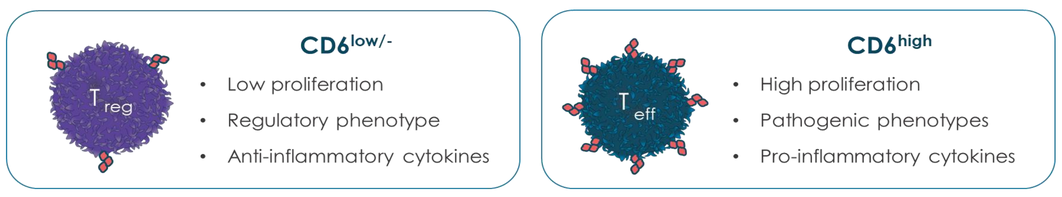
Preliminary Safety And Efficacy Of Itolizumab, A Novel Targeted Anti-CD6 Therapy, In Newly Diagnosed Severe Acute Graft-versus-host Disease: Interim Results From The EQUATE Study

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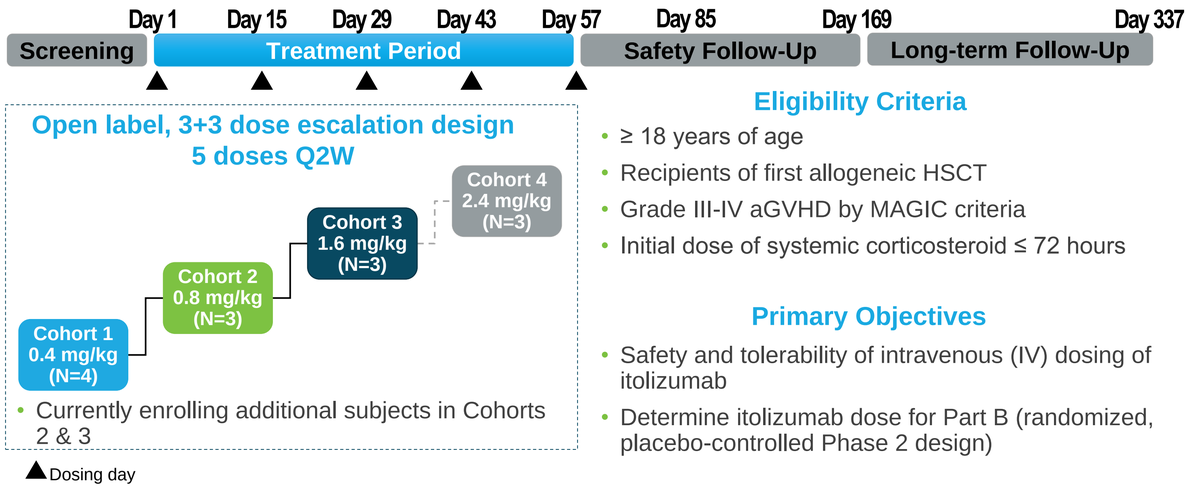
INTRODUCTION

- **CD6 is a co-stimulatory receptor** expressed on CD4 and CD8 effector T cells (T_{eff})
- Multiple CD6 ligands, including activated leukocyte cell adhesion molecule **(ALCAM), expressed on both APCs and tissues**, including the skin and GI tract
- **CD6 and ALCAM both overexpressed during GI inflammation**
- **CD6-ALCAM pathway modulates both T cell activity and trafficking**
- Prior studies validated **CD6 as a target relevant to GVHD pathogenesis**



- **Itolizumab causes antigenic modulation (shedding) of CD6 from the cell surface, thereby shifting CD4 and CD8 T cells from a CD6 high to a CD6 low phenotype**

EQUATE PART A PHASE 1B STUDY DESIGN



Eligibility Criteria

- ≥ 18 years of age
- Recipients of first allogeneic HSCT
- Grade III-IV aGVHD by MAGIC criteria
- Initial dose of systemic corticosteroid ≤ 72 hours

Primary Objectives

- Safety and tolerability of intravenous (IV) dosing of itolizumab
- Determine itolizumab dose for Part B (randomized, placebo-controlled Phase 2 design)

Data presented is from an interim analysis of subjects who completed visits through at least Day 85

DEMOGRAPHICS & GVHD DISEASE CHARACTERISTICS

	Cohort 1 (0.4 mg/kg) N=4	Cohort 2 (0.8 mg/kg) N=3	Cohort 3 (1.6 mg/kg) N=3	Total N=10
Age (years), mean (SD)	44 (18.0)	47 (21.5)	55 (7.1)	**48 (15.7)**
Sex (M), n (%)	4 (100%)	2 (67%)	3 (100%)	**9 (90%)**
Race (White/Black), n (%)	4 (100%)/0	2 (67%) /1 (33%)	3 (100%)/0	**9 (90%) /1 (10%)**
Ethnicity (Hispanic) n (%)	2 (50%)	1 (33%)	0	**3 (30%)**
Weight (kg), mean (SD)	94.3 (6.6)	84.8 (31.8)	97.2 (5.4)	**92.3 (16.5)**
Primary Disease, n (%)				
AML	2 (50%)	2 (67%)	0	**4 (40%)**
ALL	1 (25%)	1 (33%)	0	**2 (20%)**
Myelofibrosis	1 (25%)	0	1 (33%)	**2 (20%)**
Other (MDS or CMML)	0	0	2 (67%)	**2 (20%)**
Graft source, n (%)				
Peripheral blood	4 (100%)	1 (33%)	3 (100%)	**8 (80%)**
Bone Marrow	0	2 (66%)	0	**2 (20%)**
HLA matched, n (%)	2 (50%)	3 (100%)	3 (100%)	**8 (80%)**
Myeloablative conditioning, n (%)	2 (50%)	2 (67%)	1 (33%)	**5 (50%)**
Organ involvement, n (%)				
Skin	0	0	1 (33%)	**1 (10%)**
Liver	1 (25%)	0	0	**1 (10%)**
Upper GI	0	2 (67%)	0	**2 (20%)**
Lower GI	3 (75%)	3 (100%)	3 (100%)	**9 (90%)**
aGVHD Grade[1], n (%)				
III	3 (75%)	1 (33%)	3 (100%)	**7 (70%)**
IV	1 (25%)	2 (67%)	0	**3 (30%)**
MacMillan High risk Score, n (%)	4 (100%)	2 (67%)	2 (67%)	**8 (80%)**
Ann Arbor Score[2] 2/3, n (%)	0/4 (100%)	3 (100%)/0	0/3 (100%)	**3 (30%)/7 (70%)**
MAP mean (SD)	0.469 (0.148)	0.212 (0.019)	0.656 (0.271)	**0.468 (0.222)**
Prophylaxis, n (%)				
Methotrexate	3 (75%)	2 (67%)	2 (67%)	**7 (70%)**
Tacrolimus	3 (75%)	2 (67%)	2 (67%)	**7 (70%)**
Sirolimus	3 (75%)	2 (67%)	1 (33%)	**6 (60%)**

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CMML, chronic myelomonocytic lymphoma; HLA, human leukocyte antigen; M, male; SD, standard deviation; GVHD, graft versus host disease; GI, gastrointestinal; MAP; MAGIC algorithm probability.
[1]Highest clinical grade at screening or baseline
[2]Ann Arbor Score: 2, MAP 0.141-0.290; 3, MAP >0.290

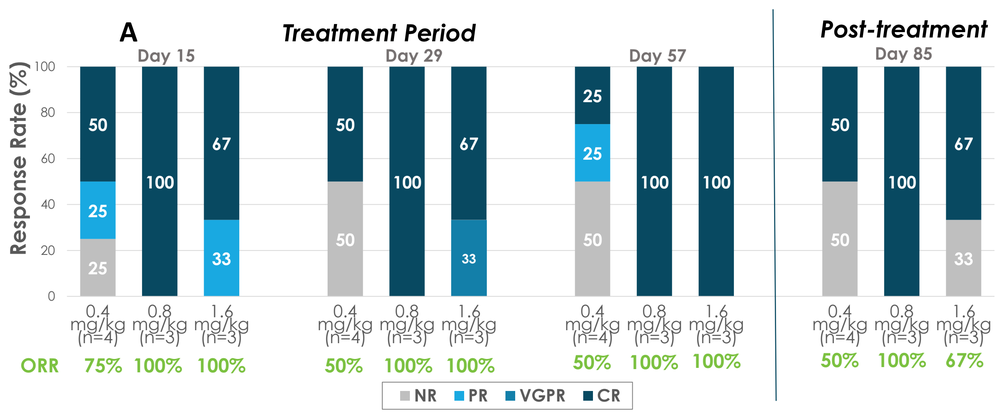
SUMMARY OF TREATMENT EMERGENT ADVERSE EVENTS

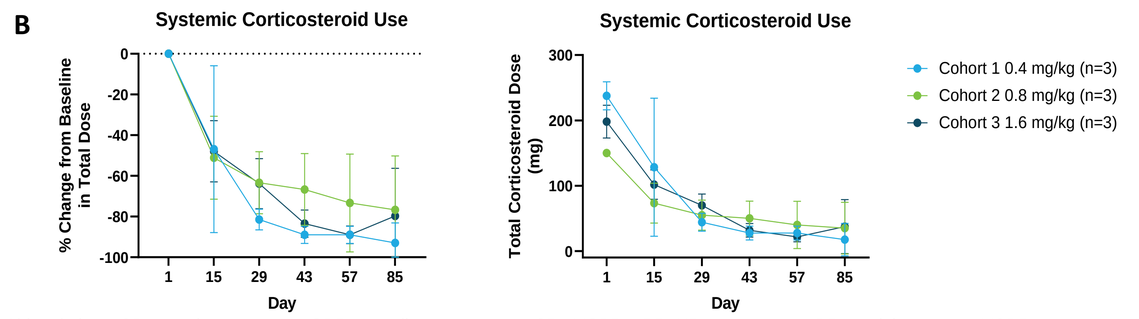
Subjects with:	Cohort 1 0.4 mg/kg n (%)	Cohort 2 0.8 mg/kg n (%)	Cohort 3 1.6 mg/kg n (%)	Total n (%)
Any AE	4 (100)	3 (100)	3 (100)	**10 (100)**
Infusion Reaction AE	1 (25.0)	0	0	**1 (10.0)**
Grade ≥3 AE	1 (25.0)	2 (66.7)	3 (100)	**6 (60.0)**
SAE	2 (50.0)	1 (33.3)	2 (66.7)	**5 (50.0)**
Infection SAE	1 (25.0)	1 (33.3)	2 (66.7)	**4 (40.0)**
Treatment Related SAE	0	1 (33.3)	1 (33.3)	**2 (20.0)**
AE Leading to Study Treatment Discontinuation	0	2 (66.7)	1 (33.3)	**3 (30.0)**
Dose Limiting Toxicity (DLT) AE	0	0	1 (33.3)	**1 (10.0)**
AE Leading to Death	0	0	1 (33.3)	**1 (10.0)**

Abbreviations: AE, adverse event; DLT, 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) ; SAE, serious adverse event

- AEs were collected through Day 169 for subjects who completed dosing and Day 85 for subjects who discontinued study treatment early
- Death was considered not related to study drug
- Infection SAEs in 1 subject each include sepsis, COVID-19, pulmonary sepsis, disseminated nocardia, fever, and skin infection
- Transient decrease in lymphocyte counts were observed in the first week

EFFICACY RESULTS

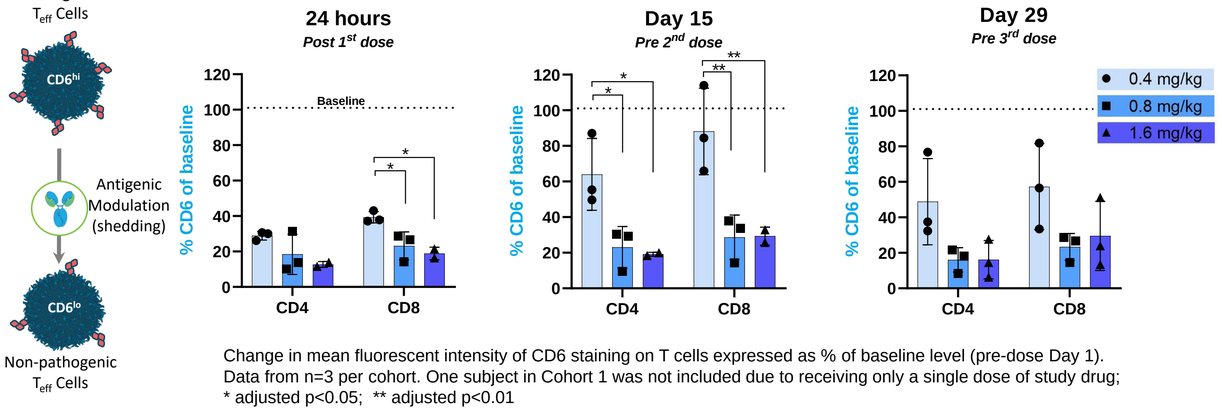




Abbreviations: CR, complete response; ORR, overall response rate= CR+ VGPR + PR; NR, no response; PR, partial response; VGPR, very good partial response based on Martin 2009 Consensus criteria

- One subject in Cohort 1 received 1 dose of study treatment; all others received between 2-5 doses
- Median % steroid dose reduction at Day 85 was 93%, 87%, and 91% for Cohorts 1, 2, and 3, respectively

DOSE-RESPONSIVE REDUCTION IN CD6 WITH ITOLIZUMAB



Change in mean fluorescent intensity of CD6 staining on T cells expressed as % of baseline level (pre-dose Day 1). Data from n=3 per cohort. One subject in Cohort 1 was not included due to receiving only a single dose of study drug; * adjusted p<0.05; ** adjusted p<0.01

- Pharmacodynamic data from first three cohorts suggests optimal dose range at 0.8 to 1.6 mg/kg

SUMMARY AND CONCLUSIONS

- **Itolizumab was generally well tolerated across all doses in high risk aGVHD patients**
  - Lymphocyte count changes are monitored carefully and are transient
  - Only one acute infusion reaction was noted early in the study (Cohort 1, first subject dosed)
  - Direct drug toxicities have not been noted; though relationship to infection in this vulnerable population will need continued assessment
- **Key findings for itolizumab**
  - Dose-dependent reduction of CD6 expression on CD4+ and CD8+ T-cells is consistent with proposed mechanism of action
  - Strong response for higher dose level cohorts (0.8 and 1.6 mg/kg) with ORR of 100% (N=6) at Day 29, most have been complete responses (one VGPR)
  - Clinical responses have been sustained through Day 57 – all subjects in CR
  - Reduction in baseline corticosteroid use at Day 29 was ~40 - 80%

Itolizumab demonstrates a favorable benefit-risk profile that supports further characterization of safety and efficacy in future studies

ACKNOWLEDGEMENTS

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REFERENCES: Consuegra-Fernandez *et al*., Cell Mol Immunol 2018; Ma *et al*., J Crohns & Colitis 2019; Soiffer *et al*., JCO 1992