RATIONALE 302: Randomized, Phase 3 study of tislelizumab vs chemotherapy as second-line treatment for advanced unresectable/metastatic esophageal squamous cell carcinoma

Lin Shen,[1*] Ken Kato,[2] Sung-Bae Kim,[3] Jaffer Ajani,[4] Kuaile Zhao,[5] Zhiyong He,[6] Xinmin Yu,[7] Yonqian Shu,[8] Qi Luo,[9] Jufeng Wang,[10] Zhendong Chen,[11] Zuoxing Niu,[12] Jong-Mu Sun,[13] Chen-Yuan Lin,[14] Hiroki Hara,[15] Roberto Pazo-Cid,[16] Christophe Borg,[17] Liyun Li,[18] Aiyang Tao,[18] Eric Van Cutsem[19]

[1]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [4]University of Texas MD Anderson Cancer Center, Houston, Texas; [5]Fudan Cancer Hospital, Shanghai, China; [6]Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fujian, China; [7]Zhejiang Cancer Hospital, Hangzhou, China; [8]Jiangsu Province Hospital, Jiangsu, China; [9]The First Affiliated Hospital of Xiamen University, Fujian, China; [10]The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [11]2nd Hospital of Anhui Medical University, Anhui, China; [12]Department of Medical Oncology, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Jinan, China; [13]Samsung Medical Center, Seoul, South Korea; [14]China Medical University Hospital, and China Medical University, Taichung, Taiwan; [15]Saitama Cancer Center, Saitama, Japan; [16]Hospital Universitario Miguel Servet, Zaragoza, Spain; BeiGene Ltd, Beijing, China; [17]Medical Oncology Department, University Hospital of Besançon, Besançon, France; [18]BeiGene Ltd, Zhongguancun Life Science Park, Beijing, China; [19]University Hospitals Gasthuisberg Leuven and KULeuven, Leuven, Belgium

**Corresponding author*

Background:

Tislelizumab (tisle) monotherapy or plus chemotherapy demonstrated antitumor activity in patients (pts) with solid tumors, including esophageal squamous cell carcinoma (ESCC) (NCT03469557 and CTR20160872).

Methods:

In this global Phase 3 study (NCT03430843), adults with histologically confirmed advanced/unresectable or metastatic ESCC whose disease progressed following prior systemic therapy with ≥1 evaluable lesion per RECIST v1.1 and an Eastern Cooperative Oncology Group performance score (ECOG PS) of ≤1 were included. Pts were randomized (1:1) to receive tisle 200 mg intravenously every 3 weeks or investigator-chosen standard chemotherapy ([ICC]; paclitaxel, docetaxel, or irinotecan) and treated until disease progression, unacceptable toxicity, or withdrawal. Stratification factors included ICC option, region, and ECOG PS. The primary endpoint was overall survival (OS) in the intent-to-treat (ITT) population. The key secondary endpoint was OS in the programmed death-ligand 1 (PD-L1)+ population (visually-estimated combined positive score [vCPS] ≥10%, by VENTANA PD-L1 SP263 assay). Other secondary endpoints included (by RECIST v1.1) progression-free survival, overall response rate (ORR), duration of response (DoR), and safety.

Results:

Overall, 512 pts (median age: 62 years; range 35-86 years) from 132 sites in 10 countries in Asia (404 pts [79%]), Europe, and North America (108 pts [21%]) were randomized to tisle (n=256) or ICC (n=256) (ITT population). Of these, 157 pts (tisle [n=89], ICC [n=68]) had vCPS ≥10% (PD-L1+ population). On 1 Dec 2020 (data cut-off), median follow-up was 8.5 months (m) with tisle and 5.8 m with ICC. The study met its primary endpoint: tisle clinically and significantly improved OS vs ICC in the ITT population (median OS: 8.6 vs 6.3 m; HR 0.70, 95% CI 0.57-0.85, p=0.0001). Tisle also demonstrated significant improvement in OS vs ICC in the PD-L1+ population (median OS: 10.3 vs 6.8 m; HR 0.54, 95% CI: 0.36-0.79, p=0.0006). Survival benefit was consistently observed across pre-defined subgroups, including baseline PD-L1 status and region. Treatment with tisle was also associated with a higher ORR (20.3% vs 9.8%) and more durable response (median DoR: 7.1 vs 4.0 m; HR 0.42, 95% CI 0.23-0.75) than ICC in the ITT population. Fewer pts had ≥Grade 3 (46% vs 68%) treatment-emergent adverse events with tisle vs ICC. Of these, fewer ≥Grade 3 AEs were treatment-related (TR) with tisle vs ICC (19% vs 56%). Fewer pts discontinued tisle vs ICC (7% vs 14%) due to a TRAE.

Conclusion:

Tisle demonstrated statistically significant and clinically meaningful improvement in OS vs ICC in pts with advanced or metastatic ESCC who had disease progression during or after first-line systemic therapy. Tisle showed a higher and longer response vs ICC. The safety profile of tisle was more favorable than ICC.