Clinical Experience in the Randomized Phase 3 SIERRA Trial: Anti-CD45 Iodine (^{131}I) Apamistamab [Iomab-B] Conditioning Enables Hematopoietic Cell Transplantation with Successful Engraftment and Acceptable Safety in Patients with Active, Relapsed/Refractory AML Not Responding to Targeted Therapies

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

Background

Older patients with relapsed/refractory (R/R) AML have had historically few therapy options to make them eligible for potentially curative hematopoietic cell transplantation (HCT).

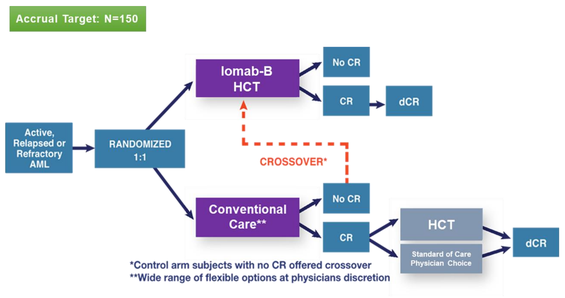
More recently, several targeted therapies have been approved. These include BCL-2 inhibitors (e.g., venetoclax), FLT-3 inhibitors (e.g., midostaurin and gilteritinib) and IDH inhibitors (e.g., ivosidenib) and are being utilized in patients with R/R AML to potentially achieve higher response rates with reduced toxicity.

Iomab-B: Iodine (^{131}I) Apamistamab

Iomab-B targets CD45, expressed on hematopoietic cells, including the majority of malignant myeloid and lymphoid cells.

Iomab-B (Iodine [^{131}I] apamistamab) delivers targeted radiation directly to leukemic cells and avoiding non-targeted tissue.

Study Design: A multi-center, phase III, open-label, randomized, controlled, optional one-way crossover study of Iomab-B versus Investigator's choice of salvage therapy in patients aged 55 years or older with active, R/R AML. Patients randomized to Conventional Care (CC) who achieve CR may proceed to allogeneic hematopoietic cell transplantation (HCT) or other standard treatment. Patients not achieving CR may crossover to receive Iomab-B.



Primary End-point: Durable Complete Remission Rate (dCR): CR/CRp at 6 months post-CR

Secondary End-points Include: Overall Survival and Event-Free Survival

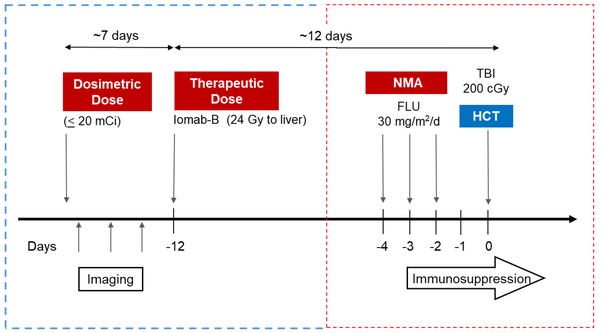
Objective

Here we report on the rates of transplant in patients treated with targeted agents and engraftment/tolerability among Iomab-B and CC patients undergoing standard HCT or crossover to Iomab-B.

SIERRA Key Eligibility Criteria

- Patients ≥ 55 years of age with active, relapsed or refractory AML, Karnofsky score ≥ 70
- Medically cleared, 8/8 HLA-matched related or unrelated donor, matching at HLA-A, HLA-B, HLA-C, and DRB-1

SIERRA Iomab-B Treatment Schedule



NMA: nonmyeloablative conditioning; FLU: fludarabine; TBI: total body irradiation; HCT: hematopoietic cell transplant

Therapeutic dose individualized based on upper limit of 24 Gy liver exposure

Patient Characteristics

Complete Enrollment, N=151			
	Iomab-B Arm (75)	**Conventional Care Arm (76)**	**Randomized to Conventional Care and Crossed Over to Iomab-B with HCT (38)**
Age median, (range)	64 (55-77)	65.5 (55-76)	64.5 (55-76)
Cytogenetic and Molecular Risk	Favorable: 5.3 % Intermediate: 32% Adverse: 61.3%	Favorable: 3.9% Intermediate: 32.9% Adverse: 63.2%	Favorable: 5.3 % Intermediate: 36.8 % Adverse: 57.9%
Disease Status at Randomization N, (%)[5]	Primary Induction Failure: 41 (54.7) First Early Relapse:17 (22.7) Relapse/Refractory: 11 (14.7) 2nd + Relapse: 6 (8)	Primary Induction Failure: 39 (51.3) First Early Relapse: 20 (26.3) Relapse/Refractory: 13 (17.1) 2nd + Relapse: 4 (5.3)	Primary Induction Failure: 18 (47.4) First Early Relapse: 11 (28.9) Relapse/Refractory: 8 (21.1) 2nd + Relapse: 1 (2.6)
% Marrow Blasts at Randomization median, (range)	30% (2-97)	20% (3-97)	**% Marrow Blasts** **At randomization:** 21.5% (3-87) **At crossover:** 32.5% (2-78)

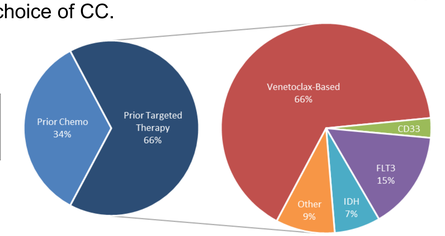
Targeted Therapy Pre & Post Enrollment

- Randomized patients received a median of 3 prior therapy regimens (range: 1-7), with 93% of patients failing at least 2 regimens prior to enrollment.
- A majority of enrolled patients (66%) had received and failed prior targeted agents, of which 66% were venetoclax-based.

Targeted Therapy Pre & Post Enrollment

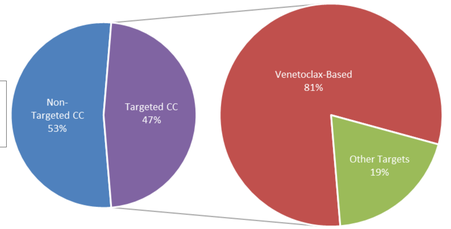
After randomization to the CC arm, 47% of patients received targeted agents, of whom 81% received venetoclax-based therapy as Investigator's choice of CC.

Pre-Enrollment
Targeted Therapies Prior to SIERRA



■ BCL-2, 66% ■ CD33, 3% ■ FLT3, 15% ■ IDH, 7% ■ Other, 9%

Post-Enrollment
Targeted Therapies on CC Arm



■ BCL-2, 81% ■ Other Targets, 19%

Thirteen (17%) of the 76 patients on the CC arm achieved CR and proceeded to standard of care HCT. Of the 63 non-responders, 28 did not respond to targeted agents, of whom 14 (50%) crossed over to receive Iomab-B/HCT (see AEs of Interest table).

Transplant Characteristics & Engraftment

Of the evaluable patients treated with Iomab-B/HCT, 100% engrafted. In the standard HCT group, there was 1 graft failure reported. Neutrophil and platelet engraftment data for all transplanted patients are presented in the table below.

Transplant Characteristics	**Iomab-B Arm (75)** 10 patients did not receive TI/HCT due to KPS decline	**Conventional Care (76)** 44 patients confirmed for crossover, 2 pending HCT, 4 did not receive TI/HCT due to KPS decline 17 patients not eligible for crossover or HCT due to KPS decline; 2 patients pending CC assessment	
	Received Iomab-B/HCT (65)	**Did not Achieve CR Crossed over to Iomab-B/HCT (38)**	**Achieved CR and received standard of care HCT (13)**
Total Iomab-B Activity median, (range)	649.5 (354-1027) mCi	606.5 (313-1013) mCi	N/A
Dose to Marrow median, (range)	15.9 (4.6-44.6) Gy	16.1 (6.3-41.8) Gy	N/A
CD34+ Cells x10^6/Kg median, (range)	5.5 (1.8-208)	5.1 (1.8-16.1)	5.03 (0.68-25.1)
Type of Graft	Marrow: 4, PBSC: 61 Related: 25, Unrelated: 40	Marrow: 2, PBSC: 36 Related: 13, Unrelated: 25	Marrow: 2, PBSC: 11 Related: 4, Unrelated: 8 Not Reported: 1
ANC Engraftment **PLT Engraftment** Median days, (range)	ANC 15 (10-32) PLT 18 (5-59) **100% engraftment**	ANC 15 (11-36) PLT 19 (2-39) **100% engraftment**	ANC 17 (2-84) PLT 17 (9-36) **92% engraftment**

Grade ≥3 Adverse Events (AEs) in ≥10% of All Patients

Adverse Event	Iomab-B Arm (N=75) N (%)	Conventional Care Arm (N=76) N (%)
Febrile Neutropenia (FN)	25 (33.3)	34 (44.7)
Sepsis[1] *p < 0.01*	4 (5.3)	18 (23.7)
Mucositis[2]	9 (12.0)	9 (11.8)
Hypertension	9 (12.0)	10 (13.2)
Pneumonia	6 (8.0)	10 (13.2)
Hypoxia	5 (6.7)	8 (10.5)
Device related infection	4 (5.3)	8 (10.5)
Acute Kidney Injury	3 (4.0)	2 (2.6)
Venoocclusive liver disease	1 (1.3)	0 (0.0)

1. "Sepsis" includes Preferred Terms of Sepsis, Septic Shock & Neutropenic Sepsis
2. "Mucositis" includes Preferred Terms of Stomatitis & Mucosal Inflammation

For patients who received targeted therapies and HCT in either crossover or standard HCT, incidences of FN, sepsis and mucositis are presented below.

Grade ≥3 AEs of Interest (All Transplanted Patients)

(Through Day 100 post-transplant)

Adverse Event	Iomab-B + HCT (65) N (%)	Crossover + HCT (38) N (%)			CC + Std HCT (13) N (%)		
		Total N=38	Crossover Post Targeted N=14	Crossover Post Non-Targeted N=24	Total N=13	Targeted CC + HCT N=8	Non-Targeted CC+HCT N=5
Febrile Neutropenia	23 (35.4)	20 (52.6)	4 (28.6).	16 (66.7)	5 (38.5)	3 (37.5)	2 (40.0)
Sepsis[1]	3 (4.6)	10 (26.3)	3 (21.4)	7 (29.2)	3 (23.1)	1 (12.5)	2 (40.0)
Mucositis[2]	8 (12.3)	6 (15.8)	2 (14.3)	4 (16.7)	3 (23.1)	2 (25.0)	1 (20.0)

1. "Sepsis" includes preferred terms: Sepsis, Septic shock and Neutropenic sepsis
2. "Mucositis" includes preferred terms: Stomatitis and Mucosal inflammation

Day +100 Transplant-Related Mortality (TRM)

	Received Iomab-B/HCT (65)	Crossed over to Iomab-B/HCT (38)	Standard of Care HCT (13)
Day +100 TRM Out of Evaluable Patients (%)	6/59[1] (10.2)	2/36[2] (5.6)	2/13 (15.4)

1. Non-evaluable patients include 5 patients still in Day 0-100 follow-up, 1 patient withdrew consent prior to Day 100
2. Non-evaluable patients include 2 patients still in Day 0-100 follow-up

Conclusions

- The majority of patients randomized to the CC group received venetoclax-based targeted therapies as Investigator's choice.
- Despite active disease with median 30% marrow blasts, patients not responding to chemotherapy and targeted therapies, including venetoclax, were able to undergo HCT with Iomab-B.
- 100% of all evaluable patients receiving Iomab-B successfully engrafted, including those crossing over to Iomab-B/HCT.
- Overall, Iomab-B was well tolerated, with a significantly lower incidence of sepsis compared to the CC group.

The SIERRA trial has completed enrollment (www.sierratrial.com or clinicaltrials.gov, NCT02665065)