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Interim Results from a Phase 1 First-in-Human Study of Flotetuzumab, a CD123 x CD3 Bispecific DART® Molecule, in AML/MDS

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Disclosure

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IL-3 Receptor α (IL-3Rα): CD123

- Low affinity ligand binding subunit of IL-3R
- Binds IL-3 and heterodimerizes with common β subunit of GM-IL-5-IL-3 receptor complex to induce proliferative and anti-apoptotic signaling
- Differentially overexpressed in 93% of AML patients
- CD123 is expressed on AML LSC
- Correlation between CD123+ cells frequency and prognosis

Disease	CD123 Positivity
AML	93%
MDS	>50%
CML	>50 - 77.5%
B-cell ALL	80 - 99%
Classical Hodgkin's Lymphoma	50 - 60 %
Hairy Cell Leukemia	100%
CLL	10%
Systemic Mastocytosis	>50 - 100%
pDC Leukemia	100%

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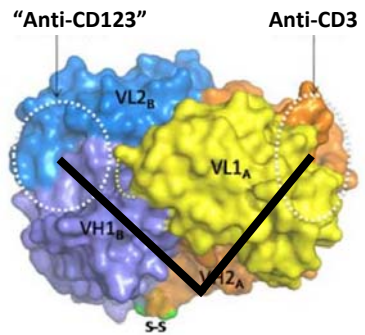
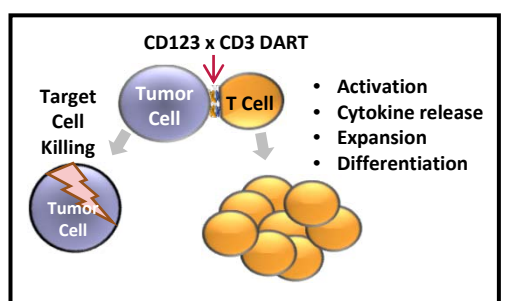
Flotetuzumab: CD123 x CD3 Bispecific DART® Protein

- DART bispecific platform
  - Multiple applications across different diseases
  - Predictable manufacturability
  - Long-term stability
  - 'Plug and Play' flexibility
  - Ability to tailor half-life and valency
- Multiple DART molecules in clinical testing
- Flotetuzumab (MGD006/S80880) mode of action: redirected T-cell killing of CD123+ Cells
- Flotetuzumab has short half-life, requiring continuous infusion





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Chichili, et al. Sci Transl Med. 2015 May 27;7(289)

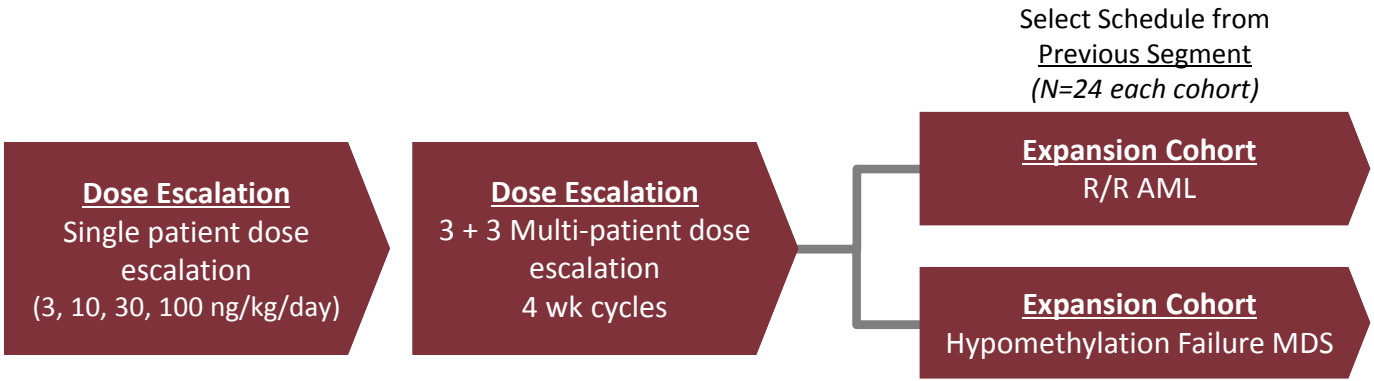
Flotetuzumab Phase 1 Study objectives

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

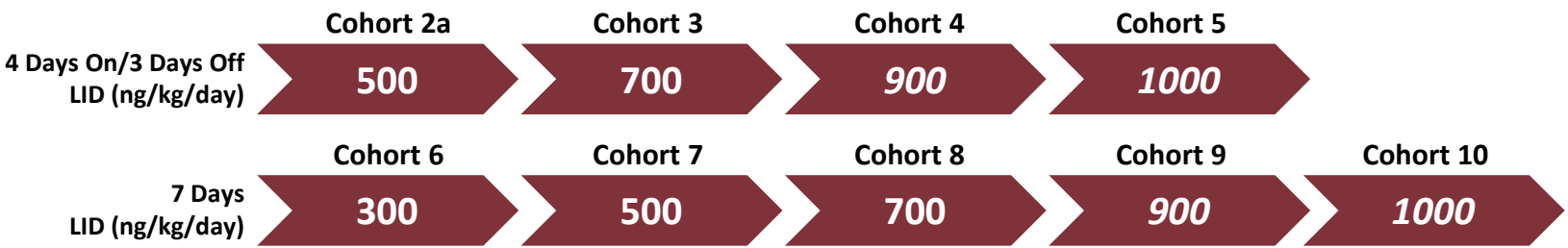
Flotetuzumab Phase 1 Key Inclusion/Exclusion Criteria

- Refractory AML unlikely to benefit from cytotoxic chemotherapy
- Patients with MDS must have experienced treatment failure with induction therapy or hypomethylating therapy and have ≥10% marrow blasts
- Prior history of allogeneic stem cell transplant is exclusionary

Flotetuzumab Phase 1 Study Design



Current Dosing Scheme in Multi-Patient Dose Escalation



Lead-in Dose	• LID: Week 1 30 ng/kg/day x 3 days, 100 ng/kg/day x 4 days
Cycle 1 Weeks 2-4	• Arm A: (Cohorts 2-5): 4-on 3-off schedule • Arm B: (Cohorts 6-10): 21 days continuous infusion
Cycle 2 and Beyond	• 4-on 3-off schedule

Flotetuzumab Phase 1 Patient Demographics

Characteristic		All Patients (n=47)*
Age	Mean ± SD	62.9 ± 14.35
	Median (Range)	64.0 (29.0, 84.0)
Gender [n(%0)]	Female	21 (44.7)
Diagnosis [n (%)]	MDS	5 (10.6)
	AML	42 (89.4)
AML Subclassification	Relapse	10 (23.8)
	Refractory	23 (54.7)
	HMA Treatment failure	9 (21.4)
AML Risk Stratification (ELN 2017)	Favorable	3 (6.8)
	Intermediate	16 (36.4)
	Adverse	25 (56.8)
MDS IPSS Risk Category	Intermediate-1	1 (20.0)
	Intermediate-2	2 (40.0)
	High	2 (40.0)

**Cutoff date: August 1, 2017 (excluding AML risk stratification, n=44 evaluable pts).*

Flotetuzumab Phase 1 Study Safety Overview*

Adverse Event	Related to Flotetuzumab	
	All (N=47)	≥ Gr 3
Infusion related reaction	36 (76.6)	6 (12.8)
Pyrexia	11 (23.4)	
Chills	7 (14.9)	
Hypotension	5 (10.6)	
Platelet count decreased	7 (14.9)	6 (12.8)
White blood cell count decreased	6 (12.8)	5 (10.6)
Lymphocyte count decreased	6 (12.8)	6 (12.8)
Anaemia	5 (10.6)	5 (10.6)
Febrile neutropenia	5 (10.6)	5 (10.6)
Hypocalcaemia	7 (14.9)	
Blood bilirubin increased	6 (12.8)	
Hypomagnesaemia	6 (12.8)	
Hypokalaemia	5 (10.6)	
Nausea	9 (19.1)	
Vomiting	6 (12.8)	
Diarrhea	5 (10.6)	
Fatigue	6 (12.8)	
Arthralgia	5 (10.6)	

**Cutoff date: August 1, 2017; Events occurring in ≥10% of the population.*

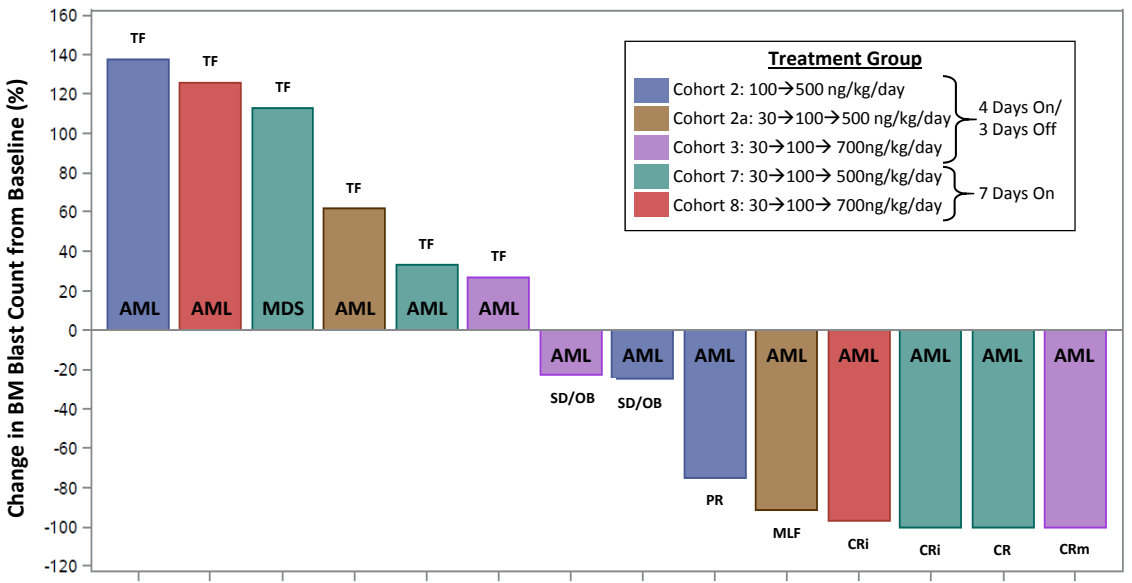
Flotetuzumab Phase 1 Safety

- Flotetuzumab has demonstrated acceptable tolerability to date
- MTDS @500ng/kg/day 7 day continuous infusion
  - DLTs @700ng/kg/day dose included Grade 3 IRR/CRS (2pts) and Grade 3 myalgia (1pt)
  - One drug-related CNS AE leading to discontinuation
- Infusion-related reaction/cytokine release syndrome (IRR/CRS)
  - Any grade: 36/47 (76.6%)
  - Grade 3 in only 6/47 (12.8%)
  - Discontinued due to IRR/CRS: 4/47 (8.5%)
- Successful intervention to decrease severity and incidence of CRS:
  - Early anti-cytokine therapy (tocilizumab) to limit CRS progression
  - Two-step LID during week 1 (30ng/kg → 100ng/kg → Target dose)

Cutoff date: August 1, 2017; Safety population = 47 pts.

Anti-Leukemic Activity at Threshold Dose ≥ 500 ng/kg

Of 14 patients treated with flotetuzumab at threshold dose ≥ 500 ng/kg/day who received ≥ one cycle of treatment and had post-treatment bone marrow biopsy



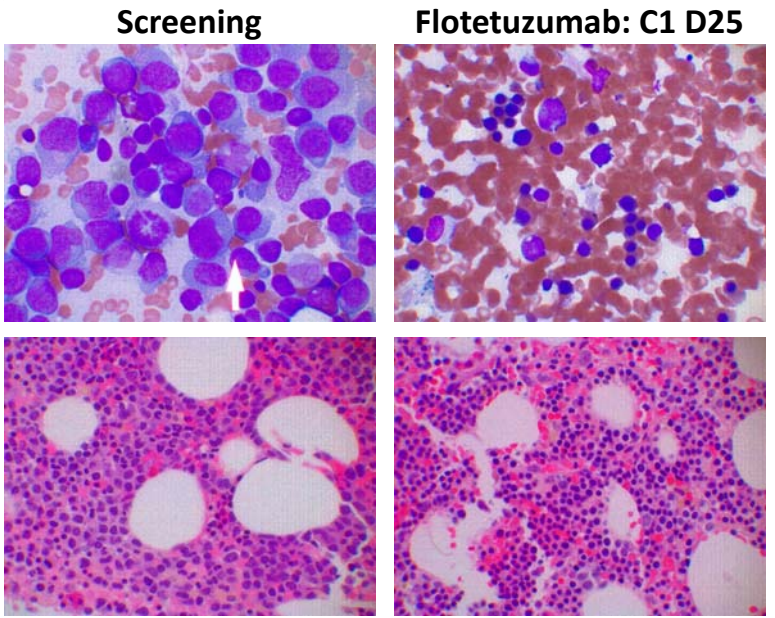
- Rapid responses after single cycle of therapy in majority of patients that respond (cycles ≤ 2)
- Anti-leukemic activity observed in 8/14 pts (57%)
- Objective resp. rate (CR/CRi/MLF/PR): 6/14 pts (43%)
- CR Rate: 4/14 (28%) (CR/CRi)

CR = Complete Response; CRm = molecular CR; CRi = Complete Response with incomplete hematological improvement; MLF = Morphologic Leukemia-free state; PR = Partial Response; SD/OB = Stable Disease/Other Anti-Leukemic Benefit; TF = Treatment Failure (ENL)

Clinical Vignette: 74 Year-Old Female AML Patient

Refractory therapy-related AML (≥ 2 induction attempts - SGN-CD33A ± Aza and 5 cycles of HMA) enrolled on cohort 3 (700ng/kg/day, 4 on /3 days off)

- <u>BM biopsy:</u>
  - 70% myeloblasts, CD13, CD34, CD117, CD123
  - Cytogenetics: 92,XXXX, t(14;21)(q22;q22)x2[4]46, XX[16]
  - *IDH1 p.R132C*
- <u>Response:</u>
  - C1D25 Morphological/Cytogenetic CR
  - C2D25 Molecular CR post-Cycle 2 of flotetuzumab loss of *IDH1*^{mut} by NGS
- In continuous CR at 3 months



Conclusions

- Flotetuzumab is a highly potent CD123 x CD3 bispecific DART molecule that redirects T-cells to kill CD123-positive AML blasts, in vitro and/or in vivo
- In patients with AML or MDS, flotetuzumab has an acceptable safety profile
  - CRS (≥ G3) and neurotoxicity, to date, compare favorably to CAR-T cells and blinatumomab
- Encouraging initial anti-leukemic activity at ≥ 500 ng/kg/day (threshold dose)
  - Objective RR (CR/CRi/MLF/PR) = 43%
- Cohort expansion (n=24 AML, n=24 MDS) now ongoing and enrolling at 11 sites in US and EU (clinical update anticipated later this year)

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