Phase 1 Cohort Expansion of Flotetuzumab, a CD123 x CD3 Bispecific DART® Protein, in Patients with Relapsed/Refractory Acute Myeloid Leukemia (AML)

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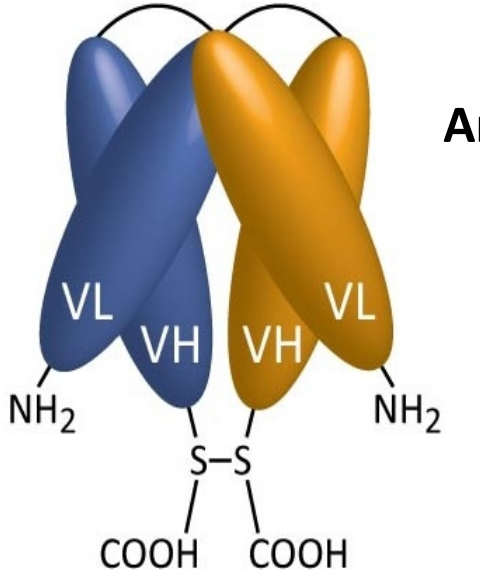
Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART® Protein

- Bivalent, investigational bispecific molecule that co-engages T cells (anti-CD3) with a tumor associated antigen (anti-CD123)
- CD123 is low affinity IL-3 receptor
  - Normally expressed on plasmacytoid dendritic cells (pDCs), basophils, monocytes, and hematopoietic progenitor cells (HPCs)
  - Over-expressed on leukemic stem cells (LSCs) in AML and other hematologic malignancies
- Flotetuzumab designed to:
  - Redirect T-cells to kill tumor cells
  - Recognize tumors independent of TCR & MHC

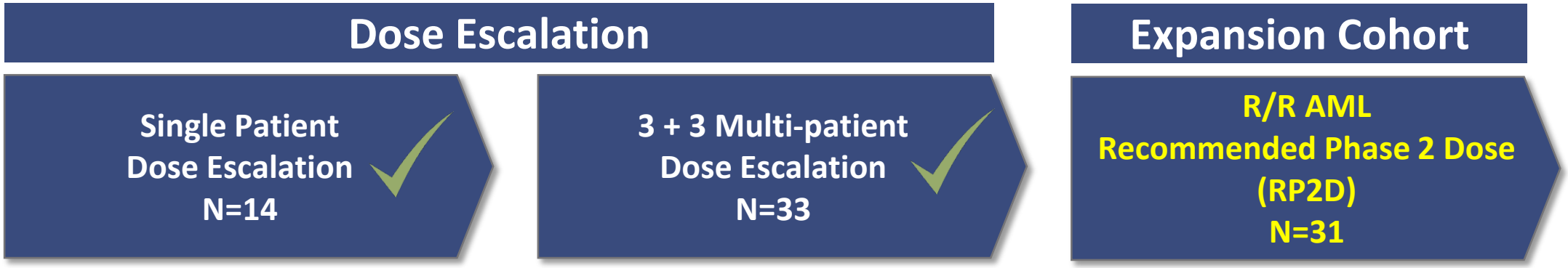
Flotetuzumab

Anti-CD3



Anti-CD123

Flotetuzumab Phase 1 Study Design



Key entry criteria

- Relapsed/Refractory AML unlikely to benefit from cytotoxic chemotherapy
  - Refractory to ≥ 2 induction attempts
  - 1st relapse with initial CR duration of < 6 months or any prior unsuccessful salvage
  - 2nd relapse or higher
  - HMA failure
- No prior allogeneic hematopoietic cell transplant

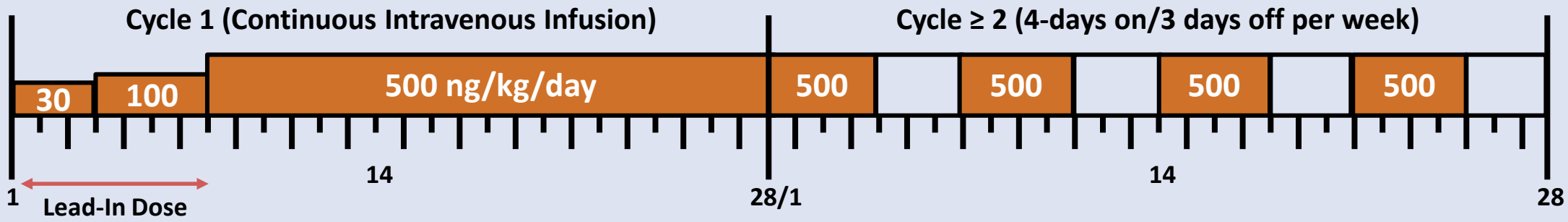
Study objectives

- Safety and preliminary clinical activity
- Optimize delivery and supportive care (manage CRS while minimizing corticosteroid use)
- Define PK, PD and PK/PD relationships

Methods

- Patients receive RP2D of 500 ng/kg/day by continuous infusion

Flotetuzumab Dose and Dosing Schedule



- Disease status assessed by modified IWG criteria
- Samples collected to investigate candidate biomarkers, including CD123 receptor density/cell (RD)
- Gene expression profiling performed using NanoString® PanCancer IO 360™ assay
  - Assessed expression of 770 genes, including 14 immune cell types and 32 immuno-oncology biological signatures in bone marrow (BM) samples

Summary of AML Patient Demographics Treated at RP2D

Characteristic		All Patients (n=31)
Age	Median (Range)	64.0 (29.0, 82.0)
Gender [n(%)]	Female	15 (48.4)
Disease Status at Time of Enrollment	**Primary Refractory§**	**19 (61.3%)**
	Relapse*	9 (29.0%)
	Failed ≤ 2 cycles of HMA	3 (9.7)
AML Risk Stratification (ELN 2017)	**Adverse**	**15 (48.4)**
	Intermediate	8 (25.8)
	Favorable	5 (16.1)
	Unknown	3 (9.7)
# Prior Lines of Therapy	Median (Range)	2.0 (1, 9)

§ Refractory includes ≥ 2 induction attempts or early relapse CR with initial duration < 6 months or refractory ≥ 4 cycles of HMA

***** Relapse includes progression after initial response to HMA/late relapse CR with duration ≥ 6 months

Data cut-off Nov. 1, 2018

Summary of Interim Safety

Treatment Related Adverse Events*	All (N=31)	Grade ≥ 3 (N=31)
Infusion related reaction/Cytokine Release Syndrome (IRR/CRS)*	29 (93.3)	4 (12.9)
Nausea	10 (32.3)	
Edema peripheral	9 (29.0)	1 (3.2)
Diarrhea	8 (25.8)	1 (3.2)
Pyrexia	8 (25.8)	
C-reactive protein increased	6 (19.4)	2 (6.5)
Dyspnea	5 (16.1)	
Headache	5 (16.1)	1 (3.2)
Hypotension	5 (16.1)	
Myalgia	5 (16.1)	2 (6.5)
Vomiting	5 (16.1)	
Alanine aminotransferase increased	4 (12.9)	2 (6.5)
Arthralgia	4 (12.9)	1 (3.2)
Decreased appetite	4 (12.9)	1 (3.2)
Edema	4 (12.9)	
Lymphocyte count decreased	7 (22.6)	6 (19.4)
Anemia	6 (19.4)	6 (19.4)
Platelet count decreased	6 (19.4)	5 (16.1)
White blood cell count decreased	5 (16.1)	5 (16.1)
Neutrophil count decreased	4 (12.9)	4 (12.9)

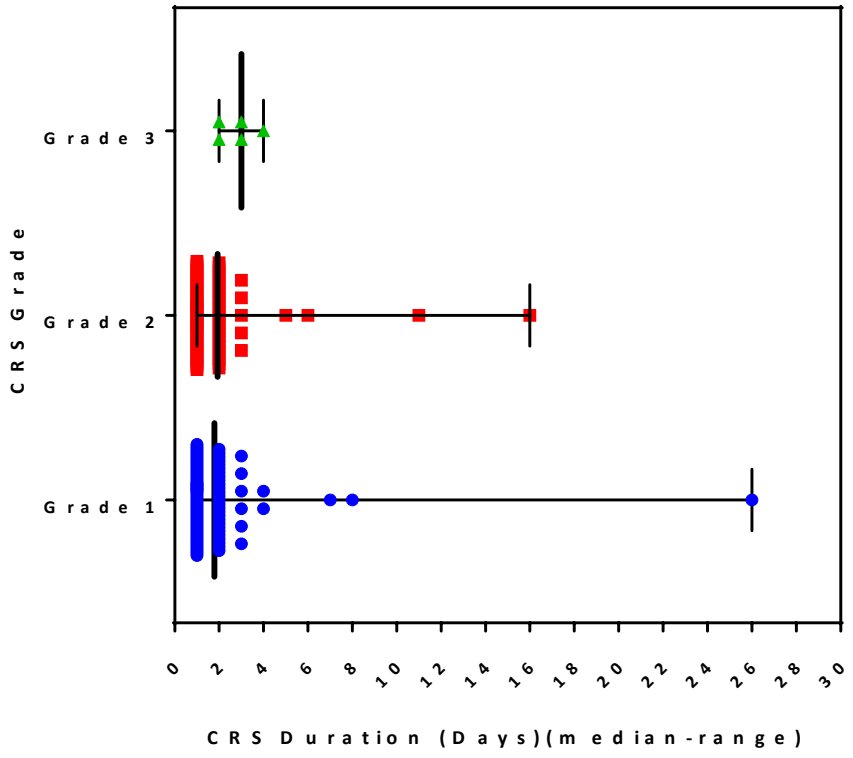
* Toxicity grading for events of IRR/CRS is based upon the modified grading scale proposed by Lee *et al*.

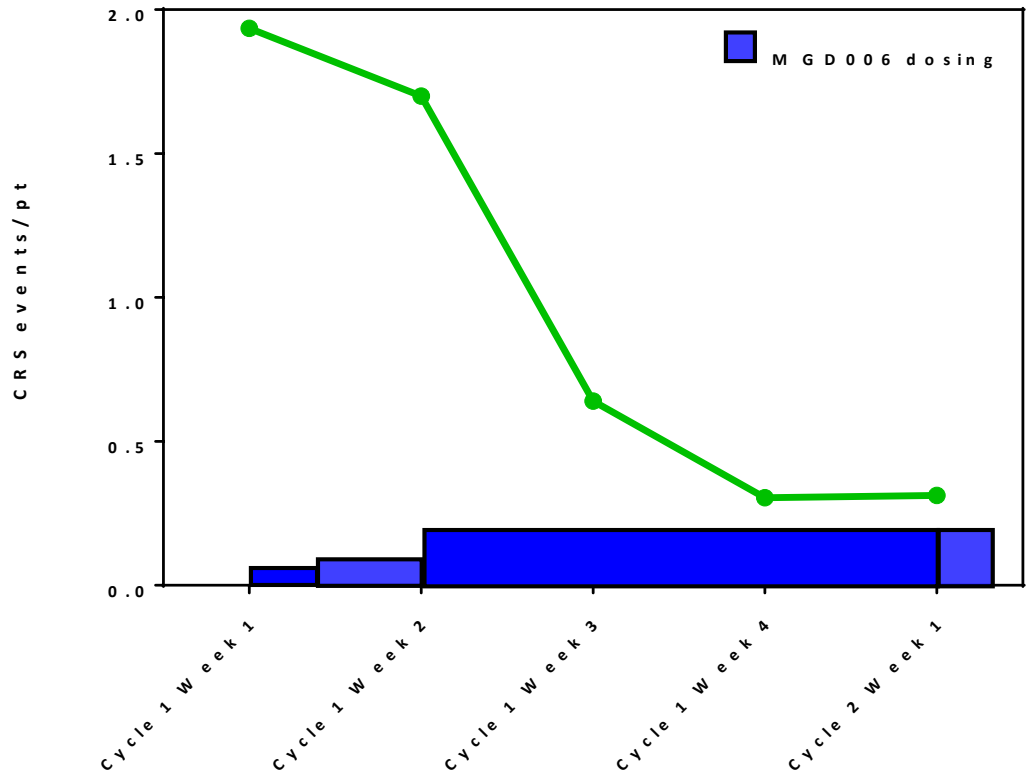
Data cut-off Nov. 1, 2018, events occurring > 10%; Toxicity grading is based on CTCAE criteria version 4.0.

Most CRS Events Were Mild to Moderate Severity and Short Duration

IRR/CRS incidence decreases with continued flotetuzumab dosing

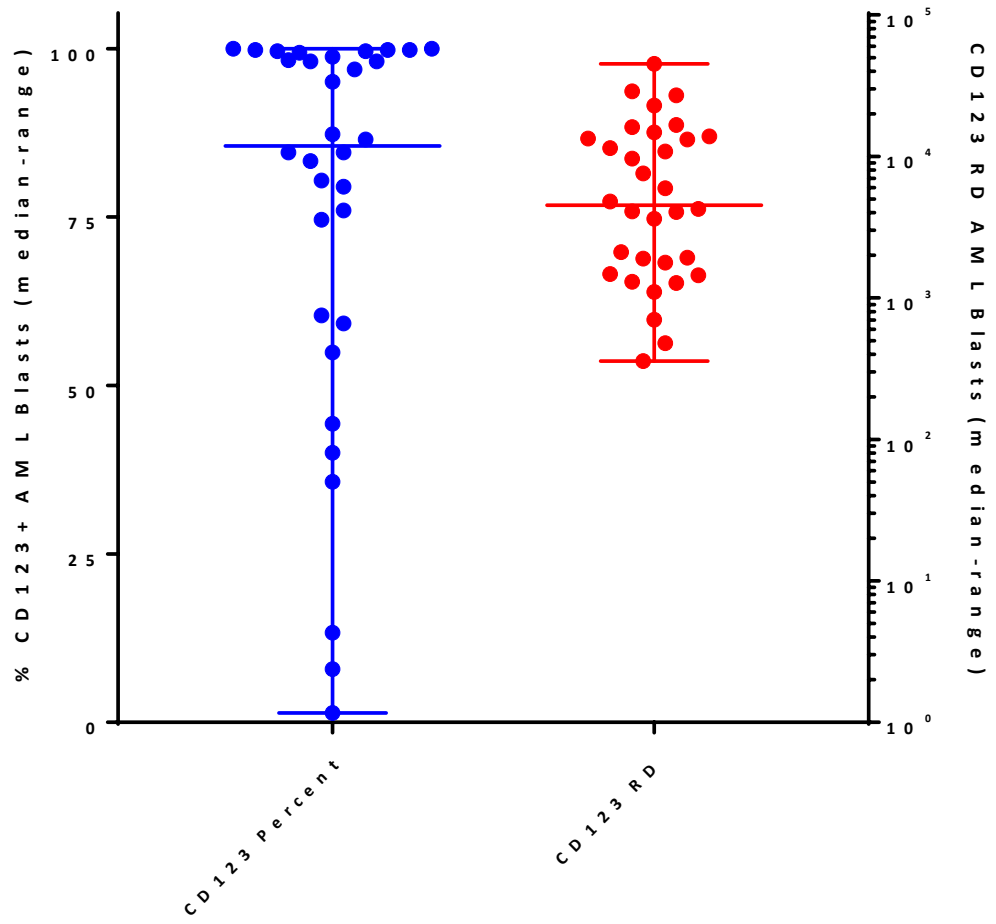
- 31 Patients treated, primarily low grade CRS (G1=25.8% (8/31), G2=58.1% (18/31), and G3=12.9% (4/31))
- Median duration Grade 1: 1 day, Grade 2: 2 days, Grade 3: 2.5 days
- CRS frequency decreased with time on treatment

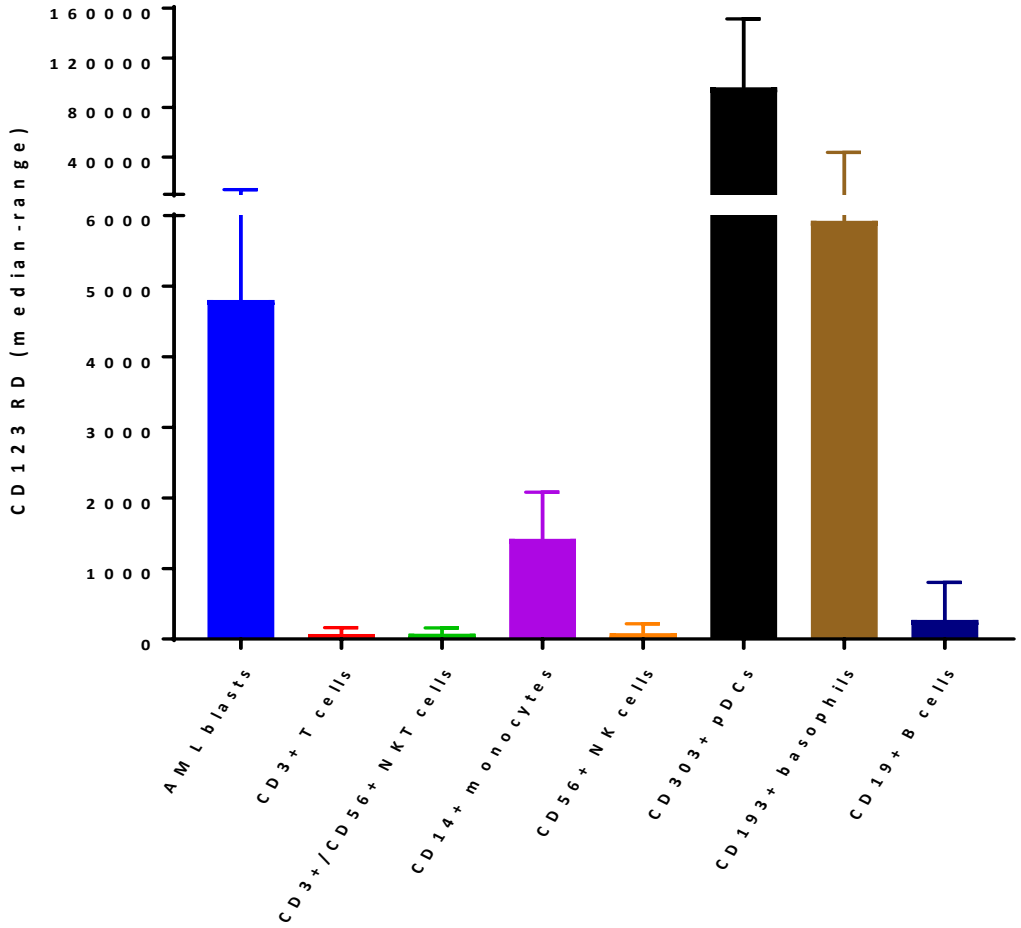




Companion presentation poster #2738

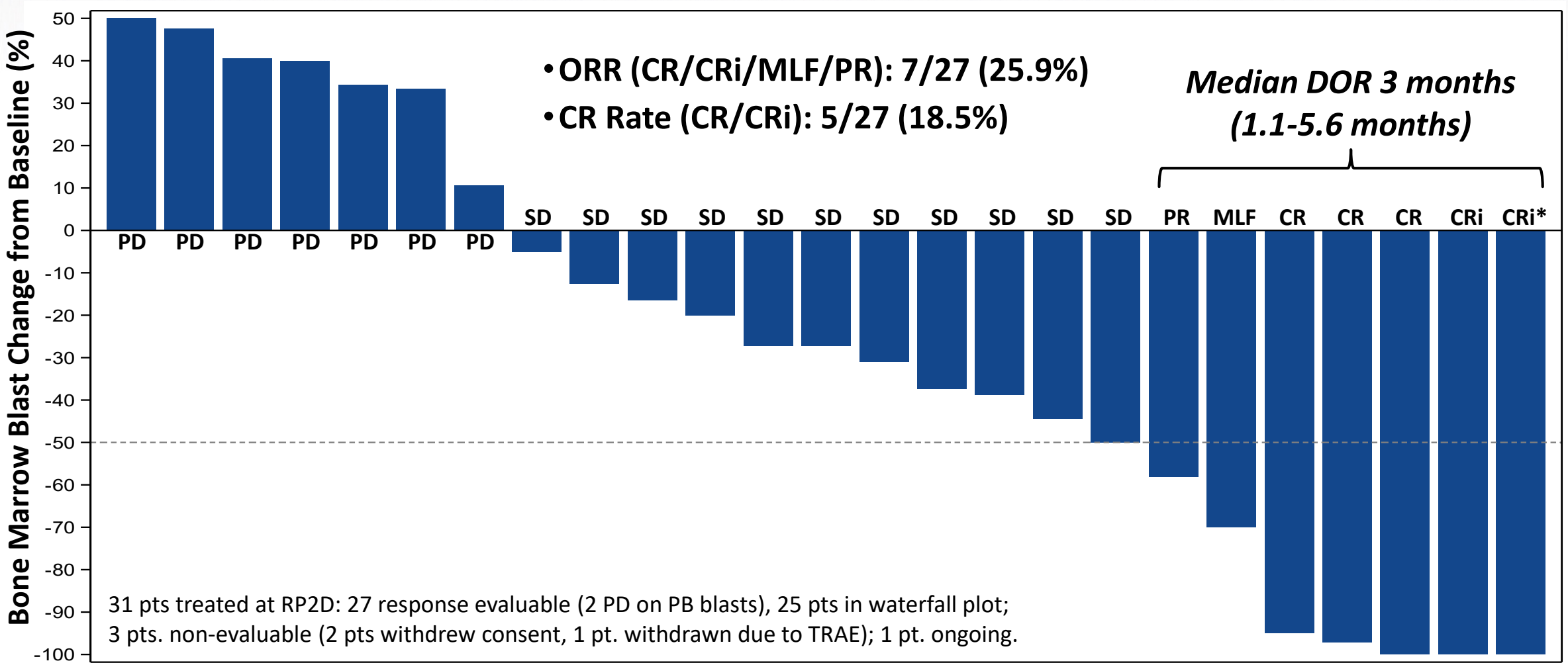
CD123 Frequency and Receptor Density (RD) on AML Blasts





- Baseline median percentage of CD123+ BM blasts 85% (range 1.4-100)
- Median CD123 receptor density on BM blasts 4084 (range 357-44998)

Flotetuzumab Activity in Overall RP2D Cohort

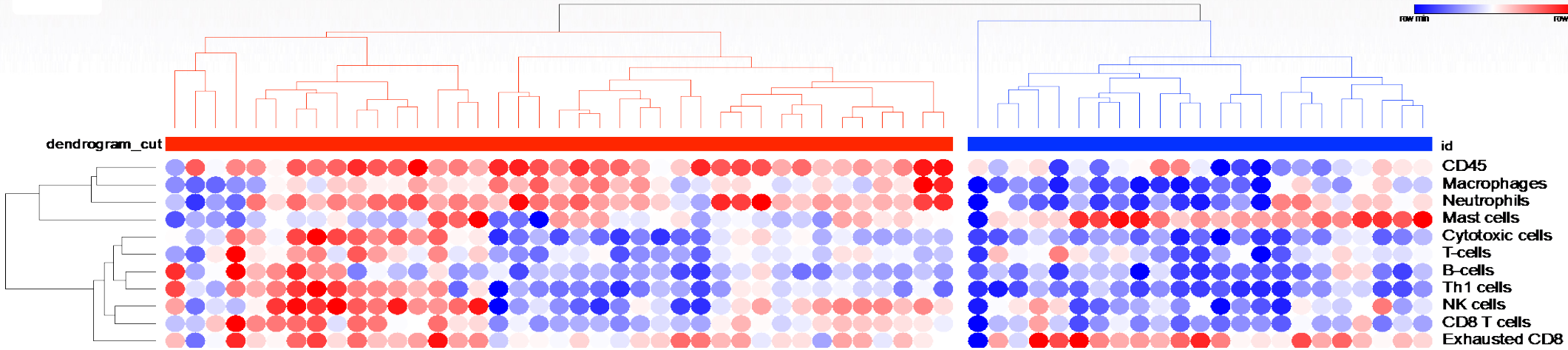


CR=Complete Response; CRi=Complete Response with incomplete hematological improvement; MLF=Morphologic Leukemia-free state; PR=Partial Response; SD=Stable Disease; PD=Treatment Failure

* Patient subsequently underwent HSCT in remission

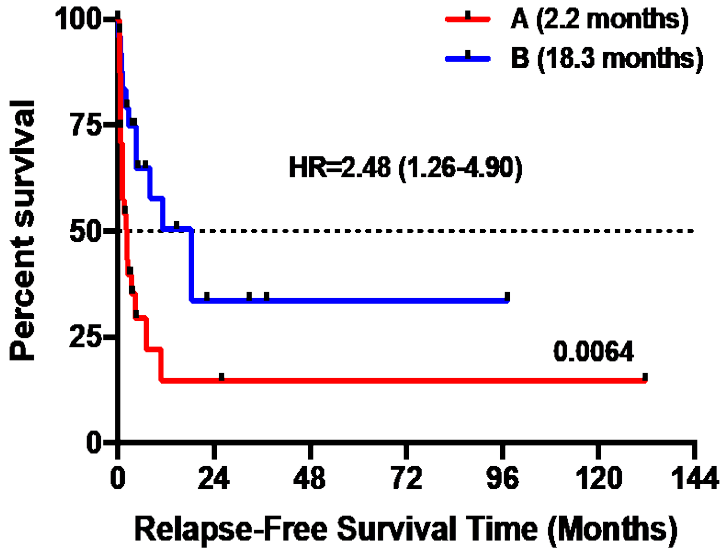
Data cut-off Nov. 1, 2018

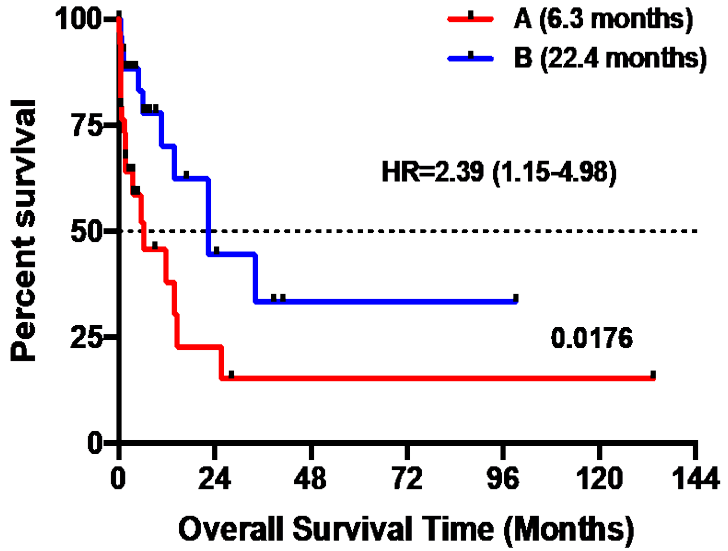
Immune-Enriched TME* Associated with Resistance to Cytotoxic CTx



Cluster A (immune-infiltrated)

Cluster B (immune-depleted)





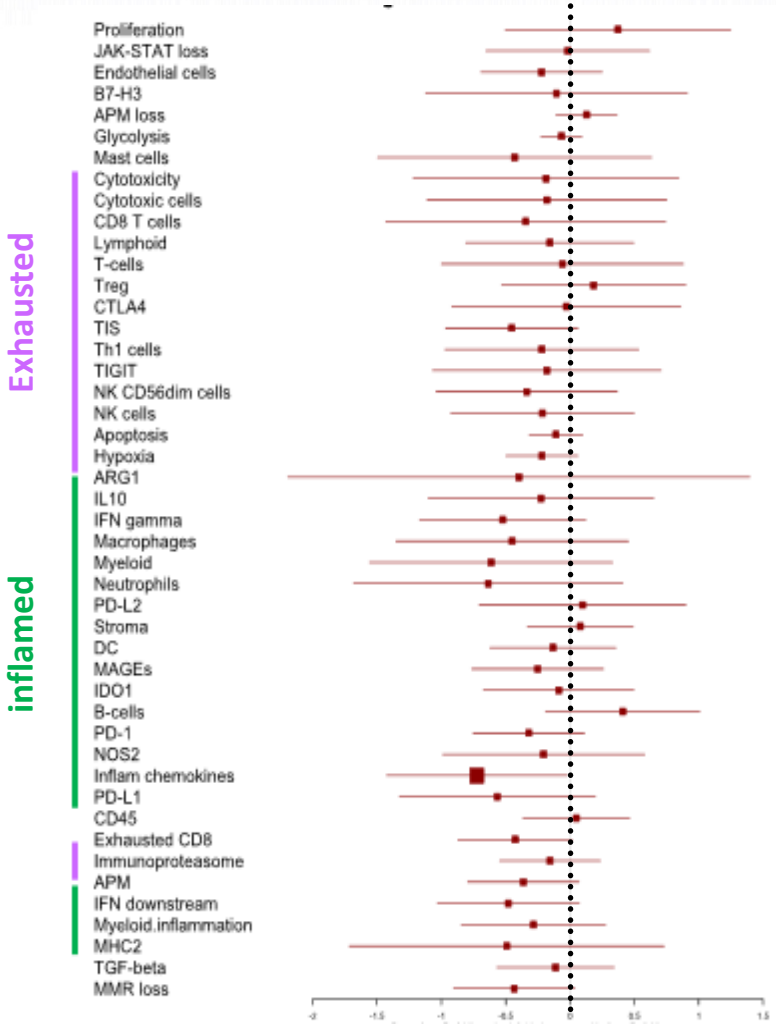
Is primary refractory AML (a potential surrogate for an immune-rich TME) associated with response to flotetuzumab?

* TME = Tumor microenvironment

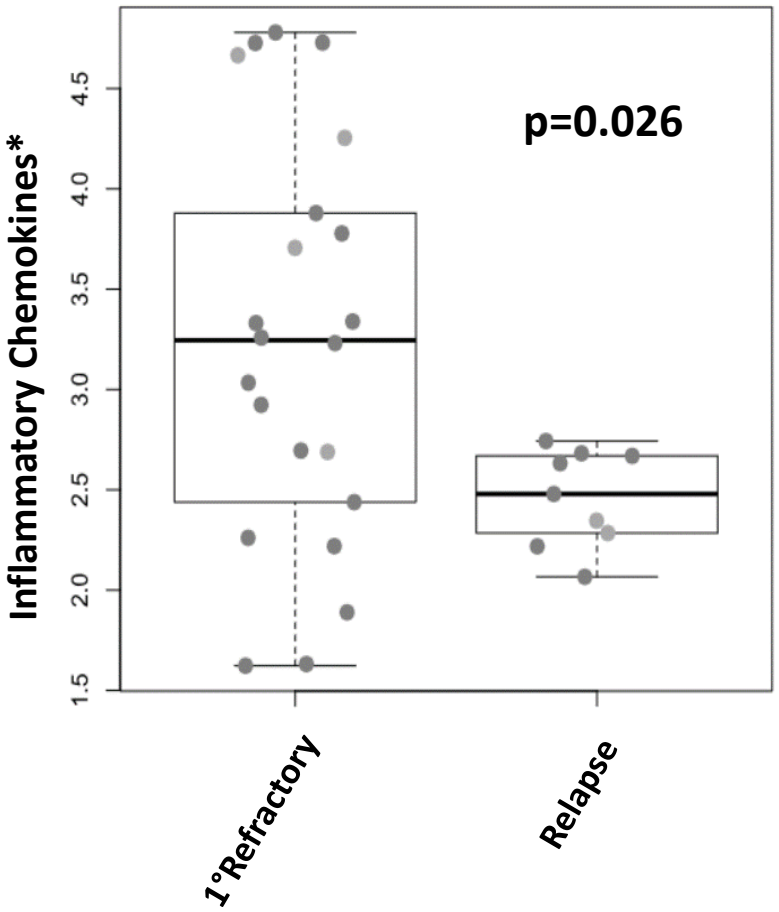
Vadakekolathu J, Patel T, Reeder S, et al. Blood 2017; 130: 3942A.

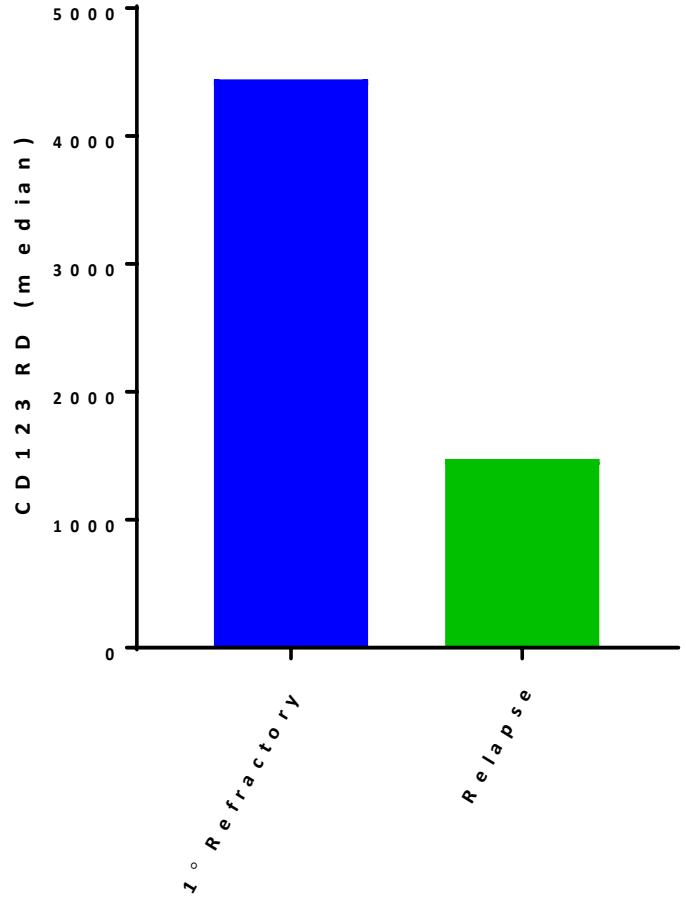
Inflammatory Signature and Increased CD123 Density in Primary Refractory AML

Log2 fold-change 1° Refractory *vs* Relapse AML*



Up in 1° Refractory AML ← log2 fold-change → Up in Relapse AML

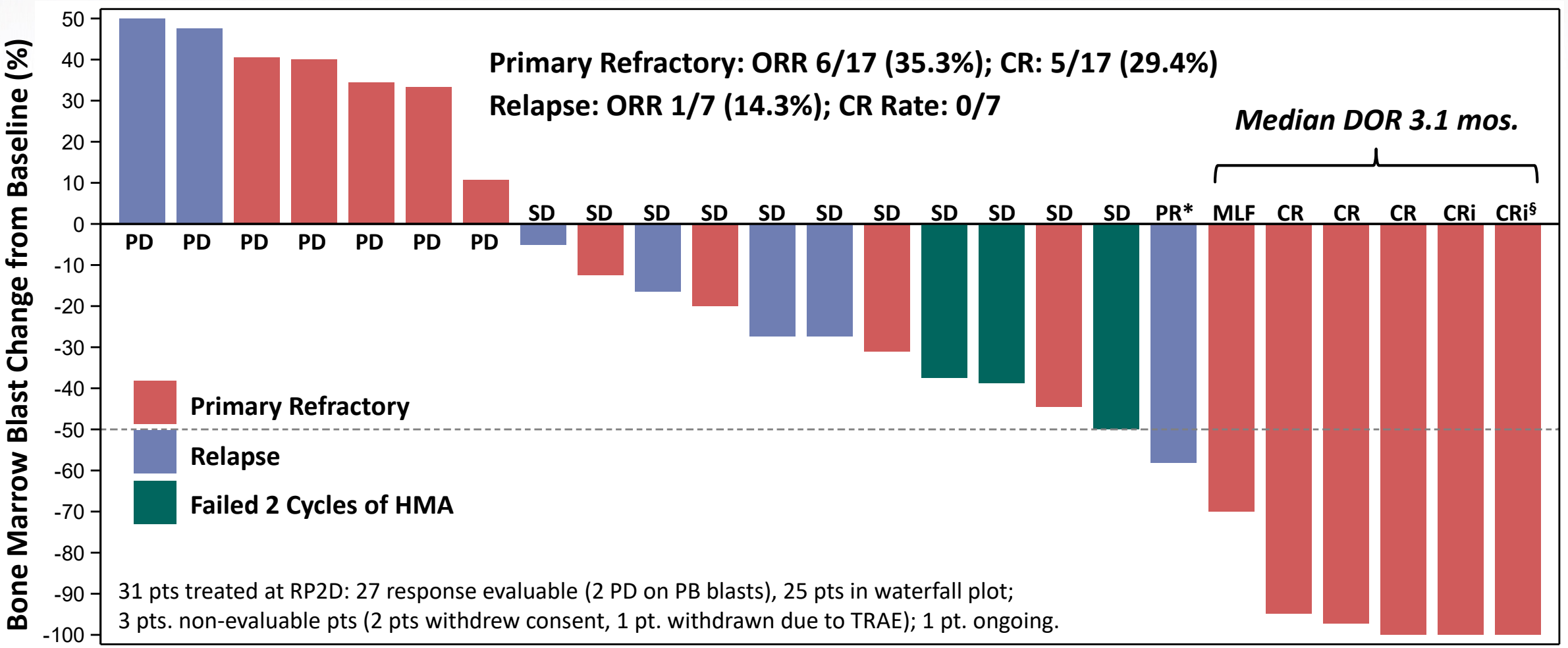




*38 baseline BM including dose escalation

Companion presentation #444, 12/2 4:30-6:00pm Grand Hall B

Primary Refractory AML Patients Were Most Responsive to Flotetuzumab



CR=Complete Response; CRi=Complete Response with incomplete hematological improvement; MLF=Morphologic Leukemia-free state; PR=Partial Response; SD=Stable Disease; PD=Treatment Failure

§ Patient subsequently underwent HSCT in remission

* Duration of response (DOR) = 1.4 months

Data cut-off Nov. 1, 2018

Anti-leukemic Activity Observed in Primary Refractory AML

Evaluable Patients	CR (CR/CRi)	ORR (CR/CRi/MLF/PR)	Benchmark (CR/CRi)
Overall R/R AML	19% (5/27)	26% (7/27)	17% [1]; 24% [2]
Primary Refractory AML	**29.4% (5/17)**	**35.3% (6/17)**	**13% [3]**
Relapse AML	0% (0/7)	14.3% (1/7)	
Failed ≤ 3 cycles HMA	0% (0/3)	0% (0/3)	
Secondary AML*	33.3% (2/6)	50.0% (3/6)	22%-32% [4]

*Secondary AML: AML therapy related AML/antecedent hematological malignancy

(1) Medeiros, et al., Clin Lymph Myel Leuk, article in press, 2018
(2) Greenberg, et al., J Clin Oncol, 2004; Montillo, et al., Amer J Hematol, 1998
(3) Kantarjian, et al., Cancer, 2018
(4) Boddu, et al, Blood Adv, 2017

Conclusions

- Flotetuzumab, an investigational DART molecule, demonstrated antileukemic activity with an acceptable safety profile
- Greater activity observed among patients with primary refractory disease
  - Inflammatory chemokines and CD123 receptor density more pronounced in primary refractory disease
- Ongoing / future studies will:
  - Expand enrollment in patients enriched for primary refractory AML
  - Further characterize potential candidate biomarkers of response
  - Investigation of lead in dosing strategy on going

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