Post-treatment neutrophil-to-lymphocyte ratio and gMDSCs as Independent prognostic factors for treatment efficacy with monoclonal antibody NEO-201 and pembrolizumab

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Methods

PBMCs and serum from cancer patients on the Phase II trial combining NEO-201 with Pembrolizumab (NCT03476681) were used to evaluate the percentage of circulating gMDSCs (flow cytometry) and arginase-1 levels (ELISA). Patients with chemo-resistant solid tumors, who were resistant to prior checkpoint inhibitor therapy, received NEO-201 1.5mg/kg every 2 weeks with pembrolizumab 400mg IV every 6 weeks (1 cycle), and were imaged for response every 2 cycles. gMDSCs percentage in PBMCs and Arginase-1 levels in serum were analyzed after treatment (C1D1), 14 days after first infusion with NEO-201 (C1D15), before cycle 2 (C2D1), and before cycle 3(C3D0). gMDSC population was defined as HLA-DR neg/CD33+/CD15+/CD14neg/CD66b. Given that NEO-201 has not been previously administered with pembrolizumab, a safety lead-in has been conducted in three subjects who received NEO-201 at 1.5 mg/kg IV every 2 weeks, and pembrolizumab 400 mg IV every 6 weeks. The safety lead-in course was 42 days in length and consisted of 1 dose of pembrolizumab and 3 doses of NEO-201.

Safety lead-in successfully completed. Expansion cohorts currently enrolling

The sample size for the expansion cohorts are calculated based on the desirable ORR (Simon minimax two-stage phase II design) for each cohort (Table 1).

Table 1: Enrollment to two-stage design per expansion cohorts

<table>
<thead>
<tr>
<th>Disease Cohort</th>
<th>Initial Stage</th>
<th>Acceptable Response Rate % (N/Total)</th>
<th>Second Stage</th>
<th>Sufficiently interesting Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>12</td>
<td>20% (1/12)</td>
<td>21</td>
<td>14.3% (3/21)</td>
</tr>
<tr>
<td>HNSCC</td>
<td>16</td>
<td>25% (2/10)</td>
<td>31</td>
<td>19.4% (6/31)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>16</td>
<td>25% (2/10)</td>
<td>31</td>
<td>19.4% (6/31)</td>
</tr>
<tr>
<td>Cervical</td>
<td>13</td>
<td>25% (3/12)</td>
<td>20</td>
<td>15% (3/20)</td>
</tr>
</tbody>
</table>

Results

2. Reduction of Quantity of Circulating gMDSCs post Treatment is Associated with Stabilization of the Disease (SD)

Based on the observation that NEO-201 recognizes and kills gMDSCs via ADCC [2], we compared the percentage of gMDSCs population from PBMCs (HLA-DRneg/CD33+/CD15+/CD14neg/CD66b) of three cancer patients with stable disease (SD) and three cancer patients with progressive disease (PD) pre and post treatment. Then, we correlated the modulations of levels of circulating gMDSCs with the clinical

Comparison of the percentage of circulating gMDSCs (HLA-DRneg/CD33+/CD15+/CD14neg/CD66b) cells between 3 cancer patients with stable (SD) and 3 cancer patients with progressive disease (PD) at different time points by flow cytometry analysis. gMDSCs were gated from alive PBMCs. Data are presented as median of percentage of viable cells expressing gMDSCs markers

Cancer patients with PD: Patient 7 (SD > 11 months) showed reduced gMDSCs (93.86%) at C3D0 compared to baseline (0.14% vs 0.228%). Patient 6 showed a marked reduction of gMDSCs (87.42%) at C1D15 compared to C1D0 (0.074% vs 0.588%). Patient 1 (SD > 8 months) showed initial increase of gMDSCs at C1D15 and C2D0 compared to C1D1 but trended down at C1D1 (0.146% vs 0.114%).

Cancer patients with PD: general uptrend of circulating gMDSCs in patients with PD.

4. Cancer Patients with PD had Higher Neutrophil-to-Lymphocyte Ratio (NLR) Compared to Cancer Patients with SD

Comparison of serum levels of arginase-1 between 3 cancer patients with stable (SD) and 3 cancer patients with progressive disease (PD). Data are presented as median of arginase-1 serum levels.

5. Characteristics of Cancer Patients with SD

Cancer patient: 50 years old with chemo-resistant metastatic gastric carcinoma.
80% tumor tissue positive for NEO-201 staining in IHC with 3+ intensity.
Stable disease for more than 6 months after first infusion with both antibodies.
Patient qualified for debulking surgery requiring exiting the study.

Head and neck squamous cell carcinoma patient:
72 years old with moderately differentiated squamous cell carcinoma.
10-15% tumor tissue positive for NEO-201 staining in IHC with 3+ intensity.
Stable disease for more than 15 months after first infusion with both antibodies.

NSCLC patient:
69 years old with metastatic lung adenocarcinoma.
50% tumor tissue positive for NEO-201 staining in IHC with 3+ intensity.
Stable disease by RECIST on Day 84.
Patient was taken off study per treating physician’s decision.

Conclusion

We compared cancer patients with SD and PD at first radiological assessment (C3D0 PRE). Among patients with SD we observed a general downtrend of circulating gMDSCs after treatment. On the other hand, there was a general uptrend of circulating gMDSCs in patients with PD. Additionally, patients with PD had NLR >10 at C2D1, suggesting moderate to severe physiological stress compared to patients with SD who had NLR level <10.

Recent studies highlight the host’s inflammatory response in tumor development and progression of various cancers. In our study, patients with SD had a downtrend of circulating gMDSCs, arginase-1 levels and normal to mild NLR compared to patients with PD, suggestive of good prognosis for treatment with NEO-201 and pembrolizumab. Ongoing enrollment in this clinical trial will validate these findings in larger cohorts.

References