Presentation # CT273

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 6% of all cancers, with class I, II, and III alterations observed at a frequency of 62.1%, 16.5%, and 17.7%, respectively.[1,2]
- Second-generation BRAF inhibitors that target BRAF V600 mutant tumors, such as dabrafenib, vemurafenib, and encorafenib, when used as monotherapy can promote RAF dimerization and paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway, potentially causing rapid disease recurrence and development of secondary malignancies.[1,3,4]
- Second-generation BRAF inhibitors combined with MAPK kinase (MEK) inhibitors to decrease paradoxical MAPK pathway activation demonstrate durable responses in BRAF V600-mutated tumors, but have high rates of pyrexia and cardiovascular, hepatic, gastrointestinal, and ocular toxicities.[1,5]
- 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 major hemorrhage, skin toxicities, reductions in growth velocity, and viral and upper respiratory infections.[6–8]
- With the exception of pediatric low-grade glioma, there are no approved therapies for non-V600 BRAF-altered tumors.
- There remains an unmet need for tolerable and efficacious targeted therapies for the treatment of BRAF-altered tumors.

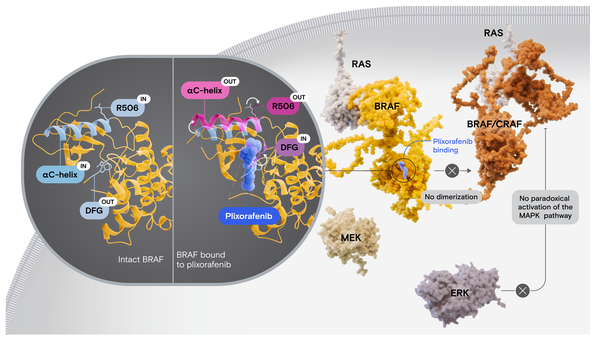
Plixorafenib (FORE8394; PLX8394)

- A novel, oral, small-molecule BRAF inhibitor that selectively inhibits BRAF V600 monomers and BRAF-containing dimers, including fusions (**Figure 1**)[9–11]
- Disrupts RAF dimerization and prevents paradoxical MAPK pathway activation, avoiding the need for combination with a MEK inhibitor[9,12,13]
- Demonstrated in vitro activity against V600 and non-V600 BRAF proteins, and antitumor activity has been observed in BRAF V600 and non-V600 nonclinical models.[9]

Phase 1/2a Study Results

- Demonstrated promising safety and clinical activity in a phase 1/2a study across a range of doses in advanced solid tumors with BRAF V600 mutations and BRAF fusions[14,15]
  - Treatment-emergent adverse events (TEAEs) occurring in ≥20% of participants included primarily low-grade liver function test changes and low-grade fatigue, nausea, diarrhea, and vomiting (**Table 1**).[14–16]
  - Antitumor activity was observed across various tumor types, including those with BRAF V600 and non-V600 alterations.[14–16]
    - In BRAF V600-mutated tumors: overall response rate (ORR) 30.2% (41.7% in a MAPK inhibitor [MAPKi]-naïve subgroup; median duration of response [mDOR] 17.8 months) (range, 3.7, 59.2; **Figure 2**)[14,16]
    - Of 14 adults with BRAF fusions, 2 had response (1 complete response [CR], DOR: 66.7+ months; 1 partial response [PR], DOR: 9.2+ months) and 7 had stable disease.[16]

Figure 1. Plixorafenib Mechanism of Action



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

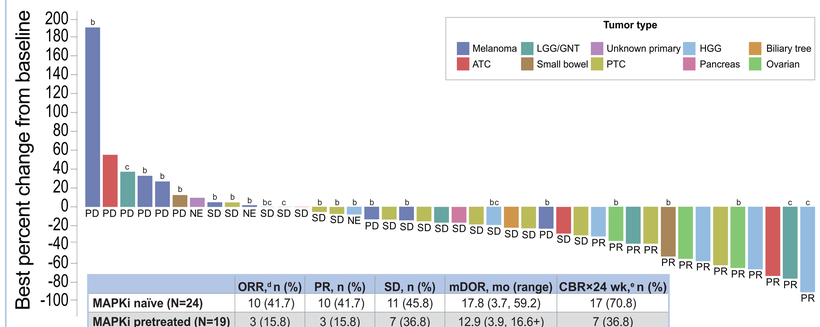
Table 1. Phase 1/2a Safety Profile[a]

		Overall (N=113)					RP2D (N=9)				
	Preferred term	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)	14 (12.4)	9 (8.0)	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)	8 (7.1)	8 (7.1)	0	20 (17.7)	0	1 (11.1)	0	0	1 (11.1)
	Hyponatremia	1 (0.9)	0	6 (5.3)	1 (0.9)	8 (7.1)	0	0	0	1 (11.1)	1 (11.1)
Symptomatic AEs	Fatigue	17 (15.0)	23 (20.4)	1 (0.9)	0	41 (36.3)	1 (11.1)	1 (11.1)	0	0	2 (22.2)
	Nausea	27 (23.9)	6 (5.3)	2 (1.8)	0	35 (31.0)	4 (44.4)	0	0	0	4 (44.4)
	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

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; G, grade; RP2D, recommended phase 2 dose; 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: Plixorafenib Best Percent Tumor Change From Baseline in BRAF V600 Adults (N=43, mITT)[a]

Excluding CRC due to known EGFR feedback loop activation with monotherapy



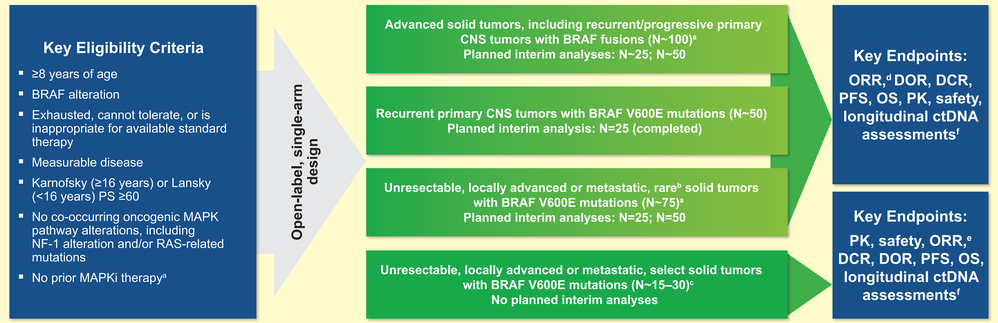
	ORR,[d] n (%)	PR, n (%)	SD, n (%)	mDOR, mo (range)	CBR×24 wk,[e] n (%)
MAPKi naïve (N=24)	10 (41.7)	10 (41.7)	11 (45.8)	17.8 (3.7, 59.2)	17 (70.8)
MAPKi pretreated (N=19)	3 (15.8)	3 (15.8)	7 (36.8)	12.9 (3.9, 16.6+)	7 (36.8)

ATC, anaplastic thyroid cancer; CBR, clinical benefit rate; CR, complete response; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; GNT, glioneuronal tumor; HGG, high-grade glioma; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase inhibitor; mDOR, median duration of response; mITT, modified intent to treat; MR, minor response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PTC, papillary thyroid cancer; RANO, Response Assessment in Neuro-oncology; SD, stable disease.
[a]One participant was excluded due to the unavailability of postbaseline assessment target lesion measurement and best response was not evaluable.
[b]Indicates prior MAPKi treatment.
[c]Reported per RANO criteria.
[d]All responses were confirmed.
[e]CBR: CR+PR+MR+(SD≥24 weeks).

PHASE 2 MASTER PROTOCOL STUDY METHODS

- 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 (**Figure 3**).

Figure 3. FORTE Basket Study



ATC, anaplastic thyroid cancer; BICR, blinded independent central review; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CSF, cerebrospinal fluid; CNS, central nervous system; 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]Plixorafenib dose to be increased to 1200 mg daily as tolerated. Participants with pediatric LGG who received prior MAPKi are eligible provided no evidence of tumor progression on treatment or within 4 weeks of discontinuation, based upon radiographic assessment. Participants with low-grade serous or serous borderline recurrent ovarian, peritoneal, or fallopian tube cancer who received one prior MAPK-targeted therapy, unless immediately preceding this study and/or with rapid progression, are also eligible.
[b]Includes ATC with 1 prior MAPKi, and rare BRAF V600-mutated tumors occurring in ≤40,000 US patients annually (**Table 2**).
[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]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.
[f]Plasma ctDNA assessments for all participants; plasma and CSF assessments for participants with primary CNS tumors.

Table 2. Examples of Rare BRAF V600E-Mutated Solid Tumors Eligible for Subprotocol C[a]

Anaplastic thyroid cancer[b]	Liver and bile duct cancers
Bladder cancer	Pancreatic acinar cell cancer
Ovarian cancer	Pancreatic neuroendocrine cancer
Gastric cancer	Small intestine cancer
Anal cancer	

[a]Not a comprehensive list; additional tumor types may be eligible.
[b]Should have received 1 prior BRAF-targeted therapy.

As of January, this trial (**NCT05503797**) is recruiting participants in **11** countries globally, with **64** sites currently activated. To date, over **100** participants are enrolled.

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.

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