MacroGenics®

Developing
Breakthrough Biologics,
Life-changing Medicines

ASH 2019 Conference Call: Flotetuzumab

December 9, 2019

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Welcome & Introduction

Scott Koenig, M.D., Ph.D.

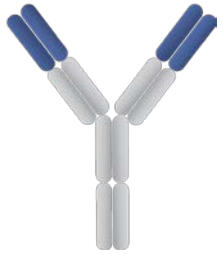
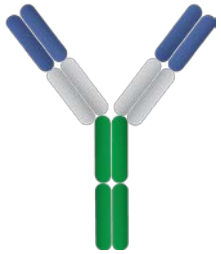
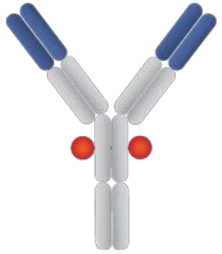
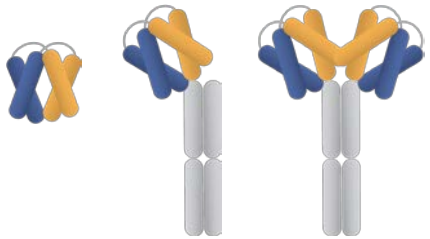
President and Chief Executive Officer, MacroGenics

ASH 2019 Flotetuzumab Conference Call Agenda

Welcome & Introduction	**Scott Koenig, M.D., Ph.D.** President & Chief Executive Officer
Immune Landscapes: Chemotherapy Resistance and Anti-Leukemic Activity of Flotetuzumab in Patients with Relapsed/Refractory AML	**Sergio Rutella, M.D., Ph.D., FRCPath** Professor, Cancer Immunotherapy, John van Geest Cancer Research Centre, Nottingham Trent University, UK
Acute Myeloid Leukemia (AML): Current Treatment Paradigm **Flotetuzumab Clinical Update:** Salvage Therapy for Primary Refractory and Early Relapsed AML Patients	**Geoff Uy, M.D.** Associate Professor, Bone Marrow Transplantation & Leukemia, Washington University School of Medicine, St. Louis
Future Development	**Jan Davidson-Moncada, M.D., Ph.D.** Senior Clinical Research Director
Key Takeaways	**Scott Koenig, M.D., Ph.D.** President & Chief Executive Officer
Q&A	

MacroGenics is Committed to Developing Life-changing Medicines

- Engineering antibodies that leverage the immune system to fight cancer
- A leader in bispecific antibodies, including redirected T-cell killing
  - Flotetuzumab (CD3 x CD123 bispecific DART® molecule) being developed in acute myeloid leukemia (AML)

Antibody	Fc-Optimized Antibody	Antibody Drug Conjugate	DART® Molecules
			
• MGA012 (anti-PD-1)	• margetuximab (anti-HER2) • enoblituzumab (anti-B7-H3)	• MGC018 (anti-B7-H3)	• **flotetuzumab (CD123 x CD3)** • MGD013 (PD-1 x LAG-3) • MGD019 (PD-1 x CTLA-4) • MGD009 (B7-H3 x CD3) • MGD007 (gpA33 x CD3)

Immune Landscapes

Sergio Rutella, M.D., Ph.D., FRCPath

Professor, Cancer Immunotherapy, John van Geest Cancer Research Centre, Nottingham Trent University, UK

NOTTINGHAM TRENT UNIVERSITY

61st ASH Annual Meeting & Exposition
Orange County Convention Centre, Orlando, FL
December 7-10, 2019

Immune Landscapes Predict Chemotherapy Resistance and Anti-Leukemic Activity of Flotetuzumab, an Investigational CD123 × CD3 Bispecific DART® Molecule, in Patients with Relapsed/Refractory Acute Myeloid Leukemia

Sergio Rutella[1,2], Jayakumar Vadakekolathu[1], Mark D. Minden[3], Tressa Hood[4], Sarah E. Church[4], Stephen Reeder[1], Heidi Altmann[5], Amy H. Sullivan[4], Elena J. Viboch[4], Tasleema Patel[6], Narmin Ibrahimova[3], Sarah E. Warren[4], Andrea Arruda[3], Yan Liang[4], Marc Schmitz[7], Alessandra Cesano[4], Peter J.M. Valk[8], Bob Löwenberg[8], A. Graham Pockley[1], Martin Bornhäuser[5], Sarah K. Tasian[6], Michael P. Rettig[9], Jan Davidson-Moncada[10], John F. DiPersio[9]

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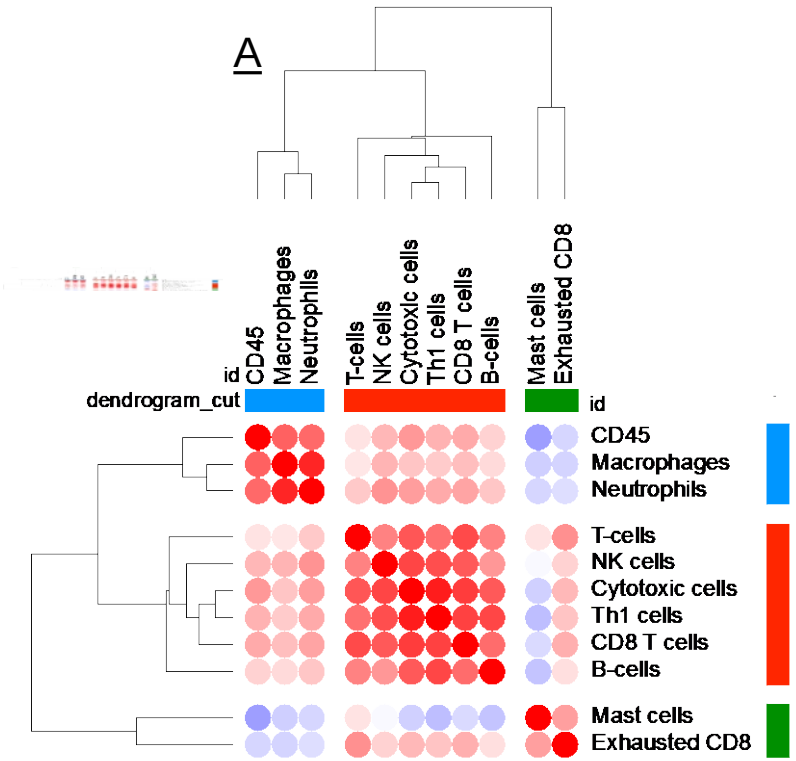
Background

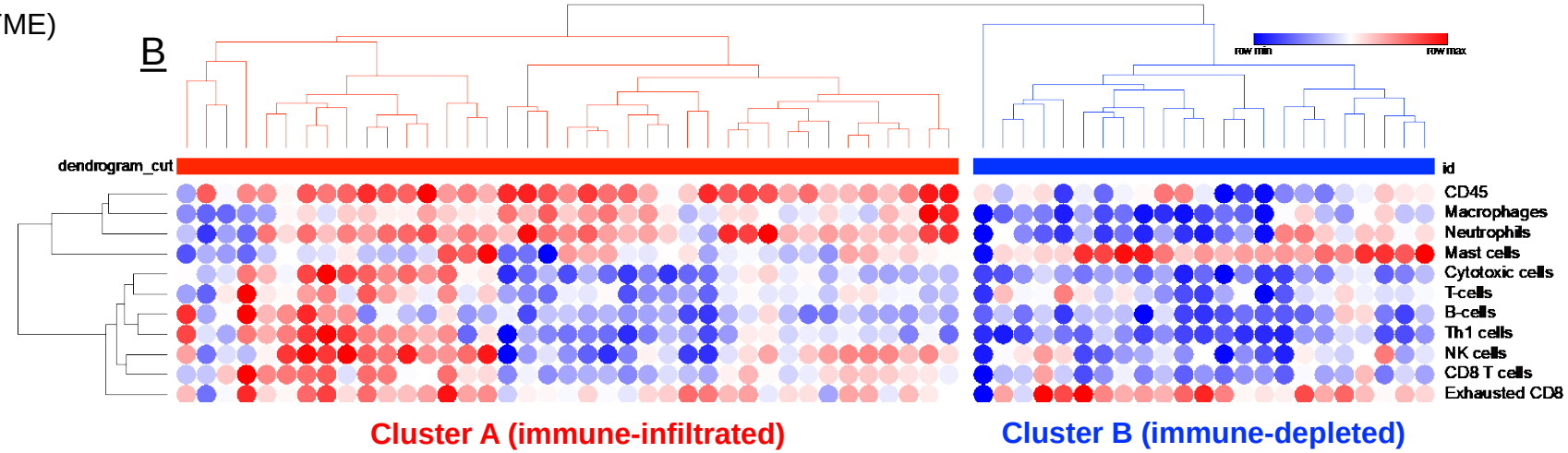
- Cytotoxic chemotherapy remains the standard-of-care for most patients with acute myeloid leukemia (AML), despite the recent approval of novel agents
- Immunotherapies such as monoclonal antibodies, bispecific molecules, immune checkpoint blockade (ICB) and CD123-CAR T cells are currently under investigation in AML
- There is an urgent need to identify predictive biomarkers in the tumor immunological microenvironment (TME)
  - IFN-γ-related mRNA profiles ("T cell-inflamed" GEP or "Tumor Inflammation Signature", TIS) predict response to pembrolizumab in multiple solid tumor types (Ayers M, et al. *JCI* 2017; Ott PA, et al. *JCO* 2019)
- Flotetuzumab, a CD123 × CD3 bispecific DART® molecule, is being tested in a phase 1 clinical trial of relapsed/refractory (R/R) AML (NCT#02152956)
- See also presentation #733. Monday, December 9, 2019: 2:45PM
  - Dr. Geoffrey Uy, Session #613. *Acute Myeloid Leukemia: Clinical Studies: Treatment of Relapsed/Refractory Disease*. Tangerine 3 (Orange County Convention Center)

Diversity of immune landscapes in AML

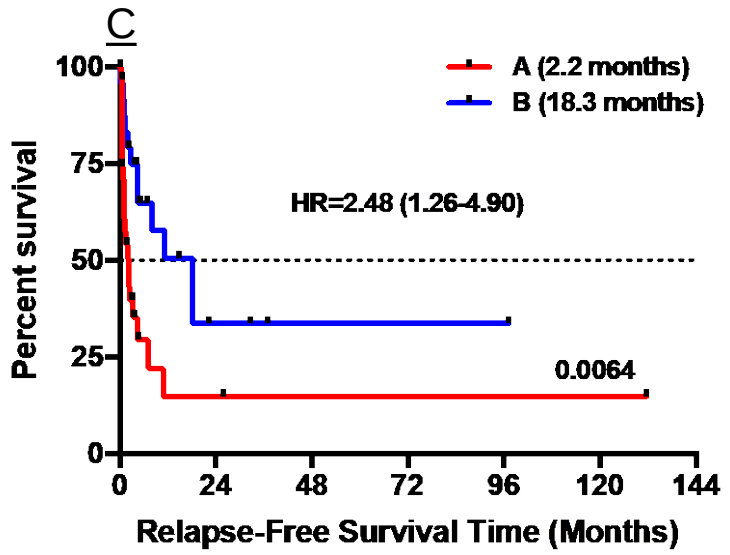
The AML tumour immunological microenvironment (TME)

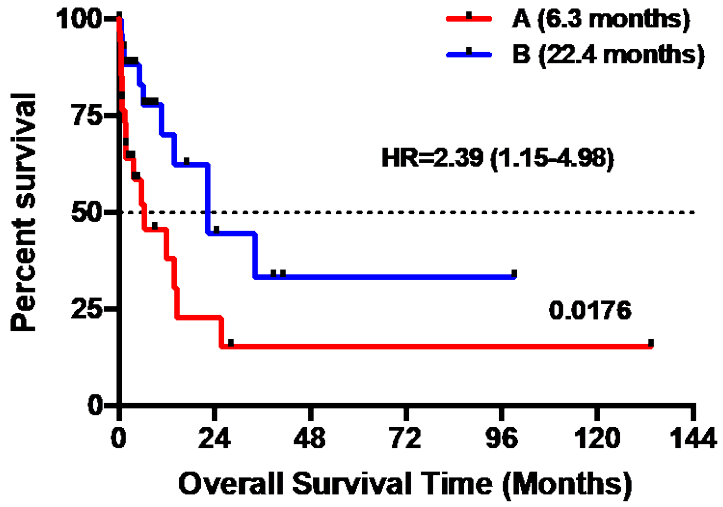
1. Innate (PMN, macrophages)
2. Adaptive (T, B, NK, CTL)
3. Mast cells, exhausted CD8⁺ T cells





Cluster A (immune-infiltrated) **Cluster B (immune-depleted)**





Discovery cohort (n=62)

34 non-promyelocytic *de novo* childhood AML
(Sarah K. Tasian, Children's Hospital of Philadelphia, USA)
28 non-promyelocytic *de novo* adult AML
(Martin Bornhäuser, Dresden, Germany)

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

Patient series and methods

Wet-lab cohorts

	PMCC*	CHOP^	SAL^^
Nr of patients	290	39	38
Age (y)	52 (18-81)	10 (0.1-20)	52.5 (23-75)
Disease status	Onset	Onset	Onset/CR/Relapse

In silico cohorts

HOVON	Beat AML Master Trial	TCGA
618	267	147
Adult	Adult	Adult
Onset	Onset	Onset

- The PanCancer Immune Profiling Panel (NanoString Technologies, Seattle, WA) was used to measure mRNA expression in bulk BM samples (n=770 immune-related genes)
- Immune signature scores and biological activity scores were calculated as pre-defined linear combinations (weighted averages) of biologically relevant gene sets
- Gene expression data have been deposited in NCBI's Gene Expression Omnibus and will be accessible through GEO Series accession number GSE134589

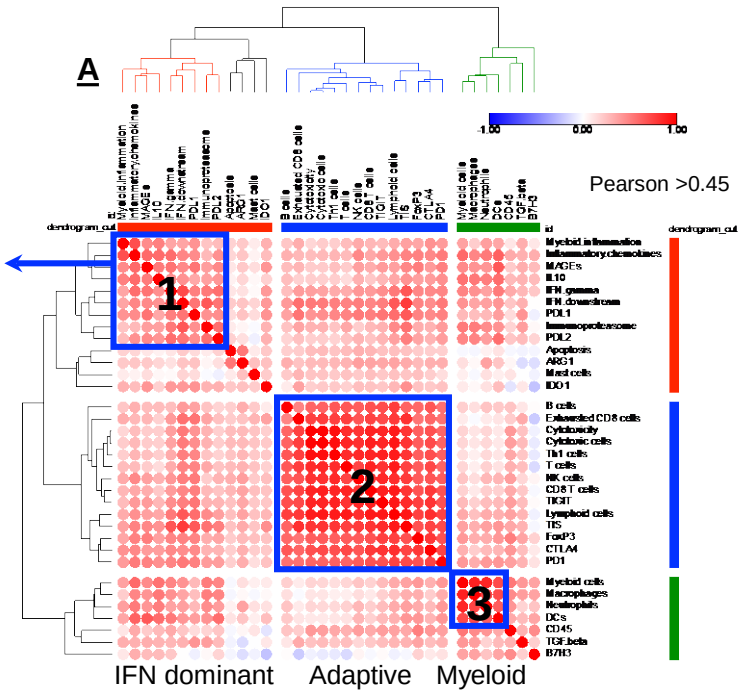
*PMCC = Princess Margaret Cancer Centre, Toronto, Canada – **Discovery cohort**
^CHOP = Children's Hospital of Philadelphia, Philadelphia, PA
^^SAL = Studienallianz Leukämie, Dresden, Germany

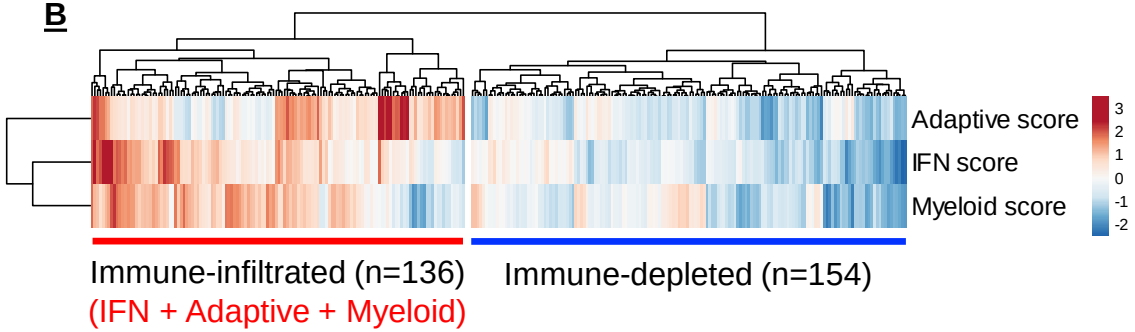
NTU

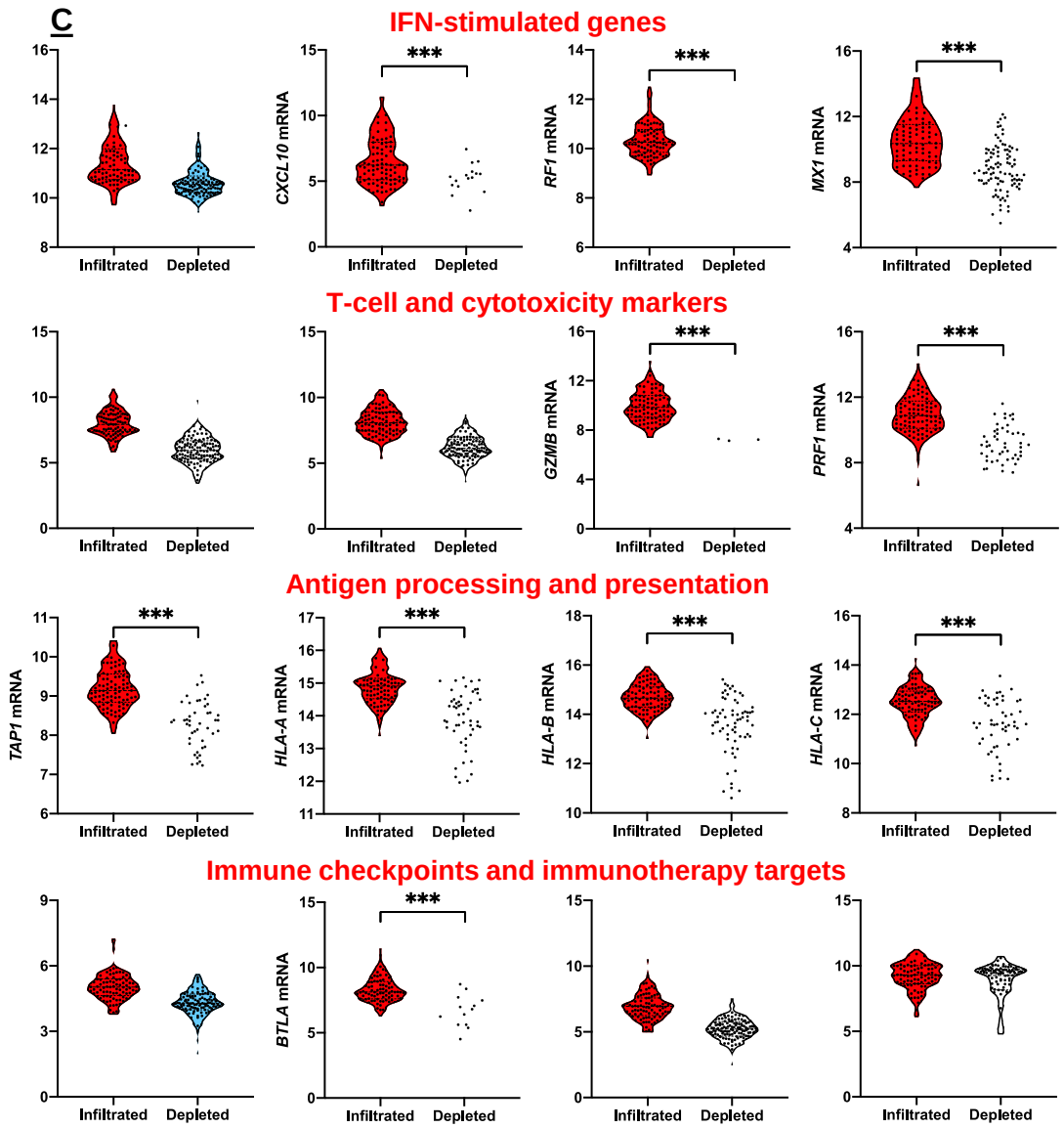
Immune landscapes assist stratification

Discovery cohort (n=290 patients)

"IFN module" gene score
Myeloid inflammation
Inflammatory chemokines
Downstream IFN signaling
IFN-γ
PDL1
PDL2
MAGEs
IL10
Immunoproteasome







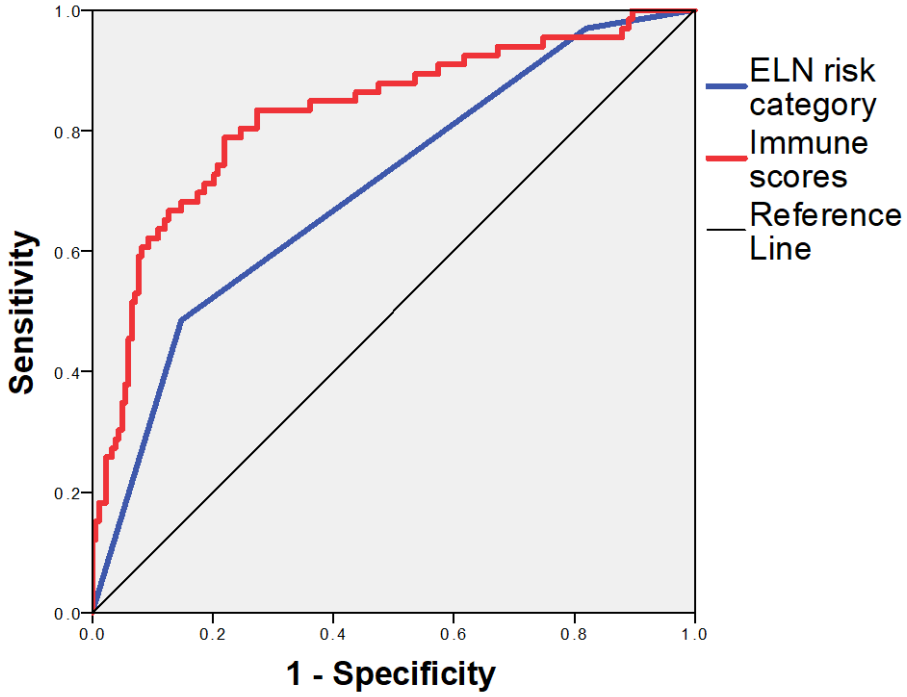
Vadakekolathu J, et al. bioRxiv 2019; DOI: 10.1101/702001. Under revision.

***P<0.05; ***P<0.001**

Prediction of chemotherapy response

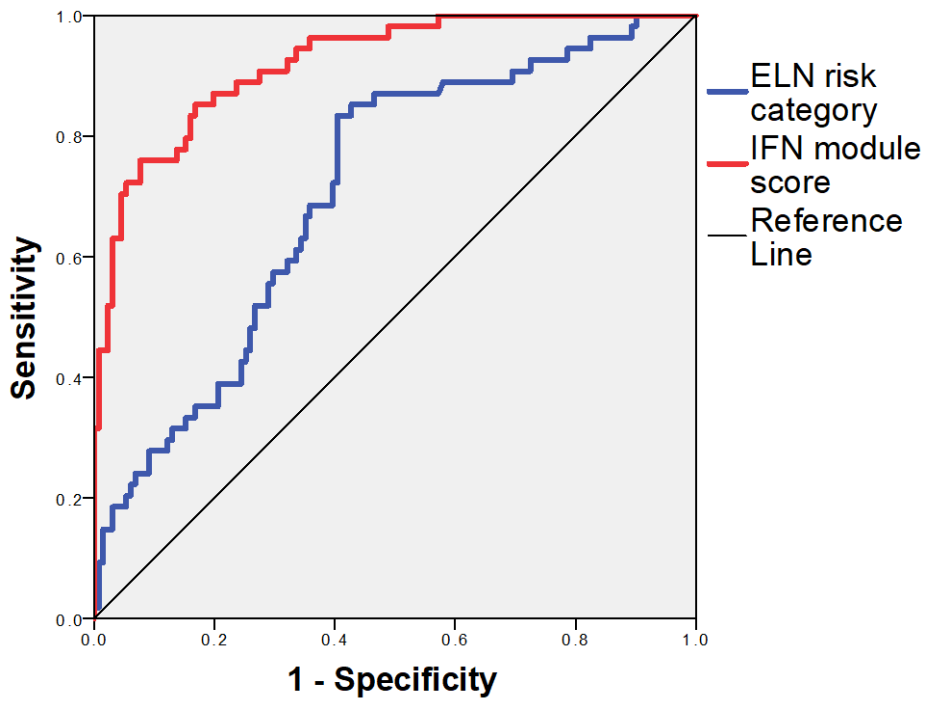
Therapy resistance (‘3+7’ backbone) was defined as failure to achieve CR in patients who survive at least 28 days (primary refractory AML) or as early relapse (less than 3 months after achieving CR)

A) PMCC discovery series (n=290)



Variable	AUROC	SE	95% CI
Immune scores	0.815	0.031	0.755-0.876
ELN risk	0.702	0.038	0.628-0.776

B) Beat-AML Master Trial validation series (n=196)



Variable	AUROC	SE	95% CI
IFN scores	0.921	0.04	0.88-0.961
ELN risk	0.709	0.021	0.629-0.788

Vadakekolathu J, et al. bioRxiv 2019; DOI: 10.1101/702001. Under revision.

Translational research question

IFN-γ-related gene signatures reflecting an immune-infiltrated TME are associated with adverse prognosis in patients with AML receiving conventional chemotherapy

Are immune-infiltrated TMEs, and IFN-γ gene signatures in particular, associated with sensitivity to targeted immunotherapy with flotetuzumab, a CD123 × CD3 DART bispecific molecule?

Flotetuzumab immunotherapy

- Immune gene expression was analyzed in a subgroup of patients (n=30/50) with relapsed/refractory AML treated with flotetuzumab (**NCT#02152956**) at RP2D (500 ng/kg/day; Uy, *et al.* ASH 2017; Uy, *et al.* ASH 2018; Rutella, *et al*. ASH 2018)
  - 30 BM samples analyzed at baseline
  - 19 BM samples analyzed “on treatment” (post-cycle 1)
- The NanoString PanCancer IO360™ assay was used to interrogate the expression of 770 genes, including the abundance of 14 immune cell types and 32 immuno-oncology signatures
  - Signature scores were calculated as pre-defined linear combinations (weighted averages) of biologically relevant gene sets

Patients and Methods

Characteristic			Patients (n=30)*
Age (median and range)			57 years (27-74)
Gender	Male		16 (53%)
	Female		14 (47%)
Disease status at study entry	Relapse (CR with initial duration >6 months)		7 (23%)
	Refractory	Primary induction failure (PIF; ≥2 induction attempts)	**17 (57%)**
		Early relapse (CR with initial duration <6 months)	6 (20%)
2017 ELN risk stratification	Favorable		6 (20%)
	Intermediate		7 (23%)
	Adverse		**17 (57%)**
Secondary AML			12 (40%)
Number of prior lines of therapy (median and range)			3 (1-9)

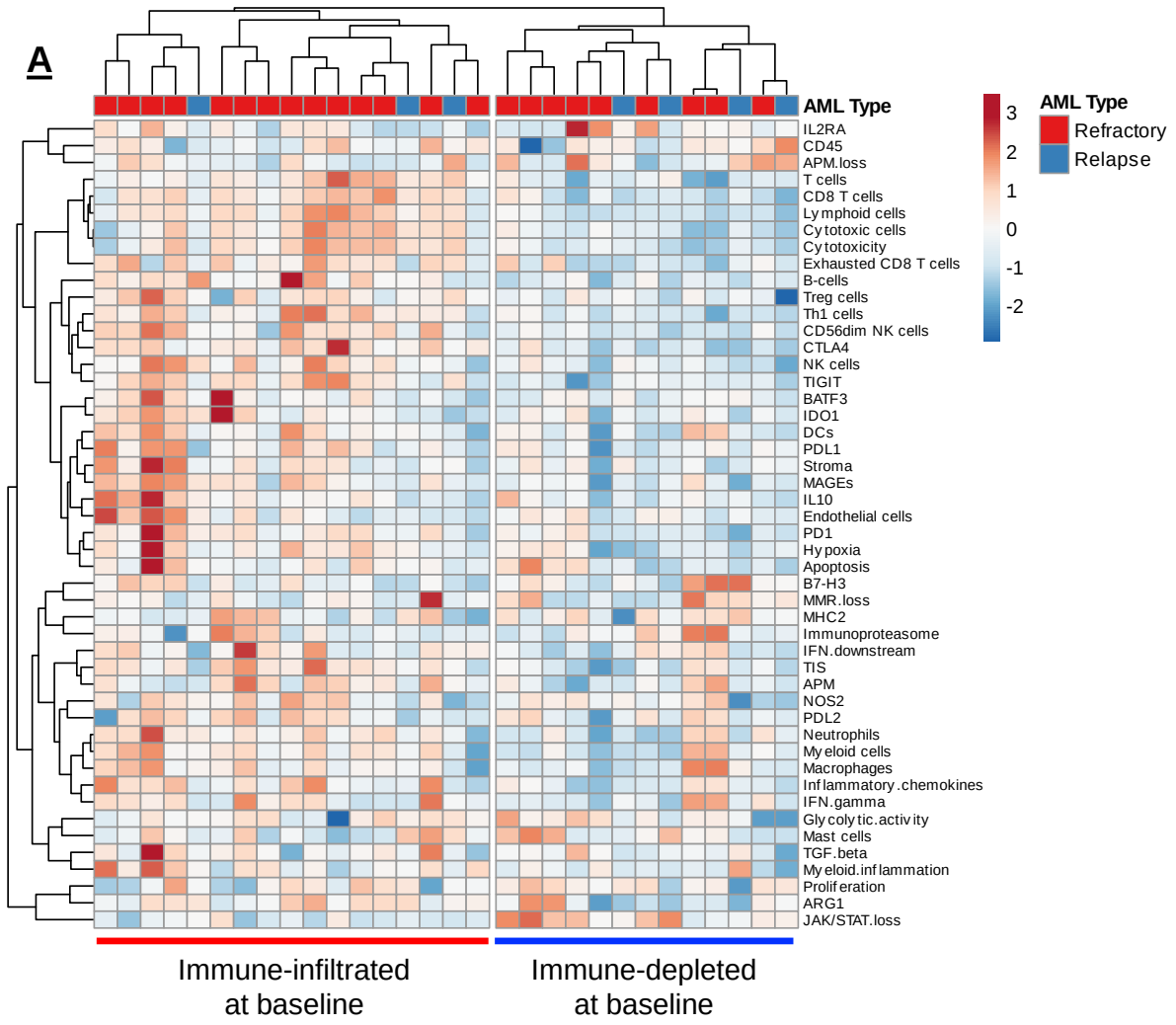
*Subgroup of 30/50 patients treated at the RP2D for whom BM samples were available

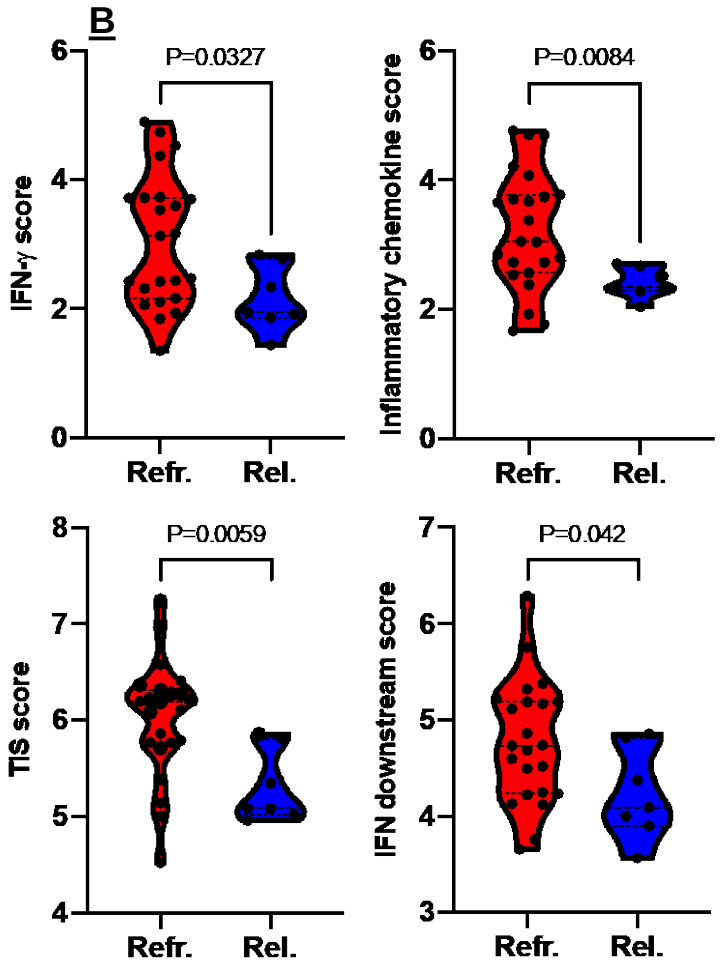
Response assessment criteria employed in analysis:

Anti-leukemic activity (ALA): CR/CRi, PR, “other benefit” (>30% decrease in BM blasts)

Non-responders (NR): treatment failure, stable disease, progressive disease

‘Hot’ TME in chemorefractory AML

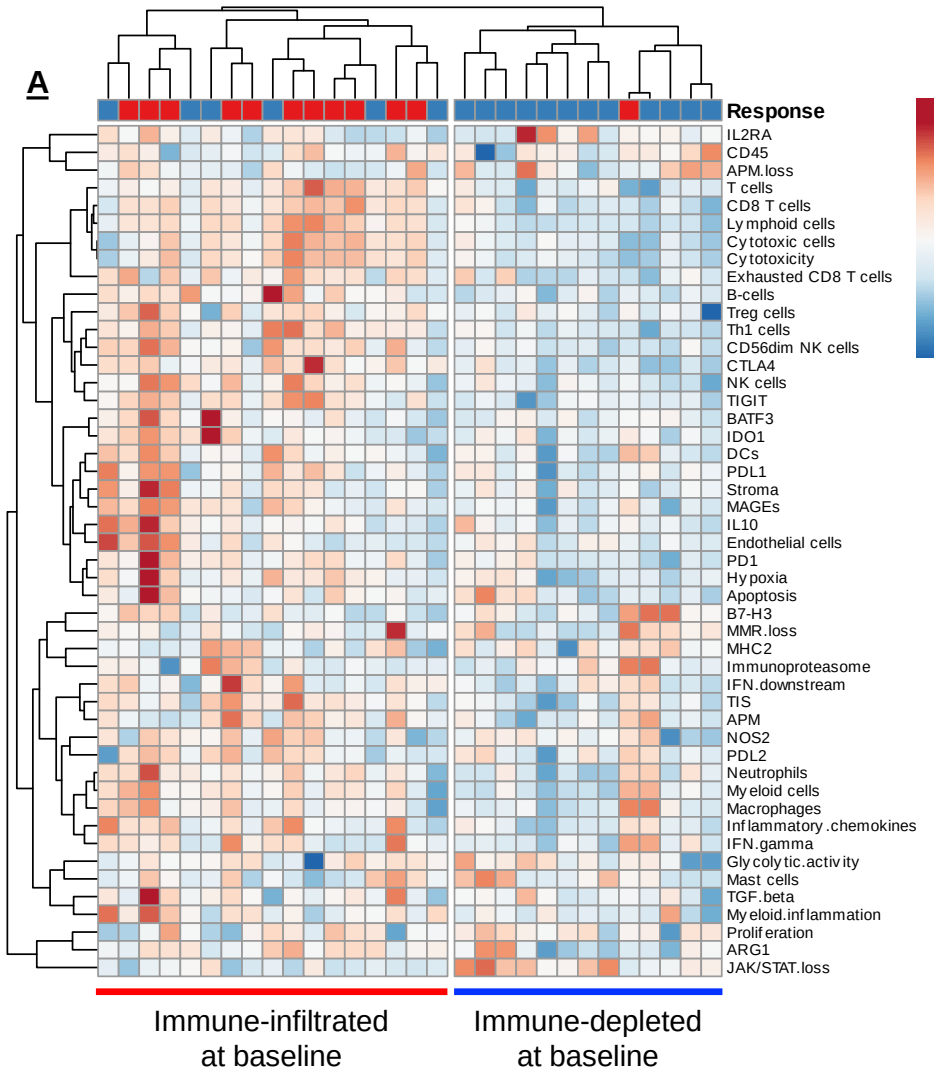


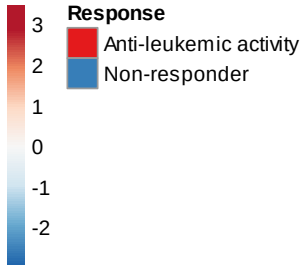


Mann Whitney *U* test for unpaired determinations
Refractory = Primary induction failure (PIF) + early relapse (ER)

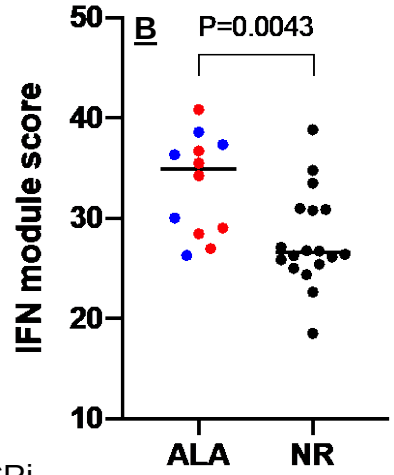
Vadakekolathu J, et al. bioRxiv 2019; DOI: 10.1101/702001. Under review.

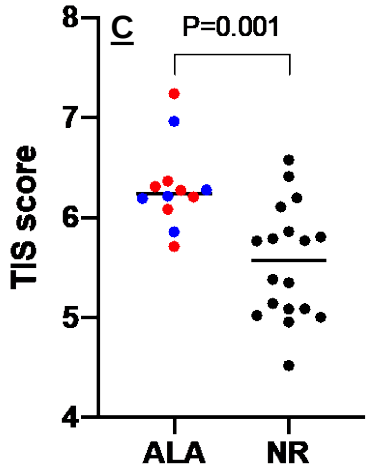
IFN-related profiles and response to flotetuzumab



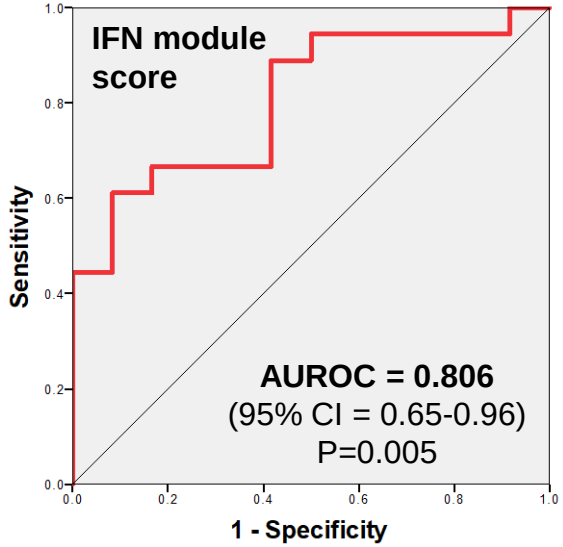


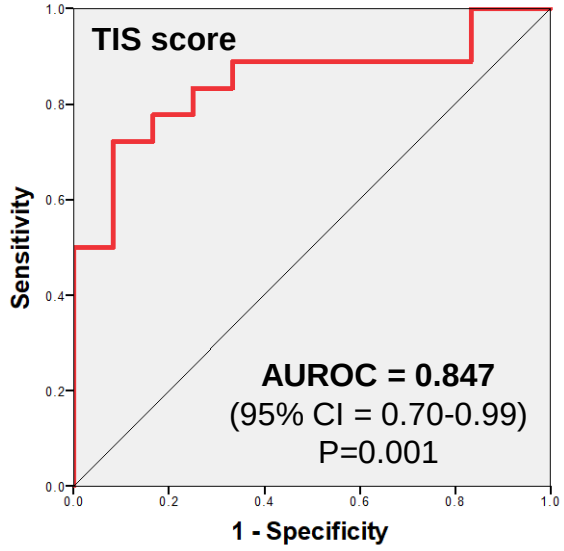
CR/CRh/CRi
PR/OB





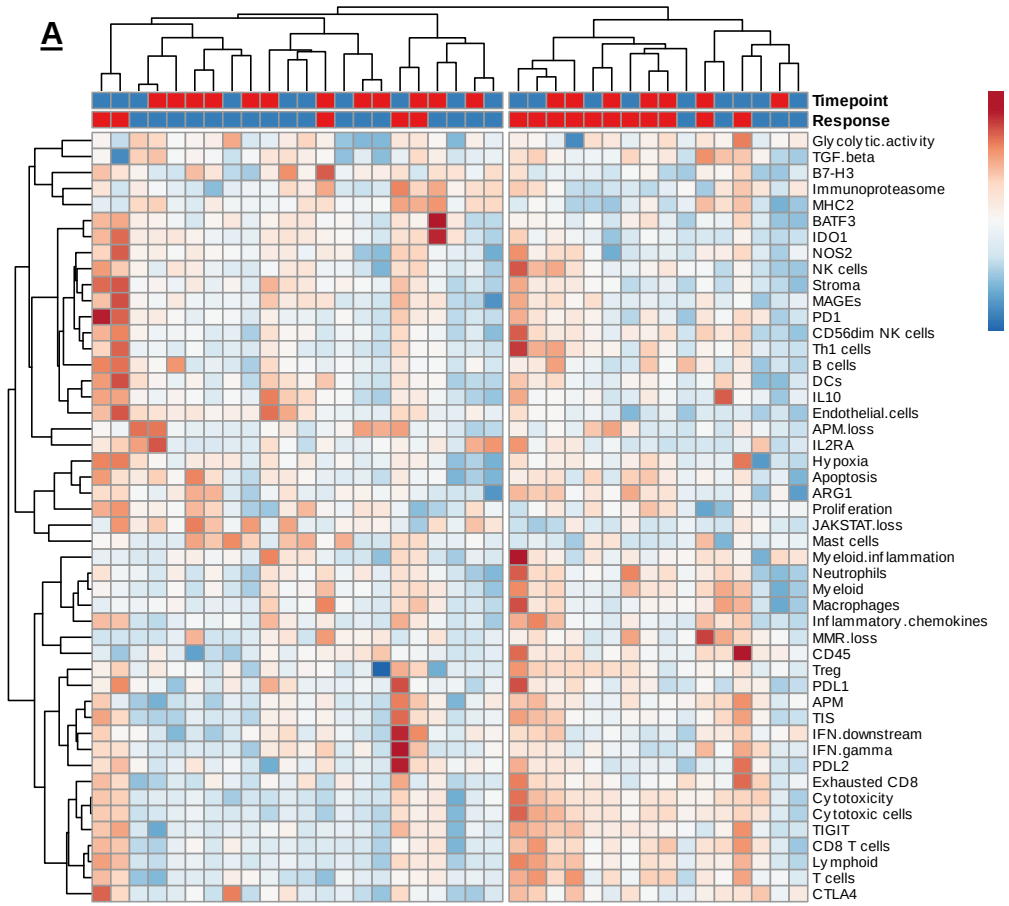
Mann Whitney *U* test for unpaired determinations



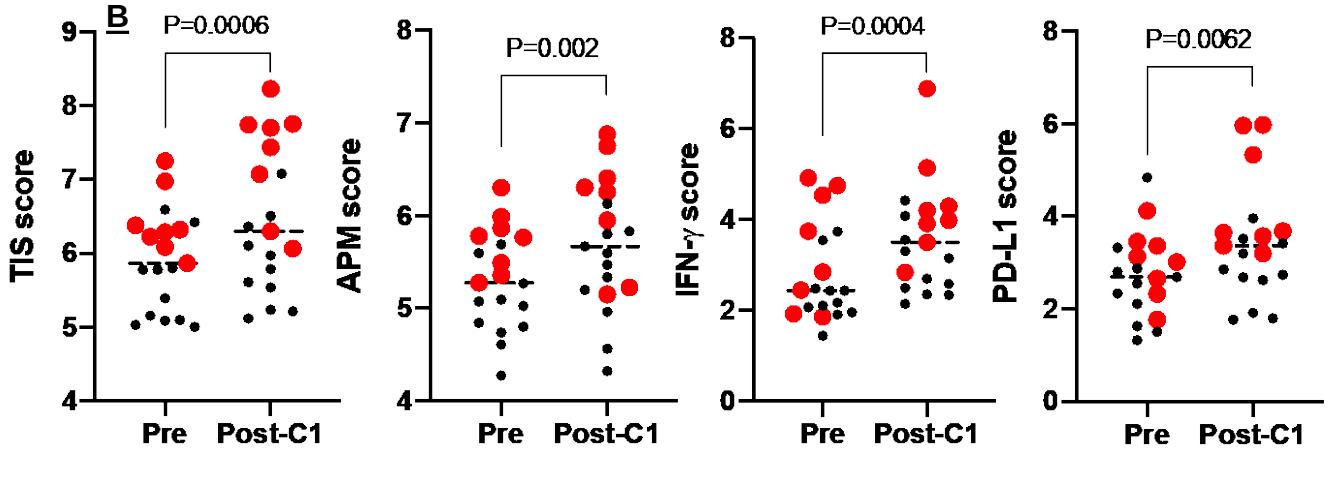


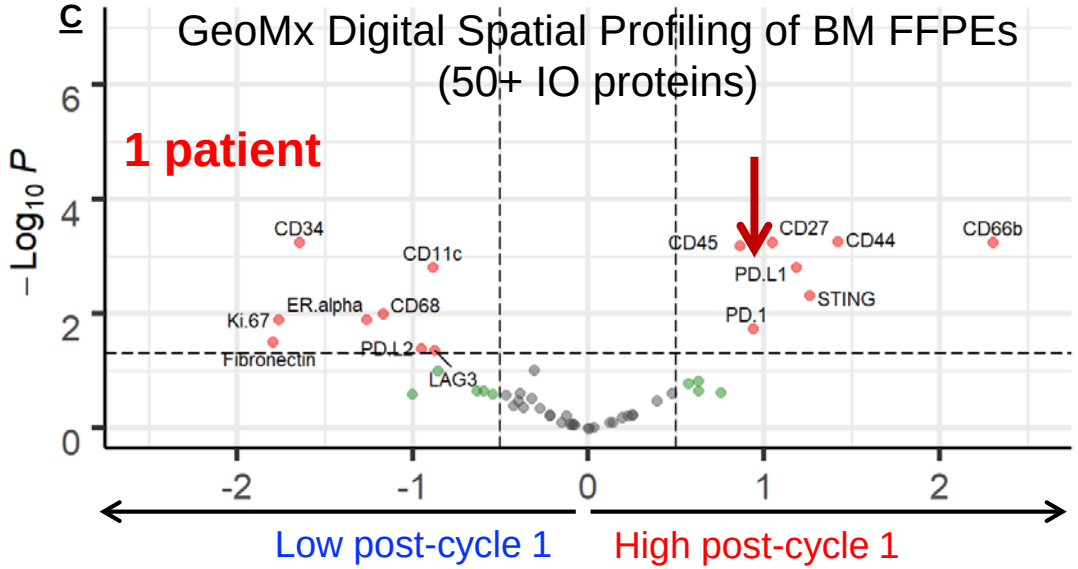
Vadakekolathu J, et al. bioRxiv 2019; DOI: 10.1101/702001. Under review.

Flotetuzumab modulates the TME



Matched baseline-post-C1 BMs available for 19 patients treated with flotetuzumab

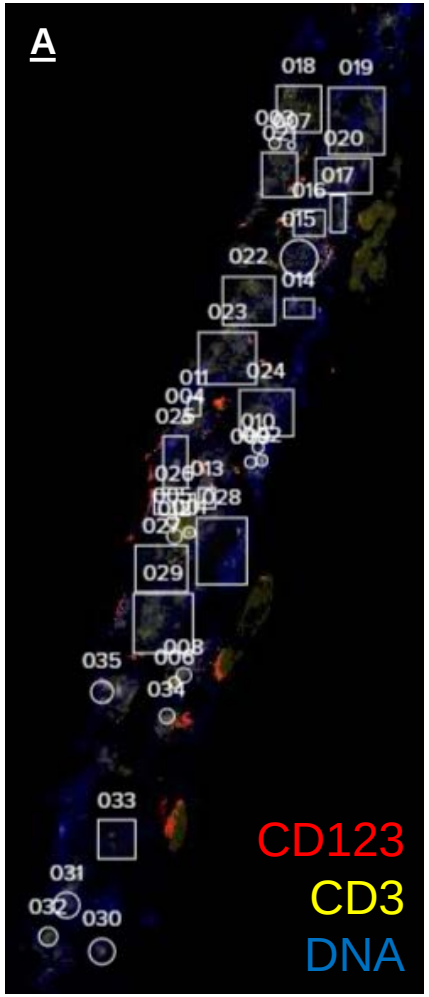




Vadakekolathu J, et al. bioRxiv 2019; DOI: 10.1101/702001. Under review and Unpublished.

Flotetuzumab modulates the TME

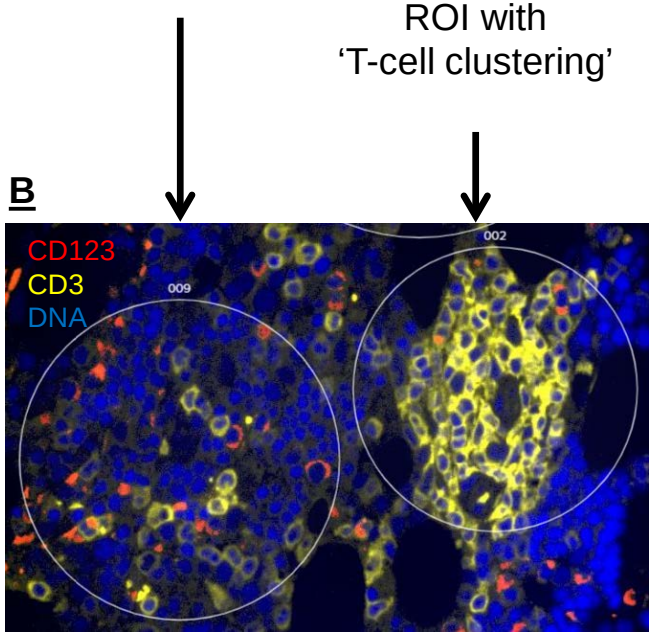
GeoMx Digital Spatial Profiling
of 2 BM FFPEs (50+ IO proteins)

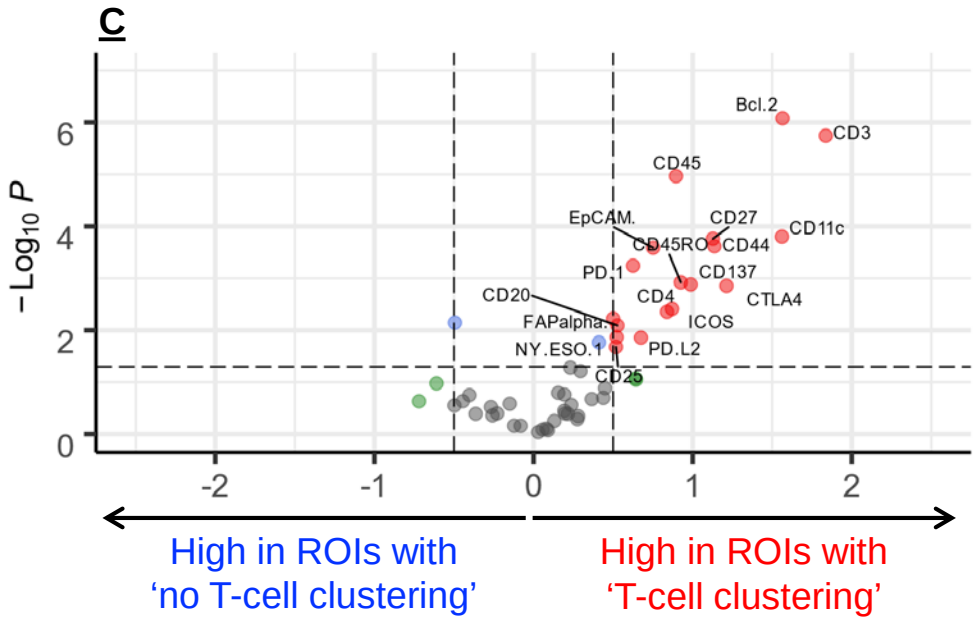


2 patients achieving CR

Region of interest (ROI) with
no ‘T-cell clustering’

ROI with
‘T-cell clustering’





Rutella S, et al. 2019 (unpublished) and Godwin JE, et al. Poster #1410. ASH 2019.

Conclusions

- Transcriptional programs that reflect high immune infiltration and IFN-γ signaling enrich in a subset of patients with AML and predict chemotherapy resistance
- IFN-γ-related mRNA profiles at baseline correlate with anti-leukemic activity of flotetuzumab at the RP2D
- A subgroup of patients with an immune-infiltrated TME show high expression of immune checkpoints, including PD-L1, suggesting potential enhanced benefit from flotetuzumab in combination with ICB
    - A phase I study of flotetuzumab combined with MGA012, an anti-PD1 antibody, is ongoing in patients with R/R AML (Wei AH, *et a*l. Poster #2662; ASH 2019)

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Co-authors and Collaborators

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Rockville, MD

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Mainstream QR funding, 2017-2019

AML Treatment Paradigm & Flotetuzumab Clinical Update

Geoffrey Uy, M.D.

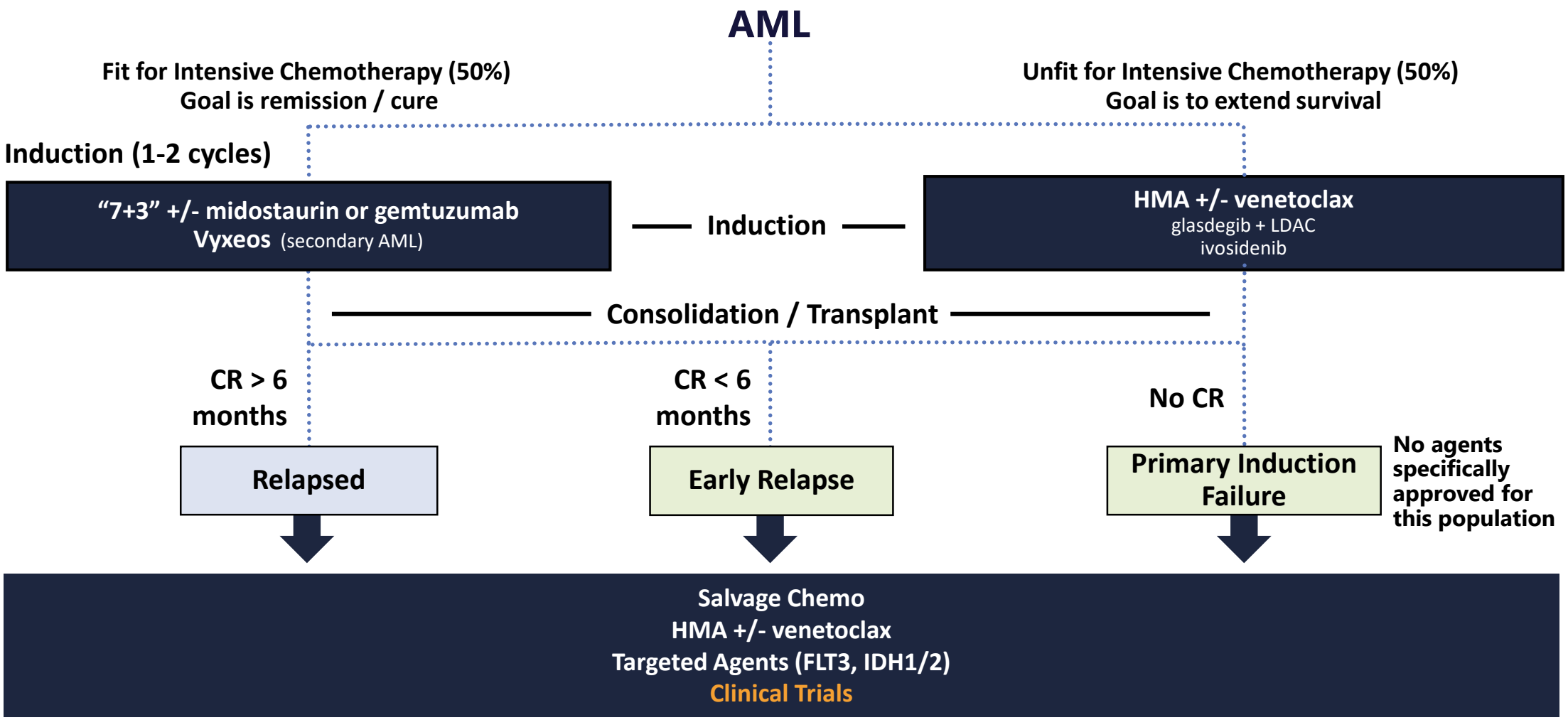
Associate Professor

Bone Marrow Transplantation & Leukemia, Washington University School of Medicine, St. Louis

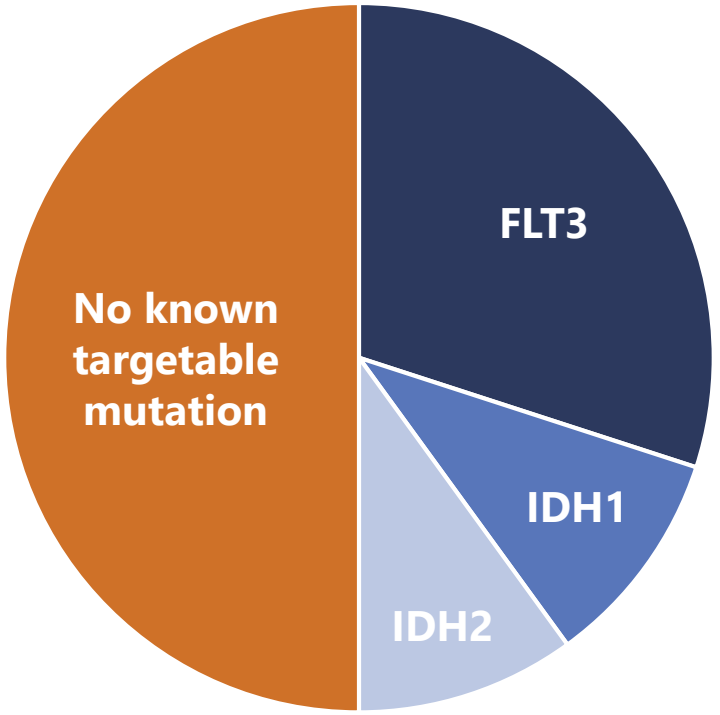
Background: Acute Myeloid Leukemia (AML)

- Hematopoietic stem cell (HSC) malignancy characterized by differentiation arrest and uncontrolled clonal proliferation of neoplastic precursors, preventing normal bone marrow hematopoiesis.
- Median age of 69 years at diagnosis.
- Nearly 20,000 new cases diagnosed per year in the US
- Approximately 40-50% of patients fail to achieve remission with intensive induction therapy (primary induction failure) or experience disease recurrence after a short remission duration (<6 months; early relapsed)
- Prognosis varies based in part on clinical features (e.g. patient age, medical comorbidities, and performance status) and underlying genetic features (cytogenetic and molecular aberrations).

Current Treatment Paradigm



At Least 50% of Patients with AML Have No Known Targetable Mutation



Cancer Facts and Figures 2019

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

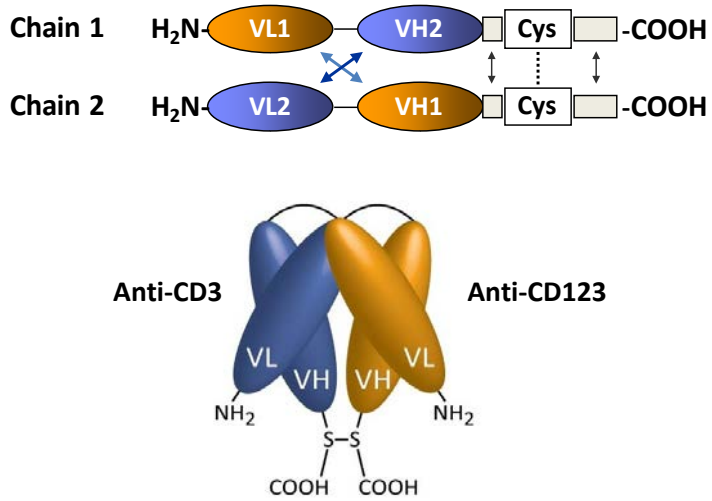
Geoffrey L. Uy, MD, Ibrahim Aldoss, MD, Matthew C Foster, MD, David A Sallman, MD, Kendra L. Sweet, MD, David A. Rizzieri, MD, Peter H. Sayre, MD, PhD, Anjali S. Advani, MD, Ashkan Emadi, MD, Matthew J. Wieduwilt, MD, PhD, Norbert Vey, MD, PhD, Fabio Ciceri, MD, Matteo Giovanni Carrabba, MD, Tamara Moyo, MD, PhD, Sarah E. Church, PhD, Michael P. Rettig, PhD, Martha L. Arellano, MD, John E. Godwin, MD, Bob Löwenberg, MD, PhD, Gerwin Huls, MD, PhD, Farhad Ravandi, MD, John Muth, MS, Kathy Tran, Ouiam Bakkacha, MD; Kenneth Jacobs, MD; Mojca Jongen-Lavrencic, MD, PhD, Erin Timmeny, Max S. Topp, MD, Stefania Paolini, MD, PhD, Kuo Guo, MSc, Teia Curtis, Jian Zhao, PhD, Jayakumar Vadakekolathu, PhD, Jon M. Wigginton, MD, Ezio Bonvini, MD, Sergio Rutella, MD, PhD, FRCPath, Roland B. Walter, MD, PhD, MS, Jan K Davidson-Moncada, MD, PhD, and John F. DiPersio, MD, PhD

ClinicalTrials.gov #NCT02152956 Abstract #733

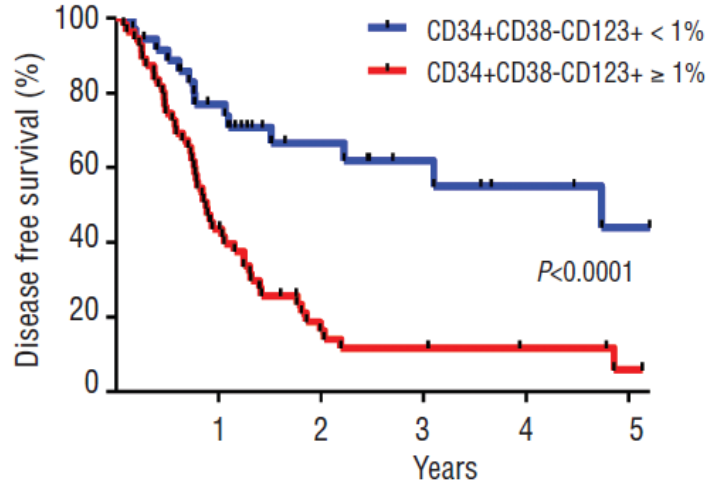
Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART® Protein

- 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

Flotetuzumab (MGD006)

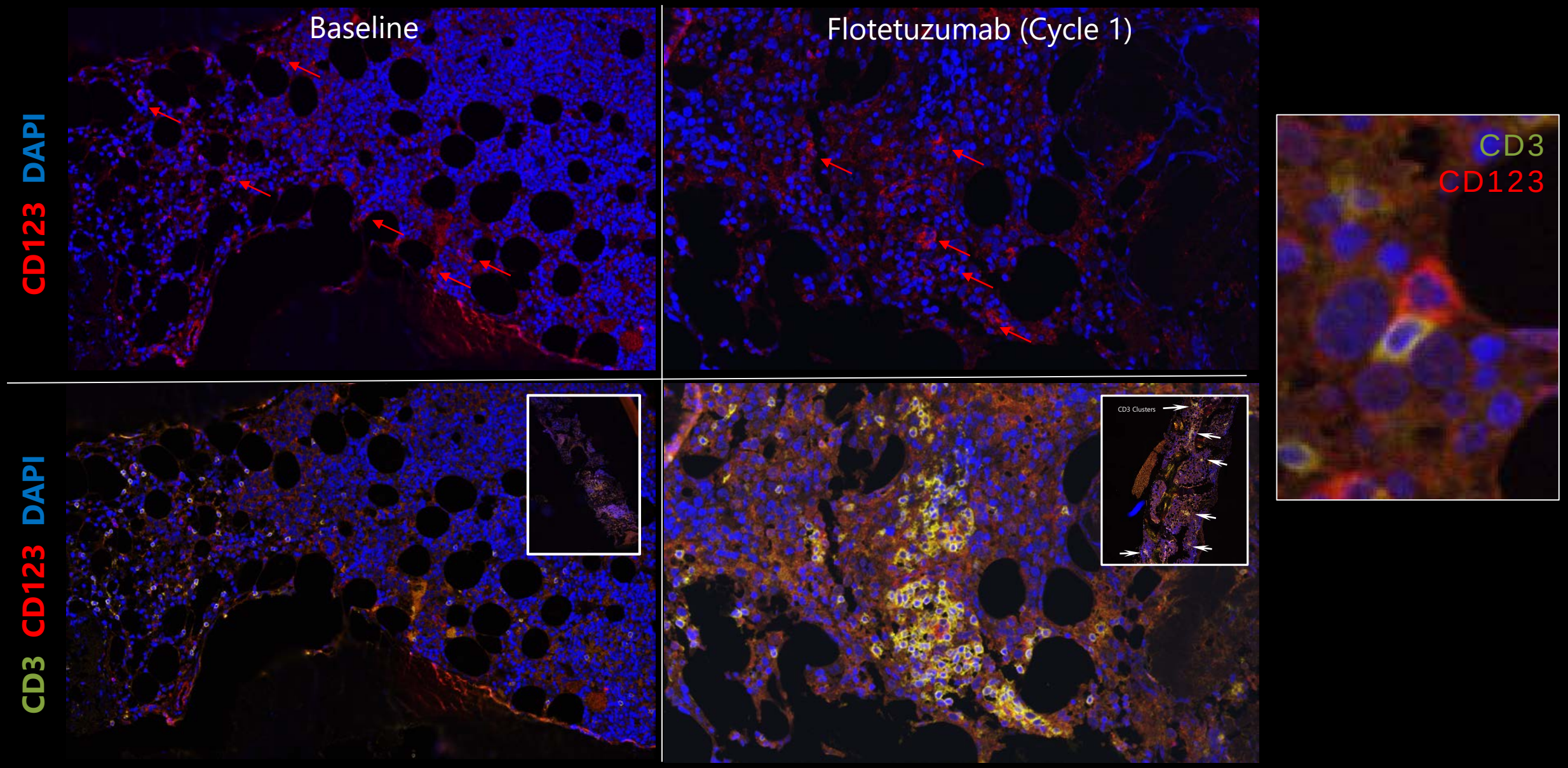


- CD123, the low-affinity IL-3 receptor (IL3Rα)
  - Normally expressed on hematopoietic progenitor cells (HPCs), plasmacytoid dendritic cells (pDCs), basophils, monocytes
  - Over-expressed on leukemic stem cells (LSCs) in AML and other hematologic malignancies
  - Increased CD123 expression associated with increased risk of relapse[1]



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

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



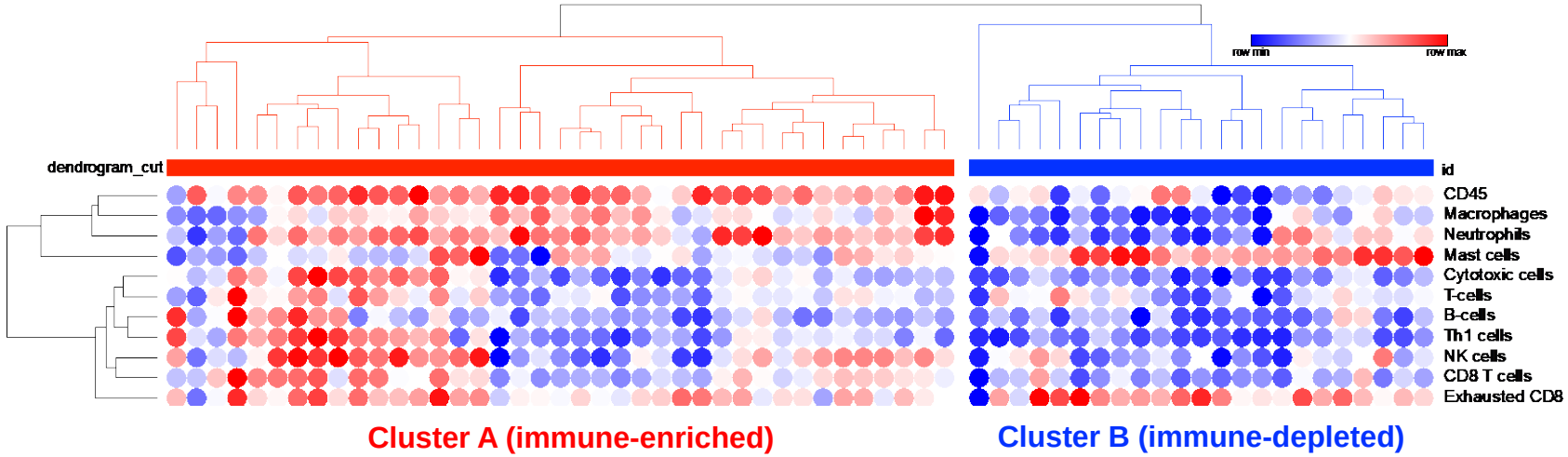
Godwin *et al,* ASH 2019, Abstract No. 1410

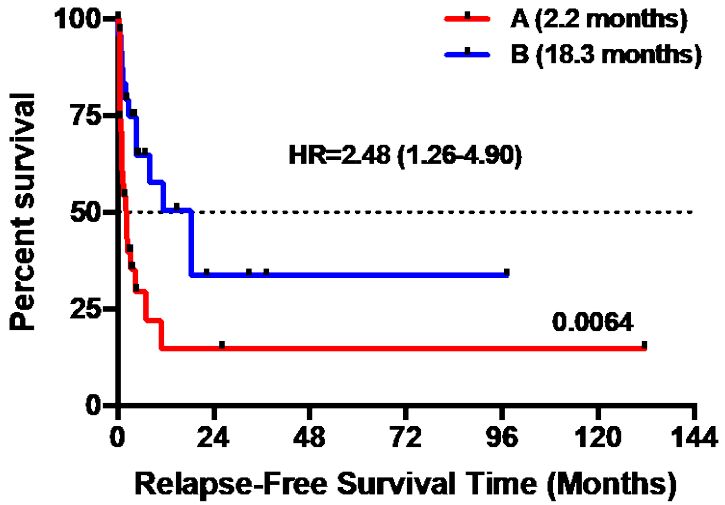
Poor outcomes for Induction Failure and Early Relapse

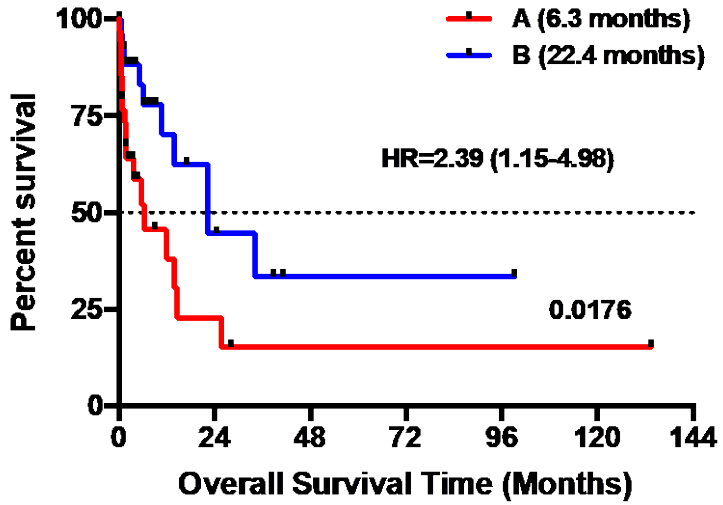
Primary induction failure (PIF) and early relapse (CR < 6 months) AML patients are unmet medical need :

- 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

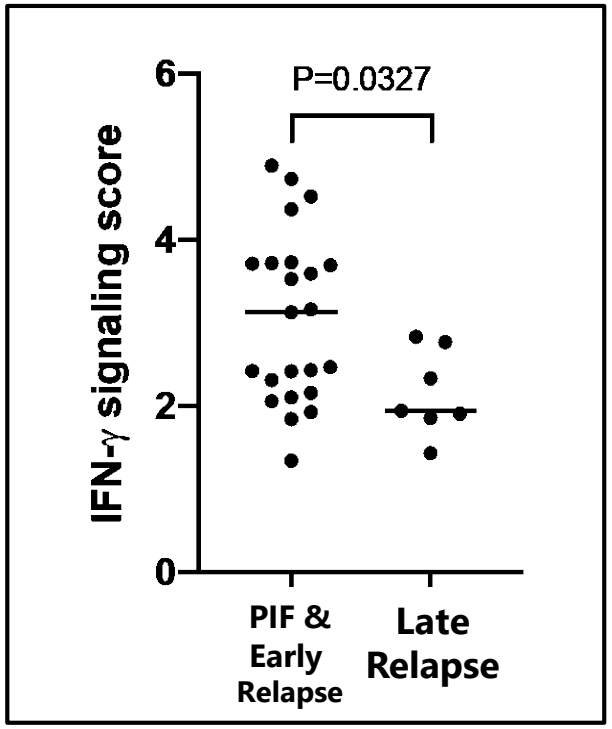




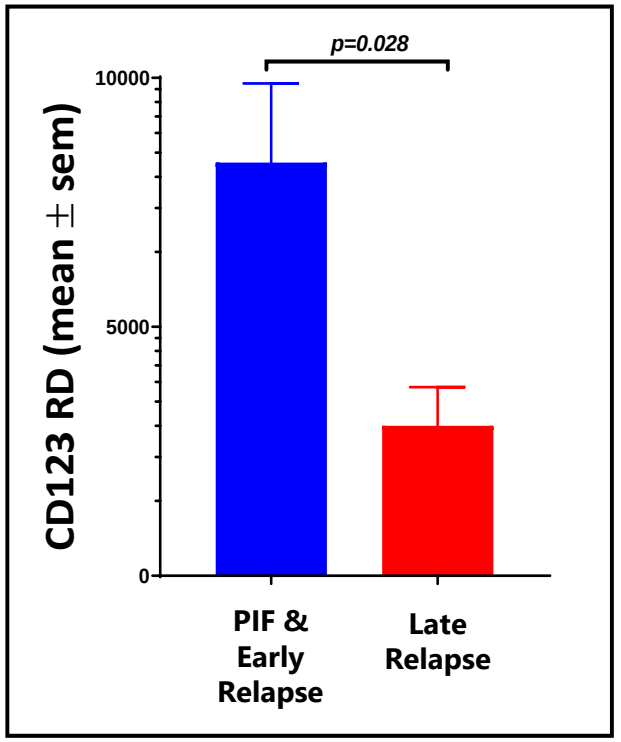


1. Vadakekolathu J et al, Blood (2017) 130: 3942A;

Higher IFN-γ and CD123 in Refractory AML Patients Treated with Flotetuzumab

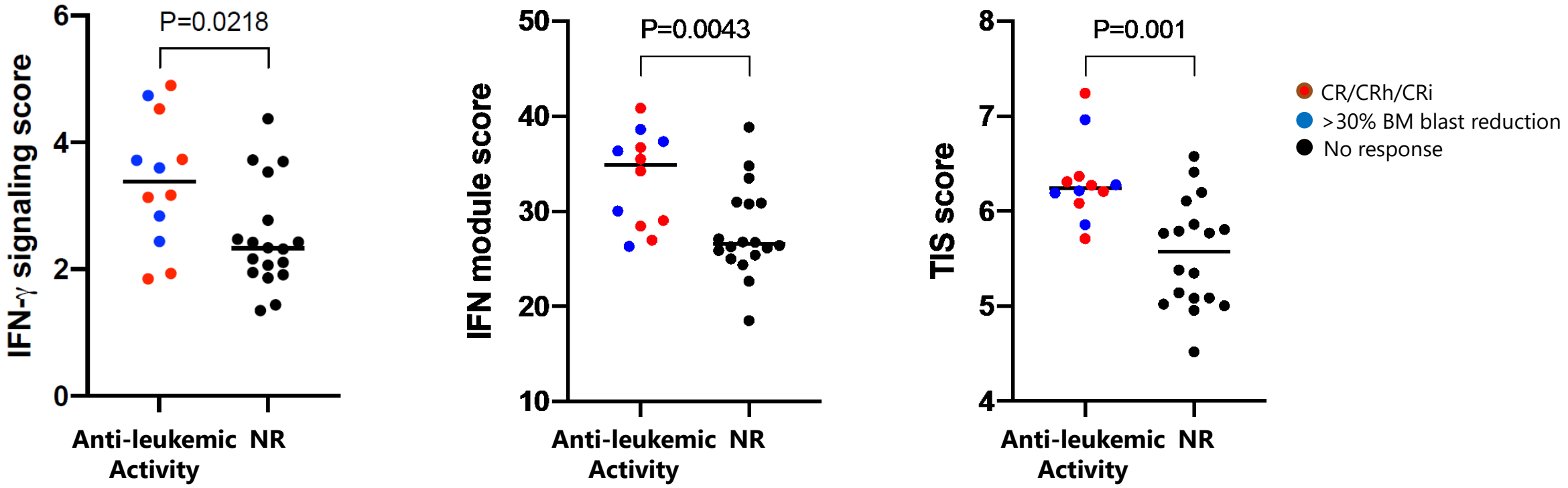


IFN-γ score (NanoString PanCancer IO 360™ panel) in baseline AML bone marrow samples (n=30; subgroup of patients treated at the RP2D for whom BM samples were available) Mann-Whitney *U* test for unpaired samples



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-γ-related Gene Signatures Associate with Flotetuzumab Activity



IFN-γ-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

Rutella et al. ASH 2019 Abstract # 460

Flotetuzumab Phase 1/2 Study Design

Expansion in primary induction failure & early relapsed AML patients

Key Entry Criteria (refractory AML population)

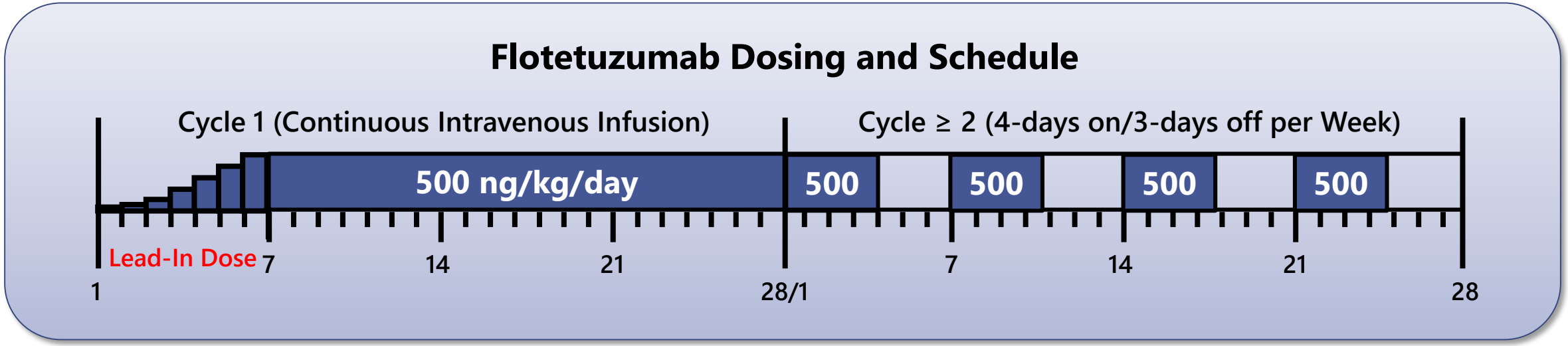
- Primary induction failure (PIF): refractory to ≥ 2 induction attempts
- Early relapse: First relapse with initial CR duration of < 6 months or any prior unsuccessful salvage
- No prior allogeneic hematopoietic cell transplant

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



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 (≥ 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 1st, 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 1st, 2019

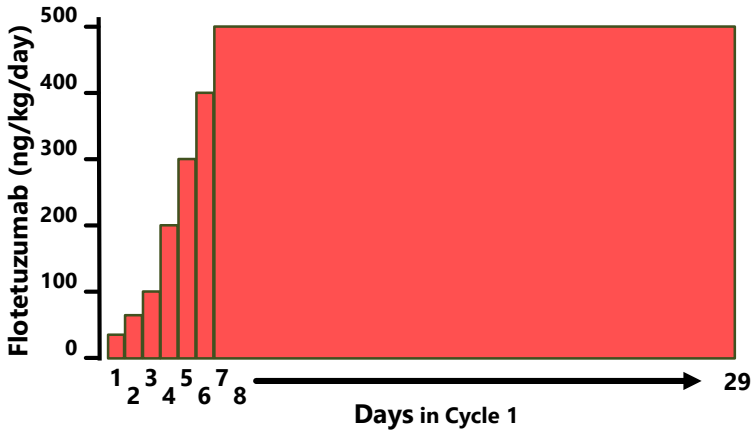
*Events occurring >10%; Toxicity grading is based on CTCAE criteria version 4.0. Toxicity grading for events of IRR/CRS is based upon the modified grading scale proposed by Lee et al.

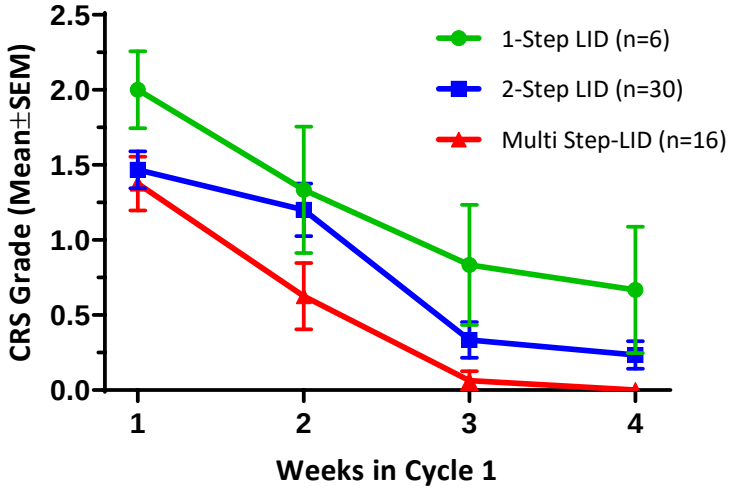
Flotetuzumab: Strategy for Mitigation of Cytokine Release Syndrome

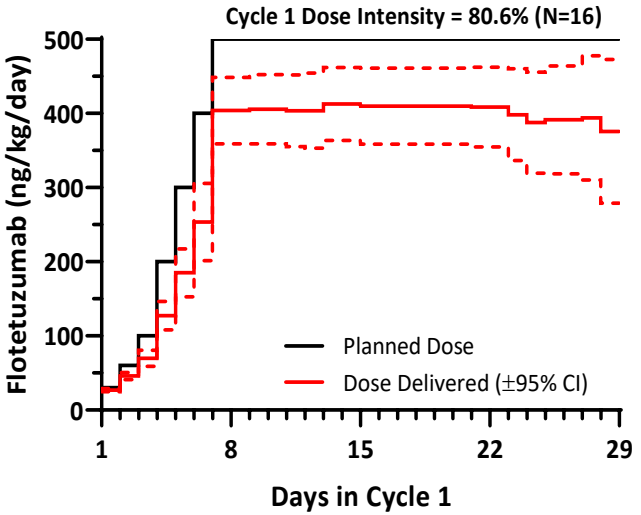
Several key interventions have helped mitigate CRS severity

- 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)



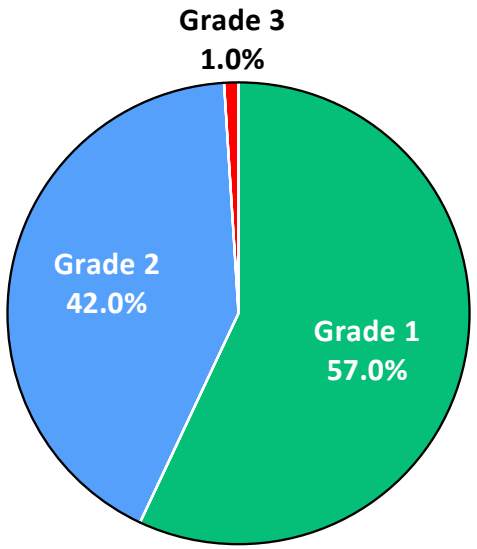




CRS Events Were Mild to Moderate in Severity in the PIF & Early Relapse AML

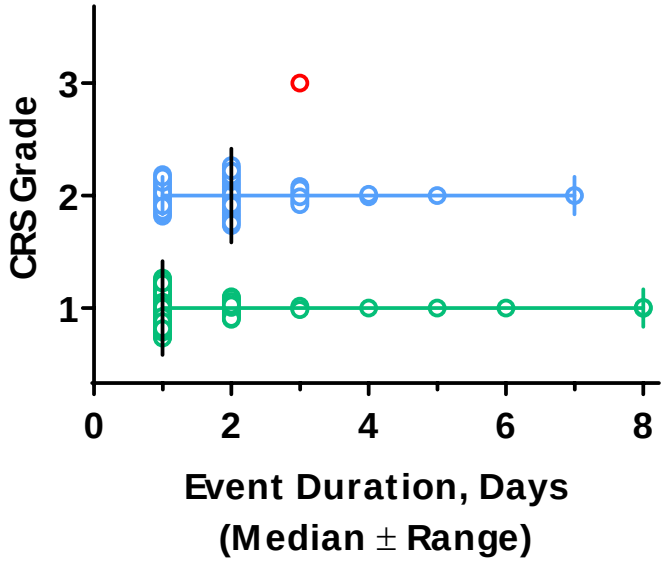
CRS was conservatively managed

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

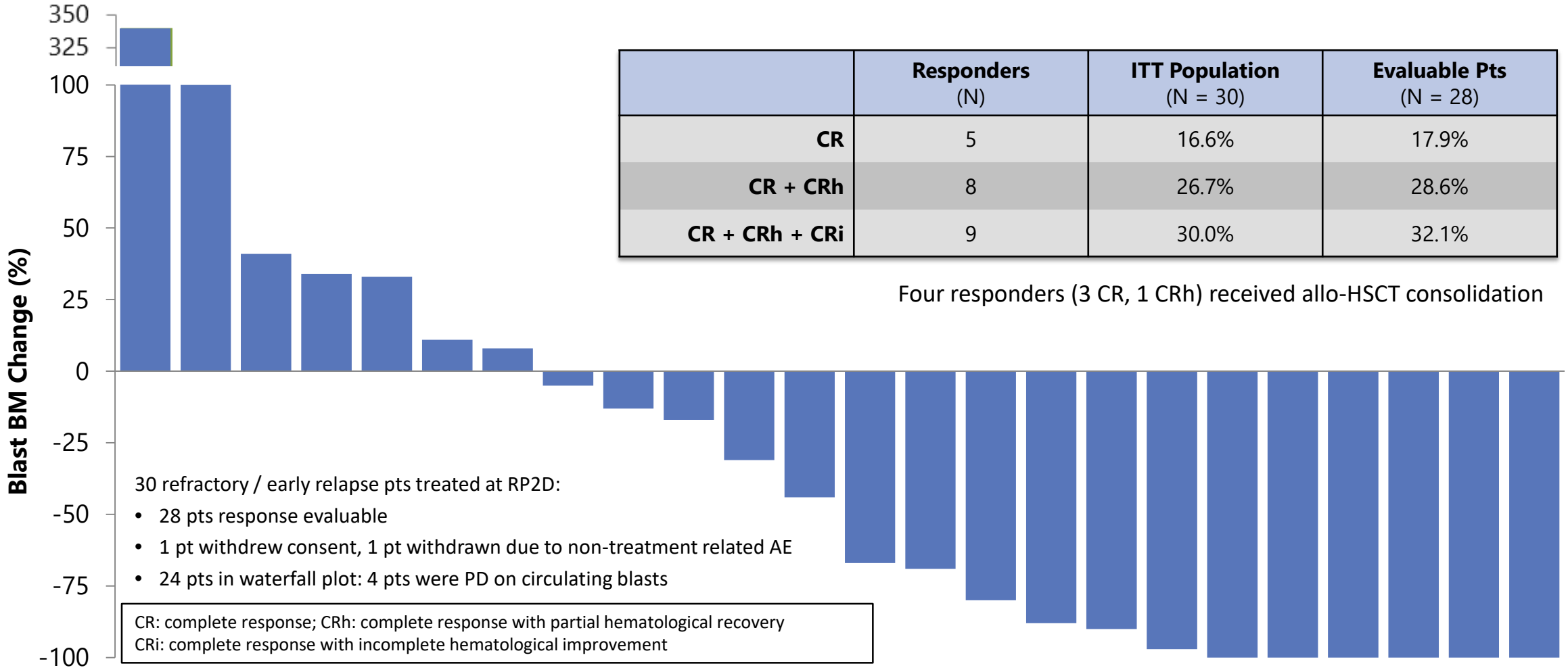
- 19/30 patients received tocilizumab (10 dose for G1, 15 doses for G2, and 1 dose for G3 events)
- 5/30 patients have required steroids (3 doses for G1 and 3 doses for G2 events)
- 2/30 patients have required vasopressors (3 doses for G2 events)

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

Benchmark analysis suggests historical CR+CRh rates in this setting of ~12.5% [1]

	Responders (N)	ITT Population (N = 30)	Evaluable Pts (N = 28)
CR	5	16.6%	17.9%
CR + CRh	8	26.7%	28.6%
CR + CRh + CRi	9	30.0%	32.1%

Four responders (3 CR, 1 CRh) received allo-HSCT consolidation



30 refractory / early relapse pts treated at RP2D:

- 28 pts response evaluable
- 1 pt withdrew consent, 1 pt withdrawn due to non-treatment related AE
- 24 pts in waterfall plot: 4 pts were PD on circulating blasts

CR: complete response; CRh: complete response with partial hematological recovery
CRi: complete response with incomplete hematological improvement

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

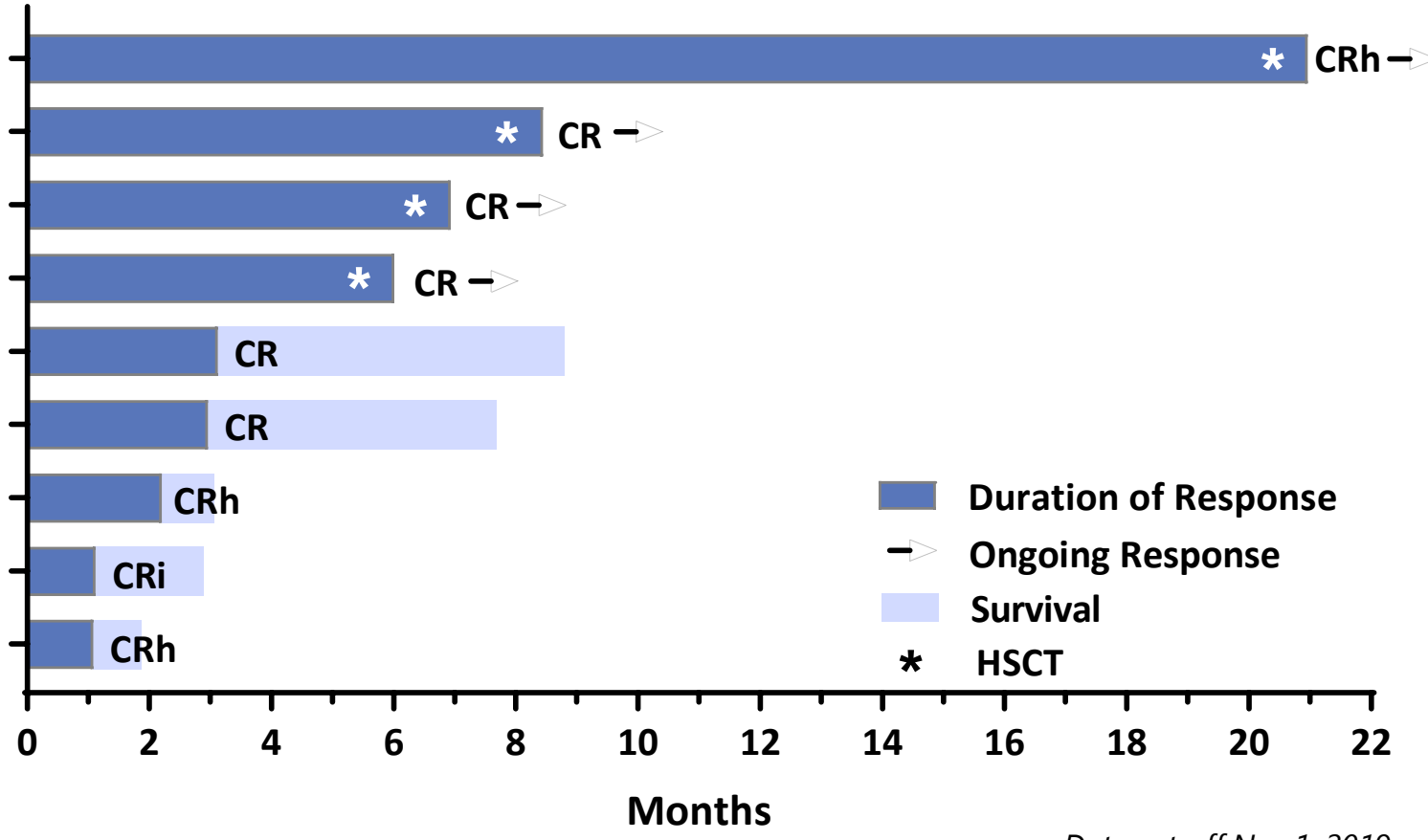
Greater response rates accrued in patients with up to 4 lines of prior therapy

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

Prior Rx Lines	Prior Rx Included:	Response to Flotetuzumab
2	7+3/HiDAC	
2	HiDAC/Venetoclax	
3	HiDAC (x2)	
2	AZA/Midostaurin	
4	HiDAC (x2)/MEC	
2	7+3 (x2)	
2	HiDAC/Venetoclax	
4	7+3/FLAG-Ida/FLAG	
4	AZA/CD33xCD3 (Amv564)	



Data cut-off Nov 1, 2019

Conclusions

- 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

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

Clinical trial teams at the study centers: Max S. Topp, MD, Universitätsklinikum Würzburg; Martin Wermke, MD,Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden; Norbert Vey, MD, Institut Paoli-Calmettes; Fabio Ciceri, MD, Matteo Carraba, MD, University Vita-Salute San Raffaele; Stefania Paolini, MD, Policlinico Sant'Orsola-Malpighi; Gerwin A. Huls, MD, University Medical Center Groningen; Bob Lowenberg, MD, Mojca Jongen-Lavrenic, MD, Erasmus University Medical Center; Geoffrey L. Uy, MD, Washington University School of Medicine; Harry Erba, MD PhD, Duke University Medical Center; Martha Arellano, MD, Emory University School of Medicine; Matthew C. Foster, MD, UNC Lineberger Comprehensive Cancer Center; John Godwin, MD, Providence Cancer Center; Farhard Ravandi-Kashani, MD, The University of Texas M D Anderson Cancer Center Department of Leukemia; Kendra Sweet, MD, Moffitt Cancer Center; Peter Sayre, MD, University of California, San Francisco; Anjali Advani, MD, Cleveland Clinic; Matthew Wieduwilt, MD, UCSD Moores Cancer Center; Ibrahim Aldoss, MD, City of Hope National Medical Center; Michael T. Byrne, DO, Vanderbilt-Ingram Cancer Center; Ashkan Emadi, MD, University of Maryland; Laura Michaelis, MD, Medical College of Wisconsin; Kristen Petit, MD, University of Michigan; Roland Walter, MD, PhD, Fred Hutchinson Cancer Research Center; Jessica Altman, MD, Northwestern Medicine

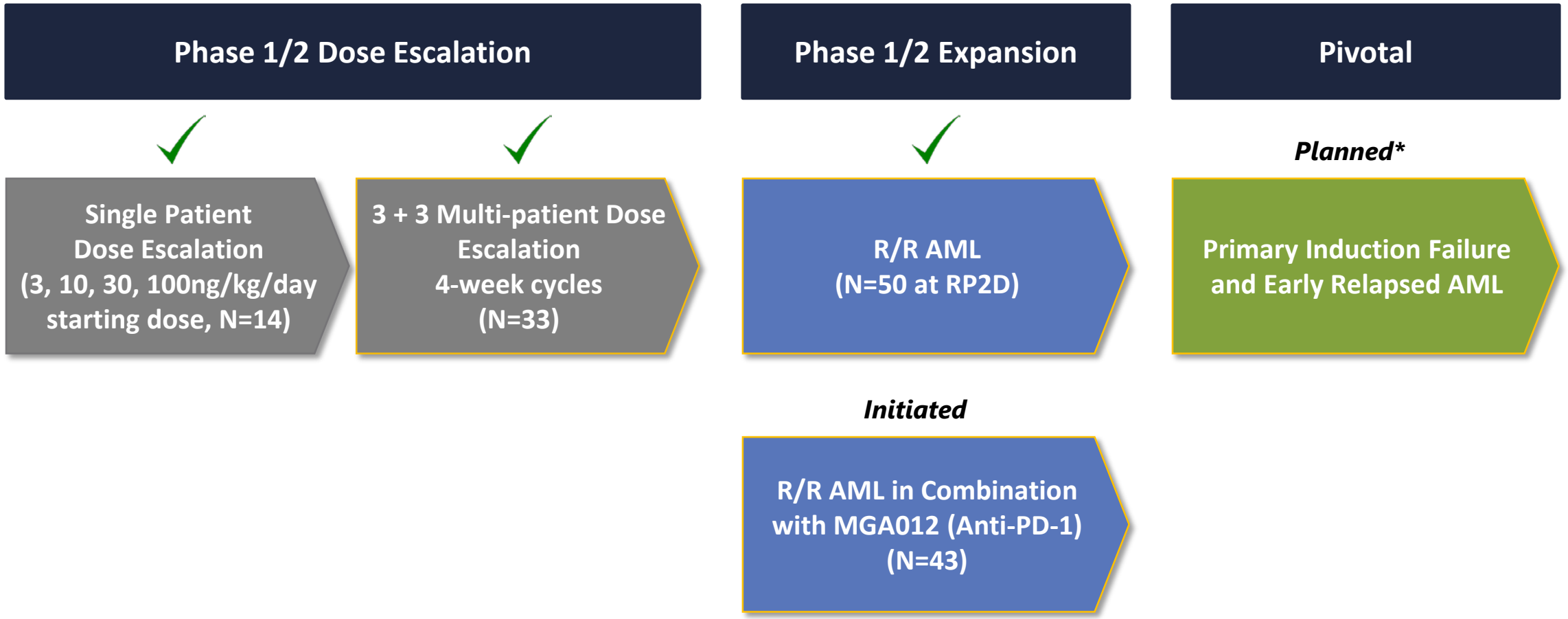
Future Development

Jan Davidson-Moncada, M.D., Ph.D.

Senior Clinical Research Director, MacroGenics

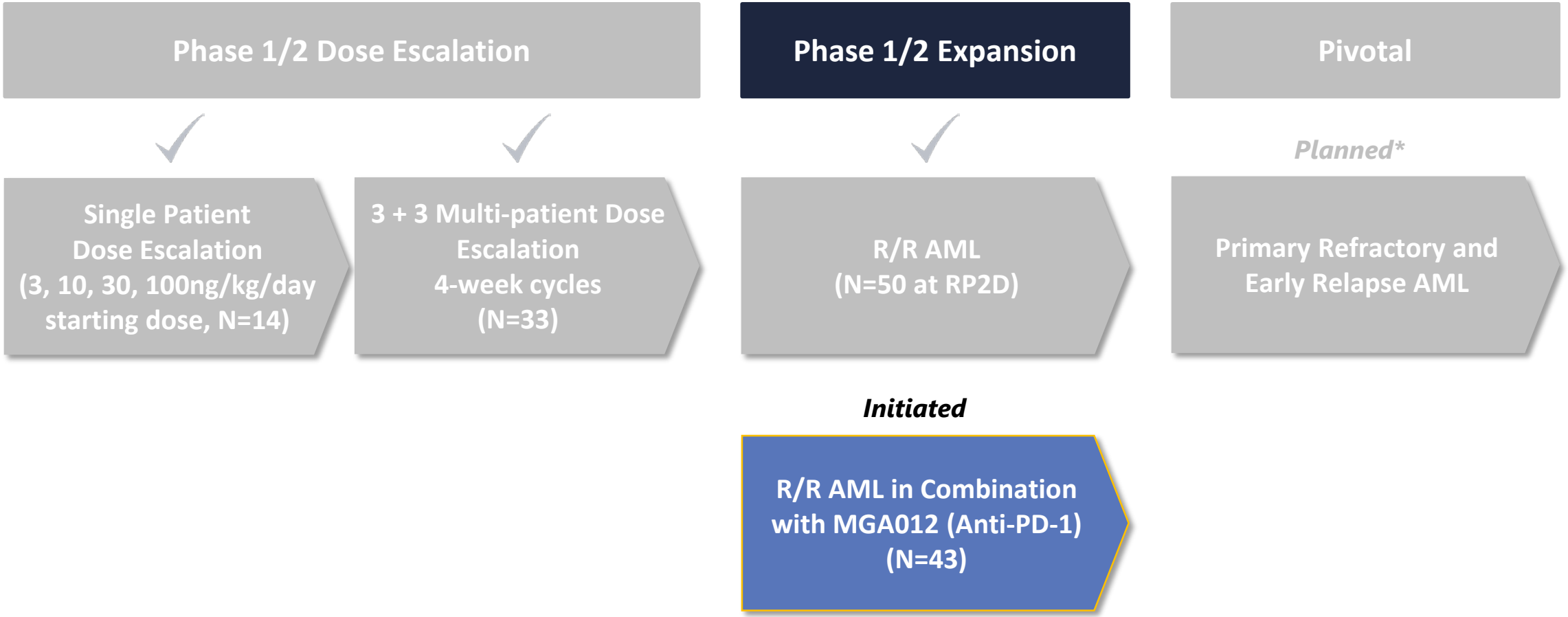
Ongoing and Planned Flotetuzumab Development

Pivotal monotherapy study planned; combination study with anti-PD-1 initiated



*Pending ongoing discussions with FDA

Strong Rationale for Combining Flotetuzumab with Anti-PD-1



*Pending ongoing discussions with FDA

MGA012 (also known as INCMGA00012) was exclusively licensed to Incyte Corporation in 2017 under a global collaboration and license agreement. MacroGenics retains the right to develop its pipeline molecules with MGA012.

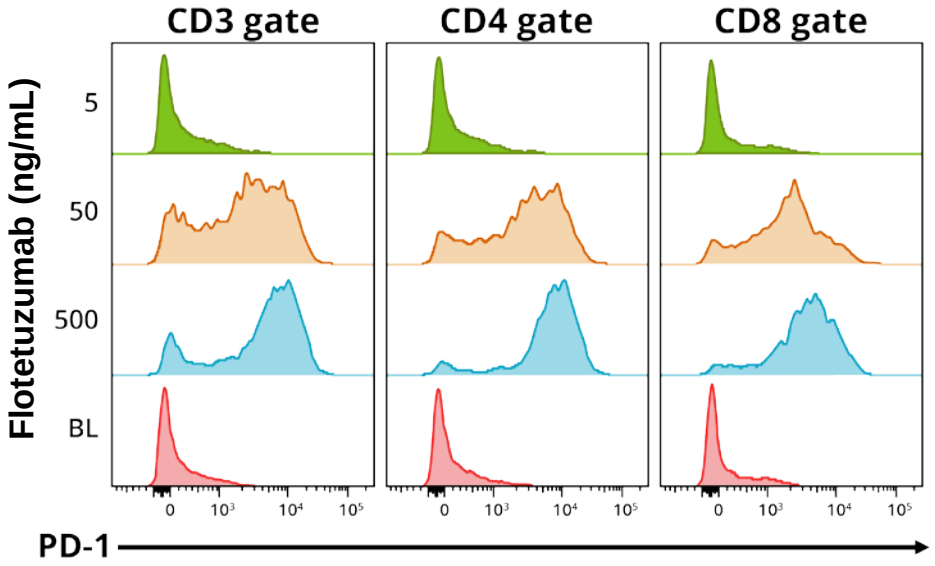
Checkpoint Blockade May Enhance Anti-leukemic Activity of Flotetuzumab

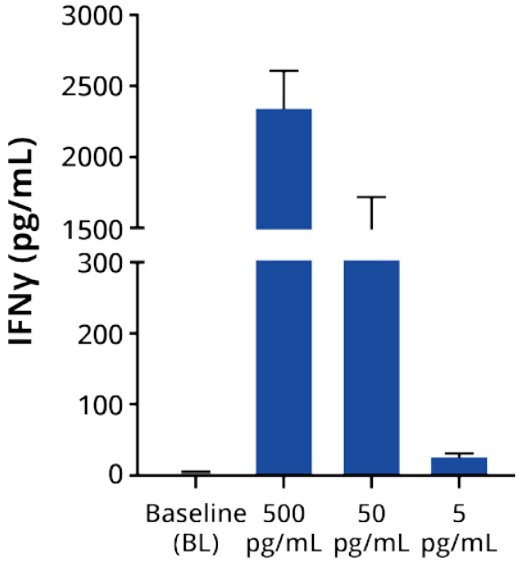
- Checkpoint inhibition has changed the paradigm of cancer therapy, however treatment of AML with anti-PD-1 mAb has not been successful.
- Patients with an immune-infiltrated tumor microenvironment show high expression of immune checkpoints, including PD-L1 in a subgroup of patients.
- Based on internal analysis, a small subset of AML patients (~10-15%) express PD-L1 at baseline.
- The challenge is how to incorporate CPI in the treatment of patients with AML.

Rutella et al, ASH 2019 (Abstract #460); Rettig et al. ASH 2017 (Abstract #1365)

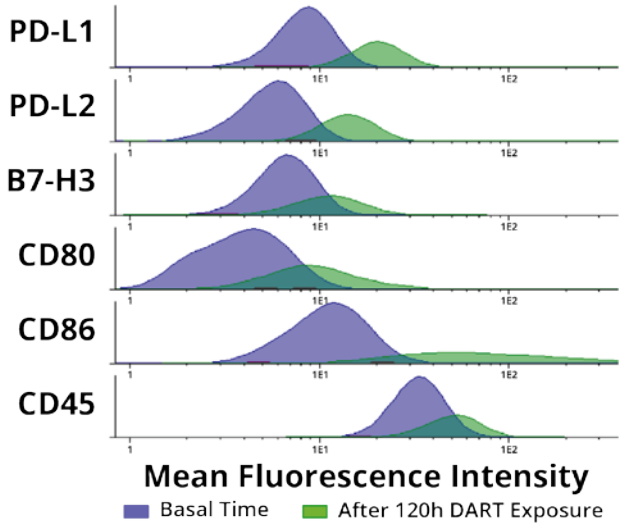
Checkpoint Molecules are Upregulated by Flotetuzumab In Vitro

CD4 and CD8 T cells from an AML patient express PD-1 after exposure to flotetuzumab



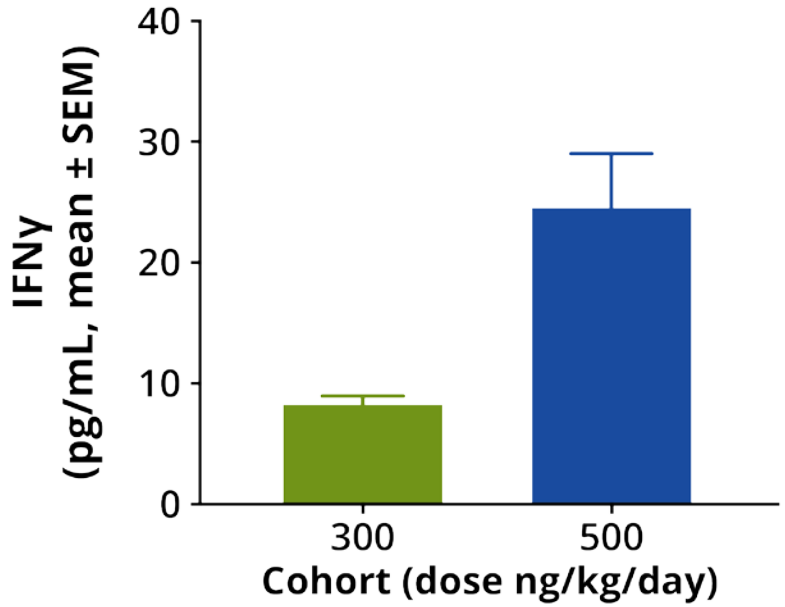


AML blasts express checkpoint molecules after exposure to flotetuzumab

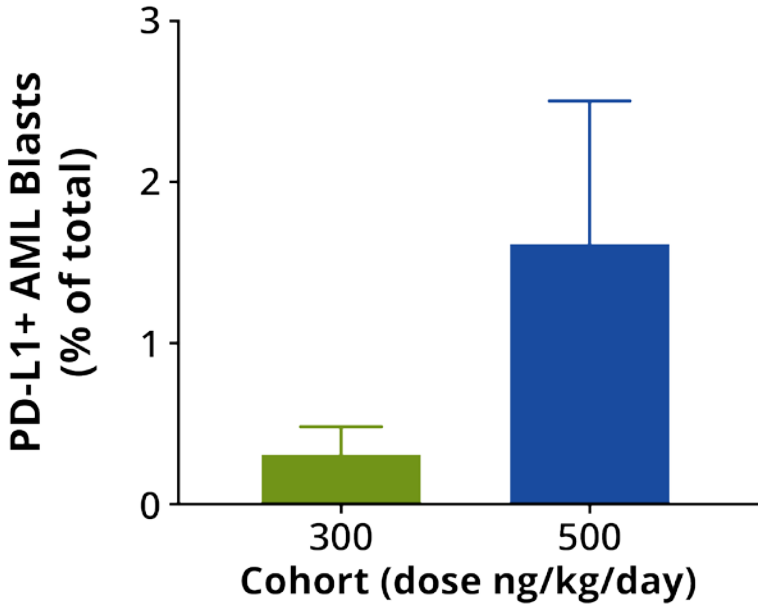


IFNγ Secretion and PD-L1 Expression in Patients Treated with Flotetuzumab

Circulating IFNγ in AML patients treated with flotetuzumab

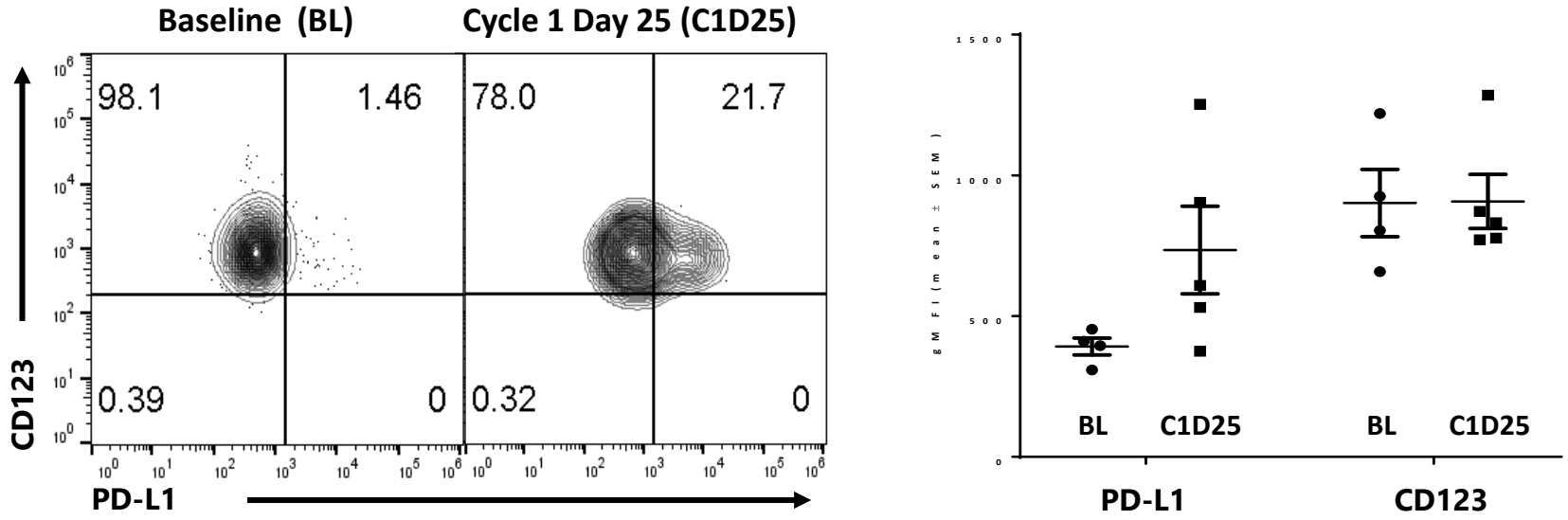


PD-L1 expression on circulating AML blasts



Flotetuzumab

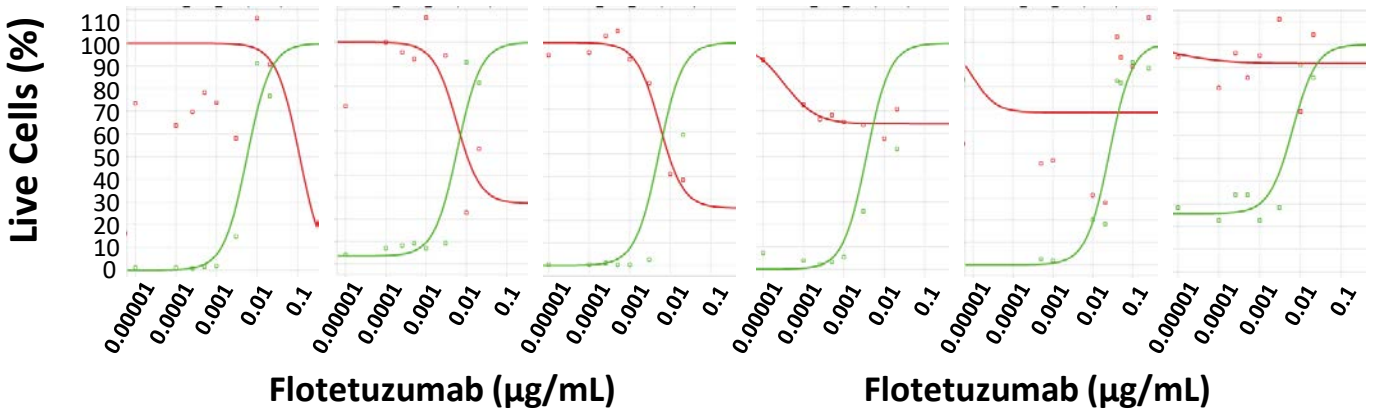
PD-L1 on Residual AML Bone Marrow Blasts After Flotetuzumab Treatment



Residual AML blasts from bone marrow of patients treated with flotetuzumab showed increased expression of PD-L1 compared to baseline

PD-L1 Expression is Associated with Decreased Flotetuzumab Activity In Vitro

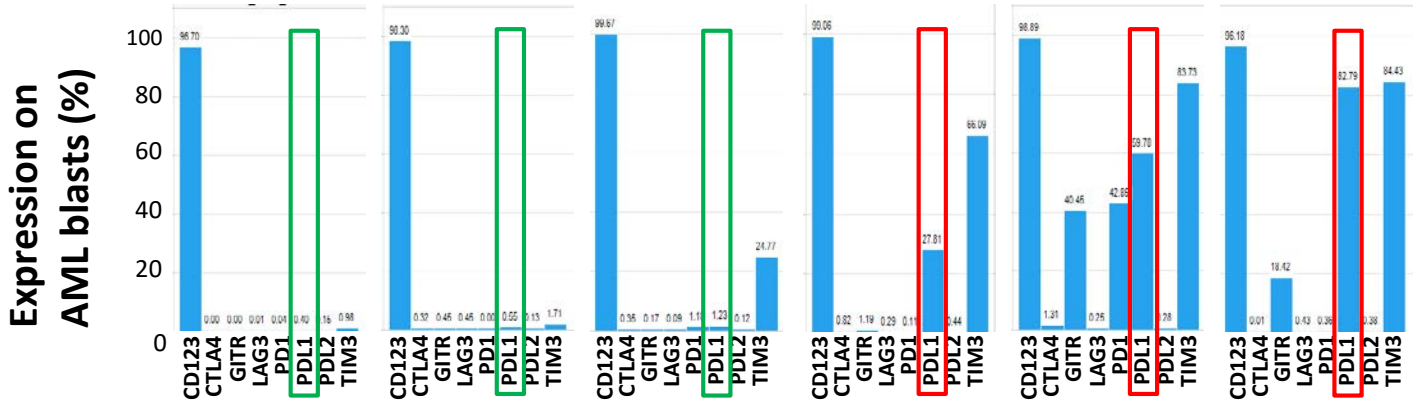
T cell activation and depletion of AML blasts by flotetuzumab in vitro.



- High anti-leukemic activity
- Low PD-L1 expression

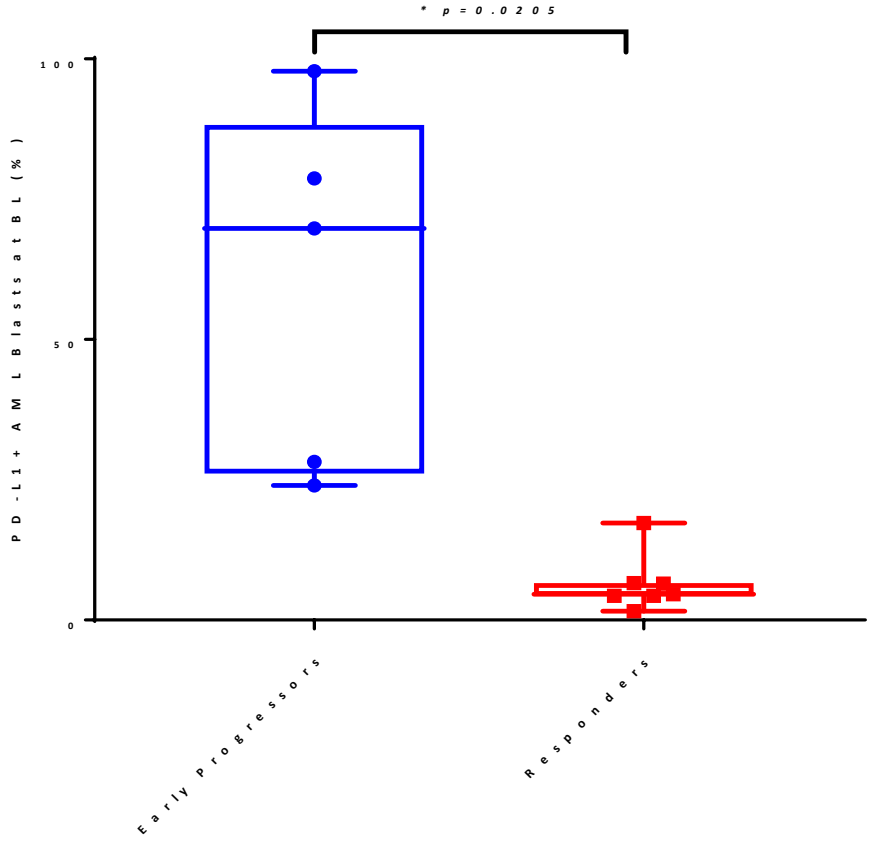
- Low anti-leukemic activity
- High PD-L1 expression

Expression of immune checkpoint inhibitors on AML blasts was associated with lower anti-leukemic activity of flotetuzumab.

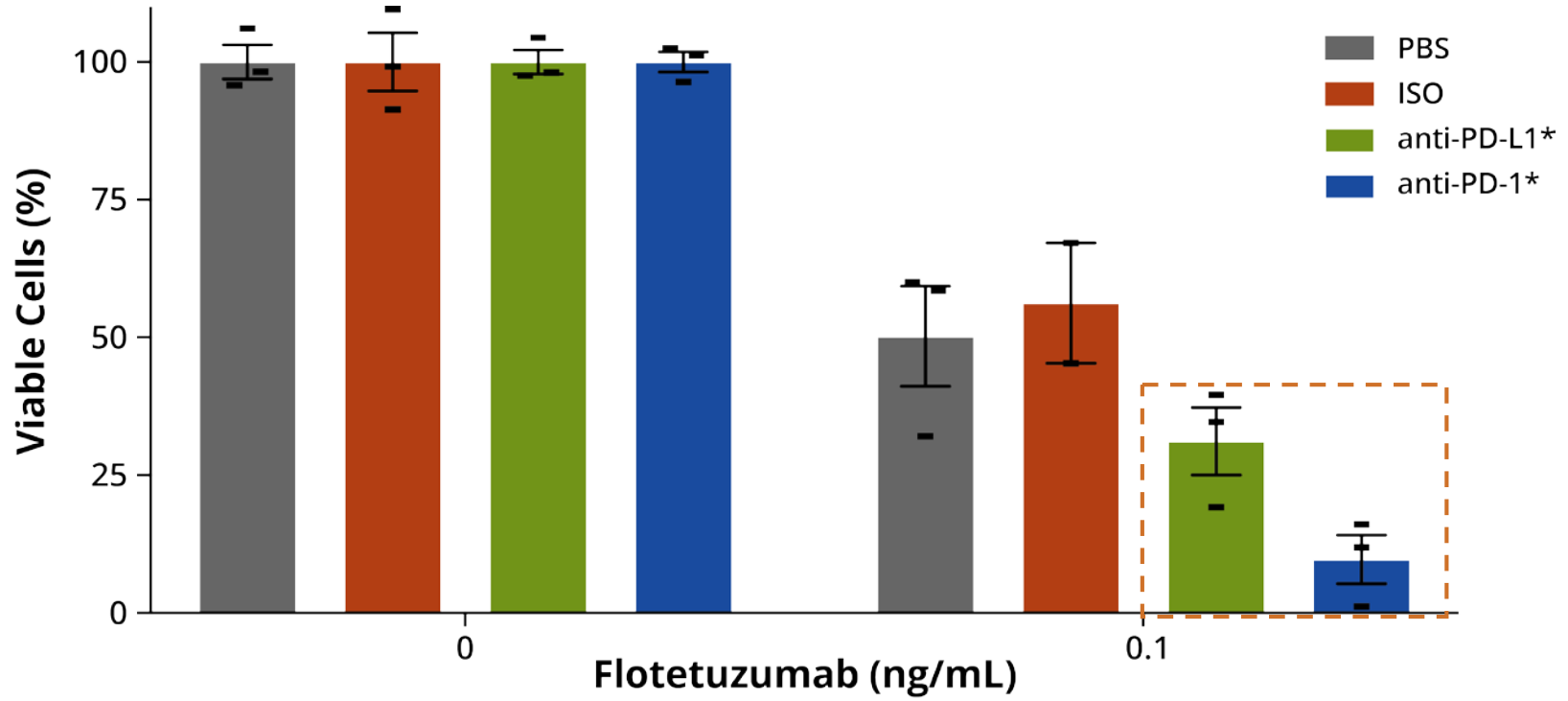


PD-L1 Expression is Associated with Decreased Flotetuzumab Activity In Vivo

Patients who progressed early (<15 days) on flotetuzumab treatment had higher baseline levels of PD-L1 on AML cells than patients who had evidence of antileukemic activity.



PD-1/PD-L1 Blockade Enhances Flotetuzumab Anti-leukemic Activity In Vitro



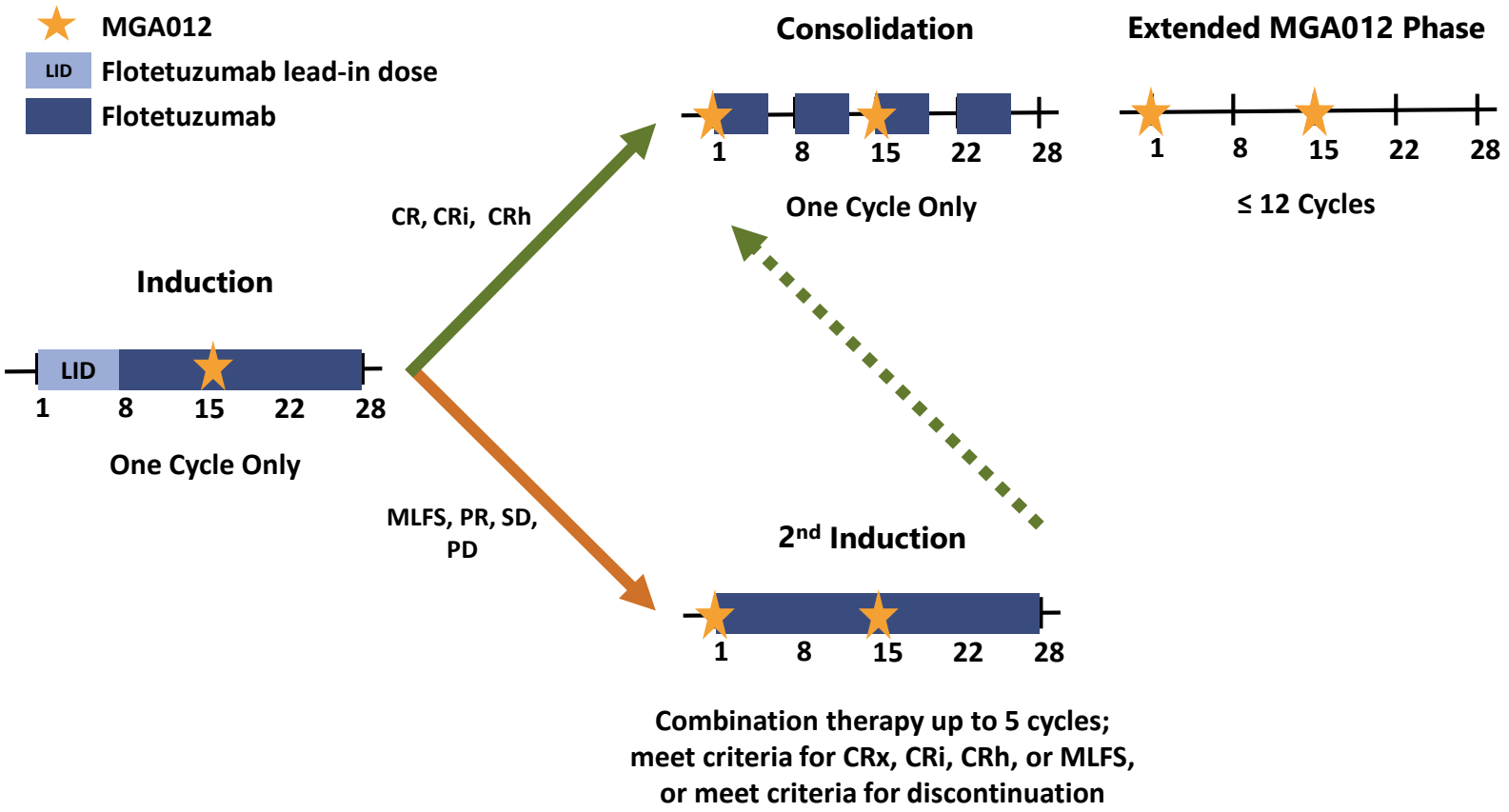
Flotetuzumab combined with an anti-checkpoint antibody showed synergistic T-cell mediated cytotoxicity of an AML cell line (KG1A)
*$p<0.05$

Checkpoint Blockade May Enhance Anti-leukemic Activity of Flotetuzumab

- Flotetuzumab, in clinical and/or preclinical studies, led to:
  - increased T cell infiltration and activation in the bone marrow,
  - enhanced secretion of IFNγ,
  - upregulation of checkpoint molecules on subset of AML blasts.
- PD-L1 is upregulated in residual AML blasts after treatment with flotetuzumab
- Flotetuzumab combined with an anti-checkpoint antibody in vitro showed synergistic T-cell mediated cytotoxicity of an AML cell line.
- Flotetuzumab combined with PD-1 inhibition aims to obviate pathways of AML resistance and harness positive changes of immune modulation induced by flotetuzumab.

Flotetuzumab + MGA012 (Anti-PD-1 mAb) Combination Study in R/R AML

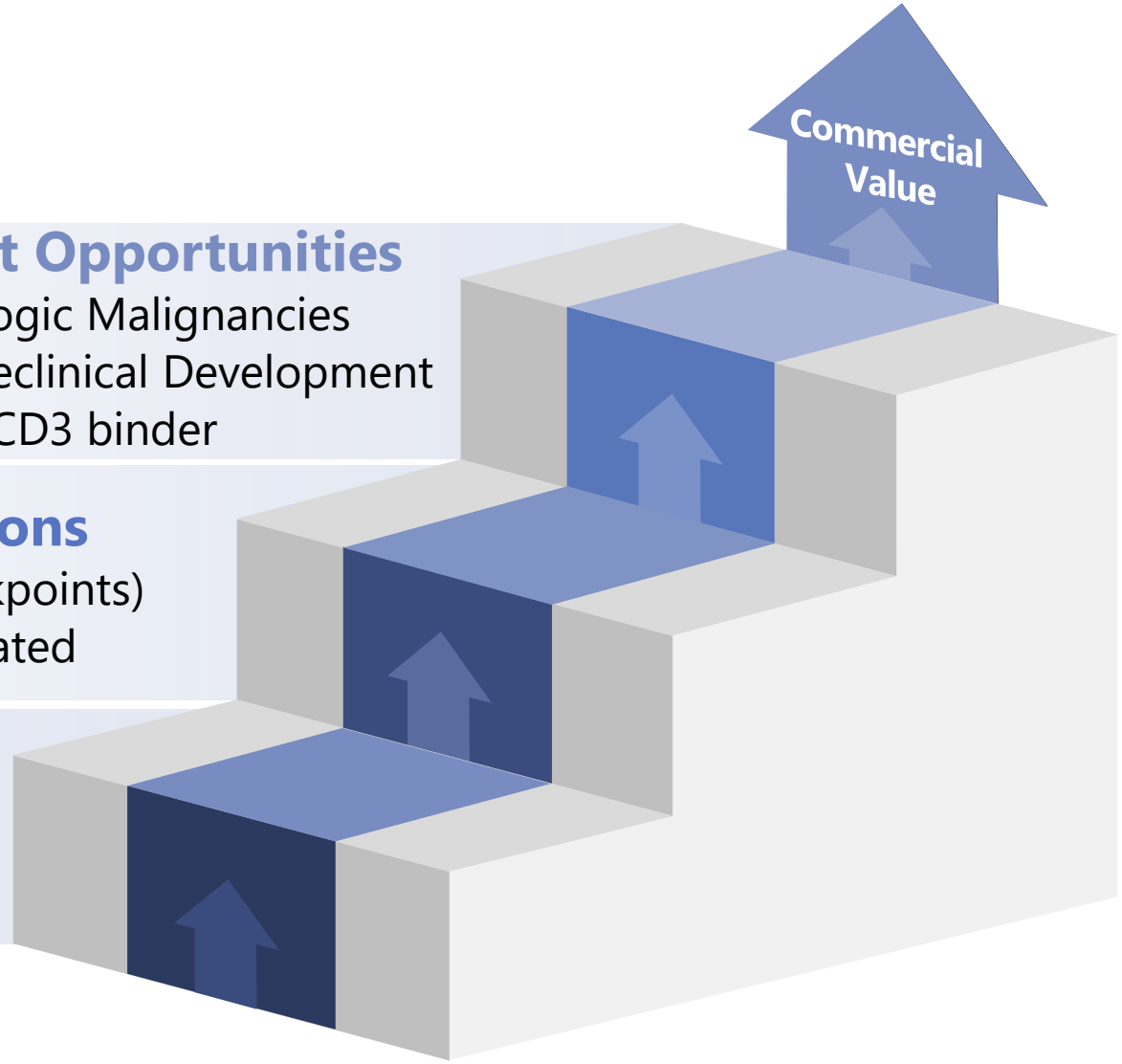
Phase 1 dose escalation study design



- **Induction** with flotetuzumab is administered by step-up, lead-in dosing, followed by continuous infusion, starting at week 2 and continuing through 28-day cycles.
- **Consolidation or second induction** with flotetuzumab based on response.
- MGA012 is administered every two weeks.
- **Maintenance** with MGA012 monotherapy for up to 12 months for eligible patients who achieved a complete remission during induction/consolidation.

Study is being conducted ex-US (in Australia, Spain and Israel).
CR=complete remission. CRh=CR with partial hematologic recovery. CRi=CR with incomplete hematological recovery. MLFS=morphologic leukemia-free state. Response evaluation determined by modified ELN 2017 criteria.

Capturing Full Potential of Flotetuzumab and CD123 x CD3 Bispecific Molecules



Future Development Opportunities

- Other CD123+ Hematologic Malignancies
- 2nd Gen. Molecule in Preclinical Development
  - Fc-bearing; alternate CD3 binder

Expand Through Combinations

- Relapsed/Refractory AML (w/checkpoints)
  - Combination with MGA012 initiated

Potential First Indication

- Primary Induction Failure/Early Relapsed AML
  - Pivotal monotherapy study being planned*

*Pending ongoing discussions with FDA

Key Takeaways

Scott Koenig, M.D., Ph.D.

President and Chief Executive Officer, MacroGenics

Flotetuzumab Potential First-in-Class Molecule for the Treatment of AML

- **Path to a potential approval in primary refractory and early relapse patients**
  - Significant anti-leukemic activity observed (~32% CR/CRh/CRi rate) in hard-to-treat population
  - Immune signature supports mechanism and may predict response
  - Pivotal study being planned, discussions with FDA ongoing, update anticipated 1H2020
- **Significant patient opportunity**
  - No agents specifically approved for primary refractory population
  - Agnostic to known, targetable, disease-associated mutations
  - Continuous infusion not a barrier to implementation and helps exposure
  - 2nd generation molecule to expand addressable indications
- **Compelling rationale for combination with anti-PD-1**
  - May enhance the effect of flotetuzumab and obviate resistance
  - Phase 1/2 study in relapsed/refractory AML initiated (ex-US)

CR=complete remission. CRh=CR with partial hematologic recovery. CRi=CR with incomplete hematological recovery.

Q&A Session

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Thank You!

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