Glofitamab, a Novel, Bivalent CD20 Targeting T-cell Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed/Refractory B-cell Lymphoma: a Phase I Trial

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SUPPLEMENTARY APPENDIX

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SUPPLEMENTARY METHODS

Complete inclusion and exclusion criteria

<u>Inclusion Criteria</u>

Patients had to meet the following criteria for study entry:

- Signed Informed Consent Form(s)

- Patient must be willing and able to comply with protocol-mandated hospitalization upon administration of the first dose of glofitamab. Patient must also be willing to comply with all study-related procedures. In Part 3, this included completion of patient reported outcome measures

- Aged ≥18 years

- Depending upon study part, a history or status of: 1) a histologically-confirmed hematological malignancy that was expected to express CD20; 2) relapse after or failure to respond to at least one prior treatment regimen; and 3) no available treatment options that were expected to prolong survival (e.g. standard chemotherapy or autologous stem cell transplant). Eligible relapsed/refractory non-Hodgkin lymphoma (NHL) patients included:

  o For Parts 1 and 2: grades 1 to 3B follicular lymphoma (FL); marginal zone lymphoma (splenic; nodal; extra-nodal); mantle cell lymphoma; diffuse large B cell lymphoma (DLBCL); primary mediastinal large B cell lymphoma (PMBCL); Richter's transformation; and/or transformed FL

  o For Part 3 expansion cohorts:

    – DLBCL cohort (DLBCL not otherwise specified, high-grade B cell lymphoma, PMBCL and DLBCL arising from FL ([transformed FL]). Patients had relapsed after or failed to respond to at least two prior

systemic treatment regimens (including at least one prior regimen containing anthracycline, and at least one containing an anti CD20-directed therapy). The Sponsor retained the option to limit the number of patients enrolled with transformed FL and PMBCL. Patients with Richter's transformation were not considered eligible for Part III. For patients in the DLBCL cohort (DLBCL not otherwise specified, high-grade B-cell lymphomas, PMBCL or transformed FL) the pathology report for the initial histopathology diagnosis had to be provided, if available. Patients with transformed FL also had to provide the pathology report at the time of disease transformation, if available. The results of all tests conducted on the tissue at initial diagnosis, including but not limited to tests assessing cell of origin, BCL2 and MYC abnormalities, were provided if performed

– FL cohort: grades 1 to 3 a FL; patients had relapsed after or failed to respond to at least two prior lines of systemic therapy and had received prior treatment with rituximab and alkylating agents. The Sponsor retained the option to enroll a minimum number of patients who are refractory to both anti-CD20 directed therapy and an alkylating agent

- Measurable disease, defined as at least one bi-dimensionally measurable nodal lesion, defined as > 1.5 cm in its longest dimension, or at least one bi-dimensionally measurable extranodal lesion, defined as > 1.0 cm in its longest dimension

- Patient had at least one measureable target lesion (> 1.5 cm) in its largest dimension by computerized tomography scan)

- Able to provide the most recent archival tumor tissue samples (formalin-fixed paraffin-embedded blocks preferred; if not available, slides accepted). Archival tumor

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tissue samples obtained preferably within 6 months and between the last dose of the last prior cancer regimen and 7 days prior to cycle 1

- In the absence of sufficient archival tissue, a fresh biopsy from a safely accessible site, per Investigator determination, were requested, providing the patient had more than one measurable target lesion

- ECOG performance status of 0 or 1

- Life expectancy (in the opinion of the Investigator) of ≥ 12 weeks

- Adverse events from prior anti-cancer therapy had resolved to grade ≤ 1

- Adequate liver function: total bilirubin ≤ 1.5 x upper limit of normal (ULN). Patients with documented history of Gilbert's Syndrome and in whom total bilirubin elevations were accompanied by elevated indirect bilirubin were eligible); aspartate transaminase/alanine transaminase ratio ≤ 3 x the ULN

- Adequate hematological function: neutrophil count of $\geq 1.5 \times 10^9$ cells/L; platelet count of ≥ 75,000/µL (and platelet transfusion free within 14 days prior to administration of obinutuzumab pretreatment [*Gpt*]); Hemoglobin ≥ 10.0 g/dL (6.2 mmol/L); transfusion free within 21 days prior to administration of *Gpt*

- Adequate renal function: serum creatinine ≤ 1.5 ULN or a creatinine clearance (CrCl) calculated by Cockroft-Gault formula of ≥ 50 mL/min for patients in whom, in the investigator's judgment, serum creatinine levels did not adequately reflect renal function

- Negative serum pregnancy test within 7 days prior to study treatment in women of childbearing potential. Women who were not of childbearing potential who were considered to be post-menopausal (≥ 12 months of non-therapy amenorrhea) or surgically sterile (absence of ovaries and/or uterus) were not required to have a pregnancy test

- Negative serologic or polymerase chain reaction (PCR) test results for acute or chronic hepatitis B virus (HBV) infection. (Note: Patients whose HBV infection status could not be determined by serologic test results had to be negative for HBV by PCR to be eligible for study participation)

- Negative test results for hepatitis C virus (HCV) and human immunodeficiency virus Note: Patients who were positive for HCV antibody had to be negative for HCV by PCR to be eligible for study participation

- Patients agreed to either remain completely abstinent or to use two effective contraceptive methods with a failure rate of < 1% per year from screening until: (a) at least 3 months after pretreatment with obinutuzumab or 2 months after the last dose of glofitamab, whichever was longer, if the patient was a male or (b) until at least 18 months after pre-treatment with obinutuzumab or 2 months after the last dose of glofitamab, whichever was longer, if patient was a female

  o For women of childbearing potential, examples of contraceptive methods with a failure rate of < 1% per year include:

    – Tubal ligation, male sterilization, hormonal implants, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices

    – Alternatively, two methods (e.g. two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide

  o For men: agreement to remain abstinent or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

    – With female partners of childbearing potential, men had to remain abstinent or use a condom plus an additional contraceptive method

that together resulted in a failure rate of < 1% per year during the

treatment period and for at least 3 months after last dose of

obinutuzumab or 2 months after the last dose of glofitamab (whichever

was longer)

  – Men had to refrain from donating sperm during this same period

  – With pregnant female partners, men had to remain abstinent or use a

    condom during the treatment period and for at least 3 months after

    last dose of obinutuzumab or 2 months after the last dose of

    glofitamab (whichever was longer) to avoid exposing the embryo

  o For both men and women, the reliability of sexual abstinence had to be

    evaluated in relation to the duration of the clinical trial and the preferred and

    usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation,

    symptothermal, or post ovulation methods) and withdrawal were not

    acceptable methods of contraception

<u>Exclusion criteria</u>

Patients who met any of the following criteria were excluded from study entry:

- Inability to comply with protocol mandated hospitalization and restrictions. Patients with

  chronic lymphatic leukemia, Burkitt lymphoma and lymphoplasmacytic lymphoma

- Patients with acute bacterial, viral, or fungal infection at baseline, confirmed by a positive

  blood culture within 72 hours prior to *Gpt* infusion or by clinical judgment in the absence

  of a positive blood culture

- Patients with known active infection, or reactivation of a latent infection, whether

  bacterial, viral (including, but not limited to, Epstein-Barr virus, cytomegalovirus, hepatitis

  B, hepatitis C, and human immunodeficiency virus), fungal, mycobacterial, or other

  pathogens (excluding fungal infections of nail beds) or any major episode of infection

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requiring hospitalization or treatment with intravenous (IV) antibiotics (for IV antibiotics this pertained to completion of last course of antibiotic treatment) within 4 weeks of dosing

- Pregnant or breastfeeding or intending to become pregnant during the study

- Prior treatment with systemic immunotherapeutic agents, including, but not limited to, radio-immunoconjugates, antibody-drug conjugates, immune/cytokines and monoclonal antibodies (e.g. anti-CTLA4, anti-PD1 and anti-PDL1) within 4 weeks or five half-lives of the drug, whichever was shorter, before *Gpt* infusion (7 days before cycle 1)

- History of treatment-emergent immune-related adverse events associated with prior immunotherapeutic agents, as follows:
  - Grade ≥ 3 adverse events with the exception of grade 3 endocrinopathy managed with replacement therapy
  - Grade 1 to 2 adverse events that did not resolve to baseline after treatment discontinuation

- Documented refractoriness to an obinutuzumab monotherapy containing regimen

- Treatment with standard radiotherapy, any chemotherapeutic agent, or treatment with any other investigational anti-cancer agent (defined as treatment for which there was no regulatory authority approved indication) within 4 weeks prior to *Gpt* infusion

- Prior solid organ transplantation

- Prior allogeneic stem-cell therapy

- Autologous stem-cell therapy within 100 days prior to *Gpt* infusion

- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

- - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone were eligible for this study
  - Patients with a history of disease-related immune thrombocytopenic purpura or autoimmune hemolytic anemia were eligible for this study
  - Patients with a history of type 1 diabetes mellitus who were well controlled (defined as a screening hemoglobin A1c < 8% and no urinary ketoacidosis) were eligible
- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
- Patient with history of confirmed progressive multifocal leukoencephalopathy
- Current or past history of central nervous system lymphoma
- Current or past history of central nervous system disease, such as stroke, epilepsy, central nervous system vasculitis, or neurodegenerative disease. Note: Patients with a history of stroke who had not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits, as judged by the investigator, were allowed
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders (bronchospasm, obstructive pulmonary disease) and known autoimmune diseases
- Major surgery or significant traumatic injury < 28 days prior to the *Gpt* infusion (excluding biopsies) or anticipation of the need for major surgery during study treatment
- Patients with another invasive malignancy in the last 2 years (with the exception of basal cell carcinoma and tumors deemed by the Investigator to be of low likelihood for recurrence)

- Significant cardiovascular disease such as New York Heart Association class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina)

- Administration of a live, attenuated vaccine within 4 weeks before *Gpt* infusion or anticipation that such a live attenuated vaccine was required during the study. (Note: Influenza vaccination had to be given during influenza season only). Patients had to not receive live, attenuated influenza vaccine (e.g. nasal spray flu vaccine) at any time during the study treatment period

- Received systemic immunosuppressive medications (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to *Gpt* infusion. Treatment with corticosteroid ≤ 25 mg/day prednisone or equivalent was allowed. Inhaled and topical steroids were permitted

- History of illicit drug or alcohol abuse within 12 months prior to screening, in the Investigator's judgment

- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug

- Finally, Investigators had to review the vaccination status of potential study patients being considered for this study and follow local disease control and prevention guidelines for adult vaccination with any other non-live vaccines intended to prevent infectious disease prior to study.

Premedication

Premedication for obinutuzumab and glofitamab consisted of anti-histamines, acetaminophen and methylprednisolone (80 mg).

Treatment schedule

In Part 1 (single-patient dose escalation), which included only three patients in single-patient cohorts, glofitamab was administered at doses of 0.005–0.045 mg. Part 2 (multiple-patient dose escalation) started when either a fixed dose of 0.81 mg was reached or a glofitamab-related Grade ≥2 AE or dose-limiting toxicity (DLT) was observed in a patient during their 4-week DLT window, whichever comes first. A minimum of three patients per cohort were enrolled.

Part 2 dose escalation started at 0.015 mg. Glofitamab was administered on day 1 and 8 of cycle 1, then on day 1 of each 14-day cycle for up to 12 cycles. Based on early pharmacokinetic data confirming a clinical half-life of glofitamab in-line with IgG antibodies, dosing at cycle 1 day 8 was omitted at doses ≥0.3 mg, and a 21-day cycle was adopted from cycle 2 at doses of ≥10 mg, for up to 12 cycles.

Based on the clinical characterization of the CRS time-course data showing that CRS events have occurred primarily following the initial dose of glofitamab, investigation of step-up dosing in Cycle 1 has been introduced as a possible additional safety measure for CRS in part 2. Step-up dosing was administered on days 1 (2.5 mg) and 8 (10 mg) of cycle 1 followed by day 1 (16 mg or 30 mg) of each subsequent 21-day cycle.

Retreatment

Patients who initially respond or have stable disease following study treatment may benefit from additional treatment. To test this further, eligible patients received retreatment with glofitamab. The study retreatment dose and schedule will be one that has been previously

demonstrated in the dose escalation to be safe, provided they meet the retreatment eligibility criteria.

Cohort Assignment Upon Retreatment

Patients who completed a Q2W (once every two weeks) dosing may continue to receive glofitamab on a Q2W dose schedule or may be switched to a Q3W (once every three weeks) dose schedule and may receive the highest glofitamab dose cleared in Part 2. In the case of emerging safety and or anti-tumor activity data, the internal monitoring committee, in consultation with study investigators may further recommend that all patients upon entering retreatment receive glofitamab combination therapy.

Follow-Up and Retreatment Eligibility

Patients who achieve partial or complete response or who have stable disease at the completion of initial glofitamab treatment (i.e., "treatment completion") should enter the 'follow-up till progression' phase, where they will be followed until disease progression, death or lost to follow-up. Patients must complete End of Treatment assessments that are required for the initial glofitamab treatment course (per schedule of assessment) before entering the 'follow-up till progression' phase of the study. While in the 'follow-up till progression' phase, patients with Investigator-assessed disease progression or disease relapse, confirmed by radiographic imaging, will be eligible for glofitamab retreatment at the highest dose found to be safe at the time of retreatment, provided they meet the "retreatment eligibility criteria". Disease progression will be confirmed by radiographic imaging, as defined by the Lugano Criteria.

Retreatment after Withdrawal Due to Progression or Pseudoprogression

Patients withdrawn from study because of apparent progression, who later achieve complete or partial response without receiving any other therapy after last dose of glofitamab are also eligible for glofitamab retreatment provided they meet the "retreatment eligibility criteria".

Patients diagnosed with "pseudoprogression" who are allowed to continue the initial treatment course, and who complete RO7082859 treatment, must also meet the "retreatment eligibility criteria" in order to receive subsequent study treatment. Likewise, if radiographic disease progression is confirmed at a subsequent tumor assessment or at end of treatment, these patients will be ineligible to receive further glofitamab treatment.

<u>Resuming Glofitamab after Prolonged Dose Delays</u>

Should a patient delay treatment for more than one cycle for reasons other than toxicity, (eg, pseudoprogression or delayed response), resuming initial treatment course may be allowed if investigator and Sponsor consider this in the best interest of the patient. As a safety measure, *Gpt* should be given 7 days prior to resuming treatment. Local and or central labs are to be collected per Schedule of Assessment.

Definition of dose-limiting toxicities

All dose-limiting toxicities that occurred during the first 28 days (ie, the 4-week dose-limiting toxicity window of treatment with glofitamab as single agent [starting from cycle 1 day 1] or in combination with obinutuzumab [starting from cycle 2 day 1]), had to be reported to the Sponsor within 24 hours. In both the monotherapy and combination therapy cohorts, any treatment delays during the first 28 days of the start of dose-limiting toxicity windows were allowed if they were less than one cycle in length; under these circumstances, the dose-limiting toxicity window was extended up to 49 days.

For dose-escalation purposes (ie, Parts 1 and 2), a dose-limiting toxicity was defined as any of the following adverse events which occurred from the time dose-limiting toxicity window begins, through 4 weeks of treatment (the dose-limiting toxicity window for Q2W and Q3W monotherapy cohorts began on cycle 1 day 1. The dose-limiting toxicity window for Q3W combination cohorts began on cycle 2 day 1):

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- Any grade ≥ 3 adverse events not considered by the Investigator to be attributable to another clearly identifiable cause, with the following exceptions:
    - Grade 3/4 lymphopenia, or grade 3/4 leukopenia, which were expected outcomes of the therapy
    - Grade 3 neutropenia that was not accompanied by an oral or tympanic temperature of ≥ 100.4°F (38°C) and improved to grade ≤ 2 (or to ≥ 80% of the baseline value, whichever was lower) without growth factor support within 1 week
    - Grade 3 thrombocytopenia that did not result in bleeding and improved to grade ≤ 2 (or to ≥ 80% of the baseline value, whichever was lower) within 1 week without platelet transfusion
    - Grade ≥ 3 infusion-related reactions, as infusion-related reactions were not considered to be dose-limiting toxicities because, on the basis of experience with monoclonal antibodies, infusion-related reactions were not dose-related events
    - Grade 3 nausea or vomiting in the absence of premedication or that could be managed with resulting resolution to grade ≤ 2 with oral or IV anti-emetics within 24 hours. Grade 3 nausea or vomiting that required total parenteral nutrition or hospitalization were not excluded and were considered dose limiting
    - Alopecia (any grade)
    - Fever > 40°C (ie, grade 3) that occurred within 48 hours of glofitamab infusion and resolved within 48 hours to > 39°C to 40°C (grade ≤ 2) and fully resolved within 1 week
    - Grade 3 arthralgia that can be adequately managed with supportive care or which resolved to grade ≤ 2 within 1 week

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- Grade 3 tumor pain that started within 24 hours of infusion and lasted less than 1 week

  - Grade 3 diarrhea that lasted for ≤ 2 days with no fever or dehydration

  - Grade 3 fatigue that lasted ≤ 3 days

  - Grade 3 fatigue lasting ≥ 3 days that resolved to grade ≤ 2 within 1 week

  - Laboratory values of grade ≥3 that were judged not clinically significant by the investigator

- Any hepatic function abnormality, based upon the following definition:

  - Aspartate aminotransferase or alanine aminotransferase (ALT) > 3 times the ULN AND total bilirubin > 2 times the ULN. Note the following exception:

    - Any aspartate aminotransferase (AST) or ALT value that was > 3 times the ULN and total bilirubin that was > 2 times the ULN (where no single value for bilirubin exceeded grade 3) that occurred in the context of grade ≤ 2 cytokine release syndrome and lasted   < 3 days was not considered dose limiting. Under these conditions, unscheduled liver function tests were performed to confirm that elevations lasted less than 3 days

  - Any grade 3 AST or ALT elevation with the following exception:

    - Any grade 3 AST or ALT elevation that occurred in the context of a grade ≤ 2 cytokine release syndrome or that lasted < 3 days was not considered dose limiting

Glofitamab dose reduction and modification

Patients received *Gpt* and glofitamab once their clinical assessment and laboratory test results are acceptable. All considerations of dose and schedule modifications were discussed with the Medical Monitor.

For patients who developed cytokine release syndrome (CRS) with associated signs and symptoms during glofitamab infusion, the infusion was discontinued immediately and not restarted, unless symptoms were limited to Grade 1 and responded to symptomatic treatment. In such cases, the dose and rate of infusion of glofitamab during subsequent cycles was determined after discussions with the Medical Monitor. For patients who may be at an increased risk of CRS, patients who experience infusion-related reactions (IRR) or CRS with their previous dose of glofitamab, or those who are at an increased risk of recurrent IRR/CRS with subsequent doses, the next dose and time of infusion was extended to up to 8 hours. Modifications to infusion time in these circumstances was also discussed with the Medical Monitor.

Initial glofitamab infusion was not started until obinutuzumab-related adverse events resolved to Grade ≤1. If a patient developed thrombocytopenia following *Gpt*, then glofitamab was not given until the platelets returned to ≥75,000/µL or to a level approved by the Medical Monitor.

Dosing was therefore resumed when hematological toxicities were Grade ≤2 and non-hematological toxicities were Grade ≤1. If a toxicity did not resolve to NCI-CTCAE Grade ≤2 for related hematological toxicities (or if thrombocytopenia related to *Gpt* was not resolved to ≥75,000/µL [or to a Medical Monitor-approved level] in advance of Cycle 1/Day 1) or to Grade ≤1 for related non-hematological toxicities and/or the patient was unable to resume treatment with glofitamab (due to the omission of 2 doses), no additional doses were administered and the patient would have been withdrawn from study treatment. It should be noted that infusions/cycles are not considered as missed but, rather, as delayed.

If treatment was delayed for more than one cycle for reasons other than toxicity, e.g. assessment of pseudoprogression or delayed response, re-continuation of treatment was

allowed if the investigator and Sponsor considered this in the best interest of the patient. As a safety measure, *Gpt*, would have been re-initiated 7 days prior to resuming treatment.

If a patient experienced recurrent toxicity of the same or higher grade following re-exposure to glofitamab, the Investigator, after discussion with the IMC, had the option to reduce the dose of glofitamab once to a lower dose level. This was done to allow patients who could potentially benefit from glofitamab to remain on the study drug. Patients receiving glofitamab who experienced a Grade 4 related non-hematological adverse event should have discontinued study treatment and were not retreated. Exceptions may be warranted after discussion with the Medical Monitor taking into consideration benefit/risk for a given individual patient and/or taking into consideration ad hoc and patient-specific risk mitigations.

SUPPLEMENTARY RESULTS

Dose-limiting toxicities

In all glofitamab cohorts, 16 dose-limiting toxicities were reported in 12 (7.0%) patients: 6 patients had cytokine release syndrome (Grade 2 in 3 patients, Grade 3 in 2 patients, and Grade 4 in 1 patient), two patients had Grade 4 neutropenia. Two patients had grade 3 tumor lysis syndrome, and one patient each had grade 3 myocardial infarction, grade 3 localized oedema, grade 3 enterocolitis bacterial and grade 4 upper airway obstruction

SUPPLEMENTARY FIGURES

Figure S1. Study design overview.
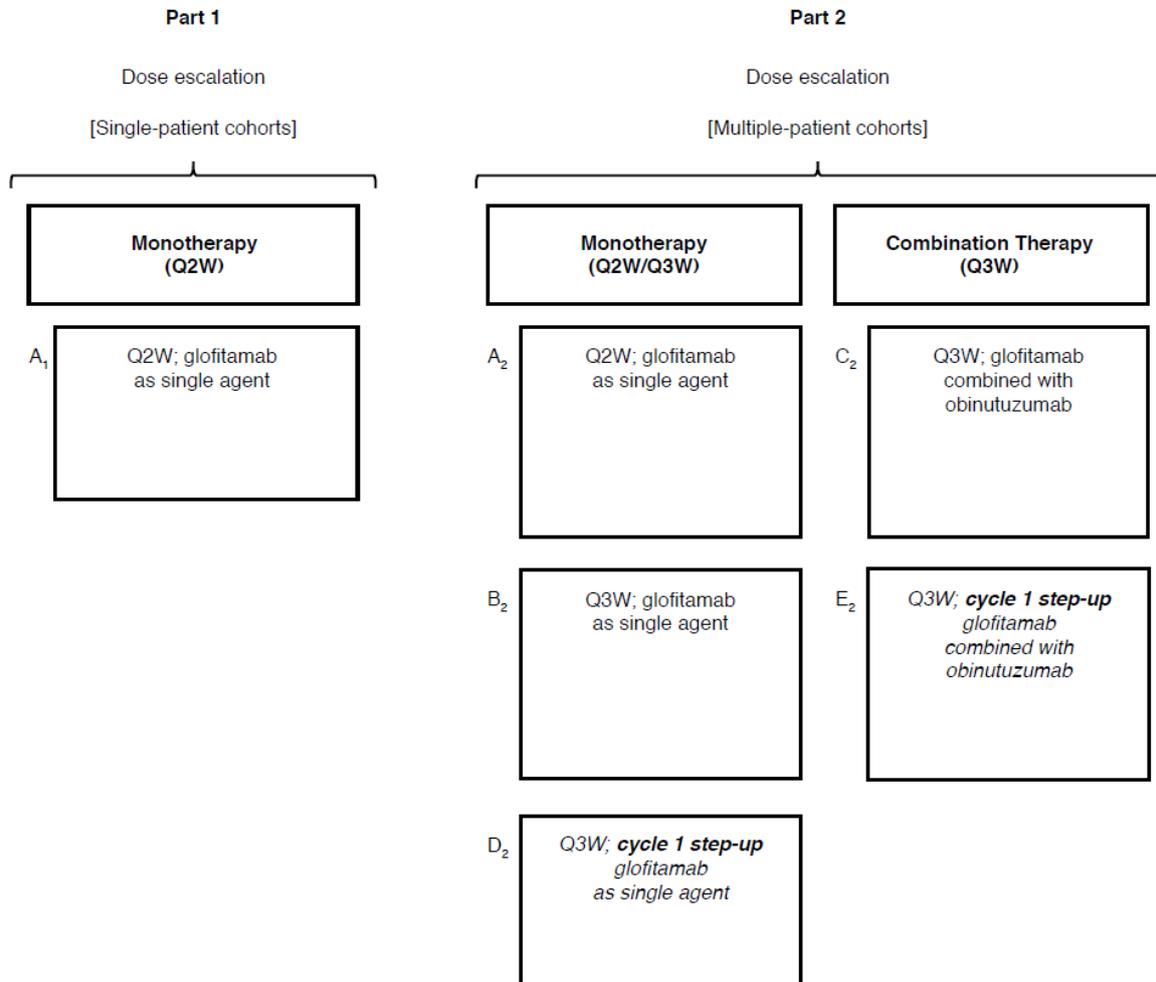
Q2W, every 2 weeks; Q3W, every 3 weeks.

Figure S2. Patient flow and disposition from the glofitamab dose-escalation part of the study in (A) patients who received glofitamab fixed and step-up doses and in patients wo received the recommended phase II dose (2.5/10/30 mg) as of August 3, 2020 (safety-evaluable population). (B) Numbers of patients in each individual dose group.

A
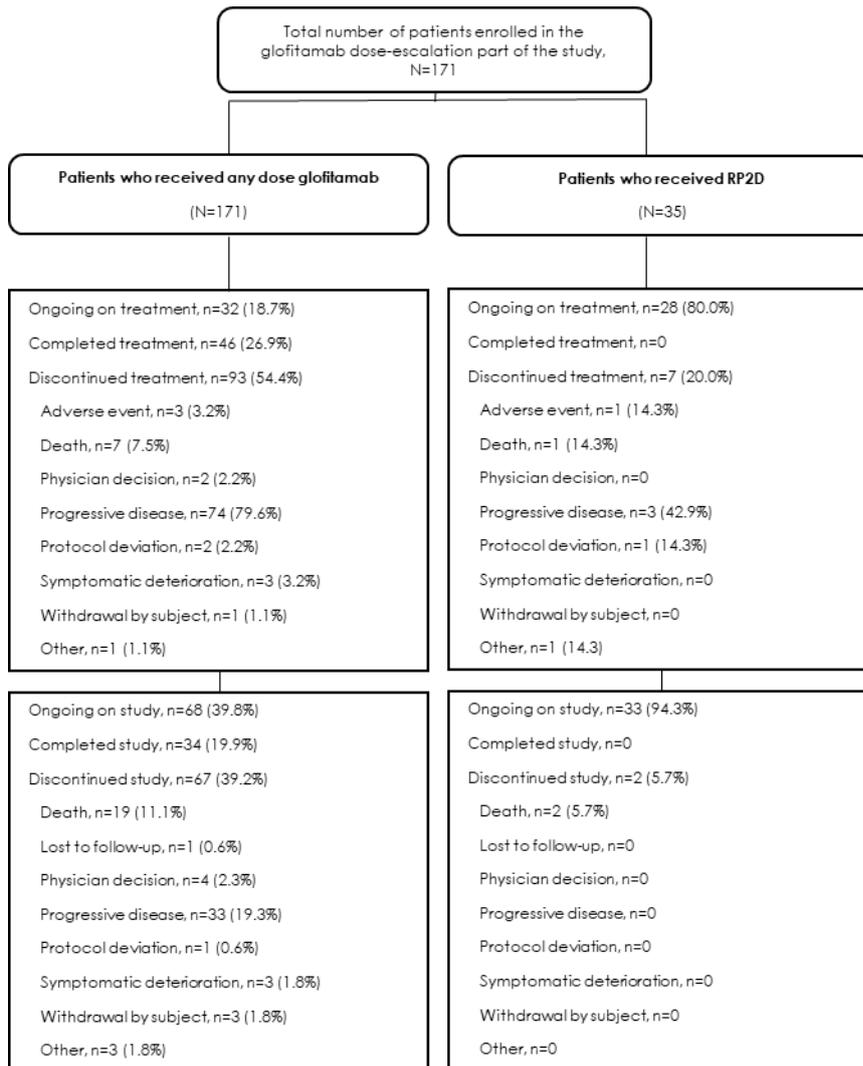
B
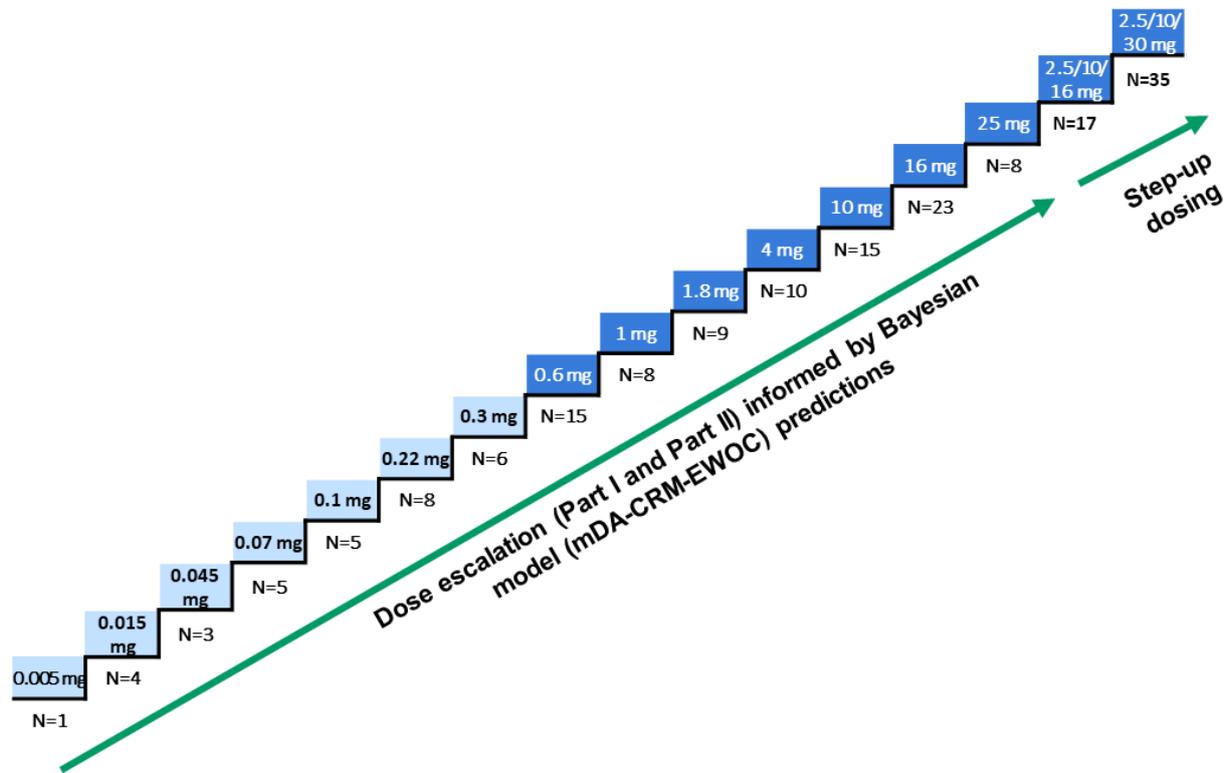
mDA-CRM-EWOC, Bayesian-modified, data-augmented, continuous reassessment method with overdose control

Figure S3. Proportion of subgroups of patients experiencing cytokine release syndrome by Lee Grade[18]
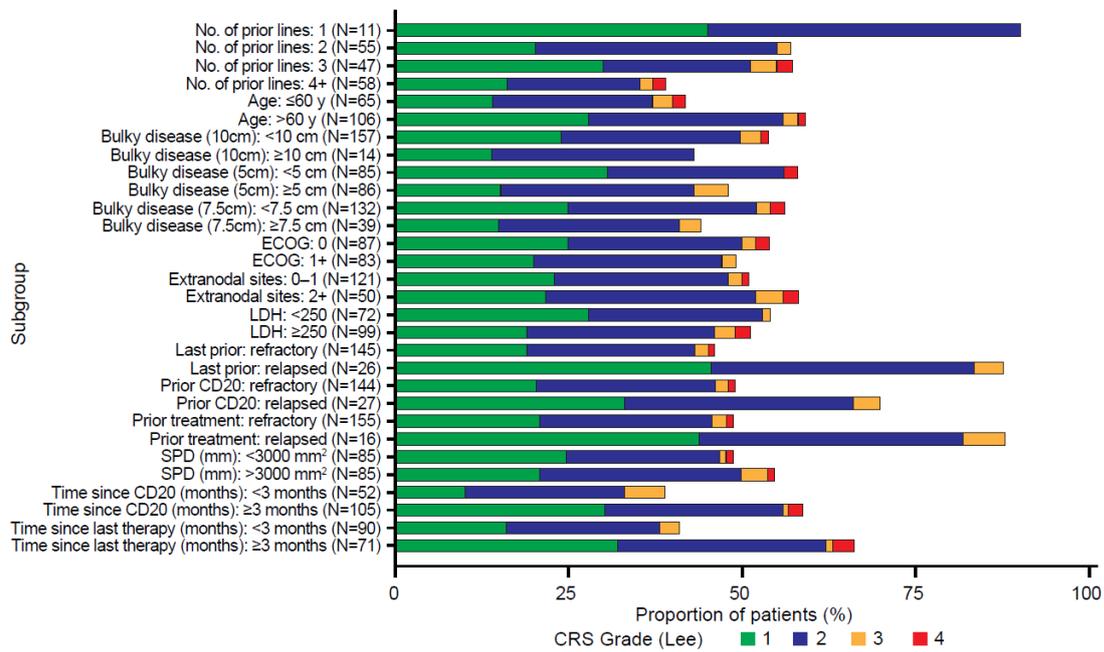
ASCT, autologous stem cell transplant, CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactase dehydrogenase; SPD, Sum of products of lesion diameters.

Figure S4. Efficacy of glofitamab in subgroups of patients who received ≥10 mg: forest plots of (A) complete and (B) overall response rates by patient subgroup in the primary efficacy population. Response rate and confidence interval calculated using Copper–Pearson method.

A

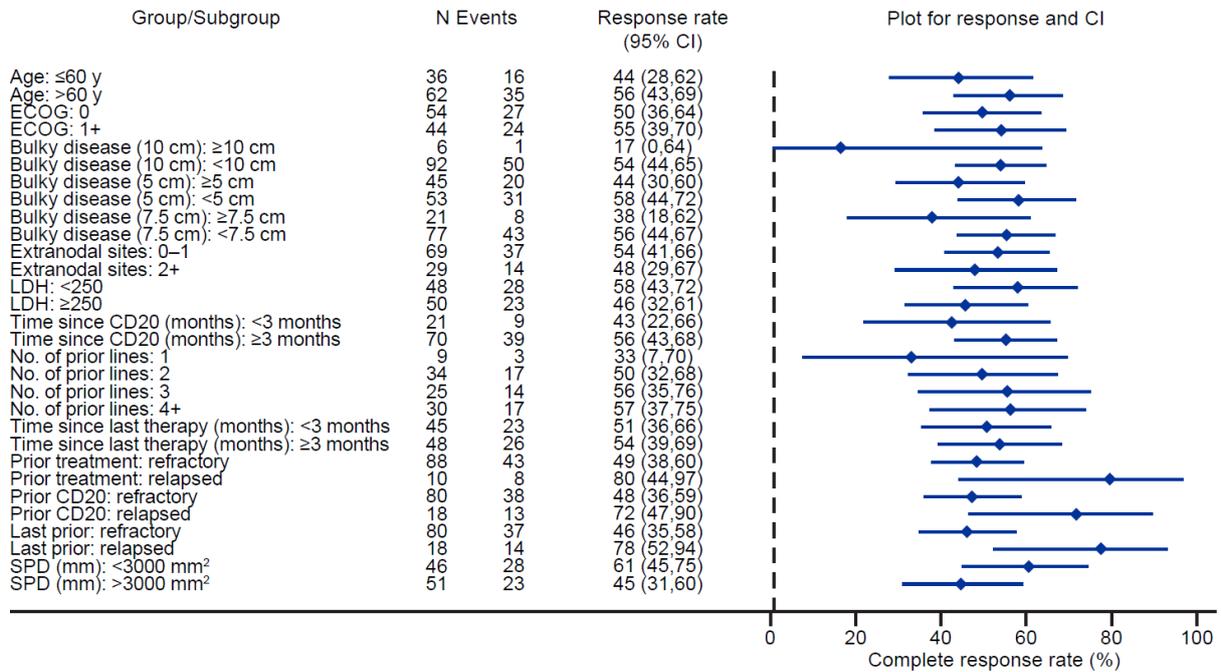| Group/Subgroup	N	Events	Response rate (95% CI)
Age: ≤60 y	36	16	44 (28,62)
Age: >60 y	62	35	56 (43,69)
ECOG: 0	54	27	50 (36,64)
ECOG: 1+	44	24	55 (39,70)
Bulky disease (10 cm): ≥10 cm	6	1	17 (0,64)
Bulky disease (10 cm): <10 cm	92	50	54 (44,65)
Bulky disease (5 cm): ≥5 cm	45	20	44 (30,60)
Bulky disease (5 cm): <5 cm	53	31	58 (44,72)
Bulky disease (7.5 cm): ≥7.5 cm	21	8	38 (18,62)
Bulky disease (7.5 cm): <7.5 cm	77	43	56 (44,67)
Extranodal sites: 0–1	69	37	54 (41,66)
Extranodal sites: 2+	29	14	48 (29,67)
LDH: <250	48	28	58 (43,72)
LDH: ≥250	50	23	46 (32,61)
Time since CD20 (months): <3 months	21	9	43 (22,66)
Time since CD20 (months): ≥3 months	70	39	56 (43,68)
No. of prior lines: 1	9	3	33 (7,70)
No. of prior lines: 2	34	17	50 (32,68)
No. of prior lines: 3	25	14	56 (35,76)
No. of prior lines: 4+	30	17	57 (37,75)
Time since last therapy (months): <3 months	45	23	51 (36,66)
Time since last therapy (months): ≥3 months	48	26	54 (39,69)
Prior treatment: refractory	88	43	49 (38,60)
Prior treatment: relapsed	10	8	80 (44,97)
Prior CD20: refractory	80	38	48 (36,59)
Prior CD20: relapsed	18	13	72 (47,90)
Last prior: refractory	80	37	46 (35,58)
Last prior: relapsed	18	14	78 (52,94)
SPD (mm): <3000 mm^2	46	28	61 (45,75)
SPD (mm): >3000 mm^2	51	23	45 (31,60)

Plot for response and CI — Complete response rate (%); axis 0, 20, 40, 60, 80, 100

B

Group/Subgroup	N	Events	Response rate (95% CI)
Age: ≤60 y	36	21	58 (41,74)
Age: >60 y	62	41	66 (53,78)
ECOG: 0	54	35	65 (51,77)
ECOG: 1+	44	27	61 (46,76)
Bulky disease (10 cm): ≥10 cm	6	1	17 (0,64)
Bulky disease (10 cm): <10 cm	92	61	66 (56,76)
Bulky disease (5 cm): ≥5 cm	45	25	56 (40,70)
Bulky disease (5 cm): <5 cm	53	37	70 (56,82)
Bulky disease (7.5 cm): ≥7.5 cm	21	10	48 (26,70)
Bulky disease (7.5 cm): <7.5 cm	77	52	68 (56,78)
Extranodal sites: 0–1	69	44	64 (51,75)
Extranodal sites: 2+	29	18	62 (42,79)
LDH: <250	48	33	69 (54,81)
LDH: ≥250	50	29	58 (43,72)
Time since CD20 (months): <3 months	21	12	57 (34,78)
Time since CD20 (months): ≥3 months	70	46	66 (53,77)
No. of prior lines: 1	9	4	44 (14,79)
No. of prior lines: 2	34	19	56 (38,73)
No. of prior lines: 3	25	17	68 (47,85)
No. of prior lines: 4+	30	22	73 (54,88)
Time since last therapy (months): <3 months	45	29	64 (49,78)
Time since last therapy (months): ≥3 months	48	30	63 (47,76)
Prior treatment: refractory	88	54	61 (50,72)
Prior treatment: relapsed	10	8	80 (44,97)
Prior CD20: refractory	80	49	61 (50,72)
Prior CD20: relapsed	18	13	72 (47,90)
Last prior: refractory	80	47	59 (47,70)
Last prior: relapsed	18	15	83 (59,96)
SPD (mm): <3000 mm^2	46	32	70 (54,82)
SPD (mm): >3000 mm^2	51	30	59 (44,72)

Plot for response and CI — Overall response rate (%); axis 0, 20, 40, 60, 80, 100
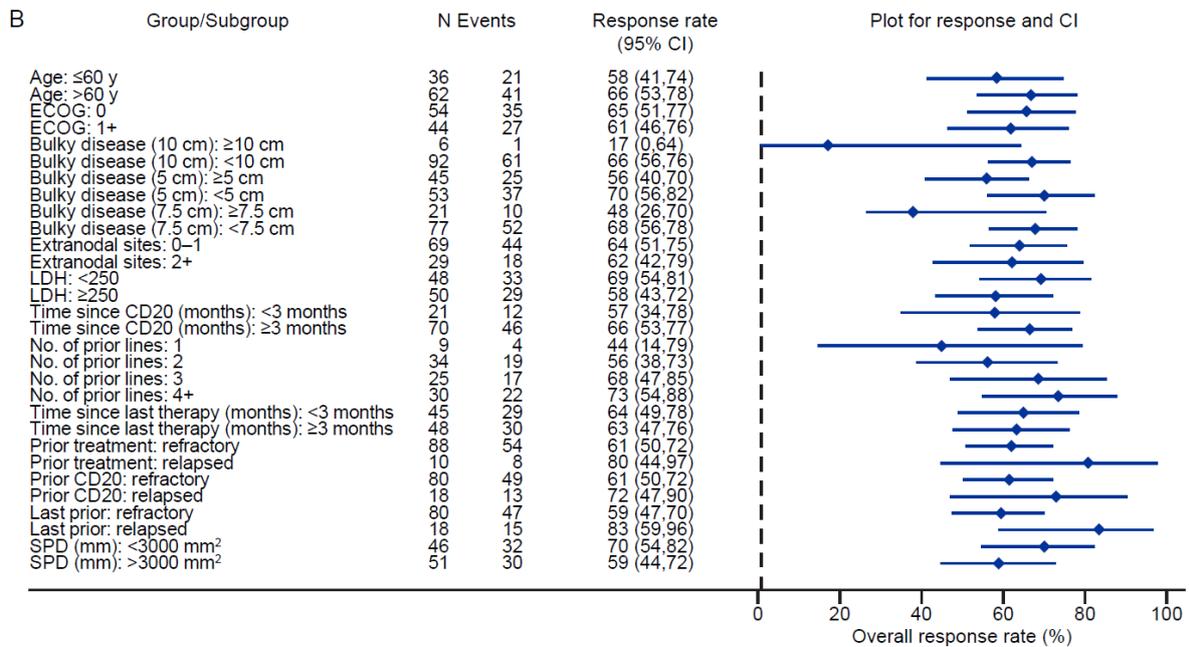
ASCT, autologous stem cell transplant, CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactase dehydrogenase; SPD, Sum of products of lesion diameters.
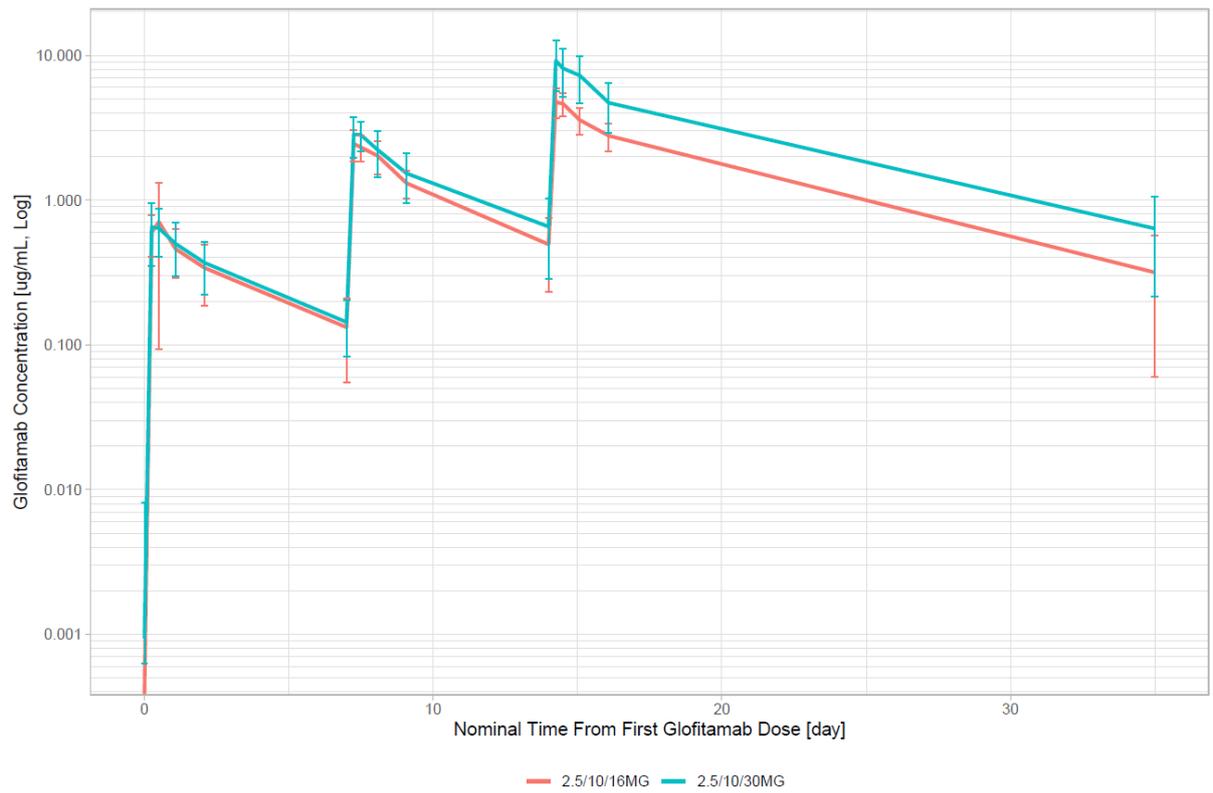
Primary efficacy population includes all patients who had a response assessment performed, who withdrew early from treatment or study, or who are still on treatment at the time of their first scheduled response.

Figure S5. Mean serum concentration-time profiles for glofitamab following cycle 1: **A**) fixed-dose, and **B**) step-up dosing administration across doses.
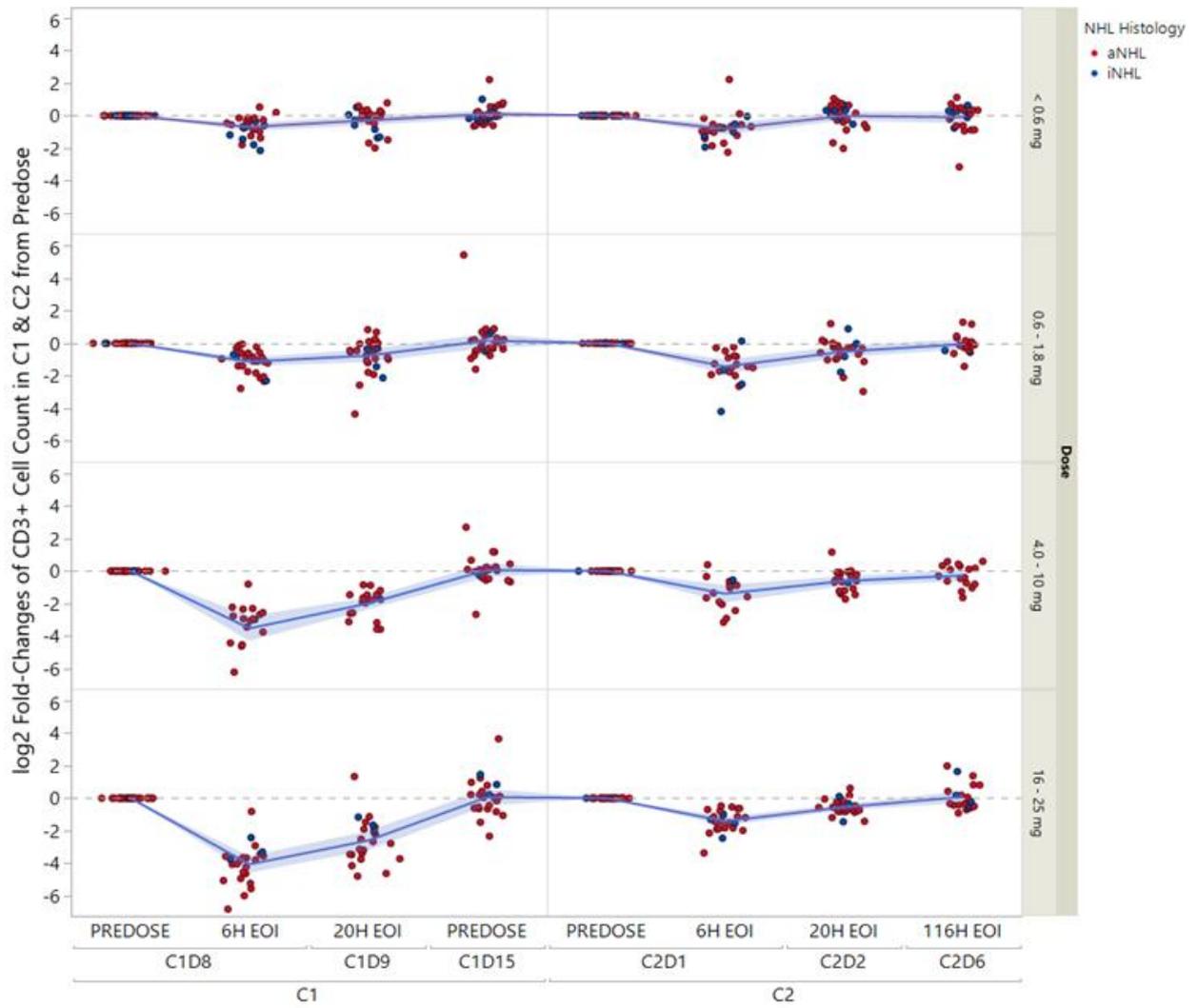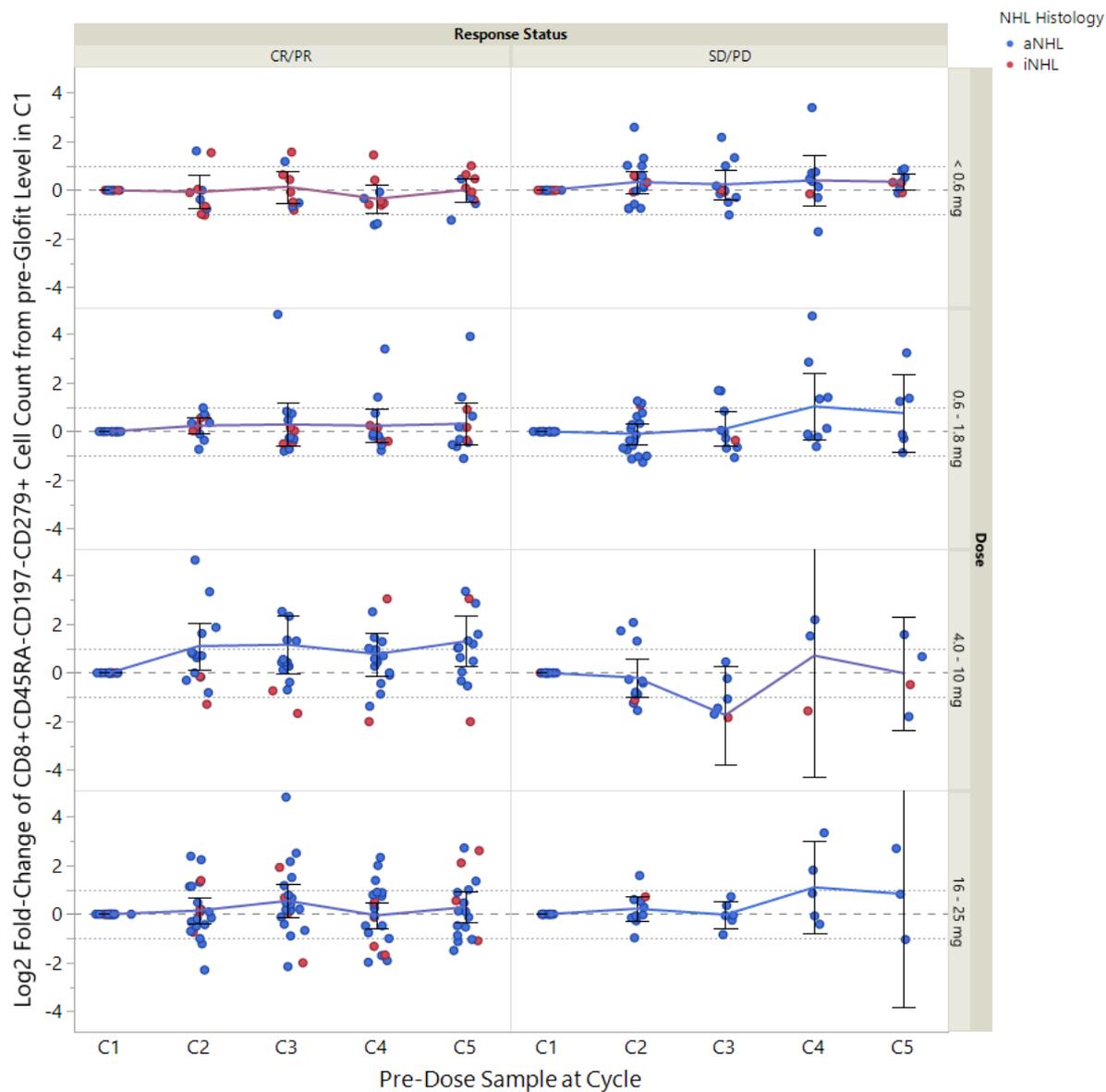
A
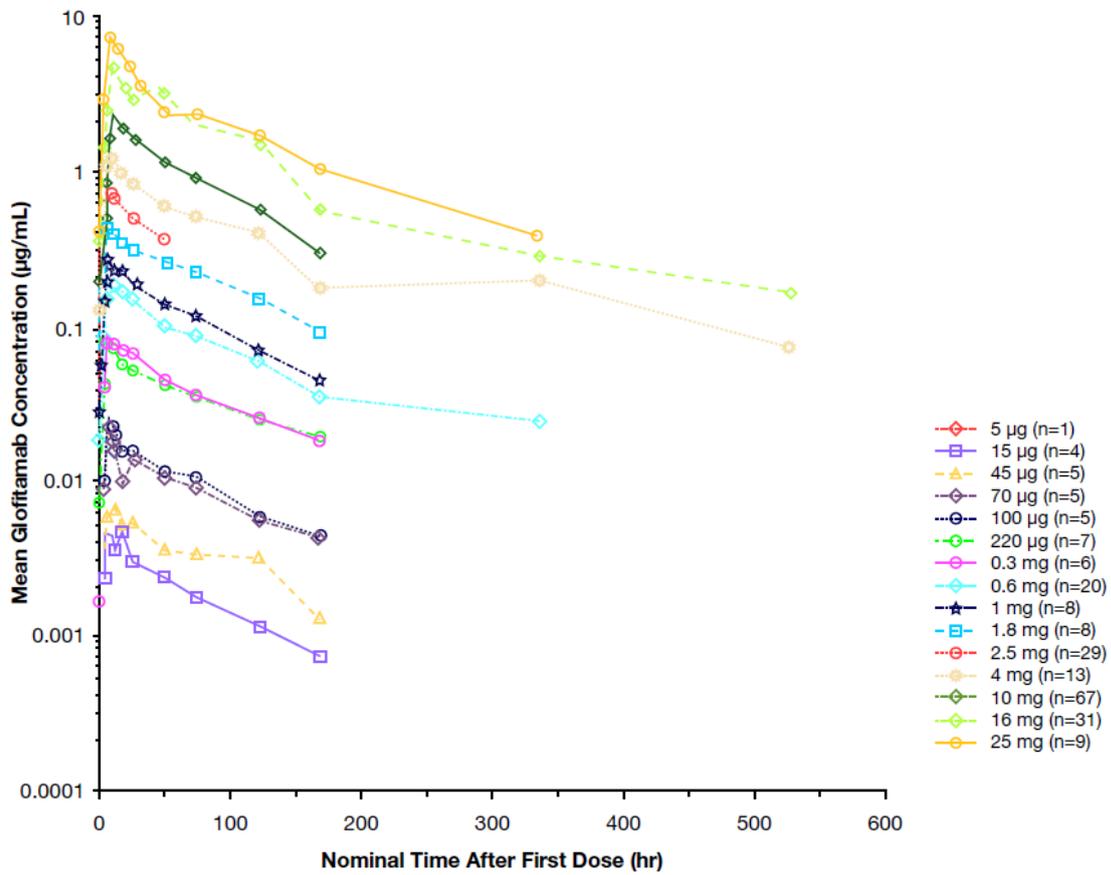
B

Figure S6. (A) Dose-dependent T-cell margination depicted by patient-specific (points) and mean (connected by solid lines, with 95% confidence intervals) fold change of CD3+ T cell count in peripheral blood from baseline at multiple time points after glofitamab dosing in cohorts who received fixed dosing. Changes are shown for indolent (blue) and aggressive (red) NHL at different doses. (B) Clinical response-dependent T-cell activation depicted by patient-specific (points) and mean (connected by solid lines, with 95% confidence intervals) fold change of PD1+ effector memory T-cell counts from baseline at each treatment cycle in cohorts who received glofitamab fixed dosing. Changes are shown in responding (CR/PR) and in non-responding (SD/PD) patients at different doses.
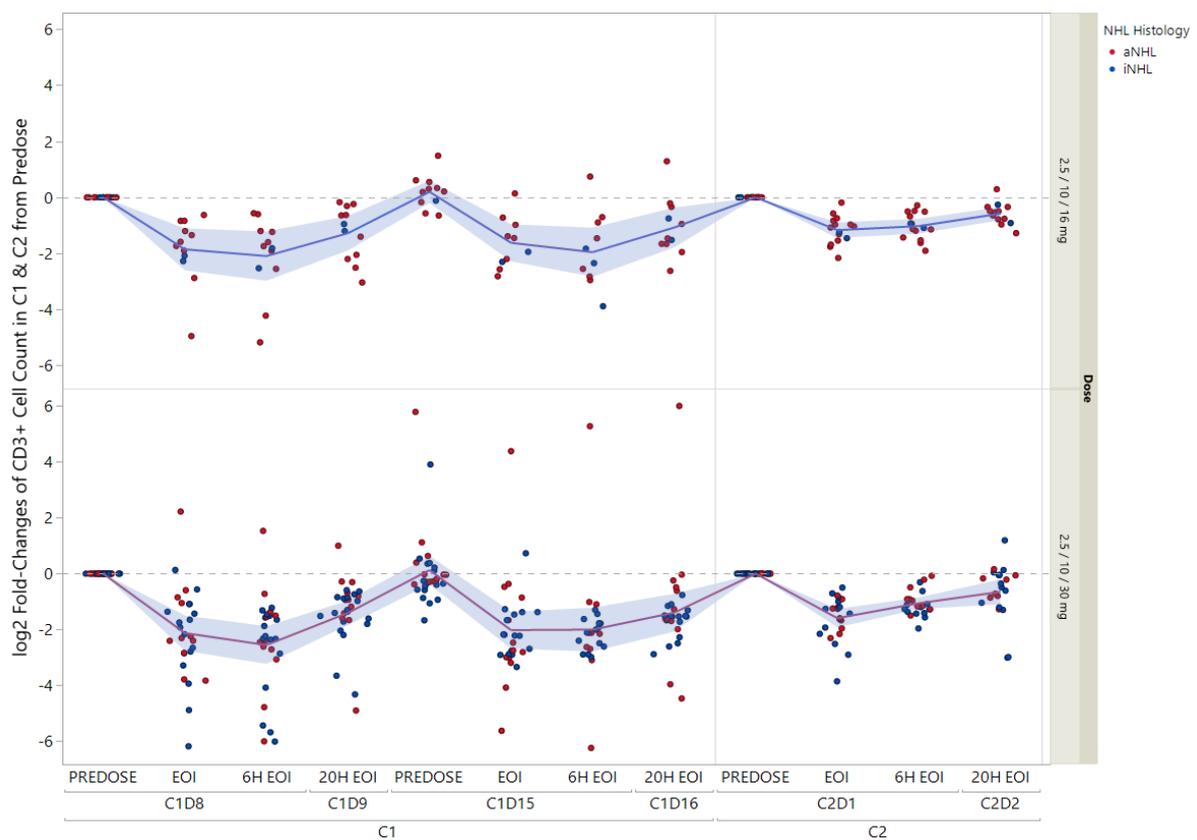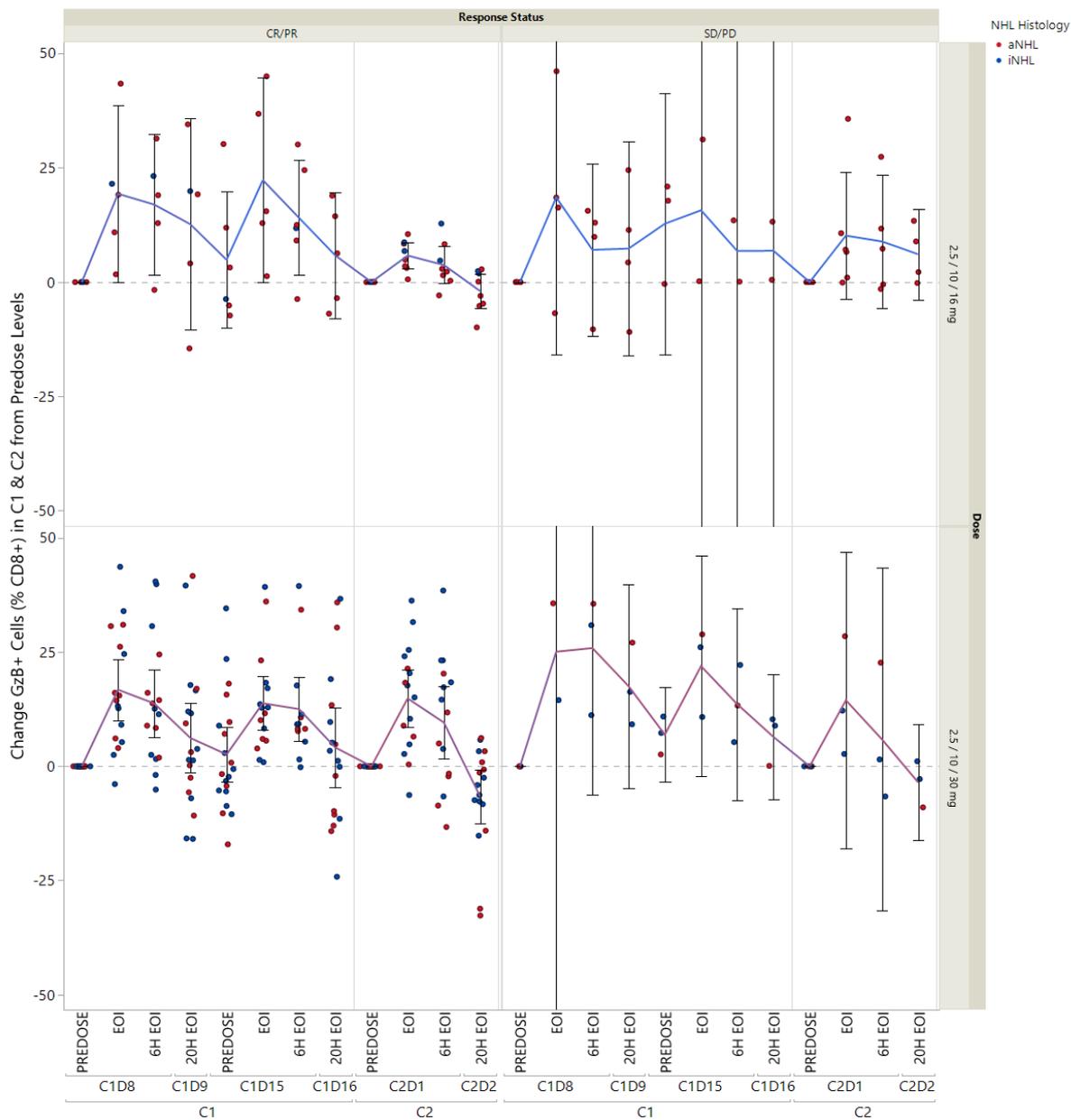
A

B

aNHL, aggressive non-Hodgkin lymphoma; CR, complete response; EOI, end of induction; iNHL, indolent non-Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; SD, stable disease.

Figure S7. (A) Dose-dependent T-cell margination depicted by patient-specific (points) and mean (connected by solid lines, with 95% confidence intervals) fold change of CD3+ T cell count in peripheral blood from baseline at multiple time points after glofitamab dosing in cohorts with step-up dosing. Changes are shown for indolent (blue) and aggressive (red) NHLs at different doses. (B) Dose-dependent T-cell activation depicted by patient-specific (points) and mean (connected by solid lines, with 95% confidence intervals) change of percentage CD8+ granzyme B+ T-cells from baseline at each treatment cycle in cohorts who received glofitamab step-up dosing. Changes are shown in responding (CR/PR) and in non-responding (SD/PD) patients at different doses.

A

B

aNHL, aggressive non-Hodgkin lymphoma; CR, complete response; EOI, end of induction; iNHL, indolent non-Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial response; SD, stable disease.

SUPPLEMENTARY TABLES

Table S1. Cytokine Release Syndrome Signs and Symptoms Occurring in ≥ 5% of Patients

Receiving Glofitamab (Safety-Evaluable Patients).

Number of Patients (%)	Glofitamab Cohorts* (N = 171)	RP2D glofitamab cohort (N = 35)
Any cytokine release syndrome symptoms	86 (50.3)	25 (71.4)
Pyrexia	79 (46.2)	25 (71.4)
Grade 1	35 (20.5)	13 (37.1)
Grade 2	39 (22.8)	11 (31.4)
Grade 3	5 (2.9)	1 (2.9)
Hypotension	42 (24.6)	6 (17.1)
Grade 1	10 (5.8)	0
Grade 2	24 (14.0)	4 (11.4)
Grade 3	8 (4.7)	2 (5.7)
Tachycardia	27 (15.8)	9 (25.7)
Grade 1	21 (12.3)	8 (22.9)
Grade 2	5 (29)	1 (2.9)

Grade 3	1 (0.6)	0
Chills	21 (12.3)	6 (17.1)
Grade 1	16 (9.4)	5 (14.3)
Grade 2	5 (2.9)	1 (2.9)
Grade 3	0	0
Hypoxia	14 (8.2)	4 (11.4)
Grade 1	4 (2.3)	2 (5.7)
Grade 2	7 (4.1)	2 (5.7)
Grade 3	3 (1.8)	0
Nausea	10 (5.8)	4 (11.4)
Grade 1	7 (4.1)	3 (8.6)
Grade 2	2 (1.2)	1 (2.9)
Grade 3	1 (0.6)	0

Table S2. Neurologic Adverse Events Occurring in ≥5% of Patients Receiving Glofitamab (Safety-Evaluable Patients).

Number of Patients (%)	Glofitamab Cohorts* (N = 171)	RP2D glofitamab cohort (N = 35)
Any neurologic adverse events	74 (43.3)	11 (31.4)
Headache	22 (12.9)	2 (5.7)
Grade 1	14 (8.2)	0
Grade 2	8 (4.7)	2 (5.7)
Grade 3	0	0
Dizziness	10 (5.8)	2 (5.7)
Grade 1	10 (5.8)	2 (5.7)
Grade 2	0	0
Grade 3	0	0