Clinical Development of Nemvaleukin Alfa (ALKS 4230) for Advanced Solid Tumors With High Unmet Need: From Design to Bench to Bedside

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INTRODUCTION

The interleukin-2 receptor pathway is a validated immuno-oncology target.

- Interleukin-2 (IL-2) has both immunosuppressive and immunostimulatory functions, mediated by its interaction with different IL-2 receptor (IL-2R) complexes (Figure 1).
  - The IL-2R α, β, and γ domains comprise the high-affinity IL-2R complex, which is expressed on vascular endothelial cells and immune suppressive regulatory T cells (T_{regs}).
  - Absence of the extracellular α domain decreases the affinity of IL-2; this intermediate-affinity IL-2R is expressed on memory $CD8^+$ T cells and natural killer (NK) cells and required for antitumor immune responses.
- Beneficial antitumor effects of IL-2 therapy require high concentrations and doses of IL-2 to activate the intermediate-affinity receptor. However, high-dose IL-2 also has a potent interaction with the high-affinity IL-2R, which is associated with immunosuppression and acute toxicities.
- A molecule that selectively binds to the intermediate-affinity IL-2R may overcome the limitations of high-dose IL-2 therapy and has the potential to work in concert with a variety of therapeutic approaches, including those that induce immunogenic cell death.
- We describe the development of nemvaleukin alfa (nemvaleukin, ALKS 4230), a novel cytokine that selectively binds the intermediate-affinity IL-2R (Figure 2).[1]

Figure 1: IL-2 Receptors

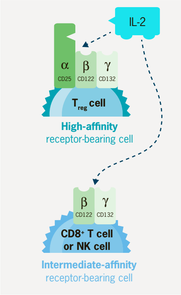
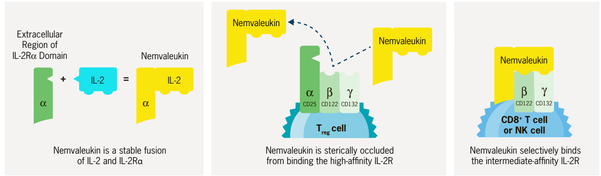


Figure 2: Rationale for Nemvaleukin Design

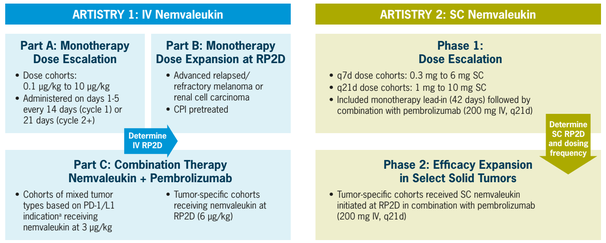


METHODS

Nemvaleukin was engineered using native IL-2 and IL-2Rα sequences to create a fusion protein sterically occluded from binding to the high-affinity IL-2R.

- Pharmacokinetic/pharmacodynamic properties of nemvaleukin were characterized in preclinical studies to confirm receptor selectivity, potency, and antitumor activity as monotherapy and in combination with oncology standards of care, and to inform dose selection for first-in-human studies.
- ARTISTRY-1 (NCT02799095) and ARTISTRY-2 (NCT03861793) were designed to determine the recommended phase 2 dose (RP2D) and maximum tolerated dose (MTD) of intravenous (IV) and subcutaneous (SC) nemvaleukin, respectively, and to characterize safety and efficacy of nemvaleukin monotherapy and in combination with the PD-1 inhibitor pembrolizumab in patients with advanced solid tumors (Figure 3).
  - Clinical data are reported as of March 2021.

Figure 3: ARTISTRY-1 and ARTISTRY-2 Study Designs



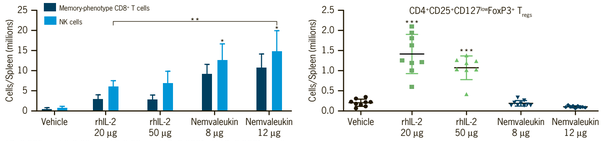
[a]PD-1/L1 indication based on approval status in US FDA label and may have changed over time.
CPI, checkpoint inhibitor; q21d, every 21 days.

RESULTS

Nemvaleukin is a stable fusion protein that is inherently active and does not require metabolic/proteolytic conversion or degrade into native IL-2.[1]

- In preclinical studies, nemvaleukin selectively binds the intermediate-affinity IL-2R and does not bind the high-affinity IL-2R.[1]
- By design, this selectivity results in preferential activation and expansion of antitumor $CD8^+$ T cells and NK cells, with minimal expansion of T_{regs}, as observed preclinically versus recombinant human IL-2 (rhIL-2) (Figure 4)[1] and confirmed clinically in ARTISTRY-1 (Figure 5A)[2] and ARTISTRY-2 (Figure 5B,C).[3]
  - Nemvaleukin monotherapy (6 μg/kg IV) increased $CD8^+$ T cells and granzyme B signal, with no change in the number of T_{regs} in the tumor microenvironment as indicated from multiplexed immunofluorescence analysis of paired biopsies taken from a melanoma patient.[4]
  - In tumor cell models, combinations of the nemvaleukin murine ortholog (m-nemvaleukin) with CPIs (anti-PD-1 or anti-CTLA-4),[5] multi-tyrosine kinase inhibitors ([TKIs] lucitanib),[6] or chemotherapy[7] enhanced survival compared with either agent alone (Figure 6).

Figure 4: Selective Expansion of NK and $CD8^+$ T Cells With Nemvaleukin Versus rhIL-2 in Preclinical Studies



*P<0.005 vs rhIL-2 20 μg, rhIL-2 50 μg. **P<0.0001. ***P<0.0001 vs all.
C57BL/6 mice were dosed SC daily for 5 days with: vehicle, rhIL-2 at 20 μg or 50 μg, or nemvaleukin at 8 μg or 12 μg (n = 12/group). Spleens from the mice were harvested on day 6, and lymphocyte populations were analyzed by flow cytometry.

Figure 5: Expansion of NK and $CD8^+$ T Cells With IV Nemvaleukin and SC Nemvaleukin in Clinical Trials

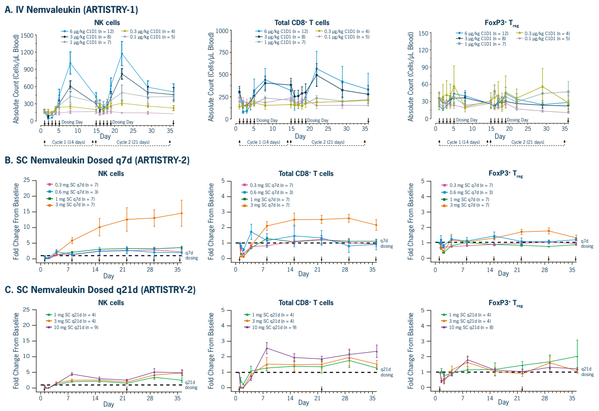
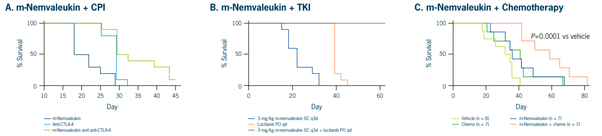


Figure 6: Antitumor Activity Observed Preclinically With Different m-Nemvaleukin Combinations



A. EMT-6 mammary carcinoma cells (5×10^6) were injected SC into female Balb/c mice (n = 9/group) on day 1. m-Nemvaleukin (16 μg) was administered SC on days 4-8 and 11-15 and anti-CTLA-4 was administered intraperitonially on day 4 (100 μg), and on days 7 and 10 (50 μg).[5] **B.** MC38 cells (5×10^5) were injected SC into C57BL/6 mice (n = 10/group) on day 1. Lucitanib was dosed qd on days 1-28 and m-nemvaleukin dosed on days 1, 4, 7, 10, 13, 16, and 19.[6] **C.** *Rb1*$^{-/-}$ *p53*$^{-/-}$ *p130*$^{-/-}$ SCLC cell lines derived from genetically engineered mouse models were orthotopically injected into mice (n = 7/group) and treated with m-nemvaleukin (6 mg/kg) SC q4d alone or with cisplatin (5 mg/kg) q1w + etoposide (10 mg/kg tiw).[7]
q1w, once weekly; qd, once daily; SCLC, small-cell lung cancer; tiw, 3 times a week.

Table 1: Safety Summary for IV Nemvaleukin Monotherapy and in Combination With Pembrolizumab (ARTISTRY-1)

Event, n (%)[a]	IV Nemvaleukin Part B (n = 62)[b]	IV Nemvaleukin + Pembrolizumab Part C (n = 128[c])
AE summary		
Any AE, regardless of causality	60 (96.8)	122 (95.3)
Grade 1-2 nemvaleukin-related AEs	59 (95.2)	113 (88.3)
Grade ≥3 nemvaleukin-related AEs	39 (62.9)	60 (46.9)
AEs leading to discontinuation[d]	3 (4.8)	10 (7.8)
AEs leading to death[e]	1 (1.6)	3 (2.3)
AEs, regardless of causality, in ≥30% of patients overall in either part of the study		
Pyrexia	37 (59.7)	73 (57.0)
Chills	30 (48.4)	79 (61.7)
Nausea	24 (38.7)	52 (40.6)
Hypotension	20 (32.3)	33 (25.8)
Fatigue	13 (21.0)	49 (38.3)
Grade ≥3 nemvaleukin-related AEs in ≥5% of patients overall in either part of the study		
Neutropenia	17 (27.4)	6 (4.7)
Neutrophil count decreased	5 (8.1)	13 (10.2)
Alanine aminotransferase increased	4 (6.5)	5 (3.9)
Anemia	4 (6.5)	15 (11.7)
Lymphocyte count decreased	1 (1.6)	10 (7.8)
Fatigue	1 (1.6)	7 (5.5)

[a]Data (as of March 19, 2021) are from an ongoing trial and are not yet final. [b]For Part B, first cycle is 14 days. [c]Includes patients who received pembrolizumab 200 mg in combination with nemvaleukin at doses of 1 μg/kg (n = 3; safety-run in), 3 μg/kg (n = 103), and 6 μg/kg (n = 22). [d]AEs leading to discontinuation that were assessed by the investigator to be related to study drug treatment include 1 case each of bronchospasm and failure to thrive in Part B and fatigue, inanition, infusion-related reaction, and pneumonitis in Part C. [e]Includes 3 deaths considered unrelated to study drug treatment: COVID-19 (Part B), acute cardiac arrest (Part C), and worsening of cancer (Part C), and 1 death due to inanition in a pancreatic cancer patient assessed by the investigator as related to nemvaleukin.

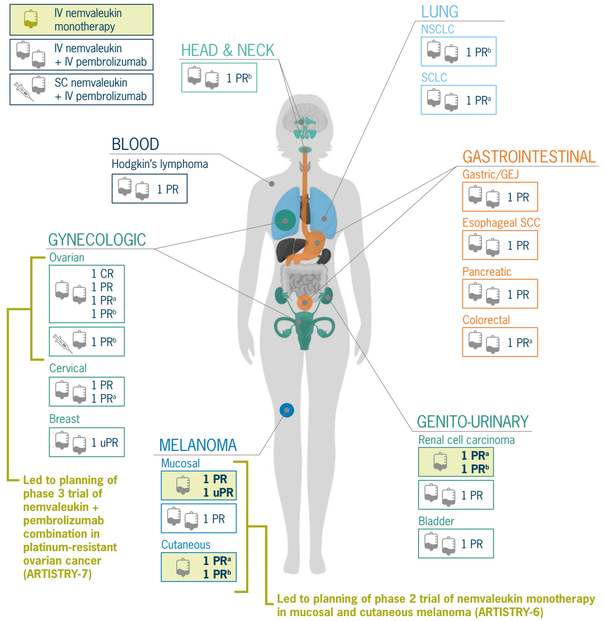
Nemvaleukin was generally well tolerated in clinical trials.

- With IV administration in ARTISTRY-1, nemvaleukin was generally well tolerated when used as monotherapy or in combination with pembrolizumab (Table 1).[8]
  - Treatment-related adverse events (AEs) have been mostly transient and manageable.
  - Neutropenia/neutrophil count decreased were the most frequently reported grade ≥3 events (Table 1) and were transient and asymptomatic.
  - The MTD has not been reached during dose escalation (Part A).[8]
- The emerging safety profile for SC nemvaleukin in phase 1 of ARTISTRY-2 was consistent with that reported for IV nemvaleukin, with no new or unanticipated safety findings observed.[9]
  - Over all doses (N = 57), most common AEs, regardless of causality, occurring in ≥30% of patients were pyrexia (50.9%), fatigue (45.6%), chills (42.1%), injection site erythema (40.4%), nausea (38.6%), and vomiting (33.3%).
  - Grade 3 or 4 nemvaleukin-related AEs occurring in ≥2 patients were lymphopenia (22.8%) and neutropenia (3.5%); no nemvaleukin-related AEs led to discontinuation or death.
  - No additive toxicity was observed with the addition of pembrolizumab to the treatment regimen.
  - The MTD was declared at 6 mg q7d and 10 mg q21d.[9]

Deep and Durable Responses With Nemvaleukin Monotherapy and in Combination With Pembrolizumab

- Based on findings from the dose escalation parts of ARTISTRY-1 and ARTISTRY-2, an RP2D of 6 μg/kg (on days 1-5 of each cycle) was declared for IV nemvaleukin[2] and 3 mg q7d for SC nemvaleukin.[9]
- In ARTISTRY-1, 30 patients with melanoma and 20 with renal cell carcinoma receiving IV nemvaleukin monotherapy at the RP2D and an additional 100 patients with various advanced solid tumors (14 ovarian) receiving combination therapy with pembrolizumab had evaluable scans at the time of the March data cut.[8]
  - Deep and durable responses were observed across multiple tumor types (Figure 7).
  - Following the March data cut, 14 additional melanoma patients have been added to the Part B cohort; data are still maturing.[10]
- ARTISTRY-2 data for patients with advanced solid tumors receiving SC nemvaleukin at RP2D in phase 2 are still maturing.[9]
  - 1 partial response ([PR], confirmed after the data cut) in a patient with high-grade serous platinum-resistant ovarian cancer has been observed, with a 47% reduction in size of total target lesions.

Figure 7: Summary of Individual Responses With Nemvaleukin Monotherapy and in Combination With Pembrolizumab in ARTISTRY-1 and ARTISTRY-2



[a]Awaiting confirmation. [b]Confirmed after the March data cut date.
CR, complete response; GEJ, gastroesophageal junction; NSCLC, non-small-cell lung cancer; SCC, squamous cell carcinoma; uPR unconfirmed PR.

CONCLUSIONS

- Emerging clinical data from ARTISTRY-1 and ARTISTRY-2 validate the design features of nemvaleukin.
- Deep and durable responses were observed with nemvaleukin monotherapy and in combination with pembrolizumab in multiple tumor types, including in areas of high unmet need such as in platinum-resistant ovarian cancer and mucosal melanoma and in the post-CPI setting.
- The observed safety profile of IV and SC nemvaleukin to date is consistent with that anticipated from the design of nemvaleukin.
- These data have led to Orphan Drug and Fast Track designations granted to nemvaleukin for the treatment of mucosal melanoma by the United States FDA and the initiation and planning of the ARTISTRY-6 (nemvaleukin monotherapy in advanced melanoma; NCT04830124) and ARTISTRY-7 (nemvaleukin + pembrolizumab in platinum-resistant ovarian cancer) studies.
- Ongoing preclinical investigations are exploring the synergistic advantages of nemvaleukin in various combinations—including with growth factor pathway inhibitors, chemotherapy, and radiation—to support future nemvaleukin clinical development plans.

REFERENCES, ACKNOWLEDGMENTS, DISCLOSURES

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Acknowledgments

The authors would like to thank all patients who are participating in these studies and their families. The study is sponsored by Alkermes, Inc. Medical writing and editorial support was provided by Parexel International, and funded by Alkermes, Inc.

Disclosures

HCL, JEL, LS, YW, YD, JRG, and JR are employees of Alkermes, Inc. IB was an employee of Alkermes, Inc. at the time of data collections.

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