

~~We claim:~~Claims

1. ~~A method of treating chronic lymphocytic leukemia (CLL) in a human subject, the method comprising administering to the subject a bispecific antibody comprising:~~

5 (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

10 (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;

15 for use in treatment of chronic lymphocytic leukemia (CLL) in a human subject, the treatment comprising administering wherein the bispecific antibody is administered to the human subject at a dose ranging from 12-60 mg in 28-day cycles.

20 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.

25 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 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).

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

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 any one of claims 4-8, wherein prior to administering the first weekly dose of 12-60 mg, a priming dose of the bispecific antibody is administered in cycle 1 of the 28-day cycles.

10. The bispecific antibody for use~~method~~ of claim 9, wherein the priming dose is administered two weeks prior to administering the first weekly dose of 12-60 mg.

11. The bispecific antibody for use~~method~~ of claim 9 or 10, wherein the priming dose is in the range of 0.05 – 0.35 mg.

12. The bispecific antibody for use~~method~~ of any one of claims 9-11, wherein said priming dose is 0.16 mg or about 0.16 mg.

13. The bispecific antibody for use~~method~~ of any one of claims 9-12, wherein after administering the priming dose and prior to administering the first weekly dose of 12-60 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 12-60 mg on days 15 and 22 of cycle 1.

15. The bispecific antibody for use~~method~~ of claim 13 or 14, wherein said intermediate dose is in the range of 0.6-1.2 mg.

16. The bispecific antibody for use~~method~~ of any one of claims 13-15, wherein said intermediate dose is 0.8 mg or about 0.8 mg.

17. The bispecific antibody for use~~method~~ of any one of claims 13-16, wherein the bispecific antibody is administered in 28-day cycles, wherein:

- a) in cycle 1, a priming dose is administered on day 1, an intermediate dose on day 8, and a full dose of 12-60 mg on days 15 and 22;
- b) in cycles 2-3, a full dose of 12-60 mg is administered on days 1, 8, 15, and 22;
- c) in cycles 4-9, a full dose of 12-60 mg is administered on days 1 and 15; and
- d) in cycle 10 and subsequent cycles, a full dose of 12-60 mg is administered on day 1.

18. The bispecific antibody for use~~method~~ of claim 17, wherein the full dose is 24 mg or about 24 mg.

19. The bispecific antibody for use~~method~~ of claim 17, wherein the full dose is 48 mg or about 48 mg.

20. The bispecific antibody for use~~method~~ of any one of claims 1-19, wherein the bispecific antibody is administered subcutaneously.

21. The bispecific antibody for use~~method~~ of any one of claims 1-20, wherein the CLL is relapsed and/or refractory CLL.

22. The bispecific antibody for use~~method~~ of any one of claims 1-21, wherein the subject is intolerant to a BTK inhibitor.

23. The bispecific antibody for use~~method~~ of any one of claims 1-22, wherein the subject has received at least two prior lines of antineoplastic therapy.

24. The bispecific antibody for use~~method~~ of claim 23, wherein at least one of the at least two prior antineoplastic therapy comprises treatment with a BTK inhibitor.

5 25. The bispecific antibody for use~~method~~ of any one of claims 1-24, wherein the CLL is refractory to a BTK inhibitor.

26. The bispecific antibody for use~~method~~ of any one of claims 1-25, wherein the CLL relapsed during treatment with a BTK inhibitor.

10 27. The bispecific antibody for use~~method~~ of any one of claims 21-26, wherein the subject has refractory and/or relapsed CLL after receiving the two prior antineoplastic therapies.

28. The bispecific antibody for use~~method~~ of any one of claims 1-27, wherein:

15 (i) the first antigen-binding region 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 comprises VHCDR1, VHCDR2, and VHCDR3
20 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.

29. The bispecific antibody for use~~composition~~~~method~~ of any one of claims 1-28, wherein:

25 (i) the first antigen-binding region 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 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
30 NO: 14.

30. The bispecific antibody for use~~method~~ of any one of claims 1-29, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1, λ (lambda) antibody.

5 31. The bispecific antibody for use~~method~~ of claim 30, 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.

10 32. The bispecific antibody for use~~method~~ of any one of claims 1-31, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1, κ (kappa) antibody.

15 33. The bispecific antibody for use~~method~~ of claim 32, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

34. The bispecific antibody for use~~method~~ of any one of claims 1-33, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

20 35. The bispecific antibody for use~~method~~ of any one of claims 1-34, wherein the bispecific antibody comprises an inert Fc region.

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

30 37. The bispecific antibody for use~~method~~ of any one of claims 1-36, 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.

5 38. The bispecific antibody for use~~method~~ of any one of claims 1-37, 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

10 (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.

15 39. The bispecific antibody for use~~method~~ of claim 38, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

20 40. The bispecific antibody for use~~method~~ of any one of claims 1-39, 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.

25 41. The bispecific antibody for use~~method~~ of any one of claims 1-40, 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.

30 42. The bispecific antibody for use~~method~~ of any one of claims 1-41, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.