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

**Eric Van Cutsem,[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] Lin Shen[19]**

[1]University Hospitals Gasthuisberg Leuven and KULeuven, Leuven, Belgium; [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, *Sungkyunkwan University School of Medicine,* 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]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China

**Background:** Tislelizumab, alone and with chemotherapy, has demonstrated antitumor activity in patients with solid tumors including esophageal squamous cell carcinoma (ESCC; NCT03469557, NCT04068519).

**Materials and methods:** This global Phase 3 study (NCT03430843) enrolled adults with histologically confirmed advanced or metastatic ESCC who progressed following prior systemic therapy. Eligible patients were randomized (1:1) to receive tislelizumab 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 intention-to-treat population. The key secondary endpoint was OS among programmed death-ligand 1–positive (PD-L1+) patients (visually-estimated combined positive score ≥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 patients (median age: 62 years; range 35-86 years) from 132 sites in 10 countries in Asia (n=404; 79%), Europe, and North America (n=108; 21%) were randomized to tislelizumab (n=256) or ICC (n=256). Of these, 157 patients (tislelizumab, n=89; ICC, n=68) were PD-L1+. As of December 1, 2020, median study follow-up was 8.5

months with tislelizumab arm and 5.8 months with ICC arm. The study met its primary endpoint: tislelizumab significantly improved OS vs ICC (median OS: 8.6 vs 6.3 months; HR 0.70, 95% CI: 0.57-0.85, *P*=0.0001). Significant OS improvement was also seen with tislelizumab in the PD-L1+ population (median OS: 10.3 vs 6.8 months; HR 0.54, 95% CI: 0.36-0.79, *P*=0.0006). Survival benefit was consistently observed across predefined subgroups, including baseline PD-L1 status and region. Tislelizumab was associated with higher ORR (20.3% vs 9.8%) and a more durable response (median DoR: 7.1 vs 4.0 months; HR 0.42, 95% CI: 0.23-0.75) than ICC. Fewer patients had Grade ≥3 treatment-emergent adverse events (AEs) (46% vs 68%) and Grade ≥3 treatment-related TEAEs (19% vs 56%) with tislelizumab vs ICC. Fewer patients discontinued tislelizumab versus ICC (7% vs 14%) due to a treatment-related TEAE.

**Conclusions:** Tislelizumab demonstrated statistically significant and clinically meaningful improvement in OS versus ICC in patients with advanced or metastatic ESCC who had disease progression during or after first-line systemic therapy. Tislelizumab showed a higher and longer response and had a more favorable safety profile compared with ICC.