Nemvaleukin Alfa in Patients With Advanced Renal Cell Carcinoma: ARTISTRY-1

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INTRODUCTION

Unmet Need

- Despite improved outcomes with checkpoint inhibitor (CPI) therapy in patients with advanced renal cell carcinoma (RCC), >60% of patients do not respond to first-line CPI monotherapy and ~40% of patients do not respond to CPI combination therapy.[1]
- For patients who progress on first-line or subsequent treatment regimens, there is a high unmet need for novel treatments with durable benefit.[2]

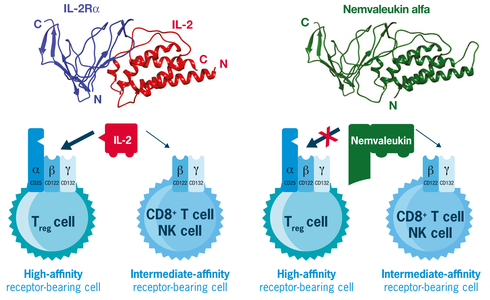
The Interleukin-2 (IL-2) Receptor Pathway Is a Validated Immuno-oncology Target for the Treatment of RCC

- High-dose IL-2 was one of the first immunotherapies to be approved for the treatment of metastatic RCC and melanoma.[3]

Nemvaleukin Alfa Is a Novel, Engineered Cytokine

- Nemvaleukin alfa (nemvaleukin; ALKS 4230) selectively binds the intermediate-affinity IL-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).[4,5]
- Nemvaleukin is under investigation for the treatment of advanced solid tumors in the ARTISTRY-1 trial (NCT02799095).
- Demonstration of single-agent activity is essential to validate the potential therapeutic benefit of nemvaleukin, as monotherapy and in combination with other agents, particularly in patients with limited treatment options, such as CPI-experienced patients with RCC.
- In clinical studies, responses were observed with nemvaleukin monotherapy in melanoma and RCC (results discussed here) and in combination with pembrolizumab in various tumor types, including breast, cervical, head and neck, gastrointestinal, genitourinary, lung, and platinum-resistant ovarian cancers.[5]
- Here we describe the antitumor activity of nemvaleukin monotherapy in patients with CPI-naive or CPI-pretreated RCC in the ARTISTRY-1 trial.

Figure 1: Cell Activation by IL-2 and Nemvaleukin



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

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

METHODS

- Patients with advanced RCC that was refractory to, or patients who were intolerant of, established therapies were enrolled into an RCC-specific cohort of ARTISTRY-1 Part B (Figure 2).
- Patients with disease progression (PD; after ≥2 cycles) or stable disease (SD; after ≥4 cycles) in Part B could be enrolled into Part C to receive nemvaleukin and pembrolizumab combination therapy.
- Final outcomes presented include antitumor activity (RECIST v1.1), pharmacodynamics, and safety as of October 29, 2021.

Figure 2: Study Design and Enrolled Patient Characteristics

Part B: RCC Cohort

Objective
Characterize the safety profile and antitumor activity of nemvaleukin at RP2D

Key Eligibility Criteria
- Advanced RCC
- Malignancy refractory to/intolerant of established therapies known to provide clinical benefit
- CPI naive or pretreated
- ECOG PS 0 or 1 with life expectancy ≥3 months
- Adequate hematologic reserve, hepatic function, and renal function

N = 27 enrolled in Part B

- Sex: male, n = 24; female, n = 3
- Median age: 69 years (range, 39-77)
- Median prior lines of therapy: 2 (range, 1-8)
- Prior CPI therapy: CPI naive, n = 12 (44%); CPI experienced, n = 15 (56%)

n = 10 rolled over to Part C

Monotherapy Dosing Regimen

Nemvaleukin 6 µg/kg IV monotherapy was administered daily for 5 days every 14 days in cycle 1 and every 21 days in cycles 2+

For up to 2 years or until disease progression or intolerable toxicity[a]

Disease progression (after ≥2 cycles) or SD (after ≥4 cycles)

Part C: Combination Therapy

Combination Dosing Regimen
IV nemvaleukin (3 µg/kg)[b] once daily for the first 5 days and pembrolizumab (200 mg) on day 1 of each 21-day cycle

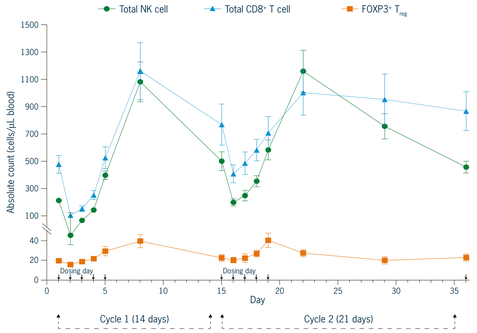
[a]Patients could continue treatment beyond 2 years according to site-specific protocol amendments.
[b]Nemvaleukin dose could be increased to 6 µg/kg if patients could tolerate the 3 µg/kg dose.
ECOG PS, Eastern Cooperative Oncology Group performance status; RP2D, recommended phase 2 dose.

RESULTS

Pharmacodynamic Activity and Safety of Nemvaleukin Monotherapy

- Twenty-seven patients with advanced RCC, 56% CPI-experienced, received nemvaleukin in Part B (≤21 cycles) (Figure 2).
- Nemvaleukin monotherapy induced robust expansion of CD8+ T and NK cells, with minimal effect on T_{regs}, in patients with advanced RCC (Figure 3).
- Safety among patients with advanced RCC was similar to that among the overall patient population.
  - One patient had an adverse event (AE; nemvaleukin-related bronchospasm) on day 22 after first infusion of nemvaleukin that resulted in treatment discontinuation (Table 1).
  - There were no deaths due to treatment-related AEs.

Figure 3: Absolute Cell Counts in Patients With Refractory RCC After Administration of Nemvaleukin 6 µg/kg IV



Each line represents mean (± standard error) in 27 patients with advanced RCC.

Table 1: Safety Summary for Nemvaleukin Monotherapy in Patients With Advanced RCC

Event, n (%)	N = 27
AE summary	
Any AE, regardless of causality	27 (100)
Any serious AE, regardless of causality	11 (40.7)
Grade 3 or 4 nemvaleukin-related AE	20 (74)
Nemvaleukin-related AEs leading to discontinuation	1 (4)
Nemvaleukin-related AEs leading to death[a]	0

AEs, n (%)	AEs (all grades, regardless of causality) in ≥30% of patients	Grade ≥3 nemvaleukin-related AEs
Pyrexia	17 (63)	0
Chills	14 (52)	1 (4)
Nausea	8 (30)	0
Anemia	8 (30)	2 (7)

[a]There was 1 AE not related to nemvaleukin leading to death.

Antitumor Activity of Nemvaleukin

- Four patients achieved partial response (PR) with nemvaleukin monotherapy (Table 2), all of whom were CPI pretreated.
- Of 23 patients with at least 1 postbaseline scan, 10 had SD as a best response and decreases in target lesions of up to 60% were observed (Table 3, Figures 4-6).
- Of the 10 patients with RCC who rolled over to Part C, 2 achieved PR with combination therapy (1 of whom also achieved PR in Part B), and 6 patients achieved SD.

Table 2: Summary of Best Response to Nemvaleukin Monotherapy by Prior CPI Exposure

	CPI naive (n = 12)	CPI pretreated (n = 11)	Total[a] (N = 23)
Best response overall, n (%)			
CR	0	0	0
PR	0	4 (36.4)	4 (17.4)[b]
SD	6 (50.0)	4 (36.4)	10 (43.5)
PD	6 (50.0)	3 (27.3)	9 (39.1)
Continuing monotherapy, n (%)			
Yes	1 (8.3)	3 (27.3)	4 (17.4)

[a]Patients with ≥1 postbaseline scan, [b]1 patient had an unconfirmed PR.
CR, complete response.

Figure 4: Changes in Sum of Target Lesions With Nemvaleukin Monotherapy

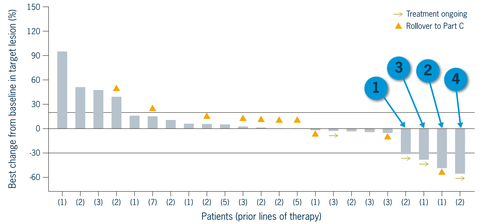


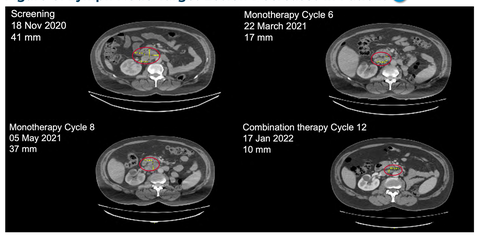
Figure 5: Duration of Treatment and Summary of Responses to Nemvaleukin Monotherapy

Table 3: Summary for Patients With PR on Nemvaleukin Monotherapy

Tumor type	Prior therapy (number of regimens)	Best overall response	Maximum decrease in target lesions	Time on therapy (weeks)
RCC 1	Sunitinib, Nivolumab (2)	uPR	31%	63
RCC 2	Ipilimumab/Nivolumab/ (Cabozantinib or Placebo) (1)	PR	48%	24 (Part B), 22 (Part C)
RCC[a] 3	Ipilimumab/Nivolumab (1)	PR	38%	33
RCC 4	Ipilimumab/Nivolumab (1)	PR	60%	24

[a]Patient discontinued after the data cut.
uPR, unconfirmed PR.

Figure 6: Lymph Node Target Lesion Decreases in Patient 2



- Patient 2, who progressed after a confirmed PR with nemvaleukin monotherapy, rolled over to Part C and achieved a confirmed PR with combination therapy.

CONCLUSIONS

- Nemvaleukin monotherapy provided evidence of single-agent tumor response in patients with advanced RCC.
- Preliminary clinical data show the potential to achieve responses in RCC with nemvaleukin plus pembrolizumab.
- Nemvaleukin was generally well tolerated as monotherapy.
- Clinical evaluation of nemvaleukin among patients with advanced RCC is ongoing.
- Evaluations of nemvaleukin in additional tumor types and in combination with other drugs are being explored, including in ARTISTRY-6 (nemvaleukin monotherapy in advanced melanoma, NCT04830124) and ARTISTRY-7 (nemvaleukin + pembrolizumab in platinum-resistant ovarian cancer, NCT05092360).

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ARTISTRY

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