Intravenous Administration of ALKS 4230 as Monotherapy and in Combination With Pembrolizumab in a Phase 1/2 Study of Patients With Advanced Solid Tumors

Ulka N. Vaishampayan,[1] Mayer N. Fishman,[2] Daniel C. Cho,[3] Christopher J. Hoimes,[4] Vamsidhar Velcheti,[4] David F. McDermott,[5] William J. Slichenmyer,[6,*] Emily L. Putiri,[7] Heather C. Losey,[7] Sean Q. Rossi,[7] Marc S. Ernstoff[8]

[1]Wayne State University, Detroit, MI; [2]Moffitt Cancer Center, Tampa, FL; [3]NYU Langone Hospitals, New York, NY; [4]Case Western Reserve University, Cleveland, OH; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Alacrita Consulting, Waltham, MA; [7]Alkermes, Inc., Waltham, MA; [8]Roswell Park Comprehensive Cancer Center, Buffalo, NY

*Employed by Alkermes, Inc. during work on the study.

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INTRODUCTION

ALKS 4230 Design and IL-2 Signaling

- ALKS 4230 is a fusion protein of circularly permuted IL-2 and IL-2Rα (Figure 1) that selectively activates the intermediate-affinity IL-2R on effector lymphocytes (Figure 2).[1-3]
- The antitumor efficacy of IL-2 derives from its stimulatory effects on effector lymphocytes (CD8+ T cells and NK cells), while IL-2-mediated stimulation of immunosuppressive CD4+ T_{regs} and the toxicity of high-dose IL-2 have limited its therapeutic utility.[1,4-6]
- Unmodified IL-2 activates high-affinity IL-2R, driving immunosuppressive T_{reg} expansion (Figure 2) and is associated with adverse effects (eg, capillary leak syndrome).[2,3,6]

Figure 1: ALKS 4230 Is a Fusion of IL-2 and IL-2Rα

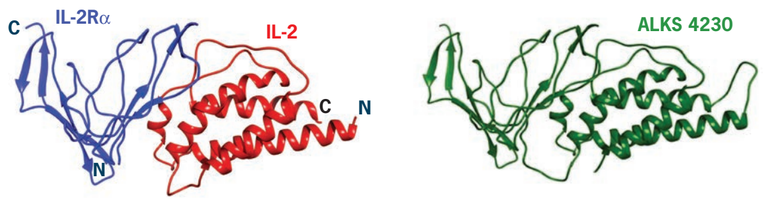
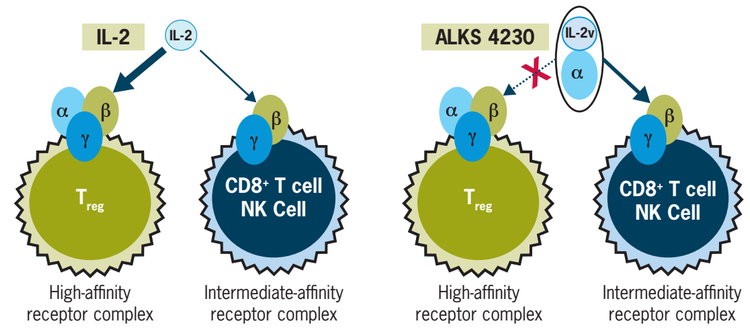


Figure 2: Cell Activation by IL-2 and ALKS 4230[1,2]



- Murine models have shown enhanced antitumor activity following administration of ALKS 4230 relative to IL-2.[3]
- ALKS 4230 displays similar potency to IL-2 on human effector lymphocytes but less potently activates T_{regs} compared with IL-2.[7]

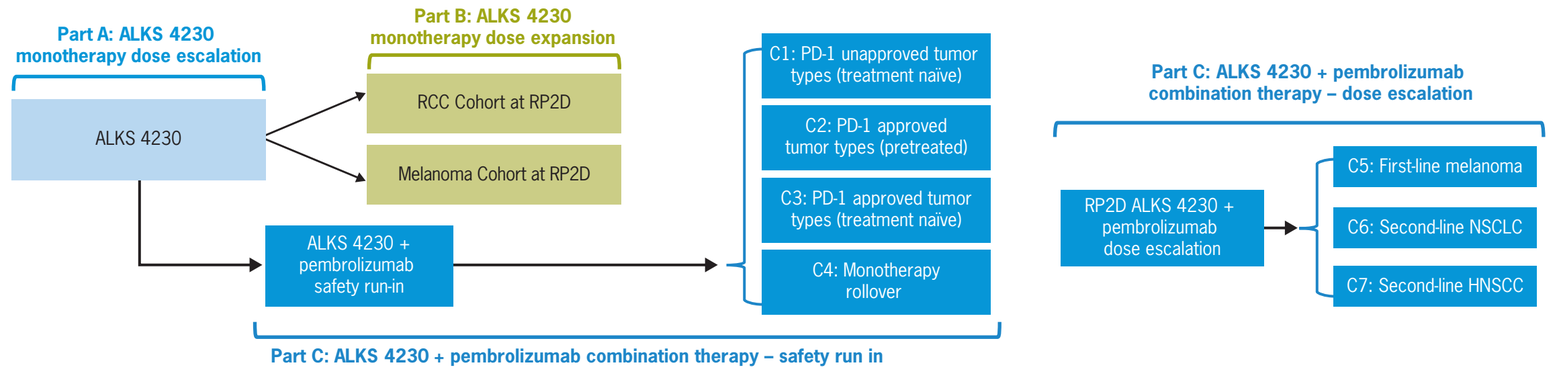
METHODS

Study Design

- Multicenter, open-label, first-in-human study (ARTISTRY-1; NCT02799095) examining the safety and efficacy of ALKS 4230, alone and in combination with pembrolizumab, in adults with advanced refractory solid tumors.
- The study design comprises 3 parts (Table 1; Figure 3); recruitment for Parts A and C is currently ongoing (Table 2).

METHODS

Figure 3: Overview of Study Design



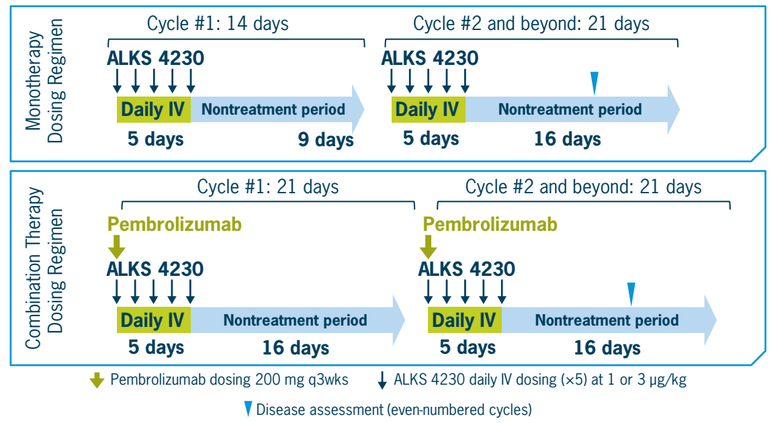
- Treatment allocation is described in Figure 4.
  - For Part C, patients will be allocated to treatment cohorts on the basis of tumor type and prior treatment with PD1/PD-L1 pathway inhibitors.
  - Patients who experience either disease progression or complete ≥ 4 cycles of ALKS 4230 monotherapy in Part A or Part B are also eligible for Part C as rollover patients.

Table 2: Key Eligibility Criteria

Inclusion Criteria[a]	Exclusion Criteria
• Advanced solid tumor, including lymphoma (Part A); diagnosis of either melanoma or RCC (Part B) • Malignancy must be refractory to/ intolerant of established therapies known to provide clinical benefit (some Part C patients must be immunotherapy naïve) • Measurable disease (Parts B and C) • ≥ 1 lesion that qualifies as a target lesion (RECIST) (Parts B and C) • ECOG performance status 0-1 with life expectancy ≥ 3 months • Adequate hematologic reserve, hepatic function, and renal function	• Active infection or fever ≥ 38.5˚C within 3 days of the first dose • Presence of active or symptomatic central nervous system metastases • Requires pharmacologic doses of corticosteroids • ECG QT interval > 470 ms (females) or > 450 ms (males) • Developed autoimmune disorders while on prior immunotherapy or are known to be positive for HIV, hepatitis B, or hepatitis C infection

[a]Cohort-specific inclusion criteria for patients whose approved tumor-types: (C1: PD-1) have progressed after chemotherapy and are approved to be treated with pembrolizumab; (C2: PD-1) have progressed on anti-PD-1/PD-L1 therapy and are approved for treatment with pembrolizumab; (C3: PD-1) have progressed after chemotherapy and are not approved to be treated with pembrolizumab; (C4: Monotherapy) have progressed while on ALKS 4320 or have received ≥ 4 cycles of ALKS 4320 monotherapy and can tolerate treatment with combination therapy; (C5: Melanoma) include unresectable locally advanced or metastatic invasive mucosal melanoma that is measurable, and are treatment naïve; (C6: 2L) include stage IIIB or IV NSCLC and have been treated with anti-PD-1-L1 therapy either as a single agent or in combination with a chemotherapy regimen and responded to treatment or had stable disease; (C7: 2L) includes subjects with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy and who are anti-PD-1/PD-L1 naïve.

Figure 4: Study Treatments



Key Study Assessments

- Primary and secondary objectives (Table 1) include:
  - Safety and tolerability
  - Antitumor activity assessed using RECIST and iRECIST guidelines
  - Pharmacokinetics
  - Pharmacodynamics and immunogenicity outcomes:
    - Circulating CD8+ T cells, T_{regs}, and NK cells in peripheral whole blood
    - Serum levels of proinflammatory cytokines
    - Anti-ALKS 4230 antibody induction

Table 1: Study Design and Primary/Secondary Objectives

Part	Tumor Type	Planned No. Patients	Primary Objective	Secondary Objective
A. Dose escalation	Advanced solid tumors	36-54[a]	• Safety/tolerability of ALKS 4230 • Maximum tolerated dose • Determination of RP2D • Dose-limiting toxicity • AE profile	• Clinical pharmacokinetic profile and immunogenicity • Clinical pharmacodynamic effects* • Antitumor activity†
B. Dose expansion	Melanoma or RCC in patients who have received prior therapies	39-105[b]	• Safety/tolerability of ALKS 4230 at RP2D • AE profile	• Clinical pharmacokinetic profile and immunogenicity • Clinical pharmacodynamic effects* • ORR and DOR
C. Combination therapy	Advanced solid tumors; 7 cohorts[d]	Up to 188[c]	• Safety/tolerability of ALKS 4230 in combination with pembrolizumab	• ORR and DOR • Clinical pharmacokinetic profile and immunogenicity • Clinical pharmacodynamic effects*

[a]3+3 study design; each dose-level cohort is intended to enroll from 3 to 6 patients. [b]n = up to 50 patients with melanoma and up to 55 patients with RCC. [c]n = up to 20 patients into each of Cohorts 1-3 based on tumor type and prior anti-PD-1 therapy; a fourth cohort of patients from Part A or B who received ≥ 4 cycles of ALKS 4230 or experienced disease progression on monotherapy. Following determination of RP2D, up to 31 patients with melanoma, up to 50 patients with NSCLC, and up to 47 patients with HNSCC may be enrolled in Cohorts 5-7. [d]Cohort 1, PD-1 unapproved tumor types (treatment naïve) = melanoma, NSCLC, HNSCC, UC, MSI-H, GC, RCC; Cohort 2, PD-1 approved tumor types (pretreated) = NSCLC, HNSCC, UC, MSI-H, GC; Cohort 3 (PD-1 approved tumor types) = NSCLC, colorectal cancer, triple-negative breast cancer, ovarian carcinoma, soft tissue sarcomas; Cohort 4, monotherapy rollover cohort (rollover patients from Part A or B); Cohort 5, first-line melanoma; Cohort 6, second-line NSCLC; Cohort 7, second-line HNSCC.
*Measurement of circulating CD8+ T cells, T_{regs}, and NK cells in peripheral whole blood and serum levels of proinflammatory cytokines. †Assessed using RECIST and iRECIST guidelines.

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Abbreviations: AE, adverse event; C, cohort; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; HNSCC, head and neck squamous cell carcinoma; IL-2, interleukin-2; IL-2R, interleukin-2 receptor; iRECIST, immune Response Evaluation Criteria In Solid Tumors; IV, intravenous; MSI-H, microsatellite instability-high cancer; NK, natural killer; NSCLC, non-small-cell lung cancer; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; ORR, objective response rate; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose; T_{regs}, regulatory T cells; UC, urothelial carcinoma

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Heather.Losey@alkermes.com

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