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Abstract #: 586 Poster Session

Multiomic profiling to identify pharmacodynamic and response biomarkers for casdozokitug with PD-L1/VEGF blockade in unresectable hepatocellular carcinoma from CHS-388-201 phase 2 study.

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Background:

Casdozokitug (CHS-388; formerly SRF388) is a novel Phase 2 clinical stage IL-27 antagonistic antibody, which inhibits immunomodulatory IL-27 signaling and restores T and NK cell effector functions, as characterized in mouse tumor models and patients with cancer. Casdozokitug treatment of solid tumor patients (NCT04374877) demonstrated acceptable safety profile and encouraging activity notably in tumors with high IL-27 expression including NSCLC and HCC[2]. A Phase 2 study (NCT05359861) of casdozokitug + atezolizumab + bevacizumab in 1L unresectable HCC (uHCC) showed an acceptable safety profile and promising antitumor activity (ORR 37.9%, CR 17.2%, mPFS 8.1 mo). Pharmacodynamic and response related biomarkers from this study were explored.

Methods:

Patients with uHCC (n=30) received casdozokitug 10 mg/kg, atezolizumab 1200 mg, and bevacizumab 15 mg/kg IV Q3W. Primary endpoints were safety and tolerability, with key secondary endpoints of ORR by RECIST1.1 and mRECIST, PFS, DoR and OS. Multiomic analyses were performed on baseline and on-treatment serum and PBMC samples to characterize biomarkers associated with casdozokitug pharmacodynamic effects and clinical outcome (response or non-response by RECIST1.1). Multiomic assessment included proteomic (MSD cytokine panels and Olink HT) and PBMC transcriptomic profiling (RNA-sequencing). Archival tumor tissue from a subset of study participants were evaluated for IL-27 expression by IHC.

Results:

Cross-platform analyses demonstrated significant immune activation. Early on-treatment

increase (> 4-fold) in serum IFNγ was associated with clinical response. On-treatment signatures associated with response included increased NK/T cell activation, IFNγ signaling and cell proliferation; along with decreased T cell diversity, monocyte signature and IL-27 co-expressed genes. Lack of response was associated with on-treatment enrichment in TGFβ signaling and angiogenesis signatures. Several circulating proteins (baseline and on-treatment) associated with response were identified. In baseline tumor tissue, higher IL-27-expression in macrophages was associated with responders (n=4) compared to non-responders (n=3).

Conclusions:
We identified pharmacodynamic and response related biomarkers following casdozokitug/atezolizumab/bevacizumab treatment in the CHS-388-201 study. Several response-associated biomarkers, particularly NK activation, showed concordance with findings from casdozokitug monotherapy and preclinical studies, supporting the contribution of effect for casdozokitug in tumor response. A randomized Phase 2 study (NCT06679985) is evaluating casdozokitug plus toripalimab/bevacizumab vs toripalimab/bevacizumab in 1L uHCC to assess treatment benefit and response biomarkers.

Track:
Pancreatic Cancer, Hepatobiliary Cancer, Neuroendocrine/Carcinoid, Small Bowel Cancer

Clinical Trial Registration Number:
NCT05359861

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Abstract Disclosures:
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