Management of Locally Advanced Unresectable or Metastatic Urothelial Carcinoma: Expert Opinion from an Indian Panel via Delphi Consensus Method

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Ind J Med Paediatr Oncol 2024;45:365–375.

Abstract

Introduction Currently, there are no guidelines for the management of locally advanced unresectable or metastatic urothelial carcinoma (mUC) from an Indian perspective. There is a lack of consensus on the utility of treatment options in first-line (1L) and second-line (2L) settings, especially in cisplatin- and platinum-unfit mUC patient subgroups.

Objective This articles aims to develop evidence-based practical consensus recommendations for the management of mUC in Indian settings.

Methods Modified Delphi consensus methodology was considered to arrive at a consensus. An expert scientific committee of 15 medical oncologists from India constituted the panel. Twelve clinically relevant questions were grouped into five categories for presentation and discussion: (1) cisplatin and platinum ineligibility criteria; (2) programmed death ligand 1 and fibroblast growth factor receptor (FGFR) testing in mUC patients; (3) treatment options in 1L settings; (4) role of switch maintenance; and (5) treatment options in 2L. Statements that reached high ($\geq$ 80%) and moderate (60–79%) levels of consensus in the first round (electronic survey) did not undergo the second Delphi round. The questions that received a low level of consensus ($<$ 60%) were discussed during the virtual meeting.

Keywords
- bladder cancer
- metastatic urothelial carcinoma
- locally advanced
- India
- management
- consensus
- Delphi

article published online
February 10, 2023

DOI https://doi.org/10.1055/s-0042-1760317.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Results Renal impairment (creatinine clearance [CrCl] < 60 mL/min) and New York Heart Association class 3 heart failure are important assessment criteria for determining cisplatin ineligibility. Patients are unfit for any platinum-based chemotherapy in case of Eastern Cooperative Oncology Group performance status> 3 or severe renal impairment (CrCl < 30 mL/min). Gemcitabine and platinum with cisplatin over carboplatin were preferred in 1L settings. In patients unfit for cisplatin-based regimens, carboplatin–gemcitabine chemotherapy was preferred over immunotherapy (atezolizumab or pembrolizumab). Selected patients who are platinum ineligible may be considered for immunotherapy. Post-induction chemotherapy, those who do not progress may be strongly considered for avelumab maintenance. Experts recommended erdafitinib in FGFR-positive mUC patients in 2L settings. In FGFR-negative patients, immunotherapy (pembrolizumab, nivolumab, or avelumab) may be preferred over chemotherapy (paclitaxel, docetaxel, or vinflunine). Enfortumab vedotin and sacituzumab govitecan may be considered for further lines of therapy.

Conclusion Expert panel consensus will offer expert guidance to oncologists/clinicians on the management of mUC in Indian settings.

Key Points

- In 1L settings, the experts preferred gemcitabine and platinum with cisplatin over carboplatin in mUC patients.
- In patients unfit for cisplatin-based regimens, carboplatin–gemcitabine chemotherapy was preferred over immunotherapy (atezolizumab or pembrolizumab). Selected patients who are platinum ineligible (cisplatin and carboplatin) may be considered for immunotherapy (atezolizumab or pembrolizumab) in 1L. Post-induction chemotherapy, those who do not progress should be strongly considered for avelumab switch maintenance.
- Erdafitinib was recommended in FGFR-positive mUC patients in 2L.
- In FGFR-negative patients, platinum-based chemotherapy was suggested in 2L for those relapsing late, immunotherapy (pembrolizumab, nivolumab, or avelumab) for those who did not receive targeted immunotherapy in 1L, and single-agent chemotherapy (paclitaxel, docetaxel, or vinflunine) for other mUC patients.

Introduction

Carcinoma of the urinary bladder is a common urological malignancy that causes substantial morbidity and mortality. As per the Global Cancer Observatory: CANCER TODAY (GLOBOCAN) statistics, bladder cancer (BC) ranked 10th in incidence, with approximately 573,000 new cases and 213,000 deaths in 2020.[1] Urothelial carcinoma (UC) is the predominant histologic type of BC and accounts for nearly 90% of all BC cases globally.[2] BC has a wide spectrum of disease severity from low-grade non–muscle-invasive BC (NMIBC) to muscle-invasive disease stage and metastatic lesions associated with poor outcomes.[3] The majority of muscle-invasive tumors are high-grade UCs. A high probability of local/systemic recurrences of muscle-invasive tumors within 36 months after local treatment of primary tumor has been observed.[4] BC diagnosed at earlier stages carry a greater chance of 5-year relative survival compared to later disease stages (►**Table 1**).[5] Overall, 5-year relative survival rate for patients diagnosed with distant metastatic UC (mUC) is roughly 6%.[5] In India, BC is ranked 17th in incidence and 19th in mortality, with significant heterogeneity in incidence rates across different regions of India.[6] The overall incidence rate of BC in India as per the National Cancer Registry Programme report is 2.25 per 100,000 annually (males: 3.67 and females: 0.83).[7] In India, BC patients are more often diagnosed with locally advanced diseases, resulting in poor outcomes. A study by Prakash et al assessed the stage distribution of patients presenting with BC ($N = 419$) to a tertiary care cancer center in Mumbai.[8] The median age of patients at diagnosis was 59 (18–88) years.[8] Around 47% of patients had NMIBC, 36% had muscle-invasive and locally advanced disease, and 17% had metastatic disease.[8] The most common sites of distant metastasis were

Table 1 Five-year relative survival rates of bladder cancer

Stage at diagnosis	5-year relative survival (%)
Stage 0: Noninvasive papillary carcinoma and carcinoma in situ	96
Stage 0–I: Localized (confined to primary sites)	70
Stage III–IV: Regional (spread to regional lymph nodes)	38
Stage IV: Distant (metastasis to lungs, liver, or bones)	6

Abbreviation: SEER: Surveillance, Epidemiology, and End Results.
Note: Adapted from: National Cancer Institute. SEER Cancer Stat Facts for bladder cancer.[5]

bone, lung, liver, pelvic peritoneum, adrenal glands, and nonregional lymph nodes.[8]

The National Comprehensive Cancer Network (NCCN) guidelines recommend either gemcitabine–cisplatin combination chemotherapy or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) with growth factor support for cisplatin-eligible mUC patients in first-line (1L) settings.[3] Subsequent switch maintenance may be considered in patients with a nonprogressive disease on 1L platinum-based chemotherapy.[3] However, a substantial proportion of mUC patients are unfit to receive cisplatin-based chemotherapy in 1L settings due to advanced age, poor performance status, impaired renal function, and presence of multiple comorbidities. Currently, there are no defined criteria to establish cisplatin and platinum ineligibility in India, and it varies among different physicians and institutes. In addition, there is a lack of consensus on the utility of different treatment options in cisplatin- and platinum-unfit patients in 1L settings and treatment options in second-line (2L) settings. In this article, we have attempted to summarize expert opinions and recommendations on (1) cisplatin and platinum ineligibility criteria, (2) programmed death ligand 1 (PD-L1) and fibroblast growth factor receptor (FGFR) testing, (3) treatment options in 1L settings, (4) role of switch maintenance after 1L platinum-containing chemotherapy, and (5) treatment options in 2L settings based on the available efficacy and safety data.

Methodology

Panel Selection

A panel of 15 medical oncologists with significant experience in managing BC patients participated in the development of the consensus article.

Evidence Review

A literature review was carried out based on data from the PubMed database to identify relevant articles between January 2001 and March 2022 using keywords such as "urothelial carcinoma," "bladder cancer," "first-line," "second-line," "maintenance," "guidelines," and "management." Twelve clinically relevant questions (►**Supplementary Material**) belonging to five major domains were drafted.

- Cisplatin/platinum ineligibility criteria.
- PD-L1 and FGFR testing.
- Treatment pattern in 1L settings.
- Role of switch maintenance.
- Treatment pattern in 2L settings and subsequent therapy.

An electronic survey link to these questions was sent to all the participants to record their views. Key articles were shortlisted and circulated among the participants before the survey. The "Oxford Centre for Evidence-Based Medicine: Levels of Evidence (LOE)" was used to define the grade or LOE of each recommendation (►**Table 2A**).[9]

Consensus Process

Modified Delphi consensus methodology was considered to arrive at a consensus.[10] ►**Table 2(B)** lists the grades of recommendation (GOR) used during the electronic voting.[11] The level of consensus (LOC) was considered "high" when $\geq$ 80% of participants agreed/strongly agreed or disagreed/strongly disagreed with a particular statement (►**Table 2C**).[12] A "moderate" LOC was achieved when 60 to 79% of participants agreed/strongly agreed or disagreed/strongly disagreed with a particular statement.[12] All the statements that reached a "moderate" and "high" LOC in the first round did not undergo the second Delphi round. The questions that received a "low" LOC ($<$ 60%) were discussed during the Delphi round 2 meeting conducted virtually on April 8, 2022. The final draft of the consensus was e-mailed to the panel for the final review.

Results

The experts ($N = 15$) analyzed evidence, including randomized clinical trials (RCTs), systematic literature reviews, and meta-analyses through a systematic search of MEDLINE (via PubMed), Cochrane Library, and guidelines (NCCN) on mUC management published between January 2001 and March 2022. Experts made their decisions based on the available evidence and current practices in India (during Delphi rounds 1 and 2).

Cisplatin Ineligibility Criteria in Locally Advanced Unresectable UC or mUC

Assessment of performance status and renal function is of utmost importance for treatment selection. The Eastern Cooperative Oncology Group performance status (ECOG PS) $\geq$ 2 criterion can strongly predict poor outcomes (increased toxicity and decreased efficacy) in mUC patients treated with cisplatin-based regimens (LOE: 1a).[13] The presence of renal impairment (creatinine clearance [CrCl] $<$ 60 mL/min) is an important exclusion criterion in clinical trials that explore cisplatin-based regimens (LOE: 1a).[13] In addition, the presence of comorbidities such as peripheral neuropathy[13,14] and hearing loss[13,15] are important criteria for determining cisplatin ineligibility (LOE: 2c). Hydration used as part of cisplatin administration can precipitate heart failure in patients with preexisting New York Heart Association (NYHA) class 3 heart failure and hence should be avoided in this subset of patients (LOE: 2c).[13,16]

Consensus/recommendations: Initial clinical evaluation should involve an assessment of medical history, hydration status, urinary obstruction, infection, and metabolic derangement. It is important that these factors are identified early and treated appropriately before deciding on eligibility for cisplatin-based chemotherapy. Experts agreed that renal impairment (CrCl $<$ 60 mL/min) and NYHA class 3 heart failure are important assessment criteria for determining cisplatin ineligibility (GOR: ++; LOC: "high"). Hearing loss of grade $\geq$ 2 should be included in the cisplatin-ineligibility criteria and an attempt should be made to perform audiometry before cisplatin administration (GOR: +; LOC: "high"). In addition, they would consider ECOG PS $\geq$ 2 and grade $\geq$ 2 peripheral neuropathy for determining cisplatin ineligibility in their daily clinical practice (GOR: ++; LOC: "moderate").

Table 2 Definitions: (A) Oxford LOE grading system, (B) grades of recommendation, and (C) level of consensus

(A) Oxford Centre for Evidence-Based Medicine: Level of evidence (LOE)		
LOE	**Therapy/prevention, etiology/harm**	**Prognosis**
1a	Systematic review (with homogeneity) of RCTs	A systematic review (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations
1b	Individual RCT (with narrow CI)	Individual inception cohort study with > 80% follow-up; clinical decision rule validated in a single population
1c	All or none	All or no case series
2a	Systematic review (with homogeneity) of cohort studies	A systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs
2b	Individual cohort study (including low-quality RCTs, < 80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of clinical decision rule or validated on split-sample only
2c	"Outcomes" research and ecological studies	"Outcomes" research
3a	Systematic review (with homogeneity) of case–control studies	
3b	Individual case–control study	
4	Case series (and poor-quality cohort and case–control studies)	Case series (and poor-quality prognostic cohort studies)
5	Expert opinion without an explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without an explicit critical appraisal, or based on physiology, bench research, or "first principles"
(B) Grade of recommendation (GOR)		
++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed	
+	This investigation or therapeutic intervention is of limited benefit for patients and can be performed	
+/−	This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge, a general recommendation cannot be given	
−	This investigation or therapeutic intervention can be of disadvantage to patients and might not be performed	
−−	This investigation or therapeutic intervention is of clear disadvantage to patients and should be avoided or omitted in any case	
(C) Level of consensus (LOC)		
High	When ≥ 80% of participants agree/strongly agree or disagree/strongly disagree with a statement	
Moderate	When 60–79% of participants agree/strongly agree or disagree/strongly disagree with a statement	
Low	When < 60% of participants agree/strongly agree or disagree/strongly disagree with a statement	

Abbreviations: CI, confidence interval; RCTs, randomized controlled trials.
Adapted from: Oxford Centre for Evidence-Based Medicine: Levels of Evidence,[9] Scharl et al, 2013,[11] and Jünger et al, 2012.[12]

Platinum Ineligibility Criteria in Locally Advanced Unresectable UC or mUC

Patients with ECOG PS > 3, CrCl < 30 mL/min, peripheral neuropathy > 3, NYHA heart failure class > 3, and a combination of ECOG PS 2 and CrCl < 30 mL/min are poor candidates for platinum-based chemotherapy (LOE: 2c).[17] Severe hearing impairment is an exclusion criterion in trials that study platinum-based regimens (LOE: 2c).[18]

Consensus/recommendations: Experts agreed that patients are unfit for any platinum-based chemotherapy in case of ECOG PS > 3 or severe renal impairment (CrCl < 30 mL/min) (GOR: ++; LOC: "high"). Assessment of grade ≥ 2 hearing loss through audiometric evaluation can be performed in patients with mUC and should be included in the platinum-ineligibility criteria (GOR: +; LOC: "high"). In addition, grade > 3 peripheral neuropathy, NYHA class > 3 heart failure, or the combination of ECOG PS 2 and CrCl < 30 mL/min should be considered for determining platinum ineligibility (GOR: ++; LOC: "moderate").

PD-L1 Testing in Locally Advanced Unresectable UC or mUC

The NCCN guidelines recommend early molecular/genomic testing to facilitate treatment decision-making in patients with locally advanced unresectable UC or mUC.[3] A systematic review by Rouanne et al highlighted the use of PD-L1 testing with use of atezolizumab (IMvigor130 [*N* = 851; SP142 assay], IMvigor210 [*N* = 119 cisplatin ineligible; SP142]), and pembrolizumab (KEYNOTE 052 [*N* = 370 cisplatin ineligible; 22C3]) in 1L settings (LOC: 1a).[19] Currently, the use of PD-L1 testing before 1L therapy is advised in mUC patients who are cisplatin ineligible and have no contraindications to the use of immunotherapy. Immune checkpoint inhibitors (ICIs) used in the 1L include atezolizumab and pembrolizumab.[3] However, in platinum-ineligible patients, checkpoint inhibitor (CPI) can be administered irrespective of PD-L1 status.[3] The NCCN guidelines do not recommend PD-L1 testing before the maintenance phase. This is based on the JAVELIN 100 phase 3 trial that was not powered to assess progression-free survival/overall survival (PFS/OS) in the PD-L1-negative mUC patients in maintenance settings (LOE: 2b).[3,20,21] In the 2L setting, PD-L1 testing is not required when assessing eligibility for treatment with ICIs (LOE: 1a).[3,19,22]

Consensus/recommendations: Experts agreed that PD-L1 testing before 1L systemic therapy can be performed in mUC patients who are ineligible to receive cisplatin chemotherapy (GOR: +; LOC: "high"). In platinum-ineligible patients, CPI can be administered irrespective of PD-L1 status (GOR: +; LOC: "high"). PD-L1 testing is not required when assessing eligibility for treatment in maintenance and 2L settings (GOR: +/−; LOC: "high").

FGFR Testing in Locally Advanced Unresectable UC or mUC

Studies have shown that FGFR3 mutation or FGFR2/3 fusion plays a significant role in the development of mUC.[23–25] Currently, FGFR testing (FGFR3 mutation or FGFR2/3 fusion) is recommended after progression on platinum-based chemotherapy by the NCCN group to plan for optimal treatment (FGFR inhibitor or PD-L1 inhibitor [for FGFR-negative patients]) based on the eligibility criteria (LOE: 1a).[3,23–25]

Consensus/recommendations: FGFR mutation testing has not shown benefit for mUC patients in 1L settings. Experts strongly opined that it is important to screen mUC patients for FGFR3 alterations or FGFR2/3 fusion before 2L systemic therapy to plan for optimal treatment (FGFR inhibitor or PD-L1 inhibitor) (GOR: ++; LOC: "high").

►**Table 3** lists recommendations on cisplatin/platinum ineligibility criteria and biomarker testing for management of locally advanced unresectable or mUC.

Treatment Pattern in 1L Settings

Patients eligible for cisplatin-based chemotherapy: The NCCN guidelines recommend either gemcitabine–cisplatin chemotherapy or ddMVAC with growth factor support for cisplatin-eligible mUC patients in 1L settings.[3]

Patients ineligible to receive cisplatin-based chemotherapy: Carboplatin–gemcitabine combination chemotherapy is recommended in cisplatin-ineligible mUC patients in 1L based on the results of phase 1/2 randomized EORTC 30986 trial (overall response rate [ORR]: 41.2%; median OS: 9.3 months) (LOE: 2b).[26] Treatment with an ICI (atezolizumab [PD-L1 inhibitor] or pembrolizumab [PD-1 inhibitor]) could be an alternative option.[3] Currently, the use of PD-L1 testing before 1L therapy is advised in mUC patients who are cisplatin ineligible and have no contraindications to the use of immunotherapy.[3] In phase 2, IMvigor210 cohort study, atezolizumab conferred significant clinical benefits in untreated cisplatin-ineligible mUC.[27] Scoring criteria designated tumors based on tumor-infiltrating immune cells (ICs): (1) IC0 (PD-L1 expression on < 1% of IC), (2) IC1 (PD-L1 expression on ≥ 1% and < 5% of IC), or (3) IC2/3 (PD-L1 expression on ≥ 5% of IC). The study demonstrated favorable durable response rates, survival, and tolerability of atezolizumab in mUC patients in 1L settings.[27] The median OS was 12.3 months in IC2/3 and 19.1 months in IC0/1 group (LOE: 2b).[27] However, in May 2018, the Food and Drug Administration (FDA) issued a safety alert for use of atezolizumab monotherapy in 1L settings due to decreased survival compared to platinum-based chemotherapy in mUC patients who have not received prior therapy and who have low PD-L1 expression.[28] The FDA has restricted the use of atezolizumab in cisplatin-unfit mUC patients with positive PD-L1 status (PD-L1 expression on ≥ 5% of IC) and mUC patients eligible for any platinum-containing chemotherapy regardless of PD-L1 expression in 1L settings.[28] On April 2021, the FDA agreed to continue the accelerated approval of atezolizumab in the frontline treatment of cisplatin-unfit mUC.[29] The efficacy and safety of pembrolizumab were assessed in the phase 2 KEYNOTE-052 trial in 1L settings.[30,31] The study demonstrated the efficacy of pembrolizumab with acceptable tolerability in cisplatin-unfit patients, most of whom were elderly, had poor performance status, or had serious comorbidities. In patients with positive PD-L1 status defined as a combined positive score (CPS) ≥ 10, the median OS was 18.5 months (95% confidence interval [CI]:12.2–28.5 months) (LOE: 2b).[30,31] Frail patients and patients with three or more comorbidities are candidates for best supportive care (BSC) alone instead of systemic therapy in 1L (LOE: 2c).[32–34]

Patients ineligible to receive any platinum-based chemotherapy (cisplatin and carboplatin): On August 2021, the FDA converted the accelerated approval of 1L pembrolizumab in

Table 3 Cisplatin-/platinum-ineligibility criteria and biomarker testing in mUC patients

(A) Cisplatin/platinum ineligibility criteria: Summary of expert recommendations
Expert recommendations on cisplatin-ineligibility criteria
• ECOG PS $\geq$ 2 (LOE: 1a; GOR: ++; LOC: 66.7%).
• CrCl < 60 mL/min (LOE: 1a; GOR: ++; LOC: 86.7%)
• Grade $\geq$ 2 peripheral neuropathy (LOE: 2c; GOR: ++; LOC: 60%)
• NYHA class 3 heart failure (LOE: 2c; GOR: ++; LOC: 80%)
• Grade $\geq$ 2 hearing loss (LOE: 2c; GOR: +; LOC: 80%)
Expert recommendations on platinum (cisplatin and carboplatin)-ineligibility criteria
• ECOG PS > 3 (LOE: 2c; GOR: ++; LOC: 80%)
• CrCl < 30 mL/min (LOE: 2c; GOR: ++; LOC: 80%)
• Grade > 3 peripheral neuropathy (LOE: 2c; GOR: ++; LOC: 60%)
• NYHA class > 3 heart failure (LOE: 2c; GOR: ++; LOC: 60%)
• ECOG PS 2 and CrCl < 30 mL/min are important criteria for determining platinum ineligibility in patients with mUC (LOE: 2c; GOR: ++; LOC: 66.7%)
• Grade $\geq$ 2 hearing loss (LOE: 2c; GOR: +; LOC: 80%)
(B) Biomarker testing in mUC: Summary of expert recommendations
PD-L1 testing before 1L systemic therapy can be performed in mUC patients who are ineligible to receive cisplatin chemotherapy. PD-L1 testing before 1L systemic therapy is not required for those who are ineligible to receive any platinum-based chemotherapy (LOE: 1a; GOR: +; LOC: 80%)
PD-L1 testing is not required when assessing eligibility for ICI maintenance in patients who have not progressed with platinum-containing chemotherapy (LOE: 2b; GOR: +/−; LOC: 80%)
PD-L1 testing is not required when assessing eligibility for treatment in 2L settings. According to current knowledge, a general recommendation cannot be given (LOE: 1a; GOR: +/−; LOC: 80%)
FGFR mutation testing has not shown benefit for mUC patients in 1L settings. A general recommendation regarding FGFR testing before 1L systemic therapy cannot be given (LOE: 2b; GOR: +/−; LOC: 80%)
It is important to screen mUC patients for FGFR alterations before 2L systemic therapy to plan for optimal treatment (LOE: 1a; GOR: ++; LOC: 80%)

Abbreviations: 1L, first-line; 2L, second-line; CrCl, creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; GOR, grade of recommendation; ICI, immune checkpoint inhibitor; LOC, level of consensus; LOE, level of evidence; mUC, metastatic urothelial carcinoma; NYHA, New York Heart Association; PD-L1, programmed death-ligand 1.

locally advanced or mUC (cisplatin-unfit patients with PD-L1 CPS $\geq$ 10 or patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status) to a full approval and revised the indication to only cover the treatment of patients who are not eligible for any platinum-containing chemotherapy.[35] Based on the FDA approvals and evidence, the recent 2022 NCCN guideline has recommended: (1) atezolizumab (for patients not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression); or (2) pembrolizumab (for patients who are not eligible for any platinum-containing chemotherapy) (LOE: 2b).[3,27,28,30,31,35]

Consensus/recommendations: Experts agreed that they would prefer carboplatin–gemcitabine chemotherapy followed by avelumab maintenance over ICI monotherapy (atezolizumab or pembrolizumab) in mUC patients with positive PD-L1 status unfit for cisplatin-based regimens in 1L settings (GOR: ++; LOC: "high"). Experts preferred ICI monotherapy (atezolizumab or pembrolizumab) over BSC in patients ineligible for any platinum-based chemotherapy (GOR: ++; LOC: "high"). BSC should be strongly preferred over ICI therapy in patients with: (1) poor performance status, (2) multiple uncontrolled comorbidities, and/or (3) poor access to therapies (GOR: ++; LOC: "high").

Role of ICI–chemotherapy combination therapy: Two trials investigated the relevance of ICI (atezolizumab or pembrolizumab) plus platinum-based chemotherapy combination in 1L settings. The first trial to report was IMvigor130, where atezolizumab plus platinum-based chemotherapy provided PFS benefit (8.2 vs. 6.3 months; $p = 0.007$); however, OS was not significant after a median follow-up of 11.8 months compared to placebo plus platinum-based chemotherapy.[36] The KEYNOTE 361 study had a similar design and investigated pembrolizumab plus platinum–gemcitabine versus chemotherapy plus placebo in 1L settings.[37] The study revealed no benefit of this combination in terms of PFS or OS.[37]

Consensus/recommendations: Experts agreed that immunotherapy (atezolizumab or pembrolizumab) plus platinum–gemcitabine chemotherapy is not suitable in mUC patients in 1L settings (GOR: −; LOC: "high").

Role of Switch Maintenance in Locally Advanced Unresectable UC or mUC After Platinum-Based Chemotherapy

The JAVELIN Bladder 100 phase 3 RCT explored the impact of switch maintenance with PD-L1 inhibitor avelumab plus BSC versus BSC alone in mUC not progressed with 1L platinum-containing chemotherapy (complete or partial response vs. stable disease).[21] Patients were categorized as having PD-L1-positive status if at least one of the three criteria were met: (1) at least 25% of tumor cells stained for PD-L1, (2) at least 25% of ICs stained for PD-L1 if more than 1% of the tumor area contained ICs, or (3) 100% of ICs stained for PD-L1 if no more than 1% of the tumor area contained ICs.[21] Addition of maintenance avelumab to BSC significantly prolonged median OS (21.4 months; 95% CI: 18.9–26.1) as compared with BSC alone (14.3 months [95% CI: 12.9–17.9]; $p = 0.001$) (LOE: 1b).[21] With extended follow-up ($\geq$ 38 months), median OS remained significantly longer in the avelumab plus BSC (23.8 months [95% CI: 19.9–28.8]) as compared to BSC alone (15.0 months [95% CI: 13.5–18.2]; $p = 0.0036$) in unresectable locally advanced UC or mUC without disease progression.[38] Another phase 2 RCT investigated the impact of switch maintenance with PD-1 inhibitor pembrolizumab in mUC patients achieving at least stable disease on 1L platinum-based chemotherapy. In this study, the OS was not significantly different (22 vs. 18.7 months) in patients randomly assigned to maintenance pembrolizumab versus placebo (LOE: 2b).[39]

Consensus/recommendations: Experts strongly recommended avelumab switch maintenance plus BSC in mUC patients with nonprogressive disease after 4 to 6 cycles of 1L platinum-containing chemotherapy (GOR: ++; LOC: "high"). They would not prefer pembrolizumab switch maintenance due to no significant OS benefit in mUC patients (GOR: −; LOC: "high"). They would consider BSC alone in patients with poor performance status and lack of access to immunotherapies (GOR: +/−; LOC: "high").

Patient profiles suitable for avelumab switch maintenance: Avelumab switch maintenance plus BSC provided an OS and PFS benefit in patients with PD-L1-positive or PD-L1-negative tumors, with a potentially greater benefit in patients with PD-L1-positive tumors.[21] Avelumab maintenance significantly prolonged OS in the PD-L1-positive mUC patients; OS at 1 year was 79.1% in the avelumab group versus 60.4% in the control group (BSC alone; $p < 0.001$) (LOE: 1b).[21] With extended follow-up ($\geq$ 38 months), median OS remained significantly longer in the avelumab plus BSC (30.9 months [95% CI: 24.0–39.8]) as compared to BSC alone (18.5 months [95% CI: 14.1–24.2]; $p = 0.0064$) in unresectable locally advanced UC or mUC patients with PD-L1-positive tumors.[38] The JAVELIN Bladder 100 phase 3 trial was not powered to assess PFS/OS in the PD-L1-negative mUC patients in maintenance settings.[21] In mUC patients with PD-L1-negative tumors, the median OS was 18.8 months (95% CI: 13.3–22.5) in the avelumab plus BSC group versus 13.7 months (95% CI: 10.8–17.8) in the BSC alone (hazard ratio: 0.85; 95% CI: 0.62–1.18) (LOE: 2b).[21] The trial demonstrated OS benefits with avelumab switch maintenance in a range of patient subgroups (categorized by age, ECOG PS 0/1, prior chemotherapy regimen, response to chemotherapy, site of baseline metastasis, CrCl) not progressed with 1L platinum-containing chemotherapy (LOE: 1b).[20,21]

Consensus/recommendations: Experts agreed that avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with ECOG 0/1, age < 65 years, regardless of PD-L1 status, CrCl, site of metastasis, and chemotherapy (gemcitabine with cisplatin or carboplatin). The patient profiles that received moderate consensus during the discussion were: (1) stable disease after 1L platinum-containing chemotherapy, (2) visceral metastasis after 1L platinum-containing chemotherapy, and (3) age $\geq$ 65 years (GOR: ++).

►**Table 4** lists the recommendations for 1L systemic therapy and switch maintenance after 1L platinum-containing chemotherapy.

Treatment Pattern in 2L and Subsequent Therapy

In the phase 3 KEYNOTE-045 RCT, pembrolizumab conferred significant OS benefits in 2L (10.3 vs. 7.4 months; $p = 0.002$) as compared to the chemotherapy group (paclitaxel, docetaxel, or vinflunine) in mUC patients who progressed during or after the receipt of platinum chemotherapy (LOE: 1b).[40] Nivolumab, a fully human immunoglobulin G4 PD-1 ICI, demonstrated clinical benefit (ORR was 19·6% [95% CI: 15.0–24.9]) in a phase 2, single-arm study in mUC patients whose disease progressed or recurred despite previous treatment with at least one platinum-based chemotherapy regimen (LOE: 2b).[41] Recently, the efficacy and safety of avelumab in 2L were assessed in phase 1b JAVELIN Solid Tumor study. Avelumab therapy resulted in a median OS of 7.0 months and a 24-month OS rate of 20.1% (LOE: 2b).[42] For management of mUC patients with FGFR alternations, the NCCN guideline recommends erdafitinib, a tyrosine kinase inhibitor of FGFR1–4, in 2L based on the promising result from the phase 2 BLC2001 study.[43] The confirmed response rate to erdafitinib therapy was 40% and the median OS was 13.8 months. Among patients who had undergone prior immunotherapy, the response rate was 59% (LOE: 2b).[43] The indication of atezolizumab was withdrawn by the FDA in March 2021 in mUC patients previously treated with platinum-based chemotherapy based on the results of the phase 3 IMvigor211 trial.[44] The trial failed to meet its primary endpoint of OS benefit in mUC patients with positive PD-L1 status (IC2/3; 11.1 vs. 10.6 months; $p = 0.41$) as compared to chemotherapy (vinflunine, paclitaxel, or docetaxel).[44,45] The NCCN guidelines recommend: (1) rechallenge with gemcitabine and cisplatin or carboplatin or MVAC in patients who relapse after a year of last platinum exposure, (2) erdafitinib in patients with FGFR3 or FGFR2 genetic alterations, or (3) ICI therapy (pembrolizumab, nivolumab, or avelumab) in patients who have not received ICI in 1L settings.[3]

Consensus/recommendations: Experts recommended erdafitinib in FGFR-positive mUC patients in 2L settings (GOR: ++; LOC: "high"). Experts agreed that in FGFR-negative patients, ICIs (pembrolizumab, nivolumab, or avelumab) may be preferred over chemotherapy (paclitaxel, docetaxel, or vinflunine).

Table 4 First-line systemic therapy and switch maintenance for locally advanced or mUC

(A) 1L systemic therapy for locally advanced unresectable UC or mUC: Summary of expert recommendations
Treatment of cisplatin-ineligible mUC patients with positive PD-L1 status Carboplatin–gemcitabine chemotherapy is preferred over ICI monotherapy (atezolizumab or pembrolizumab) in mUC patients with positive PD-L1 status deemed unfit for cisplatin-based therapy in 1L settings (LOE: 2b; GOR: ++; LOC: 80%) ***Treatment of mUC patient ineligible for any platinum-based chemotherapy (cisplatin and carboplatin ineligible)*** • ICI monotherapy (atezolizumab or pembrolizumab) can be preferred over BSC in patients ineligible for any platinum-based chemotherapy (LOE: 2b; GOR: ++; LOC: 80%) • BSC is strongly preferred over ICI therapy in patients with: (1) poor performance status; (2) multiple uncontrolled comorbidities; and/or (3) poor access to immunotherapies (LOE: 2c; GOR: ++; LOC: 80%) ***Scope of immunotherapy–chemotherapy combination in 1L treatment settings*** • Immunotherapy (atezolizumab or pembrolizumab) plus platinum–gemcitabine chemotherapy is not suitable in mUC patients in 1L treatment settings (LOE: 1b; GOR: −; LOC: 80%)
(B) Switch maintenance for locally advanced unresectable UC or mUC patients after 1L platinum-containing chemotherapy: Expert recommendations
Switch maintenance in the general population • Avelumab switch maintenance plus BSC is strongly recommended in mUC patients with the nonprogressive disease after 4–6 cycles of 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 100%) • Pembrolizumab switch maintenance is not suitable after 1L platinum-containing chemotherapy due to no OS benefit in mUC patients (LOE: 2b; GOR: −; LOC: 80%) • BSC instead of switch maintenance can be considered in patients with poor performance status and lack of access to immunotherapies (LOE: 2c; GOR: +/−; LOC: 80%)
Patient profiles suitable for avelumab switch maintenance therapy ***PD-L1 status*** • Avelumab switch maintenance plus BSC is strongly recommended in PD-L1-positive mUC patients with the nonprogressive disease after 4–6 cycles of 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 86.7%) • Avelumab switch maintenance plus BSC can be performed in PD-L1-negative mUC patients with the nonprogressive disease after 4–6 cycles of 1L platinum-containing chemotherapy (LOE: 2b; GOR: ++; LOC: 80%) **Prior chemotherapy regimen** • Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients not progressed on 1L gemcitabine–carboplatin or gemcitabine–cisplatin-based chemotherapy (LOE: 1b; GOR: ++; LOC: 93.3%) ***Response to chemotherapy*** • Avelumab switch maintenance therapy is beneficial and recommended in mUC patients with partial and complete response after 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 86.7%) • Avelumab maintenance therapy is also recommended in mUC patients with stable disease after 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 66.7%) **Type of metastases** • Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with nonvisceral metastasis after 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 86.7%) • Avelumab switch maintenance therapy is beneficial in mUC patients with visceral metastasis after 1L platinum-containing chemotherapy (LOE: 1b; GOR: ++; LOC: 73.3%) **ECOG status** Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with ECOG status 0/1 (LOE: 1b; GOR: ++; LOC: 93.3%) **CrCl** Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients regardless of CrCl (< 60 mL/min and ≥ 60 mL/min) (LOE: 1b; GOR: ++; LOC: 73.3%) **Age** • Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with age < 65 years (LOE: 1b; GOR: ++; LOC: 100%) • Avelumab switch maintenance therapy is beneficial and can be recommended in mUC patients with age ≥ 65 years (LOE: 1b; GOR: ++; LOC: 66.7%)

Abbreviations: 1L, first-line; BSC, best supportive care; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; GOR, grade of recommendation; ICI, immune checkpoint inhibitor; LOC, level of consensus; LOE, level of evidence; mUC, metastatic urothelial carcinoma; PD-L1, programmed death-ligand 1; UV, urothelial carcinoma.

Patient eligibility should be determined before therapy based on the available efficacy and safety data. On the other hand, chemotherapy (paclitaxel, docetaxel, or vinflunine) can be considered in patients who are not eligible for ICI therapy or have poor access to ICI therapy. Experts strongly opined that pembrolizumab can be preferred as it has strong phase 3 clinical evidence with OS benefit (GOR: ++; LOC: "high") as compared to nivolumab (GOR: +; LOC: "high").

Patient profiles suitable for ICI in 2L: Experts agreed that ICI therapy (pembrolizumab, nivolumab, or avelumab) is suitable and can be recommended in patients with ECOG status 0/1 (GOR: ++; LOC: "high"). In addition, ICI therapy can be considered in patients with: (1) prior cisplatin chemotherapy, (2) PD-L1 (IC 2/3), and (3) visceral disease (GOR: ++; LOC: "moderate").

Scope of antibody–drug conjugates (ADCs): In phase 3 EV-301 trial, the efficacy of enfortumab vedotin, a nectin-4-directed

ADC, was assessed in patients previously treated with platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.[46] The study demonstrated that median OS was significantly longer in the enfortumab vedotin treatment arm (12.88 months [95% CI: 10.58–15.21) as compared to the chemotherapy group (docetaxel, paclitaxel, or vinflunine) (8.97 months [95% CI: 8.05–10.74]; $p = 0.001$) (LOE: 1b).[46] Another phase 2, open-label (TROPHY-U-01) cohort study investigated the role of TROP-2-directed ADC sacituzumab govitecan in mUC patients who progress on platinum-based combination chemotherapy and ICI therapy.[47] The median OS achieved with sacituzumab govitecan therapy was 10.9 months (95% CI: 9.0–13.8 months) (LOE: 2b).[47]

Consensus/recommendations: Experts agreed that enfortumab vedotin is a suitable treatment option in patients who have previously received platinum-containing chemotherapy and progressed during or after treatment with a PD-1 or PD-L1 inhibitor (GOR: ++; LOC: "moderate"). Currently, enfortumab vedotin is available only on a compassionate basis in India. Sacituzumab govitecan is another treatment option in patients who have previously received platinum-containing chemotherapy and progressed during or after treatment with a PD-1 or PD-L1 inhibitor (GOR: ++; LOC: "low").

OS improvement from the start of 1L therapy: Experts opined that 1L platinum-based chemotherapy (4–6 cycles) followed by avelumab switch maintenance with BSC is most useful in terms of OS improvement from the start of 1L therapy and can be recommended (GOR: ++; LOC: "high").

►**Table 5** lists the recommendations for 2L systemic therapy for the management of mUC.

Discussion

Clinical and Research Implications

Treatment of UC has evolved over the last few years with improved outcomes across different disease stages. ICI and targeted therapies have emerged as new options for the treatment of persistent diseases. In India, there are no country-specific guidelines or recommendations for the management of locally advanced unresectable or mUC. Furthermore, due to the scarcity of RCTs conducted in India and the lack of local guidelines or recommendations, oncologists rely on data from the Western world. Currently, there are no defined criteria to establish cisplatin and platinum ineligibility in India, and it varies among different physicians and institutes. There is a lack of consensus on the utility of treatment options, especially in cisplatin- and platinum-unfit mUC patient subgroups. To the best of our knowledge, this is the first evidence-based practical consensus document to guide clinicians on the management of mUC in Indian settings. This consensus document will offer expert guidance to Indian oncologists and help achieve consistency in mUC management across various healthcare settings.

Strengths: The members of the panel (in the space of genitourinary oncology) were selected to best represent the breadth of knowledge and clinical expertise in the field from all over India. There was no selection bias during the development of the expert committee. All experts actively participated during the consensus process. The responses of all panelists were generated in the form of graphs (GOR vs. response in percentage) to ensure the protection of participants' data.

Table 5 Second-line systemic therapy for locally advanced or mUC

2L systemic therapy for locally advanced unresectable UC or mUC: Expert recommendations
• Erdafitinib is recommended in FGFR-positive mUC patients in 2L settings (LOE: 2b; GOR: ++; LOC: 80%) • In FGFR-negative patients, ICI (pembrolizumab, nivolumab, or avelumab) may be preferred over chemotherapy (paclitaxel, docetaxel, or vinflunine) in 2L settings. Pembrolizumab has strong phase 3 data in terms of OS and can be preferred (LOE: 1b; GOR: ++; LOC: 80%) over nivolumab (LOE: 2b; GOR: +; LOC: 80%) in 2L settings • Enfortumab vedotin is a suitable treatment option in mUC patients who have previously received platinum-containing chemotherapy and progressed during or after treatment with a PD-1 or PD-L1 inhibitor (LOE: 1b; GOR: ++; LOC: "moderate"). Currently, enfortumab vedotin is available only on a compassionate basis in India • Sacituzumab govitecan is another treatment option in patients who have previously received platinum-containing chemotherapy and progressed during or after treatment with a PD-1 or PD-L1 inhibitor (LOE: 2b; GOR: ++; LOC: "low")
Patient profiles suitable for ICI in 2L settings • ECOG PS status: ICI therapy (pembrolizumab, nivolumab, or avelumab) is suitable and can be recommended in patients with ECOG status 0/1 in 2L settings (GOR: ++; LOC: 86.7%) • PD-L1 status: ICI therapy (pembrolizumab, nivolumab or avelumab) can be considered in PD-L1 (IC 2/3 [GOR: ++; LOC: 60%] and IC 1 [GOR: +; LOC: 73.3%]) in 2L settings • First-line chemotherapy: ICI therapy (pembrolizumab, nivolumab, or avelumab) is suitable in patients with prior cisplatin chemotherapy in 2L settings (GOR: ++; LOC: 73.3%) • Extent of involvement: ICI therapy (pembrolizumab, nivolumab, or avelumab) can be considered in patients with visceral disease in 2L settings (GOR: ++; LOC: 60%)
OS improvement from the start of therapy: Expert recommendations
1L platinum-based chemotherapy (4–6 cycles) followed by avelumab switch maintenance with BSC is most useful in terms of OS improvement from the start of 1L therapy and can be recommended (GOR: ++; LOC: 100%)

Abbreviations: 2L, second-line; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; GOR, grade of recommendation; ICI, immune checkpoint inhibitor; LOC, level of consensus; LOE, level of evidence; mUC, metastatic urothelial carcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; UV, urothelial carcinoma.

Limitation: The patient's voice was not included in the consensus process.

Conclusion

In this article, we have attempted to summarize the Indian consensus on the management of locally advanced unresectable UC or mUC. Patients with treatment-naive mUC should be classified according to cisplatin and platinum eligibility based on clear definitions. In a 1L setting, the experts preferred gemcitabine and platinum with cisplatin over carboplatin. Selected patients who are platinum ineligible may be considered for atezolizumab or pembrolizumab. Post-induction chemotherapy, those who do not progress should be strongly considered for avelumab maintenance. Experts recommended screening mUC patients for FGFR3 alterations or FGFR2/3 fusion before deciding on 2L therapy. Options for 2L therapy include platinum-based chemotherapy for those relapsing late, targeted therapy with erdafitinib for patients with FGFR alterations, ICI (pembrolizumab, nivolumab, or avelumab) for those who have not received ICI in 1L settings, and single-agent chemotherapy (paclitaxel, docetaxel, or vinflunine) for others. Enfortumab vedotin and sacituzumab govitecan should be considered for further lines of therapy.

Authors' Contributions
All authors have contributed equally to the concept, design, editing, review, and finalization of manuscript.

Funding
This study is supported by Pfizer India Ltd.

Conflict of Interest
None declared.

Acknowledgment
We would like to thank BioQuest Solutions Pvt Ltd for their editorial support.

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