Toripalimab (LOQTORZI) in Nasopharyngeal Carcinoma
National Drug Monograph
September 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION		
	Description / MOA	An IgG4 monoclonal antibody directed against programmed death receptor-1 (PD-1)
	Indication Under Review[1]	1. In combination with cisplatin and gemcitabine, for 1L treatment of metastatic or recurrent locally advanced nasopharyngeal carcinoma (NPC) 2. As a single agent for recurrent unresectable of metastatic NPC with progressive disease on or after platinum-containing chemotherapy
	Dosage Regimen	1. with cisplatin and gemcitabine, toripalimab 240 mg IV every 3 weeks 2. as a single agent, toripalimab 3mg/kg IV every 2 weeks
	Dosage Forms Under Review	Injection 240 mg/6ml [40mg/ml] solution as a SDV

EFFICACY CONSIDERATIONS	**Trial**	**JUPITER-02 (NCT03581786) – 1L setting**	**POLARIS-02 (NCT02915432) – subsequent line setting**
	Design	Randomized, multicenter, DB, PC trial	Single-arm, multicenter, phase 2 trial
	Population	N=289; metastatic or recurrent, locally advanced NPC who had not received prior systemic therapy for recurrent or metastatic disease; If recurrent disease, last treatment ≥ 6 months from last treatment (radiotherapy or chemotherapy) **Excluded:** Autoimmune conditions (other than stable hypothyroidism or Type I DM) and those who require systemic immunosuppression Stratified by: ECOG PS 0 vs. 1, recurrent vs. metastatic disease	N=190; recurrent or metastatic NPC, refractory to standard chemotherapy which included (1) ≥ 2L systemic chemo (2) 1st line must have included a platinum-based regimen (3) neoadjuvant, adjuvant or concurrent chemoRT is a line of therapy if PD occurs within 6 months after end. Intolerance to chemo is not considered a line of therapy; ECOG PS 0-1 **Excluded**: active CNS metastases
	Demographic	mAge 46 yrs (38-53); 4.8% over 65 yrs; 83% male, 100% Asian (China, Taiwan, Singapore sites); 57% ECOG 0 NPC histology: 98% non-keratinizing; 1% keratinizing	mAge 46 yrs (range 22-71), male 83%; ECOG PS 1 65%; stage IVb 93%; PD-L1 positive (> 1%) 25%; s/p 1LOT 51%; s/p 2LOT 48%; NPC histology: non-keratinizing 96%; EBV DNA titer ≥ 10,000 IU/ml 55%
	Intervention	Day 1: Toripalimab 240 mg IV + Cisplatin 80mg/m2 IV every 3 weeks for up to 6 cycles; Days 1 & 8: Gemcitabine 1000 mg/m2 IV every 3 weeks for up to 6 cycles; Toripalimab 240mg IV every 3 weeks until PD or toxicity to maximum 2 years	Toripalimab 3mg/kg IV every 2 weeks until disease progression or intolerance
	Comparator	Day 1: Placebo IV + Cisplatin 80mg/m2 IV every 3 wks for up to 6 cycles; Days 1 & 8: Gemcitabine 1000 mg/m2 IV every 3 wks for up to 6 cycles; Placebo IV every 3 weeks until PD or toxicity to max 2 years	None
	Results	**Intervention vs. Comparator** **Primary: mPFS 21.4 (7.1, NE) vs. 8.2 mos (7.0, 9.5)** [HR 0.52 (95% CI 0.37-0.73); p=0.0003] **Secondary: ORR, OS** **ORR 77 (70, 84) vs. 66 (58, 74)%** CR 19 vs. 11%; PR 58 vs. 55%; p=0.0353 **mOS@36 mos: NR (38.7, NE) vs. 33.7 (27 vs. 44.2) mos;** [HR 0.63 (95% CI 0.45, 0.89); p=0.008] OS@1 yr: 91 vs. 87%; @2 yr: 78 vs. 65%; @3yr: 65 vs. 49%	Primary: ORR by Independent Review Comm (IRC) **ORR 20.5% (95% CI, 15-27); CR 2.6%; PR 18%; SD 20%** Secondary: DOR, DCR, PFS, OS **DOR 12.8 months** **DCR 40% (95% CI, 33-47)** **mPFS 1.9 months** **mOS 17.4 months** Median 8 doses received (range, 1-69)

			12 patients with genomic amplification in the 11q13 region had ORR 0%; 19 patients with ETV6 genomic alterations had ORR 5.3%
	Notes	• Standard of care is 1L cis/gem for up to 6 cycles; • Use of other ICIs (e.g. pembrolizumab, nivolumab) is based on extrapolation of toripalimab data; • **NCCN guidelines v4.2024 includes the following as preferred 1L options for recurrent, unresectable or metastatic disease (all category 1):** Cis/gem cis/gem + toripalimab cis/gem + other PD-1 inhibitor (e.g. pembro, nivo) • **VA Head & Neck Oncology Pathway includes:** cis/gem + toripalimab as 1L in patients with recurrent or metastatic NPC, who are candidates for immunotherapy and cisplatin.	• Standard of care is 1L gem/cis; no standard of care beyond 1L therapy; • First ICI approved for NPC (pembro and nivo approved in head & neck squamous cell carcinoma) • **NCCN guidelines v4.2024 includes the following as preferred subsequent line option for recurrent, unresectable or metastatic disease (category 2A):** Toripalimab (if disease progression on or after platinum-containing therapy) • **NCCN Other Recommended Regimens includes subsequent line immunotherapy (category 2B):** ➔ Nivolumab, if previously treated, recurrent or metastatic non-keratinizing disease Phase 2 (NCI-9742) N=44; @13 mos ORR 21%; 1 yr PFS 19%; 1 yr OS 59%[6] ➔ Pembrolizumab if previously treated, PD-L1+ recurrent or metastatic disease or TMB-High (≥ 10 mut/Mb) KEYNOTE-122 N=233 (pembro vs. chemo) Open-label, Phase 3 trial in PD-L1+ NPC @45 mos ORR 23 vs. 26%; OS 17 vs. 15 mos; [HR 0.90 (95% CI 0.67-1.19); p=0.2262][5] • **VA Pathway ends at NPC 1LOT, no recommendation for subsequent therapy**

SAFETY CONSIDERATIONS		
	Boxed Warnings	None
	Contraindications	None
	Other Warnings	Immune-mediated adverse reactions Infusion-Related Reactions Complications of allogeneic HSCT Embryo-fetal toxicity
	Top 5 AEs	(≥ 20%) in combo with cisplatin, gemcitabine: nausea, vomiting, decreased appetite, constipation, hypothyroidism (≥ 20%) as single agent: fatigue, hypothyroidism, musculoskeletal pain
	Drug Interactions	Prednisone-equivalent ≥ 10mg/day may diminish ICI effect

VHA PLACE IN THERAPY	• Nasopharyngeal cancers are rare in the U.S.; endemic in China, Southeast Asia, North African and Middle East; 2-3x more common in males with peak incidence around ages 50-59 years • NPC histology in U.S.: keratinizing 25%; nonkeratinizing (differentiated) 12%, (undifferentiated) 63% (subtype associated with EBV); nonkeratinizing histology is more common in Asian countries and is associated with EBV infection • Metastatic NPC carries a poor prognosis with a median overall survival of 21-29 months • Differences in study demographic make extrapolation of the data somewhat difficult; as such, the FDA requires a postmarketing commitment in which a sample size of 100 patients from the U.S and Canada, with the keratinizing subtype, reflective of the U.S. population, to further characterize the safety and efficacy of toripalimab in combination with cis/gem. Anticipated trial completion set for 12/27 and final report submission 6/2028[7] • Immune checkpoint inhibitors have not been compared in NPC setting; use of pembrolizumab and nivolumab has been based upon toripalimab data, prior to its U.S. availability • In the 1L setting, toripalimab with cis/gem demonstrates PFS and OS benefit; in the subsequent-line setting, toripalimab provides a modest 20% ORR. • In the subsequent-line setting, pembrolizumab demonstrated less toxicity compared to cytotoxic chemotherapy but did not improve OS; Nivolumab is approved as subsequent-line therapy in patients with nonkeratinizing NPC who received prior platinum-based therapy

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References

1 LOQTORZI (toripalimab) formulation [prescribing information online]. Redwood City, CA: Coherus BioSciences, Inc. October 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761240s001lbl.pdf. Accessed Aug. 20, 2024.

2 Mai Hai-Qiang, et al. Toripalimab plus chemotherapy for recurrent or metastatic Nasopharyngeal Carcinoma. JAMA 2023; 330: 1961-1970.

3 NCCN Guidelines Version 4.2024. Cancer of the Nasopharynx. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf Accessed Aug. 21, 2024

4 VHA Oncology Head and Neck Cancer V4.2024 Head and Neck Cancer - Nasopharynx Metastatic or Recurrent Disease Accessed Aug 21, 2024

5 Chan ATC, et al. Pembrolizumab monotherapy versus chemotherapy in platinum-pretreated, recurrent or metastatic NPC (KEYNOTE-122): an open-label, randomized, phase III trial. Ann Oncol 2023; 34:251-261

6 Ma BBY, et al. Antitumor Activity of Nivolumab in Recurrent and Metastatic NPC: An International, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742). J Clin Oncol 2018; 36: 1412-1418

7 Center for Drug Evaluation and Research. Application number 761240Orig1s000. Multi-disciplinary Review for LOQTORZI (toripalimab-tpzi). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761240Orig1s000MultidisciplineR.pdf Accessed Aug. 22, 2024