

# **Flotetuzumab, an Investigational CD123 x CD3 Bispecific DART® Protein, in Salvage Therapy for Primary Induction Failure and Early Relapsed Acute Myeloid Leukemia Patients**

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ClinicalTrials.gov #NCT02152956 Abstract #733

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

## • Flotetuzumab:

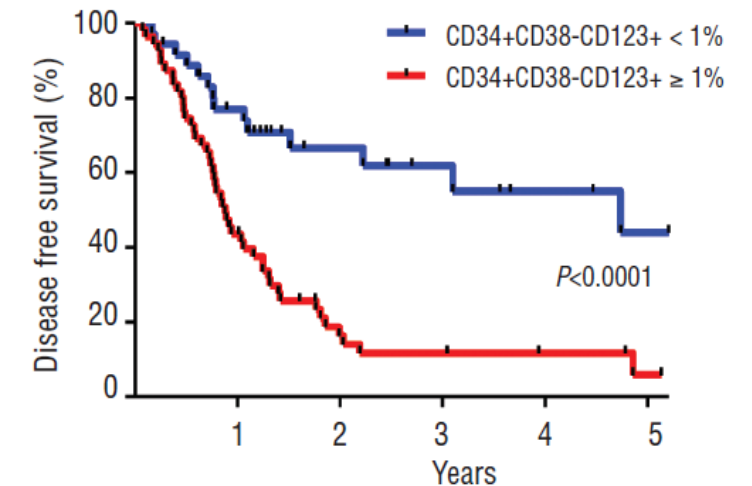
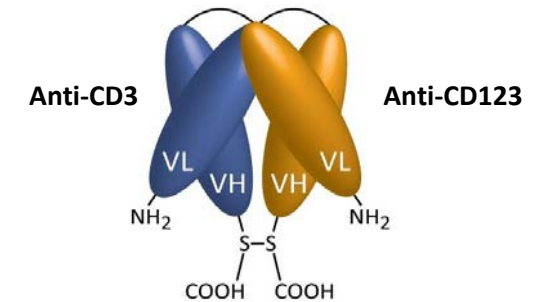
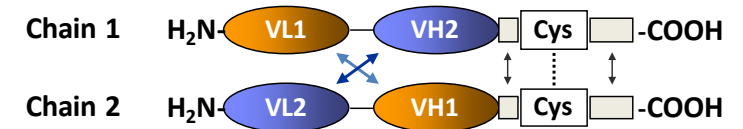
- An investigational bispecific molecule that co-engages T cells (anti-CD3) with a tumor associated antigen (CD123)
- Designed to:
  - Redirect T cells to kill tumor cells
  - Recognize tumors independent of TCR & MHC
- Currently being tested in a Phase 1/2 study in patients with AML

## • CD123, the low-affinity IL-3 receptor (IL3R $\alpha$ )

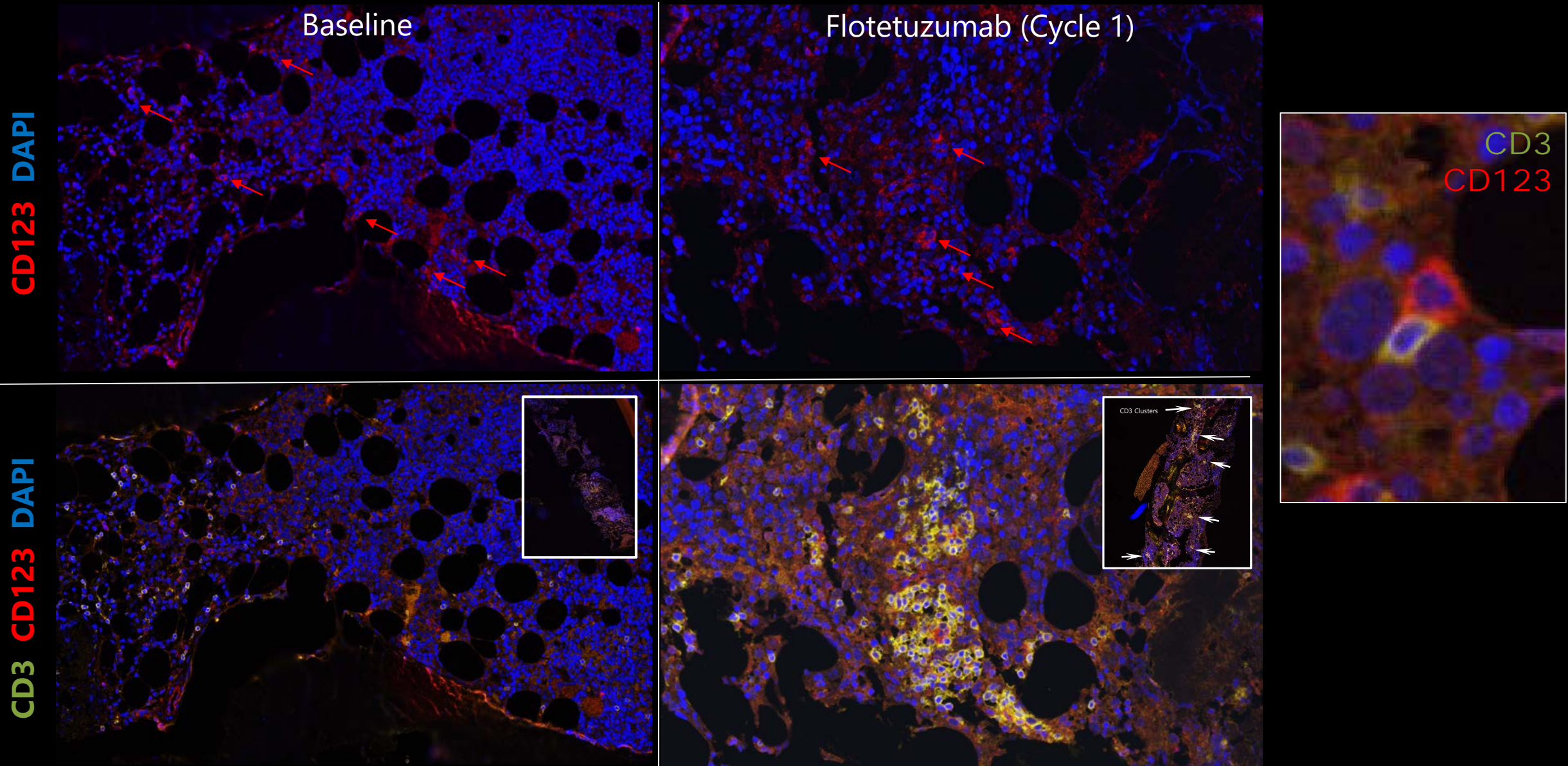
- Normally expressed on hematopoietic progenitor cells (HPCs), plasmacytoid dendritic cells (pDCs), basophils, monocytes
- Over-expressed on leukemic stem cells (LSCs) in AML and other hematologic malignancies
- Increased CD123 expression associated with increased risk of relapse<sup>1</sup>

1. Vergez F et al, Haematologica (2011) 96: 1792

## Flotetuzumab (MGD006)



# T-cell Infiltration in the Bone Marrow of a Flotetuzumab-treated Patient



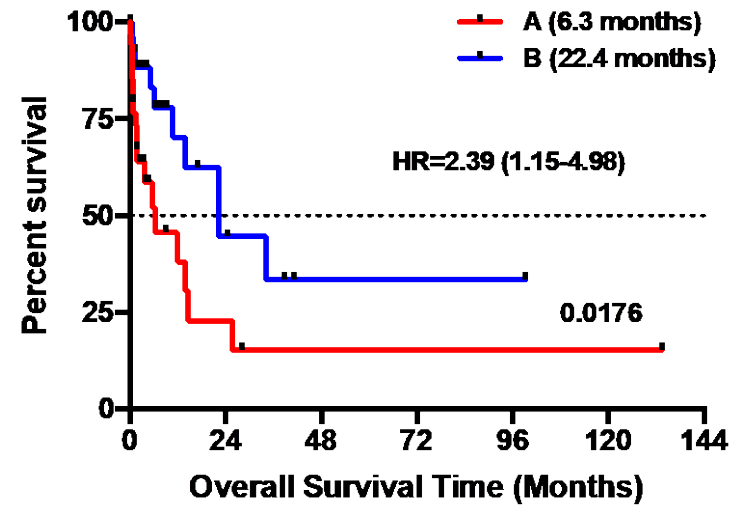
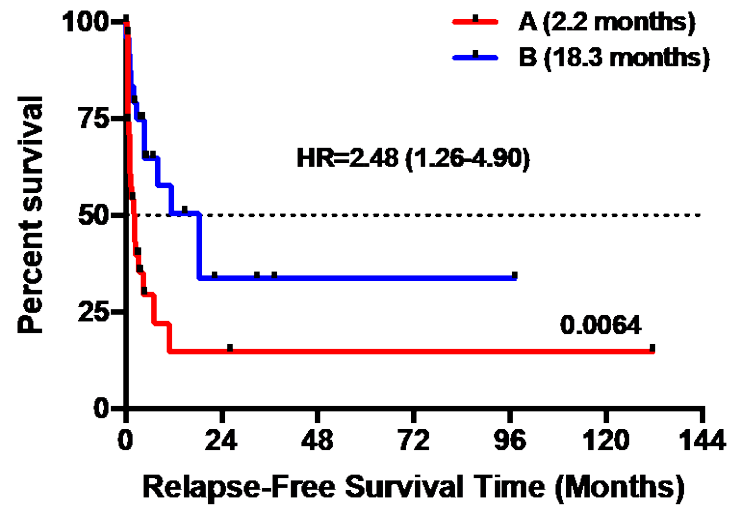
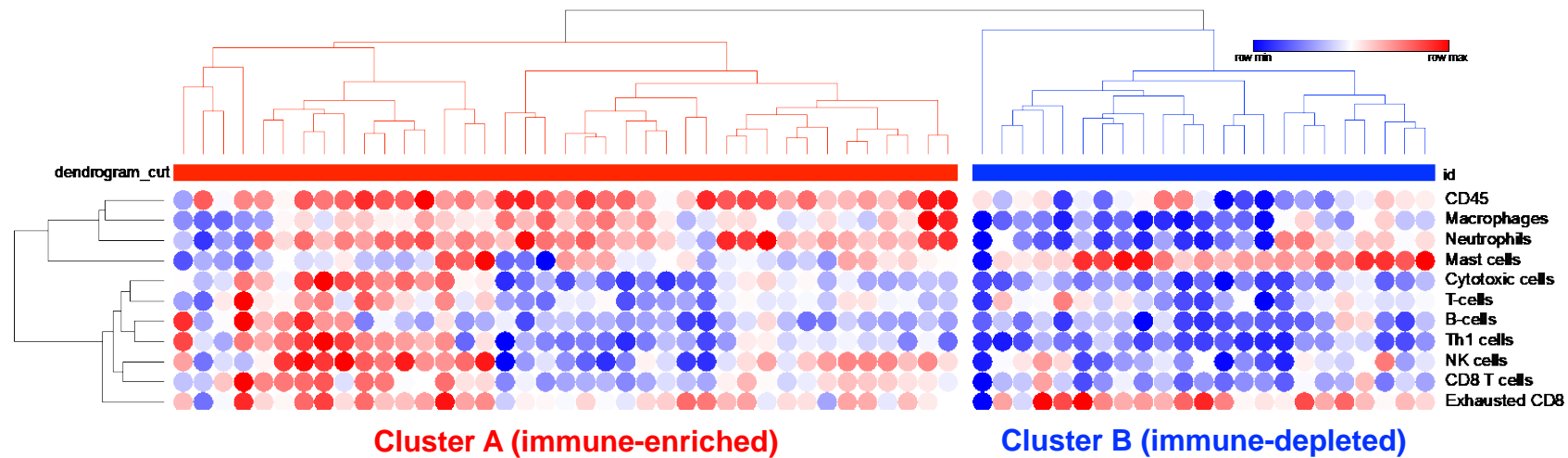
## Poor outcomes for Induction Failure and Early Relapse

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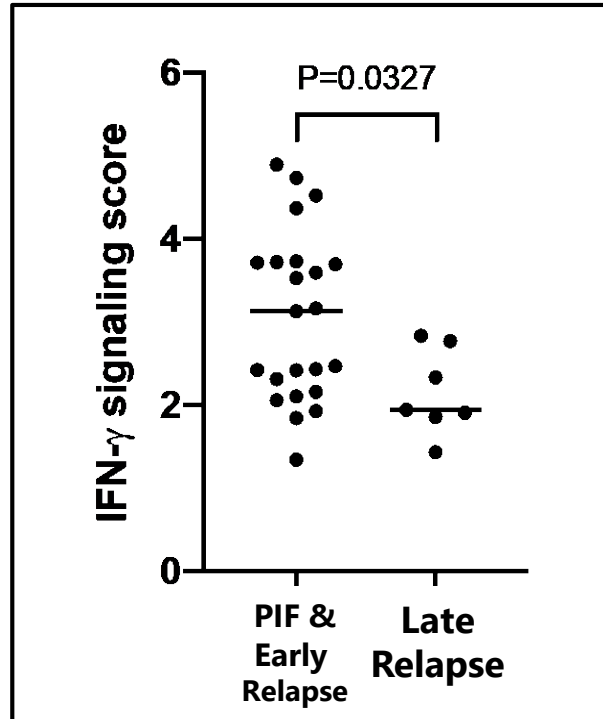
Primary induction failure (PIF) and early relapse (CR < 6 months) AML patients are unmet medical need :

- 40-50% of patients with newly diagnosed AML fail to achieve CR with intensive induction therapy or experience disease recurrence after a short remission duration (<6 months)
- Only < 15% achieve remission following first salvage with conventional chemotherapy
- Subsequent salvage attempts are nearly universally ineffective

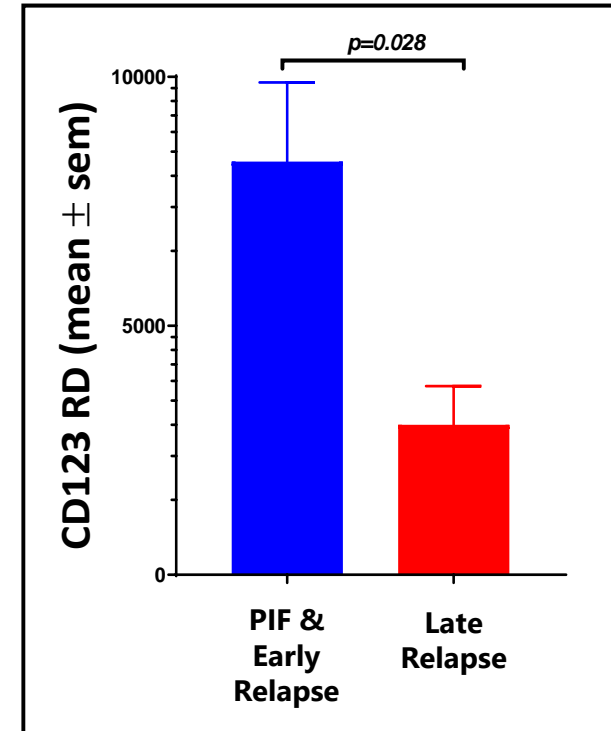
# Immune Infiltration Associated with Poor Prognosis in AML



# Higher IFN- $\gamma$ and CD123 in Refractory AML Patients Treated with Flotetuzumab

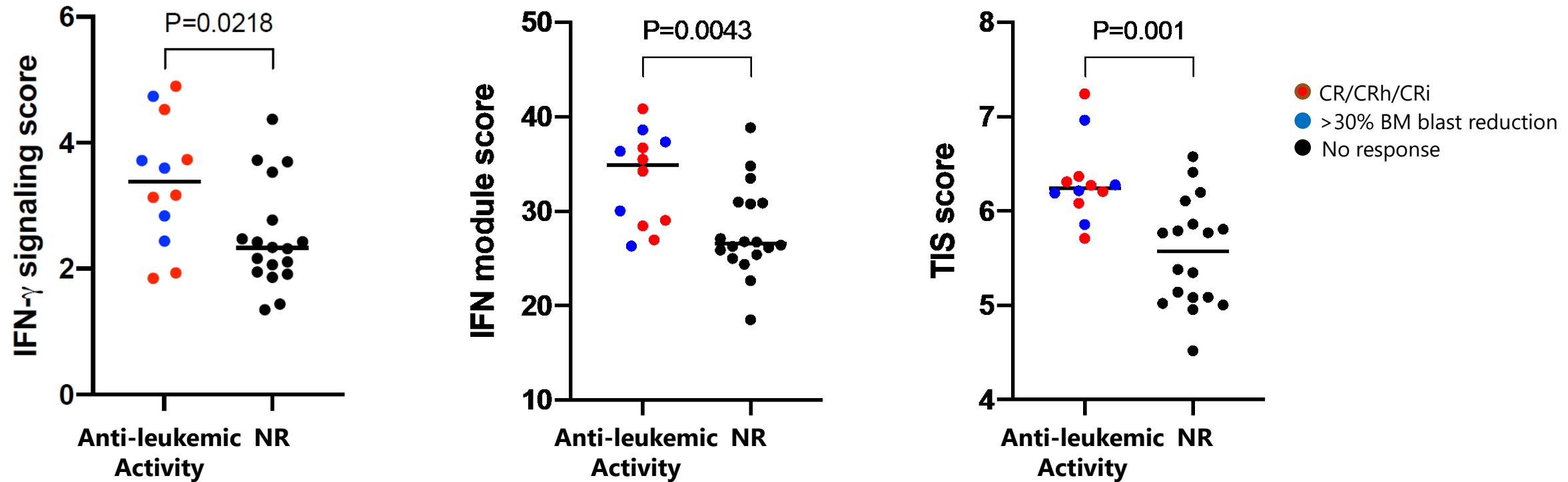


IFN- $\gamma$  score (NanoString PanCancer IO 360™ panel) in baseline AML bone marrow samples (n=30; subgroup of patients treated at the RP2D for whom BM samples were available) Mann-Whitney *U* test for unpaired samples



CD123 receptor density (no. of binding sites/cell) in primary induction failure & early relapse (n = 22) and late relapse AML (n = 7) treated at RP2D for whom data was available. Unpaired t-test

# Baseline IFN- $\gamma$ -related Gene Signatures Associate with Flotetuzumab Activity



IFN- $\gamma$ -related gene signatures (NanoString PanCancer IO 360™ panel) in baseline BM samples (NR= no response); Data shown as mean, *p*-value calculated by Mann-Whitney *U* test for unpaired determinations. Samples n=30; subgroup of patients treated at the RP2D for whom BM samples were available. TIS: Tumor Inflammation Signature

# Flotetuzumab Phase 1/2 Study Design

*Expansion in primary induction failure & early relapsed AML patients*



## Key Entry Criteria (refractory AML population)

- Primary induction failure (PIF): refractory to  $\geq 2$  induction attempts
- Early relapse: First relapse with initial CR duration of  $< 6$  months or any prior unsuccessful salvage
- No prior allogeneic hematopoietic cell transplant

## Study Objectives

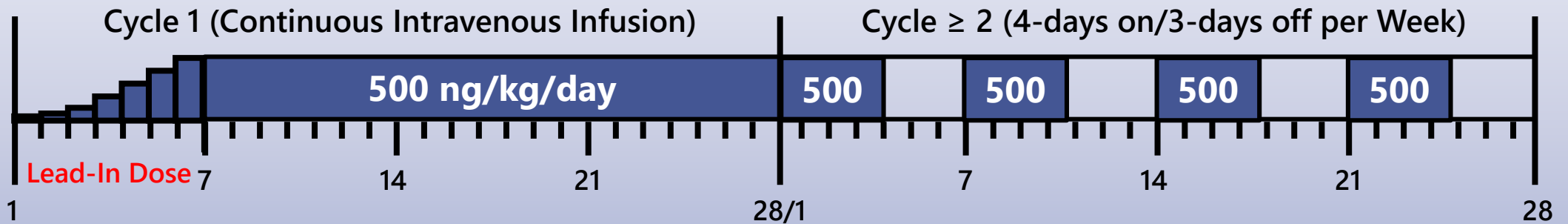
- Safety and preliminary clinical activity
- Optimize delivery and supportive care
- Define PK, PD and PK/PD relationships



# Methods

- Recommended phase 2 dose (RP2D): 500 ng/kg/day by continuous infusion
  - Lead-in dose escalation (LID) during first week of treatment
  - Pre-medication includes 10-20 mg IV dexamethasone pre-dose
- Disease status assessed by modified IWG criteria

## Flotetuzumab Dosing and Schedule



# Primary Induction Failure & Early Relapsed Patients: Demographics

Characteristic	Population (n=30)
Age, Median (range)	59 (27, 74)
Gender, Female	10 (33.3%)
Disease Status at Study Entry	
Primary Induction Failure ( $\geq 2$ induction attempts)	24 (80.0%)
Early Relapse (CR with initial duration < 6 months)	6 (20.0%)
ELN Risk Stratification (2017)	
Adverse	18 (60.0%)
Intermediate	7 (23.3%)
Favorable	5 (16.7%)
Secondary AML	12 (40.0%)
Number of Prior Lines of Therapy, median (range)	4 (1, 9)
Failed induction therapy	
Cytarabine based induction chemotherapy	21 (70.0%)
Alternative induction therapy	3 (10.0%)
Early relapse (<6 months)	
Number of patients	6 (20.0%)
Median duration of CR1 (range)	32 days (29-45)

*Data cut-off Nov 1<sup>st</sup>, 2019*

# Flotetuzumab: Phase 1/2 Population Safety

Treatment Related Adverse Events*	Total RP2D Population (n=50)		Refractory Population (n=30)	
	All n (%)	Grade ≥ 3 n (%)	All n (%)	Grade ≥ 3 n (%)
Infusion related reaction (IRR)/ Cytokine release syndrome (CRS)	48 (96.0)	4 (8.0)	30 (100)	1 ( 3.3)
Nausea	13 (26.0)		7 (23.3)	
Pyrexia	11 (22.0)		6 (20.0)	
Diarrhea	11 (22.0)		5 (16.7)	
Edema peripheral	10 (20.0)	1 ( 2.0)	6 (20.0)	
Hypotension	8 (16.0)		4 (13.3)	
Myalgia	8 (16.0)	2 ( 4.0)	4 (13.3)	
Arthralgia	7 (14.0)	1 ( 2.0)	4 (13.3)	
Dyspnea	9 (18.0)	3 ( 6.0)	2 (6.7)	2 (6.7)
Alanine aminotransferase increased	7 (14.0)	2 ( 4.0)		
C-reactive protein increased	6 (12.0)	2 ( 4.0)		
Fatigue	6 (12.0)	1 ( 2.0)		
Rash	6 (12.0)		4 (13.3)	
Lymphocyte count decreased	8 (16.0)	7 (14.0)		
White blood cell count decreased	8 (16.0)	7 (14.0)	5 (16.7)	4 (13.3)
Anemia	8 (16.0)	7 (14.0)	4 (13.3)	4 (13.3)
Platelet count decreased	7 (14.0)	7 (14.0)	4 (13.3)	4 (13.3)

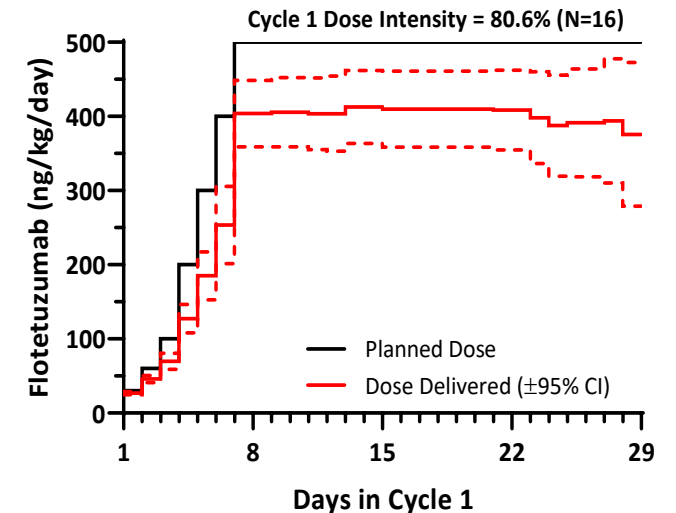
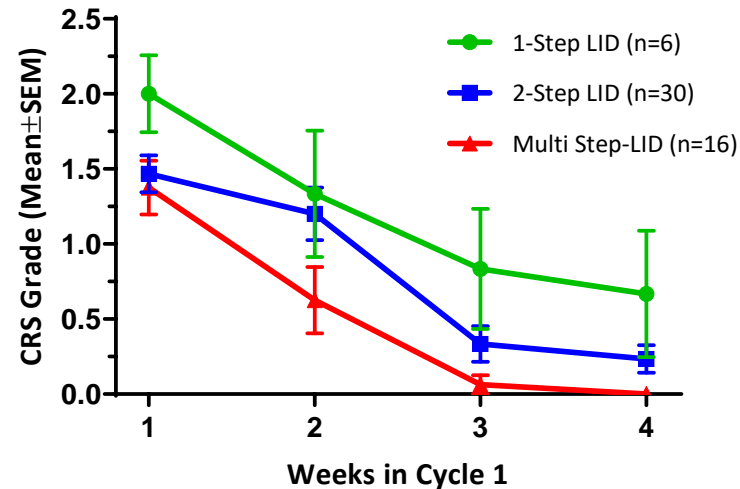
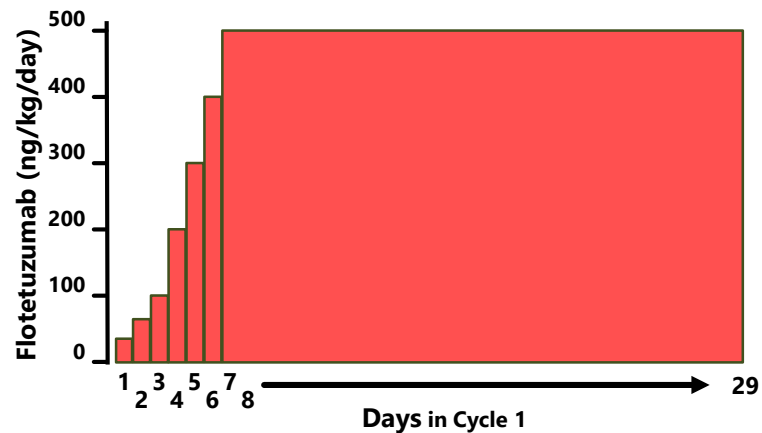
Data cut-off Nov 1<sup>st</sup>, 2019

\*Events occurring >10%; Toxicity grading is based on CTCAE criteria version 4.0. Toxicity grading for events of IRR/CRS is based upon the modified grading scale proposed by Lee et al.

# Flotetuzumab: Strategy for Mitigation of Cytokine Release Syndrome

*Several key interventions have helped mitigate CRS severity*

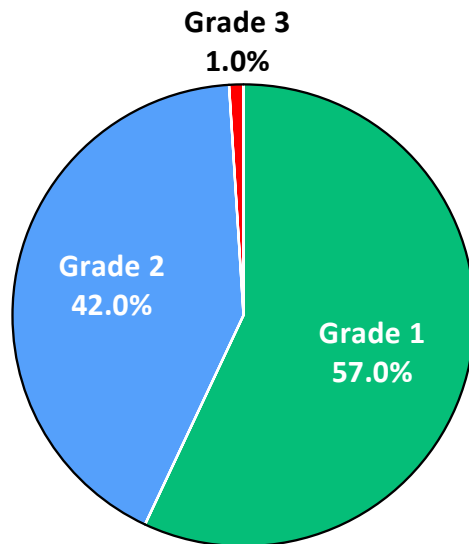
- Introduction of early use of tocilizumab to forestall CRS development and limit use of more aggressive treatments
- Sequential increment in steps of lead-in dose (LID) schedules (from 1 step, to 2-step, to multi-step LID) have decreased CRS severity and incidence and increased the total flotetuzumab dose administered (dose intensity)



# CRS Events Were Mild to Moderate in Severity in the PIF & Early Relapse AML

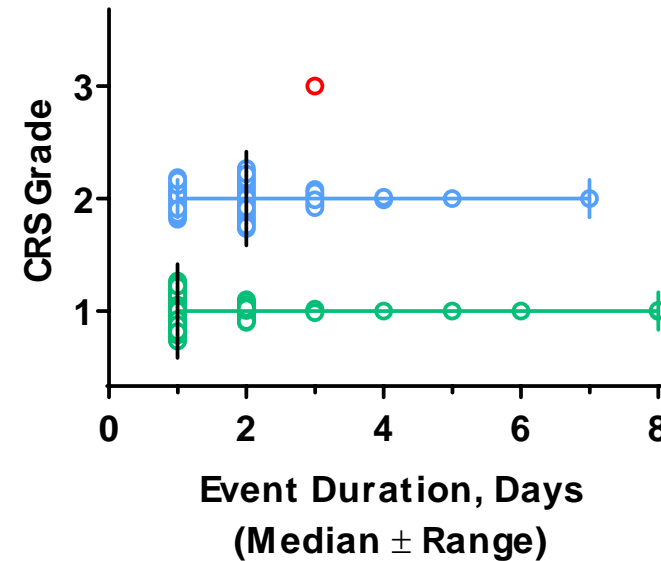
*CRS was conservatively managed*

Distribution of CRS Events by Grade



There were no grade 4 events

Duration of CRS Events by Grade



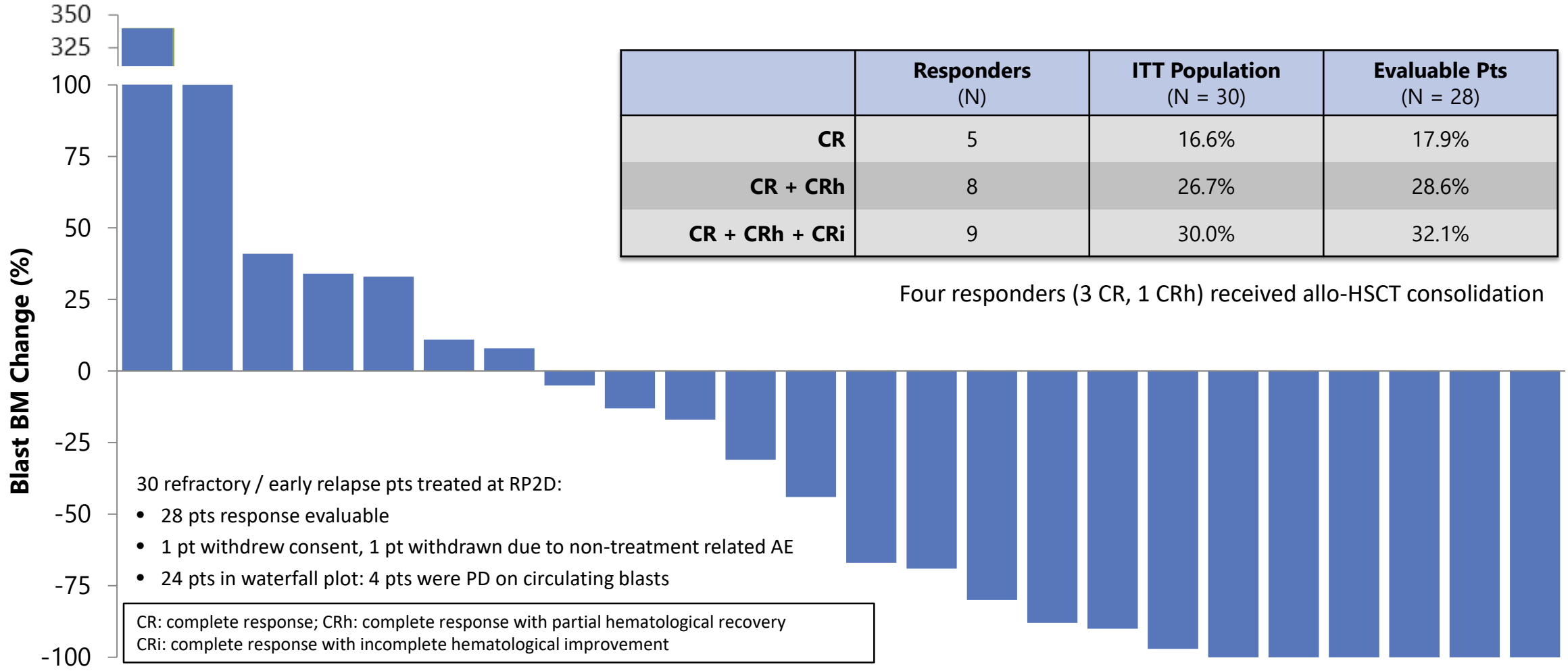
CRS events were of short duration.

Median duration: Grade 1 = 1 day; Grade 2 = 2 days; Grade 3 = 3 days

- 19/30 patients received tocilizumab (10 doses for G1, 15 doses for G2, and 1 dose for G3 events)
- 5/30 patients have required steroids (3 doses for G1 and 3 doses for G2 events)
- 2/30 patients have required vasopressors (3 doses for G2 events)

# Flotetuzumab is Active in Primary Induction Failure & Early Relapsed AML Patients

Benchmark analysis suggests historical CR+CRh rates in this setting of ~12.5% <sup>1</sup>



Data cut-off Nov 1, 2019

1. Unpublished analysis of the CLASSIC I, VALOR, ADMIRAL trials and additional trials that included venetoclax, gemtuzumab-ozogamicin, and IDH1/2 inhibitors; (n=1328): CR/CRh = 12.5% [95% CI = 7.7%, 19.6%]

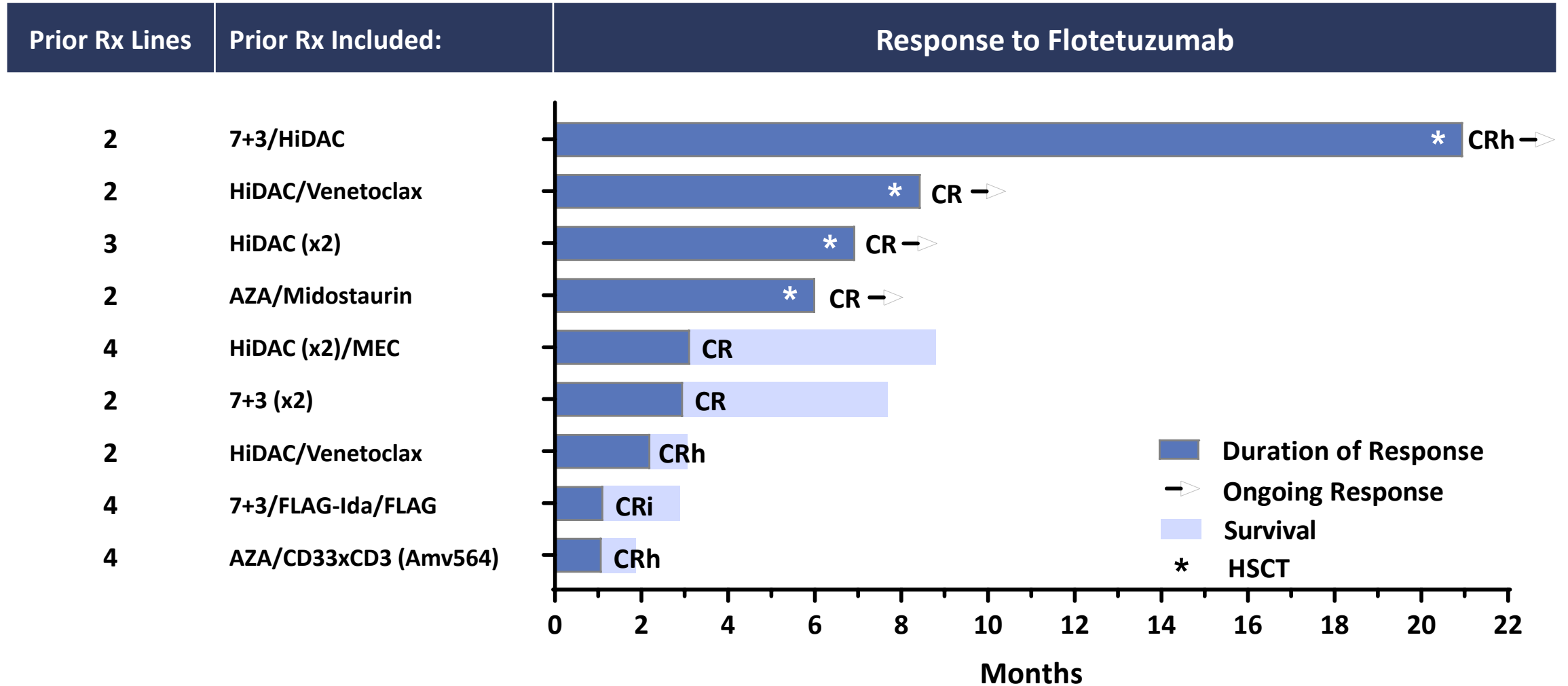
# Response to Flotetuzumab after Prior Lines of Therapy in PIF & Early Relapse AML

*Greater response rates accrued in patients with up to 4 lines of prior therapy*

Prior Lines of Tx	Flotetuzumab (CR/CRh/CRi Rate)	
	Fractional	Cumulative
2	55.6% (5/9)	
3	25.0% (1/4)	46.2% (6/13)
4	37.5% (3/8)	42.9% (9/21)
≥5	0.0% (0/7)	32.1% (9/28)

*Data cut-off Nov 1, 2019*

# Flotetuzumab: Duration of Response in PIF & Early Relapsed AML Patients



Data cut-off Nov 1, 2019



# Conclusions

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- Flotetuzumab treatment in AML showed a manageable safety profile:
  - Lead-in dosing strategies and early tocilizumab usage have helped to blunt the severity of CRS
- An IFN-related gene-expression signature in baseline BM was associated with resistance to cytotoxic chemotherapy and response to flotetuzumab
- Flotetuzumab elicited clinical response (~30% CR/CR/CRi) in heavily pretreated patients who failed AML induction therapy or showed early relapse within 6 months of induction therapy
  - Historical data indicate a best response to salvage therapy of ~12.5%
- Enrollment has been expanded in patients with primary induction failure and early relapse AML
  - Parallel analysis will continue to identify flotetuzumab response-associated biomarkers

# Acknowledgements

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*We are grateful to the patients who participated in this study and their families*

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