PLIXORAFENIB (FORE8394; PLX8394) IN CHILDREN AND ADULTS WITH RECURRENT, BRAF-ALTERED PRIMARY CENTRAL NERVOUS SYSTEM TUMORS (PCNST)

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BACKGROUND: Plixorafenib is a selective, potent BRAFi that inhibits V600 and non-V600 alterations by disrupting BRAF monomers/dimers. Plixorafenib evades paradoxical MAPK pathway activation, eliminating the need for MEKi combination, and is potentially less prone to toxicities and resistance typical of approved BRAFis. METHODS: Phase 1/2a study (NCT02428712) in children (n=5, aged 4-17 years) and adults (n=108) with BRAF-altered solid tumors assessing safety, PK, and efficacy of oral plixorafenib 900-3600mg/day ± cobicistat (PK enhancer). RESULTS: Five children, 3 LGG (1 V600E, 1 fusion, 1 amplification), 1 neuroblastoma (G469A) and 1 ND-LCH (V600E), 4-8 prior therapies, received plixorafenib 300-1200 mg/day without cobicistat. Four received BSA-adjusted dosing, which delivered lower exposures than RP2D. All had SD, with duration 66.9± months for ND-LCH. The fifth (neuroblastoma, 1200 mg/day) had PD. No DLTs, dose reductions, or LFT elevations. One had possibly related Grade 3 headache. Of 9 evaluable MAPKi-naive adults with V600E PCNST, 4/5 with HGG and 2/4 with LGG/GNT responded; ORR 67% (95% CI: 29.9-92.5), mDOR 13.9 months. Responses in patients with only non-enhancing lesions and/or pilocytic astrocytoma indicate clinically relevant CNS penetration. Responses occurred across V600 solid tumors, ORR 42% (10/24); 1-year PFS 34.4%, 2-year PFS 48.4% in the MAPKi-naive (non-CRC) subgroup. Of 14 evaluable adults with fusions, 2 responses (melanoma: CR, DOR 42.6± months; PTC: PR, DOR 4.0± months), 8 SD (5 with PCNST), 5 PD (3/5 with co-occurring driver mutations). Safety, efficacy, and PK in adults and children and insight into factors affecting plixorafenib exposure (not age or weight dependent) determined the optimal RP2D of plixorafenib as 900 mg QD with cobicistat for ages ≥10 years. CONCLUSIONS: Plixorafenib had low rates of symptomatic TEAEs with a manageable safety profile, and high ORR in MAPKi-naive BRAFV600 PCNST. A phase 2 study in children and adults is ongoing (NCT05503797).