RATIONALE-309: Updated progression-free survival (PFS), PFS after next line of treatment (PFS2), and overall survival (OS) from a Phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer (RM NPC)

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## Abstract:

**Background:**

Tislelizumab is a humanized immunoglobulin G4 anti-programmed cell death protein 1 (PD-1) monoclonal antibody (mAb). At the interim analysis (median follow-up: 10.0 months), RATIONALE-309 met its primary endpoint as first-line tislelizumab + chemotherapy significantly improved PFS, as assessed by an independent review committee (IRC), in patients with RM NPC compared with placebo plus chemotherapy. Tislelizumab + chemotherapy had an acceptable safety profile, comparable to placebo plus chemotherapy.[1] Here we report an updated analysis of PFS, PFS2, and OS with an extended median follow-up of 15.5 months.

ASCO Plenary Series 2022

**Methods:**

A total of 263 eligible patients with RM NPC were randomized 1:1 to receive tislelizumab 200 mg intravenously (IV) or placebo on Day 1, plus gemcitabine (1 g/$m^2$ IV Day 1, Day 8) plus cisplatin (80 mg/$m^2$ Day 1) every three weeks for 4–6 cycles, followed by tislelizumab or placebo every three weeks until disease progression, unacceptable toxicity or withdrawal. After IRC-confirmed disease progression, patients in the placebo arm could crossover to receive tislelizumab monotherapy. The primary endpoint was IRC-assessed PFS. Secondary endpoints included IRC-assessed objective response rate and duration of response, investigator-assessed PFS and PFS2, and OS. Biomarker analysis was an exploratory endpoint.

**Results:**

At an updated data cut-off (September 30, 2021), IRC-assessed PFS was consistent with the interim data analysis and demonstrated significant improvement for tislelizumab + chemotherapy vs placebo + chemotherapy (median PFS: 9.6 vs 7.4 months, respectively; hazard ratio [HR]=0.50; 95% confidence interval [CI]: 0.37, 0.68). Median PFS2 and OS were not reached for the tislelizumab + chemotherapy arm and were 13.9 months and 23.0 months for the placebo + chemotherapy arm, respectively. The HRs were 0.38 (95% CI: 0.25, 0.58) for PFS2 and 0.60 (95% CI: 0.35, 1.01) for OS. The association of tumor microenvironment features by gene-expression analysis with clinical benefit will be presented.

**Conclusions:**

Tislelizumab + chemotherapy showed consistent, clinically meaningful improvement in PFS compared with placebo + chemotherapy in this updated analysis. Clinically meaningful improvements in PFS2 and OS were also observed for the tislelizumab + chemotherapy arm. This is the first report of PFS2 benefit for an anti-PD-1 mAb in combination with chemotherapy in the first-line treatment setting of RM NPC. These results support the use of tislelizumab + chemotherapy as first-line therapy for RM NPC.

**Reference:** 1. Yang Y, et al. ESMO-IO Virtual Congress 2021. Oral presentation 121O.