



CD33 Program Overview and Update

Introducing Combination Study of Actimab-A + CLAG-M

February 13, 2018

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Today's Call Leaders

Dr. Ehab Atallah

Associate Professor of Medicine



Sandesh Seth

Chairman & CEO

Dr. Mark Berger

Chief Medical Officer



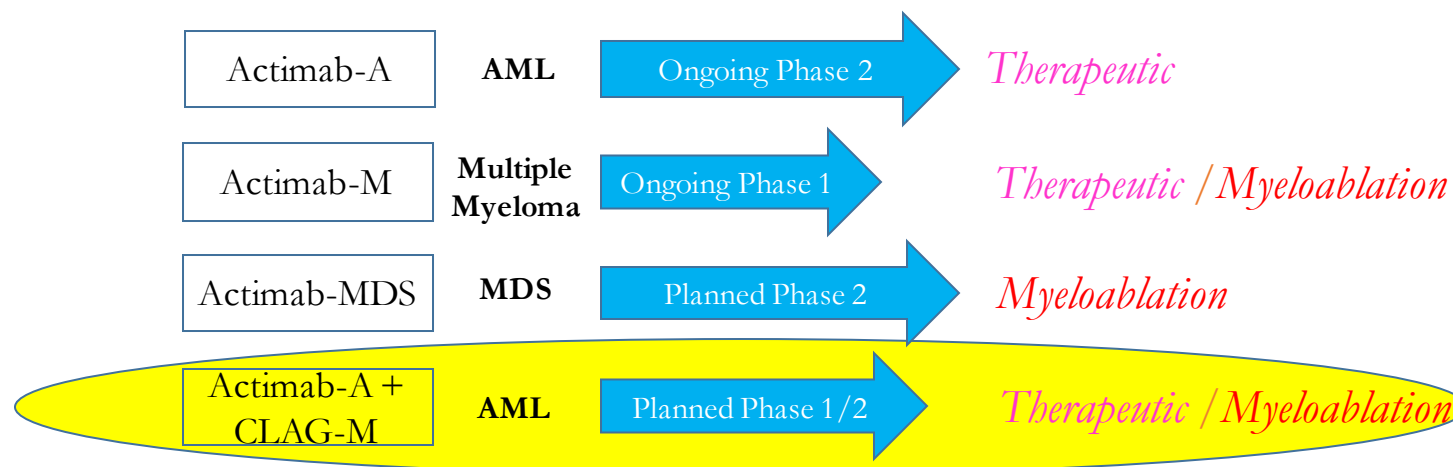
Agenda for Today's Call

	Slide Number
I. Executive Overview..... <i>Sandesh Seth</i>	5 – 6
II. CD33 Program Overview and Intro to CLAG-M <i>Mark Berger, M.D.</i>	8 – 15
III. Actimab-A + CLAG-M for Relapsed/Refractory AML..... <i>Ehab Atallah, M.D.</i>	17 – 21
IV. Outlook for CD33 Program and Summary..... <i>Sandesh Seth</i>	23 - 24
IV. Question and Answer Session..... <i>Ehab Atallah, M.D., Mark Berger, M.D. & Sandesh Seth</i>	

CD33 Program Expansion – Combination Therapy

Program Expansion Enabled By ARC Technology Capabilities Spurring Investigator Led Trials to Address Unmet Needs

- ◆ Only multi-disease CD33 asset in development
- ◆ Expansion driven by investigator support
- ◆ Highly differentiated technological approach



Actinium's CD33 Program Strategy for 2018

Objective is to extend our leadership position as the only multi-disease CD33 Program in the industry with best in class potential

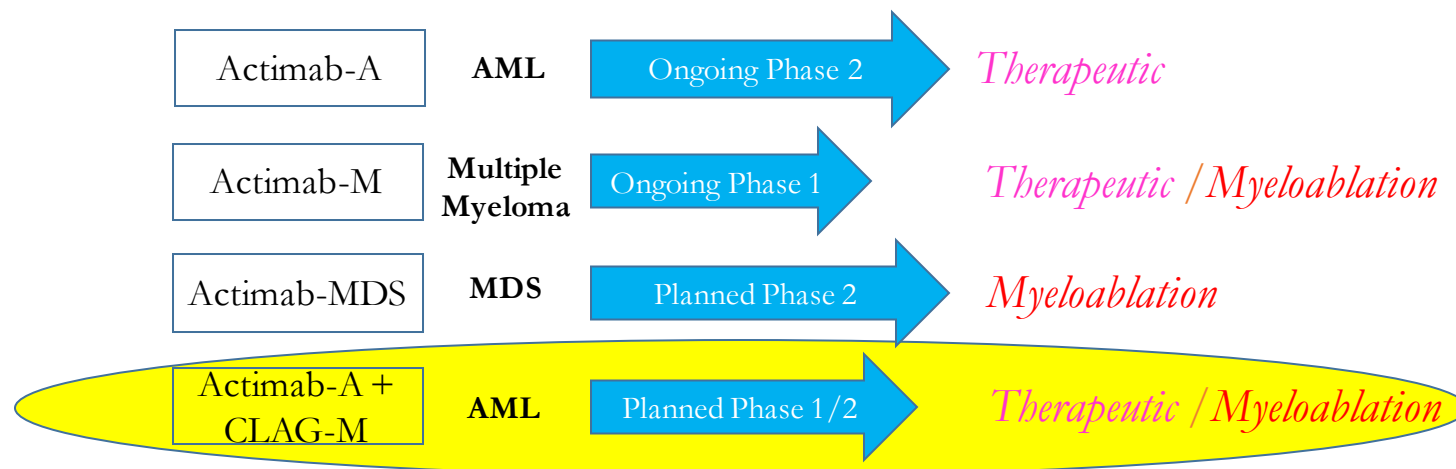
- ◆ Maximize the value of our CD33 program for 2018 by
 - Generating proof-of-concept data for the Actimab-A Phase 2 trial by mid-2018
 - Generating proof-of-concept data for the Actimab-M Phase 1 trial in 2018
 - Receiving FDA guidance for Actimab-MDS by mid 2018
 - Initiating the Actimab-MDS trial with the MDS Clinical Consortium in 2H:2018
 - Develop Actimab-A in combination [e.g. cytotoxic chemotherapy, targeted agents , immunotherapy] in preparation for further development
- ◆ Unveil new information that will further strengthen and differentiate our CD33 program and solidify its best-in-class status
- ◆ Optimize the profile of the CD33 program to enable collaborations and partnering as appropriate

CD33 Program Overview

Introduction to CLAG-M

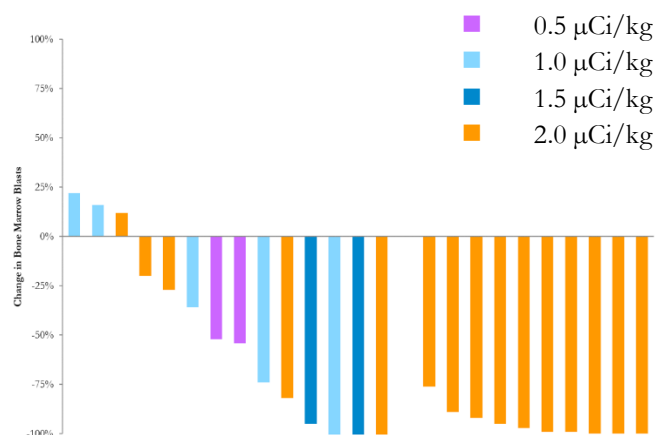
CD33 Program Birdseye View

- ♦ ARC technology has multiple advantage over other approaches
 - Minimal extramedullary toxicities – particularly no veno-occlusive disease
 - Construct is not reliant on internalization for efficacy
 - Potency of isotope results in minimal protein doses
 - Treatment consists of 1 or 2 infusions



Actimab-A: Compelling Clinical Data in AML

High blast reduction and strong response rates



Phase 1 Results²

Dose Level (µCi/kg/fraction)	Low PB patient Response Rate (CRc)
2 x 0.5	0%
2 x 1.0	33%
2 x 1.5	67%
2 x 2.0	50%

Phase 2 – ASH ‘17³

Dose Level (µCi/kg/fraction)	Response Rate (CRc) All low PB
2 x 1.5	Enrolling
2 x 2.0	69% (9/13)

- ◆ Actimab-A Phase 2 trial data was reported at ASH in December 2017
- ◆ Overall Response Rate (ORR) of 69% and median reduction in bone marrow blasts of 98%
- ◆ Median patient age of 75, with 67% having prior hematologic disease and all patients being unfit
- ◆ Minimal extramedullary toxicities, myelosuppression was prolonged given patient population
- ◆ Enrollment continuing at 1.5 µCi/kg/fraction
- ◆ Phase 2 data driving potential combinations with other therapeutic modalities

Advantages of ARC's or Antibody Radiation Conjugates

ARC technology has distinct advantages over other modalities targeting CD33

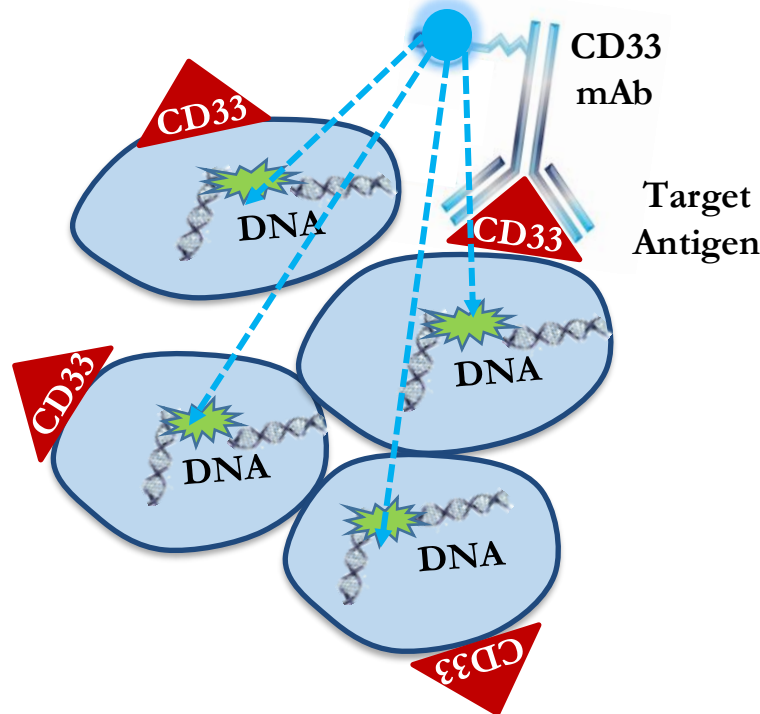
Range: .06 mm

Energy: 6 MeV

Actinium-225

CD33
mAb

Target
Antigen

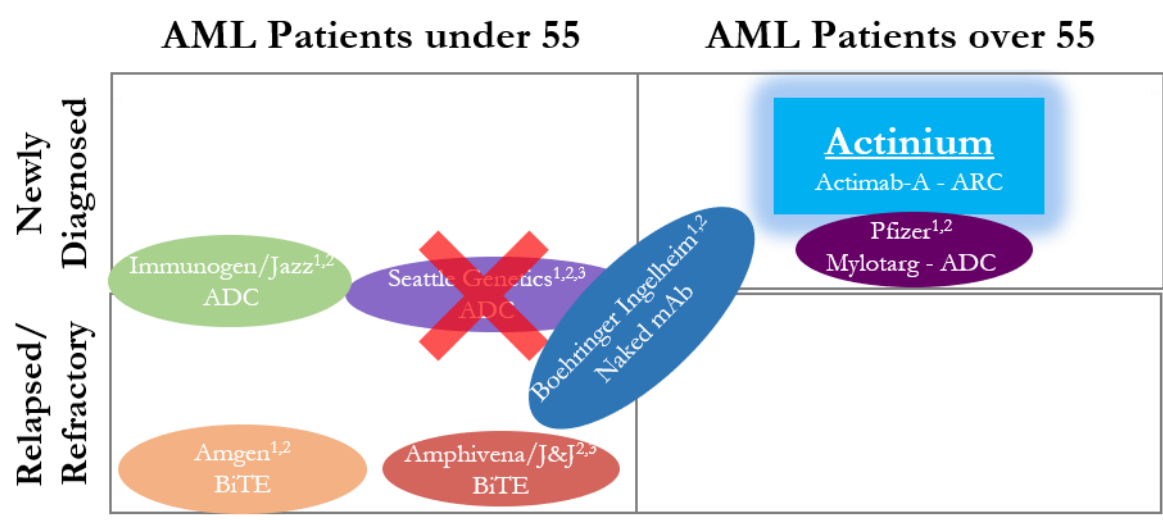


CD33 is expressed in approximately 90% of AML patients, 25%-35% of Multiple Myeloma patients and 75% of MDS patients

Advantages of the ARC approach in CD33

- ◆ ARC – Actinium Radio-Conjugate
- ◆ Very high potency - actinium-225 can kill a cell with a single alpha hit
- ◆ No internalization required unlike antibodies or ADCs
- ◆ No known resistance mechanism
- ◆ Ac-225 potentially capable of overcoming chemotherapy resistance
- ◆ High potency allows for monotherapy
- ◆ Easy administration, short infusion of one or two doses
- ◆ Short path length minimizes damage to normal cells
- ◆ Enhanced safety/tolerability allows focus on “unfit” patients

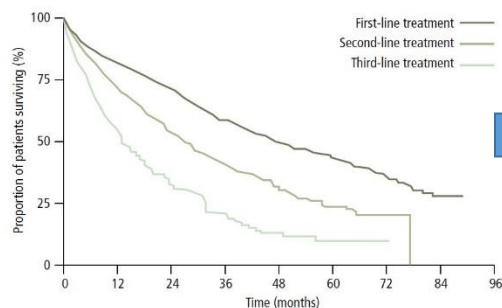
ARC's vs Other CD33 Targeting Approaches



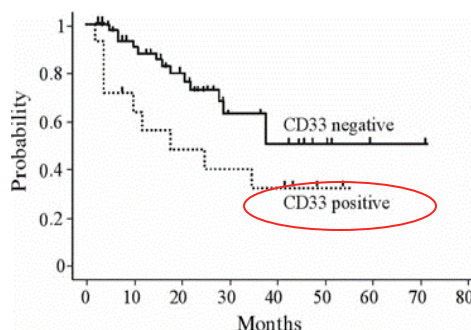
	Naked Antibodies	ADCs	Bispecifics	Actimab-A/ ARC
Monotherapy	✗	✓	✓	✓
Requires Internalization	Preferable	✓	Preferable	✗
Known Resistance Mechanism	✓	✓	✓	✗
Administration	Simple Infusion	Complex Combinations	Continuous IV	Simple 30 min Infusion
Dosing Schedule/Regimen	Complex in Combinations	Complex Combinations	Continuous IV May require pump	2 infusions 7 days apart

Actimab-M: Phase 1 Trial for Multiple Myeloma

Multiple myeloma remains incurable, limited treatment options for refractory patients



Poorer outcomes associated with CD33 expression¹



Sizeable addressable market underserved by existing treatment options

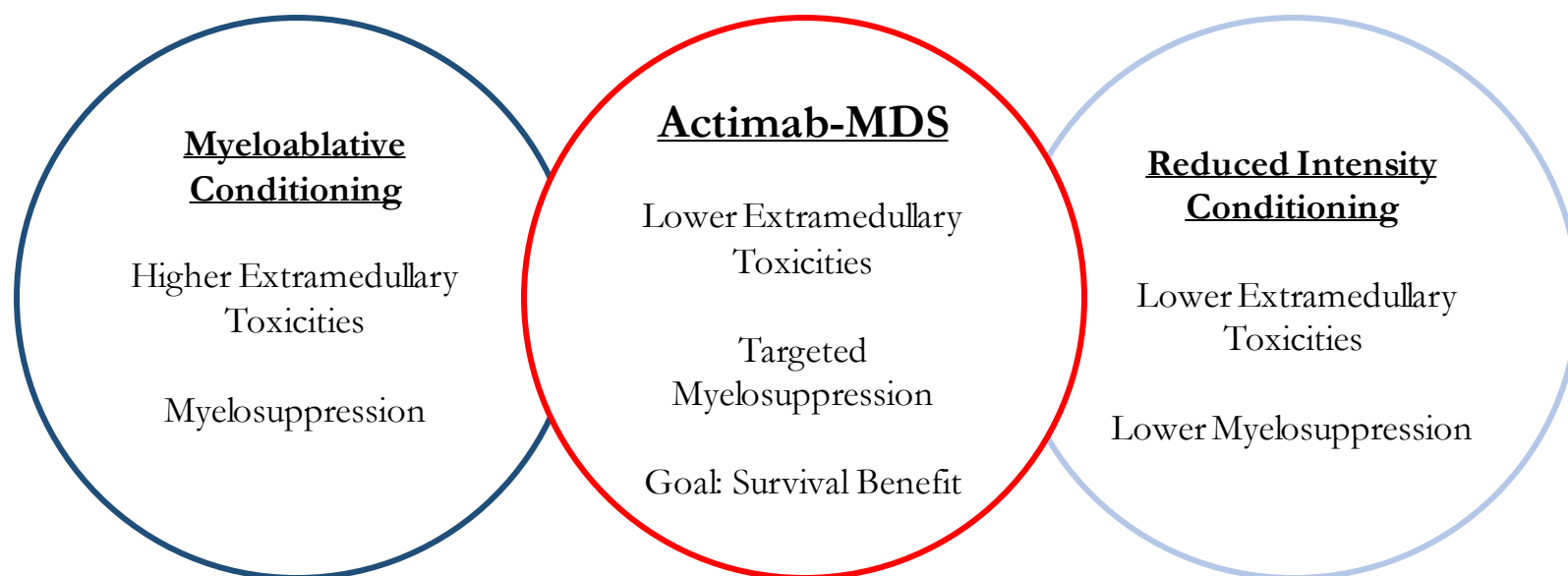
Multiple Myeloma Prevalence	Total # of Patients ³	CD33 Positive ²
US	89,600	22,400
Europe	100,000	25,000
Total	189,600	47,400

- ◆ Significant numbers ~25% - 35% of all myeloma patients have CD33 expression¹
- ◆ CD33 is a risk factor with 3-year mortality 60% greater in CD33+ patients³
- ◆ Actimab-M Proof of Concept trial data expected in 2018
- ◆ Actimab-M is the first and only trial targeting CD33 in multiple myeloma and the only alpha particle therapy for radiation sensitive multiple myeloma

1) Levy, Moshe et al "CD33 Is Expressed in a Significant Subset of Multiple Myeloma Patients in the US and May Represent a Viable Therapeutic Target." Blood 130.Suppl 1 (2017): 5378. Web. 05 Jan. 2018.
 2) H Avet-Loiseau, CD33 is expressed on plasma cells of a significant number of myeloma patients, and may represent a therapeutic target, Leukemia (2005) 19, 2021–2022.)
 3) Onyx Pharmaceuticals, SEER, NCI, ACS, Celgene, Myeloma Euronet, GLOBOCAN, CIBMTR, Kyprolis insert, W Matsui JHI estimate, Ferlay et al Eur J Cancer 2013

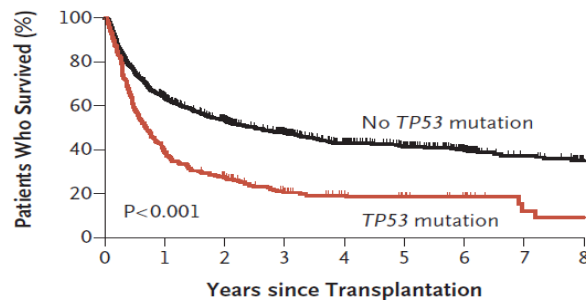
Actimab-MDS: Trial Rationale

- ◆ At 2.0 $\mu\text{Ci/kg/fraction}$ Actimab-A demonstrated prolonged myelosuppression
- ◆ Minimal extramedullary toxicities were seen at this dose level
- ◆ Dr. Gail Roboz, Director, Leukemia Program and Professor of Medicine, saw this data and came up with her “brain child” Actimab-MDS
- ◆ Actimab-MDS will leverage the strengths of our ARC approach to bridge patients with high-risk MDS to a bone marrow transplant

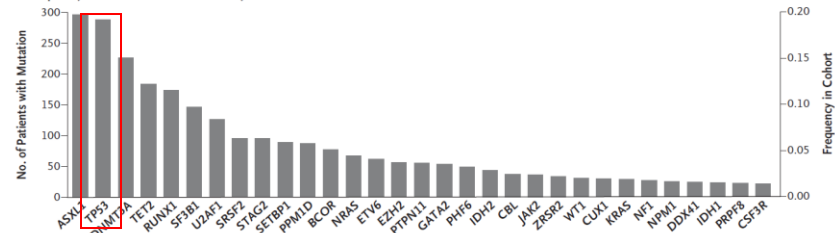


Actimab-MDS: Planned Phase 2 Trial for Myeloablation

Overall Survival, According to TP53 Mutation Status



Frequency of Driver Mutations in Study Cohort



Gail J. Roboz, M.D

Principal Investigator



NewYork-Presbyterian

THE UNIVERSITY OF TEXAS
**MD Anderson
Cancer Center**

Cleveland Clinic

**JOHNS HOPKINS
MEDICINE**

**DANA-FARBER
CANCER INSTITUTE**

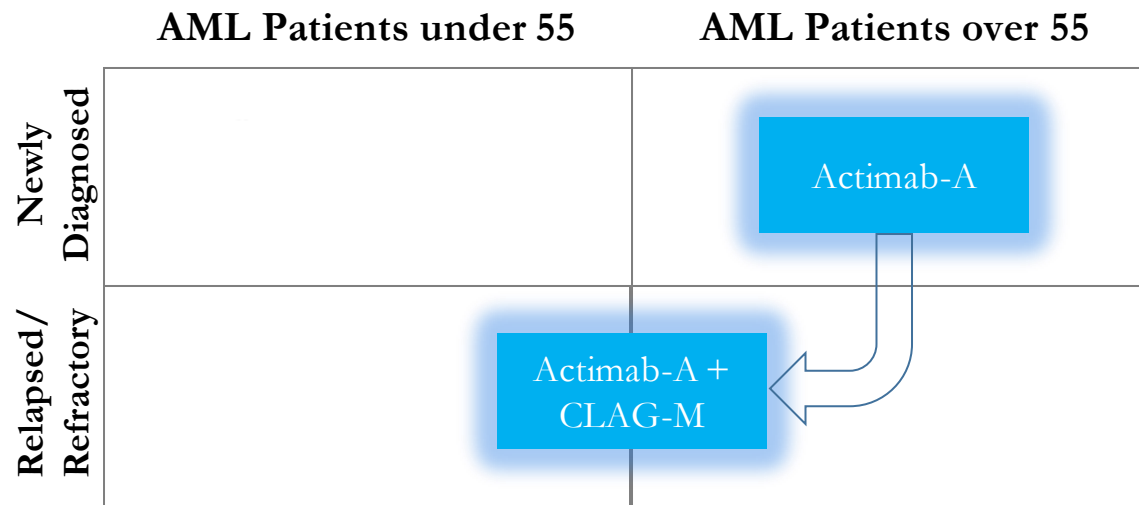
**MOFFITT
CANCER CENTER**

Phase 2 Trial Consortium

- ◆ CD33 is well expressed in 75% of MDS patients , which is a precursor disease to AML
- ◆ Median survival for higher risk MDS patients is < 2 years
- ◆ Especially high unmet medical need in p53 patients, poor survival even with SCT
- ◆ Meeting with FDA in first half 2018 and initiating trial mid-year

- 1) Lindsley, Saveer, Mar, et al, Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation, The New England Journal of Medicine 376:536-47, 2017
- 2) P53 is also referred to as TP53

Actimab-A + CLAG-M: Expanding Patient Access



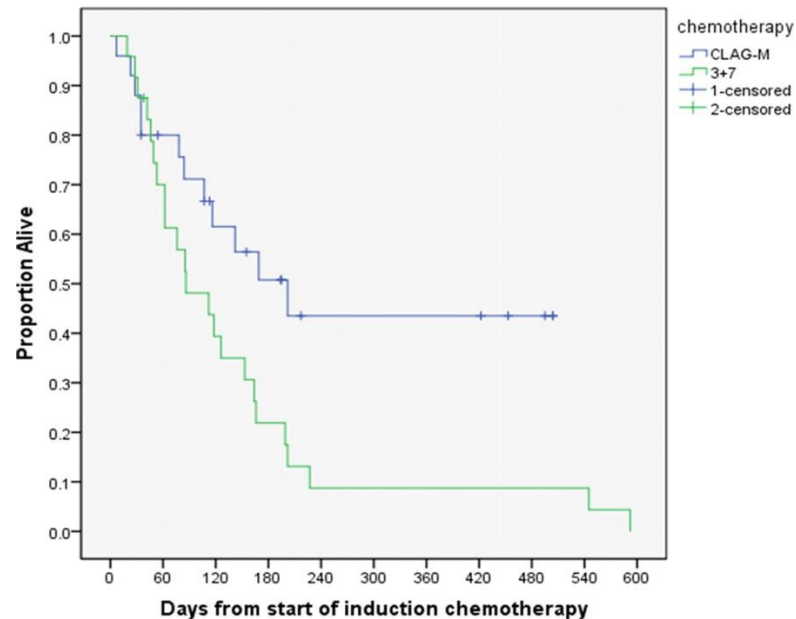
- ◆ Majority of AML patients are over the age of 55
- ◆ Of the patients below 55, ~70% relapse or become refractory to therapy
- ◆ Actimab-A + CLAG-M could be used therapeutically in patients with refractory or relapsed disease, and may also be used in patients in preparation for allogeneic transplant
- ◆ Expands addressable market beyond older, unfit patients to patients that are eligible for chemotherapy as well as younger patients
- ◆ Will demonstrate Actimab-A's ability to be used in combination
- ◆ Further expands our leadership position in development of anti-CD33 therapies

Actimab-A + CLAG-M for Relapsed/Refractory AML

What is CLAG-M?

- ◆ CLAG-M is a salvage chemotherapy regimen used increasingly at leading centers; it consists of:
 - Cladribine (approved for hairy cell leukemia)
 - Cytarabine (approved for combination use in AML)
 - G-CSF (approved for myeloid cell mobilization; stimulates AML cells to divide and thus be more susceptible to cytotoxic chemotherapy)
 - Mitoxantrone (approved for ND AML in combo with Cytarabine)
- ◆ CLAG-M showed great promise in single institution retrospective analysis of AML patients
 - CR of 38%, vs 24% for MEC
 - In primary refractory disease, CR of 46% vs 22%
 - In first relapse, CR of 37% vs 26%

Additional Data Supporting CLAG-M



- CLAG-M has proven to be effective in secondary AML patients
- Benefit seen in these patients when compared to 7+3

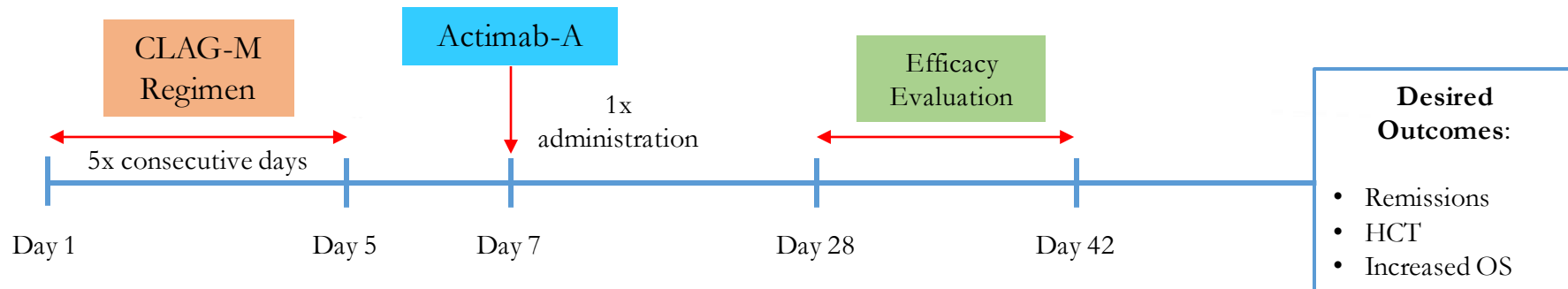
Efficacy of Cladribine, Cytarabine, G-CSF (Neupogen), Mitoxantrone (CLAG-M Regimen) Compared to Standard 3+7 (Anthracydine and Cytarabine) in Secondary Acute Myeloid Leukemia (sAML) After Azanudeosides Failure

Michael V. Jaglal, Vu H. Duong, Celeste M. Bello, Najla H Al Ali, Hugo F. Fernandez, Jeffrey E. Lancet, Alan F. List and Rami S. Komrokji
Blood 2011 118:256;

Actimab-A + CLAG-M Study Rationale

- ◆ Relapsed/refractory AML remains a significant unmet medical need
 - Majority of patients ultimately relapse / are refractory to treatment
 - For these patients, at all ages, including younger ones, access to transplant is limited
 - Regimens such as MEC, FLAG, FLAG-IDA have limited success (~15% CR in Phase 3)
- ◆ However, CLAG-M on its own in relapsed/refractory AML has some limitations
 - CR duration is short with limited gains in OS
 - Modest number of patients proceed to transplant
 - Those who do proceed to transplant mostly relapse
- ◆ There remains no single accepted standard of salvage chemotherapy regimen
- ◆ Allow more AML patients to be eligible for transplant
- ◆ Actimab-A lacks extramedullary toxicity and would allow escalated leukemic cell killing
- ◆ More patients achieving durable CR (ability of Actimab-A to kill chemo-resistant cells)
- ◆ More patients achieving CRi (ability of Actimab-A to kill chemo-resistant cells; potential transplant benefit)
- ◆ Fewer patients relapsing and longer CR duration (eliminate small clusters of leukemic cells (MRD))

Phase 1 Clinical Trial Details



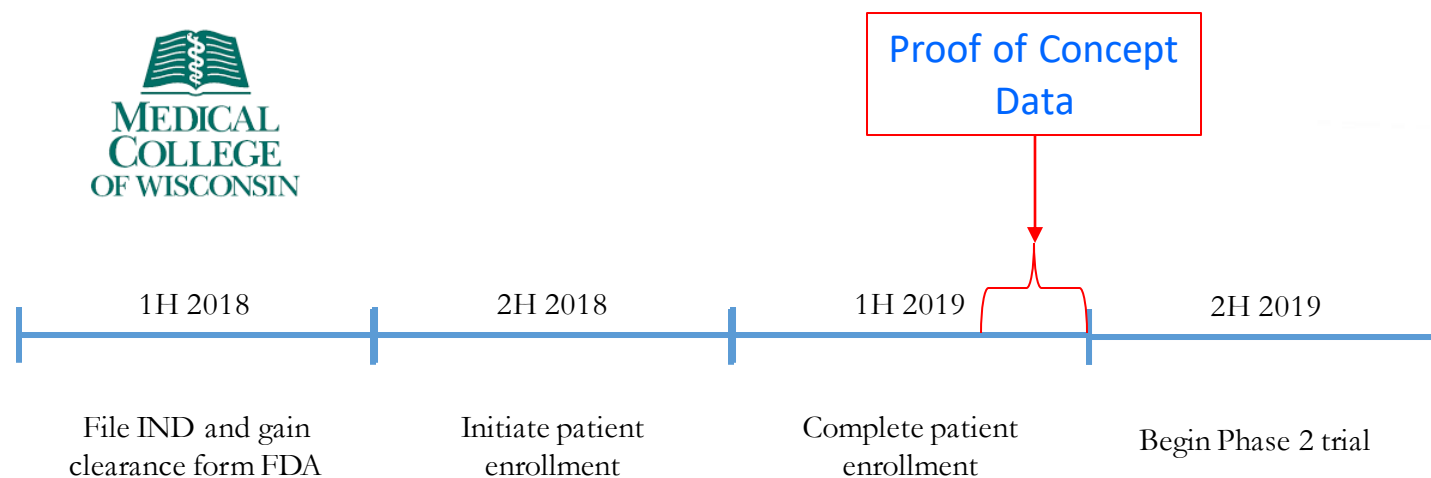
Study Design

- Single dose of Actimab-A on Day 7, CLAG-M clears blasts from peripheral blood by that time, optimizing Actimab-A efficacy
- Explore 3 dose levels (0.25, 0.50 and 0.75 uCi/kg)
- N = up to 18 subjects
- Duration: at least 1 year

Clinical considerations

- Safety monitoring (DLTs, MTD)
- Efficacy determined by CR, CRp, CRi rates; OS (1 year) and PFS
- Patients achieving at least CRi offered transplant 42 days post Actimab-A or after full peripheral blood recovery – whichever occurs sooner
- Future studies will evaluate Actimab-A + CLAG-M at MTD or higher dose for myeloablation prior to transplant

Expected Trial Timeline

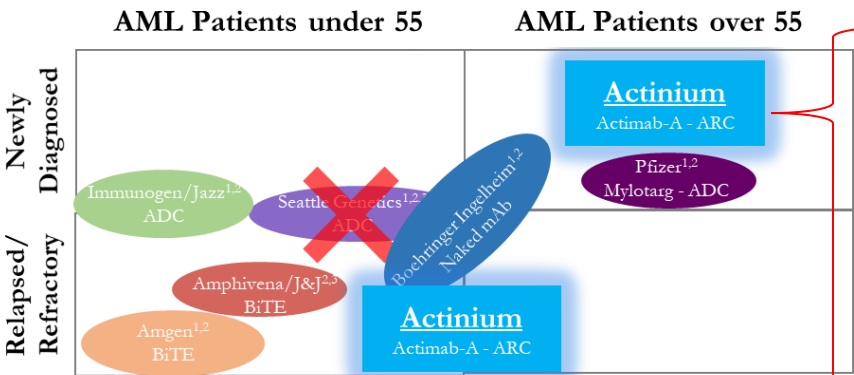


- ◆ Goal is to demonstrate proof of concept as efficiently as possible
- ◆ Medical College of Wisconsin is a leading hematology and transplant center
- ◆ Regulatory and cohort expansion updates to be provided starting in 2H:2018

Outlook for CD33 Program and Summary

Impact of Actimab-A + CLAG-M Trial

Industry focused on AML



Actinium has the only unpartnered CD33 program

Actinium's CD33 Program Expansion

Indication	Development Stage		
	Pre	1	2
AML newly diagnosed	Actimab-A		
High-risk MDS myeloablation	Actimab-MDS (planned)		
Multiple myeloma refractory	Actimab-M		
AML relapsed/refractory	Actimab-A+ CLAG-M		

CD33 Program Disease Prevalence is Meaningful To Even Large Companies

Drug	Disease	Addressable US, EU Market ⁴
Actimab-A,	AML	69,800
Actimab-M	CD33 Positive Multiple Myeloma	47,400
Actimab-MDS	MDS – SCT Prep	14,250

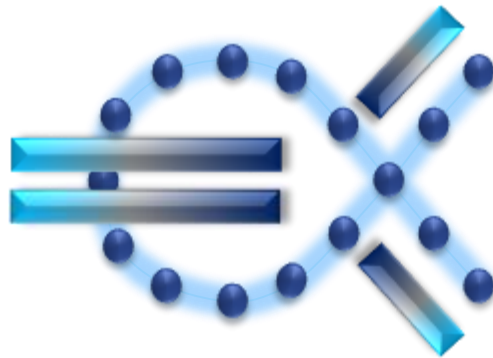
Addressable Patient Population: 131,450

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Thank-You



Actinium Pharmaceuticals, Inc.