Real-Time AI-Assisted Living Systematic Literature Review (REAL-SLR) Captures a 2025 Standard-of-Care (SOC) Shift Driven by Antibody-Drug Conjugates (ADCs) in Urothelial Carcinoma (UC): Implications for Health Technology Assessments (HTAs)

HTA78

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OBJECTIVES

- To evaluate the capability of Real-Time AI-Assisted Living Systematic Literature Review (REAL-SLR) to identify paradigm-shifting clinical evidence in UC as it emerges in real time, using a case study on ADCs

BACKGROUND

- Health technology assessments (HTAs) and payment reimbursement decisions depend on timely, comprehensive synthesis of clinical evidence aligned with evolving standards of care, typically underpinned by traditional static systematic literature reviews (SLRs)
- In urothelial cancer (UC), the rapid emergence of antibody-drug conjugates (ADC) and combination regimens culminated in a first-line standard of care (SOC) shift in 2025
- HTAs built on outdated or incomplete evidence from static SLRs risk delays or presents suboptimal data for reimbursement decisions, with direct consequences for patient access

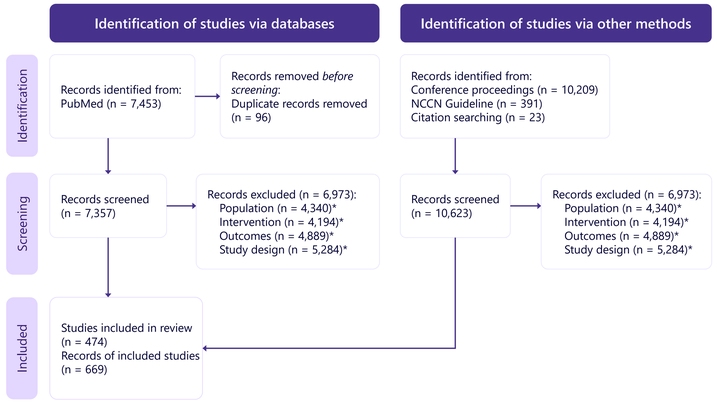
METHODS

- The UC REAL-SLR is a daily-updated, living SLR library applying standardized, protocol-driven searches with AI-assistance to support deduplication, screening, study mapping, and extraction
- The methodology of the SLR followed the Cochrane Handbook for Systematic Reviews of Interventions[1] and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[2]
- Eligibility criteria were developed using the Population, Intervention/Comparator, Outcomes, and Study design (PICOS) framework (**Table 1**). Interventional studies that evaluated any drug or procedure used for the treatment of UC and reported survival, progression, response, quality of life, or safety outcomes were included
- Daily searches were conducted using PubMed. Additional searches included conference proceedings from ASCO, ASCO GU, and ESMO, NCCN clinical guideline updates, and ClinicalTrials.gov
- Regulatory approvals and clinical guideline updates were systematically linked to individual studies to support HTA-relevant interpretation
- Identification of SOC shifts was assessed by reviewing ADC-related publications, regulatory decisions, and guideline updates incorporated during the 2025 calendar year
- Studies were classified as early evidence (phase 1, phase 1/2, or phase NR non-RCTs), investigational (phase 2 non-RCT or phase 2/3 RCT without an approved indication), or FDA approved/guideline approved

Table 1. PICOS statement

Element	Inclusion
Patient population	• Patients diagnosed with urothelial carcinoma (UC) at any stage
Intervention and Comparators	• Any intervention used for the treatment of UC including procedures (such as surgery or radiotherapy) and drugs (including biologics, cell treatments, vaccines, etc.)
Outcomes measures	• Overall survival (OS) • Progression-free survival (PFS) • Other progression measures (such as TTP, TTF, or MFS). • Response rate (including ORR, pCR, and other response outcomes) • Quality of life (including patient-reported outcomes and EQ-5D utility) • Safety/toxicity (including adverse events and discontinuations)
Study design	• Prospective Interventional studies including RCT, non-RCTs, single arm, Phase 1, Phase 1/2, Phase 2, Phase 2/3, Phase 3, Phase 4 • Pooled analyses of RCTs • Externally controlled trials
Restrictions	• English language

Figure 1. PRISMA diagram for the Prostate REAL-SLR



*Reasons for exclusion were not mutually exclusive

Figure 2. Number of studies on ADCs with publications from 2025

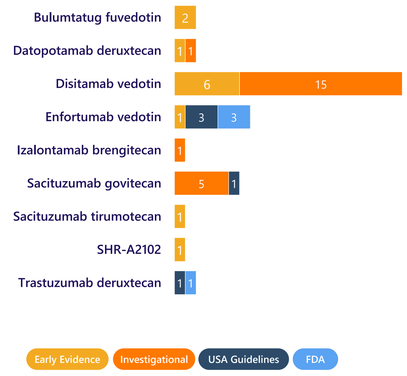


Table 2. ADC clinical trials in localized urothelial carcinoma across treatment paths and clinical stages

Treatment path	NMIBC	MIBC			UTI
Neoadjuvant	**TRUCE-04** DV+Tislelizumab	**Hope-03** DV+Tislelizumab	**ChiCTR230006820** DV	**SURE-01** SG	**Phase NR non-RCT** DV+ICI
		Phase NR non-RCT DV+Toripalimab	**Phase 2 non-RCT** DV+Gemcitabine	**SURE-02** SG+Pembrolizumab	**TRUCE-UTUC01** DV+Tislelizumab
		Phase NR non-RCT DV+Toripalimab	**RC48-C017** DV+Toripalimab	**EV-103** EV+Pembrolizumab	**DISTINCT-I** DV+Tislelizumab
		Phase NR non-RCT DV+Toripalimab	**PUNCH02** DV+Tislelizumab	**KEYNOTE-905/EV-303** EV+Pembrolizumab	
Initial treatment	**Formula-01** DV+BCG	**DECIDING-1** DV+Toripalimab+RT			
	NCT06187506 DV+BCG				
Adjuvant		**NCT06074484** DV+Cadonilimab			**Phase NR non-RCT** DV+ICI
		KEYNOTE-905/EV-303 EV+Pembrolizumab			**NCT05917158** DV+Toripalimab
					NCT06210490 DV+RT
Recurrent	**SSANTROP** SG+Sisanlimab				

Early Evidence | Investigational | FDA + USA Guidelines | FDA

Table 3: ADC clinical trials in locally advanced/metastatic urothelial carcinoma across treatment paths

Treatment path	NMIBC	MIBC			UTI
1st line	**NCT06079112** BF+Toripalimab	**TROPION-PanTumor03** DatoDXd+Rilvegostomig	NCT04073602 DV	**EV-302** EV+Pembrolizumab	EV-103 EV+Pembrolizumab
	RC48-C014 DV+Toripalimab	RC48-C016 DV+Toripalimab			
≥2nd line	**RC48-C014** DV+Toripalimab	**NCT05216965** BF	**NCT05735275** SHR-A2102	**TROPION-PanTumor03** DatoDXd+Rilvegostomig	**DESTINY-PanTumor02** Trastuzumab deruxtecan
	TROPION-PanTumor01 DatoDxd	**MK-2870-001** Sacituzumab tirumotecan	**NCT04073602** DV	**BL-B01D1-201** Izalontamab brengitecan	**TROPiCS-04** SG
	ETCTN 10483 EV+Erdafitinib				
Maintenance	**JAVELIN Bladder Medley** SG+Avelumab				

Early Evidence | Investigational | USA Guidelines | FDA + USA Guidelines

RESULTS

- 55 ADC studies were identified, and of those, 39 had publications in 2025 (Figure 2). This includes publications from the pivotal trials for the ADCs enfortumab vedotin, sacituzumab govitecan, datopotamab deruxtecan, disitamab vedotin, and trastuzumab deruxtecan
- The UC REAL-SLR integrated the addition of indications to clinical guidelines and regulatory approvals, enabling real-time visibility into SOC shifts and differences in the timing of evidence incorporation into recommendations

Regulatory approvals

- Enfortumab vedotin was the only ADC to receive a new FDA-approved indication in bladder cancer in 2025 based on the phase 3 KEYNOTE-905/EV-303 clinical trial (**Table 2**). The FDA approved enfortumab vedotin in combination with pembrolizumab as perioperative (neoadjuvant followed by adjuvant post-cystectomy) treatment for cisplatin-ineligible muscle invasive bladder cancer (MIBC)
- This approval redefines the relevant comparator set for MIBC HTAs and necessitates an updated network meta-analysis for any cisplatin-ineligible MIBC submission
- No new FDA approvals or label changes affecting bladder cancer were granted in 2025 for other ADCs. Notably, the FDA approval of sacituzumab govitecan for locally advanced/metastatic UC was withdrawn in 2024. This indication withdrawal illustrates how rapidly the comparator landscape can shift; HTAs relying on static SLRs may fail to capture such changes in time to update submissions

Updates to guideline recommendations

- Guideline recommendations for UC in 2025 occurred following FDA approvals for new indications (**Table 2, Table 3**)
- Enfortumab vedotin was the only ADC to receive a new USA guideline recommendation in bladder cancer in 2025: perioperative/sandwich enfortumab vedotin + pembrolizumab followed by radical cystectomy as a primary treatment option for patients with MIBC ineligible for cisplatin-based chemotherapy, consistent with the November 2025 FDA approval
- The December 2025 NCCN update occurred just five weeks after the FDA approval, compressing the window between regulatory action and clinical adoption, a dynamic that REAL-SLR captured in real time

Early evidence and investigational studies

- The UC REAL-SLR also identified various early-phase studies for ADC agents in 2025, indicating that the UC treatment landscape will continue to evolve (**Table 2, Table 3**). This highlights the methodological inadequacy of static SLRs as a foundation for HTA submissions in rapidly innovating therapeutic areas where evidence generation outpaces traditional review cycles
- Early phase studies for ADC agents included Disitamab vedotin+tislelizumab, Disitamab vedotin+toripalimab, Disitamab vedotin+ICI, and datopotamab deruxtecan monotherapy (**Table 2**)

CONCLUSIONS

- The UC REAL-SLR prospectively captured interventional studies upon publication, demonstrating its capacity to identify paradigm-shifting evidence in real-time
- In UC, where ADC-driven innovation altered first-line treatment in 2025, REAL-SLR provided an HTA-ready evidence foundation that reduces duplication of effort, improves transparency, and supports timely reimbursement and access decisions
- In the UC ADC case study, REAL-SLR captured a pivotal SOC shift within the same calendar year it occurred, integrating FDA approvals, NCCN guideline changes, and 39 publications, and thereby providing the complete, current evidence base that HTA submissions require to specify comparators, patient populations, and clinical outcomes
- As the treatment landscape in oncology continues to evolve and the pace of evidence generation increases, adoption of living SLR methodologies such as REAL-SLR offer a substantive advance over traditional SLR approaches, ensuring timely, current, and complete evidence for HTA submissions

ABBREVIATIONS

BCG, Bacillus Calmette-Guérin; BF, bulumtag fuvedotin; DatoDXd, datopotamab deruxtecan; DV, disitamab vedotin; EV, enfortumab vedotin; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; NR, not reported; RCT, randomized controlled trial; SG, sacituzumab govitecan; UTUC, upper tract urothelial carcinoma

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2. Page M J, McKenzie J E, Bossuyt P M, Boutron I, Hoffmann T C, Mulrow C D et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews *BMJ* 2021; 372 :n71 doi:10.1136/bmj.n71

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