AHFS Final Determination of Medical Acceptance: Tislelizumab in Combination with Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer

Drug: Tislelizumab

Off-label Use: Recurrent or metastatic nasopharyngeal cancer

Off-label Use for Review:

- Results from multicenter, randomized, double-blind, placebo-controlled, phase 3 trial

Strength of Evidence: Level 1 (high strength/quality)

Grade of Recommendation: Recommended use (accepted)

Narrative Summary:

A diagnosis of nasopharyngeal carcinoma occurs in <1 out of 100,000 individuals globally on an annual basis, with an increased incidence observed in Asian countries and males versus females.[10001] Risk factors include smoking history, heavy alcohol use, Epstein-Barr virus (EBV) exposure, Asian descent, and a family history of the cancer type.[10001] For patients with stage I-IV nonmetastatic disease, high-dose radiation therapy with chemotherapy is the usual initial treatment option.[10001] For those with metastatic and recurrent nasopharyngeal carcinoma, treatment options include radiation therapy, surgery, and chemotherapy/immunotherapy.[10001] The administration of chemotherapy/immunotherapy is considered if a patient with metastatic or recurrent disease is no longer amenable to surgery or radiation therapy per the National Cancer Institute (NCI).[10001]

A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial (RATIONALE-309) evaluated the use of tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer.[10002] RATIONALE-309 enrolled adults (18-75 years of age) with treatment-naïve histologically or cytologically confirmed recurrent or metastatic nasopharyngeal cancer regardless of programmed death-ligand 1 (PD-L1) expression.[10002] Eligible patients also had ≥1 measurable lesion per RECIST v1.1, an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, life expectancy of ≥12 weeks, and

appropriate organ function.[10002] A total of 263 patients were randomly assigned to either tislelizumab 200 mg IV (n=131) or matching placebo (n=132) every 3 weeks in combination with gemcitabine 1 g/m^2 IV given on Days 1 and 8 and cisplatin 80 mg/m^2 on Day 1.[10002] Chemotherapy was administered every 3 weeks for 4 to 6 cycles per investigator discretion.[10002] Dosage reduction of each chemotherapeutic agent was allowed twice per protocol before discontinuation.[10002] Tislelizumab dose reduction was not allowed during the study; however, temporary interruption of therapy due to adverse effects was allowed, with resumption of therapy required within 12 weeks of the last dose.[10002] Study treatment continued until disease progression, occurrence of unacceptable toxicity, or patient withdrawal.[10002] Per study protocol, patients in the tislelizumab/chemotherapy arm were allowed to continue tislelizumab monotherapy and patients in the chemotherapy alone arm were permitted to switch over to tislelizumab after disease progression.[10002] The primary study endpoint was progression-free survival (PFS) in the intention-to-treat (ITT) population as assessed by an independent review committee.[10002] Progression-free survival was defined as the time from randomization to the initial objectively documented disease progression or death from any cause, whichever occurred first.[10002] Key secondary endpoints included objective response rate (ORR), duration of response (DOR), and safety.[10002]

Baseline characteristics were comparable between the study groups.[10002] The median age of patients was 50 years, 78.3% were male, and the majority were enrolled from China (94.3%).[10002] Recurrent disease was present in 62.4% of patients and 32.7% had primary metastatic disease.[10002] The median duration of tislelizumab exposure was 35.9 weeks and the median number of tislelizumab treatment cycles was 11.[10002] Most patients in both groups had an undifferentiated, non-keratinized histology (74% in the tislelizumab/chemotherapy group and 72% in the placebo/chemotherapy group).[10002]

At the time of data cutoff for the interim analysis, the median follow-up was 10 months (range: 0.1 to 23.3 months) and 152 PFS events occurred.[10002] Additionally, 63 patients in the tislelizumab/chemotherapy arm and 37 patients in the placebo/chemotherapy arm remained on treatment.[10002] Results revealed a significantly improved modified PFS with tislelizumab/chemotherapy versus placebo/chemotherapy per independent review committee assessment (9.2 vs. 7.4 months; hazard ratio [HR] 0.52; 95% confidence interval [CI]; 0.38 to 0.73).[10002] An investigator assessment of modified PFS was consistent with these results (9.8 vs. 7.6 months; HR 0.54; 95% CI; 0.38 to 0.76).[10002] At the time of an updated data cutoff (median follow-up: 15.5 months), modified PFS as assessed by the independent review committee was consistent with the results from the interim analysis (9.6 vs. 7.4 months; HR 0.50; 95% CI; 0.37 to 0.68).[10002] A consistent PFS benefit was seen with tislelizumab/chemotherapy in almost all patient subgroups, regardless of liver metastatic status, baseline EBV level, and tumor cell PD-L1 expression level.[10002] The ORR was improved with tislelizumab/chemotherapy (69.5% vs. 55.3%); 16% of patients in the tislelizumab/chemotherapy arm versus 6.8% of patients in the placebo/chemotherapy experienced a complete response.[10002] Median DOR was prolonged for patients administered tislelizumab/chemotherapy as compared to placebo/chemotherapy (8.5 vs. 6.1 months).[10002] Overall survival (OS) was evaluated at the time of the updated data cutoff with 23 fatalities reported in the tislelizumab/chemotherapy arm and 35 in the placebo/chemotherapy

arm.[10002] The median OS was not reached in the tislelizumab/chemotherapy arm and was 23 months in the placebo/chemotherapy arm.[10002]

Treatment-emergent adverse events (TEAEs) were common in both groups; all patients in the tislelizumab/chemotherapy arm and 99.2% of patients in the placebo/chemotherapy arm experienced at least 1 TEAE.[10002] Permanent discontinuation of therapy due to a TEAE occurred in 13% of patients in the tislelizumab/chemotherapy arm and 9.1% of patients in the placebo/chemotherapy arm.[10002] Deaths related to TEAEs occurred in 5 patients in the tislelizumab/chemotherapy group and 2 patients in the placebo/chemotherapy group. [10002] One patient in the tislelizumab/chemotherapy group experienced a TEAE (myelodysplastic syndrome) leading to death considered related to tislelizumab.[10002] The most frequently occurring immune-mediated TEAE was hypothyroidism (13.7% of patients in the tislelizumab/chemotherapy arm).[10002]

Based on current evidence, tislelizumab, in combination with gemcitabine and cisplatin, as a first-line treatment for recurrent or metastatic nasopharyngeal carcinoma has Level 1 (high strength/quality) evidence supporting its use.[10002] This combination results in an improvement in PFS, ORR, and DOR with a tolerable safety profile.[10002]

Dosage

When tislelizumab is used in combination with gemcitabine and cisplatin for the treatment of recurrent or metastatic nasopharyngeal carcinoma, the usual dosage of tislelizumab administered is 200 IV every 3 weeks.[10002]

References:

10001. National Cancer Institute. Nasopharyngeal carcinoma treatment (PDQ®) – Health Professional Version. https://www.cancer.gov/types/head-and-neck/hp/adult/nasopharyngeal-treatment-pdq. Updated July 25, 2024.

10002. Yang Y, Pan J, Wang H, et al. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: a multicenter phase 3 trial (RATIONALE-309). *Cancer Cell*. 2023;41(6):1061-72.e4.

Oncology Expert Committee Voting Results and Comments:

First-Round Vote (7 of 7 committee members returned the initial ballot):

Grade of Recommendation:

Recommended use (Accepted): 4 votes

Reasonable choice (Accepted, with possible conditions): 3 votes

Not fully established (Equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Reviewer Comments on Grade of Recommendation

At this time, the use of tislelizumab plus chemotherapy and tislelizumab alone in the setting of treatment-naive patients with recurrent/metastatic nasopharyngeal cancer fulfills a similar role to toripalimab. Like tislelizumab, toripalimab may be combined with chemotherapy in the initial setting and also be used as a single-agent if the patient progresses on chemotherapy alone. Though one cannot compare the results of one study/agent to another without a direct comparison trial (due to differences in treatment population and trial design) - the PFS benefit, referenced by the Hazard ratios of the RATIONALE-309 and JUPITER-02 trials respectively, would suggest that the PFS benefit of both agents are comparable. However, toripalimab's efficacy data is more robust as the JUPITER-02 has reported overall survival benefit data whereas the RATIONALE-309 currently reports that the tislelizumab's overall survival data is immature. Therefore, while tislelizumab has demonstrated efficacy either in combo with chemotherapy or as monotherapy, toripalimab's more robust evidence would lead a prescriber use that as a first choice - this is supported by NCCN Guidelines as well (Pg. NASO-B on Head and Neck NCCN Guidelines) I would recommend the use of tislelizumab if the more established agent, toripalimab, was unable to be utilized. Toripalimab is reported to cause infusion reactions in 2-4.1% of patients, with Grade 3 reactions being rare. Patients that do experience a Grade 3 infusion reaction or above to toripalimab, however, are reasonable candidates to switch to tislelizumab.

Findings in the RATIONALE-309 study for tislelizumab had results comparable to the toripalimab +/Cis/Gem data. Tislelizumab plus chemotherapy is another reasonable choice for patients with recurrent or metastatic nasopharyngeal cancer regardless of PDL-1 expression.

Consensus Vote (6 of 7 committee members returned the consensus ballot):

Proposed Level of Evidence: Level 1 (High strength/quality)

Concur with rating: 6 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 4 votes

Reasonable choice (Accepted, with possible conditions): 2 votes

Not fully established (Equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Final Grade of Recommendation: Recommended use (accepted)

Participants:

AHFS Staff Members (writing and editing): Michael Gabay PharmD, JD, BCPS

AHFS Oncology Expert Committee Members (reviewing and voting): Donald Moore PharmD, BCOP; Andrew Li PharmD, BCOP; Jason Bergsbaken PharmD, BCOP; Christine Gegeckas RPh, BCOP; Kirollos Hanna PharmD, BCOP; Caroline Clark MSN, RN; Eve Segal PharmD, BCOP

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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