Advances in immunotherapy and targeted therapy for nasopharyngeal carcinoma: Current progress and combined approaches (Review)

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Abstract. Nasopharyngeal carcinoma (NPC), a malignancy of the head and neck closely associated with Epstein-Barr virus (EBV) infection, is highly prevalent in southern China and Southeast Asia. Traditional treatments such as radiotherapy and chemotherapy have notable limitations in the management of locally advanced, recurrent or metastatic cases. Previously, immunotherapies, such as PD-1/PD-L1 inhibitors and targeted therapies, including EGFR and VEGF inhibitors, have emerged as breakthroughs in the treatment of NPC. The synergistic effects of combining these therapies have become a prominent area of research. While existing reviews have discussed the progress in immunotherapy and targeted therapy, most focus on single therapeutic modalities and lack a systematic integration of the latest clinical data and emerging treatment approaches. The present review discussed recent clinical trial results, focusing on the synergistic mechanisms of combined immunotherapy and targeted therapy, while also exploring the predictive value of EBV-associated biomarkers. Additionally, it described cutting-edge developments such as bispecific antibodies and antibody-drug conjugates. The present article provides a comprehensive analysis of the mechanisms, clinical advancements, efficacy and safety of immunotherapy, targeted therapy and their combination in NPC, highlighting current challenges and future directions to offer precise guidance for personalized clinical treatment.

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Contents

1. Introduction

Nasopharyngeal carcinoma (NPC) is an aggressive malignancy of the head and neck closely associated with Epstein-Barr virus (EBV) infection (1), characterized by notable geographical variation. It is particularly prevalent in East and Southeast Asia, with southern China being a high-incidence region (2). Among the pathological subtypes, EBV-associated non-keratinizing squamous cell carcinoma accounts for >95% of cases in endemic areas (3), making it the primary focus of clinical treatment. In 2022, >120,000 new cases and >70,000 deaths were reported globally (4). Although the incidence of NPC has gradually declined worldwide over the past few decades, and the 5-year overall survival (OS) rate for early-stage patients has reached 94.0% (5), the deep anatomical location and non-specific clinical manifestations of the disease often result in the majority of patients being diagnosed at an advanced stage. This leads to poor prognosis, with recurrence and distant metastasis being the leading causes of death. NPC is relatively sensitive to radiotherapy and chemotherapy, with a

combination of synchronous chemoradiotherapy (CRT) being the standard treatment modality. However, some patients still experience local recurrence or distant metastasis due to radiation resistance, chemotherapy resistance or other factors. The rate of distant metastasis in newly diagnosed patients with NPC is 6-15%, and ~20% of patients with non-metastatic NPC will eventually experience recurrence or metastasis after definitive treatment (6,7). In recent years, the gemcitabine + cisplatin (GP) regimen has been recommended by major guidelines as the first-line standard treatment for recurrent and metastatic NPC (8). However, its clinical efficacy remains limited, with median progression-free survival (mPFS) and median OS (mOS) of only 7.0 and 22.1 months, respectively (6,9). Recently, the clinical breakthrough of immune checkpoint inhibitors (ICIs) and the precise development of targeted therapies have transformed the treatment landscape for NPC (10-13), offering the potential for survival improvement. Combined therapeutic strategies, particularly immunotherapy in combination with targeted therapy or chemotherapy, have demonstrated substantial synergistic potential, emerging as a key area of research in the field. However, existing reviews primarily focus on the clinical data of individual treatment modalities, offering limited in-depth analysis of the synergistic mechanisms underlying combination therapies. Furthermore, there is a lack of comprehensive integration of the latest clinical evidence, such as bispecific antibodies, antibody-drug conjugates (ADCs) and the translational challenges associated with their clinical application. The present review systematically summarized the breakthroughs in basic research, clinical evidence progress and translational application challenges in the fields of targeted therapy and immunotherapy for recurrent/metastatic NPC (R/M-NPC), with a focus on innovative combination therapies, providing novel ideas and approaches for the effective treatment of R/M-NPC in clinical practice.

2. Immunotherapy

Tumor immunotherapy is a novel strategy that aims to control and eliminate tumor cells by activating or maintaining immune cycles and restoring normal antitumor immune responses. In recent years, with the in-depth understanding of tumor immunology and breakthroughs in immune regulation technologies, immunotherapy has become a key pillar in the comprehensive treatment of NPC (14). At present, immunotherapy for NPC mainly focuses on immune checkpoint blockade therapies (such as PD-1/PD-L1 inhibitors), adoptive immune cell therapy (such as EBV-targeted CAR-T cells), cytotoxic T lymphocyte antigens, therapeutic vaccines [peptide vaccines targeting EBV latent membrane proteins (LMPs)] and immune modulation strategies. These approaches function by reshaping the antitumor immune responses of the body and overcoming tumor immune escape mechanisms, demonstrating notable efficacy in the translational treatment of R/M-NPC and locally advanced NPC.

3. PD-1/PD-L1 inhibitors

PD-1 is a membrane-bound receptor primarily expressed on the surface of immune cells such as T cells and B cells. It plays a crucial role in inhibiting T cell-mediated inflammatory responses and modulating cellular reactions to maintain immune homeostasis and promote self-tolerance. PD-L1, the ligand for PD-1, is predominantly found on the surface of tumor cells, certain immune cells and some non-immune cells. The interaction between PD-1 and PD-L1 leads to the downregulation of $CD8^+$ T lymphocyte and $CD4^+$ T lymphocyte activity via the PD-1/PD-L1 pathway, inhibiting their proliferation and ultimately suppressing their effector function within the tumor microenvironment (TME) (15). This results in diminished immune-mediated tumor cell elimination and facilitates immune evasion by the tumor.

PD-1 inhibitors primarily exert their antitumor effects by blocking the PD-1/PD-L1 signaling pathway, thereby reactivating T cell-mediated antitumor immunity. On one hand, PD-1 inhibitors specifically bind to the PD-1 molecules on the surface of T cells via their antigen-binding fragments (Fig. 1). By occupying the ligand-binding site of PD-1, these inhibitors prevent the interaction between PD-1 and PD-L1 on tumor cells, thereby disrupting the inhibitory signals transmitted through this pathway. On the other hand, once the inhibitory signals are removed, activated T cells regain proliferative capacity and secrete large amounts of cytokines such as IFN-γ and TNF-α, which directly attack tumor cells. Furthermore, activated T cells can also stimulate other immune cells, leading to a broader immune response aimed at eradicating tumor cells.

Toripalimab. Toripalimab is a recombinant humanized PD-1 monoclonal antibody, which was approved in China in 2021 and later by the US Food and Drug Administration and European Medicines Agency for the treatment of R/M-NPC. Multiple studies have demonstrated the promising application of toripalimab in locally advanced or R/M-NPC. A Phase II clinical trial investigating toripalimab in combination with concurrent CRT during the neoadjuvant and adjuvant phases for locally advanced NPC found that, compared with the placebo group receiving only CRT, the toripalimab combination group showed higher 2-year PFS (16). This suggests that early intervention with immunotherapy may reduce the risk of recurrence by activating antitumor immunity. This approach offers a novel immuno-enhancing strategy for patients with locally advanced NPC. In R/M-NPC, a Phase III trial (JUPITER-02) with 3-year survival follow-up showed that the mPFS for the toripalimab combined with gemcitabine and cisplatin (GP regimen) group was 21.4 months, extending by 13.2 months (21.4 vs. 8.2 months) (17). This result directly facilitated its approval by regulatory agencies in the U.S., China and Europe, establishing immune combination chemotherapy as the first-line standard treatment for R/M-NPC.

Camrelizumab. Camrelizumab is a humanized high-affinity anti-PD-1 immunoglobulin G4-k monoclonal antibody that has shown promising clinical potential in locally advanced or R/M-NPC. The Chinese Society of Clinical Oncology guidelines have approved camrelizumab in combination with chemotherapy as first-line treatment. In the Phase III CAPTAIN-1st study, adding camrelizumab to cisplatin and gemcitabine notably extended the PFS (9.7 vs. 6.9 months) (18). The key mechanism of action lies in the inhibition of myeloid-derived suppressor cells (MDSCs),

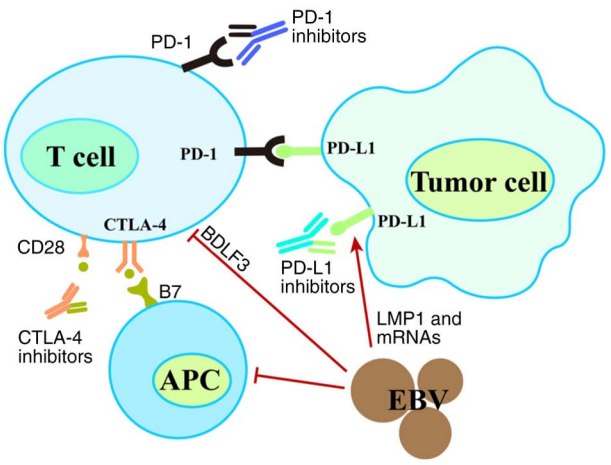

Figure 1. PD-1 binds to PD-L1, and through the PD-1/PD-L1 pathway, it reduces T lymphocyte activity and inhibits their proliferation, thereby suppressing the functional role of T lymphocytes in the tumor microenvironment. PD-1 inhibitors, by specifically recognizing and binding to PD-1 molecules on the surface of T cells via their antigen-binding fragment, and PD-L1 inhibitors, which bind to PD-L1 molecules on tumor cells, both disrupt the inhibitory signals transmitted through this pathway, thereby restoring the ability of T cells to kill tumor cells. CTLA-4 inhibitors bind to CTLA-4 on T cells, blocking the interaction between CTLA-4 and its ligand B7, thereby enhancing T cell activation and proliferation. The EBV can use BDLF3, which interferes with antigen presentation by both MHC-I and MHC-II, limiting T cell-mediated immune recognition. Viral proteins such as LMP1 and microRNAs induce PD-L1 expression, which binds to PD-1 on T cells, reducing their antitumor and antiviral responses. CTLA-4, cytotoxic T lymphocyte antigen 4; APC, antigen-presenting cell; EBV, Epstein-Barr virus; PD-(L)1, programmed cell death (ligand) protein type 1.

promotion of dendritic cell (DC) maturation and reduction of the immunosuppressive TME, which enhances the release of tumor antigens and provides additional recognition targets for camrelizumab-activated T cells, thereby augmenting antitumor efficacy. Furthermore, in the context of locally advanced NPC, the DIPPER study demonstrated that, after a median follow-up of 39 months, camrelizumab combined with the GP chemotherapy regimen exhibited superior antitumor activity and safety compared with GP chemotherapy alone (19). Compared with traditional concurrent CRT, this combination enhances tumor cell sensitivity to radiation while avoiding the risk of severe hematologic toxicity and radiation-induced mucositis, offering a safer treatment option for elderly patients or those with comorbidities who are intolerant to high-intensity therapies.

Tislelizumab. Tislelizumab is a humanized IgG4 anti-PD-1 monoclonal antibody that has demonstrated promising antitumor efficacy across a variety of malignancies. It has been approved in China for the treatment of multiple cancer types (20). In a Phase III trial (RATIONALE 309) evaluating its efficacy in untreated R/M NPC (21), the combination of tislelizumab with gemcitabine and cisplatin was compared with placebo with gemcitabine and cisplatin. In an interim analysis, the combination of tislelizumab and chemotherapy significantly prolonged PFS compared with placebo with chemotherapy. Furthermore, after progression, second-line therapy results demonstrated favorable trends for both PFS and OS in the tislelizumab combination group vs. the placebo group. The aforementioned study suggested that the combination of tislelizumab with chemotherapy substantially reduces the risk of disease progression or death, with a tolerable safety profile, offering the potential for maximum clinical benefit to patients.

Sintilimab. Sintilimab is a highly selective, fully humanized anti-PD-1 monoclonal antibody that has shown efficacy in various solid tumors (22). A recent Phase III clinical trial in China (23) found that in patients with locally advanced NPC, sintilimab combined with chemotherapy resulted in a higher PFS rate compared with the standard treatment group. However, the sintilimab group also exhibited a higher incidence of grade 3-4 adverse events. Therefore, further trials with longer follow-up are required to validate the efficacy and safety profile of sintilimab. Additionally, considerable gaps remain in the clinical exploration of sintilimab, with its indications currently limited to locally advanced NPC. Efficacy data in R/M-NPC are sparse, with only small-sample Phase II single-arm studies available. In addition, there is a lack of head-to-head comparisons with the standard GP regimen or other PD-1 inhibitors.

Nivolumab. Nivolumab is a humanized IgG4 monoclonal antibody that inhibits the PD-1 receptor on T cells, preventing its interaction with PD-L1. In the treatment of R/M-NPC, nivolumab has demonstrated considerable activity, with a superior 1-year OS rate compared with historical data from similar populations (24). A study has shown that nivolumab offers a novel treatment option for patients with platinum-resistant R/M-NPC, with a high disease control rate (DCR) and manageable safety profile (25). However, existing data mainly consist of single-arm trials with small sample sizes, making it difficult to exclude baseline differences in patient characteristics that may influence survival benefits. As such, the real-world efficacy of nivolumab in R/M-NPC requires further validation through larger cohort studies. A recent Phase II trial with long-term follow-up data has shown that nivolumab, in combination with induction chemotherapy and radiotherapy, provides effective antitumor activity with lower toxicity, offering a new combination strategy for locally advanced NPC treatment (26).

Pembrolizumab. Pembrolizumab is a humanized monoclonal IgG4 antibody that binds to the PD-1 receptor and effectively blocks its interaction with the ligand. Pembrolizumab shows promise in NPC treatment. In the Phase Ib KEYNOTE-028 study, which primarily targeted patients with multiple prior treatment failures, pembrolizumab demonstrated preliminary antitumor activity (27), providing a novel potential treatment option for patients that are chemotherapy-resistant. By contrast, in the Phase III KEYNOTE-122, which focused on patients with R/M-NPC who had failed platinum-based chemotherapy, pembrolizumab monotherapy did not show a significant difference in efficacy compared with single-agent chemotherapy (28). The differences in the efficacy results between these two studies can largely be attributed to variations in the study populations and sample sizes. KEYNOTE-028 included patients who had failed multiple lines of treatment, with a small sample size of just 27 patients, and its survival

benefits lack confirmation from large-scale real-world data. By contrast, KEYNOTE-122 was a Phase III confirmatory trial with a sample size of 233 patients, covering a broader clinical population with increased heterogeneity. The results of KEYNOTE-122 are therefore more reflective of the real-world clinical scenario and offer a more accurate assessment of the general efficacy of pembrolizumab.

KL-A167. KL-A167 is an innovative, humanized anti-PD-L1 monoclonal antibody developed in China. It has been approved by the National Medical Products Administration for treating patients with R/M-NPC who have failed second-line chemotherapy or beyond. Through targeted mutation technology for Fc segment optimization, KL-A167 eliminates ADCC and CDC effects, providing advantages such as higher stability and reduced immune evasion. A Phase II study showed that in patients with R/M-NPC who had received multiple lines of treatment and had a high tumor burden (43.9% liver with metastasis, 31.8% with ≥3 lines of chemotherapy failure), KL-A167 monotherapy achieved an overall response rate (ORR) of 26.5%, with a mPFS of 2.8 months and OS of 16.2 months, while maintaining a favorable safety profile (29). A recent secondary analysis of the aforementioned study (30,31) revealed that patients with non-liver metastasis had significantly longer PFS and OS compared with patients with liver metastasis. This finding is noteworthy, as patients with liver metastasis typically have a lower response rate to immunotherapy. However, these studies remain in the preliminary validation phase, with the existing Phase II design being a single-arm trial lacking head-to-head comparison with standard later-line treatments. This limits the ability to definitively determine its relative efficacy advantage. Furthermore, the small sample size may lead to an overestimation of efficacy. A Phase III study is currently underway and will provide further data for validation.

PD-1/PD-L1 inhibitors, when used as monotherapy or in combination with chemotherapy, CRT or as adjuvant treatment in R/M-NPC, have shown notable improvements in ORR, PFS and OS, with manageable safety profiles. The clinical trial results related to PD-1/PD-L1 inhibitors are shown in Table I. PD-1/PD-L1 inhibitors are progressively becoming central to the treatment of NPC, and combination strategies have substantially improved prognosis.

4. Cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitors

CTLA-4 is a crucial inhibitory ligand found on effector T cells. The binding of CD28 typically promotes T cell activation and proliferation (Fig. 1). After T cell activation, the expression of CTLA-4 increases, and it suppresses T cell effector functions by inhibiting CD28 receptor signaling, thereby regulating the immune response (32). The inhibitory signals of CTLA-4 are transmitted through the binding of B7-1 (CD80) and B7-2 (CD86) to antigen-presenting cells. In addition to blocking co-stimulation, CTLA-4 is also critical for T cell proliferation and NK-based cytotoxic functions. Therefore, by blocking CTLA-4 with high-affinity anti-CTLA-4 antibodies, CTLA-4 signaling can be inhibited, which enhances T cell-mediated elimination of cancer cells, promotes T cell activation and improves immune responses against cancer (33).

Ipilimumab, an anti-CTLA-4 antibody, can bind to CTLA-4 and block its interaction with its ligands, CD80/CD86, thereby enhancing T cell activation and proliferation. A study has shown that ipilimumab, in combination with nivolumab, also exhibits activity in patients with R/M-NPC who have previously received first-line combination chemotherapy (34). Subsequent studies revealed that ipilimumab treatment led to increased expression of PD-L1/PD-L2 in tumors and greater T cell infiltration, along with reduced stromal and malignant cell components (35). This suggests that ipilimumab may induce remodeling of the tumor and immune microenvironment, potentially enhancing the effectiveness of subsequent anti-PD-1 therapy.

5. PD-1/CTLA-4 bispecific antibody

Cadonilimab is a symmetric tetravalent bispecific antibody that targets both PD-1 and CTLA-4. In a prospective study, cadonilimab combined with TPC chemotherapy demonstrated significant antitumor activity in patients with RM-NPC (36). Another study reported encouraging results, showing improved ORR and PFS in patients with chemotherapy-refractory R/M-NPC (37). Recent research highlights that the combination of cadonilimab and chemotherapy outperformed previous dual ICI neoadjuvant studies (38). These findings suggest that the combination of bispecific antibodies with chemotherapy may offer a potential advantage in enhancing tumor response rates. This breakthrough indicates that the synergistic efficacy of bispecific antibodies may surpass that of dual-agent combinations, providing a novel direction for improving therapeutic outcomes in locally advanced patients. Although existing data highlight the potential of cadonilimab across various treatment settings, as a novel bispecific antibody, its long-term efficacy, stability and safety profile require further validation through large-scale clinical trials.

6. Adoptive cell immunotherapy

As most NPC cases are EBV-positive, targeting EBV antigens expressed in NPC has become a method to improve the prognosis of patients with advanced disease. The viral antigens expressed in NPC can induce specific T lymphocyte responses (39), producing EBV-specific cytotoxic T lymphocytes (EBV-CTLs) that are highly specific. The approach of extracting active immune cells from the body of the patient, followed by *ex vivo* screening and expansion, before applying them clinically is known as EBV-CTL therapy. Previous clinical trials have demonstrated that EBV-CTL therapy can offer clinical benefits (40,41). The VANCE trial in Singapore evaluated the efficacy of EBV-CTL in R/M EBV-positive NPC, with results showing no significant difference in mOS between the group receiving sequential infusion of autologous EBV-CTLs after first-line gemcitabine plus carboplatin (GC) chemotherapy and the group receiving GC chemotherapy alone (25.0 vs. 24.9 months). Although no survival advantage was observed, the VANCE trial still lays the foundation for further exploration of EBV-CTL therapy. Further clinical trials are expected in the future to further investigate the potential of EBV-CTL in the treatment of NPC (42).

Table I. List of Phase II/III clinical trials for immunotherapy in NPC.

First author/s, year	Drug (year)	Targets	Study design	Disease setting	n	Outcomes	Phase	(Refs.)
Yang *et al*, 2021	Camrelizumab	PD-1	Randomized, double-blind, camrelizumab vs. placebo in combination with gemcitabine and cisplatin	Untreated R/M-NPC	343 (camrelizumab group, n=134)	Camrelizumab group mPFS, 9.7 months; placebo group mPFS, 6.9 months; HR, 0.54	III	(18)
Yang *et al*, 2023	Tislelizumab	PD-1	Multicenter; Tislelizumab plus chemotherapy as first-line treatment	R/M NPC	263 (Tislelizumab group, n=131)	Median follow-up, 15.5 months, Tislelizumab group mPFS, 9.6 months, ORR 69.5%; placebo group mPFS, 7.4 months; placebo-chemotherapy, ORR 55.3%	III	(21)
Chan *et al*, 2023	Pembrolizumab	PD-1	Open-label, randomized, pembrolizumab monotherapy vs. chemotherapy	Platinum-pretreated R/M-NPC	233 (pembrolizumab group, n=117)	Pembrolizumab median OS, 17.2 months; chemotherapy median OS, 15.3 months; HR, 0.9	III	(28)
Liu *et al*, 2024	Sintilimab	PD-1	Multicenter, open-label, parallel-group, randomized, controlled, induction-concurrent chemoradiotherapy with or without sintilimab	Non-metastatic stage III-IVa locoregionally advanced NPC	425 (sintilimab group, n=210) `	Event-free survival	III was higher in the sintilimab group (36-month rate, 86 vs. 76%)	(23)
Liu *et al*, 2024	Toripalimab	PD-1	Randomized, single-center, double-blind, placebo-controlled	Untreated stage III or IVa NPC	150 (toripalimab group, n=100)	Median follow-up for PFS, 37.8 months; 2-year PFS for toripalimab group, 92.0%; 2-year PFS for placebo group, 74.0%; HR, 0.40	II	(16)

Table I. Continued.

First author/s, year	Drug (year)	Targets	Study design	Disease setting	n	Outcomes	Phase	(Refs.)
Xu *et al*, 2025	Nivolumab	PD-1	Multicenter, nivolumab combined with induction chemotherapy and radiotherapy	Stage III and IVa NPC	178	Median follow-up, 43 months; 3-year failure-free survival, 88.5%; 3-year OS, 97.9%	II	(26)
Shi *et al*, 2023	KL-A167 (2022)	PD-L1	Multicenter, single-arm	R/M-NPC, failed at least two lines of chemotherapy	153	ORR, 26.5%; DCR, 56.8%; mPFS, 2.8 months; median OS, 16.2 months	II	(29)
Li *et al*, 2025; Li *et al*, 2025	KL-A167 (2025)	PD-L1	Multicenter, single-arm, a secondary analysis of R/M-NPC patients treated with KL-A167	R/M-NPC, failed at least two lines of chemotherapy	153	mPFS (72 vs. 144 days) and OS (730 vs. 305 days) were significantly longer for patients with non-liver metastases.	II	(30,31)
Jiang *et al*, 2025	Cadonilimab (2025)	PD-1 and CTLA-4	Single-arm, open-label, plus TPC chemotherapy (NAB-paclitaxel, cisplatin or lobaplatin and capecitabine)	RM-NPC, failed at least one line of chemotherapy and anti-PD-1 immunotherapy	25	ORR, 68%; median DOR, 9.1 months; mPFS, 10.6 months; 12-month OS, 75.6%	II	(36)

R/M, recurrent unresectable or metastatic; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; DOR, duration of response; HR, hazard ratio; PD-(L)1, programmed cell death (ligand) protein type 1; CTLA-4, cytotoxic T-lymphocyte associated protein type 4; NPC, nasopharyngeal carcinoma; mPFS, median PFS; DCR, disease control rate.

Chimeric antigen receptor (CAR)-T cell therapy is an immunotherapy that involves genetically modifying the T cells of patients to express synthetic receptors termed CARs, which include both antigen recognition domains and intracellular signaling domains (43,44). These CAR-T cells can specifically target tumor-associated antigens through scFv, eliminating tumor cells by producing inflammatory cytokines and achieving long-lasting antitumor activity. As a highly promising innovative therapy, CAR-T cell therapy has opened novel therapeutic avenues for NPC, particularly in cases of recurrence or metastasis refractory to conventional treatments. Clinical translational research on its application in NPC is currently underway.

NK cells, a key component of the immune system, play a crucial role in tumor immune surveillance (45) by eliminating tumor cells in an antigen-independent manner. NK cells induce apoptosis through the expression of death ligands (such as TNF-α, FasL and TRAIL) and regulate immunity by producing cytokines and chemokines (including IFN-γ, IL-10, CCL3, CCL4 and CCL5). Higher NK cell activity is associated with reduced carcinogenic viral infections and increased survival rates. A Phase I study (46) of expanded NK cells combined with cetuximab for the treatment of R/M-NPC showed that, among seven treated patients, four had stable disease and three experienced progression. The disease PFS of three patients who received two NK cell treatments were 12, 13 and 19 months, respectively. Research on this combinatory strategy remains in its early stages, with current data being limited in scope and lacking controlled designs. Its efficacy in R/M-NPC remains to be further validated through larger, controlled studies. Nevertheless, the preliminary results obtained thus far have laid an important foundation for future exploration in this field.

Although adoptive cell immunotherapy has shown certain efficacy in cancer treatment, challenges remain regarding treatment-related toxicity and persistence. In CAR-T cell therapy, functional impairments and T cell exhaustion are notable obstacles, primarily due to the reduced vitality and short duration of some T cells, insufficient infiltration of effective sites and the impact of the immunosuppressive TME (47). EBV-specific CAR-T and TIL therapies offer promising breakthrough approaches for refractory NPC, targeting high-risk or recurrent patient populations. These therapies are currently in the clinical advancement phase, and more innovative strategies may emerge in the future.

7. Tumor vaccines

Virus-associated antigens are preferable targets, and EBV-positive NPC cells can express LMP and EBV nuclear antigen 1 (48). EBV antigens can directly regulate the expression of PD-L1. EBV-encoded LMPs (LMP1 and LMP2) induce high PD-L1 expression on tumor cells (Fig. 1), thereby directly inhibiting T cell cytotoxicity. Furthermore, EBV antigen stimulation of tumor cells and cells within the TME promotes the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β, which suppress pro-inflammatory responses and foster an immunosuppressive phenotype. Based on this mechanism, activating EBV-specific T cell responses through tumor vaccines can not only directly eliminate tumor cells expressing EBV antigens, but also induce long-lasting immune memory to prevent tumor relapse. DCs have the ability to present tumor antigens and can load multiple antigen-encoding mRNA constructs to efficiently activate T cells. DC vaccines have shown variable efficacy in the treatment of various malignancies, possibly related to interactions with other therapeutic agents and the functionality of bone marrow and lymphocytes (49). At present, research on DC vaccines is limited, and more clinical trials are needed to define their therapeutic efficacy.

The lipid-based LMP2-mRNA vaccine is a therapeutic vaccine for NPC. A preclinical study has shown that mice treated with three doses of the vaccine significantly suppressed tumor growth in models expressing LMP2, demonstrating its potential in combating NPC (50). A newly developed LMP2-mRNA lipid nanoparticle (C2@mLMP2) can be delivered to tumor-draining lymph nodes, inducing an increase in T cells. A study has observed that C2@mLMP2, in combination with αPD-1, exhibits strong synergistic antitumor effects (51).

Although mRNA vaccines can trigger antigen-specific T cell responses, therapeutic vaccination alone cannot achieve potent tumor suppression. A recent study found (52) that the combination of mRNA vaccines and NK cell therapy has demonstrated significant synergistic effects in humanized NPC mouse models. This combination not only leads to sustained inhibition and eradication of tumor cells, but also effectively enhances the infiltration efficiency of human T cells and NK cells into the TME, boosting their antitumor immune functions. Therefore, combining therapeutic vaccination with NK cell therapy is a promising strategy for treating EBV-positive NPC. However, the efficacy and safety of this approach still require further exploration in subsequent studies.

RNA vaccines for tumor therapy face numerous challenges in the clinical translation process (53). The inherent characteristics of tumors, including the development of resistance and immune evasion mechanisms, notably impact treatment efficacy. Practical obstacles also remain, such as the difficulty in determining optimal individualized dosing regimens, defining suitable patient populations, accurately quantifying tumor cells and addressing technical issues such as the prolonged vaccine production timeline. Currently, tumor mRNA vaccines remain in the early stages of clinical development, with preliminary studies showing promising immunogenicity and potential survival benefits. However, due to the suppressive TME and inefficient antigen presentation, monotherapy has shown limited efficacy. Therefore, combination therapy is considered a key strategy to enhance therapeutic outcomes. Future research should focus on the development of personalized tumor mRNA vaccines and the exploration of novel immunoadjuvants. Notably, the long-term efficacy of both monotherapy and combination therapy with mRNA vaccines still requires validation through large-scale, well-designed clinical trials.

8. Targeted therapy

In recent years, the rapid development of molecular biology and tumor immunology has made targeted therapy a key pillar of the comprehensive treatment of NPC (14). Currently, targeted therapies for NPC focus on several core targets,

including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and its receptor (VEGFR), EBV-related antigens, as well as abnormally activated signaling pathways such as PI3K/AKT/mTOR. Through diverse treatment approaches, such as small molecule inhibitors and monoclonal antibodies, targeted therapy precisely interferes with key biological processes such as tumor cell proliferation, angiogenesis and immune evasion. These advancements have notably improved the quality of life and prognosis of patients. The clinical trial results related to targeted therapy for NPC are shown in Table II.

Notably, multi-target combination therapies and precision medicine models based on genetic testing are driving NPC targeted therapy toward more efficient and individualized treatments. This novel approach presents a new avenue of investigation for overcoming this challenging disease.

9. EGFR pathway

EGFR is a transmembrane glycoprotein that belongs to the receptor tyrosine kinase ErbB family, which includes ErbB-1 (EGFR), ErbB-2 (HER2/neu), ErbB-3 (HER3) and ErbB-4 (HER4) (54). By binding with ligands, EGFR activates intracellular signaling pathways, such as PI3K/Akt and MAPK, to regulate cell proliferation, differentiation, survival and migration (55). In numerous tumors, EGFR is abnormally activated due to overexpression or genetic mutations, promoting tumor initiation and progression. EGFR is overexpressed in ~80% of NPC cases, enhancing tumor cell proliferation and metastasis (56). EGFR plays a crucial inhibitory role in tumor immune regulation. On one hand, activation of EGFR reduces the secretion of key pro-inflammatory cytokines, such as IL-2 and IFN-γ, by T cells, while simultaneously promoting tumor cells to strengthen their immunosuppressive phenotype, thereby directly weakening the antitumor immune response of the body. On the other hand, EGFR can upregulate the surface expression of PD-L1 on tumor cells via ERK, AKT-mTOR and STAT signaling pathways, further enhancing the inhibitory activity of the PD-1/PD-L1 immune checkpoint and ultimately reducing the clinical efficacy of ICIs in tumor treatment (57).

EGFR inhibitors can directly suppress tumor cell proliferation. Their mechanism involves competitively inhibiting the binding of extracellular ligands to EGFR after binding to EGFR, blocking the intracellular activation of EGFR, and thereby inhibiting the activation of downstream pathways related to cell proliferation, adhesion and angiogenesis, caused by EGFR activation. This results in the suppression of tumor cell growth (58), achieving antitumor effects. Currently, EGFR inhibitors used for NPC treatment in clinical practice and research include cetuximab, nimotuzumab, MRG003 and BL-B01D1.

Cetuximab. Cetuximab is a monoclonal antibody that binds to EGFR and has been used for treating EBV-related NPC. A Phase II study in R/M-NPC demonstrated that the combination of cetuximab and carboplatin achieved an ORR of 11.7% and a DCR of 60%. Notably, only 31.7% of patients experienced treatment-related toxicities, confirming the efficacy of the combination in disease control for relapsed or metastatic NPC and its acceptable safety profile in the later-line setting (59). In locally advanced NPC, the combination of cetuximab and cisplatin with intensity-modulated radiation therapy (IMRT) is also expected to improve survival rates in patients with NPC (60). However, a recent study (61) found that the overexpression of the complement regulatory protein CD55 in EBV-associated NPC cells suppressed ADCC activity, thus reducing the efficacy of cetuximab. This explains why some patients exhibit poor therapeutic outcomes and provides a direction for overcoming resistance whereby downregulating CD55 expression or combining with complement inhibitors may restore the ADCC effect of cetuximab, offering a new target for precision-targeted therapy.

Nimotuzumab. Nimotuzumab is a humanized monoclonal antibody targeting EGFR, which inhibits tumor cell proliferation and promotes apoptosis. Several clinical studies have reported clinical benefits of nimotuzumab combined with chemotherapy vs. chemotherapy alone as first-line treatment for R/M-NPC (62-64). A recent Phase II clinical study on nimotuzumab combined with docetaxel and cisplatin as first-line therapy for patients with R/M-NPC (65) found that the ORR and DCR were 65.4 and 90.4%, respectively. The majority of adverse events were grade 1-2. Grade 3/4 adverse events were primarily hematologic toxicities, including neutropenia and leukopenia. Overall, these were manageable, with no unexpected severe adverse reactions observed. These findings suggest promising efficacy, along with satisfactory tolerability and safety profiles, providing a potential treatment option for first-line therapy in R/M-NPC that balances both efficacy and safety.

Becotatug vedotin. Becotatug vedotin (MRG003) is China's first EGFR-targeted ADC. It consists of an anti-EGFR humanized monoclonal antibody conjugated with the cytotoxic drug monomethyl auristatin E via a cleavable linker VC. In 2022, results from a non-randomized clinical trial (66) indicated that MRG003 demonstrated controllable safety characteristics and promising antitumor activity in patients with EGFR-positive NPC and SCCHN (Squamous Cell Carcinoma of the Head and Neck). A 2023 study further highlighted that MRG003 exhibited satisfactory tolerability, manageable safety and showed promising efficacy in patients with 2nd/3rd-line recurrent/metastatic SCCHN who had failed prior platinum-based and PD-1/L1 inhibitor treatments (67). A Phase II clinical study presented at the 2024 European Society for Medical Oncology Asia Annual Meeting (68) showed that among 30 patients, two achieved complete remission, 18 achieved partial remission and eight had stable disease, with a DCR of 93.3%. The 6-month PFS was 76.2 and 83.3% of patients had a duration of remission lasting >6 months.

At the 2025 American Society of Clinical Oncology Annual Meeting (69), the results of a Phase IIb clinical study of the EGFR ADC MRG003 for treating advanced NPC were presented. The study involved patients with R/M-NPC who had failed at least two lines of systemic chemotherapy and PD-L1 inhibitor treatment. Patients were randomly assigned to receive MRG003 or chemotherapy (capecitabine or docetaxel). As of June 30, 2024, the ORR in the MRG003 group was significantly superior to that of the chemotherapy group, with a marked reduction in the risk of disease progression and a substantial improvement in PFS. In addition, a clear trend toward survival

Table II. List of Phase II/III clinical trials for targeted therapy in NPC.

First author/s, year	Drug	Targets	Study Design	Disease setting	n	Outcomes	Phase	(Refs.)
Chan *et al*, 2005	Cetuximab	EGFR	Multicenter, open-label, single-arm	Refractory R/M-NPC	60	ORR, 11.7%; mPFS, 81 days; median OS, 233 days	II	(59)
Chua *et al*, 2008	Gefitinib	EGFR	Single-center	R/M-NPC, failed at least 2 lines of chemotherapy	19	mPFS, 4 months; median OS, 16 months	II	(78)
Jin *et al*, 2013	Endostar	VEGF	Endostar combined with gemcitabine-cisplatin chemotherapy	M-NPC	30	Median follow-up, 13.1 months; mPFS, 19.4 months; 1-year PFS rate, 69.8%; ORR, 85.7%; OS, 90.2%	II	(93)
Li *et al*, 2020	Endostar	VEGF	Randomized, controlled, multicenter, standard chemoradiation with or without Endostar	Locally advanced NPC	114 (Endostar group, n=56)	5-year OS, 73.2%; PFS, 80.1%; FFS, 91.0%; control group, no significant difference was found	II	(94)
Xu *et al*, 2022	Endostar	VEGF	Randomized, open, multicenter, Endostar combined with PF and IMRT	Locally advanced NPC	83 (Endostar group, n=41)	Endostar group showed significantly prolonged PFS by ~4 months, no significant difference in the median overall survival was shown	II	(95)
Xu *et al*, 2024	MRG003	EGFR	MRG003 combined with pucotenlimab	R/M-NPC, failed first-line platinum-based therapy	30	Median follow-up time, 4.2 months; cORR, 66.7%; DCR, 93.3%; 6-month PFS rate, 76.2%; 6-month DOR rate, 83.3%	II	(68)
Han *et al*, 2025	Becotatug vedotin (MRG003)	EGFR	Randomized, controlled, multicenter, open-label, Becotatug vedotin vs. chemotherapy	R/M-NPC, failed ≥2 lines of systemic chemotherapy and PD-(L)1 inhibitor	173 (MRG003, n=86)	By 30 June 2024, ORR with MRG003 compared with chemotherapy was 30.2 vs. 11.5%; mPFS was 5.8 vs. 2.8 months; as of 30 December 2024, the updated mOS was 17.1 vs. 12.0 months	II	(69)

Table II. Continued.

First author/s, year	Drug	Targets	Study Design	Disease setting	n	Outcomes	Phase	(Refs.)
Yang *et al*, 2025	Izalontamab brengitecan	EGFR and HER3	Multicenter, randomized, open-label	R/M-NPC, at least to 2 standard therapies, including at least one platinum-containing regimen and PD-1/PD-L1 inhibitors	386 (iza-bren group, n=191)	Median follow-up, 7.66 months; iza-bren ORR, 54.6%; chemotherapy, 27.0%; overall survival data were not mature at data cut-off	III	(72)

R/M, recurrent unresectable or metastatic; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; FFS, failure-free survival; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; PD-(L)1, programmed cell death (ligand) protein type 1; mPFS, median PFS; NPC, nasopharyngeal carcinoma; mOS, median OS; DOR, duration of response; cORR, confirmed objective response rate.

benefit was observed in OS, particularly after excluding the interference of crossover treatments, where this advantage became even more pronounced. These results indicate that MRG003 has shown a trend toward survival benefit.

BL-B01D1. BL-B01D1 is the first EGFR-HER3 bispecific ADC, designed to specifically bind to EGFR or HER3 on the surface of tumor cells. In a Phase I clinical trial (70), BL-B01D1 showed preliminary antitumor activity and acceptable safety in patients with extensively treated advanced solid tumors. A study in 2024 found that BL-B01D1 monotherapy achieved an ORR of 54% in NPC (71). Recently, the Phase III clinical trial of the EGFR/HER3 bispecific ADC, izalontamab brengitecan (iza-bren; BL-B01D1) for NPC (study code: BL-B01D1-303) met its primary endpoint in an interim analysis, making it the first bispecific ADC drug to complete phase III studies worldwide. The results showed that, compared with chemotherapy, iza-bren significantly improved the ORR in patients with R/M-NPC, with a manageable safety profile. These findings suggest that BL-B01D1 may represent a novel therapeutic direction for this patient population (72).

In addition to directly inhibiting tumor cell proliferation, EGFR inhibitors can also influence the tumor immune microenvironment [including increased expression of MHC class I (73) and class II molecules (74) on tumor cells], thereby enhancing tumor antigen presentation. Due to these effects, EGFR inhibitors can transform an immunosuppressive TME into an immune-activated one, notably improving the effectiveness of immunotherapies. Some studies suggest (75,76) that EGFR-driven tumors may also induce the expression of PD-L1, which, when bound to PD-1, increases inhibitory signals. This may lead to the suppression of $CD8^+$ T cells expressing PD-1 receptors, hindering their immune response against tumor cells. Given these effects, combining anti-PD-L1 antibodies with EGFR inhibitors for NPC is a promising strategy.

EGFR-TKIs. EGFR-TKIs achieve targeted therapy by blocking the binding of ATP to the intracellular tyrosine kinase domain of EGFR. Gefitinib, a first-generation EGFR-TKI, a small molecule inhibitor, has been shown to exhibit intrinsic resistance in most NPC cell lines (77). A Phase II study reported that none of the patients with recurrent or metastatic NPC achieved clinical remission after gefitinib treatment, thus it is not recommended for use in NPC outside of clinical trials (78). However, other studies have suggested that EGFR-TKI treatment may increase PD-L1 expression in immune cells, making them more responsive to subsequent ICIs, indicating that EGFR-TKI treatment may influence the TME and produce favorable effects on ICI efficacy (79,80).

10. Anti-angiogenesis pathway

VEGF is a growth factor with angiogenic activity that promotes mitosis and inhibits apoptosis in endothelial cells, increases vascular permeability and facilitates cell migration. Due to these effects, VEGF plays a crucial role in regulating both normal and pathological angiogenesis processes. Studies have shown that VEGF plays an essential role in the molecular pathogenesis of tumor growth and metastasis (81). VEGF-induced abnormal vascular structures compromise tumor vessel integrity, making it difficult for T cells and DCs to infiltrate

tumor tissue. Additionally, VEGF can directly inhibit DC maturation, reducing the presentation of tumor antigens to T cells and hindering the initiation of immune responses. It also promotes the expression of PD-L1 and recruits MDSCs, thereby exacerbating immune evasion (82) and reducing the efficacy of checkpoint inhibitors. Various angiogenesis inhibitors are available for treating different types of advanced solid tumors. Numerous current treatment approaches target one or more VEGF subtypes, VEGF receptors or signaling pathways (83). Bevacizumab is an anti-VEGF-A drug, and the first humanized anti-angiogenic antibody approved for the treatment of colorectal cancer. Bevacizumab is now widely used for the treatment of NPC. A meta-analysis has shown that, among multiple clinical studies included, bevacizumab was the most effective treatment for achieving partial response in NPC (80.6%), followed by standard cancer treatments (57%), cetuximab (51.5%), nimotuzumab (31.2%) and Endostar (29.7%) (84).

In addition to its direct role in angiogenesis and tumor growth, VEGF can also induce immune suppression within the TME (85). It can suppress T-cell function, increase the recruitment of regulatory T cells (Tregs) and MDSCs, and inhibit the differentiation and activation of DCs. When VEGF levels are elevated within the TME, it further stimulates the proliferation of MDSCs and Tregs, increases VEGFR expression and inhibits T-cell activity via VEGF/VEGFR signaling. This change in the TME can, to some extent, enhance the effectiveness of immunotherapy. A preclinical study demonstrated that anti-VEGF therapy could improve the effectiveness of anti-PD-L1 treatment by improving vascular conditions. Simultaneously, anti-PD-1 or anti-PD-L1 therapies could also make anti-angiogenesis therapies more sensitive and extend their therapeutic effects (86). Furthermore, some studies have shown that, in various models, the use of bispecific anti-angiogenesis therapy could promote T-cell extravasation from tumor vessels (87,88). It could also reduce inhibitory factors on innate immune cells or those derived from innate immune cells, promoting the establishment and development of antitumor immunity, thus enhancing the activity of anti-PD-L1 treatment (89).

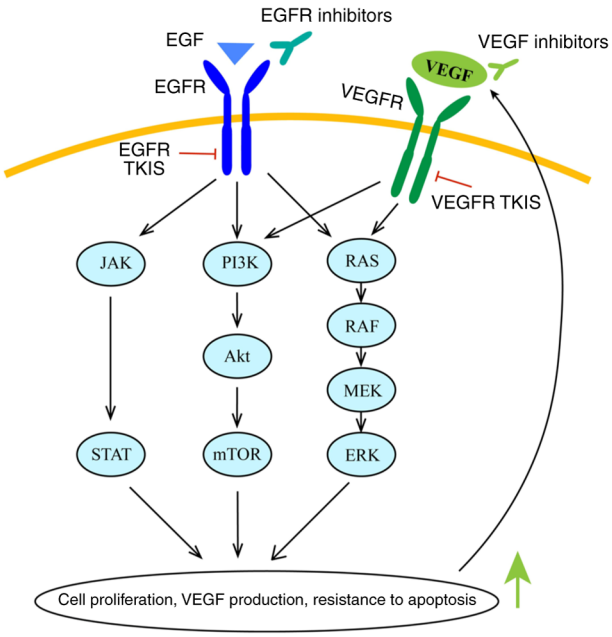

Figure 2. Upon activation by EGF, EGFR promotes cell proliferation, VEGF production and anti-apoptotic activity through the JAK/STAT, PI3K/Akt/mTOR and RAS/RAF/MEK/ERK pathways. VEGF activates VEGFR and shares these downstream signals. EGFR inhibitors/TKIs can block EGFR activation, while VEGF inhibitors/VEGFR TKIs inhibit the interaction between VEGF and VEGFR. The combination of these inhibitors can simultaneously block the upstream signaling of both pathways, synergistically suppressing tumor progression and delaying resistance. EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; TKIs, tyrosine kinase inhibitors.

11. Similarities between the EGFR and VEGF pathways

Although the EGFR and VEGF pathways target different molecules, they share key overlaps in regulating tumor immune evasion and the TME. Both pathways activate downstream PI3K and ERK signaling (Fig. 2), leading to upregulation of immune checkpoint molecules such as PD-L1 on tumor cells. Additionally, both pathways induce tumor cells to secrete factors such as IL-10 and TGF-β, which recruit Tregs, MDSCs and M2 macrophages, thereby promoting immune suppression within the TME and facilitating immune evasion. Furthermore, there is cross-activation between the two pathways, whereby the EGFR pathway can indirectly promote VEGF transcription through downstream signals, while VEGF pathway activation can enhance EGFR phosphorylation, collectively driving tumor angiogenesis and immune evasion.

12. Recombinant human endostatin

Endostar is a recombinant human endostatin that directly inhibits endothelial cell proliferation and suppresses tumor development through multiple targets, thus exerting its antitumor effects. These targets include VEGF, VEGFR-2 and platelet-derived growth factor receptor (90). Additionally, Endostar notably increases the percentage of basal membrane and pericyte coverage. It normalizes the tumor vasculature by reducing interstitial fluid pressure and vascular permeability, which in turn reduces tumor hypoxia and alters the vascular physiology within the tumor. Alleviating tumor hypoxia and improving vascular delivery may enhance the cytotoxic effects of chemotherapy drugs and ionizing radiation (91,92). Several Phase II clinical trials have confirmed that Endostar combined with chemotherapy is a safe and effective treatment for NPC and head and neck squamous cell carcinoma (93,94). The latest study indicated that, in patients with locally advanced NPC, Endostar combined with cisplatin and 5-fluorouracil chemotherapy and sequential IMRT significantly improved PFS (Endostar group, 25.6 months; control group without Endostar, 21.4 months) (95). The combination of Endostar and immunotherapy may be a promising strategy for treating NPC, although further investigation is required.

13. Combination strategies: Immunotherapy plus targeted therapy

The combination of immunotherapy and targeted therapy represents a key breakthrough in the treatment of malignant tumors, with both modalities synergistically reshaping the antitumor immune response to enhance clinical benefits. Targeted

therapies, such as anti-angiogenic agents, remodel tumor vasculature, improve oxygen supply and reduce PD-L1 expression, while also inhibiting the functions of immunosuppressive cells such as Tregs and MDSCs, and downregulating immune checkpoint molecules. Additionally, targeted therapies induce tumor metabolic stress, recruit $CD8^+$ T cells and NK cells, and enhance their cytotoxic activity, thus creating a favorable environment for immunotherapy. Immunotherapy, in turn, strengthens the antigen presentation induced by tumor immunogenic cell death through targeted drugs, complementing the cytotoxic effects of targeted therapies. It also induces stem cell-like memory T cells, enabling long-term tumor control. Together, these treatments reduce resistance, with immunotherapy clearing targeted-resistant cells and targeted therapy restoring exhausted T cell function. This combined approach inhibits tumor immune evasion and modulates the cytokine network, further reducing the risk of resistance.

Numerous clinical studies have confirmed the clinical value of this immunotherapy-targeted therapy combination strategy (Table III). For example, a recent Phase II study demonstrated that the combination of toripalimab and anlotinib in the treatment of R/M-NPC achieved a notable ORR of 37.5% and a DCR of 85.0%, with favorable tolerability. The study also indicated that the response of plasma circulating tumor DNA (ctDNA) correlates with efficacy, and ctDNA may serve as a potential biomarker for predicting the treatment response of this combination regimen (96). Several clinical trials have shown promising treatment outcomes for the combination of camrelizumab and apatinib in NPC. A Phase II study in 2023 (97) demonstrated notable disease control in patients with platinum-resistant R/M-NPC, with survival benefits even in those resistant to PD-1 inhibitors. Another Phase II study in the same year (98) demonstrated that the combination of camrelizumab and apatinib in patients with R/M-NPC resulted in a median follow-up duration of 16 months, with an ORR of 38.5%, a DCR of 61.5%, a mPFS of 6 months and a mOS of 14 months, indicating promising antitumor activity and manageable toxicity. In 2024, a study further combined this regimen with chemotherapy in patients with N3-stage NPC, achieving excellent control of distant metastasis, with the safety profile remaining within acceptable limits (99). A recent study involving pembrolizumab, with or without bevacizumab (100), directly confirmed the advantage of combination therapy, with the ORR significantly higher in the pembrolizumab and bevacizumab group compared with pembrolizumab monotherapy, clearly demonstrating the synergistic effect of anti-angiogenic drugs and PD-1 inhibitors. Additionally, the combination of PD-1 inhibitors with other targeted therapies has shown population-specific benefits. Toripalimab combined with GFH018 (101) in previously treated patients with R/M-NPC resulted in an ORR of 26.1%, a DCR of 43.5%, a mPFS of 2.0 months and a median duration of response of 7.6 months. Notably, patients who had not been previously treated with ICIs exhibited significantly improved efficacy, with substantial improvements in ORR, DCR and PFS, while even ICI-treated patients achieved some disease control. Overall, the toxicity was manageable, and there was persistent antitumor activity.

In summary, the trend towards combining immunotherapy and targeted therapy in NPC is clear. The synergistic action between PD-1 inhibitors and anti-angiogenic drugs can effectively improve disease control, with notable population heterogeneity in treatment efficacy. The exploration of biomarkers, such as ctDNA, holds promise for the precise selection of patients who may benefit. This combined strategy not only overcomes the efficacy limitations of monotherapy but also expands the research direction for precision treatment in NPC, providing personalized therapeutic options for patients with different clinical profiles.

14. Future directions

NPC, a malignancy with notable geographic clustering, exhibits highly heterogeneous biological behavior and is closely related to EBV infection, epigenetic changes and abnormal molecular signaling pathways. Precision-targeted strategies based on tumor cell surface receptors (such as EGFR), key angiogenesis factors (such as VEGF) and virus-associated antigens have become an important direction to overcome the limitations of traditional chemotherapy and radiotherapy. Additionally, the deconstruction of the immune-suppressive network in the TME provides a key entry point for immunotherapy. Therefore, integrating tumor pathological classification (keratinizing/non-keratinizing), EBV viral load, molecular markers and immune infiltration characteristics is the core prerequisite for achieving precision treatment.

In the field of targeted therapy, monoclonal antibodies targeting EGFR (such as nimotuzumab) combined with chemotherapy and radiotherapy have become the standard treatment for locally advanced NPC, notably improving local control rates. Anti-angiogenesis agents (such as bevacizumab) exhibit efficacy in delaying disease progression in recurrent and metastatic patients by blocking the VEGF pathway. In terms of immunotherapy, PD-1 inhibitors play a key role in activating T cell responses triggered by EBV-associated tumor antigens. Single-agent or combination therapies with chemotherapy or anti-angiogenesis agents have demonstrated nearly a 30% improvement in ORRs compared with traditional chemotherapy, particularly in patients that are PD-L1-positive (CPS $\geq$10) or have a high tumor mutation burden. Some of these regimens have already been recommended in international guidelines.

However, current treatments still face several challenges. Firstly, targeted therapies often encounter resistance due to compensatory activation of the EGFR pathway, tumor vascular heterogeneity and other issues. In addition, immunotherapy is only effective for ~40% of patients, and EBV-mediated immune escape and regulatory T cell infiltration in the TME may weaken efficacy. A promising development is the combination of targeted therapy with immunotherapy. For example, EGFR inhibitors can enhance T cell eliminating activity by downregulating PD-L1 expression, while the combination of CTLA-4 inhibitors and PD-1 inhibitors has shown synergistic antitumor effects in clinical studies by dual checkpoint blockade.

Future clinical research is likely to focus more on the comprehensive analysis of genomics, viral immunology and dynamic changes in the immune microenvironment, strengthening the development of novel immunotherapies

Table III. List of Phase II/III clinical trials for immunotherapy combined with targeted therapy in NPC.

First author/s, year	Drugs	Targets	Study design	Disease setting	n	Outcomes	Phase	(Refs.)
Yuan *et al*, 2023	Camrelizumab and apatinib	PD-1 and VEGFR2	Single-arm, camrelizumab plus apatinib	R/M-NPC, platinum-resistant and PD-1 inhibitor resistant	72	Platinum-resistant, median follow-up time, 23.3 months; mPFS, 12.6 months; 1-year OS, 82.5%; mOS, NA; PD-1 inhibitor resistant ORR, 34.3%; mPFS, 4.5 months; mOS, 16.2 months; 1-year OS, 68.8%	II	(97)
Mo *et al*, 2023	Camrelizumab and apatinib	PD-1 and VEGFR2	Multicenter, open-label, single-arm, apatinib combined with camrelizumab	R/M-NPC, at least to 1 standard therapy	26	Median follow-up duration, 16 months; ORR, 38.5%; DCR, 61.5%; mPFS, 6 months; mOS, 14 months	II	(98)
Liang *et al*, 2024	Camrelizumab and apatinib	PD-1 and VEGFR2	Open-label, single-arm, camrelizumab and apatinib plus chemoradiotherapy	Stage N3 NPC	49	Both 1- and 2-year DMFS rates, 98.0%; 2-year FFS, 95.9%; OS, 98.0%.	II	(99)
Zhang *et al*, 2024	Toripalimab and anlotinib	PD-1 and VEGFR	Multicenter, single-arm, toripalimab plus anlotinib	R/M-NPC	40	Median follow-up, 17.4 months; mPFS, 9.5 months; 1-year OS, 73.3%	II	(96)
Chong *et al*, 2025	Pembrolizumab and bevacizumab	PD-1 and VEGF	Randomized, open-label, pembrolizumab with or without bevacizumab	R/M-NPC	48	Bevacizumab and pembrolizumab group ORR, 58.3%; pembrolizumab group ORR, 12.5%.	II	(100)
Tang *et al*, 2025	Toripalimab and GFH018	PD-1 and TGFβRI	Multinational, open-label and single-arm, GFH018 and toripalimab combination therapy	R/M-NPC, at least to 1 standard therapy	46	ORR, 26.1%; DCR, 43.5%; mPFS, 2.0 months; median DOR, 7.6 months; without prior ICI treatment: ORR 40%, DCR 60%, mPFS 9.0 months, median DOR was not reached; previously exposed to ICIs: ORR 9.5%, DCR 23.8%	Ib/II	(101)

R/M, recurrent unresectable or metastatic; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; DOR, duration of response; DCR, disease control rate; PD-(L)1, programmed cell death (ligand) protein type 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; NPC, nasopharyngeal carcinoma; mPFS, median PFS; mOS, median OS; ICI, immune checkpoint inhibitor.

targeting EBV-specific antigens and tumor stem cell targets, and screening biomarkers to identify the patient population that would benefit most. With the clinical application of various immune inhibitors and the continuous development of novel therapeutic targets, clinical translation of cutting-edge technologies such as bispecific antibodies and adoptive cell therapy, NPC treatment is hypothesized to move from the current model of personalized targeted and immunotherapy towards a combination of targeted immunotherapy. Ultimately, this may lead to a new era of precise targeting and immune modulation in NPC therapy.

15. Conclusion

Current research has demonstrated notable progress in the development and application of targeted therapy and immunotherapy for NPC. Molecular-targeted drugs targeting key pathways such as EGFR and VEGF/VEGFR, as well as ICIs targeting PD-1/PD-L1 or CTLA-4, have shown clinically meaningful efficacy and controllable safety in the treatment of locally advanced and R/M-NPC. The combination of these novel therapies with standard CRT is changing the treatment landscape.

However, numerous challenges remain. Primary and acquired resistance to targeted therapy and immunotherapy limit the long-term effectiveness of these treatments, with only ~40% of patients achieving notable benefit from ICIs. There is an urgent need for predictive biomarkers beyond PD-L1 expression (CPS) and tumor mutational burden to improve identification of the appropriate patient populations. Although prospects are promising, numerous new approaches still need to be further validated in large-scale, randomized phase III trials.

In conclusion, the era of precision oncology for NPC is rapidly advancing, with the successful integration of targeted therapy and immunotherapy. With strong guidance from reliable biomarkers and individualized based on tumor biology, these strategies may offer new opportunities to improve survival outcomes for patients with NPC at various stages.

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ZY and HL wrote this manuscript. MC, LZ and MG collected information, revised the manuscript finally and provided some critical suggestions. RY provided general supervision and gave final approval of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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