Pembrolizumab in Patients with Metastatic Colorectal Cancer with High Tumor Mutational Burden (HTMB): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

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Background

- The TAPUR Study is a phase II basket study that evaluates the anti-tumor activity of commercially available targeted agents used in patients (pts) with advanced cancers with specific genomic alterations.
- Pembrolizumab (P) is an immune checkpoint inhibitor. HTMB is an emerging predictive biomarker for checkpoint inhibitor therapy. Results of a cohort of pts with metastatic colorectal cancer (mCRC) with HTMB defined as ≥9 mutations/megabase (Muts/Mb) treated with P are reported.

Methods

Study Design:

- Eligible pts had advanced mCRC with no remaining standard treatment options, PS 0-1, adequate organ function, and measurable disease. Treatment was assigned according to pre-specified protocol matching rules based on genomic testing performed in CLIA-certified, CAP-accredited labs selected by clinical sites.
- Pts received P at 2 mg/kg over 30 minutes (n=8) or 200 mg (n=20) every 3 weeks (wks) until disease progression. Tumor evaluations were performed at wks 8 and 16 then Q12 wks after treatment initiation.
- Primary endpoint is objective response (OR) or stable disease (SD) at 16+ wks per RECIST v1.1. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and toxicity per CTCAE. Grade 3-5 adverse events (AEs) or serious adverse events (SAEs) at least possibly related to drug are reported.

Statistical Methods:

- Simon's optimal two-stage design was used to test the null hypothesis of 15% disease control (DC) rate versus the alternative of 35%. Power and one-sided type I error rate were set at 85% and 10%, respectively.
- Design requires 10 pts in stage I and if ≥2 pts have DC (OR or SD at 16+ wks), the cohort is expanded to stage II with 28 pts. If ≥7 of 28 pts have DC, the drug is considered worthy of further study.

Results

- 28 pts were enrolled between June 2017 and November 2018 and 27 pts were evaluable; 1 pt was ineligible (without HTMB) and was therefore excluded from analyses. Baseline demographics and clinical characteristics are shown in Table 1.
- All pts in this analysis had tumors with HTMB ranging from 9 to 54 Muts/Mb as reported by a FoundationOne test (n=26) or approved by the TAPUR Molecular Tumor Board (MTB) (n=2). Tumor MS status was reported stable for 25 pts, ambiguous for 1 pt and not available for 1 pt.

Table 1: Demographics and Baseline Characteristics (N=27)

Characteristic	N (%)
Median Age, years (range)	59 (34, 79)
Sex	
Female	14 (52%)
Race	
White	18 (67%)
Black	6 (22%)
Asian	1 (4%)
Prefer not to answer	2 (7%)
ECOG Performance Status	
0	9 (33%)
1	18 (67%)
Prior systemic regimens	
1-2	6 (22%)
≥3	21 (78%)
Genomic test performed	
FoundationOne	26 (93%)
In house laboratory	1 (7%)

Clinical Outcomes:

- DC and OR were observed in 28% and 11% of pts, respectively (Table 2). Median PFS (mPFS), 1 year OS and mOS are reported in Table 2 and shown in Figure 1.
- Figure 2 shows % change from baseline in target lesions.
- Time on treatment among pts with SD and OR is shown in Figure 3.
- Safety was consistent with product label for P (Table 3).

Table 2: Clinical Outcomes of mCRC Pts with HTMB treated with P (N=27)

Clinical Outcomes	
DC rate, % (OR or SD16+) N (%), [90% CI]	8 (28%), [16%, 45%]
OR rate % (CR or PR) N (%), [95% CI]	3 (11%), [2%, 29%]
mPFS, wks, (95% CI)	9.3 (7.3, 16.1)
mOS, wks (95% CI)	51.9 (18.7, inf)
1 year OS rate, % (95% CI)	45.6 (22.2, 66.3)

Table 3: SAE/AEs at least possibly related to P experienced by 2 Pts

Grade	SAE	AEs
3	Y	acute kidney injury
3	N	fatigue, nausea, vomiting, abdominal infection, diarrhea, anorexia, colitis

Figure 1: OS and PFS in Advanced mCRC Pts with HTMB treated with P (N=27)

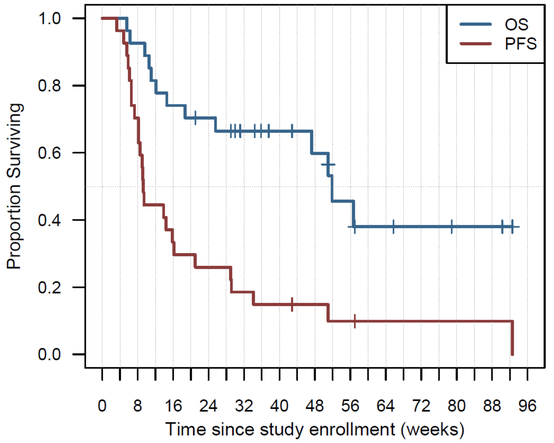


Figure 2: Best percent change from baseline in target lesion size (N=27)

Note: Mutational burden is reported above bars in Muts/Mb.

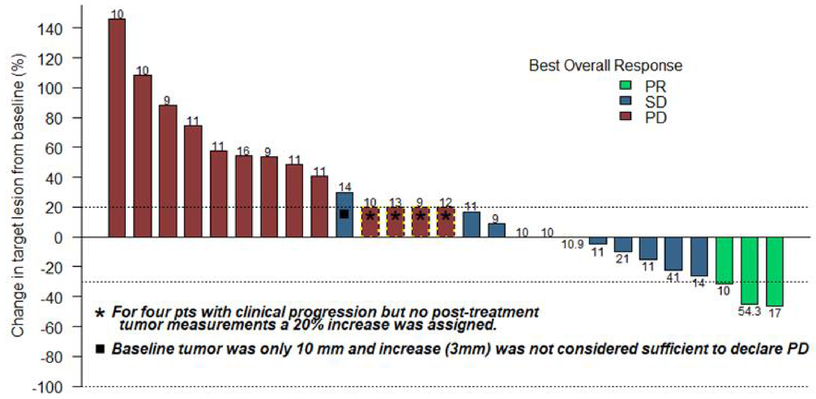
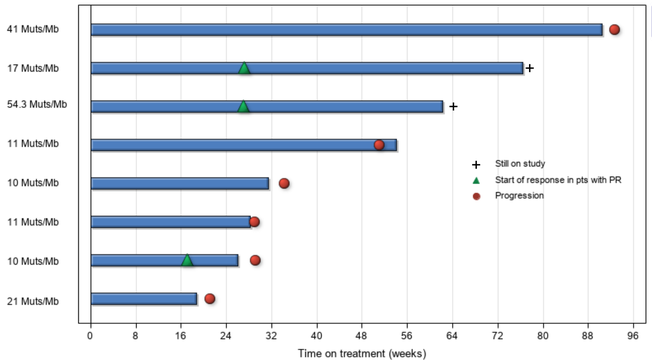


Figure 3: Time on Treatment in Pts with SD at 16 wks or OR (N=8)



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Conclusions

Monotherapy with P showed anti-tumor activity in heavily pre-treated mCRC patients with HTMB. Additional study is warranted to confirm the efficacy of P in this population.

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