

Adjuvant therapy

Role of adjuvant platinum-based chemotherapy: Adjuvant chemotherapy after radical cystectomy (RC) for patients with pT3/4 and/or LN positive disease (M0) is still debated. The main benefits include avoiding treatment in low-risk patients and not delaying surgery. Drawbacks are the inability to assess chemosensitivity, leading to potential overtreatment, and postoperative morbidity. Recent meta-analyses suggest a survival benefit for cisplatin-based chemotherapy, with a 6% improvement in overall survival (OS) at 5 years.

Role of adjuvant immunotherapy: Three phase III RCTs have evaluated PD-1/PD-L1 checkpoint inhibitors (atezolizumab, nivolumab, pembrolizumab) in muscle-invasive urothelial carcinoma (UC). The CheckMate 274 trial showed significant improvement in median disease-free survival (DFS) with nivolumab (20.8 months) vs. placebo (10.8 months) in patients with high recurrence risk, including those with pathological pT3, pT4a, or pN+ disease. Nivolumab also showed a better DFS in patients with PD-L1 expression $\geq 1\%$. Conversely, IMvigor010 trial with atezolizumab did not meet the primary DFS endpoint. **FDA has approved nivolumab for adjuvant treatment of high-risk UC patients, while EMA approval is limited to those with PD-L1 expression $\geq 1\%$.**

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Offer adjuvant nivolumab to selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Weak

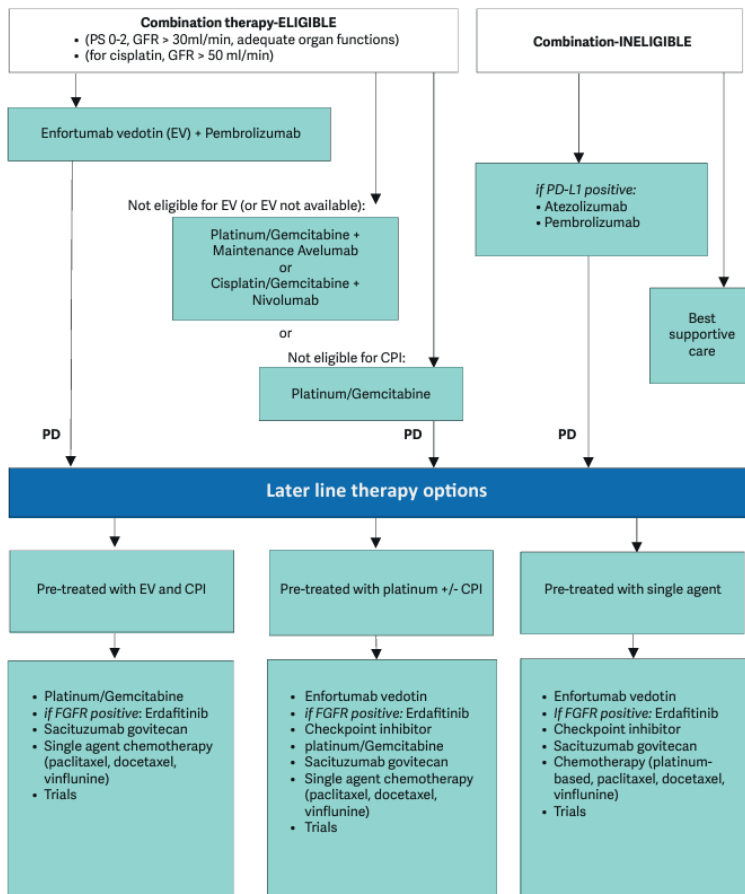
Metastatic disease

The treatment of metastatic UC has evolved significantly with the introduction of checkpoint inhibitors. Historically, cisplatin-based chemotherapy was the standard first-line treatment, **but recent trials, including EV-302/KEYNOTE A39 and Checkmate 901, have shown that immunotherapy with Pembrolizumab and Enfortumab vedotin (EV) offers improved OS and progression-free survival (PFS) compared to traditional chemotherapy, shifting the treatment paradigm for metastatic UC.**

For patients eligible for combination therapies (ECOG PS 0-2, GFR ≥ 30 ml/min), **the combination of EV + Pembrolizumab is now the standard of care.** This combination showed an overall response rate (ORR) of 67.7% and significantly improved OS, with a median of 31.5 months compared to 16.1 months with chemotherapy.

For those **ineligible for platinum-based chemotherapy, carboplatin + gemcitabine is still a preferred option**, offering effective treatment for cisplatin-unfit patients. Immunotherapy agents such as Pembrolizumab and Atezolizumab have shown effectiveness in patients who are cisplatin-ineligible, particularly those with PD-L1 positivity.

While immunotherapy has revolutionized first-line treatment, it is associated with **immune-related adverse events (AEs), which can affect various organs.** These side effects require proactive management by healthcare professionals experienced in treating immunotherapy patients to ensure safety and optimize therapeutic outcomes.



Recommendations	Strength rating
First-line treatment if eligible for combination therapy	
Use antibody drug conjugate enfortumab vedotin (EV) in combination with checkpoint inhibitor (CPI) pembrolizumab.	Strong
<i>If contraindications for EV or EV not available:</i>	Strong
Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine) followed by maintenance treatment with CPI avelumab in patients with at least stable disease on chemotherapy.	Strong
<i>If contraindications for EV (or EV not available) and cisplatin-eligible:</i>	Strong
Consider cisplatin/gemcitabine in combination with CPI nivolumab.	Strong
<i>If contraindications for checkpoint inhibitor therapy:</i>	Strong
Use platinum-containing combination chemotherapy (Cisplatin or carboplatin plus gemcitabine).	Strong
First-line treatment if not eligible for combination therapy	
Consider single agent CPI pembrolizumab or atezolizumab in case of high PD-1 expression. (for definitions see text).	Weak
Second-line treatment	
After prior EV + CPI	
Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Weak
If actionable FGFR alterations: offer erdafitinib.	Weak
Consider antibody drug conjugate sacituzumab govitecan.	Weak
Consider single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
After prior platinum-based chemotherapy +/- CPI	
Offer antibody drug conjugate enfortumab vedotin.	Strong
If actionable FGFR alterations: offer erdafitinib.	Strong
If no prior CPI: offer pembrolizumab.	Strong
Consider antibody drug conjugate sacituzumab govitecan.	Weak
Consider single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
Further treatment after EV, CPI, platinum-based therapy	
General statement: Offer treatment in clinical trials. Consider best supportive care (BSC) alone if patient is not a candidate for further cancer-specific systemic therapy.	Strong
If actionable FGFR alterations: offer Erdafitinib.	Weak

BSC = best supportive care, CPI = checkpoint inhibitor, EV = enfortumab vedotin, GC = gemcitabine plus cisplatin, FGFR = fibroblast growth factor receptor