Presentations at this year's ASCO-GU symposium addressed several updates in urothelial cancer (UC) management. In this newsletter, we present some of the advances in the use of antibody-drug conjugates (ADCs) for UC management reported this year.

Enfortumab vedotin

Several presentations provided research updates and real-world outcomes on the use of the antibody-drug conjugate (ADC) enfortumab vedotin (EV)—on its own or in combination therapy—for locally advanced or metastatic urothelial cancer (la/mUC) and upper tract urothelial cancer (UTUC).

The phase 3 **EV-302/KEYNOTE-A39 study** compared EV + pembrolizumab (EVP, n=444) against platinum-based chemotherapy (n=442) in previously untreated la/mUC patients. Initial outcomes helped establish EVP as first-line therapy for la/mUC.

Updated analysis for this trial (reflecting 2.5 years median follow-up) showed that EVP continues to demonstrate benefit over chemotherapy for both progression-free survival (PFS; median: 12.5 vs 6.3 months, respectively, $P<0.00001$) and overall survival (median 33.8 vs 15.9 months, respectively, $P<0.00001$). PFS benefit was observed regardless of cisplatin eligibility, PD-L1 expression, or the presence of metastases, including liver.

After **previously demonstrating** high uptake of EVP in the real-world setting following its accelerated approval, investigators examined real-world time on treatment (rwTOT, defined as length of time from first administration of EVP to first-line therapy discontinuation of either EV or P) in a retrospective cohort study using the Flatiron Health longitudinal database of US (predominantly cisplatin-ineligible) patients with advanced urothelial cancer treated with EVP between April 5, 2023 and March 31,2024. Among the 111 eligible patients identified:

- 41.4% (n=46) discontinued EVP
  - 23.9% (n=11) began second-line therapy
  - 65.2% (n=30) died
- 58.6% (n=65) were censored at the end of follow-up

The median rwTOT (95% CI) for EVP was 8.1 months (6.4-not reached), similar to what was reported in the EV-302 trial. Standard dosing frequency was largely maintained, despite some heterogeneity in EVP administration patterns.

Another retrospective study examined primary tumor response in patients with intact primary UTUC treated with EV or EVP between December 2017 and June 2024. Among the 22 eligible patients identified, the overall response rate (ORR) was 36.4% and the disease control rate was 72.3%, indicating promising results.

In a retrospective study of 83 patients with Ia/mUC or UTUC treated with EV or EVP between 2018 and 2024, investigators reviewed whether common toxicities seen with EV predicted treatment response. The findings showed that PFS for patients who had neuropathy, skin rash, and hyperglycemia trended higher than PFS for patients who did not experience these toxicities.

Toxicities	Median PFS, months (95% CI)	*P* value
Hyperglycemia (n=6)	15.9 (5.1–15.9)	0.03
Neuropathy (n=30)	10.6 (7.2–15.7)	0.01
Skin rash (n=32)	8.6 (7.3–20.2)	0.01
No neuropathy/skin rash/hyperglycemia (n=29)	4.5 (2.4–11.0)	—

CI, confidence interval.

Disitamab vedotin + toripalimab

The phase 2 **RC48-C017 trial** evaluated neoadjuvant treatment with disitamab vedotin (DV, formerly RC48), a HER2-targeted monoclonal antibody with MMAE payload, with perioperative toripalimab in patients with HER2-expressing muscle-invasive bladder cancer (MIBC). Earlier preliminary results showed promising efficacy and tolerability, and the updated results presented at ASCO GU 25 continue to support the use of this combination in patients with HER2-positive MIBC.

- Among the 33 evaluable patients:
    - Pathological complete response rate was 63.6% (95% CI 45.1%–79.6%)
    - Pathological response rate was 75.8% (95% CI: 57.7%–88.9%)
    - Event-free survival (EFS)
        - Median follow-up 14.1 months, median EFS not reached
        - 12 months: 92.5% (95% CI: 72.8%–98.1%)
        - 18 months: 85.9% (95% CI 60.5%–95.5%)
    - OS
        - Median follow-up 17.9 months, median OS not reached
        - 12 months, 95.5% (95% CI 83.3%–98.9%)
- Among 47 patients evaluated for safety:
    - 27.7% experienced a grade ≥3 treatment-emergent adverse event (AE)

DV is still under investigation and not currently approved for clinical use.

Similar findings were presented in a smaller single-site trial of DV + toripalimab in platinum-intolerant patients with HER2-positive locally advanced MIBC.

- Among 12 enrolled patients:
    - 10 achieved clinical complete response
    - 8 achieved pathological complete response

Nausea, alopecia, diarrhea, and tachycardia were the most common AEs reported.

Novel ADCs

SHR-A2102, a Nectin-4–targeted monoclonal antibody with a topoisomerase I inhibitor payload, was examined for safety, tolerability, and efficacy in patients with la/mUC who did not respond to or were intolerant to standard therapies. Intravenous doses ranged from 1 mg/kg to 8 mg/kg on day 1 every 3 weeks or 4 mg/kg on day 1 and day 8 every 3 weeks during dose escalation, with 6 mg/kg and 8 mg/kg selected for dose and efficacy expansions.

- 81 patients were enrolled as of October 11, 2024
    - 63 patients were in the efficacy expansion arms
- At median follow-up (5.5 months):

	6 mg/kg (n=31)	8 mg/kg (n=32)
ORR, % (95% CI)	41.9 (24.5–60.9)	50.0 (31.9–68.1)
DCR, % (95% CI)	90.3 (74.3–98.0)	84.4 (67.2–94.7)
DoR, median (95% CI), months	7.6 (2.6–8.2)	5.5 (4.2–NR)
6-month DoR rate, % (95% CI)	59.5 (23.5–83.0)	43.5 (8.3–75.7)
PFS, median (95% CI), months	5.8 (3.9–9.0)	5.8 (3.4–8.2)

ORR, overall response rate; CI, confidence interval; DCR, disease control rate; DoR, duration of response; PFS, progression-free survival; NR, not reached.

- 44.4% of patients had grade ≥3 treatment-related AEs
    - The most common (any grade) were nausea and hematologic toxicities
- 6 mg/kg had fewer toxicities than 8 mg/kg
- 6 mg/kg was established as the recommended dose

Datopotamab deruxtecan (Dato-DXd), which comprises a TROP-2 targeted monoclonal antibody with a topoisomerase I inhibitor payload, is being evaluated in patients (N=40 as of April 2024) with previously treated advanced solid tumors (including la/mUC) in the phase 1 **TROPION-PanTumor01 trial**. Eligible patients received 6 mg/kg Dato-DXd once every 3 weeks.

- At median follow-up (10.0 months):

	Dato-DXd
ORR, % (95% CI)	25.0 (12.7–41.2)
DCR, % (95% CI)	77.5 (61.5–89.2)
DoR, median (95% CI), months	NE (2.6–NE)
6-month DoR rate, % (95% CI)	76.2 (33.2–93.5)
PFS, median (95% CI), months	6.9 (2.9–NE)

ORR, overall response rate; CI, confidence interval; DCR, disease control rate; DoR, duration of response; PFS, progression-free survival; NE, not evaluable.

- 55% of patients had a grade ≥3 treatment-emergent AE
    - The most common (any grade) were stomatitis, nausea, and decreased appetite
- Findings support ongoing evaluation of Dato-DXd

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