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PERSPECTIVE

Rethinking nasopharyngeal carcinoma management: toward a low-toxicity, highly effective regimen with favorable tolerability and quality of life

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In the comprehensive treatment of locoregionally advanced nasopharyngeal carcinoma (LA-NPC), the incorporation of programmed cell death protein-1 (PD-1) blockade has been a critical breakthrough. The combination of PD-1 blockade and chemoradiotherapy markedly increases clinical efficacy among patients with LA-NPC and has revolutionized the established therapeutic intervention framework (**Table 1**).[1-8] Treatment paradigms have transitioned from survival-centered frameworks to patient-centered therapeutic strategies, thus overcoming the longstanding clinical hurdle of the considerable toxic burden of concurrent cisplatin treatment. Cisplatin frequently induces severe gastrointestinal and hematologic adverse events, alongside irreversible ototoxicity and nephrotoxicity. After platinum-based doublet or triplet induction chemotherapy, concurrent administration of cisplatin with radiotherapy exacerbates these toxic manifestations; consequently, more than 40% of patients do not complete the intended treatment course, and extensive declines in health-related quality of life (QoL) often impede patients' functional recovery and social reintegration.[4,5]

Therapeutic strategy and novelty of the DIAMOND trial

Given this clinical context, the DIAMOND trial introduced multiple innovations.[4] First, building on encouraging outcomes from the single-arm phase 2 PLATINUM trial,[5] the DIAMOND study further corroborated the efficacy and safety of toripalimab plus chemoradiotherapy without concurrent cisplatin through a multicenter phase 3 randomized controlled trial, the gold-standard design for verifying the clinical utility of novel treatment regimens. This work yielded high-grade evidence validating the concurrent cisplatin-sparing strategy and remodeled the established therapeutic framework for LA-NPC. Second, by using a rigorous 8% non-inferiority margin consistent with contemporary NPC trial designs, the trial demonstrated that the concurrent cisplatin-sparing group achieved a 3-year failure-free survival (FFS) rate of 88.3%, thus meeting the statistical non-inferiority threshold relative to the 87.6% recorded in the standard-therapy group receiving concurrent cisplatin. Moreover, the incidence of all-grade vomiting, a prespecified co-primary endpoint, was 33.6% lower in the concurrent cisplatin-sparing group than the standard-therapy group (26.2% *vs.* 59.8%), thereby indicating a substantial toxicity-related benefit. Third, the trial incorporated comprehensive patient-reported outcome (PRO) assessments *via* validated questionnaires developed by the European Organisation for Research and Treatment of Cancer and the Functional Assessment of Cancer Therapy. These PRO analyses demonstrated substantially superior global health status, alleviated gastrointestinal symptoms, preserved swallowing function, and diminished overall toxic burden among patients in the concurrent cisplatin-sparing group. An assessment based on the PRO-specific Common Terminology Criteria for Adverse Events also demonstrated that the cisplatin-sparing strategy enhanced treatment tolerance, on the basis of nausea, vomiting, constipation, and fatigue. The use of exhaustive PRO datasets notably differentiated this investigation from prior analogous clinical studies (**Table 1**).

Limitations and insights from the DIAMOND trial

The DIAMOND trial has substantially advanced chemotherapy de-escalation strategies for LA-NPC while presenting

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Table 1 Published clinical trials on PD-1 blockade in LA-NPC

First author (identifier)	Phase	Sample size (E/C)	Experimental group	Control group	Primary endpoint [HR (95% CI); *P*]*	OS [HR (95% CI); *P*]*	Tolerability	QoL
Liu et al.[1] (NCT03700476)	3	425 (210/215)	IP: sintilimab 200 mg + GP, q3w × 3; RP: DDP, q3w × 2 + sintilimab 200 mg, q3w × 3 + IMRT; AP: sintilimab 200 mg, q3w × 6	Same as the experimental group, but without sintilimab	EFS: 3-year rate, 86.0% *vs.* 76.0% [0.59 (0.38–0.92); 0.019]	3-year rate, 92% *vs.* 92% [0.86 (0.50–1.49); 0.60]	No	Yes
Liang et al.[2] (NCT03427827)	3	450 (226/224)	IP: GP, q3w × 3; RP: DDP, q3w × 2 + IMRT; AP: camrelizumab 200 mg, q3w × 12	Same as the experimental group, but without camrelizumab	EFS: 3-year rate, 86.9% *vs.* 77.3% [0.56 (0.36–0.89); 0.01]	3-year rate, 96.4% *vs.* 92.9% [0.80 (0.35–1.82); 0.59]	No	Yes
Liu et al.[3] (NCT03925090)	2	150 (100/50)	IP: toripalimab 240 mg, q2w × 2; RP: DDP, q3w × 3 + IMRT; AP: toripalimab 240 mg, q3w × 8	Same as the experimental group, but without toripalimab	PFS: 2-year rate, 92.0% *vs.* 74.0% [0.40 (0.18–0.89); 0.019]	3-year rate, 99.0% *vs.* 90.0% (NR)	No	Yes
Xu et al.[4] (NCT04907370)	3	532 (267/265)	IP: toripalimab 240 mg + GP, q3w × 3; RP: toripalimab 240 mg, q3w × 3 + IMRT; AP: toripalimab 240 mg, q3w × 11	Same as the experimental group, but with concurrent DDP	FFS: 3-year rate, 88.3% *vs.* 87.6% [0.92 (0.66–1.79); 0.73]	3-year rate, 96.1% *vs.* 96.5% [1.04 (0.52–2.08); 0.81]	Yes	Yes
Xu et al.[5] (NCT03984357)	2	152 (152/NA)	IP: nivolumab 360 mg + GP, q3w × 3; RP: nivolumab 360 mg, q3w × 3 + IMRT; AP: nivolumab 480 mg, q4w × 6	NA	FFS: 3-year rate, 88.5%	3-year rate, 97.9%	Yes	Yes
You et al.[6] (NCT04453826)	3	390 (194/196)	IP: GP, q3w × 3; RP: DDP + camrelizumab 200 mg, q3w × 2 + IMRT; AP: camrelizumab 200 mg, q3w × 17	Same as the experimental group, but without camrelizumab	PFS: 3-year rate, 83.4% *vs.* 71.3% [0.51 (0.34–0.77); 0.001]	3-year rate, 94.8% *vs.* 92.2% [0.59 (0.27–1.28); 0.19]	No	Yes
Lv et al.[7] (NCT04072107)	2	142 (110/32)	IP: GP, q3w × 3; RP: DDP, q3w × 3 + IMRT without (RATint) or with (RAThigh) sintilimab 200 mg, q3w × 3 AP: metronomic capecitabine 650 mg/m^2, p.o., bid × 6 months (RATint); sintilimab 200 mg, q3w × 9 (RAThigh)	Induction chemotherapy followed by concurrent chemoradiotherapy	FFS: 3-year rate, 89.1% *vs.* 74.4% [0.41 (0.23–0.75); 0.004]	3-year rate, 96.4% *vs.* NR [0.57 (0.18–1.78); 0.327]	No	Yes
Wang et al.[8] (NCT04782765)	2	57 (57/NA)	IP: camrelizumab 200 mg + DP, q3w × 2; RP: DDP, q3w × 2 + IMRT; AP: camrelizumab 200 mg, q3w × 12	NA	DFS: 3-year rate, 84.0%	3-year rate, 89.5%	No	No

PD-1, programmed cell death protein-1; LA-NPC, locoregionally advanced nasopharyngeal carcinoma; E/C, experimental group/control group; IP, induction phase; RP, radiotherapy phase; AP, adjuvant phase; QoL, quality of life; GP, gemcitabine-cisplatin; DDP, cisplatin; DP, docetaxel-cisplatin; IMRT, intensity-modulated radiotherapy; EFS, event-free survival; PFS, progression-free survival; FFS, failure-free survival; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; NA, not applicable; NR, not reported; q3w, once every 3 weeks; RATint, risk-adaptive therapy intermediate-risk group; RAThigh, risk-adaptive therapy high-risk group; p.o., oral administration; bid, twice per day. *Survival comparisons are presented as experimental group *vs.* control group, whereas for single-arm trials, survival outcomes are reported with the cohort as the experimental group, without reporting HR (95% CI) or *P*-values.

a set of considerations that remain open to debate.[4] Clinical implementation of the concurrent cisplatin-sparing strategy relies on continuous PD-1 blockade throughout the treatment course, favorable early response to induction-phase treatment, and high-quality implementation of radiotherapy. From a real-world perspective, current studies have not included older patients, those with multiple comorbidities, or individuals from non-endemic regions. The radiosensitizing effect of cisplatin remains irreplaceable for patients who have unsatisfactory responses to induction-phase treatment.[9,10] Furthermore, the omission of concurrent cisplatin requires prolonged courses of immunotherapy, e.g., as many as 17 cycles of PD-1 blockade with toripalimab. However, the optimal duration of PD-1 blockade remains undefined, and such prolonged exposure may increase the economic burden on patients. Cost-utility and cost-minimization analyses are warranted to define the optimal duration of adjuvant PD-1 blockade. Furthermore, the DIAMOND trial reports only 3-year follow-up data and lacks long-term survival and late toxicity results, thus restricting the extrapolation of conclusions. Core eligibility criteria may include patients with absolute contraindications to cisplatin, such as those with severe neuropathy or ototoxic injury, and patients who achieve radiological complete response and/or biological complete response after induction chemotherapy. Potential ineligible patient populations include those with poor response to induction chemotherapy, borderline renal dysfunction, and older patients with compromised physical status.

Advances in chemotherapy de-escalation regimens

The integration of immunotherapy has made chemotherapy de-escalation feasible in LA-NPC. The DIAMOND regimen comprising PD-1 blockade plus chemoradiotherapy without concurrent cisplatin has been incorporated into the Chinese Society of Clinical Oncology guidelines (version 2025) and National Comprehensive Cancer Network guidelines for China (version 2026). However, its universal applicability remains debated. A broad consensus favors balancing efficacy and toxicity to avoid inappropriate de-escalation. Individualized de-escalation guided by dynamic monitoring of Epstein–Barr virus (EBV) DNA may be a critical direction for future treatment optimization.

In parallel, chemotherapy de-escalation combined with immunotherapy has advanced in unresectable locally advanced non-small cell lung cancer (NSCLC). For patients with locoregionally advanced NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1, current studies prioritize biomarker-driven selection through positive programmed cell death-ligand 1 (PD-L1) expression.[11,12] In the DOLPHIN trial, patients with a PD-L1 tumor proportion score ≥1% received durvalumab plus definitive radiotherapy without concurrent chemotherapy, achieving a 12-month progression-free survival (PFS) rate of 72.1% and an objective response rate of 90.9%.[9] Building on previous evidence in locoregionally advanced NSCLC, the SPRINT trial used a stricter tumor proportion score ≥50% and tested induction pembrolizumab followed by risk-adapted radiotherapy alone. The 1-year PFS rate of 76% and objective response rate of 48% suggested the promise of this chemotherapy de-escalation option for patients with high PD-L1 expression.[10] For older patients with comorbidities, or those with ECOG scores ≥2 who cannot tolerate chemotherapy, studies have generally adopted a passive de-escalation approach, which involves omitting concurrent chemotherapy without mandating PD-L1 expression, to increase feasibility.

Accordingly, chemotherapy de-escalation strategies for LA-NPC are increasingly centered on risk-adapted individualized management. Robust evidence has established plasma EBV DNA as a dynamic biomarker for risk-adaptive therapy (RAT). In 2019, Lv et al. retrospectively demonstrated that longitudinal on-treatment EBV DNA kinetics can be used to monitor response and prognosis, and developed a stratification model integrating clinical stage with pretreatment EBV DNA levels.[13] On this basis, the prospective EP-SEASON study was conducted, in which blood samples were serially collected at 11 time points during treatment from 1,000 patients, and EBV DNA kinetics was comprehensively characterized throughout induction chemotherapy and radiotherapy.[14] The same research group subsequently initiated the multicenter, non-randomized phase 2 EP-STAR trial, with 58 intermediate-risk and 52 high-risk patients assigned to the RAT arm, and 32 low-risk patients receiving standard-of-care therapy. Risk-matched patients from the EP-SEASON cohort, who did not receive RAT, served as a non-randomized contemporaneous external control. The RAT arm demonstrated significantly greater 3-year FFS than the no-RAT control arm (89.1% *vs.* 74.4%). Low-risk patients receiving standard therapy achieved a 3-year FFS of 90.6%, thereby reflecting the favorable prognosis associated with early circulating tumor DNA clearance. Collectively, these findings provide high-level evidence supporting a paradigm shift from "one-size-fits-all" approach to precision therapy in LA-NPC.[7] Additionally, Li et al. conducted a randomized phase 2 non-inferiority trial comparing two *vs.* three cycles of concurrent cisplatin in patients with LA-NPC, who had baseline EBV DNA <4,000 copies/mL.[15] The two-cycle group exhibited non-inferior 3-year PFS (88.0% *vs.* 90.4%) with significantly diminished toxicity, thus directly validating the efficacy and safety of EBV DNA-guided de-escalation in low-risk patients with LA-NPC. The international multicenter NRG-HN001 trial (NCT02135042) is currently stratifying patients by end-of-treatment plasma EBV DNA detectability to guide adjuvant therapy after chemoradiotherapy: the phase 2 portion compares intensified

paclitaxel-gemcitabine with cisplatin-fluorouracil in high-risk patients with persistently detectable EBV DNA, whereas the phase 3 non-inferiority portion compares observation (no any interventions) with adjuvant cisplatin-fluorouracil in those with undetectable EBV DNA. This design is aimed at generating prospective evidence supporting EBV DNA-driven, risk-adapted de-escalation. Nevertheless, a key limitation is that the applicability of this stratification criterion remains under prospective validation in the setting of immune-chemoradiotherapy without concurrent cisplatin. An ongoing phase 3 randomized controlled trial (NCT07154069) is investigating a risk-adapted framework integrating immunotherapy. In low-risk patients (EBV DNA negative plus partial/complete response after induction chemotherapy), the trial is assessing whether omission of concurrent chemotherapy might be non-inferior to concurrent chemoradiotherapy on a backbone of induction and adjuvant immunotherapy. In high-risk patients (EBV DNA positive or have stable disease after induction chemotherapy), the trial is evaluating whether the addition of metronomic capecitabine might provide added benefits.

Clinical trial advances of PROs in LA-NPC

As LA-NPC treatment shifts toward patient-centered strategies, PROs have become a cornerstone for assessing patients' subjective treatment experiences. Through comprehensive assessment of patient well-being, social reintegration, and treatment tolerance under immune-chemoradiotherapy, PROs provide robust evidence of the clinical value of low-toxicity, highly effective regimens in optimizing patient-centered health outcomes.

Although multiple clinical trials of chemoradiotherapy with or without immunotherapy in LA-NPC have reported QoL-related results (**Table 2**),[1-7,16,17] the first dedicated PRO analysis was based on the PLATINUM trial, which demonstrated favorable results in social reintegration, QoL recovery, and tolerability with the nivolumab-based concurrent cisplatin-sparing therapy.[18] Regarding the inconsistent effects of PROs *vs.* clinician-reported outcomes on prognosis, this study identified a correlation between clinicians' under-reporting of decreased appetite and poor FFS. Moreover, this study highlighted two key unmet needs in the interpretation of toxicity and QoL data in NPC: over-reliance on clinician-reported outcomes rather than PRO data, and an exclusive focus on statistically significant differences at the expense of overlooking clinically meaningful outcomes.[18] Simultaneous analysis of QoL from both clinical and statistical perspectives enables more precise characterization of post-treatment QoL trajectories and therefore may uncover potential patterns associated with patient prognosis. The single-arm design of the PLATINUM trial permitted comparisons of only the effects of different treatment phases on QoL, and exploration of prognostic effects from the discordance between patient- and clinician-reported assessments. An ongoing dedicated PRO analysis based on the DIAMOND trial is using a randomized controlled design to directly compare PRO indicators between the concurrent cisplatin-sparing group and the standard-therapy group. This investigation is expected to deliver the most comprehensive PRO analysis in the immunotherapy era for NPC, thereby addressing the clinical demand for patient-centered treatment strategies.

In addition, PRO assessment facilitates radiotherapy optimization. A key developmental trend in NPC radiotherapy is the refinement of target volume delineation and the optimization of dose restriction strategies. This treatment concept demands stricter limitations on the irradiation dose and volume of normal tissues, including salivary glands and pharyngeal constrictors. Therefore, PRO assessment helps track the resolution of radiotherapy-related toxicities and promotes post-treatment functional recovery. A phase 3 clinical trial using a QoL questionnaire as the core PRO endpoint has indicated significantly better swallowing function at 3 years after sparing radiotherapy to the medial retropharyngeal lymph nodes, compared with standard radiotherapy.[19] A phase 2 randomized trial (NCT05834712) is innovatively exploring a mobile-based digital intervention for PRO-driven nutritional evaluation in NPC to advance the field toward digitalization and precision.

Currently, the implementation of PROs in NPC research remains relatively insufficient. Studies using validated PRO instruments remain limited, and the utilization rates are markedly below those in breast, lung, and colorectal cancers.[4,5] Systematic integration of PROs into NPC clinical trials will be essential to improve evaluation systems and capture patient-centered data reflecting the full treatment experience.

Future directions for immunotherapy in NPC

Future exploration of combination immunotherapy for NPC may follow two directions: identifying the optimal combinations of immunotherapy with different chemoradiotherapy regimens to achieve high efficacy and low toxicity (**Figure 1A**), and verifying the optimal timing for immunotherapy administration during the induction and adjuvant phases (**Figure 1B**). Traditional intravenous adjuvant chemotherapy has drawbacks of high toxicity, poor patient tolerance, and limited potential for further survival improvement. To address these challenges, Chen et al. have performed a phase 3 clinical trial validating the feasibility of oral metronomic capecitabine as an adjuvant therapy for patients with LA-NPC.[16] This well-tolerated, low-toxicity adjuvant therapy increased 1-year

Table 2 Summary of PRO reporting in chemotherapy-based trials with or without immunotherapy for LA-NPC

Study (identifier)	Sample size*	Stage	Study design	Interventional regimens	PRO scales
Liu et al.[1] (NCT03700476)	357	III–IVA, except T3–4N0 and T3N1 (AJCC 8th)	Multicenter, phase 3, RCT	GP IC + CCRT + sintilimab (induction, concurrent, and adjuvant)	EORTC QLQ-C30
Liang et al.[2] (NCT03427827)	334	T4N1M0/T1–4N2–3M0 (AJCC 8th)	Multicenter, phase 3, RCT	GP IC + CCRT + adjuvant camrelizumab	EORTC QLQ-C30
Liu et al.[3] (NCT03925090)	87	III–IVA (AJCC 8th)	single-center, phase 2, RCT	CCRT + toripalimab (induction and adjuvant)	EORTC QLQ-C30, EORTC QLQ-H&N35
Xu et al.[4] (NCT04907370)	532	T4N1M0/T1–4N2–3M0 (AJCC 8th)	Multicenter, phase 3, RCT	GP IC + IMRT + toripalimab (induction, concurrent, and adjuvant)	PRO-CTCAE, EORTC QLQ-C30, EORTC QLQ-H&N35, FACT-G, FACT-H&N
Xu et al.[5] (NCT03984357)	152	T4N1M0/T1–4N2–3M0 (AJCC 8th)	Multicenter, phase 2, single-arm	GP IC + IMRT + nivolumab (induction, concurrent, and adjuvant)	PRO-CTCAE, EORTC QLQ-C30, EORTC QLQ-H&N35, FACT-G, FACT-H&N
You et al.[6] (NCT04453826)	572	T4NxM0/TxN3M0 (AJCC 8th)	Multicenter, phase 3, RCT	GP IC + CCRT + camrelizumab (concurrent and adjuvant)	EORTC QLQ-C30
Lv et al.[7] (NCT04072107)	306	III–IVA (AJCC 8th)	Multicenter, phase 2	ctEBV DNA-guided risk-adapted therapy	EORTC QLQ-C30
Chen et al.[16] (NCT02958111)	335	III–IVA, except T3–4N0 and T3N1 (AJCC 8th)	Multicenter, phase 3, RCT	Definitive chemoradiotherapy + adjuvant metronomic capecitabine	EORTC QLQ-C30
Tang et al.[17] (NCT01540136)	145	T1–4N1–3M0/T3–4N0M0 (AJCC 7th)	Two centers, phase 3, RCT	IMRT + concurrent nedaplatin	EORTC QLQ-C30, QLQ-H&N35

PRO, patient-reported outcome; LA-NPC, locoregionally advanced nasopharyngeal carcinoma; GP, gemcitabine-cisplatin; IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; IMRT, intensity-modulated radiotherapy; MRLN, medial retropharyngeal lymph node; ctEBV, circulating tumor Epstein-Barr; AJCC, American Joint Committee on Cancer; RCT, randomized controlled trial; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, quality-of-life questionnaire core-30; QLQ-H&N35, quality-of-life questionnaire head-and-neck-35; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-H&N, Functional Assessment of Cancer Therapy-Head and Neck. *Recorded sample size is the maximum number of respondents across the different PRO questionnaires.

FFS by 9.6%, decreased the risk of recurrence or death by 50%, and effectively decreased the risk of distant metastasis. According to preclinical studies, metronomic chemotherapy exerts immunomodulatory effects and might potentially have synergistic activity with PD-1 blockade. On the basis of these results, two phase 3 randomized controlled trials have been initiated in high-risk LA-NPC to further increase survival: one trial is evaluating the addition of tislelizumab to metronomic capecitabine after definitive chemoradiotherapy to further decrease the risk of recurrence (NCT05342792), and the other is investigating whether maintenance therapy with capecitabine plus sintilimab, compared with sintilimab alone after induction immunochemotherapy, might improve survival outcomes (NCT06900218).

The "sandwich" strategy, which administers immunotherapy only during induction and adjuvant phases without concurrent radiotherapy, is the most recent advance in synergistic treatment combining immunotherapy with chemoradiotherapy. Mechanistically, radiotherapy activates the cyclic guanosine monophosphate–adenosine monophosphate synthase–stimulator of interferon genes (cGAS-STING) pathway and type I interferon response, and upregulates major histocompatibility complex-I and immune checkpoints, thereby recruiting and activating T cells. In contrast, radiotherapy may upregulate multiple immunosuppressive factors in tumor cells, enhance the function of regulatory T cells and myeloid-derived suppressor cells, and induce lymphopenia and exhaustion of effector immune cells.[20] Several phase 3 trials of PD-1/PD-L1 blockade plus chemoradiotherapy *vs.* chemoradiotherapy alone in head and neck and lung cancers have not demonstrated a significant primary survival benefit.[4,5] The "sandwich" strategy addresses the critical challenge of combination therapy by precisely balancing these two opposing effects along the temporal axis. A randomized, double-blind, placebo-controlled phase 2 study has evaluated the efficacy of this "sandwich" strategy in high-risk LA-NPC.[3] Compared

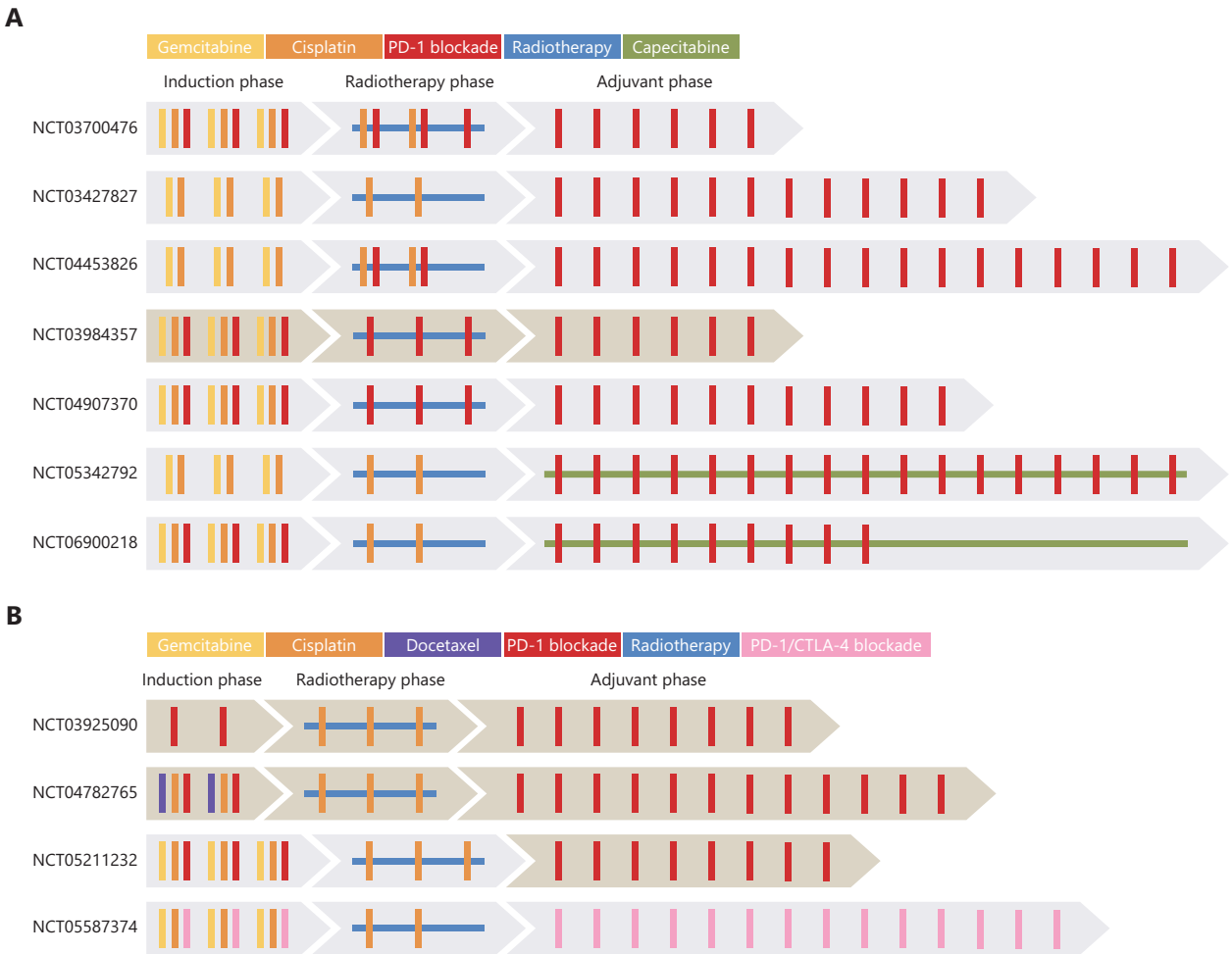

Figure 1 Summary of treatment regimens from landmark trials investigating immunotherapy combined with chemoradiotherapy in LA-NPC. (A) Immunotherapy combined with various chemotherapy regimens, including induction-concurrent chemotherapy, induction chemotherapy without concurrent cisplatin, and induction-concurrent chemotherapy followed by adjuvant capecitabine. (B) The "sandwich" strategy of immunotherapy combined with chemoradiotherapy. Under this strategy, immunotherapy is administered exclusively during induction and adjuvant phases, with no concurrent delivery during radiotherapy. Study phase is indicated by background shading: gray for phase 3 and brown for phase 2. Four phase 3 trials, CONTINUUM (NCT03700476[1]), DIPPER (NCT03427827[2]), NCT04453826[6], and DIAMOND (NCT04907370[4]), and three phase 2 trials, PLATINUM (NCT03984357[5]), NCT03925090[3], and NCT04782765,[8] have been published, whereas the remaining four phase 3 trials, NCT05342792, NCT06900218, NCT05211232, and NCT05587374, are unpublished. LA-NPC, locoregionally advanced nasopharyngeal carcinoma; PD-1, programmed cell death protein-1; CTLA-4, cytotoxic T-lymphocyte associated protein 4.

with the control group receiving concurrent chemoradiotherapy, the experimental group received two cycles of induction toripalimab and eight cycles of adjuvant toripalimab, which significantly improved 2-year PFS by 18.0% (92.0% *vs.* 74.0%), and decreased the risk of progression or death by 60%. This study has provided the first clinical validation of the "sandwich" strategy as a highly effective approach for combining immunotherapy with conventional chemoradiotherapy in high-risk LA-NPC. The BEACON trial (NCT05211232) is investigating the efficacy and safety of PD-1 blockade with tislelizumab during the induction and adjuvant phases *vs.* induction chemotherapy followed by concurrent chemoradiotherapy as the control in LA-NPC. The GEMSTONE trial (NCT05587374), which utilizes a similar study design, is exploring the "sandwich" strategy with cadonilimab, a bispecific antibody targeting both PD-1 and cytotoxic T lymphocyte-associated protein-4 (CTLA-4), in patients with LA-NPC. Both trials are expected to provide critical insights into the optimal sequencing of chemoradiotherapy and immunotherapy in the management of NPC.

Conclusions

Immunotherapy has delivered transformative breakthroughs in the management of LA-NPC. The DIAMOND trial has demonstrated that a concurrent cisplatin-sparing regimen can effectively balance efficacy and safety. The landscape of PRO research within NPC immunotherapy has rapidly expanded, and chemotherapy de-escalation approaches remain in constant evolution. Precise risk stratification using dynamic circulating EBV DNA monitoring is essential to avoid inappropriate treatment reduction. Future advances will emphasize immunotherapy combining with capecitabine and the "sandwich" strategy integrated with conventional chemoradiotherapy, with the goals of enhancing efficacy and advancing individualized patient care.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Cheng Xu.
Collected the data: Yingni Zhang, Chunxian Ou.
Wrote the paper: Yingni Zhang, Chunxian Ou.

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