# Updated Interim Results from the EQUATE Study: Preliminary Safety and Efficacy of Itolizumab, a Novel Targeted Anti-CD6 Therapy, in Newly Diagnosed Acute Graft-Versus-Host Disease

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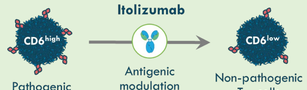
## Introduction

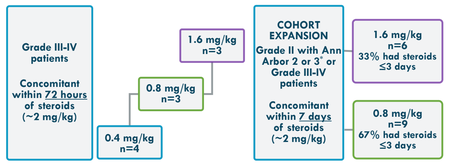
- CD6 is a target relevant to acute graft-versus-host disease (aGVHD) pathogenesis[1]
  - CD6 is a co-stimulatory receptor expressed on CD4 and CD8 T effector ($T_{eff}$) cells that modulates T cell activity and trafficking[2]
  - The CD6 ligand, activated leukocyte cell adhesion molecule (ALCAM), is expressed on antigen presenting cells and tissues, including the skin and gastrointestinal (GI) tract
  - CD6 and ALCAM are overexpressed during GI inflammation[3]
- Itolizumab, a first-in-class antibody, is a potential treatment for immuno-inflammatory diseases, including aGVHD, in which $T_{eff}$ cells play a central role
  - Itolizumab targets the CD6-ALCAM pathway by binding to CD6 domain-1, which causes CD6 shedding and results in $CD6^{low}$ T cells
  - $CD6^{low}$ T cells are hyporesponsive to stimulation, exhibiting decreased activation, proliferation, and cytokine production




## Methods

### Study Design

**Phase 1b open-label, 3+3, dose escalation study evaluating itolizumab as first-line treatment for adult subjects with aGVHD (NCT03763318)**




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

- Subjects were ≥18 years old with an initial diagnosis of aGVHD after first post-hematopoietic stem cell transplant (any conditioning regimen)
- 5 itolizumab doses intravenously (IV) bi-weekly (Day 1, 15, 29, 43 & 57)
- Subjects followed through Day 337
- Enrollment continued at 0.8 mg/kg with ≤3 days of prior steroids; no further dose escalation above 1.6 mg/kg was conducted

### 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: aGVHD overall response rate (ORR), non-relapse mortality, chronic GVHD, and durability

### Statistical Methods

- Interim data are presented here is for the first 25 subjects enrolled through 13 Oct 2021
- For Responder analyses, subjects with a partial response (PR), very good partial response (VGPR), or complete response (CR) at Day 29 were considered Day 29 Responders (n=16), whereas those with no response (NR) or progressive disease (PD) were considered Day 29 Non-Responders (n=9)
- Progression-free survival (PFS) was the time from first dose to the earliest observation of disease progression, relapse of underlying malignancy, or death
- Overall survival (OS) and PFS were assessed using Kaplan-Meier analysis

## Key Safety Results

**The adverse event (AE) profile was consistent with a severe aGVHD patient population**
- Two subjects had treatment-related infection serious AEs; one was a dose-limiting toxicity AE (sepsis)
- All infusion reaction AEs occurred with the first dose of 0.4 or 0.8 mg/kg itolizumab; subjects were able to complete dosing on Day 1
- No deaths were considered treatment-related

| Subjects, n (%) with: | Itolizumab 0.4 mg/kg N=4 | Itolizumab 0.8 mg/kg N=12 | Itolizumab 1.6 mg/kg N=9 | Total N=25 |
|---|---|---|---|---|
| **Any AE** | 4 (100) | 12 (100) | 9 (100) | **25 (100)** |
| Infusion Reaction AE | 1 (25) | 2 (17) | 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)** |
| **Deaths Unrelated to Study Treatment** | 1 (25) | 5 (42) | 5 (56) | **11 (44)** |
| AE Leading to Death | 0 | 5 (42) | 3 (33) | **8 (32)** |

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*

## Key Efficacy Results: aGVHD Response

**Responses were observed by Day 15 and maintained at Day 29**
- Highest Day 29 response rates (CR and ORR) were seen in subjects who received itolizumab within 72 hours of systemic steroid initiation
- This included a high proportion of CRs following a single dose of itolizumab (Day 15)

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

*Day 15 disease response data was not available for one subject

**Day 29 responses were durable, with most subjects maintaining response**
- Across all doses, 79% of Day 29 Responders maintained a response through Day 169, and 50% had a sustained response through Day 337

| Itolizumab | Initial aGVHD Grade | Initial Steroid Dose† ≤3 days | Treatment Period: Day 29 | Day 43 | Day 57 | Off-Treatment Follow-up Period: Day 85 | Day 169 | Day 253 | Day 337 |
|---|---|---|---|---|---|---|---|---|---|
| 0.4 mg/kg (N=2) | III | Yes | CR | CR | CR | CR | CR | PD# | -- |
| | III | Yes | CR | CR | PR | CR | CR | CR | CR |
| 0.8 mg/kg (N=7) | IV | Yes | CR | CR | CR | CR | CR | CR | CR |
| | IV | Yes | CR | CR | CR | CR | CR | CR | ● |
| | III | Yes | CR | CR | CR | CR | ND | CR | CR |
| | III | No (7 days) | CR | CR | CR | CR | CR | ● | |
| | III | Yes | CR | CR | CR | CR | CR | | |
| | III | Yes | CR | CR | CR | CR | | | |
| | II | Yes | CR | | | | | | |
| 1.6 mg/kg (N=7) | III | Yes | CR | CR | CR | PD | ● | | |
| | III | Yes | CR | CR | CR | CR | CR | ● | |
| | III | Yes | VGPR | CR | CR | CR | CR | CR | CR |
| | III | No (7 days) | CR | ● | | | | | |
| | III | No (6 days) | VGPR | ND | ND | VGPR | CR | CR | CR |
| | IV | No (4 days) | PR | CR | CR | CR | CR | CR | CR |
| | IV | Yes | CR | CR | CR | CR | PD# | -- | |

▶ Participation in study is ongoing ● Discontinued study due to primary disease relapse ● Death due to primary disease relapse ○ Unrelated AE leading to death

†Initial systemic dose of ~1-2 mg/kg prednisone or equivalent prior to itolizumab dosing; #Disease response after rescue treatment is not included

*Abbreviations: AE, adverse event; aGVHD, acute graft-versus-host disease; CR, complete response; ND, not done; ORR=PR+VGPR+CR, overall response rate; PD, progressive disease; 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*

## 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 (61%) was achieved in subjects treated with itolizumab within 72 hours of starting systemic steroids
- Responses were durable, with 79% of Day 29 Responders maintaining response through 6 months and 50% through 12 months
- Responders tapered steroids by 73% at Day 29 and 96% at Day 169
- Response at Day 29 was associated with 72% OS at 12 months and high rates of PFS
- 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 a pivotal Phase 3 study (EQUATOR), which has been initiated for the first-line treatment of aGVHD (NCT05263999)**

## Results

### Patient Demographics and Baseline Characteristics

| | 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 (Male), 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)** |

*Highest clinical grade at screening or baseline. #Score calculated at Screening.
Abbreviations: aGVHD, acute graft-versus-host disease; AML, acute myeloid leukemia; LGI, lower gastrointestinal; MAP, MAGIC Algorithm Probability; MDS, myelodysplastic syndrome; SD, standard deviation; UGI, upper gastrointestinal

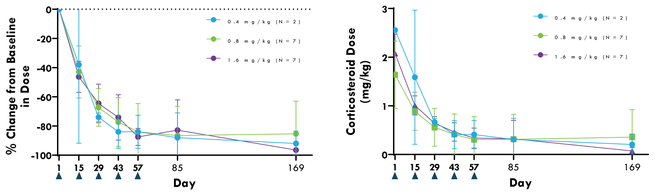
### Patient Disposition

- All subjects received 1-5 doses of itolizumab
- Study drug discontinuations after 1 dose of itolizumab were due to:
  - Need for subsequent administration of alternate anti-GVHD therapy for progressive disease (n=6)
  - AE of worsened aspiration pneumonia (n=1)
  - Physician decision (pancytopenia considered unrelated to study drug [n=1])

### Efficacy: Corticosteroid Use

**Itolizumab was associated with a clinically meaningful dose reduction in systemic steroid use**
- Most subjects continued to taper steroids through Day 169
- Median steroid dose reduction for Day 29 Responders was 73% at Day 29 and 96% at Day 169, which correlated with a median daily dose of 0.62 and 0.11 mg/kg at Days 29 and 169, respectively
- Steroids were tapered at the Investigator's discretion

**Corticosteroid Use For Day 29 Responders**



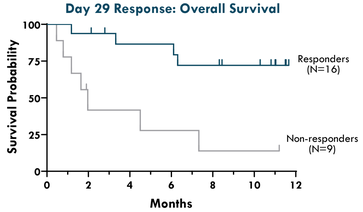

Data presented as mean (SD); equivalent prednisone dose calculated for methylprednisolone and dexamethasone to determine systemic steroid use at each visit.
▲ Represents itolizumab dosing days.

### Efficacy: Long-Term Outcomes

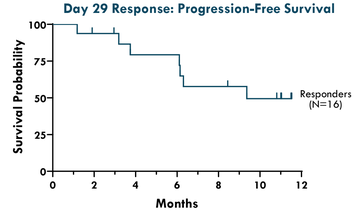
- 22 subjects were followed for 6 months (4 months post-itolizumab treatment) or discontinued from the study; 20 subjects have been followed for 12 months
- Through 6 months, 3 subjects had chronic GVHD (0.4 mg/kg: n=1 and 0.8 mg/kg: n=2)
- An additional 3 subjects developed chronic GVHD by 12 months (0.4 mg/kg: n=1 and 1.6 mg/kg: n=2)

**Day 29 Responders had improved long-term outcomes**
- Day 29 Responders had lower mortality (OS: 72%) than Non-responders (OS:14%)
- At Day 169, 12/14 (86%) Day 29 Responders were alive and 2/8 (25%) Non-responders were alive
- 7 Non-responders died during the study; 5 within 2 months of initiating itolizumab
  - 6 subjects initiated ruxolitinib after the first dose and 1 after the second dose. Of these, 5 died, 1 withdrew from the study, and 1 completed the study
- PFS was 72% at 6 months and 49% at 12 months

**Day 29 Response: Overall Survival**




**Day 29 Response: Progression-Free Survival**

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**References**
1. Soiffer RJ et al. *J Clin Oncol* 1992;10(7):1191-1200; 2. Consuegra-Fernandez M et al. *Cell Mol Immunol* 2018;17(5):493-503; 3. Ma C et al. *J Crohns Colitis* 2019;13(4):510-524.

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