Preliminary Safety and Anti-Tumor Activity of XmAb13676, an Anti-CD20 x Anti-CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia

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Introduction

The B lymphocyte-derived malignancies represent a diverse group of diseases, including non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL).[1] 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.[2] Bispecific antibodies are being tested to address the 30% of B-cell NHL cases that become resistant or refractory to anti-CD20 antibodies. XmAb13676 is a humanized bispecific antibody that binds to CD20-expressing target cells and to CD3, to recruit and activate T cells. XmAb13676 is being studied in two groups of patients with relapsed or refractory B-cell malignancies, both NHL and CLL.

Objectives

- Primary objectives: to assess safety, tolerability, dose-limiting toxicities (DLTs) and to identify the maximum tolerated dose (MTD) and/or recommended dose (RD) of XmAb13676.
- Secondary objectives: to characterize the pharmacokinetic (PK) profile, immunogenicity, and to preliminarily assess anti-tumor activity (response rates [RR], duration of response, and progression-free survival).

Methods

Study Design:

- Ongoing Phase 1, dose-escalation and expansion study to assess the safety and tolerability of XmAb13676 monotherapy
- Two-part study:
  - Part A: weekly dosing to establish a "priming dose" initially selected as 80 µg/kg and subsequently reduced to 45 µg/kg in the NHL group
  - Part B: escalating 3+3 dose cohorts with an initial "priming dose" on Cycle 1 Day 1 followed by higher step-up doses to determine MTD/RD
- Key inclusion criteria:
  - Adult (age ≥ 18 years)
  - Diagnosis of either B-cell NHL or CLL/SLL (including Richter's transformation)
  - Ineligible for or have exhausted standard therapeutic options, has refused, or is not a candidate for hematopoietic stem cell transplantation
  - Last dose of anti-CD20 antibody >4 weeks before first dose of XmAb13676
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

Results

Patient disposition, treatment exposure, baseline characteristics, and prior treatment history:

- As of 8 November 2019, 53 patients (45 Group NHL and 8 Group CLL) were treated with XmAb13676 monotherapy and are included in the safety analyses (Table 1).
- Patients with diffuse large B-cell lymphoma (DLBCL) receiving highest doses of 80-170 µg/kg are included in analyses to define clinical activity (Table 2).

Safety:

- Most events were mild or moderate in severity (Table 3).
- Nervous system disorders occurred in 26 (49.1%) patients (data not shown).
  - The most common nervous system events were dizziness (17%), headache (17%), paresthesia (9.4%), and lethargy (5.7%).
  - One (2.2%) patient experienced short-term encephalopathy (Grade 2) during a cytokine release syndrome (CRS) event that resolved concomitantly with treatment of the CRS.
  - One (2.2%) patient lost consciousness (Grade 1) during a bowel movement (likely vasovagal)
- The treatment-emergent AE (TEAE) profile for the DLBCL safety population is similar to the NHL safety population shown in Table 3 (data not shown).

Table 1: Patient Disposition

n (%)	NHL (N=45)	CLL (N=8)	Overall (N=53)
Remained on treatment	10 (22.2)	0	10 (18.9)
Discontinued treatment	35 (77.8)	8 (100.0)	43 (81.1)
Adverse event	4 (8.9)	3 (37.5)	7 (13.2)
Physician decision	2 (4.4)	0	2 (3.8)
Progressive disease	15 (33.3)	2 (25.0)	17 (32.1)
Withdrawal by patient	4 (8.9)	0	4 (7.5)
Insufficient clinical response	8 (17.8)	2 (25.0)	10 (18.9)
Other	2 (4.4)	1 (12.5)	3 (5.7)

Table 2: Baseline Characteristics and Prior Therapies - DLBCL Safety Population (80-170 µg/kg)

	Overall (N=18)
Median age, years (range)	63.5 (48, 82)
Male, n (%)	9 (50.0)
ECOG performance status, n (%)	
0	6 (33.3)
1	9 (50.00)
2	3 (16.67)
Median time since initial diagnosis, months (range)	21.5 (6, 353)
Ann Arbor Stage at enrollment n (%)	
Limited Stage II	2 (11.1)
Advanced/Stage II bulky	1 (5.6)
Advanced/Stage III	2 (11.1)
Advanced/Stage IV	11 (61.1)
Unknown	2 (11.1)
Median number of prior systemic therapy, n (range)	3 (1, 6)
Best response to last systemic therapy n(%)	
Complete remission	2 (11.1)
Partial remission	6 (33.3)
Stable disease	2 (11.1)
Progressive disease	6 (33.3)
Not assessed	2 (11.1)
Relapsed/progression after last systemic therapy n (%)*	
Yes	14 (77.8)
No	3 (16.7)
Median duration of response to last systemic therapy, weeks(range)	21.1(8, 60)

*Relapse/progression status of 1 patient is missing. Three patients (16.7%) had prior transplantation. ECOG: Eastern Cooperative Oncology Group.

Cytokine Release Syndrome (CRS):

- At least 1 CRS event occurred in 28 (52.8%) patients (Table 3):
  - Of these 28 CRS events, 25 (89%) were Grade 1 or 2 in severity (data not shown).
  - Three (5.7%) patients experienced CRS of Grade 3 or 4 in severity.
  - An additional 12 (22.6%) patients experienced other events that may have been consistent with symptoms of CRS with mild to moderate severity (Grade 1 or 2) (data not shown).
  - The most common CRS-like symptoms were pyrexia (45.3%), hypotension (20.8%), chills (18.9%), tachycardia (13.2%), and hypertension (9.4%) (data not shown).

Table 3: Summary of TEAEs

Event, n(%)	NHL (N=45)	CLL (N=8)	Overall (N=53)
Any TEAE	45 (100.0)	8 (100.0)	53 (100.0)
Any serious TEAE	24 (53.3)	5 (62.5)	29 (54.7)
Leading to drug withdrawn	4 (8.9)	3 (37.5)	7 (13.2)
Most common TEAEs (≥15%)			
Pyrexia	26 (57.8)	3 (37.5)	29 (54.7)
Cytokine release syndrome	25 (55.6)	3 (37.5)	28 (52.8)
Anemia	19 (42.2)	3 (37.5)	22 (41.5)
Diarrhea	12 (26.7)	2 (25.0)	14 (26.4)
Asthenia	10 (22.2)	3 (37.5)	13 (24.5)
Hypotension	12 (26.7)	1 (12.5)	13 (24.5)
Thrombocytopenia	11 (24.4)	2 (25.0)	13 (24.5)
Chills	11 (24.4)	1 (12.5)	12 (22.6)
Cough	10 (22.2)	2 (25.0)	12 (22.6)
Fatigue	8 (17.8)	4 (50.0)	12 (22.6)
Neutropenia	10 (22.2)	2 (25.0)	12 (22.6)
Constipation	10 (22.2)	1 (12.5)	11 (20.8)
Hypokalemia	10 (22.2)	0	10 (18.9)
Edema peripheral	6 (13.3)	4 (50.0)	10 (18.9)
Tachycardia	8 (17.8)	2 (25.0)	10 (18.9)
Dizziness	9 (20.0)	0	9 (17.0)
Dyspnea	7 (15.6)	2 (25.0)	9 (17.0)
Headache	8 (17.8)	1 (12.5)	9 (17.0)
Nausea	7 (15.6)	1 (12.5)	8 (15.1)
Upper respiratory tract infection	7 (15.6)	1 (12.5)	8 (15.1)
Grade ≥3 events, n (%)			
Any TEAE Grade ≥3	31 (68.9)	6 (75.0)	37 (69.8)
Most common TEAEs (≥5%)			
Anemia	11 (24.4)	1 (12.5)	12 (22.6)
Neutropenia	7 (15.6)	1 (12.5)	8 (15.1)
Thrombocytopenia	5 (11.1)	1 (12.5)	6 (11.3)
Lymphopenia	4 (8.9)	1 (12.5)	5 (9.4)
Cytokine release syndrome	2 (4.4)	1 (12.5)	3 (5.7)
Hypokalemia	3 (6.7)	0	3 (5.7)

Note: AEs were graded based on CTCAE version v4.03, except for CRS, which was graded according to the Lee criteria[4]

Clinical Activity

Clinical Activity:

- The data cut-off date for the analyses to define clinical activity was 8 November 2019 and includes patients whose highest dose with XmAb13676 was 80 µg/kg and above (Table 4).
- Tumor responses were assessed based on the Lugano criteria[3]
- XmAb13676 demonstrated clinical activity in DLBCL at doses of 80 µg/kg and higher (top dose tested was 170 µg/kg) in an apparently dose-dependent manner (Table 4 and Figure 1).

Pharmacodynamics:

- Serum IL-6 levels and CRS events in the NHL safety population (Figure 2)
  - Peak serum IL-6 levels are highest on the first dose of XmAb13676 (Figure 2).
  - CRS events were more frequent and generally higher grade on the first dose (Figure 2).
  - The only two Grade 3 and 4 CRS events occurred with first doses of XmAb13676 of 80 and 125 µg/kg, respectively (Figure 2).

Table 4: Best ORR with DLBCL Patients

	Safety Population
Overall	
ORR	7/18 (38.9)
CR	5/18 (27.8)
80 µg/kg	
ORR	1/4 (25.0)
CR	0
125 µg/kg*	
ORR	4/10 (40.0)
CR	4/10 (40.0)
170 µg/kg†	
ORR	2/4 (50.0)
CR	1/4 (25.0)

CR: complete response; ORR: objective response rate.
* Includes patients with 125 µg/kg flat dosing and 80/125 µg/kg step-up dosing; † step-up dosing 45/80/125/170 µg/kg

Figure 1: Tumor Response in Patients - DLBCL Safety Population

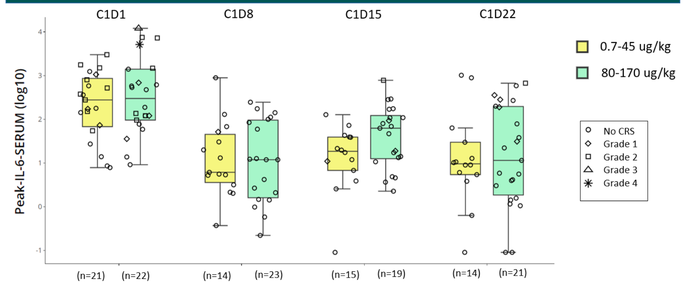
A. Best percent change from baseline in target lesions sum of products of diameters (SPD) – DLBCL safety population (80-170 ug/kg) (N=18)

CMR=complete metabolic response; PMR=partial metabolic response.
Note: One patient discontinued prior to first post-baseline disease assessment; one patient has percent change in SPD = 0 and is represented as 1% in the graph.
* step-up dosing 80/125 µg/kg; †step-up dosing 45/80/125/170 µg/kg;
One patient with negative %change in SPD had PD metabolically.

B. Time on treatment and disposition in DLBCL safety population (80-170 ug/kg)

Note: * step-up dosing 80/125 µg/kg; †step-up dosing 45/80/125/170 µg/kg (one patient discontinued after receiving 125 µg/kg)

Figure 2: Peak IL-6 Levels and CRS Grades by Dose Groups - NHL Safety Population



Conclusions

- In the ongoing dose-escalation Phase 1 study in B-cell malignancies, the CD20xCD3 bispecific antibody XmAb13676 was generally well tolerated.
  - CRS, an AE associated with this class of agents, was observed in 52.8% of patients. Other events that may have been consistent with symptoms of CRS were observed in an additional 22.6% of patients.
    - Most CRS events occurred with the first dose of XmAb13676 and were Grade 1 and 2 by the Lee criteria[4]
    - There were no Grade 3 or 4 CRS events once step-up dosing was implemented.
  - Nervous system disorders were generally mild and did not lead to discontinuation of treatment.
- XmAb13676 demonstrated clinical activity in DLBCL at doses of 80 µg/kg and higher (top dose tested was 170 µg/kg) in a dose-dependent manner.
  - In DLBCL, the objective response rate was 7/18 (38.9%), and the complete response (CR) was 5/18 (27.8%).
- Additional responses have been observed in Waldenström macroglobulinemia and Richter transformation of CLL, both CRs and both at 20 µg/kg; and in follicular lymphoma at step-up dosing to 170 µg/kg, also a CR (1/5 at 80-170 µg/kg).
- PK was dose proportional (data not shown).
- Dose escalation and schedule optimization are ongoing.

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