13676-01
ASH Poster 2021

"Phase 1 Safety and Anti-tumor Activity of Plamotamab (XmAb13676), an Anti-CD20 x Anti-CD3 Bispecific Antibody, in Subjects with Relapsed/Refractory Non-Hodgkin's Lymphoma"

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Introduction

The B lymphocyte-derived malignancies represent a diverse group of diseases, including non-Hodgkin's lymphoma (NHL). Compared to chemotherapy alone, immunochemotherapy, most commonly with the anti-CD20 antibody rituximab, led to higher response rates, higher complete remission rates, and improved survival for both indolent and aggressive histologies (1). Bispecific antibodies are being tested to address the 30% of B-cell NHL cases (2) that become resistant or refractory to anti-CD20 antibodies. XmAb13676 (plamotamab) is a humanized bispecific antibody that binds to CD20-expressing target cells and to CD3, to recruit and activate T cells, and is being studied in relapsed or refractory NHL. The data are presented here.

The primary objectives are to assess safety, tolerability, dose-limiting toxicities and to identify the maximum tolerated dose (MTD) and/or recommended dose (RD) of plamotamab. The secondary objectives are preliminarily anti-tumor activity and pharmacokinetics (PK)/pharmacodynamics.

Methods

The study is a first-in-human, multicenter, open-label, Phase 1, dose-escalation study in subjects with relapsed or refractory (R/R) NHL with a standard 3 + 3 design. This study has 3 Parts (Figure 1). Parts A and B are weight based, 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 cytokine release syndrome (CRS).

CRS and infusion related reaction (IRR) prophylaxis with dexamethasone, antihistamine, and acetaminophen was mandated prior to each administration of plamotamab.

The Recommended Dose and dosing schedule were established from Part C, allowing the diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) groups to be expanded with up to 20 evaluable subjects per expansion group.

Key inclusion criteria:

- Diagnosis of B-cell NHL in subjects 18 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 first dose of plamotamab
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

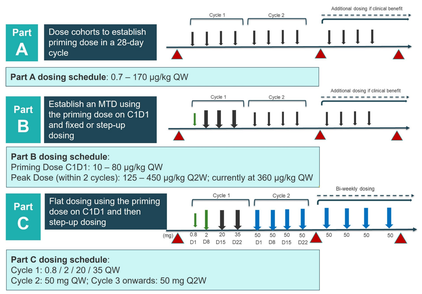


Figure 1: 13676-01 Study Schema

Results

As of data cut date, we analyzed a safety population of 50 subjects (38 DLBCL, 12 FL) for the weight-based cohorts (highest planned dose of 80 to 360 µg/kg). For Part C, the safety population was 14 subjects (8 DLBCL, 4 FL, 1 marginal zone, 1 mantle cell).

In both dosing groups, subjects were heavily pre-treated. For Part C, prior therapy included cellular therapy (9/14). 6/14 received CAR-T, 1 received NK cell therapy, and 2 received both. Discontinuations were as follows for Part C: Progressive Disease (n = 7, 50%), Death (n = 1, 7.1%), Insufficient Clinical Response (n = 2, 14.3%), Adverse Event (n = 1, 7.1%), Withdrawal by Subject (n = 1, 7.1%).

- Increases in serum concentrations of step-up dosing of plamotamab were dose proportional. Population PK analyses were performed to predict flat and Q2W exposure using concentrations from 53 subjects in Parts A and B. The RP2D of 50 mg reached trough levels potentially associated with higher response rates and reduced incidence of CRS
- Most events were mild or moderate in severity (Table 2) with a higher incidence of hematological Grade 3 TEAEs in the weight-based groups generally
- The most common TEAE was CRS
- In Part C, 12 (85.7%) subjects experienced at least 1 adverse event (AE) of ≥ Grade 3 in severity. These were generally hematological and assessed as disease-related events
- Nervous system events did not lead to subject discontinuation. The most common nervous system events were Headache (21.4% to 28%) and Dizziness (18% to 21.4%). No related neurotoxicity > Grade 2 has been observed

Median duration of response for the overall population of weight-based dosing cohorts and Part C was 225 days for DLBCL and 171 days for FL (data not shown).

	NHL Weight Based Cohorts (N = 46)	NHL – Flat Dose Cohort (Part C) (N = 14)	Overall (N = 60)
Median age, years (range)	61.5 (32, 82)	64 (36, 75)	61.5 (31, 82)
ECOG performance status, n(%)			
0	17 (34.0)	7 (50.0)	24 (37.5)
1	30 (60.0)	7 (50.0)	37 (57.8)
2	3 (6.0)	0	3 (4.7)
Time Since initial Diagnosis (Months)			
Median (range)	25.5 (6, 353)	30.5 (15, 237)	26.5 (6, 353)
Ann Arbor Stage at Baseline n (%)			
Limited/Stage I	1 (2.17)	0	1 (1.67)
Limited/Stage II	3 (6.52)	0	3 (5.00)
Limited/Stage II Bulky	2 (4.35)	0	2 (3.33)
Advanced/Stage II Bulky	1 (2.17)	0	1 (1.67)
Advanced/Stage III	9 (19.57)	1 (7.14)	10 (16.67)
Advanced/Stage IV	28 (60.87)	7 (50.00)	35 (58.33)
Unknown	2 (4.35)	6 (42.86)	8 (13.33)
Prior Transplantation n(%)	8 (17.39)		8 (13.33)
Best Response to last Systemic Therapy n(%)			
Complete Remission	8 (17.39)	3 (21.43)	11 (18.33)
Partial Remission	15 (32.61)	4 (28.57)	19 (31.67)
Stable Disease	5 (10.87)	0	5 (8.33)
Progressive Disease	15 (32.61)	7 (50.00)	22 (36.67)
Unknown	1 (2.17)	0	1 (1.67)
Not Assessed	2 (4.35)	0	2 (3.33)
Relapsed/progression after last Systemic Therapy n(%)			
Yes	37 (80.43)	14 (100.00)	51 (85.00)
No	9 (19.57)	0	9 (15.00)
Duration of Response to last Systemic Therapy (days)			
n	20	7	27
Median	133.0 (1, 1456)	56.0 (21, 336)	97.0 (1, 1456)
Number of Prior Systemic Therapies			
Median	3.0 (1, 10)	5.0 (2, 10)	4.0 (1, 10)

Table 1: Baseline Characteristics and Prior Therapies

Footnote: Data cut-off = 27 October 2021. Safety population is defined as all subjects who have received at least 1 infusion of plamotamab; NHL weight-based cohorts includes all Part B cohorts with highest planned weekly weight-based dosing of 80 to 360 µg/kg. Four NHL subjects from the weight-based cohort with primary disease of Waldenström macroglobulinemia (WM) or lymphoplasmacytic lymphoma (LPL) are not included here.

Preferred Term [a], n(%)	NHL Weight Based Cohorts (N = 50)	NHL Flat Dose Cohort (Part C) (N = 14)	Overall (N = 64)
Subjects with at least one event	50 (100.0)	14 (100.0)	64 (100.0)
Cytokine release syndrome	37 (74.0)	8 (57.1)	45 (70.3)
Pyrexia	28 (56.0)	7 (50.0)	35 (54.7)
Anaemia	21 (42.0)	7 (50.0)	28 (43.8)
Fatigue	18 (36.0)	3 (21.4)	21 (32.8)
Diarrhoea	15 (30.0)	4 (28.6)	19 (29.7)
Nausea	12 (24.0)	7 (50.0)	19 (29.7)
Cough	16 (32.0)	2 (14.3)	18 (28.1)
Headache	14 (28.0)	3 (21.4)	17 (26.6)
Hypokalaemia	14 (28.0)	3 (21.4)	17 (26.6)
Neutropenia	15 (30.0)	2 (14.3)	17 (26.6)
Decreased appetite	10 (20.0)	5 (35.7)	15 (23.4)
Thrombocytopenia	13 (26.0)	2 (14.3)	15 (23.4)
Asthenia	10 (20.0)	4 (28.6)	14 (21.9)
Constipation	12 (24.0)	2 (14.3)	14 (21.9)
Arthralgia	11 (22.0)	2 (14.3)	13 (20.3)
Dyspnoea	10 (20.0)	3 (21.4)	13 (20.3)
Oedema peripheral	9 (18.0)	4 (28.6)	13 (20.3)
Vomiting	11 (22.0)	2 (14.3)	13 (20.3)
Chills	12 (24.0)	0	12 (18.8)
Dizziness	9 (18.0)	3 (21.4)	12 (18.8)
Hypophosphataemia	10 (20.0)	2 (14.3)	12 (18.8)
Hypotension	9 (18.0)	3 (21.4)	12 (18.8)
Alanine aminotransferase increased	9 (18.0)	2 (14.3)	11 (17.2)
Back pain	8 (16.0)	3 (21.4)	11 (17.2)
Tachycardia	8 (16.0)	3 (21.4)	11 (17.2)
Hyperglycaemia	10 (20.0)	0	10 (15.6)
Grade ≥ 3 events (Safety Population > 5%)			
Subjects with at least one event	43 (86.0)	12 (85.7)	65 (81.3)
Anaemia	11 (22.0)	2 (14.3)	17 (21.3)
Neutropenia	13 (26.0)	1 (7.1)	15 (18.8)
Hypophosphataemia	8 (16.0)	0	9 (11.3)
Thrombocytopenia	8 (16.0)	1 (7.1)	9 (11.3)
Lymphopenia	6 (12.0)	2 (14.3)	8 (10.0)
Lymphocyte count decreased	6 (12.0)	0	7 (8.8)
Neutrophil count decreased	5 (10.0)	1 (7.1)	7 (8.8)
ALT increased	2 (4.0)	1 (7.1)	4 (5.0)
AST increased	2 (4.0)	1 (7.1)	4 (5.0)
Cytokine release syndrome	4 (8.0)	0	4 (5.0)
Fatigue	3 (6.0)	1 (7.1)	4 (5.0)
GGT increased	3 (6.0)	1 (7.1)	4 (5.0)
Hypertension	2 (4.0)	0	4 (5.0)
Hypokalaemia	3 (6.0)	0	4 (5.0)

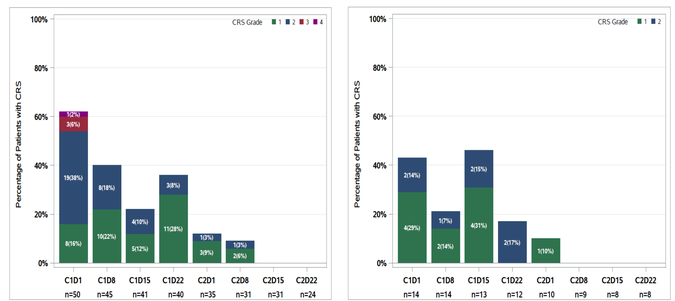
Table 2: Summary of TEAEs

Footnote: Date cut = 27 October 2021. Safety population with TEAEs > 15% frequency included here. Weight-based cohorts include highest planned weekly weight-based dosing of 80 to 360 µg/kg. Includes 4 subjects from the weight-based cohorts with primary disease of WM and LPL. Grading as per Common Terminology Criteria for Adverse Events (CTCAE)

Cytokine Release Syndrome (CRS)

- Lower frequency and less severe CRS was seen in the flat dosing Part C (57.1%) compared to the weight-based 80 to 360 µg/kg cohorts (74.0%) (Table 2)
  - Weight-based cohorts saw 4 (8%) ≥ Grade 3 CRS events on priming dose day; there was no ≥ Grade 3 CRS in Part C (Figure 2) supporting 0.8 mg as a low priming dose and the Part C schedule as a tolerable step-up strategy
  - CRS generally resolved by Cycle 2
- In Part C, the most common CRS-like symptoms were pyrexia (50%), hypotension (21.4%), and tachycardia (21.4%)
- Peak serum IL-6 levels are generally higher on the first dose and larger step-ups of plamotamab, which correlated with more frequent and higher-grade CRS (data not shown)

Figure 2: Distribution of CRS Grade by Visit – Safety Population



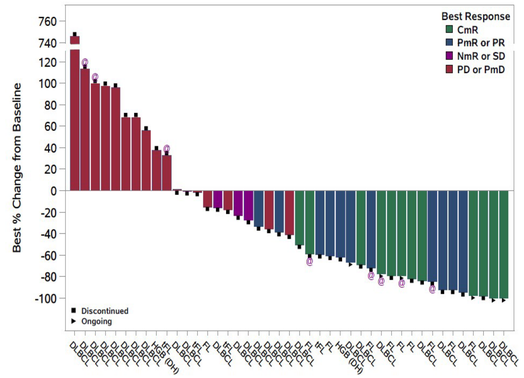
Footnote: Data cut = 27 October 2021. Weight-based cohorts includes all Part B cohorts with highest planned weekly weight-based dosing of 80 to 360 µg/kg. Adverse events with preferred term Cytokine Release Syndrome (CRS) are used in the analysis. For multiple CRS events for a subject at a dosing visit, the record with maximum CRS grade was used in the analysis. The denominator for percentages is the number of subjects (n) dosed at each visit. CRS was graded as per the ASTCT Consensus (3)

Weight-Based Cohorts	Response Rate: n/N(%)
25 µg/kg	
ORR	1/1 (100.0)
CR	0/1
80 µg/kg	
ORR	1/4 (25.0)
CR	0/4
125 µg/kg	
ORR	6/12 (50.0)
CR	5/12 (41.7)
170 µg/kg	
ORR	4/7 (57.1)
CR	2/7 (28.6)
250 µg/kg	
ORR	4/10 (40.0)
CR	1/10 (10.0)
360 µg/kg	
ORR	2/4 (50.0)
CR	1/4 (25.0)
Flat Dose Cohort, Part C	**Response Rate: n/N(%)**
50 mg	
ORR	6/9 (66.7)
CR	3/9 (33.3)
Overall	
ORR	24/47 (51.1)
CR	12/47 (25.5)

Table 3: Best ORR – DLBCL and FL

Footnote:
Data cut = 27 October 2021. Included here is the efficacy evaluable population, defined as subjects who did not withdraw prior to 2 cycles and completed at least 75% doses (6 out of 8 doses)and have post-baseline response assessment data available; or subjects who withdrew due to adverse events/death and, for subjects in Part C, reached the top dose level of 50 mg; or subjects who withdrew other than adverse events/death and have completed at least 75% doses of the first cycle (3 doses out of 4). Weight-based cohorts includes all Part B cohorts with highest planned weekly weight-based dosing of 80 to 360 µg/kg. Includes 1 subject in a 250 µg/kg top dose weight-based cohort where the subject had a response at the first dose level of 25 µg/kg in the schedule. WM and LPL subjects not shown here.
ORR = Objective response rate; CR = Complete response. Response is assessed based on Lugano Classification (4).

Figure 3: Tumor Response – DLBCL and FL (n = 47)



Footnote: Data cut = 27 October 2021. Included here is the efficacy evaluable population, as defined in Table 3.
@ = Cohort Part C.
All other subjects are from weight-based cohorts (highest planned weekly dose of 80 to 360 µg/kg).
One subject has a Percent Change in SPD = 0 and is represented as 1% in the graph. One subject from Part C did not have all post baseline target measurements but was a responder as per Lugano PET-CT 5-PS. WM and LPL subjects are not shown here.
DLBCL = Diffuse large B cell lymphoma; FL = Follicular lymphoma; CmR = Complete metabolic response; PmR = Partial metabolic response; PR = Partial response; NmR = No metabolic response; SD = Stable disease; PD = Progressive disease. Response is assessed based on Lugano Classification(4).

Conclusions

- In the ongoing Phase 1 study in B-cell malignancies, plamotamab was generally well tolerated
- There were no Grade 3 or 4 CRS events in Part C schedule, with other safety events being generally mild or moderate in severity
- Flat dosed Part C demonstrated evidence of clinical activity in R/R NHL subjects with adverse prognostic factors:
  - ORR in FL was 100% (4/4), with a complete response rate of 50% (2/4)
  - ORR in DLBCL was 40% (2/5); all DLBCL subjects received prior CAR-T
  - 2/9 responders were refractory to first-line therapy
  - Subjects were heavily pretreated with a median of 4 prior lines of therapy for FL and a median of 5 lines of therapy for DLBCL
- **Part C schedule agreed upon as RP2D by Dose Escalation Review Committee**
- Expansion groups in DLBCL and FL now opened using RP2D to further evaluate the safety and efficacy of plamotamab and is actively recruiting
- PK modelling for subcutaneous administration with less frequent dosing suggests ability to maintain trough levels to mitigate CRS (data not shown), providing an opportunity to potentially use higher doses to increase likelihood of response
- Phase 2 study in combination with tafasitamab (anti-CD19) and lenalidomide in R/R DLBCL being planned

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