Supplemental data

Inclusion and exclusion criteria

Inclusion Criteria

Part 1 (Dose Escalation)

- Male or female patients, aged 18 years or older with pathologically confirmed relapsed or refractory B cell Non-Hodgkin Lymphoma (B-NHL) who had failed or were intolerant to established therapy or for whom no other treatment options were available, in the opinion of the Investigator
- Refractory or relapsed B-NHL (per World Health Organization [WHO] Classification system)[18] defined as:
    - Diffuse large B-cell lymphoma (DLBCL)
    - Follicular lymphoma (FL)
    - Chronic lymphocytic leukemia (CLL)
    - Mantle cell lymphoma (MCL)
    - Marginal zone B-cell lymphoma (MZBCL)
    - Burkitt's lymphoma (BL)
    - Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia [WM])

Part 2 (Expansion)

Eligible histologic subtypes to be investigated in Part 2 of the study were to be determined by the Dose Escalation Steering Committee (DESC) based on evolving efficacy and safety information from Part 1. Based on DESC review of the Part 1 data, enrollment in Part 2 was not further restricted. The same relapsed or refractory B-NHL histologies listed above for Part 1 were allowed in Part 2

- Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block. An FFPE block from a current biopsy was preferred; however, archival tissue taken at initial diagnosis or any prior relapse was acceptable. If tissue block was not available, slides from an FFPE block could be acceptable for eligibility upon consultation with the Sponsor
- Measurable disease, as defined by the 2014 Lugano Classification[19]
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- Absolute neutrophil count (ANC) ≥1000/μL

- Platelet count of ≥75,000/µL.
- Hemoglobin ≥9.0 g/dL without transfusion within the 2 weeks prior to Day 1.
- Serum/plasma creatinine ≤1.5 mg/dL. If the patient had a creatinine >1.5 mg/dL, a measured creatinine clearance had to be >60 mL/min as calculated by the Cockcroft and Gault equation[24]
- Serum/plasma alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤2×the upper limit of normal (ULN); ≤5×ULN if there was liver or bone involvement
- Total serum/plasma bilirubin ≤1.5×ULN (patients with known Gilbert's syndrome could have a total bilirubin up to ≤3×ULN)
- Negative blood or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to Day 1 for women of childbearing potential
- Women of childbearing potential* had to agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of loncastuximab tesirine. Men with female partners who were of childbearing potential had to agree that they or their partners would use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient received his last dose of loncastuximab tesirine

* Women of childbearing potential were defined as sexually mature women who had not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy or who had not been postmenopausal (i.e. who had not menstruated at all) for at least 1 year.

** Highly effective forms of birth control were methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control included: Hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this was the preferred and usual lifestyle of the patient. Note: The double barrier method (e.g. synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, postovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only were not acceptable as highly effective methods of contraception.

Exclusion Criteria

Patients who met any one of the following criteria were not eligible for participation in the study:

- Patients who, in the opinion of the Investigator, had any option for other treatment for B-NHL at the current state of disease
- Active graft-versus-host disease
- Autologous or allogeneic transplant within the 60 days prior to the Screening visit.
- Known history of immunogenicity or hypersensitivity to a CD19 antibody
- Evidence of myelodysplasia or myeloid leukemia by morphology, immunostains, flow cytometry, or cytogenetics on a bone marrow aspirate or biopsy
- Known history of positive serum human ADA
- Active autoimmune disease (e.g. rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g. Wegener's granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barré syndrome and myasthenia gravis); other central nervous system (CNS) autoimmune disease (e.g. poliomyelitis, multiple sclerosis). Known seropositive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antibody to hepatitis C virus (anti-HCV) with confirmatory testing and requiring antiviral therapy (Note: Testing was not mandatory to be eligible. Testing for HCV was to be considered if the patient was at risk for having undiagnosed HCV (e.g. history of injection drug use. History of Steven's Johnson's syndrome or toxic epidermal necrolysis syndrome)
- Pregnant or breastfeeding women
- Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure greater than 115 mm Hg), unstable angina, congestive heart failure (greater than New York Heart Association class II), severe uncontrolled ventricular arrhythmias, or electrocardiographic (ECG) evidence of acute ischemia, poorly controlled diabetes, severe chronic pulmonary disease, coronary angioplasty, or myocardial infarction within 6 months prior to Screening, or uncontrolled atrial or ventricular cardiac arrhythmias
- Use of any other experimental medication(s) within 14 days or 5 half-lives but in no case less than 14 days prior to start of study treatment on Cycle 1, Day 1
- Steroid use equivalent to greater than 20 mg of prednisone within 4 weeks (28 days) prior to Day 1, except for the use of short course systemic corticosteroids (≤7 days) with a wash-out period of 1 week prior to start of study treatment on Day 1
- Major surgery, chemotherapy, systemic therapy (excluding steroids and any targeted small molecules or biologics), or radiotherapy, within 14 days or 5 half-lives (whichever was shorter) prior to Cycle 1, Day 1 treatment, except if approved by the Sponsor

- Failure to recover (to Common Terminology Criteria for Adverse Events [CTCAE] Grade 0 or Grade 1) from acute non-hematologic toxicity (except all grades alopecia or Grade 2 or lower neuropathy), due to previous therapy, prior to Screening
- Congenital long QT syndrome, or a corrected QTc interval of ≥450 ms, at the Screening visit (unless secondary to pacemaker or bundle branch block)
- Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor's Medical Monitor and the Investigator agreed and had documented that it was not exclusionary
- Any other significant medical illness, abnormality, or condition that could, in the Investigator's judgment, make the patient inappropriate for study participation or could put the patient at risk

Dose-limiting toxicities

A dose-limiting toxicity (DLT) was defined as any of the following events occurring during the first cycle of treatment, except those that were clearly due to underlying disease or extraneous causes.

A hematologic DLT was defined as:

- Grade 3 or 4 febrile neutropenia or neutropenic infection
- Grade 4 neutropenia lasting >7 days
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with clinically significant bleeding, or Grade 3
- thrombocytopenia requiring a platelet transfusion
- Grade 4 anemia

A non-hematologic DLT was defined as:

- Grade 4 tumor lysis syndrome (TLS) (Grade 3 TLS did not constitute DLT unless it led to irreversible end-organ damage).
- Grade 3 or higher AE (including nausea, vomiting, diarrhea, and electrolyte imbalances lasting more than 48 hours despite optimal therapy; excluding all grades of alopecia).
- Grade 3 or higher hypersensitivity (Appendix 12.3 of the protocol) reaction (regardless of premedication).
- Grade 2 or higher skin ulceration.

Analysis sets

Safety analysis set: All patients who received study drug.

DLT analysis set: All patients who completed at least 1 cycle in Part 1, or who discontinued before the end of the cycle but had complete DLT information.

Efficacy analysis set: All patients who received ≥1 dose of study drug and had a valid baseline and ≥1 valid post-baseline disease assessment, or had documented PD or death after the first dose of study drug and before starting subsequent anti-cancer treatment.

PK analysis set: Patients who received ≥1 dose of study drug, had sufficient concentration-time data to permit a reliable estimation of loncastuximab tesirine exposure, and who had no major/important protocol deviations.

Pharmacodynamic analysis sets:

- Analysis of CD19 expression in tumor tissue: patients who had archival tumor tissue samples available, who had received ≥1 dose of study drug, and had ≥1 value for a correlative endpoint.
- Analysis of peripheral WBC changes: US patients who had received ≥1 dose of study drug and had pre-dose and post-dose samples available.

Population PK Analysis

A population PK analysis of the study drug was performed based on serum concentrations of pyrrolobenzodiazepine (PBD)-conjugated antibody in order to obtain individual patient metrics of drug exposure. The relationship between serum concentration and frequency of treatment emergent adverse event (TEAE) categories was evaluated for 139 patients with paired data. Binomial logistic regression analysis was performed to determine the predicted probability (pp) of event for a given degree of exposure. Using PBD-conjugated antibody area under the curve (AUC) as the exposure metric, predictor variables at baseline were evaluated and included sex, age, weight (WT), body surface area (BSA), elapsed time of initial diagnosis (ELDIAGM), Eastern Cooperative Oncology Group status (ECOGB) ≥2, high risk cytogenetic phenotype (CYTHR), prior chemotherapy response (CHEMRSP), prior stem cell therapy (STMCELL), diffuse large B-cell lymphoma diagnosis at baseline (DLBCL), concomitant dexamethasone (CMDEX), and BMI. **Equation 1** was interrogated for relating probability to safety effect.

Equation 1

$$\text{logit}(p) = \log(p/(1-p) = \beta o + \beta 1 \cdot AUC + \beta 2 \cdot SEX + \beta 3 \cdot AGE + \beta 4 \cdot WT + \beta 5 \cdot BSA + \beta 6 \cdot ELDIAGM + \beta 7 \cdot ECOGB\_B + \beta 8 \cdot CYTHR + \beta 9 \cdot CHEMRSP + \beta 10 \cdot STMCELL + \beta 11 \cdot DLBCL + \beta 12 \cdot CMDEX + \beta 13 \cdot BMI$$

Supplemental Table 1. Schedule of pharmacokinetic assessments

Cycle	**Cycle 1 and 2**								**Cycle 3**				
Time	BSI, EOI	1 h, 3 h, 6 h	24 h	48 h	5 d	8 d	15 d	21 d	BSI, EOI	8 d	21 d	EOT	Follow-up (12 weeks)[b]
Time frame	Within 10%[a]	Within 10%[a]	Within 10%[a]	Within 10%[a]	±1 day	±2 days	±2 days	±3 days	Within 10%[a]	±2 days	±3 days	-	±1 week

Samples were to be collected within 10% of nominal point (e.g. 1 hour ± 6 minutes, 48 hours ± 4.8 hours) for first 48 hours; [b]blood samples were to be collected 3 months (12 weeks) after last dose of loncastuximab tesirine, unless a new anti-cancer treatment had been initiated.
BSI, before start of infusion; EOI, end of infusion, EOT, end of treatment

Supplemental Table 2. Overall response rate in all patients with B-NHL treated with loncastuximab tesirine doses 15–200 µg/kg by dose (efficacy analysis set)

	Loncastuximab tesirine dose							
	15 µg/kg (n=4)	**30 µg/kg (n=4)**	**60 µg/kg (n=4)**	**90 µg/kg (n=5)**	**120 µg/kg (n=42)**	**150 µg/kg (n=87)**	**200 µg/kg (n=34)**	**All (N=180)**
ORR, n (%)	1 (25.0)	1 (25.0)	1 (25.0)	2 (40.0)	20 (47.6)	37 (42.5)	20 (58.8)	82 (45.6)
[95% CI]	[0.6, 80.6]	[0.6, 80.6]	[0.6, 80.6]	[5.3, 85.3]	[32.0, 63.6]	[32.0, 53.6]	[40.7, 75.4]	[38.1, 53.1]
CR, n (%)	0	1 (25.0)	1 (25.0)	1 (20.0)	9 (21.4)	21 (24.1)	15 (44.1)	48 (26.7)
PR, n (%)	1 (25.0)	0	0	1 (20.0)	11 (26.2)	16 (18.4)	5 (14.7)	34 (18.9)

B-NHL, B-cell non-Hodgkin lymphoma; CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response

Supplemental Table 3. Subgroup analysis of overall response rate with loncastuximab tesirine in patients with DLBCL (efficacy analysis set: n=137)

Subgroup	ORR (n/N) [95% CI]
Sex	
Female	41.4 (24/58) [28.6, 55.1)
Male	43.0 (34/79) [31.9, 54.7]
Age group, years	
<65	34.2 (25/73) [23.5, 46.3]
65–<75	48.6 (18/37) [31.9, 65.6]
≥75	55.6 (15/27) [35.3, 74.5]
Country	
US	43.5 (37/85) [32.8, 54.7]
UK	40.0 (12/30) [22.7, 59.4]
Italy	40.9 (9/22) [20.7, 63.6]
Presence of bulky disease	
Yes	22.2 (4/18) [6.4, 47.6]
No	45.4 (54/119) [36.2, 54.8]
Presence of double/triple hit	
Yes	21.7 (5/23) [7.5, 43.7]
No	46.5 (53/114) [37.1, 56.1]
Response to first-line therapy	
Relapse	50.6 (45/89) [39.8, 61.3]
Refractory	23.3 (7/30) [9.9, 42.3]
Other[a]	33.3 (6/18) [13.3, 59.0]
Response to last-line therapy	
Relapse	53.1 (26/49) [38.3, 67.5]
Refractory	35.8 (29/81) [25.4, 47.2]
Other[a]	42.9 (3/7) [9.9, 81.6]
Number of lines of prior therapy	
≤3	45.2 (38/84) [34.3, 56.5]
>3	37.7 (20/53) [24.8, 52.1]
Transformed or de novo disease	
Transformed	45.7 (16/35) [28.8, 63.4]
De novo	41.2 (42/102) [31.5, 51.4]
Disease stage (Ann Arbor criteria)	
Stage I	42.9 (3/7) [9.9, 81.6]

Stage II	63.2 (12/19) [38.4, 83.7]
Stage III	45.5 (10/22) [24.4, 67.8]
Stage IV	37.1 (33/89) [27.1, 48.0]

[a]Other includes missing/not evaluable.

DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate

Supplemental Table 4. Pharmacokinetic parameters of loncastuximab tesirine during Cycle 1 for patients with B-NHL receiving a Q3W regimen

Dose µg/kg	C_{max} ng/mL	AUC_{last} day*ng/mL	AUC_{inf} day*ng/mL	t_{half} day	CL L/day	V_{ss} L
Conjugated antibody						
15	250 (32.6)	638 (151)	407 (44.8)	1.45 (52.5)	2.36 (42.7)	4.43 (17.9)
30	384 (36.1)	2276 (38.2)	1945 (34.7)	6.75 (23.2)	1.07 (15.3)	9.76 (51.5)
60	525 (150)	1006 (12768)	4520 (101)	5.97 (49.2)	0.621 (77.8)	4.95 (6.43)
90	705 (222)	1349 (13677)	2430 (892)	2.54 (261)	3.33 (689)	9.50 (28.6)
120	2218 (36.8)	10154 (151)	7539 (131)	4.67 (91.7)	1.05 (127)	5.66 (34.0)
150	2841 (57.7)	10329 (145)	7361 (188)	4.46 (129)	1.36 (181)	6.37 (59.3)
200	3546 (22.3)	24720 (121)	14660 (464)	9.02 (46.0)	0.998 (358)	8.71 (94.1)
Total antibody						
15	290 (27.9)	650 (187)	869 (–)	2.75 (–)	1.28 (–)	4.71 (–)
30	519 (33.1)	3028 (40.3)	–	–	–	–
60	725 (83.7)	3146 (199)	–	–	–	–
90	1060 (177)	1472 (76509)	16409 (–)	8.82 (–)	0.640 (–)	7.84 (–)
120	2648 (35.5)	13157 (93.2)	9000 (172)	4.05 (150)	1.05 (156)	5.37 (24.3)
150	3540 (60.9)	12068 (159)	8161 (180)	3.41 (203)	1.47 (178)	6.07 (41.4)
200	3998 (32.5)	26858 (129)	9162 (9232)	3.46 (1543)	2.11 (3539)	7.91 (0.318)
SG3199						
90	0.102 (–)	0.00200 (–)	–	–	–	–
120	0.0340 (49.7)	0.00200 (320)	–	–	–	–
150	0.0480 (59.3)	0.00500 (436)	0.154 (–)	0.418 (–)	627 (–)	335 (–)

200	0.0400 (72.0)	0.00400 (653)	–	–	–	–

Data are geometric mean (geometric % coefficient of variation). Accumulation index not reported for Cycle 1.

AUC_{last}, area under the concentration time curve from time 0 to last measurable timepoint in respective cycle; AUC_{inf}, area under the concentration time curve from time 0 to end of dosing interval in respective cycle; B-NHL, B-cell non-Hodgkin lymphoma; CL, apparent clearance; C_{max}, maximum observed concentration; PK, pharmacokinetics; Q3W, every 3 weeks; t_{half}, apparent terminal half-life; V_{ss}, apparent volume of distribution at steady state; –, not available

Supplemental Table 5. Pharmacokinetic parameters of loncastuximab tesirine during Cycle 2 for patients with B-NHL receiving a Q3W regimen

Dose **µg/kg**	**C_{max}** **ng/mL**	**AUC_{last}** **day*ng/mL**	**AUC_{tau}** **day*ng/mL**	**t_{half}** **day**	**CL_{ss}** **L/day**	**V_{ss}** **L**	**AI**
Conjugated antibody							
15	329 (81.1)	936 (288)	1030 (314)	3.15 (174)	0.897 (331)	3.62 (42.1)	1.11 (14.8)
30	1145 (158)	2812 (36.5)	3264 (39.7)	10.4 (40.5)	0.584 (54.3)	8.14 (79.3)	1.36 (18.6)
60	486 (377)	602 (3222048)	10545 (10.6)	15.4 (49.3)	0.389 (55.0)	8.28 (6.53)	1.67 (28.4)
90	1183 (86.3)	3183 (1802)	3227 (1611)	7.97 (146)	1.96 (1970)	7.55 (15.3)	1.38 (29.2)
120	2368 (64.9)	13522 (227)	15223 (209)	10.3 (74.1)	0.529 (194)	6.11 (45.7)	1.43 (24.8)
150*	3258 (53.7)	16547 (133)	18049 (106)	9.77 (82.2)	0.516 (99.2)	6.62 (52.5)	1.41 (24.6)
200	4160 (28.6)	44880 (40.0)	38188 (26.8)	16.2 (36.7)	0.387 (33.1)	8.62 (38.4)	1.72 (21.6)
Total antibody							
15	388 (66.7)	892 (273)	1203 (302)	2.99 (216)	0.911 (318)	3.75 (25.7)	1.13 (18.8)
30	1558 (176)	3742 (41.7)	4354 (43.4)	10.2 (40.5)	0.520 (56.1)	7.49 (102)	1.34 (18.3)
60	733 (346)	1186 (296216)	2270 (23371)	16.1 (32.0)	2.26 (33449)	7.23 (19.2)	1.69 (19.3)
90	2249 (47.3)	4282 (1759)	11043 (195)	9.55 (269)	0.665 (232)	8.44 (16.2)	1.64 (52.5)
120	2932 (50.5)	18831 (86.7)	21011 (70.0)	12.0 (80.0)	0.453 (65.8)	7.22 (49.5)	1.55 (30.4)
150*	4082 (59.1)	20087 (143)	21802 (112)	11.4 (110)	0.506 (106)	7.41 (49.7)	1.56 (30.3)
200	4941 (24.6)	52819 (43.3)	44736 (30.7)	16.5 (38.2)	0.392 (37.9)	8.50 (48.7)	1.74 (23.1)
SG3199							
90	0.0700 (22.0)	0.0180 (175)	–	–	–	–	–
120	0.0390 (30.5)	0.0180 (3038)	–	–	–	–	–
150*	0.0400 (56.1)	0.00300 (311)	–	–	–	–	–

200	0.0290 (11.7)	0.00200 (297)	–	–	–	–	–

Data are geometric mean (geometric % coefficient of variation). *In the 150 µg/kg cohort 4 patients underwent dose reduction at Cycle 2.

AI, accumulation index; AUC_{last}, area under the concentration time curve from time 0 to last measurable timepoint in respective cycle; AUC_{tau}, area under the concentration time curve from time 0 to end of dosing interval in respective cycle; B-NHL, B-cell non-Hodgkin lymphoma; CL_{ss}, apparent clearance at steady state; C_{max}, maximum observed concentration; PK, pharmacokinetics; Q3W, every 3 weeks; t_{half}, apparent terminal half-life; V_{ss}, apparent volume of distribution at steady state; –, not available

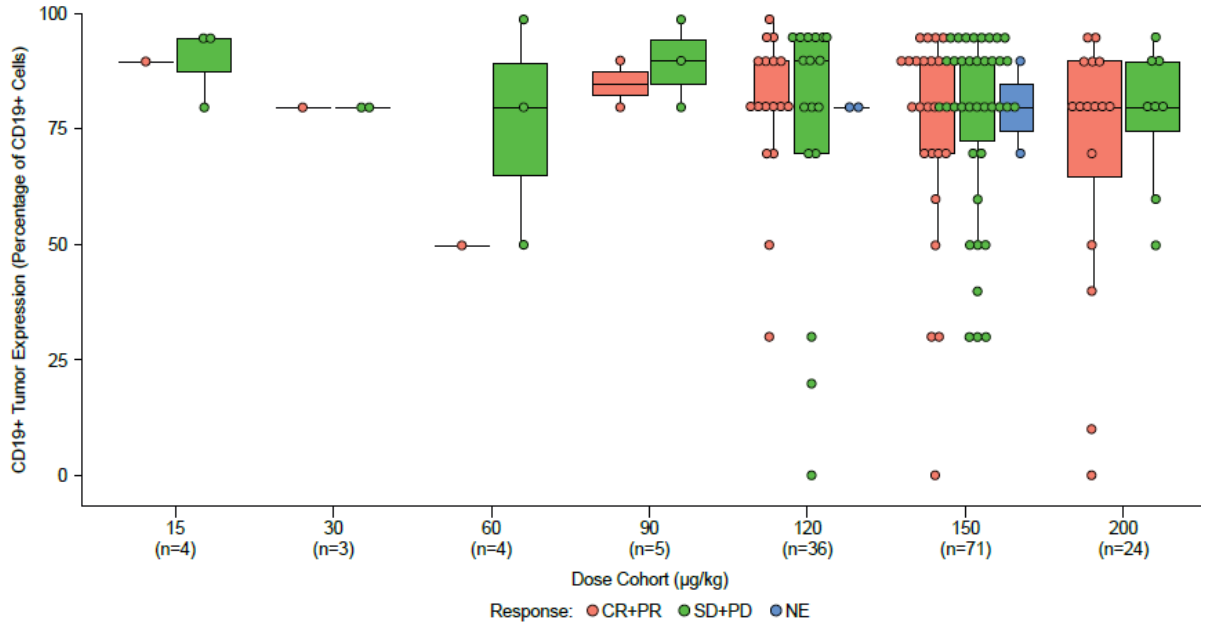
Supplemental Table 6. Predicted probabilities related to PBD-conjugated AUC and significant or clinically-relevant safety categories in patients with relapsed or refractory non-Hodgkin lymphoma

	Dose cohort (µg/kg)	15	30	60	90	120	150	200
	AUC (µg*h/L)[a]	13,723	34,898	69,203	86,231	230,378	209,757	519,473
Identified Significant TEAE Category	**Parameters modeled**	**Mean Predicted Probability (pp)**						
Edema (Grade≥3)[b,c]	STMCELL=0	0.0046	0.0050	0.0057	0.0060	0.0104	0.0096	0.0309
	STMCELL=1	0.0536	0.0578	0.0654	0.0695	0.1148	0.1070	0.2817
LFT (Grade ≥3)[d]	DLBCL=0	0.0829	0.0895	0.1013	0.1076	0.1759	0.1644	0.4018
	DLBCL=1	0.0048	0.0052	0.0059	0.0063	0.0112	0.0103	0.0343
	CHEMRSP=1	0.0829	0.0895	0.1013	0.1076	0.1759	0.1644	0.4018
	CHEMRSP=2	0.0062	0.0067	0.0077	0.0082	0.0145	0.0133	0.0442
	STMCELL=0	0.0829	0.0895	0.1013	0.1076	0.1759	0.1644	0.4018
	STMCELL=1	0.6818	0.6997	0.7275	0.7407	0.8349	0.8233	0.9409
	BMI=18.5 kg/m^2	0.0002	0.0003	0.0003	0.0003	0.0006	0.0006	0.0022
	BMI=25 kg/m^2	0.0028	0.0031	0.0036	0.0039	0.0072	0.0066	0.0249
	BMI=30 kg/m^2	0.0181	0.0199	0.0230	0.0247	0.0453	0.0415	0.1429
	BMI=35 kg/m^2	0.1075	0.1166	0.1329	0.1417	0.2361	0.2203	0.5208
	BMI=40 kg/m^2	0.4397	0.4625	0.4998	0.5183	0.6682	0.6480	0.8763
	ECOG=0	0.0829	0.0895	0.1013	0.1076	0.1759	0.1644	0.4018
	ECOG=1	0.0001	0.0001	0.0001	0.0002	0.0003	0.0003	0.0009

[a]Based on median of individual predictions from population PK analysis for respective dose cohort; [b]edema also includes effusion-related adverse events (overall p-value for model=0.0093); [c]based on model with AUC retained in model; [d]LFT included liver-related investigations, signs and symptoms (standard MEDRA query) related adverse events (overall p-value for model: <0.00001)

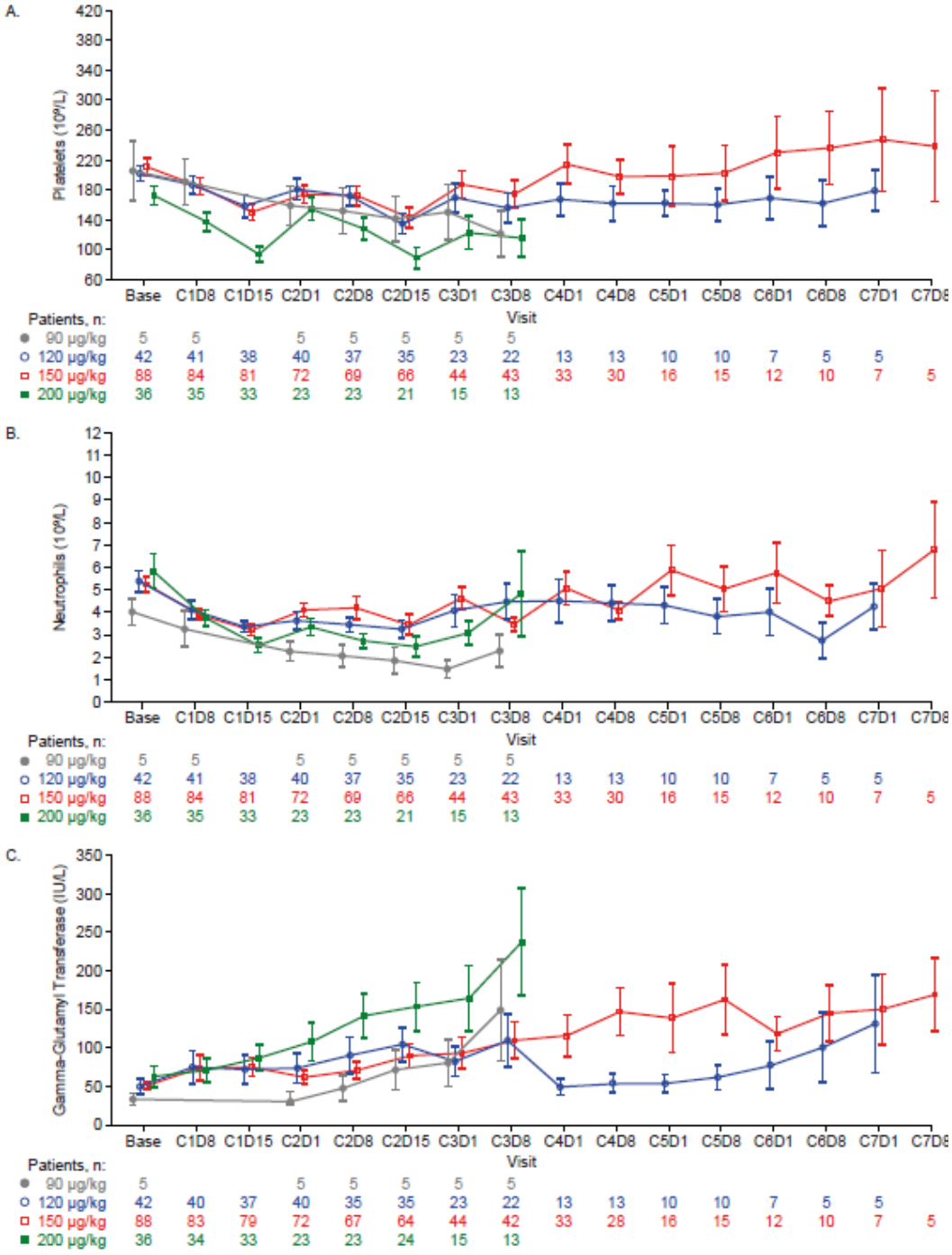
AUC, area under the curve; BMI, body mass index (kg/m^2); CHEMRSP, prior chemotherapy response (1=relapsed, 2=refractory, 9=other); DLBCL, diffuse large B-cell lymphoma (0=other, 1=DLBCL diagnosis at baseline); ECOGB, Eastern Cooperative Oncology Group status ≥2 (0=no, 1=yes); LFT, liver function test; STMCELL, prior stem cell therapy (0=no, 1=yes)

Supplemental Figure 1. Correlation between CD19 expression in pretreatment/archival tumor tissue (percentage of CD19+ cells) and clinical response by dose of loncastuximab tesirine



CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Supplemental Figure 2. Mean (SE) levels of (A) platelets (x10^9/L); (B) neutrophils (x10^9/L); and (C) gamma-glutamyltransferase levels (IU/L) by dose for loncastuximab tesirine doses ≥90 µg/kg



Baseline is defined as the last non-missing value before the initial administration of loncastuximab tesirine; values with fewer than 5 assessments of a laboratory test within a dose group are not displayed; 200 µg/kg includes patients on Q3W and Q6W dosing regimens.

C, cycle; D, day; Q3W, every 3 weeks; Q6W, every 6 weeks; SE, standard error

Supplemental data: Treatment Administration

- **Drug name:** Loncastuximab tesirine
- **Dose:** Administered intravenously over 60 minutes for the first cycle; if well-tolerated, the duration could be shortened to 30 minutes for that patient thereafter, subject to the Investigator's discretion
    - During Part 1, dose escalation from 15 µg/kg to 200 µg/kg at doses of 15, 30, 60, 90, 120, 150, or 200 µg/kg
    - During Part 2, dose expansion at doses of 120 µg/kg and 150 µg/kg; some patients in the 150 µg/kg group had their dose reduced to 75 µg/kg after 3 cycles
    - Loncastuximab tesirine treatment could be delayed for up to 21 days in any patient experiencing toxicity, until recovery to Grade 1 or baseline grade. Investigators could resume loncastuximab tesirine with 50% dose reduction based on their assessment of the patient's clinical condition and presence of clinical benefit. If the toxicity recurred in Part 1, the patient discontinued study treatment. In Part 2, the delay could be extended beyond 21 days, in consultation with the sponsor, for patients with toxicities, and loncastuximab tesirine could be resumed with 50% dose reduction. If the toxicity recurred, the dose could be reduced by a further 50%. If the toxicity occurred for a third time, the study treatment was discontinued permanently
- **Route:** Intravenous (central venous access not required)
- **Type and volume of diluent:** 5% dextrose in water (D5W). Loncastuximab tesirine was diluted into a 50 mL IV bag containing D5W at the appropriate dilution for the body mass of the patient
- **Cycle length and number of cycles, or criteria for discontinuation:**
    - Administered once every three weeks. Due to cumulative toxicity, a protocol amendment allowed patients who were receiving a 200 µg/kg dose to receive this dose every six weeks
    - There was no recommended number of cycles; patients received loncastuximab tesirine until disease progression, unacceptable toxicity, the initiation of new anti-cancer treatment, or withdrawal from the study
    - Criteria for treatment discontinuation:
        - Disease progression
        - Adverse event
        - Withdrawal of consent

        - Major protocol deviation
        - Required treatment delay >21 days (except in case of potential patient benefit, which must be approved by the Sponsor)
        - Following a dose delay due to toxicity, if the same toxicity recurred after second dose reduction, study drug was to be discontinued permanently
        - Non-compliance, including lost to follow-up
        - Pregnancy
        - Other (e.g., development of contraindications with use of the study drug)
        - The Investigator determined that it was in the best interest of the patient to discontinue the patient's participation in the study
        - Discontinuation of the study by the Sponsor
        - Death
    - Patients who experienced other significant toxicities were to be immediately and permanently withdrawn from treatment as follows:
        - Any patient who experienced a Grade 3 or higher hypersensitivity reaction, regardless of premedication, during any cycle of treatment
        - Any patient who experienced a recurrent Grade 3 or 4 toxicity, excluding hematological toxicity
        - Any patient who required a dosing delay >21 consecutive days from the planned Day 1 dosing at any time during treatment (except in case of potential patient benefit, which must have been approved by the Sponsor)
- **Premedications and concurrent medications:**
    - Prophylactic antiemetic medications, electrolyte supplementation, and other standard supportive care measures could be administered according to standard treatment center protocols
    - If a Grade 2 or higher infusion-related hypersensitivity was observed in one patient at any time during Part 1 of the study, all subsequent patients were to receive prophylactic treatment
    - Concomitant steroid use was permitted as replacement doses for patients with adrenal insufficiency, and as intranasal, inhaled, topical steroids, or local steroid injections
    - Hematopoietic growth factors were permitted; however, prophylactic use was not permitted during treatment Cycle 1

  - During Part 1, the Dose Escalation Steering Committee recommended that dexamethasone (8 mg, orally, twice daily) be added for mitigation of toxicity. In Part 2, patients were to receive dexamethasone (4 mg, orally, twice daily) on Day −1 (the day before dosing, if possible), predose on Day 1 (the day of dosing), and on Day 2 (the day after dosing)
  - Spironolactone, at standard doses, could be instituted at any time for patients with weight gain >1 kg from Cycle 1, Day 1, new or worsening edema and/or new or worsening pleural effusion. Additional diuretic support could be added if further increases in weight, edema, or pleural effusion occurred
  - Adequate patient hydration (e.g., eight to ten glasses of water or equivalent per day) was recommended
- **Patient-monitoring parameters (frequency of visits and blood draws during therapy):** Visits and blood draws occurred on Day 1, 2, 3, 5, 8, 15, and 28 for Cycles 1 and 2; on Day 1, 8, and 28 for Cycle 3 onwards; end-of-treatment, and 12-week follow-up visit. Patients who tested positive for anti-drug antibodies were to be requested to have additional blood draws during long-term follow-up.