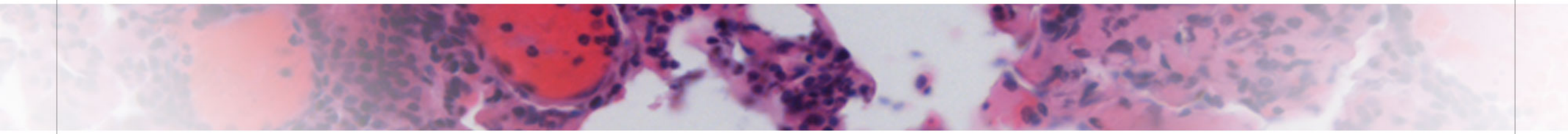
American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Complete Responses in Relapsed/ Refractory Acute Myeloid Leukemia (AML) Patients on a Weekly Dosing Schedule of Vibecotamab (XmAb®14045), a CD123 x CD3 T Cell-Engaging Bispecific Antibody; Results of a Phase 1 Study

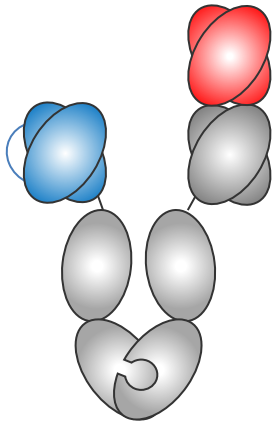
Farhad Ravandi[1], Asad Bashey[2], Wendy Stock[3], James Foran[4], Raya Mawad[5], Daniel Egan[5], William Blum[6], Raphael Clynes[7], Raman Garcha[7], Ying Ding[7], Alessandro Pastore[8], Chelsea Johnson[7], Shuo Zheng[7], Musa Yilmaz[1], and Alice S. Mims[9]

[1]U of TX-MD Anderson CC, Houston, TX; [2]Acute Leukemia and BMT Program at Northside Hospital, Atlanta, GA; [3]University of Chicago, Chicago, IL; [4]Mayo Clinic, Jacksonville, FL; [5]Swedish Cancer Institute, Seattle, WA; [6]Winship Cancer Institute, Emory University, Atlanta, GA; [7]Xencor, Inc., Monrovia, CA; [8]Novartis Institutes for Biomedical Research, Cambridge, MA; and [9]Ohio State University, Columbus, OH.

XmAb®14045 (SQZ622): CD123 x CD3 Bispecific Antibody

CD123 (IL-3 receptor α subunit) found on early hematopoietic precursor cells and basophils

CD3-binding single chain F_v domain



CD123-binding F_{ab} domain

Full-length immunoglobulin molecule designed to be dosed intermittently

Stimulates targeted T cell-mediated killing of CD123-expressing cells, regardless of T cell antigen specificity

Ablation of $F_c\gamma$ receptor binding removes potential for receptor-mediated crosslinking and non-specific activation of T cells

Frequently expressed on hematologic malignancies, including:

- Acute myelogenous leukemia (96-98% cases)
- Myelodysplastic syndrome (>50%)
- B-cell acute lymphoblastic leukemia (82-100%)

Potential target for novel therapeutic strategies

XmAb14045 Phase 1 Design

Objectives

Primary

- First infusion MTD and safety
- Second and subsequent infusion MTD and safety

Secondary

- PK, PD, immunogenicity
- Preliminary anti-tumor activity

Exploratory

- Lymphocyte subsets and T-cell activation
- Cytokine/immunologic profiles
- Effect on immune checkpoint expression
- Effect on stem cell numbers

Eligibility

Inclusion criteria

Eligible diseases:

- AML (excluding APL)
- B-cell ALL

ECOG PS 0-2

Relapsed or refractory

Prior allogeneic transplant allowed

Exclusion criteria

- Antineoplastic treatment within 2 weeks
- Known uncontrolled CNS involvement by tumor
- AST/ALT > 3.0 x ULN, Bili > 1.5, Cr > 2.0 x ULN or Clcr > 40; Absolute blast count ≥ 10K or leukostasis
- Prior therapy with CD123-directed therapies

XmAb14045 Phase 1 Design

114 subjects dosed

(as of 28OCT2020)

Safety analysis
included all subjects that received at least 1 dose of XmA*b14045*

Efficacy analysis included all patients who:

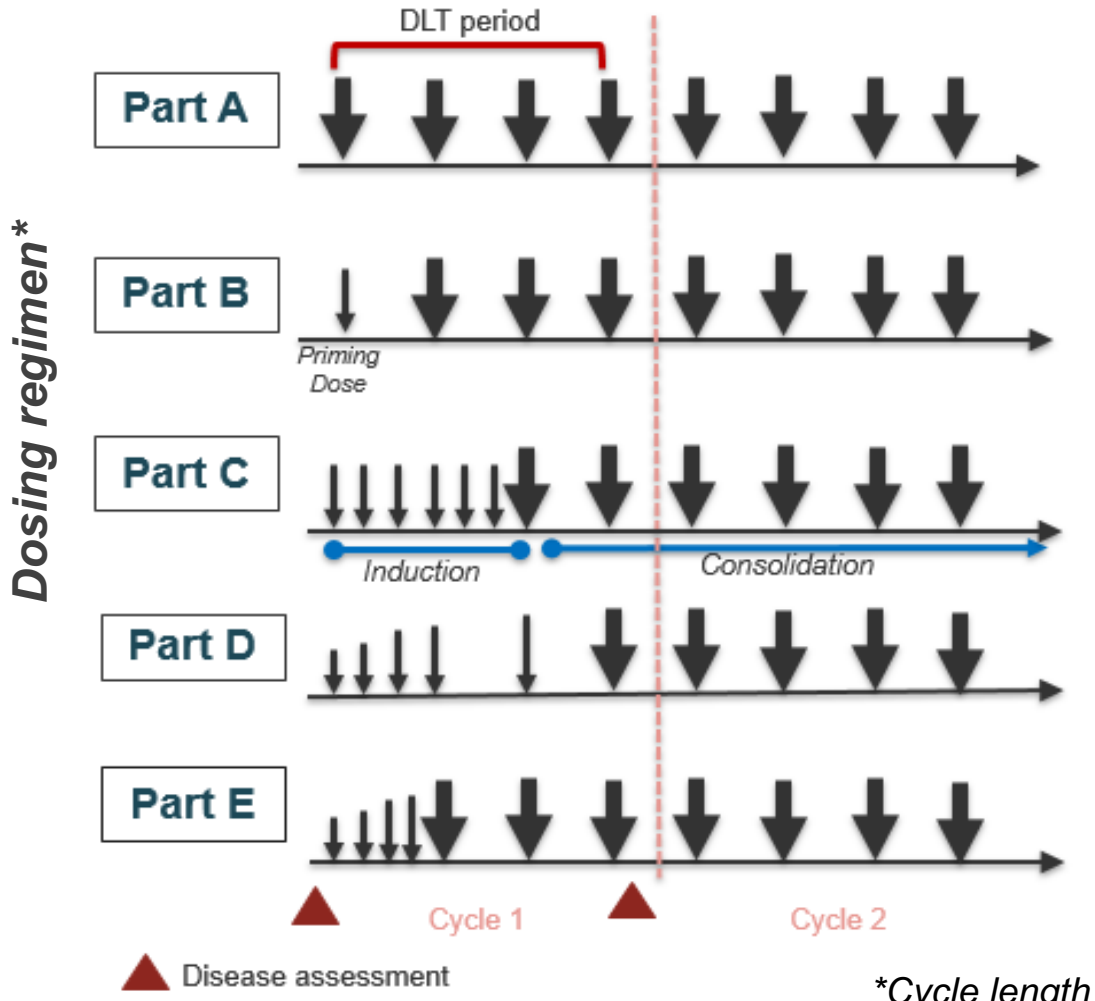
have completed at least the first cycle

(4 doses for Parts A and B; 8 doses for Part C; 6 doses for Part D; and 7 doses for Part E)

AND

had at least one post-treatment disease assessment

(occurs at the end of odd-numbered cycles)



**Cycle length = 28 days*
Doses infused over 2 hours
Intrapatient dose escalation allowed

Demographics (Safety Population)

Characteristic		All patients (n=112) (%)
Age	Median [min, max]	64 years [18, 85]
Gender	Female	53 (47)
Diagnosis	AML*	112 (100)
Time since initial diagnosis	Median [min, max]	48 weeks [3, 896]
Number of prior therapies	Median [min, max]	3 [0, 8]
History of hematopoetic stem cell transplantation		34 (30)
Refractory to last therapy (per investigator)		96 (86)
ELN risk category	Favorable	4 (4)
	Intermediate	33 (30)
	Adverse	69 (62)
	Unknown	6 (5)
Secondary leukemia		15 (13)

*One B-ALL and one CML in blast phase patient were enrolled/treated, but not included in this analysis

Data as of 28 OCT 2020

Safety Data: Related TEAEs Occurring in ≥10% of Subjects
AML Safety Population (N=112)

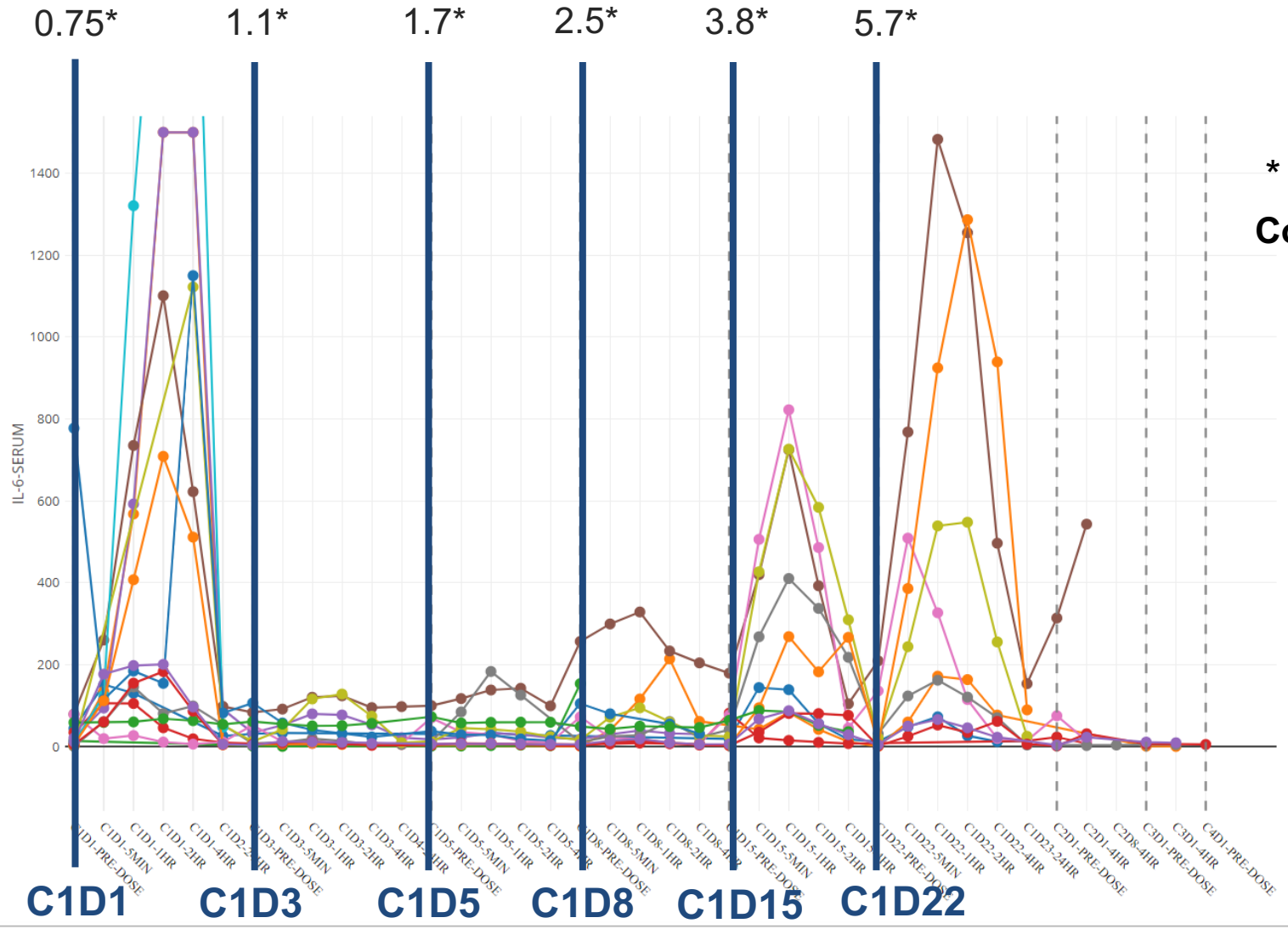
Event	Any grade (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Cytokine release syndrome*	68 (**60.7**)	8 (**7.1**)	1 (**0.9**)	1 (**0.9**)
Chills	44 (39.3)	1 (0.9)		
Pyrexia	32 (28.6)			
ALT Increased	23 (20.5)	5 (4.5)	2 (1.8)	
Sinus tachycardia	22 (19.6)			
Hypotension	21 (18.8)	3 (2.7)		
Fatigue	20 (17.9)	1 (0.9)		
AST Increased	18 (16.1)	5 (4.5)	3 (2.7)	
Nausea	18 (16.1)			
Vomiting	18 (16.1)			
Anaemia	16 (14.3)	14 (12.5)		
Headache	16 (**14.3**)	3 (**2.7**)		
GGT Increased	15 (13.4)	4 (3.6)	2 (1.8)	
Hypertension	13 (11.6)	5 (4.5)		
Lymphopenia	13 (11.6)	1 (0.9)	10 (8.9)	
Tachycardia	13 (11.6)			

Data as of 28 OCT 2020, *CRS Revised Grading System (Lee DW et al. Blood 2014;124:188)

- Primary toxicity continues to be cytokine release syndrome (CRS)
  - observed in 60.7% of subjects
- No evidence of drug-related myelosuppression
- ≥ Grade 3 transaminase elevation X 15 events
  - All but 2 events resolved within 7 days
  - Most likely to be a component of CRS
- Neurologic events: most common was headache seen in 14.3% of subjects

Safety Data: Priming Dose, Dosing Visit and IL-6 Levels

- Using IL-6 as a predictive biomarker of CRS (IL-6 > 1000 pg/ml)
- IL-6 peaks at priming dose of 0.75 µg/kg and weekly step-up dosing
- 1st week QOD dosing prevents CRS even with step-up dosing

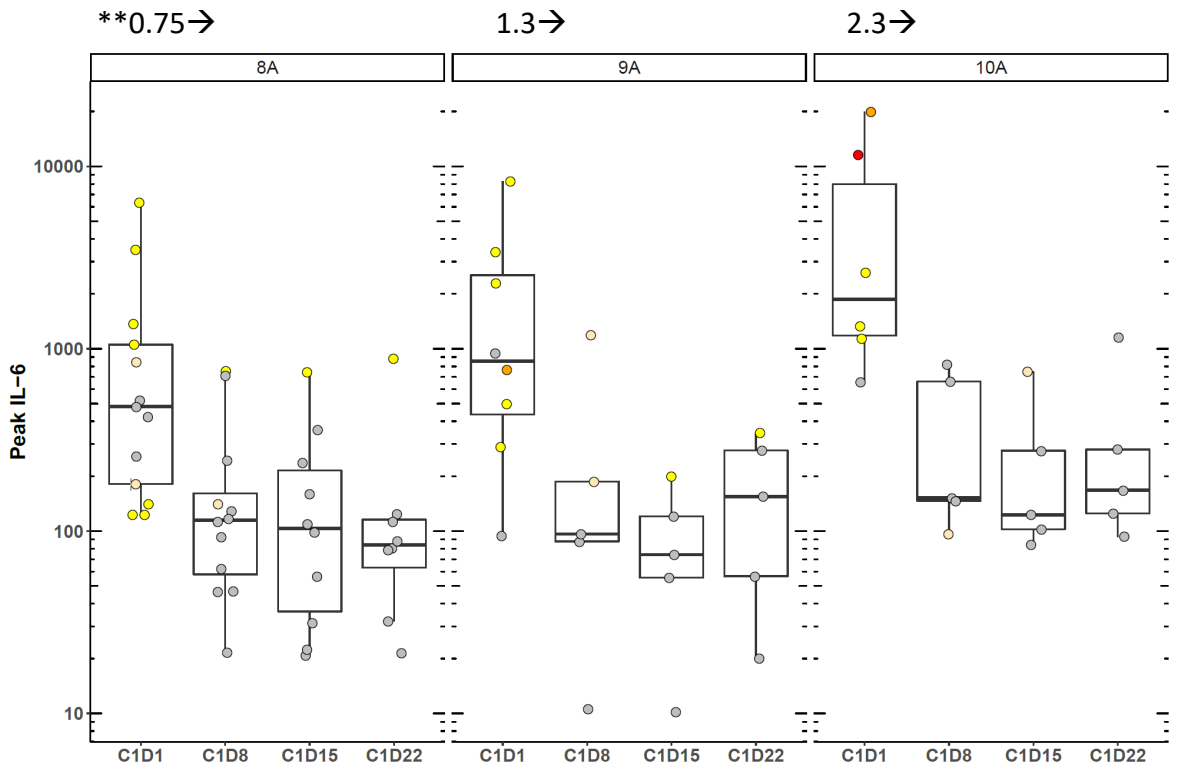


* µg/kg

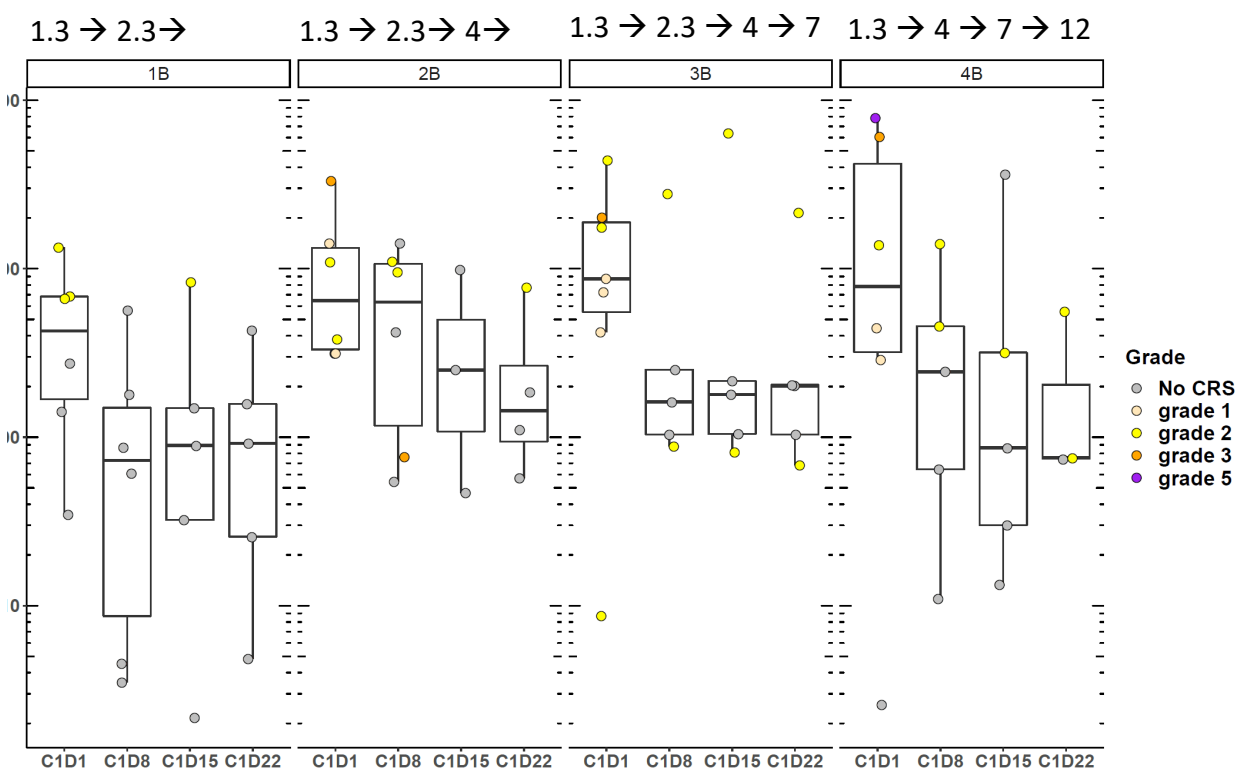
Cohort 1D

Safety Data: Weekly Dosing and IL-6 Levels

- Across all cohorts, 4.5% of stable weekly dose had IL6>1000 pg/ml *



- Across all cohorts, 15 % of weekly step-up events had IL-6>1000 pg/ml

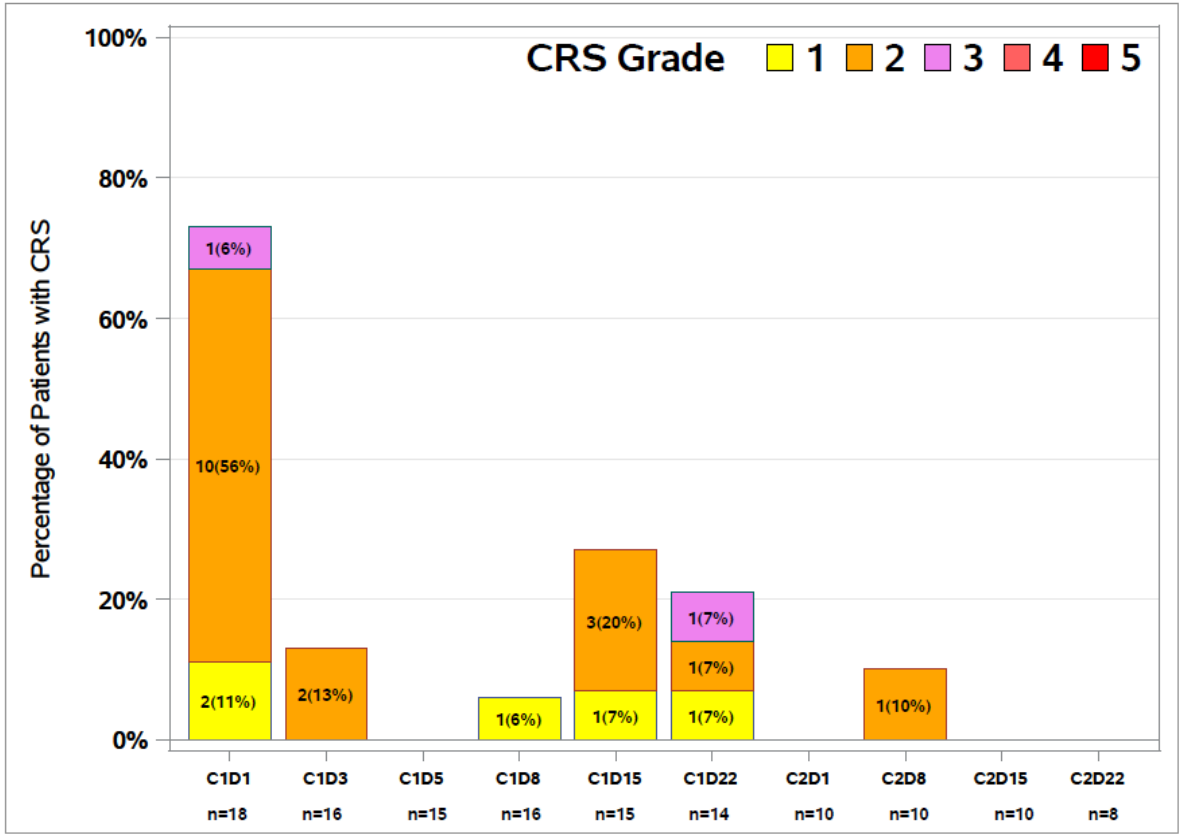


*up to 2.3ug/kg and before C2D1
**Doses in µg/kg

Safety Data: Dosing Visit and CRS

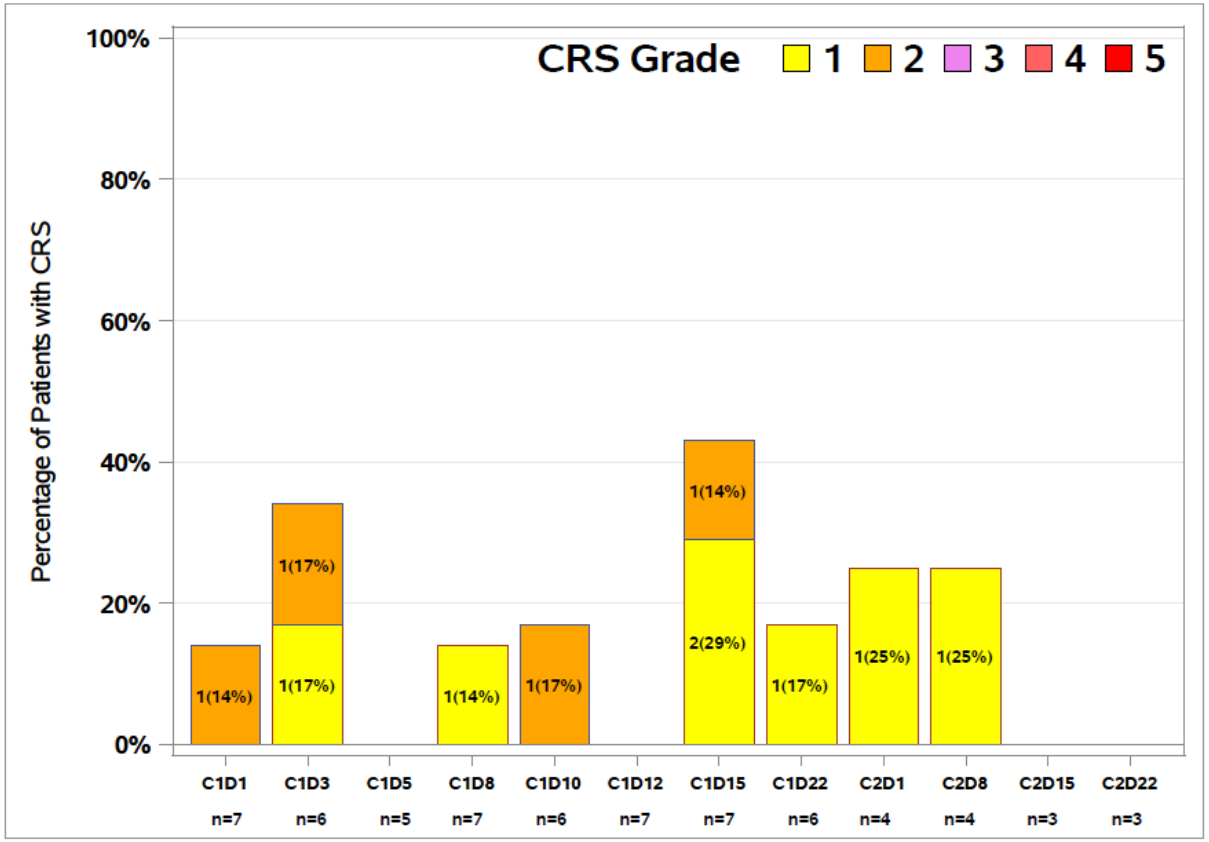
Priming Dose = 0.75 µg/kg

Figure 4.1a: Distribution of CRS Grade by Dosing visit
AML: Safety Population Cohort 1D



Priming Dose = 0.43 µg/kg

Figure 4.1a: Distribution of CRS Grade by Dosing visit
AML: Safety Population Cohort 9C



Data as of 28 OCT 2020

Increased frequency and grade of CRS in higher priming dose and in subsequent weekly step-up dosing

Safety Data: CRS Strategy for Future Cohorts and Trials

Challenge:

- Addressing the known need for priming doses in CRS complicated by the short $t^{1/2}$ of XmAb®14045; deep antigen sink

Mitigations:

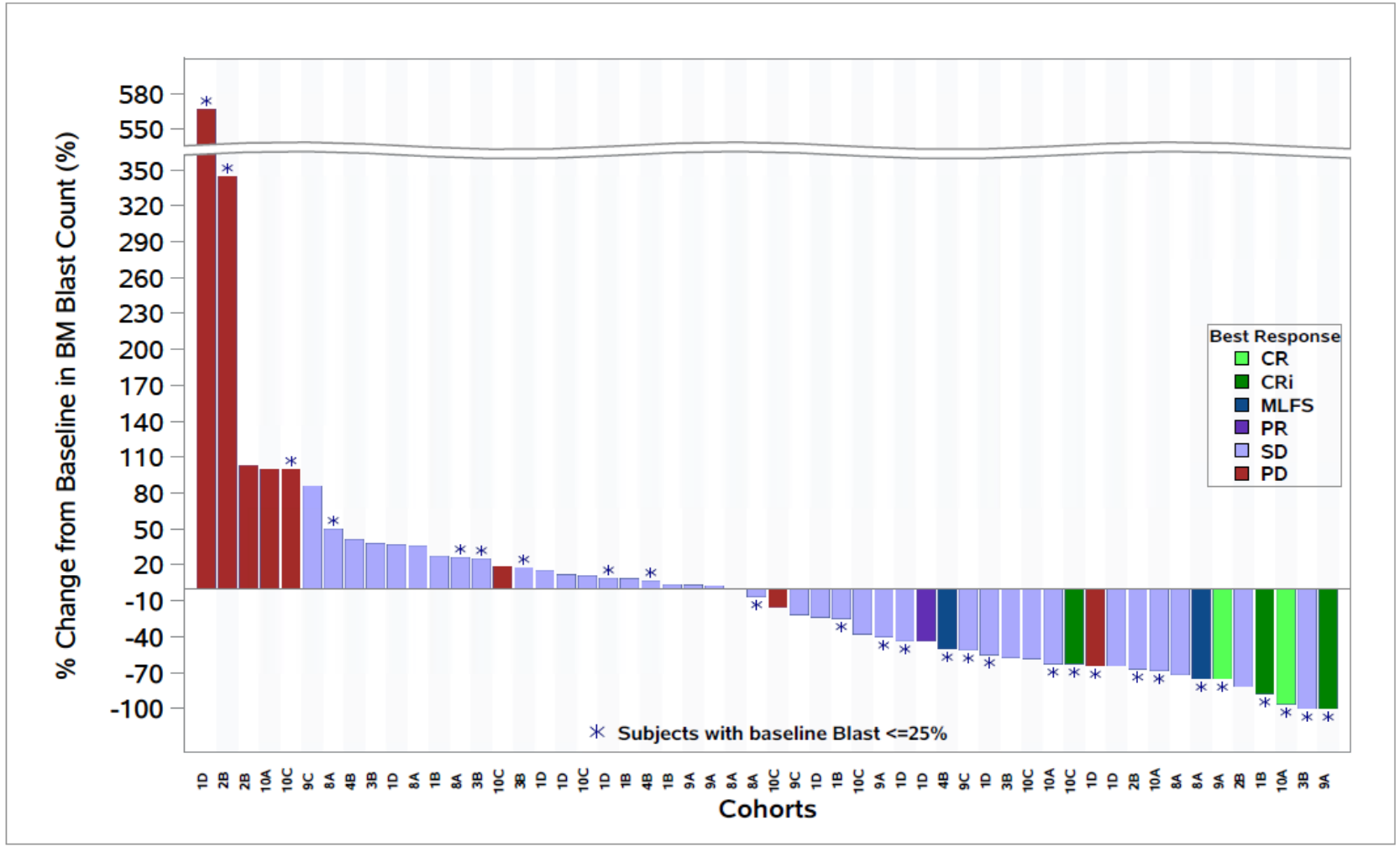
- Continued evaluation of dose and scheme
- Lowered priming dose and stop escalation prior to weekly dosing
- More frequent dosing the first week to enable higher cumulative exposure in week 1

Efficacy Data

- Objective response rate (CR + CRi+MLFS+PR) dosed at ≥0.75 µg/kg = 14.8% (8/54 patients)
- ORR in blast count ≤ 25% population = 25.9% (7/27 patients)
- Stable Disease in an additional 38 patients (70.4%)
- Reduction of marrow blasts in 52% of patients

Data as of 28 OCT 2020

Percentage change in bone marrow blasts from pretreatment baseline*

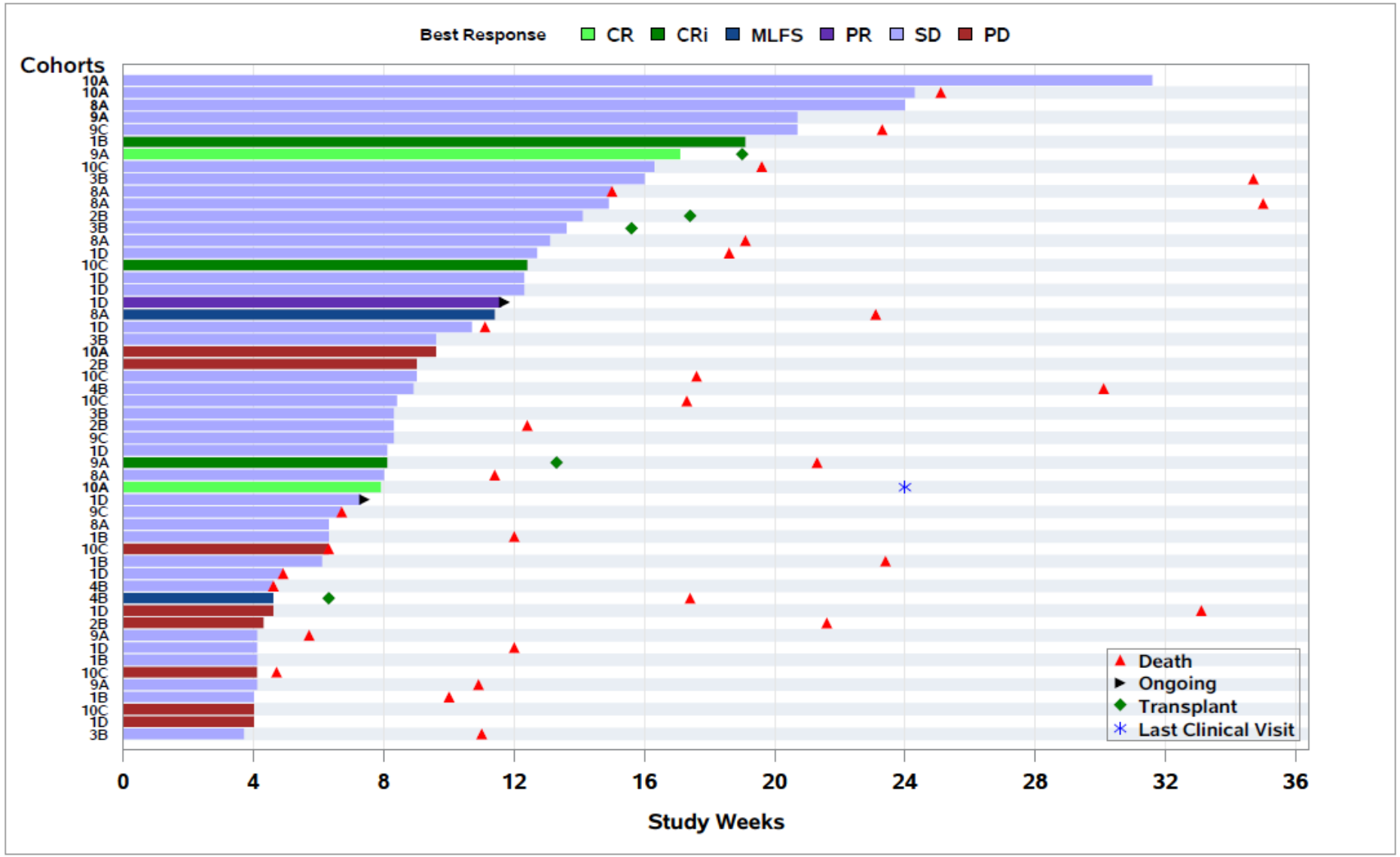


AML Evaluable Population 8A-1D Cohort (N=54)

Regarding PR response; Investigator assessment per protocol is PR, but blasts remain above the ELN response criteria of 25%

*** = subjects with ≤ 25% blasts**

Efficacy Data: Time to Treatment Discontinuation*



Data as of 28 OCT 2020

AML Evaluable Population 8A-1D Cohort (N=54)

*Regarding the PR response; Investigator assessment per protocol is PR, but blasts remain above the ELN response criteria of 25%

XmAb14045/SQZ622 Data by Cohort

Cohort	8A	9A	10A	1B	2B	3B	4B	9C	10C	1D	Proposed 1E
C1 *(Wk 1)* Cumulative Dose (µg/kg)	*3 (0.75)*	5.2 *(1.3)*	9.2 *(2.3)*	8.2 *(1.3)*	11.6	14.6	24.3 *(1.3)*	5.2 *(1.29)*	9.2 *(2.31)*	15.6 *(3.55)*	**11.48 (3.98)**
Total Efficacy Evaluable	7	5	4	5	4	5	3	3	7	11	
CR+CRi+MLFS+PR	1 (MLFS)	2 (CR, CRi)	1 (CR)	1 (CRi)	0	0	1 (MLFS)	0	1 (CRi)	2 (PR**, CR***)	
Efficacy Evaluable (≤25% blast*)	4	3	3	2	2	3	2	1	2	5	
Baseline % Blast for Responders	4%	7.5%, 10%	25%	16%			5%		8%	60%	

***Baseline aspirate or core %blast ≤25%**

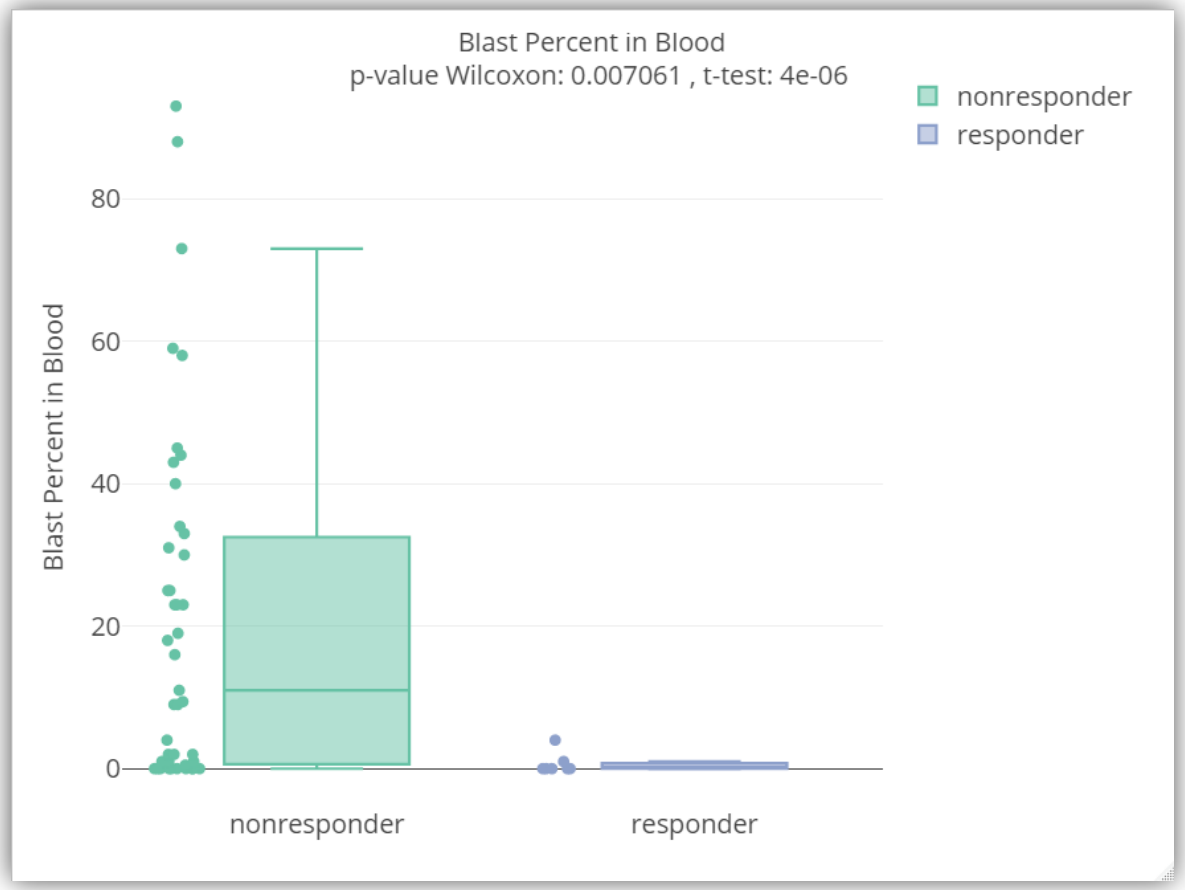
**Investigator assessment per protocol is PR, but blasts remain above the ELN response criteria of 25%

***Patient in 1D achieved CR, however, missed 2 doses so was not efficacy evaluable

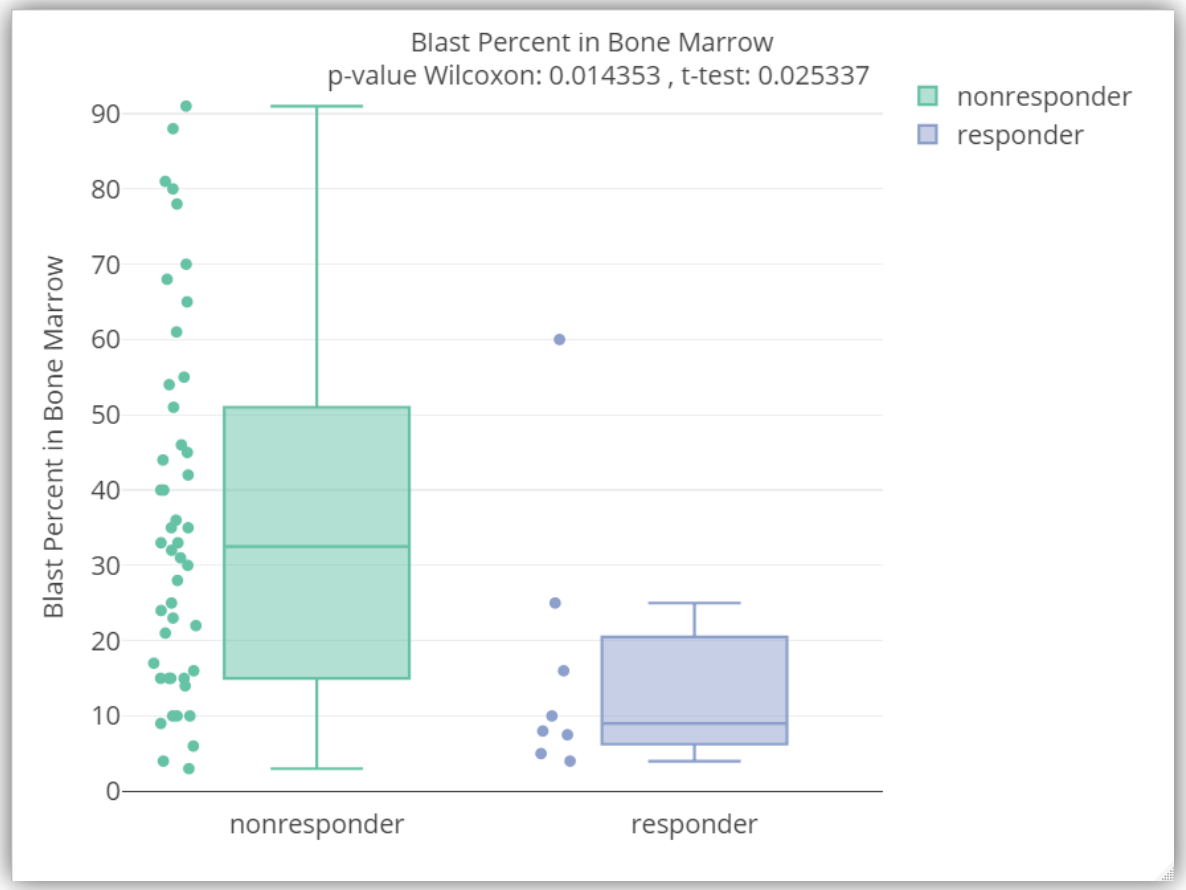
Data as of 28 OCT 2020

Responders Associated with Low absolute Blast Counts

Blood

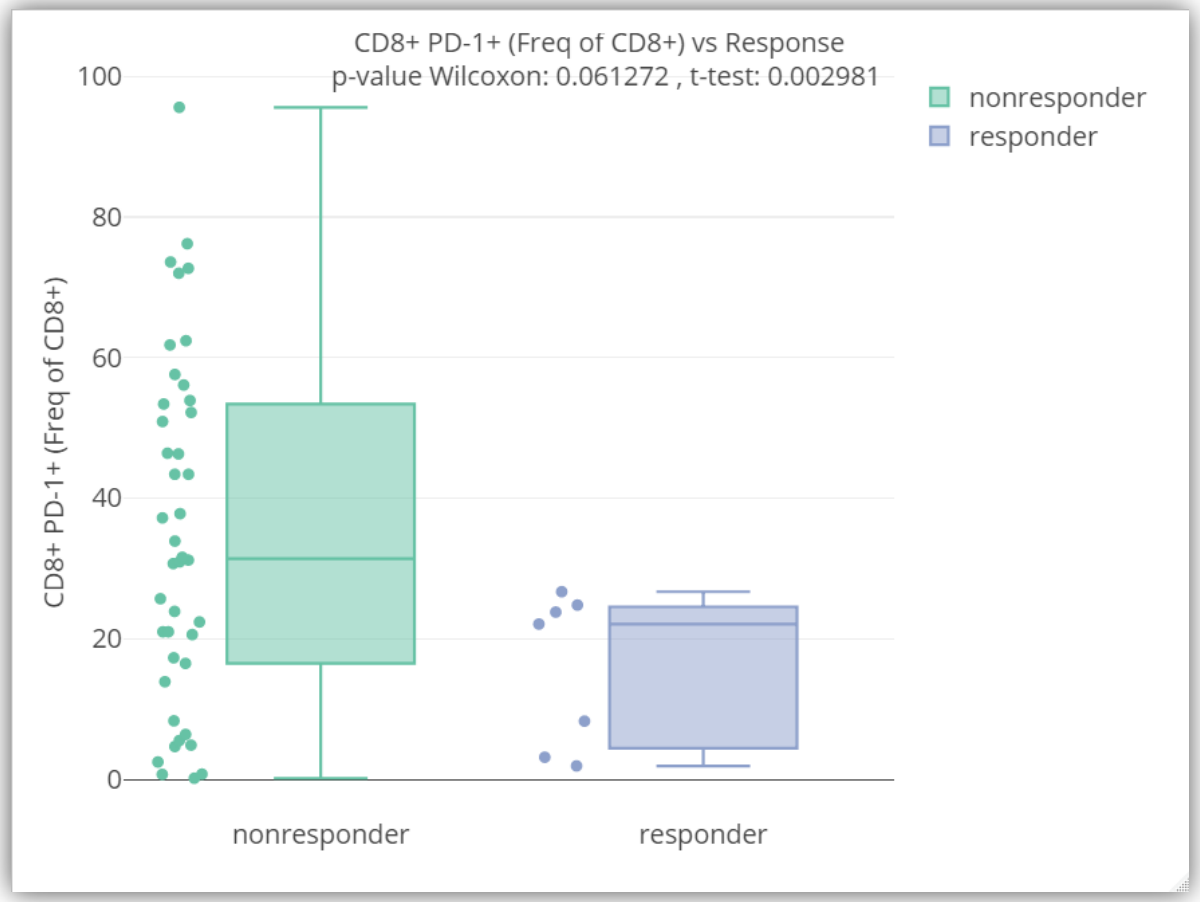


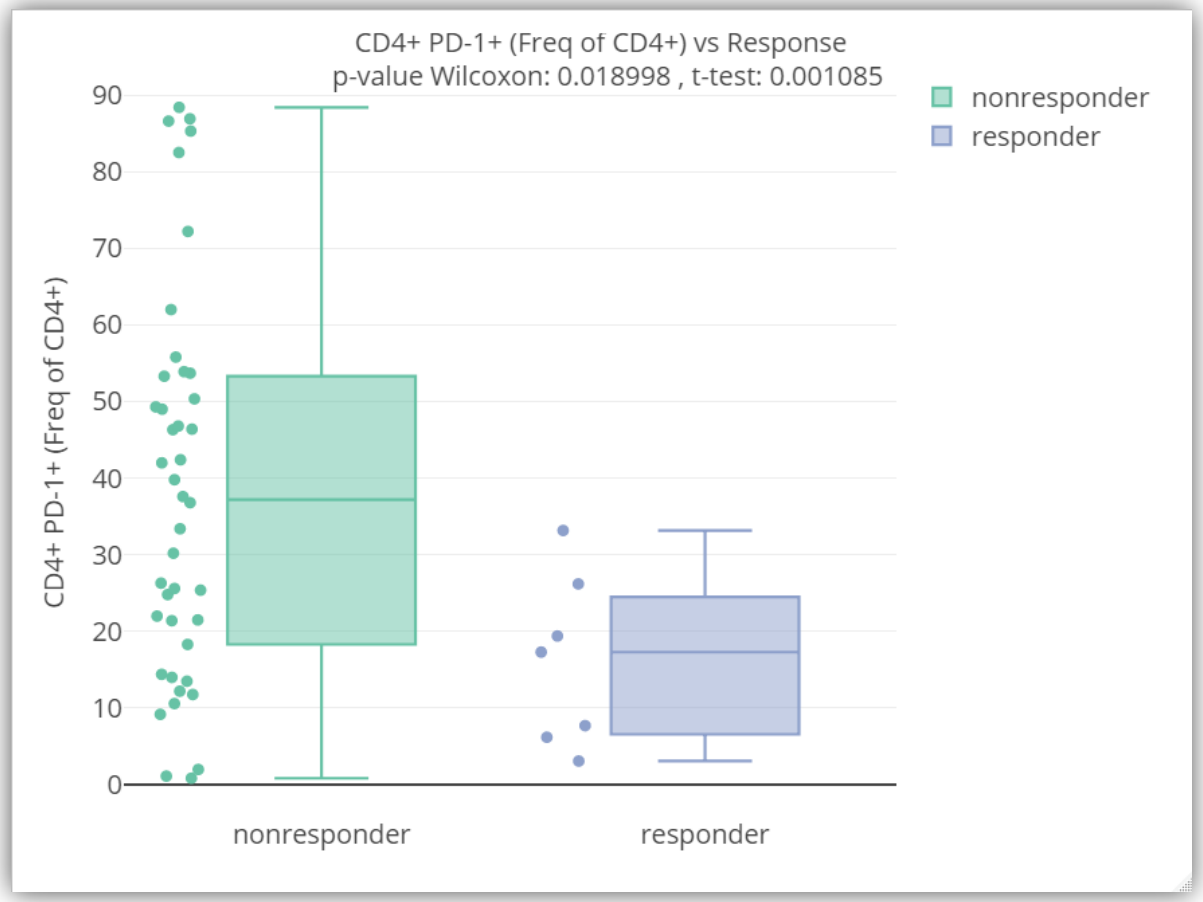
Bone Marrow



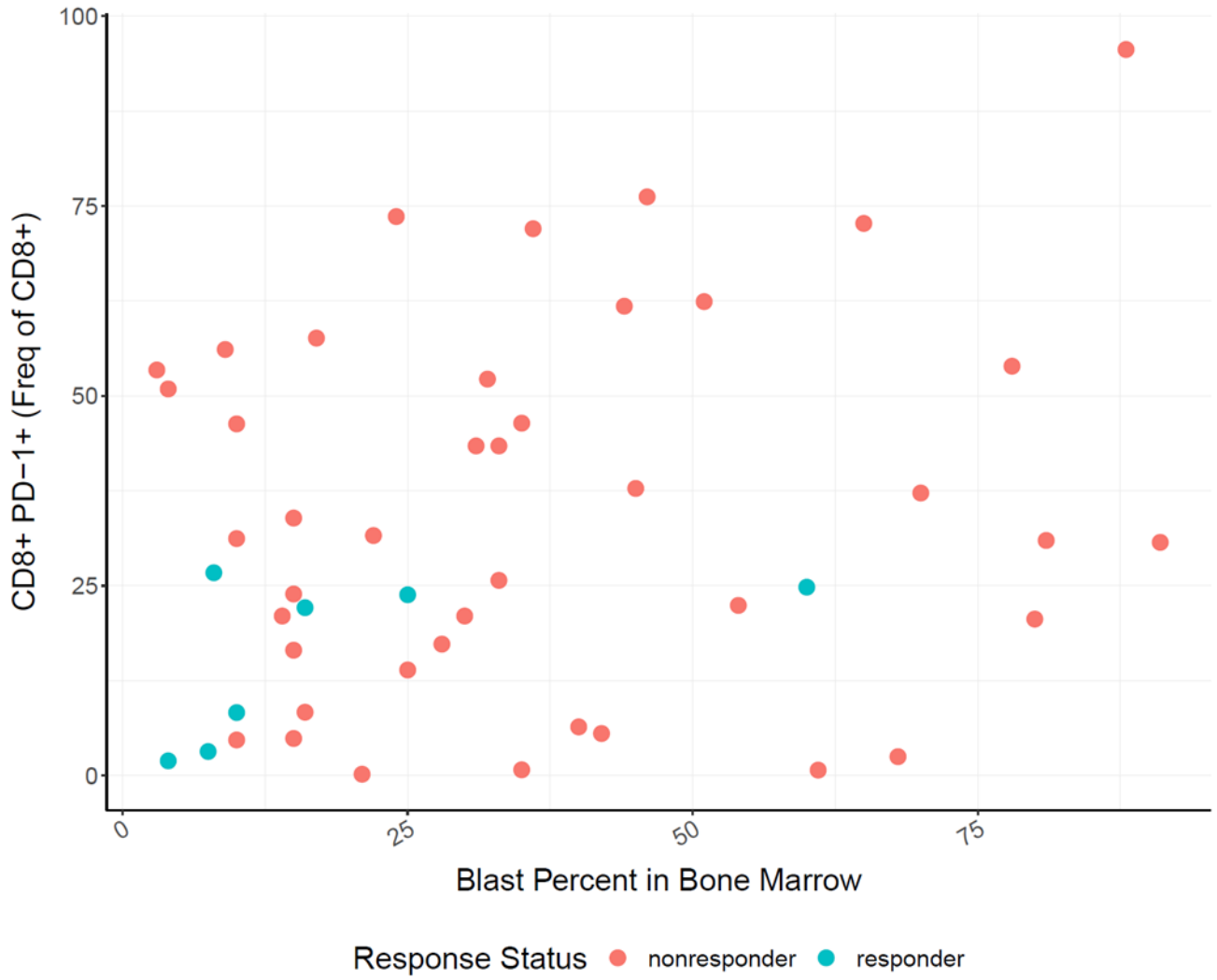
Baseline leukemic burden of bone marrow is most associated with nonresponse

Responders Associated with Low PD-1 Expression on CD8 and CD4 T Cells





AML Blast Count % in Marrow vs % PD1+ of CD8+ Cells in Blood*



- Suggests:
  - low blast and PD-1 appear to be independent predictors of response
  - 2 preliminary cut offs for selecting patients who could benefit
  - needs further study

*Efficacy evaluable population

Conclusions

- XmAb14045 has clinical activity in relapsed AML

  - ORR AML with ≤ 25% blast count = 25.9%
- Activity in low blast AML suggests potential opportunity in MDS and MRD

  - 7/8 responders had blast count ≤ 25%
- CRS is the primary toxicity of XmAb14045
- CRS mitigation strategy is effective in limiting severity

  - Lowered priming dose, intermittent dosing QOD & no weekly step ups

  - Enables bolus dosing

Acknowledgements

Participating patients and their families

MD Anderson, Houston
Farhad Ravandi MD
Musa Yilmaz MD

Ohio State University, Columbus
Alice S. Mims MD

Acute Leukemia and BMT Program at Northside Hospital, Atlanta
Asad Bashey MD PhD

Mayo Clinic Florida, Jacksonville
James M. Foran MD

University of Chicago
Wendy Stock MD

Swedish Cancer Institute, Seattle
Raya Mawad MD
Daniel Egan MD

Emory University, Atlanta
William Blum MD

Novartis, Cambridge, MA
Alessandro Pastore MD

Xencor, Inc., San Diego and Monrovia, CA
Allen Yang MD
Raman Garcha MD
Raphael Clynes MD
Chelsea Johnson BSN
Ying Ding PhD
Andrea Dawson
Shuo Zheng PhD
Salil Parab MS MBA
Selam Berhe
Kristy Colella