A Phase 1 Trial of ALKS 4230, an Engineered Cytokine Activator of NK and Effector T Cells, in Patients with Advanced Solid Tumors

Abstract #TPS3111

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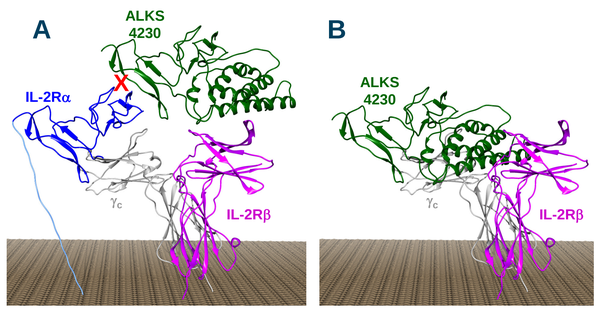
BACKGROUND

ALKS 4230 Design and IL-2 Signaling

- ALKS 4230 is an engineered fusion protein comprised of a circularly permuted interleukin-2 (IL-2) and IL-2 Receptor (IL-2R) α designed to selectively activate the intermediate-affinity (ia) IL-2R, comprised of IL-2Rβ and γ_c.
- The iaIL-2R is expressed predominantly on effector lymphocytes, which play an important role in driving antitumor immune responses.[1]
- Unmodified IL-2 activates high-affinity (ha) IL-2R, comprised of IL-2Rα, β, and γ_c, driving the expansion of haIL-2R-expressing cell types including immunosuppressive CD4$^+$ regulatory T (T_{reg}) cells at concentrations below those at which iaIL-2R bearing effector cells are activated.[2]
- The haIL-2R is also expressed on endothelial cells and may contribute to IL-2 mediated toxicity via capillary leak syndrome.[3] Thus, selective activation of the iaIL-2R by ALKS 4230 has the potential to provide enhanced tumor killing as well as improved tolerability.

FIGURE 1: ALKS 4230 is Designed to Bind Selectively to the Intermediate-Affinity IL-2 Receptor [4]



High-Affinity IL-2Rαβγ Complex
Expressed on T_{regs} and Vascular Endothelium

Intermediate-Affinity IL-2Rβγ Complex
Expressed on NK Cells and CD8 T Cells

ALKS 4230. (**A**) Due to the presence of the IL-2Rα extracellular domain, ALKS 4230 is sterically impaired from binding to the high-affinity IL-2 receptor complex. (**B**) ALKS 4230 retains ability to bind to the intermediate-affinity IL-2 receptor complex. Models are based on the solved crystal complex of IL-2 to the high-affinity IL-2 receptor complex (PDB ID 2B5I).[4]

Preclinical Results with ALKS 4230

- ALKS 4230 has similar potency to rhIL-2 on NK cells and memory CD8 T cells, but less potently activates immunosuppressive T_{regs} compared to rhIL-2, demonstrating its binding preference for cells expressing the intermediate-affinity (IL-2Rβγ) over the high-affinity (IL-2Raβγ) IL-2 receptor[5]
- ALKS 4230 induces dose-dependent selective expansion of memory CD8 T cells and cytotoxic NK cells in C57BL/6 mice and non-human primates[6]
  - ALKS 4230 does not increase CD4$^+$ T_{reg} cell numbers[6]
- ALKS 4230 exhibits a systemic dose-dependent increase after a single IV dose in cynomolgus monkeys[6]
  - Subsets of CD8 T cells and NK cells were expanded after several days of drug exposure and remained elevated for several days after the drug cleared from circulation[6]
- The murine ortholog of ALKS 4230 delays tumor growth and improves survival in multiple mouse syngeneic tumor models when used as a monotherapy and in combination with the immune checkpoint inhibitors, anti-PD-1 and anti-CTLA-4[4]

METHODS

ALKS 4230 FIH Phase 1 Overview

- ALKS 4230 is being studied in a multicenter, open-label, sequential groups FIH Phase 1 trial in subjects with advanced solid tumors.
- The trial will have 2 parts: a dose escalation part (A), followed by a dose expansion part (B)

Study Objectives

- **Part A – Dose Escalation:** To investigate the safety and tolerability of ALKS 4230 and to determine the MTD and the RP2D of ALKS 4230 in subjects with advanced solid tumors who are refractory or intolerant to therapies known to provide clinical benefit.
- **Part B – Dose Expansion:** To further characterize the safety profile of ALKS 4230 at the RP2D in subjects with specified tumor types who have previously received specified prior therapies known to provide clinical benefit.
- **Secondary objectives:** To characterize the safety profile, pharmacokinetics (PK), pharmacodynamics (PD) and evidence of antitumor activity.

Key Subject Eligibility Criteria

Inclusion Criteria	Exclusion Criteria

• Informed Consent
• ≥18 years of age
• **Histological or cytological evidence of:**
  • **A solid tumor, including lymphoma** (for Dose Escalation)
  • **A melanoma, RCC, or ovarian cancer** (for Dose Expansion)
• **Malignancy in question must be refractory to or intolerant of established therapies** known to provide clinical benefit
• Subject has measurable disease (Dose Expansion part only)
• ECOG Performance Status 0-1 and has a life expectancy of ≥ 3 months
• **Subject has adequate hematologic reserve, adequate hepatic function, and adequate renal function**
	• Subject is pregnant, breastfeeding, or planning to become pregnant during the study period
	• Active infection or fever ≥38.5ºC within 3 days of the first scheduled day of dosing for Cycle 1
	• Presence of active or symptomatic CNS metastases
	• Known hypersensitivity to any components of ALKS 4230
	• Subjects requiring pharmacologic doses of corticosteroids
	• Subjects with ECG QT interval >470 msec (females) or >450 msec (males)
	• Subjects who developed autoimmune disorders while on prior immunotherapy HIV, hepatitis B, or hepatitis C infection

Study Design

- ALKS 4230 is administered as a 30-minute intravenous infusion once daily for five days each cycle.
  - Cycle 1 will have a 9 day off period after the 5 days of dosing
  - Cycle 2 and any subsequent cycle will have a 16 day off period after the 5 days of dosing
- Cycles 1 & 2 in Part A are administered on an inpatient basis, while all of Part B and Cycles 3+ in Part A are to be administered in an outpatient setting.
- In the absence of DLTs, subjects who remain in the study may receive subsequent doses of ALKS 4230 on an outpatient basis and may continue additional treatment cycles until evidence of progressive neoplastic disease, intolerance to ALKS 4230, removal by the investigator, withdrawal of consent, or any other criteria for study removal.

Cohort and Dose Assignment

	Cohort	Dose (µg/kg)	Subjects (N)
Dose Escalation[a]	1	0.1	3[b]
	2	0.3	3[b]
	3	1	6
	4	3	6
	5	10	6
	6[a]	30	6
Dose Expansion	Melanoma	RP2D	21
	RCC (Progressed following anti-PD-1 or anti-PD-L1 therapy)	RP2D	21
	RCC (No prior checkpoint inhibitor therapy)	RP2D	21
	Ovarian	RP2D	21

[a] The starting dose was chosen based on MABEL.[7] Preclinical PK, PD and toxicology assessments support the proposed dose range and escalation scheme.[7] Additional dose escalation will be considered if the RP2D has not been reached within the proposed dose range. The dose will be escalated until reaching MTD or an Optimal Biologic Dose.

[b] If none of the 3 subjects experiences a DLT, then the next dose level will open for enrollment. If 1 of the 3 subjects experiences a DLT, then up to 3 additional subjects will be enrolled at the same dose level. If no additional DLTs are observed then the next dose level will open for enrollment. If 2 or more subjects experience DLTs at a dose level, no further dose escalations will occur

Key Study Assessments

- Safety and MTD
- Antitumor Activity (based on RECIST v. 1.1 and irRC guidelines)
- PK/PD and Immunogenicity:
  - ALKS 4230 serum concentrations and anti-drug antibodies
  - Change in CD8$^+$ T, NK, and T_{reg} cell counts in peripheral blood from baseline
  - Serum concentrations of proinflammatory cytokines

Recruitment for Part A is ongoing. NCT02799095.

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Abbreviations: DLT=dose limiting toxicity; FIH=First in Human; MABEL=minimal anticipated biological effect level; MTD=Maximum Tolerated Dose; PD-1=programmed death receptor-1; PD-L1=programmed death ligand-1; RCC=renal cell carcinoma; RP2D=recommended Phase 2 dose

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