614MO - Type II RAF Inhibitor Tovorafenib in Recurrent/Refractory (R/R) Melanoma or Other Solid Tumors with *RAF* Fusions and/or *RAF1* Amplification

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Declaration of interests

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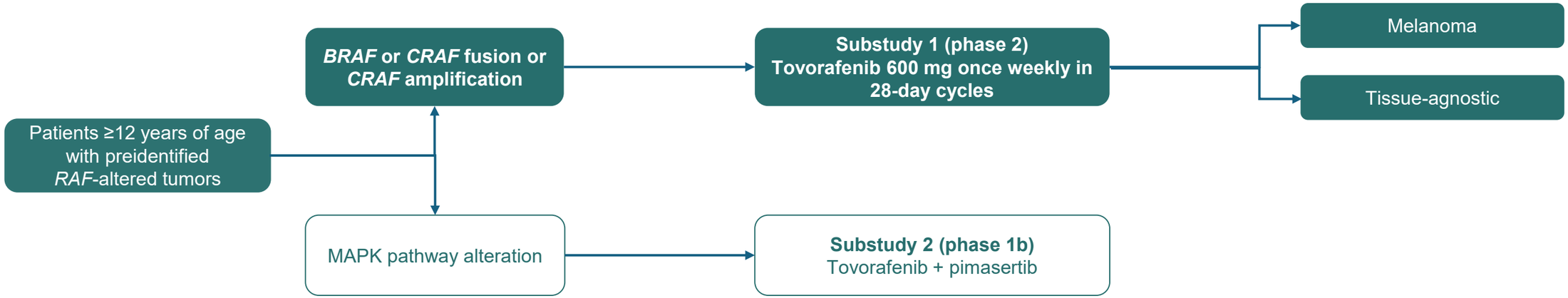
Introduction

- *BRAF* fusions and *RAF1* (*CRAF*) alterations are rare oncogenic drivers and occur in 0.5% and 1.2% of all cancers[1]
  - *BRAF* fusions have been reported in pilocytic astrocytoma, melanoma, prostate, lung, and thyroid cancers
  - *CRAF* alterations are more prevalent in melanoma, colon, lung, and endometrial adenocarcinomas, and bladder urothelial carcinoma

- Tovorafenib is an oral, selective, CNS-penetrant, type II RAF inhibitor targeting both monomeric and dimeric forms of RAF, that recently received accelerated approval by the FDA to treat relapsed or refractory pediatric low-grade glioma with *BRAF* alterations in patients ≥6 months of age[2,3]
  - A phase 1 study (NCT01425008) in adult patients with relapsed or refractory solid tumors demonstrated clinical activity in *BRAF*-mutated cancers and a recommended phase 2 dose of 600 mg once weekly[4]

- FIRELIGHT-1 (NCT04985604) is an open-label, multicenter, phase 1b/2 umbrella study of tovorafenib monotherapy or combination therapy in recurrent, progressive or refractory solid tumors harboring molecularly defined alterations of components of the MAPK pathway
  - Substudy 1 (DAY101-102a) is investigating tovorafenib monotherapy in patients with a recurrent, progressive, or refractory melanoma or other solid tumor harboring activating *BRAF* or *CRAF* fusions or *CRAF* amplification
    - Primary endpoint is investigator assessed overall response rate (ORR) per RECIST v1.1 or RANO criteria

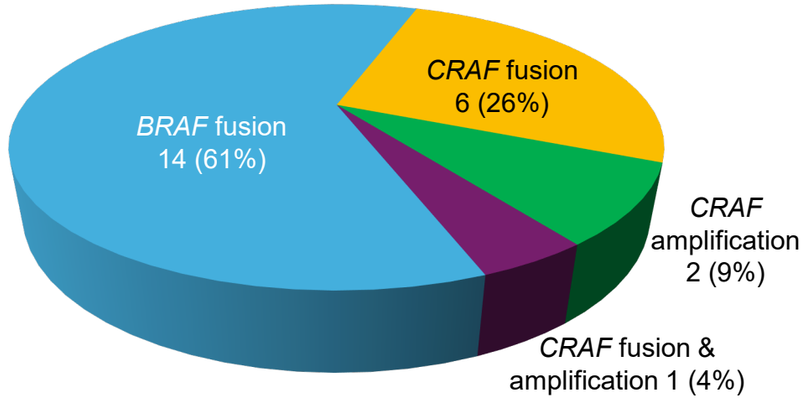


1. AACR Project GENIE Consortium. *Cancer Discov.* 2017;7(8):818-831. 2. Sun Y, et al. *Neuro Oncol.* 2017;19(6):774-785. 3. US FDA website. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tovorafenib-patients-relapsed-or-refractory-braf-altered-pediatric. Accessed Jul 16, 2024. 4. Rasco D et al., *Cancer Chemother Pharmacol.* 2023;92(1):15-18.
CNS, central nervous system; FDA, US Food & Drug Administration; MAPK, mitogen-activated protein kinase; RANO, response assessment in neuro-oncology; RECIST, response evaluation criteria in solid tumors.

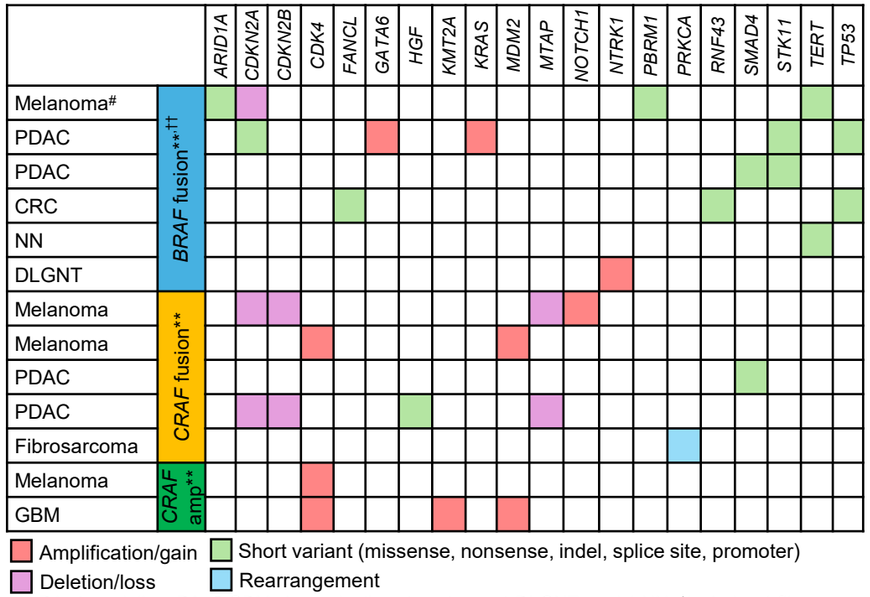
Patient characteristics

Characteristic	(N=23)
Median age, years (range)	53 (21–71)
Male, n (%)	12 (52)
Female, n (%)	11 (48)
Race, n (%)	
Asian	6 (26)
White	13 (57)
Other	2 (9)
Not reported	2 (9)
Ethnicity, n (%)	
Hispanic or Latino	2 (9)
Not Hispanic or Latino	21 (91)
Tumor type, n (%)	
Melanoma*	8 (35)
CNS†	8 (35)
PDAC	4 (17)
Sarcoma‡	2 (9)
CRC	1 (4)
Number of prior lines of systemic therapy, n (%)	
0§	2 (9)
1	8 (35)
2	4 (17)
≥3	9 (39)
ECOG performance status, n (%)	
0	9 (39)
1	14 (61)

***RAF* alterations, N=23**



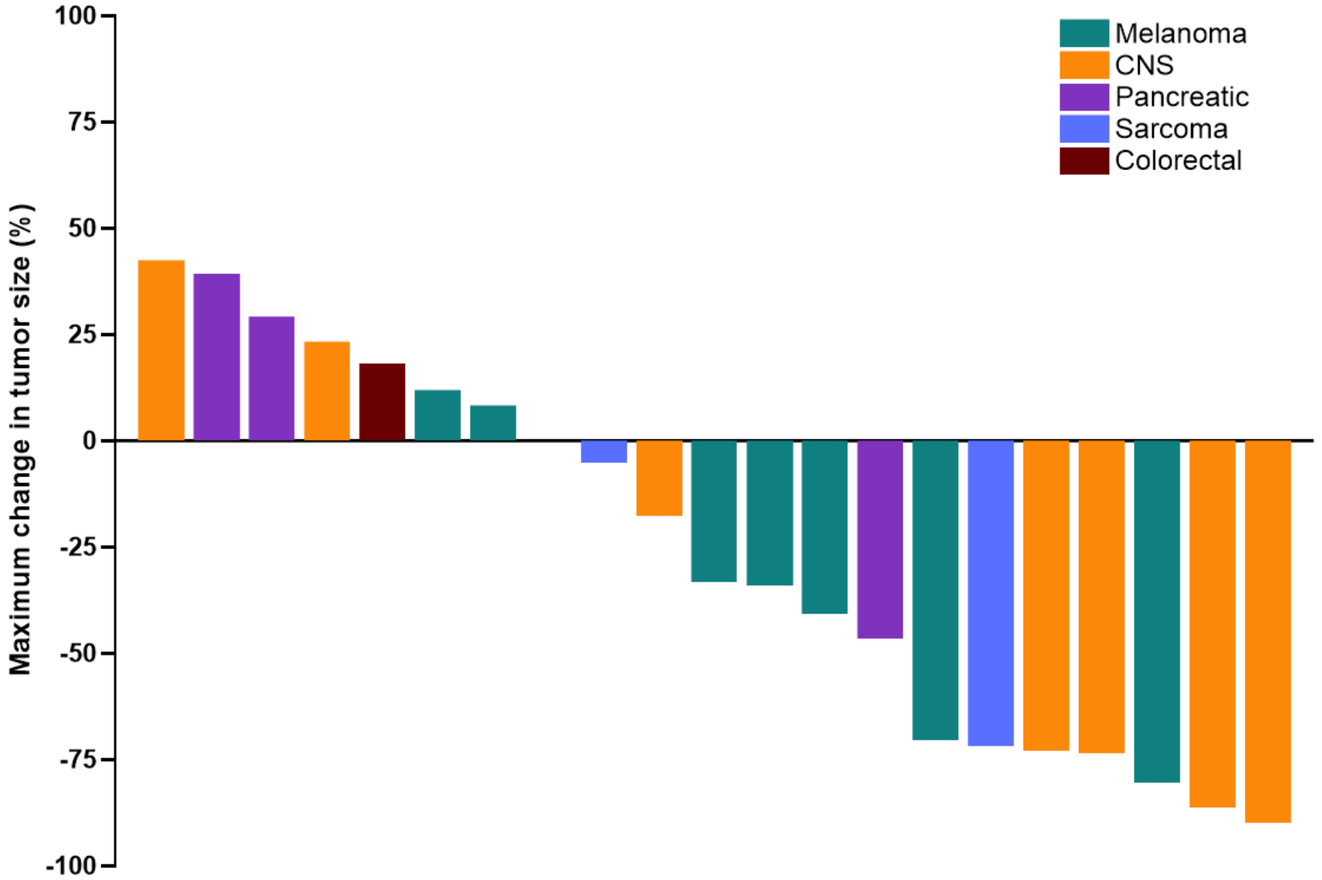
Reported co-occurring genomic findings¶



July 1, 2024 data cutoff

Percents may not add up to 100 due to rounding. *Includes 7 cutaneous non-Spitzoid and 1 malignant melanoma; †Includes 2 brain PA, 1 medullary PA, 2 GBM, 1 anaplastic astrocytoma, 1 DLGNT, and 1 NN; ‡Includes 1 fibrosarcoma and 1 spindle cell sarcoma. §One had tumor resection + prior palliative radiation, and 1 had tumor resection. ¶Reported as "potentially actionable", "biologically relevant", "pathogenic", or "likely pathogenic" on patient molecular testing reports generated in the course of routine clinical care and submitted by site investigators to support trial eligibility verification. Co-occurring genomic alterations were not observed on molecular testing reports for 10 patients (4 melanoma, 1 spindle cell sarcoma, 1 GBM, 2 brain PA, 1 medullary PA, and 1 anaplastic astrocytoma) due to variability in genes sequenced on local lab-specific NGS panels, or due to the investigator-preferred use of single analyte molecular testing assays (eg, FISH). Co-occurring genomic alterations reported as "functionally uncharacterized" or "variants of unknown significance" are not included. #Malignant. **Enrollment genomic alteration. ††Includes patients with *BRAF* duplication or rearrangement per FISH or ISH. CNS, central nervous system; CRC, colorectal adenocarcinoma; DLGNT, diffuse leptomeningeal oligodendroglial tumor (formerly known as disseminated oligodendroglial-like leptomeningeal tumor of childhood [DOGLT]); ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; GBM, glioblastoma multiforme; ISH, in situ hybridization; NGS, next generation sequencing; NN, neuroepithelial neoplasm; PA, pilocytic astrocytoma; PDAC, pancreatic ductal adenocarcinoma.

Antitumor activity of tovorafenib

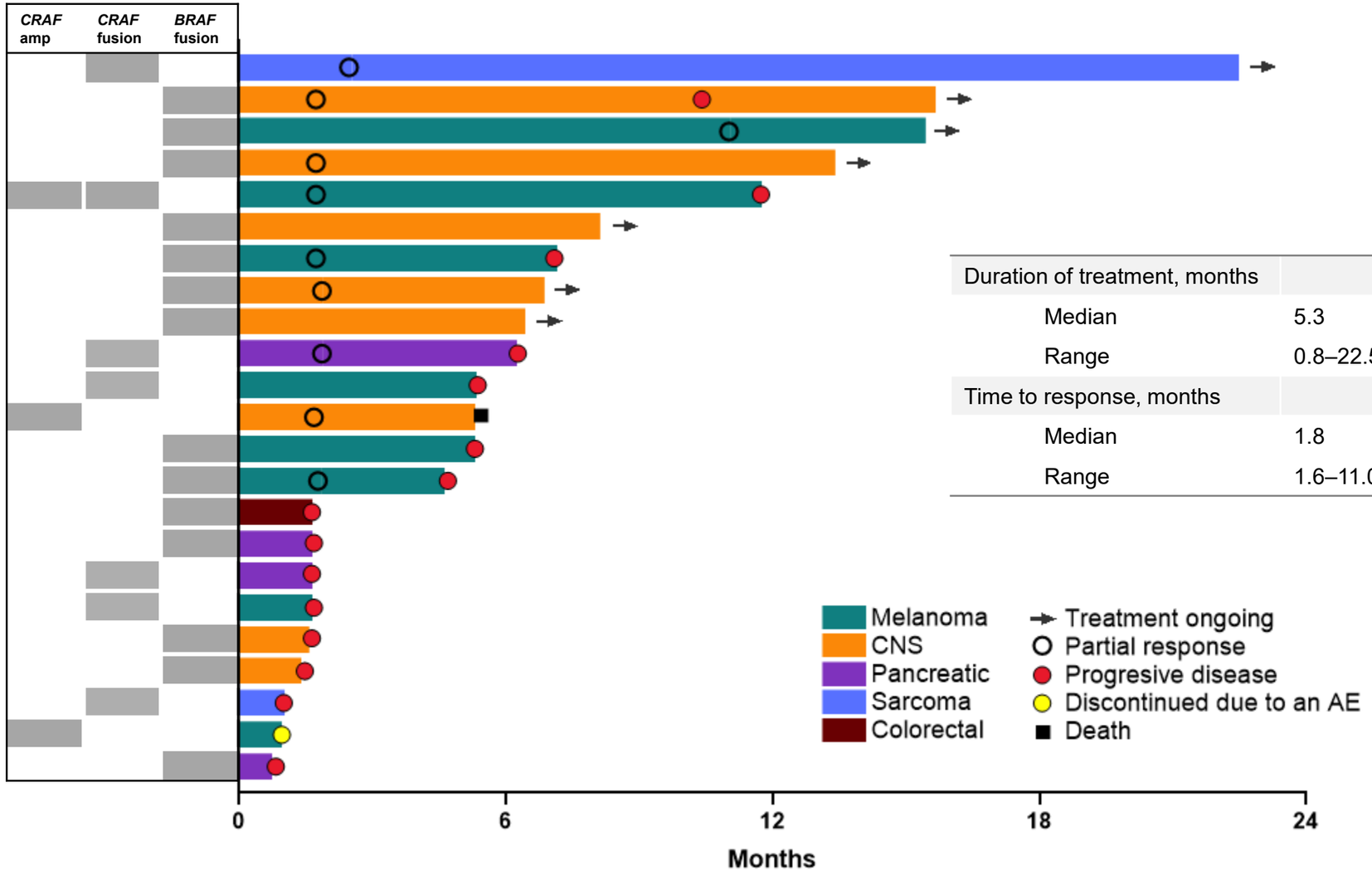


	Melanoma n=8	CNS n=8	Other n=7	All N=23
ORR (% CR + % PR), %	50	50	29	43
CBR (% CR + % PR + % SD), %	75	75	29	61
BOR, n (%)				
CR	0	0	0	0
PR	4 (50)	4 (50)	2 (29)	10 (43)
SD	2 (25)	2 (25)	0	4 (17)
PD	1 (13)	2 (25)	4 (57)	7 (30)
NE	1 (13)	0	1 (14)	2 (9)
DOR, months				
Median	5.6	9.2	-	9.2
95% CI	3.0–NE	3.5–NE	5.5–NE	3.0–NE

July 1, 2024 data cutoff.

Percents may not add up to 100 due to rounding. All responses were confirmed. Two patients, 1 with cutaneous non-Spitzoid melanoma and 1 with pancreatic ductal adenocarcinoma are not included in the waterfall as their target lesions were NE.
BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response, SD, stable disease.

Duration of therapy and response to tovorafenib



Duration of treatment, months	
Median	5.3
Range	0.8–22.5
Time to response, months	
Median	1.8
Range	1.6–11.0

July 1, 2024 data cutoff.

AE, adverse event; CNS, central nervous system.

Safety, N=23 (treatment-emergent AEs* ≥15% any grade)

	Treatment-emergent AEs		Treatment-related AEs	
Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any adverse event	23 (100)	13 (57)	21 (91)	5 (22)
Anemia	12 (52)	3 (13)	9 (39)	2 (9)
Myalgia	7 (30)	2 (9)	5 (22)	0
Pruritus	7 (30)	0	7 (30)	0
Increased blood creatine phosphokinase	6 (26)	1 (4)	6 (26)	1 (4)
Constipation	6 (26)	0	2 (9)	0
Rash	6 (26)	0	6 (26)	0
Cough	5 (22)	0	1 (4)	0
Dermatitis acneiform	5 (22)	1 (4)	5 (22)	1 (4)
Face edema	5 (22)	0	5 (22)	0
Vomiting	5 (22)	0	2 (9)	0
Asthenia	4 (17)	0	3 (13)	0
Decreased appetite	4 (17)	0	3 (13)	0
Fatigue	4 (17)	0	3 (13)	0
Hair color changes	4 (17)	0	4 (17)	0
Hypokalemia	4 (17)	1 (4)	1 (4)	1 (4)
Maculopapular rash	4 (17)	0	3 (13)	0

- 1 patient (4%) had treatment-related myalgia leading to treatment discontinuation
- 5 patients (22%) had TRAEs leading to a dose reduction; 3 dose reduced to 500 mg and 2 to 400 mg
- 7 patients (30%) had TRAEs leading to dose interruption

July 1, 2024 data cutoff.

*Per CTCAE classification, version 5.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

Summary

- Tovorafenib has single-agent tumor-agnostic clinical activity in *RAF*-altered tumors
  - Overall cohort: 43% ORR and 61% CBR, with a median DOR of 9.2 months
  - PR reported in melanoma, CNS tumors, PDAC, and spindle cell sarcoma
- Tovorafenib has a manageable safety profile
  - 5 patients (22%) had a grade ≥3 TRAE
  - 1 patient (4%) discontinued treatment due to a TRAE (myalgia)

Thank you to all patients, families, caregivers, and clinical investigators for their participation in this study

CBR, clinical benefit rate; CNS, central nervous system; DOR, duration of response; ORR, overall response rate; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; TRAE, treatment-related adverse event.