Nemvaleukin Alfa Monotherapy in Patients With Advanced Melanoma: ARTISTRY-1

Piotr Tomczak,[1] Debora S. Bruno,[2] Yan Wang,[3] Elizabeth Dorn,[3] Yangchun Du,[3] Ilda Bidollari,[3] Lei Sun,[3] Heather C. Losey,[3] Jessicca Rege,[3] David F. McDermott[4]

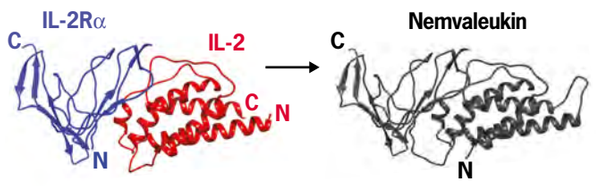
[1]Centrum Medyczne Pratia, Poznan, Poland; [2]University Hospitals, Thoracic Oncology Program, Case Comprehensive Cancer Center, Cleveland, OH, USA; [3]Alkermes, Inc., Waltham, MA, USA; [4]Beth Israel Deaconess Medical Center, Boston, MA, USA

INTRODUCTION AND METHODS

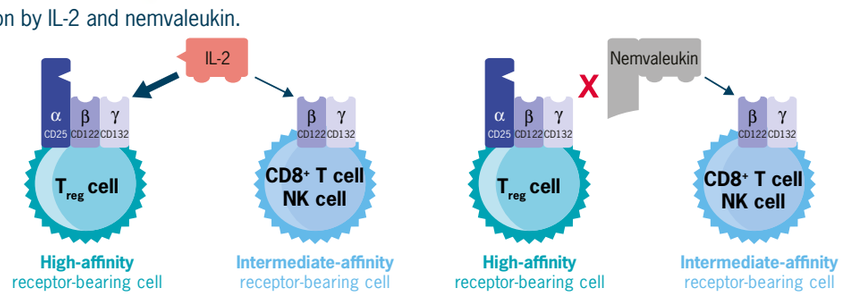
- Recent advances in melanoma treatment have been profound; however, there is variability in response to these therapies, with only a subset of patients able to achieve durable responses.
- Variability in response to immunotherapy occurs both at the individual patient level and in certain subpopulations.
- Responses to checkpoint inhibitors (CPIs) have been shown to be significantly worse for patients with mucosal melanoma, a rare and aggressive disease, compared with patients with cutaneous melanoma.[1]
- Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel engineered cytokine that selectively binds the intermediate-affinity interleukin-2 (IL-2) receptor complex to preferentially activate $CD8^+$ T and natural killer (NK) cells with minimal expansion of regulatory T cells (T_{regs}) (Figure 1).[2]
  - Nemvaleukin is designed to leverage the proven antitumor effects of the IL-2 pathway while mitigating the limitations associated with high-dose recombinant human IL-2 therapy.
- Nemvaleukin monotherapy is under investigation for the treatment of advanced melanoma in the phase 1/2 ARTISTRY-1 trial (NCT02799095).

Figure 1: Nemvaleukin Structure and Activity

A. Nemvaleukin is a covalent fusion of circularly permuted IL-2 and IL-2Rα subunit.

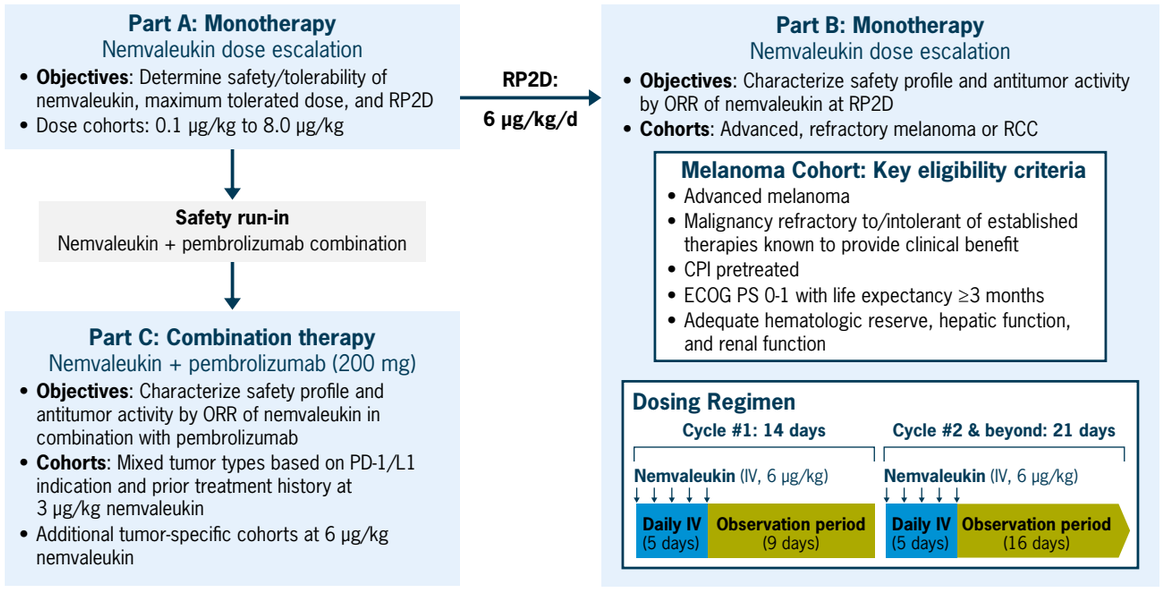


B. Cell activation by IL-2 and nemvaleukin.



- ARTISTRY-1 is an ongoing 3-part multicohort phase 1/2 trial exploring intravenous (IV) nemvaleukin as monotherapy and combined with pembrolizumab (Figure 2).
- Patients with advanced melanoma who had previously received treatment with a CPI and a targeted treatment were enrolled into a melanoma-specific cohort in Part B of the study.
- Outcomes presented include safety, pharmacodynamic effects, and antitumor activity (Response Evaluation Criteria In Solid Tumors v1.1) as of July 24, 2020.
- To evaluate changes in the tumor microenvironment, an exploratory analysis on 1 paired baseline/on-treatment biopsy was conducted.

Figure 2: Study Design and Treatment Regimens



ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; RCC, renal cell carcinoma; PD-1/L1, programmed death (ligand) 1; RP2D, recommended phase 2 dose.

RESULTS

Patient Characteristics of Part B Melanoma Cohort

- 6 patients with advanced melanoma were enrolled as of the data cut-off date.
  - The median age was 62.5 years, all were white, and 66.7% had a baseline ECOG PS of 0 at study entry.
  - 4 patients had mucosal melanoma, 1 had ocular melanoma, and 1 had unknown histology.

Safety and Tolerability of Nemvaleukin Monotherapy

- A summary of safety information is provided in Table 1.
- Most adverse events (AEs) were manageable with antipyretics and other symptomatic treatments.
  - 1 patient had a grade 3 event of transient hypotension, which was managed with fluids.
  - No AEs related to study drug led to treatment discontinuations.
- Grade ≥3 treatment-related AEs that occurred in ≥2 patients included neutrophil count decreased (Table 1).

Antitumor Activity of Nemvaleukin Monotherapy

- Among the 5 patients with evaluable scans by the data cut-off date, 1 with metastatic mucosal melanoma achieved a partial response (PR) (Figure 3, Patient A).
  - The response was accompanied by a decrease in serum lactate dehydrogenase (LDH) levels (Figure 4) and a total tumor shrinkage of approximately 40%.
  - This patient had been in the study for 57 weeks and was on treatment at the time of the data cut-off date.
- After the data cut-off date, a second patient with metastatic mucosal melanoma also achieved PR (unconfirmed) and also experienced a total tumor burden reduction of approximately 40% (Figure 3, Patient F).
  - The response was accompanied by a complete resolution of the target lesion in the right adrenal gland (Figure 5).
  - This patient has been in the study for 15 weeks and continues on treatment.

Table 1: Safety Summary for Nemvaleukin Monotherapy in the Melanoma Cohort

Preferred Term[a]	Patients (N = 6)
AEs, regardless of causality, n (%)	
Any AE	6 (100.0)
AEs leading to discontinuation[b]	1 (16.7)
Death	0
AEs in ≥3 patients	
Chills	5 (83.3)
Hypotension	4 (66.7)
Headache	4 (66.7)
Pyrexia	3 (50.0)
Nausea	3 (50.0)
Fatigue	3 (50.0)
Diarrhea	3 (50.0)
Abdominal pain	3 (50.0)
Treatment-related AEs, n (%)	
Grade 1-2	5 (83.3)
Grade ≥3	4 (66.7)
Grade ≥3 in ≥2 patients overall	
Neutrophil count decreased	2 (33.3)

[a]AEs coded using MedDRA version 19.0.
[b]1 participant discontinued due to abdominal pain (assessed as not related to nemvaleukin).

Figure 3: Patient Summaries and Antitumor Activity of Nemvaleukin Monotherapy

Patient	Diagnosis	Treatment History
A: 66-yo female	Primary urethral mucosal melanoma (Apr '17)	• Cystectomy and pelvic node dissection (Jun '17) • Adjuvant nivolumab treatment (Sep '17 – Sep '18) • Recurrence 8 months after treatment completion
B: 64-yo female	Uveal melanoma	• Nivolumab
C: 43-yo male	Unknown histology	• Nivolumab + Ipilimumab; Nivolumab; Dabrafenib + Trametinib; Vemurafenib + Cobimetinib
D: 44-yo female	Mucosal melanoma	• Nivolumab + Ipilimumab; Pembrolizumab; Encorafenib + Binimetinib; Mekinlot + Tafinlar
E: 61-yo male	Mucosal melanoma	• Peptide vaccine • Nivolumab + Ipilimumab
F: 73-yo male	Mucosal melanoma	• Adjuvant nivolumab • Progressed >9 months after treatment completion

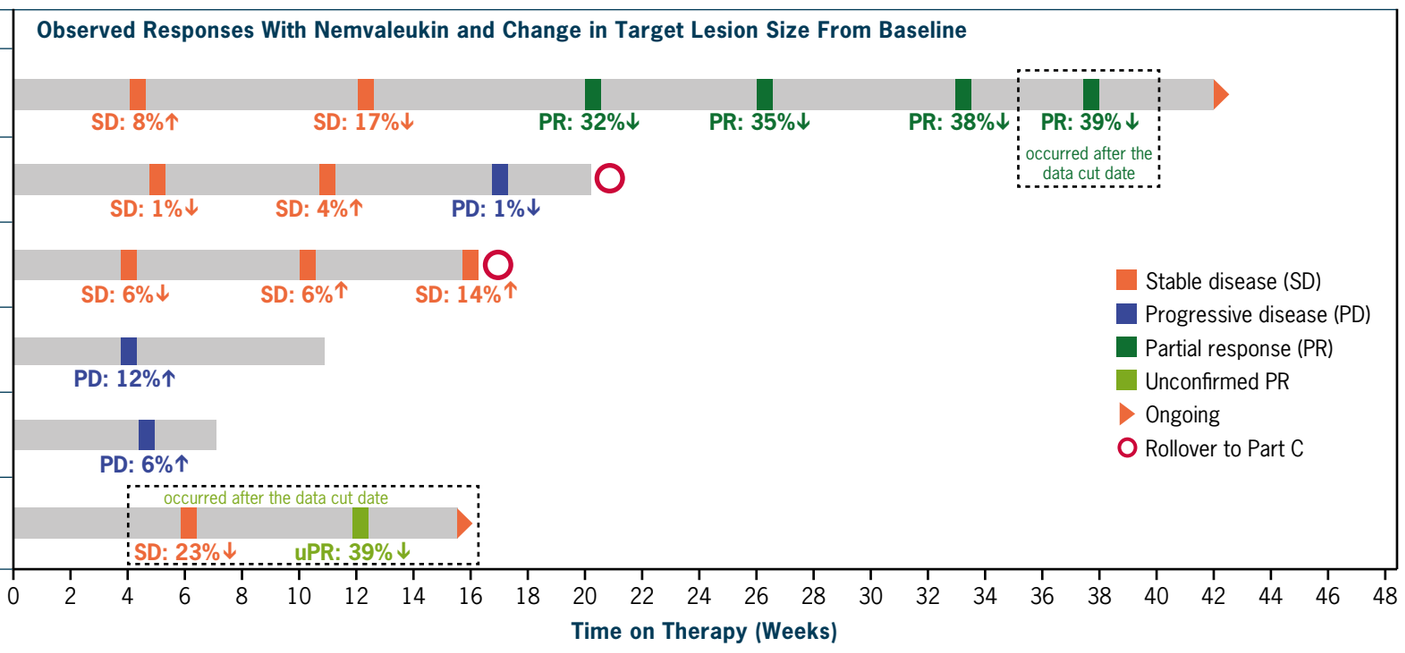


Figure 4: Reduction in Serum LDH With Nemvaleukin Monotherapy in Patient A

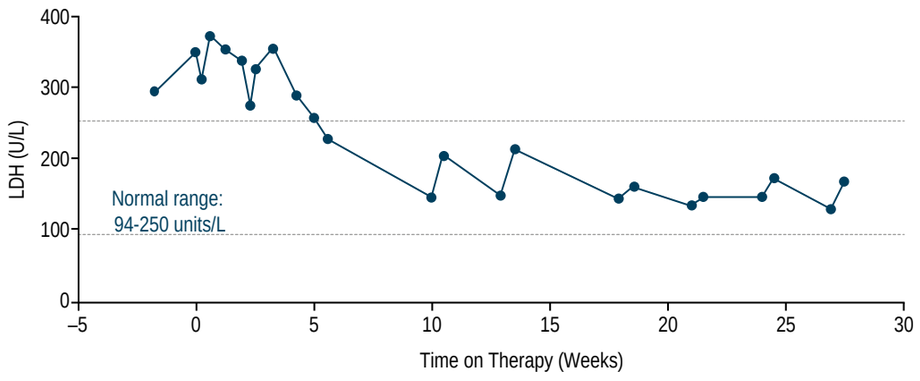
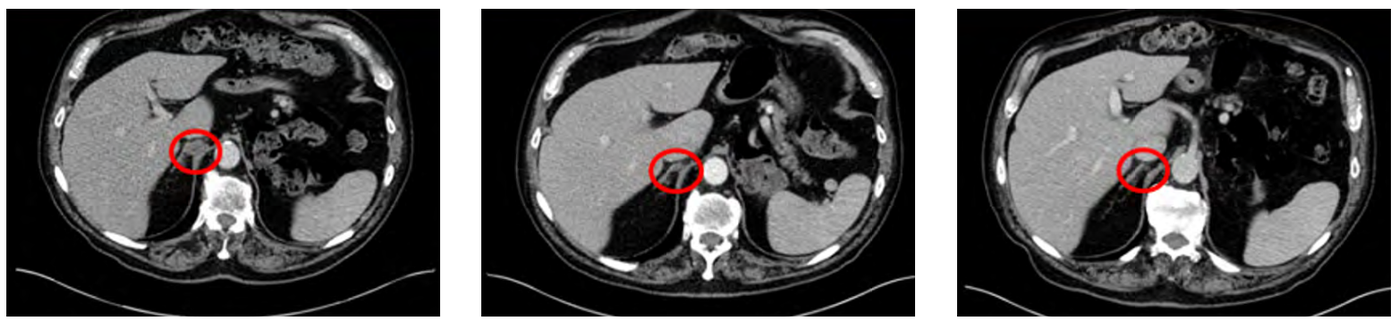


Figure 5: Resolution of Target Lesion (Right Adrenal Gland) With Nemvaleukin Monotherapy in Patient F



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

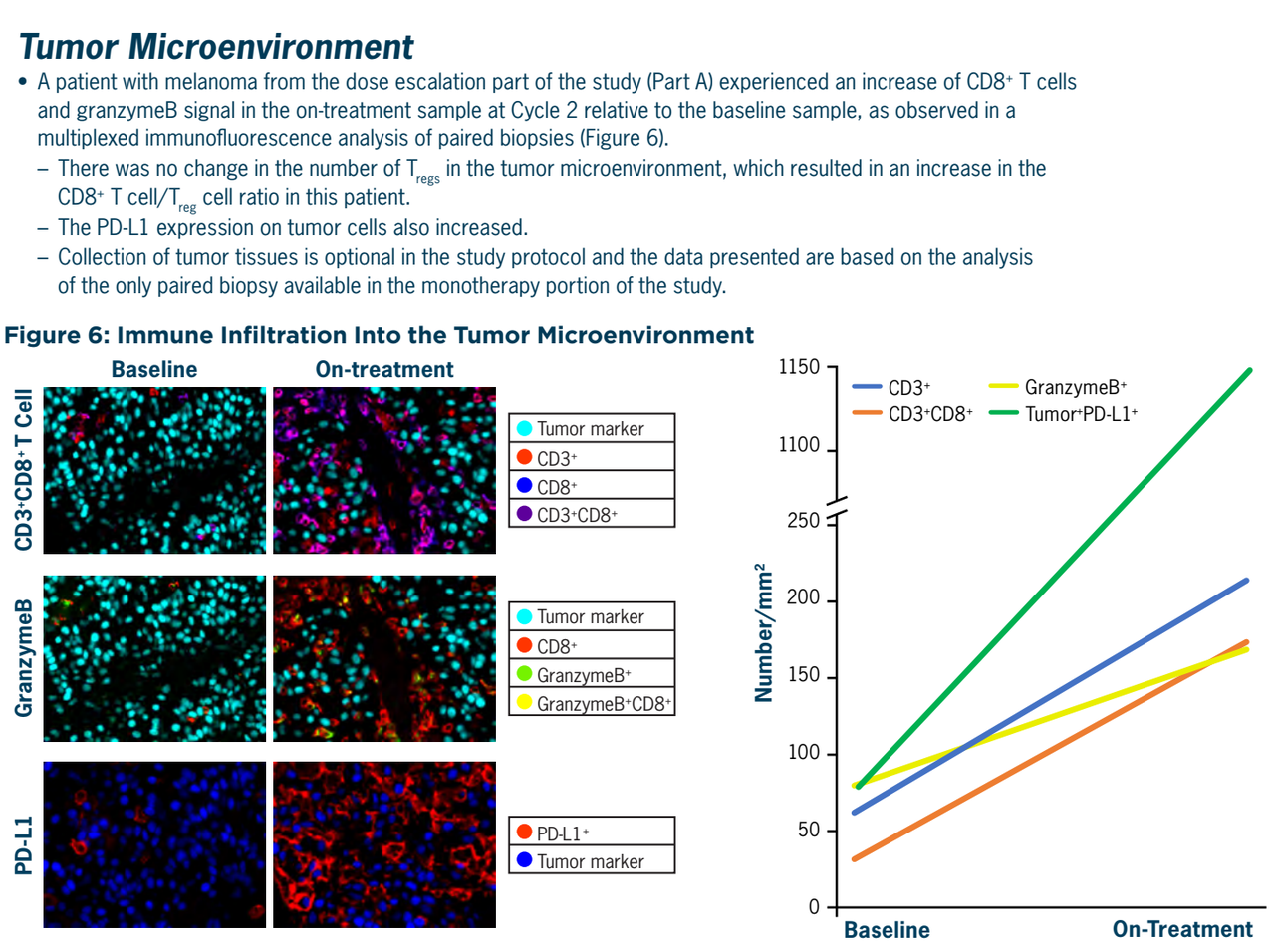
Cycle 2: **07/06/2020**
Tumor size: 6 mm

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

Tumor Microenvironment

- A patient with melanoma from the dose escalation part of the study (Part A) experienced an increase of $CD8^+$ T cells and granzymeB signal in the on-treatment sample at Cycle 2 relative to the baseline sample, as observed in a multiplexed immunofluorescence analysis of paired biopsies (Figure 6).
  - There was no change in the number of T_{regs} in the tumor microenvironment, which resulted in an increase in the $CD8^+$ T cell/T_{reg} cell ratio in this patient.
  - The PD-L1 expression on tumor cells also increased.
  - Collection of tumor tissues is optional in the study protocol and the data presented are based on the analysis of the only paired biopsy available in the monotherapy portion of the study.

Figure 6: Immune Infiltration Into the Tumor Microenvironment



CONCLUSIONS

- Nemvaleukin is a novel, investigational agent that is generally well tolerated, has demonstrated the potential for antitumor activity, and can be administered in an outpatient setting.
- Single-agent activity was observed among patients with melanoma who were previously treated with a CPI.
  - Response criteria were met to expand the monotherapy melanoma cohort, and research of nemvaleukin among patients with advanced melanoma is ongoing.
- Further validation of monotherapy and combination activity have been reported.
  - Additional responses observed with nemvaleukin monotherapy in patients with RCC are awaiting confirmation.
  - Additional responses have been observed in multiple tumor types with nemvaleukin in combination with pembrolizumab.
- The immune infiltration observed in a paired biopsy sample is consistent with serum pharmacodynamic responses[2] and demonstrates the potential for an immunostimulatory impact on the tumor microenvironment.
- Nemvaleukin will be evaluated among patients with advanced cutaneous melanoma and advanced mucosal melanoma in a planned study.
- Nemvaleukin has been granted orphan drug status for mucosal melanoma by the FDA.

REFERENCES AND ACKNOWLEDGMENTS

References

1. Gellrich FF, et al. *J Clin Med.* 2020;9(1):223.
2. Vaishampayan UN, et al. *Ann Oncol.* 2020;31(suppl4):S708-S709.

Acknowledgements and Disclosures

The authors would like to thank all of the patients who are participating in this trial and their families.
The trial is sponsored by Alkermes, Inc. Medical writing and editorial support was provided by Parexel and funded by Alkermes, Inc.

Copies of this poster obtained through this QR (Quick Response) code are for personal use only and may not be reproduced without permission of Alkermes.
For permission, contact: USMedInfo@Alkermes.com

ARTISTRY

Alkermes® Patient inspired®