TPS11578 Poster Session

Phase 1a/1b study of the safety, pharmacokinetics, and antitumor activity of ziftomenib in combination with imatinib in patients with advanced gastrointestinal stromal tumors (GIST) after imatinib failure.

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Background: GIST is the most common mesenchymal neoplasm of the digestive tract and is mainly driven by gain-of-function oncogenic mutations in the receptor tyrosine kinase KIT. Patients with GIST are typically treated with anti-KIT tyrosine kinase inhibitors (TKIs) such as imatinib. However, few patients achieve a complete response, and most eventually progress due to secondary alterations in *KIT* that cause resistance to therapy. Additional TKIs are approved in later lines but have shown only moderate clinical outcomes, highlighting the need for additional therapeutic approaches. Preclinical studies have shown that the menin-KMT2A complex epigenetically upregulates *KIT* expression in GIST cells. Ziftomenib is a potent and highly selective menin inhibitor that disrupts formation of the menin-KMT2A complex. Ziftomenib plus imatinib has demonstrated synergistic antitumor activity in imatinib-sensitive and -resistant GIST models, with reduced KIT protein levels and downstream oncogenic signaling observed in imatinib-resistant GIST patient-derived xenografts treated with the combination. Together, ziftomenib plus imatinib may enhance KIT recycling while reducing *KIT* transcription. This combination is currently being investigated clinically in patients with imatinib-sensitive and -resistant advanced GIST. **Methods:** KOMET-015 (NCT06655246) is a phase 1a/1b, open-label study to determine the safety, tolerability, recommended phase 2 dose (RP2D), and preliminary antitumor activity of ziftomenib plus imatinib (400 mg) for advanced/metastatic GIST. KOMET-015 includes dose-escalation, RP2D determination, and dose-expansion parts. Eligible patients (≥18 yrs) must have a biopsy-proven diagnosis of advanced/metastatic *KIT*-mutant GIST (T670X excluded) that progressed on imatinib (dose-escalation and RP2D determination parts), with an ECOG PS of ≤2 and measurable disease per modified RECIST (mRECIST). Dose escalation will be based on an i3+3 design to evaluate the safety and tolerability of up to 4 dose levels of ziftomenib combined with imatinib. Based on escalation, up to 2 dose levels will be selected for comparison to determine the RP2D. The dose-expansion part will examine the toxicity and preliminary clinical activity of the RP2D in patients assigned to 1 of 3 cohorts: Cohort A: patients who progressed on imatinib as immediate prior therapy, Cohort B: patients who failed imatinib and had received ≥2 lines of therapy, and Cohort C: imatinib-naive patients. Tumor response will be assessed per mRECIST. All adverse events will be recorded, monitored, and graded based on CTCAE v5.0. The trial is open and actively recruiting with sites in the United States. Clinical trial information: NCT06655246. Enrollment opens Feb 2025. Research Sponsor: Kura Oncology, Inc.