Title:

Updated efficacy and safety results from a phase 1b study of the PD-1 antagonist CS1003 combined with lenvatinib (LEN) as first-line (1L) treatment in Chinese patients (pts) with unresectable hepatocellular carcinoma (uHCC).

Submission Track & Subcategory:

Development Therapeutics - Immunotherapy & PD1/PD-L1 Inhibitor Combinations

Authors:

Lin Shen[1], Ye Guo[2], Yanqiao Zhang[3], Wei Li[4], Jifang Gong[1], Qun Li[2], Zhigang Ma[3], Nanya Wang[4], Rila Su[5], Zhongheng Cai[6], Rong Guo[6], Peiqi Li[5], Archie N.Tse[5]

1. Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China,
2. Oncology, Shanghai East Hospital, Tongji University, School of Medicine, Shanghai, China,
3. Gastroenterology, Harbin Medical University Cancer Hospital, Harbin, China,
4. Cancer center, The First Hospital of Jilin University, Changchun, China,
5. Translational Medicine and Early Development, CStone Pharmaceuticals (Su Zhou) Co., Ltd., Suzhou, China

6. Clinical Department, CStone Pharmaceuticals (Su Zhou) Co., Ltd., Suzhou, China

Background: CS1003 is a novel humanized, recombinant IgG4 anti-PD-1 monoclonal antibody. LEN, a multi-kinase inhibitor of VEGFR 1-3, FGFR 1-4, PDGFRα, RET, and KIT, is approved as 1L treatment in pts with uHCC in multiple countries. A multi-regional, double-blinded, randomized phase 3 trial (CS1003-305, NCT04194775) of CS1003/placebo in combination with LEN as 1L treatment in uHCC is underway. The preliminary efficacy and safety data from the open-label phase 1b study of CS1003 + LEN as 1L treatment in uHCC after a median 6.2 months of follow-up were previously reported at ESMO Congress 2020. Here we present the updated results with a median 18.0 months of follow-up.

Methods: Pts with uHCC, BCLC stage B or C, Child-Pugh class A, and ECOG PS ≤ 1 received 200 mg CS1003 intravenously once every 3 weeks and LEN orally (body weight ≥ 60 kg: 12 mg; < 60 kg: 8 mg) daily as 1L treatment. The primary endpoint was objective response rate (ORR) assessed by investigators per RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety. Data cutoff for this final analysis was August 13, 2021.

Results: At data cutoff, a total of 20 pts had received treatment. Compared with the last preliminary analysis, confirmed ORR was changed from 30.0% to 45.0% (95% CI: 23.06%, 68.47%) with 9 pts achieving partial response. DCR was 90.0% with 9 pts having stable disease as best overall response. DOR ranged from 4.2 to 18.7^{+} months, and median DOR in all

responders had not been reached. Median PFS was extended compared with the previous study readout from 8.4 months to 10.4 months (95% CI: 6.2, not estimable) with 6-month and 12-month PFS rates of 85.0% and 48.2%, respectively. Median OS had not been reached. All adverse events (AEs) were grade 1-3. Grade 3 AEs attributed to CS1003 and/or LEN occurred in 9 (45.0%) pts with the most common being gamma-glutamyltransferase increased (2 pts, 10.0%). Six (6) pts experienced grade 3 CS1003-related AEs, among whom, 4 pts also experienced grade 3 AEs related to LEN. Only 2 pts discontinued treatment due to AEs. There were no deaths due to AEs, and no new safety signals were identified.

Conclusions: The antitumor activity of CS1003 + LEN combination as 1L treatment in Chinese pts with uHCC remains encouraging and durable through a longer follow-up period, and the safety profile is well tolerated and manageable. The PFS is longer and the ORR is higher compared to the data previously reported, which supports further development as a combination treatment for improving outcomes in uHCC pts. The ongoing multi-regional, double-blinded, randomized, placebo-controlled, phase 3 trial (CS1003-305, NCT04194775) is currently recruiting and will further evaluate adding CS1003 to LEN as a 1L treatment in uHCC.