CLAIMS

WHAT IS CLAIMED IS:

1. 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.

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

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

5. The method 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 method of any of claims 1-5, further comprising 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 mutation in the sample.

7. 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.

8. The method of claim 7, wherein the administration further comprises combining with one or more other therapeutic agents to the subject identified with one or more of the mutations.

9. The method of claim 7 or 8, wherein 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.

10. The method of claim 9, wherein the detecting comprises performing polymerase chain reaction (PCR) or hybridization to detect one or more of the mutations.

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) 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.

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 method of any of claims 1-12, wherein the PI3K modulator is Compound 292.

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

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

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

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

20. The method of any of claims 1-6, 8-10, or 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 method of any of claims 1-6, 8-10, or 12-19, wherein the PI3K modulator is 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 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 method of any of claims 1-6, 8-10, or 12-19, wherein 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.

23. The method of any of claims 1-6, 8-10, or 12-19, wherein 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.

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

25. The 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 method of claim 24, wherein Compound 292 is 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 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 method of claim 24, wherein 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.

28. The method of any of claims 1-10 or 12-19, wherein 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.

29. The method of any of claims 1-28, 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 method of any of claims 1-28, wherein the cancer or hematologic malignancy is follicular lymphoma.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a PI3K modulator, or a pharmaceutically acceptable form thereof, alone or in combination with one or more other therapeutic agents in the manufacture of a medicament for treating cancer or hematologic malignancy in a subject having developed, or identified as having developed, resistance to a prior treatment with one or more BTK inhibitors, anti-CD20 antibodies, proteasome inhibitors, or alkylating agents.

2. Use of a PI3K modulator, or a pharmaceutically acceptable form thereof, alone or in combination with one or more other therapeutic agents in the manufacture of a medicament for treating or managing cancer or hematologic malignancy in a subject that is, or is identified as, relapsed or refractory to a prior 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, AVL-292, RN-486, GDC-0834, CGI-560, CGI-1746, HM-71224, ONO-4059, ACP-196, CNX-774, or LFM-A13.

5. The use of claim 1 or 2, wherein the prior treatment is a treatment with one or more anti-CD20 antibodies, wherein the anti-CD20 antibody is obinutuzumab, tositumomab, ^{131}I tositumomab, ^{90}Y ibritumomab, ^{111}I ibritumomab, or ofatumumab.

6. The use of claim 1 or 2, wherein the prior treatment is a treatment with one or more proteasome inhibitors or alkylating agents.

7. The use of any of the preceding claims, further comprising detecting, in a biological sample obtained from the subject, 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 mutation in the sample.

8. The use of any of the preceding claims, wherein the PI3K modulator and one or more other therapeutic agents are formulated for simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which the PI3K modulator and one or more other therapeutic agents are present.

9. Use of a PI3K modulator, or a pharmaceutically acceptable form thereof in the manufacture of a medicament for a cancer or hematologic malignancy in a subject identified as having 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.

10. The use of claim 9, wherein the PI3K modulator, or pharmaceutically acceptable form thereof, is to be administered in combination with one or more other therapeutic agents to the subject identified with one or more of the mutations.

11. The use of claim 9 or 10, wherein the subject was identified by detecting, in a biological sample obtained from the subject, 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.

12. The use of claim 11, wherein the detecting was performed by polymerase chain reaction (PCR) or hybridization to detect one or more of the mutations.

13. 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 treatment with the PI3K modulator, or a pharmaceutically acceptable form thereof, when one or more of the mutations are present in the sample.

14. The method of claim 13, wherein the subject is selected for treatment with one or more other therapeutic agents.

15. The method of claim 13 or 14, wherein the subject is to be administered a PI3K modulator, or a pharmaceutically acceptable form thereof, when one or more of the mutations are present in the sample.

16. The use or method of any of claims 1-8, 10-12, 14, or 15, wherein the other therapeutic agent is a chemotherapeutic agent or a therapeutic antibody, wherein the chemotherapeutic agent is optionally 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, and wherein the therapeutic antibody is optionally selected from anti-CD37 antibody, anti-CD20 antibody, and anti-CD52 antibody.

17. The use or method of claim 16, wherein the other therapeutic agent is an anti-CD20 antibody chosen from rituximab, obinutuzumab, tositumomab, ^{131}I tositumomab, ^{90}Y ibritumomab, ^{111}I ibritumomab, or ofatumumab.

18. The use or method of any of claims 1-8, 10-12, or 14-17, 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.

19. The use or method of any of claims 1-8, 10-12, or 14-17, wherein the PI3K modulator is formulated for administration 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 formulated for administration 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.

20. The use or method of any of claims 1-8, 10-12, or 14-17, wherein the PI3K modulator is formulated for administration 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 formulated for administration 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.

21. The use or method of any of claims 1-8, 10-12, or 14-17, wherein the PI3K modulator is formulated for administration 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 formulated for administration 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.

22. The use or method of any of claims 1-8, 10-12, or 14-17, wherein the PI3K modulator is Compound 292, or a pharmaceutically acceptable form thereof, and the other therapeutic agent is obinutuzumab.

23. The use or method of claim 22, 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.

24. The use or method of claim 22, wherein Compound 292 is formulated for administration 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 formulated for administration 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.

25. The use or method of claim 22, wherein Compound 292 is formulated for administration 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 formulated for administration 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.

26. The use or method of any of claims 1-12 or 14-17, wherein Compound 292 is formulated for administration 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 formulated for administration 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.

27. Use of a PI3K modulator, or a pharmaceutically acceptable form thereof, in the manufacture of a medicament for preventing BTK resistance in a subject having a hematologic malignancy, which subject is being treated with a BTK inhibitor.

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

29. The use or method of any of claims 1-27, wherein the cancer or hematologic malignancy is follicular lymphoma.

30. The use of any of the preceding claims, wherein the PI3K modulator is a PI3K inhibitor.

31. The use or method of any of claims 1-21 or 27-30, wherein the PI3K modulator is Compound 292.