Pembrolizumab in Patients with Metastatic Breast 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 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 breast cancer (MBC) with HTMB defined as ≥9 mutations/megabase (Muts/Mb) treated with P are reported.

Methods

Study Design:

- Eligible pts had advanced MBC 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 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. Grades 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 October 2016 and July 2018. Baseline demographics and clinical characteristics are shown in Table 1.
- All pts in this analysis had tumors with HTMB ranging from 9 to 37 Muts/Mb as reported by a FoundationOne test (n=20) or approved by the TAPUR Molecular Tumor Board (MTB) (n=8).

Table 1: Demographics and Baseline Characteristics (N=28)

Characteristic	N (%)
Median Age, years (range)	63 (36,78)
Sex	
Female	28 (100%)
Race	
White	21 (75%)
Black	6 (21%)
Asian	1 (4%)
ECOG Performance Status	
0	10 (36%)
1	18 (64%)
Prior systemic regimens	
2	2 (7%)
≥3	26 (93%)
Genomic Test Performed	
FoundationOne	20 (71%)
In house laboratory	7 (25%)
Caris MiProfile	1 (4%)

Clinical Outcomes

- DC and OR were observed in 37% and 21% of pts, respectively (Table 2). Median PFS (mPFS) and mOS are both reported in Table 2 and shown in Figure 1.
- Figure 2 shows % change from baseline in target lesions.
- There was no relationship found between PFS and Muts/Mb.
- Time on treatment among pts with response is shown in Figure 3.
- Safety was consistent with product label for P (Table 3).

Table 2: Clinical Outcomes of MBC Pts with HTMB treated with P

Clinical Outcomes	
DC (OR or SD at 16+wks) N (%), [90% CI]	10 (37%), [24%, 46%]
OR (CR or PR) N (%), [95% CI]	6 (21%), [8%, 41%]
mPFS, wks, (95% CI)	10.6 (7.7, 21.1)
mOS, wks, (95% CI)	31.6 (11.9, inf)

Table 3: Total of 6 SAE/AEs at least possibly related to P experienced by 4 Pts

Grade	SAE	AEs
3	Y	colonic obstruction, hepatic failure
3	N	weight loss, hypoalbuminemia, hyponatremia
2	Y	urinary tract infection

Figure 1: OS and PFS in Advanced MBC Pts with HTMB treated with P (N=28)

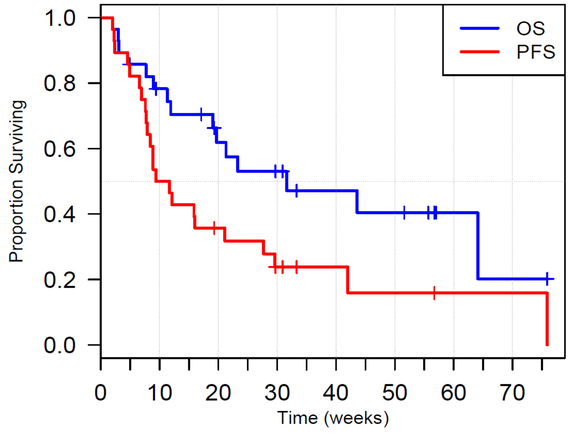


Figure 2: Best percent change from baseline in target lesion size by HER2 Status (N=28)

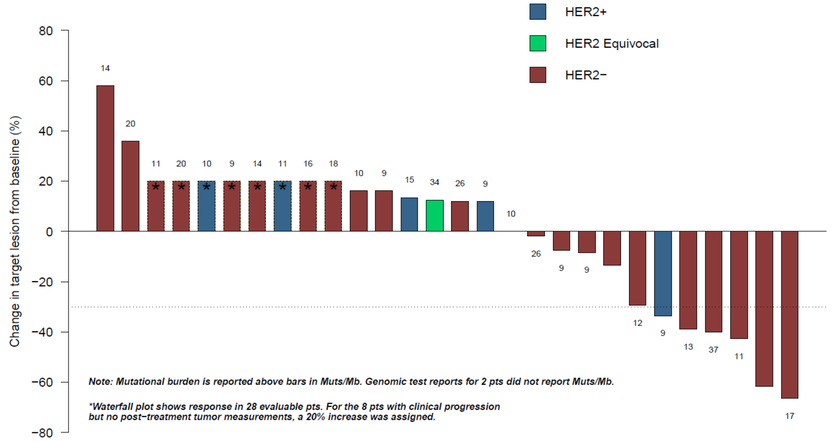
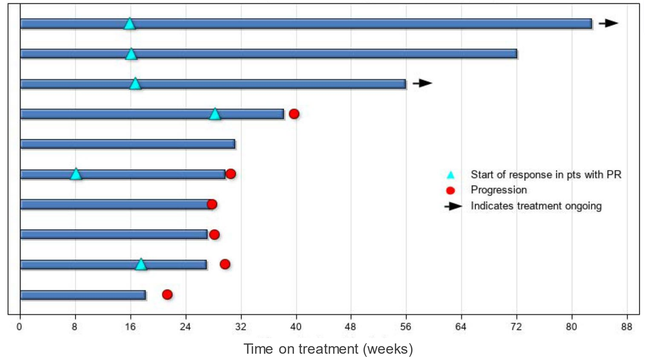


Figure 3: Time on treatment in pts with SD or objective response (N=10)



Conclusions

These results suggest monotherapy with P has anti-tumor activity in heavily pre-treated mBC pts with HTMB.

Acknowledgments

The authors would like to acknowledge the pts who participated in these cohorts as well as the following clinical lead of Merck, a TAPUR supporting pharmaceutical company: Eric Rubin, MD.