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(54) **Title:** METHODS OF TREATING CANCER PATIENTS WITH FARNESYLTRANSFERASE INHIBITORS

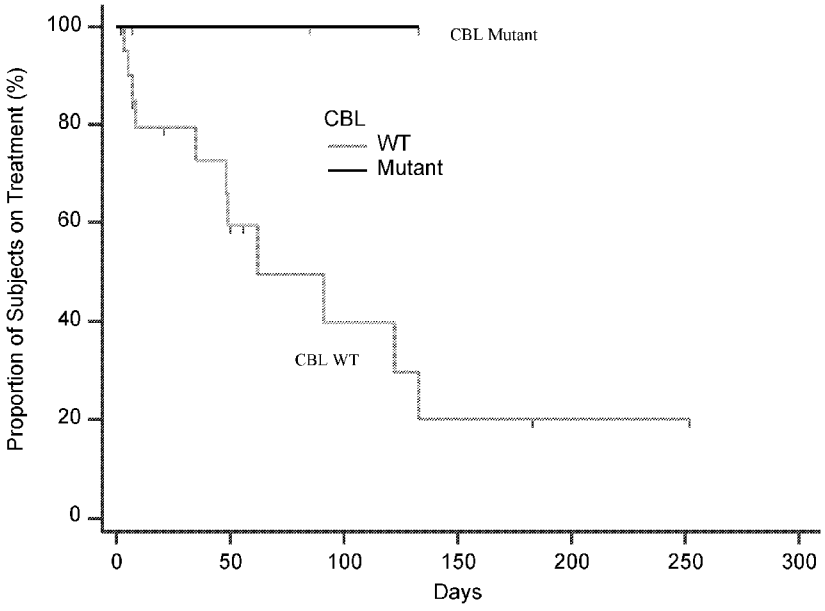

Fig. 1

(57) **Abstract:** The present invention relates to the field of molecular biology and cancer biology. Specifically, the present invention relates to methods of treating a CBL-mutant cancer in a subject with a farnesyltransferase inhibitor (FTI). The present invention also relates to methods of treating a subject with a farnesyltransferase inhibitor (FTI) that include determining whether the subject is likely to be responsive to the FTI treatment based on the mutation status of a member of the CBL family in the subject.

[Continued on next page]

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METHODS OF TREATING CANCER PATIENTS WITH FARNESYLTRANSFERASE INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/596,686, filed December 8, 2017, the entire contents of which is hereby incorporated by reference.

FIELD

[0002] The present invention relates to the field of cancer therapy. In particular, provided are methods of treating cancer, with farnesyltransferase inhibitors.

BACKGROUND

[0003] Stratification of patient populations to improve therapeutic response rate is increasingly valuable in the clinical management of cancer patients. Farnesyltransferase inhibitors (FTI) are therapeutic agents that have utility in the treatment of cancers, such as leukemia (e.g., acute myeloid leukemia (AML), chronic myelogenous leukemia (CML)) and myelodysplastic syndromes (MDS)/myeloproliferative neoplasms (MPN) (e.g., chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML)). However, patients respond differently to an FTI treatment. Therefore, methods to predict the responsiveness of a subject having cancer to an FTI treatment, or methods to select cancer patients for an FTI treatment, represent unmet needs. The methods and compositions provided herein meet these needs and provide other related advantages.

SUMMARY

[0004] Provided herein are methods of treating a CBL-mutant cancer in a subject (e.g., a human) comprising administering a farnesyltransferase inhibitor (FTI) to the subject.

[0005] In certain embodiments, provided herein are methods of treating a CBL-mutant cancer in a subject in need thereof, said method comprising administering a therapeutically

effective amount of an FTI to said subject, wherein the CBL-mutant cancer is a cancer known to have or determined to have a mutation in a member of the CBL family.

[0006] In certain embodiments, provided herein are methods of treating a CBL-mutant cancer in a subject in need thereof, said method comprising administering a therapeutically effective amount of an FTI to said subject, wherein the CBL-mutant cancer is a cancer known to have or determined to have a mutation in CBL. In some embodiments, the mutation in CBL comprises an amino acid modification (e.g., substitution or deletion) at a codon selected from a group consisting of C384, C404, R420, and E479. In some embodiments, the mutation in CBL is selected from a group consisting of E479fs, C384Y and C404Y.

[0007] In certain embodiments, provided herein are methods of treating a CBL-mutant cancer in a subject in need thereof, said method comprising administering a therapeutically effective amount of an FTI to said subject, wherein the CBL-mutant cancer is a cancer known to have or determined to have a mutation in CBLB.

[0008] In certain embodiments, provided herein are methods of treating a CBL-mutant cancer in a subject in need thereof, said method comprising administering a therapeutically effective amount of an FTI to said subject, wherein the CBL-mutant cancer is a cancer known to have or determined to have a mutation in CBLC.

[0009] In certain embodiments, the cancer treated in accordance with the methods provided herein is leukemia. In certain embodiments, the cancer treated in accordance with the methods provided herein is a myelodysplastic syndrome (MDS). In certain embodiments, the cancer treated in accordance with the methods provided herein is chronic myelomonocytic leukemia (CMML). In certain embodiments, the cancer treated in accordance with the methods provided herein is juvenile myelomonocytic leukemia (JMML). In certain embodiments, the cancer treated in accordance with the methods provided herein is acute myeloid leukemia (AML). In certain embodiments, the cancer treated in accordance with the methods provided herein is chronic myelogenous leukemia (CML).

[0010] In certain embodiments, the methods provided herein comprise a step of detecting the presence of a mutation in a member of the CBL family in a sample from the subject (e.g., prior to treatment). In some embodiments, the sample from the subject is a bone marrow sample. In

some embodiments. In some embodiments, the sample from the subject is a blood sample. In some embodiments, the sample from the subject comprises a cell or tissue of the cancer. In some embodiments, the sample is a tumor biopsy. In some embodiments, the cancer is determined to have a mutation in a member of the CBL family. In some embodiments, the mutation is detected by a method selected from the group consisting of sequencing, Polymerase Chain Reaction (PCR), DNA microarray, Mass Spectrometry (MS), Single Nucleotide Polymorphism (SNP) assay, denaturing high-performance liquid chromatography (DHPLC), and Restriction Fragment Length Polymorphism (RFLP) assay. In some embodiment, the methods provided herein comprise treating the subject if the subject is determined to have a mutation in a member of the CBL family (e.g, CBL, CBLB, and/or CBLC).

[0011] In certain embodiments, the methods provided herein comprise treating CBL-mutant cancer by administering an FTI to a subject for at least or more than 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months or 1 year. In some embodiments, an FTI is administered on days 1-21 of a 28-day treatment cycle. In some embodiment, an FTI is administered on days 1-7 of a 28-day treatment cycle. In some embodiments, an FTI is administered on days 1-7 and 15-21 of a 28-day treatment cycle. In some embodiments, an FTI is administered for at least 3 cycles or at least 6 cycles. In some embodiments, an FTI is administered twice a day. In some embodiments, the subject is or remains responsive to treatment with an FTI for at least or more than 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months or 1 year. In some embodiments, an FTI is tipifarnib. In some embodiments, an FTI (e.g., tipifarnib) is administered at a dose in the range of 200-1200 mg (e.g., orally, twice a day). In some embodiments, an FTI (e.g., tipifarnib) is administered at a dose of 900 mg twice a day (e.g., orally). In some embodiments, an FTI (e.g., tipifarnib) is administered at a dose of 600 mg twice a day (e.g., orally). In some embodiments, an FTI (e.g., tipifarnib) is administered at a dose of 400 mg twice a day (e.g., orally). In some embodiments, an FTI (e.g., tipifarnib) is administered at a dose of 300 mg twice a day (e.g., orally). In some embodiments, an FTI (e.g., tipifarnib) is administered at a dose of 200 mg twice a day (e.g., orally).

[0012] In some embodiments, the methods provided herein further comprise administering a second active agent or a support care therapy (e.g, a therapeutically effective amount of a second active agent).

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 shows proportion of subjects with CMML having wild type CBL and subjects with CMML having a mutant CBL remaining on-treatment with tipifarnib as a function of time. CBL gene status was determined for 24 patients. The figure shows that a trend (p=0.13) for longer duration of treatment with tipifarnib was observed in CMML patients with mutant CBL (N=3) as compared to those with wild type CBL (N=21). The CBL mutations detected were E479fs, C384Y, and C404Y. The median duration of treatment for the subjects with a mutant CBL has not yet reached a median value since those subjects remain in treatment. The median duration of treatment for the subjects with wild type CBL was 62 days. These data indicate that subjects with mutant CBL tumors appear to remain responsive to tipifarnib treatment longer than those with wild type CBL tumors.

DETAILED DESCRIPTION

[0014] Provided herein are methods for population selection of cancer patients for treatment with a farnesyltransferase inhibitor (FTI). The methods provided herein are based, in part, on the discovery that Casitas B cell lymphoma (*CBL*) mutation status can be used to predict responsiveness of a cancer patient to an FTI treatment.

[0015] In some embodiments, the methods provided herein include (a) determining the presence of a mutation in a member of the CBL family in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to the subject if the sample is determined to have a mutation in a member of the CBL family. In some embodiments, the methods provided herein include (a) determining the presence of a mutation in CBL, CBLB and/or CBLC in a sample from the subject, and subsequently (b)

administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to the subject if the sample is determined to have a mutation in CBL, CBLB and/or CBLC.

[0016] In some embodiments, the methods provided herein include (a) determining the presence of a *CBL* mutation in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to the subject if the sample is determined to have a *CBL* mutation. In some embodiments, the methods include determining the presence of a mutation in *CBL* selected from a group consisting of Q367, C384, T402, C404, C416, P417, R420, E479, S675, and A678 (or any combination thereof). In some embodiments, the methods include determining the presence of a mutation at a codon selected from a group consisting of C384, C404, R420, and E479 (or any combination thereof) of *CBL*. In some embodiments, the methods include determining the presence of a mutation in an amino acid of CBL selected from a group consisting of C384, C404, R420, and E479 (or any combination thereof). In some embodiments, the methods include determining the presence of one or more of the following mutations: E479fs, C384Y, and C404Y.

[0017] In some embodiments, the methods provided herein include determining the presence of a *CBLB* or a *CBLC* mutation. In some embodiments, the methods provided herein include (a) determining the presence of a *CBLB* mutation in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to the subject if the sample is determined to have a *CBLB* mutation. In some embodiments, the methods include determining the presence of a R463 mutation in *CBLB*.

[0018] In some embodiments, the methods provided herein include (a) determining the presence of a *CBLC* mutation in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to the subject if the sample is determined to have a *CBLC* mutation. In some embodiments, the methods include determining the presence of a C381 mutation in *CBLC*.

[0019] In certain embodiments, provided herein are methods of treating a cancer in a subject comprising: (a) determining the presence or absence of a mutation in a member of the CBL family in a sample from said subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject if said sample is determined to have a

mutation in a member of the CBL family. In some embodiments, said sample has a mutation in CBL. In some embodiments, said sample has a mutation in CBLB. In some embodiments, said sample has a mutation in CBLC. In certain embodiments, provided herein are methods of treating a cancer in a subject comprising: (a) determining the presence or absence of a mutation in CBL, CBLB and/or CBLC in a sample from said subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject if said sample is determined to have a mutation in CBL, CBLB and/or CBLC.

[0020] In certain embodiments, provided herein are methods of treating a cancer in a subject comprising: (a) determining the presence or absence of a *CBL* mutation in a sample from said subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject if said sample is determined to have a *CBL* mutation. In some embodiments, said *CBL* mutation comprises an amino acid substitution at a codon selected from a group consisting of Q367, C384, T402, C404, C416, P417, R420, E479, S675, and A678 (or any combination thereof). In some embodiments, said *CBL* mutation comprises an amino acid substitution at a codon selected from a group consisting of C384, C404, R420, and E479 (or any combination thereof). In some embodiments, said *CBL* mutation comprises a mutation in an amino acid of CBL selected from a group consisting of C384, C404, R420, and E479 (or any combination thereof). In some embodiments, said *CBL* mutation is one or more of the following mutations: E479fs, C384Y, and C404Y.

[0021] In certain embodiments, provided herein are methods of treating a cancer in a subject comprising: (a) determining the presence or absence of a *CBLB* mutation in a sample from said subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject if said sample is determined to have a *CBLB* mutation. In some embodiments, a CBLB mutation is in amino acid R463. In certain embodiments, provided herein are methods of treating a cancer in a subject comprising: (a) determining the presence or absence of a *CBLC* mutation in a sample from said subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject if said sample is determined to have a *CBLC* mutation. In some embodiments, a CBLC mutation is in amino acid C381.

[0022] In certain embodiments, provided herein are methods of treating a CBL-mutant cancer in a subject comprising administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject. In certain embodiments, provided herein are methods of treating a CBL-mutant cancer in a subject comprising administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject, wherein the CBL-mutant cancer is a cancer known to have or determined to have a mutation in one or more genes or proteins of the CBL family (e.g., wherein cells of the cancer have a mutation in a gene of the CBL family). The member of the CBL family can be CBL, CBLB or CBLC. In some embodiments, the CBL-mutant cancer has a mutation in an amino acid of CBL selected from a group consisting of Q367, C384, T402, C404, C416, P417, R420, E479, S675, and A678 (or any combination thereof). In some embodiments, the CBL-mutant cancer has a mutation in an amino acid of CBL selected from a group consisting of C384, C404, R420, and E479 (or any combination thereof). In some embodiments, the CBL-mutant cancer has a mutation in amino acid R463 of CBLB. In some embodiments, the CBL-mutant cancer has a mutation in amino acid C381 of CBLC.

[0023] In certain embodiments, provided herein are methods of treating a cancer in a subject in need thereof comprising selectively administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to a subject having a mutation in one or more genes of the CBL family (such as CBL, CBLB and CBLC). In some embodiments, the subject has a mutation in an amino acid of CBL selected from a group consisting of Q367, C384, T402, C404, C416, P417, R420, E479, S675, and A678 (or any combination thereof). In some embodiments, the subject has a mutation in an amino acid of CBL selected from a group consisting of C384, C404, R420, and E479 (or any combination thereof). In some embodiments, the subject has a mutation in amino acid R463 of CBLB or a mutation in amino acid C381 of CBLC.

[0024] In certain embodiments, provided herein are methods of treating a cancer in a subject comprising: (a) obtaining a tissue or plasma sample from a subject (e.g., a sample containing cancer cells such as tumor biopsy); (b) detecting the presence of a mutation in one or more members of the CBL family in the sample; (c) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to the subject determined to have a mutation in a member of the CBL family. The member of the CBL family can be CBL, CBLB or CBLC. In some embodiments, the CBL obtained from the sample has a mutation at a codon selected from a group consisting of

Q367, C384, T402, C404, C416, P417, R420, E479, S675, and A678 (or any combination thereof). In some embodiments, the CBL obtained from the sample has a mutation at a codon selected from a group consisting of C384, C404, R420, and E479 (or any combination thereof). In some embodiments, the CBLB obtained from the sample has a mutation at codon R463. In some embodiments, the CBLC obtained from the sample has a mutation at codon C381.

[0025] In certain embodiments, provided herein are methods of treating a cancer in a subject having a mutation in one or more members of the CBL family comprising administering an FTI (e.g., tipifarnib) to said subject. In certain embodiments, provided herein are methods of treating a cancer in a subject having a cancer and a mutation in one or more members of the CBL family comprising administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject. The member of the CBL family can be CBL, CBLB or CBLC. In some embodiments, the subject has a mutation in CBL, wherein the mutation is at a codon selected from a group consisting of Q367, C384, T402, C404, C416, P417, R420, E479, S675, and A678 (or any combination thereof). In some embodiments, the subject has a mutation in CBL, wherein the mutation is at a codon selected from a group consisting of C384, C404, R420, and E479 (or any combination thereof). In some embodiments, the subject has a mutation in CBLB, wherein the mutation is at codon R463. In some embodiments, the subject has a mutation in CBLC, wherein the mutation is at codon C381.

[0026] In some embodiments, the mutation in the cancer treated in accordance with the methods described herein is a mutation in CBL, and not a mutation in CBLB and CBLC. In some embodiments, the mutation in a sample from the subject treated in accordance with the methods described herein is a mutation in CBL, and not a mutation in CBLB and CBLC.

[0027] The subject can be a mammal, for example, a human. The subject can be male or female, and can be an adult, child or infant. The subject can be a patient who has cancer (e.g., has been diagnosed with a cancer).

[0028] The cancer treated in accordance with the methods provided herein can be any cancer described herein, for example, myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) (e.g., chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML)), acute myeloid leukemia (AML), or chronic myelogenous leukemia (CML). In some

embodiments, the cancer treated in accordance with the methods provided herein is MDS. In some embodiments, the cancer treated in accordance with the methods provided herein is MPN. In one embodiment, the cancer treated in accordance with the methods provided herein is CMML. In one embodiment, the cancer treated in accordance with the methods provided herein is JMML. In one embodiment, the cancer treated in accordance with the methods provided herein is AML. In one embodiment, the cancer treated in accordance with the methods provided herein is CML.

[0029] In some embodiments, the FTI is tipifarnib, arglabin, perrilyl alcohol, SCH-66336, L778123, L739749, FTI-277, L744832, CP-609,754, R208176, AZD3409, and BMS-214662. In some embodiments, the FTI is tipifarnib. It is also contemplated that a pharmaceutically acceptable salt of an FTI can be used in the methods described herein.

1. Definitions

[0030] As used herein, the articles "a," "an," and "the" refer to one or to more than one of the grammatical object of the article. By way of example, a sample refers to one sample or two or more samples.

[0031] As used herein, the term "subject" refers to a mammal. A subject can be a human or a non-human mammal such as a dog, cat, bovid, equine, mouse, rat, rabbit, or transgenic species thereof.

[0032] As used herein, the term "sample" refers to a material or mixture of materials containing one or more components of interest. A sample from a subject refers to a sample obtained from the subject, including samples of biological tissue or fluid origin, obtained, reached, or collected *in vivo* or *in situ*. A sample can be obtained from a region of a subject containing precancerous or cancer cells or tissues. Such samples can be, but are not limited to, organs, tissues, fractions and cells isolated from a mammal. Exemplary samples include lymph node, whole blood, partially purified blood, serum, bone marrow, and peripheral blood mononuclear cells ("PBMC"). A sample also can be a tissue biopsy. Exemplary samples also include cell lysate, a cell culture, a cell line, a tissue, oral tissue, gastrointestinal tissue, an organ, an organelle, a biological fluid, a blood sample, a urine sample, a skin sample, and the like.

[0033] As used herein, the term "cancer" or "cancerous" refers to the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, hematological cancers (*e.g.*, multiple myeloma, lymphoma and leukemia), and solid tumors. As used herein, the term "premalignant condition" refers to a condition associated with an increased risk of cancer, which, if left untreated, can lead to cancer. A premalignant condition can also refer to non-invasive cancer that have not progressed into aggressive, invasive stage.

[0034] As used herein, the term "treat," "treating," and "treatment," when used in reference to a cancer patient, refer to an action that reduces the severity of the cancer, or retards or slows the progression of the cancer, including (a) inhibiting the cancer growth, or arresting development of the cancer, and (b) causing regression of the cancer, or delaying or minimizing one or more symptoms associated with the presence of the cancer.

[0035] As used herein, the term "determining" refers to using any form of measurement to assess the presence of a substance, either quantitatively or qualitatively. Measurement can be relative or absolute. Measuring the presence of a substance can include determining whether the substance is present or absent, or the amount of the substance.

[0036] As used herein, the term "analyzing" a sample refers to carrying that an art-recognized assay to make an assessment regarding a particular property or characteristic of the sample. The property or characteristic of the sample can be, for example, the type of the cells in the sample, or the presence of a mutation in a gene in the sample.

[0037] As used herein, the term "administer," "administering," or "administration" refers to the act of delivering, or causing to be delivered, a compound or a pharmaceutical composition to the body of a subject by a method described herein or otherwise known in the art. Administering a compound or a pharmaceutical composition includes prescribing a compound or a pharmaceutical composition to be delivered into the body of a patient. Exemplary forms of administration include oral dosage forms, such as tablets, capsules, syrups, suspensions; injectable dosage forms, such as intravenous (IV), intramuscular (IM), or intraperitoneal (IP); transdermal dosage forms, including creams, jellies, powders, or patches; buccal dosage forms; inhalation powders, sprays, suspensions, and rectal suppositories.

[0038] As used herein, the term "selecting" and "selected" in reference to a patient is used to mean that a particular patient is specifically chosen from a larger group of patients on the basis of (due to) the particular patient having a predetermined criteria or a set of predetermined criteria, e.g., a patient having a cancer characterized by or determined to have a mutation in a member of the CBL family. Similarly, "selectively treating a patient" refers to providing treatment to a patient who is specifically chosen from a larger group of patients on the basis of (due to) the particular patient having a predetermined criteria or a set of predetermined criteria, e.g., a mutation in a gene of the CBL family. Similarly, "selectively administering" refers to administering a drug to a patient having a cancer that is specifically chosen from a larger group of patients on the basis of (due to) the particular patient having a predetermined criteria or a set of predetermined criteria (e.g., a mutation in a gene of the CBL family). By selecting, selectively treating and selectively administering, it is meant that a patient is delivered a personalized therapy for a disease or disorder, e.g., cancer, based on the patient's biology, such as the disease or disorder in the selected patient being associated with a mutation in a gene of the CBL family, rather than being delivered a standard treatment regimen based solely on having the disease or disorder (e.g., a leukemia).

[0039] As used herein, the term "therapeutically effective amount" of a compound when used in connection with a disease or disorder refers to an amount sufficient to provide a therapeutic benefit in the treatment or management of the disease or disorder or to delay or minimize one or more symptoms associated with the disease or disorder. A therapeutically effective amount of a compound means an amount of the compound that when used alone or in combination with other therapies, would provide a therapeutic benefit in the treatment or management of the disease or disorder. The term encompasses an amount that improves overall therapy, reduces or avoids symptoms, or enhances the therapeutic efficacy of another therapeutic agent. The term also refers to the amount of a compound that sufficiently elicits the biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0040] As used herein, the term "express" or "expression" when used in connection with a gene refers to the process by which the information carried by the gene becomes manifest as the

phenotype, including transcription of the gene to a messenger RNA (mRNA), the subsequent translation of the mRNA molecule to a polypeptide chain and its assembly into the ultimate protein.

[0041] As used herein, the term "biomarker" refers to a gene or a mutation in a gene that can be either present or absent in individual subjects. The presence a biomarker in a sample from a subject can indicate the responsiveness of the subject to a particular treatment, such as an FTI treatment.

[0042] As used herein, the term "responsiveness" or "responsive" when used in connection with a treatment refers to the effectiveness of the treatment in lessening or decreasing the symptoms of the disease being treated. For example, a cancer patient is responsive to an FTI treatment if the FTI treatment effectively inhibits the cancer growth, or arrests development of the cancer, causes regression of the cancer, or delays or minimizes one or more symptoms associated with the presence of the cancer in this patient.

[0043] The responsiveness to a particular treatment of a cancer patient can be characterized as a complete or partial response. "Complete response," or "CR" refers to an absence of clinically detectable disease with normalization of previously abnormal radiographic studies, bone marrow, and cerebrospinal fluid (CSF) or abnormal monoclonal protein measurements. "Partial response," or "PR," refers to at least about a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% decrease in all measurable tumor burden (i.e., the number of malignant cells present in the subject, or the measured bulk of tumor masses or the quantity of abnormal monoclonal protein) in the absence of new lesions.

[0044] A person of ordinary skill in the art would understand that clinical standards used to define CR, PR, or other level of patient responsiveness to treatments can vary for different types of cancer. For example, for hematopoietic cancers, patient being "responsive" to a particular treatment can be defined as patients who have a complete response (CR), a partial response (PR), or hematological improvement (HI) (Lancet et al., Blood 2:2 (2006)). HI can be defined as any bone marrow blast count less than 5% or a reduction in bone marrow blasts by at least half. On the other hand, patient being "not responsive" to a particular treatment can be defined as patients who have either progressive disease (PD) or stable disease (SD). Progressive disease (PD) can

be defined as either >50% increase in bone marrow or circulating blast % from baseline, or new appearance of circulating blasts (on at least 2 consecutive occasions). Stable disease (SD) can be defined as any response not meeting CR, PR, HI, or PD criteria.

[0045] As used herein, the term "likelihood" refers to the probability of an event. A subject is "likely" to be responsive to a particular treatment when a condition is met means that the probability of the subject to be responsive to a particular treatment is higher when the condition is met than when the condition is not met. The probability to be responsive to a particular treatment can be higher by, for example, 5%, 10%, 25%, 50%, 100%, 200%, or more in a subject who meets a particular condition compared to a subject who does not meet the condition.

[0046] As used herein, the term "CBL family" refers to the family of E3-ubiquitin ligases that are involved in cell signalling and promote the ubiquitination of various signalling molecules including certain receptor tyrosine kinases and SRC family kinases. Members of this family include, without limitation, CBL (or Casitas B-lineage lymphoma), CBLB and CBLC. Mutations in the gene encoding CBL have been implicated in a number of human cancers (e.g., AML). Proteins of the CBL family share a common structure that includes, from N-terminus to C-terminus: a tyrosine kinase binding domain, a linker region, and a RING finger domain (which is responsible for E3-ubiquitin ligase activity). CBL and CBLB also contain a proline-rich region involved in the recognition of SH3 proteins and the C-terminal UBA domain. Whereas CBL and CBLB regulate signalling in many tissues, CBLC is primarily expressed in epithelial cells. For information regarding CBL, CBLB and CBLC, and known mutations in CBL, CBLB and CBLC, see, for example, Aranaz et al., 2012, Haematologica 97(8):1234-1241; Makishima et al., 2012, Leukemia 26:1547-1554; and Martinelli et al., 2015, Hum. Mutat. 36:787-796, the disclosures of which are hereby incorporated by reference in their entireties.

[0047] An amino acid sequence of human CBL can be found at https://www.ncbi.nlm.nih.gov/protein/NP_005179 (NCBI Reference Sequence: NP_005179.2), and is hereby incorporated by reference in its entirety, as well as reproduced below:

MAGNVKKSSGAGGGSGSGGSGSGGLIGLMKDAFQPHHHHHHHLSPHPPGTVDKKMVEKCW
KLMDKVVRLCQNPKLALKNSPPYILDLLPDTYQHLRTILSRYEGKMETLGENEYFRVFME
NLMKKTKQTISLFKEGKERMYEENSQPRRNLTKLSLIFSHMLAELKGIFPSGLFQGDTFR
ITKADAAEFWRKAFGEKTIVPWKSFRQALHEVHPISSGLEAMALKSTIDLTCNDYISVFE
FDIFTRLFQPWSSLLRNWNSLAVTHPGYMAFLTYDEVKARLQKFIHKPGSYIFRLSCTRL

GQWAIGYVTADGNILQTIPHNKPLFQALIDGFREGFYLFPDGRNQNPDLTGLCEPTPQDH
IKVTQEQYELYCEMGSTFQLCKICAENDKDVKIEPCGHLMCTSCLTSWQESEGQGCPFCR
CEIKGTEPIVVDPFDPRGSGSLLRQGAEGAPSPNYDDDDDERADDTLFMMKELAGAKVER
PPSPFSMAPQASLPPVPPRLDLLPQRVCVPSSASALGTASKAASGSLHKDKPLPVPPTLR
DLPPPPPPDRPYSVGAESRPQRRPLPCTPGDCPSRDKLPPVPSSRLGDSWLPRPIPKVPV
SAPSSSDPWTGRELTNRHSLPFSLPSQMEPRPDVPRLGSTFSLDTSMSMNSSPLVGPECD
HPKIKPSSSANAIYSLAARPLPVPKLPPGEQCEGEEDTEYMTPSSRPLRPLDTSQSSRAC
DCDQQIDSCTYEAMYNIQSQAPSITESSTFGEGNLAAAHANTGPEESENEDDGYDVPKPP
VPAVLARRTLSDISNASSSFGWLSLDGDPTTNVTEGSQVPERPPKPFPRRINSERKAGSC
QQGSGPAASAATASPQLSSEIENLMSQGYSYQDIQKALVIAQNNIEMAKNILREFVSISS
PAHVAT
(SEQ ID NO:1)

[0048] An mRNA sequence of human CBL can be found at https://www.ncbi.nlm.nih.gov/nuccore/NM_005188 (NCBI Reference Sequence: NM_005188.3), and is hereby incorporated by reference in its entirety.

[0049] Genomic DNA sequence of human CBL can be found at https://www.ncbi.nlm.nih.gov/nuccore/291490670 (NCBI Reference Sequence: NG_016808.1), and is hereby incorporated by reference in its entirety.

[0050] Several isoforms of CBLB are known. An amino acid sequence of isoform a of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308715 (NCBI Reference Sequence: NP_001308715.1), and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MGYLCVNFIW FLGITTHRVD LKKELKFQMA NSMNGRNPGG RGGNPRKGRI LGIIDAIQDA
61 VGPPKQAAAD RRTVEKTWKL MDKVVRLCQN PKLQLKNSPP YILDILPDTY QHLRLILSKY
121 DDNQKLAQLS ENEYFKIYID SLMKKSKRAI RLFKEGKERM YEEQSQDRRN LTKLSLIFSH
181 MLAEIKAIFP NGQFQGDNFR ITKADAAEFW RKFFGDKTIV PWKVFRQCLH EVHQISSGLE
241 AMALKSTIDL TCNDYISVFE FDIFTRLFQP WGSILRNWNF LAVTHPGYMA FLTYDEVKAR
301 LQKYSTKPGS YIFRLSCTRL GQWAIGYVTG DGNILQTIPH NKPLFQALID GSREGFYLYP
361 DGRSYNPDLT GLCEPTPHDH IKVTQEQYEL YCEMGSTFQL CKICAENDKD VKIEPCGHLM
421 CTSCLTAWQE SDGQGCPFCR CEIKGTEPII VDPFDPRDEG SRCCSIIDPF GMPMLDLDDD
481 DDREESLMMN RLANVRKCTD RQNSPVTSPG SSPLAQRRKP QPDPLQIPHL SLPPVPPRLD
541 LIQKGIVRSP CGSPTGSPKS SPCMVRKQDK PLPAPPPPLR DPPPPPPERP PPIPPDNRLS
601 RHIHHVESVP SRDPPMPLEA WCPRDVFGTN QLVGCRLLGE GSPKPGITAS SNVNGRHSRV
661 GSDPVLMRKH RRHDLPLEGA KVFSNGHLGS EEYDVPPRLS PPPPVTTLLP SIKCTGPLAN
721 SLSEKTRDPV EEDDDEYKIP SSHPVSLNSQ PSHCHNVKPP VRSCDNGHCM LNGTHGPSSE
781 KKSNIPDLSI YLKGDVFDSA SDPVPLPPAR PPTRDNPKHG SSLNRTPSDY DLLIPPLGED
841 AFDALPPSLP PPPPPARHSL IEHSKPPGSS SRPSSGQDLF LLPSDPFVDL ASGQVPLPPA
901 RRLPGENVKT NRTSQDYDQL PSCSDGSQAP ARPPKPRPRR TAPEIHHRKP HGPEAALENV
961 DAKIAKLMGE GYAFEEVKRA LEIAQNNVEV ARSILREFAF PPPVSPRLNL
(SEQ ID NO:2)

[0051] An amino acid sequence of isoform b of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308717 (NCBI Reference Sequence: NP_001308717.1), and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MANSMNGRNP GGRGGNPRKG RILGIIDAIQ DAVGPPKQAA ADRRTVEKTW KLMDKVVRLC
61 QNPKLQLKNS PPYILDILPD TYQHLRLILS KYDDNQKLAQ LSENEYFKIY IDSLMKKSKR
121 AIRLFKEGKE RMYEEQSQDR RNLTKLSLIF SHMLAEIKAI FPNGQFQGDN FRITKADAAE
181 FWRKFFGDKT IVPWKVFRQC LHEVHQISSG LEAMALKSTI DLTCNDYISV FEFDIFTRLF
241 QPWGSILRNW NFLAVTHPGY MAFLTYDEVK ARLQKYSTKP GSYIFRLSCT RLGQWAIGYV
301 TGDGNILQTI PHNKPLFQAL IDGSREGFYL YPDGRSYNPD LTGLCEPTPH DHIKVTQEQY
361 ELYCEMGSTF QLCKICAEND KDVKIEPCGH LMCTSCLTAW QESDGQGCPF CRCEIKGTEP
421 IIVDPFDPRD EGSRCCSIID PFGMPMLDLD DDDDREESLM MNRLANVRKC TDRQNSPVTS
481 PGSSPLAQRR KPQPDPLQIP HLSLPPVPPR LDLIQKGIVR SPCGSPTGSP KSSPCMVRKQ
541 DKPLPAPPPP LRDPPPPPPE RPPPIPPDNR LSRHIHHVES VPSRDPPMPL EAWCPRDVFG
601 TNQLVGCRLL GEGSPKPGIT ASSNVNGRHS RVGSDPVLMR KHRRHDLPLE GAKVFSNGHL
661 GSEEYDVPPR LSPPPPVTTL LPSIKCTGPL ANSLSEKTRD PVEEDDDEYK IPSSHPVSLN
721 SQPSHCHNVK PPVRSCDNGH CMLNGTHGPS SEKKSNIPDL SIYLKGDVFD SASDPVPLPP
781 ARPPTRDNPK HGSSLNRTPS DYDLLIPPLG EDAFDALPPS LPPPPPPARH SLIEHSKPPG
841 SSSRPSSGQD LFLLPSDPFV DLASGQVPLP PARRLPGENV KTNRTSQDYD QLPSCSDGSQ
901 APARPPKPRP RRTAPEIHHR KPHGPEAALE NVDAKIAKLM GEGYAFEEVK RALEIAQNNV
961 EVARSILREF AFPPPVSPRL NL

(SEQ ID NO:3)

[0052] An amino acid sequence of isoform c of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308718 (NCBI Reference Sequence: NP_001308718.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MGYLCVNFIW FLGITTHRVD LKKELKFQMA NSMNGRNPGG RGGNPRKGRI LGIIDAIQDA
61 VGPPKQAAAD RRTVEKTWKL MDKVVRLCQN PKLQLKNSPP YILDILPDTY QHLRLILSKY
121 DDNQKLAQLS ENEYFKIYID SLMKKSKRAI RLFKEGKERM YEEQSQDRRN LTKLSLIFSH
181 MLAEIKAIFP NGQFQGDNFR ITKADAAEFW RKFFGDKTIV PWKVFRQCLH EVHQISSGLE
241 AMALKSTIDL TCNDYISVFE FDIFTRLFQP WGSILRNWNF LAVTHPGYMA FLTYDEVKAR
301 LQKYSTKPGS YIFRLSCTRL GQWAIGYVTG DGNILQTIPH NKPLFQALID GSREGFYLYP
361 DGRSYNPDLT GLCEPTPHDH IKVTQEQYEL YCEMGSTFQL CKICAENDKD VKIEPCGHLM
421 CTSCLTAWQE SDGQGCPFCR CEIKGTEPII VDPFDPRDEG SRCCSIIDPF GMPMLDLDDD
481 DDREESLMMN RLANVRKCTD RQNSPVTSPG SSPLAQRRKP QPDPLQIPHL SLPPVPPRLD
541 LIQKGIVRSP CGSPTGSPKS SPCMVRKQDK PLPAPPPPLR DPPPPPPERP PPIPPDNRLS
601 RHIHHVESVP SRDPPMPLEA WCPRDVFGTN QLVGCRLLGE GSPKPGITAS SNVNGRHSRV
661 GSDPVLMRKH RRHDLPLEGA KVFSNGHLGS EEYDVPPRLS PPPPVTTLLP SIKSCDNGHC
721 MLNGTHGPSS EKKSNIPDLS IYLKGDVFDS ASDPVPLPPA RPPTRDNPKH GSSLNRTPSD
781 YDLLIPPLGE DAFDALPPSL PPPPPPARHS LIEHSKPPGS SSRPSSGQDL FLLPSDPFVD
841 LASGQVPLPP ARRLPGENVK TNRTSQDYDQ LPSCSDGSQA PARPPKPRPR RTAPEIHHRK
901 PHGPEAALEN VDAKIAKLMG EGYAFEEVKR ALEIAQNNVE VARSILREFA FPPPVSPRLN
961 L

(SEQ ID NO:4)

[0053] An amino acid sequence of isoform d of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308719 (NCBI Reference Sequence: NP_001308719.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MALAPGPDAH AHLPPLIELK FQMANSMNGR NPGGRGGNPR KGRILGIIDA IQDAVGPPKQ
61 AAADRRTVEK TWKLMDKVVR LCQNPKLQLK NSPPYILDIL PDTYQHLRLI LSKYDDNQKL
121 AQLSENEYFK IYIDSLMKKS KRAIRLFKEG KERMYEEQSQ DRRNLTKLSL IFSHMLAEIK
181 AIFPNGQFQG DNFRITKADA AEFWRKFFGD KTIVPWKVFR QCLHEVHQIS SGLEAMALKS
241 TIDLTCNDYI SVFEFDIFTR LFQPWGSILR NWNFLAVTHP GYMAFLTYDE VKARLQKYST
301 KPGSYIFRLS CTRLGQWAIG YVTGDGNILQ TIPHNKPLFQ ALIDGSREGF YLYPDGRSYN
361 PDLTGLCEPT PHDHIKVTQE QYELYCEMGS TFQLCKICAE NDKDVKIEPC GHLMCTSCLT
421 AWQESDGQGC PFCRCEIKGT EPIIVDPFDP RDEGSRCCSI IDPFGMPMLD LDDDDDREES
481 LMMNRLANVR KCTDRQNSPV TSPGSSPLAQ RRKPQPDPLQ IPHLSLPPVP PRLDLIQKGI
541 VRSPCGSPTG SPKSSPCMVR KQDKPLPAPP PPLRDPPPPP PERPPPIPPD NRLSRHIHHV
601 ESVPSRDPPM PLEAWCPRDV FGTNQLVGCR LLGEGSPKPG ITASSNVNGR HSRVGSDPVL
661 MRKHRRHDLP LEGAKVFSNG HLGSEEYDVP PRLSPPPPVT TLLPSIKCTG PLANSLSEKT
721 RDPVEEDDDE YKIPSSHPVS LNSQPSHCHN VKPPVRSCDN GHCMLNGTHG PSSEKKSNIP
781 DLSIYLKGED AFDALPPSLP PPPPPARHSL IEHSKPPGSS SRPSSGQDLF LLPSDPFVDL
841 ASGQVPLPPA RRLPGENVKT NRTSQDYDQL PSCSDGSQAP ARPPKPRPRR TAPEIHHRKP
901 HGPEAALENV DAKIAKLMGE GYAFEEVKRA LEIAQNNVEV ARSILREFAF PPPVSPRLNL
(SEQ ID NO:5)

[0054] An amino acid sequence of isoform e of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308720 (NCBI Reference Sequence: NP_001308720.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MANSMNGRNP GGRGGNPRKG RILGIIDAIQ DAVGPPKQAA ADRRTVEKTW KLMDKVVRLC
61 QNPKLQLKNS PPYILDILPD TYQHLRLILS KYDDNQKLAQ LSENEYFKIY IDSLMKKSKR
121 AIRLFKEGKE RMYEEQSQDR RNLTKLSLIF SHMLAEIKAI FPNGQFQGDN FRITKADAAE
181 FWRKFFGDKT IVPWKVFRQC LHEVHQISSG LEAMALKSTI DLTCNDYISV FEFDIFTRLF
241 QPWGSILRNW NFLAVTHPGY MAFLTYDEVK ARLQKYSTKP GSYIFRLSCT RLGQWAIGYV
301 TGDGNILQTI PHNKPLFQAL IDGSREGFYL YPDGRSYNPD LTGLCEPTPH DHIKVTQEQY
361 ELYCEMGSTF QLCKICAEND KDVKIEPCGH LMCTSCLTAW QESDGQGCPF CRCEIKGTEP
421 IIVDPFDPRD EGSRCCSIID PFGMPMLDLD DDDDREESLM MNRLANVRKC TDRQNSPVTS
481 PGSSPLAQRR KPQPDPLQIP HLSLPPVPPR LDLIQKGIVR SPCGSPTGSP KSSPCMVRKQ
541 DKPLPAPPPP LRDPPPPPPE RPPPIPPDNR LSRHIHHVES VPSRDPPMPL EAWCPRDVFG
601 TNQLVGCRLL GEGSPKPGIT ASSNVNGRHS RVGSDPVLMR KHRRHDLPLE GAKVFSNGHL
661 GSEEYDVPPR LSPPPPVTTL LPSIKCTGPL ANSLSEKTRD PVEEDDDEYK IPSSHPVSLN
721 SQPSHCHNVK PPVRSCDNGH CMLNGTHGPS SEKKSNIPDL SIYLKGEDAF DALPPSLPPP
781 PPPARHSLIE HSKPPGSSSR PSSGQDLFLL PSDPFVDLAS GQVPLPPARR LPGENVKTNR
841 TSQDYDQLPS CSDGSQAPAR PPKPRPRRTA PEIHHRKPHG PEAALENVDA KIAKLMGEGY
901 AFEEVKRALE IAQNNVEVAR SILREFAFPP PVSPRLNL
(SEQ ID NO:6)

[0055] An amino acid sequence of isoform f of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308723 (NCBI Reference Sequence: NP_001308723.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MANSMNGRNP GGRGGNPRKG RILGIIDAIQ DAVGPPKQAA ADRRTVEKTW KLMDKVVRLC
61 QNPKLQLKNS PPYILDILPD TYQHLRLILS KYDDNQKLAQ LSENEYFKIY IDSLMKKSKR
121 AIRLFKEGKE RMYEEQSQDR RNLTKLSLIF SHMLAEIKAI FPNGQFQGDN FRITKADAAE
181 FWRKFFGDKT IVPWKVFRQC LHEVHQISSG LEAMALKSTI DLTCNDYISV FEFDIFTRLF
241 QPWGSILRNW NFLAVTHPGY MAFLTYDEVK ARLQKYSTKP GSYIFRLSCT RLGQWAIGYV
301 TGDGNILQTI PHNKPLFQAL IDGSREGFYL YPDGRSYNPD LTGLCEPTPH DHIKVTQEQY
361 ELYCEMGSTF QLCKICAEND KDVKIEPCGH LMCTSCLTAW QESDGQGCPF CRCEIKGTEP
421 IIVDPFDPRD EGSRCCSIID PFGMPMLDLD DDDDREESLM MNRLANVRKC TDRQNSPVTS
481 PGSSPLAQRR KPQPDPLQIP HLSLPPVPPR LDLIQKGIVR SPCGSPTGSP KSSPCMVRKQ
541 DKPLPAPPPP LRDPPPPPPE RPPPIPPDNR LSRHIHHVES VPSRDPPMPL EAWCPRDVFG
601 TNQLVGCRLL GEGSPKPGIT ASSNVNGRHS RVGSDPVLMR KHRRHDLPLE GAKVFSNGHL
661 GSEEYDVPPR LSPPPPVTTL LPSIKSCDNG HCMLNGTHGP SSEKKSNIPD LSIYLKGDVF
721 DSASDPVPLP PARPPTRDNP KHGSSLNRTP SDYDLLIPPL GEDAFDALPP SLPPPPPPAR
781 HSLIEHSKPP GSSSRPSSGQ DLFLLPSDPF VDLASGQVPL PPARRLPGEN VKTNRTSQDY
841 DQLPSCSDGS QAPARPPKPR PRRTAPEIHH RKPHGPEAAL ENVDAKIAKL MGEGYAFEEV
901 KRALEIAQNN VEVARSILRE FAFPPPVSPR LNL
(SEQ ID NO:7)

[0056] An amino acid sequence of isoform g of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308725 (NCBI Reference Sequence: NP_001308725.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MANSMNGRNP GGRGGNPRKG RILGIIDAIQ DAVGPPKQAA ADRRTVEKTW KLMDKVVRLC
61 QNPKLQLKNS PPYILDILPD TYQHLRLILS KYDDNQKLAQ LSENEYFKIY IDSLMKKSKR
121 AIRLFKEGKE RMYEEQSQDR TIVPWKVFRQ CLHEVHQISS GLEAMALKST IDLTCNDYIS
181 VFEFDIFTRL FQPWGSILRN WNFLAVTHPG YMAFLTYDEV KARLQKYSTK PGSYIFRLSC
241 TRLGQWAIGY VTGDGNILQT IPHNKPLFQA LIDGSREGFY LYPDGRSYNP DLTGLCEPTP
301 HDHIKVTQEQ YELYCEMGST FQLCKICAEN DKDVKIEPCG HLMCTSCLTA WQESDGQGCP
361 FCRCEIKGTE PIIVDPFDPR DEGSRCCSII DPFGMPMLDL DDDDDREESL MMNRLANVRK
421 CTDRQNSPVT SPGSSPLAQR RKPQPDPLQI PHLSLPPVPP RLDLIQKGIV RSPCGSPTGS
481 PKSSPCMVRK QDKPLPAPPP PLRDPPPPPP ERPPPIPPDN RLSRHIHHVE SVPSRDPPMP
541 LEAWCPRDVF GTNQLVGCRL LGEGSPKPGI TASSNVNGRH SRVGSDPVLM RKHRRHDLPL
601 EGAKVFSNGH LGSEEYDVPP RLSPPPPVTT LLPSIKCTGP LANSLSEKTR DPVEEDDDEY
661 KIPSSHPVSL NSQPSHCHNV KPPVRSCDNG HCMLNGTHGP SSEKKSNIPD LSIYLKGDVF
721 DSASDPVPLP PARPPTRDNP KHGSSLNRTP SDYDLLIPPL GEDAFDALPP SLPPPPPPAR
781 HSLIEHSKPP GSSSRPSSGQ DLFLLPSDPF VDLASGQVPL PPARRLPGEN VKTNRTSQDY
841 DQLPSCSDGS QAPARPPKPR PRRTAPEIHH RKPHGPEAAL ENVDAKIAKL MGEGYAFEEV
901 KRALEIAQNN VEVARSILRE FAFPPPVSPR LNL
(SEQ ID NO:8)

[0057] An amino acid sequence of isoform h of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308726 (NCBI Reference Sequence: NP_001308726.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MANSMNGRNP GGRGGNPRKG RILGIIDAIQ DAVGPPKQAA ADRRTVEKTW KLMDKVVRLC
61 QNPKLQLKNS PPYILDILPD TYQHLRLILS KYDDNQKLAQ LSENEYFKIY IDSLMKKSKR
121 AIRLFKEGKE RMYEEQSQDR RNLTKLSLIF SHMLAEIKAI FPNGQFQGDN FRITKADAAE
181 FWRKFFGDKT IVPWKVFRQC LHEVHQISSG LEAMALKSTI DLTCNDYISV FEFDIFTRLF
241 QPWGSILRNW NFLAVTHPGY MAFLTYDEVK ARLQKYSTKP GSYIFRLSCT RLGQWAIGYV
301 TGDGNILQTI PHNKPLFQAL IDGSREGFYL YPDGRSYNPD LTGLCEPTPH DHIKVTQEQY
361 ELYCEMGSTF QLCKICAEND KDVKIEPCGH LMCTSCLTAW QESDGQGCPF CRCEIKGTEP
421 IIVDPFDPRD EGSRCCSIID PFGMPMLDLD DDDDREESLM MNRLANVRKC TDRQNSPVTS
481 PGSSPLAQRR KPQPDPLQIP HLSLPPVPPR LDLIQKGIVR SPCGSPTGSP KSSPCMVRKQ
541 DKPLPAPPPP LRDPPPPPPE RPPPIPPDNR LSRHIHHVES VPSRDPPMPL EAWCPRDVFG
601 TNQLVGCRLL GEGSPKPGIT ASSNVNGRHS RVGSDPVLMR KHRRHDLPLE GAKVFSNGHL
661 GSEEYDVPPR LSPPPPVTTL LPSIKSCDNG HCMLNGTHGP SSEKKSNIPD LSIYLKGEDA
721 FDALPPSLPP PPPPARHSLI EHSKPPGSSS RPSSGQDLFL LPSDPFVDLA SGQVPLPPAR
781 RLPGENVKTN RTSQDYDQLP SCSDGSQAPA RPPKPRPRRT APEIHHRKPH GPEAALENVD
841 AKIAKLMGEG YAFEEVKRAL EIAQNNVEVA RSILREFAFP PPVSPRLNL
(SEQ ID NO:9)

[0058] An amino acid sequence of isoform i of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308728 (NCBI Reference Sequence: NP_001308728.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MANSMNGRNP GGRGGNPRKG RILGIIDAIQ DAVGPPKQAA ADRRTVEKTW KLMDKVVRLC
61 QNPKLQLKNS PPYILDILPD TYQHLRLILS KYDDNQKLAQ LSENEYFKIY IDSLMKKSKR
121 AIRLFKEGKE RMYEEQSQDR TIVPWKVFRQ CLHEVHQISS GLEAMALKST IDLTCNDYIS
181 VFEFDIFTRL FQPWGSILRN WNFLAVTHPG YMAFLTYDEV KARLQKYSTK PGSYIFRLSC
241 TRLGQWAIGY VTGDGNILQT IPHNKPLFQA LIDGSREGFY LYPDGRSYNP DLTGLCEPTP
301 HDHIKVTQEQ YELYCEMGST FQLCKICAEN DKDVKIEPCG HLMCTSCLTA WQESDGQGCP
361 FCRCEIKGTE PIIVDPFDPR DEGSRCCSII DPFGMPMLDL DDDDDREESL MMNRLANVRK
421 CTDRQNSPVT SPGSSPLAQR RKPQPDPLQI PHLSLPPVPP RLDLIQKGIV RSPCGSPTGS
481 PKSSPCMVRK QDKPLPAPPP PLRDPPPPPP ERPPPIPPDN RLSRHIHHVE SVPSRDPPMP
541 LEAWCPRDVF GTNQLVGCRL LGEGSPKPGI TASSNVNGRH SRVGSDPVLM RKHRRHDLPL
601 EGAKVFSNGH LGSEEYDVPP RLSPPPPVTT LLPSIKCTGP LANSLSEKTR DPVEEDDDEY
661 KIPSSHPVSL NSQPSHCHNV KPPVRSCDNG HCMLNGTHGP SSEKKSNIPD LSIYLKGEDA
721 FDALPPSLPP PPPPARHSLI EHSKPPGSSS RPSSGQDLFL LPSDPFVDLA SGQVPLPPAR
781 RLPGENVKTN RTSQDYDQLP SCSDGSQAPA RPPKPRPRRT APEIHHRKPH GPEAALENVD
841 AKIAKLMGEG YAFEEVKRAL EIAQNNVEVA RSILREFAFP PPVSPRLNL
(SEQ ID NO:10)

[0059] An amino acid sequence of isoform j of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308735 (NCBI Reference Sequence:

NP_001308735.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MAFLTYDEVK ARLQKYSTKP GSYIFRLSCT RLGQWAIGYV TGDGNILQTI PHNKPLFQAL
61 IDGSREGFYL YPDGRSYNPD LTGLCEPTPH DHIKVTQEQY ELYCEMGSTF QLCKICAEND
121 KDVKIEPCGH LMCTSCLTAW QESDGQGCPF CRCEIKGTEP IIVDPFDPRD EGSRCCSIID
181 PFGMPMLDLD DDDDREESLM MNRLANVRKC TDRQNSPVTS PGSSPLAQRR KPQPDPLQIP
241 HLSLPPVPPR LDLIQKGIVR SPCGSPTGSP KSSPCMVRKQ DKPLPAPPPP LRDPPPPPPE
301 RPPPIPPDNR LSRHIHHVES VPSRDPPMPL EAWCPRDVFG TNQLVGCRLL GEGSPKPGIT
361 ASSNVNGRHS RVGSDPVLMR KHRRHDLPLE GAKVFSNGHL GSEEYDVPPR LSPPPPVTTL
421 LPSIKCTGPL ANSLSEKTRD PVEEDDDEYK IPSSHPVSLN SQPSHCHNVK PPVRSCDNGH
481 CMLNGTHGPS SEKKSNIPDL SIYLKGDVFD SASDPVPLPP ARPPTRDNPK HGSSLNRTPS
541 DYDLLIPPLG EDAFDALPPS LPPPPPPARH SLIEHSKPPG SSSRPSSGQD LFLLPSDPFV
601 DLASGQVPLP PARRLPGENV KTNRTSQDYD QLPSCSDGSQ APARPPKPRP RRTAPEIHHR
661 KPHGPEAALE NVDAKIAKLM GEGYAFEEVK RALEIAQNNV EVARSILREF AFPPPVSPRL
721 NL

(SEQ ID NO:11)

[0060] An amino acid sequence of isoform k of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308737 (NCBI Reference Sequence: NP_001308737.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MAFLTYDEVK ARLQKYSTKP GSYIFRLSCT RLGQWAIGYV TGDGNILQTI PHNKPLFQAL
61 IDGSREGFYL YPDGRSYNPD LTGLCEPTPH DHIKVTQEQY ELYCEMGSTF QLCKICAEND
121 KDVKIEPCGH LMCTSCLTAW QESDGQGCPF CRCEIKGTEP IIVDPFDPRD EGSRCCSIID
181 PFGMPMLDLD DDDDREESLM MNRLANVRKC TDRQNSPVTS PGSSPLAQRR KPQPDPLQIP
241 HLSLPPVPPR LDLIQKGIVR SPCGSPTGSP KSSPCMVRKQ DKPLPAPPPP LRDPPPPPPE
301 RPPPIPPDNR LSRHIHHVES VPSRDPPMPL EAWCPRDVFG TNQLVGCRLL GEGSPKPGIT
361 ASSNVNGRHS RVGSDPVLMR KHRRHDLPLE GAKVFSNGHL GSEEYDVPPR LSPPPPVTTL
421 LPSIKCTGPL ANSLSEKTRD PVEEDDDEYK IPSSHPVSLN SQPSHCHNVK PPVRSCDNGH
481 CMLNGTHGPS SEKKSNIPDL SIYLKGEDAF DALPPSLPPP PPPARHSLIE HSKPPGSSSR
541 PSSGQDLFLL PSDPFVDLAS GQVPLPPARR LPGENVKTNR TSQDYDQLPS CSDGSQAPAR
601 PPKPRPRRTA PEIHHRKPHG PEAALENVDA KIAKLMGEGY AFEEVKRALE IAQNNVEVAR
661 SILREFAFPP PVSPRLNL

(SEQ ID NO:12)

[0061] An amino acid sequence of isoform l of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308742 (NCBI Reference Sequence: NP_001308742.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MAFLTYDEVK ARLQKYSTKP GSYIFRLSCT RLGQWAIGYV TGDGNILQTI PHNKPLFQAL
61 IDGSREGFYL YPDGRSYNPD LTGLCEPTPH DHIKVTQEQY ELYCEMGSTF QLCKICAEND
121 KDVKIEPCGH LMCTSCLTAW QESDGQGCPF CRCEIKGTEP IIVDPFDPRD EGSRCCSIID
181 PFGMPMLDLD DDDDREESLM MNRLANVRKC TDRQNSPVTS PGSSPLAQRR KPQPDPLQIP

241 HLSLPPVPPR LDLIQKGIVR SPCGSPTGSP KSSPCMVRKQ DKPLPAPPPP LRDPPPPPPE
301 RPPPIPPDNR LSRHIHHVES VPSRDPPMPL EAWCPRDVFG TNQLVGCRLL GEGSPKPGIT
361 ASSNVNGRHS RVGSDPVLMR KHRRHDLPLE GAKVFSNGHL GSEEYDVPPR LSPPPPVTTL
421 LPSIKSCDNG HCMLNGTHGP SSEKKSNIPD LSIYLKGDVF DSASDPVPLP PARPPTRDNP
481 KHGSSLNRTP SDYDLLIPPL GEDAFDALPP SLPPPPPPAR HSLIEHSKPP GSSSRPSSGQ
541 DLFLLPSDPF VDLASGQVPL PPARRLPGEN VKTNRTSQDY DQLPSCSDGS QAPARPPKPR
601 PRRTAPEIHH RKPHGPEAAL ENVDAKIAKL MGEGYAFEEV KRALEIAQNN VEVARSILRE
661 FAFPPPVSPR LNL
(SEQ ID NO:13)

[0062] An amino acid sequence of isoform m of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308745 (NCBI Reference Sequence: NP_001308745.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MAFLTYDEVK ARLQKYSTKP GSYIFRLSCT RLGQWAIGYV TGDGNILQTI PHNKPLFQAL
61 IDGSREGFYL YPDGRSYNPD LTGLCEPTPH DHIKVTQEQY ELYCEMGSTF QLCKICAEND
121 KDVKIEPCGH LMCTSCLTAW QESDGQGCPF CRCEIKGTEP IIVDPFDPRD EGSRCCSIID
181 PFGMPMLDLD DDDDREESLM MNRLANVRKC TDRQNSPVTS PGSSPLAQRR KPQPDPLQIP
241 HLSLPPVPPR LDLIQKGIVR SPCGSPTGSP KSSPCMVRKQ DKPLPAPPPP LRDPPPPPPE
301 RPPPIPPDNR LSRHIHHVES VPSRDPPMPL EAWCPRDVFG TNQLVGCRLL GEGSPKPGIT
361 ASSNVNGRHS RVGSDPVLMR KHRRHDLPLE GAKVFSNGHL GSEEYDVPPR LSPPPPVTTL
421 LPSIKSCDNG HCMLNGTHGP SSEKKSNIPD LSIYLKGEDA FDALPPSLPP PPPPARHSLI
481 EHSKPPGSSS RPSSGQDLFL LPSDPFVDLA SGQVPLPPAR RLPGENVKTN RTSQDYDQLP
541 SCSDGSQAPA RPPKPRPRRT APEIHHRKPH GPEAALENVD AKIAKLMGEG YAFEEVKRAL
601 EIAQNNVEVA RSILREFAFP PPVSPRLNL
(SEQ ID NO:14)

[0063] An amino acid sequence of isoform n of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308749 (NCBI Reference Sequence: NP_001308749.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MKYSKESDGQ GCPFCRCEIK GTEPIIVDPF DPRDEGSRCC SIIDPFGMPM LDLDDDDDRE
61 ESLMMNRLAN VRKCTDRQNS PVTSPGSSPL AQRRKPQPDP LQIPHLSLPP VPPRLDLIQK
121 GIVRSPCGSP TGSPKSSPCM VRKQDKPLPA PPPPLRDPPP PPPERPPPIP PDNRLSRHIH
181 HVESVPSRDP PMPLEAWCPR DVFGTNQLVG CRLLGEGSPK PGITASSNVN GRHSRVGSDP
241 VLMRKHRRHD LPLEGAKVFS NGHLGSEEYD VPPRLSPPPP VTTLLPSIKC TGPLANSLSE
301 KTRDPVEEDD DEYKIPSSHP VSLNSQPSHC HNVKPPVRSC DNGHCMLNGT HGPSSEKKSN
361 IPDLSIYLKG EDAFDALPPS LPPPPPPARH SLIEHSKPPG SSSRPSSGQD LFLLPSDPFV
421 DLASGQVPLP PARRLPGENV KTNRTSQDYD QLPSCSDGSQ APARPPKPRP RRTAPEIHHR
481 KPHGPEAALE NVDAKIAKLM GEGYAFEEVK RALEIAQNNV EVARSILREF AFPPPVSPRL
541 NL
(SEQ ID NO:15)

[0064] An amino acid sequence of isoform o of human CBLB can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001308751 (NCBI Reference Sequence: NP_001308751.1) and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MPMLDLDDDD DREESLMMNR LANVRKCTDR QNSPVTSPGS SPLAQRRKPQ PDPLQIPHLS
61 LPPVPPRLDL IQKGIVRSPC GSPTGSPKSS PCMVRKQDKP LPAPPPPLRD PPPPPPERPP
121 PIPPDNRLSR HIHHVESVPS RDPPMPLEAW CPRDVFGTNQ LVGCRLLGEG SPKPGITASS
181 NVNGRHSRVG SDPVLMRKHR RHDLPLEGAK VFSNGHLGSE EYDVPPRLSP PPPVTTLLPS
241 IKCTGPLANS LSEKTRDPVE EDDDEYKIPS SHPVSLNSQP SHCHNVKPPV RSCDNGHCML
301 NGTHGPSSEK KSNIPDLSIY LKGDVFDSAS DPVPLPPARP PTRDNPKHGS SLNRTPSDYD
361 LLIPPLGEDA FDALPPSLPP PPPPARHSLI EHSKPPGSSS RPSSGQDLFL LPSDPFVDLA
421 SGQVPLPPAR RLPGENVKTN RTSQDYDQLP SCSDGSQAPA RPPKPRPRRT APEIHHRKPH
481 GPEAALENVD AKIAKLMGEG YAFEEVKRAL EIAQNNVEVA RSILREFAFP PPVSPRLNL
(SEQ ID NO:16)

[0065] Exemplary mRNA sequence of human CBLB can be found at https://www.ncbi.nlm.nih.gov/nuccore/NM_170662 (NCBI Reference Sequence: NM_170662.4), and is hereby incorporated by reference in its entirety.

[0066] Genomic DNA sequence of human CBLB can be found at https://www.ncbi.nlm.nih.gov/nuccore/1244024325 (NCBI Reference Sequence: NG_055547.1), and is hereby incorporated by reference in its entirety.

[0067] At least two isoforms of CBLC are known. An amino acid sequence of isoform 1 of human CBLC can be found at https://www.ncbi.nlm.nih.gov/protein/NP_036248 (NCBI Reference Sequence: NP_036248.3), and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MALAVAPWGR QWEEARALGR AVRMLQRLEE QCVDPRLSVS PPSLRDLLPR TAQLLREVAH
61 SRRAAGGGGP GGPGGSGDFL LIYLANLEAK SRQVAALLPP RGRRSANDEL FRAGSRLRRQ
121 LAKLAIIFSH MHAELHALFP GGKYCGHMYQ LTKAPAHTFW RESCGARCVL PWAEFESLLG
181 TCHPVEPGCT ALALRTTIDL TCSGHVSIFE FDVFTRLFQP WPTLLKNWQL LAVNHPGYMA
241 FLTYDEVQER LQACRDKPGS YIFRPSCTRL GQWAIGYVSS DGSILQTIPA NKPLSQVLLE
301 GQKDGFYLYP DGKTHNPDLT ELGQAEPQQR IHVSEEQLQL YWAMDSTFEL CKICAESNKD
361 VKIEPCGHLL CSCCLAAWQH SDSQTCPFCR CEIKGWEAVS IYQFHGQATA EDSGNSSDQE
421 GRELELGQVP LSAPPLPPRP DLPPRKPRNA QPKVRLLKGN SPPAALGPQD PAPA
(SEQ ID NO:17)

[0068] An amino acid sequence of isoform 2 of human CBLC can be found at https://www.ncbi.nlm.nih.gov/protein/NP_001124324 (NCBI Reference Sequence:

NP_001124324.1), and is hereby incorporated by reference in its entirety, as well as reproduced below:

1 MALAVAPWGR QWEEARALGR AVRMLQRLEE QCVDPRLSVS PPSLRDLLPR TAQLLREVAH
61 SRRAAGGGGP GGPGGSGDFL LIYLANLEAK SRQVAALLPP RGRRSANDEL FRAGSRLRRQ
121 LAKLAIIFSH MHAELHALFP GGKYCGHMYQ LTKAPAHTFW RESCGARCVL PWAEFESLLG
181 TCHPVEPGCT ALALRTTIDL TCSGHVSIFE FDVFTRLFQP WPTLLKNWQL LAVNHPGYMA
241 FLTYDEVQER LQACRDKPGS YLYPDGKTHN PDLTELGQAE PQQRIHVSEE QLQLYWAMDS
301 TFELCKICAE SNKDVKIEPC GHLLCSCCLA AWQHSDSQTC PFCRCEIKGW EAVSIYQFHG
361 QATAEDSGNS SDQEGRELEL GQVPLSAPPL PPRPDLPPRK PRNAQPKVRL LKGNSPPAAL
421 GPQDPAPA
(SEQ ID NO:18)

[0069] mRNA sequences of human CBLC can be found at https://www.ncbi.nlm.nih.gov/nuccore/NM_012116 (NCBI Reference Sequence: NM_012116.3) and https://www.ncbi.nlm.nih.gov/nuccore/NM_001130852 (NCBI Reference Sequence: NM_001130852.1), and are hereby incorporated by reference in their entirety.

[0070] Genomic DNA sequence of human CBLC can be found at https://www.ncbi.nlm.nih.gov/nuccore/1189359003 (NCBI Reference Sequence: NG_054718.1), and is hereby incorporated by reference in its entirety.

2. FTIs, and Compositions Comprising FTIs, for Use in Cancer Treatment

2.1. *Farnesyltransferase inhibitors*

[0071] Provided herein are methods for treating a cancer with a farnesyltransferase inhibitor (FTI) in a selected cancer patient or a selected population of cancer patients. The representative FTIs roughly belong to two classes (Shen et al., Drug Disc. Today 20:2 (2015)). The FTIs in the first class have the basic framework of farnesyldiphosphate (FPP). For instance, FPP analogs with a malonic acid group (Ta) were reported to be FTIs that compete with FPP (Duez, S. et al. Bioorg. Med. Chem. 18:543–556(2010)). In addition, imidazole-containing derivatives linked by an acidic substituent and a peptidyl chain were also synthesized as bisubstrate FTIs, and the designed bisubstrate inhibitors have better affinities than FPP. The FTIs in the second class are peptidomimetic molecules, which can be divided into two groups, namely thiol and non-thiol FTIs. Regarding the thiol FTIs, for instance L-739749, a selective peptidomimetic FTI shows potent antitumor activity in nude mice without system toxicity (Kohl, N.E. et al. PNAS 91:9141–

9145(1994)). Additionally, a variety of thiol inhibitors were also developed, such as tripeptidyl FTIs (Lee, H-Y. et al. Bioorg. Med. Chem. Lett. 12:1599–1602(2002)).

[0072] For non-thiol FTIs, the heterocycles were therefore widely used to substitute the thiol group to contact with the zinc ion in the binding site. According to the structures of pharmacophoric groups, the nonthiol FTIs can be divided into three classes. The first class is featured by different monocyclic rings, such as L-778123, an FTI in Phase I clinical trials for solid tumors and lymphoma. L-778123 binds into the CAAX peptide site and competes with the CAAX substrate of farnesyltransferase. The second class is represented by tipifarnib in Phase III trials and BMS-214662 in Phase III trials, which are composed of diverse monocyclic rings and bicyclic rings (Harousseau et al. Blood 114:1166–1173 (2009)). The representative inhibitor of the third class is lonafarnib, which is active in Ras-dependent and -independent malignant tumors, and has entered Phase III clinical trials for combating carcinoma, leukemia, and myelodysplastic syndrome. Lonafarnib is an FTI with a tricycle core, which contains a central seven-membered ring fused with two six-membered aromatic rings.

[0073] Thus, FTIs as described herein can take on a multitude of forms but share the essential inhibitory function of interfering with or lessening the farnesylation of proteins implicated in cancer and proliferative diseases.

[0074] Numerous FTIs are within the scope of the invention and include those described in U.S. Pat. Nos. 5,976,851; 5,972,984; 5,972,966; 5,968,965; 5,968,952; 6,187,786; 6,169,096; 6,037,350; 6,177,432; 5,965,578; 5,965,539; 5,958,939; 5,939,557; 5,936,097; 5,891,889; 5,889,053; 5,880,140; 5,872,135; 5,869,682; 5,861,529; 5,859,015; 5,856,439; 5,856,326; 5,852,010; 5,843,941; 5,807,852; 5,780,492; 5,773,455; 5,767,274; 5,756,528; 5,750,567; 5,721,236; 5,700,806; 5,661,161; 5,602,098; 5,585,359; 5,578,629; 5,534,537; 5,532,359; 5,523,430; 5,504,212; 5,491,164; 5,420,245; and 5,238,922, the disclosures of which are hereby incorporated by reference in their entireties.

[0075] FTIs within the scope of the invention also include those described in Thomas et al., Biologics 1: 415–424 (2007); Shen et al., Drug Disc. Today 20:2 (2015); Appels et al., The Oncologist 10:565–578(2005), the disclosures of which are hereby incorporated by reference in their entireties.

[0076] In some embodiments, the FTIs include Arglabin (i.e.l(R)-10-epoxy-5(S),7(S)-guaia-3(4),11(13)-dien-6,12-olide descibed in WO-98/28303 (NuOncology Labs); perrilyl alcohol described in WO-99/45912 (Wisconsin Genetics); SCH-66336 (lonafarnib), i.e. (+)-(R)-4-[2-[4-(3,10-dibromo-8-chloro-5,6-dihydro-11H-benzo [5,6]cyclohepta[1,2-b]pyridin-11-yl)piperidin-1-yl]-2-oxoethyl]piperidine-l-carboxamide, described in U.S. Patent No. 5874442 (Schering); L778123, i.e. 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, described in WO-00/01691 (Merck); L739749, i.e. compound 2(S)-[2(S)-[2(R)-amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone described in WO-94/10138 (Merck); FTI-277, i.e., methyl {N-[2-phenyl-4-N [2(R)-amino-3-mecaptopropylamino] benzoyl]}-methionate (Calbiochem); L744832, i.e, 2S)-2-[[(2S)-2-[(2S,3S)-2-[(2R)-2-amino-3-mercaptopropyl]amino]-3-methylpentyl]oxy]-1-oxo-3-phenylpropyl]amino]-4-(methylsulfonyl)-butanoic acid 1-methylethyl ester (Biomol International L.P.); CP-609,754 (Pfizer), i.e., (R)-6-[(4-chlorophenyl)-hydroxyl-(1-methyl-1-H-imidazol-5-yl)-methyl]-4-(3-ethynylphenyl)-1-methyl-2-(1H)-quinonlinone and (R)-6-[(4-chlorophenyl)-hydroxyl-(3-methyl-3-H-imidazol-4-yl)-methyl]-4-(3-ethynylphenyl)-1-methyl-2-(1H)-quinolinone; R208176 (Johnson & Johnson), i.e., JNJ-17305457, or (R)-1-(4-chlorophenyl)-1-[5-(3-chlorophenyl)tetrazolo[1,5-a]quinazolin-7-yl]-1-(1-methyl-1H-imidazol-5-yl)methanamine; AZD3409 (AstraZeneca), i.e. (S)-isopropyl 2-(2-(4-fluorophenethyl)-5-((((2S,4S)-4-(nicotinoylthio)pyrrolidin-2-yl)methyl)amino)benzamido)-4-(methylthio)butanoate; BMS 214662 (Bristol-Myers Squibb), i.e. (R)-2,3,4,5-tetrahydro-l-(IH-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulphonyl)-1H-1,4-benzodiazapine-7-carbonitrile, described in WO 97/30992 (Bristol Myers Squibb) and Pfizer compounds (A) and (B) described in WO-00/12498 and WO-00/12499.

[0077] In some embodiments, the FTI are the non-peptidal, so-called "small molecule" therapeutics, such as are quinolines or quinoline derivatives including:

[0078] 7-(3-chlorophenyl)-9-[(4-chlorophenyl)-1H-imidazol-1-ylmethyl]-2,3-dihydro-o-1H,5H-benzo[ij]quinolizin-5-one,

[0079] 7-(3-chlorophenyl)-9-[(4-chlorophenyl)-1H-imidazol-1-ylmethyl]-1,2-dihydro-o-4H-pyrrolo[3,2,1-ij]quinoline-4-one,

[0080] 8-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl),methyl]-6-(3-chloroph-enyl)-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one, and

[0081] 8-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-6-(3-chlorophe-nyl)-2,3-dihydro-1H,5H-benzo[ij]quinolizin-5-one.

[0082] Tipifarnib is a nonpeptidomimetic FTI (Thomas et al., Biologics 1: 415–424 (2007)). It is a 4,6-disubstituted-1-methylquinolin-2-one derivative ((B)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-ch-lorophenyl)-1-methyl-2(1H)-quinolinone)) that was obtained by optimization of a quinolone lead identified from compound library screening. Tipifarnib competitively inhibits the CAAX peptide binding site of FTase and is extremely potent and highly selective inhibitor of farnesylation. Tipifarnib is not an inhibitor of geranylgeranyltransferase I. Tipifarnib has manageable safety profile as single agent therapy, is reasonably well tolerated in man and requires twice-daily dosing to obtain effective plasma concentrations.

[0083] Tipifarnib is synthesized by the condensation of the anion of 1-methylimidazole with a 6-(4-chlorobenzoyl) quinolone derivative, followed by dehydration. The quinolone intermediate was prepared in four steps by cyclization of N-phenyl-3-(3-chlorophenyl)-2-propenamide, acylation, oxidation and N-methylation. Tipifarnib was identified from Janssen's ketoconazole and retinoic acid catabolism programs as a key structural feature into Ras prenylation process. Tipifarnib is a potent inhibitor of FTase in vitro and is orally active in a variety of animal models. Single agent activity of tipifarnib was observed in unselected tumor populations (AML, MDS/CMML, urothelial cancer, breast cancer, PTCL/CTCL) although a phase III clinic study failed to demonstrate improvement in overall survival.

[0084] In some embodiments, provided herein is a method of treating cancer in a subject with an FTI or a pharmaceutical composition having FTI, or selecting a cancer patient for an FTI treatment. The pharmaceutical compositions provided herein contain therapeutically effective amounts of an FTI and a pharmaceutically acceptable carrier, diluent or excipient. In some embodiments, the FTI is tipifarnib; arglabin; perrilyl alcohol; lonafarnib (SCH-66336); L778123; L739749; FTI-277; L744832; R208176; BMS 214662; AZD3409; or CP-609,754. In some embodiments, the FTI is tipifarnib.

2.2. *FTI Formulations*

[0085] The FTI can be formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for ophthalmic or parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically the FTI is formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, e.g., Ansel Introduction to Pharmaceutical Dosage Forms, Seventh Edition 1999).

[0086] In the compositions, effective concentrations of the FTI and pharmaceutically acceptable salts is (are) mixed with a suitable pharmaceutical carrier or vehicle. In certain embodiments, the concentrations of the FTI in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms and/or progression of cancer, including haematological cancers and solid tumors.

[0087] The compositions can be formulated for single dosage administration. To formulate a composition, the weight fraction of the FTI is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the FTI provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

[0088] In addition, the FTI can be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as known in the art. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of an FTI provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

[0089] The FTI is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in in vitro and in vivo systems described herein and then extrapolated therefrom for dosages for humans.

[0090] The concentration of FTI in the pharmaceutical composition will depend on absorption, tissue distribution, inactivation and excretion rates of the FTI, the physicochemical characteristics of the FTI, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of cancer, including hematopoietic cancers and solid tumors.

[0091] In certain embodiments, a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 μg/ml. In one embodiment, the pharmaceutical compositions provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and in certain embodiments, from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

[0092] The FTI may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[0093] Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable salts thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating, retarding progression, or preventing. The concentration of active compound in the composition will depend on absorption, tissue distribution, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

[0094] The compositions are intended to be administered by a suitable route, including but not limited to orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets can be formulated. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration.

[0095] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol, dimethyl acetamide or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, pens, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

[0096] In instances in which the FTI exhibits insufficient solubility, methods for solubilizing compounds can be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate.

[0097] Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the

selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[0098] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable salts thereof. The pharmaceutically therapeutically active compounds and salts thereof are formulated and administered in unit dosage forms or multiple dosage forms. Unit dose forms as used herein refer to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit dose forms include ampules and syringes and individually packaged tablets or capsules. Unit dose forms may be administered in fractions or multiples thereof. A multiple dose form is a plurality of identical unit dosage forms packaged in a single container to be administered in segregated unit dose form. Examples of multiple dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit doses which are not segregated in packaging.

[0099] Sustained-release preparations can also be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the compound provided herein, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include iontophoresis patches, polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated compound remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37 °C, resulting in a loss of

biological activity and possible changes in their structure. Rational strategies can be devised for stabilization depending on the mechanism of action involved. For example, if the aggregation mechanism is discovered to be intermolecular S--S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[00100] Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain about 0.001% 100% active ingredient, in certain embodiments, about 0.1-85% or about 75-95%.

[00101] The FTI or pharmaceutically acceptable salts can be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

[00102] The compositions can include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable salts thereof as described herein, can also be administered together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases related to oxidative stress.

[00103] Lactose-free compositions provided herein can contain excipients that are well known in the art and are listed, for example, in the U.S. Pharmocopia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions contain an active ingredient, a binder/filler, and a lubricant in

pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose-free dosage forms contain an active ingredient, microcrystalline cellulose, pre-gelatinized starch and magnesium stearate.

[00104] Further encompassed are anhydrous pharmaceutical compositions and dosage forms containing a compound provided herein. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment and use of formulations.

[00105] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[00106] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs and strip packs.

[00107] Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric coated, sugar coated or film coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

[00108] In certain embodiments, the formulations are solid dosage forms, such as capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

[00109] Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[00110] When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[00111] Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric

coated tablets, because of the enteric coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00112] Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil in-water or water in oil.

[00113] Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

[00114] Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Examples of non aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include

lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic adds include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

[00115] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, e.g., for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be easily measured for administration.

[00116] Alternatively, liquid or semi solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g., propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

[00117] Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

[00118] In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

[00119] Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also provided herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow release or sustained release system, such that a constant level of dosage is maintained is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[00120] Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[00121] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[00122] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[00123] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[00124] The concentration of the FTI is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age,

weight and condition of the patient or animal as is known in the art. The unit dose parenteral preparations are packaged in an ampule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

[00125] Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an FTI is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

[00126] Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, such as more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

[00127] The FTI can be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

[00128] Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They can also be reconstituted and formulated as solids or gels.

[00129] The sterile, lyophilized powder is prepared by dissolving an FTI provided herein, or a pharmaceutically acceptable salt thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (including but not limited to 10-1000 mg or 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

[00130] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, about 5-35 mg, or about 9-30 mg of lyophilized powder, is added per mL of sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

[00131] Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsion or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[00132] The FTI or pharmaceutical composition having an FTI can be formulated as aerosols for topical application, such as by inhalation (see, e.g., U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a

case, the particles of the formulation will have diameters of less than 50 microns or less than 10 microns.

[00133] The FTI or pharmaceutical composition having an FTI can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered. These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

[00134] Other routes of administration, such as transdermal patches, and rectal administration are also contemplated herein. For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono , di and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. An exemplary weight of a rectal suppository is about 2 to 3 grams. Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

[00135] The FTI or pharmaceutical composition having an FTI provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, 5,639,480, 5,733,566, 5,739,108, 5,891,474, 5,922,356, 5,972,891, 5,980,945, 5,993,855, 6,045,830, 6,087,324, 6,113,943,

6,197,350, 6,248,363, 6,264,970, 6,267,981, 6,376,461,6,419,961, 6,589,548, 6,613,358, 6,699,500 and 6,740,634, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of FTI using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein.

[00136] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. In one embodiment, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. In certain embodiments, advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

[00137] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[00138] In certain embodiments, the FTI can be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used (see, Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled

release system can be placed in proximity of the therapeutic target, i.e., thus requiring only a fraction of the systemic dose (see, e.g., Goodson, Medical Applications of Controlled Release, vol. 2, pp. 115-138 (1984).

[00139] In some embodiments, a controlled release device is introduced into a subject in proximity of the site of inappropriate immune activation or a tumor. Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990). The F can be dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

[00140] The FTI or pharmaceutical composition of FTI can be packaged as articles of manufacture containing packaging material, a compound or pharmaceutically acceptable salt thereof provided herein, which is used for treatment, prevention or amelioration of one or more symptoms or progression of cancer, including hematological cancers and solid tumors, and a label that indicates that the compound or pharmaceutically acceptable salt thereof is used for treatment, prevention or amelioration of one or more symptoms or progression of cancer, including hematological cancers and solid tumors.

[00141] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, pens, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated.

2.3. *Dosages*

[00142] In some embodiments, a therapeutically effective amount of the pharmaceutical composition having an FTI is administered orally or parenterally. In some embodiments, the pharmaceutical composition having tipifarnib as the active ingredient and is administered orally in an amount of from 1 up to 1500 mg/kg daily, either as a single dose or subdivided into more than one dose, or more particularly in an amount of from 10 to 1200 mg/kg daily. In some embodiments, the pharmaceutical composition having tipifarnib as the active ingredient and is administered orally in an amount of 100 mg/kg daily, 200 mg/kg daily, 300 mg/kg daily, 400 mg/kg daily, 500 mg/kg daily, 600 mg/kg daily, 700 mg/kg daily, 800 mg/kg daily, 900 mg/kg daily, 1000 mg/kg daily, 1100 mg/kg daily, or 1200 mg/kg daily. In some embodiments, the FTI is tipifarnib.

[00143] In some embodiments, the FTI is administered at a dose of 200-1500 mg daily. In some embodiments, the FTI is administered at a dose of 200-1200 mg daily. In some embodiments, the FTI is administered at a dose of 200 mg daily. In some embodiments, the FTI is administered at a dose of 300 mg daily. In some embodiments, the FTI is administered at a dose of 400 mg daily. In some embodiments, the FTI is administered at a dose of 500 mg daily. In some embodiments, the FTI is administered at a dose of 600 mg daily. In some embodiments, the FTI is administered at a dose of 700 mg daily. In some embodiments, the FTI is administered at a dose of 800 mg daily. In some embodiments, the FTI is administered at a dose of 900 mg daily. In some embodiments, the FTI is administered at a dose of 1000 mg daily. In some embodiments, the FTI is administered at a dose of 1100 mg daily. In some embodiments, the FTI is administered at a dose of 1200 mg daily. In some embodiments, the FTI is administered at a dose of 1300 mg daily. In some embodiments, the FTI is administered at a

dose of 1400 mg daily. In some embodiments, an FTI is administered at a dose of 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1025, 1050, 1075, 1100, 1125, 1150, 1175, or 1200 mg daily. In some embodiments, the FTI is tipifarnib.

[00144] In some embodiments, the FTI is administered at a dose of 200-1400 mg b.i.d. (*i.e.*, twice a day). In some embodiments, the FTI is administered at a dose of 300-1200 mg b.i.d. In some embodiments, the FTI is administered at a dose of 300-900 mg b.i.d. In some embodiments, the FTI is administered at a dose of 600 mg b.i.d. In some embodiments, the FTI is administered at a dose of 700 mg b.i.d. In some embodiments, the FTI is administered at a dose of 800 mg b.i.d. In some embodiments, the FTI is administered at a dose of 900 mg b.i.d. In some embodiments, the FTI is administered at a dose of 1000 mg b.i.d. In some embodiments, the FTI is administered at a dose of 1100 mg b.i.d. In some embodiments, the FTI is administered at a dose of 1200 mg b.i.d. In some embodiments, an FTI is administered at a dose of 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1025, 1050, 1075, 1100, 1125, 1150, 1175, or 1200 mg b.i.d. In some embodiments, the FTI is tipifarnib.

[00145] As a person of ordinary skill in the art would understand, the dosage varies depending on the dosage form employed, condition and sensitivity of the patient, the route of administration, and other factors. The exact dosage will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active ingredient or to maintain the desired effect. Factors which can be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. During a treatment cycle, the daily dose could be varied. In some embodiments, a starting dosage can be titrated down within a treatment cycle. In some embodiments, a starting dosage can be titrated up within a treatment cycle. The final dosage can depend on the occurrence of dose limiting toxicity and other factors.

[00146] In some embodiments, the FTI is administered at a starting dose of 300 mg daily and escalated to a maximum dose of 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg,

1100 mg, or 1200 mg daily. In some embodiments, the FTI is administered at a starting dose of 400 mg daily and escalated to a maximum dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg daily. In some embodiments, the FTI is administered at a starting dose of 500 mg daily and escalated to a maximum dose of 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg daily. In some embodiments, the FTI is administered at a starting dose of 600 mg daily and escalated to a maximum dose of 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg daily. In some embodiments, the FTI is administered at a starting dose of 700 mg daily and escalated to a maximum dose of 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg daily. In some embodiments, the FTI is administered at a starting dose of 800 mg daily and escalated to a maximum dose of 900 mg, 1000 mg, 1100 mg, or 1200 mg daily. In some embodiments, the FTI is administered at a starting dose of 900 mg daily and escalated to a maximum dose of 1000 mg, 1100 mg, or 1200 mg daily. The dose escalation can be done at once, or step wise. For example, a starting dose at 600 mg daily can be escalated to a final dose of 1000 mg daily by increasing by 100 mg per day over the course of 4 days, or by increasing by 200 mg per day over the course of 2 days, or by increasing by 400 mg at once. In some embodiments, the FTI is tipifarnib.

[00147] In some embodiments, the FTI is administered at a relatively high starting dose and titrated down to a lower dose depending on the patient response and other factors. In some embodiments, the FTI is administered at a starting dose of 1200 mg daily and reduced to a final dose of 1100 mg, 1000 mg, 900 mg, 800 mg, 700 mg, 600 mg, 500 mg, 400 mg or 300 mg daily. In some embodiments, the FTI is administered at a starting dose of 1100 mg daily and reduced to a final dose of 1000 mg, 900 mg, 800 mg, 700 mg, 600 mg, 500 mg, 400 mg, or 300 mg daily. In some embodiments, the FTI is administered at a starting dose of 1000 mg daily and reduced to a final dose of 900 mg, 800 mg, 700mg, 600mg, 500 mg, 400 mg, or 300 mg daily. In some embodiments, the FTI is administered at a starting dose of 900 mg daily and reduced to a final dose of 800 mg, 700 mg, 600 mg, 500 mg, 400 mg, or 300 mg daily. In some embodiments, the FTI is administered at a starting dose of 800 mg daily and reduced to a final dose of 700 mg, 600 mg, 500 mg, 400 mg, or 300 mg daily. In some embodiments, the FTI is administered at a starting dose of 600 mg daily and reduced to a final dose of 500 mg, 400 mg, or 300 mg daily. The dose reduction can be done at once, or step wise. In some embodiments, the FTI is tipifarnib. For example, a starting dose at 900 mg daily can be reduced to a final dose of 600 mg

daily by decreasing by 100 mg per day over the course of 3 days, or by decreasing by 300 mg at once.

[00148] In some embodiments, the FTI is administered at a starting dose of 300 mg twice a day (b.i.d.) and escalated to a maximum dose of 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg b.i.d.. In some embodiments, the FTI is administered at a starting dose of 400 mg b.i.d. and escalated to a maximum dose of 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 500 mg b.i.d. and escalated to a maximum dose of 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 600 mg b.i.d. and escalated to a maximum dose of 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 700 mg b.i.d. and escalated to a maximum dose of 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 800 mg b.i.d. and escalated to a maximum dose of 900 mg, 1000 mg, 1100 mg, or 1200 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 900 mg bid and escalated to a maximum dose of 1000 mg, 1100 mg, or 1200 mg b.i.d. The dose escalation can be done at once, or step wise. For example, a starting dose at 600 mg b.i.d. can be escalated to a final dose of 1000 mg b.i.d. by increasing by 100 mg bid over the course of 4 days, or by increasing by 200 mg b.i.d. over the course of 2 days, or by increasing by 400 mg b.i.d. at once. In some embodiments, the FTI is tipifarnib.

[00149] In some embodiments, the FTI is administered at a relatively high starting dose and titrated down to a lower dose depending on the patient response and other factors. In some embodiments, the FTI is administered at a starting dose of 1200 mg b.i.d. and reduced to a final dose of 1100 mg, 1000 mg, 900 mg, 800 mg, 700 mg, 600 mg, 500 mg, 400 mg or 300 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 1100 mg b.i.d. and reduced to a final dose of 1000 mg, 900 mg, 800 mg, 700 mg, 600 mg, 500 mg, 400 mg, or 300 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 1000 mg b.i.d. and reduced to a final dose of 900 mg, 800 mg, 700 mg, 600 mg, 500 mg, 400 mg, or 300 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 900 mg b.i.d. and reduced to a final dose of 800 mg, 700 mg, 600 mg, 500 mg, 400 mg, or 300 mg b.i.d. In some embodiments, the

FTI is administered at a starting dose of 800 mg b.i.d. and reduced to a final dose of 700 mg, 600 mg, 500 mg, 400 mg, or 300 mg b.i.d. In some embodiments, the FTI is administered at a starting dose of 600 mg b.i.d. and reduced to a final dose of 500 mg, 400 mg, or 300 mg b.i.d. The dose reduction can be done at once, or step wise. In some embodiments, the FTI is tipifarnib. For example, a starting dose at 900 mg b.i.d. can be reduced to a final dose of 600 mg bid by decreasing by 100 mg b.i.d. over the course of 3 days, or by decreasing by 300 mg b.i.d. at once.

[00150] A treatment cycle can have different length. In some embodiments, a treatment cycle can be one week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months. In some embodiments, a treatment cycle is 4 weeks. A treatment cycle can have intermittent schedule. In some embodiments, a 2-week treatment cycle can have 5-day dosing followed by 9-day rest. In some embodiments, a 2-week treatment cycle can have 6-day dosing followed by 8-day rest. In some embodiments, a 2-week treatment cycle can have 7-day dosing followed by 7-day rest. In some embodiments, a 2-week treatment cycle can have 8-day dosing followed by 6-day rest. In some embodiments, a 2-week treatment cycle can have 9-day dosing followed by 5-day rest.

[00151] In some embodiments, the FTI is administered to a subject on days 1-21 of a 28-day treatment cycle (e.g., twice a day). In some embodiments, the FTI is administered on days 1-7 of a 28-day treatment cycle (e.g., twice a day). In some embodiments, the FTI is administered on days 1-7 and 15-21 of a 28-day treatment cycle (e.g., twice a day). In some embodiments, the FTI is administered for at least 3 cycles or at least 6 cycles (e.g., twice a day). In some of these embodiments, the FTI is tipifarnib, and the dose of tipifarnib is from 200 mg to 900 mg twice a day (e.g. 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, or 900 mg). In some of these embodiments, the FTI is tipifarnib, and the dose of tipifarnib is from 250 mg to 1000 mg twice a day (e.g. 250 mg, 350 mg, 450 mg, 550 mg, 650 mg, 750 mg, 850 mg, 950 mg, or 1000 mg). In some embodiments, the FTI is administered to a subject for at least or more than 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 1 year, 15 months, 1.5 years, 18 months, 2 years or 3 years. In some embodiments, the FTI is administered to a subject for at least or more than 3 months. In some embodiments, the FTI is administered to a subject

for at least or more than 6 months. In some embodiments, the FTI is administered to a subject for at least or more than 1 year. In some embodiments, the subject remains responsive to treatment with an FTI for at least or more than 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 1 year, 15 months, 1.5 years, 18 months, 2 years or 3 years. In some embodiments, the subject remains responsive to treatment with an FTI for at least or more than 3 months. In some embodiments, the subject remains responsive to treatment with an FTI for at least or more than 6 months. In some embodiments, the subject remains responsive to treatment with an FTI for at least or more than 1 year.

[00152] In some embodiments, the FTI is administered daily for 3 out of 4 weeks in repeated 4 week cycles. In some embodiments, the FTI is administered daily in alternate weeks (one week on, one week off) in repeated 4 week cycles. In some embodiments, the FTI is administered at a dose of 300 mg b.i.d. orally for 3 out of 4 weeks in repeated 4 week cycles. In some embodiments, the FTI is administered at a dose of 600 mg b.i.d. orally for 3 out of 4 weeks in repeated 4 week cycles. In some embodiments, the FTI is administered at a dose of 900 mg b.i.d. orally in alternate weeks (one week on, one week off) in repeated 4 week cycles. In some embodiments, the FTI is administered at a dose of 1200 mg b.i.d. orally in alternate weeks (days 1-7 and 15-21 of repeated 28-day cycles). In some embodiments, the FTI is administered at a dose of 1200 mg b.i.d. orally for days 1-5 and 15-19 out of repeated 28-day cycles.

[00153] In some embodiments, a 900 mg b.i.d. tipifarnib alternate week regimen can be used. Under the regimen, patients receive a starting dose of 900 mg, po, b.i.d. on days 1-7 and 15-21 of 28-day treatment cycles. In some embodiments, patients receive two treatment cycles. In some embodiments, patients receive three treatment cycles. In some embodiments, patients receive four treatment cycles. In some embodiments, patients receive five treatment cycles. In some embodiments, patients receive six treatment cycles. In some embodiments, patients receive seven treatment cycles. In some embodiments, patients receive eight treatment cycles. In some embodiments, patients receive nine treatment cycles. In some embodiments, patients receive ten treatment cycles. In some embodiments, patients receive eleven treatment cycles. In some embodiments, patients receive twelve treatment cycles. In some embodiments, patients receive more than twelve treatment cycles.

[00154] In the absence of unmanageable toxicities, subjects can continue to receive the tipifarnib treatment for up to 12 months. The dose can also be increased to 1200 mg b.i.d. if the subject is tolerating the treatment well. Stepwise 300 mg dose reductions to control treatment-related, treatment-emergent toxicities can also be included.

[00155] In some other embodiments, tipifarnib is given orally at a dose of 300 mg b.i.d. daily for 21 days, followed by 1 week of rest, in 28-day treatment cycles (21-day schedule; Cheng DT, *et al.*, *J Mol Diagn.* (2015) 17(3):251-64). In some embodiments, a 5-day dosing ranging from 25 to 1300 mg b.i.d. followed by 9-day rest is adopted (5-day schedule; Zujewski J., *J Clin Oncol.*, (2000) Feb;18(4):927-41). In some embodiments, a 7-day b.i.d. dosing followed by 7-day rest is adopted (7-day schedule; Lara PN Jr., *Anticancer Drugs.*, (2005) 16(3):317-21; Kirschbaum MH, *Leukemia.*, (2011) Oct;25(10):1543-7). In the 7-day schedule, the patients can receive a starting dose of 300 mg b.i.d. with 300 mg dose escalations to a maximum planned dose of 1800 mg b.i.d.. In the 7-day schedule study, patients can also receive tipifarnib b.i.d. on days 1–7 and days 15–21 of 28-day cycles at doses up to 1600 mg b.i.d..

[00156] In previous studies FTI were shown to inhibit the growth of mammalian tumors when administered as a twice daily dosing schedule. It was found that administration of an FTI in a single dose daily for one to five days produced a marked suppression of tumor growth lasting out to at least 21 days. In some embodiments, FTI is administered at a dosage range of 50-400 mg/kg. In some embodiments, FTI is administered at 200 mg/kg. Dosing regimen for specific FTIs are also well known in the art (e.g., U.S. Patent No. 6838467, which is incorporated herein by reference in its entirety). For example, suitable dosages for the compounds Arglabin (WO98/28303), perrilyl alcohol (WO 99/45712), SCH-66336 (U.S. Pat. No. 5,874,442), L778123 (WO 00/01691), 2(S)-[2(S)-[2(R)-amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone (WO94/10138), BMS 214662 (WO 97/30992), AZD3409; Pfizer compounds A and B (WO 00/12499 and WO 00/12498) are given in the aforementioned patent specifications which are incorporated herein by reference or are known to or can be readily determined by a person skilled in the art.

[00157] In relation to perrilyl alcohol, the medicament may be administered 1-4 g per day per 150 lb human patient. Preferably, 1-2 g per day per 150 lb human patient. SCH-66336 typically can be administered in a unit dose of about 0.1 mg to 100 mg, more preferably from about 1 mg

to 300 mg according to the particular application. Compounds L778123 and 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone may be administered to a human patient in an amount between about 0.1 mg/kg of body weight to about 20 mg/kg of body weight per day, preferably between 0.5 mg/kg of bodyweight to about 10 mg/kg of body weight per day.

[00158] Pfizer compounds A and B may be administered in dosages ranging from about 1.0 mg up to about 500 mg per day, preferably from about 1 to about 100 mg per day in single or divided (i.e. multiple) doses. Therapeutic compounds will ordinarily be administered in daily dosages ranging from about 0.01 to about 10 mg per kg body weight per day, in single or divided doses. BMS 214662 may be administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day in a single dose or in 2 to 4 divided doses.

2.4. *Combination therapies*

[00159] In some embodiments, the FTI treatment is administered in combination with radiotherapy, or radiation therapy. Radiotherapy includes using γ-rays, X-rays, and/or the directed delivery of radioisotopes to tumor cells. Other forms of DNA damaging factors are also contemplated, such as microwaves, proton beam irradiation (U.S. Patent Nos. 5,760,395 and 4,870,287; all of which are hereby incorporated by references in their entireties), and UV-irradiation. It is most likely that all of these factors affect a broad range of damage on DNA, on the precursors of DNA, on the replication and repair of DNA, and on the assembly and maintenance of chromosomes.

[00160] In some embodiments, a therapeutically effective amount of the pharmaceutical composition having an FTI is administered that effectively sensitizes a tumor in a host to irradiation. (U.S. Patent No. 6545020, which is hereby incorporated by reference in its entirety). Irradiation can be ionizing radiation and in particular gamma radiation. In some embodiments, the gamma radiation is emitted by linear accelerators or by radionuclides. The irradiation of the tumor by radionuclides can be external or internal.

[00161] Irradiation can also be X-ray radiation. Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 wk), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

[00162] In some embodiments, the administration of the pharmaceutical composition commences up to one month, in particular up to 10 days or a week, before the irradiation of the tumor. Additionally, irradiation of the tumor is fractionated the administration of the pharmaceutical composition is maintained in the interval between the first and the last irradiation session.

[00163] The amount of FTI, the dose of irradiation and the intermittence of the irradiation doses will depend on a series of parameters such as the type of tumor, its location, the patients' reaction to chemo- or radiotherapy and ultimately is for the physician and radiologists to determine in each individual case.

[00164] In some embodiments, the methods provided herein further include administering a therapeutically effective amount of a second active agent or a support care therapy. The second active agent can be a chemotherapeutic agent. A chemotherapeutic agent or drug can be categorized by its mode of activity within a cell, for example, whether and at what stage they affect the cell cycle. Alternatively, an agent can be characterized based on its ability to directly cross-link DNA, to intercalate into DNA, or to induce chromosomal and mitotic aberrations by affecting nucleic acid synthesis.

[00165] Examples of chemotherapeutic agents include alkylating agents, such as thiotepa and cyclosphosphamide; alkyl sulfonates, such as busulfan, improsulfan, and piposulfan; aziridines, such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines, including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide, and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards, such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, and uracil mustard; nitrosureas, such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics, such as the enediyne antibiotics (*e.g.,* calicheamicin, especially

calicheamicin gammalI and calicheamicin omegaI1); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authrarnycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, such as mitomycin C, mycophenolic acid, nogalarnycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin; anti-metabolites, such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues, such as denopterin, pteropterin, and trimetrexate; purine analogs, such as fludarabine, 6-mercaptopurine, thiamiprine, and thioguanine; pyrimidine analogs, such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine; androgens, such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, and testolactone; anti-adrenals, such as mitotane and trilostane; folic acid replenisher, such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids, such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSKpolysaccharide complex; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2”-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (“Ara-C”); cyclophosphamide; taxoids, *e.g.*, paclitaxel and docetaxel gemcitabine; 6-thioguanine; mercaptopurine; platinum coordination complexes, such as cisplatin, oxaliplatin, and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (*e.g.*, CPT-11); topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DMFO); retinoids, such as retinoic acid; capecitabine; carboplatin,

procarbazine,plicomycin, gemcitabine, navelbine, transplatinum, and pharmaceutically acceptable salts, acids, or derivatives of any of the above.

[00166] The second active agents can be large molecules *(e.g.*, proteins) or small molecules *(e.g.*, synthetic inorganic, organometallic, or organic molecules). In some embodiments, the second active agent is a DNA-hypomethylating agent, a therapeutic antibody that specifically binds to a cancer antigen, a hematopoietic growth factor, cytokine, anti-cancer agent, antibiotic, cox-2 inhibitor, immunomodulatory agent, anti-thymocyte globulin, immunosuppressive agent, corticosteroid or a pharmacologically active mutant or derivative thereof.

[00167] In some embodiments, the second active agent is a DNA hypomethylating agent, such as a cytidine analog (*e.g.*, azacitidine) or a 5-azadeoxycytidine (*e.g.* decitabine). In some embodiments, the second active agent is a cytoreductive agent, including but not limited to Induction, Topotecan, Hydrea, PO Etoposide, Lenalidomide, LDAC, and Thioguanine. In some embodiments, the second active agent is Mitoxantrone, Etoposide, Cytarabine, or Valspodar. In some embodiment, the second active agent is Mitoxantrone plus Valspodar, Etoposide plus Valspodar, or Cytarabine plus Valspodar. In some embodiment, the second active agent is idarubicin, fludarabine, topotecan, or ara-C. In some other embodiments, the second active agent is idarubicin plus ara-C, fludarabine plus ara-C, mitoxantrone plus ara-C, or topotecan plus ara-C. In some embodiments, the second active agent is a quinine. In some embodiments, the second active agent is dasatinib or imatinib. Other combinations of the agents specified above can be used, and the dosages can be determined by the physician.

[00168] For any specific cancer type described herein, treatments as described herein or otherwise available in the art can be used in combination with the FTI treatment. For example, drugs that can be used in combination with the FTI include belinostat (Beleodaq®) and pralatrexate (Folotyn®), marketed by Spectrum Pharmaceuticals, romidepsin (Istodax®), marketed by Celgene, and brentuximab vedotin (Adcetris®) (for ALCL), marketed by Seattle Genetics; drugs that can be used in combination with the FTI include azacytidine (Vidaza®) and lenalidomide (Revlimid®), marketed by Celgene, and decitabine (Dacogen®) marketed by Otsuka and Johnson & Johnson; drugs that can be used in combination with the FTI for thyroid cancer include AstraZeneca's vandetanib (Caprelsa®), Bayer's sorafenib (Nexavar®), Exelixis' cabozantinib (Cometriq®) and Eisai's lenvatinib (Lenvima®).

[00169] Non-cytotoxic therapies such as tpralatrexate (Folotyn®), romidepsin (Istodax®) and belinostat (Beleodaq®) can also be used in combination with the FTI treatment.

[00170] In some embodiments, the second active agent is an immunotherapy agent. In some embodiments, the second active agent is anti-PD1 antibody or anti-PDL1 antibody.

[00171] In some embodiments, it is contemplated that the second active agent or second therapy used in combination with an FTI can be administered before, at the same time, or after the FTI treatment. In some embodiments, the second active agent or second therapy used in combination with an FTI can be administered before the FTI treatment. In some embodiments, the second active agent or second therapy used in combination with an FTI can be administered at the same time as FTI treatment. In some embodiments, the second active agent or second therapy used in combination with an FTI can be administered after the FTI treatment.

[00172] The FTI treatment can also be administered in combination with a bone marrow transplant. In some embodiments, the FTI is administered before the bone marrow transplant. In other embodiments, the FTI is administered after the bone marrow transplant.

[00173] A person of ordinary skill in the art would understand that the methods described herein include using any permutation or combination of the specific FTI, formulation, dosing regimen, additional therapy to treat a subject described herein.

3. Treatment of Cancer Based on the Mutation Status of CBL

[00174] Provided herein are methods of selection of cancer patients for treatment with an FTI which are based, in part, on the discovery that the mutation status in a member of the CBL family is associated with clinical benefits of FTI and can be used to predict the responsiveness of a cancer patient to an FTI treatment. Accordingly, provided herein are methods for predicting responsiveness of a cancer patient to an FTI treatment, methods for cancer patient population selection for an FTI treatment, and methods for treating cancer in a subject with a therapeutically effective amount of an FTI, based on the mutation status of a member of the CBL family (e.g., CBL, CBLB or CBLC) in a sample from the patient. In particular, provided herein are methods for treating a CBL-mutant cancer, i.e., a cancer known to have or determined to have a mutation in a member of the CBL family. Also provided herein are methods for treating patients having a

cancer and a mutation in a member of the CBL family (such as a mutation in a member of the CBL family in a tumor cell or tissue). In some embodiments, the cancer is a hematological or hematopoietic cancer. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is a leukemia such as CMML. In some embodiments, the FTI is tipifarnib. Provided herein are also methods for treating a premalignant condition in a subject with an FTI, and methods for selecting patients with a premalignant condition for an FTI treatment based on the mutation status of a member of the CBL family (e.g., CBL, CBLB or CBLC).

[00175] In some embodiments, provided herein are methods for predicting responsiveness of a MDS patient to an FTI treatment, methods for MDS patient population selection for an FTI treatment, and methods for treating MDS in a subject with a therapeutically effective amount of an FTI, based on the mutation status of a member of the CBL family (such as CBL, CBLB and/or CBLC) in a sample from the patient (e.g., tumor sample). In some embodiments, provided herein are methods for predicting responsiveness of a MPN patient to an FTI treatment, methods for MPN patient population selection for an FTI treatment, and methods for treating MPN in a subject with a therapeutically effective amount of an FTI, based on the mutation status of a member of the CBL family (such as CBL, CBLB and/or CBLC) in a sample from the patient (e.g., tumor sample). In some embodiments, provided herein are methods for predicting responsiveness of an AML patient to an FTI treatment, methods for AML patient population selection for an FTI treatment, and methods for treating AML in a subject with a therapeutically effective amount of an FTI, based on the mutation status of a member of the CBL family (such as CBL, CBLB and/or CBLC) in a sample from the patient (e.g., tumor sample). In some embodiments, provided herein are methods for predicting responsiveness of a JMML patient to an FTI treatment, methods for JMML patient population selection for an FTI treatment, and methods for treating JMML in a subject with a therapeutically effective amount of an FTI, based on the mutation status of a member of the CBL family (such as CBL, CBLB and/or CBLC) in a sample from the patient (e.g., tumor sample).

3.1. *CBL mutation status*

[00176] In some embodiments, the cancer to be treated by methods provided herein can have a CBL mutation or mutations (e.g., one or more mutations in a member of the CBL family such as CBL, CBLB and CBLC). In some embodiments, mutation status of a gene of the CBL family

can be determined in the form of a companion diagnostic to the FTI treatment, such as the tipifarnib treatment. The companion diagnostic can be performed at the clinic site where the patient receives the tipifarnib treatment, or at a separate site. Methods provided herein or otherwise known in the art can be used to determine the mutation status of a member of the CBL family. In some embodiments, the mutation status of a gene of the CBL family can be determined by a next generation sequencing (NGS)-based assay. In some embodiments, the mutation status of a gene of the CBL family can be determined by a qualitative PCR-based assay.

[00177] Provided herein are methods of selection of cancer patients for treatment with an FTI based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein is a method of treating a cancer in a subject based on the presence of a mutation in a member of the CBL family. The method provided herein includes (a) determining the presence or absence of a mutation in a member of the CBL family in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of an FTI to the subject if the sample is determined to have a mutation in a member of the CBL family. The sample can be a tumor sample, a bone marrow sample or a plasma sample. In some embodiments, the methods include (a) determining a cancer patient to have a mutation in a member of the CBL family, and subsequently (b) administering a therapeutically effective amount of an FTI to the subject.

[00178] In some embodiments, the mutation in a member of the CBL family can be a mutation in its ring finger domain. In some embodiments, the mutation in a member of the CBL family can be a mutation in its linker domain. In some embodiments, the mutation in a member of the CBL family can be a mutation in its proline-rich domain. In some embodiments, the mutation in a member of the CBL family can be a mutation that results in the loss of its E3 unbiquitin ligase activity.

[00179] In certain embodiments, the member of the CBL family is CBL. In some embodiments, the CBL mutation is a mutation in CBL at a codon selected from the group consisting of Q367, C384, T402, C404, C416, P417, R420, E479, S675, and A678. In some embodiments, the CBL mutation is a mutation at a codon selected from the group consisting of C384, C404, R420 and E479. In some embodiments, the CBL mutation is a mutation selected from the group consisting of E479fs, C384Y, and C404Y. In one embodiment, the mutation

results in a change (e.g., a substitution or deletion) in amino acid C384 (e.g., C384Y mutation) of CBL. In one embodiment, the mutation results in a change in amino acid E479 (e.g., E479fs mutation) of CBL. In one embodiment, the mutation results in a change in amino acid C404 (e.g., C404Y mutation) of CBL. In one embodiment, the mutation results in a change in amino acid R420 (e.g., R420Q mutation) of CBL. In one embodiment, the mutation results in a change in amino acid Q367 of CBL. In one embodiment, the mutation results in a change in amino acid T402 of CBL. In one embodiment, the mutation results in a change in amino acid C416 of CBL. In one embodiment, the mutation results in a change in amino acid P417 of CBL. In one embodiment, the mutation results in a change in amino acid S675 of CBL. In one embodiment, the mutation results in a change in amino acid A678 of CBL. In some embodiments, the mutation results in a change in amino acid Q367, C384, T402, C404, C416, P417, R420, E479, S675 or A678 of CBL (SEQ ID NO:1). In some embodiments, the mutation can be a mutation in the ring finger domain of CBL. In some embodiments, the mutation can be a mutation in the linker domain of CBL. In some embodiments, the mutation can be a mutation in the proline-rich domain of CBL. In some embodiments, the mutation can be a mutation in CBL that results in the loss of the E3 unbiquitin ligase activity. In some embodiments, the mutation can be a CBL-inactivating mutation.

[00180] In certain embodiments, the member of the CBL family is CBLB. In some embodiments, the mutation can be a mutation in the ring finger domain of CBLB. In some embodiments, the mutation can be a mutation in the linker domain of CBLB. In some embodiments, the mutation can be a mutation in the proline-rich domain of CBLB. In some embodiments, the mutation can be a mutation in CBLB that results in the loss of the E3 unbiquitin ligase activity. In some embodiments, the mutation can be a CBLB-inactivating mutation. In some embodiments, the mutation results in a change in amino acid R463 of CBLB.

[00181] In certain embodiments, the member of the CBL family is CBLC. In some embodiments, the mutation can be a mutation in the ring finger domain of CBLC. In some embodiments, the mutation can be a mutation in the linker domain of CBLC. In some embodiments, the mutation can be a mutation in CBLC that results in the loss of the E3 unbiquitin ligase activity. In some embodiments, the mutation can be a CBLC-inactivating mutation. In some embodiments, the mutation results in a change in amino acid C381 of CBLC.

[00182] In some embodiments, the CBL-mutant cancer can include at least one mutation at codons selected from the group consisting of C384, C404, R420 and E479 of CBL (SEQ ID NO:1). In some embodiments, the CBL-mutant cancer can include at least two mutations at codons selected from the group consisting of C384, C404, R420 and E479 of CBL (SEQ ID NO:1).

[00183] In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in CBL (e.g., and not a mutation in CBLB and CBLC). Is some embodiments, the cancer treated in accordance with the methods described herein carries a mutant isoform of CBLB (e.g., isoform a, isoform b, isoform c, isoform d, isoform e, isoform f, isoform g, isoform h, isoform i, isoform j, isoform k, isoform, l, isoform m, isoform n, or isoform o). In some embodiments, the cancer treated in accordance with the methods described herein carries a mutant isoform of CBLC (e.g., isoform 1 or isoform 2).

[00184] The mutations in CBL, CBLB and CBLC genes can be point mutations resulting in an amino acid substitution or can be frameshift mutations (fs) resulting in a shift of the reading frame. For example, a mutation in a CBL gene can be a mutation leading to substitution of an amino acid C384, C404, R420 or E479 of CBL (SEQ ID NO:1).

[00185] In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:1 or carries a mutant SEQ ID NO:1. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:2 or carries a mutant SEQ ID NO:2. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:3 or carries a mutant SEQ ID NO:3. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:4 or carries a mutant SEQ ID NO:4. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:5 or carries a mutant SEQ ID NO:5. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:6 or carries a mutant SEQ ID NO:6. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:7 or carries a mutant SEQ ID NO:7. In some embodiments, the cancer treated in accordance with the methods

described herein has a mutation in a gene encoding SEQ ID NO:8 or carries a mutant SEQ ID NO:8. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:9 or carries a mutant SEQ ID NO:9. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:10 or carries a mutant SEQ ID NO:10. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:11 or carries a mutant SEQ ID NO:11. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:12 or carries a mutant SEQ ID NO:12. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:13 or carries a mutant SEQ ID NO:13. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:14 or carries a mutant SEQ ID NO:14. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:15 or carries a mutant SEQ ID NO:15. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:16 or carries a mutant SEQ ID NO:16. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:17 or carries a mutant SEQ ID NO:17. In some embodiments, the cancer treated in accordance with the methods described herein has a mutation in a gene encoding SEQ ID NO:18 or carries a mutant SEQ ID NO:18.

[00186] In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in CBL (e.g., and not a mutation in CBLB and CBLC). Is some embodiments, the sample from the subject treated in accordance with the methods described herein is detected to have a mutant isoform of CBLB (e.g., isoform a, isoform b, isoform c, isoform d, isoform e, isoform f, isoform g, isoform h, isoform i, isoform j, isoform k, isoform, l, isoform m, isoform n, or isoform o). In some embodiments, the sample from the subject treated in accordance with the methods described herein is detected to have a mutant isoform of CBLC (e.g., isoform 1 or isoform 2).

[00187] In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:1 or a

mutant SEQ ID NO:1. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO: 2 or a mutant SEQ ID NO:2. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:3 or a mutant SEQ ID NO:3. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:4 or a mutant SEQ ID NO:4. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:5 or a mutant SEQ ID NO:5. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:6 or a mutant SEQ ID NO:6. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:7 or a mutant SEQ ID NO:7. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:8 or a mutant SEQ ID NO:8. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:9 or a mutant SEQ ID NO:9. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:10 or a mutant SEQ ID NO:10. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:11 or a mutant SEQ ID NO:11. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:12 or a mutant SEQ ID NO:12. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:13 or a mutant SEQ ID NO:13. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:14 or a mutant SEQ ID NO:14. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:15 or a mutant SEQ ID NO:15. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a

mutation in a gene encoding SEQ ID NO:16 or a mutant SEQ ID NO:16. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:17 or a mutant SEQ ID NO:17. In some embodiments, a sample from the subject treated in accordance with the methods described herein is detected to have a mutation in a gene encoding SEQ ID NO:18 or a mutant SEQ ID NO:18.

[00188] In some embodiments, the subject treated in accordance with the methods described herein has two or more mutations in one or more genes of the CBL family (e.g., two, three, four, five or six mutations in one or more of CBL, CBLB and CBLC). In some embodiments, the subject treated in accordance with the methods described herein has one or more mutations in two or more genes of the CBL family (e.g., one or more mutations in CBL, CBLB and CBLC).

[00189] In some embodiments, the sample of a patient treated in accordance with the methods described herein is determined not to have an amino acid modification or substitution at codons C384, C404, R420 and E479 of CBL. In some embodiments, the sample from a subject being treated in accordance with methods described herein is determined to have wild type CBL. In some embodiments, the sample from a subject being treated in accordance with methods described herein is determined to have wild type CBLB. In some embodiments, the sample from a subject being treated in accordance with methods described herein is determined to have wild type CBLC. In some embodiments, the methods provided herein further include (a) determining the presence or absence of a CBL, CBLB or CBLC mutation in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of an FTI to the subject if the sample does not have a CBL, CBLB or CBLC mutation. In some embodiment, the method includes administering a therapeutically effective amount of an FTI to the subject if the sample has wild type CBL, CBLB or CBLC.

[00190] Provided herein are methods for predicting responsiveness of a cancer patient to an FTI treatment, methods for cancer patient population selection for an FTI treatment, and methods for treating cancer in a subject with a therapeutically effective amount of an FTI, based on the mutation status of CBL, CBLB and/or CBLC in a sample from the patient. In some embodiments, the method includes determining the presence or absence of a mutation in CBL, CBLB and/or CBLC in a sample from the subject prior to beginning treatment. In some embodiments, patients are selected based on the presence of a CBL, CBLB and/or CBLC

mutation. Tumors or cancers that have a CBL, CBLB or CBLC mutation indicate that the patients will likely be responsive to the FTI treatment.

[00191] Provided herein are methods for predicting responsiveness of a cancer patient to an FTI treatment, methods for cancer patient population selection for an FTI treatment, and methods for treating cancer in a subject with a therapeutically effective amount of an FTI, based on the mutation status of CBL in a sample from the patient. In some embodiments, the method includes determining the presence or absence of a mutation in CBL in a sample from the subject prior to beginning treatment. In some embodiments, patients are selected based on the presence of a CBL mutation. Tumors or cancers that have a CBL mutation indicate that the patients will likely be responsive to the FTI treatment.

[00192] As a person of ordinary skill in the art would understand, any methods described herein or otherwise known in the art for analyzing mutations can be used for determining the presence or absence of a mutation in CBL, CBLB or CBLC (or another member of the CBL family). The mutation status of CBL, CBLB or CBLC (or another member of the CBL family) can be detected at the nucleic acid or protein level. In some embodiments, the mutation status is determined by analyzing nucleic acids obtained from the sample. In some embodiments, the mutation status is determined by analyzing protein obtained from the sample.

[00193] In some embodiments, the mutation status of CBL, CBLB or CBLC (or another member of the CBL family) is determined by analyzing nucleic acids obtained from the sample. The nucleic acids may be mRNA or genomic DNA molecules from the test subject. Methods for determining the mutation status by analyzing nucleic acids are well known in the art. In some embodiments, the methods include sequencing, Polymerase Chain Reaction (PCR), DNA microarray, Mass Spectrometry (MS), Single Nucleotide Polymorphism (SNP) assay, denaturing high-performance liquid chromatography (DHPLC), or Restriction Fragment Length Polymorphism (RFLP) assay. In some embodiments, the mutation status is determined using standard sequencing methods, including, for example, Sanger sequencing, next generation sequencing (NGS). In some embodiments, the mutation status is determined using MS.

[00194] In some embodiments, the method includes determining the presence or absence of a CBL, CBLB and/or CBLC mutation by amplifying the respective CBL, CBLB and/or CBLC

nucleic acid from a sample by PCR. For example, PCR technology and primer pairs that can be used are known to the person skilled in the art. In some embodiments, primers selected for gene amplification evaluation are highly specific to avoid detecting closely related homologous genes. Following multiplex PCR amplification, the products can be purified to remove the primers and unincorporated deoxynucleotide triphosphates using PCR-M™ Clean Up System (Viogenebiotek Co., Sunnyvale, CA, USA). Purified DNA can then be semiquantified on a 1 % agarose gel in 0.5×TBE and visualized by staining with ethidium bromide. The products can then be subjected to primer extension analysis. The primer extension reaction products can then be resolved by automated capillary electrophoresis on a capillaryelectrophoresis platform, e.g. 14 µl of Hi-Di™ Formamide (Applied Biosystems) and 0.28 µl of GeneScan™- 120LIZ® Size Standard (Applied Biosystems) were added to 6 µI of primer extension products. All samples may then e.g. be analyzed on an ABI Prism 310 DNA Genetic Analyzer (Applied Biosystems) according to manufacturer's instructions using GeneScan™ 3.1 (Applied Biosystems).

[00195] Provided herein are methods of selecting a cancer patient who is likely to benefit from an FTI treatment, include determining the presence or absence of a CBL, CBLB and/or CBLC mutation by amplifying the respective CBL, CBLB and/or CBLC nucleic acid from the patient's tumor sample and sequencing the amplified nucleic acid.

[00196] In the methods provided herein, CBL, CBLB and/or CBLC nucleic acid can be obtained from the patient's tumor sample by any method known to the person skilled in the art. For example, any commercial kit may be used to isolate the genomic DNA, or mRNA from a tumor sample, such as *e.g.* the Qlamp DNA mini kit, or RNeasy mini kit (Qiagen, Hilden, Germany). For example, if mRNA was isolated from the patient's tumor sample, cDNA synthesis can be carried out prior to the methods as disclosed herein, according to any known technology in the art.

[00197] For example, the nucleic acid to be isolated from a tumor can for example be one of genomic DNA, total RNA, mRNA or poly(A)+ mRNA. For example, if mRNA has been isolated from the patient's tumor sample, the mRNA (total mRNA or poly(A)+ mRNA) may be used for cDNA synthesis according to well established technologies in prior art, such as those provided in commercial cDNA synthesis kits, *e.g.* Superscript® III First Strand Synthesis Kit. The cDNA can then be further amplified by means of *e.g.* PCR and subsequently subjected to

sequencing by *e.g.* Sanger sequencing or pyro-sequencing to determine the nucleotide sequence of *CBL, CBLB or CBLC* gene. Alternatively, the PCR product can *e.g.* also be subcloned into a TA TOPO cloning vector for sequencing. Other technologies than sequencing to determine the absence or presence of CBL, CBLB and/or CBLC mutations can be used in the methods provided herein such as *e.g.* Single Nucleotide Primer Extension (SNPE) (PLoS One. 2013 Aug 21 ;8(8):e72239); DNA microarray, Mass Spectrometry (MS) (*e.g.* matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry), Single Nucleotide Polymorphism (SNP), denaturing high-performance liquid chromatography (DHPLC), or Restriction Fragment Length Polymorphism (RFLP) assay.

[00198] For example, Single Nucleotide Polymorphism (SNP) Assay can be used for determining CBL, CBLB and/or CBLC mutation status in a sample. The SNP assay can be performed on the HT7900 from Applied Biosystems, following the allelic discrimination assay protocol provided by the manufacturer. CBL, CBLB and/or CBLC mutation status can also be determined by DHPLC or RFLP, or any other methods known in the art. Bowen *et al.*, *Blood*, 106:2113-2119 (2005); Bowen *et al.*, *Blood*, 101:2770-2774 (2003); Nishikawa *et al.*, *Clin Chim Acta.*, 318:107-112 (2002); Lin SY *et al.*, *Am J Clin Pathol.* 100:686-689 (1993); O'Leary JJ *et al.*, *J Clin Pathol.* 51:576-582 (1998).

[00199] In some embodiments, the mutation status of CBL, CBLB or CBLC (or another member of the CBL family) is determined by analyzing protein obtained from the sample. The mutated protein can be detected by a variety of immunohistochemistry (IHC) approaches, Immunoblotting assay, Enzyme-Linked Immunosorbent Assay (ELISA) or other immunoassay methods known in the art.

[00200] IHC staining of tissue sections has been shown to be a reliable method of assessing or detecting presence of proteins in a sample. Immunohistochemistry techniques utilize an antibody to probe and visualize cellular antigens in situ, generally by chromogenic or fluorescent methods. Thus, antibodies or antisera, preferably polyclonal antisera, and most preferably monoclonal antibodies that specifically target mutant CBL, CBLB and/or CBLC can be used to detect expression. The antibodies can be detected by direct labeling of the antibodies themselves, for example, with radioactive labels, fluorescent labels, hapten labels such as, biotin, or an enzyme such as horse radish peroxidase or alkaline phosphatase. Alternatively, unlabeled

primary antibody is used in conjunction with a labeled secondary antibody, comprising antisera, polyclonal antisera or a monoclonal antibody specific for the primary antibody. Immunohistochemistry protocols and kits are well known in the art and are commercially available. Automated systems for slide preparation and IHC processing are available commercially. The Ventana® BenchMark XT system is an example of such an automated system.

[00201] Standard immunological and immunoassay procedures can be found in *Basic and Clinical Immunology* (Stites & Terr eds., 7th ed. 1991). Moreover, the immunoassays can be performed in any of several configurations, which are reviewed extensively in *Enzyme Immunoassay* (Maggio, ed., 1980); and Harlow & Lane, supra. For a review of the general immunoassays, see also *Methods in Cell Biology: Antibodies in Cell Biology*, volume 37 (Asai, ed. 1993); *Basic and Clinical Immunology* (Stites & Ten, eds., 7th ed. 1991).

[00202] Assays to detect CBL, CBLB and/or CBLC mutations include noncompetitive assays, e.g., sandwich assays, and competitive assays. Typically, an assay such as an ELISA assay can be used. ELISA assays are known in the art, e.g., for assaying a wide variety of tissues and samples, including blood, plasma, serum or bone marrow.

[00203] A wide range of immunoassay techniques using such an assay format are available, see, e.g., U.S. Pat. Nos. 4,016,043, 4,424,279, and 4,018,653, which are hereby incorporated by reference in their entireties. These include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labeled antibody to a target mutant CBL, CBLB or CBLC protein. Sandwich assays are commonly used assays. A number of variations of the sandwich assay technique exist. For example, in a typical forward assay, an unlabelled antibody is immobilized on a solid substrate, and the sample to be tested brought into contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labeled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labeled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by observation

of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample.

[00204] Variations on the forward assay include a simultaneous assay, in which both sample and labeled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including any minor variations as will be readily apparent. In a typical forward sandwich assay, a first antibody having specificity for the mutant CBL protein is either covalently or passively bound to a solid surface. The solid surface may be glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride, or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (e.g. 2-40 minutes or overnight if more convenient) and under suitable conditions (e.g., from room temperature to 40° C. such as between 25° C. and 32° C. inclusive) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the mutant CBL protein. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the mutant CBL protein.

[00205] In some embodiments, flow cytometry (FACS) can be used to detect the mutant CBL, CBLB or CBLC using antibodies that specifically target the mutant CBL, CBLB or CBLC. The flow cytometer detects and reports the intensity of the fluorichrome-tagged antibody, which indicates the presence of the mutant CBL, CBLB or CBLC. Non-fluorescent cytoplasmic proteins can also be observed by staining permeablized cells. The stain can either be a fluorescence compound able to bind to certain molecules, or a fluorichrome-tagged antibody to bind the molecule of choice.

[00206] An alternative method involves immobilizing the target CBL, CBLB or CBLC protein in the sample and then exposing the immobilized target to mutant specific antibody which may or may not be labeled with a reporter molecule. Depending on the amount of target

and the strength of the reporter molecule signal, a bound target can be detectable by direct labeling with the antibody. Alternatively, a second labeled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by a labeled reporter molecule.

[00207] In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase, and alkaline phosphatase, and other are discussed herein. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable color change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labeled antibody is added to the first antibody-molecular marker complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of mutant CBL, CBLB or CBLC protein which was present in the sample. Alternately, fluorescent compounds, such as fluorescein and rhodamine, can be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labeled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic color visually detectable with a light microscope. As in the EIA, the fluorescent labeled antibody is allowed to bind to the first antibody-molecular marker complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength, the fluorescence observed indicates the presence of the molecular marker of interest. Immunofluorescence and EIA techniques are both very well established in the art and are discussed herein.

[00208] In some embodiments, the determination of the CBL, CBLB or CBLC mutation status is performed as a companion diagnostic to the FTI treatment. The companion diagnostic can be performed at the clinic site where the subject is treated. The companion diagnostic can also be performed at a site separate from the clinic site where the subject is treated.

[00209] As a person of ordinary skill in the art would understand, methods provided herein are for predicting responsiveness of a cancer patient to an FTI treatment, methods for cancer patient population selection for an FTI treatment, and methods for treating cancer in a subject with a therapeutically effective amount of an FTI, based on the mutation status of CBL, CBLB and/or CBLC (or another protein of the CBL family) in a sample from the patient. Any methods described herein or otherwise known in the art for determining the mutation status of CBL, CBLB and/or CBLC can be applied. In a preferred embodiment, methods provided herein are for predicting responsiveness of a cancer patient to an FTI treatment, methods for cancer patient population selection for an FTI treatment, and methods for treating cancer in a subject with a therapeutically effective amount of an FTI, based on the mutation status of CBL in a sample from the patient.

[00210] As provided herein, the genotype of CBL, CBLB and CBLC of a subject can be indicative of the likelihood of the subject to respond to an FTI treatment. A cancer patient who is a carrier of a mutation in CBL is likely to be responsive to an FTI treatment. Accordingly, CBL typing cancer patients, and selectively treating those who are carriers of one or more mutations in CBL, can increase the overall response rate of the cancer patients to an FTI treatment.

[00211] In some embodiments, provided herein are methods for treating cancer in a subject by administering a therapeutically effective amount of an FTI to the subject, wherein the subject (e.g., a human) is a carrier of a CBL mutation. In some embodiments, provided herein is a method for treating cancer in a subject by CBL typing the subject, and administering a therapeutically effective amount of an FTI to the subject, wherein the subject is a carrier of a CBL mutation (e.g., a mutation at amino acid C384, C404, R420 or E479 of CBL). In some embodiments, provided herein is a method for treating cancer in a subject by CBL typing the subject, and administering a therapeutically effective amount of an FTI to the subject, wherein the subject is a carrier of one or more of the following CBL mutations: Q367, C384, T402, C404,

C416, P417, R420, E479, S675, and A678. In some embodiments, the subject who is a carrier of a CBL mutation is homozygous for that mutation. In some embodiments, the subject who is a carrier of a CBL mutation is heterozygous for that mutation. In some embodiments, the CBL mutation can be a mutation selected from the group consisting of E479fs, C384Y, and C404Y. In some embodiments, the subject is a carrier of E479fs mutation. In some embodiments, the subject is a carrier of C384Y mutation. In some embodiments, the subject is a carrier of C384Y mutation. In some embodiments, the subject is not a carrier of a mutation at amino acid R420. In some embodiments, the subject who is a carrier of a C384 mutation (e.g., C384Y) is homozygous for that mutation. In some embodiments, the subject who is a carrier of a C384 mutation (e.g., C384Y) is heterozygous for that mutation. In some embodiments, the subject who is a carrier of a C404 mutation (e.g., C404Y) is homozygous for that mutation. In some embodiments, the subject who is a carrier of a C404 mutation (e.g., C404Y) is heterozygous for that mutation. In some embodiments, the subject who is a carrier of a E479 mutation (e.g., E479fs) is homozygous for that mutation. In some embodiments, the subject who is a carrier of a E479 mutation (e.g., E479fs) is heterozygous for that mutation. In some embodiments, the subject who is a carrier of a R420 mutation (e.g., R420Q) is homozygous for that mutation. In some embodiments, the subject who is a carrier of a R420 mutation (e.g., R420Q) is heterozygous for that mutation. In some embodiments, provided herein is a method for treating cancer in a subject by CBL typing the subject, and administering a therapeutically effective amount of an FTI to the subject, wherein the subject is a carrier of one or more CBLB mutations (e.g., R463). In some embodiments, provided herein is a method for treating cancer in a subject by CBL typing the subject, and administering a therapeutically effective amount of an FTI to the subject, wherein the subject is a carrier of one or more CBLC mutations (e.g., C381). In some embodiments, the subject who is a carrier of a CBLB mutation or a CBLC mutation is homozygous for that mutation. In some embodiments, the subject who is a carrier of a CBLB mutation or a CBLC mutation is heterozygous for that mutation.

[00212] The methods provided herein can be performed by any method described herein or otherwise known in the art. In some embodiments, provided herein is a method for treating cancer in a subject with an FTI by CBL typing, or selecting a cancer patient for an FTI treatment by CBL typing, wherein the CBL typing is performed by sequencing, Polymerase Chain Reaction (PCR), DNA microarray, Mass Spectrometry (MS), Single Nucleotide Polymorphism

(SNP) assay, Immunoblotting assay, or Enzyme-Linked Immunosorbent Assay (ELISA). In some embodiments, the CBL typing is performed by DNA microarray. In some embodiments, the CBL typing is performed by ELISA. In some embodiments, the CBL typing is performed by sequencing. In some embodiments, the CBL typing is performed by next generation sequencing (NGS). As a person of ordinary skill in the art would understand, the CBL typing can be performed by any method described herein or otherwise known in the art.

3.2. *Samples*

[00213] In some embodiments, methods provided herein include obtaining a sample from the subject. The sample used in the methods provided herein includes body fluids from a subject. Non-limiting examples of body fluids include blood (*e.g.*, peripheral whole blood, peripheral blood), blood plasma, bone marrow, amniotic fluid, aqueous humor, bile, lymph, menses, serum, urine, cerebrospinal fluid surrounding the brain and the spinal cord, synovial fluid surrounding bone joints.

[00214] In one embodiment, the sample is a bone marrow sample. Procedures to obtain a bone marrow sample are well known in the art, including but not limited to bone marrow biopsy and bone marrow aspiration. Bone marrow has a fluid portion and a more solid portion. In bone marrow biopsy, a sample of the solid portion is taken. In bone marrow aspiration, a sample of the fluid portion is taken. Bone marrow biopsy and bone marrow aspiration can be done at the same time and referred to as a bone marrow exam.

[00215] In some embodiments, the sample is a blood sample. The blood sample can be obtained using conventional techniques as described in, *e.g.* Innis *et al*, editors, PCR Protocols (Academic Press, 1990). White blood cells can be separated from blood samples using convention techniques or commercially available kits, *e.g.* RosetteSep kit (Stein Cell Technologies, Vancouver, Canada). Sub-populations of white blood cells, *e.g.* mononuclear cells, NK cells, B cells, T cells, monocytes, granulocytes or lymphocytes, can be further isolated using conventional techniques, *e.g.* magnetically activated cell sorting (MACS) (Miltenyi Biotec, Auburn, California) or fluorescently activated cell sorting (FACS) (Becton Dickinson, San Jose, California).

[00216] In one embodiment, the blood sample is from about 0.1 mL to about 10.0 mL, from about 0.2 mL to about 7 mL, from about 0.3 mL to about 5 mL, from about 0.4 mL to about 3.5 mL, or from about 0.5 mL to about 3 mL. In another embodiment, the blood sample is about 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 9.0 or 10.0 mL.

[00217] In some embodiments, methods provided herein include obtaining a sample from the subject. In some embodiments, the sample is a tumor sample. In some embodiments, the sample used in the present methods includes a biopsy (*e.g.*, a tumor biopsy). The biopsy can be from any organ or tissue, for example, skin, liver, lung, heart, colon, kidney, bone marrow, teeth, lymph node, hair, spleen, brain, breast, or other organs. Any biopsy technique known by those skilled in the art can be used for isolating a sample from a subject, for instance, open biopsy, close biopsy, core biopsy, incisional biopsy, excisional biopsy, or fine needle aspiration biopsy.

[00218] In certain embodiments, the sample used in the methods provided herein includes a plurality of cells. Such cells can include any type of cells, *e.g.*, stem cells, blood cells (*e.g.*, PBMCs), lymphocytes, NK cells, B cells, T cells, monocytes, granulocytes, immune cells, or tumor or cancer cells. Specific cell populations can be obtained using a combination of commercially available antibodies (*e.g.*, Quest Diagnostic (San Juan Capistrano, Calif.); Dako (Denmark)).

[00219] Samples can be analyzed at a time during an active phase of a cancer (*e.g.*, lymphoma, MDS, or leukemia), or when the cancer is inactive. In certain embodiments, more than one sample from a subject can be obtained.

[00220] In certain embodiments, the sample used in the methods provided herein is from a diseased tissue, *e.g.*, from an individual having cancer (*e.g.*, lymphoma, MDS, or leukemia). In certain embodiments. In some embodiments, the cells can be obtained from the tumor or cancer cells or a tumor tissue, such as a tumor biopsy or a tumor explants. In certain embodiments, the number of cells used in the methods provided herein can range from a single cell to about 10^9 cells. In some embodiments, the number of cells used in the methods provided herein is about 1 x 10^4, 5 x 10^4, 1 x 10^5, 5 x 10^5, 1 x 10^6, 5 x 10^6, 1 x 10^7, 5 x 10^7, 1 x 10^8, or 5 x 10^8.

[00221] In one embodiment, the sample used in the methods provided herein is obtained from the subject prior to the subject receiving a treatment for the disease or disorder. In another

embodiment, the sample is obtained from the subject during the subject receiving a treatment for the disease or disorder. In another embodiment, the sample is obtained from the subject after the subject receiving a treatment for the disease or disorder. In various embodiments, the treatment includes administering an FTI to the subject.

[00222] The number and type of cells collected from a subject can be monitored, for example, by measuring changes in morphology and cell surface markers using standard cell detection techniques such as flow cytometry, cell sorting, immunocytochemistry (*e.g.*, staining with tissue specific or cell-marker specific antibodies) fluorescence activated cell sorting (FACS), magnetic activated cell sorting (MACS), by examination of the morphology of cells using light or confocal microscopy, and/or by measuring changes in gene expression using techniques well known in the art, such as PCR and gene expression profiling. These techniques can be used, too, to identify cells that are positive for one or more particular markers. Fluorescence activated cell sorting (FACS) is a well-known method for separating particles, including cells, based on the fluorescent properties of the particles (Kamarch, 1987, Methods Enzymol, 151:150-165). Laser excitation of fluorescent moieties in the individual particles results in a small electrical charge allowing electromagnetic separation of positive and negative particles from a mixture. In one embodiment, cell surface marker-specific antibodies or ligands are labeled with distinct fluorescent labels. Cells are processed through the cell sorter, allowing separation of cells based on their ability to bind to the antibodies used. FACS sorted particles may be directly deposited into individual wells of 96-well or 384-well plates to facilitate separation and cloning.

[00223] In certain embodiments, subsets of cells are used in the methods provided herein. Methods to sort and isolate specific populations of cells are well-known in the art and can be based on cell size, morphology, or intracellular or extracellular markers. Such methods include, but are not limited to, flow cytometry, flow sorting, FACS, bead based separation such as magnetic cell sorting, size-based separation (*e.g.*, a sieve, an array of obstacles, or a filter), sorting in a microfluidics device, antibody-based separation, sedimentation, affinity adsorption, affinity extraction, density gradient centrifugation, laser capture microdissection, *etc.*

[00224] The sample can be a whole blood sample, a bone marrow sample, a partially purified blood sample, or PBMC. The sample can be a tissue biopsy or a tumor biopsy. In some

embodiments, the sample is a bone marrow sample from a cancer patient. In some embodiments, the sample is PBMCs from a cancer patient.

[00225] Methods of obtaining a sample from a subject and methods to prepare the sample for determining the mutation status of a gene or protein are well known in the art.

3.3 *Cancers*

[00226] Provided herein are methods for treating a cancer in a subject with an FTI, and methods for selecting cancer patients for an FTI treatment, based on the presence of a mutation in a member of the CBL family. Provided herein are also methods for treating a premalignant condition in a subject with an FTI, and methods for selecting patients with a premalignant condition for an FTI treatment, based on the presence of a mutation in a member of the CBL family.

[00227] In some embodiments, the methods for treating cancer in a subject include CBL, CBLB and/or CBLC- typing the subject, and administering a therapeutically effective amount of tipifarnib to the subject, wherein the subject is a carrier of a mutation in CBL, CBLB and/or CBLC.

[00228] In some embodiments, the methods for treating cancer in a subject include CBL, CBLB and/or CBLC- typing the cancer in the subject, and administering a therapeutically effective amount of tipifarnib to the subject, wherein the cancer has a mutation in CBL, CBLB and/or CBLC.

[00229] In some embodiments, provided herein are methods for treating a hematological or hematopoietic cancer in a subject with an FTI or selecting cancer patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. Hematologic cancers are cancers of the blood or bone marrow. Examples of hematological (or hematogenous) cancers include myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS), leukemia, and lymphoma. In some embodiments, the cancer is acute myeloid leukemia (AML), natural killer cell lymphoma (NK lymphoma), natural killer cell leukemia (NK leukemia), cutaneous T-Cell lymphoma (CTCL), juvenile myelomonocytic leukemia (JMML), peripheral T-cell lymphoma (PTCL), chronic myeloid leukemia (CML) or chronic myelomonocytic leukemia (CMML). In

some embodiments, the cancer is CMML. In some embodiments, the cancer is JMML. In some embodiments, the hematological or hematopoietic cancer is HPV negative.

[00230] Hematological cancers include leukemias, including acute leukemias (such as acute lymphocytic leukemia, acute myelocytic leukemia, acute myelogenous leukemia and myeloblasts, promyeiocytic, myelomonocytic, monocytic and erythroleukemia), chronic leukemias (such as chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, chronic myeloic leukemia, and chronic lymphocytic leukemia), chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, polycythemia vera, NK cell leukemia, lymphoma, NK cell lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (indolent and high grade forms), multiple myeloma, peripheral T-cell lymphomas, cutaneous T-Cell lymphoma, Waldenstrom's macroglobulinemia, heavy chain disease, myeiodysplastic syndrome, agnogenic myeloid metaplasia, familial erythrophagocytic lymphohistiocytosis, hairy cell leukemia and myelodysplasia.

[00231] In some embodiments, the hematopoietic cancer to be treated by methods provided herein can be AML, MDS, CMML, NK cell lymphoma, NK cell leukemia, CTCL, PTCL, CML. In some embodiments, the hematopoietic cancer is AML. In some embodiments, the hematopoietic cancer is MDS. In some embodiments, the MDS is lower risk MDS. In some embodiments, the hematopoietic cancer is CMML. The CMML can be low risk CMML, intermediate risk CMML, or high risk CMML. The CMML can be myelodysplastic CMML or myeloproliferative CMML. In some embodiments, the CMML is a CBL-mutant CMML. In some embodiments, the CMML is NRAS/KRAS wild type CMML. In some embodiments, the hematopoietic cancer is NK lymphoma. In some embodiments, the hematopoietic cancer is NK leukemia. In some embodiments, the hematopoietic cancer is CTCL. In some embodiments, the hematopoietic cancer is PTCL. In some embodiments, the PTCL is refractory or relapsed PTCL.

[00232] In some embodiments, provided herein are methods for treating MDS in a subject with an FTI or selecting MDS patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant MDS in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00233] MDS refers to a diverse group of hematopoietic stem cell disorders. MDS can be characterized by a cellular marrow with impaired morphology and maturation (dysmyelopoiesis), ineffective blood cell production, or hematopoiesis, leading to low blood cell counts, or cytopenias (including anemia, leukopenia, and thrombocytopenia), and high risk of progression to acute myeloid leukemia, resulting from ineffective blood cell production. *See* The Merck Manual 953 (17th ed. 1999) and List *et al.*, 1990, *J Clin. Oncol.* 8:1424.

[00234] MDS can be divided into a number of subtypes depending on at least 1) whether increased numbers of blast cells are present in bone marrow or blood, and what percentage of the marrow or blood is made up of these blasts; 2) whether the marrow shows abnormal growth (dysplasia) in only one type of blood cell (unilineage dysplasia) or in more than one type of blood cell (multilineage dysplasia); and 3) whether there are chromosome abnormalities in marrow cells and, if so, which type or types of abnormalities. MDS can also categorized based on the surface markers of the cancer cells. According to the World Health Organization, MDS subtypes include refractory cytopenia with unilineage dysplasia (RCUD), also known as refractory anemia, refractory neutropenia, or refractory thrombocytopenia; refractory anemia with ring sideroblasts (RARS); refractory cytopenia with multilineage dysplasia (RCMD), which includes RCMD-RS if multilineage dysplasia and ring sideroblasts both are present; refractory anemia with excess blasts-1 (RAEB-1) and refractory anemia with excess blasts-2 (RAEB-2) (These subtypes mean that the patients have at least 5 percent (RAEB-1) or at least 10 percent (RAEB-2) but less than 20 percent blasts in their marrow); MDS associated with isolated abnormality of chromosome 5 [del(5q)]; and unclassifiable MDS (MDS-U).

[00235] As a group of hematopoietic stem cell malignancies with significant morbidity and mortality, MDS is a highly heterogeneous disease, and the severity of symptoms and disease progression can vary widely among patients. The current standard clinical tool to evaluate risk stratification and treatment options is the revised International Prognostic Scoring System, or IPSS-R. The IPSS-R differentiates patients into five risk groups (Very Low, Low, Intermediate, High, Very High) based on evaluation of cytogenetics, percentage of blasts (undifferentiated blood cells) in the bone marrow, hemoglobin levels, and platelet and neutrophil counts. The WHO also suggested stratifying MDS patients by a del (5q) abnormality.

[00236] According to the ACS, the annual incidence of MDS is approximately 13,000 patients in the United States, the majority of which are 60 years of age or older. The estimated prevalence is over 60,000 patients in the United States. Approximately 75% of patients fall into the IPSS-R risk categories of Very Low, Low, and Intermediate, or collectively known as lower risk MDS.

[00237] The initial hematopoietic stem cell injury can be from causes such as, but not limited to, cytotoxic chemotherapy, radiation, virus, chemical exposure, and genetic predisposition. A clonal mutation predominates over bone marrow, suppressing healthy stem cells. In the early stages of MDS, the main cause of cytopenias is increased programmed cell death (apoptosis). As the disease progresses and converts into leukemia, gene mutation rarely occurs and a proliferation of leukemic cells overwhelms the healthy marrow. The disease course differs, with some cases behaving as an indolent disease and others behaving aggressively with a very short clinical course that converts into an acute form of leukemia.

[00238] An international group of hematologists, the French-American-British (FAB) Cooperative Group, classified MDS disorders into five subgroups, differentiating them from AML. *The Merck Manual* 954 (17th ed. 1999); Bennett J. M., et al., *Ann. Intern. Med.* 1985 October, 103(4): 620-5; and Besa E. C., *Med. Clin. North Am.* 1992 May, 76(3): 599–617. An underlying trilineage dysplastic change in the bone marrow cells of the patients is found in all subtypes.

[00239] There are two subgroups of refractory anemia characterized by five percent or less myeloblasts in bone marrow: (1) refractory anemia (RA) and; (2) RA with ringed sideroblasts (RARS), defined morphologically as having 15% erythroid cells with abnormal ringed sideroblasts, reflecting an abnormal iron accumulation in the mitochondria. Both have a prolonged clinical course and low incidence of progression to acute leukemia. Besa E. C., *Med. Clin. North Am.* 1992 May, 76(3): 599–617.

[00240] There are two subgroups of refractory anemias with greater than five percent mycloblasts: (1) RA with excess blasts (RAEB), defined as 6–20% myeloblasts, and (2) RAEB in transformation (RAEB-T), with 21–30% myeloblasts. The higher the percentage of myeloblasts, the shorter the clinical course and the closer the disease is to acute myelogenous leukemia. Patient transition from early to more advanced stages indicates that these subtypes are

merely stages of disease rather than distinct entities. Elderly patients with MDS with trilineage dysplasia and greater than 30% myeloblasts who progress to acute leukemia are often considered to have a poor prognosis because their response rate to chemotherapy is lower than de novo acute myeloid leukemia patients. The fifth type of MDS, the most difficult to classify, is CMML. This subtype can have any percentage of myeloblasts but presents with a monocytosis of 1000/dL or more. It may be associated with splenomegaly. This subtype overlaps with a myeloproliferative disorder and may have an intermediate clinical course. It is differentiated from the classic CML that is characterized by a negative Ph chromosome.

[00241] MDS is primarily a disease of elderly people, with the median onset in the seventh decade of life. The median age of these patients is 65 years, with ages ranging from the early third decade of life to as old as 80 years or older. The syndrome may occur in any age group, including the pediatric population. Patients who survive malignancy treatment with alkylating agents, with or without radiotherapy, have a high incidence of developing MDS or secondary acute leukemia. About 60–70% of patients do not have an obvious exposure or cause for MDS, and are classified as primary MDS patients.

[00242] The treatment of MDS is based on the stage and the mechanism of the disease that predominates the particular phase of the disease process. Bone marrow transplantation has been used in patients with poor prognosis or late-stage MDS. Epstein and Slease, 1985, *Surg. Ann.* 17:125. An alternative approach to therapy for MDS is the use of hematopoietic growth factors or cytokines to stimulate blood cell development in a recipient. Dexter, 1987, *J. Cell Sci.* 88:1; Moore, 1991, *Annu. Rev. Immunol.* 9:159; and Besa E. C., *Med. Clin. North Am.* 1992 May, 76(3): 599–617. The treatment of MDS using immunomodulatory compounds is described in U.S. Patent No. 7,189,740, the entirety of which is hereby incorporated by reference.

[00243] Therapeutic options fall into three categories including supportive care, low intensity and high intensity therapy. Supportive care includes the use red blood cell and platelet transfusions and hematopoietic cytokines such as erythropoiesis stimulating agents or colony stimulating factors to improve blood counts. Low intensity therapies include hypomethylating agents such as azacytidine (Vidaza®) and decitabine (Dacogen®), biological response modifiers such as lenalidomide (Revlimid®), and immunosuppressive treatments such as cyclosporine A or antithymocyte globulin. High intensity therapies include chemotherapeutic agents such as

idarubicin, azacytidine, fludarabine and topotecan, and hematopoietic stem cell transplants, or HSCT.

[00244] National Comprehensive Cancer Network, or NCCN, guidelines recommend that lower risk patients (IPSS-R groups Very Low, Low, Intermediate) receive supportive care or low intensity therapies with the major therapeutic goal of hematologic improvement, or HI. NCCN guidelines recommend that higher risk patients (IPSS-R groups High, Very High) receive more aggressive treatment with high intensity therapies. In some cases, high risk patients are unable to tolerate chemotherapy, and may elect lower intensity regimens. Despite currently available treatments, a substantial portion of MDS patients lack effective therapies and NCCN guidelines recommend clinical trials as additional therapeutic options. Treatment of MDS remains a significant unmet need requiring the development of novel therapies.

[00245] In some embodiments, provided herein are methods for treating MPN in a subject with an FTI or selecting MPN patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant MPN in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00246] MPN is a group of diseases that affect blood-cell formation. In all forms of MPN, stem cells in the bone marrow develop genetic defects (called acquired defects) that cause them to grow and survive abnormally. This results in unusually high numbers of blood cells in the bone marrow (hypercellular marrow) and in the bloodstream. Sometimes in MPN, the abnormal stem cells cause scarring in the marrow, called myelofibrosis. Myelofibrosis can lead to low levels of blood cells, especially low levels of red blood cells (anemia). In MPN, the abnormal stem cells can also grow in the spleen, causing the spleen to enlarge (splenomegaly), and in other sites outside the marrow, causing enlargement of other organs.

[00247] There are several types of chronic MPN, based on the cells affected. Three classic types of MPN include polycythemia vera (PV), in which there are too many RBCs; essential thrombocythemia (ET), in which there are too many platelets; primary myelofibrosis (PMF), in which fibers and blasts (abnormal stem cells) build up in the bone marrow. Other types of MPN include: chronic myeloid leukemia, in which there are too many white blood cells; chronic

neutrophilic leukemia, in which there are too many neutrophils; chronic eosinophilic leukemia, not otherwise specified, in which there are too many eosinophils (hypereosinophilia); mastocytosis, also called mast cell disease, in which there are too many mast cells, which are a type of immune system cell found in tissues, like skin and digestive organs, rather than in the bloodstream; myeloid and lymphoid neoplasms with eosinophilia and abnormalities of the PDGFRA, PDGFRB, and FGFR1 genes; and other unclassifiable myeloproliferative neoplasms.

[00248] In some embodiments, provided herein are methods for treating CMML in a subject with an FTI or selecting CMML patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. CMML is classified as a myelodysplastic/myeloproliferative neoplasm by the 2008 World Health Organization classification of hematopoietic tumors. The CMML can be myelodysplastic CMML or myeloproliferative CMML. CMML patients have a high number of monocytes in their blood (at least 1,000 per mm^3). Two classes-myelodysplastic and myeloproliferative-have been distinguished upon the level of the white blood cell count (threshold 13 G/L). Often, the monocyte count is much higher, causing their total white blood cell count to become very high as well. Usually there are abnormal cells in the bone marrow, but the amount of blasts is below 20%. About 15% to 30% of CMML patients go on to develop acute myeloid leukemia. The diagnosis of CMML rests on a combination of morphologic, histopathologic and chromosomal abnormalities in the bone marrow. The Mayo prognostic model classified CMML patients into three risk groups based on: increased absolute monocyte count, presence of circulating blasts, hemoglobin <10 gm/dL and platelets $<100 \times 10^9$/L. The median survival was 32 months, 18.5 months and 10 months in the low, intermediate, and high-risk groups, respectively. The Groupe Francophone des (GFM) score segregated CMML patients into three risk groups based on: age >65 years, WBC $>15 \times 10^9$/L, anemia, platelets $<100 \times 10^9$/L, and ASXL1 mutation status. After a median follow-up of 2.5 years, survival ranged from not reached in the low-risk group to 14.4 months in the high-risk group.

[00249] In some embodiments, provided herein are methods of treating a CBL-mutant CMML in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib. In some embodiments, the CBL-mutant CMML is a CMML that has a mutation in a member of the CBL family. In some embodiments, the CBL-

mutant CMML is a CMML that has a mutation in CBL. In some embodiments, the CBL-mutant CMML is a CMML that has a mutation in CBLB. In some embodiments, the CBL-mutant CMML is a CMML that has a mutation in CBLC.

[00250] In some embodiments, provided herein are methods of treating CMML in a subject by determining the presence or absence of a mutation in a member of the CBL family in a sample from the subject, and subsequently administering a therapeutically effective amount of the FTI to the subject if the sample is determined to have a mutation in a member of the CBL family. In some embodiments, the FTI is tipifarnib. In some embodiments, the sample is determined to have a mutation in CBL. In some embodiments, the sample is determined to have a mutation in CBLB or CBLC. In other embodiments, the sample is determined to have wild type CBL. In yet other embodiments, the sample is determined to have wild type CBLB. In yet other embodiments, the sample is determined to have wild type CBLC.

[00251] In some embodiments, provided herein are methods for predicting responsiveness of a CMML patient to an FTI treatment (e.g., tipifarnib), methods for CMML patient population selection for an FTI treatment, and methods for treating CMML in a subject with a therapeutically effective amount of an FTI, based on the mutation status of a member of the CBL family in a sample from the patient. In some embodiments, provided herein is a method of treating CMML in a subject based on the mutation status of CBL, CBLB and/or CBLC. The method provided herein includes (a) determining the presence or absence of a mutation in CBL, CBLB and/or CBLC in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of an FTI (e.g., tipifarnib) to said subject if said sample is determined to have a mutation in CBL, CBLB and/or CBLC. In some embodiments, the sample is determined to have a CBL mutation. In some embodiments, the sample is determined to have a CBLB mutation. In some embodiments, the sample is determined to have a CBLC mutation.

[00252] In some embodiments, provided herein are methods for treating leukemia in a subject with an FTI or selecting leukemia patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant leukemia in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00253] Leukemia refers to malignant neoplasms of the blood-forming tissues. Various forms of leukemias are described, for example, in U.S. Patent No. 7,393,862 and U.S. provisional patent application no. 60/380,842, filed May 17, 2002, the entireties of which are incorporated herein by reference. Although viruses reportedly cause several forms of leukemia in animals, causes of leukemia in humans are to a large extent unknown. *The Merck Manual*, 944-952 (17th ed. 1999). Transformation to malignancy typically occurs in a single cell through two or more steps with subsequent proliferation and clonal expansion. In some leukemias, specific chromosomal translocations have been identified with consistent leukemic cell morphology and special clinical features (*e.g.*, translocations of 9 and 22 in chronic myelocytic leukemia, and of 15 and 17 in acute promyelocytic leukemia). Acute leukemias are predominantly undifferentiated cell populations and chronic leukemias more mature cell forms.

[00254] Acute leukemias are divided into lymphoblastic (ALL) and non-lymphoblastic (ANLL) types. *The Merck Manual*, 946-949 (17th ed. 1999). They may be further subdivided by their morphologic and cytochemical appearance according to the French-American-British (FAB) classification or according to their type and degree of differentiation. The use of specific B- and T-cell and myeloid-antigen monoclonal antibodies are most helpful for classification. ALL is predominantly a childhood disease which is established by laboratory findings and bone marrow examination. ANLL, also known as acute myelogenous leukemia or AML, occurs at all ages and is the more common acute leukemia among adults; it is the form usually associated with irradiation as a causative agent. In some embodiments, provided herein are methods for treating a AML patient with an FTI, or methods for selecting patients for FTI treatment.

[00255] In some embodiments, provided herein are methods for treating AML in a subject with an FTI or selecting AML patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant AML in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00256] Standard procedures treat AML patients usually include 2 chemotherapy (chemo) phases: remission induction (or induction) and consolidation (post-remission therapy). The first part of treatment (remission induction) is aimed at getting rid of as many leukemia cells as possible. The intensity of the treatment can depend on a person's age and health. Intensive

chemotherapy is often given to people under the age of 60. Some older patients in good health can benefit from similar or slightly less intensive treatment. People who are much older or are in poor health are not suitable for intensive chemotherapies.

[00257] In some embodiments, the AML patient is post-remission induction. In some embodiments, the AML patient post-transplantation. In some embodiments, the AML patient is over age 60 or otherwise unfit for remission induction. In some embodiments, the AML patient is over age 65, 70, or 75. In some embodiments, the AML patient is refractory to standard chemotherapy. In some embodiments, the AML patient is a relapsed patient.

[00258] In younger patients, such as those under 60, induction often involves treatment with 2 chemo drugs, cytarabine (ara-C) and an anthracycline drug such as daunorubicin (daunomycin) or idarubicin. Sometimes a third drug, cladribine (Leustatin, 2-CdA), is given as well. The chemo is usually given in the hospital and lasts about a week. In rare cases where the leukemia has spread to the brain or spinal cord, chemo may also be given into the cerebrospinal fluid (CSF). Radiation therapy might be used as well.

[00259] Induction is considered successful if remission is achieved. However, the AML in some patients can be refractory to induction. In patients who respond to induction, further treatment is then given to try to destroy remaining leukemia cells and help prevent a relapse, which is called consolidation. For younger patients, the main options for consolidation therapy are: several cycles of high-dose cytarabine (ara-C) chemo (sometimes known as HiDAC); allogeneic (donor) stem cell transplant; and autologous stem cell transplant.

[00260] Chronic leukemias are described as being lymphocytic (CLL) or myelocytic (CML). *The Merck Manual*, 949-952 (17th ed. 1999). CLL is characterized by the appearance of mature lymphocytes in blood, bone marrow, and lymphoid organs. The hallmark of CLL is sustained, absolute lymphocytosis (> 5,000/μL) and an increase of lymphocytes in the bone marrow. Most CLL patients also have clonal expansion of lymphocytes with B-cell characteristics. CLL is a disease of middle or old age. In CML, the characteristic feature is the predominance of granulocytic cells of all stages of differentiation in blood, bone marrow, liver, spleen, and other organs. In the symptomatic patient at diagnosis, the total white blood cell (WBC) count is usually about 200,000/μL, but may reach 1,000,000/μL. CML is relatively easy to diagnose

because of the presence of the Philadelphia chromosome. Bone marrow stromal cells are well known to support CLL disease progression and resistance to chemotherapy. Disrupting the interactions between CLL cells and stromal cells is an additional target of CLL chemotherapy.

[00261] Additionally, other forms of CLL include prolymphocytic leukemia (PLL), Large granular lymphocyte (LGL) leukemia, Hairy cell leukemia (HCL). The cancer cells in PLL are similar to normal cells called prolymphocytes -- immature forms of B lymphocytes (B-PLL) or T lymphocytes (T-PLL). Both B-PLL and T-PLL tend to be more aggressive than the usual type of CLL. The cancer cells of LGL are large and have features of either T cells or NK cells. Most LGL leukemias are slow-growing, but a small number are more aggressive. HCL is another cancer of lymphocytes that tends to progress slowly, and accounts for about 2% of all leukemias. The cancer cells are a type of B lymphocyte but are different from those seen in CLL.

[00262] In some embodiments, provided herein are methods for treating chronic leukemia (e.g., CML) in a subject with an FTI or selecting a chronic leukemia patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant chronic leukemia (e.g., CML) in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00263] Juvenile myelomonocytic leukemia (JMML) is a serious chronic leukemia that affects children mostly aged 4 and under. The average age of patients at diagnosis is 2 years old. The World Health Organization has categorized JMML as a mixed myelodysplastic and myeloproliferative disorder. The JMML encompasses diagnoses formerly referred to as Juvenile Chronic Myeloid Leukemia (JCML), Chronic Myelomonocytic Leukemia of Infancy, and Infantile Monosomy 7 Syndrome.

[00264] In some embodiments, provided herein are methods for treating JMML in a subject with an FTI or selecting JMML patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant JMML in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00265] In some embodiments, provided herein are methods for treating a lymphoma in a subject with an FTI or selecting lymphoma patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant lymphoma in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00266] Lymphoma refers to cancers that originate in the lymphatic system. Lymphoma is characterized by malignant neoplasms of lymphocytes—B lymphocytes (B cell lymphoma), T lymphocytes (T-cell lymphoma), and natural killer cells (NK cell lymphoma). Lymphoma generally starts in lymph nodes or collections of lymphatic tissue in organs including, but not limited to, the stomach or intestines. Lymphoma may involve the marrow and the blood in some cases. Lymphoma may spread from one site to other parts of the body.

[00267] The treatments of various forms of lymphomas are described, for example, in U.S. Patent No. 7,468,363, the entirety of which is incorporated herein by reference. Such lymphomas include, but are not limited to, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous B-cell lymphoma, activated B-cell lymphoma, Diffuse Large B-Cell Lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL; including but not limited to FL grade I, FL grade II), follicular center lymphoma, transformed lymphoma, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma (ILL), diffuse poorly differentiated lymphocytic lymphoma (PDL), centrocytic lymphoma, diffuse small-cleaved cell lymphoma (DSCCL), peripheral T-cell lymphomas (PTCL), cutaneous T-Cell lymphoma (CTCL) and mantle zone lymphoma and low grade follicular lymphoma.

[00268] Non-Hodgkin's lymphoma (NHL) is the fifth most common cancer for both men and women in the United States, with an estimated 63,190 new cases and 18,660 deaths in 2007. Jemal A, *et al.*, *CA Cancer J Clin* 2007; 57(1):43-66. The probability of developing NHL increases with age and the incidence of NHL in the elderly has been steadily increasing in the past decade, causing concern with the aging trend of the U.S. population. *Id.* Clarke C A, *et al.*, *Cancer* 2002; 94(7):2015-2023.

[00269] DLBCL accounts for approximately one-third of non-Hodgkin's lymphomas. While some DLBCL patients are cured with traditional chemotherapy, the remainders die from the

disease. Anticancer drugs cause rapid and persistent depletion of lymphocytes, possibly by direct apoptosis induction in mature T and B cells. *See* K. Stahnke. *et al.*, *Blood* 2001, 98:3066-3073. Absolute lymphocyte count (ALC) has been shown to be a prognostic factor in follicular non-Hodgkin's lymphoma and recent results have suggested that ALC at diagnosis is an important prognostic factor in DLBCL.

[00270] DLBCL can be divided into distinct molecular subtypes according to their gene profiling patterns: germinal-center B-cell–like DLBCL (GCB-DLBCL), activated B-cell–like DLBCL (ABC-DLBCL), and primary mediastinal B-cell lymphoma (PMBL) or unclassified type. These subtypes are characterized by distinct differences in survival, chemo-responsiveness, and signaling pathway dependence, particularly the NF-κB pathway. *See* D. Kim *et al.*, *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 8082. *See* Bea S, *et al.*, *Blood* 2005; 106: 3183-90; Ngo V.N. *et al.*, *Nature* 2011; 470: 115-9. Such differences have prompted the search for more effective and subtype-specific treatment strategies in DLBCL. In addition to the acute and chronic categorization, neoplasms are also categorized based upon the cells giving rise to such disorder into precursor or peripheral. *See e.g.,* U.S. patent Publication No. 2008/0051379, the disclosure of which is incorporated herein by reference in its entirety. Precursor neoplasms include ALLs and lymphoblastic lymphomas and occur in lymphocytes before they have differentiated into either a T- or B-cell. Peripheral neoplasms are those that occur in lymphocytes that have differentiated into either T- or B-cells. Such peripheral neoplasms include, but are not limited to, B-cell CLL, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, nodal marginal zone lymphoma, splenic marginal zone lymphoma, hairy cell leukemia, plasmacytoma, Diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma. In over 95 percent of CLL cases, the clonal expansion is of a B cell lineage. *See* Cancer: Principles & Practice of Oncology (3rd Edition) (1989) (pp. 1843-1847). In less than 5 percent of CLL cases, the tumor cells have a T-cell phenotype. Notwithstanding these classifications, however, the pathological impairment of normal hematopoiesis is the hallmark of all leukemias.

[00271] PTCL consists of a group of rare and usually aggressive (fast-growing) NHLs that develop from mature T-cells. PTCLs collectively account for about 4 to 10 percent of all NHL

cases, corresponding to an annual incidence of 2,800 – 7,200 patients per year in the United States. By some estimates, the incidence of PTCL is growing significantly, and the increasing incidence may be driven by an aging population. PTCLs are sub-classified into various subtypes, each of which are typically considered to be separate diseases based on their distinct clinical differences. Most of these subtypes are rare; the three most common subtypes of PTCL not otherwise specified, anaplastic large-cell lymphoma, or ALCL, and angioimmunoblastic T-cell lymphoma, that collectively account for approximately 70 percent of all PTCLs in the United States. ALCL can be cutaneous ALCL or systemic ALCL.

[00272] For most PTCL subtypes, the frontline treatment regimen is typically combination chemotherapy, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone), or other multi-drug regimens. Patients who relapse or are refractory to frontline treatments are typically treated with gemcitabine in combination with other chemotherapies, including vinorelbine (Navelbine®) and doxorubicin (Doxil®) in a regimen called GND, or other chemotherapy regimens such as DHAP (dexamethasone, cytarabine, cisplatin) or ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin).

[00273] Because most patients with PTCL will relapse, some oncologists recommend giving high-dose chemotherapy followed by an autologous stem cell transplant to some patients who had a good response to their initial chemotherapy. Recent, non-cytotoxic therapies that have been approved for relapsed or refractory PTCL, such as pralatrexate (Folotyn®), romidepsin (Istodax®) and belinostat (Beleodaq®), are associated with relatively low objective response rates (25-27% overall response rate, or ORR) and relatively short durations of response (8.2-9.4 months). Accordingly, the treatment of relapsed/refractory PTCL remains a significant unmet medical need.

[00274] In some embodiments, provided herein are methods for treating multiple myeloma in a subject with an FTI or selecting multiple myeloma patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant multiple myeloma in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00275] Multiple myeloma (MM) is a cancer of plasma cells in the bone marrow. Normally, plasma cells produce antibodies and play a key role in immune function. However, uncontrolled growth of these cells leads to bone pain and fractures, anemia, infections, and other complications. Multiple myeloma is the second most common hematological malignancy, although the exact causes of multiple myeloma remain unknown. Multiple myeloma causes high levels of proteins in the blood, urine, and organs, including but not limited to M-protein and other immunoglobulins (antibodies), albumin, and beta-2-microglobulin. M-protein, short for monoclonal protein, also known as paraprotein, is a particularly abnormal protein produced by the myeloma plasma cells and can be found in the blood or urine of almost all patients with multiple myeloma.

[00276] Skeletal symptoms, including bone pain, are among the most clinically significant symptoms of multiple myeloma. Malignant plasma cells release osteoclast stimulating factors (including IL-1, IL-6 and TNF) which cause calcium to be leached from bones causing lytic lesions; hypercalcemia is another symptom. The osteoclast stimulating factors, also referred to as cytokines, may prevent apoptosis, or death of myeloma cells. Fifty percent of patients have radiologically detectable myeloma-related skeletal lesions at diagnosis. Other common clinical symptoms for multiple myeloma include polyneuropathy, anemia, hyperviscosity, infections, and renal insufficiency.

[00277] Bone marrow stromal cells are well known to support multiple myeloma disease progression and resistance to chemotherapy. Disrupting the interactions between multiple myeloma cells and stromal cells is an additional target of multiple myeloma chemotherapy.

[00278] In some embodiments, provided herein are methods for treating a solid tumor with an FTI based on the presence of a mutation in a member of the CBL family (such as CBL, CBLB and/or CBLC). In some embodiments, provided herein are methods selecting multiple solid tumor patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant solid tumor in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib.

[00279] Solid tumors are abnormal masses of tissue that usually do not contain cysts or liquid areas. Solid tumors can be benign or malignant. Different types of solid tumors are named for the type of cells that form them (such as sarcomas, carcinomas, and lymphomas). The solid tumor to be treated with the methods of the invention can be sarcomas and carcinomas, include fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, and other sarcomas, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, lymphoid malignancy, pancreatic cancer, breast cancer, lung cancers, ovarian cancer, prostate cancer, hepatocellular carcinoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, pheochromocytomas sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, Wilms' tumor, cervical cancer, testicular tumor, seminoma, bladder carcinoma, melanoma, and CNS tumors (such as a glioma (such as brainstem glioma and mixed gliomas), glioblastoma (also known as glioblastoma multiforme) astrocytoma, CNS lymphoma, germinoma, meduloblastoma, Schwannoma craniopharyogioma, ependymoma, pineaioma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, neuroblastoma, retinoblastoma and brain metastases). In some embodiments, the FTI is tipifarnib.

[00280] In some embodiments, provided herein are methods for treating a solid tumor with an FTI based on the presence of a mutation in a member of the CBL family (such as CBL, CBLB and/or CBLC), wherein the solid tumor is malignant melanoma, adrenal carcinoma, breast carcinoma, renal cell cancer, carcinoma of the pancreas, non-small-cell lung carcinoma (NSCLC) or carcinoma of unknown primary. In some embodiments, the FTI is tipifarnib. Drugs commonly administered to patients with various types or stages of solid tumors include, but are not limited to, celebrex, etoposide, cyclophosphamide, docetaxel, apecitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

[00281] In some embodiments, the solid tumor to be treated by methods provided herein can be thyroid cancer, head and neck cancers, urothelial cancers, salivary cancers, cancers of the upper digestive tract, bladder cancer, breast cancer, ovarian cancer, brain cancer, gastric cancer, prostate cancer, lung cancer, colon cancer, skin cancer, liver cancer, and pancreatic cancer. In

some embodiments, the bladder cancer to be treated by methods provided herein can be transitional cell carcinoma. In some embodiments, the FTI is tipifarnib.

[00282] In some embodiments, the solid tumor to be treated by methods provided herein can be selected from the groups consisting of carcinoma, melanoma, sarcoma, or chronic granulomatous disease.

[00283] In some embodiments, the solid tumor to be treated by methods provided herein can be selected from the groups consisting of thyroid cancer, head and neck cancers, or salivary gland cancer. In some embodiments, the solid tumor is thyroid cancer. In some embodiments, the thyroid cancer can be relapsed/recurrent thyroid cancer. In some embodiments, the thyroid cancer can be metastatic thyroid cancer. In some embodiments, the thyroid cancer can be advanced thyroid cancer. In some embodiments, the solid tumor is head and neck squamous cell carcinoma (HNSCC) (e.g., HPV negative HSNCC or HPV positive HSNCC). In some embodiments, the HNSCC can be HPV negative HNSCC. In some embodiments, the HNSCC can be relapsed/recurrent HNSCC. In some embodiments, the HNSCC can be metastatic HNSCC. In some embodiments, the solid tumor is salivary gland cancer. In some embodiments, the salivary gland cancer can be advanced salivary gland cancer. In some embodiments, the salivary gland cancer can be metastatic salivary gland cancer.

[00284] In some embodiments, provided herein are methods for treating premalignant conditions in a subject with an FTI or selecting premalignant condition patients for an FTI treatment based on the presence of a mutation in a member of the CBL family. In some embodiments, provided herein are methods of treating a CBL-mutant premalignant condition in a subject by administering a therapeutically effective amount of the FTI to the subject. In some embodiments, the FTI is tipifarnib. In some embodiments, the premalignant conditions to be treated by methods provided herein can be actinic cheilitis, Barrett's esophagus, atrophic gastritis, ductal carcinoma in situ, Dyskeratosis congenita, Sideropenic dysphagia, Lichen planus, Oral submucous fibrosis, Solar elastosis, cervical dysplasia, polyps, leukoplakia, erythroplakia, squamous intraepithelial lesion, a pre-malignant disorder, or a pre-malignant immunoproliferative disorder.

[00285] In some embodiments, the cancer to be treated by methods provided herein can have a CBL, CBLB or CBLC mutation. In some embodiments, the cancer to be treated by methods provided herein can be a hematologic or hematopoietic cancer with a CBL, CBLB or CBLC mutation. The hematopoietic cancer with a CBL, CBLB or CBLC mutation can be any of the hematologic or hematopoietic cancers described above. In some embodiments, the cancer to be treated by methods provided herein can be a solid tumor with a CBL, CBLB or CBLC mutation. The solid tumor with a CBL, CBLB or CBLC mutation can be any of the solid tumors described above. Methods provided herein or otherwise known in the art can be used to determine the mutation status of a CBL, CBLB and/or CBLC gene. In some embodiments, the mutation status can be determined an NGS-based assay. In some embodiments, the mutation status can be determined by a qualitative PCR-based assay. In some embodiments, mutation status of a CBL, CBLB or CBLC gene can be determined in the form of a companion diagnostic to the FTI treatment, such as the tipifarnib treatment.

[00286] In some embodiments, the treatment of cancer in accordance with the methods described herein achieves at least one, two, three, four or more of the following effects: (i) inhibition of cancer progression, (ii) increase in progression free survival, (iii) increase in tumor-free survival rate of patients; (iv) increase in duration of response to treatment, (v) reduction of tumor growth, (vi) decrease in tumor size (e.g., volume or diameter); (vii) prevention of metastasis, (viii) decrease in metastases (e.g., decrease in the number of metastases); (ix) increase in relapse free survival; (x) alleviation or reduction of one or more symptoms of cancer, and (xi) increase in symptom-free survival.

3.4. *Exemplary FTIs and dosages*

[00287] In some embodiments, provided herein is a method of treating a cancer in a subject with an FTI based on the mutation status of a member of the CBL family (such as CBL, CBLB and/or CBLC). The FTI can be any FTI described herein or otherwise known in the art. In some embodiments, the FTI is selected from the group consisting of tipifarnib, arglabin, perrilyl alcohol, lonafarnib(SCH-66336), L778123, L739749, FTI-277, L744832, CP-609,754, R208176, AZD3409, and BMS-214662. In certain embodiments, the FTI is tipifarnib.

[00288] In some embodiments, provided herein is a method of treating a hematological or hematopoietic cancer in a subject based on the mutation status of CBL, CBLB or CBLC. The

method provided herein includes (a) determining the presence or absence of a mutation in CBL, CBLB or CBLC in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of tipifarnib to said subject if said sample is determined to have a mutation in CBL, CBLB or CBLC. In some embodiments, the methods include administering the subject with another FTI described herein or otherwise known in the art. In some embodiments, the FTI is selected from the group consisting of tipifarnib, arglabin, perrilyl alcohol, lonafarnib(SCH-66336), L778123, L739749, FTI-277, L744832, CP-609,754, R208176, AZD3409, and BMS-214662.

[00289] In some embodiments, provided herein is a method of treating CMML in a subject based on the mutation status of CBL, CBLB or CBLC. The method provided herein includes (a) determining the presence or absence of a mutation in CBL, CBLB or CBLC in a sample from the subject, and subsequently (b) administering a therapeutically effective amount of tipifarnib to said subject if said sample is determined to have a mutation in CBL, CBLB or CBLC. In some embodiments, the methods include administering the subject with another FTI described herein or otherwise known in the art. In some embodiments, the FTI is selected from the group consisting of tipifarnib, arglabin, perrilyl alcohol, lonafarnib(SCH-66336), L778123, L739749, FTI-277, L744832, CP-609,754, R208176, AZD3409, and BMS-214662.

[00290] In some embodiments, the FTI is administered orally, parenterally, rectally, or topically. In some embodiments, the FTI is administered orally. In some embodiments, tipifarnib is administered orally, parenterally, rectally, or topically. In some embodiments, tipifarnib is administered orally.

[00291] In some embodiments, the FTI is administered at a dose of 1-1000 mg/kg body weight. In some embodiments, the FTI is administered twice a day. In some embodiments, the FTI is administered at a dose of 200-1200 mg twice a day. In some embodiments, the FTI is administered at a dose of 600 mg twice a day. In some embodiments, the FTI is administered at a dose of 900 mg twice a day. In some embodiments, tipifarnib is administered at a dose of 1-1000 mg/kg body weight. In some embodiments, tipifarnib is administered twice a day. In some embodiments, tipifarnib is administered at a dose of 200-1200 mg twice a day. In some embodiments, tipifarnib is administered at a dose of 300 mg twice a day. In some embodiments, tipifarnib is administered at a dose of 600 mg twice a day. In some embodiments, tipifarnib is

administered at a dose of 900 mg twice a day. In some embodiments, tipifarnib is administered at a dose in the range of 200 to 900 mg twice a day.

[00292] In some embodiments, the FTI is administered at a dose of 1-1000 mg/kg body weight. In some embodiments, the FTI is administered twice a day. In some embodiments, the FTI is administered at a dose of 200-1200 mg twice a day. In some embodiments, the FTI is administered at a dose of 300 mg twice a day. In some embodiments, the FTI is administered at a dose of 600 mg twice a day. In some embodiments, the FTI is administered at a dose of 900 mg twice a day. In some embodiments, the FTI is administered at a dose in the range of 200 to 900 mg twice a day. In some embodiments, tipifarnib is administered in treatment cycles. In some embodiments, tipifarnib is administered in alternative weeks. In some embodiments, tipifarnib is administered on days 1-7 and 15-21 of a 28-day treatment cycle. In some embodiments, tipifarnib is administered orally at a dose of 900 mg twice a day on days 1-7 and 15-21 of a 28-day treatment cycle.

[00293] In some embodiments, the FTI is administered in treatment cycles. In some embodiments, the FTI is administered in alternative weeks. In some embodiments, the FTI is administered on days 1-7 and 15-21 of a 28-day treatment cycle. In some embodiments, the FTI is administered orally at a dose of 900 mg twice a day on days 1-7 and 15-21 of a 28-day treatment cycle. In some embodiments, the FTI is administered on days 1-21 of a 28-day treatment cycle (e.g, orally at a dose of 900 mg twice a day). In some embodiments, the FTI is administered on days 1-7 of a 28-day treatment cycle (e.g, orally at a dose of 900 mg twice a day). In some embodiments, tipifarnib is administered in treatment cycles. In some embodiments, tipifarnib is administered in alternative weeks. In some embodiments, tipifarnib is administered on days 1-7 and 15-21 of a 28-day treatment cycle. In some embodiments, tipifarnib is administered orally at a dose of 900 mg twice a day on days 1-7 and 15-21 of a 28-day treatment cycle. In some embodiments, tipifarnib is administered on days 1-21 of a 28-day treatment cycle (e.g, orally at a dose of 900 mg twice a day). In some embodiments, tipifarnib is administered on days 1-7 of a 28-day treatment cycle (e.g, orally at a dose of 900 mg twice a day).

[00294] In some embodiments, the FTI is administered for at least 3 cycles. In some embodiments, the FTI is administered for at least 6 cycles. In some embodiments, the FTI is

administered for up to 12 cycles. In some embodiments, the FTI is administered orally at a dose of 900 mg twice a day on days 1-7 and 15-21 of a 28-day treatment cycle for at least three cycles. In some embodiments, tipifarnib is administered for at least 3 cycles. In some embodiments, tipifarnib is administered for at least 6 cycles. In some embodiments, tipifarnib is administered for up to 12 cycles. In some embodiments, tipifarnib is administered orally at a dose of 900 mg twice a day on days 1-7 and 15-21 of a 28-day treatment cycle for at least three cycles.

[00295] In some embodiments, the FTI is administered for at least 3 cycles. In some embodiments, the FTI is administered for at least 6 cycles. In some embodiments, the FTI is administered for up to 12 cycles. In some embodiments, the FTI is administered orally at a dose in the range of 200 mg to 900 mg twice a day on days 1-21 of a 28-day treatment cycle for at least three cycles. In some embodiments, tipifarnib is administered for at least 3 cycles. In some embodiments, tipifarnib is administered for at least 6 cycles. In some embodiments, tipifarnib is administered for up to 12 cycles. In some embodiments, tipifarnib is administered orally at a dose in the range of 200 mg to 900 mg twice a day on days 1-21 of a 28-day treatment cycle for at least three cycles.

[00296] In some embodiments, the FTI is administered for at least 3 cycles. In some embodiments, the FTI is administered for at least 6 cycles. In some embodiments, the FTI is administered for up to 12 cycles. In some embodiments, the FTI is administered orally at a dose in the range of 200 mg to 900 mg twice a day on days 1-7 of a 28-day treatment cycle for at least three cycles. In some embodiments, tipifarnib is administered for at least 3 cycles. In some embodiments, tipifarnib is administered for at least 6 cycles. In some embodiments, tipifarnib is administered for up to 12 cycles. In some embodiments, tipifarnib is administered orally at a dose in the range of 200 mg to 900 mg twice a day on days 1-7 of a 28-day treatment cycle for at least three cycles.

[00297] In some embodiments, provided herein are methods for treating CMML in a subject with a therapeutically effective amount of an tipifarnib, based on the mutation status of CBL, CBLB or CBLC in a sample from the patient. In some embodiments, provided herein is a method of treating CMML in a subject including (a) determining a sample from the subject to have a mutant CBL, CBLB or CBLC, and subsequently (b) administering tipifarnib to the subject

at a dose in the range of 200 to 900 mg twice a day on days 1-7 and 15-21 of a 28-day treatment cycle.

[00298] In some embodiments, provided herein are methods for treating CMML in a subject with a therapeutically effective amount of an tipifarnib, based on the mutation status of CBL in a sample from the patient. In some embodiments, provided herein is a method of treating CMML in a subject including (a) determining a sample from the subject to have a mutant CBL, and subsequently (b) administering tipifarnib to the subject at a dose in the range of 200 to 900 mg twice a day on days 1-7 and 15-21 of a 28-day treatment cycle.

[00299] In some embodiments, provided herein are methods for treating CMML in a subject with a therapeutically effective amount of an tipifarnib, based on the mutation status of CBL, CBLB or CBLC in a sample from the patient. In some embodiments, provided herein is a method of treating CMML in a subject including (a) determining a sample from the subject to have a mutant CBL, CBLB or CBLC, and subsequently (b) administering tipifarnib to the subject at a dose in the range of 200 to 900 mg twice a day on days 1-21 of a 28-day treatment cycle.

[00300] In some embodiments, provided herein are methods for treating CMML in a subject with a therapeutically effective amount of an tipifarnib, based on the mutation status of CBL in a sample from the patient. In some embodiments, provided herein is a method of treating CMML in a subject including (a) determining a sample from the subject to have a mutant CBL, and subsequently (b) administering tipifarnib to the subject at a dose in the range of 200 to 900 mg twice a day on days 1-21 of a 28-day treatment cycle.

[00301] In some embodiments, provided herein are methods for treating CMML in a subject with a therapeutically effective amount of an tipifarnib, based on the mutation status of CBL, CBLB or CBLC in a sample from the patient. In some embodiments, provided herein is a method of treating CMML in a subject including (a) determining a sample from the subject to have a mutant CBL, CBLB or CBLC, and subsequently (b) administering tipifarnib to the subject at a dose in the range of 200 to 900 mg twice a day on days 1-7 of a 28-day treatment cycle.

[00302] In some embodiments, provided herein are methods for treating CMML in a subject with a therapeutically effective amount of an tipifarnib, based on the mutation status of CBL in a sample from the patient. In some embodiments, provided herein is a method of treating CMML

in a subject including (a) determining a sample from the subject to have a mutant CBL, and subsequently (b) administering tipifarnib to the subject at a dose in the range of 200 to 900 mg twice a day on days 1-7 of a 28-day treatment cycle.

[00303] In some embodiments, the subject having a CBL-mutant cancer (e.g., a CBL-mutant CMML) who is selected for tipifarnib treatment receives a dose of 900 mg b.i.d. orally in alternate weeks (one week on, one week off) in repeated 4 week cycles.

[00304] In some embodiments, the subject having a CBL-mutant cancer (e.g., a CBL-mutant CMML) who is selected for tipifarnib treatment receives a dose of 600 mg b.i.d. orally in alternate weeks (one week on, one week off) in repeated 4 week cycles.

[00305] In some embodiments, the subject having a CBL-mutant cancer (e.g., a CBL-mutant CMML) who is selected for tipifarnib treatment receives a dose of 300 mg b.i.d. orally in alternate weeks (one week on, one week off) in repeated 4 week cycles.

[00306] In some embodiments, the methods further comprise administering a second therapy to the patient having a solid tumor with a mutation in a member of the CBL family. In some embodiments, the second therapy is a chemotherapy, such as cisplatin, 5-FU, carboplatin, paclitaxel, or platinum-based doublet (e.g., cisplatin/5-FU or carboplatin/paclitaxel). In some embodiments, the second therapy is an anti-EGFR antibody therapy (e.g. Cetuximab, Panitumumab, Afatinib). In some embodiments, the second therapy is taxanes, methotrexate, and/or cetuximab. In some embodiments, the second therapy is a radiation therapy. In some embodiments, the second therapy include those targeting PI3K pathway: BKM120 (buparlisib) + cetuximab, BYL719 + cetuximab, Temsirolimus + cetuximab, Rigosertib + cetuximab; those targeting MET pathway: Tivantinib + cetuximab, Ficlatuzumab + cetuximab; those targeting EGFR/HER3 pathway Afatinib + cetuximab ± paclitaxel, Patritumab; those targeting FGFR pathway: BGJ398; those targeting CDK4/6–cell cycle pathway: Palbociclib, LEE011; RTK inhibitor: Anlotinib and chemotherapy: Oral Azacitidine. In some embodiments, the second therapy is an immunotherapy, such as anti-PD1 or anti-PDL1 antibodies. In some embodiments, the second therapy is a SRC family kinase inhibitor and/or a tyrosine kinase inhibitor (e.g, dasatinib). In some embodiments, the second therapy is dasatinib. In some embodiments, the second therapy is imatinib.

6. Examples

[00307] It is understood that modifications which do not substantially affect the activity of the various embodiments of this invention are also provided within the definition of the invention provided herein. Accordingly, the following examples are intended to illustrate but not limit the present invention. All of the references cited to herein are incorporated by reference in their entireties.

EXAMPLE I

Tipifarnib Clinical Trial in CMML Patients

[00308] This example describes an ongoing Phase 2 clinical study of tipifarnib with the primary objective being to assess the antitumor activity in terms of Overall Response Rate (ORR) of tipifarnib in approximately 20 eligible subjects with chronic myelomonocytic leukemia (CMML) (ClinicalTRials.gov identifier: NCT02807272).

[00309] Subjects receive tipifarnib administered orally, twice a day (bid) for 7 days in alternating weeks (Days 1-7 and 15-21) in 28 day cycles. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. If a complete response is observed, therapy with tipifarnib will be maintained for at least 6 months beyond the start of response.

[00310] Primary outcome measures: (1) Number of patients with CMML who obtain objective response following treatment with tipifarnib [Time Frame: 1 year]; (2) Number of patients with CMML whose disease is KRAS/NRAS wild type who obtain objective response following treatment with tipfarnib. [Time Frame: 1 year]

[00311] Secondary outcome measures: rate of complete response (CR) [Time Frame: 1 year]; duration of Response [Time Frame: 1 year]; rate of progression free survival (PFS) [Time Frame: 1 year]; rate of survival [Time Frame: 1 year]; number of patients that experience Adverse Events (AEs) [Time Frame: Until 30 days following end of study]; rate of complete cytogenetic remission [Time Frame: 1 year]; rate of partial cytogenetic remission [Time Frame: 1 year]; rate of marrow response [Time Frame: 1 year].

[00312] Detailed Description:

[00313] This Phase 2 study investigates the antitumor activity in terms of ORR of tipifarnib in approximately 20 eligible subjects with CMML. This trial is planned as a single treatment trial with statistical comparison to historical ORR rate. The primary objective is to provide evidence that the TRUE underlying ORR in all subjects and/or in the KRAS/NRAS wild-type subgroup exceeds the historical rate. Only consented subjects who meet all eligibility criteria are enrolled in the study. Eligible subjects receive tipifarnib administered at a starting dose of 1200 mg or 900 mg, orally with food, bid for 7 days in alternating weeks (Days 1-7 and 15-21) in 28 day cycles. Stepwise 300 mg dose reductions to control treatment-related, treatment-emergent toxicities are allowed.

[00314] If a complete response is observed, therapy with tipifarnib is maintained for at least 6 months beyond the start of response. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. Provisions are made for the continuation of study treatment in subjects whose disease has not progressed beyond the end of the study, e.g. a single patient treatment protocol.

[00315] Determination of disease response is performed by the Investigator according to the MDS/MPN IWG criteria. Similarly, disease progression is determined based on the MDS/MPN IWG criteria. Upon disease progression, all subjects are followed approximately every 12 weeks for survival and the use of subsequent therapy until either death or 12 months after accrual of the study cohort has been completed, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.

[00316] Inclusion Criteria:

(1) Diagnosis of CMML as defined by the World Health Organization (WHO) criteria.

(2) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

(3) Subject is willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures (including bone marrow assessments).

(4) At least 1 week since the last systemic therapy regimen prior to Cycle 1 Day 1. Subjects on a stable dose of hydroxyurea for at least 2 weeks prior to Cycle 1 Day 1 may continue on hydroxyurea until Cycle 1 Day 7. Subjects must have recovered to NCI CTCAE v. 4.03 < Grade

2 from all acute toxicities (excluding Grade 2 toxicities that are not considered a safety risk by the Sponsor and Investigator) or toxicity must be deemed irreversible by the Investigator.

(5) Acceptable liver function:

(6) Total or direct bilirubin $\leq$ 2 times upper limit of normal (x ULN); does not apply to subjects with Gilbert's syndrome diagnosed as per institutional guidelines.

(7) AST (SGOT) and ALT (SGPT) $\leq$ 2.5 x ULN.

(8) Acceptable renal function with serum creatinine $\leq$ 1.5 x ULN or a calculated creatinine clearance $\geq$ 60 mL/min using the Cockcroft-Gault or Modification of Diet in Renal Disease formulas.

(9) Female subjects must be: Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or If of child-bearing plf of child-bearing potential, subject must use an adequate method of contraception consisting of two-barrier method or one barrier method with a spermicide or intrauterine device. Both females and male subjects with female partners of child-bearing potential must agree to use an adequate method of contraception for 2 weeks prior to screening, during, and at least 4 weeks after last dose of study medication. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of study medication. Not breast feeding at any time during the study.

(10) Written and voluntary informed consent understood, signed and dated.

[00317] Exclusion Criteria:

(1) Known prior progression to acute myeloid leukemia (AML) defined by at least 20% blasts in the blood or bone marrow.

(2) Myeloproliferative/myelodysplastic syndrome other than CMML. CMML with t(5;12) that have not yet received imatinib.

(3) Participation in any interventional study within 4 weeks of randomization or 5 half-lives of the prior treatment agent (whichever is longer).

(4) Ongoing treatment with an anticancer agent for CMML not contemplated in this protocol. Subjects on a stable dose of hydroxyurea for at least 2 weeks prior to Cycle 1 Day 1 may continue on hydroxyurea until Cycle 1 Day 7.

(5) Concurrent use of granulocyte macrophage colony-stimulating factor (GM-CSF).

(6) Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor.

(7) Active coronary artery disease requiring treatment, myocardial infarction within the prior year, New York Heart Association grade III or greater congestive heart failure, cerebro-vascular attack within the prior year, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.

(8) Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.

(9) Active, concurrent malignancy requiring radiation, chemotherapy, or immunotherapy (excluding non-melanoma skin cancer, adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).

(10) Active and uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy. Known infection with human immunodeficiency virus (HIV), or an active infection with hepatitis B or hepatitis C.

(11) Concomitant disease or condition that could interfere with the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.

(12) The subject has legal incapacity or limited legal capacity.

(13) Significantly altered mental status that would limit the understanding or rendering of informed consent and compliance with the requirements of this protocol. Unwillingness or inability to comply with the study protocol for any reason.

[00318] Disease assessments (bone marrow, hematology and quality of life evaluations) can be performed at screening and at the Day 22 visit (± 5 days) performed during Cycles 2, 4, 6 and every approximately 12 weeks thereafter (Cycles 9, 12, 15, etc.). Hematologic assessments,

including peripheral blood evaluations and review of transfusion requirements, can be performed at screening and at least monthly until disease progression. A screening bone marrow aspirate/biopsy is not necessary to initiate treatment in subjects who have had a bone marrow aspirate/biopsy confirming their diagnosis within 4 weeks prior to Cycle 1 Day 1 and can provide samples for the completion of study objectives. If the bone marrow aspirate is inadequate for the scheduled disease assessment, a bone marrow biopsy can be performed. Additional disease or hematologic assessments can be conducted if deemed necessary by the Investigator. The timing of the disease and hematologic assessments are maintained as much as possible independently of potential treatment cycle delays.

EXAMPLE II

Durable Responses in CBL-mutant CMML Patients

[00319] In the Phase 2 clinical study of tipifarnib in patients with CMML described in Example 1, CBL gene status was determined for 24 patients. The CBL gene status was determined in blood samples using Genoptix. FIG. 1 shows proportion of subjects with CMML having wild type CBL and subjects with CMML having a mutant CBL remaining on-treatment with tipifarnib as a function of time (days). The figure shows that a trend ($p=0.13$) for longer duration of treatment with tipifarnib was observed in CMML patients with mutant CBL (N=3) as compared to those with wild type CBL (N=21). The CBL mutations detected were E479fs, C384Y, and C404Y. The median duration of treatment for the subjects with a mutant CBL did not reach a median value at the time the data were collected since those subjects remain in treatment. The median duration of treatment for the subjects with wild type CBL was 62 days.

[00320] These data indicate that subjects with mutant CBL tumors appear to remain responsive to tipifarnib treatment longer than those with wild type CBL tumors. As shown in FIG. 1, patients with CBL-mutant cancers (such as CMML) exhibit durable responses to tipifarnib (as compared to patients having wild type CBL). Accordingly, cancer patients (in particular, CMML patients) can be selected based on mutation status of CBL for tipifarnib treatment.

EXAMPLE III

Individualized Treatment Decisions for MDS (e.g., CMML) Patients

[00321] The following procedures can be taken to determine whether an MDS (e.g., a CMML) patient is suitable for an FTI treatment, such as a tipifarnib treatment.

[00322] DNA can be extracted predominantly from bone marrow cells (mononuclear cells or buffy coat) or the peripheral blood of the patient at MDS (e.g., CMML) presentation. The mutation status of CBL, CBLB and/or CBLC is determined by DNA sequencing, using a fluorescent primer–adapted chain termination method on an ABI 3100 sequencer (Applied Biosystems, Foster City, CA). When direct sequencing is negative, PCR products are cloned (Original TA Cloning Kit; Invitrogen, Groningen, the Netherlands) and sequenced.

[00323] If the MDS (e.g., CMML) patient is determined to have a mutation in CBL, CBLB and/or CBLC (e.g., a mutation at codon C384, C404, R420 or E479 of CBL), a tipifarnib treatment is prescribed.

[00324] If a tipifarnib treatment is prescribed to the MDS (e.g., CMML) patient, the patient can simultaneously receive another treatment, such as ionizing radiation, or a second active agent or a support care therapy, as deemed fit by the oncologist. The second active agent can be a DNA-hypomethylating agent, such as azacitidine or decitabine.

EXAMPLE IV

Individualized Treatment Decisions for AML Patients

[00325] The following procedures can be taken to determine whether an AML patient is suitable for an FTI treatment, such as a tipifarnib treatment. An AML patient can be older than 60 or otherwise unfit for standard chemotherapy, or have refractory or relapsed AML.

[00326] DNA can be extracted predominantly from bone marrow cells or the peripheral blood of an AML patient. The mutation status of CBL, CBLB and/or CBLC is determined by DNA sequencing, using a fluorescent primer–adapted chain termination method on an ABI 3100 sequencer (Applied Biosystems, Foster City, CA). When direct sequencing is negative, PCR products are cloned (Original TA Cloning Kit; Invitrogen, Groningen, the Netherlands) and sequenced.

[00327] If the AML patient is determined to have a mutation in CBL, CBLB and/or CBLC (e.g., a mutation at codon C384, C404, R420 or E479 of CBL), a tipifarnib treatment is prescribed.

[00328] If a tipifarnib treatment is prescribed to the AML patient, the AML patient can simultaneously receive another treatment, a second active agent or a support care therapy, as deemed fit by the oncologist.

INCORPORATION BY REFERENCE

[00329] Various references such as patents, patent applications, and publications are cited herein, the disclosures of which are hereby incorporated by reference herein in their entireties.

CLAIMS

We claim:

1. A method of treating a CBL-mutant cancer in a subject in need thereof, said method comprising administering a therapeutically effective amount of a farnesyltransferase inhibitor (FTI) to said subject, wherein the CBL-mutant cancer is a cancer known to have or determined to have a mutation in a member of the CBL family.

2. The method of claim 1, wherein the member of the CBL family is CBL.

3. The method of claim 2, wherein the mutation in the CBL comprises an amino acid modification at a codon selected from a group consisting of C384, C404, R420, and E479.

4. The method of claim 2, wherein the mutation in the CBL is selected from a group consisting of E479fs, C384Y and C404Y.

5. The method of claim 1, wherein the member of the CBL family is CBLB.

6. The method of claim 1, wherein the member of the CBL family is CBLC.

7. The method of any one of claims 1-6, wherein the cancer is leukemia.

8. The method of any one of claims 1-6, wherein the cancer is a myelodysplastic syndrome (MDS).

9. The method of any one of claims 1-6, wherein the cancer is chronic myelomonocytic leukemia (CMML).

10. The method of any one of claims 1-6, wherein the cancer is juvenile myelomonocytic leukemia (JMML).

11. The method of any one of claims 1-6, wherein the cancer is acute myeloid leukemia (AML).

12. The method of any one of claims 1-6, wherein the cancer is chronic myelogenous leukemia (CML).

13. The method of any one of claim 1-12, comprising a step of detecting the presence of a mutation in a member of the CBL family in a sample from said subject.

14. The method of claim 13, wherein said sample is a bone marrow sample or a plasma sample.

15. The method of claim 13 or 14, wherein the mutation is detected by a method selected from the group consisting of sequencing, Polymerase Chain Reaction (PCR), DNA microarray, Mass Spectrometry (MS), Single Nucleotide Polymorphism (SNP) assay, denaturing high-performance liquid chromatography (DHPLC), and Restriction Fragment Length Polymorphism (RFLP) assay.

16. The method of any one of claims 13-15, wherein the sample is a cell or tissue of the cancer, and wherein the cancer is determined to have a mutation in a member of the CBL family.

17. The method of any one of claims 1-16, wherein the subject is responsive to treatment for at least or more than 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months or 1 year.

18. The method of any one of claims 1-17, wherein the administering is performed for at least or more than 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months or 1 year.

19. The method of any one of claims 1-18, wherein the FTI is administered on days 1-21 of a 28-day treatment cycle.

20. The method of any one of claims 1-18, wherein the FTI is administered on days 1-7 of a 28-day treatment cycle.

21. The method of any one of claims 1-18, wherein the FTI is administered on days 1-7 and 15-21 of a 28-day treatment cycle.

22. The method of any one of claims 19-21, wherein the FTI is administered for at least 3 cycles or at least 6 cycles.

23. The method of any one of claims 1-22, wherein FTI is administered twice a day.

24. The method of any one of claims 1-23, wherein the FTI is tipifarnib.

25. The method of claim 24, wherein the tipifarnib is administered at a dose of 200-1200 mg twice a day.

26. The method of claim 24, wherein tipifarnib is administered at a dose of 900 mg twice a day

27. The method of claim 24, wherein tipifarnib is administered at a dose of 600 mg twice a day.

28. The method of claim 24, wherein tipifarnib is administered at a dose of 400 mg twice a day.

29. The method of claim 24, wherein tipifarnib is administered at a dose of 300 mg twice a day.

30. The method of claim 24, wherein tipifarnib is administered at a dose of 200 mg twice a day

31. The method of any one of claims 1-30, further comprising administering a therapeutically effective amount of a second active agent or a support care therapy.

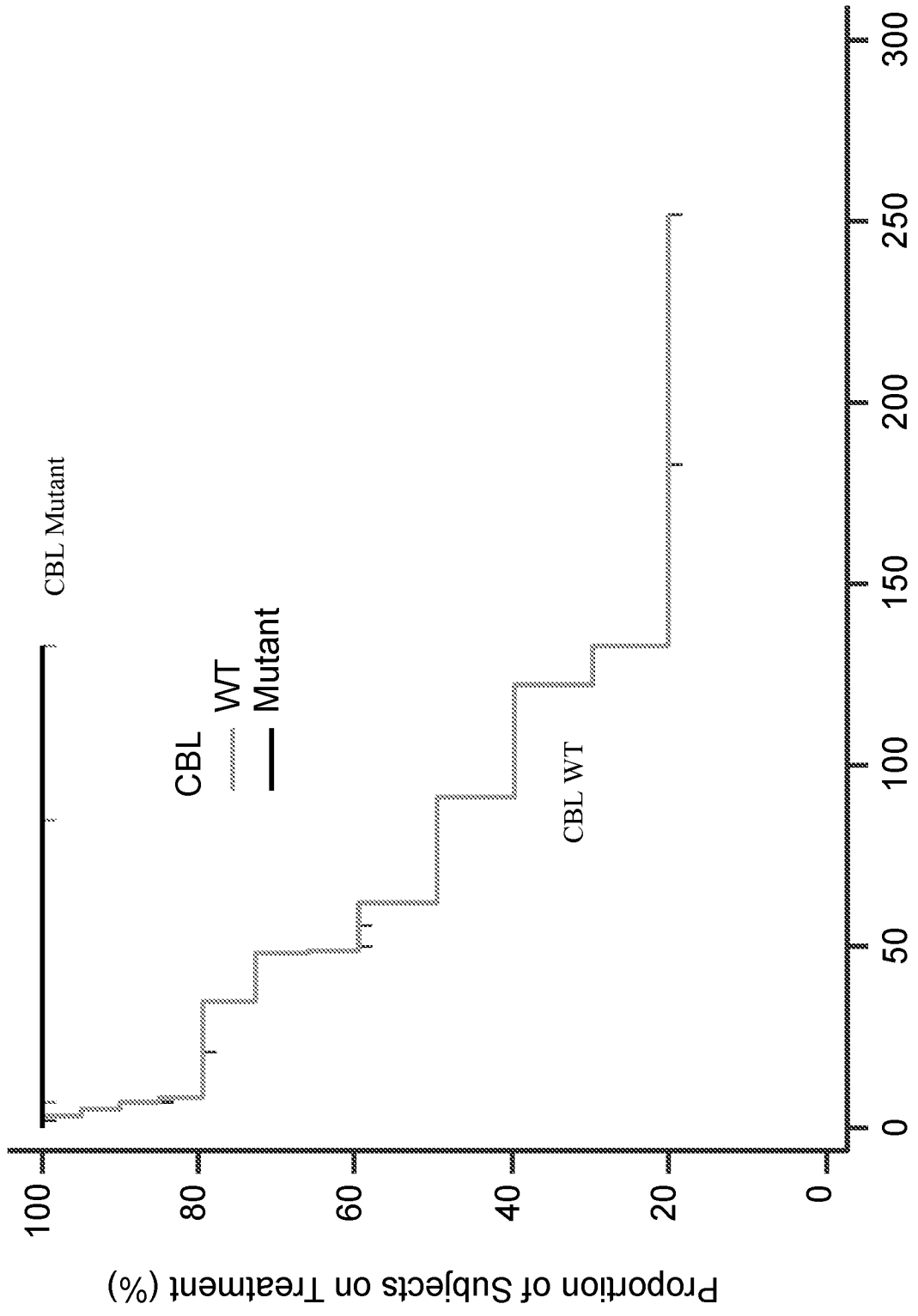
Proportion of Subjects on Treatment (%)
100
80
60
40
20
0
0
50
100
150
200
250
300
Days
CBL
WT
Mutant
CBL Mutant
CBL WT

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/064164

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6886
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/031101 A1 (KURA ONCOLOGY INC [US]) 23 February 2017 (2017-02-23) examples 2,5,7	1-8,11, 13-31
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2019	29/03/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cornelis, Karen

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ELLIOT STIEGLITZ ET AL: "Phase II/III trial of a pre-transplant farnesyl transferase inhibitor in juvenile myelomonocytic leukemia: A report from the Children's Oncology Group : Pre-HSCT Farnesyl Transferase Inhibition in JMML", PEDIATRIC BLOOD AND CANCER, vol. 62, no. 4, 1 April 2015 (2015-04-01), pages 629-636, XP055568385, US ISSN: 1545-5009, DOI: 10.1002/pbc.25342 the whole document --- H. MAKISHIMA ET AL: "CBL, CBLB, TET2, ASXL1, and IDH1/2 mutations and additional chromosomal aberrations constitute molecular events in chronic myelogenous leukemia", BLOOD, vol. 117, no. 21, 26 May 2011 (2011-05-26) , pages e198-e206, XP055568399, ISSN: 0006-4971, DOI: 10.1182/blood-2010-06-292433 --- S. SCHNITTGER ET AL: "Use of CBL exon 8 and 9 mutations in diagnosis of myeloproliferative neoplasms and myelodysplastic/myeloproliferative disorders: an analysis of 636 cases", HAEMATOLOGICA, THE HEMATOLOGY JOURNAL : OFFICIAL ORGAN OF THE EUROPEAN HEMATOLOGY ASSOCIATION, vol. 97, no. 12, 1 December 2012 (2012-12-01), pages 1890-1894, XP055568408, IT ISSN: 0390-6078, DOI: 10.3324/haematol.2012.065375 ---	1-8,11, 13-31 1-31 1-31

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/064164

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