Flotetuzumab as Salvage Therapy for Primary Induction Failure and Early Relapse Acute Myeloid Leukemia

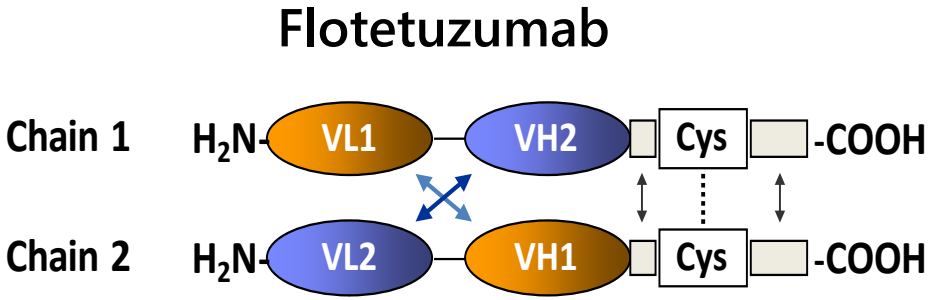
Ibrahim Aldoss, MD; Geoffrey L. Uy, MD; Norbert Vey, MD, PhD; Ashkan Emadi, MD, PhD; Peter H. Sayre, MD, PhD; Roland B. Walter, MD, PhD, MS; Matthew C Foster, MD; Martha L. Arellano, MD; John E. Godwin, MD; Matthew J. Wieduwilt, MD, PhD; Michael Byrne, DO; Laura Michaelis, MD; Patrick J. Stiff, MD; Matteo Giovanni Carrabba, MD; Patrice Chevallier, MD, PhD; Emmanuel Gyan, MD, PhD; Christian Recher MD, PhD; Anjali S. Advani, MD; Martin Wermke, MD; Harry Erba, MD, PhD; Fabio Ciceri, MD; Gerwin A Huls, MD, PhD; Mojca Jongen-Lavrencic, MD, PhD; Max S. Topp, MD, PhD; Farhad Ravandi, MD; Stefania Paolini, MD; Antonio Curti, MD, PhD; Michael P. Rettig, PhD; John Muth, MS; Teia Curtis, BA; Marybeth Collins, BS; Erin Fehr, BS; Kuo Guo, MSc; Jian Zhao, PhD; Kathy Tran, BS; Patrick Kaminker, PhD; Priyanka Patel, Pharm D.; Ouiam Bakkacha, MD; Kenneth Jacobs, MD; Maya Kostova, PhD; Jennifer Seiler, PhD, RAC; Bob Löwenberg, MD, PhD; Sergio Rutella, MD, PhD, FRCPath; Ezio Bonvini, MD; Jan K Davidson-Moncada, MD, PhD; John F. DiPersio, MD, PhD

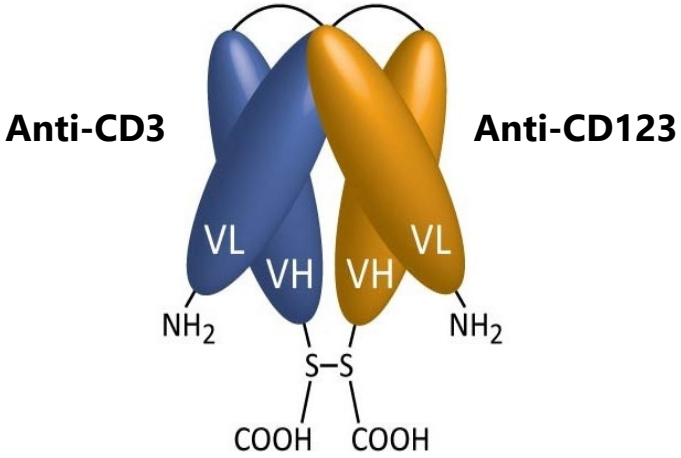
ClinicalTrials.gov #NCT02152956 Abstract # 331

Disclosures

Flotetuzumab (MGD006): CD123 × CD3 Bispecific DART® Molecule

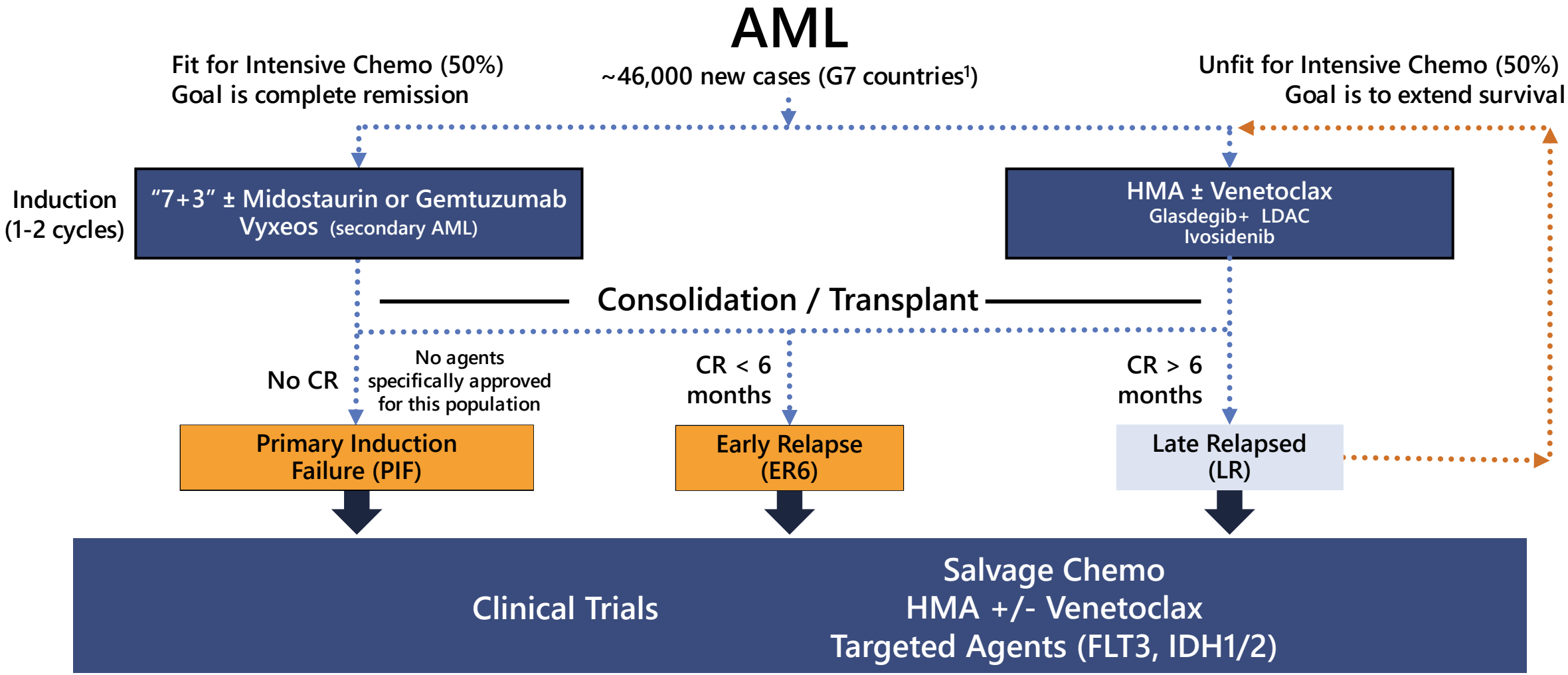
- CD123: low-affinity IL-3 receptor (IL3Rα)
  - Normally expressed on plasmacytoid dendritic cells (pDCs), basophils, monocytes and hematopoietic progenitor cells (HPCs)
  - Over-expressed on leukemic stem cells (LSCs) in AML and other hematologic malignancies
- Flotetuzumab:
  - Investigational bispecific 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
  - Phase 1 dose escalation completed[1]
  - Patients currently being enrolled in registrational study





(1) Uy, et al., Blood 2020

~50% of AML Patients Are Refractory to Induction Therapy or Have Short Remission



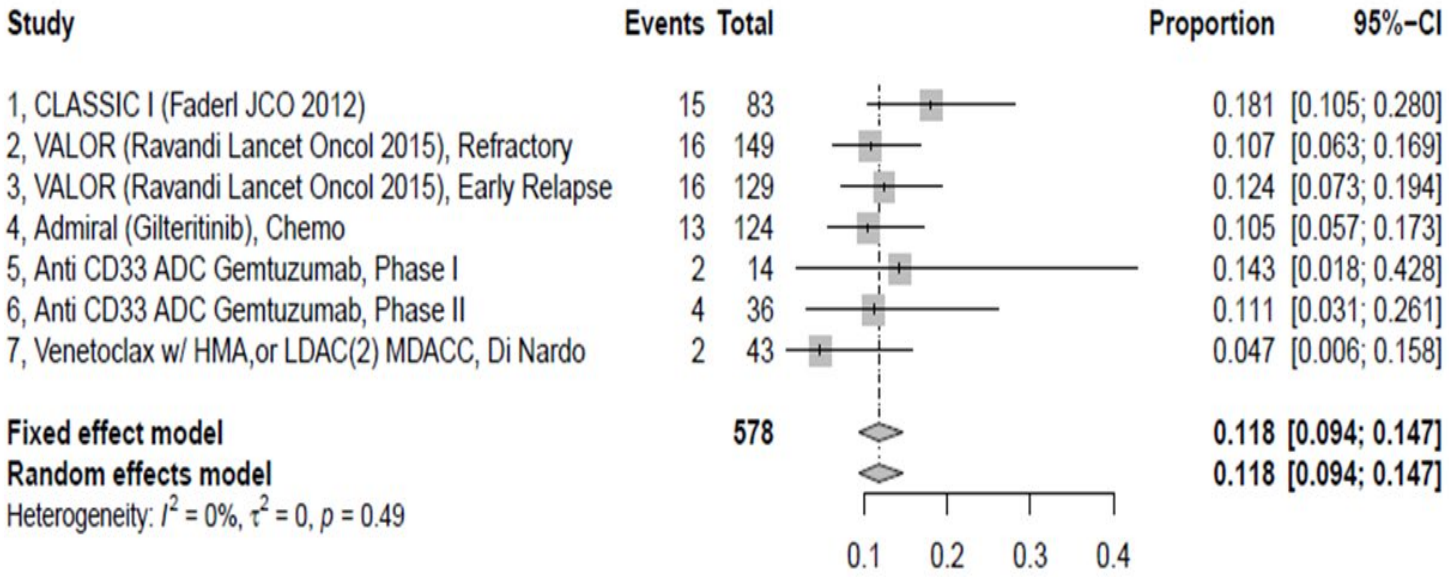
(1) G7 countries: Canada, France, Germany, Italy, Japan, United Kingdom and United States

Historical CR/CRh Rates in PIF/ER6 Range from 5% to 12%

Median expected overall survival of ~3.5 months

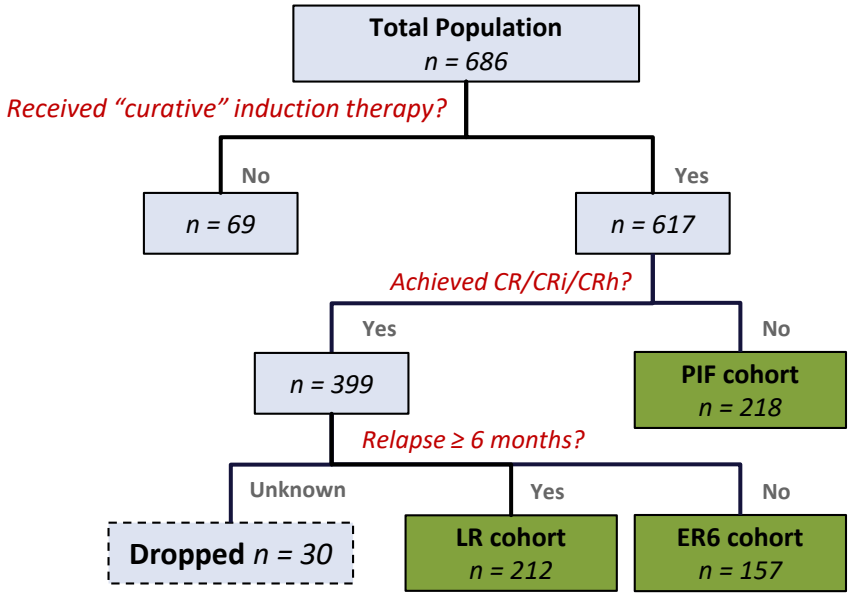
Meta-analysis of PIF/ER6 Pts (n=1328) Extracted From Published Reports[1]

CR/CRh is 11.7% [95% CI = 9.2%, 14.6%]



Aggregate PIF/ER6 Data from Clinical Trials (n=686)

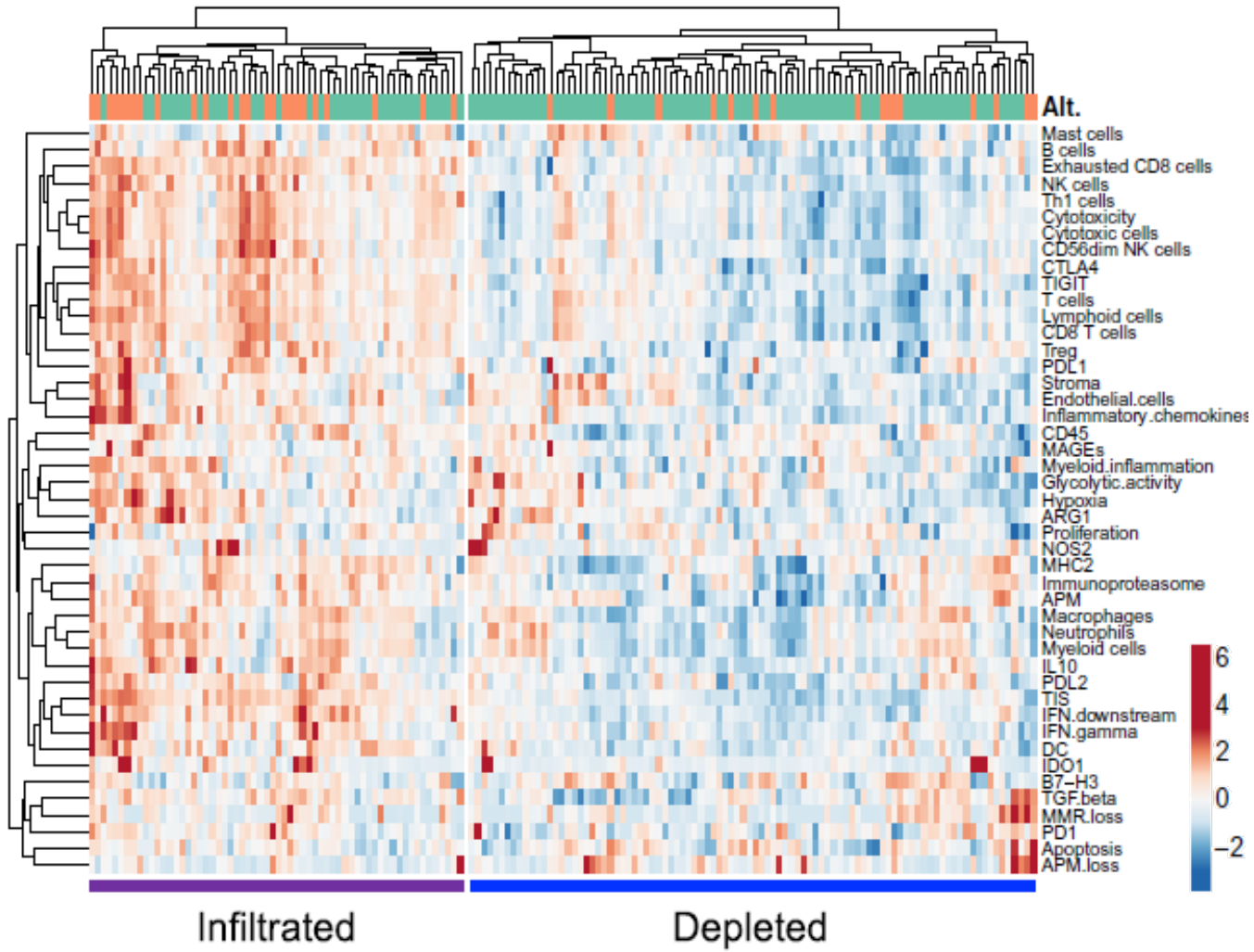
CR/CRh is 5.3%

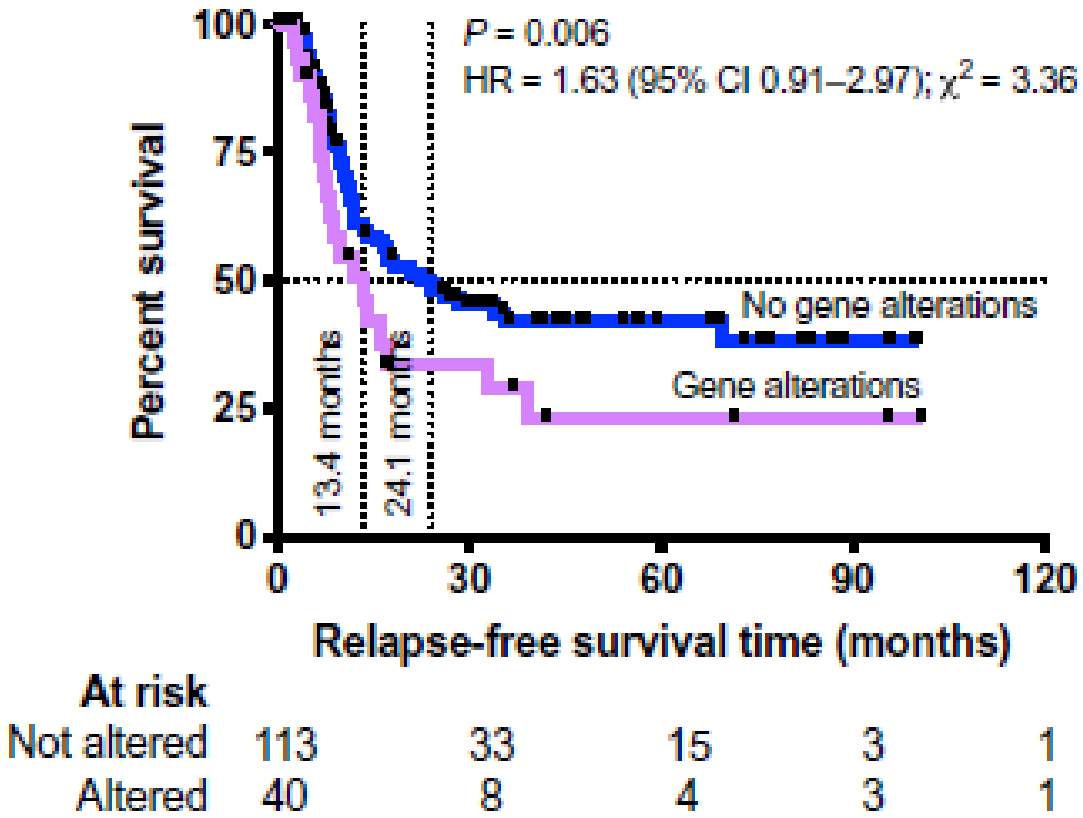


	PIF	ER6	LR
CR/CRh	4.1% (9)	7.0% (11)	11.4% (22)
	5.3% (20)		

(1) Unpublished analysis of CLASSIC I, VALOR, ADMIRAL trials and add'l trials that included venetoclax, mylotarg

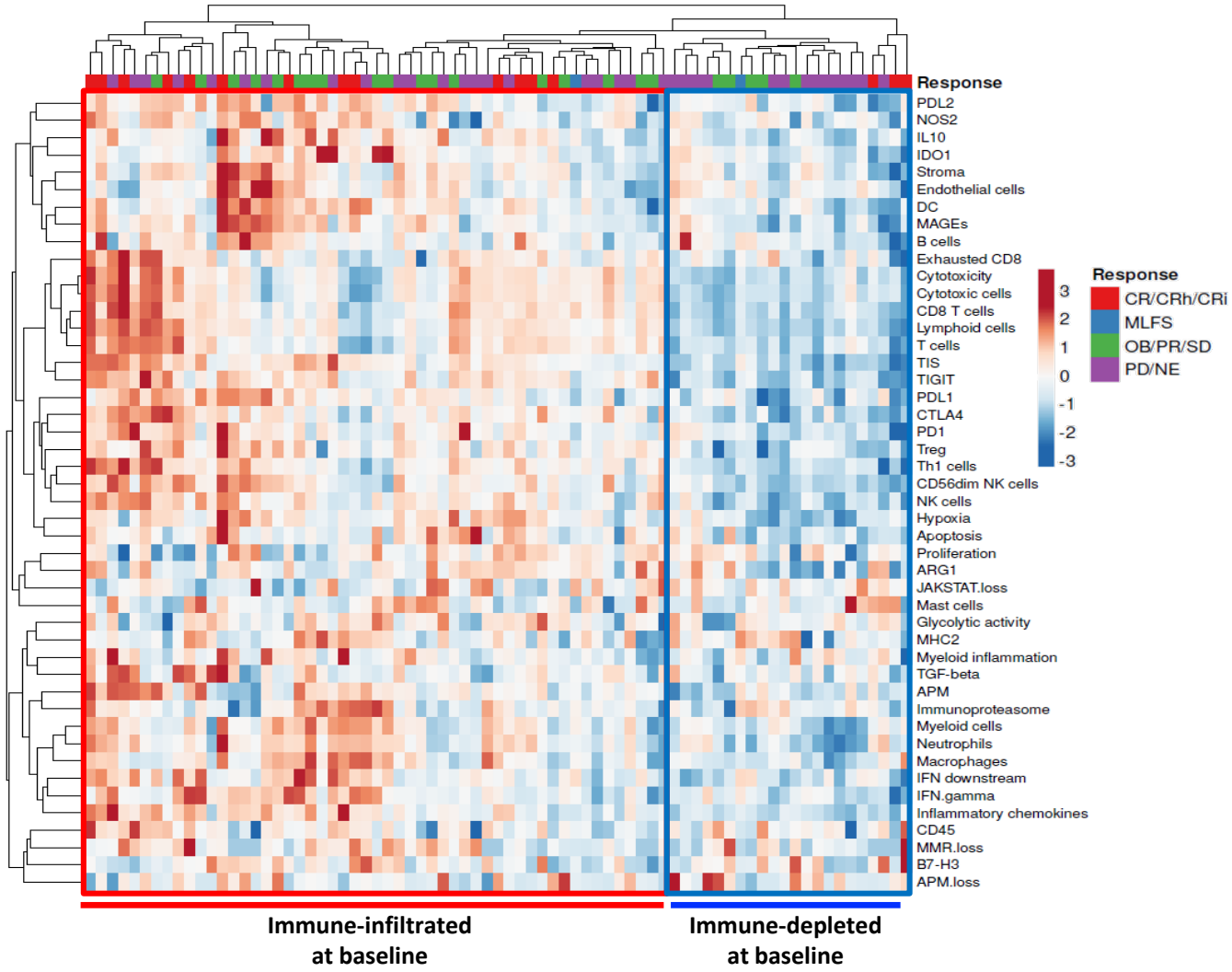
TME Immune Infiltration Associated with Cytarabine-Based Induction Failure





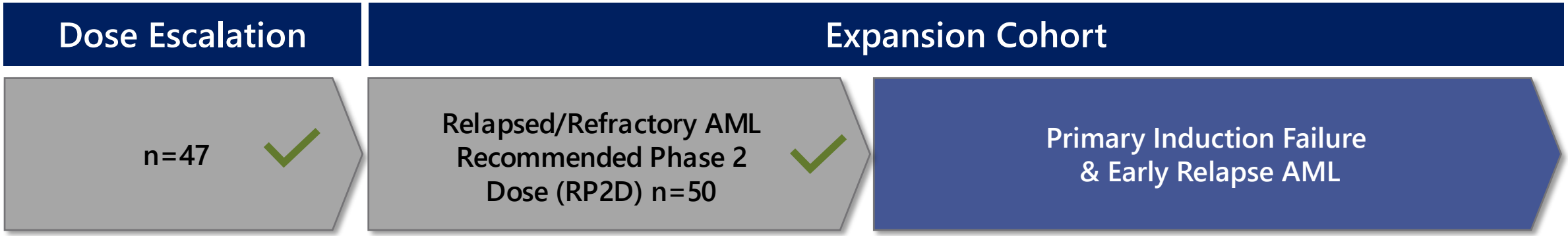
Vadakekolathu J, et al. Sci Trans Med 2020

TME Immune Infiltration Associated with Responsiveness to Flotetuzumab



% (n)	Immune Infiltrated (n=53)	Immune Depleted (n=22)
Population:		
PIF	52.8% (28)	18.2% (4)
ER6	13.2% (7)	18.2% (4)
LR	34.0% (18)	63.6% (14)
Response:		
CR/CRh/CRi	24.5% (13)	13.6% (3)
Median BM change (%)	-54%	+20%

Flotetuzumab in PIF/ER6 AML: Design of Ongoing Registrational Study



Key Entry Criteria

- **Primary Induction Failure (PIF):** refractory to cytarabine-based chemotherapy, venetoclax-based combinations or gemtuzumab ozogamicin
- **Early relapse (ER6):** First relapse with initial CR duration of < 6 months
- Maximum of 3 prior lines of therapy
- No prior allogeneic hematopoietic cell transplant

Study Objectives

- Primary: Complete remission (CR) and/or complete remission with partial hematologic recovery (CRh) rate
- Secondary: mDOR, rate of transfusion independence, time in hospital

Flotetuzumab in PIF/ER6 AML: Demographics

Analysis of all PIF/ER pts (per previous definition) treated at RP2D[1]

Characteristic	Population (n=44)[2]
Age, Median (range)	63.5 (28.0, 81.0)
Gender, Female	13 (29.5)
Disease Status at Study Entry	
Primary Induction Failure	27 (61.4)
Cytarabine based induction chemotherapy	20 (74.1)
Alternative induction therapy	7 (25.9)
Early Relapse	17 (38.6)
Median duration of CR1 (range)	3.3 months (0.8-5.7)
ELN Risk Stratification (2017)	
Adverse	32 (72.7%)
Intermediate	11 (25.0%)
Favorable	1 (2.3%)
Secondary AML	16 (36.4%)
Number of Prior Lines of Therapy, median (range)	2.0 (1.0, 3.0)
Baseline BM Blasts Median (Range)[3]	34.5 (5.0, 84)

(1) Recommended Phase 2 Dose = multistep-LID C1W1 followed by 500ng/kg/day continuous infusion through induction
(2) Including ruxolitinib mini-cohort – see Abstract # 2817: "Prophylactic Ruxolitinib for Cytokine Release Syndrome (CRS) in Relapse/Refractory (R/R) AML Patients Treated with Flotetuzumab"
(3) A patient confirmed with AML by IHC not included in baseline BM analysis

Data cut-off Nov 10th, 2020

Flotetuzumab in PIF/ER6 AML: Safety

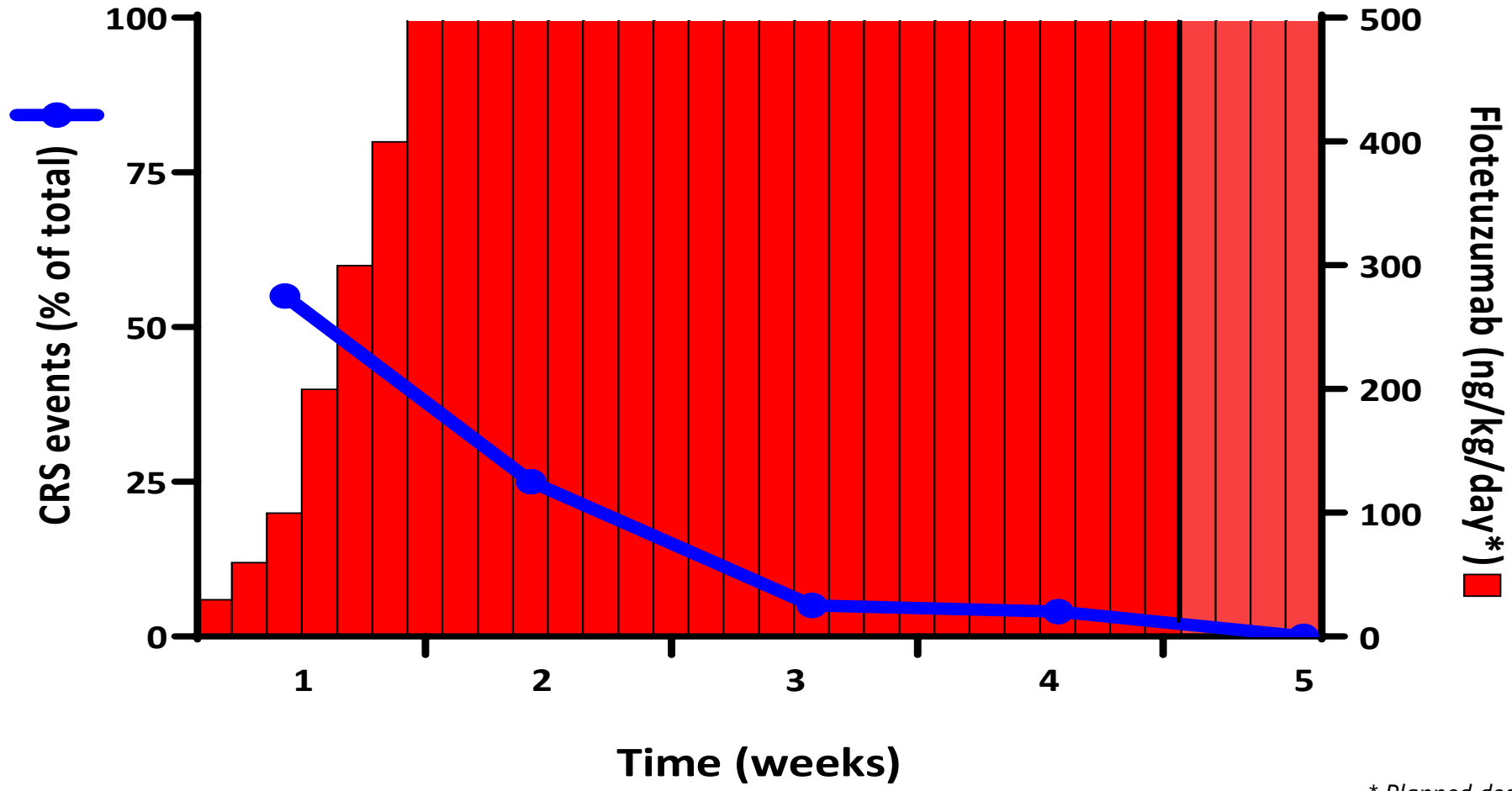
Treatment Related Adverse Events[1]	Total RP2D Population (n=44)	
	All n (%)	**Grade ≥ 3** n (%)
IRR/CRS[2]	44 (100)	1 (2.3)
Rash	17 (38.6)	
Arthralgia	11 (25.0)	
Diarrhoea	9 (20.5)	2 (4.5)
Nausea	9 (20.5)	
Pyrexia	8 (18.2)	
Decreased appetite	8 (18.2)	
Oedema peripheral	7 (15.9)	
Febrile neutropenia	6 (13.6)	6 (13.6)
Fatigue	6 (13.6)	1 (2.3)
Alanine aminotransferase increased	6 (13.6)	2 (4.5)
Aspartate aminotransferase increased	6 (13.6)	1 (2.3)
Headache	5 (11.4)	
Myalgia	5 (11.4)	

(1) Events occurring >10%; Toxicity grading is based on CTCAE criteria version 4.0
(2) Toxicity grading for events of IRR/CRS (infusion-related reaction and cytokine release syndrome) is based upon modified grading scale proposed by Lee, et al.

Data cut-off Nov 10th, 2020

CRS Frequency Decreased with Time on Treatment

- *Most CRS events (52%) occurred in first week of treatment during step-up dosing*
- Incidence of CRS progressively decreased during dosing, allowing outpatient treatment after day 8



** Planned dose; Data cut-off Nov 10th, 2020*

Neurologic Events Are of Short Duration and Fully Reversible

- *Neurologic AEs have been infrequent, and mostly mild to moderate in severity*
- *Three pts experienced Grade 3 confusion of short duration (1-2 days) that was fully reversible*

Neurological and Psychiatric Adverse Events[1] (n=44)	All Adverse Events n (%)		Treatment Related AEs n(%)	
	All	Grade ≥ 3	All	Grade ≥ 3
Headache	13 (29.5)		5 (11.4)	
Dizziness	9 (20.5)	1 (2.3)	3 (6.8)	1 (2.3)
Insomnia	8 (18.2)			
Confusional state	7 (15.9)	3 (6.8)	3 (6.8)	3 (6.8)
Anxiety	7 (15.9)		1 (2.3)	
Paraesthesia	4 (9.1)		2 (4.5)	
Tremor	4 (9.1)		2 (4.5)	
Depression	4 (9.1)	1 (2.3)		
Lethargy	3 (6.8)			

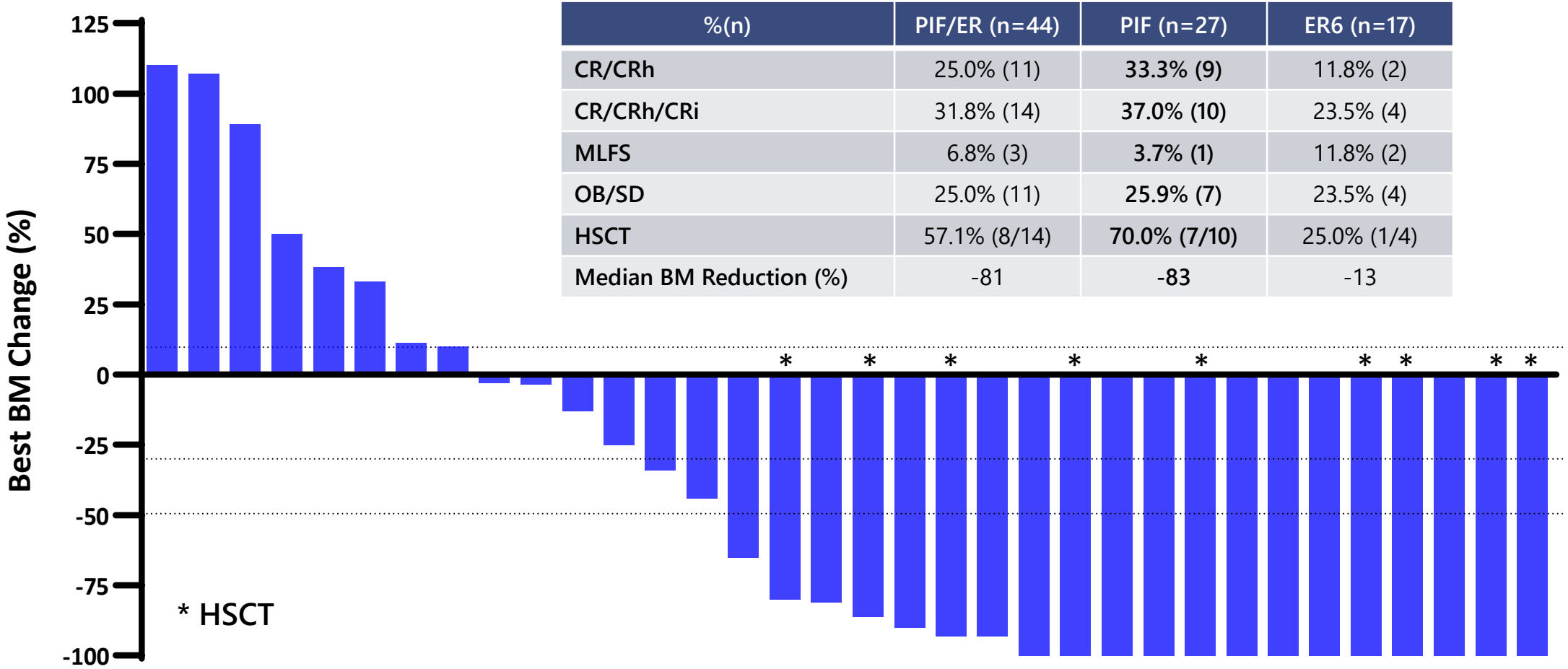
(1) Events occurring ≥2 individuals; Toxicity grading is based on CTCAE criteria version 4.0

Data cut-off Nov 10th, 2020

Flotetuzumab: Active in Primary Induction Failure & Early Relapsed AML Patients

- *59.1% (26/44) of pts had evidence of reduction in blast count with median decrease of 81.0% in BM blasts*
- *Median time to first response was 1 cycle (range: 1-3 cycles)*

%(n)	PIF/ER (n=44)	PIF (n=27)	ER6 (n=17)
CR/CRh	25.0% (11)	**33.3% (9)**	11.8% (2)
CR/CRh/CRi	31.8% (14)	**37.0% (10)**	23.5% (4)
MLFS	6.8% (3)	**3.7% (1)**	11.8% (2)
OB/SD	25.0% (11)	**25.9% (7)**	23.5% (4)
HSCT	57.1% (8/14)	**70.0% (7/10)**	25.0% (1/4)
Median BM Reduction (%)	-81	**-83**	-13



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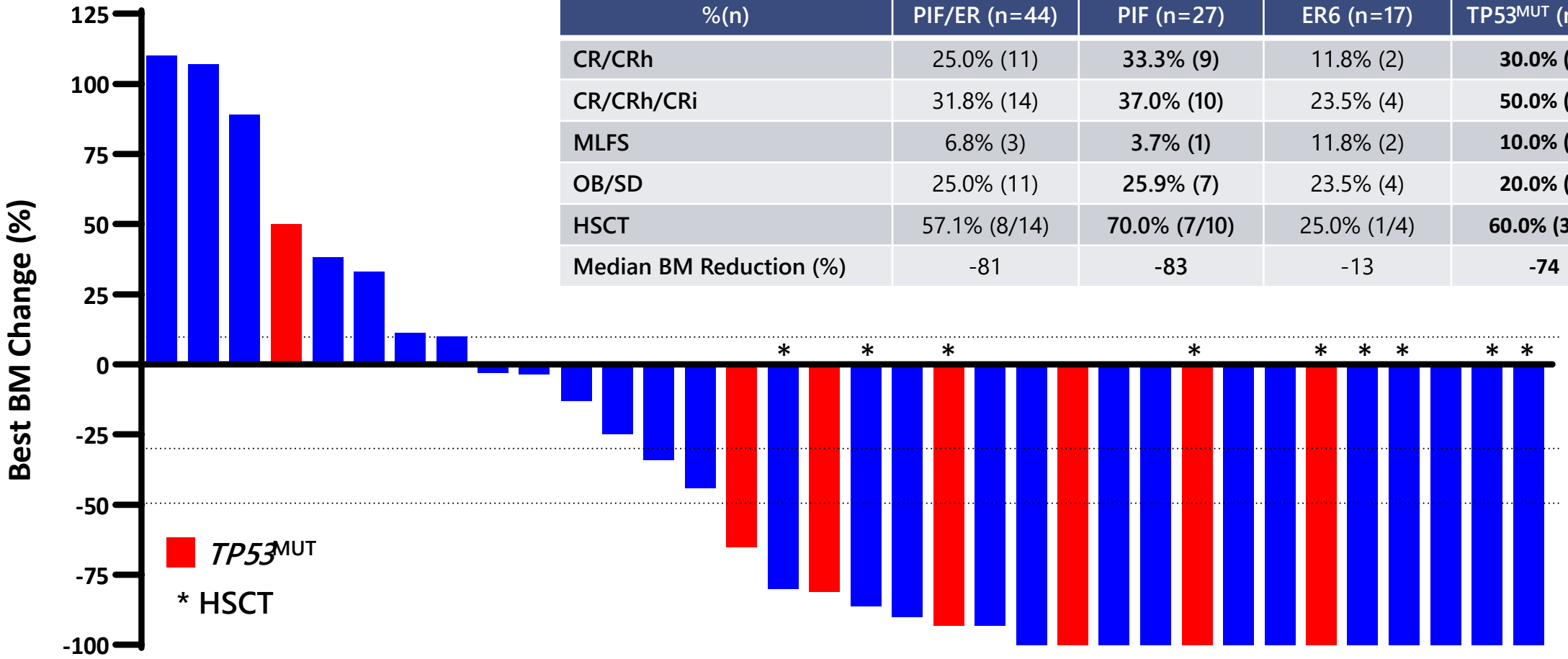
Flotetuzumab: Active in TP53^{MUT} PIF/ER6 AML Patients

- *59.1% (26/44) of pts had evidence of reduction in blast count with median decrease of 81.0% in BM blasts*
- *Median time to first response was 1 cycle (range: 1-3 cycles)*

%(n)	PIF/ER (n=44)	PIF (n=27)	ER6 (n=17)	TP53^{MUT} (n=10)
CR/CRh	25.0% (11)	**33.3% (9)**	11.8% (2)	**30.0% (3)**
CR/CRh/CRi	31.8% (14)	**37.0% (10)**	23.5% (4)	**50.0% (5)**
MLFS	6.8% (3)	**3.7% (1)**	11.8% (2)	**10.0% (1)**
OB/SD	25.0% (11)	**25.9% (7)**	23.5% (4)	**20.0% (2)**
HSCT	57.1% (8/14)	**70.0% (7/10)**	25.0% (1/4)	**60.0% (3/5)**
Median BM Reduction (%)	-81	**-83**	-13	**-74**



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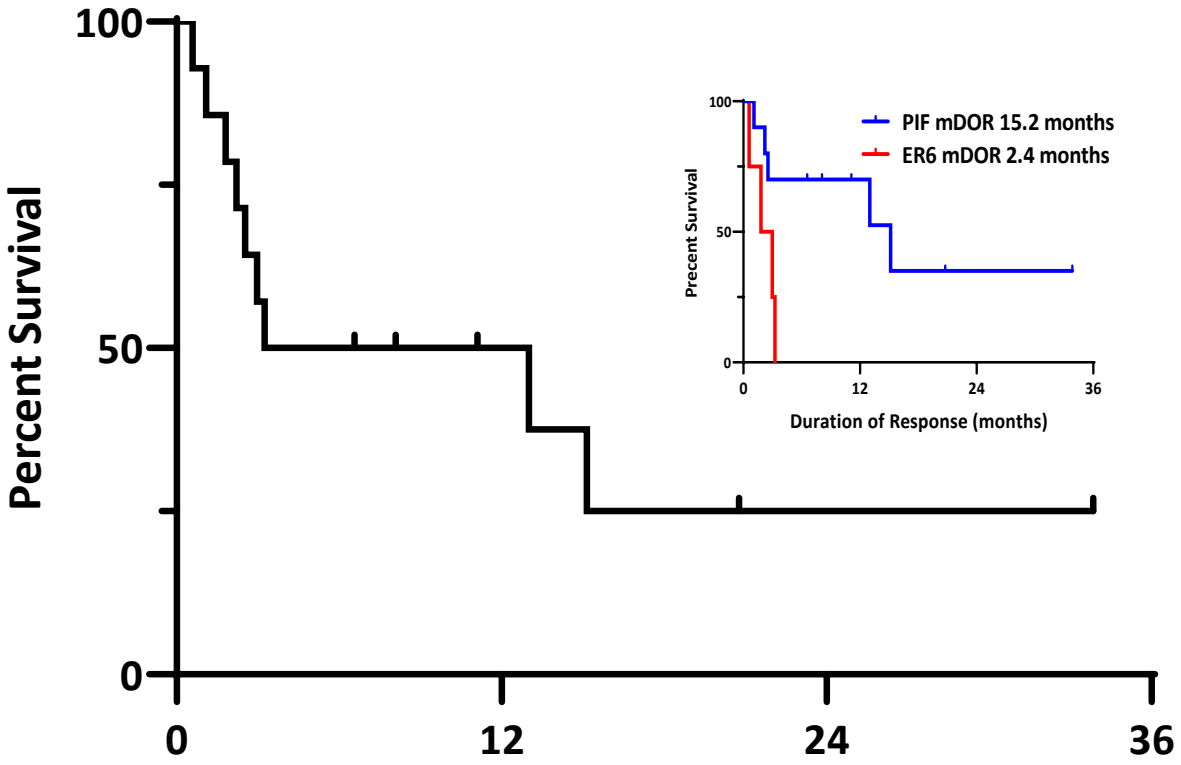
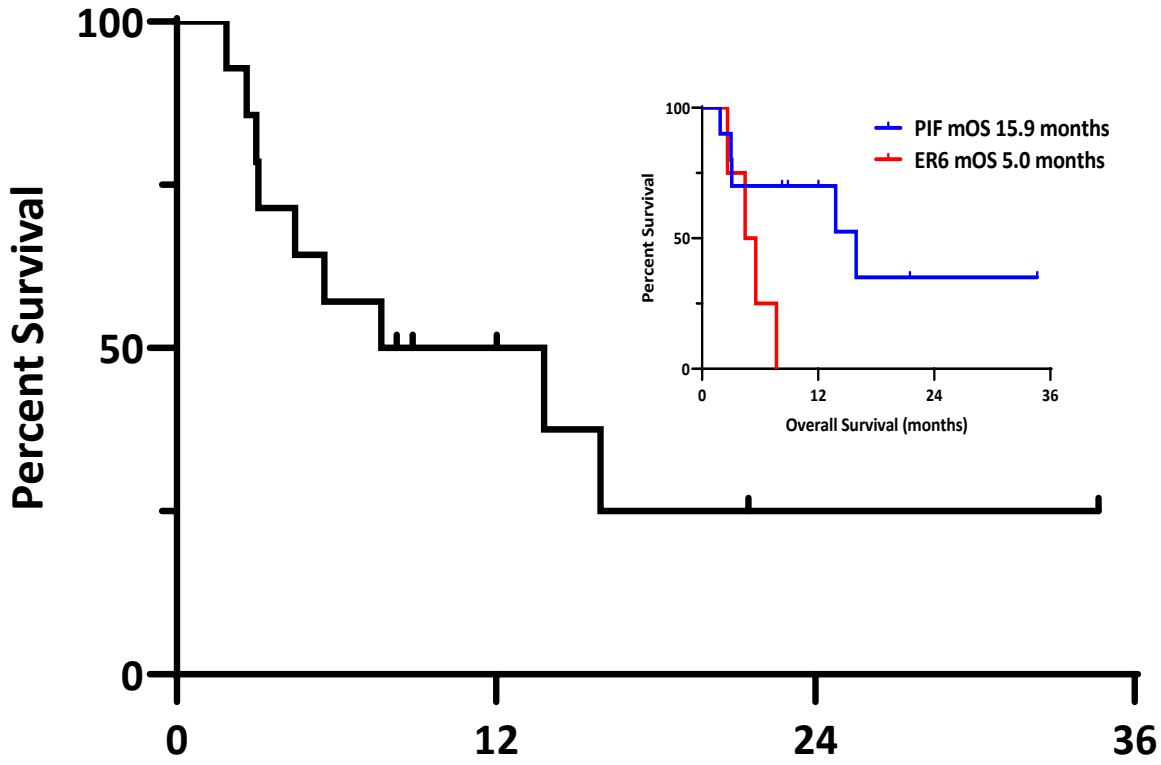
Poster Presentation Abstract ID# 136919: TP53 Abnormalities Correlate with Immune Infiltration and Associate with Response To Flotetuzumab Immunotherapy In Acute Myeloid Leukemia

Duration of Response & Overall Survival in PIF/ER6 AML Responders (CR/CRh/CRi)

Duration of Response (months)
mDOR 8.13 months



Overall Survival (months)
mOS 10.7 months



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Conclusions

- Flotetuzumab treatment in AML showed manageable safety profile
  - Manageable CRS and minimal neurological toxicity
  - Single patient with Grade 3 IRR/CRS
  - Required minimum 8-day inpatient hospitalization
- Flotetuzumab demonstrated encouraging activity in patients with PIF/ER6 AML, a population with poor prognosis and high unmet medical need
  - 31.8% Complete remission rate (CR/CRh/CRi), over half of those went on to successful stem cell transplant
  - Historical data indicate CR/CRh rate to salvage therapy of 5-12% for PIF/ER6 AML patients
- Registrational study is currently enrolling PIF/ER6 AML patients [NCT02152956]

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NANOSTRING
Sarah E. Church
Tressa Hood
Sarah E. Warren

EARLE A. CHILES RESEARCH INSTITUTE
A division of Providence Cancer Center

Carmen Ballesteros-Merino
Carlo B. Bifulco
Bernard A. Fox

JVGCRC, NTU

NTU

Sergio Rutella
Stephen Reeder (GEP)
Jayakumar Vadakekolathu (GEP)

MacroGenics Study Team

Please email your questions to ialdoss@coh.org