Impact of tislelizumab + chemotherapy versus placebo + chemotherapy on patient-reported symptoms and overall survival (OS) by programmed death-ligand 1 (PD-L1) expression in advanced or metastatic esophageal squamous cell carcinoma (ESCC): A post hoc analysis of the RATIONALE-306 trial

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ABSTRACT

Background: While improved survival has been previously demonstrated, the impact of immunotherapy on HRQoL in ESCC has not been well examined. Traditional PRO-based analyses in oncology trials, such as time to deterioration (TTD) and mixed models for repeated measures (MMRMs), are limited by discounting recurrent PRO events. Thus, we applied a 3-component joint model (JM) framework to define more clinically interpretable associations between patient-reported symptoms, treatment effects, and OS among subgroups of patients with ESCC from RATIONALE-306, which met its primary endpoint, with PD-L1 expression of ≥1%, ≥5%, and ≥10%.

Methods: The final analytic sample included 226 patients in the tislelizumab + chemotherapy arm (T+C), 242 in the placebo + chemotherapy arm (P+C) for PD-L1 ≥1%, 113 in the T+C arm and 103 in the P+C arm for PD-L1 ≥5%, and 168 in the T+C arm and 178 in the P+C arm for PD-L1 ≥10%. From EORTC QLQ-C30 and OES18, 7 key symptom domains were modeled (GHS, physical functioning, fatigue, dysphagia, pain, reflux, dietary restrictions). PRO data were collected at baseline and at every treatment cycle (up to 6 cycles), then every other cycle, and at safety follow-up, and change from baseline (CFBL) was analyzed. The joint model comprised three components: 1) linear mixed model predicting CFBL symptom scores; 2) Cox proportional hazard model (CPH) for time to OS; and 3) frailty (random effects for recurrent deterioration events [RDEs]) CPH model for time to PRO-based RDEs. Osoba (1998) 10-point threshold was used to define RDEs.

Results: Adjusted completion rates were >90% in the ITT population for both arms. Significant T+C treatment effects were observed for physical functioning in PD-L1 ≥5% (*P*=0.0476), and pain in PD-L1 ≥1% (*P*=0.0028) and PD-L1 ≥5% (*P*=0.0149) subgroups, but not in PD-L1 ≥10%. For other 5 symptoms (ie, GHS, fatigue, reflux, dysphagia, dietary restrictions), there were no statistically significant differences between treatment arms. However, T+C was associated with significant reductions in the risk of death across all 7 key symptoms and PD-L1 subgroups. As one example, with respect to interaction between pain and OS, T+C was associated with a 22% (HR, 0.78 [95% CI, 0.652-0.931]), 33% (HR, 0.67 [95% CI, 0.515-0.860]), and 47% (HR, 0.50 [95% CI, 0.344-0.720]) reduction in the risk of death in PD-L1 ≥1%, ≥5%, and ≥10%, respectively compared with P+C.

Conclusions: In this analysis, the addition of tislelizumab to chemotherapy was associated with significantly less deterioration in multiple PRO symptoms including physical functioning and pain, alongside a lower risk of death, after adjusting for recurring deterioration events using a frailty model across multiple PD-L1 expression subgroups.