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A Phase 1/2 Dose Escalation and Cohort Expansion Study of AU-007, a Human Monoclonal Antibody (mAb) That Binds to IL-2 and Inhibits CD25 Binding, Plus Low-Dose Aldesleukin in Advanced Solid Tumors

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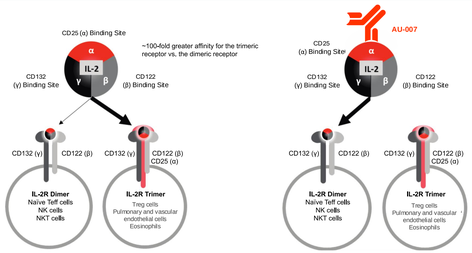
aulos

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 by leveraging 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 and Status

- This is a Phase 1/2 open label dose escalation and expansion study.
- Phase 1 dose escalation is complete. AU-007 was evaluated as monotherapy (Arm 1A); in combination with a single loading dose of low-dose, subcutaneous (SQ) aldesleukin given with the initial AU-007 dose (Arm 1B); and with both AU-007 and low-dose, SQ aldesleukin given every 2 weeks (Arm 1C). Patients receiving the single SQ aldesleukin loading dose (Arm 1B) can receive an additional SQ aldesleukin dose at the end of each 8-week cycle based on tumor growth kinetics observed on end-of-cycle scans.
- AU-007 is administered intravenously (IV) every 2 weeks (Q2W) in all cohorts and aldesleukin is administered SQ at much lower doses and much less frequently than the approved aldesleukin IV regimen.
- In Phase 1 dose escalation, patients with unresectable locally advanced or metastatic solid cancers (19 tumor histologies were eligible) who had either progressed on or were not eligible for standard/approved therapies were enrolled.
- The recommended Phase 2 dose (RP2D) of AU-007 (9 mg/kg) and SQ aldesleukin (135K IU/kg) determined in dose escalation is being evaluated in Phase 2 expansion:
  - Initial two expansion cohorts are evaluating AU-007 + a single SQ aldesleukin loading dose (Arm 2B), and AU-007 + Q2W SQ aldesleukin (Arm 2C); both cohorts evaluate patients with melanoma and renal cell carcinoma (RCC) that progressed on prior therapies.
  - Two additional expansion cohorts will enroll PD-L1+ non-small cell lung cancer (NSCLC) patients who have failed prior checkpoint inhibitor therapy. One cohort is currently enrolling patients evaluating the Arm B dosing regimen of AU-007 + SQ aldesleukin (Part 3.1) and the second cohort will enroll patients evaluating the combination of avelumab + the Arm B dosing regimen of AU-007 + SQ aldesleukin (Part 3.2), with a safety run-in (first 3 patients dosed at 9 mg/kg of AU-007 + a single SQ aldesleukin dose of 45K IU/kg as the RP2D-1 dose) followed by cohort expansion at the RP2D.
  - Monotherapy AU-007 is not being evaluated in Phase 2.
- Efficacy is evaluated based on pharmacodynamic (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	Avelumab 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					
Phase 2 Expansion		Arm 2B		Arm 2C		
		9 mg/kg	135K IU/kg	9 mg/kg	135K IU/kg	
Part 3		Part 3.1		Part 3.2		
		9 mg/kg	135K IU/kg	9 mg/kg	135K IU/kg†	800 mg

DLT Evaluation Complete **Ongoing** **Planned**

Once the dose-limiting toxicity (DLT) period was cleared in an escalation cohort, additional "backfill" patients (up to a total of 10 per cohort) were allowed to enroll in each cohort.

†Safety run-in begins at the RP2D-1, followed by RP2D and cohort expansion.

77 patients enrolled as of September 28, 2024: Arm 1A: 15; Arm 1B: 12 (1 Backfill); Arm 1C: 28 (14 Backfill); Arm 2B: 11; Arm 2C: 11.

Results

Patient Demographics	
Patient Characteristics	**N=77**
Mean age, years (range)	64.1 (33-89)
Gender, n (%)	
Male	39 (51)
Female	38 (49)
Race, n (%)	
White	67 (87)
Black	4 (5)
Asian	3 (4)
American Indian/Alaska native	1 (1)
Other	2 (3)
ECOG performance status, n (%)	
0	33 (43)
1	44 (57)
Mean number of prior therapies, n (range)	3.2 (1-10)

Data cutoff as of September 28, 2024

Tumor Histologies Evaluated in the Trial	
Cancer Diagnosis (n, %)	**N=77**
Melanoma (includes 2 uveal / 2 acral)	22 (29)
Clear cell renal cell carcinoma	15 (19)
Pancreatic cancer (escalation only)	8 (10)
Colorectal cancer (escalation only)	6 (8)
Non-small cell lung cancer	5 (6)
Head and neck squamous cell carcinoma	5 (6)
Other cancer (escalation only): Urothelial, cervical, endometrial, thyroid, gall bladder, nasopharyngeal, Merkel cell carcinoma, cutaneous squamous cell carcinoma, anal squamous cell carcinoma, hepatocellular carcinoma, leiomyosarcoma, intrahepatic bile duct carcinoma	16 (21)

Safety

Event (n, %)	AU-007 Monotherapy N=15	AU-007 + One IL-2 Dose N=23	AU-007 + IL-2 Q2W N=39	Total N=77
Any AE	**14 (93)**	**21 (91)**	**34 (87)**	**69 (90)**
Drug-Related AEs	**4 (27)**	**18 (78)**	**25 (64)**	**47 (61)**
Drug-Related SAEs	**0**	**3 (13)**	**2 (5)**	**5 (6)**
Cytokine Release Syndrome (CRS)	0	1 (Gr2)	2 (Gr2, Gr4)	3 (4)
Infusion-Related Reaction	0	1 (Gr2)	0	1 (1)
Fever	0	1 (Gr2)	0	1 (1)
Drug-Related Grade 3 or 4 AEs	**0**	**4 (17)**	**4 (10)[1]**	**8 (10)[1]**
Lymphopenia	0	3 (Gr4)	3 (1 Gr4)	6 (8)
CRS	0	0	1 (Gr4)	1 (1)
Anemia	0	0	1 (Gr3)	1 (1)
Lipase Elevation	0	1 (Gr3)	0	1 (1)
Dose-Limiting AEs	**0**	**1**	**1**	**2 (3)**

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

Drug-Related Adverse Events in > 5% of Patients | N=77		
Adverse Event	**Grade 1 or 2 n (%)**	**Grade 3 or 4 n (%)**
Chills	13 (17)	0
Pyrexia	13 (17)	0
Fatigue	12 (16)	0
Infusion-Related Reaction	8 (10)	0
Nausea	7 (9)	0
Lymphopenia	0	6 (8)
Injection Site Reaction	5 (6)	0
Headache	4 (5)	0
AST Elevation	4 (5)	0
CRS	4 (5)	1 (1)
Anemia	4 (5)	1 (1)

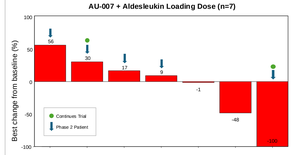
- No DLT occurred through Phase 1 dose escalation.
- Most drug-related adverse events (AEs) were Grade 1 or 2 except for:
  - Grade 3 anemia in one patient who entered study with Grade 2 anemia and had rapid disease progression, and received only 2 doses of study drug.
  - Grade 4 CRS in one patient. It resolved without tocilizumab using steroids, IV fluids, and brief vascular pressor support. This patient was noted retrospectively to have subclinical elevated IL-6 (5x) serum levels likely due to an active case of gout at baseline.
  - Grade 3 transiently elevated lipase without clinical symptoms in one patient; resolved without intervention.
  - Grade 3 or 4 transient (3-7 days) lymphopenias that were not associated with adverse outcomes in 6 patients. Transient lymphopenia is a known effect of IL-2 treatment as lymphocytes traffic out of blood and into tissue.

Early Signal of Strong Anti-Tumor Activity in Phase 1 Dose Escalation

Tumor	AU-007 Dose (mg/kg)	Dose / Regimen Aldesleukin (IU/kg)	Best Response on Prior CPI	Number of Prior Cancer Regimens	Best Objective Response (% Decrease)	Time on Treatment (Months)
HNSCC[1]	4.5	45K Q2W	PR (PD-1)	4	**-50%**	**14+[4]**
CRC (MSS)	9.0	135K Q2W	N/A	3	**-27%**	**3.3**
Bladder	4.5	45K one dose	PD (PD-L1)	1	**Metabolic CR[3]**	**18+[4]**
Bladder	4.5	270K one dose	PD (PD-1)	4	**-13%**	**4.7**
NSCLC	4.5	15K one dose[2]	PD (PD-L1)	2	**-14%**	**17.5**

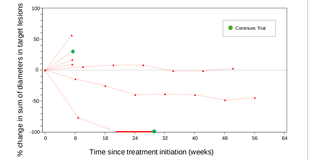
N/A Not applicable. [1]Head and neck nasopharyngeal histology. [2]Patient started on AU-007 alone and received one aldesleukin dose at the beginning of Cycle 5 (10 months on study). [3]Patient with NTL only and had highly metabolically active tumors at baseline on PET scan that became negative at Cycle 7 (14 months on study). [4]Patient continues on study therapy

Best Response in Melanoma Patients in Phase 1 and Phase 2 Receiving AU-007 Q2W + Single SQ Aldesleukin Loading Dose (Arm B Dosing Regimen)

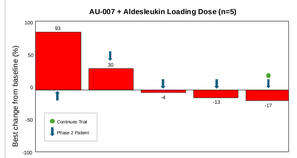


A melanoma patient who progressed on prior anti-PD-1 therapy (adjuvant) and anti-PD-1 + relatlimab has NTL only disease (so does not appear on the graph) has SD with investigator-read tumor shrinkage and continues on trial in Cycle 3 (4.7 months).

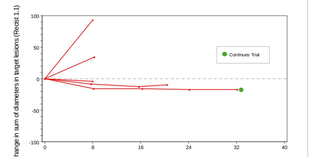
Percentage Change Over Time vs. Baseline in Melanoma Patients in Phase 1 and Phase 2 Receiving AU-007 Q2W + Single SQ Aldesleukin Loading Dose (Arm B Dosing Regimen)



Best Response in RCC Patients in Phase 1 and Phase 2 Receiving AU-007 Q2W + Single SQ Aldesleukin Loading Dose (Arm B Dosing Regimen)



Percentage Change Over Time vs. Baseline in RCC Patients in Phase 1 and Phase 2 Receiving AU-007 Q2W + Single SQ Aldesleukin Loading Dose (Arm B Dosing Regimen)

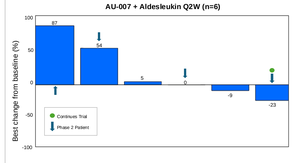


Prior Treatment and Response Status for Patients in Phase 2 Arm B Dosing Regimen

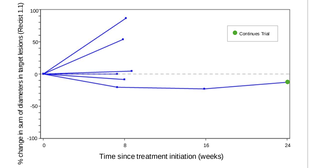
Tumor	Best Response on Prior CPI	Number of Prior Cancer Regimens	Best Response on Study	Time on Treatment (Months)
Melanoma	PD: anti-CTLA-4 + anti-PD-1	1	uPR*	8.9+
	PD: anti-PD-1	2	SD	2
	CR: anti-PD-1	2	PD	2.8+
	SD: anti-PD-1	3	PD	2
	PD: anti-PD-1 + relatlimab	2	PD	2
RCC	PD: anti-PD-1	4	SD	5.1
	PD: anti-PD-1	2	SD	7.5+
	PD: anti-PD-1	4	PD	2
	SD: anti-PD-1	4	PD	2
	PD: anti-PD-1	3	PD	2

*Patient had 76% decrease at end of Cycle 1 and was found to have a brain metastasis in Cycle 2 that was removed, and patient continues on treatment. The target lesion completely resolved (-100%) in Cycle 2.

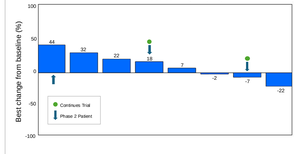
Best Response in Melanoma Patients in Phase 1 and Phase 2 Receiving AU-007 Q2W + SQ Aldesleukin Q2W (Arm C Dosing Regimen)



Percentage Change Over Time vs. Baseline in Melanoma Patients in Phase 1 and Phase 2 Receiving AU-007 Q2W + SQ Aldesleukin Q2W (Arm C Dosing Regimen)

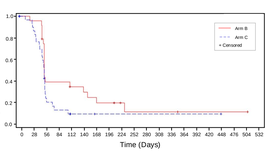


Best Response in RCC Patients in Phase 1 and Phase 2 Receiving AU-007 Q2W + SQ Aldesleukin Q2W (Arm C Dosing Regimen)



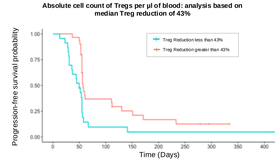
- Phase 2 expansion cohorts enroll melanoma and RCC patients to benchmark the early AU-007 + low-dose, SQ aldesleukin efficacy data against the efficacy observed with high-dose IL-2 in its approved indications.
- Durable tumor shrinkages were observed in checkpoint inhibitor (CPI) resistant or progressed RCC and melanoma, including in patients with large-volume disease.
- Two patients receiving the Arm B dosing regimen with melanoma refractory to prior anti-CTLA-4 and anti-PD-1 therapy had deep and durable tumor shrinkages: -48% reduction (on study for 13 months), and a 100% reduction in target lesions (continues on study for 8.5+ months).
- A patient with rapidly progressing acral melanoma who progressed on prior anti-PD-1 therapy received the Arm B dosing regimen for 11 months in dose escalation (4.5 mg/kg AU-007 + 135K IU/kg SQ aldesleukin) and had initial tumor growth followed by tumor reduction to below baseline tumor size.

Progression-Free Survival: All Phase 1 and 2 Patients: Arm B Loading Dose IL-2 Regimen vs. Arm C Q2W IL-2 Regimen



A Kaplan-Meier plot comparing preliminary progression-free survival (PFS) data from the Arm B vs. Arm C dosing regimens, across all patients in Phase 1 and Phase 2, demonstrates a trend to longer PFS for patients receiving the Arm B dosing regimen. Most patients with progression or death at 56 days (end of Cycle 1) are from the Phase 1 dose escalation portion of the study consisting mostly of heavily pre-treated GI cancers or cancers not typically associated with response to immunotherapies (e.g., uterine, thyroid cancers).

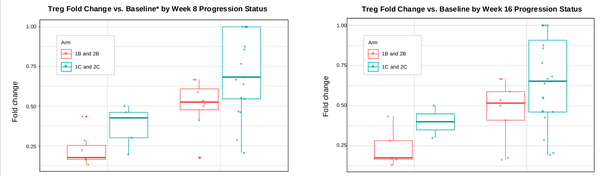
Greater Decreases in Tregs on Treatment Is Associated With Longer PFS Across Phase 1 and 2



Results are calculated by deriving the median greatest Treg decrease across all patients (excluding the first 2 days on treatment) and dividing the patients who were ≤ the median or > than the median. Patients with a Treg cell reduction greater than the median of 43% had a longer time to progression than those with a Treg cell reduction less than the median of 43%.

Patients With Greater Treg Decreases Were Less Likely to Have Progressed in Cycles 1 and 2

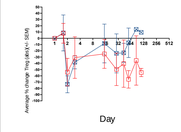
All patients who decreased Tregs less than 50% vs. baseline progressed at 8 (Cycle 1) and 16 weeks (Cycle 2)



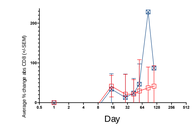
*Largest decrease in Tregs (excluding the first 2 days on treatment) expressed as a fold change vs. baseline (e.g., 0.25 is a 75% decrease) at Week 8 (Cycle 1) and Week 16 (Cycle 2).

- Absolute cell count of Tregs per µl of blood: analysis based on individual patient maximum Treg decrease while on treatment in Phase 1 and 2.
- The boxplots summarize maximum Treg decrease for each arm and progression status group showing median (line in each box) with lower and upper box boundaries corresponding to the 25th and 75th percentile.

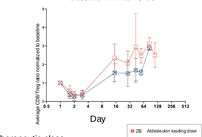
Percent Change in Tregs: Arm 2B vs. 2C



Percent Change in CD8 Cells: Arm 2B vs. 2C



CD8/Treg Ratio Fold Change Normalized to Baseline: Arm 2B vs. 2C



- AU-007 + low-dose, SQ aldesleukin continues to demonstrate a unique PD profile in the IL-2 therapeutic class.
- Peripheral Tregs decrease with both the Arm B and C dosing regimens, with 2B dosing trending toward greater and more durable decreases of Tregs.
- Peripheral CD8 cells demonstrate similar increases for the Arm B and C dosing regimens, ranging from 30-50% higher than baseline.
- The CD8/Treg ratio trends higher for the Arm B dosing regimen as the B and C regimens increase CD8 cells to the same extent while the Treg decrease is greater on the B dosing regimen.

Conclusions

- AU-007 Q2W has a tolerable and manageable safety profile as (A) monotherapy, (B) AU-007 + one loading dose of SQ aldesleukin, and (C) AU-007 + Q2W SQ aldesleukin at all doses evaluated in Phase 1 dose escalation. No dose-limiting toxicity occurred through dose escalation.
- Strong evidence of anti-tumor activity was observed in heavily pre-treated patients whose tumors progressed through checkpoint inhibitors: melanoma (prior anti-PD-1/CTLA-4), RCC (prior anti-PD-1), bladder cancer (prior anti-PD-L1), HNSCC (prior anti-PD-1), and NSCLC (prior anti-PD-L1).
- Decrease in Tregs appears to be a critical determinant of observed efficacy, with greater decreases in patients receiving a SQ aldesleukin loading dose compared to SQ aldesleukin Q2W.
- The single SQ aldesleukin loading dose regimen (Arm B dosing regimen) has been chosen as the regimen for further clinical development. Additional aldesleukin doses will be permitted at the end of each 8-week cycle if unfavorable tumor kinetics are observed. The decision to move forward with the Arm B IL-2 loading dose regimen is based on:
  - The additional IL-2 administration with the Arm C regimen does not improve efficacy vs. the Arm B regimen's one SQ aldesleukin loading dose, and patients on the Arm B regimen trend toward having deeper and more durable tumor shrinkage with prolonged PFS.
  - The Arm B regimen has a strong trend to deeper and more durable Treg decreases that are associated with longer PFS in early data, leading to a greater CD8/Treg ratio.
  - More prolonged IL-2 exposure on the Arm C dosing regimen may be driving the Teff cells to exhaustion.
  - The Arm C dosing regimen causes greater and more prolonged increases of interferon-gamma (IFN-γ) vs. the Arm B regimen. (Data not shown.) Prolonged exposure to IFN-γ may be immune suppressive.
- An additional Phase 2 cohort will evaluate AU-007 + low-dose, SQ aldesleukin combined with anti-PD-L1 avelumab in NSCLC.
- AU-007 + one administration of low-dose, SQ aldesleukin demonstrates evidence of clinical activity in melanoma following progression on prior checkpoint inhibitor therapy. Phase 2 expansion cohorts continue enrolling in melanoma and NSCLC.

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