Subcutaneous Nemvaleukin Alfa in Combination With Pembrolizumab in Patients With Refractory Solid Tumors (ARTISTRY-2)

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INTRODUCTION

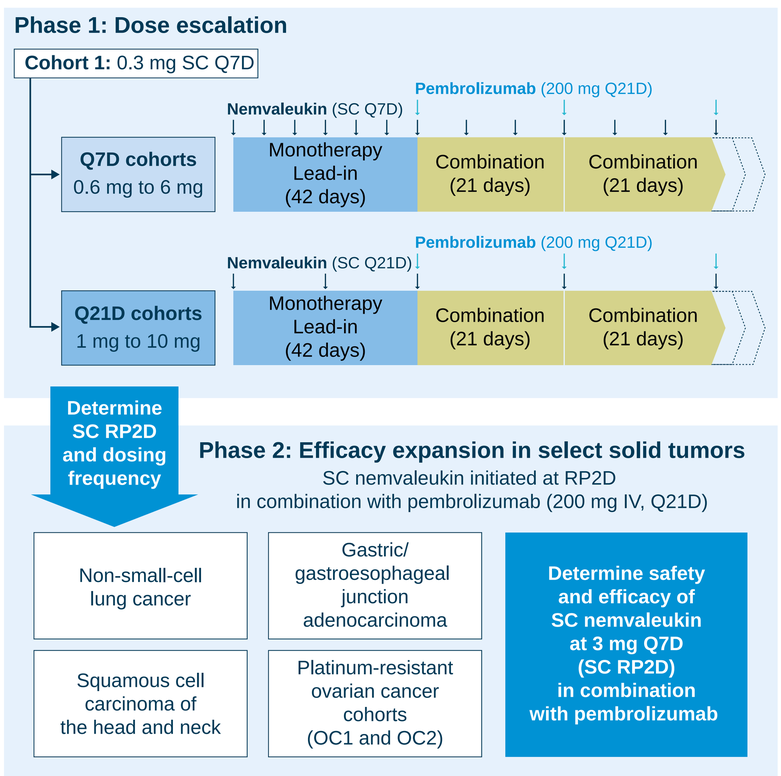
- Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds to the intermediate-affinity interleukin-2 receptor to preferentially activate antitumor CD8+ T cells and natural killer (NK) cells, with minimal expansion of immunosuppressive regulatory T cells (T_{regs})[1]
- The first-in-human ARTISTRY-1 study demonstrated antitumor activity and manageable safety with intravenous (IV) nemvaleukin (6 µg/kg/day on days 1-5 [QD×5] per 21-day cycle) monotherapy and nemvaleukin plus pembrolizumab in heavily pretreated adults with advanced solid tumors[2]
- ARTISTRY-2 (NCT03861793) is a phase 1/2 study that evaluated the safety, antitumor activity, and pharmacokinetics/pharmacodynamics of subcutaneous (SC) nemvaleukin as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors
- Based on the tolerability, pharmacodynamics, and antitumor activity from phase 1, the recommended phase 2 dose (RP2D) of SC nemvaleukin was identified as 3 mg every 7 days (Q7D)[3]
- Here we present antitumor activity and safety from phase 2 of the ARTISTRY-2 study

METHODS

Study Design and Endpoints

- The ARTISTRY-2 study design is shown in Figure 1
- In phase 2, SC nemvaleukin at the RP2D plus pembrolizumab was administered in the following advanced solid tumor cohorts: non–small-cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), gastric and gastroesophageal junction cancer (G/GEJ), and platinum-resistant ovarian cancer Cohorts 1 (OC1) and 2 (OC2)
- Key inclusion criteria for each cohort were:
  - NSCLC: checkpoint inhibitor (CPI) naive, programmed cell-death ligand 1 (PD-L1) negative (tumor proportion score <1%)
  - SCCHN: CPI pretreated
  - G/GEJ: CPI naive, 2 prior regimens that must have included a fluoropyrimidine and a platinum-based therapy
  - OC1: response to first-line platinum-based therapy lasting ≥3 months; resistant to the last platinum-based regimen; prior bevacizumab required unless deemed intolerant to or ineligible for bevacizumab
  - OC2: progression in ≤180 days following platinum-based therapy beyond first line or no response or progression during most recent platinum-based regimen; prior bevacizumab; ≤5 prior therapies in platinum-resistant setting; no prior disease-related bowel obstruction or fluid drainage of ≥500 mL in the 6 weeks prior to study drug administration
- The primary endpoints were overall response rate (ORR) per Response Evaluation Criteria In Solid Tumors v1.1 and safety
- Final results are reported as of August 17, 2023

FIGURE 1: ARTISTRY-2 study design



RESULTS

Patient Characteristics

- In phase 2, 59 patients received SC nemvaleukin plus pembrolizumab (Table 1)
- The median age was 61 years (range, 24-84), and 76% of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1
- The median number of prior lines of therapy was 3 (range, 0-12)
- Overall, 11 (19%) patients had prior CPI treatment

RESULTS (continued)

TABLE 1: Baseline characteristics

Characteristics	Overall (N=59)	OC1 (n=17)	OC2 (n=8)	NSCLC (n=11)	SCCHN (n=10)	G/GEJ (n=13)
Age (years), median (range)	61 (24-84)	58 (24-75)	60 (50-78)	67 (47-84)	69 (46-74)	61 (51-78)
Male, n (%)	29 (49)	0	0	8 (73)	9 (90)	12 (92)
ECOG PS 1, n (%)	45 (76)	13 (77)	7 (88)	7 (64)	8 (80)	10 (77)
Patients with ≥3 prior lines of therapy, n (%)	38 (64)	16 (94)	6 (75)	3 (27)	6 (60)	7 (54)
No. of prior therapies, median (range)	3 (0-12)	4 (2-12)	5 (1-7)	1 (0-6)	4 (1-10)	3 (2-6)
Pretreated with CPI, n (%)	11 (19)	0	2 (25)	0	9 (90)	0
CA-125 (U/mL),[a] mean (standard deviation)	83,636 (406,364)	4040 (7824)	312,768 (79,543)	NA	NA	NA

CA-125, cancer antigen 125; NA, not applicable.
[a]Applicable to OC cohorts only. Data are from 17 patients in OC1 and 7 patients in OC2 cohorts; CA-125 data were not available for 1 patient in the OC2 cohort.

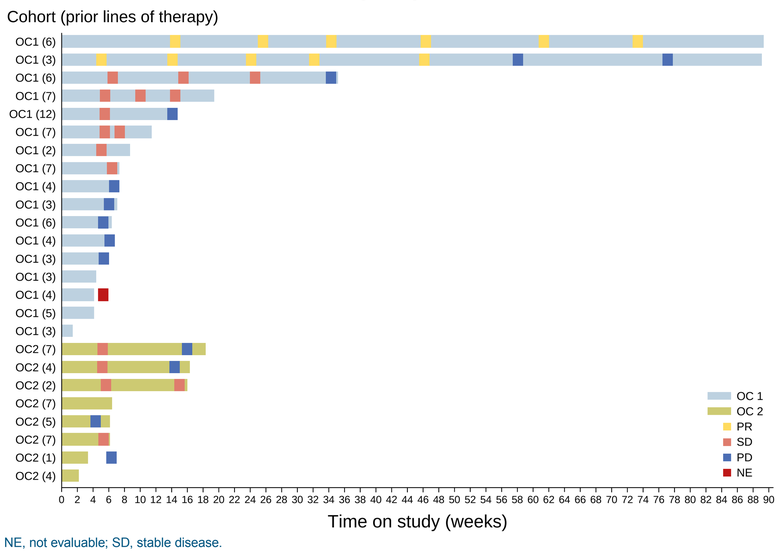
Exposure and Disposition

- Overall median (range) duration of treatment exposure was 38 days (1-617)
- Median (range) exposure was 43 days (1-617) in OC1, 29 days (8-113) in OC2, 50 days (8-113) in NSCLC, 56 days (1-316) in SCCHN, and 38 days (8-240) in G/GEJ cohorts
- At data cutoff, 1 patient had completed treatment and 58 (98%) discontinued treatment due to progressive disease (PD) (36 [61%]), adverse event (12 [20%]), patient decision (6 [10%]), death (3 [5%]), and other reasons (1 [2%])

Antitumor Activity

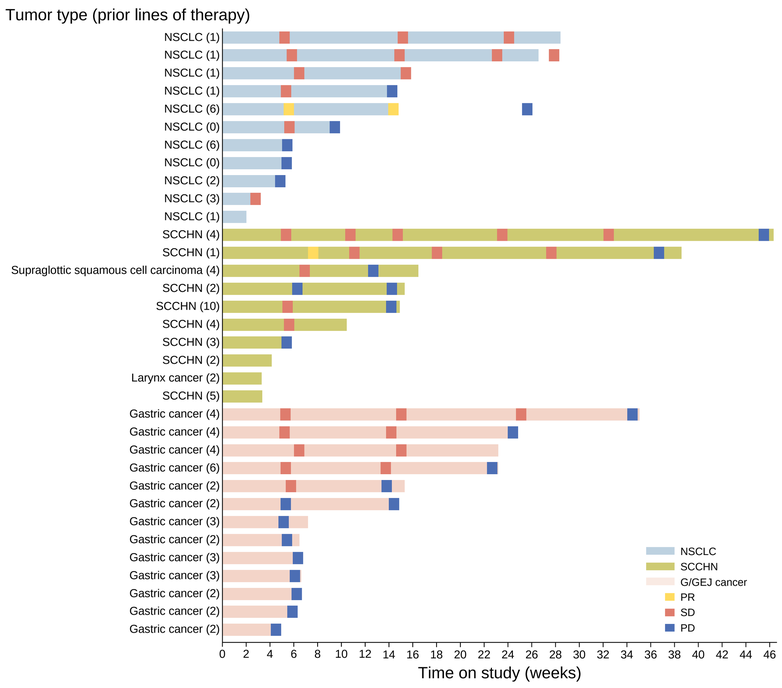
- Antitumor activity was observed, including 2 confirmed partial responses (PRs) in OC1 (2/14, ORR 14%), 1 confirmed PR in NSCLC (1/10, ORR 10%), and 1 unconfirmed PR (uPR) in SCCHN. No responses were observed in the G/GEJ or OC2 cohorts (Figures 2 and 3)
  - Confirmed responders were CPI naive
  - The unconfirmed responder was CPI pretreated

FIGURE 2: Duration of treatment by responses in OC1 and OC2 cohorts



NE, not evaluable; SD, stable disease.

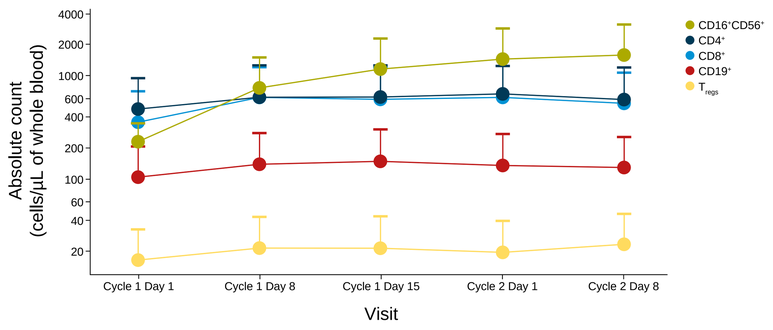
FIGURE 3: Duration of treatment by responses in NSCLC, SCCHN, and G/GEJ cohorts



Pharmacodynamics

- SC nemvaleukin demonstrated robust expansion of NK cells ($CD16^+CD56^+$) in the periphery, with an average maximum fold change of ~7 (Figure 4)
- Nominal expansion of T_{regs}, $CD8^+$ cytotoxic, and $CD4^+$ helper T cells was observed

FIGURE 4: Peripheral immune cell expansion in all tumor types after nemvaleukin plus pembrolizumab treatment



Safety

- With the exception of injection site reactions, the safety profile of SC nemvaleukin at the RP2D was consistent with that reported for IV nemvaleukin
- Most nemvaleukin-related treatment-emergent adverse events (TEAEs) were of grades 1-2 (Table 2)
- Immune-related AEs (irAEs) considered related to nemvaleukin were reported in 10% of patients, the most common of which was hypothyroidism. One patient in OC1 experienced grade 3 enterocolitis, which was assessed by the investigator as related to nemvaleukin and pembrolizumab
- One patient in the NSCLC cohort experienced a grade 5 nemvaleukin-related TEAE of pneumonitis, which was considered by the investigator as an irAE and related to nemvaleukin and pembrolizumab

TABLE 2: Safety summary

Adverse event, n (%)	Overall (N=59)
Any grade nemvaleukin-related TEAEs	58 (98)
Nemvaleukin-related grade 3 or 4 TEAEs	21 (36)
Nemvaleukin-related serious TEAEs	8 (14)
Nemvaleukin-related TEAEs leading to treatment discontinuation	7 (12)
TEAEs regardless of causality (≥25%)	
Pyrexia	31 (53)
Injection site reaction	26 (44)
Nausea	25 (42)
Decreased appetite	20 (34)
Fatigue	21 (36)
Vomiting	20 (34)
Chills	19 (32)
Aspartate aminotransferase increased	18 (31)
Nemvaleukin-related TEAEs (≥25%)	
Pyrexia	29 (49)
Injection site reaction	26 (44)
Chills	19 (32)
Nausea	19 (32)
Fatigue	17 (29)
Grade 3 or 4 nemvaleukin-related TEAEs (≥5%)	
Lymphopenia	7 (12)
Fatigue	4 (7)
Neutropenia	4 (7)

CONCLUSIONS

Limitations

- Limitations of this analysis include small sample size in each cohort and lack of a comparator arm

Conclusions

- SC nemvaleukin at the RP2D of 3 mg Q7D plus pembrolizumab was generally well tolerated and demonstrated limited antitumor activity in patients with refractory solid tumors
- The safety profile of SC nemvaleukin at the RP2D plus pembrolizumab was consistent with that reported for IV dosing, except for injection site reactions
- SC nemvaleukin demonstrated robust expansion of NK cells ($CD16^+CD56^+$), with minimal expansion of T_{regs}, consistent with its known mechanism of action
- Limited antitumor activity of SC nemvaleukin plus pembrolizumab was observed, and robustness of this regimen was less than that observed with IV nemvaleukin given QD×5, consistent with other biologics including high-dose IL-2 when administered via SC route
- Monotherapy SC nemvaleukin dosing at Q7D is being investigated in Cohort 1 of the global, phase 2 ARTISTRY-6 study (NCT04830124) in patients with cutaneous melanoma, along with separate cohorts of QD×5 and less frequent IV dosing schedules. A less frequent IV dosing schedule of nemvaleukin is also being explored in the ARTISTRY-3 study (NCT04592653)

References

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