Supplemental materials to:

Single-agent mosunetuzumab shows durable complete responses in patients with relapsed or refractory B-cell lymphomas: Phase I dose escalation study

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Contents

Supplementary Methods

Complete Inclusion and Exclusion Criteria

Inclusion Criteria

Patients had to meet the following criteria for study entry:

- Signed Informed Consent Form(s)
- Aged ≥ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Life expectancy of at least 12 weeks
- History of one of the following histologically documented hematologic malignancies that was expected to express the CD20 antigen, who had relapsed after or failed to respond to at least one prior systemic treatment regimen, and for whom there was no available therapy expected to improve survival (eg, standard chemotherapy or autologous stem cell transplant):
    - Dose-escalation cohorts:

      Grade 1-3B follicular lymphoma; marginal zone lymphoma (including splenic, nodal, and extranodal), transformed indolent non-Hodgkin lymphoma (NHL), Richter's transformation, diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, small lymphocytic lymphoma, or mantle cell lymphoma (MCL)

        - Patients with Richter's transformation who had an absolute lymphocyte count ≥ 5000 per µL were not eligible for enrollment
        - Burkitt lymphoma and lymphoplasmacytic lymphoma were not eligible diagnoses for enrollment into this study

- Interim expansion cohorts:
    - DLBCL/transformed follicular lymphoma (FL) cohort: patients must have 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). Transformed FL is an eligible diagnosis for enrollment in the DLBCL cohort but must be relapsed or refractory to standard therapies for transformed FL
    - FL cohort: grades 1-3A FL; patients must have relapsed after or failed to respond to at least two prior lines of systemic therapy and must have received prior treatment with an anti-CD20-directed therapy and an alkylating agent
    - MCL cohort: patients must have relapsed after or failed to respond to at least one prior treatment regimen containing a Bruton's tyrosine kinase (BTK) inhibitor. If BTK inhibitor was received during participation in a clinical trial, patients must have received treatment at a therapeutic dose level

- At least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension for nodal lesions, or > 1.0 cm in its largest dimension for extranodal lesions by computerized tomography scan or magnetic resonance imaging)
- For patients with DLBCL 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, and *BCL2* and *MYC* abnormalities, had to be provided, if done

- Agreement to provide tumor samples, as follows:
    - For NHL patients with more than one bi-dimensionally measurable lesion (> 1.5 cm in the largest dimension for nodal lesions, or > 1.0 cm in its largest dimension for extranodal lesions by computerized tomography scan or magnetic resonance imaging), agreement to undergo biopsy from a safely accessible site per investigator determination. Biopsies obtained at any time between the last dose of last prior anticancer therapy and the first dose of mosunetuzumab were acceptable
    - Patients who could not undergo biopsy procedures were eligible for study enrollment after confirming with the Medical Monitor. In such cases, archival tumor tissue samples (paraffin blocks or at least 15 unstained slides) had to be made available to the Sponsor
- Adverse events (AEs) from prior anticancer therapy that had resolved to grade ≤ 1
- Laboratory values, as follows:
    - Hepatic function
        - Aspartate transaminase and alanine transaminase ≤ 3 × the upper limit of normal
        - Total bilirubin ≤ 1.5 × the upper limit of normal; patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations were accompanied by elevated indirect bilirubin were eligible
    - Hematologic function

        - Platelet count ≥ 75,000 per mm^3 without transfusion within 14 days prior to first dose of mosunetuzumab
        - Absolute neutrophil count ≥ 1000 per mm^3
        - Total hemoglobin ≥ 10 g per dL without transfusion within 21 days prior to first dose of mosunetuzumab
        - Patients who did not meet the criteria for hematologic function because of extensive marrow involvement of NHL and/or disease-related cytopenias (eg, immune thrombocytopenia) could be enrolled into the study after discussion with and confirmation by the Medical Monitor
    - Serum creatinine less than the upper limit of normal or estimated creatinine clearance ≥ 60 mL per minute by the Cockcroft-Gault method or other institutional standard methods (eg, based on nuclear medicine renal scan)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use contraceptive methods that result in a failure rate of < 1% per year, and agreement to refrain from donating eggs, during the treatment period and for at least 3 months after the last dose of mosunetuzumab or tocilizumab (if applicable), whichever was longer
    - A woman was considered to be of childbearing potential if she was post-menarcheal, had not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and had not undergone surgical sterilization (removal of ovaries and/or uterus)
    - Examples of contraceptive methods with a failure rate of < 1% per year were bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices

    - The reliability of sexual abstinence was evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal were not acceptable methods of contraception
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
    - With female partners of childbearing potential or pregnant female partners, men had to remain abstinent or use a condom during the treatment period and for at least 60 days after the last dose of mosunetuzumab and tocilizumab (if applicable) to avoid exposing the embryo. Men had to refrain from donating sperm during this same period
    - The reliability of sexual abstinence was evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence and withdrawal were not acceptable methods of contraception
- Patients treated with alemtuzumab, fludarabine, cladribine, or pentostatin within 6 months before first mosunetuzumab administration could be enrolled only after confirming with the Medical Monitor.

<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 activities restrictions
- Pregnant or lactating, or intending to become pregnant during the study or within 3 months after the last dose of mosunetuzumab and tocilizumab (if applicable)
    - Women who were not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (removal of ovaries and/or uterus) had to have a negative serum pregnancy test result within 14 days prior to initiation

of study drug. If a serum pregnancy test was performed within 14 days prior to receiving first study treatment, a negative urine pregnancy test result (performed within 7 days prior to study treatment) had to be available

- Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate within 4 weeks before first mosunetuzumab administration
- Prior treatment with systemic immunotherapeutic agents for which the mechanism of action involved T cells, including but not limited to cytokine therapy and anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies, within 12 weeks or five half-lives of the drug, whichever was shorter, before first mosunetuzumab administration
- Treatment-emergent immune-related AEs associated with prior immunotherapeutic agents (eg, immune checkpoint inhibitor therapies), as follows:
    - Grade ≥ 3 AEs except for grade 3 endocrinopathy managed with replacement therapy
    - Grade 1-2 AEs that did not resolve to baseline after treatment discontinuation
    - For certain prior treatments, such as chimeric antigen receptor (CAR)-T cell therapies, patients with prior immune-related grade ≥ 3 AEs (eg, cytokine release syndrome [CRS]) could enroll after discussion with and confirmation by the Medical Monitor
- Treatment with any chemotherapeutic agent, or treatment with any other anticancer agent (investigational or otherwise) within 4 weeks or five half-lives of the drug, whichever was shorter, prior to first mosunetuzumab administration
- Treatment with radiotherapy within 2 weeks prior to the first mosunetuzumab administration. If patients had received radiotherapy within 4 weeks prior to the first mosunetuzumab administration, they had to have at least one measurable lesion

outside of the radiation field. Patients with only one measurable lesion that was previously irradiated but subsequently progressed were eligible

- Autologous stem cell transplant within 100 days prior to first mosunetuzumab administration
- Prior treatment with CAR-T therapy within 30 days before first mosunetuzumab administration
- Current eligibility for autologous stem cell transplant in patients with relapsed/refractory DLBCL or relapsed/refractory transformed FL
- Prior allogeneic stem cell transplant
- Prior solid organ transplantation
- History of autoimmune disease, including but not limited to myocarditis, pneumonitis, 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 remote history of, or well-controlled autoimmune disease, were eligible to enroll after discussion with and confirmation by the Medical Monitor
        - Patients with controlled Type 1 diabetes mellitus who were on an insulin regimen were eligible for the study
    - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone might be eligible for this study
    - Patients with a history of disease-related immune thrombocytopenic purpura or autoimmune hemolytic anemia might be eligible for this study

- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (eg, patients with psoriatic arthritis were excluded) were eligible for the study, provided all of the following conditions were met:
    - Rash had to cover < 10% of the body surface area
    - Disease was well controlled at baseline and required only low-potency topical corticosteroids
    - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months

- Patients with a history of confirmed progressive multifocal leukoencephalopathy
- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
- History of other malignancy that could affect compliance with the protocol or interpretation of the results
    - Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix were allowed
    - Patients with a malignancy that had been treated with curative intent were also allowed if the malignancy was in remission without treatment for ≥ 2 years prior to first mosunetuzumab administration
- 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

    - Patients with a history of stroke who had not experienced a stroke or transient ischemic attack in the past 2 years and had no residual neurologic deficits, as judged by the investigator were allowed
    - Patients with a history of epilepsy who had no seizures in the past 2 years while not receiving any antiepileptic medications were not allowed in the dose-escalation cohorts
- 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
- Significant active pulmonary disease (eg, bronchospasm and/or obstructive pulmonary disease)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with intravenous antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to first mosunetuzumab administration
- Known or suspected chronic active Epstein Barr Virus infection
- Recent major surgery within 4 weeks prior to first mosunetuzumab administration
    - Protocol-mandated procedures (eg, tumor biopsies and bone marrow biopsies) were permitted
- Positive serologic or polymerase chain reaction test results for acute or chronic hepatitis B virus infection
    - Patients whose hepatitis B virus infection status could not be determined by serologic test results (www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf)

had to be negative for hepatitis B virus by polymerase chain reaction to be eligible for study participation

- Acute or chronic hepatitis C virus infection
    - Patients who were positive for hepatitis C virus antibody had to be negative for hepatitis C virus by polymerase chain reaction to be eligible for study participation
- Positive serologic test results for HIV infection
- Administration of a live, attenuated vaccine within 4 weeks before first dose of study treatment or anticipation that such a live attenuated vaccine would be required during the study
    - Patients could not receive live, attenuated vaccines (eg, FluMist) while receiving study treatment or after the last dose until B-cell recovery to the normal ranges. Killed vaccines or toxoids had to be given at least 4 weeks prior to the first dose of study treatment to allow development of sufficient immunity
    - Inactivated influenza vaccination had to be given during influenza season only
    - Investigators had to review the vaccination status of potential study patients that were considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with any other non-live vaccines intended to prevent infectious diseases prior to study
- Received systemic immunosuppressive medications (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor agents) except for corticosteroid treatment ≤ 10 mg per day prednisone or equivalent within 2 weeks prior to first dose of mosunetuzumab

- Patients who received acute, systemic immunosuppressant medications (eg, a single dose of dexamethasone for nausea or B symptoms) could be enrolled in the study after discussion with and confirmation by the Medical Monitor
- The use of inhaled corticosteroids was permitted
- The use of mineralocorticoids for management of orthostatic hypotension was permitted
- The use of physiologic doses of corticosteroids for management of adrenal insufficiency was permitted

- History of illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's or Medical Monitor's judgment, precluded the patient's safe participation in and completion of the study, or which could affect compliance with the protocol or interpretation of results.

Dose Escalation in Single-Patient Cohorts in Group A

The starting dose of mosunetuzumab in Group A was 0.05 mg based on the minimum anticipated biological-effect level in humans. Initial dose escalation utilized single-patient cohorts and dose-escalation increments of ≤ 300% of the preceding dose level until one of the following scenarios occurred:

a) A dose-limiting toxicity (DLT) or any grade ≥ 2 AE not considered by the investigator to be attributable to another identifiable cause
b) An increase in the peripheral blood interleukin-6 level of > 2-fold above baseline to levels exceeding 125 pg per mL, or any 5-fold increase in peripheral blood

interleukin-6 level, that was not considered by the investigator to be attributable to another identifiable cause (eg, infection)

c) Escalation reached a dose of 2 mg, which corresponds to the human equivalent dose of the mosunetuzumab no-observed-adverse-effect level based on toxicology studies in cynomolgus monkeys

d) Review of cumulative safety data by the internal monitoring committee identified a safety concern that warranted a lower dose interval increase.

If any one of the above four conditions (a, b, c, or d) was met, whichever occurred first, dose escalation was modified as follows as long as a DLT had not occurred:

a) Dose-escalation cohorts were converted from single-patient cohorts to cohorts of at least three patients according to a standard 3+3 dose-escalation design

b) The interval increase between successive cohorts was ≤ 100% of the preceding dose level.

Definition of Dose-Limiting Toxicities (DLTs)

All DLTs, including signs and symptoms of CRS, were graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events, version 4.0. A DLT was defined as any of the following AEs occurring during the DLT assessment period:

- Any grade 4 AE not considered by the investigator to be attributable to another clearly identifiable cause, with the following exceptions:
    - Grade 4 neutropenia that was not accompanied by a temperature elevation (single oral temperature of ≥ 38.3°C [101°F] or an oral temperature of ≥ 38.0°C [100.4°F] sustained for ≥ 1 hour) and which improved to grade ≤ 2 (or to ≥ 80% of the baseline value, whichever was lower) without the use of growth factor support within 1 week

- Grade 4 lymphopenia, which was an expected outcome of therapy
- Grade 4 leukopenia, which was an expected outcome of therapy

- Any grade 3 hematologic AE not considered by the investigator to be attributable to another clearly identifiable cause, with the following exceptions:
  - Grade 3 lymphopenia, which was an expected outcome of therapy
  - Grade 3 leukopenia, which was an expected outcome of therapy
  - Grade 3 neutropenia that was not accompanied by temperature elevation (single oral temperature of ≥ 38.3°C [101°F] or an oral temperature of ≥ 38.0°C [100.4°F] sustained for ≥ 1 hour) and which improved to grade ≤ 2 (or to ≥ 80% of the baseline value, whichever was lower) without the use of growth factor support within 1 week
  - Grade 3 thrombocytopenia that improves to grade ≤ 2 (or to ≥ 80% of the baseline value, whichever was lower) within 1 week without platelet transfusion and was not associated with bleeding that was considered clinically significant by the investigator
- Any grade 3 non-hematologic AE not considered by the investigator to be attributable to another clearly identifiable cause, with the following exceptions:
  - Grade 3 nausea or vomiting in the absence of premedication or that could be managed with resulting resolution to grade ≤ 2 with oral or intravenous antiemetics within 24 hours
    - Grade 3 nausea or vomiting that required total parenteral nutrition or hospitalization was not excluded and was considered a DLT
  - Grade 3 fatigue lasting ≤ 3 days
  - Grade 3 (National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0) individual signs and symptoms of CRS that

occurred in the context of grade ≤ 2 CRS and which lasted for < 3 days were not considered DLTs

- Grade 3 laboratory abnormality that was asymptomatic and deemed by the investigator not to be clinically significant

- Any hepatic function abnormality, as defined by the following:
  - Aspartate transaminase or alanine transaminase > 3 × the upper limit of normal AND total bilirubin > 2 × the upper limit of normal
    - Any aspartate transaminase or alanine transaminase > 3 × the upper limit of normal AND total bilirubin > 2 × the upper limit of normal where no individual laboratory value exceeded grade 3 and which lasted for < 3 days was not considered a DLT
  - Any grade 3 aspartate transaminase or alanine transaminase elevation with the following exception:
    - Any grade 3 aspartate transaminase or alanine transaminase elevation lasting for < 3 days was not considered a DLT.

Definition of Maximum Tolerated Dose (MTD)

- Group A: The MTD was defined as the highest dose level resulting in DLTs in < 17% of a minimum of 6 patients
- Group B: The cumulative MTD was defined as the highest cumulative Cycle 1 dose level resulting in DLTs in < 17% of a minimum of 6 patients during the period between Cycle 1 Day 15 and Cycle 1 Day 21.

Hospitalizations, Premedication and Management of Cytokine Release Syndrome

Seventy-two-hour hospitalizations (after Cycle 1 Day 1 dose in Group A, or after Cycle 1 Day 15 dose in Group B) were required for patients enrolled in dose-escalation cohorts, but

not for patients enrolled in the interim expansion cohorts. For at least the first two cycles, patients received steroid premedication (intravenous dexamethasone 20 mg or methylprednisolone 80 mg) 1 hour before each dose of mosunetuzumab. Management of CRS included corticosteroids and anti-interleukin-6 therapy (tocilizumab) in addition to supportive care.

Additional Assessments

Pharmacokinetics and Exposure-Response Relationships

During dose-escalation, serum samples for pharmacokinetic (PK) evaluation of mosunetuzumab were obtained from Group A and B patients at the following timepoints:

- Cycle 1:
    - For Group A: on Day 1 (predose, and at the end of infusion [within 0.5 hours] and 2 [± 0.5] hours post-infusion), Day 2, Day 3, Day 4, Day 8, Day 15
    - For Group B: on Day 1 (predose, and at the end of infusion [within 0.5 hours] and 2 [± 0.5] hours post-infusion), Day 2, Day 4, Day 8 (predose, and at the end of infusion [within 0.5 hours] and 2 [± 0.5] hours post-infusion), Day 9, Day 11, Day 15 (predose, and at the end of infusion [within 0.5 hours] and 2 [± 0.5] hours post-infusion), Day 16, and Day 18
- Cycles 2-8: on Day 1 (predose and at the end of infusion [within 0.5 hours] in Cycles 2-4, 6, and 8, and at 2 [± 0.5] hours post-infusion in Cycle 4) and Day 8 (in Cycles 2-4)
- Cycles 12 and 16: Day 1 (predose)
- End of treatment: at treatment completion/end of therapy and during the post-treatment follow-up at ≥ 90 days after last study drug administration.

Serum PK data of mosunetuzumab was well described by a population two-compartmental PK model with time-dependent clearance. The apparent half-life values reported were based on non-compartmental analyses. For exposure–response characterization in patients with indolent NHL, the relationship between complete response (CR)/overall response (OR) classification and the cumulative mosunetuzumab exposure over 42 days (area under curve; AUC0–42), calculated by the population PK modeling, was determined by logistic regression. Specifically, a binary outcome was used (0 for no CR or OR, and 1 for CR or OR classification). Due to the presence of residual circulating rituximab at baseline from prior treatments (particularly in patients with aggressive NHL histologies where time since last rituximab-containing treatment is generally shorter given the aggressive nature of disease), an additional model-based exposure metric of average CD20 receptor occupancy (RO%) of mosunetuzumab was derived based on the serum PK and binding affinity (KD) of both agents to assess the target engagement level over time as defined by Equation 1. C denotes concentration.

$$RO\%(t)_{mosun} = \frac{100 * C_{mosun}}{KD_{mosun} + C_{mosun} + \frac{KD_{mosun}}{KD_{rituximab}} * C_{rituximab}}$$

(Equation 1)

RO%0-42 was determined to be an appropriate metric to characterize the exposure–response relationship for CR and OR rates in patients with aggressive NHL histologies.

From a safety perspective, the exposure-response for occurrence of grade ≥ 2 CRS during 0 to 42 days in all NHL patients pooled across histologies was described by logistic regression using the maximal value of RO% during 0 to 42 days (ie. RO%max 0-42) as the appropriate exposure metric.

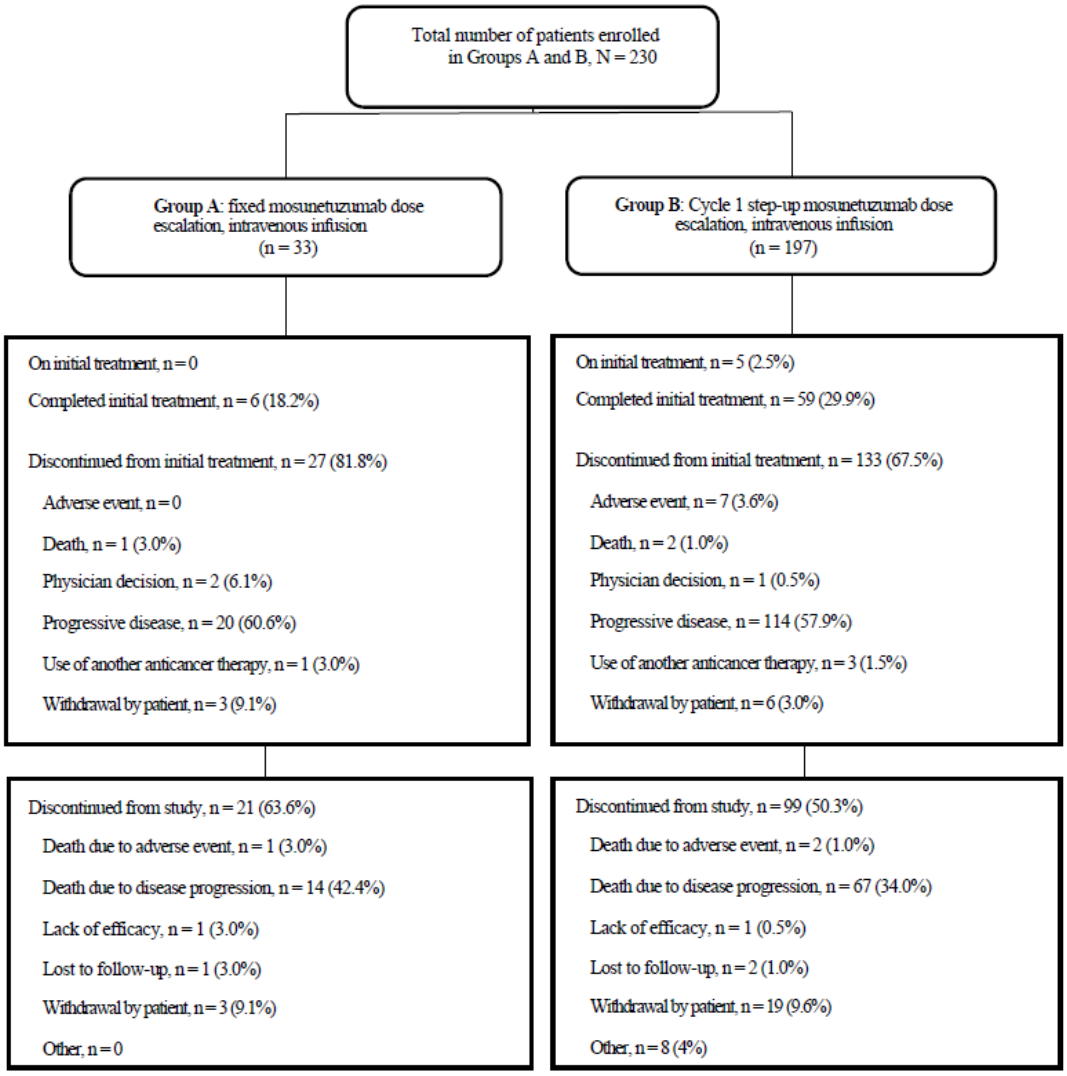
Pharmacodynamics

T-cell activation was measured in whole peripheral blood by flow cytometric determination of different cell-surface markers using a FACSCanto™ II instrument (BD Biosciences). Blood samples were drawn within 4 hours before infusion and 2 hours after the end of infusion of mosunetuzumab. Fluorescent dye-labelled monoclonal antibodies were used to detect the following cell surface markers: CD19, CD4, CD16, CD56, CD25, HLA-DR, CD69, PD-L1, and CD8.

Peripheral blood levels of interleukin-6 were monitored by ELISA. The assay was validated and the lower limit of quantification (LLOQ) was 3.13 pg/ml and the upper limit of quantification (ULOQ) was 300 pg/ml. Serum samples were collected within 4 hours before infusion start and at the end of infusion on Day 1, 8, and 15 of Cycle 1. For calculations of mean cytokine levels, values below the LLOQ were set to the LLOQ and samples above the ULOQ were set to the ULOQ.

Supplementary Figures

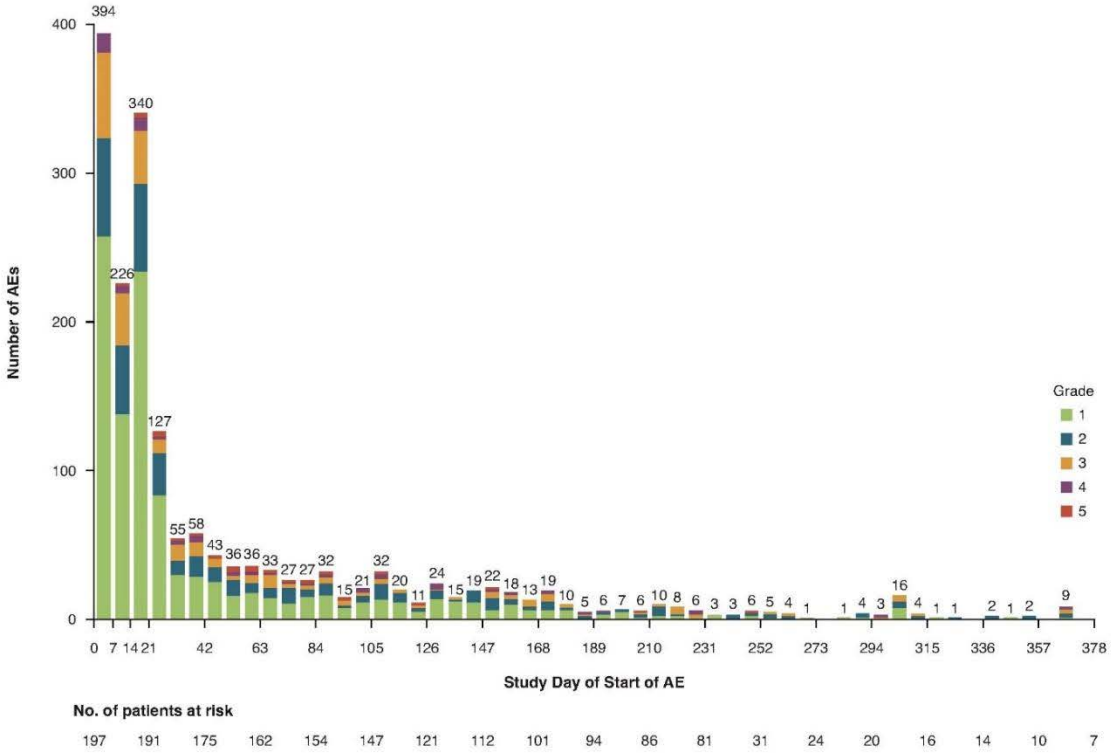
FIG S1. Patient flow and disposition.



Clinical cut-off date: January 21, 2020.

Initial treatment refers to the first 8 or 17 cycles of mosunetuzumab.

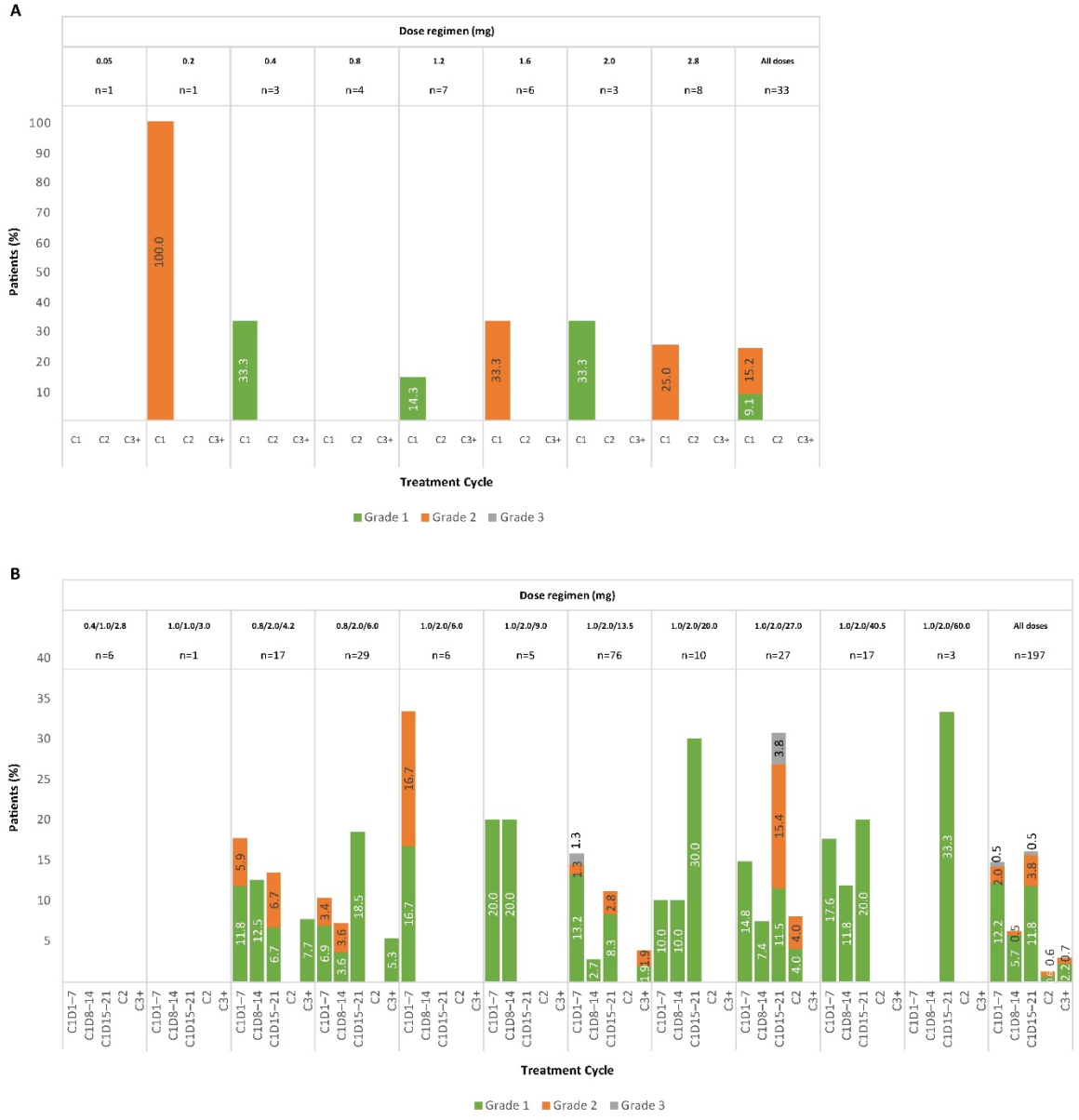
FIG S2. Distribution of onset of treatment-emergent adverse events by grade (Group B; safety population).



Clinical data cut-off: January 21, 2020.

AE, adverse event.

FIG S3. Distribution of onset of treatment-emergent cytokine release syndrome events by grade, and dose in Group A (**A**) and B (**B**) (safety population).

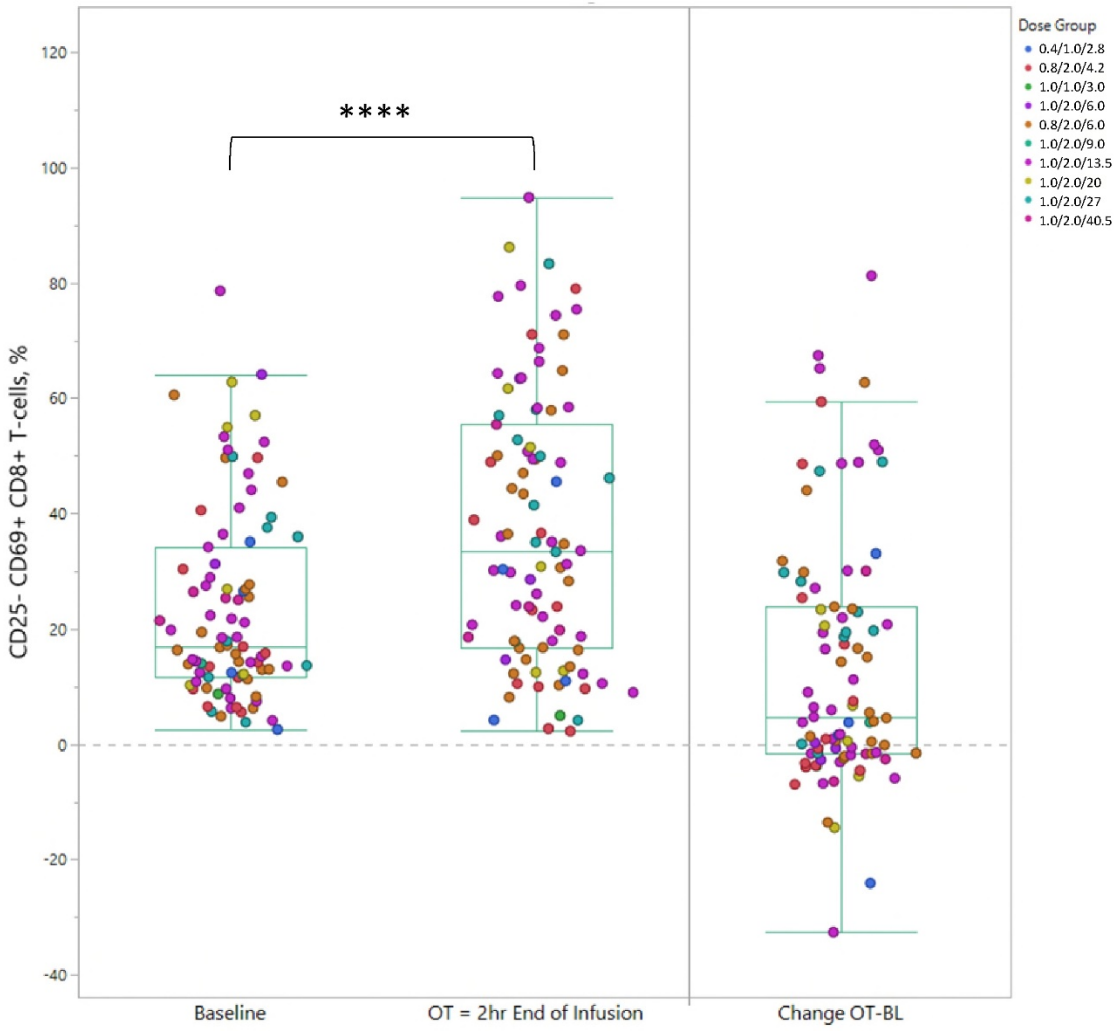


Clinical data cut-off: January 21, 2020.

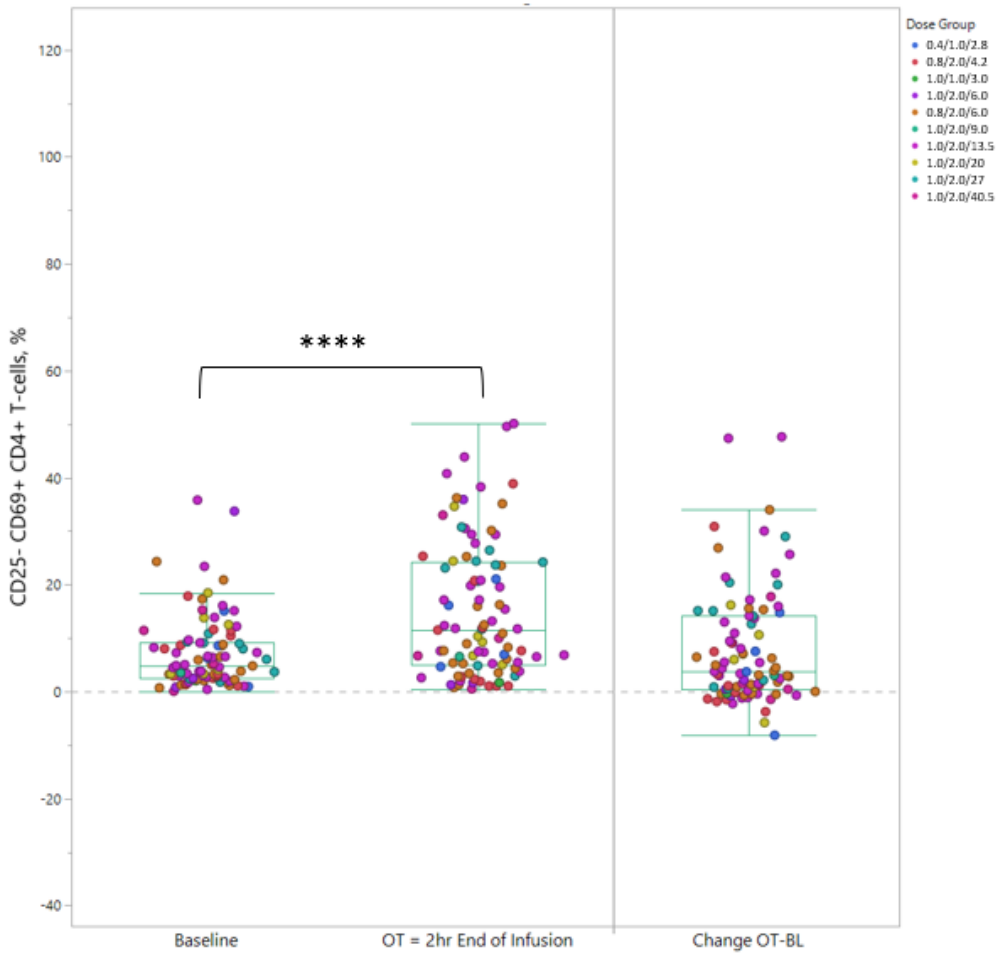
C, Cycle; D, Day.

FIG S4. Evidence of T-cell activation in peripheral (**A**) CD8+ and (**B**) CD4+ T cells in patients treated with Cycle 1 step-up dosing schedule (Group B biomarker-evaluable population).

A



B



Clinical data cut-off: January 21, 2020.

The expression of the immediate early activation marker CD69 on the surface of gated (**A**) CD8+ and (**B**) CD4+ T cell subpopulations was determined by flow cytometry at baseline and 2 hours after the first infusion and the percentages of activated, CD25-CD69+ T cell subpopulations were calculated. Values from 91 biomarker-evaluable patients are shown. Right subpanels exhibit absolute value of change from baseline to on-treatment for each patient. ****P values ($P < 0.0001$) matched pairs t-test.

BL, baseline; hr, hour; OT, on-treatment.

FIG S5. Kaplan-Meier curves for duration of response in Group B patients achieving complete response with: (A) aggressive non-Hodgkin lymphoma; and **(**B) indolent non-Hodgkin lymphoma.

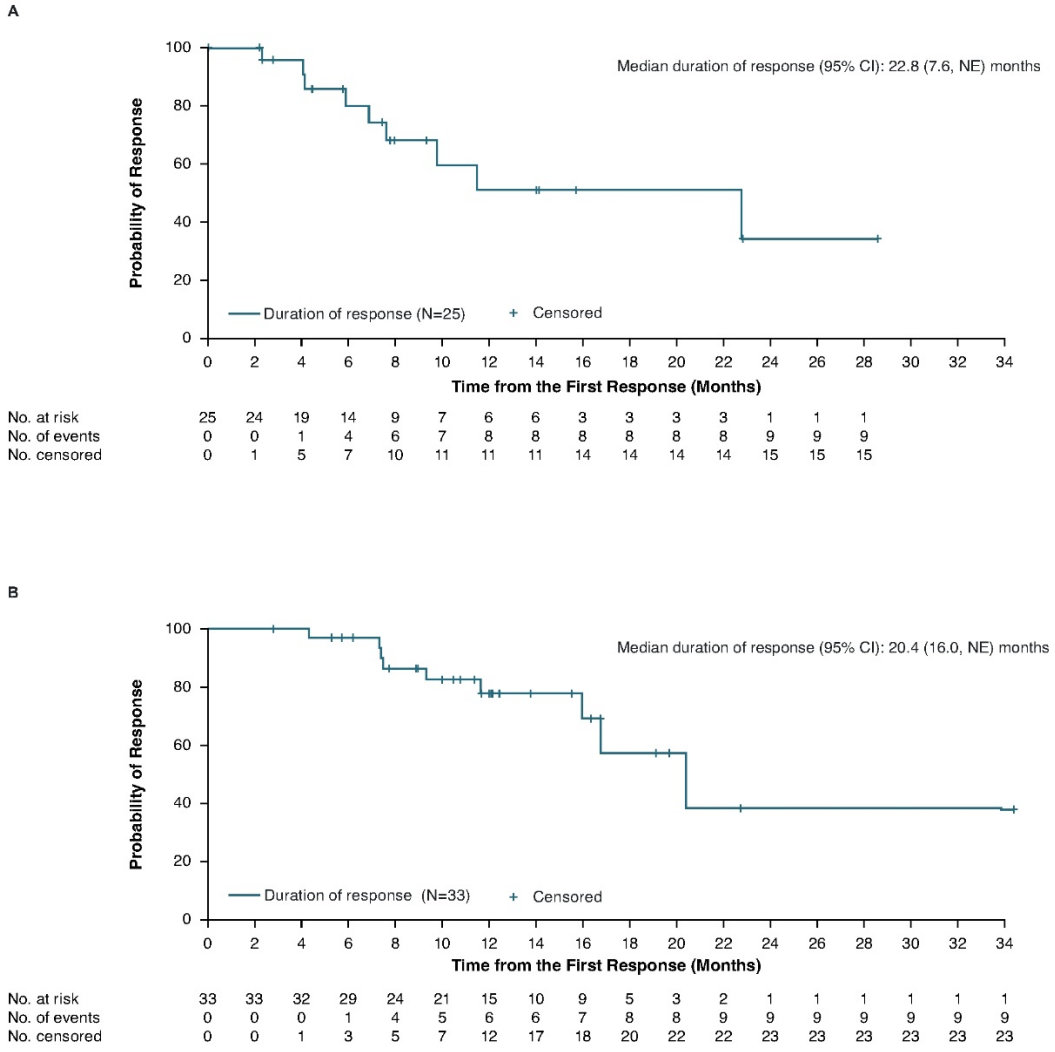
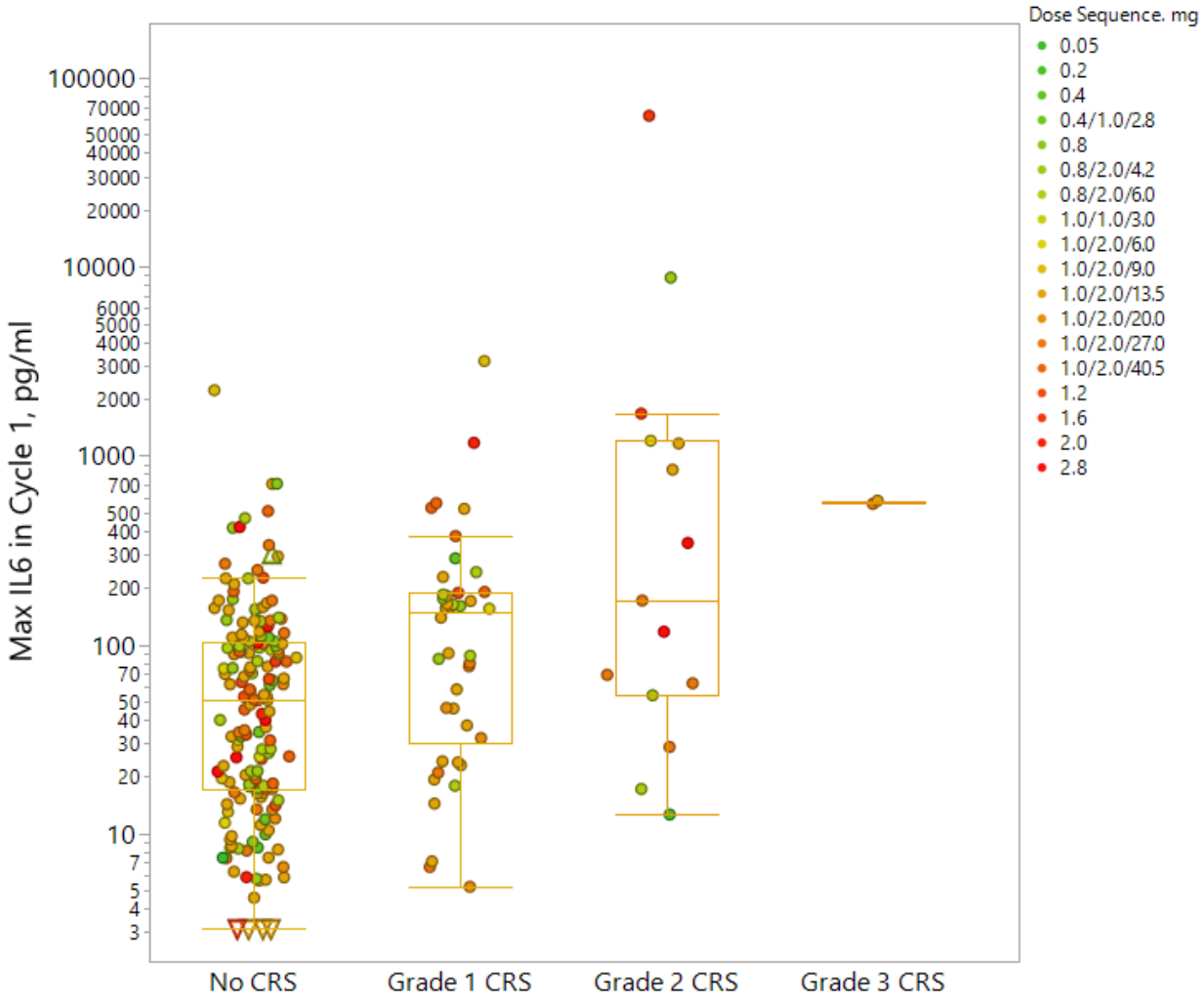
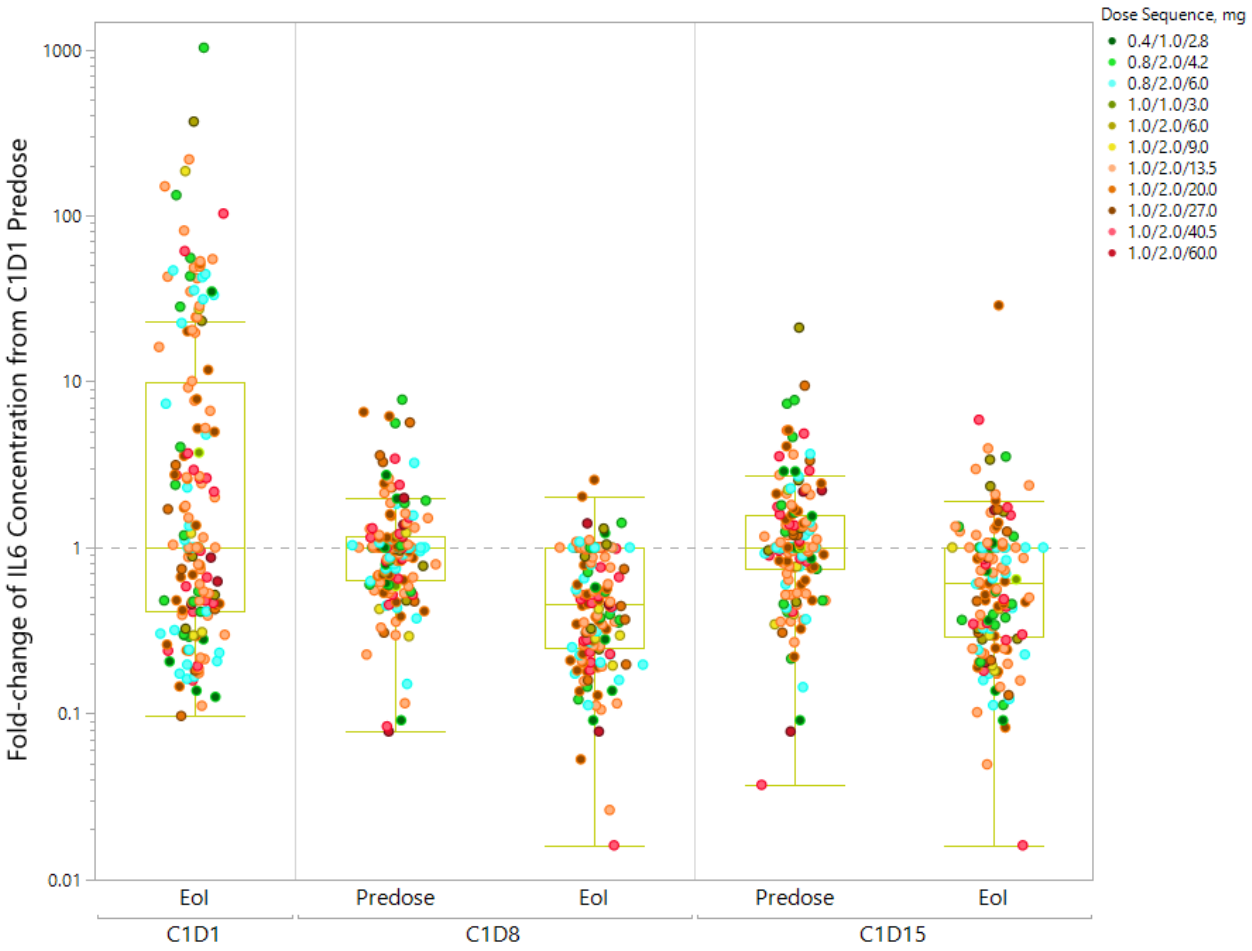


FIG S6. Interleukin-6 levels in plasma of patients treated with mosunetuzumab according to the occurrence of cytokine release syndrome. Panel (**A**) shows peak interleukin-6 levels observed during the first cycle in patients who experienced cytokine release syndrome grade 1-3 versus those who did not. A box extends from the 25th to 75th percentiles, with the bars extending to the minimum and maximum values with 1.5 times the interquartile range (difference between the 75th and 25th percentile). The horizontal line within the box indicates the median value. Panel (**B**) shows the kinetics of interleukin-6 during the first cycle in Group B patients.

A



B



Clinical data cut-off: January 21, 2020.

Δ Indicates data point above the ULOQ and plotted at the ULOQ (300 pg/ml).

∇ Indicates data point below the LLOQ and plotted at the LLOQ (3.13 pg/ml).

C, Cycle; CRS, cytokine release syndrome; D, Day; EoI, end of infusion; IL-6, interleukin-6; LLOQ, lower limit of quantification; ULOQ, upper limit of quantification.

Supplementary Tables

TABLE S1. Dose Levels and Number of Patients Enrolled in Each Cohort During the Dose-Escalation Phase

	Dose level	**Total no. of patients enrolled in the dose escalation cohort**	**No. of patients evaluable for DLT**	**No. of patients with DLT in Cycle 1**	**Total no. of patients enrolled in the interim expansion cohort**	**No. of patients enrolled in the DLBCL/trFL interim expansion cohort**	**No. of patients enrolled in the FL interim expansion cohort**	**No. of patients enrolled in the MCL interim expansion cohort**
Group A (n = 33)	0.05mg	1	1	0	0	0	0	0
	0.2mg	1	1	0	0	0	0	0
	0.4mg	3	3	0	0	0	0	0
	0.8mg	4	3	0	0	0	0	0
	1.2mg	7	3	0	0	0	0	0

	1.6mg	6	6	1	0	0	0	0
	2.0mg	3	3	0	0	0	0	0
	2.8mg	8	3	0	0	0	0	0
Group B (n = 197)	0.4/1/2.8mg	6	3	0	0	0	0	0
	0.8/2/4.2mg	10	6	1	7	6	1	0
	1/1/3mg	1	1	0	0	0	0	0
	0.8/2/6mg	10	6	1	19	12	7	0
	1/2/6mg	6	6	3*	0	0	0	0
	1/2/9mg	3	3	0	2	0	2	0
	1/2/13.5mg	6	3	0	71	20	44	7
	1/2/20mg	6	6	1	4	4	0	0
	1/2/27mg	3	3	0	23	18	0	5

	1/2/40.5mg	6	3	0	11	11	0	0
	1/2/60mg	3	3	0	0	0	0	0

In dose-escalation cohorts, if the dose level has been shown to not exceed the MTD, up to approximately 3 additional patients per dose cohort may be enrolled to obtain additional safety and pharmacodynamic data.

*Only one DLT event occurred after the Cycle 1 Day 15 dose and two DLT events after the 1mg dose. All patients treated with 1mg at Cycle 1 Day 1 were evaluated and the 1.0/2.0/6.0mg dose level did not exceed the MTD based on protocol-defined dose escalation rules.

DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicities; FL, follicular lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; tr, transformed.

TABLE S2. Patient Demographics and Baseline Disease Characteristics (Group A; Safety Population)

	Group A (n = 33)
Age – yr	
Median	64
Range	30 to 84
Male sex – no. (%)	20 (60.6)
ECOG performance status – no. (%)	
0	12 (36.4)
1	21 (63.6)
Ann Arbor stage at study entry – no. (%)	
No. of evaluable patients[*]	32
Stage I	1 (3.0)
Stage II	4 (12.1)
Stage III	10 (30.3)
Stage IV	17 (51.5)
Aggressive NHL – no. (%)	21 (63.6)
Diffuse large B-cell lymphoma	14 (42.4)
Transformed follicular lymphoma	4 (12.1)
Mantle cell lymphoma	2 (6.1)
Other[†]	1 (3.0)
Indolent NHL – no. (%)	12 (36.4)
Follicular lymphoma (grade 1-3A)	10 (30.3)
Other[‡]	2 (6.1)
Prior systemic therapies – no.	
Median	3
Range	1 to 9
Prior CAR-T therapy – no. (%)	0
Prior autologous stem cell transplant – no. (%)	10 (30.3)

Refractory to last therapy – no. (%)[§]	23 (69.7)
Refractory to prior anti-CD20 therapy – no. (%)[§]	22 (66.7)

Clinical cut-off date: January 21, 2020.

[*]Data not available for all patients by cut-off date.

[†]Richter's transformation, n = 1.

[‡]Marginal zone lymphoma, n = 1; small lymphocytic lymphoma, n = 1.

[§]Defined as not achieving a response (complete or partial response) or progressing within ≤ 6 months of applicable treatment.

CAR-T, chimeric antigen receptor T-cell; ECOG, Eastern Cooperative Oncology Group; NHL, non-Hodgkin lymphoma.

TABLE S3. Patient Demographics and Baseline Disease Characteristics (Group B, Prior CAR-T Therapy; Safety Population)

	Group B, prior CAR-T therapy (n = 19)
Age – yr	
Median	56.0
Range	30 to 76
Male sex – no. (%)	13 (68.4)
ECOG performance status – no. (%)	
0	6 (31.6)
1	13 (68.4)
Ann Arbor stage at study entry – no. (%)	
No. of evaluable patients[*]	17
Stage I	0
Stage II	1 (5.3)
Stage III	9 (47.4)
Stage IV	7 (36.8)
NHL subtype – no. (%)	
Diffuse large B-cell lymphoma	10 (52.6)
Transformed follicular lymphoma	5 (26.3)
Follicular lymphoma (grade 1-3A)	4 (21.1)
Relapsed or refractory to prior CAR-T – no. (%)	
Refractory on any	15 (78.9)
Relapsed on any (not refractory)	4 (21.1)
Prior systemic therapies – no.	
Median	5
Range	3 to 14
Prior autologous stem cell transplant – no. (%)	8 (42.1)
Refractory to last therapy – no. (%)[†]	17 (89.5)
Refractory to prior anti-CD20 therapy – no. (%)[†]	17 (89.5)

Clinical cut-off date: January 21, 2020.

*Data not available for all patients by cut-off date.

†Defined as not achieving a response (complete or partial response) or progressing within ≤ 6 months of applicable treatment.

CAR-T, chimeric antigen receptor T-cell; ECOG, Eastern Cooperative Oncology Group; NHL, non-Hodgkin lymphoma.

TABLE S4. Dose-limiting Toxicities (Safety Population in Dose-Escalation Cohorts)

Group (dose)	**Study day of DLT onset**	**DLT event(s)**	**No. of patients evaluable for DLT**	**No. of patients with DLT in Cycle 1**	**No. of patients with DLT in Cycle 1 after C1D15 dose (Group B only)**
A (1.6mg)	1 and 1	Grade 2 CRS (grade 3 AST elevation, grade 2 blood bilirubin increased) and grade 2 hypomagnesemia (2 DLTs in the same patient)	6	1	N/A
B (0.8/2.0/4.2 mg)	20 and 21	Grade 4 LFT increased and grade 3 hepatic encephalopathy (2 DLTs in the same patient)	6	1	1
B (0.8/2.0/6.0 mg)	4	Grade 3 hypotension (in the context of grade 2 worsening pleural effusion)	6	1	0
B (1.0/2.0/6.0 mg)*	4	Grade 4 neutrophil count decreased	6	3	1

B (1.0/2.0/6.0 mg)*	8	Grade 4 neutropenia			
B (1.0/2.0/6.0 mg)*	17	Grade 3 anemia			
B (1.0/2.0/20.0 mg)	1	Grade 3 hypophosphatemia	6	1	0
B (1.0/2.0/27.0 mg)	1 and 8	Grade 3 hypophosphatemia (2 DLTs in the same patient)†	3	0	0

*1.0/2.0/6.0mg dose level did not exceed the maximum tolerated dose based on protocol-defined dose-escalation rules.

†After the cut-off date, events were revised to non-DLT events.

AST, aspartate aminotransferase; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; LFT, liver function test; N/A, not applicable.

TABLE S5. Summary of Adverse Events (Group A; Safety Population)

No. of patients (%)	**Group A (n = 33)**	
Any AE	32 (97.0)	
Treatment-related AE[*]	24 (72.7)	
Serious AE, not including grade 5 malignant neoplasm progression[†]	7 (21.2)	
Treatment-related serious AE	2 (6.1)	
Grade 5 (fatal) AE, not including grade 5 malignant neoplasm progression[†]	1 (3.0)	
Any AE leading to mosunetuzumab discontinuation	1 (3.0)	
Treatment-related AE leading to mosunetuzumab treatment discontinuation	1 (3.0)	
Common (≥ 20% of patients) any-grade AEs by Preferred Term	**Any grade**	**Grade ≥ 3**
Total	32 (97.0)	17 (51.5)
Fatigue	11 (33.3)	0
Diarrhea	10 (30.3)	1 (3.0)
CRS	8 (24.2)	0
Decreased appetite	7 (21.2)	0
Headache	7 (21.2)	0
Common (> 3% of patients) serious AEs by Preferred Term		
CRS	2 (6.1)	0

Clinical cut-off date: January 21, 2020.

Serious AEs are defined as any untoward medical occurrence(s) that results in death, hospitalization or prolongation of existing hospitalization, persistent or significant

disability/incapacity or a congenital anomaly or birth defect, or any life-threatening or significant medical event in the investigator's judgement.

[*]Relationship between each AE and study treatment was determined by investigator assessment.

[†]Death attributed to progression of cancer was a reportable AE if occurring within 90 days after the last dose of study treatment and prior to the initiation of another systemic anti-cancer therapy.

AE, adverse event; CRS, cytokine release syndrome.

TABLE S6. Summary of Adverse Events (Group B, Prior CAR-T Therapy; Safety Population)

No. (%)	**Group B, prior CAR-T therapy (n = 19)**	
Any AE	19 (100.0)	
Treatment-related AE[*]	13 (68.4)	
Serious AE, not including grade 5 malignant neoplasm progression[†]	12 (63.2)	
Treatment-related serious AE[*]	5 (26.3)	
Grade 5 (fatal) AE, not including grade 5 malignant neoplasm progression[†]	1 (5.3)	
Any AE leading to mosunetuzumab discontinuation	1 (5.3)	
Treatment-related AE leading to mosunetuzumab treatment discontinuation	0	
Common (≥ 20% of patients) any-grade AEs by Preferred Term	**Any Grade**	**Grade ≥ 3**
Total	19 (100.0)	13 (68.4)
Hypophosphatemia	6 (31.6)	5 (26.3)
Neutropenia[‡]	6 (31.6)	5 (26.3)
Febrile neutropenia	1(5.3)	1 (5.3)
CRS	5 (26.3)	1 (5.3)
Hypokalemia	5 (26.3)	0
Diarrhea	4 (21.1)	0
Anemia	4 (21.1)	2 (10.5)
Chills	4 (21.1)	0
Fatigue	4 (21.1)	0
Pyrexia	4 (21.1)	0

Cough	4 (21.1)	0
Common (≥ 10% of patients) serious AEs by Preferred Term		
CRS	4 (21.1)	1 (5.3)

Clinical cut-off date: January 21, 2020.

Serious AEs are defined as any untoward medical occurrence(s) that results in death, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or a congenital anomaly or birth defect, or any life-threatening or significant medical event in the investigator's judgement.

*Relationship between each AE and study treatment was determined by investigator assessment.

†Death attributed to progression of cancer was a reportable AE if occurring within 90 days after the last dose of study treatment and prior to the initiation of another systemic anti-cancer therapy.

‡Includes the Preferred Terms neutropenia and neutrophil count decreased.

AE, adverse event; CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome.

TABLE S7. Incidence of Cytokine Release Syndrome, and Neutropenia (Safety Population)

No. (%)	**Group A (n = 33)**	**Group B (n = 197)**
Any-grade CRS*	8 (24.2)	54 (27.4)
Grade 1	3 (9.1)	41 (20.8)
Grade 2	5 (15.2)	11 (5.6)
Grade 3	0	2 (1.0)
Grade 4	0	0
Common (> 3% of patients) CRS symptoms		
Pyrexia	6 (18.2)	46 (23.4)
Grade 1	5 (15.2)	34 (17.3)
Grade 2	1 (3.0)	12 (6.1)
Grade 3	0	0
Grade 4	0	0
Chills	2 (6.1)	20 (10.2)
Grade 1	0	14 (7.1)
Grade 2	2 (6.1)	6 (3.0)
Grade 3	0	0
Grade 4	0	0
Hypotension	5 (15.2)	7 (3.6)
Grade 1	3 (9.1)	3 (1.5)
Grade 2	1 (3.0)	3 (1.5)
Grade 3	1 (3.0)	1 (0.5)
Grade 4	0	0
Headache	1 (3.0)	8 (4.1)

Grade 1	0	8 (4.1)
Grade 2	1 (3.0)	0
Grade 3	0	0
Grade 4	0	0
Tachycardia	2 (6.1)	8 (4.1)
Grade 1	2 (6.1)	4 (2.0)
Grade 2	0	4 (2.0)
Grade 3	0	0
Grade 4	0	0
Alanine aminotransferase increased	2 (6.1)	2 (1.0)
Grade 1	0	1 (0.5)
Grade 2	1 (3.0)	1 (0.5)
Grade 3	1 (3.0)	0
Grade 4	0	0
Aspartate aminotransferase increased	2 (6.1)	2 (1.0)
Grade 1	0	1 (0.5)
Grade 2	0	1 (0.5)
Grade 3	2 (6.1)	0
Grade 4	0	0
Management of CRS		
Use of tocilizumab for CRS	1 (3.0)	3 (1.5)
Use of a single vasopressor for CRS	0	1 (0.5)
Use of multiple vasopressors for CRS	0	0
Use of oxygen (low flow) for CRS	0	2 (1.0)
Use of oxygen (high flow) for CRS	0	0

Requirement of ICU admission for CRS	0	2 (1.0)
Neutropenia[†]	5 (15.2)	56 (28.4)
Grade 1	2 (6.1)	4 (2.0)
Grade 2	0	2 (1.0)
Grade 3	2 (6.1)	21 (10.7)
Grade 4	1 (3.0)	29 (14.3)
Febrile neutropenia	1 (3.0)	7 (3.6)
Grade 3	0	5 (2.5)
Grade 4	1 (3.0)	2 (1.0)
Concurrent use of growth factors for neutropenia	2 (6.1)	44 (22.3)

Clinical cut-off date: January 21, 2020.

[*]Graded according to the Modified Cytokine Release Syndrome Grading System.[15]

[†]Includes the Preferred Terms neutropenia and neutrophil count decreased.

CRS, cytokine release syndrome; ICU, intensive care unit.

TABLE S8. Summary of Efficacy (Group A; Efficacy population)

Best objective response	**Group A (n = 33)**
Overall response rate	
No. (%)	6 (18.2)
95% CI	[7.0 to 35.5]
Complete response	
No. (%)	5 (15.2)*
95% CI	[5.1 to 31.9]
Partial response	
No. (%)	1 (3.0)†
95% CI	[0.1 to 15.8]
Stable disease	
No. (%)	6 (18.2)
95% CI	[7.0 to 35.5]
Progressive disease	
No. (%)	20 (60.6)
95% CI	[42.1 to 77.1]

Clinical cut-off date: January 21, 2020.

*Histologies of complete responders included diffuse large B-cell lymphoma (n = 1), follicular lymphoma (N = 3), and transformed follicular lymphoma (n = 1). At last follow-up, remissions were ongoing at 26 months and 34 months for 2 patients with follicular lymphoma and at 38 months for the patient with diffuse large B-cell lymphoma. A third patient with follicular lymphoma who achieved complete response had their duration of response censored after the first complete response due to non-compliance. The patient with transformed follicular lymphoma progressed at 19 months.

CI, confidence interval.

TABLE S9. Investigator-Assessed Best Objective Response in High-Risk Subgroups of Patients with Aggressive or Indolent Non-Hodgkin Lymphoma (Group B; Efficacy Population)

High-risk subgroup	**No. of evaluable patients**	**Overall response rate – no. (%)**	**Complete response rate – no. (%)**
Prior CAR-T therapy	19	7 (36.8)	5 (26.3)
Diffuse large B-cell lymphoma	10	3 (30.0)	3 (30.0)
Transformed follicular lymphoma	5	0	0
Follicular lymphoma	4	4 (100.0)	2 (50.0)
Patients with follicular lymphoma			
Double refractory*	34	23 (67.6)	19 (55.9)
History of POD24†	33	25 (75.8)	18 (54.5)
PI3Ki refractory	9	8 (88.9)	7 (77.8)

Clinical cut-off date: January 21, 2020.

*Refractory to both a prior anti-CD20 antibody and an alkylating agent.

†Patients with progressive disease within 24 months of starting first-line therapy.

CAR-T, chimeric antigen receptor T-cell; PI3Ki, phosphoinositide 3-kinase inhibitor.

TABLE S10. Investigator-assessed Best Objective Response by Tumor Histology (Group B; Efficacy Population)

Best objective response	Aggressive non-Hodgkin lymphoma							Indolent non-Hodgkin lymphoma		
	DLBCL (n = 82)	**DLBCL/ MCL (n = 1)**	**FL 3B (n = 1)**	**MCL (n = 13)**	**Richter's (n = 5)**	**trFL (n = 26)**	**trMZL (n = 1)**	**FL (n = 65)**	**MZL (n = 2)**	**SLL (n = 1)**
Overall response rate										
No. (%)	27 (32.9)	0	0	4 (30.8)	3 (60.0)	11 (42.3)	0	45 (69.2)	0	0
95% CI	[22.9 to 44.2]	[0.0 to 97.5]	[0.0 to 97.5]	[9.1 to 61.4]	[14.7 to 94.7]	[23.4 to 63.1]	[0.0 to 97.5]	[56.6 to 80.1]	[0.0 to 84.2]	[0.0 to 97.5]
Complete response										
No. (%)	16 (19.5)	0	0	3 (23.1)	1 (20.0)	5 (19.2)	0	33 (50.8)	0	0
95% CI	[11.6 to 29.7]	[0.0 to 97.5]	[0.0 to 97.5]	[5.0 to 53.8]	[0.5 to 71.6]	[6.6 to 39.4]	[0.0 to 97.5]	[38.1 to 63.4]	[0.0 to 84.2]	[0.0 to 97.5]
Partial response										
No. (%)	11 (13.4)	0	0	1 (7.7)	2 (40.0)	6 (23.1)	0	12 (18.5)	0	0
95% CI	[6.9 to 22.7]	[0.0 to 97.5]	[0.0 to 97.5]	[0.2 to 36.0]	[5.3 to 85.3]	[9.0 to 43.7]	[0.0 to 97.5]	[9.9 to 30.0]	[0.0 to 84.2]	[0.0 to 97.5]
Stable disease										
No. (%)	4 (4.9)	0	0	2 (15.4)	0	2 (7.7)	1 (100.0)	11 (16.9)	2 (100.0)	0
95% CI										

	[1.3 to 12.0]	[0.0 to 97.5]	[0.0 to 97.5]	[1.9 to 45.5]	[0.0 to 52.2]	[1.0 to 25.1]	[2.5 to 100.0]	[8.8 to 28.3]	[15.8 to 100.0]	[0.0 to 97.5]
Progressive disease										
No. (%)	47 (57.3)	1 (100.0)	1 (100.0)	6 (46.2)	2 (40.0)	13 (50.0)	0	8 (12.3)	0	1 (100.0)
95% CI	[45.9 to 68.2]	[2.5 to 100.0]	[2.5 to 100.0]	[19.2 to 74.9]	[5.3 to 85.3]	[29.9 to 70.1]	[0.0 to 97.5]	[5.5 to 22.8]	[0.0 to 84.2]	[2.5 to 100.0]

Clinical cut-off date: January 21, 2020.

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; tr, transformed; Richter's, Richter's transformation; SLL, small lymphocytic lymphoma.

TABLE S11. Association Between Clinical Response and the Occurrence of CRS (Group B, Efficacy Population)

No. (%)	**Patients with CRS**	**Patients without CRS**
Aggressive NHL (n = 129)	n = 37	n = 92
Patients with response	11 (29.7)	34 (37.0)
Patients with no response	26 (70.3)	58 (63.0)
Patients with CR	7 (18.9)	18 (19.6)
Patients with no CR	30 (91.1)	74 (80.4)
Indolent NHL (n = 68)	n = 17	n = 51
Patients with response	10 (58.8)	35 (68.6)
Patients with no response	7 (41.2)	16 (31.4)
Patients with CR	6 (35.3)	27 (52.9)
Patients with no CR	11 (64.7)	24 (47.1)

Clinical cut-off date: January 21, 2020.

Fisher's exact test was used to assess the association between the CRS rate and the overall/complete response among patients with aggressive and indolent NHL. *P* values for the comparisons were > 0.05 in all cases.

CR, complete response; CRS, cytokine release syndrome; NHL, non-Hodgkin lymphoma.