Claims

1. Use of ibrutinib in the manufacture of a medicament to treat a B-cell malignancy in combination with an anti-PD-1 antibody, wherein the medicament and the anti-PD-1 antibody are administered substantially at the same time or sequentially, and wherein:

a) the B-cell malignancy is DLBCL and the subject has one or more mutations in genes selected from *KLHL14*, *RNF213*, *CSMD3*, *BCL2*, *NBPF1*, *LRP1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6;

b) the B-cell malignancy is GCB-DLBCL and the subject has one or more mutations in genes selected from *RNF213*, *NBPF1*, or a combination thereof, wherein the one or more mutations are listed in Table 16;

c) the B-cell malignancy is FL and the subject has one or more mutations in genes selected from *BCL2*, *CREBBP*, *KMT2D*, *MUC17*, *CIITA*, *FES*, *NCOA2*, *TPR*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10;

d) the B-cell malignancy is RT and the subject has one or more mutations in genes selected from *IRF2BP2*, *NBPF1*, *KLHL6*, *SETX*, *SF3B1*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14;

e) the B-cell malignancy is DLBCL and the subject does not have one or more mutations in genes selected from *TP53*, *EBF1*, *ADAMTS20*, *AKAP9*, *SOCS1*, *TNFRSF14*, *MYD88*, *NFKB1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6;

f) the B-cell malignancy is GCB-DLBCL and the subject does not have one or more mutations in genes selected from *KMT2D*, *BCL2*, *CSMD3*, *CREBBP*, *EBF1*, *SGK1*, or a combination thereof, wherein the one or more mutations are listed in Table 16;

g) the B-cell malignancy is FL and the subject does not have one or more mutations in genes selected from *CREBBP*, *KMT2D*, *BCL2*, *STAT6*, *NBPF1*, *EZH2*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10; or

h) the B-cell malignancy is RT and the subject does not have one or more mutations in genes selected from *ROS1*, *IGLL5*, *PASK*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14.

2. Use of an anti-PD-1 antibody in the manufacture of a medicament to treat a B-cell malignancy in combination with ibrutinib, wherein the medicament and the ibrutinib are administered substantially at the same time or sequentially, and wherein:

a) the B-cell malignancy is DLBCL and the subject has one or more mutations in genes selected from *KLHL14*, *RNF213*, *CSMD3*, *BCL2*, *NBPF1*, *LRP1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6;

b) the B-cell malignancy is GCB-DLBCL and the subject has one or more mutations in genes selected from *RNF213*, *NBPF1*, or a combination thereof, wherein the one or more mutations are listed in Table 16;

c) the B-cell malignancy is FL and the subject has one or more mutations in genes selected from *BCL2*, *CREBBP*, *KMT2D*, *MUC17*, *CIITA*, *FES*, *NCOA2*, *TPR*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10;

d) the B-cell malignancy is RT and the subject has one or more mutations in genes selected from *IRF2BP2*, *NBPF1*, *KLHL6*, *SETX*, *SF3B1*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14;

e) the B-cell malignancy is DLBCL and the subject does not have one or more mutations in genes selected from *TP53*, *EBF1*, *ADAMTS20*, *AKAP9*, *SOCS1*, *TNFRSF14*, *MYD88*, *NFKB1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6;

f) the B-cell malignancy is GCB-DLBCL and the subject does not have one or more mutations in genes selected from *KMT2D*, *BCL2*, *CSMD3*, *CREBBP*, *EBF1*, *SGK1*, or a combination thereof, wherein the one or more mutations are listed in Table 16;

g) the B-cell malignancy is FL and the subject does not have one or more mutations in genes selected from *CREBBP*, *KMT2D*, *BCL2*, *STAT6*, *NBPF1*, *EZH2*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10; or

h) the B-cell malignancy is RT and the subject does not have one or more mutations in genes selected from *ROS1*, *IGLL5*, *PASK*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14.

3. Use of ibrutinib and an anti-PD-1 antibody in the manufacture of a medicament to treat a B-cell malignancy, wherein:

a) the B-cell malignancy is DLBCL and the subject has one or more mutations in genes selected from *KLHL14*, *RNF213*, *CSMD3*, *BCL2*, *NBPF1*, *LRP1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6;
b) the B-cell malignancy is GCB-DLBCL and the subject has one or more mutations in genes selected from *RNF213*, *NBPF1*, or a combination thereof, wherein the one or more mutations are listed in Table 16;
c) the B-cell malignancy is FL and the subject has one or more mutations in genes selected from *BCL2*, *CREBBP*, *KMT2D*, *MUC17*, *CIITA*, *FES*, *NCOA2*, *TPR*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10;
d) the B-cell malignancy is RT and the subject has one or more mutations in genes selected from *IRF2BP2*, *NBPF1*, *KLHL6*, *SETX*, *SF3B1*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14;
e) the B-cell malignancy is DLBCL and the subject does not have one or more mutations in genes selected from *TP53*, *EBF1*, *ADAMTS20*, *AKAP9*, *SOCS1*, *TNFRSF14*, *MYD88*, *NFKB1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6;
f) the B-cell malignancy is GCB-DLBCL and the subject does not have one or more mutations in genes selected from *KMT2D*, *BCL2*, *CSMD3*, *CREBBP*, *EBF1*, *SGK1*, or a combination thereof, wherein the one or more mutations are listed in Table 16;
g) the B-cell malignancy is FL and the subject does not have one or more mutations in genes selected from *CREBBP*, *KMT2D*, *BCL2*, *STAT6*, *NBPF1*, *EZH2*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10; or
h) the B-cell malignancy is RT and the subject does not have one or more mutations in genes selected from *ROS1*, *IGLL5*, *PASK*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14.

4. The use of any one of claims 1-3, wherein the B-cell malignancy is DLBCL and the subject has one or more mutations in genes selected from *KLHL14*, *RNF213*, *CSMD3*, *BCL2*, *NBPF1*, *LRP1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6.

5. The use of claim 4, wherein the subject has one or more mutations in *KLHL14*, *RNF213*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6.

6. The use of any one of claims 1-3, wherein the B-cell malignancy is GCB-DLBCL and the subject has one or more mutations in genes selected from *RNF213*, *NBPF1*, or a combination thereof, wherein the one or more mutations are listed in Table 16.

7. The use of any one of claims 1-3, wherein the B-cell malignancy is FL and the subject has one or more mutations in genes selected from *BCL2*, *CREBBP*, *KMT2D*, *MUC17*, *CIITA*, *FES*, *NCOA2*, *TPR*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10.

8. The use of claim 7, wherein the subject has one or more mutations in *BCL2*, wherein the one or more mutations are listed in Table 8 or 10.

9. The use of any one of claims 1-3, wherein the B-cell malignancy is RT and the subject has one or more mutations in genes selected from *IRF2BP2*, *NBPF1*, *KLHL6*, *SETX*, *SF3B1*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14.

10. The use of any one of claims 1-3, wherein the B-cell malignancy is DLBCL and the subject does not have one or more mutations in genes selected from *TP53*, *EBF1*, *ADAMTS20*, *AKAP9*, *SOCS1*, *TNFRSF14*, *MYD88*, *NFKB1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6.

11. The use of any one of claims 1-3, wherein the B-cell malignancy is GCB-DLBCL and the subject does not have one or more mutations in genes selected from *KMT2D*, *BCL2*, *CSMD3*, *CREBBP*, *EBF1*, *SGK1*, or a combination thereof, wherein the one or more mutations are listed in Table 16.

12. The use of any one of claims 1-3, wherein the B-cell malignancy is FL and the subject does not have one or more mutations in genes selected from *CREBBP*, *KMT2D*, *BCL2*, *STAT6*,

*NBPF1*, *EZH2,* or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10.

13. The use of any one of claims 1-3, wherein the B-cell malignancy is RT and the subject does not have one or more mutations in genes selected from *ROS1, IGLL5, PASK,* or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14.

14. The use of claim 13, wherein the subject does not have one or more mutations in *ROS1,* wherein the one or more mutations are listed in Table 12 or 14.

15. The use of any one of the previous claims, comprising 560 mg of the ibrutinib and 3 mg/kg of the anti-PD-1 antibody.

16. The use of any one of the previous claims, wherein the anti-PD-1 antibody is administered intravenously and the ibrutinib is administered orally.

17. The use of claim 16, wherein the anti-PD-1 antibody is administered on a 14-day cycle and the ibrutinib is administered once daily.

18. The use of any one of the previous claims, wherein the anti-PD-1 antibody is nivolumab.

19. The use of any one of the previous claims, wherein the treating results in a complete response (CR) or partial response (PR) in the subject.

20. The use of any one of the previous claims, wherein the subject:

a) has DLBCL, FL, or RT (transformation from CLL/SLL only);

b) had ≥ 1 prior therapy (≥ 2 prior therapies for FL) but no more than 4 prior lines of treatment;

c) had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;

d) has measurable disease; and

e) has no prior ibrutinib or anti-PD-1 therapies.

21. A method of predicting a likelihood of responsiveness to a combination of ibrutinib and an anti-PD-1 antibody in a subject having a B-cell malignancy, wherein:

a) the B-cell malignancy is DLBCL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *KLHL14*, *RNF213*, *CSMD3*, *BCL2*, *NBPF1*, *LRP1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6;

b) the B-cell malignancy is GCB-DLBCL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *RNF213*, *NBPF1*, or a combination thereof, wherein the one or more mutations are listed in Table 16;

c) the B-cell malignancy is FL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *BCL2*, *CREBBP*, *KMT2D*, *MUC17*, *CIITA*, *FES*, *NCOA2*, *TPR*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10; or

d) the B-cell malignancy is RT and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *IRF2BP2*, *NBPF1*, *KLHL6*, *SETX*, *SF3B1*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14;

wherein the one or more mutations in the genes are indicative of responsiveness to the combination.

22. The method of claim 21, wherein the B-cell malignancy is DLBCL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *KLHL14*, *RNF213*, *CSMD3*, *BCL2*, *NBPF1*, *LRP1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6 and the one or more mutations in the genes are indicative of responsiveness to the combination.

23. The method of claim 22, wherein the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *KLHL14*, *RNF213*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6 and the one or more mutations in the genes are indicative of responsiveness to the combination.

24. The method of claim 21, wherein the B-cell malignancy is GCB-DLBCL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *RNF213*, *NBPF1*, or a combination thereof, wherein the one or more mutations are listed in Table 16 and the one or more mutations in the genes are indicative of responsiveness to the combination.

25. The method of claim 21, wherein the B-cell malignancy is FL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *BCL2*, *CREBBP*, *KMT2D*, *MUC17*, *CIITA*, *FES*, *NCOA2*, *TPR*, or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10 and the one or more mutations in the genes are indicative of responsiveness to the combination.

26. The method of claim 25, wherein the method comprises analyzing a sample from the subject for one or more mutations in *BCL2*, wherein the one or more mutations are listed in Table 8 or 10 and the one or more mutations in the genes are indicative of responsiveness to the combination.

27. The method of claim 21, wherein the B-cell malignancy is RT and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *IRF2BP2*, *NBPF1*, *KLHL6*, *SETX*, *SF3B1*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14 and the one or more mutations in the genes are indicative of responsiveness to the combination.

28. A method of predicting a likelihood of nonresponsiveness to a combination of ibrutinib and an anti-PD-1 antibody in a subject having a B-cell malignancy, wherein:

a) the B-cell malignancy is DLBCL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *TP53, EBF1*, *ADAMTS20*, *AKAP9*, *SOCS1*, *TNFRSF14*, *MYD88*, *NFKB1B*, or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6;

b) the B-cell malignancy is GCB-DLBCL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *KMT2D, BCL2, CSMD3, CREBBP, EBF1, SGK1,* or a combination thereof, wherein the one or more mutations are listed in Table 16;

c) the B-cell malignancy is FL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *CREBBP, KMT2D, BCL2, STAT6, NBPF1, EZH2,* or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10; or

d) the B-cell malignancy is RT and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *ROS1, IGLL5, PASK,* or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14;

wherein the one or more mutations in the genes is indicative of nonresponsiveness to the combination.

29. The method of claim 28, wherein the B-cell malignancy is DLBCL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *TP53, EBF1, ADAMTS20, AKAP9, SOCS1, TNFRSF14, MYD88, NFKB1B,* or a combination thereof, wherein the one or more mutations are listed in Table 4 or 6 and the one or more mutations in the genes is indicative of nonresponsiveness to the combination.

30. The method of claim 28, wherein the B-cell malignancy is GCB-DLBCL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *KMT2D, BCL2, CSMD3, CREBBP, EBF1, SGK1,* or a combination thereof, wherein the one or more mutations are listed in Table 16 and the one or more mutations in the genes is indicative of nonresponsiveness to the combination.

31. The method of claim 28, wherein the B-cell malignancy is FL and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *CREBBP, KMT2D, BCL2, STAT6, NBPF1, EZH2,* or a combination thereof, wherein the one or more mutations are listed in Table 8 or 10 and the one or more mutations in the genes is indicative of nonresponsiveness to the combination.

32. The method of claim 28, wherein the B-cell malignancy is RT and the method comprises analyzing a sample from the subject for one or more mutations in genes selected from *ROS1*, *IGLL5*, *PASK*, or a combination thereof, wherein the one or more mutations are listed in Table 12 or 14 and the one or more mutations in the genes is indicative of nonresponsiveness to the combination.

33. The method of claim 32, wherein the method comprises analyzing a sample from the subject for one or more mutations in *ROS1*, wherein the one or more mutations are listed in Table 12 or 14 and the one or more mutations are indicative of nonresponsiveness to the combination.

34. The method of any one of claims 21-33, wherein the subject:

a) has DLBCL, FL, or RT (transformation from CLL/SLL only);

b) had ≥ 1 prior therapy (≥ 2 prior therapies for FL) but no more than 4 prior lines of treatment;

c) had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2;

d) has measurable disease; and

e) has no prior ibrutinib or anti-PD-1 therapies.

35. The method of any one of claims 21-34, further comprising administering a therapeutically effective amount of the combination of ibrutinib and an anti-PD-1 antibody to the subject to thereby treat the B-cell malignancy if the subject has the one or more mutations in genes that are indicative of responsiveness to the combination and/or a lack of the one or more mutations in genes that are indicative of nonresponsiveness to the combination.

36. The method of claim 35, wherein the therapeutically effective amount of the combination of ibrutinib and the anti-PD-1 antibody comprises 560 mg of the ibrutinib and 3 mg/kg of the anti-PD-1 antibody.

37. The method of claim 35 or 36, wherein the anti-PD-1 antibody is administered intravenously and the ibrutinib is administered orally.

38. The method of claim 37, wherein the anti-PD-1 antibody is administered on a 14-day cycle and the ibrutinib is administered once daily.

39. The method of any one of the claims 35-38, wherein the anti-PD-1 antibody is nivolumab.

40. The method of any one of claims 35-39, wherein the treating results in a complete response (CR) or partial response (PR) in the subject.