Written By: Shirin Khorashadi, PharmD, BCOP
and Deborah J. Wong, MD, PhD;
Hyu Kang, MD, MPH, FACP
Institution: UCLA Hematology and Oncology; UCSF Health

Positive Quality Intervention: Toripalimab (Loqtorzi®) for Metastatic or Recurrent, Locally Advanced Nasopharyngeal Carcinoma

Description: The purpose of this PQI is to discuss clinical considerations for the use of toripalimab (Loqtorzi®) for treatment of recurrent, locally advanced nasopharyngeal carcinoma or metastatic nasopharyngeal carcinoma (RM-NPC).

Background:

Toripalimab is a humanized IgG4 monoclonal antibody against programmed death receptor-1 (PD-1). It is FDA approved in combination with cisplatin and gemcitabine as first-line treatment of adults with metastatic or with recurrent, locally advanced nasopharyngeal carcinoma (NCCN® Category 1-preferred first-line immunotherapy option). [1,2] Toripalimab is also approved as single agent therapy following disease progression on or after a platinum-containing chemotherapy for the treatment of adults with recurrent unresectable or metastatic NPC (NCCN® Category 2A-preferred subsequent-line immunotherapy).[1,2] NPC is a rare malignancy, occurring in less than 1 in every 100,000 people in the US each year. A significant proportion of NPC is related to prior Epstein-Barr Virus (EBV) infection. Therefore, in certain populations including those from Southeast Asia, the Middle East, and North Africa where EBV infection is endemic, the incidence is higher with up to 25 to 30 cases per 100,000 men and 15 to 20 cases per 100,000 women.[3]

Efficacy and safety of toripalimab has been studied in several clinical trials, including two pivotal trials, providing sufficient numbers for both safety and efficacy in recurrent, locally advanced or metastatic NPC. The international, multicenter, randomized, double-blind, phase 3 JUPITER-02 study was conducted in 289 patients in NPC-endemic regions, including mainland China, Taiwan, and Singapore. Patients with RM-NPC who were treatment naïve in the recurrent or metastatic setting were randomized (1:1) to receive toripalimab 240 mg IV (n = 146) or placebo (n = 143) in combination with gemcitabine and cisplatin for up to 6 cycles, followed by maintenance with toripalimab or placebo until disease progression, intolerable toxicity, or completion of 2 years of treatment. At final progression-free survival (PFS) analysis, toripalimab achieved a significantly longer PFS compared to the placebo group (median, 21.4 vs 8.2 months, respectively; HR, 0.52 [95% CI, 0.37-0.73]; P = 0.0003). The median overall survival (OS) was not reached in the toripalimab group, compared to 33.7 months in the placebo group (HR, 0.63 [95% CI, 0.45-0.89]; 2-sided P = .008). The most common adverse reactions when used in combination with chemotherapy include nausea (71%), vomiting (68%), decreased appetite (55%), constipation (39%), hypothyroidism (38%), rash (36%), pyrexia (32%), diarrhea (31%), and peripheral neuropathy (30%). The most common Grade 3 or 4 laboratory abnormalities were decreased neutrophils (58%), decreased lymphocytes (57%), decreased hemoglobin (50%), and decreased platelets (33%).[1,5]

POLARIS-02 was a single arm, phase II study which investigated toripalimab 3mg/kg IV once every 2 weeks in 190 patients with RM-NPC. Patients' disease was deemed refractory to standard chemotherapy or had progressed within 6 months after adjuvant chemotherapy or chemoradiotherapy. Treatment continued until disease progression, intolerable toxicity, or voluntary withdrawal of informed consent. The primary endpoint of overall response rate (ORR)was achieved in 20.5% of patients with a median duration of response (DOR) of 12.8 months, a median PFS of 1.9 months, and median OS of 17.4 months. PD-L1 status did not correlate with treatment response as ORRs were 27.1% and 19.4% in PD-L1 positive and PD-L1 negative patients, respectively (P = .31).[4] The most common adverse reactions include fatigue, hypothyroidism and musculoskeletal pain.

PQI Process:

Prior to therapy:

Written By: Shirin Khorashadi, PharmD, BCOP
and Deborah J. Wong, MD, PhD;
Hyu Kang, MD, MPH, FACP
Institution: UCLA Hematology and Oncology; UCSF Health

- Evaluate baseline labs including CBC with differential, liver function tests (AST, ALT, total bilirubin), creatinine, and thyroid function.
- Verify pregnancy status in women of reproductive potential.
    - Contraception is recommended during therapy and for 4 months after the last dose.
    - Breastfeeding is not recommended during therapy and for 4 months after the last dose.
- Identify patients with history of autoimmune disease requiring ongoing systemic immunosuppressive agents such as steroids (prednisone >10mg daily or equivalent) or previous solid organ or bone marrow transplant recipients (not included in clinical trials). Such patients should be carefully counseled and monitored regarding the risk of immune-mediated adverse events, transplanted organ rejection, and graft vs. host disease, respectively.
- Prescreen for HBV and HCV to assess the risk of reactivation and determine appropriate treatment and follow up.
- Assess cardiovascular risk factors and obtain baseline ECG, B-type natriuretic peptide, troponin, and baseline echocardiogram in high-risk patients who require long-term (>12 months) therapy.

Table 1. Toripalimab Recommended Dosage[1]

Indication	Recommended dose of toripalimab	Duration of treatment
First-line locally advanced, metastatic or recurrent NPC in combination with cisplatin and gemcitabine	240 mg IV every 3 weeks*	Until disease progression, unacceptable toxicity, or up to 24 months
Recurrent unresectable or metastatic NPC (previously treated)	3 mg/kg IV every 2 weeks	Until disease progression or unacceptable toxicity

*Given in combination with gemcitabine 1000 mg/m2 on days 1 and 8 and cisplatin 80 mg /m^2 on day 1 for up to six cycles, followed by toripalimab 240 mg every 3 weeks as maintenance thereafter.

Preparation and administration

- Toripalimab comes in 240mg/ 6mL single-dose vials
- Administer initial infusion intravenously over 60 minutes through line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter
    - Administer the drug alone. When administering in combination with chemotherapy, toripalimab should be administered prior to the chemotherapy.
- If no infusion-related reactions occur during the first infusion, subsequent infusions may be administered over 30 minutes.
- Follow the table below for guidelines regarding infusion-related adverse reaction, dosage reduction is not recommended

Table 2. Recommended adjustments for infusion-related reaction[1]

Grade 1 or 2 infusion-related reactions	Interrupt or slow the rate of infusion
Grade 3 or 4 infusion-related reactions	Stop infusion; permanently discontinue

Monitoring parameters during and after treatment with toripalimab:

- Monitor for signs and symptoms of immune-mediated reaction including pneumonitis, colitis, hepatitis,

Written By: Shirin Khorashadi, PharmD, BCOP
and Deborah J. Wong, MD, PhD;
Hyu Kang, MD, MPH, FACP
Institution: UCLA Hematology and Oncology; UCSF Health

endocrinopathies, diabetes, nephritis with renal dysfunction, ocular diseases, rash, exfoliative dermatologic conditions, myocarditis, neurologic toxicity, and solid organ transplant rejection.

- Continue to monitor liver function tests, creatinine, thyroid function, and blood glucose periodically (every 1-2 cycles of treatment).
- Consider cardiovascular risk assessment every 6 to 12 months for all patients on long-term therapy and refer to cardiologist as appropriate.
- Monitor for signs and symptoms of infusion-related reactions such as fever, chills, rigors, flushing, hypotension, and shortness of breath.

Table 3. Recommended Dosage Modifications for Immune Related Adverse Reactions (irAE)[1]

-irAE*	**Withhold toripalimab**	**Permanently discontinue toripalimab**
Pneumonitis	Grade 2**	Grade 3 or 4
Colitis	Grade 2 or 3**	Grade 4
Hepatitis with no hepatic tumor involvement	AST/ALT increase to > 3 x ULN to ≤ 8 x ULN or Total bilirubin > 1.5 x ULN to ≤ 3 x ULN**	AST/ALT increase to > 8 x ULN or Total bilirubin > 3 x ULN
Hepatitis with hepatic tumor involvement	Baseline AST/ALT > 1 x ULN to ≤ 3 x ULN and increases to > 5 X ULN up to 10 x ULN or Baseline AST/ALT > 3 x ULN to ≤ 5 x ULN and increases to > 8 x ULN up to 10 x ULN**	Baseline AST/ALT above ULN and increase to > 10 x ULN or Total bilirubin > 3 x ULN
Endocrinopathies	Grade 3 or 4 (until clinically stable)	If no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10mg per day or less within 12 weeks of initiating steroids
Nephritis with renal dysfunction	Grade 2 or 3 creatinine elevation	Grade 4 creatinine elevation
Exfoliative dermatologic conditions	Suspected SJS, TEN or DRESS	Confirmed SJS, TEN or DRESS
Myocarditis	N/a	Grade 2, 3 or 4
Neurological toxicities	Grade 2	Grade 3-4

*irAE: immune-related adverse event

**Resume after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no resolution within 12 weeks of initiating corticosteroids, or if unable to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of corticosteroid initiation

Written By: Shirin Khorashadi, PharmD, BCOP
and Deborah J. Wong, MD, PhD;
Hyu Kang, MD, MPH, FACP
Institution: UCLA Hematology and Oncology; UCSF Health

Patient-Centered Activities:

- Provide medication guide: https://loqtorzi.com/pdf/medication-guide.pdf
- Counsel patient on immune-related adverse event symptoms and when to report symptoms to oncologist and/or care team (see Supplemental Information)
    - Consider early initiation of steroids as necessary
- Schedule regular visits for blood tests (CBC w/ diff, renal function, hepatic function, thyroid function) and monitoring
- Patient Access support
    - For information about billing and coding, please call LOQTORZI Solutions™ at 1-844-483-3692
    - For-patient assistant program please refer to toripalimab solution enrollment form or contact LOQTORZI Solutions™

References:

1. Loqtorzi (toripalimab) [prescribing information]. Redwood City, CA. Coherus BioSciences, Inc.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancers V.3.2024.
3. Key Statistics for Nasopharyngeal Cancer. www.cancer.org. Retrieved August 27, 2024, from https://www.cancer.org/cancer/types/nasopharyngeal-cancer/about/key-statistics.html
4. Wang FH, et al. Efficacy, Safety, and Correlative Biomarkers of Toripalimab in Previously Treated Recurrent or Metastatic Nasopharyngeal Carcinoma: A Phase II Clinical Trial (POLARIS-02). J Clin Oncol. 2021 Mar 1;39(7):704-712. doi: 10.1200/JCO.20.02712. Epub 2021 Jan 25.
5. Mai HQ, et al. Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomized Clinical Trial. JAMA. 2023 Nov 28;330(20):1961-1970. doi: 10.1001/jama.2023.20181.

Supplemental Information:

Table 4. Adverse events patient should report to the healthcare team[1]

Lung problems • Cough • Shortness of breath • Chest pain	
Intestinal problems • Diarrhea • Stools that are black, tarry, sticky, or have blood or mucus • Severe abdominal pain or tenderness	
Liver problems • Yellowing of the skin or whites of eyes • Severe nausea or vomiting • Right-sided abdominal pain	• Dark urine (tea colored) • Bleeding or bruising more easily
Hormone gland problems • Headaches that won't go away • Eye sensitivity to light	• Notable weight gain or loss • Increased hunger or thirst

Written By: Shirin Khorashadi, PharmD, BCOP
and Deborah J. Wong, MD, PhD;
Hyu Kang, MD, MPH, FACP
Institution: UCLA Hematology and Oncology; UCSF Health

• Rapid heartbeat • Extreme fatigue	• Increase urination • Dizziness or fainting
Kidney problems	
• Decrease in amount of urine • Blood in urine	• Swelling in ankles • Loss of appetite
Skin problems	
• Rash • Itching • Skin blistering or peeling	• Painful sores or ulcers in mouth or nose or throat • Fever or flu-like symptoms • Swollen lymph nodes