Preliminary Pharmacodynamic Characterization in Patients With Platinum-Resistant Ovarian Cancer Treated With Nemvaleukin in Combination With Pembrolizumab

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Introduction

- Standard-of-care chemotherapy and anti–programmed cell death protein 1 (anti-PD1) therapy in clinical trials for platinum-resistant ovarian cancer (PROC) are associated with poor outcomes, with response rates ranging from ~6% to 20% and ~7% to 12%, respectively[1-5]
- Treatment options for patients with PROC remain limited as recent trials in PROC have mostly reported negative outcomes, highlighting a substantial unmet need for efficacious therapies for PROC[6]
- Nemvaleukin is an engineered cytokine designed to selectively bind to the intermediate-affinity interleukin-2 receptor 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}), while mitigating toxicities associated with high-dose interleukin-2[7]
- In the ARTISTRY-1 study (NCT02799095), responses to nemvaleukin, as monotherapy and in combination with pembrolizumab, have been observed in various tumor types, including breast, cervical, ovarian, gastrointestinal, head and neck, genitourinary, and lung cancers[8]
- Current data include results from an exploratory post hoc analysis of peripheral pharmacodynamic effects in patients with PROC treated with nemvaleukin plus pembrolizumab in the ARTISTRY-1 study

Methods

ARTISTRY 1 Study

- ARTISTRY-1 is a first-in-human study of intravenous (IV) nemvaleukin in patients with advanced solid tumors.[8] The study comprised 3 parts: Part A, dose escalation study to identify the recommended phase 2 dose (RP2D) of IV nemvaleukin; Part B, monotherapy with IV nemvaleukin using the RP2D dose identified from Part A; Part C, combination of nemvaleukin plus pembrolizumab[8]
- In the Part C combination cohort, patients with a variety of tumor types were enrolled to receive nemvaleukin at 3 or 6 µg/kg once daily for 5 consecutive days (Q5D) plus pembrolizumab 200 mg IV every 3 weeks
- This analysis included patients with ovarian cancer from the Part C combination cohort who received nemvaleukin at 3 µg/kg in combination with pembrolizumab
  - Nemvaleukin dosing of 3 µg/kg in these patients was based on the timing at which they entered the study as the 6 µg/kg dosing had not been evaluated at that time but was later declared as the RP2D dose
- Best overall response data are as of 27 March 2023, with scans performed every 6 (±1) weeks

Pharmacodynamic Analyses

- Whole blood samples were collected from patients with ovarian cancer at baseline (pretreatment cycle [C] 1 day [D] 1) and longitudinally (C1D8 and C2D8) and were analyzed by flow cytometry to examine immune cell modulation
- Immunophenotyping results were reported as absolute cell counts (cells/µL blood) and relative percentages for the following cells and their subtypes: NK cells, T cells, B cells, and T_{regs}

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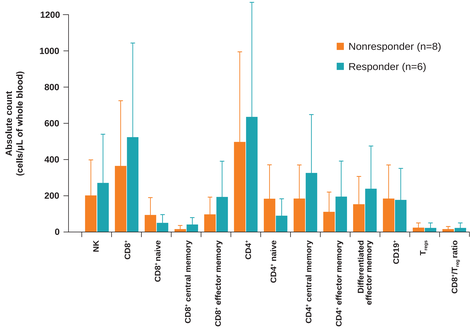
Results

- The current analysis is based on 14 of 16 patients with PROC enrolled in Part C of ARTISTRY-1
- All immune cells and their subtypes were analyzed for absolute cell counts at baseline. Figure 1 shows the average value for each in responders and nonresponders

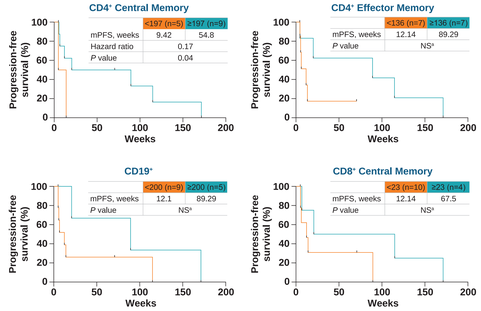
FIGURE 1: Identification of baseline immune cell types associated with response to nemvaleukin plus pembrolizumab



Data are average absolute counts for all immune cell types assessed by flow cytometry. Responder: complete/partial response (CR/PR) and stable disease (SD) >12 weeks; nonresponder: progressive disease (PD) and SD <12 weeks.

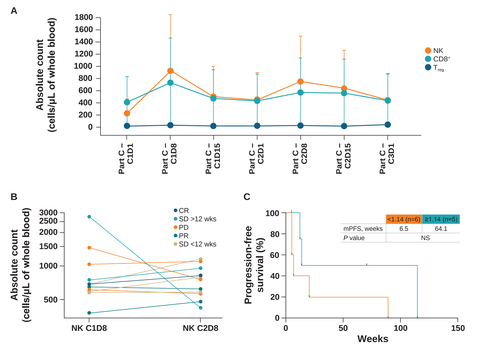
- To assess whether the absolute counts at baseline correlate with survival, cutoffs were identified for each immune cell type that gave best sensitivity and specificity for each cell type based on response data
- Based on these cutoffs, progression-free survival (PFS) was assessed with Kaplan-Meier plots using log rank test. Among all cells, higher numbers of baseline CD4$^+$ central memory cells showed significantly longer correlation with PFS; higher baseline B cells (CD19$^+$), CD8$^+$ central, and CD4$^+$ effector memory cells also showed a trend toward longer PFS (Figure 2)
- Of 14 patients at baseline, 11 had longitudinal assessments for both C1D8 and C2D8
- Nemvaleukin plus pembrolizumab treatment resulted in expansion of NK cells (~4.7-fold) and CD8$^+$ cells (~2.9-fold), with minimal change in the number of T_{regs}, consistent with the known mechanism of action of nemvaleukin (Figure 3A)
- Longitudinal assessment with limited patient data (N=11) also showed that, in the majority of responders, NK cell count at C2D8 was higher than at C1D8 compared with nonresponders (Figure 3B)
- Further, using a ratio of C2D8/C1D8 with a cutoff ≥1.14 showed that higher ratio tends to predict longer PFS (Figure 3C)

FIGURE 2: Association of baseline levels of B and memory T cells with PFS after nemvaleukin plus pembrolizumab treatment



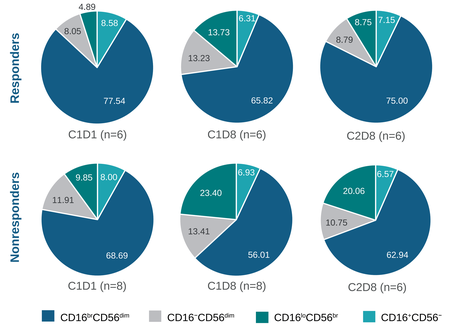
[a]*P* value was >0.05 and <0.20.
m, median. NS, not significant.

FIGURE 3: Longitudinal expansion of immune cells and correlation of NK cell ratio at C2D8/C1D8 with response and PFS



- Among all patients, the largest proportion of NK cell subtypes at all time points was the CD16^{br}/CD56^{dim} (CD56 dim) phenotype (Figure 4, blue shading)
- Following treatment, expansion of CD16^{lo}/CD56^{br} (CD56 bright) NK cells occurred in both responders and nonresponders (Figure 4, dark teal shading, statistical analysis not conducted since N is limited)
- No differences in proportion or changes with treatment of minor NK cell populations (CD16$^+$/CD56$^-$, CD16$^-$/CD56^{dim}) were observed in either responders or nonresponders (Figure 4, light teal and gray shading)

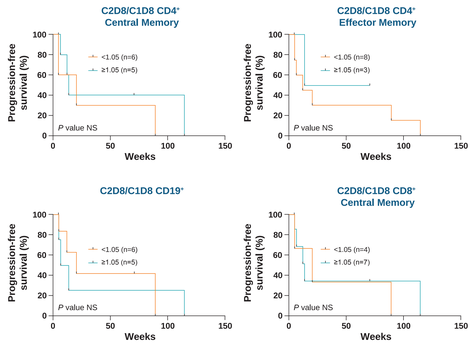
FIGURE 4: Characterization of NK cell subtypes by response status



Data shown are in percentage of NK cells (CD56$^+$/CD16$^+$) calculated from cell counts based on TBNK assay. Responder: CR/PR and SD >12 weeks; nonresponder: PD and SD <12 weeks. TBNK, T, B, NK, and T_{reg} cells along with subtypes.

- C2D8/C1D8 ratios for other cell types (those identified at baseline to be correlated with longer PFS) were not predictive of longer PFS after treatment with nemvaleukin plus pembrolizumab when evaluated via longitudinal assessment in this patient population (Figure 5)

FIGURE 5: Association of C2D8/C1D8 ratios of B and memory T cells with PFS after nemvaleukin plus pembrolizumab treatment



Conclusions

- Immune activation was observed after treatment with nemvaleukin plus pembrolizumab in PROC
- Higher numbers of baseline CD4$^+$ central memory cells showed significant correlation with longer PFS; additionally, higher numbers of B cells (CD19$^+$), CD8$^+$ central, and CD4$^+$ effector memory cells also showed a trend toward longer PFS
- NK cell ratio at C2D8/C1D8 ≥1.14 correlated with response to nemvaleukin plus pembrolizumab and trended toward longer PFS
- The largest proportion of NK cell subtypes at all time points was the CD16^{br}/CD56^{dim} (CD56 dim) phenotype
- Results of this exploratory analysis should be interpreted with caution due to limited sample size and lack of multiplicity adjustment
- Further validation of these results will be needed and explored with pharmacodynamic markers in tumor microenvironment in a larger clinical trial setting in ARTISTRY-3 (NCT04592653) and ARTISTRY-7 (NCT05092360)

References

1. Mutch D, et al. *J Clin Oncol.* 2007;25:2811-2818.
2. Awada A, et al. *OncoTargets Ther.* 2022;15:853-866.
3. Hamanishi J, et al. *J Clin Oncol.* 2021;39:3671-3681.
4. Matulonis UA, et al. *Ann Oncol.* 2019;30:1080-1087.
5. Zamarin D, et al. *J Clin Oncol.* 2020;38:1814-1823.
6. Richardson DL, et al. *JAMA Oncol.* 2023;9:851-859.
7. Lopes JE, et al. *J Immunother Cancer.* 2020;8:e000673.
8. Vaishampayan UN, et al. Oral presentation at ASCO Annual Meeting 2022. Abstract #2500.

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- Conflict of interest disclosures for all authors are available through the QR (Quick Response) code.

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Author Disclosures

I. Winer reports serving on advisory boards for GOG Partners; receiving travel stipend/honoraria for EACR travel from Regeneron; and receiving IIT collaborative funding from Chimerix for trial purposes only.

U.N. Vaishampayan reports serving as a consultant or in an advisory role for Alkermes, AAA, Bristol Myers Squibb, Exelixis, Bayer, Gilead, Seattle Genetics, Pfizer, and Genzyme; receiving research support from Bristol Myers Squibb and Merck; and receiving honoraria from Exelixis, Bayer, and Genzyme.

L. Gilbert reports serving as a consultant or in an advisory role for GlaxoSmithKline and Merck; receiving honoraria from AstraZeneca, Eisai, GlaxoSmithKline, GOG, Eisai-Merck, Merck, and Novocure; and receiving institutional research funding from Alkermes, AstraZeneca, Esperas Pharma, IMV, ImmunoGen, Tesaro/GlaxoSmithKline, Karyopharm Therapeutics, K-Group Beta Inc., Merck Sharp & Dohme, Mersana, Novocure, OncoQuest, and Roche.

S. Gandhi reports receiving honoraria from Biotheranostics and AstraZeneca.

V. Velcheti reports serving as a consultant or in an advisory role for Bristol Myers Squibb, Merck, AstraZeneca, Regeneron, G1 Therapeutics, Amgen, and GlaxoSmithKline.

R. Dalal, **S. Donatelli**, **Y. Du** and **S. Panchabhai** report being employees of and having stock options for Alkermes Inc.

J.F. Strauss reports serving as a consultant for Dialectic Therapeutics; having stock in Abbvie, Abbot, BMS, Intuitive Surgical, J&J, Merck, and Regeneron; and serving as a consultant or in an advisory role for Synlogic (institution) and Binhui Biopharmaceuticals (institution).

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