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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Bassil Dahiyat, Ph.D.

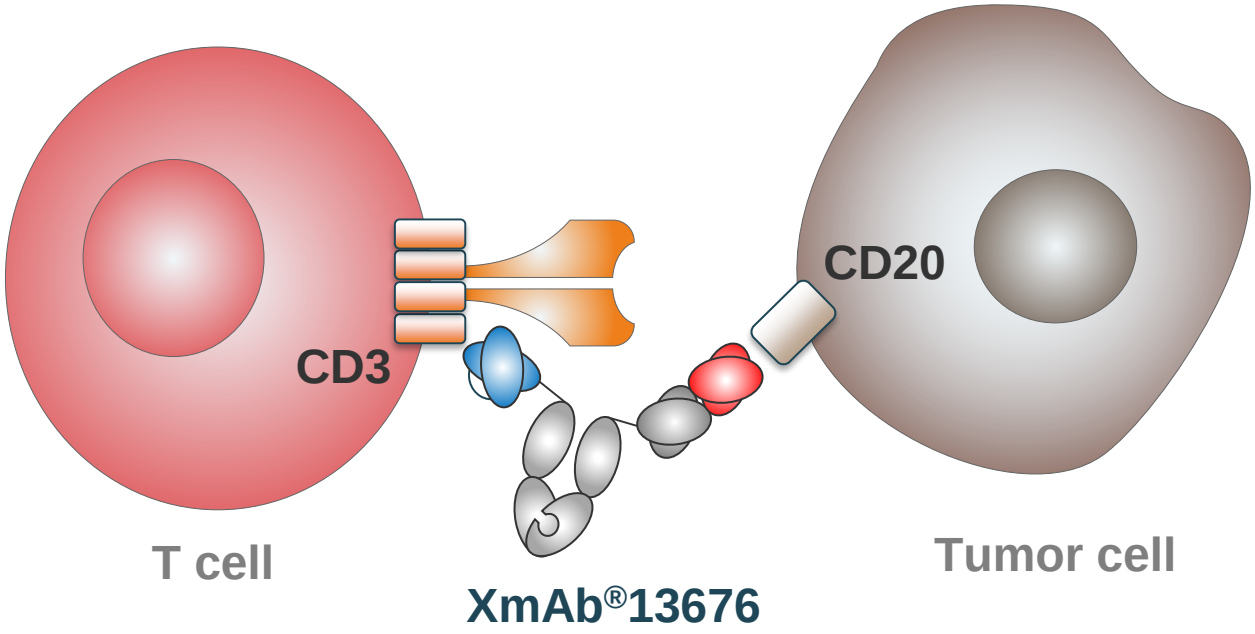
President and CEO
Xencor

Xencor's Broad Portfolio of Bispecific Antibodies and Cytokines

Program (Platform & Fc Domain)	Targets	Primary Indication	Discovery Lead	Preclinical	Phase 1	Commercial Rights
CD3 **XmAb14045** bispecific	**CD123 x CD3**	AML				xencor / NOVARTIS
CD3 **XmAb13676** bispecific	**CD20 x CD3**	B-cell cancer				xencor
CD3 **XmAb18087** bispecific	**SSTR2 x CD3**	GEP-NET GIST				xencor
TME **XmAb20717** bispecific/Xtend	**PD-1 x CTLA-4**	Oncology				xencor
CD3 **AMG 424** bispecific	**CD38 x CD3**	Myeloma				AMGEN
TME **XmAb22841** bispecific/Xtend	**CTLA-4 x LAG-3**	Oncology				xencor
TME **XmAb23104** bispecific/Xtend	**PD-1 x ICOS**	Oncology				xencor
IL **XmAb24306** bispecific/Xtend	**IL15Rβγ** (IL15/IL15Ra-Fc)	Oncology				Genentech A Member of the Roche Group
CD3 **AMG 509** 2+1 bispecific	**STEAP1 x CD3**	Prostate cancer				AMGEN
XmAb Bispecific bispecific	**Undisclosed**	Oncology				NOVARTIS

CD3 **T Cell Engager** TME **Dual Checkpoint/Co-stim** IL **Cytokine-Fc**

XmAb®13676: CD20 x CD3 Bispecific Antibody



- Potent redirection of T-cell killing toward CD20-expressing cells
- Full-length construct provides improved pharmacokinetics
- “Tunable” binding affinity allows optimization of potency and safety
- No FcγR binding prevents Fc domain-mediated CD3 crosslinking and activation

Krish Patel, M.D.

Director of the
Lymphoma Program at
Swedish Cancer Institute

Phase 1 Objectives and Eligibility

Key Objectives

- Assess safety, tolerability, and identify the MTD and/or recommended dose (RD)
- Characterize the PK profile, immunogenicity, and to preliminarily assess anti-tumor activity

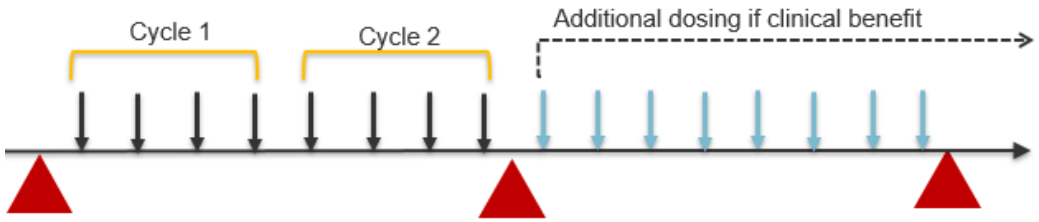
Key Inclusion Criteria

- 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
- ECOG PS of 0-2

Phase 1 Study Design:
Part A & Part B, weekly dosing, NHL & CLL groups

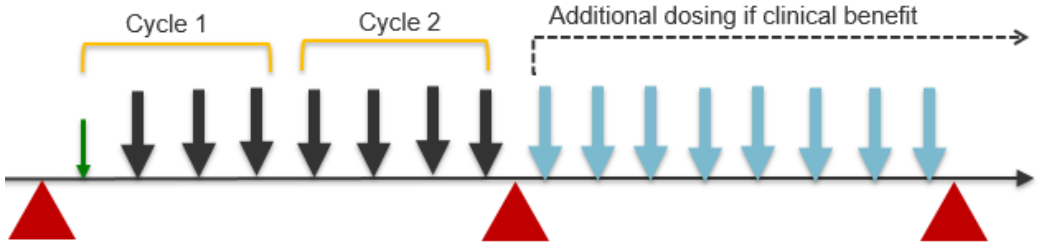
Part A

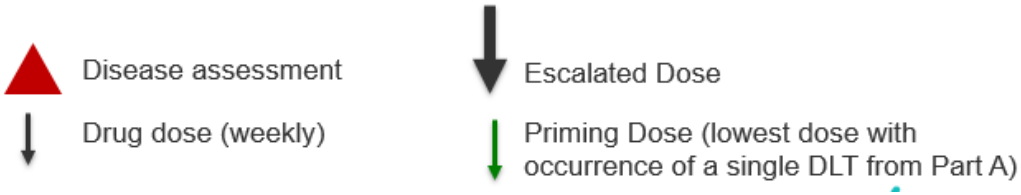
Establish dose cohorts to establish priming dose in a 28-day cycle



Part B

Establish an MTD using the priming dose on C1D1 and fixed or step-up dosing





Part A Dosing Schedule

Cohort (Part A)	Planned Weekly Dose (µg/kg)	Patients
1A	0.7	1 (+2+3)
2A	2.4	1 (+2+3)
3A	7.5	1 (+2+3)
4A*	20	3 (+3)
5A	45	3 (+3)
6A	80	3 (+3)
7A	125	3 (+3)
8A	170	3 (+3)

*CLL group is currently at Cohort 4A (20 µg/kg)

Part B Dosing Schedule - NHL

Cohort (NHL)	Dosing Schedule (µg/kg)							Patients
	C1D1 (Priming dose)	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15 +	
1B	80	125	125	125	125	125	125	3 (+3)
2B*	45	80	125	170	170	170	170	3 (+3)
3B	45	80	125	170	250	250	250	3 (+3)
4B	45	80	125	170	250	360	360	3 (+3)
5B	45	80	125	170	250	360	500	3 (+3)
Expansion	MTD or RD cohort							<20

- Priming dose determined to be 45 µg/kg for step-up dosing;
- Cohort 2B completed – dose escalation continues

XmAb13676 Phase 1 Initial Data – Patient Disposition

- 53 patients treated with XmAb13676 included in safety analysis
  - NHL: n=45
    - DLBCL patients receiving highest doses of 80-170 µg/kg included in the anti-tumor activity analysis (n=18)
  - CLL: n=8

	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)

XmAb13676 Was Generally Well Tolerated

- Most events were Grade 1 or 2
- 52.8% of patients experienced at least 1 CRS event
  - Of these CRS events, 89% were Grade 1 or 2
  - 5.7% of patients experienced Grade 3 or 4 CRS events
  - Most common symptoms were pyrexia, hypotension, chills, tachycardia and hypertension
- Nervous system disorders occurred in 49.1% of patients
  - Most common were dizziness, headache, paresthesia and lethargy
  - These events were Grade 1 or 2 in severity, except for one Grade 3 headache
  - 1 patient experienced Grade 2 short-term encephalopathy during a CRS event

Summary of Treatment-Emergent Adverse Events – Safety Evaluable

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 (Blood. 2014;124(2):188-95)

Patient Baseline Characteristics - DLBCL

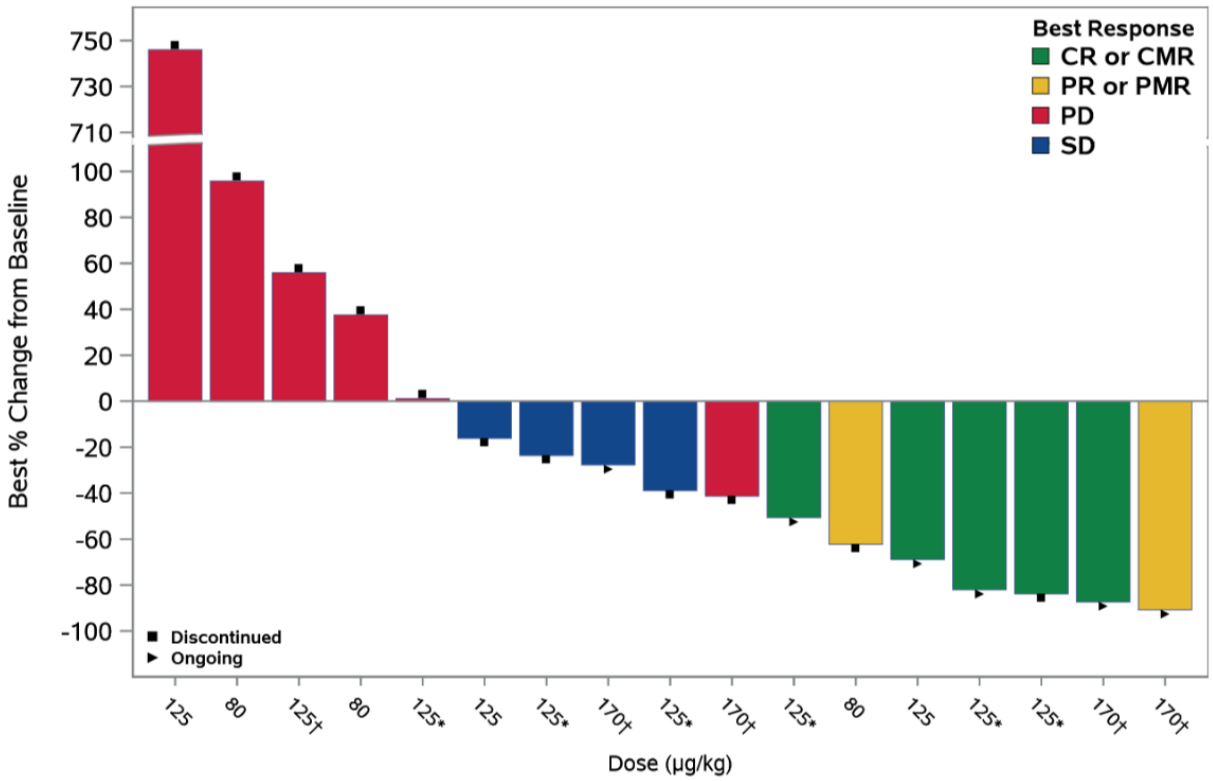
18 Patients Evaluable for Anti-Tumor Activity (Received Highest Doses of 80-170 µg/kg)

Characteristics	Overall (n=18)
Median age, years (range)	63.5 (48, 82)
Male, n (%)	9 (50.0)
ECOG performance status, n (%)	
0	6 (33.33)
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.

Encouraging Clinical Activity and Dose Dependent Activity in Initial Dosing Cohorts - DLBCL

DLBCL population with doses at 80 µg/kg or higher (N=18)



CMR: complete metabolic response; PMR: partial metabolic response.
CR: complete response; ORR: objective response rate.

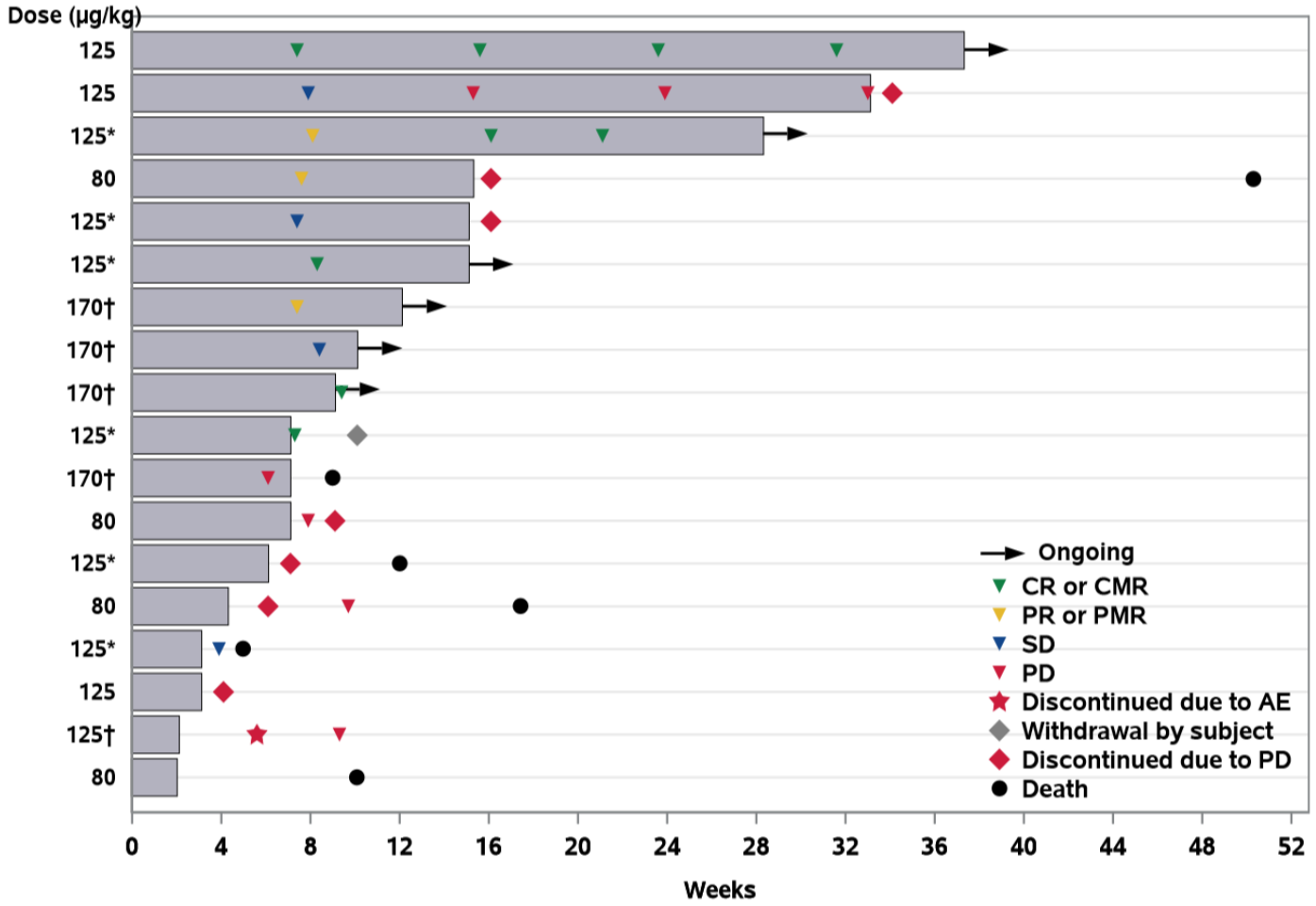
*Includes patients with 125 µg/kg flat dosing and 80/125 µg/kg step-up dosing
† step-up dosing 45/80/125/170 µg/kg.

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)

Time on Treatment - DLBCL

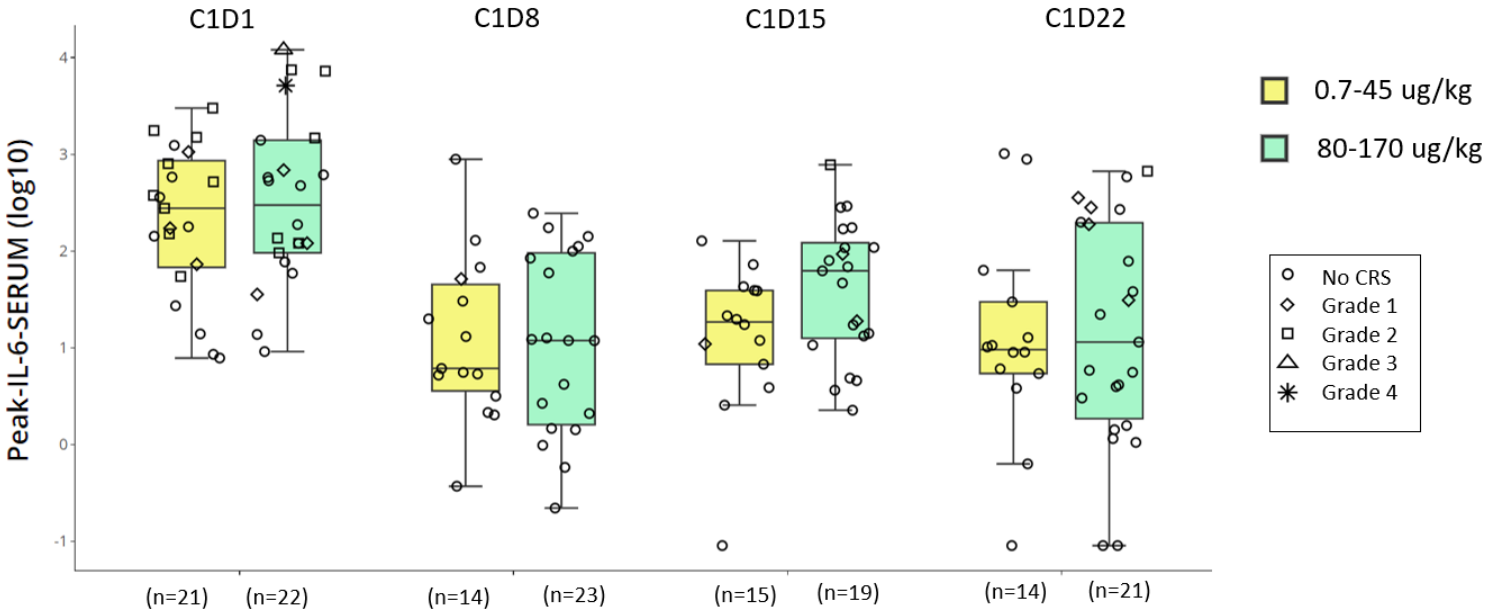
Evaluable for Anti-Tumor Activity (Received Highest Doses of 80-170 µg/kg)



CMR=complete metabolic response; PMR=partial metabolic response.

Pharmacodynamic Response

- Peak serum IL6 levels correlate to CRS symptoms
  - IL6 levels are highest on C1D1 dose
  - CRS events are more frequent and generally a higher grade at C1D1 dose



CRS Grades by NHL Dose Groups in Treatment Cycle 1

First dose (Cycle 1, Day 1 [C1D1])				
	No CRS	Grade 1	Grade 2	≥ Grade 3
> 45 mcg/kg	50.0%	13.6%	27.2%	9.1%
≤ 45 mcg/kg	42.9%	14.3%	42.9%	0%
Doses on Days 8, 15 or 22 (C1D8, C1D15 or C1D22)				
	No CRS	Grade 1	Grade 2	≥ Grade 3
> 45 mcg/kg	87.3%	9.5%	3.2%	0%
≤ 45 mcg/kg	95.3%	4.7%	0%	0%

Conclusions

- XmAb13676 was generally well tolerated
  - CRS, an AE associated with this class of agents, was observed in 52.8% of patients
  - Most CRS events occurred with the first dose of XmAb13676 and were Grade 1 and 2 by the Lee criteria
  - 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 in a dose-dependent manner
- 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 patients treated at ≥ 80µg/kg)
- PK was dose proportional
- Dose escalation and schedule optimization are ongoing

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Question & Answer

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