Updated results of a phase 1/2 study of AU-007, a monoclonal antibody (mAb) that binds to IL-2 and inhibits CD25 binding, in patients with advanced solid tumors

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Abstract 2527
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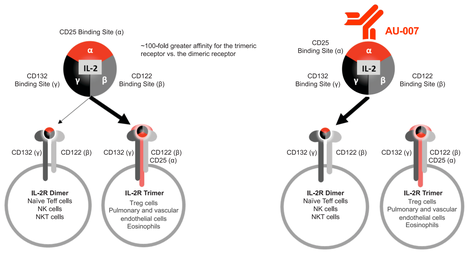
AU-007 Background

Redirects IL-2 to Effector T Cells (Teff) & NK Cells and Away From Regulatory T Cells (Tregs) and Vascular Endothelium

- AU-007 is a human IgG1 monoclonal antibody designed using artificial intelligence (Biolojic Design).
- 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 Teffs.
- 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.

Study Design

- Phase 1/2 open label dose escalation and expansion study.
- AU-007 evaluated as A) monotherapy, B) in combination with a single loading dose of low-dose aldesleukin, and C) with both AU-007 and low-dose aldesleukin given every 2 weeks (Q2W).
- Aldesleukin is administered subcutaneously, at much lower doses and much less frequently than the approved IV regimen.
- Includes adults ≥ 18 years old with any of 19 solid tumor histologies in dose escalation.
- Expansion cohorts prioritize melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC).
- Patients with unresectable locally advanced or metastatic cancer who have either progressed on or are not eligible for standard/approved therapies are eligible.
- Efficacy based on PD markers of immune stimulation and objective response; tumor assessments occur at the end of each 8-week cycle.

Enrollment Status

Phase 1 Escalation Cohort	Arm 1A	Arm 1B		Arm 1C	
	AU-007 Q2W	AU-007 Q2W	IL-2 Loading Dose	AU-007 Q2W	IL-2 Q2W
1 (1+2)	0.5 mg/kg	4.5 mg/kg	15K IU/kg	4.5 mg/kg	15K IU/kg
2 (3+3)	1.5 mg/kg	4.5 mg/kg	45K IU/kg	4.5 mg/kg	45K IU/kg
3 (3+3)	4.5 mg/kg	4.5 mg/kg	135K IU/kg	4.5 mg/kg	135K IU/kg
4 (3+3)	9 mg/kg	4.5 mg/kg	270K IU/kg	9 mg/kg	270K IU/kg
4.1 (3+3)				12 mg/kg	270K IU/kg
5 (3+3)	12 mg/kg	12 mg/kg	500K IU/kg	12 mg/kg	500K IU/kg
Phase 2 Expansion		Arm 2B		Arm 2C	
		9 mg/kg	135K IU/kg	9 mg/kg	135K IU/kg

DLT Evaluation Complete **Ongoing** **Higher aldesleukin doses can be evaluated as necessary**

Once the DLT period has cleared in an escalation cohort, additional "backfill" patients (up to a total of 10 in each escalation cohort) are allowed to enroll in each escalation cohort.

60 patients enrolled as of April 9, 2024: Arm 1A: 15; Arm 1B: 12 (1 Backfill); Arm 1C: 27 (13 Backfill); Phase 2 Expansion Arm 2B: 4; Phase 2 Expansion Arm 2C: 2.

Results

Patient Demographics

Patient Characteristics	N=59
Mean age, years (range)	63.2 (33-89)
Gender, n (%)	
Male	31 (52.5)
Female	28 (47.5)
Race, n (%)	
White	50 (84.7)
Asian	3 (5.1)
Black	3 (5.1)
American Indian/Alaska native	1 (1.7)
Other	2 (3.4)
ECOG performance status, n (%)	
0	29 (49.2)
1	30 (50.8)
Mean number of prior therapies, n (range)	3.2 (1-9)

Tumor Histologies Evaluated To Date

Cancer Diagnosis (n, %)	N=59
Melanoma (includes 2 uveal / 2 acral)	14 (23.7)
Clear cell renal cell carcinoma	8 (13.6)
Pancreatic cancer	8 (13.6)
Colorectal cancer	6 (10.2)
Head and neck squamous cell carcinoma	5 (8.5)
Non-small cell lung cancer	3 (5.1)
Urothelial cancer	2 (3.4)
Other	13 (22.0)

Data cutoff as of April 9, 2024; data available on 59 patients

Safety

Event (n, %)	AU-007 Monotherapy N=15	AU-007 + One IL-2 Dose N=16	AU-007 + IL-2 Q2W N=28	Total N=59
Any AE	**14 (93)**	**14 (88)**	**23 (82)**	**51 (86)**
Drug-Related AEs	**4 (27)**	**11 (69)**	**15 (54)**	**30 (51)**
Drug-Related SAEs	**0**	**2 (13)**	**2 (7)**	**4 (7)**
CRS	0	1 (Gr2)	2 (Gr2, Gr4)	3 (6)
Fever	0	1 (Gr2)	0	1 (2)
Drug-Related Grade 3 or 4 AEs	**0**	**3 (19)**	**3 (11)[1]**	**7 (12)**
Lymphopenia	0	3 (Gr4)	2 (Gr3, Gr4)	5 (8)
CRS	0	0	1 (Gr4)	1 (2)
Anemia	0	0	1 (Gr3)	2 (3)
Dose-Limiting AEs	**0**	**0**	**1 (3.6)**	**1 (1.7)**

[1] One patient had 2 Gr3/4 AEs: lymphopenia and anemia

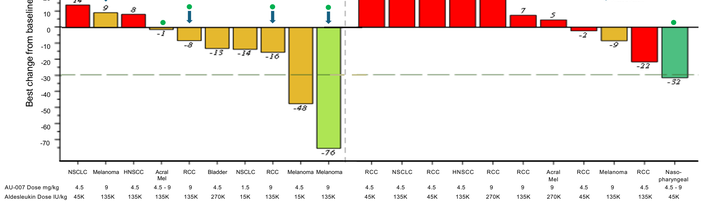
Drug-Related Adverse Events in > 5% of Patients N=59		
Adverse Event	**Grade 1 or 2 n (%)**	**Grade 3 or 4 n (%)**
Pyrexia	10 (17)	0
Fatigue	8 (14)	0
Nausea	6 (10)	0
Chills	5 (8)	0
Lymphopenia	0	5 (8)
AST Elevation	3 (5)	0
CRS	2 (3)	1 (2)

- All drug-related AEs were Grade 1 or 2 except for:
  - 1 patient with Grade 3 anemia entered study with Grade 2 anemia and had rapid disease progression receiving only 2 doses of study drug.
  - 1 patient with Grade 4 CRS that resolved quickly with steroids. This patient was noted retrospectively to have subclinical elevated IL-6 serum levels at baseline.
  - 5 patients with transient (3-7 days) Grade 3 or 4 lymphopenias that were not associated with adverse outcomes. Transient lymphopenia is a known effect of IL-2 treatment as lymphocytes traffic out of blood and into tissue.

Efficacy

Phase 1 Dose Escalation and First 4 Patients in Phase 2
AU-007 + Aldesleukin: Best Response in Tumors of Interest for Further Study

All Response Evaluable Melanoma, RCC, NSCLC, HNSCC, and Bladder Cancer Patients Who Received AU-007 + Aldesleukin

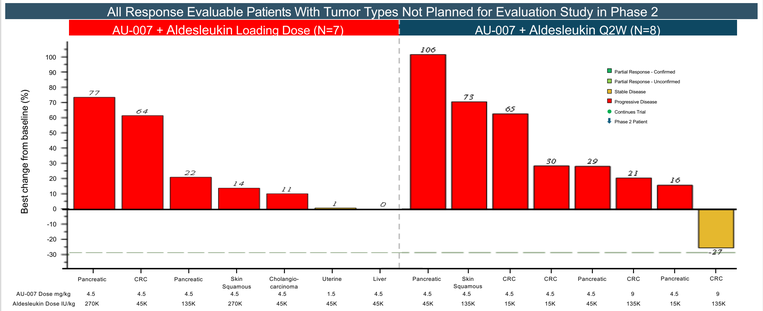


- Profound tumor shrinkage in 2 patients with metastatic melanoma of -48% and -76% (unconfirmed PR) who both had progressed on anti-CTLA-4 and anti-PD-1 antibodies.
- Tumor shrinkages observed in patients with widespread large volume disease in NSCLC, RCC, bladder cancer (metabolic CR by PET), MSI-stable colorectal cancer, and nasopharyngeal head and neck cancer (confirmed PR).
- Head and neck cancer patient with confirmed PR had reduction in a cervical bone metastasis leading to decreased arm pain and regaining function of his hand.

Not shown on graph: Patient with bladder cancer with non-measurable disease who has **METABOLIC COMPLETE RESPONSE** as measured by PET on March 25, 2024. Patient is in 1B cohort who received 4.5 mg/kg AU- 007 + one dose of 45K IU/kg IL-2 and remains on study.

Phase 1 Dose Escalation: AU-007 + Aldesleukin: Best Response in Tumors Not Planned for Study Beyond Phase 1

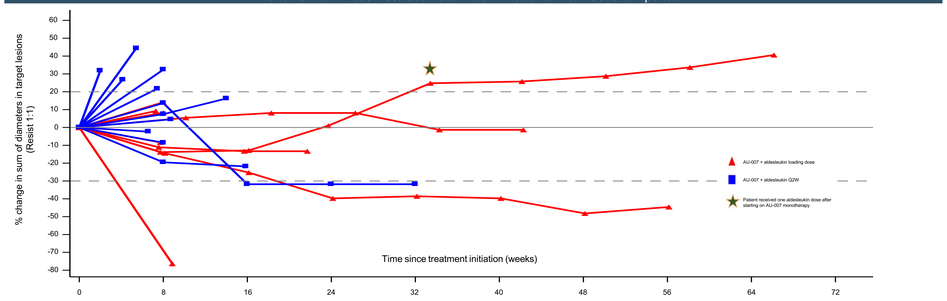
All Response Evaluable Patients With Tumor Types Not Planned for Evaluation Study in Phase 2



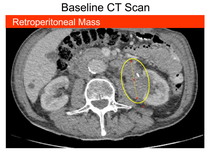
Efficacy

AU-007 + Aldesleukin: Percentage Change vs. Baseline Over Time: Tumors of Interest for Further Study in Phase 2

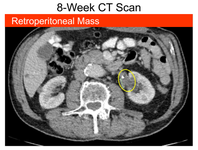
All Response Evaluable Melanoma, RCC, NSCLC, HNSCC, and Bladder Cancer Patients Who Received AU-007 + Aldesleukin
Patients From Dose Escalation and Initial 4 Patients From Cohort Expansion



Baseline CT Scan



8-Week CT Scan

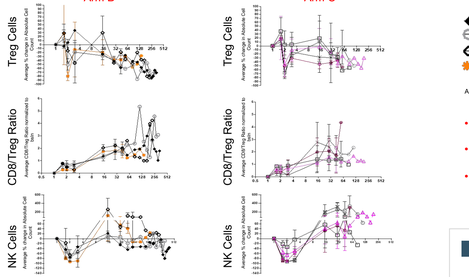


76% Shrinkage in the Target Lesions of a Melanoma Patient Whose Tumors Progressed Through Prior Anti-PD-1 + CTLA-4 Therapy

- 70-year-old man with large volume metastatic disease in the retroperitoneum.
- The patient progressed on prior combination anti-PD-1 and anti-CTLA-4 treatment December 2023.
- January 2024, the patient was the initial patient enrolled into Phase 2 expansion cohorts, receiving AU-007 (9 mg/kg) + one 135K IU/kg IL-2 dose.

Pharmacodynamics

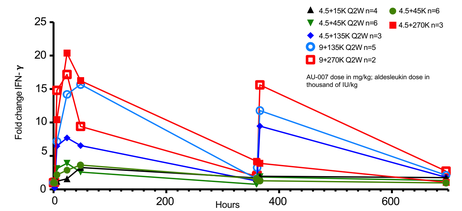
Average Percent Change in Immune Cells: Dose Escalation Cohorts



- AU-007 + aldesleukin pharmacodynamic profile remains unique in the IL-2 therapeutic class.
- AU-007 continues to demonstrate decreases in peripheral Treg cells at all AU-007 and aldesleukin dose levels evaluated on trial.
- Strong increase in peripheral CD8+/Treg cell ratios observed with both Arm B and C dosing regimens in addition to NK cell increases.

AU-007 + Low-Dose Aldesleukin Increases Levels of Circulating IFN-γ

Average Fold Change in IFN-γ From Dose Escalation Cohorts With Single (1B) or Q2W (1C) Dose Schedule of IL-2



Pharmacokinetics

Arm	AU-007 Dose (mg/kg)	N	Cmax (mg/mL)	AUClast (d*mg/mL)
1A	0.5	2	10.8 (16)	53.7 (105)
1A	1.5	3	29.6 (13)	231 (12)
1A	4.5	3	110 (15)	828 (42)
1A	9	4	255 (21)	1700 (22)
1A	12	3	282 (9.1)	1910 (39)
1B	4.5	12	132 (47)	639 (39)
1C	4.5	21	155 (42)	773 (46)
1C	9	4	223 (12)	1350 (25)

- Overall, AU-007 PK approximately dose-proportional over the dose range tested.
- T1/2 ~15 days by population PK analysis.
- In general, comparable AU-007 PK exposures alone or in combination with aldesleukin.
- No evidence of neutralizing anti-drug antibodies.

Conclusions

- AU-007 is a human IgG1 monoclonal antibody designed using artificial intelligence.
- AU-007 Q2W has a tolerable and manageable safety profile as a monotherapy evaluated up to 12 mg/kg, in combination with one aldesleukin loading dose evaluated up to 4.5 mg/kg AU-007 + 270K IU/kg aldesleukin, and in combination with aldesleukin Q2W evaluated up to 9 mg/kg AU-007 + 270K IU/kg aldesleukin.
- Manageable toxicity profile with no sign of vascular leak syndrome or pulmonary edema at all AU-007 and aldesleukin doses evaluated.
- Unique PD profile of decreasing peripheral Treg cells and significantly increasing CD8/Treg ratio demonstrates AU-007 + low-dose aldesleukin's ability to redirect IL-2 and prevent the negative feedback loop to Tregs. AU-007 + low-dose aldesleukin also substantially increases peripheral NK cells.
- Preliminary evidence of durable activity observed in mostly heavily pre-treated patients with tumors that progressed through checkpoint inhibitors, including melanoma (unconfirmed PR), bladder cancer (metabolic CR by PET), nasopharyngeal head and neck cancer (confirmed PR), NSCLC, RCC, and MSI-stable colorectal cancer.
- AU-007 PK demonstrates dose-proportionality over the dose range tested, no signs of neutralizing ADA activity, and initial T1/2 estimated to be 15+ days.
- Phase 2 expansion cohorts are ongoing in melanoma and RCC, with AU-007 given Q2W and low-dose aldesleukin given as a single loading dose or Q2W.
- Phase 2 expansion cohorts planned to evaluate AU-007 + aldesleukin in second-line PD-L1+ NSCLC, with and without the PD-L1 antibody avelumab.

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