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Initial results from dose escalation of a phase 1/2, first-in-human, open label study of AU-007, a monoclonal antibody that binds to IL-2 and prevents its binding to CD25, in patients with solid tumors

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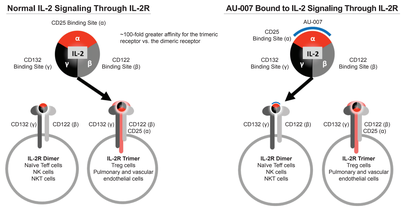
AU-007 Background

Redirects IL-2 to Teff / NK Cells and Away From Tregs and Vascular Endothelium

- AU-007 is a computationally designed (Biolojic Design), human IgG1 monoclonal antibody.
- AU-007 binds interleukin-2 (IL-2) with pM affinity and completely inhibits its binding to CD25, without hindering its binding to CD132/CD122.

Redirected IL-2 Signaling on Binding to AU-007



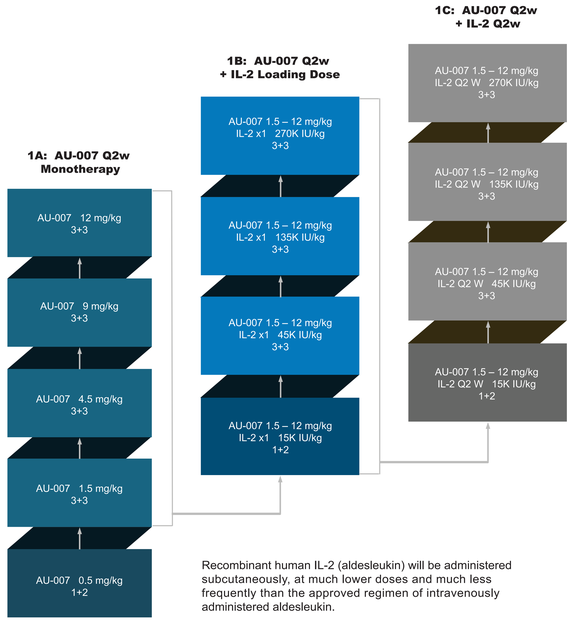
Unique MOA Addresses the IL-2 Negative Feedback Loop

- Treatments activating effector cells against tumors are undermined by an autoinhibitory loop caused by endogenous IL-2 secreted from activated T effector cells.
- AU-007 can transform the IL-2 negative feedback loop into a positive feedback loop.
- Re-engineered IL-2 therapeutics cannot address the negative feedback loop, resulting in endogenous IL-2 stimulating Treg expansion, and limiting efficacy.

AU-007 Uniquely Tips the Balance Toward Immune Activation, Away from Immune Suppression

Study Design

- AU-007 evaluated as **1A)** monotherapy, **1B)** in combination with a single loading dose of aldesleukin, or **1C)** with both AU-007 and aldesleukin given every 2 weeks (Q2w).
- AU-007 monotherapy evaluates doses sufficiently high to ensure enough AU-007 is available to bind all IL-2 molecules: both exogenously administered (aldesleukin) and endogenous IL-2.
- Patient inclusion criteria specifies any of 19 solid tumor histologies.
- Adverse events graded by the Common Terminology Criteria for Adverse Events.
- Efficacy based on PD markers of immune stimulation, total IL-2 (bound to AU-007 + free IL-2) and objective responses.
- Optional paired pre / on-treatment biopsies.
- Dose escalation began in Australia. U.S. IND cleared in October 2022, and clinical sites in the United States are being added.



Recombinant human IL-2 (aldesleukin) will be administered subcutaneously, at much lower doses and much less frequently than the approved regimen of intravenously administered aldesleukin.

Results

Patient Demographics

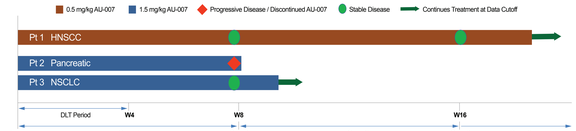
- As of the October 28 data cutoff, 4 patients have been enrolled into dose escalation, Arm 1A, AU-007 monotherapy.
- The initial patient enrolled received one dose of AU-007 but discontinued study after 10 days with deteriorating clinical condition secondary to his widespread disease. The head and neck cancer patient in Cohort 1 is the replacement for the initial patient.

Dose Escalation Patient Characteristics

Arm	Cohort	AU-007 Dose	Histology	Age / Sex	Prior Treatment / Best Response	ECOG
1A	1	0.5 mg/kg	Pt 1 Head and Neck Squamous Carcinoma (HNSCC)[1]	68 M	1) Cisplatin (adjuvant) / NA 2) AMG256[2] / PR	1
	2	1.5 mg/kg	Pt 2 Pancreatic (adenocarcinoma)	52 M	1) FOLFIRINOX / PD 2) Gemcitabine + paclitaxel / PD	0
			Pt 3 NSCLC (squamous)	82 M	1) Carboplatin + paclitaxel / PD 2) Durvalumab / PD	1

1: Head and neck cancer histology: mucoepidermoid with squamous cell component
2: IL-21 mutein x anti-PD-1 bispecific

Duration of Treatment and Efficacy Details



Efficacy Details

AU-007 Dose	Histology	Metastatic Sites	Target Lesion Sum (mm)			Non-Target Lesions	New Lesions	AU-007 Doses
			Baseline	Cycle 1	Cycle 2			
0.5 mg/kg	Head and Neck	Anterior and Posterior Pleural, Lung	59	59	61	P*	No	10
1.5 mg/kg	Pancreatic	1 Celiac and 2 Mediastinal Masses	86	82		P*	Yes	3
	NSCLC	Lung, Left and Right Adrenals	101	87		P*	No	6

* Present

Safety

- As of October 24, 2022, 4 patients have received at least one dose of AU-007.
- Only one drug-related Adverse Event (AE), Grade 1 diarrhea, has occurred in the patient with head and neck cancer receiving 0.5 mg/kg AU-007.
- The initial patient enrolled onto trial was a 60 y.o. man with nasopharyngeal carcinoma and widespread metastases to liver, lung and bone. He received one dose of AU-007 at 0.5 mg/kg but was discontinued from study after 10 days with deteriorating clinical status. This patient had no reported AEs.
- The pancreatic cancer patient experienced signs and symptoms of biliary obstruction after receiving 3 doses of AU-007. He was hospitalized for endoscopic and MRI evaluation confirming biliary outflow obstruction secondary to post-Whipple procedure stricture and potential tumor obstruction that was relieved via per-cutaneous drainage.

AU-007 Related Adverse Events

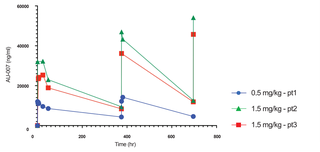
AU-007 Dose (patient number)	Tumor Histology	Event	Grade 1/2	Grade 3
0.5 mg/kg (n=1)	Head and Neck	Diarrhea	1	

Adverse Events Regardless of Causality

AU-007 Dose (patient number)	Tumor Histology	Event	Grade 1/2	Grade 3
0.5 mg/kg (n=1)	Head and Neck	Pleuritic Chest Pain	1	
		Hemoptysis	1	
		Diarrhea	1	
1.5 mg/kg (n=2)	Pancreatic	GGT Increase		1
		Increased ALP	1	
		Bilirubin Increase	1	
		Pancreatic Enzyme Decrease	1	
		Biliary Obstruction		1*
		Cancer Pain	1	
		Anemia; Upper GI Bleeding		1
		Creatinine Increase	1	
		Fatigue	1	
		Hyperglycaemia	1	
	NSCLC	Constipation	1	

* SAE: Hospitalization for per-cutaneous drainage of biliary obstruction

Pharmacokinetics

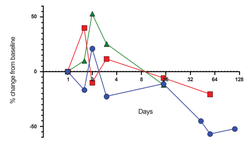


- Early pharmacokinetic profile of the first 3 patients administered monotherapy AU-007, 1 patient with 0.5 mg/kg and 2 patients with 1.5 mg/kg.
- The initial PK data demonstrate AU-007 concentration is dose proportional and has PK characteristics similar to a standard IgG1 therapeutic human monoclonal antibody.

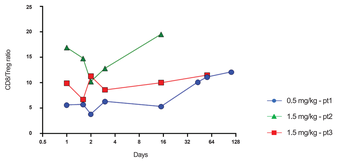
Pharmacodynamics

(A) Flow cytometry characterization of circulating Tregs (CD3+CD4+CD25+CD127 dim, Foxp3+) demonstrate an overall trend toward decreasing percentage of circulating Tregs in the first 3 patients. **(B)** The decrease in Tregs results in an increase in the CD8/Treg ratio.

A: % Change in CD4+ Treg Population

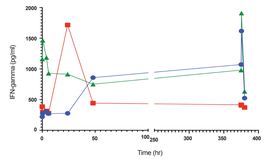


B: CD8/Treg Ratio

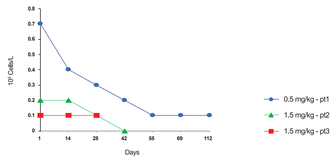


(C) Changes in interferon gamma in the peripheral blood of first 3 patients. Serum samples were taken and examined for the presence of circulating IFN-gamma using a qualified ECL technique (LLOQ 13.8 fg/ml). **(D)** Eosinophils express the same trimeric, CD25+ IL-2 receptor as Tregs and vascular endothelium. No increases in absolute eosinophil counts were observed, with 2 patients having early decreasing trends.

C: Total Circulating IFN-γ



D: Eosinophils



Conclusions:

- AU-007 is being evaluated in the second dose-level (1.5 mg/kg) of the monotherapy dose escalation cohort. In 3 evaluable patients, 1 patient at 0.5 mg/kg and 2 patients at 1.5mg/kg, the only drug related toxicity has been Grade 1 diarrhea in a single patient.
- 2 of the 3 evaluable patients have a best response of stable disease with some tumor shrinkage seen in one patient, and continue on study treatment.
- The early PK profile demonstrates characteristics similar to a standard IgG1 therapeutic human monoclonal antibody.
- Trends toward decreasing Treg cells with concordant increases in CD8/Treg ratio, initial IFN-γ increases and decreasing absolute eosinophils are consistent with the novel mechanism of action of AU-007, and consistent with the preclinical data from mice with syngeneic tumors, human PBMCs and cynomolgus monkeys treated with AU-007. In contrast, reported clinical data and preclinical data from other IL-2 therapeutics demonstrate that all other agents assessed substantially increase Tregs, likely due to the negative feedback loop, contributing to disappointing clinical efficacy findings.
- Dosing continues in Australia and the trial will be open in the U.S. in November 2022.

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