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(54) **Title:** BISPECIFIC ANTIBODY AGAINST CD3 AND CD20 IN COMBINATION THERAPY FOR TREATING FOLLICULAR LYMPHOMA

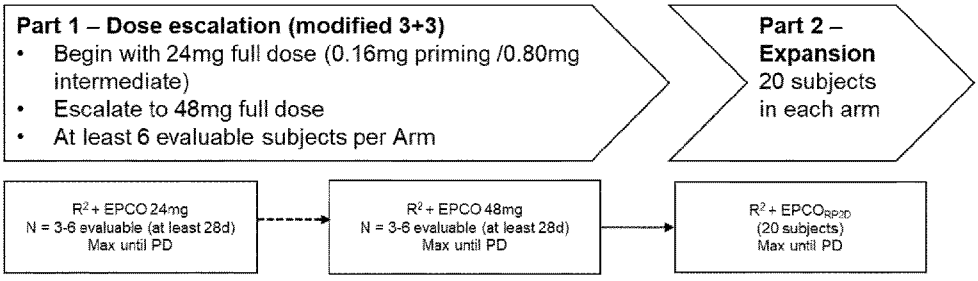

FIG. 3

(57) **Abstract:** Provided are methods of clinical treatment of follicular lymphoma (for example, relapsed and/or refractory follicular lymphoma) in human subjects using a bispecific antibody which binds to CD3 and CD20 in combination with standard of care regimens of rituximab and lenalidomide.

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BISPECIFIC ANTIBODY AGAINST CD3 AND CD20 IN COMBINATION THERAPY FOR TREATING FOLLICULAR LYMPHOMA

FIELD

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 regimen of rituximab and lenalidomide for the treatment of follicular lymphoma, for example, relapsed and/or refractory follicular lymphoma. Advantageous treatment regimens are also provided.

BACKGROUND

Follicular lymphoma is an incurable disease characterized by an indolent clinical course with a frequent need for several lines of treatment. Approximately 2 to 3% of patients per year will have histologic transformation to an aggressive lymphoma, frequently diffuse large B-cell lymphoma (DLBCL) (approximately 20% transformation at 5 years and approximately 30% transformation at 10 years). The prognosis after histologic transformation is extremely poor (median OS of 1 to 2 years) (Relander et al., *J Clin Oncol* 2010;28:2902-13; Wagner-Johnston et al., *Blood* 2015;126:851-7).

The most common first-line therapies for advanced follicular lymphoma are R-CHOP or rituximab and bendamustine (BR) (Hiddemann et al., *Blood* 2005;106:3725-32; Rummel et al., *Lancet* 2013;381:1203-10). Treatment of relapsed or refractory (R/R) follicular lymphoma is influenced by previous therapy regimens, duration of remission, and PS. Irrespective of first-line treatment choice (including R-CHOP/obinutuzumab-CHOP, BR), progression of disease at 24 months occurs in 20% of patients and is a robust predictor of poor OS, with only 35% to 50% of patients alive at 5 years. A non-cross-resistant salvage regimen is usually applied in progression of disease at 24 months, and HDT-ASCT is considered for eligible patients (Casulo et al., *Biol Blood Marrow Transplant* 2018;24:1163-71; Jurinovic et al., *Biol Blood Marrow Transplant* 2018;24:1172-9).

Several treatment options are approved for a second or later relapse of follicular lymphoma. The combination of rituximab + lenalidomide (R^2) has demonstrated impressive response rates, but with a 2-year PFS of only 50 to 60% (Leonard et al., *J Clin Oncol* 2019;37:1188-99). Treatment options for patients who have failed several lines of therapy,

including monoclonal anti-CD20 antibodies and alkylating agents, are limited. Although idelalisib is approved for double-refractory cases, it demonstrated a 1-year PFS of only 43% and several toxicities leading to treatment discontinuation (Salles et al., *Haematologica* 2017;e156).

Given the limited efficacy of and response of subjects to currently available treatment options for follicular lymphoma, new treatments for this patient population are highly desired, for example, for those who have relapsed after and/or are refractory to currently available therapies.

SUMMARY

Provided herein are methods of treating human subjects who have follicular lymphoma, for example, relapsed and/or refractory (R/R) follicular lymphoma, by administering a bispecific antibody which binds to CD3 and CD20 in combination with a standard of care regimen of rituximab and lenalidomide, in particular, advantageous clinical treatment regimens.

In one aspect, provided herein is a method of treating follicular lymphoma, for example, R/R follicular lymphoma, in a human subject, the method comprising administering to the subject the combination of epcoritamab with rituximab and lenalidomide, e.g., the method comprising administering to the subject an effective amount of rituximab, lenalidomide, and epcoritamab.

In one aspect, provided herein is a method of treating follicular lymphoma, for example, R/R follicular lymphoma in a human subject, the method comprising administering to the subject a bispecific antibody (e.g. subcutaneously) and an effective amount of rituximab (e.g., intravenously) and lenalidomide (e.g., orally), wherein the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

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

wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, lenalidomide, and the bispecific antibody are administered in 28-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), e.g., for 2.5 28-day cycles. In some embodiments, the bispecific antibody is administered once every two weeks after the weekly administration (biweekly administration), e.g., for six 28-day cycles. In some embodiments, the bispecific antibody is administered once every four weeks after the biweekly administration, e.g., for at least three 28-day cycles, e.g., until disease progression or unacceptable toxicity. 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 28-day cycle once every week (weekly administration), e.g., for one 28-day cycle. In some embodiments, after the weekly administration of rituximab, rituximab is administered once every four weeks, e.g., for four 28-day cycles. In one embodiment, rituximab is administered at a dose of 375 mg/m^2.

In some embodiments, lenalidomide is administered once a day from day 1 to day 21 of the 28-day cycles, e.g., from cycle 1 to cycle 12 of the 28-day cycles. In some embodiments, lenalidomide is administered at a dose of 15 mg in cycle 1 of the 28-day cycles. In some embodiments, lenalidomide is administered at a dose of 20 mg in cycle 2 to cycle 12 of the 28-day cycles.

In some embodiments, rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2-5), e.g., as shown in **Table 2**.

In some embodiments, administration is performed in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

In some embodiments, administration is performed in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

In some embodiments, administration is performed in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

In some embodiments, administration is performed in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

In some embodiments, the bispecific antibody is administered subcutaneously. In some embodiments, rituximab is administered intravenously. In some embodiments, lenalidomide is administered orally.

In some embodiments, the bispecific antibody, rituximab, and lenalidomide are administered sequentially. For example, if administered on the same day, (a) rituximab is administered before the bispecific antibody (e.g., days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2-5); (b) lenalidomide is administered before the bispecific antibody (e.g., days 1, 8, 15, and 22 of cycles 1-3, days 1 and 15 of cycles 4-9, and day 1 of cycles 10-12); (c) rituximab is administered before lenalidomide (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5); or (d) rituximab is administered first, lenalidomide is administered second, and the bispecific antibody is administered last (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5). In some embodiments, if administered on the same day, (a) rituximab is administered before the bispecific antibody (e.g., days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2-5); (b) lenalidomide is administered before the bispecific antibody (e.g., days 1, 8, 15, and 22 of cycles 1-3, days 1 and 15 of cycles 4-9, and day 1 of cycles 10-12); (c) lenalidomide is administered before rituximab (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5); or (d) lenalidomide is administered first, rituximab is administered second, and the bispecific antibody is administered last (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5).

In some embodiments, the subject has R/R follicular lymphoma. In some embodiments, the subject has grade 1, 2, or 3a R/R follicular lymphoma. In some embodiments, the subject has Stage II, III, or IV R/R follicular lymphoma. In some embodiments, the subject has been previously treated with at least one prior anti-neoplastic agent, e.g., an anti-CD20 antibody.

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., prednisolone at a dose of, e.g., 100 mg 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, 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., 560-1000 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 during cycle 1. In some embodiments, the prophylaxis is administered during cycle 2 when the subject experiences CRS greater than grade 1 after the last administration of the bispecific antibody in cycle 1. In some embodiments, the prophylaxis is continued in a subsequent cycle, when in the last administration of the bispecific antibody of the previous cycle, the subject experiences CRS greater than grade 1. In a further embodiment, the premedication is administered during cycle 2. In yet a further embodiment, the premedication is 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 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 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.

In some embodiments, the first antigen-binding region of the bispecific antibody comprises VHCDR1, VHCDR2, and VHCDR3 comprising the amino acid sequences set forth in SEQ ID NOs: 1, 2, and 3, respectively, and VLCDR1, VLCDR2, and VLCDR3 comprising the amino acid sequences set forth in SEQ ID NO: 4, the sequence GTN, and SEQ ID NO: 5, respectively; and the second antigen-binding region comprises VHCDR1, VHCDR2, and VHCDR3 comprising the amino acid sequences set forth in SEQ ID NOs: 8, 9, and 10, respectively, and VLCDR1, VLCDR2, and VLCDR3 comprising the amino acid sequences set forth in SEQ ID NO: 11, the sequence DAS, and SEQ ID NO: 12, respectively. In some embodiments, the first antigen-binding region of the bispecific antibody comprises a VH region comprising the amino acid sequence of SEQ ID NO: 6, and the VL region comprising the amino acid sequence of SEQ ID NO: 7; and the second antigen-binding region comprises a VH region comprising the amino acid sequence of SEQ ID NO: 13, and the VL region comprising the amino acid sequence of SEQ ID NO: 14.

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

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

Figure 1 shows T-cell activation in the presence of lenalidomide. T cells were pre-incubated with assay medium or lenalidomide in the absence or presence of CD3 crosslinking by immobilized anti-CD3 for 3 days (as indicated on the x-axes), after which upregulation of CD69, CD25, PD-1 and LAMP-1 on $CD4^+$ and $CD8^+$ T cells was determined by flow cytometry. Data shown are geomean fluorescence intensities (FI) for four donors (each circle represents one condition for one donor). Pre-incubation conditions are shown on the x-axis.

Figure 2 is a graph showing the effects of lenalidomide on Duobody-CD3xCD20-induced T-cell-mediated cytotoxicity against CD20-expressing Daudi cells. T cells were incubated with (5 or 50 μM) or without lenalidomide in the absence or presence of immobilized anti-CD3 for 3 days. T cells were then used in a cytotoxicity assay with DuoBody-CD3xCD20 or DuoBody-CD3xctrl (containing a CD3 arm and a non-binding control arm) and CD20-expressing Daudi cells as target cells (E:T ratio 2:1). Data shown are average percentages cytotoxicity ± SD of duplicates, normalized to medium control (no antibody, no lenalidomide).

Figure 3 is a schematic of the overall clinical trial design.

Figure 4 is a schematic of the dose escalation design. RP2D = Recommended Phase 2 Dose for specific combination arm.

DETAILED DESCRIPTION

Definitions

The term "immunoglobulin" as used herein refers to a class of structurally related glycoproteins consisting of two pairs of polypeptide chains, one pair of light (L) low molecular weight chains and one pair of heavy (H) chains, all four inter-connected by disulfide bonds. The structure of immunoglobulins has been well characterized (see, e.g., Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). Briefly, each heavy chain typically is comprised of a heavy chain variable region (abbreviated herein as VH or V_H) and a heavy chain constant region (abbreviated herein as CH or C_H). The heavy chain constant region typically is comprised of three domains, CH1, CH2, and CH3. The hinge region is the region between the CH1 and CH2 domains of the heavy chain and is highly flexible. Disulfide bonds in the hinge region are part of the interactions between two heavy chains in an IgG molecule. Each light chain typically is comprised of a light chain variable region (abbreviated herein as VL or V_L) and a light chain constant region (abbreviated herein as CL or C_L). The light chain constant region typically is comprised of one domain, CL. The VH and VL regions may be further subdivided into regions of hypervariability (or hypervariable regions which may be hypervariable in sequence and/or form of structurally defined loops), also termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FRs). Each VH and VL is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 (see also Chothia and Lesk *J Mol Biol* 1987;196:901-17). 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 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 about 30 minutes, at least about 45 minutes, at least about one hour, at least about two hours, at least about four hours, at least about 8 hours, at least about 12 hours, about 24 hours or more, about 48 hours or more, about 3, 4, 5, 6, 7 or more days, etc., or any other relevant functionally-defined period (such as a time sufficient to induce, promote, enhance, and/or modulate a physiological response associated with antibody binding to the antigen and/or time sufficient for the antibody to recruit an effector activity). The variable regions of the heavy and light chains of the immunoglobulin molecule contain a binding domain that interacts with an antigen. The term antibody, unless specified otherwise, also encompasses polyclonal antibodies, monoclonal antibodies (mAbs), antibody-like polypeptides, chimeric antibodies and humanized antibodies

The term "antibody fragment" or "antigen-binding fragment" as used herein refers to a fragment of an immunoglobulin molecule which retains the ability to specifically bind to an antigen, and can be generated by any known technique, such as enzymatic cleavage, peptide synthesis, and recombinant techniques. Examples of antibody fragments include (i) a Fab' or Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains, or a monovalent antibody as described in WO2007059782 (Genmab); (ii) $F(ab')_2$ fragments, bivalent fragments comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting essentially of the VH and CH1 domains; (iv) a Fv fragment consisting essentially of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward

et al., *Nature* 1989;341: 544-46), which consists essentially of a VH domain and also called domain antibodies (Holt et al; *Trends Biotechnol* 2003;21:484-90); (vi) camelid or nanobodies (Revets et al; *Expert Opin Biol Ther* 2005;5:111-24) and (vii) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they may be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain antibodies or single chain Fv (scFv), see, e.g., Bird et al., *Science* 1988;242:423-26 and Huston et al., *PNAS* 1988;85:5879-83). 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 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.

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

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.

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 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 "binding'' as used herein in the context of the binding of an antibody to a predetermined antigen typically refers to binding with an affinity corresponding to a K_D of about 10^{-6} M or less, e.g., 10^{-7} M or less, such as about 10^{-8} M or less, such as about 10^{-9} M or less, about 10^{-10} M or less, or about 10^{-11} M or even less, when determined by, e.g., BioLayer Interferometry (BLI) technology in a Octet HTX instrument using the antibody as the ligand and the antigen as the analyte, and wherein the antibody binds to the predetermined antigen with an affinity corresponding to a K_D that is at least ten-fold lower, such as at least 100-fold lower, for instance at least 1,000-fold lower, such as at least 10,000-fold lower, for instance at least

100,000-fold lower than its K_D of binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely related antigen. The amount with which the K_D of binding is lower is dependent on the K_D of the antibody, so that when the K_D of the antibody is very low, then the amount with which the K_D of binding to the antigen is lower than the K_D of binding to a non-specific antigen may be at least 10,000-fold (i.e., the antibody is highly specific).

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 CD3γ (gamma) chain (human CD3γ chain UniProtKB/Swiss-Prot No P09693, or cynomolgus monkey CD3γ UniProtKB/Swiss-Prot No Q95LI7), a CD3δ (delta) chain (human CD3δ UniProtKB/Swiss-Prot No P04234, or cynomolgus monkey CD3δ UniProtKB/Swiss-Prot No Q95LI8), two CD3ε (epsilon) chains (human CD3ε UniProtKB/Swiss-Prot No P07766, SEQ ID NO: 28); cynomolgus CD3ε UniProtKB/Swiss-Prot No Q95LI5; or rhesus CD3ε UniProtKB/Swiss-Prot No G7NCB9), and a CD3ζ-chain (zeta) chain (human CD3ζ UniProtKB/Swiss-Prot No P20963, cynomolgus monkey CD3ζ 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 CD3ε (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 CD3ε (epsilon), the second heavy and light chain pair comprises a region which binds to human CD20. The first binding region comprises the VH and VL sequences as defined by SEQ ID NOs: 6 and 7, and the second binding region comprises the VH and VL sequences as defined by SEQ ID NOs: 13 and 14. This bispecific antibody can be prepared as described in WO 2016/110576.

Antibodies comprising functional variants of the heavy chain, light chains, VL regions, VH regions, or one or more CDRs of the antibodies of the examples as also provided herein. A functional variant of a heavy chain, a light chain, VL, VH, or CDRs used in the context of an antibody still allows the antibody to retain at least a substantial proportion (at least about 90%, 95% or more) of functional features of the "reference" and/or "parent" antibody, including affinity and/or the specificity/selectivity for particular epitopes of CD20 and/or CD3, Fc inertness and PK parameters such as half-life, Tmax, Cmax. Such functional variants typically retain significant sequence identity to the parent antibody and/or have substantially similar length of heavy and light chains. The percent identity between two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % homology = # of identical positions/total # of positions x 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 “follicular lymphoma” or “FL” as used herein refers to any of several types of non-Hodgkin's lymphoma in which the lymphomatous cells are clustered into nodules or follicles. The term “follicular” is used because the cells tend to grow in a circular, or nodular, pattern in lymph nodes. The malignant cells can be characterized by activation of the Bcl2 oncogene, typically via translocation t(14;18), involving Ig heavy chain gene on chromosome 14 and the Bcl-2 on chromosome 18, and by expression of CD10, CD20, BCL2 and BCL6, but CD5 negative . FL typically has a slow disease course which persists essentially unchanged for years. FL can be classified in accordance with the WHO classification as defined in Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed. 4th). Lyon, France: IARC Press (2008) and 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), which are incorporated herein by reference.

The term “relapsed follicular lymphoma” or “relapsed FL” as used herein refers to follicular lymphoma which progressed after achieving partial (PR) or complete response (CR) to prior treatment with an anti-neoplastic therapy, such as immunochemotherapy containing an anti-CD20 antibody.

The term “refractory follicular lymphoma” or “refractory FL” as used herein refers to follicular lymphoma which was treated with an anti-neoplastic therapy but failed to achieve at least a partial response to the therapy.

The term “R/R follicular lymphoma” or “R/R FL” as used herein, unless specified otherwise, is intended to refer to relapsed and/or refractory follicular lymphoma.

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. 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 the 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 "lenalidomide" as used herein refers to a thalidomide derivative having the chemical formula $C_{13}H_{13}N_3O_3$ and chemical name: 3-(4-Amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione (Chemical Abstracts Service No. 191732-72-6). Lenalidomide is available, e.g., under the brand name Revlimid®. The term "lenalidomide" is also intended to encompass branded and generic versions (generic equivalents) of lenalidomide, 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 follicular lymphoma. Treatment may result in a complete response (CR), partial response (PR), or stable disease (SD), for example, as defined by Lugano criteria and/or LYRIC. Treatment may be continued, for example, up 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 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. For example, dosages as defined herein for the bispecific antibody (e.g., epcoritamab), i.e., 24 mg or 48 mg, administered subcutaneously can be defined as such an "effective amount" or "therapeutically effective amount". A therapeutically effective amount of an antibody may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. In some embodiments, patients treated with the methods described herein will show an improvement in ECOG performance status. A therapeutically effective amount or dosage of a drug includes a "prophylactically effective amount" or a "prophylactically effective dosage", which is any amount of the drug that, when administered alone or in combination with another therapeutic agent to a subject at risk of developing a disease or disorder (e.g., cytokine release syndrome) or of suffering a recurrence of disease, inhibits the development or recurrence of the disease.

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

The term “subject” as used herein refers to a human patient, for example, a human patient with follicular lymphoma. The terms “subject” and “patient” are used interchangeably herein.

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

“Disease progression” or “PD” as used herein refers to a situation in which one or more indices of follicular lymphoma 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 8**.

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.

Follicular lymphoma treatment regimens

Provided herein are methods of treating follicular lymphoma in a human subject using a bispecific antibody which binds to CD3 and CD20 ("anti-CD3xCD20 antibody"), e.g., an isolated anti-CD3xCD20 antibody which binds to human CD3 and human CD20, in combination with standard of care regimens of rituximab and lenalidomide. The methods are also useful for treating, e.g., relapsed and/or refractory follicular lymphoma (R/R follicular lymphoma). It is understood that the methods of treating follicular lymphoma (e.g., R/R follicular lymphoma) with a bispecific antibody which binds to both CD3 and CD20 described herein also encompass corresponding uses of the bispecific antibody for treating follicular lymphoma (e.g., R/R follicular lymphoma) in a human subject.

Accordingly, in one aspect, provided herein is a method of treating follicular lymphoma in a human subject, the method comprising administering a bispecific antibody and an effective

amount of rituximab (e.g., intravenously) and lenalidomide (e.g., orally), wherein the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

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

wherein the bispecific antibody is administered at a dose of (or a dose of about) 24 mg or 48 mg, and wherein rituximab, lenalidomide, and the bispecific antibody are administered in 28-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 28-day cycles. In one embodiment, the weekly administration of 24 or 48 mg is performed for 2.5 28-day cycles (i.e., 10 times). In one embodiment, the weekly dose of 24 mg or 48 mg is administered for 2.5 28-day cycles, on days 15 and 22 of cycle 1, and days 1, 8, 15, and 22 of cycles 2 and 3. In one embodiment, after the weekly administration, one may reduce the interval of administrating the bispecific antibody to once every two weeks (biweekly administration). In one embodiment, the biweekly administration is performed for six 28-day cycles. In some embodiments, after the biweekly administration, one may reduce the interval of administration to once every four weeks. In one embodiment, the administration once every four weeks may be performed for an extended period, for example, for at least 1 cycle, at least 2 cycles, at least 3 cycles, at least 4 cycles, at least 5 cycles, at least 6 cycles, at least 7 cycles, at least 8 cycles, at least 9 cycles, at least 10 cycles, at least 15 cycles, at least 20 cycles, or between 1-20 cycles, 1-15 cycles, 1-10 cycles, 1-5 cycles, 5-20 cycles, 5-15 cycles, or 5-10 cycles of the 28-day cycles. In a preferred embodiment, the administration once every four weeks is performed for at least three 28-day cycles. In one embodiment, the bispecific antibody is administered as monotherapy (i.e., without rituximab and lenalidomide) from cycle 13 of the 28-day cycles. In some embodiments, the bispecific antibody is administered as monotherapy from cycle 13 until disease progression (e.g., as defined by the Lugano criteria or LYRIC).

In one embodiment, the weekly dose of the bispecific antibody is administered in 28-day cycles on cycles 1-3 (which may include priming and intermediate doses, as described below), the biweekly dose of the bispecific antibody is administered on cycles 4-9, and the dose once every four weeks is administered from cycle 10 onwards, for example, on cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles, e.g., until disease progression or unacceptable toxicity is observed in the subject.

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, biweekly dose, and/or the dose every four weeks is administered is at the same level. Accordingly, when a dose of 48 mg is selected, preferably, at each weekly administration, at each biweekly administration, 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 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 cycle 1 of the 28-day cycles. In one embodiment, the priming dose is administered two weeks prior to administering the first weekly dose of 24 mg or 48 mg in cycle 1. In one embodiment, the priming dose is 0.16 mg (or about 0.16 mg) of the full-length bispecific antibody.

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

The methods described herein involve treating human subjects who have follicular lymphoma (e.g., R/R follicular lymphoma) with a bispecific antibody which binds to CD3 and CD20 in combination with a standard-of-care regimen of rituximab and lenalidomide.

In some embodiments, rituximab and lenalidomide are administered at standard-of-care dosages, e.g., as supported by clinical studies, according to local guidelines, and/or according to relevant local labels.

In some embodiments, rituximab is administered according to the product label or summary of product characteristics (see, e.g., RITUXAN® (rituximab) 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, lenalidomide is administered according to the product label or summary of product characteristics (see, e.g., REVLIMID® prescribing information, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/021880s034lbl.pdf).

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

In one embodiment, rituximab is administered once every week (weekly administration; QW) in 28-day cycles. In one embodiment, the weekly administration of rituximab is performed for one 28-day cycle (i.e., 4 times). In one embodiment, after the weekly administration of rituximab, rituximab is administered once every four weeks (Q4W) in 28-day cycles. In a further embodiment, administration of rituximab once every four weeks is performed for four 28-day cycles (i.e., 4 times).In one embodiment, lenalidomide is administered according to local guidelines and local labels. In some embodiments, lenalidomide is administered at a dose of (or a dose of about) 15 mg or 20 mg. In one embodiment, lenalidomide is administered at a dose of (or a dose of about) 15 mg. In one embodiment, lenalidomide is administered at a dose of (or a dose of about) 20 mg. In one embodiment, lenalidomide is administered as an oral dose. In one embodiment, lenalidomide is administered as a capsule for oral administration.

In one embodiment, lenalidomide is administered for 21 consecutive days (i.e., days 1-21) in 28-day cycles i.e. once a day from day 1 to day 21 of the 28-day cycles. In one embodiment, lenalidomide is administered for 12 28-day cycles (i.e., on days 1-21 of cycles 1-12 of the 28-day cycles). In one embodiment, lenalidomide is administered on days 1-21 of cycle 1 of the 28-day cycles at a dose of (or a dose of about) 15 mg. In one embodiment, lenalidomide is administered on days 1-21 of cycles 2-12 of the 28-day cycles at a dose of (or a dose of about) 20 mg. In a preferred embodiment, lenalidomide is administered on days 1-21 of cycle 1 of the 28-day cycles at a dose of (or a dose of about) 15 mg, and at a dose of (or a dose of about) 20 mg on days 1-21 of cycles 2-12 of the 28-day cycles.

In one embodiment, the dose of lenalidomide is reduced when a subject presents with lenalidomide-related toxicity (hematologic or non-hematologic) during a treatment cycle in accordance with standard of care guidelines, for example, as specified in the product label. In

some embodiments, the dose of lenalidomide is re-escalated up to the next higher dose level (up to the starting dose, e.g., 20 mg/day) if continued rituximab + lenalidomide therapy results in improved bone marrow function (i.e., the subject no longer presents with the hematologic toxicity and/or non-hematologic toxicity for at least 2 consecutive cycles and the subject has ANC $\geq 1.5 \times 10^9$/L with a platelet count $\geq 100 \times 10^9$/L at the beginning of a new cycle at the current dose level).

In certain embodiments, the bispecific antibody, rituximab, and/or lenalidomide are administered simultaneously. In some embodiments, rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2-5).

In some embodiments, the bispecific antibody, rituximab, and/or lenalidomide are administered sequentially. For instance, in one embodiment, rituximab is administered before the bispecific antibody if rituximab or the biosimilar thereof and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycle 1 of the 28-day cycles, and day 1 of cycles 2-5 of the 28-day cycles). In some embodiments, lenalidomide is administered before the bispecific antibody if lenalidomide and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycles 1-3 of the 28-day cycles, days 1 and 15 of cycles 4-9 of the 28-day cycles, and day 1 of cycles 10-12 of the 28-day cycles). In some embodiments, rituximab is administered before lenalidomide if rituximab and lenalidomide are administered on the same day (e.g., days 1, 8, and 15 of cycle 1 of the 28-day cycles, and day 1 of cycles 2-5 of the 28-day cycles). In a further embodiment, rituximab is administered first, lenalidomide is administered second, and the bispecific antibody is administered last if rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., days 1, 8, and 15 of cycle 1 of the 28-day cycles, and days 1-5 of cycles 2-5 of the 28-day cycles). In some embodiments, if administered on the same day, (a) rituximab is administered before the bispecific antibody (e.g., days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2-5); (b) lenalidomide is administered before the bispecific antibody (e.g., days 1, 8, 15, and 22 of cycles 1-3, days 1 and 15 of cycles 4-9, and day 1 of cycles 10-12); (c) lenalidomide is administered before rituximab (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5); or (d) lenalidomide is administered first, rituximab is administered second, and the bispecific antibody is administered last (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5).

In some embodiments, the subject is administered premedication and/or prophylaxis for CRS prior to administration of rituximab, lenalidomide, and the bispecific antibody.

In some embodiments, rituximab (e.g., intravenous), lenalidomide (e.g., oral), and the bispecific antibody (e.g., subcutaneous) are administered in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles (e.g., in cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles), a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

In one embodiment, rituximab (e.g., intravenous), lenalidomide (e.g., oral), and the bispecific antibody (e.g., subcutaneous) are administered in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles (e.g., in cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles), a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

In some embodiments, rituximab (e.g., intravenous), lenalidomide (e.g., oral), and the bispecific antibody epcoritamab (e.g., subcutaneous) are administered in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles (e.g., in cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles), a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

In some embodiments, rituximab (e.g., intravenous), lenalidomide (e.g., oral), and the bispecific antibody epcoritamab (e.g., subcutaneous) are administered in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles (e.g., in cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles), a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

In one embodiment, rituximab (e.g., intravenous), lenalidomide (e.g., oral), and the bispecific antibody (e.g., subcutaneous) are administered in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles (e.g., in cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles), a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5 at a dose of 375 mg/m2 or equivalent thereof; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12 at a dose of 15 mg in cycle 1 and at a dose of 20 mg in cycle 2-12.

In one embodiment, rituximab (e.g., intravenous), lenalidomide (e.g., oral), and the bispecific antibody (e.g., subcutaneous) are administered in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles (e.g., in cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles), a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5 at a dose of 375 mg/m2 or equivalent thereof; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12 at a dose of 15 mg in cycle 1 and at a dose of 20 mg in cycle 2-12.

In one embodiment, rituximab (e.g., intravenous), lenalidomide (e.g., oral), and the bispecific antibody epcoritamab (e.g., subcutaneous) are administered in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles (e.g., in cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles), a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5 at a dose of 375 mg/m2 or equivalent thereof; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12 at a dose of 15 mg in cycle 1 and at a dose of 20 mg in cycle 2-12.

In one embodiment, rituximab (e.g., intravenous), lenalidomide (e.g., oral), and the bispecific antibody epcoritamab (e.g., subcutaneous) are administered in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles (e.g., in cycles 10-15, cycles 10-20, cycles 10-25, cycles 10-30, or more cycles), a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5 at a dose of 375 mg/m2 or equivalent thereof; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12 at a dose of 15 mg in cycle 1 and at a dose of 20 mg in cycle 2-12.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 some embodiments, the subject undergoing the treatment with the methods described herein has histologically confirmed CD20+ follicular lymphoma.

In some embodiments, the subject has relapsed and/or refractory follicular lymphoma. In some embodiments, the subject has Grade 1, 2, or 3a relapsed and/or refractory follicular lymphoma. In some embodiments, the subject has relapsed and/or refractory follicular lymphoma of Stage II, III, or IV.

In another treatment, the subject has received at least one line of treatment prior to being treated with the methods described herein. For instance, in one embodiment, the subject has been previously treated with at least one prior anti-neoplastic agent prior to being treated with

the methods described herein. In some embodiments, the anti-neoplastic agent comprises an anti-CD20 antibody.

In some embodiments, 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 some embodiments, 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 ≥1.0 × 10^9/L, (b) platelet count >75 x 10^9/L, or ≥50 x 10^9/L if bone marrow infiltration or splenomegaly, (c) ALT level ≤2.5 times the ULN, (d) total bilirubin level ≤2 × ULN, (e) eGFR >50 mL/min (by Cockcroft-Gault Formula), and (f) PT, INR, and aPTT ≤ 1.5 x ULN (unless receiving anticoagulant).

In some embodiments, the subject does not have severe allergic or anaphylactic reactions to anti-CD20 antibody therapy or known allergy or intolerance to any component or excipient of the bispecific antibody.

In some embodiments, 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 >470msec.

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 follicular lymphoma, such as relapsed and/or refractory follicular lymphoma. 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 follicular lymphoma 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 8**.

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.

Subjects treated according to the methods described herein preferably experience improvement in at least one sign of follicular lymphoma. 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 or LYRIC (see, e.g., **Table 8**). 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 day as well. . In some embodiments, the prophylaxix (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. An exemplary corticosteroid suitable for use in the methods and uses described herein is prednisolone. Thus, in preferred embodiments, the corticosteroid is prednisone. In some embodiments, prednisolone is administered at an intravenous dose of 100 mg, or an equivalent thereof, including an oral dose. Exemplary corticosteroid equivalents of prednisolone, along with dosage equivalents, which can be used for CRS prophylaxis are shown in **Table 5**.

Furthermore, in some embodiments, human subjects in the methods described herein are treated with premedication to reduce reactions to injections. In one embodiment, the premedication includes the administration of antihistamines. In some embodiments, the

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

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 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 can be administered as described herein, during the first 28 day cycle of the bispecific antibody administration. In some embodiments, the premedication is administered during said first cycle.

Usually, risk of reactions during the initial treatment subsides after a few administrations, e.g., after the first four administrations (first 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 administered during the second 28-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 1. 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 prednisolone (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 optionally day 4, further prophylaxis is administered comprising the systemic administration of a corticosteroid such as prednisolone (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 28-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.

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

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 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 symptoms are treated with NSAIDs.

In some embodiments, subjects who develop Grade 2 CRS are treated with intravenous fluid boluses and/or supplemental oxygen. In some embodiments, subjects who develop Grade 2 CRS are treated with a vasopressor (e.g., norepinephrine). In some 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 some embodiments, subjects with Grade 2 CRS are treated with tocilizumab and and/or a steroid In some embodiment, the steroid is dexamethasone. In some embodiments, 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 embodiment, subjects with Grade 3 CRS are treated with tocilizumab. In some embodiments, 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 some embodiments, subjects who develop Grade 4 CRS are administered at least two vasopressors. In some embodiments, 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 some embodiments, the prophylactic treatment of TLS comprises administering allopurinol. In some embodiments, the prophylactic treatment of TLS comprises administering allopurinol and allopurinol prior to administering the bispecific antibody. In another embodiment, 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. 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, such as polysorbate 80, and having a pH of 5.3-5.6. In another embodiment, 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.

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

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

In one embodiment, lenalidomide is formulated in a pharmaceutical composition comprising pharmaceutically-acceptable excipients suitable for administration (e.g., oral administration), e.g., in accordance with local standard-of-care practice, e.g., as specified by local guidelines or local product labels. In some embodiments, lenalidomide is formulated in an oral dosage form, e.g., a capsule. In some embodiments, lenalidomide is formulated as a capsule comprising lenalidomide, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium searate.

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 CD3ε (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences within the amino acid sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences within the amino acid sequence of SEQ ID NO: 7; and

(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 some embodiments, the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises 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 some embodiments, the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a VH region comprising 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 CD3xCD20.

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

(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 CD3ε (epsilon) and comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 24, and a light chain comprising the amino acid sequence of SEQ ID NO: 25; and

(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 CD3ε (epsilon) and comprises a heavy chain comprising an amino acid sequence which is at least 85%, 90%, 95%, 98%, or 99% identical to SEQ ID NO: 24 or a heavy chain comprising the amino acid sequence of SEQ ID NO: 24, but with 1, 2, or 3 mutations (e.g., amino acid substitutions), and a light chain comprising an amino acid sequence which is at least 85%, 90%, 95%, 98%, or 99% identical to SEQ ID NO: 25 or a light

chain region comprising the amino acid sequence of SEQ ID NO: 25, but with 1, 2, or 3 mutations (e.g., amino acid substitutions); and

(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 some embodiments, the bispecific antibody is a full-length antibody with a human IgG1 constant region. 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. In one embodiment, the first binding arm of the bispecific antibody is derived from a humanized antibody, e.g., from a full-length IgG1,λ (lambda) antibody, and thus comprises a λ light chain constant region. In some embodiments, the first binding arm comprises a λ light chain constant region as defined in SEQ ID NO: 22. In some embodiments, the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody. In some embodiments, the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody, and thus may comprise a κ light chain constant region. In some embodiments, the second binding arm comprises a κ light chain constant region as defined in SEQ ID NO: 23. 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, Fcγ receptor-dependent CD3 crosslinking), by binding to Fcγ receptors, by binding to C1q, or by induction of Fc-mediated cross-linking of FcγRs. In particular, the heavy chain constant region sequence may be modified so that Fc-mediated CD69 expression is reduced by at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 99% or 100% when compared to a wild-type (unmodified) antibody, wherein said Fc-mediated CD69 expression is determined in a PBMC-based functional

assay, e.g. as described in Example 3 of WO2015001085. Modifications of the heavy and light chain constant region sequences may also result in reduced binding of C1q to said antibody. As compared to an unmodified antibody, the reduction may be by at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or 100%, and C1q binding may be determined, e.g., by ELISA. Further, the Fc region which may be modified so that the antibody mediates reduced Fc-mediated T-cell proliferation compared to an unmodified antibody by at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 99% or 100%, wherein said T-cell proliferation is measured in a PBMC-based functional assay. Examples of amino acid positions that may be modified, e.g., in an IgG1 isotype antibody, include positions L234 and L235. Thus, in one embodiment, the bispecific antibody may comprises a first heavy chain and a second heavy chain, and wherein in both the first heavy chain and the second heavy chain, the amino acid residues at the positions corresponding to positions L234 and L235 in a human IgG1 heavy chain according to Eu numbering are F and E, respectively. In addition, a D265A amino acid substitution can decrease binding to all Fcγ receptors and prevent ADCC (Shields et al., *JBC* 2001;276:6591-604). Therefore, the bispecific antibody may comprise a first heavy chain and a second heavy chain, wherein in both the first heavy chain and the second heavy chain, the amino acid residue at the position corresponding to position D265 in a human IgG1 heavy chain according to Eu numbering is A.

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 some embodiments, 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 some embodiments, 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.

With regards 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 identified herein as SEQ ID NO: 15. Consistent with the embodiments disclosed above, the bispecific antibody may comprise an IgG1 heavy chain constant region carrying the F405L substitution and may have the amino acid sequence set forth in SEQ ID NO: 17 and/or an IgG1 heavy chain constant region carrying the K409R substitution and may have the amino acid sequence set forth in SEQ ID NO: 18, and have further substitutions that render the Fc region inert or non-activating. Hence, in one embodiment, the bispecific antibody comprises a combination of IgG1 heavy chain constant regions, with the amino acid sequence of one of the IgG1 heavy chain constant regions carrying the L234F, L235E, D265A and F405L substitutions (e.g., as set forth in SEQ ID NO: 19) and the amino acid sequence of the other IgG1 heavy chain constant region carrying the L234F, L235E, D265A and K409R substitutions (e.g., as set forth in SEQ ID NO: 20). Thus, in some embodiments, 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 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 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) and/or lenalidomide (e.g., for 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 follicular lymphoma. 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 and/or lenalidomide in accordance with a standard of practice 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 CD3ε (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

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

for use in the treatment of follicular lymphoma in a human subject, wherein the treatment comprises administering the bispecific antibody and an effective amount of rituximab and lenalidomide 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, and lenalidomide are administered in 28-day cycles.

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

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

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

5. The bispecific antibody according to embodiment 4, wherein the weekly administration of 24 mg or 48 mg is performed for 2.5 28-day cycles.

6. The bispecific antibody according to any one of embodiment 4 or 5, wherein after the weekly administration, the bispecific antibody is administered once every two weeks (biweekly administration).

7. The bispecific antibody according to embodiment 6, wherein the biweekly administration is performed for six 28 day cycles.

8. The bispecific antibody according to embodiment 6 or 7, wherein after the biweekly administration, the bispecific antibody is administered once every four weeks.

9. The bispecific antibody according to embodiment 8, wherein the administration once every four weeks is performed for at least three 28-day cycles.

10. The bispecific antibody according to 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 28-day cycles.

11. The bispecific antibody according to 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 according to embodiment 10 or 11, wherein the priming dose is 0.16 mg.

13. The bispecific antibody according to 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 according to 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 days 15 and 22 of cycle 1.

15. The bispecific antibody according to embodiment 13 or 14, wherein the intermediate dose is 0.8 mg.

16. The bispecific antibody according to any one of embodiments 1-15, wherein rituximab is administered once every week (weekly administration).

17. The bispecific antibody according to embodiment 16, wherein the weekly administration of rituximab is performed for one 28-day cycle.

18. The bispecific antibody according to embodiment 16 or 17, where after the weekly administration, rituximab is administered once every four weeks.

19. The bispecific antibody according to embodiment 18, wherein the administration of rituximab once every four weeks is performed for four 28-day cycles.

20. The bispecific antibody according to any one of embodiments 1-19, wherein rituximab is administered at a dose of 375 mg/m^2 or equivalent thereof.

21. The bispecific antibody according to any one of embodiments 1-20, wherein lenalidomide is administered once a day from day 1 to day 21 of the 28-day cycles.

22. The bispecific antibody according to any one of embodiments 1-21, wherein lenalidomide is administered from cycle 1 to cycle 12 of the 28-day cycles.

23. The bispecific antibody according to any one of embodiments 1-22, wherein lenalidomide is administered at a dose of 15 mg in cycle 1 of the 28-day cycles.

24. The bispecific antibody according to any one of embodiments 1-23, wherein lenalidomide is administered at a dose of 20 mg in cycle 2 to cycle 12 of the 28-day cycles.

25. The bispecific antibody according to any one of embodiments 1-24, wherein rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2-5).

26. The bispecific antibody according to any one of embodiments 1-25, wherein the dosing schedule for the bispecific antibody, rituximab, and lenalidomide is as shown in **Table 2**.

27. The bispecific antibody according to embodiments 1, 2, and 4-26, wherein administration is performed in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

28. The bispecific antibody according to any one of embodiments 1 and 3-27, wherein administration is performed in 28-day cycles, and wherein:

(a) 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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

29. The bispecific antibody according to any one of embodiments 1-28, wherein the bispecific antibody is administered subcutaneously.

30. The bispecific antibody according to any one of embodiments 1-29, wherein rituximab is administered intravenously.

31. The bispecific antibody according to embodiments 1-30, wherein lenalidomide is administered orally.

32. The bispecific antibody according to any one of embodiments 1-31, wherein the bispecific antibody, rituximab, and lenalidomide are administered sequentially.

33. The bispecific antibody according to any one of embodiments 1-32, wherein:

(a) rituximab is administered before the bispecific antibody if rituximab and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2-5);

(b) lenalidomide is administered before the bispecific antibody if lenalidomide and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycles 1-3, days 1 and 15 of cycles 4-9, and day 1 of cycles 10-12);

(c) rituximab is administered before lenalidomide if rituximab and lenalidomide are administered on the same day (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5); or

(d) rituximab is administered first, lenalidomide is administered second, and the bispecific antibody is administered last if rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., days 1, 8, and 15 of cycle 1, and days 1-5 of cycles 2-5).

34. The bispecific antibody according to any one of embodiments 1-33, wherein the follicular lymphoma is relapsed and/or refractory follicular lymphoma.

35. The bispecific antibody according to any one of embodiment 34, wherein the subject has grade 1, 2, or 3a relapsed and/or refractory follicular lymphoma.

36. The bispecific antibody according to embodiment 34 or 35, wherein the subject has Stage II, III, or IV relapsed and/or refractory follicular lymphoma.

37. The bispecific antibody according to any one of embodiments 1-36, wherein the subject has been previously treated with at least one prior anti-neoplastic agent.

38. The bispecific antibody according to embodiment 37, wherein the at least one prior anti-neoplastic agent comprises an anti-CD20 antibody.

39. The bispecific antibody according to any one of embodiments 1-38, wherein the subject is treated with prophylaxis for cytokine release syndrome.

40. The bispecific antibody according to embodiment 39, wherein the prophylaxis comprises administering a corticosteroid to the subject.

41. The bispecific antibody according to embodiment 40, wherein the corticosteroid is administered on the same day as the bispecific antibody.

42. The bispecific antibody according to embodiment 41, wherein the corticosteroid is further administered on the second, third, and fourth days after administering the bispecific antibody.

43. The bispecific antibody according to any one of embodiments 40-42, wherein the corticosteroid is prednisolone.

44. The bispecific antibody according to embodiment 43, wherein the prednisolone is administered at an intravenous dose of 100 mg, or equivalent thereof, including oral dose.

45. The bispecific antibody according to any one of embodiments 1-44, wherein the subject is administered premedication to reduce reactions to injections.

46. The bispecific antibody according to embodiment 45, wherein the premedication comprises an antihistamine.

47. The bispecific antibody according to embodiment 46, wherein the antihistamine is diphenhydramine.

48. The bispecific antibody according to embodiment 47, wherein the diphenhydramine is administered at an intravenous or oral dose of 50 mg, or equivalent thereof.

49. The bispecific antibody according to any one of embodiments 45-48, wherein the premedication comprises an antipyretic.

50. The bispecific antibody according to embodiment 49, wherein the antipyretic is acetaminophen.

51. The bispecific antibody according to embodiment 50, wherein the acetaminophen is administered at an oral dose of 650 mg to 1000 mg, or equivalent thereof.

52. The bispecific antibody according to any one of embodiments 45-51, wherein the premedication is administered on the same day as the bispecific antibody.

53. The bispecific antibody according to any one of embodiments 39-52, wherein the prophylaxis is administered in cycle 1 of the 28-day cycles.

54. The bispecific antibody according to any one of embodiments 45-53, wherein the premedication is administered in cycle 1 of the 28-day cycles.

55. The bispecific antibody according to any one of embodiments 39-54, wherein the prophylaxis is administered during cycle 2 of the 28-day cycles when the subject experiences CRS greater than grade 1 after the last administration of the bispecific antibody in cycle 1 of the 28-day cycles.

56. The bispecific antibody according to embodiment 55, 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.

57. The bispecific antibody according to any one of embodiments 45-56, wherein the premedication is administered during cycle 2 of the 28-day cycles.

58. The bispecific antibody according to embodiment 57, wherein the premedication is administered during subsequent cycles.

59. The bispecific antibody according to any one of embodiments 1-58, wherein the subject is administered antibiotics if the subject develops Grade 1 CRS.

60. The bispecific antibody according to any one of embodiments 1-58, wherein the subject is administered a vasopressor if the subject develops Grade 2 or Grade 3 CRS.

61. The bispecific antibody according to any one of embodiments 1-58, wherein the subject is administered at least two vasopressors if the subject develops Grade 4 CRS.

62. The bispecific antibody according to any one of embodiments 1-61, wherein the subject is administered tocilizumab if the subject develops Grade 2, Grade 3, or Grade 4 CRS.

63. The bispecific antibody according to embodiment 62, wherein the subject is further administered a steroid.

64. The bispecific antibody according to embodiment 63, wherein the steroid is dexamethasone.

65. The bispecific antibody according to embodiment 63, wherein the steroid is methylprednisolone.

66. The bispecific antibody according to any one of embodiments 62-65, wherein tocilizumab is switched to an anti-IL-6 antibody (e.g., siltuximab) if the subject is refractory to tocilizumab.

67. The bispecific antibody according to any one of embodiments 62-65, wherein tocilizumab is switched to an IL-1R antagonist (e.g., anakinra) if the subject is refractory to tocilizumab.

68. The bispecific antibody according to any one of embodiments 1-67, wherein the subject is treated with prophylaxis for tumor lysis syndrome (TLS).

69. The bispecific antibody according to embodiment 68, wherein the prophylaxis for TLS comprises administering one or more uric acid reducing agents prior to administration of the bispecific antibody.

70. The bispecific antibody according to embodiment 69, wherein the one or more uric acid reducing agents comprise rasburicase and/or allopurinol.

71. The bispecific antibody according to any one of embodiments 1-70, wherein the subject achieves a complete response, a partial response, or stable disease.

72. The bispecific antibody according to any one of embodiments 1-71, 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.

73. The bispecific antibody according to any one of embodiments 1-72, 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.

74. The bispecific antibody according to any one of embodiments 1-73, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1,λ (lambda) antibody.

75. The bispecific antibody according to embodiment 74, 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.

76. The bispecific antibody according to any one of embodiments 1-75, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody.

77. The bispecific antibody according to embodiment 76, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

78. The bispecific antibody according to any one of embodiments 1-77, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

79. The bispecific antibody according to embodiments 1-78, wherein the bispecific antibody comprises an inert Fc region.

80. The bispecific antibody according to any one of embodiments 1-79, 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.

81. The bispecific antibody according to any one of embodiments 1-80, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein in the first heavy chain,

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

82. The bispecific antibody according to any one of embodiments 1-81, 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.

83. The bispecific antibody according to embodiment 82, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

84. The bispecific antibody according to any one of embodiments 1-83, 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.

85. The bispecific antibody according to any one of embodiments 1-84, 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.

86. The bispecific antibody according to any one of embodiments 1-85, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.

1a. A method of treating follicular lymphoma in a human subject, the method comprising administering to the subject a bispecific antibody an effective amount of rituximab and lenalidomide, wherein the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

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

wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, lenalidomide, and the bispecific antibody are administered in 28-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 2.5 28-day cycles.

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

7a. The method of embodiment 6a, wherein the biweekly administration is performed for six 28 day cycles.

8a. The method of embodiment 6a or 7a, wherein after the biweekly administration, the bispecific antibody is administered once every four weeks.

9a. The method of embodiment 8, wherein the administration once every four weeks is performed for at least three 28-day cycles.

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 28-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 days 15 and 22 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 week (weekly administration).

17a. The method of embodiment 16a, wherein the weekly administration of rituximab is performed for one 28-day cycle.

18a. The method of embodiment 16a or 17a, where after the weekly administration, rituximab is administered once every four weeks.

19a. The method of embodiment 18a, wherein the administration of rituximab once every four weeks is performed for four 28-day cycles.

20a. The method of any one of embodiments 1a-19a, wherein rituximab is administered at a dose of 375 mg/m^2 or equivalent thereof.

21a. The method of any one of embodiments 1a-20a, wherein lenalidomide is administered once a day from day 1 to day 21 of the 28-day cycles.

22a. The method of any one of embodiments 1a-21a, wherein lenalidomide is administered from cycle 1 to cycle 12 of the 28-day cycles.

23a. The method of any one of embodiments 1a-22a, wherein lenalidomide is administered at a dose of 15 mg in cycle 1 of the 28-day cycles.

24a. The method of any one of embodiments 1a-23a, wherein lenalidomide is administered at a dose of 20 mg in cycle 2 to cycle 12 of the 28-day cycles.

25a. The method of any one of embodiments 1a-24a, wherein rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2-5).

26a. The method of any one of embodiments 1a-25a, wherein the dosing schedule for the bispecific antibody, rituximab, and lenalidomide is as shown in **Table 2**.

27a. The method of any one of embodiments 1a, 2a, and 4a-26a, wherein administration is performed in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

28a. The method of any one of embodiments 1a and 3a-27a, wherein administration is performed in 28-day cycles, and wherein:

(a) 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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

29a. The method of any one of embodiments 1a-28a, wherein the bispecific antibody is administered subcutaneously.

30a. The method of any one of embodiments 1a-29a, wherein rituximab is administered intravenously.

31a. The method of any one of embodiments 1a-30a, wherein lenalidomide is administered orally.

32a. The method of any one of embodiments 1a-31a, wherein the bispecific antibody, rituximab, and lenalidomide are administered sequentially.

33a. The method of any one of embodiments 1a-32a, wherein:

(a) rituximab is administered before the bispecific antibody if rituximab and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2-5);

(b) lenalidomide is administered before the bispecific antibody if lenalidomide and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycles 1-3, days 1 and 15 of cycles 4-9, and day 1 of cycles 10-12);

(c) rituximab is administered before lenalidomide if rituximab and lenalidomide are administered on the same day (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5); or

(d) rituximab is administered first, lenalidomide is administered second, and the bispecific antibody is administered last if rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., days 1, 8, and 15 of cycle 1, and days 1-5 of cycles 2-5).

34a. The method of any one of embodiments 1a-33a, wherein the follicular lymphoma is relapsed and/or refractory follicular lymphoma.

35a. The method of embodiment 34, wherein the subject has grade 1a, 2a, or 3a relapsed and/or refractory follicular lymphoma.

36a. The method of embodiment 34a or 35a, wherein the subject has Stage II, III, or IV relapsed and/or refractory follicular lymphoma.

37a. The method of any one of embodiments 1a-36a, wherein the subject has been previously treated with at least one prior anti-neoplastic agent.

38a. The method of embodiment 37a, wherein the at least one prior anti-neoplastic agent comprises an anti-CD20 antibody.

39a. The method of any one of embodiments 1a-38a, wherein the subject is treated with prophylaxis for cytokine release syndrome.

40a. The method of embodiment 39a, wherein the prophylaxis comprises administering a corticosteroid to the subject.

41a. The method of embodiment 40a, wherein the corticosteroid is administered on the same day as the bispecific antibody.

42a. The method of embodiment 41a, wherein the corticosteroid is further administered on the second, third, and fourth days after administering the bispecific antibody.

43a. The method of any one of embodiments 40a-42a, wherein the corticosteroid is prednisolone.

44a. The method of embodiment 43a, wherein the prednisolone is administered at an intravenous dose of 100 mg, or equivalent thereof, including oral dose.

45a. The method of any one of embodiments 1a-44a, wherein the subject is administered premedication to reduce reactions to injections.

46a. The method of embodiment 45a, wherein the premedication comprises an antihistamine.

47a. The method of embodiment 46a, wherein the antihistamine is diphenhydramine.

48a. The method of embodiment 47a, wherein the diphenhydramine is administered at an intravenous or oral dose of 50 mg, or equivalent thereof.

49a. The method of any one of embodiments 45a-48a, wherein the premedication comprises an antipyretic.

50a. The method of embodiment 49a, wherein the antipyretic is acetaminophen.

51a. The method of embodiment 50a, wherein the acetaminophen is administered at an oral dose of 650 mg to 1000 mg, or equivalent thereof.

52a. The method of any one of embodiments 45a-51a, wherein the premedication is administered on the same day as the bispecific antibody.

53a. The method of any one of embodiments 39a-52a, wherein the prophylaxis is administered in cycle 1 of the 28-day cycles.

54a. The method of any one of embodiments 45a-53a, wherein the premedication is administered in cycle 1 of the 28-day cycles.

55a. The method of any one of embodiments 39a-54a, wherein the prophylaxis is administered during cycle 2 of the 28-day cycles when the subject experiences CRS greater than grade 1 after the last administration of the bispecific antibody in cycle 1 of the 28-day cycles.

56a. The method of embodiment 55a, 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.

57a. The method of any one of embodiments 45a-56a, wherein the premedication is administered during cycle 2 of the 28-day cycles.

58a. The method of embodiment 57a, wherein the premedication is administered during subsequent cycles.

59a. The method of any one of embodiments 1a-58a, wherein the subject is administered antibiotics if the subject develops Grade 1 CRS.

60a. The method of any one of embodiments 1a-58a, wherein the subject is administered a vasopressor if the subject develops Grade 2 or Grade 3 CRS.

61a. The method of any one of embodiments 1a-58a, wherein the subject is administered at least two vasopressors if the subject develops Grade 4 CRS.

62a. The method of any one of embodiments 1a-61a, wherein the subject is administered tocilizumab if the subject develops Grade 2, Grade 3, or Grade 4 CRS.

63a. The method of embodiment 62a, wherein the subject is further administered a steroid.

64a. The method of embodiment 63a, wherein the steroid is dexamethasone.

65a. The method of embodiment 63a, wherein the steroid is methylprednisolone.

66a. The method of any one of embodiments 62a-65a, wherein tocilizumab is switched to an anti-IL-6 antibody (e.g., siltuximab) if the subject is refractory to tocilizumab.

67a. The method of any one of embodiments 62a-65a, wherein tocilizumab is switched to an IL-1R antagonist (e.g., anakinra) if the subject is refractory to tocilizumab.

68a. The method of any one of embodiments 1a-67a, wherein the subject is treated with prophylaxis for tumor lysis syndrome (TLS).

69a. The method of embodiment 68a, wherein the prophylaxis for TLS comprises administering one or more uric acid reducing agents prior to administration of the bispecific antibody.

70a. The method of embodiment 69a, wherein the one or more uric acid reducing agents comprise rasburicase and/or allopurinol.

71a. The method of any one of embodiments 1a-70a, wherein the subject achieves a complete response, a partial response, or stable disease.

72a. The method of any one of embodiments 1a-71a, 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.

73a. The method of any one of embodiments 1a-72a, 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.

74a. The method of any one of embodiments 1a-73a, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1,λ (lambda) antibody.

75a. The method of embodiment 74a, 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.

76a. The method of any one of embodiments 1a-75a, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody.

77a. The method of embodiment 76a, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

78a. The method of any one of embodiments 1a-77a, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

79a. The method of any one of embodiments 1a-78a, wherein the bispecific antibody comprises an inert Fc region.

80a. The method of any one of embodiments 1a-79a, 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.

81a. The method of any one of embodiments 1a-80a, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein in the first heavy chain, the amino acid in the position corresponding to F405 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 is L, and wherein in the second heavy chain, the amino acid in the position corresponding to K409 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 is R, or vice versa.

82a. The method of any one of embodiments 1a-81a, 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.

83a. The method of embodiment 82a, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

84a. The method of any one of embodiments 1a-83a, 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.

85a. The method of any one of embodiments 1a-84a, 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.

86a. The method of any one of embodiments 1a-85a, wherein the bispecific antibody 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 application are expressly incorporated herein by reference.

EXAMPLES

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

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

Example 1: Anti-tumor activity of epcoritamab in the presence of anti-CD20 antibody in vivo and in NHL patient-derived samples after anti-CD20 treatment

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

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

This experiment was performed to determine the impact of lenalidomide on Duobody-CD3xCD20-induced T-cell activation and T-cell-mediated cytotoxicity.

Briefly, T cells were activated with immobilized anti-CD3 in the presence (5 or 50 μM) or absence of lenalidomide for 3 days. Crosslinking of CD3 on T cells in the presence of lenalidomide led to increased T-cell activation, measured by the upregulation of activation markers CD69, CD25 on the T cell surface, and release of granzyme B and IFNγ, compared to conditions where lenalidomide was not present (see **Figure 1**). T cells that were activated in the presence or absence of lenalidomide were subsequently tested for their cytotoxic capacity in response to epcoritamab. Higher maximum percent cytotoxicity and higher activity at lower epcoritamab concentrations were observed with T cells pre-treated with lenalidomide and anti-CD3 in a typical dose response curve, while none of the controls led to additional target cell lysis (See **Figure 2**).

This indicates that lenalidomide may enhance the T -cell activation by epcoritamab observed in patients, which in turn can lead to more efficient T cell-mediated cytotoxicity against the target cells.

Example 3: A Phase 1b, Open-Label, Safety and Efficacy Study of Epcoritamab in Combination with Standard-of-Care Rituximab and Lenalidomide for the Treatment of Relapsed/Refractory Follicular Lymphoma

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 rituximab and lenalidomide (R^2) in subjects with R/R follicular lymphoma.

Summary of Ongoing Clinical Trial with Epcoritamab

Epcoritamab as monotherapy is currently in a clinical trial for the treatment of 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.

Objectives

Dose escalation

The primary objective of the dose escalation part is to evaluate the safety and tolerability of epcoritamab in combination with R^2 (endpoints: incidence of dose-limiting toxicities (DLTs), incidence and severity of adverse events (AEs), incidence and severity of changes in laboratory values, and incidence of dose interruptions and delays).

Secondary objectives of the dose escalation part include characterizing the PK properties of epcoritamab (endpoints: PK parameters, including clearance, volume of distribution, AUC0-last, AUC0-x, Cmax, Tmax, predose values, and half-life), evaluating pharmacodynamic markers linked to efficacy and the mechanism of action of epcoritamab (endpoints: pharmacodynamic markers in blood samples and within tumor), evaluating immunogenicity (endpoint: incidence of anti-drug antibodies (ADAs) to epcoritamab), and assessing the preliminary anti-tumor activity of epcoritamab in combination with R^2 (endpoints: overall response rate (ORR) by Lugano criteria and LYRIC, duration of response (DOR) by Lugano criteria and LYRIC, time to response (TTR) by Lugano criteria and LYRIC, progression free survival (PFS) by Lugano

criteria and LYRIC, overall survival (OS), time to next anti-lymphoma therapy (TTNT), and rate and duration of minimal residual disease (MRD) negativity).

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

Expansion

The primary objective of the expansion part is to assess the preliminary anti-tumor activity of epcoritamab in combination with R^2 (endpoint: ORR by Lugano criteria).

Secondary objectives of the expansion part include evaluating the preliminary anti-tumor activity of epcoritamab in combination with R^2 (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^2 (endpoints: incidence and severity of changes in laboratory values, and incidence of dose interruptions and delays), characterizing the PK properties of epcoritamab (PK parameters, including clearance, volume of distribution, AUC0-last, AUC0-x, Cmax, Tmax, predose values, and half-life), evaluating pharmacodynamic markers linked to efficacy and mechanism of action of epcoritamab (endpoints: pharmacodynamic markers in blood samples and within tumor), and evaluating immunogenicity (endpoint: incidence of ADAs to epcoritamab).

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

Study Design Overview

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 3**. Both

parts consist of a screening period, a treatment period, a safety follow-up period, and a survival follow-up period.

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

The Part 1 dose escalation assesses the initial safety, tolerability, and clinical activity of epcoritamab in combination with R^2. Epcoritamab is initially be administered in combination with R^2 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^2 is performed in an additional 3 patients as shown in **Figure 4**.

In Part 2, epcoritamab is administered (with the dosing regimen determined in the dose escalation part) in combination with R^2. 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) until disease progression in combination with rituximab (intravenous) and lenalidomide (oral) in 4-week cycles (i.e., 28-day cycles), as follows:

Table 2. Dosing schedule

Cycle number (28-day cycle)	Epcoritamab	Rituximab	Lenalidomide
1	QW, step-up dosing	QW	Days 1-21 (15 mg)
2-3	QW	Q4W	Days 1-21 (20 mg)
4-5	Q2W	Q4W	Days 1-21 (20 mg)
6-9	Q2W	-	Days 1-21 (20 mg)
10-12	Q4W	-	Days 1-21 (20 mg)
14+	Q4W	-	-

QW: once a week (days 1, 8, 15, and 22), Q2W: once every 2 weeks (days 1 and 15) 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 day 22, and full dose in subsequent cycles. Rituximab (375 mg/m^2) is administered intravenously weekly during cycle 1, and once every 4 weeks (Q4W) for cycles 2-6. Lenalidomide is administered at 15 mg orally daily on days 1-21 of cycle 1, and at 20 mg orally daily on days 1-21 of cycles 1-13.

The order of treatments are as follows:

Table 3. Treatment administration order

Dosing order	Treatment	Dose
Pre-Meds	Pre-medications	As described in **Table 4**
1	Rituximab	375 mg/m^2
2	Lenalidomide	15 mg (cycle 1) or 20 mg (cycles 2-12) daily on Days 1-21
3	Epcoritamab	24 mg or 48 mg (as described in **Table 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 ≥1.0 × 10^9/L (growth factor use is allowed)
   b. Platelet count >75 x 10^9/L, or ≥50 x 10^9/L if bone marrow infiltration or splenomegaly
   c. ALT level ≤2.5 times the ULN
   d. Total bilirubin level ≤2 × ULN
   e. eGFR >50 mL/min (by Cockcroft-Gault Formula)
   f. PT, INR, and aPTT ≤ 1.5 x ULN, unless receiving anticoagulant
6. Histologically confirmed CD20+ FL according to the WHO 2016 classification
7. R/R FL, grade 1, 2 or 3a, stage II, III, or IV
8. Previously treated with at least 1 prior anti-neoplastic agent, including anti-CD20 antibody

9. Must have a need for treatment initiation based on symptoms and/or disease burden
10. Eligible to receive R^2

Exclusion criteria

1. FL grade 3b
2. Histologic evidence of transformation to an aggressive lymphoma
3. Contraindication to rituximab or lenalidomide
4. Prior allogeneic HSCT
5. Autologous HSCT within 3 months of the first dose of epcoritamab
6. Unwilling or unable to take aspirin prophylaxis (subjects with low or intermediate risk for thromboembolism) or prophylactic anticoagulant (if high risk for a thromboembolic event)
7. History of severe allergic or anaphylactic reactions to anti-CD20 mAb therapy or known allergy or intolerance to any component or excipient of epcoritamab
8. Prior treatment with a bispecific antibody targeting CD3 and CD20
9. Chemotherapy, radiation therapy, or major surgery within 4 weeks prior to the first dose of epcoritamab
10. Treatment with an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to the first dose of epcoritamab
11. Treatment with CAR-T therapy within 30 days prior to first dose of epcoritamab
12. Cumulative dose of corticosteroids $\geq$ 140 mg of prednisone or the equivalent within 2-week period before the first dose of epcoritamab
13. Vaccination with live vaccines within 28 days prior to the first dose of epcoritamab
14. 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 abnormalities
    b. Screening 12-lead ECG showing a baseline QTcF >470 msec
15. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results

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

17. 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

18. Active positive tests for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

19. History of HIV antibody positivity, or tests positive for HIV at screening

20. Positive test results for HTLV-1

21. Suspected active or latent tuberculosis

22. Past or current malignancy other than inclusion diagnosis, except for:

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

23. Neuropathy >grade 1

24. 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

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

26. Subject who has any condition for which participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

CRS Prophylaxis

Administration of corticosteroids for four days is performed to reduce/prevent the severity of symptoms from potential CRS for each dose of epcoritamab. For administration of epcoritamab in cycle 2 and beyond, CRS prophylaxis with corticosteroids is optional. Corticosteroid administration can 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
- 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 following completion of the DLT period (28 days from first dose of study treatment)

Table 4. Pre-medication and CRS prophylaxis

			Corticosteroids	Antihistamines	Antipyretics
Cycle 1	1st epcoritamab administration (priming dose)	Day 01*	Prednisolone 100 mg IV (or equivalent, including oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 02	Prednisolone 100 mg IV (or equivalent, including oral dose)		
		Day 03	Prednisolone 100 mg IV (or equivalent, including oral dose)		
		Day 04	Prednisolone 100 mg IV (or equivalent, including oral dose)		
	2nd epcoritamab administration (intermediate dose)	Day 08*	Prednisolone 100 mg IV (or equivalent including oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 09	Prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 10	Prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 11	Prednisolone 100 mg IV (or		

			Corticosteroids	Antihistamines	Antipyretics
			equivalent, including oral dose)		
	3rd epcoritamab administration (full dose)	Day 15*	At least prednisolone 100 mg IV (or equivalent including oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 16	At least prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 17	At least prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 18	Prednisolone 100 mg IV (or equivalent, including oral dose)		

			Corticosteroids	Antihistamines	Antipyretics
Cycle 1	4th epcoritamab administration (full dose)	Day 22	At least prednisolone 100 mg IV (or equivalent including oral dose)	Diphenhydramine 50 mg IV or oral (PO) (or equivalent)	Paracetamol (acetaminophen) 650 to 1000 mg PO (or equivalent)
		Day 23	At least prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 24	At least prednisolone 100 mg IV (or equivalent including oral dose)		
		Day 25	Prednisolone 100 mg IV (or equivalent, including oral dose)		
Cycle 2	5th epcoritamab administration (full dose)	Day 29*	If CRS > grade 1 occurs following the 4th epcoritamab administration, 4-day consecutive corticosteroid administration is continued in Cycle 2 until epocoritamab 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^2, the premedication is administered prior to epcoritamab dose and corticosteroid prophylaxis is continued for 3 days following the epcoritamab administration.

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

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

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

1. Fever is defined as temperature ≥38.0°C not attributable to any other cause, with or without constitutional symptoms (eg, myalgia, arthralgia, malaise). In subjects who have CRS receiving antipyretics, anticytokine therapy, and/or corticosteroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. Both systolic blood pressure and mean arterial pressure are acceptable for blood pressure measurement. No specific limits are required, but hypotension should be determined on a case-by-case basis, accounting for age and the subject's individual baseline, i.e., a blood pressure that is below the normal expected for an individual in a given environment.
3. Intubation of a subject without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not by definition grade 4 CRS.

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

Table 7: Grading and Management of Cytokine Release Syndrome

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

* Consider intervening earlier in specific cases. For example, an elderly patient with prolonged fever (> 72 hours) or very high fever (> 40.5°C/104.9°F) may not tolerate the resulting sinus tachycardia as well as a younger patient, so tocilizumab may be indicated.

† Tocilizumab (anti-IL-6R) remains the only first-line anticytokine therapy approved for CRS. If there is no improvement in symptoms within 6 hours, or if the patient starts to deteriorate after initial improvement, a second dose of tocilizumab should be administered along with a dose of corticosteroids. For patients being refractory to tocilizumab (3 administrations), additional anticytokine therapy such as siltuximab (anti-IL-6) or anakinra (anti-IL-1R) may be considered. However, such use is entirely anecdotal and, as such, is entirely at the discretion of the treating physician.

‡ Consider dexamethasone over methylprednisolone due to improved CNS penetration even in absence of neurotoxicity, as high-grade CRS is correlated with risk of concurrent or subsequent ICANS. If concurrent ICANS is observed, dexamethasone should be preferred.
Source: (Varadarajan I, Kindwall-Keller 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 TLS occur, supportive therapy, including rasburicase, is used.

Dose Modification Guidance and Safety Management

There will be no dose modification for epcoritamab (see **Figure 4** for exceptions in the dose escalation cohorts) or rituximab, although they may be held depending on any toxicities subjects develop during their use.

For R-lenalidomide, if the dose is reduced for a hematologic DLT, the dose can be re-escalated up to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued R^2 therapy results in improved bone marrow function (i.e., no hematologic toxicity of grade 4 neutropenia or febrile neutropenia, or grade 4 thrombocytopenia, and no non-hematologic toxicity of grade 3 rash, grade 4 rash or blistering, thrombosis/embolism ≥grade 3, constipation ≥3, hypo/hyperthyroidism ≥grade 2, grade 3 or 4 peripheral neuropathy, and other ≥grade 3 lenalidomide-related AEs, for at least two consecutive cycles, and an ANC $\geq 1.5 \times 10^9$/L with a platelet count $\geq 100 \times 10^9$/L at the beginning of a new cycle at the current dose level).

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.

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

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

Radiographic Assessments

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

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

Bone Marrow Assessments

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.

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 8**) to inform decisions on continuation of treatment.

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.

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.

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.

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

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

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

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

LYRIC

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

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

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

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 ≥ 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) ≥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).

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

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

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

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

Table 8. LYRIC

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

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

Patient-reported Outcomes

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

Study Assessments

Results:

As of June 28, 2021, 16 patients were treated with the combination of epcoritamab + R2 (3 patients treated with epcoritamab 24 mg and 13 with 48 mg) and were evaluable for safety. Five patients completed at least 7 weeks of therapy and were evaluable for efficacy. A median of 3

cycles per patient have been administered. Fourteen (88%) patients remain on treatment. Median age was 68 years (range, 52–81), 10 (63%) patients were female, and 11 (69%) had 1 prior line of therapy (range in all 16 pts, 1–3 prior lines). All patients received prior immunochemotherapy, 6 (38%) had disease progression ≤2 years prior to baseline, and 6 (38%) had disease progression ≤2 years after initial treatment (POD24). Cytokine release syndrome (CRS) occurred in 31% of patients (5/16) and was of grade 1/2 in all cases. The median time to onset of CRS was 15 days (study day 16; range, 5–16) and median time to resolution was 2 days; no patient required tocilizumab. Other adverse events (AEs) reported in >15% of pts were injection-site reaction (25%; 4/16), constipation (19%; 3/16), cough (19%; 3/16), diarrhea (19%; 3/16), and stomatitis (19%; 3/16; all grade 1/2). No immune effector cell–associated neurotoxicity syndrome events or fatal adverse effects (AEs) were observed. Five (31%) patients required hospitalization due to serious AEs (grade 1 CRS related to epcoritamab in 3 pts; unrelated grade 2 mania in 1 patient; unrelated grade 3 pneumonia in 1 patient; and unrelated grade 3 atrial flutter in 1 of the patients with CRS). All 5 response-evaluable patients achieved an objective response by week 7, with 4 achieving complete metabolic response. All 5 responders had stage IV disease at baseline, 3 had a FL International Prognostic Index of 4/5, 3 had received >2 prior lines of therapy, and 2 had POD24 with first-line therapy.

As of September 8, 2021, a total of 29 patients have been dosed. The expansion phase 48mg is opened on 17Jun21. 6 responders were observed in escalation phase and 13 responders in expansion phase. The most common related AEs were CRS and Injection Site Reaction. Majority of CRS are Grade 1/2. Two episode of Grade 3 CRS were reported, both recovered and only one reported with tocilizumab treatment. These data are preliminary and non-validated and unclean data and response data were not completely entered by site.

Conclusion:

These preliminary data suggest that epcoritamab can be safely combined with R^2 with a manageable toxicity profile, with no new safety signals or unexpected AEs. The relatively lower incidence of CRS with the combination compared with single-agent epcoritamab is notable and warrants further analysis. The novel chemotherapy-free combination demonstrated encouraging

preliminary activity with early responses in all evaluable pts by week 7, including a majority of patients with high-risk features.

Table 9: 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	EVKLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKSSLYLQMNNLKTEDTAMYYCVRHGNFGNSYVSWFAYWGQGTLVTVSS
7	huCD3 VL1	QAVVTQEPSFSVSPGGTVTLTCRSSTGAVTTSNYANWVQQTPGQAFRGLIGGTNKRAPGVPARFSGSLIGDKAALTITGAQADDESIYFCALWYSNLWVFGGGTKLTVL
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	EVQLVESGGGLVQPDRSLRLSCAASGFTFHDYAMHWVRQAPGKGLEWVSTISWNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDIQYGNYYYGMDVWGQGTTVTVSS

14	VL CD20 – 7D8	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIY DASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPITF GQGTRLEIK
15	IgG1 heavy chain constant region – WT (amino acids positions 118-447 according to EU numbering). *CH3 region italics*	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAK*GQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*
16	IgG1-LFLEDA heavy chain constant region (amino acids positions 118-447 according to EU numbering).	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE**FE**GGPSVFLFPPKPKDTLMISRTPEVTCV VV**A**VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
17	IgG1 F405L (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS F**L**LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
18	IgG1-K409R (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYS**R**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
19	IgG1 -LFLEDA-F405L (FEAL) (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPE**FE**GGPSVFLFPPKPKDTLMISRTPEVTCV VV**A**VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE

		EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
20	IgG1 -LFLEDA-K409R (FEAR) (amino acids positions 118-447 according to EU numbering)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCV VVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
21	IgG1 CH3 region	GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG
22	Constant region human lambda LC	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECS
23	Constant region human kappa LC	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
24	huCD3-LFLEDA-F405L (FEAL) heavy chain	EVKLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLE WVARIRSKYNNYATYYADSVKDRFTISRDDSKSSLYLQMNNLKTEDTA MYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFLLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG
25	huCD3 VL+CL light chain	QAVVTQEPSFSVSPGGTVTLTCRSSTGAVTTSNYANWVQQTPGQAF RGLIGGTNKRAPGVPARFSGSLIGDKAALTITGAQADDESIYFCALWYS NLWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS
26	CD20-7D8-LFLEDA-K409R (FEAR) heavy chain	EVQLVESGGGLVQPDRSLRLSCAASGFTFHDYAMHWVRQAPGKGLE WVSTISWNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDIQYGNYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKST

		SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPA PE**FE**GGPSVFLFPPKPKDTLMISRTPEVTCVVV**A**VSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS**R**LTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPG
27	CD20 – 7D8 VL+CL light chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIY DASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPITF GQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
28	Human CD3 (epsilon)	MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSISGTTVI LTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSG YYVCYPRGSKPEDANFYLYLRARVCENCMEMDVMSVATIVIVDICITG GLLLLVYYWSKNRKAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDY EPIRKGQRDLYSGLNQRRI
29	Human CD20	MTTPRNSVNGTFPAEPMKGPIAMQSGPKPLFRRMSSLVGPTQSFFM RESKTLGAVQIMNGLFHIALGGLLMIPAGIYAPICVTVWYPLWGGIM YIISGSLLAATEKNSRKCLVKGKMIMNSLSLFAAISGMILSIMDILNIKIS HFLKMESLNFIRAHTPYINIYNCEPANPSEKNSPSTQYCYSIQSLFLGILS VMLIFAFFQELVIAGIVENEWKRTCSRPKSNIVLLSAEEKKEQTIEIKEEV VGLTETSSQPKNEEDIEIIPIQEEEEEETETNFPEPPQDQESSPIENDSSP

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

Claims

1. A method of treating follicular lymphoma in a human subject, the method comprising administering to the subject a bispecific antibody an effective amount of rituximab and lenalidomide, wherein the bispecific antibody comprises:

(i) a first binding arm comprising a first antigen-binding region which binds to human CD3ε (epsilon) and comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises the CDR1, CDR2 and CDR3 sequences that are in the VH region sequence of SEQ ID NO: 6, and the VL region comprises the CDR1, CDR2 and CDR3 sequences that are in the VL region sequence of SEQ ID NO: 7; and

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

wherein the bispecific antibody is administered at a dose of 24 mg or 48 mg, and wherein rituximab, lenalidomide, and the bispecific antibody are administered in 28-day cycles.

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

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

4. The method of any one of claims 1-3, wherein the 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 2.5 28-day cycles.

6. The method of claim 4 or 5, wherein after the weekly administration, the bispecific antibody is administered once every two weeks (biweekly administration).

7. The method of claim 6, wherein the biweekly administration is performed for six 28 day cycles.

8. The method of claim 6 or 7, wherein after the biweekly administration, the bispecific antibody is administered once every four weeks.

9. The method of claim 8, wherein the administration once every four weeks is performed for at least three 28-day cycles.

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 28-day cycles.

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.

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.

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 days 15 and 22 of cycle 1.

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

16. The method of any one of claims 1-15, wherein rituximab is administered once every week (weekly administration).

17. The method of claim 16, wherein the weekly administration of rituximab is performed for one 28-day cycle.

18. The method of claim 16 or 17, where after the weekly administration, rituximab is administered once every four weeks.

19. The method of claim 18, wherein the administration of rituximab once every four weeks is performed for four 28-day cycles.

20. The method of any one of claims 1-19, wherein rituximab is administered at a dose of 375 mg/m^2 or equivalent thereof.

21. The method of any one of claims 1-20, wherein lenalidomide is administered once a day from day 1 to day 21 of the 28-day cycles.

22. The method of any one of claims 1-21, wherein lenalidomide is administered from cycle 1 to cycle 12 of the 28-day cycles.

23. The method of any one of claims 1-22, wherein lenalidomide is administered at a dose of 15 mg in cycle 1 of the 28-day cycles.

24. The method of any one of claims 1-23, wherein lenalidomide is administered at a dose of 20 mg in cycle 2 to cycle 12 of the 28-day cycles.

25. The method of any one of claims 1-24, wherein rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., on days 1, 8, and 15 of cycle 1, and on day 1 of cycles 2-5).

26. The method of any one of claims 1-25, wherein the dosing schedule for the bispecific antibody, rituximab, and lenalidomide is as shown in **Table 2**.

27. The method of any one of claims 1, 2, and 4-26, wherein administration is performed in 28-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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 24 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 24 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 24 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

28. The method of any one of claims 1 and 3-27, wherein administration is performed in 28-day cycles, and wherein:

(a) 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 days 15 and 22;

(ii) in cycles 2 and 3, a dose of 48 mg is administered on days 1, 8, 15, and 22;

(iii) in cycles 4-9, a dose of 48 mg is administered on days 1 and 15; and

(iv) in cycle 10 and subsequent cycles, a dose of 48 mg is administered on day 1;

(b) rituximab is administered on days 1, 8, 15, and 22 in cycle 1, and day 1 in cycles 2-5; and

(c) lenalidomide is administered on days 1-21 in cycles 1-12.

29. The method of any one of claims 1-28, wherein the bispecific antibody is administered subcutaneously.

30. The method of any one of claims 1-29, wherein rituximab is administered intravenously.

31. The method of any one of claims 1-30, wherein lenalidomide is administered orally.

32. The method of any one of claims 1-31, wherein the bispecific antibody, rituximab, and lenalidomide are administered sequentially.

33. The method of any one of claims 1-32, wherein:

(a) rituximab is administered before the bispecific antibody if rituximab and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2-5);

(b) lenalidomide is administered before the bispecific antibody if lenalidomide and the bispecific antibody are administered on the same day (e.g., days 1, 8, 15, and 22 of cycles 1-3, days 1 and 15 of cycles 4-9, and day 1 of cycles 10-12);

(c) rituximab is administered before lenalidomide if rituximab and lenalidomide are administered on the same day (e.g., days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-5); or

(d) rituximab is administered first, lenalidomide is administered second, and the bispecific antibody is administered last if rituximab, lenalidomide, and the bispecific antibody are administered on the same day (e.g., days 1, 8, and 15 of cycle 1, and days 1-5 of cycles 2-5).

34. The method of any one of claims 1-33, wherein the follicular lymphoma is relapsed and/or refractory follicular lymphoma, such as grade 1, 2, or 3a relapsed and/or refractory follicular lymphoma or such as Stage II, III, or IV relapsed and/or refractory follicular lymphoma.

35. The method of any one of claims 1-34, 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.

36. The method of any one of claims 1-35, 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.

37. The method of any one of claims 1-35, wherein the first binding arm of the bispecific antibody is derived from a humanized antibody, preferably from a full-length IgG1,λ (lambda) antibody.

38. The method of claim 37, 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.

39. The method of any one of claims 1-38, wherein the second binding arm of the bispecific antibody is derived from a human antibody, preferably from a full-length IgG1,κ (kappa) antibody.

40. The method of claim 39, wherein the second binding arm comprises a κ light chain constant region comprising the amino acid sequence set forth in SEQ ID NO: 23.

41. The method of any one of claims 1-40, wherein the bispecific antibody is a full-length antibody with a human IgG1 constant region.

42. The method of any one of claims 1-41, wherein the bispecific antibody comprises an inert Fc region.

43. The method of any one of claims 1-42, 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.

44. The method of any one of claims 1-43, wherein the bispecific antibody comprises a first heavy chain and a second heavy chain, wherein in the first heavy chain, the amino acid in the position corresponding to F405 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 is L, and wherein in the second heavy chain, the amino acid in the position corresponding to K409 in the human IgG1 heavy chain constant region of SEQ ID NO: 15 is R, or *vice versa*.

45. The method of any one of claims 1-44, 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*.

46. The method of claim 45, wherein the bispecific antibody comprises heavy chain constant regions comprising the amino acid sequences of SEQ ID NOs: 19 and 20.

47. The method of any one of claims 1-46, 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.

48. The method of any one of claims 1-47, 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.

49. The method of any one of claims 1-48, wherein the bispecific antibody is epcoritamab, or a biosimilar thereof.

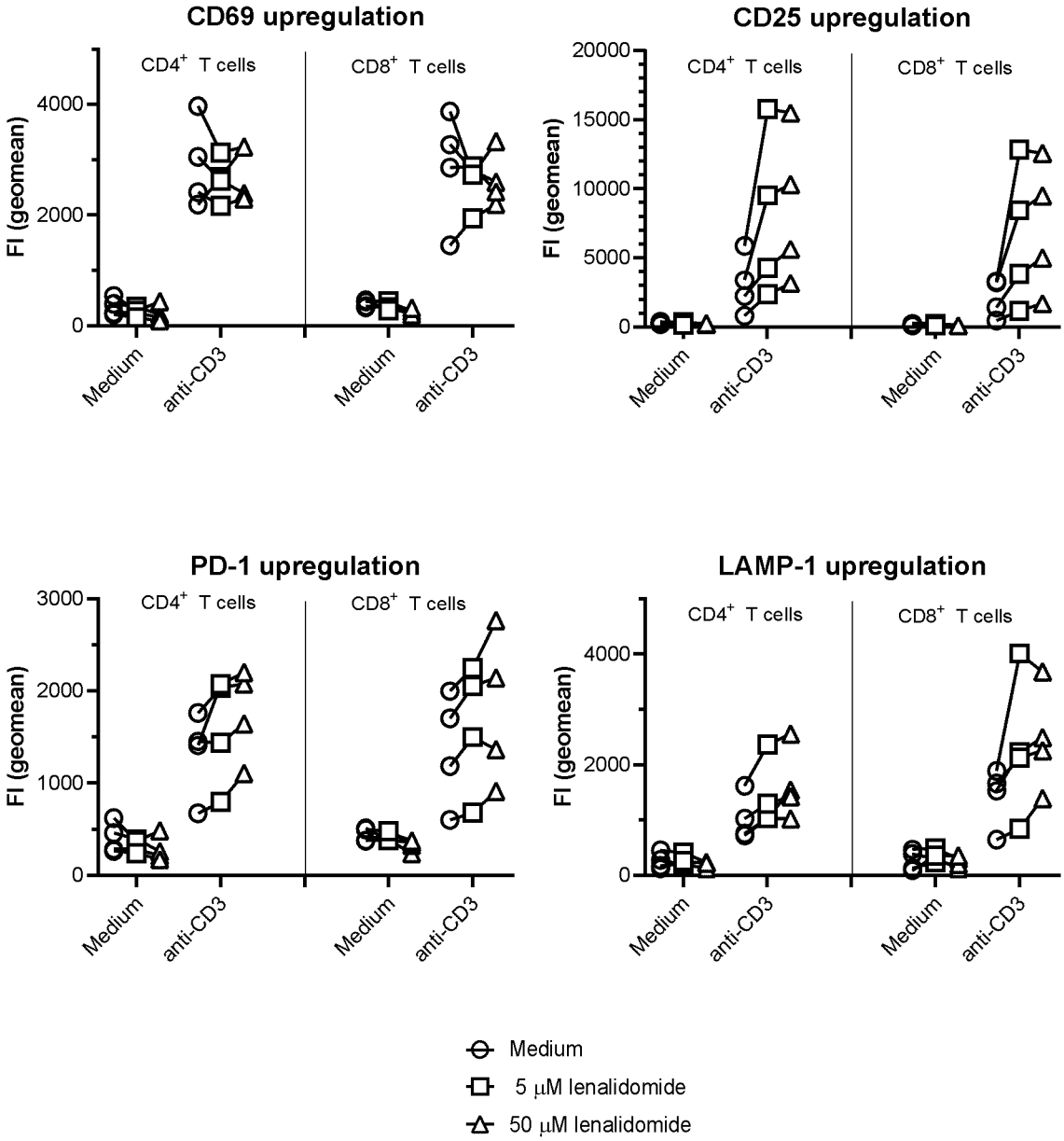
CD69 upregulation
CD25 upregulation
PD-1 upregulation
LAMP-1 upregulation
CD4+ T cells
CD8+ T cells
FI (geomean)
Medium
anti-CD3
Medium
5 μM lenalidomide
50 μM lenalidomide

FIG. 1

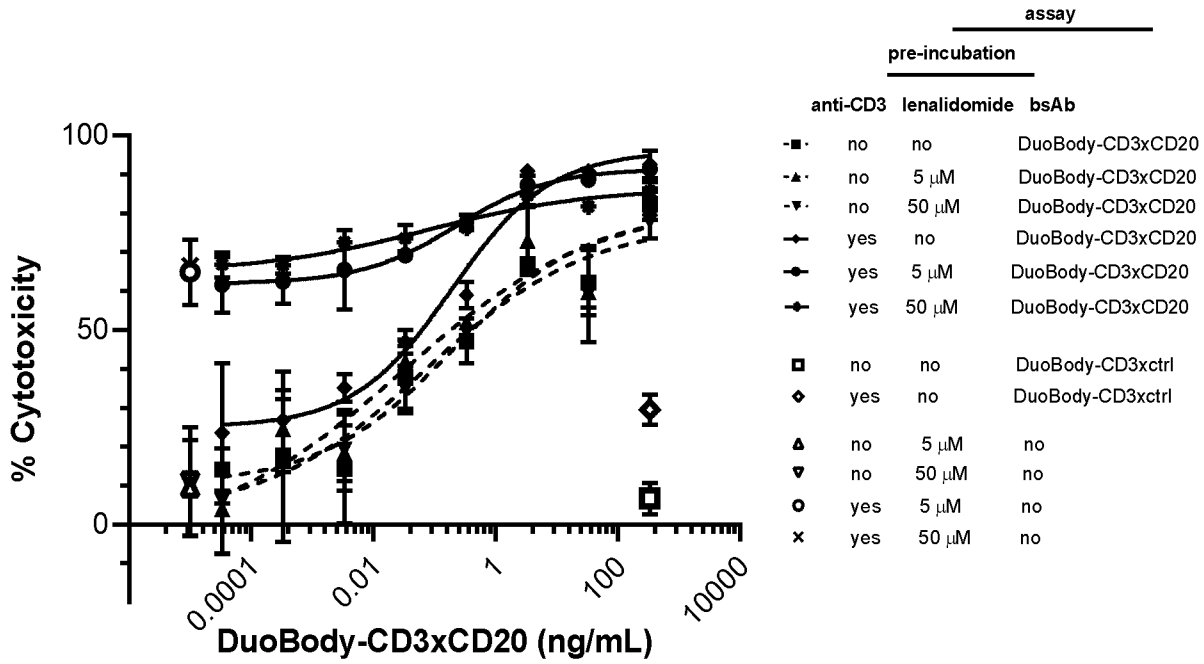
% Cytotoxicity
100
50
0
0.0001
0.01
1
100
10000
DuoBody-CD3xCD20 (ng/mL)
assay
pre-incubation
anti-CD3
lenalidomide
bsAb
no no DuoBody-CD3xCD20
no 5 μM DuoBody-CD3xCD20
no 50 μM DuoBody-CD3xCD20
yes no DuoBody-CD3xCD20
yes 5 μM DuoBody-CD3xCD20
yes 50 μM DuoBody-CD3xCD20
no no DuoBody-CD3xctrl
yes no DuoBody-CD3xctrl
no 5 μM no
no 50 μM no
yes 5 μM no
yes 50 μM no

FIG. 2

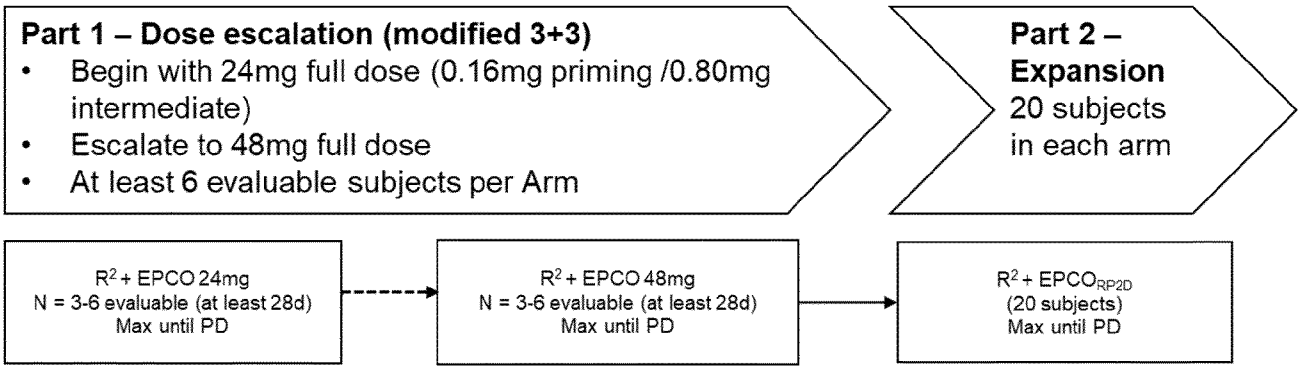
Part 1 – Dose escalation (modified 3+3)
• Begin with 24mg full dose (0.16mg priming /0.80mg intermediate)
• Escalate to 48mg full dose
• At least 6 evaluable subjects per Arm
Part 2 – Expansion
20 subjects in each arm
R2 + EPCO 24mg
N = 3-6 evaluable (at least 28d)
Max until PD
R2 + EPCO 48mg
N = 3-6 evaluable (at least 28d)
Max until PD
R2 + EPCORP2D
(20 subjects)
Max until PD

FIG. 3

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

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/075017

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61P35/02 C07K16/28
ADD. A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MORSCHHAUSER FRANCK ET AL: "Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma", THE NEW ENGLAND JOURNAL OF MEDICINE, vol. 379, no. 10, 6 September 2018 (2018-09-06), pages 934-947, XP055855089, US ISSN: 0028-4793, DOI: 10.1056/NEJMoa1805104 the whole document	1-48

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 October 2021	09/11/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Galli, Ivo

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATRICK J. ENGELBERTS ET AL: "DuoBody-CD3xCD20 induces potent T-cell-mediated killing of malignant B cells in preclinical models and provides opportunities for subcutaneous dosing", EBIOMEDICINE, vol. 52, 1 February 2020 (2020-02-01), page 102625, XP055762370, NL ISSN: 2352-3964, DOI: 10.1016/j.ebiom.2019.102625 cited in the application the whole document	1-48
A	VAN DER HORST HILMA J ET AL: "Duobody-CD3xCD20 Induces Potent Anti-Tumor Activity in Malignant Lymph Node B Cells from Patients with DLBCL, FL and MCL Ex Vivo, Irrespective of Prior Treatment with CD20 Monoclonal Antibodies", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 134, 13 November 2019 (2019-11-13), page 4066, XP086675260, ISSN: 0006-4971, DOI: 10.1182/BLOOD-2019-125765 cited in the application the whole document	1-48
A	WO 2016/110576 A1 (GENMAB AS [DK]) 14 July 2016 (2016-07-14) the whole document	1-48

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2021/075017

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2021/075017

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 49(completely); 1-46(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 49(completely); 1-46(partially)

Claim 1 lacks clarity because it does not define the CDRs of the constructs. Moreover, in the case of fine-tuning of medical regimens, small differences in affinity to the target can cause great changes in the outcome. The few data presented concern epcoritamab, and not more generic constructs for which there is no support and disclosure in the sense of Art. 5-6 PCT. Claims 1-46 have been interpreted (and the search restricted) as concerning epcoritamab. (Claims 47-48 are deemed to refer to epcoritamab as such.)
Claim 49 concerns undefined and undisclosed "biosimilars". As none have been disclosed, not even for epcoritamab, it is not possible to carry out a meaningful search.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/075017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016110576 A1	14-07-2016	AU 2016205967 A1	27-07-2017
		BR 112017014551 A2	15-05-2018
		CA 2973159 A1	14-07-2016
		CN 107660214 A	02-02-2018
		EA 201791554 A1	29-12-2017
		EP 3242682 A1	15-11-2017
		JP 6853176 B2	31-03-2021
		JP 2018508188 A	29-03-2018
		JP 2021104020 A	26-07-2021
		KR 20170128222 A	22-11-2017
		SG 11201705496S A	30-08-2017
		UA 120286 C2	11-11-2019
		US 2017355767 A1	14-12-2017
		US 2020199231 A1	25-06-2020
		WO 2016110576 A1	14-07-2016