

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) dexamethasone, (c) cytarabine, and (d) oxaliplatin/carboplatin, wherein the 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 the treatment of diffuse large B-cell lymphoma (DLBCL) in a human subject, wherein the treatment comprises administering the bispecific antibody and an effective amount of rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin to the human subject, and wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, 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 subject is planned to receive autologous stem cell transplant (ASCT).

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

6. The bispecific antibody for use~~method~~ of claim 5, wherein the weekly administration of 24 mg or 48 mg is performed for three and one-third 21-day cycles.

7. The bispecific antibody for use~~method~~ of claim 5 or 6, wherein after the weekly administration, if high-dose therapy (HDT) for ASCT does not occur following the fourth 21-day cycle, then the bispecific antibody is administered once every two weeks (biweekly administration) as a monotherapy in 28-day cycles until ASCT is performed.

8. The bispecific antibody for use~~method~~ of claim 7, wherein the biweekly administration is performed until ASCT is performed or for five 28-day cycles, whichever is earlier.

9. The bispecific antibody for use~~method~~ of claim 8, wherein if after five 28-day cycles of biweekly administration ASCT has not been performed, then the bispecific antibody is administered once every four weeks in 28-day cycles.

10. The bispecific antibody for use~~method~~ of claim 9, wherein the administration once every four weeks is performed until ASCT is performed.

11. The bispecific antibody for use~~method~~ of any one of claims 5-10, 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.

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

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

14. The bispecific antibody for use~~method~~ of any one of claims 11-13, 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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15. The bispecific antibody for use~~method~~ of claim 14, 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.

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

17. The bispecific antibody~~method~~ of any one of claims 1-6 and 11-16, wherein rituximab is administered once every three weeks.

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

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

20. The bispecific antibody for use ~~method~~ of any one of claims 1-6 and 11-19, wherein dexamethasone is administered once a day from day 1 to day 4 of the 21-day cycles.

25 21. The bispecific antibody for use~~method~~ of claim 20, wherein dexamethasone is administered for three 21-day cycles.

22. The bispecific antibody for use~~method~~ of any one of claims 1-21, wherein dexamethasone is administered at a dose of 40 mg/day.

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23. The bispecific antibody for use~~method~~ of any one of claims 1-6 and 11-22, wherein cytarabine is administered twice every three weeks.

24. The bispecific antibody for use~~method~~ of claim 23, wherein the administration of cytarabine twice every three weeks is performed for three 21-day cycles.

25. The bispecific antibody for use~~method~~ of any one of claims 1-6 and 11-24, wherein cytarabine is administered at a dose of 2 g/m².

26. The bispecific antibody for use~~method~~ of any one of claims 1-6 and 11-25, wherein cytarabine is administered a total of twice over days 1-3 of a 21-day cycle.

27. The bispecific antibody for use~~method~~ of claim 26, wherein the second administration of cytarabine is performed 12 hours after initiation of the first administration of cytarabine.

28. The bispecific antibody for use~~method~~ of any one of claims 1-6 and 11-27, wherein oxaliplatin is administered once every three weeks.

29. The bispecific antibody for use~~method~~ of claim 28, wherein the administration of oxaliplatin once every three weeks is performed for three 21-day cycles.

30. The bispecific antibody for use~~method~~ of any one of claims 1-6 and 11-29, wherein oxaliplatin is administered at a dose of 100 mg/m².

31. The bispecific antibody for use~~method~~ of any one of claims 1-6 and 11-27, wherein carboplatin is administered once every three weeks.

32. The bispecific antibody for use~~method~~ of claim 31, wherein the administration of carboplatin once every three weeks is performed for three 21-day cycles.

33. The bispecific antibody for use~~method~~ of any one of claims 1-6, 11-27, 31, and 32, wherein carboplatin is administered at a dose of $AUC = 5 \text{ mg/ml/min}$, as determined using Calvert's formula.

5 34. The bispecific antibody for use~~method~~ of any one of claims 1-6 and 11-33, wherein rituximab, dexamethasone, and oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day.

35. The bispecific antibody for use~~method~~ of claim 34, wherein cytarabine is administered the
10 day after rituximab, dexamethasone, oxaliplatin/carboplatin, and the bispecific antibody are administered.

36. The bispecific antibody for use~~method~~ of any one of claims 1-35, wherein the dosing
15 schedule for rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody is as shown in Table 2.

37. The bispecific antibody for use~~method~~ of any one of claims 1, 2, 4-6, and 11-36, wherein:
(a) the bispecific antibody is administered in 21-day cycles as follows:

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

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

(b) rituximab is administered in 21-day cycles on day 1 in cycles 1-3;

(c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

25 (d) cytarabine is administered in 21-day cycles on day 1 or days 1-2 or day 2 or days 2-3
in cycles 1-3; and

(e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

38. The bispecific antibody for use~~method~~ of any one of claims 1, 3-6, and 11-36, wherein:

30 (a) the bispecific antibody is administered in 21-day cycles 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; and

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

5 (b) rituximab is administered in 21-day cycles on day 1 in cycles 1-3;

(c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

(d) cytarabine is administered in 21-day cycles on day 1 or days 1-2 or day 2 or days 2-3 in cycles 1-3; and

(e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

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39. The bispecific antibody for use~~method~~ of claim 37 or 38, wherein the bispecific antibody is administered once every two weeks in 28-day cycles from cycle 5 to cycle 9 or to when ASCT is performed, whichever is earlier.

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40. The bispecific antibody for use~~method~~ of claim 39, wherein if ASCT is not performed by the end of cycle 9, the bispecific antibody is administered once every four weeks in 28-day cycles from cycle 10 to when ASCT is performed.

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

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

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

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

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45. The bispecific antibody for use~~method~~ of any one of claims 1-44, wherein oxaliplatin is administered intravenously.

46. The bispecific antibody for use~~method~~ of any one of claims 1-45, wherein carboplatin is administered intravenously.

47. The bispecific antibody for use~~method~~ of any one of claims 1-46, wherein rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody are administered sequentially.

48. The bispecific antibody for use~~method~~ of any one of claims 1-47, wherein dexamethasone is administered first, rituximab is administered second, oxaliplatin/carboplatin is administered third, the bispecific antibody is administered fourth, and cytarabine is administered last.

49. The bispecific antibody for use~~method~~ of claim 48, wherein dexamethasone, rituximab, oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day, and cytarabine is administered the next day.

50. The bispecific antibody for use~~method~~ of any one of claims 1-49, wherein the DLBCL is double-hit or triple-hit DLBCL.

51. The bispecific antibody for use~~method~~ of any one of claims 1-49, wherein the DLBCL is follicular lymphoma Grade 3B.

52. The bispecific antibody for use~~method~~ of any one of claims 1-51, wherein the subject has relapsed after at least one prior therapy.

53. The bispecific antibody for use~~method~~ of any one of claims 1-52, wherein the subject is refractory to at least one prior therapy.

54. The bispecific antibody for use~~method~~ of any one of claims 1-53, 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.

55. The bispecific antibody for use~~method~~ of any one of claims 1-54, 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.

56. The bispecific antibody for use~~method~~ of any one of claims 1-55, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1, λ (lambda) antibody.

57. The bispecific antibody for use~~method~~ of claim 56 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.

58. The bispecific antibody for use~~method~~ of any one of claims 1-57, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1, κ (kappa) antibody.

59. The bispecific antibody for use~~method~~ of claim 58, 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 60. The bispecific antibody for use~~method~~ of any one of claims 1-59, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

61. The bispecific antibody for use~~method~~ of any one of claims 1-60, wherein the bispecific antibody comprises an inert Fc region.

10 62. The bispecific antibody for use~~method~~ of any one of claims 1-61, 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.

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

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

65. The bispecific antibody for use~~method~~ of claim 64, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

66. The bispecific antibody for use~~method~~ of any one of claims 1-65, 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.

67. The bispecific antibody for use~~method~~ of any one of claims 1-66, 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.

68. The bispecific antibody for use~~method~~ of any one of claims 1-67, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.