Pattern of Natural Killer (NK) Cell ($CD16^+CD56^+$) Expansion Correlates With Response Outcomes With Nemvaleukin Alfa Treatment

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Abstract #740

INTRODUCTION

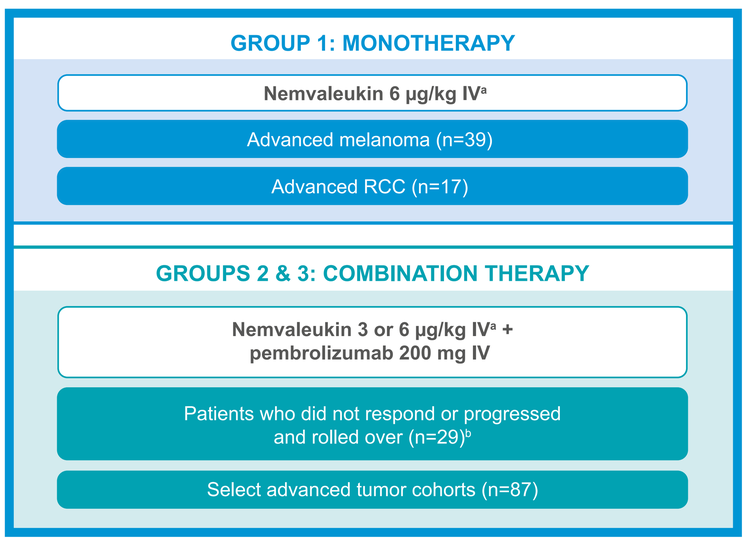
- Nemvaleukin alfa (nemvaleukin) is a novel, engineered cytokine designed to leverage antitumor effects of the interleukin-2 (IL-2) pathway while mitigating potential toxicity that would limit its use[1]
- Nemvaleukin selectively binds to the intermediate-affinity IL-2 receptor (IL-2R) and is sterically occluded from binding to the high-affinity IL-2R[1]
- Because of this molecular design, nemvaleukin treatment leads to preferential expansion of antitumor $CD8^+$ T cells and natural killer (NK) cells, with minimal expansion of immunosuppressive regulatory T cells (T_{regs})[2]
- In the ARTISTRY-1 study (NCT02799095), responses to nemvaleukin, as monotherapy and in combination with pembrolizumab, have been observed in various tumor types, including melanoma, Hodgkin's lymphoma, and breast, cervical, ovarian, gastrointestinal, head and neck, genitourinary, and lung cancers[2]
- Identifying potential biomarkers that may serve as early predictors of clinical antitumor activity during nemvaleukin treatment is of significant interest
- We present results from an exploratory biomarker analysis of immunophenotyping data from ARTISTRY-1

METHODS

Trial Design

- ARTISTRY-1 is a first-in-human study of intravenous nemvaleukin, as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors
- For the purpose of this analysis, patients were classified into the following groups based on the treatment they received (Figure 1):
  - Group 1: patients with melanoma and renal cell carcinoma (RCC) treated with nemvaleukin monotherapy (6 µg/kg; majority pretreated with checkpoint inhibitor therapy)
  - Group 2: patients from Group 1 and 2 patients from the dose escalation cohort who experienced progressive disease (PD) after 2 cycles or stable disease (SD) after 4 cycles and rolled over to combination therapy (nemvaleukin 3 µg/kg and pembrolizumab)
  - Group 3: patients with various solid tumors treated with combination therapy (nemvaleukin 3 or 6 µg/kg and pembrolizumab)

FIGURE 1: Biomarker analysis patient groups



IV, intravenous.
[a]Nemvaleukin daily for 5 days, then off treatment for 9 days (cycle 1) or 16 days (cycle 2+). [b]Group 2 includes 27 patients from Group 1 and 2 patients from the ARTISTRY-1 dose escalation cohort.

Biomarker Analyses and Time Points

- Immunophenotyping of whole blood was conducted by flow cytometry, and results were reported as absolute cell counts (cells/µL) and relative percentages for the following cells and their subtypes: T_{regs}, T cells, $CD19^+$, NK cells
- Time points: day (D) 1 of each cycle (C); C1D8, first time point that shows immune expansion; C2D8, next time point when immune expansion reaches maximum, plateaus, or decreases
- Group 1 was a training set used to identify biomarkers predictive of antitumor activity, perform analytical validation, and analyze the association with demographic and clinical characteristics; Groups 2 and 3 were used to test the predictive ability of the biomarker during combination treatment
- Scans occurred every 6 (±1) weeks
- Best overall response (BOR) assessment is as of March 27, 2023, and includes confirmed and unconfirmed responses
- Treatment cycles were 21 days, except C1 Group 1 (14 days)

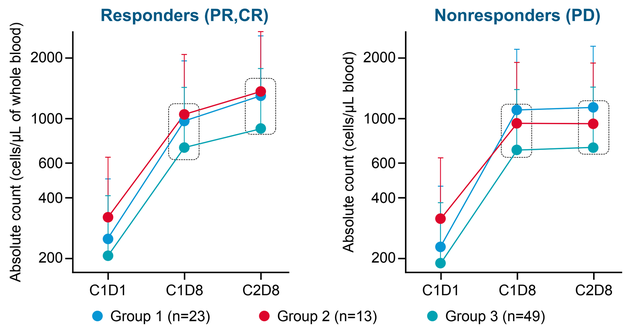
RESULTS

Identification of Biomarker of Response to Nemvaleukin

- Among all the cell types analyzed, the ratio of absolute count for NK cells (defined by $CD16^+/CD56^+$) at C2D8/C1D8 was identified as a potential predictive marker of response in all treatment groups
- No other cell types (T cells and subtypes, $CD19^+$, T_{regs}) analyzed showed a consistent trend as a biomarker in all 3 groups
- NK cells showed a greater expansion at C2D8 in patients with a partial/complete response (PR/CR) compared with those with PD after similar initial expansion at C1D8 (Figure 2)

RESULTS (continued)

FIGURE 2: NK ($CD16^+/CD56^+$) cell expansion at C1D8 and C2D8 in patients[a] with a PR/CR vs PD



[a]Group 1: 8 patients had PR/CR, 15 had PD; Group 2: 4 patients had PR/CR, 9 had PD; Group 3: 15 patients had PR/CR, 34 had PD.

Predictive Value of NK Cell Ratio at C2D8/C1D8 for Response to Nemvaleukin Monotherapy

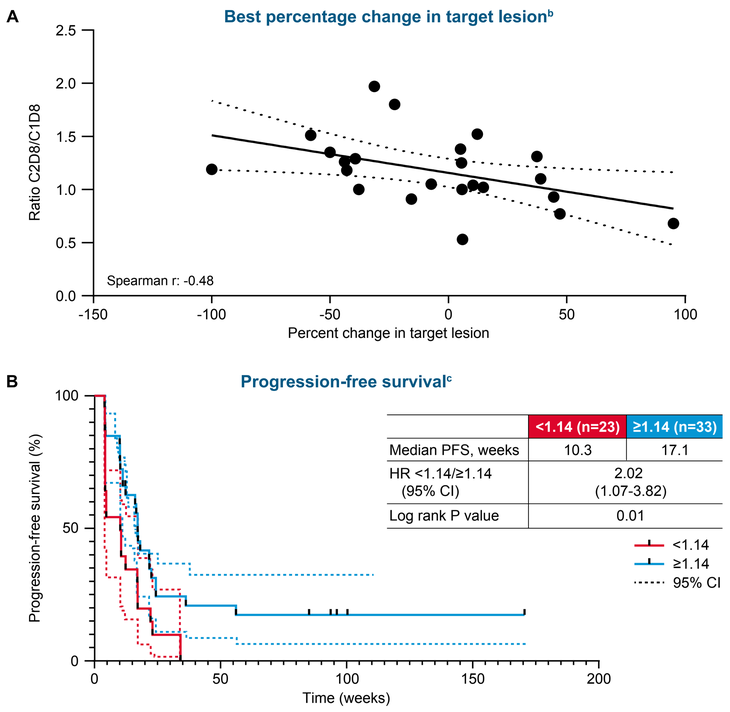
- The ratio of absolute count for NK cells (defined by $CD16^+/CD56^+$) at C2D8/C1D8 was identified as a potential predictive marker of response
- Analytical validation of this biomarker in Group 1 (monotherapy cohort) can be seen using BOR (Table 1), best percentage change in target lesion (Figure 3A), and progression-free survival (PFS; Figure 3B)
- A cutoff of ≥1.14 for the NK cell ratio at C2D8/C1D8 demonstrated a strong negative predictive value (NPV), correlated with a greater decrease in target lesion, and showed a statistically significant difference in PFS

TABLE 1: Analytical validation of the C2D8/C1D8 NK cell ratio in the Group 1 monotherapy cohort[a] using BOR[b]

	Includes only CR/PR and PD patients			Includes CR/PR, PD, and SD patients		
Group 1 Melanoma and RCC (cutoff 1.14)	**PR/CR**	**PD**	**Total**	**Responders PR/CR/SD >12 wks**	**Nonresponders PD/SD <12 wks**	**Total**
C2D8/C1D8 ratio > cutoff	7	5	12	21	12	33
C2D8/C1D8 ratio < cutoff	1	10	11	8	15	23
Total	8	15	23	29	27	56
	Sensitivity, 87.5%; Specificity, 67% PPV, 58%; NPV, 91%			**Sensitivity, 72%; Specificity, 55% PPV, 64%; NPV, 65%**		
Group 1 Only melanoma (cutoff 1.14)	**PR/CR**	**PD**	**Total**	**Responders PR/CR/SD >12 wks**	**Nonresponders PD/SD <12 wks**	**Total**
C2D8/C1D8 ratio > cutoff	5	4	9	15	9	24
C2D8/C1D8 ratio < cutoff	0	5	5	5	10	15
Total	5	9	14	20	19	39
	Sensitivity, 100%; Specificity, 55% PPV, 55%; NPV, 100%			**Sensitivity, 75%; Specificity, 53% PPV, 63%; NPV, 67%**		
Group 1 Only RCC (cutoff 1.14)	**PR/CR**	**PD**	**Total**	**Responders PR/CR/SD >12 wks**	**Nonresponders PD/SD <12 wks**	**Total**
C2D8/C1D8 ratio > cutoff	2	1	3	6	3	9
C2D8/C1D8 ratio < cutoff	1	5	6	3	5	8
Total	3	6	9	9	8	17
	Sensitivity, 66%; Specificity, 83% PPV, 66%; NPV, 83%			**Sensitivity, 67%; Specificity, 63% PPV, 67%; NPV, 63%**		

max, maximum; min, minimum; PPV, positive predictive value; RP2D, recommended phase 2 dose.
[a]Patients received nemvaleukin 6 µg/kg RP2D; median number of cycles, 6 (min-max, 2-52); median duration of treatment, 19.6 weeks (min-max, 5-178). [b]BOR includes confirmed and unconfirmed responses.

FIGURE 3: Analytical validation of the C2D8/C1D8 NK cell ratio in the Group 1 monotherapy cohort[a]

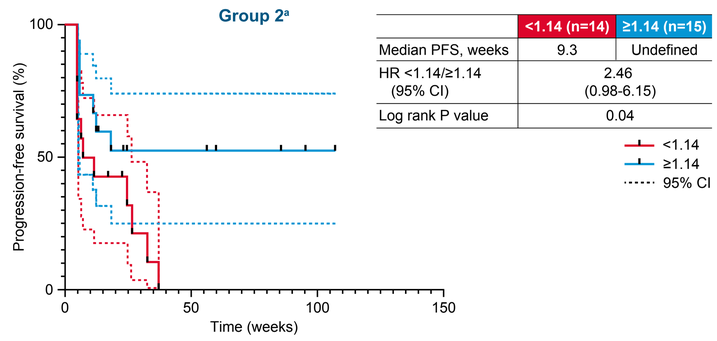


CI, confidence interval; HR, hazard ratio.
[a]Patients received nemvaleukin 6 µg/kg RP2D; median number of cycles, 6 (min-max, 2-52); median duration of treatment, 19.6 weeks (min-max, 5-178). [b]Includes total N=23 (PR, 8; PD, 15). [c]Includes total N=56 (PR, 8; SD, 33; PD, 15).

Predictive Value of the NK Cell Ratio at C2D8/C1D8 for Response to Nemvaleukin Combination Therapy

- A cutoff of ≥1.14 for the NK cell ratio at C2D8/C1D8 also demonstrated a significant difference in PFS for the Group 2 and Group 3 combination cohorts (Figure 4)
- Subgroup analysis of patients in Cohort 3 based on prior PD-1 treatment (pretreated vs naive) revealed that the trend for the biomarker was consistent in both groups, with a higher NK cell ratio predicting longer PFS, although caveats remain of multiple confounding variables such as different tumor types, different doses of nemvaleukin (3 or 6 µg/kg), and different prior lines of treatment (data not shown)

FIGURE 4: PFS by the C2D8/C1D8 NK cell ratio is predictive of response in the combination therapy cohort



[a]Patients received nemvaleukin 3 µg/kg and pembrolizumab; median number of cycles received, 8 (min-max, 2-32); median duration of treatment, 26.1 weeks (min-max, 6.3-111.1). [b]Patients received nemvaleukin 3 or 6 µg/kg and pembrolizumab; median number of cycles received, 5 (min-max, 2-43); median duration of treatment, 17.1 weeks (min-max, 4-137.1)

Analysis of the C2D8/C1D8 NK Cell Ratio by Patient Baseline Characteristics

- Logistic regression analysis, adjusting for baseline NK cell numbers, age, sex, and prior treatment lines, for patients with melanoma in Group 1 showed the NK cell ratio as the only predictor associated with response (defined as CR/PR and SD >12 weeks; data not shown)

Characterization of NK Cell Subtypes Following Nemvaleukin Treatment

- The largest proportion of NK cells in all groups at baseline, C1D8, and C2D8 were the $CD16^{bright}CD56^{dim}$ cytotoxic phenotype (Figure 5)
- The proportion of $CD16^{low}CD56^{bright}$ NK cells expanded in all groups with nemvaleukin treatment

FIGURE 5: Characterization of NK cell subtypes

Patients with SD were excluded from this analysis.

CONCLUSIONS

Limitations

- Limitations of this analysis include the small sample size

Conclusions

- NK cell expansion emerged as a novel predictive biomarker of response to nemvaleukin in melanoma and other solid tumors, offering early insight into treatment effect
- The predictive value of NK cell expansion was consistent across patient subgroups by baseline characteristics (age, sex, and prior treatment)
- Prospective validation of NK cell expansion in larger ongoing studies is warranted

References

1. Lopes JE, et al. *J Immunother Cancer.* 2020;8(1):e000673.
2. Vaishampayan UN, et al. Oral presentation at the ASCO Annual Meeting 2022. Abstract #2500.

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