Cobimetinib Plus Vemurafenib in Patients With Solid Tumors With *BRAF* Mutations: Results From the Targeted Agent and Profiling Utilization Registry Study

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ABSTRACT

PURPOSE The Targeted Agent and Profiling Utilization Registry Study is a phase II basket study evaluating antitumor activity of commercially available targeted agents in patients with advanced cancers with genomic alterations known to be drug targets. The results in a cohort of patients with solid tumors with *BRAF* mutations treated with cobimetinib plus vemurafenib are reported.

METHODS Eligible patients had measurable disease (RECIST v.1.1), Eastern Cooperative Oncology Group performance status 0-2, adequate organ function, and no standard treatment options. The primary end point was disease control (DC), defined as complete response (CR) or partial response (PR) or stable disease of at least 16-weeks duration (SD16+). Low-accruing histology-specific cohorts with *BRAF* mutations treated with cobimetinib plus vemurafenib were collapsed into a single histology-pooled cohort for this analysis. The results were evaluated on the basis of a one-sided exact binomial test with a null DC rate of 15% versus 35% (power, .82; α, .10). The secondary end points were objective response (OR), progression-free survival, overall survival, duration of response, duration of stable disease, and safety.

RESULTS Thirty-one patients with solid tumors with *BRAF* mutations were enrolled. Twenty-eight patients were evaluable for efficacy. Patients had tumors with *BRAF* V600E (n = 26), K601E (n = 2), or other (n = 3) mutations. Two patients with CR (breast and ovarian cancers; V600E), 14 with PR (13 V600E, one N581I), and three with SD16+ (two V600E, one T599_V600insT) were observed with a DC rate of 68% ($P < .0001$; one-sided 90% CI, 54 to 100) and an OR rate of 57% (95% CI, 37 to 76). Nineteen patients experienced ≥one drug-related grade 3-5 adverse event or serious adverse event including one death attributed to treatment-related kidney injury.

CONCLUSION Cobimetinib plus vemurafenib showed antitumor activity in patients with advanced solid tumors with *BRAF* V600E mutations; additional study is warranted to confirm the antitumor activity in tumors with non-V600E *BRAF* mutations.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

The *BRAF* gene encodes the BRAF protein, a serine/threonine kinase that regulates the mitogen-activated protein kinase (MAPK) pathway, which modulates cell growth and division. The most common *BRAF* mutation, *BRAF* V600E, constitutively activates the kinase. *BRAF* is mutated in 40% of melanomas, and the *BRAF* V600E mutation comprises more than 90% of *BRAF* mutations in melanoma.[1,2] An analysis of the AACR GENIE database demonstrated that *BRAF* V600E mutations are also found frequently (>30%) in thyroid cancer and less commonly in colorectal cancer (CRC; 7.6%), cholangiocarcinoma (1.5%), and non–small-cell lung cancer (NSCLC; 1.3%).[3]

Vemurafenib, an ATP-competitive inhibitor of mutant *BRAF* V600E, improved overall survival (OS) and progression-free survival (PFS) compared with treatment with dacarbazine in patients with unresectable or metastatic melanoma bearing *BRAF* V600E mutations.[4,5] This led to the approval of vemurafenib by the US Food and Drug Administration (FDA) in 2011. The limited efficacy observed with single-agent vemurafenib in *BRAF* V600E–mutant CRC raised concerns

CONTEXT

Key Objective

The Targeted Agent and Profiling Utilization Registry Study aims to evaluate the antitumor activity of US Food and Drug Administration (FDA)–approved drugs used outside of their approved indication(s) in patients with advanced cancers with potentially actionable genomic variants. This cohort assessed whether the combination of vemurafenib, a BRAF inhibitor, plus cobimetinib, a MEK inhibitor, is efficacious in patients with solid tumors with *BRAF* mutations.

Knowledge Generated

The combination of cobimetinib plus vemurafenib demonstrated antitumor activity in heavily pretreated patients with *BRAF*-mutated solid tumors, primarily *BRAF* V600E.

Relevance

The FDA approval of dabrafenib plus trametinib for patients with advanced solid tumors with a *BRAF* V600E mutation with no satisfactory alternative treatment options demonstrates the benefit of the combination of BRAF and MEK inhibitors for this indication. The results of this study build upon these findings and demonstrate the efficacy of cobimetinib plus vemurafenib in patients with various solid tumors with *BRAF* mutations.

about the antitumor activity of BRAF inhibitors.[6] However, a basket trial of vemurafenib in patients with solid tumors harboring a *BRAF* V600E mutation demonstrated a 33% overall response rate (ORR) and a 42% clinical benefit rate (CBR), suggesting that *BRAF* V600E is an actionable alteration across many tumor types.[7]

Preclinically, inhibition of BRAF induced MEK inhibitor–sensitive but RAF inhibitor–resistant ERK activation.[8] This paradoxical ERK activation limited antitumor efficacy and contributed to toxicity. This established the rationale for clinical testing of BRAF/MEK inhibitor combinations, and the FDA has now approved three such combinations for treating advanced metastatic melanoma: vemurafenib and cobimetinib (2015), dabrafenib and trametinib (2022), and encorafenib and binimetinib (2018).

These combinations improved patient OS and PFS and lead to precision oncology trials targeting members of the MAPK pathway.[9-11] For example, the combination of vemurafenib and cobimetinib, a highly selective small molecule inhibitor of MEK, exhibited an ORR of 68% in patients with melanoma.[11]

The Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a phase II basket study evaluating the antitumor activity of commercially available targeted agents in patients with advanced cancers with genomic alterations known to be drug targets. We report the results in a cohort of patients with solid tumors with *BRAF* mutations treated with cobimetinib plus vemurafenib.

METHODS

The rationale, general design, and eligibility criteria of this trial were reported previously.[12] The methods specific to the data collection and analysis of a cohort, defined in TAPUR as a group of patients with the same tumor genomic target, histology, and study treatment received, have been previously reported for other cohorts.[13-17]

Patients

Eligible patients were required to meet both general and drug-specific eligibility criteria. General eligibility criteria included advanced or metastatic solid tumors measurable according to RECIST version 1.1.,[18] Eastern Cooperative Oncology Group performance status of 0-2, and a protocol-specified genomic target identified by a Clinical Laboratory Improvement Amendments–certified and College of American Pathologists or NY State–accredited laboratory. Patients with *BRAF* V600D/E/K/R mutations without mutations in *MAP2K1*, *MAP2K2*, *MEK1*, *MEK2*, or *NRAS* were eligible for this study. Other *BRAF* mutations were acceptable if approved by the TAPUR Molecular Tumor Board (MTB). The TAPUR MTB is an ASCO-appointed group of experts in clinical oncology, pathology, genomics and cancer biology, and pharmacology, among others. Each case submitted to the MTB is thoroughly reviewed against relevant preclinical and clinical research, established gene mutation knowledge bases to assess the pathogenicity of the mutation, and the mechanism of action of various treatment options in or outside of the TAPUR study. Patients matched to cobimetinib plus vemurafenib must have been 18 years or older with no previous treatment with any BRAF or MEK inhibitor. Prior treatment with EGFR inhibitors was permitted. Patients with melanoma were excluded. Additional drug-specific exclusion criteria have been previously reported.[19]

Patients were treated with cobimetinib 60 mg orally once daily for 21 days followed by 7 days off and vemurafenib 960 mg orally twice daily until clinical and/or radiographic evidence of progressive disease or withdrawal because of unacceptable toxicity, patient preference, or physician recommendation.

TABLE 1. Baseline Demographic and Clinical Characteristics (N = 31)

Characteristic	No. (%)[a]
Age, years, median (range)	63 (31-79)
Sex	
Female	20 (65)
Male	11 (35)
Race[b]	
Asian or Asian American	1 (3)
Black or African American	1 (3)
White	27 (87)
Other	1 (3)
Prefer not to answer	1 (3)
Ethnicity[b]	
Hispanic or Latino	1 (3)
Not Hispanic or Latino	29 (94)
Prefer not to answer	1 (3)
ECOG performance status	
0	7 (23)
1	20 (64)
2	4 (13)
Prior treatments	
Prior radiation therapy	
No	14 (45)
Yes	17 (55)
Prior systemic therapies	
0	2 (7)
1	7 (23)
2	6 (19)
≥3	16 (52)
Genomic test performed	
Caris MI Profile X	4 (13)
FoundationOne	11 (35)
FoundationOne CDx	4 (13)
In-house laboratory test[c]	7 (23)
Other[d]	5 (16)
BRAF genomic alterations	
V600E	26 (84)
K601E[e]	1 (3)
K601E[e]/R603Q[e,f]	1 (3)
G469V[e]	1 (3)
N581I[e]	1 (3)
T599_V600insT[e]	1 (3)
Primary tumor	
Ovary	6 (19)
Neuroendocrine carcinoma[g]	5 (16)
Breast	4 (13)
Pancreas	3 (10)
Cholangiocarcinoma	2 (6)
NSCLC	2 (6)
Angiosarcoma	1 (3)
Clear cell sarcoma	1 (3)
Colon	1 (3)
GIST[h]	1 (3)
HCC	1 (3)
Malignant neoplasm, site unspecified	1 (3)
Melanoma[i]	1 (3)
Malignant phyllodes tumor of breast	1 (3)
Prostate	1 (3)

(continued in next column)

TABLE 1. Baseline Demographic and Clinical Characteristics (N = 31) (continued)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; MI-ONCOSEQ, Michigan Oncology Sequencing Center; MTB, Molecular Tumor Board; NCI, National Cancer Institute; NGS, next-generation sequencing; NCI-MATCH, National Cancer Institute Molecular Analysis for Therapy Choice; NSCLC, non–small-cell lung cancer; PNET, primitive neuroectodermal tumor; TAPUR, Targeted Agent and Profiling Utilization Registry; VUS, variant of unknown significance.

[a]Percentages may not sum to 100% because of rounding.

[b]Race and ethnicity were self-identified.

[c]In-house laboratory tests include 50-Gene Somatic Mutation Analysis Panel (MD Anderson Cancer Center), CS-Focus GIST Panel by NGS (Cedars-Sinai Medical Center), MI-ONCOSEQ (Michigan Medicine Pathology), Solid Tumor Genomic Assay (MD Anderson Cancer Center), and Solid Tumor Genomic Sequencing Panel (Center for Personalized Diagnostics, Perelman School of Medicine at the University of Pennsylvania).

[d]Genomic tests in the "other" category include BRAF Mutation Analysis and Ewing/PNET, EWSR1 FISH Analysis (Quest Diagnostics Nichols Institute), FoundationOne Liquid (Foundation Medicine), FoundationOne Heme (Foundation Medicine), NCI-MATCH NGS Assay (Molecular Characterization Laboratory, NCI), and xO Onco-seq Panel (Tempus).

[e]Approved by the TAPUR MTB.

[f]VUS.

[g]Primary tumor sites reported include pancreas (1), colon (1), and site unspecified (3).

[h]Tumor had a *KIT* W557_K558del mutation.

[i]During data validation and verification, one patient was found to have a primary melanoma of the vulva, was deemed ineligible and unevaluable, and was removed from the efficacy analyses. The patient was included in safety analyses and demographics since the patient received at least one dose of treatment.

Patients who were eligible but unevaluable were those for whom data on the primary end point were not available because of leaving the study before radiographic assessment; these patients were not included in the efficacy analyses but were included in safety analyses.

Study End Points

The primary end point was investigator assessment of disease control (DC), defined as objective response (OR) or stable disease of at least 16-weeks duration (SD16+) from the initiation of study treatment as determined by RECIST

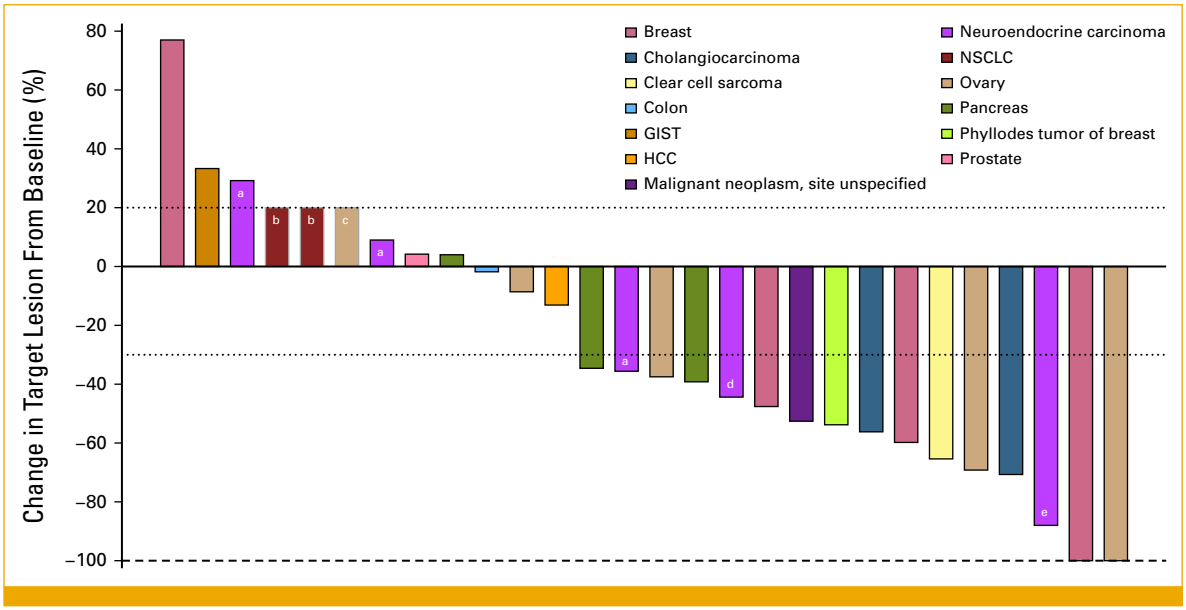

FIG 1. Maximum percent change from baseline in target lesions (n = 28). Color coding indicates primary tumor origin. All evaluable patients are included in this figure, including one patient who died due to acute kidney injury, a known side effect of vemurafenib treatment. [a]Neuroendocrine carcinoma, site unspecified. [b]For two patients with clinical progression but no post-treatment tumor measurements, a 20% increase was assigned. [c]For one patient who ended treatment due to death related to study treatment but no post-treatment tumor measurements, a 20% increase was assigned. [d]Neuroendocrine carcinoma of colon. [e]Neuroendocrine carcinoma of pancreas. GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; NSCLC, non–small-cell lung cancer.

version 1.1.[18] The assessment of complete response (CR) is based on radiographic assessment of measured target lesions and recorded nontarget lesions only. The secondary end points were OR, PFS, OS, duration of response, duration of SD, and safety. Duration of response was defined as the time from the participant's first documented OR until disease progression and was censored at the last time the patient was known to be progression free. Duration of SD was defined as the time from initiation of study treatment until disease progression. PFS was measured from the time of initiation of study treatment until clinical progression, radiographic progression, or death, whichever occurred first, and was censored at the last clinical evaluation at which the patient was still alive and progression free. OS was measured from time of initiation of study treatment until death from any cause or censored on the date of last follow-up of the surviving patients. Radiographic assessment and clinical evaluation for response were performed at 8 weeks and 16 weeks after treatment initiation and then every 12 weeks thereafter while the patient remained on treatment. DC was determined on the basis of the best response reported at 16 weeks after treatment initiation or later. An independent review of imaging studies was not performed. All serious adverse events (SAEs) and treatment-related adverse events (AEs) of grade 3-5 were reported according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical Considerations

Low-accruing individual histology-specific cohorts of patients with *BRAF*-mutant solid tumors who were treated with cobimetinib plus vemurafenib were collapsed into a single cohort for this analysis. The primary objective was assessed on the basis of an exact binomial test with a null DC rate of .15 and one-sided α of .10. For this cohort of 28 evaluable patients, the null hypothesis was rejected if at least eight patients had DC. This design has a power of 82% if the true DC rate is .35. A one-sided 90% CI is also provided for the DC rate. Kaplan-Meier curves were used to estimate the PFS and OS distributions. Other efficacy end point estimates used 95% CIs. All patients receiving at least one dose of study treatment were included in the safety analysis.

Trial Oversight

The study protocol was approved by a central institutional review board and, in some cases, by a local institutional review board at participating sites. Patients provided written consent before any screening activities or data collection began. The study was designed by ASCO staff with input from ASCO volunteer members, patient advocates, and participating pharmaceutical companies. The TAPUR Data and Safety Monitoring Board (DSMB) is an ASCO-appointed independent board that meets biannually to monitor the study and review the safety and efficacy findings. In this

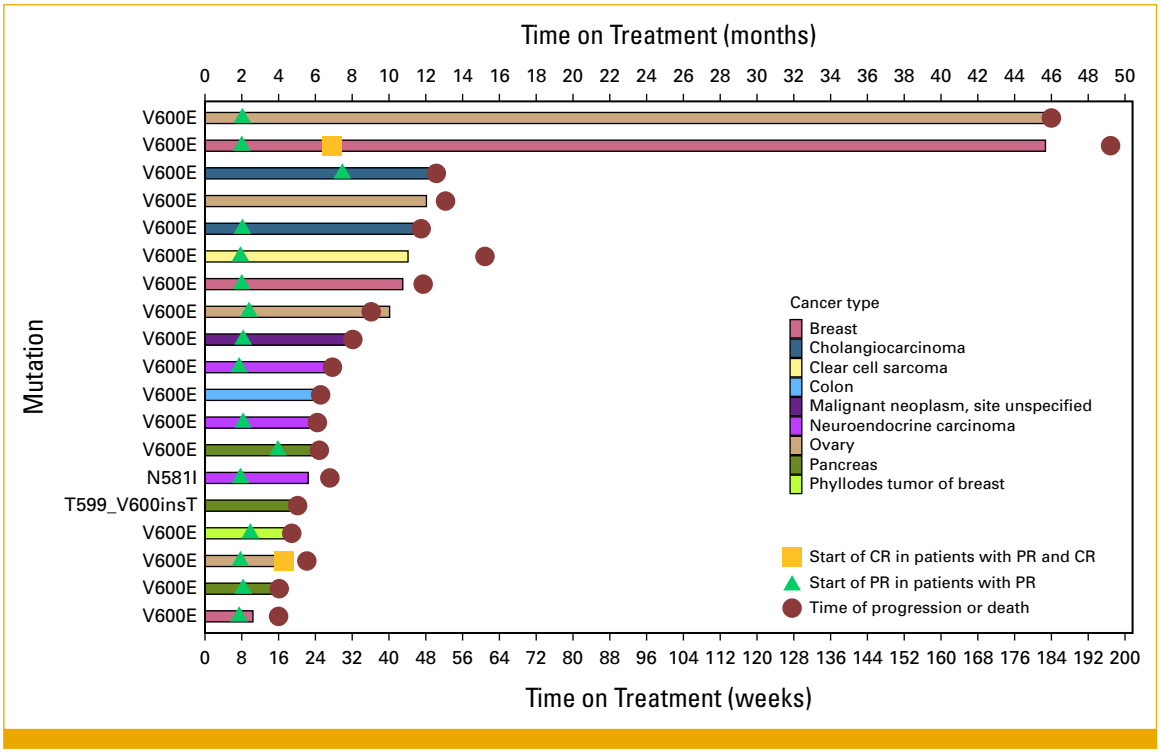

FIG 2. Time on treatment of 19 patients with OR or SD16+. Color coding indicates primary tumor origin. Sites for neuroendocrine carcinoma include pancreas (1), colon (1), and site unspecified (3). CR, complete response; OR, objective response; PR, partial response; SD16+, stable disease of at least 16-weeks duration.

cohort, multiple groups of patients with *BRAF* mutations treated with cobimetinib plus vemurafenib were collapsed into a single histology-pooled group. After review, the DSMB approved release of the outcome data reported herein.

RESULTS

Patient Characteristics

Thirty-one patients with solid tumors, representing 15 tumor types, were enrolled from December 2016 to January 2021 across 18 clinical sites (68% were enrolled from community-based sites). Twenty-eight patients were evaluable and were included in the efficacy analyses. Two patients left the study before the protocol-specified radiographic assessment at week 8 and were unevaluable while one patient was ineligible.

Patient characteristics are summarized in Table 1. Twenty-six of 31 patients (84%) had a tumor with a *BRAF* V600E mutation. Two patients had tumors with a *BRAF* K601E mutation, one of whom also had a *BRAF* R603Q mutation. The remaining three patients had tumors with unique *BRAF* mutations (G469V, N581I, and T599_V600insT). The two most common tumor types were ovary (19%) and neuroendocrine carcinoma of varying sites (16%). During data validation and verification, one patient was found to have primary melanoma of the vulva and was, therefore, deemed ineligible and removed from efficacy analyses. Genomic alterations, tumor types, and responses for all patients are shown in Appendix Table A1.

Efficacy Results

Of 28 evaluable patients, two had CR, 14 had a partial response (PR), and three had SD16+. The DC rate was 68% (one-sided 90%, 54 to 100), and the OR rate was 57% (95% CI, 37 to 76). The null hypothesis of a 15% DC rate was rejected ($P < .0001$).

Seventeen of 19 patients with DC had tumors with a *BRAF* V600E mutation while the other two had tumors with an N581I (PR, neuroendocrine carcinoma, site unspecified) and a T599_V600insT (SD16+, pancreas) mutation. The two patients with CR had ER+/HER2− invasive ductal carcinoma and ovarian cancer with V600E mutations.

Maximum percent change in target lesion size from baseline is shown in Figure 1. Time on treatment for patients with a best response of OR or SD16+ is shown in Figure 2, and percent change in tumor burden over time for 28 patients is shown in Figure 3. The duration of response on study for the two patients with CR was 5 (ovary, left study because of rising creatinine levels) and 170 (invasive ductal carcinoma in the breast) weeks. The median duration of response for the patients with PR was 21 weeks (range, 8-176). Among the

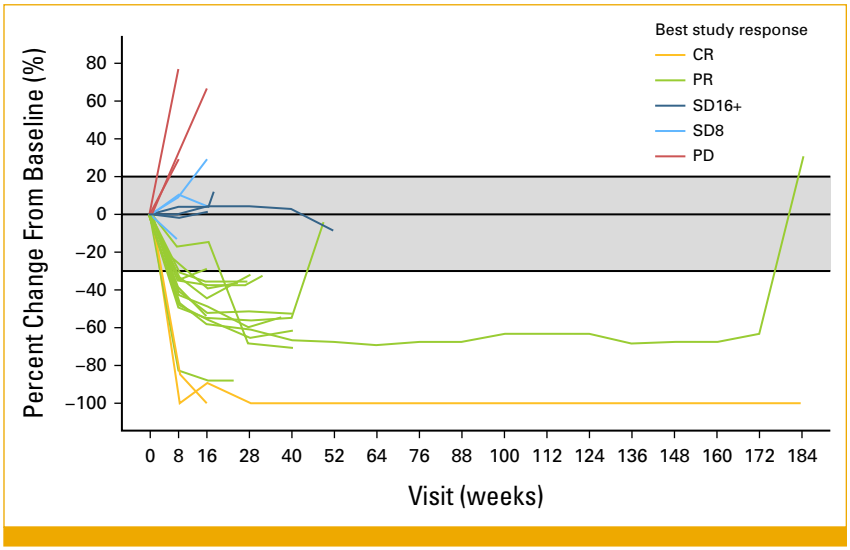

FIG 3. Spider plot of percent change from baseline in tumor burden during cobimetinib plus vemurafenib treatment in 28 patients with solid tumors with *BRAF* mutations. Three patients were not evaluable or had only a baseline visit because of leaving the study early and are not included in the spider plot: one enrolled on study, received treatment, and was later found to be ineligible, one had an unreportable AE, and one chose to discontinue participation in the study. Color coding in the plot showing CR, PR, SD16+, SD8, and PD indicates best response observed during the period of observation. AE, adverse event; CR, complete response; PD, progressive disease; PR, partial response; SD8, stable disease at the 8-week follow-up visit; SD16+, stable disease of at least 16-weeks duration.

three patients with a best response of SD16+, the duration of SD was 20, 25, and 53 weeks, respectively.

The median PFS for all evaluable patients was 23 weeks (95% CI, 13 to 28), and the median OS was 61 weeks (95% CI, 34 to 114), as shown in Figures 4A and 4B.

Safety Results

Drug-related grade 3-5 AEs and SAEs were reported in 19 of 31 patients (61%) included in the safety analysis (Table 2); drug-related SAEs were reported in 11 patients (35%). Two patients discontinued treatment because of AEs and were not evaluable: one experienced a grade 2 AE of rash, fatigue, dysgeusia, pain, and anorexia, and one experienced an unrelated grade 4 SAE of sepsis. One patient died from treatment-related acute kidney injury which is a known side effect of vemurafenib.

Of 19 patients with drug-related AEs, six had dose adjustments and 11 had dose discontinuations. Those with dose discontinuations may have also experienced dose adjustments before discontinuation. Among 31 patients assessed for safety, 18 had dose adjustments or discontinuation regardless of the AE's relatedness to treatment, 10 of whom experienced DC. Dose adjustment was defined as an instance in which the treating physician changed treatment dosing for a patient because of an AE, and dose discontinuation was defined as an instance in which the treating physician temporarily or permanently stopped treatment for a patient because of an AE.

DISCUSSION

Genomic testing is increasingly used to inform the care of patients with advanced cancer. Multiple genotype-matched therapies are now FDA-approved for several disease types and tumor-agnostic biomarker-matched therapies, including agents targeted to *NTRK* and *RET* fusions, *BRAF* V600E mutations, and tumors with microsatellite instability-high status, and high tumor mutational burden are available for patients with any solid tumor. Recently, the ASCO Guideline Committee released a provisional clinical opinion on the clinical utility of genomic testing recommending that multigene panel testing be performed in patients with advanced solid tumors whenever more than one genomic biomarker has been linked to an approved therapy.[3] They concluded that tumor agnostic approvals provide a rationale for genomic testing in all solid tumors and may identify additional targets in diseases without disease-specific drug approvals. Our study confirms that routine genomic testing can identify patients with actionable *BRAF* mutations in various cancers.

In the past decade, BRAF inhibitors have been approved for multiple *BRAF* V600-mutant tumors, as either monotherapy

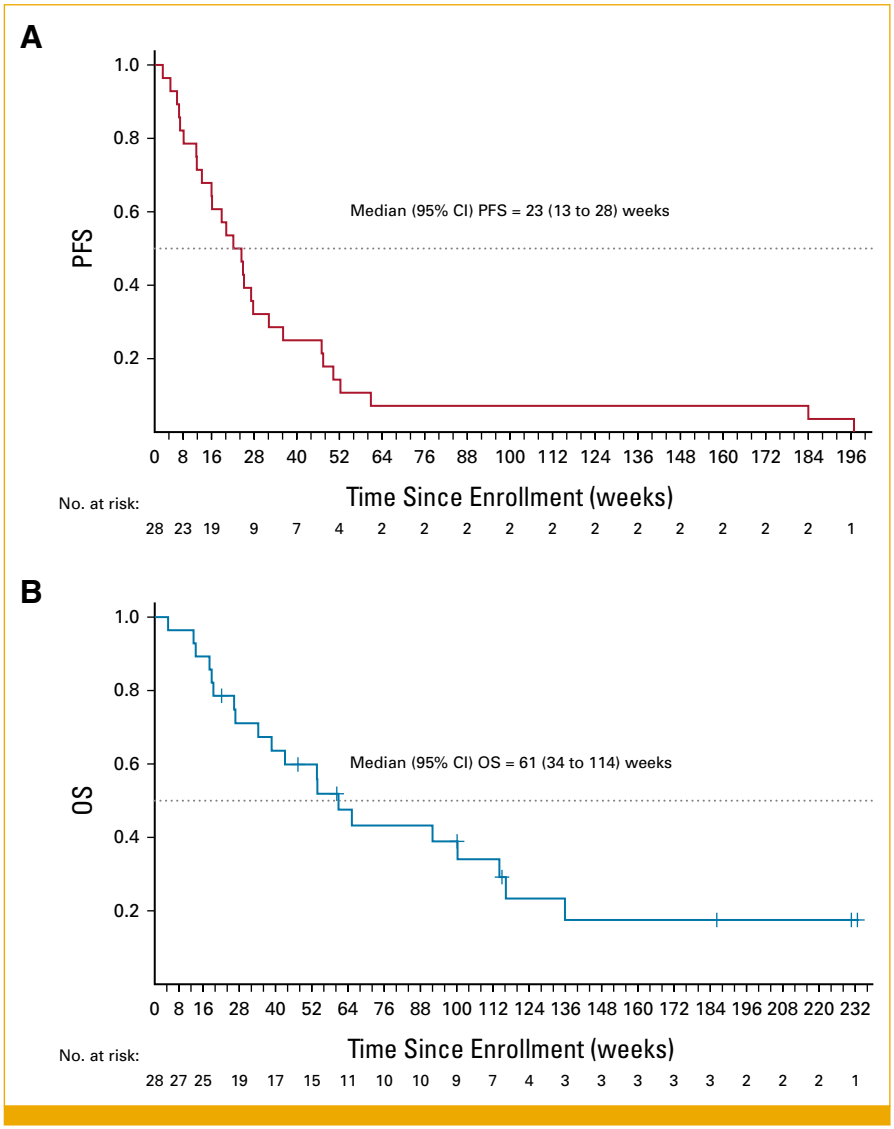

FIG 4. (A) PFS and (B) OS in 28 patients with solid tumors with *BRAF* mutations treated with cobimetinib plus vemurafenib. OS, overall survival; PFS, progression-free survival.

(vemurafenib for Erdheim-Chester disease) or in combination with MEK inhibitors (dabrafenib plus trametinib for anaplastic thyroid cancer, NSCLC, and unresectable or metastatic solid tumors) and in combination with EGFR inhibitors (encorafenib and cetuximab for CRC).[20-22] In our study, cobimetinib plus vemurafenib demonstrated an OR rate of 57%, with responses and prolonged SD in multiple tumor types where vemurafenib, alone or in combination, has not yet been approved, notably breast cancer, ovarian cancer, and cholangiocarcinoma. AEs were consistent with known side effects of the drug combination. Our findings provide further evidence that *BRAF* V600 is an actionable driver mutation across multiple tumor types.

The VE-BASKET study enrolled 208 patients, 172 of whom were included in the efficacy analysis to investigate the efficacy of vemurafenib in *BRAF* V600E-mutant tumors.[7,23] The study demonstrated an ORR of 33% and a CBR of 42%. The cohort presented here demonstrated higher antitumor activity, with an OR rate of 57% and a DC rate of 68%. Our observed median PFS of 23 weeks (5.75 months) comports with the VE BASKET trial, which reported a median PFS of 5.8 months.[7] However, the patients included in this study were more heavily pretreated, with 52% having had three or more lines of systemic therapy, compared with 26% in the VE–BASKET trial. In addition, this study had few patients with lung cancer or cholangiocarcinoma, diseases where *BRAF* V600E mutations are more common and for which BRAF/MEK combination therapy (dabrafenib/trametinib) has already demonstrated efficacy.[24,25]

The phase II, open-label Rare Oncology Agnostic Research (ROAR) basket trial, which enrolled patients with *BRAF* V600E–mutated rare cancers (ClinicalTrials.gov identifier: NCT02034110), demonstrated activity of dabrafenib in combination with trametinib that led to initial FDA approvals

TABLE 2. Summary of Drug-Related Grade 3-4 AEs and SAEs

AE	Total No. of Events	Patients Experiencing Non-SAE Grade 3-4 AEs, No. (%)[a]	Patients Experiencing SAEs, No. (%)
Rash, maculopapular	5	4 (13)	1 (3)[b]
Acute kidney injury	3	—	3 (10)[c]
Alkaline phosphatase increase	3	2 (6)	—
Anemia	3	2 (6)	—
Hypophosphatemia	3	1 (3)	—
Multiple SCCs of skin	3	1 (3)	—
Aspartate aminotransferase increase	2	2 (6)	—
CPK increase	2	1 (3)	—
Diarrhea	2	1 (3)	1 (3)[b]
GGT increase	2	2 (6)[d]	—
Hypokalemia	2	2 (6)	—
Treatment-related secondary malignancy	2	1 (3)	—
Abdominal pain	1	—	1 (3)[b]
Alanine aminotransferase increase	1	1 (3)	—
Bilirubin increase	1	—	1 (3)[b]
Constipation	1	—	1 (3)[b]
Fatigue	1	—	1 (3)[e]
Fever	1	—	1 (3)[b]
Lymphocyte count decrease	1	1 (3)	—
Nausea	1	—	1 (3)[b]
Platelet count decrease	1	1 (3)	—
Syncope	1	—	1 (3)[e]
Upper GI hemorrhage	1	—	1 (3)[b]

NOTE. Among 31 patients assessed for safety, 19 patients experienced at least one grade 3-4 AE or SAE at least possibly related to treatment.
Abbreviations: AE, adverse event; CPK, creatine phosphokinase; GGT, gamma-glutamyl transferase; SAE, serious adverse event; SCC, squamous cell carcinoma.
[a]Patients may have experienced one or more events.
[b]Hospitalization (inpatient/prolonged).
[c]One patient had a grade 5 death due to event and hospitalization (inpatient/prolonged) for two patients.
[d]Grade 4 AE.
[e]Incapacitation/disruption to normal life.

in NSCLC and anaplastic thyroid cancer.[24] This trial also demonstrated antitumor activity in rare cancers including adenocarcinoma of the small intestine (ORR, 67%), low-grade glioma (ORR, 54%), high-grade glioma (ORR, 33%), hairy cell leukemia (ORR, 89%), and multiple myeloma (ORR, 50%).[26] The NCI-MATCH (ClinicalTrials.gov identifier: NCT02465060) study included 29 patients with various tumor types harboring *BRAF* V600E mutations and reported an ORR of 38% (90% CI, 22.9 to 54.9).[27] Although, we report a higher OR rate, the similar CIs (57% [95% CI, 37 to 76]) in these studies suggest that either dabrafenib plus trametinib or cobimetinib plus vemurafenib are reasonable treatment options for patients with tumors with *BRAF* V600E mutations.

The collective data from the ROAR basket trial, NCI-MATCH trial, and the 36 pediatric patients from the CTMT212X2101 study (ClinicalTrials.gov identifier: NCT02124772),[28] in which a 25% ORR was observed in response to combination dabrafenib and trametinib, supported the tumor-agnostic FDA approval for dabrafenib plus trametinib.[29] For the 131 adult patients, 54 (41%; 95% CI, 33 to 50) experienced OR. The studies enrolled patients with 24 tumor types. Among the highest representative tumor types, ORR was 46% for biliary tract cancer, 33% for high-grade glioma, and 50% for low-grade glioma. TAPUR patients with various tumor types, including ER+ breast cancer, cholangiocarcinoma, CRC, neuroendocrine tumors (various sites), ovarian cancer, pancreatic cancer, and clear cell sarcoma, had ORs and/or clinical benefit, in some cases of several years' duration, providing further support for the efficacy of this treatment strategy across multiple tumor types.

Over the past few years, our understanding of *BRAF* signaling has significantly improved. *BRAF* mutations are subdivided into three classes on the basis of the activation mechanism of ERK signaling. Class I mutations (V600) signal as active monomers while class II mutations signal as active dimers. Class III mutants are often kinase impaired or dead and promote MAPK signaling in cooperation with RAS.[30,31] Importantly, vemurafenib is ineffective at inhibiting MAPK

signaling in cancer cells when the pathway is activated by class II and III *BRAF* mutations. In our study, patients were eligible if they had a *BRAF* V600E mutation; however, patients with other *BRAF* alterations were enrolled following review by the TAPUR MTB leading to inclusion of two patients with tumors harboring class II mutations (K601E and G469V) and one with a tumor with a class III mutation (N581I).[32,33]

Interestingly, the patient in this study with a neuroendocrine tumor (site unspecified) harboring a *BRAF* N581I mutation had a PR. *BRAF* N581I is an inactivating mutation insensitive to vemurafenib/BRAF inhibition but sensitive to MEK inhibition.[31] Thus, the antitumor activity observed in this patient was likely attributable to cobimetinib, further highlighting the potential benefit of this combinatorial approach. Our study enrolled five patients with neuroendocrine tumors harboring *BRAF* mutations, three of whom obtained PRs. Another patient with a pancreatic tumor with a *BRAF* p.T599_V600insT mutation had a duration of SD of 20 weeks. Previous reports have documented sensitivity to BRAF/MEK inhibitors in patients with tumors harboring this mutation.[34-36]

There are limitations to this study. Patients were enrolled on the basis of local testing using a variety of genomic testing platforms, although this was intended in the design of TAPUR to try to replicate real-world clinical practice. However, not all genomic tests had the same coverage or depth of sequencing, resulting in variation in the mutational profiles reported for individual patients. As a result, we were unable to systematically evaluate the contribution of coalterations to treatment efficacy. In addition, during the study period, dabrafenib plus trametinib was FDA-approved for anaplastic thyroid and NSCLC, limiting the accrual of these sensitive tumor types to our study. Finally, our study did not have a control arm, and we were unable to assess the individual contributions of vemurafenib and cobimetinib. However, we are encouraged that patients with multiple different *BRAF*-mutant tumor types exhibited clinical benefit at a time when few other treatment options were available for them.

In summary, the TAPUR Study demonstrated that *BRAF* mutations (most commonly V600E) can be identified in many tumor types in patients undergoing routine genomic testing. Cobimetinib plus vemurafenib combination therapy had a toxicity profile consistent with the drug labels and showed antitumor activity in patients with multiple tumor types with advanced solid tumors with *BRAF* V600E mutations. Responses seen in patients with non-V600E mutations warrant further study to confirm antitumor activity.

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APPENDIX

TABLE A1. Molecular Alterations and Response for Patients With Solid Tumors and *BRAF* Mutations Sorted by Best Response on Study

Primary *BRAF* Mutation	Primary Tumor Type	Genomic Test Performed	Comutation(s)[a]	Best Response
V600E	Breast	Tempus xO Onco-seq Panel	*AKT1* E17K	CR
V600E	Ovary	FoundationOne	*NF1* A2532V[b]	CR
N581I	Neuroendocrine carcinoma, site unspecified	Caris MI Profile X	—	PR
V600E	Ovary	FoundationOne	—	PR
V600E	Neuroendocrine carcinoma, pancreas	NCI-MATCH NGS Assay (MOCHA)	—	PR
V600E	Ovary	Caris MI Profile X	—	PR
V600E	Breast	FoundationOne	*CCND1* amplification *PTEN* R159fs*21, and S170fs*13	PR
V600E	Phyllodes tumor of the breast	FoundationOne	*PTEN* R233* *CDKN2A* p16INK4a R58*, and p14ARF P72L	PR
V600E	Cholangiocarcinoma	FoundationOne	—	PR
V600E	Pancreas	Solid Tumor Genomic Sequencing Panel	*PIK3CA* H1047R and H1047Y	PR
V600E	Clear cell sarcoma	BRAF Mutation Analysis and Ewing/PNET, EWSR1 FISH Analysis	—	PR
V600E	Malignant neoplasm, site unspecified	Caris MI Profile X	*PTEN* L345fs	PR
V600E	Neuroendocrine carcinoma, colon	FoundationOne CDx	*CDK6* amplification *MYC* amplification	PR
V600E	Cholangiocarcinoma	FoundationOne CDx	*PTEN* N69fs*30	PR
V600E	Breast	Solid Tumor Genomic Assay	*PIK3CA* H1047R	PR
V600E	Pancreas	Solid Tumor Genomic Assay	—	PR
T599_V600insT	Pancreas	FoundationOne	*CDKN2A* p16INK4a E120fs*26 *MYC* S362F[b]	SD16+
V600E	Colon	FoundationOne	*PTEN* loss	SD16+
V600E	Ovary	FoundationOne CDx	—	SD16+
V600E	Neuroendocrine carcinoma, small cell	FoundationOne	*RAF1* V316M[b]	SD8
K601E	Prostate	FoundationOne	*AKT1* E17K	SD8
V600E	HCC	FoundationOne CDx	—	SD8
V600E	Breast	MI-ONCOSEQ	—	PD
K601E, R603Q[b]	Melanoma[c]	FoundationOne	*MAP2K2* amplification *CDKN2A/B* loss	PD
V600E	NSCLC	FoundationOne	*PIK3CA* H1065fs*6+	PD
G469V	Angiosarcoma	FoundationOne Heme	—	PD
V600E	Neuroendocrine carcinoma, site unspecified	Caris MI Profile X	*CDKN2A* L64fs	PD
V600E	NSCLC	FoundationOne Liquid	*NF1* Y491fs*20	PD
V600E	GIST	CS-Focus GIST Panel by NGS	—	PD
V600E	Ovary	50-Gene Somatic Mutation Analysis Panel	—	PD
V600E	Ovary	Solid Tumor Genomic Assay	—	PD

Abbreviations: CR, complete response; FISH, fluorescence in situ hybridization; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; MI-ONCOSEQ, Michigan Oncology Sequencing Center; NCI-MATCH, National Cancer Institute Molecular Analysis for Therapy Choice; NGS, next-generation sequencing; NSCLC, non–small-cell lung cancer; PD, progressive disease; PNET, primitive neuroectodermal tumor; PR, partial response; SD8, stable disease at the 8-week follow-up; SD16+, stable disease of at least 16-weeks duration; VUS, variant of unknown significance.

[a]Comutations in the following genes were queried: *AKT1*, *AKT2*, *CCND1*, *CDK4*, *CDK6*, *CDKN2A*, *CYP3A4*, *EGFR*, *ERBB2*, *ETS1*, *KRAS*, *MAP2K1*, *MAP2K2*, *MAPK1*, *MAPK3*, *MET*, *MTOR*, *MYC*, *NF1*, *NRAS*, *PDGFRB*, *PIK3CA*, *PTEN*, and *RAF1*.

[b]VUS.

[c]During data validation and verification one patient was found to have primary melanoma of the vulva, was deemed ineligible and unevaluable, and was removed from the efficacy analyses. The patient was included in safety analyses and demographics since the patient received at least one dose of treatment.