Tislelizumab (TIS) + chemotherapy (CT) versus placebo (PBO) + CT in advanced or metastatic esophageal squamous cell carcinoma (ESCC): programmed death-ligand 1 (PD-L1) biomarker analysis from the RATIONALE-306 study

Authors: David Tougeron,[1]* Eric Raymond,[2] Jianming Xu,[3] Ken Kato,[4] Richard Hubner,[5] Yongqian Shu,[6] Sook Ryun Park,[7] Takashi Kojima,[8] Lucjan Wyrwicz,[9] David Tougeron,[10] Karen Geboes,[11] Eric Van Cutsem,[12] Roberto Pazo Cid,[13] Aziz Zaanan,[14] Sue-Anne McLachlan,[15] Hongqian Wu,[16] Jingwen Shi,[17] Liyun Li,[18] Shican Yan,[18] Harry H. Yoon,[19] on behalf of the RATIONALE-306 Investigators

Affiliations: [1]CHU de Poitiers, Service d'hépato-gastro-entérologie, Poitiers, France; [2]Centre Hospitalier Paris Saint-Joseph, Paris, France; [3]Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; [4]National Cancer Center Hospital, Tokyo, Japan; [5]Department of Medical Oncology, The Christie NHS Foundation Trust/Division of Cancer Sciences, University of Manchester, Manchester, UK; [6]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [7]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]National Cancer Center Hospital East, Chiba, Japan; [9]Maria Sklodowska-Curie National Cancer Research Institute, Warsaw, Poland; [10]Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [11]UZ Gent, Gent, Belgium; [12]University Hospitals Gasthuisberg / Leuven & KULeuven, Leuven, Belgium; [13]Hospital Universitario Miguel Servet, Zaragoza, Spain; [14]Hôpital Européen Georges Pompidou, Digestive Oncology, Paris, France; [15]St Vincent's Hospital Melbourne, Melbourne, Victoria, Australia; [16]Global Statistics and Data Science, BeiGene USA, Inc., Ridgefield Park, NJ, USA; [17]Clinical Biomarker, BeiGene (Beijing) Co., Ltd., Beijing, China; [18]Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [19]Mayo Clinic, Rochester, MN, USA.

ABSTRACT

Introduction: TIS (an anti–programmed cell death protein-1 antibody) + CT demonstrated significant overall survival (OS) benefit versus PBO + CT as first-line (1L) therapy for advanced ESCC in all randomized patients (stratified hazard ratio [HR] 0.66) and patients with PD-L1 tumor area positivity (TAP) score ≥10% (stratified HR 0.62) in the phase 3 RATIONALE-306 study (NCT03783442). Sustained survival benefit was observed at 3 years follow-up. Here we report exploratory analyses of OS by PD-L1 expression status and concordance of PD-L1 TAP and combined positive score (CPS).

Patients and Methods: Adults with advanced ESCC were randomized (1:1) to TIS 200 mg intravenously or PBO every 3 weeks + investigator-chosen CT (platinum + fluoropyrimidine or platinum + paclitaxel) until disease progression or intolerable toxicity. The primary endpoint was OS. Tissue samples were stained using the VENTANA PD-L1 (SP263) assay. PD-L1 expression was assessed by TAP and rescored post hoc by CPS. OS with different PD-L1 cutoffs, concordance between TAP and CPS at multiple cutoffs, interclass correlation coefficient (ICC), and Cohen's Kappa were investigated.

Results: Among 647 randomized patients, PD-L1 status was evaluable in 542 for TAP and 537 for CPS. 223/34%, 135/21%, 123/19%, and 61/9% of patients had PD-L1 TAP score ≥10%, 5 to <10%, 1 to <5% and <1%, respectively. After a minimum 3-year follow-up, OS improvement with TIS + CT versus PBO + CT was seen in PD-L1 subgroups with TAP score ≥1%, while small subgroup size with TAP score <1% limited interpretation (**Table**). OS results defined by TAP and CPS were similar. ICC between TAP and CPS was 0.85 (95% confidence interval [CI] 0.80-0.88). TAP and CPS scores showed substantial concordance in overall percentage agreement and Cohen's Kappa.

Conclusion: Exploratory PD-L1 subgroup results, with prior results from all randomized patients, support TIS + CT as a new 1L treatment option for patients with advanced ESCC. The concordance of

TAP and CPS scoring methods indicate that both are viable clinical measurements of PD-L1 expression in patients with ESCC.

Table

	Event/Total		OS, Unstratified Hazard Ratio (95% CI)
PD-L1 status	**TIS + CT**	**PBO + CT**	
TAP score			
≥10%	90/116	85/107	0.71 (0.53-0.95)
5 to <10%	38/56	66/79	0.50 (0.33-0.75)
1 to <5%	50/59	56/64	0.86 (0.59-1.26)
<1%	32/36	22/25	1.21 (0.70-2.08)
Unknown	40/59	35/48	0.65 (0.41-1.02)
CPS			
≥10	85/115	93/113	0.64 (0.48-0.86)
5 to <10	39/54	51/61	0.72 (0.47-1.09)
1 to <5	52/64	60/73	0.71 (0.49-1.03)
<1	28/31	23/26	1.36 (0.78-2.38)
Unknown	43/62	37/50	0.66 (0.42-1.02)
PD-L1 concordance between TAP and CPS	**Overall % agreement, (95% CI)**		**Cohen's Kappa, (95% CI)**
TAP 1% versus CPS 1	97 (96-98)		0.85 (0.77-0.92)
TAP 5% versus CPS 5	85 (82-88)		0.67 (0.60-0.73)
TAP 10% versus CPS 10	89 (87-92)		0.78 (0.72-0.83)