ARTISTRY-2: A Phase 1/2 Study of Subcutaneously Administrated ALKS 4230 as Monotherapy and in Combination With Pembrolizumab in Patients With Advanced Solid Tumors

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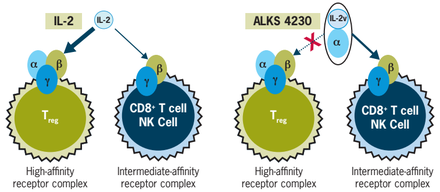
INTRODUCTION

- ALKS 4230 is an engineered fusion protein of circularly permuted interleukin-2 (IL-2) and IL-2 receptor-α (IL-2Rα) that selectively expands natural killer (NK) and cytotoxic (CD8+) T cells (Figure 1).
- The high doses of IL-2 required for antitumor efficacy are associated with regulatory T cell (T_{reg}) expansion, which may limit efficacy, and lead to acute toxicities, which may be life threatening.[1,2]
- ALKS 4230 exhibited enhanced pharmacokinetic (PK) and selective pharmacodynamic properties, with improved antitumor efficacy relative to IL-2 in preclinical studies.[3]

Figure 1: ALKS 4230 Structure and Activity

(A) ALKS 4230 is a covalent fusion of circularly permuted IL-2 and IL-2Rα

(B) Cell activation by IL-2 and ALKS 4230



- Intravenous (IV) dosing of ALKS 4230 is being evaluated in ARTISTRY-1 (NCT02799095), which has enrolled more than 50 patients to date (see poster P447).
- Here, we present ARTISTRY-2 (NCT03861793), a study of subcutaneous (SC) ALKS 4230 that is currently enrolling.
- Rationale for exploration of SC dosing in addition to IV formulation:
  - Lower peak serum drug concentrations with a prolonged exposure profile, which may result in an improved tolerability and safety profile.
  - Lymphatic absorption, which may facilitate direct immunologic effects.
  - A more convenient dosing schedule than daily inpatient IV dosing.

METHODS

- ARTISTRY-2 is a phase 1/2 study of ALKS 4230, administered SC as monotherapy and in combination with the anti–programmed cell death protein 1 antibody pembrolizumab in patients with advanced solid tumors (Table 1, Figure 2).

FIGURE 2: ARTISTRY-2 Study Sites

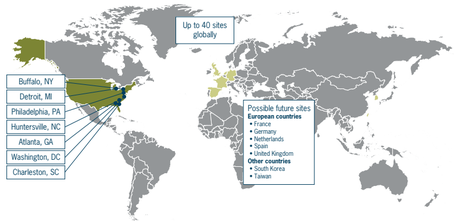


Table 1: Key Inclusion and Exclusion Criteria

Inclusion Criteria[a]	Exclusion Criteria[a]
• Advanced solid tumor (phases 1 and 2); specified tumor types (phase 2)	• Active infection or fever ≥ 38.5°C within 3 days of the first dose
• Recovered from the effects of any prior chemotherapy, immunotherapy, radiotherapy, or surgery	• Presence of active or symptomatic CNS metastases
• Adequate hematologic reserve, hepatic function, and renal function	• Requirement of pharmacologic doses of corticosteroids
• ECOG PS of 0 or 1	• Prior development of autoimmune disorders while on immunotherapy or known positivity for HIV, hepatitis B, or hepatitis C infection

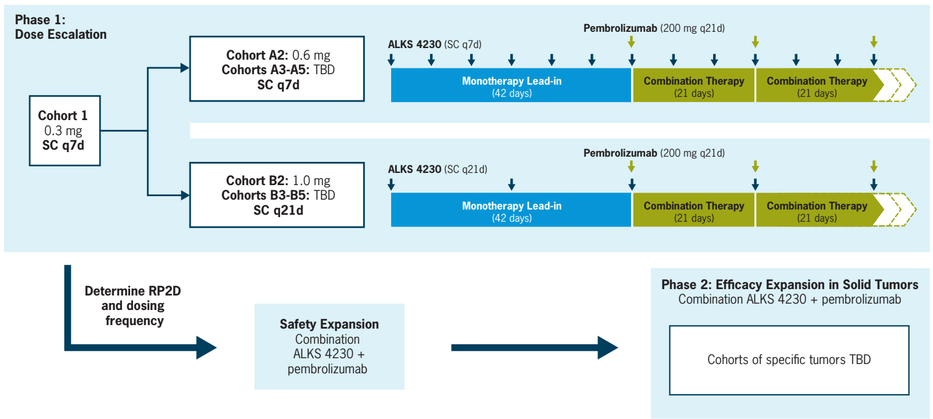
[a]Additional criteria apply.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status.

- In phase 1 (dose escalation), multiple ascending doses of SC ALKS 4230 will be administered every 7 (q7d) or 21 (q21d) days during a 6-week lead-in period (Figure 3).
  - Injection site locations will include the back of the arm, the thigh, and the abdomen.
  - If the patient tolerates ALKS 4230 monotherapy, pembrolizumab, administered as an IV infusion over 30 minutes q21d, will be added to the ongoing ALKS 4230 regimen.
- In phase 2 (dose expansion), ALKS 4230 will be administered SC at the recommended phase 2 dose (RP2D) in combination with pembrolizumab in tumor-specific cohorts (Figure 3).
- Outcomes include the RP2D, safety, PK, pharmacodynamics, immunogenicity, and antitumor activity (Table 2).
- Efficacy endpoints include overall response rate, disease control rate, duration of response, time to response, and progression-free survival and overall survival at 6- and 12-month milestones.
- Preliminary data from the fully enrolled dose escalation Cohort 1 as of August 2, 2019, are presented.

TABLE 2: Study Objectives

Phase	Tumor Type	Expected no. of Patients	Primary Objectives	Secondary Objectives
Phase 1: Dose escalation	Advanced solid tumors	33-75	• Safety and tolerability • Identify RP2D	• Describe dose-limiting toxicity • PK and immunogenicity • Pharmacodynamics • Antitumor activity
Phase 2: Dose expansion	Advanced solid tumors	91-182	• Safety and tolerability of SC ALKS 4230 at RP2D in combination with pembrolizumab	• Antitumor activity • PK and immunogenicity • Pharmacodynamics

FIGURE 3: Study Design and Treatment Regimens



TBD, to be determined.

PRELIMINARY RESULTS

Enrollment

- In the fully enrolled initial cohort at the once-weekly 0.3 mg dose of ALKS 4230 (N = 7):
  - Patients were aged between 28 and 82 years at enrollment.
  - 6 of 7 patients currently remain on therapy.
    - Duration of treatment ranged from 43+ days to 141+ days (data cut: August 2, 2019).
  - As of October 2019, dosing at next dose escalation cohorts (0.6 mg q7d and 1.0 mg q21d) is ongoing.

Initial Safety Findings

- The most common adverse events (AEs) (by preferred term, regardless of relationship to study drugs) were fatigue (n = 4), chills (n = 3), injection site erythema (n = 3), injection site pruritus (n = 3), nausea (n = 3), and pyrexia (n = 3); all other AEs occurred in ≤ 2 patients each.
- 6 of 7 patients (86%) had mild symptoms at the injection site, mostly grade 1 injection site erythema and pruritus; 1 patient experienced grade 2 injection site pain.
- 1 grade ≥ 3 AE occurred: lymphopenia (transient; likely related to ALKS 4230 mechanism of action).
- No patient discontinued treatment due to an AE.
- Review of safety data from Cohort 1 (0.3 mg SC q7d) permitted dose escalation to Cohort A2 (0.6 mg SC q7d) and Cohort B2 (1.0 mg SC q21d).

CONCLUSIONS

- ARTISTRY-2 is an ongoing study and clinical sites are actively recruiting.
- Initial signals of favorable tolerability were observed in the relatively small sample of patients with advanced solid tumors enrolled to date.
- As the study continues, data from additional patients and maturation of the data will allow us to more fully understand the therapeutic potential of SC ALKS 4230 in this setting.

References

1.Sim GC, et al. *J Clin Invest*. 2014;124:99-110.
2.Choudry H, et al. *BioMed Res Int*. 2018, Article ID 9056173:1-7.
3.Losey HC, et al. *Cancer Res*. 2017;77(13 Suppl). Abstract 591.

Disclosures

Study funding was provided by Alkermes, Inc.
Writing and editorial support was provided by Parexel, funded by Alkermes, Inc.

ARTISTRY

Alkermes Patient inspired