EUROPEAN UROLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Words of Wisdom

Re: Disitamab Vedotin plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer

Sheng X, Zeng G, Zhang C, et al.

N Engl J Med 2025;393:2324–37

Experts' summary:
The phase 3 RC48-C016 trial evaluated disitamab vedotin (RC48), a HER2-directed antibody-drug conjugate (ADC), combined with toripalimab versus standard gemcitabine + platinum chemotherapy as first-line treatment for HER2-expressing advanced urothelial carcinoma [1]. HER2 expression was identified via immunohistochemistry or gene amplification, and only patients with measurable HER2 positivity were enrolled. The combination of RC48 and toripalimab significantly improved progression-free survival and overall survival in comparison to chemotherapy, which suggests a clinically meaningful advantage for biologically selected therapy. Safety was manageable and consistent with known profiles of ADCs and checkpoint inhibitors. These findings highlight HER2 as a potentially actionable biomarker in urothelial carcinoma and position HER2-directed ADC + ICI combinations as a promising therapeutic strategy. However, the study population was exclusively Chinese, which may limit the applicability to broader global settings. Overall, the trial marks an important step towards biomarker-guided treatment in urothelial cancer.

Experts' comments:
RC48-C016 provides compelling evidence that HER2-targeted therapy may reshape the treatment landscape for urothelial carcinoma. The dual strategy of an ADC + immune checkpoint inhibition is biologically attractive and clinically promising, and nearly doubled survival outcomes in comparison to gemcitabine + platinum chemotherapy. However, several considerations temper immediate enthusiasm.

First, the control arm may reflect a standard of care that is becoming outdated in the post–EV-302 era, as enfortumab vedotin plus pembrolizumab is increasingly considered a reference first-line regimen [2]. Thus, the magnitude of the benefit observed may partly reflect comparison with a suboptimal control rather than superiority over contemporary therapy. Second, the exclusively Chinese population limits generalizability given potential differences in tumor biology, HER2 prevalence, and access to subsequent treatments.

Biologically, HER2 expression in urothelial carcinoma is heterogeneous, observed in 10–15% of tumors, and lacks universally accepted testing standards or cutoffs [3]. It remains unclear whether the efficacy of RC48 extends to HER2-low disease, as seen in breast or gastric cancer [4], or is confined to "true" HER2-positive tumors. In addition, mechanisms of resistance to HER2-directed ADCs, heterogeneous antigen expression, internalization dynamics, and bystander effects remain poorly defined and require deeper investigation [5].

From a clinical perspective, the RC48-C016 trial is hypothesis-generating rather than practice-changing. Global validation, biomarker harmonization, and trials comparing HER2-directed strategies with modern immunotherapy + ADC combinations are essential before HER2 can be considered a standard first-line target.

HER2-guided therapy has reached the starting line in urothelial cancer; crossing the finish line will require international cooperation, robust diagnostics, and evidence that any benefit extends beyond narrowly selected populations.

Conflicts of interest: The authors have nothing to disclose.

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https://doi.org/10.1016/j.eururo.2026.01.006

Please cite this article as: G. Roviello, S. Mancini and L. Antonuzzo, Re: Disitamab Vedotin plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.01.006

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Associate Editor:
George Thalmann

Accepted 1 January 2026

Please cite this article as: G. Roviello, S. Mancini and L. Antonuzzo, Re: Disitamab Vedotin plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.01.006