Care Med. (2009) 179(7):542–48; Randis *et al.* Eur J Immunol. (2008) 38(5):1215–24), mast cells (Ali *et al.* Nature (2004) 431(7011):1007–11; Kim *et al.* Trends Immunol. (2008) 29(10):493–501; Lee *et al.* FASEB J. (2006) 20(3):455–65), and NK cells (Guo *et al*. J Exp Med. (2008) 205(10):2419–35; Kim *et al.* Blood (2007) 110(9):3202–08; Saudemont *et al.* Proc Natl Acad Sci U S A. (2009) 106(14):5795–800; Tassi *et al.* Immunity. (2007) 27(2):214–27).

[0010] Both PI3K-δ and -γ are believed to be important for the development and persistence of autoimmune disease and hematologic malignancies.

[0011] There remains a significant need for improved therapy for cancers such as hematologic malignancies.

SUMMARY

[0012] Provided herein are methods, compositions, and kits for treating or preventing cancers or diseases, such as hematologic malignancies, which have a high expression level of one or more isoform(s) of PI3K (*e.g.*, PI3K-δ and/or PI3K-γ). In one example, the methods, compositions, and kits provided herein relate to administering an isoform-selective PI3K modulator (*e.g.*, a compound provided herein, which selectively reduces or inhibits the activity of one or more PI3K isoform(s), *e.g.*, PI3K-δ and/or PI3K-γ), alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human, having a cancer or disease, such as a hematologic malignancy, which has a high expression level of the one or more PI3K isoform(s).

[0012a] In one aspect, the present disclosure refers to the use of a PI3K modulator, or a pharmaceutically acceptable form thereof, in the manufacture of a medicament for treating or managing cancer or hematologic malignancy in a subject who is identified to have received a prior treatment and who developed resistance to the prior treatment, wherein said medicament is to be administered alone or in combination with one or more other therapeutic agents.

[0012b] In another aspect, the present disclosure refers to the use of a PI3K modulator, or a pharmaceutically acceptable form thereof, in the manufacture of a medicament for treating a subject with a cancer or hematologic malignancy, wherein the subject is identified with one or more mutations selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation.

[0012c] In yet another aspect, the present disclosure refers to method of selecting a subject diagnosed with a cancer or hematologic malignancy as a candidate for treatment with a therapeutically effective amount of a

PI3K modulator, or a pharmaceutically acceptable form thereof, comprising: (a) detecting the presence or absence of one or more mutations selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation in a sample obtained from the subject, wherein the presence of one or more of the mutations indicates that the subject is a candidate for treatment with a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof; and (b) selecting the subject for administration with a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof, when one or more of the mutations are present in the sample.

[0013] In one example, provided herein are methods, compositions, and kits for treating or preventing a specific type of cancer or disease, such as, a specific type of hematologic malignancy, which has a high expression level of one or more isoform(s) of PI3K. In one example, provided herein are methods, compositions, and kits for treating or preventing a specific sub-type of cancer or disease, such as, a specific sub-type of hematologic malignancy, which has a high expression level of one or more isoform(s) of PI3K. In one example, the specific type or specific sub-type of cancer or hematologic malignancy has a high expression of PI3K isoform(s), including one or more of PI3K-δ or PI3K-γ, or a combination thereof. In one example, the specific type or specific sub-type of cancer or hematologic malignancy has a high expression of PI3K-δ, or PI3K-γ, or both PI3K-δ and PI3K-γ.

[0014] In one example, the methods, compositions, and kits comprise, or relate to, the step of selecting a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of hematologic malignancy, for treatment, using a biomarker provided herein (*e.g.*, selecting a specific type or sub-type of cancer or hematologic malignancy that has a high expression level of one or more isoform(s) of PI3K as determined using a biomarker provided herein). In one example, the methods, compositions, and kits comprise, or relate to, the step of administering to a subject having a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of hematologic malignancy, which has a high expression level of one or more isoform(s) of PI3K, a PI3K modulator that selectively modulates (*e.g.*, selectively inhibits) the PI3K isoform(s) that is highly expressed in the specific type or subtype of disease.

[0015] In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of hematologic malignancy, which has a high expression level of PI3K-δ. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of a hematologic malignancy, which has a high expression level

of PI3K-γ. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of a hematologic malignancy, which has a high expression level of PI3K-δ and PI3K-γ. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of a hematologic malignancy, which has a high expression level of PI3K-γ and PI3K-α. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of a hematologic malignancy, which has a high expression level of PI3K-γ and PI3K-β. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of a hematologic malignancy, which has a high expression level of PI3K-δ and PI3K-α. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of a hematologic malignancy, which has a high expression level of PI3K-δ and PI3K-β. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of a hematologic malignancy, which has a high expression level of PI3K-δ, PI3K-γ, and PI3K-α. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific type, or a specific sub-type, of cancer or disease, *e.g.*, a specific type, or a specific sub-type, of a hematologic malignancy, which has a high expression level of PI3K-δ, PI3K-γ, and PI3K-β.

[0016] In one example, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, such as, a hematologic malignancy, wherein the particular patient or group of patients has(ve) a high expression level of one or more isoform(s) of PI3K. In one example, the PI3K isoform includes one or more of PI3K-δ or PI3K-γ, or a combination thereof. In one example, the specific patient or group of patients, having a cancer or a hematologic malignancy, has(ve) a high expression of PI3K-δ or PI3K-γ, or both PI3K-δ and PI3K-γ.

[0017] In one example, the methods, compositions, and kits comprise, or relate to, the step of selecting a patient or group of patients having a cancer or disease for treatment, using a biomarker provided herein (*e.g.*, selecting a patient or group of patients that has(ve) a high expression level of one or more isoform(s) of PI3K as determined using a biomarker provided herein). In one example, the methods, compositions, and kits comprise, or relate to, the step of administering to the patient or group of patients having a high expression level of one or more isoform(s) of PI3K, a PI3K modulator that selectively modulates (*e.g.*, selectively inhibits) the PI3K isoform(s) that is/are highly expressed in the patient(s).

[0018] In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, that has a high expression level of PI3K-δ. In specific examples, provided herein are methods, compositions, and kits

for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, that has a high expression level of PI3K-γ. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, which has a high expression level of PI3K-δ and PI3K-γ. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, which has a high expression level of PI3K-γ and PI3K-α. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, which has a high expression level of PI3K-γ and PI3K-β. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, which has a high expression level of PI3K-δ and PI3K-α. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, which has a high expression level of PI3K-δ and PI3K-β. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, which has a high expression level PI3K-δ, PI3K-γ, and PI3K-α. In specific examples, provided herein are methods, compositions, and kits for treating or preventing a specific patient or group of patients, having a cancer or disease, *e.g.*, a hematologic malignancy, which has a high expression level of PI3K-δ, PI3K-γ, and PI3K-β.

[0019] In certain examples, the expression level of one or more than one particular PI3K isoform in a cancer or a disease (*e.g.*, a hematologic malignancy), or a patient or a group of patients, can be determined by detecting the expression level of protein of a particular PI3K isoform, or DNA of a particular PI3K isoform, or RNA of a particular PI3K isoform, for example, using a method provided herein or a method known in the art. In other examples, the expression level of one or more than one particular PI3K isoform in a cancer or a disease (*e.g.*, a hematologic malignancy), or a patient or a group of patients, can be determined by measuring a biomarker provided herein (*e.g.*, a signaling pathway biomarker, a protein mutation biomarker, a protein expression biomarker, a gene mutation biomarker, a gene expression biomarker, a cytokine biomarker, a chemokine biomarker, or a biomarker for particular cancer cells, among others). In yet another example, the expression level of one or more than one particular PI3K isoform in a cancer or a disease (*e.g.*, a hematologic malignancy), or a patient or a group of patients, can be determined based on information known in the art or based on prior studies on the cancer or disease (*e.g.*, a hematologic malignancy), or prior testing of the patient or group of patients.

[0020] In one example, the methods, compositions and kits provided herein relate to administering a PI3K modulator (*e.g.*, a compound that selectively reduces the activity of one or more PI3K isoform(s)), alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human. In one example, the PI3K modulator is selective toward one or more isoform(s) of PI3K over the other isoform(s) of PI3K. In one example, the PI3K modulator (*e.g.*, a compound provided herein) is selective toward

PI3K-δ; selective toward PI3K-γ; selective toward PI3K-δ and PI3K-γ; selective toward PI3K-γ and PI3K-α; selective toward PI3K-γ and PI3K-β; selective toward PI3K-δ and PI3K-α; selective toward PI3K-δ and PI3K-β; selective toward PI3K-δ, PI3K-γ, and PI3K-α; or selective toward PI3K-δ, PI3K-γ, and PI3K-β; over other PI3K isoform(s). In one example, the selectivity of the PI3K modulator (*e.g.*, a compound provided herein) for one isoform of PI3K over another isoform of PI3K is about 2-fold, about 5-fold, about 10-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, about 200-fold, about 300-fold, about 400-fold, about 500-fold, about 1000-fold, about 2000-fold, about 5000-fold, about 10000-fold, or greater than about 10000-fold. In one example, the selectivity of a compound provided herein for one isoform of PI3K over another isoform of PI3K is greater than about 2-fold, greater than about 5-fold, greater than about 10-fold, greater than about 20-fold, greater than about 30-fold, greater than about 40-fold, greater than about 50-fold, greater than about 100-fold, greater than about 200-fold, greater than about 300-fold, greater than about 400-fold, greater than about 500-fold, greater than about 1000-fold, greater than about 2000-fold, greater than about 5000-fold, or greater than about 10000-fold.

[0021] In certain examples, the selectivity of a PI3K modulator (*e.g.*, a compound provided herein) for one or more PI3K isoform(s) over other PI3K isoform(s) can be determined by measuring the activity of the PI3K modulator toward PI3K isoforms (*e.g.*, PI3K-α, PI3K-β, PI3K-δ, and/or PI3K-γ), for example, using a method provided herein or a method known in the art.

[0022] In one example, provided herein is a method of treating or managing cancer or hematologic malignancy in a subject who developed resistance to a prior treatment comprising identifying a subject who received prior treatment and administering to the subject a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof, alone or in combination with one or more other therapeutic agents.

[0023] In one example, the prior treatment is a treatment with one or more BTK inhibitors, anti-CD20 antibodies, proteasome inhibitors, or alkylating agents. In one example, the prior treatment is treatment with one or more BTK inhibitors.

[0024] In one example, the BTK inhibitor is ibrutinib (1-[(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) or AVL-292 (N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide). In one example, the BTK inhibitor is RN-486 (6-cyclopropyl-8-fluoro-2-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-2H-isoquinolin-1-one), GDC-0834 ([R-N-(3-(6-(4-(1,4-dimethyl-3-oxopiperazin-2-yl) phenylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide]), CGI-560 (N-[3-(8-anilinoimidazo[1,2-a]pyrazin-6-yl)phenyl]-4-tert-butylbenzamide), CGI-1746 (4-(tert-butyl)-N-(2-methyl-3-(4-methyl-6-((4-(morpholine-4-carbonyl)phenyl)amino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide), HM-71224, ONO-4059, ACP-196, CNX-774 (4-(4-((4-((3-acrylamidophenyl)amino)-5-fluoropyrimidin-2-yl)amino)phenoxy)-N-methylpicolinamide), or LFM-A13 (2Z-cyano-N-(2,5-dibromophenyl)3-hydroxy-2-butenamide).

[0025] In one example, the method provided herein further comprises obtaining a biological sample from the subject and detecting the presence of one or more mutations selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutationin the sample.

[0026] In one example, the prior treatment is treatment with one or more proteasome inhibitors. In one example, the proteasome inhibitor is bortezomib. In one example, the prior treatment is treatment with one or more alkylating agents. In one example, the alkylating agent is nitrogen mustard. In one example, the prior treatment is treatment with one or more anti-CD20 antibodies. In one example, wherein the anti-CD20 antibody is rituximab, obinutuzumab, tositumomab, ^{131}I tositumomab, ^{90}Y ibritumomab, ^{111}I ibritumomab, or ofatumumab.

[0027] In one example, provided herein is a method of treating a subject with a cancer or hematologic malignancy comprising:

identifying a subject with one or more mutations selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation; and

administering a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof, to the subject identified with one or more of the mutations.

[0028] In another example, the administration further comprises combining with one or more other therapeutic agents to the subject identified with one or more of the mutations.

[0029] In one example, the identifying comprises obtaining a biological sample from the subject and detecting one or more mutations selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine

to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation in the sample. In one example, the detecting comprises performing polymerase chain reaction (PCR) or hybridization to detect one or more of the mutations.

[0030] In one example, provided herein is a method of selecting a subject diagnosed with a cancer or hematologic malignancy as a candidate for treatment with a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof, comprising:

(a) detecting the presence or absence of one or more mutations selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation in a sample obtained from the subject, wherein the presence of one or more of the mutations indicates that the subject is a candidate for treatment with a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof; and

(b) administering to the subject a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof, when one or more of the mutations are present in the sample.

[0031] In one example, the administration further comprises combining with one or more other therapeutic agents to the subject identified with one or more of the mutations.

[0032] In one example, the PI3K modulator is Compound 292. In another example, the PI3K modulator is or CAL-101 (GS-1101, idelalisib, (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one).

[0033] In one example, the other therapeutic agent is a chemotherapeutic agent or a therapeutic antibody. In one example, the chemotherapeutic agent is selected from mitotic inhibitors, alkylating agents, anti-metabolites, proteasome inhibitor, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

[0034] In one example, the therapeutic antibody is selected from anti-CD37 antibody, anti-CD20 antibody, and anti-CD52 antibody. In one example, the therapeutic antibody is anti-CD20 antibody. In one example, the anti-CD20 antibody is rituximab, obinutuzumab, tositumomab, ^{131}I tositumomab, ^{90}Y ibritumomab, ^{111}I ibritumomab, or ofatumumab. In one example, the anti-CD20 antibody is obinutuzumab.

[0035] In one example, the molar ratio of the PI3K modulator to the other therapeutic agent is about 500:1, about 250:1, about 100:1, about 50:1, about 25:1, about 20:1, about 19:1, about 18: 1, about 17:1, about 16:1, about 15:1, about 14:1, about 13:1, about 12:1, about 11:1, about 10:1, about 5:1, about 4:1, about 3:1, about 2:1, or about 1:1.In one example, the PI3K modulator is administered at a daily dosage of about 0.1 mg to about 75 mg,

about 1 mg to about 75 mg, about 5 mg to about 75 mg, about 5 mg to about 60 mg, about 10 mg to about 60 mg, about 20 mg to about 60 mg, about 30 mg to about 60 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 10 mg, about 20 mg, or about 50 mg; or at a twice daily dosage of about 0.1 mg to about 75 mg, about 1 mg to about 75 mg, about 5 mg to about 75 mg, about 5 mg to about 60 mg, about 5 mg to about 50 mg, about 5 mg, about 10 mg, about 20 mg, about 25 mg, or about 50 mg; and

the other therapeutic agent is administered at a daily dosage of about 0.1 mg to about 10,000 mg, about 0.1 mg to about 7500 mg, about 0.1 mg to about 5000 mg, about 1 mg to about 2500 mg, about 1 mg to about 1500 mg, about 10 mg to about 1000 mg, about 500 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, about 900 mg to about 1000 mg, or about 1000.

[0036] .

[0037] In one example, the PI3K modulator is administered at a daily dosage of about 0.1 mg to about 500 mg, about 1 mg to about 500 mg, about 100 mg to about 500 mg, about 150 mg to about 500 mg, about 200 mg to about 500 mg, about 200 mg to about 400 mg, or about 250 mg to about 350 mg; and

obinutuzumab is administered at a daily dosage of about 0.1 mg to about 10,000 mg, about 0.1 mg to about 7500 mg, about 0.1 mg to about 5000 mg, about 1 mg to about 2500 mg, about 1 mg to about 1500 mg, about 10 mg to about 1000 mg, about 500 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, or about 900 mg to about 1000 mg.

[0038] In one example, the PI3K modulator is administered at an amount to reach maximum plasma concentration at steady state (Cmaxss) at about 1000 ng/mL to about 5000 ng/mL, about 1000 ng/mL to about 4000 ng/mL, about 1000 ng/mL to about 3000 ng/mL, about 1000 ng/mL to about 2500 ng/mL, or about 1400 ng/mL to about 2200 ng/mL; and

the other agent is administered at an amount to reach Cmaxss at about 100 ng/mL to about 1000 ng/mL, about 250 ng/mL to about 1000 ng/mL, about 500 ng/mL to about 1000 ng/mL, about 600 ng/mL to about 1000 ng/mL, about 700 ng/mL to about 1000 ng/mL, about 740 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 900 ng/mL, or about 750 ng/mL to about 800 ng/mL.

[0039] In one example, the PI3K modulator is administered at an amount to reach an area under the plasma concentration-time curve at steady-state (AUCss) at about 5000 ng/mL*hr to about 10000 ng/mL*hr, about 5000 ng/mL*hr to about 9000 ng/mL*hr, about 6000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr, about 7500 ng/mL*hr, about 8000 ng/mL*hr, about 8500 ng/mL*hr , about 8600 ng/mL*hr, about 8700 ng/mL*hr, or about 8800 ng/mL*hr; and

the other agent is administered at an amount to reach an AUCss at about 1000 ng/mL*hr to about 5000 ng/mL*hr, about 2000 ng/mL*hr to about 5000 ng/mL*hr, about 3000 ng/mL*hr to about 5000 ng/mL*hr, about 4000 ng/mL*hr to about 5000 ng/mL*hr, or about 4000 ng/mL*hr to about 4500 ng/mL*hr.

[0040] In one example, the PI3K modulator is Compound 292, or a pharmaceutically acceptable form thereof, and the other therapeutic agent is obinutuzumab.

[0041] In another example, the PI3K modulator is CAL-101, or a pharmaceutically acceptable form thereof, and the other therapeutic agent is obinutuzumab.

[0042] In one example, the molar ratio of Compound 292 to obinutuzumab is about 500:1, about 250:1, about 100:1, about 50:1, about 25:1, about 20:1, about 19:1, about 18: 1, about 17:1, about 16:1, about 15:1, about 14:1, about 13:1, about 12:1, about 11:1, about 10:1, about 5:1, about 4:1, about 3:1, about 2:1, or about 1:1. In one example, the molar ratio is 25:1 to about 1:1. In one example, the molar ratio is about 20:1 to about 5:1. In one example, the molar ratio is about 20:1 to about 10:1. In one example, the molar ratio is about 20:1, about 19:1, about 18:1, about 17:1, about 16:1, or about 15:1. In one example, the molar ratio is about 16:1. In one example, the molar ratio is about 17:1.

[0043] In one example, the molar ratio of CAL-101 to obinutuzumab is about 500:1, about 250:1, about 100:1, about 50:1, about 25:1, about 20:1, about 19:1, about 18: 1, about 17:1, about 16:1, about 15:1, about 14:1, about 13:1, about 12:1, about 11:1, about 10:1, about 5:1, about 4:1, about 3:1, about 2:1, or about 1:1. In one example, the molar ratio is about 150:1 to about 50:1. In one example, the molar ratio is about 150:1 to about 75:1. In one example, the molar ratio is about 125:1 to about 75:1. In one example, the molar ratio is about 110:1 to about 90:1. In one example, the molar ratio is about 100:1.

[0044] In one example, Compound 292 is administered at a daily dosage of about 0.1 mg to about 75 mg, about 1 mg to about 75 mg, about 5 mg to about 75 mg, about 5 mg to about 60 mg, about 10 mg to about 60 mg, about 20 mg to about 60 mg, about 30 mg to about 60 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 10 mg, about 20 mg, or about 50 mg; or at a twice daily dosage of about 0.1 mg to about 75 mg, about 1 mg to about 75 mg, about 5 mg to about 75 mg, about 5 mg to about 60 mg, about 5 mg to about 50 mg, about 5 mg, about 10 mg, about 20 mg, 25 mg, or about 50 mg; and obinutuzumab is administered at a daily dosage of about 0.1 mg to about 10,000 mg, about 0.1 mg to about 7500 mg, about 0.1 mg to about 5000 mg, about 1 mg to about 2500 mg, about 1 mg to about 1500 mg, about 10 mg to about 1000 mg, about 500 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, about 900 mg to about 1000 mg, or about 1000 mg.

[0045] In one example, Compound 292 is administered at a daily dosage of about 5 mg to about 60 mg, about 15 mg to about 60 mg, about 20 mg to about 60 mg, about 30 mg to about 60 mg, or about 40 mg to about 60 mg. In one example, Compound 292 is administered at a daily dosage of about 50 mg. In one example, Compound 292 is administered at a twice daily at a dosage of about 5 mg to about 30 mg, about 15 mg to about 30 mg, or about 20 mg to about 30 mg. In one example, Compound 292 is administered at twice daily at a dosage of about 25 mg. In one example, obinutuzumab is administered at a daily dosage of about 500 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, or about 900 mg to about 1000 mg. In one example, obinutuzumab is administered at a daily dosage of about 1000 mg.

[0046] In one example, CAL-101 is administered at a daily dosage of about 0.1 mg to about 500 mg, about 1 mg to about 500 mg, about 100 mg to about 500 mg, about 150 mg to about 500 mg, about 200 mg to about 500 mg, about 200 mg to about 400 mg, or about 250 mg to about 350 mg; and

[0047] obinutuzumab is administered at a daily dosage of about 0.1 mg to about 10,000 mg, about 0.1 mg to about 7500 mg, about 0.1 mg to about 5000 mg, about 1 mg to about 2500 mg, about 1 mg to about 1500 mg, about 10 mg to about 1000 mg, about 500 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, or about 900 mg to about 1000 mg. In one example, CAL-101 is administered at a daily dosage of about 200 mg to about 500 mg, about 200 mg to about 400 mg, or about 250 mg to about 350 mg. In one example, CAL-101 is administered at a daily dosage of about 300 mg. In one example, CAL-101 is administered at twice daily at a dosage of about 10 mg to about 250 mg, about 75 mg to about 200 mg, about 100 mg to about 200 mg, or about 125 mg to about 1750 mg. In one example, CAL-101 is administered twice daily at a dosage of about 150 mg. In one example, obinutuzumab is administered at a daily dosage of about 500 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, or about 900 mg to about 1000 mg. In one example, obinutuzumab is administered at a daily dosage of about 1000 mg.

[0048] In one example, Compound 292 is administered at an amount to reach is administered at an amount to reach Cmaxss at about 1000 ng/mL to about 5000 ng/mL, about 1000 ng/mL to about 4000 ng/mL, about 1000 ng/mL to about 3000 ng/mL, about 1000 ng/mL to about 2500 ng/mL, or about 1400 ng/mL to about 2200 ng/mL; and

obinutuzumab is administered at an amount to reach Cmaxss at about 100 ng/mL to about 1000 ng/mL, about 250 ng/mL to about 1000 ng/mL, about 500 ng/mL to about 1000 ng/mL, about 600 ng/mL to about 1000 ng/mL, about 700 ng/mL to about 1000 ng/mL, about 740 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 900 ng/mL, or about 750 ng/mL to about 800 ng/mL.

[0049] In one example, Compound 292 is administered at an amount to reach is administered at an amount to reach Cmaxss at about 1500 ng/mL to about 1000 ng/mL, about 1500 ng/mL to about 1200 ng/mL, about 1500 ng/mL to about 1300 ng/mL, or about 1500 ng/mL to about 1400 ng/mL. In one example, Compound 292 is administered at an amount to reach is administered at an amount to reach Cmaxss at about 1487 ng/mL. In one example, Cmaxss is at least 700 ng/mL, at least 1000 ng/mL, at least 1200 ng/mL, at least 1400 ng/mL, at least 1450 ng/mL, or at least 1480 ng/mL. In one example, obinutuzumab is administered at an amount to reach Cmaxss at about 750 ng/mL to about 900 ng/mL, about 750 ng/mL to about 850 ng/mL, or about 750 ng/mL to about 800 ng/mL. In one example, obinutuzumab is administered at an amount to reach Cmaxss at about 741 ng/mL. In one example, Cmaxss is at least 200 ng/mL, at least 500 ng/mL, at least 600 ng/mL, at least 700 ng/mL, at least 720 ng/mL, or at least 740 ng/mL.

[0050] In one example, CAL-101 is administered at an amount to reach is administered at an amount to reach Cmaxss at about 1000 ng/mL to about 5000 ng/mL, about 1000 ng/mL to about 4000 ng/mL, about 1000 ng/mL to about 3000 ng/mL, about 1000 ng/mL to about 2500 ng/mL, or about 1400 ng/mL to about 2200 ng/mL; and obinutuzumab is administered at an amount to reach Cmaxss at about 100 ng/mL to about 1000 ng/mL, about 250 ng/mL to about 1000 ng/mL, about 500 ng/mL to about 1000 ng/mL, about 600 ng/mL to about 1000 ng/mL,

about 700 ng/mL to about 1000 ng/mL, about 740 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 900 ng/mL, or about 750 ng/mL to about 800 ng/mL.

[0051] In one example, CAL-101 is administered at an amount to reach is administered at an amount to reach Cmaxss at about 1000 ng/mL to about 2500 ng/mL, 1500 ng/mL to about 2500, or about 2000 ng/mL to about 2500 ng/mL. In one example, CAL-101 is administered at an amount to reach is administered at an amount to reach Cmaxss at about 2200 ng/mL. In one example, the Cmaxss is at least 1000 ng/mL, at least 1500 ng/mL, at least 1750 ng/mL, at least 2000 ng/mL, at least 2100 ng/mL, at least 2150 ng/mL, at least 2175 ng/mL, or at least 2200 ng/mL. In one example, obinutuzumab is administered at an amount to reach Cmaxss at about 750 ng/mL to about 900 ng/mL, about 750 ng/mL to about 850 ng/mL, or about 750 ng/mL to about 800 ng/mL. In one example, obinutuzumab is administered at an amount to reach Cmaxss at about 741 ng/mL. In one example, Cmaxss is at least 200 ng/mL, at least 500 ng/mL, at least 600 ng/mL, at least 700 ng/mL, at least 720 ng/mL, or at least 740 ng/mL.

[0052] In one example, Compound 292 is administered at an amount to reach an AUCss at about 5000 ng/mL*hr to about 10000 ng/mL*hr, about 5000 ng/mL*hr to about 9000 ng/mL*hr, about 6000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr, about 7500 ng/mL*hr, about 8000 ng/mL*hr, about 8500 ng/mL*hr , about 8600 ng/mL*hr, about 8700 ng/mL*hr, or about 8800 ng/mL*hr; and obinutuzumab is administered at an amount to reach an AUCss at about 1000 ng/mL*hr to about 5000 ng/mL*hr, about 2000 ng/mL*hr to about 5000 ng/mL*hr, about 3000 ng/mL*hr to about 5000 ng/mL*hr, about 4000 ng/mL*hr to about 5000 ng/mL*hr, or about 4000 ng/mL*hr to about 4500 ng/mL*hr.

[0053] In one example, Compound 292 is administered at an amount to reach an AUCss at about 7000 ng/mL*hr to about 9000 ng/mL*hr or about 8000 ng/mL*hr to about 8500 ng/mL*hr. In one example, Compound 292 is administered at an amount to reach an AUCss at about 8600 ng/mL*hr, about 8700 ng/mL*hr, or about 8800 ng/mL*hr. In one example, Compound 292 is administered at an amount to reach an AUCss at about 8787 ng/mL*hr. In one example, obinutuzumab is administered at an amount to reach an AUCss at about 3000 ng/mL*hr to about 5000 ng/mL*hr, about 4000 ng/mL*hr to about 5000 ng/mL*hr, or about 4000 ng/mL*hr to about 4500 ng/mL*hr. In one example, obinutuzumab is administered at an amount to reach an AUCss at about 4044 ng/mL*hr.

[0054] In one example, CAL-101 is administered at an amount to reach an AUCss at about 5000 ng/mL*hr to about 10000 ng/mL*hr, about 5000 ng/mL*hr to about 9000 ng/mL*hr, about 6000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr, about 7500 ng/mL*hr, about 8000 ng/mL*hr, about 8500 ng/mL*hr , about 8600 ng/mL*hr, about 8700 ng/mL*hr, or about 8800 ng/mL*hr; and obinutuzumab is administered at an amount to reach an AUCss at about 1000 ng/mL*hr to about 5000 ng/mL*hr, about 2000 ng/mL*hr to about 5000 ng/mL*hr, about 3000 ng/mL*hr to about 5000 ng/mL*hr, about 4000 ng/mL*hr to about 5000 ng/mL*hr, or about 4000 ng/mL*hr to about 4500 ng/mL*hr.

[0055] In one example, CAL-101 is administered at an amount to reach AUCss at about 6000 ng/mL*hr to about 9000 ng/mL*hr, about 6000 ng/mL*hr to about 8000 ng/mL*hr, about 6000 ng/mL*hr to about 7500

ng/mL*hr, or about 6500 ng/mL*hr to about 7500 ng/mL*hr. In one example, CAL-101 is administered at an amount to reach AUCss at about 7000 ng/mL*hr. In one example, obinutuzumab is administered at an amount to reach an AUCss at about 3000 ng/mL*hr to about 5000 ng/mL*hr, about 4000 ng/mL*hr to about 5000 ng/mL*hr, or about 4000 ng/mL*hr to about 4500 ng/mL*hr. In one example, obinutuzumab is administered at an amount to reach an AUCss at about 4044 ng/mL*hr.

[0056] In one example, the cancer or hematologic malignancy is CLL, Waldenström macroglobulinemia (WM), mantle cell, NHL, iNHL, diffuse large B-cell lymphoma, or T-cell lymphoma. In another example, the cancer or hematologic malignancy is follicular lymphoma.

[0057] In one example, provided herein is a method of treating or preventing a specific cancer or disease, such as, a hematologic malignancy (*e.g.*, a specific type, or a specific sub-type, of hematologic malignancy), which has a high expression level of one or more isoform(s) of PI3K, wherein the method comprises: (1) determining the expression level of one or more PI3K isoform(s) in the cancer or disease; (2) selecting a treatment agent (*e.g.*, a PI3K modulator having a particular selectivity profile for one or more PI3K isoform(s)), based on the expression levels of PI3K isoforms in the cancer or disease to be treated; and (3) administering the treatment agent to a patient having the cancer or disease, alone or in combination with one or more other agents or therapeutic modalities. In one example, the expression level of one or more PI3K isoform(s) in the cancer or disease can be measured by determining the expression level of PI3K isoform protein, DNA, and/or RNA; or by measuring one or more biomarkers provided herein (*e.g.*, a signaling pathway biomarker, a protein mutation biomarker, a protein expression biomarker, a gene mutation biomarker, a gene expression biomarker, a cytokine biomarker, a chemokine biomarker, or a biomarker for particular cancer cells, among others). In other examples, the expression level of one or more PI3K isoform(s) in the cancer or disease can be determined based on information known in the art or information obtained in prior studies on the cancer or disease.

[0058] Certain cancer or disorder, *e.g.*, a hematologic malignancy (*e.g.*, a specific type, or a specific sub-type, of hematologic malignancy), can exhibit heterogeneity in PI3K isoform expression among patient populations. In one example, provided herein is a method of treating or preventing a specific patient or group of patients, having a cancer or disease, such as, a hematologic malignancy, wherein the method comprises: (1) determining the expression levels of one or more PI3K isoform(s) in the patient or group of patients having the cancer or disease; (2) selecting a treatment agent (*e.g.*, a PI3K modulator having a particular selectivity profile for one or more PI3K isoform(s)) based on the expression levels of PI3K isoforms in the patient(s) to be treated; and (3) administering the treatment agent to the patient(s), alone or in combination with one or more other agents or therapeutic modalities. In one example, the expression level of one or more PI3K isoform(s) in the patient or group of patients can be measured by determining the expression level of PI3K isoform protein, DNA, and/or RNA in the patient or group of patients; or by measuring one or more biomarkers provided herein in the patient or group of patients (*e.g.*, a signaling pathway biomarker, a protein mutation biomarker, a protein expression biomarker, a gene mutation biomarker, a gene expression biomarker, a cytokine biomarker, a chemokine biomarker, or a biomarker for

particular cancer cells, among others). In other examples, the expression level of one or more PI3K isoform(s) in the patient or group of patients can be determined based on information known in the art or information obtained in prior testing of the patient or group of patient(s).

[0059] In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-δ over the other isoforms of PI3K. In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-γ over the other isoforms of PI3K. In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-δ and PI3K-γ over the other isoforms of PI3K. In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-γ and PI3K-α over the other isoforms of PI3K. In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-γ and PI3K-β over the other isoforms of PI3K. In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-δ and PI3K-α over the other isoforms of PI3K. In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-δ and PI3K-β over the other isoforms of PI3K. In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-δ, PI3K-γ, and PI3K-α over other isoform of PI3K. In specific examples, the methods, compositions and kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective toward PI3K-δ, PI3K-γ, and PI3K-β over other isoform of PI3K.

[0060] In one example, the methods, compositions, or kits provided herein relate to administering a PI3K modulator, alone or in combination with one or more other agents or therapeutic modalities, to a subject, *e.g.*, a mammalian subject, *e.g.*, a human; wherein the PI3K modulator is selective for one or more PI3K isoform(s) over

other isoforms of PI3K (*e.g.*, PI3K-δ selective, PI3K-γ selective, or PI3K-δ and PI3K-γ selective); and the subject being treated has a high expression level of the particular PI3K isoform(s) (*e.g.*, high expression of PI3K-δ, high expression of PI3K-γ, or high expression of both PI3K-δ and PI3K-γ). Without being limited to a particular theory, the methods, compositions, or kits provided herein can provide reduced side effects and/or improved efficacy. Thus, in one example, provided herein is a method of treating or preventing a cancer or disease, such as hematologic malignancy, or a specific type or sub-type of cancer or disease, such as a specific type or sub-type of hematologic malignancy, having a high expression level of one or more isoform(s) of PI3K, wherein the adverse effects associated with administration of PI3K inhibitors are reduced.

[0061] In one example, provided herein is a method of treating or preventing a cancer or disease, such as hematologic malignancy, or a specific type or sub-type of cancer or disease, such as a specific type or sub-type of hematologic malignancy, with a PI3K-γ selective inhibitor, wherein the adverse effects associated with administration of inhibitors for other isoform(s) of PI3K (*e.g.*, PI3K-α or PI3K-β) are reduced. In one example, provided herein is a method of treating or preventing a cancer or disease, such as hematologic malignancy, or a specific type or sub-type of cancer or disease, such as a specific type or sub-type of hematologic malignancy, with a PI3K-γ selective inhibitor, at a lower (*e.g.*, by about 10%, by about 20%, by about 30%, by about 40%, by about 50%, by about 60%, by about 70%, or by about 80%) dose as compared to treatment with a PI3K-γ non-selective or less selective inhibitor (*e.g.*, a PI3K pan inhibitor (*e.g.*, PI3K-α, β, γ, δ)).

[0062] In one example, the methods, compositions, or kits provided herein relate to administering a PI3K modulator, in combination with one or more second active agent(s), *e.g.*, one or more cancer therapeutic agent(s). In one example, the second active agents that can be used in the methods, compositions, or kits provided herein include, but are not limited to, one or more of: a BTK inhibitor, such as, *e.g.*, ibrutinib, RN-486 (6-cyclopropyl-8-fluoro-2-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-2H-isoquinolin-1-one), GDC-0834 ([R-N-(3-(6-(4-(1,4-dimethyl-3-oxopiperazin-2-yl) phenylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide]), CGI-560 (N-[3-(8-anilinoimidazo[1,2-a]pyrazin-6-yl)phenyl]-4-tert-butylbenzamide), CGI-1746 (4-(tert-butyl)-N-(2-methyl-3-(4-methyl-6-((4-(morpholine-4-carbonyl)phenyl)amino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide), HM-71224(Hammi Pharmaceticals), ONO-4059 (Ono Pharmaceuticals Co., LTD), CNX-774 (4-(4-((4-((3-acrylamidophenyl)amino)-5-fluoropyrimidin-2-yl)amino)phenoxy)-N-methylpicolinamide), LFM-A13 (2Z-cyano-N-(2,5-dibromophenyl)3-hydroxy-2-butenamide) and AVL-292 (N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide), which can also be referred to as CC-292 ; an HDAC inhibitor, such as, *e.g.*, belinostat, vorinostat, panobinostat, or romidepsin; an mTOR inhibitor, such as, *e.g.,* everolimus (RAD 001); a proteasome inhibitor, such as, *e.g.*, bortezomib or carfilzomib; a JAK inhibitor or a JAK/STAT inhibitor, such as, *e.g.*, Tofacitinib, INCB16562, or AZD1480; a BCL-2 inhibitor, such as, *e.g.*, ABT-737, ABT-263, or Navitoclax; a MEK inhibitor, such as, *e.g.*, AZD8330 or ARRY-424704; an anti-folate, such as, *e.g.*, pralatrexate; a farnesyl transferase inhibitor, such as, *e.g.*, tipifarnib; an antibody or a biologic agent, such as,

e.g., obinutuzumab (GA101), alemtuzumab, rituximab, ofatumumab, or brentuximab vedotin (SGN-035); an antibody-drug conjugate, such as, *e.g.*, inotuzumab ozogamicin, or brentuximab vedotin; a cytotoxic agent, such as, *e.g.*, bendamustine, gemcitabine, oxaliplatin, cyclophosphamide, vincristine, vinblastine, anthracycline (*e.g.*, daunorubicin or daunomycin, doxorubicin, or actinomycin or dactinomycin), bleomycin, clofarabine, nelarabine, cladribine, asparaginase, methotrexate, or pralatrexate; or other anti-cancer agents or chemotherapeutic agents, such as, *e.g.*, fludarabine, ibrutinib, fostamatinib, lenalidomide, thalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, or R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin or Hydroxydaunomycin, Vincristine or Oncovin, Prednisone). Additional examples of second active agents are provided herein elsewhere.

[0063] Without being limited by a particular theory, in one example, the cancer or disease being treated or prevented, such as a blood disorder or hematologic malignancy, has a high expression level of one or more PI3K isoform(s) (*e.g.*, PI3K-α, PI3K-β, PI3K-δ, or PI3K-γ, or a combination thereof). In one example, the cancer or disease that can be treated or prevented by methods, compositions, or kits provided herein includes a blood disorder or a hematologic malignancy, including, but not limited to, myeloid disorder, lymphoid disorder, leukemia, lymphoma, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), mast cell disorder, and myeloma (*e.g.*, multiple myeloma), among others. In one example, the blood disorder or the hematologic malignancy includes, but is not limited to, acute lymphoblastic leukemia (ALL), T-cell ALL (T-ALL), B-cell ALL (B-ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), blast phase CML, small lymphocytic lymphoma (SLL), CLL/SLL, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), B-cell NHL, T-cell NHL, indolent NHL (iNHL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), aggressive B-cell NHL, B-cell lymphoma (BCL), Richter's syndrome (RS), T-cell lymphoma (TCL), peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), transformed mycosis fungoides, Sézary syndrome, anaplastic large-cell lymphoma (ALCL), follicular lymphoma (FL), Waldenström macroglobulinemia (WM), lymphoplasmacytic lymphoma, Burkitt lymphoma, multiple myeloma (MM), amyloidosis, MPD, essential thrombocytosis (ET), myelofibrosis (MF), polycythemia vera (PV), chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome (MDS), high-risk MDS, and low-risk MDS. In one example, the hematologic malignancy is relapsed. In one example, the hematologic malignancy is refractory. In one example, the cancer or disease is in a pediatric patient (including an infantile patient). In one example, the cancer or disease is in an adult patient. Additional examples of a cancer or disease being treated or prevented by methods, compositions, or kits provided herein are described herein elsewhere.

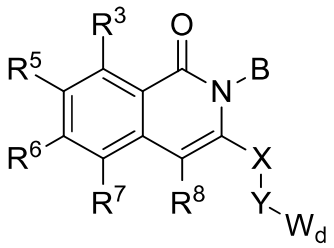
[0064] In one example, the cancer or disease being treated or prevented, such as a blood disorder or hematologic malignancy, has a high expression level of PI3K-δ and/or PI3K-γ, which includes, but is not limited to, CLL, CLL/SLL, blast phase CLL, CML, DLBCL, MCL, B-ALL, T-ALL, multiple myeloma, B-cell lymphoma, CTCL (*e.g.*, mycosis fungoides or Sézary syndrome), AML, Burkitt lymphoma, follicular lymphoma (FL), Hodgkin lymphoma, ALCL, or MDS.

[0065] In one example, provided herein is a PI3K modulator, as a single agent or in combination with one or more additional therapies, for use in a method, composition, or kit provided herein, to ameliorate cancer or hematologic disease, such as a hematologic malignancy (*e.g.*, by decreasing one or more symptoms associated with the cancer or hematologic disease) in a subject, *e.g.*, a mammalian subject. Symptoms of cancer or hematologic disease that can be ameliorated include any one or combination of symptoms of cancer or hematologic disease, as known the art and/or as disclosed herein. Experimental conditions for evaluating the effects of a PI3K modulator in ameliorating cancer or hematologic disease in animal models of cancer or hematologic disease are provided herein or are known in the art.

[0066] In one example, provided herein is a method of reducing a symptom associated with cancer or hematologic disease, such as a hematologic malignancy, in a biological sample, comprising contacting the biological sample with a PI3K modulator, *e.g.*, a compound provided herein (*e.g.*, a compound of Formula I, *e.g.*, Compound 292) or a pharmaceutically acceptable form thereof (*e.g.*, an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof), in an amount sufficient to reduce the symptom associated with cancer or hematologic disease.

[0067] In one example, provided herein is a method of treating or preventing cancer or hematologic disease (*e.g.*, a hematologic malignancy) in a subject, comprising administering an effective amount of a PI3K modulator, *e.g.*, a compound provided herein (*e.g.*, a compound of Formula I, *e.g.*, Compound 292), or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

[0068] In one example, the compound is a compound of Formula I, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof:

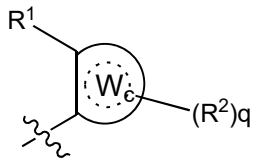


Formula I

wherein

W_d is heterocycloalkyl, aryl or heteroaryl;

B is alkyl or a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4;

X is absent or –$(CH(R^9))_z$–, and z is an integer of 1;

Y is absent, or -$N(R^9)$-;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy, or nitro;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy, or nitro;

R^5, R^6, R^7, and R^8 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy, or nitro; and

each instance of R^9 is independently hydrogen, alkyl, cycloalkyl, or heterocycloalkyl.

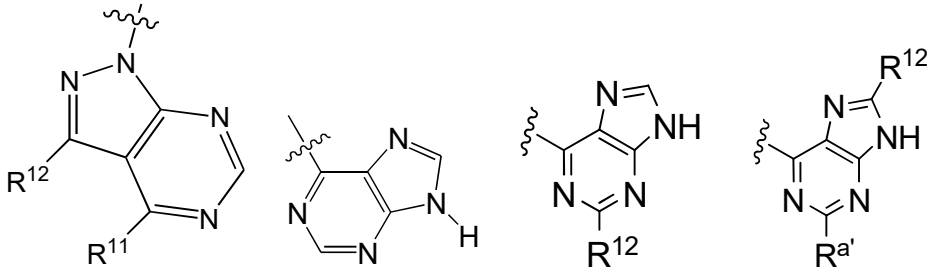
[0069] In some examples, when both X and Y are present then Y is –NH–.

[0070] In some examples, X is absent or is –$(CH(R^9))_z$–, and z is independently an integer of 1, 2, 3, or 4; and Y is absent, -O-, -S-, -S(=O)-, -$S(=O)_2$-, -$N(R^9)$-, -C(=O)-$(CHR^9)_z$-, -C(=O)-, -$N(R^9)$(C=O)-, -$N(R^9)$(C=O)NH-, or-$N(R^9)C(R^9)_2$-.

[0071] In some examples, -X- is -CH_2-, -$CH(CH_2CH_3)$-, or -$CH(CH_3)$-.

[0072] In some examples, -X-Y- is -CH_2-$N(CH_3)$-, -CH_2-$N(CH_2CH_3)$-, -$CH(CH_2CH_3)$-NH-, or -$CH(CH_3)$-NH-.

[0073] In some examples, W_d is a pyrazolopyrimidine of Formula III(a), or a purine of Formula III(b), Formula III(c) or Formula III(d):

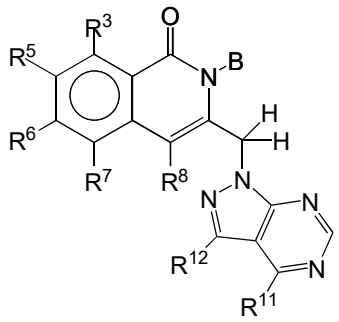


Formula III(a) Formula III(b) Formula III(c) Formula III(d)

wherein $R^{a'}$ of Formula III(d) is hydrogen, halo, phosphate, urea, a carbonate, amino, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl; R^{11} of Formula III(a) is H, alkyl, halo, amino, amido, hydroxy, or alkoxy; and R^{12} of Formula III(a), Formula III(c) or Formula III(d) is H, alkyl, alkynyl, alkenyl, halo, aryl,

heteroaryl, heterocycloalkyl, or cycloalkyl. In some examples, W_d is a pyrazolopyrimidine of Formula III(a), wherein R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is cyano, amino, carboxylic acid, or amido.

[0074] In some examples, a compound of Formula I has the structure of Formula IV:

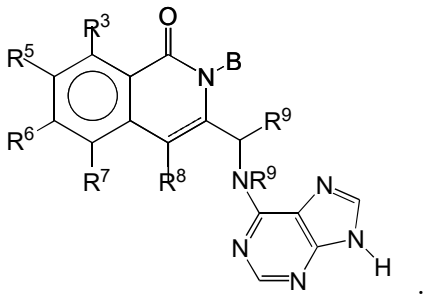


Formula IV

wherein R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In some examples, the compound of Formula I has the structure of Formula IV wherein R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is cyano, amino, carboxylic acid, or amido.

[0075] In some examples, R^{11} is amino. In some examples, R^{12} is alkyl, alkenyl, alkynyl, heteroaryl, aryl, or heterocycloalkyl. In some examples, R^{12} is cyano, amino, carboxylic acid, amido, monocyclic heteroaryl, or bicyclic heteroaryl.

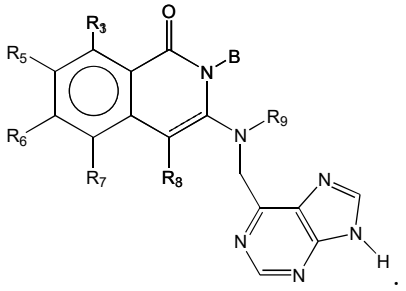
[0076] In some examples of a compound of Formula I, the compound has the structure of Formula V:



Formula V

[0077] In some examples, $-NR^9-$ is $-N(CH_2CH_3)CH_2-$ or $-N(CH_3)CH_2-$.

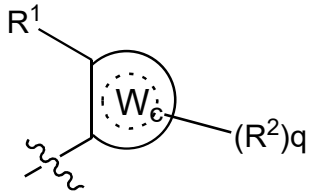
[0078] In some examples of a compound of Formula I, the compound has a structure of Formula VI:



Formula VI

[0079] In some examples, R^3 is -H, -CH_3, -Cl, or -F, and R^5, R^6, R^7, and R^8 are independently hydrogen.

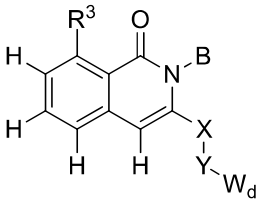
[0080] In some examples, B is a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4.

[0081] In one example, the PI3 kinase modulator is a compound, or a pharmaceutically acceptable salt thereof, having the structure of Formula I-1:



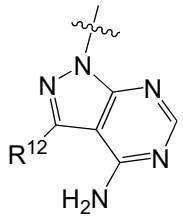
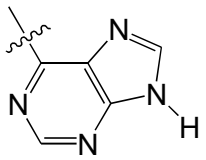
Formula I-1

wherein B is a moiety of Formula II;

wherein W_c in B is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4;

X is absent or $-(CH(R^9))_z-$, and z is an integer of 1;

Y is absent, or -$N(R^9)$-;

when Y is absent, W_d is:  , or when Y is present, W_d is:  ;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

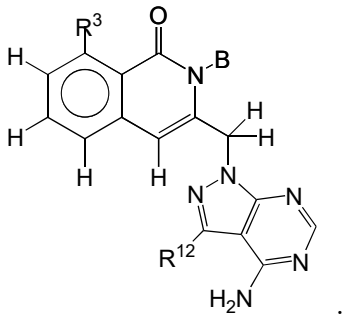
R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy, or nitro;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy, or nitro;

each instance of R^9 is independently hydrogen, C_1-C_{10} alkyl, cycloalkyl, or heterocycloalkyl; and

R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

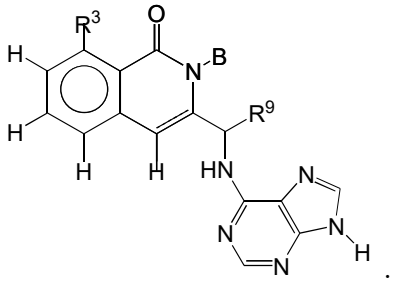
[0082] In some examples, a compound of Formula I or Formula I-1 has the structure of Formula IV-A:



Formula IV-A

[0083] In some examples, R^{12} is substituted benzoxazole.

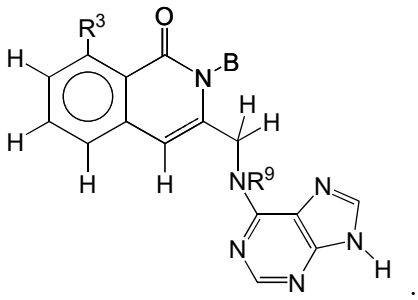
[0084] In some examples, a compound of Formula I or Formula I-1 has the structure of Formula V-A:



Formula V-A

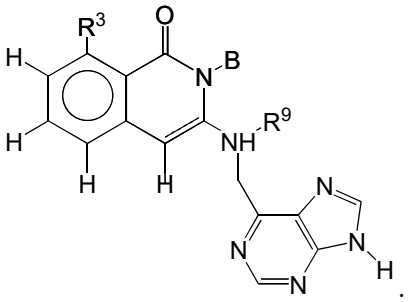
[0085] In some examples, a compound of Formula I or Formula I-1 has the structure of Formula IV-A or Formula V-A.

[0086] In some examples, a compound of Formula I or Formula I-1 has the structure of Formula V-B:



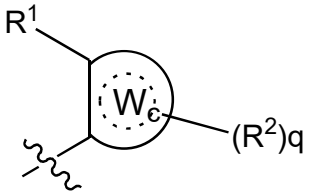
Formula V-B

[0087] In some examples, a compound of Formula I or Formula I-1 has the structure of Formula VI-A:



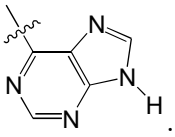
Formula VI-A

[0088] In some examples, a compound of Formula I or Formula I-1 is a compound wherein B is a moiety of Formula II:



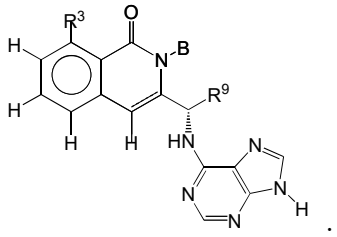
Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; q is an integer of 0 or 1; R^1 is hydrogen, alkyl, or halo; R^2 is alkyl or halo; and R^3 is hydrogen, alkyl, or halo. In some examples, when both X and Y are present then Y is –NH–. In other examples, R^3 is -H, -CH_3, -CH_2CH_3, -CF_3, -Cl or -F. In other examples, R^3 is methyl or chloro.

[0089] In some examples, X is –$(CH(R^9))_z$–, wherein R^9 is methyl and z is 1; and W_d is .

[0090] In some examples of a compound of Formula I or Formula I-1, the compound is predominately in an (S)- stereochemical configuration.

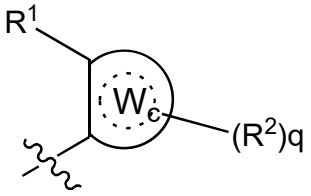
[0091] In some examples of a compound of Formula I or Formula I-1, the compound has a structure of Formula V-A2:



Formula V-A2

[0092] In some examples, R^{12} is a monocyclic heteroaryl, bicyclic heteroaryl, or heterocycloalkyl.

[0093] In some examples, B is a moiety of Formula II:



Formula II

wherein W_c is aryl or cycloalkyl.

[0094] In some examples, the compound of Formula I is a polymorph Form C of Compound 292 as disclosed herein.

[0095] In some examples, the compound inhibits or reduces the activity of a class I PI3K. In certain examples, the class I PI3K is p110 α, p110 β, p110 γ, or p110 δ.

[0096] In some examples, the compound inhibits one or more class I PI3K isoforms selected from the group consisting of PI3 kinase-α, PI3 kinase-β, PI3 kinase-γ, and PI3 kinase-δ.

[0097] In some examples, the compound selectively inhibits a class I PI3 kinase-δ isoform, as compared with other class I PI3 kinase isoforms. In some examples, the compound selectively inhibits a class I PI3 kinase-γ isoform, as compared with other class I PI3 kinase isoforms. In some examples, the compound selectively inhibits a class I PI3 kinase-δ and a PI3 kinase-γ isoform, as compared with other class I PI3 kinase isoforms.

[0098] In some examples, a pharmaceutical composition is used, wherein the composition comprises a pharmaceutically acceptable excipient and one or more compounds of any formulae provided herein, including but not limited to Formula I, I-1, and IV to XVIII (including IV-A, V, V-A, V-A2, V-B, VI, and VI-A, among others). In some examples, the composition is a liquid, solid, semi-solid, gel, or an aerosol form.

[0099] In some examples, two or more PI3K modulators (*e.g.*, two or more PI3K modulators described herein) are administered in combination. In one example, the PI3K modulators are administered concurrently. In another example the modulators are administered sequentially. For example, a combination of *e.g.*, Compound 292 and a second PI3K modulator, can be administered concurrently or sequentially. In one example, the second PI3K modulator, is administered first, followed, with or without a period of overlap, by administration of Compound 292. In another example, Compound 292 is administered first, followed, with or without a period of overlap, by administration of the second PI3K modulator.

[00100] In other examples, a PI3K modulator (*e.g.*, one or more PI3K modulators described herein) are administered in combination with one or more than one additional therapeutic agent, such as a cancer therapeutic agent described herein. In one example, the PI3K modulator and the second agent are administered concurrently. In another example the PI3K modulator and the second agent are administered sequentially. For example, a combination of *e.g.*, Compound 292 and a second agent, can be administered concurrently or sequentially. In one example, the second agent, is administered first, followed, with or without a period of overlap, by administration of

Compound 292. In another example, Compound 292 is administered first, followed, with or without a period of overlap, by administration of the second agent.

[00101] In one example, the subject treated is a mammal, *e.g.*, a primate, typically a human (*e.g.*, a patient having, or at risk of having, cancer or hematologic disorder, such as hematologic malignancy, as described herein). In some examples, the subject treated is in need of PI3 kinase inhibition (*e.g.*, has been evaluated to show elevated PI3K levels or alterations in another component of the PI3K pathway). In one example, the subject previously received other treatment (*e.g.*, a treatment for cancer or a treatment for hematologic disorder).

[00102] In some examples, the PI3K modulator is administered as a pharmaceutical composition comprising the PI3K modulator, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00103] In certain examples, the PI3K modulator is administered or is present in the composition, *e.g.*, the pharmaceutical composition.

[00104] The PI3K modulators described herein can be administered to the subject systemically (*e.g.*, orally, parenterally, subcutaneously, intravenously, rectally, intramuscularly, intraperitoneally, intranasally, transdermally, or by inhalation or intracavitary installation). Typically, the PI3K modulators are administered orally.

[00105] In one example, the PI3K modulator is Compound 292, as disclosed in Table 4, or a pharmaceutically acceptable salt thereof. Compound 292, or a pharmaceutically acceptable salt thereof, can be administered orally. Other routes of administration are also provided herein.

[00106] The methods and compositions provided herein can, optionally, be used in combination with other therapies (*e.g.*, one or more agents, surgical procedures, or radiation procedures). Any combination of one or more PI3K modulator(s) and one or more other agents or therapies can be used. The PI3K modulator(s) and other therapies can be administered before treatment, concurrently with treatment, post-treatment, or during remission of the disease. In one example, a second agent is administered simultaneously or sequentially with the PI3K modulator.

[00107] In one example, provided herein is a biomarker (*e.g.*, a diagnostic biomarker, a predictive biomarker, or a prognostic biomarker), for use in treating or preventing a cancer or disease (*e.g.*, a hematologic malignancy) described herein. In one example, the biomarker provided herein include, but are not limited to: a target biomarker, a signaling pathway biomarker, a protein mutation biomarker, a protein expression biomarker, a gene mutation biomarker, a gene expression biomarker, a cytokine biomarker, a chemokine biomarker, or a biomarker for particular cancer cells. In one example, the biomarker can be used to evaluate a particular type of cancer or disease, or a particular patient or group of patients. In one example, the biomarker involves immunohistochemistry (IHC) of a particular protein target. In one example, the biomarker involves the RNA (*e.g.*, mRNA) (*e.g.*, in situ hybridization (ISH) of mRNA) of a particular protein target. In one example, the biomarker involves the DNA of a particular protein target, including genetic alteration such as somatic mutation, copy number

alterations such as amplification or deletion, and chromosomal translocation as well as epigenetic alteration such as methylation and histone modification. In one example, the biomarker involves micro-RNA (miRNA) which regulates expression of a particular protein target. In one example, the biomarker involves measurement of a protein/protein modification. In one example, the biomarker involves measurement of a non-protein marker, such as, *e.g.*, metabolomics. In one example, the biomarker is measured by ELISA, western blot, or mass spectroscopy. In one example, the biomarker is a serum biomarker. In one example, the biomarker is a blood biomarker. In one example, the biomarker is a bone marrow biomarker. In one example, the biomarker is a sputum biomarker. In one example, the biomarker is a urine biomarker. In one example, the biomarker involves bio-matrixes, including, but not limited to, serum, blood, bone marrow, sputum, or urine.

[00108] In exemplary examples, the biomarker provided herein is a target biomarker, such as, *e.g.*, a biomarker to determine the protein and/or RNA expression of one or more particular PI3K isoform; *e.g.*, a biomarker for PI3K-α expression, for PI3K-β expression, for PI3K-δ expression, or for PI3K-γ expression, or combinations thereof. In other examples, the biomarker could be DNA alteration of one or more particular PI3K isoforms (*e.g.*, mutation, copy number variation, or epigenetic modification).

[00109] In exemplary examples, the biomarker provided herein is a signaling pathway biomarker, such as, *e.g.*, a PTEN pathway biomarker and/or a biomarker of signaling pathway activation such as pAKT, pS6, and/or pPRAS40 (*e.g.*, an IHC biomarker, a DNA alteration biomarker, a DNA deletion biomarker, or a DNA mutation biomarker). In exemplary examples, the biomarker provided herein is a mutation biomarker, such as, a protein mutation biomarker or a gene mutation biomarker, to assess the mutation of one or more targets, such as, *e.g.*, IGH7, KRAS, NRAS, A20, CARD11, CD79B, TP53, CARD11, MYD88, GNA13, MEF2B, TNFRSF14, MLL2, BTG1, EZH2, NOTCH1, JAK1, JAK2, PTEN, FBW7, PHF6, IDH1, IDH2, TET2, FLT3, KIT, NPM1, CEBPA, DNMT3A, BAALC, RUNX1, ASXL1, IRF8, POU2F2, WIF1, ARID1A, MEF2B, TNFAIP3, PIK3R1, MTOR, PIK3CA, PI3Kδ, and/or PI3Kγ. In exemplary examples, the biomarker provided herein is an expression biomarker, such as, a protein expression biomarker, a gene expression biomarker, to assess the expression of one or more targets, or the upregulation or downregulation of a pathway, such as, *e.g.*, pERK IHC biomarker or pERK expression biomarker, for example, to assess RAS or PI3K pathway activation.

[00110] In exemplary examples, the biomarker provided herein is a cytokine biomarker (*e.g.*, serum cytokine biomarkers or other cytokine biomarkers provided herein). In exemplary examples, the biomarker provided herein is a chemokine biomarker (*e.g.*, serum chemokine biomarkers or other chemokine biomarkers provided herein).

[00111] In exemplary examples, the biomarker provided herein is a biomarker for cancer cells (*e.g.*, a particular cancer cell line, a particular cancer cell type, a particular cell cycle profile).

[00112] In exemplary examples, the biomarker provided herein relates to gene expression profiling of a patient or group of patients, *e.g.*, as a predictive biomarker for PI3Kδ and/or PI3Kγ pathway activation, or as a predictive biomarker for response to a treatment described herein. In exemplary examples, the biomarker provided

herein relates to a gene expression classifier, *e.g.*, as a predictive biomarker for PI3Kδ and/or PI3Kγ expression or activation (*e.g.*, differential expression or activation in the ABC, GCB, oxidative phosphorylation (Ox Phos), B-cell receptor/proliferation (BCR), or host response (HR) subtypes of DLBCL).

[00113] In one example, the methods provided herein can further include the step of evaluating a subject, *e.g.*, for one or more signs or symptoms or biological concomitants of cancer or hematologic disorder, as disclosed herein, *e.g.*, evaluate a biomarker described herein in the subject. In some examples, one or more of these biological concomitants or biomarkers correlate with improved likelihood of response of a subject to a particular therapy. In some examples, one or more of these biological concomitants or biomarkers correlate with reduced side effect in a subject to a particular therapy.

[00114] In one example, the methods provided herein can further include the step of monitoring the subject, *e.g.*, for a change (*e.g.*, an increase or decrease) in levels of one or more signs or symptoms or biological concomitants of cancer or hematologic disorder, as disclosed herein, *e.g.*, a biomarker described herein. In some examples, one or more of these biological concomitants or biomarkers correlate with a decrease in one or more clinical symptoms associated with cancer or hematologic disorder. In some examples, one or more of these biological concomitants or biomarkers correlate with improved likelihood of response in a subject to a particular therapy. In some examples, one or more of these biological concomitants or biomarkers correlate with reduced side effect in a subject to a particular therapy.

[00115] In some examples, a normalization or change (*e.g.*, a decrease in an elevated level or increase in a diminished level) of a biological concomitant or biomarker is indicative of treatment efficacy and/or is predictive of improvement in clinical symptoms. In some examples, the subject is monitored for a change in a biological concomitant or biomarker (*e.g.*, a decrease or increase of a biological concomitant or biomarker, which can be indicative of treatment efficacy).

[00116] In one example, the subject can be evaluated or monitored in one or more of the following periods: prior to beginning of treatment; during the treatment; or after one or more elements of the treatment have been administered. Evaluation and monitoring can be used to determine the need for further treatment with the same PI3K modulator, alone or in combination with, another agent, or for additional treatment with additional agents, or for adjusted dosing regimen of the same PI3K modulator.

[00117] In one example, the methods provided herein can further include the step of analyzing a nucleic acid or protein from the subject, *e.g.*, analyzing the genotype of the subject. In one example, a PI3K protein, or a nucleic acid encoding a PI3K protein, and/or an upstream or downstream component(s) of a PI3K signaling pathway is analyzed. The nucleic acid or protein can be detected in any biological sample (*e.g.*, blood, urine, circulating cells, a tissue biopsy or a bone marrow biopsy) using any method disclosed herein or known in the art. For example, the PI3K protein can be detected by systemic administration of a labeled form of an antibody to PI3K followed by imaging.

[00118] The analysis can be used, *e.g.*, to evaluate the suitability of, or to choose between alternative treatments, *e.g.*, a particular dosage, mode of delivery, time of delivery, inclusion of adjunctive therapy, *e.g.*, administration in combination with a second agent, or generally to determine the subject's probable drug response phenotype or genotype. The nucleic acid or protein can be analyzed at any stage of treatment. In one example, the nucleic acid or protein can be analyzed at least prior to administration of the PI3K modulator and/or agent, to thereby determine appropriate dosage(s) and treatment regimen(s) of the PI3K modulator (*e.g.*, amount per treatment or frequency of treatments) for prophylactic or therapeutic treatment of the subject.

[00119] In certain examples, the methods provided herein further include the step of detecting an altered PI3K level in a patient, prior to, or after, administering a PI3K modulator to the patient. The PI3K level can be assessed in any biological sample, *e.g.*, blood, urine, circulating cells, or a tissue biopsy. In some examples, the PI3K level is assessed by systemic administration of a labeled form of an antibody to PI3K followed by imaging.

[00120] In another example, provided herein is a composition, *e.g.*, a pharmaceutical composition, that includes one or more PI3K modulators, *e.g.*, a PI3K modulator as described herein, and one or more agents (*e.g.*, a second active agent as disclosed herein). The composition can further include a pharmaceutically-acceptable carrier or excipient.

[00121] In another example, provided herein is a composition for use, or the use, of a PI3K modulator, alone or in combination with a second agent or a therapeutic modality described herein for the treatment of a cancer or disorder, such as a hematologic malignancy, as described herein.

[00122] In another example, provided herein are therapeutic kits that include a PI3K modulator, alone or in combination with one or more additional agents, and instructions for use in the treatment of a cancer or disorder, such as a hematologic malignancy, as described herein.

INCORPORATION BY REFERENCE

[00123] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference in their entirety and to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[00124] **FIG. 1** depicts the PK/PD relationship of mean drug plasma concentration and mean % reduction from pre-dose for basophil activation over time, following single dose administration of Compound 292 in human.

[00125] **FIG. 2** depicts the PK/PD relationship of mean drug plasma concentration and mean % reduction from pre-dose for basophil activation over time, following multiple dose administration of Compound 292 in human.

[00126] **FIG. 3** depicts the pharmacodynamic response versus concentration of Compound 292 in human.

[00127] **FIG. 4** depicts the steady state (C2D1) plasma concentrations over time after administration of Compound 292 in human.

[00128] **FIG. 5** depicts AKT phosphorylation in CLL/SLL cells of Compound 292.

[00129] **FIG. 6** depicts changes in tumor size after administration of Compound 292 in human.

[00130] **FIG. 7** depicts rapid onset of clinical activity of Compound 292 in CLL/SLL patients.

[00131] **FIG. 8** depicts clinical activity of Compound 292 in T-cell lymphoma patients.

[00132] **FIG. 9** depicts clinical activity of Compound 292 in a T-cell lymphoma patient.

[00133] **FIG. 10** depicts percent changes in measurable disease in patients with peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma.

[00134] **FIG. 11** depicts percent changes in measurable disease in patients with aggressive NHL (aNHL), Hodgkin's lymphoma and mantle cell lymphoma (MCL).

[00135] **FIG. 12** depicts percent changes in measurable disease in patients with indolent NHL (iNHL). iNHL patients included patients with follicular lymphoma, Waldenstrom macroglobulinemia (lymphoplasmacytic lymphoma) and marginal zone lymphoma (MZL).

[00136] **FIG. 13** depicts months on study by subject and diagnosis for patients treated with Compound 292.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a PI3K modulator, or a pharmaceutically acceptable form thereof, in the manufacture of a medicament for treating or managing cancer or hematologic malignancy in a subject who is identified to have received a prior treatment and who developed resistance to the prior treatment, wherein said medicament is to be administered alone or in combination with one or more other therapeutic agents.

2. The use of claim 1, wherein the prior treatment is a treatment with one or more BTK inhibitors, anti-CD20 antibodies, proteasome inhibitors, or alkylating agents.

3. The use of claim 1 or 2, wherein the prior treatment is treatment with one or more BTK inhibitors.

4. The use of claim 3, wherein the BTK inhibitor is ibrutinib or AVL-292.

5. The use of claim 3, wherein the BTK inhibitor is RN-486, GDC-0834, CGI-560, CGI-1746, HM-71224, ONO-4059, ACP-196, CNX-774, or LFM-A13.

6. The use of any of claims 1-5, wherein one or more mutations are detectable in a biological sample obtained from the subject, the one or more mutations being selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation in the sample.

7. Use of a PI3K modulator, or a pharmaceutically acceptable form thereof, in the manufacture of a medicament for treating a subject with a cancer or hematologic malignancy, wherein

the subject is identified with one or more mutations selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation.

8. The use of claim 7, wherein said medicament is to be administered in combination with one or more other therapeutic agents to the subject identified with one or more of the mutations.

9. The use of claim 7 or 8, wherein theone or more mutations are detectable in a biological sample obtained from the subject, the one or more mutations being selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation in the sample.

10. The use of claim 9, wherein the one or more of the mutations are detectable by performing polymerase chain reaction (PCR) or hybridization.

11. A method of selecting a subject diagnosed with a cancer or hematologic malignancy as a candidate for treatment with a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof, comprising:

(a) detecting the presence or absence of one or more mutations selected from cysteine to serine mutation on residue 481 of BTK (C481S), cysteine to phenylalanine mutation on residue 481 of BTK (C481F), arginine to tryptophan mutation on residue 665 of PLCgamma2 gene (R665W), histidine to leucine mutation on residue 257 of PLCgamma2 gene (H257L), methionine to arginine mutation on residue 1141 of PLCgamma2 gene (M1141R), serine to phenylalanine mutation on residue 707 of the PLCgamma2 gene (S707F), leucine to phenylalanine mutation on residue 845 of the PLCgamma2 gene (L845F), serine to tyrosine mutation on residue 707 of the PLCgamma2 gene (S707Y), histidine to arginine mutation on residue 244 of the PLCgamma2 gene (H244R), and WHIM-like CXCR4 mutation in a sample obtained from the subject, wherein the presence of one or more of the mutations indicates that the subject is a candidate for treatment with a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof; and

(b) selecting the subject for administration with a therapeutically effective amount of a PI3K modulator, or a pharmaceutically acceptable form thereof, when one or more of the mutations are present in the sample.

12. The method of claim 11, wherein the administration further comprises combining with one or more other therapeutic agents to the subject identified with one or more of the mutations.

13. The use of any of claims 1-10, or the method of claim 11 or 12, wherein the PI3K modulator is Compound 292.

14. The use of any of claims 1-6, 8-10, or 13, or the method of claim 12 or 13, wherein the other therapeutic agent is a chemotherapeutic agent or a therapeutic antibody.

15. The use or method of claim 14, wherein the chemotherapeutic agent is selected from mitotic inhibitors, alkylating agents, anti-metabolites, proteasome inhibitor, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

16. The use or method of claim 14, wherein the therapeutic antibody is selected from anti-CD37 antibody, anti-CD20 antibody, and anti-CD52 antibody.

17. The use or method of claim 16, wherein the therapeutic antibody is anti-CD20 antibody.

18. The use or method of claim 17, wherein the anti-CD20 antibody is rituximab, obinutuzumab, tositumomab,^{131}I tositumomab, ^{90}Y ibritumomab, ^{111}I ibritumomab, or ofatumumab.

19. The use or method of claim 18, wherein the anti-CD20 antibody is obinutuzumab.

20. The use of any of claims 1-6, 8-10, 13-19, or the method of any of claims 12-19, wherein the molar ratio of the PI3K modulator to the other therapeutic agent is about 500:1, about 250:1, about 100:1, about 50:1, about 25:1, about 20:1, about 19:1, about 18: 1, about 17:1, about 16:1, about 15:1, about 14:1, about 13:1, about 12:1, about 11:1, about 10:1, about 5:1, about 4:1, about 3:1, about 2:1, or about 1:1.

21. The use of any of claims 1-6, 8-10, 13-19, or the method of any of claims 12-19, wherein the PI3K modulator is to be administered at a daily dosage of about 0.1 mg to about 150 mg, about 1 mg to about 100 mg, about 5 mg to about 75 mg, about 5 mg to about 60 mg, about 10 mg to about 60 mg, about 20 mg to about 60 mg, about 30 mg to about 60 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 10 mg, about 20 mg, or about 50 mg; or at a twice daily dosage of about 0.1 mg to about 75 mg, about 1 mg to about 75 mg, about 5 mg to about 75 mg, about 5 mg to about 60 mg, about 5 mg to about 50 mg, about 5 mg, about 10 mg, about 20 mg, about 25 mg, or about 50 mg; and

the other therapeutic agent is to be administered at a daily dosage of about 0.1 mg to about 10,000 mg, about 0.1 mg to about 7500 mg, about 0.1 mg to about 5000 mg, about 1 mg to about 2500 mg, about 1 mg to about 1500 mg, about 10 mg to about 1000 mg, about 500 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, about 900 mg to about 1000 mg, or about 1000.

22. The use of any of claims 1-6, 8-10, 13-19, or the method of any of claims 12-19, wherein the PI3K modulator is to be administered at an amount to reach maximum plasma concentration at steady state (Cmaxss) at about 1000 ng/mL to about 5000 ng/mL, about 1000 ng/mL to about 4000 ng/mL, about 1000 ng/mL to about 3000 ng/mL, about 1000 ng/mL to about 2500 ng/mL, or about 1400 ng/mL to about 2200 ng/mL; and

the other agent is to be administered at an amount to reach Cmaxss at about 100 ng/mL to about 1000 ng/mL, about 250 ng/mL to about 1000 ng/mL, about 500 ng/mL to about 1000 ng/mL, about 600 ng/mL to about 1000 ng/mL, about 700 ng/mL to about 1000 ng/mL, about 740 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 900 ng/mL, or about 750 ng/mL to about 800 ng/mL.

23. The use of any of claims 1-6, 8-10, 13-19, or the method of any of claims 12-19, wherein the PI3K modulator is to be administered at an amount to reach an area under the plasma concentration-time curve at steady-state (AUCss) at about 5000 ng/mL*hr to about 10000 ng/mL*hr, about 5000 ng/mL*hr to about 9000 ng/mL*hr, about 6000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr, about 7500 ng/mL*hr, about 8000 ng/mL*hr, about 8500 ng/mL*hr , about 8600 ng/mL*hr, about 8700 ng/mL*hr, or about 8800 ng/mL*hr; and

the other agent is to be administered at an amount to reach an AUCss at about 1000 ng/mL*hr to about 5000 ng/mL*hr, about 2000 ng/mL*hr to about 5000 ng/mL*hr, about 3000 ng/mL*hr to about 5000 ng/mL*hr, about 4000 ng/mL*hr to about 5000 ng/mL*hr, or about 4000 ng/mL*hr to about 4500 ng/mL*hr.

24. The use of any of claims 1-6, 8-10, 13-19, or the method of any of claims 12-19, wherein the PI3K modulator is Compound 292, or a pharmaceutically acceptable form thereof, and the other therapeutic agent is obinutuzumab.

25. The use or method of claim 24, wherein the molar ratio of Compound 292 to obinutuzumab is about 500:1, about 250:1, about 100:1, about 50:1, about 25:1, about 20:1, about 19:1, about 18: 1, about 17:1, about 16:1, about 15:1, about 14:1, about 13:1, about 12:1, about 11:1, about 10:1, about 5:1, about 4:1, about 3:1, about 2:1, or about 1:1.

26. The use or method of claim 24, wherein Compound 292 is to be administered at a daily dosage of about 0.1 mg to about 150 mg, about 1 mg to about 100 mg, about 5 mg to about 75 mg, about 5 mg to about 60 mg, about 10 mg to about 60 mg, about 20 mg to about 60 mg, about 30 mg to about 60 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 10 mg, about 20 mg, or about 50 mg; or at a twice daily dosage of about 0.1 mg to about 75 mg, about 1 mg to about 75 mg, about 5 mg to about 75 mg, about 5 mg to about 60 mg, about 5 mg to about 50 mg, about 5 mg, about 10 mg, about 20 mg, 25 mg, or about 50 mg; and

obinutuzumab is to be administered at a daily dosage of about 0.1 mg to about 10,000 mg, about 0.1 mg to about 7500 mg, about 0.1 mg to about 5000 mg, about 1 mg to about 2500 mg, about 1 mg to about 1500 mg,

about 10 mg to about 1000 mg, about 500 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, about 900 mg to about 1000 mg, or about 1000 mg.

27. The use or method of claim 24, wherein Compound 292 is to be administered at an amount to reach Cmaxss at about 1000 ng/mL to about 5000 ng/mL, about 1000 ng/mL to about 4000 ng/mL, about 1000 ng/mL to about 3000 ng/mL, about 1000 ng/mL to about 2500 ng/mL, or about 1400 ng/mL to about 2200 ng/mL; and

obinutuzumab is to be administered at an amount to reach Cmaxss at about 100 ng/mL to about 1000 ng/mL, about 250 ng/mL to about 1000 ng/mL, about 500 ng/mL to about 1000 ng/mL, about 600 ng/mL to about 1000 ng/mL, about 700 ng/mL to about 1000 ng/mL, about 740 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 1000 ng/mL, about 750 ng/mL to about 900 ng/mL, or about 750 ng/mL to about 800 ng/mL.

28. The use of any of claims 1-6, 8-10, 13-19, or the method of any of claims 12-19, wherein Compound 292 is to be administered at an amount to reach an AUCss at about 5000 ng/mL*hr to about 10000 ng/mL*hr, about 5000 ng/mL*hr to about 9000 ng/mL*hr, about 6000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr to about 9000 ng/mL*hr, about 7000 ng/mL*hr, about 7500 ng/mL*hr, about 8000 ng/mL*hr, about 8500 ng/mL*hr , about 8600 ng/mL*hr, about 8700 ng/mL*hr, or about 8800 ng/mL*hr; and

obinutuzumab is to be administered at an amount to reach an AUCss at about 1000 ng/mL*hr to about 5000 ng/mL*hr, about 2000 ng/mL*hr to about 5000 ng/mL*hr, about 3000 ng/mL*hr to about 5000 ng/mL*hr, about 4000 ng/mL*hr to about 5000 ng/mL*hr, or about 4000 ng/mL*hr to about 4500 ng/mL*hr.

29. The use of any of claims 1-6, 8-10, 13-28, or the method of any of claims 12-28, wherein the cancer or hematologic malignancy is CLL, Waldenström macroglobulinemia (WM), mantle cell, NHL, iNHL, diffuse large B-cell lymphoma, or T-cell lymphoma.

30. The use of any of claims 1-6, 8-10, 13-28, or the method of any of claims 12-28, wherein the cancer or hematologic malignancy is follicular lymphoma.