INPLASY

Comparative Effectiveness of First-Line Therapies in Advanced Urothelial Carcinoma: A Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025100112

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 October 2025 and was last updated on 28 October 2025.

INTRODUCTION

Review question / Objective The optimal first-line therapy for advanced urothelial carcinoma (UC) remains uncertain due to limited direct comparisons across regimens. This study aimed to compare the efficacy and safety of first-line systemic therapies using network meta-analysis (NMA).

Condition being studied Urothelial carcinoma (UC) is the predominant histologic subtype of malignancies arising in the urinary tract, accounting for more than 90% of cases [1]. According to GLOBOCAN estimates, 614,298 new bladder cancer cases and 220,596 bladder cancer deaths occurred worldwide in 2022, underscoring its public health impact. At diagnosis, about 6% of patients present with distant disease in the United States and the five-year relative survival for distant stage is 9%, highlighting the poor outcomes once the disease becomes advanced [2]. Even among non–muscle-invasive disease, recurrence rates remain high, with 15–61% at one year and 31–78% at five years, indicating substantial risk across the disease continuum [3].

METHODS

Search strategy Pubmed:

(urothelial carcinoma OR bladder cancer OR transitional cell carcinoma OR upper tract urothelial carcinoma OR UTUC) AND (chemotherapy OR cisplatin OR carboplatin OR gemcitabine OR docetaxel OR paclitaxel OR nab-paclitaxel OR methotrexate OR vinblastine OR doxorubicin OR MVAC OR GC OR PGC OR chemoimmunotherapy OR chemo-immunotherapy OR immunotherapy plus chemotherapy OR immunotherapy OR immune checkpoint inhibitor OR ICI OR ICIs OR ICB OR PD-1 OR PD1 OR PD-L1 OR PDL1 OR CTLA-4 OR CTLA4 OR anti-PD-1 OR anti-PD-L1 OR anti-CTLA-4 OR pembrolizumab OR nivolumab OR atezolizumab OR durvalumab OR avelumab OR tremelimumab OR ipilimumab OR keytruda OR opdivo OR tecentriq OR imfinzi OR bavencio OR yervoy OR antibody-drug conjugate OR ADC OR ADCs OR enfortumab vedotin OR EV OR padcev OR NECTIN4 OR NECTIN-4 OR sacituzumab govitecan OR SG OR trodelvy OR TROP2 OR TROP-2 OR disitamab vedotin OR RC48 OR HER2 OR ERBB2 OR trastuzumab deruxtecan OR T-DXd OR datopotamab deruxtecan OR Dato-DXd) AND (randomized controlled trial OR RCT OR phase II OR phase III) AND("first-line" OR "initial treatment" OR "untreated")

Embase:

('urothelial carcinoma'/exp OR 'bladder cancer'/exp OR 'transitional cell carcinoma'/exp OR 'upper urinary tract cancer'/exp OR ((urothelial NEXT/1 carcinoma) OR (transitional NEXT/1 cell NEXT/1 carcinoma) OR (upper NEXT/1 tract NEXT/1 urothelial NEXT/1 carcinoma) OR UTUC OR (bladder NEXT/1 cancer) OR (bladder NEXT/1 carcinoma)):ti,ab,kw) AND (chemotherapy:ti,ab,kw OR chemotherap*:ti,ab,kw OR cisplatin:ti,ab,kw OR carboplatin:ti,ab,kw OR gemcitabine:ti,ab,kw OR docetaxel:ti,ab,kw OR paclitaxel:ti,ab,kw OR (nab NEXT/1 paclitaxel):ti,ab,kw OR methotrexate:ti,ab,kw OR vinblastine:ti,ab,kw OR doxorubicin:ti,ab,kw OR MVAC:ti,ab,kw OR (gemcitabine NEAR/3 cisplatin):ti,ab,kw OR PGC:ti,ab,kw OR chemoimmunotherapy:ti,ab,kw OR 'chemo-immunotherapy':ti,ab,kw OR (immunotherapy NEAR/3 chemotherapy):ti,ab,kw OR immunotherapy:ti,ab,kw OR ('immune checkpoint inhibitor*':ti,ab,kw OR ICI:ti,ab,kw OR ICIs:ti,ab,kw OR ICB:ti,ab,kw) OR ('PD-1':ti,ab,kw OR PD1:ti,ab,kw OR 'PD-L1':ti,ab,kw OR PDL1:ti,ab,kw OR 'CTLA-4':ti,ab,kw OR CTLA4:ti,ab,kw OR pembrolizumab:ti,ab,kw OR nivolumab:ti,ab,kw OR atezolizumab:ti,ab,kw OR durvalumab:ti,ab,kw OR avelumab:ti,ab,kw OR tremelimumab:ti,ab,kw OR ipilimumab:ti,ab,kw OR keytruda:ti,ab,kw OR opdivo:ti,ab,kw OR tecentriq:ti,ab,kw OR imfinzi:ti,ab,kw OR bavencio:ti,ab,kw OR yervoy:ti,ab,kw) OR ('antibody drug conjugate':ti,ab,kw OR 'antibody-drug conjugate':ti,ab,kw OR ADC:ti,ab,kw OR ADCs:ti,ab,kw OR 'enfortumab vedotin':ti,ab,kw OR EV:ti,ab,kw OR padcev:ti,ab,kw OR NECTIN4:ti,ab,kw OR 'NECTIN-4':ti,ab,kw OR 'sacituzumab govitecan':ti,ab,kw OR SG:ti,ab,kw OR trodelvy:ti,ab,kw OR TROP2:ti,ab,kw OR 'TROP-2':ti,ab,kw OR 'disitamab vedotin':ti,ab,kw OR RC48:ti,ab,kw OR HER2:ti,ab,kw OR ERBB2:ti,ab,kw OR 'trastuzumab deruxtecan':ti,ab,kw OR 'T-DXd':ti,ab,kw OR 'datopotamab deruxtecan':ti,ab,kw OR 'Dato-DXd':ti,ab,kw)) AND ('randomized controlled trial'/exp OR 'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR random*:ti,ab,kw OR (double NEAR/1 blind*):ti,ab,kw OR (single NEAR/1 blind*):ti,ab,kw) AND ('first-line':ti,ab,kw OR (first NEXT/1 line):ti,ab,kw OR 'initial treatment':ti,ab,kw OR untreated:ti,ab,kw OR 'treatment-naive':ti,ab,kw OR 'treatment naïve':ti,ab,kw) AND [english]/lim AND [humans]/lim AND [1974-2025]/py

Cochrane Library:

#1 MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees

#2 MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees

#3 MeSH descriptor: [Ureteral Neoplasms] explode all trees

#4 (urothelial NEAR/3 carcinoma):ti,ab,kw

OR (transitional NEAR/2 cell NEAR/2 carcinoma):ti,ab,kw

OR (upper NEAR/2 tract NEAR/2 urothelial NEAR/2 carcinoma):ti,ab,kw

OR UTUC:ti,ab,kw

OR (bladder NEAR/1 cancer):ti,ab,kw

OR (bladder NEAR/1 carcinoma):ti,ab,kw

#5 #1 OR #2 OR #3 OR #4

#6 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees

#7 MeSH descriptor: [Immunotherapy] explode all trees

#8 MeSH descriptor: [Immunoconjugates] explode all trees

#9 MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees.

Participant or population Patients with locally advanced or metastatic urothelial carcinoma.

Intervention Eligible interventions included chemotherapy, ICIs, their combinations, or novel agents such as ADCs.

Comparator Comparators could be any other active treatment, including chemotherapy, ICIs or placebo.

Study designs to be included Randomized controlled trials.

Eligibility criteria We included randomized controlled trials (RCTs) investigating first-line systemic treatments for patients with locally advanced or metastatic urothelial carcinoma (UC). Eligible interventions included chemotherapy, ICIs, their combinations, or novel agents such as ADCs. Comparators could be any other active treatment, including chemotherapy, ICIs or placebo. Studies were required to report at least one relevant outcome, including OS, PFS, ORR, or grade ≥3 adverse events (AEs). Trials were excluded if they were single-arm, retrospective, non-randomized, or lacked key outcome data. For studies with overlapping populations, the most complete and up-to-date data were retained for analysis.

Information sources Electronic databases.

Main outcome(s) OS, PFS, ORR, or grade ≥3 adverse events (AEs).

Quality assessment / Risk of bias analysis The risk of bias (RoB) was assessed using the Cochrane Collaboration's RoB tool for RCTs.

Strategy of data synthesis The NMA was performed under a frequentist framework using random-effects models. Network geometry was visualized to assess the structure of treatment comparisons. Consistency was examined using a design-by-treatment interaction model, and transitivity was evaluated through comparison of clinical and methodological characteristics across studies. Treatments were ranked using the surface under the cumulative ranking curve (SUCRA). All analyses were performed using R software (version 4.5.0).

Subgroup analysis
1. cisplatin-eligible patients and cisplatin-ineligible patients
2. age
3. gender
4. PD-L1 status
5. ECOG
6. specific treatment regimens.

Sensitivity analysis Not applicable.

Country(ies) involved China.

Keywords Urothelial carcinoma; First-line therapy; Immune checkpoint inhibitor; Antibody–drug conjugate; Network meta-analysis.

Contributions of each author

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