FPN 943P: Atezolizumab plus talazoparib in patients with solid tumors with *BRCA1/2* alterations: 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 the antitumor activity of commercially available targeted agents in patients (pts) with advanced cancers with specific genomic alterations.
- Pts with *BRCA1/2*-altered cancers may benefit from atezolizumab plus talazoparib (A+T) due to the induction of synthetic lethality (T), which can enhance genomic instability and sensitize the tumor to immunomodulation via PD-L1 blockade (A).
- **Results of a cohort of pts with solid tumors with *BRCA1/2* alterations treated with A+T are reported.**

Methods

Study Design:

- **Eligible pts:** Advanced solid tumors, no standard treatment (tx) options, no prior tx with PARP, PD-1/PD-L1 or CTLA-4 inhibitors, ECOG PS 0-2, adequate organ function, measurable disease. Tx assigned according to prespecified matching rules based on genomic tests selected by sites. For most pts, the genomic test performed did not distinguish between germline and somatic mutation (mut).
- Pts received 1200 mg IV of A every 3 weeks (wks) concurrently with 1 mg of T orally daily until disease progression, unacceptable toxicity or pt or physician choice to discontinue.
- **Primary endpoint:** Disease control (DC) defined as objective response (OR) or stable disease (SD) of at least 16+ wks (SD16+) per RECIST v1.1.
- **Secondary endpoints:** OR, progression-free survival (PFS), overall survival (OS), duration of response (DOR), duration of SD, and toxicity per CTCAE. Grade 3-5 adverse events (AE) or serious adverse events (SAE) at least possibly related to A+T are reported.
- DOR is defined as time from pt's first documented OR to progressive disease (PD). Duration of SD is defined as time from tx start to PD.

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%.
- At least 7 of 28 pts must achieve DC to reject null hypothesis and consider tx worthy of further study.

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Results

- 29 pts enrolled May 2021 to May 2024. 2 pts were not evaluable for efficacy. 7 pts (24%) had *BRCA1* mut; 18 (62%) had *BRCA2* mut, 1 (3%) had *BRCA1* deletion (del), 2 (7%) had *BRCA2* del, 1 (3%) had both *BRCA1* and *BRCA2* del and *BRCA2* mut. Demographics and clinical characteristics are summarized in **Table 1**.
- **Outcomes**: 9 pts (33%) had partial response (PR) and 6 pts (22%) had SD16+ **(Table 2 and 3)**. Median duration of PR was 47 wks (range, 12-128) and of SD for pts with SD16+ was 44 wks (range, 28-147).
- **Safety:** 12 pts (41%) had ≥1 tx-related SAE or grade 3-5 AE. All were consistent with drug labels except for generalized muscle weakness, thromboembolic event, oral mucositis, hyponatremia, confusion, UTI, sepsis, sinus tachycardia, pancreatitis.

Table 1. Baseline Characteristics (N=29)

Characteristic		N (%)[a]
Median Age	Years (range)	56 (40, 80)
Sex	Female	19 (66)
Race	Asian/Asian American	1 (3)
	Black or African American	2 (7)
	White	21 (72)
	Other	3 (10)
	Prefer not to answer	2 (7)
Ethnicity	Hispanic or Latino	4 (14)
	Not Hispanic or Latino	24 (83)
	Prefer not to answer	1 (3)
ECOG PS	0	14 (48)
	1	15 (52)
Prior Systemic Regimens	0	1 (3)
	1	6 (21)
	2	7 (24)
	≥3	15 (52)
Prior Platinum Therapy	Yes	15 (52)
	No	14 (49)
Primary Tumor Origin	Breast	11 (38)
	Pancreas	9 (31)
	Cholangiocarcinoma	2 (7)
	NSCLC	2 (7)
	Gallbladder	1 (3)
	Prostate	1 (3)
	Small intestine	1 (3)
	Thymus	1 (3)
	Unspecified	1 (3)

[a]Percentages may not sum to 100% due to rounding.

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Table 2. Tumor Origin and Alterations of Pts Meeting Response Criteria (n=15)

Pt[a]	Response	Primary Tumor Origin	*BRCA1/2* Alteration[a]	MS/ PD-L1 Status[b]	Muts/Mb[b]	Co-alterations[c, d]
A	PR	Breast	*BRCA1* D1475fs	MS stable (MSS), PD-L1 negative	11.5	--
B	PR	Breast	*BRCA1* del *BRCA2* del, L2092fs	MSS, PD-L1 negative	6	*ERBB2* amplification *RAD51C* E375*[e]
C	PR	Breast	*BRCA1* S1450*	MSS, PD-L1 positive	1	*RB1* exon 14 rearrangement *POLE* R2259Q[e] *PARP1* L1013M[e]
D	PR	Breast	*BRCA1* splice site 213-11T>G	MSS, PD-L1 positive	1	*PTEN* I135K
E	PR	Breast	*BRCA2* I2627F	NT	NT	--
F	PR	Pancreas	*BRCA1* del	NT	NT	--
G	PR	Pancreas	*BRCA1* F1571fs	MSS, PD-L1 NT	4	*KRAS* G12D
H	PR	Pancreas	*BRCA2* S2670L[f]	MSS, PD-L1 positive	2.1	*KRAS* G12R *ATM* E223G[e]
I	PR	NSCLC	*BRCA2* P606_K607>L*	MSS, PD-L1 negative	10	*EGFR* E709_T710>D *CHEK2* T367fs*15 *FANCA* C1142fs*1 *POLE* S1353G[e] *BARD1* S376L[e] *ATRX* L2395F[e]
J	SD16+	Breast	*BRCA2* T308fs	MSS, PD-L1 NT	4.2	*PTEN* M1? *RUNX1* F416fs
K	SD16+	NSCLC	*BRCA1* Q1467fs, N1272H[e]	MSS, PD-L1 negative	NT	*EGFR* D770_N771insSVD *ERBB2* E553*[e]
L	SD16+	Cholangiocarcinoma	*BRCA2* splice site 7007+2T>C	NT	NT	*ATM* R2547_S2549 del *STK11* G163R *ERBB3* R55G[e]
M	SD16+	Cholangiocarcinoma	*BRCA2* S641fs*3	MSS, PD-L1 NT	4	--
N	SD16+	Gallbladder	*BRCA2* Q2655*	MSS, PD-L1 high	7	*ERBB2* G776delinsLC
O	SD16+	Thymus	*BRCA2* R1512H	MSS[e], PD-L1 negative	1.6[e]	*TOP2A* splice site 22-2A>G *MSH2* Y43C[e]

[a]Pt letter corresponds to letter/bar in Figure 2.
[b]MSI, TMB, and PD-L1 status are listed unless not tested (NT).
[c]Unless otherwise specified, germline or somatic status was not reported.
[d]The list of genes reviewed for inclusion are available upon request.
[e]Variant of unknown significance.
[f]Germline.

Table 3: Efficacy Outcomes (n=27)

DC rate, % (1-sided 90% CI), p-value	56 (35, 100), p=0.0001
OR rate, % (95% CI)	33 (17, 54)
Median PFS, wks (95% CI)	28 (8, 41)
Median OS, wks (95% CI)	92 (23, 133)

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

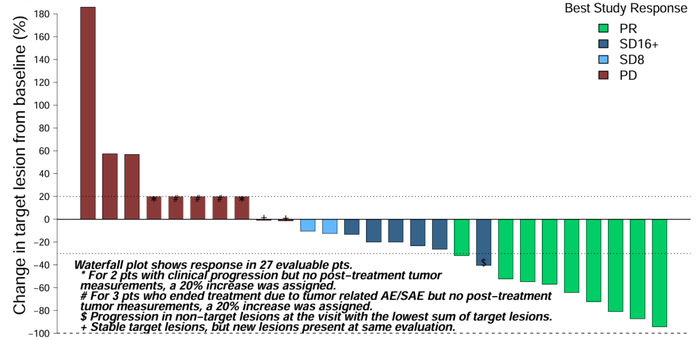


Figure 2: Time on Tx in Pts with PR or SD16+ (n=15)

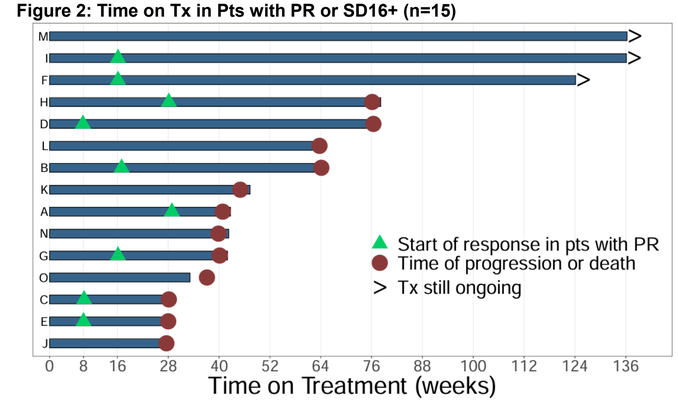
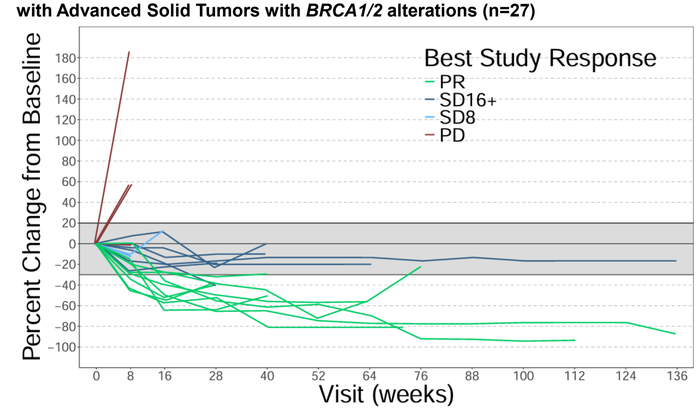


Figure 3: Percent Change from Baseline of Tumor Burden During A+T Tx in Pts with Advanced Solid Tumors with *BRCA1/2* alterations (n=27)



Conclusion

A+T met the prespecified criteria to declare antitumor activity in pts with solid tumors with *BRCA1/2* alterations. Additional study is warranted to confirm the efficacy of A+T and whether A adds to T alone.