Abstract 5548: Nivolumab plus Ipilimumab in Patients with Ovarian Cancer with BRCA1/2 Mutations: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

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Background:
• TAPUR is a phase II basket study that evaluates antitumor activity of commercially available targeted agents in patients (pts) with advanced cancers with specific genomic alterations.
• Results of a cohort of pts with ovarian cancer (OC) with BRCA1/2 mutations (mut) treated with nivolumab plus ipilimumab (N+I) are reported.

Methods:
Study Design:
• Eligible pts: Advanced OC, ECOG performance status (PS) 0-2, adequate organ function, measurable disease and no standard treatment (tx) options. Tx was assigned according to prespecified protocol matching rules based on genomic testing performed in CLIA-certified, CAP-accredited labs selected by clinical sites. PS-1 status was not routinely reported.
• Pts received I at 3 mg/kg every three weeks (wks) for four doses with N at 1 mg/kg IV every three wks for four doses. N alone was then continued at 240 mg every two wks or 480 mg every four wks until disease progression, unacceptable toxicity or pt or physician choice to discontinue.
• Primary endpoint: Disease control (DC) determined by investigator assessment of objective response (OR) or stable disease (SD) of at least 16 wks duration (SD16+) per RECIST v1.1. Confirmation of response was not required, and response was based on measured target lesions only as CA-125 levels were not routinely reported.
• Secondary endpoints: Progression-free survival (PFS), overall survival (OS), duration of response, duration of SD, and toxicity per CTCAE v4.0. Grade 3-5 adverse events (AEs) or serious adverse events (SAEs) at least possibly related to tx were reported.

Statistical Methods:
• Simon’s optimal two-stage design was used to test the null hypothesis of 15% DC rate vs. alternative of 35%. Power = 85%; 1-sided α = 10%. The p-value was calculated based on the Simon’s two-stage design.
• At least seven of 28 pts must achieve DC to reject null hypothesis and consider response to N+I in this patient population.

Results:
• 62 pts enrolled from September 2017 to October 2019. Six pts were not evaluable.
• 33 pts enrolled in the cohort (95% CI: 27 to 39).
• 27 (13, 36); p=0.169
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Conclusion: Nivolumab plus ipilimumab did not meet prespecified criteria to declare a signal of activity in patients with ovarian cancer and BRCA1/2 mutations.

Future Direction: The observation of six partial responses, some long-lasting, supports further study to identify additional predictive biomarkers of response to N+I in this patient population.

Table 1. Duration of PR and Mut of Pts Meeting Response Criteria (n=6)

<table>
<thead>
<tr>
<th>Response</th>
<th>Duration of PR</th>
<th>Mut</th>
<th>Comutations</th>
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<tbody>
<tr>
<td>PR</td>
<td>80 wks</td>
<td>BRCA1 E1213* and BRCA2 K3326* (VUS)</td>
<td>RAD51 rearrangementa</td>
</tr>
<tr>
<td>PR</td>
<td>62 wks</td>
<td>BRCA1 R1751X deletion</td>
<td>--</td>
</tr>
<tr>
<td>PR</td>
<td>14 wks</td>
<td>BRCA2 A9385* and N888_K1025del</td>
<td>ARID1A Q321fs*70 ATM S1691Rb FANCL L59Pb</td>
</tr>
<tr>
<td>PR</td>
<td>8 wks</td>
<td>BRCA1 Ser1253Argf*10</td>
<td>--</td>
</tr>
<tr>
<td>PR</td>
<td>unknownc</td>
<td>BRCA1 Q1127*</td>
<td>--</td>
</tr>
<tr>
<td>PR</td>
<td>unknownd</td>
<td>BRCA2 S1982_A1991K and S1982fs*22</td>
<td>ATM MB1218e FANCF K324eb FANCL L808eb</td>
</tr>
</tbody>
</table>

aThe following genes were examined: ARID1A, ATM, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, and WRN. bVariant of unknown significance (VUS). cPt ended study shortly after achieving PR due to an AE of neuropathy. dPt ended study shortly after achieving PR due to a grade 4 SAE of hypokalemia.

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Table 2: Efficacy Outcomes (n=27)

<table>
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<tr>
<th>DC rate, % (90% CI)</th>
<th>27 (13, 36); p=0.169</th>
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<tbody>
<tr>
<td>OR rate, % (95% CI)</td>
<td>22 (9, 42)</td>
</tr>
<tr>
<td>Median PFS, wks (95% CI)</td>
<td>8.1 (8.0, 8.3)</td>
</tr>
<tr>
<td>Median OS, wks (95% CI)</td>
<td>45 (20, 133)</td>
</tr>
<tr>
<td>Median duration of PR, wks (95% CI)</td>
<td>38 (8, inf)</td>
</tr>
</tbody>
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*OR rate differs from DC as the DC rate accounts for the Simon’s two-stage design.

Figure 1: Best Percent Change from Baseline in Target Lesion Size (n=27)

Figure 2: Time on Tx in Pts with OR and SD16+ (n=6)

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