Phase 1/2 Study of Subcutaneously Administered ALKS 4230, a Novel Engineered Cytokine, as Monotherapy and in Combination With Pembrolizumab, in Patients With Advanced Solid Tumors: ARTISTRY-2

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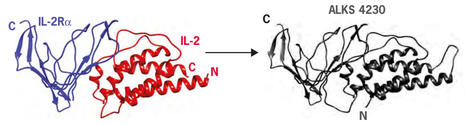
INTRODUCTION

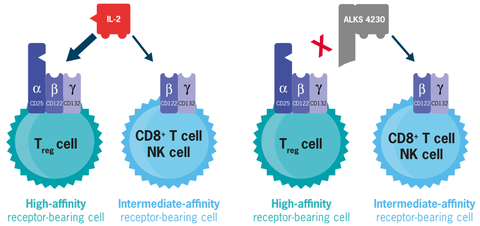
- ALKS 4230 is a novel engineered cytokine designed to selectively expand natural killer (NK) and cytotoxic CD8+ T cells by activating the intermediate-affinity IL-2 receptor (IL-2R) (Figure 1).
- High doses of IL-2 are required to induce the activation of the intermediate-affinity IL-2R for antitumor activity; however, this also leads to activation of the high-affinity IL-2R, which is associated with regulatory T cell (T_{reg}) expansion and may lead to life-threatening acute toxicities.[1]
- Intravenous (IV) dosing of ALKS 4230 has shown encouraging antitumor activity and acceptable tolerability, as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors (ARTISTRY-1, NCT02799095; see Poster 689).[2]
- Subcutaneous (SC) dosing may provide an alternative administration option for patients.

Figure 1: ALKS 4230 Structure and Activity

A. ALKS 4230 is a fusion protein of circularly permuted IL-2 and IL-2Rα.



B. ALKS 4230 is designed to selectively bind only to the intermediate-affinity IL-2R complex.



RESULTS

Patient Characteristics

- 43 patients have been treated with ALKS 4230 across 8 assigned dose escalation cohorts, with SC doses ranging from 0.3 mg to 10 mg across both dosing regimens (Table 1).
  - The median (range) number of prior therapies was 4 (0-17).
  - 42% of patients were previously treated with immunotherapy.
  - Median (range) age at study entry was 61.0 (28-82) years.
  - 16 patients (37.2%) are male.
- Patient tumor indications were mixed; the most common tumor types included colon cancer (n = 8), ovarian cancer (n = 5), and lung cancer (n = 4).
- 30 patients (69.8%) completed lead-in monotherapy and initiated combination therapy.

Safety and Tolerability

- The maximum tolerated dose and RP2D for SC administration have not yet been determined.
  - 6 mg q7d, 6 mg q21d, and 10 mg q21d cohorts are ongoing.
- Overall, across both treatment periods, injection site reactions (ISRs) were the most commonly reported adverse events (AEs).
- AEs, regardless of causality, occurred in 42 (97.7%) patients during the monotherapy lead-in period and in 28 (65.1%) during the combination period (Table 1).
- Overall, across both treatment periods, 16 patients (37.2%) experienced grade ≥ 3 AEs assessed by the investigator as being related to ALKS 4230, with lymphopenia (25.6%) as the only AE reported in ≥ 2 patients.
- 1 patient experienced dose-limiting AEs while receiving 10 mg q21d ALKS 4230 (grade 3 nausea, vomiting, and fatigue).
- Additionally, 1 patient experienced a treatment-related serious AE (SAE) (grade 3 tumor flare manifesting as a colonic obstruction).

Table 1: Summary of AEs

Patients With an AE, n (%)	q7d					q21d			q7d + q21d Overall (N = 43)
	0.3 mg (n = 7)	0.6 mg (n = 3)	1 mg (n = 7)	3 mg (n = 7)	6 mg (n = 3)	1 mg (n = 4)	3 mg (n = 4)	10 mg (n = 8)	
Overall, both treatment periods									
Any AE	7 (100)	3 (100)	7 (100)	7 (100)	3 (100)	4 (100)	4 (100)	7 (87.5)	42 (97.7)
Grade ≥ 3 TRAEs	1 (14.3)	0	4 (57.1)	4 (57.1)	2 (66.7)	1 (25.0)	1 (25.0)	3 (37.5)	16 (37.2)
Related ISR AEs[a]	5 (71.4)	1 (33.3)	3 (42.9)	5 (71.4)	1 (33.3)	3 (75.0)	3 (75.0)	6 (75.0)	27 (62.8)
Monotherapy lead-in period									
Any AE	7 (100)	3 (100)	7 (100)	7 (100)	3 (100)	4 (100)	4 (100)	7 (87.5)	42 (97.7)
AEs occurring in ≥ 20% of the overall population									
Pyrexia	3 (42.9)	0	2 (28.6)	4 (57.1)	0	0	4 (100)	4 (50.0)	17 (39.5)
Fatigue	4 (57.1)	1 (33.3)	2 (28.6)	2 (28.6)	1 (33.3)	0	2 (50.0)	3 (37.5)	15 (34.9)
Chills	3 (42.9)	0	2 (28.6)	3 (42.9)	1 (33.3)	0	2 (50.0)	4 (50.0)	15 (34.9)
Nausea	3 (42.9)	0	2 (28.6)	3 (42.9)	1 (33.3)	0	1 (25.0)	4 (50)	14 (32.6)
Lymphopenia	1 (14.3)	0	3 (42.9)	3 (42.9)	0	1 (25.0)	1 (25.0)	2 (25.0)	11 (25.6)
Combination period									
Any AE	7 (100)	2 (66.7)	6 (85.7)	3 (42.9)	0	3 (75.0)	3 (75.0)	4 (50.0)	28 (65.1)
AEs occurring in ≥ 15% of the overall population									
Lymphopenia	0	0	3 (42.9)	1 (14.3)	0	2 (50.0)	0	2 (25.0)	8 (18.6)
Fatigue	3 (42.9)	0	2 (28.6)	1 (14.3)	0	1 (25.0)	0	0	7 (16.3)

[a]ISRs include the following preferred terms: injection site reaction, injection site erythema, injection site pain, injection site pruritus, injection site swelling, injection site discoloration, injection site inflammation, injection site irritation, and injection site warmth.
TRAE, treatment-related AE.

Clinical Results

- Median (range) duration of treatment was 65 (1-562) days.
- 23 of 33 evaluable patients treated in the study so far achieved stable disease.
  - 1 patient with ovarian cancer (low-grade Mullerian mesenchymal tumor) has been receiving study treatment for > 6 months (number of prior therapies was 1).
  - 1 patient with head and neck squamous cell carcinoma (malignant neoplasm of lacrimal gland and duct) has been receiving study treatment for > 12 months (number of prior therapies was 4).

Pharmacokinetics/Pharmacodynamics

- Systemic exposure to ALKS 4230 increased with increasing dose (Figure 3), resulting in a dose-dependent increase in circulating NK and CD8+ T cells, with minimal impact on T_{regs} (Figure 4).
  - Accompanying dose-dependent transient elevation of serum IFNγ and, to a lesser extent, IL-6 concentrations were also observed (Figure 3).
  - Relative to IV ALKS 4230, there was a greater increase in serum IFNγ and a smaller increase in serum IL-6 concentrations.

Figure 3: Serum Concentrations After the First Dose in Monotherapy Lead-in Period

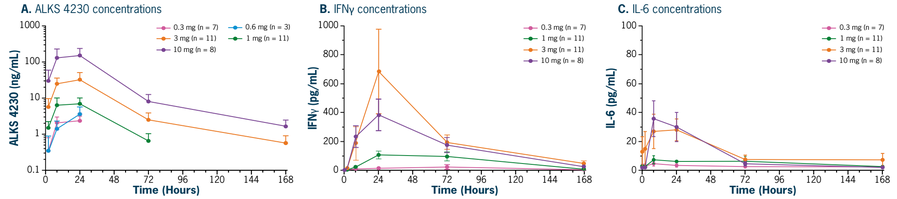
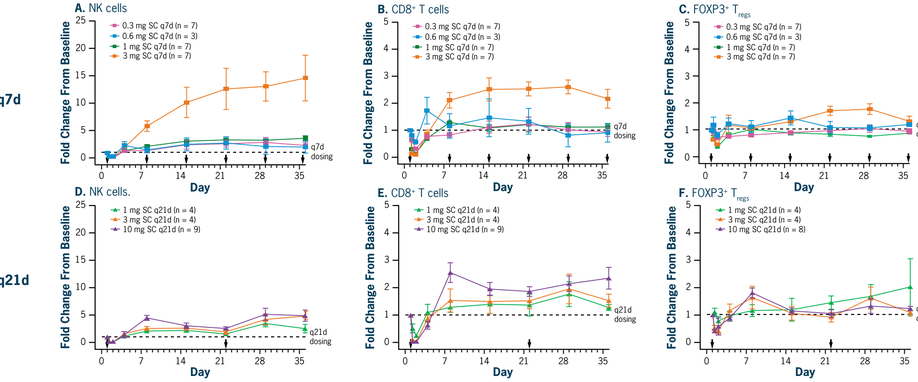


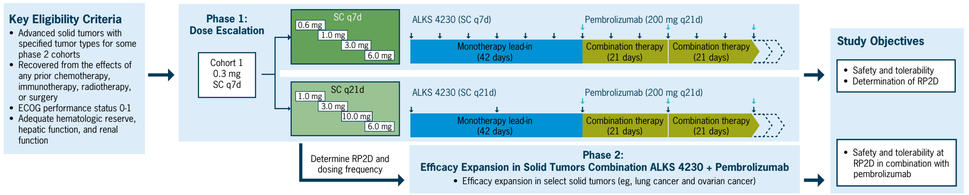
Figure 4: ALKS 4230 Pharmacodynamics by Dosing Regimen



METHODS

- ARTISTRY-2 (NCT03861793) is an ongoing phase 1/2 study of SC ALKS 4230 ± pembrolizumab.
- Phase 1 is an ongoing dose escalation during which cohort-specific doses of SC ALKS 4230 are administered.
- Each patient assigned to a given cohort receives ALKS 4230 at a single dose level and on a schedule of either every 7 days (q7d) or every 21 days (q21d).
  - Intrapatient dose escalation is allowed.
- The dosing schedule included a 6-week lead-in monotherapy period followed by combination with IV pembrolizumab 200 mg q21d (Figure 2).
- Safety, tolerability, and pharmacokinetic/pharmacodynamic data from dose escalation up to a dose of 10 mg, as of 9/29/2020, are reported in his poster.

Figure 2: Study Design and Dosing Schedule



ECOG, Eastern Cooperative Oncology Group; RP2D, recommended phase 2 dose.

CONCLUSIONS

- ALKS 4230 is a promising investigational agent for the treatment of advanced solid tumors.
- Subcutaneously administered ALKS 4230 in the doses studied has an acceptable safety and tolerability profile consistent with the anticipated pharmacological effect and what is observed with IV ALKS 4230.
- Pharmacodynamic results show dose-dependent increases in NK cell and CD8+ T cell activation and minimal increase in immunosuppressive markers, such as FOXP3+ T_{regs}.
- Clinical benefit is noted, even in immunotherapy-pretreated patients; 11 patients continued on therapy past 6 months.
- The study, including dose escalation, is ongoing.
- Maximum tolerated dose and RP2D for SC ALKS 4230 have not yet been determined.

REFERENCES AND ACKNOWLEDGMENTS

References

1. Lopes J, et al. *J Immunother Cancer.* 2020;8:e000673.
2. Vaishampayan UN, et al. *Ann Oncol.* 2020;31(suppl 4):S708-S709.

Acknowledgments

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ARTISTRY

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