2022 ASCO® ANNUAL MEETING

ASCO TAPUR™
Targeted Agent and Profiling Utilization Registry Study

Cobimetinib plus Vemurafenib in patients with solid tumors with *BRAF* mutation

Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

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BRAF Mutation in Solid Tumors

- *BRAF* is mutated in a wide range of human cancers[1]
- Clinical activity of BRAF inhibitors has been observed in nonmelanoma cancers with BRAF V600E mutations, such as NSCLC, Erdheim-Chester disease or Langerhans'-cell histiocytosis, anaplastic thyroid cancer, and cholangiocarcinoma[2]
- Resistance to BRAF inhibitors can arise due to MAPK reactivation and MAPK- independent signaling[3]
- Combining BRAF and MEK inhibitors improves PFS in patients with metastatic melanoma with BRAF V600 mutations compared to BRAF inhibition alone[3,4]
- We evaluated the combination of Cobimetinib + Vemurafenib in patients with various solid tumors with *BRAF* mutations

[1]Davies H et al. Nature 2002; 417(6892):949-954
[2]Subbiah V et al. Cancer Discov 2020; 10(5): 657–663
[3]Flaherty KT et al. N Engl J Med 2012; 367:1694-1703
[3]Long GV et al. N Engl J Med 2014; 371:1877-1888

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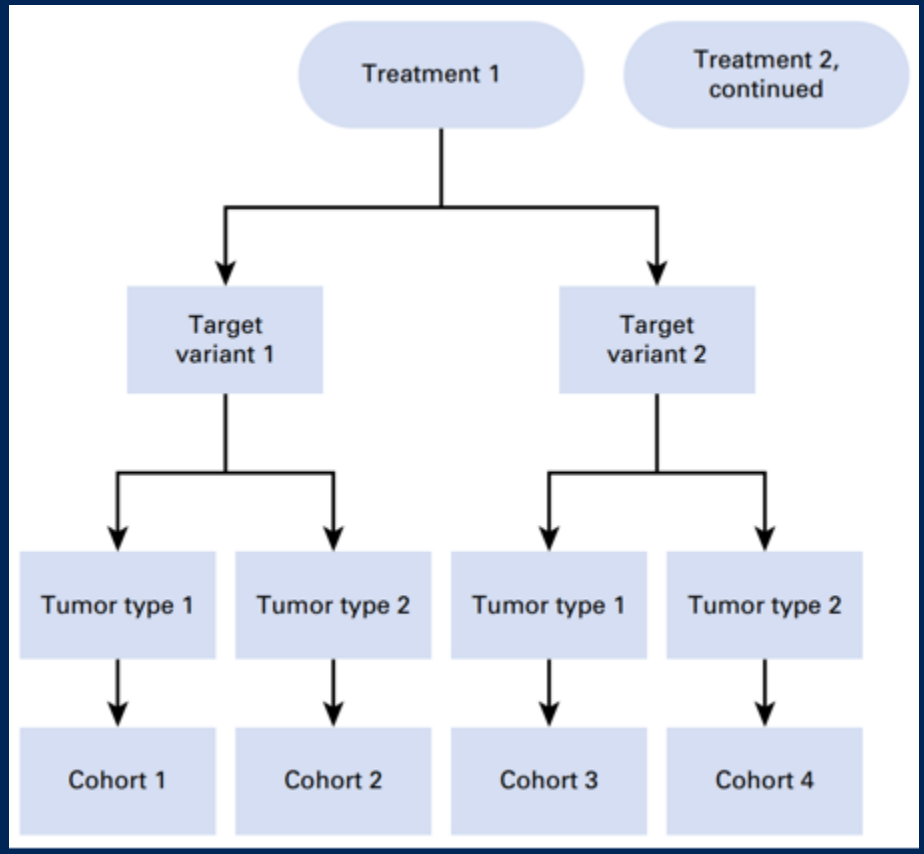
TAPUR Study

- Non-randomized, phase II, basket trial
- 17 current treatments
- 85+ genomic targets
- Any advanced and/or metastatic solid tumors
- Pre-specified genomic matching rules and broad eligibility criteria
- Virtual Molecular Tumor Board



Mangat PK et al. JCO Precision Oncology 2018; 2: 1-14

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Primary Objective and Study Endpoints

- **Objective:** Evaluate the anti-tumor activity of commercially available targeted agents in patients with advanced cancers with specific genomic alterations outside of FDA-approved uses
- **Primary Endpoint**: Disease control (DC): objective response (OR) or stable disease of at least 16 weeks duration (SD16+) per RECIST v1.1
- Secondary Endpoints:
  - Objective response
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Duration of response
  - Grade 3-5 adverse events (AEs) or serious adverse events (SAEs) at least possibly related to study treatment

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Study Design

- Slow accruing histology-specific cohorts with the same genomic target and treatment are collapsed into one histology-pooled cohort for this analysis
- For histology-pooled cohorts with 28 evaluable patients, results are evaluated based on a one-sided exact binomial test
- Null Hypothesis: Disease control rate (DCR) ≤15%
- Sample size (N=28) achieves 82% power with a one-sided alpha of 0.10 based on an alternative hypothesized DCR of 35%

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Key Eligibility Criteria and Treatment Administration

- Eligibility
  - Advanced solid tumors
  - ECOG Performance Status 0-2
  - Adequate organ function
  - Measurable disease in accordance with RECIST v1.1
  - Genomic test performed in CLIA-certified, CAP-accredited laboratory
  - BRAF V600E/D/K/R mutation or other *BRAF* mutation approved by the Molecular Tumor Board; no *MAP2K1/2*, *MEK1/2*, *NRAS* mutation
  - No prior treatment with a BRAF or MEK inhibitor
- Cobimetinib, 60 mg orally daily for 21 days, 7 days off and Vemurafenib, 960 mg orally every 12 hours daily until disease progression, unacceptable toxicity or patient withdrawal

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Demographics and Clinical Characteristics (N=31)

Characteristic[1]		
Age, years	Median (range)	63 (31, 79)
Sex, N (%)	Female	20 (65)
Race, N (%)	Asian/Asian American	1 (3)
	Black or African American	1 (3)
	White	27 (87)
	Other	1 (3)
	Prefer not to answer	1 (3)
Ethnicity, N (%)	Hispanic or Latino	1 (3)
	Not Hispanic or Latino	29 (94)
	Prefer not to answer	1 (3)
ECOG, PS, N (%)	0-1	27 (87)
	2	4 (13)
Number of prior systemic treatments, N (%)	0-2	15 (48)
	≥3	16 (52)

Characteristic[1]	
Genomic alteration, N (%)	
BRAF V600E	26 (84)
BRAF K601E[2]	1 (3)
BRAF K601E[2]/R603Q[2,3]	1 (3)
BRAF G469V[2]	1 (3)
BRAF N581I[2]	1 (3)
BRAF T599_V600insT[2]	1 (3)

[1]Percentages may not sum to 100% due to rounding
[2]As approved by the Molecular Tumor Board
[3]Variant of unknown significance

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Primary Tumor Origin (N=31)

Primary Tumor Origin[1]	
Site	**N (%)**
Ovary	6 (19)
Neuroendocrine carcinoma	5 (16)
Breast	4 (13)
Pancreas	3 (10)
Cholangiocarcinoma	2 (6)
NSCLC	2 (6)
Angiosarcoma	1 (3)
Colon	1 (3)
GIST	1 (3)
Hepatocellular carcinoma	1 (3)
Malignant neoplasm, site unspecified	1 (3)
Melanoma[2]	1 (3)
Malignant phyllodes tumor of breast	1 (3)
Prostate	1 (3)
Soft tissue sarcoma	1 (3)

[1]Percentages may not sum to 100% due to rounding
[2]During data validation and verification the patient was found to be ineligible and unevaluable and removed from primary endpoint analysis

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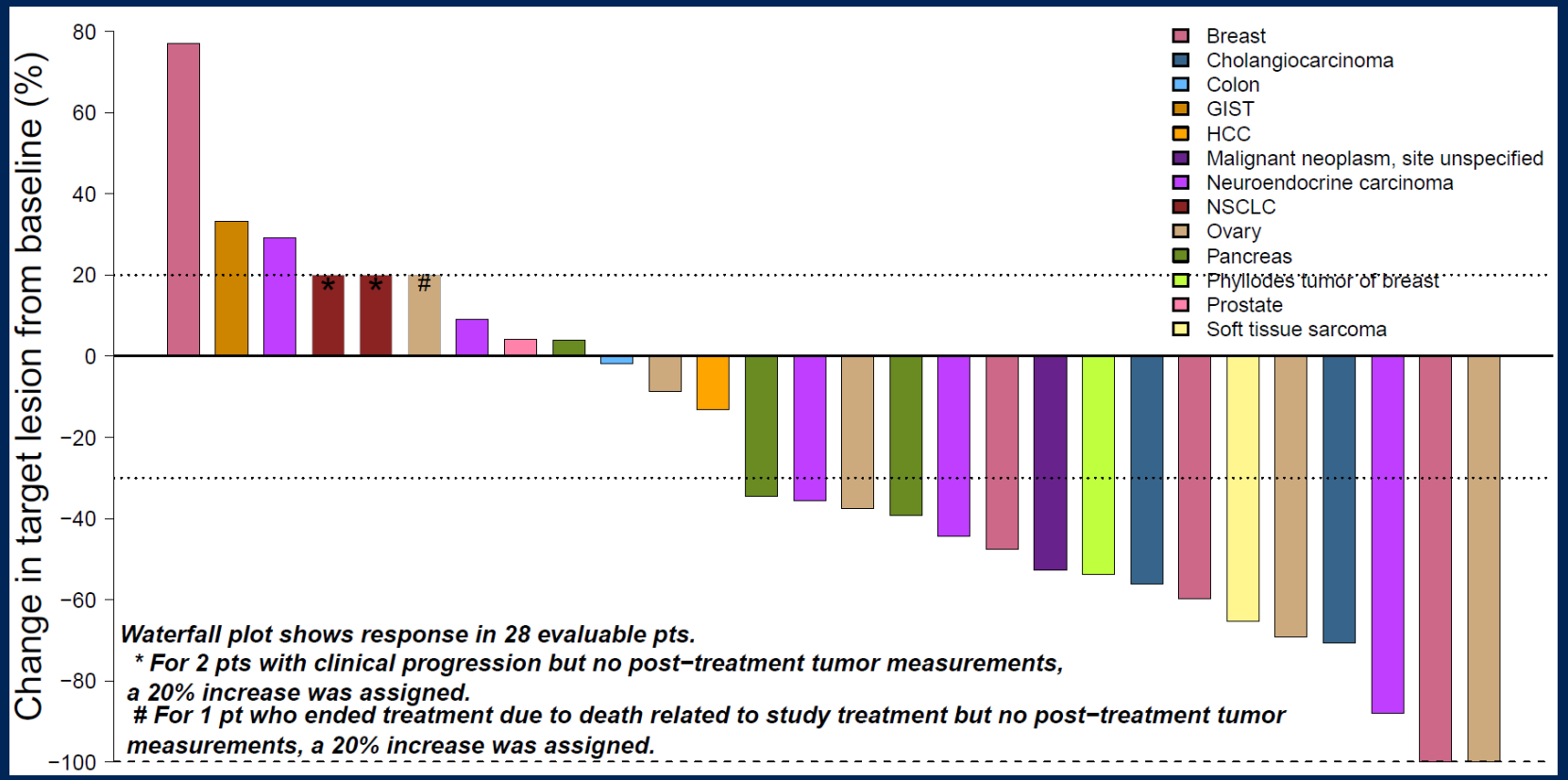
Efficacy Outcomes

Efficacy Outcomes (N=28)	
DC rate, % (one-sided 90% CI)	68 (54, 100)
OR rate, % (95% CI)	57 (37, 76)

Best percent change from baseline target lesion size (N=28)



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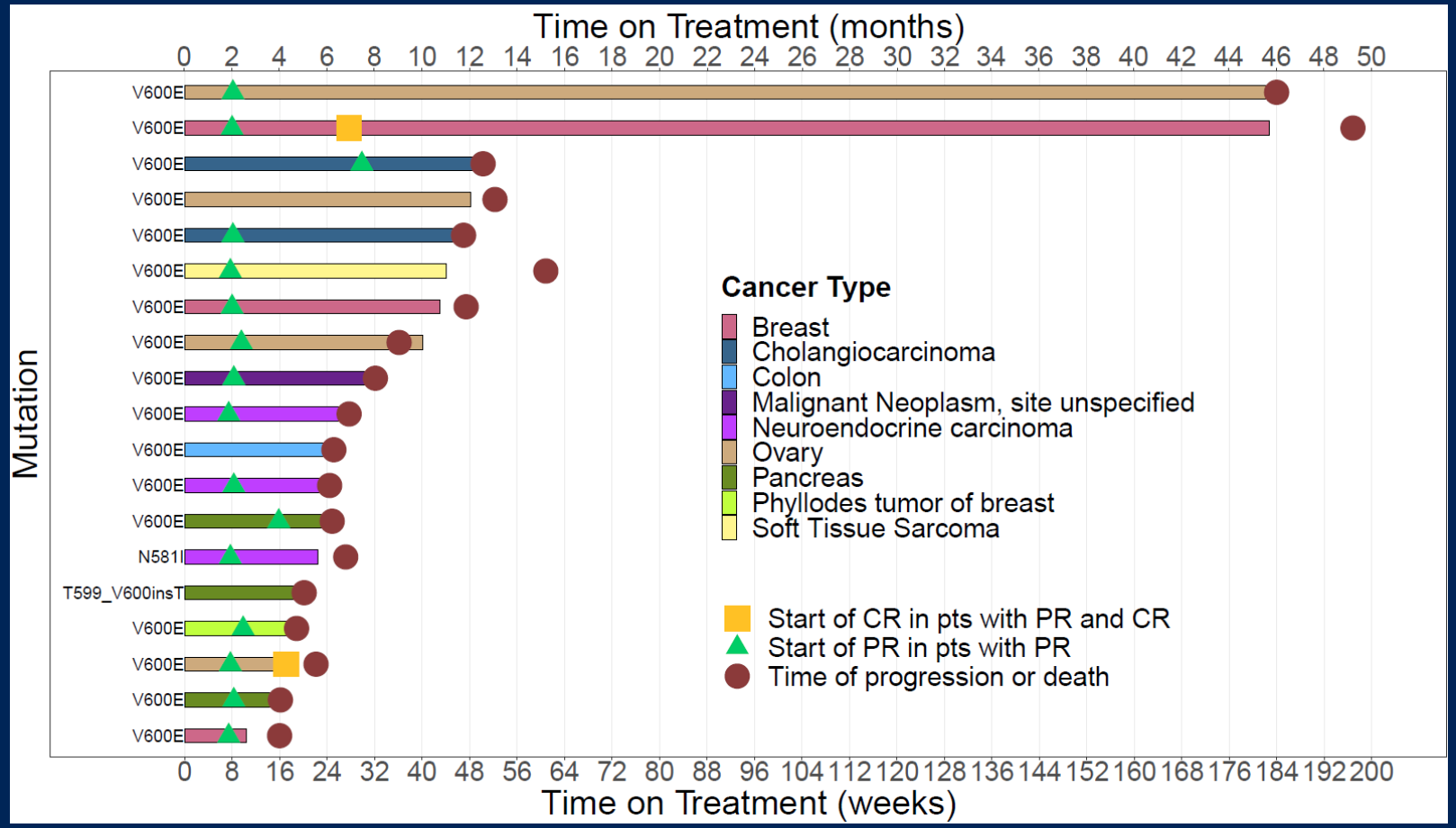
Time on Treatment in Patients with SD16+ or OR (N=19)

Duration of Response	
Duration of OR, weeks (N=16)	20.5 (8.0, 189.9)



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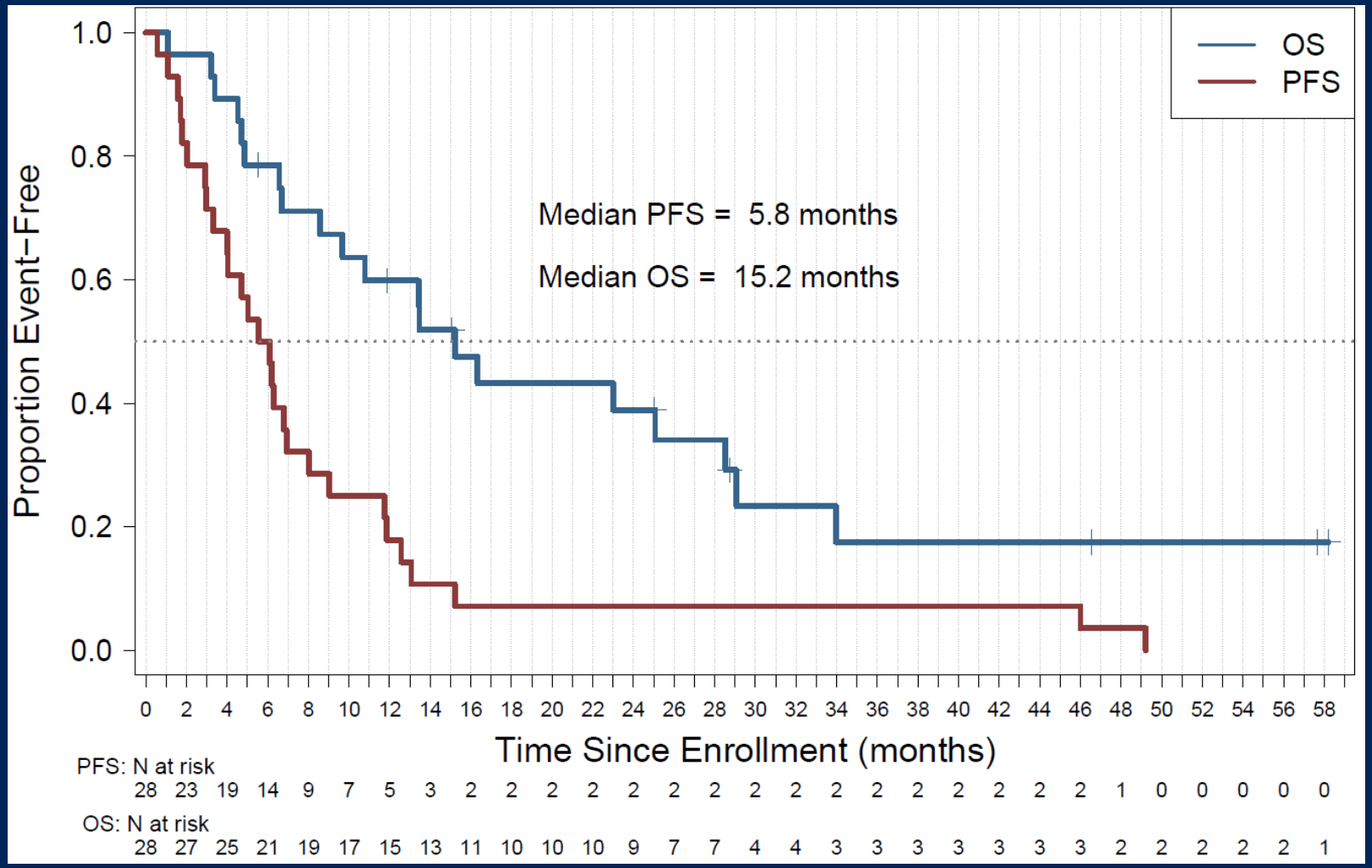
Progression Free Survival and Overall Survival (N=31)



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Toxicity Outcomes (N=31)

Grade	SAE	Pts experiencing SAE, N (%)[1]
Grade 1	Fever	1 (3)
Grade 2	Abdominal pain Constipation Fatigue	1 (3) 1 (3) 1 (3)
Grade 3	Acute kidney injury Bilirubin Diarrhea Nausea Rash Syncope Upper GI hemorrhage	2 (6) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3)
Grade 5	Acute kidney injury	1 (3)

[1] Pts may have experienced >1 event

Grade	AE	Pts experiencing AE, N (%)[1]
Grade 3	Rash Anemia Hypokalemia Alk Phos. AST ALT CPK Diarrhea GGT Hypophosphatemia Lymphocyte count decreased Multiple SCCs of skin Platelet count decreased Treatment related secondary malignancy	4 (13) 2 (6) 2 (6) 2 (6) 2 (6) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3) 1 (3)
Grade 4	GGT	1 (3)

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Summary

- *BRAF* mutations occur commonly in melanoma and at low frequency in many other solid tumors
- For those patients with OR or SD16+, sites of primary tumor origin included breast, cholangiocarcinoma, colon, unknown primary, neuroendocrine carcinoma, ovary, pancreas, and soft tissue sarcoma
- Our data (OR 57%) confirm efficacy of Cobimetinib + Vemurafenib in multiple tumor types with BRAF V600E mutation
- Toxicity is consistent with known side effects of this drug combination

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Single Agent vs Combination BRAF Inhibition in non-Melanoma Solid Tumors [14]

	Vemurafenib basket trial[1]	TAPUR Study
Treatment	Vemurafenib	Cobimetinib+Vemurafenib
Tumor characteristics	Non-melanoma BRAF V600 mutation-positive solid tumors	*BRAF* mutation-positive solid tumors
Number of patients enrolled	208	31
Number of patients included in efficacy analysis	172	28
Number of sites of primary tumor origin	16	15
Number of patients with ≥3 prior systemic therapies (%)	45 (26)	16 (52)
Clinical Benefit Rate[2] [Vem basket trial; (95% CI)] or DC rate [TAPUR (one-sided 90% CI)]	42 (34, 50)	68 (54, 100)
OR rate, % (95% CI)	33 (26, 40)	57 (37, 76)
Median PFS, months (95% CI)	5.8 (5.4, 7.6)	5.8 (3.3, 6.9)
Median OS, months (95% CI)	17.6 (13.0, 28.2)	15.2 (8.5, 28.5)
Number of patients with Grade ≥3 AE/SAEs (%)	126 (73)	17 (55)

[1]Subbiah V et al. Cancer Discov 2020; 10(5): 657–663

[2]Defined as confirmed partial response or stable disease lasting ≥6 months

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Conclusions

- Cobimetinib + Vemurafenib demonstrated evidence of anti-tumor activity in patients with a variety of advanced solid tumors with BRAF V600E with variable response durations ranging from a few weeks to >1 year
- Activity was demonstrated in multiple tumor types without current approvals for BRAF/MEK inhibitors
- Our data suggest the possibility that the combination of Cobimetinib + Vemurafenib may be more efficacious and less toxic than Vemurafenib alone, but a prospective RCT would be necessary to determine this with certainty

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- The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Santa Monica, CA
- Cancer Treatment Centers of America – Chicago, part of City of Hope, Zion, IL
- Inova Schar Cancer Institute, Fairfax, VA
- Sanford Health, Sioux Falls, SD
- University of Michigan Rogel Comprehensive Cancer Center, Ann Arbor, MI
- Michigan Cancer Research Consortium, Ypsilanti, MI
- Fox Chase Cancer Center, Philadelphia, PA
- Sutter Sacramento Medical Center, Sacramento, CA
- Sylvester Comprehensive Cancer Center, University Of Miami Miller School Of Medicine, Plantation, FL
- Cancer Treatment Centers of America – Atlanta, part of City of Hope, Newnan, GA
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