**Recurrent patient-reported outcome (PRO)-based symptomatic deterioration predicts progression-free survival (PFS): Results from RATIONALE-305**

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**Background:** PRO-based symptom scores are routinely employed in time to deterioration (TTD) analyses. In contrast to PFS, the recurrent nature of PRO symptom deterioration may result in endpoints with "transient" terminal event times. The TTD framework forces a single-event solution onto a recurrent event problem. Recurrent event survival models remedy this limitation. Thus, we present a joint survival model (JM) linking recurrent PRO-based deterioration to PFS assessed by investigator (progression or death).

**Methods:** RATIONALE-305 (NCT03777657) was a randomized phase 3 trial of tislelizumab (TIS) + chemotherapy (chemo) vs. placebo (PBO) + chemo as first-line treatment for patients (pts) with locally advanced, unresectable, or metastatic gastric/gastroesophageal junction (GEJ) adenocarcinoma. EORTC QLQ-C30 and QLQ-STO22 symptom endpoints were modeled. Osoba's 10pt threshold was used to define PRO-based deterioration events from treatment cycles 2 to 38. Emphasis in abstract is placed on recurrent UGI deterioration (R UGI-D) events modeled with frailty cox models and PFS modeled via Cox proportional hazards models within a JM. The PFS model adjusted the R UGI-D model for informative missing PRO data. R UGI-D frailties predicted PFS. Pts were censored without R UGI-D events by Cycle 38 or time of disease progression or if they remained progression free to end of study.

**Results:** Of the 896 pts, 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. Higher rates of R UGI-D events predicted increased risk of progression/death (HR 3.38, $P<0.00001$), irrespective of treatment. In contrast to PBO + chemo, TIS + chemo was not associated with significantly increased risk of R UGI-D events but was associated with a 27% reduction in risk of progression/death (HR 0.73, $P=0.007$). Similar findings were observed between recurrent deterioration in appetite, fatigue, and pain/discomfort and PFS.

**Conclusions:** This analysis demonstrated that recurrent PRO deterioration was strongly predictive of PFS in pts with advanced gastric/GEJ cancer.