Nemvaleukin Alfa Combination Therapy for Gastrointestinal (GI) Cancers: Preclinical Evidence and Clinical Data From the ARTISTRY-1 Trial

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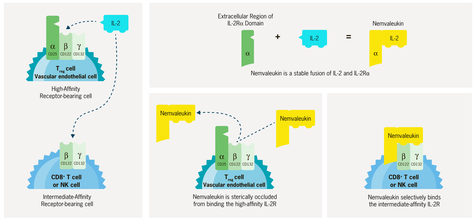
INTRODUCTION

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[1] (Figure 1).
  - IL-2 potently activates the high-affinity IL-2R, which is expressed on immunosuppressive regulatory T cells (T_{regs}), is upregulated on vascular endothelial cells, and is associated with a high incidence of acute toxicities, including capillary leak syndrome.[1]
  - Preferential activation of high-affinity IL-2R-expressing cells by IL-2 leads to expansion of T_{regs}, which may counteract antitumor activity.[1]
- High concentrations of IL-2 are required to activate the intermediate-affinity receptor and elicit beneficial antitumor effects.[1]

Figure 1: Cell Activation by IL-2 and Nemvaleukin



Nemvaleukin Alfa Is a Novel, Engineered Cytokine

- Nemvaleukin alfa (nemvaleukin) selectively binds the intermediate-affinity IL-2R, preferentially activating and expanding antitumor CD8$^+$ T and natural killer (NK) cells, with minimal expansion of T_{regs} (Figure 1).[1]
- Inherently active, nemvaleukin neither requires metabolic/proteolytic conversion nor degrades into native IL-2.

Preclinical and Clinical Studies Support the Potential for the Broad Use of Nemvaleukin, Including in GI Cancers

- Preclinical studies confirmed receptor selectivity and antitumor activity of nemvaleukin alone and with checkpoint inhibitors and informed dose selection for the first-in-human ARTISTRY-1 study.
- The phase 1/2 ARTISTRY-1 study (NCT02799095) is investigating intravenous (IV) nemvaleukin alone and in combination with pembrolizumab in patients with advanced solid tumors, including GI tumors.
  - Responses to nemvaleukin + pembrolizumab were observed in multiple tumor types that have not typically shown robust response to checkpoint inhibitor therapy, including breast, cervical, head and neck, GI, genitourinary, lung, and platinum-resistant ovarian cancers.[2,3]
- Here we further describe the clinical outcomes of patients with GI cancers enrolled in ARTISTRY-1.
- Based on the positive results from ARTISTRY-1 described here, other combination regimens are also under investigation, including combinations with tyrosine kinase inhibitors (TKIs)—a drug class indicated for some GI cancers.
  - Lenvatinib is an inhibitor of vascular endothelial growth factor (VEGF) receptors (VEGFR1-3), fibroblast growth factor receptors (FGFR1-4), platelet-derived growth factor receptor α (PDGFRα), and RET and KIT proto-oncogenes.[4]
  - High levels of VEGF are associated with an immunosuppressive tumor microenvironment and diminished response to high-dose IL-2.[5]
  - Combining immunotherapies with TKIs may provide a synergistic benefit to augment antitumor effects.[6]

CLINICAL EVALUATION IN ADVANCED GI CANCER

Study Design

- Eligible patients with GI cancers who had progressed on prior therapy were enrolled into cohorts of mixed tumor types to receive combination therapy in Part C of ARTISTRY-1 (Figure 2).
- Outcomes presented include antitumor activity (RECIST v1.1) and safety as of August 31, 2021, data cutoff.

Figure 2: Study Design of ARTISTRY-1 Part C: Nemvaleukin Plus Pembrolizumab Combination Therapy

Objective
Characterize the safety profile and antitumor activity (ORR) of nemvaleukin in combination with pembrolizumab

Dosing Regimen
Nemvaleukin IV once daily (3 µg/kg for GI cohort; 6 µg/kg [RP2D] for melanoma, NSCLC, and HNSCC cohorts) for the first 5 days plus pembrolizumab 200 mg IV on day 1 of each 21-day cycle

Key Eligibility Criteria for the 4 Cohorts Enrolling Patients With GI Cancers

- Advanced solid tumors
- Malignancy refractory to or intolerant of established therapies known to provide clinical benefit
- ≥ 1 lesion that may qualify as a target lesion
- ECOG PS 0 or 1
- Life expectancy ≥ 3 months
- Adequate hematologic reserve, hepatic function, and renal function

PD-1/L1 unapproved

PD-1/L1 approved (PD-1/L1 pretreated)

PD-1/L1 approved (PD-1/L1 treatment naive)

Rollover from Part A (monotherapy dose escalation)

ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD-1/L1, programmed death (ligand) 1; RP2D, recommended phase 2 dose.

Figure 3: Enrolled Patient Characteristics

N = 26 patients with GI cancers enrolled

Colon/colorectal, n = 14
Esophageal SCC, n = 4[a]
Esophageal adenocarcinoma, n = 1
Hepatocellular, n = 3
Pancreatic, n = 3
Gastric, n = 1

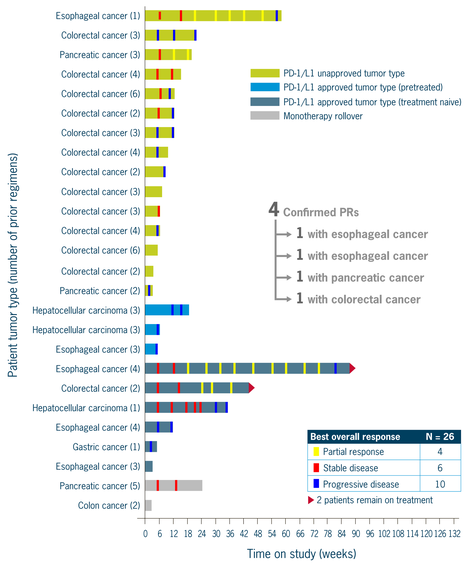
- Median age: 55 years (range, 26-82)
- Median prior lines of therapy: 3 (range, 1-6)
- ECOG PS: 0 (n = 6) or 1 (n = 20)
- Median cycles of nemvaleukin + pembrolizumab received: 3 (range, 1-24)

[a]One patient was previously miscategorized as having gastric/GEJ cancer instead of esophageal adenocarcinoma, based on their prior treatment. GEJ, gastroesophageal junction; SCC, squamous cell carcinoma.

Antitumor Activity of Nemvaleukin Plus Pembrolizumab

- Twenty of 26 patients were evaluable.
- Four patients had confirmed partial responses (PR) (Figure 4), with decreases in target lesion size from baseline ranging from 39% to 63%.
  - 1 PR in a patient with esophageal adenocarcinoma on treatment for 85+ weeks
  - 1 PR in a patient with esophageal SCC
  - 1 PR in a patient with microsatellite instability-high (MSI-H) colorectal cancer on treatment for 42+ weeks
  - 1 PR in a patient with pancreatic cancer on treatment for 18 weeks
- Six patients had stable disease (Figure 4).

Figure 4: Duration of Treatment and Summary of Responses to Nemvaleukin Plus Pembrolizumab Combination Therapy



Safety of Nemvaleukin Plus Pembrolizumab

- Of the 26 patients with GI cancers, 96% had grade 1 or 2 nemvaleukin-related adverse events (AEs), 50% had grade 3 or 4 nemvaleukin-related AEs, and 19% had AEs leading to discontinuation.
- The safety profile for the patients with GI cancers (n = 26) was consistent with that reported for the full mixed tumor type cohort (N = 160).
  - For the patients with GI cancers (n = 26), most frequent grade ≥ 3 nemvaleukin-related AEs were aspartate aminotransferase increased (15%), lymphocyte count decreased (12%), neutrophil count decreased (12%), anemia (12%), fatigue (12%), alanine aminotransferase increased (8%), and hypertension (8%).
  - For the full mixed tumor type cohort (N = 160), most frequent grade ≥ 3 nemvaleukin-related AEs were anemia, neutropenia, neutrophil count decreased, lymphocyte count decreased, aspartate aminotransferase increased, and hypertension.

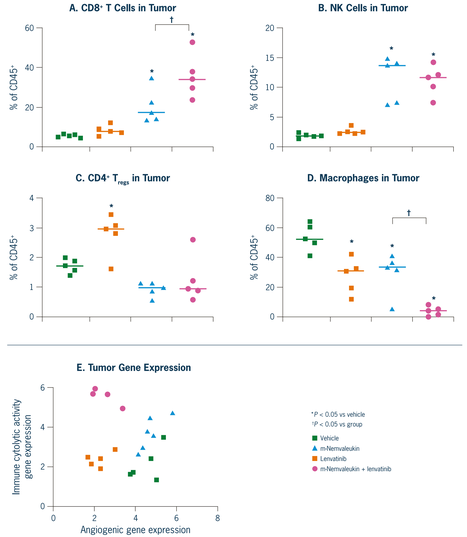
BEYOND CPIs: PRECLINICAL EVALUATION OF NOVEL COMBINATIONS IN ADVANCED GI CANCER

Based on the positive clinical outcomes in ARTISTRY-1, preclinical evaluation of additional combination partners were initiated using the mouse ortholog of nemvaleukin (m-nemvaleukin; RBD 1462)

m-Nemvaleukin Plus Lenvatinib in MC38 Murine Cancer Models

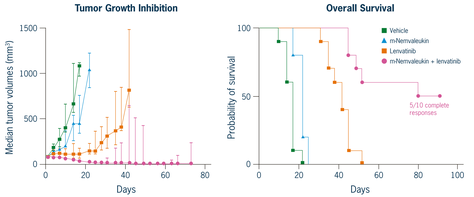
- When compared with vehicle or with either monotherapy alone, the combination of m-nemvaleukin plus lenvatinib:
  - Increased immunostimulatory CD8$^+$ T cells and decreased immunosuppressive macrophages in tumor (Figure 5A-D);
  - Showed evidence of enhanced antitumor mechanisms via increased expression of immune cytolytic genes and decreased expression of an angiogenic gene in tumor (Figure 5E);
  - Improved tumor growth inhibition and survival (Figure 6).

Figure 5: Immune Cell Subsets and Tumor Gene Expression in Mice Treated With m-Nemvaleukin Plus Lenvatinib



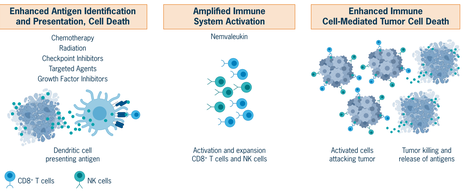
Combinations of m-nemvaleukin plus lenvatinib were evaluated in a mouse colon adenocarcinoma (MC38) model. Flow cytometric and RNA-Seq analyses of samples from C57BL/6 mice were collected on day 7 (following treatment described in Figure 6 legend). Single-cell suspensions were made from tumors and were stained for expression of select markers and analyzed via flow cytometry. Gene expression was measured from isolated RNA using the Ampliseq mouse Transcriptome kit.

Figure 6: Antitumor Efficacy of m-Nemvaleukin Plus Lenvatinib in Tumor Model



In a tumor model, C57BL/6 mice were subcutaneously implanted with MC38 cells and treated with one of the following: m-nemvaleukin plus lenvatinib, m-nemvaleukin plus vehicle, lenvatinib plus vehicle, or vehicle alone.

Figure 7: Proposed Nemvaleukin Mechanism of Immune System Activation in Combination With Agents Used in the Treatment of GI Cancers



Nemvaleukin is proposed to work synergistically and complementarily with other agents used to treat GI cancers, including chemotherapy, radiation therapy, and biologic agents. Alone, these therapies result in immunogenic tumor cell death and tumor antigen release, which stimulates the immune system. Nemvaleukin is proposed to amplify this immune response, activating and expanding both adaptive and innate immune cells (CD8$^+$ T cells and NK cells, respectively) to drive cell-mediated tumor cell death in a durable manner due to resulting antitumor immunity.

m-Nemvaleukin Plus Lucitanib in MC38 Murine Cancer Models[7]

- When compared with vehicle or with either monotherapy alone, the combination of m-nemvaleukin plus lucitanib:
  - Increased CD8$^+$ T cells in tumor;
  - Inhibited tumor growth and improved survival;
  - Increased expression of immune cytolytic genes and decreased expression of an angiogenic gene.

CONCLUSIONS

- Emerging clinical data show that responses in GI tumors may be achieved with nemvaleukin in combination with pembrolizumab with an acceptable safety profile.
- Preclinical evidence of antitumor activity of nemvaleukin with TKIs warrants further exploration of nemvaleukin in combination with TKIs for patients with GI cancers.

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ARTISTRY