ALKS 4230, an Engineered IL-2 Fusion Protein, in Monotherapy Dose-Escalation and Combination Therapy With Pembrolizumab in Patients With Solid Tumors: ARTISTRY-1 Trial

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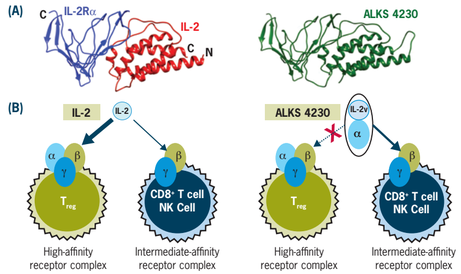
INTRODUCTION

- 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 and selective pharmacodynamic properties with improved antitumor efficacy relative to IL-2 in preclinical studies.[3]
- Here we present preliminary data from ARTISTRY-1 (NCT02799095), a study of intravenous (IV) ALKS 4230 in patients with advanced solid tumors.[4]
- Subcutaneous (SC) dosing of ALKS 4230 is being evaluated in the ongoing ARTISTRY-2 trial (NCT03861793; see poster P441).

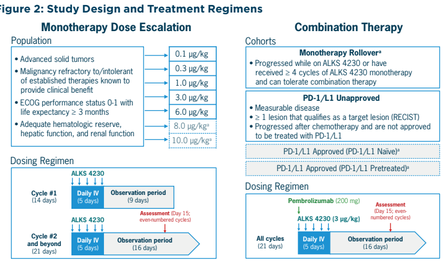
Figure 1: ALKS 4230 Structure and Activity. (A) ALKS 4230 is a covalent fusion of circularly permuted IL-2 and IL-2Rα; (B) cell activation by IL-2 and ALKS 4230



METHODS

- ARTISTRY-1 is a phase 1/2 study investigating intravenous ALKS 4230 as monotherapy and in combination with the anti–programmed cell death protein 1 (anti-PD-1) antibody pembrolizumab, and consists of 3 parts: a monotherapy dose escalation, monotherapy dose expansion in renal cell carcinoma and melanoma cohorts, and combination therapy.
  - For monotherapy dose escalation, ALKS 4230 is administered by IV infusion (over 30 min), once daily for 5 days (Figure 2).
  - For combination therapy, the same regimen of IV ALKS 4230 is administered with pembrolizumab; cohorts were enrolled based on tumor type, anti-PD-1 or anti–programmed death-ligand 1 (anti-PD-L1) indication, and rollover from monotherapy (Figure 2).
- Outcomes measured include the monotherapy recommended phase 2 dose (RP2D), safety, pharmacodynamics, and antitumor activity (Response Evaluation Criteria In Solid Tumors [RECIST] 1.1).
- Data from the first 5 fully enrolled monotherapy dose escalation cohorts and from the monotherapy rollover and PD-1/L1 unapproved cohorts of the combination therapy phase as of August 2, 2019, are presented.

Figure 2: Study Design and Treatment Regimens



*Still enrolling.
ECOG, Eastern Cooperative Oncology Group.

RESULTS FROM ALKS 4230 MONOTHERAPY

Safety Findings: Monotherapy Dose Escalation

- 36 patients received ALKS 4230 monotherapy at doses up to 6 µg/kg/d.
  - The maximum tolerated dose of ALKS 4230 has not been reached and dose escalation is ongoing.
- The most frequently reported adverse events (AEs), regardless of relationship to ALKS 4230, were pyrexia (75%) and chills (72%); the majority were grades 1-2.
- Other AEs showing possible dose relationship included nausea (36%), hypotension (31%), headache (19%), and confusional state (14%).
- Grade ≥ 3 AEs considered related to ALKS 4230 by the investigator are shown in Table 1.
- 1 death, from aspiration pneumonia, was considered unrelated to ALKS 4230 by the investigator.

Table 1: Grade ≥ 3 AEs Considered Related to ALKS 4230

Preferred Term, n (%)	0.1 µg/kg n = 5	0.3 µg/kg n = 4	1 µg/kg n = 7	3 µg/kg n = 8	6 µg/kg n = 12	Total N = 36
Any AE	0	0	0	5 (62.5)	6 (50.0)	11 (30.6)
Neutrophil count decreased	0	0	0	2 (25.0)	2 (16.7)	4 (11.1)
Lymphocyte count decreased	0	0	0	1 (12.5)	1 (8.3)	2 (5.6)
White blood cell count decreased	0	0	0	2 (25.0)	0	2 (5.6)
Pyrexia	0	0	0	0	2 (16.7)	2 (5.6)
Aspartate aminotransferase increased	0	0	0	0	1 (8.3)	1 (2.8)
Diarrhea	0	0	0	1 (12.5)	0	1 (2.8)
Febrile neutropenia	0	0	0	1 (12.5)	0	1 (2.8)
Neutropenia	0	0	0	0	1 (8.3)	1 (2.8)
Hypoalbuminemia	0	0	0	1 (12.5)	0	1 (2.8)
Hyperbilirubinemia	0	0	0	1 (12.5)	0	1 (2.8)
Cholangitis	0	0	0	1 (12.5)	0	1 (2.8)
Jaundice cholestatic	0	0	0	1 (12.5)	0	1 (2.8)

Identification of Monotherapy RP2D

- The monotherapy RP2D (primary objective) in this heavily pretreated, refractory population was established as 6 µg/kg/d.

Antitumor Activity: Monotherapy Dose Escalation

- ALKS 4230 induced dose-dependent increases in circulating NK and CD8+ T cells with negligible, non-dose-dependent effects on T_{reg} (Figure 3).
- Among the 27 patients with evaluable scans, 14 (52%) had stable disease (Figure 4).
  - 1 patient with heavily pretreated pancreatic adenocarcinoma had prolonged stable disease and continued on ALKS 4230 6 µg/kg/d therapy for 6+ months (Figure 4, Table 2, Patient A).
- No objective response was reported with ALKS 4230 monotherapy.

Figure 3: ALKS 4230 Pharmacokinetic and Pharmacodynamic Data

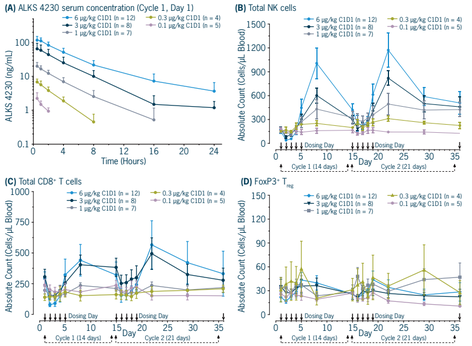
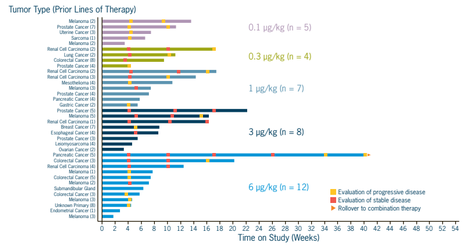


Figure 4: ALKS 4230 Monotherapy: Duration of Treatment by Overall Response (RECIST 1.1)



RESULTS FROM ALKS 4230 COMBINATION THERAPY

Safety Findings: ALKS 4230 Combination Therapy

- 26 patients received ALKS 4230 in combination with pembrolizumab.
- The most frequently reported AEs, regardless of relationship to ALKS 4230, were chills (n = 17 [65%]), pyrexia (n = 16 [62%]), and nausea (n=11 [42%]); all other AEs occurred in < 10 patients.
- Grade ≥ 3 AEs considered related to ALKS 4230 by the investigator occurred in 7 patients: infusion-related reactions (n = 2 [8%]); lymphocyte count decreased (n = 2 [8%]); and anemia, aspartate aminotransferase increased, confusion, dehydration, and fatigue (n = 1 [4%] each).

Antitumor Activity: ALKS 4230 Combination Therapy

- Among the 26 patients (n = 1 monotherapy rollover; n = 25 PD-1/L1 unapproved; 18 patients had evaluable scans; 12 of the 18 (67%) had stable disease or better over the course of treatment (Figure 5).
  - 1 patient with ovarian cancer had a confirmed partial response (PR) (Table 2, Patient B).
  - 1 patient with triple negative breast cancer showed > 50% reduction in target lesion size (Figure 6, Table 2, Patient C).

Table 2: Description of Selected Patients With Clinical Benefit

Patient	Treatment History	On-study benefits
A Male (70 yo) with pancreatic cancer	• 5 prior lines • Most recent: abraxane and gemcitabine	• Reduction in CA19-9 from 2571 U/mL (baseline) to 673 U/mL while on monotherapy • Received monotherapy for 10 months and combination therapy for 4.5 months; the patient had 6 months of stable disease on monotherapy • Maintained ECOG performance status of 1 throughout the study
B Female (48 yo) with high-grade ovarian cancer PD-L1-positive; BRCA wild type	• 5 prior lines • Most recent: carboplatin and docetaxel	• PR (60% decrease in target lesions) at Cycle 4; confirmed partial response at Cycle 6 • Normalization of CA-125 at Cycle 4 and continues in the normal range: 282 U/mL (screening) to 12.6 U/mL (Cycle 10) • Tolerated therapy well
C Female (47 yo) with triple negative breast cancer	• 8 prior lines • Most recent: carboplatin and gemcitabine	• 32% decrease in target lesions at Cycle 2; 53% at Cycle 8 • Decrease in target lesions and in small new lesions qualified patient iPR by iRECIST criteria • Tolerated therapy well; grade 1 AEs and intermittent grade 2 tachycardia early on

Figure 5: Results of ALKS 4230 Combination Therapy With Pembrolizumab (RECIST 1.1)

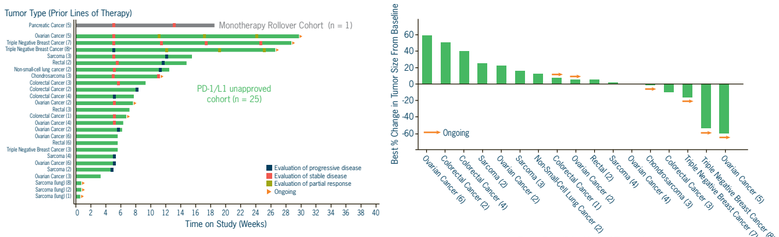
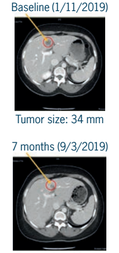


Figure 6: Triple Negative Breast Cancer Patient With > 50% Decrease in Target Lesion in the Liver on ALKS 4230 and Pembrolizumab Therapy



[a]Patient with triple negative breast cancer had a decrease in sum of target lesion diameters ≥ 30% classified as immune unconfirmed progressive disease due to small new lesions in Cycle 2. Subsequent shrinkage of both target lesion and small new lesions classified as immune partial response (iPR) in Cycle 4 and beyond.

CONCLUSIONS

- ARTISTRY-1 is an ongoing study, with clinical sites actively recruiting additional cohorts.
- In patients with advanced solid tumors, ALKS 4230 selectively expanded CD8+ T cells and NK cells with negligible, non-dose dependent T_{reg} expansion.
- The IV monotherapy RP2D was established as 6 µg/kg/d.
- Safety and pharmacodynamic data enabled selection of the 3 µg/kg dose for initial evaluation in combination with pembrolizumab.
- ALKS 4230 is a promising agent with evidence of acceptable tolerability and preliminary clinical benefit both as monotherapy and in combination with pembrolizumab.

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Disclaimer

Data may change as more patient data are available.

Acknowledgments and Disclosures

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ARTISTRY

Alkermes Patient inspired

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