Randomized, Global, Phase 3 Study of Tislelizumab (TIS) + Chemotherapy (chemo) vs Placebo (PBO) + chemo as First-line (1L) Treatment for Advanced/Metastatic Esophageal Squamous Cell Carcinoma (ESCC): RATIONALE-306

Authors:

Richard Hubner,[1] Jianming Xu,[2] Ken Kato,[3] Eric Raymond,[4] Yongqian Shu,[5] Yueyin Pan,[6] Yi Jiang,[7] Jingdong Zhang,[8] Sook Ryun Park,[9] Takashi Kojima,[10] Chen-Yuan Lin,[11] Evgeny Gotovkin,[12] Lucjan Wyrwicz,[13] Ryu Ishihara,[14] Hongqian Wu,[15] Yanyan Peng,[16] Lei Wang,[17] Liyun Li,[17] Harry H. Yoon[18]

Affiliations:

[1]*Department of Medical Oncology, The Christie NHS Foundation Trust/Division of Cancer Sciences, University of Manchester, Manchester, UK;*

[2]*Fifth Medical Center, Chinese PLA General Hospital, Beijing, China;*

[3]*National Cancer Center Hospital, Tokyo, Japan;*

[4]*Centre Hospitalier Paris Saint-Joseph, Paris, France;*

[5]*The First Affiliated Hospital of Nanjing Medical University, Nanjing, China;*

[6]*Anhui Provincial Hospital, Hefei, China;*

[7]*Cancer Hospital of Shantou University Medical College, Shantou, China;*

[8]*Liaoning Cancer Hospital, Shenyang, China;*

[9]*Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea;*

[10]*National Cancer Center Hospital East, Chiba, Japan;*

[11]*China Medical University Hospital, and China Medical University, Taichung, Taiwan;*

[12]*Ivanovo Regional Oncology Dispensary, Ivanovo, Russia;*

[13]*Maria Sklodowska-Curie National Cancer Research Institute, Warsaw, Poland;*

[14]*Osaka International Cancer Institute, Osaka, Japan;*

[15]*Global Statistics and Data Science, BeiGene USA, Inc., Ridgefield Park, NJ, USA;*

[16]*Clinical Biomarker, BeiGene (Shanghai) Co., Ltd., Shanghai, China;*

[17]*Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China;*

[18]*Mayo Clinic, Rochester, MN, USA*

Background: At interim analysis (IA) of RATIONALE-306 (NCT03783442), 1L TIS + chemo demonstrated a statistically significant, clinically meaningful improvement in overall survival (OS) vs PBO + chemo, with a manageable safety profile, in patients (pts) with advanced/metastatic ESCC. Here, we report updated efficacy and safety data with minimum (min) 2 years' follow-up.

Methods: Adults with unresectable locally advanced recurrent/metastatic ESCC and no prior systemic treatment for advanced disease were enrolled and randomized (1:1; stratified by region, prior definitive therapy, and investigator [INV]-chosen chemo) to receive TIS 200 mg (Arm A) or PBO (Arm B) IV Q3W + chemo (platinum + fluoropyrimidine or platinum + paclitaxel), until disease progression, intolerable toxicity, or withdrawal. The primary endpoint was OS in the intent-to-treat population. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DoR) per INV, and safety.

Results: 649 pts were randomized (Arm A n=326, Arm B n=323). At data cutoff (Dec 31, 2022), min study follow-up was 25.2 months; improvements in OS, PFS, ORR, and DoR in Arm A vs B (**Table**) were maintained relative to the IA. Similar to the IA, incidences of any-grade (96.6% vs 96.3%) or ≥grade 3 (66.7% vs 64.5%) treatment-related adverse events (TRAEs) were comparable between Arms A and B, respectively; treatment-emergent adverse events leading to treatment discontinuation were higher in Arm A (31.8%) vs B (22.1%). In Arm A vs B, respectively, serious TRAEs occurred in 29.3% vs 19.6% of pts; TRAEs leading to death occurred in 1.9% and 1.2%.

Conclusions: After min 2 years' follow-up, 1L TIS + chemo continued to demonstrate clinically meaningful improvements in OS and PFS and durable tumor response benefit vs PBO + chemo in pts with advanced/metastatic ESCC, with no new safety signals.

	Arm A: TIS + chemo (n=326)	**Arm B: PBO + chemo (n=323)**
mOS, mo (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)
HR (95% CI)	0.67 (0.56, 0.80)	
24-mo OS, % (95% CI)	37.9 (32.5, 43.2)	25.0 (20.2, 30.0)
mPFS, mo (95% CI)[a]	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)	0.61 (0.51, 0.73)	
24-mo PFS, % (95% CI)	18.1 (13.6, 23.1)	7.2 (4.4, 11.0)
ORR, % (95% CI)[a]	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
mDoR, mo (95% CI)[a]	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
24-mo DoR, % (95% CI)	19.6 (13.9, 25.9)	10.1 (5.0, 17.1)

[a]Per INV.
CI, confidence interval; HR, hazard ratio; m, median; mo, months.