TPS4216 **Poster Session**

Phase II trial of zanzalintinib (XL-092) in combination with durvalumab and tremelimumab in unresectable hepatocellular carcinoma (ZENOBIA).

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Background: Despite the evolving novel treatment options, the prognosis for advanced hepatocellular carcinoma (HCC) remains poor, with a 4-year survival rate of approximately 25%. Immune checkpoint inhibitors (ICIs), including the combination of durvalumab (Durva) & tremelimumab (Treme), represents the current standard-of-care for frontline HCC treatment. However, therapy resistance, either primary or secondary, often arises due to the immunosuppressive tumor microenvironment (TME). VEGFR is a well-established therapeutic target in HCC. Cabozantinib (Cabo), a multi-target tyrosine kinase inhibitor (TKI), is approved for later-line use per the CELESTIAL trial, and it also demonstrated significant TME modulation through antiangiogenic effects. A Phase II study (CHECKMATE 040) reported an impressive objective response rate (ORR) of 29% with the combination of ipilimumab/nivolumab and Cabo but noted high toxicity rates. Zanzalintinib (Zanza) is a novel TKI targeting VEGFR, MET, & TAM kinases (TYRO3, AXL, MER), key mediators of angiogenesis, tumor growth, metastasis, and TME immunosuppression. With a target profile similar to Cabo but an improved pharmacokinetic profile & a shorter half-life (16–22 hours), Zanza has demonstrated potential synergy with ICIs in preclinical and early-phase trials, suggesting enhanced sensitivity by fostering an immune-permissive TME. This phase II study evaluates the safety & efficacy of Zanza combined with Durva and Treme in HCC. **Methods:** This open-label, non-randomized Phase II trial consists of two parallel cohorts. Eligible patients must have unresectable HCC, be treatment-naïve in the unresectable setting, & have ECOG performance status of 0-1. Exclusion criteria include Child-Pugh score >7, known autoimmune diseases, heightened risk of gastrointestinal perforation or fistula formation, and known gastric or esophageal varices. The study begins with a safety lead-in phase of 9–12 patients to establish the recommended Phase II dose. The two cohorts aim to explore the optimal sequential strategy for combining Zanza with Durva & Treme. Cohort A: Zanza is administered during Cycle 1, followed by Durva + Treme in Cycle 2. Cohort B: Durva + Treme is administered during Cycle 1, followed by Zanza and Durva in Cycle 2. Both cohorts will continue with Zanza and Durva in subsequent cycles. A total of 40 participants (20 per cohort) will be enrolled. The primary endpoint is the ORR assessed by imRECIST 1.1. Secondary endpoints include the conversion rate to resectable or transplant-eligible disease, disease control rate, median PFS and OS, and landmark PFS & OS at 6, 12, 24, and 36 months. Safety and tolerability will also be evaluated. Comprehensive translational analyses include bulk RNA sequencing, spatial transcriptomics of baseline tumor biopsies, & serial ctDNA monitoring. Trial enrollment commenced in December 2024. Clinical trial information: NCT06698250. Research Sponsor: Exelixis.