Enhanced efficacy of anti-VEGFR2/taxane therapy after progression on immune checkpoint inhibition (ICI) in patients with metastatic gastroesophageal adenocarcinoma (mGEA).

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Abstract

Background:
Most pts with mGEA do not respond to ICI or anti-VEGFR2 (semotuzumab) in combination (RAM/TAX)1,2. We unexpectedly observed durable responses in 2 patients on RAM/TAX after progression on an ICI trial (NCT05999913). We performed a pilot to examine if ICI impacts efficacy of subsequent RAM/TAX in a larger cohort and explored alterations in the tumor microenvironment.

Methods:
All patients with mGEA at Mayo Clinic who received RAM/TAX (2014-15) were included (N = 87). Outcomes were best objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS). Chi-square and multivariate (MV) logistic and Cox regression were used.

Results:
15 consecutive patients with measurable mGEA received ICI immediately followed by RAM/TAX after rRECIST progression. Most patients (95%) did not respond to ICI. Yet on RAM/TAX, ORR was 73%. In these patients (who received ICI followed by RAM/TAX), PFS on RAM/TAX was longer than on last chemotherapy before ICI (12.3 vs 3.0 m, P < .001). Outcomes on RAM/TAX in these patients were significantly better than in patients who received RAM/TAX alone (see Table). Associations were strengthened after adjusting for total lines of therapy, line of therapy of RAM/TAX, age, and ECOG PS. Exploratory analysis of paired tumor biopsies collected pre-ICI and on RAM/TAX revealed that the frequency of intratumoral immunosuppressive FOXP3+ Tregs decreased on RAM/TAX, whereas the frequency of antitumor CD8+ T cells was preserved.

Conclusions:
RAM/TAX immediately preceded by ICI was associated with significantly higher OS, PFS, ORR, and DOR than RAM/TAX alone, suggesting ICI may enhance efficacy of subsequent anti-VEGFR2/taxane therapy. This novel sequence of therapy will be tested prospectively in a new randomized phase 2 trial (NCT04069273).

Table 1: Patient baseline characteristics (n=87).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RAM/TAX with preceding ICI</th>
<th>RAM/TAX without preceding ICI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58.8 (18.5%)</td>
<td>62.9 (19.5%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Male</td>
<td>16 (18.5%)</td>
<td>83 (95%)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS 0-1 before RAM/TAX</td>
<td>16 (18.5%)</td>
<td>80 (85%)</td>
<td>0.004</td>
</tr>
<tr>
<td>RAM/TAX 2+</td>
<td>17 (20%)</td>
<td>59 (67%)</td>
<td></td>
</tr>
<tr>
<td>Total lines of therapy (median)</td>
<td>3</td>
<td>3 (range 1-14)</td>
<td>0.004</td>
</tr>
<tr>
<td>Tumor diff, poor</td>
<td>11 (13%)</td>
<td>44 (51%)</td>
<td>0.012</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>4 (12%)</td>
<td>11 (15%)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*Includes 4 pts with non-measurable disease

With preceding ICI Without preceding ICI P

n = 19  n = 68

<table>
<thead>
<tr>
<th>Response</th>
<th>RAM/TAX with preceding ICI</th>
<th>RAM/TAX without preceding ICI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>58%</td>
<td>18%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DOR</td>
<td>10.5 m</td>
<td>4.3 m</td>
<td>.021</td>
</tr>
<tr>
<td>OS</td>
<td>15.0 m</td>
<td>7.6 m</td>
<td>.003</td>
</tr>
</tbody>
</table>

Figures:

Figure 1 - Analytic Approach: 4 regimens and 2 key comparisons.

Figure 2 - Best response assessment of target lesions.

Figure 3 - Immunohistomorphometric analysis from a responder: substantial reduction (post vs. pre-Treatment) in intratumoral density of intratumoral progression (CD8+ T cells), with preserved density of antitumor CD8+ T cells.

Figure 4 - Overall survival (OS): RAM/TAX with vs. without preceding ICI.

Figure 5 - Progression-free survival (PFS): RAM/TAX with vs. without preceding ICI.

Figure 6 - Progression-free survival (PFS): RAM/TAX with preceding ICI vs. last chemo before ICI.

Figure 7 - Progression-free survival (PFS): RAM/TAX with preceding ICI vs. last chemo before ICI.

Key:
- 1 Includes 4 pts with non-measurable disease
- 2 Percent 95% CI
- 3 Logrank
- 4 HR 95% CI

References: