RATIONALE 302: Randomized, Phase 3 study of tislelizumab vs chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma

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Objective:

Patients (pts) with advanced or metastatic esophageal squamous cell carcinoma (ESCC) have a poor prognosis and limited options after first-line chemotherapy. Tislelizumab (TIS) has previously demonstrated activity in pts with solid tumors, including ESCC.

Methods:

In this global Phase 3 study (NCT03430843), adults with advanced or metastatic ESCC whose disease progressed after prior systemic therapy and who had an ECOG PS of ≤1, were randomized (1:1) to receive TIS 200 mg IV Q3W or investigator-chosen standard chemotherapy (ICC) until disease progression or unacceptable toxicity. Stratification factors were ICC option, region, and ECOG PS. Primary endpoint was overall survival (OS) in the intent-to-treat (ITT) population. The key secondary endpoint was OS in the programmed death ligand-1 (PD-L1+) population (visually-estimated combined positive score [vCPS] ≥10%, by VENTANA PD-L1 SP263 assay). Other secondary endpoints were progression-free survival (PFS), overall response rate (ORR), duration of response (DoR), and safety.

Results:

In the ITT population, 512 pts (median age: 62 [range: 35–86] years) from 10 countries in Asia (404 pts [79%]) and Europe/North America (108 pts [21%]) were randomized to TIS (n=256) or ICC (n=256). Of these, 157 pts (TIS [n=89], ICC [n=68]) had vCPS ≥10% (PD-L1+ population). As of Dec 1, 2020, median follow-up was 8.5 months (m) with TIS and 5.8 m with ICC. TIS statistically and clinically improved OS vs ICC in the ITT population (median OS: 8.6 vs 6.3 m; HR 0.70, 95% CI 0.57–0.85, p=0.0001) and in the PD-L1+ population (median OS: 10.3 vs 6.8 m; HR 0.54, 95% CI 0.36–0.79, p=0.0006). Survival benefit was observed across pre-defined subgroups, including PD-L1 status and region. TIS pts demonstrated higher ORR (20.3% vs 9.8%) and more durable responses (median DoR: 7.1 vs 4.0 m; HR 0.42, 95% CI 0.23–0.75) than ICC in the ITT population. TIS pts had fewer ≥Grade 3 (46% vs 68%) TEAEs, fewer treatment-related ≥Grade 3 AEs (19% vs 56%), and fewer TRAE-related discontinuations (7% vs 14%).

Conclusion:

2L TIS demonstrated statistically and clinically meaningful improvement in OS vs ICC and a higher and longer response in pts with advanced or metastatic ESCC following prior systemic therapy. The safety profile of TIS was more favorable than ICC. Benefits were seen across subgroups including age, region, gender, and smoking status.

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