Clinical Outcomes of Ovarian Cancer Patients Treated With ALKS 4230, a Novel Engineered Cytokine, in Combination With Pembrolizumab: ARTISTRY-1 Trial

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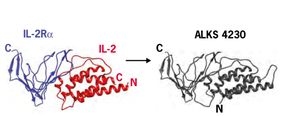
Poster 689

INTRODUCTION

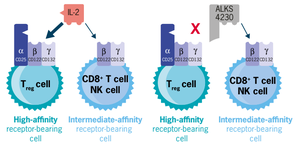
- ALKS 4230 is a novel engineered cytokine designed to selectively expand natural killer (NK) and cytotoxic CD8+ T cells by activating the intermediate-affinity IL-2 receptor (IL-2R) (Figure 1).
- High doses of IL-2 are required to induce the activation of the intermediate-affinity IL-2R complex and subsequent antitumor activity; however, this also leads to activation of the high-affinity receptor complex, which is associated with regulatory T cell (T_{reg}) expansion and may lead to severe acute toxicities.[1]
- The ongoing ARTISTRY-1 trial (NCT02799095) has shown encouraging antitumor activity and acceptable tolerability of ALKS 4230 among patients with advanced solid tumors, including ovarian cancer.[2]
- Ovarian cancer is a poorly immunogenic tumor type that does not typically respond to treatment with single-agent checkpoint inhibitors.[3]
  - Approximately 75% of women diagnosed with ovarian cancer already have metastatic disease at the time of diagnosis and prognosis is poor.[4]
- We report a detailed analysis of ovarian cancer patients who received combination therapy in ARTISTRY-1 and an update on results from ARTISTRY-1.

Figure 1: ALKS 4230 Structure and Activity

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



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



METHODS

- ARTISTRY-1 is an ongoing 3-part multicohort phase 1/2 trial exploring intravenous (IV) ALKS 4230 as monotherapy and combined with pembrolizumab in patients with advanced solid tumors (Figure 2).
- The recommended phase 2 dose (RP2D) for IV ALKS 4230 was determined to be 6 µg/kg in the dose escalation portion of the trial.
- Outcomes are presented as of 9/29/2020 and include a detailed analysis of ovarian cancer patients enrolled in the Part C cohort of mixed programmed death (ligand) 1 (PD-1/L1) unapproved tumor types who had progressed on prior chemotherapy.

Figure 2: Study Design (Part C), Combination Treatment Regimen, and Patient Characteristics

Objectives of Part C[a]: Combination Therapy
- Characterize safety profile and antitumor activity by ORR of ALKS 4230 in combination with pembrolizumab

Key Eligibility Criteria
- Advanced solid tumors
- Malignancy refractory to/intolerant of established therapies known to provide clinical benefit
- ECOG performance status 0-1 with life expectancy ≥ 3 months
- Adequate hematologic reserve, hepatic function, and renal function

Cohorts
- Mixed tumor types based on PD-1/L1 indication and prior treatment history at 3 µg/kg ALKS 4230
- Additional tumor-specific cohorts at 6 µg/kg ALKS 4230

PD-1/L1 Unapproved Cohort (n = 42)
- 9 different tumor types represented, with the most common being colorectal cancer, ovarian cancer, and sarcoma
- Median age was 57.0 years; most patients were white (81.0%) and had a baseline ECOG performance status of 1 (78.6%) at study entry
- Median number of prior lines of therapy was 3 (range, 1-11)

Ovarian Cancer Patients (n = 15)
- Subset of PD-1/L1 unapproved cohort
- Median number of prior regimens was 4 (range, 2-11)
- All have received previous treatment with platinum-based regimens

Combination Dosing Regimen

[a]Part A of the trial was a dose escalation phase 1 trial, the results of which have been previously reported. This part of the trial is currently ongoing at 8 µg/kg in order to establish the maximum tolerated dose. Part B of the trial is a monotherapy (6 µg/kg) dose expansion in melanoma and RCC patients that is currently ongoing.
ECOG, Eastern Cooperative Oncology Group; RCC, renal cell carcinoma; ORR, objective response rate.

RESULTS IN OVARIAN CANCER PATIENTS FROM PD-1/L1 UNAPPROVED COHORT

Safety and Tolerability

- Among patients in the PD-1/L1 unapproved cohort, treatment-related adverse events (TRAEs) have generally been transient and manageable, with the majority being grade 1 or 2 in severity (Table 1).
  - The most commonly reported AEs (≥ 50%) were chills, pyrexia, and nausea.
  - Chills and pyrexia were mostly manageable with antipyretics and other symptomatic treatments.
  - No cases of hypotension have required the use of vasopressors to date.
  - 1 patient discontinued due to a TRAE (inanition in a pancreatic cancer patient).
- Among the 15 ovarian cancer patients, the ALKS 4230 safety profile was consistent with that observed across patients in the PD-1/L1 cohort.
  - Grade ≥ 3 AEs related to treatment with ALKS 4230 (in ≥ 2 patients), as assessed by the investigator, included anemia (n = 4; 26.7%) and fatigue (n = 2; 13.3%).

Table 1: Safety Summary

Preferred Term[a]	PD-1/L1 Unapproved (N = 42) (Includes 15 Ovarian Cancer Patients)
AE summary, n (%)	
Any TEAE	42 (100)
Grade 1-2 TRAE[b]	42 (100)
Grade ≥ 3 TRAE[b]	20 (47.6)
TEAEs leading to discontinuation	5 (11.9)
Death[c]	2 (4.8)
AEs regardless of causality in ≥ 25% of patients overall, n (%)	
Chills	33 (78.6)
Pyrexia	32 (76.2)
Nausea	24 (57.1)
Fatigue	18 (42.9)
Hypotension	17 (40.5)
Tachycardia	16 (38.1)
Constipation	15 (35.7)
Decreased appetite	12 (28.6)
Anemia	12 (28.6)
Vomiting	12 (28.6)
Abdominal pain	11 (26.2)
Grade ≥ 3 AEs related to ALKS 4230 in ≥ 2 patients overall, n (%)[b]	
Anemia	6 (14.3)
Fatigue	5 (11.9)
Neutrophil count decreased	3 (7.1)
Lymphocyte count decreased	3 (7.1)
Infusion-related reaction	2 (4.8)

[a]AEs coded using MedDRA version 19.0. [b]As assessed by the investigator. [c]Two deaths occurred in pancreatic cancer patients; one was due to the underlying cancer and assessed by the investigator as not related to treatment, the other was due to inanition in a heavily pretreated patient and assessed by the investigator as related to ALKS 4230.
TEAE, treatment-emergent AE (these are AEs regardless of causality).

Antitumor Activity Among Patients With Ovarian Cancer

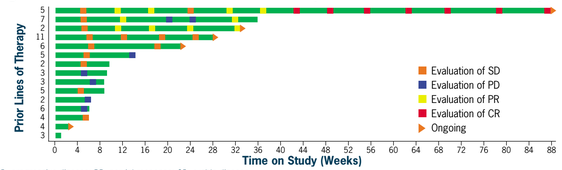
- Among 13 evaluable ovarian cancer patients with ≥ 1 assessment, 9 experienced disease control/stable disease at first scan and 4 experienced disease progression (Figure 3).
  - 9 patients had high-grade serous ovarian cancer, 1 patient had low-grade serous ovarian cancer, 1 patient had a sex cord-stromal tumor, and 3 patients were missing histology details but had advanced ovarian cancer.
  - 9 patients were negative for *BRCA* mutations, 1 patient had a *BRCA1* mutation, 1 patient had a *BRCA2* mutation, and the remainder of patients are awaiting *BRCA* status.
  - 5 patients experienced tumor shrinkage over 4 or more cycles (> 20 weeks); of these, all were platinum-resistant as assessed by the investigator, all had high-grade serous histology, 4 were negative for *BRCA* mutations (1 was unknown), and 1 (who achieved complete response [CR]) had PD-L1-positive tumor (Table 2, Figure 3, and Figure 4).

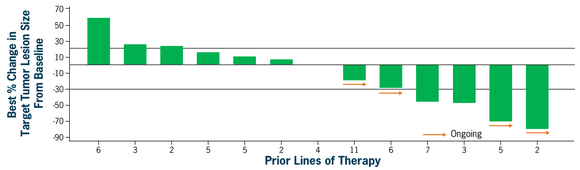
Table 2: Description of Selected Ovarian Cancer Patients With on-Study Clinical Benefit

Patient (Age)	Prior Therapies	Maximum Reduction of Target Lesions (%)	Overall Response (Investigator Assessment)	CA125 (U/mL) Response From Baseline	Time on ALKS 4230
Ovarian cancer 1 (48)	CBP/PAC/BEV, CDDP/GEM, CBP/PLD, PCA, CBP/DOC	-70.0	CR[a]	Normalized from 282 to 24.5 at cycle 4	> 87 weeks ▶ Ongoing
Ovarian cancer 2 (83)	CBP/PAC/DOC, CBP/DOC/NIR/TAM	-79.4 (Figure 4)	PR	Normalized from 125 to 16 at cycle 4	> 30 weeks ▶ Ongoing
Ovarian cancer 3 (60)	CBP/PAC, CBP/PLD, CBP/BEV, PAC/BEV, BEV, PLD	-44.7	uPR	Reduced from 1400 to 260 at cycle 4	34 weeks
Ovarian cancer 4 (75)	CBP/PAC, PLD/BEV, CBP/GEM, TOP, NIR	-28.1	SD	Reduced from 493 to 245 at cycle 5	> 22 weeks ▶ Ongoing
Ovarian cancer 5 (83)	CBP/PAC, CBP, CBP/PAC/CAP, CBP/PLD, CBP/PLD	-18.3	SD	Normal at baseline at 10.6	> 26 weeks ▶ Ongoing

[a]CR due to node shrinkage to < 10 mm short axis, which is considered normal.
BEV, bevacizumab; CAP, capecitabine; CA125, cancer antigen 125; CBP, carboplatin; CDDP, cisplatin; DOC, docetaxel; GEM, gemcitabine; NIR, niraparib; PAC, paclitaxel; PCA, paclitaxel albumin; PLD, pegylated liposomal doxorubicin hydrochloride; TAM, tamoxifen; TOP, topotecan; uPR, unconfirmed PR.

Figure 3: Duration of Treatment and Overall Responses With Combination Therapy in Ovarian Cancer Patients

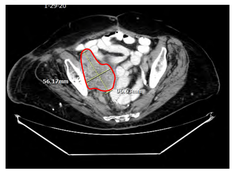




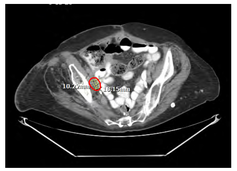
PD, progressive disease; PR, partial response; SD, stable disease.

Figure 4: Ovarian Cancer Patient 2 (Table 2) With 79% Decrease in Target Lesions on ALKS 4230 and Pembrolizumab Combination Therapy

A. Right hemipelvic mass

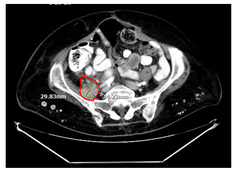


Baseline (1/29/2020) Tumor size: 97 mm

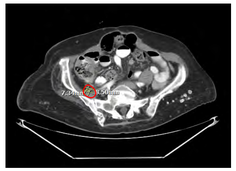


Cycle 10 (9/15/2020) Tumor size: 18 mm

B. Right retroperitoneal mass



Baseline (1/29/2020) Tumor size: 34 mm



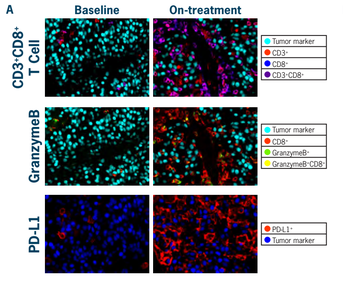
Cycle 10 (9/15/2020) Tumor size: 9 mm

SUPPORTIVE DATA FROM OTHER TUMOR TYPES

Findings From Other Tumor Types: Tumor Microenvironment

- Multiplexed immunofluorescence analysis of paired biopsies taken from a melanoma patient who received 6 ug/kg ALKS 4230 monotherapy showed an increase of CD8+ T cells and granzymeB signal in cycle 2 of the on-treatment sample relative to the baseline sample (Figure 5).
  - There was no change in the number of T_{regs} in the tumor microenvironment, which resulted in an increase in the CD8+ T cell/T_{reg} cell ratio in this patient.
  - The PD-L1 expression on tumor cells also increased (Figure 5).

Figure 5: Immune Infiltration Into the Tumor Microenvironment



Findings From Other Tumor Types: Antitumor Activity

- Objective responses have been observed in patients with other tumor types who received combination treatment with ALKS 4230 and pembrolizumab:
  - 1 patient with cervical cancer (observed after previous 8/7/2020 data cut).
  - 1 patient with triple-negative breast cancer.
  - 1 patient with pancreatic cancer.
  - 2 patients with esophageal cancer (1 each with adenocarcinoma and squamous cell carcinoma).
- Furthermore, objective responses were observed in 2 PD-1 experienced melanoma patients (1 confirmed, 1 unconfirmed [observed after previous 7/24/2020 data cut]) who received ALKS 4230 as monotherapy.
  - Both patients had metastatic mucosal melanoma.
  - Both patients had received prior nivolumab adjuvant therapy and had relapsed > 9 months after completing nivolumab therapy.
  - Response criteria were met for the expanded monotherapy melanoma cohort.

CONCLUSIONS

- The demonstration in a melanoma patient of lymphocytic infiltration in the tumor microenvironment and the increased PD-L1 positivity observed are supportive of the results achieved from the combination of ALKS 4230 with an immune checkpoint inhibitor in ovarian cancer patients. High CD8+ T cell/T_{reg} cell ratios, independent of treatment type, have been reported to be associated with better prognosis among multiple tumor types, including ovarian tumors.[5]
- Objective responses with ALKS 4230 and pembrolizumab combination therapy were observed in some patients with heavily pretreated, platinum-resistant ovarian cancer, a cancer type that does not robustly respond to treatment with single-agent checkpoint inhibitors.
- The combination of ALKS 4230 and pembrolizumab was generally well tolerated.
- This regimen could represent a new therapeutic option for ovarian cancer patients.
- A prospective study to evaluate ALKS 4230 in combination with pembrolizumab among platinum-resistant and bevacizumab-experienced ovarian cancer patients is being planned.

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ARTISTRY

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