TPS2091 **Poster Session**

FORTE: A phase 2 master protocol assessing plixorafenib for BRAF-altered cancers.

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Background: Plixorafenib (FORE8394; PLX8394) is a novel, oral, small-molecule BRAF inhibitor highly selective for BRAF V600 monomers and BRAF-containing dimers. Plixorafenib binding disrupts RAF dimerization, targeting both BRAF V600 mutations and fusions, thereby preventing paradoxical activation and avoiding the need for combination with a MEK inhibitor. In a phase 1/2a study, plixorafenib demonstrated promising safety and clinical activity across a range of doses tested in tumors with BRAF V600 mutations or fusions. The most common adverse events (AEs) included predominantly low-grade liver function test changes and grade 1 fatigue, nausea, diarrhea, and vomiting. **Methods:** The FORTE Phase 2 basket study is currently enrolling patients ≥10 years of age into 4 sub-protocols. Study details are shown in theTable. Eligible patients have received prior therapy for advanced disease, have measurable disease, and have a Karnofsky (≥16 years) or Lansky (<16 years) Performance Score of ≥60 at study entry. All patients receive plixorafenib continuous dosing, in some cohorts coadministered with cobicistat, a pharmacokinetic (PK) booster. Prior MAPK inhibitor therapy is excluded unless otherwise specified below. As of January 2025, the trial is recruiting participants in 9 countries globally, with 54 sites activated. Clinical trial information: NCT05503797. Research Sponsor: Fore Biotherapeutics.

	Sub-Protocol A	Sub-Protocol B	Sub-Protocol C	Sub-Protocol D
Patient Population	Advanced solid and primary CNS tumors harboring BRAF fusions	BRAF V600-mutated recurrent primary CNS tumors	Rare[1] BRAF V600-mutated advanced solid tumors	BRAF V600-mutated melanoma[2] or thyroid cancer without anaplastic or undifferentiated components
Planned Enrollment	~100	~50	~75	~12
Design	Single-arm, open-label, Bayesian optimal phase 2 design			1:1 randomized, open-label crossover design to compare plixorafenib administered alone and with PK booster
Planned Efficacy Interim Analyses	N=25 N=50	N=25	N=25 N=50	None
Primary Endpoint	ORR[3]			Intra-patient PK
Key Secondary Endpoints	DOR, DCR, PFS, OS, PK, Safety			Safety, ORR, DOR, DCR, PFS, OS, Safety
Key Exploratory Endpoint	Longitudinal ctDNA assessments[4]			

[1]BRAF V600-mutated tumors occurring in ≤40,000 US patients annually (eg, ovarian/gynecologic cancers, cholangiocarcinoma, small intestinal/gastrointestinal cancers other than colorectal adenocarcinoma, neuroendocrine cancers).
[2]Patients with melanoma should have received and not tolerated a prior BRAF inhibitor.
[3]Response assessed by BICR using 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 cycle 1 day 1, every 9 weeks for 48 weeks, then every 12 weeks.
[4]Plasma for all patients; plasma and CSF for patients with primary CNS tumors.