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(54) **BISPECIFIC ANTIBODY AGAINST CD3 AND CD20 IN COMBINATION THERAPY FOR TREATING DIFFUSE LARGE B-CELL LYMPHOMA**

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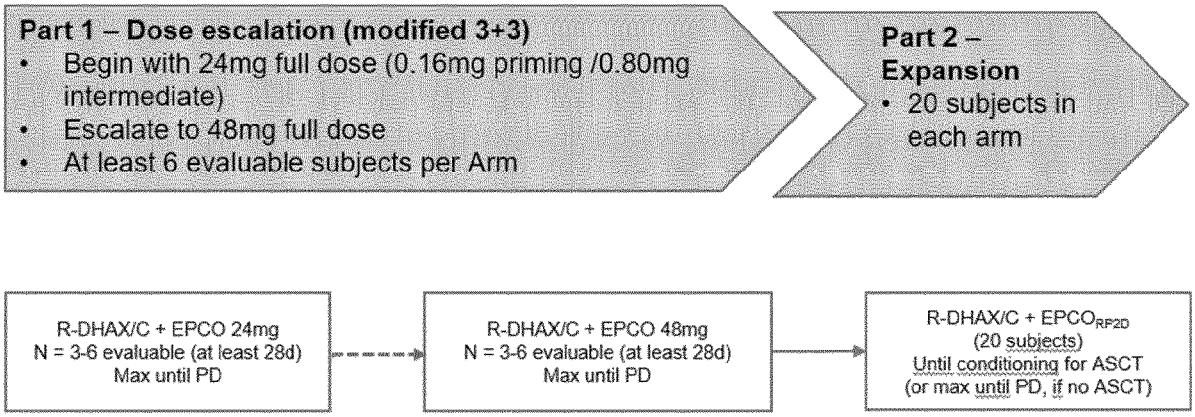
(57) **ABSTRACT**

Provided are methods of clinical treatment of diffuse large B-cell lymphoma (DLBCL) (e.g., relapsed and/or refractory DLBCL eligible for autologous stem cell transplant) in human subjects using a bispecific antibody which binds to CD3 and CD20 in combination with standard of care regimen of R-DHAX/C (rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin).

Specification includes a Sequence Listing.



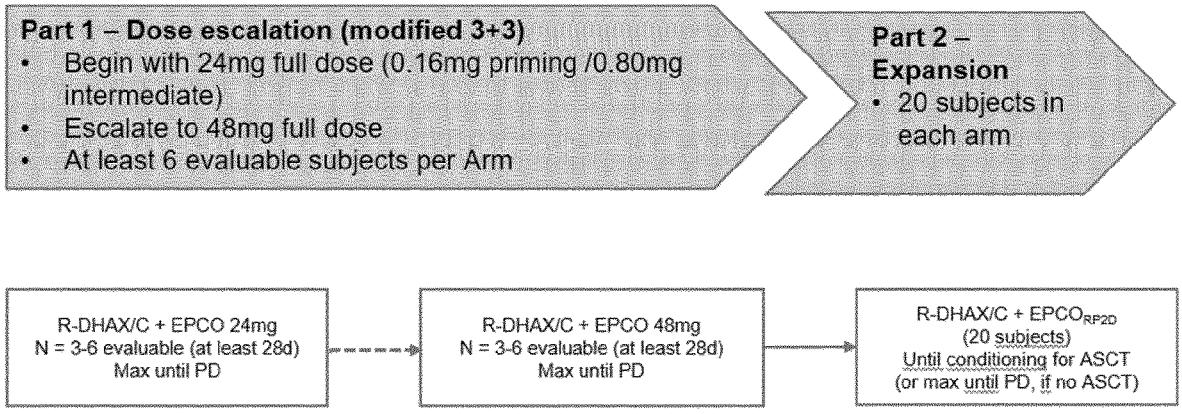

Part 1 – Dose escalation (modified 3+3)
• Begin with 24mg full dose (0.16mg priming /0.80mg intermediate)
• Escalate to 48mg full dose
• At least 6 evaluable subjects per Arm
Part 2 – Expansion
• 20 subjects in each arm
R-DHAX/C + EPCO 24mg
N = 3-6 evaluable (at least 28d)
Max until PD
R-DHAX/C + EPCO 48mg
N = 3-6 evaluable (at least 28d)
Max until PD
R-DHAX/C + EPCO$_{RP2D}$
(20 subjects)
Until conditioning for ASCT
(or max until PD, if no ASCT)

FIG. 1

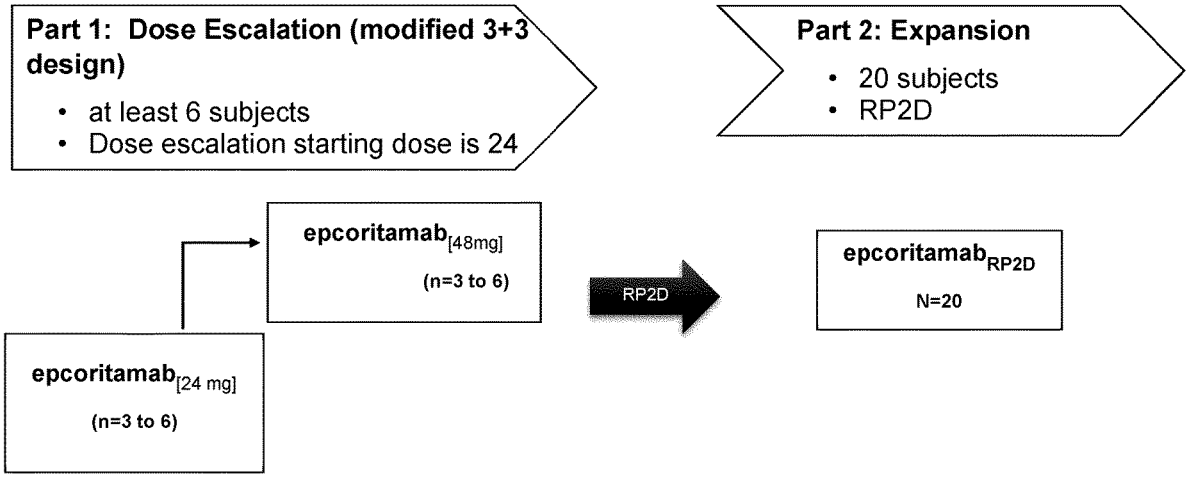

Part 1: Dose Escalation (modified 3+3 design)
• at least 6 subjects
• Dose escalation starting dose is 24
Part 2: Expansion
• 20 subjects
• RP2D
epcoritamab[48mg]
(n=3 to 6)
epcoritamab[24 mg]
(n=3 to 6)
RP2D
epcoritamabRP2D
N=20

FIG. 2

BISPECIFIC ANTIBODY AGAINST CD3 AND CD20 IN COMBINATION THERAPY FOR TREATING DIFFUSE LARGE B-CELL LYMPHOMA

FIELD

[0001] The present invention relates to bispecific antibodies targeting both CD3 and CD20 and the use of such antibodies in combination with a standard of care R-DHAX/C (rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin) regimen for the treatment of diffuse large B-cell lymphoma (DLBCL), for example, recurrent and/or relapsed (R/R) DLBCL (e.g., R/R DLBCL eligible for autologous stem cell transplant (ASCT)). Advantageous treatment regimens are also provided.

BACKGROUND

[0002] DLBCL is the most common non-Hodgkin lymphoma (NHL), and the standard first-line therapy is R-CHOP. The cure rate of this combination for the overall population of newly-diagnosed DLBCL is between 60% and 70% (Sehn et al., *Blood* 2007; 109:1867-61). Attempts to improve upon outcomes of first-line therapy, including intensification of dose and addition of other agents to intensify the regimen, have failed to provide sufficient evidence to alter standard of care.

[0003] Risk factors impacting rates of CR to first-line treatment, disease relapse, and OS are included in the International Prognostic Index (IPI) or Revised-IPI (R-IPI): age >60 years, ECOG >1 or KPS <60, LDH >ULN; extranodal disease >1 (2 or more), and disease Stage 3 or 4 (Project et al., *N Engl J Med* 1993; 329:987-994; Sehn et al., supra). While patients in the good risk group (1-2 IPI factors) have a 4-year PFS of 80% following standard first-line R-CHOP, the 45% of patients in the poor risk (high risk) group (3-5 IPI factors) only achieve a 4-year PFS and OS of 55% (Sehn et al., supra).

[0004] Approximately 35% of patients with DLBCL are either primary refractory to or relapse following standard frontline chemoimmunotherapy. In this group, the only option for long-term survival is salvage chemotherapy, such as rituximab combined with DHAX (dexamethasone, cytarabine and oxaliplatin) or DHAC (dexamethasone, cytarabine and carboplatin), followed by high-dose therapy (HDT) with ASCT (Tixier et al., *Hematol Oncol* 2017; 35:584-90). However, only half of patients with R/R DLBCL are eligible to receive HDT-ASCT, and among those who are transplant-eligible, some are insensitive to salvage therapy, precluding the ASCT procedure. Finally, a significant proportion of patients relapse following HDT-ASCT treatment, with approximately 45% progressing within 3 years (Gisselbrecht et al., *J Clin Oncol* 2010; 28:4184-90). Overall, less than 10% of patients with R/R DLBCL can expect cure with standard secondary therapies. For the patients who relapse after or are ineligible for HDTASCT, there are palliative treatment options, with the goal of achieving remission and prolonging survival. However, there is no consensus gold standard, and patients will normally be offered nonintensive (e.g., R-GemOx, BR) or other palliative intervention (sequential single agent chemotherapy, local radiation therapy for focal symptoms). The recently approved CAR-T cell therapies demonstrate a durable response in only a small subset of patients (Locke et al., Lancet Oncol 2019; 20:31-42; Schuster et al., *N Engl J Med* 2019; 380:45-56). However, access to this highly specialized intervention is limited.

[0005] Given the limited efficacy of and response of subjects to currently available treatments, particular those who have relapsed or are refractory to currently available treatments, novel and effective therapies are needed.

SUMMARY

[0006] Provided herein are methods of treating human subjects who have DLBCL, for example, refractory and/or relapsed (R/R) DLBCL (e.g., R/R DLBCL eligible for ASCT), by administering a bispecific antibody which binds to CD3 and CD20 in combination with a standard of care R-DHAX/C regimen, in particular, advantageous clinical treatment regimens.

[0007] In one aspect, provided herein is a method of treating diffuse large B-cell lymphoma (DLBCL) in a human subject, the method comprising administering to the subject the combination of epcoritamab with R-DHAX/C, e.g., the method comprising administering to the subject an effective amount of (a) rituximab, (b) dexamethasone, (c) cytarabine, (d) oxaliplatin/carboplatin, and (f) epcoritamab.

[0008] In one aspect, provided herein is 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:

[0009] (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

[0010] (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;

[0011] 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.

[0012] In some embodiments, the bispecific antibody is administered at a dose of (or about) 24 mg. In some embodiments, the bispecific antibody is administered at a dose of (or about) 48 mg.

[0013] In one embodiment, the subject is planned to receive autologous stem cell transplant (ASCT).

[0014] In one embodiment, the bispecific antibody is administered once every week at a dose of 24 mg or 48 mg (weekly administration/weekly dose) in 21-day cycles, e.g., for three and one-third 21-day cycles (i.e., day 15 of cycle 1 and days 1, 8, and 15 of cycles 2-4). In some embodiments, the bispecific antibody is administered once every two weeks in 28-day cycles after the weekly administration if ASCT is not performed on the fourth 21-day cycle, e.g., until

ASCT is performed or for five 28-day cycles, whichever is earlier. In some embodiments, the bispecific antibody is administered once every four weeks in 28-day cycles until ASCT is performed if, after five 28-day cycles of biweekly administration, ASCT has not been performed. In a further embodiment, a priming dose (e.g., 0.16 mg or about 0.16 mg) of the bispecific antibody is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg. In some embodiments, after administering the priming dose and prior to administering the weekly dose of 24 mg or 48 mg, an intermediate dose (e.g., 0.8 mg or about 0.8 mg) of the bispecific antibody is administered. In some embodiments, the priming dose is administered one week before the intermediate dose, and the intermediate dose is administered one week before the first weekly dose of 24 mg or 48 mg.

[0015] In some embodiments, rituximab is administered in a 21-day cycle once every three weeks, e.g., for three 21-day cycles. In some embodiments, rituximab is administered at a dose of 375 mg/m^2.

[0016] In some embodiments, dexamethasone is administered once a day from day 1 to day 4 in 21-day cycles, e.g., for three 21-day cycles. In some embodiments, dexamethasone is administered at a dose of 40 mg/day.

[0017] In some embodiments, cytarabine is administered twice every three weeks in 21-day cycles, e.g., for three 21-day cycles. In some embodiments, cytarabine is administered at a dose of 2 g/m^2. In some embodiments, the dose of 2 g/m^2 is administered a total of twice over days 1-2 of the 21-day cycles. In a further embodiment, the second administration of cytarabine on day 2 of a 21-day cycle is performed 12 hours after initiation of the first administration of cytarabine on day 1 of the 21-day cycle. In some embodiments, the dose of 2 g/m^2 is administered a total of twice over days 2-3. In some embodiments, the second administration of cytarabine on day 3 of a 21-day cycle is performed 12 hours after initiation of the first administration of cytarabine on day 2 of the 21-day cycle.

[0018] In some embodiments, oxaliplatin is administered in a 21-day cycle once every three weeks, e.g., for three 21-day cycles. In some embodiments, oxaliplatin is administered at a dose of 100 mg/m^2.

[0019] In some embodiments, carboplatin is administered in a 21-day cycle once every three weeks, e.g., for three 21-day cycles. In some embodiments, oxaliplatin is administered at a dose of AUC=5 mg/ml/min, as determined using Calvert's formula.

[0020] In some embodiments, rituximab, dexamethasone, oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day (e.g., on day 1 of cycles 1-3), e.g., as shown in Table 2. In some embodiments, cytarabine is administered the day after rituximab, dexamethasone, oxaliplatin/carboplatin, and the bispecific antibody are administered.

[0021] In some embodiments, administration is performed in 21-day cycles, wherein

[0022] (a) the bispecific antibody is administered as follows:

[0023] (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; and

[0024] (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

[0025] (b) rituximab is administered in 21-day cycles on day 1 of cycles 1-3;

[0026] (c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0027] (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

[0028] (e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0029] In some embodiments, administration is performed in 21-day cycles, wherein

[0030] (a) the bispecific antibody is administered as follows:

[0031] (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

[0032] (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

[0033] (b) rituximab is administered in 21-day cycles on day 1 of cycles 1-3;

[0034] (c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0035] (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

[0036] (e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0037] In some embodiments, administration is performed in 21-day cycles, wherein

[0038] (a) the bispecific antibody epcoritamab is administered as follows:

[0039] (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; and

[0040] (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

[0041] (b) rituximab is administered in 21-day cycles on day 1 of cycles 1-3;

[0042] (c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0043] (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

[0044] (e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0045] In some embodiments, administration is performed in 21-day cycles, wherein

[0046] (a) the bispecific antibody epcoritamab is administered as follows:

[0047] (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

[0048] (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

[0049] (b) rituximab is administered in 21-day cycles on day 1 of cycles 1-3;

[0050] (c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0051] (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

[0052] (e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0053] In one embodiment, the bispecific antibody is administered once every two weeks in 28-day cycles (i.e., switching from 21-day cycles to 28-day cycles) from cycle 5 to cycle 9 or to when ASCT is performed, whichever is earlier. In some embodiments, if ASCT is not performed by the end of cycle 9 of the 28-day cycles, then the bispecific antibody is administered once every four weeks in 28-day cycles from cycle 10 to when ASCT is performed.

[0054] In some embodiments, the bispecific antibody is administered subcutaneously. In some embodiments, rituximab is administered intravenously. In some embodiments, dexamethasone is administered intravenously or orally. In a further embodiment, cytarabine is administered intravenously. In yet a further embodiment, oxaliplatin is administered intravenously. In some embodiments, carboplatin is administered intravenously.

[0055] In some embodiments, the bispecific antibody, rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin are administered sequentially. For example, dexamethasone is administered first, rituximab is administered second, oxaliplatin/carboplatin is administered third, the bispecific antibody is administered fourth, and cytarabine is administered last. In some embodiments, dexamethasone, rituximab, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day. In some embodiments, dexamethasone, rituximab, oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day, and the first dose of cytarabine is administered on the same day and the second dose of cytarabine is administered on the next day. In some embodiments, dexamethasone, rituximab, oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day, and the first dose of cytarabine is administered on the next day and the second dose of cytarabine is administered on the day after the first dose (e.g., over days 1-2 or days 2-3 of a 21-day cycle). In some embodiments, the DLBCL is double-hit or triple-hit DLBCL. In some embodiments, the DLBCL is follicular lymphoma Grade 3B. In some embodiments, the subject has relapsed after at least one prior therapy. In a further embodiment, the subject is refractory to at least one prior therapy.

[0056] In some embodiments, the subject is treated with prophylaxis for cytokine release syndrome (CRS). In some embodiments, the prophylaxis comprises administering a corticosteroid (e.g., dexamethasone at a dose of, e.g., 40 mg/day or equivalent thereof, including oral dose) on, for example, the same day as the bispecific antibody. In some embodiments, the corticosteroid is further administered on the second, third, and fourth days after administering the bispecific antibody. In some embodiments, for the methods described herein involving administering dexamethasone as part of the R-DHAX/C regimen on days 1-4 of each 21-day cycle, no additional prophylaxis for CRS is administered on days 1-4, since the dexamethasone component of R-DHAX/C serves as the corticosteroid component of CRS prophylaxis (i.e., there is no double-dosing of the corticosteroid). However, in such embodiments, a corticosteroid such as prednisolone or its equivalent may be administered for CRS prophylaxis on days for which the bispecific antibody is administered but R-DHAX/C is not administered (i.e., prednisolone or its equivalent is administered on days 8-11 and 15-18 of the first 21-day cycle, and optionally on days 8-11 and 15-18 of the second 21-day cycle (or later cycles) if, e.g., CRS >Grade 1 remains at the end of the previous cycle).

[0057] In some embodiments, if the dexamethasone from R-DHAX/C is administered more than 120 minutes before administration of the bispecific antibody, then the subject is administered prednisolone or an equivalent as CRS prophylaxis about 30-120 minutes prior to administration of the bispecific antibody.

[0058] In some embodiments, the subject is administered premedication, such as antihistamine (e.g., diphenhydramine, intravenously or orally at a dose of, e.g., 50 mg or equivalent thereof) and/or antipyretic (e.g., acetaminophen at a dose of, e.g., 650-1000 mg), to reduce reactions to injections. In some embodiments, the premedication is administered on the same day as the bispecific antibody.

[0059] In some embodiments, the prophylaxis and premedication are administered in cycle 1 and start of cycle 2 of the 21-day cycles (i.e., together with the first dose of the bispecific antibody on day 1 in cycle 2). In some embodiments, the prophylaxis is administered during the second and third administrations of the bispecific antibody during cycle 2 of the 21-day cycles when the subject experiences CRS greater than grade 1 after the first administration of the bispecific antibody in cycle 2 of the 21-day cycles. In some embodiments, the prophylaxis is continued in a subsequent cycle, when in the last administration of the bispecific antibody of the previous cycle, the subject experiences CRS greater than grade 1. In a further embodiment, the premedication and prophylaxis are administered during cycle 2 of the 21-day cycles. In yet a further embodiment, the premedication and prophylaxis are administered during subsequent cycles.

[0060] In some embodiments, the subject is administered antibiotics if the subject develops Grade 1 CRS. In some embodiments, the subject is administered a vasopressor if the subject develops Grade 2 or Grade 3 CRS. In some embodiments, the subject is administered at least two vasopressors if the subject develops Grade 4 CRS.

[0061] In some embodiments, the subject is administered tocilizumab if the subject develops Grade 2, Grade 3, or Grade 4 CRS. In some embodiments, the subject is further administered a steroid (e.g., dexamethasone or methylprednisolone). In some embodiments, tocilizumab is switched to an anti-IL-6 antibody (e.g., siltuximab) or an IL-1R antagonist (e.g., anakinra) if the subject is refractory to tocilizumab.

[0062] In some embodiments, the subject is administered prophylaxis for tumor lysis syndrome (TLS). In some embodiments, the prophylaxis for TLS comprises administering one or more uric acid reducing agents prior to administration of the bispecific antibody. In some embodiments, rasburicase and/or allopurinol is administered as the uric acid reducing agent. In some embodiments, when a subject shows signs of TLS, supportive therapy, such as rasburicase, may be used.

[0063] In some embodiments, the subject treated with the methods described herein achieves a complete response, a partial response, or stable disease, e.g., as defined by the Lugano criteria or LYRIC.

[0064] In some embodiments, 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 the second antigen-binding region 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.

[0065] In some embodiments, 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 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 NO: 14.

[0066] In some embodiments, the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1,λ (lambda) antibody (e.g., SEQ ID NO: 22). In some embodiments, the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody (e.g., SEQ ID NO: 23). In some embodiments, the bispecific antibody is a full-length antibody with a human IgG1 constant region.

[0067] In some embodiments, the bispecific antibody comprises an inert Fc region, for example, an Fc region in which 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. In some embodiments, the bispecific antibody comprises substitutions which promote bispecific antibody formation, for example, 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. In some embodiments, the bispecific antibody has both an inert Fc region (e.g., substitutions at L234, L235, and D265 (e.g., L234F, L235E, and D265A)) and substitutions which promote bispecific antibody formation (e.g., F405L and K409R). In a further embodiment, the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

[0068] In some embodiments, the bispecific antibody comprises a first heavy chain and a first light chain comprising (or consisting of) the amino acid sequences set forth in SEQ ID NOs: 24 and 25, respectively, and a second heavy chain and a second light chain comprising (or consisting of) the amino acid sequences set forth in SEQ ID NOs: 26 and 27, respectively. In some embodiments, the bispecific antibody is epcoritamab, or a biosimilar thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0069] FIG. **1** is a schematic of the overall clinical trial design.

[0070] FIG. **2** is a schematic of the dose escalation design.

DETAILED DESCRIPTION

[0071] The term "immunoglobulin" as used herein refers to a class of structurally related glycoproteins consisting of two pairs of polypeptide chains, one pair of light (L) low molecular weight chains and one pair of heavy (H) chains, all four inter-connected by disulfide bonds. The structure of immunoglobulins has been well characterized (see, e.g., Fundamental Immunology Ch. **7** (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). Briefly, each heavy chain typically is comprised of a heavy chain variable region (abbreviated herein as VH or V_H) and a heavy chain constant region (abbreviated herein as CH or C_H). The heavy chain constant region typically is comprised of three domains, CH1, CH2, and CH3. The hinge region is the region between the CH1 and CH2 domains of the heavy chain and is highly flexible. Disulfide bonds in the hinge region are part of the interactions between two heavy chains in an IgG molecule. Each light chain typically is comprised of a light chain variable region (abbreviated herein as VL or V_L) and a light chain constant region (abbreviated herein as CL or C_L). The light chain constant region typically is comprised of one domain, CL. The VH and VL regions may be further subdivided into regions of hypervariability (or hypervariable regions which may be hypervariable in sequence and/or form of structurally defined loops), also termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FRs). Each VH and VL is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 (see also Chothia and Lesk *J Mol Biol* 1987; 196:90117). Unless otherwise stated or contradicted by context, CDR sequences herein are identified according to IMGT rules (Brochet X., *Nucl Acids Res* 2008; 36:W503-508; Lefranc M P., *Nucl Acids Res* 1999; 27:209-12; www.imgt.org/). Unless otherwise stated or contradicted by context, reference to amino acid positions in the constant regions is according to the EU-numbering (Edelman et al., *PNAS.* 1969; 63:78-85; Kabat et al., Sequences of Proteins of Immunological Interest, Fifth Edition. 1991 NIH Publication No. 91-3242). For example, SEQ ID NO: 15 sets forth amino acids positions 118-447, according to EU numbering, of the IgG1 heavy chain constant region.

[0072] The term "amino acid corresponding to position . . . " as used herein refers to an amino acid position number in a human IgG1 heavy chain. Corresponding amino acid positions in other immunoglobulins may be found by alignment with human IgG1. Thus, an amino acid or segment in one sequence that "corresponds to" an amino acid or segment in another sequence is one that aligns with the other amino acid or segment using a standard sequence alignment program such as ALIGN, ClustalW or similar, typically at default settings and has at least 50%, at least 80%, at least 90%, or at least 95% identity to a human IgG1 heavy chain. It is within the ability of one of ordinary skill in the art to align a sequence or segment in a sequence and thereby determine the corresponding position in a sequence to an amino acid position according to the present invention.

[0073] The term "antibody" (Ab) as used herein in the context of the present invention refers to an immunoglobulin molecule which has the ability to specifically bind to an antigen under typical physiological conditions with a half-life of significant periods of time, such as at least about 30 minutes, at least about 45 minutes, at least about one hour, at least about two hours, at least about four hours, at least about 8 hours, at least about 12 hours, about 24 hours or more, about 48 hours or more, about 3, 4, 5, 6, 7 or more

days, etc., or any other relevant functionally-defined period (such as a time sufficient to induce, promote, enhance, and/or modulate a physiological response associated with antibody binding to the antigen and/or time sufficient for the antibody to recruit an effector activity). The variable regions of the heavy and light chains of the immunoglobulin molecule contain a binding domain that interacts with an antigen. The term antibody, unless specified otherwise, also encompasses polyclonal antibodies, monoclonal antibodies (mAbs), antibody-like polypeptides, chimeric antibodies and humanized antibodies.

[0074] The term "antibody fragment" or "antigen-binding fragment" as used herein refers to a fragment of an immunoglobulin molecule which retains the ability to specifically bind to an antigen, and can be generated by any known technique, such as enzymatic cleavage, peptide synthesis, and recombinant techniques. Examples of antibody fragments include (i) a Fab' or Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains, or a monovalent antibody as described in WO2007059782 (Genmab); (ii) $F(ab')_2$ fragments, bivalent fragments comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting essentially of the VH and CH1 domains; (iv) a Fv fragment consisting essentially of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., *Nature* 1989; 341: 54446), which consists essentially of a VH domain and also called domain antibodies (Holt et al; *Trends Biotechnol* 2003; 21:484-90); (vi) camelid or nanobodies (Revets et al; *Expert Opin Biol Ther* 2005; 5:111-24) and (vii) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they may be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain antibodies or single chain Fv (scFv), see, e.g., Bird et al., *Science* 1988; 242:42326 and Huston et al., *PNAS* 1988; 85:587983). Such single chain antibodies are encompassed within the term antibody fragment unless otherwise noted or clearly indicated by context.

[0075] The term "antibody-binding region" or "antigen-binding region" as used herein refers to the region which interacts with the antigen and comprises both the VH and the VL regions. The term antibody when used herein refers not only to monospecific antibodies, but also multispecific antibodies which comprise multiple, such as two or more, e.g., three or more, different antigen-binding regions. The term antigen-binding region, unless otherwise stated or clearly contradicted by context, includes fragments of an antibody that are antigen-binding fragments, i.e., retain the ability to specifically bind to the antigen.

[0076] As used herein, the term "isotype" refers to the immunoglobulin class (for instance IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM) that is encoded by heavy chain constant region genes. When a particular isotype, e.g., IgG1, is mentioned, the term is not limited to a specific isotype sequence, e.g., a particular IgG1 sequence, but is used to indicate that the antibody is closer in sequence to that isotype, e.g. IgG1, than to other isotypes. Thus, e.g., an IgG1 antibody may be a sequence variant of a naturally-occurring IgG1 antibody, which may include variations in the constant regions.

[0077] The term "bispecific antibody" or "bs" or "bsAb" as used herein refers to an antibody having two different antigen-binding regions defined by different antibody sequences. A bispecific antibody can be of any format.

[0078] The terms "half molecule", "Fab-arm", and "arm", as used herein, refer to one heavy chain-light chain pair.

[0079] When a bispecific antibody is described as comprising a half-molecule antibody "derived from" a first parental antibody, and a half-molecule antibody "derived from" a second parental antibody, the term "derived from" indicates that the bispecific antibody was generated by recombining, by any known method, said half-molecules from each of said first and second parental antibodies into the resulting bispecific antibody. In this context, "recombining" is not intended to be limited by any particular method of recombining and thus includes all of the methods for producing bispecific antibodies described herein, including for example recombining by half-molecule exchange (also known as "controlled Fab-arm exchange"), as well as recombining at nucleic acid level and/or through co-expression of two half-molecules in the same cells.

[0080] The term "full-length" as used herein in the context of an antibody indicates that the antibody is not a fragment but contains all of the domains of the particular isotype normally found for that isotype in nature, e.g., the VH, CH1, CH2, CH3, hinge, VL and CL domains for an IgG1 antibody. A full-length antibody may be engineered. An example of a "full-length" antibody is epcoritamab.

[0081] The term "Fc region" as used herein refers to an antibody region consisting of the Fc sequences of the two heavy chains of an immunoglobulin, wherein said Fc sequences comprise at least a hinge region, a CH2 domain, and a CH3 domain.

[0082] The term "heterodimeric interaction between the first and second CH3 regions" as used herein refers to the interaction between the first CH3 region and the second CH3 region in a first-CH3/second-CH3 heterodimeric protein.

[0083] The term "homodimeric interactions of the first and second CH3 regions" as used herein refers to the interaction between a first CH3 region and another first CH3 region in a first-CH3/first-CH3 homodimeric protein and the interaction between a second CH3 region and another second CH3 region in a second-CH3/second-CH3 homodimeric protein.

[0084] The term "isolated antibody" as used herein refers to an antibody which is substantially free of other antibodies having different antigenic specificities. In a preferred embodiment, an isolated bispecific antibody that specifically binds to CD20 and CD3 is in addition substantially free of monospecific antibodies that specifically bind to CD20 or CD3.

[0085] The term "CD3" as used herein refers to the human Cluster of Differentiation **3** protein which is part of the T-cell co-receptor protein complex and is composed of four distinct chains. CD3 is also found in other species, and thus, the term "CD3" is not limited to human CD3 unless contradicted by context. In mammals, the complex contains a CD3γ (gamma) chain (human CD3γ chain UniProtKB/Swiss-Prot No P09693, or cynomolgus monkey CD3γ UniProtKB/Swiss-Prot No Q95LI7), a CD36 (delta) chain (human CD36 UniProtKB/Swiss-Prot No P04234, or cynomolgus monkey CD36 UniProtKB/Swiss-Prot No Q95LI8), two CD3ε (epsilon) chains (human CD3ε UniProtKB/Swiss-Prot No P07766, SEQ ID NO: 28); cynomolgus CD3ε UniProtKB/Swiss-Prot No Q95LI5; or rhesus CD3ε

UniProtKB/Swiss-Prot No G7NCB9), and a CD3-chain (zeta) chain (human CD3 UniProtKB/Swiss-Prot No P20963, cynomolgus monkey CD3 UniProtKB/Swiss-Prot No Q09TK0). These chains associate with a molecule known as the T-cell receptor (TCR) and generate an activation signal in T lymphocytes. The TCR and CD3 molecules together comprise the TCR complex.

[0086] The term "CD3 antibody" or "anti-CD3 antibody" as used herein refers to an antibody which binds specifically to the antigen CD3, in particular human CD3ε (epsilon).

[0087] The term "human CD20" or "CD20" refers to human CD20 (UniProtKB/Swiss-Prot No P11836, SEQ ID NO: 29) and includes any variants, isoforms, and species homologs of CD20 which are naturally expressed by cells, including tumor cells, or are expressed on cells transfected with the CD20 gene or cDNA. Species homologs include rhesus monkey CD20 (*Macaca mulatta*; UniProtKB/Swiss-Prot No H9YXP1) and cynomolgus monkey CD20 (*Macaca fascicularis*; UniProtKB No G7PQ03).

[0088] The term "CD20 antibody" or "anti-CD20 antibody" as used herein refers to an antibody which binds specifically to the antigen CD20, in particular to human CD20.

[0089] The term "CD3xCD20 antibody", "anti-CD3xCD20 antibody", "CD20xCD3 antibody" or "anti-CD20xCD3 antibody" as used herein refers to a bispecific antibody which comprises two different antigen-binding regions, one of which binds specifically to the antigen CD20 and one of which binds specifically to CD3.

[0090] The term "DuoBody-CD3xCD20" as used herein refers to an IgG1 bispecific CD3xCD20 antibody comprising a first heavy and light chain pair as defined in SEQ ID NO: 24 and SEQ ID NO: 25, respectively, and comprising a second heavy and light chain pair as defined in SEQ ID NO: 26 and SEQ ID NO: 27. The first heavy and light chain pair comprises a region which binds to human CD3ε (epsilon), the second heavy and light chain pair comprises a region which binds to human CD20. The first binding region comprises the VH and VL sequences as defined by SEQ ID NOs: 6 and 7, and the second binding region comprises the VH and VL sequences as defined by SEQ ID NOs: 13 and 14. This bispecific antibody can be prepared as described in WO 2016/110576.

[0091] Antibodies comprising functional variants of the heavy chain, light chains, VL regions, VH regions, or one or more CDRs of the antibodies of the examples as also provided herein. A functional variant of a heavy chain, a light chain, VL, VH, or CDRs used in the context of an antibody still allows the antibody to retain at least a substantial proportion (at least about 90%, 95% or more) of functional features of the "reference" and/or "parent" antibody, including affinity and/or the specificity/selectivity for particular epitopes of CD20 and/or CD3, Fc inertness and PK parameters such as half-life, Tmax, Cmax. Such functional variants typically retain significant sequence identity to the parent antibody and/or have substantially similar length of heavy and light chains. The percent identity between two sequences is a function of the number of identical positions shared by the sequences (i.e.,% homology=# of identical positions/total # of positions×100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The percent identity between two nucleotide or amino acid sequences may e.g. be determined using the algorithm of E. Meyers and W. Miller, Comput. Appl. Biosci 4, 11-17 (1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences may be determined using the Needleman and Wunsch, *J Mol Biol* 1970; 48:444-453 algorithm. Exemplary variants include those which differ from heavy and/or light chains, VH and/or VL, and/or CDR regions of the parent antibody sequences mainly by conservative substitutions; e.g., 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or 1 of the substitutions in the variant may be conservative amino acid residue replacements.

[0092] Conservative substitutions may be defined by substitutions within the classes of amino acids reflected in the following table:

TABLE 1

Amino acid residue classes for conservative substitutions

Acidic Residues	Asp (D) and Glu (E)
Basic Residues	Lys (K), Arg (R), and His (H)
Hydrophilic Uncharged Residues	Ser (S), Thr (T), Asn (N), and Gln (Q)
Aliphatic Uncharged Residues	Gly (G), Ala (A), Val (V), Leu (L), and Ile (I)
Non-polar Uncharged Residues	Cys (C), Met (M), and Pro (P)
Aromatic Residues	Phe (F), Tyr (Y), and Trp (W)

[0093] Unless otherwise indicated, the following nomenclature is used to describe a mutation: i) substitution of an amino acid in a given position is written as, e.g., K409R which means a substitution of a Lysine in position 409 with an Arginine; and ii) for specific variants the specific three or one letter codes are used, including the codes Xaa and X to indicate any amino acid residue. Thus, the substitution of Lysine with Arginine in position 409 is designated as: K409R, and the substitution of Lysine with any amino acid residue in position 409 is designated as K409X. In case of deletion of Lysine in position 409 it is indicated by K409*.

[0094] The term "humanized antibody" as used herein refers to a genetically engineered non-human antibody, which contains human antibody constant domains and non-human variable domains modified to contain a high level of sequence homology to human variable domains. This can be achieved by grafting of the six non-human antibody CDRs, which together form the antigen binding site, onto a homologous human acceptor framework region (FR) (see WO92/22653 and EP0629240). In order to fully reconstitute the binding affinity and specificity of the parental antibody, the substitution of framework residues from the parental antibody (i.e., the non-human antibody) into the human framework regions (back-mutations) may be required. Structural homology modeling may help to identify the amino acid residues in the framework regions that are important for the binding properties of the antibody. Thus, a humanized antibody may comprise non-human CDR sequences, primarily human framework regions optionally comprising one or more amino acid back-mutations to the non-human amino acid sequence, and fully human constant regions. The VH and VL of the CD3 arm that is used herein in DuoBody-CD3xCD20 represents a humanized antigen-binding region. Optionally, additional amino acid modifications, which are not necessarily back-mutations, may be applied to obtain a

humanized antibody with preferred characteristics, such as affinity and biochemical properties.

[0095] The term "human antibody" as used herein refers to antibodies having variable and constant regions derived from human germline immunoglobulin sequences. Human antibodies may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The VH and VL of the CD20 arm that is used in DuoBody-CD3xCD20 represents a human antigen-binding region. Human monoclonal antibodies of the invention can be produced by a variety of techniques, including conventional monoclonal antibody methodology, e.g., the standard somatic cell hybridization technique of Kohler and Milstein, *Nature* 256: 495 (1975). Although somatic cell hybridization procedures are preferred, in principle, other techniques for producing monoclonal antibody can be employed, e.g., viral or oncogenic transformation of B-lymphocytes or phage display techniques using libraries of human antibody genes. A suitable animal system for preparing hybridomas that secrete human monoclonal antibodies is the murine system. Hybridoma production in the mouse is a very well-established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. Fusion partners (e.g., murine myeloma cells) and fusion procedures are also known. Human monoclonal antibodies can thus be generated using, e.g., transgenic or transchromosomal mice or rats carrying parts of the human immune system rather than the mouse or rat system. Accordingly, in one embodiment, a human antibody is obtained from a transgenic animal, such as a mouse or a rat, carrying human germline immunoglobulin sequences instead of animal immunoglobulin sequences. In such embodiments, the antibody originates from human germline immunoglobulin sequences introduced in the animal, but the final antibody sequence is the result of said human germline immunoglobulin sequences being further modified by somatic hypermutations and affinity maturation by the endogenous animal antibody machinery (see, e.g., Mendez et al. *Nat Genet* 1997; 15:146-56). The VH and VL regions of the CD20 arm that is used in DuoBody-CD3xCD20 represents a human antigen-binding region.

[0096] The term "biosimilar" (e.g., of an approved reference product/biological drug) as used herein refers to a biologic product that is similar to the reference product based on data from (a) analytical studies demonstrating that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; (b) animal studies (including the assessment of toxicity); and/or (c) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is approved and intended to be used and for which approval is sought (e.g., that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product). In some embodiments, the biosimilar biological product and reference product utilizes the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product. In some embodiments, the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product. In some embodiments, the route of administration, the dosage form, and/or the strength of the biological product are the same as those of the reference product. A biosimilar can be, e.g., a presently known antibody having the same primary amino acid sequence as a marketed antibody, but may be made in different cell types or by different production, purification, or formulation methods.

[0097] The term "reducing conditions" or "reducing environment" as used herein refers to a condition or an environment in which a substrate, here a cysteine residue in the hinge region of an antibody, is more likely to become reduced than oxidized.

[0098] The term "recombinant host cell" (or simply "host cell") as used herein is intended to refer to a cell into which an expression vector has been introduced, e.g., an expression vector encoding an antibody described herein. Recombinant host cells include, for example, transfectomas, such as CHO, CHO-S, HEK, HEK293, HEK-293F, Expi293F, PER.C6 or NS0 cells, and lymphocytic cells.

[0099] The term "diffuse large B-cell lymphoma" or "DLBCL" as used herein refers to a neoplasm of the germinal center B lymphocytes with a diffuse growth pattern and a high-intermediate proliferation index. DLBCLs represent approximately 30% of all lymphomas. Subtypes of DLBCL seem to have different outlooks (prognoses) and responses to treatment. DLBCL can affect any age group but occurs mostly in older people (the average age is mid-60s). "Double hit" and "triple hit" DLBCL refers to DLBCL with MYC and BCL2 and/or BCL6 translocations, falling under the category of high-grade B cell lymphoma (HGBCL) with MYC and BCL2 and/or BCL6 translocations, in accordance with the WHO 2016 classification (Swerdlow S H, Campo E, Harris N L, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised ed. 4th). Lyon, France: IARC Press (2017), the contents of which are herein incorporated by reference). Follicular lymphoma grade 3B is also often considered to be equivalent to DLBCL and thus treated as such.

[0100] The term "relapsed DLBCL" as used herein refers to DLBCL which progressed after achieving partial response (PR) or complete response (CR) to prior treatment with an anti-neoplastic therapy.

[0101] The term "refractory DLBCL" as used herein refers to DLBCL which was treated with at least one prior anti-neoplastic therapy but failed to achieve at least a partial response to the therapy.

[0102] The term "R/R DLBCL" as used herein, unless specified otherwise, is intended to refer to relapsed and/or refractory DLBCL

[0103] The term "R-DHAX/C" as used herein refers to "R-DHAX" or "R-DHAC". "R-DHAX" refers to a drug combination containing rituximab, dexamethasone, cytarabine, and oxaliplatin. "R-DHAC" refers to a drug combination containing rituximab, dexamethasone, cytarabine, and carboplatin. As used herein, "oxaliplatin/carboplatin" is

intended to refer to oxaliplatin or carboplatin. The term "R-DHAX/C" is also intended to encompass regimens in which the rituximab component is replaced with a biosimilar thereof, and/or branded or generic versions (generic equivalents) of dexamethasone, cytarabine, oxaliplatin, and/or carboplatin, as well as pharmaceutically acceptable salts, isomers, racemates, solvates, complexes and hydrates, anhydrate forms thereof, and any polymorphic or amorphous forms thereof or combinations thereof, are used in the methods described herein.

[0104] The term "rituximab" (CAS Number: 174722-31-7; DrugBank—DB00073; Kyoto Encyclopedia of Genes and Genomes (KEGG) entry D02994) as used herein refers to a genetically engineered chimeric human gamma 1 murine constant domain containing monoclonal antibody against human CD20. The chimeric antibody contains human gamma 1 constant domains and is referred to as "C2B8" in U.S. Pat. No. 5,736,137 (the entire content of which is herein incorporated by reference). Rituximab is commercially available, for example, as Rituxan®, MabThera®, or Zytux®. In certain embodiments of the methods described herein, rituximab can be replaced with a biosimilar thereof. Accordingly, it will be understood that the term "rituximab" is intended to encompass biosimilars of rituximab. Also encompassed by the term "rituximab" are antibodies which have CDRs, variable regions, or heavy and light chains of rituximab. Non-limiting examples of biosimilars of rituximab include Truxima® (rituximab-abbs), Ruxience® (rituximab-pvvr), and Rixathon®. The biosimilar may be administered according to a standard of care dosage, or at a dose equivalent to the standard of care dosage specified for rituximab.

[0105] The term "dexamethasone" as used herein is an anti-inflammatory glucocorticoid. Its chemical names include, e.g., (11β,16α)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione (CAS No. 50-02-2) and 9α-Fluoro-16α-methylprednisolone. Dexamethasone is marketed under tradenames such as Decadron®, Dexamethasone Intensol®, Dexamethasone Oral Solution USP Intensol®, and Baycadron®. The term "dexamethasone" is also intended to encompass branded and generic versions (generic equivalents) of dexamethasone, as well as pharmaceutically acceptable salts, isomers, racemates, solvates, complexes and hydrates, anhydrate forms thereof, and any polymorphic or amorphous forms thereof or combinations thereof.

[0106] The term "cytarabine" as used herein refers to a compound comprising a cytosine base and a arabinose sugar that is converted into Arabinofuranosylcytosine triphosphate in vivo. Cytarabine is also known as known as cytosine arabinoside or Ara-C (Arabinofuranosyl Cytidine) (CAS No. 147-94-4). Cytarabine is commercially available, for example, under the tradenames, e.g., Cytosar-U®, Tarabine PFS®, and Depocyt®. The term "cytarabine" is also intended to encompass branded and generic versions (generic equivalents) of cytarabine, as well as pharmaceutically acceptable salts, isomers, racemates, solvates, complexes and hydrates, anhydrate forms thereof, and any polymorphic or amorphous forms thereof or combinations thereof.

[0107] "Oxaliplatin" refers to a platinum-based drug that acts as a DNA cross-linking agent to effectively inhibit DNA replication and transcription, resulting in cytotoxicity which is cell-cycle non-specific. Oxaliplatin may be referred to as, e.g., [SP-4-2-(1R-trans)]-(1,2-cyclohexanediamine-N,N')[ethanedioata(2-)-O,O']platinum; [(1R,2R)-cyclohexane-1,2-diamine](ethanedioato-O,O')platinum(II). Oxaliplatin has the chemical formula $C_8H_{14}N_2O_4Pt$ (CAS No. 61825-94-3), and is commercially available, for example, under the tradenames Eloxatin® and Oxaliplatin Novaplus®. The term "oxaliplatin" is also intended to encompass branded and generic versions (generic equivalents) of oxaliplatin, as well as pharmaceutically acceptable salts, isomers, racemates, solvates, complexes and hydrates, anhydrate forms thereof, and any polymorphic or amorphous forms thereof or combinations thereof.

[0108] "Carboplatin" is a platinum coordination compound that is used as a cancer chemotherapeutic agent. Carboplatin may be referred to as, e.g., cis-diammine (1,1-cyclobutanedicarboxylato) platinum (II). Carboplatin has the chemical formula $C_6H_{12}N_2O_4Pt$ (CAS No. 41575-94-4), and is commercially available, for example, under the tradenames Paraplatin®, CARBOplatin®, Paraplatin NovaPlus®, Carboplatin Novaplus®. The term "carboplatin" is also intended to encompass branded and generic versions (generic equivalents) of carboplatin, as well as pharmaceutically acceptable salts, isomers, racemates, solvates, complexes and hydrates, anhydrate forms thereof, and any polymorphic or amorphous forms thereof or combinations thereof.

[0109] Dosing for carboplatin can be determined using "Calvert's formula," which is based on a subject's glomerular filtration rate (GFR in mL/min) and carboplatin target area under the concentration versus time curve (AUC in mg/mLmin). Calvert's formula is as follows:

$$\text{Total dose (mg)} = (\text{target } AUC) \times (GFR + 25)$$

[0110] The term "autologous stem cell transplant" or "ASCT" as used herein refers to stem cells that are collected from an individual and given back to that the individual.

[0111] The term "treatment" refers to the administration of an effective amount of a therapeutically active antibody described herein for the purpose of easing, ameliorating, arresting or eradicating (curing) symptoms or disease states such as DLBCL. Treatment may result in a complete response (CR), partial response (PR), or stable disease (SD), for example, as defined by Lugano criteria and/or LYRIC. Treatment may be continued, for example, up until ASCT is performed or disease progression, whichever occurs first.

[0112] The term "administering" or "administration" as used herein refers to the physical introduction of a composition (or formulation) comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Preferred routes of administration for antibodies described herein include intravenous, intraperitoneal, intramuscular, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as in vivo electroporation. Alternatively, a therapeutic agent described herein can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration,

for example, intranasally, orally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods. In the methods described herein, the bispecific antibody (e.g., epcoritamab) is administered subcutaneously. Other agents used in combination with the bispecific antibody, such as for R-DHAX/C, cytokine release syndrome prophylaxis, and/or tumor lysis syndrome (TLS) prophylaxis, may be administered via other routes, such as intravenously or orally.

[0113] The term "effective amount" or "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. For example, dosages as defined herein for the bispecific antibody (e.g., epcoritamab), i.e., 24 mg or 48 mg, administered subcutaneously can be defined as such an "effective amount" or "therapeutically effective amount". A therapeutically effective amount of an antibody may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. In some embodiments, patients treated with the methods described herein will show an improvement in ECOG performance status. A therapeutically effective amount or dosage of a drug includes a "prophylactically effective amount" or a "prophylactically effective dosage", which is any amount of the drug that, when administered alone or in combination with another therapeutic agent to a subject at risk of developing a disease or disorder (e.g., cytokine release syndrome) or of suffering a recurrence of disease, inhibits the development or recurrence of the disease.

[0114] The term "inhibits growth" of a tumor as used herein includes any measurable decrease in the growth of a tumor, e.g., the inhibition of growth of a tumor by at least about 10%, for example, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 99%, or 100%.

[0115] The term "subject" as used herein refers to a human patient, for example, a human patient with DLBCL. The terms "subject" and "patient" are used interchangeably herein.

[0116] The term "buffer" as used herein denotes a pharmaceutically acceptable buffer. The term "buffer" encompasses those agents which maintain the pH value of a solution, e.g., in an acceptable range and includes, but is not limited to, acetate, histidine, TRIS® (tris (hydroxymethyl) aminomethane), citrate, succinate, glycolate and the like. Generally, the "buffer" as used herein has a pKa and buffering capacity suitable for the pH range of about 5 to about 6, preferably of about 5.5.

[0117] "Disease progression" or "PD" as used herein refers to a situation in which one or more indices of DLBCL show that the disease is advancing despite treatment. In one embodiment, disease progression is defined based on the Lugano Response Criteria for Malignant Lymphoma ("Lugano criteria") and/or Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC). Details regarding the Lugano criteria/classification system, including definitions for complete response (CR), partial response (PR), no response/stable disease (NR/SD), and progressive disease (PD) are provided in Cheson et al. *J Clin Oncol* 2014; 32:3059-68, the contents of which are incorporated by reference herein (see, in particular, Table 3 in Cheson et al., 2014). Details regarding LYRIC are provided in Table 9.

[0118] A "surfactant" as used herein is a compound that is typically used in pharmaceutical formulations to prevent drug adsorption to surfaces and or aggregation. Furthermore, surfactants lower the surface tension (or interfacial tension) between two liquids or between a liquid and a solid. For example, an exemplary surfactant can significantly lower the surface tension when present at very low concentrations (e.g., 5% w/v or less, such as 3% w/v or less, such as 1% w/v or less such as 0.4% w/v or less, such as below 0.1% w/v or less, such as 0.04% w/v). Surfactants are amphiphilic, which means they are usually composed of both hydrophilic and hydrophobic or lipophilic groups, thus being capable of forming micelles or similar self-assembled structures in aqueous solutions. Known surfactants for pharmaceutical use include glycerol monooleate, benzethonium chloride, sodium docusate, phospholipids, polyethylene alkyl ethers, sodium lauryl sulfate and tricaprylin (anionic surfactants); benzalkonium chloride, citrimide, cetylpyridinium chloride and phospholipids (cationic surfactants); and alpha tocopherol, glycerol monooleate, myristyl alcohol, phospholipids, poloxamers, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbintan fatty acid esters, polyoxyethylene sterarates, polyoxyl hydroxystearate, polyoxylglycerides, polysorbates such as polysorbate 20 or polysorbate 80, propylene glycol dilaurate, propylene glycol monolaurate, sorbitan esters sucrose palmitate, sucrose stearate, tricaprylin and TPGS (Nonionic and zwitterionic surfactants).

[0119] A "diluent" as used herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of dilutions of the pharmaceutical composition or pharmaceutical formulation (the terms "composition" and "formulation" are used interchangeably herein). Preferably, such dilutions of the composition dilute only the antibody concentration but not the buffer and stabilizer. Accordingly, in one embodiment, the diluent contains the same concentrations of the buffer and stabilizer as is present in the pharmaceutical composition of the invention. Further exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution which is preferably an acetate buffer, sterile saline solution such as water for injection, Ringer's solution or dextrose solution. In one embodiment the diluent comprises or consists essentially of acetate buffer and sorbitol.

[0120] As used herein, the term "about" refers to a value that is no more than 10% above and no more than 10% below a specified value.

DLBCL Treatment Regimens

[0121] Provided herein are methods of treating DLBCL in a human subject using a bispecific antibody which binds to CD3 and CD20 ("anti-CD3xCD20 antibody"), e.g., an isolated anti-CD3xCD20 antibody such as epcoritamab which binds to human CD3 and human CD20, in combination with a standard of care regimen of R-DHAX (rituximab, dexamethasone, cytarabine, and oxaliplatin) or R-DHAC (rituximab, dexamethasone, cytarabine, and carboplatin) (referred to herein as "R-DHAX/C"). The methods are useful for treating, e.g., relapsed and/or refractory (R/R) DLBCL. It is

understood that the methods of treating DLBCL (e.g., R/R DLBCL, such as R/R DLBCL eligible for ASCT) with a bispecific antibody which binds to both CD3 and CD20 described herein also encompass corresponding uses of the bispecific antibody for treating DLBCL in a human subject (e.g., R/R DLBCL, such as R/R DLBCL eligible for ASCT).

[0122] Accordingly, in one aspect, provided herein is a method of treating DLBCL in a human subject, the method comprising administering a bispecific antibody and an effective amount of (a) rituximab, (b) dexamethasone, (c) cytarabine, and (d) oxaliplatin/carboplatin, wherein the bispecific antibody comprises:

[0123] (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

[0124] (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;

[0125] wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin, and the bispecific antibody are administered in 21-day cycles.

[0126] In some embodiments, the bispecific antibody is administered at a dose of (or a dose of about) 24 mg. In some embodiments, the bispecific antibody is administered at a dose of (or a dose of about) 48 mg.

[0127] In some embodiments, the bispecific antibody is a full length antibody. In other embodiments, the bispecific antibody is an antibody with an inert Fc region. In yet other embodiments, the bispecific antibody is a full length antibody with an inert Fc region.

[0128] With regard to the dose of (or dose of about) 24 mg or 48 mg of the bispecific antibody that is to be administered, or any other specified dose, it is understood that this amount refers to the amount of a bispecific antibody representing a full-length antibody, such as epcoritamab as defined in the Examples section. Hence, one may refer to administering a dose of a bispecific antibody of 24 mg as administering a dose of a bispecific antibody described herein, wherein the dose corresponds to a dose of 24 mg of epcoritamab. One of ordinary skill in the art can readily determine the amount of antibody to be administered when, for example, the antibody used differs substantially in molecular weight from the molecular weight of a full-length antibody such as epcoritamab. For instance, the amount of antibody can be calculated by dividing the molecular weight of the antibody by the weight of a full-length antibody such as epcoritamab and multiplying the outcome thereof with the specified dose as described herein. As long as the bispecific antibody (e.g., a functional variant of DuoBody CD3xCD20) has highly similar features as DuoBody CD3xCD20, with regard to plasma half-life, Fc inertness, and/or binding characteristics for CD3 and CD20, i.e., with regard to CDRs and epitope binding features, such antibodies are suitable for use in the methods provided herein at a dose described for a full-length antibody such as epcoritamab.

[0129] In some embodiments, the subject is planned to receive ASCT. In one embodiment, the bispecific antibody is administered once a week (weekly administration/weekly dose) in 21-day cycles. In some embodiments, the weekly dose of 24 mg or 48 mg is administered for three and one-third 21-day cycles (i.e., 10 times; on day 15 of cycle 1, and days 1, 8, and 15 of cycles 2-4). In some embodiments, after the weekly administration, if ASCT is not performed on the fourth 21-day cycle, then the bispecific antibody is administered once every two weeks (biweekly administration) as a monotherapy (i.e., without R-DHAX/C) in 28-day cycles until ASCT is performed. In yet some embodiments, the biweekly administration is performed until ASCT is performed or for five 28-day cycles, whichever is earlier. 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. The administration once every four weeks may be performed for an extended period, e.g., until ASCT is performed or until disease progression, for example, for at least 1 cycle, at least 2 cycles, at least 3 cycles, at least 4 cycles, at least 5 cycles, at least 6 cycles, at least 7 cycles, at least 8 cycles, at least 9 cycles, at least 10 cycles, at least 11 cycles, at least 12 cycles, at least 13 cycles, at least 14 cycles, at least 15 cycles, such as between 1-20 cycles, 1-19 cycles, 1-18 cycles, 1-17 cycles, 1-16 cycles, 1-15 cycles, 1-14 cycles, 1-13 cycles, 1-12 cycles, 1-10 cycles, 1-5 cycles, 5-20 cycles, 5-15 cycles, 5-10 cycles 10-20 cycles, 10-15 cycles, or 15-20 cycles. In one embodiment, the administration once every four weeks is performed until cycle 14 or until ASCT is performed or until disease progression (e.g., as defined by the Lugano criteria or LYRIC), whichever is earlier. In one embodiment, the weekly administration of the bispecific antibody (21-day cycle) is performed in the cycle during which the subject is receiving a conditioning regimen+ ASCT (e.g., in cycle 4 of the 21-day cycles).

[0130] In one embodiment, the weekly dose of the bispecific antibody is administered in 21-day cycles on cycles 1-4 (which may include priming and intermediate doses, as described below), the dose once every two weeks of the bispecific antibody is administered in 28-day cycles on cycles 5-9 (i.e., switched from 21-day cycles to 28-day cycles starting on cycle 5), and the dose once every four weeks is administered in 28-day cycles from cycle 10 onwards, for example, on cycles 10-14 or until ASCT is performed, whichever is earlier. In some embodiments, the dose once every four weeks extends past cycle 14, e.g., until ASCT is performed or until disease progression or unacceptable toxicity is observed.

[0131] It is understood that the doses referred to herein may also be referred to as a full or a flat dose in the scenarios above wherein, e.g., the weekly dose, the biweekly dose, and/or the dose every four weeks is administered at the same level. Accordingly, when a dose of 48 mg is selected, preferably, at each weekly administration, at each biweekly administration, and at each administration every four weeks, the same dose of 48 mg is administered. Prior to administering the dose, a priming or a priming and subsequent intermediate (second priming) dose may be administered. This may be advantageous as it may help mitigate cytokine

release syndrome (CRS) risk and severity, a side-effect that can occur during treatment with the bispecific anti-CD3xCD20 antibody described herein. Such priming, or priming and intermediate doses, are at a lower dose as compared with the flat or full dose.

[0132] Accordingly, in some embodiments, prior to administering the weekly dose of 24 mg or 48 mg, a priming dose of the bispecific antibody may be administered. In one embodiment, the priming dose is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg in cycle 1. In one embodiment, the priming dose is 0.16 mg (or about 0.16 mg) of the full-length bispecific antibody.

[0133] In some embodiments, after administering the priming dose and prior to administering the weekly dose of 24 mg or 48 mg, an intermediate dose of said bispecific antibody is administered. In one embodiment, the priming dose is administered one week before the intermediate dose (i.e., on day 1 of cycle 1), and the intermediate dose is administered one week before the first weekly dose of 24 mg or 48 mg (i.e., on day 8 of cycle 1). In one embodiment, the intermediate dose is 800 μg (0.8 mg) or about 800 μg (0.8 mg) of the full-length bispecific antibody.

[0134] The methods described herein involve treating human subjects who have DLBCL with a bispecific antibody which binds to CD3 and CD20 in combination with a standard-of-care regimen of R-DHAX/C (rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin).

[0135] In some embodiments, rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin are administered at standard-of-care dosages for R-DHAX/C, e.g., as supported by clinical studies, according to local guidelines, and/or according to relevant local labels.

[0136] In some embodiments, rituximab is administered according to relevant local product labels or summary of product characteristics (see, e.g., RITUXAN® (rituximab) prescribing information, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/103705s54141b1.pdf). In some embodiments, a biosimilar of rituximab is used in place of rituximab in the methods described herein.

[0137] In some embodiments, dexamethasone is administered according to relevant local product labels or summary of product characteristics (see, e.g., Dexamethasone Sodium Phosphate Injection, prescribing information, available at www.accessdata.fda.gov/drugsatfda_docs/label/2014/40572s0021b1edt.pdf).

[0138] In some embodiments, cytarabine is administered according to relevant local product labels or summary of product characteristics (see, e.g., CYTARABINE® (cytarabine injection, solution) prescribing information, available at labeling.pfizer.com/ShowLabeling.aspx?id=4397).

[0139] In some embodiments, oxaliplatin is administered according to relevant local product labels or summary of product characteristics (see, e.g., ELOXATIN® prescribing information, available at www.accessdata.fda.gov/drugsatfda_docs/label/2020/021759s0231bl.pdf).

[0140] In some embodiments, carboplatin is administered according to relevant local product labels or summary of product characteristics (see, e.g., PARAPLATIN® prescribing information, available at www.accessdata.fda.gov/drugsatfda_docs/label/2010/020452s0051b1.pdf).

[0141] In one embodiment, rituximab is administered according to local guidelines and local labels. In some embodiments, rituximab is administered at a dose of (or a dose of about) 375 mg/m^2. In some embodiments, rituximab is administered intravenously.

[0142] In one embodiment, rituximab is administered once every three weeks (Q3W) in 21-day cycles. In some embodiments, administration of rituximab once every three weeks is performed for three 21-day cycles (i.e., 3 times).

[0143] In one embodiment, dexamethasone is administered according to local guidelines and local labels. In another embodiment, dexamethasone is administered at a dose of (or a dose of about) 40 mg (e.g., 40 mg/day). In some embodiments, dexamethasone is administered intravenously. In a further embodiment, dexamethasone is administered orally.

[0144] In one embodiment, dexamethasone is administered once a day for four consecutive days (i.e., days 1-4) in 21-day cycles. In some embodiments, dexamethasone is administered for three 21-day cycles (e.g., on days 1-4 of cycles 1-3 of the 21-day cycles).

[0145] In one embodiment, cytarabine is administered according to local guidelines and local labels. In another embodiment, cytarabine is administered at a dose of (or a dose of about) 2 g/m^2. In some embodiments, the dose of 2 g/m^2 is administered twice, wherein the second administration of cytarabine is performed 12 hours or about 12 hours after initiation of the first administration. In a further embodiment, cytarabine is administered a total of twice over day 1, or days 1-2, or day 2, or days 2-3 of a 21-day cycle. Preferably, the total of two doses are administered over days 1-2 of a 21-day cycle. However, it can be contemplated that cytarabine is administered on day 2 and on day 3 as administration may be delayed for various reasons. Hence, in one embodiment, cytarabine can be administered a total of twice over any of days 1-3, with an interval of about 12 hours between administrations. For example, cytarabine may be administered a total of twice on the same day (e.g., day 1 of, e.g., cycle 1; or day 2 of e.g. cycle 2), or a total of twice on consecutive days (e.g., days 1-2 of, e.g., cycle 1, or days 2-3 of, e.g., cycle 1). In a further embodiment, cytarabine is administered intravenously. In one embodiment, cytarabine is administered a total of twice every three weeks (Q3W) in 21-day cycles. In another embodiment, administration of cytarabine twice every three weeks is performed for three 21-day cycles (i.e., six total administrations). In some embodiments, cytarabine is administered twice on day 1 of such a 21-day cycle. In another embodiment, cytarabine is administered for a first time on day 1 and a second time on day 2 of such a 21-day cycle. In some embodiments, cytarabine is administered twice on day 2 of such a 21-day cycle. In another embodiment, cytarabine is administered for a first time on day 2 and a second time on day 3 of such a 21-day cycle.

[0146] In one embodiment, oxaliplatin is administered according to local guidelines and local labels. In another embodiment, oxaliplatin is administered at a dose of (or a dose of about) 100 mg/m^2. In some embodiments, oxaliplatin is administered intravenously.

[0147] In one embodiment, oxaliplatin is administered once every three weeks (Q3W) in 21-day cycles. In some embodiments, administration of oxaliplatin once every three weeks is performed for three 21-day cycles (i.e., three times).

[0148] In one embodiment, carboplatin is administered according to local guidelines and local labels. In another embodiment, carboplatin is administered at a dose of (or a

dose of about) AUC=5 mg/ml/min, for example, using Calvert's formula. In some embodiments, carboplatin is administered intravenously.

[0149] In one embodiment, carboplatin is administered once every three weeks (Q3W) in 21-day cycles. In some embodiments, administration of carboplatin once every three weeks is performed for three 21-day cycles (i.e., 3 times).

[0150] In one embodiment, the dose of cytarabine is reduced from 2 $g/m^2 \times 2$ (i.e., 2 g/m^2 twice) when a subject presents with severe neutropenia (ANC $<0.2 \times 10^9/L$; reduce dose to 1 $g/m^2 \times 2$), severe thrombocytopenia (platelets $<20 \times$ 109/L; reduce dose to 1 $g/m^2 \times 2$), sepsis associated with neutropenia (reduce dose to 0.5 $g/m^2 \times 1$), and if the subject has a serum creatinine 1.5-3.0 mg/mL (hold cytarabine).

[0151] The dose of oxaliplatin may be reduced when a subject presents with neuropathy (worsening compared to baseline). In one embodiment, the dose of cytarabine is reduced to 75 mg/m^2 when the subject presents with severe paresthesia (increase in severity from baseline) lasting between 7 and 13 days after each administration. See, for example, Table 8 for dose modification criteria or cytarabine. In some embodiments, oxaliplatin is stopped if a subject presents with abnormal results from neurological examination nor if a subject experiences significant paresthesia lasting for 14 days or more. Oxaliplatin can be restarted at a dose of 75 mg/m^2 once symptoms improve.

[0152] In certain embodiments, the bispecific antibody, rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin are administered simultaneously.

[0153] In one embodiment, the bispecific antibody, rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin are administered sequentially. For instance, in one embodiment, dexamethasone is administered first, rituximab is administered second, oxaliplatin/carboplatin is administered third, the bispecific antibody is administered fourth, and cytarabine is administered last. In another embodiment, the bispecific antibody, rituximab, dexamethasone, and oxaliplatin/carboplatin are administered on the same day, and cytarabine is administered the next day.

[0154] In some embodiments, the subject is administered premedication and/or prophylaxis for CRS prior to administration of rituximab, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody. In one embodiment, the dexamethasone component of the R-DHAX/C regimen is used as the corticosteroid in CRS prophylaxis.

[0155] In one embodiment, rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody are administered according to the following schedule:

[0156] (a) the bispecific antibody is administered in 21-day cycles as follows:

[0157] (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; and

[0158] (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

[0159] (b) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0160] (c) 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

[0161] (d) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0162] In one embodiment, rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody are administered according to the following schedule:

[0163] (a) the bispecific antibody is administered in 21-day cycles as follows:

[0164] (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

[0165] (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

[0166] (b) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0167] (c) 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

[0168] (d) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0169] In one embodiment, rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody epcoritamab are administered according to the following schedule:

[0170] (a) the bispecific antibody epcoritamab is administered in 21-day cycles as follows:

[0171] (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; and

[0172] (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

[0173] (b) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0174] (c) 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

[0175] (d) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0176] In one embodiment, rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody epcoritamab are administered according to the following schedule:

[0177] (a) the bispecific antibody epcoritamab is administered in 21-day cycles as follows:

[0178] (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

[0179] (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

[0180] (b) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0181] (c) 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

[0182] (d) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0183] In one embodiment, rituximab (e.g. intravenously), dexamethasone (e.g. intravenously or orally), cytarabine, oxaliplatin/carboplatin (e.g. intravenously), and the bispecific antibody (e.g. subcutaneously) are administered according to the following schedule:

[0184] (a) the bispecific antibody is administered in 21-day cycles as follows:

[0185] (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; and

[0186] (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

[0187] (b) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3 at a dose of 100 mg/m^2 and a dose of AUC=5 mg/ml/min as determined using Calvert's formula, respectively;

[0188] (c) cytarabine is administered twice in 21-day cycles on day 1 or days 1-2 or day 2 or days 2-3 in cycles 1-3 at a dose of 2 g/m^2; and

[0189] (d) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3 at a dose of 40 mg/day.

[0190] In one embodiment, rituximab (e.g. intravenously), dexamethasone (e.g. intravenously or orally), cytarabine, oxaliplatin/carboplatin (e.g. intravenously), and the bispecific antibody (e.g. subcutaneously) are administered according to the following schedule:

[0191] (a) the bispecific antibody is administered in 21-day cycles as follows:

[0192] (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

[0193] (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

[0194] (b) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3 at a dose of 100 mg/m^2 and a dose of AUC=5 mg/ml/min as determined using Calvert's formula, respectively;

[0195] (c) cytarabine is administered twice in 21-day cycles on day 1 or days 1-2 or day 2 or days 2-3 in cycles 1-3 at a dose of 2 g/m^2; and

[0196] (d) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3 at a dose of 40 mg/day.

[0197] In one embodiment, rituximab (e.g. intravenously), dexamethasone (e.g. intravenously or orally), cytarabine, oxaliplatin/carboplatin (e.g. intravenously), and the bispecific antibody epcoritamab (e.g. subcutaneously) are administered according to the following schedule:

[0198] (a) the bispecific antibody epcoritamab is administered in 21-day cycles as follows:

[0199] (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; and

[0200] (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

[0201] (b) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3 at a dose of 100 mg/m^2 and a dose of AUC=5 mg/ml/min as determined using Calvert's formula, respectively;

[0202] (c) cytarabine is administered twice in 21-day cycles on day 1 or days 1-2 or day 2 or days 2-3 in cycles 1-3 at a dose of 2 g/m^2; and

[0203] (d) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3 at a dose of 40 mg/day.

[0204] In one embodiment, rituximab (e.g. intravenously), dexamethasone (e.g. intravenously or orally), cytarabine, oxaliplatin/carboplatin (e.g. intravenously), and the bispecific antibody epcoritamab (e.g. subcutaneously) are administered according to the following schedule:

[0205] (a) the bispecific antibody epcoritamab is administered in 21-day cycles as follows:

[0206] (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

[0207] (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

[0208] (b) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3 at a dose of 100 mg/m^2 and a dose of AUC=5 mg/ml/min as determined using Calvert's formula, respectively;

[0209] (c) cytarabine is administered twice in 21-day cycles on day 1 or days 1-2 or day 2 or days 2-3 in cycles 1-3 at a dose of 2 g/m^2; and

(d) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3 at a dose of 40 mg/day. In some embodiments, the subject is planned to receive ASCT. In one embodiment, if the subject has not received ASCT by the end of cycle 4 of the 21-day cycles, then 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. In another embodiment, if ASCT is not performed by cycle 9, the bispecific antibody is administered once every four weeks in 28-day cycles from cycle 10, for example, from cycle 10 to cycle 15, from cycle 10 to cycle 17, from cycle 10 to cycle 20 or until ASCT is performed or until disease progression, whichever is earlier. In some embodiments, once ASCT is performed, administration of the bispecific antibody is stopped.

[0210] Accordingly, in one embodiment, following the 4 21-day cycles, the bispecific antibody is administered as monotherapy in 28-day cycles until the subject receives ASCT as follows:

[0211] (e) in cycle 5-9 a dose of 24 mg is administered on days 1 and 15;

[0212] (f) from cycle 10 of the 28-day cycles a dose of 24 mg is administered on day 1.

In one embodiment, following the 4 21-day cycles, the bispecific antibody is administered as monotherapy in 28-day cycles until the subject receives ASCT as follows:

[0213] (e) in cycle 5-9 a dose of 48 mg is administered on days 1 and 15;

[0214] (f) from cycle 10 of the 28-day cycles a dose of 48 mg is administered on day 1.

[0215] In one embodiment, the subject undergoing the treatment with the methods described herein has documented DLBCL (de novo or histologically transformed from indolent lymphomas, except for CLL) according to the WHO 2016 classification (Swerdlow S H, Campo E, Harris N L, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised ed. 4th). Lyon, France: IARC Press (2017), the contents of which are herein incorporated by reference). In another embodiment, the subject has DLBCL, NOS (not otherwise specified). In another embodiment, the subject has "double hit" or "triple hit" DLBCL, which are classified in WHO 2016 as HGBCL, with MYC and BCL2 and/or BCL6 translocations. In some embodiments, the subject has follicular lymphoma Grade 3B. In a further embodiment, the subject has relapsed or is

refractory to at least one prior therapy. In yet a further embodiment, the subject is eligible to receive high-dose therapy (HDT)-ASCT.

[0216] In one embodiment, the subject has an Eastern Cooperative Oncology Group (ECOG) performance status (ECOG PS) of 0, 1, or 2. Information regarding ECOG PS scores can be found in, e.g., Oken et al, *Am J Clin Oncol* 1982 December; 5(6):649-55).

[0217] In one embodiment, the subject has measurable disease as defined as (a)≥1 measurable nodal lesion (long axis >1.5 cm and short axis >1.0 cm) or ≥1 measurable extra-nodal lesion (long axis >1 cm) on CT or MRI.

[0218] In one embodiment, the subject has acceptable organ function as defined as: (a) ANC ≥1.0×109/L, (b) platelet count ≥75×109/L, or ≥50×109/L if bone marrow infiltration or splenomegaly, (c) ALT level ≤2.5 times the ULN, (d) total bilirubin level ≤2×ULN, (e) eGFR >50 mL/min (by Cockcroft-Gault Formula), and (f) PT, INR, and aPTT ≤1.5×ULN (unless receiving anticoagulant).

[0219] In one embodiment, the subject does not have severe allergic or anaphylactic reactions to anti-CD20 antibody therapy, any component of DHAX/C (i.e., dexamethasone, cytarabine, and oxaliplatin/carboplatin), or the bispecific antibody, or known allergy or intolerance to any component or excipient of rituximab, DHAX/C, and/or the bispecific antibody.

[0220] In one embodiment, the subject does not have clinically significant cardiac disease, including (a) myocardial infarction within one year prior to the first dose of the bispecific antibody, or unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, NYHA class III-IV), cardiac arrhythmia (CTCAE Version 4 Grade 2 or higher), or clinically significant ECG abnormalities, and/or (b) 12-lead ECG showing a baseline QTcF >470 msec.

[0221] A human subject receiving a treatment described herein may be a patient having one or more of the inclusion criteria set forth in Example 2, or not having one or more of the exclusion criteria set forth in Example 2.

[0222] The methods described herein are advantageous for treating DLBCL, such as R/R DLBCL (e.g., R/R DLBCL in subjects who are eligible for ASCT). The treatment is maintained continuously using, e.g., the treatment regimens described herein, until ASCT is performed, or until progressive disease develops or unacceptable toxicity occurs.

[0223] The response of subjects with DLBCL to treatment using the methods described herein may be assessed according to the Lugano Response Criteria for Malignant Lymphoma (also referred to as "Lugano criteria" herein) and/or Lymphoma Response to Immunomodulatory Therapy Criteria (also referred to as "LYRIC" herein), as described in Example 2. In one embodiment, complete response (CR), partial response (PR), and stable disease (SD) are assessed using the Lugano criteria. In some embodiments, patients showing disease progression, also referred to as progressive disease (PD), according to the Lugano criteria are further evaluated according to LYRIC. Details regarding the Lugano criteria/classification system, including definitions for complete response, partial response, no response/stable disease, and progressive disease are provided in Cheson et al. *J Clin Oncol* 2014; 32:3059-68 (see, in particular, Table 3 in Cheson et al., 2014). Details regarding LYRIC are provided in Table 9.

[0224] In some embodiments, subjects are treated with the methods described herein until they show disease progression (PD), e.g., as defined by Lugano criteria and/or LYRIC. In some embodiments, the subjects are treated with the methods described herein until they receive ASCT

[0225] Subjects treated according to the methods described herein preferably experience improvement in at least one sign of DLBCL. In one embodiment, improvement is measured by a reduction in the quantity and/or size of measurable tumor lesions. In some embodiments, lesions can be measured on CT, PET-CT, or MRI films. In some embodiments, cytology or histology can be used to evaluate responsiveness to a therapy. In some embodiments, bone marrow aspirate and bone marrow biopsy can be used to evaluate response to therapy.

[0226] In one embodiment, the subject treated exhibits a complete response (CR), a partial response (PR), or stable disease (SD), as defined by the Lugano criteria or LYRIC (Table 9). In some embodiments, the methods described herein produce at least one therapeutic effect chosen from prolonged survival, such as progression-free survival or overall survival, optionally compared to another therapy or placebo.

[0227] Cytokine release syndrome (CRS) can occur when methods are used in human subjects that utilize immune cell- and bispecific antibody-based approaches that function by activation of immune effector cell, such as by engaging CD3 (Lee et al., *Biol Blood Marrow Transplant* 2019; 25:625-38, which is incorporated herein by reference). Hence, in some embodiments, CRS mitigation is performed together with the methods described herein. As part of CRS mitigation, the selection of a priming dose and/or intermediate dose is performed prior to administering the full dose (e.g., 24 or 48 mg), as described herein. CRS can be classified in accordance with standard practice (e.g. as outlined in Lee et al., *Biol Blood Marrow Transplant* 2019; 25:625-38, which is incorporated herein by reference). CRS may include excessive release of cytokines, for example of proinflammatory cytokines, e.g., IL-6, TNF-alpha, or IL-8, that may result in adverse effects like fever, nausea, vomiting and chills. Thus, despite the unique anti-tumor activity of bispecific antibodies such as epcoritamab, their immunological mode of action may trigger unwanted "side" effects, i.e., the induction of unwanted inflammatory reactions. Hence, patients may be further subjected to a concomitant treatment, prophylaxis, and/or premedication with, e.g., analgesics, antipyretics, and/or anti-inflammatory drugs to mitigate possible CRS symptoms.

[0228] Accordingly, in one embodiment, human subjects in the methods described herein are treated with prophylaxis for CRS. In some embodiments, the prophylaxis includes the administration of a corticosteroid. In one embodiment, the prophylaxis is administered on the same day as the bispecific antibody. The prophylaxis can also be administered on the subsequent day as well, more preferably on subsequent days 2, 3, and 4. It is understood that days 2, 3 and 4 when relating to further medication, such as prophylaxis, is relative to the administration of the bispecific antibody which is administered on day 1. For example, when in a cycle the antibody is administered on day 15, and prophylaxis is also administered, the prophylaxis corresponding to days 2, 3 and 4 are days 16, 17, and 18 of the cycle. In some embodiments, the prophylaxis is administered on the day when the bispecific antibody is administered and on subsequent days 2-4. When

said prophylaxis is administered on the same day as the bispecific antibody, the prophylaxis is preferably administered 30-120 minutes prior to said administration of the bispecific antibody. The corticosteroid for use in CRS prophylaxis for the methods described herein is preferably prednisolone. In some embodiments, the dexamethasone component of R-DHAX/C is used as the corticosteroid component of the CRS prophylaxis. In some embodiments, prednisolone is administered at an intravenous dose of 100 mg, or an equivalent thereof, including an oral dose. Exemplary corticosteroid equivalents of prednisolone, along with dosage equivalents, which can be used for CRS prophylaxis are shown in Table 5.

[0229] With regard to CRS prophylaxis when the bispecific antibody (e.g., epcoritamab) is administered on days when R-DHAX/C is also administered (e.g., day 1 of each 21-day cycle), it is understood that the R-DHAX/C regimen already provides the corticosteroid component for the CRS prophylaxis (i.e., dexamethasone or equivalent), as well as the subsequent administration of corticosteroids in CRS prophylaxis for, e.g., subsequent days 2, 3, and 4. If, however, the bispecific antibody is not administered within about 30-120 minutes of administration of the dexamethasone component of R-DHAX/C, then, in some embodiments, an additional dose of corticosteroid for CRS prophylaxis may be administered on that day. On subsequent days, however, e.g., days 2, 3, and 4 after day 1 when R-DHAX/C and the bispecific antibody were administered, only one dose of dexamethasone is administered (i.e., the dose serves as both CRS prophylaxis for the bispecific antibody and a component of the R-DHAX/C regimen). On days when the bispecific antibody is administered without R-DHAX/C (e.g., days 8 and 15 of the 21-day cycles), dexamethasone or an equivalent is administered as CRS prophylaxis, e.g., together with premedication (e.g., antihistamine/antipyretic), as described below.

[0230] In one embodiment, when dexamethasone is administered as a part of the R-DHAX/C regimen on days 1-4 of a 21-day cycle (e.g., cycle 1), and the bispecific antibody is administered on day 1 of that cycle, no additional corticosteroid is administered for CRS prophylaxis, provided that the dexamethasone component of R-DHAX/C is administered about 30-120 minutes before the bispecific antibody is administered (i.e., no double dosing of the corticosteroid is performed). In some embodiments, when dexamethasone is administered as a part of the R-DHAX/C regimen on days 1-4 of a 21-day cycle (e.g., cycle 1), and the bispecific antibody is administered on day 1 of that cycle, a further corticosteroid (e.g., prednisolone 100 mg or equivalent thereof) is administered as CRS prophylaxis before the bispecific antibody is administered if the dexamethasone component of R-DHAX/C is administered more than 120 minutes before the bispecific antibody is administered. In some embodiments, if R-DHAX/C is withheld on day 1 of a 21-day cycle, and thus the dexamethasone component of the R-DHAX/C regimen is not administered to the subject on the same day as the bispecific antibody, then the subject is administered a corticosteroid such as prednisolone or its equivalent for CRS prophylaxis.

[0231] Furthermore, in some embodiments, human subjects in the methods described herein are treated with premedication to reduce reactions to injections. In one embodiment, the premedication includes the administration of antihistamines. In some embodiments, the premedication includes the administration of antipyretics. In a further embodiment, the premedication includes systemic administration of antihistamines and antipyretics.

[0232] An exemplary antihistamine suitable for use in premedication is diphenhydramine. In one embodiment, diphenhydramine is administered at an intravenous or oral dose 50 mg, or an equivalent thereof. An exemplary antipyretic suitable for use in premedication is acetaminophen. In one embodiment, acetaminophen is administered at an oral dose of 650-1000 mg, or equivalent thereof. In some embodiments, the premedication is administered on the same day as the bispecific antibody, for example, prior to the injection with the bispecific antibody, e.g., 30-120 minutes prior to administration of the bispecific antibody.

[0233] Premedication and/or prophylaxis for CRS can be administered at least in the initial phase of the treatment. In some embodiments, premedication and/or prophylaxis is administered during the first four administrations of the bispecific antibody. For example, the prophylaxis and/or premedication can be administered as described herein, during the three administrations of the bispecific antibody in the first 21-day cycle and first administration of the bispecific antibody of the second 21-day cycle. In one embodiment, on day 1 of the first and second 21-day cycles, the dexamethasone component of the R-DHAX/C regimen serves as the corticosteroid for prophylaxis of CRS.

[0234] Usually, risk of reactions during the initial treatment subsides after a few administrations, e.g., after the first four administrations (three administrations in first cycle and first administration in second cycle). Hence, when the human subject does not experience CRS with the fourth administration, prophylaxis for CRS may be stopped. However, CRS prophylaxis may continue, particularly when the human subject experiences a CRS greater than grade 1. Likewise, premedication may also optionally continue. CRS grading can be performed as described in Tables 6 and 7.

[0235] In a further embodiment, in the methods described herein, the prophylaxis for CRS is continued in the second 21-day cycle when the human subject experiences CRS greater than grade 1 after the fourth administration of the bispecific antibody in cycle 2 (i.e., day 1 of cycle 2 of the 21-day cycles). Furthermore, the prophylaxis can be continued during a subsequent cycle, when in the last administration of the bispecific antibody of the previous cycle, the human subject experiences CRS greater than grade 1. Any premedication may be optionally administered during the second cycle. Further premedication may be optionally administered during subsequent cycles as well.

[0236] In one embodiment, premedication and prophylaxis for CRS is administered, including an antihistamine such as diphenhydramine (e.g., at an intravenous or oral dose 50 mg, or an equivalent thereof), an antipyretic such as acetaminophen (e.g., at an oral dose of 650-1000 mg, or an equivalent thereof), and a corticosteroid such as prednisolone (e.g., at an intravenous or oral dose of 100 mg, or an equivalent thereof). In some embodiments, the premedication and prophylaxis is administered 30-120 minutes prior to administration of the bispecific antibody. On subsequent days 2, 3, and 4, further prophylaxis is administered comprising the systemic administration of a corticosteroid such as prednisolone (e.g., at an intravenous or oral dose of 100 mg, or an equivalent thereof). In some embodiments, the premedication and prophylaxis schedule preferably is administered during the first four administrations of the

bispecific antibody, e.g., during the first 21-day cycle and start of the second 21-day cycle of bispecific antibody administration described herein. Furthermore, subsequent cycles, in case of, e.g., CRS greater than grade 1 occurring during the last administration of the prior cycle, can include the same administration schedule, wherein the premedication as part of the administration schedule is optional. As discussed above, however, the corticosteroid component of the CRS prophylaxis may not be administered to the subject during the first administration of the bispecific antibody, on day 1 and subsequent days 2-4, of each 21-day cycle if dexamethasone is administered as part of the R-DHAX/C regimen.

[0237] During the treatment of a human subject with DLBCL using the doses and treatment regimens described herein, CRS can be well managed while at the same time effectively controlling and/or treating the DLBCL. As described in the Examples, subjects treated with the methods described herein may experience manageable CRS. In some cases, subjects receiving the treatment described herein may develop CRS of grade 1 as defined in accordance with standard practice. In other cases, subjects may develop manageable CRS of grade 2 as defined in accordance with standard practice. Hence, subjects receiving the treatments described herein may have manageable CRS of grade 1 or grade 2 during as defined in accordance with standard practice. In accordance with standard classification for CRS, a grade 1 CRS includes a fever to at least 38° C., no hypotension, no hypoxia, and a grade 2 CRS includes a fever to at least 38° C. plus hypotension, not requiring vasopressors and/or hypoxia requiring oxygen by low flow nasal cannula or blow by. Such manageable CRS can occur during cycle 1. Human subjects receiving the treatments described herein may also have CRS greater than grade 2 during the treatments as defined in accordance with standard practice. Hence, human subjects receiving the treatments described herein may also have CRS of grade 3 during said treatments as defined in accordance with standard practice. Such manageable CRS may further occur during cycle 1 and subsequent cycles.

[0238] Human subjects treated according to the methods described herein may also experience pyrexia, fatigue, and injection site reactions. They may also experience neurotoxicity, partial seizures, agraphia related to CRS, or confusional state related to CRS.

[0239] As mentioned above, subjects may develop CRS during treatment with the methods described herein, despite having received CRS prophylaxis. CRS grading criteria are described in Tables 6 and 7.

[0240] In one embodiment, subjects who develop Grade 1 CRS are treated with antibiotics if they present with infection. In some embodiments, the antibiotics are continued until neutropenia, if present, resolves. In some embodiments, subjects with Grade 1 CRS who exhibit constitutional symptoms are treated with NSAIDs.

[0241] In one embodiments, subjects who develop Grade 2 CRS are treated with intravenous fluid boluses and/or supplemental oxygen. In some embodiments, subjects who develop Grade 2 CRS are treated with a vasopressor. In some embodiments, subjects with Grade 2 CRS with comorbidities are treated with tocilizumab (a humanized antibody against IL-6 receptor, commercially available as, e.g., ACTEMRA®) and/or steroids (e.g., dexamethasone or its equivalent of methylprednisolone). In a further embodiment, a subject who presents with concurrent ICANS is administered dexamethasone. In yet a further embodiment, if the subject does not show improvement in CRS symptoms within, e.g., 6 hours, or if the subject starts to deteriorate after initial improvement, then a second dose of tocilizumab is administered together with a dose of corticosteroids. In some embodiments, if the subject is refractory to tocilizumab after three administrations, then additional cytokine therapy, e.g., an anti-IL-6 antibody (e.g., siltuximab) or an IL-1R antagonist (e.g., anakinra) is administered to the subject.

[0242] In one embodiment, subjects who develop Grade 3 CRS are treated with vasopressor (e.g., norepinephrine) support and/or supplemental oxygen. In some embodiments, subjects with Grade 3 CRS are treated with tocilizumab, or tocilizumab in combination with steroids (e.g., dexamethasone or its equivalent of methylprednisolone). In some embodiments, a subject who presents with concurrent ICANS is administered dexamethasone. In a further embodiment, if the subject is refractory to tocilizumab after three administrations, then additional cytokine therapy, e.g., an anti-IL-6 antibody (e.g., siltuximab) or an IL-1R antagonist (e.g., anakinra) is administered to the subject.

[0243] In one embodiment, subjects who develop Grade 4 CRS are treated with vasopressor support and/or supplemental oxygen (e.g., via positive pressure ventilation, such as CPAP, BiPAP, intubation, or mechanical ventilation). In some embodiments, the subject is administered at least two vasopressors. In some embodiments, the subject is administered tocilizumab and a steroid. In a further embodiment, a subject who presents with concurrent ICANS is administered dexamethasone. In yet a further embodiment, if the subject is refractory to tocilizumab after three administrations, then additional cytokine therapy, e.g., an anti-IL-6 antibody (e.g., siltuximab) or an IL-1R antagonist (e.g., anakinra) is administered to the subject.

[0244] In some embodiments, the human subject receives prophylactic treatment for tumor lysis syndrome (TLS). Classification and grading of tumor lysis syndrome can be performed using methods known in the art, for example, as described in Howard et al. *N Engl J Med* 2011; 364:1844-54, and Coiffier et al., *J Clin Oncol* 2008; 26:2767-78. In some embodiments, prophylactic treatment of TLS comprises administering uric acid reducing agents prior to administering the bispecific antibody. Exemplary uric acid reducing agents include rasburicase and allopurinol. Accordingly, in one embodiment, the prophylactic treatment of TLS comprises administering rasburicase and/or allopurinol prior to administering the bispecific antibody. In some embodiments, when the subject shows signs of TLS, supportive therapy, such as rasburicase, may be used.

[0245] Subjects being administered rituximab according to the methods described herein can be treated with supportive therapies. In one embodiment, supportive therapies include, but are not limited to, (a) premedication with acetaminophen (e.g., 650 mg orally), diphenhydramine (e.g., 50-100 mg intravenously or orally), and steroids, for example, 30-60 minutes prior to starting each rituximab infusion, (b) prophylactic treatment for Pneumocystis carinii pneumonia, (c) CNS prophylaxis according to standard local practice (e.g., methotrexate), (d) low-dose aspirin (e.g., 70-100 mg daily) or another prophylactic antithrombotic treatment for subjects without a prior history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 5

years of initiating treatment and considered to be at standard risk for thrombosis, and/or (e) anticoagulation therapy for subjects with a prior medical history of DVT or PE within 5 years of initiating treatment.

[0246] In one embodiment, the bispecific antibody is administered subcutaneously, and thus is formulated in a pharmaceutical composition such that it is compatible with subcutaneous (s.c.) administration, i.e., having a formulation and/or concentration that allows pharmaceutical acceptable s.c. administration at the doses described herein. In some embodiments, subcutaneous administration is carried out by injection. For example, formulations for DuoBody CD3xCD20 that are compatible with subcutaneous formulation and can be used in the methods described herein have been described previously (see, e.g., WO2019155008, which is incorporated herein by reference). In some embodiments, the bispecific antibody may be formulated using sodium acetate trihydrate, acetic acid, sodium hydroxide, sorbitol, polysorbate 80, and water for injection, and have a pH of 5.5 or about 5.5. In some embodiments, the bispecific antibody is provided as a 5 mg/mL or 60 mg/mL concentrate. In other embodiments, the desired dose of the bispecific antibody is reconstituted to a volume of about 1 mL for subcutaneous injection.

[0247] In one embodiment, a suitable pharmaceutical composition for the bispecific antibody can comprise the bispecific antibody, 20-40 mM acetate, 140-160 mM sorbitol, and a surfactant, such as polysorbate 80, and having a pH of 5.3-5.6. In some embodiments, the pharmaceutical formulation may comprise an antibody concentration in the range of 5-100 mg/mL, e.g., 48 or 60 mg/mL of the bispecific antibody, 30 mM acetate, 150 mM sorbitol, 0.04% w/v polysorbate 80, and have a pH of 5.5. Such a formulation may be diluted with, e.g., the formulation buffer to allow proper dosing and subcutaneous administration.

[0248] The volume of the pharmaceutical composition is appropriately selected to allow for subcutaneous administration of the antibody. For example, the volume to be administered is in the range of about 0.3 mL to about 3 mL, such as from 0.3 mL to 3 mL. The volume to be administered can be 0.5 mL, 0.8 mL, 1 mL, 1.2 mL, 1.5 ml, 1.7 mL, 2 mL, or 2.5 mL, or about 0.5 mL, about 0.8 mL, about 1 mL, about 1.2 mL, about 1.5 ml, about 1.7 mL, about 2 mL, or about 2.5 mL. Accordingly, in one embodiment, the volume to be administered is 0.5 mL or about 0.5 mL. In some embodiments, the volume to be administered is 0.8 mL or about 0.8 mL. In some embodiments, the volume to be administered is 1 mL or about 1 mL. In some embodiments, the volume to be administered is 1.2 mL or about 1.2 mL. In some embodiments, the volume to be administered is 1.5 mL or about 1.5 mL. In some embodiments, the volume to be administered is 1.7 mL or about 1.7 mL. In some embodiments, the volume to be administered is 2 mL or about 2 mL. In some embodiments, the volume to be administered is 2.5 mL or about 2.5 mL.

[0249] In one embodiment, rituximab is formulated in a pharmaceutical composition comprising pharmaceutically-acceptable excipients for administration (e.g., intravenous administration) in accordance with local standard-of-care practice, e.g., as specified by local guidelines or local product labels. For example, in some embodiments, rituximab is provided as a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration. In one embodiment, rituximab is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. In some embodiments, rituximab is formulated in polysorbate 80 (0.7 mg/mL), sodium citrate dihydrate (7.35 mg/mL), sodium chloride (9 mg/mL), and water, at a pH of 6.5, for injection.

[0250] In one embodiment, individual components of the DHAX/C regimen (i.e., dexamethasone, cytarabine, oxaliplatin, and carboplatin) are formulated in a pharmaceutical composition comprising pharmaceutically-acceptable excipients for administration (e.g., intravenous administration) in accordance with local standard-of-care practice, e.g., as specified by local guidelines or local product labels, or as directed by the manufacturer. In some embodiments, dexamethasone, cytarabine, oxaliplatin, and carboplatin are diluted from a stock solution, or reconstituted if in lyophilized form, according to, e.g., instructions in the product label (e.g., with 0.9% saline solution). In some embodiments, dexamethasone is formulated in a pharmaceutical composition for oral administration.

[0251] In one embodiment, the bispecific antibody used in the methods described herein comprises:

[0252] (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 within the amino acid sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences within the amino acid sequence of SEQ ID NO: 7; and

[0253] (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 within the amino acid sequence of SEQ ID NO: 13, and the VL region comprises the CDR1, CDR2 and CDR3 sequences within the amino acid sequence SEQ ID NO: 14.

[0254] CDR1, CDR2 and CDR3 regions can be identified from variable heavy and light chain regions using methods known in the art. The CDR regions from said variable heavy and light chain regions can be annotated according to IMGT (see Lefranc et al., *Nucleic Acids Research* 1999; 27:209-12, 1999] and Brochet. *Nucl Acids Res* 2008; 36:W503-8).

[0255] In some embodiments, the bispecific antibody comprises:

[0256] (i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises VHCDR1, VHCDR2 and VHCDR3 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

[0257] (ii) a second binding arm comprising a second antigen-binding region which binds to human CD20 and 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.

[0258] In some embodiments, the bispecific antibody comprises:

[0259] (i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a VH region comprising the amino acid sequence of SEQ ID NO: 6, and a VL region comprising the amino acid sequence of SEQ ID NO: 7; and

[0260] (ii) a second binding arm comprising a second antigen-binding region which binds to human CD20 and comprises a VH region comprising the amino acid sequence of SEQ ID NO: 13, and a VL region comprising the amino acid sequence of SEQ ID NO: 14.

[0261] In one embodiment, the bispecific antibody is a full-length antibody and may have an inert Fc region. In some embodiments, the first binding arm for CD3 is derived from a humanized antibody, e.g., from a full-length IgG1,λ (lambda) antibody such as H1L1 described in WO2015001085, which is incorporated herein by reference, and/or the second binding arm for CD20 is derived from a human antibody, e.g., from a full-length IgG1,κ (kappa) antibody such as clone 7D8 as described in WO2004035607, which is incorporated herein by reference. The bispecific antibody may be produced from two half molecule antibodies. Each of the two half molecule antibodies comprising, e.g., the respective first and second binding arms set forth in SEQ ID NOs: 24 and 25, and SEQ ID NOs: 26 and 27. The half-antibodies may be produced in CHO cells and the bispecific antibodies generated by, e.g., Fab-arm exchange. In one embodiment, the bispecific antibody is a functional variant of DuoBody CD3xCD20.

[0262] Accordingly, in some embodiments, the bispecific antibody comprises (i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a VH region comprising an amino acid sequence which is at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 6 or a VH region comprising the amino acid sequence of SEQ ID NO: 6, but with 1, 2, or 3 mutations (e.g., amino acid substitutions), and a VL region comprising an amino acid sequence which is at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 7 or a VL region comprising the amino acid sequence of SEQ ID NO: 7, but with 1, 2, or 3 mutations (e.g., amino acid substitutions); and

[0263] (ii) a second binding arm comprising a second antigen-binding region which binds to human CD20 and comprises a VH region comprising an amino acid sequence which is at least 85%, 90%, 95%, 98%, or 99% identical to SEQ ID NO: 13 or a VH region comprising the amino acid sequence of SEQ ID NO: 13, but with 1, 2, or 3 mutations (e.g., amino acid substitutions), and a VL region comprising an amino acid sequence which is at least 85%, 90%, 95%, 98%, or 99% identical to SEQ ID NO: 14 or a VL region comprising the amino acid sequence of SEQ ID NO: 14, but with 1, 2, or 3 mutations (e.g., amino acid substitutions).

[0264] In one embodiment, the bispecific antibody comprises:

[0265] (i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 24, and a light chain comprising the amino acid sequence of SEQ ID NO: 25; and

[0266] (ii) a second binding arm comprising a second antigen-binding region which binds to human CD20 and comprises a VH region comprising the amino acid sequence of SEQ ID NO: 26, and a VL region comprising the amino acid sequence of SEQ ID NO: 27.

[0267] In some embodiments, the bispecific antibody comprises (i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a heavy chain comprising an amino acid sequence which is at least 85%, 90%, 95%, 98%, or 99% identical to SEQ ID NO: 24 or a heavy chain comprising the amino acid sequence of SEQ ID NO: 24, but with 1, 2, or 3 mutations (e.g., amino acid substitutions), and a light chain comprising an amino acid sequence which is at least 85%, 90%, 95%, 98%, or 99% identical to SEQ ID NO: 25 or a light chain region comprising the amino acid sequence of SEQ ID NO: 25, but with 1, 2, or 3 mutations (e.g., amino acid substitutions); and

[0268] (ii) a second binding arm comprising a second antigen-binding region which binds to human CD20 and comprises a heavy chain comprising an amino acid sequence which is at least 85%, 90%, 95%, 98%, or 99% identical to SEQ ID NO: 26 or a heavy chain comprising the amino acid sequence of SEQ ID NO: 26, but with 1, 2, or 3 mutations (e.g., amino acid substitutions), and a light chain comprising an amino acid sequence which is at least 85%, 90%, 95%, 98%, or 99% identical to SEQ ID NO: 27 or a light chain region comprising the amino acid sequence of SEQ ID NO: 27, but with 1, 2, or 3 mutations (e.g., amino acid substitutions).

[0269] Various constant regions or variants thereof may be used in the bispecific antibody. In one embodiment, the antibody comprises an IgG constant region, such as a human IgG1 constant region, e.g., a human IgG1 constant region as defined in SEQ ID NO: 15, or any other suitable IgG1 allotype. In one embodiment, the first binding arm of the bispecific antibody is derived from a humanized antibody, e.g., from a full-length IgG1,λ (lambda) antibody, and thus comprises a λ light chain constant region. In some embodiments, the first binding arm comprises a λ light chain constant region as defined in SEQ ID NO: 22. In some embodiments, the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody, and thus may comprise a κ light chain constant region. In some embodiments, the second binding arm comprises a κ light chain constant region as defined in SEQ ID NO: 23.

[0270] It is understood that the constant region portion of the bispecific antibody may comprise modifications that allow for efficient formation/production of bispecific antibodies and/or provide for an inert Fc region. Such modifications are well known in the art.

[0271] Different formats of bispecific antibodies are known in the art (reviewed by Kontermann, *Drug Discov Today* 2015; 20:838-47; MAbs, 2012; 4:182-97). Thus, the bispecific antibody used in the methods and uses described herein are not limited to any particular bispecific format or method of producing it. For example, bispecific antibodies may include, but are not limited to, bispecific antibodies with complementary CH3 domains to force heterodimerization, Knobs-into-Holes molecules (Genentech, WO9850431), CrossMAbs (Roche, WO2011117329), or

electrostatically-matched molecules (Amgen, EP1870459 and WO2009089004; Chugai, US201000155133; Oncomed, WO2010129304).

[0272] Preferably, the bispecific antibody comprises an Fc-region comprising a first heavy chain with a first Fc sequence comprising a first CH3 region, and a second heavy chain with a second Fc sequence comprising a second CH3 region, wherein the sequences of the first and second CH3 regions are different and are such that the heterodimeric interaction between said first and second CH3 regions is stronger than each of the homodimeric interactions of said first and second CH3 regions. Further details on these interactions and how they can be achieved are provided in e.g. WO2011131746 and WO2013060867 (Genmab), which are hereby incorporated by reference. In one embodiment, the bispecific antibody comprises in the first heavy chain (i) the amino acid L in the position corresponding to F405 in the human IgG1 heavy chain constant region of SEQ ID NO: 15, and comprises in the second heavy chain the amino acid R in the position corresponding to K409 in the human IgG1 heavy chain constant region of SEQ ID NO: 15, or vice versa.

[0273] Bispecific antibodies may comprise modifications in the Fc region to render the Fc region inert, or non-activating. Thus, in the bispecific antibodies disclosed herein, one or both heavy chains may be modified so that the antibody induces Fc-mediated effector function to a lesser extent relative to the bispecific antibody which does not have the modification. Fc-mediated effector function may be measured by determining Fc-mediated CD69 expression on T cells (i.e. CD69 expression as a result of CD3 antibody-mediated, Fcγ receptor-dependent CD3 crosslinking), by binding to Fcγ receptors, by binding to C1q, or by induction of Fc-mediated cross-linking of FcγRs. In particular, the heavy chain constant region sequence may be modified so that Fc-mediated CD69 expression is reduced by at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 99% or 100% when compared to a wild-type (unmodified) antibody, wherein said Fc-mediated CD69 expression is determined in a PBMC-based functional assay, e.g. as described in Example 3 of WO2015001085. Modifications of the heavy and light chain constant region sequences may also result in reduced binding of C1q to said antibody. As compared to an unmodified antibody, the reduction may be by at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or 100%, and C1q binding may be determined, e.g., by ELISA. Further, the Fc region which may be modified so that the antibody mediates reduced Fc-mediated T-cell proliferation compared to an unmodified antibody by at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 99% or 100%, wherein said T-cell proliferation is measured in a PBMC-based functional assay. Examples of amino acid positions that may be modified, e.g., in an IgG1 isotype antibody, include positions L234 and L235. Thus, in one embodiment, the bispecific antibody may comprises a first heavy chain and a second heavy chain, and wherein in both the first heavy chain and the second heavy chain, the amino acid residues at the positions corresponding to positions L234 and L235 in a human IgG1 heavy chain according to Eu numbering are F and E, respectively. In addition, a D265A amino acid substitution can decrease binding to all Fcγ receptors and prevent ADCC (Shields et al., JBC 2001; 276:6591-604). Therefore, the bispecific antibody may comprise a first heavy chain and a second heavy chain, wherein in both the first heavy chain and the second heavy chain, the amino acid residue at the position corresponding to position D265 in a human IgG1 heavy chain according to Eu numbering is A.

[0274] In one embodiment, in the first heavy chain and second heavy chain of the bispecific antibody, the amino acids in the positions corresponding to positions L234, L235, and D265 in a human IgG1 heavy chain, are F, E, and A, respectively. An antibody having these amino acids at these positions is an example of an antibody having an inert Fc region, or a non-activating Fc region.

[0275] With regard to the bispecific antibodies described herein, those which have the combination of three amino acid substitutions L234F, L235E and D265A and in addition the K409R or the F405L mutation, as described above, may be referred to with the suffix "FEAR" or "FEAL", respectively.

[0276] An amino acid sequence of a wild type IgG1 heavy chain constant region may be identified herein as SEQ ID NO: 15. Consistent with the embodiments disclosed above, the bispecific antibody may comprise an IgG1 heavy chain constant region carrying the F405L substitution and may have the amino acid sequence set forth in SEQ ID NO: 17 and/or an IgG1 heavy chain constant region carrying the K409R substitution and may have the amino acid sequence set forth in SEQ ID NO: 18, and have further substitutions that render the Fc region inert or non-activating. Hence, in one embodiment, the bispecific antibody comprises a combination of IgG1 heavy chain constant regions, with the amino acid sequence of one of the IgG1 heavy chain constant regions carrying the L234F, L235E, D265A and F405L substitutions (e.g., as set forth in SEQ ID NO: 19) and the amino acid sequence of the other IgG1 heavy chain constant region carrying the L234F, L235E, D265A and K409R substitutions (e.g., as set forth in SEQ ID NO: 20).

[0277] In some embodiments, the bispecific antibody used in the methods and uses described herein comprises a first binding arm comprising a heavy chain and a light chain as defined in SEQ ID NOs: 24 and 25, respectively, and a second binding arm comprising a heavy chain and a light chain as defined in SEQ ID NOs: 26 and 27, respectively. Such an antibody is referred to herein as DuoBody CD3xCD20. Also, variants of such antibodies are contemplated use in the methods and uses as described herein. In some embodiments, the bispecific antibody is epcoritamab (CAS 2134641-34-0), or a biosimilar thereof.

Kits

[0278] Also provided herein are kits which include a pharmaceutical composition containing a bispecific antibody which binds to CD3 and CD20 in accordance with the invention, such as DuoBody CD3xCD20 or epcoritamab, and a pharmaceutically-acceptable carrier, in a therapeutically effective amount adapted for use in the methods described herein. The kits may also include a pharmaceutical composition containing rituximab (e.g., for intravenous administration), dexamethasone (e.g., for intravenous or oral administration), cytarabine (e.g., for intravenous administration), and/or oxaliplatin/carboplatin (e.g., for intravenous administration). The kits optionally also can include instructions, e.g., comprising administration schedules, to allow a practitioner (e.g., a physician, nurse, or patient) to admin-

ister the composition or compositions contained therein to a patient with DLBCL. The kit also can include a syringe or syringes.

[0279] Optionally, the kits include multiple packages of the single-dose pharmaceutical compositions each containing an effective amount of the bispecific antibody for a single administration in accordance with the methods described herein. They may also include multiple packages of single dose pharmaceutical compositions containing a dose of rituximab, dexamethasone, cytarabine, and/or oxaliplatin/carboplatin in accordance with a standard of care regimen. Instruments or devices necessary for administering the pharmaceutical composition(s) also may be included in the kits.

Further Embodiments

[0280] 1. A bispecific antibody comprising:

[0281] (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

[0282] (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;

[0283] 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 the bispecific antibody, dexamethasone, cytarabine, and oxaliplatin/carboplatin are administered in 21-day cycles.

[0284] 2. The bispecific antibody of embodiment 1, wherein the bispecific antibody is administered at a dose of 24 mg.

[0285] 3. The bispecific antibody of embodiment 1, wherein the bispecific antibody is administered at a dose of 48 mg.

[0286] 4. The bispecific antibody of any one of embodiments 1-3, wherein the subject is planned to receive autologous stem cell transplant (ASCT).

[0287] 5. The bispecific antibody of any one of embodiments 1-4, wherein the bispecific antibody is administered once every week (weekly administration).

[0288] 6. The bispecific antibody of embodiment 5, wherein the weekly administration of 24 mg or 48 mg is performed for three and one-third 21-day cycles.

[0289] 7. The bispecific antibody of embodiment 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.

[0290] 8. The bispecific antibody of embodiment 7, wherein the biweekly administration is performed until ASCT is performed or for five 28-day cycles, whichever is earlier.

[0291] 9. The bispecific antibody of embodiment 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.

[0292] 10. The bispecific antibody of embodiment 9, wherein the administration once every four weeks is performed until ASCT is performed.

[0293] 11. The bispecific antibody of any one of embodiments 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.

[0294] 12. The bispecific antibody of any one of embodiment 11, wherein the priming dose is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg.

[0295] 13. The bispecific antibody of embodiment 11 or 12, wherein the priming dose is 0.16 mg.

[0296] 14. The bispecific antibody of any one of embodiments 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.

[0297] 15. The bispecific antibody of embodiment 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.

[0298] 16. The bispecific antibody of embodiment 14 or 15, wherein the intermediate dose is 0.8 mg.

[0299] 17. The bispecific antibody of any one of embodiments 1-6 and 11-16, wherein rituximab is administered once every three weeks.

[0300] 18. The bispecific antibody of embodiment 17, wherein the administration of rituximab once every three weeks is performed for three 21-day cycles.

[0301] 19. The bispecific antibody of any one of embodiments 1-18, wherein rituximab is administered at a dose of 375 mg/m^2.

[0302] 20. The bispecific antibody of any one of embodiments 1-6 and 11-19, wherein dexamethasone is administered once a day from day 1 to day 4 of the 21-day cycles.

[0303] 21. The bispecific antibody of embodiment 20, wherein dexamethasone is administered for three 21-day cycles.

[0304] 22. The bispecific antibody of any one of embodiments 1-21, wherein dexamethasone is administered at a dose of 40 mg/day.

[0305] 23. The bispecific antibody of any one of embodiments 1-6 and 11-22, wherein cytarabine is administered twice every three weeks.

[0306] 24. The bispecific antibody of embodiment 23, wherein the administration of cytarabine twice every three weeks is performed for three 21-day cycles.

[0307] 25. The bispecific antibody of any one of embodiments 1-6 and 11-24, wherein cytarabine is administered at a dose of 2 g/m^2.

[0308] 26. The bispecific antibody of any one of embodiments 1-6 and 11-25, wherein cytarabine is administered a total of twice over days 1-3 of a 21-day cycle.

[0309] 27. The bispecific antibody of embodiment 26, wherein the second administration of cytarabine is performed 12 hours after initiation of the first administration of cytarabine.

[0310] 28. The bispecific antibody of any one of embodiments 1-6 and 11-27, wherein oxaliplatin is administered once every three weeks.

[0311] 29. The bispecific antibody of embodiment 28, wherein the administration of oxaliplatin once every three weeks is performed for three 21-day cycles.

[0312] 30. The bispecific antibody of any one of embodiments 1-6 and 11-29, wherein oxaliplatin is administered at a dose of 100 mg/m^2.

[0313] 31. The bispecific antibody of any one of embodiments 1-6 and 11-27, wherein carboplatin is administered once every three weeks.

[0314] 32. The bispecific antibody of embodiment 31, wherein the administration of carboplatin once every three weeks is performed for three 21-day cycles.

[0315] 33. The bispecific antibody of any one of embodiments 1-6, 11-27, 31, and 32, wherein carboplatin is administered at a dose of AUC=5 mg/ml/min, as determined using Calvert's formula.

[0316] 34. The bispecific antibody of any one of embodiments 1-6 and 11-33, wherein rituximab, dexamethasone, and oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day.

[0317] 35. The bispecific antibody of embodiment 34, wherein cytarabine is administered the day after rituximab, dexamethasone, oxaliplatin/carboplatin, and the bispecific antibody are administered.

[0318] 36. The bispecific antibody of any one of embodiments 1-35, wherein the dosing schedule for rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody is as shown in Table 2.

[0319] 37. The bispecific antibody of any one of embodiments 1, 2, 4-6, and 11-36, wherein:

[0320] (a) the bispecific antibody is administered in 21-day cycles as follows:

[0321] (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; and

[0322] (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

[0323] (b) rituximab is administered in 21-day cycles on day 1 in cycles 1-3;

[0324] (c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0325] (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

[0326] (e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0327] 38. The bispecific antibody of any one of embodiments 1, 3-6, and 11-36, wherein:

[0328] (a) the bispecific antibody is administered in 21-day cycles as follows:

[0329] (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

[0330] (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

[0331] (b) rituximab is administered in 21-day cycles on day 1 in cycles 1-3;

[0332] (c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0333] (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

[0334] (e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0335] 39. The bispecific antibody of embodiment 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.

[0336] 40. The bispecific antibody of embodiment 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.

[0337] 41. The bispecific antibody of any one of embodiments 1-40, wherein the bispecific antibody is administered subcutaneously.

[0338] 42. The bispecific antibody of any one of embodiments 1-41, wherein rituximab is administered intravenously.

[0339] 43. The bispecific antibody of any one of embodiments 1-42, wherein dexamethasone is administered intravenously or orally.

[0340] 44. The bispecific antibody of any one of embodiments 1-43, wherein cytarabine is administered intravenously.

[0341] 45. The bispecific antibody of any one of embodiments 1-44, wherein oxaliplatin is administered intravenously.

[0342] 46. The bispecific antibody of any one of embodiments 1-45, wherein carboplatin is administered intravenously.

[0343] 47. The bispecific antibody of any one of embodiments 1-46, wherein rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody are administered sequentially.

[0344] 48. The bispecific antibody of any one of embodiments 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.

[0345] 49. The bispecific antibody of embodiment 48, wherein dexamethasone, rituximab, oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day, and cytarabine is administered the next day.

[0346] 50. The bispecific antibody of any one of embodiments 1-49, wherein the DLBCL is double-hit or triple-hit DLBCL.

[0347] 51. The bispecific antibody of any one of embodiments 1-49, wherein the DLBCL is follicular lymphoma Grade 3B.

[0348] 52. The bispecific antibody of any one of embodiments 1-51, wherein the subject has relapsed after at least one prior therapy.

[0349] 53. The bispecific antibody of any one of embodiments 1-52, wherein the subject is refractory to at least one prior therapy.

[0350] 54. The bispecific antibody of any one of embodiments 1-53, wherein the subject is treated with prophylaxis for cytokine release syndrome (CRS).

[0351] 55. The bispecific antibody of any one of embodiment 54, wherein the prophylaxis comprises administering a corticosteroid to the subject.

[0352] 56. The bispecific antibody of embodiment 55, wherein the corticosteroid is administered on the same day as the bispecific antibody.

[0353] 57. The bispecific antibody of embodiment 56, wherein the corticosteroid is further administered on the second, third, and fourth days after administering the bispecific antibody.

[0354] 58. The bispecific antibody of any one of embodiments 55-57, wherein the corticosteroid is prednisolone.

[0355] 59. The bispecific antibody of embodiment 58, wherein the prednisolone is administered at an intravenous dose of 100 mg, or equivalent thereof, including oral dose.

[0356] 60. The bispecific antibody of embodiment 58 or 59, wherein predniosolone is administered on days 8-11 and 15-18 of cycle 1 of the 21-day cycles.

[0357] 61. The bispecific antibody of any one of embodiments 55-57, wherein the dexamethasone from R-DHAX/C serves as the corticosteroid for prophylaxis for CRS.

[0358] 62. The bispecific antibody of embodiment 61, wherein if the dexamethasone from R-DHAX/C is administered more than 120 minutes before administration of the bispecific antibody, then the subject is administered prednisolone or an equivalent about 30-120 minutes prior to administration of the bispecific antibody.

[0359] 63. The bispecific antibody of any one of embodiments 1-62, wherein the subject is administered premedication to reduce reactions to injections.

[0360] 64. The bispecific antibody of embodiment 63, wherein the premedication comprises an antihistamine.

[0361] 65. The bispecific antibody of embodiment 64, wherein the antihistamine is diphenhydramine.

[0362] 66. The bispecific antibody of embodiment 65, wherein the diphenhydramine is administered at an intravenous or oral dose of 50 mg, or equivalent thereof.

[0363] 67. The bispecific antibody of any one of embodiments 63-66, wherein the premedication comprises an antipyretic.

[0364] 68. The bispecific antibody of embodiment 67, wherein the antipyretic is acetaminophen.

[0365] 69. The bispecific antibody of embodiment 68, wherein the acetaminophen is administered at an oral dose of 650 mg to 1000 mg, or equivalent thereof.

[0366] 70. The bispecific antibody of any one of embodiments 63-69, wherein the premedication is administered on the same day as the bispecific antibody.

[0367] 71. The bispecific antibody of any one of embodiments 54-70, wherein the prophylaxis is administered in cycle 1 and start of cycle 2 of the 21-day cycles.

[0368] 72. The bispecific antibody of any one of embodiments 63-71, wherein the premedication is administered in cycle 1 and start of cycle 2 of the 21-day cycles.

[0369] 73. The bispecific antibody of any one of embodiments 54-72, wherein the prophylaxis is administered during the second and third administrations of the bispecific antibody during cycle 2 of the 21-day cycles when the subject experiences CRS greater than grade 1 after the first administration of the bispecific antibody in cycle 2 of the 21-day cycles.

[0370] 74. The bispecific antibody of embodiment 73, wherein the prophylaxis is continued in a subsequent cycle, when in the last administration of the bispecific antibody of the previous cycle, the subject experiences CRS greater than grade 1.

[0371] 75. The bispecific antibody of any one of embodiments 63-74, wherein the premedication is administered during cycle 2 of the 21-day cycles.

[0372] 76. The bispecific antibody of embodiment 75, wherein the premedication is administered during subsequent cycles.

[0373] 77. The bispecific antibody of any one of embodiments 1-76, wherein the subject is administered antibiotics if the subject develops Grade 1 CRS.

[0374] 78. The bispecific antibody of any one of embodiments 1-76, wherein the subject is administered a vasopressor if the subject develops Grade 2 or Grade 3 CRS.

[0375] 79. The bispecific antibody of any one of embodiments 1-76, wherein the subject is administered at least two vasopressors if the subject develops Grade 4 CRS.

[0376] 80. The bispecific antibody of any one of embodiments 1-79, wherein the subject is administered tocilizumab if the subject develops Grade 2, Grade 3, or Grade 4 CRS.

[0377] 81. The bispecific antibody of embodiment 80, wherein the subject is further administered a steroid.

[0378] 82. The bispecific antibody of embodiment 81, wherein the steroid is dexamethasone.

[0379] 83. The bispecific antibody of embodiment 81, wherein the steroid is methylprednisolone.

[0380] 84. The bispecific antibody of any one of embodiments 80-83, wherein tocilizumab is switched to an anti-IL-6 antibody (e.g., siltuximab) if the subject is refractory to tocilizumab.

[0381] 85. The bispecific antibody of any one of embodiments 80-83, wherein tocilizumab is switched to an IL-1R antagonist (e.g., anakinra) if the subject is refractory to tocilizumab.

[0382] 86. The bispecific antibody of any one of embodiments 1-85, wherein the subject is treated with prophylaxis for tumor lysis syndrome (TLS).

[0383] 87. The bispecific antibody of embodiment 86, wherein the prophylaxis for TLS comprises administering one or more uric acid reducing agents prior to administration of the bispecific antibody.

[0384] 88. The bispecific antibody of embodiment 87, wherein the one or more uric acid reducing agents comprise rasburicase and/or allopurinol.

[0385] 89. The bispecific antibody of any one of embodiments 1-88, wherein the subject achieves a complete response, a partial response, or stable disease.

[0386] 90. The bispecific antibody of any one of embodiments 1-89, wherein:

[0387] (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

[0388] (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.

[0389] 91. The bispecific antibody of any one of embodiments 1-90, wherein:

[0390] (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

[0391] (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.

[0392] 92. The bispecific antibody of any one of embodiments 1-91, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1,λ (lambda) antibody.

[0393] 93. The bispecific antibody of embodiment 92 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.

[0394] 94. The bispecific antibody of any one of embodiments 1-93, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody.

[0395] 95. The bispecific antibody of embodiment 94, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

[0396] 96. The bispecific antibody of any one of embodiments 1-95, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

[0397] 97. The bispecific antibody of any one of embodiments 1-96, wherein the bispecific antibody comprises an inert Fc region.

[0398] 98. The bispecific antibody of any one of embodiments 1-97, 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.

[0399] 99. The bispecific antibody of any one of embodiments 1-98, 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.

[0400] 100. The bispecific antibody of any one of embodiments 1-99, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein

[0401] (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

[0402] (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.

[0403] 101. The bispecific antibody of embodiment 100, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

[0404] 102. The bispecific antibody of any one of embodiments 1-101, 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.

[0405] 103. The bispecific antibody of any one of embodiments 1-102, 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.

[0406] 104. The bispecific antibody of any one of embodiments 1-103, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.

[0407] The present disclosure is further illustrated by the following examples, which should not be construed as further limiting. The contents of all figures and all references, Genbank sequences, journal publications, patents, and published patent applications cited throughout this application are expressly incorporated herein by reference.

[0408] 1a. 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:

[0409] (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

[0410] (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;

[0411] 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.

[0412] 2a. The method of embodiment 1a, wherein the bispecific antibody is administered at a dose of 24 mg.

[0413] 3a. The method of embodiment 1a, wherein the bispecific antibody is administered at a dose of 48 mg.

[0414] 4a. The method of any one of embodiments 1a-3a, wherein the subject is planned to receive autologous stem cell transplant (ASCT).

[0415] 5a. The method of any one of embodiments 1a-4a, wherein the bispecific antibody is administered once every week (weekly administration).

[0416] 6a. The method of embodiment 5a, wherein the weekly administration of 24 mg or 48 mg is performed for three and one-third 21-day cycles.

[0417] 7a. The method of embodiment 5a or 6a, 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.

[0418] 8a. The method of embodiment 7a, wherein the biweekly administration is performed until ASCT is performed or for five 28-day cycles, whichever is earlier.

[0419] 9a. The method of embodiment 8a, 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.

[0420] 10a. The method of embodiment 9a, wherein the administration once every four weeks is performed until ASCT is performed.

[0421] 11a. The method of any one of embodiments 5a-10a, 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.

[0422] 12a. The method of embodiment 11a, wherein the priming dose is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg.

[0423] 13a. The method of embodiment 11a or 12a, wherein the priming dose is 0.16 mg.

[0424] 14a. The method of any one of embodiments 11a-13a, 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.

[0425] 15a. The method of embodiment 14a, 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.

[0426] 16a. The method of embodiment 14a or 15a, wherein the intermediate dose is 0.8 mg.

[0427] 17a. The method of any one of embodiments 1a-6a and 11a-16a, wherein rituximab is administered once every three weeks.

[0428] 18a. The method of embodiment 17a, wherein the administration of rituximab once every three weeks is performed for three 21-day cycles.

[0429] 19a. The method of any one of embodiments 1a-18a, wherein rituximab is administered at a dose of 375 mg/m^2.

[0430] 20a. The method of any one of embodiments 1a-6a and 11a-19a, wherein dexamethasone is administered once a day from day 1 to day 4 of the 21-day cycles.

[0431] 21a. The method of embodiment 20a, wherein dexamethasone is administered for three 21-day cycles.

[0432] 22a. The method of any one of embodiments 1a-21a, wherein dexamethasone is administered at a dose of 40 mg/day.

[0433] 23a. The method of any one of embodiments 1a-6a and 11a-22a, wherein cytarabine is administered twice every three weeks.

[0434] 24a. The method of embodiment 23a, wherein the administration of cytarabine twice every three weeks is performed for three 21-day cycles.

[0435] 25a. The method of any one of embodiments 1a-6a and 11a-24a, wherein cytarabine is administered at a dose of 2 g/m^2.

[0436] 26a. The method of any one of embodiments 1a-6a and 11a-25a, wherein cytarabine is administered a total of twice over days 1-3 of a 21-day cycle.

[0437] 27a. The method of embodiment 26a, wherein the second administration of cytarabine is performed 12 hours after initiation of the first administration of cytarabine.

[0438] 28a. The method of any one of embodiments 1a-6a and 11a-27a, wherein oxaliplatin is administered once every three weeks.

[0439] 29a. The method of embodiment 28a, wherein the administration of oxaliplatin once every three weeks is performed for three 21-day cycles.

[0440] 30a. The method of any one of embodiments 1a-6a and 11a-29a, wherein oxaliplatin is administered at a dose of 100 mg/m^2.

[0441] 31a. The method of any one of embodiments 1a-6a and 11a-27a, wherein carboplatin is administered once every three weeks.

[0442] 32a. The method of embodiment 31a, wherein the administration of carboplatin once every three weeks is performed for three 21-day cycles.

[0443] 33a. The method of any one of embodiments 1a-6a, 11a-27a, 31a, and 32a, wherein carboplatin is administered at a dose of AUC=5 mg/ml/min, as determined using Calvert's formula.

[0444] 34a. The method of any one of embodiments 1a-6a and 11a-33a, wherein rituximab, dexamethasone, and oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day.

[0445] 35a. The method of embodiment 34a, wherein cytarabine is administered the day after rituximab, dexamethasone, oxaliplatin/carboplatin, and the bispecific antibody are administered.

[0446] 36a. The method of any one of embodiments 1a-35a, wherein the dosing schedule for rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody is as shown in Table 2.

[0447] 37a. The method of any one of embodiments 1a, 2a, 4a-6a, and 11a-36a, wherein:

[0448] (a) the bispecific antibody is administered in 21-day cycles as follows:

[0449] (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; and

[0450] (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;

[0451] (b) rituximab is administered in 21-day cycles on day 1 in cycles 1-3;

[0452] (c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0453] (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

[0454] (e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0455] 38a. The method of any one of embodiments 1a, 3a-6a, and 11a-36a, wherein:

[0456] (a) the bispecific antibody is administered in 21-day cycles as follows:

[0457] (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

[0458] (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;

[0459] (b) rituximab is administered in 21-day cycles on day 1 in cycles 1-3;

[0460] (c) oxaliplatin/carboplatin is administered in 21-day cycles on day 1 in cycles 1-3;

[0461] (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

[0462] (e) dexamethasone is administered in 21-day cycles on days 1-4 in cycles 1-3.

[0463] 39a. The method of embodiment 37a or 38a, 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.

[0464] 40a. The method of embodiment 39a, 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.

[0465] 41a. The method of any one of embodiments 1a-40a, wherein the bispecific antibody is administered subcutaneously.

[0466] 42a. The method of any one of embodiments 1a-41a, wherein rituximab is administered intravenously.

[0467] 43a. The method of any one of embodiments 1a-42a, wherein dexamethasone is administered intravenously or orally.

[0468] 44a. The method of any one of embodiments 1a-43a, wherein cytarabine is administered intravenously.

[0469] 45a. The method of any one of embodiments 1a-44a, wherein oxaliplatin is administered intravenously.

[0470] 46a. The method of any one of embodiments 1a-45a, wherein carboplatin is administered intravenously.

[0471] 47a. The method of any one of embodiments 1a-46a, wherein rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin, and the bispecific antibody are administered sequentially.

[0472] 48a. The method of any one of embodiments 1a-47a, 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.

[0473] 49a. The method of embodiment 48a, wherein dexamethasone, rituximab, oxaliplatin/carboplatin, and the bispecific antibody are administered on the same day, and cytarabine is administered the next day.

[0474] 50a. The method of any one of embodiments 1a-49a, wherein the DLBCL is double-hit or triple-hit DLBCL.

[0475] 51a. The method of any one of embodiments 1a-49a, wherein the DLBCL is follicular lymphoma Grade 3B.

[0476] 52a. The method of any one of embodiments 1a-51a, wherein the subject has relapsed after at least one prior therapy.

[0477] 53a. The method of any one of embodiments 1a-52a, wherein the subject is refractory to at least one prior therapy.

[0478] 54a. The method of any one of embodiments 1a-53a, wherein the subject is treated with prophylaxis for cytokine release syndrome (CRS).

[0479] 55a. The method of embodiment Ma, wherein the prophylaxis comprises administering a corticosteroid to the subject.

[0480] 56a. The method of embodiment 55a, wherein the corticosteroid is administered on the same day as the bispecific antibody.

[0481] 57a. The method of embodiment 56a, wherein the corticosteroid is further administered on the second, third, and fourth days after administering the bispecific antibody.

[0482] 58a. The method of any one of embodiments 55a-57a, wherein the corticosteroid is prednisolone.

[0483] 59a. The method of embodiment 58a, wherein the prednisolone is administered at an intravenous dose of 100 mg, or equivalent thereof, including oral dose.

[0484] 60a. The method of embodiment 58a or 59a, wherein predniosolone is administered on days 8-11 and 15-18 of cycle 1 of the 21-day cycles.

[0485] 61a. The method of any one of embodiments 55a-57a, wherein the dexamethasone from R-DHAX/C serves as the corticosteroid for prophylaxis for CRS.

[0486] 62a. The method of embodiment 61, wherein if the dexamethasone from R-DHAX/C is administered more than 120 minutes before administration of the bispecific antibody, then the subject is administered prednisolone or an equivalent about 30-120 minutes prior to administration of the bispecific antibody.

[0487] 63a. The method of any one of embodiments 1-62a, wherein the subject is administered premedication to reduce reactions to injections.

[0488] 64a. The method of embodiment 63a, wherein the premedication comprises an antihistamine.

[0489] 65a. The method of embodiment 64a, wherein the antihistamine is diphenhydramine.

[0490] 66a. The method of embodiment 65a, wherein the diphenhydramine is administered at an intravenous or oral dose of 50 mg, or equivalent thereof.

[0491] 67a. The method of any one of embodiments 63a-66a, wherein the premedication comprises an antipyretic.

[0492] 68a. The method of embodiment 67a, wherein the antipyretic is acetaminophen.

[0493] 69a. The method of embodiment 68a, wherein the acetaminophen is administered at an oral dose of 650 mg to 1000 mg, or equivalent thereof.

[0494] 70a. The method of any one of embodiments 63a-69a, wherein the premedication is administered on the same day as the bispecific antibody.

[0495] 71a. The method of any one of embodiments 54a-70a, wherein the prophylaxis is administered in cycle 1 and start of cycle 2 of the 21-day cycles.

[0496] 72a. The method of any one of embodiments 63a-71a, wherein the premedication is administered in cycle 1 and start of cycle 2 of the 21-day cycles.

[0497] 73a. The method of any one of embodiments 54a-72a, wherein the prophylaxis is administered during the second and third administrations of the bispecific antibody during cycle 2 of the 21-day cycles when the subject

experiences CRS greater than grade 1 after the first administration of the bispecific antibody in cycle 2 of the 21-day cycles.

[0498] 74a. The method of embodiment 73a, wherein the prophylaxis is continued in a subsequent cycle, when in the last administration of the bispecific antibody of the previous cycle, the subject experiences CRS greater than grade 1.

[0499] 75a. The method of any one of embodiments 63a-74a, wherein the premedication is administered during cycle 2 of the 21-day cycles.

[0500] 76a. The method of embodiment 75a, wherein the premedication is administered during subsequent cycles.

[0501] 77a. The method of any one of embodiments 1a-76a, wherein the subject is administered antibiotics if the subject develops Grade 1 CRS.

[0502] 78a. The method of any one of embodiments 1a-76a, wherein the subject is administered a vasopressor if the subject develops Grade 2 or Grade 3 CRS.

[0503] 79a. The method of any one of embodiments 1a-76a, wherein the subject is administered at least two vasopressors if the subject develops Grade 4 CRS.

[0504] 80a. The method of any one of embodiments 1a-79a, wherein the subject is administered tocilizumab if the subject develops Grade 2, Grade 3, or Grade 4 CRS.

[0505] 81a. The method of embodiment 80a, wherein the subject is further administered a steroid.

[0506] 82a. The method of embodiment 81a, wherein the steroid is dexamethasone.

[0507] 83a. The method of embodiment 81a, wherein the steroid is methylprednisolone.

[0508] 84a. The method of any one of embodiments 80a-83a, wherein tocilizumab is switched to an anti-IL-6 antibody (e.g., siltuximab) if the subject is refractory to tocilizumab.

[0509] 85a. The method of any one of embodiments 80a-83a, wherein tocilizumab is switched to an IL-1R antagonist (e.g., anakinra) if the subject is refractory to tocilizumab.

[0510] 86a. The method of any one of embodiments 1a-85a, wherein the subject is treated with prophylaxis for tumor lysis syndrome (TLS).

[0511] 87a. The method of embodiment 86a, wherein the prophylaxis for TLS comprises administering one or more uric acid reducing agents prior to administration of the bispecific antibody.

[0512] 88a. The method of embodiment 87a, wherein the one or more uric acid reducing agents comprise rasburicase and/or allopurinol.

[0513] 89a. The method of any one of embodiments 1a-88a, wherein the subject achieves a complete response, a partial response, or stable disease.

[0514] 90a. The method of any one of embodiments 1a-89a, wherein:

[0515] (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

[0516] (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.

[0517] 91a. The method of any one of embodiments 1a-90a, wherein:

[0518] (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

[0519] (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.

[0520] 92a. The method of any one of embodiments 1a-91a, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1,λ (lambda) antibody.

[0521] 93a. The method of embodiment 92a 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.

[0522] 94a. The method of any one of embodiments 1a-93a, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody.

[0523] 95a. The method of embodiment 94a, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

[0524] 96a. The method of any one of embodiments 1a-95a, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

[0525] 97a. The method of any one of embodiments 1a-96a, wherein the bispecific antibody comprises an inert Fc region.

[0526] 98a. The method of any one of embodiments 1a-97a, 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.

[0527] 99a. The method of any one of embodiments 1a-98a, 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.

[0528] 100a. The method of any one of embodiments 1a-99a, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein

[0529] (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

[0530] (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.

[0531] 101a. The method of embodiment 100a, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

[0532] 102a. The method of any one of embodiments 1a-101a, 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.

[0533] 103a. The method of any one of embodiments 1a-102a, 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.

[0534] 104a. The method of any one of embodiments 1a-103a, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.

EXAMPLES

DuoBody-CD3xCD20

[0535] DuoBody-CD3xCD20 is a bsAb recognizing the T-cell antigen CD3 and the B-cell antigen CD20. DuoBody-CD3xCD20 triggers potent T-cell-mediated killing of CD20-expressing cells. DuoBody-CD3xCD20 has a regular IgG1 structure.

[0536] Two parental antibodies, IgG1-CD3-FEAL, a humanized IgG1λ, CD3ε-specific antibody having heavy and light chain sequences as listed in SEQ ID NOs: 24 and 25, respectively, and IgG1-CD20-FEAR, derived from human IgG1κ CD20-specific antibody 7D8 having heavy and light chain sequences as listed in SEQ ID NOs: 26 and 27, respectively, were manufactured as separate biological intermediates. Each parental antibody contains one of the complementary mutations in the CH3 domain required for the generation of DuoBody molecules (F405L and K409R, respectively). The parental antibodies comprised three additional mutations in the Fc region (L234F, L235E and D265A; FEA). The parental antibodies were produced in mammalian Chinese hamster ovary (CHO) cell lines using standard suspension cell cultivation and purification technologies. DuoBody-CD3xCD20 was subsequently manufactured by a controlled Fab-arm exchange (cFAE) process (Labrijn et al. 2013, Labrijn et al. 2014, Gramer et al. 2013). The parental antibodies are mixed and subjected to controlled reducing conditions. This leads to separation of the parental antibodies that, under re-oxidation, re-assemble. This way, highly pure preparations of DuoBody-CD3xCD20 (~93-95%) were obtained. After further polishing/purification, final product was obtained, close to 100% pure. The DuoBody-CD3xCD20 concentration was measured by absorbance at 280 nm, using the theoretical extinction coefficient ε=1.597 $mL \cdot mg^{-1}cm^{-1}$. The final product was stored at 4° C. The product has an international proprietary name of epcoritamab.

[0537] Epcoritamab is prepared (5 mg/mL or 60 mg/mL) as a sterile clear colorless to slightly yellow solution supplied as concentrate for solution for subcutaneous (SC) injection. Epcoritamab contains buffering and tonicifying agents. All excipients and amounts thereof in the formulated product are pharmaceutically acceptable for subcutaneous injection products. Appropriate doses are reconstituted to a volume of about 1 mL for subcutaneous injection.

Example 1: Anti-Tumor Activity of Epcoritamab in the Presence of Anti-CD20 Antibody In Vivo and in NHL Patient-Derived Samples after Anti-CD20 Treatment

[0538] The effects of the presence of an anti-CD20 antibody on the anti-tumor activity of epcoritamab in a humanized mouse xenograft model has been previously described in Engelberts et al., *E Bio Medicine* 2020; 52:10265, as summarized below.

[0539] Epcoritamab was found to effectively reduce tumor growth in the xenograft model (NOD-SCID mice injected with CD20-expressing Raji-luc tumor cells and PBMCs), even in the presence of an excess of a rituximab variant with an inert Fc domain (IgG1-RTX-FEAR, containing L234F, L235E, D265A, and K409R mutations). Rituximab and IgG1-CD20, of which the CD20 arm of epcoritamab is derived, compete for CD20 binding even though they bind to a different epitope, indicating that epcoritamab is able to induce effective anti-tumor activity in the presence of circulating anti-CD20 antibodies that can compete for target binding.

[0540] Furthermore, epcoritamab induced T-cell-mediated cytotoxicity in primary DLBCL and follicular lymphoma patient biopsies taken a certain amount of time after administration of an anti-CD20 antibody (Van der Horst et al., *Blood* 2019; 134 (Supplement 1):4066). Even in a biopsy taken 2 weeks after administering the anti-CD20 antibody, epcoritamab was able to induce up to 40% tumor cell kill.

Example 2: A Phase 1b, Open-Label, Safety and Efficacy Study of Epcoritamab in Combination with Standard-of-Care R-DHAX/C for the Treatment of Relapsed or Refractory (R/R) DLBCL Eligible for Autologous Stem Cell Transplant (ASCT)

[0541] An open-label, 2-part (dose escalation and expansion), multinational, multicenter interventional study is conducted to evaluate the safety, tolerability, PK, pharmacodynamics/biomarkers, immunogenicity, and preliminary efficacy of epcoritamab in combination with a standard of care regimen of R-DHAX/C in subjects with R/R DLBCL eligible for ASCT.

Summary of Ongoing Clinical Trial with Epcoritamab

[0542] Epcoritamab as monotherapy is currently in a clinical trial for the treatment of relapsed/refractory (R/R) (ClinicalTrials.gov Identifier: NCT03625037). Preliminary data suggest that the drug is tolerated at doses up to at least 48 mg, including 60 mg, in R/R B-NHL patients, with no dose-limiting toxicities reported.

Objectives

Dose Escalation

[0543] The primary objective of the dose escalation part is to evaluate the safety and tolerability of epcoritamab in combination with R-DHAX/C (endpoints: incidence of dose-limiting toxicities (DLTs), incidence and severity of

adverse events (AEs), incidence and severity of changes in laboratory values, and incidence of dose interruptions and delays).

[0544] Secondary objectives of the dose escalation part include characterizing the PK properties of epcoritamab (endpoints: PK parameters, including clearance, volume of distribution, AUC0-last, AUC0-x, Cmax, Tmax, predose values, and half-life), evaluating pharmacodynamic markers linked to efficacy and the mechanism of action of epcoritamab (endpoints: pharmacodynamic markers in blood samples and within tumor), evaluating immunogenicity (endpoint: incidence of anti-drug antibodies (ADAs) to epcoritamab), and assessing the preliminary anti-tumor activity of epcoritamab in combination with R-DHAX/C (endpoints: overall response rate (ORR) by Lugano criteria and LYRIC, duration of response (DOR) by Lugano criteria and LYRIC, time to response (TTR) by Lugano criteria and LYRIC, progression free survival (PFS) by Lugano criteria and LYRIC, overall survival (OS), time to next anti-lymphoma therapy (TTNT), and rate and duration of minimal residual disease (MRD) negativity).

[0545] Exploratory objectives of the dose escalation part include assessing potential biomarkers predictive of clinical response to epcoritamab (endpoints: CD3, CD20, and other molecular/phenotypic markers pre-treatment and during treatment, DNA mutation status, and gene profile).

Expansion

[0546] The primary objective of the expansion part is to assess the preliminary anti-tumor activity of epcoritamab in combination with R-DHAX/C (endpoint: ORR by Lugano criteria).

[0547] Secondary objectives of the expansion part include evaluating the preliminary anti-tumor activity of epcoritamab in combination with R-DHAX/C (endpoints: endpoints: DOR by Lugano criteria and LYRIC, TTR by Lugano criteria and LYRIC, PFS by Lugano criteria and LYRIC, ORR by LYRIC, OS, TTNT, and rate and duration of minimal residual disease (MRD) negativity), further evaluating the safety and tolerability of epcoritamab in combination with R-DHAX/C (endpoints: incidence and severity of changes in laboratory values, and incidence of dose interruptions and delays), characterizing the PK properties of epcoritamab (PK parameters, including clearance, volume of distribution, AUC0-last, AUC0-x, Cmax, Tmax, predose values, and half-life), evaluating pharmacodynamic markers linked to efficacy and mechanism of action of epcoritamab (endpoints: pharmacodynamic markers in blood samples and within tumor), and evaluating immunogenicity (endpoint: incidence of ADAs to epcoritamab).

[0548] Exploratory objectives of the expansion part include assessing potential biomarkers predictive of clinical response to epcoritamab (endpoints: expression of CD20 in tumors, evaluation of molecular and genetic tumor markers, immune populations, phenotype and function in tumors and blood, and DNA mutation status and gene profile), and evaluating patient-reported outcomes (PROs) (endpoint: changes in lymphoma symptoms and general health status as evaluated by the FACT-Lym).

Study Design Overview

[0549] The trial is conducted in 2 parts: dose escalation (Part 1) and expansion (Part 2). Subjects participate in only one part. A schematic of the overall trial design is shown in FIG. **1**. Both parts consist of a screening period, a treatment period, a safety follow-up period, and a survival follow-up period.

Dose Escalation (Part 1) and Expansion (Part 2)

[0550] The Part 1 dose escalation assesses the initial safety, tolerability, and clinical activity of epcoritamab in combination with R-DHAX/C. Epcoritamab is initially be administered in combination with R-DHAX/C in a 3-subject cohort. DLTs are evaluated during the first 28 days. Depending on the number of DLTs observed in the initial 3 subjects, administration of epcoritamab (full dose: 48 mg or 24 mg) in combination with R-DHAX/C is performed in an additional 3 subjects as shown in FIG. **2**.

[0551] In Part 2, epcoritamab is administered (with the dosing regimen determined in the dose escalation part) in combination with R-DHAX/C. The expansion will include 20 subjects in order to evaluate the preliminary clinical activity of the combination, in addition to safety, tolerability, PK, pharmacodynamic, and immunogenicity data.

[0552] In both Part 1 and Part 2, epcoritamab is administered as a subcutaneous (SC) injection (24 mg or 48 mg; step-up dosing) in combination with R-DHAX/C until ASCT or disease progression, whichever occurs first, as follows:

TABLE 2

Dosing schedule		
Cycle number	Epcoritamab	Standard of care
21-day cycles		
1	QW, step-up dosing	R-DHAX/C – Q3W
2-3	QW	R-DHAX/C – Q3W
4	QW	Conditioning + ASCT*
28-day cycles (if conditioning/ASCT delayed)		
5-9	Q2W	—
10+	Q4W	—

QW: once a week (days 1, 8, and 15),

Q2W: once every two weeks (days 1 and 8),

Q3W: once every three weeks (day 1),

Q4W: once every four weeks (day 1)

*If ASCT delayed, then epcoritamab given until ASCT or disease progression. No epcoritamab is given after ASCT.

[0553] A step-up dosing method is used for epcoritamab to mitigate the potential for CRS: priming dose (0.16 mg) on cycle 1 day 1, followed by intermediate dose (0.8 mg) on cycle 1 day 8, full dose (24 mg or 48 mg) on cycle 1 day 15, and full dose in subsequent cycles. Rituximab (375 mg/m^2) is administered intravenously on day 1 once every 3 weeks (Q3W) for cycles 1-3. Dexamethasone (40 mg) is administered intravenously or orally on days 1-4 of a cycle once every 3 weeks (Q3W) for cycles 1-3. Cytarabine (2 g/m^2) is administered intravenously on day 1 (usually over 3 hours), repeated after 12 hours (may result in a second dose on day 2 depending on timing of first dose), once every 3 weeks (Q3W) for cycles 1-3. Oxaliplatin (for DHAX) (100 mg/m^2) is administered intravenously on day 1 once every 3 weeks (Q3W) for cycles 1-3. Carboplatin (for DHAC) (AUC=5 mg/ml/min; Calvert's formula) is administered intravenously on day 1 once every 3 weeks (Q3W) for cycles 1-3.

[0554] The order of treatments are as follows:

TABLE 3

Treatment administration order		
Dosing order	Treatment	Dose
Pre-Meds	Pre-medications (dexamethasone component of R-DHAX/C may serve as corticosteroid premedication)	As described in Table 4
1	Dexamethasone	40 mg
2	Rituximab	375 mg/m^2
3	(a) Oxaliplatin or (b) Carboplatin	(a) 100 mg/m^2; (b) AUC = 5 mg/ml/min on day 1
4	Epcoritamab	24 mg or 48 mg
5	Cytarabine	2 g/m^2 (x2) on day 1, or 2 g/m^2 on day 1 and 2 g/m^2 on day 2

Inclusion Criteria

[0555] 1. Subject must be at least 18 years of age

[0556] 2. ECOG PS score of 0, 1, or 2

[0557] 3. CD20-positive NHL representative tumor biopsy

[0558] 4. Measurable disease defined as ≥1 measurable nodal lesion (long axis >1.5 cm and short axis >1.0 cm) or ≥1 measurable extra-nodal lesion (long axis >1.0 cm) on CT or MRI

[0559] 5. Acceptable organ function at screening defined as:

[0560] a. ANC $\geq 1.0\times10^9$/L (growth factor use is allowed)

[0561] b. Platelet count $>75\times10^9$/L, or $\geq 50\times10^9$/L if bone marrow infiltration or splenomegaly

[0562] c. ALT level ≤2.5 times the ULN

[0563] d. Total bilirubin level ≤2×ULN

[0564] e. eGFR >50 mL/min (by Cockcroft-Gault Formula)

[0565] f. PT, INR, and aPTT ≤1.5×ULN, unless receiving anticoagulant

[0566] 6. Documented DLBCL (de novo or histologically transformed from indolent lymphomas, except for CLL) according to the 2016 WHO classification, including:

[0567] a. DLBCL, NOS

[0568] b. "Double hit" or "triple hit" DLBCL (technically classified in WHO 2016 as HGBCL, with MYC and BCL2 and/or BCL6 translocations)—Other double-/triple-hit lymphomas are not eligible

[0569] c. FL Grade 3B

[0570] 7. Relapsed or refractory to at least one prior therapy

[0571] 8. Eligible to receive HDT-ASCT

[0572] 9. Eligible to receive R-DHAX/C.

Exclusion Criteria

[0573] 1. Contraindication to any of the individual drugs in the R-DHAX/C regimen

[0574] 2. History of severe allergic or anaphylactic reactions to anti-CD20 mAb therapy or known allergy or intolerance to any component or excipient of epcoritamab

[0575] 3. Prior treatment with a bispecific antibody targeting CD3 and CD20

[0576] 4. Chemotherapy, radiation therapy, or major surgery within 4 weeks prior to the first dose of epcoritamab

[0577] 5. Treatment with an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to the first dose of epcoritamab

[0578] 6. Treatment with CAR-T therapy within 30 days prior to first dose of epcoritamab

[0579] 7. Cumulative dose of corticosteroids ≥140 mg of prednisone or the equivalent within 2-week period before the first dose of epcoritamab

[0580] 8. Vaccination with live vaccines within 28 days prior to the first dose of epcoritamab

[0581] 9. Clinically significant cardiac disease, including:

[0582] a. Myocardial infarction within 1 year prior to the first dose of epcoritamab, or unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV), cardiac arrhythmia (CTCAE Version 4 Grade 2 or higher), or clinically significant ECG abnormalities

[0583] b. Screening 12-lead ECG showing a baseline QTcF >470 msec

[0584] 10. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results

[0585] 11. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at trial enrollment or significant infections within 2 weeks prior to the first dose of epcoritamab

[0586] 12. CNS lymphoma or known CNS involvement by lymphoma at screening as confirmed by MRI/CT scan of the brain and, if clinically indicated, by lumbar puncture

[0587] 13. Active positive tests for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

[0588] 14. History of HIV antibody positivity, or tests positive for HIV at screening

[0589] 15. Positive test results for HTLV-1

[0590] 16. Suspected active or latent tuberculosis

[0591] 17. Past or current malignancy other than inclusion diagnosis, except for:

[0592] a. Cervical carcinoma of Stage 1B or less

[0593] b. Non-invasive basal cell or squamous cell skin carcinoma

[0594] c. Non-invasive, superficial bladder cancer

[0595] d. Prostate cancer with a current PSA level <0.1 ng/mL

[0596] e. Any curable cancer with a CR of >2 years duration

[0597] 18. Neuropathy >grade 1

[0598] 19. Female who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this trial or within 12 months after the last dose of epcoritamab

[0599] 20. Male who plans to father a child while enrolled in this trial or within 12 months after the last dose of epcoritamab

[0600] 21. Subject who has any condition for which participation would not be in the best interest of the

subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

CRS Prophylaxis

[0601] Administration of corticosteroids for four days is performed to reduce/prevent the severity of symptoms from potential CRS for each dose of epcoritamab. Dexamethasone in the R-DHAX/C regimen serves as the corticosteroid component of the CRS prophylaxis regimen for days 1-4 of cycle 1 of the 21-day cycles, but not days 8-11 and 15-18 of cycle 1 of the 21-day cycles, which will use prednisolone 100 mg or equivalent. For administration of epcoritamab in cycle 2 and beyond, CRS prophylaxis is optional. Dexamethasone administration can be either intravenous or oral route with recommended dose or equivalent.

[0602] Supportive therapies recommended for treatments containing rituximab include:

[0603] Premedication with acetaminophen (650 mg orally), diphenhydramine (50 to 100 mg IV or orally), and steroids, 30 to 60 minutes before starting each rituximab infusion, to attenuate infusion reactions

[0604] Prophylactic treatment for Pneumocystis carinii pneumonia

[0605] Central nervous system (CNS) prophylaxis; subjects with 1) involvement of 2 extranodal sites and elevated LDH, or 2) lymphomatous involvement of the bone marrow, testis, or a para-meningeal site are considered to be at high risk of developing CNS disease and should receive CNS prophylaxis. CNS prophylaxis with IV methotrexate is permitted following completion of the DLT period (28 days from first dose of study treatment)

TABLE 4

Pre-medication and CRS prophylaxis

			Corticosteroids	Antihistamines	Antipyretics
Cycle 1	1st epcoritamab administration (priming dose)	Day 01*	Dexamethasone 40 mg (IV or oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 02	Dexamethasone 40 mg (IV or oral dose)		
		Day 03	Dexamethasone 40 mg (IV or oral dose)		
		Day 04	Dexamethasone 40 mg (IV or oral dose)		
	2nd epcoritamab administration (intermediate dose)	Day 08*	Prednisolone 100 mg IV (or equivalent including oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 09	Prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 10	Prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 11	Prednisolone 100 mg IV (or equivalent including oral dose)		
	3$_{rd}$ epcoritamab administration (full dose)	Day 15*	Prednisolone 100 mg IV (or equivalent including oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 16	Prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 17	Prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 18	Prednisolone 100 mg IV (or equivalent including oral dose)		
Cycle 2	4th epcoritamab administration (full dose)	Day 22	Dexamethasone 40 mg (IV or oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 23	Dexamethasone 40 mg (IV or oral dose)		
		Day 24	Dexamethasone 40 mg (IV or oral dose)		
		Day 25	Dexamethasone 40 mg (IV or oral dose)		
	5th epcoritamab administration (full dose)	Day 29* Day 30	If CRS > grade 1 occurs following the 4th epcoritamab administration, 4-day consecutive corticosteroid	Optional	Optional

TABLE 4-continued

Pre-medication and CRS prophylaxis			
	Corticosteroids	Antihistamines	Antipyretics
	administration is continued in Cycle 2 until epcoritamab dose is given without subsequent CRS event.		

*30 minutes to 2 hours prior to administration of epcoritamab

Note:

If epcoritamab dose is administered more than 24 h after the start of R-DHAX/C, the premedication is administered prior to epcoritamab dose and corticosteroid prophylaxis is continued for 3 days following the epcoritamab administration.

TABLE 5

Corticosteroid Dose Equivalents - Conversion Table	
Glucocorticoid	Approximate equivalent dose (mg)
Short-acting	
Cortisone (PO)	500
Hydrocortisone (IV or PO)	400
Intermediate-acting	
Methylprednisolone (IV or PO)	80
Prednisolone (PO)	100
Prednisone (IV or PO)	100
Triamcinolone (IV)	80
Long-acting	
Betamethasone (IV)	15
Dexamethasone (IV or PO)	15

Supportive Care for Cytokine Release Syndrome

[0606] CRS is graded according to the ASTCT grading for CRS (Tables 6 and 7), and for treatment of CRS, subjects should receive supportive care. Supportive care can include, but is not limited to,

[0607] Infusion of saline

[0608] Systemic glucocorticosteroid, antihistamine, antipyrexia

[0609] Support for blood pressure (vasopressin, vasopressors)

[0610] Support for low-flow and high-flow oxygen and positive pressure ventilation

[0611] Monoclonal antibody against IL-6R, e.g., IV administration of tocilizumab

[0612] Monoclonal antibody against IL-6, e.g., IV siltuximab if not responding to repeated tocilizumab.

TABLE 6

Grading and Management of Cytokine Release Syndrome

Harmonized definitions and grading criteria for CRS, per the American Society for Transplantation and Cellular Therapy (ASTCT), formerly American Society for Blood and Marrow Transplantation, (ASBMT), are presented below.

Grading of Cytokine Release Syndrome

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever[1]	≥38.0° C.	≥38.0° C.	≥38.0° C.	≥38.0° C.	Death due to CRS in which another cause is not the principle factor leading to this outcome
With hypotension	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring ≥2 vasopressors (excluding vasopressin)	
And/or hypoxia[2]	None	Requiring low-flow (≤6 L/minute) nasal cannula or blow-by	Requiring high-flow (>6 L/minute) nasal cannula, facemask, nonrebreather mask, or venturi mask	Requiring positive pressure ventilation[3] (eg, CPAP, BiPAP, intubation and mechanical ventilation)	

Abbreviations: BiPAP, Bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; IV, intravenous.

Note:

organ toxicities or constitutional symptoms associated with CRS may be graded according to CTCAE but they do not influence CRS grading.

[1]Fever is defined as temperature ≥38.0° C. not attributable to any other cause, with or without constitutional symptoms (eg, myalgia, arthralgia, malaise). In subjects who have CRS receiving antipyretics, anticytokine therapy, and/or corticosteroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[2]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5° C., hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. Both systolic blood pressure and mean arterial pressure are acceptable for blood pressure measurement. No specific limits are required, but hypotension should be determined on a case-by-case basis, accounting for age and the subject's individual baseline, i.e., a blood pressure that is below the normal expected for an individual in a given environment.

[3]Intubation of a subject without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not by definition grade 4 CRS.

Source: Adapted from Lee et al., *Biol Blood Marrow Transplant* 2019; 25: 625-638

TABLE 7

Grading and Management of Cytokine Release Syndrome

CRS grade	Management
1	Fever: Patients with a new fever should be admitted to the hospital if not already. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until and potential neutropenia resolve. Constitutional symptoms may be helped by NSAIDs. Tocilizumab: No*. Steroids: No.
2	Fever: As per grade 1. Hypotension: Immediate clinical evaluation and intervention is warranted. At the first confirmed decrease ≥ 20% from baseline systolic, diastolic or mean arterial pressure or evidence of worsening perfusion, administer an IV fluid bolus (20 mL/kg up to 1 L). Consider a vasopressor and administer no later than after the 3rd IV fluid bolus due the vasodilatation and capillary leak associated with CRS. Hypoxia: Consider X-ray or CT-scan if hypoxic and/or tachypneic. Administer oxygen by low-flow nasal cannula (≤6 L/min) or blow-by. Tocilizumab: No* (yes, if the patient has comorbidities†). Steroids: No (consider, if the patient has comorbidities‡).
3	Fever: As per grade 1. Hypotension: Immediate clinical evaluation and intervention is warranted. Administer a vasopressor (norepinephrine), with or without vasopressin, as most patients with CRS have peripheral vasodilation. Hypoxia: Administer oxygen by high-flow nasal cannula (>6 L/min), facemask, non-breather mask, or Venturi mask. Tocilizumab: Yes†. Steroids: Consider‡.
4	Fever: As per grade 1. Hypotension: Immediate clinical evaluation and intervention is warranted. Administer at least 2 vasopressors, with or without vasopressin, as most patients with CRS have peripheral vasodilation. Hypoxia: Positive pressure (e.g. CPAP, BiPAP, intubation, and mechanical ventilation). Tocilizumab: Yes†. Steroids: Yes‡.

*Consider intervening earlier in specific cases. For example, an elderly patient with prolonged fever (>72 hours) or very high fever (>40.5° C./104.9° F.) may not tolerate the resulting sinus tachycardia as well as a younger patient, so tocilizumab may be indicated.
†Tocilizumab (anti-IL-6R) remains the only first-line anticytokine therapy approved for CRS. If there is no improvement in symptoms within 6 hours, or if the patient starts to deteriorate after initial improvement, a second dose of tocilizumab should be administered along with a dose of corticosteroids. For patients being refractory to tocilizumab (3 administrations), additional anticytokine therapy such as siltuximab (anti-IL-6) or anakinra (anti-IL-1R) may be considered. However, such use is entirely anecdotal and, as such, is entirely at the discretion of the treating physician.
‡Consider dexamethasone over methylprednisolone due to improved CNS penetration even in absence of neurotoxicity, as high-grade CRS is correlated with risk of concurrent or subsequent ICANS. If concurrent ICANS is observed, dexamethasone should be preferred.
Source: Varadarajan I, Kindwall-Keller T L, Lee D W (2020). Management of cytokine release syndrome. In: Chimeric antigen receptor T-cell therapies for cancer (Chapter 5). Elsevier 2020)

Tumor Lysis Syndrome Prevention and Management

[0613] For prophylactic treatment of tumor lysis syndrome, subjects receive hydration and uric acid reducing agents prior to the administration of epcoritamab. If signs of tumor lysis syndrome (TLS) occur, supportive therapy, including rasburicase, is used.

Dose Modification Guidance and Safety Management

[0614] There will be no dose modification for epcoritamab (see FIG. **2** for exceptions in the dose escalation cohorts), although it may be held or discontinued depending on the nature of toxicities (and grade of toxicities) subjects develop during their use.

[0615] Dose modifications for rituximab, dexamethasone, cytarabine, oxaliplatin, and carboplatin should be done in accordance with the respective product labels in situations that differ from dose modification recommendations provided below.

Rituximab

[0616] Rituximab should be held for any Grade 4 toxicity or for any rituximab-related, clinically significant, unmanageable Grade 3 adverse event. Rituximab should be held until the adverse event returns to baseline or resolves completely.

DHAX/C

[0617] Table 8 describes the dose reduction steps for R-DHAX/C

TABLE 8

R-DHAX/C Dose Reduction Steps

Event	Cytarabine
Severe neutropenia ANC < 0.2 × 10^9/L	1 g/m^2 × 2
Severe thrombocytopenia Platelets < 20 × 10^9/L	1 g/m^2 × 2
Sepsis associated with neutropenia	0.5 g/m^2 × 1
Serum creatinine	Hold
1.5-2.0 mg/mL	Hold
2.1-3.0 mg/mL	

[0618] For oxaliplatin dose reduction for neuropathy (worsening compared with baseline):

[0619] No dose reduction for paresthesia lasting between 1 and 6 days after each administration.

[0620] Reduce dose to 75 mg/m^2 in the event of significant paresthesia (increase in severity from baseline) lasting between 7 and 13 days after each administration. In the event of abnormal results by neurologic examination or if a subject experiences significant paresthesia lasting for 14 days or more, oxaliplatin should be stopped until symptoms improve and then restarted at a dose of 75 mg/m^2. In the event of pharyngolaryngeal dysesthesia, the duration of the oxaliplatin infusion should be prolonged from 2 to 6 hours.

Study Assessments

Demographics and Baseline Assessments

[0621] Demographic details of subjects are collected, as is information such as date of lymphoma diagnosis, Ann Arbor Staging at diagnosis, including constitutional symptoms (B symptoms), and prior evidence of CD20 positivity. Medical history, information regarding prior and concomitant medications, concomitant procedures, and prior cancer therapies and surgeries (including prior anti-cancer therapy for NHL, such as surgery, radiotherapy, chemo-radiotherapy, and systemic treatment regimens), are also collected.

Efficacy Assessments

[0622] Eligible subjects have at least 1 measurable site of disease (as indicated in the inclusion criteria) for disease evaluations. Measurable sites of lymphoma are defined as lymph nodes, lymph node masses, or extranodal sites. Measurements are determined by imaging evaluation, with up to 6 measurable sites followed as target lesions for each subject. Sites not measurable as defined above are considered assessable by objective evidence of disease (i.e., radiographic imaging, physical examination, or other procedures). Examples of assessable disease include, e.g., bone marrow involvement, bone lesions, effusions, or thickening of bowel wall.

Tumor and Bone Marrow Biopsies

[0623] Two fresh core tumor biopsies are collected before treatment with epcoritamab (during the screening period) and 2 fresh core tumor biopsies at the start of cycle 2 day 15 (±1 week) for all subjects with accessible tumors. An archival tumor biopsy, if collected within 3 months prior to enrollment, is acceptable if a fresh biopsy at screening cannot be collected. The biopsy can be a whole lymph node or a core biopsy. Tumor biopsies should be FFPE. Tumor biopsies are examined for MRD assessment and exploratory biomarkers.

Radiographic Assessments

[0624] An FDG PET-CT scan (or CT/MRI and FDG PET when PET-CT scan not available) is performed during Screening. For subjects with FDG-avid tumors at Screening, all subsequent disease assessments include FDG-PET using the 5-point scale described in Barrington et al. (*J Clin Oncol* 2014; 32:3048-58; Score 1: No uptake; Score 2: Uptake ≤mediastinum; Score 3: Update >mediastinum but ≤liver; Score 4: Uptake moderately higher than liver; Score 5: Uptake markedly higher than liver and/or new lesions; Score X: new areas of update unlikely to be related to lymphoma). For subjects with non-avid or variably FDG-avid tumors, CT scan with IV contrast of neck/chest/abdomen/pelvis/additional known lesions may be performed. The CT component of the PET-CT may be used in lieu of a standalone CT/MRI, if the CT component is of similar diagnostic quality as a contrast enhanced CT performed without PET. If contrast enhanced PET-CT is not available, a standalone diagnostic CT/MRI and a standard FDG-PET is performed. Subjects who are intolerant of IV CT contrast agents undergo CT scans with oral contrast.

[0625] MRI can be used to evaluate sites of disease that cannot be adequately imaged using CT or for subjects intolerant of CT contrast agents. In cases where MRI is the imaging modality of choice, the MRI is obtained at screening and at all subsequent response evaluations.

Bone Marrow Assessments

[0626] A bone marrow biopsy (archival or fresh), with or without aspirate, is obtained at screening for all patients to document bone marrow involvement with lymphoma. A bone marrow biopsy obtained as routine SOC may be used if taken up to 42 days before first dose of epcoritamab. If bone marrow aspirate is obtained, determination of bone marrow involvement can be confirmed by flow cytometry. A bone marrow biopsy is taken (1) at screening; (2) for subjects with bone marrow involvement at screening who later achieve CR by imaging—bone marrow evaluation includes morphological examination and either flow cytometry or IHC, if warranted, to confirm the presence or absence (complete remission) of lymphoma; (3) for subjects with bone marrow involvement documented at screening who later achieve CR by imaging—a portion of the aspirate collected to confirm CR will be used for MRD assessments.

Minimal Residual Disease Assessment

[0627] MRD is assessed by tracking the presence of DNA that encodes the B cell receptor (BCR) expressed specifically by the cancer cells. The DNA sequence of this BCR is identified by tumor biopsy submitted at screening. After the start of treatment, blood samples are taken at fixed timepoints and at the time of CR to assess whether the amount of cancer DNA is declining, as a potential measure of (early) response, and to assess MRD. As an exploratory analysis, when a subject reaches a metabolic/radiologic CR and has bone marrow involvement documented at screening, a portion of the aspirate collected to confirm CR is used to assess MRD.

Disease Response and Progressive Disease Assessment

[0628] Disease response is assessed according to both Lugano criteria (described in Cheson et al., *J Clin Oncol* 2014; 32:3059-68 (see, in particular, Table 3 in Cheson et al., 2014) and LYRIC (Table 9) to inform decisions on continuation of treatment.

[0629] Endpoint definitions are as follows:

[0630] Overall response rate (ORR), is defined as the proportion of subjects who achieve a response of PR or CR, prior to initiation of subsequent therapy.

[0631] Time to response (TTR), is defined among responders, as the time between first dose (from day 1, cycle 1) of epcoritamab and the initial documentation of PR or CR.

[0632] Duration of response (DOR), is defined among responders, as the time from the initial documentation of PR or CR to the date of disease progression or death, whichever occurs earlier.

[0633] Progression-free survival (PFS), is defined as the time from the first dosing date (day 1, cycle 1) of epcoritamab and the date of disease progression or death, whichever occurs earlier.

[0634] Overall survival (OS), is defined as the time from the first dosing date (day 1, cycle 1) of epcoritamab and the date of death.

[0635] Time to next anti-lymphoma therapy (TTNT), is defined as the number of days from day 1 of cycle 1 to the first documented administration of subsequent anti-lymphoma therapy.

[0636] MRD negativity rate, is defined as the proportion of subjects with at least 1 undetectable MRD result according to the specific threshold, prior to initiation of subsequent therapy.

Lugano criteria (see, e.g., Cheson et al., *J Clin Oncol* 2014; 32:3059-68, for definitions of complete response, partial response, no response/stable disease, and progressive disease)

(a) Target and Non-Target Lesions

[0637] Target lesions for the Lugano criteria include up to 6 of the largest dominant nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters and are preferably from different body regions representative of the subject's overall disease burden, including mediastinal and retroperitoneal disease, where applicable. At baseline, a measurable node is >15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the six representative target lesions. At baseline, measurable extranodal lesions should be >10 mm in LDi.

[0638] All other lesions (including nodal, extranodal, and assessable disease) may be followed as non-target lesions (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

(b) Split Lesions and Confluent Lesions

[0639] Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease (PD). The LDi and smallest diameter (SDi) are no longer needed to determine progression.

LYRIC

[0640] Clinical studies have shown that cancer immunotherapies may result in early apparent radiographic progression (including the appearance of new lesions), followed by a delayed response. As this initial increase in tumor size might be caused by immune-cell infiltration in the setting of a T-cell response, this progression may not be indicative of true disease progression and is therefore called "pseudoprogression" (Wolchok et al., *Clin Cancer Res* 2009; 15:7412-20).

[0641] The current Lugano response assessment criteria (Cheson et al., *J Clin Oncol* 2014; 32:3059-68) does not take pseudoprogression into account, and there is a significant risk of premature discontinuation of a potentially efficacious immunomodulatory drug following the observation of an atypical response. Atypical responses are characterized either by the early progression of existing lesions, later followed by response, or by the development of new lesions, with or without tumor shrinkage elsewhere.

[0642] LYRIC is a modification of the Lugano response assessment criteria, which has been adapted to immune-based therapies, and it implements a new, mitigating response category: the "indeterminate response" (IR) designation (Cheson et al., *Blood* 2016; 128:2489-96). This IR designation was introduced to potentially identify "atypical response" cases until confirmed as flare/pseudoprogression or true PD by either biopsy or subsequent imaging.

[0643] A subject who shows PD according Lugano criteria/classification will be considered to have IR in 1 or more of the 3 following circumstances:

[0644] IR (1): Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥50% of up to 6 target lesions in the first 12 weeks of therapy, without clinical deterioration.

[0645] IR (2): Appearance of new lesions or growth of one or more existing lesion(s)≥50% at any time during treatment; occurring in the context of lack of overall progression (SPD <50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment.

[0646] IR (3): Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number.

[0647] It is possible that, at a single time point, a subject could fulfill criteria for both IR(1) or IR(2) and IR(3): for example, there could be a new FDG-avid lesion in the absence of overall progression (IR[2]), and, at the same time, increase in FDG uptake of a separate lesion (IR[3]). In such cases, the designation of IR(1) or IR (2) should take priority (e.g., IR[2] in the above example).

TABLE 9

LYRIC				
	CR	PR	SD	PD
LYRIC	Same as Lugano Classification	Same as Lugano Classification	Same as Lugano Classification	As with Lugano with the following exceptions: IR Categories: IR (1): ≥50% increase in SPD in first 12 weeks of therapy IR (2): <50% increase in SPD with a) New lesion(s), or b) ≥50% increase of 1 lesion or set of lesions at any time during treatment IR (3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

[0648] Subjects categorized as having any of the IR types receive repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated, and the subject should be considered to have true PD with the following considerations:

[0649] Follow-up IR(1): In case of IR(1), comparison should be made between the first IR(1) and the current SPD. The IR(1) will become PD if: (a) SPD increases by ≥10% from first IR1 AND (b) an increase of ≥5 mm (in either dimension) of ≥1 lesion for lesions ≤2 cm and >10 mm for lesions >2 cm, to be consistent with Lugano criteria.

[0650] Follow-up IR(2): In case of IR(2), the new or growing lesion(s) is added to the target lesion(s), up to a total of no more than 6 total lesions. The IR(2) will become PD if: (a)≥50% increase in SPD (newly defined set of target lesions) from nadir value.

[0651] Follow-up IR(3): The IR(3) will become PD if lesion with increased FDG uptake also shows size increase.

Clinical Safety Assessments

[0652] Safety is assessed by measuring adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and ECOG performance status. Also assessed are immune effector cell-associated neurotoxicity syndrome (e.g., as described by Lee et al., *Biol Blood Marrow Transplant* 2019; 25:625-638), constitutional symptoms (B symptoms), tumor flare reaction, and survival.

Patient-Reported Outcomes

[0653] Patient-reported outcomes are evaluated using the FACT-Lym health-related quality of life (QOL) questionnaire, which assesses QOL in lymphoma patients.

Preliminary Results

[0654] As of Sep. 8, 2021, a total of 22 patients had been dosed. The expansion phase 48 mg was opened on 28 June 21. 4 responders were observed in escalation phase and 0 in expansion phase. The most common related AEs are Thrombocytopenia and CRS. All CRS were Grade 1/2. One episode of Grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) was reported where the patient recovered. These data are preliminary and non-validated and unclean data and response data were not completely entered by site.

TABLE 10

Summary of Sequences

SEQ ID	Description	Sequence
1	huCD3 VH CDR1	GFTFNTYA
2	huCD3 VH CDR2	IRSKYNNYAT
3	huCD3 VH CDR3	VRHGNFGNSYVSWFAY
4	huCD3 VL CDR1	TGAVTTSNY
–	huCD3 VL CDR2	GTN
5	huCD3 VL CDR3	ALWYSNLWV
6	huCD3 VH1	EVKLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLE WVARIRSKYNNYATYYADSVKDRFTISRDDSKSSLYLQMNNLKTEDTA MYYCVRHGNFGNSYVSWFAYWGQGTLVTVSS
7	huCD3 VL1	QAVVTQEPSFSVSPGGTVTLTCRSSTGAVTTSNYANWVQQTPGQAF RGLIGGTNKRAPGVPARFSGSLIGDKAALTITGAQADDESIYFCALWYS NLWVFGGGTKLTVL

TABLE 10-continued

Summary of Sequences

SEQ ID	Description	Sequence
8	VH CD20-7D8 CDR1	GFTFHDYA
9	VH CD20-7D8 CDR2	ISWNSGTI
10	VH CD20-7D8 CDR3	AKDIQYGNYYYGMDV
11	VL CD20-7D8 CDR1	QSVSSY
—	VL CD20-7D8 CDR2	DAS
12	VL CD20-7D8 CDR3	QQRSNWPIT
13	VH CD20-7D8	EVQLVESGGGLVQPDRSLRLSCAASGFTFHDYAMHWVRQAPGKGLE WVSTISWNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDIQYGNYYYGMDVWGQGTTVTVSS
14	VL CD20- 7D8	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIY DASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPITF GQGTRLEIK
15	IgG1 heavy chain constant region-WT (amino acids positions 118-447 according to EU numbering). CH3 region italics	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAK*GQPREPQVYTLPPSRE* *EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS* *FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*
16	IgG1-LFLEDA heavy chain constant region (amino acids positions 118-447 according to EU numbering).	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE**FE**GGPSVFLFPPKPKDTLMISRTPEVTCV VV**A**VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
17	IgG1 F405L (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS F**L**LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
18	IgG1-K409R (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYS**R**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
19	IgG1-LFLEDA-F405L (FEAL) (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE**FE**GGPSVFLFPPKPKDTLMISRTPEVTCV VV**A**VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS F**L**LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
20	IgG1-LFLEDA-K409R (FEAR) (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE**FE**GGPSVFLFPPKPKDTLMISRTPEVTCV VV**A**VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYS**R**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
21	IgG1 CH3 region	GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG

TABLE 10-continued

Summary of Sequences

SEQ ID	Description	Sequence
22	Constant region human lambda LC	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECS
23	Constant region human kappa LC	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
24	huCD3-LFLEDA-F405L (FEAL) heavy chain	EVKLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLE WVARIRSKYNNYATYYADSVKDRFTISRDDSKSSLYLQMNNLKTEDTA MYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPE**FE**GGPSVFLFPPKPKDTLMISRTPEVTCVVV**A**VSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSF**L**LYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG
25	huCD3 VL + CL light chain	QAVVTQEPSFSVSPGGTVTLTCRSSTGAVTTSNYANWVQQTPGQAF RGLIGGTNKRAPGVPARFSGSLIGDKAALTITGAQADDESIYFCALWYS NLWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS
26	CD20-7D8-LFLEDA-K409R (FEAR) heavy chain	EVQLVESGGGLVQPDRSLRLSCAAS<u>GFTFHDYA</u>MHWVRQAPGKGLE WVST<u>ISWNSGTI</u>GYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYC<u>AKDIQYGNYYYGMDV</u>WGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPA PE**FE**GGPSVFLFPPKPKDTLMISRTPEVTCVVV**A**VSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS**R**LTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPG
27	CD20-7D8 VL + CL light chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIY DASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPITF GQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
28	Human CD3 (epsilon)	MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSISGTTVI LTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSG YYVCYPRGSKPEDANFYLYLRARVCENCMEMDVMSVATIVIVDICITG GLLLLVYYWSKNRKAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDY EPIRKGQRDLYSGLNQRRI
29	Human CD20	MTTPRNSVNGTFPAEPMKGPIAMQSGPKPLFRRMSSLVGPTQSFFM RESKTLGAVQIMNGLFHIALGGLLMIPAGIYAPICVTVWYPLWGGIM YIISGSLLAATEKNSRKCLVKGKMIMNSLSLFAAISGMILSIMDILNIKIS HFLKMESLNFIRAHTPYINIYNCEPANPSEKNSPSTQYCYSIQSLFLGILS VMLIFAFFQELVIAGIVENEWKRTCSRPKSNIVLLSAEEKKEQTIEIKEEV VGLTETSSQPKNEEDIEIIPIQEEEEEETETNFPEPPQDQESSPIENDSSP

[0655] Bold and underlined are FE; A; L and R, corresponding to positions 234 and 235; 265; 405 and 409, respectively, said positions being in accordance with EU-numbering. In variable regions, said CDR regions that were annotated in accordance with IMGT definitions are underlined.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 29

<210> SEQ ID NO 1
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence

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<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 1

Gly Phe Thr Phe Asn Thr Tyr Ala
1 5

<210> SEQ ID NO 2
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 2

Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr
1 5 10

<210> SEQ ID NO 3
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 3

Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr
1 5 10 15

<210> SEQ ID NO 4
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 4

Thr Gly Ala Val Thr Thr Ser Asn Tyr
1 5

<210> SEQ ID NO 5
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 5

Ala Leu Trp Tyr Ser Asn Leu Trp Val
1 5

<210> SEQ ID NO 6
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy chain variable region sequence 1

<400> SEQUENCE: 6

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

-continued

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Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210> SEQ ID NO 7
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Light chain variable region sequence

<400> SEQUENCE: 7

Gln Ala Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1               5                   10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Thr Pro Gly Gln Ala Phe Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Asp Asp Glu Ser Ile Tyr Phe Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210> SEQ ID NO 8
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 8

Gly Phe Thr Phe His Asp Tyr Ala
1               5


<210> SEQ ID NO 9
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 9

Ile Ser Trp Asn Ser Gly Thr Ile
1               5
```

-continued

<210> SEQ ID NO 10
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 10

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 11
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 11

Gln Ser Val Ser Ser Tyr
1 5

<210> SEQ ID NO 12
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR sequence

<400> SEQUENCE: 12

Gln Gln Arg Ser Asn Trp Pro Ile Thr
1 5

<210> SEQ ID NO 13
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy chain variable region sequence

<400> SEQUENCE: 13

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Asp Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe His Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Trp Asn Ser Gly Thr Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 14
<211> LENGTH: 107
<212> TYPE: PRT

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<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Light chain variable region sequence

<400> SEQUENCE: 14

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> SEQ ID NO 15
<211> LENGTH: 329
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 15

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

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Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325


<210> SEQ ID NO 16
<211> LENGTH: 329
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy chain constant region

<400> SEQUENCE: 16

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Ala Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240
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```
Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325


<210> SEQ ID NO 17
<211> LENGTH: 329
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy chain constant region

<400> SEQUENCE: 17

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
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```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325


<210> SEQ ID NO 18
<211> LENGTH: 329
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy chain constant region

<400> SEQUENCE: 18

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270
```

-continued

```
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325


<210> SEQ ID NO 19
<211> LENGTH: 329
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy chain constant region

<400> SEQUENCE: 19

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Ala Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu
        275                 280                 285
```

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```
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325


<210> SEQ ID NO 20
<211> LENGTH: 329
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy chain constant region

<400> SEQUENCE: 20

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Ala Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300
```

-continued

```
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> SEQ ID NO 21
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

```
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
1               5                   10                  15

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            20                  25                  30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        35                  40                  45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    50                  55                  60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65                  70                  75                  80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                85                  90                  95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            100                 105
```

<210> SEQ ID NO 22
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

```
Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1               5                   10                  15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
            20                  25                  30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
        35                  40                  45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
    50                  55                  60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65                  70                  75                  80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
                85                  90                  95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
            100                 105
```

<210> SEQ ID NO 23
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15
```

-continued

```
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105


<210> SEQ ID NO 24
<211> LENGTH: 454
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody heavy chain

<400> SEQUENCE: 24

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20                  25                  30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255
```

-continued

```
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Ala Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
    290                 295                 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

Leu Ser Leu Ser Pro Gly
    450


<210> SEQ ID NO 25
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody light chain

<400> SEQUENCE: 25

Gln Ala Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1               5                   10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Thr Pro Gly Gln Ala Phe Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Asp Asp Glu Ser Ile Tyr Phe Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140
```

-continued

```
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205

Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 26
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody heavy chain

<400> SEQUENCE: 26

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Asp Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe His Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Thr Ile Ser Trp Asn Ser Gly Thr Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Val Ser
            260                 265                 270
```

-continued

```
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210> SEQ ID NO 27
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody light chain

<400> SEQUENCE: 27

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
                85                  90                  95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160
```

-continued

```
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 28
<211> LENGTH: 207
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 28

Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1               5                   10                  15

Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
            20                  25                  30

Gln Thr Pro Tyr Lys Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr
        35                  40                  45

Cys Pro Gln Tyr Pro Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys
    50                  55                  60

Asn Ile Gly Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp
65                  70                  75                  80

His Leu Ser Leu Lys Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr
                85                  90                  95

Val Cys Tyr Pro Arg Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu
            100                 105                 110

Tyr Leu Arg Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Val Met
        115                 120                 125

Ser Val Ala Thr Ile Val Ile Val Asp Ile Cys Ile Thr Gly Gly Leu
    130                 135                 140

Leu Leu Leu Val Tyr Tyr Trp Ser Lys Asn Arg Lys Ala Lys Ala Lys
145                 150                 155                 160

Pro Val Thr Arg Gly Ala Gly Ala Gly Gly Arg Gln Arg Gly Gln Asn
                165                 170                 175

Lys Glu Arg Pro Pro Pro Val Pro Asn Pro Asp Tyr Glu Pro Ile Arg
            180                 185                 190

Lys Gly Gln Arg Asp Leu Tyr Ser Gly Leu Asn Gln Arg Arg Ile
        195                 200                 205


<210> SEQ ID NO 29
<211> LENGTH: 297
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 29

Met Thr Thr Pro Arg Asn Ser Val Asn Gly Thr Phe Pro Ala Glu Pro
1               5                   10                  15

Met Lys Gly Pro Ile Ala Met Gln Ser Gly Pro Lys Pro Leu Phe Arg
            20                  25                  30

Arg Met Ser Ser Leu Val Gly Pro Thr Gln Ser Phe Phe Met Arg Glu
        35                  40                  45
```

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```
Ser Lys Thr Leu Gly Ala Val Gln Ile Met Asn Gly Leu Phe His Ile
    50                  55                  60

Ala Leu Gly Gly Leu Leu Met Ile Pro Ala Gly Ile Tyr Ala Pro Ile
65                  70                  75                  80

Cys Val Thr Val Trp Tyr Pro Leu Trp Gly Gly Ile Met Tyr Ile Ile
                85                  90                  95

Ser Gly Ser Leu Leu Ala Ala Thr Glu Lys Asn Ser Arg Lys Cys Leu
            100                 105                 110

Val Lys Gly Lys Met Ile Met Asn Ser Leu Ser Leu Phe Ala Ala Ile
        115                 120                 125

Ser Gly Met Ile Leu Ser Ile Met Asp Ile Leu Asn Ile Lys Ile Ser
    130                 135                 140

His Phe Leu Lys Met Glu Ser Leu Asn Phe Ile Arg Ala His Thr Pro
145                 150                 155                 160

Tyr Ile Asn Ile Tyr Asn Cys Glu Pro Ala Asn Pro Ser Glu Lys Asn
                165                 170                 175

Ser Pro Ser Thr Gln Tyr Cys Tyr Ser Ile Gln Ser Leu Phe Leu Gly
            180                 185                 190

Ile Leu Ser Val Met Leu Ile Phe Ala Phe Phe Gln Glu Leu Val Ile
        195                 200                 205

Ala Gly Ile Val Glu Asn Glu Trp Lys Arg Thr Cys Ser Arg Pro Lys
    210                 215                 220

Ser Asn Ile Val Leu Leu Ser Ala Glu Glu Lys Lys Glu Gln Thr Ile
225                 230                 235                 240

Glu Ile Lys Glu Glu Val Val Gly Leu Thr Glu Thr Ser Ser Gln Pro
                245                 250                 255

Lys Asn Glu Glu Asp Ile Glu Ile Ile Pro Ile Gln Glu Glu Glu Glu
            260                 265                 270

Glu Glu Thr Glu Thr Asn Phe Pro Glu Pro Pro Gln Asp Gln Glu Ser
        275                 280                 285

Ser Pro Ile Glu Asn Asp Ser Ser Pro
    290                 295
```

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 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;

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 method of claim **1**, wherein the bispecific antibody is administered at a dose of 24 mg.

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

4. The method of any one of claims **1-3**, wherein the subject is planned to receive autologous stem cell transplant (ASCT).

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

6. The 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 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 bis-

pecific antibody is administered once every two weeks (biweekly administration) as a monotherapy in 28-day cycles until ASCT is performed.

8. The 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 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 method of claim **9**, wherein the administration once every four weeks is performed until ASCT is performed.

11. The 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 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 method of claim **11** or **12**, wherein the priming dose is 0.16 mg.

14. The 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.

15. The 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 of cycle 1.

16. The method of claim **14** or **15**, wherein the intermediate dose is 0.8 mg.

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

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

19. The method of any one of claims **1-18**, wherein rituximab is administered at a dose of 375 mg/m^2.

20. The 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.

21. The method of claim **20**, wherein dexamethasone is administered for three 21-day cycles.

22. The method of any one of claims **1-21**, wherein dexamethasone is administered at a dose of 40 mg/day.

23. The method of any one of claims **1-6** and **11-22**, wherein cytarabine is administered twice every three weeks.

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

25. The method of any one of claims **1-6** and **11-24**, wherein cytarabine is administered at a dose of 2 g/m^2.

26. The 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 method of claim **26**, wherein the second administration of cytarabine is performed 12 hours after initiation of the first administration of cytarabine.

28. The method of any one of claims **1-6** and **11-27**, wherein oxaliplatin is administered once every three weeks.

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

30. The method of any one of claims **1-6** and **11-29**, wherein oxaliplatin is administered at a dose of 100 mg/m^2.

31. The method of any one of claims **1-6** and **11-27**, wherein carboplatin is administered once every three weeks.

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

33. The method of any one of claims **1-6**, **11-27**, **31**, and **32**, wherein carboplatin is administered at a dose of AUC=5 mg/ml/min, as determined using Calvert's formula.

34. The 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 method of claim **34**, wherein cytarabine is administered the day after rituximab, dexamethasone, oxaliplatin/carboplatin, and the bispecific antibody are administered.

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

37. The 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 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;
(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 method of any one of claims **1**, **3-6**, 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 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;
(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.

39. The 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.

40. The 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.

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

42. The method of any one of claims **1-41**, wherein rituximab is administered intravenously.

43. The method of any one of claims **1-42**, wherein dexamethasone is administered intravenously or orally.

44. The method of any one of claims **1-43**, wherein cytarabine is administered intravenously.

45. The method of any one of claims **1-44**, wherein oxaliplatin is administered intravenously.

46. The method of any one of claims **1-45**, wherein carboplatin is administered intravenously.

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

48. The 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 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 method of any one of claims **1-49**, wherein the DLBCL is double-hit or triple-hit DLBCL.

51. The method of any one of claims **1-49**, wherein the DLBCL is follicular lymphoma Grade 3B.

52. The method of any one of claims **1-51**, wherein the subject has relapsed after at least one prior therapy.

53. The method of any one of claims **1-52**, wherein the subject is refractory to at least one prior therapy.

54. The 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 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 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 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 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 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.

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

62. The 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, respectively.

63. The 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 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 method of any one of claims **1-63**, 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.

65. The 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 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 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 method of any one of claims **1-67**, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.

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