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. PD-L1 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 are 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 tx worthy of further study.

Results:

- 33 pts enrolled from September 2017 to October 2019. Six pts were not evaluable for efficacy: one pt was found to be ineligible after enrolling for having no measurable disease, five pts discontinued tx before the first post-baseline tumor evaluation due to an AE or SAE.
- **Demographics**: Median age 59 (range, 47-86); 100% female; 79% self-identified as White, 6% as Black/African American, 3% as Asian/Asian American, 9% preferred not to answer, 3% as Other; 94% as not Hispanic or Latino.
- **Clinical characteristics:** 97% PS 0-1, 3% PS 2; 91% received ≥3 prior systemic regimens; 28/33 pts (85%) had platinum therapy as one of their three most recent therapies and 21/33 pts (64%) were treated with PARP inhibitor(s) as one of their three most recent therapies.

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.

- **Alterations**: 20 pts (61%) had *BRCA1* mut; 10 (30%) had *BRCA2* mut, and three pts (9%) had both *BRCA1* and *BRCA2* muts.
- **Outcomes**: Six pts had PR for a DC rate of 27% (90% CI: 13 to 36) (**Table 1 and 2**). The null hypothesis was not rejected (p=0.169).
- **Safety:** 17 pts (52%) had ≥1 SAE or grade 3 AE at least possibly related to N+I, including acute kidney injury, ALT/AST increase, colitis, dehydration, diarrhea, E. coli, ejection fraction decrease, elevated liver enzymes and lipase, fever, hyponatremia, hypokalemia, nausea/vomiting, pneumonitis and rash.

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

Response	Duration of PR	Mut	Comutations[a]
PR	80 wks	*BRCA1* E1213* and *BRCA2* K3326* (VUS)	*RAD51* rearrangement[b]
PR	62 wks	*BRCA1* R1751X deletion	--
PR	14 wks	*BRCA2* A938fs* and N888_K1025del	*ARID1A* Q321fs*70 *ATM* S1691R[b] *FANCL* L59P[b]
PR	8 wks	*BRCA1* Ser1253Argfr*10	--
PR	unknown[c]	*BRCA1* Q1227*	--
PR	unknown[d]	*BRCA2* S1982_A1991>K and S1982fs*22	*ATM* M812I[b] *FANCF* K324E[b] *FANCL* L80V[b]

[a] The 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*. [b] Variant of unknown significance (VUS) [c] Pt ended study shortly after achieving PR due to an AE of neuropathy. [d] Pt ended study shortly after achieving PR due to a grade 4 SAE of hypokalemia.

Funding supported by Bristol Myers Squibb (BMS). The authors would like to thank the patients who participated in this cohort, the clinical centers and staff, and Cynthia Brogdon, RN, PhD, clinical lead of BMS, a TAPUR supporting pharmaceutical company.

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Table 2: Efficacy Outcomes (n=27)

DC rate, % (90% CI)	27 (13, 36); p=0.169
OR rate, % (95% CI)[a]	22 (9, 42)
Median PFS, wks (95% CI)	8.1 (8.0, 8.3)
Median OS, wks (95% CI)	45 (20, 133)
Median duration of PR, wks (95% CI)	38 (8, inf)

[a] OR rate differs from DC rate 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)

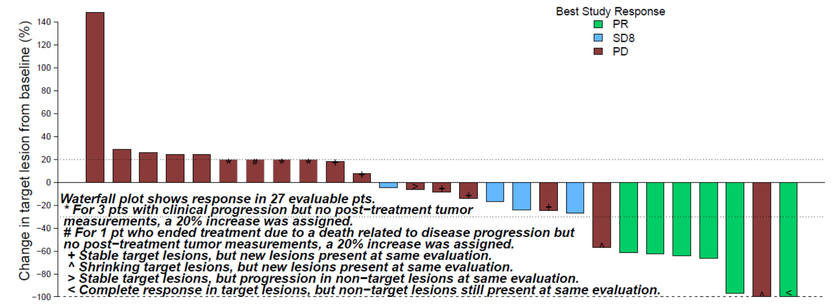

Figure 2: Time on Tx in Pts with OR or SD16+ (n=6)