TPS11579 Poster Session

SARC044: A phase II trial of bezuclastinib in combination with sunitinib in patients with GIST who progressed on sunitinib monotherapy.

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Background: Gastrointestinal stromal tumors (GIST) are commonly driven by mutations in the receptor tyrosine kinase *KIT*. Resistance to approved tyrosine kinase inhibitors (TKIs) arises from additional KIT mutations in the ATP-binding pocket (AP) and activation loop (AL). No single approved TKI broadly suppresses all resistant clones, and overlapping VEGFR inhibition and toxicity limits TKI combinations. The type I TKI bezuclastinib ("BEZ," CGT9486) inhibits KIT AL resistance mutations, does not inhibit VEGFR, and has complimentary activity with sunitinib ("SUN," inhibitor of KIT AP resistance mutations). The first-in-human study (PLX121-01) and ongoing Peak trial (NCT05208047) evaluated BEZ+SUN showing promising safety and efficacy in GIST. SARC044 investigates BEZ+SUN in patients (pts) with SUN-resistant, KIT-mutant GIST, and correlatives aim to determine mechanisms of response and resistance (NCT06208748). **Methods:** SARC044 is a multi-center, open label, single-arm phase II trial enrolling up to 40 adult pts with KIT exon 9 or 11-mutant GIST resistant to imatinib and SUN. After TKI washout (baseline, "b/l"), pts initiate BEZ 600 mg daily for 2 weeks, then add SUN 37.5 mg daily, taking both drugs continuously (28-day cycles) until mRECISTv1.1 progression or unmanageable toxicity. Response evaluations (RE) are performed every 8 weeks (wk) through 15 months (mo) on study, then every 12 wk. Circulating tumor DNA (ctDNA) is collected at b/l, cycle 1 day 15 (C1D15), C2D1, C3D1, and progression. Targeted exome sequencing (TES) of ctDNA will track primary/resistant KIT mutation dynamics across therapy. ^{18}FDG PET/CTs are performed in 20 pts at b/l, C1D15, and C2D1, which guide a biopsy of a resistant tumor. TES, allele-specific and long-read PCR (to detect AP+AL mutation phasing), and immunoblotting (evaluating KIT pathway activation) will be performed on tissue. EORTC QLQ-C30 surveys collect pt-reported outcomes (PRO) at b/l, on treatment, and at progression. The primary endpoint is median progression-free survival (mPFS) and secondary endpoints include overall survival at 1 and 2 years, clinical benefit rate at 16 wk, adverse event rate, PRO, and KIT mutation profile in ctDNA and tissue. 35 evaluable pts achieves 83% power ($p<0.05$, one-sided) in a one-sample log-rank test to detect a mPFS of 6.5 mo vs 4 mo (historic control). Expected accrual is 12 mo across 4 sites in the United States with ~36 mo to study completion. Clinical trial information: NCT06208748. Research Sponsor: Cogent Biosciences; Life Raft Group; Brown Family Fund; Conquer Cancer©, the ASCO Foundation.