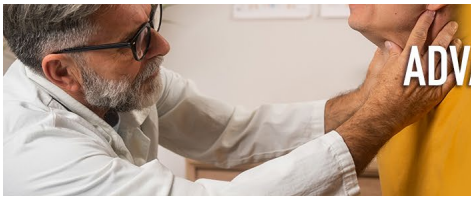

ADVANCES IN RECURRENT / METASTATIC NASOPHARYNGEAL CARCINOMA: IMMUNOTHERAPY AND BIOMARKERS

Editor's Note: This is a transcript of an online course released in September 2024.
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Module 1: Patient Selection and Treatment Considerations for Currently Approved Therapies

Nasopharyngeal carcinoma (NPC) is a rare head and neck cancer. In most parts of the world, the annual incidence of NPC is less than 1 case per 100,000 people. However, the rate is as high as 20 cases per 100,000 people in Southeast Asia and Southern China. Other areas with higher NPC rates include the Middle East, North Africa, and the Arctic.[1]

Risk factors for development of NPC include Epstein-Barr virus (EBV) infection, smoking, alcohol, and intake of salt-preserved foods such as fish.[2,3] EBV is a particularly important risk factor; NPC risk appears to increase as EBV antibody levels increase.[2] In regions where NPC is endemic, EBV contributes to 95% of NPC incidences compared to 20% in non-endemic areas.[4] Men are 2 to 3 times more likely to develop NPC than women. NPC risk slowly increases with age, but can occur at any age. In areas where NPC incidence is high, peak age at diagnosis is between 45 and 59 years. In areas with lower incidence, cases more often occur in young adults (age 15 to 24 years) and then peak again at ages 65 to 79 years.[1] Overall, NPC incidence and mortality rates in most countries have decreased over the past decades, likely due to environmental and lifestyle changes.[1] However, incidence and mortality rates are expected to increase by 35% and 42%, respectively, by the year 2040 in Southeastern Asia and China, primarily due to population growth and aging.[2]

Due to its location and non-specific clinical presentation, NPC is most often diagnosed at the locally advanced or metastatic stage, with up to 15% diagnosed with distant metastatic disease.[3,5,6] Early stage and locally advanced, non-metastatic NPC generally carry a good prognosis, with 5-year survival rates of 82% and 72%, respectively.[7] Treatment typically includes radiation alone in earlier stages and concurrent chemoradiation with or without adjuvant or induction chemotherapy in more advanced stages.[8] However, 10% to 20% of patients experience recurrence after initial treatment with resulting poor prognosis.[9,10] For patients with distant recurrence and metastatic disease, the median overall survival is approximately 20 months, with a 5-year survival rate of less than 40%.[5,11]

Standard first-line treatment for inoperable/recurrent and metastatic disease includes platinum doublet chemotherapy, with the combination of cisplatin/gemcitabine as the preferred regimen.[12,13] The duration of response is an average of 7 months.[14] There isn't a standard treatment option after progression on chemotherapy; current options include single agent chemotherapy or immunotherapy.[13]

The tumor microenvironment of NPC consists of high expression of programmed death ligand 1 (PD-L1) and abundant lymphocytic infiltration. Consequently, there is a strong biologic rationale for incorporating immunotherapy in NPC treatment.[15] PD-L1 and programmed cell death protein 1 (PD-1) are checkpoint proteins; PD-L1 is found on tumor cells and activated immune cells and PD-1 is found on T cells and natural killer (NK) cells. Binding of PD-1 to PD-L1 stops the immune system from attacking tumor cells. Blocking the binding of these two checkpoint proteins by either PD-1 or PD-L1 inhibition restores immune function and allows T cells to destroy tumor cells (Click for PD-1 inhibitor mechanism of action).[16]

Toripalimab-tpzi is a PD-1-blocking antibody that binds to a different site on PD-1 compared to other PD-1 inhibitors, allowing for potentially stronger inhibition.[17] Toripalimab is the first FDA-approved immunotherapy for NPC and is approved for use in combination with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced NPC.[18] The approval of toripalimab for first-line treatment of NPC in combination with cisplatin and gemcitabine was based on the results of the JUPITER-02 trial in which patients were randomized to receive toripalimab or placebo in combination with gemcitabine and cisplatin for 6 cycles, followed by maintenance with toripalimab or placebo until disease progression, intolerable toxicity, or completion of 2 years of treatment. The primary outcome of progression-free survival (PFS) was significantly longer in the toripalimab group compared to placebo **(Table 1)**. Overall survival was also significantly improved in the toripalimab group.[19] Camrelizumab and tislelizumab are additional investigational PD-1 inhibitors being studied in the first-line setting for recurrent/metastatic NPC in combination with gemcitabine and cisplatin with preliminary results showing improved PFS and objective response rate (ORR) compared to placebo.[20,21] (**Table 1**) These trials are ongoing, but both agents are now approved in China for recurrent/metastatic NPC.[22]

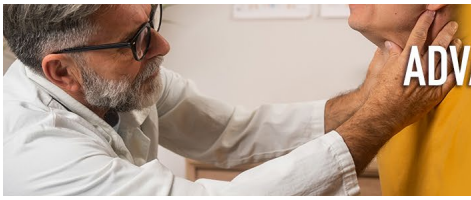

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Table 1. Summary of Clinical Trials Assessing Immunotherapy in Combination with Chemotherapy in Recurrent/Metastatic NPC

First-line setting					
Clinical trial	**Intervention**	**Comparator**	**Median follow-up**	**Primary outcome**	**Secondary outcomes**
JUPITER-02[19]	Toripalimab + gemcitabine/ cisplatin→ toripalimab maintenance	Placebo + gemcitabine/ cisplatin→ placebo maintenance	36 mos	**PFS** 21.4 vs 8.2 mos (HR 0.52 [95% CI 0.37-0.73], *P*<0.001)	**ORR** 78.8% vs 67.1% (*P*=0.02)
					OS NR vs 33.7 mos (HR 0.63 [95% CI, 0.45-0.89], *P*=0.008)
CAPTAIN-1st[20]	Camrelizumab + gemcitabine/ cisplatin→ camrelizumab maintenance	Placebo + gemcitabine/ cisplatin→ placebo maintenance	10.2 mos	**PFS** 9.7 vs 6.9 mos (HR 0.54 [95% CI 0.39-0.76], *P*=0.0002)	**ORR** 87.3% vs 80.6%
					***OS**
RATIONALE-309[21]	Tislelizumab + gemcitabine/ cisplatin→ tislelizumab maintenance	Placebo + gemcitabine/ cisplatin→ placebo maintenance	15.5 mos	**PFS** 9.6 vs 7.4 mos (HR 0.50 [95% CI 0.37-0.68, *P*<0.0001])	**ORR** 69.5% vs 55.3%
					****OS** NR vs 23 mos (HR 0.60 [95% CI 0.35-1.01]

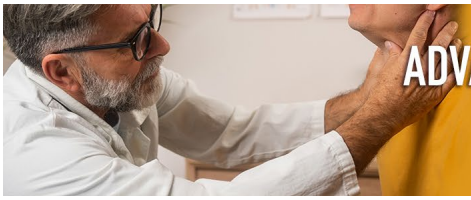
NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
*Results are too immature to report at this time.**Preliminary OS results.

Toripalimab also received approval as monotherapy for adults with recurrent unresectable or metastatic NPC with disease progression on or after platinum-containing chemotherapy.[23] This approval was based on the results of the POLARIS-02 trial. The primary efficacy outcome of ORR was 20.5% with toripalimab. Secondary efficacy outcomes were significantly better with toripalimab, with a median duration of response of 12.8 months, median PFS of 1.9 months, and median OS of 17.4 months.[24] Toripalimab is now an NCCN category 1 preferred regimen when used in combination with cisplatin and gemcitabine for first-line treatment of recurrent or metastatic disease and as a single agent for subsequent-line treatment.[13]

The substitution of other PD-1 inhibitors for toripalimab is controversial.[12] The NCCN guidelines allow for the use of pembrolizumab or nivolumab in combination with cisplatin and gemcitabine based on extrapolation from results of the JUPITER-02 trial and ongoing trials with other investigational anti-PD1 antibodies.[13,19–21] Treatment with pembrolizumab or nivolumab in combination with gemcitabine and cisplatin are NCCN category 2A recommendations, while first-line treatment with toripalimab in combination with chemotherapy is an NCCN category 1 recommendation. Nivolumab and pembrolizumab are also options as monotherapy for subsequent-line treatment options.[13] Both have been studied independently as subsequent therapy in nonrandomized studies with response rates of 20% to 25%, similar to toripalimab.[25–27] The controversy of substitution for toripalimab will likely remain as more PD-1 inhibitors are studied in the subsequent-line setting. In the KEYNOTE-122 trial, pembrolizumab failed to show superiority over chemotherapy in the second-line platinum pre-treated setting.[28] In patients who are not tumor mutational burden-high (TMB-H), pembrolizumab and nivolumab are both considered NCCN category 2B recommendations for subsequent treatment in specific scenarios, while toripalimab is considered a preferred category 2A recommendation.[13]

Module 1 Key Concepts:

- Addition of immunotherapy to first-line cisplatin/gemcitabine in patients with recurrent/metastatic NPC significantly improves progression-free survival.
- Toripalimab is the first and only PD-1 inhibitor approved in combination with gemcitabine and cisplatin for the first-line treatment of adults with metastatic or recurrent, locally advanced NPC, as well as monotherapy for adults with recurrent unresectable or metastatic NPC with disease progression on or after platinum-containing chemotherapy.
- Substitution of other PD-1 inhibitors (nivolumab, pembrolizumab) for toripalimab can be considered, although the evidence for use of these agents with chemotherapy is not as strong as with toripalimab.



ADVANCES IN RECURRENT / METASTATIC NASOPHARYNGEAL CARCINOMA: IMMUNOTHERAPY AND BIOMARKERS

Module 2: Use of Biomarkers

EBV plays an important role in the development, prognosis, and progression of NPC.[29] Plasma EBV DNA has been used as an indicator of response to induction chemotherapy or radiation and for residual disease monitoring.[13] For patients with locally advanced NPC, high initial levels of plasma EBV or persistently elevated levels near or at the end of induction chemotherapy or definitive treatment are associated with significantly poorer outcomes, including increased mortality and distant metastasis.[13,30] A new emphasis has been placed on designing NPC clinical trials that incorporate an EBV DNA assay as part of the trial design to define disease burden and tailor the therapeutic strategy.[15]

For patients with nonkeratinizing or undifferentiated histology, EBV testing via tumor or blood can be considered during the initial work-up. Testing methods include in situ hybridization (ISH) for EBV-encoded RNA (EBER) and immunohistochemical staining for latent membrane protein (LMP). ISH for EBER tends to be more sensitive than LMP. Evaluation of EBV DNA load may be quantified using PCR targeting of EBV DNA with tests such as Bam HI-W, Epstein-Barr virus nuclear antigen (EBNA), or LMP. Some centers use EBV DNA levels to determine prognosis and monitor residual disease.[13] However, there are no standardized testing recommendations for EBV DNA and little consensus exists on sample preparation, assay specifications, and cutoffs.[13,15]

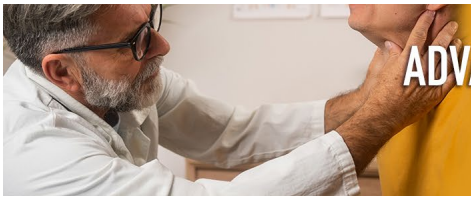
Human papillomavirus (HPV) infection has been associated with NPC in case studies and small case series. HPV-associated NPC appears to have better local control and survival prognosis than non-virally associated NPC. However, current data is limited and conflicting regarding its impact on treatment outcomes. Routine HPV testing is not currently recommended by the NCCN guidelines.[13]

There are no well-established biomarkers for immunotherapy in NPC. The predictive value of PD-L1 expression and tumor mutational burden (TMB) is also unclear in this disease.[29] Pembrolizumab is listed as a category 2A option in the NCCN guidelines for patients with metastatic NPC with previously treated tumor mutational burden-high (TMB-H) disease based on the results of the KEYNOTE-158 trial. It should be noted, however, that no patients with NPC were included in KEYNOTE-158.[13,31] In the JUPITER-02 trial, OS results were consistent, regardless of PD-L1 expression. However, more patients in the toripalimab group experienced EBV DNA copy number reduction to an undetectable level compared with placebo. In addition, fewer patients experienced EBV DNA copy number rebound, consistent with the higher percentage of patients treated with toripalimab that achieved long-term clinical benefits. In this study, EBV DNA copy number rebound preceded disease progression by a median of 1.9 months, suggesting that EBV DNA copy number rebound may be used to predict disease progression.[19] In the POLARIS-02 trial, patients with PD-L1 positivity had a numerically, but not statistically, better ORR (27.1% vs 19.1%). TMB also had no predictive value for response. However, patients with a lower EBV baseline titer (<10,000 IU/mL) had a numerically higher, but not statistically significant, ORR than those with higher baseline titers. In addition, patients with a ≥50% decrease in EBV DNA copy number from baseline to day 28 had a significantly better ORR than those with a <50% decrease (48% vs 5.7%). Lastly, patients who initially responded to toripalimab, but later had disease progression, had at least a 100% plasma EBV titer increase occurring at a median of 3 months before radiographic identification of disease progression. The JUPITER-02 and POLARIS-02 results support the positive association of plasma EBV DNA copy number reduction with improved disease control with immunotherapy.[24]

A recent systematic review and meta-analysis confirmed that patients with NPC and lower plasma EBV DNA level had higher ORR and longer median PFS.[29] Moreover, those with post-treatment EBV DNA decreases correlated with a better response to immunotherapy. However, PD-L1 expression and TMB did not correlate with clinical outcomes.[29] Clinical studies are also evaluating whether treatment can be adapted based on clinical efficacy and EBV DNA response in patients with locally advanced NPC.[32]

Module 2 Key Concepts

- Higher EBV DNA levels at diagnosis and at the end of treatment are associated with significantly poorer outcomes including increased mortality and distant metastases; however, there are currently no standardized testing recommendations.
- There is currently no clear role for HPV, PD-L1, or TMB testing in patients with NPC.

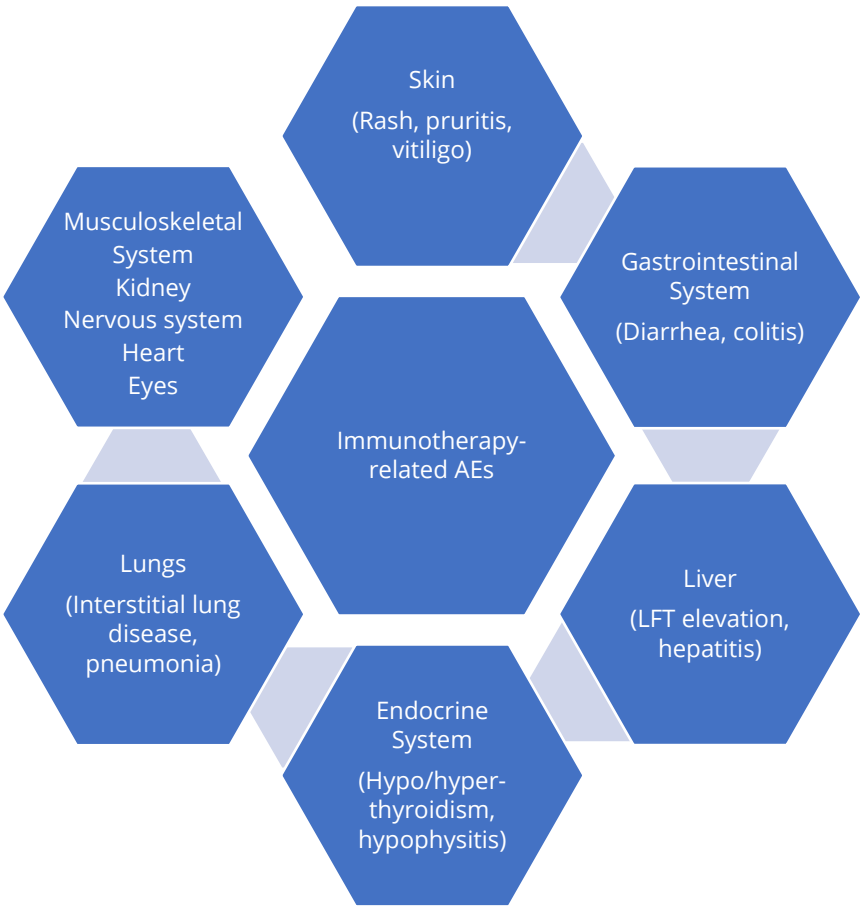


ADVANCES IN RECURRENT / METASTATIC NASOPHARYNGEAL CARCINOMA: IMMUNOTHERAPY AND BIOMARKERS

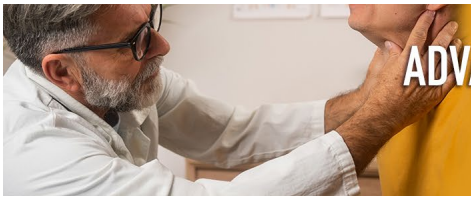
Module 3: Toxicity Monitoring

Although immunotherapy is perceived as less toxic than chemotherapy, it comes with its own set of unique toxicities called immune-related adverse events (irAEs). These irAEs occur as a result of uncontrolled activation of T cells, resulting in inflammation.[33] In addition, combining immunotherapy with chemotherapy presents an added challenge in differentiating between chemotherapy- and immunotherapy-related AEs. PD-1 inhibitor-related side effects can affect any organ in the body, although the gastrointestinal tract, skin, liver, lungs, and endocrine system are most often affected.[34] (**Figure**). In general, the reported overall incidence of any-grade irAE with PD-1/PD-L1 inhibitors is up to 30% based on reports from phase III trials. In addition, a meta-analysis of anti-PD-1/PD-L1 agents reported the incidence of any-grade irAEs at 26.8% and grade 3 irAEs at 6.1%.[33,35]

Figure. Immunotherapy-Related Adverse Events (irAEs) Associated with PD-1 Inhibitor Treatment



In the JUPITER-02 trial, addition of toripalimab to chemotherapy did not increase the incidence of all adverse events (AEs) or grade ≥3 AEs, however, the incidence of irAEs was increased in the toripalimab group.[19] IrAEs occurred in 54.1% of patients treated with toripalimab compared to 21.7% of patients in the placebo group. Toripalimab caused irAEs such as pneumonitis, colitis, hepatitis, dermatitis, and hypothyroidism. IrAEs seen more often with toripalimab included hypothyroidism, upper respiratory tract infections, and pneumonia. Grade ≥3 AEs occurred in 9.6% of patients who received toripalimab compared to 1.4% of patients who received placebo.[18,19] In the POLARIS-02 trial, treatment-related adverse events (TRAEs) occurred in 74% of patients treated with toripalimab. The main TRAEs included hypothyroidism (23.7%), hyperthyroidism (2.6%), abnormal liver function (1.6%), interstitial lung disease (1.6%), dermatomyositis (0.5%), and autoimmune myocarditis (0.5%). Grade 3-5 TRAEs occurred in 14% of patients.[24] In general, addition of a PD-1 inhibitor to chemotherapy has resulted in a manageable safety profile, with reported toxicities in line with expected irAEs.[36]



Guidelines are available on the appropriate management of patients who experience irAEs. Depending on the grade of the irAE, typical management includes temporary or permanent suspension of the PD-1 inhibitor and administration of corticosteroids or other immunosuppressive therapy such as infliximab, vedolizumab, mycophenolate mofetil, intravenous immunoglobulin (IVIG), and plasmapheresis. Select endocrinopathies often can be managed with hormone replacement without the need for immunosuppression.[13,34]

Immune-related toxicities require multidisciplinary management to facilitate early detection and diagnosis, which are critical to successful patient management. Diagnosis and management of certain irAEs may require the input of non-oncology specialists such as dermatologists, endocrinologists, gastroenterologists, and pulmonologists (**Figure**). Nurses and pharmacists can play a key role in patient education on irAEs. Patient education can improve patient adherence by decreasing anxiety, incorporating the patient as an active participant in their own care, and educating patients on symptom management. The involvement of non-oncology specialists may be particularly helpful for patients with high-risk features like pre-existing autoimmune disorders, organ transplant, or who have a history of irAEs. The management of patients with severe irAEs requires adoption of standardized treatment protocols and close collaboration among ICU clinicians, organ specialists, and oncologists to ensure optimal patient outcomes. In the case of irAE-induced organ failure, ICU admission should be considered due to potential for reversal with treatment.[37] Institutions have implemented successful multidisciplinary consult teams dedicated to guiding clinical care, distributing knowledge to providers less familiar with irAEs, and standardizing irAE management.[38]

Module 3 Key Concepts

- Toripalimab does not increase the risk of overall AEs or grade ≥3 AEs when added to chemotherapy; however, rates of irAEs such as hypothyroidism are higher.
- The management of patients who experience an irAE includes temporary or permanent discontinuation of the PD-1 inhibitor and initiation of corticosteroids or other immunosuppressive therapy. Interprofessional, multidisciplinary management of irAEs can aid in early detection and optimal treatment of irAEs.

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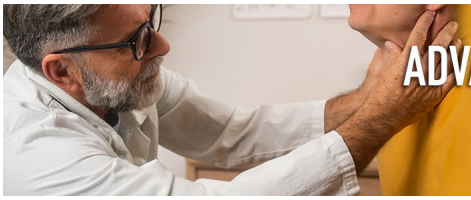

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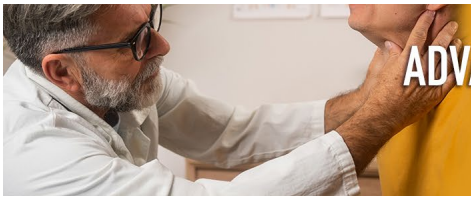

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