Rapid reduction of peripheral blasts in older patients with refractory acute myeloid leukemia (AML) using reinduction with single agent anti-CD45 targeted iodine (^{131}I) apamistamab [Iomab-B] radioimmunotherapy in the phase III SIERRA trial.

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SIERRA
STUDY OF IOMAB-B IN ELDERLY RELAPSED/REFRACTORY AML

Background & Rationale

The SIERRA trial is a prospective, randomized, phase 3, open-label, ongoing multicenter trial for patients aged ≥55 years with active, relapsed/refractory (R/R) AML evaluating allogeneic hematopoietic cell transplantation (HCT) versus conventional care (CC). Recent preliminary data demonstrated robust donor engraftment in all patients treated with Iomab-B (Agura *et al,* Blood 2018 132:1017) despite active disease. Rapid peripheral blast clearance is predictive of CR and RFS after cytotoxic chemotherapy for AML (Elliot *et al,* Blood 2007 110:4172; Gianfaldoni *et al,* BJH 2006 134:54). In the present study we characterize the anti-leukemic effect and rate of peripheral disease reduction by single-agent Iomab-B.

Hypothesis

We hypothesize that successful engraftment following HCT may be related to myeloablation and anti-leukemic activity by single agent Iomab-B prior to RIC.

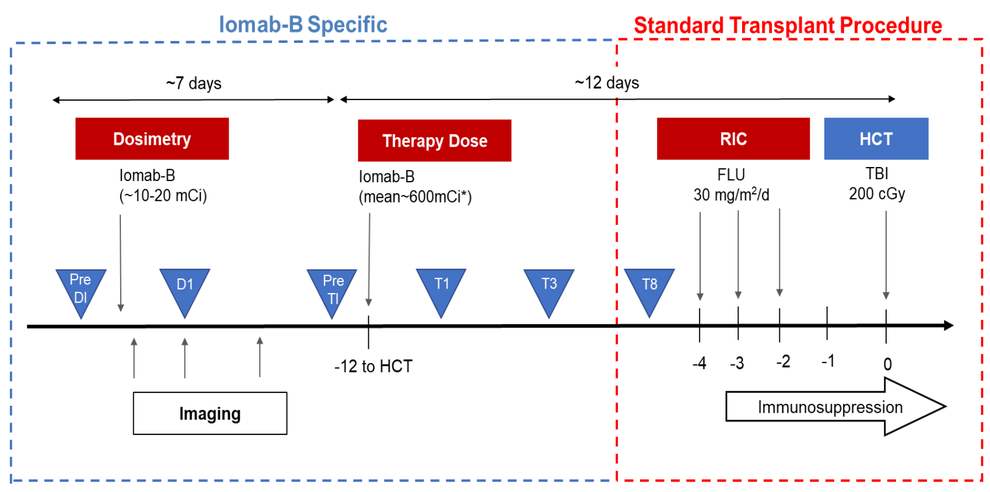
Methods

Patients are randomized to receive Iomab-B and HCT or to a CC therapy including approved targeted agents followed by HCT if in remission. Majority of patients (79%) in the CC arm did not achieve CR and the study allowed crossover to receive Iomab-B.

Results

Data were evaluated for the first 25% of patients (N = 38). 29 patients received Iomab-B, either directly (N = 19) or via crossover (N = 10). Median baseline marrow blasts were 30% (4-74) for Iomab-B and 24% (6-70%) for CC, which increased to 45% (10-70%) at crossover. Peripheral blast data was available in 16 patients (Iomab-B 7, Crossover 9). By day 3 post-Iomab-B, blasts were reduced by 98% with 100% reduction by day 8 (assuming 0% blasts due to lack of differential at WBC 0.1). All patients engrafted with ANC at a median of 13 days (9-22 days). Patients treated with hydroxyurea versus without were analyzed together as well as separately and showed similar results. One patient received hydroxyurea post-Iomab-B therapeutic infusion.

Figure 2: Iomab-B and Peripheral Blood Draw Schedule



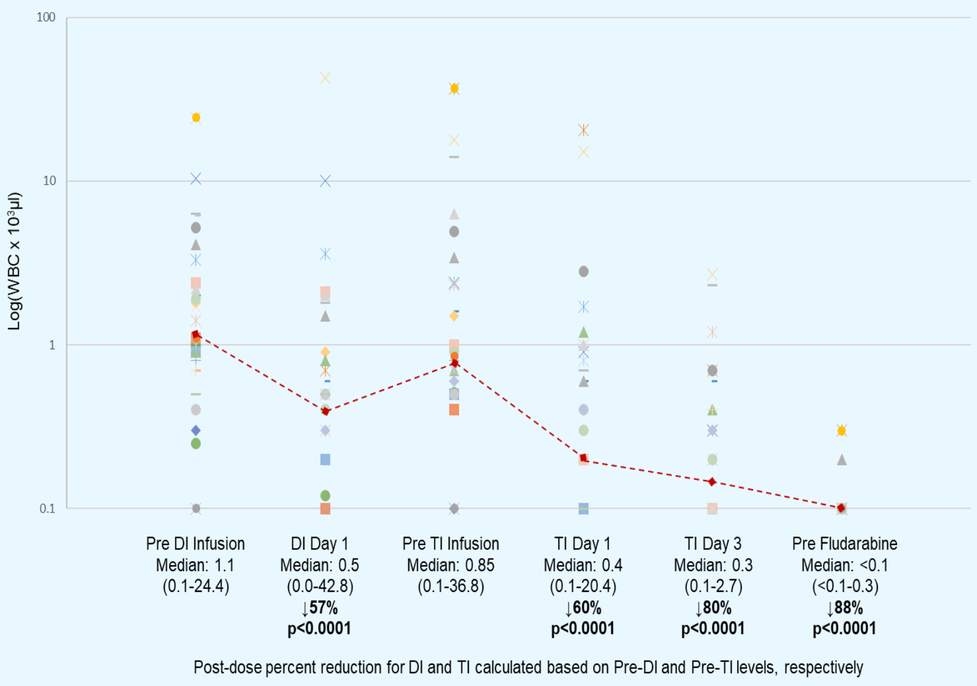
RIC: Reduced Intensity Conditioning FLU: Fludarabine TBI: Total Body Irradiation HCT: Hematopoietic Cell Transplant

*Therapy dose individualized and calculated based on upper limit of 24 Gy liver exposure
Median 17 Gy dose delivered to bone marrow

Table 2: WBC, Absolute Lymphocyte and Absolute Blast Reduction Post Iomab-B

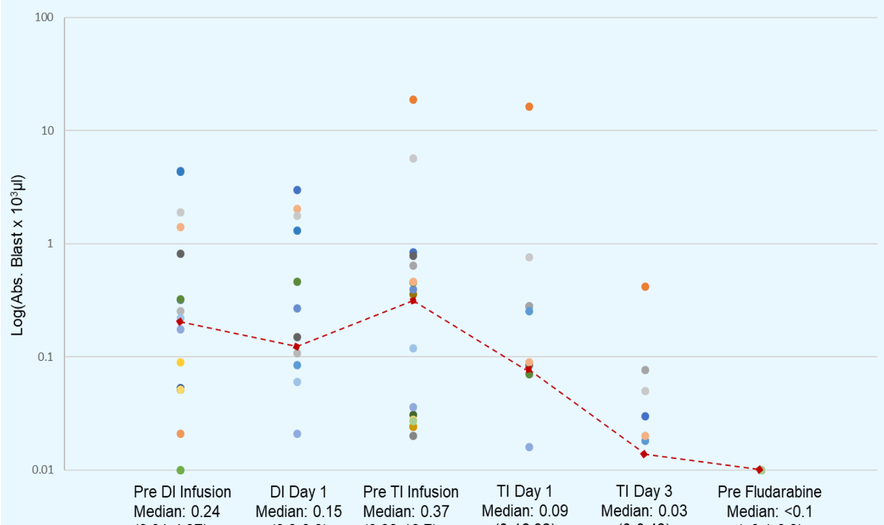
Time Point Assessments	WBC x 10^3 µL (N=30)^	% Reduction	Absolute Lymphocyte x 10^3 µL (N=27)^	% Reduction	Absolute Blast x 10^3 µL (N=16**)	% Reduction
Pre Dosimetry Infusion (Pre DI)	1.10 (0.1 – 24.4)	-	0.5 (0.05 – 3.33)	-	0.24 (0.01 – 4.37)	-
Day 1 Post Dosimetry (D1)	0.5 (N=29) (0.0 – 42.8)	57% *(p < 0.0001)*	0.15 (N=20) (0.00 – 1.8)	67% *(p < 0.0001)*	0.15 (N=13) (0.0 – 3.0)	63% *(p < 0.02)*
Pre Therapy Infusion (Pre TI)	0.85 (N=28) (0.1 - 36.8)	-	0.33 (N=23) (0.08 – 1.2)	-	0.37 (N=16) (0.02 – 18.7)	-
Day 1 Post Therapy (T1)	0.4 (N=28) (<0.1 – 20.4)	60% *(p < 0.0001)*	0.1 (N=14) (0.00 – 1.02)	81% *(p < 0.0001)*	0.09 (N=11) (0 – 16.32)	80% *(p < 0.0001)*
Day 3 Post Therapy (T3)	0.3 (N=26) (<0.1 – 2.7)	80% *(p < 0.0001)*	0.03 (N=13) (0.00 – 0.11)	90% *(p < 0.0001)*	0.03 (N=8) (0 – 0.42)	98% *(p < 0.0001)*
Day 8 Post Therapy (T8, Pre FLU Conditioning)	0.1 (N=28) (<0.1 – 0.3)	88% *(p < 0.0001)*	0.02 (N=3) (0.01 – 0.02)	*WBC <0.1 with no differential reported**	0.0* (N=16)	*WBC <0.1 with no differential reported**

Figure 3: WBC Reduction Following Iomab-B Treatment



Post-dose percent reduction for DI and TI calculated based on Pre-DI and Pre-TI levels, respectively

Figure 5: Absolute Blast Reduction Following Iomab-B Treatment



Post-dose percent reduction for DI and TI calculated based on Pre-DI and Pre-TI levels, respectively

Table 3: Engraftment Data

Median (range)	Randomized to Iomab-B and transplanted (N=18/19)^	Randomized to Conventional Care (N=19)	
		Achieved CR and received standard of care transplant (N=4)	Did not achieve CR Crossed over to Iomab-B arm and transplanted (N=10/15) ^^
Days to ANC Engraftment	13 (9-22)***	Not collected	13 (9-20)
Days to Platelet Engraftment	16 (13-26)***	Not collected	17 (10-20)**
Full Donor Chimerism (>95% prior to day 100)	17/18 (1 patient 65% donor)	n/a	9/10 (1 patient 86% donor)
Days to HCT (Post Randomization)	28 (23-38)	67 (66-86)	66 (57-161)****
Dose Delivered to Bone Marrow	18 (8.2-32) Gy 616 (397-1027) mCi	n/a	16 (6.3-20) Gy 518 (313-1008) mCi

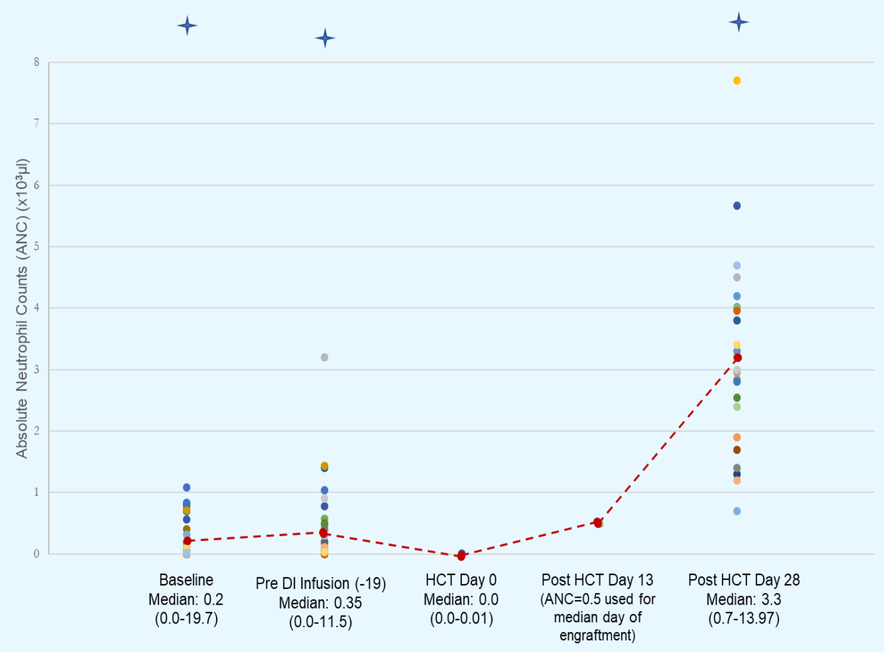
^ 1 patient had unfavorable dosimetry ^^ 5 patients ineligible for transplant

Key Data Highlights:

- Despite high blast count all patients receiving Iomab-B successfully engrafted
- 15/19 (79%) of patients in the control arm failed to achieve complete remission
- 10/15 (67%) of eligible patients in the control arm crossed-over to receive Iomab-B
- Faster time to transplant in patients randomized to Iomab-B (28 days) vs. conventional care (67 days)
- If on conventional care arm, no delay to HCT with crossover to Iomab-B

** N=2 patients, platelet engraftment data not available; *** ANC engraftment data not available (N=2), platelet engraftment data not available (N=3);
****1 patient at 161 days had delayed transplant due to infection & respiratory failure, received Iomab & transplant when stable

Figure 6: Successful ANC Engraftment and Recovery Post Iomab-B and HCT



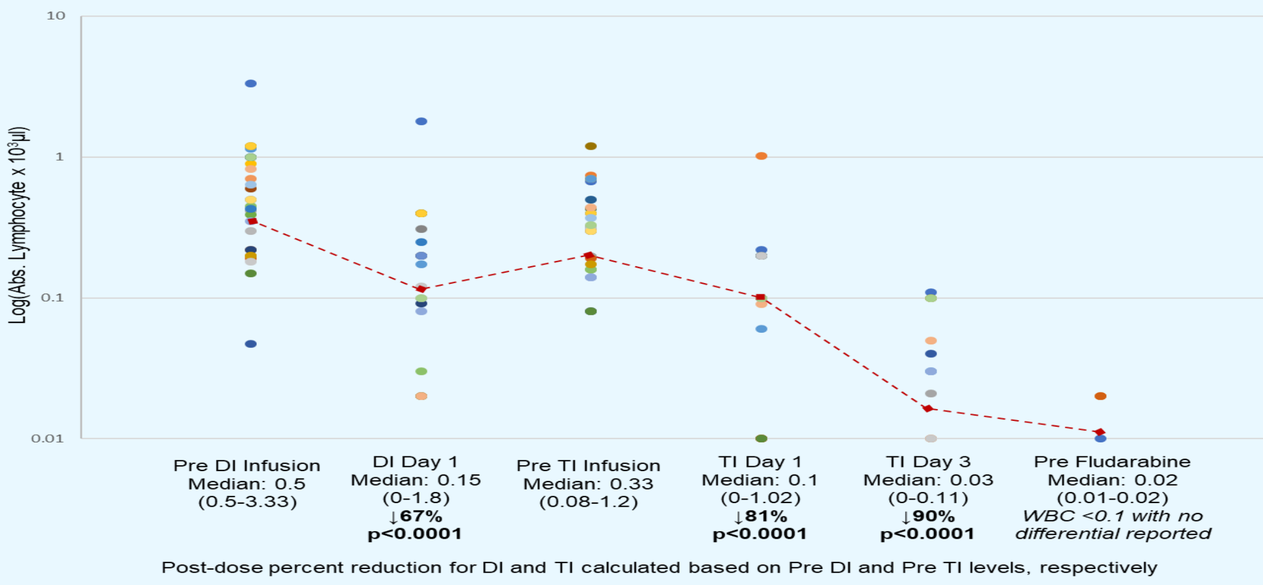
ANC data points > 8 x10^3 are not plotted in graph but have been included in data

Table 1: Patient Demographics

Ongoing Phase 3 SIERRA Trial (N=38)	Randomized to Iomab-B Study Arm (N=19)	Randomized to Conventional Care (N=19)	Randomized to Conventional Care and Crossed Over (N=10)
Age (median, range)	62 (55-72)	64 (55-76)	63 (58-72)
Disease Status At Randomization	Primary Induction Failure (10) First Early Relapse (1) Relapsed / Refractory (4) 2nd / Subsequent Relapse (3) ***1 patient not entered*	Primary Induction Failure (6) First Early Relapse (1) Relapsed / Refractory (8) 2nd / Subsequent Relapse (4)	Primary Induction Failure (3) First Early Relapse (0) Relapsed / Refractory (6) 2nd / Subsequent Relapse (1)
% Bone Marrow Blasts at Randomization (median, range)	30% (4*-74)	26% (6-97)	Marrow Blasts At randomization: 24% (6-70) At Crossover: 45% (10-70)

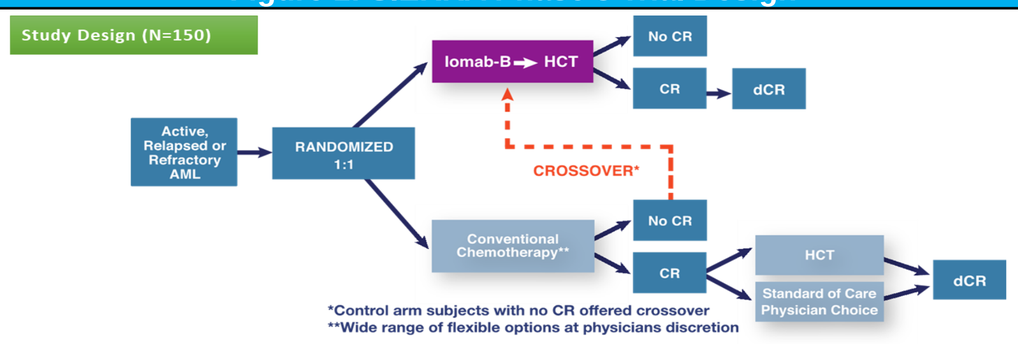
*1 patient with peripheral blasts at screening

Figure 4: Lymphocyte Reduction Following Iomab-B Treatment



Post-dose percent reduction for DI and TI calculated based on Pre DI and Pre TI levels, respectively

Figure 1: SIERRA Phase 3 Trial Design



Primary End-point: Durable Complete Response Rate (dCR): morphologic CR lasting ≥180 days
Secondary End-point: 1-year Overall Survival

Key Eligibility Criteria:

Active, relapsed or refractory AML defined as:
- Primary induction failure (PIF) after ≥2 cycles of chemotherapy
- First early relapse after remission < 6 months
- Refractory to salvage combination chemotherapy with high-dose cytarabine
- Second or subsequent relapse

- **Bone marrow blast count ≥ 5% or the presence of peripheral blasts**
- **≥ 55 years of age**
- Karnofsky score ≥ 70
- An 8/8 allele-level, related or unrelated, medically cleared HSC donor matching at HLA-A, HLA-B, HLA-C, and DRB-1

Conclusions

- Targeted radioimmunotherapy with single-agent Iomab-B rapidly decreases peripheral blasts by 98% by day 3 in chemotherapy refractory AML.
- Iomab-B conditioning leads to myeloablation in older patients with active disease (up to a median of 45% blasts in the marrow) as demonstrated by engraftment in all patients.
- Successful engraftment after Iomab-B and HCT benefits patients who had prolonged neutropenia due to active and refractory disease prior to transplant.
- While efficacy data is not yet available for these patients, rapid peripheral blast reduction is encouraging as prior studies utilizing cytotoxic chemotherapy suggest a relationship between the rate of disease reduction and disease response. Enrollment is ongoing.

For Questions or Comments Relating to the SIERRA Trial, Please Contact: SIERRA.ACTINIUM@actiniumpharma.com

For more information about the SIERRA Trial, Please Visit: www.sierratrial.com