Abstract 127: Nivolumab plus ipilimumab (N+I) in patients (pts) with colorectal cancer (CRC) with *BRCA1/2* alterations (alts): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

ASCO TAPUR
Targeted Agent and Profiling Utilization Registry Study

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Background:

- TAPUR is a phase II basket study that evaluates the antitumor activity of commercially available targeted agents in pts with advanced cancers with specific genomic alts.
- **Results of a cohort of pts with CRC with *BRCA1/2* alts treated with N+I are reported.**

Methods:

Study Design:

- **Eligible pts:** Advanced CRC, ECOG performance status (PS) 0-2, adequate organ function, measurable disease, and no standard treatment (tx) options. 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 mutations (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) of at least 16 wks duration (SD16+) per RECIST v1.1. Confirmation of response was not required.
- **Secondary endpoints:** OR, progression-free survival (PFS), overall survival (OS), duration of response, duration of SD are reported. Grade 3-5 adverse events (AEs) or serious adverse events (SAEs) per CTCAE at least possibly related to tx are reported. Duration of response 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 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 the null hypothesis and consider tx worthy of further study.

Results:

- 33 pts enrolled from October 2017 to September 2023. Pt demographics and clinical characteristics are shown in **Table 1.**
- Pts had adenocarcinoma (n=32) or CRC not otherwise specified (n=1) with the following sidedness: 11 (33%) right, 9 (27%) rectal, 6 (18%) undetermined, 5 (15%) left, 2 (6%) not reported.
- **Alterations:** 20 (61%) had *BRCA2* mut; 6 (18%) had *BRCA1* deletion (del); 6 pts (18%) had *BRCA1* mut; 1 (3%) had co-occurring *BRCA1* del and *BRCA2* mut.
- PD-L1 status was positive for 4 pts, low for 2 pts, negative for 9 pts, not reported for 9 pts, and not tested for 9 pts. Tumor mutational burden (TMB) was not reported for 6 pts, undetermined for 3 pts, ≤10 mut per megabase (mut/Mb) for 21 pts, and >10 mut/Mb for 3 pts. Microsatellite status (MS) was stable in 27 pts, undetermined in 3, and not reported in 2, and not detected in 1.
- **Outcomes**: 3 pts were not evaluable for efficacy. Of 30 evaluable pts, 1 (3%) had PR (recorded at the final study visit) and 4 pts (13%) had SD16+. Median duration of SD was 33 wks (range, 17-44) for the 4 pts with SD16+ **(Table 2)**. DC rate was 24% (90% CI, 9 to 100) and OR rate was 3% (95% CI, <1 to 17). The null DC rate failed to be rejected (p=0.33) **(Table 3)**. No pts with DC had *POLE* or *POLD1* co-alts.
- **Safety:** 12 pts (36%) had ≥1 grade 3-4 AE or SAE, all of which were consistent with the drug labels, except: encephalopathy (3%), generalized muscle weakness (3%), hypophosphatemia (3%), hypotension (3%), INR increase(3%), leukocytosis (3%), proteinuria (3%), and sinus tachycardia (3%).

Conclusion: Nivolumab + Ipilimumab did not meet prespecified criteria to declare a signal of activity in heavily pretreated patients with CRC with *BRCA1/2* alterations.

Future Direction: Other treatments should be considered for these patients, including treatments offered in clinical trials.

Table 1. Demographic and Clinical Characteristics (N=33)

Characteristic		No (%)
Median Age	Years (range)	64 (31-76)
Sex	Female	11 (33)
Race	Asian/Asian American	1 (3)
	Black or African American	6 (18)
	White	21 (64)
	More than one race	1 (3)
	Other	2 (6)
	Prefer not to answer	2 (6)
Ethnicity	Hispanic	1 (3)
	Not Hispanic or Latino	29 (88)
	Prefer not to answer	3 (9)
ECOG PS	0	10 (30)
	1	20 (61)
	2	3 (9)
Prior Systemic Regimens[a]	1-2	6 (18)
	≥3	27 (82)

[a] 29 pts received platinum therapy and no pts received a PARP inhibitor as one of their 3 most recent therapies prior to TAPUR.

Table 2. Tumor Sidedness and Alterations of Pts Meeting Response Criteria (n=5)

Response	Sidedness	Time on Tx (wks)	*BRCA1/2* Alteration	MS/TMB/PD-L1 Status
PR	Right	11	*BRCA1* deletion exons 16-18	MS Stable TMB 4 mut/Mb PD-L1 Not Tested
SD16+	Right	26	*BRCA2* H2074N[a]	MS and TMB Cannot be Determined PD-L1 Not Reported
SD16+	Left	42	*BRCA2* V1532fs	MS Stable TMB and PD-L1 Not Reported
SD16+	Right	11	*BRCA2* E2878*	MS Stable TMB 5 mut/Mb PD-L1 Low (CPS 2%)
SD16+	Rectal	35	*BRCA2* L583fs	MS Stable TMB Not Reported PD-L1 Positive (CPS 30%)

[a] Variant of unknown significance

Table 3: Efficacy Outcomes (n=30)

DC rate, % (1-sided 90% CI) (p-value)	24 (9, 100), p=0.33
OR rate, % (95% CI)	3 (<1, 17)
Median PFS, wks (95% CI)	8 (7, 9)
Median OS, wks (95% CI)	19 (11, 25)

Figure 1: Best Percent Change from Baseline in Target Lesion Size (n=30)

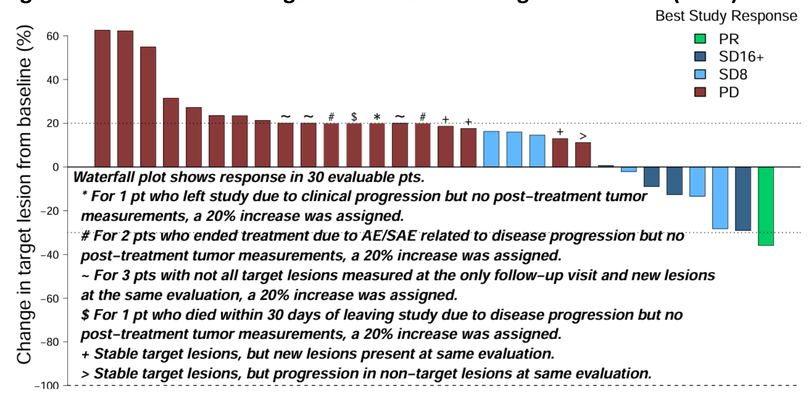
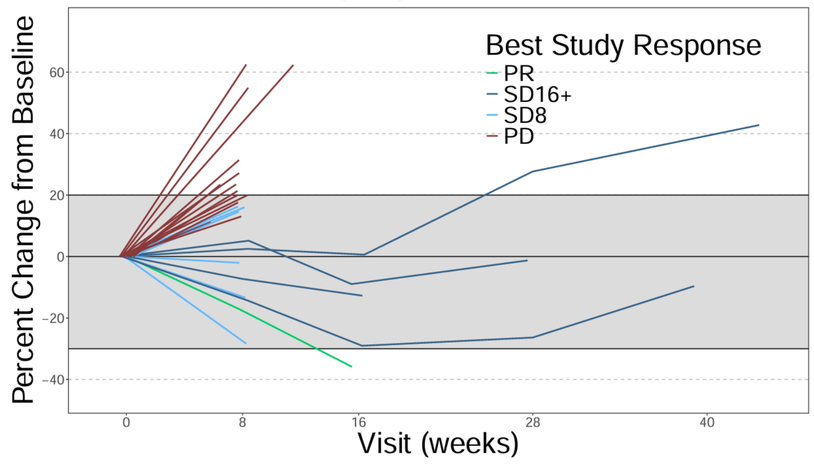


Figure 2: Percent Change from Baseline of Tumor Burden During Tx of N+I in Pts with CRC with *BRCA1/2* alts (n=26)



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