Assessment of Safety and Immunologic Activity of Nemvaleukin Alfa in Patients With Advanced Solid Tumors Treated With Less Frequent Intravenous Dosing (ARTISTRY-3)

Sarina A. Piha-Paul,[1] Justin A. Call,[2] Alexander I. Spira,[3] Aránzazu Manzano,[4] Emiliano Calvo,[5] Maria de Miguel,[5] Shwetha Asha,[6] Yangchun Du,[6] Clifford DiLea,[6] Bhaskar Rege,[6] Rita Dalal,[6] Sonali Panchabhai,[6] Nehal J. Lakhani[7]

[1]Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]START Mountain Region, West Valley City, UT; [3]NEXT Oncology Virginia, Fairfax, VA; [4]UTEC Hospital Clínico San Carlos, Madrid, Spain; [5]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain, [6]Alkermes, Inc., Waltham, MA; [7]START Midwest, Grand Rapids, MI

Abstract #744

INTRODUCTION

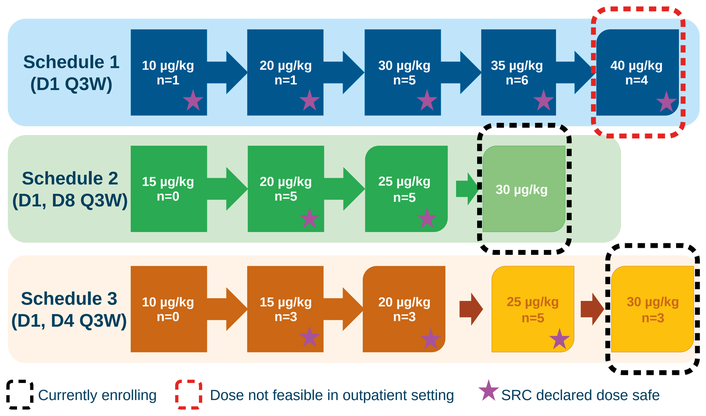
- Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine designed to selectively bind the intermediate-affinity interleukin-2 (IL-2) receptor and thus preferentially expand antitumor CD8$^+$ T and natural killer (NK) cells, with minimal effect on immunosuppressive regulatory T cells (T_{regs})[1]
- In the ARTISTRY-1 study, intravenous (IV) nemvaleukin 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]
- One goal of the ARTISTRY-3 study was to identify a more flexible IV dosing schedule of nemvaleukin that will be more patient- and provider-friendly with a benefit-risk profile similar to that of the QD×5 IV 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 of 6 µg/kg or 3 µg/kg QD×5 in a 21-day cycle[3]
- We report preliminary results from Cohort 2 of ARTISTRY-3 (NCT04592653), evaluating the safety and tolerability of less frequent IV dosing of nemvaleukin in advanced solid tumors

METHODS

Study Design and Endpoints

- ARTISTRY-3 is an ongoing phase 1/2, open-label study
- Escalating doses of nemvaleukin are being 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 methodology (BOIN) design, with modifications to accommodate open enrollment
- Dose escalation decisions were based on predefined safety parameters of dose-limiting toxicity (DLT) evaluated during the first cycle 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 in the first 2 cycles post treatment
- The primary endpoint is incidence of DLTs; secondary endpoints include efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and safety

FIGURE 1: ARTISTRY-3 Cohort 2 (Part A) study design using BOIN design for dose escalation



D, day; Q3W, every 3 weeks.
BOIN design for dose escalation, with modifications to accommodate open enrollment.
The maximum tolerated dose is determined using a Bayesian logistic regression after completion of dose escalation.
The maximum sample size is 30 patients per schedule. For all schedules, additional higher dose levels may continue in increments of 5 µg/kg from the highest dose (if tolerable) for at least 1 to 2 dose levels.

Key Patient Eligibility Criteria

- Adult patients (≥18 years) with an Eastern Cooperative Oncology Group performance status of 0 or 1 and histologically/cytologically confirmed diagnosis of select malignant solid tumors having at least 1 lesion that qualifies as a target lesion per Response Evaluation Criteria In Solid Tumors 1.1 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

Exposure

- 41 patients with solid tumors have been enrolled across dosing schedules
- As of April 21, 2023, the overall median duration of exposure across the 3 dosing schedules was 22.0 days (range, 1-154)

Safety

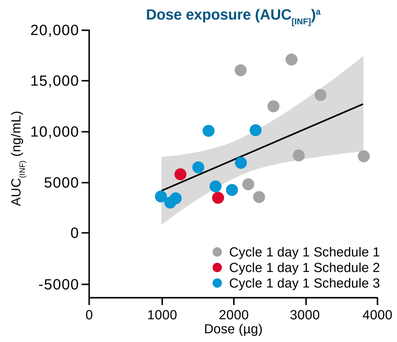
- All doses of IV nemvaleukin in schedule 1 were tolerable
- The 40 µg/kg dose, although tolerable, was considered not feasible in outpatient settings due to delayed cytokine release syndrome events
- The most common (≥20%) treatment-emergent adverse events were nausea, vomiting, abdominal pain, cytokine release syndrome, and fatigue
- No new safety signals were identified in review of higher doses of the less frequent IV dosing schedule
- No DLTs have been reported at this time

RESULTS (continued)

Pharmacokinetics

- Maximum serum concentrations of nemvaleukin were generally reached at the end of infusion and declined with time in a log-linear manner
- Nemvaleukin exposure (maximum plasma concentration [C_{max}] and area under the curve from time zero to infinity [$AUC_{(INF)}$]) increased with increasing dose; evidence of nonlinearity was not observed (Figure 2)

FIGURE 2: Nemvaleukin exposure-dose relationship for dosing Schedules 1, 2, and 3 and PK parameters



C1D1 Geometric mean PK parameters by schedule and dose group

Schedule	Dose group µg/kg	C_{max} (n) ng/mL	T_{max} [b] (n) h	C_{last} (n) ng/mL	T_{last} [b] (n) h	$T_{1/2}$ (n) h	AUC_{last} (n) h·ng/mL	$AUC_{(INF)}$ (n) h·ng/mL
1	30	769 (5)	0.8 (5)	2.6 (5)	69 (5)	8.5 (5)	10,849 (5)	10,896 (5)
1	35	601 (6)	0.6 (6)	6.4 (6)	70 (6)	10.0 (2)	3829 (6)	4152 (2)
1	40	850 (4)	1.4 (4)	2.5 (4)	74 (4)	10.2 (4)	13,830 (4)	13,875 (4)
2	20	430 (2)	0.6 (2)	1.1 (2)	70 (2)	9.4 (2)	4472 (2)	4488 (2)
3	15	402 (3)	1.0 (3)	1.2 (3)	70 (3)	10.5 (3)	4670 (3)	4691 (3)
3	20	466 (3)	0.6 (3)	1.5 (3)	72 (3)	9.9 (3)	5348 (3)	5369 (3)
3	25	394 (4)	2.0 (4)	3.8 (4)	71 (4)	9.0 (3)	4400 (4)	5900 (3)

AUC_{last}, AUC from dosing to last measured concentration; C_{last}, last observed quantifiable concentration; C, cycle; T_{last}, time to C_{last}; $T_{1/2}$, half-life; T_{max}, time to C_{max}.
Nemvaleukin (10-30 µg/kg) was administered by IV infusion in 30 minutes on day 1 (Schedule 1) or days 1 and 8 (Schedule 2) or days 1 and 4 (Schedule 3) of every 21-day 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. PK data presented include data available until August 8, 2023, for all schedules.
[a]Linear equation of the presented graph is Y = 3.63X + 914, adjusted R-sq = 0.209, n=22, *P*=0.0188.
[b]Median, n = number of patients in each group.

Pharmacodynamics

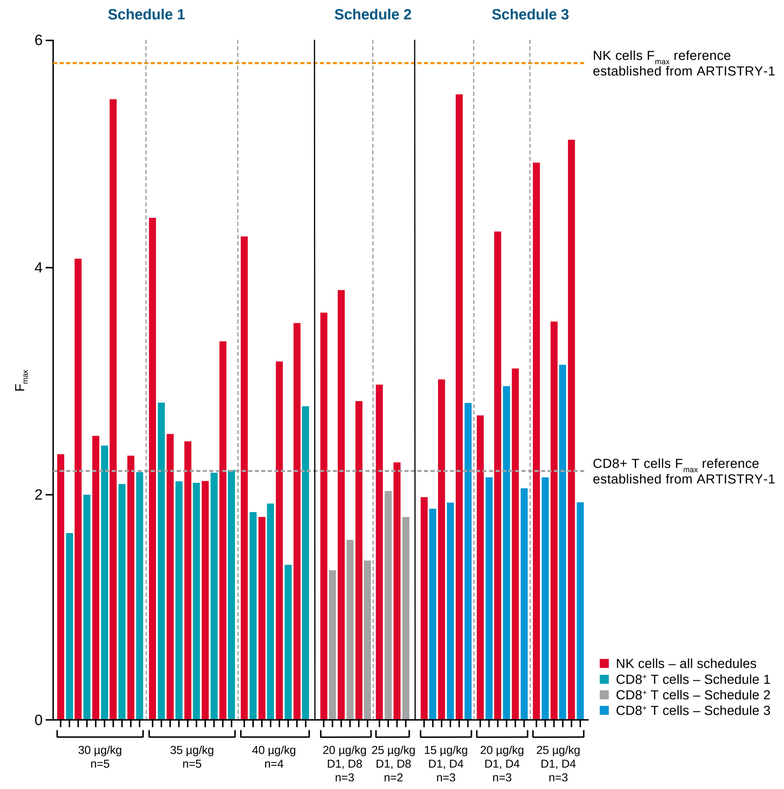
ARTISTRY-1: Reference Data

- In the monotherapy cohort (melanoma and renal cell carcinoma) of ARTISTRY-1 in which single-agent activity of nemvaleukin was demonstrated, the maximum fold change from baseline for NK and CD8$^+$ T cells was 5.8- and 2.2-fold, respectively. The time point for maximum expansion was observed at cycle 2 day 8 in the majority of patients (data not shown)

ARTISTRY-3: All Schedules Data

- Based on the reference values from ARTISTRY-1, the following PD metrices were considered for evaluating immune cell expansion in ARTISTRY-3:
  - NK cells: at least 3-fold maximum expansion from baseline (preferred in cycle 2 and beyond) and ratio of absolute counts at cycle 2 day 8/cycle 1 day 8 >1
  - CD8$^+$ T cells: at least 2-fold maximum expansion from baseline (preferred in cycle 2 and beyond) and ratio of absolute counts at cycle 2 day 8/cycle 1 day 8 >1
- Based on these metrices, expansion of NK and CD8$^+$ T cells was observed at all less frequent IV dosing schedules (Figure 3)
- Since 3 different dosing schedules with various tumor types are included, the time point for maximum fold change varied

FIGURE 3: Maximum fold change in NK and CD8$^+$ T cells



F_{max}, maximum fold change from baseline.
Orange and gray dotted lines indicate maximum fold change in levels of NK and CD8$^+$ T cells, respectively, observed with IV QD×5 dosing.

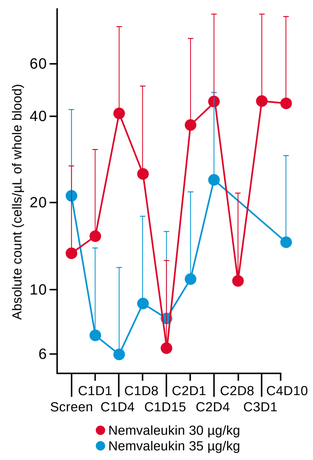
ARTISTRY-3: Schedule 1 RP2D

- Enrollment in Schedule 1 is complete. All 3 doses in this schedule were evaluated and the SRC agreed on 35 µg/kg as the RP2D for this schedule
  - The 35 µg/kg dosing resulted in more favorable expansion of both NK and CD8$^+$ T cells compared with 30 µg/kg dosing; T_{reg} expansion was minimal at both doses tested (Figure 4)
  - Additionally, analysis of proliferating cells (Ki67$^+$) and activation markers (CXCR3, ICOS, PD-1) for each immune cell type revealed higher proliferation with 35 µg/kg versus 30 µg/kg. The proportion of anergic dysfunctional NK cells was significantly lower with nemvaleukin 35 µg/kg versus 30 µg/kg at both baseline and on-treatment longitudinal assessments (data not shown)

FIGURE 4: Expansion of NK cells, CD8$^+$ T cells, and T_{regs} in Schedule 1

Patient	Schedule	Dose	Tumor type	NK cells Total cycles	NK cells Max FC	NK cells Max TP	NK cells C2D8/C1D8	CD8$^+$ T cells Max FC	CD8$^+$ T cells Max TP	CD8$^+$ T cells C2D8/C1D8
1	1	30 µg/kg	Cutaneous melanoma	2	2.34	C2D4		1.65	C2D4	
2	1	30 µg/kg	Ovarian cancer	8	4.07	C2D4		1.98	C8D1	
3	1	30 µg/kg	Mucosal melanoma	2	2.50	C2D4	0.85	2.42	C1D8	0.93
4	1	30 µg/kg	Esophageal cancer	1	2.19	C1D4		2.08	C1D4	
5	1	30 µg/kg	Ovarian cancer	1	2.33	C1D8		2.19	C1D8	
Patient	Schedule	Dose	Tumor type	Total cycles	Max FC	Max TP	C2D8/C1D8	Max FC	Max TP	C2D8/C1D8
1	1	35 µg/kg	Endometrial cancer	2	4.43	C2D8	1.39	2.80	C1D8	0.66
2	1	35 µg/kg	Ovarian cancer	2	2.52	C2D4		2.10	C2D4	
3	1	35 µg/kg	Pancreatic cancer	1	2.46	C1D15		2.09	C1D8	
4	1	35 µg/kg	Mucosal melanoma	4	2.10	C2D4		2.18	C1D15	
5	1	35 µg/kg	Ovarian cancer	2	3.34	C2D4		2.22	C1D4	
Patient	Schedule	Dose	Tumor type	Total cycles	Max FC	Max TP	C2D8/C1D8	Max FC	Max TP	C2D8/C1D8
1	1	40 µg/kg	Pancreatic cancer	1	4.27	C1D8		1.83	C1D8	
2	1	40 µg/kg	Ovarian cancer	2	1.79	C1D15		1.91	C1D8	
3	1	40 µg/kg	Endometrial cancer	2	3.16	C2D4		1.37	C2D1	
4	1	40 µg/kg	Gastric adenocarcinoma	1	3.50	C1D15		2.77	C1D15	

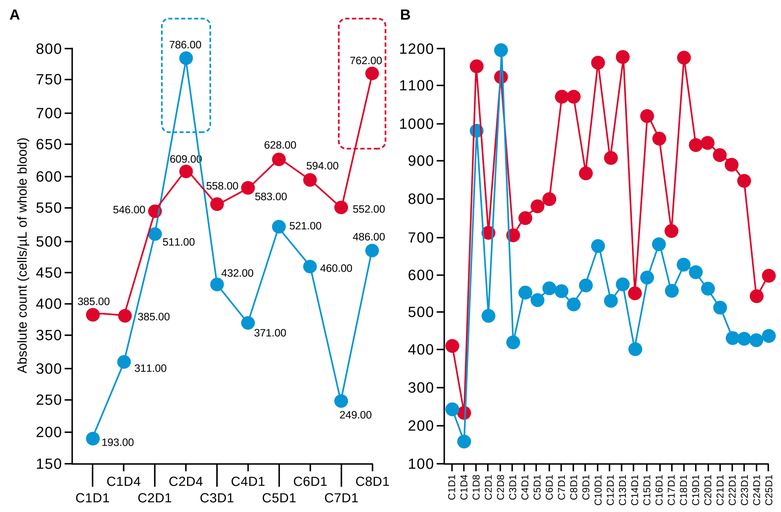
FC, fold change; TP, time point.



Efficacy Outcomes

- In Schedule 1, a heavily pretreated patient with ovarian cancer receiving nemvaleukin at 30 µg/kg was reported to have stable disease for 8 cycles
- Real-time cell expansion analysis showed maximum expansion of NK cells occurring in cycle 2 day 4 and sustained expansion of CD8$^+$ T cells in later cycles (Figure 5A)
- A similar profile of NK and CD8$^+$ T cell expansion was seen in responders (best overall response: partial response) from ARTISTRY-1 (Figure 5B). This correlation of response and immune cell expansion serves as proof of concept for the clinical activity of less frequent IV dosing (only once per 21 days) compared with QD×5 per 21 days dosing

FIGURE 5: Expansion of NK cells and CD8$^+$ T cells in a patient with stable disease over 8 cycles



CONCLUSIONS

Limitations

- The trial is ongoing, and data are based on results available at the time of data cutoff

Conclusions

- Nemvaleukin was tolerable at all doses tested in the less frequent IV dosing schedules, and the safety profile of IV nemvaleukin in Schedule 1 was consistent with its known mechanism of action and as expected in patients with relapsed/refractory solid tumors
- Preliminary analyses demonstrated immunologic activity with all 3 less frequent IV dosing schedules of nemvaleukin
- Expansion of NK cells and CD8$^+$ T cells, with minimal expansion of T_{regs}, was observed
- Based on the analysis of safety, PK, PD, and efficacy data, the 35 µg/kg dose was determined to be the RP2D for Schedule 1
- Dose escalation in Schedules 2 and 3 is ongoing, and the RP2D will be assessed after completion

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, The Netherlands.

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