

Claims

1. ~~A method of treating diffuse large B-cell lymphoma (DLBCL) in a human subject, the method comprising administering to the subject a bispecific antibody, and an effective amount of (a) rituximab, (b) cyclophosphamide, (c) doxorubicin, (d) vincristine and (e) prednisone, wherein the a-bispecific antibody comprises:~~

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (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 diffuse large B-cell lymphoma (DLBCL) in a human subject, the treatment comprising administering to the subject the bispecific antibody, and an effective amount of (a) rituximab, (b) cyclophosphamide, (c) doxorubicin, (d) vincristine and (e) prednisone, wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered in 21-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 three and one-third 21-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 three weeks.

7. The bispecific antibody for use~~method~~ of claim 6, wherein the administration once every three weeks is performed for two or four 21-day cycles.

8. The bispecific antibody for use~~method~~ of claim 7, wherein after the administration once every three weeks, the bispecific antibody is administered once every four weeks in 28-day cycles.

9. The bispecific antibody for use~~method~~ of claim 8, wherein the administration once every four weeks is performed for up to one year total duration of treatment with the bispecific antibody.

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 21-day cycles.

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.

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.

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 day 15 of cycle 1.

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

16. The bispecific antibody for use~~method~~ of any one of claims 1-15, wherein rituximab is administered once every three weeks.

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17. The bispecific antibody for use~~method~~ of claim 16, wherein the administration of rituximab once every three weeks is performed for six or eight 21-day cycles.

18. The bispecific antibody for use~~method~~ of any one of claims 1-17, wherein rituximab is administered at a dose of 375 mg/m².

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19. The bispecific antibody for use~~method~~ of any one of claims 1-18, wherein cyclophosphamide is administered once every three weeks.

20. The bispecific antibody for use~~method~~ of claim 19, wherein the administration of cyclophosphamide once every three weeks is performed for six or eight 21-day cycles.

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21. The bispecific antibody for use~~method~~ of any one of claims 1-20, wherein cyclophosphamide is administered at a dose of 750 mg/m².

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22. The bispecific antibody for use~~method~~ of any one of claims 1-21, wherein doxorubicin is administered once every three weeks.

23. The bispecific antibody for use~~method~~ of claim 22, wherein the administration of doxorubicin once every three weeks is performed for six or eight 21-day cycles.

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24. The bispecific antibody for use~~method~~ of any one of claims 1-23, wherein doxorubicin is administered at a dose of 50 mg/m².

25. The bispecific antibody for use~~method~~ of any one of claims 1-24, wherein vincristine is administered once every three weeks.

26. The bispecific antibody for use~~method~~ of claim 25, wherein the administration of vincristine once every three weeks is performed for six or eight 21-day cycles.

27. The bispecific antibody for use~~method~~ of any one of claims 1-26, wherein vincristine is administered at a dose of 1.4 mg/m².

28. The bispecific antibody for use~~method~~ of any one of claims 1-27, wherein prednisone is administered once a day from day 1 to day 5 of the 21-day cycles.

29. The bispecific antibody for use~~method~~ of claim 28, wherein prednisone is administered for six or eight 21-day cycles.

30. The bispecific antibody for use~~method~~ of any one of claims 1-29, wherein prednisone is administered at a dose of 100 mg/day.

31. The bispecific antibody for use~~method~~ of any one of claims 1-30, wherein rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered on the same day (e.g., on day 1 of cycles 1-6 or cycles 1-8 of the 21-day cycles).

32. The bispecific antibody for use~~method~~ of any one of claims 1-31, wherein the dosing schedule for rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody is as shown in **Table 2**.

33. The bispecific antibody for use~~method~~ of any one of claims 1, 2, and 4-32, wherein administration is performed in 21-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 day 15;

(ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

5 (iii) in cycles 5 and 6, a dose of 24 mg is administered on day 1;

(b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-6; and

(c) prednisone is administered on days 1-5 in cycles 1-6.

10 34. The bispecific antibody for use~~method~~ of any one of claims 1 and 3-32, wherein administration is performed in 21-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 48 mg is administered on day 15;

15 (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

(iii) in cycles 5 and 6, a dose of 48 mg is administered on day 1;

(b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-6; and

(c) prednisone is administered on days 1-5 in cycles 1-6.

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35. The bispecific antibody for use~~method~~ of claim 33 or 34 wherein the bispecific antibody is administered once every four weeks in 28-day cycles on day 1 from cycle 7.

25 36. The bispecific antibody for use~~method~~ of any one of claims 1, 2, and 4-32, wherein administration is performed in 21-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 day 15;

(ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

30 (iii) in cycles 5-8, a dose of 24 mg is administered on day 1;

(b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-8; and

(c) prednisone is administered on days 1-5 in cycles 1-8.

5 37. The bispecific antibody for use~~method~~ of any one of claims 1 and 3-32, wherein administration is performed in 21-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 48 mg is administered on day 15;

10 (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

(iii) in cycles 5-8, a dose of 48 mg is administered on day 1;

(b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-8; and

(c) prednisone is administered on days 1-5 in cycles 1-8.

15 38. The bispecific antibody for use~~method~~ of claim 36 or 37, wherein the bispecific antibody is administered once every four weeks in 28-day cycles on day 1 from cycle 9.

20 39. The bispecific antibody for use~~method~~ of any one of claims 1-38, wherein the bispecific antibody is administered subcutaneously.

40. The bispecific antibody for use~~method~~ of any one of claims 1-39, wherein rituximab is administered intravenously.

25 41. The bispecific antibody for use~~method~~ of any one of claims 1-40, wherein cyclophosphamide is administered intravenously.

42. The bispecific antibody for use~~method~~ of any one of claims 1-41, wherein doxorubicin is administered intravenously.

43. The bispecific antibody for use~~method~~ of any one of claims 1-42, wherein vincristine is administered intravenously.

44. The bispecific antibody for use~~method~~ of any one of claims 1-43, wherein prednisone is administered intravenously or orally.

45. The bispecific antibody for use~~method~~ of any one of claims 1-44, wherein rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered sequentially.

46. The bispecific antibody for use~~method~~ of any one of claims 1-45, wherein prednisone is administered first, rituximab is administered second, cyclophosphamide is administered third, doxorubicin is administered fourth, vincristine is administered fifth, and the bispecific antibody is administered last if rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered on the same day.

47. The bispecific antibody for use~~method~~ of any one of claims 1-46, wherein the DLBCL is double-hit or triple-hit DLBCL.

48. The bispecific antibody for use~~method~~ of any one of claims 1-47, wherein the DLBCL is follicular lymphoma Grade 3B.

49. The bispecific antibody for use~~method~~ of any one of claims 1-48, wherein the subject has an International Prognostic Index (IPI) score or Revised-IPI score ≥ 3 .

50. The bispecific antibody for use~~method~~ of any one of claims 1-49, wherein the subject has not received prior therapy for DLBCL or follicular lymphoma Grade 3B.

51. The bispecific antibody for use~~method~~ of any one of claims 1-50, 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.

52. The bispecific antibody for use~~method~~ of any one of claims 1-51, 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.

53. The bispecific antibody for use~~method~~ of any one of claims 1-52, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1, λ (lambda) antibody.

54. The bispecific antibody for use~~method~~ of claim 53, 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.

55. The bispecific antibody for use~~method~~ of any one of claims 1-54, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1, κ (kappa) antibody.

56. The bispecific antibody for use~~method~~ of claim 55, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

57. The bispecific antibody for use~~method~~ of any one of claims 1-56, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

58. The bispecific antibody for use~~method~~ of any one of claims 1-57, wherein the bispecific antibody comprises an inert Fc region.

59. The bispecific antibody for use~~method~~ of any one of claims 1-58, 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, respectively.

60. The bispecific antibody for use~~method~~ of any one of claims 1-59, 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 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.

61. The bispecific antibody for use~~method~~ of any one of claims 1-60, wherein the bispecific 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 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.

62. The bispecific antibody for use~~method~~ of claim 61, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

5 63. The bispecific antibody for use~~method~~ of any one of claims 1-62, 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.

10 64. The bispecific antibody for use~~method~~ of any one of claims 1-63, 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.

15 65. The bispecific antibody for use~~method~~ of any one of claims 1-64, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.