Plamotamab: First Presentation of Subcutaneous Administration in a Phase 1 Dose-Escalation Study in Heavily Pretreated R/R NHL Patients Who Had Prior CAR-T Cell Therapy

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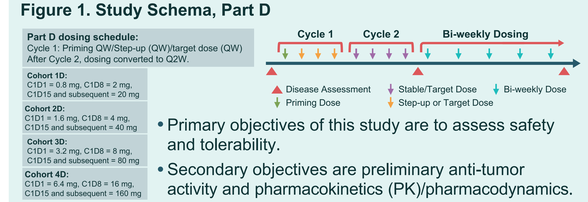
Introduction

- Plamotamab is a CD20 x CD3 T-cell engaging bispecific antibody. This is a Phase 1, first-in-human, multiple-dose, dose-escalation study designed in 4 parts, using intravenous (IV) administration in Parts A, B and C, and subcutaneous (SC) administration in Part D.
- In the dose-escalation phase of the Phase 1 study (XmAb13676-01; NCT02924402), plamotamab was administered intravenously with a step-up priming regimen. It was well tolerated with manageable cytokine release syndrome (CRS) 70.5% mainly at priming (29.5%, Grade 1; 40.9%, Grade 2; no Grade ≥ 3/4), ICANS 1.5%, and demonstrated evidence of clinical activity (objective response rate [ORR] was 52%) in patients with large B-cell lymphoma (LBCL)[1].
- Recommended dose (RD) from Part C Cohort 1C was used to model dosing for SC administration for Part D.
- Plamotamab was evaluated in various subtypes of B-cell non-Hodgkin lymphoma (NHL), including LBCL, mantle cell lymphoma, and Waldenström macroglobulinemia.
- We report results from the SC Part D dose escalation.

Methods

Figure 1. Study Schema, Part D



- Primary objectives of this study are to assess safety and tolerability.
- Secondary objectives are preliminary anti-tumor activity and pharmacokinetics (PK)/pharmacodynamics.

C = cycle; D = day. Part D shown here. The study schema for Parts A, B, and C utilizing IV dosing was previously described in ASH 2022[1].
Data cut: 12 August 2024

Results

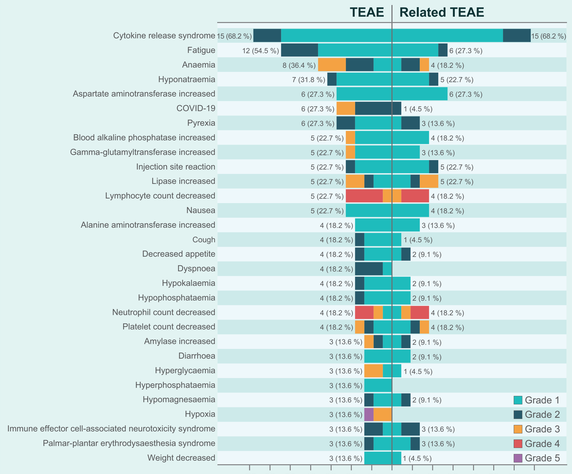
Table 1. Demographics and Baseline Characteristics of Part D

Categories	Overall (N=22)
Median age (range), years	67.0 (27, 9)
Male, n (%)	16 (72.7)
Baseline ECOG	
0/1	8 (36.3)/ 14 (63.6)
Modified Ann Arbor stage at baseline, n (%)	
Limited: Stage I/Stage II	1 (4.5)/1 (4.5)
Advanced: Stage III/ Stage IV	3 (13.6)/ 14 (63.6)
Unknown/ Not applicable	2 (9.1)/ 1 (4.5)
Median time since initial diagnosis, months Min, max	33.2 9.0, 171.9
Median number of prior systemic therapies (range)	4.0 (2–10)
Refractory to last therapy, n (%)	13 (59.1)
Prior autologous transplantation, n (%)	4 (18.2)
Prior CAR-T, n (%)	18 (81.8)
Primary disease at enrollment, n (%)	
DLBCL	15 (68.2)
GCB DLBCL	4 (18.2)
Non-GBC DLBCL	1 (4.5)
DLBCL, unknown cell origin	8 (36.4)
Primary cutaneous DLBCL, leg type	1 (4.5)
T-cell/Histiocyte-rich large B-cell lymphoma	1 (4.5)
HGBCL	5 (22.7)
HGBCL w/MYC and BCL2 and/or BCL6 rearrangements	4 (18.2)
HGBCL, NOS	1 (4.5)
Mantle cell lymphoma	1 (4.5)
Waldenström macroglobulinemia	1 (4.5)

BCL2/BCL6 = B-cell lymphoma 2 and 6; CAR-T = chimeric antigen receptor-modified T-cell therapy; DLBCL = diffuse large B-cell therapy; ECOG = Eastern Cooperative Oncology Group; GCB = germinal center B cell; HGBCL = high-grade B-cell lymphoma; NOS = not otherwise specified.
Unknown/Not applicable: with 2 patients no data available \ 1 patient with Waldenström.
Data cut: 12 August 2024.

Safety and Tolerability: Part D

Figure 2. Treatment-Emergent AEs in ≥ 10% of Patients



- Related TEAEs in >20% include CRS (68%), fatigue (55%), anemia (36%), hyponatremia (32%), and AST increased, COVID-19, pyrexia (27%).
- Grade ≥3 AEs include lymphopenia (23%), neutrophil count decreased (14%), anemia and hypoxia (14%).
- 3 ICANS events occurred in Part D. All events were Grade 1 and 2 and resolved within the same day.
  - 5 events occurred in Parts A–D of the study (n=154; 3.2%).
  - 4 out of 5 ICANS events occurred at the same study site.
- Grade 5 hypoxia event occurred on Day 163 and was assessed as unlikely related to plamotamab and occurred in a patient with a serious adverse event of exacerbation of prior history of congestive heart failure.

CTCAE v4.03 was used for grading toxicities. The ASTCT CRS Consensus Grading (Lee, 2019[2]) was used for grading CRS. Immune Effector Cell- Associated Encephalopathy score was used for grading ICANS.
Data cut: 12 August 2024

Cytokine Release Syndrome

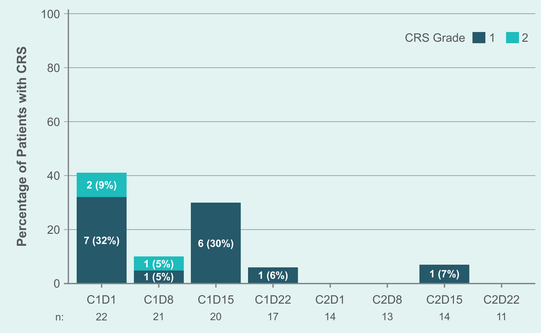
Table 2. CRS by Preferred Term and Maximum Severity for Part D

Preferred Term	Overall (N=22)
Maximum Severity, n (%)[a]	
Number of Patients with at Least One IRR/CRS TEAE[b]	18 (81.8)
Grade 1	14 (63.6)
Grade 2	4 (18.2)
Cytokine Release Syndrome	15 (68.2)
Grade 1	12 (54.5)
Grade 2	3 (13.6)

CRS = cytokine release syndrome; IRR = infusion-related reaction.
The ASTCT CRS Consensus Grading (Lee, 2019[2]) was used for grading CRS. Note: A patient with multiple adverse events within a preferred term is only counted once with maximum grade in this preferred term.
[a]All treatment-emergent adverse event (TEAE) terms were coded using MedDRA version 26.1.
[b]TEAEs are defined as events with onset dates on or after the start of study treatment or events that are present before the first infusion of plamotamab and subsequently worsen in severity.

Safety and Tolerability: CRS

Figure 3. Distribution of CRS Grade by Visit: Safety Population (n = 22)



- Most of the CRS occurred at the first priming dose; no CRS > Grade 1 occurred after C1D8.
- Event of CRS at C2D15 visit is due to repriming dose after dose interruption for upper respiratory infection (Covid-19).

The ASTCT CRS Consensus Grading (Lee, 2019[2]) was used for grading CRS. Adverse Events with preferred term Cytokine Release Syndrome (CRS) are used in the analysis. For multiple CRS events for a subject at a dosing visit, the record with maximum CRS grade was used in the analysis. The denominator for percentages is the number of patients (n) dosed at each visit.
EDC Data transfer date: 12 August 2024.

Best Objective Response Rate

Table 3. BOR and ORR in Part D (Efficacy-evaluable Population)

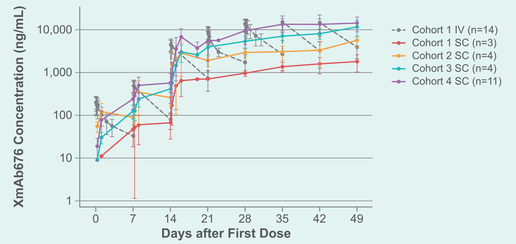
Response Category	LBCL Overall (N=17)
ORR[a] 95% CI	9/17 (52.9) (27.8, 77.0)
ORR Prior CAR-T[a,b] 95% CI	7/14 (50.0) (23.0, 76.9)
Best Overall Response, n (%)[c]	
Complete Response	4 (23.5)
Partial Response	5 (29.4)
Progressive Disease	7 (41.2)
Not Evaluable	1 (5.9)
Duration of Response (in months)	
Duration of Response (min-max)	5.5 (2–11)
Prior CAR-T	
Yes	14/17 (82.4)
DLBCL[d]	5/10 (50.0)

- Includes 17 evaluable patients (defined as patients with LBCL [DLBCL, HGBCL, and T-cell rich lymphoma] who completed at least the first cycle of plamotamab and had at least 1 post-baseline assessment available). In patients with DLBCL, the ORR was 43% and the CR rate was 14%.

BOR = best overall response rate; CAR-T = chimeric antigen receptor T-cell therapy; LBCL = large B-cell lymphoma; ORR = objective response rate. [a]ORR is defined as the proportion of patients achieving partial or complete response of PR or better including minor response. [b]Denominator is the number of patients with Post CAR-T in each indication. [c]Best overall response is defined per Lugano classification[3] and is the best response recorded during the study. [d]DLBCL patients with prior CAR-T.
Generated on 24 September 2024.

Exposure Response

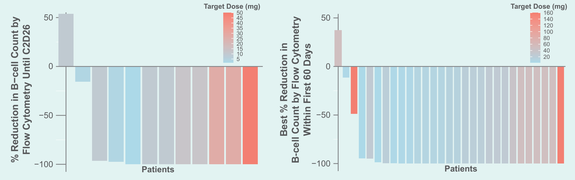
Figure 4. Plamotamab Pharmacokinetic Profile Post SC Administration



- Based on the preliminary population PK model, C_{max} was reduced by approximately 8-fold post SC administration compared to IV administration.
- The terminal half-life of plamotamab was approximately 14 days post SC administration, supporting a Q2W dosing regimen post Cycle 2.

IV PK profile is included in the figure for comparison.

Figure 5. Significant Reduction in B-cell Count



- Absolute CD19+ B-cell count in bone marrow (on C1D1 and C1D26) and whole blood (on C1D1 and timepoints up to C55D1) measured by flow cytometry.
- >90% decrease in B-cells in both bone marrow (baseline vs. postdose) and whole blood across the dose cohorts.

C = cycle; D = day. Figure includes patients from Parts A–D. No bone marrow samples were collected in Part D. Patients with LBCL were included if their baseline B-cell count was >10 cell/μL.

Conclusions

- Plamotamab was generally well tolerated across all SC dose levels in Part D with no Grade 3+ CRS events. Most CRS occurred with the first priming dose and less frequently at subsequent step-up doses.
- SC administration of plamotamab reduced C_{max} compared to IV.
- Robust reduction occurred in B-cell counts across all dose levels of plamotamab in whole blood in Parts A-D and in both whole blood and bone marrow in Parts A–C (bone marrow not collected in Part D).
- Plamotamab demonstrated evidence of clinical activity (ORR = 53%; efficacy-evaluable population) in patients with LBCL despite adverse prognostic factors such as prior CAR-T and being heavily pretreated (median 4 prior lines).
- The SC Part D dose escalation was completed with evidence of response with manageable CRS (no Grade ≥3/4).

References

1. Patel K, et al. *Blood* 2022;140 (Supplement 1): 9470–9472.
2. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25(4):625-638.
3. Cheson, BD, et al. *J Clin Oncol* 2014;32(27):3059-3068.

Acknowledgments

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