NEIHULIZUMAB (ALTB-168) IN PATIENTS WITH STEROID-REFRACTORY ACUTE GRAFT-VERSUS-HOST-DISEASE (SR-aGVHD) or TREATMENT-REFRACTORY ACUTE GRAFT-VERSUS-HOST-DISEASE (TR-aGVHD)

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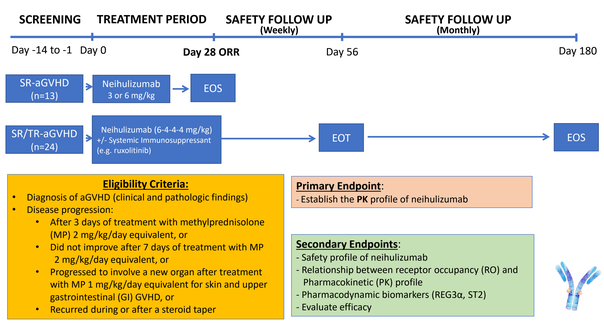
INTRODUCTION

- **Neihulizumab** (**ALTB-168,** former name AbGn-168H) represents a novel immune checkpoint agonistic antibody that binds to human CD162 (PSGL-1), leading to downregulation of activated T cells. Results of early-phase trials of neihulizumab have suggested a benefit in patients with treatment refractory auto-immune conditions, including psoriasis, psoriatic arthritis and ulcerative colitis.

- Acute GVHD (aGVHD) is a T-cell mediated disorder that may develop after allogeneic hematopoietic cell transplantation. Up to 60% of patients have an unsatisfactory response to steroids, the standard first-line treatment. For patients with steroid-refractory aGVHD (SR-aGVHD), outcomes remain poor despite the approval of ruxolitinib. For patients who have not benefitted from a systemic treatment in addition to corticosteroids (treatment-refractory aGVHD), the outcome is dismal. Development of novel therapies for the treatment of SR- and TR-aGVHD is needed. Therefore, we conducted a Phase I study of neihulizumab in patients with SR- and TR-aGVHD.

STUDY DESIGN



Eligibility Criteria:
- Diagnosis of aGVHD (clinical and pathologic findings)
- Disease progression:
  - After 3 days of treatment with methylprednisolone (MP) 2 mg/kg/day equivalent, or
  - Did not improve after 7 days of treatment with MP 2 mg/kg/day equivalent, or
  - Progressed to involve a new organ after treatment with MP 1 mg/kg/day equivalent for skin and upper gastrointestinal (GI) GVHD, or
  - Recurred during or after a steroid taper

Primary Endpoint:
- Establish the **PK** profile of neihulizumab

Secondary Endpoints:
- Safety profile of neihulizumab
- Relationship between receptor occupancy (RO) and Pharmacokinetic (PK) profile
- Pharmacodynamic biomarkers (REG3α, ST2)
- Evaluate efficacy

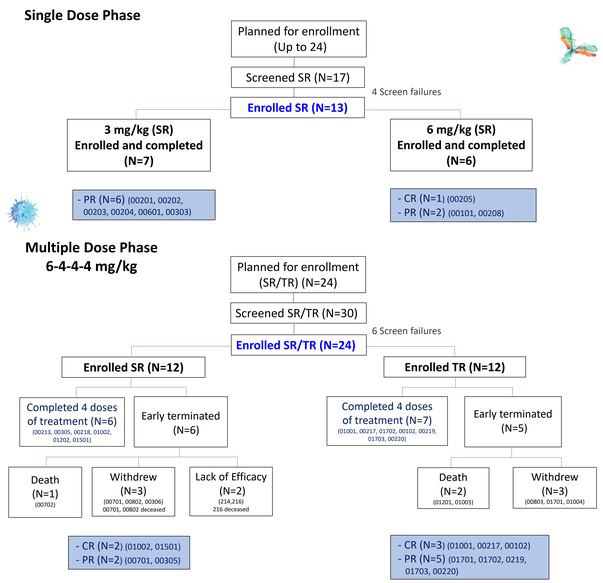
RESULTS

Demographics and Baseline Characteristics

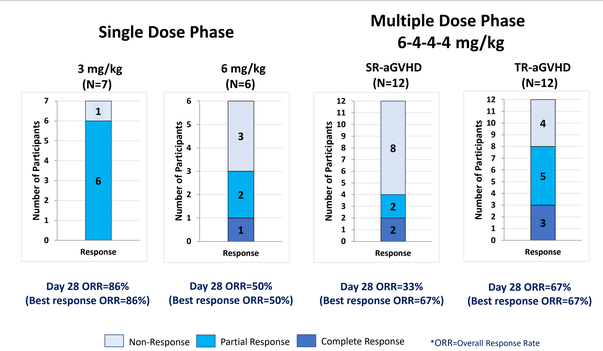
	Single Dose Phase		Multiple Dose Phase	
			6-4-4-4 mg/kg	
	3 mg/kg (N=7)	6 mg/kg (N=6)	SR-aGVHD (N=12)	TR-aGVHD (N=12)
Age				
Median (range)	57 (38-72)	59 (56-64)	65 (55-75)	53 (23-70)
Gender				
Male	5 (71)	3 (50)	6 (50)	8 (67)
Female	2 (29)	3 (50)	6 (50)	4 (33)
Race				
Black or African American	0	0	2 (17)	1 (8)
White	7 (100)	6 (100)	8 (67)	10 (83)
Other	0	0	2 (17)	1 (8)
aGVHD grade				
Grade I-II	6 (86)	4 (67)	3 (25)	6 (50)
Grade III-IV	1 (14)	2 (33)	9 (75)	6 (50)
aGVHD organ involvement				
Skin only[1]	6 (86)	4 (67)	2 (17)	3 (25)
(Lower) GI only	0	0	5 (42)	4 (33)
Liver only	0	0	2 (17)	2 (17)
Skin and (lower) GI	1 (14)	1 (14)	3 (25)	3 (25)
Skin, (lower) GI and Liver	0	1 (14)	0	0
Prior treatment with ruxolitinib	0	0	0	11(92)
Underlying disease				
Acute Myeloid Leukemia	1 (14)	2 (33)	6 (50)	5 (42)
Myelodysplastic Syndrome	1 (14)	2 (33)	1 (8)	3 (25)
Acute Lymphoblastic Leukemia	1 (14)	2 (33)	0	1 (8)
Lymphoma	2 (29)	0	0	1 (8)
Others	2 (29)	0	5 (42)	2 (17)
Donor type				
Related	2 (29)	1 (17)	5 (42)	7 (58)
Unrelated	5 (71)	5 (83)	7 (58)	5 (42)
Conditioning regimen				
Myeloablative	2 (29)	4 (67)	7 (58)	6 (50)
Reduced Intensity	5 (71)	2 (33)	5 (42)	4 (33)
Non-Myeloablative	0	0	0	2 (17)
Stem cell type				
Peripheral blood	5 (71)	5 (83)	11 (92)	10 (83)
Bone marrow	2 (29)	1 (17)	1 (8)	0 (0)
Umbilical cord blood	0 (0)	0 (0)	0 (0)	2 (17)

[1]Skin involvement was a requirement in Single Dose Phase

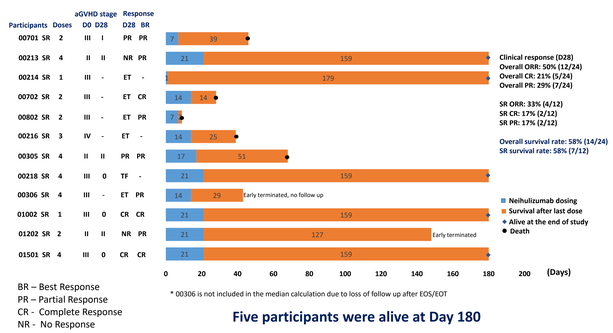
Participant Disposition



Efficacy Overview of Neihulizumab – Day 28



Duration of Neihulizumab Treatment & Survival – SR-aGVHD

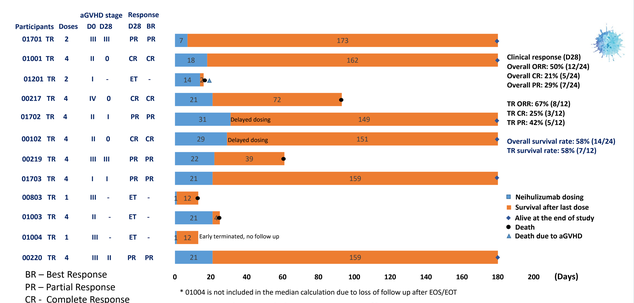


BR – Best Response
PR – Partial Response
CR - Complete Response
NR - No Response

* 00306 is not included in the median calculation due to loss of follow up after EOS/EOT

Five participants were alive at Day 180

Duration of Neihulizumab Treatment & Survival – TR-aGVHD



BR – Best Response
PR – Partial Response
CR - Complete Response
NR - No Response

* 01004 is not included in the median calculation due to loss of follow up after EOS/EOT

Six participants were alive at Day 180

Ruxolitinib Treatment Duration Prior to Neihulizumab

Participants (TR-aGVHD)	Neihulizumab (number of doses)	Ruxolitinib Treatment (prior to neihulizumab treatment)	Organ of Persistent GVHD	
			Prior to neihulizumab	After neihulizumab
01701	4	11	Liver (3)	Liver (2)
01001	4	18	GI (1)	GI (0)
01201	3	6	Skin (2)	Skin (4)
00217	4	4	Skin (4)/GI (2)	Skin (0)/GI (0)
01702	4	14	Skin (3)	Skin (1)
00219	4	30	Liver (3)	Liver (2)
01703	4	42	Skin (2)	Skin (1)
00803	2	6	GI (3)	GI (3)
01003	3	11	GI (1)	GI (4)
01004	1	4	Skin (3)/GI (3)	Skin (3)/GI (3)
00220	4	6	GI (2)	GI (1)
Median		**11 (4 - 42) Days**		

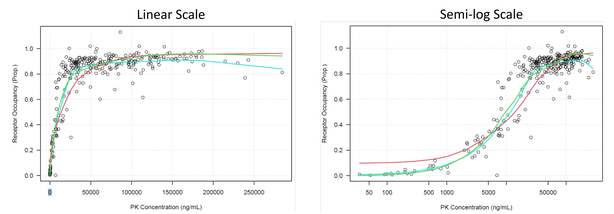
Steroid Reduction after Neihulizumab Treatment

Multiple Dose Phase

Participants	Efficacy (Day 28)	Steroid Treatment
00701 (SR)	PR	Methylprednisolone (35 mg, Q12H) → Prednisone (10 mg, QOD)
01501 (SR)	PR	Prednisone (60-195 mg, QD) → Methylprednisolone (40-150 mg, QD)
01001 (TR)	CR	Methylprednisolone (53 mg, QD) → Prednisone (45mg, QD)
00217 (TR)	CR	Methylprednisolone (50 mg, Q12H) → Prednisone (40 mg, QD)
01702 (TR)	PR	Prednisone (20 mg, QD)→ (15 mg, QD)
00102 (TR)	CR	Prednisone (90 mg, BID) → (45 mg, QD)
00219 (TR)	PR	Methylprednisolone (60 mg, BID)→ (25 mg QD)
00220 (TR)	PR	Prednisone (15 mg, QOD) → (10 mg, QD)

Correlation of PK & RO

- **Receptor Occupancy vs. Neihulizumab Concentration**



Receptor Occupancy	Present Analysis (Sigmoidal Emax)
50%	8.98 μg/mL
80%	29.98 μg/mL
85%	40.58 μg/mL
90%	60.68 μg/mL

Safety Overview

Overall Adverse Events (AEs)

Participants with AE	Single Dose Phase		Multiple Dose Phase (6-4-4-4 mg/kg)	
	3 mg/kg (N=7)	6 mg/kg (N=6)	SR-aGVHD (N=12)	TR-aGVHD (N=12)
Any Adverse Event	6 (86%)	6 (100%)	10 (83%)	12 (100%)
Serious Adverse Event	2 (29%)	2 (33%)	5 (42%)	10 (83%)
Dose Limiting Toxicity	0	0	2 (17%)	3 (25%)
Death	0	0	0	0

Most Frequent AEs (occurred in ≥ 2 participants)

Grade 3-4 adverse events observed ≥ 2 participants	Single Dose Phase		Multiple Dose Phase (6-4-4-4 mg/kg)	
	3 mg/kg (N=7)	6 mg/kg (N=6)	SR-aGVHD (N=12)	TR-aGVHD (N=12)
Anemia	-	-	5 (42%)	3 (25%)
Adenovirus	-	-	2 (17%)	-
Diarrhea	-	-	-	2 (17%)
Fatigue	-	-	2 (17%)	-
Hyperkalemia	-	-	-	2 (17%)
Hypocalcemia	-	-	-	-
Hypokalemia	-	-	2 (17%)	2 (17%)
Hyponatremia	2 (29%)	-	-	2 (17%)
Hypotension	-	-	-	2 (17%)
Ileus	-	-	-	2 (17%)
Lymphocyte count decreased	3 (43%)	3 (50%)	-	2 (17%)
Platelet count decreased	2 (29%)	3 (50%)	5 (42%)	3 (25%)
White blood decreased	2 (29%)	-	2 (17%)	-

SUMMARY

- Participants with SR-aGVHD disease achieved an ORR of 67% and CR of 17% as measured by Best Response
- In the TR-aGVHD cohort, median exposure to ruxolitinib was 11 days prior to study entry
- Participants with TR-aGVHD (11 of 12 concomitant ruxolitinib) achieved an ORR of 67% and CR of 25% at Day 28
- 5 participants in the SR-aGVHD and 6 participants in the TR-aGVHD cohort were alive at the end of study visit (Day 180)
- Corticosteroid reductions were achieved in a significant portion of TR-aGVHD participants
- Safety results were comparable between the SR and TR cohorts

CONCLUSIONS

- ✓ A promising efficacy signal was observed, including participants that previously failed ruxolitinib treatment and subsequently received neihulizumab in combination with ruxolitinib
- ✓ Median survival benefits in TR-aGVHD participants compare favorably to historical controls
- ✓ Neihulizumab was well tolerated, with similar safety profiles observed when given alone or in combination with ruxolitinib
- ✓ These data support further development of neihulizumab as a potential novel treatment for patients with SR- or TR-aGVHD

CONTACT INFORMATION

- This study was sponsored by AltruBio, Inc.
- Clinical trial identification: NCT03327857
- Contact information: jesse.hall@altrubio.com