ARTISTRY-6: Nemvaleukin Alfa Monotherapy in Patients With Advanced Mucosal and Cutaneous Melanoma

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BACKGROUND

Nemvaleukin Alfa (Nemvaleukin, ALKS 4230) Is a Novel, Engineered Cytokine

- Designed to selectively bind the intermediate-affinity interleukin-2 receptor (IL-2R) to preferentially activate CD8+ T and natural killer (NK) cells with minimal expansion of regulatory T cells (T_{regs}) (Figure 1).[1]
- Nemvaleukin has been granted orphan drug designation and fast track designation for the treatment of mucosal melanoma by the United States FDA.
- In the ongoing ARTISTRY-1 study (NCT02799095), intravenous (IV) nemvaleukin monotherapy at the recommended phase 2 dose (RP2D) of 6 µg/kg demonstrated durable antitumor activity in patients with advanced melanoma, including mucosal melanoma, previously treated with a checkpoint inhibitor (CPI).[2]
  - Among the 44 patients with evaluable scans, decreases in tumor burden of up to 46% have been observed with nemvaleukin monotherapy (Figure 2).
  - Additional responses with nemvaleukin monotherapy have been achieved in patients with advanced renal cell carcinoma previously treated with a CPI.[2]
- In the ongoing ARTISTRY-2 study (NCT03861793), subcutaneous (SC) nemvaleukin at the RP2D of 3 mg every 7 days (q7d) demonstrated pharmacodynamic effects consistent with those of IV nemvaleukin.[3]
- IV and SC nemvaleukin were generally well tolerated, with largely similar safety profiles consistent with its mechanism of action.

Advanced Cutaneous and Mucosal Melanoma Represent Tumor Types With Vast Unmet Needs

- Despite improved outcomes for melanoma patients with the introduction of CPIs, ~50% of patients do not respond to monotherapy and ~40% do not respond to combinations.
  - A subset of responders ultimately progress and have limited treatment options, underscoring a high unmet need for novel treatments with durable benefit.
- Patients with mucosal melanoma exhibit response rates and progression-free survival times ~2 times lower than those with cutaneous melanoma.

References, Acknowledgments, Disclosure

References

1. Lopes JE, et al. *J Immunother Cancer.* 2020;8(1):e000673.
2. Boni V, et al. *J Clin Oncol.* 2021;39(Suppl 15):abstr 2513.
3. Hamid O, et al. *J Clin Oncol.* 2021;39(Suppl 15):abstr 2552.
4. Tomczak P, et al. Poster presented at World Congress of Melanoma, 2021.

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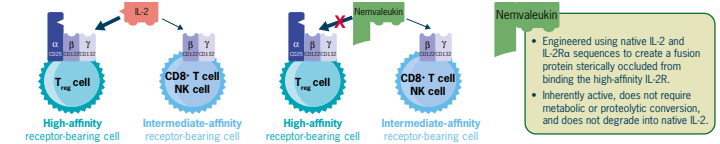
Disclosures

RC has consulted for BMS, Castle Biosciences, Compugen, Foundation Medicine, Immunocore, I-Mab, Incyte, Merck, Roche/Genentech, PureTech Health, Sanofi Genzyme, and Sorrento Therapeutics; served on advisory boards for Aura Biosciences, Chimeron, and Rgenix; and received research funding from Amgen, Astellas, AstraZeneca, Bayer, Bellicum, BMS, Corvus, Eli Lilly, Immunocore, Incyte, Macrogenics, Merck, Mirati, Novartis, Pfizer, Plexxikon, Roche/Genentech.

ARTISTRY

Alkermes Patient Inspired

Figure 1. Cell Activation by IL-2 and Nemvaleukin



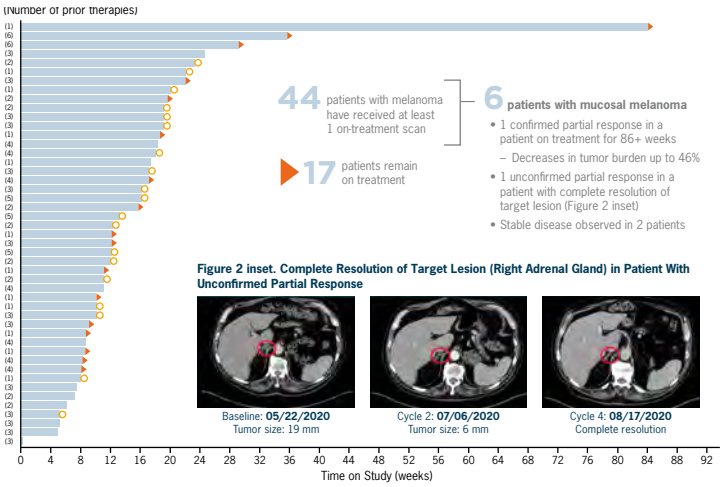
Nemvaleukin

- Engineered using native IL-2 and IL-2Rα sequences to create a fusion protein sterically occluded from binding the high-affinity IL-2R.
- Inherently active, does not require metabolic or proteolytic conversion, and does not degrade into native IL-2.

IL-2

- IL-2 has both immunosuppressive and immunostimulatory functions, mediated by its interaction with different IL-2R complexes.
- The intermediate-affinity IL-2R consists of IL-2Rβ and IL-2Rγ domains, is constitutively expressed on memory CD8+ T cells and NK cells, and is required for antitumor immune responses. The presence of a third extracellular domain, IL-2Rα, increases the affinity of IL-2; this high-affinity IL-2R is constitutively expressed on T_{regs} and induced on effector T cells, NK cells, and vascular endothelial cells.
- The beneficial antitumor effects of IL-2 therapy, achieved through activation of the intermediate-affinity IL-2R (which requires high concentrations for binding), are counterbalanced by more potent interaction with the high-affinity IL-2R, which is associated with immunosuppression and acute toxicities.

Figure 2. Nemvaleukin Monotherapy: Duration of Treatment at RP2D in Patients With Melanoma From ARTISTRY-1 (as of Data Cut Date of 29 June 2021)



44 patients with melanoma have received at least 1 on-treatment scan

17 patients remain on treatment

6 patients with mucosal melanoma

- 1 confirmed partial response in a patient on treatment for 86+ weeks
  - Decreases in tumor burden up to 46%
- 1 unconfirmed partial response in a patient with complete resolution of target lesion (Figure 2 inset)
- Stable disease observed in 2 patients

○ Rollover to Part C of ARTISTRY-1 (combination of nemvaleukin with pembrolizumab)

Figure 2 inset. Complete Resolution of Target Lesion (Right Adrenal Gland) in Patient With Unconfirmed Partial Response

Baseline: **05/22/2020** Tumor size: 19 mm

Cycle 2: **07/06/2020** Tumor size: 6 mm

Cycle 4: **08/17/2020** Complete resolution

METHODS

ARTISTRY-6 (NCT04830124)

A phase 2, global, multicenter, cohort study of nemvaleukin alfa monotherapy administered subcutaneously in patients with advanced cutaneous melanoma or intravenously in patients with advanced mucosal melanoma who have previously received anti-PD-(L)1 therapy

Patient Population

Adults aged ≥18 years with confirmed diagnosis of unresectable and/or metastatic melanoma.

- ECOG performance status of 0 or 1.
- Adequate hematologic reserve and hepatic and renal function.
- Measurable lesion (≥1) that qualifies as a target lesion (RECIST 1.1).
- Prior treatment with anti-PD-(L)1 therapy with or without anti-CTLA-4 therapy,
  - With best objective response of partial response or complete response or with stable disease (RECIST 1.1 or iRECIST).
  - Patients with progressive disease may be eligible if they received anti-PD-(L)1 therapy for ≥12 weeks.
  - No more than 1 other prior regimen of systemic anti-neoplastic therapy (eg, targeted therapy, chemotherapy); previous adjuvant and/or neoadjuvant therapy counts as 1 prior regimen.
  - Patients with *BRAF* mutations may or may not have received prior targeted therapy.
- Prior treatment with talimogene laherparepvec (TVEC) is allowed provided that last exposure to TVEC was ≥28 days prior to first exposure to nemvaleukin and that all injection site reactions to TVEC have resolved.
  - TVEC shall not be considered a prior line of systemic anti-neoplastic therapy, nor shall it be considered a systemic immunomodulatory agent.

Dosing Regimen

Cohort 1: SC nemvaleukin (3 mg) once q7d

Cohort 2: IV nemvaleukin (6 µg/kg) on days 1-5 followed by 9 days off treatment (cycle 1) or 16 days off treatment (cycle 2+)

Patients will continue to receive nemvaleukin until disease progression or intolerable toxicity.

Primary Objective

To evaluate the antitumor activity of nemvaleukin by centralized reviewers' assessment of overall response rate (ORR) based on RECIST 1.1 separately for patients with advanced cutaneous (Cohort 1) and mucosal (Cohort 2) melanoma.

Secondary Objectives (Evaluated Separately for Cohort 1 and Cohort 2)

- To evaluate the antitumor activity (other than by centrally assessed ORR), safety, and tolerability of nemvaleukin.

Exploratory Objectives (Evaluated Separately for Cohort 1 and Cohort 2)

- To evaluate overall survival, durable and immune durable response rates, and health-related quality of life with nemvaleukin, and pharmacokinetics, immunogenicity, and pharmacodynamic effects of nemvaleukin.
- To describe changes in post-treatment patient blood and/or tumor tissue samples and identify properties that may predict response or nonresponse to nemvaleukin monotherapy.

The Study is Actively Recruiting

- As of October 2021, enrolling in South Korea, United States
- Study countries in planning: Australia, Canada, Italy, Spain, Taiwan, United Kingdom

Cohort 1

(Target N = 40)

- Advanced **cutaneous** melanoma
- No more than 5 patients with acral melanoma will be enrolled

Cohort 2

(Target N = 70)

- Advanced **mucosal** melanoma

Key Exclusion Criteria

- Uveal melanoma
- Prior IL-2-based or IL-15-based cytokine therapy
- Exposure, including intralesional, to IL-12 or analogs thereof