Cobimetinib + Vemurafenib in Patients with Colorectal Cancer with BRAF V600E Mutations: 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.
- Results of a cohort of metastatic colorectal cancer (mCRC) pts with *BRAF V600E* mutations treated with cobimetinib plus vemurafenib (C+V) are reported.

Methods

Study Design:

- Pts with advanced mCRC with no remaining treatment options, PS 0-2, adequate organ function, and measurable disease were eligible. 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 C at 60 mg orally once daily for 21 days, followed by 7 days off, and V at 960 mg orally twice daily until disease progression. Tumor evaluations were performed at 8 and 16 weeks (wks) then Q12 wks after treatment initiation.
- Primary endpoint is disease control (DC) defined as 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% 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, the cohort is expanded to stage II with 28 pts. If ≥7 of 28 pts have DC, the treatment is considered worthy of further study.

Results

- 30 pts were enrolled between August 2016 and August 2018. Two pts were not evaluable for efficacy as 1 pt self-discontinued the treatment for unknown reasons and 1 pt stopped treatment due to an AE. Baseline demographics and clinical characteristics are shown in Table 1.
- All pts had *BRAF V600E* mutations.

Table 1: Demographics and Baseline Characteristics (N=30)

Characteristic	N (%)
Median Age, years (range)	62 (37, 77)
Sex	
Female	19 (63%)
Race	
White	28 (94%)
Black	1 (3%)
Prefer not to answer	1 (3%)
ECOG Performance Status	
0	7 (23%)
1	17 (57%)
2	6 (20%)
Prior systemic regimens	
1-2	11 (37%)
≥3	19 (63%)
Genomic test performed	
FoundationOne	10 (34%)
Other	8 (27%)
In house laboratory	7 (23%)
Caris MiProfile	4 (13%)
Guardant Health	1 (3%)

Clinical Outcomes:

- DC and OR were observed in 57% and 29%, respectively (Table 2). Median PFS (mPFS) 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 C+V (Table 3).

Table 2: Clinical Outcomes of mCRC Pts with *BRAF V600E* mutations treated with C+V (N=28)

Clinical Outcomes	
DC rate, (OR or SD 16+wks) N (%), [90% CI]	16 (57%), [43%, 67%]
OR rate, (CR or PR) N (%), [95% CI]	8 (29%), [13%, 49%]
mPFS, wks (95% CI)	15.8 (14.4, 18.1)
mOS, wks (95% CI)	38.9 (26.1, 49.4)

Table 3: SAE/AEs at least possibly related to C+V experienced by 13 Pts

Grade	SAE	AEs
3	N	ALT increase, anemia, AST increase, diarrhea, GGT increase, hypophosphatemia, lymphocyte decrease, photosensitivity, rash maculo-papular
3	Y	diarrhea, dyspnea, fatigue, hypercalcemia, upper gastrointestinal hemorrhage
2	Y	vomiting

Figure 1: OS and PFS in Pts with Advanced mCRC with *BRAF V600E* Mutations Treated with C+V (N=28)

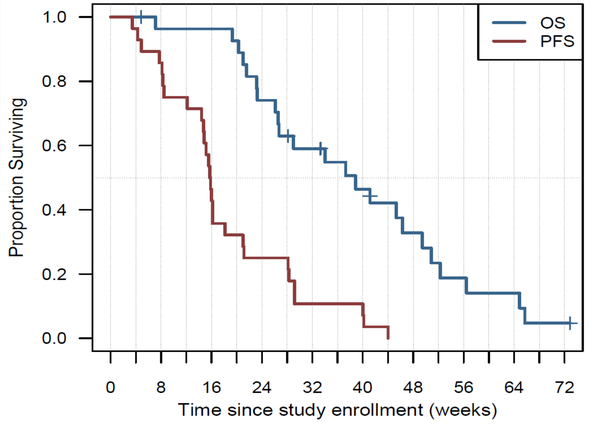


Figure 2: Best percent change from baseline in target lesion size (N=28)

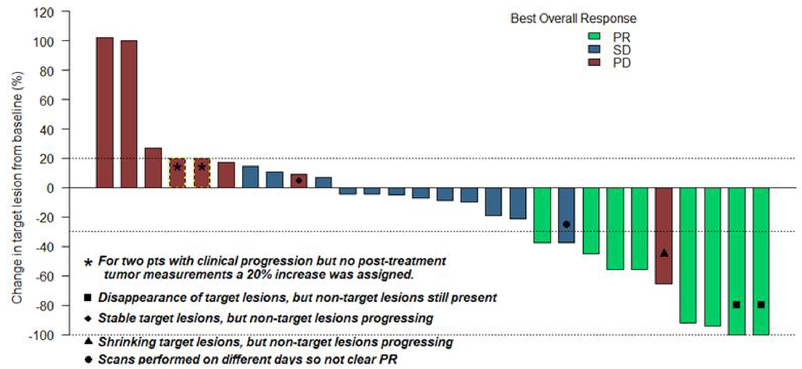
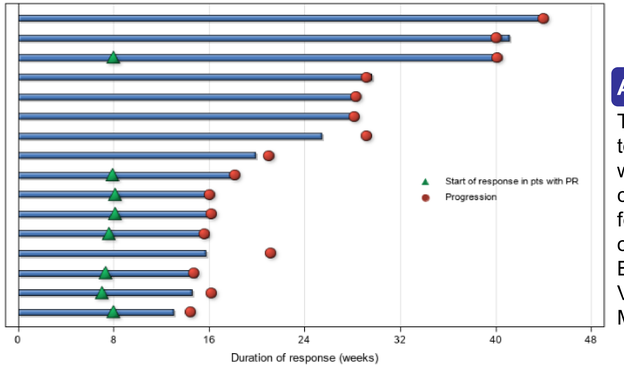


Figure 3: Time on Treatment in Pts with SD or OR (N=16)



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Conclusions

The combination of C+V demonstrated evidence of anti-tumor activity in heavily pre-treated pts with mCRC with *BRAF V600E* mutations. Further study is warranted to confirm the efficacy of C+V in this population.

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