Efficacy of BRAF Inhibitor Plixorafenib (FORE8394) in Recurrent, Primary Central Nervous System Tumors (PCNST)

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Disclosures

- Advisory Board Member: Servier Pharmaceuticals, Rigel Pharmaceuticals, and AnHeart Therapeutics.

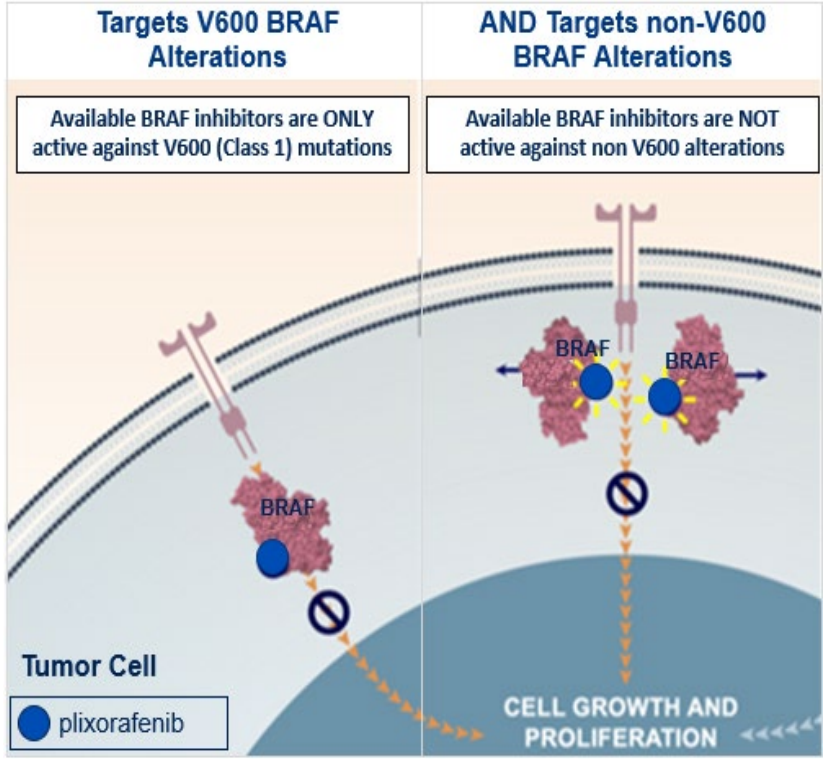
BRAF mutations and primary CNS tumors (PCNSTs)

- Targeting BRAF V600 mutation has demonstrated clinical benefit across solid tumor types[1]
- BRAF alterations are found in ~7% of all CNS tumors[1]
- Median overall survival rates for adults with recurrent BRAFV600+ HGG and LGG are 6.8 months and 9.5 months, respectively[2]
- In adult BRAF V600+ PCNST, response rates include 25% with vemurafenib single-agent therapy[3] and 33% (HGG) to 50% (LGG) with combination of dabrafenib and trametinib[4,5]
  - DOR of 3.9–44 months in HGG and 6–29 months in LGG have been observed[4,5]
- Approved BRAF inhibitors can have a challenging safety profile (nausea, pyrexia, and rash)[6,7], have discontinuation of up to 30%[7], and require administration with a MEK inhibitor

Plixorafenib (FORE8394; PLX8394): an investigational oral BRAF inhibitor[8,9]

- Selective, potent activity for mutant BRAF, minimal effects on wild type BRAF, ARAF, and CRAF
- Novel MOA: targets V600 and non-V600 alterations by disrupting BRAF monomers and BRAF-BRAF and BRAF-CRAF heterodimers, without inducing RAF dimer formation
- Evades paradoxical activation of the MAPK pathway, eliminating the need for combination with a MEK inhibitor
- Not sensitive to some of the resistance mechanisms of the currently approved BRAFi

Plixorafenib Novel MOA



We report the safety of plixorafenib in patients with PCNSTs and the prespecified subgroup efficacy analysis in the MAPKi-naïve PCNST BRAF V600 population

ARAF, A-raf proto-oncogene, serine/threonine kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; BRAFi, BRAF inhibitor; CNS, central nervous system; CRAF, proto-oncogene c-RAF; DOR, duration of response; HGG, high-grade glioma; LGG, low-grade glioma; MAPK, mitogen-activated protein kinases; MEKi, MAPK kinase inhibitor; MOA, mechanism of action; ORR, objective response rate; RAF, rapidly accelerated fibrosarcoma.

1. Bouchè V et al. *Front Oncol* 2021;11:772052; **2.** Andrews LJ et al. *Neuro Oncol* 2022;24:528–40; **3.** Kaley T et al. *J Clin Oncol* 2018;36:3477–84; **4.** Tafinlar. Prescribing Information. Novartis; 2013. Accessed Nov 6, 2023. https://www.novartis.com/us-en/sites/novartis_us/files/tafinlar.pdf; **5.** Gouda M and Subbiah V. *Am Soc Clin Oncol Educ Book* 2023;43:e404770; **6.** Chen P et al. *Onco Targets Ther* 2017;10:5391–403; **7.** Garutti M et al. *Cancers* 2023;15:141; **8.** Yao Z et al. *Nat Med* 2019;25:284–91; **9.** Tutuka CSA et al. *Mol Cancer* 2017;16:112.

Study Design (NCT02428712)

- Phase 1/2a, first-in-class, open-label, single-arm, multicenter study
- Dose escalation (3+3 design) followed by dose expansion
  - Dose escalation (included patients ≥4 y with advanced cancer or LCH)
  - Dose optimization & extension (included patients ages ≥10 y with class 1 or 2 BRAF-altered tumors)
- The optimal dose (RP2D) was established as 900 mg QD with the PK booster cobicistat 150 mg QD, based on PK, efficacy, and safety data (ASCO 2023)

N=113[a]
Evaluated doses of 900–3600 mg/day ± PK booster

51% received dose levels > the RP2D

Key inclusion criteria
- Adults/children ≥10 y
- Advanced unresectable solid or BRAF-altered CNS tumors
- No available standard therapy

Overall patient population[a] (N=113)
- 64 (57%) had V600+ disease
- 34 (30%) had received ≥1 prior MAPK-targeted regimen

→

PCNST[b] (independent of BRAF alteration; safety subgroup) (n=22)
- 15 had a V600+ BRAF mutation
- 13/15 were V600+ with ≥1 postbaseline assessment
- 9/13 were MAPKi naïve (efficacy subgroup)

→

PCNST[b] BRAFV600+ **and** MAPKi treatment naïve (n=9)

→

LGG/GNT (n=4)
- Neuroepithelial-GNT (n=1)
- Ganglioglioma-GNT (n=1)
- Pilocytic astrocytoma (n=1)
- Xanthoastrocytoma (n=1)

HGG (n=5)
- Anaplastic astrocytoma (n=1)
- Glioblastoma (n=4)

[a]All patients who received ≥1 dose of plixorafenib.
[b]For patients with PCNST, tumor assessments were performed using RECIST 1.1 or RANO HGG or LGG criteria based on the protocol under which the patient was enrolled.

ASCO, American Society of Clinical Oncology; GNT, glioneuronal tumor; LCH, Langerhans cell histiocytosis; MAPKi, MAPK inhibitor; PK, pharmacokinetics; QD, once daily; RANO, response assessment in neuro-oncology; RECIST, response evaluation criteria in solid tumours; RP2D, recommended phase 2 dose.

Patient Baseline Characteristics

Demographics		Overall (N=113)	PCNST safety subgroup (n=22)	PCNST V600+ MAPKi naïve (n=9)
Age, years	Median (min, max)	57.0 (4, 86)	41.5 (4, 80)	43.0 (21, 80)
	<18 years, n (%)	5 (4.4)	3 (13.6)	0
	18 to <65 years, n (%)	66 (58.4)	18 (81.8)	8 (88.9)
	≥65 years, n (%)	42 (37.2)	1 (4.5)	1 (11.1)
Sex, n (%)	Male	59 (52.2)	9 (40.9)	4 (44.4)
Race, n (%)	White	101 (89.4)	18 (81.8)	7 (77.8)
	Black/African American	5 (4.4)	2 (9.1)	1 (11.1)
	Asian	3 (2.7)	1 (4.5)	1 (11.1)
	Missing	4 (3.5)	1 (4.5)	0
Ethnicity, n (%)	Hispanic or Latino	12 (10.6)	5 (22.7)	1 (11.1)
ECOG PS, n (%)	0	43 (38.1)	11 (50.0)	6 (66.7)
	1	65 (57.5)	9 (40.9)	3 (33.3)
	≥2	5 (4.4)	2 (9.1)	0

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Baseline Prior Treatments & Disease Characteristics

Treatment history	PCNST (n=22)	PCNST V600+ MAPKi naïve (n=9)
Months from diagnosis to first dose		
Median (range)	32.4 (5.2, 182.3)	22.5 (5.2, 182.3)
Months on last treatment		
Median (range)	7.0 (2.0, 46.0)	11.3 (6.3, 46.0)
Months from last treatment to enrollment/first dose		
Median (range)	2.7 (0.8, 79.9)	9.5 (1.9, 79.9)
Prior lines of systemic therapy, n (%)		
0	6 (27.3)	2 (22.2)
1	7 (31.8)	6 (66.7)
2	0	0
≥3	9 (40.9)	1 (11.1)
Prior anticancer therapies, n (%)		
Systemic therapy		
Bevacizumab	4 (18.2)	1 (11.1)
Temozolomide	16 (72.7)	7 (77.8)
MAPK inhibitor	5 (22.7)	0
Checkpoint inhibitor	1 (4.5)	0
Surgery	19 (86.4)	7 (77.8)
Radiation therapy	15 (68.2)	7 (77.8)

Disease characteristics	PCNST V600+ MAPKi naïve (n=9)
Histology	
Glioblastoma	4
Anaplastic astrocytoma	1
Pilocytic astrocytoma	1
Xanthoastrocytoma	1
Neuroepithelial-GNT	1
Ganglioglioma-GNT	1
WHO CNS grade (most recent prior to study entry)	
I	3
II	1
III	1
IV	4
Primary location(s) at diagnosis	
Temporal lobe	6
Brain stem	2
Parietal lobe	1
IDH wild type	9

Disposition & Safety Profile

Overall Population (N=113)

Reasons for treatment discontinuation

- 86 (76.1%) discontinued due to RECIST/RANO-defined PD or clinical disease progression
- 9 (8%) withdrew from the study
- 5 (4%) due to AE (4 considered not related to plixorafenib)
- 3 (2.7%) due to other reason
- 1 (0.9%) due to physician decision

Dose reductions due to TRAEs: 8 (7%)

Only one patient discontinued plixorafenib due to TRAE

- Grade 3 bilirubin; dose: 1800 mg BID with PK booster

No fatal treatment-related adverse events

86 patient-years of plixorafenib exposure

PCNST Population (N=22)

Reasons for treatment discontinuation

- 16 (72.7%) discontinued due to RECIST/RANO-defined PD or clinical disease progression
- 1 (4.5%) withdrew from the study
- 1 (4.5%) due to AE considered not related to treatment
- 1 (4.5%) due to other reason

No patient discontinued due to TRAE

Treatment-emergent AES in PCNST (across dose levels)

- TEAEs in ≥20% were limited to LFT changes, G1 increased creatinine, fatigue, headache, and nausea
- Grade ≥3 TEAEs occurring in >1 patient included ALT increase (4 patients, all grade 3) and headache (2 patients, both grade 3)

16 patient-years of plixorafenib exposure

AE, adverse event; ALT, alanine transaminase; BID, twice daily; G, grade; LFT, liver function test; PD, progressive disease; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Safety Profile (Overall Population and at the RP2D)

Most Common TEAEs[a] in the Overall Population

	Preferred term	All dose levels (N=113)					RP2D (n=9)				
		G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	Any grade n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	Any grade n (%)
Lab abnormality AEs	Increased ALT	24 (21.2)	15 (13.3)	8 (7.1)	1 (0.9)	48 (42.5)	4 (44.4)	1 (11.1)	1 (11.1)	0	6 (66.7)
	Increased AST	26 (23.0)	13 (11.5)	3 (2.7)	0	42 (37.2)	4 (44.4)	1 (11.1)	0	0	5 (55.6)
	Increased blood bilirubin	4 (3.5)	7 (6.2)	9 (8.0)	0	20 (17.7)	0	1 (11.1)	0	0	1 (11.1)
Symptomatic AEs	Fatigue	17 (15.0)	22 (19.5)	1 (0.9)	0	40 (35.4)	1 (11.1)	1 (11.1)	0	0	2 (22.2)
	Nausea	26 (23.0)	6 (5.3)	2 (1.8)	0	34 (30.1)	3 (33.3)	0	0	0	3 (33.3)
	Diarrhea	15 (13.3)	7 (6.2)	4 (3.5)	0	26 (23.0)	2 (22.2)	0	0	0	2 (22.2)
	Vomiting	11 (9.7)	11 (9.7)	1 (0.9)	0	23 (20.4)	0	0	0	0	0

[a]≥20% for all grade and/or ≥5% for grade ≥3 TEAEs.

A low frequency of grade ≥2 symptomatic TEAEs were observed across all dose levels (up to 3600 mg/day with PK booster) and at the RP2D of 900 mg QD with the PK booster

At the RP2D:

- No DLTs
- LFT changes are predominantly low grade
- Maximizes dose intensity early in treatment
- Symptomatic AEs were almost all grade 1
- 7 of the 9 patients had PCNSTs

AST; aspartate transaminase; DLT, dose-limiting toxicity; G2, grade 2; G3, grade 3; G4, grade 4.

Known MAPK Inhibitor Toxicities, Contrasted With Plixorafenib TEAEs

Dabrafenib/Trametinib Common Events (≥20%)[1]

TEAEs, %	All		Grade 3/4	
	Dabr/Tram[a] (N=206)	Plixorafenib (N=113)	Dabr/Tram[a] (N=206)	Plixorafenib (N=113)
Pyrexia	55	7	4.9	0
Fatigue[b]	50	36	5	0.9
Nausea	40	30	1.5	1.8
Rash[b]	40	12	2.4	0
Chills	30	0.9	0.5	0
Headache	30	15	1.5	1.8
Hemorrhage[b]	29	11	4.4	1.8
Cough[b]	29	15	0	0
Vomiting	27	20	1.5	0.9
Constipation	27	17	0	0
Diarrhea	26	23	2.9	3.5
Myalgia[b]	24	11	0.5	1.8
Arthralgia	23	12	0.5	1.8
Peripheral edema[b]	22	12	0	0.9

In contrast to treatment with BRAFi/MEKi therapies, TEAEs with plixorafenib:

- **Rash & pyrexia:** grade 1 only; none led to plixorafenib reductions
- **Ocular:** no uveitis or retinal detachment based on TEAE and eye exams
- **Cardiovascular:** no TEAE of left ventricular ejection fraction reduction
- **Lack of paradoxical MAPK pathway activation:** no related events of hyperkeratosis or secondary skin cancers

1) Supports novel MOA, designed to avoid the need to combine with a MEK inhibitor
2) Supports a more tolerable profile without the burden of additional monitoring for CV, ocular, or dermatologic effects

[a]NCI CTCAE version 4.0. Dabrafenib/trametinib data are per Tafinlar USPI, BRAF V600E+ tumors (N=206).
[b]Combined incidence for TEAEs as listed in the Tafinlar USPI.

CV, cardiovascular; Dabr, dabrafenib; NCI CTCAE, National Cancer Institute common terminology criteria for adverse events; Tram, trametinib; USPI, United States prescribing information.

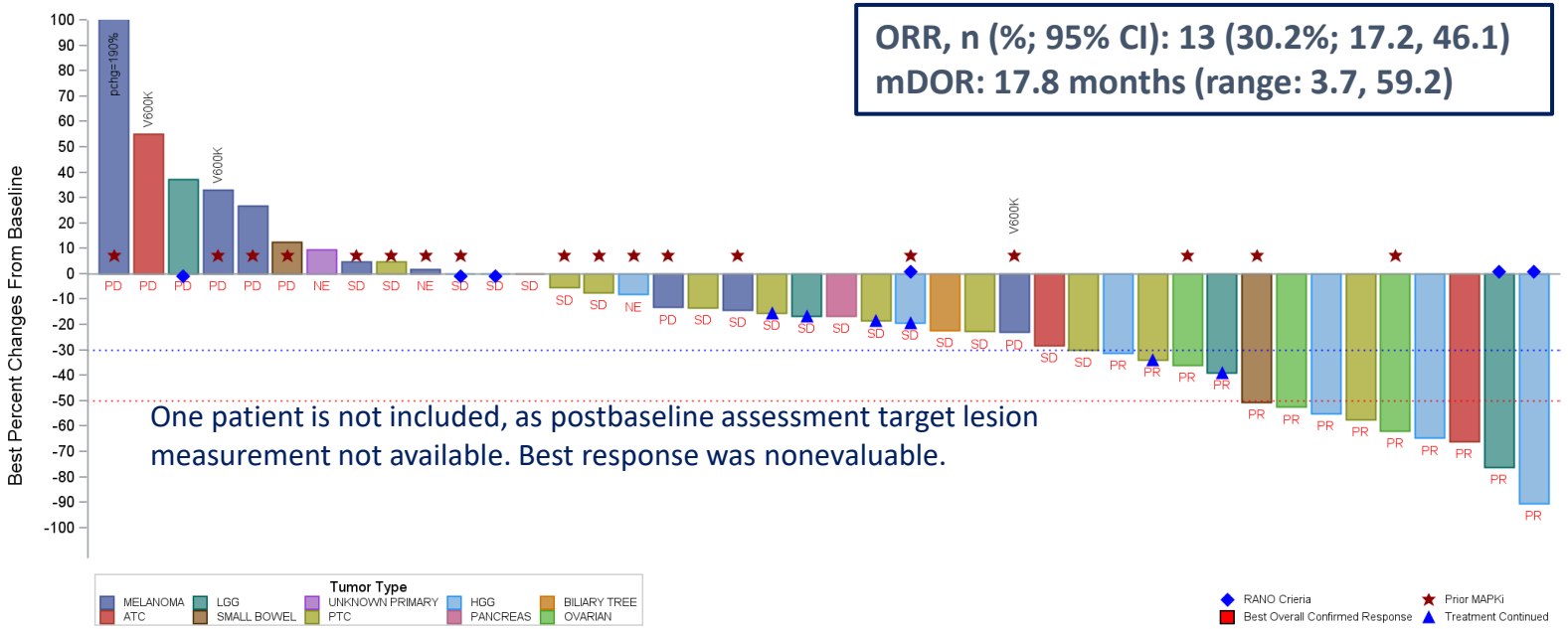
1. Tafinlar. Prescribing Information. Table 14. Novartis; 2013. Accessed Nov 6, 2023. https://www.novartis.com/us-en/sites/novartis_us/files/tafinlar.pdf;

Summary of Efficacy in Evaluable Adults With V600-mutated Tumors

Plixorafenib Best Percent Tumor Change From Baseline in V600+ Adults (N=43, mITT)

Excluding CRC Due to Known Intrinsic Resistance Through EGFR Pathway

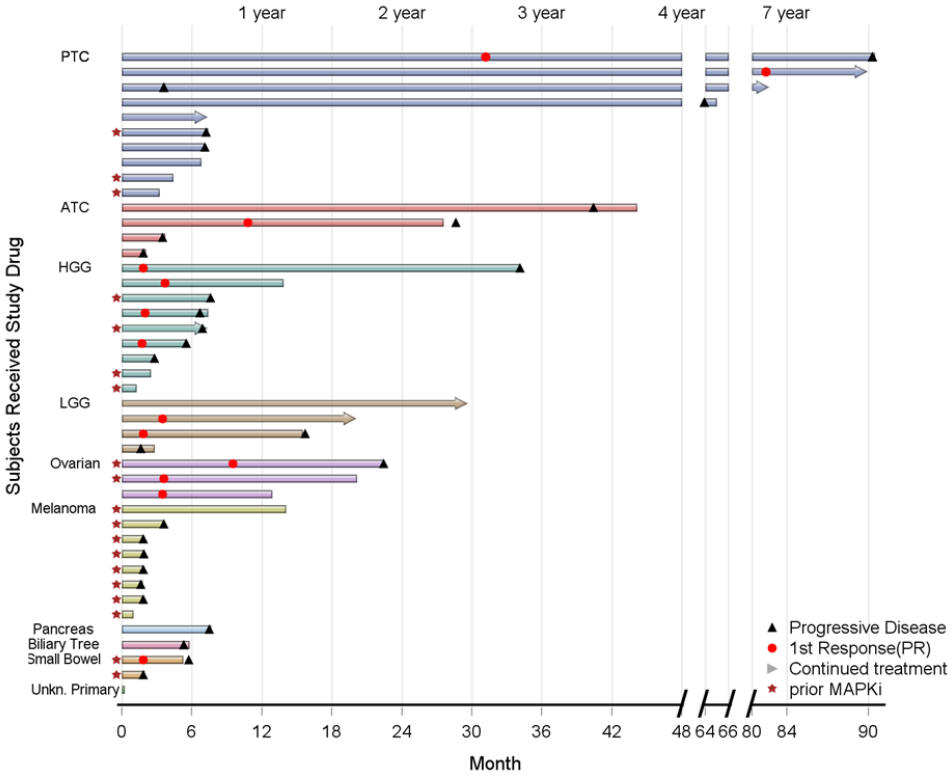
ORR, n (%; 95% CI): 13 (30.2%; 17.2, 46.1)
mDOR: 17.8 months (range: 3.7, 59.2)



One patient is not included, as postbaseline assessment target lesion measurement not available. Best response was nonevaluable.

Plixorafenib Treatment Duration

Efficacy Evaluable Adults with V600+ Tumors



Median time to response: 3.5 months

	ORR[a] n (%)	PR n (%)	SD n (%)	mDOR (range)	6-month DOR rate, n (%)[b]	CBRx24wks[c] n (%)
MAPKi naïve (n=24)	10 (41.7)	10 (41.7)	11 (45.8)	17.8 months (3.7, 59.2)	8 (80.0)	17 (70.8)
MAPKi pretreated (n=19)	3 (15.8)	3 (15.8)	7 (36.8)	12.9 months (3.9, 16.6+)	2 (66.6)	7 (36.8)

Antitumor activity was observed in various tumor types

[a]All responses were confirmed.
[b]6-month DOR rate: % of responders with DOR ≥6 months.
[c]CBR: CR+PR+MR+(SD≥24 weeks).

ATC, anaplastic thyroid carcinoma; CBR, clinical benefit rate; cPR, confirmed partial response; CRC, colorectal cancer; DOR, duration of response; EGFR, epidermal growth factor receptor; mDOR, median DOR; MR, minor response; mITT, modified intent to treat; NR, not reached; ORR, overall response rate; PR, partial response; PTC, papillary thyroid carcinoma; SD, stable disease; Unkn, unknown.

Efficacy in V600+ MAPKi-naïve PCNST

	LGG (n=4)	HGG (n=5)
Median follow-up, months (range)	17.8 (2.8, 29.5)	7.9 (2.8, 34.1)
Confirmed response, n (%)		
PR	2 (50.0)	4 (80.0)
SD	1 (25.0)	1 (20.0)
PD	1 (25.0)	0
ORR, n (%)	2 (50.0)	4 (80.0)
DOR range, months	13.2+, 13.9	3.7, 32.3
6-month DOR rate, n (%)[b]	2/2 (100.0)	2/4 (50.0)
CBRx24wks[a], n (%)	3 (75.0)	4 (80.0)
mPFS, months (range)	NE (1.6, 27.8+)	6.7 (2.8, 34.1)

[a]CBRx24wks: CR+PR+MR+(SD≥24 weeks).
[b]≥6-month DOR rate: % of responders with DOR ≥6 months.

ORR: 6/9 had PR (66.7%; 95% CI: 29.9, 92.5)

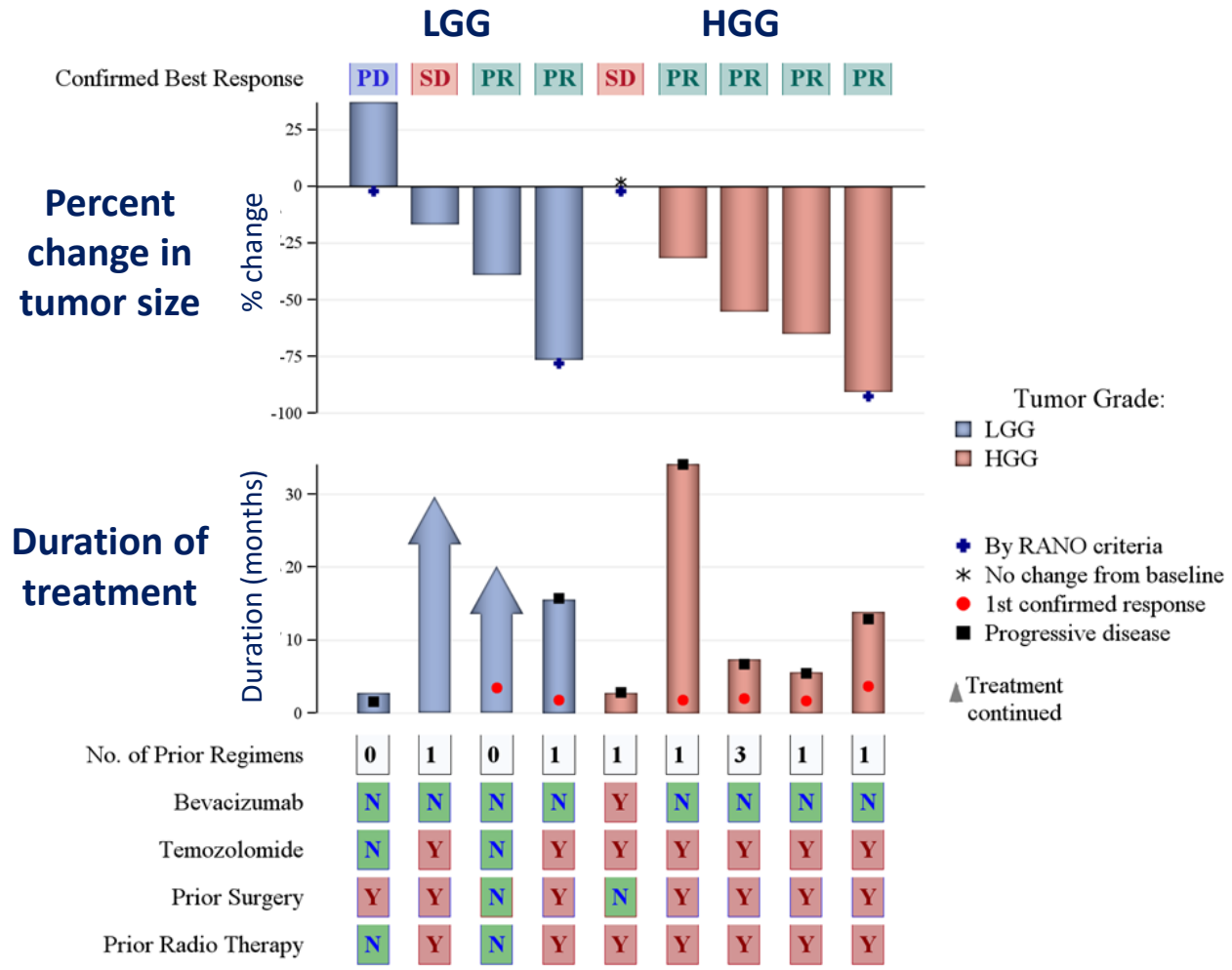
Response or SDx24weeks: 78%

Duration of response: 13.9 months (median)

*Exploratory retrospective blinded independent review.
All responses were confirmed.

CI, confidence interval; CR, complete response; mPFS, median progression-free survival; NA, not applicable; NE; not evaluable.

Efficacy and Treatment Duration by Patient



Responses occurred in both LGG and HGG and included:

- Pilocytic astrocytoma (n=1)
- Patients with only nonenhancing lesions (n=2*)

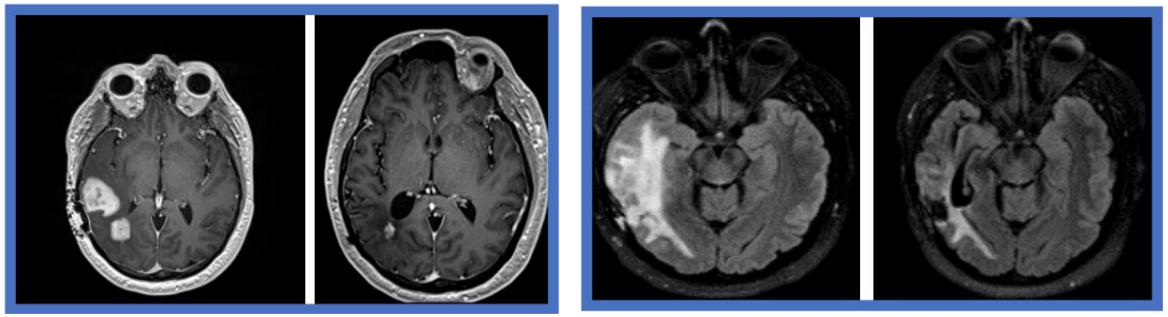
Provides evidence of clinically relevant CNS penetration

Clinical Vignettes in V600+ MAPKi treatment-naïve HGG and LGG

47-year-old male with recurrent WHO grade 4 V600E+ glioblastoma

- S/p resection & RT with concurrent TMZ, 5 adjuvant cycles (presented with disease progression)
- Treated with plixorafenib 900 mg QD + cobicistat (4-week cycles)
- PR by RANO at 3.7 months
- Continues treatment 13.8+ months

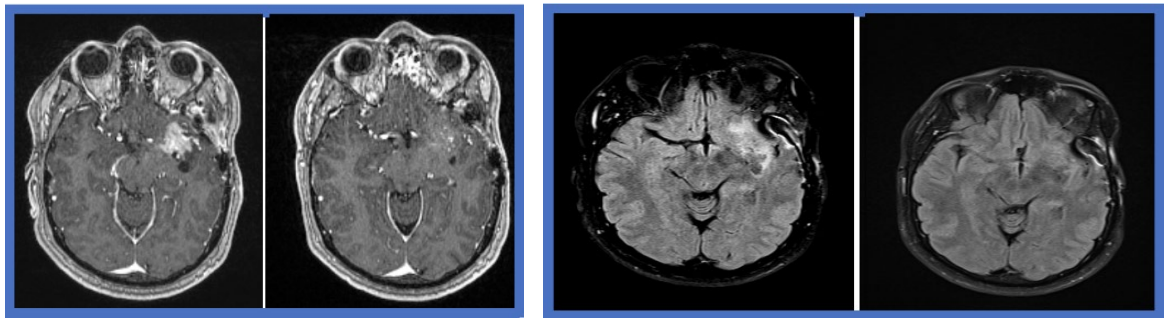
Screening **Cycle 11** **Screening** **Cycle 11**



37-year-old male with recurrent V600E+ xanthoastrocytoma

- Dx'd 14 years ago, s/p 2 resections, RT with concurrent TMZ, followed by TMZ cycles. POD with a 3rd resection
- Treated with plixorafenib 900 mg QD + cobicistat
- PR after 1.8 months
- Continues treatment 19+ months

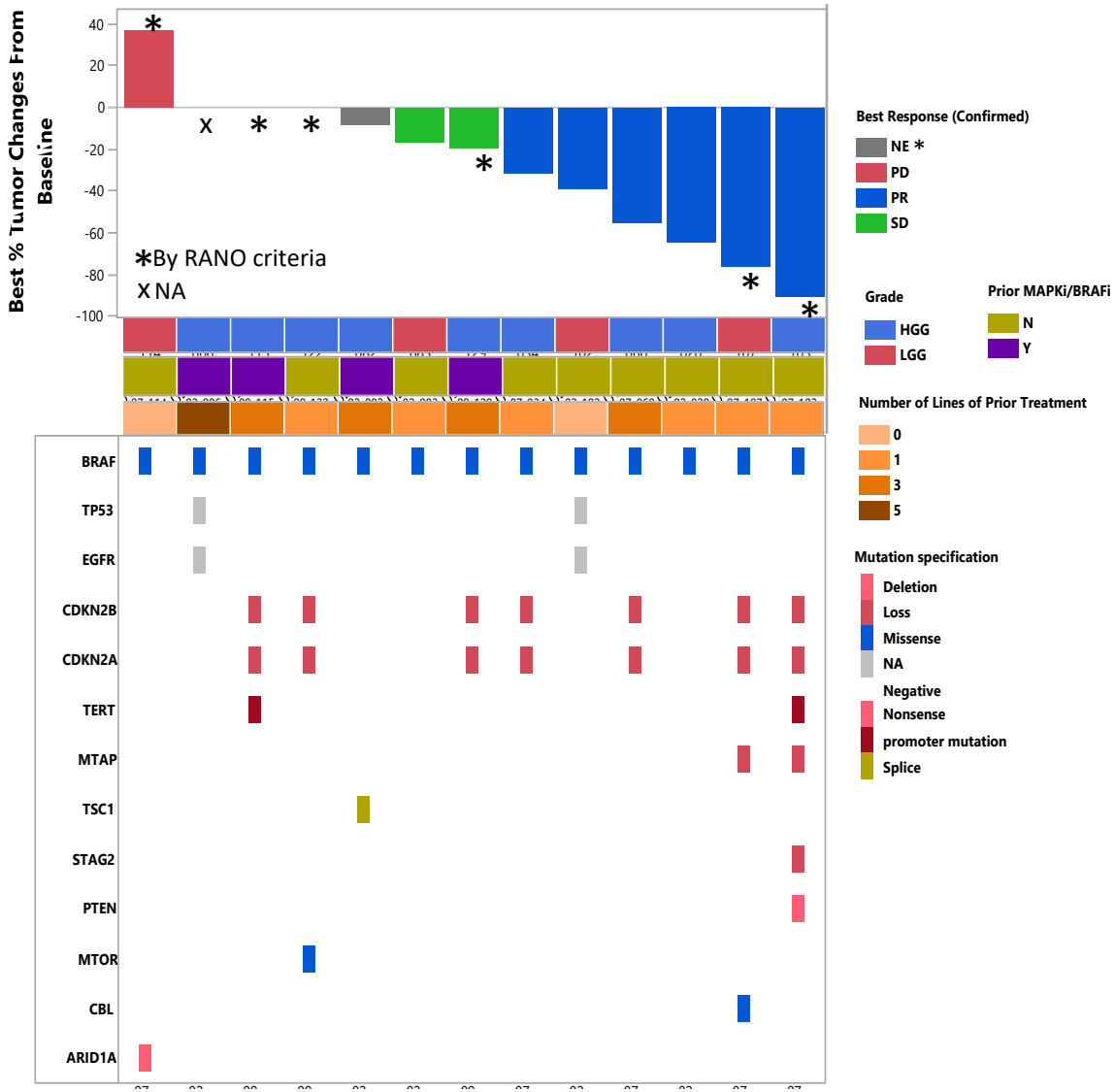
Screening **Cycle 16** **Screening** **Cycle 16**



Dx'd, diagnosed; POD, progression of disease; RT, radiotherapy; S/P, status post; TMZ, temozolomide.

Baseline Genomics in Evaluable Adults With BRAF V600E-mutated PCNST (N=13)

- 9/13 are within the MAPKi-naïve subgroup
  - The one PD had concomitant driver mutation
- 4/13 are in the MAPKi-pretreated subgroup and were heavily pretreated
  - 3–5 lines of prior systemic therapy
  - 3 received prior RT and surgery
  - 1 received 3 prior MAPKi treatments with documented PD following MAPKi treatment
- 7 (54%) had CDKN2A/B deletion; 4 of the 6 responses occurred with CDKN2A/B deletion
- Responses were observed in 1/1 patient with PTEN deletion and 2/2 patients with MTAP deletion
- No trend for increased molecular heterogeneity was observed between the MAPKi-naïve– and MAPKi-pretreated subgroups



*NE: the only postbaseline response assessment was SD and <42 days from baseline.

ARID1A, AT-rich interacting domain-containing protein 1A gene; CBL, casitas B lineage lymphoma; CDKN2A/2B, cyclin-dependent kinase inhibitor 2A/2B; MTAP, S-methyl-5'-thioadenosine phosphorylase; MTOR, mammalian/mechanistic target of rapamycin; PTEN, phosphatase and tensin homolog; STAG2, stromal antigen 2; TD, treatment duration; TERT, telomerase; TSC1, tuberous sclerosis 1.

Conclusions

- Plixorafenib has a tolerable safety profile with a low frequency of ≥grade 2 symptomatic AEs and minimal toxicities relative to approved BRAF inhibitors
- The safety profile in patients with PCNST was consistent with that observed in the overall population
  - Headache was the only symptomatic grade 3 or higher TEAE occurring in >5% of patients
- Promising single-agent activity against BRAF V600 altered tumors (30% ORR; 42% in MAPKi naïve), including PCNST (67% ORR in MAPKi naïve)
- The phase 2 Forte study is ongoing to confirm these findings in adults and children aged ≥10 years with PCNSTs harboring BRAF V600E mutations (NCT05503797)

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