Impact of tislelizumab + chemotherapy versus placebo + chemotherapy on patient-reported symptoms and disease progression by programmed death-ligand 1 expression in gastroesophageal adenocarcinoma: a post hoc analysis of the RATIONALE-305 trial

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ABSTRACT

Background: The relationship between patient-reported outcome (PRO)-based symptom scores, recurrent PRO-based symptomatic deterioration events (RDEs), and terminal events such as progression-free survival (PFS) are rarely examined in the oncology therapeutic domain. Thus, we applied a 3-component joint model (JM) framework aiming to illuminate more clinically interpretable associations between PRO-based treatment effects, RDEs, and PFS among subgroups of patients with programmed death-ligand 1 (PD-L1) expression of ≥1%, ≥5%, and ≥10%.

Methods: The final analytic sample included 378 patients in the tislelizumab + chemotherapy arm (T+C) vs 401 in the placebo + chemotherapy arm (P+C) for the PD-L1 ≥1% subgroup, 238 in the T+C arm vs 237 in the P+C for the PD-L1 ≥5% subgroup, and 118 in the T+C arm vs 125 in the P+C arm for the PD-L1 ≥10% subgroup. Symptom domain scores from the EORTC QLQ-C30 and QLQ-STO22 symptom were modeled. Change from baseline (CFBL) in each domain was analyzed every cycle up to cycle 6, then every other cycle thereafter (up to cycle 25). The joint model was applied to all PD-L1 subgroups and comprised three components: 1) linear mixed model (LMM) predicting CFBL symptom scores, 2) Cox proportional hazard (CPH) model for disease progression (PFS as terminal event), and 3) frailty (random effects for RDEs) CPH model for time to PRO-based RDEs. Osoba's 10-point threshold was used to define RDEs.

Results: In the LMM, significant treatment efficacy for the T+C arm compared with the P+C arm was observed for the GHS/QoL (*P*=0.0080) and dietary restriction scores (*P*=0.0475) in the PD-L1 ≥5% subgroup. In the PD-L1 ≥1% subgroup, compared with the P+C arm, the T+C arm was associated with less worsening in pain/discomfort (*P*=0.0376), upper gastrointestinal symptoms (*P*=0.0088), and dietary restrictions (*P*=0.0352). In the CPH model, the average hazard ratio indicated that compared with the P+C arm, the T+C arm was associated with a reduction in risk of disease progression across all PRO domains and PD-L1 subgroups. Lastly, the PRO-based RDE frailty predictions were strongly associated with PFS risk in the PD-L1 ≥1% and ≥5% subgroups for GHS/QoL, and in the PD-L1 ≥1% subgroup for physical functioning, fatigue, dysphagia-odynophagia, pain/discomfort, and dietary restrictions, as well as for pain/discomfort and dietary restrictions in the PD-L1 ≥5% subgroup.

Conclusions: Through the 3-component JM, PRO-based effects were detected and demonstrated strong associations between PRO-based RDEs, and investigator-assessed PFS among varying PD-L1 expression levels. This framework may be a promising alternative for analyzing and interpreting PRO data in the context of PFS.