Recommended Phase 2 Dose (RP2D) of Nemvaleukin Alfa in Patients With Advanced Solid Tumors Treated With Less Frequent Intravenous Dosing (ARTISTRY-3)

Poster 2587

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Take Aways

- Nemvaleukin demonstrated PD proof of mechanism in all 3 schedules and was tolerable at all doses tested
- Nemvaleukin RP2D for less frequent dosing was selected to be 30 µg/kg (days 1 and 8, Q3W)

Conclusions

- Nemvaleukin was tolerable at all doses tested in the less frequent IV dosing schedules, and no DLTs were observed
- The safety profile of nemvaleukin in all schedules was consistent with its known mechanism of action and was as expected in patients with relapsed/refractory solid tumors
- Expansion of NK cells and CD8$^+$ T cells, with minimal expansion of T_{regs}, was observed across all schedules
- Based on the analysis of safety, PK, and PD, the 30 µg/kg dose (on days 1 and 8 Q3W) was determined to be the RP2D
- The new dosing regimen, a shift from 5 daily infusions (days 1-5) Q3W to 2 infusions (on days 1 and 8) Q3W, did not result in additional observed tolerability issues compared with previous studies of nemvaleukin

Background

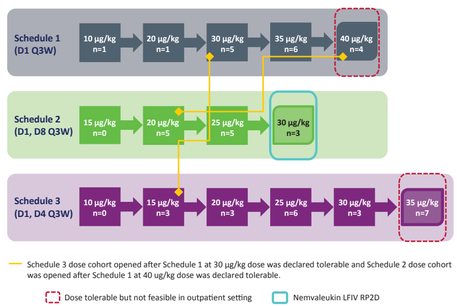
- Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine designed to selectively bind the intermediate-affinity interleukin-2 (IL-2) receptor and thus preferentially expand antitumor CD8$^+$ T and natural killer (NK) cells, with minimal effect on immunosuppressive regulatory T cells (T_{regs})[1]
- In the ARTISTRY-1 study, intravenous (IV) nemvaleukin once daily on days 1-5 (QD×5) in 21-day cycles showed antitumor activity across multiple tumor types as monotherapy at the recommended phase 2 dose (RP2D) of 6 µg/kg and in combination with pembrolizumab at doses of 3 and 6 µg/kg[2]
- Expansion of circulating CD8$^+$ T and NK cells was observed, with minimal effect on T_{regs}[2]
- The ARTISTRY-3 study aimed to identify a more flexible IV dosing schedule of nemvaleukin that will be more patient- and provider-friendly than the QD×5 regimen
- Quantitative systems pharmacology modeling was used to predict the dose levels with a less frequent IV dosing regimen needed to achieve an extent of CD8$^+$ and NK cell expansion comparable to that achieved with 6 µg/kg or 3 µg/kg QD×5 in a 21-day cycle[3]
- We report results from Cohort 2 of ARTISTRY-3 (NCT04592653), evaluating the safety and tolerability of less frequent IV dosing of nemvaleukin monotherapy in advanced solid tumors and the selection of RP2D

Methods

Study Design and Endpoints

- ARTISTRY-3 is an ongoing phase 1/2, open-label study
- Escalating doses of nemvaleukin were evaluated across 3 schedules in 21-day cycles as follows: Schedule 1: dosing on day 1, Schedule 2: dosing on days 1 and 8, and Schedule 3: dosing on days 1 and 4 (**Figure 1**)
- Dose escalation in Cohort 2 was based on Bayesian optimal interval (BOIN) design and on predefined safety parameters of dose-limiting toxicity (DLT) evaluated during the first cycle (21 days) by the safety review committee (SRC)
- Pharmacodynamic (PD) assessments included absolute counts and relative percentages of immune cells and their subtypes (T, B, NK, T_{reg}) analyzed in whole blood by flow cytometry at baseline and post treatment. Paired biopsies to assess modulation of immune cells were collected at baseline and on cycle 2 day 8
- The primary endpoint was incidence of DLTs; secondary endpoints included objective response rate, pharmacokinetics (PK), PD, and safety

Figure 1. ARTISTRY 3 Cohort 2 (Part A) study design followed BOIN design for dose escalation



D, day; LFIV, less frequent intravenous; Q3W, every 3 weeks.
BOIN design for dose escalation, with modifications to accommodate open enrollment.
The maximum sample size was 30 patients per schedule. For all schedules, additional higher dose levels could continue in increments of 5 µg/kg from the highest dose (if tolerable and PK/PD parameters were not saturated) for at least 1 to 2 dose levels.

Key Patient Eligibility Criteria

- Adult patients (≥18 years) with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and histologically/cytologically confirmed diagnosis of select malignant solid tumors having at least 1 qualifying target (per Response Evaluation Criteria In Solid Tumors version 1.1 [RECIST v1.1]) were included
- The following key exclusion criteria were applied: active infection within 3 days of first scheduled dose for cycle 1, active autoimmune disease(s) requiring systemic treatment within the past 2 years, primary central nervous system malignancy, or prior IL-2- or IL-15-based therapy

Results

Patient Characteristics

- As of April 21, 2024 (data cutoff), 52 patients have been treated: 17, 13, and 22 in Schedules 1, 2, and 3, respectively (**Table 1**)
- The median age was 60 years (range, 31-83), and 73% of patients had ECOG PS of 1
- The median number of prior lines of therapy was 4 (range, 1-14)

Table 1. Baseline characteristics

Characteristics	All schedules combined (N=52)
Age (years), median (range)	60 (31-83)
Female, n (%)	37 (71)
ECOG PS 1, n (%)	38 (73)
No. of prior therapies, median (range)	4 (1-14)
Patients with ≥3 prior lines of therapy, n (%)	36 (69)
Tumor type, n (%)	
Ovarian cancer	8 (15)
Pancreatic cancer	7 (13)
Mucosal melanoma	4 (8)
Cutaneous melanoma	4 (8)
Biliary tract tumor[a]	4 (8)
Cervical cancer	4 (8)
Epithelial tumor of the fallopian tube, peritoneum, or ovaries	4 (8)
Other[b]	17 (33)
Primary tumor present, n (%)	37 (71)
Stage IV disease, n (%)	43 (83)
Tumor Proportion Score (TPS), mean (SD)[c]	13 (24)
Mutation status, n (%)	
BRCA mutation present / absent[d]	0 (0) / 16 (31)
HRD deficient / proficient[e]	3 (6) / 2 (4)
BRAF^{V600} mutation present / absent[f]	2 (4) / 19 (37)
KIT mutation present / absent[g]	1 (2) / 16 (31)
NRAS mutation present / absent[h]	3 (6) / 13 (25)

HRD, homologous recombination deficiency; SD, standard deviation.
[a]Including intra- and extrahepatic cholangiocarcinoma, gall bladder, ampullary type. [b]Includes gastric and gastroesophageal junction adenocarcinoma, n=3; endometrial cancer, n=2; esophageal cancer (squamous and adeno cell type), n=2; metastatic or advanced breast cancer, n=2; triple-negative breast cancer, n=1; adenocarcinoma of the left ovary, n=1; borderline mucinous ovarian carcinoma, n=1; high-grade serous adenocarcinoma of the ovary, n=1; metastatic multifocal vulvar melanoma, n=1; nodular melanoma, n=1; vulvar melanoma, n=2. [c]Assessed in 8 patients. [d]Missing or unknown, n=36. [e]Missing, n=47. [f]Unknown, n=31. [g]Missing or unknown, n=35. [h]Unknown, n=36.

Exposure

- Overall median (range) duration of treatment exposure was 25 days (1-228)
- The median duration of exposure was 21 days (range, 1-154) for Schedule 1, 29 days (range, 1-187) for Schedule 2, and 41 days (range, 1-228) for Schedule 3
- At data cutoff, 49 (94%) patients had discontinued treatment; the primary reason for treatment discontinuation was progressive disease

Safety

- No DLTs were observed across dosing schedules
- All evaluated nemvaleukin doses were declared tolerable by the SRC
- Nemvaleukin doses at 40 µg/kg (Schedule 1) and 35 µg/kg (Schedule 3), although tolerable, were considered not feasible in outpatient settings due to delayed incidence of cytokine release syndrome events occurring after 4 to 6 hours
- The most common (≥25%) nemvaleukin-related TEAEs were infusion-related reaction, cytokine release syndrome, pyrexia, nausea, hypotension, and neutropenia (**Table 2**)
- 5 patients (10%) experienced nemvaleukin-related grade 3-4 events: anemia (Schedule 2) and neutropenia, lymphopenia, cytokine release syndrome, and decreased white blood cell count (all Schedule 3) (Table 2)
- No new safety signals were identified in review of higher doses of the less frequent IV dosing schedule
- No differences in safety profiles were observed across the 3 schedules, although sample sizes were small

Pharmacokinetics

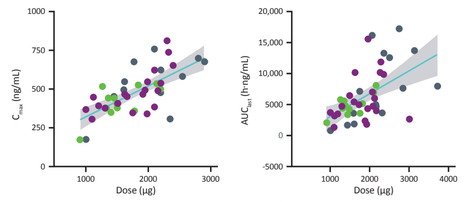
- Compartment model independent PK analysis on sparse data showed that maximum nemvaleukin serum concentration (C_{max}) was reached at the end of the 30-minute infusion and declined with time in a biphasic pattern
- Nemvaleukin exposure (C_{max} and area under the concentration-time curve from time zero to last quantifiable concentration [AUC_{last}]) increased with increasing dose; evidence of nonlinearity was not observed (**Figure 2**, **Table 3**)
- Exposures after repeated administrations were similar to those at the first dose; accumulation was not observed

Table 2. Safety summary

Adverse events, n (%)	Schedule 1 (n=17)	Schedule 2 (n=13)	Schedule 3 (n=22)
Any-grade nemvaleukin-related TEAEs	11 (65)	13 (100)	20 (91)
Nemvaleukin-related grade 3 or 4 TEAEs	0 (0)	1 (8)	4 (18)
Nemvaleukin-related serious TEAEs	0 (0)	1 (8)	1 (5)
Nemvaleukin-related TEAEs leading to treatment discontinuation	0 (0)	0 (0)	0 (0)
TEAEs regardless of causality (≥25%)			
Infusion-related reaction	3 (18)	5 (39)	5 (23)
Cytokine release syndrome	5 (29)	4 (31)	8 (36)
Fatigue	4 (24)	3 (23)	9 (41)
Nausea	6 (35)	3 (23)	6 (27)
Pyrexia	1 (6)	3 (23)	6 (27)
Vomiting	5 (29)	2 (15)	2 (9)
Hypotension	2 (12)	1 (8)	6 (27)
Neutropenia	1 (6)	0 (0)	6 (27)
Nemvaleukin-related TEAEs (≥25%)			
Infusion-related reaction	3 (18)	5 (38)	5 (23)
Cytokine release syndrome	5 (29)	4 (31)	8 (36)
Pyrexia	1 (6)	3 (23)	6 (27)
Nausea	5 (29)	2 (15)	5 (23)
Hypotension	2 (12)	1 (8)	6 (27)
Neutropenia	1 (6)	0 (0)	6 (27)
Nemvaleukin-related grade 3 or 4 TEAEs			
Anemia	0 (0)	1 (8)[a]	0 (0)
Neutropenia	0 (0)	0 (0)	3 (14)[b]
Lymphopenia	0 (0)	0 (0)	1 (5)[c]
Cytokine release syndrome	0 (0)	0 (0)	1 (5)[c]
White blood cell count decreased	0 (0)	0 (0)	1 (5)[d]

TEAE, treatment-emergent adverse event.
[a]One event at nemvaleukin 20 µg/kg. [b]One event each at nemvaleukin 25 µg/kg, 30 µg/kg, and 35 µg/kg. [c]One event at nemvaleukin 35 µg/kg. [d]One event at nemvaleukin 30 µg/kg.

Figure 2. Nemvaleukin exposure–dose relationship at cycle 1 day 1



C, cycle.
To determine nemvaleukin in serum (lower level of quantification 0.5 ng/mL), blood was collected at predetermined times. A model-independent PK analysis was performed with evaluable interim data from the ongoing study.

Table 3. Mean (SD) PK parameters at cycle 1 day 1, by schedule and dose group

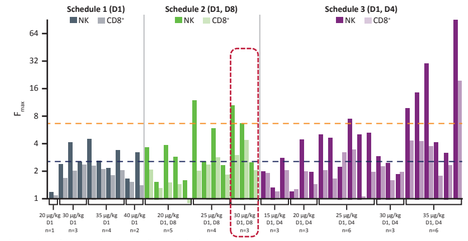
Schedule	Dose group µg/kg (n)	C_{max} ng/mL (SD)	T_{max}[a] h	C_{last} ng/mL (SD)	T_{last}[a] h	AUC_{last} h·ng/mL (SD)
1	10 (1)	175 (n/a)	0.5	33 (n/a)	8	704 (n/a)
1	20 (1)	547 (n/a)	0.6	111 (n/a)	8	1775 (n/a)
1	30 (5)	879 (583)	0.8	3 (2)	69	12,243 (6424)
1	35 (6)	697 (476)	0.6	17 (36)	71	5592 (4114)
1	40 (4)	1009 (538)	0.6	3 (1)	74	14,931 (5653)
2	20 (4)	357 (141)	0.8	1 (1)	71	3819 (1536)
2	25 (5)	419 (68)	0.6	1 (0)	70	4665 (636)
2	30 (3)	491 (48)	0.6	12 (19)	71	6032 (2445)
3	15 (3)	431 (33)	0.6	1 (0)	70	5511 (3913)
3	20 (3)	506 (265)	0.6	2 (1)	72	5961 (3560)
3	25 (6)	420 (113)	0.6	32 (48)	71	4351 (2239)
3	30 (3)	461 (77)	0.5	5 (6)	73	4578 (720)
3	35 (5)	620 (158)	0.6	55 (75)	70	7461 (5969)

C_{last}, last observed quantifiable concentration; n/a, not applicable; T_{last}, time of the last quantifiable concentration; T_{max}, time to C_{max}.
[a]Values are median. The entire concentration-time profile and estimation of the terminal log-linear decline phase (λ_z) could not be optimally captured. Therefore, subsequently planned PK parameters that require λ_z could not be computed.

Pharmacodynamics

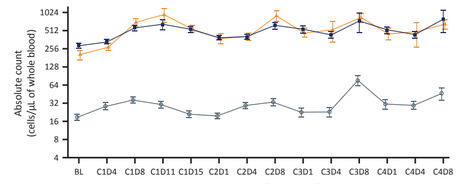
- Expansion of NK and CD8$^+$ T cells was observed at all less frequent IV dosing schedules of nemvaleukin, with the best expansion seen at 30 µg/kg dose at days 1 and 8 (**Figure 3**)
- T_{reg} expansion was minimal at all doses tested (**Figure 4**)

Figure 3. Maximum fold change in NK and CD8$^+$ T cells after nemvaleukin treatment



F_{max}, maximum fold change from baseline (beyond cycle 1).
Gold and blue dotted lines indicate maximum fold change in levels of NK and CD8+ T cells, respectively, observed with nemvaleukin IV QD×5 dosing in ARTISTRY-1.

Figure 4. Immune cell expansion after nemvaleukin treatment



BL, baseline; SE, standard error.
Values are mean ± SE. Data are combined from all patients across dosing schedules.

Recommended Phase 2 Dose

- After comprehensive review of all the safety, PK, PD, and efficacy parameters across all schedules and doses, the nemvaleukin 30 µg/kg day 1, day 8 dose was selected as the RP2D for less frequent IV dosing
- The 7-day window between 2 doses offers time for recovery and was considered more tolerable than the day 1, day 4 regimen
- Nemvaleukin 30 µg/kg day 1, day 8 will be evaluated in the open-label extension of the ARTISTRY-6 study that will evaluate the antitumor activity of nemvaleukin as monotherapy and in combination with pembrolizumab in patients with advanced cutaneous melanoma

Efficacy

- There were 46 patients in the efficacy-evaluable population
- In this heavily pretreated mixed-tumor phase 1 population, no objective responses were seen; 5 patients had stable disease for at least 3 months (with tumor types: cervical [n=3], epithelial [n=1], biliary [n=1])
- 2 patients remain on study treatment, with ongoing stable disease of 1.3 months and 5.6 months as of data cutoff
- 1 patient with stage IV vulvar melanoma (baseline target lesion of 66 mm) showed 9% reduction in target lesion at the end of cycle 2 following administration of only 1 dose of nemvaleukin 35 µg/kg
- 1 patient with metastatic breast cancer (*BRCA* WT, ER+, PR+, HER2-; baseline target lesion of 71.5 mm) showed 25% reduction in target lesion at the end of cycle 2 following administration of nemvaleukin 20 µg/kg (Schedule 3)

References

1. Lopes JE, et al. *J Immunother Cancer*. 2020;8(1):e000673.
2. Vaishampayan U, et al. *J Clin Oncol*. 2022;40(16_suppl). Abstract #2500.
3. Sun L, et al. Poster presented at the Quantitative Systems Pharmacology Conference; April 20-22, 2022; Leiden, Netherlands.

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