

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

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

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

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  $\geq 1$  evaluable lesion per RECIST v1.1 and an Eastern Cooperative Oncology Group performance score (ECOG PS) of  $\leq 1$  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]  $\geq 10\%$ , 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  $\geq$ 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  $\geq$ Grade 3 (46% vs 68%) treatment-emergent adverse events with tisle vs ICC. Of these, fewer  $\geq$ 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.