FPN 942P: Atezolizumab plus talazoparib in patients with solid tumors with non-*BRCA1/2* DNA damage repair gene mutations: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

CJ Calfa[1], M Rothe[2], PK Mangat[2], E Garrett-Mayer[2], CM Reynolds[3], RC Wadlow[4], MD Chen[5], NR Ammakkanavar[6], MS Pelster[7], E Pisick[8], K Yost Butler[9], OV Crysler[10], CA Thomas[11], AL Jackson[12], T Philip[13], A Gregory[2], DC Hinshaw[2], GN Grantham[2], S Halabi[14], RL Schilsky[2]

[1]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL; [2]American Society of Clinical Oncology, Alexandria, VA; [3]Michigan Cancer Research Consortium, Ypsilanti, MI; [4]Inova Schar Cancer Institute, Fairfax, VA; [5]Sutter Cancer Research Consortium, Palo Alto, CA; [6]Community MD Anderson Cancer Center, Indianapolis, IN; [7]Sarah Cannon Research Institute, Nashville, TN; [8]City of Hope Chicago, Zion, IL; [9]Cancer Research Consortium of West Michigan, Grand Rapids, MI; [10]University of Michigan Rogel Comprehensive Cancer Center, Ann Arbor, MI; [11]Jackson Laboratory-Maine Cancer Genomics Initiative, Bar Harbor, ME; [12]University of Cincinnati Medical Center, Cincinnati, OH; [13]Northwell Health Cancer Institute, Lake Success, NY; [14]Duke University Medical Center, Durham, NC

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 DNA damage repair (DDR) gene (other than *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 non-*BRCA1/2* DDR (non-*BRCA*) mutations (mut) 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.
- 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.
- **The following non-*BRCA* muts were match criteria for the cohort: *ATM*, *ATR*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*.** For most pts, the genomic test performed did not distinguish between germline and somatic muts.
- **Primary endpoint:** Disease control (DC) defined as objective response (OR) or stable disease (SD) or at least16+ 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.

Results

- 30 pts enrolled from June 2021 to April 2023. 2 pts were not evaluable for efficacy. Demographics and clinical characteristics are outlined in **Table 1**.

Results Continued

- **Outcomes**: 3 pts (11%) had SD16+ and 3 (11%) had OR, including 2 partial responses (PRs) and 1 complete response (CR) **(Table 2 and 3).** The CR was documented at the final study visit. Durations of PR were 22 and 11 wks and of SD in pts with SD16+ were 25, 36, and 41 wks.
- **Safety:** 10 pts (33%) had ≥1 tx-related SAE or grade 3-4 AE. All were consistent with drug labels except for bilirubin increase, confusion, disseminated intravascular coagulation, hepatic failure, thromboembolic event.

Table 1. Baseline Characteristics (N=30)

Characteristic		N (%)[a]
Median Age	Years (range)	60 (41, 79)
Sex	Female	22 (73)
Race	Asian/Asian American	6 (20)
	Black or African American	4 (13)
	White	20 (67)
Ethnicity	Hispanic or Latino	3 (10)
	Not Hispanic or Latino	27 (90)
ECOG PS	0	15 (50)
	1	14 (47)
	2	1 (3)
Prior Systemic Regimens	1	4 (13)
	2	8 (27)
	≥3	18 (60)
Prior Platinum Therapy	Yes	16 (53)
	No	14 (47)
DDR Genes (# pts with gene muts)[b]	*ATM*	11 (37)
	CHEK2	11 (37)
	CDK12	6 (20)
	NBN	3 (10)
	ATR	2 (7)
	MRE11A	2 (7)
	PALB2	2 (7)
	FANCA	1 (3)
	MLH1	0 (0)
	RAD51C	0 (0)
Primary Tumor Origin	Breast	9 (30)
	Pancreas	4 (13)
	Gallbladder	3 (10)
	NSCLC	3 (10)
	Ovary	3 (10)
	Ampulla	1 (3)
	Carcinoid tumor of lung	1 (3)
	Cholangiocarcinoma	1 (3)
	Endometrium	1 (3)
	Esophagus	1 (3)
	Head and neck	1 (3)
	Prostate	1 (3)
	Small intestine	1 (3)

[a]Percentages may not sum to 100% due to rounding.
[b]Pts may have had muts in more than one qualifying DDR gene.

Table 2. Tumor Origin and Alterations of Pts Meeting Response Criteria (n=6)

Pt[a]	Response	Primary Tumor Origin	Non-*BRCA1/2* Mutation	MS/PD-L1 Status[b]	Muts/Mb[b]	Co-alterations[c,d]
A	CR	Ovary	*ATM* W2042*	MS stable (MSS), PD-L1 positive	5.3	*BRCA2* V950I[e] *CREBBP* P937L[e]
B	PR	Breast	*ATM* Q1970*	MSS, PD-L1 NT	5.7	*EGFR* amplification
C	PR	Uterus	*ATR* V219fs*1 *NBN* T452P[e]	MSS, PD-L1 negative	3	*PIK3CA* R108H *ATR2* V2191fs*1
D	SD16+	Breast	*CHEK2* W93fs	MSS, PD-L1 NT	9.6	*EGFR* I646M[e] E319K[e] *ERBB2* E1021K[e] *MTOR* G663W[e] *PIK3CA* C420R, Q546R *PTEN* Q245*
E	SD16+	Breast	*CDK12* D962fs	MSS, PD-L1 positive	19	*RAF1* G162E[e] *POLQ* splice site 1109-8delT[e]
F	SD16+	Lung neuroendocrine	*CDK12* S863S *CHEK2* L183S	MSS, PD-L1 negative	8.9	*PTEN* N184K[e]

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

Table 3: Efficacy Outcomes (n=28)

DC rate, % (1-sided 90% CI), p-value	27 (12, 100), p=0.19
OR rate, % (95% CI)	11 (2, 28)
Median PFS, wks (95% CI)	9 (8, 10)
Median OS, wks (95% CI)	41 (21, 72)

Figure 1: Best Percent Change from Baseline in Target Lesion Size (n=28)

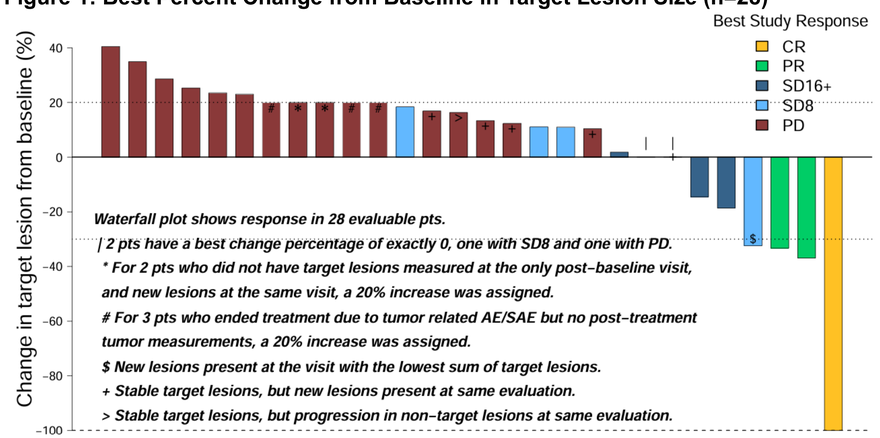


Figure 2: Time on Tx in Pts with SD16+ or OR (n=6)

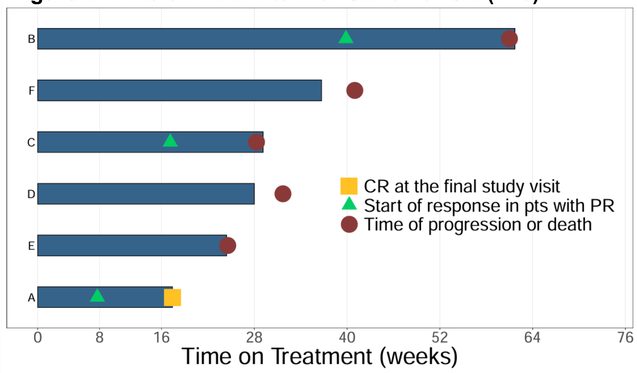
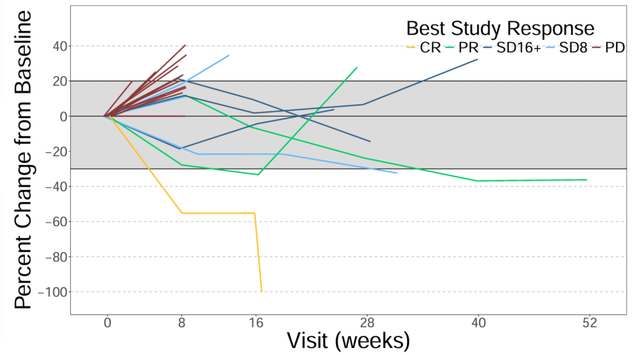


Figure 3: Percent Change from Baseline of Tumor Burden During Tx of A+T in Pts with Advanced Solid Tumors with Non-*BRCA* Alterations (n=28)



Conclusion

A+T did not meet the prespecified criteria to declare antitumor activity in pts with solid tumors with non-*BRCA* mutations. However, the observation of six pts with DC, some long lasting, supports further study to identify better predictive biomarkers of response to A+T in this pt population.

CJ Calfa DOI: No declarations

Funding provided by Genentech and Pfizer. The authors would like to thank the patients who participated in this cohort, the clinical centers and staff.

Contact: TAPURPublications@asco.org