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SIERRA Clinical Trial Dosimetry Results Support Low Dose Anti-CD45 Iodine (131I) Apamistamab [Iomab-B] for Targeted Lymphodepletion Prior to Adoptive Cell Therapy

Rajneesh Nath, MD[1], Eileen M Geoghegan, PhD[2], Matthew L Ulrickson, MD[1], Jennifer A Spross[2], Renee H Lichtenstein[2], Sandy Konerth[3], Darrell R Fisher, PhD[3], Qing Liang, PhD[2], Dale L Ludwig, PhD[2], Vijay Reddy, MD, PhD[2], Mark S Berger, MD[2], Boglarka Gyurkocza, MD[4]

[1]Banner MD Anderson Cancer Center, Gilbert, AZ; [2]Actinium Pharmaceuticals, New York, NY; [3]Versant Medical Physics, Kalamazoo, MI; [4]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Introduction: Nearly all adoptive cell therapies currently being evaluated in the clinic, including CAR-T, tumor infiltrating lymphocytes (TIL), and TCR-based cell therapies, require lymphodepletion to remove cellular cytokine sinks and create a favorable cytokine environment for the incoming transferred cells to proliferate. Targeted conditioning with an antibody radio-conjugate directed to CD45 represents a promising and potentially more effective alternative to the commonly used fludarabine/cyclophosphamide chemotherapy lymphodepletion regimen.

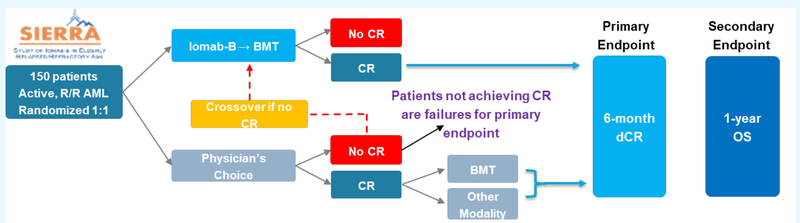
Methods: SIERRA is an ongoing Phase 3 multicenter trial evaluating anti-CD45 Iodine (131-I) Apamistamab [Iomab-B] (131-I Apamistamab) as targeted conditioning prior to HCT in active, relapsed or refractory acute myeloid leukemia (r/r AML). Prior to administration of the therapeutic dosage, dosimetry is performed using a tracer amount of Iomab-B (range from 7-20 mCi, median 10 mCi) in an out-patient setting to calculate the appropriate patient-specific therapeutic infusion. Blood sample analysis from 56 evaluable Iomab-B treated patients collected pre-dosimetric infusion (Pre-DI), post-dosimetric infusion (Post-DI), day 1 post-dosimetric infusion (D1 post-DI), and pre-therapeutic infusion (Pre-TI, range 6-14 days post-dosimetry) was assessed to determine if residual Iomab-B had any significant effect on blood counts in support of its use as a transient targeted lymphodepletion agent.

Results: From these data, a significant but transient decrease in lymphocytes and white blood cells was observed compared to pre-DI values. An 85% decrease of lymphocytes was observed at the post-DI time point, a 67% decrease at day 1 post-DI, and a 43% decrease at the time of therapeutic infusion. Peripheral blasts were also transiently decreased at the post-DI time point (35%), indicating that low dose Iomab-B may exert an anti-tumor effect in these patients. Interestingly, the levels of platelets, hematocrit, and neutrophils were unchanged at the Pre-TI time point compared to Pre-DI, reflecting the comparatively lower surface antigen levels of CD45 on these cell types. In addition, data from Iomab-B treated patients was used to calculate the radiation absorbed dose to bone marrow to determine an appropriate amount of Iomab-B that would not impart more than 2 Gy, a threshold that is considered to be non-myeloablative. This analysis determined that approximately 75 mCi Iomab-B could be administered as a non-myeloablative amount and has been proposed as the starting dose for a clinical trial using Iomab-B for targeted lymphodepletion prior to CAR-T. Additional calculations were performed to model the clearance of Iomab-B to determine at what time post-infusion a CAR-T could be administered without the amount of residual radiation to bone marrow exceeding a safe level (0.25 Gy). Based on clinical data from the SIERRA trial, the average effective half-time of Iomab-B was 45.1 hours and the time frame for CAR-T administration following 75 mCi of Iomab-B was approximately 147 hours (~ 6 days). While administration of radiopharmaceuticals often requires special safety precautions, these proposed doses for Iomab-B would be amenable to outpatient administration without the need for isolation or special monitoring.

Conclusions: Despite the importance of lymphodepletion prior to adoptive cell therapies, there has been very little optimization of this step. Clinical data collected using a low dose of Iomab-B for dosimetry has demonstrated that this method of lymphodepletion is specifically targeted to CD45+ immune cells, may have an anti-tumor effect, and can be administered in an outpatient setting. These clinical and logistical attributes are attractive characteristics for lymphodepletion and supportive of using Iomab-B as a novel lymphodepletion regimen prior to adoptive cell therapies such as CAR-T.

Figure 1: Phase 3 SIERRA Clinical Trial Design

A)



B)

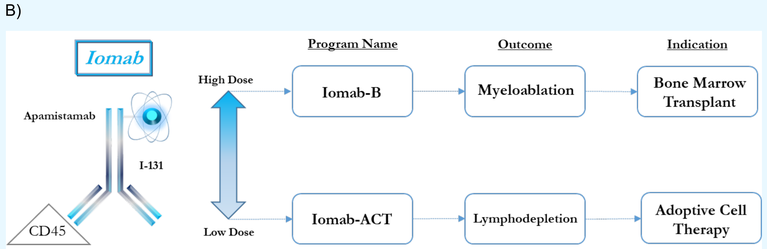


Figure 1: A) Schematic of the SIERRA Phase 3 clinical trial. Patients are randomized 1:1 to receive either conventional chemotherapy or Iomab-B. Patients who receive conventional chemotherapy are eligible to crossover to the Iomab-B arm if a CR is not achieved. B) Figure demonstrating the relationship between high dose (Iomab-B) and low dose (Iomab-ACT) 131-I Apamistamab and its use for myeloablative conditioning or lymphodepletion.

Disclosures: RN: Astellas: Consultancy; Daiichi Sankyo: Consultancy; Actinium: Consultancy. EMG: Actinium Pharmaceuticals: Employment. JAS: Actinium Pharmaceuticals: Employment, Equity Ownership. RHL: Actinium Pharmaceuticals: Employment, Equity Ownership. SK: Versant Medical Physics and Radiation Safety: Consultancy. DRF: Versant Medical Physics and Radiation Safety: Employment. QL: Actinium Pharmaceuticals: Employment. DLL: Actinium Pharmaceuticals: Employment, Equity Ownership. VR: Actinium Pharmaceuticals: Employment. MSB: Actinium Pharmaceuticals, Inc: Employment, Equity Ownership. BG: Actinium Pharmaceuticals: Research Funding.

Figure 2: SIERRA Trial Treatment Schematic

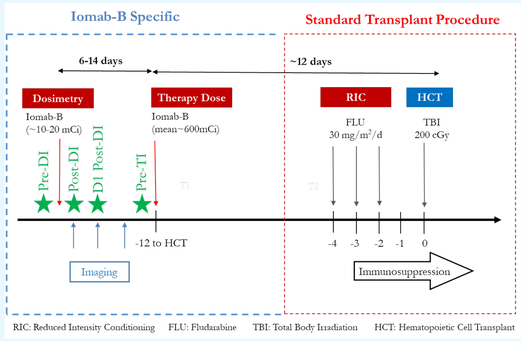


Figure 2: Schematic of relevant time points throughout the dosimetry infusion (DI) and the therapeutic infusion (TI) of Iomab-B. Blood samples were taken prior to DI (pre-DI), at the completion of infusion approximately 6 hours post initiation of DI (post-DI), 24 hours post-DI (D1 Post-DI), and immediately before TI (range 6-14 days).

Tables 1-3: Depletion of Various Blood Counts Pre- and Post-Dosimetry

1) All Iomab-B Treated Patients

Time Point Assessments	WBC x 10^3 µL	% Change*	Absolute Lymphocyte x 10^3 µL	% Change	Absolute Blasts x 10^3 µL	% Change	Platelets x 10^3 µL	% Change	Absolute Neutrophils x 10^3 µL	% Change	Hemato-crit (%)	% Change	Hemo-globin g/dL	% Change
Pre Dosimetry Infusion (Pre-DI)	1.8 (N = 54) (<0.1 – 36.5)	-	0.62 (N = 50) (0 – 8.1)	-	0.18 (N = 39) (0 – 10.83)	-	32.50 (N = 54) (3.00 - 229.00)	-	0.41 (N = 51) (0.0 - 19.50)	-	24.7 (N = 53) (15.9 – 39.5)	-	8.2 (N = 53) (5.6 – 13.1)	-
Post Dosimetry Infusion (Post-DI)	0.8 (N = 48) (<0.1 – 48)	**↓-46%** (-92 – 97%) p < 0.0001	0.1 (N = 23) (0.0 – 2.0)	**↓-85%** (-100 – -42%) p < 0.0001	0.19 (N = 15) (0.0 – 2.85)	**↓-35%** (-88 – 97%) p = 0.035	20.00 (N = 48) (2.00 - 174.00)	**↓-34%** (-93 – 135%) p < 0.0001	0.32 (N = 29) (0.0 - 21.40)	↓-12% (-100 – 345%) p = 0.97	24.8 (N = 47) (19 – 37)	0% (-26 – 23%) p = 0.75	8.5 (N = 47) (6.1 – 12.1)	↑1.4% (-24 – 24%) p = 0.33
Day 1 Post Dosimetry (D1 Post-DI)	0.83 (N = 51) (0 – 47.1)	**↓-29%** (-100 – 164%) p = 0.0001	0.2 (N = 37) (0 – 3.3)	**↓-67%** (-100 – 147%) p < 0.0001	0.27 (N = 23) (0 – 15.9)	↓-31% (-100 – 81%) p = 0.09	27.00 (N = 52) (7.00 - 158.00)	↓-28% (-73 – 467%) p < 0.53	0.20 (N = 23) (0.0 - 33.40)	↓-26% (-100 – 265%) p = 0.63	23.9 (N = 51) (17.7 – 37.3)	**↓-5%** (-23 – 30%) p = 0.01	8.0 (N = 51) (6.5 – 12.5)	**↓-4.6%** (-21 – 32%) p = 0.03
Pre Therapy Infusion (Pre-TI)	1.0 (N = 46) (0.1 – 36.8)	↓-19% (-97 – 4000%) p = 0.37	0.4 (N = 37) (0.08 – 1.33)	**↓-43%** (-93 – 236%) p = 0.019	0.39 (N = 21) (0 – 18.8)	↓-34% (-87 – 411%) p = 0.68	34.00 (N = 47) (9.00 - 147.00)	↓-9% (-83 – 766%) p = 0.20	0.36 (N = 40) (0.0 - 10.40)	↓-14% (-91 – 2929 %) p = 0.25	24.5 (N = 46) (18.4 – 34.1)	↓-3% (-31 – 70%) p = 0.98	8.15 (N = 46) (6.5 – 12)	↓-5% (-30 – 76%) p = 0.88

Values in table are median, sample size, and range (min-max).
* All percent change values are relative to pre-DI timepoint and reflect the median change and range.

2) Randomized to Iomab-B

% Change vs Pre-DI (Median)	WBC	Absolute Lymphocytes	Absolute Blasts	Platelets	Absolute Neutrophils	Hematocrit	Hemoglobin	RBC
Post-DI	-43.43	-76.47	-34.8	-27.33	-4.55	0	1.4	0.6
N	30	13	7	30	16	29	29	30
p-value	***<0.0001***	***<0.0001***	0.335	***0.0012***	0.7337	0.9075	0.5719	0.5262
DI Day 1	-28.76	-59.09	-37.11	-28	-23.86	-5.15	-4.64	-4
N	33	25	12	33	25	32	29	33
p-value	***0.0112***	***0.0014***	0.223	0.6829	0.6853	***0.0212***	0.0632	0.1282
Pre-TI	-22.22	-50	-14.04	-9.36	-25	-5.02	-6.33	-4.27
N	30	23	8	30	23	29	32	30
p-value	0.3928	0.1572	0.6473	0.3985	0.3176	0.9968	0.9457	0.3278

3) Crossover to Iomab-B

% Change vs Pre-DI (Median)	WBC	Absolute Lymphocytes	Absolute Blasts	Platelets	Absolute Neutrophils	Hematocrit	Hemoglobin	RBC
Post-DI	-51.28	-86.05	-37.82	-36.96	-32.8	0.54	1.33	0.4
N	18	9	6	18	10	18	18	18
p-value	***0.0003***	***<0.0001***	***0.0334***	***<0.0001***	0.3781	0.7394	0.4329	0.5785
DI Day 1	-36.93	-84.26	-30.7	-28.92	-58.77	-3.06	-4.35	-3.45
N	18	11	9	19	13	19	19	19
p-value	***0.0019***	***<0.0001***	0.2987	0.3432	***0.0069***	0.2378	0.2558	0.3095
Pre-TI	-11.27	-42.8	-50.64	-7.37	12.81	-0.47	3.19	2.1
N	16	12	6	17	12	17	17	17
p-value	0.6896	***0.0171***	0.9775	0.2298	0.177	0.9801	0.8396	0.9756

Tables 1-3: Blood sample analysis from 56 evaluable Iomab-B treated patients collected Pre-DI, Post-DI, D1 post-DI, and Pre-TI were assessed to determine if low dose (median 10mCi) 131-I Apamistamab had any significant effect on blood counts. Overall data is presented in Table 1, data from patients who were randomized to Iomab-B are presented in Table 2, and patients who were initially randomized to conventional chemotherapy and later crossed over to the Iomab-B arm are presented in Table 3.

Figure 3: Depletion of Lymphocytes Pre- and Post-Dosimetry

Time Post-Infusion	0 hr	~ 6 hr	24 hr	6-14 days
Median:	0.62	0.1	0.2	0.4
Percent Decrease (vs. 0 hr)	-	85%*	67%*	43%*

Figure 3: Absolute lymphocyte counts from AML patients treated with 131-I Apamistamab in the Phase 3 SIERRA trial before and after single-dose dosimetry show that low doses of Iomab-B can result in transient lymphodepletion. Red line represents median value of absolute lymphocytes for each time point. *p < 0.05

Table 4: Rationale for 75 mCi Starting Dose of 131-I Apamistamab for Lymphodepletion

131-I Activity Administered	Total marrow dose to infinite time (cGy)	Time post-infusion (hours) after which the remaining absorbed dose will not exceed 25 cGy	Days post-infusion
25mCi	67	69	2.9
50 mCi	134	118	4.9
75 mCi	**200**	**147**	**6.1**
100 mCi	267	167	7.0
150 mCi	401	194	8.1
200 mCi	534	216	9.0

Table 4: Data from dosimetry were used to calculate the total absorbed dose of radiation to the bone marrow for various doses of 131-I Apamistamab. These calculations revealed that an administered dose of 75 mCi of 131-I Apamistamab would deliver approximately 200 cGy to the bone marrow, the threshold that is considered non-myeloablative.

Figure 4: Determination of Safe Waiting Time Post-131-I Apamistamab Administration

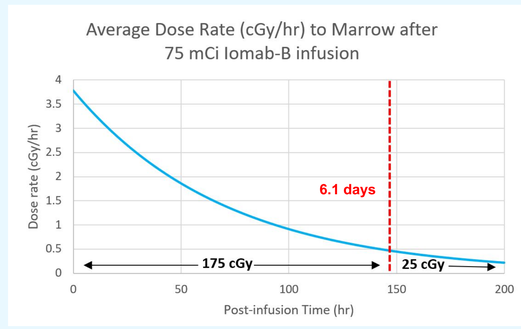


Figure 4: In addition to determining a safe starting dose, dosimetry data were used to calculate at what time post-administration of 131-I Apamistamab the remaining absorbed dose to the marrow will not exceed approximately 25 cGy. Current scientific data suggests that doses of less than 100 cGy do not result in long term chromosomal instability in the bone marrow (Zyuzikov et al. 2012 Radiobiology and Environmental Security), therefore an assumption was made that approximately 25 cGy is a safe residual dose to bone marrow at the time of an adoptive cell therapy administration. Using this 25 cGy target for an administered dose of 75 mCi of 131-I Apamistamab, a waiting time of approximately 147 hours or 6.1 days was calculated. The average effective half-time of Iomab-B was around 45.1 hours.

Figure 5: Clearance of 131-I Apamistamab and Determination of Ideal Window for Administration of an Adoptive Cell Therapy

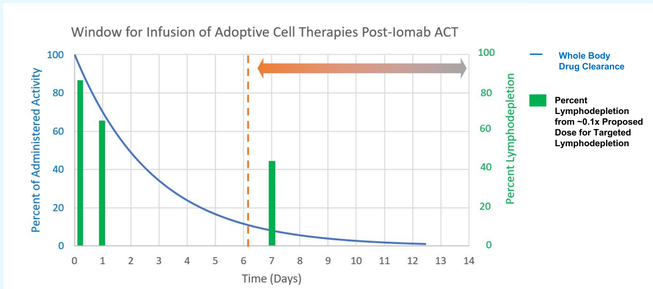


Figure 5: The whole body clearance profile of 131-I Apamistamab was plotted on the left axis while the percent depletion of lymphocytes following dosimetric infusion was plotted on the right axis. Post-DI is plotted at 6 hrs, D1 Post-DI at Day 1, and Pre-TI is represented at Day 7 (range 6-14) in hatched green bars. 6.1 days, the time at which the remaining absorbed dose is 25 cGy, is plotted in dotted orange line, and represents the beginning of the window for ideal administration of an adoptive cell therapy such as CAR-T post-Iomab-ACT mediated lymphodepletion.

Conclusions

- Data from the dosimetry infusion (median 10mCi) in the SIERRA clinical trial was used to model the dose of radiation delivered to marrow and the clearance profile of 131-I Apamistamab.
- Modeling predicts that approximately 75mCi is an appropriate starting dosage that will not exceed the 2 Gy threshold for non-myeloablative dose of radiation to the bone marrow.
- Blood samples taken before and after dosimetry demonstrate a transient depletion of WBCs, lymphocytes, and blasts, but with little effect on neutrophils, platelets, and hematocrit.
- Lymphodepletion results were similar for patients randomized to Iomab-B and for those who crossed over to the Iomab-B arm.
- Based on the clearance of 131-I Apamistamab, an adoptive cell therapy such as CAR-T could be administered after around 6 days post-lymphodepletion with a 75mCi dosage.
- Targeted lymphodepletion with 131-I Apamistamab represents a promising strategy to achieve safe and transient lymphodepletion prior to adoptive cell therapies such as CAR-T.