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

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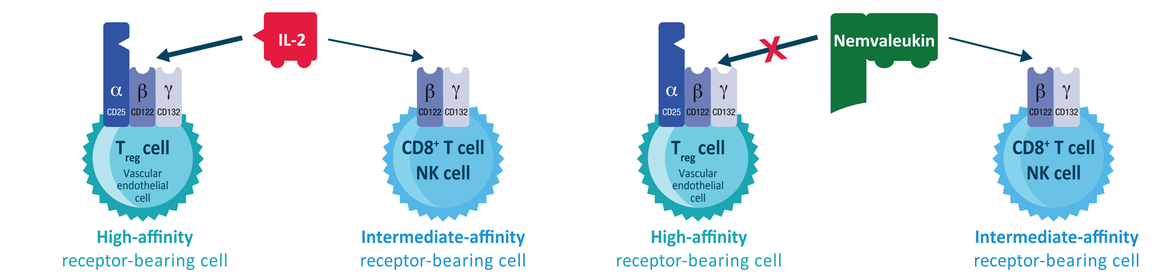
INTRODUCTION

Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine (Figure 1)[1]

- Nemvaleukin monotherapy for mucosal melanoma has been granted Orphan Drug and Fast Track designations by the US FDA, and an Innovation Passport by the Medicines and Healthcare products Regulatory Agency of the United Kingdom under the Innovative Licensing and Access Pathway[2]
- In the ARTISTRY-1 study (NCT02799095), intravenous (IV) nemvaleukin monotherapy at the recommended phase 2 dose (RP2D) of 6 µg/kg on days 1-5 per 21-day cycle demonstrated durable antitumor activity in patients with advanced melanoma, including mucosal melanoma, previously treated with a checkpoint inhibitor (CPI) (Figure 2)[3]
  - Additional responses with nemvaleukin monotherapy have been achieved in patients with advanced renal cell carcinoma previously treated with a CPI
  - Nemvaleukin was generally well tolerated, with a low incidence of treatment-related discontinuations
- In the ARTISTRY-2 study (NCT03861793), subcutaneous (SC) nemvaleukin monotherapy at the RP2D of 3 mg every 7 days (Q7D) demonstrated pharmacodynamic effects consistent with those of IV nemvaleukin[4]
- The ARTISTRY-3 study (NCT04592653) is evaluating less frequent IV nemvaleukin administration in patients with advanced solid tumors[5]

Figure 1: Cell activation by IL-2 and nemvaleukin



IL-2

- Preferential activation 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

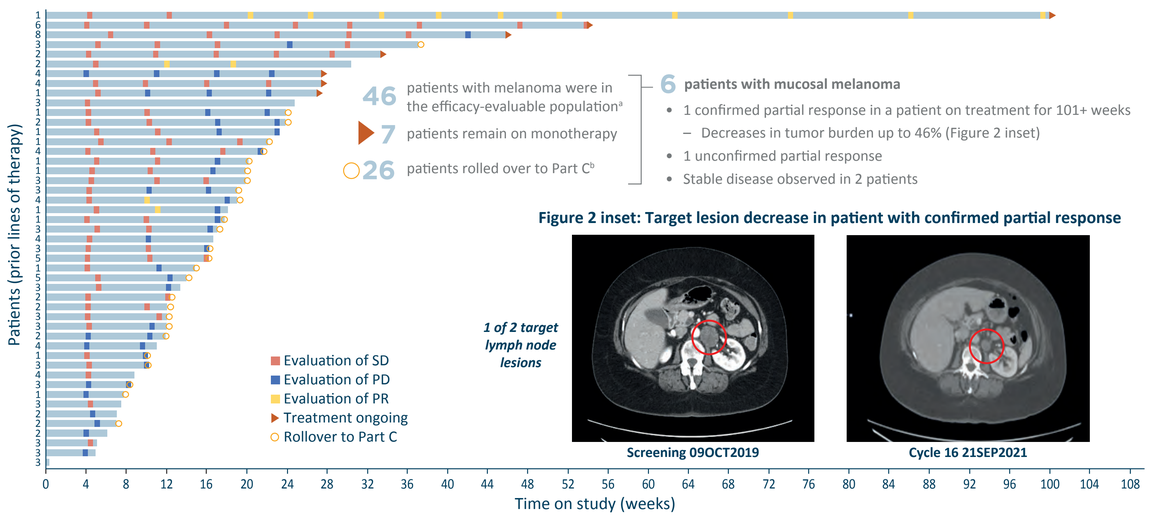
- Stable fusion protein designed to harness the validated IL-2 pathway biology
  - Intrinsically active immediately upon systemic entry; does not degrade into native IL-2
- Designed to selectively bind to the intermediate-affinity IL-2R to:
  - Preferentially activate memory cytotoxic CD8+ T cells and 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

IL-2, interleukin-2; IL-2R, IL-2 receptor; NK, natural killer; T_{reg}, regulatory T cell.

Advanced cutaneous and mucosal melanoma represent tumor types with vast unmet needs

- Although the introduction of CPIs led to improved outcomes for patients with melanoma, ~50% do not respond to monotherapy and ~40% do not respond to combination therapy[6]
  - 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

Figure 2: Duration of nemvaleukin monotherapy and responses at RP2D in patients with melanoma from ARTISTRY-1 (data cut date 29 October 2021)



PD, progressive disease; PR, partial response; SD, stable disease.
[a]1 patient with mucosal melanoma discontinued prior to first scan (patient request). [b]Part C of the ARTISTRY-1 study is a combination therapy dose expansion cohort (nemvaleukin 3 or 6 µg/kg IV + pembrolizumab 200 mg IV). Patients could roll over to Part C upon progression or stable disease (after ≥4 cycles) on monotherapy.

ARTISTRY-6 STUDY DESIGN

ARTISTRY-6 (NCT04830124) is actively recruiting

An ongoing phase 2, global, multicenter, open-label cohort study of nemvaleukin monotherapy in patients with advanced cutaneous melanoma or advanced musocal 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
  - Eastern Cooperative Oncology Group performance status of 0 or 1
  - Adequate hematologic reserve and hepatic and renal function
  - Measurable lesion (≥1) that qualifies as a target lesion (Response Evaluation Criteria In Solid Tumors [RECIST v1.1])
- Prior treatment with anti–programmed death (ligand) 1 (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 v1.1 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 antineoplastic 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 antineoplastic therapy, nor shall it be considered a systemic immunomodulatory agent

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

Cohort 3[a] Target N=66
(33 per dosing schedule)
- Advanced cutaneous melanoma
- No patients with acral melanoma will be enrolled

[a]Added as a protocol amendment.

Key exclusion criteria

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

Dosing regimen

Cohort 1: nemvaleukin 3 mg SC once Q7D of a 21-day cycle

Cohort 2: nemvaleukin 6 µg/kg IV on days 1-5 followed by 9 days off treatment (cycle 1 , 14 days) or 16 days off treatment (cycle 2+, 21 days)

Cohort 3: nemvaleukin IV in 2 less frequent dosing schedules – 1 dose/21-day cycle (Schedule 1) or 2 doses/21-day cycle (Schedule 2 or Schedule 3, based on less frequent IV RP2D established in ARTISTRY-3)

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

All objectives evaluated separately for Cohort 1, Cohort 2, Cohort 3 (Schedule 1), and Cohort 3 (Schedule 2 or 3)

Primary objective

- To evaluate the antitumor activity of nemvaleukin by assessment of overall response rate (ORR) based on RECIST v1.1

Secondary objectives

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

Exploratory objectives

- 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

ARTISTRY

ClinicalTrials.gov ID: NCT04830124

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