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Methods for assessing and treating leukemia

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(56) Related Art

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Rowinsky EK et al, Journal of Clinical Oncology, Vol 17, 1999, pages 3631-3652

Abstract of the Invention

METHODS FOR ASSESSING AND TREATING CANCER

Methods for treating cancer, and preferably hematological malignancy, patients include analyzing gene expression profiles and/or molecular markers of a patient to determine whether the patient is likely to respond to treatment with farnesyl transferase inhibitor (FTI) and, optionally, other therapeutics. The methods are also useful for monitoring patient therapy and for selecting a course of therapy. Genes modulated in response to FTI treatment are provided and are used in formulating the profiles.

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COMPLETE SPECIFICATION

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Invention Title: METHODS FOR ASSESSING AND TREATING LEUKEMIA

The following statement is a full description of this invention, including the best method of performing it known to me:-

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METHODS FOR ASSESSING AND TREATING LEUKEMIA

BACKGROUND

This invention relates to diagnostics, prognostics, and treatments for cancer based on the detection of molecular markers and/or gene expression analysis.

Some molecules, such as Ras, that are implicated in cancers must be farnesylated by the farnesyl transferase enzyme in order to interact with the inner leaflet of the plasma membrane of the cell and become involved in various signaling pathways. However, Ras is not the only protein implicated in cancer that has a CAAX box that is prenylated. Farnesyl transferase inhibitors (FTIs) are therapeutic agents that inhibit the covalent attachment of the carbon farnesyl moieties to the C-terminal CAAX motif of various proteins. They have utility in the treatment of cancers and proliferative disorders such as hematological malignancies. Hematological malignancies such as leukemias, lymphomas, and myelomas (e.g, acute myeloid leukemia; AML) are among the diseases that can most beneficially be addressed with FTIs. Solid tumors such as breast cancer and glioblastomas may also be treated with FTIs.

As is true in the case of many treatment regimens, some patients respond to treatment with FTIs and others do not. Prescribing the treatment to a patient who is unlikely to respond to it is not desirable. Thus, it would be useful to know how a patient could be expected to respond to such treatment before a drug is administered so that non-responders would not be unnecessarily treated and so that those with the best chance of benefiting from the drug are properly treated and monitored. Further, of those who respond to treatment there may be varying degrees of response. Treatment with therapeutics other than FTIs or treatment with therapeutics in addition to FTIs may be beneficial for those patients who would not respond to FTIs or in whom response to FTIs alone is less than desired.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a method of determining whether a patient will respond to treatment with a farnesyl transferase inhibitor (FTI) by analyzing the presence or expression of the LBC oncogene (SEQ ID NO: 2).

It is preferred that the analysis of the expression of a gene that is differentially modulated in the presence of an FTI.

Preferably, there are articles comprising a medium with which gene expression profiles of the patient indicative of the FTI response are determined.

Preferably, there are kits comprising reagents used for nucleic acid arrays, including cDNA arrays or oligonucleotide arrays.

Preferably, there is a diagnostic kit comprising molecular markers that distinguish responders from non-responders to FTI treatment.

Preferably, there is a combination comprising the use of an FTI for the preparation of a pharmaceutical composition in the therapeutic treatment of said patient and an active agent.

It is preferred that the gene expression profiles are obtained from a group of genes correlating to more than one nucleic acid sequence of Seq. ID. No 1-18.

It is preferred that said reagents for detecting the presence or expression of the LBC oncogene (SEQ ID NO:2).

There is a method of treating a cancer patient with an FTI. In one such method, the presence or absence of a molecular marker is determinative of whether the patient is likely to respond to the FTI. The patient is treated with an FTI if they are likely to respond. If the patient is not likely to respond to treatment with an FTI, then it may be withheld. The gene expression profiles are obtained for a set of genes that are predictive of FTI response. The presence of a molecular marker and gene expression profiles are used in combination to determine likelihood of response to FTI treatment. Preferably, the expression profiles are used in combination with leukemic blast counts and/or leukemic cell antigen expression to determine likelihood of response to FTI treatment. Preferably, the samples used in the assays are obtained from bone marrow.

Preferably, a cancer patient is monitored for treatment with an FTI in which the patient's gene expression profile and/or the presence of a molecular marker is analyzed to determine whether the patient is responding to the FTI and treating a patient with the FTI if they are likely to respond in a desirable fashion.

Preferably, a patient is treated if the gene expression profile shows modulation of one or more particular genes indicative of FTI responders.

Preferably, a patient is treated if the gene expression profile shows modulation of one or more particular genes indicative of FTI responders and either a bone marrow blast cell count of 0 – 60%, or the presence of less than 60% of cells having positive expression of the CD33 cell surface antigen and/or the presence of less than 10% of cells having positive expression of the CD34 cell surface antigen.

Preferably, the molecular marker is one or more of the following: the lbc oncogene; AHR; DKFZp667G2110; IDS; GPR105; TEM6; TNFSF13; SVIL; KIAA0680; FRAG1; DKFZp566B213; KIAA1036; BTG3; MAPK8IP3; ARHH; and NPTX2. The marker can also be OPN3 and/or IL3RA in combination with one or more of the above.

Preferably, the FTI is a quinilone or quinoline derivative.

Preferably, the FTI is (R)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone).

Such articles include gene expression profiles or representations of them. The representations can be fixed in computer readable media. Other articles include nucleic acid arrays used to determine the gene expression profiles and devices and components for practicing other nucleic acid detection technologies.

Such kits include reagents for detecting the expression of genes and/or the presence of a molecular marker that distinguish responders from non-responders to FTI treatment. The kits can include instructions.

Preferably, there is a method of treating a cancer patient comprises administering an FTI and a therapeutic composition that modulates the MAPK/ERK signaling pathways, TGFβ, WNT, Rho, or apoptotic pathways.

Preferably, the patient is treated with an FTI and a therapeutic composition selected from the group consisting of tyrosine kinase inhibitors, MEK kinase

inhibitors, PI3K kinase inhibitors, MAP kinase inhibitors, apoptosis modulators and combinations thereof.

Preferably, the gene expression profile and/or the presence or absence of a molecular marker of a patient is analyzed to determine whether the patient would likely benefit from the combination of an FTI and another drug. The patient is then treated with such combination or, if the patient is unlikely to respond to an FTI, the patient is treated with another drug such as one selected from the group consisting of tyrosine kinase inhibitors; MEK kinase inhibitors; PI3K kinase inhibitors; MAP kinase inhibitors; and apoptosis-modulators; and combinations thereof.

Preferably, the gene expression profile and/or the presence of a molecular marker of a patient is analyzed to determine whether the patient would likely benefit from the combination of an FTI and another form of therapy. The patient is then treated with such combination or, if the patient is unlikely to respond to an FTI, the patient is treated with another therapy without the inclusion of an FTI.

BRIEF DESCRIPTION OF DRAWINGS

Fig 1 is a graphical presentation of a Kaplan-Meier analysis of patients with high and low CD33 antigen expression.

Fig 2 is a graphical presentation of a Kaplan-Meier analysis of patients with high and low blast counts.

Fig 3A is a graphical presentation of a Kaplan-Meier survival analysis of patients using clinical response classifiers.

Fig 3B is a graphical presentation of a Kaplan-Meier survival analysis of patients using oncoLBC gene expression to classify patients.

Fig 3C is a graphical presentation of a Kaplan-Meier survival analysis of patients using oncoLBC and AHR gene expressions to classify patients.

DETAILED DESCRIPTION

The therapeutic agents referred to in this specification are FTIs. They take on a multitude of forms but share the essential inhibitory function of interfering with or lessening the farnesylation of proteins implicated in cancer and proliferative diseases. Preferably, the FTIs are those indicated for the treatment of solid tumors such as glioblastoma and breast cancer. More preferably, the FTIs are indicated for the treatment of hematological malignancies such as leukemias, lymphomas, and myelomas. Most preferably, the FTIs are contemplated for use in AML, myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), and multiple myeloma (MM). In the case of hematological malignancies, a patient who responds to an FTI is one in whom a reduction of more than 50% of blast cells is seen in bone marrow following treatment with the FTI. In solid tumors, a patient who responds to an FTI is one in whom their tumor ceases to grow. Response in patients with solid tumor can alternatively be measured according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria as such term is commonly used in oncology.

Numerous FTIs are within the scope of the invention and include those described in U.S. Patents: 5,976,851 to Brown et al; 5,972,984 to Anthony et al.; 5,972,966 to deSolms; 5,968,965 to Dinsmore et al.; 5,968,952 to Venet et al.; 6,187,786 to Venet et al.; 6,169,096 to Venet et al.; 6,037,350 to Venet et. al.; 6,177,432 to Angibaud et al.; 5,965,578 to Graham et al.; 5,965,539 to Sebti et al.; 5,958,939 to Afonso et al.; 5,939,557 to Anthony et al.; 5,936,097 to Commercon et al.; 5,891,889 to Anthony et al.; 5,889,053 to Baudin et al.; 5,880,140 to Anthony; 5,872,135 to deSolms; 5,869,682 to deSolms; 5,861,529 to Baudoin; 5,859,015 to Graham et al.; 5,856,439 to Clerc; 5,856,326 to Anthony et al.; 5,852,010 to Graham et al.; 5,843,941 to Marsters et al.; 5,807,852 to Doll; 5,780,492 to Dinsmore et al.; 5,773,455 to Dong et al.; 5,767,274 to Kim et al.; 5,756,528 to Anthony et al.; 5,750,567 to Baudoin et al.; 5,721,236 to Bishop et al,; 5,700,806 to Doll et al.; 5,661,161 to Anthony et al.; 5,602,098 to Sebti et al.; 5,585,359 to Breslin et al.; 5,578,629 to Ciccarone et al.; 5,534,537 to Ciccarone et al.; 5,532,359 to Marsters et al.; 5,523,430 to Patel et al.; 5,504,212 to de Solms et al.; 5,491,164 to deSolms et al.; 5,420,245 to Brown et al.; and 5,238,922 to Graham et al. each of which is incorporated herein by reference. Non-peptidal, so-called "small molecule" therapeutics are preferred. More preferred FTIs are quinolines or quinoline derivatives such as:

7-(3-chlorophenyl)-9-[(4-chlorophenyl)-1H-imidazol-1-ylmethyl]-2,3-dihydro- 1H,5H-benzo[ij]quinolizin-5-one,

7-(3-chlorophenyl)-9-[(4-chlorophenyl)-1H-imidazol-1-ylmethyl]-1,2-dihydro- 4H-pyrrolo[3,2,1-ij]quinoline-4-one,

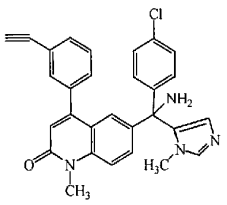
8-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl),methyl]-6-(3-chlorophen yl)-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one, and

8-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-6-(3-chloropheny l)-2,3-dihydro-1H,5H-benzo[ij]quinolizin-5-one.

The most preferred FTI is (R)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone), described in U.S. Patent 6,420,387 to Venet et al as the (+) enantiomer.

Another preferred FTI is (-)-5-(3-chlorophenyl)-α-(4-chlorophenyl)-α-(1-methyl-1*H*-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine and its pharmaceutically acceptable acid addition salts, described in WO 01/98302.

Other useful FTIs include Arglabin (i.e.1(R)-10-epoxy-5(S),7(S)-guaia-3(4),11(13)-dien-6,12-olide descibed in WO-98/28303; perrilyl alcohol described in WO-99/45912; SCH-66336, i.e. (+)-(R)-4-[2-[4-(3,10-dibromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide, described in U.S. Patent No. 5874442 ; L778123, i.e. 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, described in WO-00/01691; compound 2(S)-[2(S)-[2(R)-amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone described in WO-94/10138; and BMS 214662, i.e. (R)-2,3,4,5-tetrahydro-1-(IH-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulphonyl)-1H-1,4-benzodiazapine-7-carbonitrile, described in WO 97/30992; CP 609754, i.e. N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, described in US Patent 5,747,498; and 6-[amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethynyl-phenyl)-1-methyl-1H-quinolin-2-one described in WO-00/12499:



The mere presence of nucleic acid sequences having the potential to express proteins or peptides ("genes") within the genome is not determinative of whether a protein or peptide is expressed in a given cell. Whether or not a given gene capable of expressing proteins or peptides or transcribing RNA does so and to what extent such expression or transcription occurs, if at all, is determined by a variety of complex factors. Nevertheless, assaying gene expression can provide useful information about the cellular response to a given stimulus such as the introduction of a drug or other therapeutic agent. Relative indications of the degree to which genes are active or inactive can be found in such gene expression profiles. In some instances, the presence of a molecular marker can, by itself or with the use of gene expression information, provide useful information about treatment efficacy too. The gene expression profiles and molecular markers of this invention are used to identify and treat patients who will likely benefit from FTI therapy or exclude patients from FTI therapy where the patient likely would experience little or no beneficial response to the drug or therapy.

Cancers, including hematological malignancies, typically arise from mutations in a variety of genes. The same type of cancer may arise as a result of, or coincident with, one or more mutations that differ from those of another patient having the same type of cancer. The fact that there are often multiple molecular bases underlying the same cancers is consistent with the observation that some therapies that affect one patient do not necessarily equally affect another patient with the same type of cancer. Further, from a diagnostic point of view, the presence of particular mutations such as translocations, deletions, or SNPs can have powerful implications. In some instances, such molecular markers are themselves useful indicators for diagnosis, prognosis, or treatment response determinations. This is particularly true where the molecular mutations can be associated with response to particular treatments. In the instant invention, cancers coincident with the absence of the lbc oncogene (the lymphoid blast crisis oncogene) respond to FTI treatment. Therefore, the expression of this gene, the lack of expression of the gene and its presence

or absence are useful in predicting resistance to FTI treatment prior to actually prescribing such treatment.

The lbc oncogene (Seq. ID No. 2) is a chimera derived from the fusion of an lbc proto-oncogene (Seq. ID No. 23-27) on chromosome 15q with an unrelated sequence originating in chromosome 7q. The truncation of the proto-oncogene at the C-terminus of the sequence results in the gene gaining transforming ability. This tructation could also arise from other mechanisms other than a translocation. For example, aberrant splicing could result in RNA transcripts with C-terminus truncations. The gene has a number of expression products including mRNA and a protein (Seq. ID No. 29, Human LBC protein, Genbank Accession number GI: 29791897). While the precise manner in which the lbc oncogene functions is not completely understood, it is clear that it can be present in a range of tissues including skeletal muscle, heart, lung, prostate, ovary, small intestine, and hematopoietic cells. Treatment of cancers originating in tissues where the oncogene could be manifested (but is not) is within the scope of this invention.

There is great flexibility available in formatting the assays of this invention because the gene is the product of a truncation and because it produces recognizable expression products. Not only can the absence of the gene or its products be used, but so too can detection of the modulated expression of this gene. Thus, a gene expression profile can include this gene. Preferably, the absence or modulation of the gene is used as an indicator of FTI treatment response in hematological malignancies, more preferably in leukemias, and most preferably in AML

Where identification of the lbc oncogene as a molecular marker is undertaken, any suitable method of detection may be used. The presence of the molecular marker is indicative of a poor prognosis for treatment with an FTI and its absence is indicative of an greater likelihood of response to such treatment. Methods useful for detecting the presence of the lbc oncogene include any method for detecting known mutant genes or sequences including, without limitation, the single strand conformation polymorphism technique, chemical and thermal denaturing gradient analysis, chemical and enzymatic cleavage methods, mass spectrometry, RFLP and allele specific amplification, ratiometric PCR, bead-based and microarray-based systems as well as in situ hybridization, heteroduplex analysis, and microarray analysis, ELISA, western, FACS, antibody-based techniques, methylation-based PCR, and SNP detection.

The most preferred method for detecting the presence or absence of the lbc oncogene is via PCR. In this method, cells are first obtained from the patient according to

routine sample preparation methods. Where the malignancy is hematological, a simple peripheral blood sample or a bone marrow sample is preferable. RNA is then extracted according to well-accepted procedures and amplified as follows. Target sequences are amplified using, e.g., 250 nM of primers and 250 nM of Taqman probe in ABI Taqman buffer. Thermal cycling is conducted at 50°C for 2 minutes, 95°C for 10 minutes, followed by 50 cycles of 95°C for 15 minutes and 62°C for 1 minute. Examples of the primers and probe are shown in Table 1.

This technique measures the amount of LBC transcript present in the sample. Measured quantities can be normalized by running similar RT-PCR experiments in which the same samples are used to amplify endogenous control genes such as HPRT.

Table 1

Name	Sequence (5'-3')
LBC forward	GGTCAGATGTTTGCCAAGGAA
LBC reverse	TCTTCAGAAACACACTCCCATCAC
LBC TaqMan probe	TGAAACGGAAGAAGCTTGTA

Another method for determining the presence or absence of the lbc oncogene is to assay the length of the RNA transcript. Since the LBC oncogene has a 3' translocation the transcript length will be shorter than the LBC proto-oncogene transcript. This end point is favored as a diagnostic. To diagnose the transcript size a forward primer homologous to both the proto- and onco LBC transcripts is used (eg LBC forward primer from above Table 1) in conjunction with a reverse primer homologous to the universal poly A tail of RNA transcripts. Preferably initial cDNA synthesis will incorporate an additional unique sequence tag 3' of the polyA sequence to confer additional specificity for the PCR reaction.

If the genomic translocation is being measured then genomic DNA will be isolated using standard techniques and PCR primers used that are specific for the lbc oncogene. For example, the forward primer homologous for both the onco- and proto-LBC genes could be used in conjunction with the polyA sequence as described above. Alternatively, the reverse primer could be homologous to the 3' translocated sequence. The readout would be the size of the amplicon where presence of the oncogene is consistent with a shorter product than the protooncogene, or presence or absence of an oncoLBC-specific amplicon.

Assays for the lbc oncogene status of the cell also can determine normal/abnormal tissue distribution for diagnostic purposes using techniques such as Immunohistochemical analysis (IHC). For example, the antibodies to lbc protein may be used in conjunction with both fresh-frozen and formalin-fixed, paraffin-embedded tissue blocks prepared for study by immunohistochemistry (IHC). Each tissue block may consist of 50 mg of residual "pulverized" tumor.

Briefly, frozen-sections may be prepared by rehydrating 50 ng of frozen pulverized tumor at room temperature in PBS in small plastic capsules; pelleting the particles by centrifugation; resuspending them in a viscous embedding medium (OCT); inverting the capsule and pelleting again by centrifugation; snap-freezing in -70°C. isopentane; cutting the plastic capsule and removing the frozen cylinder of tissue; securing the tissue cylinder on a cryostat microtome chuck; and cutting 25-50 serial sections containing intact tumor cells.

Permanent-sections may be prepared by a similar method involving rehydration of the 50 mg sample in a plastic microfuge tube; pelleting; resuspending in 10% formalin for 4 hours fixation; washing/pelleting; resuspending in warm 2.5% agar; pelleting; cooling in ice water to harden the agar; removing the tissue/agar block from the tube; infiltrating and embedding the block in paraffin; and cutting up to 50 serial permanent sections.

For the immunohistochemical assay, the sections are overlaid with a blocking solution containing: 3% bovine serum albumin (BSA) in PBS or other blocking reagents. The blocking reagents include non-specific serum or dry milk. The blocking treatment is allowed to proceed for 1 hr. at room temperature. Anti-lbc protein antibody is diluted with PBS buffer containing 3% BSA, 0.1% TRITON X.TM.-100, t-octylphenoxypolyethoxyethanol, at a ratio of 1:100. The sample sections are generally overlaid with the antibody solution for 16 hrs. at 4°C. The duration and temperature conditions may be varied according to the antibody selected and the material tested. The optimal conditions should be determined empirically. The antibody treated sections are then washed three times in PBS for 15 min. each to remove unbound antibody and then overlaid with PBS containing 3% BSA and a secondary antibody at a dilution of 1:2000. The secondary antibodies may be coupled to a chromogenic enzyme such as: horseradish peroxidase, alkaline phosphatase, fluorescein iso-thiocyanate, or other suitable enzymes. Alternatively, the secondary antibody may be conjugated to biotin and used in conjunction with chromophore-labeled avidin.

Another exemplary method for detecting the presence of the lbc oncogene is via in situ hybridization. Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue or biological structure to be analyzed; (2) prehybridization treatment of the biological structure to increase accessibility of target DNA, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization and (5) detection of the hybridized nucleic acid fragments. The reagent used in each of these steps and the conditions for use vary depending on the particular application.

In this case, a hybridization solution comprising at least one detectable nucleic acid probe capable of hybridizing to the lbc oncogene (at its chromosomal locus) is contacted with the cell under hybridization conditions. Any hybridization is then detected and compared to a predetermined hybridization pattern from normal or control cells. Preferably, the probes are alpha-centromeric probes. Such probes can be made commercially available from a number of sources (e.g., from Visys Inc., Downers Grove, IL). In a preferred embodiment, the hybridization solution contains a multiplicity of probes, specific for an area on the chromosome that corresponds to the translocation of the sequences that make up the chimera (e.g., 15q24-25).

Hybridization protocols suitable for use with the methods of the invention are described, e.g., in Albertson (1984) EMBO J. 3: 1227-1234; Pinkel (1988) Proc. Natl. Acad. Sci. USA 85: 9138-9142; EPO Pub. No. 430,402; Methods in Molecular Biology, Vol. 33: In Situ Hybridization Protocols, Choo, ed., Humana Press, Totowa, N.J. (1994), etc. In one particularly preferred embodiment, the hybridization protocol of Pinkel et al. (1998) Nature Genetics 20:207-211 or of Kallioniemi (1992) Proc. Natl Acad Sci USA 89:5321-5325 (1992) is used. Methods of optimizing hybridization conditions are well known (see, e.g., Tijssen (1993) Laboratory Techniques in Biochemistry and Molecular Biology, Vol. 24: Hybridization With Nucleic Acid Probes, Elsevier, N.Y.).

In a preferred embodiment, background signal is reduced by the use of a detergent (e.g., C-TAB) or a blocking reagent (e.g., sperm DNA, cot-1 DNA, etc.) during the hybridization to reduce non-specific binding. In a particularly preferred embodiment, the hybridization is performed in the presence of about 0.1 to about 0.5 mg/ml DNA (e.g., cot-1 DNA).

The probes may be prepared by any method known in the art, including synthetically or grown in a biological host. Synthetic methods include oligonucleotide synthesis, riboprobes, and PCR.

The probe may be labeled with a detectable marker by any method known in the art. Methods for labeling probes include random priming, end labeling, PCR and nick translation. Enzymatic labeling is conducted in the presence of nucleic acid polymerase, three unlabeled nucleotides, and a fourth nucleotide which is either directly labeled, contains a linker arm for attaching a label, or is attached to a hapten or other molecule to which a labeled binding molecule may bind. Suitable direct labels include radioactive labels such as ^{32}P, ^{3}H, and ^{35}S and non-radioactive labels such as fluorescent markers, such as fluorescein, Texas Red, AMCA blue, lucifer yellow, rhodamine, and the like; cyanin dyes which are detectable with visible light; enzymes and the like. Labels may also be incorporated chemically into DNA probes by bisulfite-mediated transamination or directly during oligonucleotide synthesis.

Fluorescent markers can readily be attached to nucleotides with activated linker arms which have been incorporated into the probe. Probes may be indirectly labeled by the methods disclosed above, by incorporating a nucleotide covalently linked to a hapten or other molecule such as biotin or digoxygenin, and performing a sandwich hybridization with a labeled antibody directed to that hapten or other molecule, or in the case of biotin, with avidin conjugated to a detectable label. Antibodies and avidin may be conjugated with a fluorescent marker, or with an enzymatic marker such as alkaline phosphatase or horseradish peroxidase to render them detectable. Conjugated avidin and antibodies are commercially available from companies such as Vector Laboratories (Burlingame, Calif.) and Boehringer Mannheim (Indianapolis, Ind.).

The enzyme can be detected through a colorimetric reaction by providing a substrate for the enzyme. In the presence of various substrates, different colors are produced by the reaction, and these colors can be visualized to separately detect multiple probes. Any substrate known in the art may be used. Preferred substrates for alkaline phosphatase include 5-bromo-4-chloro-3-indolylphosphate (BCIP) and nitro blue tetrazolium (NBT). The preferred substrate for horseradish peroxidase is diaminobenzoate (DAB).

Fluorescently labelled probes suitable for use in the in situ hybridization methods of the invention are preferably in the range of 150-500 nucleotides long. Probes may be DNA or RNA, preferably DNA.

Hybridization of the detectable probes to the cells is conducted with a probe concentration of 0.1-500 ng/µl, preferably 5-250 ng/µl. The hybridization mixture will preferably contain a denaturing agent such as formamide. In general, hybridization is carried out at 25°C - 45°C, more preferably at 32°C - 40°C, and most preferably at 37°C - 38°C. The time required for hybridization is about 0.25-96 hours, more preferably 1-72 hours, and most preferably for 4-24 hours. Hybridization time will be varied based on probe concentration and hybridization solution content which may contain accelerators such as hnRNP binding protein, trialkyl ammonium salts, lactams, and the like. Slides are then washed with solutions containing a denaturing agent, such as formamide, and decreasing concentrations of sodium chloride or in any solution that removes unbound and mismatched probe.

The temperature and concentration of salt will vary depending on the stringency of hybridization desired. For example, high stringency washes may be carried out at 42°C - 68°C, while intermediate stringency may be in the range of 37°C - 55°C, and low stringency may be in the range of 30°C - 37°C. Salt concentration for a high stringency wash may be 0.5-1 times SSC (0.15M NaCl, 0.015M Na citrate), while medium stringency may be 1.-4times., and low stringency may be 2-6 times SSC.

The detection incubation steps, if required, should preferably be carried out in a moist chamber at 23°C - 42°C, more preferably at 25°C - 38°C and most preferably at 37 - 38°C. Labeled reagents should preferably be diluted in a solution containing a blocking reagent, such as bovine serum albumin, non-fat dry milk, or the like. Dilutions may range from 1:10-1:10,000, more preferably 1:50-1:5,000, and most preferably at 1:100-1:1,000. The slides or other solid support should be washed between each incubation step to remove excess reagent.

Slides may then be mounted and analyzed by microscopy in the case of a visible detectable marker, or by exposure to autoradiographic film in the case of a radioactive marker. In the case of a fluorescent marker, slides are preferably mounted in a solution that contains an antifade reagent, and analyzed using a fluorescence microscope. Multiple nuclei may be examined for increased accuracy of detection.

Additionally, assays for the expression product of the lbc oncogene can also be used to determine whether the lbc oncogene mutation has occurred. Most preferably, such assays are immunoassays. Immunoassays, in their most simple and direct sense, are binding assays. Certain preferred immunoassays are the various types of enzyme linked

immunosorbent assays (ELISAs) and radioimmunoassays (RIA) known in the art. Immunohistochemical detection using tissue sections is also particularly useful.

In one exemplary ELISA, anti-oncolbc protein -specific antibodies are immobilized onto a selected surface exhibiting protein affinity, such as a well in a polystyrene microtiter plate. Then, a test composition containing the desired antigen, such as a clinical sample, is added to the wells. After binding and washing to remove non-specifically bound immune complexes, the bound antigen may be detected. Detection is generally achieved by the addition of another antibody, specific for the desired antigen, that is linked to a detectable label. This type of ELISA is a simple "sandwich ELISA". Detection may also be achieved by the addition of a second antibody specific for the desired antigen, followed by the addition of a third antibody that has binding affinity for the second antibody, with the third antibody being linked to a detectable label.

Variations of ELISA techniques are well known. In one such variation, the samples containing the desired antigen are immobilized onto the well surface and then contacted with the antibodies of the invention. After binding and appropriate washing, the bound immune complexes are detected. Where the initial antigen specific antibodies are linked to a detectable label, the immune complexes may be detected directly. Again, the immune complexes may be detected using a second antibody that has binding affinity for the first antigen specific antibody, with the second antibody being linked to a detectable label.

Competitive ELISAs are also possible in which test samples compete for binding with known amounts of labeled antigens or antibodies. The amount of reactive species in the unknown sample is determined by mixing the sample with the known labeled species before or during incubation with coated wells. The presence of reactive species in the sample acts to reduce the amount of labeled species available for binding to the well and thus reduces the ultimate signal.

Antigen or antibodies may also be linked to a solid support, such as in the form of plate, beads, dipstick, membrane or column matrix, and the sample to be analyzed applied to the immobilized antigen or antibody. In coating a plate with either antigen or antibody, one will generally incubate the wells of the plate with a solution of the antigen or antibody, either overnight or for a specified period. The wells of the plate will then be washed to remove incompletely adsorbed material. Any remaining available surfaces of the wells are then "coated" with a nonspecific protein that is antigenically neutral with regard to the test antisera. These include bovine serum albumin (BSA), casein and solutions of milk powder.

The coating allows for blocking of nonspecific adsorption sites on the immobilizing surface and thus reduces the background caused by nonspecific binding of antisera onto the surface.

In ELISAs, it is customary to use a secondary or tertiary detection means rather than a direct procedure. Thus, after binding of the antigen or antibody to the well, coating with a non-reactive material to reduce background, and washing to remove unbound material, the immobilizing surface is contacted with the clinical or biological sample to be tested under conditions effective to allow immune complex (antigen/antibody). This can include diluting the antigens and antibodies with solutions such as BSA, bovine gamma globulin (BGG) and phosphate buffered saline (PBS)/Tween. These added agents also tend to assist in the reduction of nonspecific background. Detection of the immune complex then requires a labeled secondary binding ligand or antibody, or a secondary binding ligand or antibody in conjunction with a labeled tertiary antibody or third binding ligand.

Following all incubation steps in an ELISA, the contacted surface is washed so as to remove non-complexed material. Washing often includes washing with a solution of PBS/Tween, or borate buffer. Following the formation of specific immune complexes between the test sample and the originally bound material, and subsequent washing, the occurrence of even minute amounts of immune complexes may be determined.

To provide a detecting means, the second or third antibody will have an associated label to allow detection. Preferably, this will be an enzyme that will generate color development upon incubating with an appropriate chromogenic substrate. Thus, for example, one will desire to contact and incubate the first or second immune complex with a urease, glucose oxidase, alkaline phosphatase or hydrogen peroxidase-conjugated antibody for a period of time and under conditions that favor the development of further immune complex formation, e.g., incubation for 2 hours at room temperature in a PBS-containing solution such as PBS-Tween.

After incubation with the labeled antibody, and subsequent to washing to remove unbound material, the amount of label is quantified, e.g., by incubation with a chromogenic substrate such as urea and bromocresol purple and H_2O_2, in the case of peroxidase as the enzyme label. Quantification is then achieved by measuring the degree of color generation, e.g., using a visible spectra spectrophotometer. Alternatively, the label may be a chemiluminescent one. The use of such labels is described in U.S. Pat. Nos. 5,310,687, 5,238,808 and 5,221,605.

In embodiments of the invention in which gene expression is detected for determining response to FTIs, the use of gene expression portfolios is most preferred. A portfolio of genes is a set of genes grouped so that expression information obtained about them provides the basis for making a clinically relevant judgment such as a diagnosis, prognosis, or treatment choice. In this case, gene expression portfolios can be fashioned to help make therapeutic decisions regarding the use of FTIs in cancer patients.

It is most preferred to detect the expression of the lbc oncogene as part of a gene expression profile with one or more other genes whose differential expression is indicative of likelihood of response to FTI treatment. In this aspect of the invention, the gene expression profiles are made up the lbc oncogene (also referred to as AKAP13). One or more of the following genes can also be used, most preferably, in combination with the lbc oncogene: AHR, DKFZp667G2110, IDS, OPN3, GPR105, TEM6, TNFSF13, SVIL, IL3RA, KIAA0680, FRAG1, DKFZp566B213 , KIAA1036, BTG3, MAPK8IP3, ARHH, NPTX2 (Seq ID No. 1, 3-18). OPN3 and IL3RA are used in combination with one or more other genes and preferably, the profile includes two or more of any of the genes. The most preferred gene expression profile detects the differential expression of lbc oncogene and AHR. Variants, such as splice variants, of the aforementioned genes are also useful in this application.

Preferred methods for establishing gene expression profiles (including those used to arrive at the explication of the relevant biological pathways) include determining the amount of RNA that is produced by a gene that can code for a protein or peptide or transcribe RNA. This is best accomplished by reverse transcription PCR (RT-PCR), competitive RT-PCR, real time RT-PCR, differential display RT-PCR, Northern Blot analysis and other related tests. While it is possible to conduct these techniques using individual PCR reactions, it is often desirable to amplify copy DNA (cDNA) or copy RNA (cRNA) produced from mRNA and analyze it via microarray. A number of different array configurations and methods for their production are known to those of skill in the art and are described in U.S. Patents such as: 5,445,934; 5,532,128; 5,556,752; 5,242,974; 5,384,261; 5,405,783; 5,412,087; 5,424,186; 5,429,807; 5,436,327; 5,472,672; 5,527,681; 5,529,756; 5,545,531; 5,554,501; 5,561,071; 5,571,639; 5,593,839; 5,599,695; 5,624,711; 5,658,734; and 5,700,637; the disclosures of which are herein incorporated by reference.

Microarray technology allows for the measurement of the steady-state mRNA level of thousands of genes simultaneously thereby presenting a powerful tool for identifying the effect of FTIs on cell biology and the likely effect of treatment based on analysis of such

effects. Two microarray technologies are currently in wide use. The first are cDNA arrays and the second are oligonucleotide arrays. Although differences exist in the construction of these chips, essentially all downstream data analysis and output are the same. The product of these analyses are typically measurements of the intensity of the signal received from a labeled probe used to detect a cDNA sequence from the sample that hybridizes to a nucleic acid sequence at a known location on the microarray. Typically, the intensity of the signal is proportional to the quantity of cDNA, and thus mRNA, expressed in the sample cells. A large number of such techniques are available and useful. Preferred methods for determining gene expression can be found in US Patents 6,271,002 to Linsley, et al.; 6,218,122 to Friend, et al.; 6,218,114 to Peck, et al.; and 6,004,755 to Wang, et al., the disclosure of each of which is incorporated herein by reference.

Analysis of the expression levels is conducted by comparing such intensities. This is best done by generating a ratio matrix of the expression intensities of genes in a test sample versus those in a control sample. For instance, the gene expression intensities from a tissue that has been treated with a drug can be compared with the expression intensities generated from the same tissue that has not been treated with the drug. A ratio of these expression intensities indicates the fold-change in gene expression between the test and control samples.

Gene expression profiles can also be displayed in a number of ways. A common method is to arrange a ratio matrix into a graphical dendogram where columns indicate test samples and rows indicate genes. The data is arranged so genes that have similar expression profiles are proximal to each other. The expression ratio for each gene is visualized as a color. For example, a ratio less than one (indicating down-regulation) may appear in the blue portion of the spectrum while a ratio greater than one (indicating up-regulation) may appear as a color in the red portion of the specrtum. Commercially available computer software programs are available to display such data including "GENESPRINT" from Silicon Genetics, Inc. and "DISCOVERY" and "INFER" software from Partek, Inc.

The genes that are differentially expressed are either up regulated or down regulated in diseased cells following treatment with an FTI, or in responders versus non-responders prior to treatment, as deduced by an assessment of gene expression as described above. Up regulation and down regulation are relative terms meaning that a detectable difference (beyond the contribution of noise in the system used to measure it) is found in the amount of expression of the genes relative to some baseline. In this case, the baseline

is the measured gene expression of the untreated diseased cell. The genes of interest in the treated diseased cells are then either up regulated or down regulated relative to the baseline level using the same measurement method. Preferably, levels of up and down regulation are distinguished based on fold changes of the intensity measurements of hybridized microarray probes. A 1.5 fold difference is preferred for making such distinctions. That is, before a gene is said to be differentially expressed in treated versus untreated diseased cells, the treated cell is found to yield at least 1.5 times more, or 1.5 times less intensity than the untreated cells. A 1.7 fold difference is more preferred and a 2 or more fold difference in gene expression measurement is most preferred.

One method of the invention involves comparing gene expression profiles for various genes to determine whether a person is likely to respond to the use of a therapeutic agent. Having established the gene expression profiles that distinguish responder from nonresponder, the gene expression profiles of each are fixed in a medium such as a computer readable medium as described below. A patient sample is obtained that contains diseased cells (such as hematopoietic blast cells in the case of AML) is then obtained. Most preferably, the samples are of bone marrow and are extracted from the patient's sternum or iliac crest according to routine methods before the patient has been treated with drug. Preferably the bone marrow aspirate is processed to enrich for leukemic blast cells using routine methods. Sample RNA is then obtained and amplified from the diseased patient cell and a gene expression profile is obtained, preferably (in the case of a large gene portfolio) via micro-array, for genes in the appropriate portfolios. The expression profiles of the samples are then compared to those previously determined as responder and non-responder. If the sample expression patterns are consistent with an FTI responder expression pattern then treatment with an FTI could be indicated (in the absence of countervailing medical considerations). If the sample expression patterns are consistent with an FTI non-responder expression pattern then treatment with an FTI would not be indicated. When a small number of genes are used in the portfolio such as when the single gene, lymphoid blast crisis oncogene (oncoLBC, Seq. ID No. 2), is used, a simple nucleic acid amplification and detection scheme are most preferred methods of measuring the modulation of the gene. In such a case, PCR, NASBA, rolling circle, LCR, and other amplification schemes known to skilled artisans can be used with PCR being most preferred. Where the portfolios include a large number of genes or it is desirable to measure the expression of numerous other genes then it is preferred to assess the expression patterns based on intensity measurements of micro-arrays as described above.

In similar fashion, gene expression profile analysis can be conducted to monitor treatment response. In one aspect of this method, gene expression analysis as described above is conducted on a patient treated with an FTI at various periods throughout the course of treatment. If the gene expression patterns are consistent with a responder then the patient's therapy is continued. If it is not, then the patient's therapy is altered as with additional therapeutics such as tyrosine kinase inhibitor, changes to the dosage, or elimination of FTI treatment. Such analysis permits intervention and therapy adjustment prior to detectable clinical indicia or in the face of otherwise ambiguous clinical indicia.

With respect to the molecular markers of the invention, a number of other formats and approaches are available for diagnostic use. Methylation of genomic regions can affect gene expression levels. For example, hypermethylation of gene promoter regions can constitutively down-regulate gene expression whereas hypomethylation can lead to an increase in steady-state mRNA levels. As such, detection of methylated regions associated to genes predictive of drug response can be used as an alternative method for diagnosing gene expression levels. Such methods are known to those skilled in the art. Alternatively, single nucleotide polymorphisms (SNPs) that are present in promoter regions can also affect transcriptional activity of a gene. Therefore, detection of these SNPs by methods known to those skilled in the art can also be used as a diagnostic for detecting genes that are differentially expressed between responders and non-responders.

The distinction between responder and non-responder can also be advantageously made with the additional assay of the proportion of bone marrow leukemic blasts present prior to treatment and/or the presence of cell surface antigens such as CD33 and/or CD34. Low expression of CD33 and CD34 surface antigens indicates an increased likelihood of response to FTI treatment. This is most conveniently measured as the percent of cells in a sample that express such antigens with responders having about 60% or less of such cells expressing CD33 and about 15% or less expressing CD34. A percentage of such cells exceeding 60% expressing CD33 or 15% CD34 antigens indicates that the patient is likely a non-responder to FTI treatment. Further, a sample taken as described above in which the percentage of cells that are blast cells is less than about 60% is likely to respond to FTI treatment while those with blast cell counts that exceed this percentage is not. Determinations of percent of CD33+, CD34+, and blast cell count are conducted according to any of the well known methods and are most efficiently conducted using standard pathological tests and preparations conducted in most clinical laboratories.

Articles of this invention are representations of the gene expression profiles useful for treating, diagnosing, prognosticating, staging, and otherwise assessing diseases. Preferably they are reduced to a medium that can be automatically read such as computer readable media (magnetic, optical, and the like). The articles can also include instructions for assessing the gene expression profiles in such media. For example, the articles may comprise a CD ROM having computer instructions for comparing gene expression profiles of the portfolios of genes described above. The articles may also have gene expression profiles digitally recorded therein so that they may be compared with gene expression data from patient samples. Alternatively, the profiles can be recorded in different representational format. Clustering algorithms such as those incorporated in "DISCOVERY" and "INFER" software from Partek, Inc. mentioned above can best assist in the visualization of such data.

Additional articles according to the invention are kits for conducting the assays described above. Each such kit would preferably include instructions in human or machine readable form as well as the reagents typical for the type of assay described. These can include, for example, nucleic acid arrays (e.g. cDNA or oligonucleotide arrays), as described above, configured to discern the gene expression profiles of the invention. They can also contain reagents used to conduct nucleic acid amplification and detection including, for example, reverse transcriptase, reverse transcriptase primer, a corresponding PCR primer set, a thermostable DNA polymerase, such as Taq polymerase, and a suitable detection reagent(s), such as, without limitation, a scorpion probe, a probe for a fluorescent 5'nuclease assay, a molecular beacon probe, a single dye primer or a fluorescent dye specific to double-stranded DNA, such as ethidium bromide. Kits for detecting surface antigens contain staining materials or are antibody based cased including components such as buffer, anti-antigenic antibody, detection enzyme and substrate such as Horse Radish Peroxidase or biotin-avidin based reagents. Kit components for detecting blast cells generally include reagents for conducting flow cytometry, blast cell adhesion assays, and other commonly practiced blast cell assays.

As described in the pending application of the inventor entitled, METHODS FOR ASSESSING AND TREATING LEUKEMIA, and filed October 30, 2002 (Serial Number 10/283975), in addition to the FTIs that are preferred, the preferred drugs of this invention are those that modulate the MAPK/ERK signaling pathways, TGFβ, WNT or apoptotic pathways. These include, without limitation, tyrosine kinase inhibitors, MEK kinase inhibitors, P13K kinase inhibitors, MAP kinase inhibitors, apoptosis modulators and

combinations thereof. Exemplary drugs that are most preferred among these are the "GLEEVEC" tyrosine kinase inhibitor of Novartis, U-0126 MAP kinase inhibitor, PD-098059 MAP kinase inhibitor, SB-203580 MAP kinase inhibitor, and antisense, ribozyme, and DNAzyme, Bcl-XL, and anti-apoptotics. Examples of other useful drugs include, without limitation, the calanolides of US Patent 6,306,897; the substituted bicyclics of US Patent 6,284,764; the indolines of US Patent 6,133,305; and the antisense oligonucleotides of US Patent 6,271,210.

The FTI may also be used in combination with other conventional anti-cancer agents for example selected from platinum coordination compounds for example cisplatin or carboplatin, taxane compounds for example paclitaxel or docetaxel, camptothecin compounds for example irinotecan or topotecan, anti-tumor vinca alkaloids for example vinblastine, vincristine or vinorelbine, anti-tumor nucleoside derivatives for example 5-fluorouracil, gemcitabine or capecitabine, nitrogen mustard or nitrosourea alkylating agents for example cyclophosphamide, chlorambucil, carmustine or lomustine, anti-tumor anthracycline derivatives for example daunorubicin, doxorubicin or idarubicin; HER2 antibodies for example trastzumab; and anti-tumor podophyllotoxin derivatives for example etoposide or teniposide; and antiestrogen agents including estrogen receptor antagonists or selective estrogen receptor modulators preferably tamoxifen, or alternatively toremifene, droloxifene, faslodex and raloxifene, or aromatase inhibitors such as exemestane, anastrozole, letrazole and vorozole.

The FTI can administered to a patient as described above in conjunction with irradiation; such treatment is may be especially beneficial as farnesyl transferase inhibitors can act as radiosensitisers for example as described in International Patent Specification WO 00/01411, enhancing the therapeutic effect of such irradiation. Irradiation means ionizing radiation and in particular gamma radiation, especially that emitted by linear accelerators or by radionuclides that are in common use today. The irradiation of the tumor by radionuclides can be external or internal.

Preferably, the administration of the farnesyl transferase inhibitor commences up to one month, in particular up to 10 days or a week, before the irradiation of the tumor. Additionally, it is advantageous to fractionate the irradiation of the tumor and maintain the administration of the farnesyl transferase inhibitor in the interval between the first and the last irradiation session. The amount of farnesyl protein transferase inhibitor, the dose of irradiation and the intermittence of the irradiation doses will depend on a series of parameters such as the type of tumor, its location, the patients' reaction to chemo- or

radiotherapy and ultimately is for the physician and radiologists to determine in each individual case. Thus, cancer therapy according to the inventive method also includes, for a host harboring a tumor, administering a radiation-sensitizing effective amount of a farnesyl protein transferase inhibitor according to the invention before, during or after administering radiation to said host in the proximity to the tumor.

As noted, the drugs of the instant invention can be therapeutics directed to gene therapy or antisense therapy or RNA interference. Oligonucleotides with sequences complementary to a mRNA sequence can be introduced into cells to block the translation of the mRNA, thus blocking the function of the gene encoding the mRNA. The use of oligonucleotides to block gene expression is described, for example, in, Strachan and Read, Human Molecular Genetics, 1996, incorporated herein by reference.

These antisense molecules may be DNA, stable derivatives of DNA such as phosphorothioates or methylphosphonates, RNA, stable derivatives of RNA such as 2'-*O*-alkylRNA, or other antisense oligonucleotide mimetics. Antisense molecules may be introduced into cells by microinjection, liposome encapsulation or by expression from vectors harboring the antisense sequence.

In the case of gene therapy, the gene of interest can be ligated into viral vectors that mediate transfer of the therapeutic DNA by infection of recipient host cells. Suitable viral vectors include retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, polio virus and the like. Alternatively, therapeutic DNA can be transferred into cells for gene therapy by non-viral techniques including receptor-mediated targeted DNA transfer using ligand-DNA conjugates or adenovirus-ligand-DNA conjugates, lipofection membrane fusion or direct microinjection. These procedures and variations thereof are suitable for *ex vivo* as well as *in vivo* gene therapy. Protocols for molecular methodology of gene therapy suitable for use with the gene is described in Gene Therapy Protocols, edited by Paul D. Robbins, Human press, Totawa NJ, 1996.

The FTI may be used to treat various types of cancer including lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), prostate cancer including the advanced disease, hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)),

thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumor of the skin (e.g. keratoacanthomas), breast carcinoma (e.g. advanced breast cancer), kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

Pharmaceutically useful compositions comprising the drugs of this invention may be formulated according to known methods such as by the admixture of a pharmaceutically acceptable carrier. Examples of such carriers and methods of formulation may be found in Remington's Pharmaceutical Sciences. To form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain an effective amount of the drug. The effective amount of the drug may vary according to a variety of factors such as the individual's condition, weight, sex and age. Other factors include the mode of administration. The pharmaceutical compositions may be provided to the individual by a variety of routes such as subcutaneous, topical, oral and intramuscular.

The drugs of this invention include chemical derivatives of the base molecules of the drug. That is, they may contain additional chemical moieties that are not normally a part of the base molecule. Such moieties may improve the solubility, half-life, absorption, etc. of the base molecule. Alternatively the moieties may attenuate undesirable side effects of the base molecule or decrease the toxicity of the base molecule. Examples of such moieties are described in a variety of texts, such as Remington's Pharmaceutical Sciences.

Compounds identified according to the methods disclosed herein may be used alone at appropriate dosages defined by routine testing in order to obtain optimal inhibition or activity while minimizing any potential toxicity. In addition, co-administration or sequential administration of other agents may be desirable.

The drugs of this invention can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for administration. For example, the drugs can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to

those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a modulating agent.

The daily dosage of the products may be varied over a wide range from 0.01 to 1,000 mg per patient, per day. For oral administration, the compositions are preferably provided in the form of scored or unscored tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0001 mg/kg to about 100 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 10 mg/kg of body weight per day. The dosages are adjusted when combined to achieve desired effects. On the other hand, dosages of these various agents may be independently optimized and combined to achieve a synergistic result wherein the pathology is reduced more than it would be if either agent were used alone.

Advantageously, compounds or modulators used in the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds or modulators for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concurrently, or they each can be administered at separately staggered times.

The dosage regimen utilizing the compounds or modulators in the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular drug employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentrations of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

The drugs of this invention can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include, without limitation, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

For liquid forms the active drug component can be combined in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. Other dispersing agents that may be employed include glycerin and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations, which generally contain suitable preservatives, are employed when intravenous administration is desired.

The drugs in the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Drugs in the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The drugs in the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropylmethacryl-amidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyl-eneoxidepolylysine substituted with palmitoyl residues. Furthermore, the drugs in the present invention may be coupled to a class of biodegradable polymers

useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydro-pyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

For oral administration, the drugs may be administered in capsule, tablet, or bolus form or alternatively they can be mixed with feed. The capsules, tablets, and boluses are comprised of the active ingredient in combination with an appropriate carrier vehicle such as starch, talc, magnesium stearate, or di-calcium phosphate. These unit dosage forms are prepared by intimately mixing the active ingredient with suitable finely-powdered inert ingredients including diluents, fillers, disintegrating agents, and/or binders such that a uniform mixture is obtained. An inert ingredient is one that will not react with the drugs and which is non-toxic to the animal being treated. Suitable inert ingredients include starch, lactose, talc, magnesium stearate, vegetable gums and oils, and the like. These formulations may contain a widely variable amount of the active and inactive ingredients depending on numerous factors such as the size and type of the animal species to be treated and the type and severity of the infection. The active ingredient may also be administered by simply mixing the compound with the feedstuff or by applying the compound to the surface of the foodstuff.

The compounds or modulators may alternatively be administered parenterally via injection of a formulation consisting of the active ingredient dissolved in an inert liquid carrier. Injection may be either intramuscular, intraruminal, intratracheal, or subcutaneous. The injectable formulation consists of the active ingredient mixed with an appropriate inert liquid carrier. Acceptable liquid carriers include the vegetable oils such as peanut oil, cotton seed oil, sesame oil and the like as well as organic solvents such as solketal, glycerol formal and the like. As an alternative, aqueous parenteral formulations may also be used. The vegetable oils are the preferred liquid carriers. The formulations are prepared by dissolving or suspending the active ingredient in the liquid carrier such that the final formulation contains from 0.005 to 10% by weight of the active ingredient.

The invention is further illustrated by the following nonlimiting examples.

Examples

In the nonprophetic examples, AML patients were administered 600 mg of(R)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone) (referred to as Zarnestra) at a starting oral dose of 600 mg b.i.d. for the first 21 days of each 28 day cycle in AML. Subjects were enrolled into two cohorts, those with relapsed AML and those with refractory AML. A total of 257 patients (135 relapsed and 117 refractory) were treated.

Response to Zarnestra treatment was defined as patients who had an objective response (CR, CRp, or PR) as shown in Table 2, or patients who demonstrated stable disease and anti-leukemic activity (decrease of >50% of leukemic blast cells) as determined by either central review or the clinical site. Anti-leukemic activity is defined as any bone marrow blast count less than 5% or a reduction in bone marrow blasts by at least half.

Table 2

Response	Criteria
Complete Response (CR)	Neutrophil count > 1,000/μL **AND** < 5% blasts in bone marrow aspirate **AND** platelet count > 100,000/μL and no extramedullary disease.
Complete Response-incomplete platelet recovery (CRp)	Meets all the criteria for CR except recovery up to 100,000/μL platelets, but have sufficient bone marrow recovery to be platelet transfusion independent.
Partial Response (PR)	At least a 50% decrease in bone marrow blasts **AND** partial recovery of neutrophil count (> 500/μL) **AND** platelet count > 50,000/μL.
Stable Disease (SD)	Any response not meeting CR, CRp, PR or PD Criteria **AND** absence of clinical deterioration.
Progressive Disease (PD)	> 50% increase in bone marrow blasts OR circulating blasts OR interval development of circulating blasts that persists on at least two consecutive occasions OR interval development of extramedullary disease.

Example 1. Microarray Analysis

Bone marrow samples were collected from consenting patients both before and after treatment with Zarnestra FTI (active ingredient, (R)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone), diluted with PBS and centrifuged with Ficoll-diatrizoate (1.077g/ml). White blood cells were washed twice with PBS, resuspended in FBS with 10% DMSO and immediately frozen at -80°C. Samples were thawed at 37°C and 10X volume of RPMI with 20% FBS was added drop-wise over a period of 5 min. Cells were centrifuged at 500g for 10 min and resuspended in 10 ml PBS with 2 mM EDTA and 0.5% BSA. Samples were then passed through a 70 μM filter (Becton Dickinson Labware, Franklin lakes, NJ) to remove any cell clumps. Cell viability was determined by trypan blue dye exclusion assay. The mean viability of the bone marrow samples upon thawing was 35% (range 0-96%). Due to the relatively low number of viable cells present the samples were not further enriched for myeloid cells. Approximately $2x10^5$ cells were double labeled with CD33-FITC and CD34-PE antibodies (Becton Dickinson Biosciences Pharmingen, San Diego, CA) and FACS analysis was performed.

Total RNA was extracted from cell samples using the RNeasy Kit (Qiagen, Santa Clarita, CA). Synthesis of cDNA and cRNA were performed according to Affymetrix (Santa Clara, CA) protocols. Two rounds of linear amplification was performed since the RNA yield for several samples was less than 1 μg. For hybridization, 11 μg of cRNA were fragmented randomly by incubation at 94°C for 35 min in 40 mM Tris-acetate, pH 8.1, 100 mM potassium acetate, and 30 mM magnesium acetate. Fragmented cRNA was hybridized to U133A arrays at 45°C for 16 h in a rotisserie oven set at 60 rpm. Following hybridization, arrays were washed (with 6x SSPE and 0.5x SSPE containing Triton X-100 (0.005%)), and stained with streptavidin-phycoerythrin (SAPE; Molecular Probes, Eugene, OR). Quantification of bound labeled probe was conducted using the Agilent G2500A GeneArray scanner (Agilent Technologies, Palo Alto, CA).

The total fluorescence intensity for each array was scaled to the uniform value of 600. Chip performance was quantitated by calculating a signal to noise ratio (raw average signal/noise). Chips were removed from further analysis if their signal-to-noise ratio was less than 5. Genes were only included in further analysis if they were called "present" in at least 10% of the chips. Approximately 12,000 Affymetrix probe sets remained following

this cut-off. The quality of the gene expression data was further controlled by identifying outliers based on principal components analysis and by analyzing the normal distributions of the gene intensities.

Chi-squared tests and Student's t-test were used to identify correlations between patient response and patient co-variates, mutational status, CD33 and CD34 antigen expression, leukemic blast counts, and gene expression. To identify genes that could predict response with high sensitivity, a percentile analysis was employed. For example, genes that were up- or down-regulated in all responders compared to at least 40% of non-responders were identified. Genes that did not reveal significant p-values ($P < 0.05$) based on a two-tailed Student's t-test (unequal variance) were removed. The predictive value of the top gene(s) was analyzed by a leave-one-out cross validation method. Here, one sample was removed from the data set and the marker was reselected from the 12,000 genes. The predictive value of this gene was then tested on the left-out sample using a linear discriminant analysis. Sensitivity was calculated as the number of true positives divided by the sum of true positives plus false negatives. Specificity was calculated as the number of true negatives divided by the sum of true negatives and false positives. Positive predictive value was calculated as the number of true positives divided by the sum of true positives and false positives. Negative predictive value was calculated as the number of true negatives divided by the sum of false negatives and true negatives.

Univariate cox proportional hazard models were used to assess the association of each parameter (genes or blast counts) with patient survival outcome. The coefficient estimate of each parameter from the cox model measures the strength of such association. When more than one gene was used a multivariate hazard model was employed. The classifier that distinguishes responders from non-responders was defined as:

$$b1*x1 + b2*x2 + b3*x3 + ...$$

where b1, b2, b3 are coefficient estimates from the cox model, and x2, x2, x3 are standardized parameter values (blast counts or $\log_{10}$ of gene expression values).

Receiver operator curves (ROC) were used to choose appropriate thresholds for each classifier, requiring a sensitivity of at least 90%. The ROC diagnostic calculates the sensitivity and specificity for each parameter. In addition, gene markers were first ranked for their ability to stratify good outcome from poor outcome using a training set of 29

randomly chosen samples. The predictive value of each gene was then tested on the remaining 29 samples. This allowed for the identification of genes with the most robust predictive values.

Example 2: Leukemic Cell Antigen Expression

Leukemic blast cells are known to express the surface antigens CD33 and CD34. 95% and 55% of patient bone marrow leukemic cells were positive for CD33 and CD34, respectively. The mean percentage of cells expressing the antigens in each sample was 13% for CD34 and 43% for CD33. Chi-squared analysis was performed to investigate the correlation between the level of antigen expression and patient outcome. Cutoffs of 15% and 60% were chosen for CD34 and CD33 levels, respectively. Low expression (positive in less than about 15% of the cell population for CD34 and positive in less than about 60% of the cell population for CD33) of CD33 and CD34 correlated with patient response to Zarnestra™ ($p=0.137$, $p=0.052$, respectively). High expression of both antigens (positive in more than about 15% of the cell population for CD34 and positive in less than about 60% of the cell population for CD33) was also positively correlated with high blast counts. A Kaplan Meier analysis also indicated that high CD33 expression correlated with poor overall survival (Fig. 1).

Example 3: Leukemic Blast Count Analysis

The analysis of CD33 and CD34 antigen expression suggested that the level of leukemic blast cells correlated with patient response. The average value of the site and DCL blast count measurements were calculated and a Student's t-test was performed to investigate if blast counts correlated with patient response in the AML patients. From a total of 199 evaluable patients, 24 of which had a CR, CRp, PR, or SD, the percentage of blasts correlated significantly with patient outcome ($p = 0.0006$). Responders had a lower number of blasts (mean 34%) than those with progressive disease (mean 51%). Only one of the 24 total responders (defined as having SD) had a blast count higher than 60%. Chi-squared analysis for all evaluable patients also found a significant correlation between high blast counts and resistance to treatment ($\chi^2 = 9.53$).

A Kaplan-Meier analysis found that those patients with a low level of blast counts (<60%) had a significantly better overall survival than those with high blast counts (Fig. 2). These

analyses indicate that patients with blast counts higher than approximately 60% will be unlikely to respond to Zarnestra™.

Example 4: Identification of genes that are differentially expressed between responders and non-responders

Bone marrow samples were obtained for gene expression analysis from 80 patients prior to drug treatment. Of the 80 base-line samples, 14 were removed from the analysis since they came from non-evaluable patients. Samples were enriched for myeloid cells, processed for messenger RNA (the molecules that encode for gene-specific proteins), and hybridized to the Affymetrix U133A gene chip. 58 of the 66 samples passed additional quality control measures following hybridization to the U133A chip. The gene expression data was integrated with the clinical information and retrospective analyses were performed to identify genes that could stratify responders from non-responders with a high level of sensitivity. Several gene markers were identified that are useful in predicting response to Zarnestra™ (Table 3). In the case of the lymphoid blast crisis oncogene (oncoLBC) the predictive value of this gene was calculated for the dataset using a leave-one-out cross validation (Table 3). The oncoLBC gene expression levels were able to capture all of the clinically identified responders while removing over half of the non-responders.

Table 3: Genes Differentially Expressed in Responders versus Non-Responders

Title	Gene Symbol	ttest	Ratio*	RefSeq	Seq. ID No.
aryl hydrocarbon receptor	AHR	2.55E-06	0.39	NM_001621	1
A kinase (PRKA) anchor protein 13 (oncoLBC)	AKAP13	6.13E-05	0.51	NM_006738	2
hypothetical protein DKFZp667G2110	DKFZp667G2110	6.93E-05	0.71	NM_153605	3
iduronate 2-sulfatase (Hunter syndrome)	IDS	0.00024	0.36	NM_000202	4
opsin 3 (encephalopsin, panopsin)	OPN3	0.000643	0.54	NM_014322	5
G protein-coupled receptor 105	GPR10 5	0.000876	0.34	NM_014879	6
tumor endothelial marker 6	TEM6	0.001031	0.62	NM_022748	7
tumor necrosis factor (ligand) superfamily, member 13	TNFSF13	0.001042	0.59	NM_003808	8
Supervillin	SVIL	0.001457	0.62	NM_003174	9
interleukin 3 receptor, alpha (low affinity)	IL3RA	0.001984	0.40	NM_002183	10
KIAA0680 gene product	KIAA0680	0.002616	0.57	NM_014721	11
FGF receptor activating protein 1	FRAG1	0.00299	1.24	NM_014489	12
cDNA DKFZp566B213	DKFZp566B213	0.012011	1.50		13
KIAA1036 protein	KIAA1036	0.012621	0.72	NM_014909	14
BTG family, member 3	BTG3	0.016594	1.48	NM_006806	15
mitogen-activated protein kinase 8 interacting protein 3	MAPK8IP3	0.018174	1.39	NM_015133	16
ras homolog gene family, member H	ARHH	0.027219	1.64	NM_004310	17
neuronal pentraxin II	NPTX2	0.033468	0.14	NM_002523	18

*Ratios indicate fold-change in responders compared to non-responders

Table 4: Leave-one-out cross validation using oncoLBC as a marker of response.

		Gold Std	
		Resp .	Non -resp .
Test	Predict response	14	20
	Predict non-resp.	0	24
	Total	14	44

Sensitivity	= 100%
Specificity	= 55%
Positive predictive value	= 41%
Negative predictive value	= 100%

A survival analysis showed that patients who were classified as responders based on oncoLBC expression (Fig 3A, p = 0.00841) significantly outperformed patient classification using the clinical data (Fig 3B, p = 0.0827). This was due to the oncoLBC marker identifying a subset of non-responders with an increased overall survival. Based on the Cox hazard model, combining the oncoLBC and a second gene marker, the aryl hydrocarbon receptor (AHR), increased the specificity and positive predictive value to 75% and 56%, respectively (Fig. 3C). These results indicated that using either the oncoLBC alone, or in combination with the AHR gene presents an effective array for predicting response to Zarnestra™ treatment.

A leave-one-out cross validation using the oncoLBC and aryl hydrocarbon receptor (AHR) as markers was also performed. When using the cut-off to identify the highest sensitivity and best specificity the PPV and sensitivity remained the same. Results of leave-one out cross validation of other gene combinations are shown in Table 5. This illustrates that combinations of markers can improve the predictive value of this method.

Table 5

markers	sensitivity	specificity	PPV	NPV	prior probability*
LBC, AHR, katanin, IDS, DKFZp667G2110	100	73	54	100	0.32
LBC, katanin, DKFZp667G2110	100	70	52	100	0.47
LBC, AHR, DKFZp667G2110	100	66	48	100	0.23
LBC, AHR, IDS, DKFZp667G2110	100	66	48	100	0.28
LBC, AHR, IDS	100	61	45	100	0.2
LBC, katanin	100	61	45	100	0.41
LBC, DKFZp667G2110	100	57	42	100	0.2
katanin	100	56	42	100	0.49
LBC	100	55	41	100	0.4
LBC, AHR	100	55	41	100	0.19
LBC, IDS, katanin	100	55	41	100	0.38
LBC, AHR, katanin	100	52	40	100	0.18
LBC, IDS	100	50	39	100	0.38
IDS	100	50	39	100	0.42
DKFZp667G2110	100	45	37	100	0.39
AHR	100	45	37	100	0.17
AHR, katanin	100	43	36	100	0.17

Furthermore, stratification of patients using the LBC and AHR classifier showed a similar difference in median survival time between the two patient populations compared with using the oncoLBC gene or the clinical response definitions (Fig. 4C). These results indicated that using either the oncoLBC alone, or in combination with the AHR gene could be used as effective biomarkers for predicting response to ZARNESTRA in the current dataset.

A Cox hazard model was used to analyze other combinations of markers in stratifying poor survivors from good survivors (Table 6). Here, data from 51 patients was used since only this number of patient samples had CD33 and CD34 antigen levels measured. A sensitivity of greater than 90% was used in determining the appropriate cut-offs for the markers. The use of multiple markers can improve the difference in median survival times of the 2 survival groups.

Table. 6

Markers*	P-value	Median survival poor (days)	Median survival good (days)	Delta (days)	Sens (%)	Spec (%)
LBC	0.0098	64	177	113	91	65
CD33	0.0029	40	105	65	91	23
CD34	0.643	64	103	39	91	35
AHR	0.12	59	106	47	91	53
% blasts #	0.1241	60	103	43	91	38
LBC + % Blasts	0.00223	59	154	95	93	61
LBC + AHR	0.0111	71	171	100	91	73
LBC + CD33	0.00266	71	182	111	91	73
LBC + CD34	0.00038	64	192	128	91	80
LBC + AHR + CD34	0.003	71	213	142	91	83
LBC + AHR + CD33	0.00062	64	192	128	91	80

Example 5: Antibodies (Prophetic)

An lbc oncogene-derived peptide is synthesized, coupled to keyhole limpet hemocyanin, and used to immunize rabbits for production of polyclonal antibodies. The sera are tested for reactivity against the corresponding peptide with ELISA, and the positive batches are affinity-purified. The purified antibody specifically detects the peptide that has the epitope in tissue sections. This is verified by complete abolishment of the signal if the corresponding peptide is added simultaneously with the antibody. In addition to this polyclonal antibody, which works well in immunohistochemistry, monoclonal antibodies able to detect the protein in its natural fold are produced. To produce monoclonal antibodies, a purified antigen, produced in mammalian cells to ensure natural fold and posttranslational modifications, is generated. The antigen, lbc onco protein-IgG constant part fusion protein, is expressed in mouse myeloma cells, and the protein is purified using the Fc part as bait. This purified antigen is recognized in Western blot by the C-terminal polyclonal antibody. The antigen is used to generate mouse monoclonal antibodies against lbc peptides by selecting out of the positive clones those that produce antibodies that react against lbc peptide instead of the IgG constant part.

Kits for the clinical identification of lbc oncogene can be readily fashioned employing these and similar antibodies. Such kits would include antibodies directed to lbc peptide identification (and hence, lbc oncogene), appropriate indicator reagents (e.g.,

enzymes, labels, and the like), and (optionally) other reagents useful in the clinical application of such a kit such as dilution buffers, stabilizers, and other materials typically used in such assays.

Example 6: In situ hybridization (Prophetic)

Formalin fixed paraffin embedded tissue samples are cut into 5-7 μm thick sections, mounted on silane coated glass slides, and incubated at 37°C over night and at 65°C for 30 min before deparaffinating twice for 10 min in xylene. Thereafter the samples are rehydrated through a graded series of ethanol solutions (100 to 70%), and rinsed twice for 5 min in phosphate buffered saline (PBS pH 7.0), treated twice for 5 min with 0.1 mol/L glysine in PBS, permeabilized for 15 min with 0.3% Triton X-100 in PBS. The sections are treated with proteinase K (Finnzymes, Helsinki, Finland) treatment (μg/ml, in TE buffer; 100 mmol/L Tris-HCl, 50 mmol/L EDTA, pH 8.0) at 37°C for 30 min, postfixed in 3% paraformaldehyde in PBS at 4°C for 5 min and rinsed twice in PBS. Positive charges are blocked by soaking the slides in 0.25% (v/v) acetic anhydride, 100 mmol/L triethanolamine, pH 8.0, twice for 5 min. The slides are equilibrated in 4xSSC, 50% (v/v) deionized formamide at 37°C for 10 min.

Probes are prepared by ligating a PCR-amplified 0.4 kb lbc oncogene cDNA insert into the pCR-II vector using a TA cloning kit (Invitrogen, San Diego CA, USA). The templates for lbc oncogene antisense or sense RNA probes are generated by linearizing the appropriate vector construct (in 3' to 5' direction or 5' to 3' direction, respectively). An RNA Labeling Kit (Boehringer-Mannheim) is used to generate digoxygenin labeled RNA probes by in vitro transcription. The hybridization is performed overnight at 45°C using a hybridization mixture containing 1xDenhart's solution (0.2g/L Ficoll Type 400, Pharmacia), 0.2g/L polyvinylpyrrolidone, 0.2g/L bovine serum albumin (fraction V; Sigma), 40% formamide, 10% dextran sulfate, 4xSSC, 10 mmol/L dithiothreitol, 1mg/mL yeast tRNA, 1 mg/mL herring sperm DNA and 300 ng/mL digoxygenin-labeled RNA probe. After hybridization, the tissue sections are washed at 37°C twice for 5 min in 2xSSC and once for 15 min in 60% formamide, 0.2xSSC, followed by two 5 minute rinses in 2xSSC at room temperature and two 10 minute washes in 100 mmol/L Tris-HCl, pH 8.0, 150 mmol/L NaCl. The signal detection is carried out using 1:250 alkaline phosphatase-conjugated sheep antidigoxygenin fab fragments (Boehringer Mannheim). The signal is

visualized by incubating the sections with NBT/BCIP Stock Solution (Boehringer Mannheim) for 1.5 hours.

Lbc oncogene-positive cells seen in the tumorigenic cells of cancer patients indicates that response to an FTI is unlikely.

Example 7: Immunohistochemistry (Prophetic)

An affinity-purified polyclonal antibody against the C-terminal peptide of lbc oncogene is used for the immunohistochemical detection and localization of lbc oncogene. Four μm sections from formalin-fixed and paraffin embedded normal and tumor tissue is mounted on 3-aminopropyl-triethoxy-silane (APES, Sigma, St. Louis, MO, U.S.A) coated slides. The sections are deparaffinized and rehydrated in graded concentrations of ethanol and treated with methanolic peroxide (0.5% hydrogen peroxide in absolute methanol) for 30 minutes at room temperature to block the endogenous peroxidase activity. Antigen retrieval is done in a microwave oven twice for 5 minutes (650W). An Elite ABC Kit (Vectastain, Vector Laboratories, Burlingame, CA, U.S.A) is used for immunoperoxidase staining. The lbc peptide antibody is used at an optimal dilution of 1:2000. Both the biotinylated second antibody and the peroxidase-labeled avidin-biotin complex are incubated on the sections for 30 minutes. The dilutions are made in PBS (pH 7.2), and all incubations are carried out in a moist chamber at room temperature. Between the different staining steps the slides are rinsed three times with PBS. The peroxidase staining is visualized with a 3-amino-9-ethylcarbazole (Sigma) solution (0.2 mg/ml in 0.05 M acetate buffer containing 0.03% hydrogen peroxide, pH 5.0) at room temperature for 15 minutes. Finally, the sections are lightly counterstained with Mayer's haematoxylin and mounted with aqueous mounting media (Aquamount, BDH). In control experiments the primary antibodies are replaced with the IgG fraction of normal rabbit serum or the primary antibody was preabsorbed with the lbc peptide. These stainings indicate the presence of the lbc oncogene in a subset of cells.

Example 8: Enzyme Immunoassay (Prophetic)

Immunoassays are prepared for the lbc protein or characteristic peptides related to the lbc oncogene. Antigen standards comprising a digest of colon tumor specimens (shown to contain the antigen by immunoperoxidase staining) are used. Human white blood cells from AML patients. The specimens are pooled and homogenized in 10 volumes of 10 mM Tris buffer, pH 7.4, containing 0.2% (w/v) sodium deoxycholate at 4C.

The homogenate is quickly brought to 37 C and the following reagents (final concentration) are added while stirring: 1 mM cysteine (Sigma), 1 mM EDTA (Sigma), and papain (0.8 unit/ml) (Boehringer-Mannheim, Indianapolis, Ind.). After 5 minutes, digestion is stopped by the addition of 5 mM iodoacetamide (Sigma). The homogenate is centrifuged at 100,000Xg for 1 hour at 4C, then extensively dialyzed against 10 mM Tris/0.9% NaCl solution buffer, pH 7.4, containing phenylmethysulfonyl fluoride and aminocaproic acid, each at 10 mM. The homogenate is frozen in small aliquots at a concentration of 0.5 mg of protein/mi.

The dose response curve that will be generated for the immunoassay procedure measuring lbc protein or peptides demonstrates linearity between antigen input of 100ng to 100µg/ml. For serum analysis, the range is 1ng to 1000ng/ml, since these samples are diluted 10-fold prior to assay.

Solid-phase preparations of the antibodies described the examples above are prepared using CNBr-activated Sepharose (Pharmacia). Microtiter plates (Nunc I Immunoplates; Grand Island Biological Co., Grand Island, N.Y.) are coated with the antibodies (200 µl /well) in 50 mM carbonate-bicarbonate buffer, pH 9.6, for 18 hours at 4°C. After removal of the antibody solution, residual protein binding sites on the plastic are blocked by the addition of 200 µl of assay buffer [PBS containing 1% (v/v) rabbit *serum* and 1% (w/v) bovine albumin]. After 1 hour of incubation at room temperature, the coated plates are used immediately for the assay procedure.

To perform the assay, 200 µl samples, diluted in assay buffer, are applied for 1-5 hours at 37°C. After 3 washes using assay buffer, 200 µl of the antibody covalently conjugated to horseradish peroxidase (Sigma, Type VI) is applied to each well for 1.5 hours at 37°C. The conjugate is diluted to a concentration of 0.5 µg of immunoglobulin per ml of PBS containing 10% (v/v) murine serum. Following a wash procedure as above, 200 µl of substrate per well are applied for 0.5 hours at room temperature. Substrate solution contains 0.4 mg of o-phenylenediamine per ml of pH 5.0 citrate buffer and 0.003% hydrogen peroxide. The reaction is stopped by addition of 50 µl of 2N sulfuric acid, and absorbance is monitored at 488 nM using an enzyme assay plate reader (Fisher Scientific Co., Pittsburgh, Pa.).

The percentage of bound enzyme conjugate is calculated by the formula:
$(B-B_0)(B_t-B_0)(100)$

where B=absorbance of the sample, B_1 =maximal absorbance, and B_0 =absorbance of the blank. Each assay is performed in triplicate using a standard digest and 26-fold diluted serum samples diluted in assay buffer. Specificity of the immunoassay is examined by substituting various antibody reagents at the solid phase, including an antibody to an unrelated protein and nonimmune rabbit serum. Of the solid phase antibodies only antibody prepared according to the examples above bind antigen at high dilutions.

Levels of serum lbc protein are detected for normal control subjects, patients with benign and malignant hematological disorders.

Sera obtained from apparently healthy individuals exhibits no lbc protein. Only 5% of the samples express serum antigen at the limit of detection or above, and this value is chosen as the cutoff for elevated serum levels. Cancer patients below the cutoff are likely to respond to treatment with an FTI.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form or suggestion that the prior art forms part of the common general knowledge in Australia.

EDITORIAL NOTE

APPLICATION NUMBER 2004202980

The following pages 40 to 102 are attached at the end as the Gene Sequence

The claims defining the invention are as follows:-

1. A method of determining whether a patient will respond to treatment with a farnesyl transferase inhibitor (FTI) by analyzing the presence or expression of the LBC oncogene (SEQ ID NO: 2).

2. The method according to claim 1 further including the analysis of the expression of a gene that is differentially modulated in the presence of an FTI.

3. The method according to claim 2 wherein the analysis is of the expression of more than one gene in addition to the LBC oncogene.

4. The method according to claim 2 wherein the gene is selected from the group consisting of SEQ ID NOs: 1, 3-18 and 29.

5. The method according to claim 4 wherein the gene is SEQ ID NO: 1 or SEQ ID NO: 3.

6. The method according to claim 1 wherein a patient in whom the LBC oncogene is determined to be absent or is not expressed is treated with an FTI.

7. The method according to claim 1 wherein a patient in whom the LBC oncogene is determined to be present or expressed is treated with an agent other than an FTI.

8. The method according to claim 1 further comprising the step of determining whether the patient samples used to determine response to the FTI includes cell surface antigens selected from the group consisting of CD33 and CD34.

9. The method according to claim 8 wherein the presence of cells having said surface antigens is prognostic of response to FTI treatment.

10. The method according to claim 1 further comprising the step of determining the percentage of cells in the patient sample used to determine response to the FTI that includes blast cells.

11. Articles when used in the method according to claim 1, comprising a medium with which gene expression profiles of the patient indicative of the FTI response are determined.

12. The articles according to claim 11, wherein the gene expression profiles are obtained from a group of genes correlating to more than one nucleic acid sequence of Seq. ID. No 1-18.

13. Articles when used in the method according to claim 1, comprising representations of gene expression profiles in the form of computer readable media.

14. Kits when used in the method according to claim 1, comprising reagents used for nucleic acid arrays, including cDNA arrays or oligonucleotide arrays.

15. Kits when used in the method according to claim 1, comprising reagents used for nucleic acid amplification or detection are selected from any one of the group consisting of: reverse transcriptase; reverse transcriptase primer; a PCR primer; a DNA polymerase; a scorpion probe; a fluorescent 5" nuclease assay probe; a molecular beacon probe; a single dye primer; and a fluorescent dye.

16. Kits when used in the method according to claim 1, further including reagents for detecting the expression of genes, selected from the group consisting of SEQ. ID. No's: 1, 3-18 and 29 and their variants.

17. Kits when used in the method according to claim 1, further including reagents for the detection of cell surface antigens are selected from the group consisting of CD33 and CD34.

18. Kits when used in the method according to claim 1, further including reagents for the detection of blast cells.

19. A diagnostic kit when used in the method according to claim 1, comprising molecular markers that distinguish responders from non-responders to FTI treatment.

20. The diagnostic kit according to claim 19, wherein the molecular markers are selected from any one of the group consisting of: lbc oncogene; AHR; DKFZp667G2110; IDS; GPR105; TEM6; TNFSF13; SVIL; KIAA0680; FRAG1; DKFZp566B213; KIAA1036; BTG3; MAPK8IP3; ARHH; and NPTX2.

21. A combination when used in the method according to claim 1, comprising the use of an FTI for the preparation of a pharmaceutical composition in the therapeutic treatment of said patient and an active agent.

22. The combination according to claim 21, wherein the active agent is selected from any one or a combination of: tyrosine kinase inhibitors; MEK kinase inhibitors; PI3K kinase inhibitors; MAP kinase inhibitors; and apoptosis-modulators.

23. A method of determining whether a patient will respond to treatment with a farnesyl transferase inhibitor (FTI) substantially as hereinbefore described.

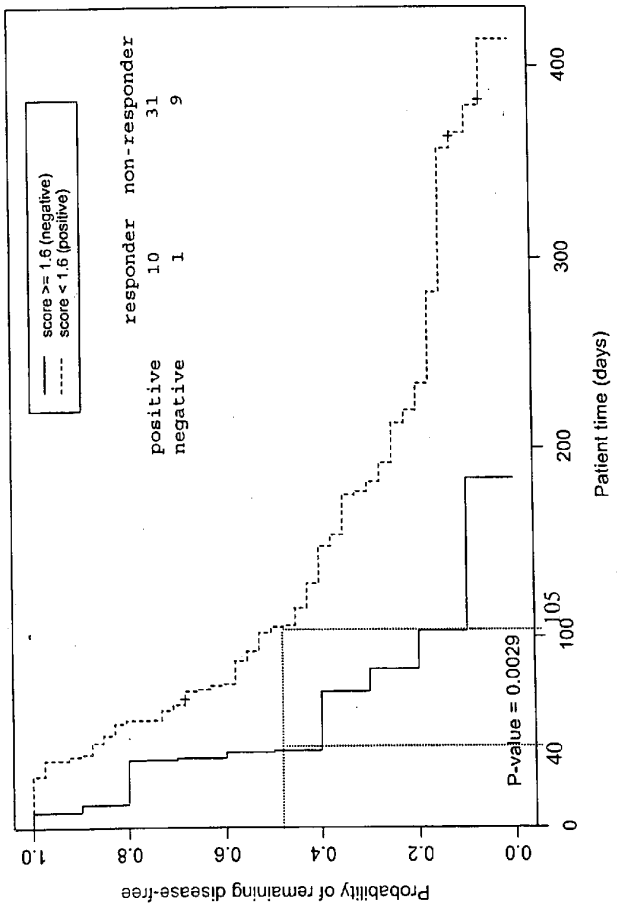
24. A method of determining whether a patient will respond to treatment with a farnesyl transferase inhibitor (FTI) substantially as hereinbefore described with reference to any one of the Examples.

25. The articles according to claim 11, substantially as hereinbefore described with reference to any one of the Examples.

26. The kits according to claim 14, substantially as hereinbefore described with reference to any one of the Examples.

27. The diagnostic kit according to claim 19, substantially as hereinbefore described with reference to any one of the Examples.

28. The combination according to claim 21, substantially as hereinbefore described with reference to any one of the Examples.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score < 1.6 (positive)
responder non-responder
positive 10 31
negative 1 9
P-value = 0.0029
Probability of remaining disease-free
Patient time (days)
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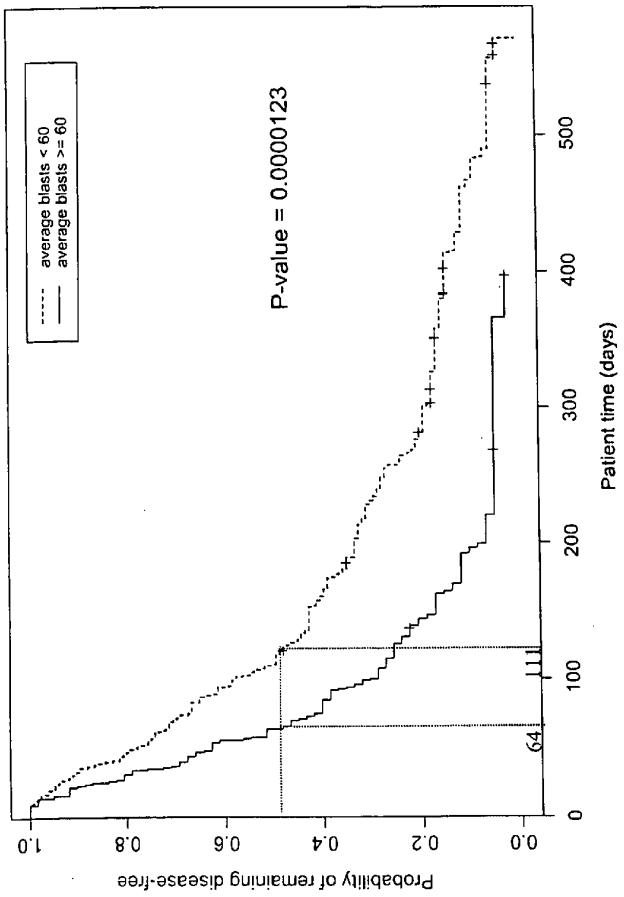
0.4
0.6
0.8
1.0
0
40
100
105
200
300
400

Fig 1.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average blasts >= 60
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Probability of remaining disease-free
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0.2
0.4
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400
500
Patient time (days)
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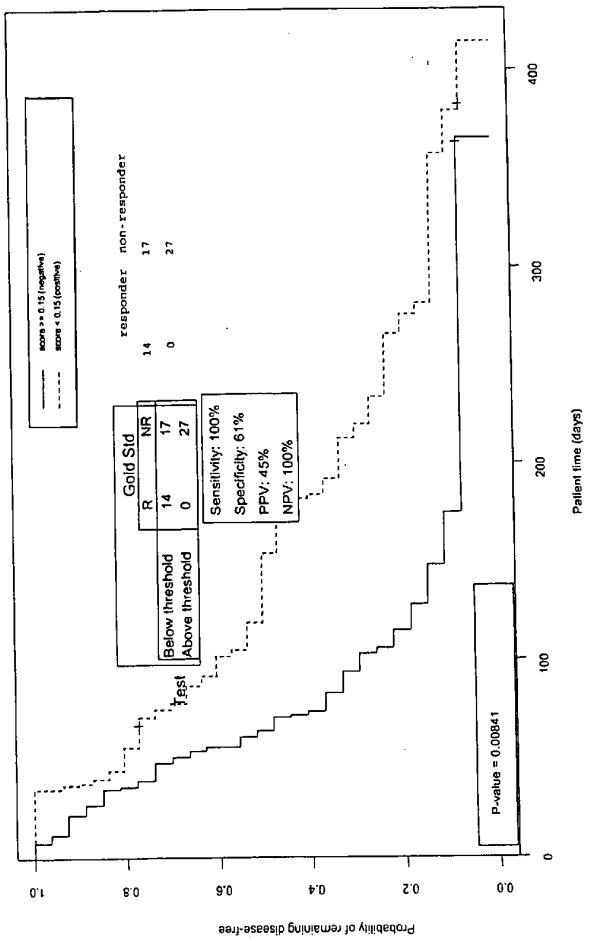
1

Fig 2.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score < 0.15 (positive)
responder non-responder
14 17
0 27
Gold Std
R NR
Below threshold 14 17
Above threshold 0 27
Test
Sensitivity: 100%
Specificity: 61%
PPV: 45%
NPV: 100%
P-value = 0.00841
Probability of remaining disease-free
Patient time (days)
0.0
0.2
0.4
0.6
0.8
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Fig. 3A

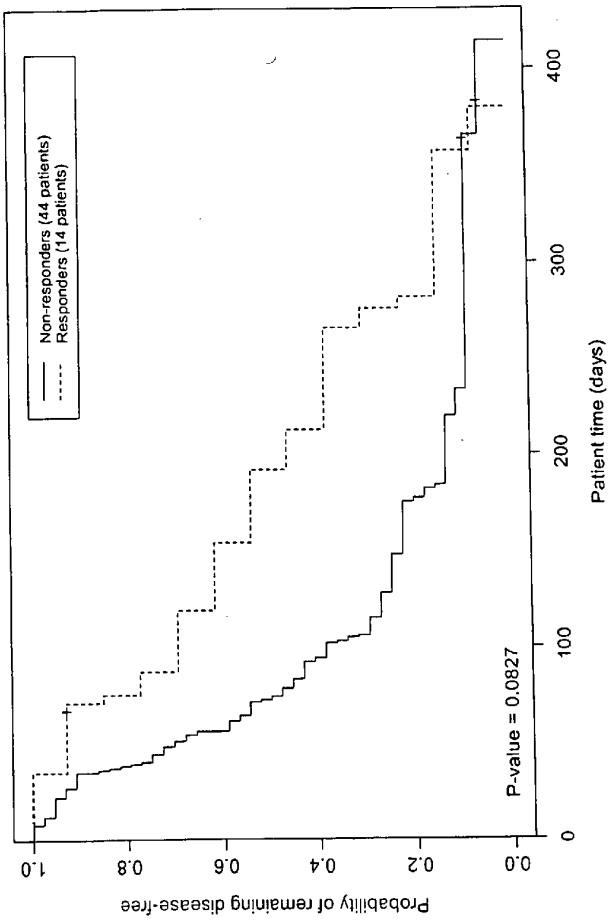
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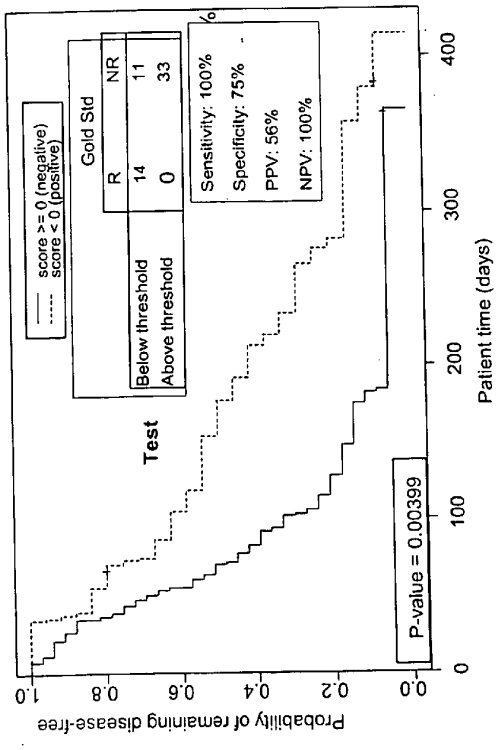
Fig. 3B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NR
Test
Below threshold
Above threshold
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PPV: 56%
NPV: 100%
%
P-value = 0.00399
Probability of remaining disease-free
Patient time (days)
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Figure 3C

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<120> METHODS FOR ASSESSING AND TREATING CANCER

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