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Clinical Studies Update

Is HER2 the New NECTIN4 in Advanced Urothelial Cancer?

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1. Introduction

Antibody-drug conjugates (ADCs) are transforming the treatment landscape for metastatic urothelial carcinoma (mUC). These drugs combine the cytotoxic effect of chemotherapy with antibody targeting, achieving a powerful yet precise effect. UC has traditionally had limited therapeutic options and poor prognosis; just 5% of patients with mUC survive beyond 5 years [1].

Following the groundbreaking phase 3 EV-302 trial, enfortumab vedotin (EV) combined with pembrolizumab has superseded platinum-containing chemotherapy as standard-of-care first-line therapy [2,3]. In the platinum-refractory setting, both EV and sacituzumab govitecan (SG) monotherapy have been approved for unselected patients by the US Food and Drug Administration (FDA). A personalised therapy approach targeting *HER2* is currently being explored.

2. HER2: an emerging biomarker in UC

Poor outcomes in UC have driven efforts to identify potential therapeutic targets. Following the success of EV, which is a NECTIN4-targeted antibody linked to monomethyl auristatin E (MMAE), there has been ongoing interest in the development of new ADCs. *HER2* is a membrane-bound tyrosine kinase receptor involved in cell proliferation that is encoded by the *ERBB2* oncogene. *HER2* amplification and overexpression have been identified in several cancers, which led to the development of a number of targeted therapies that improve outcomes, most notably in breast and gastric malignancies [4].

HER2 has been identified as a therapeutic target in UC. It has been reported that *HER2* mutation and amplification rates are in the region of 6–17%, while the incidence of *HER2* overexpression has ranged from 6% to 80% [5]. The definition of *HER2* positivity in UC requires greater attention. *HER2* positivity has traditionally been defined as an immunohistochemistry (IHC) score of 3+, or a score of 2+ with gene amplification confirmed via fluorescence in situ hybridisation (FISH) testing. This scoring system was based on single-agent anti-*HER2* therapies in breast cancer [6]. ADCs are able to deliver cytotoxic agents to cells with low *HER2* levels (IHC 1+ or 2+ and FISH-negative), so it is likely that more patients will benefit from this therapeutic approach. Further work is needed to determine a standard for *HER2* evaluation in UC.

The relationship between *HER2* overexpression in UC and prognosis remains controversial. Studies have shown that *HER2* mutations were more frequent in micropapillary UC, an aggressive subtype, and that the rate of overexpression was higher in lymph node metastases than in primary bladder tumours [7,8]. However, as studies used varying definitions and methods for determining *HER2* positivity, this has yet to be confirmed. Moreover studies have found no correlation between *HER1/2* status and overall survival (OS) [9]. Recent studies have examined the relationship between *HER2* and PD-L1 expression. The combined positive score for tumour and immune-cell PD-L1 expression

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Table 1 – A summary of phase 2 and 3 clinical trials of approved ADCs targeting NECTIN4 and HER2 in metastatic urothelial carcinoma

ADC	Payload	Trial	Line	Drug vs control	N	Outcomes (primary end point)
NECTIN4						
EV	MMAE	**EV-201** Phase 2	C1: prior platinum and ICI C2: prior ICI, platinum-naïve	EV	219	ORR: C1 44%, C2 52%
		EV-301 Phase 3	2nd/3rd line	EV vs docetaxel or vinflunine or paclitaxel	608	mOS: 12.8 vs 8.9 mo HR 0.70 (95% CI 0.56–0.89); p = 0.001
		EV-302 Phase 3	1st line	EV/P vs platinum + gemcitabine	886	mOS: 31.5 vs 16.1 mo HR 0.47 (95% CI 0.38–0.58); p = 0.001
HER2						
T-DXd	TOP1 inhibitor	DESTINY-PanTumor02 Phase 2	2nd line	T-DXd	267 (41 BC)	ORR: 37.1% overall, 39% BC
DV	MMAE	RC48-C005/C009 Phase 2	2nd line	DV	107	ORR: 50.5%
		RC48-C014 Phase 1b/2	1st line (cisplatin-ineligible) and 2nd line	DV + toripalimab	41	Preliminary ORR: 76.7%

ADC = antibody-drug conjugate; BC = bladder cancer; C1 = cohort 1; C2 = cohort 2; CI = confidence interval; DV = disitamab vedotin; EV = enfortumab vedotin; EV/P = EV + pembrolizumab; HR = hazard ratio; MMAE = monomethyl auristatin E; ICI = immune checkpoint inhibitor; mOS = median overall survival for drug versus control; ORR = overall response rate; T-DXd = trastuzumab deruxtecan.

on IHC was inversely associated with *HER2* IHC expression [10]. This calls into question the combination approach, although there is controversy regarding the PD-L1 biomarker in UC.

3. Targeting HER2 in UC

Trials investigating *HER2*-targeted single agents and tyrosine kinase inhibitors (TKIs) have not shown promising outcomes in mUC. A phase 3 trial investigated the use of maintenance lapatinib, a TKI targeting *HER2*, in patients with no progression following first-line chemotherapy and positive *HER1/2* status (IHC 2+ or 3+). No improvement in OS was observed in comparison to placebo (hazard ratio 0.96, 95% confidence interval [CI] 0.70–1.31; p = 0.8) [9]. Other studies explored the addition of trastuzumb to first-line platinum-based chemotherapy in mUC. Patients were eligible if they tested positive for *HER2* overexpression (IHC 2+ or 3+), which had to be confirmed via FISH. Only 13.3% of the 563 patients screened were deemed to be *HER2*-positive, which the authors attributed to the stringent eligibility criteria. The trial found no improvement in OS with addition of trastuzumab to first-line chemotherapy and highlighted the need for a consensus in defining *HER2*-positive UC [11].

4. HER2 as an ADC target

HER2 has shown promise as an ADC target in mUC. Trastuzumab deruxtecan (T-DXd) is an ADC composed of an anti-*HER2* monoclonal antibody linked to a TOP1 inhibitor payload. T-DXd is the first *HER2*-targeted ADC to be granted accelerated approval by the FDA for pretreated, *HER2*-positive (IHC 3+) UC [12] following results from the phase 2 DESTINY-PanTumour02 basket trial (NCT04482309). Among the 41 mUC patients recruited, the overall response rate (ORR) was 39% (95% CI 24.2–55.5%) [13]. With T-DXd becoming a treatment option for mUC patients in the USA, there is a need to define *HER2* expression in this tumour type and ensure routine screening.

Disitamab vedotin (DV) is an ADC composed of hertuzumab, a *HER2*-targeted monoclonal antibody, conjugated to MMAE. Two phase 2 trials conducted in China, RC48-C005 (NCT03507166) and RC48-C009 (NCT03809013), demonstrated the efficacy and tolerability of DV monotherapy in patients with *HER2*-positive (IHC 3+ or 2+) mUC refractory to standard first-line therapy [14,15]. A combined analysis demonstrated an ORR of 50.5% (95% CI 40.6–60.3%) and median OS of 14.2 mo (95% CI 9.7–18.8) [16]. An ORR of 39.6% was observed in the *HER2*-low group (IHC 2+ and FISH-negative), indicating the potential of DV in mUC with low or even negative *HER2* expression. These studies led to approval of DV monotherapy for chemotherapy-refractory *HER2*-positive mUC in China in 2022. Work is under way in China to establish whether combination of DV with the anti-PD-1 antibody toripalimab has an additive effect. Provisional results from a phase 2 trial (NCT04264936) that recruited patients regardless of *HER2* or PD-L1 IHC status have demonstrated an ORR of 73.2% [17]. Addition of immune checkpoint inhibitors to ADCs continues to show promise, even though PD-L1 expression is inversely associated with *HER2* IHC expression.

5. Are ADCs targeting HER2 the new EV?

HER2 can be targeted in UC via at least two ADCs with different cytotoxic payloads (Table 1). Toxicity is both target- and payload-dependent, as T-DXd and DV have distinct toxicity profiles. T-DXd is more commonly associated with haematological toxicity, while DV causes neuropathy and fatigue. *HER2*-targeted ADCs avoid the skin toxicity seen with NECTIN4-targeted EV. In the *HER2*-high population (IHC 2+ and FISH-positive, or IHC 3+) indirect comparisons between *HER2*-targeted ADCs and EV are not possible because of low numbers, but both treatments appear to be at least as good as standard chemotherapy. The response in the *HER2*-low population is less clear (IHC2+ and FISH-negative, or IHC 1+), although some efficacy is evident, which highlights the likely bystander effect of ADCs. Further evaluation is under way in a randomised phase 2 trial (NCT04879329) examining responses to DV in both first-

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and second-line settings in patients with either *HER2*-high or *HER2*-low status [18]. The study will also evaluate DV together with pembrolizumab in the first-line cohort to determine whether responses echo those seen in EV-302.

With better molecular characterisation across various treatment settings, it is likely that the use of ADCs will expand and that the choice of an ADC for an individual patient will become personalised. Trials exploring combination therapy using ADCs with differing targets and cytotoxic payloads are under way.

Conflicts of interest: The authors have nothing to disclose.

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