A Phase 1 Study of Plamotamab, an Anti-CD20 x Anti-CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Non-Hodgkin's Lymphoma: Recommended Dose Safety/Efficacy Update and Escalation Exposure-Response Analysis

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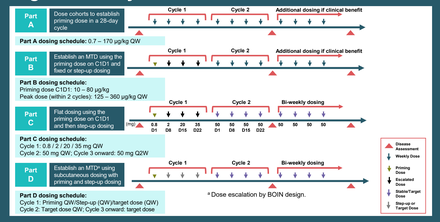
Introduction

- Non-Hodgkin's lymphoma (NHL) cases that become resistant or refractory after ≥ 2 therapies have a poor prognosis. Patients need an effective, well-tolerated, off-the-shelf treatment option.
- Plamotamab is a humanized bispecific antibody that recruits cytotoxic T cells to kill CD20-expressing malignant cells. In the dose-escalation phase of an ongoing first-in-human Phase 1 study (XmAb13676-01; NCT02924402), plamotamab was well tolerated with manageable cytokine release syndrome (CRS) and demonstrated evidence of clinical activity in heavily pre-treated patients with relapsed/refractory (R/R) NHL.[1]
- Primary objectives of this study are to assess safety, tolerability, and dose-limiting toxicities and to identify the maximum tolerated dose and/or recommended dose (RD) of plamotamab. Secondary objectives are preliminary anti-tumor activity and pharmacokinetics (PK)/pharmacodynamics.
- We report exposure-response (ER) analyses of the dose-escalation cohorts (Parts A, B and C) from the same study. We also report safety and efficacy results from the follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) escalation (Part C) and expansion cohorts at the proposed RD regimen.

Methods

Figure 1. Study Schema



- Parts A and B are weight-based dosing, and Part C is a flat, step-up dose regimen with biweekly dosing from Cycle 3 Day 1, enabling a more convenient dosing schedule.
- Part C uses a priming dose level of 0.8 mg, which was informed by Parts A and B to mitigate CRS.
- RD from Part C Cohort 1C was used in the DLBCL and FL expansion groups; n = 20 each.
- ER analysis was conducted based on exposure metrics calculated using population PK (popPK) model for plamotamab vs observed responses related to efficacy/safety from Parts A (n = 39), B (n = 43), and C (n = 14).
- Data are presented on all patients enrolled and treated at RD by 30 June 2022 (Part C and Expansion, n = 44) with a data cutoff of 24 August 2022 and 30 new patients at the RD since the ASH 2021 presentation.[1]

Key Inclusion Criteria

- B-cell NHL in patients aged 18 years or older.
- Ineligible for or have exhausted standard therapeutic options and not a candidate for or refusing hematopoietic stem cell transplantation.
- Last dose of anti-CD20 antibody > 4 weeks before plamotamab.
- ECOG performance status of 0 to 2.
- Diagnoses for expansion cohorts were limited to DLBCL and FL.

Methods for Exposure-Response Analysis

- Analysis was based on exposure metrics calculated using popPK model for plamotamab vs observed efficacy/safety responses from Parts A, B, and C.
- At data cutoff (10 Nov 2021) of Parts A, B, and C only, data were available from patients who received at least 1 dose of plamotamab in the second cycle and were evaluable for CRS and for efficacy and safety at the target dose.
- To account for CD20 binding competition between plamotamab and rituximab, the exposure metric receptor occupancy was calculated using the formula as provided by Li et al. ASH 2019.[2]
- ER plots are divided into intervals (dashed green lines) indicating tertiles of the corresponding exposure metrics. Open squares at each interval indicate the observed rates with 95% CIs from binominal distributions. Black lines are the modeled average trend based on linear regression model when the response variable is peak IL-6 and logistic regression model when response variables are CRS, AEs, or clinical response; shaded areas represent the 95% CI of the modeled ER relationship.

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Results

Table 1. Baseline Characteristics of Patients Treated at RD

	Overall (N = 44)		Overall (N = 44)
Median age (range), years	69.0 (36, 86)	Prior CAR-T n (%)	22 (50.00)
Male, n (%)	28 (63.64)	Primary disease at enrollment	
Baseline ECOG		DLBCL/HGBCL	32 (70.45)
0/1/2	17 (38.64)/24 (54.55)/3 (6.82)	DLBCL, NOS	6 (18.75)
Ann Arbor stage at baseline, n (%)		DLBCL, ABC	7 (21.88)
Limited: Stage I/Stage II/Stage II bulky	2 (4.55)/3 (6.82)/1 (2.27)	DLBCL, GCB	5 (15.63)
Advanced: Stage III/Stage IV	4 (9.09)/34 (77.27)	DLBCL, other[a]	8 (25.00)
Median time since initial diagnosis, months	38.0	HGBCL	6 (18.75)
Median number of prior systemic therapies	4.0	Follicular lymphoma	10 (22.72)
Refractory to last therapy, n (%)	21 (47.73)	Mantle cell lymphoma	1 (2.27)
Prior transplantation, n (%)	5 (11.36)	Nodal marginal zone lymphoma	1 (2.27)

[a] DLBCL, other: DLBCL associated with chronic inflammation (n = 2); DLBCL, unknown type (n = 2); EBV-positive DLBCL, NOS (n = 1); primary cutaneous DLBCL, leg type (n = 1); T-cell/histiocyte-rich LBCL (n = 1); primary mediastinal B-cell lymphoma (n = 1).

Safety and Tolerability in the RD Cohort

Table 2. All AEs in >15% of Patients

Preferred Term,[a] n (%)	Overall (N = 44)
Patients with at least 1 TEAE	44 (100.0)
CRS	31 (70.5)
Pyrexia	18 (40.9)
Anaemia	16 (36.4)
Nausea	15 (34.1)
Neutropenia	15 (34.1)
Asthenia	11 (25.0)
Diarrhoea	10 (22.7)
Hypokalaemia	9 (20.5)
Hypophosphataemia	9 (20.5)
Hypotension	9 (20.5)
Thrombocytopenia	9 (20.5)
COVID-19	8 (18.2)
Constipation	8 (18.2)
Fatigue	8 (18.2)
Vomiting	8 (18.2)
AST increased	7 (15.9)
Decreased appetite	7 (15.9)

[a] All AE terms were coded using MedDRA version 25.0. Grading is per Common Terminology Criteria for Adverse Events (CTCAE).

Table 3. Grade ≥3 AEs in >1 Patient

Preferred Term,[a] n (%)	Overall (N = 44)
Patients with at least 1 TEAE Grade ≥3	31 (70.5)
Neutropenia	11 (25.0)
Anaemia	7 (15.9)
Lymphopenia	5 (11.4)
Thrombocytopenia	4 (9.1)
Hypophosphataemia	3 (6.8)
WBC count decreased	3 (6.8)
ALT increased	2 (4.5)
COVID-19	2 (4.5)
Fatigue	2 (4.5)
Hypercalcaemia	2 (4.5)
Hypokalaemia	2 (4.5)
Pneumocystis jirovecii pneumonia	2 (4.5)
Sepsis	2 (4.5)

[a] All AE terms were coded using MedDRA version 25.0. Grading is per Common Terminology Criteria for Adverse Events (CTCAE).

- Grade 3 ICANS occurred in 1 patient (1/44, 2.3%).
- At the RD, 9/44 (20.5%) patients discontinued due to AEs of COVID-19 (4/44, 9.1%), carpal tunnel syndrome, Clostridioides difficile infection, neutropenia, palmar-plantar erythrodysaesthesia syndrome, and Pneumocystis jirovecii pneumonia (1 patient each, 2.3%).

Cytokine Release Syndrome at RD

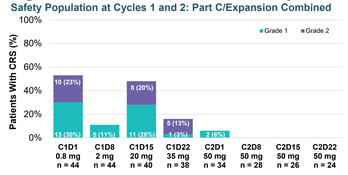
Table 4. Frequency and Duration of CRS

	Overall (N = 44)
CRS event, n (%)	31 (70.5)
Grade 1	13 (29.5)
Grade 2	18 (40.9)
Grade 3/4	0 (0.0)
Median time from start of last dose to onset of CRS, hours	25.97
Median duration of CRS, hours	14.75
CRS leading to treatment discontinuation, n (%)	0 (0.0)
Treated with tocilizumab, n (%)	15 (34.1)
Treated with steroids, n (%)[a]	13 (29.5)

[a] Part C/Expansion includes all patients treated at the RD.

Figure 2. Distribution of CRS Grade by Visit

Safety Population at Cycles 1 and 2: Part C/Expansion Combined



- No Grade 3 CRS observed.
- CRS generally resolved by Cycle 2.
- Median time to onset ~24 hours.

For this analysis, AEs with preferred term cytokine release syndrome (CRS) are used. For a patient with multiple CRS events at a dosing visit, the record with maximum CRS grade is used. The denominator for percentages is the number of patients (n) dosed at each visit. CRS was graded per the ASTCT consensus criteria.

Best Objective Response Rate – DLBCL and FL at RD

Table 5A. Efficacy Evaluable Population

Efficacy Evaluable Population	DLBCL/HGBCL (n = 25)	FL (n = 8)	Overall (N = 33)
ORR,[a] n/N (%)	13/25 (52.0)	7/8 (87.5)	20/33 (60.6)
Complete response	6/25 (24.0)	4/8 (50.0)	10/33 (30.3)
Partial response	7/25 (28.0)	3/8 (37.5)	10/33 (30.3)
Median duration of response, days[b]	126	NR	126
Median duration of follow-up, days	169	191	169
Post CAR-T, n/N (%)	16/25 (64.0)	1/8 (12.5)	17/33 (51.5)
ORR,[c]	8/16 (50.0)	0	8/17 (47.1)
CR rate	4/16 (25.0)	0	4/17 (23.5)

Table 5B. Intent-to-Treat Population

ITT Population	DLBCL/HGBCL (n = 32)	FL (n = 10)	Overall (N = 42)
ORR[a] n/N (%)	14/32 (43.8)	8/10 (80.0)	22/42 (52.4)
Complete response	6/32 (18.8)	4/10 (40.0)	10/42 (23.8)
Partial response	8/32 (25.0)	4/10 (40.0)	14/42 (28.6)
Median duration of response, days[b]	126	NR	126
Median duration of follow-up, days	132	191	166.5
Post CAR-T, n/N (%)	20/32 (62.5)	1/10 (10.0)	21/42 (50.0)
ORR[c]	8/20 (40.0)	0	8/21 (38.1)
CR rate	4/20 (20.0)	0	4/21 (19.0)

HGBCL = high-grade B-cell lymphoma; NR = not reached.

Patients enrolled before 30 June 2022. Efficacy evaluable population is defined as patients who reached the top dose level of 50 mg and, in addition, who did not withdraw prior to 2 cycles and completed at least 75% of doses (6 of 8 doses) and have post-baseline response assessment data available; or patients who withdrew due to AEs/death; or who withdrew other than AEs/death and have completed at least 75% of doses of the first cycle (3 of 4 doses). Intent-to-treat (ITT) population is defined as all treated patients.

[a] By Lugano criteria; objective response rate (ORR) is defined as the proportion of patients achieving a best overall response of PR or better. [b] Kaplan-Meier estimate; Duration of response is defined as time from initial response (PR or better) to first documentation of relapse (recurrence after CR) or progression (after PR) or death, whichever comes first. Patients who terminated the study without documented progression will be censored at the last tumor assessment date. [c] Denominator is the number of patients with post CAR-T in each indication.

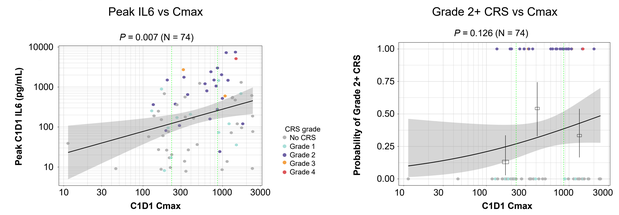
Exposure-Response

CRS After First Dose

Population: Parts A, B, and C (dose-escalation cohorts, both weight-based and flat dosing).

- Positive trend observed between plamotamab Cmax post first dose and peak IL6 levels as well as Grade 2+ CRS events.
- Minimal IL6 increases and Grade 2+ CRS events observed in the lowest tertile.
  - Lowest tertile represented by plamotamab Cmax ~< 230 ng/m.

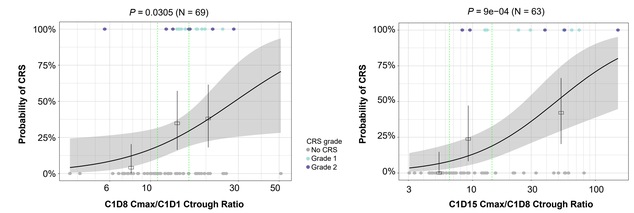
Figure 3. Exposure-Response Plot of CRS at First Dose



CRS After Step-up Doses

- As post-dose Cmax after step-up doses did not correlate significantly with incidence of any-grade CRS after the 2nd or 3rd dose (data not shown), the utility of the $Cmax_{post}/Ctrough_{pre}$ fold-increase in serum plamotamab associated with each step-up was explored as a metric to predict probability of CRS.
- The ratio of post-dose Cmax to pre-dose Ctrough is a significant predictor of any-grade CRS after 2nd and 3rd dose.

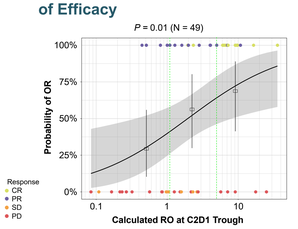
Figure 4. Exposure-Response Plot of CRS After Step-up Doses



Exposure vs Clinical Response

- Significant correlation between plamotamab exposure metric that accounts for competition for CD20 binding between rituximab and plamotamab vs ORR.

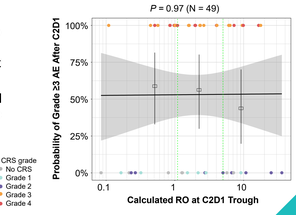
Figure 5. Exposure-Response Plot of Efficacy



Exposure-Safety Response at Target Dose

- Lack of correlation between plamotamab exposure metric vs Grade ≥3 AEs post target dose.
- Indicates the potential for a wide therapeutic window at the target dose.

Figure 6. Exposure-Response Plot of Safety



Conclusions

- Plamotamab was generally well tolerated with no Grade 3+ CRS events at RD.
- RD demonstrated evidence of clinical activity (ORR = 60.6%; efficacy evaluable population) in DLBCL/HGBCL and FL patients despite adverse prognostic factors such as prior CAR-T (50%), heavily pre-treated (median 4 prior lines), and 30% with poor risk histology (HGBCL and ABC-DLBCL).
- The RD of 50 mg reached the trough levels potentially associated with higher response rates and without incidence of high-grade CRS.
- ER analysis for CRS identifies the safety exposure limits after both priming (Cmax) and step-up dosing (Cmax/Ctrough) to avoid high-grade CRS events.
- ER analysis for efficacy indicates an increase in ORR with increasing exposure but a flat relationship for exposure vs high-grade AEs post administration of target dose.

Future Directions

- Cohort to accelerate titration to IV RD now actively recruiting (Part C Cohort 2C).
- Cohorts for subcutaneous administration to further improve safety and efficacy profile now actively recruiting (Part D).
- Phase 2 study in combination with tafasitamab (anti-CD19) and lenalidomide in R/R DLBCL underway (Protocol XmAb13676-03, NCT05328102, ASH 2022 abstract # 5503).

References

1. Patel K, et al. *Blood* 2021;138(Supplement 1): 2494.
2. Li CC, et al. *Blood* 2019;134 (Supplement 1): 1285.

Acknowledgments

We wish to thank the patients and their families and all the investigators' site staff for their contribution to this study. We also wish to thank Michael Chiarella, Selam Berhe, Huaiyu Sun, Matthew Guo, Rose Morton, Phuong Lee, Kristy Colella, and Pamela Boltz from Xencor. This study was funded by Xencor, Inc. Medical writing and editorial support was provided by Parexel and funded by Xencor, Inc.

Presented at the American Society of Hematology Annual Meeting and Exposition, New Orleans, LA, USA, December 10–13, 2022