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

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Background

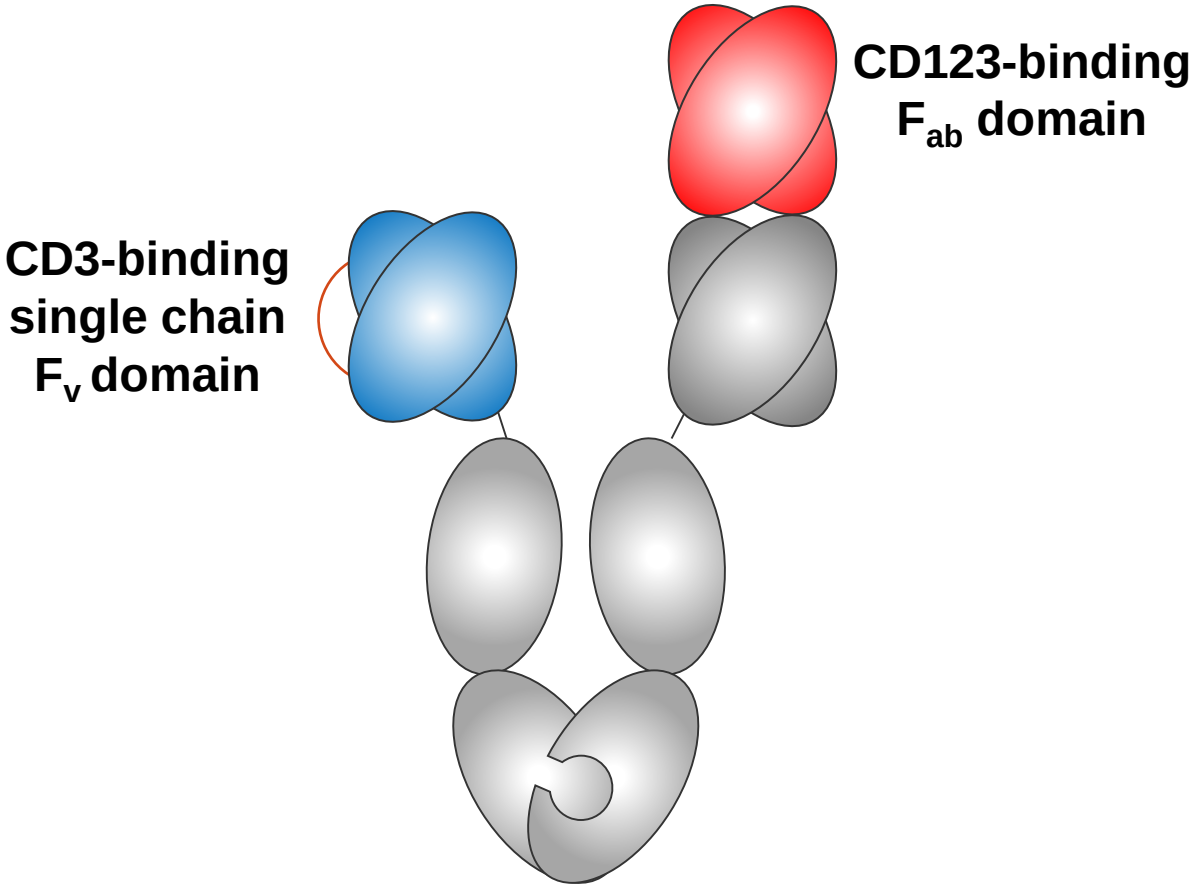
CD123 (IL-3 receptor α subunit) found on early hematopoietic precursor cells and basophils

Frequently expressed on hematologic malignancies, including:

- Acute myelogenous leukemia – 96-98% of cases
- Myelodysplastic syndrome – >50%
- B-cell acute lymphoblastic leukemia – 82-100%
- Blastic plasmacytoid dendritic cell neoplasm – 83-100%
- Chronic myelogenous leukemia – 75-100%
- Hairy cell leukemia – 95-100%

Potential target for novel therapeutic strategies

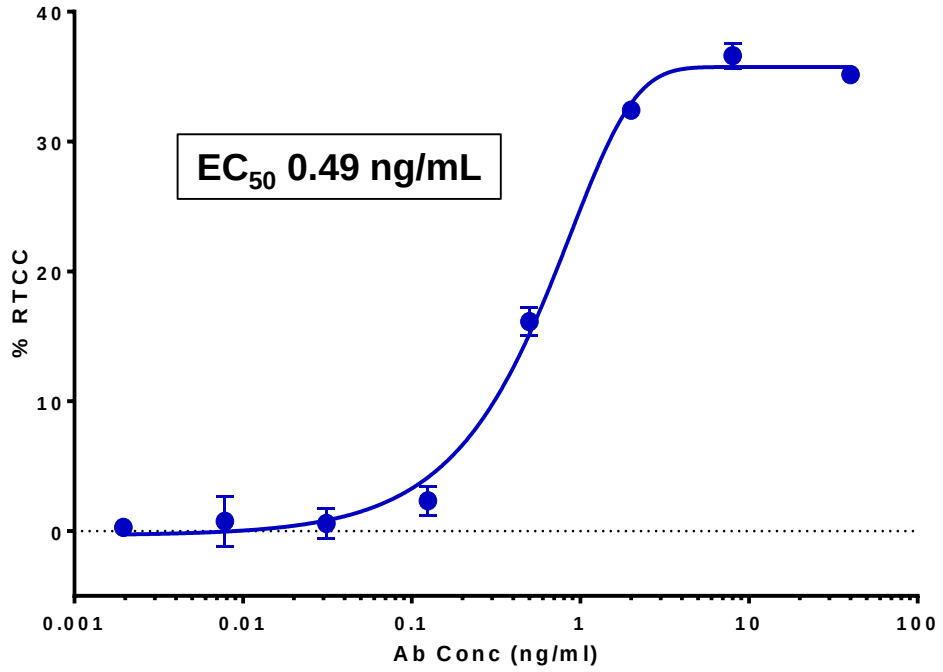
XmAb®14045 (SQZ622): CD123 x CD3 Bispecific Antibody



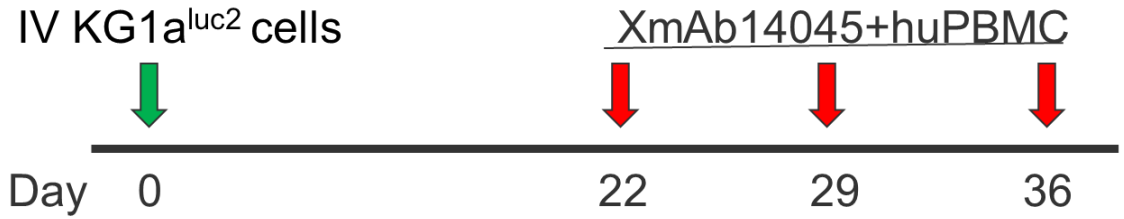
- Full-length immunoglobulin molecule designed to be dosed intermittently, in contrast to smaller constructs that are referred to as “DART” or “BiTE” bispecific antibodies that require a continuous infusion
- Stimulates targeted T cell-mediated killing of CD123-expressing cells, regardless of T cell antigen specificity
- Ablation of $F_c\gamma$ receptor binding removes potential for receptor-mediated crosslinking and activation of T cells

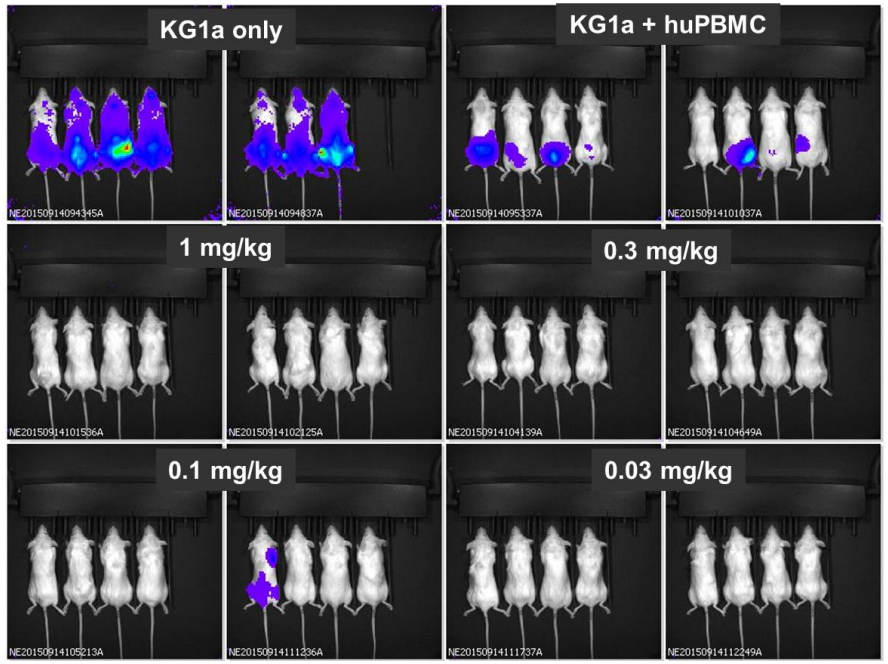
XmAb14045: CD123 x CD3: Potent in Vitro Killing

Redirected human T-cell cytotoxicity of human PBMC (effector cells) against KG-1a AML cells at increasing XmAb14045 concentrations



Immunodeficient NSG mice →





XmAb14045 Phase 1 Design: Objectives and Eligibility

Objectives

Primary

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

Secondary

- Pharmacokinetics, pharmacodynamics, immunogenicity
- Preliminary anti-tumor activity

Exploratory

- Lymphocyte subsets and T-cell activation
- Cytokine/immunologic profiles (IL-2, IL-6, IL-10, gamma-IFN, CRP, etc.)
- Effect on immune checkpoint expression
- Effect on stem cell numbers

Inclusion criteria

Eligible diseases

- AML (excluding PML)
- B-cell ALL
- Blastic plasmacytoid dendritic neoplasm
- Blast crisis CML

ECOG PS 0-2

Relapsed or refractory

Prior allogeneic transplant allowed

Exclusion criteria

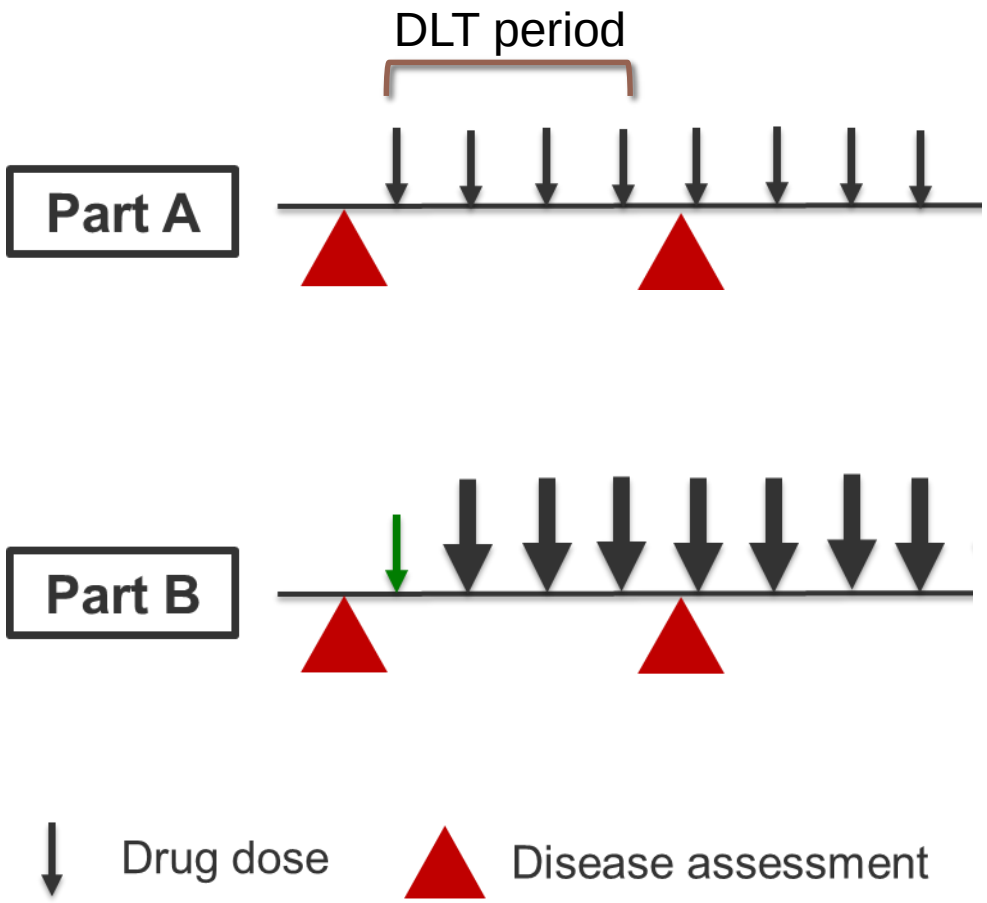
Antineoplastic treatment within 2 weeks

Known uncontrolled CNS involvement by tumor

AST/ALT > 3.0x ULN, Bili > 1.5, Cr > 2.0x ULN or Clcr > 40; WBC ≥ 10K or leukostasis

History of therapy with CD123-directed therapies

XmAb14045 Phase 1 Design



- Weekly doses infused over 2 hours
- Cycle length was 28 days
- 15 planned dose cohorts for Part A starting at 0.003 µg/kg
- Disease assessments occurred at the end of odd-numbered cycles
- DLT period — Days 1-22
- Subject could receive additional cycles of therapy if the investigator felt there was clinical benefit
- Intrapatient dose escalation was allowed

XmAb14045 Phase 1 Design

- 66 subjects dosed as of 19 Oct 2018
- Efficacy analysis included:
  - all subjects that received 4 weekly doses of XmAb14045 at ≥1.3 µg/kg (dose level at which activity was initially seen)
  - had at least one post-treatment disease assessment
- Safety analysis included all subjects that received at least 1 dose of XmAb14045

Cohorts	Cycle 1				Cycle 2+	Dosed	Efficacy Evaluable
	Day 1	Day 8	Day 15	Day 22			
9A	1.3	1.3	1.3	1.3	1.3	8	5
10A	2.3	2.3	2.3	2.3	2.3	5	4
1B	1.3	2.3	2.3	2.3	2.3	6	5
2B	1.3	2.3	2.3	4	4	6	4

All doses in µg/kg

Demographics (Safety Population)

Characteristic		All patients (n=66)
Age	Median [min, max]	61 years [18, 85]
Gender	Female	30 (46%)
Diagnosis	AML*	66 (100%)
Time since initial diagnosis	Median [min, max]	49 weeks [3, 879]
Number of prior therapies	Median [min, max]	3 [1, 8]
History of hematopoetic stem cell transplantation		20 (30%)
Refractory to last therapy (per investigator)		57 (86%)
ELN risk category	Favorable	3 (5%)
	Intermediate	22 (33%)
	Adverse	35 (53%)
	Unknown	6 (9%)
Secondary leukemia		7 (11%)

*one B-ALL patient was enrolled/treated, but not included in this analysis.

Safety

Related Treatment Emergent Adverse Events Occurring in ≥10% of Subjects (n=66)

Event	All	≥ Grade 3
Cytokine release syndrome*	36 (55%)	4 (6%)
Chills	26 (39%)	
Fever	18 (27%)	
Tachycardia	14 (21%)	
Increased ALT	12 (18%)	5 (8%)
Anemia	11 (17%)	9 (14%)
Hypotension	11 (17%)	1 (2%)
Fatigue	10 (15%)	1 (2%)
Hypertension	9 (14%)	3 (5%)
Increased AST	8 (12%)	2 (3%)
Lymphopenia	7 (11%)	5 (8%)
Nausea	7 (11%)	
Vomiting	7 (11%)	

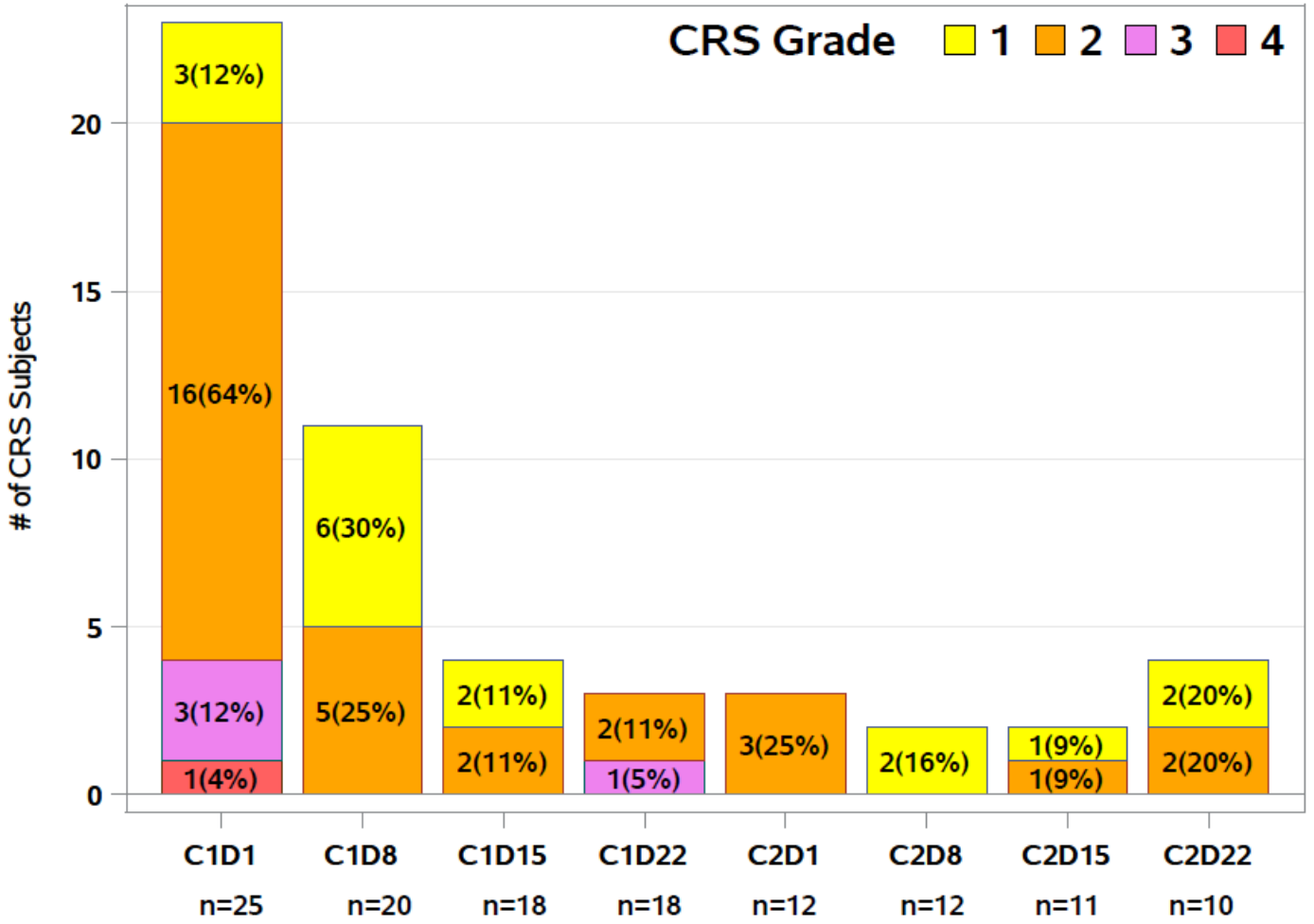
*CRS Revised Grading System (Lee DW et al. Blood 2014;124:188)

- Primary toxicity was cytokine release syndrome (CRS), observed in 55% of subjects. Additional events occurring within 24 hours of dosing consistent with CRS were seen in 29% (chills, fever, tachycardia, hypotension, etc.)
- No clear evidence of drug-related myelosuppression
- Grade 3 transaminase elevation occurring within 24 hours of drug infusion was seen in 5 patients
  - All resolved within 7 days
  - Only 1 patient developed hyperbilirubinemia (Gr 1)
  - No clear relationship with dose
  - Most often seen with the first dose of XmAb14045
- Recurrent infusion-related back or head pain in 4 patients, managed with analgesics
- Neurologic events: 5 patients developed transient infusion-related cognitive changes and 1 patient manifested paresthesias

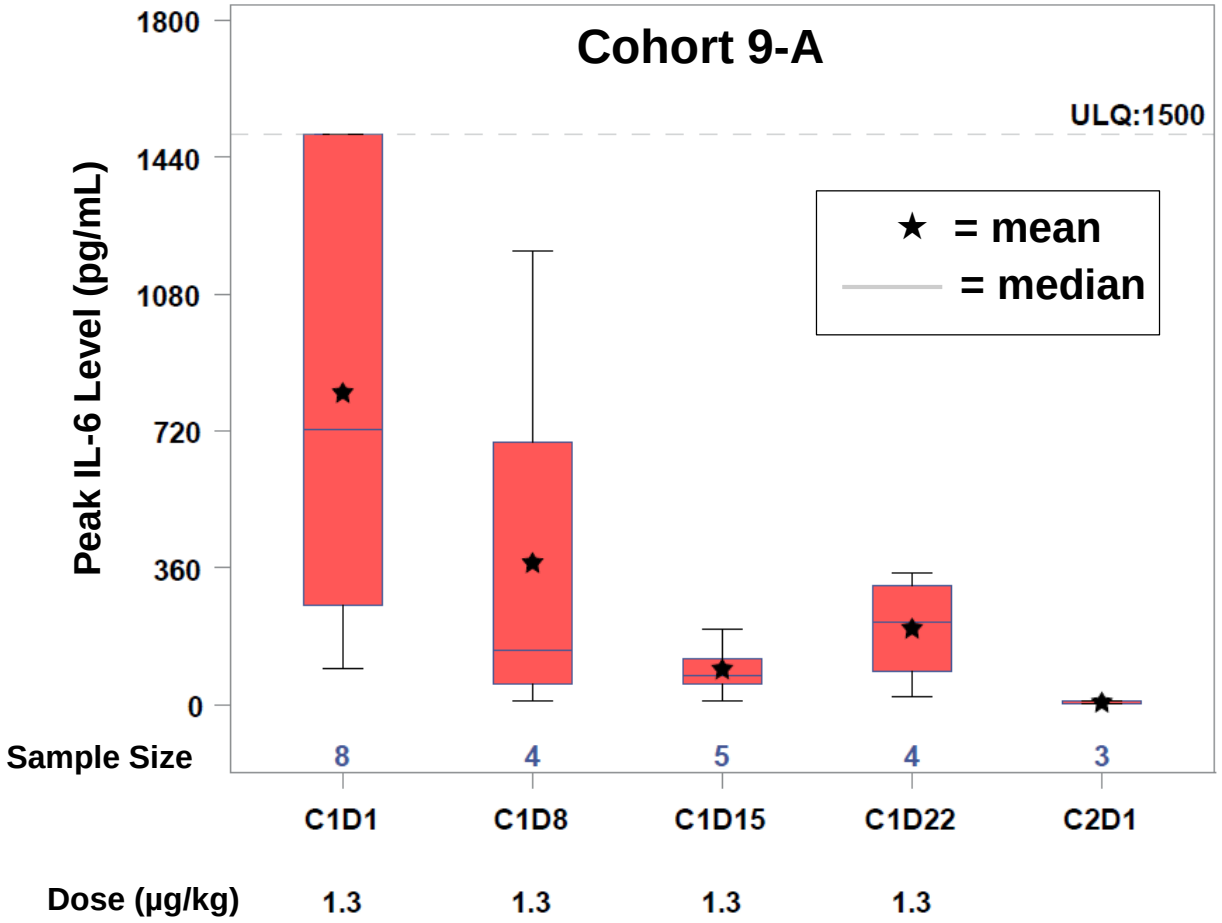
Cytokine Release Syndrome and Premedications

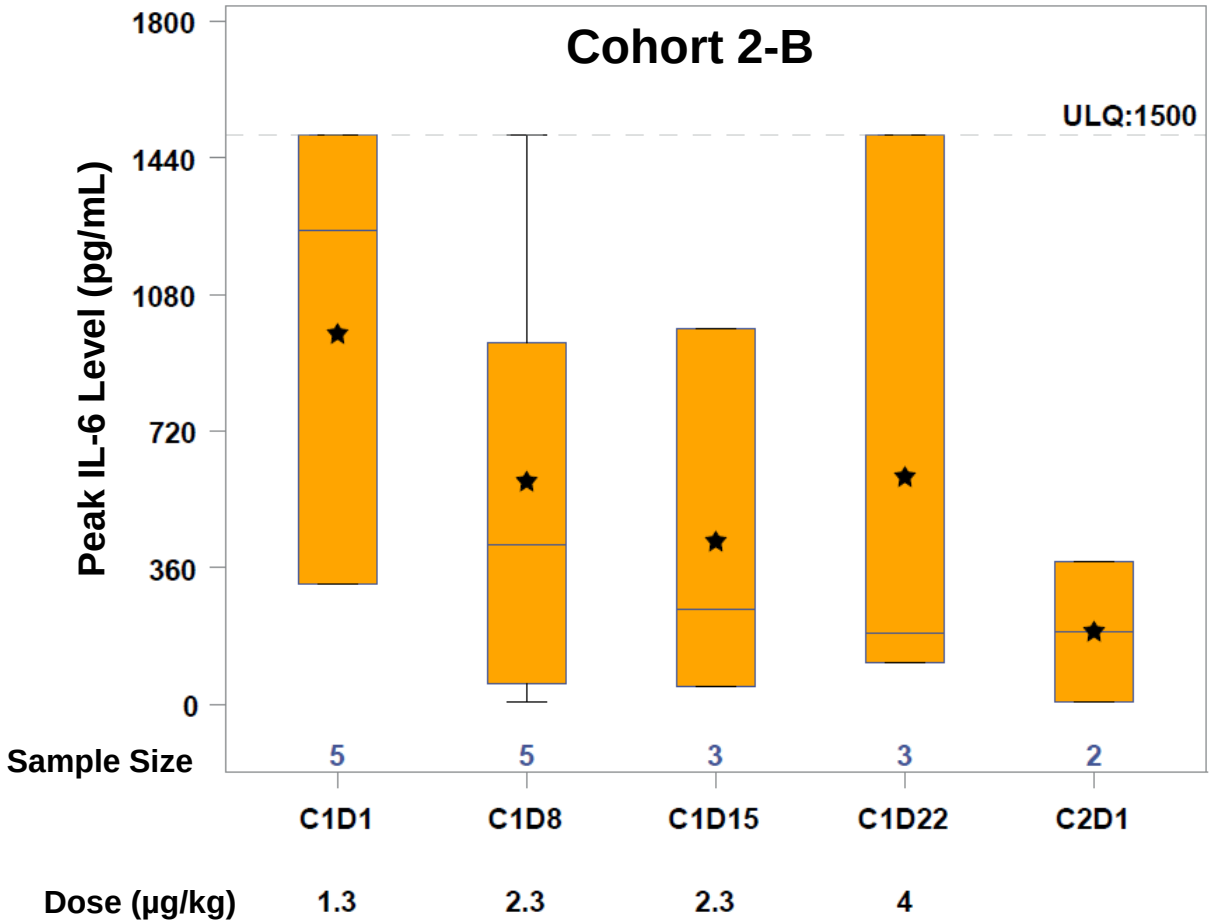
- No premedication was given for early cohorts
- Standard premedications were added for Cohort 4A (0.075 µg/kg):
  - Dexamethasone 10-20 mg IV
  - Diphenhydramine 50 mg po
  - Acetaminophen 500 mg po
- All episodes of CRS began within 1-4 hours of the start of drug infusion and usually resolved within 1-4 hours
- CRS was generally more severe on the initial dose, accounting for most ≥ Grade 3 episodes

CRS severity by infusion (Cohorts 9A-2B)



Cytokine Release Syndrome: Peak Serum IL-6 by Infusion

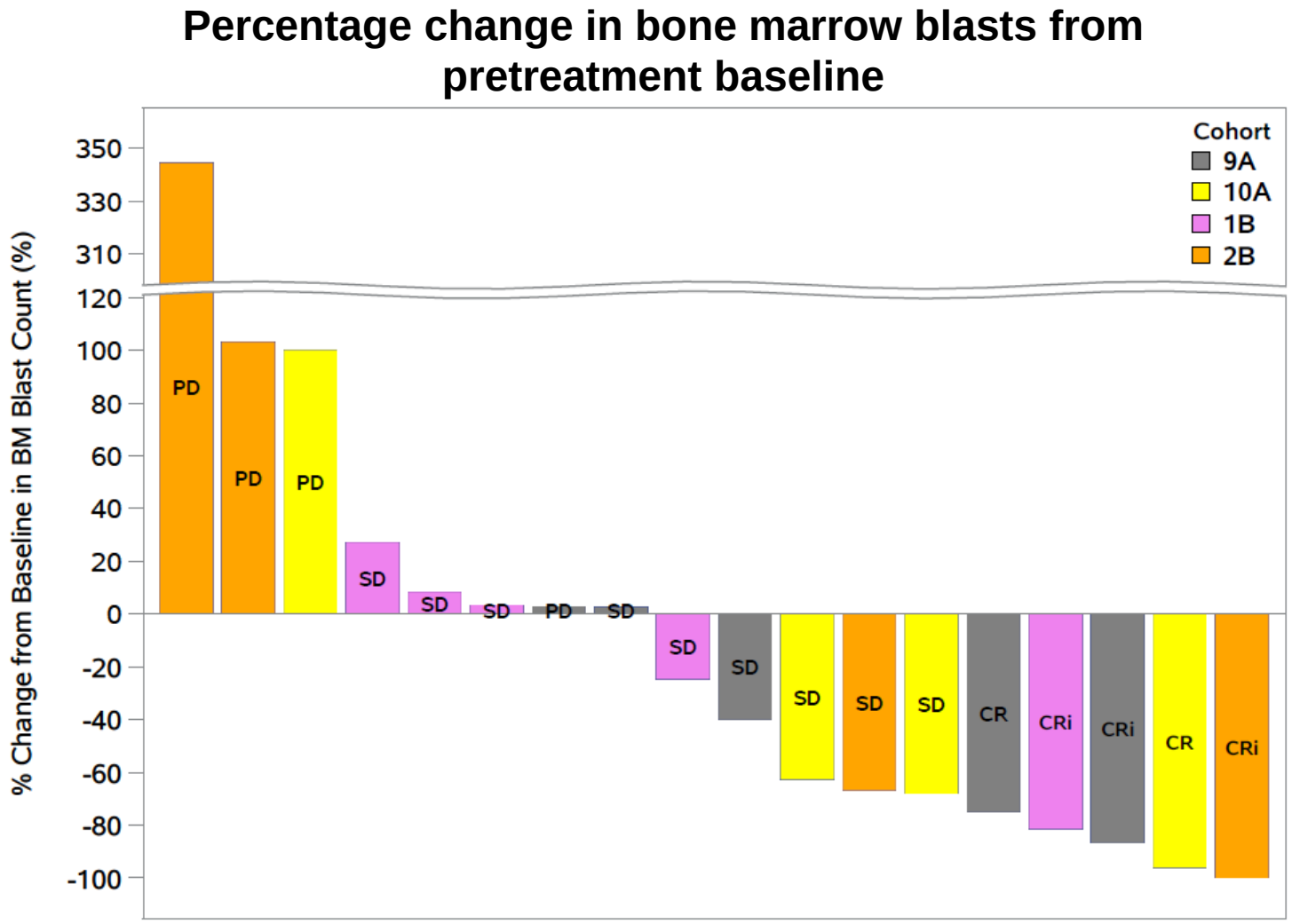




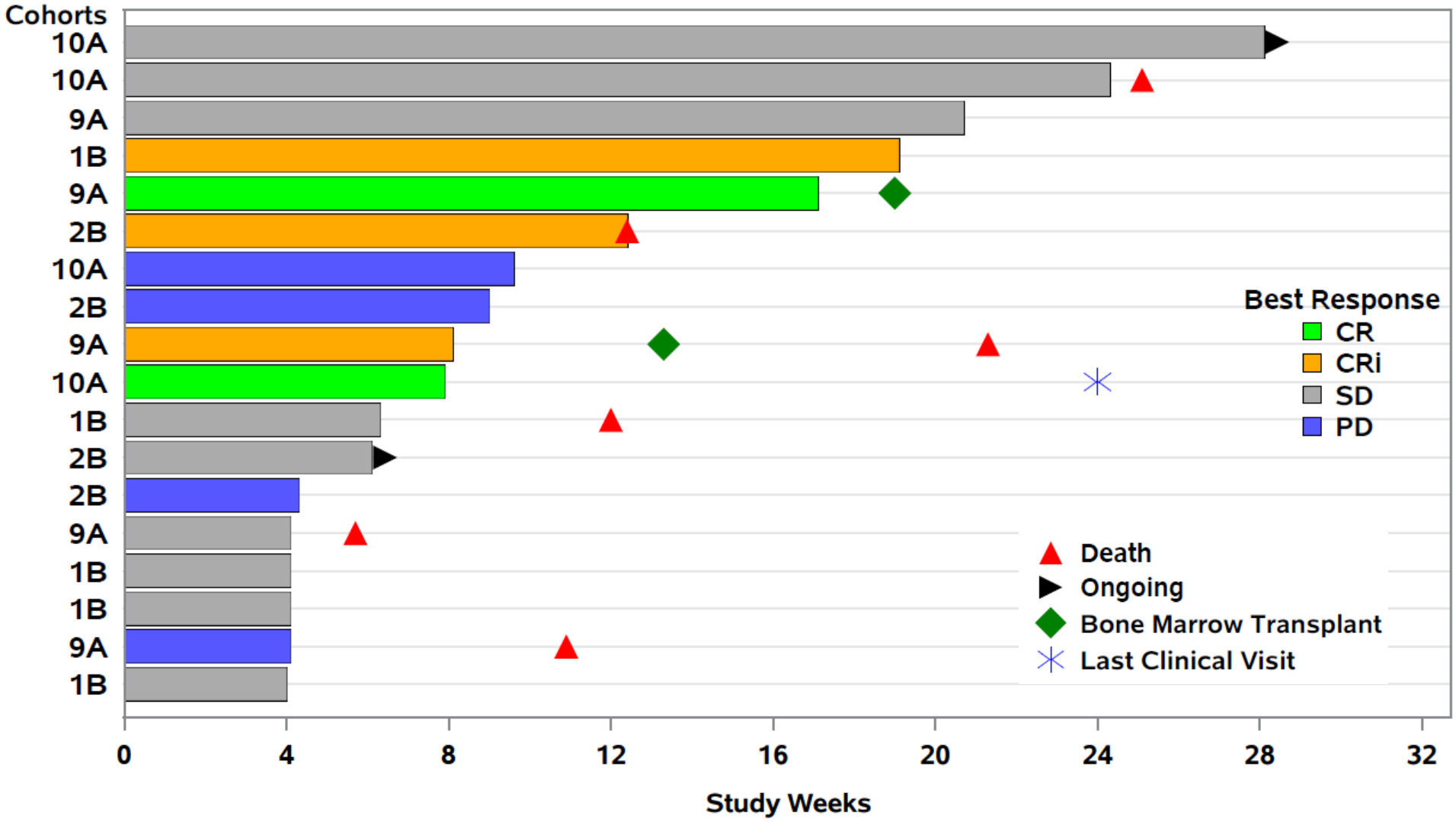
Upper limit of quantification for IL-6 = 1500 pg/mL

Preliminary Efficacy Data

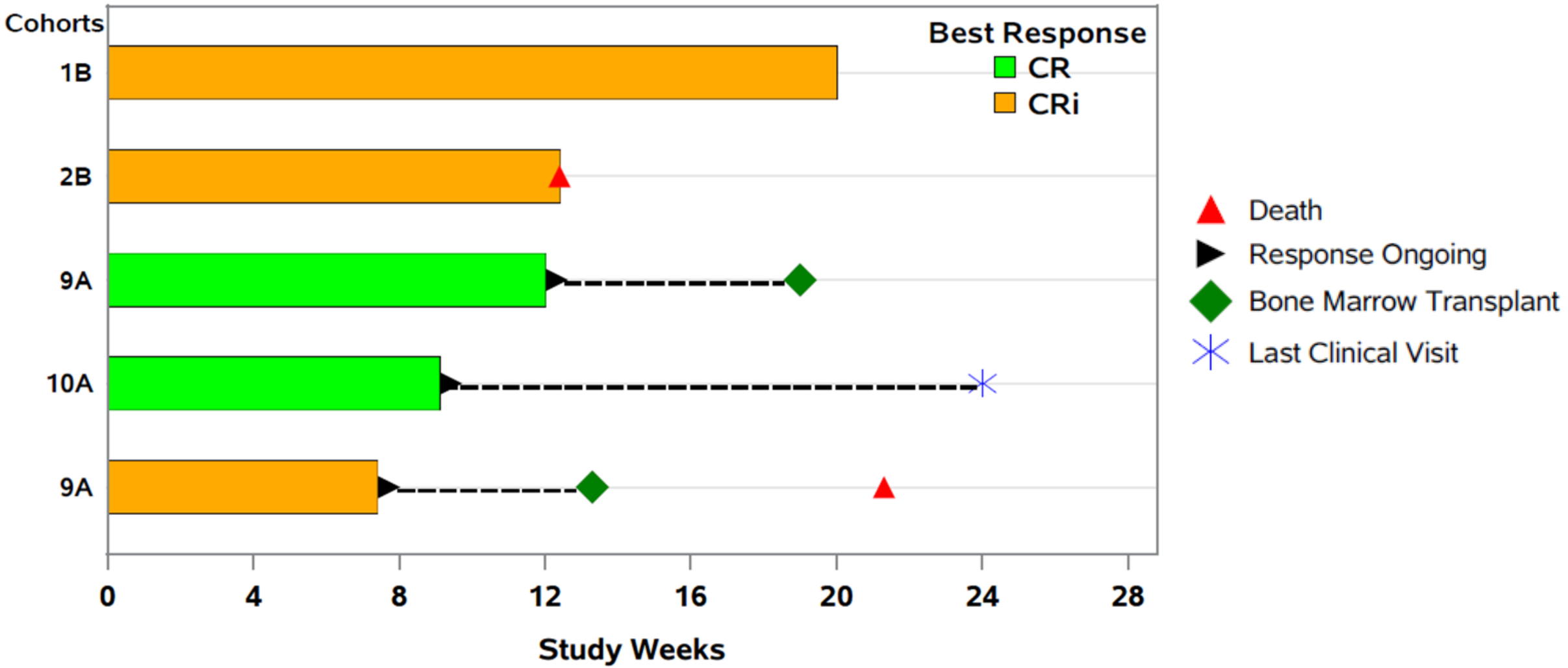
- Objective response rate (CR + CRi) in 5/18 patients (28%) dosed at ≥1.3 µg/kg
- Stable Disease lasting for >3 months in an additional 3 patients (17%)
- Reduction of marrow blasts in 56% of patients
- Blast reduction occurred within the first cycle, although clinical hematologic recovery (CRi→CR) sometimes required 1-2 additional cycles



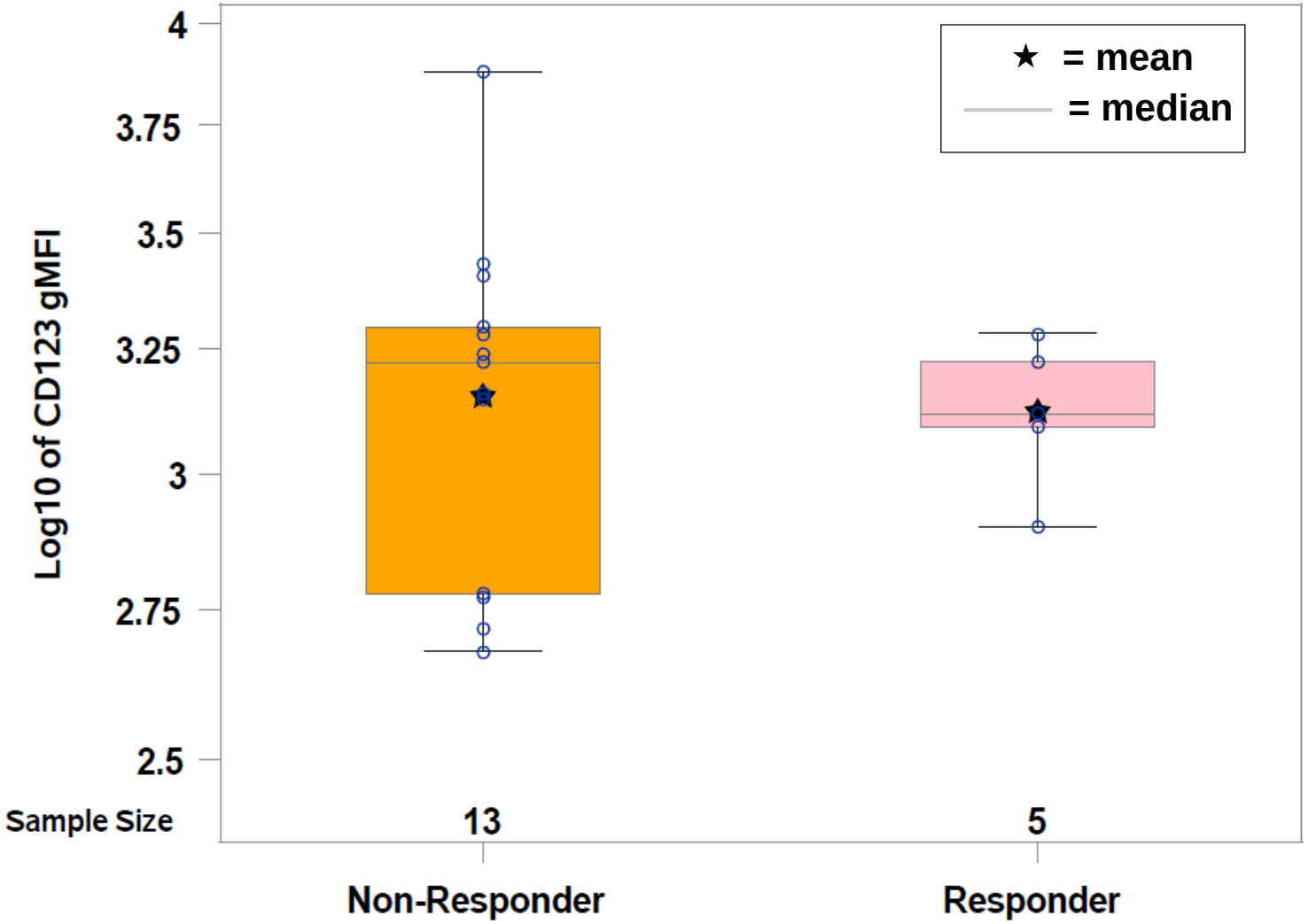
Time to Treatment Discontinuation



Responders (CR and CRi)



Blast CD123 Expression: Responders vs. Non-Responders



CD123 mean fluorescent intensity of marrow leukemic blasts by flow cytometry prior to XmAb14045 administration was not significantly different between responders and non-responders

Conclusions

- XmAb14045 at the dose and schedule studied is well tolerated and has clinical activity in relapsed AML
- Antibody construct with full-length Fc region permits weekly dosing
- Cytokine release syndrome is the primary toxicity of XmAb14045; management with premedication and the use of a priming dose and step-up dosing is effective in limiting its severity
- No clear evidence of myelosuppression was observed even after prolonged administration
- Clinically significant responses were achieved in relapsed/refractory AML allowing allogeneic stem cell transplant
- Dose escalation and schedule optimization continues

Acknowledgments

Participating patients and their families

MD Anderson, Houston
Farhad Ravandi MD
Hagop M. Kantarjian MD
Koichi Takahashi MD

Ohio State University, Columbus
Alice S. Mims MD
Bhavana Bhatnagar DO

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

Emory University, Atlanta
William Blum MD

Novartis, Cambridge, MA
K. Gary J. Vanasse MD

Xencor, Inc., San Diego and Monrovia, CA
Wayne Saville MD
Chelsea M. Johnson BSN
Maria Winter
Andrea Dawson
Thomas Ly PhD
Salil Parab MS MBA
Smitha Mullapudi MS
Caiyan Li PhD
Paul Foster MD