Nemvaleukin Alfa Monotherapy and in Combination With Pembrolizumab in Patients With Advanced Solid Tumors: ARTISTRY-1

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*At time of study

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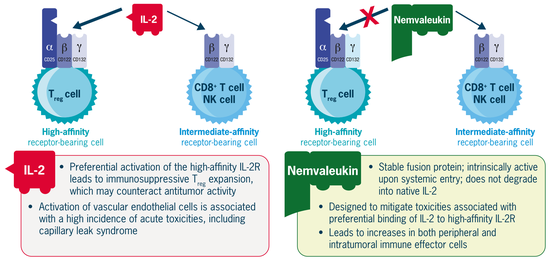
INTRODUCTION

- Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel 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]
- The US FDA has granted nemvaleukin Fast Track designation for treatment of mucosal melanoma and platinum-resistant ovarian cancer (PROC), and Orphan Drug designation for mucosal melanoma

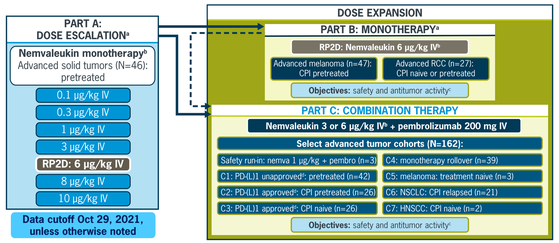
Figure 1: Mechanism of action of nemvaleukin



METHODS

- **ARTISTRY-1 (NCT02799095)** is a 3-part, first-in-human, phase 1/2 study of intravenous (IV) nemvaleukin as monotherapy and in combination with pembrolizumab (Figure 2)

Figure 2: ARTISTRY-1 study design and patient population



[a]Patients from Parts A and B could roll over to Part C upon progression or stable disease (after ≥4 cycles) on monotherapy. [b]Nemvaleukin daily for 5 days, then off treatment for 9 days (cycle 1) or 16 days (cycle 2+). [c]ORR assessed by investigator (RECIST v1.1). [d]Nemvaleukin 3 µg/kg/d in C1-C4, 6 µg/kg/d in C5-C7. PD-(L)1 approved/unapproved indication based on US FDA prescribing information and may have changed over time.
C1-7, Cohort 1-7; CPI, checkpoint inhibitor; HNSCC, head and neck squamous cell carcinoma; nemva, nemvaleukin; NSCLC, non–small cell lung cancer; ORR, overall response rate (complete response [CR] + partial response [PR]); PD-(L)1, programmed death (ligand) 1; pembro, pembrolizumab; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose.

RESULTS

Part A

- Nemvaleukin maximum tolerated dose was not reached; 1 patient had a dose-limiting toxicity (grade 4 acute kidney injury) at 10 µg/kg IV
- RP2D was determined to be 6 µg/kg IV on days 1 to 5 of a 21-day cycle

Pharmacokinetics and pharmacodynamics

- Immune cell expansion data from 12 patients who received nemvaleukin 6 µg/kg IV in Part A showed proof of principle for preferential expansion of CD8+ T cells and NK cells by nemvaleukin, with minimal effect on T_{regs}

RESULTS (CONT)

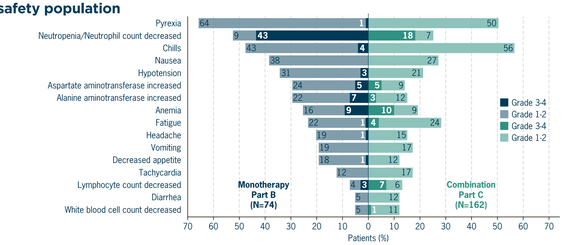
Parts B and C: patient baseline demographics and prior therapies

- Patients in Part B had a median age of 67 years, had received a median of 2 prior lines of therapy (range, 1-8), and 41% and 59% of patients had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and 1, respectively
  - Histologies in the melanoma cohort (n=47) were cutaneous (n=30), mucosal (n=7), uveal (n=6), and acral (n=4); 96% of patients were CPI pretreated
- Patients in Part C had a median age of 62 years, had received a median of 3 prior lines of therapy (range, 1-9), and 31% and 69% of patients had ECOG PS of 0 and 1, respectively

Safety summary: Parts B and C

- Nemvaleukin safety profile was consistent with its mechanism of action
- Monotherapy safety profile was similar to that of combination therapy, with no additive toxicity
- Most frequently observed grade 3-4 treatment-related adverse event (TRAE): neutropenia (includes neutropenia and neutrophil count decreased)
  - Median duration 4 days; not associated with risk of serious infections or febrile neutropenia
- Proportion of patients with TRAEs leading to discontinuation: 3% (monotherapy), 4% (combination)
- No event of capillary leak syndrome reported to date

Figure 3: Summary of most frequent TRAEs (≥10% in either cohort) in the safety population

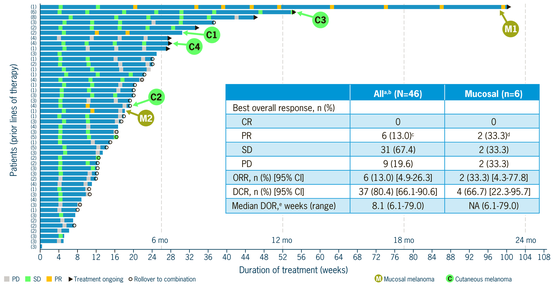


Part C includes patients who received nemvaleukin at 1, 3, or 6 µg/kg IV in combination with pembrolizumab 200 mg IV.

Antitumor activity with nemvaleukin monotherapy

- Durable, clinically meaningful antitumor activity was observed in melanoma and RCC (Figures 4 and 5)
- All responders had progressed on prior CPI therapy
- In the melanoma cohort (46 evaluable patients), there were 6 PRs (2 unconfirmed and 1 awaiting confirmation)
  - Data from this cohort supported the design of the ARTISTRY-6 study
- In the RCC cohort (22 evaluable patients), there were 4 PRs (1 unconfirmed)

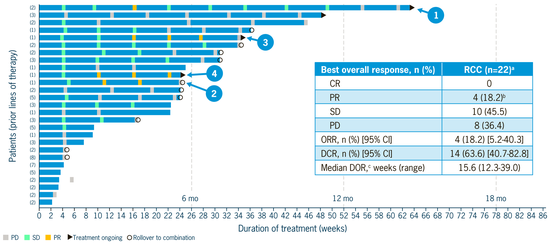
Figure 4: Duration of nemvaleukin monotherapy and responses in melanoma



	All[a,b] (N=46)	Mucosal (n=6)
Best overall response, n (%)		
CR	0	0
PR	6 (13.0)[c]	2 (33.3)[d]
SD	31 (67.4)	2 (33.3)
PD	9 (19.6)	2 (33.3)
ORR, n (%) [95% CI]	6 (13.0) [4.9-26.3]	2 (33.3) [4.3-77.8]
DCR, n (%) [95% CI]	37 (80.4) [66.1-90.6]	4 (66.7) [22.3-95.7]
Median DOR,[e] weeks (range)	8.1 (6.1-79.0)	NA (6.1-79.0)

Responses per RECIST v1.1.
Patients with a response are indicated with circles and arrows. [a]1 patient did not meet tumor-evaluable criteria. [b]Patients with mucosal, cutaneous, uveal, acral included in All. [c]Includes 3 confirmed PRs (1 occurred after data cutoff date), 2 unconfirmed PRs, and 1 PR awaiting confirmation (occurred after data cutoff date). [d]1 confirmed PR. [e]DOR for Part B only and does not include patients who rolled over to Part C; some patients may still be on treatment.
CI, confidence interval; DCR, disease control rate (CR+PR+SD); DOR, duration of response; PD, progressive disease; SD, stable disease.

Figure 5: Duration of nemvaleukin monotherapy and responses in RCC



Best overall response, n (%)	RCC (n=22)[a]
CR	0
PR	4 (18.2)[b]
SD	10 (45.5)
PD	8 (36.4)
ORR, n (%) [95% CI]	4 (18.2) [5.2-40.3]
DCR, n (%) [95% CI]	14 (63.6) [40.7-82.8]
Median DOR,[c] weeks (range)	15.6 (12.3-39.0)

Responses per RECIST v1.1. Patients with a response are indicated with circles and arrows.
[a]5 patients did not meet tumor-evaluable criteria. [b]Includes 3 confirmed PRs and 1 unconfirmed PR. [c]DOR is for Part B only and does not include rollover to Part C; some patients may still be on treatment.

Antitumor activity with nemvaleukin plus pembrolizumab

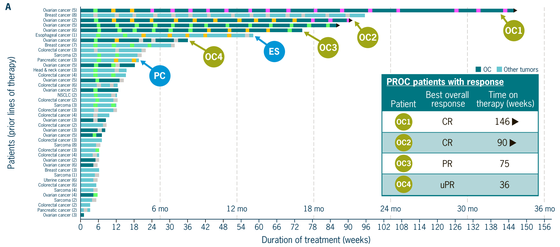
- The antitumor evaluable population comprised 137 patients
- Durable antitumor activity was observed in PD-(L)1 unapproved and approved cohorts (Table 1, Figure 6A, B)
- Responders had received between 1 and 6 prior lines of therapy
- Antitumor activity was observed in various tumor types
  - PROC (n=14): ORR 28.6%; DCR 71.4%; 2 CRs and 2 PRs (1 unconfirmed); median DOR 53.4 weeks

Table 1: Summary of best response to combination treatment

	Overall[a] Cohorts: C1-C7 (N=137)	PD-(L)1 unapproved Cohort: C1 (n=36)	PD-(L)1 approved	
		PD-(L)1 pretreated Cohort: C2 (n=22)	PD-(L)1 naive Cohort: C3 (n=21)	
Best overall response,[b] n (%)				
CR	4 (2.9)	2 (5.6)	0	1 (4.8)
PR	18 (13.1)	4 (11.1)	1 (4.5)	6 (28.6)
SD	60 (43.8)	14 (38.9)	10 (45.5)	7 (33.3)
PD	55 (40.1)	16 (44.4)	11 (50.0)	7 (33.3)
ORR, n (%) 95% CI	22 (16.1) 10.3-23.3	6 (16.7) 6.4-32.8	1 (4.5) 0.1-22.8	7 (33.3) 14.6-57.0
DCR, n (%) 95% CI	82 (59.9) 51.1-68.1	20 (55.6) 38.1-72.1	11 (50.0) 28.2-71.8	14 (66.7) 43.0-85.4
Median DOR, weeks Range	23.2 0.1-132.1	27.6 8.3-79.1	NE	26.1 6.9-63.1

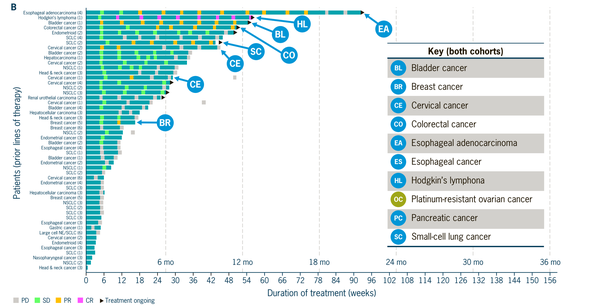
[a]The Overall column includes patients from all 7 cohorts included in Part C. [b]Responses include confirmed and unconfirmed responses (per RECIST v1.1); percentages are based on patients in the evaluable population.
NE, not evaluable.

Figure 6: Duration of treatment and summary of responses in PD-(L)1 unapproved (A) and approved (B) cohorts with combination therapy



PD-(L)1 approved/unapproved indication based on US FDA prescribing information and may have changed over time. Responses per RECIST v1.1; patients with a response are indicated with circles and arrows.
See key in panel B.

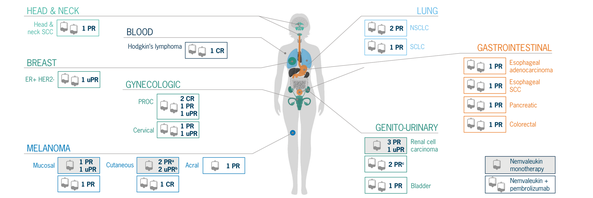
Figure 6 (cont)



PD-(L)1 approved/unapproved indication based on US FDA prescribing information and may have changed over time. Responses per RECIST v1.1; patients with a response are indicated with circles and arrows. NE, neuroendocrine; SCLC, small-cell lung cancer; uPR, unconfirmed PR.

- Responses were observed across a range of tumor types with both nemvaleukin monotherapy and in combination with pembrolizumab

Figure 7: Summary of individual responses in Parts B and C per RECIST v1.1



*1 PR occurred after the data cutoff date. [a]Includes 1 PR awaiting confirmation (occurred after the data cutoff date). [b]Includes 1 patient who had a PR on monotherapy.
Responses per RECIST v1.1. ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; SCC, squamous cell carcinoma.

CONCLUSIONS

- Nemvaleukin is a novel cytokine designed to expand the therapeutic potential of high-dose IL-2
  - Dose-dependent expansion of CD8+ and NK cells to a level consistent with high-dose IL-2 and minimal non–dose-dependent effect on T_{regs} was observed
- Nemvaleukin was generally well tolerated, with a manageable safety profile
- Monotherapy activity was demonstrated in melanoma and RCC, tumor types in which high-dose IL-2 has proven activity
- Responses were observed with nemvaleukin + pembrolizumab in heavily pretreated patients across a range of tumors (including CPI-unapproved and post-CPI failure)
- 43 patients remain on therapy across the study
- Data support ongoing global registrational studies
  - ARTISTRY-6 (NCT04830124): nemvaleukin monotherapy in mucosal and cutaneous melanoma
  - ARTISTRY-7 (NCT05092360): nemvaleukin + pembrolizumab in PROC

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Reference

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