NEIHULIZUMAB (ABGN-168H) IN PATIENTS WITH STEROID-REFRACTORY ACUTE GRAFT-VERSUS-HOST-DISEASE (SR-AGVHD): PRELIMINARY RESULTS OF A PHASE I STUDY

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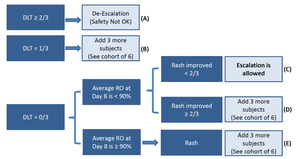
Background

- **Neihulizumab (AbGn-168H)** is a humanized monoclonal antibody which binds to human CD162 (PSGL-1) and preferentially induces apoptosis of late stage activated T cells. It has been tested in T-cell mediated inflammatory diseases including psoriasis, psoriatic arthritis and ulcerative colitis.
- Acute GvHD (aGvHD) is a T-cell mediated disorder after allogeneic hematopoietic cell transplantation. Up to 60% of patients have unsatisfactory response of steroid, the standard first-line treatment. For patients with steroid-refractory aGvHD (sr-aGvHD), no consensus exists regarding treatment, and outcomes remain poor. Development of agents for treatment of sr-aGvHD is a significant unmet medical need. Therefore, we conduct a Phase I study of Neihulizumab in patients with sr-aGvHD.

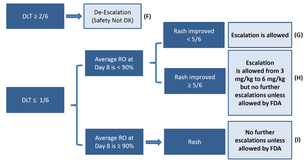
Study Design

- This is an open label, single dose and dose escalation study in a window design with "3+3" scheme to assess Neihulizumab in patients with sr-aGvHD.
- Escalation route is determined by (1) DLT, (2) Receptor occupancy (RO) and (3) Skin rash improvement
- Dose: 3 mg/kg, 6 mg/kg, 9 mg/kg or 12 mg/kg, single dose.

Dose Escalation Scheme - Cohort of 3



Dose Escalation Scheme - Cohort of 6



Study Objectives

Primary Objective:
- To establish the pharmacokinetic (PK) profile of Neihulizumab.

Secondary Objective:
- To establish the safety profile.
- To evaluate the relationship between receptor occupancy (RO) and PK.
- To investigate the relevance of regenerating islet–derived 3-alpha (REG3α) and suppression of tumorigenicity 2 (ST2) as pharmacodynamics (PD) biomarkers.
- To evaluate signs of efficacy and to determine the immunogenicity.

Key Inclusion Criteria

Patients with any grade sr-aGvHD involving the skin, with or without other organ involvement. Sr-aGvHD was defined as aGvHD that

- worsened after 2 days during treatment with ≥ 1mg/kg prednisone (or equivalent) or
- persisted after 7 days during treatment with > 0.4 mg/kg prednisone (or equivalent) or
- worsened while tapering steroid treatment at doses > 0.4 mg/kg prednisone (or equivalent).

Patient Enrollment

Table 1. Demographics and baseline characteristics

		3 mg/kg (N = 6+1[a])	6 mg/kg (N = 6)	Overall (N = 13)
Median Age (range)		60 (38-72)	58 (56-64)	60 (38-72)
Gender	Female	2 (29%)	3 (50%)	5 (38%)
	Male	5 (71%)	3 (50%)	8 (62%)
Primary disease	AML	1 (14%)	1 (17%)	2 (15%)
	CMML	1 (14%)	-	1 (8%)
	ALL	1 (14%)	3 (50%)	4 (31%)
	CLL	1 (14%)	-	1 (8%)
	CTCL	1 (14%)	-	1 (8%)
	HL	1 (14%)	-	1 (8%)
	MDS	1 (14%)	2 (33%)	3 (23%)
Conditioning Regimen	Myeloablative	2 (29%)	4 (67%)	6 (46%)
	Reduced Intensity	5 (71%)	2 (33%)	7 (54%)
Donor Status	Related	2 (29%)	1 (17%)	3 (23%)
	Non-related	5 (71%)	5 (83%)	10 (77%)
Stem cell type	Bone Marrow	2 (29%)	1 (17%)	3 (23%)
	Peripheral Blood	5 (71%)	5 (83%)	10 (77%)
Enrollment aGvHD Grade	Grade I	1 (14%)	1 (17%)	2 (15%)
	Grade II	5 (71%)	3 (50%)	8 (62%)
	Grade III	1 (14%)	2 (33%)	3 (23%)
Organ Involvement	Skin	7 (100%)	6 (100%)	13 (100%)
	GI track, lower	1 (14%)	2 (33%)	3 (23%)
	Liver	0 (0%)	1 (17%)	1 (8%)

[a] *Including one subject initially assigned to the 6 mg/kg cohort. Due to infusion reaction, approximately 50% of study drug was administered.*

Safety Overview

Table 2. Overall adverse events (AEs)

	3 mg/kg (N = 6+1[a])	6 mg/kg (N = 6)
AEs	7 (100%)	6 (100%)
Serious AEs	2 (29%)	2 (33%)
DLT	1 (14%)	0 (0%)
Death	0 (0%)	0 (0%)

[a] *Including one subject initially assigned to the 6 mg/kg cohort. Due to infusion reaction, approximately 50% of study drug was administered.*

Table 3. Most frequent AEs (occurred in ≥ 2 subjects)

Most frequent AEs	3 mg/kg (N = 6+1[a])	Grade				6 mg/kg (N = 6)	Grade			
		1	2	3	4		1	2	3	4
Lymphocyte decreased	4 (57%)	1	1	1	1	5 (83%)		2	1	2
Platelet decreased	3 (43%)		2		1	3 (50%)			2	1
Hyperglycemia	4 (57%)		2	2		2 (33%)			2	
Hypoalbuminemia	3 (43%)	2	1			2 (33%)	2			
Alanine aminotransferase increased	2 (29%)	2				3 (50%)	2	1		
Hypertension	3 (43%)	1	1	1		2 (33%)	1	1		
Hypocalcemia	2 (29%)	1	1			3 (50%)	2	1		
Hypophosphatemia	3 (43%)		2	1		2 (33%)		1	1	
White blood cell count decreased	2 (29%)				2	2 (33%)		1	1	
Anemia	2 (29%)		1	1		2 (33%)	1	1		
Hyperkalemia	2 (29%)	1	1			2 (33%)	2			
Edema limbs						2 (33%)	2			
Neutrophil count decreased	2 (29%)		1		1					
Aspartate aminotransferase increased	2 (29%)	2								
Fever	2 (29%)	2								
Headache	2 (29%)	2								
Hyperuricemia	2 (29%)	1			1					
Hypomagnesemia	2 (29%)	2								
Hyponatremia	2 (29%)			2						
Insomnia	2 (29%)		1	1						

[a] *Including one subject initially assigned to the 6 mg/kg cohort. Due to infusion reaction, approximately 50% of study drug was administered.*

Safety Overview

Table 4. Related AEs

Related AEs	3 mg/kg (N = 6+1[a])	Grade				6 mg/kg (N = 6)	Grade			
		1	2	3	4		1	2	3	4
Lymphocyte decreased	4 (57%)	1	1	1	1	1 (14%)		1		
Platelet decreased	2 (29%)		2							
Hyponatremia	2 (29%)			2		1 (14%)	1			
Hypertension						1 (14%)	1			
Infusion reaction	1 (14%)		1							

[a] *Including one subject initially assigned to the 6 mg/kg cohort. Du to infusion reaction, approximately 50% of study drug was administered.*

Table 5. SAE and DLT

Cohort	Subject	SAE	Severity	Causality	DLT
3 mg/kg	Subject 2	Hyponatremia	Grade 3	Possibly related	DLT
	Subject 5	Presyncope	Grade 3	Definitely not related	
6 mg/kg	Subject 11	aGvHD progression	Grade 3	Definitely not related	
	Subject 13	aGvHD progression	Grade 3	Definitely not related	

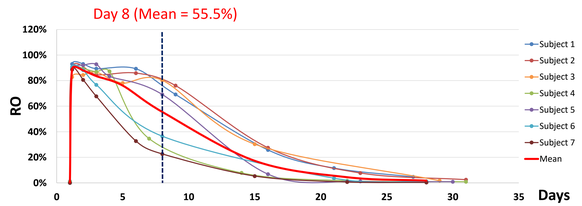
Efficacy Overview of Neihulizumab

Efficacy outcome	3 mg/kg (N=6+1[a])	6 mg/kg (N=6)	Total (N=13)
Overall best response	7 (100%)	3 (50%)	10 (77%)
Complete response	1 (14%)	1 (17%)	2 (15%)
Partial response	6 (86%)	2 (33%)	8 (62%)
Failure	0 (0%)	3 (50%)	3 (23%)

[a] *Including one subject initially assigned to the 6 mg/kg cohort. Due to infusion reaction, approximately 50% of study drug was administered.*

Receptor Occupancy

3 mg/kg cohort



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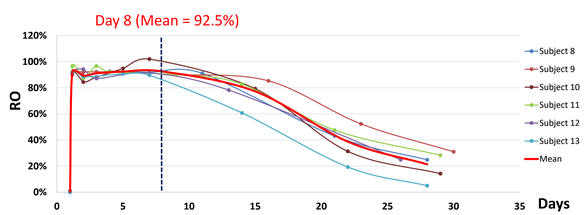
6 mg/kg cohort



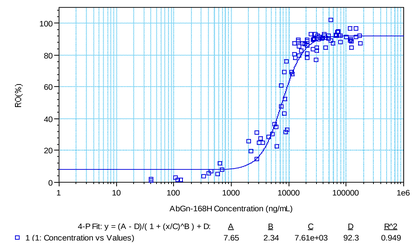
Pharmacokinetic Parameters of Neihulizumab

Parameters	3 mg/kg		6 mg/kg	
	N[a]	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
C_{max}, μg/mL	7	47.1 (15.3)	6	174.3 (54.6)
T_{max}, hour	7	4.4 (3.4)	6	3.2 (2.8)
AUC_{0-t}, μg.h/mL	7	$4.7x10^3$ ($1.6x10^3$)	6	$1.9x10^4$ ($3.6x10^3$)
AUC_{0-inf}, μg.h/mL	7	$4.7x10^3$ ($1.6x10^3$)	6	$2.0x10^4$ ($3.8x10^3$)
$t_{1/2}$, hour	7	72.1 (14.2)	6	116.9 (20.2)
λz (Kel) , $hour^{-1}$	7	0.01 (0.002)	6	0.006 (0.001)
MRT, hour	7	100.8 (25.2)	6	141.9 (27.0)
Vd, L	7	5.8 (1.5)	6	4.1 (0.8)

[a] *Including one subject initially assigned to the 6 mg/kg cohort. Due to infusion reaction, approximately 50% of study drug was administered.*

Correlation of PK & RO

AbGn-168H plasma concentration ≥ 35 μg/mL is required to reach 90% RO saturation.



RO	Conc. (μg/mL)
29%	4.78
50%	7.61
80%	16.23
85%	20.87
90%	35.11

Conclusions and Future Directions

- Safety results suggested that Neihulizumab is well-tolerated in patients with sr-aGvHD.
  (1) Most AEs observed are typical for patients with sr-aGvHD and with severity mild to moderate.
  (2) Most frequently reported AE is lymphocyte decrease.
  (3) Hyponatremia was the only (possibly) related SAE and the only DLT.
  (4) No death.
- A promising efficacy signal was observed with 77% of patients improving at least 1 stage after administration of single dose of Neihulizumab without increasing the steroid dose or starting other systemic treatment.
- With dose escalation to 6 mg/kg, RO was maintained at ≥ 90% throughout the first week after administration. No further dose escalation is planned.
- These results support continued testing of Neihulizumab in patients with sr-aGvHD with multiple dosing to further assess safety and efficacy.

Other Information/ Acknowledgements

- This study is sponsored by AbGenomics
- Clinical trial identification: NCT03327857
- Contact information: shihyao.lin@abgenomics.com