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PERSPECTIVE

The conditional promise of dual-epitope HER2 antibody-drug conjugates in breast cancer

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In the landscape of neoadjuvant therapy for breast cancer, achieving a pathologic complete response (pCR) to improve long-term survival remains the paramount clinical objective[1]. Although traditional dual human epidermal growth factor receptor 2 (HER2)-targeted therapies combined with chemotherapy have improved pCR rates in HER2-positive breast cancer[2], their associated systemic toxicities and current efficacy plateaus have compelled researchers to seek more precise alternative strategies.

Antibody-drug conjugates (ADCs) have transformed the treatment of advanced HER2-positive and HER2-low breast cancer and are now being actively explored in earlier stages of disease. The architecture of an ADC comprises three core components: a specific monoclonal antibody, a stable linker, and a cytotoxic payload[3,4]. Its mechanism of action involves four coordinated steps: recognition and binding to tumor surface antigens; internalization *via* receptor-mediated endocytosis; intracellular lysosomal trafficking and degradation; and linker cleavage to release the payload, thereby inducing apoptosis in the target cell[5].

Traditional single-epitope HER2 ADCs, such as ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), have achieved notable clinical success in both the salvage setting for advanced disease and the adjuvant setting for high-risk patients[6,7]. Despite the success of single-epitope HER2 ADCs, resistance, heterogeneous HER2 expression, variable internalization, and treatment-related toxicities remain important challenges.

To overcome the efficacy and resistance bottlenecks of traditional ADCs, dual-epitope (or biparatopic) HER2 ADCs have emerged as a novel molecular architecture. These agents, distinct from conventional ADCs, are engineered to simultaneously target two non-overlapping epitopes, such as extracellular domain 2 (ECD2) and extracellular domain 4 (ECD4) of HER2 on a single molecular scaffold, to alter receptor spatial conformation and biophysical dynamics[8]. This Perspective reviews the mechanistic rationale and early clinical evidence for dual-epitope HER2 ADCs in breast cancer, paying particular attention to their potential translation into neoadjuvant therapy.

Mechanistic rationale: the promise and limits of dual-epitope engagement

Resistance to single-epitope ADCs primarily arises from target antigen downregulation and aberrant vesicular trafficking[9]. Concurrently, dysregulated endocytosis, such as impaired lysosomal degradation or active receptor recycling pathways, decreases the intracellular release of the payload. Single-epitope ADCs heavily rely on the spontaneous endocytosis of high-abundance HER2 on the tumor surface; diminished antigen density or stagnant internalization dynamics compromise their efficacy. Therefore, a molecular design capable of actively breaching the receptor internalization threshold is required.

Bispecific ADCs use dual-target or dual-epitope antibodies to enhance binding affinity and address target heterogeneity; they have stable, cleavable linkers to ensure precise intralysosomal release; and incorporate topoisomerase I inhibitors (TOP1i) with bystander effects to replace traditional microtubule inhibitors, thereby widening the therapeutic window. Within this landscape, distinguishing between "dual-target" (targeting two different proteins) and "dual-epitope" (or biparatopic, simultaneously targeting two non-overlapping domains on the same protein) is crucial. For example, in current dual-epitope HER2 ADCs, the antibody backbone concurrently binds the extracellular domains ECD2 (the pertuzumab-binding site) and ECD4 (the trastuzumab-binding site) of HER2[8,10].

The two binding arms of the antibody trans-bind to ECD2 and ECD4 on adjacent HER2 receptors, and subsequently

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induce high-order receptor clustering on the cell membrane[8]. This spatial reconfiguration alters the distributional state of the receptors and promotes the formation of stable cross-linked complexes, thus enhancing receptor-mediated endocytosis. This clustered state improves endocytic efficiency and skews the trafficking of receptor complexes toward the lysosomal pathway rather than recycling back to the plasma membrane[11]. Within lysosomes, the ADC undergoes proteolytic cleavage and release of the cytotoxic payload, thereby resulting in direct tumor cell death while affecting adjacent tumor cells *via* the bystander effect (**Figure 1**)[5]. The ability of dual-epitope ADCs to mitigate resistance mechanisms might therefore lie in coupling receptor clustering with altered intracellular trafficking. By promoting active internalization and lysosomal routing, this design has potential to increase payload release in tumors with diminished or heterogeneous HER2 expression, while partially addressing resistance associated with impaired endocytosis or receptor recycling.

Overall, dual-epitope HER2 binding has potential to promote receptor clustering and alter intracellular trafficking, thereby providing a mechanistic rationale for improving ADC internalization and payload delivery. However, these effects are unlikely to be uniform across agents and tumor contexts, because they depend on antibody geometry, HER2 expression heterogeneity, linker stability, conjugation strategy, payload properties, and drug-to-antibody ratio (DAR). Importantly, receptor clustering increases the opportunity for ADC internalization, but the amount of cytotoxic drug delivered by each

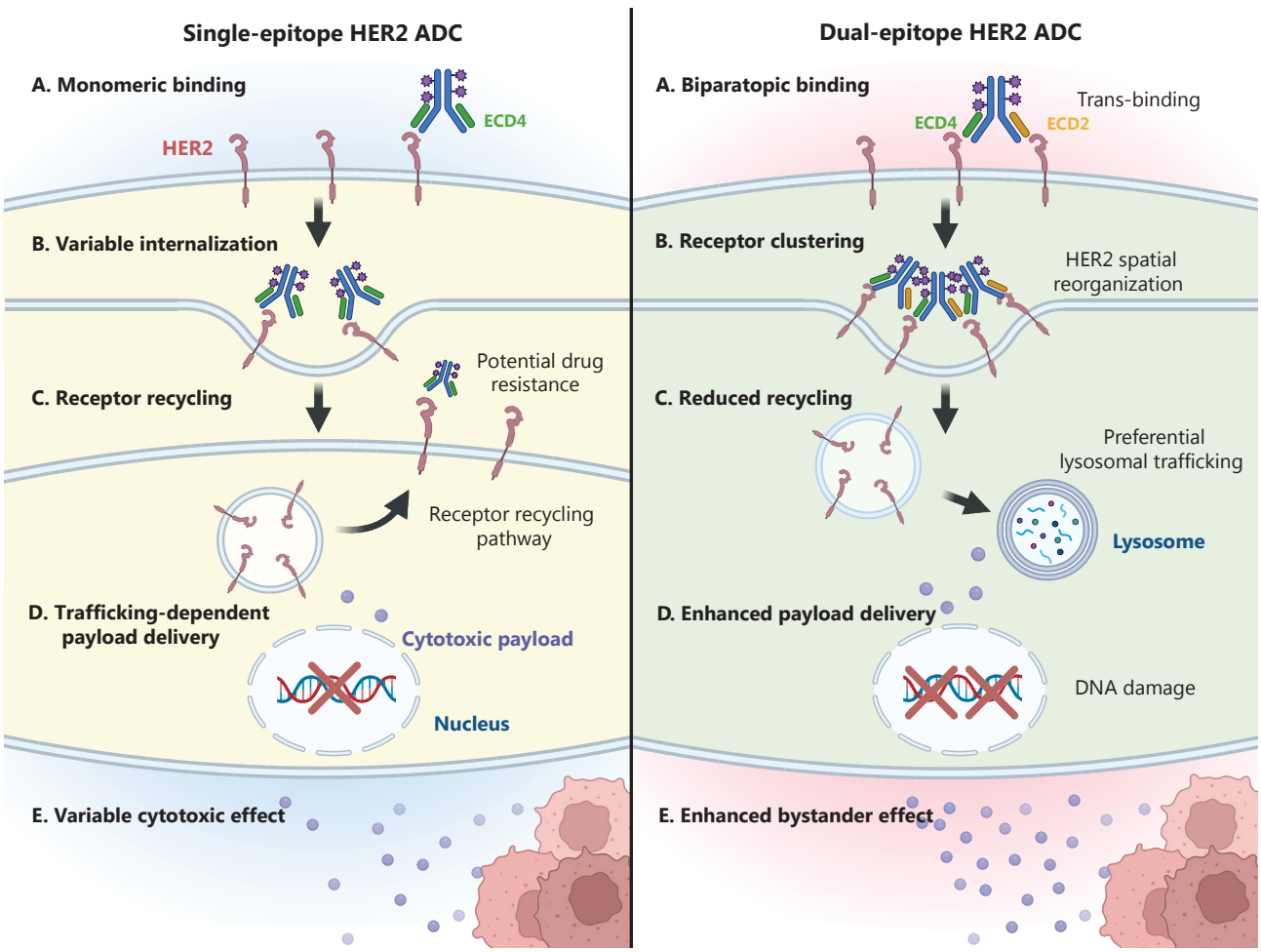


Figure 1 Conceptual schematic of HER2 receptor engagement and trafficking by single-epitope and dual-epitope ADCs. In single-epitope HER2 ADCs, (A) monomeric binding is followed by (B) variable internalization, (C) potential receptor recycling, (D) trafficking-dependent payload delivery, and (E) payload-dependent cytotoxic effects. In dual-epitope HER2 ADCs, (A) biparatopic binding may promote (B) receptor clustering, (C) decreased receptor recycling and preferential lysosomal trafficking, (D) enhanced payload delivery, and (E) potential bystander effects. Created with BioRender.com (www.biorender.com). ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; ECD2, extracellular domain 2; ECD4, extracellular domain 4.

internalized receptor complex is further influenced by DAR and linker-payload stability. Site-specific glycan conjugation, as exemplified by JSKN003, might improve ADC homogeneity and hydrophilicity, thereby resulting in lower aggregation risk than that with less site-controlled conjugation approaches. TOP1i payloads might also broaden cytotoxic activity by inducing DNA damage and enabling bystander killing. Therefore, the DAR 4 design of JSKN003 and DAR 6 design of TQB2102 should be interpreted in the broader context of ADC therapeutic index optimization. Compared with high-DAR platforms such as T-DXd (DAR 8), lower or intermediate DAR designs might have lower hydrophobicity, aggregation risk, clearance, and systemic toxicity, while preserving sufficient payload delivery through receptor-clustering-driven internalization.

Clinical evidence: balancing efficacy and safety

Clinical evidence for dual-epitope HER2 ADCs remains heterogeneous across agents and disease settings. Most available data were generated in advanced or metastatic cohorts, whereas direct neoadjuvant evidence is currently limited and comes primarily from TQB2102. Early studies, nevertheless, have provided useful information on how antibody format, linker-payload design, DAR, and payload class influence efficacy and safety. The four representative agents and their core clinical evidence are summarized in **Table 1**.

ZW49: proof-of-concept limited by ocular toxicity

ZW49 is a dual-epitope ADC targeting ECD2 and ECD4 of HER2. It uses a protease-cleavable linker to site-specifically conjugate a microtubule inhibitor (N-acyl sulfonamide auristatin) to the antibody, with an average DAR of approximately 2.

In a phase I clinical trial (NCT03821233) in patients with HER2-positive advanced solid tumors, the objective response rate (ORR) in the 2.5 mg/kg recommended dose cohort reached 31%, and the disease control rate (DCR) was 72%[12]. No interstitial lung disease (ILD) or treatment-related deaths were observed. However, ocular toxicity, including grade ≥2 keratitis and blurred vision, emerged as a clinically relevant dose-limiting toxicity. Therefore, the absence of ILD does not necessarily translate into a broad therapeutic window for curative-intent development.

The clinical development of ZW49 has been discontinued because of an unfavorable benefit–risk profile. Although this agent provided an early proof of concept for biparatopic HER2 engagement, its auristatin-based payload was associated with ocular toxicity, and its relatively low DAR (~2) might have limited payload delivery. Therefore, dual-epitope binding alone is insufficient to ensure clinical success without an optimized linker-payload system and tolerability profile.

MEDI4276: potent payload offset by a narrow therapeutic window

MEDI4276 is a biparatopic tetravalent ADC targeting HER2 ECD2 and ECD4. It site-specifically conjugates a microtubule inhibitor, tubulysin, *via* a maleimidocaproyl linker to the antibody, thus yielding an average DAR of approximately 4.

In a phase I clinical trial (NCT02576548) enrolling patients with HER2-positive advanced breast and gastric cancers, the ORR among 32 patients with breast cancer was 9.4%[13]. Notably, the three patients who achieved an objective response had previously developed resistance to trastuzumab, pertuzumab, and T-DM1. However, the drug exhibited intolerable toxicity at doses greater than 0.3 mg/kg. At the 0.9 mg/kg dose, dose-limiting toxicity (DLT) characterized by grade 3 elevations in liver function metrics emerged, among which elevated aspartate aminotransferase (AST) was most prevalent. This hepatotoxicity might reflect not only tubulysin potency but also linker-related instability and premature payload exposure, thereby underscoring the importance of linker chemistry in determining systemic tolerability.

MEDI4276 was discontinued because of a narrow therapeutic window and dose-limiting hepatotoxicity. The low maximum tolerated dose limited target saturation, and contributed to high clearance and a short half-life. Together, these data illustrate how a potent microtubule-disrupting payload and suboptimal systemic tolerability can offset the theoretical advantages of biparatopic receptor engagement.

JSKN003: TOP1i-based design with manageable safety profile

JSKN003, a dual-epitope HER2-targeting ADC, uses site-specific glycan conjugation technology to attach a TOP1i *via* a dibenzocyclooctyne tetrapeptide linker, thus resulting in an average DAR of approximately 4.

In a phase I clinical study (NCT05494918) in pretreated patients with advanced solid tumors, preliminary data have suggested that JSKN003 has a manageable safety profile[14]. The ORR and DCR for the entire cohort were 50.0% and 90.6%, respectively. Within the breast cancer cohort, the ORR for HER2-positive patients was 80.0% (4/5), whereas the HER2-low population achieved an ORR of 40.0% (4/10). Treatment-related adverse events (TRAEs) occurred in 27 patients (84.4%), and grade 3 TRAEs occurred in 2 patients (6.3%); diarrhea and nausea were the most common TRAEs and were grade 1–2. Within the dose-escalation range up to 8.4 mg/kg, no DLTs were observed. Only one case of grade 2 ILD was reported in the entire cohort, although longer follow-up and larger randomized datasets are required to define the true incidence of rare toxicities.

JSKN003 has advanced to two phase III trials: NCT06846437, conducting a head-to-head comparison with T-DM1 in HER2-positive advanced breast cancer, and NCT06079983,

Table 1 Overview of representative dual-epitope HER2 ADCs

Agent	Target	Linker	Payload	DAR	Clinical trial	Efficacy	Safety	Status	Limitation	Reference
ZW49	Dual-epitope HER2 ADC targeting ECD2/ECD4	Protease-cleavable linker; site-specific conjugation	N-acyl sulfonamide auristatin	2	HER2-positive advanced solid tumors; phase I, NCT03821233	ORR 31%, DCR 72% at 2.5 mg/kg recommended dose cohort	No ILD or treatment-related deaths; grade ≥2 keratitis/blurred vision	Discontinued	Ocular toxicity, low DAR, unfavorable benefit-risk profile	[12]
MEDI4276	Dual-epitope HER2 ADC targeting ECD2/ECD4	Maleimidocaproyl linker; site-specific conjugation	Tubulysin	4	HER2-positive advanced breast/ gastric cancer; phase I, NCT02576548	ORR 9.4% among patients with breast cancer	Grade 3 AST elevation; dose-limiting hepatotoxicity	Discontinued	Narrow therapeutic window, low MTD, high clearance/ short half-life	[13]
JSKN003	Dual-epitope HER2 ADC targeting ECD2/ECD4	Site-specific glycan conjugation; DBCO tetrapeptide linker	TOP1i	4	Pretreated advanced solid tumors; phase I, NCT05494918	Overall ORR 50.0%; HER2-positive breast cancer ORR 80.0%; HER2-low ORR 40.0%	One case grade 2 ILD; grade 3 TRAEs in 6.3% of patients	Phase III: NCT06846437; NCT06079983	Early-phase data; limited breast cancer sample; rare toxicities need larger datasets	[14]
TQB2102	Dual-epitope HER2 ADC targeting ECD2/ECD4	Enzyme-cleavable linker	TOP1i	6	Advanced solid tumors; phase 1, NCT05735496	ORR 41.2% among 165 previously treated patients	One case grade 2 ILD; no DLTs; main grade ≥3 TRAEs were hematologic	Phase III: NCT06561607 (HER2-low advanced breast cancer)	Direct neoadjuvant evidence mainly phase II; no head-to-head comparison; EFS/ OS immature	[15]
					HER2-low breast cancer; phase 1b, NCT06115902	ORR 53.4%, with 44.4% in patients previously treated with other ADCs	No ILD events; grade ≥3 TRAEs in 41.1% of patients			[16]
					HER2-positive neoadjuvant therapy; phase 2, NCT06198751	tpCR 57.7%–76.9% across dose-cycle cohorts	Grade ≥3 TRAEs 23.1%–30.8%; no treatment-related deaths; low ILD incidence			[17]

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; DCR, disease control rate; DLT, dose-limiting toxicity; EFS, event-free survival; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; tpCR, total pathologic complete response; TRAE, treatment-related adverse event; TOP1i, topoisomerase I inhibitor; DBCO, dibenzocyclooctyne (site-specific conjugation chemistry). ECD2, extracellular domain 2; ECD4, extracellular domain 4; MTD, maximum tolerated dose. Clinical efficacy and safety data are derived from early-phase studies, selected cohorts, or conference-reported datasets where indicated; cross-trial comparisons should be interpreted cautiously.

targeting the HER2-low population against physician's choice chemotherapy.

TQB2102: direct neoadjuvant evidence with encouraging tpCR signals

TQB2102 is a recombinant humanized anti-HER2 dual-epitope ADC that simultaneously targets ECD2 and ECD4. It uses an enzyme-cleavable linker to conjugate a TOP1i payload to the antibody, and it achieves a precisely controlled DAR of 6. Among the agents reviewed herein, TQB2102 currently has the most direct evidence supporting the exploration of dual-epitope HER2 ADCs in the neoadjuvant setting.

In a phase 1 trial for advanced solid tumors (NCT05735496), the overall ORR among 165 previously treated patients was 41.2%[15]. Among ten patients with HER2-positive metastatic breast cancer with brain metastases, seven achieved a partial response, and one achieved a complete response in brain lesions. No DLTs were observed, and only one case of mild (grade 2) ILD was reported.

In a phase 1b trial (NCT06115902), the ORR in the HER2-low breast cancer cohort was 53.4% (39/73), and the 7.5 mg/kg group achieved an ORR of 58.3%[16]. Among patients with refractory cases previously treated with other ADCs, the ORR remained clinically meaningful, at 44.4%. This cohort reported no ILD events, and primary toxicities were limited to manageable hematologic events and gastrointestinal reactions.

On the basis of these advanced-disease signals, TQB2102 has been further explored in the neoadjuvant setting. In a phase II trial (NCT06198751) evaluating the neoadjuvant treatment of early-stage HER2-positive breast cancer, 104 patients demonstrated favorable total pathologic complete response (tpCR) rates[17]. The rates were 57.7% for the 6.0 mg/kg (6 cycles) group, and peaked at 76.9% for the 6.0 mg/kg (8 cycles) group, 61.5% for the 7.5 mg/kg (6 cycles) group, and 69.2% for the 7.5 mg/kg (8 cycles) group. The incidence of grade ≥3 TRAEs ranged from 23.1% to 30.8%, and no treatment-related deaths occurred. However, these pCR/tpCR findings should be interpreted cautiously, because survival endpoints, including event-free survival (EFS) and overall survival (OS), remain immature.

TQB2102 has also entered phase III evaluation in HER2-low advanced breast cancer (NCT06561607). Its DAR 6 design and TOP1i payload support continued investigation, but its role in chemotherapy-sparing neoadjuvant strategies remains investigational and requires randomized comparison with contemporary HER2-directed regimens.

TQB2102 in the neoadjuvant landscape: comparison with contemporary HER2-directed strategies

The tpCR signal observed with TQB2102 should be interpreted within a rapidly evolving neoadjuvant ADC landscape. DESTINY-Breast11 reported pCR rates of 67.3% with T-DXd followed by paclitaxel, trastuzumab, and pertuzumab (T-DXd-THP) and 56.3% with dose-dense doxorubicin/cyclophosphamide followed by THP (ddAC-THP); adjudicated ILD/pneumonitis occurred in 4.4% and 5.1% of patients, respectively[18]. For SHR-A1811, FASCINATE-N reported pCR rates of 63.2% (55/87) with monotherapy, 62.5% (55/88) with SHR-A1811 plus pyrotinib, and 64.4% (58/90) with paclitaxel/carboplatin plus trastuzumab and pertuzumab (PCbHP), with grade ≥3 TRAEs of 44.8%, 71.6%, and 38.8%, respectively[19]. In MUKDEN 07, the tpCR rates were 72.4% (21/29) with SHR-A1811 monotherapy and 77.1% (27/35) with SHR-A1811 plus pyrotinib; the most common grade ≥3 TRAEs were neutropenia with monotherapy and neutropenia, diarrhea, and leukopenia with combination therapy, and no treatment-related deaths occurred[20]. These cross-trial data support further evaluation, but not superiority, of dual-epitope ADCs as investigational chemotherapy-sparing or response-adapted neoadjuvant strategies.

Future directions for neoadjuvant development

Future development should focus on clinically feasible biomarker refinement, rational expansion beyond HER2-positive disease, response-adapted treatment design, and rigorous safety monitoring under curative intent (**Figure 2**).

Refining biomarkers and diagnostic strategies

Clinically scalable approaches, including multiplex immunofluorescence, targeted spatial proteomics, quantitative digital pathology, and HER2 heterogeneity scoring on core biopsies, may provide intermediate tools for patient selection. Dynamic markers such as early MRI response and ctDNA clearance have potential to further support response-adapted escalation or de-escalation strategies. Single-cell sequencing and spatial transcriptomics might also help define HER2 heterogeneity, receptor-trafficking states, and immune microenvironmental changes; however, these platforms remain difficult to routinely implement because of their cost, tissue requirements, and lack of standardized interpretation.

Expanding indications and optimizing combination strategies

Expansion into HER2-low, HER2-ultralow, or selected triple-negative breast cancer is biologically plausible, because enhanced receptor clustering and membrane-permeable TOP1i payloads might improve drug delivery and bystander killing in heterogeneous tumors. However, these populations are diagnostically complex. HER2-low and HER2-ultralow classification is affected by interobserver variability, spatial

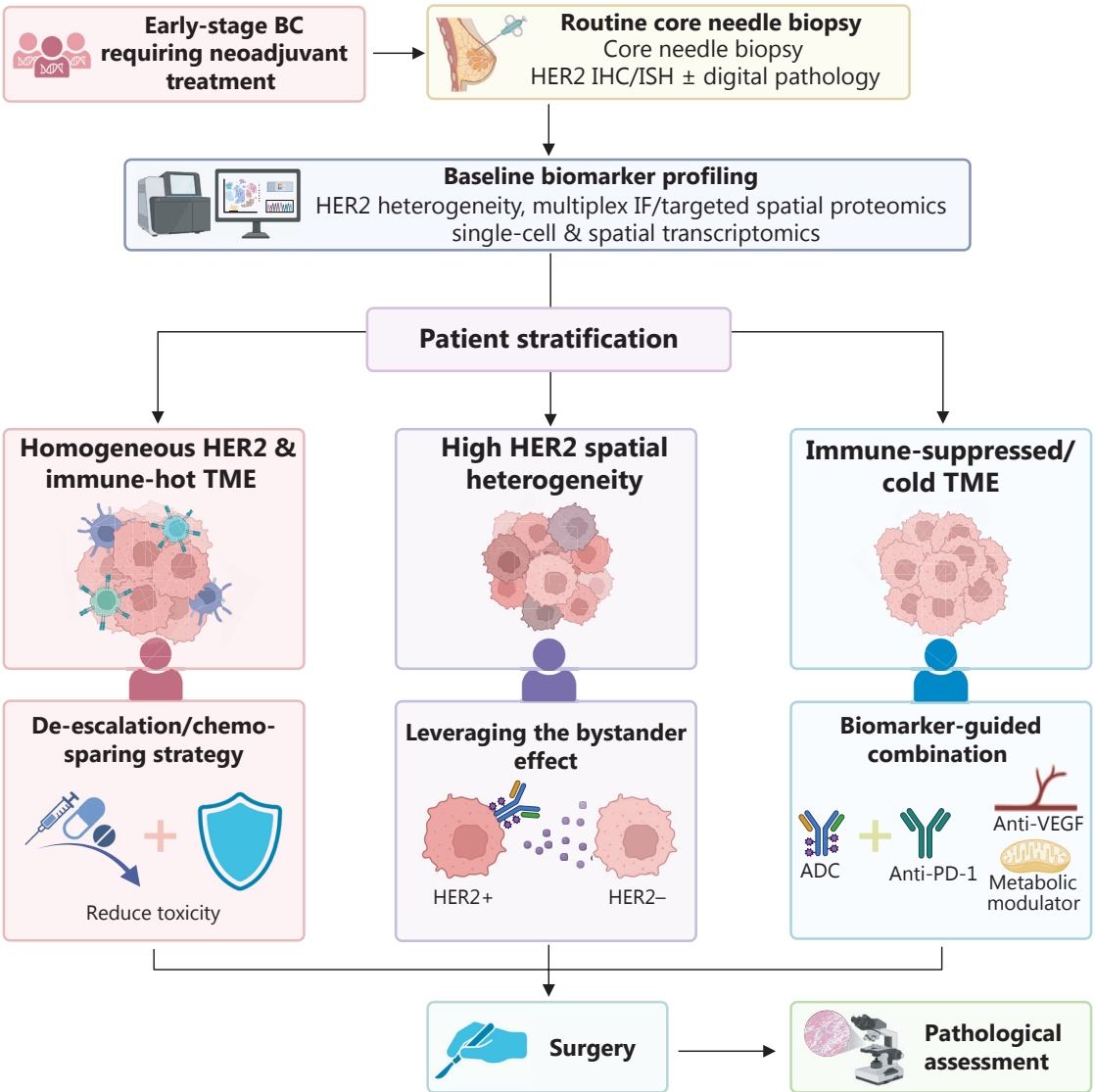


Figure 2 Proposed biomarker-guided framework for neoadjuvant development of dual-epitope HER2 ADCs. Routine core needle biopsy defines HER2 status by IHC/ISH, whereas baseline biomarker profiling can be used to assess HER2 heterogeneity and immune/spatial features. Patients may be stratified into HER2-homogeneous immune-hot tumors for de-escalation or chemotherapy-sparing strategies; spatially heterogeneous tumors for approaches leveraging the bystander effect; and immune-suppressed or cold tumors for biomarker-guided combinations with ADCs, immune checkpoint inhibitors, anti-VEGF therapy, or metabolic modulators. Surgery and pathological assessment enable response evaluation and provide material for further translational analysis. Created with BioRender.com (www.biorender.com). ADC, antibody-drug conjugate; BC, breast cancer; HER2, human epidermal growth factor receptor 2; IF, immunofluorescence; IHC, immunohistochemistry; ISH, in situ hybridization; TME, tumor microenvironment; PD-1, programmed cell death protein 1; VEGF, vascular endothelial growth factor.

heterogeneity, and sampling bias, and most TNBCs have low or unstable HER2 expression. Therefore, expansion beyond HER2-positive disease should require quantitative HER2 assessment, spatial heterogeneity metrics, and prospective subgroup validation. Anti-angiogenic agents or metabolic modulators may also be explored in biomarker-defined settings when vascular or metabolic features contribute to immune exclusion or resistance.

Maintaining the safety baseline in the curative setting

In curative-intent neoadjuvant therapy, pCR gains must be weighed against acute and long-term toxicities. ADC-based de-escalation might decrease exposure to conventional chemotherapy, particularly anthracyclines, but it does not eliminate treatment-related toxicity. Benefit-risk assessment should

therefore consider both overlapping cytotoxic effects and platform-associated risks, including ocular toxicity with auristatin-based ADCs and ILD/pneumonitis with TOP1i-based HER2 ADCs. Future trials should predefine toxicity monitoring and management strategies, and should evaluate treatment completion, surgical feasibility, EFS, OS, and patient-reported outcomes.

Conclusions

Dual-epitope HER2 ADCs are an emerging strategy linking biparatopic HER2 engagement with modern linker-payload engineering. By promoting receptor clustering, internalization, and lysosomal trafficking, these agents provide a mechanistic rationale for improving payload delivery, although these effects vary across constructs and tumor contexts. Early experience with ZW49 and MEDI4276 highlights the importance of payload and linker tolerability, whereas JSKN003 and TQB2102 suggest that TOP1i-based designs might offer a more favorable therapeutic window. However, current neoadjuvant evidence remains limited, and potential chemotherapy-sparing or response-adapted roles require phase III randomized validation with mature survival and safety outcomes against contemporary HER2-directed regimens.

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Conflicts of interest

Dr. Li participated as an investigator in a clinical study of TQB2102 sponsored by Chia Tai Tianqing Pharmaceutical Group Co., Ltd. No funding from Chia Tai Tianqing Pharmaceutical Group Co., Ltd. or any other pharmaceutical company was received for the preparation of this Perspective. The remaining authors declare no potential conflicts of interest.

Author contributions

Conceived and designed the manuscript: Junjie Li, Ruoqing Wang
Performed literature review and evidence synthesis: Ruoqing Wang, Shuhao Jiang
Prepared the figures and table: Ruoqing Wang
Wrote the original draft: Ruoqing Wang, Shuhao Jiang
Reviewed and edited the manuscript: Qun Zhang, Junjie Li
Supervised the work and acquired funding: Junjie Li.

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