

Claims

1. ~~A method of treating follicular lymphoma in a human subject, the method comprising administering to the subject a bispecific antibody an effective amount of rituximab and lenalidomide, wherein the bispecific antibody comprises:~~

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

(ii) a second binding arm comprising a second antigen-binding region which binds to human CD20 and comprises a VH region and a VL region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 13, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 14;

for use in treatment of follicular lymphoma in a human subject, the treatment comprising administering to the subject the bispecific antibody and an effective amount of rituximab and lenalidomide, wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, lenalidomide, and the bispecific antibody are administered in 28-day cycles.

2. The bispecific antibody for use~~method~~ of claim 1, wherein the bispecific antibody is administered at a dose of 24 mg.

3. The bispecific antibody for use~~method~~ of claim 1, wherein the bispecific antibody is administered at a dose of 48 mg.

4. The bispecific antibody for use~~method~~ of any one of claims 1-3, wherein the bispecific antibody is administered once every week (weekly administration).

5. The bispecific antibody for use~~method~~ of claim 4, wherein the weekly administration of 24 mg or 48 mg is performed for 2.5 28-day cycles.

6. The bispecific antibody for use~~method~~ of claim 4 or 5, wherein after the weekly administration, the bispecific antibody is administered once every two weeks (biweekly administration).

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7. The bispecific antibody for use~~method~~ of claim 6, wherein the biweekly administration is performed for six 28 day cycles.

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8. The bispecific antibody for use~~method~~ of claim 6 or 7, wherein after the biweekly administration, the bispecific antibody is administered once every four weeks.

9. The bispecific antibody for use~~method~~ of claim 8, wherein the administration once every four weeks is performed for at least three 28-day cycles.

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10. The bispecific antibody for use~~method~~ of any one of claims 4-9, wherein prior to the weekly administration of 24 mg or 48 mg, a priming dose of the bispecific antibody is administered in cycle 1 of the 28-day cycles.

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11. The bispecific antibody for use~~method~~ of claim 10, wherein the priming dose is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg.

12. The bispecific antibody for use~~method~~ of claim 10 or 11, wherein the priming dose is 0.16 mg.

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13. The bispecific antibody for use~~method~~ of any one of claims 10-12, wherein after administering the priming dose and prior to administering the first weekly dose of 24 mg or 48 mg, an intermediate dose of the bispecific antibody is administered.

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14. The bispecific antibody for use~~method~~ of claim 13, wherein the priming dose is administered on day 1 and the intermediate dose is administered on day 8 before the first weekly dose of 24 mg or 48 mg on days 15 and 22 of cycle 1.

15. The bispecific antibody for use~~method~~ of claim 13 or 14, wherein the intermediate dose is 0.8 mg.

5 16. The bispecific antibody for use method of any one of claims 1-15, wherein rituximab is administered once every week (weekly administration).

17. The bispecific antibody for use~~method~~ of claim 16, wherein the weekly administration of rituximab is performed for one 28-day cycle.

10 18. The bispecific antibody for use~~method~~ of claim 16 or 17, where after the weekly administration, rituximab is administered once every four weeks.

15 19. The bispecific antibody for use~~method~~ of claim 18, wherein the administration of rituximab once every four weeks is performed for four 28-day cycles.

20. The bispecific antibody for use~~method~~ of any one of claims 1-19, wherein rituximab is administered at a dose of 375 mg/m² or equivalent thereof.

20 21. The bispecific antibody for use composition~~method~~ of any one of claims 1-20, wherein lenalidomide is administered once a day from day 1 to day 21 of the 28-day cycles.

22. The bispecific antibody for use~~method~~ of any one of claims 1-21, wherein lenalidomide is administered from cycle 1 to cycle 12 of the 28-day cycles.

25 23. The bispecific antibody for use~~method~~ of any one of claims 1-22, wherein lenalidomide is administered at a dose of 15 mg in cycle 1 of the 28-day cycles.

30 24. The bispecific antibody for use~~method~~ of any one of claims 1-23, wherein lenalidomide is administered at a dose of 20 mg in cycle 2 to cycle 12 of the 28-day cycles.

25. The bispecific antibody for use~~method~~ of any one of claims 1-24, wherein rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2-5).

26. The bispecific antibody for use~~method~~ of any one of claims 1-25, wherein the dosing schedule for the bispecific antibody, rituximab, and lenalidomide is as shown in **Table 2**.

27. The bispecific antibody for use~~method~~ of any one of claims 1, 2, and 4-26, wherein administration is performed in 28-day cycles, and wherein:

(a) the bispecific antibody is administered as follows:

(i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 24 mg is administered on days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5;

and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

28. The bispecific antibody for use~~method~~ of any one of claims 1 and 3-27, wherein administration is performed in 28-day cycles, and wherein:

(a) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 48 mg is administered on days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5;

and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

29. The bispecific antibody for use~~method~~ of any one of claims 1-28, wherein the bispecific antibody is administered subcutaneously.

30. The bispecific antibody for use~~method~~ of any one of claims 1-29, wherein rituximab is administered intravenously.

31. The bispecific antibody for use~~method~~ of any one of claims 1-30, wherein lenalidomide is administered orally.

32. The bispecific antibody for use~~method~~ of any one of claims 1-31, wherein the bispecific antibody, rituximab, and lenalidomide are administered sequentially.

33. The bispecific antibody for use~~method~~ of any one of claims 1-32, wherein:

(a) rituximab is administered before the bispecific antibody if rituximab and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2-5);

(b) lenalidomide is administered before the bispecific antibody if lenalidomide and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycles 1-3, days 1 and 15 of cycles 4-9, and day 1 of cycles 10-12);

(c) rituximab is administered before lenalidomide if rituximab and lenalidomide are administered on the same day (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5); or

(d) rituximab is administered first, lenalidomide is administered second, and the bispecific antibody is administered last if rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., days 1, 8, and 15 of cycle 1, and days 1-5 of cycles 2-5).

34. The bispecific antibody for use~~method~~ of any one of claims 1-33, wherein the follicular lymphoma is relapsed and/or refractory follicular lymphoma, such as grade 1, 2, or 3a relapsed and/or refractory follicular lymphoma or such as Stage II, III, or IV relapsed and/or refractory follicular lymphoma.

35. The bispecific antibody for use~~method~~ of any one of claims 1-34, wherein:

(i) the first antigen-binding region of the bispecific antibody comprises VHCDR1, VHCDR2, and VHCDR3 comprising the amino acid sequences set forth in SEQ ID NOs: 1, 2, and 3, respectively, and VLCDR1, VLCDR2, and VLCDR3 comprising the amino acid sequences set forth in SEQ ID NO: 4, the sequence GTN, and SEQ ID NO: 5, respectively; and

(ii) the second antigen-binding region of the bispecific antibody comprises VHCDR1, VHCDR2, and VHCDR3 comprising the amino acid sequences set forth in SEQ ID NOs: 8, 9, and 10, respectively, and VLCDR1, VLCDR2, and VLCDR3 comprising the amino acid sequences set forth in SEQ ID NO: 11, the sequence DAS, and SEQ ID NO: 12, respectively.

36. The bispecific antibody for use~~method~~ of any one of claims 1-35, wherein:

(i) the first antigen-binding region of the bispecific antibody comprises a VH region comprising the amino acid sequence of SEQ ID NO: 6, and the VL region comprising the amino acid sequence of SEQ ID NO: 7; and

(ii) the second antigen-binding region of the bispecific antibody comprises a VH region comprising the amino acid sequence of SEQ ID NO: 13, and the VL region comprising the amino acid sequence of SEQ ID NO: 14.

37. The bispecific antibody for use~~method~~ of any one of claims 1-35, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1, λ (lambda) antibody.

38. The bispecific antibody for use~~method~~ of claim 37, wherein the first binding arm of the bispecific antibody comprises a λ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 22.

39. The bispecific antibody for use~~method~~ of any one of claims 1-38, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1, κ (kappa) antibody.

40. The bispecific antibody for use~~method~~ of claim 39, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

5 41. The bispecific antibody for use~~method~~ of any one of claims 1-40, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

42. The bispecific antibody for use~~method~~ of any one of claims 1-41, wherein the bispecific antibody comprises an inert Fc region.

10 43. The bispecific antibody for use~~method~~ of any one of claims 1-42, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein in both the first and second heavy chains, the amino acids in the positions corresponding to positions L234, L235, and D265 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 are F, E, and A,
15 respectively.

44. The bispecific antibody for use~~method~~ of any one of claims 1-43, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein in the first heavy chain, the amino acid in the position corresponding to F405 in the human IgG1 heavy chain constant
20 region of SEQ ID NO: 15 is L, and wherein in the second heavy chain, the amino acid in the position corresponding to K409 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 is R, or *vice versa*.

45. The bispecific antibody for use~~method~~ of any one of claims 1-44, wherein the bispecific
25 antibody comprises a first heavy chain and a second heavy chain, wherein

(i) in both the first and second heavy chains, the amino acids in the positions corresponding to positions L234, L235, and D265 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 are F, E, and A, respectively, and

(ii) in the first heavy chain, the amino acid in the position corresponding to F405 in the
30 human IgG1 heavy chain constant region of SEQ ID NO: 15 is L, and wherein in the second heavy

chain, the amino acid in the position corresponding to K409 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 is R, or *vice versa*.

46. The bispecific antibody for use~~method~~ of claim 45, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

47. The bispecific antibody for use~~method~~ of any one of claims 1-46, wherein the bispecific antibody comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 24 and 25, respectively, and a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 26 and 27, respectively.

48. The bispecific antibody for use~~method~~ of any one of claims 1-47, wherein the bispecific antibody comprises a heavy chain and a light chain consisting of the amino acid sequence of SEQ ID NOs: 24 and 25, respectively, and a heavy chain and a light chain consisting of the amino acid sequence of SEQ ID NOs: 26 and 27, respectively.

49. The bispecific antibody for use~~method~~ of any one of claims 1-48, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.