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Disitamab vedotin plus tislelizumab as nephron-sparing therapy for high-risk upper tract urothelial carcinoma: The phase II DISTINCT-I trial

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Background

Radical nephroureterectomy (RNU) remains standard for localized high-risk upper tract urothelial carcinoma (UTUC), while functional nephron preservation has emerged as a universal clinical priority to optimize long-term patient outcomes. This phase II trial (DISTINCT-I) evaluates a novel kidney-sparing strategy combining endoscopic Thulium laser ablation/ureteral segmental resection with perioperative HER2-targeted therapy (disitamab vedotin [DV]) plus immune checkpoint inhibitors (ICIs) in high-risk UTUC.

Methods

This ongoing study (NCT05912816, initiated September 2023 at Renji Hospital/Tianjin Second Hospital) enrolled high-risk UTUC patients (N0-1[M0], absolute/relative renal preservation indications: solitary kidney or eGFR <60 mL/min/1.73m^2). Protocol: endoscopic biopsy followed by 2-4 cycles of DV (2.0 mg/kg) + tislelizumab (200 mg) Q3W induction, then kidney-sparing surgery. Primary endpoint: 1-year kidney-intact event-free survival (KI-EFS; events: local recurrence, metastasis, death). Secondary endpoints: clinical complete response (cCR), renal function preservation (ΔeGFR), safety (CTCAE v5.0).

Results

Among 20 enrolled patients (19 completed treatment, median follow-up: 13 months), HER2 status by biopsy IHC: 3+ (n=6), 2+ (n=2), 1+ (n=7), 0 (n=4). Kidney-sparing procedures: ureteral segmental resection (n=5), endoscopic ablation (n=9), RNU (n=5). One recurrence post-ablation required salvage RNU at 6 months. KI-EFS at 1 year: 68.4% (13/19). cCR rate at 3 months: 73.7% (14/19). Treatment cycles completed: 4 (n=16), 3 (n=2), 2 (n=1). Tumor response: CR (n=4), PR (n=9), SD (n=4), PD (n=1). No grade ≥3 systemic toxicities observed.

Conclusions

The DV-ICI combination with kidney-sparing surgery demonstrates promising tumor downstaging (73.7% cCR) and nephron preservation (68.4% 1-year KI-EFS) in high-risk UTUC, with favorable safety. HER2 overexpression (3+/2+: 42.1%) may correlate with enhanced response, warranting biomarker validation. This paradigm challenges RNU dominance in selected patients.

Clinical trial identification

NCT05912816.

Legal entity responsible for the study

The authors.

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Disclosure

All authors have declared no conflicts of interest.

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