TPS4214 Poster Session

PROSPERO: A phase 3 randomized, placebo (Pbo)-controlled study of amezalpat (TPST-1120), a peroxisome proliferator-activated receptor a (PPARα) inhibitor, in combination with atezolizumab + bevacizumab (AB) for patients (pts) with unresectable or metastatic hepatocellular carcinoma (mHCC) not previously treated with systemic therapy.

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Background: PPARα is a fatty acid ligand-activated transcription factor that regulates genes involved in fatty acid oxidation (FAO), angiogenesis, and inflammation. In HCC and other tumor types, PPARα signaling promotes tumor growth and also modulates the tumor immune microenvironment to suppress antitumor immunity. Amezalpat (TPST-1120) is an investigational PPARα antagonist that inhibits FAO, targeting the bioenergetic requirements of cancer cells and restoring anticancer immune pathways. HCC has the highest PPARα expression of any major tumor type. In preclinical studies of HCC, including ß-catenin activated disease, amezalpat exhibits anti-cancer activity as a single agent and demonstrates complementary efficacy in combination with PD-L1 and VEGF inhibitors. In an ongoing global randomized Phase 1b/2 study in pts with unresectable or mHCC not previously treated with systemic therapy, amezalpat in combination with atezolizumab + bevacizumab (TPST-AB) was tolerable and was associated with a clinically meaningful improvement in multiple efficacy endpoints, including overall survival (OS) and confirmed objective response rate (ORR), compared to AB alone. Here we describe a follow-up pivotal Phase 3 study to evaluate the safety and efficacy of TPST-AB vs Pbo plus AB (Pbo-AB) in pts with unresectable or mHCC (NCT06680258). **Methods:** This Phase 3, global, randomized, double-blind study will enroll ~740 pts with unresectable or mHCC. Key eligibility criteria include no prior systemic therapy (prior locoregional therapy allowed), ECOG PS 0-1, Child-Pugh Class A, and measurable disease by RECIST v1.1; pts with fibrolamellar/sarcomatoid HCC, mixed cholangiocarcinoma/HCC, and untreated active HBV are not eligible. Pts will be randomized 1:1 to receive oral amezalpat 600 mg or Pbo twice daily along with the approved doses of atezolizumab and bevacizumab every 3 weeks, until unacceptable toxicity or loss of clinical benefit. Randomization will be stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (y/n), baseline α-fetoprotein ($<$ 400 vs $\geq$400 ng/mL), and baseline ECOG PS (0 vs 1). The primary efficacy endpoint is OS. Key secondary efficacy endpoints include progression-free survival and ORR (RECIST v1.1). Exploratory analyses will include outcome by PD-L1 expression and ß-catenin mutational status. Interim analyses for futility (30% OS events) and efficacy (70% OS events) are planned. Findings of this pivotal study will inform the efficacy and safety profile of amezalpat added to AB vs AB alone in pts with unresectable or mHCC not previously treated with systemic therapy. Clinical trial information: NCT06680258. Research Sponsor: Tempest Therapeutics, Inc.