Poster # 225

FORTE: A Phase 2 Master Protocol Assessing Plixorafenib for BRAF-Altered Cancers

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BACKGROUND

- v-raf murine sarcoma viral oncogene homolog B1 (BRAF) alterations occur in about 6% of all cancers, with class I, II, and III alterations observed at a frequency of approximately 62%, 17%, and 18%, respectively.[1,2]
- BRAF alterations have been observed in approximately 6% of pediatric cancers, with about 74% of brain tumors harboring known-activating BRAF alterations.[3]
- Primary CNS cancers represent the most common cause of cancer death in children aged 0–14 years, with a 5-year survival rate of about 69%.[4]
- BRAF inhibitors (BRAFi) combined with MEK inhibitors (MEKi) demonstrate durable responses in BRAF V600-mutated tumors but have high rates of pyrexia and cardiovascular, hepatic, gastrointestinal, and ocular toxicities.[1,5]
- Overall, BRAFi/MEKi have a similar efficacy and safety profile in adults and children and have been approved down to 1 year of age.[6,7]
- The type II/pan-RAF inhibitor, tovorafenib, shows benefit in relapsed or refractory pediatric low-grade glioma with BRAF fusions or V600 mutations but confers the risk of hemorrhage, skin toxicities, reductions in growth velocity, and viral and upper respiratory infections.[8–10]

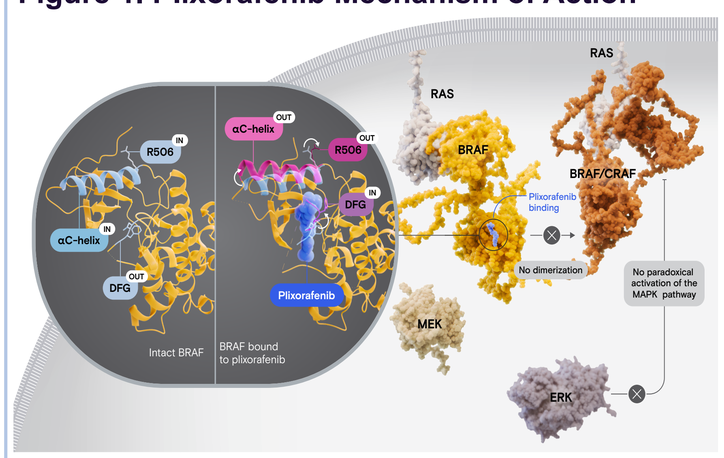
Plixorafenib (FORE8394; PLX8394)

- A novel, oral, small-molecule BRAF inhibitor that selectively inhibits mutated BRAF V600 monomers and BRAF-containing dimers, including fusions (**Figure 1**)[11–13]
- Disrupts RAF dimerization and prevents paradoxical MAPK pathway activation, avoiding the need for combination with a MEK inhibitor[11,14,15]

Phase 1/2a Study Results

- Demonstrated promising safety and clinical activity in a phase 1/2a study in patients ≥10 years of age with advanced solid tumors with BRAF V600 mutations and BRAF fusions[16,17]
  - Safety profile is distinct from available BRAFis/RAFis (**Table 1**) with no observed secondary malignancies, hyperkeratosis, uveitis, retinal detachment, left ventricular ejection fraction reduction, hemorrhage, hair, skin, or nail changes, or growth deficiencies.[8–10,16–18]
  - Antitumor activity was observed across various tumors and BRAF alterations.[16–18]
    - In BRAF V600E-mutated tumors (N=39), overall response rate (ORR) was 33.3% (43.5% in a MAPK inhibitor [MAPKi]-naïve subgroup); median duration of response (mDOR) of 17.8 months; 76.9% with DOR ≥6 months.
    - Of the 9 participants with BRAF V600 MAPKi-naïve CNS tumors, 6 (66.7%) had PR; mDOR of 12 months; 66.7% with DOR ≥6 months (**Figure 2**).
    - Of 14 adults with BRAF fusions, 2 had response (1 complete response [CR], DOR: 69.9+ months; continued treatment under a single-participant investigational new drug [sIND], with total duration of treatment of 75.7 months; 1 partial response [PR], DOR: 12.9+ months) and 7 had stable disease (SD).[18]

Figure 1. Plixorafenib Mechanism of Action



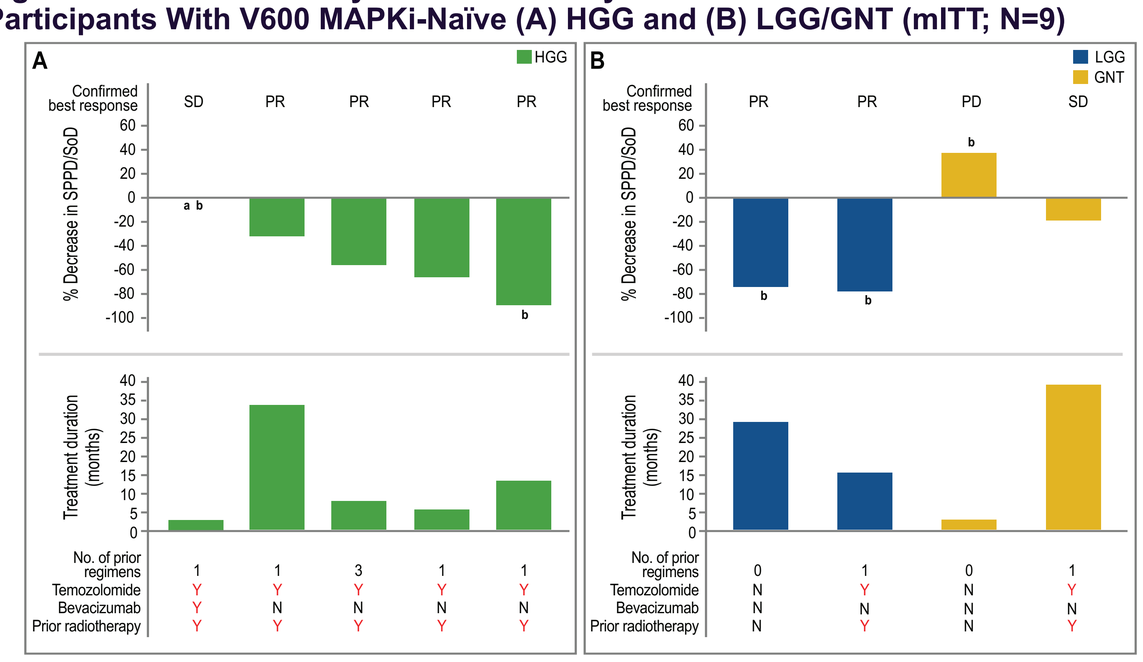
BRAF, v-raf murine sarcoma viral oncogene homolog B1; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase.

Table 1. Phase 1/2a Safety Profile[a]

	Preferred term	Overall (N=113) G1, n (%)	G2, n (%)	G3, n (%)	G4, n (%)	Any grade, n (%)
Lab abnormality AEs	Increased ALT	24 (21.2)	14 (12.4)	9 (8.0)	1 (0.9)	48 (42.5)
	Increased AST	26 (23.0)	13 (11.5)	3 (2.7)	0	42 (37.2)
	Increased blood bilirubin	4 (3.5)	8 (7.1)	8 (7.1)	0	20 (17.7)
	Hyponatremia	1 (0.9)	0	6 (5.3)	1 (0.9)	8 (7.1)
Symptomatic AEs	Fatigue	17 (15.0)	23 (20.4)	1 (0.9)	0	41 (36.3)
	Nausea	27 (23.9)	6 (5.3)	2 (1.8)	0	35 (31.0)
	Diarrhea	15 (13.3)	7 (6.2)	4 (3.5)	0	26 (23.0)
	Vomiting	11 (9.7)	11 (9.7)	1 (0.9)	0	23 (20.4)

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; G, grade; TEAE, treatment-emergent AE.
[a]Shown are the most common TEAEs in the overall population (≥20% any grade and/or ≥5% grade ≥3 TEAEs).

Figure 2. Phase 1/2a Study Results: Efficacy and Treatment Duration for Participants With V600 MAPKi-Naïve (A) HGG and (B) LGG/GNT (mITT; N=9)



GNT, glioneuronal tumor; HGG, high-grade glioma; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase pathway inhibitor; mITT, modified intent to treat; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-oncology; SD, stable disease; SoD; sum of diameters; SPPD; sum product of perpendicular diameter.
[a]Unchanged from baseline.
[b]Maximal decrease in SPPD and confirmed best response are based on RANO criteria.

Phase 1/2a Pediatric Demographics, Clinical Characteristics, and Treatment History

Age range, year	Sex, n (%) Female	Male	Tumor types	BRAF alteration	Prior lines of treatment, median (range)	Plixorafenib BID dosing Range, mg/m²	Flat, mg
4–17	2 (40)	3 (60)	• LGG (n=3)[a,b] • Neuroblastoma (n=1) • LCH-ND (n=1)	• V600E, AMP, Fusion (all n=1) • Class II • V600E	5 (4–8)[c]	250–500	600

AMP, amplification; BID, twice daily; LCH-ND, Langerhans cell histiocytosis-neurodegenerative; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase pathway inhibitor.
[a]Two participants with pilocytic astrocytoma and 1 with pilomyxoid astrocytoma.
[b]One participant (LGG; pilocytic astrocytoma) had an amplification and was excluded from the efficacy-evaluable population.
[c]One participant with LGG (AMP) and 1 participant with LCH-ND had 1 and 2 prior MAPKi therapies, respectively.

Safety (n=5) and Efficacy (n=4) in Pediatric Participants

- No dose-limiting toxicities occurred in pediatric participants.
- Among the 4 participants receiving body surface area (BSA)-adjusted dosing, 2 experienced 1 or more treatment-emergent adverse events (TEAEs) leading to plixorafenib dose interruption (all grade 3: gastroenteritis-norovirus and headache in 1 participant, neutropenia in 1 participant); there were no grade 4 or 5 TEAEs.
- Although phase 1/BSA-adjusted dosing provided exposures lower than the optimal dose, 3/3 participants had SD (n=1 each: BRAF V600 Langerhans cell histiocytosis-neurodegenerative [LCH-ND], BRAF V600 low-grade glioma [LGG], BRAF fusion LGG).
  - The 1 participant with LCH-ND transitioned to compassionate use and has been on treatment for 6.5+ years with significant functional improvement.[19]
- 1 participant treated in phase 2a with plixorafenib 600 mg BID (2 dose levels below the optimal dose) had PD (neuroblastoma class II nonfusion BRAF alteration).

Clinical Pharmacokinetics[20]

- Dose-adjusted AUC and C_{max} were comparable between adult and pediatric participants.
- Exposure was not dependent on age (4–86 years) or weight (18–132 kg).
- The model-informed optimal dose was determined based upon efficacy, safety, PK, and PD.
- The optimal dose for patients ≥10 years of age was determined to be 900 mg daily with a PK booster, or 1800 mg daily without, in the fasted state.

FORTE BASKET STUDY METHODS

A phase 2, open-label, single-arm, multicenter study to assess the safety and efficacy of plixorafenib in adult and pediatric participants (≥8 years of age) with cancer-harboring BRAF alterations (**Figure 3**)

Figure 3. FORTE Basket Study[a]

Key Eligibility Criteria
- ≥8 years of age
- BRAF alteration
- Exhausted, cannot tolerate, or is inappropriate for available standard therapy
- Measurable disease
- Karnofsky (≥16 years) or Lansky (<16 years) PS ≥60
- No co-occurring oncogenic MAPK pathway alterations, including NF-1 alteration and/or RAS-related mutations
- No evidence of MAPKi resistance

Open-label, single-arm design

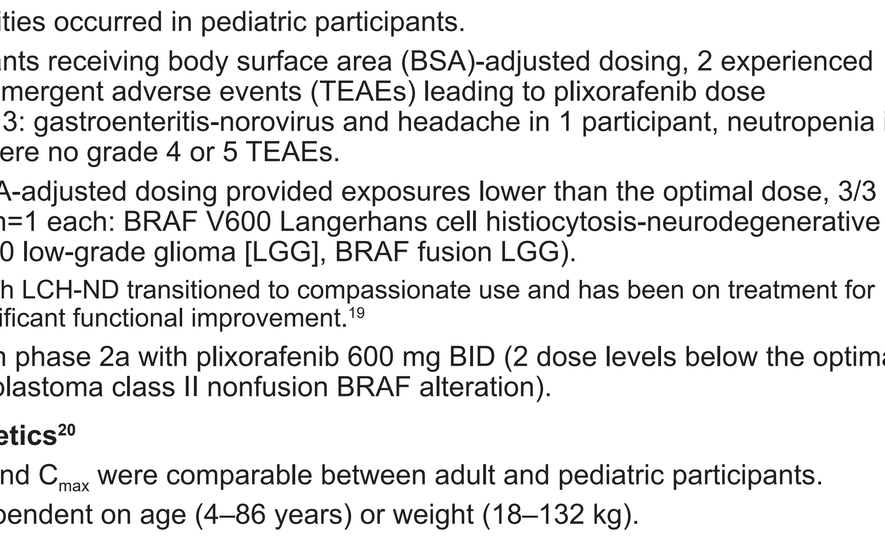
- Advanced solid tumors, including recurrent/progressive primary CNS tumors with BRAF fusions (N~100) Planned interim analyses: N~25; N~50
- Recurrent primary CNS tumors with BRAF V600E mutations (N~50) Planned interim analysis: N=25 (completed)
- Unresectable, locally advanced or metastatic, rare[b] solid tumors with BRAF V600E mutations (N~75) Planned interim analyses: N=25; N=50
- Unresectable, locally advanced or metastatic, select solid tumors with BRAF V600E mutations (N~15–30)[c] No planned interim analyses

Key Endpoints: ORR,[d] DOR, DCR, PFS, OS, PK, safety, longitudinal ctDNA assessments[e]

Key Endpoints: PK, safety, ORR,[f] DCR, DOR, PFS, OS, longitudinal ctDNA assessments[e]

ATC, anaplastic thyroid cancer; BICR, blinded independent central review; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CNS, central nervous system; CSF, cerebrospinal fluid; ctDNA, circulating tumor DNA; DCR, disease control rate; DOR, duration of response; HGG, high-grade glioma; LGG, low-grade glioma; MAPK, mitogen-activated protein kinase; MAPKi, MAPK inhibitor; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PS, performance score; RANO, Response Assessment in Neuro-oncology; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]All participants in the subprotocols receive plixorafenib 900 mg once daily (within 30 minutes following a meal) until progressive disease, unacceptable toxicity, or treatment discontinuation.
[b]Includes ATC with 1 prior MAPKi, and rare BRAF V600-mutated tumors occurring in ≤40,000 US patients annually.
[c]MAPKi-naïve thyroid cancer, and solid tumors with ≤1 prior MAPKi not otherwise eligible for other cohorts (eg, advanced cutaneous melanoma, primary CNS tumors, NSCLC, ovarian cancer, and others).
[d]Response assessed by BICR using either RECIST v1.1 for solid tumors or RANO HGG or LGG for primary CNS tumors. ORR for primary CNS tumors using RANO 2.0 is an exploratory endpoint. Tumors assessed at baseline, every 6 weeks for 48 weeks, then every 9 weeks for 48 weeks, then every 12 weeks.
[e]Plasma ctDNA assessments for all participants; plasma and CSF assessments for participants with primary CNS tumors.
[f]Response assessed by BICR using either RECIST v1.1 for solid tumors or RANO HGG or LGG for primary CNS tumors. ORR for primary CNS tumors using RANO 2.0 is an exploratory endpoint. Tumors assessed at baseline, every 9 weeks for 48 weeks, then every 12 weeks.

As of May 2026, this trial (**NCT05503797**) is recruiting participants in **12** countries globally, with **64** sites currently activated. To date, over **100** participants are enrolled across CNS tumor types, including 5 participants <18 years of age with low-grade glioma.



On March 27, 2026, Breakthrough Therapy Designation was granted by the US FDA to plixorafenib for the treatment of adults with recurrent or progressive BRAF V600E-mutated high-grade glioma.

References
1. Gouda MA, Subbiah V. *ESMO Open* 2023;8:100788; **2.** Owsley J et al. *Exp Biol Med* 2021;246:31–9; **3.** Rankin A et al. *Oncologist* 2021;26:e153-e163; **4.** Ostrom QT et al. *Neuro Oncol* 2023;25(S4):iv1–iv99; **5.** Heinzerling L et al. *ESMO Open* 2019;4:e000491; **6.** Subbiah V et al. *Nat Med* 2023;29:1103–12; **7.** Tafinlar. Prescribing information. Novartis Pharmaceuticals Corporation; 2026. https://www.novartis.com/us-en/sites/novartis_us/files/tafinlar.pdf; **8.** Kilburn LB et al. *Nat Med* 2023;30:207–17; **9.** Rasco DW et al. *Cancer Chemother Pharmacol* 2023;92:15–28; **10.** Ojemba. Package insert. Day One Biopharmaceuticals; 2025; **11.** Yao Z et al. *Nat Med* 2019;25:284–91; **12.** Janku F et al. *J Clin Oncol* 2018;36:2583; **13.** de la Fuente MI et al. Oral presentation presented at SNO 2023; **14.** Tutuka CSA et al. *Mol Cancer* 2017;16:112; **15.** Zhang C et al. *Nature* 2015;526:583–6; **16.** de la Fuente MI et al. Poster presented at ISPNO 2024; **17.** de la Fuente MI et al. Oral presentation presented at ASCO 2023; **18.** Rodón J et al. Poster presented at OCRS 2024; **19.** Yi JS et al. *JCO Precis Oncol* 2025;9:e2500225; **20.** Sherman EJ et al. Poster presented at ASCO 2023.

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