Itolizumab, a Novel Targeted Anti-CD6 Therapy, in Combination with Corticosteroids, is Well Tolerated, with Rapid Pharmacodynamic and Clinical Response in Newly Diagnosed Acute Graft-Versus-Host Disease

POSTER 2891

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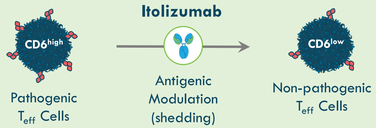
Introduction

- **CD6 is a co-stimulatory receptor** expressed on CD4 and CD8 T effector (T_{eff}) cells and modulates **T cell activity and trafficking**[1]
- The CD6 ligand, activated leukocyte cell adhesion molecule (ALCAM), is **expressed on antigen presenting cells and tissues**, including the skin and gastrointestinal (GI) tract
- CD6 and ALCAM are both **overexpressed during GI inflammation**[2]
- Prior clinical studies validated CD6 as a target relevant to acute graft-versus-host disease (aGVHD) pathogenesis[3]
- **Itolizumab** is a first-in-class antibody therapeutic targeting the CD6-ALCAM pathway by binding to domain-1 of CD6, causing CD6 shedding, and producing $CD6^{low}$ T cells (Figure 1)
- $CD6^{low}$ T cells are hyporesponsive to stimulation, exhibiting decreased activation, proliferation and cytokine production (see *ASH poster #995*)
- Itolizumab is being evaluated as a treatment for immuno-inflammatory disease in which T_{eff} cells play a central role, including aGVHD

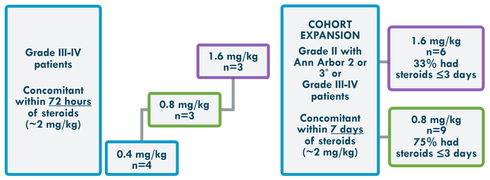
FIGURE 1. ITOLIZUMAB INDUCES CD6 SHEDDING AND PRODUCES $CD6^{LOW}$ NON-PATHOGENIC T EFFECTOR CELLS



Methods

Study Design

EQUATE — **Phase 1b open-label, 3+3, dose escalation study (NCT03763318)**
5 itolizumab doses intravenously (IV) bi-weekly (Days 1, 15, 29, 43 & 57)
Subjects followed through Day 337



*Ann Arbor Score: 1, MAGIC Algorithm Probability (MAP) <0.141; 2, MAP 0.141-0.290; 3, MAP >0.290

- Here we present interim data for 25 subjects who enrolled through 13 Oct 2021
- **EQUATE is continuing to enroll patients at 0.8 mg/kg with ≤ 3 days of prior steroids**; no further dose escalation above 1.6 mg/kg is anticipated

Objectives

Primary Objectives
- Assess the safety and tolerability of IV dosing of itolizumab
- Determine optimal IV dose level(s) of itolizumab

Secondary Objectives
- Characterize the pharmacokinetics and pharmacodynamics of itolizumab
- Assess the clinical activity of itolizumab: GVHD ORR (overall response rate), non-relapse mortality, chronic GVHD, and durability

Statistical Methods

- Data were summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables

Pharmacodynamic and Immunophenotyping Methods

- Fresh whole blood was collected at clinical sites for peripheral blood mononuclear cell isolation
- Flow cytometry staining panels were developed to assess T cell, B cell, innate and myeloid cell populations

Results

Patient Demographics and Baseline Characteristics

- Baseline characteristics were similar across dose groups, with 96% of subjects having Grade III or IV aGVHD (TABLE 1)

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS BY DOSE GROUP

	Itolizumab 0.4 mg/kg N=4	Itolizumab 0.8 mg/kg N=12	Itolizumab 1.6 mg/kg N=9	TOTAL N=25
Age (years), Mean (SD)	44 (18.0)	60(12.4)	55 (13.0)	**55 (14.0)**
Sex (M), n (%)	4 (100)	7 (58)	5 (56)	**16 (64)**
Race (White), n (%)	4 (100)	9 (75)	8 (89)	**21 (84)**
Primary Disease, n (%)				
AML	2 (50)	6 (50)	2 (22)	**10 (40)**
MDS	0	3 (25)	2 (22)	**5 (20)**
Other	2 (50)	3 (25)	5 (56)	**10 (40)**
Graft Source, n (%)				
Peripheral Blood	4 (100)	10 (83)	9 (100)	**23 (92)**
Bone Marrow	0	2 (17)	0	**2 (8)**
aGVHD Clinical Grade*, n (%)				
II	0	1(8)	0	**1 (4)**
III	3 (75)	7 (58)	6 (67)	**16 (64)**
IV	1 (25)	4 (33)	3 (33)	**8 (32)**
Organ Involvement, n (%)				
Skin	1 (25)	4 (33)	4 (44)	**9 (36)**
Liver	1 (25)	0	1 (11)	**2 (8)**
UGI	1 (25)	8 (67)	2 (22)	**11 (44)**
LGI	4 (100)	10 (83)	7 (78)	**21 (84)**
Minnesota High Risk Score#, n (%)	4 (100)	8 (67)	7 (78)	**19 (76)**
Ann Arbor Score 2 or 3*, n (%)	4 (100)	12 (100)	8 (89)	**24 (96)**

Ann Arbor Score: 1, MAP <0.141; 2, MAP 0.141-0.290; 3, MAP >0.290.
*Highest clinical grade at screening or baseline. #Score calculated at Screening.
Interim data; subject to change. Includes data for subjects enrolled through 13 Oct 2021.
Abbreviations: aGVHD, acute graft-vs-host disease; AML, acute myeloid leukemia; LGI, lower gastrointestinal; M, male; MAP, MAGIC Algorithm Probability; MDS, myelodysplastic syndrome; SD, standard deviation; UGI, upper gastrointestinal.

Patient Disposition

- All subjects received 1-5 doses of itolizumab
- Discontinuations of study drug after one dose of itolizumab were due to:
  - Requiring subsequent administration of alternate anti-GVHD therapy for progressive disease (n=6)
  - Adverse event (AE) unrelated to study drug (n=2)

Safety

- The AE profile was consistent with the aGVHD patient population (TABLE 2)
- Two subjects had treatment-related infection serious adverse events (SAEs), one of which was a dose-limiting toxicity AE of sepsis
- There were 8 AEs leading to death, however, none were considered treatment-related

TABLE 2. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS BY DOSE

Subjects with:	Itolizumab 0.4 mg/kg N=4 n (%)	Itolizumab 0.8 mg/kg N=12 n (%)	Itolizumab 1.6 mg/kg N=9 n (%)	TOTAL N=25 n (%)
Any AE	4 (100)	11 (92)	9 (100)	**24 (96)**
Infusion reaction AE	1 (25)	2 (17)	0 (0.0)	**3 (12)**
Infection AEs	3 (75)	6 (50)	7 (78)	**16 (64)**
CTCAE Grade ≥3 AE	2 (50)	9 (75)	9 (100)	**20 (80)**
AE Leading to Study Treatment Discontinuation	0	2 (17)	4 (44)	**6 (24)**
Infection AEs With treatment discontinuation	0	1 (8)	2 (22)	**3 (12)**
SAE	2 (50)	6 (50)	8 (89)	**16 (64)**
Infection SAE	1 (25)	3 (25)	6 (67)	**10 (40)**
Treatment-related SAE	0	1 (8)	1 (11)	**2 (8)**
Dose-Limiting Toxicity AE	0	0	1 (11)	**1 (4)**
AE Leading to Death	0	5 (42)	3 (33)	**8 (32)**
Deaths related to study treatment	0	0	0	**0**

Interim data; subject to change. Includes data for subjects enrolled through 13 Oct 2021.
AEs were collected through Day 169 for subjects who completed dosing and Day 85 for subjects who discontinued study treatment early.
Treatment-related defined as possibly related, probably related, or related by the Investigator.
Dose-Limiting Toxicity defined as ≥ Grade 3 infusion reaction or clinical finding associated with hypersensitivity or any ≥ Grade 3 AE that is not related to underlying disease that is at least possibly related to study treatment as per the investigator.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event

Efficacy

Responses observed by day 15 and maintained at day 29
- The highest complete response (CR) rate was seen in subjects who received itolizumab within 72 hours of systemic steroid initiation (TABLE 3).

TABLE 3. DISEASE RESPONSE AT DAY 15 AND DAY 29

	Early response: Day 15			Response endpoint: Day 29			Response endpoint: Day 29 *Itolizumab dosed ≤ 72 hours of steroid initiation*		
	N	CR n (%)	ORR n (%)	N	CR n (%)	ORR n (%)	N	CR n (%)	ORR n (%)
0.4 mg/kg (N=4)	4	2 (50)	3 (75)	4	2 (50)	2 (50)	4	2 (50)	2 (50)
0.8 mg/kg (N=12)	11*	6 (55)	7 (64)	12	7 (58)	7 (58)	9	6 (67)	6 (67)
1.6 mg/kg (N=9)	9	4 (44)	7 (78)	9	4 (44)	7 (78)	5	3 (60)	4 (80)
TOTAL (N=25)	**24***	**12 (50)**	**17 (71)**	**25**	**13 (52)**	**16 (64)**	**18**	**11 (61)**	**12 (67)**

*Day 15 disease response data was not available for one subject
Interim data; subject to change. Includes data for subjects enrolled through 13 Oct 2021.
Abbreviations: CR, complete response; ORR=PR+VGPR+CR, overall response rate; PR, partial response; VGPR, very good partial response defined as achieving all the criteria for skin, liver, and gut involvement per Martin 2009 Consensus criteria without meeting the criteria for CR

Six-month Outcomes: Responses were sustained in long-term follow-up
- 22 subjects have been studied for 6 months (4 months post-itolizumab treatment) or have met the endpoint
- Responses were durable from Day 29 through Day 169 (TABLE 4)
- 12 out of 14 (86%) responders (i.e., subjects with partial response [PR], very good partial response [VGPR], or CR at Day 29) were alive at Day 169; whereas only 2 out of 8 (25%) of non-responders (i.e., subjects with no response [NR] or progressive disease [PD] at Day 29) were alive at Day 169

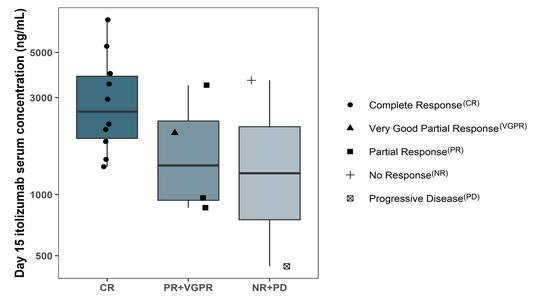
TABLE 4. SIX-MONTH RESPONSE AND SURVIVAL OUTCOMES

	6-month Response		6-month Survival	
	CR at Day 169 n (%)	Durable response* n (%)	Overall Survival n (%)	NRM n (%)
0.4 mg/kg (N=4)	2 (50)	2 (50)	3 (75)	1 (25)
0.8 mg/kg (N=9)	5 (56)	5 (56)	5 (56)	4 (44)
1.6 mg/kg (N=9)	4 (44)	4 (44)	6 (67)	3 (33)
TOTAL (N=25)	**11 (50)**	**11 (50)**	**14 (64)**	**8 (36)**

*Durable response is defined as PR, CR, or VGPR from Day 29 through Day 169.
Interim data; subject to change. Includes data for subjects enrolled through 13 Oct 2021.
Abbreviation: CR, complete response, NRM, non-relapse mortality

Exposure-response relationship at day 15 (exploratory)
- Itolizumab trough concentrations were higher in subjects who achieved a CR at Day 15 compared to those who did not achieve a CR (FIGURE 2)

FIGURE 2. ITOLIZUMAB TROUGH CONCENTRATIONS AFTER THE FIRST DOSE BY CLINICAL RESPONSE CATEGORY AT DAY 15

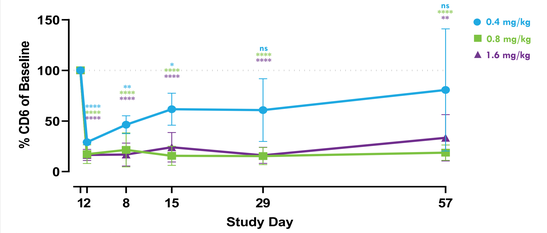


Shapes represent subject-level data as denoted in the legend. In the boxplots, the bold line represents the median, the lower and upper hinges correspond to the first and third quartiles, and the lower and upper whiskers extend to the smallest and largest values, respectively, within 1.5 times the interquartile range. Interim data; subject to change.

Pharmacodynamics

- Itolizumab significantly reduced the surface levels of CD6 on CD4+ T cells by 24 hours after the first dose (FIGURE 3)
- At 0.4 mg/kg, CD6 trended toward baseline by Day 15; at higher doses, CD6 remained significantly reduced ($p<0.0001$)
- Similar results were observed in CD8+ T cells

FIGURE 3. SURFACE LEVELS OF CD6 ON CD4+ T CELLS



*p < 0.05, **p<0.01, ***p<0.001, ****p<0.0001
Interim data; subject to change. Includes data for subjects enrolled through 13 Oct 2021.

Immunophenotyping

- By Day 15 following the first dose, itolizumab 0.8 and 1.6 mg/kg increased the ratio of T regulatory (T_{reg}) to T_{eff} cells (FIGURE 4)
- In addition, at Day 15, a decrease in the T cell activation marker programmed cell death protein 1 (PD-1) on T_{eff} cells was observed at all 3 doses, suggesting that itolizumab reduces the activation state of T cells (FIGURE 5)

FIGURE 4. DAY 15 T_{REG} TO T_{EFF} CELL RATIO†

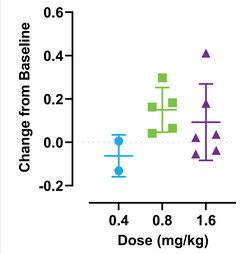
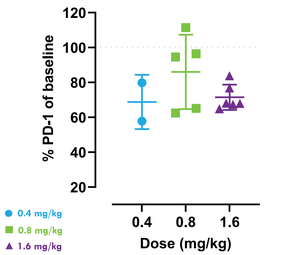


FIGURE 5. PD-1 ON T_{EFF} AT DAY 15†



Interim data; subject to change.
T_{reg} cells were identified by CD4+CD127-CD25+ cells and T_{eff} cells were identified by low/negative expression of CD45RA
†N = 13; Data not shown if there were < 50 events in the population of interest.

Conclusions

- Itolizumab treatment was associated with high rates of overall clinical response
  - At Day 29 CR was 52% and ORR was 64% across all doses
  - The highest Day 29 CR of 61% was achieved in subjects treated within 72 hours of systemic steroids
  - Early Day 15 CR response was achieved in 50% of subjects and was associated with higher itolizumab concentrations
- Responses were durable with 50% CR and 36% NRM at Day 169
- Dose-dependent reduction of CD6 expression on CD4+ T cells and increase in the T_{reg} to T_{eff} cell ratio are consistent with the mechanism of action of itolizumab
- Itolizumab was well tolerated across all doses, in the context of a severe aGVHD population

ITOLIZUMAB OFFERS A FAVORABLE BENEFIT-RISK PROFILE THAT SUPPORTS EVALUATION IN FUTURE STUDIES

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Disclosures

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