Patient-reported outcome (PRO)-based recurrent upper gastrointestinal (GI) deterioration predicts overall survival (OS): Results from RATIONALE 305.

Authors: Daniel Serrano,[1*] Hui Xu,[2] Tao Sheng,[3] Liyun Li,[2] Gisoo Barnes,[3] Do-Youn Oh[4]

[1]The Psychometrics Team, Sheridan, WY, USA,
[2]BeiGene (Beijing) Co., Ltd, Beijing, China,
[3]BeiGene, USA. Inc., San Mateo, CA, USA,
[4]Seoul National University Hospital, Cancer Research Institute, Seoul, Korea.

Background: PRO symptom scores are routinely employed in time to deterioration (TTD) or time until definite deterioration (TUDD) analyses. In contrast to OS, TTD/TUDD endpoints have ambiguous or “transient” terminal event times due to the potential recurrent nature of PRO symptom deterioration. TTD and TUDD attempt to force a single-event solution onto a recurrent event problem. An alternative is using recurrent event survival models to model the entire set of repeated deteriorations. Another criticism of the TTD/TUDD framework is that missing data due to death or dropout compromise these endpoints. To address these issues, this analysis presents a joint survival model (JM) linking recurrent PRO symptom deterioration to OS.

Methods: RATIONALE 305 was a randomized, double-blind, placebo-controlled, phase 3 trial comparing efficacy and safety of tislelizumab + chemotherapy (chemo) vs. placebo + chemo as a first-line treatment for patients with locally advanced, unresectable, or metastatic gastric/gastroesophageal junction adenocarcinoma.

Anchor-based meaningful-within patient change thresholds defining EORTC-STO22 upper GI symptom deterioration (UGI-D) was computed using change from baseline to Cycle 24 data. Using this threshold, unique recurrent UGI-D (R UGI-D) events were coded from Cycle 2 to Cycle 38. OS and R UGI-D events were modeled via Cox and Cox frailty proportional hazards, respectively, within a JM. The OS model adjusted the R UGI-D model for missing PRO data. The R UGI-D event frailty prediction of OS was used to evaluate the relationship between R UGI-D events and OS. Patients were censored: within the R UGI-D component of the JM without R UGI-D event by Cycle 38 and at the time of death; within the OS component of the JM if they survived to end of observation. All analyses were conducted using the JMBayes2 package in R version 4.3.2.

Results: Of the 896 patients, 514 (57.4%), 254 (28.3%), 83 (9.3%), 26 (2.9%), 16 (1.8%), and 3 (0.3%) experienced zero (censored), one, two, three, four, and five R UGI-D events, respectively.

Results showed that R UGI-D events were associated with lower OS (*P*<0.0001) irrespective of treatment. Tislelizumab + chemo was not associated with increased risk of R UGI-D events (*P*=0.95015); tislelizumab + chemo was associated with a 21% reduction in the risk of death event (HR 0.79; *P*<0.01) versus placebo + chemo.

Conclusions: Recurrent event models may provide a more coherent framework for PRO-based TTD endpoints. This research demonstrated that recurrent PRO-based deterioration events were strongly and negatively associated with OS.