

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 June 2008 (05.06.2008)

PCT

(10) International Publication Number
WO 2008/066498 A1

(51) International Patent Classification:

C12N 15/52 (2006.01) *C12N 9/00* (2006.01)
C07K 16/00 (2006.01) *C07K 14/71* (2006.01)
C07K 16/40 (2006.01) *C07K 16/30* (2006.01)
C07K 14/47 (2006.01) *C12N 15/12* (2006.01)
C07K 16/28 (2006.01)

(21) International Application Number:

PCT/SG2007/000412

(22) International Filing Date:

3 December 2007 (03.12.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/868,173 1 December 2006 (01.12.2006) US

(71) Applicant (for all designated States except US):

AGENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH [SG/SG]; 20 Biopolis Way #07-01, Centros, Singapore 138668 (SG).

(72) Inventors; and

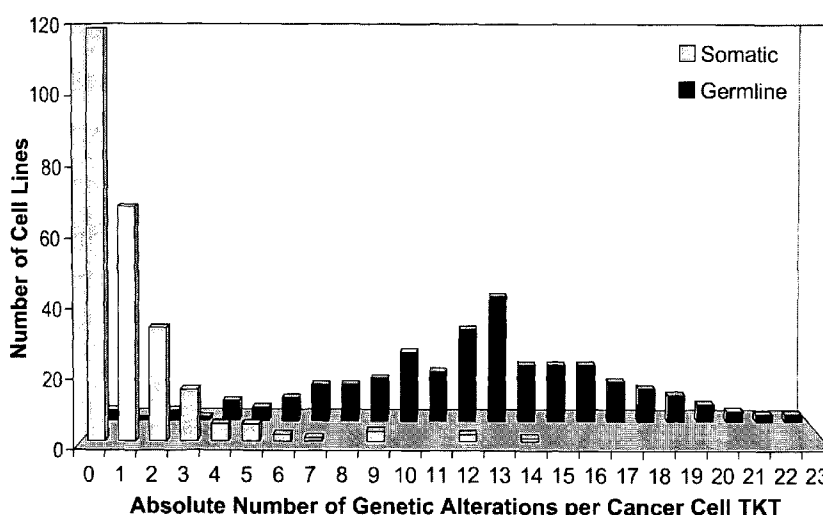
(75) **Inventors/Applicants (for US only):** **ULLRICH, Axel** [DE/DE]; Brunnstr. 5, 80331 Munich (DE). **RUHE, Jens** [DE/SG]; 21 Telok Blangah Drive, #19-06, Singapore 109258 (SG). **HART, Stefan** [DE/SG]; 135 Sunset Way, #06-15, Singapore 597152 (SG). **STREIT, Sylvia** [DE/SG]; 21 Telok Blangah Drive, #19-06, Singapore 109258 (SG). **WONG, Chee Hong** [SG/SG]; Block 52 Strathmore Avenue, #38-237, Singapore 141052 (SG). **CHUA, Boon Tin** [SG/SG]; Block 151 Yung Ho Road, #10-85, Singapore 610151 (SG).

(74) **Agent:** **SCHIWECK, Wolfram**; Viering, Jentschura & Partner LLP, P.O. Box 1088, Rochor Post Office, Rochor Road, Singapore 911833 (SG).

(81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,

[Continued on next page]

(54) Title: CANCER-RELATED PROTEIN KINASES



(57) **Abstract:** The present invention relates to mutant kinase polypeptides and kinase variants selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSFR1, CSK, DDR1, DDR2, EGFR, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRFB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, SYK, TEC, TEK, TIE, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3, YES1, and ZAP70, nucleotide sequences encoding the mutant kinase polypeptides and kinase variants, as well as various products and methods useful for the diagnosis and treatment of various kinase-related diseases and conditions, including the screening for and identification of novel protein kinase modulators.

WO 2008/066498 A1



PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,
ZM, ZW.

PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
- *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

CANCER-RELATED PROTEIN KINASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application makes reference to and claims the benefit of priority of an application for "Cancer-Related Protein Kinases" filed on December 01, 2006 with the United States Patent and Trademark Office and there duly assigned the serial number US60/868,173. The contents of said application filed on December 01, 2006 is incorporated herein by reference for all purposes, including an incorporation of any element or part of the description, claims or drawings not contained herein and referred to in Rule 20.5(a) of the PCT, pursuant to Rule 4.18 of the PCT.

FIELD OF THE INVENTION

[0002] The present invention relates to mutant protein kinases, nucleotide sequences encoding the mutated protein kinases, their use for the diagnosis and treatment of various kinase-related diseases and conditions and the design and identification of novel protein kinase inhibitors.

BACKGROUND OF THE INVENTION

[0003] The following description of the background of the invention is provided to aid in understanding the invention, but is not admitted to be or to describe prior art to the invention.

[0004] Cancer is the second most common cause of death in developed countries and is a rising health problem in less developed parts of the world. The diagnosis of cancer is connected to great physical and mental suffering for affected individuals and poses a significant burden on the health care system. For many tumors, conventional management strategies, such as surgery, radiation therapy and chemotherapy, have high toxicity with limited efficacy. Thus, an in-depth understanding of the molecular genetics underlying individual malignancies will greatly facilitate the cancer therapeutic problem is now commonly accepted among investigators in the field.

[0005] Autonomous cell growth resulting in tissue invasion and metastasis is the defining feature of all malignant neoplasms. Cancers do not necessarily arise solely as a result of an accelerated rate of cell proliferation. Rather they are the consequence of an imbalance between the rate of cell-cycle progression (cell division) and cell growth (cell mass) on one hand and programmed cell death (apoptosis) on the other. Researchers now recognize that aberrant cellular signal transduction pathways play a vital role in driving this imbalance and hence in malignant transformation.

[0006] Cellular signal transduction is a fundamental mechanism whereby external stimuli

that regulate diverse cellular processes are relayed to the interior of cells. One of the key biochemical mechanisms of signal transduction involves the reversible phosphorylation of proteins, which enables regulation of the activity of mature proteins by altering their structure and function.

[0007] Thus, one of the most critical groups of signaling molecules involved in normal and abnormal cellular regulation are the protein kinases, a family of enzymes that catalyze the phosphorylation of amino acid residues of various target molecules. This process controls fundamental cellular processes including cell cycle, migration, metabolism, proliferation, differentiation, and survival.

[0008] Protein kinases are one of the largest families of eukaryotic proteins with several hundred known members. These proteins share a 250-300 amino acid long kinase domain that can be subdivided into 12 distinct subdomains that includes the common catalytic core structure. These conserved protein motifs have recently been exploited using PCR-based cloning strategies leading to a significant expansion of the known kinases.

[0009] The best-characterized protein kinases in eukaryotes phosphorylate proteins on the hydroxyl moiety of serine, threonine and/or tyrosine residues. These kinases largely fall into two groups, those specific for phosphorylating serines and threonines, and those specific for phosphorylating tyrosines. Some kinases, referred to as "dual specificity" kinases, are able to phosphorylate on tyrosine as well as serine/threonine residues.

[0010] Protein kinases can also be characterized by their location within the cell. Some kinases are transmembrane receptor-type proteins capable of directly altering their catalytic activity in response to the external environment such as the binding of a ligand. Others are non-receptor-type proteins lacking any transmembrane domain. They can be found in a variety of cellular compartments from the inner surface of the cell membrane to the nucleus.

[0011] Many kinases are involved in regulatory cascades wherein their substrates may include other kinases whose activities are regulated by their phosphorylation state. Ultimately the activity of some downstream effector is modulated by phosphorylation resulting from activation of such a pathway.

[0012] Protein tyrosine phosphorylation, mediated by protein tyrosine kinases, is a key mechanism underlying signal transduction pathways that regulate fundamental cellular processes such as proliferation, differentiation, motility and cell survival. Deregulation of kinase activity, caused by genetic alterations, modulated expression levels, or the loss of negative regulatory control mechanisms has been described for various members of the tyrosine kinase family, and in many cases has been implicated in the development of human

cancer (Blume-Jensen, P., & Hunter, T., Nature 411, 355-365 (2001)). Consequently, tyrosine kinases have become rational targets for therapeutic intervention using both monoclonal antibodies and small molecule drugs.

[0013] First hints for genetically modified tyrosine kinases to be involved in the development of cancer came from viral oncogenes which in several cases have been shown to represent altered versions of cellular receptor tyrosine kinases. The avian erythroblastosis gene v-erbB for example has been identified as a truncated and mutated version of the human epidermal growth factor receptor EGFR (e.g. Downward, J., et al. Nature 311, 483-485, (1984)), which for the first time connected an animal oncogene with a human gene that encoded a cell growth controlling membrane protein. Furthermore, v-fms was found to represent a deleted form of the macrophage CSF-1 receptor (Coussens, L., et al. Nature 320, 277-280 (1986); Sherr, C. J., et al., Cell 41, 665-676 (1985)), and the identified truncations, deletions and mutations were speculated to form the genetic basis for the conversion of a proto-oncogene into an oncogene that can cause malignant cancer in animals.

[0014] These observations stimulated a massive search for genetic alterations of tyrosine kinases in human cancer. Several deletions and point mutations were described that result in increased catalytic activity of the EGFR. The most prevalent in tumors was found to be EGFRvIII, an EGFR deletion mutant that lacks exons 2-7, which can arise from gene rearrangement or alternative mRNA splicing (Malden, L. T., et al., Cancer Res 48, 2711-2714 (1988)). Amplification of the HER2 gene (Coussens, L., et al., Science 230, 1132-1139 (1985)) - another member of the EGFR family - was discovered as a genetic abnormality occurring in 30% of invasive human breast cancer, and a significant correlation between HER2 overexpression in tumors and reduced patient survival could be demonstrated (Slamon, D. J., et al., Science 235, 177-182 (1987)). These findings established HER2 as a prognostic marker and led to evaluate the concept of target-specific cancer therapy. In 1998, it culminated in the FDA-approval of Herceptin, a humanized monoclonal against HER2 and the first targeted anti-kinase therapeutic agent based on genomic research.

[0015] Since then it became more and more obvious that even single genetic changes were able to mediate oncogenic potential to a given kinase. This was first shown for neu, the rat homologue of the human HER2 gene, where the replacement of a single valine within the transmembrane domain by glutamic acid resulted in activation of p185 and tumorigenic activity of the modified neu proto-oncogene (Bargmann, C. I., et al., Cell 45, 649-657 (1986)). Other very well known genetic variations in tyrosine kinase genes that are associated with cancer are the BCR-ABL oncogene, a reciprocal translocation between chromosomes 9 and 22 in chronic myelogenous leukaemia (CML), and KIT receptor point mutations in

gastrointestinal stromal tumors (GISTs) (Corless, C. L., et al., J Mol Diagn. 6, 366-370 (2004)) – both being targeted by the small molecule imatinib (Gleevec, Novartis) (Demetri, G. D., Eur. J Cancer 38 Suppl 5, S52-S59 (2002); Peggs, K. & Mackinnon, S., N. Engl. J Med. 348, 1048-1050 (2003)).

[0016] In addition to their significant role in disease initiation or progression, specific mutations could be shown to mediate and thus predict sensitivity towards specific small molecule inhibitors such as imatinib or gefitinib (Iressa, AstraZeneca). Two independent groups recently described the identification of mutations clustered around the ATP binding pocket of the EGFR kinase domain and demonstrated their occurrence primarily in patients with Iressa-responsive lung cancer (Lynch, T. J., et al., N. Engl. J Med. 350, 2129-2139 (2004); Paez, J. G., et al., Science 304, 1497-1500 (2004)).

[0017] Therefore, significant efforts have been undertaken to screen for mutations in tyrosine kinase encoding genes on the level of genomic DNA, and comprehensive studies focusing on the kinase domain in colorectal cancer (Bardelli, A., et al., Science 300, 949 (2003)) or selected tumor types (Bignell, G., et al., Genes, Chromosomes & Cancer 45:42–46 (2006) (2006); Davies, H., et al., et al., Cancer Res. 65:17, 7591-7595 (2005); Stephens, P., et al., Nature 431:525-526 (2004)) have recently been reported.

[0018] For decades the traditional approach to identify cancer genes was to hand-pick likely candidates and then search for mutations within them. But since the completion of the draft human genome sequence in 2000, scientists have had the tools to go after cancer mutations in a more global and systematic way.

[0019] Scientists of the post-genome era can examine the sequences of thousands of genes in cancer cells. But because of the expense and technical limitations of current sequencing technologies, groups have for now been focusing on specific sets of genes rather than attempting to go after all of them at once.

[0020] DNA sequencing, although a major component, is only one part of the process of finding cancer mutations. Indeed cancer can arise from small mutations in the DNA sequences, changes in the number of copies of specific genes, rearrangements affecting entire chromosomes, and even from tumor viruses that land inside or next to human genes. In addition, epigenetic changes are also thought to play a role in cancer.

[0021] However, the large variation in molecular changes from one tumor to another, and even within the same tumor from one cell to another, has long been an obstacle for the development of effective therapies. Recent studies provided the first clear demonstration of the vast array of mutations present in cancer cells and identified close to 200 mutations in protein

kinase genes in lung tumors, indicating that many mutated protein kinases may be contributing to lung cancer development but that mutations in any one gene are infrequent.

[0022] For some tumors one will thus find high frequency mutations that will make good drug targets, but many will be a mixture of different low frequency mutations.

[0023] Beyond the challenge of obtaining accurate DNA sequence on such large scale, researches have to sift through the hundreds of changes identified in any one set of genes and determine which are specific to cancer and which are normal changes that occur in DNA of any individual (polymorphisms).

[0024] This problem can be addressed by comparing each cancer sequence to that of DNA taken from normal cells of the same patient. Polymorphisms should be present in both samples whereas cancer-specific changes should be present only in the cancer DNA.

[0025] The present invention relates to the identification of protein kinase mutations prevalent in human malignancies as well as methods of use of such mutated protein kinases. The invention further relates to germline variations in kinase genes that are related to tumor development and progression.

SUMMARY OF THE INVENTION

[0026] Thus, in a first aspect the invention provides an isolated, enriched, or purified nucleic acid molecule. The nucleic acid molecule encodes a mutant of a protein kinase polypeptide. The protein kinase is one of FGFR4, FGFR1, Tyro3, TEC, CSK and Ack1. Further, the mutant of the protein kinase polypeptide encoded by the nucleic acid molecule includes at least one mutation of FGFR4 Y367C, FGFR1 P252S, Tyro3 S531L, Tyro3 P822L, TEC L89R, TEC W531R, TEC P587L, CSK Q26X and ACK1 S985N.

[0027] In a second aspect invention provides a method of identifying a cell that is resistant to apoptosis inducing reagents, i.e. a cell that is chemoresistant. The method includes measuring in the cell the expression of the protein kinase Tyro3, or identifying the amino acid at position 531 and/or 822 of the expressed protein kinase Tyro3, or identifying the amino acid at position 89, 531 and/or 587 of the expressed protein kinase TEC. Where the method includes measuring in the cell the expression of the protein kinase Tyro3 the result of the measurement obtained is further compared with that of a control measurement. An increased expression of protein kinase Tyro3 indicates resistance of the cell to apoptosis inducing reagents. Where the method includes identifying the amino acid at position 531 and/or 822 of the expressed protein kinase Tyro3, the presence of Leucine at position 531 instead of Serine and/or the presence of Leucine at position 822 instead of Proline indicates increased resistance

of the cell to apoptosis inducing reagents. Where the method includes identifying the amino acid at position 89, 531 and/or 587 of the expressed protein kinase Tec, the presence of Arginine at position 89 instead of Leucine, the presence of Arginine at position 531 instead of Tryptophan, and/or the presence of Leucine at position 587 instead of Proline indicates increased resistance of the cell to apoptosis inducing reagents.

[0028] In a third aspect invention provides a method of identifying a cell that has a predisposition to transform into a cancer cell. The method includes either identifying the amino acid at position 367 of the expressed protein kinase FGFR4 and/or the amino acid at position 252 of the expressed protein kinase FGFR1, or identifying the amino acid at position 362 of the expressed protein kinase TYK2, or identifying the amino acid at position 26 of the expressed protein kinase C-terminal Src kinase (CSK), and/or identifying the amino acid at position 985 of the expressed protein kinase Ack1. Where the method includes identifying the amino acid at position 367 of the expressed protein kinase FGFR4 and/or the amino acid at position 252 of the expressed protein kinase FGFR1, the presence of Cysteine at position 367 of the expressed protein kinase FGFR4 instead of Tyrosine and/or the presence of Serine at position 252 of the expressed protein kinase FGFR1 instead of Proline indicates an increased predisposition to transform into a cancer cell. Where the method includes identifying the amino acid at position 362 of the expressed protein kinase TYK2, the presence of Phenylalanine at position 362 of the expressed protein kinase TYK2 instead of Valine indicates an increased predisposition to transform into a cancer cell. Where the method includes identifying the amino acid at position 26 of the expressed protein kinase C-terminal Src kinase (CSK), the presence of an amino acid different from Glutamine at position 26 of the expressed protein kinase CSK indicates an increased predisposition to transform into a cancer cell. Where the method includes identifying the amino acid at position 985 of the expressed protein kinase Ack1, the presence of Asparagine at position 985 of the expressed protein kinase Ack1 instead of Serine indicates an increased predisposition to transform into a cancer cell.

[0029] In a fourth aspect the invention provides an isolated, enriched, or purified nucleic acid molecule encoding a mutant kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and

ZAP70.

[0030] The mutant kinase polypeptides encoded by the nucleic acid molecules according to the invention include at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3

G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

[0031] In some embodiments, the invention features isolated, enriched, or purified nucleic acid molecules encoding a mutant kinase polypeptide comprising, consisting essentially of or consisting of a nucleotide sequence that: (a) encodes a polypeptide having the amino acid sequence set forth in SEQ ID Nos: 1-256 or any variant, isoform or fragment thereof, with the proviso that the mutated position or region is retained; (b) is the complement of the nucleotide sequence of (a).

[0032] In another embodiment, the invention is directed to an isolated, enriched, or purified nucleic acid molecule encoding a kinase polypeptide variant selected from the group consisting of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70.

[0033] The kinase variant encoded by the nucleic acid molecules according to the invention includes at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delins-PWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813_C814insQ, ROS C76fsX, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598fsX5, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX,

[0034] In some embodiments, the invention features isolated, enriched, or purified nucleic acid molecules encoding a kinase variant comprising, consisting essentially of or consisting of a nucleotide sequence that: (a) encodes a polypeptide having the amino acid sequence set forth in SEQ ID Nos: 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641 or any variant, isoform or fragment thereof, with the proviso that the altered position or region is retained; (b) is the complement of the nucleotide sequence of (a).

[0035] The nucleic acid may be isolated from a natural source by cDNA cloning or by subtractive hybridization. The natural source may be mammalian, for example, of murine, human, porcine, canine, or bovine origin. The polypeptide can be isolated from every suitable sample, including cultured cells, a biopsy, blood, semen, or any tissue derived from an organ, for example, skin, liver, pancreas to name only a few illustrative examples. In another aspect, the nucleic acid may be synthesized by the triester method or by using an automated DNA synthesizer.

[0036] In other embodiments, the invention features isolated, enriched, or purified nucleic acid molecules encoding mutant kinase polypeptides, further comprising a vector or promoter effective to initiate transcription in a host cell.

[0037] In a fifth aspect the invention also features a recombinant nucleic acid, for instance in a cell or an organism. The recombinant nucleic acid may include, consist essentially of or consist of a sequence set forth in SEQ ID Nos: 257-512, 643-646, 649, 654-655, 657-658, 663, 667-668, 673, 677-680, 692, 701-703, 713-717, 719-721, 728, 730-731, 737, 746, 750-751, 753-754, 756, 760, 762-764, 767, and 770-771, or a functional derivative thereof and, optionally, a vector or a promoter effective to initiate transcription in a host cell. The recombinant nucleic acid can alternatively contain a transcriptional initiation region functional in a cell, a sequence complementary to an RNA sequence encoding a kinase polypeptide and a transcriptional termination region functional in a cell. Specific vectors and host cell combinations are discussed herein.

[0038] In yet other embodiments, the nucleic acid is useful for the design of hybridization probes to facilitate identification and cloning of mutated kinase polypeptides or kinase variants, the design of PCR probes to facilitate cloning of mutated kinase polypeptides or kinase variants, obtaining antibodies to mutated kinase polypeptide or kinase variants, and designing antisense oligonucleotides.

[0039] In a sixth aspect, the invention provides a nucleic acid probe for the detection of a nucleic acid that encodes a mutant kinase polypeptide in a sample. The mutant kinase

polypeptide is selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, comprising at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK

L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V. The nucleic acid probe may include, consist essentially of or consist of a nucleotide base sequence that will hybridize to the mutated region of the nucleic acid sequence set forth in any of SEQ ID Nos: 257-512 or a functional derivative thereof.

[0040] In a seventh aspect, the present invention also features a nucleic acid probe for the detection of nucleic acid that encodes a kinase variant in a sample. The altered kinase polypeptide is one of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70 comprising at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813_C814insQ, ROS C76fsX, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598fsX5, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70

K186fsX. In some embodiments, the nucleic acid probe includes, consists essentially of or consists of a nucleotide base sequence that will hybridize to the mutated region of the nucleic acid sequence set forth in any of SEQ ID Nos: 643-646, 649, 654-655, 657-658, 663, 667-668, 673, 677-680, 692, 701-703, 713-717, 719-721, 728, 730-731, 737, 746, 750-751, 753-754, 756, 760, 762-764, 767, and 770-771, or a functional derivative thereof.

[0041] Methods for using the probes of the invention include detecting the presence or amount of mutated or altered kinase RNA in a sample by contacting the sample with a nucleic acid probe under conditions such that hybridization occurs and detecting the presence or amount of the probe bound to kinase RNA. The nucleic acid duplex formed between the probe and a nucleic acid sequence coding for a kinase polypeptide may be used in the identification of the sequence of the nucleic acid detected. In certain embodiment, kits for performing such methods may be constructed to include a container means having disposed therein a nucleic acid probe.

[0042] The present invention also relates to the use of a set of the mutant kinase polypeptides, the nucleic acids encoding the mutant kinase polypeptides, and the nucleic acid probes of the invention as molecular markers for the diagnosis of proliferative diseases or disorders in a subject. Such a method may also be useful to predict the risk of cancer with high predictive accuracy and/or to choose an adequate therapy. Moreover, such a method may also be useful to monitor the course of a treatment regimen and/or to predict the risk or cancer recurrence.

[0043] Thus, the present invention also encompasses a method that allows predicting or diagnosing proliferative diseases or disorders, such as cancer, in a subject comprising the steps of (a) obtaining a biological sample from the subject; and (b) detecting the expression of one or more nucleic acid molecules encoding the mutant kinase polypeptides of the invention in said sample.

[0044] In one embodiment of the invention, these two or more nucleic acid molecules the expression of which is to be detected includes, consist essentially of or consist of at least one of the nucleotide sequences set forth in SEQ ID Nos: 257-512, or complements and fragments thereof. Such a combination of two ore more of these molecular markers may be utilized for the risk prediction or diagnosis of cancer in a subject. Any combination of at least two of the above nucleic acid molecules may be used for this analysis. For example, in some embodiments, a combination of at least 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 50, 60, 70, 80, 90 or more of the nucleotide sequences set forth in SEQ ID Nos: 257-512 may be used for said diagnostic purpose.

[0045] In another aspect, the invention is also directed to the use of a set of kinase variants, i.e. kinases that include germline alterations such as single nucleotide polymorphisms, the nucleic acids encoding these kinase variants, and nucleic acid probes for the nucleic acids encoding these kinase variants as molecular markers for the diagnosis of proliferative diseases or disorders in a subject. Such a method may also be useful to predict the risk of cancer development and/or metastasis with high predictive accuracy. Further, such method may also allow to choose an adequate therapy, monitor the course of a treatment regimen and/or to predict the risk of cancer recurrence.

[0046] Suitable kinase variants include, but are not limited to AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813_C814insQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76fsX, RYK N96S, RYK F516L, Styk G204S, TEK P346Q, TEK , V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598fsX5, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del

[0047] Thus, the present invention also encompasses a method that allows predicting or

diagnosing proliferative diseases or disorders, such as cancer, in a subject. The method includes the steps of (a) obtaining a biological sample from the subject; and (b) detecting the expression of one or more nucleic acid molecules encoding the kinase variants of the invention in said sample.

[0048] In one embodiment of the invention, these one or more nucleic acid molecules the expression of which is to be detected include, consist essentially of or consist of at least one of the nucleotide sequences set forth in SEQ ID Nos: 643-772 or complements and fragments thereof. Such a combination of two or more of these molecular markers may be utilized for the risk prediction or diagnosis of cancer in a subject. Any combination of at least two of the above nucleic acid molecules may be used for this analysis. For example, in some embodiments, a combination of at least 5, 7, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90 or all 91 of the nucleotide sequences set forth in SEQ ID Nos: 643-772 may be used for said diagnostic purpose.

[0049] In still another aspect, the invention provides a recombinant cell or tissue comprising a nucleic acid molecule encoding a kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, including at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R,

EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V. In such cells, the nucleic acid may be under the control of the genomic regulatory elements, or may be under the control of one or more heterologous regulatory elements including a heterologous promoter. In certain embodiments, the kinase polypeptide is a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID Nos: 1-256, or the corresponding full-length amino acid sequence, wherein said fragment includes the mutated region.

[0050] Alternatively, the present invention provides a recombinant cell or tissue comprising a nucleic acid molecule encoding a kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70 including at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRFA L221F, PDGFRFA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813_C814insQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76fsX, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598fsX5, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del. In such cells, the nucleic acid may be under the control of the genomic regulatory elements, or may be under the control of one or more heterologous regulatory elements including a heterologous promoter. In certain embodiments, the kinase polypeptide is a fragment of the protein encoded

by the amino acid sequence set forth in SEQ ID Nos: 513-642, or the corresponding full-length amino acid sequence, wherein said fragment includes the mutated region.

[0051] In still another aspect, the invention provides an isolated, enriched, or purified mutant kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, including at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S,

INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

[0052] In some embodiments, the mutant kinase polypeptide is a fragment of the protein with the amino acid sequence set forth in SEQ ID Nos: 1-256, or the corresponding full-length amino acid sequences, with the proviso that the mutation is included in said fragment. Also included are variants and isoforms of the mutant kinases of the invention.

[0053] The invention further provides an isolated, enriched, or purified kinase variant selected from the group consisting of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70 including at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON

R627fsX23, RON R813_C814insQ, ROS C76fsX, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598fsX5, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX.

[0054] In certain embodiments, the kinase variant is a fragment of the protein with the amino acid sequence set forth in SEQ ID Nos.: 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641, or the corresponding full-length amino acid sequences as well as isoforms thereof, with the proviso that the mutation is included in said fragment.

[0055] The polypeptide can be isolated from a natural source by methods well-known in the art. The natural source may be mammalian, for example, of murine, human, porcine, canine, or bovine origin. The polypeptide can be isolated from every suitable sample, including cultured cells, a biopsy, blood, semen, or any tissue derived from an organ, for example, skin, liver, pancreas to name only a few illustrative examples. In another embodiment the polypeptide may be synthesized using an automated polypeptide synthesizer.

[0056] In certain embodiments the invention includes the above mutant kinases and kinase variants, wherein the mutant kinases or kinase variants are of recombinant origin. For example, the mutant kinases and kinase variants of the invention may be expressed in a heterologous expression system.

[0057] In a further aspect, the invention provides an antibody (*e.g.*, a monoclonal or polyclonal antibody) having specific binding affinity only for a mutant kinase polypeptide or a mutant kinase polypeptide domain or fragment, where the polypeptide is selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, including at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL

M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK

A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

[0058] Also included in the present invention are antibodies (*e.g.*, monoclonal or polyclonal antibodies) having specific binding affinity only for a kinase variant or a kinase variant domain or fragment, where the polypeptide is selected from the group consisting of the or the group AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70 including at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSFR1 H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRFA L221F, PDGFRFA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813_C814insQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76fsX, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598fsX5, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2

G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del.

[0059] Antibodies or antibody fragments having specific binding affinity only for a mutant kinase polypeptide or a kinase variant of the invention may be used in methods for detecting the presence and/or amount of mutant kinase polypeptide or kinase variant in a sample by probing the sample with the antibody under conditions suitable for kinase-antibody immuno-complex formation and detecting the presence and/or amount of the antibody conjugated to the kinase polypeptide. The antibodies of the invention are thus capable of differentiating between the mutant/variant and the native form of a kinase polypeptide.

[0060] Diagnostic kits for performing such methods may be constructed to include antibodies or antibody fragments specific for the kinase as well as a conjugate of a binding partner of the antibodies or the antibodies themselves. Diagnostic kits for performing such methods may be constructed to include a first container containing the antibody and a second container having a conjugate of a binding partner of the antibody and a label, such as, for example, a radioisotope. The diagnostic kit may also include notification of an FDA approved use and instructions therefor.

[0061] An antibody or antibody fragment with specific binding affinity only for a mutant kinase polypeptide or a kinase variant of the invention can be isolated, enriched, or purified from a prokaryotic or eukaryotic organism. Routine methods known to those skilled in the art enable production of antibodies or antibody fragments, in both prokaryotic and eukaryotic organisms. Purification, enrichment, and isolation of antibodies, which are polypeptide molecules, are described above.

[0062] In a further aspect, the invention relates to methods for identifying a compound that modulates kinase activity comprising: (a) contacting a kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, including at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1

G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90,

ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V, with a test substance; (b) measuring the activity of said polypeptide; and (c) determining whether said substance modulates the activity of said polypeptide.

[0063] In addition to applying the above method to the mutant kinase polypeptides of the invention, such a method may also be suitable to test compounds for their activity for the kinase variants of the invention. These kinase variants include, but are not limited to AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70. These kinases include at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRFA L221F, PDGFRFA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813_C814insQ, RON

R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76fsX, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598fsX5, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del.

[0064] In another aspect, the invention refers to methods for identifying a substance that modulates kinase activity in a cell comprising the steps of: (a) expressing a kinase polypeptide in a cell, wherein said polypeptide is selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, including at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER

Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V, (b) adding a test substance to said cell; and (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

[0065] Alternatively, kinase variants may be used in such a method, wherein the kinase variants include at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES

P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813_C814insQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76fsX, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598fsX5, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del.

[0066] In yet another aspect, the invention provides methods for treating or preventing a proliferative disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a mutant kinase selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70. The mutant kinase includes at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR

A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1

A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V. In some embodiments the disease is cancer.

[0067] In another embodiment, the method for treating or preventing a proliferative disease or disorder includes administering to a patient in need of such treatment a substance that modulates the activity of a kinase variant associated with such a disease or disorder, the kinase variant being selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70. These kinases include at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813_C814insQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76fsX, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598fsX5, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3

Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del .

[0068] The present invention also provides a method for screening for human cells containing a mutant kinase polypeptide of the invention or an equivalent sequence. The method involves identifying the mutant polypeptide in human cells using techniques that are routine and standard in the art, such as those described herein for identifying the mutant kinases of the invention (*e.g.*, cloning, Southern or Northern blot analysis, in situ hybridization, PCR amplification, etc.).

[0069] Thus, in a further aspect, the invention encompasses methods for the detection of a nucleic acid encoding a mutant kinase polypeptide or a kinase variant in a sample as a diagnostic tool for diseases or disorders, wherein the method includes the steps of: (a) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to

(i) a nucleic acid target region of a mutant kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, with these mutant kinases including at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2

R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V; or

(ii) a nucleic acid target region of a kinase variant selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRA, PDGFRB,

PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70, with these kinases including at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813_C814insQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76fsX, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598fsX5, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del. The probe includes the nucleic acid sequence that encodes the mutant kinase polypeptide or the kinase variant, fragments thereof, or the complements of the sequences and fragments; and (b) detecting the presence or amount of the probe:target region hybrid as an indication of the disease.

[0070] In certain embodiments of the invention, the disease or disorder is a proliferative disease or disorder, for example, cancer.

[0071] In certain embodiments the nucleic acid probes of the invention hybridizes to a kinase target region encoding at least 6, 12, 75, 90, 105, 120, 150, 200, 250, 300 or 350 contiguous amino acids of the sequence set forth in SEQ ID Nos: 1-256 and 513-642, or the

corresponding full-length amino acid sequence, or a functional derivative thereof, with the proviso that the mutated region is included. Hybridization conditions should be such that hybridization occurs only with the kinase genes in the presence of other nucleic acid molecules. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. Typically, such conditions prevent hybridization of nucleic acids having one or more mismatches in 20 contiguous nucleotides.

[0072] The diseases that could be diagnosed by detection of mutated or altered kinase nucleic acid in a sample may include cancers. The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well-known in the art and can be readily adapted in order to obtain a sample that is compatible with the method utilized.

[0073] The summary of the invention described above is not limiting and other features and advantages of the invention will be apparent from the following detailed description of the invention, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0074] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0075] **Figure 1A** shows the origin of tissue samples and number of tumor cell lines derived thereof, **Fig. 1B** patterns of genetic alterations for 5 skin-derived tumor cell lines and **Fig. 1C** the number of somatic (bright) or germline (dark) alterations in the characterization of the tyrosine kinase transcriptome of tumor cell lines.

[0076] **Figure 2** illustrates the genetic alterations of the FGFR4 gene detected in tumor cell lines and control samples.

[0077] **Figure 3A** depicts the rates of germline alterations of non-synonymous polymorphisms identified in the TKT of 276 cancer cell lines and control samples (MS= missense substitution, NS= nonsense substitution, DEL= deletion, INS= insertions). **Fig 3B** shows the domain localization of identified polymorphisms. **Fig 3C** depicts the tissue distribution of germline variations (BL= bladder; BS= bone and soft tissue; BA= brain; BE= breast; CV= cervix and vulva; CO= colon; EP= endometrium and placenta; HN= head and

neck; HL= hematopoietic and lymphoid system; KI= kidney; LI= liver; LU= lung; OV= ovary; PA= pancreas; PR= prostate; SK= skin; ST= stomach; TE= testes; TY= thyroid, NO= normal control samples).

[0078] Figure 4 depicts the diverging occurrence rates of polymorphisms in different tumor types and/or control samples. The frequency of homozygous (HO; dark bar) and heterozygous (HE; light bar) carriers of (A) EGFR R521K, (B) TYK2 V362F and (C) TNK1 M598delinsEVRSHX was determined. Only tissue origins (for abbreviations see legend to Fig. 1, supra) with an expression of the corresponding gene in at least 10 samples have been selected for this analysis.

[0079] Figure 5 depicts the distributions of non-synonymous somatic mutations identified in all transcribed PTK genes from 254 tumor cell lines. **A**, rates of somatic mutations. The allocation to missense (MS) or nonsense (NS) substitutions, deletions (DEL) and insertions (INS) as well as frequency categories (1, 2-5, 6-10 or more than 10 affected samples) is shown. **B**, domain localization of identified mutations. The localization within defined domains or other protein regions is indicated. **C**, tissue distribution of sporadic alterations. For each somatic mutation, the tissue distribution (see legend to Fig. 3 for abbreviations) was determined (Fig. 35) and presented here for text-related examples. Paired numerals indicate the number of mutated and expression-positive cell lines within a given tumor type. Novel somatic mutations are highlighted in bold type.

[0080] Figure 6 is an illustration of known and novel genetic alterations in selected genes. **A**, SYK. The domain organization and location of genetic alterations is displayed. **B**, sequence comparison of FGFR1-4. For FGFR1-4, the general domain organization (middle) and sequence comparisons of the linker region connecting the IG-D2- and IG-D3-domain (top) as well as a part of the extracellular juxtamembrane region (bottom) are illustrated. Genetic alterations identified in the cell line screen are illustrated below, known sequence variants are depicted above the graphical representation of the domain structure. Polymorphisms are underlined and somatic mutations are not highlighted. Numbers in parenthesis indicate the number of affected non-related cell lines. (SH2: Src Homolgy 2 Domain; TK: Tyrosine Kinase Domain; S: Signal Peptide; TM: Transmembrane Domain; IG: Immunoglobulin-Like Domain).

[0081] Figure 7 shows overexpression of FGFR4 in hepatocellular carcinoma (HCC) patients (n= 57) in the tumor vs. the adjacent normal tissue as determined by real-time PCR.

[0082] Figure 8 shows the corresponding Ct values of the detected FGFR4 overexpression shown in Fig. 7.

[0083] **Figure 9** shows that a single nucleotide polymorphism, G388R is highly represented in the Asian population, including HCC patients.

[0084] **Figure 10** depicts alpha-fetoprotein (AFP) levels in HCC patients, an oncofetal protein serving as a diagnostic marker for hepatocellular carcinoma. In patients with hepatoma, the incidence of elevated AFP levels correlates with tumor burden (60-70% of HCC patients exhibit AFP elevation). Fig. 10 shows that the homozygous 388Arg genotype correlates with an increased AFP secretion at the point of tumor resection.

[0085] **Figure 11** shows elevated AFP production caused by stimulation of FGFR4 in the HCC cell line HuH7 using 50 and 100 ng/ml of the specific ligand FGF19.

[0086] **Figure 12** shows elevated AFP production caused by stimulation of FGFR4 in the HCC cell line HepG2 using 50 and 100 ng/ml of the specific ligand FGF19.

[0087] **Figure 13** depicts gene silencing of FGFR4 by siRNA. A= control siRNA, B= FGFR4 siRNA.

[0088] **Figure 14** shows AFP production in HuH7 cells after gene silencing of FGFR4 by siRNA.

[0089] **Figure 15** shows AFP production in HuH7 cells after exposure to 0, 1, 5 and 10 μ M of the commercially available non-selective FGFR inhibitor PD173074. SF= serum free

[0090] **Figure 16** depicts the viability of HuH7 exposed to the FGFR inhibitor PD173074. An exquisite anti-proliferative effect can be observed.

[0091] **Figure 17** depicts a decreased Tyrosinphosphorylation of TEC mutants. Reduced tyrosine phosphorylation was observed for TEC L89R, TEC W531R and TEC P587L, but not TEC R563K (IP = immunoprecipitation, IB = immunoblot, α -HA = anti Hemagglutinin antibody, α -PY = anti phosphor tyrosin antibody).

[0092] **Figure 18** illustrates the genetic alterations of TEC-kinase identified by the present inventors (TEC L89R, TEC W531R and TEC P587L).

[0093] **Figure 19** shows a decreased MAPK signaling of TEC mutants indicated by decreased MAPK phosphorylation. No activation of the MAPK pathway was observed for TEC L89R, TEC W531R and TEC P587L.

[0094] **Figure 20** depicts a c-fos gene reporter assay (HEK293 cells, 18h), performed to compare TEC wt with TEC mutants. TEC kinase is involved in B-cell receptor induced c-fos promoter activity (Aoki, N., et al., *J Biol Chem.* 2004 Mar 12; 279(11):10765-10775 (2004), Epub 2003 Dec 16). Overexpression of TEC wt and TEC R563K showed enhanced luciferase

expression but not TEC L89R, TEC W531R, TEC P589L and TEC KM.

[0095] Figure 21 depicts a decreased Stat3 activation of the TEC mutants.

[0096] Figure 22 shows an *in vitro* Ubiquitination assay Hek293 transfected with myc-Ubiquitin and Flag-protein of interest. An exchange of amino acid 985 from Serine to Asparagine resulted in a protein of higher stability that is less sensitive to ubiquitination.

[0097] Figure 23 shows the overexpression of TYK2 mutants in HEK293 cells.

[0098] Figure 24 depicts tumor cell lines, control cell lines, and tissues from healthy individuals. The name, origin, reference number, and supplier/source of the tumor cell lines, normal cell lines, and tissues from healthy individuals analyzed in the screen are specified. Related tumor cell lines are indicated by parenthesized asterisks and identical numerals. (ATCC: The American Type Culture Collection, Manassas (VA), USA; DKFZ: Tumorbank Deutsches Krebsforschungszentrum, Heidelberg, Germany; DSMZ: German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany; ECACC: The European Collection of Cell Cultures, Porton Down, Salisbury, UK)

[0099] Figure 25 lists the primary tumor samples used, identifiers for the 55 primary kidney, prostate and breast cancer samples are listed.

[0100] Figure 26 shows the primers used for PCR amplification and sequencing of PTK genes.

[0101] Figure 27 shows the primers used for PCR amplification and sequencing of PTK gene fragments using genomic DNA as template.

[0102] Figure 28 indicates the NCBI accession numbers of PTK reference sequences. Accession numbers of NCBI (<http://www.ncbi.nlm.nih.gov>) sequence files that served as references for sequences alignments are listed.

[0103] Figure 29 lists the genetic alterations identified in all cDNA samples. Sequence differences occurring in all cDNA samples analyzed are shown. References for previously described alterations are provided. Homozygosity (HO) or heterozygosity (HE) is indicated.

[0104] Figure 30 shows the characterization of each tumor- and control cell line with regard to somatic and germline alterations in the transcripts of PTK genes. Somatic mutations are underlined.

[0105] Figure 31 depicts the characterization of PTK genes with regard to identified somatic and germline alterations in the transcripts of 276 tumor cell lines and control samples. For each tyrosine kinase gene, the spectrum of identified genetic alterations and the

corresponding patterns of affected tumor cell lines or control samples are presented. Receptor- and non-receptor tyrosine kinase genes reflect the categorization into subfamilies, cancer cell lines are subdivided according to their tissue origin. The total sample number carrying a given sequence variant is indicated. Heterozygosity is indicated by a hash.

[0106] **Figure 32** lists the SEQ ID Nos for both the amino acid sequences (“protein”) and the nucleic acid sequences (“nt”) of the identified somatic alterations.

[0107] **Figure 33** lists the SEQ ID Nos for both the amino acid sequences (“protein”) and the nucleic acid sequences (“nt”) of the identified germline alterations.

[0108] **Figure 34** specifies the frameshift alterations and insertions. Detailed amino acid sequence information is provided for selected frameshift (fs) alterations and insertions. Nomenclature of sequence alterations is based on suggestions by the Human Genome Variation Society (HGVS; Kong-Beltran, M., et al., Cancer Res, 66: 283-289 (2006)).

[0109] **Figure 35** depicts the domain localization and tissue distribution of identified polymorphisms (abbreviations for the Ig-like domain: [A] = H199_Q247delins48; [B] = T311_Q422del (Bounacer, et al, 2002, supra)*).

[0110] **Figure 36** shows the genetic alterations analyzed in primary tumor samples.

[0111] **Figure 37** depicts the domain localization and tissue distribution of identified somatic mutations.

[0112] **Figure 38** depicts the absolute numbers of somatic mutations in transcribed PTK genes from 254 tumor cell lines.

[0113] **Figure 39** depicts the normalized mutational frequencies of transcribed PTK genes. Somatic mutation frequencies - normalized with respect to the expression status among the 254 tumor cell lines - are provided for each PTK gene and expressed as number of mutations per 1 Mb of cDNA.

DETAILED DESCRIPTION OF THE INVENTION

[0114] The present invention relates to altered kinase polypeptides, nucleic acids encoding such polypeptides, cells containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. The present invention is based upon the identification of mutant kinase polypeptides and kinase variants involved in human malignancies. The polypeptides and nucleic acids of the invention may be produced using well-known and standard synthesis techniques when given the sequences presented herein.

[0115] The term "nucleic acid molecule" as used herein refers to any nucleic acid in any possible configuration, such as single stranded, double stranded or a combination thereof. Nucleic acids include for instance DNA molecules, RNA molecules, analogues of the DNA or RNA generated using nucleotide analogues or using nucleic acid chemistry, locked nucleic acid molecules (LNA), protein nucleic acids molecules (PNA) and tecto-RNA molecules (e.g. Liu, B., et al., J. Am. Chem. Soc. 126, 4076-4077 (2004)). LNA has a modified RNA backbone with a methylene bridge between C4' and O2', providing the respective molecule with a higher duplex stability and nuclease resistance. DNA or RNA may be of genomic or synthetic origin. A respective nucleic acid may furthermore contain non-natural nucleotide analogues and/or be linked to an affinity tag or a label.

[0116] Many nucleotide analogues are known and can be used in nucleic acids used in the methods of the invention. A nucleotide analogue is a nucleotide containing a modification at for instance the base, sugar, or phosphate moieties. As an illustrative example, a substitution of 2'-OH residues of siRNA with 2'F, 2'O-Me or 2'H residues is known to improve the *in vivo* stability of the respective RNA. Modifications at the base moiety include natural and synthetic modifications of A, C, G, and T/U, different purine or pyrimidine bases, such as uracil-5-yl, hypoxanthin-9-yl, and 2-aminoadenin-9-yl, as well as non-purine or non-pyrimidine nucleotide bases. Other nucleotide analogues serve as universal bases. Universal bases include 3-nitropyrrole and 5-nitroindole. Universal bases are able to form a base pair with any other base. Base modifications often can be combined with for example a sugar modification, such as for instance 2'-O-methoxyethyl, e.g. to achieve unique properties such as increased duplex stability.

I. The Nucleic Acids of the Invention

[0117] As mentioned above, the invention also relates to nucleic acid molecules that encode a mutant protein kinase polypeptide. In some embodiments the mutant protein kinase polypeptide is one of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70. These mutant kinases include one or more of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L,

ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS

D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

[0118] In another aspect, the invention is directed to a nucleic acid molecule encoding a protein kinase polypeptide variant. In some embodiments the protein kinase polypeptide variant is one of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70 and includes at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRFA L221F, PDGFRFA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813_C814insQ, ROS C76fsX, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598fsX5, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX.

[0119] In certain aspects of the invention, the nucleic acid molecules may be isolated, enriched, or purified. The mutant kinase polypeptide encoded by said nucleic acid molecules may include, consist essentially of or consist of the amino acid sequence set forth in SEQ ID Nos: 1-256, 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641. Also included are nucleic acids encoding mutant kinase polypeptide fragments of said amino acid sequences set forth in SEQ ID Nos: 1-256, 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641, as long as the mutation or mutated region is retained. In some embodiments, these fragments are at least 10, at least 15, at least 20, at least 30 or at least 35 amino acids long.

[0120] By "isolated" in reference to a nucleic acid is meant a polymer of nucleotides

conjugated to each other, including DNA and RNA, that is isolated from a natural source or that is synthesized. The isolated nucleic acids of the present invention are not found in a pure or separated state in nature. Use of the term "isolated" indicates that a naturally occurring sequence has been removed from its normal cellular (*i.e.*, chromosomal) environment. Thus, the sequence may be in a cell-free solution or placed in a different cellular environment. The term does not imply that the sequence is the only nucleotide chain present, but that it is essentially free (about 90 - 95% pure at least) of non-nucleotide material naturally associated with it, and thus is distinguished from isolated chromosomes.

[0121] By the use of the term "enriched" in reference to nucleic acid is meant that the specific DNA or RNA sequence constitutes a significantly higher fraction (2 - 5 fold) of the total DNA or RNA present in the cells or solution of interest than in normal or diseased cells or in the cells from which the sequence was taken. This could be achieved by reducing the amount of other DNA or RNA present, or by increasing the amount of the specific DNA or RNA sequence, or by a combination of the two. However, it should be noted that being enriched does not imply that there are no other DNA or RNA sequences present, it merely defines that the relative amount of the sequence of interest has been significantly increased.

[0122] The term "significant" is used to indicate that the level of increase is useful to the person making such an increase, and generally means an increase relative to other nucleic acids of about at least about 2 fold, such as at least about 5 to about 10 fold or even more. The term does also not imply that there is no DNA or RNA from other sources present. As an illustrative example, another source of DNA may, for example, include a yeast or bacterial genome, or a cloning vector. This term distinguishes from naturally occurring events, such as viral infection, or tumor type growths, in which the level of one mRNA may be naturally increased relative to other species of mRNA. That is, the term is meant to cover only those situations in which a person has intervened to elevate the proportion of the desired nucleic acid.

[0123] It is also advantageous for some purposes that a nucleotide sequence be present in purified form. The term "purified" in reference to nucleic acid does not require absolute purity (such as a homogeneous preparation). Instead, it represents an indication that the sequence is relatively more pure than in the natural environment (compared to the natural level this level should be at least 2-5 fold greater, *e.g.*, in terms of mg/ml). Individual clones isolated from a cDNA library may be purified to electrophoretic homogeneity. The claimed DNA molecules obtained from these clones could be obtained directly from total DNA or from total RNA. The cDNA clones are not naturally occurring, rather they are typically obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The construction of a

cDNA library from mRNA involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection of the cells carrying the cDNA library. Thus, the process which includes the construction of a cDNA library from mRNA and isolation of distinct cDNA clones yields an approximately 10^6 -fold purification of the native message. Thus, purification of at least one order of magnitude, including two or three orders, and more, such as four or five orders of magnitude is expressly contemplated.

[0124] By a "mutant kinase polypeptide" as used herein is meant a protein kinase polypeptide including a somatic mutation. Such a mutation may be a deletion, insertion or substitution of one or more amino acids. In some embodiments, the term refers to a contiguous sequence of at least about 50, such as about 100, about 200, or about 300 amino acids set forth in the amino acid sequence of SEQ ID Nos: 1-256, or the corresponding full-length amino acid sequence, with the proviso that the desired mutation is included in said amino acid sequence. In case the mutation leads to a premature stop codon in the nucleotide sequence encoding the mutant kinase polypeptide, the sequence may even be shorter than the above 50 amino acids. The kinase polypeptide can be encoded by a full-length nucleic acid sequence, i.e. the complete coding sequence of the respective gene, or any portion of the full-length nucleic acid sequence, as long as the mutation of the polypeptide is retained.

[0125] The amino acid sequences will be substantially similar to the sequences shown in SEQ ID Nos: 1-256, or to fragments thereof. A sequence that is substantially similar to any one of the sequences of SEQ ID Nos: 1-256 or fragment thereof will in some embodiments have at least about 80, such as at least about 90% identity (in some embodiments at least about 95% or 99-100%) to the sequence of SEQ ID Nos: 1-256, with the proviso that the desired mutation is retained.

[0126] The term "kinase variant" or "protein kinase polypeptide variant" relates to a kinase polypeptide that includes a germline alteration. Such an alteration may be a deletion, insertion or substitution of one or more amino acids, and may include single nucleotide polymorphisms (SNPs). While such alterations may themselves not be pathological, they may play a role in the predisposition, development and progression of proliferative diseases and disorders, for example human malignancies. In the context of the present invention, the term 'kinase variant' in some embodiments refers to a contiguous sequence of at least about 50, such as about 100, about 200, or about 300 amino acids set forth in the amino acid sequence of SEQ ID Nos: 513-642, or the corresponding full-length amino acid sequence, with the proviso that said alteration is included in said amino acid sequence. In case the mutation leads to a premature stop codon in the nucleotide sequence encoding the kinase variant, the sequence

may even be shorter than the above 50 amino acids. The kinase polypeptide can be encoded by a full-length nucleic acid sequence, i.e. the complete coding sequence of the respective gene, or any portion of the full-length nucleic acid sequence, as long as the alteration of the polypeptide is retained.

[0127] The amino acid sequences will be substantially similar to the sequences shown in SEQ ID Nos: 513-642 or to fragments thereof. A sequence that is substantially similar to any one of the sequences of SEQ ID Nos: 513-642 or fragment thereof will in some embodiments have at least 80, such as at least 90% identity (in some embodiments at least 95% or 99-100%) to the sequence of SEQ ID Nos: 513-642, with the proviso that the altered position or sequence is retained.

[0128] By "identity" is meant a property of sequences that measures their similarity or relationship. Identity is measured by dividing the number of identical residues by the total number of residues and gaps and multiplying the product by 100.

[0129] "Gaps" are spaces in an alignment that are the result of additions or deletions of amino acids. Thus, two copies of exactly the same sequence have 100% identity, but sequences that are less highly conserved, and have deletions, additions, or replacements, may have a lower degree of identity. Those skilled in the art will recognize that several computer programs are available for determining sequence identity using standard parameters, for example Blast (Altschul, *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402), Blast2 (Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410), and Smith-Waterman (Smith, *et al.* (1981) *J. Mol. Biol.* 147:195-197).

[0130] The term "mutated" or "mutant" in reference to a nucleic acid or a polypeptide refers to the exchange, deletion, or insertion of one or more nucleotides or amino acids, respectively, compared to the naturally occurring nucleic acid or polypeptide.

[0131] The term "altered" or "variant" in reference to a nucleic acid or polypeptide refers to polymorphisms, i.e. the exchange, deletion, or insertion of one or more nucleotides or amino acids, respectively, compared to the predominant form of the respective nucleic acid or polypeptide.

[0132] Also encompassed by the present invention are nucleic acid molecules substantially complementary to the above nucleic acid molecules. "Substantially complementary" as used herein refers to the fact that a given nucleic acid molecule is at least 90, at least 95, or 99 or 100% complementary to another nucleic acid. The term "complementary" or "complement" refers to two nucleotides that can form multiple favorable interactions with one another. Such favorable interactions include Watson-Crick base pairing. A nucleotide sequence is the

complement of another nucleotide sequence if all of the nucleotides of the first sequence are complementary to all of the nucleotides of the second sequence.

[0133] The nucleic acids according to the invention may be isolated from a natural source by cDNA cloning or subtractive hybridization or other routine techniques known to a person skilled in the art. The natural source may be any organism. As an illustrative example, the nucleic acids may be isolated from a mammalian source. It may for example be of human origin. The natural source can include blood, semen, or tissue.

[0134] The term "mammalian" refers to any mammal, for example, species such as mice, rats, rabbits, guinea pigs, sheep, and goats, cats, dogs, monkeys, apes, and humans.

[0135] The nucleic acids of the invention may also be synthetic, meaning being synthesized by the triester method or by using an automated DNA synthesizer.

[0136] The above nucleic acid molecules of the invention encoding mutant kinase polypeptides, may further include a vector or promoter effective to initiate transcription in a host cell. The recombinant nucleic acid can alternatively contain a transcriptional initiation region functional in a cell, a sequence complementary to an RNA sequence encoding a kinase polypeptide and a transcriptional termination region functional in a cell. Specific vectors and host cell combinations are discussed herein. Thus, the present invention also encompasses nucleic acids of recombinant origin, such as a cell or an organism.

[0137] The term "vector" relates to a single or double-stranded circular nucleic acid molecule that can be transfected into cells and replicated within or independently of a cell genome. A circular double-stranded nucleic acid molecule can be cut and thereby linearized upon treatment with restriction enzymes. An assortment of nucleic acid vectors, restriction enzymes, and the knowledge of the nucleotide sequences cut by restriction enzymes are readily available to those skilled in the art. A nucleic acid molecule encoding a kinase can be inserted into a vector by cutting the vector with restriction enzymes and ligating the two pieces together.

[0138] The term "promoter" as used herein, refers to nucleic acid sequence needed for gene sequence expression. Promoter regions vary from organism to organism, but are well known to persons skilled in the art for different organisms. For example, in prokaryotes, the promoter region contains both the promoter (which directs the initiation of RNA transcription) as well as the DNA sequences which, when transcribed into RNA, will signal synthesis initiation. Such regions will normally include those 5'-non-coding sequences involved with initiation of transcription and translation, such as the TATA box, capping sequence, CAAT sequence, and the like.

[0139] The nucleic acids according to the invention may include, consist essentially of or

consist of the nucleotide sequence set forth in any one of SEQ ID Nos: 257-512. Alternatively, the nucleic acids of the invention may also include, consists essentially of or consist of the nucleotide sequence set forth in any one of SEQ ID Nos: 643-646, 649, 654-655, 657-658, 663, 667-668, 673, 677-680, 692, 701-703, 713-717, 719-721, 728, 730-731, 737, 746, 750-751, 753-754, 756, 760, 762-764, 767, and 770-771.

[0140] Included within the scope of this invention are the functional equivalents of the herein-described isolated nucleic acid molecules. The degeneracy of the genetic code permits substitution of certain codons by other codons that specify the same amino acid and hence would give rise to the same protein. The nucleic acid sequence can vary substantially since, with the exception of methionine and tryptophan, the known amino acids can be coded for by more than one codon. Thus, portions or all of the kinase genes of the invention could be synthesized to give a nucleic acid sequence significantly different from that shown in SEQ ID Nos: 257-512, 643-646, 649, 654-655, 657-658, 663, 667-668, 673, 677-680, 692, 701-703, 713-717, 719-721, 728, 730-731, 737, 746, 750-751, 753-754, 756, 760, 762-764, 767, and 770-771. The encoded amino acid sequence thereof would, however, be preserved.

[0141] In addition, the nucleic acid sequence may include a nucleotide sequence which results from the addition, deletion or substitution of at least one nucleotide to the 5'-end and/or the 3'-end of the nucleic acid formula shown in SEQ ID Nos: 257-512, 643-646, 649, 654-655, 657-658, 663, 667-668, 673, 677-680, 692, 701-703, 713-717, 719-721, 728, 730-731, 737, 746, 750-751, 753-754, 756, 760, 762-764, 767, and 770-771, or a derivative thereof. Any nucleotide or polynucleotide may be used in this regard, provided that its addition, deletion or substitution does not alter the amino acid sequence of SEQ ID Nos: 1-256, 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641, which is encoded by the nucleotide sequence. For example, the present invention is intended to include any nucleic acid sequence resulting from the addition of ATG as an initiation codon at the 5'-end of the inventive nucleic acid sequence or its derivative, or from the addition of TTA, TAG or TGA as a termination codon at the 3'-end of the inventive nucleotide sequence or its derivative. Moreover, the nucleic acid molecule of the present invention may, as necessary, have restriction endonuclease recognition sites added to its 5'-end and/or 3'-end.

[0142] Such functional alterations of a given nucleic acid sequence afford an opportunity to promote secretion and/or processing of heterologous proteins encoded by foreign nucleic acid sequences fused thereto. All variations of the nucleotide sequence of the kinase genes of the invention and fragments thereof permitted by the genetic code are, therefore, included in this invention.

[0143] Further, it is possible to delete codons or to substitute one or more codons with codons other than degenerate codons to produce a structurally modified polypeptide, but one which has substantially the same utility or activity as the polypeptide produced by the unmodified nucleic acid molecule. As recognized in the art, the two polypeptides are functionally equivalent, as are the two nucleic acid molecules that give rise to their production, even though the differences between the nucleic acid molecules are not related to the degeneracy of the genetic code.

II. Nucleic acid probes, methods, and kits for the detection of mutant kinases.

[0144] The nucleic acid molecules of the invention are also useful for the design of hybridization probes to facilitate identification and cloning of mutated kinase polypeptides or kinase variants, the design of PCR probes to facilitate cloning of mutated kinase polypeptides or kinase variants, obtaining antibodies directed against mutated kinase polypeptides and kinase variants, and designing antisense oligonucleotides.

[0145] Therefore, the invention is also directed to nucleic acid probes for the detection of nucleic acid molecules encoding a mutant kinase polypeptide or a kinase polypeptide variant in a sample.

[0146] The mutant kinase polypeptide may in some embodiments be selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, and may include at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R,

EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K,

VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

[0147] The nucleic acid probes of the invention may include, consist essentially of or consist of nucleotide sequences that will hybridize to a target region in the nucleic acid sequence set forth in any of SEQ ID Nos: 257-512, or a functional equivalent thereof. The target region the nucleic acid probes of the invention are binding to include the mutation or mutated region, indicated in Fig. 32.

[0148] In another embodiment, the nucleic acid probe may be suitable for the detection of kinase variants selected from the group of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70 and including at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813_C814insQ, ROS C76fsX, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598fsX5, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX.

[0149] The kinase "target region" is the nucleotide base sequence set forth in SEQ ID Nos: 257-512, 643-646, 649, 654-655, 657-658, 663, 667-668, 673, 677-680, 692, 701-703, 713-717, 719-721, 728, 730-731, 737, 746, 750-751, 753-754, 756, 760, 762-764, 767, and 770-771 or the corresponding full-length sequences, a functional derivative thereof, or a fragment thereof to which the nucleic acid probe will specifically hybridize, as long as said nucleotide base sequence includes any one of the above indicated mutations or alterations. Specific hybridization indicates that in the presence of other nucleic acids the probe only hybridizes detectably with the target region of the mutant kinase or kinase variant of the invention.

[0150] A nucleic acid probe of the present invention may be used to probe a sample or a chromosomal/cDNA library by usual hybridization methods to detect the presence of nucleic acid molecules of the present invention. A chromosomal DNA or cDNA library may be prepared from appropriate cells according to methods well established in the art.

[0151] In order to obtain nucleic acid probes having nucleotide sequences which

correspond to altered portions of the amino acid sequence of the polypeptide of interest, chemical synthesis can be carried out. The synthesized nucleic acid probes may be first used as primers in a polymerase chain reaction (PCR) carried out in accordance with recognized PCR techniques, essentially according to standard PCR Protocols utilizing the appropriate template, in order to obtain the probes of the present invention.

[0152] One skilled in the art will readily be able to design such probes based on the sequence disclosed herein using methods of computer alignment and sequence analysis well known in the art. The hybridization probes of the present invention can be labeled by standard labeling techniques such as with a radiolabel, enzyme label, fluorescent label, biotin-avidin label, chemiluminescence, and the like. After hybridization, the probes may be visualized using known methods.

[0153] The nucleic acid probes of the present invention include RNA, as well as DNA probes, such probes being generated using techniques known in the art. The nucleic acid probe may be immobilized on a solid support. Examples of such solid supports include, but are not limited to, plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, and acrylic resins, such as polyacrylamide and latex beads. Techniques for coupling nucleic acid probes to such solid supports are well known in the art.

[0154] The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well known in the art and can be readily adapted in order to obtain a sample which is compatible with the method utilized.

[0155] One method of detecting the presence of nucleic acids of the invention in a sample includes (a) contacting said sample with the above-described nucleic acid probe under conditions such that hybridization occurs, and (b) detecting the presence of said probe bound to said nucleic acid molecule. One skilled in the art would select the nucleic acid probe according to techniques known in the art as described above. Samples to be tested include but should not be limited to RNA samples of human tissue.

[0156] The above method may also utilize a set of the nucleic acid probes of the invention to simultaneously detect the presence of the nucleic acids of the invention in a sample. Such a method may be useful for the diagnosis of proliferative diseases or disorders in a subject and may also be useful to predict the risk of cancer with high predictive accuracy and/or to choose an adequate therapy.

[0157] The set of nucleic acid probes utilized in such a method of the invention may be chosen in view of the condition to be detected and may include nucleic acid probes for all or any subset of the nucleic acid molecules that are implicated by the present invention in the predisposition, development and progression of cancer, including the nucleotide sequences set forth in SEQ ID Nos: 257-512 and 643-772. Such a subset may include at least 2, for example at least 5, 7, 10, 12, 16, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350 or any other number, for example all of the above sequences.

[0158] For the above method one or more nucleic acid probes may be bound to or immobilized on a solid support. Said solid support may be a chip, for example a DNA microchip.

[0159] A kit for detecting the presence of nucleic acids of the invention in a sample includes at least one container means having disposed therein the above-described nucleic acid probe. The kit may further include other containers that include one or more of the following: wash reagents and reagents capable of detecting the presence of bound nucleic acid probe. Examples of detection reagents include, but are not limited to radiolabeled probes, enzymatic labeled probes (horseradish peroxidase, alkaline phosphatase), and affinity labeled probes (biotin, avidin, or streptavidin).

[0160] In detail, a compartmentalized kit includes any kit in which reagents are included in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allow the efficient transfer of reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the probe or primers used in the assay, containers which contain wash reagents (such as phosphate buffered saline, Tris buffers, and the like), and containers which contain the reagents used to detect the hybridized probe, bound antibody, amplified product, or the like. One skilled in the art will readily recognize that the nucleic acid probes described in the present invention can readily be incorporated into one of the established kit formats which are well known in the art.

III. DNA constructs including a nucleic acid molecule of the invention and cells containing these constructs.

[0161] The invention further describes a recombinant cell or tissue including a nucleic acid molecule according to the invention, as detailed above.

[0162] In such cells, the nucleic acid may be under the control of the genomic regulatory elements, or may be under the control of heterologous regulatory elements including a heterologous promoter.

[0163] The term "heterologous" refers to the relationship between two or more nucleic acid or protein sequences that are derived from different sources. For example, a promoter is heterologous with respect to a transcribable polynucleotide sequence if such a combination is not normally found in nature. In addition, a particular sequence may be "heterologous" with respect to a cell or organism in that it encodes a protein or is included in a protein, for example a recombinant protein, that is not normally expressed by the host cell, tissue, or species. Such a heterologous protein accordingly generally is or has been inserted into the respective host cell, tissue, or species. Accordingly, a heterologous promoter is not normally coupled *in vivo* transcriptionally to the coding sequence for the kinase polypeptides.

[0164] Therefore, the present invention also relates to a recombinant DNA molecule including, 5' to 3', a promoter effective to initiate transcription in a host cell and the above-described nucleic acid molecules. In addition, the present invention relates to a recombinant DNA molecule including a vector and an above-described nucleic acid molecule. The present invention also relates to a nucleic acid molecule including a transcriptional region functional in a cell, a sequence complementary to an RNA sequence encoding an amino acid sequence corresponding to the above-described polypeptide, and a transcriptional termination region functional in said cell. The above-described molecules may be isolated and/or purified DNA molecules.

[0165] The present invention further relates to a cell or organism that contains an above-described nucleic acid molecule and thereby is capable of expressing a polypeptide. The polypeptide may be purified from cells which have been altered to express the polypeptide. A cell is said to be "altered to express a desired polypeptide" when the cell, through genetic manipulation, is made to produce a protein which it normally does not produce or which the cell normally produces at lower levels. One skilled in the art can readily adapt procedures for introducing and expressing either genomic, cDNA, or synthetic sequences into either eukaryotic or prokaryotic cells.

[0166] A nucleic acid molecule, such as DNA, is said to be "capable of expressing" a polypeptide if it contains nucleotide sequences which contain transcriptional and translational regulatory information and such sequences are "operably linked" to nucleotide sequences which encode the polypeptide. An operable linkage is a linkage in which the regulatory DNA sequences and the DNA sequence sought to be expressed are connected in such a way as to

permit gene sequence expression. The precise nature of the regulatory regions needed for gene sequence expression may vary from organism to organism, but shall in general include a promoter region which, in prokaryotes, contains both the promoter (which directs the initiation of RNA transcription) as well as the DNA sequences which, when transcribed into RNA, will signal synthesis initiation. Such regions will normally include those 5'-non-coding sequences involved with initiation of transcription and translation, such as the TATA box, capping sequence, CAAT sequence, and the like.

[0167] If desired, the non-coding region 3' to the sequence encoding a mutant kinase of the invention may be obtained by the above-described methods. This region may be retained for its transcriptional termination regulatory sequences, such as termination and polyadenylation. Thus, by retaining the 3'-region naturally contiguous to the DNA sequence encoding a kinase of the invention, the transcriptional termination signals may be provided. Where the transcriptional termination signals are not satisfactorily functional in the expression host cell, then a 3' region functional in the host cell may be substituted.

[0168] Two DNA sequences (such as a promoter region sequence and a sequence encoding a mutant kinase of the invention) are said to be operably linked if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region sequence to direct the transcription of a gene sequence encoding a kinase of the invention, or (3) interfere with the ability of the gene sequence of a kinase of the invention to be transcribed by the promoter region sequence.

[0169] Thus, a promoter region would be operably linked to a DNA sequence if the promoter were capable of effecting transcription of that DNA sequence. Thus, to express a gene encoding a mutant kinase of the invention, transcriptional and translational signals recognized by an appropriate host are necessary.

[0170] The present invention encompasses the expression of a gene encoding a kinase of the invention (or a functional derivative thereof) in either prokaryotic or eukaryotic cells. Prokaryotic hosts are, generally, very efficient and convenient for the production of recombinant proteins and are, therefore, one type of expression system for mutant kinases of the invention. Prokaryotes most frequently are represented by various strains of *E. coli*. However, other microbial strains may also be used, including other bacterial strains.

[0171] In prokaryotic systems, plasmid vectors that contain replication sites and control sequences derived from a species compatible with the host may be used. Examples of suitable plasmid vectors may include pBR322, pUC118, pUC119 and the like; suitable phage or

bacteriophage vectors may include γ gt10, γ gt11 and the like; and suitable virus vectors may include pMAM-neo, pKRC and the like. In some embodiments the selected vector of the present invention has the capacity to replicate in the selected host cell.

[0172] Recognized prokaryotic hosts include bacteria such as *E. coli*, *Bacillus*, *Streptomyces*, *Pseudomonas*, *Salmonella*, *Serratia*, and the like. However, under such conditions, the polypeptide will not be glycosylated. The prokaryotic host must be compatible with the replicon and control sequences in the expression plasmid.

[0173] To express a kinase of the invention (or a functional derivative thereof) in a prokaryotic cell, it is necessary to operably link the sequence encoding the kinase of the invention to a functional prokaryotic promoter. Such promoters may be either constitutive or regulatable (*i.e.*, inducible or derepressible). Examples of constitutive promoters include the *int* promoter of bacteriophage λ , the *bla* promoter of the β -lactamase gene sequence of pBR322, and the *cat* promoter of the chloramphenicol acetyl transferase gene sequence of pPR325, and the like. Examples of inducible prokaryotic promoters include the major right and left promoters of bacteriophage λ (P_L and P_R), the *trp*, *recA*, *lacZ*, *lacI*, and *gal* promoters of *E. coli*, the α -amylase (Ulmanen *et al.*, J. Bacteriol. 162:176-182, 1985) and the ζ -28-specific promoters of *B. subtilis* (Gilman *et al.*, Gene Sequence 32:11-20, 1984), and the promoters of the bacteriophages of *Bacillus*, and *Streptomyces* promoters (Ward *et al.*, Mol. Gen. Genet. 203:468-478, 1986). Prokaryotic promoters are reviewed by Glick (Ind. Microbiol. 1:277-282, 1987), Cenatiempo (Biochimie 68:505-516, 1986), and Gottesman (Ann. Rev. Genet. 18:415-442, 1984).

[0174] Proper expression in a prokaryotic cell also requires the presence of a ribosome-binding site upstream of the gene sequence-encoding sequence. Such ribosome-binding sites are disclosed, for example, by Gold *et al.* (Ann. Rev. Microbiol. 35:365-404, 1981). The selection of control sequences, expression vectors, transformation methods, and the like are dependent on the type of host cell used to express the gene. As used herein, "cell", "cell line", and "cell culture" may be used interchangeably and all such designations include progeny. Thus, the words "transformants" or "transformed cells" include the primary subject cell and cultures derived therefrom, without regard to the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. However, as defined, mutant progeny have the same functionality as that of the originally transformed cell.

[0175] Host cells which may be used in the expression systems of the present invention are not strictly limited, provided that they are suitable for use in the expression of the kinase

polypeptide of interest. Suitable hosts may often include eukaryotic cells. Examples of eukaryotic hosts include, but are not limited to, yeast, fungi, insect cells, mammalian cells either *in vivo*, or in tissue culture. Mammalian cells which may be useful as hosts include for example HeLa cells, cells of fibroblast origin such as VERO or CHO-K1, or cells of lymphoid origin and their derivatives. In some embodiments the mammalian host cells include any, including all human cancer cell lines.

[0176] Another suitable host is an insect cell, for example the *Drosophila* larvae. Using insect cells as hosts, the *Drosophila* alcohol dehydrogenase promoter can be used (Rubin, Science 240:1453-1459, 1988). Alternatively, baculovirus vectors can be engineered to express large amounts of kinases of the invention in insect cells (Jasny, Science 238:1653, 1987).

[0177] Any of a series of yeast expression systems can be utilized which incorporate promoter and termination elements from the actively expressed sequences coding for glycolytic enzymes that are produced in large quantities when yeast are grown in mediums rich in glucose. Known glycolytic gene sequences can also provide very efficient transcriptional control signals. Yeast provides substantial advantages in that it can also carry out post-translational modifications. A number of recombinant DNA strategies exist utilizing strong promoter sequences and high copy number plasmids, which can be utilized for production of the desired proteins in yeast. Yeast recognizes leader sequences on cloned mammalian genes and secretes peptides bearing leader sequences (*i.e.*, pre-peptides). Several possible vector systems are available for the expression of kinases of the invention in a mammalian host.

[0178] A wide variety of transcriptional and translational regulatory sequences may be employed, depending upon the nature of the host. The transcriptional and translational regulatory signals may be derived from viral sources, such as adenovirus, bovine papilloma virus, cytomegalovirus, simian virus, or the like, where the regulatory signals are associated with a particular gene sequence which has a high level of expression. Alternatively, promoters from mammalian expression products, such as actin, collagen, myosin, and the like, may be employed. Transcriptional initiation regulatory signals may be selected which allow for repression or activation, so that expression of the gene sequences can be modulated. Of interest are regulatory signals which are temperature-sensitive so that by varying the temperature, expression can be repressed or initiated, or are subject to chemical (such as metabolite) regulation.

[0179] Expression of mutant kinases of the invention in eukaryotic hosts requires the use

of eukaryotic regulatory regions. Such regions will, in general, include a promoter region sufficient to direct the initiation of RNA synthesis. Examples of a suitable eukaryotic promoter include, but are not limited to, the promoter of the mouse metallothionein I gene sequence (Hamer *et al.*, J. Mol. Appl. Gen. 1:273-288, 1982); the TK promoter of Herpes virus (McKnight, Cell 31:355-365, 1982); the SV40 early promoter (Benoist *et al.*, Nature 290:304-31, 1981); and the yeast gal4 gene sequence promoter (Johnston *et al.*, Proc. Natl. Acad. Sci. (USA) 79:6971-6975, 1982; Silver *et al.*, Proc. Natl. Acad. Sci. (USA) 81:5951-5955, 1984).

[0180] Translation of eukaryotic mRNA is initiated at the codon which encodes the first methionine. For this reason, it may be desired to ensure that the linkage between a eukaryotic promoter and a DNA sequence which encodes a kinase of the invention (or a functional derivative thereof) does not contain any intervening codons which are capable of encoding a methionine (*i.e.*, AUG). The presence of such codons results either in the formation of a fusion protein (if the AUG codon is in the same reading frame as the kinase of the invention coding sequence) or a frame-shift mutation (if the AUG codon is not in the same reading frame as the kinase of the invention coding sequence).

[0181] A nucleic acid molecule encoding a kinase of the invention and an operably linked promoter may be introduced into a recipient prokaryotic or eukaryotic cell either as a nonreplicating DNA or RNA molecule, which may either be a linear molecule or a closed covalent circular molecule. Since such molecules are incapable of autonomous replication, the expression of the gene may occur through the transient expression of the introduced sequence. Alternatively, permanent expression may occur through the integration of the introduced DNA sequence into the host chromosome.

[0182] A vector may be employed which is capable of integrating the desired gene sequences into the host cell chromosome. Cells which have stably integrated the introduced DNA into their chromosomes can be selected by also introducing one or more markers which allow for selection of host cells which contain the expression vector. The marker may provide for prototrophy to an auxotrophic host, biocide resistance, *e.g.*, antibiotics, or heavy metals, such as copper, or the like. The selectable marker gene sequence can either be directly linked to the DNA gene sequences to be expressed, or introduced into the same cell by co-transfection. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include splice signals, as well as transcription promoters, enhancers, and termination signals. cDNA expression vectors incorporating such elements include those described by Okayama (Mol. Cell. Biol. 3:280, 1983).

[0183] The introduced nucleic acid molecule can be incorporated into a plasmid or viral

vector capable of autonomous replication in the recipient host. Any of a wide variety of vectors may be employed for this purpose. Factors of importance in selecting a particular plasmid or viral vector include: the ease with which recipient cells that contain the vector may be recognized and selected from those recipient cells which do not contain the vector; the number of copies of the vector which are desired in a particular host; and whether it is desirable to be able to "shuttle" the vector between host cells of different species.

[0184] An illustrative example of a prokaryotic vector is a plasmid, such as a plasmid capable of replication in *E. coli* (such as, for example, pBR322, ColEI, pSC101, pACYC 184, π VX). *Bacillus* plasmids include pC194, pC221, pT127, and the like. Suitable *Streptomyces* plasmids include p1J101 (Kendall *et al.*, J. Bacteriol. 169:4177-4183, 1987), and streptomyces bacteriophages such as ϕ C31. *Pseudomonas* plasmids are reviewed by John *et al.* (Rev. Infect. Dis. 8:693-704, 1986), and Izaki (Jpn. J. Bacteriol. 33:729-742, 1978).

[0185] Examples of an eukaryotic plasmid include, but are not limited to, BPV, vaccinia, SV40, 2-micron circle, and the like, or their derivatives. Such plasmids are well known in the art (e.g. Broach, Cell 28:203-204, 1982; Bollon *et al.*, J. Clin. Hematol. Oncol. 10:39-48, 1980).

[0186] Once the vector or nucleic acid molecule containing the construct(s) has been prepared for expression, the DNA construct(s) may be introduced into an appropriate host cell by any of a variety of suitable means, *i.e.*, transformation, transfection, conjugation, protoplast fusion, electroporation, particle gun technology, calcium phosphate-precipitation, direct microinjection, and the like. After the introduction of the vector, recipient cells are grown in a selective medium, which selects for the growth of vector-containing cells. Expression of the cloned gene(s) results in the production of a kinase of the invention, or fragments thereof. This can take place in the transformed cells as such, or following the induction of these cells to differentiate. A variety of incubation conditions can be used to form the peptide of the present invention. It may be desired to use conditions that mimic physiological conditions.

[0187] The term "transfecting" defines a number of methods to insert a nucleic acid vector or other nucleic acid molecules into a cellular organism. These methods involve a variety of techniques, such as treating the cells with high concentrations of salt, an electric field, detergent, or DMSO to render the outer membrane or wall of the cells permeable to nucleic acid molecules of interest or use of various viral transduction strategies.

IV. Proteins of the invention

[0188] The mutant kinase polypeptides of the invention are selected from the group

consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, and include at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK

L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V and may be isolated, enriched or purified.

[0189] Also included are kinase variants that are selected from the group consisting of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70 and including at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813_C814insQ, ROS C76fsX, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598fsX5, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX. These kinase variants may also be isolated, enriched or purified.

[0190] By "isolated" in reference to a polypeptide is meant a polymer of amino acids (2 or more amino acids) conjugated to each other, including polypeptides that are isolated from a

natural source or that are synthesized. The isolated polypeptides of the present invention are unique in the sense that they are not found in a pure or separated state in nature. Use of the term "isolated" indicates that a naturally occurring sequence has been removed from its normal cellular environment. Thus, the sequence may be in a cell-free solution or placed in a different cellular environment. The term does not imply that the sequence is the only amino acid chain present, but that it is essentially free (about 90 - 95% pure at least) of non-amino acid material naturally associated with it.

[0191] By the use of the term "enriched" in reference to a polypeptide is meant that the specific amino acid sequence constitutes a significantly higher fraction (2 - 5 fold) of the total amino acid sequences present in the cells or solution of interest than in normal or diseased cells or in the cells from which the sequence was taken. This could be caused by preferential reduction in the amount of other amino acid sequences present, or by a preferential increase in the amount of the specific amino acid sequence of interest, or by a combination of the two. However, it should be noted that enriched does not imply that there are no other amino acid sequences present. The term merely defines that the relative amount of the sequence of interest has been significantly increased. The term significant here is used to indicate that the level of increase is useful to the person making such an increase, and generally means an increase relative to other amino acid sequences of about at least 2-fold, for example at least about 5- to 10-fold or even more. The term also does not imply that there is no amino acid sequence from other sources. The other source of amino acid sequences may, for example, include amino acid sequence encoded by a yeast or bacterial genome, or a cloning vector. The term is meant to cover only those situations in which man has intervened to increase the proportion of the desired amino acid sequence.

[0192] It is also advantageous for some purposes that an amino acid sequence be in purified form. The term "purified" in reference to a polypeptide does not require absolute purity (such as a homogeneous preparation); instead, it represents an indication that the sequence is relatively purer than in the natural environment. Compared to the natural level this level should be at least 2-5 fold greater (*e.g.*, in terms of mg/ml). Purification of at least one order of magnitude, such as about two or three orders, including for example about four or five orders of magnitude is expressly contemplated. It may be desired to obtain the substance at least essentially free of contamination at a functionally significant level, for example about 90%, about 95%, or 99% pure.

[0193] Explicitly falling within the scope of the present invention are fragments of mutant kinase polypeptides with any one of the amino acid sequences set forth in SEQ ID Nos: 1-256, or the corresponding full-length amino acid sequences thereof, as long as said fragments

include one of the mutations set forth in Fig. 32. The mutant kinase polypeptide fragments contain at least 30, 35, 40, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID Nos: 1-256, provided that the mutation of interest is included in said protein fragment.

[0194] Also encompassed by the present invention are kinase variants with any one of the amino acid sequences set forth in SEQ ID Nos: 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641 and fragments thereof, as long as said fragment include the alteration indicated in Fig. 33. Such fragments may have a length of at least 30, 35, 40, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID Nos: 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641 with the proviso that said fragment includes the altered sequence position or region.

[0195] In case a mutation or polymorphism leads to a premature stop codon, the mutated or altered kinase may be even shorter than 30 amino acids. However, such mutants and variants are also considered to fall within the scope of the present invention.

[0196] Also intended to fall within the scope of the present invention, are splice variants of the above mutant kinase polypeptides. Said splice variants may significantly differ from the above amino acid sequences, however, the functional domain architecture, for example the kinase domain, as well as the mutated region have to be retained in such variants. Such splice variants may lead to isoforms of the mutated kinase or kinase variant and may differ from the known form, for example, by an extended or shortened C- or N-terminus or the insertion or deletion of an amino acid sequence stretch. However, the sequence homology and sequence identity between the splice variants/isoforms is sufficiently high so that the skilled person is readily aware that the kinase in question is a mere isoform and not another kinase of the same family. Due to differing lengths of the isoforms, the mutated or altered position may be conserved but the numbering may be changed.

[0197] By "fragment" in reference to a polypeptide is meant any amino acid sequence present in a kinase polypeptide, as long as it is shorter than the full length sequence and includes the alteration to be detected.

[0198] A variety of methodologies known in the art can be utilized to obtain the polypeptides of the present invention. The polypeptides may be purified from tissues or cells that naturally produce the polypeptides. Alternatively, the above-described isolated nucleic acid fragments could be used to express the recombinant kinase polypeptides of the invention in any organism.

[0199] By "recombinant kinase polypeptide" is meant a polypeptide produced by recombinant DNA techniques such that it is distinct from a naturally occurring polypeptide either in its location (*e.g.*, present in a different cell or tissue than found in nature), purity or structure. Generally, such a recombinant polypeptide will be present in a cell in an amount different from that normally observed in nature.

[0200] Any eukaryotic organism can be used as a source for the polypeptides of the invention, as long as the source organism naturally contains such polypeptides. As used herein, "source organism" refers to the original organism from which the amino acid sequence of the subunit is derived, regardless of the organism the subunit is expressed in and ultimately isolated from.

[0201] As a further alternative the polypeptides of the invention may be synthesized using an automated polypeptide synthesizer.

[0202] One skilled in the art can readily follow known methods for isolating proteins in order to obtain the polypeptides free of natural contaminants. These include, but are not limited to: size-exclusion chromatography, HPLC, ion-exchange chromatography, and immuno-affinity chromatography.

V. Antibodies, methods of their use and kits for the detection of mutant kinase polypeptides

[0203] Also encompassed by the invention are antibodies having specific binding affinity only for a mutant kinase polypeptide, or domain or fragment thereof, with the mutant kinase polypeptide being selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70 and including at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N,

CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26,

TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

[0204] Furthermore, also included are antibodies having specific binding affinity only for a kinase variant, or domain or fragment thereof, with the kinase variant being selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70 and including at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins16, PDGFRA L221F, PDGFRA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813_C814insQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76fsX, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598fsX5, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1

P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del.

[0205] By "specific binding affinity" is meant that the antibody binds to the target kinase polypeptide with greater affinity than it binds to other polypeptides under specified conditions. Antibodies or antibody fragments are polypeptides that contain regions that can bind other polypeptides. The term "specific binding affinity" describes an antibody that binds to a mutant kinase polypeptide with significantly greater affinity than it binds to other polypeptides, e.g. the native kinase, under specified conditions.

[0206] The term "polyclonal" refers to antibodies that are heterogenous populations of antibody molecules derived from the sera of animals immunized with an antigen or an antigenic functional derivative thereof. For the production of polyclonal antibodies, various host animals may be immunized by injection with the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species.

[0207] "Monoclonal antibodies" are substantially homogenous populations of antibodies to a particular antigen. They may be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. Monoclonal antibodies may be obtained by methods well known to those skilled in the art (see for example, Köhler et al., *Nature* 256:495-497 (1975), and U.S. Patent No. 4,376,110, both of which are hereby incorporated by reference herein in their entirety including any figures, tables, or drawings).

[0208] The term "antibody fragment" refers to a portion of an antibody, often the hypervariable region and portions of the surrounding heavy and light chains that displays specific binding affinity for a particular molecule. A hypervariable region is a portion of an antibody that physically binds to the polypeptide target.

[0209] The term "domain" refers to a region of a polypeptide which contains a particular function. For instance, N-terminal or C-terminal domains of signal transduction proteins can serve functions including, but not limited to, binding molecules that localize the signal transduction molecule to different regions of the cell or binding other signaling molecules directly responsible for propagating a particular cellular signal. Some domains can be expressed separately from the rest of the protein and function by themselves, while others must remain part of the intact protein to retain function. The latter are termed functional regions of proteins and also relate to domains.

[0210] An antibody of the invention may be isolated by comparing its binding affinity to a mutant kinase or kinase variant of the invention with its binding affinity to other polypeptides. Those which bind selectively to a mutant kinase or kinase variant of the invention would be

chosen for use in methods requiring a distinction between a kinase of the invention and other polypeptides. Such methods could include, but should not be limited to, the analysis of altered kinase expression in tissue containing other polypeptides.

[0211] The mutant kinases and kinase variants of the present invention can be used in a variety of procedures and methods, such as for the generation of antibodies and for use in identifying pharmaceutical compositions. One skilled in the art will recognize that if an antibody is desired, a mutant kinase or kinase variant according to the invention could be generated as described herein and used as an immunogen. The antibodies of the present invention include monoclonal and polyclonal antibodies, as well fragments of these antibodies, and humanized forms. Humanized forms of the antibodies of the present invention may be generated using one of the procedures known in the art such as chimerization or CDR grafting.

[0212] In general, techniques for preparing monoclonal antibodies and hybridomas are well known in the art. Any animal (mouse, rabbit, and the like) which is known to produce antibodies can be immunized with the selected polypeptide. Methods for immunization are well known in the art. Such methods include subcutaneous or intraperitoneal injection of the polypeptide. One skilled in the art will recognize that the amount of polypeptide used for immunization will vary based on the animal which is immunized, the antigenicity of the polypeptide and the site of injection.

[0213] The polypeptide may be modified or administered in an adjuvant in order to increase the peptide antigenicity. Methods of increasing the antigenicity of a polypeptide are well known in the art. Such procedures include coupling the antigen with a heterologous protein (such as globulin or β -galactosidase) or through the inclusion of an adjuvant during immunization.

[0214] For monoclonal antibodies, spleen cells from the immunized animals are removed, fused with myeloma cells, such as SP2/0-Ag14 myeloma cells, and allowed to become monoclonal antibody producing hybridoma cells. Any one of a number of methods well known in the art can be used to identify the hybridoma cell which produces an antibody with the desired characteristics. These include screening the hybridomas with an ELISA assay, western blot analysis, or radioimmunoassay (Lutz *et al.*, Exp. Cell Res. 175:109-124, 1988). Hybridomas secreting the desired antibodies are cloned and the class and subclass are determined using procedures known in the art.

[0215] For polyclonal antibodies, antibody-containing antisera is isolated from the immunized animal and is screened for the presence of antibodies with the desired specificity using one of the above-described procedures. The above-described antibodies may be

detectably labeled. Antibodies can be detectably labeled through the use of radioisotopes, affinity labels (such as biotin, avidin, and the like), enzymatic labels (such as horse radish peroxidase, alkaline phosphatase, and the like) fluorescent labels (such as FITC or rhodamine, and the like), paramagnetic atoms, and the like. Procedures for accomplishing such labeling are well-known in the art, for example, *see* Stemberger *et al.*, J. Histochem. Cytochem. 18:315, 1970; Bayer *et al.*, Meth. Enzym. 62:308-, 1979; Engval *et al.*, Immunol. 109:129-, 1972; Goding, J. Immunol. Meth. 13:215-, 1976. The labeled antibodies of the present invention can be used for *in vitro*, *in vivo*, and *in situ* assays to identify cells or tissues which express a specific peptide.

[0216] The above-described antibodies may also be immobilized on a solid support. Examples of such solid supports include plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, acrylic resins and such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art. The immobilized antibodies of the present invention can be used for *in vitro*, *in vivo*, and *in situ* assays as well as in immunochromatography.

[0217] The present invention also relates to a method of detecting a mutant kinase polypeptide or kinase variant in a sample, including: (a) contacting the sample with an above-described antibody, under conditions such that immunocomplexes form, and (b) detecting the presence of said antibody bound to the polypeptide. In detail, the methods include incubating a test sample with one or more of the antibodies of the present invention and assaying whether the antibody binds to the test sample. The presence of a mutant kinase or kinase variant of the invention in a sample may indicate disease.

[0218] Conditions for incubating an antibody with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the antibody used in the assay. One skilled in the art will recognize that any one of the commonly available immunological assay formats (such as radioimmunoassays, enzyme-linked immunosorbent assays, diffusion based Ouchterlony, or rocket immunofluorescent assays) can readily be adapted to employ the antibodies of the present invention..

[0219] The immunological assay test samples of the present invention include cells, protein or membrane extracts of cells, or biological fluids such as blood, serum, plasma, or urine. The test samples used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed.

[0220] Methods for preparing protein extracts or membrane extracts of cells are well

known in the art and can be readily be adapted in order to obtain a sample which is testable with the system utilized.

[0221] Diagnostic kits for performing such methods may contain all the necessary reagents to carry out the previously described methods of detection. The kit may include antibodies or antibody fragments specific for the mutant kinase or kinase variant as well as a conjugate of a binding partner of the antibodies or the antibodies themselves. Diagnostic kits for performing such methods may be constructed to include a first container containing the antibody and a second container having a conjugate of a binding partner of the antibody and a label, such as, for example, a radioisotope. In another embodiment, the kit further includes one or more other containers including one or more of the following: wash reagents and reagents capable of detecting the presence of bound antibodies.

[0222] Examples of detection reagents include, but are not limited to, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the chromophoric, enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. The compartmentalized kit may be as described above for nucleic acid probe kits. One skilled in the art will readily recognize that the antibodies described in the present invention can readily be incorporated into one of the established kit formats which are well known in the art.

VI. Exemplary protein kinase mutants and of the invention and their use

[0223] In one aspect the present invention relates to an isolated, enriched, or purified nucleic acid molecule that encodes a mutant of a protein kinase polypeptide with the protein kinase polypeptide being one of FGFR4, FGFR1, Tyro3, TEC, CSK and Ack1.

[0224] FGFR1 and FGFR4 are members of the fibroblast growth factor transmembrane receptor family. FGF-receptors stimulate growth of many cell types and are inter alia involved in tissue repair, wound healing and angiogenesis. The FGF receptors include a variety of splice variants. Each receptor and receptor splice variant is activated by a unique set of fibroblast growth factors (see Powers, C.M., et al., Endocr. Relat. Cancer 7:165-197 (2000), incorporated herein by reference in its entirety). Cellular signaling pathways by FGF receptors have recently been reviewed by Eswarakumar et al (Cytokine & Growth Factor Reviews 16, 139-149 (2005), incorporated herein by reference in its entirety). Fibroblast growth factor receptors are known to activate the Ras-MAPK, the PLC γ -PKC, the PI3K-Akt and the p38 MAPK pathways. They are also known to play a role in tumor development and progression. FGFR1 and FGFR4 are overexpressed in clinical prostate cancer and suppression of FGFR4

expression blocks prostate cancer proliferation (Sahadevan, K., et al. J. Pathology 213: 82-90 (2007), incorporated herein by reference in its entirety).

[0225] In one aspect the invention relates to a nucleic acid molecule that encodes FGFR4 Y367C. This nucleic acid accordingly encodes an FGFR protein that has at position 367 Cysteine rather than Tyrosine, as would be the case for the wild type protein. This amino acid is highly conserved throughout the FGFR family and located within the extracellular domain of the receptor. The amino acid exchange may facilitate receptor dimerization, thereby augmenting receptor activation and resulting in a basal receptor activation.

[0226] The present inventors have further identified an amino acid exchange at position 388 of FGFR4 as a single nucleotide polymorphism that is highly represented in Asian HCC patients compared to the Caucasian population. A respective protein has Arginine instead of Glycine at position 388. Furthermore, the homozygous genotype encoding Arginine at position 388 correlates with an increased secretion of a diagnostic marker for hepatocellular carcinoma.

[0227] In another aspect the invention also relates to a nucleic acid molecule that encodes FGFR1 P252S. Amino acid position 252 is highly conserved. The present inventors found a heterozygous exchange in the melanoma cell line MeWo in this position. This amino acid change may lead to receptor activation by influencing ligand binding. Without being bound by theory it is believed that the presence of a serine residue, providing a hydroxyl group, is likely to induce the formation of additional hydrogen bonds.

[0228] Tyro3, another receptor protein-tyrosine kinase, is a member of the Axl family, the members of which play an important role in spermatogenesis, immunoregulation, and phagocytosis. Tyro3 proteins are also known to be essential for mammalian development. The crystal structure of the N-terminal Ig domain pair of Tyro3 has been reported by Heiring et al. (J. Biol. Chem., 279, 8, 6952-6958, (2004)). In one aspect the invention relates to a nucleic acid molecule that encodes Tyro3 P822L. This nucleic acid accordingly encodes a Tyro 3 protein that has at position 822 Leucine rather than Proline, as would be the case for the wild type protein.

[0229] The present inventors observed that overexpression of Tyro3 in HEK293 cells confers resistance to apoptosis upon treatment with TNF α /actinomycin-D. Furthermore, overexpression of mutants S531L and P822L instead of wildtype Tyro3 enhanced anti-apoptotic effects. Tyro3 may perturb mitochondrial apoptotic signaling through the modulation of BCL2 family members. The present invention thus relates to the detection of Tyro3 expression, and particularly the occurrence of mutants S531L and P822L as genetic

markers for chemoresistance. Inhibitors of Tyro3 signaling may be a promising adjuvant with other chemotherapeutic agents.

[0230] In a further aspect the invention also relates to a nucleic acid molecule that encodes TEC L89R, TEC W531R or TEC P587L. The first of these nucleic acids accordingly encodes a TEC protein that has at position 89 Arginine rather than Leucine, as would be the case for the wild type protein. This exchange is located in the pleckstrin homology domain of TEC. The second of these nucleic acids accordingly encodes a TEC protein that has at position 531 Arginine rather than Tryptophan, as would be the case for the wild type protein. This exchange is located in the kinase domain of TEC. The third of these nucleic acids encodes a TEC protein that has at position 587 Leucine rather than Proline, as would be the case for the wild type protein. This exchange is located in the kinase domain of TEC, too. The inventors have identified the corresponding proteins, encoded by these nucleic acids, as showing a decreased tyrosine phosphorylation compared to the wild type protein (see Fig. 17). Furthermore, the corresponding proteins are not able to activate MAPK signaling (Fig. 19), c-fos (Fig. 20) and Stat3 (Fig. 21).

[0231] TEC is a member of a family of intracellular tyrosine kinases of the same name, that includes Txk, Bmx, Itk, and Btk. TEC is involved in cell growth and differentiation and performs an essential role in antigen receptor signaling of T and B lymphocytes. It is important in phospholipase C γ activation following antigen receptor stimulation. TEC is activated via phosphatidylinositol 3,4,5-trisphosphate generation by phosphatidylinositol 3-kinase (PI 3-kinase), and trans-phosphorylation by a Src family PTK, which activates the kinase domain of the protein. TEC is also involved in cytoskeleton reorganization by increasing actin polymerization and formation of stress fibers. The solution structure of the TEC Src homology 3 domain, which mediates interactions with proline-rich sequences (including in an intramolecular manner), was determined using NMR spectroscopy by Pursglove et al. (*J. Biol. Chem.*, 277, 1, 755-762 (2002)). A tyrosine within this domain is phosphorylated during T cell signaling, a mechanism that depends on SH2-mediated interactions with the kinase domain (Joseph, R.E., *Biochemistry*, 46, 18, 5595-5603 (2007)). TEC is known to signal constitutively when over-expressed in lymphocyte cell lines.

[0232] Tyrosine kinase 2 (Tyk2) is a Janus kinase transducing signals of cytokines. Tyk2 is known to play an important role in IFN-induced apoptosis of pro-B cells. Tyk2 is constitutively tyrosine phosphorylated in the leukemogenic cell line RH/K34 (Samaana, A., & Mahana, W., *Immunology Letters* 109, 2, 113-119(2007)). Tyk2 has been shown to play an important role in urokinase-type plasminogen activator-induced prostate cancer cell invasion (Ide, H., et al., *Biochem. Biophys. Res. Commun.* doi:10.1016/j.bbrc.2007.08.160 (2007),

incorporated herein by reference in its entirety). The present inventors identified a differential occurrence of TYK2 F362 allele carriers in tumor cell lines (Fig. 4B) with an under-representation of the TYK2 F362 allele in control samples. These data indicate a tumor-promoting function, including a cancer-promoting function, of TYK2 F362. Illustrative examples of a respective tumor include, but are not limited to, leukemia, melanoma, and glioma. The present invention thus also relates to the detection of TYK2 F362.

[0233] Ack1 is a nonreceptor tyrosine kinase that binds exclusively to activated Cdc42-GTP, a Rho family small G protein, but not to Rac or Rho (for an investigation on its biochemical properties see e.g. Yokoyama, N. et al., J. Biol. Chem., 278, 48, 47713-47723). Ack1 has a kinase domain, an SH3 domain, a Cdc42/Rac-interactive binding (CRIB) domain, and a proline-rich C terminus. The C terminus has been shown to be involved in the interaction with the epidermal growth factor receptor (Shen, F., et al., Molecular Biology of the Cell, 18, 732-742 (2007), incorporated herein by reference in its entirety). Ack1 is Tyrosine phosphorylated by signaling via growth factors, cell adhesion, and muscarinic receptors. Ack1 has been shown to play an important role in cancer cell survival, as well as in tumor formation and metastasis (Mahajan, N.P., et al., Cancer Research 65, 10514-10523 (2005); van der Horst, E.H., Proc. Natl. Acad. Sci. U.S.A. 102, 44, 15901-15906 (2005)). MacKeigan et al. (Nat. Cell Biol. 7, 591-600 (2005)) identified Ack1 as an anti-apoptotic gene in an RNAi screen. Sustained activation of Ack-1 has been reported to be tumorigenic (Mahajan, 2005, supra; Mahajan, N.P., et al., Proc. Natl. Acad. Sci. U.S.A. 104, 20, 8438-8443 (2007), incorporated herein by reference in its entirety). Ack1 has also been shown to include an ubiquitin association domain at its C-terminus where it is ubiquitinated and leading to its proteosomal degradation (Shen et al., 2007, supra). The present inventors show that the somatic variant of Ack1, that has at position 985 Serine rather than Asparagin, as would be the case for the wild type protein, is less sensitive to ubiquitination, suggesting the stabilization of this oncogenic kinase.

[0234] In this regard the invention also provides a method of identifying a cell having a predisposition to turn tumorigenic, including to transform into a cancer cell. The cell may in some embodiments be derived from an organism such as a mammal, a fish, an amphibian, or a bird. Examples of a mammal include, but are not limited to, a rat, a mouse, a rabbit, a Guinea pig, an opossum, a dog, a cat, a chimpanzee, a rhesus monkey, a cattle (cow), a marmoset and a human. The cell may for example be cultured. The cell may also be included in an organism such as a mammal (see above for examples), a fish, an amphibian, or a bird. In such embodiments the method may be or may be included in diagnosing the risk of developing a neoplasm in a subject. It may be or be included in diagnosis of a tumor such as cancer.

[0235] A respective method may include identifying the amino acid at position 367 of the expressed protein kinase FGFR4. The presence of Cysteine at position 367 indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. A respective method may also include identifying the amino acid at position 388 of the expressed protein kinase FGFR4. The presence of Arginine at position 388 instead of Glycine indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. In some embodiments such a cell is a liver cell. In some embodiments a method where the amino acid at position 388 of the expressed protein kinase FGFR4 is identified, the genotype of the gene encoding the FGFR4 receptor in the cell is further determined. A homozygous genotype FGFR4 388Arg, i.e. where the cell is homozygously encoding FGFR4 with Arginine at position 388, indicates an increased predisposition to transform into a cancer cell.

[0236] A respective method may also include identifying the amino acid at position 252 of the expressed protein kinase FGFR1. The presence of Serine at position 252 instead of Proline indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. A respective method may also include identifying the amino acid at position 388 of the expressed protein kinase FGFR4. Such a cell is typically a hepatocyte. The presence of Arginine at position 388 instead of Glycine indicates an increased predisposition to transform into a hepatocellular carcinoma cell. A respective method may also include identifying the amino acid at position 531 and/or 822 of the expressed protein kinase Tyro3. The presence of Leucine at position 531 instead of Serine and/or the presence of Leucine at position 822 instead of Proline indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. A respective method may also include identifying the amino acid at position 89 of the expressed protein kinase TEC. The presence of Arginine at position 89 instead of Leucine indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. In some embodiments such a cell is a stomach cell. A respective method may also include identifying the amino acid at position 531 of the expressed protein kinase TEC. The presence of Arginine at position 531 instead of Tryptophan indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. In some embodiments such a cell is a T cell. A respective method may also include identifying the amino acid at position 587 of the expressed protein kinase TEC. The presence of Leucine at position 587 instead of Proline indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. In some embodiments such a cell is a lung cell. Such a method may also include identifying the amino acid at position 362 of the expressed protein kinase TYK2. The presence of Phenylalanine at position 362 instead of Valine indicates an

increased predisposition to turn tumorigenic, including to transform into a cancer cell. In some embodiments such a cell is a brain cell or a cell of the hematopoietic/lymphoid system. A respective method may also include identifying the amino acid at position 26 of the expressed protein kinase C-terminal Src kinase (CSK). The presence of an amino acid different from Glutamine at position 26 indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. In some embodiments such a cell is a colon cell. A respective method may also include identifying the amino acid at position 985 of the expressed protein kinase Ack1. The presence of Asparagine at position 985 instead of Serine indicates an increased predisposition to turn tumorigenic, including to transform into a cancer cell. In some embodiments such a cell is a kidney cell.

[0237] A method of identifying a cell that has a predisposition to turn tumorigenic, including to transform into a cancer cell, may be used in combination with any other diagnostic or prognostic method, e.g. a method of cancer prognosis or diagnosis. As an illustrative example, where the cell of interest is a liver cell, the level of the marker protein alpha-fetoprotein may be determined (see above and below). The method of the invention may also be combined with any other desired method. In some embodiments a method according to the present invention may be combined with detecting the expression of one or more marker genes of the respective tissue type of the cell in question. Any such combination may also be carried out with a respective method of identifying a cell that is resistant to apoptosis inducing reagents (see below).

[0238] In this regard the invention further provides a method of identifying a cell that is resistant to apoptosis inducing reagents, i.e. a cell that is chemoresistant. A respective method may include measuring in the cell the expression of the protein kinase Tyro3. Such a method further includes comparing the result of the measurement obtained with the result of a control measurement. An increased expression of protein kinase Tyro3 indicates resistance of the cell to apoptosis inducing reagents. A respective method may include identifying the amino acid at position 531 of the expressed protein kinase Tyro3. The presence of Leucine at position 531 instead of Serine indicates increased resistance of the cell to apoptosis inducing reagents. A respective method may include identifying the amino acid at position 822 of the expressed protein kinase Tyro3. The presence of Leucine at position 822 instead of Proline indicates increased resistance of the cell to apoptosis inducing reagents. Furthermore, a respective method may include identifying the amino acid at position 89 of the expressed protein kinase TEC. The presence of Arginine at position 89 instead of Leucine indicates increased resistance of the cell to apoptosis inducing reagents. In some embodiments the respective cell is a T cell. A respective method may also include identifying the amino acid at

position 531 of the expressed protein kinase TEC. The presence of Arginine at position 531 instead of Tryptophan indicates increased resistance of the cell to apoptosis inducing reagents. In some embodiments the respective cell is a T cell. A respective method may include identifying the amino acid at position 587 of the expressed protein kinase TEC. The presence of Leucine at position 587 instead of Proline indicates increased resistance of the cell to apoptosis inducing reagents. In some embodiments the respective cell is a T cell. One of the amino acid exchanges as described above may for instance confer chemoresistance through enhancing antiapoptotic effects in a cell, including a cancer cell. It is understood that any of the methods described above may be combined.

VII. Identification of compounds modulating mutant kinase activity

[0239] Encompassed by the instant disclosure are also methods for the identification of a compound capable of modulating the activity of a mutant protein kinase polypeptide or protein kinase polypeptide variant of the invention. Said mutant kinase polypeptide or protein kinase variant is selected from the ones detailed above.

[0240] The term “kinase activity”, as used herein, may relate to the catalytic activity of a kinase and thus define the rate at which a kinase catalytic domain phosphorylates a substrate. Catalytic activity can be measured, for example, by determining the amount of a substrate converted to a phosphorylated product as a function of time. Catalytic activity can be measured by methods of the invention by holding time constant and determining the concentration of a phosphorylated substrate after a fixed period of time. Phosphorylation of a substrate occurs at the active site of a protein kinase. The active site is normally a cavity in which the substrate binds to the protein kinase and is phosphorylated. The term “kinase activity” may also relate to the binding of a kinase to a natural binding partner that may, but must not include phosphorylation.

[0241] The term "kinase catalytic domain" refers to a region of the protein kinase that is typically 25-300 amino acids long and is responsible for carrying out the phosphate transfer reaction from a high-energy phosphate donor molecule such as ATP or GTP to itself (autophosphorylation) or to other proteins (heterologous phosphorylation). The catalytic domain of protein kinases is made up of 12 subdomains that contain highly conserved amino acid residues, and are responsible for proper polypeptide folding and for catalysis. The catalytic domain can be identified following, for example, a Smith-Waterman alignment of the protein sequence against the non-redundant protein database.

[0242] The term “substrate” as used herein refers to a molecule phosphorylated by a

kinase of the invention. Kinases phosphorylate substrates on serine/threonine or tyrosine amino acids. The molecule may be another protein or a polypeptide.

[0243] By “functional” domain is meant any region of the polypeptide that may play a regulatory or catalytic role as predicted from amino acid sequence homology to other proteins or by the presence of amino acid sequences that may give rise to specific structural conformations (*i.e.* coiled-coils).

[0244] The term “modulates” refers to the ability of a compound to alter the function of a mutated kinase or kinase variant of the invention. A modulator typically activates or inhibits the activity of a mutated kinase or kinase variant of the invention depending on the concentration of the compound exposed to the kinase. In some embodiments the modulator inhibits the activity of a mutated kinase or kinase variant of the invention. The compound may be capable of differentiating between a native and mutant form and/or between the distinct variants of said kinase.

[0245] The term “activates” refers to increasing the cellular activity of the kinase. The term “inhibits” refers to decreasing the cellular activity of the kinase. Kinase activity may be the interaction with a natural binding partner, including phosphorylation.

[0246] The term “modulates” also refers to altering the function of mutant kinases of the invention by increasing or decreasing the probability that a complex forms between the kinase and a natural binding partner. A modulator may increase or decrease the probability that such a complex forms between the kinase and the natural binding partner depending on the concentration of the compound exposed to the kinase. In some embodiments the modulator decreases the probability that a complex forms between the kinase and the natural binding partner.

[0247] The term “complex” refers to an assembly of at least two molecules bound to one another. Signal transduction complexes often contain at least two protein molecules bound to one another. For instance, a protein tyrosine receptor protein kinase, GRB2, SOS, RAF, and RAS assemble to form a signal transduction complex in response to a mitogenic ligand.

[0248] The term “natural binding partner” refers to polypeptides, lipids, small molecules, or nucleic acids that bind to kinases in cells. The natural binding partner may be a nucleotide, such as ATP or GTP or an analogue thereof, or a protein. In some embodiments it is a protein that is involved in signal transduction pathways. A change in the interaction between a kinase and a natural binding partner can manifest itself as an increased or decreased probability that the interaction forms, or an increased or decreased concentration of kinase/natural binding partner complex.

[0249] Such a method includes the steps of: (a) contacting a mutant kinase polypeptide or kinase variant of the invention with a test substance; (b) measuring the activity of said polypeptide; and (c) determining whether said substance modulates the activity of said polypeptide.

[0250] Also within the scope of the invention are methods for the identification of mutant kinase polypeptide or kinase variant modulating compounds in a cell. Said method includes (a) expressing a mutant kinase polypeptide or kinase variant in a cell; (b) adding a test substance to said cell; and (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

[0251] In one embodiment, the cells used for such a method are cancer cells, for instance a cancer cell line. Examples for cells that may be suitable for such a method are those identified in the Examples section of the present invention, i.e. the cells in which the mutant kinases or kinase variants were first identified.

[0252] The term “expressing” as used herein refers to the production of mutant kinases or kinase variants of the invention from a nucleic acid vector containing kinase genes within a cell. The nucleic acid vector is transfected into cells using well-known techniques in the art as described herein.

[0253] The invented methods thus also relate to the detection of an agonist or antagonist of mutant kinase or kinase variant activity including incubating cells that produce a mutant kinase of the invention in the presence of a compound and detecting changes in the level of kinase activity. The compounds thus identified would produce a change in activity indicative of the presence of the compound. The compound may be present within a complex mixture, for example, serum, body fluid, or cell extracts. Once the compound is identified it can be isolated using techniques well known in the art.

[0254] The present invention also encompasses a method of agonizing (stimulating) or antagonizing kinase associated activity in a cell and/or in an organism such as a mammal (see below for examples) including administering to said cell and/or organism an agonist or antagonist to a kinase of the invention in an amount sufficient to effect said agonism or antagonism. As an illustrative example a protein kinase inhibitor (see also below) or protein kinase activator in form of a synthetic small organic compound may be used for this purpose. Recent overviews on protein kinase inhibitors have for instance been given by Dancey & Sausville (Nature Reviews Drug Discovery 2, 4, 296-313 (2007)), Thaimattam et al. (Current Pharmaceutical Design 13, 2751-2765 (2007)) and Liao (J. Med. Chem 50, 3, 409-424 (2007)).

[0255] In some embodiments agonizing (stimulating) or antagonizing kinase associated activity in a mammal includes stimulating or reducing the expression or amplification of the respective protein kinase. Methods of stimulating or reducing the expression or amplification of a protein are well known in the art. As an illustrative example, agonizing kinase associated activity may in some embodiments be achieved by expression of a corresponding heterologous kinase. Tissue selective expression of such a heterologous kinase, for example expression only in the liver, may be achieved by using the microRNA present in the respective cell or organism in controlling expression, as described by Brown et al. (Nature Biotechnology doi:10.1038/nbt1372 (2007)).

[0256] As a further illustrative example, in some embodiments of the present method of the invention the expression of the respective protein kinase is reduced by means of a non-coding nucleic acid molecule, such as for example an aptamer or a Spiegelmer® (described in WO 01/92655). A non-coding nucleic acid molecule may also be an nc-RNA molecule (see e.g. Costa, FF, *Gene* (2005), 357, 83-94 for an introduction on natural nc-RNA molecules). Examples of nc-RNA molecules include, but are not limited to, an anti-sense-RNA molecule, an L-RNA Spiegelmer®, a silencer-RNA molecule (such as the double-stranded Neuron Restrictive Silencer Element), a micro RNA (miRNA) molecule, a short hairpin RNA (shRNA) molecule, a small interfering RNA (siRNA) molecule, a repeat-associated small interfering RNA (rasiRNA) molecule or an RNA that interacts with Piwi proteins (piRNA) (for a brief review see e.g. Lin, H., *Science* (2007) 316, 397).

[0257] The use of small interfering RNAs has become a tool to “knock down” specific genes. An overview on the differences between the use of synthetic small organic compounds and RNAi has been given by Weiss et al. (Nature Chem. Biol. 3, 12, 739-744 (2007)). Small interfering RNA makes use of gene silencing or gene suppression through RNA interference (RNAi), which occurs at the posttranscriptional level and involves mRNA degradation. RNA interference represents a cellular mechanism that protects the genome. SiRNA molecules mediate the degradation of their complementary RNA by association of the siRNA with a multiple enzyme complex to form what is called the RNA-induced silencing Complex (RISC). The siRNA becomes part of RISC and is targeted to the complementary RNA species which is then cleaved. This leads to the loss of expression of the respective gene (for a brief overview see Zamore, PD, & Haley, B, Science 309, 1519-1524 [2005]). This technique has for example been applied to silencing parasitic DNA sequences, such as the cleavage of HIV RNA, as disclosed in US patent application 2005/0191618.

[0258] A typical embodiment of such a siRNA for the current invention includes an in vitro or in vivo synthesized molecule of 10 to 35 nucleotides, in some embodiments 15 to 25

nucleotides. A respective si-RNA molecule may be directly synthesized within a cell of interest (including a cell that is part of a microorganism and an animal). It may also be introduced into a respective cell and/or delivered thereto. An illustrative example of delivering a siRNA molecule into selected cells in vivo is its non-covalent binding to a fusion protein of a heavy-chain antibody fragment (Fab) and the nucleic acid binding protein protamin (Song, E. et al., Nature Biotech. 23, 6, 709-717 [2005]). In an embodiment of the present invention siRNA molecules are used to induce a degradation of mRNA molecules encoding one or more protein kinases of interest.

[0259] A method of treating diseases in a mammal with a modulator of mutant kinase or kinase variant activity including administering the compound to a mammal in an amount sufficient to modulate mutant kinase or kinase variant associated functions is also encompassed in the present application.

[0260] In an effort to discover novel treatments for diseases, biomedical researchers and chemists have designed, synthesized, and tested molecules that inhibit the function of protein kinases. Some small organic molecules form a class of compounds that modulate the function of protein kinases. Examples of molecules that have been reported to inhibit the function of protein kinases include, but are not limited to, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT WO 92/20642, published November 26, 1992 by Maguire *et al.*), vinylene-azaindole derivatives (PCT WO 94/14808, published July 7, 1994 by Ballinari *et al.*), 1-cyclopropyl-4-pyridyl-quinolones (U.S. Patent No. 5,330,992), styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1), seleoindoles and selenides (PCT WO 94/03427, published February 17, 1994 by Denny *et al.*), tricyclic polyhydroxylic compounds (PCT WO 92/21660, published December 10, 1992 by Dow), and benzylphosphonic acid compounds (PCT WO 91/15495, published October 17, 1991 by Dow *et al.*).

[0261] Compounds that can traverse cell membranes and are resistant to acid hydrolysis are potentially advantageous as therapeutics as they can become highly bioavailable after being administered orally to patients. However, many of these protein kinase inhibitors only weakly inhibit the function of protein kinases. In addition, many inhibit a variety of protein kinases and will cause multiple side-effects as therapeutics for diseases.

[0262] Other examples of substances capable of modulating kinase activity include, but are not limited to, indolinones, tyrphostins, quinazolines, quinoxolines, and quinolines. The indolinones, quinazolines, tyrphostins, quinolines, and quinoxolines referred to above include

well known compounds such as those described in the literature.

[0263] For example, representative publications describing indolinone compounds include WO 96/22976 (published August 1, 1996 by Ballinari *et al.*), U.S. Patent Application Serial Nos. 08/702,232 and 08/485,323 by Tang *et al.*, and International Patent Publication WO 96/22976 by Ballinari *et al.*; all of which are incorporated herein by reference in their entirety, including any drawings.

[0264] Publications relating to the use of quinazolines as kinase function modulators include Barker *et al.*, EPO Publication No. 0 520 722 A1; Jones *et al.*, U.S. Patent No. 4,447,608; Kabbe *et al.*, U.S. Patent No. 4,757,072; Kaul and Vougioukas, U.S. Patent No. 5,316,553; Kreighbaum and Comer, U.S. Patent No. 4,343,940; Pegg and Wardleworth, EPO Publication No. 0 562 734 A1; Barker *et al.*, Proc. of Am. Assoc. for Cancer Research 32:327 (1991); Bertino, J.R., Cancer Research 3:293-304 (1979); Bertino, J.R., Cancer Research 9(2 part 1):293-304 (1979); Curtin *et al.*, Br. J. Cancer 53:361-368 (1986); Fernandes *et al.*, Cancer Research 43:1117-1123 (1983); Ferris *et al.* J. Org. Chem. 44(2):173-178; Fry *et al.*, Science 265:1093-1095 (1994); Jackman *et al.*, Cancer Research 51:5579-5586 (1981); Jones *et al.* J. Med. Chem. 29(6):1114-1118; Lee and Skibo, Biochemistry 26(23):7355-7362 (1987); Lemus *et al.*, J. Org. Chem. 54:3511-3518 (1989); Ley and Seng, Synthesis 1975:415-522 (1975); Maxwell *et al.*, Magnetic Resonance in Medicine 17:189-196 (1991); Mini *et al.*, Cancer Research 45:325-330 (1985); Phillips and Castle, J. Heterocyclic Chem. 17(19):1489-1596 (1980); Reece *et al.*, Cancer Research 47(11):2996-2999 (1977); Sculier *et al.*, Cancer Immunol. and Immunother. 23:A65 (1986); Sikora *et al.*, Cancer Letters 23:289-295 (1984); Sikora *et al.*, Analytical Biochem. 172:344-355 (1988); all of which are incorporated herein by reference in their entirety, including any drawings.

[0265] Quinoxalines are, for example, described in Kaul and Vougioukas, U.S. Patent No. 5,316,553, incorporated herein by reference in its entirety, including any drawings.

[0266] Quinolines are described in Dolle *et al.*, J. Med. Chem. 37:2627-2629 (1994); MaGuire, J. Med. Chem. 37:2129-2131 (1994); Burke *et al.*, J. Med. Chem. 36:425-432 (1993); and Burke *et al.* BioOrganic Med. Chem. Letters 2:1771-1774 (1992), all of which are incorporated by reference in their entirety, including any drawings.

[0267] Tyrphostins are described in Allen *et al.*, Clin. Exp. Immunol. 91:141-156 (1993); Anafi *et al.*, Blood 82:12:3524-3529 (1993); Baker *et al.*, J. Cell Sci. 102:543-555 (1992); Bilder *et al.*, Amer. Physiol. Soc. pp. 6363-6143:C721-C730 (1991); Brunton *et al.*, Proceedings of Amer. Assoc. Cancer Rsch. 33:558 (1992); Bryckaert *et al.*, Experimental Cell Research 199:255-261 (1992); Dong *et al.*, J. Leukocyte Biology 53:53-60 (1993); Dong *et al.*,

J. Immunol. 151(5):2717-2724 (1993); Gazit et al., J. Med. Chem. 32:2344-2352 (1989); Gazit et al., J. Med. Chem. 36:3556-3564 (1993); Kaur et al., Anti-Cancer Drugs 5:213-222 (1994); Kaur et al., King et al., Biochem. J. 275:413-418 (1991); Kuo et al., Cancer Letters 74:197-202 (1993); Levitzki, A., The FASEB J. 6:3275-3282 (1992); Lyall et al., J. Biol. Chem. 264:14503-14509 (1989); Peterson et al., The Prostate 22:335-345 (1993); Pillemer et al., Int. J. Cancer 50:80-85 (1992); Posner et al., Molecular Pharmacology 45:673-683 (1993); Rendu et al., Biol. Pharmacology 44(5):881-888 (1992); Sauro and Thomas, Life Sciences 53:371-376 (1993); Sauro and Thomas, J. Pharm. and Experimental Therapeutics 267(3):119-1125 (1993); Wolbring et al., J. Biol. Chem. 269(36):22470-22472 (1994); and Yoneda et al., Cancer Research 51:4430-4435 (1991); all of which are incorporated herein by reference in their entirety, including any drawings.

[0268] Other compounds that could be used as modulators include oxindolinones such as those described in U.S. patent application Serial No. 08/702,232 filed August 23, 1996, incorporated herein by reference in its entirety, including any drawings.

[0269] Other substances that modulate the activity of the mutant kinases may include antisense oligonucleotides and antibodies.

VIII. Methods of use of the molecules of the invention

[0270] The present invention also includes a method for screening for human cells containing a mutant kinase polypeptide or kinase polypeptide variant of the invention or an equivalent sequence. The method involves identifying the mutant kinase polypeptide or kinase variant in human cells using techniques that are routine and standard in the art (*e.g.*, cloning, Southern or Northern blot analysis, in situ hybridization, PCR amplification, etc.).

[0271] Also provided are methods for treating or preventing a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a mutant kinase or kinase variant of the invention. Methods of identifying such compounds have been discussed above. In some embodiments the disease or disorder to be treated or prevented involves an aberrant signal transduction pathway, for example an aberrant kinase function due to a mutation or germline alteration. The disease or disorder to be treated or prevented with the methods of the invention may for example be cancer.

[0272] If the aberrant kinase function is due to a mutation, the mutation can be an activating mutation, i.e. a mutation that leads to the constitutive activation of the kinase. Such a mutation may for example impair the intermolecular or intramolecular regulation of the kinase.

[0273] Alternatively, a germline alteration in a kinase gene, as disclosed and discussed above, may also lead to an altered function of a kinase. This altered function may include deregulation of the kinase, enhanced activity, and increased or decreased sensitivity against natural binding partners or drugs, such as known kinase modulating compounds. Such changes of the function of the kinase by germline alterations may inter alia lead to a predisposition for the development of a proliferative disease, such as cancer, as tumor development and progression naturally depend on an accumulation of a number of aberrations, of which alteration of kinase function may be only one aspect.

[0274] The term “preventing” refers to decreasing the probability that an organism contracts or develops an abnormal condition.

[0275] The term “treating” refers to having a therapeutic effect and at least partially alleviating or abrogating an abnormal condition in the organism.

[0276] The term “administering” relates to a method of incorporating a compound into cells or tissues of an organism.

[0277] The term “signal transduction pathway” refers to the molecules that propagate an extracellular signal through the cell membrane to become an intracellular signal. This signal can then stimulate a cellular response. The polypeptide molecules involved in signal transduction processes are typically protein kinases, more specifically receptor and non-receptor protein tyrosine kinases, serine/threonine kinases and dual specificity kinases. Also involved are typically receptor and non-receptor protein phosphatases, nucleotide exchange factors, and transcription factors. Signal transduction may be mediated via a variety of signaling domains, including but not limited to SRC homology 2 and 3 domains (SH2 and SH3), phosphotyrosine binding domains (PTB), pleckstrin homology domains (PH), proline-rich regions, coiled-coil structures, WW domains, etc., all of which are known to the person skilled in the art.

[0278] The term “therapeutic effect” refers to the inhibition or activation of factors causing or contributing to the abnormal condition. A therapeutic effect relieves to some extent one or more of the symptoms of the abnormal condition.

[0279] The term “aberration” or “aberrant”, in conjunction with the function of a kinase in a signal transduction process, refers to a kinase that is over- or under-expressed in an organism, altered such that its catalytic activity is lower or higher than wild-type protein kinase activity, altered such that it can no longer interact with a natural binding partner, is no longer modified by another protein kinase or protein phosphatase, or no longer interacts with a natural binding partner.

[0280] The abnormal condition caused by a mutant kinase polypeptide or kinase variant of the invention may be prevented or treated when the cells or tissues of the organism exist within the organism or outside of the organism. Cells existing outside the organism can be maintained or grown in cell culture dishes. For cells harbored within the organism, many techniques exist in the art to administer compounds, including (but not limited to) oral, parenteral, dermal, injection, and aerosol applications. For cells outside of the organism, multiple techniques exist in the art to administer the compounds, including (but not limited to) cell microinjection techniques, transformation techniques, and carrier techniques.

[0281] The abnormal condition can also be prevented or treated by administering a compound to a group of cells having an aberration in a signal transduction pathway to an organism. The effect of administering a compound on organism function can then be monitored. The organism may or instance be a mammal, such as a mouse, a rat, a rabbit, a guinea pig, a goat, a monkey or an ape. In some embodiments the organism is a human.

[0282] The term “abnormal condition” refers to a function in the cells or tissues of an organism that deviates from their normal functions in that organism. An abnormal condition can relate to cell proliferation, cell differentiation, or cell survival.

[0283] Abnormal cell proliferative conditions include cancer, fibrotic and mesangial disorders, abnormal angiogenesis and vasculogenesis, wound healing, psoriasis, diabetes mellitus, and inflammation. Furthermore, said proliferative disorders can relate to conditions in which programmed cell death (apoptosis) pathways are abrogated. As a number of protein kinases are associated with the apoptosis pathways, aberrations in the function of any one of the protein kinases could lead to cell immortality.

[0284] Other methods included in the invention are useful for the detection of a mutant kinase polypeptide or kinase variant in a sample as a diagnostic tool for diseases or disorders. Such a method may include the steps of: (a) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a target region of a nucleic acid encoding a mutant kinase polypeptide or kinase variant of the invention or the complement thereof; and (b) detecting the presence or amount of the probe:target region hybrid as an indication of the disease or disorder.

[0285] The disease or disorder involving a kinase mutant or kinase variant may be a proliferative disease or disorder, for example cancer.

[0286] In some embodiments the nucleic acid probe hybridizes to a mutant kinase target region that encodes at least about 10, about 15, about 20, about 30, about 40, about 50, about 75, about 100, about 150, about 200, about 250, about 300 or about 350 contiguous amino

acids of the sequence set forth in SEQ ID NO: 1-256 or 513-642, or the corresponding full-length amino acid sequence, or a functional derivative thereof, with the proviso that the target region includes one of the mutations or alterations set forth in Figures 32 and 33. Hybridization conditions should be such that hybridization occurs only with the kinase genes in the presence of other nucleic acid molecules. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. It may be desired to use conditions that prevent hybridization of nucleic acids that have one or more mismatches in a sequence of about 20 contiguous nucleotides.

[0287] The diseases that may be diagnosed by detection of a kinase nucleic acid in a sample may include a cancer. The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well-known in the art and can be readily adapted in order to obtain a sample that is compatible with the method utilized.

IX. Pharmaceutical formulations and routes of administration

[0288] The compounds described herein can be administered to a human patient per se, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, latest edition". Exemplary routes include, but are not limited to, oral, transdermal, and parenteral delivery.

[0289] Suitable routes of administration may, for example, include depot, oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

[0290] Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a solid tumor, often in a depot or sustained release formulation.

[0291] Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor.

[0292] Pharmaceutical compositions that include the compounds of the present invention

may be manufactured in a manner that is itself known, e. g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0293] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0294] For injection, the agents of the invention may be formulated in aqueous solutions, for instance in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0295] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[0296] Pharmaceutical preparations for oral use can be obtained by adding a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP).

[0297] If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0298] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0299] Pharmaceutical preparations that can be used orally include push-fit capsules made

of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0300] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e. g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0301] The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e. g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0302] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0303] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing

conventional suppository bases such as cocoa butter or other glycerides.

[0304] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0305] A pharmaceutical carrier for the hydrophobic compounds of the invention is a co-solvent system including benzyl alcohol, a non-polar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the non-polar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD: D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution.

[0306] This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics.

[0307] Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity non-polar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0308] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0309] The pharmaceutical compositions also may include suitable solid or gel phase carriers or excipients.

[0310] Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0311] Many of the kinase modulating compounds of the invention may be provided as salts with pharmaceutically compatible counter-ions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms.

[0312] Pharmaceutical compositions suitable for use in the present invention include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0313] For any compound used in the methods of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture (i. e., the concentration of the test compound which achieves a half-maximal inhibition of the kinase activity). Such information can be used to more accurately determine useful doses in humans.

[0314] Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50} . It may be desired to use compounds that exhibit high therapeutic indices. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e. g., Fingl, et al. (1975) *The Pharmacological Basis of Therapeutics* Chapter 1 page 1).

[0315] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data; e.g., the concentration necessary to achieve 50-90% inhibition of the kinase. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

[0316] Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, for example from about 30 to about 90%, such as from about 50 to about 90%.

[0317] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration. The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

[0318] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for instance include metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compound for human or veterinary administration. Such notice, for example, may be the labeling approved by the U. S. Food and Drug Administration or other government agency for prescription drugs, or the approved product insert.

[0319] Compositions including a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Suitable conditions indicated on the label may include, for example, treatment of cancer.

[0320] In order that the invention may be readily understood and put into practical effect, particular embodiments will now be described by way of the following non-limiting examples.

EXEMPLARY EMBODIMENTS OF THE INVENTION

[0321] Fig. 1 depicts a characterization of tumor cell lines with regard to genetic

alterations in the tyrosine kinase transcriptome (TKT). **Fig. 1A:** samples. The tissue origins and number of tumor cell lines derived thereof are summarized. **Fig. 1B:** patterns of genetic alterations. For each of the 254 tumor and 7 control cell lines, the specific pattern of non-synonymous genetic alterations within the tyrosine kinase transcriptome is provided (Fig. 30) and exemplarily shown for 5 skin-derived tumor cell lines. Germline polymorphisms and somatic mutations are highlighted in blue and yellow, respectively. **Fig. 1C:** genetic alterations per TKT. The number of tumor cell lines with the indicated number of somatic (light) or germline (dark) alterations detected therein is illustrated.

[0322] Fig. 2 depicts a characterization of protein tyrosine kinase genes with regard to genetic alterations detected in the transcripts of 276 tumor cell lines and control samples. As exemplified here for FGFR4, the spectrum of identified genetic alterations and the corresponding patterns of affected tumor cell lines or control samples was determined for each tyrosine kinase gene (Fig. 31). The total sample number carrying a given sequence variant is indicated, and affected cancer cell lines are subdivided according to their tissue origin. Somatic mutations are underlined, the remaining entries are germline polymorphisms. Heterozygosity is indicated by a hash, the other samples are homozygous carriers of the respective alteration.

[0323] Fig. 3 shows the distributions of non-synonymous polymorphisms identified in the TKT of 276 cancer cell lines and control samples. **Fig. 3A:** rates of germline alterations. The rates of missense (MS) or nonsense (NS) substitutions, deletions (DEL) and insertions (INS) subdivided into four frequency categories (1, 2-5, 6-10 or more than 10 affected samples) are summarized. **Fig. 3B:** domain localization of identified polymorphisms. The number of polymorphisms detected in distinct domains or other protein regions is indicated. **Fig. 3C:** tissue distribution of germline variations. The tissue distribution (BL: bladder; BS: bone and soft tissue; BA: brain; BE: breast; CV: cervix and vulva; CO: colon; EP: endometrium and placenta; HN: head and neck; HL: hematopoietic and lymphoid system; KI: kidney; LI: liver; LU: lung; OV: ovary; PA: pancreas; PR: prostate; SK: skin; ST: stomach; TE: testes; TY: thyroid, NO: normal control samples) was determined for all polymorphisms (Fig. 33) and presented here for those described in the text. Paired numerals indicate the number of carriers of the indicated variant as a subset of all cell lines with the same tissue origin that express the corresponding gene regardless of its genotype. Novel germline alterations are highlighted in bold type, parenthesized numbers refer to the following references that associate respective polymorphisms with cancer: 1.: Ullrich, A., et al., *Nature*, 313: 756-761, 1985; 2: Galland, F., et al., *Oncogene*, 8: 1233-1240, 1993; 3: Schmidt, L. S., et al. *J Urol*, 172: 1256-1261, 2004; 4: Gimm, O., et al., *J Clin Endocrinol Metab*, 84: 2784-2787, 1999; 5: Greco, A., et al. *Am J*

Hum Genet, 64: 1207-1210, 1999; 6: Walter, J. W., et al. Genes Chromosomes Cancer, 33: 295-303, 2002; 7: Walters, D. K., et al., Cancer Cell, 10: 65-75, 2006; 8: Xie, D., et al. J Natl Cancer Inst, 92: 412-417, 2000; 9: Bange, J., et al., Cancer Res, 62: 840-847, 2002; 10: Tjin, E. P., et al., Blood, 107: 760-768, 2006; 11: Lee, J. H., et al., Oncogene, 19: 4947-4953, 2000; 12: Bounacer, A., et al. Br J Cancer, 86: 1929-1936, 2002; 13: Sturla, L. M., et al., Br J Cancer, 89: 1276-1284, 2003; 14: Ma, P. C., et al., Cancer Res, 65: 1479-1488, 2005; 15: Moriai, T., et al., Proc Natl Acad Sci U S A, 91: 10217-10221, 1994; 16: Collesi, C., et al. Mol Cell Biol, 16: 5518-5526, 1996; 17: Lynch, T. J., Bell, et al., N Engl J Med, 350: 2129-2139, 2004; 18: Huusko, P., et al., Nat Genet, 36: 979-983, 2004; 19: Beghini, A., et al. Hematol J, 3: 157-163, 2002; 20: Kong-Beltran, M., et al. Cancer Res, 66: 283-289, 2006; 21: Reindl, C., et al. Blood, 107: 3700-3707, 2006.

[0324] Figure 4 depicts the diverging occurrence rates of polymorphisms in different tumor types and/or control samples. The frequency of homozygous (HO; dark bar) and heterozygous (HE; light bar) carriers of EGFR R521K, TYK2 V362F and TNK1 M598delinsEVRSHX was determined. Only tissue origins (for abbreviations see legend to Fig. 1, supra) with an expression of the corresponding gene in at least 10 samples have been selected for this analysis.

[0325] Figure 5 depicts the distributions of non-synonymous somatic mutations identified in all transcribed PTK genes from 254 tumor cell lines. **A**, rates of somatic mutations. The allocation to missense (MS) or nonsense (NS) substitutions, deletions (DEL) and insertions (INS) as well as frequency categories (1, 2-5, 6-10 or more than 10 affected samples) is shown. **B**, domain localization of identified mutations. The localization within defined domains or other protein regions is indicated. **C**, tissue distribution of sporadic alterations. For each somatic mutation, the tissue distribution (see legend to Fig. 3 for abbreviations) was determined (Fig. 37) and presented here for text-related examples. Paired numerals indicate the number of mutated and expression-positive cell lines within a given tumor type. Novel somatic mutations are highlighted in bold type, numbers in parenthesis refer to references given in the legend of Fig. 3 that associate respective mutations with cancer.

[0326] Figure 6 is an illustration of known and novel genetic alterations in selected genes. **A**, SYK. The domain organization and location of genetic alterations is displayed. **B**, sequence comparison of FGFR1-4. For FGFR1-4, the general domain organization (middle) and sequence comparisons of the linker region connecting the IG-D2- and IG-D3-domain (top) as well as a part of the extracellular juxtamembrane region (bottom) are illustrated. Genetic alterations identified in our cell line screen are illustrated below, known sequence variants are

depicted above the graphical representation of the domain structure. Polymorphisms are underlined, the remaining marked positions are somatic mutations. Numbers in parenthesis indicate the number of affected non-related cell lines. (SH2: Src Homology 2 Domain; TK: Tyrosine Kinase Domain; S: Signal Peptide; TM: Transmembrane Domain; IG: Immunoglobulin-Like Domain)

[0327] FGFR4 transcript is overexpressed (> 2 -fold) in 1/3 of hepatocellular carcinoma (HCC) patients ($n = 57$) in the tumor vs. the adjacent normal tissue as determined by real-time PCR (Fig. 7, Fig. 8). The threshold cycle (C_t) value shown in Fig. 8 is scored as the cycle number where the fluorescence level crosses a predefined threshold value. The C_t value assigned to a particular sample thus reflects the point during the reaction at which a sufficient number of amplicons have accumulated, in that well, to be at a statistically significant point above the baseline. A lower C_t value accordingly reflects a higher relative gene expression.

[0328] A single nucleotide polymorphism, G388R is highly represented in Asian population (including HCC patients) and the homozygous 388Arg genotype correlates with an increased alpha-fetoprotein (a diagnostic marker for HCC) secretion in the respective patients at the point of tumor resection (Fig. 9, Fig. 10). Subsequent *in vitro* investigations revealed that stimulation of FGFR4 in HCC cell lines using a specific ligand, FGF19, elevated AFP production by the cells (Figure 11, Fig. 12). Gene silencing as well the administration of a commercially available non-selective FGFR inhibitor (Fig. 13, Fig. 14), PD173074 blocks AFP production (Figure 15). Furthermore, this inhibitor exhibited exquisite anti-proliferative effect on HCC cell lines vs. non-cancerous cell line, HEK293 (data not shown, $LD_{50} > 50$ micromolar, see also Figure 16). Hence, it is postulated that FGFR4 activity contributes to normal-to-tumor progression of HCC and may be a viable target for pharmacological intervention.

[0329] TEC phosphorylation was shown after SCF, GM-CSF, IL-3, IL-6 stimulation. The TEC-kinase (66kDa) is involved in cytoskeleton reorganization by increasing actin polymerization and formation of stress fibers (phalloidin). The TEC PH domain was found to bind Vav, a specific nucleotide exchange factor for Rho, Rac and Cdc42 (Machide, M., et al., Oncogene, Aug 17;11(4):619-25 (1995)). Furthermore, TEC physically associates with c-kit through a region that contain a proline-rich motif, amino terminal of the SH3 domain. (Tang, B., et al., Mol Cell Biol. 1994 Dec;14(12):8432-8437). TEC activates transcription factor such as NF-KappaB, c-Jun, c-Fos, Elk1 and SRF.

[0330] The genetic alterations identified in a cell line screen performed by the present inventors are illustrated in Fig. 18.

Mutations (all of somatic origin)

- **L89R** AGS (heterozygous), mutation in pleckstrin homology domain
- **W531R** Jurkat (homozygous), mutation in kinase domain
- **P587L** NCI-H661 (heterozygous), mutation in kinase domain
- R563K** published somatic alteration

[0331] Subsequent *in vitro* investigation demonstrated that TEC L89R, W531R and P587L have decreased Tyrosine phosphorylation compared to TEC wt (Figure 17). In addition, these somatic alterations are incapable of activating MAPK signaling (Figure 19), c-fos (Figure 20) and Stat3 activation (Figure 21). Two publications support the finding that the W531R alteration abolishes kinase activity: It is shown that in Jak2 conversion of W1020 (corresponding W531 in TEC) abolished Jak2 kinase activity (Sandberg, E.M., et al., Mol. Cell. Biochem. Oct;265(1-2):161-169 (2004)). Furthermore, disruption of W352 in CSK (corresponding W531 in TEC) leads to a 90 % decrease in CSK activity (Lee, S., et al., Biochemistry Oct 8;41(40):12107-12114 (2002)).

[0332] A possible advantage of the T-cell lymphoma harboring the inactivating TEC W531R somatic mutation may be as follows: DNA damaging agents induce activation of AP-1 in T Lymphocytes and subsequent apoptosis (Kasibhatla, S., et al, Mol Cell. 1998 Mar;1(4): 543-51 (1988)). S. Kasibhatla et al. showed that treatment of Jurkat cells with Topoisomerase II inhibitors (etoposide, teniposide) or UV-B irradiation leads to activation c-fos mediated FasL expression followed by the induction of apoptosis. Etoposide (Etopophos, Eposin, Vepesid, VP-16) is used as a form of chemotherapy for various malignancies including lymphoma. Without being bound by theory it is postulated that TEC W531R may lead to resistance to etoposide treatment of T-cell Lymphoma (e.g. Jurkat cells) by decreasing Fas Ligand expression.

Tyro3 and mutants expression exhibit enhanced anti-apoptotic effects

[0333] Overexpression of Tyro3 in HEK293 confers resistance to the apoptosis upon treatment with TNF α /actinomycin-D. Furthermore, overexpression of mutants S531L and P822L instead of wildtype Tyro3 enhanced anti-apoptotic effects. Preliminary data suggests that Tyro3 may perturb mitochondrial apoptotic signaling through the modulation of BCL2 family members. Hence, it is suggested that Tyro3 expression, and particularly the occurrence of mutants S531L and P822L may be a genetic marker for chemoresistance. Inhibitors of Tyro3 signaling may be a promising adjuvant with other chemotherapeutic agents.

Somatic mutation in Ack1

[0334] Ack1, also known as activated Cdc42- associated kinase 1, is a non receptor tyrosine kinase implicated in cancer progression. Sequencing effort initiated by Singapore OncoGenome programme has identified single base mutation that resulted in homozygous amino acid change from serine to Asparagine at amino acid 985 of kidney cancer line A498. *In vitro* ubiquitination assay in Hek 293 cells shows that mutation of 985 from serine to Asparagine resulted in a stable protein that is less sensitive to ubiquitination (Fig. 22).

Alterations in TYK2 lead to decreased kinase activity.

[0335] A clearly differential occurrence of TYK2 F362 allele carriers was observed in brain- (75%) and hematopoietic/lymphoid system- (67%) derived tumor cell lines compared to control tissues (31%) or other tumor types (Fig. 4B). The under-representation of the TYK2 F362 allele in control samples indicates a tumor-promoting function with particular relevance for leukemia, melanoma, and glioma.

[0336] The skipping of entire exons in the cytoplasmic kinases TYK2 and TXK, TYK2 E971fsX67 and TXK Y414fsX15, for instance, results in frame shifts and premature translation termination in the tyrosine kinase domains, and thus most likely is associated with catalytic inactivation. The truncated TYK2 variant that lacks 206 aa of the kinase domain including the catalytic site and the activation loop may also impose a dominant negative effect on cell signals. Interestingly, Stoiber et al. reported that TYK2-deficient mice developed B and T lymphoid leukemia with higher incidence and shortened latency as a result of decreased cytotoxic capacity of TYK2^{-/-} NK and NKT cells and thus impaired tumor surveillance (Stoiber, D., et al., J Clin Invest 114:1650-1658 (2004)). Since NK activity as part of the innate immune system mediates tumor rejection in general, the significance of TYK2 loss-of-function might not be restricted to hematopoietic malignancies, but may also be important for other cancer types. Consistent with this possibility, the inventors detected TYK2 E971fsX67 in cancer cells derived from various tissues including breast, cervix/vulva, colon, endometrium, lung, and pancreas (Fig. 3C) as well as 33 clinical breast, prostate, and kidney cancer specimens. Its occurrence in the control cell line BPH-1 suggests potential germline origin. Hence, the TYK2 E971fsX67 splice variant may also represent a prognostic marker for cancer patients and support therapeutic decision making.

FGFR4 Y367C

[0337] The somatic mutation FGFR4 Y367C identified within the extracellular domain FGFR4 Y367C possibly augment receptor activation by receptor dimerization. The novel FGFR4 Y367C mutation was detected as a homozygous genotype in the breast cancer cell line

MDA-MB-453, and the affected Y367 residue in the extracellular juxtamembrane domain is highly conserved throughout the FGFR family. Remarkably, homologous substitutions in FGFR1 (Y372C), FGFR2 (Y375C) and FGFR3 (Y373C) were shown to cause various osteogenic deficiency syndromes (Wilkie, A.O., Cytokine Growth Factor Rev 16:187-203 (2005)) through the formation of intermolecular disulfide bonds that force receptor dimerization and activation. Ligand-independent, constitutive receptor activation has been confirmed in vitro for FGFR1 Y372C (White, K.E., et al., Am J Hum Genet 76:361-367 (2005)) and FGFR3 Y373C (d'Avis, P.Y., et al., Cell Growth Differ; 9:71-78 (1998)). Furthermore, the oncogenic potential of the FGFR3 Y373C variant has been demonstrated and was suggested to contribute to tumor progression of multiple myeloma (Chesi, M., Blood, 97:729-736 (2001)). Thus, it is most likely that Y367C as the homologous FGFR4 variant also results in basal receptor activation, which strongly indicates an important role of this mutant in cancer.

FGFR1 P252S

[0338] FGFR1 P252S may lead to receptor activation by influencing ligand binding. The highly conserved FGFR1 P252 residue the inventors found to be heterozygously exchanged with hydrophilic serine in the melanoma cell line MeWo has previously been shown to be replaced by threonine in lung cancer (Davies, H., et al., Cancer Res; 65:7591-7595 (2005)) and arginine in patients with Pfeiffer syndrome (Muenke, M., et al., Nat Genet;8:269-274 (1994)). The crystal structure of the homologous activating FGFR2 mutant, FGFR2 P252R, revealed the formation of 3 additional hydrogen bonds with complexed fibroblast growth factor 2 (FGF2). They were predicted to increase the receptor's affinity for its specific ligand as well as to allow binding of a different set of ligands (Ibrahimi, O.A., et al., Proc Natl Acad Sci U S A;98:7182-7187 (2001)). Since the hydroxy group of the P252-replacing serine residue in FGFR1 also has a high potential to form additional hydrogen bonds, the somatic FGFR1 P252S substitution may represent a gain-of-function mutation with analogous functional consequences as for FGFR2 P252R. This is particularly intriguing in the context of studies demonstrating that blockage of FGFR1 or bFGF function was associated with suppressed proliferation and survival of melanoma cells (Wang, Y, & Becker, D., Nat Med; 3:887-893 (1997)).

CSK Q26X may lead to downregulation of Tumor Suppressor Activity

[0339] The heterozygous CSK Q26X nonsense substitution detected in the colon cancer cell lines DLD-1 and HCT-15 is consistent with reduced protein levels of this negative regulator of SRC-family kinases that were reported for ~60% of human colon cancer cases

with elevated SRC activity (Rengifo-Cam, W., et al., *Oncogene*; 23:289-297 (2004)). These data indicate a significant role of CSK nonsense mutations in the development and/or progression of colon carcinoma and therefore strongly suggest the inclusion of SRC kinase inhibitors in the therapeutic regimen of this prevalent malignancy.

EXAMPLES

Samples

[0340] Samples of primary invasive breast carcinomas were obtained from the archives of the Department of Pathology of the Technical University of Munich, Germany (Prof. H. Hoefler) and the Department of Oncology of the University of Chieti, Italy (Dr. S. Iacobelli). Kidney tissue materials of tumors and healthy tissue as well as prostate cancer tissue were obtained from the Urology Department of the Klinikum Darmstadt, Germany (Prof. S. Peter). 14 cDNAs of normal tissue (spleen, testes, ovary, kidney, skeletal muscle, colon, prostate, bladder, cervix, pancreas, liver, brain, lung, gastric) derived from different individuals were purchased from Ambion.

[0341] Genomic DNA of 90 blood samples derived from non-cancer patients was purchased from Coriell Institute for Medical Research (Camden, NJ, USA).

cDNA Synthesis

[0342] Total RNA was isolated according to the method described by Puissant and Houdebine.

[0343] Cancer cell lines were cultured according to conditions by the American Type Culture Collection (ATTC, <http://www.atcc.org>).

[0344] After homogenization of the cultured human cancer cells (80 % confluency) or the primary tissue in a denaturing solution (4M guanidine thiocyanate, 25mM sodium citrate, 0.5% Sarkosyl, 0.1M β -mercaptoethanol, 10mM EDTA), the homogenate was sequentially mixed with 2M sodium acetate (pH 4.0), saturated phenol and finally with chloroform. The mixture was centrifuged and the upper phase was isopropanol precipitated, resuspended in denaturing solution and again reprecipitated with isopropanol. Following ethanol washing the pellet was resuspended in H₂O and incubated at 65°C for 5 min. The quality of the total RNA was tested by gel electrophoresis.

[0345] For the extraction of poly(A)⁺RNA, total RNA was denatured at 70 °C (5min) and applied to a oligo-dT-cellulose column along with a washing buffer (10 mM Tris/HCl pH7.4,

0.5M NaCl, 1mM EDTA, 0.5 % SDS). Following several washing steps the poly(A)⁺RNA was eluted (10 mM Tris/HCl pH7.4, 1mM EDTA, 0.5% SDS) and precipitated with ethanol.

[0346] The conversion of the poly(A)⁺RNA into the complementary DNA (cDNA) was performed using the AMV reverse transcriptase (Promega AMV-RT) and oligo(dT) polymers and oligonucleotides (dNTP). After the synthesis the cDNA was purified using Qiagen PCR purification columns and eluted in 50μl.

PCR and Sequencing

[0347] For each cell line and control sample, whole cell cDNA was prepared and used for the amplification and direct sequencing of the complete PTK coding region. Primers for PCR amplification (and sequencing) were designed using Primer3 program (http://www-genome.wi.mit.edu/cgi-bin/primer/primer3_www.cgi), and were synthesized by Prologo (Singapore). PCR amplification was performed on cDNA from 265 early passage cell lines, placenta and 14 normal tissues (Ambion). PCR optimization was done in the first step with a cDNA pool of different cell lines, second step with 6/8 different individual cell lines, before being dispensed into a 96-well culture plate. Direct sequencing was done using a 96 capillary automated sequencing apparatus (ABI 3730XL).

Analysis of Mutations

[0348] Sequence traces were assembled and analyzed to identify potential genomic alterations using the Mutation Surveyor software package (SoftGenetics, State College, PA). The tyrosine kinase gene sequences were aligned with the NCBI reference sequence (Fig. 24) and identified alterations were compared with the literature or public databases such as the NCBI SNP database (<http://www.ncbi.nlm.nih.gov>), the Ensemble Genome Browser (<http://www.ensembl.org>), the UniProtKB/Swiss-Prot database (<http://ca.expasy.org>) the SNP500Cancer database, and KinMutBase (http://bioinf.uta.fi/KinMutBase/main_frame.html).

[0349] Despite the lack of normal tissue counterparts for the established tumor cell lines, it was attempted to define the identified PTK transcript variations as somatic or germline sequence differences. Those sequence differences were defined as germline polymorphisms that were either detected in our 22 controls or were previously reported as hereditary variants in the databases named above or the literature. If genetic alterations occurred neither in the 16 normal tissues nor in one of the cited databases, it was defined as a somatic mutation. Besides zygosity, cell line-specific variant profiles thus indicate germline or somatic origin of the

individual TKT sequence variations. Representative examples are displayed for the skin-derived tumor cell lines A-375, BOW-G, C-32, C8161, and Colo-16 (Fig. 1B). The characterization of all cell lines can be found in Fig. 30.

Gene Identification

[0350] The coding sequences of the analyzed RTK and TK genes were retrieved from NCBI (www.ncbi.gov). NCBI accession numbers are provided in Fig. 28.

Results

[0351] In order to comprehensively characterize widely-used tumor cell lines with regard to non-silent alterations in all expressed tyrosine kinase genes, the inventors evaluated the sequence of the entire tyrosine kinase transcriptome of 254 established cancer cell lines (Fig. 28). These cell lines were derived from 19 different tissue origins (Fig. 1A), controls included 7 non-tumorigenic cell lines and 15 tissues from different organs of healthy individuals.

Identification of 422 non synonymous genetic alterations in the TKT of 258 cancer cell lines

[0352] Based on the above data, the absolute number and distribution of TKT-linked somatic mutations and germline polymorphisms was determined within the entire tumor cell line panel. In total, 72.08 Mb of cDNA sequence encoding the entire protein tyrosine kinase gene family of 59 receptor tyrosine kinases and 32 cytoplasmic protein tyrosine kinases were analyzed. 39.85 Mb of reverse transcribed mRNA were amplified that, apart from IRR, MUSK, FGR and SRMS for which no PCR product from any of the cDNA samples was obtained, represent the entire protein tyrosine kinome expressed within the 280 samples examined. With this analysis numerous silent DNA sequence differences (not presented and further analyzed) and 389 non-synonymous genetic alterations were identified that were amplifiable and represent the detectable TKT of all samples. The majority of these - namely 359 sequence differences - were missense single base substitutions that caused amino acid changes, whereas only two somatic base replacements resulted in the generation of translational termination codons. Furthermore, 43 deletions and 18 insertions were detected. Remarkably, 65 sequence differences to the NCBI database occurred in all cDNA samples analyzed, strongly indicating that these variants actually represent the wild-type rather than genetic alterations (not shown) and were possibly caused by sequencing errors in the human genome database or the fact that the database entries represent individual sequence variants.

[0353] The basis for the discrimination between sporadically occurring somatic mutations and hereditary germline alterations or polymorphisms was formed by the 22 control samples of tissues from healthy individuals and non-tumorigenic cell lines, and by the extensive variant information obtained from public databases such as the NCBI SNP database (<http://www.ncbi.nlm.nih.gov>), Ensemble Genome Browser (<http://www.ensembl.org>), the UniProtKB/Swiss-Prot database (<http://ca.expasy.org>), or the SNP500Cancer database (<http://snp500gov.nci.nih.gov>). Those genetic alterations that were either identified in the control samples or have been reported as polymorphisms in one of the databases or the literature were considered as germline alterations.

[0354] For polymorphisms, a Gaussian-like distribution was observed, with an average of 12.3 sequence variations per cancer cell line. In contrast, somatic mutations were unevenly distributed (Fig. 1C). No somatic alterations were detected in the TKT of 119 cancer cell lines, consistent with kinome mutations entirely absent in subsets of recently screened breast cancer, lung carcinoid, and testicular germ-cell tumor samples (Stephens et al., *Nat Genet* 37:590-592(2005); Davies et al., *Cancer Res* 65:7591-7595(2005); Bignell et al., *Genes Chromosomes Cancer* 2006;45:42-6). In contrast, high frequencies of 9 to 14 somatic mutations in the transcribed tyrosine kinomes of LNCaP, Jurkat, MeWo, MKN1, HCT-15 and DLD-1 might reflect a mutator phenotype (Stephens et al., 2005, supra). They are in agreement with sequence data of 24 cancer genes in the NCI-60 cell line panel that also showed HCT-15 to be one of the most frequently mutated tumor cell lines (Ikediobi et al., *Mol Cancer Ther* 5:2606-12 (2006)). With intermediate mutation rates for the other tumor cell lines, our data indicate an accumulation of somatic mutations in PTK transcripts of various cancer cell lines which may contribute to the progression characteristics of certain cancers.

[0355] As alternative to the allocation to cell line-specific variant profiles, these sequence differences were grouped by genes and PTK subfamilies. Each variation was thereby specified regarding the spectrum of affected cell lines as well as the zygosity status and the presumable somatic versus germline origin. These data are shown for FGFR4 (Fig. 2) that will be discussed below. The full information for all transcript variants and PTK genes can be obtained from Fig. 31 – Fig. 33.

Tykiva Database for cancer cell line TKT analysis

[0356] Additionally, all data on the identified PTK transcript variants are compiled in the database designated “Tykiva” (*tyrosine kinome variant*; <http://tykiva.bii.a-star.edu.sg>). Transcript variants can be specifically retrieved for each of the 254 tumor cell lines, 19 tissue origins/tumor types, or any of the 90 PTK genes. Somatic or germline origin is indicated, and

other cell lines carrying the same variant are referred to. In graphical gene representations, the localization of all detected variants is displayed in the context of the reference amino acid sequence as well as predicted protein domain structures according to Swiss-Prot data. Optionally projectable to the major known isoforms, these illustrations cross-reference our data to variant information from the NCBI SNP database¹⁰, the Ensemble Genome Browser, the Swiss-Prot and the GenBank databases, the KinMutBase, the IDbases, and the literature. By that, they include the current knowledge of non-silent genetic variations in PTK genes.

[0357] The expressed PTK variants may define cell line-specific signaling characteristics and cancer-related cell properties. In the following sections, tissue distribution and localization of each polymorphism and somatic mutation within the respective protein sequence are therefore addressed. Based on these data and the current literature, potential functional and/or clinical relevance for some of the identified genetic variants are discussed.

[0358] The genetic alterations analyzed in primary tumor samples are shown in **Fig. 36**. All non-conservative genetic alteration that were found at least twice in the panel of 276 cell lines and control samples with at least one cell line being derived from breast-, kidney- or prostate cancer were analyzed for occurrence in cDNA obtained from 55 primary breast carcinomas, 55 prostate cancer specimens, 55 kidney cancer specimens, 50 healthy kidney tissues and in genomic DNA derived from blood of 90 non-cancer donors. The number of carriers per sample group is provided for each alteration. Genetic alterations considered somatic as a result of the cell line screen are indicated with asterisks.

Characterization of 155 PTK gene sequence polymorphisms

[0359] According to the above definition of somatic and germline sequence variants, 155 of the 389 identified alterations were classified as sequence polymorphisms. They include 131 SNPs, 16 germline deletions, and 8 insertions. Their overall frequencies and localization in distinct protein domains are summarized in Figs. 3A and 3B. Moreover, the occurrence frequency of each polymorphism in individual tumor types or control samples was determined. Occurrence frequency was thereby defined as the fraction of carriers of a given sequence variant and the number of cell lines with the same tissue origin that express the corresponding gene regardless of its genotype (paired numbers in Fig. 3C and Fig. 35). It therefore reflects the expression aspect of respective genes and alterations, as addressed by our cDNA analysis.

[0360] Of the 131 missense substitutions, 100 had been reported previously. However, only 12 of them, as well as 2 deletions, have been connected with cancer so far (Fig. 35). Noteworthy, 5 of 8 novel deletions involve entire exons (Fig. 35) and most likely represent

splice variants. Such variants could preferentially be detected because of the use of cDNA as sequencing target. Moreover, other transcription-related mechanisms such as epigenetic gene silencing or mRNA stability are also reflected by cDNA, and genetic alterations identified therein are thus likely to be expressed within the cell. However, a disadvantage of our approach is that it does not detect fusion kinase gene- or amplified kinase transcripts.

[0361] In order to verify the *in vivo*-relevance of the sequence variations detected in tumor cell lines, cDNA from 165 primary breast, kidney and prostate cancer specimens was analyzed as well as blood DNA from 90 healthy individuals for the occurrence of a representative subset of our identified genetic alterations. This subset was defined as all non-conservative sequence changes that were found at least twice in our panel of cell lines and control samples with at least one cell line originating from breast, kidney, or prostate cancer. All but 2 of the 46 polymorphisms that fulfilled these criteria could be verified in patient sample cDNAs or blood DNA (Fig. 36), hence confirming the *in vivo*-relevance of sequence variations in tumor cell lines.

[0362] Noteworthy, some novel polymorphisms have been reported as somatic mutations in the literature before. VEGFR2 P1147S, a non-conservative substitution within the catalytic domain of VEGFR2/KDR, for example, has been described as somatic mutation in hemangioma specimens (Walter et al. (2002) Genes Chromosomes Cancer 33: 295-303). This variant was identified in skeletal muscle tissue from a healthy control individual, clearly demonstrating its germline origin and supporting the assumption that various alterations reported earlier as somatic mutations might actually represent germline polymorphisms.

Cancer relevance of identified polymorphisms

[0363] More and more evidence has accumulated over the past years that indicates that genetic polymorphisms can significantly influence clinical parameters of human cancers. In order to provide first information on possible structural or functional consequences of individual polymorphisms the location of all identified polymorphisms within the respective protein sequence is presented herein. In Fig. 37, germline alterations in regions coding for the different domains, including kinase-, the transmembrane- and the juxtamembrane domains, are displayed. Furthermore, the tissue origins a given polymorphism has been found in are indicated (BL: bladder; BS: bone and soft tissue; BA: brain; BE: breast; CV: cervix and vulva; CO: colon; EP: endometrium and placenta; HN: head and neck; HL: hematopoietic and lymphoid system; KI: kidney; LI: liver; LU: lung; OV: ovary; PA: pancreas; PR: prostate; SK: skin; ST: stomach; TE: testes; TY: thyroid, NO: normal control samples).

[0364] Two polymorphisms in the cytoplasmic tyrosine kinase TYK2 and TXK transcripts, TYK2 E971fsX67 and TXK Y414fsX15, are remarkable because of their frequency and localization. TYK2 E971fsX67 and TXK Y414fsX15 were found in different cDNAs, and thus represent relatively frequent germline alterations. Both variations affect the tyrosine kinase domain, and in both cases, the deletion represents the loss of an entire exon associated with a frame shift and the generation of a premature translation termination site. For TYK2 E971FsX67, exon 19 beginning with the N-terminal Glu⁹⁷¹ was deleted, and in conjunction with the frame shift (fs) leading to a STOP-codon after another 67 amino acid residues, this resulted in the loss of the major part of the catalytic domain including the catalytic and the activation loop. The deletion of exon 13 in TXK (TXK Y414fsX15) also results in a truncated variant lacking the functional kinase activation loop and the subsequent C-terminal region, and thus is also very likely to be associated with disruption of catalytic activity.

[0365] The polymorphic in-frame deletion NTRK3 G466_Y529delinsD was found to affect the juxtamembrane membrane of this RTK in two brain, breast and skin tumor cell lines each as well as in three lung cancer and one control cell line. With exception of 12 amino acid residues that are most proximal to the transmembrane domain and 8 residues preceding the kinase domain, this deletion of exon 13 results in the loss of the entire juxtamembrane region. All deletions were detected in one allele only.

[0366] The single nucleotide polymorphism ACK1 P725L is among the novel germline variants the one with the highest frequency. It was detected in 80 different cancer cell line cDNA samples. Interestingly, Pro⁷²⁵ is one of the proline residues that define the affected region of ACK1 as a proline-rich domain. Similarly, in the cytoplasmic tyrosine kinase FAK the proline-rich domain was found to be affected by L926delinsPWRL. In contrast to ACK1 where Pro⁷²⁵ was replaced by an isoleucine, the substitution of FAK Lys⁹²⁶ by the polypeptide PWRL led to the insertion of an additional proline. In both cases the affinity and/or specificity for interacting binding proteins might be modulated.

[0367] In addition to the localization within the protein, strikingly different frequencies in particular tumor types might provide another hint for the potential cancer relevance of a given sequence alteration. The present inventors therefore determined the number of cDNA samples carrying a given germline variation of the reference sequence and the fraction of cell lines that express the corresponding gene (indicated by paired numbers in Fig. 37). As can be seen from Fig. 37 the representation frequency of several polymorphisms varies significantly in tumor cell lines of different tissue origins indicating the possibility of respective differential functional relevance.

[0368] Some of the identified polymorphisms have previously been associated with non-proliferative diseases. Respective functional modulations may, because of the pleiotropic effects of many PTKs, also be relevant for cancer. This is exemplified by the V722I transversion in the pseudokinase domain of JAK3 that the inventors identified as a rare heterozygous polymorphism in the head and neck cancer cell lines SCC-10A and SCC-10B (Fig. 3C). First reported in patients with autosomal recessive T-B+ SCID syndrome (Schumacher, R.F., et al., Hum Genet 106:73-79 (2000)), its recent detection in an acute megakaryoblastic leukemia (AMKL) patient and the capacity to transform Ba/F3 cells (Walters et al., Cancer Cell 10:65-75 (2006)) support a potential role in cancer. Another example is NTRK1 R780Q which the inventors found in the colon-, ovarian-, and head and neck cancer cell lines Caco2, SK-OV-8 and SCC-9 (Fig. 3C), respectively. This SNP affects the same arginine residue whose replacement with proline was shown to be associated with “congenital insensitivity to pain with Anhidrosis (CIPA)” and abrogation of catalytic tyrosine kinase activity in vitro (Greco et al., Am J Hum Genet 64:1207-10 (1999)). Assuming a similar loss-of-function for the NTRK1 Q780 isotype, this variant may exert anti-apoptotic and hence pro-oncogenic effects, as expression of NTRK1 wild type was associated with induction of apoptosis and a favorable prognosis of neuroblastoma patients (Lavoie et al., J Biol Chem 280:29199-207 (2005)).

[0369] Cancer relevance was also established for MET T1010I which represents a biomarker for MET inhibitor efficacy (Jagadeeswaran et al. Cancer Res 66:352-61 (2006)) and was originally reported as a somatic gain-of-function mutation in small- and non-small cell lung cancers (SCLC, NSCLC; Ma et al., Cancer Res 63:6272-6281 (2003)) and malignant pleural mesotheliomas (MPM; Jagadeeswaran et al., 2006, supra). Its detection in 4 of our 90 blood control DNAs (Fig. 36), however, confirmed previous hints for potential germline occurrence (Tengs et al., Cancer Lett 239:227-233 (2006)). Moreover, the identification of MET T1010I in the prostate carcinoma cell line TSU-PR1 and a primary prostate tumor as well as in the brain-, breast-, colon-, hematopoietic- and skin cancer cell lines IHR-32, DAL, LS-123, U-266, and Colo-829, respectively (Fig. 3C and Fig. 36), suggests enhanced MET signaling in these tumor cell lines and expands the currently reported spectrum of affected tumor types.

Polymorphism Frequencies in Cancer Cells versus Normal Tissues

[0370] Differential occurrence rates of sequence polymorphisms in particular cancer types and/or normal tissues may indicate tumor suppressive or promoting effects. In order to address the potential relevance of all polymorphism for certain tumor types, their occurrence

frequencies in tissue types and control samples was compared (Fig. 3C and Fig. 35). Only some examples are displayed in Fig. 4. For EGFR R521K, a relative over-representation of the EGFR K521 allele in cDNAs of normal control samples (55%), colon (52%), and head and neck (69%) tumor cell lines was detected (Fig. 4A) This indicates a possible tumor suppressive activity of the EGFR K521 isotype which apparently is not relevant to colon cancer and head and neck cancer. An attenuated growth response to EGFR ligands and reduced induction of the proto-oncogenes FOS, JUN, and MYC in EGFR K521, but not EGFR R521 expressing cells (Moriai et al., Proc Natl Acad Sci U S A 91:10217-10221 (1994)), and an increased risk of local recurrence after chemoradiation treatment for rectal cancer patients with at least one EGFR R521 allele (Zhang et al., Clin Cancer Res 11:600-5 (2005)) support these conclusions. Similarly, a clearly differential occurrence of TYK2 F362 allele carriers was observed in brain- (75%) and hematopoietic/lymphoid system- (67%) derived tumor cell lines compared to control tissues (31%) or other tumor types (Fig. 4B). The novel polymorphism TNK M598delinsEVRSHX was found at low frequencies in control samples (5%) and cancer cells of several tissue origins, but occurred in 62% of blood-, 55% of skin- and, even more prominent, 80% of brain-derived tumor cell lines (Fig. 4C) In contrast to EGFR R521K, the under-representation of the TYK2 F362 allele and the TNK insertion in control samples indicates a tumor-promoting function with particular relevance for leukemia, melanoma, and glioma. It can be expected that, as for EGFR R521K (Zhang et al., 2005, supra) or FGFR4 G388R (Bange et al., Cancer Res 62:840-847 (2002)), the correlation with clinical parameters will assign therapeutic and/or predictive value to many of such unequally distributed alleles.

[0371] The domain localization and tissue distribution of identified polymorphisms is depicted in Fig. 35. The localization in distinct protein domains and the tissue distribution (BL: bladder; BS: bone and soft tissue; BA: brain; BE: breast; CV: cervix and vulva; CO: colon; EP: endometrium and placenta; HN: head and neck; HL: hematopoietic and lymphoid system; KI: kidney; LI: liver; LU: lung; OV: ovary; PA: pancreas; PR: prostate; SK: skin; ST: stomach; TE: testes; TY: thyroid, NO: normal control samples) was determined for all polymorphisms. Paired numerals reflect the number of carriers of the indicated isotype as a subset of all cell lines within the given tissue origin that express the corresponding gene regardless of its genotype. Novel germline alterations are highlighted in bold type, polymorphisms located in the pseudokinase domain of JAK-family members are indicated as (ps), and skipping of entire exons is marked by asterisks. Parenthesized numbers refer to references given in the legend of Fig. 3 that associate indicated polymorphisms with cancer.

Polymorphisms affecting the kinase domain

[0372] The localization of genetic alterations within the respective protein sequence may be indicative of structural and/or functional consequences. The skipping of entire exons in the cytoplasmic kinases TYK2 and TXK, TYK2 E971fsX67 and TXK Y414fsX15, for instance, results in frame shifts and premature translation termination in the tyrosine kinase domains, and thus most likely is associated with catalytic inactivation. The truncated TYK2 variant that lacks 206 aa of the kinase domain including the catalytic site and the activation loop may also impose a dominant negative effect on cell signals. Interestingly, Stoiber et al. reported that TYK2-deficient mice developed B and T lymphoid leukemia with higher incidence and shortened latency as a result of decreased cytotoxic capacity of TYK2^{-/-} NK and NKT cells and thus impaired tumor surveillance (Stoiber et al., *J Clin Invest* 114:1650-1658 (2004)). Since NK activity as part of the innate immune system mediates tumor rejection in general, the significance of TYK2 loss-of-function might not be restricted to hematopoietic malignancies, but may also be important for other cancer types. Consistent with this possibility, TYK2 E971fsX67 was detected in cancer cells derived from various tissues including breast, cervix/vulva, colon, endometrium, lung, and pancreas (Fig. 3C) as well as 33 clinical breast, prostate, and kidney cancer specimens. Its occurrence in the control cell line BPH-1 suggests potential germline origin. Hence, the TYK2 E971fsX67 splice variant may also represent a prognostic marker for cancer patients and support therapeutic decision making.

[0373] Overall, these examples point at the potential role of sequence polymorphisms as genetic parameters that may contribute to a patient-specific definition of disease predisposition, rate of progression, or responsiveness to therapeutic agents. In conjunction with simple detectability in blood samples, this renders polymorphisms to be highly valuable biomarkers for diagnostic patient characterization.

Identification of 256 somatic mutations in cancer cell lines

[0374] Of all sequence differences, 234 were undetectable in any of the control samples or public databases and were thus defined as somatic mutations. However, because of the lack of cell line-specific normal tissue controls, the possibility cannot be excluded that some actually represent rare germline polymorphisms. The somatic mutations are composed of 210 missense and 2 nonsense single nucleotide substitutions as well as 19 deletions and 3 insertions. While the majority (186) occurred once, 53 were found 2 to 5 times, and 3 in 6 to 10 tumor cell lines (Fig. 5A). Among the twice occurring somatic mutations, 20 were detected in cell lines originating from the same tumor donor (Fig. 24). They may be considered single mutations,

thus adding up to a total of 206 non-recurring mutational events. As for the polymorphisms, all somatic TKT alterations are presented in the context of the respective protein domains and tumor types. Further, the ratio of affected and expression-positive cell lines are presented for each tissue origin (Figs. 5B and 5C and Fig. 37).

[0375] The domain localization and tissue distribution of identified somatic mutations are summarized in **Fig. 37**. Somatic mutations are characterized with regard to their localization within the protein and the tissue origin (BL: bladder; BS: bone and soft tissue; BA: brain; BE: breast; CV: cervix and vulva; CO: colon; EP: endometrium and placenta; HN: head and neck; HL: hematopoietic and lymphoid system; KI: kidney; LI: liver; LU: lung; OV: ovary; PA: pancreas; PR: prostate; SK: skin; ST: stomach; TE: testes; TY: thyroid, NO: normal control samples) of affected cell lines. The first of the paired numerals provided for a given somatic mutation and particular tumor type indicates the number of mutated cell lines, the second numeral refers to the number of expression-positive cell lines. Somatic mutations affecting the activation loop (a), the catalytic loop (c), the P-loop (p) or the pseudokinase (ps) domain are indicated. Novel somatic mutations are highlighted in bold type, skipping of entire exons is indicated by asterisks. Numbers in parenthesis refer to references given in the legend of Fig. 3 (*supra*) that associate indicated mutations with cancer.

[0376] Consistent with SYK A353T to represent one of the 2 most prevalent mutations, the tumor suppressive tyrosine kinase SYK turned out to be the most frequently mutated kinase within our panel of 254 tumor cell lines. When absolute numbers of somatic mutations were compared, SYK scored highest with mutations detected in 11 non-related tumor cell lines (Fig. 38). After normalization with respect to the PTK transcription status, SYK showed the highest mutation rate of 30.3 sporadic alterations per 1 MB expressed coding sequence, followed by NTRK1, EPHA2, and FLT3 (Fig. 39). The domain organization of SYK and the known and novel genetic alterations are illustrated in Fig. 6A.

Somatic mutations with possible oncogenic potential

[0377] Somatic mutations clustering in the EGFR kinase domain (EGFR G719S, L858R, L861Q and others) have recently been reported for patients with Gefitinib-responsive NSCLC and were shown to enhance tyrosine kinase activity and sensitivity to Gefitinib *in vitro* (Paez et al., Science 304:1497-1500 (2004); Lynch et al., N Engl J Med 350:2129-2139 (2004); Pao et al., Proc Natl Acad Sci U S A 101:13306-13311 (2004)). The present inventors found the EGFR G719S mutation to be heterozygously expressed in the colon cancer cell line SW-48 (Fig. 5C, Fig. 24 and Fig. 25). This demonstrates the existence of Iressa sensitivity-mediating

mutations in cancers other than NSCLC and, in particular, suggests colon cancer as another potential indication for Gefitinib therapy.

[0378] Similar to EGFR L858R and Gefitinib, the KIT N822K mutation which the inventors confirmed in the AML cell line KASUMI-1 (Beghini et al., Hematol J, 3:157-163 (2002)) was reported to mediate sensitivity to Gleevec (Heinrich et al., J Clin Oncol 21:4342-4349 (2003)). The enhanced *in vitro* receptor activation shown for these EGFR and KIT mutations (30, 34) might be related to their location within the regulatory activation loop. In this respect, the sporadic variations FLT3 R849H, TEK A1006T, ABL G417E, ARG K450R, and TEC W531R which the inventors detected homo- or heterozygously in BM-1604, SK-MEL-2, MM-Leh, Caki-2, and Jurkat (Fig. 5C) are particularly intriguing as they are located in the activation loop as well. By inference, these mutations may also have a higher probability to modulate the TK catalytic activity and/or related signaling pathways within the respective tumor cell lines.

[0379] The 18 somatic mutations that the present inventors identified in intracellular juxtamembrane domains (Fig. 36) might affect functionally important elements that mediate downregulation of RTK activity. The in-frame deletion MET D981_E1027del as a result of exon 14 skipping, for instance, leads to the loss of c-Cbl E3-ligase binding, decreased ubiquitination, and prolonged ligand-dependent cell signaling *in vitro* and *in vivo* (Kong-Beltran et al.; Cancer Res 66:283-289 (2006)). While MET D981_E1027del was confirmed in the NSCLC cell line NCI-H596, its homozygous detection in breast and stomach cancer cell lines MDA-MB-415 and Hs746, respectively (Fig. 5C), provides evidence for its occurrence in tumor types other than the reported NSCLC (*ibid*; Ma et al.; Cancer Res 65:1479-1488 (2005)). Presuming enhanced sensitivity to anti-MET therapeutics that MET D981_E1027del was suggested to mediate (Kong-Beltran et al., 2006, *supra*), the findings disclosed herein extend the potential clinical relevance for this deletion.

[0380] The somatic mutations that the present inventors identified within the extracellular domain of two FGFR family members, FGFR1 P252S and FGFR4 Y367C (Figs. 5C and 6B), possibly augment receptor activation by influencing ligand binding and receptor dimerization, respectively. The highly conserved FGFR1 P252 residue that the present inventors found to be heterozygously exchanged with hydrophilic serine in the melanoma cell line MeWo has previously been shown to be replaced by threonine in lung cancer (Davies et al., Cancer Res 65:7591-7595 (2005)) and arginine in patients with Pfeiffer syndrome (Muenke et al., Nat Genet 8:269-274 (1994)). The crystal structure of the homologous activating FGFR2 mutant, FGFR2 P252R, revealed the formation of 3 additional hydrogen bonds with complexed fibroblast growth factor 2 (FGF2). They were predicted to increase the receptor's affinity for

its specific ligand as well as to allow binding of a different set of ligands (Ibrahimi et al., Proc Natl Acad Sci U S A 98:7182-7187 (2001)). Since the hydroxy group of the P252-replacing serine residue in FGFR1 also has a high potential to form additional hydrogen bonds, the somatic FGFR1 P252S substitution may represent a gain-of-function mutation with analogous functional consequences as for FGFR2 P252R. This is particularly intriguing in the context of studies demonstrating that blockage of FGFR1 or bFGF function was associated with suppressed proliferation and survival of melanoma cells (Wang & Becker Nat Med 3:887-93 (1997)).

[0381] The novel FGFR4 Y367C mutation was detected as a homozygous genotype in the breast cancer cell line MDA-MB-453, and the affected Y367 residue in the extracellular juxtamembrane domain is highly conserved throughout the FGFR family. Remarkably, homologous substitutions in FGFR1 (Y372C), FGFR2 (Y375C) and FGFR3 (Y373C) were shown to cause various osteogenic deficiency syndromes (Wilkie, Cytokine Growth Factor Rev 16:187-203 (2005)) through the formation of intermolecular disulfide bonds that force receptor dimerization and activation. Ligand-independent, constitutive receptor activation has been confirmed in vitro for FGFR1 Y372C (White et al., Am J Hum Genet 76:361-367 (2005)) and FGFR3 Y373C (d'Avis et al., Cell Growth Differ 9:71-78 (1998)). Furthermore, the oncogenic potential of the FGFR3 Y373C variant has been demonstrated and was suggested to contribute to tumor progression of multiple myeloma (Chesi et al.; Blood 97:729-736 (2001)). Thus, it is most likely that Y367C as the homologous FGFR4 variant also results in basal receptor activation, which strongly indicates an important role of this mutant in cancer.

Nonsense Substitutions Abrogate Tumor Suppressor Activity

[0382] Downregulation of tumor suppressive activity is expected for the 2 nonsense substitutions that the present inventors detected in EPHB2 and CSK (Fig. 5C). Q722X-mediated truncation and kinase inactivation of EPHB2 in the two prostate cancer cell lines BM-1604 and DU-145 supports mutational inactivation to be involved in progression of prostate cancer as proposed by Huusko et al. They showed suppressed growth and colony formation of DU-145 cells upon reconstitution with functional EPHB2 (Huusko et al., Nat Genet 36:979-983 (2004)). The heterozygous CSK Q26X nonsense substitution detected in the colon cancer cell lines DLD-1 and HCT-15 is consistent with reduced protein levels of this negative regulator of SRC-family kinases that were reported for ~60% of human colon cancer cases with elevated SRC activity (Rengifo-Cam et al., Oncogene 23:289-97 (2004)). These data indicate a significant role of CSK nonsense mutations in the development and/or

progression of colon carcinoma and therefore strongly suggest the inclusion of SRC kinase inhibitors in the therapeutic regimen of this prevalent malignancy.

[0383] The examples discussed above represent only a partial extract of our overall data. Other genetic alterations affecting less investigated PTKs such as members of the AATYK-, DDR-, EPH-, ROR-, ROS- or FRK families, as well as tyrosine kinases that more recently captured scientific attention such as HER3 or ACK1, have been found (Figures 25 - 29). Their identification shall support novel functional investigations towards the understanding of the therapeutic value of these kinases.

Low Redundancy of PTK Gene Mutations in Human Tumors

[0384] In agreement with results from previous studies (Stephens et al., 2005, supra; Davies et al., 2005, supra; Bignell et al., 2006, supra; Stephens et al., 2004, supra; Bardelli et al., 2003, supra; Thomas et al., 2007, supra; Greenman et al., 2007, supra; Sjoblom et al., Science 314:268-274 (2006)), the analysis of 254 cancer cell lines and additional primary tumors presented here indicates that mutational patterns might be quite unique for the majority of human tumors, and that the frequency of specific somatic mutations in PTKs is low. Data mining of public databases and the literature revealed that only 9 of all sporadic alterations identified in our study have been described before (Fig. 37). Among them are KIT N822K and VEGFR1 R781Q as the 2 only ones that were picked up in the currently most comprehensive mutational kinome analysis of human cancer samples (Greenman et al., 2007, supra). The low redundancy of somatic mutations is furthermore reflected by the non-recurrence that the present inventors found for 206 of the 256 mutational events within our panel of tumor cell lines.

[0385] Consistent with this picture, none of the 7 somatic representatives of our exemplary subset of non-conservative and more frequent alterations found in at least one breast-, kidney-, or prostate cancer cell line could be detected in any of the 165 primary breast-, kidney- and prostate cancer specimens (Fig. 36). In fact, two genetic alterations, YES K113Q and TYRO3 E489K, were found in blood controls and therefore must be considered rare germline alterations.

[0386] Despite the low redundancy of individual mutations, 70 of the tyrosine kinase genes turned out to carry at least one somatic mutation. Although most of our mutations require further experimental evaluation to determine their cancer relevance and in some cases may turn out to represent "passenger" rather than "driver" mutations, this broad incidence of sporadic alterations underscores the central importance of the entire PTK family in

oncogenesis. Moreover, it provides further compelling support for the development of multi-targeted kinase inhibitors or combination of complementary therapeutics as cancer treatments which may be adapted to the pathological and genetic parameters of an individual patient. The extensive characterization of established tumor cell lines with respect to transcriptional profiles of genetic variations in this currently most promising cancer target family will aid in the selection of suitable cell systems, data interpretation and target validation, and thereby support preclinical development of novel targeted cancer drugs.

Cell culture, Plasmids

[0387] HEK293, Jurkat E6.1, HuH7, HepG2, MCF-7 and MDA-MB-231 cells were purchased from ATCC (Manassas, VA). HEK 293, HuH7 and MCF-7 were maintained in DMEM (high glucose) medium supplemented with sodium pyruvate and 10 % FCS. Jurkat E6.1 and MDA-MB-231 were maintained in RPMI supplemented with L-glutamine, sodium pyruvate and 10 % FCS. HepG2 was maintained in MEM supplemented with non-essential amino acids, L-glutamine, sodium pyruvate and 10 % FCS. All cell culture reagents were from Invitrogen (Carlsbad, CA) unless otherwise stated.

[0388] Full-length cDNAs encoding TEC were amplified by PCR from a human placenta cDNA library and subcloned into pcDNA3 (Invitrogen, Carlsbad, CA). Generation of mutants was performed using QuikChange Site-Directed Mutagenesis Kit from Stratagene (La Jolla, USA). The expression construct for human Ack1 (pXJ40-Ack1-Flag) was a gift from Edward Manser (IMCB, A*STAR, Singapore).

Sample preparation:

[0389] Fifty seven adjacent normal tissue were obtained from resected livers of patients from the National University Hospital (patient's consent for collection of tissue was obtained prior operation). The tumor and normal liver tissues were visually separated. Both tumor and normal tissue were cut into small pieces and flash frozen in liquid nitrogen immediately after being harvested from patients. The frozen tissues were later stored in -80 °C. RNA extraction from frozen tissue was carried out by TriZol method as described previously (Chomczynski, P., & Sacchi, N., Nat Protoc 1:581-5 [2006]).

mRNA purification

[0390] mRNA was purified from total RNA (50 µg per sample) using the Oligotex mRNA kit (Qiagen, Valencia, CA) performed according to manufacturer's protocol. The resulting mRNA from the Oligotex columns was eluted with two volumes of 50 µL of the elution buffer supplied in the kit. To purify and concentrate the eluant, 2 µL of pellet paint (Merck,

Darmstadt, Germany) and 10 μ L of 3M sodium acetate were first added to enhance visualization of the produce before precipitating overnight with 200 μ L of absolute ethanol at -20 °C. The resultant mRNA was pelleted by spinning at 13,000 rpm for 30 min and subsequently washed with another volume of 80 % ethanol. The final precipitate was air-dried and re-dissolved in 10 μ L of RNase-free water.

First strand cDNA synthesis

[0391] The purified mRNA (4 μ L) from above was mixed gently with 1 μ L of OligoDT15 primer (100 μ M, Roche, Basel, Switzerland) in a 1.5 mL microcentrifuge tube and incubated at 70 °C for 2 min. After cooling on ice, 15 μ L of reverse transcription mix containing 4 μ L of 5X RT buffer, 2.4 μ L of $MgCl_2$, 1 μ L dNTP (10 mM), 1 μ L RNase inhibitor, 1 μ L ImProm-II RT (Promega) and 5.6 μ L of water was added. The reaction was maintained at 42 °C for 1 h and was quenched with 75 μ L of TE buffer. The resultant cDNAs were purified with QiaQuick PCR purification kit (Qiagen).

Sequencing and mutational analysis:

[0392] Primers for PCR amplification of cDNA samples (and sequencing) were designed using Primer3 program (http://www-genome.wi.mit.edu/cgi-bin/primer/primer3_www.cgi), and were synthesized by Proligo (SigmaAldrich, Singapore). PCR reactions were optimized as previously described for FGFR4. Direct sequencing was done using a 96 capillary automated sequencing apparatus (ABI 3730XL). Sequence traces were assembled and analyzed to identify potential genomic alterations using the Mutation Surveyor software package (SoftGenetics, State College, PA). The entire coding sequence of FGFR4 was aligned to the NCBI reference sequence (NM_002011.2) and identified alterations were compared to known mutations in the literature (in publications) or public databases such as NCBI SNP database (<http://www.ncbi.nlm.nih.gov>), the Ensemble Genome Browser (<http://www.ensembl.org>), the UniProtKB/Swiss-Prot database (<http://ca.expasy.org>) and KinMutBase (http://bioinf.uta.fi/KinMutBase/main_frame.html).

Quantitative Real-time PCR

[0393] Quantitative RT-PCR was carried out using an Applied Biosystems 7300 Real-time PCR system (ABI, Foster City, CA) with pre-optimized TaqMan Gene Expression Assay for human FGFR4 and human GAPDH as the housekeeping control. The thermal cycling condition included an initial denaturation step at 95 °C for 10 min, followed by 40 cycles at 95 °C for 15 s and 60 °C for 60 s. The samples were prepared in triplicate with 4 μ L of prediluted cDNA (2-10 fold) samples each. Data were obtained as an average CT value, and

subsequently normalized against GAPDH endogenous control as ΔC_T . Expression changes in FGFR4 transcripts between the normal and the corresponding tumor tissue were expressed as fold change using $2^{(\text{difference in } \Delta C_T \text{ between pairs})}$.

Ligand stimulation assay

[0394] HepG2 or HuH7 cells were seeded into 96-well plates and allowed to attach overnight. They were serum-starved for 24 h before addition of heparin. Two hours later, FGF19 (R&D Systems, Minneapolis, MN, 50-100 ng/mL final concentration) was administered. After 8 hours, aliquots of the supernatant were harvested for AFP ELISA assay as described below. Similar FGF19 stimulations were performed in 10 cm dishes for immunoblot detection of phospho-FRS2 α .

Immunoprecipitation, Immunoblot assay

[0395] All fractions collected were assayed for protein concentration using a BCA protein assay kit (Pierce, Rockford, IL). Lysates were pre-cleared by centrifugation at 13 000 r.p.m. for 10 min at 4 °C. For immunoprecipitation, supernatants were diluted with an equal volume of HNTG buffer (Seedorf, K., et al., J Biol Chem. Jun 10; 269(23):16009-16014 (1994)) and subsequently immunoprecipitated using the respective antibodies and 20 μ l of protein A/G–Sephrose for 4 h at 4 °C. Precipitates were washed three times with 0.5 ml of HNTG buffer, suspended in SDS sample buffer and boiled for 3 min.

[0396] For the immunoblot assay, sample proteins (30-50 μ g) or the immunoprecipitated samples were resolved by denaturing electrophoresis using 7.5 % SDS-PAGE and transferred to nitrocellulose membranes for 2 h at 5 V using Trans-Blot SD Semi-Dry Transfer Cell (Bio-Rad). Immunodetection was by chemiluminescence (SuperSignal West Dura Extended, Pierce) using specific antibodies diluted in PBS with 0.05% (v/v) Tween 20 and 5% (w/v) powdered milk. Anti-phospho-FRS2 α anti-HA, anti-phospho-MAPK, anti-MAPK, anti-phospho-Stat3, anti-Stat3 were from Cell Signaling Technology (Beverly, MA); anti-Ack1, anti-myc and anti-FGFR4 were from Santa Cruz Biotechnology (Santa Cruz, CA); anti- β -actin controls and anti-TEC were from Abcam (Cambridge, UK); anti-4G10 and anti-TYK2 were from Upstate (Lake Placid, New York, USA); anti-Hsp60, anti-Flag were from Sigma (St Louis, USA). Secondary anti-mouse and anti-rabbit horseradish peroxidase conjugated secondary antibodies (Pierce) were used at 1:10000 dilution.

AFP ELISA assay

[0397] Supernatants from the respective FGF19 stimulation and siRNA experiments were

subjected to AFP ELISA assay using the DELFIA hAFP kit (Perkin Elmer, Boston, MA), performed according to manufacturer's protocol. The readout was converted to concentration (ng/mL) using the standard curve derived from the solutions provided in the kit. AFP production by the cells was subsequently normalized to the number of cells in each well. The cell number was determined by ATP bioluminescence Cell-Titer Glo assay (Promega, Madison, WI) using protocol as described by the manufacturer.

Gene silencing by siRNA

[0398] HuH7 cells were grown on 24-well plate to 50% confluence before transfection with siRNA (small interfering RNAs). Custom-made ON-TARGETplus siRNA designed for silencing *FGFR4* (Accession number: NM_002011) expression was purchased from Dharmacon. A microcentrifuge tube containing 1.3 μ L of 20 μ M siRNA and 40.2 μ L complete growth medium was prepared (Tube A). Simultaneously, another tube containing 1 μ L oligofectamine (Invitrogen) and 7.5 μ L growth medium was also prepared (Tube B). Both tubes were incubated at room temperature for 5 min before combining the contents and left to stand for another 20 min. Next, each well of HuH7 cells was replaced with fresh serum-free medium (200 μ L). The combined volume of the siRNA transfection mix (50 μ L) was added to the well and incubated at 37 °C. After 4 h, the samples were loaded with another 250 μ L of growth medium containing 20 % serum. Immunoblot and AFP ELISA assays were subsequently performed after 72 h incubation of the cells with the FGFR4 silencing complex.

c-fos gene reporter assay

[0399] HEK-293 cells (2×10^4 /96-well) were transiently transfected with 0.2 μ g of the pfos/luc reporter plasmid (Yamashita et al., Blood 91, 1496-1507 (1998)) and 0.1 μ g of expression plasmids for TEC or its mutants. 24 hours after transfection luciferase activity was measured with the use of the dual luciferase assay system (Promega, Madison, WI).

Ubiquitination Assay

[0400] 3.5×10^6 Hek 293 cells were seeded on 10 cm dish. Cells were co-transfected with 7.5 μ g Myc-tagged Ubiquitin and 10 μ g Flag-tagged Ack1, Ack1 S985N, Mop1 and EphA5, using LipofectamineTM 2000 (Invitrogen, San Diego, CA) according to the manufacturer's instructions.

[0401] 20 hours post transfection, cells are incubated with 10 μ M MG132 (Sigma, St Louis, MO) for 8 hours and lysed by RIPA buffer. 500 μ g of protein lysate were used for immunoprecipitation with 2 μ g anti-myc antibody at 4 degrees Celsius overnight. IP samples

were washed and denatured with SDS-lysis buffer (50 mM Tris-HCl pH 6.8, 100 mM DTT, 2 % SDS) and separated on a 7.5 % SDS-PAGE gel. Co-IP proteins were detected using anti-Flag antibodies.

MG132 Treatment

[0402] 1×10^6 HepG2 cells were seeded on 6 well plate the day before treatment. Cells were incubated with 10 μ M MG132 (Sigma, St Louis, MO) and harvested according to time course. 30 μ g cell lysate was separated with a 7.5 % SDS-PAGE gel.

[0403] The listing or discussion of a previously published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

[0404] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0405] One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. Further, it will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. The molecular complexes and the methods, procedures, treatments, molecules, specific compounds described herein are presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention are defined by the scope of the claims.

[0406] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms “comprising”, “consisting essentially of” and “consisting of” etc. shall be read expansively and without limitation, and are not limited to only the listed components they directly reference, but include also other non-specified components or elements. As such they may be exchanged with each other. Additionally, the terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or

portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

[0407] Other embodiments are within the following claims. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

Claims

What is claimed is:

1. An isolated, enriched, or purified nucleic acid molecule encoding a mutant of a protein kinase polypeptide, wherein the protein kinase polypeptide is selected from the group consisting of FGFR4, FGFR1, Tyro3, TEC, CSK and Ack1, and

wherein the mutant of the protein kinase polypeptide encoded by the nucleic acid molecule comprises at least one mutation selected from the group consisting of FGFR4 Y367C, FGFR1 P252S, Tyro3 S531L, Tyro3 P822L, TEC L89R, TEC W531R, TEC P587L, CSK Q26X and ACK1 S985N.

2. A method of identifying a cell that is resistant to apoptosis inducing reagents (chemoresistant), the method comprising:

- measuring in the cell the expression of the protein kinase Tyro3 and comparing the result of the measurement obtained with that of a control measurement, wherein an increased expression of protein kinase Tyro3 indicates resistance of the cell to apoptosis inducing reagents;
- identifying the amino acid at position 531 and/or 822 of the expressed protein kinase Tyro3, wherein the presence of Leucine at position 531 instead of Serine and/or the presence of Leucine at position 822 instead of Proline indicates increased resistance of the cell to apoptosis inducing reagents; and/or
- identifying the amino acid at position 89, 531 and/or 587 of the expressed protein kinase Tec, wherein the presence of Arginine at position 89 instead of Leucine, the presence of Arginine at position 531 instead of Tryptophan, and/or the presence of Leucine at position 587 instead of Proline indicates increased resistance of the cell to apoptosis inducing reagents.

3. The method of claim 2, wherein the amino acid at position 531 of the expressed protein kinase TEC is identified and wherein the cell is a T cell.

4. The method of claim 2, wherein the amino acid at position 89 of the expressed protein kinase TEC is identified and wherein the cell is a stomach cell.

5. The method of claim 2, wherein the amino acid at position 587 of the expressed protein kinase TEC is identified and wherein the cell is a lung cell.

6. A method of identifying a cell having a predisposition to transform into a cancer cell, the method comprising measuring in the cell the expression of the protein kinase Tyro3, and comparing the result of the measurement obtained with that of a control measurement, wherein an increased expression of protein kinase Tyro3 indicates a predisposition to transform into a cancer cell.

7. A method of identifying a cell having a predisposition to transform into a cancer cell, the method comprising:

- identifying the amino acid at position 367 of the expressed protein kinase FGFR4 and/or the amino acid at position 252 of the expressed protein kinase FGFR1, wherein the presence of Cysteine at position 367 of the expressed protein kinase FGFR4 instead of Tyrosine and/or the presence of Serine at position 252 of the expressed protein kinase FGFR1 instead of Proline indicates an increased predisposition to transform into a cancer cell;
- identifying in the cell, the cell being a liver cell, the amino acid at position 388 of the expressed protein kinase FGFR4, wherein the presence of Arginine at position 388 instead of Glycine indicates an increased predisposition to transform into a hepatocellular carcinoma cell;
- identifying the amino acid at position 362 of the expressed protein kinase TYK2, wherein the presence of Phenylalanine at position 362 of the expressed protein kinase TYK2 instead of Valine indicates an increased predisposition to transform into a cancer cell;
- identifying the amino acid at position 26 of the expressed protein kinase C-terminal Src kinase (CSK), wherein the presence of an amino acid different from Glutamine at position 26 of the expressed protein kinase CSK indicates an increased predisposition to transform into a cancer cell; and/or
- identifying the amino acid at position 985 of the expressed protein kinase Ack1, wherein the presence of Asparagine at position 985 of the expressed protein kinase Ack1 instead of Serine indicates an increased predisposition to transform into a cancer cell.

8. The method of claim 7, wherein the amino acid at position 362 of the expressed protein kinase TYK2 is identified and wherein the cell is a brain cell or a cell of the hematopoietic/lymphoid system.

9. The method of claim 7, wherein the amino acid at position 26 of the expressed protein kinase CSK is identified and wherein the cell is a colon cell.

10. The method of claim 7, wherein the presence of Asparagine at position 985 of

protein kinase Ack1 renders the protein kinase less susceptible to ubiquitination, thereby rendering the protein kinase more durable than protein kinase Ack1 comprising Serine at position 985, and wherein the cell is a kidney cell..

11. The method of claim 7, wherein the amino acid at position 388 of the expressed protein kinase FGFR4 is identified, and wherein further the genotype of the gene encoding the FGFR4 receptor in the liver cell is determined, wherein the homozygous genotype FGFR4 388Arg indicates an increased predisposition to transform into a hepatocellular carcinoma cell.

12. An isolated, enriched, or purified nucleic acid molecule encoding a mutant protein kinase polypeptide, wherein the mutant protein kinase polypeptide is selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, and wherein said mutant kinase polypeptide encoded by said nucleic acid molecule comprises at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6

L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

13. The nucleic acid molecule according to claim 12, wherein the nucleic acid molecule (a) encodes a polypeptide having the amino acid sequence set forth in SEQ ID Nos: 1-256 or any fragment thereof lacking one or more segments of amino acid residues, with the proviso that the mutated region is retained; or (b) is the complement of the nucleotide sequence of (a).

14. The nucleic acid molecule according to claim 12 or 13, wherein the nucleic acid molecule comprises a nucleic acid sequence as set forth in any of SEQ ID No. 257-512, or the complement thereof.

15. An isolated, enriched, or purified nucleic acid molecule encoding a protein kinase polypeptide variant, wherein the protein kinase polypeptide variant is selected from the group consisting of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70 and wherein said protein kinase polypeptide variant encoded by said nucleic acid molecule comprises at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins14, PDGFRFA L221F, PDGFRFA¹ S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813delinsRQ, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598delinsEVRSHX, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX.

16. The nucleic acid molecule according to claim 15, wherein the nucleic acid molecule (a) encodes a polypeptide having the amino acid sequence set forth in SEQ ID Nos: 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641 or any fragment thereof lacking one or more segments of amino acid residues, with the proviso that the altered region is retained; or (b) is the complement of the nucleotide sequence of (a).

17. The nucleic acid molecule according to claim 15 or 16, wherein the nucleic acid molecule comprises a nucleic acid sequence as set forth in any of SEQ ID No. 643-646, 649, 654-655, 657-658, 663, 667-668, 673, 677-680, 692, 701-703, 713-717, 719-721, 728, 730-731, 746, 750-751, 753-754, 756, 760, 762-764, 767, and 770-771, or the complement thereof.

18. The nucleic acid molecule according to any one of claims 1 and 12 to 17, wherein the nucleic acid molecule is isolated from a natural source.

19. The nucleic acid molecule of claim 18, wherein the natural source is mammal.
20. The nucleic acid molecule of claim 19, wherein the mammal is a human.
21. The nucleic acid molecule according to any one of claims 1 and 12 to 17, wherein the nucleic acid molecule is of recombinant origin.
22. The nucleic acid molecule according to any one of claims 1 and 12 - 21, wherein the nucleic acid molecule is RNA or DNA.
23. The nucleic acid molecule according to any one of claims 1 and 12 - 22, wherein the nucleic acid molecule further comprises a vector or promoter effective to initiate transcription in a host cell.
24. A nucleic acid probe for the detection of a nucleic acid molecule encoding a mutant kinase polypeptide in a sample, wherein the mutant kinase polypeptide is selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, and wherein said mutant kinase polypeptide encoded by said nucleic acid molecule comprises at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K,

EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V, wherein said nucleic acid probe contains a nucleotide base sequence that will hybridize to the mutated region of said nucleic acid sequence.

25. The nucleic acid probe according to claim 24, wherein the nucleic acid probe contains a nucleotide base sequence that will hybridize to the mutated region of the nucleic acid sequence set forth in any of SEQ ID Nos: 257-512, or a functional derivative thereof.

26. A nucleic acid probe for the detection of a nucleic acid molecule encoding a protein kinase polypeptide variant in a sample, wherein said protein kinase polypeptide variant is selected from the group consisting of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70, and wherein said protein kinase polypeptide variant encoded by said nucleic acid molecule comprises at least one of the alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins14, PDGFRA L221F, PDGFRA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813delinsRQ, ROS C76_R77ins9, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598delinsEVRSHX, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX, wherein said nucleic acid probe contains a nucleotide base sequence that will hybridize to the mutated region of said nucleic acid sequence.

27. The nucleic acid probe according to claim 26, wherein the nucleic acid probe contains a nucleotide base sequence that will hybridize to the altered region of the nucleic acid sequence set forth in any of SEQ ID Nos: 643-646, 649, 654-655, 657-658, 663, 667-668, 673, 677-680, 692, 701-703, 713-717, 719-721, 728, 730-731, 737, 746, 750-751, 753-754, 756, 760, 762-764, 767, and 770-771, or a functional derivative thereof.

28. A method for detecting the presence or amount of nucleic acid molecule encoding a mutant kinase polypeptide or a kinase polypeptide variant in a sample comprising the steps of a) contacting the sample with a nucleic acid probe according to any one of claims 12-15 under conditions such that hybridization occurs and b) detecting the presence or amount of the probe bound to nucleic acid molecules encoding a mutant kinase polypeptide.

29. The method according to claim 28, wherein the method includes the use of at least two nucleic acid probes according to any one of claims 24-27, in order to simultaneously detect the presence or amount of at least two nucleic acid molecules encoding a mutant kinase polypeptide or kinase variant in a sample.

30. The method according to claim 29, wherein a subset of at least 5, 10, 15, 20, 30, 40, 50 or more nucleic acid probes is used to simultaneously detect the presence or amount of at least 5, 10, 15, 20, 30, 40, 50 or more nucleic acid molecules encoding a mutant kinase polypeptide or kinase polypeptide variant in a sample.

31. The method of any one of claims 28-30, wherein the nucleic acid probe is immobilized on or bound to a solid support.

32. The method according to claim 31, wherein said solid support is a DNA microchip.

33. A kit for performing the methods of any one of claims 28-30, including a container means having disposed therein one or more nucleic acid probes according to any one of claims 24-27.

34. A solid support having immobilized thereon one or more of the nucleic acid probes according to any one of claims 24-27.

35. The solid support according to claim 34, wherein the solid support is a DNA microchip.

36. A recombinant cell or tissue comprising a nucleic acid molecule according to any one of claims 1 and 12-23.

37. The recombinant cell or tissue according to claim 36, wherein the nucleic acid molecule is under the control of genomic regulatory elements or heterologous regulatory elements including a heterologous promoter.

38. An isolated, enriched, or purified mutant kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK,

FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, wherein said mutant kinase polypeptide comprises at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M,

LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

39. The mutant kinase polypeptide according to claim 38, wherein the mutant kinase polypeptide comprises an amino acid sequence as set forth in SEQ ID Nos: 1-256 or a fragment thereof, with the proviso that said fragment includes said mutation.

40. The mutant kinase polypeptide according to claim 38, wherein the mutant kinase polypeptide comprises at least 30, 35, 40, 45, 50, 60, 100, 200, or 300 contiguous amino acids of the amino acid sequence set forth in SEQ ID Nos: 1-256, provided that said polypeptide includes said mutation.

41. An isolated, enriched, or purified kinase polypeptide variant selected from the group consisting of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRB, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70, wherein said kinase polypeptide variant comprises at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins14, PDGFRA L221F, PDGFRA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG,

PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813delinsRQ, ROS C76_R77ins9, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598delinsEVRSHX, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX.

42. The kinase polypeptide variant according to claim 41, wherein the kinase polypeptide variant comprises an amino acid sequence as set forth in SEQ ID Nos: 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641 or a fragment thereof, with the proviso that said fragment includes said alteration.

43. The kinase polypeptide variant according to claim 38, wherein the kinase polypeptide variant comprises at least 30, 35, 40, 45, 50, 60, 100, 200, or 300 contiguous amino acids of the amino acid sequence set forth in SEQ ID Nos: 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641, provided that said polypeptide includes said alteration.

44. The kinase polypeptide according to any one of claims 38-43, wherein the polypeptide is isolated from a natural source or being of recombinant origin.

45. The kinase polypeptide according to claim 44, wherein the natural source is a mammal.

46. The kinase polypeptide according to claim 45, wherein the mammal is a human.

47. A monoclonal or polyclonal antibody or antibody fragment having specific binding affinity only for a mutant kinase polypeptide or a mutant kinase polypeptide domain or fragment, said mutant kinase polypeptide, polypeptide domain or fragment being selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, and fragments and domains thereof, wherein said

mutant kinase polypeptide, polypeptide domain or fragment comprises at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3

A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

48. The antibody or antibody fragment according to claim 47, wherein the antibody is directed against a mutant kinase polypeptide comprising the amino acid sequence set forth in any one of SEQ ID Nos: 1-256 or fragments thereof, with the proviso that said fragment includes said mutation.

49. A monoclonal or polyclonal antibody or antibody fragment having specific binding affinity only for a kinase polypeptide variant or a kinase polypeptide variant domain or fragment, said kinase polypeptide variant, polypeptide domain or fragment being selected from the group consisting of AATYK (AATK), ACK1, AXL, CCK4, EPHA1, EPHA2, EPHA3, EPHB3, FAK, FES, HER2, LMTK2 (AATYK2/BREK), MATK, MER, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RON, ROS, RYK, TEK, TNK1, TXK, TYK2, VEGFR1, VEGFR2, VEGFR3, and ZAP70, and fragments and domains thereof, wherein said kinase polypeptide variant, polypeptide domain or fragment comprises at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ACK1 P725L, AXL G517S, CCK4 P693L, CCK4 A777V, CCK4 S795R, EPHA1 S936L, EPHA2 R876H, EPHA3 I564V, EPHB3 R514Q, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, HER2 R1161Q, LMTK2 S910I, MATK A496T, MER E823Q, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins14, PDGFRA L221F, PDGFRA S478P, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, RON Q473_D515del, RON R627fsX23, RON R813delinsRQ, ROS C76_R77ins9, RYK F516L, TEK V600L, TNK1 D472_R473del, TNK1 M598delinsEVRSHX, TXK R63C, TXK Y414fsX15, TYK2 E971fsX67, VEGFR1 Y642H,

VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 C482R, VEGFR3 R1321Q and ZAP70 K186fsX.

50. The antibody or antibody fragment according to claim 49, wherein the antibody is directed against a kinase polypeptide variant comprising the amino acid sequence set forth in any one of SEQ ID Nos: 513-516, 519, 524-525, 527-528, 533, 537-538, 543, 547-550, 562, 571-573, 583-587, 589-591, 598, 600-601, 607, 616, 620-621, 623-624, 626, 630, 632-634, 637, and 640-641 or fragments thereof, with the proviso that said fragment includes said alteration.

51. A method for detecting the presence and/or amount of at least one mutant kinase polypeptide or kinase polypeptide variant in a sample, comprising the steps of a) probing the sample with the antibody according to any one of claims 47-50 under conditions suitable for kinase-antibody immunocomplex formation and b) detecting the presence and/or amount of the antibody bound to the kinase polypeptide.

52. A kit for performing the method of claim 51, including an antibody or an antibody fragment according to any one of claims 47-50.

53. The kit of claim 52, further comprising a conjugate of a binding partner of the antibody or antibody fragment.

54. The kit of claim 53, wherein said conjugate of a binding partner of the antibody or antibody fragment includes a detectable label.

55. A method for identifying a compound that modulates kinase activity in vitro comprising the steps of: (a) contacting a kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, wherein said kinase polypeptide comprises at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG

K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R,

ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V, or any functional fragment thereof, with the proviso that said fragment includes the mutated region, with a test substance; (b) measuring the activity of said polypeptide; and (c) determining whether said substance modulates the activity of said polypeptide.

56. The method according to claim 55, wherein said kinase polypeptide comprises any one of the amino acid sequences set forth in SEQ ID Nos: 1-256 or any functional fragment thereof, with the proviso that said fragment includes the mutated region.

57. A method for identifying a compound that modulates kinase activity in vitro comprising the steps of: (a) contacting a kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70, wherein said kinase polypeptide comprises at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3

P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins14, PDGFRA L221F, PDGFRA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813delinsRQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76_R77ins9, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598delinsEVRSHX, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del, or any functional fragment thereof, with the proviso that said fragment includes the altered region, with a test substance; (b) measuring the activity of said polypeptide; and (c) determining whether said substance modulates the activity of said polypeptide.

58. The method according to claim 57, wherein said kinase polypeptide comprises any one of the amino acid sequences set forth in SEQ ID Nos: 513-642 or any functional fragment thereof, with the proviso that said fragment includes the altered region

59. A method for identifying a compound that modulates kinase activity in vivo comprising the steps of: (a) expressing a kinase polypeptide in a cell, wherein said polypeptide is selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, wherein said kinase polypeptide comprises at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V,

ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H,

ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V, or any functional fragment thereof, with the proviso that said fragment includes the mutated region; (b) adding a test substance to said cell; and (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

60. The method according to claim 59, wherein said kinase polypeptide comprises any one of the amino acid sequences set forth in SEQ ID Nos: 1-256 or any functional fragment thereof, with the proviso that said fragment includes the mutated region.

61. A method for identifying a compound that modulates kinase activity in vivo comprising the steps of: (a) expressing a kinase polypeptide in a cell, wherein said polypeptide is selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70, wherein said kinase polypeptide comprises at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3

P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins14, PDGFRA L221F, PDGFRA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813delinsRQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76_R77ins9, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598delinsEVRSHX, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del, or any functional fragment thereof, with the proviso that said fragment includes the altered region; (b) adding a test substance to said cell; and (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

62. The method according to claim 61, wherein said kinase polypeptide comprises any one of the amino acid sequences set forth in SEQ ID Nos: 513-642 or any functional fragment thereof, with the proviso that said fragment includes the altered region

63. A method for treating or preventing a proliferative disease or disorder by administering to a subject in need of such treatment a substance that modulates the activity of a kinase selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, wherein said kinase polypeptide comprises at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N,

ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N, CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H,

ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T, TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V.

64. The method according to claim 63, wherein said kinase polypeptide comprises any one of the amino acid sequences set forth in SEQ ID Nos: 1-256.

65. A method for treating or preventing a proliferative disease or disorder by administering to a subject in need of such treatment a substance that modulates the activity of a kinase selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70, wherein said kinase polypeptide comprises at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins14, PDGFRA L221F, PDGFRA S478P,

PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813delinsRQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76_R77ins9, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598delinsEVRSHX, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del.

66. The method according to claim 65, wherein said kinase polypeptide comprises any one of the amino acid sequences set forth in SEQ ID Nos: 513-642.

67. A method for the diagnosis of a proliferative disease or disorder or the risk prediction of developing a proliferative disease or disorder in a subject, said disease or disorder being characterized by an abnormality in a signal transduction pathway due to aberrant protein kinase function, wherein said method comprises : (a) providing a biological sample from said subject; (b) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a target region of a nucleic acid molecule encoding a mutant kinase polypeptide selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, BMX, BRK, BTK, CCK4, CSK, DDR1, DDR2, EGFR, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FER, FES, FGFR1, FGFR2, FGFR4, FLT3, FRK, FYN, HER2, HER3, HER4, IGF1R, INSR, ITK, JAK1, JAK2, JAK3, LCK, LMTK2 (AATYK2/BREK), LYN, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, SYK, TEC, TEK, TIE, TNK1, TYK2, TYRO3, VEGFR1, VEGFR2, YES1, and ZAP70, wherein the mutant kinase polypeptide encoded by said nucleic acid molecule comprises at least one of the mutations AATYK F1195C, ABL1 G417E, ABL1 N789S, ABL1 G883fsX12, ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ALK G1580V, ARG E332K, ARG V345A, ARG K450R, ARG M657I, ARG P665T, ARG R668C, ARG Q696H, ARG K930R, ARG S968F, ARG Q994H, AXL M569I, AXL M589K, AXL G835V, BMX A150D, BMX S254del, BMX N267I, BRK W78fsX58, BTK M489I, BTK W588C, CCK4 D106N,

CCK4 T410S, CCK4 M746L, CCK4 Q913H, CSK Q26X, DDR1 R60C, DDR1 V100A, DDR1 R248W, DDR2 M117I, DDR2 R478C, EGFR N115K, EGFR A289V, EGFR P332S, EGFR I646L, EGFR T678M, EGFR P753S, EGFR E922K, EGFR A1118T, EPHA2 R315Q, EPHA2 H333R, EPHA2 G391R, EPHA2 P460L, EPHA2 H609Y, EPHA2 M631T, EPHA2 G662S, EPHA2 V747I, EPHA2 L836R, EPHA2 E911K, EPHA2 V936M, EPHA2 R950W, EPHA3 S46F, EPHA3 E53K, EPHA3 A777G, EPHA4 V234F, EPHA4 S803A, EPHA4 M877V, EPHA5 N81T, EPHA5 E85K, EPHA5 A672T, EPHA5 V891L, EPHA5 A957T, EPHA5 R981L, EPHA6 N291H, EPHA6 G513E, EPHA6 L622F, EPHB1 A39V, EPHB1 I837M, EPHB2 A83V, EPHB2 S98R, EPHB2 V136M, EPHB2 R270Q, EPHB2 P273L, EPHB2 R369Q, EPHB2 E686K, EPHB2 V762L, EPHB3 P6del, EPHB3 A517V, EPHB4 P231S, EPHB4 V547M, EPHB4 D576G, EPHB4 I610T, EPHB4 E890D, EPHB4 A955V, EPHB6 G353_E471del, EPHB6 A369T, EPHB6 L580F, EPHB6 E615K, EPHB6 A647V, EPHB6 S785R, EPHB6 R811C, FAK S329I, FAK Q440R, FAK A472V, FAK P901S, FER I240T, FER Q526L, FER Q599R, FES M323V, FES L690M, FES V724M, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 G539_K540del, FGFR2 I526T, FGFR4 Y367C, FLT3 V194M, FLT3 D358V, FLT3 V557I, FLT3 G757E, FLT3 R849H, FRK R64Q, FRK G119A, FRK R406H, FYN E521K, HER2 G518V, HER2 A830V, HER2 E930D, HER2 G1015E, HER2 A1216D, HER3 N126K, HER3 R611W, HER3 R667H, HER3 R1077W, HER3 R1089W, HER3 P1142H, HER3 L1177I, HER4 L753V, HER4 G936R, IGF1R T104M, IGF1R Y201H, IGF1R N209S, INSR L991I, ITK R448H, JAK1 I363V, JAK1 R494C, JAK1 N849fsX16, JAK2 F85S, JAK2 A377E, JAK2 L383P, JAK2 G571S, JAK2 E592K, JAK2 R1063H, JAK2 N1108S, JAK3 G62fsX47, JAK3 M511I, JAK3 P693L, JAK3 E698K, LCK L36fsX8, LCK F151S, LCK R484W, LMTK2 Q238P, LMTK2 A251T, LMTK2 G518V, LMTK2 D523Y, LMTK2 M758V, LMTK2 D793G, LMTK2 R828Q, LMTK2 L879M, LMTK2 A1008V, LYN F130V, MER E831Q, MET T17I, MET P366S, MET S691L, NTRK1 P453fsX15, NTRK1 L585fsX73, NTRK1 G595E, NTRK1 R748W, NTRK2 A586V, NTRK2 V622I, NTRK2 A647fsX54, NTRK3 V530fsX6, NTRK3 G608D, NTRK3 A631fsX33, PDGFRA G79D, PTK-9 D258E, PTK-9 K265R, PTK-9 N333S, PYK2 S9I, PYK2 C395Y, PYK2 E404Q, PYK2 D424Y, PYK2 E798Q, PYK2 M885L, PYK2 T978M, RET A750T, RON F574fsX23, RON Q955H, RON A1022_K1090del, RON V1070fsX12, ROR1 R185H, ROR1 R429Q, ROR1 S870I, ROR1 P883S, ROR2 R302H, ROR2 C389R, ROR2 D390fsX46, ROR2 P548S, ROS R187M, ROS D709fsX16, ROS Q865fsX90, ROS A1443S, RYK H250R, RYK R504H, RYK A559T, SYK M34fsX3, SYK I262L, SYK E315K, SYK A353T, SYK R520S, SYK V622A, TEC L89R, TEC W531R, TEC P587L, TEK A615T,

TEK A1006T, TIE S470L, TIE M871T, TNK1 A299D, TYK2 A53T, TYK2 S340fsX26, TYK2 R701T, TYK2 D883N, TYK2 R901Q, TYK2 A928V, TYK2 P1104A, TYRO3 S324C, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L, VEGFR1 G203W, VEGFR1 S437L, VEGFR1 A673V, VEGFR1 R781Q, VEGFR1 M938V, VEGFR2 E107K, VEGFR2 P1280S, YES1 K113Q, ZAP70 T155M, and ZAP70 M549V; and (c) detecting the presence or amount of the probe:target region hybrid as an indication of or predisposition to the disease or disorder.

68. The method according to claim 67, wherein the mutant kinase polypeptide encoded by said nucleic acid molecule comprises at least one of the amino acid sequences set forth in SEQ ID Nos: 1-256.

69. The method according to claim 67 or 68, wherein the nucleic acid probe comprises any one of the nucleotide sequences set forth in SEQ ID Nos: 257-512, or a complement or fragment thereof, with the proviso that the fragment covers said mutation.

70. A method for the diagnosis of a proliferative disease or disorder or the risk prediction of developing a proliferative disease or disorder in a subject, said disease or disorder being characterized by an abnormality in a signal transduction pathway due to aberrant protein kinase function, wherein said method comprises : (a) providing a biological sample from said subject; (b) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a target region of a nucleic acid molecule encoding a kinase polypeptide variant selected from the group consisting of AATYK (AATK), ABL1, ACK1, ALK, ARG, AXL, CCK4, CSFR1, EGFR, EPHA1, EPHA10, EPHA2, EPHA3, EPHA7, EPHB2, EPHB3, EPHB4, EPHB6, FAK, FES, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FRK, FYN, HER2, HER3, JAK2, JAK3, LMTK2 (AATYK2/BREK), MATK, MER, MET, NTRK1, NTRK2, NTRK3, PDGFRFA, PDGFRB, PTK-9, PYK2, RET, RON, ROR1, ROR2, ROS, RYK, STYK, TEK, TNK1, TXK, TYK2, TYRO3, VEGFR1, VEGFR2, VEGFR3 and ZAP70, wherein the kinase polypeptide variant encoded by said nucleic acid molecule comprises at least one of the germline alterations AATYK G600C, AATYK G641S, AATYK F1163S, AATYK T1227M, ABL1 P829L, ABL1 S991L, ACK1 P725L, ACK1 R1038H, ALK K1491R, ALK D1529E, ARG K959R, AXL G517S, CCK4 P693L, CCK4 E745D, CCK4 A777V, CCK4 S795R, CSF1R H362R, EGFR R521K, EPHA1 A160V, EPHA1 V900M, EPHA1 S936L, EPHA10 L629P, EPHA10 V645I, EPHA10 G749E, EPHA2 R876H, EPHA3 I564V, EPHA3 R914H, EPHA3 W924R, EPHA7 I138V, EPHB2 P128A, EPHB3 R514Q, EPHB4 P231S, EPHB6 G107S, EPHB6 S309A, FAK T416fsX, FAK

L926delinsPWRL, FES P397R, FES S72_K129del, FES E413fsX131, FGFR1 V427_T428del, FGFR2 M71T, FGFR2 H199_Q247del, FGFR3 T311_Q422del, FGFR4 V10I, FGFR4 L136P, FGFR4 G388R, FLT3 M227T, FRK G122R, FYN D506E, HER2 I655V, HER2 R1161Q, HER2 P1170A, HER3 S1119C, JAK2 L393V, JAK3 P132T, JAK3 P151R, JAK3 V722I, LMTK2 P30A, LMTK2 L780M, LMTK2 S910I, MATK A496T, MER E823Q, MER V870I, MET N375S, MET R988C, MET T1010I, MET V1238I, NTRK1 H604Y, NTRK1 G613V, NTRK1 R780Q, NTRK2 D466fsX14, NTRK3 E402_F410delinsV, NTRK3 G466_Y529delinsD, NTRK3 R711_V712ins14, PDGFRA L221F, PDGFRA S478P, PDGFRB P345S, PDGFRB T464M, PTK-9 E195_V196insRPEDHIG, PYK2 G414V, PYK2 K838T, PYK2 V739_R780del, RET D489N, RET G691S, RET R982C, RON N440S, RON R523Q, RON Q473_D515del, RON R627fsX23, RON Y884_Q932del, RON R813delinsRQ, RON R1335G, ROR1 M518T, ROR2 T245A, ROR2 V819I, ROS T145P, ROS R167Q, ROS I537M, ROS S1109L, ROS D2213N, ROS K2228Q, ROS S2229C, ROS C76_R77ins9, RYK N96S, RYK F516L, STYK G204S, TEK P346Q, TEK V486I, TEK V600L, TNK1 D472_R473del, TNK1 M598V, TNK1 M598delinsEVRSHX, TXK R63C, TXK R336Q, TXK Y414fsX15, TYK2 V362F, TYK2 G363S, TYK2 I684S, TYK2 E971fsX67, TYRO3 I346N, VEGFR1 Y642H, VEGFR1 E982A, VEGFR1 P1201L, VEGFR2 V297I, VEGFR2 Q472H, VEGFR2 C482R, VEGFR2 P1147S, VEGFR3 Q890H, VEGFR3 R1321Q, ZAP70 K186fsX, and ZAP70 P296_S301del; and (c) detecting the presence or amount of the probe:target region hybrid as an indication of or predisposition to the disease or disorder.

71. The method according to claim 70, wherein the mutant kinase polypeptide encoded by the nucleic acid molecule comprises at least one of the amino acid sequences set forth in SEQ ID Nos: 513-642.

72. The method according to claim 70 or 71, wherein said nucleic acid probe comprises any one of the nucleotide sequences set forth in SEQ ID Nos: 643-772, or a complement or fragment thereof, with the proviso that the fragment covers said mutation.

73. The method according to any one of claims 63 to 72, wherein said subject is a human.

74. The method according to any one of claims 63 to 73, wherein the proliferative disease or disorder is cancer.

1/306

Fig. 1A

Tissue Origin of Cell Lines	Number of Cell Lines
bladder (BL)	5
bone and soft tissue (BS)	4
brain (BA)	16
breast (BE)	22
cervix and vulva (CV)	11
colon (CO)	23
endometrium and placenta	3
head and neck (HN)	13
hematopoietic and lymphoid system (HL)	24
kidney (KI)	9
liver (LI)	4
lung (LU)	22
ovary (OV)	11
pancreas (PA)	17
prostate (PR)	6
skin (SK)	53
stomach (ST)	5
testes (TE)	3
thyroid (TY)	3
normal tissue (NO)	22

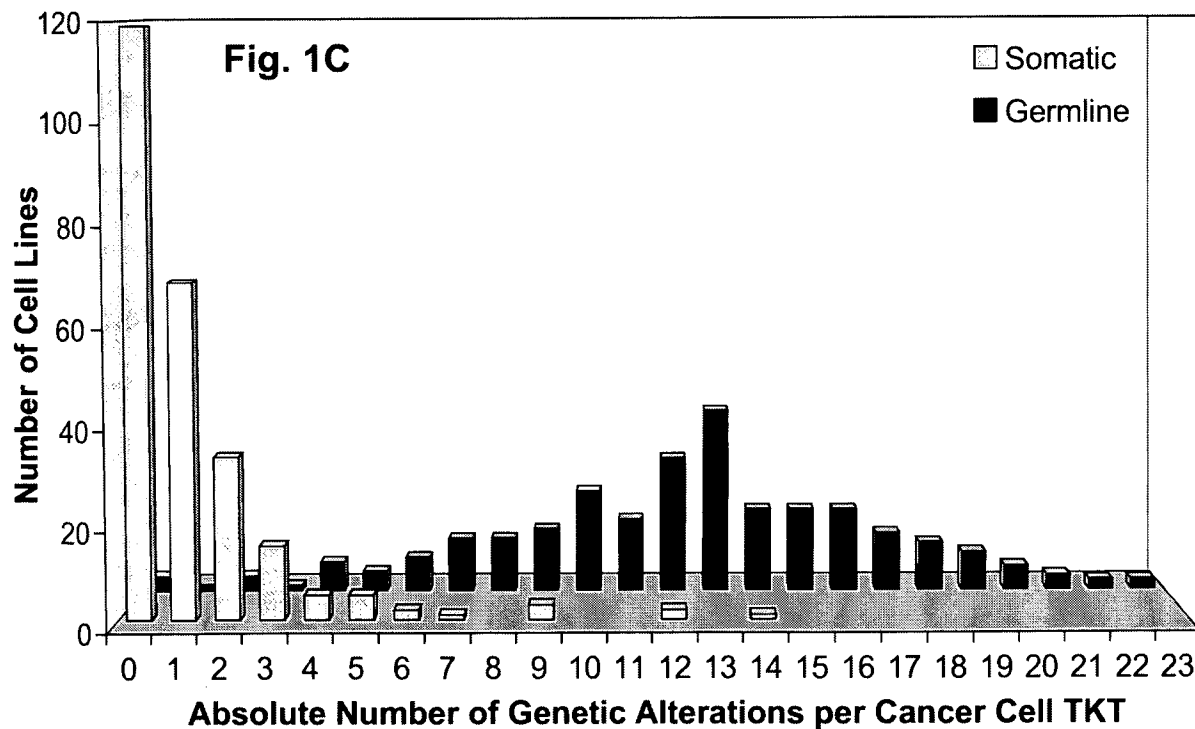
Fig. 1B: Skin (continued on next page)

A-375			BOW-G			C-32		
ALK	K1491R#		TYRO3	I346N#		TYRO3	I346N#	
ALK	D1529E#		HER2	I655V#		EGFR	R521K#	
TYRO3	I346N#		HER2	P1170A		HER2	P1170A	
EGFR	R521K#		FGFR4	G388R		EPHA3	W924R#	
HER2	P1170A#		ROR1	M518T		RON	R1335G#	
EPHA3	W924R#		TEK1	P346Q		ROR1	M518T	
EPHA5	E85K		VEGFR2	E107K#		VEGFR2	Q472H#	
CCK4	T410S#		VEGFR2	V297I#		LMTK2	P30A#	
ROR1	M518T		LMTK2	L780M#		TNK1	M598delinsEVRSHX	
NTRK3	E402_F410delinsV#		ARG	M657I#		TYK2	I684S#	
NTRK3	R711_V712ins14#		TYK2	S340fsX26#				
ACK1	P725L#		TNK1	M598delinsEVRSHX#				
			PYK2	K838T#				

2/306

Fig. 1B (continued from prev. page): Skin

C-8161		Colo-16	
TYRO3	I346N#	HER2	P1170A#
HER2	P1170A	ROR1	M518T#
EPHA2	R876H#	ROR2	T245A
RON	R813delinsRQ#	ACK1	P725L#
ROR1	M518T	PYK2	K838T#
STYK1	G204S	FRK	G122R#
TNK1	M598delinsEVRSHX#		
PYK2	K838T		
FES	S72_K129del		



3/306

Gene	Mu- tation	Total Number	Bladder	Bone and Soft Tissue	Brain	Breast	Cervix and Vulva	Colon	Endome- trium and Placenta	Head and Neck	Hemato- poietic and Lymphoid System	
FGFR4	V10I	8		RD, I TE-671, I				LS-174T, I # LS-180, I #	JAR, I #		OCI-AML5, I	
FGFR4	L136P	37	SCaBER, P	SaOS2, P #		BT-474, P BT-483, P # MB-157, P MB-415, P		HCT-116, P # LS-123, P # LS-174T, P # LS-180, P # LoVo, P SW-837, P			HL-60, P K-562, P # PLB-985, P U-266, P	
FGFR4	Y367C	1				MB-453, C						
FGFR4	G388R	58	TCCSUP, R		SHSY5Y, R # SK-N-SH, R # SW-1088, R # U-1240, R U-1242, R	Hs-578T, R MB-361, R # MB-453, R SK-BR-3, R	Ms 751, R	Caco2, R SW-403, R #		SCC-4, R SCC-22B, R SCC-22A, R	EM-2, R M-Mac-1, R # M-Mac-6, R #	
....												

Fig. 2

4/306

Fig. 3A

Frequency	MS	NS	DEL	INS	Total
1x	36	0	2	1	39
2-5x	28	0	1	0	29
6-10x	17	0	2	1	20
>10x	50	0	11	6	67
Total	131	0	16	8	155

Fig. 3B

Protein Domains and Number of Polymorphisms therein					
Kinase	30	Cysteine-Rich	1	SH2	3
Transmembrane	3	Immunoglobulin	10	IPT/TIG	1
Juxtamembrane	13	Signal Peptide	1	Frizzled	1
FN Type III	8	Sema	3	WIF	1
SAM	3	Proline-Rich	9	Other	67

Fig. 3C

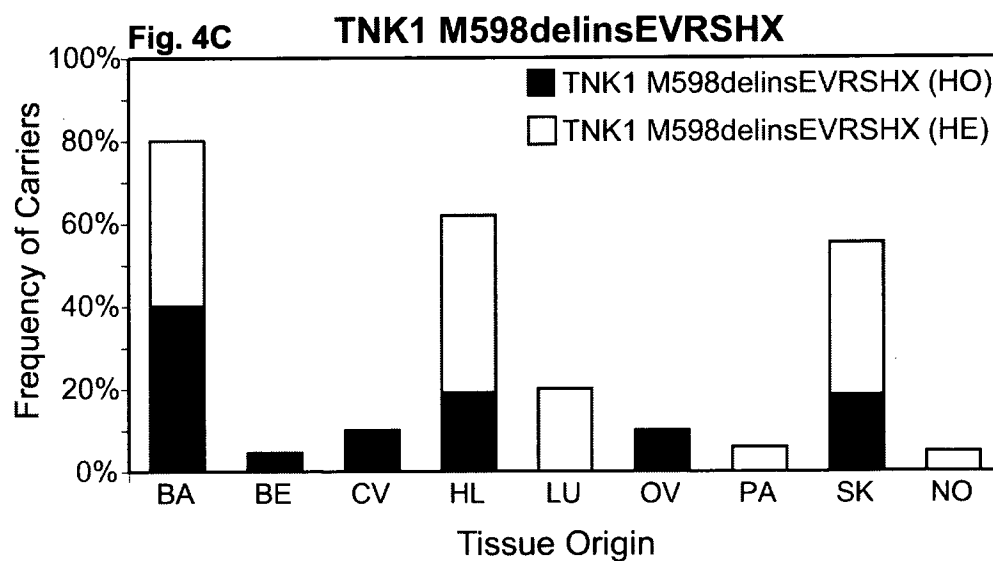
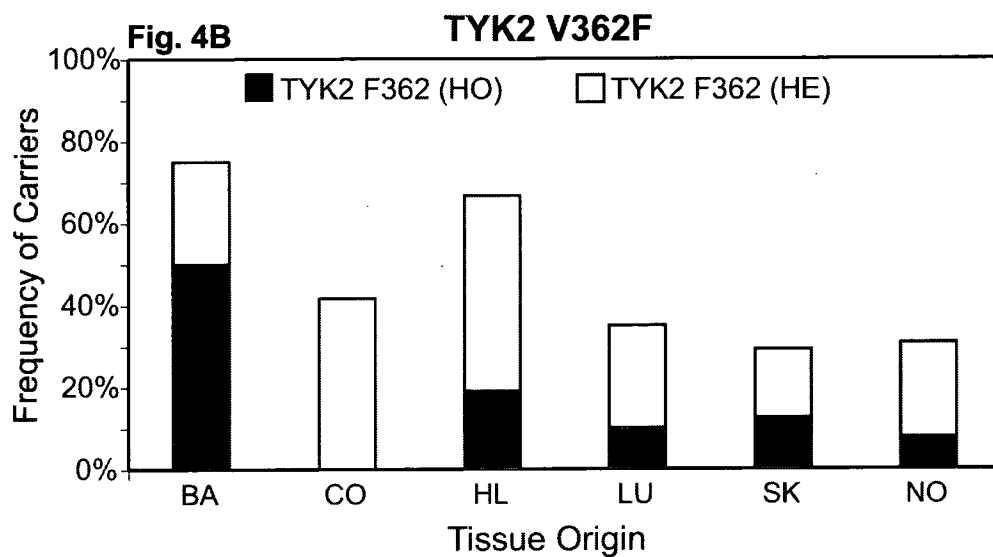
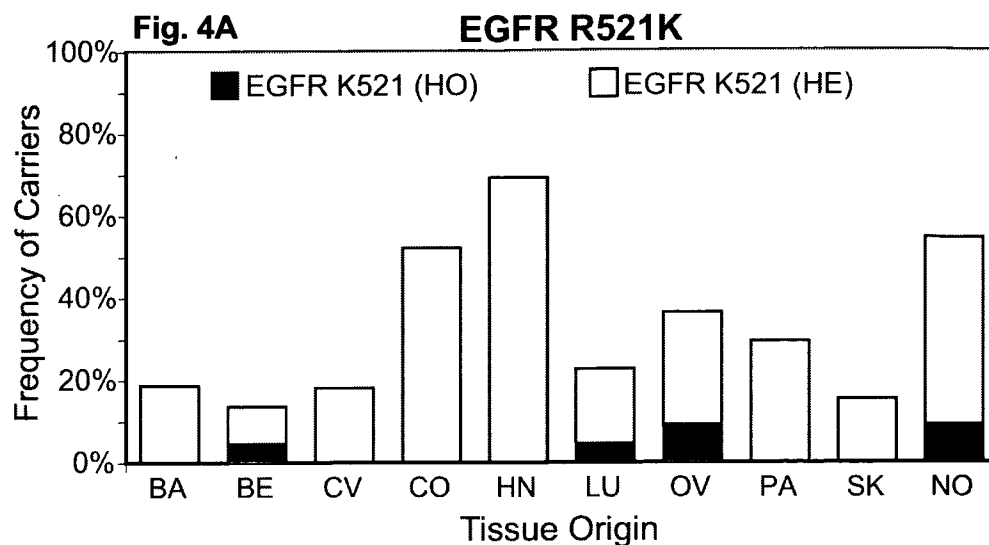
Gene	Germline Alteration	Tissue Origin						
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)
EGFR	R521K (SI 15)		1/2	3/16	3/22	2/11	12/23	1/3
FGFR4	G388R (SI 9)	1/4		5/14	4/11	1/8	2/13	
MET	R988C (SI 10)							
MET	T1010I (SI 11)			1/15	3/21		1/22	
NTRK1	R780Q (SI 5)						1/18	
ROR1	M518T	2/4	4/4	13/15	14/15	8/9	18/23	3/3
ROR2	T245A		1/1	5/5	2/4	3/3	1/2	1/1
TYRO3	I346N	2/4	3/4	9/15	1/9	3/8	4/16	3/3
JAK3	V722I (SI 7)							
TNK1	M598delinsEVRSHX		2/2	12/15	1/22	1/10		
TXK	R336Q	1/5			1/20		3/23	
TXK	Y414fsX15			3/10	4/19	1/9	2/22	
TYK2	E971fsX67				5/17	1/11	3/21	1/3
TYK2	V362F	1/4	4/4	9/12	2/4	2/9	5/12	

5/306

Fig. 3C (continued from prev. page)

Gene	Germline Alteration	Tissue Origin												
		HN (13)	HL (24)	KI (9)	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)	NO (22)
EGFR	R521K (SI 15)	9/13		7/9	2/4	5/22	4/11	5/17	2/6	8/52	2/6	2/2		12/22
FGFR4	G388R (SI 9)	3/12	3/13	3/8	2/3	6/17	2/5	4/9	2/6	11/45	1/1			8/19
MET	R988C (SI 10)					1/20								1/19
MET	T1010I (SI 11)		1/13						1/6	1/50				
NTRK1	R780Q (SI 5)	1/12					1/11							
ROR1	M518T	7/10	9/10	7/8	2/3	15/21	7/10	14/16	5/6	44/51	4/5	1/3		21/22
ROR2	T245A	1/3	2/7	4/4	1/1	2/4	3/3	1/1		3/4		1/1		3/8
TYRO3	I346N	3/12	7/23	2/8	1/4	7/22	3/6	7/12		18/46				12/21
JAK3	V722I (SI 7)	2/7												
TNK1	M598delinsEVRSHX		13/21	4/9	1/4	4/20	1/10	1/17	1/6			1/3		1/21
TXK	R336Q	4/10			1/4		2/11			2/45	1/7			1/20
TXK	Y414fsX15		9/24	2/4		2/16		3/15		1/39	2/4		2/3	2/19
TYK2	E971fsX67					1/22		2/14				1/2		1/21
TYK2	V362F		14/21	6/9	1/4	7/20		2/9		7/24				4/13

6/306



7/306

Fig. 5A

Frequency	MS	NS	DEL	INS	Total
1x	171	0	7	2	180
2-5x	38	2	11	1	52
6-10x	1	0	1	0	2
>10x	0	0	0	0	0
Total	210	2	19	3	234

Fig. 5B

Protein Domains and Number of Somatic Mutations therein					
Kinase	71	Cysteine-Rich	6	Src-homology 2	4
Transmembrane	4	Immunoglobulin	7	Src-homology 3	3
Juxtamembrane	17	Signal Peptide	2	Other	95
FN type III	10	Sema	1		
SAM	5	Proline-Rich	9		

Fig. 5C (continued on next page)

Gene	Somatic Mutations	Tissue Origin						
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)
EGFR	G719S (SI 17)						1/21	
EPHB2	Q722X (SI 18)							
FGFR1	P252S							
FGFR4	Y367C				1/14			
FLT3	R849H							
KIT	N822K (SI 19)							
MET	D981_E1027del (SI 20)				1/22			
RON	A1022_K1090del				1/17			
TEK	A1006T							
TYRO3	E489K				1/8			
ABL1	G417E							
ARG	K450R							
CSK	Q26X						2/18	
TEC	W531R							
YES1	K113Q				1/9		1/19	

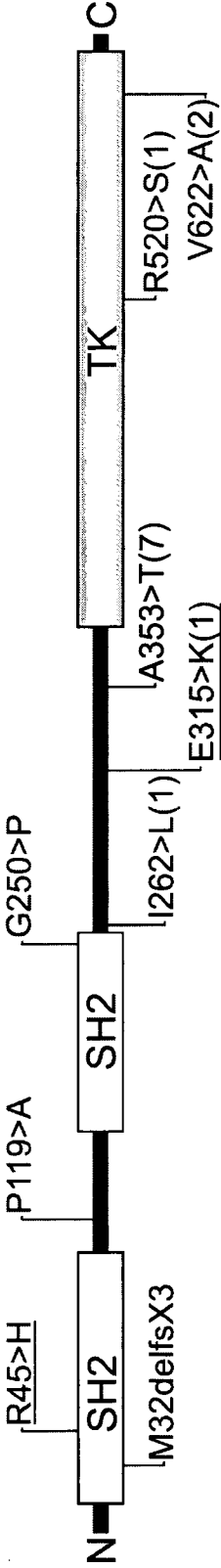
8/306

Gene	Somatic Mutations	Tissue Origin											
		HN (13)	HL (24)	KI (9)	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
EGFR	G719S (SI 17)								2/6				
EPHB2	Q722X (SI 18)									1/38			
FGFR1	P252S												
FGFR4	Y367C												
FLT3	R849H								1/2				
KIT	N822K (SI 19)		1/13										
MET	D981_E1027del (SI 20)					1/22				1/5			
RON	A1022_K1090del												
TEK	A1006T									1/31			
TYRO3	E489K								2/5				
ABL1	G417E												
ARG	K450R			1/9						1/51			
CSK	Q26X												
TEC	W531R		1/24										
YES1	K113Q			1/9									

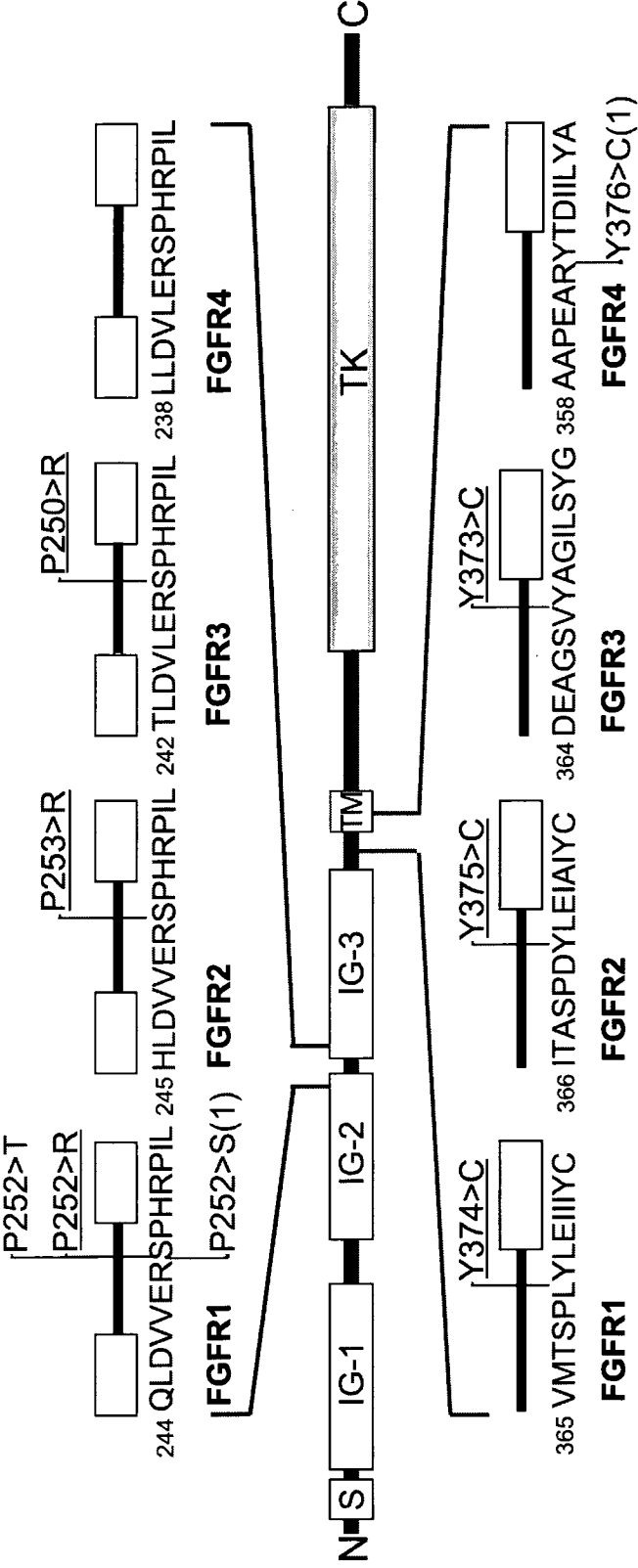
Fig. 5C (continued from prev. page)

Fig. 6

A SYK



B FGFR

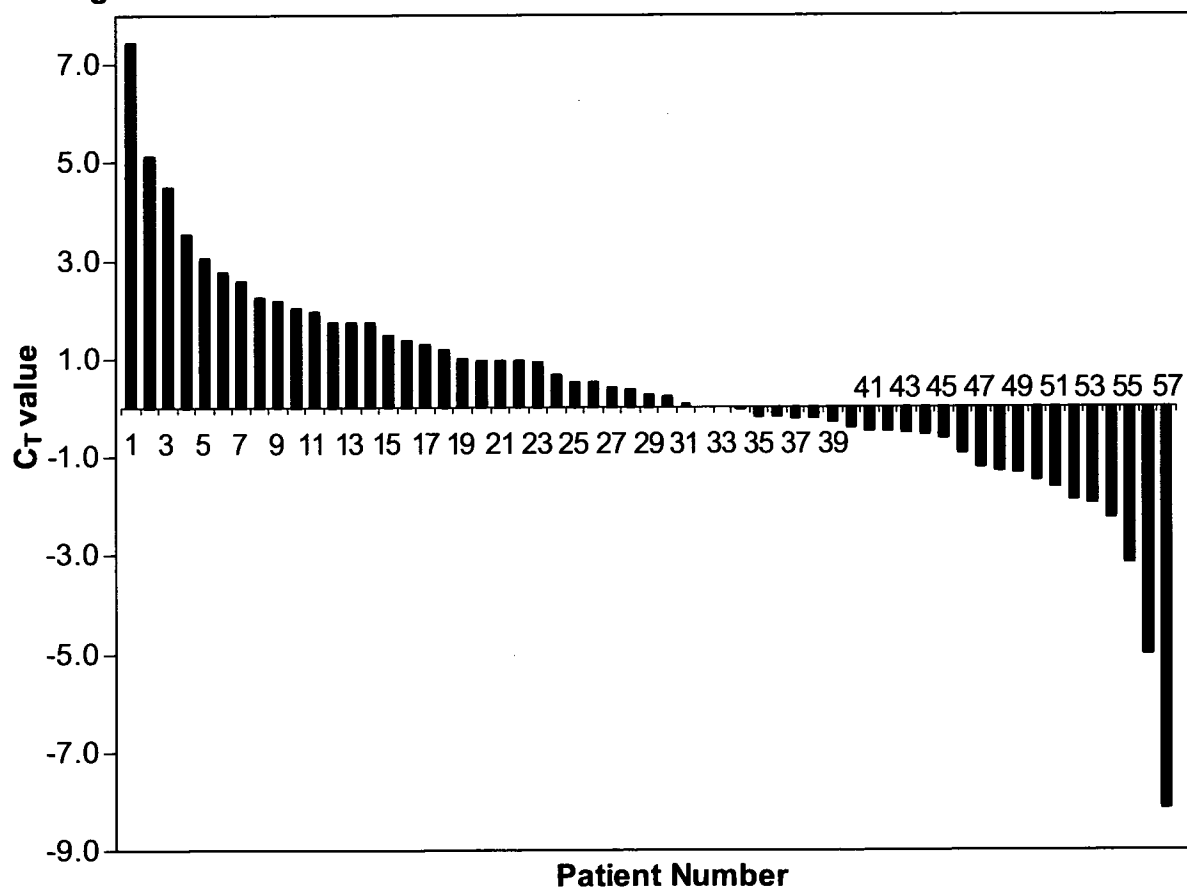


10/306

Fig. 7

FGFR4 expression-fold change			
Fold change	<0.5	0.5-2.0	>2.0
No. of patients	11	28	18
% of patients	19.3%	49.1%	31.6%

Fig. 8 Expression Changes Between Normal and Tumor Tissues

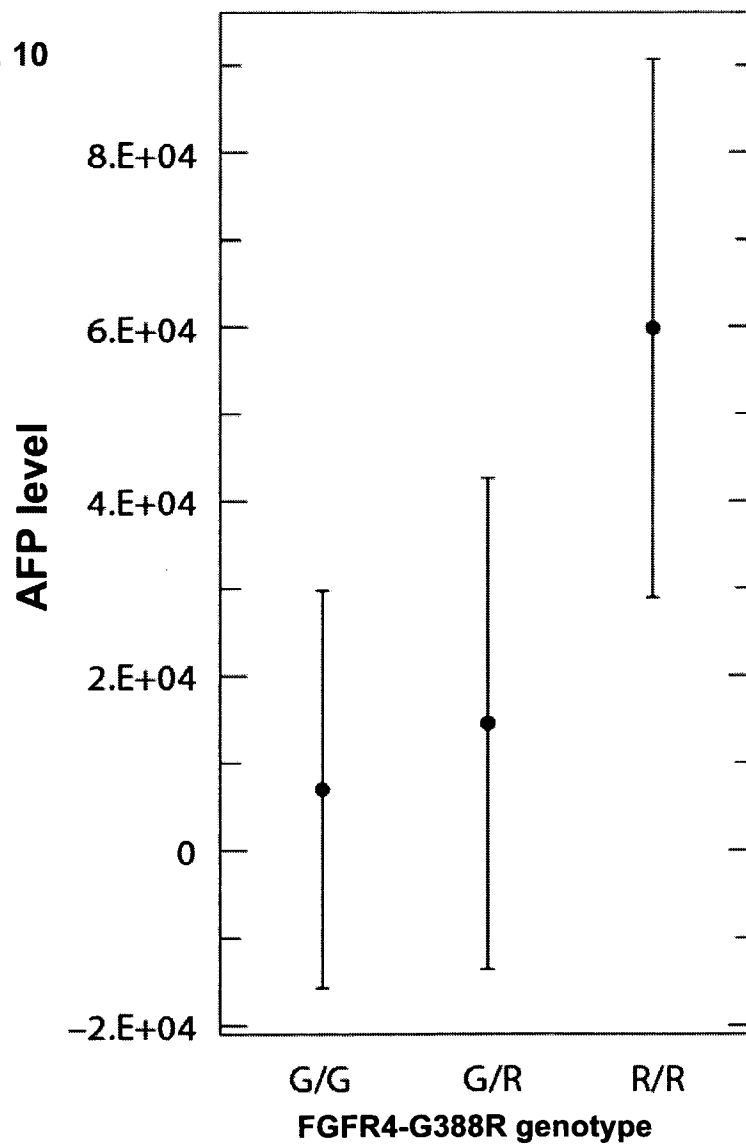


11/306

Fig. 9

FGFR4-G388R		
Genotype	HCC samples	Control Asian population
GG	46.6% (27/58)	34.1% (30/88)
GR	29.3% (17/58)	43.2% (38/88)
RR	24.1% (14/58)	22.7% (20/88)

Fig. 10



12/306

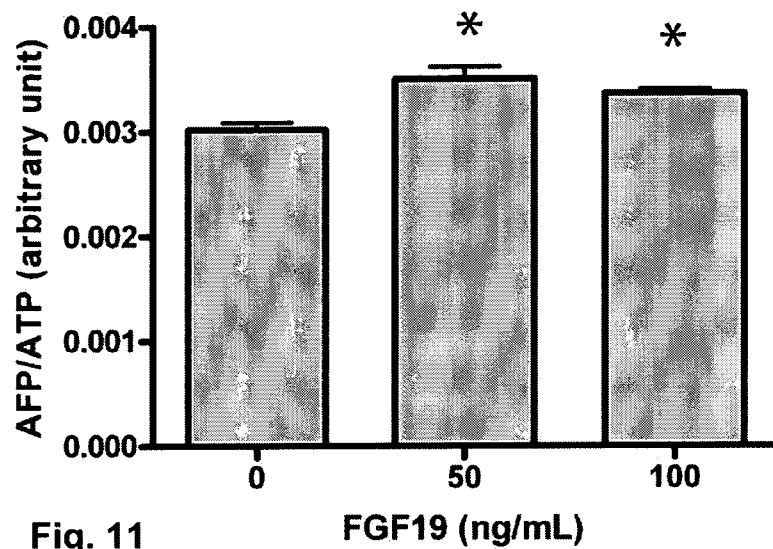
FGF19 stimulation of AFP production in HuH7

Fig. 11

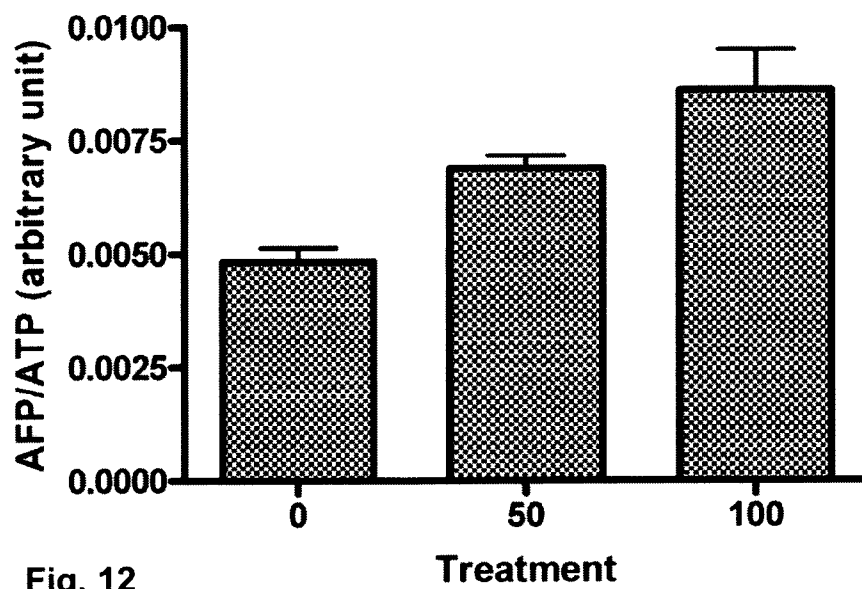
FGF19 stimulation of AFP production in HepG2

Fig. 12

13/306

Fig. 13

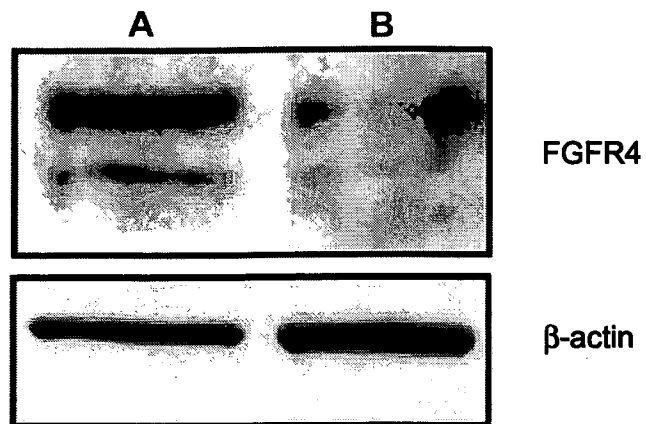


Fig. 14

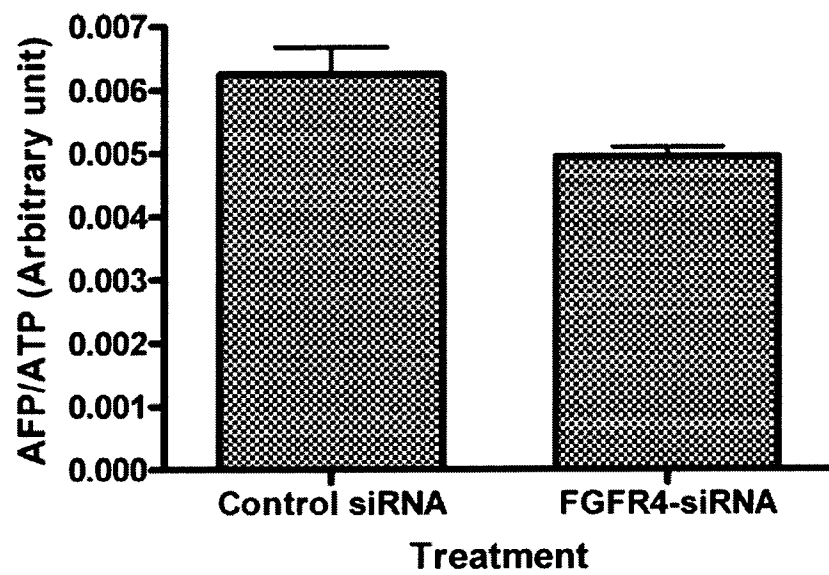
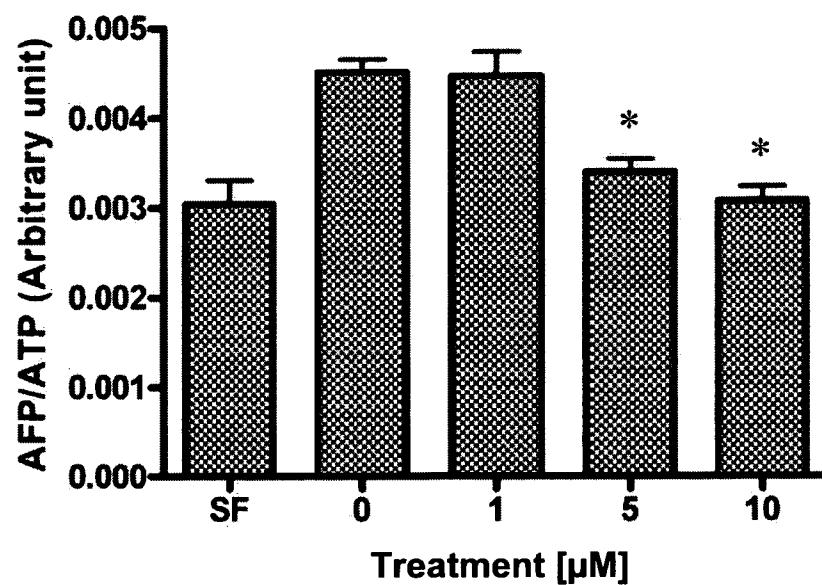


Fig. 15



14/306

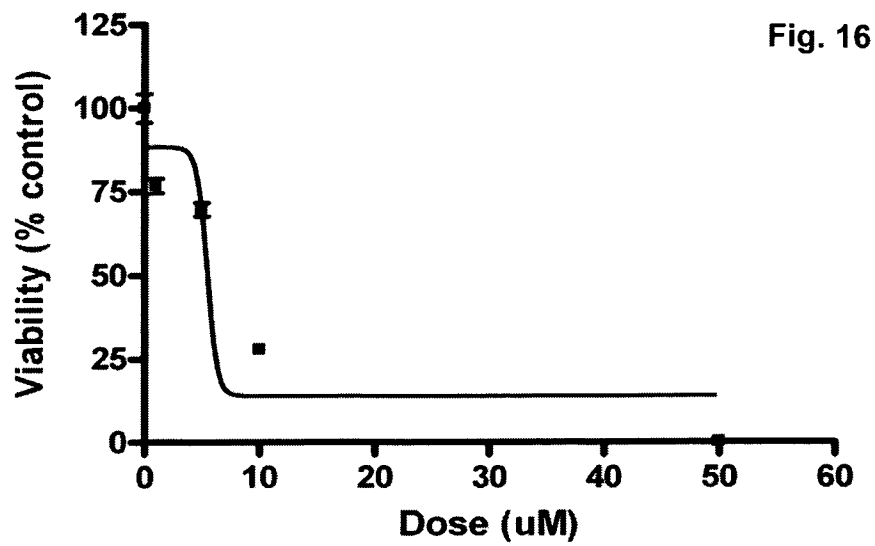
Dose-response of PD173074 in HuH7 cells

Fig. 17A

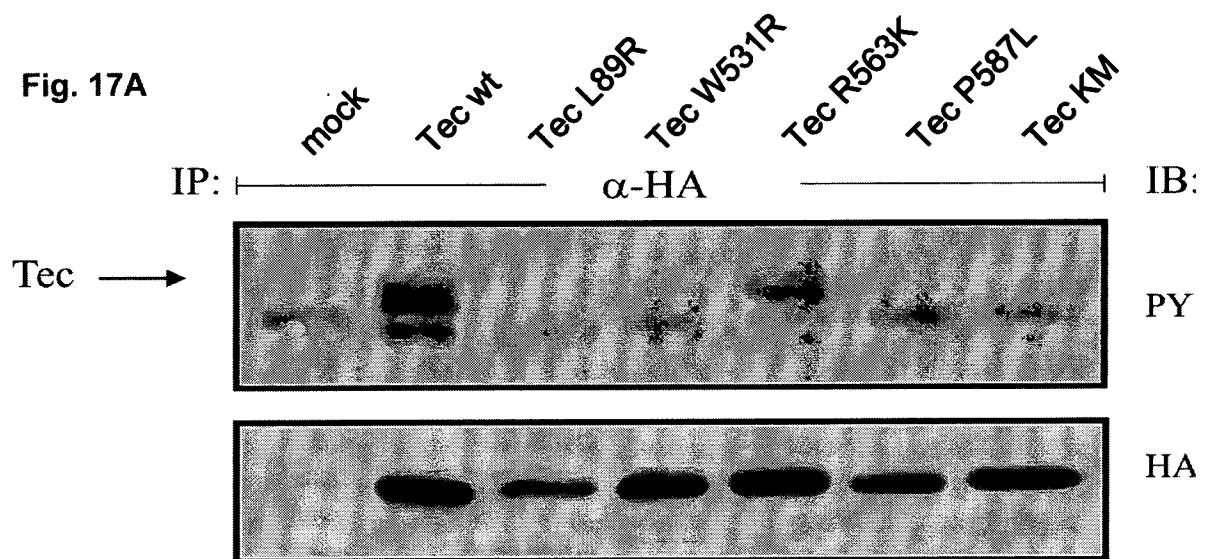
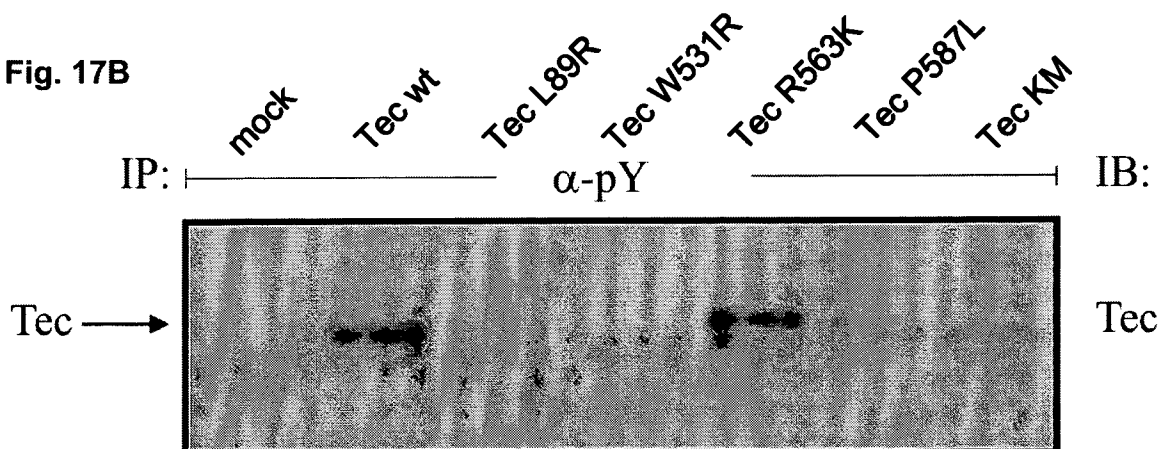


Fig. 17B



TEC (Cytoplasmic Protein Tyrosine Kinase)



NM_003215.1 Tyrosine-protein kinase Tec (EC 2.7.1.112),
also known as PSCTK4 with 1 isoform

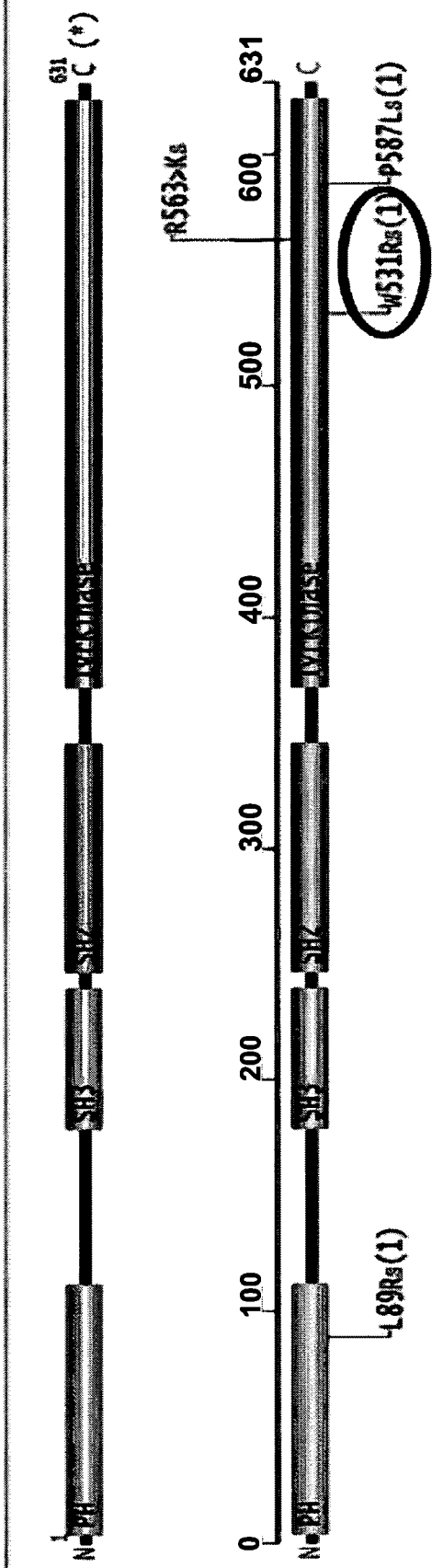


Fig. 18

Fig. 19

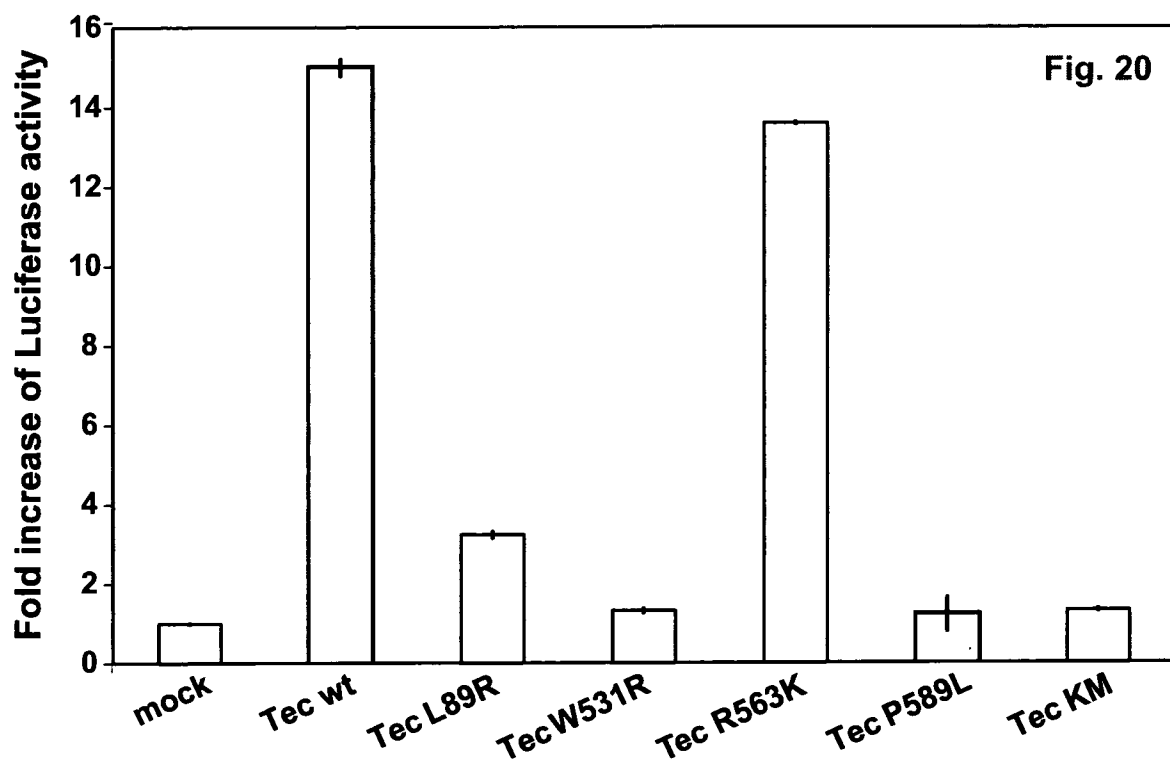
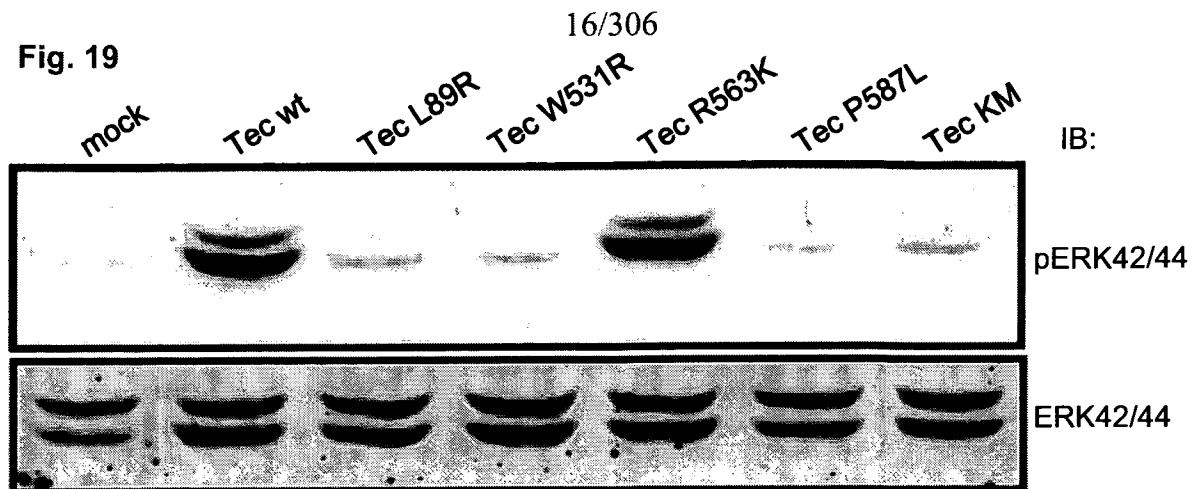
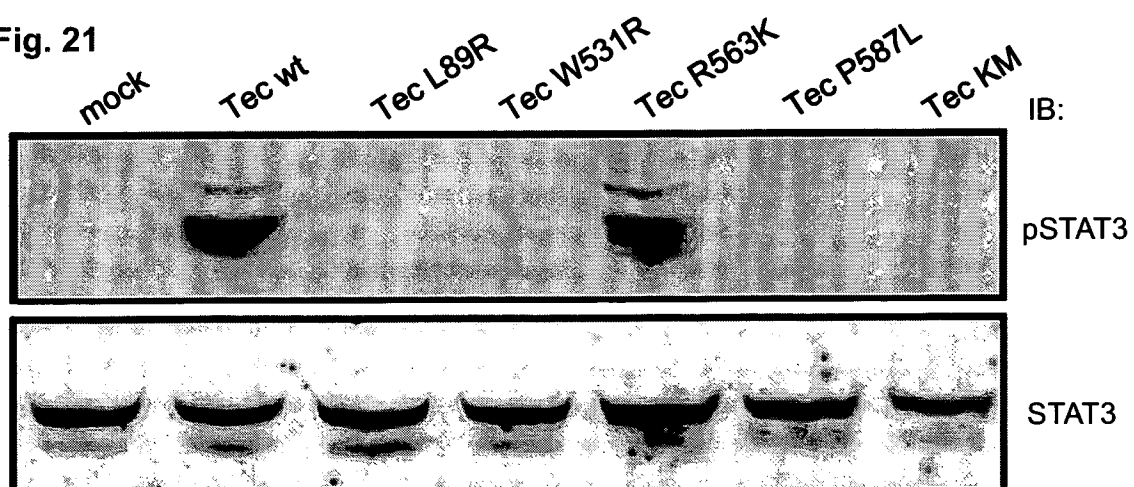


Fig. 21



17/306

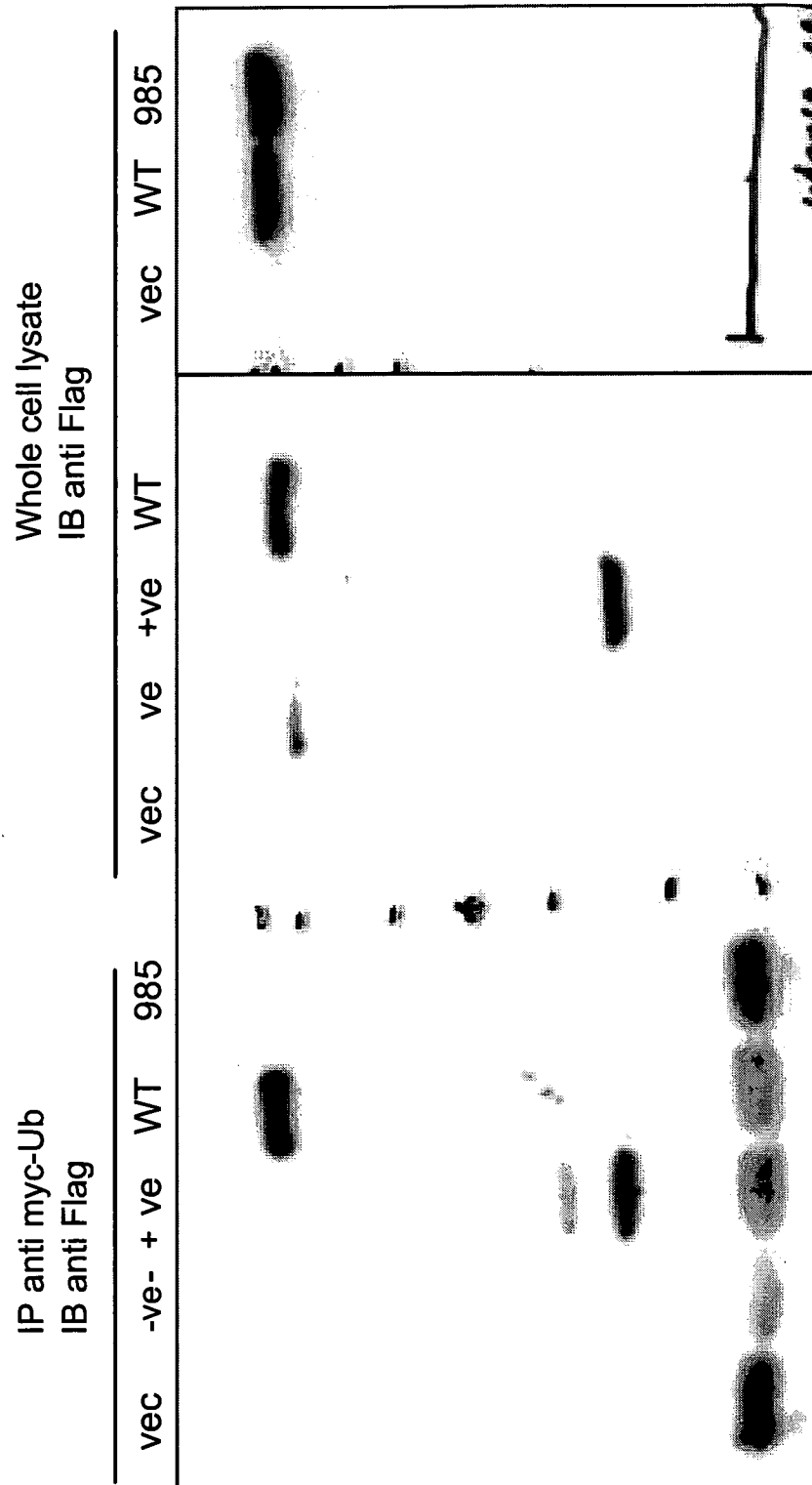


Fig. 22

18/306

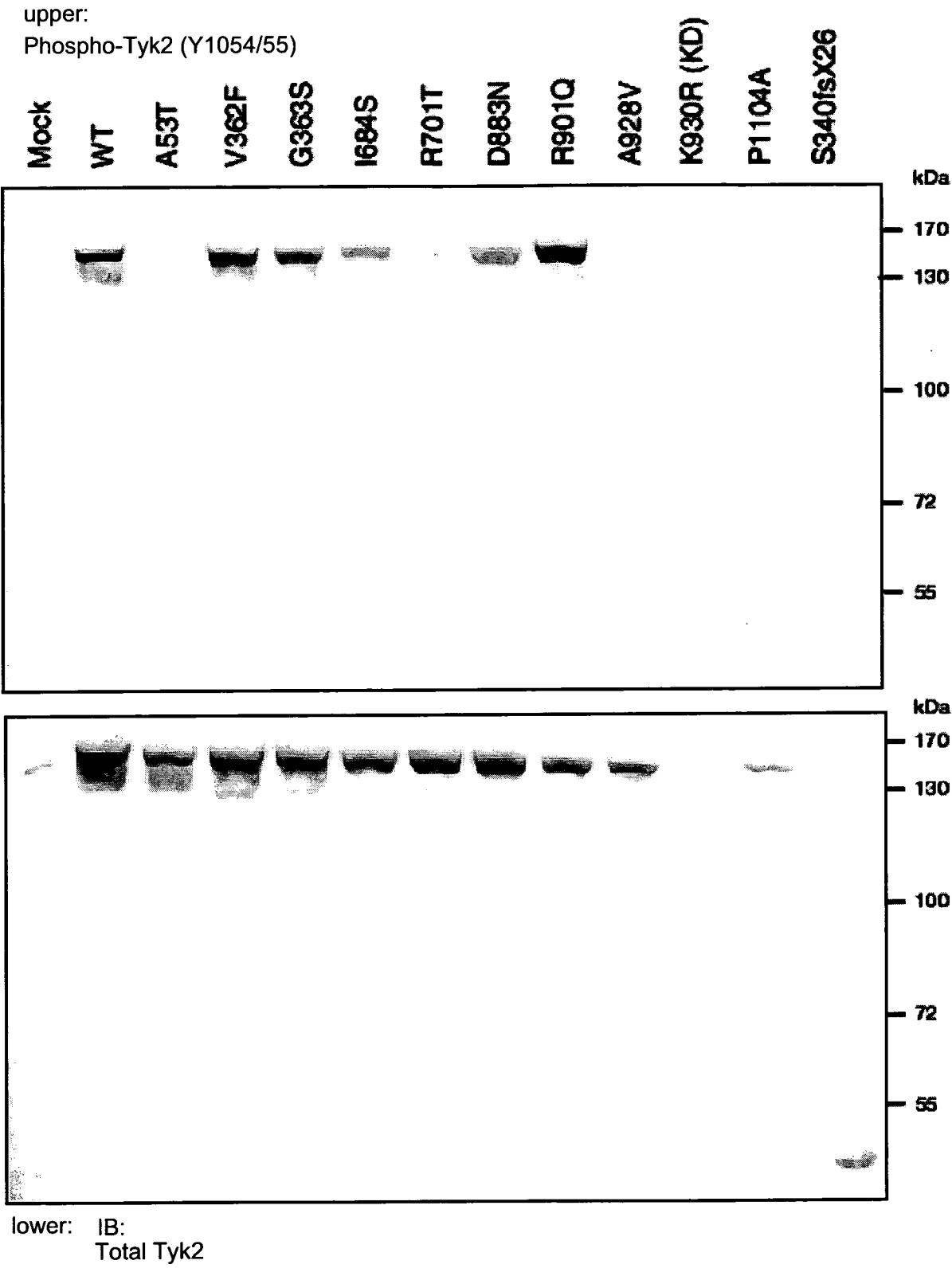


Fig. 23

19/306

Fig. 24

Name	Origin	ATCC/DSMZ number	Obtained from
Bladder			
HT-1376	bladder carcinoma	CRL-1472	DSMZ
RT-4	bladder transitional-cell papilloma	HTB-2	DSMZ
SCaBER	bladder squamous cell carcinoma	HTB-3	ATCC
T-24	bladder transitional-cell carcinoma	HTB-4	DSMZ
TCCSUP	bladder transitional-cell carcinoma	HTB-5	DSMZ
Bone and Soft Tissue			
MG-63	osteosarcoma	CRL-1427	Ambion
RD (*1)	rhabdomyosarcoma	CCL-136	ATCC
SaOS2	osteosarcoma	HTB-85	Ambion
TE-671 (*1)	rhabdomyosarcoma	ACC-263	DSMZ
Brain			
1321N1	astrocytoma	CRL-1620	ECACC
A172	glioblastoma		ATCC
CCF-STTG1	astrocytoma		ECACC
IMR-32	neuroblastoma		DSMZ
SF-126	glioblastoma		Rutka et al., 1987
SF-763	glioblastoma		Tissue Bank of the Brain Tumor Research Center, UCSF, CA, USA
SF-767	glioblastoma	CRL-2266 HTB-11 HTB-12 CRL-1690 HTB-15 HTB-16 HTB-17	Tissue Bank of the Brain Tumor Research Center, UCSF, CA, USA
SH-SY-5Y	neuroblastoma		ATCC
SK-N-SH	neuroblastoma		ATCC
SW-1088	astrocytoma		ATCC
T-98 G	glioblastoma		ATCC
U-118-MG	glioblastoma		ATCC
U-138-MG	glioblastoma		ATCC
U-373	glioblastoma		ATCC
U-1240	glioblastoma		Nister et al., 1988
U-1242	glioblastoma		Nister et al., 1988

(cont. on next page)

20/306

Fig. 24 (cont. from prev. page)

Name	Origin	ATCC/DSMZ number	Obtained from
Breast			
BT-20	breast carcinoma	HTB-19	ATCC
BT-474	breast ductal carcinoma	HTB-20	ATCC
BT-483	breast ductal carcinoma	HTB-121	ATCC
BT-549	breast ductal carcinoma	HTB-122	ATCC
DAL	breast carcinoma		Pier Giorgio Natali Regina Elena Cancer Institute, Rome, Italy
DU-44-75	breast carcinoma	HTB-123	ATCC
HBL-100	breast epithelial cell line, tandemly integrated SV40 virus genome	HTB-124	ATCC
Hs-578T	breast ductal carcinoma	HTB-126	ECACC
MCF-7	breast carcinoma	HTB-22	ATCC
MDA-MB-157	breast medullary carcinoma	HTB-24	ECACC
MDA-MB-175VII	breast ductal carcinoma	HTB-25	ATCC
MDA-MB-231	breast carcinoma	HTB-26	ATCC
MDA-MB-361	breast carcinoma	HTB-27	ATCC
MDA-MB-415	breast carcinoma	HTB-128	DKFZ
MDA-MB-435S	breast ductal carcinoma	HTB-129	ATCC
MDA-MB-436	breast carcinoma	HTB-130	ATCC
MDA-MB-453	breast carcinoma	HTB-131	ATCC
MDA-MB-468	breast carcinoma	HTB-132	ATCC
SK-BR-3	breast carcinoma	HTB-30	ATCC
T-47D	breast ductal carcinoma	HTB-133	ATCC
ZR-75-1	breast ductal carcinoma	CRL-1500	ATCC
ZR-75-30	breast ductal carcinoma	CRL-1504	ATCC
Cervix and Vulva			
A-431	vulva epidermoid carcinoma	CRL-1555	ATCC
C-33A	cervix carcinoma	HTB-31	ATCC
C-4II	cervix carcinoma	CRL-1595	ATCC
Ca Ski	cervix carcinoma	CRL-1550	ATCC
HeLa S3	cervix carcinoma	CCL-2.2	ATCC
HT3	cervix carcinoma	HTB-32	ATCC
ME-180	cervix squamous cell carcinoma	HTB-33	ATCC
MES-SA	uterus sarcoma	CRL-1976	Ambion
MS 751	cervix squamous cell carcinoma	HTB-34	ATCC
SiHa	cervix carcinoma	HTB-35	ATCC
SW-954	vulva squamous cell carcinoma	HTB-117	ATCC

(cont. on next page)

21/306

Fig. 24 (cont. from prev. page)

Name	Origin	ATCC/DSMZ number	Obtained from
Colon			
CaCo2	colon carcinoma	HTB-37	ATCC
COLO 320DM	colon carcinoma	CCL-220	ATCC
DLD-1 (*2)	colon carcinoma	CCL-221	ATCC
HCT-15 (*2)	colon carcinoma	CCL-225	ATCC
HCT-116	colon carcinoma	CCL-247	ATCC
LoVo	colon carcinoma	CCL-229	ATCC
LS-123	colon carcinoma	CCL-255	ATCC
LS-174T (*3)	colon carcinoma	CL-188	ATCC
LS-180 (*3)	colon carcinoma	CL-187	ATCC
NCI-H498	ileum-cecum carcinoma	CCL-254	ATCC
SK-CO-1	colon carcinoma	HTB-39	ATCC
SNU-C2B	cecum carcinoma	CCL-250	ATCC
SW-48	colon carcinoma	CCL-231	ATCC
SW-403	colon carcinoma	CCL-230	ATCC
SW-480 (*4)	colon carcinoma	CCL-228	ATCC
SW-620 (*4)	colon carcinoma	CCL-227	ATCC
SW-837	rectum carcinoma	CCL-235	ATCC
SW-948	colon carcinoma	CCL-237	ATCC
SW-1116	colon carcinoma	CCL-233	ATCC
SW-1417	colon carcinoma	CCL-238	ATCC
SW-1463	rectum carcinoma	CCL-249	ATCC
T-84	colon carcinoma	CCL-248	ATCC
WiDr	colon carcinoma	CCL-218	ATCC
Endometrium and Placenta			
JAR	placenta choriocarcinoma	HTB-144	ATCC
KLE	endometrium carcinoma	CRL-1622	ATCC
RL95-2	endometrium adenocarcinoma	CRL-1671	ATCC
Head and Neck			
FaDu	pharynx squamous cell carcinoma	HTB-43	ATCC
HLaC-78	larynx squamous cell carcinoma		Zenner et al., 1979
HLaC-79	larynx squamous cell carcinoma		Zenner et al., 1979
SCC-4	tongue squamous cell carcinoma	CRL-1624	ATCC
SCC-9	tongue squamous cell carcinoma	CRL-1629	ATCC
SCC-15	tongue squamous cell carcinoma	CRL-1623	ATCC
SCC-25	tongue squamous cell carcinoma	CRL-1628	ATCC
UM-SCC-10A (*5)	pharynx squamous cell carcinoma		Vlock et al., 1989
UM-SCC-10B (*5)	pharynx squamous cell carcinoma		Vlock et al., 1989

(cont. on next page)

22/306

Fig. 24 (cont. from prev. page)

Name	Origin	ATCC/DSMZ number	Obtained from
Head and Neck (continued)			
UM-SCC-17A (*6)	larynx squamous cell carcinoma		Vlock et al., 1989
UM-SCC-17B (*6)	larynx squamous cell carcinoma		Vlock et al., 1989
UM-SCC-22A (*7)	pharynx squamous cell carcinoma		Vlock et al., 1989
UM-SCC-22B (*7)	pharynx squamous cell carcinoma		Vlock et al., 1989
Hematopoietic and Lymphoid System			
Daudi	Burkitt's lymphoma	CCL-213	ATCC
EM-2	chronic myeloid leukemia	ACC-135	DSMZ
HL-60	acute promyelocytic leukemia	CCL-240	DSMZ
IM-9	EBV-immortalised B-lymphoblastoid cells	CCL-159	ATCC
Jurkat	T-cell leukemia	ACC-282	Ambion
K-562	chronic myeloid leukemia	CCL-243	ATCC
KASUMI-1	acute myeloid leukemia	ACC-220	DSMZ
KG 1	acute myeloid leukemia	CRL-8031	ATCC
M-07e	acute megakaryoblastic leukemia	ACC-104	DSMZ
MEG-01	chronic myeloid leukemia, megakaryoblastic crisis	CRL-2021	ATCC
MOLM1	chronic myeloid leukemia, megakaryoblastic crisis		Matsuoka et al., 1997
Mono-Mac-1 (*8)	acute monocytic leukemia	ACC-252	DSMZ
Mono-Mac-6 (*8)	acute monocytic leukemia	ACC-124	DSMZ
MV4-11	acute myelomonocytic leukemia	CRL-9591 (HTB-189)	DSMZ
NB-4	acute promyelocytic leukemia	ACC-207	DSMZ
OCI-AML5	acute myeloid leukemia	ACC-247	DSMZ
PLB-985	acute promyelocytic leukemia (derivate of HL-60)	ACC-139	DSMZ
Raji	Burkitt's lymphoma	CCL-86	ATCC
RF-1 (*9)	B-cell lymphoma		Ji et al, 2002
RF-48 (*9)	B-cell lymphoma		Ji et al, 2002
TF-1	acute erythroleukemia	CRL-2003	ATCC
THP-1	acute monocytic leukemia	TIB-202	DSMZ
U-266	multiple myeloma (IgE secreting)	ACC-9	DSMZ
U-937	lymphocytic lymphoma	CRL-1593	ATCC

(cont. on next page)

23/306

Fig. 24 (cont. from prev. page)

Name	Origin	ATCC/DSMZ number	Obtained from
Kidney and Adrenal Gland			
769-p	kidney carcinoma	CRL-1923	ATCC
786-0	kidney carcinoma	CRL-1933	ATCC
A-498	kidney carcinoma	HTB-44	ATCC
A-704	kidney carcinoma	HTB-45	ATCC
ACHN	kidney carcinoma	CRL-1611	ATCC
CaKi-1	kidney clear cell carcinoma	HTB-46	ATCC
CaKi-2	kidney clear cell carcinoma	HTB-47	ATCC
G401	Wilms tumor	CRL-1441	Ambion
SW-13	adrenal cortex adenocarcinoma	CCL-105	ATCC
Liver			
HepG-2	hepatocellular carcinoma	HB-8065	ATCC
Hs 817. T	hepatocellular carcinoma	CRL-7549	ATCC
Hu-H7	hepatocellular carcinoma		Nakabayashi et al., 1982
SK-HEP-1	hepatocellular carcinoma	ACC-141	DSMZ
Lung			
A-427	lung carcinoma	ACC-234	DSMZ
A-549	lung carcinoma	CCL185	DKFZ
Calu-1	lung epidermoid carcinoma	HTB-54	ATCC
Calu-3	lung adenocarcinoma	HTB-55	ATCC
Calu-6	anaplastic carcinoma, probably lung	HTB-56	ATCC
NCI-H69	lung small cell carcinoma	HTB-119	ATCC
NCI-H82	lung small cell carcinoma	HTB-175	ATCC
NCI-H128	lung small cell carcinoma	HTB-120	ATCC
NCI-H146	lung small cell carcinoma	HTB-173	ATCC
NCI-H209	lung small cell carcinoma	HTB-172	ATCC
NCI-H292	lung mucoepidermoid carcinoma	CRL-1848	ATCC
NCI-H345	lung small cell carcinoma	HTB-180	ATCC
NCI-H441	lung papillary adenocarcinoma	HTB-174	ATCC
NCI-H446	lung small cell carcinoma	HTB-171	ATCC
NCI-H460	lung large cell carcinoma	HTB-177	ATCC
NCI-H510A	lung small cell carcinoma	HTB-184	ATCC
NCI-H520	lung squamous cell carcinoma	HTB-182	ATCC
NCI-H596	lung adenosquamous carcinoma	HTB-178	ATCC
NCI-H661	lung large cell carcinoma	HTB-183	ATCC
SK-LU-1	lung adenocarcinoma	HTB-57	ATCC
SK-MES-1	lung squamous cell carcinoma	HTB-58	ATCC
SW-900	lung squamous cell carcinoma	HTB-59	ATCC

(cont. on next page)

24/306

Fig. 24 (cont. from prev. page)

Name	Origin	ATCC/DSMZ number	Obtained from
Ovary			
A2780	ovary adenocarcinoma		ECACC 93112519
CaOv-3	ovary papillary adenocarcinoma	HTB-75	ATCC
CaOv-4	ovary adenocarcinoma	HTB-76	ATCC
IGROV-1	ovary adenocarcinoma		Benard et al., 1985
MDAH-2774	ovary adenocarcinoma	CRL-10303	ATCC
OAW-42	ovary carcinoma		DKFZ
OVCAR-3	ovary adenocarcinoma	HTB-161	ATCC
PA-1	ovary adenocarcinoma	CRL-1572	ATCC
Sk-OV-3	ovary adenocarcinoma	HTB-77	ATCC
Sk-OV-6	ovary adenocarcinoma		Ludwig Institute for Cancer Research Memorial Sloan Kettering Cancer Center New York, USA
Sk-OV-8	ovary adenocarcinoma		Provencher et al., 1993
Pancreas			
818-4	pancreas carcinoma		Schmiegel et al., 1993
818-7	pancreas adenocarcinoma		Schmiegel et al., 1993
AsPC-1	pancreas adenocarcinoma	CRL-1682	ATCC
BxPC-3	pancreas adenocarcinoma	CRL-1687	ATCC
Capan-1	pancreas adenocarcinoma	HTB-79	DKFZ
Capan-2	pancreas adenocarcinoma	HTB-80	DKFZ
CFPAC-1	pancreas adenocarcinoma	CRL-1918	ATCC
Colo-357	pancreas carcinoma		Kalthoff et al., 1991
DANG-G	pancreas carcinoma	ACC-249	DSMZ
Hs 766T	pancreas carcinoma	HTB-134	ATCC
Mia-PaCa2	pancreas carcinoma	CRL-1420	ATCC
PANC-1	pancreas epitheloid carcinoma	CRL-1469	ATCC
PANC TU1	pancreas carcinoma		Kalthoff et al., 1991
PaTu 8902	pancreas carcinoma	ACC-179	DSMZ
PaTu 8988t	pancreas carcinoma	ACC-162	DSMZ
PT-45P1	pancreas carcinoma		Kalthoff et al., 1991
SW 850	pancreas carcinoma		Kalthoff et al., 1991
Prostate			
BM-1604 (*10)	prostate adenocarcinoma	ACC-298	DSMZ
DU-145 (*10)	prostate carcinoma	HTB-81	ATCC
LNCaP.FGC	prostate adenocarcinoma	CRL-1740	ATCC

(cont. on next page)

25/306

Fig. 24 (cont. from prev. page)

Name	Origin	ATCC/DSMZ number	Obtained from
Prostate (continued)			
PC-3	prostate adenocarcinoma	CRL-1435	ATCC
PPC-1	prostate adenocarcinoma		Chen, 1993
TSU-PR1	prostate adenocarcinoma		Dr. Isaacs, Johns Hopkins Oncology Center Baltimore, USA
Skin			
A-375	malignant melanoma	CRL-1619	ATCC
BOW-G	melanosarcoma		DKFZ
C-32	malignant melanoma, amelanotic	CRL-1585	ATCC
C-8161	malignant melanoma, amelanotic		Welch et al., 1991
Colo-16	skin squamous cell carcinoma		Moore et al., 1975
Colo-829	malignant melanoma	CRL-1974	ATCC
F-01	melanoblastoma		DKFZ
G-361	malignant melanoma	CRL-1424	ATCC
Hs-294T	malignant melanoma	HTB-140	ATCC
Hs-695T	malignant melanoma, amelanotic	HTB-137	ATCC
HT-144	malignant melanoma	HTB-63	ATCC
IGR-39	malignant melanoma		DSMZ
KA-II	malignant melanoma		Soruri et al., 1998
Malme 3M	malignant melanoma	HTB-64	ATCC
Mel Gerl	malignant melanoma		L. Ziegler
Mel JUSO	malignant melanoma		DSMZ
MeWo	malignant melanoma	HTB-65	ATCC
MM-031-I	malignant melanoma		Koerner et al., submitted
MM-194-G	malignant melanoma		Schulten et al., 2002
MM-195-H	malignant melanoma		Schulten et al., 2002
MM-201-B	malignant melanoma		Schulten et al., 2002
MM-232-E	malignant melanoma		Schulten et al., 2002
MM-254-C	malignant melanoma		Schulten et al., 2002
MM-358-A	malignant melanoma		Schulten et al., 2002
MM-Alb	malignant melanoma		Koerner et al., submitted
MM-Alt	malignant melanoma		Koerner et al., submitted
MM-Arn	malignant melanoma		Koerner et al., submitted
MM-Du	malignant melanoma		Koerner et al., submitted
MM-Leh	malignant melanoma		Koerner et al., submitted
MM-Lo	malignant spreading melanoma		Koerner et al., submitted
MM-Su	superficial spreading melanoma		Koerner et al., submitted

(cont. on next page)

26/306

Fig. 24 (cont. from prev. page)

Name	Origin	ATCC/DSMZ number	Obtained from
Skin (continued)			
MRI-H221	malignant melanoma	HTB-66	DKFZ
RPMI 7951	malignant melanoma		ATCC
SBCL 2	malignant melanoma		The Wistar Institute Philadelphia
SK-MEL-1	malignant melanoma	HTB-67	ATCC
SK-MEL-2	malignant melanoma	HTB-68	ATCC
SK-MEL-3	malignant melanoma	HTB-69	ATCC
SK-MEL-5	malignant melanoma	HTB-70	ATCC
SK-MEL-24	malignant melanoma	HTB-71	ATCC
SK-MEL-28	malignant melanoma	HTB-72	ATCC
SK-MEL-31	malignant melanoma	HTB-73	ATCC
WM-35	malignant melanoma	CRL-2807	ATCC
WM-115 (*11)	primary melanoma	CRL-1675	ATCC
WM-239A (*11)	primary melanoma	CRL-1676 CRL-2809 CRL-2806	The Wistar Institute Philadelphia, PA, USA
WM-266-4 (*11)	primary melanoma		ATCC
WM-1617	primary melanoma		ATCC
WM-793	malignant melanoma		ATCC
WM-852	malignant melanoma		The Wistar Institute Philadelphia
WM-902B	primary melanoma		The Wistar Institute Philadelphia, PA, USA
WM-983A (*12)	primary melanoma		The Wistar Institute Philadelphia, PA, USA
WM-983B (*12)	primary melanoma		The Wistar Institute Philadelphia, PA, USA
WM-1205	malignant melanoma		The Wistar Institute Philadelphia
WM-1341D	primary melanoma		The Wistar Institute Philadelphia, PA, USA
Stomach			
AGS	stomach adenocarcinoma	CRL-1739	ATCC
Hs746T	stomach carcinoma	HTB-135	ATCC
KATO III	stomach carcinoma, signet ring cell type	HTB-103	ATCC
MKN-1	stomach carcinoma		Wallasch et al., 2002
MKN-28	stomach carcinoma		Wallasch et al., 2002

(cont. on next page)

27/306

Fig. 24 (cont. from prev. page)

Name	Origin	ATCC/DSMZ number	Obtained from
Testes			
Cates 1B	embryonal testis carcinoma	HTB-104	ATCC
NT2	teratocarcinoma	CRL-1973	ATCC
Tera-2	embryonal carcinoma	HTB-106	ATCC
Thyroid			
FTC-133 (*13)	thyroid carcinoma		ECACC 94060901
FTC-238 (*13)	thyroid carcinoma		ECACC 94060902
TT	thyroid carcinoma, medullary type		ECACC 92050721
Non-Cancer Cell Lines and Primary Cells			
As-745	breast epithelial cells		Martha R. Stampfer Life Science Division Lawrence Berkely National Library, CA, USA
BPH-1	prostate hyperplasia	ACC-143	DSMZ
HaCaT	keratinocytes		Boukamp et al., 1988
HEK-293	kidney embryonic	CRL-1573	ATCC
Hs 1.Li	liver cells	CRL-7821	ATCC
HuVeC	vesicular endothelial cells	CRL-1730	ATCC
MCF-10A	breast epithelial cells	CRL-10317	ATCC
Normal Tissues			
bladder			Ambion
brain			Ambion
colon			Ambion
cervix			Ambion
kidney			Ambion
liver			Ambion
lung			Ambion
ovary			Ambion
pancreas			Ambion
placenta			Ambion
prostate			Ambion
skeletal			Ambion
spleen			Ambion
stomach			Ambion
testes			Ambion

28/306

Fig. 25

Kidney Carcinoma	Prostate Carcinoma	Breast Carcinoma
2t	4t	4992-92t
4t	7t	5296-92t
6t	8t	5382-92t
8t	10t	6177-92t
10t	14t	6735-92t
12t	16t	8074-92t
14t	18t	9456-92t
16t	19t	9519-92t
18t	20t	9633-92t
20t	21t	9994-92t
22t	22t	10555-92t
24t	23t	10670-92t
26t	24t	10681-92t
28t	25t	10781-92t
30t	26t	10808-92t
32t	29t	11189-92t
34t	31t	11526-92t
36t	32t	11697-92t
38t	34t	11808-92t
40t	35t	11820-92t
42t	37t	12015-92t
44t	38t	12120-92t
46t	39t	12166-92t
48t	40t	13932-92t
52t	42t	14002-92t
54t	43t	16353-92t
64t	45t	8335-93t
70t	48t	8481-93t
74t	51t	8566-93t
76t	52t	8786-93t
78t	53t	9145-93t
83t	55t	9354-93t
85t	56t	10150-93t
87t	57t	11218-93t
88t	59t	13232-93t
90t	60t	14879-93t
92t	65t	14t
93t	68t	16t
94t	69t	38t
97t	70t	72t
99t	71t	97t

(cont. on next page)

29/306

Fig. 25 (cont. from prev. page)

Kidney Carcinoma	Prostate Carcinoma	Breast Carcinoma
100t	72t	145t
101t	73t	148t
102t	76t	161t
103t	80t	177t
104t	81t	181t
105t	88t	23t
106t	91t	25t
107t	101t	3433t
108t	102t	3539t
109t	103t	3631t
110t	107t	3632t
111t	108t	3637t
112t	109t	3638t
113t	111t	3640t

Identifiers for the 55 primary kidney, prostate and breast cancer samples are listed.

Fig. 26

Gene	Oligo-name	Sequence
Receptor Tyrosine Kinases		
ALK family		
ALK	ALK-1	AGCAGTGTAACGGCCTCCTC
	ALK-2	CTCTGGGCATCTCCTTAGAACG
	ALK-3	AGTATTCCCCTCCACTGCATGA
	ALK-4	AACCTGTCAGACACATCGAGGA
	ALK-5	CTATGAAGGCTTGAGCCTGTGG
	ALK-6	GTCTCCCACCCCCACTTCTT
	ALK-7	GTGGAGGTGGCTGGAATGATA
	ALK-8	GTCTCTCGGAGGAAGGACTTGA
	ALK-9	AGCAAATTCAACCACCAGAACA
	ALK-10	AGAGGAGGTGGTAGGCAGAGGT
	ALK-11	CCTGAAGACAGGCCCAACTTT
	ALK-12	TTGGTCTCTGGTTTGTGAAGGA
LTK	LTK-1	TGGCAAAATGAGCTGTCAACTT
	LTK-2	GGATACTCCATCTTCCCCATCA
	LTK-3	CCCCGAGAACTGGAGAACC
	LTK-4	CCAGACATCAGTTCCAGCAGAA
	LTK-5	CTCAGGATGAGCTGGATTTCTT
	LTK-6	CTCAGTGCCTCAGTCCTTACCC

(cont. on next page)

30/306

Fig. 26 (cont. from prev page)

(cont. on next page)

Gene	Oligo-name	Sequence
AXL family		
AXL	AXL-1	AAGTCTGGGAGTGAGGGAAGG
	AXL-2	CTCAGGTTGAAGGGGGTGT
	AXL-3	TGAGGATGAACAGGATGACTGG
	AXL-4	GATAAGGGGTGTGAGGATGGAG
	AXL-5	CGGAGCTGGAGGTGGCTTGG
	AXL-6	GCCTTCCATCACAGCTCCAAA
	AXL-7	AAGCTGCGGGATGTGATGGTGG
	AXL-8	AAATCTCTGTTCTCCACGCCG
	AXL-9	TCGCCAAGATGCCAGTCAAGTG
	AXL-10	GCTGCAAGTGGGGATAAGGC
MER	MER-1	ATCCGTCCGGAGAGAAATTACA
	MER-2	GAGGGAATTGCTTTGATGTTGA
	MER-3	GGGCTGACCGTGTCCC
	MER-4	CCTCACTGASCTCCCAAGC
	MER-5	CCTTGCCATCAGAAAAAGAGT
	MER-6	GTGGCCATGGAGAAGATAGTCA
	MER-7	ATGACTGTCTGTGTTGCGGACT
	MER-8	CAGCAGAAGAATTGGCTTGATTT
TYRO3	TYRO3-1	CTCCCTCCCGCTCCCTTC
	TYRO3-2	CGCACCTGAGGCTGTAGTT
	TYRO3-3	CCTGTGCCCCCCTTTACCTGC
	TYRO3-4	GGCCACGTGTGGATGGTCAAAC
	TYRO3-5	CCGGTCCTTCAATCGAGAAAG
	TYRO3-6	GTGTCATGATCTCCACATGGT
	TYRO3-7	TGACAGTGTGTGTGGCTGACTT
	TYRO3-8	CTTGGGAGGACTACACAGGAG
DDR family		
DDR1	DDR1-1	CCTGCAGAGATGCTGCCCCCACC
	DDR1-2	GGAAGCGACATTCCACCCCGCC
	DDR1-3	GAGCTCTATGGCTGCCTCTGGA
	DDR1-4	AGAGGTGAACCGTCAGCTCCTCTT
	DDR1-5	ATCATTGCCCTCATGCTCTGG
	DDR1-6	GAGGTCGCCGTTCTCCATGT
	DDR1-7	AAGAATGCCAGCTTCTCCTTGTTCT
	DDR1-8	CACCTGCAGTCTCACTGCCTCTATT
DDR2	DDR2-1	AAGTTCCAAGGTTTGTGGCTTGAAT
	DDR2-2	TGCTGTATCCAACAGCTCCATCATA
	DDR2-3	CGACCACTCCATGAATGTGTGTATG
	DDR2-4	ATGCTAGAATCACTTGGCAGGGAAA
	DDR2-5	CATCTTTATCCTCCTGGCCATCATT
	DDR2-6	GGTGTAAGTACAGTGCGTACATCG
	DDR2-7	CAAGGACCCAAACATCATCCATCTA
	DDR2-8	TATATGAGTCAGGGGTAGGGAGTGG

31/306

Fig. 26 (cont. from prev page)

Gene	Oligo-name	Sequence
EGFR family		
EGFR	EGFR-1	CTCCGTCCAGTATTGATCG
	EGFR-2	CGCAGGTGGCACCAAAGC
	EGFR-3	GCTCTACAACCCCAACCACG
	EGFR-4	CTGTGCAGGTGATGTTTCATGG
	EGFR-5	GTGCCACCCAGAGTGCCTG
	EGFR-6	CCGCACCCAGCAGTTTGGC
	EGFR-7	CCTGGCAGCCAGGAACG
	EGFR-8	GGGCTCATACTATCCTCCG
HER2	HER2-1	CTCCCAGCCGGGTCCAGCC
	HER2-2	GCATGGACTCAAACGTGTCTGTG
	HER2-3	CCTGCCTCCACTTCAACCACAG
	HER2-4	CGGCATTCTCCACGCACTCC
	HER2-5	GAGGACGAGTGTGTGGGCGAG
	HER2-6	AGAGGCAGCCATAGGGCATAAG
	HER2-7	GAAGCATACGTGATGGCTGGTG
	HER2-8	CAGGTCCCCACCGCCACTCC
	HER2-9	GTGGATGCTGAGGAGTATCTGG
	HER2-10	CCCACCTCTTGATGCCAGCAG
HER3	HER3-1	CTCTTGCCCTCGATGTCCTAGCC
	HER3-2	GGATGTTTGATCCACCACAAAGTTA
	HER3-3	GTACCTCGCTGTCCACAGCCTC
	HER3-4	GCCCGAGCCATTGCATGTGGC
	HER3-5	GCCCATGAGGCCGAATGCTTC
	HER3-6	GCCACCTGAACCTGACTGG
	HER3-7	GCATAGAAACCTGGCTGCCC
	HER3-8	GGAATGGTAGGCGCTATCTCCG
	HER3-9	GGAGAAAGTGTCAATGTGTAG
	HER3-10	CCTCTAAAGGCACTAGCTGCC
HER4	HER4-1	CACGGGATCTGAGACTTCCAA
	HER4-2	CCAGTTGAAAGGTGGTTGGATTGTA
	HER4-3	GCATGAATTTCAATGACAGTGGAG
	HER4-4	GAGAGCACTTTGTACAGTTGTCAGG
	HER4-5	GTGAATTTCTGGGAGTTTGAGAATG
	HER4-6	TTTTTCATCTCCTTCCAAGAGTCTG
	HER4-7	GGGCTAGCCAGACTCTTGGAA
	HER4-8	GTTTCCTGACATGGGGGTGTA
	HER4-9	TTCCAGAGCAAGAATTGACTCG
	HER4-10	AGGAAGACCACCAGAGAAAGAGAG

(cont. on next page)

32/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
EPH family		
EPHA1	EPHA1-1	GCCACTGTCCCAGGTCCCG
	EPHA1-2	CGTGAGACAATGGGGTGTG
	EPHA1-3	CTGTCCGGGTCTTCTACCAG
	EPHA1-4	CAGCCCTGACACTCCATTTT
	EPHA1-5	TGAGGTGTTCCCAGTGTGAG
	EPHA1-6	CCTCAGGGTCCCTCGATAC
	EPHA1-7	CCTGCCCCTCTGTATGAGC
	EPHA1-8	GGGAGTGACCATGAGCGACC
EPHA2	EPHA2-1	GGATCGGACCGAGAGCGAG
	EPHA2-2	CAGGGCACTCCAAGCAGGG
	EPHA2-3	CCATTGGGCAGTGCCTGTGCC
	EPHA2-4	GCACCAGAAGCAGGACCACACC
	EPHA2-5	CGCTGTCCCCGGAGGGATCTGG
	EPHA2-6	GCTCCACACGTCGCTGGC
	EPHA2-7	CAAGATCCCCATCCGCTGGAC
	EPHA2-8	GCATGGCACAGCAGGGAGG
EPHA3	EPHA3-1	GCGAGCGGAGCATGGTAACTTC
	EPHA3-2	CTCTTTCTTCATAGCCAGCATTGC
	EPHA3-3	CAGTCCCTGGTGGAGGTTAG
	EPHA3-4	AGGCTTGAGGCTACTGATGG
	EPHA3-5	AAATCCGAGCCCGAACAGCC
	EPHA3-6	TCAAGATGTTCCGAGCAGCGAG
	EPHA3-7	CCACCCCAATATCATTCGAC
	EPHA3-8	CACTTCCGTCCAGAAGCACT
EPHA4	EPHA4-1	ATAGAAGCGGCAGGAGCAG
	EPHA4-2	TGCTTAATGGCCCTACATCC
	EPHA4-3	ACCATTGCTGCTGATGAGA
	EPHA4-4	CAAGTTCACAGATGTCTCGTTG
	EPHA4-5	CTCTATGCCCTGCACCCGTCC
	EPHA4-6	CGCCCACTGCATACCTCACC
	EPHA4-7	CCAAGCAGTGCGAGAGTTTGCC
	EPHA4-8	CCACATAACGATTCCATAGCTCC
	EPHA4-9	CAACTTGGTCTGCAAAGTGTCTG
	EPHA4-10	ATTAAAGTGCATGGATGAGGTAAAC
EPHA5	EPHA5-1	CTCGGGACAGCGGCACC
	EPHA5-2	AACACGGTCACCAAGATCAA
	EPHA5-3	GACTGGGGACCTGTAAGGAA
	EPHA5-4	GAGATGGCATTCCGAGGAG
	EPHA5-5	TGAGGAAGCTTCAACCTCTTG
	EPHA5-6	GGGGTGGTTTCAAACCTCAA
	EPHA5-7	TACAGCAGCAGGCTATGGTG
	EPHA5-8	GTGAACTGCCCATCGTTTTT

(cont. on next page)

33/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
EPH family (cont.)		
EPHA6	EPHA6-1	CCAATCGGGACAAGAAGAAG
	EPHA6-2	TGTCAGCAGAGGCAAGAAGA
	EPHA6-3	CCATCCTACCCAGAACACCT
	EPHA6-4	AACCAGCCAATCTCCATCAG
	EPHA6-5	ACGGGGTTCTTGTGTGAAGA
	EPHA6-6	AAGGATGGCAGCATAAGTGG
	EPHA6-7	CGGGGTTCTTGTGTGAAGAG
	EPHA6-8	TGGAGGGAAGCATTTCATCT
EPHA7	EPHA7-1	ACTTGCAGGCAGCAAACAC
	EPHA7-2	CCTCTGCACTGCTGACACAT
	EPHA7-3	TGCTGGTCCATTATTGAGAACTT
	EPHA7-4	GTTCCCTTTGATCTTTCTCGT
	EPHA7-5	AGCGGAGTGTGAGCCTTTC
	EPHA7-6	GCATTCCTACTAACTGAATGACTG
	EPHA7-7	TCATGGAAAATGGAGCCCTA
	EPHA7-8	AGGACCCAGGACATCACTTG
EPHA8	EPHA8-1	CTGCGCTCTGGGTCGTCAC
	EPHA8-2	TGTGTCCCGCTCCTCTGAGT
	EPHA8-3	CTACCTGGCCTTCCAGGAC
	EPHA8-4	GCCTCGATCCAGAAGGAGTA
	EPHA8-5	GCCCACATGAACTACTCCTTCT
	EPHA8-6	GAGAGCCGTTCTCCATGTACTC
	EPHA8-7	CATCAAGGCCCTCAAAGC
	EPHA8-8	ACCATGCCCAGAGAGGAGTAT
EPHA10	EPHA10-1	GGACTGACAGCTCGGTCTGC
	EPHA10-2	ACAGGCTTCGCAGAAAGTCAC
	EPHA10-3	TTCTCCACACTGGTGGAAGTG
	EPHA10-4	ATCTGAAAGACGTAGCGGGTAG
	EPHA10-5	CCGATACTACGAGAAGGGTCAG
	EPHA10-6	AAGTGGCCAAACTGAAGTGTCT
	EPHA10-7	TATCTGTCAGAGATGGGCTACG
	EPHA10-8	AGTTAGCCAAGGCGTTCAGACT
EPHB1	EPHB1-1	CGCGAAAGGATACCGAGAAG
	EPHB1-2	CTCATAGCCAGGCTTGCAAGT
	EPHB1-3	CCCATCAAACCTCTACTGCAACG
	EPHB1-4	GAAGCACATCTTGCCACTGAAC
	EPHB1-5	AGACCAACACAGCAAGGATTGA
	EPHB1-6	GACACCTTGACACACCAGGTTAC
	EPHB1-7	AATTATGTGCATCGGGACCTG
	EPHB1-8	AGGTCCGGTTGATTCTTCACTG

(cont. on next page)

34/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
EPH family (cont.)		
EPHB2	EPHB2-1	CGTGGAAGAAACGCTAATGGAC
	EPHB2-2	ACTCCAGCATGAGGGAGGTCT
	EPHB2-3	GTCAATGAGACCTCCCTCATGC
	EPHB2-4	CAGGTGTGGCTCTTGGTCACGAC
	EPHB2-5	GGCTACACGGAGAAGCAGCGC
	EPHB2-6	GAGAATGTCCTCCATCATCATCTG
	EPHB2-7	GCCAAATTGTCAACACGCTAGA
	EPHB2-8	ATTGGACACATCGCATGAATCT
EPHB3	EPHB3-1	CCCTCCTCTCTCCTGGATCTCCT
	EPHB3-2	CTTGAGTGGCACCACACCT
	EPHB3-3	CGCGCCTTCTACAAGAAGTGT
	EPHB3-4	TGCCCTCGCTCTTCTCAAAGTA
	EPHB3-5	CAGCAGCCTCACCTATCCTG
	EPHB3-6	AGTTCATCTCGGACAGGTACTTC
	EPHB3-7	AGTTCATGGAAACTGCGCCCTG
	EPHB3-8	AGTCCAAGAGTCCGAAAGTCCAG
EPHB4	EPHB4-1	GCCCAGGGAGAGTCAGACC
	EPHB4-2	CACTTGGTGTTCCTCAGC
	EPHB4-3	AGCTGACTGTGAACCTGACTCG
	EPHB4-4	GCCCTTCTCATGGTATTTGACC
	EPHB4-5	CCGGGTGACGCGGTCCTCAC
	EPHB4-6	CGTAGCTCATCTCGGCAAGGT
	EPHB4-7	AGTTCATGGAGAACGGCGCCCT
	EPHB4-8	ACTGCGGGGCCGGTCCTCCTG
EPHB6	EPHB6-1	GAAGATGTCCCATGGCTACTG
	EPHB6-2	CGACAGCTACCATCCACTTGC
	EPHB6-3	CCTTTGCTTCCTTTCCAGAGAC
	EPHB6-4	GTGAAGGAGTGGGATTCTGTCTT
	EPHB6-5	GACCAGACCAATGGGAACATC
	EPHB6-6	CTTGACACCAAGTGGCTATTTC
	EPHB6-7	CTGACGGAGTTCATGGAGCTT
	EPHB6-8	ACGTCCCACATGTCCCTTCT
FGFR family		
FGFR1	FGFR1-1	GAGCCTTGTCACCAACCTCTAACTG
	FGFR1-2	AGCATCTGAAACATTGACGGAGAAG
	FGFR1-3	ACCTGCTGCAGCTTCGCTGT
	FGFR1-4	ACCTTGTAGCCTCCAATTCTGTGGT
	FGFR1-5	CCCAGAAAAGATGGAAAAGAAAT
	FGFR1-6	AGAGTGATGGGAGAGTCCGATAG
	FGFR1-7	GTACGGCAGCATCAACCACACATAC

(cont. on next page)

35/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
FGFR family (cont.)		
FGFR1	FGFR1-8	TCTTCGGGAAGCTCATACTCAGAGA
	FGFR1-9	TGGAGATCATCATCTATTGCACAGG
	FGFR1-10	AGGCCAAAGTCTGCTATCTTCATCA
	FGFR1-11	GAGTATCTGGCCTCCAAGAAGTGC
	FGFR1-12	GCAGGGGCTGTGGGTGAGGG
FGFR2	FGFR2-1	GGCCCTCCTTCAGTTTAGTTGA
	FGFR2-2	CATCCAGGTGGTACGTGTGATT
	FGFR2-3	GAAAAACGGGAAGGAGTTTAAGCAG
	FGFR2-4	TGAAGAGAGGCGTGTGTGTTATCCTC
	FGFR2-5	AGCTCCTCCATGAACTCCAAC
	FGFR2-6	CAAAACATTTCTGGCTGCTAAAT
	FGFR2-7	TCCTATGACATTAACCGTGTTCC
	FGFR2-8	AACTGCTTGAACGTTGGTCTCT
	FGFR2-9	GGAACTTTTTAAGCTGCTGAAGG
	FGFR2-10	AAGTGGAGACAACAAGCTCTGG
FGFR3	FGFR3-1	GAGCCACTGGATGTGGG
	FGFR3-2	GAGCCACTGGATGTGGG
	FGFR3-3	CCAGACGGCGGTGCTGGG
	FGFR3-4	CCGCAGGTTACCCTTGGC
	FGFR3-5	CGGACCTGGTGTCTGAGATGG
	FGFR3-6	CGGGGAGTGGCTGTGCACC
FGFR4	FGFR4-1	GGCAGTTGGTGGGAAGTCCAGC
	FGFR4-2	GTGGGGCTGGGCATCGC
	FGFR4-3	GTGGGCAGCATCCGCTATAACTAC
	FGFR4-4	AACTCCCATAGTGGGTCGAGAGGTA
	FGFR4-5	AGTTCTCCCTGGAGTCAGGCTCTT
	FGFR4-6	GGCCGTTGCTGGTTTTCTTATAGTA
	FGFR4-7	GGTGTCTGCACCCAGGAAGG
	FGFR4-8	CCAGCCTATGTGCCTGCACAG
INSR family		
IGF1R	IGF1R-1	AAAGGGAATTTTCATCCCAAATAAAAG
	IGF1R-2	GCACTCGCCGTCGTGGATCAC
	IGF1R-3	CTATGCCGGTGTCTGTGTGC
	IGF1R-4	CAGGGCTTCAGCCCATGTAG
	IGF1R-5	CAGAGTATGATGGGCAGGATGC
	IGF1R-6	CTTCTCAGCCTCGTGGTTGC
	IGF1R-7	GAGAACTGTCATTTCTAACCTTCG
	IGF1R-8	CTCTGTGGACGAACTTATTGGCG
	IGF1R-9	ACCTCCAAGCCTGAGCAAGATGATT
	IGF1R-10	GGAGGCTTGTGAATGGATTGTT

(cont. on next page)

36/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
INSR family (cont.)		
INSR	INSR-1	CAGCGCCGCGCGCCTGATC
	INSR-2	GTTCTTGCAATTTGTGGTGCAGG
	INSR-3	CGTACTACCACTTCCAGGACTG
	INSR-4	GTCTACCACCGTCCAAGTGTG
	INSR-5	CCCCTTATCAGAATGTGACGGAG
	INSR-6	TGCCACACTGCACCGTTCCTC
	INSR-7	CGACACTTCACGGGCTATCGC
	INSR-8	CAGAGAACGGAGGTAGCTCTTC
	INSR-9	GCCTCCTGGGAGTGGTGTCC
	INSR-10	AACCAGAGGAAAGCGAAAATGGG
IRR	IRR-1	CAGAGTCACCGGGAGGAGAGC
	IRR-2	CAGGACTCATACTGGTAGGTGC
	IRR-3	AGTGCTGCCACACCGAATGC
	IRR-4	ACGTGCTCTGTGGCGTTCTGG
	IRR-5	AGACCGCATCCTGCTACGCTG
	IRR-6	GTGGTTGCAGGCATGGATGTGC
	IRR-7	CGAGATCCAGGAGGACAAGGTG
	IRR-8	CATGGTGACACTTGAAGGCTTTC
	IRR-9	CTGAAGACGGTGAATGAGCTGGC
	IRR-10	TCAGTGCCCTGGACCCCCATTTTG
MET family		
MET	MET-1	CCACTGGTTCCTGGGCACCG
	MET-2	GCAATCCAGAGTTTATGG
	MET-3	CTTCTTGACGGTCCAAAG
	MET-4	CCTTGTAGATTGCAGGC
	MET-5	CGGAGGAATGCCTGAGC
	MET-6	GCAGATTCAGCTGTTGC
	MET-7	GGCATGTCAACATCGC
	MET-8	GCCCTCTTCCTATGACTTC
	MET-9	CCAGTAGCCTGATTGTGC
	MET-10	GTGTGGACTGTTGC
RON	RON-1	GGATCCTCTAGGGTCCCAGCTC
	RON-2	GCCGGCTGTACAGTCAGGAAGTAT
	RON-3	GCCCAAGCATCTTGTCTCCTACAGT
	RON-4	ACTGTCACCCAGTGAGAAGTTGGAC
	RON-5	GACAACGTACAGTGGCACACAT
	RON-6	GGGGTGTGGCACATAAAAGCTG
	RON-7	CTGATAGCAGTGCAACCCCTCTTT
	RON-8	CAGGGGGCAGACAACCATGT

(cont. on next page)

37/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
MET family (cont.)		
RON	RON-9 RON-10 RON-11 RON-12	GCCAACCTAGTTCCACG GCTGATGAGGTCCTTCACG CTATATGTGCCACGGTGACCT CCATTTACCTATTGCCTCTGAAA
MUSK family		
MUSK	MUSK-1 MUSK-2 MUSK-3 MUSK-4 MUSK-5 MUSK-6	CCAGAAGGAACTTCGTCC GGCAGTACTGAACTTCTCC CAGGACTCTACACATGCATAGC CCTTGGATACTCCAGGCTGAG CCAGAGGATGCCGGCTCCTTC CCTTAGACACTCACAGTTCCTC
PDGFR family		
CSF1R	CSF1R-1 CSF1R-2 CSF1R-3 CSF1R-4 CSF1R-5 CSF1R-6 CSF1R-7 CSF1R-8	CCAGTGCAGAGGAGAGGAAC TGAGGGTCAGGACTTTTTGG AGCCAGCAGCGTTGATGATGTTA TGGTACTTGGGCTTCTGCTT GGGCCTTCATACCCATCTCT ATCTTGGCCACATGACCATT GCTTCACTTCTCCAGCCAAG CCTCACCTTCCCAAGTTTCA
FLT3	FLT3-1 FLT3-2 FLT3-3 FLT3-4 FLT3-5 FLT3-6 FLT3-7 FLT3-8	TTTTCTGCAATGATATTTGGGACT TGCCACTGATGATACAAAAGCA CAAACCTCTCAGACCACATTGC AGGGGCCTGGAGAGTTTAAAAG AAGCCATAAAAGGGTTCTGGT CGAGCCAATCCAAAGTCACATA TCCAATCACATCCAAATTCCAG TTAGGGATAGGTGGAGGGATGA
KIT	KIT-1 KIT-2 KIT-3 KIT-4 KIT-5 KIT-6 KIT-7 KIT-8	GATCCCATCGCAGCTACC TGGCATAACACATGAACACTCC CTGTTGTGTCTGTGTCCAAAGC CAATCAGCAAAGGAGTGAACAG CCAGTGGATGTGCAGACACTAA TTCTAAGTCTAGGGCCAACCTCG AGCAGGAAGATCATGCAGAAG CCCCTATCCTGGAGTTGGA

(cont. on next page)

38/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
PDGFR family (cont.)		
PDGFRA	PDGFRA-1	CGGAGGAGAAGTTTCCCAG
	PDGFRA-2	GGTAGCCTGGCGGGCAGC
	PDGFRA-3	GCCACGGTGAAAGACAGTGGAG
	PDGFRA-4	GGCAGCTGCATCGGGTC
	PDGFRA-5	CCGAGGTATGAAATTCGCTG
	PDGFRA-6	CACGGGCAGAAAGGTACTG
	PDGFRA-7	GGCCTGGCCAGAGACATCATGC
	PDGFRA-8	GGATCCAGAGGTGGCCCCAG
PDGFRB	PDGFRB-1	GCCCACACCAGAAGCCATCAG
	PDGFRB-2	CTCCGTCACATTGCAGG
	PDGFRB-3	CCTTACCACATCCGCTCCATC
	PDGFRB-4	GGCCGTCAGAGCTCACAGAC
	PDGFRB-5	CATCCTCATCATGCTTTGGC
	PDGFRB-6	CGAGTCCCGCATGATGTCTC
	PDGFRB-7	CCTGGCGGCTAGGAACGTGC
	PDGFRB-8	CAGGCCAGGCCAGGAGATGC
PTK7 family		
CCK4	CCK4-1	CGGGGACTCGGAGGTACT
	CCK4-2	GACCTGCCTCAATCCATTTG
	CCK4-3	GTCCTCCCAGGATGCACTGC
	CCK4-4	GCGGTTAGTGATGGGAGTC
	CCK4-5	CCATTGCCAGTTCTCAGCCC
	CCK4-6	GCCAGCGTCATCTCGAGTC
	CCK4-7	GCCGAGAGAAGCCCACTATTAAG
	CCK4-8	AGTAGAACATGAGGCCAGCA
	CCK4-9	GATTCAGTGGAAGGCAAGGAC
	CCK4-10	AGATCCACATATTCCAGCACCAT
	CCK4-11	CCTGGCAAAGGCTCAGGGCTTGG
	CCK4-12	GCCCATCATGCTGTGAGCTTC
RET family		
RET	RET-1	CTAGCCGCAGTCCCTCCAG
	RET-2	GTCCTCCTTCCGCTTGAAGTC
	RET-3	GTGACCGTGTACGACGAGGA
	RET-4	AGTCCTGAGGGCAAATGTTGAT
	RET-5	GGATCACCAGGAACTTCTCCAC
	RET-6	CAGATACTGCATCCCCTGTGAG
	RET-7	CTCACCATGGGCGACCTC
	RET-8	AGCTGCTGAGACTTCCCAA

(cont. on next page)

39/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
ROR family		
ROR1	ROR1-1	AGGGAGCAGGTTAGAGGGACA
	ROR1-2	CAGTTTCAGCCTCATCAGAATCA
	ROR1-3	CTGTGCCACTATGCCTTCCCG
	ROR1-4	AGGCTTCTTGTTGAAATTCCATCC
	ROR1-5	GAGTGTGCCTTTGGAAAAATCTA
	ROR1-6	GAGCTTGTGTGACTTGAGAGTCC
	ROR1-7	AGCTCTTACCATGCTCTGAAGAC
	ROR1-8	GCGATGTCTGCTAAATGAGAACC
ROR2	ROR2-1	GGGAGAAGGAGGAGCGGACG
	ROR2-2	CTCTCCAGCACCTCGCACTCG
	ROR2-3	ATCCTTCTGCCACTTCGTGTTT
	ROR2-4	CGTGCGAACAGTAGCTGAAGAT
	ROR2-5	AGCTGGTCTGCGTGGTGTGTC
	ROR2-6	AGCTGGTCTGCGTGGTGTGTC
	ROR2-7	CATGATCGAGTGCTGGAACGAG
	ROR2-8	CTGAGTATGGTGTCTTCTCAAAGG
ROS family		
ROS1	ROS1-1	CAAACAAAGCAAATCCATCAGC
	ROS1-2	TCTGCTTCTGGACCCTCACC
	ROS1-3	TGCAGGGACACAGAGAACCA
	ROS1-4	CAGGTCACATCCCACGATGA
	ROS1-5	TCCTACCTCGCATCCCCTTT
	ROS1-6	TCCACCAACTGAATCCACCA
	ROS1-7	TTTGTGTGGCTGCTGAATGG
	ROS1-8	TTGCAGCATTTTCCACTTGGT
	ROS1-9	GGGCCCCAAAACATCTCTGT
	ROS1-10	TGCAGAATTCCGTGCAAGGT
	ROS1-11	TGACTGGATTTC AAGGCACCTC
	ROS1-12	ATGAGCTGCACTGCCTCTGG
	ROS1-13	CAGGAAAAACAGCTCTGACTTGAA
	ROS1-14	TTGGACTTCCATGTGCAAACA
	ROS1-15	GCACTTCAAATAATTTACAGAACCAGA
	ROS1-16	TGCATCCGTTCCAAGTAGACA
	ROS1-17	CCTTGGTTGACCTTGTAGACCTG
	ROS1-18	TTTGGAGTTATAGACCACCATGACA
RYK family		
RYK	RYK-1	CGGCCGACGCTCCTCTTC
	RYK-2	CGTTCTTCTCTATCCGCAAGGT
	RYK-3	CAGACGACTCAGTATCTGAGAGCA
	RYK-4	TGGAGAGGAGTCAGACGTAGGC

(cont. on next page)

40/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
TIE family		
TEK1	TEK1-1	CAAACCGCTGGGTTTTTGAA
	TEK1-2	CCCATAGGGGTCAGGGAGAC
	TEK1-3	TGCACACGTTTGGCAGAACT
	TEK1-4	CGAGCTTGGAATATTGGTTGC
	TEK1-5	ATCGGACTCCCTCCTCCAAG
	TEK1-6	GCATCCATCCGTAACCCATC
	TEK1-7	GTGATTGGGGAGGGCAATTT
	TEK1-8	TCCTTTGGCAGAGGCATGTT
TIE	TIE-1	CAGTCAGGCCCCACAGCATCT
	TIE-2	ATAGGGGTCTGGGAGGCAGA
	TIE-3	TGAACAGGCCTGCAGAGAGG
	TIE-4	ACAGGCGCAGCAGGAAAC
	TIE-5	CTGCGAGTGAGCTGGTCCTT
	TIE-6	TTCTCCCGCAAAGTCACGAT
	TIE-7	GATCAAGAAGGACGGGCTGA
	TIE-8	CAGCAGAGCCACGTTCTGG
TRK family		
NTRK1	NTRK1-1	AGCTGGGAGCGCACAGAC
	NTRK1-2	CGTTGACCTGAACAGAGACCT
	NTRK1-3	CTGGGAGGAGGAGGGACT
	NTRK1-4	CAAGGAGCAGCGTAGAAAGG
	NTRK1-5	GTCAACAACGGCAACTACAC
	NTRK1-6	CCACATCCTCCCCACCG
	NTRK1-7	AGATGCTGGTGGCTGTCAA
	NTRK1-8	CTATGGGGGATGCTGAGG
NTRK2	NTRK2-1	GAGTTAAGAGAGCCGCAAGC
	NTRK2-2	GGTCTGAGGTTGGAGATTCTG
	NTRK2-3	TGTAGTGTGGCAGGTGATCC
	NTRK2-4	TTGGAGATGTGATGGAGTGG
	NTRK2-5	TCTCGGTCTATGCTGTGGTG
	NTRK2-6	ACATCCCAAAGTCCCCGATT
	NTRK2-7	GTGAAGACCCTGAAGGATGC
	NTRK2-8	TGAGGAGTACGTTGGGAAGG
NTRK3	NTRK3-1	AGACGCTGAAGGATTTTGC
	NTRK3-2	AAGCCATTGTCCTCACTCGT
	NTRK3-3	ACGAGAGGGTGACAATGCTG
	NTRK3-4	CAATGACAGGGATGCGAGT
	NTRK3-5	GCTTTTGCCTGTGTCCTGTT
	NTRK3-6	CTGTAATAATCCGTGCTGTAGA
	NTRK3-7	CGACCAAGGACAAGATGCT
	NTRK3-8	GAGGTGGAAGGGAGATGTGA

(cont. on next page)

41/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
VEGFR family		
VEGFR1	VEGFR1-1	GATTACCCGGGGAAGTGTT
	VEGFR1-2	CGCCTTACGGAAGCTCTCTTAT
	VEGFR1-3	CCACGCCCAGTCAAATTACTTA
	VEGFR1-4	TTCTTCCCACAGTCCCAACTTT
	VEGFR1-5	GCAACATGGGAAACAGAATTGA
	VEGFR1-6	CACACTGCTCATCCAAAGGAAC
	VEGFR1-7	GCGACTCTCTTCTGGCTCCTAT
	VEGFR1-8	TGGAGACCCACCTAAGGAGAAG
	VEGFR1-9	CCCGATTATGTGAGAAAAGGA
	VEGFR1-10	TGGCTCCCATGGAAAGATAAAG
VEGFR2	VEGFR2-1	CTGTGCGCTCAACTGTCCT
	VEGFR2-2	TGGGTTTTTAGGTCTCGGTTT
	VEGFR2-3	TTGTCGTTGTAGGGTATAGGATTT
	VEGFR2-4	CTCCTCTCCCGACTTTGTTG
	VEGFR2-5	GAGGACTTCCAGGGAGGAAA
	VEGFR2-6	CATGACGATGGACAAGTAGCC
	VEGFR2-7	CCCAGGAAAAGACGAACTTG
	VEGFR2-8	AAATTGTTTCTGGGGCCATC
	VEGFR2-9	GAAGAACGTGGTTAAATCTGTGA
	VEGFR2-10	CTCATGTGATGTCCGGGAGT
VEGFR3	VEGFR3-1	GACGGCCTGGTGAGTGACTACT
	VEGFR3-2	GTTGTTGGCCTTGACACATAC
	VEGFR3-3	CCAACAGACCCACACAGAACTC
	VEGFR3-4	CGTACTTGTAGCTGTCGGCTTG
	VEGFR3-5	TCTGCCATGTACAAGTGTGTGG
	VEGFR3-6	GCTGGCATCGTAGGACAGGTAT
	VEGFR3-7	GGTCCTCCTCCTCCTCATCTTC
	VEGFR3-8	CCCAGAGAGAAGATCTCCAGA
	VEGFR3-9	CTGAAAGCATCTTCGACAAGGT
	VEGFR3-10	AGTCTGCAGAGAGGGAAGAGGA
AATYK family		
AATYK	AATYK-1	GACGTGTACGTCCTGCCACTC
	AATYK-2	CACACAGGTAGGACAGCAGCAG
	AATYK-3	CTGGTACGAGGTGATGCAGTTCT
	AATYK-4	CTCGAAGAAGGCAGGACAGAAG
	AATYK-5	ACTACCCTCGCAGAAGCTTGG
	AATYK-6	CTGGACGTGTCGGTGAAGAT
	AATYK-7	AGCAGTGAGGATGAGGACACG
	AATYK-8	AACTCAGAGCTGTTGCCTTCTGAT
	AATYK-9	CTCCAGTTTTTCCTGCTGAC
	AATYK-10	ACCTTCTCGGTCACCATCCTC

(cont. on next page)

42/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
ROR family		
LMTK2	LMTK2-1	GTTTGGCAGAAGCAACGTGT
	LMTK2-2	TTCAGGTCACCCAAGTCACA
	LMTK2-3	GCGATTCCCTACCTCCTGGT
	LMTK2-4	TTCGGTCACGGTGAGGACTT
	LMTK2-5	GCCGAACACAAACAGCAGAG
	LMTK2-6	GGATCAAAATTATCTTGGTGCATAA
	LMTK2-7	AAGCCCCGTAAGATTTTTGACA
	LMTK2-8	AGTCCGAGGAGAGGGCAGAC
	LMTK2-9	CCAGCAGGGTGAGTGTAGGG
	LMTK2-10	AGGCAAGGAGTTTCGTTTCGTG
	LMTK2-11	CTTAGCAGCGGCGATGACTT
	LMTK2-12	AGCAAATGGCGAGTGGATGT
LMTK3	LMTK3-1	GCGCGTTTTTGGTGGAAG
	LMTK3-2	ATTGGCAGGGAGACCTCAG
	LMTK3-3	GTCGGCTTCAAGGAATTTGA
	LMTK3-4	CAGGGACCAGATGTTGCTCT
	LMTK3-5	GCCACAGCAACTACAAGGA
	LMTK3-6	GTCCAGGGGGTCCCAGTC
	LMTK3-7	CGAGTACTACATCCGCTTGA
	LMTK3-8	AGGGACCCCTTCCTCCTC
	LMTK3-9	GAGACCGAGACCCCTTTTTC
	LMTK3-10	GTTCCAGCGTCCCGTTCT
	LMTK3-11	GAGAAGACGCCCCGAGAGTT
	LMTK3-12	GTGGAAGGAGACCATCTTGC
	LMTK3-13	AACAGCGAGCAGATCAAAGC
	LMTK3-14	CCGTCATCCACAGAGGATTC
Styk family		
STYK1	STYK1-1	ACCTGGCTCAGGAAATGCAG
	STYK1-2	AATTCCAGCGCCAAAAGGAC
	STYK1-3	AGGCTGCTGCACTGAAAAGC
	STYK1-4	TTGTGTCCCTGGGAAAGACC
Non-Receptor Tyrosine Kinases		
A6 family		
PTK-9	PTK9-1	GGAGGAGCAGCCACTTCCTG
	PTK9-2	CGGCTCTTGCACTAGAATACA
	PTK9-3	GGGTGTGGACACTAAGCATCAA
	PTK9-4	CGCTATGAAAACAGTGTGACAAAA

(cont. on next page)

43/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
ABL family		
ABL1	ABL1-1	TTTCAGCATCCCCTGTGAAT
	ABL1-2	AGGGCTTCATGTTCCACAAA
	ABL1-3	CAGGGAAGAAGGAATCATCG
	ABL1-4	TGGTGTCCCTCCTTCAAGTC
	ABL1-5	GAGGGCGTGTGGAAGAAATA
	ABL1-6	CCTGCAGCAAGGTACTCACA
	ABL1-7	GAAATCCACCAAGCCTTTGA
	ABL1-8	AGAGCCGGCTTCTCACTTTT
	ABL1-9	CAGTCCACGGGAAGACAGTT
	ABL1-10	GGGTTTTCCGAAGAGACACTC
	ABL1-11	CACGTTGCCATCAGCATC
	ABL1-12	GGAGCAGGAACTCCACAGAT
ARG	ARG-1	AGCCGAGGAGGAATGTGAC
	ARG-2	GGGGGACACACCATAGACTG
	ARG-3	GAGCTTGTACACCATCACTCCAC
	ARG-4	AATGCTGGAGTCATGGAACATGG
	ARG-5	GTGGGAAATTGCTACCTATGGA
	ARG-6	CCCTGAGGACATGGAAGATGTA
	ARG-7	AAACTCTACATCTTCCATGTCCTC
	ARG-8	CCTCCCAGCTTTCCCACT
	ARG-9	CCTACAGAAGAGCCAACTGCCC
	ARG-10	TTCCCTCTCCCCTCAGAAAT
ACK family		
ACK1	ACK1-1	AAGGGGACGCAGGATGTAG
	ACK1-2	GTCCAACAACGATCCCAGAG
	ACK1-3	AACCTCATCCGCCTCTACG
	ACK1-4	TGTGGATGAAGCTGTTCTGC
	ACK1-5	CTCGCAACGTGGTGACCT
	ACK1-6	CCTCATGCACTCCTGCTGTA
	ACK1-7	GCCCAGGATGAGGATGACT
	ACK1-8	GCTCGGGCAGCAAGTAATAG
	ACK1-9	CTGCCTGTGCCTCTGCTG
	ACK1-10	TGGTTTCCTCCCAGTCTGTC
TNK1	TNK1-1	TAGGGCCTGCCCTGAGC
	TNK1-2	ACCCCAAACATCCACACG
	TNK1-3	CCATCAAGGTGGCTGACTTCGGGC
	TNK1-4	GGGCTCCAGGCATTCCCATGGGGTG
	TNK1-5	CAGCCCTCTAGGGAGAGGC
	TNK1-6	GGGACCTAGGCTTTTCATGC

(cont. on next page)

44/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
CSK family		
CSK	CSK-1	TCTCCTTGCACCCATACCTC
	CSK-2	GAGCTGCACCAGGTTGCTAT
	CSK-3	TTACCGAGGGAACAAAGTCG
	CSK-4	ACAGGTGGGTCCAAGAGAGA
MATK	MATK-1	CTGTGACCACTTGCTCAGTGTG
	MATK-2	GATATTCTTCACGGCCACCTTT
	MATK-3	GTGGAGCATTACAGCAAGGACA
	MATK-4	GCCGCACTCTCCACTCTCTC
FAK family		
FAK	FAK-1	GTGAGGCGTGGGAGGAAG
	FAK-2	ATCCAGCTTGAACCAAGAGC
	FAK-3	ACCCACCAGAGGAGTGGAATA
	FAK-4	AGCCGGCAGTACCCATCTATTA
	FAK-5	GAGATCCTGTCTCCAGTCACAG
	FAK-6	CCGAGCAGCAATGTCCC
	FAK-7	CCTGTATGCCTATCAGCTTAG
	FAK-8	CAGCGCTGATCTTCTTCC
	FAK-9	GTTGCCAACCCATCTG
	FAK-10	GCTGGTGGAAGGCTAGAG
PYK2	PYK-1	CGGCCGACTTACCTGTACTTG
	PYK-2	TTCCGGAGCTGTTGGTAAAAAT
	PYK-3	GAAGCCGAGTGGAGGTATGA
	PYK-4	CAGCCTCTGCTAGGGATGAG
	PYK-5	CTTCCAGCAGTACGCCTCGC
	PYK-6	CACGCAGTTGATGCTCTCCAGG
	PYK-7	CTCACCTCGTGCTGTACTCAC
	PYK-8	CCATCTGCTTCTGCTGTTTGTCC
	PYK-9	CTCCCGTTAACTCACTGCACAC
	PYK-10	ATCTTTGTCACCGTCACCCTGT
FES family		
FER	FER-1	GCTGATTAGAAGGCTC
	FER-2	CCACATGATCTCATTTGCC
	FER-3	GAACAACGGCTGCTAAAG
	FER-4	GCCCAGTAATTCTCCC
	FER-5	GGTGTAGTTCTGCTGAATCC
	FER-6	CCTGAAGGCTGAGTTTGG

(cont. on next page)

45/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
FES family (cont.)		
FES	FES-1	AGGCCGTCCCAGGAGCAG
	FES-2	GCAGGAAGCCTTGGTACTCA
	FES-3	GCACGAGGAGATGGCTTG
	FES-4	ATCCCACAGCACCGACAG
	FES-5	AAGTTCTCGCTCCCTCCAC
	FES-6	AGGCTGCATAGACCCCATC
	FES-7	TACAGCCACCCCAACATCG
	FES-8	AGGGACACAGAGAGGACACG
FRK family		
BRK	BRK-1	CCTGGGCCCCAAGTATGTG
	BRK-2	AACCCGAAGTCCCCAACTTT
	BRK-3	ATTGGGATGACTGGGAGAGG
	BRK-4	GTATTGGACGCAGACACTCCAC
FRK	FRK-1	AGGTGGATCGCAGAGACTAAGG
	FRK-2	TCATTTGGATCCATTGAACCTG
	FRK-3	GTGGACCAATGGGAGATAGACC
	FRK-4	AAACTGATTGTGCAGTTGGTTGA
SRMS	SRMS-1	GCCCAGCGTGGTGACCCC
	SRMS-2	CACAGGCTCCCCGCCCGAGCAC
	SRMS-3	GAAGGGCCTGCGGCACGAGCGG
	SRMS-4	GAGGACTCAGGGGTGGCATCTG
JAK family		
JAK1	JAK1-1	AACACTGGACAGCTGAATAAATG
	JAK1-2	TCGTAGTAGAGAACGTTTCCACC
	JAK1-3	ACTTCCATGTTACTGATTTTCATCAGA
	JAK1-4	GATCACTTTTATCTTCTTCTCTTCAG
	JAK1-5	CACGAGAACACACATCTATTCTGG
	JAK1-6	GCTATGTGGTTACCTCCACTCTC
	JAK1-7	CAGCCAACTGAAGTGGAC
	JAK1-8	TTGATAATCTGTGGAATTTAAATG
JAK2	JAK2-1	GCAGGCAACAGGAACAAGATGTG
	JAK2-2	ACCACTTCCAGGTTCTTTTACTTC
	JAK2-3	TTTTGACAAGGAAGCGAATAAGG
	JAK2-4	TTGGCCAAGGCTTTCATTAAATA
	JAK2-5	GTACCAACCTCACCAACATTACAG
	JAK2-6	CTATCCTCATATTTGGTAACATGTC
	JAK2-7	CTTTCAGAGCCATCATACGAGATC
	JAK2-8	ATCTACTTTGGTCTCAGAATGAAGG

(cont. on next page)

46/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
JAK family (cont.)		
JAK3	JAK3-1	CGCCCTTCGAAAGTCCAG
	JAK3-2	GCCTGCTTGATGCTAATGTCTA
	JAK3-3	CAAGGAGCAGGGTGAGTG
	JAK3-4	CAAGGGGGTTCTGGACACA
	JAK3-5	ACTCCCAGCACTTCTTCTGC
	JAK3-6	GGCCTTTGTCCTCCAGATAGT
	JAK3-7	TGCTGCTGAAGGTCATGGATGC
	JAK3-8	GCTGAAAGTCCCTCTGCTGGTC
	JAK3-9	CTGCCAAGACCCACGAT
	JAK3-10	TCACACAGCCAGTCAACAGA
TYK2	TYK2-1	CTGAGGCCCAGAATTGCTAAGT
	TYK2-2	CACTGTCCCGGATGTAGCAG
	TYK2-3	TGGTCATGGTCAAATACCTAGCC
	TYK2-4	CATGATGATGAGATTGGAGGTTTC
	TYK2-5	GATGACTGCTTCTCTCTGCGTC
	TYK2-6	CGGAGGGACTGCGGCTCTGC
	TYK2-7	GGGAGGAGCGGGTGGAGAGG
	TYK2-8	GTCCAGCAGCACGTTGCGCGC
	TYK2-9	ACCAAGGCGAGAAGTCGCTGC
	TYK2-10	TGGAGCAGGGAGCAGGAGGC
Src-A family		
FGR	FGR-1	CCCTGTTCAATTGCCCTGTAT
	FGR-2	CGATGAGCAGGTTGCACAG
	FGR-3	GCAGCACTACATGGAGGTGAAT
	FGR-4	GGAAGAACAGCTCTGGGGATT
FYN	FYN-1	CCAGTCCTGCCTCTGTTGTAGA
	FYN-2	CGATGAAAACACAAAGGTAAGGTC
	FYN-3	GATCAAGAGACTGGGAAATGGGC
	FYN-4	CTCAGTGTACGTTAGACTAGGAC
SRC	SRC-1	CGAGACCCCTGACTCCACACC
	SRC-2	GCCCAGCTTGACCTCCAGCC
	SRC-3	TGGCCTACTACTCCAAACACG
	SRC-4	CAGGATCCAAGCCGAGAAG
YES1	YES-1	GATTTGATAATGGGCTGC
	YES-2	GCTTCTGGCATCATTGTACC
	YES-3	CATGGAATGGAACCACGAAAG
	YES-4	GCAACCATATCTGGGATTC

(cont. on next page)

47/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
Src-B family		
BLK	BLK-1	TGGGACTGGCTTTTGCTTTA
	BLK-2	GGCACCTTTGTTGGTTTCAC
	BLK-3	TAGATCACAGGGTCGGAAGG
	BLK-4	TTCATGCGCTCAATGTATGC
	BLK-5	CGAGTACATGGCCAGAGGAT
	BLK-6	GTCTGAGAAAAGGGCACAGG
HCK	HCK-1	ATCAGAGGCTTAGAGGCGAGTG
	HCK-2	TCTTCTCCAGCTTGAGGGATTG
	HCK-3	GACGGGCTCTGCCAGAAA
	HCK-4	GGGAGTAGGAAGGGGGTGTG
LCK	LCK-1	TGGCTGCAGCTCACACC
	LCK-2	GTTGCAGCTGCTTCATGAGGT
	LCK-3	AGGTGTGGATGGGGTACTACAAC
	LCK-4	TCATGTGCAGAGTCCATATGTGC
LYN	LYN-1	TGAACTCAAGTCACCGTGGAGC
	LYN-2	CAAGCCTTTTCACCAACTTGATGG
	LYN-3	CTTGTATTAGTCCCAAGCCACAG
	LYN-4	GCACATGAAATCATAAGTGCAACC
SYK family		
SYK	SYK-1	GCTGGAGAGCGAGGAGGAG
	SYK-2	TGAGATTATTCCACCCGCTGA
	SYK-3	GGAGGCCGTCCACAACCTCC
	SYK-4	GCCCATAGGAGAATGCTTCC
	SYK-5	GGTACGCTCCGGAATGCATC
	SYK-6	GCTCCTGTGATCAAAGGCAGC
ZAP-70	ZAP70-1	TCAGAACCGGCTCTCCATT
	ZAP70-2	AGGCCTCCTTCAGGCAGTA
	ZAP70-3	GCCGAGCGCAAACCTTTACT
	ZAP70-4	CACATTGCTCACAGGGATCT
	ZAP70-5	ACCAGCTGGACAACCCCTA
	ZAP70-6	GTAAGCAATGCCCTCAGCTC
TEC family		
BMX	BMX-1	TGGTGCCTCAAAGCAGTAAC
	BMX-2	GCAACATCTTCACTGCTGCT
	BMX-3	CCCAGCCACCATCTTCAAGTA
	BMX-4	GTAATTCAGCAAGCAGCCATTG
	BMX-5	CCATCCCAAGCTGGTTAAAT
	BMX-6	TCAGGAGCAGCATAAACAAA

(cont. on next page)

48/306

Fig. 26 (cont. from prev. page)

Gene	Oligo-name	Sequence
TEC family		
BTK	BTK-1	TCAATGCATCTGGGAAGCTA
	BTK-2	GCCCATTTTTATCTCGTGCT
	BTK-3	AAAAGGTTGTGGCCCTTTATGA
	BTK-4	GTCTCGGTGAAGGAACTGCTTT
	BTK-5	GGAAATTGATCCAAAGGACCTG
	BTK-6	GCCTTTGCTCAGAAGCCACTAT
ITK	ITK-3	ACTGCCTGCTGGACAGTTCT
	ITK-4	GCACCAGTTTGGGATGAGAG
	ITK-5	ACCCCTCAGAGCTCACTTTTGT
	ITK-6	GGTGGCAGCTTCTAATGCTCTA
TEC	TEC-1	AGCCGGTTCAGCCAGAATAC
	TEC-2	CCCGTTACGTAATTACTTGGGATA
	TEC-3	CACCCGGATGTGAAAAATACAA
	TEC-4	CTCACCCTCCAAACAGTCCAC
	TEC-5	CCAGTCAACCAGGCTTGTACAC
	TEC-6	CCTCGAGTAACCATGGTTACCAC
	TEC-7	TCCTCCGACAGAGACAAGGT
	TEC-8	TCAAGTGCCTGAGGAATGAA
TXK	TXK-1	AGTAGAGCACCGCAGAAGAACT
	TXK-2	TGAAATCCTCTTCAGACATGGA
	TXK-3	GGTGAATGGCGGTACATATCC
	TXK-4	GGGTTGGCATTCTGTTTC

Fig. 27

Gene	Genetic Variations	Oligo-name	Sequence
Receptor Tyrosine Kinases			
AXL family			
TYRO3	I346N	TYRO3-2-1	TGTGCCTCTCAGAGCTGTTT
		TYRO3-2-2	GCTTATACTCCAGGAGAGTGGAGA
	E489K	TYRO3-1-5	GGGAGAGGCAGGTAATGATG
		TYRO3-1-6	CTGATTCCTGAGCCAAAACC

(cont. on next page)

49/306

Fig. 27 (cont. from prev. page)

Gene	Genetic Variations	Oligo-name	Sequence
EPH family			
EPHA2	M631T	EPHA2-2-1 EPHA2-2-2	CATCCATCCTGTGTCACTCG GACAGAGCCCCTGCTAAGTG
EPHA3	W924R	EPHA3-1-1 EPHA3-1-2	TGTCTCCCTTTGGTGTTTTT TCATGTCAAGCCAAGAAAGTT
EPHA5	A672T R981L	EPHA5-G-C3 EPHA5-G-C4 EPHA5-G-D1 EPHA5-G-D2	GCTGGTCCTTGCAGTTGAAT TCACTTTGAATGCAAGCCAAT CCACGGCCCATAGTTTACATTAG TTCTTTGAGAGCTGCCACACAT
EPHA10	G749E	EPHA10-1-1 EPHA10-1-2	CACAGGAAGCACCTTGATGA GGTGTAGACAGCCTCTGATCG
EPHB2	Q722X	EPHB2-G-C3 EPHB2-G-C4	CCTGTGTTCTCACCACCACTCT TAGGTGGGGTCTGAGGTATCGT
EPHB4	I610T	EPHB4-G-C3 EPHB4-G-C4	GGGTTTGGGGCTAAAAGCTATG ATTGCCACACAGCTCTCCTTCT
FGFR family			
FGFR1	V427_T428Del	FGFR1-G-B2-5 FGFR1-G-B2-6	GAGTGA CTTCACAGCCAGATG CCCTGCATCTCTGCACTTCTAA
FGFR4	G388R	FGFR4-G-B1-1 FGFR4-G-B1-2	CTACAGCTTCCTCCGTGTGTGT GCAAAGTGGGAGACTTGTTCT
MET family			
MET	T1010I / D981_E1027del	MET-G-D3 MET-G-D4	ATTGTCGTCGATTCTTGTGTGC CCTGGATTGTAAAAGAGAGCTTCG
RON	R523Q R627fsX23 R813RQ R1335G Y884_Q932del A1022_K1090del	RON-G-C1-3 RON-G-C1-4 RON-G-C1-5 RON-G-C1-6 RON-G-C2-1 RON-G-C2-2 RON-G-E3 RON-G-E4 RON-G-D1 RON-G-D2 RON-G-D5 RON-G-D6	TGTGGGATCACAGACTCTCCAT AGCCTGTCCCACTCTTACCTGT GCATGCATCTAGGCCTGTGTAA CAGACACTCAGTCCCATTGACC ACTGCCTCTTTGCCCACTCT ATTAGCCAGGAACCCACCT GGAAGGCAGGACTGGAACAGTA GTTCTGGACGCACATTCATCTC GGTGGCAGGGAATCTGAGTG GCACCACTCTACCCAGGATATG ACCAAGGATTCTCTTTCCACAG GTCTCGATCTCCTGACCTCAT

(cont. on next page)

50/306

Fig. 27 (cont. from prev. page)

Gene	Genetic Variations	Oligo-name	Sequence
PDGFR family			
FLT3	M227T	FLT3-G-A1 FLT3-G-A2	TGGGCTTGTTTACCTTTTGACC TGCATTTACTGTGACCTGAAGGA
ROR family			
ROR1	M518T	ROR1-G-C1 ROR1-G-C2	AGAATTGGGTGAGTGTGCCTTT TATTCCATGCCAGCTGCAATCT
ROR2	T245A	ROR2-G-A3 ROR2-G-A4	CTGCAAATCAGAGCAGGTGATG ACATTTCAAGGGCCCTACACTC
ROS family			
ROS1	C76fsX D2213N/ K2228Q / S2229C	ROS1-G-A3 ROS1-G-A4 ROS1-G-I3 ROS1-G-I4	CCTGCAGTGAGCCACAAGACT CCTTCCGTGACCTCTAGTCACAT AAAATGACCCTACCTGGGTTATCA CTTGAGGTCCAAACTGGTGTGT
TRK family			
NTRK1	L585fsX82 H604Y/ G613V	NTRK1-G-D3 NTRK1-G-D4 NTRK1-G-D5 NTRK1-G-D6	GGTGGCTGTCAAGGTGAGAC CCTTCCTGATCTTTCTTGGTGT CATCTGGAGTTCAAGGAGCTG GTGCTGTAGATATCCCTGCTCA
NTRK3	E402_F410delinsV G466_Y529delinsD R711_V712ins16	NTRK3-G-B1 NTRK3-G-B2 NTRK3-G-C7 NTRK3-G-C8 NTRK3-G-D1 NTRK3-G-D2	ACTGCATCGAGTTTGTGGTG CAGTGTGCCCTAACATGCAC TTGTGATGGGAACAGTAGTTGG TGGCTCAGGCTATTCTTCAAGT AATGATCCTTGTGGATGGACAG GAAGCACGTAAGAACACAATGC
VEGFR family			
VEGFR2	Q472H / C482R	VEGFR2-G-B3 VEGFR2-G-B4	GTAGGCTGCGTTGGAAGTTATT CCATCCTTCCATTAAAGAGAGA
VEGFR3	G890H	VEGFR3-G-D1 VEGFR3-G-D2	CCGTACAGCTCACCTGCAACT TGGGAGGGGGAGGGTTACTA
AATYK family			
AATYK	F1163S	AATYK-G-C3 AATYK-G-C4	CTTCTGTCCTGCCTTCTTCG CACTACTGGCTGTCTCTGTCCA

(cont. on next page)

51/306

Fig. 27 (cont. from prev. page)

Gene	Genetic Variations	Oligo-name	Sequence
Non-receptor Tyrosine Kinases			
ABL family			
ABL1	S991L	ABL1-G-E1 ABL1-G-E2	GAGTCTGGTTGATGCTGTGAAC CAGAACGTGTAGAGGTTTTTGC
ACK family			
TNK1	D472_R473del M598delinsEVRSHX	TNK1-G-B1 TNK1-G-B2 TNK1-G-C1 TNK1-G-C2	GGACAGGACCAGAGTGAAGC AGGATGCCAGCAGACAGAAT AAAGAAAACCCCCACACAATC GTCGGGACCTTGTTCTGGTT
FAK family			
FAK	L926PWL	FAK-G-D1 FAK-G-D2	TGGGAATCATTCTCTCTCACCA ACCCCAAGCATCCTGGTTTAAT
PYK2	G414V K838T	PYK2-G-B1 PYK2-G-B2 PYK2-G-D3 PYK2-G-D4	CTTCTCCTCCTACCCCCTTG GCTCCCTCTGAAGGCTAGGT GCACCCATCTGTGTCCTCTT TCAGGAAAAGGGCCATGTAG
FES family			
FES	S72_K129del E413fsX131	FES-G-A1 FES-G-A2 FES-G-B1 FES-G-B2	TGTATCTGCCTTCTCCTTCCTC TCCTCTCCCTGACTCTCAGAAC AGAGGCAAGTGCTGCAAGA GAACTTGGGGCGGAAGAT
FRK family			
FRK	G122R	FRK-G-A1 FRK-G-A2	TCAGGACCTCTCAGACAGAACA CCTTTTTGGCTTCACTTTCTC
JAK family			
TYK2	I684S E971fsX19	TYK2-G-C3 TYK2-G-C4 TYK2-G-D1 TYK2-G-D2	CCCCAACTCACTTTCAACC ACAGGCCACACACCAGGTA GTTCTTGGCATCTGGGTGAG AGCCCAAGCTGAAGAGGAAG

(cont. on next page)

52/306

Fig. 27 (cont. from prev. page)

Gene	Genetic Variations	Oligo-name	Sequence
SRC-A family			
YES-1	K113Q	YES1-G-A1 YES1-G-A2	TTTCCCTCTGATAGGTGGTGTTA ATACGACTGGAAGCAGACCATAA
SYK family			
ZAP70	K186fsX P296_S301del	ZAP70-G-A1 ZAP70-G-A2 ZAP70-G-B1 ZAP70-G-B2	CCACCATGCACAACTACCTG CCAACTGCACACTCACGTCT CCCTAGAGTCCACCCTCATGT CAAACCTGCTGTGAGACAGACATC
TEC family			
BMX	S251del	BMX-G-B3 BMX-G-B4	GGGCAAATCCAGTCAAGATG CATGGATGCTGGCTAGGAAT
TXK	R336Q Y414fsX15	TXK-G-B1 TXK-G-B2 TXK-G-B7 TXK-G-B8	CAGGAAAGGAAATCTGCTTGA CCTGGCATACTCAGTAGCA TTGTTTGGGGAGGAAACATT CTCTGCGGAGTGGAACACTT

Fig. 28

Receptor Tyrosine Kinases

Gene	Gbk-file	Gene	Gbk-file
ALK family		FGFR family	
ALK	NM_004304.3	FGFR1	NM_000604.2
LTK	NM_002344.3	FGFR2	NM_023031.1
AXL family		FGFR3	NM_000142.2
AXL	NM_021913.2	FGFR4	NM_002011.2
MER	NM_006343.1	INSR family	
TYRO3	NM_006293.2	IGF1R	NM_000875.2
DDR family		INSR	NM_000208.1
DDR1	NM_013994.1	IRR	NM_014215.1
DDR2	NM_006182.1	MET family	
EGFR family		MET	NM_000245.1
EGFR	NM_005228.2	RON	NM_002447.1
HER2	NM_004448.2		
HER3	NM_001982.2		
HER4	NM_005235.1		

(cont. on next page)

53/306

Fig. 28 (cont. from prev. page)

Receptor Tyrosine Kinases (cont.)

Gene	Gbk-file	Gene	Gbk-file
EPH family		ROR family	
EPHA1	NM_005232.2	ROR1	NM_005012.1
EPHA2	NM_004431.2	ROR2	NM_004560.2
EPHA3	NM_005233.3	ROS family	
EPHA4	NM_004438.2	ROS1	NM_002955.2
EPHA5	NM_004439.3	RYK family	
EPHA6	XM_114973.4	RYK	NM_002958.1
EPHA7	NM_004440.2	TIE family	
EPHA8	NM_020526.2	TEK1	NM_000459.1
EPHA10	AJ872185.1	TIE	NM_005424.2
EPHB1	NM_004441.2	TRK family	
EPHB2	NM_017449.1	NTRK1	NM_002529.2
EPHB3	NM_004443.3	NTRK2	NM_006180.2
EPHB4	NM_004444.3	NTRK3	NM_002530.1
EPHB6	NM_004445.1	VEGFR family	
MUSK family		VEGFR1	NM_002019.2
MUSK	NM_005592.1	VEGFR2	NM_002253.1
PDGFR family		VEGFR3	NM_182925.1
CSF1R	NM_005211.2	AATYK family	
FLT3	Z26652.1	AATYK	XM_290778.1
KIT	NM_000222.1	LMTK2	NM_014916.2
PDGFRA	NM_006206.2	LMTK3	XM_055866.6
PDGFRB	NM_002609.2	STYK family	
PTK7 family		STYK1	NM_018423.1
CCK4	NM_002821.3		
RET family			
RET	NM_020975.2		

Non-Receptor Tyrosine Kinases

Gene	Gbk-file	Gene	Gbk-file
A6 family		ACK family	
PTK-9	NM_002822.3	ACK1	NM_005781.4
ABL family		TNK1	NM_003985.1
ABL1	NM_007313.2	CSK family	
ARG	NM_007314.1	CSK	NM_004383.1
		MATK	NM_139355.1

(cont. on next page)

54/306

Fig. 28 (cont. from prev. page)

Non-Receptor Tyrosine Kinases (cont.)

Gene	Gbk-file
FAK family	
FAK	NM_005607.3
PYK2	NM_173174.1
FES family	
FER	NM_005246.1
FES	NM_002005.2
FRK family	
BRK	NM_005975.2
FRK	NM_002031.2
SRMS	NM_080823.2
JAK family	
JAK1	NM_002227.1
JAK2	NM_004972.2
JAK3	NM_000215.2
TYK2	NM_003331.3

Gene	Gbk-file
SRC-A family	
FGR	NM_005248.1
FYN	NM_002037.3
SRC	NM_005417.3
YES1	NM_005433.3
SRC-B family	
BLK	NM_001715.2
HCK	NM_002110.2
LCK	NM_005356.2
LYN	NM_002350.1
SYK family	
SYK	NM_003177.3
ZAP-70	NM_001079.3
TEC family	
BMX	NM_001721.4
BTK	NM_000061.1
ITK	NM_005546.3
TEC	NM_003215.1
TXK	NM_003328.1

Fig. 29

Receptor Tyrosine Kinases

Gene	Alteration	Reference
ALK family		
ALK	I1461V	HO dbSNP:1670283
AXL family		
MER	G328S	HO dbSNP:7604639
MER	R466K	HO dbSNP:3811635
MER	I518V	HO dbSNP:1131246
MER	H628Q	HO dbSNP:1131246
MER	R794A	HO dbSNP:1131246
MER	P888S	HO dbSNP:1131246

Gene	Alteration	Reference
DDR family		
DDR1	DEL506-542	HE Isoform 2
DDR1	DEL666-671	HO Isoform 2
DDR2	S642A	HO Isoform 2
EGFR family		
HER3	G1064E	HO Isoform 2
EPH family		
EPHA1	A398G	HO Isoform 2
EPHA5	E232K	HO Isoform 2
EPHA5	F563SV	HE Isoform 2
EPHA5	DEL597-619	HO Isoform 2

(cont. on next page)

55/306

Fig. 29 (cont. from prev. page)

Receptor Tyrosine Kinases (cont.)				Non-Receptor Tyrosine Kinases							
Gene		Alteration		Reference		Gene		Alteration		Reference	
FGFR family				ABL family							
FGFR1	DEL148-149	HE	Isoform 14, 15, 18	ARG	DEL53-73	HO					
FGFR2	R497G	HO									
INSR family				ACK family							
IGF1R	DEL928-929	HE	dbSNP:7508518	ACK1	M984MLQ	HO					
INSR	H171Y	HO		TNK1	G36E	HO	Isoform 1				
INSR	T448I	HO		TNK1	S65R	HO	Isoform 1				
INSR	K492Q	HO		TNK1	T94S	HO	Isoform 1				
INSR	DEL744-755 (short isoform)	HO/HE		TNK1	Q252L	HO	Isoform 1				
MET family				TNK1				T288A	HO	Isoform 1	
MET	DEL755-772	HO		TNK1	P325A	HO	Isoform 1				
RON	G209A	HO		TNK1	P347L	HO	Isoform 1				
PDGFR family				TNK1				S348C	HO	Isoform 1	
FLT3	R78G	HO		TNK1	A391V	HO	Isoform 1				
KIT	DEL509-512	HE		TNK1	D424G	HO	Isoform 1				
KIT	DEL715	HE		TNK1	T443A	HO	Isoform 1				
ROS family				TNK1				E561K	HO	Isoform 1	
ROS1	G223GQ	HE		TNK1	W604G	HO	Isoform 1				
RYK family				TNK1				L635H	HO	Isoform 1	
RYK	N251S	HE		TNK1	DEL411-415	HO	Isoform 2				
TIE family				FES family							
TEK1	I695T	HO		FER	V439L	HO					
TEK1	DELV788	HE		JAK family							
TRK family				JAK1	D338H	HO					
NTRK1	DEL393-398	HO		JAK1	F356Y	HO					
VEGFR family				JAK1	R846_T852del	HO					
VEGFR1	L779F	HO		JAK1	E886EG	HO					
VEGFR3	P745R	HO	(2)	TYK2	S1016A	HO	dbSNP:17851123				
VEGFR3	R752K	HO	(2)	SRC-B family							
VEGFR3	P753A	HO	(2)	LCK	P87Q	HO					
VEGFR3	V1128L	HO	(2)	TEC family							
VEGFR3	H1146R	HO	dbSNP:1130379	TEC	F514V	HO					

56/306

Fig. 30

Bladder

HT-1376		T-24	
HER2	P1170A	HER2	I655V
RON	R523Q	EPHA1	V900M#
RON	R1335G#	FGFR2	M71T#
FRK	G122R	RON	R523Q#
		RON	R627fsX5#
		RON	R813delinsRQ#
		RON	Y884_Q932del14
		RON	R1335G#
		ROR1	M518T#
		NTRK1	H604Y#
		NTRK1	G613V#
		TYK2	V362F#
		TXK	R336Q#
RT-4		TCCSUP	
MER	V870I#	HER2	I655V
TYRO3	I346N#	TYRO3	I346N#
HER2	P1170A	HER2	P1170A
EPHA10	G749E	EPHA2	G391R
RON	R523Q#	FGFR2	H199_Q247delins48
RON	R813RQins#	FGFR4	G388R
RON	R1335G#	RON	R523Q#
RET	G691S#	RON	R813delinsRQ#
LMTK2	L780M	RON	Y884_Q932del14
ACK1	P725L#	RON	R1335G#
PYK2	K838T#	PDGFRA	S478P
<u>BRK</u>	<u>W78fsX58#</u>	ROS1	C76_R77ins9
TYK2	G363S	ROS1	D2213N#
		NTRK3	E402_F410delinsV#
		LMTK2	L780M#
		ACK1	P725L#
		FRK	G122R
SCaBER			
ALK	D1529E#		
HER2	P1170A#		
<u>EPHA5</u>	<u>A957T</u>		
FGFR2	M71T#		
FGFR4	L136P		
RON	R523Q		
RON	R813delinsRQ#		
ROR1	M518T		
RYK	N96S		
STYK1	G204S#		
TNK1	M598V		
FRK	G122R#		

(cont. on next page)

57/306

Fig. 30 (continued)

Bone and Soft Tissue

		SaOS2	
MG-63		ALK	K1491R#
ALK	K1491R#	ALK	D1529E#
ALK	D1529E#	EGFR	R521K#
TYRO3	I346N	HER2	P1170A
HER2	P1170A#	FGFR2	H199_Q247delins48
FGFR2	H199_Q247delins48	FGFR4	L136P#
RON	R523Q	RON	R1335G
RON	R627fsX5#	ROR1	M518T
RON	R813delinsRQ#	ROR2	T245A
CCK4	A777V#	ROR2	V819I
ROR1	M518T	ROS1	C76_R77ins9#
ROR2	V819I#	ROS1	D2213N#
RYK	N96S	ROS1	K2228Q#
LMTK2	L780M	ROS1	S2229C#
ACK1	P725L#	RYK	N96S#
TYK2	V362F#	NTRK3	E402_F410delinsV#
TYK2	P1104A#	LMTK2	L780M
RD		ACK1	P725L#
TYRO3	I346N	PYK2	K838T
HER2	I655V	TYK2	V362F#
HER2	P1170A#	ZAP-70	K186fsX#
HER2	A1216D#	TE-671	
FGFR2	H199_Q247delins48	TYRO3	I346N
FGFR4	V10I	HER2	I655V
RET	G691S	HER2	P1170A#
ROR1	M518T#	HER2	A1216D#
AATYK	T1227M#	FGFR2	H199_Q247delins48
ACK1	P725L#	FGFR4	V10I
TNK1	M598delinsEVERSHX#	RET	G691S
PYK2	D424Y#	ROR1	M518T#
PYK2	K838T#	NTRK3	G466_Y529delinsD#
TYK2	V362F	AATYK	T1227M#
		ACK1	P725L#
		TNK1	M598delinsEVERSHX#
		PYK2	D424Y#
		PYK2	K838T#
		TYK2	V362F

(cont. on next page)

58/306

Fig. 30 (continued)

Brain

A172		1321N1	
EGFR	R521K#	TYRO3	I346N
HER2	I655V#	HER3	S1119C#
HER2	P1170A	RON	Y884_Q932del14
RON	R813delinsRQ#	RON	R1335G#
RON	R1335G#	ROR1	M518T
CSF1R	H362R	ROR2	V819I
ROR1	M518T#	RYK	N96S
ROS1	S1109L#	NTRK3	E402_F410delinsV#
ROS1	K2228Q#	NTRK3	G466_Y529delinsD#
ROS1	S2229C#	LMTK2	L780M#
RYK	N96S	STYK1	G204S#
AATYK	G600C#	ACK1	P725L#
LMTK2	L780M#	TNK1	M598delinsEVERSHX
TNK1	M598delinsEVERSHX	TYK2	V362F
PYK2	K838T		

CCF-STTG1		IMR-32	
TYRO3	I346N#	TYRO3	I346N#
HER2	I655V	HER2	P1170A
HER2	P1170A	FGFR2	H199_Q247delins48
EPHA3	W924R#	MET	T1010I#
FGFR2	H199_Q247delins48	RON	R1335G#
RON	R523Q	PDGFRA	G79D
CCK4	T410S#	CCK4	E745D#
ROR1	M518T#	ROR1	M518T#
ROR2	T245A	ROR2	V819I
ROR2	V819I	NTRK3	E402_F410delinsV#
ROS1	C76_R77ins9#	LMTK2	L780M
ROS1	T145P#	ACK1	P725L#
ROS1	I537M#	TNK1	M598delinsEVERSHX#
ROS1	D2213N#	FAK	T416fsX#
ROS1	K2228Q#	FAK	L926delinsPWRL#
ROS1	S2229C#	PYK2	K838T#
NTRK3	E402_F410delinsV#	TXK	Y414fsX15#
LMTK2	L780M#		
ACK1	P725L#		
TNK1	M598delinsEVERSHX#		

(cont. on next page)

59/306

Fig. 30 (continued)

Brain (cont.)

SF-126		SF-767	
TYRO3	I346N	ALK	K1491R#
EGFR	R521K#	ALK	D1529E#
HER2	P1170A	TYRO3	I346N#
EPHA2	R876H	EGFR	R521K#
EPHA3	W924R#	HER2	I655V
RON	R523Q	HER2	P1170A
RON	R813delinsRQ#	<u>HER4</u>	<u>L753V#</u>
RON	R1335G#	RON	R523Q
ROR1	M518T	RON	R813delinsRQ
ROS1	T145P	ROR2	T245A
ROS1	S1109L#	ROR2	V819I
ROS1	D2213N#	RYK	N96S
ROS1	K2228Q#	LMTK2	L780M
ROS1	S2229C#	STYK1	G204S#
NTRK3	E402_F410delinsV#	ABL1	S991L#
STYK1	G204S	PYK2	K838T
PYK2	K838T#	TYK2	V362F
TYK2	V362F	TYK2	I684S
TYK2	I684S#		
SF-763		SH-SY-5Y	
ALK	K1491R#	ALK	D1529E
ALK	D1529E#	HER2	I655V#
HER2	P1170A#	HER2	P1170A
EPHA3	W924R#	FGFR2	H199_Q247delins48
EPHA10	G749E#	FGFR4	G388R#
<u>EPHB4</u>	<u>V547M#</u>	RON	R627fsX5
RON	R627fsX5#	RON	R1335G#
RON	R813delinsRQ#	PDGFRA	S478P#
CCK4	A777V	ROR1	M518T#
ROR1	M518T#	ROR2	V819I#
RYK	N96S	RYK	N96S
<u>RYK</u>	<u>R504H#</u>	NTRK3	E402_F410delinsV#
AATYK	G600C#	LMTK2	L780M
STYK1	G204S#	FAK	T416fsX#
ABL1	S991L#	PYK2	K838T#
<u>PYK2</u>	<u>E404Q</u>	TYK2	I684S#
BMX	S254del#	FYN	D506E#
TXK	Y414fsX15#	TXK	Y414fsX15#

(cont. on next page)

60/306

Fig. 30 (continued)

Brain (cont.)

SK-N-SH		SW-1088	
HER2	P1170A	ALK	K1491R
FGFR2	H199_Q247delins48#	ALK	D1529E#
FGFR4	G388R#	TYRO3	I346N#
PDGFRA	S478P#	HER2	P1170A
ROR1	M518T#	<u>EPHB6</u>	<u>G353_E471del#</u>
ROR2	T245A	FGFR2	H199_Q247delins48
ROR2	V819I#	FGFR4	G388R#
ROS1	C76_R77ins9#	ROR2	T245A
NTRK3	E402_F410delinsV#	ROR2	V819I
LMTK2	L780M	ROS1	C76_R77ins9#
ARG	K930R#	ROS1	T145P#
<u>ACK1</u>	<u>G947D#</u>	ROS1	I537M#
TNK1	M598delinsEVERSHX#	ROS1	D2213N#
FAK	T416fsX#	ROS1	K2228Q#
PYK2	K838T#	ROS1	S2229C#
<u>JAK3</u>	<u>G62fsX44#</u>	RYK	N96S
TYK2	V362F	NTRK3	E402_F410delinsV#
TYK2	I684S#	LMTK2	L780M#
<u>SYK</u>	<u>A353T#</u>	ACK1	P725L#
ZAP-70	K186fsX#	TNK1	M598delinsEVERSHX#
ZAP-70	P296_S301del#	PYK2	K838T#
		TYK2	V362F#
		TYK2	I684S#
T-98 G		U-118-MG	
HER2	P1170A	ALK	D1529E
RON	R523Q	TYRO3	I346N
RON	F574fX23#	RON	R523Q#
ROR1	M518T	RON	R1335G#
ROS1	C76_R77ins9#	ROR1	M518T
RYK	N96S	RYK	N96S
NTRK3	E402_F410delinsV#	NTRK3	402_F410delinsV#
LMTK2	L780M	NTRK3	R711_V712ins15#
STYK1	G204S#	VEGFR2	Q472H
ACK1	P725L#	LMTK2	P30A#
TNK1	M598delinsEVERSHX#	LMTK2	L780M#
PYK2	K838T	ACK1	P725L#
TYK2	V362F	TNK1	598delinsEVERSHX
TYK2	I684S#	PYK2	K838T#
		TYK2	V362F#
		ZAP-70	P296_S301del#

(cont. on next page)

61/306

Fig. 30 (continued)

Brain (cont.)

U-138-MG

ALK	K1491R#
TYRO3	I346N
RON	R1335G#
ROR1	M518T
RYK	N96S
NTRK3	E402_F410delinsV#
AATYK	G600C
LMTK2	L780M
STYK1	G204S#
ACK1	P725L#
TNK1	M598delinsEVERSHX
TYK2	V362F#
ZAP-70	P296_S301del#

U-373

no genetic
alteration identified

U-1240

<u>EGFR</u>	<u>P332S</u>
HER2	I655V#
HER2	P1170A#
<u>EPHA2</u>	<u>G662S#</u>
EPHA5	A672T
FGFR2	H199_Q247delins48
FGFR4	G388R
RON	R1335G#
RET	G691S
ROR1	M518T#
ROR2	V819I
RYK	N96S#
NTRK1	H604Y#
NTRK1	G613V#
NTRK3	E402_F410delinsV#
AATYK	G600C#
STYK1	G204S
TNK1	M598delinsEVERSHX#
PYK2	K838T
TYK2	V362F

U-1242

ALK	K1491R#
TYRO3	I346N#
HER2	I655V
EPHA3	R914H#
FGFR2	H199_Q247delins48
FGFR4	G388R
RON	R1335G
CCK4	A777V#
ROR1	M518T
ROR2	T245A#
ROR2	V819I#
ROS1	C76_R77ins9#
ROS1	T145P
ROS1	S1109L#
RYK	N96S
NTRK3	E402_F410delinsV#
VEGFR2	Q472H#
LMTK2	L780M#
ACK1	P725L#
TNK1	M598delinsEVERSHX
PYK2	K838T

Breast

BT-20

TYRO3	E489K
<u>RON</u>	<u>A1022_K1090del</u>
ROR1	M518T

BT-474

FGFR4	L136P
RON	Y884_Q932del14
RON	R1335G
ROR1	M518T
NTRK3	E402_F410delinsV#
TYK2	E971fsX67#

(cont. on next page)

62/306

Fig. 30 (continued)

Breast (cont.)

BT-483		HBL-100	
HER2	P1170A	ALK	K1491R#
EPHA1	V900M#	ALK	D1529E
FGFR4	L136P#	EGFR	R521K#
RON	R1335G#	HER2	I655V#
NTRK3	E402_F410delinsV#	HER2	P1170A
NTRK3	R711_V712ins15#	EPHA1	V900M#
LMTK2	L780M#	RON	R627fsX5#
STYK1	G204S#	RON	R1335G
JAK2	L393V#	ROR1	M518T#
TYK2	E971fsX67#	ROR2	T245A
TXK	Y414fsX15#	ROR2	V819I
		RYK	N96S
		ROS1	C76_R77ins9#
		NTRK3	E402_F410delinsV
		<u>LMTK2</u>	<u>M758V#</u>
		LMTK2	L780M
		<u>JAK2</u>	<u>N1108S#</u>
		TYK2	V362F#
BT-549		Hs-578T	
EPHA5	A672T	HER2	P1170A
ROR1	M518T#	EPHA3	W924R#
NTRK3	E402_F410delinsV#	FGFR4	G388R
NTRK3	G466_Y529delinsD#	RON	R1335G#
LMTK2	L780M	ROR1	M518T#
TYK2	E971fsX67#	ROS1	C76_R77ins9
		NTRK3	E402_F410delinsV#
		NTRK3	G466_Y529delinsD#
		ACK1	P725L#
DAL		MCF-7	
MET	T1010I#	ALK	D1529E
LMTK2	L780M#	RON	R523Q#
ACK1	P725L#	ROR1	M518T
FAK	L926delinsPWRL#	LMTK2	L780M
		FYN	D506E#
		BMX	S254del#
DU-44-75			
HER3	S1119C#		
EPHA1	V900M		
MET	T1010I		
RON	R1335G#		
CCK4	P693L#		
FAK	T416fsX#		
FAK	926delinsPWRL#		

(cont. on next page)

63/306

Fig. 30 (continued)

Breast (cont.)

MDA-MB-157	
HER2	P1170A
EPHA2	M631T#
EPHA3	W924R
FGFR4	L136P
FLT3	M227T#
ROR1	M518T
NTRK3	E402_F410delinsV#
LMTK2	L780M#
TNK1	M598V
TXK	Y414fsX15#

MDA-MB-175-VII	
HER2	P1170A#
EPHA2	M631T#
ROR1	M518T
NTRK3	E402_F410delinsV#
NTRK3	R711_V712ins15#
VEGFR2	V297I
LMTK2	R828Q#
STYK1	G204S
TNK1	M598V

MDA-MB-231	
HER2	P1170A
EPHA1	V900M
MET	T1010I#
TXK	R336Q#

MDA-MB-361	
<u>EGFR</u>	T678M#
HER2	P1170A
FGFR4	G388R#
RON	R523Q
LMTK2	L780M
STYK1	G204S#
ACK1	P725L#
TYK2	E971fsX67#

MDA-MB-415	
HER2	P1170A
<u>EPHA5</u>	R981L
FGFR4	L136P
<u>MET</u>	D981_E1027del
ROR1	M518T
ROS1	C76_R77ins9#
NTRK3	R711_V712ins15#
AATYK	G600C
LMTK2	L780M
TYK2	E971fsX67#
TXK	Y414fsX15#

MDA-MB-435S	
HER3	S1119C#
EPHA3	W924R#
<u>EPHA4</u>	M877V#
RON	R523Q
ROR1	M518T#
RYK	N96S
NTRK3	R711_V712ins15#
<u>VEGFR1</u>	R781Q
STYK1	G204S#
TNK1	M598delinsEVERSHX
FAK	L926delinsPWRL#
PYK2	K838T#
FRK	G122R
TYK2	V362F
TYK2	I684S#
TYK2	P1104A#
FYN	D506E

MDA-MB-436	
EGFR	R521K
HER2	P1170A
FGFR1	DELTA28_V429#
FGFR2	H199_Q247delins48
RON	R1335G
RET	G691S#

(cont. on next page)

64/306

Fig. 30 (continued)

Breast (cont.)

MDA-MB-436 (cont.)

ROR1	M518T
RYK	N96S
NTRK1	H604Y#
NTRK1	G613V#
NTRK3	E402_F410delinsV#
NTRK3	R711_V712ins15#
VEGFR2	V297I#
VEGFR3	Q890H
STYK1	G204S#
<u>PYK2</u>	<u>C395Y</u>
PYK2	K838T
YES1	K113Q#

MDA-MB-453

<u>FGFR4</u>	<u>Y367C</u>
FGFR4	G388R
RON	R1335G#
ROR1	M518T
NTRK3	E402_F410delinsV#
NTRK3	R711_V712ins15#
LMTK2	L780M#
ACK1	P725L#
BMX	S254del#

MDA-MB-468

RON	R1335G
ROR1	M518T#
VEGFR2	V297I
TNK1	M598V
TXK	Y414fsX15#

SK-BR-3

MER	V870I#
FGFR4	G388R
RON	R1335G
NTRK3	E402_F410delinsV#
LMTK2	L780M
STYK1	G204S#

T-47D

HER2	P1170A
RON	R1335G#
ROR2	T245A
ROS1	D2213N#
ROS1	K2228Q#
ROS1	S2229C#
AATYK	G600C

ZR-75-1

TYRO3	I346N#
EGFR	R521K#
HER2	P1170A#
EPHA10	G749E
RON	R523Q#
RON	R627fsX5#
RON	R813delinsRQ#
RON	R1335G#
CCK4	E745D
ROR2	V819I
RYK	N96S
NTRK3	E402_F410delinsV#
AATYK	G600C
LMTK2	L780M#
STYK1	G204S#
ACK1	P725L#

ZR-75-30

MER	V870I#
RON	R813delinsRQ#
RON	R1335G
ROR1	M518T
STYK1	G204S
FAK	L926delinsPWRL#

(cont. on next page)

65/306

Fig. 30 (continued)

Cervix

A-431	
RON	R1335G
<u>CCK4</u>	<u>D106N#</u>
ROR1	M518T
ROS1	C76_R77ins9
AATYK	G600C
LMTK2	S910I#
STYK1	G204S#
ACK1	P725L#
JAK2	L393V
TNK1	M598V#

C-33A	
TYRO3	I346N#
<u>DDR1</u>	<u>R248W#</u>
HER2	P1170A
HER3	S1119C#
EPHA5	A672T#
FGFR2	H199_Q247delins48
RON	R1335G#
ROR1	M518T
ROR2	V819I#
ROS1	S1109L#
RYK	N96S
NTRK3	E402_F410delinsV#
STYK1	G204S#
<u>ARG</u>	<u>R668C#</u>
<u>TNK1</u>	<u>A299D</u>
<u>FAK</u>	<u>S329I#</u>
PYK2	G414V#
PYK2	K838T#
ZAP-70	K186fsX#

C-4II	
ALK	K1491R#
ALK	D1529E#
EGFR	R521K#
HER2	I655V#

C-4II	
HER2	P1170A#
HER3	S1119C#
RON	R523Q#
RON	R813delinsRQ#
RON	R1335G#
CCK4	T410S#
ROR1	M518T
ROR2	T245A
ROR2	V819I
LMTK2	L780M
STYK1	G204S
ACK1	P725L#
FRK	G122R
TYK2	V362F
TYK2	I684S

Ca Ski	
HER2	I655V#
HER2	P1170A
RON	R523Q
RON	R813delinsRQ#
ROR1	M518T
ROR2	T245A
ROR2	V819I
ROS1	D2213N#
ROS1	K2228Q#
ROS1	S2229C#
RYK	N96S
ACK1	P725L#
<u>FRK</u>	<u>R64Q#</u>
ZAP-70	P296_S301#

HeLa S3	
<u>EGFR</u>	<u>I646L#</u>
HER2	I655V#
HER2	P1170A#
<u>INSR</u>	<u>L991I</u>

(cont. on next page)

66/306

Fig. 30 (continued)

Cervix

HeLa S3 (cont.)		ME-180 (cont.)	
RON	N440S#	TYK2	V362F
RON	R523Q#	TYK2	I684S#
RON	R627fsX5#		
RON	R813delinsRQ#		MES-SA
RON	R1335G#	TYRO3	I346N#
ROR1	M518T	HER2	P1170A
ROR2	V819I	HER3	S1119C#
LMTK2	S910I#	FGFR2	H199_Q247delins48
STYK1	G204S#	RON	R813delinsRQ#
ZAP-70	P296_S301del#	ROR1	M518T
		ROS1	C76_R77ins9
	HT3	TEK1	V486I
ALK	K1491R#	ABL1	S991L#
ALK	D1529E#	TNK1	M598delinsEVERSHX
HER2	I655V#	PYK2	K838T#
HER2	P1170A	<u>SYK</u>	<u>A353T#</u>
RYK	N96S	ZAP-70	P296_S301del#
AATYK	F1163S#		
LMTK2	P30A#		MS 751
LMTK2	L780M#	ALK	K1491R#
STYK1	G204S#	ALK	D1529E#
TNK1	M598V	HER2	P1170A
PYK2	K838T	EPHA1	V900M#
TXK	Y414fsX15#	<u>EPHB6</u>	<u>G353_E471del#</u>
		FGFR4	G388R
	ME-180	RON	R523Q
TYRO3	I346N#	RON	R627fsX23#
HER2	I655V	RON	R813delinsRQ#
HER2	P1170A	CCK4	E745D#
RON	R523Q	ROR1	M518T
RON	R627fsX5#	LMTK2	L780M#
RON	R813delinsRQ#	RYK	N96S#
ROR2	T245A	AATYK	F1163S#
ROR2	V819I	STYK1	G204S#
LMTK2	L780M	<u>ARG</u>	<u>P665T#</u>
STYK1	G204S#	PYK2	K838T
ABL1	S991L#	TYK2	E971fsX67#
PYK2	K838T		

(cont. on next page)

67/306

Fig. 30 (continued)

Cervix (cont.)		COLO 320DM	
SiHa			
EGFR	R521K#	ALK	D1529E#
HER2	P1170A	TYRO3	I346N#
RON	R523Q	EGFR	R521K#
RON	R627fsX5#	HER2	P1170A
RON	R813delinsRQ#	EPHA3	R914H#
ROR1	M518T#	EPHA3	W924R
ROR2	V819I	ROR1	M518T
ROS1	R167Q	AATYK	G600C#
TNK1	D472_R473del	LMTK2	L780M#
PYK2	K838T	FAK	L926delinsPWRL#
FRK	G122R	PYK2	K838T
		<u>JAK1</u>	<u>R494C#</u>
		ZAP-70	P296_S301del#
SW-954		DLD-1	
HER2	P1170A#	ALK	K1491R
HER3	S1119C#	ALK	D1529E
RYK	N96S	EGFR	R521K#
LMTK2	L780M#	HER2	P1170A#
STYK1	G204S	<u>HER3</u>	<u>N126K#</u>
TNK1	M598V	<u>HER3</u>	<u>R667H#</u>
FES	DELS72_K129	HER3	S1119C#
TYK2	G363S#	<u>HER3</u>	<u>P1142H#</u>
ZAP-70	K186fsX#	EPHA2	R876H#
ZAP-70	P296_S301del#	EPHA10	G749E#
Colon		EPHB3	A517V#
CaCo2		<u>FGFR1</u>	<u>A268S</u>
EGFR	R521K#	RON	R813delinsRQ#
FGFR4	G388R	RON	R1335G#
RON	R813delinsRQ#	ROR1	M518T
RON	R1335G	<u>ROR1</u>	<u>S870I#</u>
ROR2	V819I	RYK	N96S
NTRK1	R780Q#	NTRK3	E402_F410delinsV#
AATYK	G600C	<u>VEGFR1</u>	<u>G203W</u>
LMTK2	L780M	AATYK	G600C
STYK1	G204S#	LMTK2	L780M
ACK1	P725L#	<u>LMTK2</u>	<u>L879M#</u>
PYK2	K838T	STYK1	G204S#
<u>JAK1</u>	<u>I363V</u>		
ZAP-70	P296_S301del#		

(cont. on next page)

68/306

Fig. 30 (continued)

Colon (cont.)

DLD-1 (cont.)

<u>CSK</u>	<u>Q26X#</u>
<u>FER</u>	<u>I240T#</u>
<u>FES</u>	<u>L690M#</u>
<u>FRK</u>	<u>G122R</u>
<u>FYN</u>	<u>E521K#</u>
<u>LCK</u>	<u>F151S#</u>
<u>SYK</u>	<u>A353T#</u>

HCT-15

<u>ALK</u>	<u>K1491R</u>
<u>ALK</u>	<u>D1529E</u>
<u>TYRO3</u>	<u>P822L#</u>
<u>EGFR</u>	<u>R521K#</u>
<u>HER2</u>	<u>P1170A#</u>
<u>HER3</u>	<u>N126K#</u>
<u>HER3</u>	<u>R667H#</u>
<u>HER3</u>	<u>P1142H#</u>
<u>EPHA2</u>	<u>R876H#</u>
<u>FGFR1</u>	<u>A268S</u>
<u>RON</u>	<u>R813delinsRQ#</u>
<u>RON</u>	<u>R1335G#</u>
<u>ROR1</u>	<u>M518T</u>
<u>ROR1</u>	<u>S870I#</u>
<u>RYK</u>	<u>N96S</u>
<u>NTRK3</u>	<u>E402_F410delinsV#</u>
<u>AATYK</u>	<u>G600C</u>
<u>LMTK2</u>	<u>L780M</u>
<u>STYK1</u>	<u>G204S#</u>
<u>ARG</u>	<u>Q994H#</u>
<u>CSK</u>	<u>Q26X#</u>
<u>FER</u>	<u>I240T#</u>
<u>FRK</u>	<u>G122R</u>
<u>JAK2</u>	<u>L383P#</u>
<u>FYN</u>	<u>E521K#</u>
<u>SYK</u>	<u>A353T#</u>

HCT-116

<u>AXL</u>	<u>M589K</u>
<u>TYRO3</u>	<u>I346N#</u>
<u>DDR2</u>	<u>M117I#</u>
<u>HER2</u>	<u>P1170A</u>
<u>EPHB6</u>	<u>A647V#</u>
<u>FGFR3</u>	<u>T311_Q422del11</u>
<u>FGFR4</u>	<u>L136P#</u>
<u>RON</u>	<u>R813delinsRQ#</u>
<u>ROR1</u>	<u>M518T#</u>
<u>ROR2</u>	<u>R302H#</u>
<u>NTRK3</u>	<u>E402_F410delinsV</u>
<u>NTRK3</u>	<u>A631fsX33#</u>
<u>VEGFR2</u>	<u>Q472H#</u>
<u>LMTK2</u>	<u>L780M#</u>
<u>ACK1</u>	<u>M393T#</u>
<u>TNK1</u>	<u>D472_R473del#</u>
<u>FES</u>	<u>E413fsX131</u>
<u>FRK</u>	<u>G122R#</u>
<u>TYK2</u>	<u>V362F#</u>
<u>TYK2</u>	<u>G363S#</u>
<u>TYK2</u>	<u>E971fsX67#</u>
<u>LCK</u>	<u>R484W#</u>
<u>ZAP-70</u>	<u>P296_S301del#</u>
<u>TXK</u>	<u>Y414fsX15#</u>

LoVo

<u>ALK</u>	<u>G1580V#</u>
<u>DDR1</u>	<u>V100A#</u>
<u>EGFR</u>	<u>R521K#</u>
<u>HER2</u>	<u>P1170A</u>
<u>EPHA1</u>	<u>A160V#</u>
<u>EPHA3</u>	<u>W924R</u>
<u>EPHA6</u>	<u>G513E#</u>
<u>FGFR2</u>	<u>H199_Q247delins48#</u>
<u>FGFR4</u>	<u>L136P</u>
<u>RON</u>	<u>R813delinsRQ#</u>

(cont. on next page)

69/306

Fig. 30 (continued)

Colon (cont.)

LoVo (cont.)

ROR1	M518T
ROS1	C76_R77ins9
TEK1	V600L
LMTK2	L780M#
FAK	.926delinsPWRL#
PYK2	K838T
FRK	G122R
TYK2	V362F#
TYK2	P1104A#
ZAP-70	P296_S301del#

LS-123

ALK	K1491R
ALK	D1529E
FGFR4	L136P#
MET	T1010I
RON	R813delinsRQ#
FLT3	M227T
CCK4	T410S#
ROR1	M518T
RYK	N96S
AATYK	G600C
LMTK2	L780M
PYK2	K838T
FES	E413fsX131
ZAP-70	P296_S301del#

LS-174T

ALK	K1491R#
ALK	D1529E#
EGFR	R521K#
HER2	P1170A
<u>EPHB3</u>	<u>P6del</u>
EPHB6	S309A#
FGFR4	V10I#
FGFR4	L136P#
RON	R523Q#
RON	R627fsX5#
RON	R813delinsRQ#
ROR1	M518T
RYK	N96S#

LS-174T (cont.)

TEK1	V600L
AATYK	G600C#
LMTK2	L780M#
<u>ABL1</u>	<u>G883fsX12#</u>
FAK	L926delinsPWRL#
PYK2	K838T
TYK2	V362F#
<u>LYN</u>	<u>F130V#</u>
<u>SYK</u>	<u>M34fsX3#</u>
ZAP-70	P296_S301del#

LS-180

ALK	K1491R#
ALK	D1529E#
EGFR	R521K#
HER2	P1170A
<u>EPHB3</u>	<u>P6del</u>
EPHB6	S309A#
FGFR2	H199_Q247delins48#
FGFR4	V10I#
FGFR4	L136P#
RON	R523Q
RON	R627fsX5#
RON	R813delinsRQ#
<u>ROR1</u>	<u>R185H#</u>
ROR1	M518T
RYK	N96S#
TEK1	V600L
<u>TEK1</u>	<u>A615T#</u>
AATYK	G600C#
LMTK2	L780M#
<u>ABL1</u>	<u>G883fsX12#</u>
FAK	L926delinsPWRL#
PYK2	K838T
TYK2	V362F#
<u>LYN</u>	<u>F130V#</u>
<u>SYK</u>	<u>M34fsX3#</u>

(cont. on next page)

70/306

Fig. 30 (continued)

Colon (cont.)

NCI-H498

EGFR	R521K#
HER2	I655V
HER2	P1170A
<u>EPHA2</u>	<u>H333R#</u>
RON	R627fsX5#
RON	R813insRQ#
ROR1	M518T
AATYK	F1163S
LMTK2	L780M#
FAK	L926delinsPWRL#
PYK2	K838T
FRK	G122R#
<u>JAK2</u>	<u>N1108S#</u>
TYK2	V362F#
TXK	R336Q#

SK-CO-1

ALK	D1529E
EGFR	R521K#
HER2	P1170A#
RON	R813insRQ#
ROR1	M518T
ROS1	R167Q
LMTK2	P30A#
<u>LMTK2</u>	<u>A1008V#</u>
TNK1	D472_R473del#
FAK	L926delinsPWRL#
PYK2	K838T

SNU-C2B

ALK	K1491R
ALK	D1529E
EGFR	R521K#
ROR1	M518T
TEK1	V600L

SW-48

TYRO3	I346N#
<u>EGFR</u>	<u>G719S#</u>
HER2	I655V#
<u>EPHB4</u>	<u>I610T#</u>
RON	R813insRQ#

SW-48 (cont.)

RON	R1335G#
ROR1	M518T#
<u>NTRK1</u>	<u>L585fsX73#</u>
AATYK	G600C#
LMTK2	L780M
STYK1	G204S#
<u>ACK1</u>	<u>R127H#</u>
ZAP-70	P296_S301Ddel#

SW-403

ALK	K1491R#
TYRO3	I346N#
HER2	P1170A#
FGFR4	G388R#
RON	R813insRQ#
RON	R1335G
AATYK	G600C#
LMTK2	L780M#
PYK2	K838T

SW-480

ALK	D1529E
HER2	P1170A
RON	R813insRQ#
RON	R1335G
ROR1	M518T
ROR2	T245A
ROR2	V819I#
LMTK2	L780M
ACK1	P725L
FAK	L926delinsPWRL#
PYK2	G414V
FRK	G122R
ZAP-70	P296_S301del#

SW-620

ALK	D1529E
HER2	P1170A
RON	R813insRQ#
RON	R1335G#
ROR1	M518T

(cont. on next page)

71/306

Fig. 30 (continued)

Colon (cont.)

SW-620 (cont.)

LMTK2	L780M#
ACK1	P725L
FAK	L926delinsPWRL#
PYK2	G414V
FRK	G122R
ZAP-70	P296_S301del#

SW-837

ALK	K1491R
ALK	D1529E
EGFR	R521K#
HER2	P1170A
FGFR4	L136P
LMTK2	L780M
PYK2	K838T
FER	Q526L#
TYK2	I684S
TYK2	E971fsX67#
YES1	K113Q
TXK	R336Q#

SW-948

ALK	K1491R#
EGFR	R521K#
HER2	I655V
HER2	P1170A
EPHB6	S785R
RON	R813insRQ#
ROR1	M518T
TNK1	M598V
FAK	.926delinsPWRL#
PYK2	K838T
FRK	G122R#
FRK	R406H#

SW-1116

no genetic
alteration identified

SW-1417

ALK	D1529E
HER2	P1170A
HER3	S1119C#
RON	R1335G#
FLT3	M227T
ROR1	M518T#
TXK	Y414fsX15#

SW-1463

HER2	I655V#
HER2	P1170A
EPHA10	G749E#
RON	R523Q
RON	R813insRQ#
RON	R1335G
CCK4	A777V#
ROR1	M518T#
STYK1	G204S
ACK1	P725L#
TNK1	M598V
PYK2	K838T
FRK	G122R#

T-84

HER2	P1170A
ROS1	D709fsX16#
NTRK2	A647fsX54#
LMTK2	L780M
STYK1	G204S#
FRK	G122R

WiDr

EPHA2	E911K#
RON	R523Q#
RON	Y884_Q932del14
RON	R1335G
ROR1	M518T#
ROS1	Q865fsX90#
LMTK2	L780M#
STYK1	G204S#
FAK	L926delinsPWRL#
TYK2	E971fsX67#
TXK	R336Q#

(cont. on next page)

72/306

Fig. 30 (continued)

Endometrium and Placenta

JAR	
TYRO3	I346N#
HER2	P1170A#
HER3	S1119C#
EPHA1	V900M#
FGFR4	V10I#
RON	R523Q#
RON	R627fsX5#
RON	R813delinsRQ#
RON	R1335G#
PDGFRB	T464M#
ROR1	M518T#
ROR2	T245A
ROR2	P548S#
ROR2	V819I
VEGFR3	Q890H#
LMTK2	L780M#
TNK1	M598V
FAK	L926delinsPWRL#
TYK2	E971fsX67#
FYN	D506E#

KLE	
TYRO3	I346N
HER2	I655V
EPHA3	W924R
FGFR2	H199_Q247delins48
RON	R813delinsRQ#
RON	R1335G
FLT3	M227T
ROR1	M518T
RYK	N96S
VEGFR2	Q472H#
LMTK2	L780M#
TYK2	I684S
ZAP-70	P296_S301del#

RL95-2	
MER	V870I#
TYRO3	I346N#
<u>EGFR</u>	<u>A289V#</u>
EGFR	R521K#
<u>HER2</u>	<u>G518E#</u>

RL95-2	
HER2	P1170A
<u>EPHA2</u>	<u>R950W#</u>
RON	R813delinsRQ#
RON	R1335G
FLT3	M227T#
RET	G691S#
ROR1	M518T
LMTK2	L780M
STYK1	G204S#
PYK2	K838T#
FRK	G122R
<u>JAK2</u>	<u>F85S#</u>
<u>BTK</u>	<u>M489I</u>

Head and Neck

FaDu	
EGFR	R521K#
HER2	P1170A
AATYK	G600C
STYK1	G204S#
TNK1	M598V#

HLaC-78	
EGFR	R521K#
HER2	P1170A#
ROR1	M518T
ROR2	T245A
ROR2	V819I
LMTK2	L780M#
<u>LMTK2</u>	<u>D793G#</u>
ACK1	P725L#
PYK2	K838T#

HLaC-79	
HER2	P1170A#
<u>INSR</u>	<u>L991I</u>
RON	N440S
RON	R813delinsRQ#
RON	R1335G#
ROR1	M518T#

(cont. on next page)

73/306

Fig. 30 (continued)

Head and Neck (cont.)

HLaC-79 (cont.)		SCC-15 (cont.)	
ROR2	V819I	AATYK	G600C#
LMTK2	S910I#	LMTK2	L780M#
STYK1	G204S#	FRK	G122R#
SCC-4		SCC-25	
ALK	K1491R#	ALK	D1529E#
ALK	D1529E#	TYRO3	I346N
EGFR	R521K#	EGFR	R521K#
EPHB4	E890D#	HER2	P1170A#
FGFR4	G388R	RON	R627fsX5#
RON	R1335G	RON	R813delinsRQ#
ROR1	M518T	RON	R1335G
ROS1	C76_R77ins9#	ROR1	M518T
SCC-9		LMTK2	L780M#
ALK	D1529E#	STYK1	G204S#
HER2	P1170A	ACK1	P725L#
EPHA5	N81T#	FRK	G122R#
ROS1	C76_R77ins9#	UM-SCC-10A	
NTRK1	R780Q#	ALK	K1491R#
AATYK	G600C#	HER2	P1170A
STYK1	G204S#	EPHA3	W924R#
PYK2	K838T	EPHB2	R270Q#
FRK	G122R	RET	G691S#
BMX	S254del#	ROR1	M518T
SCC-15		NTRK3	E402_F410delinsV#
ALK	D1529E	ROS1	S1109L#
EGFR	R521K#	LMTK2	L780M
HER2	P1170A	PYK2	K838T
EPHA3	R914H#	FRK	G122R#
EPHA3	W924R#	JAK3	V722I#
EPHA7	I138V#	TXK	R336Q#
MET	N375S#	UM-SCC-10B	
RON	R813delinsRQ#	ALK	K1491R#
RON	R1335G	HER2	P1170A
CCK4	T410S	EPHA3	W924R
ROR1	M518T	EPHB2	R270Q#
ROS1	D2213N#	RET	G691S
ROS1	K2228Q#	ROR1	M518T
ROS1	S2229C#	NTRK3	E402_F410delinsV#

(cont. on next page)

74/306

Fig. 30 (continued)

Head and Neck (cont.)

UM-SCC-10B (cont.)

NTRK3	R711_V712 ins14#
ROS1	S1109L#
LMTK2	L780M
PYK2	K838T
FRK	G122R#
JAK3	V722I#
TXK	R336Q#

UM-SCC-17A

EGFR	R521K#
HER2	P1170A
HER3	L1177I#
EPHB2	S98R#
RON	R813delinsRQ#
RON	Y884_Q932del#
RON	R1335G#
RET	G691S#
AATYK	G600C#
LMTK2	L780M
STYK1	G204S#
ACK1	P725L#
PYK2	K838T#
FRK	G122R#

UM-SCC-17B

EGFR	N115K#
EGFR	R521K#
HER2	P1170A
HER3	L1177I#
EPHA5	N81T
EPHB2	S98R#
RON	R627fsX5#
RON	Y884_Q932del#
RON	R1335G#
RET	G691S#
AATYK	G600C
LMTK2	L780M
STYK1	G204S#
ACK1	P725L
FRK	G122R#

UM-SCC-22A

TYRO3	I346N#
EGFR	R521K#
HER2	P1170A#
EPHA5	N81T#
FGFR4	G388-R
RON	R813delinsRQ#
RET	G691S#
ROR2	V819I
ROS1	C76_R77ins9
AATYK	G600C#
LMTK2	L780M
PYK2	K838T
TXK	R336Q#

UM-SCC-22B

TYRO3	I346N#
EGFR	R521K#
HER2	P1170A#
EPHA5	N81T#
FGFR4	G388R
RON	R813delinsRQ#
RET	G691S#
ROR2	V819I
AATYK	G600C#
LMTK2	L780M
PYK2	K838T
TXK	R336Q#

Hematopoietic and Lymphoid System

Daudi

ALK	D1529E
MER	V870I#
HER2	R1161Q#
EPHA3	W924R
RON	R523Q
RON	R813delinsRQ#
FLT3	M227T
FLT3	G757E

(cont. on next page)

75/306

Fig. 30 (continued)

Hematopoietic and Lymphoid System

Daudi (cont.)

RET	G691S#
ROR1	M518T
NTRK3	E402_F410delinsV#
LMTK2	L780M#
ABL1	S991L#
TNK1	M598V#
FAK	L926delinsPWRL#
PYK2	K838T#
JAK3	G62fsX44#
ZAP-70	K186fsX#
ZAP-70	P296_S301del#

EM-2

ALK	D1529E
MER	V870I#
TYRO3	I346N#
HER2	P1170A#
EPHB4	E890D#
FGFR4	G388R
RON	R523Q#
RON	R1335G#
FLT3	M227T
ROS1	C76_R77ins9#
LMTK2	L780M#
STYK1	G204S#
ACK1	P725L#
PYK2	V739_R780del
TYK2	V362F#
<u>ZAP-70</u>	<u>M549V#</u>
TXK	Y414fsX15#

HL-60

ALK	D1529E
HER2	P1170A#
FGFR4	L136P
RYK	N96S
LMTK2	L780M#
TNK1	M598delinsEVERSHX#
PYK2	V739_R780del
PYK2	K838T#
TYK2	V362F#
TYK2	I684S#
TXK	Y414fsX15#

IM-9

TYRO3	I346N#
HER2	P1170A
EPHA3	R914H#
EPHA3	W924R#
RON	R523Q
RON	R813delinsRQ#
RON	R1335G#
FLT3	M227T#
ROR1	M518T
<u>NTRK2</u>	<u>A647fsX54#</u>
NTRK3	E402_F410delinsV
NTRK3	R711_V712ins14#
LMTK2	P30A#
ACK1	P725L#
ACK1	R1038H#
TNK1	M598delinsEVERSHX#
PYK2	V739_R780del
FRK	G122R#
TYK2	V362F#
TYK2	P1104A#

Jurkat

ALK	K1491R
ALK	D1529E
MER	V870I#
HER2	P1170A
EPHA5	N81T#
<u>EPHB6</u>	<u>A369T</u>
<u>CCK4</u>	<u>Q913H#</u>
RYK	N96S
NTRK3	E402_F410delinsV#
<u>VEGFR1</u>	<u>A673V#</u>
VEGFR1	M938V#
LMTK2	L780M#
ACK1	S699N#
ACK1	P725L#
FAK	L926delinsPWRL#
PYK2	V739_R780del#
PYK2	K838T#
<u>FES</u>	<u>V724M#</u>
SYK	M34fsX3

(cont. on next page)

76/306

Fig. 30 (continued)

Hematopoietic and Lymphoid System

Jurkat (cont.)		KG 1	
<u>ZAP-70</u>	T155M#	ALK	D1529E
<u>ITK</u>	R448H#	TYRO3	I346N#
<u>TEC</u>	W531R	<u>EPHA2</u>	V747I#
		EPHB6	S309A
		FGFR1	V427_T428del#
		FGFR2	H199_Q247delins48
		RON	R627fsX5#
		FLT3	M227T
		FLT3	V557I
		ROR1	M518T
		ROS1	S1109L
		RYK	N96S
		STYK1	G204S
		FAK	L926delinsPWRL#
		PYK2	V739_R780del#
		<u>SYK</u>	I262L#
		ZAP-70	P296_S301del#
K-562		M-07e	
HER3	R611W#	ALK	K1491R#
EPHA1	V900M#	TYRO3	I346N#
FGFR4	L136P#	HER2	P1170A#
RON	R813delinsRQ#	RON	R1335G#
ROR1	M518T#	CSF1R	H362R#
ROS1	S1109L	STYK1	G204S#
RYK	N96S	ACK1	P725L#
NTRK3	402_F410delinsV#	TNK1	M598V
NTRK3	R711_V712ins14#	TNK1	M598delinsEVERSHX
LMTK2	L780M	PYK2	K838T#
<u>LMTK2</u>	D793G#	FES	M323V#
STYK1	G204S	TYK2	G363S#
PYK2	K838T#	ZAP-70	P296_S301del#
TYK2	V362F#	TXK	Y414fsX15#
TXK	Y414fsX15#		
KASUMI-1		MEG-01	
HER2	P1170A#	CSF1R	H362R
<u>IGF1R</u>	T104M#	NTRK3	E402_F410delinsV
RON	R523Q#	VEGFR2	Q472H
RON	R627fsX5#	VEGFR3	Q890H
RON	R813delinsRQ#	TNK1	M598delinsEVERSHX
CSF1R	H362R#	FAK	L926delinsPWRL#
FLT3	M227T		
<u>KIT</u>	N822K#		
RET	D489N#		
RYK	N96S#		
PYK2	K838T#		
TYK2	V362F		
<u>TYK2</u>	R701T#		
ZAP-70	P296_S301#		
TXK	Y414fsX15#		

(cont. on next page)

77/306

Fig. 30 (continued)

Hematopoietic and Lymphoid System (cont.)

MEG-01 (cont.)

PYK2	K838T#
FRK	G122R#
TYK2	V362F
TXK	Y414fsX15#

MOLM1

HER2	P1170A#
CSF1R	H362R
ROR1	M518T
AATYK	G600C#
TNK1	M598delinsEVERSHX#
PYK2	V739_R780del#
TXK	Y414fsX15#

Mono-Mac-1

TYRO3	I346N#
HER2	P1170A
FGFR4	G388R#
RON	R813delinsRQ#
CSF1R	H362R#
FLT3	V194M#
FLT3	M227T
FLT3	V592A#
ROR2	T245A
ROR2	V819I
TEK1	V600L#
LMTK2	L780M#
ACK1	P725L#
PYK2	V739_R780del
PYK2	K838T#
TYK2	V362F
TYK2	G363S#
TYK2	P1104A#
ZAP-70	K186fsX#

Mono-Mac-6

TYRO3	I346N#
HER2	P1170A
FGFR4	G388R#
RON	R813delinsRQ#
CSF1R	H362R#

Mono-Mac-6 (cont.)

FLT3	M227T
FLT3	V592A
ROR2	T245A
ROR2	V819I
ROS1	C76_R77ins9#
TEK1	V600L#
AATYK	G600C#
LMTK2	L780M
ACK1	P725L#
TNK1	M598delinsEVERSHX#
PYK2	V739_R780del#
PYK2	K838T#
TYK2	V362F
TYK2	G363S#
TYK2	P1104A#
ZAP-70	K186fsX#

MV4-11

HER2	P1170A#
RON	R627fsX5#
FLT3	M227T
RET	G691S#
NTRK3	E402_F410delinsV#
NTRK3	R711_V712ins14#
STYK1	G204S#
ACK1	P725L#
TNK1	M598delinsEVERSHX#
FAK	L926delinsPWRL#
PYK2	V739_R780del
PYK2	K838T#

NB-4

MER	V870I#
HER2	P1170A
ROR2	V819I#
ROS1	T145P
ROS1	S1109L
LMTK2	L780M#
STYK1	G204S#
ACK1	P725L#
TNK1	M598delinsEVERSHX
PYK2	V739 R780del#

(cont. on next page)

78/306

Fig. 30 (continued)

Hematopoietic and Lymphoid System (cont.)

NB-4 (cont.)		Raji	
PYK2	K838T#	HER2	P1170A
TYK2	V362F#	EPHA1	A160V#
TXK	Y414fsX15#	EPHA1	V900M#
OCI-AML5		EPHB4	E890D#
TYRO3	I346N	RON	R1335G#
HER2	P1170A	FLT3	M227T
FGFR4	V10I#	RYK	N96S
RON	R1335G#	NTRK3	R711_V712ins14#
ROR1	M518T	LMTK2	L780M
ROR2	V819I	ACK1	R1038H#
ROS1	T145P	TNK1	598delinsEVERSHX
ROS1	S1109L#	PYK2	S9I
ROS1	D2213N#	PYK2	V739_R780del#
ROS1	K2228Q#	PYK2	K838T
ROS1	S2229C#	FES	S72_K129del
RYK	N96S	JAK3	M511I#
NTRK3	E402_F410delinsV#	TYK2	V362F#
NTRK3	R711_V712ins14#	TYK2	P1104A#
AATYK	F1163S	ZAP-70	K186fsX#
TNK1	M598delinsEVERSHX#	ZAP-70	P296_S301del#
PYK2	V739_R780del	RF-1	
TYK2	V362F#	ALK	K1491R#
TYK2	P1104A#	HER2	P1170A#
PLB-985		FGFR1	G539_K540del#
ALK	D1529E	RON	R1335G#
HER2	P1170A#	FLT3	M227T#
FGFR4	L136P	ROR1	M518T
RYK	N96S	ROS1	T145P
NTRK3	R711_V712ins14	ROS1	I537M#
AATYK	G600C#	ROS1	D2213N#
LMTK2	L780M#	ROS1	K2228Q#
TNK1	M598delinsEVERSHX#	ROS1	S2229C#
PYK2	V739_R780del#	LMTK2	L780M
PYK2	K838T#	FAK	L926delinsPWRL
TYK2	V362F#	PYK2	V739_R780del
TYK2	I684S#	TYK2	V362F#
TXK	Y414fsX15#	TYK2	I684S#
		ZAP-70	P296_S301del#

(cont. on next page)

79/306

Fig. 30 (continued)

Hematopoietic and Lymphoid System (cont.)

RF-48		U-266	
ALK	K1491R#	EPHA3	W924R
HER2	P1170A#	FGFR4	L136P
<u>FGFR1</u>	<u>G539_K540del#</u>	MET	T1010I
FLT3	M227T#	RON	R813delinsRQ#
ROR1	M518T	RON	R1335G#
ROS1	I537M#	ROR2	V819I
ROS1	D2213N#	AATYK	G600C
ROS1	K2228Q#	LMTK2	L780M
ROS1	S2229C#	ACK1	P725L#
LMTK2	L780M	PYK2	V739_R780del#
TNK1	M598delinsEVERSHX#	PYK2	K838T
FAK	L926delinsPWRL	FES	E413fsX131#
PYK2	V739_R780del	FRK	G122R#
TYK2	V362F#	TYK2	G363S#
TYK2	I684S#	ZAP-70	K186fsX#
		ZAP-70	P296_S301del#
TF-1		U-937	
HER2	P1170A#	EPHA1	V900M#
EPHA7	I138V#	FGFR2	M71T#
RON	R523Q	RON	R523Q#
RON	R627fsX5#	CCK4	P693L#
ROR1	M518T#	NTRK3 4	02_F410delinsV#
ROR2	V819I	STYK1	G204S#
<u>RYK</u>	<u>A559T#</u>	ACK1	R1038H#
NTRK3	E402_F410delinsV#	PYK2	K838T#
NTRK3	R711_V712ins14#		
LMTK2	P30A#	Kidney	
STYK1	G204S#	769-p	
TNK1	M598delinsEVERSHX#	EGFR	R521K#
PYK2	K838T#	HER2	P1170A#
ZAP-70	P296_S301del#	FGFR2	H199_Q247delins48
THP-1		FGFR4	L136P
ALK	K1491R#	FLT3	M227T
ALK	D1529E	ROR1	M518T#
<u>TYRO3</u>	<u>N788T#</u>	<u>ROS1</u>	<u>R187M</u>
PDGFRB	P345S#	NTRK3	R711_V712ins14
TNK1	M598V	LMTK2	L780M
PYK2	V739_R780del	TNK1	M598delinsEVERSHX#
PYK2	K838T#	FAK	L926delinsPWRL#
FES	S72_K129del	PYK2	K838T#
<u>JAK3</u>	<u>G62fsX44#</u>	TYK2	V362F#

(cont. on next page)

80/306

Fig. 30 (continued)

Kidney (cont.)

769-p (cont.)		A-498 (cont.)	
TYK2	G363S#	AATYK	G600C
YES1	K113Q#	LMTK2	L780M#
TXK	Y414fsX15#	ACK1	S985N
786-0		TNK1	D472_R473DEL#
HER2	I655V#	FAK	L926delinsPWRL#
HER2	P1170A	FES	E413fsX131
FGFR2	H199_Q247delins48	FRK	G122R
FGFR4	V10I	TYK2	V362F#
RON	R523Q	TYK2	P1104A#
ROR1	M518T	SYK	R520S#
ROR2	T245A	ZAP-70	P296_S301DEL#
ROR2	V819I	A-704	
RYK	N96S	TYRO3	I346N#
NTRK3	E402_F410delinsV#	EGFR	R521K#
AATYK	G600C#	HER2	I655V#
LMTK2	L780M	HER3	S1119C#
STYK1	G204S	EPHA3	W924R#
TNK1	M598delinsEVERSHX#	EPHB4	I610T#
PYK2	K838T	FGFR4	G388R#
TYK2	V362F#	RON	R523Q#
TYK2	I684S#	RON	R813delinsRQ#
TXK	Y414fsX15DEL#	RON	R1335G#
A-498		ROR1	M518T#
ALK	K1491R#	ROR2	T245A
ALK	D1529E#	ROR2	V819I#
TYRO3	I346N#	ROS1	C76_R77ins9
EGFR	R521K#	NTRK1	L585fsX73#
HER2	P1170A	AATYK	G600C#
EPHA3	W924R	LMTK2	L780M#
FGFR2	H199_Q247delins48	STYK1	G204S#
FGFR2	I526T#	ARG	V345A#
RON	R523Q	FES	E413fsX131#
RON	R627fsX5#	ZAP-70	P296_S301DEL#
RON	R813delinsRQ#	ACHN	
ROR1	M518T	ALK	D1529E#
ROS1	C76_R77ins9	EGFR	R521K#
RYK	N96S	HER2	I655V
NTRK3	R711_V712ins14#	HER2	P1170A
		EPHA1	V900M#

(cont. on next page)

81/306

Fig. 30 (continued)

Kidney (cont.)

ACHN (cont.)	
EPHA2	P460L
FGFR2	H199_Q247delins48
FGFR4	G388R
RON	R813delinsRQ#
RON	R1335G
FLT3	M227T
ROR1	M518T
RYK	N96S
NTRK3	E402_F410delinsV#
VEGFR3	Q890H#
LMTK2	L780M
ZAP-70	P296_S301DEL#

Caki-1	
MER	V870I#
EGFR	R521K#
HER2	P1170A#
FGFR2	199_Q247delins48
FGFR4	L136P#
MET	V1238I
RON	R1335G
ROR1	M518T#
ROS1	C76_R77ins9#
RYK	N96S
TEK1	V600L
NTRK3	R711_V712ins14#
AATYK	G600C#
AATYK	F1163S
LMTK2	L780M
ACK1	P725L#
PYK2	K838T
TYK2	V362F#
ZAP-70	K186fsX#
ZAP-70	P296_S301DEL#

CAKI-2	
ALK	D1529E#
EGFR	R521K
HER2	P1170A
FGFR2	H199_Q247delins48
FGFR4	G388R#
RON	R627fsX5#

CAKI-2 (cont.)	
RON	R1335G
FLT3	M227T
ROR1	M518T
ROR2	T245A
ROR2	V819I
RYK	N96S
TEK1	V600L
NTRK3	E402_F410delinsV#
LMTK2	L780M#
ARG	K450R#
ACK1	P725L
PYK2	K838T
TYK2	V 362 F#
ZAP-70	P296_S301DEL#

G401	
DDR1	R60C#
EGFR	R521K#
HER2	P1170A#
RYK	N96S
NTRK1	H604Y#
NTRK1	G613V#
NTRK3	E402_F410delinsV#
AATYK	G600C
AATYK	F1163S#
LMTK2	L780M#
ABL1	S991L#
TNK1	M598delinsEVERSHX
PYK2	K838T
FES	S72_K129DEL
TYK2	V362F#
BMX	S254DEL#

SW-13	
MER	V870I#
HER2	P1170A
FGFR4	L136P#
FLT3	M227T
ROR2	T245A
ROR2	V819I
RYK	N96S
NTRK3	E402_F410delinsV#

(cont. on next page)

82/306

Fig. 30 (continued)

SW-13		Hu-H7	
VEGFR3	Q890H#	ALK	K1491R#
AATYK	G600C#	EGFR	R521K#
AATYK	F1163S	HER2	P1170A
LMTK2	L780M	FGFR2	H199_Q247delins48
ACK1	P725L	FGFR4	G388R
TNK1	M598delinsEVERSHX	RON	R813delinsRQ#
ZAP-70	K186fsX#	RET	G691S#
ZAP-70	P296_S301DEL#	AATYK	G600C
Liver		LMTK2	P30A#
HepG-2		STYK1	G204S#
ALK	K1491R#	TNK1	M598V
EGFR	R521K#	PYK2	K838T
HER2	P1170A#	ZAP-70	K186fsX#
EPHB4	P231S#	SK-HEP-1	
FGFR4	G388R	ALK	K1491R
ROR1	M518T	ALK	D1529E#
AATYK	G600C#	HER2	P1170A#
LMTK2	L780M#	EPHA10	G749E
TNK1	M598delinsEVERSHX	FGFR4	L136P
PYK2	V739_R780DEL	RON	R1335G#
PYK2	K838T#	ROR1	M518T#
TYK2	V362F#	ROR2	T245A
TYK2	I684S#	ROR2	V819I
ZAP-70	K186fsX#	NTRK1	H604Y#
HS 817.T		NTRK1	G613V#
TYRO3	I346N#	NTRK3	E402_F410delinsV#
HER2	P1170A#	AATYK	G600C#
EPHA10	L629P#	LMTK2	L780M#
EPHA10	V645I#	STYK1	G204S#
EPHB1	A39V#	ACK1	P725L
IGF1R	Y201H#	Lung	
RON	R813delinsRQ#	A-427	
RON	Y884_Q932DEL	MER	V870I
RON	R1335G	TYRO3	S324C#
RYK	N96S	TYRO3	I346N#
STYK1	G204S	EGFR	R521K#
FAK	L926delinsPWRL#	HER2	P1170A#
FRK	G122R	EPHA3	W924R#
TXK	R336Q#	RON	R813delinsRQ#
		FLT3	M227T

(cont. on next page)

83/306

Fig. 30 (continued)

Lung (cont.)

A-427 (cont.)		Calu-1 (cont.)	
RET	G691S#	ROS1	T145P
RYK	N96S	ROS1	S1119L
VEGFR3	Q890H#	ROS1	D2213N#
AATYK	G600C#	ROS1	K2228Q#
AATYK	T1227M#	ROS1	S2229C#
ACK1	P725L	RYK	N96S
FAK	L926delinsPWRL#	NTRK1	H604Y#
PYK2	K838T#	NTRK1	G613V#
		NTRK3	E402_F410delinsV#
		AATYK	G600C
		AATYK	F1163S#
		ARG	K959R#
		ACK1	P725L#
		PYK2	K838T
		TYK2	V362F#
A-549		Calu-3	
EGFR	R521K#	AXL	G835V
HER2	P1170A#	TYRO3	I346N#
EPHA10	G749E	EGFR	R521K
FGFR2	H199_Q247delins48	RON	R813delinsRQ#
FGFR4	G388R#	CCK4	A777V#
RON	R813delinsRQ#	ROS1	C76_R77ins9#
RON	R1335G	LMTK2	L780M
RET	G691S#	STYK1	G204S#
ROR1	M518T	FAK	L926delinsPWRL#
ROR2	V819I	TYK2	V362F#
ROS1	C76_R77ins9#	TYK2	P1104A#
ROS1	D2213N#		
ROS1	K2228Q#		
ROS1	S2229C#		
RYK	N96S		
NTRK3	E402_F410delinsV#		
VEGFR3	Q890H#		
AATYK	G600C		
AATYK	F1163S		
STYK1	G204S		
FAK	L926delinsPWRL#		
PYK2	K838T#		
FRK	G122R#		
Calu-1		Calu-6	
HER2	P1170A	ALK	D1529E#
RON	R813delinsRQ#	TYRO3	I346N
CSF1R	H362R#	HER2	P1170A
PDGFRB	P345S#	EPHB6	G107S#
ROR1	M518T#	FGFR2	H199_Q247delins48
ROR2	V819I	FGFR4	G388R
ROS1	C76_R77ins9#	RON	R1335G
		RET	G691S#
		ROR1	M518T
		ROR2	T245A
		STYK1	G204S

(cont. on next page)

84/306

Fig. 30 (continued)

Lung (cont.)

Calu-6 (cont.)		NCI-H128	
ACK1	P725L#	TYRO3	I346N
TNK1	M598delinsEVERSHX#	HER3	S1119C#
FAK	T416fsX#	FGFR4	L136P
FAK	L926delinsPWRL#	RON	R1335G
		ROR1	M518T
		ROR2	V819I
		ROS	S1109L
		NTRK3	E402_F410delinsV#
		AATYK	T1227M
		LMTK2	L780M#
		TNK1	M598EVERSHIins#
		FAK	T416fsX#
		FAK	L926delinsPWRL#
		PYK2	K838T#
		JAK2	A377E#
		ZAP-70	K186fsX#
NCI-H69		NCI-H146	
ALK	D1529E	TYRO3	I346N
HER2	P1170A	EPHA3	W924R#
FGFR4	L136P	FGFR4	G388R
MET	R988C#	RYK	N96S
RON	R813delinsRQ#	NTRK3	E402_F410delinsV#
RET	G691S	AATYK	G600C
ROR1	M518T	AATYK	F1163S
ROR2	C389R#	LMTK2	L780M
ROR2	V819I	ACK1	P725L
RYK	N96S	FAK	T416fsX#
NTRK2	A586V#	PYK2	K838T#
AATYK	F1163S#	TYK2	A53T#
AATYK	F1195C#	TYK2	V362F#
LMTK2	L780M#		
TNK1	D472_R473del		
PYK2	K838T		
NCI-H82		NCI-H209	
HER2	P1170A	ALK	K1491R#
EPHA3	W924R#	ALK	D1529E
FGFR2	H199_Q247delins48	HER2	I655V
FGFR4	G388R	RON	R813delinsRQ#
RON	R1335G#	RON	R1335G
NTRK1	R748W	ROR1	M518T
NTRK3	E402_F410delinsV	NTRK1	H604Y
LMTK2	L780M#	NTRK1	G613V
STYK1	G204S#		
ARG	K930R#		
FAK	T416fsX#		
FAK	L926delinsPWRL#		
FRK	G122R		

(cont. on next page)

85/306

Fig. 30 (continued)

NCI-H209 (cont.)		NCI-H441	
NTRK3	E402_F410delinsV#	EGFR	R521K#
STYK1	G204S#	HER2	P1170A
ACK1	P725L	HER3	S1119C
FAK	T416fsX#	<u>EPHA2</u>	<u>R315Q#</u>
TXK	Y414fsX15#	EPHA2	Q391R#
		EPHA10	G749E
		RON	R813delinsRQ#
		RON	R1335G
		<u>FLT3</u>	<u>V592A#</u>
		ROR1	M518T
		ROS1	K2228Q#
		ROS1	S2229C#
		RYK	N96S#
		VEGFR2	V297I#
		VEGFR2	Q472H#
		PYK2	K838T#
NCI-H292		NCI-H446	
ALK	K1491R#	ALK	D1529E
ALK	D1529E	HER2	I655V
HER2	P1170A#	HER2	P1170A#
EPHA1	A160V#	FGFR2	H199_Q247delins48
RON	R627fsX5#	FGFR4	L136P
RON	R813delinsRQ#	CCK4	E745D#
RON	R1335G#	RYK	N96S
CCK4	A777V#	NTRK3	E402_F410delinsV#
ROR1	M518T#	VEGFR3	Q890H
RYK	N96S	AATYK	G600C
VEGFR2	V297I#	LMTK2	L780M#
LMTK2	P30A#	ACK1	P725L#
<u>LMTK2</u>	<u>Q238P#</u>	TNK1	D472_R473del
TNK1	M598V#	FAK	T416fsX#
JAK3	P132T	FAK	L926delinsPWRL#
		PYK2	K838T
		ZAP-70	K186fsX#
		BMX	S254DEL#
NCI-H345		NCI-H460	
ALK	D1529E#	TYRO3	I346N
HER2	I655V	HER2	I655V#
HER2	P1170A	HER2	P1170A
EPHA2	R876H#	EPHA3	W924R#
<u>EPHB1</u>	<u>I837M</u>	FGFR4	G388R
<u>EPHB2</u>	<u>V762L#</u>		
<u>FGFR1</u>	<u>G539 K540del#</u>		
FGFR4	G388R#		
RON	R813delinsRQ#		
ROR1	M518T#		
NTRK3	402_F410delinsV#		
VEGFR3	Q890H#		
AATYK	F1163S		
LMTK2	L780M#		
TNK1	38delinsEVERSHX#		
FAK	T416fsX#		
FAK	926delinsPWRL#		
PYK2	K838T		

(cont. on next page)

86/306

Fig. 30 (continued)

NCI-H460 (cont.)		NCI-H520 (cont.)	
RON	R813delinsRQ#	LMTK2	L780M
ROR1	M518T	TYK2	V362F#
RYK	N96S	FYN	D506E#
NTRK3	E402_F410delinsV#	NCI-H596	
VEGFR3	Q890H#	ALK	K1491R#
AATYK	G600C	ALK	D1529E
LMTK2	L780M#	HER2	P1170A
PTK-9	K265R#	FGFR2	99_Q247delins48#
ARG	K930R#	<u>MET</u>	<u>D981_E1027del</u>
FAK	L926delinsPWRL#	RON	R523Q#
PYK2	K838T	RON	R627fsX5#
FRK	G122R	RON	R813delinsRQ#
NCI-H510A		ROR2	V819I
EGFR	R521K#	ROS1	K2228Q#
HER2	P1170A	ROS1	S2229C#
EPHA10	G749E#	RYK	N96S
RON	R627fsX5#	VEGFR2	V297I#
CCK4	E745D#	PYK2	K838T
ROR1	M518T	FES	S72_K129del
ROR2	V819I	<u>JAK2</u>	<u>N1108S#</u>
NTRK1	H604Y#	TYK2	V362F#
NTRK1	G613V#	NCI-H661	
NTRK3	E402_F410delinsV#	ALK	K1491R#
NTRK3	G466_Y529delinsD#	HER2	P1170A#
LMTK2	L780M#	EPHA10	L629P#
STYK1	G204S#	FGFR2	H199_Q247delins48
FAK	T416fsX#	FGFR4	L136P
TYK2	E971fsX67#	RON	R813delinsRQ#
NCI-H520		RON	R1335G
HER2	P1170A	RET	G691S
EPHA3	W924R#	ROR1	M518T#
RON	R813delinsRQ#	ROR2	T245A
RON	R1335G	<u>ROR2</u>	<u>D390fsX44#</u>
CCK4	A777V	ROS1	C76_R77ins9
RET	G691S#	ROS1	S1109L
ROR2	V819I	<u>ROS1</u>	<u>A1443S</u>
RYK	N96S	RYK	N96S
NTRK3	E402_F410delinsV#	NTRK3	E402_F410delinsV#
NTRK3	G466_Y529delinsD#	AATYK	G600C
VEGFR2	V297I	AATYK	F1163S#
VEGFR2	Q472H	LMTK2	L780M

(cont. on next page)

87/306

Fig. 30 (continued)

NCI-H661 (cont.)		SK-MES-1	
TNK1	M598delinsEVERSHX#	TYRO3	I346N#
FAK	L926delinsPWRL#	HER2	P1170A
PYK2	K838T	HER4	G936R#
JAK3	E698K	EPHA5	V891L#
TYK2	V362F	RON	R813delinsRQ#
TEC	P587L	RON	R1335G
		CCK4	E745D
		RET	G691S#
		ROR1	M518T
		ROS1	S1109L
		NTRK3	E402_F410delinsV#
		NTRK3	G466_Y529delinsD#
		VEGFR2	Q472H#
		STYK1	G204S
		PYK2	K838T
		FRK	G122R#
		JAK3	G62fsX44#
		TYK2	P1104A
SK-LU-1		Ovary	
ALK	K1491R#	A2780	
ALK	D1529E#	ALK	K1491R#
HER2	P1170A	EPHA2	M631T#
EPHB6	S309A	EPHA3	W924R
RON	R1335G	STYK1	G204S
RET	G691S#	TNK1	M598delinsEVRSHX
ROR1	M518T	PYK2	K838T
ROR2	V819I	ZAP-70	P296_S301del#
NTRK3	E402_F410delinsV#		
VEGFR2	Q472H	CaOv-3	
VEGFR3	Q890H#	ALK	D1529E#
LMTK2	L780M	TYRO3	I346N#
PYK2	K838T	HER2	P1170A
FRK	G122R#	EPHA3	W924R#
TYK2	V362F	EPHA5	A672T#
LCK	L36fsX8	EPHA10	G749E#
ZAP-70	K186fsX#	RON	R523Q
		RON	R627fsX5#
		RON	R813delinsRQ#
		FLT3	M227T
		RET	G691S#
		RET	R982C
		ROR1	M518T
SW-900			
ALK	D1529E		
HER2	P1170A		
RON	R813delinsRQ#		
RON	R1335G		
ROR1	M518T		
ROS1	D2213N#		
TIE	S470L#		
NTRK3	V530fsX6		
LMTK2	L780M		
ACK1	P725L		
FAK	L926delinsPWRL#		
PYK2	G414V		
BRK	W78fsX58#		
FRK	G122R#		
TXK	Y414fsX15#		

(cont. on next page)

88/306

Fig. 30 (continued)

Ovary (cont.)

CaOv-3 (cont.)	
ROR2	V819I
VEGFR3	Q890H
LMTK2	L780M
STYK1	G204S#
CaOv-4	
ALK	K1491R#
ALK	D1529E#
HER2	P1170A
EPHA3	W924R#
RON	R813delinsRQ#
RON	R1335G
FLT3	M227T
ROR1	M518T#
NTRK3	E402_F410delinsV
STYK1	G204S
ACK1	P725L
FAK	L926delinsPWRL#
PYK2	K838T#
FRK	G122R
MDAH-2774	
HER2	P1170A
EPHA2	V936M#
EPHA3	W924R
EPHA6	L622F#
FGFR1	G539_K540del#
FGFR2	H199_Q247delins48#
RON	R813delinsRQ#
RON	R1335G
ROR2	T245A
ROR2	V819I#
NTRK3	E402_F410delinsV#
LMTK2	L780M#
ACK1	P725L
FAK	A472V#
BTK	W588C

IGROV-1

ALK	D1529E
TYRO3	I346N#
HER2	P1170A
HER3	S1119C#
EPHB4	A955V#
EPHB6	G353_E471del#
FGFR2	H199_Q247delins48
FGFR4	G388R#
RON	R523Q#
RON	R627fsX5#
RON	R813delinsRQ#
RON	R1335G#
RET	A750T#
ROR1	R429Q#
ROR1	M518T
RYK	N96S
TIE	M871T#
LMTK2	L780M
STYK1	G204S
ABL1	S991L#
ACK1	P725L#
PYK2	K838T
JAK1	N849fsX16
TYK2	R901Q#
TXK	R336Q#

OAW-42

TYRO3	I346N
HER2	P1170A#
EPHA10	G749E
FGFR2	199_Q247delins48
FGFR4	G388R#
RON	R813delinsRQ#
RON	R1335G#
CCK4	T410S#
ROR1	M518T
LMTK2	L780M#
ACK1	P725L#
FAK	.926delinsPWRL#
TXK	R336Q#

(cont. on next page)

89/306

Fig. 30 (continued)

Ovary (cont.)

OVCAR-3

EPHA3	W924R#
FGFR4	L136P
RON	R813delinsRQ#
RON	R1335G
FLT3	M227T
ROR1	M518T
ROR2	V819I
LMTK2	L780M#
PYK2	K838T#
FRK	G122R
JAK2	R1063H

PA-1

EGFR	R521K#
HER2	P1170A#
EPHA3	W924R
FGFR2	H199_Q247delins48
RON	R1335G
FLT3	M227T
FLT3	V557I#
RET	G691S#
ROR1	M518T
ROR2	T245A#
VEGFR2	V297I#
LMTK2	L780M#
STYK1	G204S#
<u>PTK-9</u>	<u>N333S#</u>
TNK1	D472_R473del#
ZAP-70	P296_S301del#

Sk-OV-3

ALK	K1491R#
ALK	D1529E#
EGFR	R521K#
HER2	P1170A
EPHA1	V900M
EPHA3	W924R
RON	R813delinsRQ#
RON	R1335G
ROR1	M518T
LMTK2	L780M
STYK1	G204S#
ACK1	P725L

SK-OV-6

EGFR	R521K
PYK2	K838T
FRK	G122R#

SK-OV-8

EGFR	R521K#
EPHA3	W924R#
ROR2	T245A#
ROR2	V819I
NTRK1	R780Q#
LMTK2	L780M
STYK1	G204S
ACK1	P725L#
FRK	G122R#

Pancreas

818-4

TYRO3	I346N
<u>EGFR</u>	<u>E922K</u>
HER2	P1170A
RON	R813delinsRQ#
RON	R1335G#
FLT3	M227T
ROR1	M518T#
AATYK	F1163S#
TNK1	M598V
FES	S72_K129del
ZAP-70	P296_S301del#

A-818-7

TYRO3	I346N#
HER2	P1170A
FGFR4	L136P
RON	R627fsX5#
RON	R813delinsRQ#
RON	R1335G#
ROR1	M518T#
ROS1	I537M#
TNK1	M598V

(cont. on next page)

90/306

Fig. 30 (continued)

Pancreas (cont.)

AsPC-1

ALK	K1491R
ALK	D1529E#
EGFR	R521K#
HER2	P1170A#
EPHA10	G749E#
FGFR4	G388R#
RON	R813delinsRQ#
RON	R1335G#
CCK4	T410S#
CCK4	M746L#
ROR1	M518T
RYK	N96S
LMTK2	L780M
STYK1	G204S
ACK1	P725L#
FRK	G122R
TYK2	V362F
TYK2	I684S

BxPC-3

MER	V870I#
HER2	P1170A#
FGFR4	G388R#
RON	R1335G
ROR1	M518T
AATYK	G600C
ACK1	P725L#

Capan-1

<u>MER</u>	<u>E831Q#</u>
MER	V870I#
TYRO3	I346N#
HER2	P1170A
RON	R523Q
RON	R813delinsRQ#
RON	R1335G#
CCK4	P693L#
ROR1	M518T
ACK1	P725L#
FAK	L926delinsPWRL#
PYK2	K838T#
<u>FRK</u>	<u>G119A</u>
FRK	G122R#

Capan-2

FGFR1	V427_T428del#
RON	R523Q#
RON	R813delinsRQ#
RON	R1335G#
ROR1	M518T
AATYK	G600C
LMTK2	L780M#
STYK1	G204S#
ACK1	R1038H#
PYK2	K838T
FRK	G122R

CFPAC-1

ALK	K1491R
ALK	D1529E
TYRO3	I346N#
HER2	P1170A#
HER3	S1119C
EPHA10	G749E#
FGFR4	L136P
RON	R813delinsRQ#
RON	R1335G
ROR1	M518T
LMTK2	L780M#
ACK1	P725L#
PYK2	K838T
FRK	G122R#

COLO-357

<u>FLT3</u>	<u>V592A</u>

DANG-G

ALK	K1491R#
ALK	D1529E
EGFR	R521K#
HER2	P1170A
RON	R813delinsRQ#
RON	Y884_Q932del
RON	R1335G
ROR1	M518T#
STYK1	G204S#

(cont. on next page)

91/306

Fig. 30 (continued)

Pancreas (cont.)

DANG-G (cont.)		PANC TU1	
FRK	G122R#	TYRO3	I346N
FYN	D506E#	<u>HER2</u>	<u>G1015E#</u>
Hs 766T		HER2	P1170A
TYRO3	I346N#	HER3	S1119C#
EGFR	R521K#	FGFR4	G388R#
HER2	P1170A	RON	R813delinsRQ#
RON	R813delinsRQ#	RON	R1335G
RON	R1335G	ROR1	M518T
ROR1	M518T#	RYK	N96S
NTRK3	E402_F410delinsV#	LMTK2	L780M#
LMTK2	L780M#	TNK1	D472_R473del
STYK1	G204S	PYK2	K838T
PYK2	K838T	TXK	Y414fsX15#
FES	S72_K129del	PaTu 8902	
Mia-PaCa2		ALK	D1529E
HER2	P1170A	TYRO3	I346N
EPHA10	G749E	HER2	P1170A
<u>EPHB2</u>	<u>R369Q</u>	HER3	S1119C#
FGFR2	H199_Q247delins48	FGFR1	V427_T428del#
RET	G691S	FGFR4	L136P
ROR1	M518T	RON	R813delinsRQ#
RYK	N96S	RON	R1335G
LMTK2	L780M#	PDGFRA	S478P#
ABL1	S991L	<u>NTRK1</u>	<u>P453fsX15#</u>
TNK1	M598delinsEVRSHX#	LMTK2	L780M#
PYK2	K838T	TNK1	D472_R473del
TXK	Y414fsX15#	PYK2	K838T
PANC-1		TYK2	E971fsX67#
EGFR	R521K#	ZAP-70	P296_S301del#
HER2	P1170A	PaTu 8988T	
EPHA7	I138V#	HER2	P1170A
RON	Y884_Q932del	EPHA1	V900M#
RON	R1335G	EPHA3	W924R
ROR1	M518T	RON	R813delinsRQ#
LMTK2	L780M#	TEK1	V600L
PYK2	K838T	LMTK2	L780M
FRK	G122R#	ACK1	P725L#
TYK2	E971fsX67#	TXK	Y414fsX15#

(cont. on next page)

92/306

Fig. 30 (continued)

Pancreas (cont.)		Prostate	
PT-45P1		BM-1604	
ALK	K1491R#	ALK	D1529E
ALK	D1529E#	EGFR	R521K#
HER2	P1170A#	HER2	P1170A#
EPHA2	R876H#	<u>EPHB2</u>	<u>Q722X#</u>
EPHA7	I138V#	<u>EPHB6</u>	<u>L580F#</u>
RON	R523Q#	<u>FLT3</u>	<u>R849H</u>
RON	R813delinsRQ#	FGFR2	K199_D247del#
RON	Y884_Q932del	ROR1	M518T
RON	R1335G#	LMTK2	L780M#
ROR1	M518T#	PYK2	K838T
ROR2	V819I	<u>PYK2</u>	<u>M885L#</u>
LMTK2	L780M#	FRK	G122R#
ACK1	P725L#	<u>SYK</u>	<u>V622A</u>
TYK2	V362F	DU-145	
TYK2	P1104A#	EGFR	R521K#
ZAP-70	P296-S301del#	HER2	P1170A#
SW 850		<u>EPHB2</u>	<u>Q722X#</u>
ALK	D1529E#	<u>EPHB6</u>	<u>L580F#</u>
EGFR	R521K#	FGFR2	K199_D247del#
HER2	P1170A#	FGFR4	L136P#
HER3	S1119C#	RON	R523Q
EPHA2	G391R#	RON	R627fsX5#
FGFR4	G388R#	ROR1	M518T
RON	R523Q#	LMTK2	L780M#
RON	R627fsX5#	PYK2	K838T#
RON	R1335G#	<u>PYK2</u>	<u>M885L#</u>
CCK4	T410S#	FRK	G122R#
<u>CCK4</u>	<u>M746L#</u>	<u>SYK</u>	<u>V622A#</u>
ROR1	M518T	LNCAP.FGC	
ROR2	T245A	<u>HER2</u>	<u>E930D#</u>
LMTK2	L780M	HER2	P1170A
STYK1	G204S	HER3	S1119C#
ACK1	P725L#	EPHA1	V900M#
FRK	G122R	EPHA7	I138V
TYK2	I684S	EPHA10	G749E#
		<u>EPHB4</u>	<u>D576G#</u>
		<u>FGFR1</u>	<u>R78H#</u>
		FLT3	M227T
		FLT3	D358V#
		NTRK1	H604Y
		NTRK1	G613V#

(cont. on next page)

93/306

Fig. 30 (continued)

Prostate (cont.)

LNCAP.FGC (cont.)		PPC-1 (cont.)	
LMTK2	G518V#	ACK1	P725L
LMTK2	D523Y#	PYK2	K838T
LMTK2	L780M#	FRK	G122R#
ABL1	N789S#		
ABL1	S991L#		
ACK1	R748W#		
FER	Q599R#		
FYN	D506E#		
BMX	A150D		
ZAP-70	P296_S301del#		
PC-3		TSU-PR1	
TYRO3	E489K#	HER2	I655V
HER2	I655V	HER2	P1170A#
HER3	S1119C#	HER3	S1119C#
EPHA1	V900M#	EPHA3	A777G
EPHA3	R914H#	EPHA3	W924R
EPHA3	W924R	EPHB2	P273L#
EPHA10	G749E	HER2	I655V
FGFR4	G388R	HER2	P1170A#
RON	R523Q#	HER3	S1119C#
RON	R627fsX5#	EPHA3	A777G
RON	R813delinsRQ#	EPHA3	W924R
RON	R1335G#	EPHB2	P273L#
ROR1	M518T	FGFR2	K199_D247del
ROS1	C76_R77ins9#	MET	T1010I#
VEGFR2	Q472H#	RON	R1335G
VEGFR2	C482R#	ROR1	M518T#
AATYK	G600C#	NTRK1	H604Y
ACK1	P725L#	NTRK1	G613V
PYK2	K838T	TNK1	598delinsEVRSHX
FRK	G122R		
PPC-1		Skin	
ALK	D1529E#	A-375	
TYRO3	E489K#	ALK	K1491R#
HER2	I655V	ALK	D1529E#
EPHA1	V900M#	TYRO3	I346N#
EPHA3	R914H#	EGFR	R521K#
EPHA3	W924R	HER2	P1170A#
FGFR4	G388R	EPHA3	W924R#
RON	R627fsX5#	EPHA5	E85K
RON	R1335G#	CCK4	T410S#
ROR1	M518T	ROR1	M518T
		NTRK3	E402_F410delinsV#
		NTRK3	R711_V712ins14#
		ACK1	P725L#

(cont. on next page)

94/306

Fig. 30 (continued)

Skin (cont.)

BOW-G	
TYRO3	I346N#
HER2	I655V#
HER2	P1170A
FGFR4	G388R
ROR1	M518T
TEK1	P346Q
VEGFR2	E107K#
VEGFR2	V297I#
LMTK2	L780M#
ARG	M657I#
TYK2	S340fsX26#
TNK1	M598delinsEVRSHX#
PYK2	K838T#

C-32	
TYRO3	I346N#
EGFR	R521K#
HER2	P1170A
EPHA3	W924R#
RON	R1335G#
ROR1	M518T
VEGFR2	Q472H#
LMTK2	P30A#
TNK1	M598delinsEVRSHX
TYK2	I684S#

C-8161	
TYRO3	I346N#
HER2	P1170A
EPHA2	R876H#
RON	R813delinsRQ#
ROR1	M518T
STYK1	G204S
TNK1	M598delinsEVRSHX#
PYK2	K838T
FES	S72_K129del

Colo-16	
HER2	P1170A#
ROR1	M518T#
ROR2	T245A
ACK1	P725L#
PYK2	K838T#
FRK	G122R#

Colo-829	
ALK	D1529E#
TYRO3	I346N
HER2	I655V
HER2	P1170A#
EPHA2	R876H
EPHA5	N81T#
MET	N375S#
MET	T1010I#
ROR1	M518T#
VEGFR2	V297I#
VEGFR2	Q472H#
LMTK2	L780M#
PYK2	K838T#

F-01	
EPHA3	W924R#
FGFR2	K199_D247del
FGFR4	G388R#
RET	G691S
ROR1	M518T#
AATYK	G600C
AATYK	F1163S
LMTK2	L780M
TNK1	M598delinsEVRSHX
FAK	L926delinsPWRL#
PYK2	K838T#
FRK	G122R#
ZAP-70	P296_S301del#

G-361	
ALK	K1491R#
ALK	D1529E
EGFR	R521K#
HER2	P1170A#
HER3	S1119C#
EPHA3	W924R#
RON	R1335G#
ROR1	M518T#
ROS1	K2228Q#
ROS1	S2229C#
NTRK3	E402_F410delinsV

(cont. on next page)

95/306

Fig. 30 (continued)

Skin (cont.)

G-361 (cont.)		HT-144 (cont.)	
AATYK	G600C	NTRK3	E402_F410delinsV#
FRK	G122R#	LMTK2	L780M
TYK2	S340fsX26#	STYK1	G204S
HS-294T		TNK1	M598delinsEVRSHX#
HER2	P1170A	PYK2	K838T
HER3	S1119C#	IGR-39	
EPHA3	W924R#	ALK	D1529E
RON	R813delinsRQ#	EGFR	R521K#
ROR1	M518T#	EPHA3	R914H#
ROS1	C76_R77ins9#	EPHA3	W924R
ROS1	T145P	FGFR4	G388R
ROS1	S1109L	RON	R813delinsRQ#
ROS1	D2213N#	ROR1	M518T
NTRK3	E402_F410delinsV#	NTRK3	402_F410delinsV#
NTRK3	R711_V712ins14#	NTRK3	R711_V712ins14#
VEGFR2	Q472H#	VEGFR1	S437L
ACK1	P725L#	LMTK2	L780M
PYK2	K838T	PYK2	K838T#
FRK	G122R#	FRK	G122R#
HS-695T		KA-II	
EPHA3	W924R	HER2	P1170A#
FGFR4	G388R#	FGFR4	G388R#
MET	N375S#	RON	V1070fsX12
RON	R813delinsRQ#	ROR1	M518T#
FLT3	M227T	LMTK2	P30A#
CCK4	T410S	LMTK2	L780M#
ROR1	M518T	PTK-9	D258E#
RYK	N96S	ABL1	S991L
NTRK3	E402_F410delinsV#	FRK	G122R
TNK1	M598delinsEVRSHX#	TXK	R336Q#
PYK2	K838T#	ZAP-70	P296_S301del#
HT-144		Malme-3M	
ALK	D1529E#	HER2	P1170A#
TYRO3	I346N#	EPHA3	R914H#
HER2	P1170A#	EPHA3	W924R#
HER3	S1119C#	RON	R1335G#
FGFR1	V427_T428del#	ROR1	M518T
ROR1	M518T#	NTRK3	E402_F410delinsV
NTRK1	H604Y#	VEGFR2	V297I#
NTRK1	G613V#	STYK1	G204S#

(cont. on next page)

96/306

Fig. 30 (continued)

Skin (cont.)

Malme-3M (cont.)

ACK1	P725L#
FRK	G122R#
Mel- Ger	
TYRO3	I346N
HER2	P1170A#
EPHA3	W924R
FGFR4	L136P
ROR1	M518T#
ROS1	S1109L
TEK1	P346Q
NTRK3	E402_F410delinsV#
AATYK	G600C#
LMTK2	L780M
STYK1	G204S#
TNK1	M598delinsEVRSHX#
PYK2	K838T

Mel JUSO

ALK	K1491R#
HER2	P1170A#
RON	R1335G
CCK4	P693L#
<u>NTRK1</u>	<u>G595E#</u>
NTRK3	E402_F410delinsV
LMTK2	L780M
TNK1	M598delinsEVRSHX
PYK2	K838T#
FRK	G122R#

MEWO

EGFR	R521K#
HER2	P1170A#
<u>EPHA2</u>	<u>L836R#</u>
<u>EPHA3</u>	<u>S46F#</u>
<u>EPHA3</u>	<u>E53K#</u>
EPHA3	W924R#
<u>EPHB6</u>	<u>E615K#</u>
<u>EPHB6</u>	<u>R811C#</u>
<u>FGFR1</u>	<u>P252S#</u>
<u>MET</u>	<u>P366S#</u>
RON	R813delinsRQ#
ROR1	M518T
VEGFR2	Q472H#

MEWO (cont.)

AATYK	G600C
LMTK2	L780M#
<u>ARG</u>	<u>S968F#</u>
TNK1	M598delinsEVRSHX#
FES	S72_K129del
<u>TYK2</u>	<u>D883N#</u>
SYK	E315K
TXK	R336Q#

MM-031-I

HER3	L1177I#
EPHA2	R876H
EPHA3	W924R#
RON	R1335G#
ROR1	M518T
AATYK	F1163S
LMTK2	L780M
ACK1	P725L#
TNK1	598delinsEVRSHX
<u>PYK2</u>	<u>E798Q#</u>
PYK2	K838T

MM-194-G

HER2	P1170A
FGFR2	H199_Q247delins48
FGFR4	L136P
RON	R1335G
TEK1	V600L

MM-195-H

HER2	P1170A#
HER2	A1216D#
EPHA5	A672T#
ROR1	M518T
AATYK	G600C#
LMTK2	L780M
STYK1	G204S#
PYK2	K838T#

MM-201-B

ALK	K1491R
ALK	D1529E
HER2	P1170A#
FGFR2	H199_Q247delins48

(cont. on next page)

97/306

Fig. 30 (continued)

Skin (cont.)

MM-201-B (cont.)		MM-A1b	
ROR1	M518T#	HER2	P1170A
ROS1	I537M#	EPHA3	W924R
NTRK3	E402_F410delinsV#	EPHA5	N81T#
LMTK2	L780M#	RON	R1335G
STYK1	G204S#	PDGFRA	S478P#
TYK2	V362F#	ROR1	M518T#
TYK2	G363S#	LMTK2	L780M
TYK2	P1104A#	ACK1	P725L#
		ACK1	R1038H#
		TYK2	V362F#
MM-232-E		MM-A1t	
HER3	L1177I#	HER2	I655V#
EPHA2	R876H	HER2	P1170A
EPHA3	W924R#	EPHA2	R876H#
AATYK	F1163S	<u>EPHB2</u>	<u>R369Q</u>
LMTK2	L780M	VEGFR2	Q472H#
ACK1	P725L#	AATYK	F1163S
TNK1	M598delinsEVRSHX	LMTK2	L780M
<u>PYK2</u>	<u>E798Q#</u>	PYK2	K838T
PYK2	K838T	TYK2	V362F
MM-254-C		TYK2	A928V#
TYRO3	I346N	ZAP-70	P296_S301del#
HER2	P1170A	MM-Arn	
EPHA2	G391R#	ALK	K1491R#
EPHA5	N81T#	ALK	D1529E#
FGFR4	G388R#	DDR2	R478C
RON	R813delinsRQ#	<u>EGFR</u>	<u>E922K#</u>
ROR1	M518T	HER2	I655V
NTRK3	E402_F410delinsV	HER2	P1170A
STYK1	G204S#	HER3	S1119C
<u>ARG</u>	<u>E332K#</u>	FGFR4	G388R
<u>ACK1</u>	<u>H37Y#</u>	<u>MET</u>	<u>S691L#</u>
<u>ACK1</u>	<u>E111K#</u>	RON	R1335G#
FAK	L926delinsPWRL#	ROR1	M518T
MM-358-A		RYK	N96S
ALK	K1491R	LMTK2	L780M
ALK	D1529E	ACK1	P725L
HER2	P1170A	TNK1	M598delinsEVRSHX#
<u>EPHA2</u>	<u>H609Y#</u>	PYK2	K838T#
FGFR4	L136P	<u>SYK</u>	<u>A353T#</u>
ROR1	M518T#		
AATYK	G600C#		

(cont. on next page)

98/306

Fig. 30 (continued)

Skin (cont.)

MM-Du		MM-Su	
ALK	D1529E#	ALK	D1529E#
TYRO3	I346N	EPHA1	V900M#
ROR1	M518T	MRI-H221	
RYK	N96S	TYRO3	I346N#
NTRK1	H604Y#	HER2	P1170A
NTRK1	G613V#	EPHA3	W924R#
VEGFR2	P1280S#	RON	R813delinsRQ#
LMTK2	L780M#	RON	R1335G#
TNK1	M598delinsEVRSHX#	CCK4	T410S#
PYK2	K838T	RET	G691S
TYK2	V362F	ROR1	M518T#
ZAP-70	T155M#	NTRK1	P453fsX15#
MM-Leh		NTRK3	E402_F410delinsV#
HER2	P1170A	NTRK3	R711_V712ins14#
EPHA3	W924R#	TNK1	D472_R473del
EPHB2	E686K#	PYK2	K838T#
FGFR4	L136P	TYK2	I684S#
ROR1	M518T	RPMI 7951	
ROS1	S1109L	TYRO3	I346N#
VEGFR1	M938V#	EPHA3	W924R#
STYK1	G204S#	FGFR4	L136P
ABL1	G417E#	MET	T17I
ACK1	P725L#	PDGFRA	S478P
TYK2	I684S#	ROR1	M518T
SYK	A353T#	ROS1	C76_R77ins9
MM-Lo		NTRK3	E402_F410delinsV#
EPHA2	G391R#	AATYK	G600C
EPHA3	W924R#	STYK1	G204S#
ROR1	M518T	ACK1	P725L#
RYK	H250R#	TNK1	M598delinsEVRSHX#
NTRK3	402_F410delinsV#	PYK2	K838T
LMTK2	P30A#	TYK2	S340fsX26#
LMTK2	L780M#	ZAP-70	P296_S301del#
STYK1	G204S	SK-MEL-1	
ACK1	P725L#	ROR1	M518T
FAK	P901S	AATYK	G600C#
TYK2	V362F	LMTK2	L780M#
TYK2	I684S#	STYK1	G204S#

(cont. on next page)

99/306

Fig. 30 (continued)

Skin (cont.)

SBCL2		SK-MEL-24	
<u>AXL</u>	<u>M569I#</u>	ALK	K1491R#
TYRO3	I346N	ALK	D1529E#
EGFR	R521K#	HER2	P1170A
HER2	I655V#	<u>HER3</u>	<u>R1077W#</u>
HER2	P1170A	EPHA3	W924R#
EPHA3	W924R#	RON	R1335G
FGFR4	G388R#	TEK1	V600L
RON	R523Q	NTRK1	H604Y#
RON	R627fsX5#	NTRK1	G613V
RON	R813delinsRQ#	NTRK3	E402_F410delinsV#
<u>ROR1</u>	<u>P883S</u>	LMTK2	L780M#
RYK	N96S#	TNK1	M598delinsEVRSHX#
NTRK3	E402_F410delinsV#	PYK2	K838T#
ACK1	P725L#	SK-MEL-28	
TNK1	D472_R473del#	<u>EGFR</u>	<u>P753S#</u>
PYK2	K838T#	EPHA3	W924R#
FES	S72_K129del	ROR1	M518T
JAK2	L393V	NTRK3	R711_V712ins14#
TYK2	V362F#	LMTK2	L780M
SK-MEL-2		STYK1	G204S#
HER2	P1170A#	PYK2	K838T#
RON	R1335G	FRK	G122R
ROR1	M518T	<u>JAK2</u>	<u>E592K#</u>
TEK1	A1006T#	<u>JAK3</u>	<u>P693L#</u>
NTRK3	402_F410delinsV#	SK-MEL-31	
LMTK2	P30A#	ALK	D1529E#
LMTK2	L780M#	TYRO3	I346N#
STYK1	G204S	HER2	P1170A#
SK-MEL-3		EPHA3	W924R
ALK	D1529E#	RON	R1335G
HER2	P1170A	ROR1	M518T
SK-MEL-5		TEK1	V600L
TYRO3	I346N	NTRK3	E402_F410delinsV#
HER2	P1170A#	LMTK2	L780M
NTRK1	H604Y#	STYK1	G204S
NTRK1	G613V#	PYK2	K838T#
NTRK3	E402_F410delinsV#	FRK	G122R#
LMTK2	L780M#		
FAK	L926delinsPWRL#		

(cont. on next page)

100/306

Fig. 30 (continued)

Skin (cont.)

WM-35

MER	V870I#
HER2	P1170A
EPHA3	W924R#
RON	R523Q
ROR1	M518T#
ROS	C76_R77ins9
NTRK2	A647fsX54
NTRK3	402_F410delinsV#
LMTK2	L780M#
PYK2	K838T#

WM-115

ALK	K1491R#
ALK	D1529E
AXL	G517S#
HER2	I655V
HER2	P1170A#
FGFR1	G539_K540del#
RON	R1335G
PDGFRA	S478P#
ROR1	M518T
ROS1	R167Q
RYK	N96S
NTRK3	E402_F410delinsV#
NTRK3	R711_V712ins14#
AATYK	T1227M#
LMTK2	L780M#
BMX	N267I

WM-239A

ALK	K1491R#
ALK	D1529E
AXL	G517S#
HER2	I655V
HER2	P1170A#
FGFR1	G539_K540del#
RON	R1335G
PDGFRA	S478P#
ROR1	M518T
ROS1	C76_R77ins9
RYK	N96S
NTRK3	E402_F410delinsV#
AATYK	T1227M#

WM-239A (cont.)

LMTK2	L780M#
BMX	N267I

WM-266-4

ALK	K1491R#
ALK	D1529E
AXL	G517S#
HER2	I655V
HER2	P1170A#
FGFR1	G539_K540del#
RON	R813delinsRQ#
RON	R1335G
PDGFRA	S478P#
ROR1	M518T
RYK	N96S
AATYK	T1227M#
LMTK2	L780M#
BMX	N267I

WM-793

EGFR	R521K#
HER2	P1170A
EPHA3	W924R#
RON	R813delinsRQ#
RON	R1335G#
ROR1	M518T
ROR2	T245A
ROR2	V819I
ROS1	I537M#
NTRK3	E402_F410delinsV#
NTRK3	G466_Y529delinsD#
VEGFR2	V297I#
LMTK2	L780M
STYK1	G204S#
TNK1	M598delinsEVRSHX
PYK2	K838T
TYK2	V362F#
TYK2	G363S#
TXK	Y414fsX15#

(cont. on next page)

101/306

Fig. 30 (continued)

Skin (cont.)

WM-852

HER2	P1170A#
EPHA3	W924R#
EPHA4	V234F#
RON	R1335G#
ROR1	M518T
ROR2	T245A
ROR2	V819I
NTRK3	E402_F410delinsV#
LMTK2	L780M
ACK1	P725L#
TNK1	A299D
PYK2	K838T#
FRK	G122R#

WM-902B

ALK	K1491R#
TYRO3	I346N#
EGFR	R521K#
HER2	P1170A
HER3	S1119C#
EPHA3	R914H#
EPHA3	W924R#
PDGFRA	S478P
ROR1	M518T
NTRK3	402_F410delinsV#
AATYK	G600C#
LMTK2	P30A#
LMTK2	L780M#
TNK1	598delinsEVRSHX#
PYK2	K838T
ZAP-70	P296_S301del#

WM-983A

TYRO3	I346N#
TYRO3	S531L#
HER2	P1170A
HER3	L1177I#
EPHA5	A672T#
FGFR4	G388R#
ROR1	M518T
RYK	N96S
NTRK3	E402_F410delinsV
AATYK	F1163S#

WM-983A (cont.)

LMTK2	L780M
TNK1	M598delinsEVRSHX#
PYK2	T978M#
FES	S72_K129del#
ZAP-70	P296_S301del#

WM-983B

TYRO3	I346N#
TYRO3	S531L#
HER2	P1170A
HER3	L1177I#
EPHA5	A672T#
FGFR4	G388R#
ROR1	M518T
RYK	N96S
NTRK3	E402_F410delinsV#
AATYK	F1163S#
LMTK2	L780M
TNK1	M598delinsEVRSHX#
PYK2	T978M#
FES	S72_K129del#
ZAP-70	P296_S301del#

WM-1205

HER2	P1170A
EPHA3	W924R#
RON	R1335G#
ROR1	M518T
ROS1	I537M#
NTRK3	E402_F410delinsV#
NTRK3	G466_Y529delinsD#
VEGFR2	V297I#
LMTK2	L780M
TNK1	M598delinsEVRSHX#
PYK2	K838T

WM-1341D

HER2	P1170A
HER3	S1119C#
EPHA5	A672T#
FGFR4	G388R#
ROR1	M518T
NTRK3	E402_F410delinsV
NTRK3	G608D

(cont. on next page)

102/306

Fig. 30 (continued)

Skin (cont.)		Hs746T (cont.)	
WM-1341D (cont.)		<u>NTRK1</u>	<u>P453fsX15#</u>
STYK1	G204S	NTRK3	E402_F410delinsV
ACK1	P725L#	AATYK	G600C
PYK2	K838T	LMTK2	L780M
ZAP-70	P296_S301del#	ACK1	R1038H
WM-1617		FRK	G122R
ALK	K1491R#	TXK	Y414fsX15#
TYRO3	I346N#	KATO III	
HER2	P1170A	ALK	K1491R
EPHA3	W924R#	ALK	D1529E
EPHA5	N81T#	EGFR	R521K
ROR1	M518T#	HER2	P1170A
ROR2	V819I	FGFR4	G388R#
NTRK3	E402_F410delinsV#	RON	R813delinsRQ#
<u>NTRK3</u>	<u>G608D</u>	RON	Y884_Q932del
NTRK3	R711_V712ins14	ROR1	M518T
TNK1	M598delinsEVERSHX	AATYK	G600C
ZAP-70	P296_S301del#	<u>ACK1</u>	<u>A634T#</u>
Stomach		TNK1	M598V
AGS		FES	S72_K129del
HER2	P1170A#	ZAP-70	P296_S301del#
HER3	S1119C#	BMX	S254del#
RON	R813delinsRQ#	MKN-1	
NTRK3	E402_F410delinsV	ALK	K1491R#
LMTK2	L780M#	ALK	D1529E#
STYK1	G204S	EGFR	R521K#
TNK1	D472_R473del#	HER2	P1170A#
TEC	L89R#	HER3	N126K#
TXK	R336Q#	<u>HER3</u>	<u>R667H#</u>
Hs746T		<u>HER3</u>	<u>R1089W#</u>
ALK	D1529E	EPHA2	G391R#
HER2	P1170A	EPHA2	R876H#
EPHA5	R981L	<u>EPHA4</u>	<u>S803A#</u>
<u>MET</u>	<u>D981_E1027del</u>	<u>EPHA6</u>	<u>N291H#</u>
RON	R523Q	EPHB2	A83V#
RON	R813delinsRQ#	<u>EPHB2</u>	<u>V136M#</u>
RON	R1335G	<u>FGFR1</u>	<u>A268S</u>
ROR1	M518T	<u>IGF1R</u>	<u>N209S#</u>
ROS1	C76_R77ins9#	RON	R813delinsRQ#
		RON	R1335G#
		ROR1	M518T

(cont. on next page)

103/306

Fig. 30 (continued)

Stomach (cont.)	
MKN-1 (cont.)	
ROR1	S870I#
LMTK2	L780M
STYK1	G204S#
FAK	Q440R#
FRK	G122R
SYK	A353T#
MKN-28	
ROR1	M518T
TNK1	M598V#
FRK	G122R
TXK	Y414fsX15#
Testes	
Cates 1B	
ALK	K1491R#
ALK	D1529E
DDR1	R60C#
HER2	P1170A#
RYK	N96S
NTRK1	H604Y#
NTRK1	G613V#
NTRK3	E402_F410delinsV#
AATYK	F1163S#
LMTK2	L780M#
ABL1	S991L#
PYK2	K838T
TNK1	M598delinsEVRSHX
NT2	
EGFR	R521K#
HER2	I655V
HER3	S1119C
RYK	N96S
NTRK3	E402_F410delinsV#
VEGFR2	Q472H
VEGFR3	Q890H#
AATYK	F1163S
STYK1	G204S
TNK1	D472_R473del
PYK2	K838T#
TYK2	E971fsX67#

NT2 (cont.)	
ZAP-70	P296_S301del#
BMX	S254del#
Tera-2	
EGFR	R521K#
HER2	I655V
HER2	P1170A
HER3	S1119C
FGFR2	K199_D247del
RON	R1335G#
ROR1	M518T#
ROR2	T245A#
ROR2	V819I
NTRK3	E402_F410delinsV#
VEGFR2	Q472H
VEGFR3	Q890H
PYK2	K838T#
TNK1	D472_R473del

Thyroid

FTC-133	
ALK	D1529E#
EGFR	A1118T#
HER2	A830V
HER2	P1170A
HER3	S1119C#
EPHA2	R876H
ROS1	C76_R77ins9#
ROS1	T145P
ROS1	S1109L
RYK	N96S
TEK1	V600L
NTRK2	V622I
VEGFR2	Q472H
LMTK2	A251T
LMTK2	L780M
ABL1	P829L#
ACK1	P731L
PYK2	K838T
FRK	G122R#
ZAP-70	K186fsX#
TXK	Y414fsX15#

(cont. on next page)

104/306

Fig. 30 (continued)

Thyroid (cont.)		Non-Cancer Cell Lines	
FTC-238		As-745	
ALK	D1529E#	EGFR	R521K#
<u>EGFR</u>	<u>A1118T#</u>	HER2	P1170A
<u>HER2</u>	<u>A830V</u>	EPHA3	W924R
HER2	P1170A	RON	R627fsX5#
HER3	S1119C#	RON	R813delinsRQ#
EPHA2	R876H	CSF1R	H362R
ROS1	C76_R77ins9	CCK4	A777V#
ROS1	T145P	ROR1	M518T
ROS1	S1109L	ROS1	C76_R77ins9
RYK	N96S	RYK	N96S
TEK1	V600L	LMTK2	L780M
VEGFR2	Q472H	STYK1	G204S#
LMTK2	L780M#	ACK1	P725L
<u>ARG</u>	<u>Q696H#</u>	PYK2	K838T#
<u>ACK1</u>	<u>P731L</u>	FRK	G122R#
PYK2	K838T	TNK1	D472_R473del#
FRK	G122R#		
<u>JAK2</u>	<u>G571S#</u>		
TXK	Y414fsX15#		
TT		BPH-1	
ALK	D1529E#	ALK	K1491R#
HER2	P1170A#	ALK	D1529E#
RET	R982C	TYRO3	I346N#
NTRK1	H604Y#	EPHA2	R876H#
NTRK1	G613V#	CCK4	A777V#
NTRK3	E402_F410delinsV#	ROR1	M518T#
VEGFR2	Q472H#	ROS1	T145P
AATYK	F1163S	ROS1	S1109L
LMTK2	L780M	ROS1	D2213N#
STYK1	G204S	ROS1	K2228Q#
ACK1	P725L#	ROS1	S2229C#
FAK	T416fsX#	LMTK2	L780M
FAK	L926delinsPWRL#	STYK1	G204S#
FRK	G122R	ACK1	P725L#
TYK2	A53T#	PYK2	K838T#
ZAP-70	K186fsX#	FES	S72_K129del
		FRK	G122R
		TYK2	E971fsX67#

(cont. on next page)

105/306

Fig. 30 (continued)

Non-Cancer Cell Lines (cont.)

HaCaT		Hs 1.Li	
ALK	D1529E#	ALK	K1491R#
TYRO3	I346N#	ALK	D1529E#
HER2	P1170A	TYRO3	I346N#
EPHA3	W924R	EGFR	R521K#
RON	R627fsX5#	HER2	I655V#
RON	R813delinsRQ#	HER2	P1170A#
RON	R1335G	EPHB3	R514Q#
ROR1	M518T	FGFR4	L136P#
LMTK2	L780M	PDGFRA	S478P#
STYK1	G204S#	RET	D489N#
ACK1	P725L#	RET	G691S#
PYK2	K838T#	ROR1	M518T
HEK-293		RYK	N96S#
MER	E823Q#	NTRK3	E402_F410delinsV#
EGFR	R521K#	NTRK3	G466_Y529delinsD#
HER2	P1170A#	VEGFR1	Y642H#
FGFR2	K199_D247del	VEGFR2	V297I#
FGFR4	G388R#	AATYK	G600C#
RON	R627fsX5#	LMTK2	L780M#
RON	R813delinsRQ#	STYK1	G204S#
RON	R1335G	PYK2	K838T#
ROR1	M518T	ZAP-70	K186fsX#
ROR2	T245A	HuVeC	
ROR2	V819I	TYRO3	I346N#
RYK	N96S	HER2	P1170A
RYK	F516L#	FGFR4	L136P
NTRK3	E402_F410delinsV#	MET	R988C#
VEGFR1	P1201L#	RON	R627fsX5
VEGFR3	Q890H#	RON	R1335G#
VEGFR3	R1321Q#	ROR1	M518T#
LMTK2	P30A#	TEK1	P346Q#
LMTK2	L780M	VEGFR2	V297I#
ACK1	P725L#	VEGFR3	Q890H
PYK2	K838T#	LMTK2	L780M#
FES	E413fsX131	ACK1	P725L#
ZAP-70	K186fsX#	TNK1	598delinsEVRSHX#
		PYK2	K838T
		FES	S72_K129del
		TYK2	I684S#

(cont. on next page)

106/306

Fig. 30 (continued)

Non-Cancer Cell Lines (cont.)

MCF-10A

EGFR	R521K#	ROS1	C76_R77ins9#
HER2	I655V#	RYK	N96S
HER2	P1170A#	AATYK	G600C#
HER3	S1119C#	LMTK2	L780M#
EPHA1	V900M#	ACK1	P725L
RON	R627fsX5#	ACK1	R1038H#
RON	R813delinsRQ#	TYK2	V362F#
RON	R1335G	TYK2	I684S#
CCK4	S795R#	TXK	R336Q#
ROR1	M518T#		

Fig. 31

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
Receptor Tyrosine Kinases					
ALK family					
ALK	K1491R	67		SaOS2, R #	SF-763, R # SF-767, R # SW-1088, R U-1242, R # U-138, R #
ALK	D1529E	93	SCaBER, E #	MG63, E # SaOS2, E #	SF-763, E # SF-767, E # SH-SY-5Y, E SW-1088, E # U-118, E
ALK	G1580V	1			
Abbreviations:			Skeletal Muscle	S. Muscle	
MDA-MB	MB		Mono-Mac	M-Mac	
UM-SCC	SCC		PA-TU	PT	
			Colo 320DM	C. 320DM	

(cont. on next page)

107/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
Receptor Tyrosine Kinases					
ALK family					
ALK	K1491R	HBL-100, R #	C-4II, R # HT-3, R # Ms 751, R #	DLD-1, R HCT-15, R LS-123, R LS-174T, R # LS-180, R # SNU-C2B, R SW-403, R # SW-837, R SW-948, R #	
ALK	D1529E	HBL-100, E MCF-7, E	C-4II, E # HT-3, E # Ms 751, E #	C. 320DM, E # DLD-1, E HCT-15, E LS-123, E LS-174T, E # LS-180, E # SK-CO-1, E SNU-C2B, E SW-1417, E SW-480, E SW-620, E SW-837, E	
ALK	G1580V	1		LoVo, V #	

108/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
Receptor Tyrosine Kinases					
ALK family					
ALK	K1491R	SCC-4, R #	Jurkat, R	A-498, R #	HepG-2, R #
		SCC-10A, R #	M-07e, R #		Hu-H7, R #
		SCC-10B, R #	MG63, R #		SK-HEP-1, R
			RF-1, R #		
			RF-48, R #		
			THP-1, R #		
ALK	D1529E	SCC-15, E	Daudi, E	A-498, E #	SK-HEP-1, E
		SCC-25, E #	EM-2, E	ACHN, E #	
		SCC-4, E #	HL-60, E	CaKi-2, E #	
		SCC-9, E #	Jurkat, E		
			KG-1, E		
			PLB-985, E		
			THP-1, E		

109/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
Receptor Tyrosine Kinases					
ALK family					
ALK	K1491R	NCI-H209, R #	2780, R #	AsPC-1, R	
		NCI-H292, R #	CaOV-4, R #	CFPAC-1, R	
		NCI-H596, R #	SK-OV-3, R #	DANG-G, R #	
		NCI-H661, R #		PT-45P1, R #	
		SK-LU-1, R #			
ALK	D1529E	Calu-6, E #	CaOV-3, E #	AsPC-1, E #	BM-1604, E
		NCI-H209, E	CaOV-4, E #	CFPAC-1, E	PPC-1, E #
		NCI-H292, E	IGROV-1, E	DANG-G, E	
		NCI-H345, E #	SK-OV-3, E #	PT-8902, E	
		NCI-H446, E		PT-45P1, E #	
		NCI-H596, E		SW-850, E #	
		NCI-H69, E			
		SK-LU-1, E #			
		SW-900, E			
ALK		G1580V			

110/306

Fig. 31 (continued)

Gene Alteration Skin			Stomach	Testes	Thyroid	Normal Tissue
Receptor Tyrosine Kinases						
ALK family						
ALK	K1491R	A-375, R # G-361, R # MM-201-B, R MM-358-A, R MM-Arn, R # Mel Juso, R # SK-MEL-24, R # WM-115, R # WM-1617, R # WM-239A, R # WM-266-4, R # WM-902B, R #	KATO III, R MKN-1, R #	Cates 1B, R #		BPH-1, R # Bladder, R # Cervix, R # Colon, R # Gastric, R # Hs 1.Li, R # Placenta, R # Prostate, R #
ALK	D1529E	A-375, E # Colo829, E # G-361, E HT-144, E # IGR-39, E MM-201-B, E MM-358-A, E MM-Arn, E # MM-Du, E # MM-Su, E # SK-MEL-24, E # SK-MEL-3, E # SK-MEL-31, E # WM-115, E WM-239A, E WM-266-4, E	HS-746T, E KATO III, E MKN-1, E #	Cates 1B, E	FTC133, E # FTC238, E # TT, E #	BPH-1, E # Bladder, E Cervix, E Colon, E # Gastric, E # HaCaT, E # Hs 1.Li, E # Ovary, E # Prostate, E
ALK	G1580V					

111/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
AXL family					
AXL	G517S	4			
AXL	M569I	1			
AXL	M589K	1			
AXL	G835V	1			
MER	E823Q	1			
MER	E831Q	1			
MER	V870I	14	RT-4, I #		
TYRO3	S324C	1			
TYRO3	I346N	85	RT-4, N # TCCSUP, N #	RD, N TE-671, N	1321N1, N CCF-STTG1, N # IMR-32, N # SF-126, N SF-767, N # SW-1088, N # U-118, N U-1242, N # U-138, N
TYRO3	E489K	3			
TYRO3	S531L	2			
TYRO3	N788T	1			
TYRO3	P822L	1			

112/306

Fig. 31 (continued)

Gene Alteration Breast			Cervix and Vulva	Colon	Endo- metrium and Placenta	Head and Neck
AXL family						
AXL	G517S					
AXL	M569I					
AXL	M589K			<u>HCT-116, K</u>		
AXL	G835V					
MER	E823Q					
MER	E831Q					
MER	V870I	SK-BR-3, I # ZR-75-30, I #			RL95-2, I #	
TYRO3	S324C					
TYRO3	I346N	ZR-75-1, N #	C-33A, N # ME-180, N # MES-SA, N #	C. 320DM, N HCT-116, N # SW-403, N # SW-48, N #	JAR, N # KLE, N RL95-2, N #	SCC-25, N SCC-22A, N # SCC-22B, N #
TYRO3	E489K	BT-20, K				
TYRO3	S531L					
TYRO3	N788T					
TYRO3	P822L			<u>HCT-15, L #</u>		

113/306

Fig. 31 (continued)

Gene	Alteration	Hemato- poietic and Lymphoid System	Kidney	Liver	Lung
AXL family					
AXL	G517S				
AXL	M569I				
AXL	M589K				
AXL	G835V				<u>Calu-3, V</u>
MER	E823Q				
MER	E831Q				
MER	V870I	Daudi, I # EM-2, I # Jurkat, I # NB-4, I #	CaKi-1, I # SW13, I #		A-427, I
TYRO3	S324C				<u>A-427, C #</u>
TYRO3	I346N	EM-2, N # IM-9, N # KG-1, N # M-07e, N # MG63, N M-Mac-1, N # M-Mac-6, N # OCI-AML5, N	A-498, N # A-704, N #	Hs 817.T, N #	A-427, N # Calu-3, N # Calu-6, N NCI-H128, N NCI-H146, N NCI-H460, N SK-MES-1, N #
TYRO3	E489K				
TYRO3	S531L				
TYRO3	N788T	THP-1, T #			
TYRO3	P822L				

114/306

Fig. 31 (continued)

Gene	Alteration	Ovary	Pancreas	Prostate	Skin
AXL family					
AXL	G517S				WM-115, S # WM-239A, S # WM-266-4, S # <u>SBCL2, I #</u>
AXL	M569I				
AXL	M589K				
AXL	G835V				
MER	E823Q				
MER	E831Q		<u>Capan-1, Q #</u>		
MER	V870I		BxPC-3, I # Capan-1, I #		WM-35, I
TYRO3	S324C				
TYRO3	I346N	CaOV-3, N # IGROV-1, N # OAW-42, N	A-818-7, N # A-818-7, N # CFPAC-1, N # Capan-1, N # Hs 766T, N # PT-8902, N Panc TU1, N		A-375, N # BOW-G, N # C-32, N # C-8161, N # Colo829, N HT-144, N # MM-254-C, N MM-Du, N MRI-H221, N # RPMI7951, N # SBCL2, N SK-MEL-31, N # SK-MEL-5, N WM-1617, N # WM-902B, N # WM-983A, N # WM-983B, N #
TYRO3	E489K			PC-3, K # PPC-1, K #	
TYRO3	S531L				<u>WM-983A, L #</u> <u>WM-983B, L #</u>
TYRO3	N788T				
TYRO3	P822L				

115/306

Fig. 31 (continued)

Gene	Alteration	Stomach	Testes	Thyroid	Normal Tissue
AXL family					
AXL	G517S				Ovary, S #
<u>AXL</u>	<u>M569I</u>				
<u>AXL</u>	<u>M589K</u>				
<u>AXL</u>	<u>G835V</u>				
MER	E823Q				HEK-293, Q #
<u>MER</u>	<u>E831Q</u>				
MER	V870I				
<u>TYRO3</u>	<u>S324C</u>				
TYRO3	I346N				BPH-1, N # Brain, N # Cervix, N # Gastric, N # HaCaT, N # Hs 1.Li, N # HuVeC, N # Lung, N Ovary, N # Placenta, N #
TYRO3	E489K				
<u>TYRO3</u>	<u>S531L</u>				
<u>TYRO3</u>	<u>N788T</u>				
<u>TYRO3</u>	<u>P822L</u>				

116/306

Fig. 31 (cont.)												
Gene	Alte- ration	Total Number	Bladder	Bone and Soft Tissue	Brain	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta	Head & Neck	Hemato- poietic and Lymphoid System	Kidney
DDR family												G401, C #
DDR1	R60C	2						LoVo, A #				
DDR1	V100A	1										
DDR1	R248W	1					C-33A, W #					
DDR2	M117I	1						HCT-116, I #				
DDR2	R478C	1										
Gene	Alte- ration	Liver	Lung	Ovary	Pancreas	Prostate	Skin	Stomach	Testes	Thyroid	Normal Tissue	
DDR1	R60C											Cates 1B, C #
DDR1	V100A											
DDR1	R248W											
DDR2	M117I											
DDR2	R478C											
												MM-Arn, C

(cont. on next page)

117/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
EGFR family					
<u>EGFR</u>	<u>N115K</u>	<u>1</u>			
<u>EGFR</u>	<u>A289V</u>	<u>1</u>			
<u>EGFR</u>	<u>P332S</u>	<u>1</u>			<u>U-1240, S #</u>
<u>EGFR</u>	<u>R521K</u>	<u>80</u>		SaOS2, K #	A172, K # SF-126, K # SF-767, K #
<u>EGFR</u>	<u>I646L</u>	<u>1</u>			
<u>EGFR</u>	<u>T678M</u>	<u>1</u>			
<u>EGFR</u>	<u>G719S</u>	<u>1</u>			
<u>EGFR</u>	<u>P753S</u>	<u>1</u>			
<u>EGFR</u>	<u>E922K</u>	<u>2</u>			
<u>EGFR</u>	<u>A1118T</u>	<u>2</u>			
<u>HER2</u>	<u>G518E</u>	<u>1</u>			
<u>HER2</u>	<u>I655V</u>	<u>47</u>	T-24, V TCCSUP, V	RD, V TE-671, V	A172, V # CCF-STTG1, V SF-767, V SH-SY-5Y, V # U-1240, V # U-1242, V

118/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
EGFR family					
<u>EGFR</u>	<u>N115K</u>				
<u>EGFR</u>	<u>A289V</u>				<u>RL95-2, V #</u>
<u>EGFR</u>	<u>P332S</u>				
<u>EGFR</u>	<u>R521K</u>	HBL-100, K # MB-436, K ZR-75-1, K #	C-4II, K # SiHa, K #	Caco2, K # C. 320DM, K # DLD-1, K # HCT-15, K # LS-174T, K # LS-180, K # LoVo, K # NCI-H498, K # SK-CO-1, K # SNU-C2B, K # SW-837, K # SW-948, K #	RL95-2, K #
<u>EGFR</u>	<u>I646L</u>		<u>HeLa S3, L #</u>		
<u>EGFR</u>	<u>T678M</u>	<u>MB-361, M #</u>			
<u>EGFR</u>	<u>G719S</u>			<u>SW-48, S #</u>	
<u>EGFR</u>	<u>P753S</u>				
<u>EGFR</u>	<u>E922K</u>				
<u>EGFR</u>	<u>A1118T</u>				
<u>HER2</u>	<u>G518E</u>				<u>RL95-2, E #</u>
<u>HER2</u>	<u>I655V</u>	HBL-100, V #	C-4II, V # Ca Ski, V # HT-3, V # HeLa S3, V # ME-180, V	NCI-H498, V SW-1463, V # SW-48, V # SW-948, V	KLE, V

119/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
EGFR family					
<u>EGFR</u>	<u>N115K</u>	<u>SCC-17B, K #</u>			
<u>EGFR</u>	<u>A289V</u>				
<u>EGFR</u>	<u>P332S</u>				
EGFR	R521K	FaDu, K #		769-P, K #	HepG-2, K #
		HLaC-78, K #		A-498, K #	Hu-H7, K #
		SCC-15, K #		A-704, K #	
		SCC-25, K #		ACHN, K #	
		SCC-4, K #		CaKi-1, K #	
		SCC-17A, K #		CaKi-2, K	
		SCC-17B, K #		G401, K #	
		SCC-22A, K #			
		SCC-22B, K #			
<u>EGFR</u>	<u>I646L</u>				
<u>EGFR</u>	<u>T678M</u>				
<u>EGFR</u>	<u>G719S</u>				
<u>EGFR</u>	<u>P753S</u>				
<u>EGFR</u>	<u>E922K</u>				
<u>EGFR</u>	<u>A1118T</u>				
<u>HER2</u>	<u>G518E</u>				
HER2	I655V			786-0, V #	
				A-704, V #	
				ACHN, V	

120/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
EGFR family					
<u>EGFR</u>	<u>N115K</u>				
<u>EGFR</u>	<u>A289V</u>				
<u>EGFR</u>	<u>P332S</u>				
EGFR	R521K	A-427, K # A-549, K # Calu-3, K NCI-H441, K # NCI-H510A, K #	PA-1, K # SK-OV-3, K # SK-OV-6, K SK-OV-8, K #	AsPC-1, K # DANG-G, K # Hs 766T, K # PANC-1, K # SW-850, K #	BM-1604, K # DU-145, K #
<u>EGFR</u>	<u>I646L</u>				
<u>EGFR</u>	<u>T678M</u>				
<u>EGFR</u>	<u>G719S</u>				
<u>EGFR</u>	<u>P753S</u>				
<u>EGFR</u>	<u>E922K</u>			<u>818-4, K</u>	
<u>EGFR</u>	<u>A1118T</u>				
<u>HER2</u>	<u>G518E</u>				
HER2	I655V	NCI-H209, V NCI-H345, V NCI-H446, V NCI-H460, V #			PC-3, V PPC-1, V TSU-PR1, V

121/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
EGFR family						
<u>EGFR N115K</u>						
<u>EGFR A289V</u>						
<u>EGFR</u>	<u>P332S</u>					
EGFR	R521K	A-375, K # C-32, K # G-361, K # IGR-39, K # MeWo, K # SBCL2, K # WM-793, K # WM-902B, K #	KATO III, K MKN-1, K #	NT-2, K # Tera-2, K #		As-745, K # Bladder, K # Colon, K # Gastric, K HEK-293, K # Hs 1.Li, K # Kidney, K # MCF-10A, K # Placenta, K # Prostate, K S. Muscle, K # Spleen, K #
<u>EGFR</u>	<u>I646L</u>					
<u>EGFR</u>	<u>T678M</u>					
<u>EGFR</u>	<u>G719S</u>					
<u>EGFR</u>	<u>P753S</u>	SK-MEL-28, S #				
<u>EGFR</u>	<u>E922K</u>	MM-Arn, K #				
<u>EGFR</u>	<u>A1118T</u>				FTC133, T # FTC238, T #	
<u>HER2</u>	<u>G518E</u>					
HER2	I655V	BOW-G, V # Colo829, V MM-Alt, V # MM-Arn, V SBCL2, V # WM-115, V WM-239A, V WM-266-4, V		NT-2, V Tera-2, V		Colon, V # Hs 1.Li, V # Lung, V # MCF-10A, V # Ovary, V Testes, V

122/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
EGFR family (cont.)					
<u>HER2</u>	<u>A830V</u>	<u>2</u>			
<u>HER2</u>	<u>E930D</u>	<u>1</u>			
<u>HER2</u>	<u>G1015E</u>	<u>1</u>			
HER2	R1161Q	2			
HER2	P1170A	214	HT-1376, A RT-4, A SCaBER, A # TCCSUP, A	SaOS2, A TE-671, A # RD, A #	A172, A CCF-STTG1, A IMR-32, A SF-126, A SF-763, A # SF-767, A SH-SY-5Y, A SK-N-SH, A SW-1088, A T-98G, A U-1240, A #

123/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
EGFR family					
<u>HER2</u>	<u>A830V</u>				
<u>HER2</u>	<u>E930D</u>				
<u>HER2</u>	<u>G1015E</u>				
HER2	R1161Q				
HER2	P1170A	BT-483, A	C-33A, A	C. 320DM, A	JAR, A #
		HBL-100, A	C-4II, A #	DLD-1, A #	RL95-2, A
		Hs-578T, A	Ca Ski, A	HCT-116, A	
		MB-157, A	HT-3, A	HCT-15, A #	
		MB-175-VII, A #	HeLa S3, A #	LS-174T, A	
		MB-231, A	ME-180, A	LS-180, A	
		MB-361, A	MES-SA, A	LoVo, A	
		MB-415, A	Ms 751, A	NCI-H498, A	
		MB-436, A	SW 954, A #	SK-CO-1, A #	
		T-47D, A	SiHa, A	SW-1417, A	
		ZR-75-1, A #		SW-1463, A	
				SW-403, A #	
				SW-480, A	
				SW-620, A	
				SW-837, A	
				SW-948, A	
				T-84, A	

124/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
<u>HER2</u>	<u>A830V</u>				
<u>HER2</u>	<u>E930D</u>				
<u>HER2</u>	<u>G1015E</u>				
HER2	R1161Q		Daudi, Q #		
HER2	P1170A	FaDu, A	EM-2, A #	769-P, A #	HepG-2, A #
		HLaC-78, A #	HL-60, A #	786-0, A	Hs 817.T, A #
		HLaC-79, A #	IM-9, A	A-498, A	Hu-H7, A
		SCC-15, A	Jurkat, A	ACHN, A	SK-HEP-1, A
		SCC-25, A #	Kasumi-1, A #	CaKi-1, A #	
		SCC-9, A	M-07e, A #	CaKi-2, A	
		SCC-10A, A	MG63, A #	G401, A #	
		SCC-10B, A	MOLM-1, A #	SW13, A	
		SCC-17A, A	MV4-11, A #		
		SCC-17B, A	M-Mac-1, A		
		SCC-22A, A #	M-Mac-6, A		
		SCC-22B, A #	NB-4, A		
			OCI-AML5, A		
			PLB-985, A #		
			Raji, A		
			RF-1, A #		
			RF-48, A #		
			TF-1, A #		

125/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
<u>HER2</u>	<u>A830V</u>				
<u>HER2</u>	<u>E930D</u>				<u>LNCaP, D #</u>
<u>HER2</u>	<u>G1015E</u>			<u>Panc TU1, E #</u>	
<u>HER2</u>	<u>R1161Q</u>				
<u>HER2</u>	<u>P1170A</u>	A-427, A # A-549, A # Calu-1, A Calu-6, A NCI-H292, A # NCI-H345, A NCI-H441, A NCI-H446, A # NCI-H460, A NCI-H510A, A NCI-H520, A NCI-H596, A NCI-H661, A # NCI-H69, A NCI-H82, A SK-LU-1, A SK-MES-1, A SW-900, A	2774, A CaOV-3, A CaOV-4, A IGROV-1, A OAW-42, A # PA-1, A # SK-OV-3, A	818-4, A A-818-7, A AsPC-1, A # BxPC-3, A # CFPAC-1, A # Capan-1, A DANG-G, A Hs 766T, A Mia-PaCa2, A PT-8902, A PANC-1, A PT-45P1, A # PT-8988T, A Panc TU1, A SW-850, A #	BM-1604, A # DU-145, A # LNCaP.FGC, A TSU-PR1, A #

126/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
HER2	A830V				<u>FTC133, V</u>	
					<u>FTC238, V</u>	
HER2	E930D					
HER2	G1015E					
HER2	R1161Q					Kidney, Q #
HER2	P1170A	A-375, A # BOW-G, A C-32, A C-8161, A Colo829, A # G-361, A # HT-144, A # Hs-294T, A KA-II, A # MALME-3M, A # MM-194-G, A MM-195-H, A # MM-201-B, A # MM-254-C, A MM-358-A, A MM-Alb, A MM-Alt, A MM-Arn, A MM-Leh, A MRI-H221, A MeWo, A # Mel Ger, A # Mel Juso, A # SBCL2, A SK-MEL-2, A # SK-MEL-24, A SK-MEL-3, A SK-MEL-31, A # SK-MEL-5, A # WM-115, A # WM-1205, A WM-1341D, A WM-1617, A WM-239A, A # WM-266-4, A # WM-35, A WM-793, A WM-852, A # WM-902B, A WM-983A, A WM-983B, A Colo-16, A #	AGS, A # HS-746T, A KATO III, A MKN-1, A #	Cates 1B, A # Tera-2, A	FTC133, A FTC238, A TT, A #	As-745, A Bladder, A Brain, A Cervix, A # Colon, A # Gastric, A # HEK-293, A # HaCaT, A Hs 1.Li, A # HuVeC, A Liver, A Lung, A MCF-10A, A # Ovary, A # Pancreas, A Placenta, A # Prostate, A S. Muscle, A # Testes, A #

127/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
EGFR family (cont.)					
HER2	A1216D	3		RD, D # TE-671, D #	
<u>HER3</u>	<u>N126K</u>	<u>3</u>			
<u>HER3</u>	<u>R611W</u>	<u>1</u>			
<u>HER3</u>	<u>R667H</u>	<u>3</u>			
<u>HER3</u>	<u>R1077W</u>	<u>1</u>			
<u>HER3</u>	<u>R1089W</u>	<u>1</u>			
HER3	S1119C	36			1321N1, C #
<u>HER3</u>	<u>P1142H</u>	<u>2</u>			
HER3	L1177I	6			
<u>HER4</u>	<u>L753V</u>	<u>1</u>			<u>SF-767, V #</u>
<u>HER4</u>	<u>G936R</u>	<u>1</u>			
EPH family					
EPHA1	A160V	4			
EPHA1	V900M	20	T-24, M #		
EPHA1	S936L	1			
<u>EPHA2</u>	<u>R315Q</u>	<u>1</u>			
<u>EPHA2</u>	<u>H333R</u>	<u>1</u>			
EPHA2	G391R	6	TCCSUP, R		

128/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
HER2	A1216D				
<u>HER3</u>	<u>N126K</u>			<u>DLD-1, K #</u>	
				<u>HCT-15, K #</u>	
<u>HER3</u>	<u>R611W</u>				
<u>HER3</u>	<u>R667H</u>			<u>DLD-1, H #</u>	
				<u>HCT-15, H #</u>	
<u>HER3</u>	<u>R1077W</u>				
<u>HER3</u>	<u>R1089W</u>				
HER3	S1119C	DU-44-75, C #	C-33A, C #	DLD-1, C #	JAR, C #
		MB-435S, C #	C-4II, C #	SW-1417, C #	
			MES-SA, C #		
			SW 954, C #		
<u>HER3</u>	<u>P1142H</u>			<u>DLD-1, H #</u>	
				<u>HCT-15, H #</u>	
HER3	L1177I				
<u>HER4</u>	<u>L753V</u>				
<u>HER4</u>	<u>G936R</u>				
EPH family					
EPHA1	A160V			LoVo, V #	
EPHA1	V900M	BT-483, M #	Ms 751, M #		JAR, M #
		DU-44-75, M			
		HL-100, M #			
EPHA1	S936L	MB-231, M			
<u>EPHA2</u>	<u>R315Q</u>				
<u>EPHA2</u>	<u>H333R</u>			<u>NCI-H498, R #</u>	
EPHA2	G391R				

129/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
HER2	A1216D				
<u>HER3</u>	<u>N126K</u>				
<u>HER3</u>	<u>R611W</u>		<u>K-562, W #</u>		
<u>HER3</u>	<u>R667H</u>				
<u>HER3</u>	<u>R1077W</u>				
<u>HER3</u>	<u>R1089W</u>				
HER3	S1119C			A-704, C #	
<u>HER3</u>	<u>P1142H</u>				
HER3	L1177I	SCC-17A, I # SCC-17B, I #			
<u>HER4</u>	<u>L753V</u>				
<u>HER4</u>	<u>G936R</u>				
EPH family					
EPHA1	A160V		Raji, V #		
EPHA1	V900M		K-562, M # Raji, M # U-937, M #	ACHN, M #	
EPHA1	S936L				
<u>EPHA2</u>	<u>R315Q</u>				
<u>EPHA2</u>	<u>H333R</u>				
EPHA2	G391R				

130/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
HER2	A1216D				
<u>HER3</u>	<u>N126K</u>				
<u>HER3</u>	<u>R611W</u>				
<u>HER3</u>	<u>R667H</u>				
<u>HER3</u>	<u>R1077W</u>				
<u>HER3</u>	<u>R1089W</u>				
HER3	S1119C	NCI-H128, C # NCI-H441, C	IGROV-1, C #	CFPAC-1, C PT-8902, C # Panc TU1, C # SW-850, C #	LNCaP.FGC, C # PC-3, C # TSU-PR1, C #
<u>HER3</u>	<u>P1142H</u>				
HER3	L1177I				
<u>HER4</u>	<u>L753V</u>				
<u>HER4</u>	<u>G936R</u>	<u>SK-MES-1, R #</u>			
EPH family					
EPHA1	A160V	NCI-H292, V #			
EPHA1	V900M		SK-OV-3, M	PT-8988T, M #	LNCaP, M # PC-3, M # PPC-1, M #
EPHA1	S936L				
<u>EPHA2</u>	<u>R315Q</u>	<u>NCI-H441, Q #</u>			
<u>EPHA2</u>	<u>H333R</u>				
EPHA2	G391R	NCI-H441, R #		SW-850, R #	

131/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue				
HER2	A1216D	MM-195-H, D #	MKN-1, K #	NT-2, C Tera-2, C	FTC133, C # FTC238, C #	Bladder, C # Liver, C # MCF-10A, C # Pancreas, C #				
HER3	N126K									
HER3	R611W									
HER3	R667H									
HER3	R1077W	SK-MEL-24, W #	MKN-1, W #							
HER3	R1089W									
HER3	S1119C	G-361, C # HT-144, C # Hs-294T, C # MM-Arn, C WM-1341D, C # WM-902B, C #								
HER3	P1142H									
HER3	L1177I	MM-031-I, I # MM-232-E, I # WM-983A, I # WM-983B, I #								
HER4	L753V									
HER4	G936R									
EPH family										
EPHA1	A160V	MM-Su, M #				Placenta, V Cervix, M MCF-10A, M # Placenta, M # Spleen, L #				
EPHA1	V900M									
EPHA1	S936L									
EPHA2	R315Q									
EPHA2	H333R									
EPHA2	G391R	MM-254-C, R # MM-Lo, R #	MKN-1, R #							

132/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
<u>EPHA2</u>	<u>P460L</u>	<u>1</u>			
<u>EPHA2</u>	<u>H609Y</u>	<u>1</u>			
<u>EPHA2</u>	<u>M631T</u>	<u>3</u>			
<u>EPHA2</u>	<u>G662S</u>	<u>1</u>			<u>U-1240, S #</u>
<u>EPHA2</u>	<u>V747I</u>	<u>1</u>			
<u>EPHA2</u>	<u>L836R</u>	<u>1</u>			
<u>EPHA2</u>	<u>R876H</u>	<u>16</u>			SF-126, H
<u>EPHA2</u>	<u>E911K</u>	<u>1</u>			
<u>EPHA2</u>	<u>V936M</u>	<u>1</u>			
<u>EPHA2</u>	<u>R950W</u>	<u>1</u>			
<u>EPHA3</u>	<u>S46F</u>	<u>1</u>			
<u>EPHA3</u>	<u>E53K</u>	<u>1</u>			
<u>EPHA3</u>	<u>I564V</u>	<u>1</u>			
<u>EPHA3</u>	<u>A777G</u>	<u>1</u>			
<u>EPHA3</u>	<u>R914H</u>	<u>15</u>			U-1242, H #
<u>EPHA3</u>	<u>W924R</u>	<u>74</u>			CCF-STTG1, R # SF-126, R # SF-763, R #

133/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>EPHA2</u>	<u>P460L</u>				
<u>EPHA2</u>	<u>H609Y</u>				
<u>EPHA2</u>	<u>M631T</u>	MB-157, T # MB-175-VII, T #			
<u>EPHA2</u>	<u>G662S</u>				
<u>EPHA2</u>	<u>V747I</u>				
<u>EPHA2</u>	<u>L836R</u>				
<u>EPHA2</u>	<u>R876H</u>			DLD-1, H # HCT-15, H #	
<u>EPHA2</u>	<u>E911K</u>			<u>WiDr, K #</u>	
<u>EPHA2</u>	<u>V936M</u>				
<u>EPHA2</u>	<u>R950W</u>				<u>RL95-2, W #</u>
<u>EPHA3</u>	<u>S46F</u>				
<u>EPHA3</u>	<u>E53K</u>				
<u>EPHA3</u>	<u>I564V</u>				
<u>EPHA3</u>	<u>A777G</u>				
<u>EPHA3</u>	<u>R914H</u>			C. 320DM, H #	
<u>EPHA3</u>	<u>W924R</u>	Hs-578T, R # MB-157, R MB-435S, R #		C. 320DM, R KLE, R LoVo, R	

134/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
<u>EPHA2</u>	<u>P460L</u>			<u>ACHN, L</u>	
<u>EPHA2</u>	<u>H609Y</u>				
<u>EPHA2</u>	<u>M631T</u>				
<u>EPHA2</u>	<u>G662S</u>				
<u>EPHA2</u>	<u>V747I</u>		<u>KG-1, I #</u>		
<u>EPHA2</u>	<u>L836R</u>				
<u>EPHA2</u>	<u>R876H</u>				
<u>EPHA2</u>	<u>E911K</u>				
<u>EPHA2</u>	<u>V936M</u>				
<u>EPHA2</u>	<u>R950W</u>				
<u>EPHA3</u>	<u>S46F</u>				
<u>EPHA3</u>	<u>E53K</u>				
<u>EPHA3</u>	<u>I564V</u>				
<u>EPHA3</u>	<u>A777G</u>				
<u>EPHA3</u>	<u>R914H</u>	SCC-15, H #	IM-9, H #		
<u>EPHA3</u>	<u>W924R</u>	SCC-15, R # SCC-10A, R # SCC-10B, R	Daudi, R IM-9, R # U-266, R	A-498, R A-704, R #	

135/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
<u>EPHA2</u>	<u>P460L</u>				
<u>EPHA2</u>	<u>H609Y</u>				
<u>EPHA2</u>	<u>M631T</u>		2780, T #		
<u>EPHA2</u>	<u>G662S</u>				
<u>EPHA2</u>	<u>V747I</u>				
<u>EPHA2</u>	<u>L836R</u>				
<u>EPHA2</u>	<u>R876H</u>	NCI-H345, H #		PT-45P1, H #	
<u>EPHA2</u>	<u>E911K</u>				
<u>EPHA2</u>	<u>V936M</u>		<u>2774, M #</u>		
<u>EPHA2</u>	<u>R950W</u>				
<u>EPHA3</u>	<u>S46F</u>				
<u>EPHA3</u>	<u>E53K</u>				
<u>EPHA3</u>	<u>I564V</u>				
<u>EPHA3</u>	<u>A777G</u>				TSU-PR1, G
<u>EPHA3</u>	<u>R914H</u>				PC-3, H # PPC-1, H #
<u>EPHA3</u>	<u>W924R</u>	A-427, R # NCI-H146, R # NCI-H460, R # NCI-H520, R # NCI-H82, R #	2774, R 2780, R CaOV-3, R # CaOV-4, R # OVCAR-3, R # PA-1, R SK-OV-3, R SK-OV-8, R #	PT-8988T, R	PC-3, R PPC-1, R TSU-PR1, R

136/306

136/306

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue	
EPHA2	P460L	MM-358-A, Y #	MKN-1, H #		FTC133, H FTC238, H	BPH-1, H # Kidney, H # Ovary, H #	
EPHA2	H609Y						
EPHA2	M631T						
EPHA2	G662S						
EPHA2	V747I						
EPHA2	L836R						MeWo, R #
EPHA2	R876H						C-8161, H # Colo829, H MM-031-I, H MM-232-E, H MM-Alt, H #
EPHA2	E911K						
EPHA2	V936M						
EPHA2	R950W						
EPHA3	S46F	MeWo, F #					
EPHA3	E53K	MeWo, K #					
EPHA3	I564V	IGR-39, H # MALME-3M, H # WM-902B, H #				S. Muscle, V # Bladder, H # Brain, H # Liver, H # Ovary, H # S. Muscle, H # Testes, H # As-745, R Bladder, R # Brain, R # Cervix, R # Gastric, R # HaCaT, R Liver, R # Lung, R # Ovary, R Placenta, R # Prostate, R # S. Muscle, R # Testes, R #	
EPHA3	A777G						
EPHA3	R914H						
EPHA3	W924R	A-375, R # C-32, R # F-01, R # G-361, R # Hs-294T, R # Hs-695T, R IGR-39, R MALME-3M, R # MM-031-I, R # MM-232-E, R # MM-Alb, R MM-Leh, R # MM-Lo, R # MRI-H221, R # MeWo, R # Mel Ger, R RPMI7951, R # SBCL2, R # SK-MEL-24, R # SK-MEL-28, R # SK-MEL-31, R WM-1205, R # WM-1617, R # WM-35, R # WM-793, R # WM-852, R # WM-902B, R #					

Fig. 31 (continued)

Fig. 31 (continued)

137/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
<u>EPHA4</u>	<u>V234F</u>	<u>1</u>			
<u>EPHA4</u>	<u>S803A</u>	<u>1</u>			
<u>EPHA4</u>	<u>M877V</u>	<u>1</u>			
<u>EPHA5</u>	<u>N81T</u>	<u>9</u>			
<u>EPHA5</u>	<u>E85K</u>	<u>1</u>			
<u>EPHA5</u>	<u>A672T</u>	<u>8</u>			U-1240, T
<u>EPHA5</u>	<u>V891L</u>	<u>1</u>			
<u>EPHA5</u>	<u>A957T</u>	<u>1</u>	<u>SCaBER, T</u>		
<u>EPHA5</u>	<u>R981L</u>	<u>2</u>			
<u>EPHA6</u>	<u>N291H</u>	<u>1</u>			
<u>EPHA6</u>	<u>G513E</u>	<u>1</u>			
<u>EPHA6</u>	<u>L622F</u>	<u>1</u>			
<u>EPHA7</u>	<u>I138V</u>	<u>7</u>			
<u>EPHA10</u>	<u>L629P</u>	<u>2</u>			
<u>EPHA10</u>	<u>V645I</u>	<u>1</u>			
<u>EPHA10</u>	<u>G749E</u>	<u>17</u>	<u>RT-4, E</u>		SF-763, E #
<u>EPHB1</u>	<u>A39V</u>	<u>1</u>			
<u>EPHB1</u>	<u>I837M</u>	<u>1</u>			
<u>EPHB2</u>	<u>A83V</u>	<u>1</u>			

138/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>EPHA4</u>	<u>V234F</u>				
<u>EPHA4</u>	<u>S803A</u>				
<u>EPHA4</u>	<u>M877V</u>	<u>MB-435S, V #</u>			
<u>EPHA5</u>	<u>N81T</u>				
<u>EPHA5</u>	<u>E85K</u>				
<u>EPHA5</u>	<u>A672T</u>	<u>BT-549, T</u>	<u>C-33A, T #</u>		
<u>EPHA5</u>	<u>V891L</u>				
<u>EPHA5</u>	<u>A957T</u>				
<u>EPHA5</u>	<u>R981L</u>	<u>MB-415, L</u>			
<u>EPHA6</u>	<u>N291H</u>				
<u>EPHA6</u>	<u>G513E</u>			<u>LoVo, E #</u>	
<u>EPHA6</u>	<u>L622F</u>				
<u>EPHA7</u>	<u>I138V</u>				
<u>EPHA10</u>	<u>L629P</u>				
<u>EPHA10</u>	<u>V645I</u>				
<u>EPHA10</u>	<u>G749E</u>	<u>ZR-75-1, E</u>		<u>DLD-1, E #</u> <u>SW-1463, E #</u>	
<u>EPHB1</u>	<u>A39V</u>				
<u>EPHB1</u>	<u>I837M</u>				
<u>EPHB2</u>	<u>A83V</u>				

139/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
<u>EPHA4</u>	<u>V234F</u>				
<u>EPHA4</u>	<u>S803A</u>				
<u>EPHA4</u>	<u>M877V</u>				
<u>EPHA5</u>	<u>N81T</u>	SCC-9, T # SCC-17B, T SCC-22A, T # SCC-22B, T #	Jurkat, T #		
<u>EPHA5</u>	<u>E85K</u>				
<u>EPHA5</u>	<u>A672T</u>				
<u>EPHA5</u>	<u>V891L</u>				
<u>EPHA5</u>	<u>A957T</u>				
<u>EPHA5</u>	<u>R981L</u>				
<u>EPHA6</u>	<u>N291H</u>				
<u>EPHA6</u>	<u>G513E</u>				
<u>EPHA6</u>	<u>L622F</u>				
<u>EPHA7</u>	<u>I138V</u>	SCC-15, V #	TF-1, V #		
	<u>L629P</u>				Hs 817.T, P #
	<u>V645I</u>				Hs 817.T, I #
	<u>G749E</u>				SK-HEP-1, E
<u>EPHB1</u>	<u>A39V</u>				
<u>EPHB1</u>	<u>I837M</u>				
<u>EPHB2</u>	<u>A83V</u>				<u>Hs 817.T, V #</u>

140/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
<u>EPHA4</u>	V234F				
<u>EPHA4</u>	S803A				
<u>EPHA4</u>	M877V				
<u>EPHA5</u>	N81T				
<u>EPHA5</u>	E85K				
<u>EPHA5</u>	A672T		CaOV-3, T #		
<u>EPHA5</u>	V891L	SK-MES-1, L #			
<u>EPHA5</u>	A957T				
<u>EPHA5</u>	R981L				
<u>EPHA6</u>	N291H				
<u>EPHA6</u>	G513E				
<u>EPHA6</u>	L622F		2774, F #		
<u>EPHA7</u>	I138V			PANC-1, V # PT-45P1, V #	LNCaP, V
<u>EPHA10</u>	L629P	NCI-H661, P #			
<u>EPHA10</u>	V645I				
<u>EPHA10</u>	G749E	A-549, E NCI-H441, E NCI-H510A, E #	CaOV-3, E # OAW-42, E	AsPC-1, E # CFPAC-1, E # Mia-PaCa2, E	LNCaP, E # PC-3, E
<u>EPHB1</u>	A39V				
<u>EPHB1</u>	I837M	NCI-H345, M			
<u>EPHB2</u>	A83V				

141/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
EPHA4	V234F	WM-852, F #	MKN-1, A #			
EPHA4	S803A					
EPHA4	M877V					
EPHA5	N81T	Colo829, T # MM-254-C, T # MM-Alb, T WM-1617, T #				
EPHA5	E85K	A-375, K				
EPHA5	A672T	MM-195-H, T # WM-1341D, T # WM-983A, T # WM-983B, T #				
EPHA5	V891L					
EPHA5	A957T					
EPHA5	R981L		HS-746T, L			
EPHA6	N291H		MKN-1, H #			
EPHA6	G513E					S. Muscle, V # Spleen, V # Testes, E #
EPHA6	L622F					
EPHA7	I138V					
EPHA10	L629P					
EPHA10	V645I					
EPHA10	G749E					
EPHB1	A39V					
EPHB1	I837M					
EPHB2	A83V		MKN-1, V #			

142/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
<u>EPHB2</u>	<u>S98R</u>	<u>2</u>			
<u>EPHB2</u>	<u>P128A</u>	<u>1</u>			
<u>EPHB2</u>	<u>V136M</u>	<u>2</u>			
<u>EPHB2</u>	<u>R270Q</u>	<u>2</u>			
<u>EPHB2</u>	<u>P273L</u>	<u>1</u>			
<u>EPHB2</u>	<u>R369Q</u>	<u>2</u>			
<u>EPHB2</u>	<u>E686K</u>	<u>1</u>			
<u>EPHB2</u>	<u>Q722X</u>	<u>2</u>			
<u>EPHB2</u>	<u>V762L</u>	<u>1</u>			
<u>EPHB3</u>	<u>P6del</u>	<u>2</u>			
<u>EPHB3</u>	<u>R514Q</u>	<u>1</u>			
<u>EPHB3</u>	<u>A517V</u>	<u>1</u>			
<u>EPHB4</u>	<u>P231S</u>	<u>1</u>			
<u>EPHB4</u>	<u>V547M</u>	<u>1</u>			<u>SF-763, M #</u>
<u>EPHB4</u>	<u>D576G</u>	<u>1</u>			
<u>EPHB4</u>	<u>I610T</u>	<u>2</u>			
<u>EPHB4</u>	<u>E890D</u>	<u>3</u>			
<u>EPHB4</u>	<u>A995V</u>	<u>1</u>			
<u>EPHB6</u>	<u>G107S</u>	<u>1</u>			
<u>EPHB6</u>	<u>S309A</u>	<u>4</u>			
<u>EPHB6</u>	<u>G353_E471del</u>	<u>3</u>			<u>SW-1088, - #</u>
<u>EPHB6</u>	<u>A369T</u>	<u>1</u>			
<u>EPHB6</u>	<u>L580F</u>	<u>2</u>			
<u>EPHB6</u>	<u>E615K</u>	<u>1</u>			
<u>EPHB6</u>	<u>A647V</u>	<u>1</u>			
<u>EPHB6</u>	<u>S785R</u>	<u>1</u>			
<u>EPHB6</u>	<u>R811C</u>	<u>1</u>			

143/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>EPHB2</u>	<u>S98R</u>				
<u>EPHB2</u>	<u>P128A</u>				
<u>EPHB2</u>	<u>V136M</u>				
<u>EPHB2</u>	<u>R270Q</u>				
<u>EPHB2</u>	<u>P273L</u>				
<u>EPHB2</u>	<u>R369Q</u>				
<u>EPHB2</u>	<u>E686K</u>				
<u>EPHB2</u>	<u>Q722X</u>				
<u>EPHB2</u>	<u>V762L</u>				
<u>EPHB3</u>	<u>P6del</u>			<u>LS-174T, -</u>	
<u>EPHB3</u>	<u>R514Q</u>			<u>LS-180, -</u>	
<u>EPHB3</u>	<u>A517V</u>			<u>DLD-1, V #</u>	
<u>EPHB4</u>	<u>P231S</u>				
<u>EPHB4</u>	<u>V547M</u>				
<u>EPHB4</u>	<u>D576G</u>				
<u>EPHB4</u>	<u>I610T</u>			<u>SW-48, T #</u>	
<u>EPHB4</u>	<u>E890D</u>				
<u>EPHB4</u>	<u>A995V</u>				
<u>EPHB6</u>	<u>G107S</u>				
<u>EPHB6</u>	<u>S309A</u>			<u>LS-174T, A #</u>	
				<u>LS-180, A #</u>	
<u>EPHB6</u>	<u>G353_E471del</u>		<u>Ms 751, A #</u>		
<u>EPHB6</u>	<u>A369T</u>				
<u>EPHB6</u>	<u>L580F</u>				
<u>EPHB6</u>	<u>E615K</u>				
<u>EPHB6</u>	<u>A647V</u>			<u>HCT-116, V #</u>	
<u>EPHB6</u>	<u>S785R</u>			<u>SW-948, R</u>	
<u>EPHB6</u>	<u>R811C</u>				

144/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
<u>EPHB2</u>	<u>S98R</u>	<u>SCC-17A, R #</u>			
		<u>SCC-17B, R #</u>			
<u>EPHB2</u>	<u>P128A</u>				
<u>EPHB2</u>	<u>V136M</u>				
<u>EPHB2</u>	<u>R270Q</u>	<u>SCC-10A, Q #</u>			
		<u>SCC-10B, Q #</u>			
<u>EPHB2</u>	<u>P273L</u>				
<u>EPHB2</u>	<u>R369Q</u>				
<u>EPHB2</u>	<u>E686K</u>				
<u>EPHB2</u>	<u>Q722X</u>				
<u>EPHB2</u>	<u>V762L</u>				
<u>EPHB3</u>	<u>P6del</u>				
<u>EPHB3</u>	<u>R514Q</u>				
<u>EPHB3</u>	<u>A517V</u>				
<u>EPHB4</u>	<u>P231S</u>				<u>HepG-2, S #</u>
<u>EPHB4</u>	<u>V547M</u>				
<u>EPHB4</u>	<u>D576G</u>				
<u>EPHB4</u>	<u>I610T</u>			<u>A-704, T #</u>	
<u>EPHB4</u>	<u>E890D</u>	<u>SCC-4, D #</u>	<u>EM-2, D #</u>		
			<u>Raji, D #</u>		
<u>EPHB4</u>	<u>A995V</u>				
<u>EPHB6</u>	<u>G107S</u>				
<u>EPHB6</u>	<u>S309A</u>		<u>KG-1, A</u>		
<u>EPHB6</u>	<u>G353_E471del</u>				
<u>EPHB6</u>	<u>A369T</u>		<u>Jurkat, T</u>		
<u>EPHB6</u>	<u>L580F</u>				
<u>EPHB6</u>	<u>E615K</u>				
<u>EPHB6</u>	<u>A647V</u>				
<u>EPHB6</u>	<u>S785R</u>				
<u>EPHB6</u>	<u>R811C</u>				

145/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
<u>EPHB2</u>	<u>S98R</u>				
<u>EPHB2</u>	<u>P128A</u>				
<u>EPHB2</u>	<u>V136M</u>				
<u>EPHB2</u>	<u>R270Q</u>				
<u>EPHB2</u>	<u>P273L</u>				<u>TSU-PR1, L #</u>
<u>EPHB2</u>	<u>R369Q</u>			<u>Mia-PaCa2, Q</u>	
<u>EPHB2</u>	<u>E686K</u>				
<u>EPHB2</u>	<u>Q722X</u>				<u>BM-1604, *</u>
<u>EPHB2</u>	<u>V762L</u>				<u>DU-145, *</u>
<u>EPHB3</u>	<u>P6del</u>	<u>NCI-H345, L #</u>			
<u>EPHB3</u>	<u>R514Q</u>				
<u>EPHB3</u>	<u>A517V</u>				
<u>EPHB4</u>	<u>P231S</u>				
<u>EPHB4</u>	<u>V547M</u>				
<u>EPHB4</u>	<u>D576G</u>				<u>LNCaP, G #</u>
<u>EPHB4</u>	<u>I610T</u>				
<u>EPHB4</u>	<u>E890D</u>				
<u>EPHB4</u>	<u>A995V</u>		<u>IGROV-1, V #</u>		
<u>EPHB6</u>	<u>G107S</u>	<u>Calu-6, S #</u>			
<u>EPHB6</u>	<u>S309A</u>	<u>SK-LU-1, A</u>			
<u>EPHB6</u>	<u>G353_E471del</u>		<u>IGROV-1, - #</u>		
<u>EPHB6</u>	<u>A369T</u>				
<u>EPHB6</u>	<u>L580F</u>				<u>BM-1604, F #</u>
					<u>DU-145, F #</u>
<u>EPHB6</u>	<u>E615K</u>				
<u>EPHB6</u>	<u>A647V</u>				
<u>EPHB6</u>	<u>S785R</u>				
<u>EPHB6</u>	<u>R811C</u>				

146/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
<u>EPHB2</u>	<u>S98R</u>	MM-Alt, Q MM-Leh, K #	MKN-1, M #			Kidney, A #
<u>EPHB2</u>	<u>P128A</u>					
<u>EPHB2</u>	<u>V136M</u>					
<u>EPHB2</u>	<u>R270Q</u>					
<u>EPHB2</u>	<u>P273L</u>					
<u>EPHB2</u>	<u>R369Q</u>					
<u>EPHB2</u>	<u>E686K</u>					
<u>EPHB2</u>	<u>Q722X</u>					
<u>EPHB2</u>	<u>V762L</u>					
<u>EPHB3</u>	<u>P6del</u>					
<u>EPHB3</u>	<u>R514Q</u>		Hs 1.Li, Q #			
<u>EPHB3</u>	<u>A517V</u>					
<u>EPHB4</u>	<u>P231S</u>					
<u>EPHB4</u>	<u>V547M</u>					
<u>EPHB4</u>	<u>D576G</u>					
<u>EPHB4</u>	<u>I610T</u>					
<u>EPHB4</u>	<u>E890D</u>					
<u>EPHB4</u>	<u>A995V</u>					
<u>EPHB6</u>	<u>G107S</u>					
<u>EPHB6</u>	<u>S309A</u>					
<u>EPHB6</u>	<u>G353_E471del</u>					
<u>EPHB6</u>	<u>A369T</u>					
<u>EPHB6</u>	<u>L580F</u>					
<u>EPHB6</u>	<u>E615K</u>	MeWo, K #				
<u>EPHB6</u>	<u>A647V</u>	MeWo, C #				
<u>EPHB6</u>	<u>S785R</u>					
<u>EPHB6</u>	<u>R811C</u>					

147/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
FGFR family					
FGFR1	R78H	1			
FGFR1	P252S	1			
FGFR1	A268S	3			
FGFR1	T428_V429del	5			
FGFR1	G539_K540del	7			
FGFR2	M71T	3	SCaBER, T # T-24, T #		
FGFR2	H199_Q247delins48	54	TCCSUP, -	MG63, - RD, - SaOS2, - TE-671, -	CCF-STTG1, - IMR-32, - SH-SY-5Y, - SK-N-SH, - # SW-1088, - U-1240, - U-1242, -
FGFR2	I526T	1			
FGFR3	T311_Q422del	1			
FGFR4	V10I	8		RD, I TE-671, I	
FGFR4	L136P	37	SCaBER, P	SaOS2, P #	

148/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
FGFR1	R78H				
FGFR1	P252S				
FGFR1	A268S			DLD-1, S	
				HCT-15, S	
FGFR1	T428_V429del	MB-436, - #			
FGFR1	G539 K540del				
FGFR2	M71T				
FGFR2	H199_Q247delins48	MB-436, -	C-33A, - MES-SA, -	LS-180, - # LoVo, - #	KLE, -
FGFR2	I526T				
FGFR3	T311_Q422del			HCT-116, -	
FGFR4	V10I			LS-174T, I # LS-180, I #	JAR, I #
FGFR4	L136P	BT-474, P BT-483, P # MB-157, P MB-415, P		HCT-116, P # LS-123, P # LS-174T, P # LS-180, P # LoVo, P SW-837, P	

149/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
FGFR1	R78H				
FGFR1	P252S				
FGFR1	A268S				
FGFR1	T428_V429del		KG-1, - #		
FGFR1	G539_K540del		RF-1, - # RF-48, - #		
FGFR2	M71T		U-937, T #		
FGFR2	H199_Q247delins48		KG-1, -	769-P, - 786-0, - A-498, - ACHN, - CaKi-1, - CaKi-2, -	Hu-H7, -
FGFR2	I526T			A-498, T #	
FGFR3	T311_Q422del				
FGFR4	V10I		OCI-AML5, I#	786-0, I	
FGFR4	L136P		HL-60, P K-562, P # PLB-985, P U-266, P	769-P, P CaKi-1, P # SW13, P #	SK-HEP-1, P

150/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
FGFR1	R78H				LNCaP, H #
FGFR1	P252S				
FGFR1	A268S				
FGFR1	T428_V429del			Capan-2, - # PT-8902, - #	
FGFR1	G539_K540del	NCI-H345, - #	2774, - #		
FGFR2	M71T				
FGFR2	H199_Q247delins48	A-549, - Calu-6, - NCI-H446, - NCI-H596, - # NCI-H661, - NCI-H82, -	2774, - # IGROV-1, - OAW-42, - PA-1, -	Mia-PaCa2, -	BM-1604, - # DU-145, - # TSU-PR1, -
FGFR2	I526T				
FGFR3	T311_Q422del				
FGFR4	V10I				
FGFR4	L136P	NCI-H128, P NCI-H446, P NCI-H661, P NCI-H69, P	OVCAR-3, P	A-818-7, P CFPAC-1, P PT-8902, P	

151/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
FGFR1	R78H					
FGFR1	P252S	MeWo, S #				
FGFR1	A268S		MKN-1, S			
FGFR1	T428_V429del	HT-144, - #				
FGFR1	G539_K540del	WM-115, - #				
		WM-239A, - #				
		WM-266-4, - #				
FGFR2	M71T					
FGFR2	H199_Q247delins48	F-01, - MM-194-G, - MM-201-B, -		Tera-2, -		Bladder, - # Brain, - Cervix, - Colon, - Gastric, - # HEK-293, - Kidney, - Liver, - # Ovary, - Testes, -
FGFR2	I526T					
FGFR3	T311_Q422del					
FGFR4	V10I					Colon, I #
FGFR4	L136P	MM-194-G, P MM-358-A, P MM-Leh, P Mel Ger, P RPMI7951, P				Hs 1.Li, P # HuVeC, P Kidney, P

152/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
FGFR4	Y367C	1			
FGFR4	G388R	58	TCCSUP, R		SH-SY-5Y, R # SK-N-SH, R # SW-1088, R # U-1240, R U-1242, R
INSR family					
IGF1R	T104M	1			
IGF1R	Y201H	1			
IGF1R	N209S	1			
INSR	L991I	2			
MET family					
MET	T17I	1			
MET	P366S	1			
MET	N375S	4			
MET	S691L	1			
MET	D981_F1027del	3			
MET	R988C	2			
MET	T1010I	8			IMR-32, I #
MET	V1238I	1			
RON	N440S	2			
RON	Q473_D515del	1			
RON	R523Q	57	HT-1376, Q RT-4, Q # SCaBER, Q T-24, Q # TCCSUP, Q #	MG63, Q	CCF-STTG1, Q SF-126, Q SF-767, Q T-98G, Q U-118, Q #

153/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
FGFR4	Y367C	MB-453, C			
FGFR4	G388R	Hs-578T, R MB-361, R # MB-453, R SK-BR-3, R	Ms 751, R	Caco2, R SW-403, R #	
INSR family					
IGF1R	T104M				
IGF1R	Y201H				
IGF1R	N209S				
INSR	L991I		HeLa S3, I		
MET family					
MET	T17I				
MET	P366S				
MET	N375S				
MET	S691L				
MET	D981_F1027del	MB-415,			
MET	R988C				
MET	T1010I	DAL, I # DU-44-75, I MB-231, I #		LS-123, I	
MET	V1238I				
RON	N440S		HeLa S3, S #		
RON	Q473_D515del				
RON	R523Q	MCF-7, Q # MB-361, Q MB-435S, Q ZR-75-1, Q #	C-4II, Q # Ca Ski, Q HeLa S3, Q # ME-180, Q Ms 751, Q SiHa, Q	LS-174T, Q # LS-180, Q SW-1463, Q WiDr, Q #	JAR, Q #

154/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
FGFR4	Y367C				
FGFR4	G388R	SCC-4, R SCC-22B, R SCC-22A, R	EM-2, R M-Mac-1, R #ACHN, R M-Mac-6, R #CaKi-2, R #	A-704, R #	HepG-2, R Hu-H7, R
INSR family					
IGF1R	T104M		Kasumi-1, M #		
IGF1R	Y201H				Hs 817.T, H #
IGF1R	N209S				
INSR	L991I	HLaC-79, I			
MET family					
MET	T17I				
MET	P366S				
MET	N375S	SCC-15, S #			
MET	S691L				
MET	D981_E1027del				
MET	R988C				
MET	T1010I		U-266, I		
MET	V1238I			CaKi-1, I	
RON	N440S	HLaC-79, S			
RON	Q473_D515del				
RON	R523Q		Daudi, Q EM-2, Q # IM-9, Q Kasumi-1, Q # TF-1, Q U-937, Q #	786-0, Q A-498, Q A-704, Q #	

155/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
FGFR4	Y367C				
FGFR4	G388R	A-549, R # Calu-6, R NCI-H146, R NCI-H345, R # NCI-H460, R NCI-H82, R	IGROV-1, R # OAW-42, R #	AsPC-1, R # BxPC-3, R # Panc TU1, R # SW-850, R #	PC-3, R PPC-1, R
INSR family					
IGF1R	T104M				
IGF1R	Y201H				
IGF1R	N209S				
INSR	L991I				
MET family					
MET	T17I				
MET	P366S				
MET	N375S				
MET	S691L				
MET	D981_E1027del	NCI-H596, -			
MET	R988C	NCI-H69, C #			
MET	T1010I				TSU-PR1, I #
MET	V1238I				
RON	N440S				
RON	Q473_D515del				
RON	R523Q	NCI-H596, Q #	CaOV-3, Q IGROV-1, Q #	Capan-1, Q Capan-2, Q # PT-45P1, Q # SW-850, Q #	DU-145, Q PC-3, Q #

156/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
FGFR4	Y367C					
FGFR4	G388R	BOW-G, R F-01, R # Hs-695T, R # IGR-39, R KA-II, R # MM-254-C, R # MM-Arn, R SBCL2, R # WM-1341D, R # WM-983A, R # WM-983B, R #	KATO III, R #			Bladder, R Colon, R # Gastric, R # HEK-293, R # Liver, R # Lung, R # Ovary, R # S. Muscle, R
INSR family						
IGF1R	T104M					
IGF1R	Y201H					
IGF1R	N209S		MKN-1, S #			
INSR	L991I					
MET family						
MET	T17I	RPMI7951, I				
MET	P366S	MeWo, S #				
MET	N375S	Colo829, S # Hs-695T, S #				Colon, S #
MET	S691L	MM-Arn, L #				
MET	D981_F1027del		HS-746T, -			
MET	R988C					HuVeC, C #
MET	T1010I	Colo829, I #				
MET	V1238I					
RON	N440S					
RON	Q473_D515del					Bladder, - #
RON	R523Q	SBCL2, Q # WM-35, Q	HS-746T, Q			Bladder, Q Cervix, Q Colon, Q Gastric, Q # Kidney, Q # Liver, Q # Lung, Q Ovary, Q Prostate, Q Testes, Q #

157/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
RON	F574fsX23	1			T-98G,#
RON	R627fsX5	38	T-24,#	MG63,#	SF-763,# SH-SY-5Y,#
RON	R813delinsRQ	115	RT-4, # SCaBER, # T-24, # TCCSUP, #	MG63, #	A172, # SF-126, # SF-763, # SF-767, #
RON	Y884_Q932del	12	T-24, - TCCSUP, -		1321N1, -
RON	A1022 K1090del	1			
RON	V1070fsX12	1			
RON	R1335G	128	HT-1376, G # RT-4, G # T-24, G # TCCSUP, G #	SaOS2, G	1321N1, G # A172, G # IMR-32, G # SF-126, G # SH-SY-5Y, G # U-118, G # U-1240, G # U-1242, G U-138, G #

Fig. 31 (continued)

158/306

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
RON	F574fsX23				
RON	R627fsX5	HBL-100, # ZR-75-1, #	HeLa S3, # ME-180, # Ms 751, # SiHa, #	LS-174T, # LS-180, # NCI-H498, #	JAR, #
RON	R813delinsRQ	ZR-75-1, # ZR-75-30, #	C-4II, # Ca Ski, # HeLa S3, # ME-180, # MES-SA, # Ms 751, # SiHa, #	Caco2, # DLD-1, # HCT-116, # HCT-15, # LS-123, # LS-174T, # LS-180, # LoVo, # NCI-H498, # SK-CO-1, # SW-1463, # SW-403, # SW-48, # SW-480, # SW-620, # SW-948, #	JAR, # KLE, # RL95-2, #
RON	Y884_Q932del	BT-474, -			
RON	A1022_K1090del	BT-20, -			
RON	V1070fsX12				
RON	R1335G	BT-474, G BT-483, G # DU-44-75, G # HBL-100, G Hs-578T, G # MB-436, G MB-453, G # MB-468, G SK-BR-3, G T-47D, G # ZR-75-1, G # ZR-75-30, G	C-33A, G # C-4II, G # HeLa S3, G # A-431, G	Caco2, G DLD-1, G # HCT-15, G # SW-1417, G # SW-1463, G SW-403, G SW-48, G # SW-480, G SW-620, G # WiDr, G	JAR, G # KLE, G RL95-2, G

159/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
RON	<u>F574fsX23</u>				
RON	R627fsX5	SCC-25,# SCC-17B,#	KG-1,# Kasumi-1,# MV4-11,# TF-1,#	A-498,# CaKi-2,#	
RON	R813delinsRQ	HLaC-79, # SCC-15, # SCC-25, # SCC-17A, # SCC-22A, # SCC-22B, #	Daudi, # IM-9, # K-562, # Kasumi-1, # M-Mac-1, # M-Mac-6, # U-266, #	A-498, # A-704, # ACHN, #	Hs 817.T, # Hu-H7, #
RON	Y884_Q932del	SCC-17A, -# SCC-17B, -#			Hs 817.T, -
RON	<u>A1022_K1090del</u>				
RON	<u>V1070fsX12</u>				
RON	R1335G	HLaC-79, G # SCC-15, G SCC-25, G SCC-4, G SCC-17A, G # SCC-17B, G #	EM-2, G # IM-9, G # M-07e, G # OCI-AML5, G Raji, G # RF-1, G # U-266, G #	A-704, G # ACHN, G CaKi-1, G CaKi-2, G	Hs 817.T, G SK-HEP-1, G

160/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
RON	F574fsX23				
RON	R627fsX5	NCI-H292, # NCI-H510A, # NCI-H596, #	CaOV-3, # IGROV-1, #	A-818-7, # SW-850, #	DU-145, # PC-3, # PPC-1, # PC-3, #
RON	R813delinsRQ	A-427, # A-549, # Calu-1, # Calu-3, # NCI-H209, # NCI-H292, # NCI-H345, # NCI-H441, # NCI-H460, # NCI-H520, # NCI-H596, # NCI-H661, # NCI-H69, # SK-MES-1, # SW-900, #	2774, # CaOV-3, # CaOV-4, # IGROV-1, # OAW-42, # OVCAR-3, # SK-OV-3, #	818-4, # A-818-7, # AsPC-1, # CFPAC-1, # Capan-1, # Capan-2, # DANG-G, # Hs 766T, # PT-8902, # PT-45P1, # PT-8988T, # Panc TU1, #	
RON	Y884_Q932del	DANG-G, - PANC-1, - PT-45P1, -			
RON	A1022_K1090del				
RON	V1070fsX12				
RON	R1335G	A-549, G Calu-6, G NCI-H128, G NCI-H209, G NCI-H292, G # NCI-H441, G NCI-H520, G NCI-H661, G NCI-H82, G # SK-LU-1, G SK-MES-1, G SW-900, G	2774, G CaOV-4, G IGROV-1, G # OAW-42, G # OVCAR-3, G PA-1, G SK-OV-3, G	818-4, G # A-818-7, G # AsPC-1, G # BxPC-3, G CFPAC-1, G Capan-1, G # Capan-2, G # DANG-G, G Hs 766T, G PT-8902, G PANC-1, G PT-45P1, G # Panc TU1, G SW-850, G #	

161/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
RON	F574fsX23	SBCL2, # WM-266-4, # C-8161, # Hs-294T, # Hs-695T, # IGR-39, # MM-254-C, # MRI-H221, # MeWo, # SBCL2, # WM-266-4, # WM-793, #		AGS, # HS-746T, # KATO III, # MKN-1, # KATO III, -		As-745, # HEK-293, # HaCaT, # HuVeC, # As-745, # Bladder, # Colon, # Gastric, # HEK-293, # HaCaT, # Kidney, # Liver, # MCF-10A, # S. Muscle, # Testes, #
RON	R627fsX5					
RON	R813delinsRQ					
RON	Y884_Q932del					
RON	A1022_K1090del					
RON	V1070fsX12		KA-II,			
RON	R1335G	PC-3, G # PPC-1, G # TSU-PR1, G	C-32, G # G-361, G # MALME-3M, G # MM-031-I, G # MM-194-G, G MM-Alb, G MM-Am, G # MRI-H221, G # Mel Juso, G SK-MEL-2, G SK-MEL-24, G SK-MEL-31, G WM-115, G WM-1205, G # WM-239A, G WM-266-4, G WM-793, G # WM-852, G #	HS-746T, G MKN-1, G #	Tera-2, G #	Gastric, G # HEK-293, G HaCaT, G HuVeC, G # Kidney, G # Liver, G # MCF-10A, G Placenta, G # Testes, G #

162/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
PDGFR family					
CSF1R	H362R	11			A172, R
FLT3	V194M	1			
FLT3	M227T	36			
FLT3	D358V	1			
FLT3	V557I	2			
FLT3	V592A	4			
FLT3	G757E	1			
FLT3	R849H	1			
KIT	N822K	1			
PDGFRA	G79D	1			IMR-32, D
PDGFRA	L221F	1			

163/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
CSF1R	H362R				
FLT3	V194M				
FLT3	M227T	MB-157, T #		LS-123, T SW-1417, T	KLE, T RL95-2, T #
FLT3	D358V				
FLT3	V557I				
FLT3	V592A				
FLT3	G757E				
FLT3	R849H				
KIT	N822K				
PDGFRA	G79D				
PDGFRA	L221F				

164/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
CSF1R	H362R		Kasumi-1, R # M-07e, R # MEG-01, R MOLM-1, R M-Mac-1, R # M-Mac-6, R #		
FLT3	V194M		M-Mac-1, M #		
FLT3	M227T		Daudi, T EM-2, T IM-9, T # KG-1, T Kasumi-1, T MV4-11, T M-Mac-1, T M-Mac-6, T Raji, T RF-1, T # RF-48, T #	769-P, T ACHN, T CaKi-2, T SW13, T	
FLT3	D358V				
FLT3	V557I		KG-1, I		
FLT3	V592A		M-Mac-1, A #		
			M-Mac-6, A		
FLT3	G757E		Daudi, E		
FLT3	R849H				
KIT	N822K		Kasumi-1, K #		
PDGFRA	G79D				
PDGFRA	L221F				

165/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
CSF1R	H362R	Calu-1, R #			
FLT3	V194M				
FLT3	M227T	A-427, T	CaOV-3, T CaOV-4, T OVCAR-3, T PA-1, T	818-4, T	LNCaP, T
FLT3	D358V				LNCaP, V #
FLT3	V557I		PA-1, I #		
FLT3	V592A	NCI-H441, A #		Colo-357, A	
FLT3	G757E				
FLT3	R849H				BM-1604, H
KIT	N822K				
PDGFRA	G79D				
PDGFRA	L221F				

166/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
CSF1R	H362R					As-745, R Gastric, R # Kidney, R #
FLT3	V194M					
FLT3	M227T	Hs-695T, T				Bladder, T # Cervix, T # Gastric, T # Kidney, T # Liver, T # Prostate, T Spleen, T Testes, T #
FLT3	D358V					
FLT3	V557I					
FLT3	V592A					
FLT3	G757E					
FLT3	R849H					
KIT	N822K					
PDGFRA	G79D					
PDGFRA	L221F					Placenta, F

167/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
PDGFRA	S478P	13	TCCSUP, P		SH-SY-5Y, P # SK-N-SH, P #
PDGFRB	P345S	2			
PDGFRB	T464M	2			
PTK7 family					
CCK4	D106N	1			
CCK4	T410S	10			CCF-STTG1, S #
CCK4	P693L	4			
CCK4	E745D	6			IMR-32, D #
CCK4	M746L	2			
CCK4	A777V	10		MG63, V #	SF-763, V U-1242, V #
CCK4	S795R	1			
CCK4	Q913H	1			
RET family					
RET	D489N	2			
RET	G691S	33	RT-4, S #	RD, S TE-671, S	U-1240, S

168/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
PDGFRA	S478P				
PDGFRB	P345S				
PDGFRB	T464M				JAR, M #
PTK7 family					
CCK4	D106N		A-431, N #		
CCK4	T410S		C-4II, S #	LS-123, S #	
CCK4	P693L	DU-44-75, L #			
CCK4	E745D	ZR-75-1, D	Ms 751, D #		
CCK4	M746L				
CCK4	A777V			SW-1463, V #	
CCK4	S795R				
CCK4	Q913H				
RET family					
RET	D489N				
RET	G691S	MB-436, S #			RL95-2, S #

169/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
PDGFRA	S478P				
PDGFRB	P345S		THP-1, S #		
PDGFRB	T464M				
PTK7 family					
<u>CCK4</u>	<u>D106N</u>				
CCK4	T410S	SCC-15, S			
CCK4	P693L		U-937, L #		
CCK4	E745D				
<u>CCK4</u>	<u>M746L</u>				
CCK4	A777V				
CCK4	S795R				
<u>CCK4</u>	<u>Q913H</u>		Jurkat, H #		
RET family					
RET	D489N		Kasumi-1, N #		
RET	G691S	SCC-10A, S #	Daudi, S #		Hu-H7, S #
		SCC-10B, S	MV4-11, S #		
		SCC-17A, S #			
		SCC-17B, S #			
		SCC-22A, S #			
		SCC-22B, S #			

170/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
PDGFRA	S478P			PT-8902, P #	
PDGFRB	P345S	Calu-1, S #			
PDGFRB	T464M				
PTK7 family					
CCK4	D106N				
CCK4	T410S		OAW-42, S #	AsPC-1, S # SW-850, S #	
CCK4	P693L			Capan-1, L #	
CCK4	E745D	NCI-H446, D # NCI-H510A, D # SK-MES-1, D			
CCK4	M746L			AsPC-1, L # SW-850, L #	
CCK4	A777V	Calu-3, V # NCI-H292, V # NCI-H520, V			
CCK4	S795R				
CCK4	Q913H				
RET family					
RET	D489N				
RET	G691S	A-427, S # A-549, S # Calu-6, S # NCI-H520, S # NCI-H661, S NCI-H69, S SK-LU-1, S # SK-MES-1, S #	CaOV-3, S # PA-1, S #	Mia-PaCa2, S	

171/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
PDGFRA	S478P	MM-A1b, P # RPMI7951, P WM-115, P # WM-239A, P # WM-266-4, P # WM-902B, P				Hs 1.Li, P # Kidney, P # Placenta, P
PDGFRB	P345S					
PDGFRB	T464M					Kidney, M #
PTK7 family						
CCK4	D106N					
CCK4	T410S	A-375, S # Hs-695T, S MRI-H221, S #				
CCK4	P693L	Mel Juso, L #				
CCK4	E745D					
CCK4	M746L					
CCK4	A777V					As-745, V # BPH-1, V # Spleen, V #
CCK4	S795R					MCF-10A, R #
CCK4	Q913H					
RET family						
RET	D489N					Hs 1.Li, N #
RET	G691S	F-01, S MRI-H221, S				Cervix, S # Colon, S Gastric, S # Hs 1.Li, S # Pancreas, S #

172/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
<u>RET</u>	<u>A750T</u>	<u>1</u>			
RET	R982C	3			
ROR family					
<u>ROR1</u>	<u>R185H</u>	<u>1</u>			
<u>ROR1</u>	<u>R429Q</u>	<u>1</u>			
ROR1	M518T	198	SCaBER, T T-24, T #	SaOS2, T RD, T # TE-671, T # MG63, T	1321N1, T A172, T # CCF-STTG1, T # IMR-32, T # SF-126, T SF-763, T # SH-SY-5Y, T # SK-N-SH, T # T-98G, T U-118, T U-1240, T # U-1242, T U-138, T

173/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>RET</u>	<u>A750T</u>				
RET	R982C				
ROR family					
<u>ROR1</u>	<u>R185H</u>			<u>LS-180, H #</u>	
<u>ROR1</u>	<u>R429Q</u>				
ROR1	M518T	BT-20, T	C-33A, T	C. 320DM, T	JAR, T #
		BT-474, T	C-4II, T	DLD-1, T	KLE, T
		BT-549, T #	Ca Ski, T	HCT-116, T #	RL95-2, T
		HBL-100, T #	HeLa S3, T	HCT-15, T	
		Hs-578T, T #	MES-SA, T	LS-123, T	
		MCF-7, T	Ms 751, T	LS-174T, T	
		MB-157, T	SiHa, T #	LS-180, T	
		MB-175-VII, T	A-431, T	LoVo, T	
		MB-415, T		NCI-H498, T	
		MB-435S, T #		SK-CO-1, T	
		MB-436, T		SNU-C2B, T	
		MB-453, T		SW-1417, T #	
		MB-468, T #		SW-1463, T #	
		ZR-75-30, T		SW-48, T #	
				SW-480, T	
				SW-620, T	
				SW-948, T	
				WiDr, T #	

174/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
<u>RET</u>	<u>A750T</u>				
RET	R982C				
ROR family					
<u>ROR1</u>	<u>R185H</u>				
<u>ROR1</u>	<u>R429Q</u>				
ROR1	M518T	HLaC-78, T	Daudi, T	769-P, T #	HepG-2, T
		HLaC-79, T #	IM-9, T	786-0, T	SK-HEP-1, T
		SCC-15, T	K-562, T #	A-498, T	
		SCC-25, T	KG-1, T	A-704, T #	
		SCC-4, T	MOLM-1, T	ACHN, T	
		SCC-10A, T	OCI-AML5, T	CaKi-1, T #	
		SCC-10B, T	RF-1, T	CaKi-2, T	
			RF-48, T		
			TF-1, T #		

175/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
RET	A750T		IGROV-1, T #		
RET	R982C		CaOV-3, C		
ROR family					
ROR1	R185H				
ROR1	R429Q		IGROV-1, Q #		
ROR1	M518T	A-549, T Calu-1, T # Calu-6, T NCI-H128, T NCI-H209, T NCI-H292, T # NCI-H345, T # NCI-H441, T NCI-H460, T NCI-H510A, T NCI-H661, T # NCI-H69, T SK-LU-1, T SK-MES-1, T SW-900, T	CaOV-3, T CaOV-4, T # IGROV-1, T OAW-42, T OVCAR-3, T PA-1, T SK-OV-3, T	818-4, T # A-818-7, T # AsPC-1, T BxPC-3, T CFPAC-1, T Capan-1, T Capan-2, T DANG-G, T # Hs 766T, T # Mia-PaCa2, T PANC-1, T PT-45P1, T # Panc TU1, T SW-850, T	BM-1604, T DU-145, T PC-3, T PPC-1, T TSU-PR1, T #

Fig. 31 (continued)

176/306

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
RET	A750T				TT, C	Colon, C
RET	R982C					
ROR family						
ROR1	R185H					
ROR1	R429Q					
ROR1	M518T	A-375, T BOW-G, T C-32, T C-8161, T Colo829, T # F-01, T # G-361, T # HT-144, T # Hs-294T, T # Hs-695T, T IGR-39, T KA-II, T # MALME-3M, T MM-031-I, T MM-195-H, T MM-201-B, T # MM-254-C, T MM-358-A, T # MM-Alb, T # MM-Arn, T MM-Du, T MM-Leh, T MM-Lo, T MRI-H221, T # MeWo, T Mel Ger, T # RPMI7951, T SK-MEL-1, T SK-MEL-2, T SK-MEL-28, T SK-MEL-31, T WM-115, T WM-1205, T WM-1341D, T WM-1617, T # WM-239A, T WM-266-4, T WM-35, T # WM-793, T WM-852, T WM-902B, T WM-983A, T WM-983B, T Colo-16, T #	HS-746T, T KATO III, T MKN-1, T MKN-28, T	Tera-2, T #	As-745, T BPH-1, T # Bladder, T # Brain, T Cervix, T # Colon, T Gastric, T # HEK-293, T HaCaT, T Hs 1.Li, T HuVeC, T # Kidney, T # Liver, T # Lung, T MCF-10A, T # Ovary, T # Pancreas, T # Placenta, T # S. Muscle, T # Spleen, T # Testes, T #	

177/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
<u>ROR1</u>	<u>S870I</u>	<u>3</u>			
<u>ROR1</u>	<u>P883S</u>	<u>1</u>			
<u>ROR2</u>	<u>T245A</u>	<u>34</u>		SaOS2, A	CCF-STTG1, A SF-767, A SK-N-SH, A SW-1088, A U-1242, A #
<u>ROR2</u>	<u>R302H</u>	<u>1</u>			
<u>ROR2</u>	<u>C389R</u>	<u>1</u>			
<u>ROR2</u>	<u>D390fsX44</u>	<u>1</u>			
<u>ROR2</u>	<u>P548S</u>	<u>1</u>			
<u>ROR2</u>	<u>V819I</u>	<u>65</u>		SaOS2, I # MG63, I #	1321N1, I CCF-STTG1, I IMR-32, I SF-767, I SH-SY-5Y, I # SK-N-SH, I # SW-1088, I U-1240, I U-1242, I #
ROS family					
<u>ROS1</u>	<u>C76_R77ins9</u>	<u>41</u>	TCCSUP, -	SaOS2, - #	CCF-STTG1, - # SK-N-SH, - # SW-1088, - # T-98G, - # U-1242, - #

178/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>ROR1</u>	<u>S870I</u>			DLD-1, I #	
				HCT-15, I #	
<u>ROR1</u>	<u>P883S</u>				
ROR2	T245A	HBL-100, A T-47D, A	C-4II, A Ca Ski, A ME-180, A	SW-480, A	JAR, A
<u>ROR2</u>	<u>R302H</u>			HCT-116, H #	
<u>ROR2</u>	<u>C389R</u>				
<u>ROR2</u>	<u>D390fsX44</u>				
ROR2	P548S				JAR, S #
ROR2	V819I	HBL-100, I ZR-75-1, I	C-33A, I # C-4II, I Ca Ski, I HeLa S3, I ME-180, I SiHa, I	Caco2, I SW-480, I #	JAR, I
ROS family					
ROS1	C76_R77ins9	HBL-100, - # Hs-578T, - MB-415, - #	MES-SA, - A-431, -	LoVo, -	

179/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
<u>ROR1</u>	<u>S870I</u>				
<u>ROR1</u>	<u>P883S</u>				
ROR2	T245A	HLaC-78, A	M-Mac-1, A M-Mac-6, A	786-0, A A-704, A CaKi-2, A SW13, A	SK-HEP-1, A
<u>ROR2</u>	<u>R302H</u>				
<u>ROR2</u>	<u>C389R</u>				
<u>ROR2</u>	<u>D390fsX44</u>				
ROR2	P548S				
ROR2	V819I	HLaC-78, I HLaC-79, I SCC-22A, I SCC-22B, I	M-Mac-1, I M-Mac-6, I NB-4, I # OCI-AML5, I TF-1, I U-266, I	786-0, I A-704, I # CaKi-2, I SW13, I	SK-HEP-1, I
ROS family					
ROS1	C76_R77ins9	SCC-4, - # SCC-9, - # SCC-22A, -	EM-2, - # M-Mac-6, - #	A-498, - A-704, - CaKi-1, - #	

180/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
<u>ROR1</u>	<u>S870I</u>				
<u>ROR1</u>	<u>P883S</u>				
ROR2	T245A	Calu-6, A NCI-H661, A	2774, A PA-1, A # SK-OV-8, A #	SW-850, A	
<u>ROR2</u>	<u>R302H</u>				
<u>ROR2</u>	<u>C389R</u>	NCI-H69, R #			
<u>ROR2</u>	<u>D390fsX44</u>	NCI-H661#			
ROR2	P548S				
ROR2	V819I	A-549, I Calu-1, I NCI-H128, I NCI-H510A, I NCI-H520, I NCI-H596, I NCI-H69, I SK-LU-1, I	2774, I # CaOV-3, I OVCAR-3, I SK-OV-8, I	PT-45P1, I	
ROS family					
ROS1	C76_R77ins9	A-549, - # Calu-1, - # Calu-3, - # NCI-H661, -			PC-3, - #

181/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
ROR1	S870I		MKN-1, I #			
ROR1	P883S	SBCL2, S				
ROR2	T245A	WM-793, A WM-852, A Colo-16, A		Tera-2, A #		HEK-293, A Ovary, A Testes, A
ROR2	R302H					
ROR2	C389R					
ROR2	D390fsX44					
ROR2	P548S					
ROR2	V819I	WM-1617, I WM-793, I WM-852, I		Tera-2, I		Bladder, I Colon, I Gastric, I # HEK-293, I Kidney, I # Liver, I Lung, I Ovary, I Placenta, I Prostate, I # Testes, I
ROS family						
ROS1	C76_R77ins9	Hs-294T, - # RPMI7951, - WM-239A, - WM-35, -	HS-746T, - #		FTC133, - # FTC238, -	As-745, - As-745, - # Gastric, - # Lung, - # MCF-10A, - # Placenta, - Prostate, - # Testes, - #

182/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
ROS1	T145P	13			CCF-STTG1, P # SF-126, P # SW-1088, P # U-1242, P #
ROS1	R167Q	3			
ROS1	R187M	1			
ROS1	I537M	8			CCF-STTG1, M # SW-1088, M #
ROS1	D709fsX16	1			
ROS1	Q865fsX90	1			
ROS1	S1109L	21			A172, L # SF-126, L # U-1242, L #
ROS1	A1443S	1			
ROS1	D2213N	20	TCCSUP, N #	SaOS2, N #	CCF-STTG1, N # SF-126, N # SW-1088, N #
ROS1	K2228Q	22		SaOS2, Q #	A172, Q # CCF-STTG1, Q # SF-126, Q # SW-1088, Q #
ROS1	S2229C	22		SaOS2, C #	A172, C # CCF-STTG1, C # SF-126, C # SW-1088, C #

183/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
ROS1	T145P				
ROS1	R167Q		SiHa, Q	SK-CO-1, Q	
<u>ROS1</u>	<u>R187M</u>				
ROS1	I537M				
<u>ROS1</u>	<u>D709fsX16</u>			<u>T-84#</u>	
<u>ROS1</u>	<u>Q865fsX90</u>			<u>WiDr,</u>	
<u>ROS1</u>	<u>S1109L</u>		<u>C-33A, L #</u>		
<u>ROS1</u>	<u>A1443S</u>				
ROS1	D2213N	T-47D, N #	Ca Ski, N #		
ROS1	K2228Q	T-47D, Q #	Ca Ski, Q #		
ROS1	S2229C	T-47D, Q #	Ca Ski, C #		

184/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
ROS1	T145P		NB-4, P # OCI-AML5, P RF-1, P		
ROS1	R167Q				
ROS1	R187M			769-P, M	
ROS1	I537M		RF-1, M # RF-48, M #		
ROS1	D709fsX16				
ROS1	Q865fsX90				
ROS1	S1109L	SCC-10A, L	K-562, L		
		SCC-10B, L	KG-1, L NB-4, L OCI-AML5, L		
ROS1	A1443S				
ROS1	D2213N	SCC-15, N #	OCI-AML5, N # RF-48, N # RF-1, N #		
ROS1	K2228Q	SCC-15, Q #	OCI-AML5, Q # RF-48, Q # RF-1, Q #		
ROS1	S2229C	SCC-15, C #	OCI-AML5, C # RF-48, C # RF-1, C #		

185/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
ROS1	T145P	Calu-1, P			
ROS1	R167Q				
ROS1	R187M				
ROS1	I537M			A-818-7, M #	
ROS1	D709fsX16				
ROS1	Q865fsX90				
ROS1	S1109L	Calu-1, L			
		NCI-H128, L			
		NCI-H661, L			
		SK-MES-1, L			
ROS1	A1443S	NCI-H661, S			
ROS1	D2213N	A-549, N #			
		Calu-1, N #			
		SW-900, N #			
ROS1	K2228Q	A-549, Q #			
		Calu-1, Q #			
		NCI-H441, Q #			
		NCI-H596, Q #			
ROS1	S2229C	A-549, C #			
		Calu-1, C #			
		CCI-H441, C #			
		CCI-H596, C #			

186/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
ROS1	T145P	Hs-294T, P			FTC133, P FTC238, P	BPH-1, P Brain, P
ROS1	R167Q	WM-115, Q				
ROS1	R187M					
ROS1	I537M	MM-201-B, M # WM-1205, M # WM-793, M #				
ROS1	D709fsX16					
ROS1	Q865fsX90					
ROS1	S1109L	Hs-294T, L			FTC133, L	Brain, L #
		MM-Leh, L Mel Ger, L			FTC238, L	BPH-1, L
ROS1	A1443S					
ROS1	D2213N	Hs-294T, N #				BPH-1, N # Bladder, N # Brain, N # Lung, N # Prostate, N #
ROS1	K2228Q	G-361, N #				BPH-1, Q # Bladder, Q # Brain, Q # Lung, Q # Prostate, Q #
ROS1	S2229C	G-361, C #				Spleen, Q # BPH-1, Q # Bladder, Q # BraiC, Q # LuCg, Q # Prostate, Q # SpleeC, Q #

187/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
RYK family					
RYK	N96S	83	SCaBER, S	SaOS2, S # MG63, S	1321N1, S A172, S SF-763, S SF-767, S SH-SY-5Y, S SW-1088, S T-98G, S U-118, S U-1240, S # U-1242, S U-138, S
RYK	H250R	1			
RYK	R504H	1			SF-763, H #
RYK	F516L	1			
RYK	A559T	1			
TIE family					
TEK1	P346Q	4			
TEK1	V486I	2			
TEK1	V600L	15			
TEK1	A615T	1			
TEK1	A1006T	1			
TIE	S470L	1			
TIE	M871T	1			

188/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
RYK family					
RYK	N96S	HBL-100, S	C-33A, S	DLD-1, S	KLE, S
		MB-435S, S	Ca Ski, S	HCT-15, S	
		MB-436, S	HT-3, S	LS-123, S	
		ZR-75-1, S	Ms 751, S #	LS-174T, S #	
			SW 954, S	LS-180, S #	
<u>RYK</u>	<u>H250R</u>				
<u>RYK</u>	<u>R504H</u>				
RYK	F516L				
<u>RYK</u>	<u>A559T</u>				
TIE family					
TEK1	P346Q				
TEK1	V486I		MES-SA, I		
TEK1	V600L			LS-174T, L	
				LS-180, L	
				LoVo, L	
				SNU-C2B, L	
<u>TEK1</u>	<u>A615T</u>			LS-180, T #	
<u>TEK1</u>	<u>A1006T</u>				
<u>TIE</u>	<u>S470L</u>				
<u>TIE</u>	<u>M871T</u>				

189/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
RYK family					
RYK	N96S		HL-60, S Jurkat, S K-562, S KG-1, S Kasumi-1, S # OCI-AML5, S PLB-985, S Raji, S	786-0, S A-498, S ACHN, S CaKi-1, S CaKi-2, S G401, S SW13, S	Hs 817.T, S
<u>RYK</u>	<u>H250R</u>				
<u>RYK</u>	<u>R504H</u>				
RYK	F516L				
<u>RYK</u>	<u>A559T</u>		<u>TF-1, T #</u>		
TIE family					
TEK1	P346Q				
TEK1	V486I				
TEK1	V600L		M-Mac-1, L # M-Mac-6, L #	CaKi-1, L CaKi-2, L	
<u>TEK1</u>	<u>A615T</u>				
<u>TEK1</u>	<u>A1006T</u>				
<u>TIE</u>	<u>S470L</u>				
<u>TIE</u>	<u>M871T</u>				

190/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
RYK family					
RYK	N96S	A-427, S A-549, S Calu-1, S NCI-H146, S NCI-H292, S NCI-H441, S # NCI-H446, S NCI-H460, S NCI-H520, S NCI-H596, S NCI-H661, S NCI-H69, S	IGROV-1, S	AsPC-1, S Mia-PaCa2, S Panc TU1, S	
RYK	H250R				
RYK	R504H				
RYK	F516L				
RYK	A559T				
TIE family					
TEK1	P346Q				
TEK1	V486I				
TEK1	V600L			PT-8988T, L	
TEK1	A615T				
TEK1	A1006T				
TIE	S470L	SW-900, L #			
TIE	M871T		IGROV-1, T #		

191/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
RYK family						
RYK	N96S	Hs-695T, S MM-Arn, S MM-Du, S SBCL2, S # WM-115, S WM-239A, S WM-266-4, S WM-983A, S WM-983B, S		NT-2, S Cates 1B, S	FTC133, S FTC238, S	As-745, S Gastric, S HEK-293, S Hs 1.Li, S # Kidney, S Liver, S MCF-10A, S Ovary, S Testes, S
RYK	H250R	MM-Lo, R #				
RYK	R504H					
RYK	F516L					HEK-293, L #
RYK	A559T					
TIE family						
TEK1	P346Q	BOW-G, Q Mel Ger, Q				Brain, Q # HuVeC, Q #
TEK1	V486I					Kidney, I #
TEK1	V600L	MM-194-G, L SK-MEL-24, L SK-MEL-31, L			FTC133, L FTC238, L	S. Muscle, L #
TEK1	A615T					
TEK1	A1006T	SK-MEL-2, T #				
TIE	S470L					
TIE	M871T					

192/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
TRK family					
<u>NTRK1</u>	<u>P453fsX15</u>	<u>3</u>			
<u>NTRK1</u>	<u>L585fsX73</u>	<u>2</u>			
<u>NTRK1</u>	<u>G595E</u>	<u>1</u>			
NTRK1	H604Y	18	T-24, Y #		U-1240, V #
NTRK1	G613V	18	T-24, V #		U-1240, V #
<u>NTRK1</u>	<u>R748W</u>	<u>1</u>			
NTRK1	R780Q	3			
<u>NTRK2</u>	<u>A586V</u>	<u>1</u>			
<u>NTRK2</u>	<u>V622I</u>	<u>1</u>			
<u>NTRK2</u>	<u>A647fsX54</u>	<u>3</u>			
NTRK3	E402_F410delinsV	115	TCCSUP, V #	SaOS2, V #	1321N1, V # CCF-STTG1, V # IMR-32, V # SF-126, V # SH-SY-5Y, V # SK-N-SH, V # SW-1088, V # T-98G, V # U-118, V # U-1240, V # U-1242, V # U-138, V #
NTRK3	G466_Y529delinsD	10		TE-671, D #	1321N1, D #

193/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
TRK family					
<u>NTRK1</u>	<u>P453fsX15</u>				
<u>NTRK1</u>	<u>L585fsX73</u>			SW-48, #	
<u>NTRK1</u>	<u>G595E</u>				
NTRK1	H604Y	MB-436, Y #			
NTRK1	G613V	MB-436, V #			
<u>NTRK1</u>	<u>R748W</u>				
NTRK1	R780Q			Caco2, Q #	
<u>NTRK2</u>	<u>A586V</u>				
<u>NTRK2</u>	<u>V622I</u>				
<u>NTRK2</u>	<u>A647fsX54</u>			T-84, #	
NTRK3	E402_F410delinsV	BT-474, V #	C-33A, V #	DLD-1, V #	
		BT-483, V #		HCT-116, V	
		BT-549, V #		HCT-15, V #	
		HBL-100, V			
		Hs-578T, V #			
		MB-157, V #			
		MB-175-VII, V #			
		MB-436, V #			
		MB-453, V #			
		SK-BR-3, V #			
		ZR-75-1, V #			
NTRK3	G466_Y529delinsD	BT-549, D #			
		Hs-578T, D #			

194/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
TRK family					
NTRK1	<u>P453fsX15</u>				
NTRK1	<u>L585fsX73</u>			A-704, #	
NTRK1	<u>G595E</u>				
NTRK1	H604Y			G401, Y #	SK-HEP-1, V
NTRK1	G613V			G401, Y #	SK-HEP-1, V
NTRK1	<u>R748W</u>				
NTRK1	R780Q	SCC-9, Q #			
NTRK2	<u>A586V</u>				
NTRK2	<u>V622I</u>				
NTRK2	<u>A647fsX54</u>		IM-9, #		
NTRK3	E402_F410delinsV	SCC-10A, V # SCC-10B, V #	Daudi, V # IM-9, V Jurkat, V # K-562, V # MEG-01, V # MV4-11, V # OCI-AML5, V # TF-1, V # U-937, V #	786-0, V # ACHN, V # CaKi-2, V # G401, V # SW13, V #	SK-HEP-1, V
NTRK3	G466_Y529delinsD				

195/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
NTRK1	P453fsX15			PT-8902, #	
NTRK1	L585fsX73				
NTRK1	G595E				
NTRK1	H604Y	Calu-1, Y # NCI-H209, Y NCI-H510A, Y #			LNCaP, Y TSU-PR1, Y
NTRK1	G613V	Calu-1, Y # NCI-H209, Y NCI-H510A, Y #			LNCaP, Y TSU-PR1, Y
NTRK1	R748W	NCI-H82, W			
NTRK1	R780Q		SK-OV-8, Q #		
NTRK2	A586V	NCI-H69, V #			
NTRK2	V622I				
NTRK2	A647fsX54				
NTRK3	E402_F410delinsV	A-549, V # Calu-1, V # NCI-H128, V # NCI-H146, V # NCI-H209, V # NCI-H345, V # NCI-H446, V # NCI-H460, V # NCI-H510A, V # NCI-H520, V # NCI-H661, V # NCI-H82, V SK-LU-1, V # SK-MES-1, V #	2774, V # CaOV-4, V	Hs 766T, V #	
NTRK3	G466_Y529delinsD	NCI-H510A, D # NCI-H520, D # SK-MES-1, D #			

196/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
NTRK1	P453fsX15	MRI-H221#	HS-746T#			
NTRK1	L585fsX73					
NTRK1	G595E	Mel Juso, E #				
NTRK1	H604Y	HT-144, Y # MM-Du, Y # SK-MEL-24, Y # SK-MEL-5, Y #		Cates 1B, Y #	TT, Y #	Colon, Y # Gastric, Y #
NTRK1	G613V	HT-144, Y # MM-Du, Y # SK-MEL-24, Y # SK-MEL-5, Y #		Cates 1B, V #	TT, V #	Colon, V # Gastric, V #
NTRK1	R748W					
NTRK1	R780Q					
NTRK2	A586V					
NTRK2	V622I				FTC133.I	
NTRK2	A647fsX54	WM-35,				
NTRK3	E402_F410delinsV	A-375, V # G-361, V HT-144, V # Hs-294T, V # Hs-695T, V # IGR-39, V # MALME-3M, V MM-201-B, V # MM-254-C, V MM-Lo, V # MRI-H221, V # Mel Ger, V # Mel Juso, V RPMI7951, V # SBCL2, V # SK-MEL-2, V # SK-MEL-24, V # SK-MEL-31, V # SK-MEL-5, V # WM-115, V # WM-1205, V # WM-1341D, V WM-1617, V # WM-239A, V # WM-35, V # WM-793, V # WM-852, V # WM-902B, V # WM-983A, V WM-983B, V #	AGS, V HS-746T, V	NT-2, V # Cates1B, V # Tera-2, V #	TT, V #	Bladder, V # Brain, V # Cervix, V # Colon, V # Gastric, V # HEK-293, V # Hs 1.Li, V # Kidney, V # Liver, V # Lung, V # Ovary, V # Pancreas, V # Prostate, V # S. Muscle, V # Spleen, V # Testes, V #
NTRK3	G466_Y529delinsD	WM-1205, D # WM-793, D #				Hs 1.Li, D #

197/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
NTRK3	V530fsX6	1			
NTRK3	G608D	2			
NTRK3	A631fsX33	2			
NTRK3	R711_V712ins14	31			U-118, #
VEGFR family					
VEGFR1	G203W	1			
VEGFR1	S437L	1			
VEGFR1	Y642H	1			
VEGFR1	A673V	1			
VEGFR1	R781Q	1			
VEGFR1	M938V	2			
VEGFR1	E982A	1			
VEGFR1	P1201L	1			
VEGFR2	E107K	1			
VEGFR2	V297I	16			
VEGFR2	Q472H	24			U-118, H U-1242, H #
VEGFR2	C482R	2			
VEGFR2	P1147S	1			

198/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>NTRK3</u>	<u>V530fsX6</u>				
<u>NTRK3</u>	<u>G608D</u>				
<u>NTRK3</u>	<u>A631fsX33</u>			HCT-116	
<u>NTRK3</u>	<u>R711_V712ins14</u>	BT-483, # MB-175-VII, # MB-415, # MB-435S, # MB-436, # MB-453, #			
VEGFR family					
<u>VEGFR1</u>	<u>G203W</u>			DLD-1, W	
<u>VEGFR1</u>	<u>S437L</u>				
<u>VEGFR1</u>	<u>Y642H</u>				
<u>VEGFR1</u>	<u>A673V</u>				
<u>VEGFR1</u>	<u>R781Q</u>	MB-435S, Q			
<u>VEGFR1</u>	<u>M938V</u>				
<u>VEGFR1</u>	<u>E982A</u>				
<u>VEGFR1</u>	<u>P1201L</u>				
<u>VEGFR2</u>	<u>E107K</u>				
<u>VEGFR2</u>	<u>V297I</u>	MB-175-VII, I MB-436, I # MB-468, I			
<u>VEGFR2</u>	<u>Q472H</u>			HCT-116, H #KLE, H #	
<u>VEGFR2</u>	<u>C482R</u>				
<u>VEGFR2</u>	<u>P1147S</u>				

199/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
<u>NTRK3</u>	<u>V530fsX6</u>				
<u>NTRK3</u>	<u>G608D</u>				
<u>NTRK3</u>	<u>A631fsX33</u>				
NTRK3	R711_V712ins14	SCC-10B #	IM-9, # K-562, # MV4-11, # OCI-AML5, # PLB-985, - Raji, # TF-1, #	769-P, - A-498, # CaKi-1, #	
VEGFR family					
<u>VEGFR1</u>	<u>G203W</u>				
<u>VEGFR1</u>	<u>S437L</u>				
VEGFR1	Y642H				
VEGFR1	A673V		Jurkat, V #		
<u>VEGFR1</u>	<u>R781Q</u>				
VEGFR1	M938V		Jurkat, V #		
VEGFR1	E982A				
VEGFR1	P1201L				
<u>VEGFR2</u>	<u>E107K</u>				
VEGFR2	V297I				
VEGFR2	Q472H		MEG-01, H		
VEGFR2	C482R				
VEGFR2	P1147S				

200/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
NTRK3	V530fsX6	SW-900			
NTRK3	G608D				
NTRK3	A631fsX33				
NTRK3	R711_V712ins14				
VEGFR family					
VEGFR1	G203W				
VEGFR1	S437L				
VEGFR1	Y642H				
VEGFR1	A673V				
VEGFR1	R781Q				
VEGFR1	M938V				
VEGFR1	E982A				
VEGFR1	P1201L				
VEGFR2	E107K				
VEGFR2	V297I	NCI-H292, I # NCI-H441, I # NCI-H520, I NCI-H596, I #	PA-1, I #		
VEGFR2	Q472H	NCI-H441, H # NCI-H520, H SK-LU-1, H SK-MES-1, H #			PC-3, H #
VEGFR2	C482R				PC-3, R #
VEGFR2	P1147S				

201/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
NTRK3	V530fsX6					
NTRK3	G608D	WM-1341D, D				
		WM-1617, D				
NTRK3	A631fsX33					
NTRK3	R711_V712ins14	A-375, # Hs-294T, # IGR-39, # MRI-H221, # SK-MEL-28, # WM-115, # WM-1617				Bladder, # Brain, # Cervix, # Gastric, # Lung, # S. Muscle, #
VEGFR family						
VEGFR1	G203W					
VEGFR1	S437L	IGR-39, L				
VEGFR1	Y642H					Hs 1.Li, H #
VEGFR1	A673V					
VEGFR1	R781Q					
VEGFR1	M938V	MM-Leh, V #				
VEGFR1	E982A					Kidney, A #
VEGFR1	P1201L					HEK-293, L #
VEGFR2	E107K	BOW-G, K #				
VEGFR2	V297I	BOW-G, I # Colo829, I # MALME-3M, I # WM-1205, I # WM-793, I #				Hs 1.Li, I # HuVeC, I # Ovary, I
VEGFR2	Q472H	C-32, H # Colo829, H # Hs-294T, H # MM-Alt, H # MeWo, H #		NT-2, H Tera-2, H	FTC133, H FTC238, H TT, H #	Cervix, H # Ovary, H Prostate, H Testes, H # Prostate, R # S. Muscle, S #
VEGFR2	C482R					
VEGFR2	P1147S					

202/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
VEGFR2	P1280S	1			
VEGFR3	Q890H	20			
VEGFR3	R1321Q	1			
AATYK family					
AATYK	G600C	64			A172, C # SF-763, C # U-1240, C # U-138, C
AATYK	G641S	1			
AATYK	F1163S	26			
AATYK	F1195C	1			
AATYK	T1227M	9		RD, M # TE-671, M #	

203/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>VEGFR2</u>	<u>P1280S</u>				
VEGFR3	Q890H	MB-436, H			JAR, H #
VEGFR3	R1321Q				
AATYK family					
AATYK	G600C	MB-415, C T-47D, C ZR-75-1, C	A-431, C	Caco2, C C. 320DM, C # DLD-1, C HCT-15, C LS-123, C LS-174T, C # LS-180, C # SW-403, C # SW-48, C #	
AATYK	G641S				
AATYK	F1163S		HT-3, S # Ms 751, S #	NCI-H498, S	
<u>AATYK</u>	<u>F1195C</u>				
AATYK	T1227M				

204/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
VEGFR2	P1280S				
VEGFR3	Q890H		MEG-01, H	ACHN, H # SW13, H #	
VEGFR3	R1321Q				
AATYK family					
AATYK	G600C	FaDu, C SCC-15, C # SCC-9, C # SCC-17A, C # SCC-17B, C SCC-22A, C # SCC-22B, C #	MOLM-1, C # M-Mac-6, C # PLB-985, C # U-266, C	786-0, C # A-498, C A-704, C # CaKi-1, C # G401, C SW13, C #	HepG-2, C # Hu-H7, C SK-HEP-1, C
AATYK	G641S				
AATYK	F1163S		OCI-AML5, S	CaKi-1, S G401, S # SW13, S	
AATYK	F1195C				
AATYK	T1227M				

205/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
<u>VEGFR2</u>	<u>P1280S</u>				
VEGFR3	Q890H	A-427, H # A-549, H # NCI-H345, H # NCI-H446, H NCI-H460, H # SK-LU-1, H #	CaOV-3, H		
VEGFR3	R1321Q				
AATYK family					
AATYK	G600C	A-427, C # A-549, C Calu-1, C NCI-H146, C NCI-H446, C NCI-H460, C NCI-H661, C		BxPC-3, C Capan-2, C	PC-3, C #
AATYK	G641S				
AATYK	F1163S	A-549, S Calu-1, S # NCI-H146, S NCI-H345, S NCI-H661, S # NCI-H69, S #		818-4, S	
<u>AATYK</u>	<u>F1195C</u>	<u>NCI-H69, C #</u>			
AATYK	T1227M	A-427, M # NCI-H128, M			

206/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
VEGFR2	P1280S	MM-Du, S #		NT-2, H # Tera-2, H		HEK-293, H # HuVeC, H Kidney, H Ovary, H # S. Muscle, H # Testes, H # HEK-293, Q #
VEGFR3	Q890H					
VEGFR3	R1321Q					
AATYK family						
AATYK	G600C	F-01, C G-361, C MM-195-H, C # MM-358-A, C # MeWo, C Mel Ger, C # RPMI7951, C SK-MEL-1, C # WM-902B, C #	HS-746T, C KATO III, C			Brain, C # Colon, C # Gastric, C # Hs 1.Li, C # MCF-10A, C # S. Muscle, C #
AATYK	G641S					Gastric, S #
AATYK	F1163S	F-01, S MM-031-I, S MM-232-E, S MM-Alt, S WM-983A, S # WM-983B, S #		NT-2, S Cates 1B,S#	TT, S	Liver, S # Prostate, S # Testes, S #
AATYK	F1195C					
AATYK	T1227M	WM-115, M # WM-239A, M # WM-266-4, M #				Lung, M # Prostate, M #

207/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
LMTK2	P30A	13			U-118, A #
LMTK2	Q238P	1			
LMTK2	A251T	1			
LMTK2	G518V	1			
LMTK2	D523Y	1			
LMTK2	M758V	1			
LMTK2	L780M	180	RT-4, M TCCSUP, M #	MG63, M SaOS2, M	1321N1, M # A172, M # CCF-STTG1, M # IMR-32, M SF-767, M SH-SY-5Y, M SK-N-SH, M SW-1088, M # T-98G, M U-118, M # U-1242, M # U-138, M
LMTK2	D793G	2			
LMTK2	R828Q	1			
LMTK2	L879M	1			
LMTK2	S910I	6			

208/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
LMTK2	P30A		HT-3, A #	SK-CO-1, A #	
<u>LMTK2</u>	<u>Q238P</u>				
<u>LMTK2</u>	<u>A251T</u>				
<u>LMTK2</u>	<u>G518V</u>				
<u>LMTK2</u>	<u>D523Y</u>				
<u>LMTK2</u>	<u>M758V</u>	<u>HBL-100, V #</u>			
LMTK2	L780M	BT-483, M #	C-4II, M	Caco2, M	JAR, M #
		BT-549, M	HT-3, M #	C. 320DM, M	KLE, M #
		DAL, M #	ME-180, M	DLD-1, M	RL95-2, M
		HBL-100, M	Ms 751, M #	HCT-116, M #	
		MCF-7, M	SW 954, M #	HCT-15, M	
		MB-157, M #		LS-123, M	
		MB-361, M		LS-174T, M #	
		MB-415, M		LS-180, M #	
		MB-453, M #		LoVo, M #	
		SK-BR-3, M		NCI-H498, M #	
		ZR-75-1, M #		SW-403, M #	
				SW-48, M	
				SW-480, M	
				SW-620, M #	
				SW-837, M	
				T-84, M	
				WiDr, M #	
<u>LMTK2</u>	<u>D793G</u>				
<u>LMTK2</u>	<u>R828Q</u>	<u>MB-175-VII, Q #</u>			
<u>LMTK2</u>	<u>L879M</u>			DLD-1, M #	
LMTK2	S910I		HeLa S3, I #		
			A-431, I #		

209/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
LMTK2	P30A		IM-9, A # TF-1, A #		Hu-H7, A #
<u>LMTK2</u>	<u>Q238P</u>				
<u>LMTK2</u>	<u>A251T</u>				
<u>LMTK2</u>	<u>G518V</u>				
<u>LMTK2</u>	<u>D523Y</u>				
<u>LMTK2</u>	<u>M758V</u>				
LMTK2	L780M	HLaC-78, M #	Daudi, M #	769-P, M	HepG-2, M #
		SCC-15, M #	EM-2, M #	786-0, M	SK-HEP-1, M
		SCC-25, M #	HL-60, M #	A-498, M #	
		SCC-10A, M	Jurkat, M #	A-704, M #	
		SCC-10B, M	K-562, M	ACHN, M	
		SCC-17A, M	M-Mac-1, M #	CaKi-1, M	
		SCC-17B, M	M-Mac-6, M	CaKi-2, M #	
		SCC-22A, M	NB-4, M #	G401, M #	
		SCC-22B, M	PLB-985, M #	SW13, M	
			Raji, M		
			RF-1, M		
			RF-48, M		
			U-266, M		
<u>LMTK2</u>	<u>D793G</u>	<u>HLaC-78, G #</u>	<u>K-562, G #</u>		
<u>LMTK2</u>	<u>R828Q</u>				
<u>LMTK2</u>	<u>L879M</u>				
LMTK2	S910I	HLaC-79, I #			

210/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
LMTK2	P30A	NCI-H292, A #			
<u>LMTK2</u>	<u>Q238P</u>	<u>NCI-H292, P #</u>			
<u>LMTK2</u>	<u>A251T</u>				
<u>LMTK2</u>	<u>G518V</u>				LNCaP, V #
<u>LMTK2</u>	<u>D523Y</u>				LNCaP, Y #
<u>LMTK2</u>	<u>M758V</u>				
LMTK2	L780M	Calu-3, M NCI-H128, M # NCI-H146, M NCI-H345, M # NCI-H446, M # NCI-H460, M # NCI-H510A, M # NCI-H520, M NCI-H661, M NCI-H69, M # NCI-H82, M # SK-LU-1, M SW-900, M	2774, M # CaOV-3, M IGROV-1, M OAW-42, M # OVCAR-3, M # PA-1, M # SK-OV-3, M SK-OV-8, M	AsPC-1, M CFPAC-1, M # Capan-2, M # Hs 766T, M # Mia-PaCa2, M # PT-8902, M # PANC-1, M # PT-45P1, M # PT-8988T, M Panc TU1, M # SW-850, M	BM-1604, M # DU-145, M # LNCaP.FGC, M
<u>LMTK2</u>	<u>D793G</u>				
<u>LMTK2</u>	<u>R828Q</u>				
<u>LMTK2</u>	<u>L879M</u>				
LMTK2	S910I				

Fig. 31 (continued)

211/306

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
LMTK2	P30A	C-32, A # KA-II, A # MM-Lo, A # SK-MEL-2, A # WM-902B, A #				HEK-293, A #
LMTK2	Q238P					
LMTK2	A251T				FTC133, T	
LMTK2	G518V					
LMTK2	D523Y					
LMTK2	M758V					
LMTK2	L780M	BOW-G, M # Colo829, M # F-01, M HT-144, M IGR-39, M KA-II, M # MM-031-I, M MM-195-H, M MM-201-B, M # MM-232-E, M MM-Alb, M MM-Alt, M MM-Arn, M MM-Du, M # MM-Lo, M # MeWo, M # Mel Ger, M Mel Juso, M SK-MEL-1, M # SK-MEL-2, M # SK-MEL-24, M # SK-MEL-28, M SK-MEL-31, M SK-MEL-5, M # WM-115, M # WM-1205, M WM-239A, M # WM-266-4, M # WM-35, M # WM-793, M WM-852, M WM-902B, M # WM-983A, M WM-983B, M	AGS, M # HS-746T, M MKN-1, M	Cates1B, M #	FTC133, M FTC238, M # TT, M	As-745, M BPH-1, M Bladder, M # Brain, M # Cervix, M # Colon, M Gastric, M # HEK-293, M HaCaT, M Hs 1.Li, M # HuVeC, M # Liver, M Lung, M # MCF-10A, M # Pancreas, M # Prostate, M # S. Muscle, M Spleen, M Testes, M #
LMTK2	D793G					
LMTK2	R828Q					
LMTK2	L879M					
LMTK2	S910I					Colon, I Kidney, I # S. Muscle, I

212/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
<u>LMTK2</u>	<u>A1008V</u>	<u>1</u>			
STYK family					
STYK1	G204S	99	SCaBER, S #		1321N1, S # SF-126, S SF-763, S # SF-767, S # T-98G, S # U-1240, S U-138, S #
Non-Receptor Tyrosine Kinases					
A6 family					
<u>PTK-9</u>	<u>E195_V196insRSEDHIG</u>	<u>1</u>			
<u>PTK-9</u>	<u>D258E</u>	<u>1</u>			
<u>PTK-9</u>	<u>K265R</u>	<u>1</u>			
<u>PTK-9</u>	<u>N333S</u>	<u>1</u>			

213/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>LMTK2</u>	<u>A1008V</u>			<u>SK-CO-1, V#</u>	
STYK family					
STYK1	G204S	BT-483, S #	C-33A, S #	Caco2, S #	RL95-2, S #
		MB-175-VII, S	C-4II, S	DLD-1, S #	
		MB-361, S #	HT-3, S #	HCT-15, S #	
		MB-435S, S #	HeLa S3, S #	SW-1463, S	
		MB-436, S #	ME-180, S #	SW-48, S #	
		SK-BR-3, S #	Ms 751, S #	T-84, S #	
		ZR-75-1, S #	SW 954, S	WiDr, S #	
		ZR-75-30, S	A-431, S #		
Non-Receptor Tyrosine Kinases					
A6 family					
PTK-9	E195_V196insRSEDHIG				
PTK-9	<u>D258E</u>				
PTK-9	<u>K265R</u>				
PTK-9	<u>N333S</u>				

214/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
<u>LMTK2</u>	<u>A1008V</u>				
STYK family					
STYK1	G204S	FaDu, S #	EM-2, S #	786-0, S	Hs 817.T, S
		HLaC-79, S #	K-562, S	A-704, S #	Hu-H7, S #
		SCC-25, S #	KG-1, S		SK-HEP-1, S
		SCC-9, S #	M-07e, S #		
		SCC-17A, S #	MV4-11, S #		
		SCC-17B, S #	NB-4, S #		
			TF-1, S #		
			U-937, S #		
Non-Receptor Tyrosine Kinases					
A6 family					
PTK-9	E195_V196insRSEDHIG				
<u>PTK-9</u>	<u>D258E</u>				
<u>PTK-9</u>	<u>K265R</u>				
<u>PTK-9</u>	<u>N333S</u>				

215/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
<u>LMTK2</u>	<u>A1008V</u>				
STYK family					
STYK1	G204S	A-549, S	2780, S	AsPC-1, S	
		Calu-3, S #	CaOV-3, S #	Capan-2, S #	
		Calu-6, S	CaOV-4, S	DANG-G, S #	
		NCI-H209, S #	IGROV-1, S	Hs 766T, S	
		NCI-H510A, S #	PA-1, S #	SW-850, S	
		NCI-H82, S #	SK-OV-3, S #		
		SK-MES-1, S	SK-OV-8, S		
Non-Receptor Tyrosine Kinases					
A6 family					
PTK-9	E195_V196insRSEDHIG				
<u>PTK-9</u>	<u>D258E</u>				
<u>PTK-9</u>	<u>K265R</u>	<u>NCI-H460, R #</u>			
<u>PTK-9</u>	<u>N333S</u>		<u>PA-1, S #</u>		

216/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
LMTK2	<u>A1008V</u>					
STYK family						
STYK1	G204S	C-8161, S HT-144, S MALME-3M, S # MM-195-H, S # MM-201-B, S # MM-254-C, S # MM-Leh, S # MM-Lo, S Mel Ger, S # RPMI7951, S # SK-MEL-1, S # SK-MEL-2, S SK-MEL-28, S # SK-MEL-31, S WM-1341D, S WM-793, S #	AGS, S MKN-1, S #	NT-2, S	TT, S	As-745, S # BPH-1, S # Cervix, S Colon, S # HaCaT, S # Hs 1.Li, S # Lung, S # Ovary, S # Placenta, S #
Non-Receptor Tyrosine Kinases						
A6 family						
PTK-9	E195 V196ins- RSEDHIG					Brain, #
PTK-9	<u>D258E</u>	<u>KA-II, E #</u>				
PTK-9	<u>K265R</u>					
PTK-9	<u>N333S</u>					

217/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
ABL family					
<u>ABL1</u>	<u>G417E</u>	<u>1</u>			
<u>ABL1</u>	<u>N789S</u>	<u>1</u>			
<u>ABL1</u>	<u>P829L</u>	<u>1</u>			
<u>ABL1</u>	<u>G883fsX12</u>	<u>2</u>			
<u>ABL1</u>	<u>S991L</u>	<u>14</u>			SF-763, L # SF-767, L #
<u>ARG</u>	<u>E332K</u>	<u>1</u>			
<u>ARG</u>	<u>V345A</u>	<u>1</u>			
<u>ARG</u>	<u>K450R</u>	<u>1</u>			
<u>ARG</u>	<u>M657I</u>	<u>1</u>			
<u>ARG</u>	<u>P665T</u>	<u>1</u>			
<u>ARG</u>	<u>R668C</u>	<u>1</u>			
<u>ARG</u>	<u>Q696H</u>	<u>1</u>			
<u>ARG</u>	<u>K930R</u>	<u>3</u>			SK-N-SH, R #
<u>ARG</u>	<u>K959R</u>	<u>1</u>			
<u>ARG</u>	<u>S968F</u>	<u>1</u>			
<u>ARG</u>	<u>Q994H</u>	<u>1</u>			
ACK family					
<u>ACK1</u>	<u>H37Y</u>	<u>1</u>			
<u>ACK1</u>	<u>E111K</u>	<u>1</u>			
<u>ACK1</u>	<u>R127H</u>	<u>1</u>			
<u>ACK1</u>	<u>M393T</u>	<u>1</u>			
<u>ACK1</u>	<u>A634T</u>	<u>1</u>			
<u>ACK1</u>	<u>S699N</u>	<u>1</u>			

218/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
ABL family					
<u>ABL1</u>	<u>G417E</u>				
<u>ABL1</u>	<u>N789S</u>				
<u>ABL1</u>	<u>P829L</u>				
<u>ABL1</u>	<u>G883fsX12</u>			<u>LS-174T, #</u>	
				<u>LS-180, #</u>	
<u>ABL1</u>	<u>S991L</u>		<u>ME-180, L #</u>		
			<u>MES-SA, L #</u>		
<u>ARG</u>	<u>E332K</u>				
<u>ARG</u>	<u>V345A</u>				
<u>ARG</u>	<u>K450R</u>				
<u>ARG</u>	<u>M657I</u>				
<u>ARG</u>	<u>P665T</u>		<u>Ms 751, T #</u>		
<u>ARG</u>	<u>R668C</u>		<u>C-33A, C #</u>		
<u>ARG</u>	<u>Q696H</u>				
<u>ARG</u>	<u>K930R</u>				
<u>ARG</u>	<u>K959R</u>				
<u>ARG</u>	<u>S968F</u>				
<u>ARG</u>	<u>Q994H</u>			<u>HCT-15, H #</u>	
ACK family					
<u>ACK1</u>	<u>H37Y</u>				
<u>ACK1</u>	<u>E111K</u>				
<u>ACK1</u>	<u>R127H</u>			<u>SW-48, H #</u>	
<u>ACK1</u>	<u>M393T</u>	<u>DAL, L #</u>		<u>HCT-116, T #</u>	
<u>ACK1</u>	<u>A634T</u>				
<u>ACK1</u>	<u>S699N</u>				

219/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
ABL family					
<u>ABL1</u>	<u>G417E</u>				
<u>ABL1</u>	<u>N789S</u>				
<u>ABL1</u>	<u>P829L</u>				
<u>ABL1</u>	<u>G883fsX12</u>				
<u>ABL1</u>	<u>S991L</u>		Daudi, L #	G401, L #	
<u>ARG</u>	<u>E332K</u>				
<u>ARG</u>	<u>V345A</u>			A-704, A #	
<u>ARG</u>	<u>K450R</u>			CaKi-2, R #	
<u>ARG</u>	<u>M657I</u>				
<u>ARG</u>	<u>P665T</u>				
<u>ARG</u>	<u>R668C</u>				
<u>ARG</u>	<u>Q696H</u>				
<u>ARG</u>	<u>K930R</u>				
<u>ARG</u>	<u>K959R</u>				
<u>ARG</u>	<u>S968F</u>				
<u>ARG</u>	<u>Q994H</u>				
ACK family					
<u>ACK1</u>	<u>H37Y</u>				
<u>ACK1</u>	<u>E111K</u>				
<u>ACK1</u>	<u>R127H</u>				
<u>ACK1</u>	<u>M393T</u>				
<u>ACK1</u>	<u>A634T</u>				
<u>ACK1</u>	<u>S699N</u>		Jurkat, N #		

220/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
ABL family					
<u>ABL1</u>	<u>G417E</u>				
<u>ABL1</u>	<u>N789S</u>				<u>LNCaP, S #</u>
<u>ABL1</u>	<u>P829L</u>				
<u>ABL1</u>	<u>G883fsX12</u>				
<u>ABL1</u>	<u>S991L</u>		<u>IGROV-1, L #</u>	<u>Mia-PaCa2, L</u>	<u>LNCaP, L #</u>
<u>ARG</u>	<u>E332K</u>				
<u>ARG</u>	<u>V345A</u>				
<u>ARG</u>	<u>K450R</u>				
<u>ARG</u>	<u>M657I</u>				
<u>ARG</u>	<u>P665T</u>				
<u>ARG</u>	<u>R668C</u>				
<u>ARG</u>	<u>Q696H</u>				
<u>ARG</u>	<u>K930R</u>	<u>NCI-H460, R #</u>			
		<u>NCI-H82, R #</u>			
<u>ARG</u>	<u>K959R</u>	<u>Calu-1, R #</u>			
<u>ARG</u>	<u>S968F</u>				
<u>ARG</u>	<u>Q994H</u>				
ACK family					
<u>ACK1</u>	<u>H37Y</u>				
<u>ACK1</u>	<u>E111K</u>				
<u>ACK1</u>	<u>R127H</u>				
<u>ACK1</u>	<u>M393T</u>				
<u>ACK1</u>	<u>A634T</u>				
<u>ACK1</u>	<u>S699N</u>				

221/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
ABL family						
<u>ABL1</u>	G417E	MM-Leh, E #				
<u>ABL1</u>	N789S					
<u>ABL1</u>	P829L				FTC133, L #	
<u>ABL1</u>	G883fsX12					
<u>ABL1</u>	S991L	KA-II, L		Cates 1B, L #		Liver, L # Ovary, L # Prostate, L #
<u>ARG</u>	E332K	MM-254-C, K #				
<u>ARG</u>	V345A					
<u>ARG</u>	K450R					
<u>ARG</u>	M657I	BOW-G, I #				
<u>ARG</u>	P665T					
<u>ARG</u>	R668C					
<u>ARG</u>	Q696H				FTC238, H #	
<u>ARG</u>	K930R					
<u>ARG</u>	K959R					
<u>ARG</u>	S968F	MeWo, F #				
<u>ARG</u>	Q994H					
ACK family						
<u>ACK1</u>	H37Y	MM-254-C, Y #				
<u>ACK1</u>	E111K	MM-254-C, K #				
<u>ACK1</u>	R127H					
<u>ACK1</u>	M393T					
<u>ACK1</u>	A634T		KATO III, T #			
<u>ACK1</u>	S699N					

222/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
ACK1	P725L	89	RT-4, L # TCCSUP, L #	MG63, L # SaOS2, L # RD, L # TE-671, L #	1321N1, L #
					CCF-STTG1, L #
					IMR-32, L #
					SW-1088, L #
					T-98G, L #
					U-118, L #
					U-1242, L #
					U-138, L #
ACK1	P731L	2			
ACK1	R748W	1			
ACK1	G947D	1			SK-N-SH, D #
ACK1	S985N	1			
ACK1	R1038H	10			
TNK1	A299D	2			
TNK1	D472_R473del	15			
TNK1	M598V	23	SCaBER, V		

223/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
ACK1	P725L	DAL, L # Hs-578T, L # MB-361, L # MB-453, L # ZR-75-1, L #	C-4II, L # Ca Ski, L # A-431, L #	Caco2, L # SW-1463, L # SW-480, L SW-620, L	
ACK1	P731L				
ACK1	R748W				
ACK1	G947D				
ACK1	S985N				
ACK1	R1038H				
TNK1	A299D		C-33A, D		
TNK1	D472_R473del		SiHa, -	HCT-116, - # SK-CO-1, - #	
TNK1	M598V	MB-157, V MB-175-VII, V MB-468, V	HT-3, V SW 954, V A-431, V #	SW-1463, V SW-948, V	JAR, V

224/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
ACK1	P725L	HLaC-78, L #	EM-2, L #	CaKi-1, L #	SK-HEP-1, L
		SCC-25, L #	IM-9, L #	CaKi-2, L	
		SCC-17A, L #	Jurkat, L #	SW13, L	
		SCC-17B, L	M-07e, L #		
			MV4-11, L #		
			M-Mac-1, L #		
			M-Mac-6, L #		
			NB-4, L #		
			U-266, L #		
ACK1	P731L				
ACK1	R748W				
ACK1	G947D				
ACK1	S985N			A-498, N	
ACK1	R1038H		IM-9, H #		
			Raji, H #		
			U-937, H #		
TNK1	A299D				
TNK1	D472_R473del			A-498, - #	
TNK1	M598V	FaDu, V #	Daudi, V #		Hu-H7, V
			M-07e, V		
			THP-1, V		

225/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
ACK1	P725L	A-427, L	2774, L	AsPC-1, L #	PC-3, L #
		Calu-1, L #	CaOV-4, L	BxPC-3, L #	PPC-1, L
		Calu-6, L #	IGROV-1, L #	CFPAC-1, L #	
		NCI-H146, L	OAW-42, L #	Capan-1, L #	
		NCI-H209, L	SK-OV-3, L	PT-45P1, L #	
		NCI-H446, L #	SK-OV-8, L #	PT-8988T, L #	
		SW-900, L		SW-850, L #	
ACK1	P731L				
ACK1	R748W				LNCaP, W #
ACK1	G947D				
ACK1	S985N				
ACK1	R1038H			Capan-2, H #	
TNK1	A299D				
TNK1	D472_R473del	NCI-H446, -	PA-1, - #	PT-8902, -	
		NCI-H69, -		Panc TU1, -	
TNK1	M598V	NCI-H292, V #		818-4, V	
				A-818-7, V	

226/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
ACK1	P725L	A-375, L # Hs-294T, L # MALME-3M, L # MM-031-I, L # MM-232-E, L # MM-A1b, L # MM-Arn, L MM-Leh, L # MM-Lo, L # RPMI7951, L # SBCL2, L # WM-1341D, L # WM-852, L # Colo-16, L #			TT, L #	As-745, L BPH-1, L # Colon, L # Gastric, L # HEK-293, L # HaCaT, L # HuVeC, L # Liver, L # MCF-10A, L
ACK1	P731L					FTC133, L
ACK1	R748W					FTC238, L
ACK1	G947D					
ACK1	S985N					
ACK1	R1038H	MM-A1b, H #	HS-746T, H			Kidney, H MCF-10A, H # Placenta, H # Spleen, H #
TNK1	A299D	WM-852, D				
TNK1	D472_R473del	MRI-H221, - SBCL2, - #	AGS, - #	NT-2, - Tera-2, -		As-745, - #
TNK1	M598V		KATO III, V MKN-28, V #			Kidney, V S. Muscle, V # Spleen, V #

227/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
TNK1	M598delinsEVRSHX	64		RD, # TE-671, #	1321N1, A172, CCF-STTG1, # IMR-32, # SK-N-SH, # SW-1088, # T-98G, # T-98G, U-118, U-1240, # U-1242, U-138,
CSK family					
CSK	Q26X	2			
MATK	A496T	3			
FAK family					
FAK	S329I	1			
FAK	T416fsX	13			IMR-32, E # SH-SY-5Y, E # SK-N-SH, E #
FAK	Q440R	1			
FAK	A472V	1			
FAK	P901S	1			

228/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
TNK1	M598delinsEVRSHX	MB-435S,	MES-SA,		
CSK family					
CSK	Q26X			DLD-1, *	
				HCT-15, *	
MATK	A496T				
FAK family					
FAK	S329I		C-33A, I #		
FAK	T416fsX	DU-44-75, E #			
FAK	Q440R				
FAK	A472V				
FAK	P901S				

229/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
TNK1	M598delinsEVRSHX		HL-60, # IM-9, # M-07e, MEG-01, MOLM-1, # MV4-11, # M-Mac-6, # NB-4, OCI-AML5, # PLB-985, # Raji, RF-48, # TF-1, #	769-P, # 786-0, # G401, SW13,	HepG-2,
CSK family					
CSK	<u>Q26X</u>				
MATK	A496T				
FAK family					
FAK	<u>S329I</u>				
FAK	T416fsX				
FAK	<u>Q440R</u>				
FAK	<u>A472V</u>				
FAK	<u>P901S</u>				

230/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
TNK1	M598delinsEVRSHX	Calu-6, # NCI-H128, # NCI-H345, # NCI-H661, #	2780,	Mia-PaCa2, #	TSU-PR1,
CSK family					
CSK	Q26X				
MATK	A496T				
FAK family					
FAK	S329I				
FAK	T416fsX	Calu-6, E # NCI-H128, E # NCI-H146, E # NCI-H209, E # NCI-H345, E # NCI-H446, E # NCI-H510A, E # NCI-H82, E #			
FAK	Q440R				
FAK	A472V		2774, V #		
FAK	P901S				

231/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
TNK1	M598delinsEVRSHX	BOW-G, # C-32, C-8161, # F-01, HT-144, # Hs-695T, # MM-031-I, MM-232-E, MM-Arn, # MM-Du, # MeWo, # Mel Ger, # Mel Juso, RPMI7951, # SK-MEL-24, # WM-1205, # WM-1617, WM-793, WM-902B, # WM-983A, # WM-983B, #		Cates 1B,		HuVeC, #
CSK family						
CSK	Q26X					
MATK	A496T					Bladder, T # Colon, T # S. Muscle, T #
FAK family						
FAK	S329I					
FAK	T416fsX				TT, E #	
FAK	Q440R		MKN-1, R #			
FAK	A472V					
FAK	P901S	MM-Lo, S				

232/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
FAK	L926delinsPWRL	52			IMR-32, #
<u>PYK2</u>	<u>S9I</u>	<u>1</u>			
<u>PYK2</u>	<u>C395Y</u>	<u>1</u>			
<u>PYK2</u>	<u>E404Q</u>	<u>1</u>			<u>SF-763, Q</u>
<u>PYK2</u>	<u>G414V</u>	<u>6</u>			
<u>PYK2</u>	<u>D424Y</u>	<u>2</u>		<u>RD, Y #</u>	
				<u>TE-671, Y #</u>	
<u>PYK2</u>	<u>V739_R780del</u>	<u>21</u>			
<u>PYK2</u>	<u>E798Q</u>	<u>2</u>			

233/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
FAK	L926delinsPWRL	DAL, #		C. 320DM, #	JAR, #
		DU-44-75, #		LS-174T, #	
		MB-435S, #		LS-180, #	
		ZR-75-30, #		LoVo, #	
				NCI-H498, #	
				SK-CO-1, #	
				SW-480, #	
				SW-620, #	
				SW-948, #	
				WiDr, #	
<u>PYK2</u>	<u>S9I</u>				
<u>PYK2</u>	<u>C395Y</u>	MB-436, Y			
<u>PYK2</u>	<u>E404Q</u>				
<u>PYK2</u>	<u>G414V</u>	ZR-75-1, V	C-33A, V #	SW-480, V	
				SW-620, V	
<u>PYK2</u>	<u>D424Y</u>				
<u>PYK2</u>	<u>V739_R780del</u>				
<u>PYK2</u>	<u>E798Q</u>				

234/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
FAK	L926delinsPWRL		Daudi, # Jurkat, # KG-1, # MEG-01, # MV4-11, # RF-1, RF-48, Raji, I	769-P, # A-498, #	Hs 817.T, #
<u>PYK2</u>	<u>S9I</u>				
<u>PYK2</u>	<u>C395Y</u>				
<u>PYK2</u>	<u>E404Q</u>				
<u>PYK2</u>	<u>G414V</u>				
<u>PYK2</u>	<u>D424Y</u>				
<u>PYK2</u>	<u>V739_R780del</u>		EM-2, - HL-60, - IM-9, - Jurkat, - # KG-1, - # MOLM-1, - # MV4-11, - M-Mac-1, - M-Mac-6, - # NB-4, - # OCI-AML5, - PLB-985, - # Raji, - # RF-1, - RF-48, - THP-1, - U-266, - #		HepG-2, -
<u>PYK2</u>	<u>E798Q</u>				

235/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
FAK	L926delinsPWRL	A-427, #	CaOV-4, #	Capan-1, #	
		A-549, #	OAW-42, #		
		Calu-3, #			
		Calu-6, #			
		NCI-H128, #			
		NCI-H345, #			
		NCI-H446, #			
		NCI-H460, #			
		NCI-H661, #			
		NCI-H82, #			
		SW-900, #			
<u>PYK2</u>	<u>S9I</u>				
<u>PYK2</u>	<u>C395Y</u>				
<u>PYK2</u>	<u>E404Q</u>				
PYK2	G414V	SW-900, V			
<u>PYK2</u>	<u>D424Y</u>				
PYK2	V739_R780del				
<u>PYK2</u>	<u>E798Q</u>				

236/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
FAK	L926delinsPWRL	F-01, # MM-254-C, # SK-MEL-5, #			TT, #	Brain, # Colon, # Gastric, # Kidney, # Liver, # Prostate, # S. Muscle, # Testes, #
PYK2	S9I					
PYK2	C395Y					
PYK2	E404Q					
PYK2	G414V					Brain, V #
PYK2	D424Y					
PYK2	V739_R780del					Lung, - # Placenta, - # Spleen, -
PYK2	E798Q	MM-031-I, Q #				
		MM-232-E, Q #				

237/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
PYK2	K838T	149	RT-4, T #	SaOS2, T	A172, T
				RD, T #	IMR-32, T #
				TE-671, T #	SF-126, T #
					SF-767, T
					SH-SY-5Y, T #
					SK-N-SH, T #
					SW-1088, T #
					T-98G, T
					U-118, T #
					U-1240, T
					U-1242, T
<u>PYK2 M885L</u>		<u>2</u>			
<u>PYK2 T978M</u>		<u>3</u>			

238/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
PYK2	K838T	MB-435S, T #	C-33A, T #	Caco2, T	RL95-2, T #
		MB-436, T	HT-3, T	C. 320DM, T	
			ME-180, T	LS-123, T	
			MES-SA, T #	LS-174T, T	
			Ms 751, T	LS-180, T	
			SiHa, T	LoVo, T	
				NCI-H498, T	
				SK-CO-1, T	
				SW-1463, T	
				SW-403, T	
				SW-837, T	
				SW-948, T	
<u>PYK2</u>	<u>M885L</u>				
<u>PYK2</u>	<u>T978M</u>				

239/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
PYK2	K838T	HLaC-78, T #	Daudi, T #	769-P, T #	HepG-2, T #
		SCC-9, T	HL-60, T #	786-0, T	Hu-H7, T
		SCC-10A, T	Jurkat, T #	CaKi-1, T	
		SCC-10B, T	K-562, T #	CaKi-2, T	
		SCC-17A, T #	Kasumi-1, T #	G401, T	
		SCC-22A, T	M-07e, T #		
		SCC-22B, T	MEG-01, T #		
			MV4-11, T #		
			M-Mac-1, T #		
			M-Mac-6, T #		
			NB-4, T #		
			PLB-985, T #		
			Raji, T		
			TF-1, T #		
			THP-1, T #		
			U-266, T		
			U-937, T #		
<u>PYK2</u>	<u>M885L</u>				
<u>PYK2</u>	<u>T978M</u>				

240/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
PYK2	K838T	A-427, T #	2780, T	CFPAC-1, T	BM-1604, T
		A-549, T #	CaOV-4, T #	Capan-1, T #	DU-145, T #
		Calu-1, T	IGROV-1, T	Capan-2, T	PC-3, T
		NCI-H128, T #	OVCAR-3, T #	Hs 766T, T	PPC-1, T
		NCI-H146, T #	SK-OV-6, T	Mia-PaCa2, T	
		NCI-H345, T		PT-8902, T	
		NCI-H441, T #		PANC-1, T	
		NCI-H446, T		Panc TU1, T	
		NCI-H460, T			
		NCI-H596, T			
		NCI-H661, T			
		NCI-H69, T			
		SK-LU-1, T			
		SK-MES-1, T			
PYK2	M885L				BM-1604, L #
					DU-145, L #
<u>PYK2</u>	<u>T978M</u>				

241/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
PYK2	K838T	BOW-G, T # C-8161, T Colo829, T # F-01, T # HT-144, T Hs-294T, T Hs-695T, T # IGR-39, T # MM-031-I, T MM-195-H, T # MM-232-E, T MM-Alt, T MM-Arn, T # MM-Du, T MRI-H221, T # Mel Ger, T Mel Juso, T # RPMI7951, T SBCL2, T # SK-MEL-24, T # SK-MEL-28, T # SK-MEL-31, T # WM-1205, T WM-1341D, T WM-35, T # WM-793, T WM-852, T # WM-902B, T Colo-16, T #		NT-2, T # Cates 1B, T Tera-2, T #	FTC133, T FTC238, T	As-745, T # BPH-1, T # Bladder, T Cervix, T # Colon, T # Gastric, T # HEK-293, T # HaCaT, T # Hs 1.Li, T # HuVeC, T Liver, T Lung, T Ovary, T # Placenta, T # Prostate, T # S. Muscle, T # Testes, T #
PYK2	M885L					
PYK2	T978M	WM-983A, M # WM-983B, M #				

242/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
FES family					
<u>FER</u>	<u>I240T</u>	<u>2</u>			
FER	Q526L	1			
<u>FER</u>	<u>Q599R</u>	<u>1</u>			
FES	S72_K129del	17			
FES	M323V	1			
FES	P397R	1			
FES	E413fsX131	8			
<u>FES</u>	<u>L690M</u>	<u>1</u>			
<u>FES</u>	<u>V724M</u>	<u>1</u>			
FRK family					
<u>BRK</u>	<u>W78fsX58</u>	<u>2</u>	<u>RT-4, #</u>		
<u>FRK</u>	<u>R64Q</u>	<u>1</u>			
<u>FRK</u>	<u>G119A</u>	<u>1</u>			
FRK	G122R	74	HT-1376, R		
			SCaBER, R #		
			TCCSUP, R		

243/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>FER</u>	<u>I240T</u>			DLD-1, T #	
				HCT-15, T #	
FER	Q526L			SW-837, L #	
<u>FER</u>	<u>Q599R</u>				
FES	S72_K129del		SW 954, -		
FES	M323V				
FES	P397R				
FES	E413fsX131			HCT-116, LS-123,	
<u>FES</u>	<u>L690M</u>			<u>DLD-1, M #</u>	
<u>FES</u>	<u>V724M</u>				
FRK family					
<u>BRK</u>	<u>W78fsX58</u>				
<u>FRK</u>	<u>R64Q</u>		Ca Ski, Q #		
<u>FRK</u>	<u>G119A</u>				
FRK	G122R	MB-435S, R	C-4II, R SiHa, R	DLD-1, R HCT-116, R # HCT-15, R LoVo, R NCI-H498, R # SW-1463, R # SW-480, R SW-620, R SW-948, R # T-84, R	RL95-2, R

244/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato - poietic and Lymphoid System	Kidney	Liver
FES family					
<u>FER</u>	<u>I240T</u>				
<u>FER</u>	<u>Q526L</u>				
<u>FER</u>	<u>Q599R</u>				
FES	S72_K129del		Raji, -	G401, -	
FES	M323V		M-07e, V #		
FES	P397R				
FES	E413fsX131		U-266,	A-498, A-704,	
<u>FES</u>	<u>L690M</u>				
<u>FES</u>	<u>V724M</u>		Jurkat, M #		
FRK family					
<u>BRK</u>	<u>W78fsX58</u>				
<u>FRK</u>	<u>R64Q</u>				
<u>FRK</u>	<u>G119A</u>				
FRK	G122R	SCC-15, R # SCC-25, R # SCC-9, R SCC-10A, R # SCC-10B, R # SCC-17A, R # SCC-17B, R #	IM-9, R # MEG-01, R # U-266, R #	A-498, R	Hs 817.T, R

245/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
FES family					
<u>FER</u>	<u>I240T</u>				
FER	Q526L				
<u>FER</u>	<u>Q599R</u>				LNCaP, R #
FES	S72_K129del	NCI-H596, -		818-4, - Hs 766T, -	
FES	M323V				
FES	P397R				
FES	E413fsX131				
<u>FES</u>	<u>L690M</u>				
<u>FES</u>	<u>V724M</u>				
FRK family					
<u>BRK</u>	<u>W78fsX58</u>	<u>SW-900, #</u>			
<u>FRK</u>	<u>R64Q</u>				
<u>FRK</u>	<u>G119A</u>			Capan-1, A	
FRK	G122R	A-549, R # NCI-H460, R NCI-H82, R SK-LU-1, R # SK-MES-1, R # SW-900, R #	CaOV-4, R OVCAR-3, R SK-OV-6, R # SK-OV-8, R #	AsPC-1, R CFPAC-1, R # Capan-1, R # Capan-2, R DANG-G, R # PANC-1, R # SW-850, R	BM-1604, R # DU-145, R # PC-3, R PPC-1, R #

246/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
FER	<u>I240T</u>					
FER	<u>Q526L</u>					
FER	<u>Q599R</u>					
FES	S72_K129del	C-8161, - MeWo, - SBCL2, - WM-983A, - # WM-983B, - #	KATO III, -			Colon, - HuVeC, - S. Muscle, - BPH-1, -
FES	M323V					Colon, R #
FES	P397R					HEK-293, Cervix, Prostate,
FES	E413fsX131					
FES	<u>L690M</u>					
FES	<u>V724M</u>					
FRK family						
BRK	<u>W78fsX58</u>					
FRK	<u>R64Q</u>					
FRK	<u>G119A</u>					
FRK	G122R	F-01, R # G-361, R # Hs-294T, R # IGR-39, R # KA-II, R MALME-3M, R # Mel Juso, R # SK-MEL-28, R SK-MEL-31, R # WM-852, R # Colo-16, R #	HS-746T, R MKN-1, R MKN-28, R		FTC133, R # FTC238, R # TT, R	As-745, R # BPH-1, R Gastric, R # Liver, R # Ovary, R S. Muscle, R # Testes, R #

247/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
<u>FRK</u>	<u>R406H</u>	<u>1</u>			
JAK family					
<u>JAK1</u>	<u>I363V</u>	<u>1</u>			
<u>JAK1</u>	<u>R494C</u>	<u>1</u>			
<u>JAK1</u>	<u>N849fsX16</u>	<u>1</u>			
<u>JAK2</u>	<u>F85S</u>	<u>1</u>			
<u>JAK2</u>	<u>A377E</u>	<u>1</u>			
<u>JAK2</u>	<u>L383P</u>	<u>1</u>			
<u>JAK2</u>	<u>L393V</u>	<u>3</u>			
<u>JAK2</u>	<u>E592K</u>	<u>1</u>			
<u>JAK2</u>	<u>G571S</u>	<u>1</u>			
<u>JAK2</u>	<u>R1063H</u>	<u>1</u>			
<u>JAK2</u>	<u>N1108S</u>	<u>3</u>			
<u>JAK3</u>	<u>G62fsX44</u>	<u>4</u>			<u>SK-N-SH #</u>
<u>JAK3</u>	<u>P132T</u>	<u>1</u>			
<u>JAK3</u>	<u>P151R</u>	<u>1</u>			
<u>JAK3</u>	<u>M511I</u>	<u>1</u>			
<u>JAK3</u>	<u>P693L</u>	<u>1</u>			
<u>JAK3</u>	<u>E698K</u>	<u>1</u>			
<u>JAK3</u>	<u>V722I</u>	<u>2</u>			
<u>TYK2</u>	<u>A53T</u>	<u>2</u>			
<u>TYK2</u>	<u>S340fsX26</u>	<u>3</u>			

248/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
<u>FRK</u>	<u>R406H</u>			<u>SW-948, H #</u>	
JAK family					
<u>JAK1</u>	<u>I363V</u>			<u>Caco2, V</u>	
<u>JAK1</u>	<u>R494C</u>			<u>C. 320DM, C #</u>	
<u>JAK1</u>	<u>N849fsX16</u>				
<u>JAK2</u>	<u>F85S</u>				<u>RL95-2, S #</u>
<u>JAK2</u>	<u>A377E</u>				
<u>JAK2</u>	<u>L383P</u>			<u>HCT-15, P #</u>	
<u>JAK2</u>	<u>L393V</u>	<u>BT-483, V #</u>	<u>A-431, V</u>		
<u>JAK2</u>	<u>E592K</u>				
<u>JAK2</u>	<u>G571S</u>				
<u>JAK2</u>	<u>R1063H</u>				
<u>JAK2</u>	<u>N1108S</u>	<u>HBL-100, S #</u>		<u>NCI-H498, S #</u>	
<u>JAK3</u>	<u>G62fsX44</u>				
<u>JAK3</u>	<u>P132T</u>				
<u>JAK3</u>	<u>P151R</u>				
<u>JAK3</u>	<u>M511I</u>				
<u>JAK3</u>	<u>P693L</u>				
<u>JAK3</u>	<u>E698K</u>				
<u>JAK3</u>	<u>V722I</u>				
<u>TYK2</u>	<u>A53T</u>				
<u>TYK2</u>	<u>S340fsX26</u>				

249/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
<u>FRK</u>	<u>R406H</u>				
JAK family					
<u>JAK1</u>	<u>I363V</u>				
<u>JAK1</u>	<u>R494C</u>				
<u>JAK1</u>	<u>N849fsX16</u>				
<u>JAK2</u>	<u>F85S</u>				
<u>JAK2</u>	<u>A377E</u>				
<u>JAK2</u>	<u>L383P</u>				
<u>JAK2</u>	<u>L393V</u>				
<u>JAK2</u>	<u>E592K</u>				
<u>JAK2</u>	<u>G571S</u>				
<u>JAK2</u>	<u>R1063H</u>				
<u>JAK2</u>	<u>N1108S</u>				
<u>JAK3</u>	<u>G62fsX44</u>		<u>Daudi #</u>		
			<u>THP-1 #</u>		
<u>JAK3</u>	<u>P132T</u>				
<u>JAK3</u>	<u>P151R</u>				
<u>JAK3</u>	<u>M511I</u>		<u>Raji, I #</u>		
<u>JAK3</u>	<u>P693L</u>				
<u>JAK3</u>	<u>E698K</u>				
<u>JAK3</u>	<u>V722I</u>	SCC-10A, I #			
		SCC-10B, I #			
<u>TYK2</u>	<u>A53T</u>				
<u>TYK2</u>	<u>S340fsX26</u>				

250/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
<u>FRK</u>	<u>R406H</u>				
JAK family					
<u>JAK1</u>	<u>I363V</u>				
<u>JAK1</u>	<u>R494C</u>				
<u>JAK1</u>	<u>N849fsX16</u>		<u>IGROV-1</u>		
<u>JAK2</u>	<u>F85S</u>				
<u>JAK2</u>	<u>A377E</u>	NCI-H128, E #			
<u>JAK2</u>	<u>L383P</u>				
<u>JAK2</u>	<u>L393V</u>				
<u>JAK2</u>	<u>E592K</u>				
<u>JAK2</u>	<u>G571S</u>				
<u>JAK2</u>	<u>R1063H</u>		<u>OVCAR-3, H</u>		
<u>JAK2</u>	<u>N1108S</u>	NCI-H596, S #			
<u>JAK3</u>	<u>G62fsX44</u>	<u>SK-MES-1 #</u>			
<u>JAK3</u>	<u>P132T</u>	NCI-H292, T			
<u>JAK3</u>	<u>P151R</u>				
<u>JAK3</u>	<u>M511I</u>				
<u>JAK3</u>	<u>P693L</u>				
<u>JAK3</u>	<u>E698K</u>	NCI-H661, K			
<u>JAK3</u>	<u>V722I</u>				
<u>TYK2</u>	<u>A53T</u>	<u>NCI-H146, T #</u>			
<u>TYK2</u>	<u>S340fsX26</u>				

251/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
<u>FRK</u>	<u>R406H</u>					
JAK family						
<u>JAK1</u>	<u>I363V</u>					
<u>JAK1</u>	<u>R494C</u>					
<u>JAK1</u>	<u>N849fsX16</u>					
<u>JAK2</u>	<u>F85S</u>					
<u>JAK2</u>	<u>A377E</u>					
<u>JAK2</u>	<u>L383P</u>					
<u>JAK2</u>	<u>L393V</u>	SBCL2, V				
<u>JAK2</u>	<u>E592K</u>	SK-MEL-28, K#				
<u>JAK2</u>	<u>G571S</u>				FTC238, S #	
<u>JAK2</u>	<u>R1063H</u>					
<u>JAK2</u>	<u>N1108S</u>					
<u>JAK3</u>	<u>G62fsX44</u>					
<u>JAK3</u>	<u>P132T</u>					
<u>JAK3</u>	<u>P151R</u>					Testes, R #
<u>JAK3</u>	<u>M511I</u>					
<u>JAK3</u>	<u>P693L</u>	SK-MEL-28, L#				
<u>JAK3</u>	<u>E698K</u>					
<u>JAK3</u>	<u>V722I</u>					
<u>TYK2</u>	<u>A53T</u>				TT, T #	
<u>TYK2</u>	<u>S340fsX26</u>	G-361, #				
	<u>BOW-G, #</u>					
	<u>RPMI7951, #</u>					

252/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
TYK2	V362F	64	T-24, F #	MG63, F #	1321N1, F
				SaOS2, F #	SF-126, F
				RD, F	SF-767, F
				TE-671, F	SK-N-SH, F
					SW-1088, F #
					T-98G, F
					U-118, F #
					U-1240, F
					U-138, F #
TYK2	G363S	10	RT-4, S #		
TYK2	I684S	26			SF-126, S #
					SF-767, S
					SH-SY-5Y, S #
					SK-N-SH, S #
					SW-1088, S #
TYK2	R701T	1			T-98G, S #
TYK2	D883N	1			
TYK2	R901Q	1			
TYK2	A928V	1			
TYK2	E971fsX67	15			
TYK2	P1104A	13		MG63, A #	

253/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
TYK2	V362F	HBL-100, F # MB-435S, F	C-4II, F ME-180, F	HCT-116, F # LS-174T, F # LS-180, F # LoVo, F # NCI-H498, F #	
TYK2	G363S		SW 954, S #	HCT-116, S #	
TYK2	I684S	MB-435S, S #	C-4II, S ME-180, S #	SW-837, S	KLE, S
TYK2	R701T				
TYK2	D883N				
TYK2	R901Q				
TYK2	A928V				
TYK2	E971fsX67	BT-474 # BT-483 # BT-549 # MB-415 # MB-361 #	Ms 751 #	SW-837 # WiDr # HCT-116 #	JAR #
TYK2	P1104A	MB-435S, A #		LoVo, A #	

254/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato-poietic and Lymphoid System	Kidney	Liver
TYK2	V362F		EM-2, F #	769-P, F #	HepG-2, F #
			HL-60, F #	786-0, F #	
			IM-9, F #	A-498, F #	
			K-562, F #	CaKi-1, F #	
			Kasumi-1, F	CaKi-2, F #	
			MEG-01, F	G401, F #	
			M-Mac-1, F #		
			M-Mac-6, F #		
			NB-4, F #		
			OCI-AML5, F #		
			PLB-985, F #		
			Raji, F #		
			RF-1, F #		
			RF-48, F #		
TYK2	G363S		M-07e, S #	769-P, S #	
			M-Mac-1, S #		
			M-Mac-6, S #		
			U-266, S #		
TYK2	I684S		HL-60, S #	786-0, S #	HepG-2, S #
			PLB-985, S #		
			RF-1, S #		
			RF-48, S #		
TYK2	R701T		Kasumi-1, T #		
TYK2	D883N				
TYK2	R901Q				
TYK2	A928V				
TYK2	E971fsX67				
TYK2	P1104A		IM-9, A #	A-498, A #	
			M-Mac-1, A #		
			M-Mac-6, A #		
			OCI-AML5, A #		
			Raji, A #		

255/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
TYK2	V362F	Calu-1, F # Calu-3, F # NCI-H146, F # NCI-H520, F # NCI-H596, F # NCI-H661, F SK-LU-1, F		AsPC-1, F PT-45P1, F	
TYK2	G363S				
TYK2	I684S			AsPC-1, S SW-850, S	
<u>TYK2</u>	<u>R701T</u>				
<u>TYK2</u>	<u>D883N</u>				
<u>TYK2</u>	<u>R901Q</u>		IGROV-1, Q #		
TYK2	A928V				
TYK2	E971fsX67	NCI-H510A #		PT-8902 # PANC-1 #	
TYK2	P1104A	Calu-3, A # SK-MES-1, A		PT-45P1, A #	

256/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
TYK2	V362F	MM-201-B, F # MM-Alb, F # MM-Alt, F MM-Du, F MM-Lo, F SBCL2, F # WM-793, F #				Colon, F Gastric, F # Liver, F # MCF-10A, F #
TYK2	G363S	MM-201-B, S # WM-793, S #				
TYK2	I684S	C-32, S # MM-Leh, S # MM-Lo, S # MRI-H221, S #				HuVeC, S # MCF-10A, S # Placenta, S #
TYK2	R701T					
TYK2	D883N	MeWo, N #				
TYK2	R901Q					
TYK2	A928V	MM-Alt, V #				
TYK2	E971fsX67			NT-2 #		BPH-1 #
TYK2	P1104A	MM-201-B, A #				

257/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
SRC-A family					
FYN	D506E	7			SH-SY-5Y, E #
<u>FYN</u>	<u>E521K</u>	<u>2</u>			
YES1	K113Q	3			
SRC-B family					
<u>LCK</u>	<u>L36fsX8</u>	<u>1</u>			
<u>LCK</u>	<u>F151S</u>	<u>1</u>			
<u>LCK</u>	<u>R484W</u>	<u>1</u>			
<u>LYN</u>	<u>F130V</u>	<u>2</u>			
SYK family					
<u>SYK</u>	<u>M34fsX3</u>	<u>3</u>			
<u>SYK</u>	<u>I262L</u>	<u>1</u>			
SYK	E315K	1			
<u>SYK</u>	<u>A353T</u>	<u>7</u>			SK-N-SH, T #
<u>SYK</u>	<u>R520S</u>	<u>1</u>			
<u>SYK</u>	<u>V622A</u>	<u>2</u>			
<u>ZAP-70</u>	<u>T155M</u>	<u>2</u>			
ZAP-70	K186fsX	20		SaOS2, - #	SK-N-SH, - #

258/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
SRC-A family					
FYN	D506E	MCF-7, E # MB-435S, E			JAR, E #
FYN	E521K			DLD-1, K # HCT-15, K #	
YES1	K113Q	MB-436, Q #		SW-837, Q	
SRC-B family					
LCK	L36fsX8				
LCK	F151S			DLD-1, S #	
LCK	R484W			HCT-116, W #	
LYN	F130V			LS-174T, V # LS-180, V #	
SYK family					
SYK	M34fsX3			LS-174T, # LS-180, #	
SYK	I262L				
SYK	E315K				
SYK	A353T		MES-SA, T #	DLD-1, T #	
SYK	R520S				
SYK	V622A				
ZAP-70	T155M				
ZAP-70	K186fsX		C-33A, - # SW 954, - #		

259/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
SRC-A family					
FYN	D506E				
FYN	E521K				
YES1	K113Q			769-P, Q #	
SRC-B family					
LCK	L36fsX8				
LCK	F151S				
LCK	R484W				
LYN	F130V				
SYK family					
SYK	M34fsX3		Jurkat, -		
SYK	I262L		KG-1, L #		
SYK	E315K				
SYK	A353T				
SYK	R520S			A-498, S #	
SYK	V622A				
ZAP-70	T155M		Jurkat, M #		
ZAP-70	K186fsX		Daudi, - #	CaKi-1, - #	HepG-2, - #
			M-Mac-1, - #	SW13, - #	Hu-H7, - #
			M-Mac-6, - #		
			Raji, - #		
			U-266, - #		

260/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
SRC-A family					
FYN	D506E	NCI-H520, E #		DANG-G, E #	LNCaP, E #
<u>FYN</u>	<u>E521K</u>				
YES1	K113Q				
SRC-B family					
<u>LCK</u>	<u>L36fsX8</u>	<u>SK-LU-1</u>			
<u>LCK</u>	<u>F151S</u>				
<u>LCK</u>	<u>R484W</u>				
<u>LYN</u>	<u>F130V</u>				
SYK family					
<u>SYK</u>	<u>M34fsX3</u>				
<u>SYK</u>	<u>I262L</u>				
<u>SYK</u>	<u>E315K</u>				
<u>SYK</u>	<u>A353T</u>				
<u>SYK</u>	<u>R520S</u>				
<u>SYK</u>	<u>V622A</u>				BM-1604, A
					<u>DU-145, A #</u>
<u>ZAP-70</u>	<u>T155M</u>				
ZAP-70	K186fsX	NCI-H128, - #			
		NCI-H446, - #			
		SK-LU-1, - #			

261/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
SRC-A family						
<u>FYN</u>	<u>D506E</u>					
<u>FYN</u>	<u>E521K</u>					
<u>YES1</u>	<u>K113Q</u>					
SRC-B family						
<u>LCK</u>	<u>L36fsX8</u>					
<u>LCK</u>	<u>F151S</u>					
<u>LCK</u>	<u>R484W</u>					
<u>LYN</u>	<u>F130V</u>					
SYK family						
<u>SYK</u>	<u>M34fsX3</u>					
<u>SYK</u>	<u>I262L</u>					
<u>SYK</u>	<u>E315K</u>	MeWo, K				
<u>SYK</u>	<u>A353T</u>	MM-Arn, T #	MKN-1, T #			
		<u>MM-Leh, T #</u>				
<u>SYK</u>	<u>R520S</u>					
<u>SYK</u>	<u>V622A</u>					
<u>ZAP-70</u>	<u>T155M</u>	MM-Du, M #				
<u>ZAP-70</u>	<u>K186fsX</u>				FTC133, - # TT, - #	HEK-293, - # Hs 1.Li, - #

262/306

Fig. 31 (continued)

Gene	Alteration	Total Number	Bladder	Bone and Soft Tissue	Brain
ZAP-70	P296_S301del	55			SK-N-SH, - # U-118, - # U-138, - #
ZAP-70	M549V	1			
TEC family					
BMX	A150D	1			
BMX	S254del	10			SF-763, - #
BMX	N267I	3			
BTK	M489I	1			
BTK	W588C	1			
ITK	R448H	1			
TEC	L89R	1			
TEC	W531R	1			
TEC	P587L	1			
TXK	R63C	1			
TXK	R336Q	16	T-24, Q #		
TXK	Y414fsX15	33			IMR-32, # SF-763, # SH-SY-5Y, #

263/306

Fig. 31 (continued)

Gene	Alteration	Breast	Cervix and Vulva	Colon	Endo- metrium and Placenta
ZAP-70	P296_S301del		Ca Ski, - # HeLa S3, - # MES-SA, - # SW 954, - #	Caco2, - # C. 320DM, - # HCT-116, - # LS-123, - # LS-174T, - # LoVo, - # SW-48, - # SW-480, - # SW-620, - #	KLE, - #
ZAP-70	M549V				
TEC family					
BMX	A150D				
BMX	S254del	MCF-7, - # MB-453, - #			
BMX	N267I				
BTK	M489I				RL95-2, I
BTK	W588C				
ITK	R448H				
TEC	L89R				
TEC	W531R				
TEC	P587L				
TXK	R63C				
TXK	R336Q	MB-231, Q #		NCI-H498, Q # SW-837, Q # WiDr, Q #	
TXK	Y414fsX15	BT-483, # MB-157, # MB-415, # MB-468, #	HT-3, #	HCT-116, # SW-1417, #	

264/306

Fig. 31 (continued)

Gene	Alteration	Head and Neck	Hemato- poietic and Lymphoid System	Kidney	Liver
ZAP-70	P296_S301del		Daudi, - # KG-1, - # Kasumi-1, - # M-07e, - # Raji, - # TF-1, - # U-266, - #	A-498, - # A-704, - # ACHN, - # CaKi-1, - # CaKi-2, - # SW13, - #	
ZAP-70	M549V		EM-2, V #		
TEC family					
BMX	A150D				
BMX	S254del	SCC-9, - #		G401, - #	
BMX	N267I				
BTK	M489I				
BTK	W588C				
ITK	R448H		Jurkat, H #		
TEC	L89R				
TEC	W531R		Jurkat, R		
TEC	P587L				
TXK	R63C				
TXK	R336Q	SCC-10A, Q # SCC-10B, Q # SCC-22A, Q # SCC-22B, Q #			Hs 817.T, Q #
TXK	Y414fsX15		EM-2, # HL-60, # K-562, # Kasumi-1, # M-07e, # MEG-01, # MOLM-1, # NB-4, # PLB-985, #	769-P, # 786-0, #	

265/306

Fig. 31 (continued)

Gene	Alteration	Lung	Ovary	Pancreas	Prostate
ZAP-70	P296_S301del		2780, - # PA-1, - #	818-4, - # PT-8902, - # PT-45P1, - #	LNCaP.FGC, -
ZAP-70	M549V				
TEC family					
BMX	A150D				LNCaP, D
BMX	S254del	NCI-H446, - #			
BMX	N267I				
BTK	M489I				
BTK	W588C		2774, C		
ITK	R448H				
TEC	L89R				
TEC	W531R				
TEC	P587L	NCI-H661, L			
TXK	R63C				
TXK	R336Q		IGROV-1, Q # OAW-42, Q #		
TXK	Y414fsX15	NCI-H209, # SW-900, #		Mia-PaCa2, # PT-8988T, # Panc TU1, #	

266/306

Fig. 31 (continued)

Gene	Alteration	Skin	Stomach	Testes	Thyroid	Normal Tissue
ZAP-70	P296_S301del	F-01, - # KA-II, - # MM-Ait, - # RPMI7951,-# WM-1341D,-# WM-1617,-# WM-902B,-# WM-983A,-# WM-983B,-#	KATO III,-# RF-1, - #	NT-2, - #		Cervix, - # Colon, - # Gastric, - # Kidney, - # Liver, - # Ovary, - # Prostate, - #
ZAP-70	M549V					
TEC family						
BMX	A150D					
BMX	S254del		KATO III,-#	NT-2, - #		Liver, - # Prostate, - #
BMX	N267I	WM-115, I				
		WM-239A, I				
		WM-266-4, I				
BTK	M489I					
BTK	W588C					
ITK	R448H					
TEC	L89R		AGS, R #			
TEC	W531R					
TEC	P587L					
TXK	R63C					Spleen, C #
TXK	R336Q	KA-II, Q # MeWo, Q #	AGS, Q #			MCF-10A, Q #
TXK	Y414fsX15		HS-746T, # MKN-28, #		FTC133, # FTC238, #	Ovary, # S. Muscle, #

267/306

Fig. 32

Gene	Somatic mutations		Sequence Listing #	
	amino acids	nucleotides	Protein	nt
AATK	F1195C	T3751G	1	270
ABL1	G417E	G1689A	2	271
ABL1	N789S	A2805G	3	272
ABL1	G883fsX12	nt3083DEL	4	273
ACK1	H37Y	C652T	5	274
ACK1	E111K	G874A	6	275
ACK1	R127H	G923A	7	276
ACK1	M393T	T1721C	8	277
ACK1	A634T	G2443A	9	278
ACK1	S699N	G2639A	10	279
ACK1	P731L	C2735T	11	280
ACK1	R748W	C2785T	12	281
ACK1	G947D	G3383A	13	282
ACK1	S985N	G3497A	14	283
ALK	G1580V	G5646T	15	284
ARG	E332K	G1198A	16	285
ARG	V345A	T1238C	17	286
ARG	K450R	A1553G	18	287
ARG	M657I	G2175A	19	288
ARG	P665T	C2197A	20	289
ARG	R668C	C2206T	21	290
ARG	Q696H	G2292C	22	291
ARG	K930R	A2993G	23	292
ARG	S968F	C3107T	24	293
ARG	Q994H	G3186T	25	294
AXL	M569I	G2165A	26	295
AXL	M589K	T2224A	27	296
AXL	G835V	G2962T	28	297
BMX	A150D	C550A	29	298
BMX	S254del	nt863-865del	30	299
BMX	N267I	A901T	31	300
BRK	W78fsX58	nt271-392DEL	32	301
BTK	M489I	G1630A	33	302
BTK	W588C	G1927T	34	303
CARK	L259F		35	304
CARK	S591fsX74		36	305
CARK	N627fsX24		37	306
CARK	N627fsX19		38	307
CARK	N627fsX29		39	308
CARK	E662K		40	309
CARK	G708fsX24		41	310
CARK	G708fsX19		42	311
CARK	R752L		43	312
CARK	S784fsX6		44	313

(cont. on next page)

268/306

Fig. 32 (cont.)

Gene	Somatic mutations		Sequence Listing #	
	amino acids	nucleotides	Protein	nt
CARK	S784fsX5		45	314
CARK	S784fsX18		46	315
CARK	G811fsX5		47	316
CCK4	D106N	G514A	48	317
CCK4	T410S	A1426T	49	318
CCK4	M746L	A2434C	50	319
CCK4	Q913H	G2937T	51	320
CSK	Q26X	C488T	52	321
DDR1	R60C	C514T	53	322
DDR1	V100A	T635C	54	323
DDR1	R248W	C1078T	55	324
DDR2	M117I	G704A	56	325
DDR2	R478C	C1785T	57	326
EGFR	N115K	T511A	58	327
EGFR	A289V	C1032T	59	328
EGFR	P332S	C1160T	60	329
EGFR	I646L	A2102C	61	330
EGFR	T678M	C2199T	62	331
EGFR	P753S	C2423T	63	332
EGFR	E922K	G2930A	64	333
EGFR	A1118T	G3518A	65	334
EPHA2	R315Q	G1081A	66	335
EPHA2	H333R	A1135G	67	336
EPHA2	G391R	G1308A	68	337
EPHA2	P460L	C1516T	69	338
EPHA2	H609Y	C1962T	70	339
EPHA2	M631T	T2029C	71	340
EPHA2	G662S	G2121A	72	341
EPHA2	V747I	G2376A	73	342
EPHA2	L836R	T2644G	74	343
EPHA2	E911K	G2868A	75	344
EPHA2	V936M	G2943A	76	345
EPHA2	R950W	C2985T	77	346
EPHA3	S46F	C362T	78	347
EPHA3	E53K	G382A	79	348
EPHA3	A777G	C2555G	80	349
EPHA4	V234F	G742T	81	350
EPHA4	S803A	T2449G	82	351
EPHA4	M877V	A2671G	83	352
EPHA5	N81T	A291C	84	353
EPHA5	E85K	G302A	85	354
EPHA5	A672T	G2063A	86	355
EPHA5	V891L	G2720T	87	356

(cont. on next page)

269/306

Fig. 32 (cont.)

Gene	Somatic mutations		Sequence Listing #	
	amino acids	nucleotides	Protein	nt
EPHA5	A957T	G2918A	88	357
EPHA5	R981L	G2991T	89	358
EPHA6	N291H	A871C	90	359
EPHA6	G513E	G1538A	91	360
EPHA6	L622F	C1864T	92	361
EPHB1	A39V	C330T	93	362
EPHB1	I837M	C2725G	94	363
EPHB2	A83V	C266T	95	364
EPHB2	S98R	C312A	96	365
EPHB2	V136M	G424A	97	366
EPHB2	R270Q	G827A	98	367
EPHB2	P273L	C836T	99	368
EPHB2	R369Q	G1124A	100	369
EPHB2	E686K	G2074A	101	370
EPHB2	V762L	G2302T	102	371
EPHB3	P6del	nt455-457del	103	372
EPHB3	A517V	C1987T	104	373
EPHB4	P231S	C1066T	105	374
EPHB4	V547M	G2014A	106	375
EPHB4	D576G	A2102G	107	376
EPHB4	I610T	T2204C	108	377
EPHB4	E890D	G3045T	109	378
EPHB4	A955V	C3239T	110	379
EPHB6	G353_E471del	nt1856-2212del	111	380
EPHB6	A369T	G1903A	112	381
EPHB6	L580F	G2538T	113	382
EPHB6	E615K	G2641A	114	383
EPHB6	A647V	C2738T	115	384
EPHB6	S785R	C3153A	116	385
EPHB6	R811C	C3229T	117	386
FAK	S329I	G1139T	118	387
FAK	Q440R	A1472G	119	388
FAK	A472V	C1568T	120	389
FAK	P901S	C2854T	121	390
FER	I240T	T1103C	122	391
FER	Q526L	A1961T	123	392
FER	Q599R	A2180G	124	393
FES	M323V	A1042G	125	394
FES	L690M	C2143A	126	395
FES	V724M	G2245A	127	396
FGFR1	R78H	G959A	128	397
FGFR1	P252S	C1480T	129	398
FGFR1	A268S	G1528T	130	399
FGFR1	G539_K540del	nt2341-2346del	131	400

(cont. on next page)

270/306

Fig. 32 (cont.)

Gene	Somatic mutations		Sequence Listing #	
	amino acids	nucleotides	Protein	nt
FGFR2	I526T	T2162C	132	401
FGFR4	Y367C	A1256G	133	402
FLT3	V194M	G580A	134	403
FLT3	D358V	A1073T	135	404
FLT3	V557I	G1669A	136	405
FLT3	G757E	G2270A	137	406
FLT3	R849H	G2546A	138	407
FRK	R64Q	G638A	139	408
FRK	G119A	G803C	140	409
FRK	R406H	G1664A	141	410
FYN	E521K	G2140A	142	411
HER2	G518E	G1791A	143	412
HER2	A830V	C2727T	144	413
HER2	E930D	G3028T	145	414
HER2	G1015E	G3282A	146	415
HER2	A1216D	C3885A	147	416
HER3	N126K	C571A	148	417
HER3	R611W	C2024T	149	418
HER3	R667H	G2193A	150	419
HER3	R1077W	C3422T	151	420
HER3	R1089W	C3458T	152	421
HER3	P1142H	C3618A	153	422
HER3	L1177I	C3722A	154	423
HER4	L753V	C2290G	155	424
HER4	G936R	G2839A	156	425
IGF1R	T104M	C356T	157	426
IGF1R	Y201H	T646C	158	427
IGF1R	N209S	A671G	159	428
INSR	L991I	C3077A	160	429
ITK	R448H	G1425A	161	430
JAK1	I363V	A1162G	162	431
JAK1	R494C	C1555T	163	432
JAK1	N849fsX16	nt2614DEL	164	433
JAK2	F85S	T748C	165	434
JAK2	A377E	C1624A	166	435
JAK2	L383P	T1642C	167	436
JAK2	G571S	G2205A	168	437
JAK2	E592K	G2268A	169	438
JAK2	R1063H	G3682A	170	439
JAK2	N1108S	A3817G	171	440
JAK3	G62fsX44	nt244-367DEL	172	441
JAK3	M511I	G1592A	173	442
JAK3	P693L	C2137T	174	443
JAK3	E698K	G2151A	175	444

(cont. on next page)

271/306

Fig. 32 (cont.)

Gene	Somatic mutations		Sequence Listing #	
	amino acids	nucleotides	Protein	nt
LCK	L36fsX8	nt155(CAGGCGACGGGCCTTTGGGA GGGTAAGAATGCAACCAGAAGAATG ACCGCCTACAGCCTTGAAAGAAGAG TGGCCTCTCCCTGAAATACAAAGGA AAACCCAGAGAGGGGAAGGAATCT CCTAAGATCCA)INS	176	445
LCK	F151S	T503C	177	446
LCK	R484W	C1501T	178	447
LMTK2	Q238P	A1006C	179	448
LMTK2	A251T	G1044A	180	449
LMTK2	G518V	G1846T	181	450
LMTK2	D523Y	G1860T	182	451
LMTK2	M758V	A2565G	183	452
LMTK2	D793G	A2671G	184	453
LMTK2	R828Q	G2776A	185	454
LMTK2	L879M	C2928A	186	455
LMTK2	A1008V	C3316T	187	456
LYN	F130V	T685G	188	457
MER	E831Q	G2628C	189	458
MET	T17I	C238T	190	459
MET	P366S	C1284T	191	460
MET	S691L	C2260T	192	461
NTRK1	P453fsX15	nt1355-1632DEL	193	462
NTRK1	L585fsX73	nt1753DEL	194	463
NTRK1	G595E	G1784A	195	464
NTRK1	R748W	C2242T	196	465
NTRK2	A586V	C2239T	197	466
NTRK2	V622I	G2346A	198	467
NTRK2	A647fsX54	nt2421-2655DEL	199	468
NTRK3	V530fsX6	nt1741(ACTCAGCACACACATGTTAG AAAACACTGGGTTATAGTGTGATCA GAAGCTTTTAAAGAAGAATCAAGCA GGATGTGTTTCGTCAACCACCCACTT CTTATATCAAGAAACCACCACACCC AGCACGCTACCCAGCTCTAGGCTCA GCCCTCACTTCTGCCTTCTACGTAG AGTCAGAAAAAATTCTGGTTGCTGA TGGATAGACACTCTTGTGAAGATCA GGAAACCTTCGCTGTGATATCTCAG AAGAAAATGA)INS	200	469
NTRK3	G608D	G1978A	201	470
NTRK3	A631fsX33	nt2046-2289DEL	202	471
PDGFRA	G79D	G630A	203	472
ptk9	D258E	T802G	204	473

(cont. on next page)

272/306

Fig. 32 (cont.)

Gene	Somatic mutations		Sequence Listing #	
	amino acids	nucleotides	Protein	nt
ptk9	K265R	A822G	205	474
ptk9	N333S	A1026G	206	475
PYK2	S9I	G834T	207	476
PYK2	C395Y	G1992A	208	477
PYK2	E404Q	G2018C	209	478
PYK2	D424Y	G2078T	210	479
PYK2	E798Q	G3200C	211	480
PYK2	M885L	A3461T	212	481
PYK2	T978M	C3741T	213	482
RET	A750T	G2443A	214	483
RON	F574fsX23	nt1748-2073DEL	215	484
RON	Q955H	G2893T	216	485
RON	A1022_K1090del	nt3093-3299del	217	486
RON	V1070fsX12	nt3234-3297DEL	218	487
ROR1	R185H	G929A	219	488
ROR1	R429Q	G1661A	220	489
ROR1	S870I	G2984T	221	490
ROR1	P883S	C3022T	222	491
ROR2	R302H	G1104A	223	492
ROR2	C389R	T1364C	224	493
ROR2	D390fsX44	nt1369-1402DEL	225	494
ROR2	P548S	C1841T	226	495
ROS	R187M	G759T	227	496
ROS	D709fsX16	nt2322-2343DEL	228	497
ROS	Q865fsX90	nt2793-3168DEL	229	498
ROS	A1443S	G4526T	230	499
RYK	H250R	A852G	231	500
RYK	R504H	G1614A	232	501
RYK	A559T	G1778A	233	502
SYK	M34fsX3	nt242(GG)INS	234	503
SYK	I262L	A931C	235	504
SYK	E315K	G1090A	236	505
SYK	A353T	G1204A	237	506
SYK	R520S	C1705A	238	507
SYK	V622A	T2012C	239	508
TEC	L89R	T383G	240	509
TEC	W531R	T1708C	241	510
TEC	P587L	C1877T	242	511
TEK	A615T	G1991A	243	512
TEK	A1006T	G3164A	244	513
TIE	S470L	C1488T	245	514
TIE	M871T	T2691C	246	515
TNK1	A299D	C1012A	247	516
TYK2	A53T	G498A	248	517

(cont. on next page)

273/306

Fig. 32 (cont.)

Gene	Somatic mutations		Sequence Listing #	
	amino acids	nucleotides	Protein	nt
TYK2	S340fsX26	nt1354-1708DEL	249	518
TYK2	R701T	G2443C	250	519
TYK2	D883N	G2988A	251	520
TYK2	R901Q	G3043A	252	521
TYK2	A928V	C3124T	253	522
TYK2	P1104A	C3651G	254	523
TYRO3	S324C	A1194T	255	524
TYRO3	E489K	G1689A	256	525
TYRO3	S531L	C1816T	257	526
TYRO3	N788T	A2587C	258	527
TYRO3	P822L	C2689T	259	528
VEGFR1	G203W	G856T	260	529
VEGFR1	S437L	C1559T	261	530
VEGFR1	A673V	C2267T	262	531
VEGFR1	R781Q	G2591A	263	532
VEGFR1	M938V	A3061G	264	533
VEGFR2	E107K	G622A	265	534
VEGFR2	P1280S	C4141T	266	535
YES1	K113Q	A558C	267	536
ZAP70	T155M	C671T	268	537
ZAP70	M549V	A1852G	269	538

Fig. 33

Gene	Germline alterations		Sequence Listing#	
	amino acids	nucleotides	Protein	nt
AATYK	G600C	G1965T	539	667
AATYK	G641S	G2088A	540	668
AATYK	F1163S	T3655C	541	669
AATYK	T1227M	C3847T	542	670
ABL1	P829L	C2925T	543	671
ABL1	S991L	C3411T	544	672
ACK1	P725L	C2717T	545	673
ACK1	R1038H	G3656A	546	674
ALK	K1491R	A5379G	547	675
ALK	D1529E	C5494G	548	676
ARG	K959R	A3080G	549	677
AXL	G517S	G2007A	550	678
CCK4	P693L	C2276T	551	679

(cont. on next page)

274/306

Fig. 33 (cont.)

Gene	Germline alterations		Sequence Listing#	
	amino acids	nucleotides	Protein	nt
CCK4	E745D	G2433C	552	680
CCK4	A777V	C2528T	553	681
CCK4	S795R	C2583G	554	682
CSF1R	H362R	A1377G	555	683
EGFR	R521K	G1728A	556	684
EPHA1	A160V	C566T	557	685
EPHA1	V900M	G2785A	558	686
EPHA1	S936L	C2894T	559	687
EPHA10	L629P	T1972C	560	688
EPHA10	V645I	G2019A	561	689
EPHA10	G749E	G2332A	562	690
EPHA2	R876H	G2764A	563	691
EPHA3	I564V	A1915G	564	692
EPHA3	R914H	G2966A	565	693
EPHA3	W924R	T2995C	566	694
EPHA7	I138V	A625G	567	695
EPHB2	P128A	C400G	568	696
EPHB3	R514Q	G1978A	569	697
EPHB6	G107S	G1117A	570	698
EPHB6	S309A	T1723G	571	699
FAK	T416fsX	nt1398(ATGAAATTAGTGGGGACGA)INS	572	700
FAK	L926delinsPWRL	nt2929(CCATGGAGGC)INS	573	701
FES	S72_K129del	nt289-462del	574	702
FES	P397R	C1265G	575	703
FES	E413fsX131	nt1311(GCCTGGCCACCCGCTGACGTCT GTCCCTGGCCTCAG)INS	576	704
FGFR1	V427_T428del	nt2007-2012del	577	705
FGFR2	M71T	T797C	578	706
FGFR2	H199_Q247del	nt1179-1325del	579	707
FGFR4	V10I	G184A	580	708
FGFR4	L136P	T563C	581	709
FGFR4	G388R	G1318A	582	710
FLT3	M227T	T680C	583	711
FRK	G122R	G811A	584	712
FYN	D506E	C2097G	585	713
HER2	I655V	A2201G	586	714
HER2	R1161Q	G3720A	587	715
HER2	P1170A	C3746G	588	716
HER3	S1119C	A3548T	589	717
JAK2	L393V	C1671G	590	718
JAK3	P132T	C453A	591	719
JAK3	P151R	C511G	592	720
JAK3	V722I	G2223A	593	721
LMTK2	P30A	C381G	594	722

(cont. on next page)

275/306

Fig. 33

Gene	Germline alterations		Sequence Listing#	
	amino acids	nucleotides	Protein	nt
LMTK2	L780M	T2631A	595	723
LMTK2	S910I	G3022T	596	724
MATK	A496T	G1885A	597	725
MER	E823Q	G2604C	598	726
MER	V870I	G2745A	599	727
MET	N375S	A1312G	600	728
MET	R988C	C3150T	601	729
MET	T1010I	C3217T	602	730
MET	V1238I	G3900A	603	731
NTRK1	H604Y	C1810T	604	732
NTRK1	G613V	G1838T	605	733
NTRK1	R780Q	G2339A	606	734
NTRK3	E402_F410delinsV	nt1360-1383del	607	735
NTRK3	G466_Y529delinsD	nt1552-1740del	608	736
NTRK3	R711_V712ins16	nt2288(GCTCTTTAATCCATCTGGAAATG ATTTTGTATATGGTGTGAG)INS	609	737
PDGFRA	L221F	C1055T	610	738
PDGFRA	S478P	T1826C	611	739
PDGFRB	P345S	C1389T	612	740
PDGFRB	T464M	C1747T	613	741
ptk9	E195_V196ins RPEDHIG	nt612(AGAGACCAGAGGATCATATTGG) INS	614	742
PYK2	G414V	G2049T	615	743
PYK2	V739_R780del	nt3024-3149del	616	744
PYK2	K838T	A3321C	617	745
RET	D489N	G1660A	618	746
RET	G691S	G2266A	619	747
RET	R982C	C3139T	620	748
RON	N440S	A1347G	621	749
RON	Q473_D515del	nt1445-1573del	622	750
RON	R523Q	G1596A	623	751
RON	R627fsX23	nt1907-2073DEL	624	752
RON	R813_C814insQ	nt2467(GCAG)INS	625	753
RON	Y884_Q932del	nt2678-2824del	626	754
RON	R1335G	A4031G	627	755
ROR1	M518T	T1928C	628	756
ROR2	T245A	A932G	629	757
ROR2	V819I	G2654A	630	758
ROS	C76fsX	nt427(GAATGATACTTATGCCACCGTTTG TGAG)INS	631	759
ROS	T145P	A632C	632	760
ROS	R167Q	G699A	633	761
ROS	I537M	A1810G	634	762
ROS	S1109L	C3525T	635	763

(cont. on next page)

276/306

Fig. 33

Gene	amino acids	Germline alterations		Sequence Listing#	
		nucleotides		Protein	nt
ROS	D2213N		G6836A	636	764
ROS	K2228Q		A6881C	637	765
ROS	S2229C		C6885G	638	766
RYK	N96S		A390G	639	767
RYK	F516L		C1651G	640	768
Styk	G204S		G879A	641	769
TEK	P346Q		C1185A	642	770
TEK	V486I		G1604A	643	771
TEK	V600L		G1946T	644	772
TNK1	D472_R473del		nt1529-1534del	645	773
TNK1	M598V		A1908G	646	774
TNK1	M598fsX5	nt1906(AGGTGAGGTCTCACTGAAATGG CCTGGTGTCCAGAAAGGGCTACAGGCA GGGGCAAGGCCCTGAGTGAGGCTTTGT TTGTCCCA)INS		647	775
TXK	R63C		C273T	648	776
TXK	R336Q		G1093A	649	777
TXK	Y414fsX15		nt1326-1444DEL	650	778
TYK2	V362F		G1425T	651	779
TYK2	G363S		G1428A	652	780
TYK2	I684S		T2392G	653	781
TYK2	E971fsX67		nt3251-3369DEL	654	782
TYRO3	I346N		T1261A	655	783
VEGFR1	Y642H		T2173C	656	784
VEGFR1	E982A		A3194C	657	785
VEGFR1	P1201L		C3851T	658	786
VEGFR2	V297I		G1192A	659	787
VEGFR2	Q472H		A1719T	660	788
VEGFR2	C482R		T1747C	661	789
VEGFR2	P1147S		C3742T	662	790
VEGFR3	Q890H		G2690C	663	791
VEGFR3	R1321Q		G3982A	664	792
ZAP70	K186fsX		nt763-772DEL	665	793
ZAP70	P296_S301del		nt1095-1112del	666	794

277/306

Somatic alterations

Gene	Alteration	Amino Acid Sequence
RON	F574fsX23	del F574GASADSSATPLWPTGRRRLSHS*
RON	V1070fsX12	del V1070ATLELSTTENT*
ROR2	D390fsX44	del D390EWGFCTSWSPASQFHWSSLAFFSWFACAGISRRLRPHRSGDS*
ROS1	D709fsX16	del D708ASTTVTRKATFLCGC*
ROS1	Q865fsX90	del
NTRK1	A453fsX15	del A453TEGGVRECSAGLPT*
NTRK1	L585fsX73	del L585CSWSSSICGTGTSTASSDPMDPSCWLVRMMWLQAPWWGSCWPWLARSLRGWCTWRVVCILCTGTWPHATV*
NTRK2	A647fsX54	del A647SVATQCCPFAGCLQRASCTGNSRRKATSGAWGSCCGRFSPMANSPGTSCQTMR*
NTRK3	V530fsX6	ins V530SAHTC*
NTRK3	A631fsX33	del A631WEDTPCSPFAGCLLKASCTGSSLQRVMYGASG*
ABL1	G883fsX12	del G883APARAPPRSPE*
BRK	W78fsX58	del W78AGHAGCAALQDLAACRGPAAPERGGVLPQPARACELPQGPEPVP RPAAAGRALPEARA*
JAK1	N849fsX16	del N849TSQLKWTPHILRSAS*
JAK3	G62fsX44	del G62AFTSPIGLGWRSATASGYARIWPVLSLTCQSWSTSLPSTAVTW*
TYK2	S340fsX26	del S340HLCRPSCGPRTACTSFTGAPATPTA*
LCK	L36fsX8	ins L36GDGPLGG*
SYK	M34fsX3	ins M34HE*

Germline alterations

Gene	Alteration	Amino Acid Sequence
FGFR2	H199_Q247delins48	H199_Q247delinsAAGVNTTDKEIEVLYIRNVTFEDAGEYTCLAGNSIGISFHSAWLTVLP
RON	R627fsX5	del R627RSQC*
ROS	C76_R77ins9	ins C76CNDTYATVCE
NTRK3	R711_V712 ins14	ins R711RLEFNPSGNDFCIWCE
FES	E413fsX131	ins E413PGHPLTSPVGLRSRSEGEHPWRSLRATSQESSAPSSRSLHRCSSFRRCRSPCMSSCGTTGPSRGQRW
TYK2	E971fsX67	del E971HGLSALAALHPPRPSRAQRAAGQRAQGDRLWPSQGRARRPRVLP RARGWGQPRVLCPRVPEGV*
TXK	Y414fsX15	del Y414SFNVGSFYRRKNAF*

Fig. 34

278/306

Fig. 35

Gene	Germline Alteration	Tissue Origin								
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)
Kinase Domain										
MER	E823Q									
EPHA2	M631T				2/22					
EPHA3	A777G									
EPHA10	V645I									
EPHA10	G749E	1/2		1/2	1/2		2/12			
EPHB4	E890D								1/13	2/20
MET	V1238I (3)									
RON	R1335G	4/5	1/4	9/12	12/19	4/8	10/21	3/3	6/12	7/21
RET	R982C									
ROR1	M518T	2/4	4/4	13/15	14/15	8/9	18/23	3/3	7/10	9/10
ROR2	P548S							1/1		
ROS1	D2213N	1/2	1/1	3/7	1/7	1/3			1/5	3/6
RYK	F516L									
NTRK1	H604Y (4)	1/2		1/15	1/5					
NTRK1	G613V (5)	1/2		1/15	1/5					
NTRK1	R780Q (5)						1/18		1/12	
VEGFR1	M938V									1/13
VEGFR1	E982A									
VEGFR2	P1147S (6)									
VEGFR3	Q890H				1/1			1/2		1/5
STYK	G204S	1/5		7/9	8/10	8/10	7/17	1/3	6/12	8/16
JAK2	R1063H									
JAK3	V722I (7) (ps)								2/7	
TYK2	I684S (ps)			6/16	1/8	2/11	1/20	1/3		4/24
TYK2	A928V									
TYK2	E971fsX67*				5/17	1/11	3/21	1/3		
TYK2	P1104A		1/4		1/19		1/21			5/24
FYN	D506E			1/14	2/22			1/2		
TXK	R336Q	1/5			1/20		3/23		4/10	
TXK	Y414fsX15*			3/10	4/19	1/9	2/22			9/24

(cont. on next page)

279/306

Fig. 35 (cont.)

Gene	Germline Alteration	KI (9)	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)	NO (22)
Kinase Domain												
MER	E823Q				1/11							1/19
EPHA2	M631T						1/4					
EPHA3	A777G											
EPHA10	V645I	1/2										
EPHA10	G749E	1/3		3/18	2/4	3/8	2/5					1/6
EPHB4	E890D											
MET	V1238I (3)	1/6										
RON	R1335G	4/6	2/4	12/21	7/10	14/16	3/4	18/41	2/5	1/2		9/14
RET	R982C				1/5						1/3	1/15
ROR1	M518T	7/8	2/3	15/21	7/10	14/16	5/6	44/51	4/5	1/3		21/22
ROR2	P548S											
ROS1				3/4				1/3				5/10
RYK	F516L		1/22									
NTRK1	H604Y (4)	1/8	1/2	3/22			2/6	4/38	1/3	1/3	1/3	2/17
NTRK1	G613V (5)	1/8	1/2	3/22			2/6	4/38	1/3	1/3	1/3	2/17
NTRK1	R780Q (5)				1/11							
VEGFR1	M938V							1/36				
VEGFR1	E982A											1/20
VEGFR2	P1147S (6)	2/3		6/8	1/1							1/17
VEGFR3	Q890H	2/6	3/3	7/19	7/10	5/12			2/2			6/14
STYK	G204S				1/11			16/32	2/4	1/1	1/2	9/18
JAK2	R1063H											
JAK3	V722I (7) (ps)	1/9	1/4			2/14		4/47		3/21		
TYK2	I684S (ps)							1/48				
TYK2	A928V			1/22		2/14		1/2				1/21
TYK2	E971fsX67*	1/9		2/20		1/6		1/52				
TYK2	P1104A			1/22		1/15	1/6					
FYN	D506E				2/11							
TXK	R336Q	2/4	1/4	2/16		3/15		2/45	1/7			1/20
TXK	Y414fsX15*							1/39	2/4	2/3		2/19

(cont. on
next page)

280/306

Fig. 35 (cont.)

Gene	Germline Alteration	Tissue Origin									
		BL	BS	BA	BE	CV	CO	EP	HN	HL	KI
		(5)	(4)	(16)	(22)	(11)	(23)	(3)	(13)	(24)	(9)
		Transmembrane Domain									
HER2	I655V (8)	2/5	2/4	6/13	1/14	5/7	4/21	1/3			3/8
EPHA3	I564V										
FLT3	V557I									1/17	
FGFR4	G388R (9)	1/4		5/14	4/11	1/8	2/13		3/12	3/13	3/8

Gene	Germline Alteration	Tissue Origin									
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)	NO (22)
		Transmembrane Domain									
HER2	I655V (8)		4/21			3/6	8/39		2/3		6/19
EPHA3	I564V										1/18
FLT3	V557I			1/8							
FGFR4	G388R (9)	2/3	6/17	2/5	4/9	2/6	11/45	1/1			8/19

Gene	Germline Alteration	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	
		Juxtamembrane Domain									
AXL	G517S										
DDR2	R478C										
EPHA10	L629P										
EPHA5	A672T			1/10	1/8	1/4					
EPHB6	A647V						1/16				
FGFR1	V427_T428del				1/5					1/14	
MET	R988C (10)										
MET	T1010I (11)			1/15	3/21		1/22			1/13	
CCK4	E745D			1/16	1/13	1/6					
CCK4	A777V			2/16			1/20		1/14		
CCK4	S795R										
RET	G691S (12)	1/2	2/2	1/7	1/2			1/1	6/10	2/12	
NTRK3	G466_Y529delinsD*		1/2	1/11	2/9						

(cont. on next page)

281/306

Gene	Germline Alteration	Tissue Origin										
		KI	LI	LU	OV	PA	PR	SK	ST	TE	TY	NO
		(9)	(4)	(22)	(11)	(17)	(6)	(53)	(5)	(3)	(3)	(22)

Fig. 35 (cont.)

Juxtamembrane Domain

AXL	G517S							3/33				1/18
DDR2	R478C							1/29				
EPHA10	L629P		1/3	1/4				4/34				
EPHA5	A672T				1/3							
EPHB6	A647V											
FGFR1	V427_T428del					2/4		1/39				1/19
MET	R988C (10)			1/20				1/6				
MET	T1010I (11)							1/50				
CCK4	E745D			3/21								3/19
CCK4	A777V			3/22								1/20
CCK4	S795R											5/17
RET	G691S (12)		1/3	8/12	2/6	1/2		2/17				1/16
NTRK3	G466_Y529delinsD*			3/14				2/19				

Gene	Germline Alteration	Tissue Origin													
		BS	BA	BE	CV	CO	EP	HN	HL	KI	LI	LU	OV	PA	PR
		(5)	(4)	(16)	(22)	(11)	(23)	(3)	(13)	(24)	(9)	(4)	(22)	(11)	(17)
		(5)	(4)	(16)	(22)	(11)	(23)	(3)	(13)	(24)	(9)	(4)	(22)	(11)	(17)

Fibronectin Type III Domain															
TYRO3	I346N	2/4	3/4	9/15	1/9	3/8	4/16	3/3	3/12	7/23	2/8	1/4	7/22	3/6	7/12
EPHA2	G391R	1/4											1/14		
EPHB3	R514Q														
ROS1	T145P		4/5							3/7			1/5		
ROS1	R167Q					1/3	1/3								
ROS1	S1109L		3/9			1/11		2/10	4/15			4/18			
TEK	V486I					1/8									
TEK	V600L						4/15		2/6	2/8				1/2	

(cont. on next page)

282/306

Fig. 35 (cont.)		Tissue Origin														(cont. on next page)								
		Gene	Germline Alteration	BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)	LI (4)	LU (22)								OV (11)	PA (17)
SAM-Domain																								
EPHA1	S936L																						1/22	
EPHA3	R914H					1/12					1/11	1/14						2/4	3/50				6/18	
EPHA3	W924R					3/11	3/11		2/8	1/2	3/9	3/13	2/4		5/14	8/9	1/7	3/4	27/49				13/21	
Cysteine-Rich Domain																								
EPHB6	S309A								2/12		1/21				1/15									
Ig-Like Domain																								
FGFR2	M71T	2/5										1/16												
FGFR2	[A]	1/5	4/4	7/10	1/7			2/7	2/17	1/2		1/1	6/7	1/2	6/11	4/9	1/9	3/4	3/9		1/1		10/15	
FGFR3	[B]								1/1															
CSF1R	H362R					1/5						6/17			1/4								3/17	
PDGFRA	G79D					1/10																	1/14	
PDGFRA	L221F																							
VEGFR1	Y642H														1/16									
VEGFR2	V297I														4/16	1/8			5/35				3/20	
VEGFR2	Q472H			2/7					1/1	1/1		1/2			4/8			1/1	5/29		2/2	3/3	4/15	
VEGFR2	C482R																	1/1					1/15	
Sema Domain																								
MET	N375S (14)										1/12								2/49				1/17	
RON	N440S							1/7			1/11													
RON	Q473_D515del*																						1/14	
IPT/TIG Domain																								
RON	R627fsX5*	1/4	1/1	3/6	2/4	4/6	3/5	1/2	2/2	4/7	2/6		3/3	2/2	2/5	3/3	1/2						6/15	
FZ-Domain																								
ROR2	T245A		1/1	5/5	2/4	3/3	1/2	1/1	1/3	2/7	4/4	1/1	2/4	3/3	1/1		3/4				1/1		3/8	
Wif-Domain																								
RYK	N96S	1/1	2/2	11/11	4/5	5/7	5/5	1/3	8/11	7/9	1/3	12/13	1/2	3/3			9/10				2/2	2/2	9/9	
Signal Peptide																								
FGFR4	V10I	2/2						2/6	1/1		1/4		1/5										1/5	

283/306

Fig. 35 (cont.)

Gene	Germline Alteration	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
Proline-Rich Domain											
ROR2	V819I		2/3	9/10	2/2	6/6	2/5	1/1	4/5	6/7	4/4
ABL1	P829L										
ABL1	S991L			2/14		2/10				1/21	1/9
ARG	K930R			1/15							
ARG	K959R										
ACK1	P725L	2/4	4/4	8/15	5/19	3/11	4/21		4/12	9/23	3/9
FAK	L926delinsPWRL			1/14	4/22		10/19	1/3		7/11	2/9
PYK2	V739_R780del*									17/24	
PYK2	K838T	1/4	3/4	11/15	2/5	6/10	12/20	1/3	7/14	17/24	5/9

Gene	Germline Alteration	Tissue Origin									
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)	NO (22)
Proline-Rich Domain											
ROR2	V819I	1/1	8/13	4/5	1/1		3/3		1/1		11/13
ABL1	P829L									1/3	
ABL1	S991L			1/4	1/11	1/5	1/38		1/2		3/18
ARG	K930R		2/22								
ARG	K959R		1/21								
ACK1	P725L	1/4	7/22	6/11	7/17	2/6	14/50			1/3	9/20
FAK	L926delinsPWRL	1/2	11/22	2/11	1/13		3/52			1/3	8/20
PYK2	V739_R780del*	1/4									
PYK2	K838T	2/4	14/22	5/11	8/15	4/6	29/45		3/3	2/3	17/21

Gene	Germline Alteration	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
SH2-Domain											
FER	Q526L				1/22						
ZAP70	K186fsX		1/1	1/4		2/2				5/15	2/7
FRK	G122R	3/5			1/4	2/9	10/18	1/3	7/13	3/6	1/7

Gene	Germline Alteration	Tissue Origin									
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)	NO (22)
SH2-Domain											
FER	Q526L										
ZAP70	K186fsX	2/2	3/7							2/2	2/13
FRK	G122R	1/3	6/16	4/10	7/12	4/5	11/32	3/5		3/3	7/13

(cont. on next page)

284/306

Fig. 35 (cont.)

Gene	Germline Alteration	Tissue Origin								
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)
Other Domains										
ALK	K1491R		2/3	5/13	1/19	3/11	9/20		3/9	5/11
ALK	D1529E	1/5	2/3	5/13	2/18	3/8	12/19		6/10	7/9
MER	V870I	1/3			2/20			1/3		4/22
DDR1	V100A						1/12			
EGFR	R521K (15)		1/2	3/16	3/22	2/11	12/23	1/3	9/13	
HER2	R1161Q									1/24
HER2	P1170A	4/5	4/5	11/15	11/19	10/11	17/21	2/3	12/14	17/21
HER2	A1216D		2/3							
HER3	S1119C			1/5	2/18	4/11	2/20	1/3		
HER3	L1177I								2/13	
EPHA1	A160V						1/12			1/4
EPHA1	V900M	1/4			4/19	1/7		1/3		3/22
EPHA2	R876H			1/16			2/22			
EPHA5	N81T								4/9	1/4
EPHA7	I138V								1/10	1/3
EPHB2	P128A									
EPHB6	G107S									
FGFR4	L136P	1/1	1/3		4/5		6/14			4/11
RON	R523Q	5/5	1/1	5/7	4/6	6/6	4/7	1/2		6/10
RON	R813delinsRQ	4/4	1/1	4/5	2/2	7/8	16/18	3/3	6/8	7/10
RON	Y884_Q932del (16)*	2/4		1/4	1/5		1/9		2/14	
FLT3	M227T				1/5		2/9	2/2		11/18
FLT3	D358V									
PDGFRA	S478P	1/1		2/3						
PDGFRB	P345S									1/5
PDGFRB	T464M							1/2		
CCK4	T410S			1/16		1/9	1/23		1/14	
CCK4	P693L				1/9					1/18
RET	D489N									1/6
ROS1	C76_R77ins9	1/1	1/1	5/5	3/3	2/3	1/3		3/4	2/6
ROS1	I537M			2/8						2/13
ROS1	K2228Q		1/1	4/8	1/7	1/3			1/5	3/6
ROS1	S2229C		1/1	4/8	1/7	1/3			1/5	3/6
TEK	P346Q									
NTRK3	E402_F410delinsV*	1/1	1/2	12/13	11/14	1/2	3/8		2/7	9/12
NTRK3	R711_V712 ins14			1/12	6/11				1/2	7/10
VEGFR1	P1201L									
VEGFR3	R1321Q									
AATYK	G600C			4/7	3/6	1/3	9/10		7/13	4/11
AATYK	G641S									
AATYK	F1163S					2/3	1/7			1/7
AATYK	T1227M		2/3							
LMTK2	P30A			1/11		1/10	1/19			2/19

(cont. on next page)

Fig. 35 (cont.)

285/306

Gene	Germline Alteration	Tissue Origin										
		KI (9)	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)	NO (22)
				Other Domains								
ALK	K1491R	1/9	3/5	5/19	3/8	4/15		12/43	2/3	1/3		8/21
ALK	D1529E	3/9	1/4	9/19	4/8	6/16	2/5	16/37	3/3	1/3	3/4	9/19
MER	V870I	2/9		1/21		2/17		1/48				
DDR1	V100A											
EGFR	R521K (15)	7/9	2/4	5/22	4/11	5/17	2/6	8/52	2/6	2/2		12/22
HER2	R1161Q											1/22
HER2		8/9	4/4	18/22	7/11	15/16	4/6	42/52	4/5	2/3	3/3	19/22
HER2	A1216D							1/50				
HER3	S1119C	1/8		2/17	1/10	4/15	3/5	6/47	1/7	2/3	2/3	4/17
HER3	L1177I							4/49				
EPHA1	A160V			1/7								1/3
EPHA1	V900M	1/6			1/10	1/15	3/5	1/22				3/22
EPHA2	R876H			1/21		1/18		5/52	1/5		2/3	3/22
EPHA5	N81T							4/39				
EPHA7	I138V					2/6	1/5					2/15
EPHB2	P128A											1/22
EPHB6	G107S			1/19								
FGFR4	L136P	3/8	1/3	4/15	1/3	3/5		5/12				3/5
RON	R523Q	3/6		1/2	2/3	4/6	2/3	2/3	1/1			10/15
RON	R813delinsRQ	3/4	2/2	15/18	7/9	12/13	1/1	10/17	4/4			11/14
RON	Y884_Q932del (16)*		1/1			3/13			1/4			
FLT3	M227T	4/4		1/2	4/8	1/2	1/3	1/4				8/11
FLT3	D358V						1/3					
PDGFRA	S478P					1/4		6/38				3/15
PDGFRB	P345S			1/6								
PDGFRB	T464M											1/13
CCK4	T410S				1/11	2/18		3/36				
CCK4	P693L					1/14		1/32				
RET	D489N											1/7
ROS1	C76_R77ins9	3/3		4/5			1/1	4/7	1/1		2/2	8/10
ROS1	I537M					1/11		3/24				
ROS1	K2228Q			4/6				1/3				6/7
ROS1	S2229C			4/6				1/3				6/7
TEK	P346Q							2/34				2/19
NTRK3	E402_F410delinsV*	5/5	1/1	14/15	2/5	1/1		30/34	2/2	3/3	1/3	16/16
NTRK3	R711_V712 ins14	3/6						7/24				6/17
VEGFR1	P1201L											1/17
VEGFR3	R1321Q											1/5
AATYK	G600C	6/8	3/4	7/16		2/10	1/1	9/16	2/2			6/7
AATYK	G641S											1/8
AATYK	F1163S	3/4		6/17		1/2		6/10		2/2	1/1	3/8
AATYK	T1227M			2/9				3/11				2/8
LMTK2	P30A		1/3	1/20				5/15				1/12

(cont. on next page)

286/306

Fig. 35 (cont.)

Gene	Germline Alteration	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
		Other Domains									
LMTK2	L780M	2/5	2/4	12/15	11/21	5/10	17/20	3/3	9/15	13/21	9/9
LMTK2	S910I					2/11			1/11		
PTK9	E195_V196insRSEDHIG										
ACK1	R1038H									3/23	
TNK1	D472_R473del					1/9	2/19				1/7
TNK1	M598V	1/5			3/22	3/11	2/22	1/3	1/13	3/22	
TNK1	M598delinsEVRSHX		2/2	12/15	1/22	1/10				13/21	4/9
MATK	A496T										
FAK	T416fsX			3/15	1/17						
PYK2	G414V				1/9	1/11	2/19				
FES	S72_K129del*					1/2				2/15	1/1
FES	M323V									1/19	
FES	P397R										
FES	E413fsX131						2/3			1/18	2/3
JAK2	A377E										
JAK2	L393V				1/21	1/11					
JAK3	P132T (7)										
JAK3	P151R										
TYK2	V362F	1/4	4/4	9/12	2/4	2/9	5/12			14/21	6/9
TYK2	G363S	1/4				1/9	1/12			4/20	1/9
SYK	E315K										
ZAP70	P296_S301del			3/4		4/4	9/9	1/1		8/13	6/6
BMX	S254del			1/7	2/5				1/12		1/8
TXK	R63C										

(cont. on next page)

287/306

Fig. 35 (cont.)

Tissue Origin

[illegible]

288/306

Fig. 36

Confirmed Alterations		Breast	Prostate	Kidney	Blood
Gene	Alteration				
TYRO3	I346N	18	19	15	48
EPHA3	W924R	8	13	19	30
EPHA10	G749E	1	5	7	25
FGFR1	T428_V429del	7	2	0	n.a.
FGFR4	G388R	10	16	29	46
MET	T1010I	0	1	1	4
RON	R523Q	30	34	35	67
RON	R627fsX23	3	5	4	n.a.
RON	R813delinsRQ	20	40	41	n.a.
RON	Y884_Q932del	34	48	40	n.a.
RON	R1335G	32	31	34	66
FLT3	M227T	13	28	38	n.a.
ROR1	M518T	17	39	47	41
ROR2	T245A	17	29	28	55
ROS1	C76_R77ins9	10	40	30	n.a.
ROS1	D2213N	0	13	7	n.a.
ROS1	K2228Q	0	15	6	n.a.
ROS1	S2229C	0	15	6	n.a.
NTRK1	H604Y	5	3	4	n.a.
NTRK1	G613V	5	3	4	n.a.
NTRK3	E402_F410del	37	48	53	n.a.
NTRK3	R711_V712ins14	9	1	5	n.a.
VEGFR2	Q472H	10	20	23	35
VEGFR2	C482R	3	4	3	10
VEGFR3	G890H	8	26	36	n.a.
AATYK	F1163S	4	24	22	n.a.
ABL1	S991L	0	0	3	n.a.
TNK1	M598delinsEVERSHX	4	0	0	n.a.
FAK	T416fsX	1	1	0	n.a.
FAK	L926delinsPWRL	3	32	29	n.a.
PYK2	G414V	1	0	0	1
PYK2	K838T	17	20	31	75
FES	S72_K129del	3	25	30	n.a.
FES	E413fsx131	15	30	35	n.a.
FRK	G122R	5	25	33	n.a.
TYK2	I684S	6	5	4	n.a.
TYK2	E971fsX67	15	17	1	n.a.
YES	K113Q*	0	1	0	1
ZAP-70	K186fsX	5	0	2	n.a.
ZAP-70	P296_S301	12	26	22	n.a.
BMX	S254del	3	1	1	n.a.
TXK	R336Q	5	2	4	19
TXK	Y414fsX15	5	7	13	n.a.

(cont. on next page)

289/306

Fig. 36 (cont.)

Not Confirmed Alterations

Gene	Alteration				
EPHA5	R981L	0	0	0	0
EPHB2	Q722X	0	0	0	0
EPHB4	I610T	0	0	0	0
MET	D981_E1027del	0	0	0	n.a.
NTRK1	L585fsX73	0	0	0	n.a.
TYRO3	E489K*	0	0	0	1
EPHA2	M631T	0	0	0	1
EPHA5	A672T	0	0	0	7
NTRK3	G466_Y529delinsD	0	0	0	n.a.
TNK1	D472_R473	0	0	0	n.a.

Fig. 37

Gene	Somatic Mutation	Tissue Origin										
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)	LI (4)
Kinase Domain												
AXL	M569I											
AXL	M589K						1/10					
MER	E831Q											
TYRO3	S531L											
TYRO3	N788T									1/24		
EGFR	G719S (P)(17)						1/21					
EGFR	P753S											
EGFR	E922K											
HER2	A830V											
HER2	E930D							1/6				
HER4	L753V			1/2								
HER4	G936R											
EPHA2	G662S			1/15								
EPHA2	V747I									1/2		
EPHA2	L836R											
EPHA4	S803A											
EPHA4	M877V				1/22							
EPHA5	V891L											
EPHB1	I837M											
EPHB2	E686K											
EPHB2	Q722X (18)											
EPHB2	V762L											
EPHB6	S785R(c)						1/20					

(cont. on next page)

290/306

Fig. 37 (cont.)

Gene	Somatic Mutation	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Kinase Domain									
AXL	M569I					1/41			
AXL	M589K								
MER	E831Q			1/16					
TYRO3	S531L					2/45			
TYRO3	N788T								
EGFR	G719S (P)(17)								
EGFR	P753S					1/37			
EGFR	E922K			1/16		1/33			
HER2	A830V						2/3		
HER2	E930D								
HER4	L753V								
HER4	G936R	1/19							
EPHA2	G662S								
EPHA2	V747I								
EPHA2	L836R					1/49			
EPHA4	S803A						1/4		
EPHA4	M877V								
EPHA5	V891L	1/14							
EPHB1	I837M	1/18							
EPHB2	E686K					1/39			
EPHB2	Q722X (18)				2/6				
EPHB2	V762L	1/22							
EPHB6	S785R(c)								

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
Kinase Domain											
EPHB6	R811C (a)										
FGFR1	G539_K540del									2/13	
FGFR2	I526T										1/3
KIT	N822K (a)(19)									1/13	
FLT3	G757E									1/18	
FLT3	R849H (a)										
CCK4	Q913H									1/12	
RYK	R504H (a)				1/15						
RYK	A559T									1/23	
TEK	A1006T (a)										
TIE	M871T										
NTRK1	L585fsX73						1/17				1/7
NTRK1	G595E										

(cont. on next page)

291/306

Fig. 37 (cont.)

Fig. 3 (Cont.)

Gene	Somatic Mutation	Tissue Origin								
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Kinase Domain										
EPHB6	R811C (a)						1/30			
FGFR1	G539_K540del		1/21	1/10			3/42			
FGFR2	I526T									
KIT	N822K (a)(19)									
FLT3	G757E									
FLT3	R849H (a)					1/2				
CCK4	Q913H									
RYK	R504H (a)									
RYK	A559T									
TEK	A1006T (a)						1/31			
TIE	M871T			1/9						
NTRK1	L585fsX73									
NTRK1	G595E						1/32			

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
Kinase Domain											
NTRK1	R748W										
NTRK2	A586V										
NTRK2	V622I										
NTRK2	A647fsX54						1/11			1/1	
NTRK3	G608D										
LMTK2	Q238P										
LMTK2	A251T										
ABL1	G417E (a)										
ARG	E332K										
ARG	V345A										1/9
ARG	K450R (a)										1/9
ACK1	R127H						1/21				
TNK1	A299D					1/8					
FAK	A472V										
FER	Q599R										
FES	L690M						1/21				
FES	V724M									1/24	
FRK	R406H						1/19				
JAK2	G571S (ps)										
JAK2	E592K (ps)										
JAK2	N1108S				1/23		1/21				
JAK3	P693L (ps)										

(cont. on next page)

292/306

Fig. 37 (cont.)

Gene	Somatic Mutation	Tissue Origin								
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Kinase Domain										
NTRK1	R748W		1/22							
NTRK2	A586V		1/11							
NTRK2	V622I									1/2
NTRK2	A647fsX54						1/23			
NTRK3	G608D						2/25			
LMTK2	Q238P		1/22							
LMTK2	A251T									1/3
ABL1	G417E (a)						1/51			
ARG	E332K						1/49			
ARG	V345A									
ARG	K450R (a)									
ACK1	R127H									
TNK1	A299D						1/25			
FAK	A472V			1/11						
FER	Q599R					1/6				
FES	L690M									
FES	V724M									
FRK	R406H									
JAK2	G571S (ps)									1/3
JAK2	E592K (ps)						1/53			
JAK2	N1108S		1/22							
JAK3	P693L (ps)						1/34			

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
Kinase Domain											
JAK3	E698K (ps)										
TYK2	R701T (ps)									1/24	
TYK2	R901Q										
FYN	E521K						2/21				
LCK	R484W						1/4				
SYK	R520S (a)										1/5
SYK	V622A										
ZAP70	M549V									1/22	
BTK	M489I							1/3			
BTK	W588C										
ITK	R448H									1/3	
TEC	W531R (a)									1/24	
TEC	P587L										

(cont. on next page)

293/306

Fig. 37 (cont.)

Fig. 37 (cont.)

Gene	Somatic Mutation	Tissue Origin									
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)	
Kinase Domain											
JAK3	E698K (ps)		1/19								
TYK2	R701T (ps)										
TYK2	R901Q			1/10							
FYN	E521K										
LCK	R484W										
SYK	R520S (a)										
SYK	V622A					2/4					
ZAP70	M549V										
BTK	M489I										
BTK	W588C			1/10							
ITK	R448H										
TEC	W531R (a)										
TEC	P587L		1/22								

Gene	Somatic Mutation	Tissue Origin																	
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)
Transmembrane Domain																			
EGFR	I646L					1/9													
EPHB4	V547M			1/14															
EPHB6	L580F														2/5				
RYK	H250R																1/27		

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
Fibronectin Type III Domain											
TYRO3	S324C										
EPHA2	H333R						1/22				
EPHA2	P460L										1/7
EPHA6	L622F										
EPHB2	R369Q										
EPHB3	A517V						1/19				
EPHB6	A369T									1/11	
ROS1	R187M										1/4
TEK	A615T						1/16				
TIE	S470L										

(cont. on next page)

294/306

Fig. 37 (cont.)

Gene	Somatic Mutation	Tissue Origin								
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Fibronectin Type III Domain										
TYRO3	S324C		1/20							
EPHA2	H333R									
EPHA2	P460L									
EPHA6	L622F			1/10						
EPHB2	R369Q				1/15		1/26			
EPHB3	A517V									
EPHB6	A369T									
ROS1	R187M									
TEK	A615T									
TIE	S470L		1/5							

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
SAM- Domain											
EPHA2	E911K						1/21				
EPHA2	V936M										
EPHA2	R950W							1/3			
EPHA5	R981L				1/7						
EPHB4	A955V										

Gene	Somatic Mutation	Tissue Origin								
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
SAM- Domain										
EPHA2	E911K									
EPHA2	V936M			1/11						
EPHA2	R950W									
EPHA5	R981L							1/3		
EPHB4	A955V			1/11						

(cont. on next page)

295/306

Fig. 37 (cont.)

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
Juxtamembrane Domain											
TYRO3	E489K				1/8						
EGFR	T678M				1/19						
HER3	R667H						2/23				
EPHA2	H609Y										
EPHB4	D576G										
EPHB4	I610T						1/20				1/9
EPHB6	E615K										
INSR	L991I					1/6			1/12		
MET	D981_E1027del (20)*				1/22						
RON	A1022_K1090del*				1/17						
RON	V1070fsX12										
FLT3	V592A (21)									2/22	
CCK4	M746L										
RET	A750T										
ROR1	R429Q										
NTRK1	P453fsX15*										
VEGFR1	R781Q				1/5						

Gene	Somatic Mutation	Tissue Origin								
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Juxtamembrane Domain										
TYRO3	E489K					2/5				
EGFR	T678M									
HER3	R667H							1/6		
EPHA2	H609Y						1/52			
EPHB4	D576G					1/5				
EPHB4	I610T									
EPHB6	E615K						1/22			
INSR	L991I									
MET	D981_E1027del (20)*		1/22					1/5		
RON	A1022_K1090del*									
RON	V1070fsX12						1/20			
FLT3	V592A (21)		1/15		1/9					
CCK4	M746L				2/13					
RET	A750T			1/3						
ROR1	R429Q			1/10						
NTRK1	P453fsX15*				1/7		1/19	1/2		
VEGFR1	R781Q									

(cont. on next page)

296/306

Fig. 37 (cont.)

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)

Cysteine-Rich Domain

EPHA2	R315Q
EPHA4	V234F
EPHA6	G513E
EPHB2	R270Q
EPHB2	P273L
EPHB4	P231S

1/6

2/13

Gene	Somatic Mutation	Tissue Origin							
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)

Cysteine-Rich Domain

EPHA2	R315Q
EPHA4	V234F
EPHA6	G513E
EPHB2	R270Q
EPHB2	P273L
EPHB4	P231S

1/14

1/45

1/6

1/4

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)

Ig-Like Domain

FGFR1	R78H
FGFR1	A268S
CCK4	D106N
VEGFR1	G203W
VEGFR1	S437L
VEGFR1	A673V
VEGFR2	E107K

2/14

1/9

1/7

1/9

Gene	Somatic Mutation	Tissue Origin							
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)

Ig-Like Domain

FGFR1	R78H
FGFR1	A268S
CCK4	D106N
VEGFR1	G203W
VEGFR1	S437L
VEGFR1	A673V
VEGFR2	E107K

1/5

1/5

1/35

1/29

(cont. on next page)

297/306

Fig. 37 (cont.)

Gene	Somatic Mutation	Tissue Origin															
		BL	BS	BA	BE	CV	CO	EP	HN	HL	KI	LI	LU	OV	PA	PR	SK
		(5)	(4)	(16)	(22)	(11)	(23)	(3)	(13)	(24)	(9)	(4)	(22)	(11)	(17)	(6)	(53)
Signal Peptide																	
EPHB3	P6del																
MET	T17I																1/50

Gene	Somatic Mutation	Tissue Origin															
		BL	BS	BA	BE	CV	CO	EP	HN	HL	KI	LI	LU	OV	PA	PR	SK
		(5)	(4)	(16)	(22)	(11)	(23)	(3)	(13)	(24)	(9)	(4)	(22)	(11)	(17)	(6)	(53)
Sema Domain																	
MET	P366S																1/49

Gene	Somatic Mutation	Tissue Origin									
		BL	BS	BA	BE	CV	CO	EP	HN	HL	KI
		(5)	(4)	(16)	(22)	(11)	(23)	(3)	(13)	(24)	(9)
Proline-Rich Domain											
ABL1	G883fsX12										2/17
ARG	S968F										
ARG	Q994H										1/21
ACK1	A634T										
ACK1	S699N										1/24
ACK1	P731L										
ACK1	R748W										
ACK1	G947D										1/10
FAK	P901S										

Gene	Somatic Mutation	Tissue Origin							
		LI	LU	OV	PA	PR	SK	ST	TE
		(4)	(22)	(11)	(17)	(6)	(53)	(5)	(3)
Proline-Rich Domain									
ABL1	G883fsX12								
ARG	S968F								1/50
ARG	Q994H								
ACK1	A634T								1/6
ACK1	S699N								
ACK1	P731L								2/3
ACK1	R748W								
ACK1	G947D								
FAK	P901S								1/49

(cont. on next page)

298/306

Fig. 37 (cont.)

Figure 1 (cont.)

		Tissue Origin																		
Gene	Somatic Mutation	BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
SH2-Domain																				
JAK1	R494C						1/18													
LCK	F151S						1/15													
LYN	F130V						2/23													
FRK	G119A														1/1					
		Tissue Origin																		
Gene	Somatic Mutation	BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
SH3-Domain																				
ACK1	M393T						1/20													
FRK	R64Q					1/10														
YES1	K113Q				1/9		1/19				1/9									
		Tissue Origin																		
Gene	Somatic Mutation	BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)									
Other Domain																				
ALK	G1580V										1/12									
AXL	G835V																			
TYRO3	P822L										1/20									
DDR1	R60C																		1/3	
DDR1	R248W									1/6										
DDR2	M117I										1/9									
EGFR	N115K														1/13					
EGFR	A289V (22)													1/3						
EGFR	P332S						1/16													
EGFR	A1118T (22)																			
HER2	G518E													1/3						
HER2	G1015E																			
HER3	N126K										2/21									
HER3	R611W																1/11			
HER3	R1077W																			
HER3	R1089W																			
HER3	P1142H										2/23									
EPHA3	S46F																			
EPHA3	E53K																			
EPHA5	E85K																			
EPHA5	A957T					1/3														
EPHA6	N291H																			
EPHB1	A39V																			
EPHB2	A83V																			

(cont. on next page)

299/306

Fig. 37 (cont.)

		Tissue Origin								
Gene	Somatic Mutation	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Proline-Rich Domain										

Proline-Rich Domain

ALK	G1580V									
AXL	G835V		1/13							
TYRO3	P822L									
DDR1	R60C								1/1	
DDR1	R248W									
DDR2	M117I									
EGFR	N115K									
EGFR	A289V (22)									
EGFR	P332S									
EGFR	A1118T (22)									2/3
HER2	G518E									
HER2	G1015E				1/14					
HER3	N126K							1/4		
HER3	R611W									
HER3	R1077W						1/49			
HER3	R1089W							1/5		
HER3	P1142H									
EPHA3	S46F						1/44			
EPHA3	E53K						1/37			
EPHA5	E85K						1/36			
EPHA5	A957T									
EPHA6	N291H							1/2		
EPHB1	A39V									
EPHB2	A83V	1/2						1/7		

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
Other Domain											

Other Domain

EPHB2	S98R								2/13		
EPHB2	V136M										
EPHB6	G353_E471del			1/3		1/6					
FGFR1	P252S										
FGFR4	Y367C				1/14						
IGF1R	T104M									1/21	
IGF1R	Y201H										
IGF1R	N209S										
MET	S691L										
RON	F574fsX23*			1/13							
FLT3	V194M									1/18	

(cont. on next page)

300/306

Fig. 37 (cont.)

		Tissue Origin								
Gene	Somatic Mutation	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Other Domain										
EPHB2	S98R									
EPHB2	V136M							1/7		
EPHB6	G353_E471del			1/4						
FGFR1	P252S						1/38			
FGFR4	Y367C									
IGF1R	T104M									
IGF1R	Y201H	1/4								
IGF1R	N209S							1/3		
MET	S691L						1/43			
RON	F574fsX23*									
FLT3	V194M									

Gene	Somatic Mutation	Tissue Origin									
		BL (5)	BS (4)	BA (16)	BE (22)	CV (11)	CO (23)	EP (3)	HN (13)	HL (24)	KI (9)
Other Domain											
ROR1	R185H						1/16				
ROR1	S870I						2/7				
ROR1	P883S										
ROR2	R302H						1/5				
ROR2	C389R										
ROR2	D390fsX44										
ROS1	D709fsX16						1/10				
ROS1	Q865fsX90 *						1/10				
ROS1	A1443S										
NTRK3	V530fsX6										
NTRK3	A631fsX33*						1/5				
VEGFR2	P1280S										
AATYK	F1195C										
LMTK2	G518V										
LMTK2	D523Y										
LMTK2	M758V				1/22						
LMTK2	D793G								1/10	1/19	
LMTK2	R828Q				1/21						
LMTK2	L879M						1/22				
LMTK2	A1008V						1/20				
PTK-9	D258E										
PTK-9	K265R										
PTK-9	N333S										
ABL1	N789S										

(cont. on next page)

301/306

Fig. 37 (cont.)

Gene	Somatic Mutation	Tissue Origin								
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Other Domain										
ROR1	R185H									
ROR1	S870I							1/7		
ROR1	P883S						1/49			
ROR2	R302H									
ROR2	C389R		1/10							
ROR2	D390fsX44		1/11							
ROS1	D709fsX16									
ROS1	Q865fsX90 *									
ROS1	A1443S		1/9							
NTRK3	V530fsX6									
NTRK3	A631fsX33*									
VEGFR2	P1280S						1/32			
AATYK	F1195C		1/8							
LMTK2	G518V					1/6				
LMTK2	D523Y					1/6				
LMTK2	M758V									
LMTK2	D793G									
LMTK2	R828Q									
LMTK2	L879M									
LMTK2	A1008V									
PTK-9	D258E						1/51			
PTK-9	K265R		1/21							
PTK-9	N333S			1/11						
ABL1	N789S					1/5				

Gene	Somatic Mutation	Tissue Origin									
		BL	BS	BA	BE	CV	CO	EP	HN	HL	KI
		(5)	(4)	(16)	(22)	(11)	(23)	(3)	(13)	(24)	(9)
Other Domain											
ARG	M657I										
ARG	P665T					1/10					
ARG	R668C					1/9					
ARG	Q696H										
ACK1	H37Y										
ACK1	E111K										
ACK1	S985N										1/8
CSK	Q26X						2/18				
FAK	S329I					1/11					
FAK	Q440R										
PYK2	S9I									1/24	

(cont. on next page)

302/306

Fig. 37 (cont.)

		Tissue Origin								
Gene	Somatic Mutation	LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Other Domain										
ARG	M657I						1/50			
ARG	P665T									
ARG	R668C									
ARG	Q696H									1/3
ACK1	H37Y						1/48			
ACK1	E111K						1/48			
ACK1	S985N									
CSK	Q26X									
FAK	S329I									
FAK	Q440R							1/6		
PYK2	S9I									

Gene	Somatic Mutation	Tissue Origin									
		BL	BS	BA	BE	CV	CO	EP	HN	HL	KI
		(5)	(4)	(16)	(22)	(11)	(23)	(3)	(13)	(24)	(9)
Other Domain											
PYK2	C395Y				1/8						
PYK2	E404Q			1/14							
PYK2	D424Y		2/3								
PYK2	E798Q										
PYK2	M885L										
PYK2	T978M										
FER	I240T						2/20				
BRK	W78fsX58*	1/3									
JAK1	I363V						1/18				
JAK1	N849fsX16										
JAK2	F85S							1/3			
JAK2	L383P						1/22				
JAK3	G62fsX44*			1/6						2/18	
JAK3	M511I									1/17	
TYK2	A53T										
TYK2	S340fsX26*										
TYK2	D883N										
LCK	L36fsX8										
SYK	I262L									1/22	
SYK	M34fsX3						2/21			1/23	
SYK	A353T			1/11		1/6	2/21				
ZAP70	T155M									1/11	
BMX	A150D										
BMX	N267I										
TEC	L89R										

(cont. on next page)

303/306

Fig. 37 (cont.)

Fig. 37 (cont.)

Gene	Somatic Mutation	Tissue Origin								
		LI (4)	LU (22)	OV (11)	PA (17)	PR (6)	SK (53)	ST (5)	TE (3)	TY (3)
Other Domain										
PYK2	C395Y									
PYK2	E404Q									
PYK2	D424Y									
PYK2	E798Q						2/48			
PYK2	M885L					2/6				
PYK2	T978M						2/49			
FER	I240T									
BRK	W78fsX58*		1/9							
JAK1	I363V									
JAK1	N849fsX16			1/1						
JAK2	F85S									
JAK2	L383P									
JAK3	G62fsX44*		1/10							
JAK3	M511I									
TYK2	A53T		1/21							1/3
TYK2	S340fsX26*						3/16			
TYK2	D883N						1/48			
LCK	L36fsX8		1/18							
SYK	I262L									
SYK	M34fsX3									
SYK	A353T						2/15	1/7		
ZAP70	T155M						1/3			
BMX	A150D					1/6				
BMX	N267I						3/47			
TEC	L89R							1/7		

Fig. 38

Receptor Tyrosine Kinases

Gene	mutations	Gene	mutations	Gene	mutations
ALK family		DDR family		EPH family	
ALK	1	DDR1	3	EPHA1	0
LTK	0	DDR2	1	EPHA2	10
				EPHA3	2
				EPHA4	3
				EPHA5	5
				EPHA6	3
				EPHA7	0
				EPHA8	0
				EPHA10	0
AXL family		EGFR family			
AXL	3	EGFR	10		
MER	1	HER2	4		
TYRO3	4	HER3	8		
		HER4	2		

(cont. on next page)

304/306

Fig. 38 (cont.)

Receptor Tyrosine Kinases (cont.)

Gene	mutations	Gene	mutations	Gene	mutations
EPH family (cont.)		PDGFR family		TIE family	
EPHB1	2	CSF1R	0	TEK1	2
EPHB2	10	FLT3	6	TIE	2
EPHB3	2	KIT	1	TRK family	
EPHB4	6	PDGFRA	0	NTRK1	7
EPHB6	8	PDGFRB	0	NTRK2	5
FGFR family		PTK7 family		NTRK3	5
FGFR1	8	CCK4	4	VEGFR family	
FGFR2	1	RET family		VEGFR1	4
FGFR3	0	RET	1	VEGFR2	2
FGFR4	1	ROR family		VEGFR3	0
INSR family		ROR1	5	AATYK family	
IGF1R	3	ROR2	3	AATYK	1
INSR	2	ROS family		LMTK2	10
IRR	-	ROS1	4	LMTK3	0
MET family		RYK family		STYK family	
MET	6	RYK	3	STYK1	0
RON	3				
MUSK family					
MUSK	-				

Non-Receptor Tyrosine Kinases

Gene	mutations	Gene	mutations	Gene	mutations
A6 family		FES family		SRC-B family	
PTK-9	3	FER	2	BLK	0
ABL family		FES	2	HCK	0
ABL1	3	FRK family		LCK	3
ARG	9	BRK	2	LYN	1
ACK family		FRK	3	SYK family	
ACK1	10	SRMS	-	SYK	11
TNK1	2	JAK family		ZAP-70	3
CSK family		JAK1	3	TEC family	
CSK	1	JAK2	7	BMX	2
MATK	0	JAK3	7	BTK	2
FAK family		TYK2	8	ITK	1
FAK	4	SRC-A family		TEC	3
PYK2	8	FGR	0	TXK	0
		FYN	1		
		SRC	0		
		YES1	0		

305/306

Fig. 39

Receptor Tyrosine Kinases

Gene	mutations/Mb	Gene	mutations/Mb	Gene	mutations/Mb
ALK family		FGFR family		ROR family	
ALK	3.3	FGFR1	13.3	ROR1	7.6
LTK	0.0	FGFR2	2.2	ROR2	13.6
AXL family		FGFR3	0.0	ROS family	
AXL	5.3	FGFR4	2.3	ROS1	5.1
MER	1.7	INSR family		RYK family	
TYRO3	6.6	IGF1R	5.1	RYK	11.4
DDR family		INSR	2.3	TIE family	
DDR1	11.9	IRR	-	TEK1	14.5
DDR2	2.6	MET family		TIE	11.7
EGFR family		MET	6.3	TRK family	
EGFR	11.6	RON	4.9	NTRK1	24.9
HER2	4.2	MUSK family		NTRK2	15.8
HER3	9.4	MUSK	-	NTRK3	9.4
HER4	9.6	PDGFR family		VEGFR family	
EPH family		CSF1R	0.0	VEGFR1	7.1
EPHA1	0.0	FLT3	16.2	VEGFR2	4.6
EPHA2	16.9	KIT	2.8	VEGFR3	0.0
EPHA3	4.4	PDGFRA	0.0	AATYK family	
EPHA4	5.3	PDGFRB	0.0	AATYK	4.0
EPHA5	12.2	PTK7 family		LMTK2	13.0
EPHA6	8.9	CCK4	5.2	LMTK3	0.0
EPHA7	0.0	RET family		STYK family	
EPHA8	0.0	RET	4.0	STYK1	0.0
EPHA10	0.0				
EPHB1	10.0				
EPHB2	13.0				
EPHB3	4.0				
EPHB4	11.2				
EPHB6	16.0				

(cont. on next page)

306/306

Fig. 39 (cont.)

Non-Receptor Tyrosine Kinases

Gene	mutations/Mb	Gene	mutations/Mb	Gene	mutations/Mb
A6 family		FES family		SRC-B family	
PTK-9	8.3	FER	3.2	BLK	0.0
		FES	7.4	HCK	0.0
ABL family		FRK family		LCK	8.5
ABL1	6.2			LYN	2.7
ARG	10.0	BRK	10.7		
ACK family		FRK	9.9	SYK family	
ACK1	11.6	SRMS	-	SYK	30.5
TNK1	6.1			ZAP-70	8.5
CSK family		JAK family		TEC family	
CSK	3.3	JAK1	3.4	BMX	5.4
MATK	0.0	JAK2	7.5	BTK	4.3
FAK family		JAK3	15.3	ITK	6.3
FAK	4.1	TYK2	8.9	TEC	3.9
PYK2	8.6	SRC-A family		TXK	0.0
		FGR	0.0		
		FYN	2.2		
		SRC	0.0		
		YES1	0.0		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2007/000412

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C12N 15/52 (2006.01) *C07K 16/00* (2006.01) *C07K 16/40* (2006.01)
C07K 14/47 (2006.01) *C07K 16/28* (2006.01) *C12N 9/00* (2006.01)
C07K 14/71 (2006.01) *C07K 16/30* (2006.01) *C12N 15/12* (2006.01))

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Chemical Abstracts Registry File - Sequences corresponding to mutants ACK1 H37Y, ACK1 E111K, ACK1 R127H, ACK1 M393T, ACK1 A634T, ACK1 S699N, ACK1 P725L, ACK1 P731L, ACK1 R748W, ACK1 G947D, ACK1 S985N, ACK1 R1038H, CSK Q26X, FGFR1 R78H, FGFR1 P252S, FGFR1 A268S, FGFR1 V427_T428del, FGFR1 G539_K540del, FGFR4 V10I, FGFR4 L136P, FGFR4 Y367C, FGFR4 G388R, TEC L89R, TEC W531R, TEC P587L, TYRO3 S324C, TYRO3 I346N, TYRO3 E489K, TYRO3 S531L, TYRO3 N788T, TYRO3 P822L

GenomeQuest Protein databases – Sequence corresponding to TYRO3 with keywords tumour, cancer, malignant

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/074485 A1 (RESEARCH ASSOCIATION FOR BIOTECHNOLOGY and ZOEGENE CORPORATION), 2 September 2004 See SEQ ID NO: 22 & Chemical Abstracts Abstract Number AN 141:237775 & Chemical Abstracts Registry Number RN 680966-95-4 & GenPept Accession Number BAD18675 & GenBank Accession Number AK131539	15-23, 26-37, 41-46, 49-54, 57-58, 61-62

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
31 March 2008

Date of mailing of the international search report
14 APR 2008

Name and mailing address of the ISA/AU
 AUSTRALIAN PATENT OFFICE
 PO BOX 200, WODEN ACT 2606, AUSTRALIA
 E-mail address: pct@ipaustalia.gov.au
 Facsimile No. +61 2 6283 7999

Authorized officer
ANDREW BRYCE
 AUSTRALIAN PATENT OFFICE
 (ISO 9001 Quality Certified Service)
 Telephone No : (02) 6283 3132

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2007/000412

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/031001 A2 (CHIRON CORPORATION), 7 April 2005 See Abstract; SEQ ID NOs: 433, 435, 439 and 443; Claims 45, 49 and 50 & Chemical Abstracts Registry Number RN 848962-96-9 & Chemical Abstracts Registry Number RN 848962-98-1 & Chemical Abstracts Registry Number RN 848963-02-0 & Chemical Abstracts Registry Number RN 848963-06-4	57-58, 61-62, 65-66, 70-74
X	US 2006/0194265 A1 (Morris et al.), 31 August 2006 See Abstract; SEQ ID NOs: 433, 435, 439 and 443; Claims 57, 61 and 62 & Chemical Abstract Registry Number RN 906028-18-0 & Chemical Abstract Registry Number RN 906028-21-5 & Chemical Abstract Registry Number RN 906028-25-9 & Chemical Abstract Registry Number RN 906028-30-6	57-58, 61-62, 65-66, 70-74
X	Ezzat S. et al. "Targeted expression of a human pituitary tumor-derived isoform of FGF receptor-4 recapitulates pituitary tumorigenesis" Journal of Clinical Investigation (2002) 109 (1): 69-78 See page 77, column 1, paragraphs 1 and 4; Figure 1 & Chemical Abstract Registry Number RN 402909-69-7 & GenPept Accession Number AAK51435 & GenBank Accession Number AF359246.	57-58, 61-62, 65-66, 70-74
X	Ron D. et al. "Fibroblast Growth Factor Receptor 4 Is a High Affinity Receptor for Both Acidic and Basic Fibroblast Growth Factor but Not for Keratinocyte Growth Factor" Journal of Biological Chemistry (1993) 268 (8): 5388-5394 See page 5394, column 1; Figures 1 and 2	57-58, 61-62, 65-66, 70-74
X	WO 2002/031198 A2 (AVALON PHARMACEUTICALS), 18 April 2002 See SEQ ID NOs: 13 and 14; Claim 9	6
X	WO 2003/065006 A2 (MILLENNIUM PHARMACEUTICALS, INC.), 7 August 2003 See Gene ID 1686 on page 16	6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2007/000412

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2005-198640 A (BIOMARKER SCIENCE CO. LTD.), 28 July 2005 See SEQ ID NO: 15 & Chemical Abstracts Abstract Number AN 143:166667 & Chemical Abstracts Registry Number RN 483593-57-3	57-58, 61-62, 65-66, 70-74
A	Kostrzewa M. and Müller U. "Genomic structure and complete sequence of the human FGFR4 gene" Mammalian Genome (1998) 9 (2): 131-135 See page 134, column 1, paragraph 1; Figure 4	57-58, 61-62, 65-66, 70-74

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2007/000412**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
Claims 1-74 as far as they relate to ACK1, CSK, FGFR1, FGFR4, TEC and TYRO3.
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

Supplemental Box

(To be used when the space in any of Boxes I to IV is not sufficient)

Continuation of Box No: III

The International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, consideration has been given to those features which can potentially distinguish the claimed combination of features from the prior art. Where different claims have different distinguishing features they define different inventions.

This International Searching Authority has found that there are different inventions as follows:

1. Claims 1-74 (partially), insofar as they relate to **FGFR4**. It is considered that the isolated, enriched or purified nucleic acid molecules encoding a mutant/variant of FGFR4 protein kinase polypeptide and the associated recombinant cell or tissue, the isolated, enriched or purified mutant/variant FGFR4 polypeptides, and the associated probes, antibodies, kits, methods of use, and methods of treatment and diagnosis, comprise a first distinguishing feature.
2. Claims 1-74 (partially), insofar as they relate to **FGFR1**. It is considered that the isolated, enriched or purified nucleic acid molecule encoding a mutant/variant FGFR1 protein kinase polypeptide and the associated recombinant cell or tissue, the isolated, enriched or purified mutant/variant FGFR1 polypeptides, and the associated probes, antibodies, kits, methods of use, and methods of treatment and diagnosis, comprise a second distinguishing feature.
3. Claims 1-74 (partially), insofar as they relate to **Tyros3**. It is considered that the isolated, enriched or purified nucleic acid molecule encoding a mutant/variant Tyros3 protein kinase polypeptide and the associated recombinant cell or tissue, the isolated, enriched or purified mutant/variant Tyros3 polypeptides, and the associated probes, antibodies, kits, methods of use, and methods of treatment and diagnosis, comprise a third distinguishing feature.
4. Claims 1-74 (partially), insofar as they relate to **TEC**. It is considered that the isolated, enriched or purified nucleic acid molecule encoding a mutant/variant TEC protein kinase polypeptide and the associated recombinant cell or tissue, the isolated, enriched or purified mutant/variant TEC polypeptides, and the associated probes, antibodies, kits, methods of use, and methods of treatment and diagnosis, comprise a fourth distinguishing feature.
5. Claims 1-74 (partially), insofar as they relate to **CSK**. It is considered that the isolated, enriched or purified nucleic acid molecule encoding a mutant/variant CSK protein kinase polypeptide and the associated recombinant cell or tissue, the isolated, enriched or purified mutant/variant CSK polypeptides, and the associated probes, antibodies, kits, methods of use, and methods of treatment and diagnosis, comprise a fifth distinguishing feature.
6. Claims 1-74 (partially), insofar as they relate to **ACK1**. It is considered that the isolated, enriched or purified nucleic acid molecule encoding a mutant/variant ACK1 protein kinase polypeptide and the associated recombinant cell or tissue, the isolated, enriched or purified mutant/variant ACK1 polypeptides, and the associated probes, antibodies, kits, methods of use, and methods of treatment and diagnosis, comprise a sixth distinguishing feature.
- 7-81. Claims 1-74 (partially), insofar as they relate to **each and every one of the additional protein kinases** identified in the claims. It is considered that each additional isolated, enriched or purified nucleic acid molecule encoding a mutant/variant protein kinase polypeptide and associated recombinant cell or tissue, the isolated, enriched or purified mutant/variant protein kinase polypeptides, the associated probes, antibodies, kits, methods of use, and methods of treatment and diagnosis, comprise a further distinguishing feature.

(Continued on next sheet)

Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: III

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

The only feature common to the inventions identified above is that they all relate to a mutant/variant protein kinase. However this concept is not novel in the light of a large number of documents, including the following:

- Schmidt, L. *et al* (1997) *Nature Genetics* 16: 68-73
- Mulligan, L. M. *et al* (1993) *Nature* 363: 458-460
- Cappellen, D. *et al* (1999) *Nature Genetics* 23: 18-20
- Stadler, C. R. *et al* (June 2006) *Cellular Signalling* 18: 783-794
- Neumann, H. P. H. *et al* (2002) *New England Journal of Medicine* 19: 1459-1466
- Baumgartner-Parzer, S. M. *et al* (2005) *The Journal of Clinical Endocrinology & Metabolism* 90(11): 6232-36
- Satioglu-Tufan, N. L. *et al* (May 2006) *World Journal of Gastroenterology* 12(20): 3283-3287
- James, M. R. *et al* (2005) *Journal of Investigative Dermatology* 125(6): 1252-1258
- Schnittger, S. *et al* (April 2006) *Genes Chromosomes and Cancer* 45(4): 332-337
- Stephens, L. A. *et al* (2005) *Thyroid* 15(2): 100-104
- Lo, Y. L. *et al* (2005) *International Journal of Cancer* 115(2): 276-283
- Bange, J. *et al* (2002) *Cancer Research* 62: 840-847

Note also that all of the above relate to the variant/mutant protein kinase in the context of cancer.

This means that the common feature cannot constitute a special technical feature within the meaning of PCT Rule 13.2, second sentence, since it makes no contribution over the prior art.

Because the common feature does not satisfy the requirement for being a special technical feature it follows that it cannot provide the necessary technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention *a posteriori*.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2007/000412

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2004074485	JP	2006174701				
WO	2005031001	AU	2002337943	AU	2002364052	AU	2002364708
		AU	2002367390	AU	2003218331	AU	2003219959
		AU	2003220178	AU	2003224641	AU	2003225750
		AU	2003225826	AU	2003230669	AU	2003299645
		AU	2003299646	AU	2003299897	AU	2003303638
		AU	2004213432	AU	2004213452	AU	2004276821
		CA	2465921	CA	2468316	CA	2470844
		CA	2471840	CA	2477225	CA	2477974
		CA	2479719	CA	2479721	CA	2479723
		CA	2479727	CA	2479731	CA	2508944
		CA	2510311	CA	2511817	CA	2513137
		CA	2516128	CA	2516138	CA	2539709
		EP	1469769	EP	1469870	EP	1476067
		EP	1490388	EP	1490500	EP	1490688
		EP	1490689	EP	1490690	EP	1509539
		EP	1558623	EP	1581244	EP	1581542
		EP	1583501	EP	1587405	EP	1587476
		EP	1592708	EP	1594893	EP	1685157
		US	2002182586	US	2003022255	US	2003064383
		US	2003087252	US	2003099963	US	2003165878
		US	2003194702	US	2003216558	US	2003232334
		US	2004072154	US	2004072264	US	2004126762
		US	2004166490	US	2004170982	US	2004180344
		US	2004197778	US	2004219528	US	2005090434
		US	2005202442	US	2006040262	US	2006121454
		US	2006134623	US	2006154250	US	2006166213
		US	2006177861	US	2006194265	US	2006204982
		US	2006211015	US	2006228710	US	2007037145
		US	2007071757	US	2007149449	US	2007212351
		US	2007218071	US	2007237770	US	2007274990
		WO	03008583	WO	03035837	WO	03039484

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2007/000412

		WO	03045230	WO	03053224	WO	03057146
		WO	03071933	WO	03073826	WO	03079977
		WO	03080639	WO	03080853	WO	03081250
		WO	03081251	WO	2004058146	WO	2004058288
		WO	2004060301	WO	2004060304	WO	2004074320
		WO	2004074321				
US	2006194265	AU	2002337943	AU	2002364052	AU	2002364708
		AU	2002367390	AU	2003218331	AU	2003219959
		AU	2003220178	AU	2003224641	AU	2003225750
		AU	2003225826	AU	2003230669	AU	2003299645
		AU	2003299646	AU	2003299897	AU	2003303638
		AU	2004213432	AU	2004213452	AU	2004276821
		CA	2465921	CA	2468316	CA	2470844
		CA	2471840	CA	2477225	CA	2477974
		CA	2479719	CA	2479721	CA	2479723
		CA	2479727	CA	2479731	CA	2508944
		CA	2510311	CA	2511817	CA	2513137
		CA	2516128	CA	2516138	CA	2539709
		EP	1469769	EP	1469870	EP	1476067
		EP	1490388	EP	1490500	EP	1490688
		EP	1490689	EP	1490690	EP	1509539
		EP	1558623	EP	1581244	EP	1581542
		EP	1583501	EP	1587405	EP	1587476
		EP	1592708	EP	1594893	EP	1685157
		US	2002182586	US	2003022255	US	2003064383
		US	2003087252	US	2003099963	US	2003165878
		US	2003194702	US	2003216558	US	2003232334
		US	2004072154	US	2004072264	US	2004126762
		US	2004166490	US	2004170982	US	2004180344
		US	2004197778	US	2004219528	US	2005090434
		US	2005202442	US	2006040262	US	2006121454
		US	2006134623	US	2006154250	US	2006166213
		US	2006177861	US	2006204982	US	2006211015
		US	2006228710	US	2007037145	US	2007071757
		US	2007149449	US	2007212351	US	2007218071
		US	2007237770	US	2007274990	WO	03008583
		WO	03035837	WO	03039484	WO	03045230

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2007/000412

	WO	03053224	WO	03057146	WO	03071933	
	WO	03073826	WO	03079977	WO	03080639	
	WO	03080853	WO	03081250	WO	03081251	
	WO	2004058146	WO	2004058288	WO	2004060301	
	WO	2004060304	WO	2004074320	WO	2004074321	
	WO	2005031001					
WO	0231198	AU	13084/02	CA	2425643	EP	1399584
		US	2004072192				
WO	03065006	AU	2003225535	EP	1468118	US	2003157082
		US	2005080343	US	2007078088		
JP	2005198640	NONE					
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.							
END OF ANNEX							