Abstract 715: Nivolumab plus ipilimumab in patients with pancreatic cancer with *BRCA1/2* mutations: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

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Targeted Agent and Profiling Utilization Registry Study

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PJ Hosein[1], M Rothe[2], PK Mangat[2], E Garrett-Mayer[2], AD Baron[3], TL Cannon[4], E Pisick[5], E Hobbs[6], KF Mileham[7], M Tinguely[8], M Frimer[9], PJ Gold[10], KA Klute[11], SC Rogers[12], V Sahai[13], DPS Sohal[14], SP Thomas[15], JD Winegarden[16], GN Grantham[2], A Gregory[2], DC Hinshaw[2], S Halabi[17], 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]California Pacific Medical Center, San Francisco, CA; [4]Inova Schar Cancer Institute, Fairfax, VA; [5]City of Hope Chicago, Zion, IL; [6]Providence Health and Services, Portland, OR; [7]Levine Cancer Institute, Atrium Health, Charlotte, NC; [8]Sanford Roger Maris Cancer Center, Fargo, ND; [9]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Northwell Health, New Hyde Park, NY; [10]Swedish Cancer Institute, Seattle, WA; [11]University of Nebraska Medical Center, Omaha, NE; [12]UF Health, Gainesville, FL; [13]University of Michigan Rogel Cancer Center, Ann Arbor, MI; [14]University of Cincinnati Cancer Center, Cincinnati, OH; [15]Kaiser Permanente Vallejo Medical Center, Vallejo, CA; [16]Michigan Cancer Research Consortium, Ypsilanti, MI; [17]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 and specific genomic alterations.
- Pts with pancreatic cancer (PC) with *BRCA1/2* mutations (mut) were treated with nivolumab plus ipilimumab (N+I) based on the hypothesis that these muts confer immunotherapy responsiveness due to increased genomic instability (higher tumor mutational burden [TMB] and genome-wide loss of heterozygosity compared to wild-type pts).[1,2]

Methods:

Study Design:

- **Eligible pts:** Advanced PC, ECOG performance status (PS) 0-2, adequate organ function, measurable disease, and no standard treatment (tx) options or prior immune checkpoint inhibitor tx. Tx was assigned according to prespecified matching rules based on genomic tests performed in CLIA-certified, CAP-accredited labs selected by sites. For most pts, the genomic test performed did not distinguish between germline and somatic mut.
- Pts received N at 1 mg/kg IV every 3 weeks (wks) in combination with I at 3 mg/kg every 3 wks for 4 doses. N was then continued at 240 mg every 2 wks or 480 mg every 4 wks until disease progression, unacceptable toxicity or pt or physician choice to discontinue.
- **Primary endpoint:** Disease control (DC) defined by investigator assessment of objective response (OR) or stable disease (SD) at 16+ wks (SD16+) per RECIST v1.1. Confirmation of response was not required. The assessment of complete response (CR) is based on radiographic assessment of target lesions and recorded nontarget lesions only. CA 19-9 levels were not routinely collected.
- **Secondary endpoints:** OR, progression-free survival (PFS), overall survival (OS), duration of response (DOR), and toxicity per CTCAE. For toxicity, grade 3-5 adverse events (AEs) or serious adverse events (SAEs) at least possibly related to N+I 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% to achieve power of 85% with 1-sided α of 10%.
- At least 7 of 28 pts must achieve DC to reject the null hypothesis and consider tx worthy of further study.

Results:

- 32 pts enrolled between October 2017 to March 2023. Pt demographics and clinical characteristics are outlined in **Table 1.**
- 29 pts had adenocarcinoma, 2 pts had acinar cell carcinoma and 1 pt had poorly differentiated carcinoma.
- PD-L1 status was not reported for 28 pts, negative for 2 pts, and low (tumor proportion score 1-49%) for 2 pts. TMB was not reported for 14 pts, undetermined for 3 pts, less than 10 muts per megabase (Muts/Mb) for 14 pts, and greater than 10 Muts/Mb for 1 pt (15 Muts/Mb). Microsatellite status was stable in 17 pts, not reported in 14 and undetermined in 1.
- 15 pts received a PARP inhibitor (olaparib) as one of their 3 most recent therapies prior to TAPUR.
- **Alterations:** 8 pts (25%) had *BRCA1* mut; 22 (69%) had *BRCA2* mut; and 2 (6%) had both *BRCA1/2* mut.
- **Outcomes**: 4 pts were not evaluable for efficacy. Of the 28 evaluable pts, 1 had CR, 3 had partial response (PR) and 4 had SD16+. All pts with DC had adenocarcinoma.
- Duration of CR for 1 pt was 329 wks as of November 20, 2024. Durations of PR for 3 pts were 175, 7 and 2 wks. Median duration of SD for pts with SD16+ was 31 wks (range, 24-34).
- **Safety:** 17 pts (53%) had ≥1 tx-related SAE or grade 3-4 AE. All AEs and SAEs were consistent with N+I labels, except generalized muscle weakness and lymphopenia.

Conclusion: Nivolumab plus ipilimumab met prespecified criteria to declare clinical activity in heavily pretreated patients with pancreatic cancer with *BRCA1/2* mutations.

Future Direction: Additional study is warranted to confirm the efficacy of nivolumab plus ipilimumab in this patient population.

Table 1. Clinical Characteristics (N=32)

Characteristic		No. (%)[a]
Age (years)	Median (range)	66 (37-80)
Sex	Female	15 (47)
Race[b]	White Other Prefer not to answer	27 (84) 3 (9) 2 (6)
Ethnicity[b]	Not Hispanic or Latino Hispanic or Latino Prefer not to answer	27 (84) 4 (13) 1 (3)
ECOG PS	0 1 2	16 (50) 15 (47) 1 (3)
Prior Systemic Regimens for metastatic disease	0 1-2 >2	1 (3) 9 (28) 22 (69)

[a]Percentages may not sum to 100 due to rounding.
[b]Race and ethnicity are self-selected by the patient. No additional information is collected.

Table 2. Pts Meeting Response Criteria and Corresponding Alterations (n=8)

Response	Time to progression (wks)	*BRCA* Mutation[a]	Co-alterations[b,c]
CR	345[d]	*BRCA1* Q1756fs*74	*KRAS* G12D
PR	202	*BRCA2* V1283fs	*KRAS* G12R
PR	16	*BRCA1* exon 23 rearrangement	*KRAS* G12D
PR	18	*BRCA2* N136fs*16	*KRAS* G12R
SD16+	34	*BRCA2* L638fs*9	--
SD16+	34	*BRCA1* exon 13 ins 6kb (germline)	--
SD16+	28	*BRCA2* R645fs, K3326*	--
SD16+	24	*BRCA1* E23fs	--

[a]Unless otherwise specified, germline or somatic status was not reported.
[b]Of the following genes assessed: *ARID1A, ATR, ATRX, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, KRAS, MLH1, MRE11A, NBN, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L.*
[c]Variants of Unknown Significance are not included.
[d]Censored at last known tx date.

Table 3: Efficacy Outcomes (n=28)

DC rate, % (1-sided 90% CI) (p-value)	31 (18, 100) (0.044)
OR rate, % (95% CI)	14 (4, 33)
Median PFS, wks (95% CI)	9 (7, 16)
Median OS, wks (95% CI)	34 (14, 46)
Duration of CR, wks (n=1)	329
Duration of PR, wks (n=3)	2, 7, 175
Median duration of SD for pts with SD16+, wks (n=4)	31 (24, 34)

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

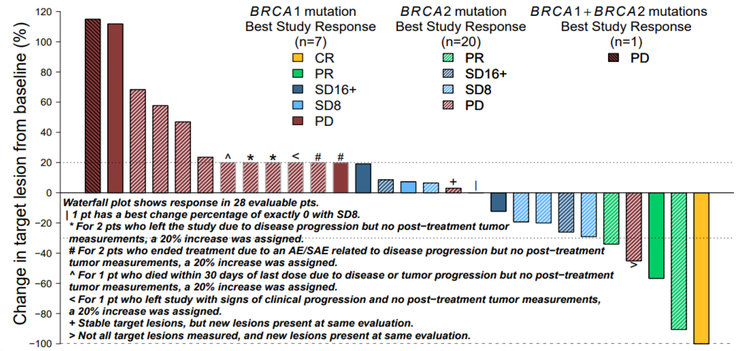
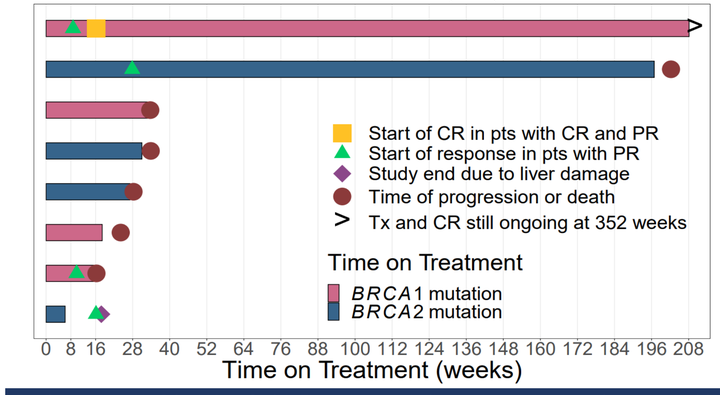


Figure 2: Time on Tx in Pts with OR and SD16+ (n=8)



Funding supported by Bristol Myers Squibb. The authors would like to acknowledge the patients who participated in this cohort and the clinical centers and staff. **Contact:** TAPURPublications@asco.org

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