A First in Human Study of AO-176, a Highly Differentiated Anti-CD47 Antibody, in Patients with Advanced Solid Tumors

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INTRODUCTION

- AO-176 is a humanized IgG2 antibody that specifically targets CD47
- Expressed by multiple tumor types, CD47 binds to signal regulatory protein α (SIRPα) on phagocytes, including macrophages and dendritic cells
- AO-176 has negligible binding to red blood cells (RBC)

AO-176: A HIGHLY DIFFERENTIATED NEXT-GENERATION HUMANIZED ANTI-CD47 MAB

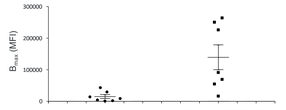
	Conventional Anti-CD47 Blocker	AO-176	Potential Advantages
Blocks CD47/SIRPα & Induces Phagocytosis	✓	✓	
Lower Binding to Normal Cells	✗	✓	Safety
Better Binding in Tumor Environment (Low pH)	✗	✓	Safety + Efficacy
Direct Killing & DAMP[1] Induction	✗	✓	Efficacy

[1] DAMP = Damage-associated molecular patterns

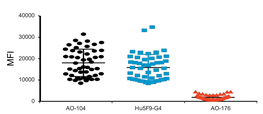
Figure 1: AO-176 Exhibits Lower Binding to Normal Cells and Increased Tumor Targeting at Acidic pH by Flow Cytometry

LOWER BINDING TO NORMAL CELLS AND NEGLIGIBLE BINDING TO RBC

Normal Cells (Epithelial, Muscle, Endothelial, Neutrophils, Platelets, T Cells and RBC)

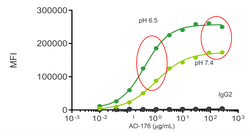


Comparison of Maximal RBC Binding from ~50 Normal Donors

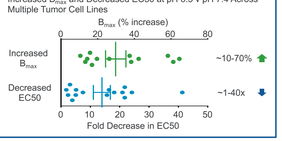


HIGHER TUMOR CELL BINDING IN ACIDIC TUMOR MICROENVIRONMENT

SNU-1 Gastric Cancer



Increased B_{max} and Decreased EC50 at pH 6.5 v pH 7.4 Across Multiple Tumor Cell Lines



- AO-176 does not induce hemolysis or hemagglutination
- There is negligible binding to donor-derived RBC at concentrations as high as 1 mg/mL
- Increased binding & affinity at acidic pH may correlate with higher receptor occupancy (RO) in tumor vs normal cells
- B_{max} ranges in various tumor lines from 10-70% increase
- Lower RO in the periphery is expected

OBJECTIVES

Safety, dose-limiting toxicity (DLT) and recommended Phase 2 dose (RP2D), antitumor activity, pharmacokinetic (PK) parameters and exploratory biomarkers

METHODS

- In a Phase 1/2 first-in-human study (NCT03834948) of AO-176, patients with advanced solid tumors associated with high CD47 expression and an ECOG PS of 0-1 were enrolled into escalating dose cohorts of AO-176 given IV every 7 days (three weekly doses of AO-176 constituted 1 treatment cycle)
- Patients were not selected for study based on tumor CD47 expression
- The trial used a classic 3+3 design
- Dose levels of 1, 3, 10, 20 and 20 (using step-up dosing) mg/kg were evaluated in >250 infusions
- The DLT period was cycle 1 for patients in Cohorts 1-4 (dose level 1, 3, 10, 20 mg/kg), and through the first 2 cycles for patients in Cohort 5 (dose levels 20 mg/kg with step-up dosing)
- Adverse events (AEs) were assessed per the CTCAE v5.0 (published 17 November 2017)
- Exploratory biomarkers included baseline tumor CD47, CD3, CD8, PD-L1 (28-8) and CD68 by IHC and RO measured on platelets and peripheral blood mononuclear cells (PBMC) by flow cytometry
- Data cutoff date: March 29, 2021

Figure 2: Phase 1 Dose Escalation

COHORT	1	2	3	4	5
Dose (mg/kg) in 21-day cycles (n=3-6)	1	3	10	20	STEP UP DOSE TO 20

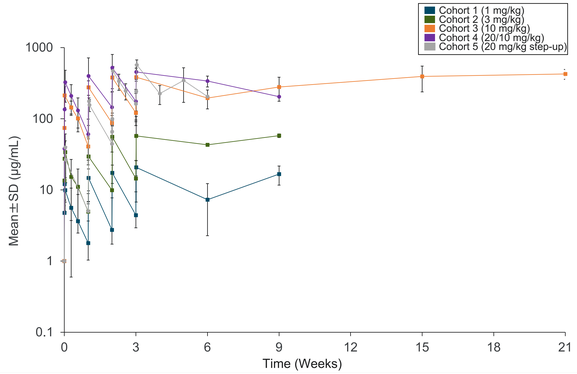
RESULTS

Table 1: Demographics (N=27)

Category		Safety Population
Age (Years)	Median (Range)	64 (35-81)
Gender	Female % (n)	67 (18)
Primary Diagnosis	Epithelial Ovarian/Fallopian Tube % (n)	26 (7)
	Gastric/GEJ % (n)	19 (5)
	Endometrial % (n)	15 (4)
	Non-Small Cell Lung % (n)	15 (4)
	Castration Resistant Prostate Cancer % (n)	7 (2)
	Pleural Mesothelioma, Papillary Thyroid, Head and Neck % (n=1 each)	11 (3)
CD47	Median H-Score (n)	170 (25)
ECOG	PS 1 % (n)	67 (18)
Prior Therapies[1]	Median (range)	4 (1-7)

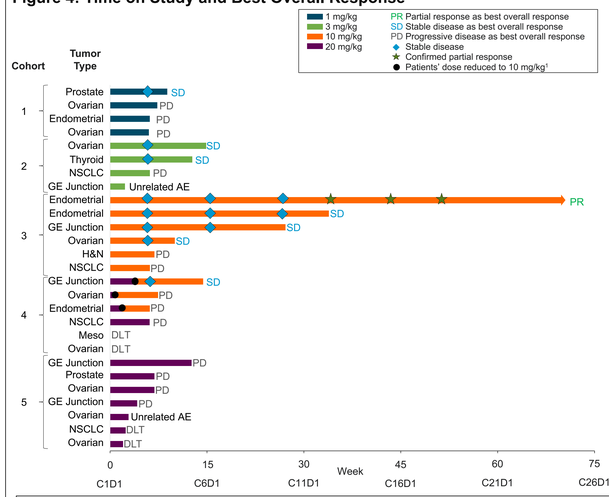
[1] For metastatic disease

Figure 3: AO-176 Pharmacokinetics and Pharmacodynamics



- AO-176 demonstrates linear and predictable pharmacokinetics
- Maximum, peripheral AO-176 RO is reached at RP2D
- AO-176 platelet RO confirms submaximal binding to normal cells (~60% on PBMC and ~50% on platelets) but higher RO on tumor is expected due to enhanced binding of AO-176 in acidic microenvironments and higher expression of CD47 on tumor cells
- Compared to other CD47 drugs, reduced binding to normal cells minimizes AO-176 sink effect as well as potential target-related cytotoxicity

Figure 4: Time on Study and Best Overall Response



Of the 7 patients with SD as a best response, 6 remained on treatment for >12 weeks

[1] Patients originally at 20mg/kg were dose reduced to 10mg/kg due to observations of G4 IRR in other patients at this dose level, in an abundance of caution

Patient with Endometrial Carcinoma Who Had Not Responded to Any of 4 Prior Systemic Regimens Had a Confirmed PR and Remains on Study for >1 Year

Table 2: Treatment History

Line #	Agent(s)	Dates	Best Response	D/C[1] Reason
1	Paclitaxel + Carboplatin	Nov 2014 – Jun 2015	NA[1]	Completed Course
2	MLN1117[2] + MLN0128[3]	Jul 2016 – Apr 2018	PD[1]	PD[1]
3	Gemcitabine	Jun 2018 – Dec 2018	PD[1]	PD[1]
4	Rebastinib[4] + Paclitaxel	Jan 2019 – Nov 2019	SD[1]	AE[1] (Retinal Vein Occlusion)

[1] D/C=Discontinuation, NA=Not available, PD=Progressive disease, SD=Stable disease, AE=Adverse event; 2 PI3K alpha inhibitor; 3 MTORC 1/2 inhibitor; 4 TIE2 inhibitor; 5 Cytotoxic cells

Figure 5: Target Lesion Change Over Time

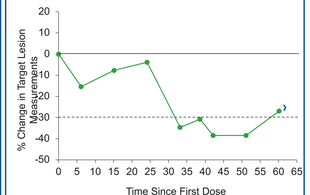
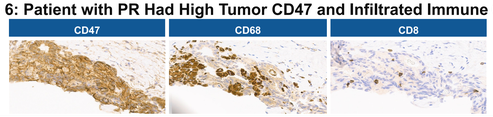


Figure 6: Patient with PR Had High Tumor CD47 and Infiltrated Immune Cells



- The patient with PR had a high baseline tumor CD47 H-score of 220 which was in the population top quartile (above)
- All patients but one had baseline tumors expressing CD47 and all had tumor infiltrating macrophages and CD8+[5] T cells

Table 3: Recommended Phase 2 Dose & Dose-Limiting Toxicity

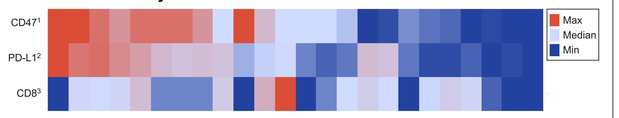
Cohort	Dose Level (mg/kg)	Number of Patients (27 total)	Number of Patients with Dose-Limiting Toxicity
1	1	4	0
2	3	4	0
3 (RP2D)	10	6	0
4	20	6	2 (Gr 4 IRRs)
5	Step Up Dosing 3→10→20	7	2 (1 Gr 4 thrombocytopenia and 1 cerebrovascular accident)

Table 4: Incidence of Treatment-Emergent Adverse Events (TEAE) Irrespective of Grade Related to Study Treatment with Incidence Rate ≥10% (N=27)

Preferred Term	n (%)
Number of patients with at least one event	24 (89%)
Infusion related reaction	9 (33%)
Thrombocytopenia	7 (26%)
Anemia (no evidence of hemolysis or hemagglutination)	7 (26%)
Nausea	5 (19%)
Fatigue	4 (15%)

- Subsequent IRRs were eliminated using additional pre-medication and a 6-hour infusion in cycle 1. Dexamethasone tapering and shortening of the infusion duration to 2 hours was successful in all patients after cycle 1
- The only G3+TEAE occurring in ≥10% of patients was asymptomatic, brief thrombocytopenia (22%) not associated with clinically significant bleeding and no platelet transfusions were required

Figure 7: Higher Tumor CD47 Expression Associated with High PD-L1 and Low CD8 Infiltrate in Study Patients Baseline Tumors



AO-176 will be tested in combination with pembrolizumab in select tumor types (opening 2H 2021)

[1] CD47: % of tumor with 2+ or 3+; 2 PD-L1: # of positive tumor cells, lymphocytes and macrophages/# viable cells; 3 CD8: avg count per 40X field

CONCLUSIONS

- AO-176 is a well-tolerated, differentiated anti-CD47 therapeutic
- Durable anti-tumor activity has been observed
- The recommended phase 2 dose is 10 mg/kg
- Maximum, peripheral AO-176 RO of ~60% is reached at RP2D, demonstrating reduced binding to normal cells
- Evaluations of AO-176 in combination with paclitaxel in patients with select solid tumors (NCT03834948) and as a single-agent in patients with multiple myeloma (NCT04445701) are ongoing

Table 5: AO-176 Ongoing and Planned[1] Clinical Studies

Therapeutic Program	Treatment	Preclinical	Phase 1	Phase 2	Phase 3
AO-176 Anti-CD47 Antibody: Select Solid Tumors; AO-176-101 Phase 1/2 Multiple Cohorts	Monotherapy		Ongoing		
	Combination with Chemotherapy		Ongoing		
	Combination with Pembrolizumab		Planned		
AO-176 Anti-CD47 Antibody: Multiple Myeloma; AO-176-102 Phase 1/2 Multiple Cohorts	Monotherapy		Ongoing		
	Combination with Standard Therapies		Planned		

[1] Other hematologic and solid tumor indications are planned

Note: Data is unaudited and subject to change

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