RATIONALE 309: A randomized, global, double-blind, Phase 3 trial of tislelizumab (TIS) vs placebo, plus gemcitabine + cisplatin (GP), as 1L treatment for recurrent/metastatic nasopharyngeal cancer (RM-NPC)

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Background

TIS is an anti-PD-1 antibody engineered to minimize FcγR binding, a mechanism of T-cell clearance and potential anti-PD-1 resistance. TIS demonstrated antitumor activity in NPC as a single agent in a Phase 1/2 study (CTR20160872). This randomized, double-blind, Phase 3 study evaluated TIS + GP vs placebo + GP as 1L treatment for RM-NPC (NCT03924986).

Methods

Eligible pts with RM-NPC were randomized 1:1 to receive TIS (Arm A) or placebo (Arm B) (200 mg IV D1) plus G (1 g/m^2 IV D1, D8) and P (80 mg/m^2 D1) every three weeks (Q3W) for 4–6 cycles followed by TIS or placebo Q3W until disease progression, unacceptable toxicity, or withdrawal. After disease progression, patients in Arm B could crossover to receive TIS monotherapy. The primary endpoint was independent review committee-assessed progression-free survival (PFS_{IRC}). Secondary endpoints included objective response rate (ORR_{IRC}), duration of response (DoR_{IRC}), investigator-assessed PFS (PFS_{INV}), and safety.

Results

A total of 263 pts were randomized to Arm A (n=131) and Arm B (n=132). At the interim analysis (data cut-off: Mar 26, 2021), median follow-up was 10.0 months (m). Median PFS_{IRC} was significantly longer for Arm A vs B (HR 0.52 [95% CI: 0.38, 0.73]; median PFS: 9.2 vs 7.4 m; p<0.0001). PFS benefit in Arm A was consistent across most subgroups. PFS_{INV} was consistent with PFS_{IRC} (HR 0.54 [0.38, 0.76]; median 9.8 vs 7.6 m). ORR_{IRC} and median DoR_{IRC} were 69.5% and 8.5 m (Arm A) and 55.3% and 6.1 m (Arm B), with 21 (16.0%) and 9 (6.8%) patients achieving complete response, respectively. The 12-month PFS_{IRC} event-free rate was 35.7% (Arm A) and 12.2% (Arm B). Safety is described in the **Table**.

Conclusions

TIS + GP significantly prolonged PFS vs GP alone as 1L therapy for RM-NPC. ORR and DoR were increased for TIS + GP vs GP alone. The safety profile of TIS + GP was manageable and consistent with previous reports, with no new safety signals identified.

Table: Summary of TEAEs

%	Arm A (n=131)	Arm B (n=132)
≥ 1 TEAE	100.0	99.2
≥ Grade 3 TEAE	80.9	81.8
Serious TEAE	27.5	33.3
TEAE leading to discontinuation of TIS/placebo	5.3	3.8
≥ Grade 3 immune-mediated TEAE	2.3	-

TEAE, treatment emergent adverse event; TIS, tislelizumab.