Antitumor Activity of Dostarlimab by PD-L1 and Tumor Mutational Burden in Patients with Mismatch Repair Deficient and Proficient Tumors in the GARNET Trial

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Background

Dostarlimab is a programmed death receptor 1 (PD-L1)-blocking antibody that is approved in the US as a monotherapy in adult patients with the following: - Microsatellite instability-high (MSI-H) tumors - MSI-H tumors and PD-L1 ≥10% (A2) advanced/recurrent EC, and - MSI-H tumors and PD-L1 ≥10% (A1) recurrent or advanced endometrial cancer (EC) that has progressed on or after prior treatment with a platinum-containing regimen - dMMR recurrent or advanced solid tumors that have progressed on or after prior treatment and who have no satisfactory Alternative treatment options

In the EU, dostarlimab is approved as a monotherapy in adult patients with recurrent or advanced dMMR/microsatellite instability-high (MSI-H) EC that has progressed on or after treatment with a platinum-containing regimen

- Along with dMMR/MSI-H, tumor microsatellite/burden (TMB) and combined positive score (CPS) are biomarkers associated with higher response rates to anti-PD-L1 therapy

Conclusions

- High expression of programmed death ligand 1 (PD-L1) and high TMB (TMB-H) are more common in dMMR tumors, however, a subset of mismatch repair proficient (dMMR) tumors are also TMB-H (40%). Some MMRp tumors (5%) are also TMB-H.

- Most dMMR tumors are also TMB-H (40%). Some MMRp tumors (5%) are also TMB-H.

- TMB-H occurs in <5% of dMMR tumors and in <40% of MMRp tumors

- In dMMR tumors there is considerable overlap of PD-L1-H and TMB-H; however, most PD-L1-H tumors are not TMB-H.

- Most TMB-H tumors are PD-L1-H, regardless of MMR status.

- In the MMRp patients, the sample size was not sufficient to determine if TMB alone, or PD-L1 and TMB together, may predict response

- Differences in the distribution of TMB and CPS scores by cohort existed, and future research may refine the optimal cutoff points for each tumor type or an overall cutoff

- In summary, patients with high neocarcinogenesis (PD-L1-H) and/or inflamed microenvironment (PD-L1-H) have increased objective response rate (ORR) compared to tumors with an absence of these features

Methods

- GARNET (NCT02715284) is a phase 1, multicenter, open-label, single-arm study of dostarlimab in patients with advanced/recurrent solid tumors (Figure 1)

- Three expansion cohorts enrolled patients based on MMR status (A1, A2) and dMMR status, and dMMR patients with ≥10 mutations/Mb

- Patients received dostarlimab 500 mg every 3 weeks for 4 cycles, then 500 mg every 6 weeks until disease progression or discontinuation

- TMB and PD-L1 were explored as biomarkers

- TMB status was determined by Foundation One test; TMB ≥10 mutations/Mb

- PD-L1 status was determined by Veneris assay; PD-L1-H was defined as ≥1% expression

- The study was not powered to assess antitumor activity subgroup

Results

- Overall, 351 patients were enrolled into the 3 cohorts for this analysis:

  - cohort A: 115, MMRp (cohort A1) and dMMR (cohort A2)
  - cohort F: 69, dMMR (cohort F)

- 58 patients with dMMR, 138 patients with dMMRp, and 68 patients with dMMR or dMMRp (cohort A2) were evaluable for analysis

- 79 patients with dMMR, 107 patients with MMRp, and 69 patients with dMMR or dMMRp had known CPS scores

Objective

- Here we report a post hoc analysis of antitumor activity by PD-L1 expression and TMB in patients with dMMRp and MMRp solid tumors in the GARNET trial

Table 1. Tumor Types Enrolled in Cohorts A1, A2, and F

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Tumor Type</th>
<th>Patients (N)</th>
<th>TMB ≤9</th>
<th>TMB ≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>MMRp (PD-L1-H)</td>
<td>115</td>
<td>94</td>
<td>21</td>
</tr>
<tr>
<td>A2</td>
<td>MMRp (PD-L1-H)</td>
<td>115</td>
<td>94</td>
<td>21</td>
</tr>
<tr>
<td>A2</td>
<td>dMMR (PD-L1-H)</td>
<td>115</td>
<td>94</td>
<td>21</td>
</tr>
<tr>
<td>A2</td>
<td>dMMR (PD-L1-L)</td>
<td>115</td>
<td>94</td>
<td>21</td>
</tr>
<tr>
<td>F</td>
<td>dMMR (PD-L1-H)</td>
<td>69</td>
<td>56</td>
<td>13</td>
</tr>
<tr>
<td>F</td>
<td>dMMR (PD-L1-L)</td>
<td>69</td>
<td>56</td>
<td>13</td>
</tr>
</tbody>
</table>

- TMB and PD-L1-H were common in dMMR solid tumors; PD-L1-H was more common than TMB-H in MMRp EC (Figure 2A)

- The majority of TMB-H tumors were also PD-L1-H (Figure 2B)

- In the dMMR cohorts (A2 and F) the majority of patients with PD-L1-H were also TMB-H

- Although 38% of patients with PD-L1-H were PD-L1-L, only a small number of patients in that cohort were TMB-H; thus, the majority of PD-L1-H patients with dMMR or dMMRp EC were TMB-L

Results (cont’d)