RATIONALE-309 (NCT03924986) – A Phase 3 Trial Comparing Anti-PD-1 Antibody Tislelizumab Combined with Chemotherapy Versus Chemotherapy Alone as First-Line Treatment for Patients with Recurrent or Metastatic Nasopharyngeal Cancer

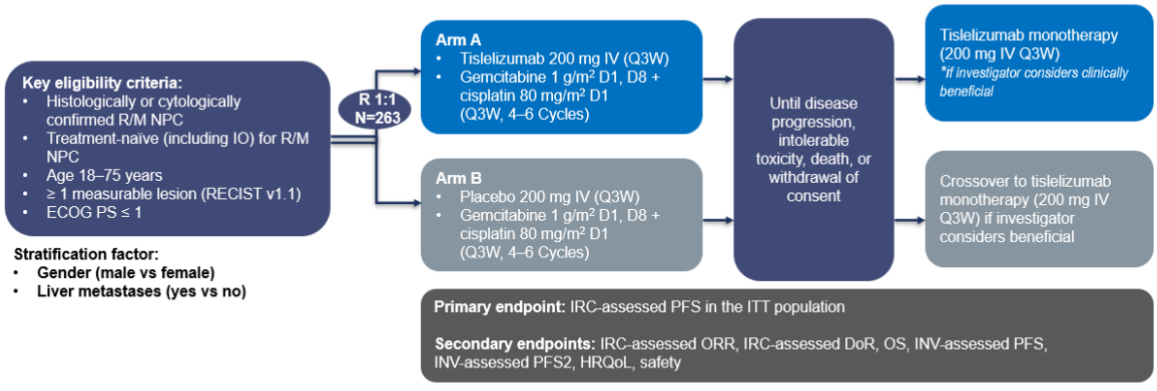
ABOUT THE TRIAL

The RATIONALE-309 trial evaluates the efficacy and safety of tislelizumab combined with gemcitabine plus cisplatin versus placebo combined with gemcitabine plus cisplatin as first line treatment for recurrent or metastatic nasopharyngeal cancer (R/M NPC).[i]

Nasopharyngeal carcinoma (NPC) is a rare cancer in which malignant cells form in the tissues of the nasopharynx and accounts for approximately 133,000 new diagnoses and 80,000 deaths per year worldwide.[ii]

R/M NPC exhibits a high prevalence in Southeast Asia, among other emerging markets.[ii]

TRIAL DESIGN[i,iii]



D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IO, immunotherapy; IRC, independent review committee; ITT, intention-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment; Q3W, every 3 weeks; RECIST, response evaluation criteria in solid tumours; RM NPC, recurrent or metastatic nasopharyngeal carcinoma

- Randomized, multicenter, double-blind, placebo-controlled[i]
- 1:1 assignment to tislelizumab 200 mg intravenously (IV) or placebo on day 1, plus gemcitabine (1 g/m^2 IV D1, D8), plus cisplatin (80 mg/m^2 day 1) every 3 weeks for 4–6 cycles, followed by tislelizumab or placebo every 3 weeks (Q3W) until disease progression, unacceptable toxicity, or withdrawal[i]
- Stratified randomization by gender, liver metastases[i]
- A total of 263 patients were enrolled in the trial, with 131 and 132 randomized to Arm A and Arm B, respectively, with balanced baseline characteristics between both arms[i]

- Patients in the placebo arm could crossover to tislelizumab monotherapy if disease progression was confirmed and the investigator considers clinically beneficial[i]

Primary Efficacy Endpoint:
Progression Free Survival as assessed by an Independent Review Committee (IRC) per RECIST v1.1[i]

Secondary endpoints: IRC-assessed overall response rate (ORR), as well as duration of response (DoR), overall survival (OS), investigator-assessed PFS, time to second objective disease progression (PFS2), and safety.[i,iii]

Study Results:

Interim results from the trial were presented at the 2021 European Society for Medical Oncology Immuno-Oncology (ESMO I-O) Congress. The study is currently active, not recruiting. Updated efficacy analyses presented at the 2022 Annual ASCO meeting showed that, at a median follow-up of 15.5 months, tislelizumab in combination with chemotherapy continued to demonstrate a clinically significant progression-free survival (PFS) benefit over chemotherapy alone for patients with R/M NPC.[iii]

Patients administered a 200 mg Q3W dose of tislelizumab in combination with chemotherapy achieved a median PFS of 9.6 months (stratified hazard ratio (HR)=0.50 [CI: 0.37, 0.68]) compared to 7.4 months for patients dosed with placebo control and chemotherapy, as assessed by an independent review committee (IRC).[iii] A positive overall survival (OS) trend was also observed with median OS not yet reached in the tislelizumab combination arm and 23 months for the chemotherapy plus placebo arm (HR=0.60 [95% CI: 0.35, 1.01]). For patients treated with tislelizumab plus chemotherapy, median PFS2 was not yet reached compared to 13.9 months for those treated with placebo plus chemotherapy (HR=0.38 [95% CI: 0.25, 0.58])[iii]

The safety profile of the tislelizumab and chemotherapy combination was generally manageable and consistent with known risks of each treatment agent.[iii]

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[i] Yang, Y., Pan, J., Wang, H., RATIONALE 309: A randomized, global, double-blind, phase III trial of tislelizumab (TIS) vs placebo, plus gemcitabine + cisplatin (GP), as first-line treatment for recurrent/metastatic nasopharyngeal cancer (RM-NPC). Annals Of Oncology Vol 32_suppl 7, (December 1, 2021) S1430

[ii] Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/4-Nasopharynx-fact-sheet.pdf. Accessed May 24, 2022

[iii] Zhang, L., Yang, Y., Pan, J., et. al. RATIONALE-309: Updated progression-free survival (PFS), PFS after next line of treatment, and overall survival from a phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer. Journal of Clinical Oncology Vol. 40, no. 36_suppl (April 20, 2022) 384950-384950.