

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

FIELD

5 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-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen for the treatment of diffuse large B-cell lymphoma (DLBCL), for example, previously untreated high-risk DLBCL. Advantageous treatment regimens are also provided.

BACKGROUND

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
15 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.

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,
20 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*).

25 Given the limited efficacy and long-term response of poor risk subjects to currently available treatments, novel and effective treatments are needed.

SUMMARY

Provided herein are methods of treating human subjects who have DLBCL, for example,
30 previously untreated DLBCL (e.g., DLBCL with high-risk features (e.g., IPI or R-IPI ≥ 3)), by

administering a bispecific antibody which binds to CD3 and CD20 in combination with a standard of care R-CHOP regimen, in particular, advantageous clinical treatment regimens.

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-CHOP, e.g., the method comprising administering to the subject an effective amount of (a) rituximab, (b) cyclophosphamide, (c) doxorubicin, (d) vincristine, (e) prednisone, and (f) epcoritamab.

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) cyclophosphamide, (c) doxorubicin, (d) vincristine, (e) prednisone, wherein the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

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

wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered in 21-day cycles.

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.

In one embodiment, the bispecific antibody is administered once every week at a dose of 24 mg or 48 mg (weekly administration/dose), 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 three weeks after the weekly administration, e.g., for two or

four 21-day cycles. In some embodiments, the bispecific antibody is administered once every four weeks after the administration once every three weeks in 28-day cycles, e.g., for up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP (i.e., from cycle 1). 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.

In some embodiments, rituximab is administered in a 21-day cycle once every three weeks, e.g., for six or eight 21-day cycles. In some embodiments, rituximab is administered at a dose of 375 mg/m².

In some embodiments, cyclophosphamide is administered in a 21-day cycle once every three weeks, e.g., for six or eight 21-day cycles. In some embodiments, cyclophosphamide is administered at a dose of 750 mg/m².

In some embodiments, doxorubicin is administered in a 21-day cycle once every three weeks, e.g., for six or eight 21-day cycles. In some embodiments, doxorubicin is administered at a dose of 50 mg/m².

In some embodiments, vincristine is administered in a 21-day cycle once every three weeks, e.g., for six or eight 21-day cycles. In some embodiments, vincristine is administered at a dose of 1.4 mg/m².

In some embodiments, prednisone is administered once a day from day 1 to day 5 of the 21-day cycles, e.g., for six or eight 21-day cycles. In some embodiments, prednisone is administered at a dose of 100 mg/day.

In some embodiments, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered on the same day (e.g., on day 1 of cycles 1-6 or day 1 of cycles 1-8), e.g., as shown in **Table 2**.

In some embodiments, administration is performed in 21-day cycles, wherein (a) the bispecific antibody is administered as follows:

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

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

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

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

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

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

10 (a) the bispecific antibody is administered as follows:

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

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

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

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

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

20 In one embodiment, the bispecific antibody is administered once every four weeks in 28-day cycles from cycle 7, wherein the bispecific antibody is administered on day 1 of each cycle.

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

(a) the bispecific antibody is administered as follows:

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

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

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

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

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

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

(a) the bispecific antibody is administered as follows:

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

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

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

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

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

10 In one embodiment, the bispecific antibody is administered once every four weeks in 28-day cycles from cycle 9, wherein the bispecific antibody is administered on day 1 of each cycle..

In some embodiments, the bispecific antibody is administered subcutaneously. In some embodiments, rituximab is administered intravenously. In some embodiments, cyclophosphamide is administered intravenously. In a further embodiment, doxorubicin is administered intravenously. In yet a further embodiment, vincristine is administered intravenously. In some embodiments, prednisone is administered intravenously or orally.

15 In some embodiments, the bispecific antibody, rituximab, cyclophosphamide, doxorubicin, and vincristine are administered sequentially. For example, if administered on the same day, prednisone is administered first, rituximab is administered second, cyclophosphamide is administered third, doxorubicin is administered fourth, vincristine is administered fifth, and the bispecific antibody is administered last.

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 an International Prognostic Index (IPI) score or Revised IPI score ≥ 3 .

25 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., prednisone at a dose of, e.g., 100 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 prednisone as part of the R-CHOP regimen on days 1-5 of each 21-day cycle, no

additional prophylaxis for CRS is required, since the prednisone component of R-CHOP serves already 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 prednisone or its equivalent may be administered for CRS prophylaxis on days for which the bispecific antibody is administered but R-CHOP is not administered (i.e., prednisone 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).

In some embodiments, if the prednisone from R-CHOP is administered more than 120 minutes before administration of the bispecific antibody, then the subject is administered prednisone or an equivalent as CRS prophylaxis about 30-120 minutes prior to administration of the bispecific antibody.

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.

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 prophylaxis and premedication are administered during cycle 2 of the 21-day cycles. In yet a further embodiment, the prophylaxis and premedication are administered during subsequent cycles.

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.

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
5 subject is refractory to tocilizumab.

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
10 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.

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.

15 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
20 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.

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
25 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.

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:
30 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.

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.

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

Figures 1A-1D are graphs showing the minimal effects of CHOP components on DuoBody CD3xCD20-induced T-cell-mediated cytotoxicity. **Figure 1A:** DuoBody CD3xCD20 + cyclophosphamide, **Figure 1B:** DuoBody CD3xCD20 + doxorubicin, **Figure 1C:** DuoBody CD3xCD20 + vincristine, **Figure 1D:** DuoBody CD3xCD20 + prednisone. Left panels show DuoBody CD3xCD20 dose-response curves for one representative donor. Right panels show the results for 4 donors, at 333 ng/mL DuoBody CD3xCD20.

Figure 2 is a schematic of the overall clinical trial design.

Figure 3 is a schematic of the dose escalation design.

DETAILED DESCRIPTION

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 V_H or V_H) and a heavy chain constant region (abbreviated herein as C_H 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 V_L or V_L) and a light chain constant region (abbreviated herein as C_L or C_L). The light chain constant region typically is comprised of one domain, CL. The V_H and V_L 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 V_H and V_L 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 MP., *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.

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
5 determine the corresponding position in a sequence to an amino acid position according to the present invention.

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
10 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
15 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. An antibody as generated can possess any isotype.

The term “antibody fragment” or “antigen-binding fragment” as used herein refers to a
20 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
25 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
30 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).
5 Such single chain antibodies are encompassed within the term antibody fragment unless otherwise noted or clearly indicated by context.

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
10 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.

15 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
20 sequence variant of a naturally-occurring IgG1 antibody, which may include variations in the constant regions.

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.

25 The terms “half molecule”, “Fab-arm”, and “arm”, as used herein, refer to one heavy chain-light chain pair.

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
30 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.

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.

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.

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.

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.

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.

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 CD3 γ (gamma) chain (human CD3 γ chain UniProtKB/Swiss-Prot No P09693, or cynomolgus monkey CD3 γ UniProtKB/Swiss-Prot No Q95LI7), a CD3 δ (delta) chain (human CD3 δ UniProtKB/Swiss-Prot No P04234, or cynomolgus monkey CD3 δ UniProtKB/Swiss-Prot No Q95LI8), two CD3 ϵ

(epsilon) chains (human CD3 ϵ UniProtKB/Swiss-Prot No P07766, SEQ ID NO: 28); cynomolgus CD3 ϵ UniProtKB/Swiss-Prot No Q95LI5; or rhesus CD3 ϵ UniProtKB/Swiss-Prot No G7NCB9), and a CD3 ζ -chain (zeta) chain (human CD3 ζ UniProtKB/Swiss-Prot No P20963, cynomolgus monkey CD3 ζ 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.

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 CD3 ϵ (epsilon).

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).

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.

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.

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 CD3 ϵ (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.

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, T_{max}, C_{max}. 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.

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)

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*.

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.

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.

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.

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.

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.

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. DLBCL represents 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 SH, Campo E, Harris NL, 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.

The term “R-CHOP” as used herein refers to a drug combination containing rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. The term “R-CHOP” 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 cyclophosphamide, doxorubicin, vincristine, and/or prednisone, 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.

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. Patent 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.

The term “cyclophosphamide” as used herein refers to a nitrogen mustard alkylating agent with the chemical name 2H-1,3,2-Oxazaphosphorin-2-amine, N,N-bis(2-chloroethyl)tetrahydro-, 2-oxide (CAS No. 50-18-0) and has the chemical formula $C_7H_{15}Cl_2N_2O_2P$. It is marketed under trade names such as Endoxan®, Cytosan®, Neosar®, Procytox®, and Revimmune®. The term “cyclophosphamide” is also intended to encompass branded and generic versions (generic equivalents) of cyclophosphamide, 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.

The term “doxorubicin” as used herein refers to an anthracycline antibiotic, closely related to the natural product daunomycin, and like all anthracyclines, it works by intercalating DNA. Doxorubicin is marketed under trade names such as Adriamycin PFS®, Adriamycin RDF®, or Rubex®. Typically, the drug is administered intravenously, in the form of hydrochloride salt (e.g., as doxorubicin hydrochloride). Doxorubicin hydrochloride has the chemical name 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, hydrochloride, (8S,10S)- (CAS No. 25316-40-9), and has the chemical formula $C_{27}H_{29}NO_{11} \cdot HCl$. The term “doxorubicin” is also intended to encompass branded and generic versions (generic equivalents) of doxorubicin, 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.

The term “vincristine” (also known as leurocristine) as used herein refers to a vinca alkaloid chemotherapy agent used to treat various types of cancer. It is marketed under trade names such as Oncovin® and Vincasar PFS®. Liposomally formulated vincristine sulfate is marketed under the trade name Marquibo®. The term “vincristine” is also intended to encompass branded and generic versions (generic equivalents) of vincristine, 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.

“Prednisone” is a synthetic glucocorticoid with anti-inflammatory and immunosuppressive properties. It is a prodrug that is metabolized in the liver to prednisolone, the active form of the drug. Prednisone is marketed under trade names such as Deltasone®,

Liquid Pred[®], Rayos[®], and Orasone[®], among others. Prednisone has the chemical name 17,21-dihydroxypregna-1,4-diene-3,11,20-trione (CAS No. 53-03-2). The term “prednisone” is also intended to encompass branded and generic versions (generic equivalents) of prednisone, 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.

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, for up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP, or up to disease progression or unacceptable toxicity.

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-CHOP, cytokine release syndrome

prophylaxis, and/or tumor lysis syndrome (TLS) prophylaxis, may be administered via other routes, such as intravenously or orally.

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.

5 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
10 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
15 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.

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
20 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%.

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.

25 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
30 about 6, preferably of about 5.5.

“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 11**.

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).

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.

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

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-CHOP (i.e., rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The methods are useful for treating, e.g., previously untreated, high-risk (IPI or R-IPI ≥ 3) DLBCL. It is understood that the methods of treating DLBCL (e.g., newly-diagnosed, previously untreated, high-risk (IPI or R-IPI 3-5) DLBCL) with a bispecific antibody which binds to both CD3 and CD20 described herein also encompass corresponding uses of the bispecific antibody for treating DLBCL (e.g., newly-diagnosed, previously untreated, high-risk (IPI or R-IPI 3-5) DLBCL) in a human subject.

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) cyclophosphamide, (c) doxorubicin, (d) vincristine, and (e) prednisone, wherein the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

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

wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered in 21-day cycles.

In some embodiments, the bispecific antibody is a full-length antibody. In some embodiments, the bispecific antibody is an antibody with an inert Fc region. In some embodiments, the bispecific antibody is a full-length antibody with an inert Fc region.

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.

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.

In some embodiments, the dose of bispecific antibody is administered once every week (weekly administration) in 21-day cycles. In one embodiment, 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 one embodiment, the weekly dose of 24 mg is administered
5 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 one embodiment, the weekly dose of 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, one may reduce the interval of administration to once every three weeks. In one embodiment, the administration once every
10 three weeks is performed for two or four 21-day cycles (i.e., two or four times, respectively). In one embodiment, the administration once every three weeks is performed for two 21-day cycles (i.e., two times). In one embodiment, the administration once every three weeks is performed for four 21-day cycles (i.e., two times). In some embodiments, after the administration once every three weeks in 21-day cycles, one may reduce the interval of administration to once every four
15 weeks in 28-day cycles i.e. after the administration once every three weeks, the bispecific antibody is administered once every four weeks in 28-day cycles. In some embodiments, the administration once every four weeks in 28-day cycles is performed for up to one year total duration of treatment with the bispecific antibody. In one embodiment, the administration once every four weeks in 28-day cycles may be performed for an extended period, for example, for at
20 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, or 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,
25 or 15-20 cycles. In some embodiments, the bispecific antibody is administered once every four weeks from cycle 7 or cycle 9 (i.e., cycle starting after the bispecific antibody + R-CHOP combination has ended) to cycle 17 of the 28-day cycles. In some embodiments, the bispecific antibody is administered once every four weeks from cycle 7 or cycle 9 for up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP. In a further
30 embodiment, the bispecific antibody is administered from cycle 7 or cycle 9 of the 28-day cycles

until disease progression (e.g., as defined by the Lugano criteria or LYRIC) or unacceptable toxicity.

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),
5 the dose once every three weeks of the bispecific antibody is administered in 21-day cycles on cycles 5-6 or 5-8, and the dose once every four weeks is administered in 28-day cycles from cycle 7 or 9 onwards, for example, on cycles 7-17 or 9-17, or more cycles, e.g., for up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP, or until disease progression or unacceptable toxicity is observed in the subject. In some embodiments,
10 the dose once every four weeks in 28-day cycles is administered on cycles 7-17 or 9-17.

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, dose once every three weeks, 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 administration once every three
15 weeks, and 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
20 intermediate doses, are at a lower dose as compared with the flat or full dose.

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-
25 length bispecific antibody. In one embodiment, the priming dose of 0.16 mg is administered two weeks prior to administering the first weekly dose of 24 mg in cycle 1. In one embodiment, the priming dose of 0.16 mg is administered two weeks prior to administering the first weekly dose of 48 mg in cycle 1.

In some embodiments, after administering the priming dose and prior to administering
30 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). Thus, 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. In one embodiment, the intermediate dose is 5 800 µg (0.8 mg) or about 800 µg (0.8 mg) of the full-length bispecific antibody. In one embodiment, the priming dose of 0.16 mg is administered one week before the intermediate dose (i.e., on day 1 of cycle 1) of 0.8 mg, and the intermediate dose is administered one week before the first weekly dose of 24 mg (i.e., on day 8 of cycle 1). In one embodiment, the priming dose of 0.16 mg is administered one week before the intermediate dose (i.e., on day 1 of cycle 1) of 10 0.8 mg, and the intermediate dose is administered one week before the first weekly dose of 48 mg (i.e., on day 8 of cycle 1).

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 rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

15 In some embodiments, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone are administered at standard-of-care dosages for R-CHOP, e.g., as supported by clinical studies, according to local guidelines, and/or according to relevant local labels.

For example, in some embodiments, rituximab is administered according to relevant local product labels or summary of product characteristics (see, e.g., RITUXAN® (rituximab) 20 prescribing information, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/103705s5414lbl.pdf). In some embodiments, a biosimilar of rituximab is used in place of rituximab in the methods described herein.

In some embodiments, cyclophosphamide is administered according to relevant local 25 product labels or summary of product characteristics (see, e.g., CYCLOPHOSPHAMIDE injection prescribing information, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf).

In some embodiments, doxorubicin is administered according to relevant local product labels or summary of product characteristics (see, e.g., ADRIAMYCIN (DOXOrubicin HCl) for 30 Injection (lyophilized) and ADRIAMYCIN (DOXOrubicin HCL) Injection (0.9% sodium chloride and water) prescribing information, available at

www.accessdata.fda.gov/drugsatfda_docs/label/2012/062921s022lbl.pdf; Doxorubicin Hydrochloride for Injection and Doxorubicin Hydrochloride Injection prescribing information available at www.accessdata.fda.gov/drugsatfda_docs/label/2010/050467s070lbl.pdf).

5 In some embodiments, vincristine is administered according to relevant local product labels or summary of product characteristics (see, e.g., VinCRISTine Sulfate Injection prescribing information, available at www.accessdata.fda.gov/drugsatfda_docs/label/2014/071484s042lbl.pdf).

In some embodiments, prednisolone is administered in place of prednisone in the R-CHOP regimen.

10 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/m². In some some embodiments, rituximab is administered intravenously.

In one embodiment, rituximab is administered once every three weeks. In some embodiments, rituximab is administered once every three weeks (Q3W) in 21-day cycles. In 15 some embodiments, administration of rituximab once every three weeks is performed for six or eight 21-day cycles (i.e., six or eight times, respectively). In preferred embodiments, rituximab is administered intravenously once every three weeks for six 21-day cycles (i.e., six times) at a dose of 375 mg/m². In preferred embodiments, rituximab is administered intravenously once every three weeks for eight 21-day cycles (i.e., eight times) at a dose of 375 mg/m².

20 In some embodiments, cyclophosphamide is administered according to local guidelines and local labels. In some embodiments, cyclophosphamide is administered at a dose of (or a dose of about) 750 mg/m². In some embodiments, cyclophosphamide is administered intravenously. In some embodiments, cyclophosphamide is administered once every three weeks. In some embodiments, rituximab is administered once every three weeks (Q3W) in 21- 25 day cycles. In some embodiment, administration of cyclophosphamide once every three weeks is performed for six or eight 21-day cycles (i.e., six or eight times, respectively). In a preferred embodiment, cyclophosphamide is administered intravenously once every three weeks for six 21-day cycles (i.e., six times) at a dose of 750 mg/m². In another preferred embodiment, cyclophosphamide is administered intravenously once every three weeks for eight 21-day cycles 30 (i.e., eight times) at a dose of 750 mg/m².

In some embodiments, doxorubicin is administered according to local guidelines and local labels. In some embodiments, doxorubicin is administered at a dose of (or a dose of about) 50 mg/m². In some embodiments, doxorubicin is administered intravenously. In some embodiments, doxorubicin is administered once every three weeks. In some embodiments, doxorubicin is administered once every three weeks (Q3W) in 21-day cycles. In some 5 embodiments, administration of doxorubicin once every three weeks is performed for six or eight 21-day cycles (i.e., six or eight times, respectively). In a preferred embodiment, doxorubicin is administered intravenously once every three weeks for six 21-day cycles (i.e., six times) at a dose of 50 mg/m². In another preferred embodiment, doxorubicin is administered intravenously 10 once every three weeks for eight 21-day cycles (i.e., eight times) at a dose of 50 mg/m².

In some embodiments, vincristine is administered according to local guidelines and local labels. In some embodiments, vincristine is administered at a dose of (or a dose of about) 1.4 mg/m². In some embodiments, the maximum dose of vincristine administered to the subject is below 2 mg. In a further embodiment, vincristine is administered intravenously. In some 15 embodiments, vincristine is administered once every three weeks. In some embodiments, vincristine is administered once every three weeks (Q3W) in 21-day cycles. In some embodiments, administration of vincristine once every three weeks is performed for six or eight 21-day cycles (i.e., six or eight times). In a preferred embodiment, vincristine is administered intravenously once every three weeks for six 21-day cycles (i.e., six times) at a dose of less than 20 2 mg/m². In another preferred embodiment, vincristine is administered intravenously once every three weeks for eight 21-day cycles (i.e., eight times) at a dose of less than 2 mg/m². In a most preferred embodiment, vincristine is administered intravenously once every three weeks for six 21-day cycles (i.e., six times) at a dose of 1.4 mg/m². In another most preferred embodiment, vincristine is administered intravenously once every three weeks for eight 21-day cycles (i.e., 25 eight times) at a dose of 1.4 mg/m².

In a preferred embodiment, rituximab is preferably administered at a dose of 375 mg/m², cyclophosphamide is preferably administered at a dose of 750 mg/m², doxorubicin is preferably administered at a dose of 50 mg/m², vincristine is preferably administered at a dose of 1.4 mg/m², wherein rituximab, cyclophosphamide, doxorubicin and vincristine is preferably 30 administered intravenously once every three weeks for six 21-day cycles.

In some embodiments, prednisone is administered according to local guidelines and local labels. In some embodiments, prednisone is administered at a dose of (or a dose of about) 100 mg. In some embodiment, prednisone is administered intravenously and/or orally. In some embodimentss, prednisone is administered intravenously. In some embodiments, prednisone is administered orally.

In one embodiment, prednisone is administered once a day for five consecutive days (i.e., days 1-5) in 21-day cycles. In one embodiment, prednisone is administered for six or eight 21-day cycles (e.g., on days 1-5 of cycles 1-6 or cycles 1-8 of the 21-day cycles). In one embodiment, prednisone is administered once a day on days 1-5 in 21-day cycles. In some embodiments, prednisone is administered once a day for five consecutive days (i.e., days 1-5) for six or eight 21-day cycles (e.g., on days 1-5 of cycles 1-6 or cycles 1-8 of the 21-day cycles). In a preferred embodiment, prednisone is administered intravenously once a day for five consecutive days (i.e., days 1-5) for six 21-day cycles (e.g., on days 1-5 of cycles 1-6 of the 21-day cycles) at a dose of 100 mg/day. In another preferred embodiment, prednisone is administered intravenously once a day for five consecutive days (i.e., days 1-5) for eight 21-day cycles (e.g., on days 1-5 of cycles 1-8 of the 21-day cycles) a dose of 100 mg/day. In another preferred embodiment, prednisone is administered orally once a day for five consecutive days (i.e., days 1-5) for six 21-day cycles (e.g., on days 1-5 of cycles 1-6 of the 21-day cycles) at a dose of 100 mg/day. In another preferred embodiment, prednisone is administered orally once a day for five consecutive days (i.e., days 1-5) for eight 21-day cycles (e.g., on days 1-5 of cycles 1-8 of the 21-day cycles) a dose of 100 mg/day. In another preferred embodiment, prednisone is administered intravenously and/or orally once a day for five consecutive days (i.e., days 1-5) for six 21-day cycles (e.g., on days 1-5 of cycles 1-6 of the 21-day cycles) at a dose of 100 mg/day. In another preferred embodiment, prednisone is administered intravenously and/or orally once a day for five consecutive days (i.e., days 1-5) for eight 21-day cycles (e.g., on days 1-5 of cycles 1-8 of the 21-day cycles) a dose of 100 mg/day. In one embodiment, the dose of cyclophosphamide or doxorubicin is reduced when a subject presents with cyclophosphamide- or doxorubicin-related hematological toxicities during a treatment cycle in accordance with standard of care guidelines, for example, as specified in the product label. See, for example, **Table 8** for dose modification criteria or cyclophosphamide and doxorubicin (see also **Table 9**).

In one embodiment, the dose of vincristine is reduced when a subject presents with impaired hepatic function, e.g., using serum bilirubin levels as a marker. For example, if a subject has serum bilirubin levels of 2-3 mg/dL, then the dose of vincristine is reduced to 75% of the normal dose. If a subject has serum bilirubin levels of >3.0 mg/dL, then the dose of
5 vincristine is reduced to 50% of the normal dose. Vincristine can be re-escalated when hyperalbuminemia improves.

In one embodiment, the dose of prednisone (or equivalent) is reduced according to local prescribing information. For example, when a subject develops an adverse event related to corticosteroid and cannot tolerate the 100 mg/day dose (or equivalent), then the dose may be
10 reduced to no less than 80 mg/day. In some embodiments, the dose reduction of prednisone (or equivalent) is performed in a tapering regimen.

In certain embodiments, the bispecific antibody, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone are administered simultaneously.

In other embodiments, the bispecific antibody, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone are administered sequentially. For instance, in some
15 embodiments, the bispecific antibody, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone are administered on the same day. In one embodiment, when the bispecific antibody and R-CHOP are administered on the same day, prednisone is administered first, rituximab is administered second, cyclophosphamide is administered third, doxorubicin is
20 administered fourth, vincristine is administered fifth, and the bispecific antibody is administered last.

In some embodiments, the subject is administered premedication and/or prophylaxis for CRS prior to administration of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody. In one embodiment, the prednisone component of the
25 R-CHOP regimen is used as the corticosteroid in CRS prophylaxis.

In one embodiment, rituximab (e.g., intravenous), cyclophosphamide (e.g., intravenous), doxorubicin (e.g., intravenous), vincristine (e.g., intravenous), prednisone (e.g., intravenous or oral), and the bispecific antibody (e.g., subcutaneous) are administered in 21-day cycles, wherein:

30 (a) the bispecific antibody is administered as follows:

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

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

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

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

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

In one embodiment, rituximab (e.g., intravenous), cyclophosphamide (e.g., intravenous), doxorubicin (e.g., intravenous), vincristine (e.g., intravenous), prednisone (e.g., intravenous or
10 oral), and the bispecific antibody (e.g., subcutaneous) are administered in 21-day cycles, wherein:

(a) the bispecific antibody is administered as follows:

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

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

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

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

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

20 In the two embodiments above, the bispecific antibody is administered once every four weeks in 28-day cycles from cycle 7 (e.g., from cycle 7-cycle 15, from cycle 7 to cycle 17, from cycle 7 to cycle 20, or from cycle 7 up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP). In the two embodiments above, rituximab is preferably administered at a dose of 375 mg/m², cyclophosphamide is preferably administered at a dose of
25 750 mg/m², doxorubicin is preferably administered at a dose of 50 mg/m², vincristine is preferably administered at a dose of 1.4 mg/m² and prednisone is preferably administered at a dose of 100 mg/day.

In one embodiment, rituximab (e.g., intravenous), cyclophosphamide (e.g., intravenous), doxorubicin (e.g., intravenous), vincristine (e.g., intravenous), prednisone (e.g., intravenous or
30 oral), and the bispecific antibody (e.g., subcutaneous) are administered in 21-day cycles, wherein:

(a) the bispecific antibody is administered as follows:

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

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

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

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

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

10 In one embodiment, rituximab (e.g., intravenous), cyclophosphamide (e.g., intravenous), doxorubicin (e.g., intravenous), vincristine (e.g., intravenous), prednisone (e.g., intravenous or oral), and the bispecific antibody (e.g., subcutaneous) are administered in 21-day cycles, wherein:

(a) the bispecific antibody is administered as follows:

15 (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;

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

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

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

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

In the two embodiments above, the bispecific antibody is administered once every four weeks in 28-day cycles from cycle 9 (e.g., from cycle 9-cycle 15, from cycle 9 to cycle 17, from cycle 9 to cycle 20, or for up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP). In the two embodiments above, rituximab is preferably administered
25 at a dose of 375 mg/m², cyclophosphamide is preferably administered at a dose of 750 mg/m², doxorubicin is preferably administered at a dose of 50 mg/m², vincristine is preferably administered at a dose of 1.4 mg/m² and prednisone is preferably administered at a dose of 100 mg/day.

30 In one embodiment, rituximab (e.g., intravenous), cyclophosphamide (e.g., intravenous), doxorubicin (e.g., intravenous), vincristine (e.g., intravenous), prednisone (e.g., intravenous or

oral), and the bispecific antibody epcoritamab (e.g., subcutaneous) are administered in 21-day cycles, wherein:

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

- (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 24 mg is administered on day 15;
- (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;
- (iii) in cycles 5-6, a dose of 24 mg is administered on day 1;

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

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

In one embodiment, rituximab (e.g., intravenous), cyclophosphamide (e.g., intravenous), doxorubicin (e.g., intravenous), vincristine (e.g., intravenous), prednisone (e.g., intravenous or oral), and the bispecific antibody epcoritamab (e.g., subcutaneous) are administered in 21-day cycles, wherein:

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

- (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 48 mg is administered on day 15;
- (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;
- (iii) in cycles 5-6, a dose of 48 mg is administered on day 1;

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

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

In the two embodiments above, the bispecific antibody epcoritamab is further administered once every four weeks in 28-day cycles from cycle 7 (e.g., from cycle 7-cycle 15, from cycle 7 to cycle 17, from cycle 7 to cycle 20, or from cycle 9 up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP). In the two embodiments above, rituximab is preferably administered at a dose of 375 mg/m², cyclophosphamide is preferably administered at a dose of 750 mg/m², doxorubicin is preferably administered at a dose of 50 mg/m², vincristine is preferably administered at a dose of 1.4 mg/m² and prednisone is preferably administered at a dose of 100 mg/day.

In one embodiment, rituximab (e.g., intravenous), cyclophosphamide (e.g., intravenous), doxorubicin (e.g., intravenous), vincristine (e.g., intravenous), prednisone (e.g., intravenous or oral), and the bispecific antibody epcoritamab (e.g., subcutaneous) are administered in 21-day cycles, wherein:

- 5 (a) the bispecific antibody epcoritamab is administered as follows:
 - (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 24 mg is administered on day 15;
 - (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;
 - (iii) in cycles 5-8, a dose of 24 mg is administered on day 1;
- 10 (b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-8; and
- (c) prednisone is administered on days 1-5 in cycles 1-8.

In one embodiment, rituximab (e.g., intravenous), cyclophosphamide (e.g., intravenous), doxorubicin (e.g., intravenous), vincristine (e.g., intravenous), prednisone (e.g., intravenous or oral), and the bispecific antibody epcoritamab (e.g., subcutaneous) are administered in 21-day cycles, wherein:

- 15 (a) the bispecific antibody epcoritamab is administered as follows:
 - (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 48 mg is administered on day 15;
 - 20 (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;
 - (iii) in cycles 5-8, a dose of 48 mg is administered on day 1;
- (b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-8; and
- (c) prednisone is administered on days 1-5 in cycles 1-8.

- 25 In the two embodiments above, the bispecific antibody epcoritamab is further administered once every four weeks in 28-day cycles from cycle 9 (e.g., from cycle 9-cycle 15, from cycle 9 to cycle 17, from cycle 9 to cycle 20, or from cycle 9 up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP). In the two embodiments above, rituximab is preferably administered at a dose of 375 mg/m², cyclophosphamide is preferably administered at a dose of 750 mg/m², doxorubicin is preferably administered at a dose of 50 mg/m², vincristine is
- 30

preferably administered at a dose of 1.4 mg/m² and prednisone is preferably administered at a dose of 100 mg/day.

In some embodiments, subjects considered to be at risk of thrombosis are administered prophylactic antithrombotic treatment, such as low-dose aspirin (e.g., 70-100 mg daily). In certain embodiments, subjects with a prior history of deep vein thrombosis (DVT) or pulmonary embolism (PE) are administered anticoagulation therapy.

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. Accordingly, in one embodiment, the subject has DLBCL, NOS (not otherwise specified). In some embodiments, 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 one embodiment, the subject with DLBCL has a Revised International Prognostic Index (R-IPI) score ≥ 3 , such as an R-IPI score of 3, 4, or 5. IPI risk factors include (1) Ann Arbor Stage III or IV, (2) age >60 years, (3) Lactate dehydrogenase level elevated, (4) ECOG performance score ≥ 2 , and (5) more than 1 extranodal site. R-IPI scoring is based on the number of above risk factors (1)-(5). R-IPI risk groups are categorized as Very good (0 IPI risk factors), Good (1 or 2 IPI risk factors), and Poor (3-5 IPI risk factors). R-IPI applies to subjects with newly diagnosed DLBCL who are receiving R-CHOP as first-line therapy. See, e.g., Information regarding the R-IPI is available, e.g., in Sehn et al., *Blood* 2007;109:1857-71.

In one embodiment, the subject with DLBCL has not received prior therapy for DLBCL or follicular lymphoma Grade 3B.

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 Dec;5(6):649-55).

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.

In some embodiments, the subject has acceptable organ function as defined as: (a) ANC $\geq 1.0 \times 10^9/L$, (b) platelet count $>75 \times 10^9/L$, or $\geq 50 \times 10^9/L$ if bone marrow infiltration or

splenomegaly, (c) ALT level ≤ 2.5 times the ULN, (d) total bilirubin level $\leq 2 \times$ ULN, (e) eGFR > 50 mL/min (by Cockcroft-Gault Formula), and (f) PT, INR, and aPTT $\leq 1.5 \times$ ULN (unless receiving anticoagulant).

In one embodiment, the subject does not have severe allergic or anaphylactic reactions to anti-CD20 antibody therapy, any component of CHOP (i.e., cyclophosphamide, doxorubicin, vincristine, and prednisone), or the bispecific antibody, or known allergy or intolerance to any component or excipient of rituximab, CHOP, and/or the bispecific antibody.

In one embodiment, the subject has not received prior therapy for DLBCL (with the exception of nodal biopsy). In some embodiments, the subject does not have a contraindication to any individual drug in the R-CHOP regimen.

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.

A human subject receiving a treatment described herein may be a patient having one or more of the inclusion criteria set forth in Example 3, or not having one or more of the exclusion criteria set forth in Example 3.

The methods described herein are advantageous for treating DLBCL, such as previously untreated, high risk (IPI or R-IPI ≥ 3) DLBCL. The treatment is maintained continuously using, e.g., the treatment regimens described herein. However, treatment may be terminated when progressive disease develops or unacceptable toxicity occurs.

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 3. 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 11**.

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 one embodiment, subjects are treated with the methods described herein until they show disease progression (PD) as defined by both Lugano criteria and LYRIC. In some embodiments, the subjects are treated with the methods described herein for up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP.

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.

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 and/or LYRIC (see, e.g., **Table 11**). 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.

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.

Accordingly, in one embodiment, human subjects in the methods described herein are treated with prophylaxis for CRS. In preferred embodiments, the prophylaxis includes the administration of a corticosteroid to the subject. In one embodiment, the prophylaxis (e.g. corticosteroid) is administered on the same day as the bispecific antibody. The prophylaxis (e.g. corticosteroid) can also be administered on the subsequent days as well. In some embodiments, the prophylaxis (e.g. corticosteroid) is further administered 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 prednisone, as it is a component of the R-CHOP regimen. Thus, in preferred embodiments, the corticosteroid is prednisone. In some embodiments, prednisone 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**.

With regard to CRS prophylaxis when the bispecific antibody (e.g., epcoritamab) is administered on days when R-CHOP is also administered (e.g., day 1 of each 21-day cycle), it is understood that the R-CHOP regimen already provides the corticosteroid component for the CRS prophylaxis (i.e., prednisone 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 prednisone component of R-CHOP, 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-CHOP and the bispecific antibody were administered, only one dose of prednisone is administered (i.e., the dose serves as both CRS prophylaxis for the bispecific antibody and a component of the R-CHOP regimen). On days
5 when the bispecific antibody is administered without R-CHOP (e.g., days 8 and 15 of the 21-day cycles), prednisone or an equivalent is administered as CRS prophylaxis, e.g., together with premedication (e.g., antihistamine/antipyretic), as described below.

In one embodiment, when prednisone is administered as a part of the R-CHOP regimen on days 1-5 of a 21-day cycle (e.g., cycle 1), and the bispecific antibody is administered on day 1
10 of that cycle, no additional corticosteroid is administered for CRS prophylaxis, provided that the prednisone component of R-CHOP 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 prednisone is administered as a part of the R-CHOP regimen on days 1-5 of a 21-day cycle (e.g., cycle 1), and the bispecific antibody is administered on day 1 of that cycle,
15 a further corticosteroid (e.g., prednisone 100 mg or equivalent thereof) is administered as CRS prophylaxis before the bispecific antibody is administered if the prednisone component of R-CHOP is administered more than 120 minutes before the bispecific antibody is administered. In some embodiments, if R-CHOP is withheld on day 1 of a 21-day cycle, and thus the prednisone component of the R-CHOP regimen is not administered to the subject on the same day as the
20 bispecific antibody, then the subject is administered a corticosteroid such as prednisone or its equivalent for CRS prophylaxis.

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
25 premedication includes the administration of antipyretics. In a further embodiment, the premedication includes systemic administration of antihistamines and antipyretics.

An exemplary antihistamine suitable for use in premedication is diphenhydramine. Thus, in one embodiment, the antihistamine for use in premedication is diphenhydramine. In one embodiment, diphenhydramine is administered at an intravenous or oral dose 50 mg, or an
30 equivalent thereof. An exemplary antipyretic suitable for use in premedication is acetaminophen. Thus, in one embodiment, the antipyretic 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. In some embodiments, the antihistamine (e.g. diphenhydramine) 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 in an intravenous or oral dose of (or about) 50 mg. In some embodiments, the antipyretic (e.g. acetaminophen) 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 in an oral dose of (or about) 650-1000mg. In some embodiments, the antihistamine (e.g. diphenhydramine) and the antipyretic (e.g. acetaminophen) are 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 in an intravenous or oral dose of (or about) 50 mg and an oral dose of (or about) 650-1000mg, respectively.

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 prednisone component of the R-CHOP regimen serves as the corticosteroid for prophylaxis of CRS.

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. Thus, in some embodiments, the premedication and/or prophylaxis is administered in cycle 1 and start of cycle 2 of the 21-day cycles. In some embodiments, the premedication is administered in cycle 1 and start of cycle 2 of the 21-day cycles. In some embodiments, the prophylaxis is administered in cycle 1 and start of cycle 2 of the 21-day cycles. 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**.

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

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 prednisone (e.g., at an intravenous 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 prednisone (e.g., at an intravenous 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 prednisone is administered as part of the R-CHOP regimen.

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
5 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
10 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
15 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.

20 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.

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

In a preferred embodiment, subjects who develop Grade 1 CRS are treated with antibiotics if they present with infection i.e. the subject is administered antibiotics if the subject develops Grade 1 CRS. In some embodiments, the antibiotics are continued until neutropenia, if present, resolves. In some embodiments, subjects with Grade 1 CRS who exhibit constitutional
30 symptoms are treated with NSAIDs.

In one embodiment, subjects who develop Grade 2 CRS are treated with intravenous fluid boluses and/or supplemental oxygen. In one embodiment, subjects who develop Grade 2 CRS are treated with a vasopressor (e.g., norepinephrine). In one embodiment, subjects with Grade 2 CRS with comorbidities are treated with tocilizumab (a humanized antibody against IL-6 receptor, commercially available as, e.g., ACTEMRA®). In one embodiment, subjects with Grade 2 CRS are treated with tocilizumab and a steroid. In one embodiment, the steroid is dexamethasone. In one embodiment, the steroid is 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.

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. In one embodiment, subjects with Grade 3 CRS are treated with 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.

In one embodiment, subjects who develop Grade 4 CRS are treated with vasopressor (e.g., norepinephrine) support and/or supplemental oxygen (e.g., via positive pressure ventilation, such as CPAP, BiPAP, intubation, or mechanical ventilation). In one embodiment, subjects who develop Grade 4 CRS are administered at least two vasopressors. In one embodiment, subjects who develop Grade 4 CRS are administered tocilizumab and a steroid (e.g., dexamethasone or its equivalent of methylprednisolone). In a further embodiment, a subject who presents with concurrent ICANS is administered dexamethasone. 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. In some embodiments, tocilizumab is switched to an IL-6 antibody (e.g., siltuximab) if the subject is refractory to tocilizumab. In some embodiments, tocilizumab is switched to an IL-1R antagonist (e.g., anakinra) if the subject is refractory to tocilizumab.

In some embodiments, the human subject receives prophylactic treatment for tumor lysis syndrome (TLS) i.e. the subject is treated with prophylaxis for 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, prophylaxis (prophylactic treatment) of TLS comprises administering one or more 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. In one embodiment, the prophylactic treatment of TLS comprises administering allopurinol. In one embodiment, the prophylactic treatment of TLS comprises administering allopurinol and 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.

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.

In one embodiment, the bispecific antibody used in the methods described herein 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.

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.

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, 10 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.

15 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 20 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 25 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.

In one embodiment, rituximab is formulated in a pharmaceutical composition comprising pharmaceutically-acceptable excipients for administration (e.g., intravenous administration) in 30 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.

In one embodiment, cyclophosphamide, doxorubicin, vincristine, and prednisone 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, cyclophosphamide, doxorubicin, vincristine, and prednisone 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, prednisone is formulated in a pharmaceutical composition for oral administration.

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

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences 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

(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.

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).

In one embodiment, the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (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

(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.

In one embodiment, the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a 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

(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.

In one embodiment, the bispecific antibody is a full-length antibody. In some embodiments, the bispecific antibody have an inert Fc region. In some embodiments, the bispecific antibody is a full-length antibody and 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, wherein 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 CD3 $\times$ CD20.

Accordingly, in some embodiments, the bispecific antibody comprises (i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a 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

(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).

In one embodiment, the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a 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

(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.

In some embodiments, the bispecific antibody comprises (i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a 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

(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).

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 bispecific antibody is a full-length antibody with a human IgG1 constant region. In one embodiment, the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1, λ (lambda) antibody. 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 one embodiment, the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1, κ (kappa) antibody. In one embodiment 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. In a preferred embodiment, the first binding arm comprises a λ light chain constant region as defined in SEQ ID NO: 22 and the second binding arm comprises a κ light chain constant region as defined in SEQ ID NO: 23.

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.

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).

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.

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, Fc γ receptor-dependent CD3 crosslinking), by binding to Fc γ receptors, by binding to C1q, or by induction of Fc-mediated cross-linking of Fc γ Rs. 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 comprise 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.

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. In one embodiment, 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. In one embodiment, 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. In a preferred embodiment, 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.

5 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.

 An amino acid sequence of a wild type IgG1 heavy chain constant region may be
10 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
15 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
20 SEQ ID NO: 20). Thus, in one embodiment, the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

 In preferred 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
25 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 embodiment, the bispecific antibody comprising a heavy chain and a light chain consisting of the amino acid sequences set forth in SEQ ID NOs: 24 and 25, respectively, and a heavy chain and a light chain consisting of the amino acid
30 sequences set forth in SEQ ID NOs: 26 and 27, respectively. In some embodiments, the bispecific antibody is epcoritamab (CAS 2134641-34-0), or a biosimilar thereof.

Kits

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), cyclophosphamide (e.g., for intravenous administration), doxorubicin (e.g., for intravenous administration), vincristine (e.g., for intravenous administration), and/or prednisone (e.g., for intravenous or oral 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 administer the composition or compositions contained therein to a patient with DLBCL. The kit also can include a syringe or syringes.

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, cyclophosphamide, doxorubicin, vincristine, and/or prednisone 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

1. A bispecific antibody comprising:
 - (i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

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

for use in the treatment of diffuse large B-cell lymphoma (DLBCL) in a human subject, wherein the treatment comprises administering the bispecific antibody and an effective amount of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone to the human subject, wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein the bispecific antibody, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone are administered in 21-day cycles.

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

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

4. The bispecific antibody of any one of embodiments 1-3, wherein the bispecific antibody is administered once every week (weekly administration).

5. The bispecific antibody of embodiment 4, wherein the weekly administration of 24 mg or 48 mg is performed for three and one-third 21-day cycles.

6. The bispecific antibody of embodiment 4 or 5, wherein after the weekly administration, the bispecific antibody is administered once every three weeks.

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

8. The bispecific antibody of embodiment 7, wherein after the administration once every three weeks, the bispecific antibody is administered once every four weeks in 28-day cycles.
9. The bispecific antibody of embodiment 8, wherein the administration once every four weeks is performed for up to one year total duration of treatment with the bispecific antibody.
10. The bispecific antibody of any one of embodiments 4-9, wherein prior to the weekly administration of 24 mg or 48 mg, a priming dose of the bispecific antibody is administered in cycle 1 of the 21-day cycles.
11. The bispecific antibody of embodiment 10, wherein the priming dose is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg.
12. The bispecific antibody of embodiment 10 or 11, wherein the priming dose is 0.16 mg.
13. The bispecific antibody of any one of embodiments 10-12, wherein after administering the priming dose and prior to administering the first weekly dose of 24 mg or 48 mg, an intermediate dose of the bispecific antibody is administered.
14. The bispecific antibody of embodiment 13, wherein the priming dose is administered on day 1 and the intermediate dose is administered on day 8 before the first weekly dose of 24 mg or 48 mg on day 15 of cycle 1.
15. The bispecific antibody of embodiment 13 or 14, wherein the intermediate dose is 0.8 mg.
16. The bispecific antibody of any one of embodiments 1-15, wherein rituximab is administered once every three weeks.
17. The bispecific antibody of embodiment 16, wherein the administration of rituximab once every three weeks is performed for six or eight 21-day cycles.

18. The bispecific antibody of any one of embodiments 1-17, wherein rituximab is administered at a dose of 375 mg/m².
19. The bispecific antibody of any one of embodiments 1-18, wherein cyclophosphamide is administered once every three weeks.
20. The bispecific antibody of embodiment 19, wherein the administration of cyclophosphamide once every three weeks is performed for six or eight 21-day cycles.
21. The bispecific antibody of any one of embodiments 1-20, wherein cyclophosphamide is administered at a dose of 750 mg/m².
22. The bispecific antibody of any one of embodiments 1-21, wherein doxorubicin is administered once every three weeks.
23. The bispecific antibody of embodiment 22, wherein the administration of doxorubicin once every three weeks is performed for six or eight 21-day cycles.
24. The bispecific antibody of any one of embodiments 1-23, wherein doxorubicin is administered at a dose of 50 mg/m².
25. The bispecific antibody of any one of embodiments 1-24, wherein vincristine is administered once every three weeks.
26. The bispecific antibody of embodiment 25, wherein the administration of vincristine once every three weeks is performed for six or eight 21-day cycles.
27. The bispecific antibody of any one of embodiments 1-26, wherein vincristine is administered at a dose of 1.4 mg/m².

28. The bispecific antibody of any one of embodiments 1-27, wherein prednisone is administered once a day from day 1 to day 5 of the 21-day cycles.
29. The bispecific antibody of embodiment 28, wherein prednisone is administered for six or
5 eight 21-day cycles.
30. The bispecific antibody of any one of embodiments 1-29, wherein prednisone is administered at a dose of 100 mg/day.
- 10 31. The bispecific antibody of any one of embodiments 1-30, wherein rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered on the same day (e.g., on day 1 of cycles 1-6 or cycles 1-8 of the 21-day cycles).
32. The bispecific antibody of any one of embodiments 1-31, wherein the dosing schedule for
15 rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody is as shown in **Table 2**.
33. The bispecific antibody of any one of embodiments 1, 2, and 4-32, wherein administration is performed in 21-day cycles, and wherein:
- 20 (a) the bispecific antibody is administered as follows:
- (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 24 mg is administered on day 15;
 - (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;
 - (iii) in cycles 5 and 6, a dose of 24 mg is administered on day 1;
- 25 (b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-6; and
- (c) prednisone is administered on days 1-5 in cycles 1-6.
34. The bispecific antibody of any one of embodiments 1 and 3-32, wherein administration is
30 performed in 21-day cycles, and wherein:
- (a) the bispecific antibody is administered as follows:

- (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 48 mg is administered on day 15;
 - (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;
 - (iii) in cycles 5 and 6, a dose of 48 mg is administered on day 1;
- 5 (b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-6; and
- (c) prednisone is administered on days 1-5 in cycles 1-6.

35. The bispecific antibody of embodiment 33 or 34 wherein the bispecific antibody is
10 administered once every four weeks in 28-day cycles on day 1 from cycle 7.

36. The bispecific antibody of any one of embodiments 1, 2, and 4-32, wherein administration is performed in 21-day cycles, and wherein:

- (a) the bispecific antibody is administered as follows:
 - 15 (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 24 mg is administered on day 15;
 - (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;
 - (iii) in cycles 5-8, a dose of 24 mg is administered on day 1;
- (b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1
20 in cycles 1-8; and
- (c) prednisone is administered on days 1-5 in cycles 1-8.

37. The bispecific antibody of any one of embodiments 1 and 3-32, wherein administration is performed in 21-day cycles, and wherein:

- 25 (a) the bispecific antibody is administered as follows:
 - (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 48 mg is administered on day 15;
 - (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;
 - (iii) in cycles 5-8, a dose of 48 mg is administered on day 1;
- 30 (b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-8; and

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

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

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39. The bispecific antibody of any one of embodiments 1-38, wherein the bispecific antibody is administered subcutaneously.

40. The bispecific antibody of any one of embodiments 1-39, wherein rituximab is administered intravenously.

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41. The bispecific antibody of any one of embodiments 1-40, wherein cyclophosphamide is administered intravenously.

42. The bispecific antibody of any one of embodiments 1-41, wherein doxorubicin is administered intravenously.

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43. The bispecific antibody of any one of embodiments 1-42, wherein vincristine is administered intravenously.

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44. The bispecific antibody of any one of embodiments 1-43, wherein prednisone is administered intravenously or orally.

45. The bispecific antibody of any one of embodiments 1-44, wherein rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered sequentially.

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46. The bispecific antibody of any one of embodiments 1-45, wherein prednisone is administered first, rituximab is administered second, cyclophosphamide is administered third, doxorubicin is administered fourth, vincristine is administered fifth, and the bispecific antibody is

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administered last if rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered on the same day.

47. The bispecific antibody of any one of embodiments 1-46, wherein the DLBCL is double-
5 hit or triple-hit DLBCL.

48. The bispecific antibody of any one of embodiments 1-47, wherein the DLBCL is follicular lymphoma Grade 3B.

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

50. The bispecific antibody of any one of embodiments 1-49, wherein the subject has not received prior therapy for DLBCL or follicular lymphoma Grade 3B.
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51. The bispecific antibody of any one of embodiments 1-50, wherein the subject is treated with prophylaxis for cytokine release syndrome (CRS).

52. The bispecific antibody of embodiment 51, wherein the prophylaxis comprises
20 administering a corticosteroid to the subject.

53. The bispecific antibody of embodiment 52, wherein the corticosteroid is administered on the same day as the bispecific antibody.

25 54. The bispecific antibody of embodiment 53, wherein the corticosteroid is further administered on the second, third, and fourth days after administering the bispecific antibody.

55. The bispecific antibody of any one of embodiments 52-54, wherein the corticosteroid is prednisone.
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56. The bispecific antibody of embodiment 55, wherein the prednisone is administered at an intravenous dose of 100 mg, or equivalent thereof, including oral dose.
57. The bispecific antibody of any one of embodiments 52-54, wherein the prednisone from
5 R-CHOP serves as the corticosteroid for prophylaxis for CRS.
58. The bispecific antibody of embodiment 57, wherein if the prednisone from R-CHOP is administered more than 120 minutes before administration of the bispecific antibody, then the subject is administered prednisone or an equivalent about 30-120 minutes prior to administration
10 of the bispecific antibody.
59. The bispecific antibody of any one of embodiments 1-58, wherein the subject is administered premedication to reduce reactions to injections.
- 15 60. The bispecific antibody of embodiment 59, wherein the premedication comprises an antihistamine.
61. The bispecific antibody of embodiment 60, wherein the antihistamine is diphenhydramine.
- 20 62. The bispecific antibody of embodiment 61, wherein the diphenhydramine is administered at an intravenous or oral dose of 50 mg, or equivalent thereof.
63. The bispecific antibody of any one of embodiments 59-62, wherein the premedication comprises an antipyretic.
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64. The bispecific antibody of any one of embodiment 63, wherein the antipyretic is acetaminophen.
65. The bispecific antibody of embodiment 64, wherein the acetaminophen is administered at
30 an oral dose of 650 mg to 1000 mg, or equivalent thereof.

66. The bispecific antibody of any one of embodiments 59-65, wherein the premedication is administered on the same day as the bispecific antibody.
67. The bispecific antibody of any one of embodiments 51-66, wherein the prophylaxis is administered in cycle 1 and start of cycle 2 of the 21-day cycles.
68. The bispecific antibody of any one of embodiments 59-66, wherein the premedication is administered in cycle 1 and start of cycle 2 of the 21-day cycles.
69. The bispecific antibody of any one of embodiments 51-68, 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.
70. The bispecific antibody of embodiment 69, 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.
71. The bispecific antibody of any one of embodiments 59-70, wherein the premedication is administered during cycle 2 of the 21-day cycles.
72. The bispecific antibody of embodiment 71, wherein the premedication is administered during subsequent cycles.
73. The bispecific antibody of any one of embodiments 1-72, wherein the subject is administered antibiotics if the subject develops Grade 1 CRS.
74. The bispecific antibody of any one of embodiments 1-72, wherein the subject is administered a vasopressor if the subject develops Grade 2 or Grade 3 CRS.

75. The bispecific antibody of any one of embodiments 1-72, wherein the subject is administered at least two vasopressors if the subject develops Grade 4 CRS.
76. The bispecific antibody of any one of embodiments 1-75, wherein the subject is administered tocilizumab if the subject develops Grade 2, Grade 3, or Grade 4 CRS.
77. The bispecific antibody of embodiment 76, wherein the subject is further administered a steroid.
78. The bispecific antibody of embodiment 77, wherein the steroid is dexamethasone.
79. The bispecific antibody of embodiment 77, wherein the steroid is methylprednisolone.
80. The bispecific antibody of any one of embodiments 76-79, wherein tocilizumab is switched to an anti-IL-6 antibody (e.g., siltuximab) if the subject is refractory to tocilizumab.
81. The bispecific antibody of any one of embodiments 76-79, wherein tocilizumab is switched to an IL-1R antagonist (e.g., anakinra) if the subject is refractory to tocilizumab.
82. The bispecific antibody of any one of embodiments 1-81, wherein the subject is treated with prophylaxis for tumor lysis syndrome (TLS).
83. The bispecific antibody of embodiment 82, wherein the prophylaxis for TLS comprises administering one or more uric acid reducing agents prior to administration of the bispecific antibody.
84. The bispecific antibody of embodiment 83, wherein the one or more uric acid reducing agents comprise rasburicase and/or allopurinol.
85. The bispecific antibody of any one of embodiments 1-84, wherein the subject achieves a complete response, a partial response, or stable disease.

86. The bispecific antibody of any one of embodiments 1-85, 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.
87. The bispecific antibody of any one of embodiments 1-86, 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.
88. The bispecific antibody of any one of embodiments 1-87, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1, λ (lambda) antibody.
89. The bispecific antibody of embodiment 88, 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.
90. The bispecific antibody of any one of embodiments 1-89, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1, κ (kappa) antibody.

91. The bispecific antibody of embodiment 90, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.
92. The bispecific antibody of any one of embodiments 1-91, wherein the bispecific antibody
5 is a full-length antibody with a human IgG1 constant region.
93. The bispecific antibody of any one of embodiments 1-92, wherein the bispecific antibody comprises an inert Fc region.
- 10 94. The bispecific antibody of any one of embodiments 1-93, 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.
- 15 95. The bispecific antibody of any one of embodiments 1-94, 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
20 vice versa.
96. The bispecific antibody of any one of embodiments 1-95, 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
25 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
30 constant region of SEQ ID NO: 15 is R, or vice versa.

97. The bispecific antibody of embodiment 96, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

98. The bispecific antibody of any one of embodiments 1-97, wherein the bispecific antibody
5 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.

99. The bispecific antibody of any one of embodiments 1-98, wherein the bispecific antibody
10 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.

100. The bispecific antibody of any one of embodiments 1-99, wherein the bispecific antibody
15 is epcoritamab, or a biosimilar thereof.

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
20 application are expressly incorporated herein by reference.

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) cyclophosphamide, (c) doxorubicin, (d) vincristine and (e) prednisone, wherein
25 the a bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3
30 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, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered in 21-day cycles.

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

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

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

5a. The method of embodiment 4a, wherein the weekly administration of 24 mg or 48 mg is performed for three and one-third 21-day cycles.

6a. The method of embodiment 4a or 5a, wherein after the weekly administration, the bispecific antibody is administered once every three weeks.

7a. The method of embodiment 6a, wherein the administration once every three weeks is performed for two or four 21-day cycles.

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

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

10a. The method of any one of embodiments 4a-9a, 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.

11a. The method of embodiment 10a, wherein the priming dose is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg.

12a. The method of embodiment 10a or 11a, wherein the priming dose is 0.16 mg.

13a. The method of any one of embodiments 10a-12a, 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.

14a. The method of embodiment 13a, 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.

15a. The method of embodiment 13a or 14a, wherein the intermediate dose is 0.8 mg.

16a. The method of any one of embodiments 1a-15a, wherein rituximab is administered once every three weeks.

17a. The method of embodiment 16a, wherein the administration of rituximab once every three weeks is performed for six or eight 21-day cycles.

18a. The method of any one of embodiments 1a-17a, wherein rituximab is administered at a dose of 375 mg/m².

19a. The method of any one of embodiments 1a-18a, wherein cyclophosphamide is administered once every three weeks.

20a. The method of embodiment 19a, wherein the administration of cyclophosphamide once
5 every three weeks is performed for six or eight 21-day cycles.

21a. The method of any one of embodiments 1a-20a, wherein cyclophosphamide is administered at a dose of 750 mg/m^2 .

10 22a. The method of any one of embodiments 1a-21a, wherein doxorubicin is administered once every three weeks.

23a. The method of embodiment 22a, wherein the administration of doxorubicin once every three weeks is performed for six or eight 21-day cycles.
15

24a. The method of any one of embodiments 1a-23a, wherein doxorubicin is administered at a dose of 50 mg/m^2 .

25a. The method of any one of embodiments 1a-24a, wherein vincristine is administered once
20 every three weeks.

26a. The method of embodiment 25a, wherein the administration of vincristine once every three weeks is performed for six or eight 21-day cycles.

25 27a. The method of any one of embodiments 1a-26a, wherein vincristine is administered at a dose of 1.4 mg/m^2 .

28a. The method of any one of embodiments 1a-27a, wherein prednisone is administered once a day from day 1 to day 5 of the 21-day cycles.
30

29a. The method of embodiment 28a, wherein prednisone is administered for six or eight 21-day cycles.

30a. The method of any one of embodiments 1a-29a, wherein prednisone is administered at a
5 dose of 100 mg/day.

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

10

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

15 33a. The method of any one of embodiments 1a, 2a, and 4a-32a, wherein administration is performed in 21-day cycles, and wherein:

(a) the bispecific antibody is administered as follows:

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

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

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

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

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

25

34a. The method of any one of embodiments 1a and 3a-32a, wherein administration is performed in 21-day cycles, and wherein:

(a) the bispecific antibody is administered as follows:

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

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

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

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

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

5

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

36a. The method of any one of embodiments 1a, 2a, and 4a-32a, wherein administration is performed in 21-day cycles, and wherein:

10 (a) the bispecific antibody is administered as follows:

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

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

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

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

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

20 37a. The method of any one of embodiments 1 and 3a-32a, wherein administration is performed in 21-day cycles, and wherein:

(a) the bispecific antibody is administered as follows:

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

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

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

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

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

30

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

39a. The method of any one of embodiments 1a-38a, wherein the bispecific antibody is administered subcutaneously.

40a. The method of any one of embodiments 1a-39a, wherein rituximab is administered intravenously.

41a. The method of any one of embodiments 1a-40a, wherein cyclophosphamide is administered intravenously.

42a. The method of any one of embodiments 1a-41a, wherein doxorubicin is administered intravenously.

43a. The method of any one of embodiments 1a-42a, wherein vincristine is administered intravenously.

44a. The method of any one of embodiments 1a-43a, wherein prednisone is administered intravenously or orally.

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

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

- 47a. The method of any one of embodiments 1a-46a, wherein the DLBCL is double-hit or triple-hit DLBCL.
- 48a. The method of any one of embodiments 1a-47a, wherein the DLBCL is follicular lymphoma Grade 3B.
- 49a. The method of any one of embodiments 1a-48a, wherein the subject has an International Prognostic Index (IPI) score or Revised-IPI score ≥ 3 .
- 50a. The method of any one of embodiments 1a-49a, wherein the subject has not received prior therapy for DLBCL or follicular lymphoma Grade 3B.
- 51a. The method of any one of embodiments 1a-50a, wherein the subject is treated with prophylaxis for cytokine release syndrome (CRS).
- 52a. The method of embodiment 51a, wherein the prophylaxis comprises administering a corticosteroid to the subject.
- 53a. The method of embodiment 52a, wherein the corticosteroid is administered on the same day as the bispecific antibody.
- 54a. The method of embodiment 53a, wherein the corticosteroid is further administered on the second, third, and fourth days after administering the bispecific antibody.
- 55a. The method of any one of embodiments 52a-54a, wherein the corticosteroid is prednisone.
- 56a. The method of embodiment 55a, wherein the prednisone is administered at an intravenous dose of 100 mg, or equivalent thereof, including oral dose.
- 57a. The method of any one of embodiments 52a-54a, wherein the prednisone from R-CHOP serves as the corticosteroid for prophylaxis for CRS.

58a. The method of embodiment 57a, wherein if the prednisone from R-CHOP is administered more than 120 minutes before administration of the bispecific antibody, then the subject is administered prednisone or an equivalent about 30-120 minutes prior to administration of the
5 bispecific antibody.

59a. The method of any one of embodiments 1a-58a, wherein the subject is administered premedication to reduce reactions to injections.

10 60a. The method of embodiment 59a, wherein the premedication comprises an antihistamine.

61a. The method of embodiment 60a, wherein the antihistamine is diphenhydramine.

62a. The method of embodiment 61a, wherein the diphenhydramine is administered at an
15 intravenous or oral dose of 50 mg, or equivalent thereof.

63a. The method of any one of embodiments 59a-62a, wherein the premedication comprises an antipyretic.

20 64a. The method of embodiment 63a, wherein the antipyretic is acetaminophen.

65a. The method of embodiment 64a, wherein the acetaminophen is administered at an oral dose of 650 mg to 1000 mg, or equivalent thereof.

25 66a. The method of any one of embodiments 59a-65a, wherein the premedication is administered on the same day as the bispecific antibody.

67a. The method of any one of embodiments 51a-66a, wherein the prophylaxis is administered in cycle 1 and start of cycle 2 of the 21-day cycles.
30

68a. The method of any one of embodiments 59a-66a, wherein the premedication is administered in cycle 1 and start of cycle 2 of the 21-day cycles.

69a. The method of any one of embodiments 51a-68a, 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.

70a. The method of embodiment 69a, 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.

71a. The method of any one of embodiments 59a-70a, wherein the premedication is administered during cycle 2 of the 21-day cycles.

72a. The method of embodiment 71a, wherein the premedication is administered during subsequent cycles.

73a. The method of any one of embodiments 1a-72a, wherein the subject is administered antibiotics if the subject develops Grade 1 CRS.

74a. The method of any one of embodiments 1a-72a, wherein the subject is administered a vasopressor if the subject develops Grade 2 or Grade 3 CRS.

75a. The method of any one of embodiments 1a-72a, wherein the subject is administered at least two vasopressors if the subject develops Grade 4 CRS.

76a. The method of any one of embodiments 1a-75a, wherein the subject is administered tocilizumab if the subject develops Grade 2, Grade 3, or Grade 4 CRS.

77a. The method of embodiment 76a, wherein the subject is further administered a steroid.

- 78a. The method of embodiment 77a, wherein the steroid is dexamethasone.
- 79a. The method of embodiment 77a, wherein the steroid is methylprednisolone.
- 5 80a. The method of any one of embodiments 76a-79a, wherein tocilizumab is switched to an anti-IL-6 antibody (e.g., siltuximab) if the subject is refractory to tocilizumab.
- 81a. The method of any one of embodiments 76a-79a, wherein tocilizumab is switched to an
10 IL-1R antagonist (e.g., anakinra) if the subject is refractory to tocilizumab.
- 82a. The method of any one of embodiments 1a-81a, wherein the subject is treated with prophylaxis for tumor lysis syndrome (TLS).
- 15 83a. The method of embodiment 82a, wherein the prophylaxis for TLS comprises administering one or more uric acid reducing agents prior to administration of the bispecific antibody.
- 84a. The method of embodiment 83a, wherein the one or more uric acid reducing agents comprise rasburicase and/or allopurinol.
- 20 85a. The method of any one of embodiments 1a-84a, wherein the subject achieves a complete response, a partial response, or stable disease.
- 86a. The method of any one of embodiments 1a-85a, wherein:
- 25 (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,
30 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.

87a. The method of any one of embodiments 1a-86a, wherein:

5 (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.

88a. The method of any one of embodiments 1a-87a, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1, λ (lambda) antibody.

15

89a. The method of embodiment 88a, 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.

20 90a. The method of any one of embodiments 1a-89a, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1, κ (kappa) antibody.

91a. The method of embodiment 90a, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

25

92a. The method of any one of embodiments 1a-91a, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

30 93a. The method of any one of embodiments 1a-92a, wherein the bispecific antibody comprises an inert Fc region.

94a. The method of any one of embodiments 1a-93a, 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
5 IgG1 heavy chain constant region of SEQ ID NO: 15 are F, E, and A, respectively.

95a. The method of any one of embodiments 1a-94a, 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
10 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.

96a. The method of any one of embodiments 1a-95a, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein
15 (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
20 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.

97a. The method of embodiment 96, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.
25

98a. The method of any one of embodiments 1a-97a, 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.
30

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

5

100a. The method of any one of embodiments 1a-99a, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.

EXAMPLES

10 DuoBody-CD3xCD20

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.

Two parental antibodies, IgG1-CD3-FEAL, a humanized IgG1 λ , CD3 ϵ -specific antibody
15 having heavy and light chain sequences as listed in SEQ ID NOs: 24 and 25, respectively, and IgG1-CD20-FEAR, derived from human IgG1 κ 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
20 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).
25 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
30 extinction coefficient $\epsilon = 1.597 \text{ mL} \cdot \text{mg}^{-1} \cdot \text{cm}^{-1}$. The final product was stored at 4°C. The product has an international proprietary name of epcoritamab.

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.

- 5 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**

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 described in Engelberts et al., *EBioMedicine* 2020;52:10265, as summarized below.

- 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.

- 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 anti-CD20 antibody, epcoritamab was able to induce up to 40% tumor cell kill.

Example 2: Impact of CHOP on in vitro T cell-mediated cytotoxicity induced by epcoritamab

- CHOP is often used to treat DLBCL and FL. This experiment was performed to test the impact of CHOP components separately to evaluate each component's effect on epcoritamab-induced T-cell-mediated cytotoxicity.

Briefly, T cells were pre-incubated with cyclophosphamide, doxorubicin, vincristine, or prednisone for 16 hours and subsequently used in a cytotoxicity assay with epcoritamab and CD20-expressing Daudi cells as target cells (E:T ratio 2:1), in which cyclophosphamide, doxorubicin, vincristine, or prednisone was added in the same concentration as during pre-incubation, respectively. Data are presented as percent viable target cells (CD4-CD8-CD22+), normalized to medium control (no Ab, no CHOP component). Since doxorubicin pre-treatment affected the viability of the T cells, not all concentrations of epcoritamab could be tested.

Figures 1A-1D show in the left panels dose response curves for DuoBody-CD3xCD20 for a representative donor, the right panels show the response to a dose of 333 ng/ml of DuoBody-CD3xCD20 for four different donors, with and without various concentrations of the CHOP components. Pretreatment of T cells with cyclophosphamide, vincristine, or prednisone, respectively, did not impact T cell viability (data not shown). As said, pretreatment with doxorubicin led to a reduction in T cell viability (not shown), though the degree observed in-vitro appeared exaggerated as compared with what was observed in patients treated with R-CHOP (*Oncology* 2016;91: 302–10 and *Hematol Oncol* 2011;29:5–9). As shown in **Figures 1A, 1C, and 1D**, T cells pretreated with cyclophosphamide (A), vincristine (C), or prednisone (D) were able to mediate an epcoritamab-induced cytotoxic response against the CD20-expressing target cells, as shown by the dose-dependent cytotoxicity (in the left panels) and the very low percentages of viable B cells left after incubation (in the right panels). As shown in **Figure 1B**, the remaining T cells pre-treated with doxorubicin were also able to mediate epcoritamab-induced cytotoxicity against target cells indicating that the remaining T cells were functional.

Taken together, the data and observations above show that epcoritamab can be combined with CHOP and R-CHOP, as rituximab does not interfere with epcoritamab activity, to induce highly effective anti-tumor activity against CD20-expressing target cells.

Example 3: A Phase 1b, Open-Label, Safety and Efficacy Study of Epcoritamab in Combination with Standard-of-Care R-CHOP for the Treatment of Previously Untreated, High-risk (IPI or R-IPI ≥ 3) DLBCL

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-CHOP in subjects with previously untreated DLBCL.

Summary of Ongoing Clinical Trial with Epcoritamab

5 Epcoritamab as monotherapy is currently in a clinical trial for the treatment of relapsed/refractory (R/R) B-NHL (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.

10 **Objectives**

Dose escalation

The primary objective of the dose escalation part is to evaluate the safety and tolerability of epcoritamab in combination with R-CHOP (endpoints: incidence of dose-limiting toxicities (DLTs), incidence and severity of adverse events (AEs), incidence and severity of changes in
15 laboratory values, and incidence of dose interruptions and delays).

Secondary objectives of the dose escalation part include characterizing the PK properties of epcoritamab (endpoints: PK parameters, including clearance, volume of distribution, AUC_{0-last}, AUC_{0-x}, C_{max}, T_{max}, predose values, and half-life), evaluating pharmacodynamic markers linked to efficacy and the mechanism of action of epcoritamab (endpoints: pharmacodynamic
20 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-CHOP (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
25 criteria and LYRIC, overall survival (OS), time to next anti-lymphoma therapy (TTNT), and rate and duration of minimal residual disease (MRD) negativity).

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

Expansion

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

5 Secondary objectives of the expansion part include evaluating the preliminary anti-tumor activity of epcoritamab in combination with R-CHOP (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-CHOP (endpoints: incidence and severity of changes in laboratory values, and incidence of dose
10 interruptions and delays), characterizing the PK properties of epcoritamab (PK parameters, including clearance, volume of distribution, AUC_{0-last}, AUC_{0-x}, C_{max}, T_{max}, 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).

15 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
20 health status as evaluated by the FACT-Lym).

Study Design Overview

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 **Figure 2**. Both
25 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)

The Part 1 dose escalation assesses the initial safety, tolerability, and clinical activity of
30 epcoritamab in combination with R-CHOP. Epcoritamab is initially be administered in combination with R-CHOP 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-CHOP is performed in an additional 3 subjects as shown in **Figure 3**.

In Part 2, epcoritamab is administered (with the dosing regimen determined in the dose-escalation part) in combination with R-CHOP. 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.

In both Part 1 and Part 2, epcoritamab is administered as a subcutaneous (SC) injection (24 mg or 48 mg; step-up dosing) for up to one year total duration of treatment with the bispecific antibody from initiation of R-CHOP, with 6 (Table 2a), or 8 (Table 2b) of the cycles in combination with R-CHOP, as follows:

Table 2(a). Dosing schedule (6 cycles with R-CHOP)

Cycle number	Epcoritamab	R-CHOP
21-day cycles		
1	QW, step-up dosing	Q3W
2-4	QW	Q3W
5-6	Q3W	Q3W
28-day cycles		
7+	Q4W	-

Table 2(b). Dosing schedule (8 cycles with R-CHOP)

Cycle number	Epcoritamab	R-CHOP
21-day cycles		
1	QW, step-up dosing	Q3W
2-4	QW	Q3W
5-8	Q3W	Q3W
28-day cycles		
9+	Q4W	-

QW: once a week (days 1, 8, and 15), Q3W: once every 3 weeks (day 1), Q4W: once every 4 weeks (day 1)

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/m²) is administered intravenously on day 1 once every three weeks (Q3W) for cycles 1-6 or 1-8. Cyclophosphamide (750 mg/m²) is administered intravenously on day 1 once every three weeks (Q3W) of cycles 1-6 or 1-8. Doxorubicin (50 mg/m²) is administered intravenously on day 1 once every three weeks (Q3W) of cycles 1-6 or 1-8. Vincristine (1.4 mg/m², with a recommended cap of 2 mg) is administered intravenously on day 1 once every three weeks (Q3W) of cycles 1-6 or 1-8. Prednisone (100 mg/day) is administered intravenously or orally on five consecutive days (days 1-5) every three weeks (Q3W) of cycles 1-6 or 1-8.

The order of treatments are as follows:

Table 3. Treatment administration order

Dosing order	Treatment	Dose
Pre-Meds	Pre-medications (prednisone component of R-CHOP may serve as corticosteroid premedication/CRS prophylaxis)	As described in Table 4
1	Prednisone	100 mg
2	Rituximab*	375 mg/m ²
3	Cyclophosphamide*	750 mg/m ²
4	Doxorubicin* (hydroxydaunomycin)	50 mg/m ²
5	Vincristine* (Oncovin®)	1.4 mg/m ² (max. 2 mg)
6	Epcoritamab	24 mg or 48 mg

*Intravenous components of R-CHOP may be administered over 2 days, with subsequent epcoritamab administration on day 2.

Inclusion criteria

1. Subject must be at least 18 years of age

2. ECOG PS score of 0, 1, or 2
3. CD20-positive NHL at representative tumor biopsy
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
5. Acceptable organ function at screening defined as:
 - a. ANC $\geq 1.0 \times 10^9/L$ (growth factor use is allowed)
 - b. Platelet count $> 75 \times 10^9/L$, or $\geq 50 \times 10^9/L$ if bone marrow infiltration or splenomegaly
 - c. ALT level ≤ 2.5 times the ULN
 - d. Total bilirubin level $\leq 2 \times$ ULN
 - 10 e. eGFR > 50 mL/min (by Cockcroft-Gault Formula)
 - f. PT, INR, and aPTT $\leq 1.5 \times$ ULN, unless receiving anticoagulant
6. Documented DLBCL (de novo or histologically transformed from indolent lymphomas, except for CLL) according to the 2016 WHO classification, including:
 - a. DLBCL, NOS
 - 15 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
 - c. FL Grade 3B
7. International Prognostic Index score ≥ 3
- 20 8. No prior therapy for DLBCL (or FL Grade 3B) other than corticosteroids, not exceeding the threshold listed in exclusion criterion 8.
9. Eligible to receive R-CHOP. For subjects aged ≥ 80 years, confirm they are eligible to receive R-CHOP according to protocol, without preplanned dose reductions.
10. LVEF within institutional normal limits by multiple-gated acquisition scan (MUGA) or
- 25 echocardiography at screening.

Exclusion criteria

1. Prior therapy for DLBCL with the exception of nodal biopsy
2. Contraindication to any of the individual drugs in the R-CHOP regimen
- 30 3. History of severe allergic or anaphylactic reactions to anti-CD20 mAb therapy or known allergy or intolerance to any component or excipient of epcoritamab

4. Prior treatment with a bispecific antibody targeting CD3 and CD20
5. Chemotherapy, radiation therapy, or major surgery within 4 weeks prior to the first dose of epcoritamab
6. Treatment with an investigational drug within 4 weeks or 5 half-lives, whichever is longer,
5 prior to the first dose of epcoritamab
7. Treatment with CAR-T therapy within 30 days prior to first dose of epcoritamab
8. Cumulative dose of corticosteroids ≥ 140 mg of prednisone or the equivalent within 2-week period before the first dose of epcoritamab
9. Vaccination with live vaccines within 28 days prior to the first dose of epcoritamab
- 10 10. Clinically significant cardiac disease, including:
 - 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
15 abnormalities
 - b. Screening 12-lead ECG showing a baseline QTcF >470 msec
11. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results
12. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding
20 fungal infections of nail beds) at trial enrollment or significant infections within 2 weeks prior to the first dose of epcoritamab
13. 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
14. Active positive tests for hepatitis B virus or hepatitis C virus indicating acute or chronic
25 infection
15. History of HIV antibody positivity, or tests positive for HIV at screening
16. Positive test results for HTLV-1
17. Suspected active or latent tuberculosis
18. Past or current malignancy other than inclusion diagnosis, except for:
30
 - a. Cervical carcinoma of Stage 1B or less
 - b. Non-invasive basal cell or squamous cell skin carcinoma

- c. Non-invasive, superficial bladder cancer
 - d. Prostate cancer with a current PSA level < 0.1 ng/mL
 - e. Any curable cancer with a CR of > 2 years duration
19. Neuropathy >grade 1
- 5 20. 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
21. Male who plans to father a child while enrolled in this trial or within 12 months after the last dose of epcoritamab
22. Subject who has any condition for which participation would not be in the best interest of
- 10 the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

CRS Prophylaxis

- Administration of corticosteroids for four days is performed to reduce/prevent the
- 15 severity of symptoms from potential CRS for each dose of epcoritamab. Prednisone in the R-CHOP regimen serves as the corticosteroid component of the CRS prophylaxis regimen on 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 CRS prophylaxis. For administration of epcoritamab in cycle 2 and beyond, CRS prophylaxis is optional. Prednisone administration can
- 20 be either intravenous or oral route with recommended dose or equivalent.

Supportive therapies recommended for treatments containing rituximab include:

- 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
- 25
- Prophylactic treatment for pneumocystis carinii pneumonia
 - 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
- 30 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	1 st epcoritamab administration (priming dose)	Day 01*	Prednisone 100 mg (or equivalent, IV or oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 02	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 03	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 04	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 05	Prednisone 100 mg (or equivalent IV or oral dose)		
	2 nd epcoritamab administration (intermediate dose)	Day 08*	Prednisone 100 mg (or equivalent IV or oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 09	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 10	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 11	Prednisone 100 mg (or equivalent IV or oral dose)		
	3 rd epcoritamab administration (full dose)	Day 15*	Prednisone 100 mg (or equivalent IV or oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 16	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 17	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 18	Prednisone 100 mg (or equivalent IV or oral dose)		

			Corticosteroids	Antihistamines	Antipyretics
Cycle 2	4 th epcoritamab administration (full dose)	Day 22	Prednisone 100 mg (or equivalent IV or oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 23	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 24	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 25	Prednisone 100 mg (or equivalent IV or oral dose)		
		Day 26	Prednisone 100 mg (or equivalent IV or oral dose)		
	5 th epcoritamab administration (full dose)	Day 29*	If CRS > grade 1 occurs following the 4 th epcoritamab administration, 4-day consecutive corticosteroid administration is continued in Cycle 2 until epcoritamab dose is given without subsequent CRS event.	Optional	Optional
		Day 30			

*30 minutes to 2 hours prior to administration of epcoritamab

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

5

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

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,

- Infusion of saline
- Systemic glucocorticosteroid, antihistamine, antipyrexia
- Support for blood pressure (vasopressin, vasopressors)
- Support for low-flow and high-flow oxygen and positive pressure ventilation
- Monoclonal antibody against IL-6R, e.g., IV administration of tocilizumab
- 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	

With hypotension	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring ≥ 2 vasopressors (excluding vasopressin)	Death due to CRS in which another cause is not the principle factor leading to this outcome
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 $\geq 38.0^{\circ}\text{C}$ 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 $\geq 20\%$ 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 ($> 40.5^{\circ}\text{C}/104.9^{\circ}\text{F}$) 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 TL, Lee DW (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

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

There will be no dose modification for epcoritamab (see **Figure 3** 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.

Dose modifications for rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone should be done in accordance with the respective product labels in situations that differ from dose modification recommendations provided below.

Treatment-emergent adverse events of R-CHOP combination therapy predominantly comprise hematologic toxicities (such as neutropenia, leucopenia, thrombocytopenia, and anemia). Nonhematologic disorders such as asthenia, sensory disturbance, mucositis, alopecia, sepsis, dyspnea, back pain, hyperglycemia, hypersensitivity, and cardiac disorders have all also been observed when treatment with R-CHOP has been administered. It is not always easy to assess the role of any 1 agent in these events; therefore, it is at the investigator's discretion to decide if 1 or more agents are causal.

The start of a new cycle may be delayed on a weekly basis until recovery of toxicity to a level allowing continuation of therapy. A subject whose cycle is delayed should be assessed weekly for resolution of toxicity. If toxicity persists after a 2-week cycle delay that is related to 1 specific drug (vincristine, doxorubicin, etc.), the offending drug should continue to be withheld and the new cycle should be started with the remaining drugs. If R-CHOP chemotherapy is delayed, treatment with epcoritamab should be continued during the delay phase (provided the reason for delay is not toxicity potentially related to epcoritamab therapy).

Subjects who discontinue any component of R-CHOP without disease progression will continue epcoritamab for up to 16 cycles or until one or more of the following discontinuation criteria are met: (a) unacceptable AE, (b) subject non-compliance, (c) pregnancy, (d) subject request to discontinue treatment, (e) clinical progression, or (f) radiographic evidence of disease progression.

The following parameters must be met on the first day of each cycle (other than Cycle 1):

- Platelet count $>75 \times 10^9/L$, or $\geq 50 \times 10^9/L$ if bone marrow infiltration or splenomegaly (prior platelet transfusion is allowed)
- Hemoglobin ≥ 8 g/dL (≥ 4.96 mmol/L) (prior red blood cell transfusion or recombinant human erythropoietin use is allowed)
- ANC $\geq 1.0 \times 10^9/L$ (growth factor use is allowed)

Rituximab

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.

Cyclophosphamide

Dose adjustments for cyclophosphamide follow the local prescribing information. The most common adverse events experienced with cyclophosphamide are hematological toxicities; myelosuppression with leucopenia, anemia, and thrombocytopenia may occur. The lowest leukocyte and platelet levels occur in the first to second week after treatment is started. Recovery usually occurs within 3 to 4 weeks after treatment is started. Following treatment with cyclophosphamide, hemorrhagic cystitis and hematuria may occur. These may necessitate interruption of dosing.

The dose of cyclophosphamide should be adjusted on Day 1 of the subsequent cycle of dosing when subjects develop hematological toxicities thought to be causally related to cyclophosphamide.

Table 8. Dose Modification for Cyclophosphamide and Doxorubicin for Hematological Toxicities

ANC and Neutropenia (any time during cycle)	Platelet count ^a	Dose Given (on next cycle)
$\geq 1 \times 10^9/\text{L}$	$> 75 \times 10^9/\text{L}$	100% of the designated dose
$> 0.5 \times 10^9/\text{L}$ and no febrile neutropenia	$> 50 \times 10^9/\text{L}$	100% of the designated dose after recovery of ANC to $1.5 \times 10^9/\text{L}$ and platelets to $100 \times 10^9/\text{L}$
$< 0.5 \times 10^9/\text{L}$ and/or febrile neutropenia (ANC $< 0.5 \times 10^9/\text{L}$ + fever $\geq 38.5^\circ\text{C}$)	N/A	Initiation of G-CSF for all subsequent cycles is recommended
$< 0.5 \times 10^9/\text{L}$ and/or febrile neutropenia (ANC $< 0.5 \times 10^9/\text{L}$ + fever $\geq 38.5^\circ\text{C}$ despite growth factors)	$< 50 \times 10^9/\text{L}$	25% dose reduction for subsequent cycles
Recurrence of $< 0.5 \times 10^9/\text{L}$ and/or febrile neutropenia (ANC $< 0.5 \times 10^9/\text{L}$ + fever $\geq 38.5^\circ\text{C}$ despite growth factors)	Recurrence of $< 50 \times 10^9/\text{L}$	Additional 25% dose reduction for subsequent cycles
Third episode of $< 0.5 \times 10^9/\text{L}$ and/or febrile neutropenia (ANC $< 0.5 \times 10^9/\text{L}$ + fever $\geq 38.5^\circ\text{C}$ despite growth factors)	Third episode of $< 50 \times 10^9/\text{L}$	Discontinue

Abbreviations: ANC=absolute neutrophil count; DLBCL=diffuse large B-cell lymphoma; G-CSF=granulocyte colony-stimulating factor.

-
- a. Dose reductions due to low platelet counts or ANC's are not required in subjects with thrombocytopenia or neutropenia due to bone marrow infiltration from DLBCL who entered the trial with platelet counts $<75 \times 10^9/L$ or neutrophil counts $<1.0 \times 10^9/L$.

Doxorubicin

Dose adjustments for doxorubicin follow the provided prescribing information. The recommended lifetime cumulative dose limit of doxorubicin is 450 to 550 mg/m^2 . The maximum dose given for each subject is 300 to 400 mg/m^2 , depending on the number of cycles given. Dose-limiting toxicities of doxorubicin therapy are mucositis, myelosuppression, and cardiotoxicity. Myelosuppression includes leucopenia, thrombocytopenia, and anemia, reaching nadir at 10 to 14 days after treatment. The dose of doxorubicin should be adjusted on Day 1 of the subsequent cycle of dosing when subjects develop hematological toxicities thought to be causally related to doxorubicin (see **Table 8** above).

- 10 Cardiotoxicity as an arrhythmia can occur directly after administration and ECG changes may last up to 2 weeks after administration. Cardiotoxicity may, however, occur several weeks or months after administration. Doxorubicin is metabolized by the liver and excreted in bile. Impairment of liver function results in slower excretion of the drug and consequently increased retention and accumulation in the plasma and tissues, resulting in enhanced clinical toxicity.
- 15 Doxorubicin dosage is reduced if hepatic function is impaired, as shown in **Table 9**.

Table 9. Dose Modification of Doxorubicin for Hepatic Function Impairment

Serum Bilirubin Levels*	Recommended Dose
2.0-3.0 mg/dL	50% normal dose
>3.0 mg/dL	25% normal dose

*When bilirubin elevation is attributable to hepatotoxicity

Vincristine

- Dose adjustments for vincristine must follow the provided prescribing information. The
- 20 vincristine dosage is reduced if hepatic function is impaired, as shown in **Table 10**.

Table 10: Dose Modification for Vincristine for Hepatic Function Impairment

Serum Bilirubin Levels*	Recommended Dose
2.0-3.0 mg/dL	75% normal dose
>3.0 mg/dL	50% normal dose

*When bilirubin elevation is attributable to hepatotoxicity

Vincristine doses is re-escalated when hyperbilirubinemia improves. These dose reductions are not required in subjects with Gilbert syndrome and in cases where the increase of bilirubin is due to non-hepatic reasons.

Neurologic toxicity is the most common adverse event experienced with vincristine and is related to dose and age. In case of severe neurotoxicity (Grade ≥ 3), vincristine should not be administered, especially if there are signs of paresthesia or paresis. For grade 3 neuropathy, treatment may be resumed at 50% of the dose when symptoms subside. Vincristine is reduced by 25% for any episode of ileus/constipation requiring hospitalization. Vincristine is permanently discontinued for Grade 4 neuropathy of any type.

Prednisone (or Equivalent)

Dose adjustments for prednisone (or equivalent) follow the provided prescribing information. Subjects administered high-dose prednisone or equivalent are monitored carefully as there is a relatively higher risk of developing or exacerbating some conditions (e.g., bacterial infections, viral infections, systemic mycoses, hypertension, diabetes mellitus, and gastrointestinal conditions such as peptic ulcers, pancreatitis, and diverticulitis).

In the event that a subject develops an adverse event related to corticosteroid and is not able to tolerate prednisone 100 mg (or equivalent), the dose is adjusted to a level specific to that subject but should be no less than prednisone 80 mg per day (so that the subject still receives a high dose of corticosteroid). In exceptional circumstances, a subject may not tolerate sudden steroid withdrawal after 5 days of therapy. In such an instance, a tapering regimen of is indicated.

Study Assessments

Demographics and Baseline Assessments

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.

10 **Efficacy Assessments**

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

20 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
25 examined for MRD assessment and exploratory biomarkers.

Radiographic Assessments

An FDG PET-CT scan (or CT/MRI and FDG PET when PET-CT scan not available) is performed during Screening. For subjects with FDGavid tumors at Screening, all subsequent
30 disease assessments include FDGPET using the 5-point scale described in Barrington et al. (*J Clin Oncol* 2014;32:3048-58; Score 1: No uptake; Score 2: Uptake $\leq$ mediastinum; Score 3:

Update > mediastinum but $\leq$ 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). If contrast enhanced PETCT is not available, a standalone diagnostic CT/MRI and a standard FDGPET is performed. Subjects who are intolerant of IV CT contrast agents undergo CT scans with oral contrast.

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.

10 Bone Marrow Assessments

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

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.

30

Disease Response and Progressive Disease Assessment

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 11) to inform decisions on continuation of treatment.

5 Endpoint definitions are as follows:

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.

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.

10 **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.

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.

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

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.

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.

20

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

25 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

30 LDi.

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

- 5 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
- 10 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 LD_i and smallest diameter (SD_i) are no longer needed to determine progression.

15 LYRIC

- 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
- 20 and is therefore called “pseudoprogression” (Wolchok et al., *Clin Cancer Res* 2009;15:7412-20).

- 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
- 25 progression of existing lesions, later followed by response, or by the development of new lesions, with or without tumor shrinkage elsewhere.

- 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
- 30 designation was introduced to potentially identify “atypical response” cases until confirmed as flare/pseudoprogression or true PD by either biopsy or subsequent imaging.

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

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

IR (2): Appearance of new lesions or growth of one or more existing lesion(s) $\geq 50\%$ 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.

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

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 11. 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): $\geq 50\%$ increase in SPD in first 12 weeks of therapy IR (2): $< 50\%$ increase in SPD with a) New lesion(s), or b) $\geq 50\%$ 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

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

5 considerations:

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 $\geq 10\%$ 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.

10 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) $\geq 50\%$ increase in SPD (newly defined set of target lesions) from nadir value.

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

15

Clinical Safety Assessments

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*

20 *Blood Marrow Transplant* 2019;25:625-638), constitutional symptoms (B symptoms), tumor flare reaction, and survival.

Patient-reported Outcomes

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

Preliminary results

30 As of 15 Jul 2021, 9 patients have been treated with the combination of epcoritamab + R-CHOP (4 with epcoritamab 24 mg; 5 with 48 mg) with 4 patients completing ≥ 6 cycles. Median age was 66 years (range 56–78). All patients had stage III–IV disease. At data cutoff, all patients

remained on treatment with a median follow-up of 12.2 weeks (range 2.2–28.2). The most common treatment-emergent adverse events were cytokine release syndrome (CRS) (56%, all grade 1/2), anemia (42%, all grade 2/3), neutropenia (42%, all grade 3/4), fatigue (33%, all grade 1/2), and peripheral neuropathy (33%, all grade 1/2). Notably, no grade ≥ 3 CRS events or cases of febrile neutropenia were reported. No dose-limiting toxicities had been observed. Four patients have had ≥ 1 response assessment, with 3 achieving confirmed complete metabolic response (CMR; all in the epcoritamab 24 mg dose-escalation cohort) and 1 patient achieving confirmed partial metabolic response (epcoritamab 48 mg cohort) by week 6; 2 of the 3 patients with CMR had response assessments at 6 months, and both remained in CMR at that time. Both dose cohorts have been cleared by the Dose Escalation Committee and Safety Committee, and the expansion part had been opened to enroll additional patients.

As of September 8, 2021, 24 patients had been dosed. The expansion phase 48 mg was opened on June 30, 2021. 7 responders were observed in dose escalation. The most common related AEs were CRS and Anemia. Majority of CRS were Grade 1/2. There was one episode of Grade 3 CRS, which was treated with tocilizumab and recovered. These data are preliminary and non-validated and unclear data and response data were not completely entered by site.

Conclusions:

These preliminary data suggest that epcoritamab in combination with R-CHOP has a manageable safety profile with no new safety signals. Adverse events were similar to those previously reported for epcoritamab monotherapy and R-CHOP. All evaluable patients achieved early responses, with all pts remaining on treatment. Updated and additional data from patients treated in the expansion phase will be presented.

Table 12: 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	EVKLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWWVRQAPGKGLE WVARIRSKYNNYATYYADSVKDRFTISRDDSKSSLYLQMNNLKTEDTA MYVCVRHGNFGNSYVSWFAYWGQGTLLTVSS
7	huCD3 VL1	QAVVTQEPSFSVSPGGTVTLTCSRSTGAVTTSNYANWVQQTGQAF RGLIGGTNKRAPGVPARFSGSLIGDKAALTITGAQADDESIYFCALWYS NLWVFGGGTKLTVL
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	EVQLVESGGGLVQPDRLRLSCAASGFTFHDYAMHWWVRQAPGKGLE WVSTISWNSGTIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAL YYCAKDIQYGNYYYGMDVWGQGTLLTVSS
14	VL CD20 – 7D8	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIY DASNRATGIPARFSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPITF GQGTREIK
15	IgG1 heavy chain constant region – WT (amino acids positions 118-447 according to EU numbering). <i>CH3 region italics</i>	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
16	IgG1-LFLEDA heavy chain constant region	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVPSSSLGTQTYICNVNHKPSNTKVDK

	(amino acids positions 118-447 according to EU numbering).	RVEPKSCDKTHTCPPCPAPE <u>FE</u> GGPSVFLFPPKPKDTLMISRTPEVTCV VV <u>A</u> VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
17	IgG1 F405L (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE <u>LL</u> GGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDS F <u>LL</u> YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
18	IgG1-K409R (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE <u>LL</u> GGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDS FFLYS <u>R</u> LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
19	IgG1 -LFLEDA-F405L (FEAL) (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE <u>FE</u> GGPSVFLFPPKPKDTLMISRTPEVTCV VV <u>A</u> VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDS F <u>LL</u> YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
20	IgG1 -LFLEDA-K409R (FEAR) (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE <u>FE</u> GGPSVFLFPPKPKDTLMISRTPEVTCV VV <u>A</u> VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDS FFLYS <u>R</u> LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
21	IgG1 CH3 region	GQPREPQVYTLPPSREMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG

22	Constant region human lambda LC	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
23	Constant region human kappa LC	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
24	huCD3-LFLEDA-F405L (FEAL) heavy chain	EVKLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKSSLYLQMNNLKTEDTAMYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNTKVDKRVKPKCDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVAVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFLLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
25	huCD3 VL+CL light chain	QAVVTQEPFSVSPGGTVTLTCSRSTGAVTTSNYANWVQQTGQAFRGLIGGTNKRAGVPPARFSGSLIGDKAALTITGAQADDESIYFCALWYSNLWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS
26	CD20-7D8-LFLEDA-K409R (FEAR) heavy chain	EVQLVESGGGLVQPDRSLRLSCAASGFTFHDYAMHWVRQAPGKGLEWVSTISWNSGTIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCAKDIQYGNYYYGMDVWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPSNTKVDKRVKPKCDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVAVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
27	CD20 – 7D8 VL+CL light chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYDASNRATGIPARFSGSGSGTDFTLTISLEPEDFAVYYCQQRSNWPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

28	Human CD3 (epsilon)	MQSGTHWRVLGLCLLSVGWVGQDGNEEMGGITQTPYKVSISGTTVI LTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSG YYVCYPRGSKPEDANFYLYLRARVCENCMEMDVMSVATIVIVDICITG GLLLLVYYWSKNRKAKAKPVTRGAGAGGRQGRQNKERPPVPNPDPY EPIRKGQRDLYSGLNQRR
29	Human CD20	MTTPRNSVNGTFPAEPMKGPIAMQSGPKPLFRRMSSLVGPTQSFFM RESKTLGAVQIMNGLFHIALGGLLMIPAGIYAPICVTWVYPLWGGIM YIISGSLLAATEKNSRKCLVKGKMIMNSLSLFAAISGMILSIMDILNIKIS HFLKMESLNFIRAHTPYINIYNCEPANPSEKNPSTQYCYSIQSLFLGILS VMLIAFFQELVIAGIVENEWKRTCSRPKSNIVLLSAEEKKEQTIEIKEEV VGLTETSSQPKNEEDIEIPIQEEEEETETNFPEPPQDQESSPIENDSSP

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

5 underlined.

Claims

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

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3 ϵ (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the
10 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
15 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, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered in 21-day cycles.

20

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.

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

5. The method of claim 4, wherein the weekly administration of 24 mg or 48 mg is performed for three and one-third 21-day cycles.

30

6. The method of claim 4 or 5, wherein after the weekly administration, the bispecific antibody is administered once every three weeks.
7. The method of claim 6, wherein the administration once every three weeks is performed
5 for two or four 21-day cycles.
8. The method of claim 7, wherein after the administration once every three weeks, the bispecific antibody is administered once every four weeks in 28-day cycles.
- 10 9. The method of claim 8, wherein the administration once every four weeks is performed for up to one year total duration of treatment with the bispecific antibody.
10. The method of any one of claims 4-9, wherein prior to the weekly administration of 24 mg or 48 mg, a priming dose of the bispecific antibody is administered in cycle 1 of the 21-day cycles.
15
11. The method of claim 10, wherein the priming dose is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg.
12. The method of claim 10 or 11, wherein the priming dose is 0.16 mg.
20
13. The method of any one of claims 10-12, wherein after administering the priming dose and prior to administering the first weekly dose of 24 mg or 48 mg, an intermediate dose of the bispecific antibody is administered.
- 25 14. The method of claim 13, wherein the priming dose is administered on day 1 and the intermediate dose is administered on day 8 before the first weekly dose of 24 mg or 48 mg on day 15 of cycle 1.
15. The method of claim 13 or 14, wherein the intermediate dose is 0.8 mg.
30

16. The method of any one of claims 1-15, wherein rituximab is administered once every three weeks.
17. The method of claim 16, wherein the administration of rituximab once every three weeks
5 is performed for six or eight 21-day cycles.
18. The method of any one of claims 1-17, wherein rituximab is administered at a dose of 375 mg/m².
- 10 19. The method of any one of claims 1-18, wherein cyclophosphamide is administered once every three weeks.
20. The method of claim 19, wherein the administration of cyclophosphamide once every three weeks is performed for six or eight 21-day cycles.
15
21. The method of any one of claims 1-20, wherein cyclophosphamide is administered at a dose of 750 mg/m².
22. The method of any one of claims 1-21, wherein doxorubicin is administered once every
20 three weeks.
23. The method of claim 22, wherein the administration of doxorubicin once every three weeks is performed for six or eight 21-day cycles.
- 25 24. The method of any one of claims 1-23, wherein doxorubicin is administered at a dose of 50 mg/m².
25. The method of any one of claims 1-24, wherein vincristine is administered once every three
30 weeks.

26. The method of claim 25, wherein the administration of vincristine once every three weeks is performed for six or eight 21-day cycles.
27. The method of any one of claims 1-26, wherein vincristine is administered at a dose of 1.4 mg/m².
28. The method of any one of claims 1-27, wherein prednisone is administered once a day from day 1 to day 5 of the 21-day cycles.
29. The method of claim 28, wherein prednisone is administered for six or eight 21-day cycles.
30. The method of any one of claims 1-29, wherein prednisone is administered at a dose of 100 mg/day.
31. The method of any one of claims 1-30, wherein rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered on the same day (e.g., on day 1 of cycles 1-6 or cycles 1-8 of the 21-day cycles).
32. The method of any one of claims 1-31, wherein the dosing schedule for rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody is as shown in **Table 2**.
33. The method of any one of claims 1, 2, and 4-32, wherein administration is performed in 21-day cycles, and wherein:
- (a) the bispecific antibody is administered as follows:
- (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 24 mg is administered on day 15;
- (ii) in cycles 2-4, a dose of 24 mg is administered on days 1, 8, and 15;
- (iii) in cycles 5 and 6, a dose of 24 mg is administered on day 1;
- (b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-6; and

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

34. The method of any one of claims 1 and 3-32, wherein administration is performed in 21-day cycles, and wherein:

5 (a) the bispecific antibody is administered as follows:

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

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

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

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

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

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

36. The method of any one of claims 1, 2, and 4-32, wherein administration is performed in 21-day cycles, and wherein:

(a) the bispecific antibody is administered as follows:

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

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

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

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

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

37. The method of any one of claims 1 and 3-32, wherein administration is performed in 21-day cycles, and wherein:

30 (a) the bispecific antibody is administered as follows:

- (i) in cycle 1, a priming dose of 0.16 mg is administered on day 1, an intermediate dose of 0.8 mg is administered on day 8, and a dose of 48 mg is administered on day 15;
 - (ii) in cycles 2-4, a dose of 48 mg is administered on days 1, 8, and 15;
 - (iii) in cycles 5-8, a dose of 48 mg is administered on day 1;
- 5 (b) rituximab, cyclophosphamide, doxorubicin, and vincristine are administered on day 1 in cycles 1-8; and
- (c) prednisone is administered on days 1-5 in cycles 1-8.

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

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

15 40. The method of any one of claims 1-39, wherein rituximab is administered intravenously.

41. The method of any one of claims 1-40, wherein cyclophosphamide is administered intravenously.

20 42. The method of any one of claims 1-41, wherein doxorubicin is administered intravenously.

43. The method of any one of claims 1-42, wherein vincristine is administered intravenously.

44. The method of any one of claims 1-43, wherein prednisone is administered intravenously
25 or orally.

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

30 46. The method of any one of claims 1-45, wherein prednisone is administered first, rituximab is administered second, cyclophosphamide is administered third, doxorubicin is administered

fourth, vincristine is administered fifth, and the bispecific antibody is administered last if rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and the bispecific antibody are administered on the same day.

5 47. The method of any one of claims 1-46, wherein the DLBCL is double-hit or triple-hit DLBCL.

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

10

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

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

51. The method of any one of claims 1-50, wherein:

20 (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

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

52. The method of any one of claims 1-51, wherein:

30 (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.

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

54. The method of claim 53, wherein the first binding arm of the bispecific antibody comprises
10 a λ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 22.

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

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

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

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

59. The method of any one of claims 1-58, wherein the bispecific antibody comprises a first
25 heavy chain and a second heavy chain, wherein in both the first and second heavy chains, the amino acids in the positions corresponding to positions L234, L235, and D265 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 are F, E, and A, respectively.

60. The method of any one of claims 1-59, wherein the bispecific antibody comprises a first
30 heavy chain and a second heavy chain, wherein in the first heavy chain, the amino acid in the position corresponding to F405 in the human IgG1 heavy chain constant region of SEQ ID NO:

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

61. The method of any one of claims 1-60, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein

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

(ii) in the first heavy chain, the amino acid in the position corresponding to F405 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 is L, and wherein in the second heavy chain, the amino acid in the position corresponding to K409 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 is R, or vice versa.

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

63. The method of any one of claims 1-62, wherein the bispecific antibody comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 24 and 25, respectively, and a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 26 and 27, respectively.

64. The method of any one of claims 1-63, wherein the bispecific antibody comprises a heavy chain and a light chain consisting of the amino acid sequence of SEQ ID NOs: 24 and 25, respectively, and a heavy chain and a light chain consisting of the amino acid sequence of SEQ ID NOs: 26 and 27, respectively.

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

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