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PERSPECTIVE

A bispecific EGFR × HER3 antibody–drug conjugate for later-line recurrent or metastatic nasopharyngeal carcinoma: insights from BL-B01D1-303

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First-line immunochemotherapy has reshaped the treatment landscape for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC). In many NPC endemic regions, platinum-based chemotherapy combined with PD-1/PD-L1 blockade is now considered the standard first-line approach (**Figure 1**)[1-4]. However, treatment after disease progression remains poorly defined. Clinical practice varies across regions, and no globally accepted standard has been established[5,6]. The phase 3 BL-B01D1-303 trial is therefore important because it evaluates a novel treatment for an increasingly common patient population: patients with R/M NPC who have received both platinum-based chemotherapy and immune checkpoint blockade, yet effective later-line options remain limited. In this heavily pretreated population, izalontamab brengitecan (iza-bren; BL-B01D1), a bispecific EGFR × HER3 antibody–drug conjugate (ADC), resulted in better responses and progression-free survival (PFS) in comparison to chemotherapy[7]. These findings support iza-bren as a later-line option after platinum and PD-1/PD-L1 blockade, particularly for patients who require tumor shrinkage and have adequate bone marrow reserve to tolerate treatment.

Defining the later-line treatment landscape

The definition of late-line treatment needs to be clarified. In regions where first-line immunochemotherapy is standard for NPC, later-line treatment is increasingly administered after progression on immunotherapy, while in some settings, patients continue to receive salvage treatment after progression on chemotherapy alone. These populations may differ substantially in prior treatment exposure, bone marrow reserve, access to subsequent care, and treatment goals.

This distinction is important for clinical interpretation. Patients who experience NPC progression on first-line gemcitabine/cisplatin and PD-1 inhibitor represent a clinically distinct population from those who received chemotherapy alone due to unavailability of immunotherapy. In clinical practice, later-line treatment selection depends not only on the line of therapy but also on the urgency of disease control, the risk of toxicity, the tolerance of prior therapy, and the feasibility of subsequent treatment.

BL-B01D1-303 enrolled patients with R/M NPC who had received at least two prior lines of systemic therapy, including platinum-based chemotherapy and PD-1/PD-L1 inhibitors. This is now a common scenario in clinical practice: patients have already been exposed to the two principal systemic treatment backbones for advanced NPC but may still require effective tumor reduction.

Current salvage options, including taxanes, capecitabine, gemcitabine, and platinum rechallenge, usually provide limited and short-lived benefits[5,6,8]. Addressing the unmet need for these patients requires not simply another active agent but a treatment that induce meaningful tumor responses without causing severe toxicity. This benefit–risk balance is particularly important in NPC because many patients have received prior radiotherapy and multiple courses of cytotoxic therapy and may have symptomatic metastatic disease.

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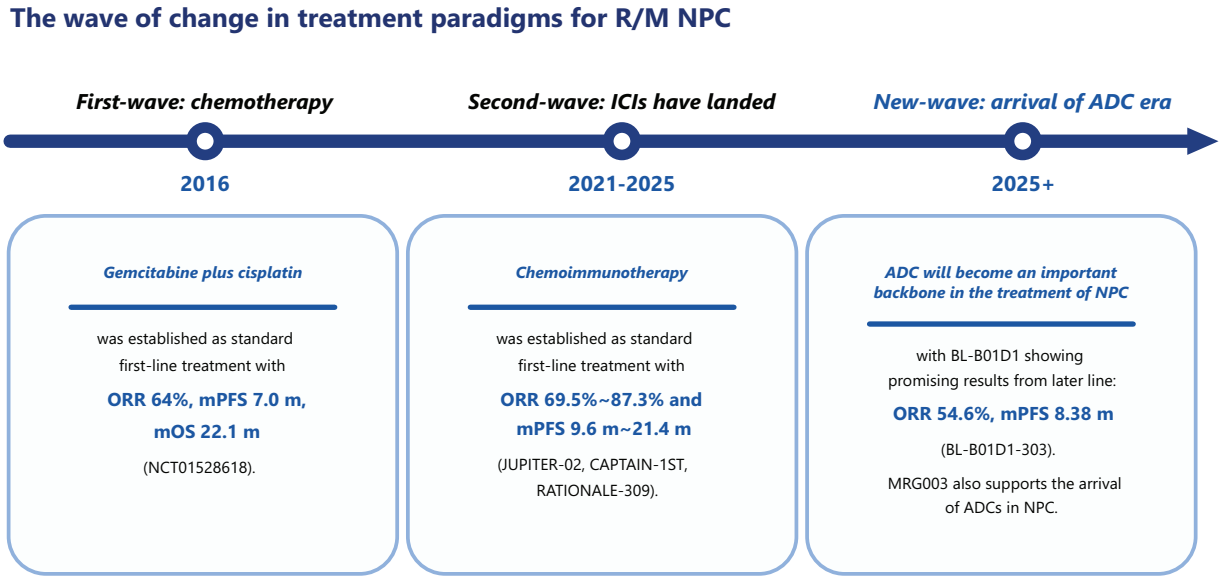

Figure 1 Treatment for recurrent or metastatic nasopharyngeal carcinoma. This timeline summarizes three successive treatment waves in R/M NPC. First-wave: chemotherapy. The timeline begins in 2016, when gemcitabine plus cisplatin was established as standard first-line treatment for R/M NPC, with an ORR of 64%, mPFS of 7.0 months, and mOS of 22.1 months in NCT01528618. Second-wave: ICIs have landed. From 2021 to 2025, chemoimmunotherapy was established as a first-line standard, with ORRs of 69.5%–87.3% and mPFS of 9.6–21.4 months across JUPITER-02, CAPTAIN-1ST, and RATIONALE-309. New-wave: arrival of the ADC era. From 2025 onwards, ADCs represented an emerging treatment backbone for NPC: BL-B01D1 showed later-line activity in the BL-B01D1-303 trial, with an ORR of 54.6% and mPFS of 8.38 months, and the MRG003 data provide additional evidence supporting the use of ADCs for NPC treatment. ADC, antibody–drug conjugate; ICI, immune checkpoint inhibitor; m, months; mOS, median overall survival; mPFS, median progression-free survival; NPC, nasopharyngeal carcinoma; ORR, objective response rate; R/M, recurrent or metastatic.

BL-B01D1-303 in later-line NPC: established efficacy and unresolved issues

At the time of study design, no standard later-line regimen existed; physician's choice of chemotherapy (PCC) was therefore used as the control. The ADC-naive study population had already received the principal systemic backbones now used for advanced NPC in many regions, while cumulative exposure to prior therapy may have reduced treatment tolerance, which underscores the need to interpret efficacy alongside safety[9].

Iza-bren showed clinically meaningful efficacy relative to chemotherapy (**Figure 2**). On blinded independent central review, the objective response rate (ORR) was 54.6% with iza-bren *vs.* 27.0% with chemotherapy. Median PFS was 8.38 months with iza-bren *vs*. 4.34 months with chemotherapy, and the median duration of response (DoR) was 8.51 months *vs*. 4.76 months. In this heavily pretreated population, concordant improvements in ORR, PFS, and DoR support the antitumor efficacy of iza-bren relative to chemotherapy.

Earlier evidence for ADCs in NPC and related solid tumors came largely from early-phase, single-arm studies or conference reports[9-14]. BL-B01D1-303 advances the evidence base for bispecific ADCs in NPC from early-phase and single-arm observations to a disease-specific randomized phase 3 trial and provides the first disease-specific data in this setting. Although the trial findings do not establish iza-bren as a default later-line option, they provide stronger evidence to support its use after platinum-based chemotherapy and PD-1/PD-L1 blockade.

Several trial features should be considered when interpreting these results. BL-B01D1-303 had an open-label design, which was a pragmatic choice because iza-bren and PCC differ in administration routes and treatment schedules; blinding would have required a complex double-dummy approach. This design does not invalidate the efficacy findings, as objective responses and PFS were assessed *via* blinded independent central review, which reduces the risk that knowledge of treatment assignment biases assessment of the radiographic endpoint. Nevertheless, blinded image review cannot eliminate the potential effects of treatment awareness on adverse-event reporting, supportive care, dose modifications, treatment

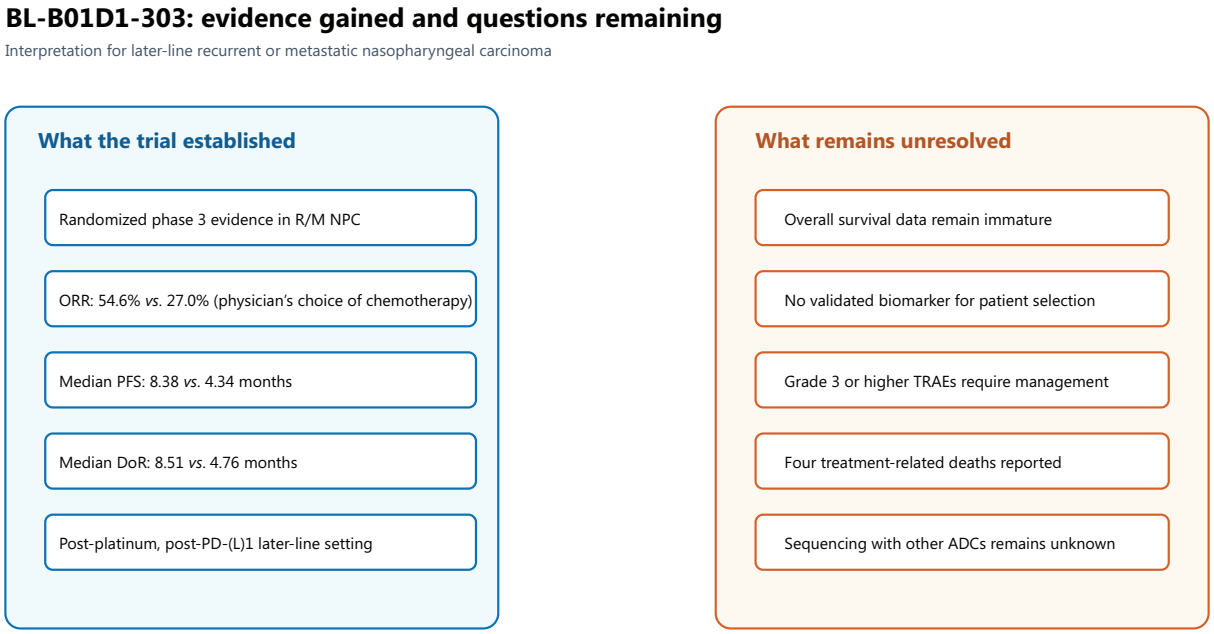

Figure 2 What BL-B01D1-303 established and what remains unresolved in later-line NPC. (1) Established evidence. In patients with R/M NPC previously treated with platinum-based chemotherapy and PD-1/PD-L1 blockade, iza-bren improved ORR, PFS, and DoR in comparison to physician's choice of chemotherapy in a randomized phase 3 trial. (2) Unresolved questions. OS data remain immature. BL-B01D1-303 did not mandate prospective collection of tumor tissue for central testing of EGFR or HER3 expression. Therefore, correlations between baseline target expression and either response or survival outcomes cannot be assessed. Samples were also not prospectively collected for baseline or longitudinal assessment of plasma EBV DNA, leaving its value for response monitoring or prediction of ADC benefits unclear. The high incidence of grade ≥3 TRAEs and four treatment-related deaths necessitate careful patient selection, monitoring, supportive care, and dose modification. In addition, patients previously treated with an EGFR- or HER3-directed ADC or an ADC containing a TOP1 inhibitor payload were excluded. The trial therefore does not establish how iza-bren should be used after another ADC, whether the target or payload class should guide ADC sequencing, or which ADC should be selected first when multiple approved options are available. ADC, antibody–drug conjugate; DoR, duration of response; EBV, Epstein-Barr virus; EGFR: epidermal growth factor receptor; HER3: human epidermal growth factor receptor 3; NPC, nasopharyngeal carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/M, recurrent or metastatic; TRAE, treatment-related adverse event.

discontinuation, or patient-reported outcomes. Given that no standard later-line regimen existed when the trial was designed, and considering the established activity of capecitabine, gemcitabine, and docetaxel, these agents were chosen as pragmatic comparators. The trial therefore provides a contemporaneous phase 3 estimate of chemotherapy efficacy in heavily pretreated R/M NPC. However, the control arm was heterogeneous, and efficacy for the chemotherapy regimen selected was not reported. BL-B01D1-303 thus establishes the benefit of iza-bren over PCC overall but does not define its relative effect against each individual salvage regimen. In addition, all participants were enrolled in an endemic region in which undifferentiated nonkeratinizing NPC predominates. It remains unknown whether the efficacy and toxicity profile of iza-bren extends to non-endemic regions, particularly to populations in which keratinizing NPC is more common. Evaluation in more diverse populations is needed because prior treatment patterns, access to PD-1/PD-L1 inhibitors and ADCs, and practices for supportive care may differ across regions.

Iza-bren in later-line NPC: managing hematologic toxicity and refining patient selection

Toxicity is a key consideration when interpreting the trial results. Treatment-related adverse events (TRAEs) of grade ≥3 occurred in 80% of patients in the iza-bren group and 62% in the PCC group. The predominant severe toxicities were hematological, including anemia (50%), and decreases in white blood-cell (43%), platelet (43%), and neutrophil (38%) counts. The incidence of serious TRAEs was 43% in the iza-bren arm and 27% in the PCC arm. Four treatment-related deaths occurred in the iza-bren group, attributed to febrile

neutropenia in two patients, thrombocytopenia in one patient, and unknown cause in one patient. Serious nonhematologic TRAEs were less frequent, including asthenia, nausea, decreased appetite, constipation, hypoalbuminemia, and stomatitis. Interstitial lung disease (ILD) was uncommon: two patients (1%) developed grade 2 ILD, and no grade ≥3 events or ILD-related deaths occurred in the iza-bren group. These findings identify myelosuppression, infection, and bleeding as central considerations in patient selection and clinical decision-making. Therefore, the decision to use iza-bren cannot be based on efficacy alone. Until survival data have matured, shared decision-making should balance the probability of a tumor response against severe hematologic toxicity and treatment-related mortality.

In routine practice, complete blood counts should be monitored regularly, with particular attention to patients with limited bone marrow reserve or prior myelosuppressive therapy. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was permitted after individual risk assessment, and secondary prophylaxis was recommended after febrile neutropenia or grade ≥3 neutropenia. In the trial, prophylactic G-CSF was administered to 93% of patients in the iza-bren group. Clinically significant cytopenia warrants treatment interruption and supportive care. For grade 4 neutropenia or febrile neutropenia, the study protocol required treatment interruption until recovery, followed by a one-dose level reduction. For grade 3 or 4 anemia and thrombocytopenia, management options included treatment delay, red cell or platelet support as clinically indicated, and dose reduction based on the severity and time to recovery. After dose reduction, re-escalation was not permitted. TRAEs led to dose interruption in 61.4% of patients and dose reduction in 41.8%; permanent discontinuation occurred in 3%. Management of hematological toxicity frequently involved prophylactic and supportive measures, treatment interruption, and dose reduction; however, the occurrence of fatal febrile neutropenia and thrombocytopenia underscores the need for early recognition and intervention.

Patients with R/M NPC who experience disease progression on platinum-based chemotherapy and PD-1/PD-L1 blockade are most likely to be considered for iza-bren, particularly those who would benefit from tumor shrinkage and have adequate performance status and bone marrow reserve. Persistent cytopenia, recurrent infections, poor nutritional status, and prior myelosuppressive therapy may limit the feasibility of iza-bren treatment. Prior radiotherapy and multiple lines of systemic therapy do not necessarily preclude iza-bren treatment, but warrant careful baseline assessment and early dose management. For these patients, the key question is not whether iza-bren elicits a response, but whether it can be safely administered at a sufficient dose and duration to yield clinically meaningful benefit.

Rationale for an EGFR × HER3 bispecific ADC and its limitations

The first-in-human study of BL-B01D1 demonstrated the feasibility and preliminary antitumor activity of this bispecific ADC in patients with advanced solid tumors. The BL-B01D1-303 trial subsequently evaluated the agent in a disease-specific randomized phase 3 setting. The key question is whether dual EGFR × HER3 targeting provides a clinically meaningful advantage over single-target EGFR approaches; a potential rationale for such an advantage could be broader tumor cell engagement. In principle, EGFR and HER3 may be heterogeneously expressed across tumor cells and lesions. Because iza-bren can bind to either receptor, it may deliver the Topoisomerase 1 (TOP1) inhibitor (Ed-04) payload to EGFR-dominant, HER3-dominant, and dual-positive cells, whereas an EGFR-directed monospecific ADC remains dependent on EGFR expression. Preclinical studies indirectly support this possibility, but there is no specific proof for the NPC setting. In prostate cancer models, expression of either receptor increased BL-B01D1 sensitivity, with the greatest sensitivity in cells expressing both receptors[15]. Iza-bren also resulted in greater inhibition of tumor growth than either parental anti-EGFR or anti-HER3 ADCs with the same linker and payload in selected xenograft models of colorectal and pancreatic cancers[16].

Beyond broader target engagement, another potential advantage of dual targeting may involve modulation of Erythroblastic Oncogene B (ERBB) signaling. EGFR and HER3 are members of the ERBB receptor family and are frequently coexpressed in several epithelial tumor types. Through heterodimerization with other ERBB receptors, particularly HER2, EGFR and HER3 can cooperatively activate downstream pathways such as Phosphatidylinositol 3-Kinase-Protein Kinase B and Mitogen-Activated Protein Kinases. In models of EGFR-mutated non–small cell lung cancer (NSCLC), EGFR inhibition can increase cell-surface HER3 by relieving negative feedback, whereas residual activity of EGFR or other ERBB family members may continue to support HER3 signaling[17]. Consistent with this biology, dual EGFR–HER3 antibodies suppressed compensatory signaling more broadly than antibodies targeting either receptor alone in models of EGFR-inhibitor–resistant NSCLC and head and neck squamous-cell carcinoma[18]. These findings suggest that dual EGFR × HER3 targeting could combine receptor-mediated payload delivery with suppression of compensatory ERBB signaling. Whether these effects confer a clinically meaningful advantage over single-target ADCs in NPC remains to be established.

Broader binding does not necessarily translate into effective killing of tumor cells. The antibody component largely determines target recognition and receptor-mediated uptake, whereas the Ed-04 payload induces DNA damage and cell death after intracellular release. In prostate cancer cell-line assays, the unconjugated parental bispecific antibody SI-B001

showed minimal cytotoxicity, whereas BL-B01D1 retained cytotoxic activity, which suggests that pathway blockade alone could not account for cytotoxicity[15]. Exploratory analyses of a limited panel of small-cell lung cancer cell lines suggested that EGFR abundance was primarily associated with endolysosomal uptake, whereas HER3 abundance was more closely linked to cytotoxic sensitivity[19]. Resistance can also arise after payload release. In prostate cancer models, Adenosine triphosphate Binding Cassette Subfamily G Member 2 (ABCG2) upregulation reduced BL-B01D1 sensitivity, whereas ABCG2 inhibition restored it[15]. The antitumor activity of iza-bren may therefore depend on three separate factors: receptor availability, intracellular payload delivery, and sensitivity to Ed-04.

Future mechanistic studies should address three questions. First, tumor specimens should be analyzed to determine whether spatial patterns of EGFR/HER3 expression are associated with clinical outcomes. Second, studies in NPC models comparing iza-bren with SI-B001 and matched single-target ADCs should investigate whether bispecificity enhances signaling suppression, broadens tumor-cell coverage, or improves Ed-04 delivery. Third, when resistance develops, paired baseline and progression samples should be analyzed to determine whether resistance is associated with loss of receptor expression, impairment of ADC internalization or payload release, or reduced sensitivity to Ed-04.

ADC selection in R/M NPC: beyond response rates

ADCs have entered clinical practice in China for previously treated R/M NPC (**Table 1**). Becotatug vedotin (MRG003), an EGFR-directed ADC containing monomethyl auristatin E (MMAE), and iza-bren are both approved treatment options in China[7,11-13]. In a phase 2a single-arm study, MRG003 achieved an ORR of 42%, a disease control rate of 81%, median DoR of 8.0 months, median PFS of 5.8 months, and median OS of 15.8 months; grade ≥3 TRAEs occurred in 39% of patients, and no treatment-related deaths were reported. Interim results from a randomized phase 2b study presented at the 2025 American Society of Clinical Oncology conference revealed an ORR of 30.2% *vs*. 11.5%, median PFS of 5.8 *vs*. 2.8 months, and interim OS of 17.1 *vs*. 12.0 months for MRG003 *vs*. PCC. Together, these studies support clinically meaningful antitumor activity with EGFR-directed ADC therapy in heavily pretreated R/M NPC.

The studies of MRG003 and iza-bren differ substantially in trial design, patient population, and follow-up duration. Accordingly, the available evidence does not permit a reliable ranking of the two agents. The availability of both agents has expanded later-line treatment options for patients with previously treated R/M NPC in China. Iza-bren differs from MRG003 in both target design (dual targeting of EGFR × HER3 rather than EGFR alone) and payload class. The key question is not whether one response rate is higher than another across trials, but whether differences in target design and payload class offer distinct clinical options[7,9,11-13].

The ADC payload may also influence treatment selection. The tolerability of ADCs with MMAE and TOP1 inhibitor payloads may differ in patients with limited bone marrow reserve after prior therapy. Current evidence in NPC does not support payload-based sequencing, but it underscores the need to consider toxicity when selecting an ADC. In BL-B01D1-303, iza-bren was associated with severe hematologic toxicity and treatment-related mortality. In the phase 2a study of MRG003, grade ≥3 TRAEs occurred in 39% of patients and there were no treatment-related deaths[12]. These findings do not constitute a head-to-head safety comparison between ADCs with MMAE and TOP1 inhibitor payloads; nevertheless, the toxicity data reported may influence treatment selection. Even among ADCs with a TOP1 inhibitor payload, toxicity profiles can differ substantially. ILD is a major safety concern with deruxtecan-containing ADCs in breast, gastric, and other solid tumors[20]. In BL-B01D1-303, two patients (1%) receiving iza-bren developed grade 2 ILD, with no grade ≥3 ILD observed in that group. In the chemotherapy group, two patients (1%) developed grade 3 ILD.

YL201, a B7-H3-directed ADC with a TOP1 inhibitor payload, represents a non-EGFR ADC approach in NPC[14]. In a phase 1/1b study, the NPC cohort comprised 70 heavily pretreated patients; all had received prior anti-PD-1 therapy and platinum-based chemotherapy, and 84.3% had received at least two prior lines of systemic therapy. The ORR was 48.6% and the disease control rate was 92.9%. These YL201 data provide an early signal of clinical activity for a non-EGFR ADC in NPC. However, the role of YL201 in NPC remains to be fully defined as current data derive from an early-phase pan-tumor study rather than an NPC-specific randomized trial. An NPC-specific phase 3 trial of YL201 is ongoing. Efforts to define the clinical role of this agent will require evidence on whether target expression, payload sensitivity, and toxicity profiles can identify a distinct patient population that would benefit from EGFR-based ADCs. At present, these ADCs should be regarded as complementary development pipelines rather than interchangeable options.

Clinical studies are also evaluating ADC-based combinations and earlier-line treatment. Although NPC-specific clinical evidence is lacking, preclinical data from ADCs with a TOP1 inhibitor payload indicate that tumor-selective DNA damage may induce immunogenic cell-death signals, activate Cyclic guanosine monophosphate-adenosine monophosphate synthase-Stimulator of interferon genes/Type I Interferons pathways, and enhance Major Histocompatibility Complex/Human Leukocyte Antigen class I expression, dendritic-cell activation, and $CD8^+$ T-cell recruitment/function. These findings provide a mechanistic rationale for combining ADC with PD-1 blockade[21-25]. ADC plus immunotherapy is being

Table 1 ADC landscape relevant to recurrent or metastatic nasopharyngeal carcinoma

Study	Target/payload	Stage	Population/setting	Key data	Safety
BL-B01D1-303 (iza-bren)[7]	EGFR × HER3/ TOP1 inhibitor payload	Published randomised phase 3; approved in China	R/M NPC after at least 2 systemic lines including platinum and PD-1/ PD-L1 inhibitor	ORR 54.6% *vs*. 27.0%; mPFS 8.38 *vs*. 4.34 months; median DoR 8.51 *vs*. 4.76 months	Grade ≥3 TRAEs 80%; common grade ≥3 events were hematologic (anemia 50%, decrease in WBCs 43%, decrease in platelet count 43%, decrease in neutrophil count 38%); 4 treatment-related deaths
MRG003 randomised trial (Magic-M001)[11]	EGFR/MMAE payload	Phase 2b; approved in China	Heavily pretreated R/M NPC *vs*. capecitabine or docetaxel	ORR 30.2% *vs*. 11.5%; mPFS 5.8 *vs*. 2.8 months; interim mOS 17.1 *vs*. 12.0 months	Grade ≥3 TRAEs 45.3% (decrease in WBC count 9.3%, decrease in neutrophil count 9.3%, hyponatremia 9.3%); 3 deaths due to AEs reported
MRG003 phase 2a[12]	EGFR/MMAE payload	Published, phase 2a	Previously treated R/M NPC, including patients after PD-1/PD-L1 and multiple chemotherapy lines	ORR 42%; median DoR 8.0 months; mPFS 5.8 months; mOS 15.8 months	Grade ≥3 TRAEs 39%; no treatment-related deaths reported
YL201 phase 1/1b NPC cohort[14]	B7-H3/TOP1 inhibitor payload	Published, phase 1/1b	Heavily pretreated advanced solid tumours; NPC subgroup had prior anti-PD-L1 and platinum, and 84.3% had at least 2 prior systemic lines	ORR 48.6%; DCR 92.9%	Overall study grade ≥3 TRAEs included a decrease in neutrophil count (31.7%), decrease in WBC count (29.5%), and anemia (25.0%)
YL201 (NCT06629597)	B7-H3/TOP1 inhibitor payload	Recruiting, phase 3	R/M NPC after prior PD-(L)1 inhibitor and at least 2 lines of chemotherapy	N/A	N/A
MRG003 + pucotenlimab (Magic-C002, NCT06976190)	EGFR ADC + PD-1 inhibitor	Recruiting, phase 3	R/M NPC after prior standard therapy	N/A	N/A
MRG003 + pucotenlimab first-line study (NCT07381699)	EGFR ADC + PD-1 inhibitor	Not yet recruiting, phase 2	First-line R/M NPC	N/A	N/A

ADC, antibody–drug conjugate; DCR, disease control rate; DoR, duration of response; MMAE, monomethyl auristatin E; NPC, nasopharyngeal carcinoma; ORR, objective response rate; mOS, median overall survival; mPFS, median progression-free survival; R/M, recurrent or metastatic; TRAE, treatment-related adverse event; AE, adverse event; WBC, white blood cell; N/A, not applicable.

evaluated in patients with R/M NPC previously treated with standard therapy, while other trials are assessing ADC-based strategies in earlier treatment lines. These trials will help determine whether ADCs should remain primarily as later-line options or move into earlier treatment lines. Until data from these studies have matured, no definitive conclusion can be drawn regarding the optimal ADC position in the NPC treatment sequence.

Predictive biomarkers and treatment sequencing for ADCs in NPC: unresolved issues

There has been no validation of any predictive biomarker to guide ADC selection in NPC. According to previous studies, an informative biomarker strategy need to combine multiple factors: target expression in tumor tissue, response to prior therapy, disease kinetics, metastatic pattern, and dynamic biomarkers such as circulating tumor DNA or plasma Epstein–Barr virus (EBV) DNA.

Plasma EBV DNA is an established biomarker for prognostic assessment and disease monitoring in NPC, but its predictive value for specific treatments, including ADCs, remains uncertain. BL-B01D1-303 did not prospectively collect samples for EBV DNA analysis, so neither baseline nor longitudinal EBV DNA analyses were performed. Accordingly, the trial cannot determine whether baseline EBV DNA levels or early changes during treatment are associated with responses, PFS, or a durable clinical benefit from iza-bren. Future trials of ADCs in NPC should prospectively incorporate baseline and serial assessment of plasma EBV DNA, ideally alongside tumor target expression and clinical variables, to determine whether EBV DNA can complement radiographic assessment or contribute to patient selection.

The key unresolved question is whether tumor EGFR or HER3 expression is associated with benefit from iza-bren[26]. Eligibility and stratification in BL-B01D1-303 did not require EGFR or HER3 expression. The protocol did not mandate prospective collection of tumor tissue for central EGFR/HER3 testing, so baseline target expression was not systematically assessed. The trial therefore cannot assess associations between EGFR or HER3 expression and objective responses or PFS. Future trials should prospectively evaluate quantitative levels and spatial patterns of EGFR/HER3 expression in relation to response, survival, and toxicity. Exploratory biomarker data from other early-phase ADC trials are hypothesis-generating. In the phase 1 study of MRG003, immunohistochemical EGFR expression was assessed in relation to overall response, PFS, and OS. Outcomes were numerically more favorable in the group with the highest EGFR expression; however, the subgroups were small and histologically heterogeneous, and the analysis did not establish a clinically usable cutoff[27]. The phase 1/1b study of YL201 found no clear association between objective responses and either tumor B7-H3 expression or soluble B7-H3 levels[14].

Treatment sequencing is another clinical challenge. BL-B01D1-303 excluded patients previously treated with EGFR-directed or HER3-directed ADCs or with ADCs carrying TOP1 inhibitor payloads. The efficacy and safety of iza-bren after prior ADC therapy are therefore unknown. As multiple ADCs become available for R/M NPC, this evidence gap will become increasingly relevant. Patients treated with EGFR-directed ADC before iza-bren may differ from the ADC-naive population enrolled in BL-B01D1-303 in terms of both the likelihood of benefit and the risk of toxicity. Prior exposure to ADC with TOP1 payload may also raise concerns about cross-resistance and cumulative marrow toxicity. These uncertainties will affect treatment selection as multiple ADCs become routinely available. Prospective sequencing studies are necessary to guide ADC selection after prior exposure to a particular target or payload class.

These questions have direct implications for routine practice as multiple ADCs become available. Clinicians need evidence to determine which ADC to use first, whether the target or payload class would influence subsequent treatment, and how to manage patients who retain good performance status after disease progression on an ADC. The available evidence does not yet answer these questions, which should therefore be prioritized in future clinical studies.

Later-line NPC in the ADC era: what comes next?

The immediate clinical priority is to define the position of iza-bren in the treatment sequence. Current evidence supports consideration of iza-bren after platinum-based chemotherapy and PD-1/PD-L1 blockade in ADC-naive patients who require tumor shrinkage and can tolerate intensive monitoring for myelosuppression. The BL-B01D1-303 results do not establish iza-bren as the preferred option over another approved ADC or define treatment after prior ADC exposure. This position may change as ADCs move into earlier treatment lines or as stronger evidence emerges for other ADCs. Based on current evidence, iza-bren utility after platinum-based chemotherapy and PD-1/PD-L1 blockade is the best-supported clinical application of this ADC.

Future studies should address treatment selection in addition to antitumor activity. If MRG003, iza-bren, and YL201 are all available as later-line options, evidence will be needed to determine which ADC to use first, how to treat patients after progression on an ADC, and whether the target or payload class would influence subsequent treatment. For iza-bren, the data most relevant to clinical implementation comprise baseline status (particularly marrow reserve), treatment

modifications (dose reductions and discontinuations), safety events (severe infections and treatment-related mortality), and outcomes with subsequent therapies. These data will be important for further estimates of the response rate.

The increasing use of first-line immunochemotherapy has changed the clinical context in which later-line trials are interpreted. ADCs have expanded later-line treatment options in China, but their clinical use will require disease-specific evidence, careful management of safety, and a clear understanding of the limitations of current data. In this context, BL-B01D1-303 provides a randomized benchmark for interpreting future ADC studies in NPC.

Conclusions

Trial BL-B01D1-303 provides randomized phase 3 evidence that iza-bren improves ORR, PFS, and DoR in comparison to PCC in ADC-naive patients with R/M NPC previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitors. Clinical use must balance these efficacy gains against substantial hematological toxicity and treatment-related mortality. Future studies should identify the patients who are most likely to benefit, characterize those at risk of severe toxicity, and determine how iza-bren should be sequenced as other ADCs become available.

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Conflict of interest statement

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Author contributions

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Wrote the paper: Huaqiang Zhou, Jiayi Shen, Jiaqing Liu, Li Zhang, Yunpeng Yang.
Draft revision and critical review: Huaqiang Zhou, Li Zhang, Yunpeng Yang.

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