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Use of beta-catenin as a biomarker for treating cancers using anti-Dkk-1 antibody

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(54) Title: USE OF BETA-CATENIN AS A BIOMARKER FOR TREATING CANCERS USING ANTI-DKK-1 ANTIBODY

(57) Abstract: A method of treating a cancer in a subject in need thereof is disclosed. The cancer can be an esophageal cancer, a uterine cancer, a liver cancer, or a cholangiocarcinoma. The method comprises administering to the subject an effective amount of an anti-Dkk-1 antibody or antigen binding-fragment thereof, wherein the subject is determined to have a constitutively activating mutation of the beta-catenin protein.

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USE OF BETA-CATENIN AS A BIOMARKER FOR TREATING CANCERS USING ANTI-DKK-1 ANTIBODY

RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/413,198, filed on October 26, 2016. The entire teachings of the above application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Cancer remains an important public health threat with poor prognosis and limited treatment available for many types. There is a significant unmet need for therapies that can increase efficacy in treating cancers, particularly esophageal cancer, uterine cancer, liver cancer, and cholangiocarcinoma or bile duct cancer. The present application provides such therapies.

[0002a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of the common general knowledge in the field.

[0002b] Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

SUMMARY OF THE INVENTION

[0003] The present invention relates to a method of treating cancers (*e.g.*, esophageal adenocarcinoma) in a subject in need of treatment.

[0003a] In an aspect, the invention provides a method of treating a subject suffering from a cancer, comprising the steps of:

determining that the subject has a constitutively activating mutation in a beta-catenin protein (SEQ ID NO: 2) in a cancer sample; and

administering to the subject determined to have the constitutively activating mutation in a beta-catenin protein (SEQ ID NO: 2) an effective amount of an anti-Dkk-1 antibody or antigen binding-fragment thereof,

wherein the cancer is an esophageal cancer or a uterine cancer

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wherein the anti-Dkk-1 antibody or antigen binding-fragment thereof comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity determining regions (CDRs) LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2 and HCDR3, wherein LCDR1 has the amino acid sequence of SEQ ID NO: 6, LCDR2 has the amino acid sequence of SEQ ID NO: 7, wherein Xaa at position 2 is Ala and Xaa at position 6 is Ile, LCDR3 has the amino acid sequence of SEQ ID NO: 8, wherein Xaa at position 4 is Glu, HCDR1 has the amino acid sequence of SEQ ID NO: 9, HCDR2 has the amino acid sequence of SEQ ID NO: 10, and an HCDR3 has the amino acid sequence of SEQ ID NO: 11, wherein Xaa at position 4 is Asn, and

wherein the mutation is a deletion of Exons 2, 3, and 4 (SEQ ID NOs: 3, 4, and 5) or is any one of the mutations of amino acid residues of SEQ ID NO:2 selected from D32G, D32N, D32Y, G34E, G34R, G34V, S37F, I35S, S33C, S33F, S33Y, S37A, S37C, S37P, S45C, S45F, T41A, T41I, S33A, K335T, D32A, D32V, H36P, S33P, S45Y, S37Y, S45P, T42_K49del, K335I, N387I, or N387K.

[0004] In another aspect, the present invention is a method of treating a cancer in a subject in need thereof. The cancer can be an esophageal cancer, a uterine cancer, a liver cancer, or a cholangiocarcinoma. Alternatively, the cancer can be a stomach cancer. The method comprises administering to the subject a therapeutically effective amount of an anti-Dkk-1 antibody or antigen binding-fragment thereof, wherein the subject is determined to have a constitutively activating mutation of the beta-catenin protein (SEQ ID NO:2).

[0005] In another aspect, the present invention is a method of treating a subject suffering from a cancer. The cancer can be an esophageal cancer, a uterine cancer, a liver cancer, or a cholangiocarcinoma. Alternatively, the cancer can be a stomach cancer. The method com-

prises the steps of obtaining a sample of a neoplastic cell from the subject; determining a sequence of the beta-catenin protein in the sample; and administering to the subject a therapeutically effective amount of an anti-Dkk-1 antibody or antigen binding-fragment thereof if the sequence of a beta-catenin protein (SEQ ID NO: 2) includes a constitutively activating mutation.

[0006] In yet another aspect, the present invention is a method of treating a cancer in a subject in need thereof. The cancer can be an esophageal cancer, a uterine cancer, a liver cancer, or a cholangiocarcinoma. Alternatively, the cancer can be a stomach cancer. The method comprises administering to the subject a therapeutically effective amount of an anti-Dkk-1 antibody or antigen binding-fragment thereof, wherein the subject has a constitutively activating mutation of the beta-catenin protein (SEQ ID NO: 2).

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The foregoing will be apparent from the following more particular description of example embodiments of the invention, as illustrated in the accompanying drawings. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating embodiments of the present invention.

[0008] FIG. 1 is a table presenting the analysis of CTNNB1 (beta-catenin) protein mutational data in patients subject to DKN-01 therapy.

[0009] FIG. 2A is a plot indicating the change (in percent of size) in the lesion size in Patient 105-023 suffering from esophageal cancer and put on a combination therapy of Paclitaxel and DKN-01. Patient 105-023 was shown to have a deletion of exons 2 through 4 of the CTNNB1 (beta catenin) gene.

[0010] FIG. 2B is a tomographic image of the target lesion of Patient 105-023 at the inception of the study and at cycle 10.

[0011] FIG. 3A through 3F illustrate the sequence of the human CTNNB1 gene.

[0012] FIG. 4A through 4D collectively represent Table 1 which shows examples of mutations of the beta-catenin protein.

DETAILED DESCRIPTION OF THE INVENTION

[0013] A description of example embodiments of the invention follows.

[0014] Dickkopf-1 (Dkk-1) is a protein that acts as a natural inhibitor of the canonical Wnt/β-catenin signaling pathway. The Wnt pathway influences a number of biological processes such as cell growth, cell proliferation, stem cell maintenance, cell differentiation, cell polarity, bone development, and adult tissue homeostasis.

[0015] In a canonical Wnt/β-catenin signaling pathway, extracellular Wnt ligand binds to its cognate receptor "Frizzled," and further recruits transmembrane lipoproteins LPR5 and LPR6 (low-density lipoprotein receptor-related proteins 5 and 6) co-receptors. Formation of a Wnt/Frizzled/LPR5/6 complex triggers several intracellular signaling cascades, including the one mediated by the β-catenin protein, a gene product of the CTNNB1 gene. In particular, the formation of a Wnt/Frizzled/LPR5/6 complex results in stabilization of cytoplasmic level of beta-catenin due to the inhibition of the beta-catenin phosphorylation. While phosphorylated beta-catenin is degraded in the cytoplasm, unphosphorylated beta-catenin translocates to the nucleus, where it enhances target gene expression of, *e.g.*, cyclin D1, c-myc, c-jun, cyclooxygenase-2, matrix metalloproteinase-7, vascular endothelial growth factor, and survivin, among other growth factors. Absent the signal from the Wnt/Frizzled/LPR5/6 complex, beta-catenin is phosphorylated by intracellular kinases, such as glycogen synthase kinase 3β (GSK3β) and casein kinas I (CKI). Transduction of a signal from the Wnt/Frizzled/LPR5/6 complex inhibits this phosphorylation.

[0016] Extracellular Dkk-1 binds to the LPR5/6 co-receptors and prevents Wnt ligand binding. This results in resuming of beta-catenin phosphorylation and its subsequent degradation, thus inhibiting canonical Wnt signaling pathway.

[0017] See URL "https://www.ncbi.nlm.nih.gov/gene/1499" for the nucleotide sequence and genomic (chromosomal) coordinates of human CTNNB1. Briefly, genomic (chromosomal) coordinates of CTNNB1 gene are chr3:41,240,942-41,281,939. All coordinates are from build GRCh37/hg19. Nucleotide sequence of CTNNB1 is provided in SEQ ID NO: 1 (includes exons, indicated by capital letters). The gene product of human CNNTB1 gene, referred herein as beta-catenin or beta-catenin protein, is a protein having the sequence provided by SEQ ID NO: 2 (UniProt accession No. P35222). Of particular interest are Exons 2, 3, and 4, corresponding in SEQ ID NO: 2 to amino acid residues 1 through 4 (Exon 2), 5-81 (Exon 3), and 82-165 (Exon 4). The amino acid sequences of the Exons 2 through 4 are provided by SEQ ID Nos: 3, 4, and 5, respectively.

[0018] As used herein, "a constitutively activating mutation of a beta-catenin protein" refers to a mutation of the amino acid sequence of beta-catenin that results in an elevated cellular level of beta-catenin functionally capable of transducing a signal to the cell nucleus, when compared to a wild type protein. Examples of constitutively activating mutations of beta-catenin include mutations that result in its inability to be phosphorylated by GSK3-beta kinase and/or casein kinase I in the absence of the Wnt/Frizzled/LPR5/6 complex. Examples of such mutations include: deletions of Exons 2 through 4, deletion of or within Exon 3, and mutations of the serine and threonine residues that are phosphorylated in the absence of the Wnt/Frizzled/LPR5/6 complex, such as Ser33, Ser37, Thr41, and Ser45 of SEQ ID NO: 2.

[0019] In various embodiments, a mutation of the beta-catenin protein is selected from the mutations listed in Table 1, represented in FIGs. 4A through 4D.

[0020] As those of skill in the art will recognize, "esophageal cancer" as used herein refers to cancer of the esophagus as well as the gastro-esophageal junction. As commonly used in the art, esophageal cancer comprises esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Generally, ESCC refers to cancer that originates in squamous cells, which cells line the esophagus in approximately upper 2/3 of the organ. EAC refers to cancer that originates in gland cells, which replace an area of squamous cells (*e.g.*, in Barrett's esophagus), typically in the lower 1/3 of the esophagus. As such, esophageal adenocarcinoma as used herein refers to adenocarcinoma of the esophagus as well as the gastro-esophageal junction.

[0021] "Uterine cancer" is any type of cancer that emerges from the tissue of the uterus. It can refer to several types of cancer, with cervical cancer (arising from the lower portion of the uterus) being the most common type.

[0022] "Liver cancer," also known as hepatic cancer and primary hepatic cancer, is cancer that starts in the liver. Cancer which has spread from elsewhere to the liver, known as liver metastasis, is more common than that which starts in the liver. Primary liver cancer is globally the sixth most frequent cancer (6%) and the second leading cause of death from cancer (9%).

[0023] "Cholangiocarcinoma" or bile duct cancer is a form of cancer that is composed of mutated epithelial cells (or cells showing characteristics of epithelial differentiation) that originate in the bile ducts which drain bile from the liver into the small intestine. The rates of chlonagiocarcinoma have been rising worldwide over the past few decades. Cholangiocarcinoma is considered to be an incurable and rapidly lethal cancer unless both the primary tumor

and any metastases can be fully removed by surgery. No potentially curative treatment exists except surgery, but most people have advanced stage disease at presentation and are inoperable at the time of diagnosis.

[0024] "Stomach cancer" also called *gastric cancer*, is a cancer that starts in the stomach. About 90% to 95% of cancers of the stomach are adenocarcinomas. When the term stomach cancer or gastric cancer is used, it almost always refers to an adenocarcinoma. These cancers develop from the cells that form the innermost lining of the stomach (known as the mucosa).

[0025] The term "effective amount" means an amount of a therapeutic agent, *e.g.* an antibody, that is effective in prophylactically or therapeutically treating the indicated disorder. An "effective amount" may also refer to an amount of a combination of therapeutic agents that is therapeutically or prophylactically sufficient to treat the target disorder. An effective amount will depend on the age, gender, and weight of the patient, the current medical condition of the patient, and the nature of the esophageal cancer being treated. Those of skill in the art will be able to determine appropriate dosages depending on these and other factors.

[0026] It has now been discovered that cancer patients suffering from certain cancers and who have a constitutively activating mutation within the beta-catenin protein (SEQ ID NO: 2) are expected to be more responsive to an anti-Dkk-1 antibody therapy than patients who do not have such a mutation. Accordingly, the present invention relates to a method of treating cancers (*e.g.*, esophageal cancer, uterine cancer, liver cancer, and cholangiocarcinoma) in a subject in need of treatment comprising administering an effective amount of an anti-Dkk-1 antibody, or antigen binding-fragment thereof, wherein the subject is determined to have a constitutively activating mutation of a beta-catenin protein (SEQ ID NO:2).

Dkk-1 Antibody

[0027] Dkk-1 antibodies have been described previously (see, *e.g.*, U.S. Patent Nos. 8,148,498 and 7,446,181, incorporated by reference herein in their entireties). The Dkk-1 antibody or antigen-binding fragment thereof disclosed herein relates to human engineered antibodies that bind to a human Dkk-1 comprising the amino acid sequence set for in SEQ ID NO: 27, or fragments thereof. The present Dkk-1 antibodies are therapeutically useful Dkk-1 antagonists possessing a number of desirable properties. For example, the Dkk-1 antibodies block Dkk-1 mediated inhibition of alkaline phosphatase, a marker or osteoblast activity, as well as treat various types of cancer (*e.g.*, non-small cell lung cancer).

[0028] A full-length antibody as it exists naturally is an immunoglobulin molecule comprising 2 heavy (H) chains and 2 light (L) chains interconnected by disulfide bonds. The amino terminal portion of each chain includes a variable region of about 100-110 amino acids primarily responsible for antigen recognition via the complementarity determining regions (CDRs) contained therein. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function.

[0029] The CDRs are interspersed with regions that are more conserved, termed framework regions ("FR"). Each light chain variable region (LCVR) and heavy chain variable region (HCVR) is composed of 3 CDRs and 4 FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The 3 CDRs of the light chain are referred to as "LCDR1, LCDR2, and LCDR3" and the 3 CDRs of the heavy chain are referred to as "HCDR1, HCDR2, and HCDR3." The CDRs contain most of the residues which form specific interactions with the antigen. The numbering and positioning of CDR amino acid residues within the LCVR and HCVR regions is in accordance with the well-known Kabat numbering convention.

[0030] Light chains are classified as kappa or lambda, and are characterized by a particular constant region as known in the art. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, and define the isotype of an antibody as IgG, IgM, IgA, IgD, or IgE, respectively. IgG antibodies can be further divided into subclasses, e.g., IgG1, IgG2, IgG3, IgG4. Each heavy chain type is characterized by a particular constant region with a sequence well known in the art.

[0031] As used herein, the term "monoclonal antibody" (Mab) refers to an antibody that is derived from a single copy or clone including, for example, any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Mabs of the present invention preferably exist in a homogeneous or substantially homogeneous population. Complete Mabs contain 2 heavy chains and 2 light chains.

[0032] Unless specified otherwise, the term “Dkk-1 antibody” encompasses both a full-length antibody as well as an antigen binding-fragment of the Dkk-1 antibody.

[0033] "Antigen-binding fragments" of such monoclonal antibodies include, for example, Fab fragments, Fab' fragments, $F(ab')_2$ fragments, and single chain Fv fragments. Monoclonal antibodies and antigen-binding fragments thereof can be produced, for example, by recombinant technologies, phage display technologies, synthetic technologies, *e.g.*, CDR-grafting, or combinations of such technologies, or other technologies known in the art. For example, mice

can be immunized with human DKK-1 or fragments thereof, the resulting antibodies can be recovered and purified, and determination of whether they possess binding and functional properties similar to or the same as the antibody compounds disclosed herein can be assessed by the methods known in the art. Antigen-binding fragments can also be prepared by conventional methods. Methods for producing and purifying antibodies and antigen-binding fragments are well known in the art and can be found, for example, in Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 5-8 and 15, ISBN 0-87969-314-2.

[0034] Monoclonal Dkk-1 antibodies disclosed herein are engineered to comprise framework regions that are substantially human or fully human surrounding CDRs derived from a non-human antibody. "Antigen-binding fragments" of such human engineered antibodies include, for example, Fab fragments, Fab' fragments, $F(ab')_2$ fragments, and single chain Fv fragments. "Framework region" or "framework sequence" refers to any one of framework regions 1 to 4. Human engineered antibodies and antigen-binding fragments thereof encompassed by the antibodies disclosed herein include molecules wherein any one or more of framework regions 1 to 4 is substantially or fully human, *i.e.,* wherein any of the possible combinations of individual substantially or fully human framework regions 1 to 4, is present. For example, this includes molecules in which framework region 1 and framework region 2, framework region 1 and framework region 3, framework region 1, 2, and 3, *etc.*, are substantially or fully human. Substantially human frameworks are those that have at least about 80% sequence identity to a known human germline framework sequence. Preferably, the substantially human frameworks have at least about 85%, about 90%, about 95%, or about 99% sequence identity to a known human germline framework sequence.

[0035] Human engineered antibodies in addition to those disclosed herein exhibiting similar functional properties can be generated using several different methods. The specific antibody compounds disclosed herein can be used as templates or parent antibody compounds to prepare additional antibody compounds. In one approach, the parent antibody compound CDRs are grafted into a human framework that has a high sequence identity with the parent antibody compound framework. The sequence identity of the new framework will generally be at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% identical to the sequence of the corresponding framework in the parent antibody compound. This grafting may result in a reduction in binding affinity compared to that of the

parent antibody. If this is the case, the framework can be back-mutated to the parent framework at certain positions based on specific criteria disclosed by Queen *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:2869. Additional references describing methods useful in humanizing mouse antibodies include U.S. Pat. Nos. 4,816,397; 5,225,539, and 5,693,761; computer programs ABMOD and ENCAD as described in Levitt (1983) *J. Mol. Biol.* 168:595-620; and the method of Winter and co-workers (Jones *et al.* (1986) *Nature* 321:522-525; Riechmann *et al.* (1988) *Nature* 332:323-327; and Verhoeyen *et al.* (1988) *Science* 239:1534-1536). Methods for identifying residues to consider for back-mutation are known in the art (see, *e.g.,* U.S. Patent No. 8,148,498).

[0036] The methods provided herein relate to the use of a Dkk-1 antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity determining regions (CDRs) LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2 and HCDR3, wherein LCDR1 has the amino sequence of SEQ ID NO: 6, HCDR1 has the amino sequence of SEQ ID NO: 9, and HCDR2 has the amino sequence of SEQ ID NO: 10.

[0037] In one embodiment, the Dkk-1 antibody comprises a LCDR1 having the amino sequence of SEQ ID NO: 6, LCDR2 having the amino sequence of SEQ ID NO: 7, LCDR3 having the amino sequence of SEQ ID NO: 8, HCDR1 having the amino sequence of SEQ ID NO: 9, HCDR2 having the amino sequence of SEQ ID NO: 10, and HCDR3 having the amino sequence of SEQ ID NO: 11.

[0038] In another embodiment, the Dkk-1 antibody comprises a LCVR having the amino acid sequence of SEQ ID NO: 12 and a HCVR having the amino acid sequence of SEQ ID NO: 13. In a particular embodiment, the LCVR comprises the amino acid sequence of SEQ ID NO: 16 and the HCVR comprises the amino acid sequence of SEQ ID NO: 17.

[0039] In further embodiments, the Dkk-1 antibody comprises a heavy chain (HC) having the amino acid sequence of SEQ ID NO: 22 and a light chain (LC) having the amino acid sequence of SEQ ID NO: 23. The Dkk-1 antibody or antigen binding-fragment thereof comprising the HC and LC amino acid sequence of SEQ ID NO: 22 and SEQ ID NO: 23, respectively, is referred to herein as DKN-01. In particular, DKN-01 has the molecular/empirical formula C_{6394} H_{9810} N_{1698} O_{2012} S_{42} and a molecular weight of 144015 Daltons (intact).

[0040] In certain embodiments, the Dkk-1 antibody disclosed herein is an IgG_4 antibody with a neutralizing activity against human Dkk-1 comprising the sequence set forth in SEQ

ID NO: 27, of a fragment thereof. For example, canonical Wnt signaling is important for osteoblast differentiation and activity. Wnt-3a combined with BMP-4 induces pluripotent mouse C2C12 cells to differentiate into osteoblasts with a measurable endpoint of alkaline phosphatase ("AP"), a marker of osteoblast activity. Dkk-1, an inhibitor of canonical Wnt signaling, inhibits the differentiation and production of AP. Neutralizing Dkk-1 antibodies prevent Dkk-1-mediated inhibition of AP. Antibodies which block Dkk-1 inhibitory activity prevent the loss of AP activity (see U.S. Patent No. 8,148,498). In a particular embodiment, the Dkk-1 antibody possessing neutralizing activity is DKN-01, which is an IgG_4 antibody.

[0041] The Dkk-1 antibodies disclosed herein possess high affinity (Kd) to Dkk-1 (*e.g.*, human Dkk-1, SEQ ID NO: 27), as described in U.S. Patent No. 8,148,498. For example, the present Dkk-1 antibodies possess a Kd of between $0.5x10^{-12}$ M and $3.0x10^{-11}$ M, at 37 °C.

Modes of Administration

[0042] The Dkk-1 antibody and chemotherapeutic agents for use in the methods or compositions of the invention can be formulated for parenteral, oral, transdermal, sublingual, buccal, rectal, intranasal, intrabronchial or intrapulmonary administration.

[0043] For parenteral administration, the compounds for use in the methods or compositions of the invention can be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose and/or infusion (e.g., continuous infusion). Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing and/or dispersing agents can be used.

[0044] For oral administration the compounds can be of the form of tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.*g.*, magnesium stearate, talc or silica); disintegrates (*e.g.*, sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). If desired, the tablets can be coated using suitable methods. Liquid preparation for oral administration can be in the form of solutions, syrups or suspensions. The liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters

or ethyl alcohol); and preservatives (*e.g.*, methyl or propyl p-hydroxy benzoates or sorbic acid).

[0045] For buccal administration, the compounds for use in the methods or compositions of the invention can be in the form of tablets or lozenges formulated in a conventional manner.

[0046] For rectal administration, the compounds for use in the methods or compositions of the invention can be in the form of suppositories.

[0047] For sublingual administration, tablets can be formulated in conventional manner.

[0048] For intranasal, intrabronchial or intrapulmonary administration, conventional formulations can be employed.

[0049] Further, the compounds for use in the methods or compositions of the invention can be formulated in a sustained release preparation. For example, the compounds can be formulated with a suitable polymer or hydrophobic material which provides sustained and/or controlled release properties to the active agent compound. As such, the compounds for use in the method of the invention can be administered in the form of microparticles, for example, by injection or in the form of wafers or discs by implantation. Various methods of formulating controlled release drug preparations are known in the art.

[0050] Administration of a compound, or pharmaceutically acceptable salt thereof, or a composition comprising one or more compound (or pharmaceutical salt thereof) of the invention useful to practice the methods described herein, can be continuous, hourly, four times daily, three time daily, twice daily, once daily, once every other day, twice weekly, once weekly, once every two weeks, once a month, or once every two months, or longer, or some other intermittent dosing regimen.

[0051] Examples of administration of a compound, or a composition comprising one or more compound (or pharmaceutical salt thereof) of the invention include peripheral administration. Examples of peripheral administration include oral, subcutaneous, intraperitoneal, intramuscular, intravenous, rectal, transdermal, or intranasal forms of administration.

[0052] As used herein, peripheral administration includes all forms of administration of a compound or a composition comprising a compound of the instant invention which excludes intracranial administration. Examples of peripheral administration include, but are not limited to, oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous or subcutaneous injection, extended release, slow release implant, depot and the like), nasal, vaginal, rectal, sublingual or topical routes of administration, including transdermal patch applications and the like.

Combination Therapy

[0053] The Dkk-1 antibody disclosed herein can be used for treating esophageal cancer in combination with a second amount of a chemotherapeutic agent (sometime referred to herein as a "second agent"). Such combination administration can be by means of a single dosage form which includes a Dkk-1 antibody and the second agent, such single dosage form including a tablet, capsule, spray, inhalation powder, injectable liquid or the like. Combination administration can comprise a further second agent (*e.g.,* chemotherapeutic agent) in addition to the single dosage form. Alternatively, combination administration can be by means of administration of two different dosage forms, with one dosage form containing a Dkk-1 antibody, and the other dosage form including a second amount of a chemotherapeutic agent. In this instance, the dosage forms may be the same or different. Without wishing to limit combination therapies, the following exemplifies certain combination therapies which may be employed. It is understood that additional chemotherapeutic agents beyond the required second amount of a chemotherapeutic agent can be employed in the method described herein.

[0054] The second amount of the chemotherapeutic agent (sometimes referred to herein as the second agent) can be administered before, simultaneously with, or after the administration of a Dkk-1 antibody. Accordingly, a Dkk-1 antibody and a second agent can be administered together in a single formulation or can be administered in separate formulations, *e.g.*, either simultaneously or sequentially, or both. For example, if a Dkk-1 antibody and a second agent are administered sequentially in separate compositions, the Dkk-1 antibody can be administered before or after the chemotherapeutic agent. The duration of time between the administration of a Dkk-1 antibody and the second amount of the chemotherapeutic agent will depend on the nature of the chemotherapeutic agent. In certain embodiments, the Dkk-1 antibody can precede or follow a chemotherapeutic agent immediately, or after some duration of time deemed to be appropriate by a skilled practitioner.

[0055] In addition, the Dkk-1 antibody and the second amount of the chemotherapeutic agent may or may not be administered on similar dosing schedules. For example, the Dkk-1 antibody and the chemotherapeutic agent may have different half-lives and/or act on different time-scales such that the Dkk-1 antibody is administered with greater frequency than the chemotherapeutic agent or vice-versa. For example, the Dkk-1 antibody and the chemotherapeutic agent can be administered together (*e.g.*, in a single dosage or sequentially) on one

day, followed by administration of only the chemotherapeutic agent (or a different chemotherapeutic) a set number of days later. The number of days in between administration of therapeutic agents can be appropriately determined according to the safety and pharmacodynamics of each drug. Either the Dkk-1 antibody or the chemotherapeutic agent can be administered acutely or chronically.

[0056] As used herein, an "effective amount" refers to an amount of a therapeutic agent or a combination of therapeutic agents that is therapeutically or prophylactically sufficient to treat the target disorder. An effective amount will depend on the age, gender, and weight of the patient, the current medical condition of the patient, and the nature of the esophageal cancer being treated. Those of skill in the art will be able to determine appropriate dosages depending on these and other factors.

[0057] Suitable doses per administration for a Dkk-1 antibody include doses of about or greater than about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, or about 3,000 mg. Each suitable dose can be administered over a period time deemed appropriate by a skilled practitioner. For example, each suitable dose can be administered over a period of about 30 minutes and up to about 1 hour, about 2 hours, about 3, hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, or about 8 hours. In a particular embodiment, a suitable dose for Dkk-1 antibody can be about 150 mg administered over a period of about 30 minutes and

up to about 2 hours. Another suitable dose for the Dkk-1 antibody can be about 300 mg administered over a period of about 30 minutes and up to about 2 hours.

[0058] Suitable doses per administration for a second amount of chemotherapeutic agent can be determined based on the recommended dosing found on the label. When paclitaxel in the second amount of the chemotherapeutic agent used doses of about or greater than about 8 mg/m^2, 10 mg/m^2, about 15 mg/m^2, about 20 mg/m^2, about 25 mg/m^2, about 30 mg/m^2, about 35 mg/m^2, about 40 mg/m^2, about 45 mg/m^2, about 50 mg/m^2, about 55 mg/m^2, about 60 mg/m^2, about 65 mg/m^2, about 70 mg/m^2, about 75 mg/m^2, about 80 mg/m^2, about 85 mg/m^2, about 90 mg/m^2, about 95 mg/m^2, about 100 mg/m^2, about 105 mg/m^2, about 110 mg/m^2, about 120 mg/m^2, about 130 mg/m^2, about 140 mg/m^2, about 150 mg/m^2, about 160 mg/m^2, about 170 mg/m^2, about 180 mg/m^2, about 190 mg/m^2, about 200 mg/m^2, about 225 mg/m^2, about 250 mg/m^2, about 275 mg/m^2, about 300 mg/m^2, about 600 mg/m^2 or about 800 mg/m^2. For example, a suitable dose per administration of paclitaxel is about 80 mg/m^2 over a period of about 1 hour.

[0059] An effective amount can be achieved in the methods or compositions of the invention by coadministering a first amount of a Dkk-1 antibody (or a pharmaceutically acceptable salt, hydrate or solvate thereof) and a second amount of at least one chemotherapeutic agent. In one embodiment, the Dkk-1 antibody and the chemotherapeutic agent are each administered in a respective effective amount (*e.g.*, each in an amount which would be therapeutically effective if administered alone). In another embodiment, the Dkk-1 antibody and the chemotherapeutic agent are each administered in an amount which alone does not provide a therapeutic effect (a sub-therapeutic dose). In yet another embodiment, the Dkk-1 antibody can be administered in an effective amount, while the chemotherapeutic agent is administered in a sub-therapeutic dose. In still another embodiment, the Dkk-1 antibody can be administered in a sub-therapeutic dose, while the chemotherapeutic agent is administered in an effective amount.

[0060] As used herein, the term "subject" refers to a mammal, preferably a human, but can also mean an animal in need of veterinary treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like).

[0061] As used herein "treating" includes achieving, partially or substantially, delaying, inhibiting or preventing the progression of clinical indications related to the cancer being treated. For example, "treating" includes reduction in tumor growth, or prevention of further

growth, as detected by standard imaging methods known in the art, including, for example, computed tomography (CT) scan, magnetic resonance imaging (MRI), chest x-ray, and CT/positron emission tomography (CT/PET) scans, and evaluated according to guidelines and methods known in the art. For example, responses to treatment can be evaluated through the Response Evaluation Criteria in Solid Tumors (RECIST) (Revised RECIST Guideline version 1.1; see Eisenhauer *et al.*, *Eur. J. Cancer* 45(2):228-47, 2009). Thus, in some embodiments, "treating" refers to a Complete Response (CR), which is defined according to the RECIST guideline as the disappearance of all target lesions, or a Partial Response (PR), which is defined as at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. Other means for evaluating tumor response to treatment include evaluation of tumor markers and evaluation of performance status (*e.g.*, assessment of creatinine clearance; see Cockcroft and Gault, *Nephron.* 16:31-41, 1976).

Pharmaceutical Composition

[0062] The Dkk-1 antibody and chemotherapeutic agents disclosed herein can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the antibody, or one or more chemotherapeutic agents, or both, and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated.

[0063] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with

acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0064] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL(TM) (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0065] Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a Dkk-1antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0066] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form

of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0067] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0068] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid- derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

[0069] For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0070] The compounds can also be prepared in the form of suppositories (*e.g.,* with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0071] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to

methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0072] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0073] While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

EXEMPLIFICATION

Example 1 – Detection of Constitutively Activating Mutations of CTNNB1 Gene

[0074] Biopsy samples can be obtained from a patient for determination of the sequence of the beta-catenin gene. Gene sequencing is well within the purview of a person of ordinary skill in the art, and can be accomplished using commercially available products, such as the Archer® VariantPlex Solid Tumor kit available from ArcherDX, Inc. of Boulder, CO, and next generation sequencing platforms such as one avalaible from Illumina, Inc. of San Diego CA (Worldwide Headquarters). Comparison can be done to publically available genetic sequence of the gene, *e.g.* at the NCBI database.

Example 2 – Detection of Constitutively Activating Mutations of beta-Catenin Protein

[0075] Phosphorylation status of beta-catenin can be determined by western blot analysis with antibodies that recognize the phosphorylated form of beta-catenin. Stabilization and activation of beta-catenin can be determined by western blot demonstrating an increase in cellular protein levels and by immunofluorescence demonstrating nuclear localization of beta-catenin. Measuring the expression of downstream beta-catenin target genes or an exogenous beta-catenin reporter gene construct can be utilized to determine the activation status of beta-catenin.

Example 3 – CTNNB1 Mutational Data in Patients Subject to DKN-01 Therapy

Clinical Study of the Paclitaxel /DKN-01 Combination Therapy

[0076] Patients were selected for a clinical investigation of the combination DKN-01/Paclitaxel® therapy designed as a phase 1 non-randomized, dose-escalating, open label, multicenter study.

[0077] Patients with histologically confirmed recurrent or metastatic esophageal or gastro-esophageal junction adenocarcinoma were selected. Each patient reported on in Table 1 was placed on a 28-day treatment cycle: 300 mg of DKN-01 antibody on days 1 and 15; 80 mg/m^2 of Paclitaxel® on days 1, 8, 15, and 22.

[0078] DKN-01 was administered intravenously (IV) over a minimum of 30 minutes and up to a maximum of 2 hours without interruption. Paclitaxel® was administered IV over 1 hour on days 1, 8, 15 and 22 of each cycle according to standard clinical practice. Standard of care premedication for paclitaxel was given prior to administration. Sequence of administration: pre-medication for paclitaxel, DKN-01, pactlitaxel. DKN-01 was administered first followed by paclitaxel on Days 1 and 15 when both drugs were delivered.

[0079] Biopsy samples, collected prior to commencement of the study, were subject to gene expression analysis.

[0080] Radiological tumor assessment was perfomed. At a minimum, a computerized tomography (CT) scan of the chest, abdomen and pelvis had been conducted for tumor assessment with documentation of one or more metastatic tumors measurable on radiographic imaging as defined by Response Evaluation Criteria in Solid Tumors (RECIST). Whenever feasible, the preferred imaging modality throughout the study was CT/PET scans. Baseline radiographic tumor assessments were conducted within 28 days prior to day 1 of cycle 1 and subsequent tumor assessments were performed after every even numbered cycle.

[0081] The following response criteria were used:

[0082] Complete Response (CR): Disappearance of all lesions. Any pathological lymph nodes had reduction in short axis to <10 mm. Tumor marker results were normalized.

[0083] Partial Response (PR): At least a 30% decrease in the sum of diameter of lesions, taking as reference the baseline sum diameters.

[0084] Progressive Disease (PD): At least a 20% increase in the sum of the diameters of lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum demonstrated an absolute

increase of at least 5 mm. The appearance of one or more new lesions was also considered progression.

[0085] Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Result Analysis

[0086] Analysis of beta-catenin mutations was performed on patients subjected to the combination therapy of Paclitaxel® and DKN-01 according to the methods described above. The results are presented in FIG. 1. As can be seen, the beta-catenin mutations resulting from deletion of Exons 2-4, S45F and T41I are found in patients exhibiting a partial response or at least stable disease.

[0087] This data demonstrates that an activating mutation of beta-catenin is a bi-omarker predictor of a therapeutic response to an anti-Dkk-1 antibody administration.

Example 4 – Case Study of Patient 105-023: β-Catenin Activating Mutations is a Bi-omarker for DKN-01 Sensitivity in Esophageal Cancer Therapy

[0088] As shown in FIG. 1, Patient 105-023, suffering from a GEJ adenocarcinoma ma-lignancy, exhibited the highest reduction in tumor volume. Clinical data pertaining to Patient 105-023 was further analyzed.

[0089] Patient 105-023 experienced a tumor regression of 73% over the course of four-teen 28-day treatment cycles. The results are illustrated in FIG. 2A and FIG. 2B. FIG. 2A shows a plot of tumor volume in Patient 105-023 as a function of the number of cycles of treatment (cycles are denoted by start dates). Patient 105-023 received 300 mg of DKN-01 on Days 1 and 15 and 80 mg/m2 of paclitaxel weekly during a 28-Day Cycle for the first 10 cycles. During Cycle 10 paclitaxel was discontinued; however the response continued to deepen. FIG. 2B is a computerized tomography image demonstrating a reduction in the size of the primary lesion in Patient 105-023 from baseline to Cycle 10. Arrow denotes the pri-mary lesion.

[0090] As can be seen from the data, Patient 105-023 discontinued paclitaxel in Cycle 10 and has continued to have a deepening response to DKN-01 monotherapy. Genetic analysis of a biopsy sample from this patient's tumor (performed using the methods described in Ex-ample 1 by employing a FoundationOne® Panel, commercially available from Foundation

Medicine, Inc., Cambridge, MA) indicated the presence of a β-catenin exon 2-4 deletion that results in constitutive activation.

[0091] This data further supports the finding that an activating mutation of beta-catenin is a biomarker predictor of a therapeutic response to an anti-Dkk-1 antibody administration.

SEQUENCES

The genomic DNA sequence of CTNNB1 – SEQ ID NO: 1

[0092] SEQ ID NO: 1, shown in FIGs. 3A through 3F, represents the sequence of human CTNNB1 gene having the chromosomal coordinates chr3:41,240,942-41,281,939. All coordinates are from build GRCh37/hg19. 5'UTR and 3'UTR exons are not included. Capital letters are the exons, lower case letters are introns. Exons 2, 3, and 4 are underlined and superscripted.

Amino Acid Sequence of beta-Catenin Protein – SEQ ID NO: 2

[0093] SEQ ID NO: 2, below, is the amino acid sequence of human beta-catenin, a 781 amino acid protein UniProt Database ID – P35222 (http://www.uniprot.org/uniprot/P35222). Exons 2, 3, and 4 are underlined and superscripted.

```
2  4 3   10          20          30          40          50
MATQ ADLMEL DMAMEPDRKA AVSHWQQQSY LDSGIHSGAT TTAPSLSGKG
         60          70          80  4       90         100
NPEEEDVDTS QVLYEWEQGF SQSFTQEQVA DIDGQYAMTR AQRVRAAMFP
        110         120         130         140         150
ETLDEGMQIP STQFDAAHPT NVQRLAEPSQ MLKHAVVNLI NYQDDAELAT
        160         170         180         190         200
RAIPELTKLL NDEDQVVVNK AAVMVHQLSK KEASRHAIMR SPQMVSAIVR
        210         220         230         240         250
TMQNTNDVET ARCTAGTLHN LSHHREGLLA IFKSGGIPAL VKMLGSPVDS
        260         270         280         290         300
VLFYAITTLH NLLLHQEGAK MAVRLAGGLQ KMVALLNKTN VKFLAITTDC
        310         320         330         340         350
LQILAYGNQE SKLIILASGG PQALVNIMRT YTYEKLLWTT SRVLKVLSVC
        360         370         380         390         400
SSNKPAIVEA GGMQALGLHL TDPSQRLVQN CLWTLRNLSD AATKQEGMEG
        410         420         430         440         450
LLGTLVQLLG SDDINVVTCA AGILSNLTCN NYKNKMMVCQ VGGIEALVRT
        460         470         480         490         500
VLRAGDREDI TEPAICALRH LTSRHQEAEM AQNAVRLHYG LPVVVKLLHP
        510         520         530         540         550
PSHWPLIKAT VGLIRNLALC PANHAPLREQ GAIPRLVQLL VRAHQDTQRR
        560         570         580         590         600
TSMGGTQQQF VEGVRMEEIV EGCTGALHIL ARDVHNRIVI RGLNTIPLFV
        610         620         630         640         650
QLLYSPIENI QRVAAGVLCE LAQDKEAAEA IEAEGATAPL TELLHSRNEG
        660         670         680         690         700
VATYAAAVLF RMSEDKPQDY KKRLSVELTS SLFRTEPMAW NETADLGLDI
        710         720         730         740         750
GAQGEPLGYR QDDPSYRSFH SGGYGQDALG MDPMMEHEMG GHHPGADYPV
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      760         770         780
DGLPDLGHAQ DLMDGLPPGD SNQLAWFDTD L
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Exons of beta-Catenin Protein

[0094] The amino acid number range does not correspond exactly to the exons as marked in SEQ ID NO: 1 because of the splicing of the transcript. For example the first base "G" of the codon for amino acid #5 is in exon 2 and second and third bases "CT" are in Exon 3.

[0095] Highlighted residues of Exon 3 (in bold and underlined) indicate GSK3B and CK1α phosphorylation sites that stabilize beta-catenin when they are mutated or deleted): S33, S37, T41, S45. (*See* de La Coste A, Romagnolo B, Billuart P, Renard CA, Buendia MA, Soubrane O, et al. (1998). Somatic mutations of the beta-catenin gene are frequent in mouse and human hepatocellular carcinomas. Proc Natl Acad Sci U S A 95: 8847-8851; and Xu W, & Kimelman D (2007). Mechanistic insights from structural studies of beta-catenin and its binding partners. J Cell Sci 120: 3337-3344.)

Exon 1 (Non-Coding)

Exon 2 – SEQ ID NO: 3 (amino acids 1-4 of SEQ ID NO: 2)
MATQ (SEQ ID NO: 3)

Exon 3 – SEQ ID NO: 4 (amino acids 5-81 of SEQ ID NO: 2)
ADLMELDMAMEPDRKAAVSHWQQQSYLD**S**GIH**S-**
GAT**T**TAP**S**LSGKGNPEEEDVDTSQVLYEWEQGFSQSFTQEQVAD (SEQ ID NO: 4)

Exon 4 – SEQ ID NO: 5 (amino acids 82-165 of SEQ ID NO: 2)
IDGQYAMTRAQRVRAAMFPETLDEGMQIPSTQFDAAHPTNVQRLAEPSQMLKHAV-
VNLINYQDDAELATRAIPELTKLLNDEDQ (SEQ ID NO: 5)

[0096] LCDR1
His Ala Ser Asp Ser Ile Ser Asn Ser Leu His (SEQ ID NO: 6)

[0097] LCDR2
Tyr Xaa Arg Gln Ser Xaa Gln (SEQ ID NO: 7)
wherein **Xaa** at position 2 is Gly or Ala; and **Xaa** at position 6 is Ile or Glu

[0098] LCDR3

Gln Gln Ser Xaa Ser Trp Pro Leu His (SEQ ID NO: 8)

wherein **Xaa** at position 4 is Glu or Ala

[0099] HCDR1

Gly Phe Thr Phe Ser Ser Tyr Thr Met Ser (SEQ ID NO: 9)

[00100] HCDR2

Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val Lys (SEQ ID NO: 10)

[00101] HCDR3

Pro Gly Tyr Xaa Asn Tyr Tyr Phe Asp Ile (SEQ ID NO: 11)

wherein **Xaa** at position 4 is His or Asn

[00102] LCVR

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Xaa Arg Gln Ser Xaa Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Xaa Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys (SEQ ID NO: 12)

wherein **Xaa** at position 51 is Gly or Ala; **Xaa** at position 55 is Ile or Glu and **Xaa** at position 92 is Glu or Ala.

[00103] HCVR

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Pro Gly Tyr Xaa Asn Tyr Tyr Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 13)

wherein **Xaa** at position 102 is His or Asn

[00104] LCVR

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Gly Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Glu Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys (SEQ ID NO: 14)

[00105] HCVR

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Pro Gly Tyr His Asn Tyr Tyr Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 15)

[00106] LCVR

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Ala Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Glu Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys (SEQ ID NO: 16)

[00107] HCVR

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Pro Gly Tyr Asn Asn Tyr Tyr Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser (SEQ ID NO: 17)

[00108] LCVR

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro

Arg Leu Leu Ile Tyr Tyr Gly Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ala Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys (SEQ ID NO: 18)

[00109] LCVR

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Ala Arg Gln Ser Glu Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ala Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys (SEQ ID NO: 19)

[00110] HC

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Pro Gly Tyr His Asn Tyr Tyr Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly (SEQ ID NO: 20)

[00111] LC

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Gly Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Glu Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys (SEQ ID NO: 21)

[00112] HC

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Pro Gly Tyr Asn Asn Tyr Tyr Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly (SEQ ID NO: 22)

[00113] LC

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Ala Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Glu Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys (SEQ ID NO: 23)

[00114] HC

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Pro Gly Tyr His Asn Tyr Tyr Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly (SEQ ID NO: 24)

[00115] LC

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Gly Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ala Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys (SEQ ID NO: 25)

[00116] LC

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Tyr Ala Arg Gln Ser Glu Gln Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ala Ser Trp Pro Leu His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys (SEQ ID NO: 26)

[00117] Human Dkk-1 Amino Acid Sequence

Thr Leu Asn Ser Val Leu Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro Pro Leu Gly Gly Ala Ala Gly His Pro Gly Ser Ala Val Ser Ala Ala Pro Gly Ile Leu Tyr Pro Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn Tyr Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu Tyr Cys Ala Ser Pro Thr Arg Gly Gly Asp Ala Gly Val Gln Ile Cys Leu Ala Cys Arg Lys Arg

Arg Lys Arg Cys Met Arg His Ala Met Cys Cys Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Val Ser Ser Asp Gln Asn His Phe Arg Gly Glu Ile Glu Glu Thr Ile Thr Glu Ser Phe Gly Asn Asp His Ser Thr Leu Asp Gly Tyr Ser Arg Arg Thr Thr Leu Ser Ser Lys Met Tyr His Thr Lys Gly Gln Glu Gly Ser Val Cys Leu Arg Ser Ser Asp Cys Ala Ser Gly Leu Cys Cys Ala Arg His Phe Trp Ser Lys Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His Arg Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys Gly Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser Asn Ser Ser Arg Leu His Thr Cys Gln Arg His (SEQ ID NO: 27)

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CLAIMS

1. A method of treating a subject suffering from a cancer, comprising the steps of:

determining that the subject has a constitutively activating mutation in a beta-catenin protein (SEQ ID NO: 2) in a cancer sample; and

administering to the subject determined to have the constitutively activating mutation in a beta-catenin protein (SEQ ID NO: 2) an effective amount of an anti-Dkk-1 antibody or antigen binding-fragment thereof,

wherein the cancer is an esophageal cancer or a uterine cancer

wherein the anti-Dkk-1 antibody or antigen binding-fragment thereof comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity determining regions (CDRs) LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2 and HCDR3, wherein LCDR1 has the amino acid sequence of SEQ ID NO: 6, LCDR2 has the amino acid sequence of SEQ ID NO: 7, wherein Xaa at position 2 is Ala and Xaa at position 6 is Ile, LCDR3 has the amino acid sequence of SEQ ID NO: 8, wherein Xaa at position 4 is Glu, HCDR1 has the amino acid sequence of SEQ ID NO: 9, HCDR2 has the amino acid sequence of SEQ ID NO: 10, and an HCDR3 has the amino acid sequence of SEQ ID NO: 11, wherein Xaa at position 4 is Asn, and

wherein the mutation is a deletion of Exons 2, 3, and 4 (SEQ ID NOs: 3, 4, and 5) or is any one of the mutations of amino acid residues of SEQ ID NO:2 selected from D32G, D32N, D32Y, G34E, G34R, G34V, S37F, I35S, S33C, S33F, S33Y, S37A, S37C, S37P, S45C, S45F, T41A, T41I, S33A, K335T, D32A, D32V, H36P, S33P, S45Y, S37Y, S45P, T42_K49del, K335I, N387I, or N387K.

2. The method of Claim 1, further including administering an effective amount of a chemotherapeutic agent.

3. The method of Claim 2, wherein the chemotherapeutic agent is a taxane, paclitaxel, docetaxel, carbazitaxel, gemcitabine, carboplatin, cisplatin, oxaliplatin, fluorouracil, capecitabine, or tegafor, or any functional analog thereof.

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4. The method of any one of claims 1 to 3, wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 16 and the HCVR comprises the amino acid sequence of SEQ ID NO: 17.

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5. The method of Claim 4, wherein the anti-Dkk-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 22 and a light chain comprising the amino acid sequence of SEQ ID NO: 23.

6. The method of any one of Claims 1 to 5, wherein the subject is a human.

7. The method of Claim 1, wherein the mutation includes a deletion of Exons 2, 3, and 4 (SEQ ID NOs: 3, 4, and 5).

8. The method of Claim 1, wherein the mutation is a mutation of any one of the amino acid residues selected from Ser33, Ser37, Thr41, and Ser45 of the protein of SEQ ID NO: 2.

9. The method of Claim 1, wherein the esophageal cancer is a cancer of the gastro-esophageal junction.

Patient ID	Response[1]	Cycles on Treatment[1]	CTNNB1 Mutation	Predicted Effect	Allelic Frequency	Gene Panel
105-023	PR (-73%)	16+ cycles (on going)	Exon 2-4 deletion	Stabilizing	Unknown	Foundation One
104-004	PR (-67%)	13+ cycles (on going)	Not detected	NA	NA	Archer VariantPlex Solid Tumor
108-003	PR (-40%)	10 cycles (off treatment)	C-term truncation: Q27Ter	Unknown	6%	Archer VariantPlex Solid Tumor
109-008	PR (-35%)	3+ cycles (on going)	S45F	Stabilizing	2%	Archer VariantPlex Solid Tumor
109-003	SD (-7%)	9+ cycles (on going)	I35N T41I	Most likely stabilizing Stabilizing	3% 4%	Archer VariantPlex Solid Tumor
104-014	SD (-6%)	4+ cycles (on going)	Not detected	NA	NA	Solid Tumor Hotspot NGS
109-001	SD (-2%)	3 cycles (off treatment)	Not detected	NA	NA	Archer VariantPlex Solid Tumor
104-016	PD (13%)	2 cycles (off treatment)	Not detected	NA	NA	Guardant 360
104-017	PD (8%)	2 cycles (off treatment)	Not detected	NA	NA	Foundation One
104-020	PD (69%)	2 cycles (off treatment)	Not detected	NA	NA	Archer VariantPlex Solid Tumor
104-018	PD (90%)	2 cycles (off treatment)	D6N	Most likely no effect	11%	Archer VariantPlex Solid Tumor
104-023	PD (260%)	2 cycles (off treatment)	Not detected	NA	NA	Archer VariantPlex Solid Tumor

[1] Response as of 8/3/16, best response. Cycles are 28 day periods – treatment delays may prolong or adjust these durations.
Legend: Partial response (PR). Stable disease (SD). Progressive disease (PD).
[2]For the Archer VariantPlex Solid Tumor Gene Panel, the Archer Analysis (version 4.1.0.5) default parameters were used to identify CTNNB1 mutations

FIG. 1

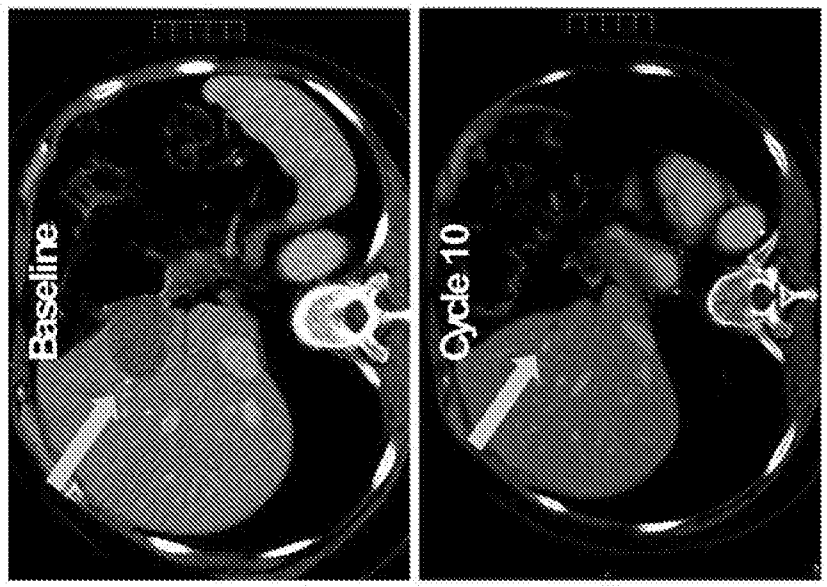
Baseline
Cycle 10

FIG. 2B

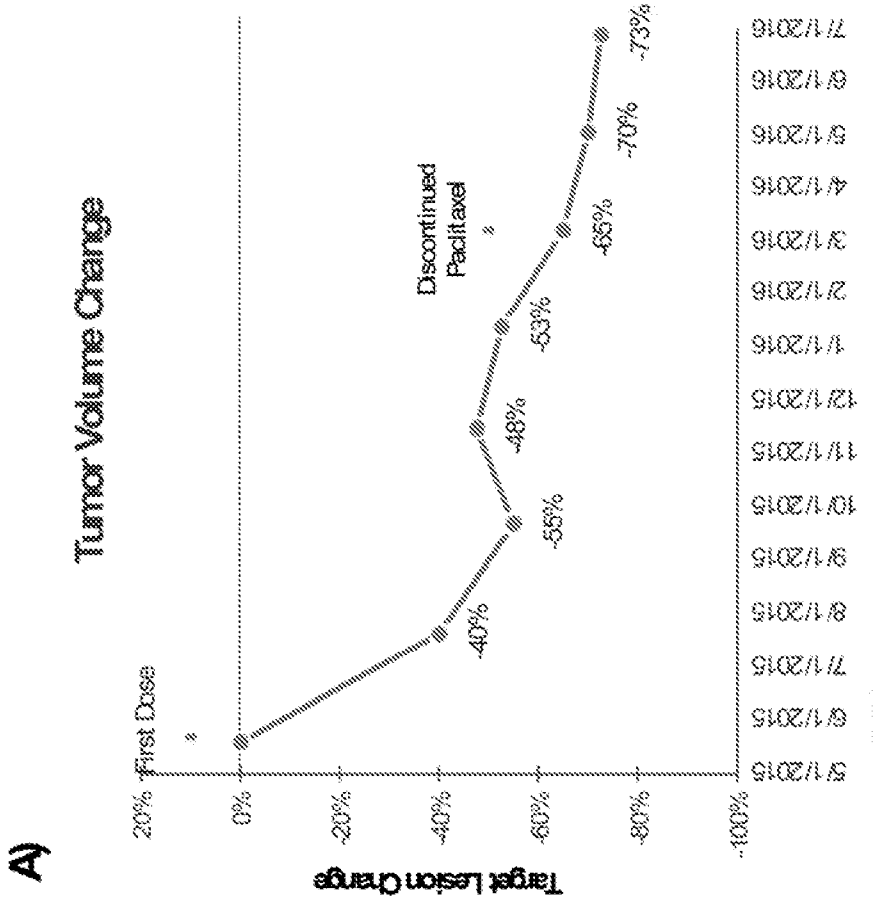
A)
Tumor Volume Change
Target Lesion Change
20%
0%
-20%
-40%
-60%
-80%
-100%
First Dose
-40%
-55%
-48%
-53%
-65%
-70%
-73%
Discontinued Paclitaxel
5/1/2015
6/1/2015
7/1/2015
8/1/2015
9/1/2015
10/1/2015
11/1/2015
12/1/2015
1/1/2016
2/1/2016
3/1/2016
4/1/2016
5/1/2016
6/1/2016
7/1/2016

FIG. 2A

CTNNB1 genomic DNA sequence (includes introns)
(SEQ ID NO: 1)

Exon 2
ATGGCTACTCAAGgtttgtgtcattaaatctttagttactgaattggggc 50
tctgcttcgttgccattaagccagtctggctgagatcccccctgctttcct
ctctccctgcttacttgtcaggctacctttttgctccatttttctgctcact
cctcctaatggcttggtgaaatagcaaacaagccaccagcaggaatctag
tctggatgactgcttctggagcctggatgcagtaccattcttccactgat
tcagtgagtaactgttaggtggttccctaagggattaggtatttcatcac
tgagctaaccctggctatcattctgcttttcttggctgtctttcagattt
gactttatttctaaaaatatttcaatgggtcatatcacagattcttttttt
tttaaattaaagtaacatttccaatctactaatgctaatactgtttcgta 400
Exon 3
tttatagCTGATTTGATGGAGTTGGACATGGCCATGGAACCAGACAGAAA
AGCGGCTGTTAGTCACTGGCAGCAACAGTCTTACCTGGACTCTGGAATCC 500
ATTCTGGTGCCACTACCACAGCTCCTTCTCTGAGTGGTAAAGGCAATCCT
GAGGAAGAGGATGTGGATACCTCCCAAGTCCTGTATGAGTGGGAACAGGG
ATTTTCTCAGTCCTTCACTCAAGAACAAGTAGCTGgtaagagtattattt
ttcattgccttactgaaagtcagaatgcagttttgagaactaaaaagtta
gtgtataatagtttaaataaaatgttgtggtgaagaaaagagagtaatag
caatgtcacttttaccatttaggatagcaaatacttaggtaaatgctgaa
Exon 4
ctgtggatagtgagtgttgaattaacctttccagATATTGATGGACAGT 850
ATGCAATGACTCGAGCTCAGAGGGTACGAGCTGCTATGTTCCCTGAGACA
TTAGATGAGGGCATGCAGATCCCATCTACACAGTTTGATGCTGCTCATCC
CACTAATGTCCAGCGTTTGGCTGAACCATCACAGATGCTGAAACATGCAG 1000
TTGTAAACTTGATTAACTATCAAGATGATGCAGAACTTGCCACACGTGCA
ATCCCTGAACTGACAAAACTGCTAAATGACGAGGACCAGgtaagcaatga
catagctagctttttagtctgctttgaagtaaatgctcaaggggagtagt
ttcagaatgtctacccaataccagtacttgaaaactaacgatgtttctga
attcctgtattacagGTGGTGGTTAATAAGGCTGCAGTTATGGTCCATCA
GCTTTCTAAAAAGGAAGCTTCCAGACACGCTATCATGCGTTCTCCTCAGA
TGGTGTCTGCTATTGTACGTACCATGCAGAATACAAATGATGTAGAAACA
GCTCGTTGTACCGCTGGGACCTTGCATAACCTTTCCCATCATCGTGAGGG
CTTACTGGCCATCTTTAAGTCTGGAGGCATTCCTGCCCTGGTGAAAATGC
TTGGgtaagaaaacatgtcagaatgcttgaagctaaaaagtagaagagta 1500
tactcacaatatttctgatgaggctttttttcttcttcccagTTCACCAGT
GGATTCTGTGTTGTTTTATGCCATTACAACTCTCCACAACCTTTTATTAC
ATCAAGAAGGAGCTAAAATGGCAGTGCGTTTAGCTGGTGGGCTGCAGAAA
ATGGTTGCCTTGCTCAACAAAACAAATGTTAAATTCTTGGCTATTACGAC
AGACTGCCTTCAAATTTTAGCTTATGGCAACCAAGAAAGCAAGgtaagag
aattattctttatgtggttttcatggagcattggacacctccagtgtcat
gtcattccatgcagtgttcctaacctttttggcaccagggaccagtttcg
tggaaaacagtttttccatgaatgggttgtgggaatggtttctggatgac
accattccacctcagataatcaggcattagattctcatagggagcgtgca
gcctagatcctcgcatgtgcagtccacactagggtttctactcctatga 2000
gactctcatggtgcagttgatctgacaggaggtagagctcaagccaggta
atgctcgctcacctgccacttacctcctgctgtgcagcccagttcatttc
tgttcttttaaatttttgagtttccatatgtaaagcactatgcgaagtag
tagggatatggtaggcaagcttctcttcacactttgttcttaggtggga
tgtagatgttgggaataataacctaatatttaatttgtgtagtgggaaga 2250

FIG. 3A

agtggggctatgagggcacataacacaagttgaaactgactctttttgag 2300
ggttcaaggagacctcttggaggaagtgatagttgagttcagtgttcaag
gatgagaagggattcactaggtgaaggttaggtgagaaaacaacatcttt
gaaacgaaggaaggagatggaaagttttgggaatttaagaaatactaata
gtaaggaggaagaaaggtttgaggtgaggctattgagatagacttagcag 2500
atctcatagggctttgtagagcatgtttaaaagcacaatgggaaatttca
gcagaagcctgaaatgatgaaatttgtttttagaaaattggggcagtgtt
gaaagggaagatatacagggaatgaaaggacaagcatgaatgatcatttt
atggtatctgtttttaaggtggatataattaggaaaattaaagggccaaa
tgatgaggagttaagtgccagttctggttcaaattttcagtgaatcagtt
ttgatataactttcatcttagggcattactcttgcctaccaacatagttt
ctaaatttttttctttggtgtgatcactgtgggaagaaggaaattgggc
ccaaactgatacattgtttggaggactgggatgtctgaatttgagtggaa
tgctttaaaaggacaagttggatagggccccagtatgggggtctgagtga
tggggtccaggaatacatttaggtccaatggcaagctggctgaaattctt 3000
gtataataaaataggttggtaatatggctcttctcagacatgtgatcaag
attccttgactaacaagatatatatatatatctttctagCTCATCATACT
GGCTAGTGGTGGACCCCAAGCTTTAGTAAATATAATGAGGACCTATACTT
ACGAAAAACTACTGTGGACCACAAGCAGAGTGCTGAAGGTGCTATCTGTC
TGCTCTAGTAATAAGCCGGCTATTGTAGAAGCTGgtaagtatatgtatct
attctgagtcttgtgtatagcatctgcagttctaattagattacttttct
taggaaaaggtggtagaactttaactactgaaaataaatggtcctattca
gtttgcagccaagatttacattcagagtacctgtcatctggattgtagct
aaatatttaaggctagtttaggtagagttcttattatccatcaaaaatga
tggcatatgttttgcttaataaaatttgtttgtaatttcagttttgagta 3500
aacctaagatttgctaacagagctgtgaatttataggagaaaagacaaat
tctaatatagtacagttttatgtaaagtgattgctttattagtagatgct
catgagcagtttttgttttgttttaacttttaggttccgggtaatgtgca
ggcttgttatataggtaaattgcatgtcacaggggtttcgtgtgcagatt
attttgtcacccaggcagtaagtattgtacccaataggtagtttttcagt
tctttacctcccacccgtaagtaggccccagtgtctgttgttcccttctt
tgtgcccgtgtgtactcagtgtttacctcccacttataagtgagaacatg
tggtatttggtttttctattcctatgttagtttgcttaggataatggcctc
cagctccatccatgttgctgaggaagacatcttggtatttttttatggct
gcttagtattccatagtatatatgtaccacatttttctttatctagtctac 4000
cattgatgggcatttaggttaattccatatctttgctattgtgaataatg
ctgcagtgaacatatgcatgcatgtgtctttatggtaaaaagatttcttt
ttctttgggcatatacctaataataggattgctggattgaatggtaattc
tgtcaggtttttgagaaatcaccaaattgctttccacaatggctgaact
aatttacttttcccaccagcagtgtataagcattctcttttctcagcaacc
tcaccagcatctgtcatttttgacttttttattagtagccattctaactg
gtgtgagacggtatctcattgtggttttgatttgcatttctctaatgatc
agtgatgtcgagcttttcttcatatgtttcttggccacttgtatgtcttc
ttttgaaaagtgtctgttcatgtcctttgcccacttttaatggggttgt
tctttttgcttgttaatttaagtttattgtaaactctggatattagacc 4500
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aagctctttatactgtcccatttgtcagtttttgttttttgttgcaacttc
tcttggcatcttcgtcatgaaatctttgccaggtcttatgtccagaatgg
tatttcctaggttatcttgcagagtttttacagttttaagttttatattt
aagtctttaatccattctgagttgatttttgtacatcatgtaaggatggg
gtgcagtttcaatcttggatgtggctagccagttatcccagcaccattta 4750

FIG. 3B

```
ttgaatagggagtcctttccccattgcttgtttttgtttacttgttaggt 4800
gtgcggcctaacttctgggctttctttttctgttccattggtctctgtgtc
tgtttgtataccagtaccatgctgtgattgtaaccttgtattaacagtat
agcttgaagttgggtaaagtgattcctccagttttgttctttttgcttag
gattgccttggctattcaggctctttttttgggttcatatgaatttttaaa 5000
tagtttttttttaattatgtgaagaatgccattggtagtttggtaggaat
agcattgaatctgtgaattgctttgggctgtatggccattttaacaatat
tgattcttcctgccatgaaatagaatgtttttttcatttgttggtgtcatc
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gtgtatgttggcaattgggggaaaagaatagatggtttgtactagggcctc
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ggctggcaacacttacttttctcacttattgagagtaattttacttggga
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gagggaaaaggtctccttgaaaaggggatgttaagtgggactgcaggatg 6500
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ggttcctataagatagttactactcatggagtttattcatgctttattcc
agctttggagccatagatacagaatactttggtcagtttggaaggctagg 7350
```

FIG. 3C

```
tgggatccaaattctaaacggttcctcagggttatactaaagtatttcta 7400
ttatcttaaaaggatgctgagacactttcgatggttgtttatcaatagca
aagcatcacagtggtgtgtttaaaatattaataatagcattgtatagatt 7500
aacagtttgaatgaccaaaagctagaagaccagactactgagatgttaca
ggctttttaggaatgaaatagtttgctttttagaactcaatagcaaagggca
gatgtctgagatgcctgaaagaatcatagaatgtaataatataggagcta
agggagcaaccaaaaaacggtttgtggaggggacaacattggtaccatgaa
gataaaatggaaccctcagaaggcatccttaatttttgaacataataattt
aagaagctgacttaaagtgacttaaaaggtcagtaggtagctggaaatgt
atgatactagaatgcaagagaggcaggctagagatttggaagtttccctc
ttagtatataggggtaagggcagcagggaaggggaggtagaggtgccaca
gagtcatctgtatgggacttttttttttaccctagaactgctgaatcaga
atgtgtgtgttttaaagtctctgtaggccattctgatggacatctggggt 8000
taaaatccattctcttagagttaatagttatgtaaaggggagggaatgaag
tcttaaagaggggaaagaaggtagtcatttcacaaatactgagcatcctg
atcatcagtcttacgcagatcattctattagtagctggagctactatgaa
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acctcatctgaggaaataaaacagacccgaaagatgaaggagacaaggaa
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gaagttaatctactatgtgggcattgggcttccatttatactcctttgcc
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cttggaacacatgttttgtagtcagtgaattgtataaagtccctgacagt 8500
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tagcttctttaggtctttagtcagatgtcaccttcacagtgaggtgacct
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ctttaatatcatctgacatactgtatggttttagtttattgtatattttt
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aggaacagtagctatttgagagtttgtcactagtgaggtgaactggcaaa
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agaacagatatttaggattgataggcacttctagctaatgactagggcct
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ATCTTTCAGATGCTGCAACTAAACAGgtaaattctgagtaaactggtgcc
atgggaatagagtcaagatgagtatgtgcttgtactgaccatctgttttt
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TGGGTTCAGATGATATAAATGTGGTCACCTGTGCAGCTGGAATTCTTTCT
AACCTCACTTGCAATAATTATAAGAACAAGATGATGGTCTGCCAAGTGGG
TGGTATAGAGGCTCTTGTGCGTACTGTCCTTCGGGCTGGTGACAGGGAAG 9500
ACATCACTGAGCCTGCCATCTGTGCTCTTCGTCATCTGACCAGCCGACAC
CAAGAAGCAGAGATGGCCCAGAATGCAGTTCGCCTTCACTATGGACTACC
AGTTGTGGTTAAGCTCTTACACCCACCATCCCACTGGCCTCTGATAAAGg
taaattgtcaaagtagaatttaccttttgttgcagaattgaaaatgaagca
tctctagctgttggatggctgtctaagcatagtgatcaataagtaggaat
tgtattccttagtaagtaggaagtatggctgcgataggggtaagattctg
aaatgtttgtgtagtcagaactacttttagttgataccaatagatttagt
gtggtgggaattttagggtaagaaaatgattttgttgagttgtatgccag 9900
```

FIG. 3D

```
ttcttccttctgtttttcagGCTACTGTTGGATTGATTCGAAATCTTGCC 9950
CTTTGTCCCGCAAATCATGCACCTTTGCGTGAGCAGGGTGCCATTCCACG 10000
ACTAGTTCAGTTGCTTGTTCGTGCACATCAGGATACCCAGCGCCGTACGT
CCATGGGTGGGACACAGCAGCAATTTGTGgtaggtaaattcttacagtga
tacctggctatctaaaaggaatgcataaatccaaaggatcctgaacttct
ttctttggtcattggttcccccatccgtcttcctgaagagctaatgaca
aagtaaataaataaataattacacatttctatggctgcagagaaaataag
gcatagtgtggccccagtgatatttccttggacacgtccttcacatggtc
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gactttaagaccttattaggttagtttagaaaacaaagatggagcctacc
agaacagatgttaggaatctcattttgctggttgctttgtgtatgtactc
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cttttctaggaagaagagagtttttgtgtccttgtaagaatcaagttatt
tataaaagctgctaaatgtagcagaataataacccctttaaaaactcaaa
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atgtaaaagaaaaacgttgacatagtctgagcattactttctcatcttct
ctttttatatacctttacccagaatgattggtgcccttactgtaggaaa
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ggggaggggtgctgctttgaattagtgctgccaggaggcctcttttcagt
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cctcaaactttacagaggagaatgccctgtttgttaaccatgtttctttt 11500
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CTTCACATCCTAGCTCGGGATGTTCACAACCGAATTGTTATCAGAGGACT
AAATACCATTCCATTGTTTGTGCAGgtatgttttaagtgaagtgttctag
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ggaatgtttgcaccacagtgggggggcttgccatgttttagctttagattt
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AGGAAGCTGCAGAAGCTATTGAAGCTGAGGGAGCCACAGCTCCTCTGACA
GAGTTACTTCACTCTAGGAATGAAGGTGTGGgtaagtaaaaaggaaccaa
agcctttagcagatgtgtacattgaagtctcagtttttcctcaagggcct
ttttctccttgtctcttagCGACATATGCAGCTGCTGTTTTGTTCCGAAT
GTCTGAGGACAAGCCACAAGATTACAAGAAACGGCTTTCAGTTGAGCTGA
CCAGCTCTCTCTTCAGAACAGAGCCAATGGCTTGGAATGAGgtagggaaa 12500
```

FIG. 3E

```
tgtgagcagttatttatctggtagtttcctagagcaggtatggcagcttg 12550
ttctttcctctcaaaacacttagtacacattcatttgcattgatgtttcc
ctggcttgagtatttcttctttatgctgtctagcaactgctctgaggaag
aactataatacaagctttaaagagtctgttcagaatcattacaaataagt
tgtgttatttaaaattataattcataagggagaaagatgaaaaatgttac
cagattaaagaagatttttcaaaaggatgtaaggaaagaggcagtgttaa
acactgttaagaggacagtttatcagtatttttactaaactttaataaa
acttttctatttgaatttctgctatgaatttttcttcagcatttgtcctc
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GCTGATCTTGGACTTGATATTGGTGCCCAGGGAGAACCCCTTGGATATCG
CCAGGATGgtatgtgtctcatatttctcgattaactccagatcaagctaa
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actcctgtttctaggctcagatctcgggtgggtttttacatagttgcatt
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catctgcttctacctaattatgaaaccactaaagcgcagattcttactgt
gagaaataacatgtcaaccctaagataaaatatgttgaggtttcatggaa
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ccctgactcttctagATCCTAGCTATCGTTCTTTTCACTCTGGTGGATAT
GGCCAGGATGCCTTGGGTATGGACCCCATGATGGAACATGAGATGGGTGG 15000
CCACCACCCTGGTGCTGACTATCCAGTTGATGGGCTGCCAGATCTGGGGC
ATGCCCAGGACCTCATGGATGGGCTGCCTCCAGGTGACAGCAATCAGCTG 15100
GCCTGGTTTGATACTGACCTGTAA                             15124
```

FIG. 3F

Uterine Tumor ID	CTNNB1 Mutation
TCGA-AP-A0LV-01	D32G
TCGA-BK-A0CB-01	D32G
TCGA-AX-A05U-01	D32N
TCGA-A5-A0GV-01	D32N
TCGA-BG-A0VX-01	D32N
TCGA-BS-A0T9-01	D32N
TCGA-A5-A0GX-01	D32Y
TCGA-B5-A0K6-01	D32Y
TCGA-BG-A0W2-01	D32Y
TCGA-D1-A17S-01	D32Y
TCGA-AX-A05W-01	G34E
TCGA-A5-A0VQ-01	G34E
TCGA-A5-A0GN-01	G34R
TCGA-AP-A0LL-01	G34R
TCGA-BG-A0MU-01	G34R
TCGA-B5-A11F-01	G34R
TCGA-D1-A102-01	G34R
TCGA-D1-A17N-01	G34R
TCGA-BS-A0WQ-01	G34V
TCGA-D1-A17M-01	G34V,D32N
TCGA-AX-A0J0-01	M553V,S37F
TCGA-D1-A16R-01	Q623E,I35S
TCGA-B5-A0JY-01	R453Q,D32N
TCGA-AX-A062-01	S33C
TCGA-BG-A0MO-01	S33C
TCGA-A5-A0R9-01	S33C
TCGA-BS-A0UT-01	S33C
TCGA-D1-A0ZN-01	S33C
TCGA-AP-A05N-01	S33F
TCGA-AX-A05T-01	S33F
TCGA-A5-A0GU-01	S33F

Esophageal Tumor ID	CTNNB1 Mutation
TCGA-R6-A6XQ-01	S33A
TCGA-R6-A8WG-01	S37F
TCGA-LN-A7HX-01	R90L
TCGA-L5-A4OJ-01	V136A
TCGA-L5-A8NM-01	X561_splice
TCGA-L5-A8NR-01	Q68* (nonsense/truncating)
TCGA-R6-A8W5-01	E571* (nonsense/truncating)
TCGA-VR-AA4G-01	S681F
TCGA-V5-A7RB-01	K335T

Liver Tumor ID	CTNNB1 Mutation
TCGA-DD-AACP-01	D32A,S33Y
TCGA-EP-A2KC-01	D32G
TCGA-G3-A5SL-01	D32G
TCGA-DD-A73D-01	D32G
TCGA-ED-A7PZ-01	D32G
TCGA-G3-AAV1-01	D32G
TCGA-DD-AACB-01	D32G
TCGA-DD-AAW1-01	D32G
TCGA-UB-A7MD-01	D32N
TCGA-G3-AAV5-01	D32N
TCGA-DD-AAVY-01	D32N
TCGA-DD-A73E-01	D32V
TCGA-MI-A75H-01	D32V
TCGA-RC-A6M4-01	D32V
TCGA-CC-A7IK-01	D32V
TCGA-CC-A7IL-01	D32V
TCGA-DD-A4NF-01	D32Y
TCGA-G3-AAV3-01	D32Y
TCGA-DD-AAW2-01	E54D,T41A
TCGA-EP-A3RK-01	G34E
TCGA-ZS-A9CG-01	G34R
TCGA-DD-AAC8-01	G34R
TCGA-DD-A119-01	G34V
TCGA-G3-A3CJ-01	G34V
TCGA-CC-A9FW-01	G34V
TCGA-DD-A1EL-01	H36P
TCGA-DD-A4NI-01	H36P
TCGA-DD-AACD-01	H36P
TCGA-G3-A3CK-01	H36P,S33P
TCGA-ZP-A9D4-01	I35S
TCGA-DD-AACX-01	

FIG. 4A

TCGA-A5-A0GW-01	S33F
TCGA-D1-A0ZU-01	S33F
TCGA-D1-A17C-01	S33F
TCGA-AP-A0LN-01	S33Y
TCGA-B5-A0K7-01	S33Y
TCGA-B5-A0JT-01	S33Y
TCGA-D1-A165-01	S33Y
TCGA-AP-A0LG-01	S37A
TCGA-B5-A11V-01	S37A
TCGA-BS-A0V7-01	S37A
TCGA-AP-A0LJ-01	S37C
TCGA-B5-A0K0-01	S37C
TCGA-BG-A0LW-01	S37C
TCGA-AX-A0IS-01	S37C
TCGA-D1-A15Z-01	S37C
TCGA-D1-A17T-01	S37C
TCGA-BG-A0M3-01	S37C,S646F
TCGA-A5-A0GM-01	S37F
TCGA-BG-A0MG-01	S37F
TCGA-BG-A0VT-01	S37F
TCGA-D1-A0ZQ-01	S37F
TCGA-D1-A16B-01	S37F
TCGA-D1-A16Q-01	S37F
TCGA-D1-A17R-01	S37F
TCGA-BG-A0MI-01	S37P
TCGA-AP-A0LE-01	S37P
TCGA-B5-A121-01	S45C
TCGA-BS-A0TG-01	S45F
TCGA-B5-A11Z-01	T41A
TCGA-A5-A0GI-01	T41I
TCGA-BS-A0UJ-01	T41I
TCGA-B5-A11U-01	T41I
TCGA-DD-AAVP-01	I35S
TCGA-EP-A12J-01	S33A
TCGA-FV-A4ZQ-01	S33C
TCGA-ED-A7XP-01	S33C
TCGA-G3-AAV4-01	S33C
TCGA-DD-AAE3-01	S33C
TCGA-DD-AAVX-01	S33C
TCGA-XR-A8TF-01	S33F
TCGA-DD-AACA-01	S33F
TCGA-DD-A116-01	S33P
TCGA-DD-A39V-01	S33P
TCGA-G3-A6UC-01	S33P
TCGA-DD-AADE-01	S33P,S45Y
TCGA-CC-A5UD-01	S33Y
TCGA-DD-AADD-01	S33Y
TCGA-KR-A7K0-01	S37A
TCGA-DD-AAEK-01	S37A
TCGA-UB-A7MC-01	S37C
TCGA-DD-AADG-01	S37C
TCGA-BW-A5NQ-01	S37F
TCGA-5C-A9VG-01	S37F
TCGA-DD-AAD0-01	S37Y
TCGA-4R-AA8I-01	S45F
TCGA-LG-A9QD-01	S45F
TCGA-ZP-A9CV-01	S45F
TCGA-3K-AAZ8-01	S45F
TCGA-BC-A10U-01	S45F,S45Ffs*5
TCGA-O8-A75V-01	S45P
TCGA-RG-A7D4-01	S45P
TCGA-NI-A8LF-01	S45P
TCGA-G3-AAV2-01	S45P
TCGA-G3-AAV6-01	S45P

FIG. 4B

TCGA-8G-A187-01	T41I
TCGA-AP-A059-01	V199I
TCGA-BS-A0V8-01	K170M
TCGA-B5-A11E-01	K354T
TCGA-AP-A054-01	M688T
TCGA-AP-A0LM-01	R535Q
TCGA-AP-A056-01	R587Q,D712N
TCGA-AX-A0J1-01	R710H
TCGA-D1-A103-01	A215T

TCGA-2Y-A9H1-01	S45P
TCGA-WX-AA47-01	S45P
TCGA-DD-AAEE-01	S45P
TCGA-DD-AAEH-01	S45P
TCGA-DD-AAVQ-01	S45P
TCGA-DD-AAW3-01	S45P
TCGA-DD-A4NK-01	S45Y
TCGA-5R-AA1C-01	S45Y
TCGA-DD-A11D-01	T41A
TCGA-2Y-A9HB-01	T41A
TCGA-DD-AACJ-01	T41A
TCGA-DD-AADU-01	T41A
TCGA-DD-AAE9-01	T41A
TCGA-EP-A26S-01	T41I
TCGA-2Y-A9HA-01	T41I
TCGA-CC-A7IH-01	T42_K49del
TCGA-DD-A1EA-01	L31_I35del
TCGA-DD-A1ED-01	V136A
TCGA-CC-5262-01	W383C
TCGA-G3-A5SJ-01	Y333F
TCGA-DD-A39Y-01	K181Rfs*28
TCGA-DD-A1EJ-01	K335I
TCGA-DD-A3A4-01	K335I
TCGA-DD-A4NL-01	K335I
TCGA-MI-A75C-01	K335I
TCGA-DD-AACK-01	K335I
TCGA-K7-A6G5-01	K335T
TCGA-DD-A39W-01	L139F
TCGA-G3-A25Z-01	L405F
TCGA-DD-A1EE-01	L405F,K335I
TCGA-DD-A73A-01	N387I
TCGA-EP-A3JL-01	N387K

FIG. 4C

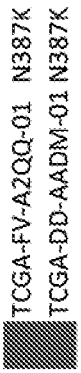

FIG. 4D