ARTISTRY-3: Effect of Nemvaleukin Alfa With a Less Frequent IV Dosing Schedule as Monotherapy and in Combination With Pembrolizumab and Impact on the Tumor Microenvironment in Patients With Advanced Solid Tumors

Poster # TPS2684

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INTRODUCTION

Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel engineered cytokine

- Nemvaleukin is an engineered cytokine designed to selectively bind to the intermediate-affinity interleukin-2 receptor (IL-2R) for preferential activation and expansion of tumor-killing CD8+ T cells and natural killer (NK) cells, with minimal expansion of regulatory T cells (T_{regs}) (Figure 1)[1]
- Nemvaleukin is designed to leverage antitumor effects of the IL-2 pathway while mitigating potential toxicity that would limit its use[1]

Nemvaleukin showed activity of interest in the ARTISTRY-1 trial

- In ARTISTRY-1, the recommended phase 2 dose (RP2D) for nemvaleukin monotherapy of 6 µg/kg intravenously (IV) on days 1 to 5 of a 21-day cycle elicited durable and deep responses in patients with advanced melanoma and renal cell carcinoma[2]
- Responses with nemvaleukin plus pembrolizumab were also observed in multiple tumor types, including cervical, gastrointestinal, genitourinary, and platinum-resistant ovarian cancers[2]
- Nemvaleukin was generally well tolerated and did not show any additive toxicity to that already established with pembrolizumab alone[2]

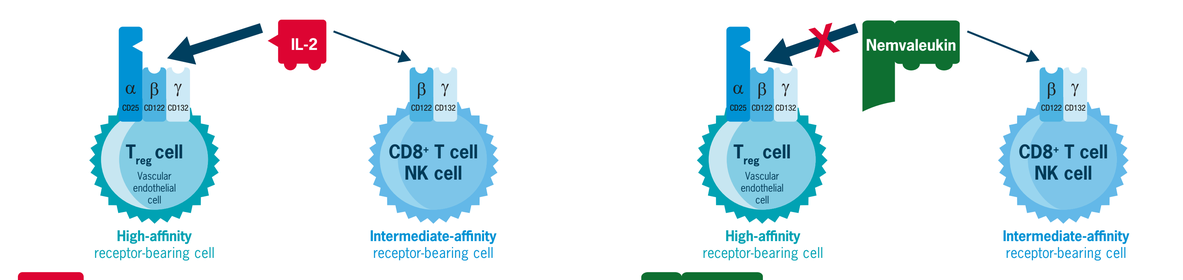
Cohort 1 of ARTISTRY-3: effect of nemvaleukin on the tumor microenvironment (TME)

- The TME plays an important role in tumor responses to immunotherapy; Cohort 1 of ARTISTRY-3 is evaluating treatment-emergent changes in the TME and peripheral blood immunophenotypes after treatment with nemvaleukin monotherapy and in combination with pembrolizumab
- Cohort 1 enrollment is on pause to initiate Cohort 2 enrollment and will resume when a less frequent IV RP2D has been established

Cohort 2 of ARTISTRY-3: less frequent IV dosing for nemvaleukin

- The current dosing schedule for nemvaleukin (6 µg/kg IV on days 1-5 of a 21-day cycle) has shown efficacy for both monotherapy and combination therapy
- A less frequent dosing schedule will provide flexibility in scheduling for patients, caregivers, and clinics and potentially minimize risks and visits to medical facilities
- Cohort 2 of ARTISTRY-3 (added as a protocol amendment) will evaluate the safety and tolerability of higher doses of nemvaleukin administered at a less frequent dosing schedule of 1 or 2 doses per cycle

Figure 1: Cell activation by IL-2 and nemvaleukin



IL-2

- Potently activates the high-affinity IL-2R, which is preferentially expressed on immunosuppressive T_{regs} and vascular endothelial cells
- Preferential binding of high-affinity IL-2R by high-dose IL-2 leads to expansion of T_{regs}, which may counteract antitumor activity as well as stimulate vascular endothelial cells
- Activation of vascular endothelial cells is associated with high incidence of acute toxicities, including capillary leak syndrome

Nemvaleukin

- Stable fusion protein designed to harness the validated IL-2 pathway biology
- Intrinsically active immediately upon systemic entry; does not degrade into native IL-2
- Designed to selectively bind the intermediate-affinity IL-2R to:
  - Preferentially activate memory cytotoxic CD8+ T cells and NK cells without expanding CD4+ T_{regs}
  - Mitigate toxicities associated with preferential binding of IL-2 to high-affinity IL-2R
- Leads to increases in both peripheral and intratumoral immune effector cells

ARTISTRY-3 STUDY DESIGN

Methodology and cohorts

- ARTISTRY-3 (NCT04592653) is a phase 1/2, open-label study with 2 cohorts
- Key eligibility criteria for both cohorts are presented in Table 1

TABLE 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
Age ≥18 years	Currently pregnant or breastfeeding, or planning to become pregnant during study period
Histologically/cytologically confirmed diagnosis of select malignant solid tumor	An active infection or fever ≥38.5°C within 3 days of the first scheduled dose for cycle 1
≥1 accessible lesion for biopsy; ≥1 lesion that qualifies as a target lesion based on RECIST v1.1	Active autoimmune disease(s) requiring systemic treatment within the past 2 years or a history of clinically severe autoimmune disease (replacement therapy not excluded)
ECOG PS of 0 or 1; estimated life expectancy ≥3 months	Known hypersensitivity to any components of nemvaleukin or pembrolizumab
Adequate hematologic reserve and adequate hepatic and renal function	Requirement for pharmacologic doses of systemic corticosteroids (>10 mg prednisone daily or equivalent)
1-3 prior FDA-approved targeted therapies	Primary CNS malignancy
Cohort 1: cutaneous melanoma, RCC, TNBC, MSS colorectal cancer, MSI-H solid tumors, or ovarian cancer	Prior IL-2–based or IL-15–based protein therapy at any time
Cohort 2: tumor types with previous demonstrated clinical activity with nemvaleukin (with or without pembrolizumab)[a]	Unstable medical condition

[a]Tumor types eligible for Cohort 2 include epithelial tumor of the fallopian tube, peritoneum, or ovaries, cervical cancer, endometrial cancer, non-small-cell lung adenocarcinoma, small-cell lung cancer, gastric and gastroesophageal junction adenocarcinoma, esophageal cancer (squamous and adeno cell type), pancreatic cancer, biliary tract tumor (including intra- and extrahepatic cholangiocarcinoma, gall bladder, ampullary type), cutaneous melanoma, mucosal melanoma, head and neck squamous cell carcinoma, or metastatic or advanced breast cancer.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology group performance status; FDA, US Food and Drug Administration; MSI-H, microsatellite instability–high; MSS, microsatellite stable; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria In Solid Tumors; TNBC, triple-negative breast cancer.

ARTISTRY-3 STUDY DESIGN (CONT)

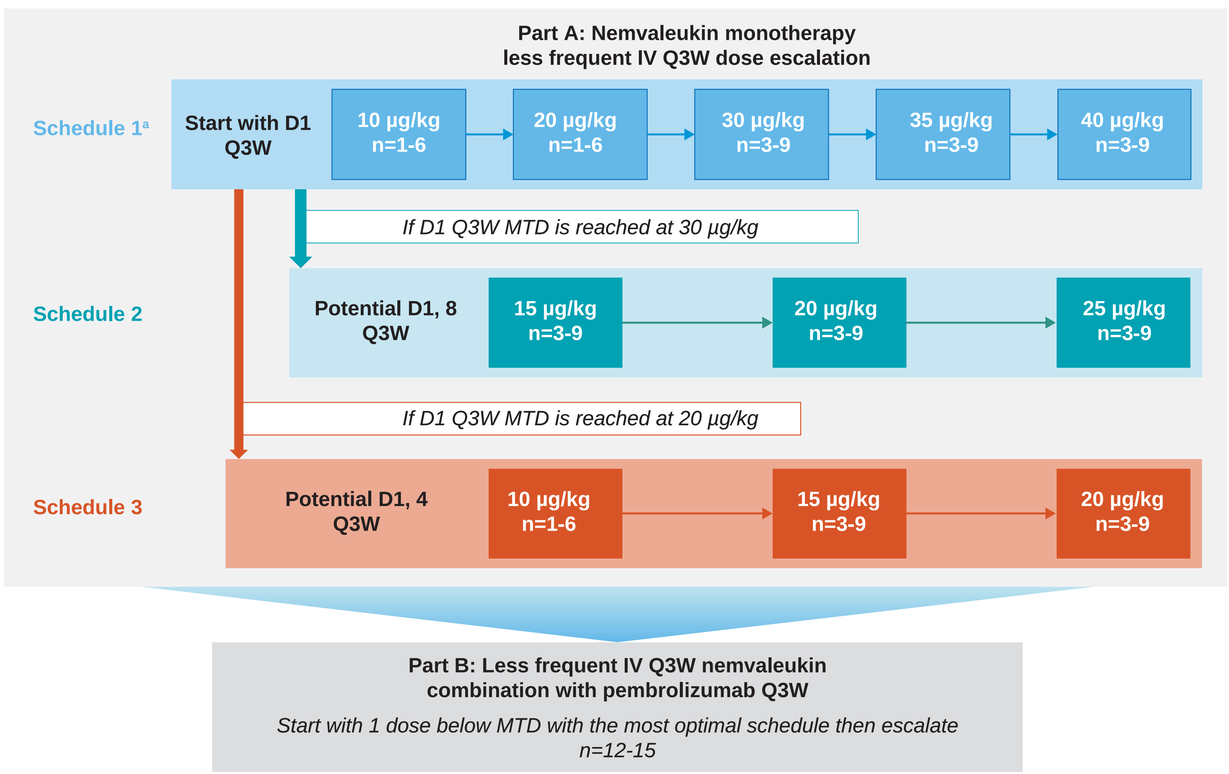
Cohort 1

- For Cohort 1, 2 cycles of nemvaleukin were administered during a 5-week monotherapy lead-in period, followed by treatment with nemvaleukin in combination with pembrolizumab. The focus of this cohort is to understand the effect of nemvaleukin on changes in the TME
- Cohort 1 enrollment is on pause to initiate Cohort 2 enrollment and will resume when a less frequent IV RP2D has been established; when Cohort 1 enrollment is resumed, patients will receive lead-in monotherapy at a dose selected based on results from Cohort 2
- Tumor biopsies are being collected pretreatment (within 21 days before start of treatment), during nemvaleukin monotherapy treatment (cycle 2), and, optionally, during combination treatment

Cohort 2

- Nemvaleukin will be administered at various doses and schedules to identify a safe and tolerable less frequent dosing schedule for nemvaleukin monotherapy (Part A) and for combination therapy with pembrolizumab (Part B, Figure 2)
- A quantitative system pharmacology model was applied to identify a less frequent schedule for nemvaleukin dosing
- Cohort 2 will assess safety and tolerability of nemvaleukin in an escalating fashion at 1 dose per 21-day cycle and 2 doses per 21-day cycle to achieve optimal pharmacokinetic/pharmacodynamic parameters
- The Bayesian optimal interval methodology design with modifications to accommodate open enrollment will be applied to facilitate dose escalation decisions

Figure 2: Cohort 2 study design



[a]Schedule 1 accommodates de-escalating to half doses of 15 or 25 µg/kg if the dose-limiting toxicity (DLT) criteria are met for a dose above either of these respective doses, and de-escalation is recommended.
D, day; MTD, maximum tolerated dose; Q3W, every 3 weeks.

Primary objectives and endpoints

- Cohort 1: effects of nemvaleukin monotherapy on the TME evaluated as changes in density (cell counts per mm^2) and/or ratios of immune cells based on immunohistochemistry and/or immunofluorescence analysis in the TME between pretreatment and on-treatment paired tumor biopsies
- Cohort 2: RP2D of a less frequent IV dosing schedule of nemvaleukin monotherapy and MTD of nemvaleukin and pembrolizumab combination therapy; primary endpoint is incidence of DLTs from the first dose through the end of the DLT observation period

Secondary/exploratory objectives

- Clinical antitumor activity: overall response rate, duration of response, progression-free survival, overall survival
- Safety of nemvaleukin monotherapy and in combination with pembrolizumab
- Clinical pharmacokinetics and immunogenicity of nemvaleukin monotherapy
- Correlative biomarkers of nemvaleukin monotherapy and in combination with pembrolizumab
- Cohort 1: effects of nemvaleukin plus pembrolizumab on the TME

REFERENCES AND ACKNOWLEDGMENTS

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