# BLADDER CANCER

CHI Formulary Indication Review

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Council of Health Insurance

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# Abbreviations

| | |
|---|---|
| 5-FU | 5-Fluorouracil |
| ASCO | American Society of Clinical Oncology |
| ASTRO | American Society for Radiation Oncology |
| AUA | American Urological Association |
| BCG | Bacillus Calmette Guerin |
| BSC | Best Supportive Care |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CBC | Complete Blood Count |
| CPS | Combined Positive Score |
| CrCl | Creatinine Clearance |
| CT | Computer Tomography |
| CTAE | Common Terminology Criteria for Adverse Events |
| CUA | Canadian Urological Association |
| ddMVAC | Dose-dense Methotrexate/Vinblastine/Doxorubicin/Cisplatin |
| EAU | European Association of Urology |
| ECOG | Eastern Cooperative Oncology Group |
| ESMO | European Society of Medical Oncology |
| GC | Gemcitabine/Cisplatin |
| GFR | Glomerular Filtration Rate |
| HAS | Haute Autorité de Santé |
| HR | Hazard Ratio |
| HTA | Health Technology Assessment |
| ICER | Incremental Cost-Effectiveness Ratio |
| ICI | Immune Checkpoint Inhibitor |
| IQWIG | Institute for Quality and Efficiency in Healthcare |
| KSA | Kingdom of Saudi Arabia |
| MIBC | Muscle Invasive Bladder Cancer |
| MRI | Magnetic Resonance Imaging |
| NAC | Neoadjuvant Chemotherapy |
| NICE | National Institute for Health and Care Excellence |
| NMIBC | Non-Muscle Invasive Bladder Cancer |
| NCCN | National Comprehensive Cancer Network |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PD | Peritoneal Dialysis |
| PD-1 | Programmed Cell Death Protein-1 |
| PD-L1 | Programmed Death Ligand-1 |
| PLND | Pelvic Lymph Node Dissection |

| | |
|---|---|
| pERC | pan-Canadian Oncology Drug Review Expert Review Committee |
| PET | Positron Emission Tomography |
| PFS | Progression-Free Survival |
| QALY | Quality-Adjusted Life Years |
| QoL | Quality of Life |
| RC | Radical Cystectomy |
| RT | Radiotherapy |
| SIC | Single Instillation of Chemotherapy |
| SUO | Society of Urologic Oncology |
| TURBT | Transurethral resection of bladder tumor |
| UC | Urothelial Carcinoma |

# Executive Summary

Bladder cancer is the most common malignancy involving the urinary system. Urothelial (transitional cell) carcinoma is the predominant histologic type in the United States and Europe, where it accounts for 90% of all bladder cancers. Bladder cancer is the 6th most common cancer in the United States, with an estimate of 82,290 new cases in 2023, accounting for 4.2% of all new cancer cases[1]. It is rarely diagnosed in individuals younger than 40 years. Given that the median age at diagnosis is 73 years[1], medical comorbidities are a frequent consideration in patient management. Risk factors for developing bladder cancer include male sex, white race, smoking, personal or family history of bladder cancer, pelvic radiation, environmental/occupational exposures, exposure to certain drugs, chronic infection or irritation of the urinary tract, and certain medical conditions including obesity and diabetes[2,3,4,5]. While diabetes mellitus appears to be associated with an elevated risk of developing bladder cancer[3], treatment with metformin may be associated with improved prognosis in patients with bladder cancer and diabetes[6]. Certain genetic syndromes, most notably Lynch syndrome, may also predispose an individual to urothelial carcinoma[7].

The clinical spectrum of bladder cancer can be divided into three categories that differ in prognosis, management, and therapeutic aims.

- The first category consists of **non-muscle invasive bladder cancer** (NMIBC), for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage.
- The second group encompasses **muscle invasive bladder cancer** (MIBC). The goal of therapy is to determine whether the bladder should be removed or if it can be preserved without compromising survival, and to determine if the primary lesion can be managed independently or if patients are at high risk for distant spread requiring systemic approaches to improve the likelihood of cure.
- The critical concern for the third group, consisting of **metastatic disease**, is how to prolong and maintain quality of life[8].

Patients with urothelial bladder cancer typically present with **painless hematuria**. The presence of unexplained hematuria in adults requires evaluation that is based on risk of malignancy.

The goal of the **diagnostic evaluation** is to determine the diagnosis, site, and extent of cancer, and the presence or absence of muscle invasive disease. It includes the following[8,9,10,11,12,13,14,15]:

- **Urinalysis –** The urinalysis should include a microscopic and gross examination as well as a dipstick chemical test.
- **Cystoscopy –** Cystoscopy is the initial procedure for both the diagnosis and management of urothelial malignancy. Cystoscopy is used to establish the diagnosis, assess whether or not muscle invasion is present, and provide initial therapy for non-muscle invasive lesions.
- **Urine cytology –** Urine cytology is widely used in combination with cystoscopy to assess for the presence of carcinoma in situ and to evaluate for the presence of upper urinary tract lesions.
- **TURBT –** Transurethral resection of bladder tumor (TURBT) along with examination under anesthesia is required in order to determine histology, depth of invasion, and potential involvement beyond the bladder.
- **Bladder biopsy –** Bladder biopsies of normal-appearing metastatic urothelial carcinoma are required in patients with an otherwise unexplained positive urine cytology.
- **Imaging –** For patients with muscle-invasive disease, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) and laboratory evaluation is indicated to assess the extent of pelvic disease and exclude the presence of distant metastases.

**Stage** is the most important independent prognostic variable for assessing the probability of progression and survival. The standard approach is the tumor, node, metastasis (TNM) staging system, which requires cystectomy. For patients who will undergo neoadjuvant therapy, clinical staging is appropriate[8-15].

In the **Kingdom of Saudi Arabia, the overall incidence of bladder cancer between 2008 and 2017 was 1.4 per 100 000 persons, according to a retrospective cohort study from the Saudi Cancer registry** (SCR)[16]. The registry contained 3750 patients with bladder cancer. **The mean age was 62.3 (15.0) years, and the majority** (58.6%) **were 60 years or older**, **males** (82.2%) and **Saudi** (71.3%)[16]. Most were married (77.8%). Almost a third (29.9%) resided in the central region. Most of the tumors were multifocal (85.6%) and urothelial carcinoma (89.9%) of various grades. The squamous cell carcinoma incidence ranged from 0.05 to 0.09 per 100 000, and the adenocarcinoma from 0.02 to 0.06 per 100 000. **The mortality rate was 16.3%** (n=610, with 12 unknowns). Of the deceased group, 579 (94.92%) died due to the cancer. **The mean interval in years from diagnosis to death for the deceased group due to cancer was 0.92 (0.90) years**[16]**.** Urothelial carcinoma had a notably higher rate of grade IV tumors compared to adenocarcinoma and squamous cell carcinoma. A significant difference in survival was observed by age group, **the group with the longest mean survival was the 19 to 39 years age group**, and the **shortest was in the older and younger groups** (mean of 6.75 years in ≥60 years group vs. 1.99 years

in the ≤18 years group[16]. There was a significant difference in survival between genders: **the male group had a higher mean survival compared to the female group** (5.49 years vs. 4.99 years)[16]. **Saudis had longer mean survival years compared with the non-Saudis** (5.33 years vs. 3.98, respectively, P<.001). The highest mean survival years occurred in the western region, and the lowest in the southern region (5.81 years compared to 4.71 years, respectively, P=.015). The location with the **highest mean survival** was the **lateral wall of the urinary bladder**, and the **lowest the anterior wall** (6.54 years vs. 2.36 years)[16]. Mean survival for urothelial carcinoma was higher than for the groups with adenocarcinoma and squamous cell carcinoma (5.51 years vs. 3.59 and 3.64 years, respectively, (P<.001). **The longest mean survival occurred in patients who had localized tumors**; the lowest in the group with distant metastasis (6.46 years vs. 2.26 years, respectively, (P<.001)[16]. The factors significantly associated with decreased survival were age, squamous cell carcinoma, Grade III, Grade IV, regional: direct extension, regional: lymph node extension, regional: lymph node and direct extension, and distant metastasis[16].

This report compiles all clinical and economic evidence related to bladder cancer and associated complications according to the relevant sources. The ultimate objective of issuing bladder cancer guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to bladder cancer patients in Saudi Arabia.** The main focus of the review was on Saudi, North American, and European guidelines issued within the last five years in addition to recent systematic reviews and meta-analysis.

**Treatment strategies** for patients with bladder cancer are outlined in the below sections[8-15]:

### A. Non-Muscle Invasive Bladder Cancer (NMIBC)

Primary tumors without muscle invasion (Ta and T1 lesions) are generally managed initially with **TURBT**[8-15].

- A **single instillation of intravesical chemotherapy** is recommended to be administered within 24 hours of surgery (ideally within 6 hours)[8-15].
- **Gemcitabine** (Recommendation Level A, Evidence Level II) and **mitomycin** (Recommendation Level A, Evidence Level II) are the preferred agents for intravesical chemotherapy in this setting[8-15].
- The subsequent management of NMIBC will be based on the American Urological Association/ Society of Urologic Oncology (AUA/SUO) risk stratification[10] (Table 1) with the caution that an individual patient within each of the risk groups may have specific features that can influence care decisions[8,10].

**Table 1.** AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer. Adapted from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol. 2016;196(4):1021-1029. doi:10.1016/j.juro.2016.06.049.

| Low Risk | Intermediate Risk | High Risk |
|---|---|---|
| ▪ Papillary urothelial neoplasm of low malignant potential<br>▪ Low grade urothelial carcinoma<br>- Ta and<br>- ≤3 cm and<br>- Solitary | ▪ Low grade urothelial carcinoma<br>- T1 or<br>- >3 cm or<br>- Multifocal or Recurrence within 1 year<br>▪ High grade urothelial carcinoma<br>- Ta and<br>- ≤3 cm and<br>- Solitary | ▪ High grade urothelial carcinoma<br>- CIS or<br>- T1 or<br>- >3 cm or<br>- Multifocal<br>▪ Very high-risk features (any):<br>- BCG unresponsive<br>- Variant histologies<br>- Lymphovascular invasion<br>- Prostatic urethral invasion |

### A.1. Patients with low-risk NMBC:

- The risk of recurrence or progression is low following TURBT and no further treatment is necessary, although a single instillation of intravesical chemotherapy immediately post-TURBT can be helpful in reducing the risk of recurrence.
- An appropriate surveillance schedule is recommended for early detection of disease recurrence. If the initial follow-up surveillance cystoscopy is negative within 4 months of TURBT, the next cystoscopy is recommended 6 to 9 months later and then yearly for up to 5 years[8-15].

### A.2. Patients with intermediate-risk NMBC:

- After TURBT and immediate intravesical chemotherapy, **a 6-week induction course of intravesical therapy** is recommended[8-15].
- **Gemcitabine** (Recommendation Level A, Evidence Level I) and **mitomycin** (Recommendation Level A, Evidence Level I) are the preferred agents for **induction intravesical chemotherapy**[8-15].
- **Gemcitabine** is preferred over **mitomycin** based on toxicity profiles and lower cost. In addition, in systematic reviews and meta-analyses,

gemcitabine has shown superior efficacy compared to mitomycin, in that it demonstrated reduced rates of recurrence and progression[8].

- Intravesical **Bacillus-Calmette-Guerin (BCG)** is also an option for adjuvant intravesical chemotherapy. The availability of BCG should be considered in decision-making as it may be prioritized for treatment of higher risk disease[8-15].

### A.3. Patients with high-risk NMBC:

- High-risk NMIBC has a relatively high risk for recurrence and progression towards more invasiveness.
- Treatment options for high-risk NMIBC depend on whether the tumor has previously been shown to be unresponsive or intolerant to BCG.
- For BCG-naïve NMIBC, the options are **cystectomy** or **BCG**. When *very high-risk features* are present, **cystectomy** is preferred because of the high risk for progression to a more advanced stage, while **BCG** is preferred when these are *not present*.
- **BCG** is the preferred treatment recommendation for **BCG-naïve, high-risk NMIBC without very-high-risk features** (Recommendation Level A, Evidence Level I) [8-15].
- There are concerns regarding potentially severe local and systemic side effects and the inconsistent availability of BCG.

- All patients are at risk for recurrence both in the bladder and elsewhere in the urothelium, and **long-term surveillance is required** following initial therapy. For intermediate and high-risk NMIBC, follow-up is recommended with a urinary cytology and cystoscopy at 3- to 6-month intervals for the first 2 years, and at longer intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high-risk tumors[8-15].
- Post-treatment of Recurrent or Persistent Disease:
  - ***Patients with Positive Cystoscopy***: Patients under surveillance after initial TURBT, who show a documented recurrence by positive cystoscopy, should undergo another TURBT to reclassify the AUA/SUO risk group. Patients should be treated and followed as indicated based on the risk of their recurrent disease[8-15].
  - ***Patients with Positive Cytology***: In patients without a documented recurrence but with initial positive cytology and negative cystoscopy and imaging, it may be appropriate to repeat the cytology test within 3 months.

- If subsequent cytology tests are positive, selected mapping biopsies including transurethral resection of the prostate (TURP) may be considered. In addition, the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract. If available, enhanced cystoscopy should be considered[8-15].
- If the selected mapping **biopsy of the bladder is positive**, then the recommendation is to administer **intravesical BCG** followed by **maintenance BCG (preferred)** if a complete response is seen[8-15].
    - For tumors that are unresponsive to BCG or for persistent or recurrent disease post-BCG treatment, the subsequent management options include **cystectomy**, changing the intravesical agent, or participation in a clinical trial.
    - **Pembrolizumab** is also an option for patients with BCG-unresponsive, high-risk, NMIBC with Tis, with or without papillary tumors, who are ineligible for or have elected not to undergo cystectomy, although the data are currently not mature enough to determine if pembrolizumab can be considered curative in this setting[8-15].
    - Nadofaragene firadenovec-vncg is indicated for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS (with or without papillary) (Recommendation Level A, Evidence Level II) and may also be considered for patients with BCG-unresponsive, high-risk, NMIBC with high-grade papillary Ta/T1 only tumors without CIS (Recommendation Level A, Evidence Level II)[8].
    - Non-cystectomy candidates with recurrent or persistent cTa or cT1 disease may also consider concurrent **chemoradiotherapy** as an option[8].
    - For patients with disease that does not respond or shows an incomplete response to treatment following a change in intravesical agent, subsequent management is cystectomy[8].
- If the bladder, prostate, and upper tract continue to show negative results on further evaluation, additional follow-up is indicated after 3 months, then at longer intervals. If BCG was given previously, maintenance BCG may be considered.

## B. Muscle-Invasive Bladder Cancer (MIBC)

**Radical cystectomy** with urinary diversion is the **treatment of choice** for patients with muscle invasive disease[8-15].

### B.1. Treatment of Stage II and IIIA Tumors

- **Neoadjuvant chemotherapy** – **Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy** improves overall survival (OS) and is the standard of care (Recommendation Level A, Evidence Level I)[8-15].
    - **ddMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles** is the preferred regimen for neoadjuvant chemotherapy (Recommendation Level A, Evidence Level II)[8-15].
    - **GC (gemcitabine/cisplatin)** is another alternative for neoadjuvant chemotherapy (Recommendation Level A, Evidence Level II)[8-15].
    - Partial cystectomy along with neoadjuvant cisplatin-based chemotherapy can be considered for stage II (cT2, N0) disease with a single tumor in a suitable location and no presence of Tis. Partial cystectomy is not an option for patients with stage III disease.
- **Adjuvant therapy** – Patients who receive initial treatment with definitive surgery and are at high risk for recurrence based on pathologic staging or those who have residual muscle-invasive cancer after neoadjuvant chemotherapy and cystectomy may be candidates for adjuvant therapy (Recommendation Level A, Evidence Level II)[8-15].
    - Available systemic agents include cisplatin-based chemotherapy **(ddMVAC with growth factor support for 3-6 cycles [preferred]; GC)** and **immunotherapy (nivolumab)** (Recommendation Level A, Evidence Level II)[8-15].
    - If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered.
    - If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered.
    - Adjuvant RT is another option for patients with tumors that are T3–4, or with positive nodes or margins, following surgery (Recommendation Level B, Evidence Level II)[8-15].

- **Trimodality therapy (TMT)** – For patients unable or unwilling to undergo radical cystectomy with urinary diversion for muscle invasive urothelial bladder cancer, trimodality therapy (TMT) incorporating complete TURBT combined with radiation therapy (RT) plus chemotherapy may offer an alternative bladder-sparing approach[8-15].
  - Based on clinical practice and strength of the data, the following **radiosensitizing regimens** are preferred for organ-preserving chemoradiation: **5-FU plus mitomycin C** or **cisplatin** alone (Recommendation Level A, Evidence Level II). **Cisplatin plus 5-FU**, **cisplatin plus paclitaxel**, or **low-dose gemcitabine** may be considered as alternative regimens (Recommendation Level A, Evidence Level II)[8-15].
  - After a complete TURBT, 60 to 66 Gy of external beam RT (EBRT) is administered. Two doses of concurrent radiosensitizing chemotherapy may be given at weeks 1 and 4 (although weekly schedules are possible as well). Alternatively, an induction dose of 40 to 45 Gy radiotherapy may be given following complete TURBT[8-15].
- In patients with **extensive comorbid disease** or poor performance status who are non-cystectomy candidates, treatment options include concurrent **chemoradiation** (preferred) (Recommendation Level A, Evidence Level I) or **radiotherapy** alone[8-15].
  - TURBT is another option for patients with stage II disease who are non-cystectomy candidates.
  - The overall tumor status should be reassessed 2 to 3 months after treatment. If no tumor is evident, the patient should be observed. If tumor is observed, systemic therapy, concurrent chemoradiotherapy or radiotherapy alone (if no prior radiotherapy), TURBT with or without intravesical therapy, or best supportive care may be given.

### B.2. Treatment of Stage IIIB Tumors

- Primary treatment for stage IIIB (cT1–T4a, N2–3) disease can include either **down staging systemic therapy** or **concurrent chemoradiotherapy** (with the agents mentioned in the previous section) [8-15].
- Subsequent disease management depends on the response to primary treatment[8-15].
  - Patients who received downstaging systemic therapy and had a complete disease response may then be subsequently treated with cystectomy or chemoradiotherapy or may be observed until disease relapse.
    - Patients who received downstaging systemic therapy and showed a partial response may be treated with cystectomy or

chemoradiotherapy (for persistent disease confined to the bladder) or treated as metastatic disease with additional lines of systemic therapy (for distant disease).

- Patients who had disease progression following primary downstaging systemic therapy may be treated as with metastatic disease, with additional lines of systemic therapy.

- Patients with complete disease response following concurrent chemoradiotherapy should be observed until disease relapse.
    - Disease with partial responses to concurrent chemoradiotherapy may be subsequently treated with surgical consolidation (for residual disease confined to the bladder), consideration of intravesical BCG (for Tis, Ta, or T1 residual disease), or treated as metastatic disease with systemic therapy (for remaining disease outside the bladder).
    - Progression following concurrent chemoradiotherapy may be treated as metastatic disease with systemic therapy.

### B.3. Treatment of Stage IVA Tumors

- For patients with stage IVA disease, treatment options differ depending on the presence of distant metastasis (M0 vs. M1a).
- Primary treatment recommendations for **patients with M0 disease** include **systemic therapy** or **concurrent chemoradiotherapy** followed by evaluation with cystoscopy, EUA, TURBT, and imaging of the abdomen and pelvis[8-15].
    - If no evidence of tumor is present after primary treatment, the patient may be treated with consolidation systemic therapy or adjuvant treatment with chemoradiotherapy may be initiated if the patient did not receive prior radiotherapy.
    - In general, stage IVA disease is considered unresectable. However, in patients with disease that responds to treatment, cystectomy may be an option if the tumor becomes technically resectable.
    - If residual disease is noted on evaluation after primary therapy, systemic therapy or cystectomy is recommended. Systemic therapy may include targeted therapy, chemoradiotherapy (if no prior radiotherapy), or chemotherapy.
- **Patients with M1a disease** should receive **systemic therapy** as primary treatment[8-15].

- Those select patients with metastatic disease treated with curative intent should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic imaging.
- If a complete response is noted following primary treatment of metastatic disease, consolidative local therapy with concurrent chemoradiotherapy or cystectomy may be considered in select cases.
- If the disease remains stable or progresses following primary therapy, these patients should follow treatment for metastatic disease.

### B.4. Follow-up

- Follow-up after a cystectomy should include urine cytology, liver function tests, creatinine, and electrolytes. Imaging of the chest, upper tract abdomen, and pelvis should be conducted at intervals based on the risk of recurrence. Patients should be monitored annually for vitamin B12 deficiency if a continent urinary diversion was created.
- Additionally, continued monitoring of the urothelium with cystoscopy and urinary cytologies with or without mapping biopsy is a routine part of the management of all cases in which the bladder is preserved[8-15].

### B.5. Recurrent or Persistent Disease

- Metastatic or local recurrence of muscle invasive disease may be managed with **cystectomy**, **systemic therapy**, or **palliative TURBT** and **best supportive care**[8-15].
- Subsequent-line therapy for metastatic disease or local recurrence includes systemic therapy, chemoradiotherapy (if no previous RT), or RT.
- **Chemotherapy** is sometimes combined with **palliative radiation** to treat metastases or pelvic recurrence after cystectomy. However, concurrent chemotherapy is inappropriate if high-dose radiation (>3 Gy fractions) is used[8-15].
    - The radiosensitizing chemotherapy regimens remain controversial in this setting. Possible options include cisplatin (Recommendation Level A, Evidence Level II); docetaxel or paclitaxel (Recommendation Level B, Evidence Level II); 5-FU with or without mitomycin C (Recommendation Level B, Evidence Level II); capecitabine (Recommendation Level C, Evidence Level III); and low-dose gemcitabine (Recommendation Level B, Evidence Level II) [8-15].
    - Radiotherapy alone can also be considered as a subsequent-line therapy for patients with metastatic disease or local recurrence following

cystectomy, especially in selected cases with regional-only recurrence or with clinical symptoms.

### C. Metastatic (Stage IVB) Bladder Cancer

- For patients with advanced unresectable and metastatic urothelial carcinoma, treatment options include **platinum-based chemotherapy**, **checkpoint inhibitor immunotherapy**, and **targeted therapies**[8-15].
- Patients with metastatic urothelial carcinoma who are **eligible for a cisplatin-containing regimen** should receive either **GC (gemcitabine/cisplatin)** or **ddMVAC (dose dense methotrexate/vinblastine/doxorubicin, cisplatin)** with growth factor support as first-line therapy for 4-6 cycles (Recommendation Level A, Evidence Level I) [8-15].
  - A patient who is ineligible for cisplatin, but eligible for **carboplatin**, should preferentially receive gemcitabine in combination with carboplatin first line (Recommendation Level A, Evidence Level I) [8-15].
  - If there is no progression on a first-line platinum-containing chemotherapy, **avelumab maintenance therapy is preferred** (Recommendation Level A, Evidence Level I) [8-15].
- For patients with metastatic urothelial carcinoma who are **ineligible for a cisplatin-containing chemotherapy**:
  - **Pembrolizumab** is a **preferred first-line option for patients who are not eligible for any platinum-containing chemotherapy** or **who have disease progression within 12 months** of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Recommendation Level A, Evidence Level II)[8-15].
  - **Pembrolizumab in combination with enfortumab vedotin** can also be used in previously untreated cisplatin-ineligible patients[8], based on positive results from the KEYNOTE-869 clinical trial.
  - **Atezolizumab** is another, **less-preferred first-line treatment option** for patients who are not eligible for cisplatin-containing chemotherapy and **whose tumors express PD-L1** (Recommendation Level B, Evidence Level II) or in patients who are not eligible for any platinum-containing chemotherapy **regardless of PD-L1 expression** (Recommendation Level C, Evidence Level III) [8-15].
  - Several chemotherapy regimens, including **gemcitabine**, alone or in combination with **paclitaxel**, or the combination of **ifosfamide, doxorubicin, and gemcitabine** may also be appropriate first-line treatment options for some patients (Recommendation Level A, Evidence Level II) [8-15].

- The available **second-line options depend on what was given as the first line**.
  - If a platinum-based chemotherapy was given first-line, **pembrolizumab** (Recommendation Level A, Evidence Level I), **nivolumab**, **avelumab**, **erdafitinib** (if eligible based on FGFR3 or FGFR2 genetic alterations), or **enfortumab vedotin** are preferred second-line treatment options (Recommendation Level A, Evidence Level II). These recommendations also pertain to patients who receive a non-platinum chemotherapy first-line[8-15].
  - If progression-free survival was more than **1 year** following treatment with a platinum-containing regimen, **retreatment with platinum** may be considered[8-15].
  - If a **checkpoint inhibitor was given first-line**, preferred second-line options include **enfortumab vedotin** or **gemcitabine/carboplatin** for those who are cisplatin-ineligible or **GC** or **ddMVAC** with growth factor support for those who are cisplatin-eligible (Recommendation Level A, Evidence Level II). Other regimens may also be appropriate in the second-line setting[8-15].
- For **subsequent therapy**, after treatment with a platinum-based therapy and a checkpoint inhibitor, if the patient is eligible for these, the preferred regimens are **enfortumab vedotin** (Recommendation Level A, Evidence Level I) or **erdafitinib**, if eligible based on FGFR3/FGFR2 testing results. A number of chemotherapy regimens and the antibody-drug conjugate, **sacituzumab govitecan**, are also recommended options in this setting (Recommendation Level A, Evidence Level II)[8-15]. **Vinflunine** is approved in Europe for second-line treatment of urothelial cancer based on one phase III trial that showed a **survival benefit** over best supportive care. However, vinflunine is not approved in the United States[12].

A **summary of drugs used** for the management of NMIBC, early stage MIBC, and locally advanced or metastatic bladder cancer is illustrated in tables 1, 2, and 3[8-15].

**Table 2.** Drugs Used in the Management of Non-Muscle Invasive Bladder Cancer

| Management of Non-Muscle Invasive Bladder Cancer | | | | |
|---|---|---|---|---|
| **Medication** | **Indication** | **Line of Therapy** | **Recommendation** | **Evidence** |
| **Gemcitabine (intravesical)** | Intravesical therapy post-TURBT (preferred) | **1st** | A | I |

| | | | | |
|---|---|---|---|---|
| | First-line treatment of NMIBC (induction) | | | |
| **Mitomycin C (intravesical)** | Intravesical therapy post-TURBT<br>First-line treatment of NMIBC (induction) | **1st** | A | I |
| **Bacillus-Calmette-Guerin (BCG) (intravesical)** | First-line treatment of high-risk NMIBC (preferred)<br>Second-line treatment of NMIBC in patients with positive cytology | **1st**<br>**2nd** | A<br>A | I<br>II |
| **Pembrolizumab** | Treatment of BCG-unresponsive, high-risk, NMIBC in patients who are ineligible for or have elected not to undergo cystectomy. | **2nd** | A | II |
| **Nadofaragene firadenovec** | Treatment of high-risk BCG-unresponsive NMIBC with carcinoma in situ (CIS) with or without papillary tumors in adults. | **2nd** | A | II |

**Table 3.** Drugs Used in the Management of Early-Stage Muscle-Invasive Bladder Cancer.

| **Management of Early-Stage Muscle-Invasive Bladder Cancer** | | | | |
|---|---|---|---|---|
| **Medication** | **Indication** | **Line of Therapy** | **Recommendation** | **Evidence** |
| **Methotrexate** | First-line treatment of early stage MIBC (preferred) | **1st** | A | II |
| **Vinblastine** | First-line treatment of early stage MIBC (preferred) | **1st** | A | II |
| **Doxorubicin** | First-line treatment of early stage MIBC (preferred) | **1st** | A | II |

| | | | | |
|---|---|---|---|---|
| **Cisplatin** | First-line treatment of early stage MIBC (preferred) | **1st** | A | II |
| **Gemcitabine** | First-line treatment of early stage MIBC | **1st** | A | II |
| **Nivolumab** | Adjuvant treatment of early-stage MIBC following resection | **1st** | A | II |
| **5-Fluorouracil** | First-line treatment of early stage MIBC in combination with RT | **1st** | A | II |
| **Mitomycin C** | First-line treatment of early stage MIBC in combination with RT | **1st** | A | II |

**Table 4.** Drugs Used in the Management of Locally Advanced/Metastatic Bladder Cancer.

| **Management of Locally Advanced/Metastatic Bladder Cancer** | | | | |
|---|---|---|---|---|
| **Medication** | **Indication** | **Line of Therapy** | **Recommendation** | **Evidence** |
| **Methotrexate** | First-line treatment of locally advanced/metastatic MIBC (preferred)<br>Second-line treatment of locally advanced/ metastatic MIBC | **1st**<br>**2nd** | A<br>A | I<br>II |
| **Vinblastine** | First-line treatment of locally advanced/metastatic MIBC (preferred)<br>Second-line treatment of locally advanced/ metastatic MIBC | **1st**<br>**2nd** | A<br>A | I<br>II |

| | | | | |
|---|---|---|---|---|
| **Doxorubicin** | First-line treatment of locally advanced/metastatic MIBC (preferred)<br>Second-line treatment of locally advanced/ metastatic MIBC | **1st**<br>**2nd** | A<br>A | I<br>II |
| **Cisplatin** | First-line treatment of locally advanced/metastatic MIBC (preferred)<br>Second-line treatment of locally advanced/ metastatic MIBC | **1st**<br>**2nd** | A<br>A | I<br>II |
| **Gemcitabine** | First-line treatment of locally advanced/metastatic MIBC (preferred)<br>Second-line treatment of locally advanced/ metastatic MIBC | **1st**<br>**2nd** | A<br>A | I<br>II |
| **Avelumab** | First-line maintenance treatment of locally advanced/metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy (preferred)<br>Second-line treatment of locally advanced/ metastatic MIBC post platinum-containing therapy (preferred) | **1st**<br>**2nd** | A<br>A | I<br>II |
| **Carboplatin** | First-line treatment of locally advanced/ metastatic MIBC in patients not eligible for | **1st** | A | I |

| | | | | |
|---|---|---|---|---|
| | cisplatin-containing therapy (preferred) | | | |
| **Pembrolizumab** | First-line treatment of locally advanced/ metastatic MIBC in patients not eligible for platinum-containing therapy (preferred)<br>Second-line treatment of locally advanced/ metastatic MIBC post platinum-containing therapy (preferred) | **1st**<br>**2nd** | A<br>A | II<br>I |
| **Paclitaxel** | First-line treatment of locally advanced/ metastatic MIBC in patients not eligible for platinum-containing therapy<br>Second and later-line treatment of locally advanced/ metastatic MIBC post platinum-containing therapy | **1st**<br>**2nd**<br>**3rd** | A<br>A<br>A | II<br>II<br>II |
| **Atezolizumab** | First-line treatment of locally advanced/ metastatic MIBC in patients not eligible for platinum-containing therapy whose tumors express PD-L1<br>(or regardless of PD-1 status; lack of evidence) | **1st** | B<br>C | II<br>III |
| **Ifosfamide** | First-line treatment of locally advanced/ metastatic MIBC in patients not eligible for platinum-containing (useful in certain circumstances) | **1st** | A | II |

| | | | | |
|---|---|---|---|---|
| **Nivolumab** | Second-line treatment of locally advanced/ metastatic MIBC post platinum-containing therapy (preferred) | **2nd** | A | II |
| **Vinflunine** | Second-line treatment of locally advanced/ metastatic MIBC post platinum-containing therapy | **2nd** | B | II |
| **Enfortumab vedotin** | Second and subsequent-line treatment of locally advanced/ metastatic MIBC post platinum-containing therapy or checkpoint inhibitor therapy (preferred) | **2nd**<br>**3rd** | A<br>A | II<br>II |
| **Erdafitinib** | Second and subsequent-line treatment of locally advanced/ metastatic MIBC post platinum-containing therapy or checkpoint inhibitor therapy in patients with FGFR3 or FGFR2 genetic alterations (preferred) | **2nd**<br>**3rd** | A<br>A | II<br>II |
| **Docetaxel** | Second-line treatment of locally advanced/ metastatic MIBC post platinum-containing therapy | **2nd**<br>**3rd** | A<br>A | II<br>II |
| **Sacituzumab govitecan** | Third and later-line treatment of early stage MIBC | **3rd** | A | II |

All the medications in the standard of care therapy are available on the Saudi Market, except mitomycin C, enfortumab vedotin, erdafitinib, vinflunine, and nadofaragene firadenovec. Section 3 provides a full description of each treatment

protocol with a final statement on the place in therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA), reflecting specific drug class role in the bladder cancer therapeutic landscape.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in bladder cancer were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health, Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). A summary of these recommendations is shown in section 3.

The summary of the HTA recommendations for atezolizumab, avelumab, nivolumab, pembrolizumab, and enfortumab vedotin are shown in table 5 below[17-41].

**Table 5.** HTA Recommendations for Urothelial Carcinoma of the Bladder

| Medication | Agency | HTA Recommendation |
|---|---|---|
| **Atezolizumab** | NICE[17,18] | 10/2021: Atezolizumab is **recommended**, within its marketing authorization, as an option for **untreated locally advanced or metastatic urothelial cancer** in adults whose tumors express **PD-L1 at a level of 5% or more** and when **cisplatin-containing chemotherapy is unsuitable**.<br>- Atezolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life.<br>- The cost-effectiveness estimates are likely to be within what NICE considers an acceptable use of NHS resources. So, atezolizumab is recommended.<br>06/2018: Atezolizumab is **recommended** as an option for treating **locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy**, only if atezolizumab is stopped at **2 years** of uninterrupted treatment or earlier if the disease progresses |

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| | | - Atezolizumab **meets NICE's criteria to be considered a life-extending treatment** at the end of life.<br>- Although there are uncertainties in the economic model, the most plausible **cost effectiveness estimates for atezolizumab compared with taxanes are within the range NICE considers an acceptable use** of NHS resources. |
| | IQWIG[19,20] | 03/2019: **Added benefit not proven** of atezolizumab versus chemotherapy in adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable and whose tumors have a PD-L1 expression ≥ 5% (first-line indication).<br>12/2017: **Hint of considerable added benefit** of atezolizumab versus chemotherapy (vinflunine or platinum-based chemotherapy) in adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy (second-line indication) |
| **Avelumab** | HAS[21] | 03/2021: **Favorable opinion for reimbursement** as monotherapy for the **first-line maintenance treatment** of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free **following platinum-based chemotherapy**.<br>- Therapeutic improvement compared to supportive care.<br>- Moderate clinical added value (CAV III) compared to supportive care |
| | NICE[22] | 11/2022: **Avelumab is recommended** as an option for **maintenance treatment of locally advanced or metastatic urothelial cancer that has not progressed after platinum-based chemotherapy** in adults, only if it is stopped at **5 years** of uninterrupted treatment or earlier if the disease progresses. |

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| | | - Avelumab meets NICE's criteria to be considered a life-extending treatment at the end of life.<br>- The ICER with a 5-year stopping rule and 1 year treatment effect cap is within the range usually considered cost effective for end of life treatments. |
| | CADTH[23] | 03/2021: The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) **conditionally recommends reimbursement of avelumab** plus best supportive care (BSC) for the first-line **maintenance treatment** of patients with histologically confirmed, **unresectable, locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based** induction chemotherapy if: · cost-effectiveness is improved to an acceptable level · feasibility of adoption (budget impact) is addressed.<br>- **There is a net clinical benefit of avelumab plus BSC compared to BSC only** based on statistically significant and clinically meaningful improvements in overall survival (OS), progression-free survival (PFS), a manageable toxicity profile, and no apparent detriment in quality of life (QoL).<br>- pERC concluded that avelumab in combination with BSC **is not considered cost-effective** at the submitted price versus BSC alone.<br>- The incremental cost-effectiveness ratio (ICER) for avelumab with BSC versus BSC alone was $278,373 per quality-adjusted life year (QALY). At a willingness-to-pay threshold of $50,000 per QALY, **a price reduction of at least 83% is required for avelumab with BSC to be cost-effective**. |
| | IQWIG[24] | 05/2021: There is an **indication of minor added benefit** of avelumab in comparison with best supportive care (BSC) for adults with locally |

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| | | advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy. |
| | PBAC[25] | 03/2022: **Recommended** for the maintenance treatment of locally advanced (Stage III) or metastatic (Stage IV) urothelial carcinoma in patients whose disease has not progressed following first-line platinum-based chemotherapy |
| **Nivolumab** | HAS[26] | 10/2022: **Favorable opinion** in the **adjuvant treatment of adult patients with muscle-invasive urothelial carcinoma at high risk of recurrence** after complete removal, whose tumor cells express **PD-L1 at a threshold of ≥ 1%**: who received neoadjuvant chemotherapy; or who did not receive neoadjuvant chemotherapy and were ineligible for and/or refused cisplatin-based adjuvant chemotherapy.<br>- Substantial clinical benefit in this restricted indication only<br>- Minor clinical added value (CAV IV) |
| | NICE[27,28] | 08/2022: **Nivolumab is recommended** as an option for the **adjuvant treatment of muscle-invasive urothelial cancer that is at high risk of recurrence** after radical resection in adults whose tumors **express PD-L1 at a level of 1% or more when platinum-based chemotherapy is not suitable**.<br>- **Nivolumab is cost effective only when adjuvant platinum-based chemotherapy is unsuitable**.<br>07/2018: **Nivolumab is not recommended**, within its marketing authorization, for treating **locally advanced unresectable or metastatic urothelial carcinoma in adults who have had platinum-containing therapy**.<br>- The most plausible ICERs were somewhere between £58,791 per QALY gained (compared with paclitaxel) and £78,869 per QALY gained (compared with docetaxel), **above what NICE** |

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|---|---|---|
| | | **normally considers to be acceptable for end-of-life treatments**. |
| | CADTH[29] | 08/2022: pERC recommends that nivolumab be **reimbursed** as a **monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma** who are at **high risk of recurrence** after undergoing radical resection of UC only if the conditions below are met:<br>• Pathologic evidence of UC at high risk of recurrence based on pathologic staging of radical surgery tissue<br>• Evidence of no recurrence confirmed before initiating therapy<br>• Muscle-invasive UC at disease diagnosis<br>- Evidence from the CheckMate-274 trial demonstrated that adjuvant treatment with nivolumab resulted in a **statistically and clinically significant improvement in disease free survival** in patients with characteristics listed in this condition.<br>- In patients who had received neoadjuvant chemotherapy or were not able to receive adjuvant chemotherapy, the **ICER for nivolumab was $112,386 per QALY when compared with observation**. A **price reduction of at least 56%** would be required for nivolumab to be able to achieve an ICER of $50,000 per QALY compared to observation. |
| | IQWIG[30] | 07/2022: **Added benefit not proven** of nivolumab **in comparison with platinum-containing chemotherapy** in adult patients with muscle-invasive urothelial carcinoma with tumor cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are eligible for cisplatin-containing therapy for adjuvant treatment.<br>**Hint of minor benefit versus watchful waiting** in patients who are not eligible for cisplatin-containing therapy. |

| | | |
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| | PBAC[31] | 03/2022: **Not recommended** for the **adjuvant treatment** of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection |
| **Pembrolizumab** | HAS[32] | 02/2018: **High clinical benefit** for the monotherapy treatment of adults with **locally advanced or metastatic urothelial cancer having received prior platinum salt-based chemotherapy** urothelial cancer and **minor clinical added value** compared to chemotherapy in terms of overall survival.<br>- **Preferred therapeutic option over chemotherapy for second- and third-line treatments for these patients**.<br>- However, pembrolizumab increases the risk of death in the first two months of treatment compared to chemotherapy. |
| | NICE[33] | 04/2021: **Pembrolizumab is not recommended**, within its marketing authorization, for treating **locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy**.<br>- Pembrolizumab **meets NICE's criteria to be considered a life-extending treatment at the end of life**.<br>- However, the most plausible ICER for pembrolizumab compared with docetaxel and paclitaxel is likely to be over £50,000 per QALY gained **which is above the range that NICE normally considers a cost-effective use of NHS resources** for a life-extending treatment at the end of life. |
| | CADTH[34,35] | 10/2019: pERC **does not recommend the reimbursement** of pembrolizumab for **the first line treatment** of adult patients with **locally advanced or metastatic urothelial carcinoma** who are not eligible for cisplatin-containing chemotherapy and whose tumors express programmed death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 10), or in patients who are |

| | | |
|---|---|---|
| | | not eligible for any platinum-containing chemotherapy regardless of PD-L1 status (first-line indication).<br>- While pERC acknowledged that there is an unmet need for effective treatments in this setting, the Committee concluded that **there was considerable uncertainty in the magnitude of clinical benefit of pembrolizumab** compared with appropriate comparators with regard to outcomes important to decision-making such as OS, PFS, and quality of life (QoL), given the limitations in the evidence from the available phase II clinical trial.<br>- pERC **could not draw a conclusion on the cost-effectiveness of pembrolizumab** compared with gemcitabine plus carboplatin or single-drug chemotherapy due to the uncertainty surrounding the incremental survival benefits used in the economic model.<br>03/2018: pERC **recommends the reimbursement** of pembrolizumab for **the treatment** of patients with **locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy**, **conditional of cost-effectiveness being improved** to an acceptable level (second-line indication).<br>- There is a **net clinical benefit with pembrolizumab** compared with chemotherapy, based on a clinical meaningful improvement in OS, an acceptable toxicity profile, and high unmet need for effective treatments, while maintaining QoL.<br>- However, pERC noted that **at the submitted price, pembrolizumab could not be considered cost-effective compared with chemotherapy**. |

| | | |
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| | IQWIG[36,37] | 06/2021: There is an **indication of considerable added benefit** of pembrolizumab in comparison with chemotherapy in locally advanced or metastatic urothelial carcinoma in **adults who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a CPS ≥ 10** (first-line treatment).<br>01/2018: Patients with locally advanced or metastatic urothelial carcinoma **after pretreatment with a platinum-based chemotherapy** (second-line setting): **indication of considerable added benefit**. |
| | PBAC[38] | 11/2022: **Not recommended** for locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer |
| **Enfortumab Vedotin** | CADTH[39] | 01/2022: The CADTH pERC recommends that enfortumab vedotin be **reimbursed** for the treatment of adult patients with **unresectable, locally advanced or metastatic UC** who have **previously received a platinum-containing chemotherapy and a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor therapy**<br>- Evidence from Study EV-301 demonstrated that enfortumab vedotin resulted in significant improvements in OS, PFS, and ORR in patients with locally advanced or metastatic UC who had previously been treated with a platinum-containing chemotherapy in the neoadjuvant or adjuvant, locally advanced or metastatic setting, as well as a PD-1 or PD-L1 inhibitor in the locally advanced or metastatic setting.<br>- The **ICER for enfortumab vedotin is $506,439 when compared with taxanes**. A **price reduction of 93%** would be required for enfortumab vedotin to be able to achieve an ICER of $50,000 per QALY compared to a taxane. |

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| | IQWIG[40] | 08/2022: There is a **hint of minor added benefit** of enfortumab vedotin in comparison with vinflunine or cisplatin/gemcitabine chemotherapy for adults with locally advanced or metastatic urothelial carcinoma **who have received prior platinum-containing chemotherapy and a PD1 or PD-L1 inhibitor and for whom chemotherapy is suitable**.<br>**Added benefit not proven** in comparison with BSC for adults with locally advanced or metastatic urothelial carcinoma **who have received prior platinum-containing chemotherapy and a PD1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable**. |
| | PBAC[41] | 03/2023: **Recommended** for the treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer who have progressed on or after a platinum-containing chemotherapy regimen and either PD-1 inhibitor or a PD-L1 inhibitor. |

# Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

## 1.1 KSA Guidelines

### 1.1.1 Saudi Oncology Society and Saudi Urology Association Combined Clinical Management Guidelines for Urothelial cell Carcinoma of the Urinary Bladder (2017)

The Saudi oncology society and Saudi urology association published in 2017 an updated combined clinical management guideline for urothelial urinary bladder cancer[42]. The key recommendations of the guidelines are outlined in the below sections:

#### 1.1.1.1 Staging

The Tumor Node Metastasis (TNM) staging for bladder cancer system is used[42].

#### 1.1.1.2 Grading

The World Health Organization grading of urinary tumors 2016 is used with the following categories[42]:

- Non-invasive urothelial lesions:
  - Urothelial carcinoma *in situ*
  - Papillary urothelial carcinoma, low grade
  - Papillary urothelial carcinoma, high grade
  - Papillary urothelial neoplasm of low malignant potential.
- Urothelial papilloma
- Inverted urothelial papilloma
- Urothelial proliferation of uncertain malignant potential (hyperplasia)
- Urothelial dysplasia
- Invasive urothelial tumor

#### 1.1.1.3 Pathology reporting

Surgical pathology reporting must include the following[42]:

- The histological tumor type
- The presence or absence of lamina propria and muscularis propria
- The depth of invasion (i.e., pathological T stage)

- The presence or absence of carcinoma in situ (CIS)
- The grade of tumor
- Any urothelial carcinoma variant

#### 1.1.1.4 Initial evaluation

- History and physical examination, complete blood count, renal function, urine cytology, and bladder ultrasonography[42].
- Initial diagnostic cystoscopy should be done with transurethral bladder tumor resection (TURBT) to achieve complete resection if possible[42].
- Imaging of the upper tract should be done by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) urogram[42].
- If the cystoscopy findings confirm the invasive disease, CT or MRI of abdomen and pelvis, as well as chest imaging are recommended[42].

#### 1.1.1.5 Management of NMIBC

- If the findings of the diagnostic cystoscopy are suggestive of a noninvasive bladder tumor[42]:
  - Conduct TURBT to achieve complete resection, if possible
  - Repeat TURBT within 2–4 weeks, indicated if the resection was incomplete, the disease is high-grade Ta or T1, or if no muscle examination was performed.
  - Administer a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin/doxorubicin) within 24 h of TURBT, unless perforation is suspected.
  - Provide further treatment according to risk stratification.
- Risk stratification for non-muscle invasive urothelial bladder carcinoma[42]:
  - Risk depends on the following factors: T stage, the presence of CIS, grade, recurrence rate, number of tumors, and tumor size
  - Low - risk, non-muscle, invasive bladder cancer (NMIBC) (solitary small volume, low-grade Ta)
  - Intermediate risk NMIBC (multifocal and/or large volume low-grade Ta, recurrence at 3 months)
  - High-risk NMIBC (high-grade Ta, all T1, CIS)
- Management of low-risk NMIBC– Surveillance cystoscopy (3–6 months) intervals[42]
- Management of intermediate risk NMIBC[42]:

- Intravesical bacillus Calmette–Guerin (BCG) or mitomycin induction (weekly for 6 weeks)
- Surveillance cystoscopy and cytology
- Upper tract imaging every 2 years or as indicated.

- Management of high-risk non-muscle, invasive bladder cancer, including carcinoma *in situ*[42]:
  - Intravesical BCG or mitomycin induction (weekly for 6 weeks) and maintenance therapy (3 weekly injections) at 3, 6, 12, 18, 24, 30, and 36 months from induction
  - Close surveillance cystoscopy, cytology, and upper tract imaging iii. Consider early cystectomy in selected patients.
- Recurrence of non-muscle invasive disease[42]:
  - TURBT
  - Adjuvant intravesical therapy if not given before or as a second induction
  - If two inductions of adjuvant intravesical therapy were given before, then consider changing the intravesical therapy
  - Consider early cystectomy in recurrent CIS, T1, and high-grade disease with prior treatment with no >2 inductions of intravesical therapy.
- Positive urine cytology without gross evidence of disease[42]:
  - Multiple biopsies of the bladder and prostatic urethra
  - Selective cytology of the upper tract
  - Upper tract imaging (CT, MRI, or retrograde pyelogram)
  - Ureteroscopy if suspicion of upper tract tumor
- Repeat TURBT within 2–4 weeks is indicated if incomplete resection, high-grade, pathological T1, or there is no muscle in specimen[42].

#### 1.1.1.6 Management of muscle invasive bladder cancer

- Staging should include complete blood count, renal function and serum electrolytes, liver function test including alkaline phosphatase, imaging of the chest, abdomen, and pelvis (CT or MRI), bone scan if elevated alkaline phosphatase or symptoms of bone pain[42].
- Clinical T2–T4a disease with negative lymph nodes[42]
  - Neoadjuvant cisplatin-based combination chemotherapy

        - Considered in clinical T2
        - Strongly recommended in clinical T3.
    - Radical cystectomy with extended lymphadenectomy (open, laparoscopic, or Robotic) is considered the standard treatment
    - Bilateral pelvic lymphadenectomy should be performed and include at a minimum common, internal and external iliac, and obturator nodes
    - Bladder preservation with tri-modality combination of maximum TURBT followed concurrent chemoradiation with early radical cystectomy in failure is an alternative to upfront radical cystectomy in selected patients with solitary disease, no CIS, no hydronephrosis, normal renal function, and adequate bladder capacity
    - In patient undergoing bladder preservation, early evaluation is recommended after 45 Gy, if there is residual/recurrent tumor than consider cystectomy and if there is the complete response then complete radiotherapy to 60–65 Gy total dose
    - Patients who are not candidate for radical treatment, consider TURBT and/or palliative radiotherapy
    - After surgery with positive lymph nodes or pathological T3 or T4 disease, consider adjuvant cisplatin-based combination chemotherapy if no neoadjuvant was given.
- Clinical T4b or positive locoregional lymph node disease[42]
    - Cisplatin-based combination chemotherapy or chemoradiation
    - Reevaluate the response during the treatment with imaging and/or TURBT
    - If chemoradiation was used:
        - Observation for patients who achieved complete response
        - If partial response consider cystectomy.
    - If cisplatin-based combination chemotherapy was used[42]:
        - In responding patients, consider cystectomy or chemoradiation
        - In non-responding patients, consider chemoradiation.

#### 1.1.1.6 Metastatic Disease

- Chemotherapy is the mainstay of treatment.
- Patients with normal renal function and fit for chemotherapy (PS 0–2) are treated with combination cisplatin and gemcitabine for a maximum of 6 cycles[42].
- Patients with decreased renal function and/or unfit (PS 3) are treated with combination of carboplatin and gemcitabine or single-agent gemcitabine, carboplatin, or atezolizumab[42].
- There is no standard, second-line therapy; patients who relapse or progress on the first-line may be given atezolizumab, vinflunine, or taxanes as second-line chemotherapy[42].
- Patients who present with local recurrence may benefit from palliative radiation therapy[42].

## 1.2 North American Guidelines

### 1.2.1 National Comprehensive Cancer Network (NCCN) Bladder Cancer Clinical Practice Guidelines (Version 3.2023)

The National Comprehensive Cancer Network (NCCN) published its updated recommendations for the management of Bladder Cancer in May 2023, including recommendations for the diagnosis, evaluation, treatment, and follow-up[8].

#### a) Clinical Presentation and Workup

The most common presenting symptom in patients with bladder cancer is microscopic or gross hematuria, although urinary frequency due to irritation or a reduced bladder capacity can also develop. Less common symptoms are a urinary tract infection, upper tract obstruction or pain notably in patients with more advanced lesions[8].

Patients presenting with symptoms should be evaluated with office **cystoscopy** to determine if a lesion is present. Enhanced cystoscopy may be used if available. If a lesion is documented, the patient should be scheduled for a **transurethral resection of the bladder tumor (TURBT)** to confirm the diagnosis and determine the extent of disease within the bladder. **Urine cytology** may also be obtained around the time of cystoscopy[8].

Table 6 summarizes the workup recommendations for patients with suspicion of bladder cancer as per NCCN guidelines[8].

**Table 6.** Workup Recommendations for Patients with Suspected Bladder Cancer (NCCN Guidelines)

| **Initial Evaluation** |
|---|
| ▪ History and physical (H&P)<br>▪ Consider germline testing and genetic counselor referral especially if younger age at presentation (<45 years) or family history of colon/endometrial cancer<br>▪ Office cystoscopy, enhanced if available<br>▪ Consider cytology<br>▪ Abdominal/pelvic imaging (CT scan or MRI) that includes imaging of upper urinary tract collecting system before transurethral resection of bladder tumor (TURBT)<br>▪ Screen and actively promote smoking cessation |
| **Primary Evaluation/Surgical Treatment** |
| ▪ Examination under anesthesia (EUA) (bimanual)<br>▪ TURBT<br>▪ Single-dose intravesical chemotherapy within 24 hours of TURBT<br>o Gemcitabine (preferred) (category 1) or<br>o Mitomycin (category 1)<br>▪ Imaging of upper tract collecting system, if not previously done |

### b) Pathology and Staging

- The most commonly used staging system is the tumor, node, metastasis (TNM) staging system by the AJCC.
- The NCCN Guidelines divide treatment recommendations for urothelial carcinoma of the bladder according to non-muscle invasive disease (Ta, T1, and Tis) and muscle invasive disease (≥T2 disease) (Table 7). Patient bladder function, comorbidities, and life expectancy are also important considerations[8].

**Table 7.** Clinical Staging of Bladder Cancer (NCCN guidelines)

| **Presumptive Clinical Stage** |
|---|
| ▪ Non-muscle invasive bladder cancer (NMIBC) (CTa, CT1, Tis)<br>▪ Muscle invasive bladder cancer (MIBC) (Stage II, IIIa, IIIb, IVa, Metastatic)<br>o Complete blood count (CBC) |

- Chemistry profile, including alkaline phosphatase
- Chest imaging
- Bone imaging if clinical suspicion or symptoms of bone metastases

### c) Non-Muscle Invasive Bladder Cancer (NMIBC)

The NCCN Panel recommends management of NMIBC based on American Urological Association/ Society of Urologic Oncology (AUA/SUO) risk stratification (c.f Table 1) with the caveat that an individual patient within each of the risk strata may have more or less concerning feature that can influence care decisions[8].

- After the initial TURBT shows NMIBC, a repeat TURBT is recommended for visually incomplete or high-volume tumors and for high-grade NMIBC, which is found to be T1 on the initial TURBT.
- Repeat TURBT may also be considered for select patients with high-grade Ta on initial TURBT, particularly if the tumor is large and/or there was no muscle present in the initial TURBT specimen.
- If muscle invasive disease is found during repeat TURBT, then additional staging for muscle invasive disease and appropriate treatment depending on stage should be followed.
- Treatment for non-muscle invasive disease often includes **intravesical therapy** or, for those at particularly high risk, **cystectomy**[8].

#### c.1 Treatment of Low-Risk NMIBC

- For these tumors, risk of recurrence or progression is low following TURBT and no further treatment is necessary, although a single instillation of intravesical chemotherapy immediately post-TURBT can be helpful in reducing the risk of recurrence[8].
- An appropriate surveillance schedule is recommended for early detection of disease recurrence.

#### c.2 Treatment of Intermediate-Risk NMIBC

- Although a complete TURBT alone can eradicate intermediate-risk NMIBC, there is a relatively high risk for recurrence.
- A single instillation of chemotherapy is recommended to be administered within 24 hours of surgery (ideally within 6 hours) [8].
- After TURBT and immediate intravesical chemotherapy, the panel recommends a 6-week induction course of intravesical therapy[8].

- Gemcitabine (preferred) (category 1) and mitomycin (category 1) are the most commonly used agents in the United States for intravesical chemotherapy[8].
- **Gemcitabine** is preferred over **mitomycin** based on toxicity profiles and lower cost. In addition, in systematic reviews and meta-analyses, gemcitabine has shown superior efficacy compared to mitomycin, in that it demonstrated reduced rates of recurrence and progression[8].
- BCG is also an option for adjuvant intravesical chemotherapy. The availability of BCG should be considered in decision-making as it may be prioritized for treatment of higher risk disease[8].

### c.3 Treatment of High-Risk NMIBC

- High-risk NMIBC has a relatively high risk for recurrence and progression towards more invasiveness.
- Treatment options for high-risk NMIBC depend on whether the tumor has previously been shown to be unresponsive or intolerant to BCG.
- For BCG-naïve NMIBC, the options are cystectomy or BCG. When very high-risk features are present, cystectomy is preferred because of the high risk for progression to a more advanced stage, while BCG is preferred when these are not present. BCG is also a category 1 recommendation for BCG-naïve, high-risk NMIBC without very-high-risk features[8].
- Toxicity and shortage of BCG[8]:
    - There are concerns regarding potentially severe local and systemic side effects and the inconsistent availability of BCG. BCG induces a systemic, nonspecific, immunostimulatory response leading to secretion of proinflammatory cytokines. This causes patients to experience flu-like symptoms that may last 48 to 72 hours.
    - Installation of BCG into the bladder also mimics a urinary tract infection and may produce intense local discomfort.
    - The side effects of treatment have translated to patient refusal of BCG therapy. Dysuria has been reported in 60% of patients in clinical trials.
    - However, the side effects are treatable in almost all cases and no increase in toxicity has been reported with cumulative doses. Symptom management with single-dose, short-term quinolones and/or anticholinergics have been reported to reduce adverse events.
- For some patients, BCG is not an option due to side effects or a tumor that is BCG-resistant. For these patients, cystectomy is preferred although other intravesical chemotherapy or pembrolizumab are other options[8].

### c.4 Surveillance

- For intermediate and high-risk NMIBC, follow-up is recommended with a urinary cytology and cystoscopy at 3- to 6-month intervals for the first 2 years, and at longer intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high-risk tumors[8].
- For patients with low-risk NMIBC, if the initial follow-up surveillance cystoscopy is negative within 4 months of TURBT, the next cystoscopy is recommended 6 to 9 months later and then yearly for up to 5 years[8].
- Follow-up cystoscopy after 5 years should only be performed based on clinical indication. Beyond baseline imaging, upper tract imaging is not indicated without symptoms for patients with low-risk NMIBC[8].

### c.5 Post-treatment of Recurrent or Persistent Disease

- *Treatment of Patients with Positive Cystoscopy:* Patients under surveillance after initial TURBT, who show a documented recurrence by positive cystoscopy, should undergo another TURBT to reclassify the AUA/SUO risk group. Patients should be treated and followed as indicated based on the risk of their recurrent disease[8].
- *Treatment of Patients with Positive Cytology:* In patients without a documented recurrence but with initial positive cytology and negative cystoscopy and imaging, it may be appropriate to repeat the cytology test within 3 months[8].
    - If subsequent cytology tests are positive, selected mapping biopsies including transurethral resection of the prostate (TURP) may be considered. In addition, the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract. If available, enhanced cystoscopy should be considered.
    - If the bladder, prostate, and upper tract continue to show negative results on further evaluation, additional follow-up is indicated after 3 months, then at longer intervals. If BCG was given previously, maintenance BCG may be considered.
- If the selected mapping **biopsy of the bladder is positive**, then the recommendation is to administer **intravesical BCG** followed by **maintenance BCG (preferred)** if a complete response is seen[8].
    - For tumors that are unresponsive to BCG or for persistent or recurrent disease post-BCG treatment, the subsequent management options include **cystectomy**, changing the intravesical agent, or participation in a clinical trial.

- **Pembrolizumab** is also an option for patients with BCG-unresponsive, high-risk, NMIBC with Tis, with or without papillary tumors, who are ineligible for or have elected not to undergo cystectomy, although the data are currently not mature enough to determine if pembrolizumab can be considered curative in this setting[8].
- Non-cystectomy candidates with recurrent or persistent cTa or cT1 disease may also consider concurrent **chemoradiotherapy** as an option (category 2A for cT1, category 2B for cTa) [8].
- **Valrubicin** is approved for CIS that is refractory to BCG, although panelists disagree on its value[8].
- For patients with disease that does not respond or shows an incomplete response to treatment following a change in intravesical agent, subsequent management is cystectomy.

### d) Muscle Invasive Urothelial Bladder Cancer

#### d.1 Treatment of Stage II and IIIA Tumors

- Primary surgical treatment for stage II and IIIA disease is a **radical cystectomy and pelvic lymphadenectomy**. **Neoadjuvant chemotherapy** is recommended (category 1)[8].
  - Partial cystectomy along with **neoadjuvant cisplatin-based chemotherapy** can be considered for stage II (cT2, N0) disease with a single tumor in a suitable location and no presence of Tis. Partial cystectomy is not an option for patients with stage III disease.
  - If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered.
  - If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered (as per NCCN guidelines).
  - Adjuvant RT is another option for patients with tumors that are T3–4, or with positive nodes or margins, following surgery (category 2B) [8].
- **Bladder preservation with maximal TURBT followed by concurrent chemoradiotherapy** is another category 1 primary treatment option for these patients[8].
  - Based on clinical practice and strength of the data, the following radiosensitizing regimens are preferred for organ-preserving

chemoradiation: 5-FU plus mitomycin C or cisplatin alone. Cisplatin plus 5-FU, cisplatin plus paclitaxel, or low-dose gemcitabine may be considered as alternative regimens[8].

- After a complete TURBT, 60 to 66 Gy of external beam RT (EBRT) is administered. Two doses of concurrent radiosensitizing chemotherapy may be given at weeks 1 and 4 (although weekly schedules are possible as well). Alternatively, an induction dose of 40 to 45 Gy radiotherapy may be given following complete TURBT.

- In patients with extensive comorbid disease or poor performance status who are non-cystectomy candidates, treatment options include **concurrent chemoradiation** (preferred, category 1) or **radiotherapy** alone[8].
  - TURBT is another option for patients with stage II disease who are non-cystectomy candidates.
  - Based on high-level evidence showing superiority to radiotherapy alone, the NCCN Panel recommends chemoradiotherapy as the preferred option for these patients.
  - The overall tumor status should be reassessed 2 to 3 months after treatment. If no tumor is evident, the patient should be observed. If tumor is observed, systemic therapy, concurrent chemoradiotherapy or radiotherapy alone (if no prior radiotherapy), TURBT with or without intravesical therapy, or best supportive care may be given.

### d.2 Treatment of Stage IIIB Tumors

- Primary treatment for stage IIIB (cT1–T4a, N2–3) disease can include either down staging systemic therapy or concurrent chemoradiotherapy.
- Subsequent disease management depends on the response to primary treatment.
- Patients who received downstaging systemic therapy and had a complete disease response may then be subsequently treated with cystectomy or chemoradiotherapy or may be observed until disease relapse[8].
  - Patients who received downstaging systemic therapy and showed a partial response may be treated with cystectomy or chemoradiotherapy (for persistent disease confined to the bladder) or treated as metastatic disease with additional lines of systemic therapy (for distant disease).
  - Patients who had disease progression following primary downstaging systemic therapy may be treated as with metastatic disease, with additional lines of systemic therapy.

- Patients with complete disease response following concurrent chemoradiotherapy should be observed until disease relapse[8].
    - Disease with partial responses to concurrent chemoradiotherapy may be subsequently treated with surgical consolidation (for residual disease confined to the bladder), consideration of intravesical BCG (for Tis, Ta, or T1 residual disease), or treated as metastatic disease with systemic therapy (for remaining disease outside the bladder).
    - Progression following concurrent chemoradiotherapy may be treated as metastatic disease with systemic therapy.

The systemic therapy treatment recommendations for muscle invasive early-stage bladder cancer and radiosensitizing chemotherapy regimens according to NCCN guidelines are outlined in tables 8 and 9.

**Table 8.** Systemic Therapy Regimens for Muscle Invasive Early-Stage Bladder Cancer (NCCN Guidelines)

| **Neoadjuvant Chemotherapy** | |
|---|---|
| **Preferred Regimen** | **Other Recommended Regimens** |
| ▪ ddMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles | ▪ Gemcitabine and cisplatin for 4 cycles |
| **Adjuvant Chemotherapy** | |
| **No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)** | **Previous platinum-based neoadjuvant therapy (ypT2–ypT4a or ypN+)** |
| ▪ Preferred regimen<br>- ddMVAC with growth factor support for 3–6 cycles<br>▪ Other recommended regimens<br>- Gemcitabine and cisplatin for 4 cycles<br>- Nivolumab | ▪ Other recommended regimens<br>- Nivolumab |

*All recommendations are Category 2A unless specified otherwise.*

**Table 9.** Radiosensitizing Chemotherapy Regimens for Bladder Cancer (NCCN guidelines)

| **Radiosensitizing Chemotherapy Regimens** |
|---|

| Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|
| ▪ Cisplatin<br>▪ Low-dose Gemcitabine<br>▪ 5-Fluorouracil (5-FU) and mitomycin | ▪ Cisplatin and 5-FU<br>▪ Cisplatin and paclitaxel | ▪ Taxane (docetaxel or paclitaxel) (category 2B)<br>▪ 5-FU (category 2B)<br>▪ Capecitabine (category 3) |

*All recommendations are category 2A unless specified otherwise.*

### d.3 Treatment of Stage IVA Tumors

- For patients with stage IVA disease, treatment options differ depending on the presence of distant metastasis (M0 vs. M1a)[8].
    - Primary treatment recommendations for patients with M0 disease include systemic therapy or concurrent chemoradiotherapy followed by evaluation with cystoscopy, EUA, TURBT, and imaging of the abdomen and pelvis[8].
    - If no evidence of tumor is present after primary treatment, the patient may be treated with consolidation systemic therapy or adjuvant treatment with chemoradiotherapy may be initiated if the patient did not receive prior radiotherapy.
    - In general, stage IVA disease is considered unresectable. However, in patients with disease that responds to treatment, cystectomy may be an option if the tumor becomes technically resectable.
    - If residual disease is noted on evaluation after primary therapy, systemic therapy or cystectomy is recommended. Systemic therapy may include targeted therapy, chemoradiotherapy (if no prior radiotherapy), or chemotherapy.
- Patients with M1a disease should receive systemic therapy as primary treatment[8].
    - Those select patients with metastatic disease treated with curative intent should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic imaging.
    - If a complete response is noted following primary treatment of metastatic disease, consolidative local therapy with concurrent chemoradiotherapy or cystectomy may be considered in select cases.

- If the disease remains stable or progresses following primary therapy, these patients should follow treatment for metastatic disease.

### d.4 Follow-up

- Follow-up after a cystectomy should include urine cytology, liver function tests, creatinine, and electrolytes. Imaging of the chest, upper tract abdomen, and pelvis should be conducted at intervals based on the risk of recurrence. Patients should be monitored annually for vitamin B12 deficiency if a continent urinary diversion was created[8].
- Additionally, continued monitoring of the urothelium with cystoscopy and urinary cytologies with or without mapping biopsy is a routine part of the management of all cases in which the bladder is preserved[8].

### d.5 Recurrent or Persistent Disease

- Metastatic or local recurrence of muscle invasive disease may be managed with cystectomy, systemic therapy, or palliative TURBT and best supportive care[8].
- A positive cytology with no evidence of disease in the bladder should prompt retrograde selective washings of the upper tract and a biopsy of the prostatic urethra.
    - For patients with a preserved bladder, local recurrence or persistent disease should be evaluated as a new cancer. Recurrences are treated based on the extent of disease at relapse, with consideration of prior treatment.
    - As previously discussed, Tis, Ta, or T1 tumors are generally managed with intravesical therapy or cystectomy.
    - If no response is noted following intravesical treatment, a cystectomy is advised. Invasive disease is generally managed with radical cystectomy, and a second attempt at bladder preservation is not advisable.
    - Cystectomy may not be possible in a patient who has undergone a full course of EBRT and has bulky residual disease. For these patients, systemic therapy or palliative TURBT and best supportive care is advised.
- Subsequent-line therapy for metastatic disease or local recurrence includes systemic therapy, chemoradiotherapy (if no previous RT), or RT[8].
- Chemotherapy is sometimes combined with palliative radiation to treat metastases or pelvic recurrence after cystectomy. However, concurrent chemotherapy is inappropriate if high-dose radiation (>3 Gy fractions) is used[8].

- The radiosensitizing chemotherapy regimens remain controversial in this setting. Possible options include cisplatin (category 2A); docetaxel or paclitaxel (category 2B); 5-FU with or without mitomycin C (category 2B); capecitabine (category 3); and low-dose gemcitabine (category 2B) [8].
- Radiotherapy alone can also be considered as a subsequent-line therapy for patients with metastatic disease or local recurrence following cystectomy, especially in selected cases with regional-only recurrence or with clinical symptoms[8].

### e) Metastatic (Stage IVB) Urothelial Bladder Cancer

- Based on the available data, the NCCN Panel recommends that patients with metastatic urothelial carcinoma who are eligible for a cisplatin-containing regimen receive either **GC** (gemcitabine/cisplatin) or **ddMVAC** (dose dense methotrexate/vinblastine/doxorubicin, cisplatin) with growth factor support as first-line therapy. Both of these regimens are supported by category 1 data[8].
- A patient who is ineligible for cisplatin, but eligible for carboplatin, should preferentially receive gemcitabine in combination with carboplatin first-line[8].
- If there is no progression on a first-line platinum-containing chemotherapy, **avelumab maintenance therapy is preferred** (category 1)[8].
- For patients with metastatic urothelial carcinoma who are ineligible for a cisplatin-containing chemotherapy, **pembrolizumab** is also a preferred first-line option for patients who are not eligible for any platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy[8].
- **Atezolizumab** is another, non-preferred first-line treatment option for patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (category 2B) or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression (category 3)[8].
- Several chemotherapy regimens, including gemcitabine, alone or in combination with paclitaxel, or the combination of ifosfamide, doxorubicin, and gemcitabine may also be appropriate first-line treatment options for some patients[8].
- Clinical trial enrollment is recommended by the NCCN Panel for all patients when appropriate but is strongly recommended for second-line and subsequent therapies.
- The available *second-line options* depend on what was given as first-line.

- If a platinum-based chemotherapy was given first-line, pembrolizumab, nivolumab, avelumab, erdafitinib (if eligible on the basis of FGFR3 or FGFR2 genetic alterations), or enfortumab vedotin are preferred second-line treatment options[8]. **Pembrolizumab** is supported by category 1 level data in this setting. These recommendations also pertain to patients who receive a non-platinum chemotherapy first-line.
- If progression-free survival was more than 1 year following treatment with a platinum-containing regimen, retreatment with platinum may be considered[8].
- If a checkpoint inhibitor was given first-line, preferred second-line options include enfortumab vedotin or gemcitabine in combination with carboplatin for those who are cisplatin-ineligible or GC or ddMVAC with growth factor support for those who are cisplatin-eligible. Other regimens may also be appropriate in the second-line setting[8].
- For *subsequent therapy*, after treatment with a platinum-based therapy and a checkpoint inhibitor, if the patient is eligible for these, the preferred regimens are enfortumab vedotin or erdafitinib, if eligible based on FGFR3/FGFR2 testing results. **Enfortumab vedotin** is supported by category 1 level data in this setting. A number of chemotherapy regimens and the antibody-drug conjugate, sacituzumab govitecan, are also recommended options in this setting[8].
- **The NCCN Panel voted to remove atezolizumab and durvalumab as treatment options for patients with metastatic urothelial carcinoma in the post-platinum setting** in response to the voluntary withdrawals of the manufacturers of the indications after lack of efficacy in clinical studies[8].

The first and subsequent-line systemic therapy treatment recommendations for muscle invasive locally-advanced or metastatic (stage IV) bladder cancer according to NCCN guidelines are outlined in tables 10 and 11[8].

**Table 10.** First-Line Systemic Therapy Regimens for Locally Advanced or Metastatic Bladder Cancer (Stage IV) (NCCN Guidelines)

| **First-Line Therapy for Locally Advanced or Metastatic Disease (Stage IV)**<br>*Cisplatin Eligible* |
|---|
| **Preferred regimens**<br>▪ Gemcitabine and cisplatin (category 1) followed by avelumab maintenance therapy (category 1) |

| | | |
|---|---|---|
| ▪ ddMVAC with growth factor support (category 1) followed by avelumab maintenance therapy (category 1) | | |
| **First-Line Therapy for Locally Advanced or Metastatic Disease (Stage IV)** *Cisplatin Ineligible* | | |
| **Preferred Regimens** | **Other Recommended Regimens** | **Useful in Certain Circumstances** |
| ▪ Gemcitabine and carboplatin followed by avelumab maintenance therapy (category 1)<br>▪ Pembrolizumab (for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)<br>▪ Pembrolizumab and enfortumab vedotin-ejfv | ▪ Gemcitabine<br>▪ Gemcitabine and paclitaxel<br>▪ Atezolizumab (only for patients whose tumors express PD-L1) (category 2B) | ▪ Ifosfamide, doxorubicin, and gemcitabine (for patients with good kidney function and good performance status)<br>▪ Atezolizumab (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 3) |

*All recommendations are category 2A unless specified otherwise.*

**Table 11.** Second-Line Systemic Therapy for Locally Advanced or Metastatic Bladder Cancer (Stage IV) (NCCN Guidelines)

| **Second-Line Therapy for Locally Advanced or Metastatic Disease (Stage IV)** *Post-platinum or other chemotherapy* | | |
|---|---|---|
| **Preferred Regimens** | **Other Recommended Regimens** | **Useful in Certain Circumstances** |
| **Preferred regimen**<br>▪ Pembrolizumab (category 1 post-platinum)<br>***Alternative preferred regimens***<br>▪ Immune checkpoint inhibitor | ▪ Paclitaxel or docetaxel<br>▪ Gemcitabine<br>▪ Pembrolizumab and enfortumab vedotin-ejfv (category 2B) | ▪ Ifosfamide, doxorubicin, and gemcitabine<br>▪ Gemcitabine and paclitaxel<br>▪ Gemcitabine and cisplatin |

| | | |
|---|---|---|
| ▪ Nivolumab<br>▪ Avelumab<br>▪ Erdafitinib<br>▪ Enfortumab vedotin-ejfv | | ▪ ddMVAC with growth factor support |

| **Second-Line Therapy for Locally Advanced or Metastatic Disease (Stage IV)**<br>*Post-checkpoint inhibitor* | | |
|---|---|---|
| **Preferred Regimens** | **Other Recommended Regimens** | **Useful in Certain Circumstances** |
| **Preferred regimens for cisplatin ineligible, chemotherapy naïve:**<br>▪ Enfortumab vedotin-ejfv<br>▪ Gemcitabine and carboplatin<br>**Preferred regimens for cisplatin eligible, chemotherapy naïve**<br>▪ Gemcitabine and cisplatin<br>▪ ddMVAC with growth factor support<br>▪ Erdafitinib | ▪ Erdafitinib (FGFR 2 or 3 positive)<br>▪ Paclitaxel or docetaxel<br>▪ Gemcitabine | ▪ Ifosfamide, doxorubicin, and gemcitabine<br>▪ Gemcitabine and paclitaxel |

| **Subsequent-Line Therapy for Locally Advanced or Metastatic Disease (Stage IV)** | |
|---|---|
| **Preferred Regimens** | **Other Recommended Regimens** |
| ▪ Enfortumab vedotin-ejfv<br>▪ Erdafitinib | ▪ Sacituzumab govitecan-hziy<br>▪ Gemcitabine<br>▪ Paclitaxel or docetaxel<br>▪ Ifosfamide, doxorubicin, and gemcitabine<br>▪ Gemcitabine and paclitaxel<br>▪ Gemcitabine and cisplatin<br>▪ ddMVAC with growth factor support |

***Participation in clinical trials of new agents is recommended.***

*All recommendations are considered category 2A unless specified otherwise.*

### 1.2.2 American Society of Clinical Oncology (ASCO)/American Society for Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO): Guideline for Treatment of Non-Metastatic Muscle Invasive Bladder Cancer (2017, Amended 2020)

The American Urological Association (AUA), American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) published in 2020 their joint multi-disciplinary, evidence-based guideline for clinically non-metastatic muscle-invasive bladder cancer focuses on the evaluation, treatment, and surveillance of muscle-invasive bladder cancer guided toward curative intent[9]. The key and strength of recommendations of the guidelines are outlined in the below sections.

#### a) Initial Patient Evaluation and Counseling

- Prior to treatment consideration, a full history and physical exam should be performed, including an exam under anesthesia at the time of transurethral resection of bladder tumor (TURBT) for a suspected invasive cancer. (Clinical Principle)[9]
- Prior to muscle-invasive bladder cancer (MIBC) management, clinicians should perform a complete staging evaluation, including imaging of the chest and cross sectional imaging of the abdomen and pelvis with intravenous contrast if not contraindicated. Laboratory evaluation should include a comprehensive metabolic panel (complete blood count, liver function tests, alkaline phosphatase and renal function). (Clinical Principle)[9]
- An experienced genitourinary pathologist should review the pathology of a patient when variant histology is suspected or if muscle invasion is equivocal (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, extensive squamous or glandular differentiation). (Clinical Principle)[9]
- For patients with newly diagnosed MIBC, curative treatment options should be discussed before determining a plan of therapy that is based on both patient comorbidity and tumor characteristics. Patient evaluation should be completed using a multidisciplinary approach. (Clinical Principle)[9]
- Prior to treatment, clinicians should counsel patients regarding complications and the implications of treatment on quality of life (e.g., impact on continence, sexual function, fertility, bowel dysfunction, metabolic problems). (Clinical Principle)[9]

### b) Treatment

#### b.1 Neoadjuvant/Adjuvant Chemotherapy

- Utilizing a multidisciplinary approach, **clinicians should offer cisplatin-based neoadjuvant chemotherapy to eligible radical cystectomy patients prior to cystectomy**. (Strong Recommendation; Evidence Level: Grade B)[9]
- **Clinicians should not prescribe carboplatin-based neoadjuvant chemotherapy** for clinically resectable stage cT2-T4aN0 bladder cancer. Patients ineligible for cisplatin-based NAC should proceed to definitive locoregional therapy. (Expert Opinion)[9]
- Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from neoadjuvant chemotherapy. (Expert Opinion)[9]
- Eligible patients who have not received cisplatin-based neoadjuvant chemotherapy and have non-organ confined (pT3/T4and/or N+) disease at cystectomy should be offered adjuvant cisplatin- based chemotherapy. (Moderate Recommendation; Evidence Level: Grade C)[9]

#### b.2 Radical Cystectomy

- Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (M0) MIBC. (Strong Recommendation; Evidence Level: Grade B)[9]
- When performing a standard radical cystectomy, clinicians should remove the bladder, prostate, and seminal vesicles in males and should remove the bladder, uterus, fallopian tubes, ovaries, and anterior vaginal wall in females. (Clinical Principle)[9]
- Clinicians should discuss and consider sexual function preserving procedures for patients with organ-confined disease and absence of bladder neck, urethra, and prostate (male) involvement. (Moderate Recommendation; Evidence Level: Grade C)[9]
- In patients undergoing radical cystectomy, ileal conduit, continent cutaneous, and orthotopic neobladder urinary diversions should all be discussed. (Clinical Principle)[9]
- In patients receiving an orthotopic urinary diversion, clinicians must verify a negative urethral margin. (Clinical Principle)[9]

### b.3 Perioperative Surgical Management

- Clinicians should attempt to optimize patient performance status in the perioperative setting. (Expert Opinion)[9]
- Perioperative pharmacologic thromboembolic prophylaxis should be given to patients undergoing radical cystectomy. (Strong Recommendation; Evidence Level: Grade B)[9]
- In patients undergoing radical cystectomy μ -opioid antagonist therapy should be used to accelerate gastrointestinal recovery, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)[9]
- Patients should receive detailed teaching regarding care of urinary diversion prior to discharge from the hospital (Clinical Principle)[9]

### b.4 Pelvic Lymphadenectomy

- Clinicians must perform a bilateral pelvic lymphadenectomy at the time of any surgery with curative intent. (Strong Recommendation; Evidence Level: Grade B)[9]
- When performing bilateral pelvic lymphadenectomy, clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes (standard lymphadenectomy). (Clinical Principle)[9]

### b.5 Bladder Preserving Approaches

- For patients with newly diagnosed non-metastatic MIBC who desire to retain their bladder, and for those with significant comorbidities for whom radical cystectomy is not a treatment option, clinicians should offer bladder preserving therapy when clinically appropriate. (Clinical Principle)[9]
- In patients under consideration for bladder preserving therapy, maximal debulking TURBT and assessment of multifocal disease/carcinoma in situ should be performed. (Strong Recommendation; Evidence Level: Grade C)[9]
- Patients with MIBC who are medically fit and consent to radical cystectomy should not undergo partial cystectomy or maximal TURBT as primary curative therapy. (Moderate Recommendation; Evidence Level: Grade C)[9]
- For patients with MIBC, clinicians should not offer radiation therapy alone as a curative treatment. (Strong Recommendation; Evidence Level: Grade C)[9]
- For patients with MIBC who have elected multi-modal bladder preserving therapy, clinicians should offer maximal TURBT, chemotherapy combined with external beam radiation therapy, and planned cystoscopic re-evaluation. (Strong Recommendation; Evidence Level: Grade B)[9]

- **Radiation sensitizing chemotherapy regimens should include cisplatin or 5- fluorouracil and mitomycin C**. (Strong Recommendation; Evidence Level: Grade B.)
- Following completion of bladder preserving therapy, the clinician should perform regular surveillance with CT scans, cystoscopy and urine cytology. (Strong Recommendation; Evidence Level: Grade C)[9]
- Clinicians should obtain chest imaging and cross sectional imaging of the abdomen and pelvis with CT or MRI at 6-12 month intervals for 2-3 years and then may continue annually. (Expert Opinion)[9]

#### c) Patient Surveillance and Follow Up

- Following therapy for MIBC, patients should undergo laboratory assessment at three-to-six-month intervals for two to three years and then annually thereafter. (Expert Opinion)[9]
- Following radical cystectomy in patients with a retained urethra, clinicians should monitor the urethral remnant for recurrence. (Expert Opinion)[9]

### 1.2.3 American Urological Association/Society of Urologic Oncology (AUA/SUO): Joint Guideline for the Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer (2016, Amended 2020)

The American Urological Association (AUA) and the Society of Urologic Oncology (SUO) published in 2020 their most updated guideline for treatment of non-muscle invasive bladder cancer[10].

#### a) Diagnosis

- At the time of resection of suspected bladder cancer, a clinician should perform a thorough cystoscopic examination of a patient's entire urethra and bladder that evaluates and documents tumor size, location, configuration, number, and metastatic urothelial carcinoma abnormalities. (Clinical Principle)[10]
- At initial diagnosis of a patient with bladder cancer, a clinician should perform complete visual resection of the bladder tumor(s), when technically feasible. (Clinical Principle)[10]
- A clinician should perform upper urinary tract imaging as a component of the initial evaluation of a patient with bladder cancer. (Clinical Principle)[10]
- In a patient with a history of NMIBC with normal cystoscopy and positive cytology, a clinician should consider prostatic urethral biopsies and upper

tract imaging, as well as enhanced cystoscopic techniques (blue light cystoscopy, when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)[10]

### b) Risk Stratification

- At the time of each occurrence/recurrence, a clinician should assign a clinical stage and classify a patient accordingly as "low-," "intermediate-," or "high-risk." (Moderate Recommendation; Evidence Strength: Grade C) (c.f. table 1)[10]

### c) Variant Histologies

- An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regards to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of LVI. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- If a bladder sparing approach is being considered in a patient with variant histology, then a clinician should perform a restaging TURBT within four to six weeks of the initial TURBT. (Expert Opinion)[10]
- Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy. (Expert Opinion)[10]

### d) Urine Markers after Diagnosis of Bladder Cancer

- In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)[10]
- In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)[10]
- In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)[10]

### e) TURBT/Repeat Resection: Timing, Technique, Goal, Indication

- In a patient with non-muscle invasive disease who underwent an incomplete initial resection (not all visible tumor treated), a clinician should perform repeat transurethral resection or endoscopic treatment of all remaining tumor if technically feasible. (Strong Recommendation; Evidence Strength: Grade B)[10]

- In a patient with high-risk, high-grade Ta tumors, a clinician should consider performing repeat transurethral resection of the primary tumor site within six weeks of the initial TURBT. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- In a patient with T1 disease, a clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT. (Strong Recommendation; Evidence Strength: Grade B)[10]

#### f) Intravesical Therapy; BCG/Maintenance; Chemotherapy/BCG Combinations

- In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., gemcitabine, mitomycin C) within 24 hours of TURBT[10].
- In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative intravesical chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)[10]
- In a low-risk patient, a clinician should not administer induction intravesical therapy. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- In an intermediate-risk patient a clinician should consider administration of a six-week course of induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)[10]
- In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)[10]
- In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)[10]
- In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)[10]

### g) BCG Relapse and Salvage Regimens

- In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)[10]
- In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, a clinician should offer a second course of BCG. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- A clinician should not prescribe additional BCG to a patient who is intolerant of BCG or has documented recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- In a patient with persistent or recurrent intermediate- or high-risk NMIBC within 12 months of completion of adequate BCG therapy (two induction courses or one induction course plus one maintenance cycle) who is unwilling or unfit for cystectomy, a clinician may recommend clinical trial enrollment or offer alternative intravesical therapy (e.g., valrubicin, gemcitabine, docetaxel, combination chemotherapy) when clinical trials are unavailable. A clinician may also offer systemic immunotherapy with pembrolizumab to a patient with CIS within 12 months of completion of adequate BCG therapy. (Expert Opinion)[10]

### h) Role of Cystectomy in NMIBC

- In a patient with Ta low- or intermediate-risk disease, a clinician should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (Clinical Principle)[10]
- In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a

clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)[10]

### i) Enhanced Cystoscopy

- In a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)[10]
- In a patient with NMIBC, a clinician may consider use of NBI to increase detection and decrease recurrence. (Conditional Recommendation; Evidence Strength: Grade C)[10]

### j) Risk Adjusted Surveillance and Follow-up Strategies

- After completion of the initial evaluation and treatment of a patient with NMIBC, a clinician should perform the first surveillance cystoscopy within three to four months. (Expert Opinion)[10]
- For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)[10]
- In an asymptomatic patient with a history of low-risk NMIBC, a clinician should not perform routine surveillance upper tract imaging. (Expert Opinion)[10]
- In a patient with a history of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), a clinician may consider in-office fulguration as an alternative to resection under anesthesia. (Expert Opinion)[10]
- For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. (Expert Opinion)[10]
- For a high-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter. (Expert Opinion)[10]
- For an intermediate- or high-risk patient, a clinician should consider performing surveillance upper tract imaging at one-to-two-year intervals. (Expert Opinion)[10]

### 1.2.4 Canadian Urological Association (CUA) Guideline on the Management of Non-Muscle-Invasive Bladder Cancer (2021)

The Canadian Urological Association (CUA) published their guidelines for treatment of both non-muscle invasive bladder cancer (2021)[11] and muscle invasive bladder cancer (joint statement with the Genitourinary Medical Oncologists of Canada (GUMOC) (2019)[12]. The key treatment recommendations for non-muscle invasive bladder cancer are outlined in this section, while the CUA/GUMOC guidelines for muscle invasive bladder cancer are detailed in section 1.2.5.

#### a) Transurethral resection

- Patients presenting with a bladder tumor should undergo initial TURBT for diagnostic confirmation and pathological evaluation (LE 2, strong recommendation).
- Initial TURBT aims for complete tumor resection with sampling of the underlying detrusor muscle as the first step of curative-intent treatment of NMIBC (LE 2, strong recommendation). Patients with presumed low-grade (LG) Ta or CIS might be spared from muscle sampling at initial TURBT (LE 3, weak recommendation).
- When available, blue light cystoscopy (BLC) (LE 1, weak recommendation) or narrow band imaging (LE 2, weak recommendation) can increase tumor detection at first TURBT and reduce recurrence risk.
- A restaging TURBT should be performed in patients with T1 NMIBC, or when a complete resection was not achieved with the first TURBT (LE 2, strong recommendation). Re-staging TURBT is not required in patients who will proceed to radical cystectomy (RC) based on the findings of the first TURBT.
- In select cases of high-grade (HG) Ta tumors (e.g., large and/or multiple tumors), a restaging TURBT can be considered (LE 3, weak recommendation).
- The suggested window for a restaging TURBT is within six weeks of the first resection (LE 3, weak recommendation).
- Patients presenting with a positive urine cytology, but normal-appearing bladder at WLC and normal upper urinary tract imaging are at higher risk of harboring occult CIS and should undergo random bladder biopsies (or use of BLC with directed biopsies) (LE 2, strong recommendation).
- Biopsies or transurethral resection of the prostatic urethra should be included with random bladder biopsies in the presence of a positive bladder urine cytology, but normal-appearing bladder at WLC and normal upper tract imaging (LE 3, strong recommendation).

- Prostatic urethral biopsies (or a transurethral resection) can also be considered in the presence of extensive bladder CIS or tumor at the bladder neck or trigone (LE 3, weak recommendation).
- Patients with prostatic urethral involvement (PUI) with CIS restricted to the urethral metastatic urothelial carcinomaosa can be managed conservatively with transurethral resection of the prostate (TURP) plus intravesical bacillus Calmette-Guérin (BCG) (LE 3, weak recommendation). Repeat prostatic urethral biopsies after induction BCG should be considered (LE 3, weak recommendation). RC can be discussed as an alternative option (LE 4, weak recommendation).
- In patients with HG T1 or CIS extending into the prostatic ducts, RC should be considered (LE 3, weak recommendation). TURP followed by intravesical BCG is an alternative option. In this instance, close follow up with repeat prostatic urethral biopsies after induction BCG should be considered (LE 3, weak recommendation).
- In patients with prostatic stromal invasion, neoadjuvant cisplatin-based chemotherapy followed by RC is recommended (LE 3, strong recommendation; refer to CUA guideline on MIBC)[11].

### b) Single instillation of chemotherapy (SIC) post-TURBT

- SIC (with mitomycin-C, epirubicin, doxorubicin, pirarubicin, or gemcitabine) should be offered to all patients with presumed low-risk NMIBC at TURBT and should be administered within 24 hours after endoscopic resection (LE 1, strong recommendation).
- SIC is recommended for intermediate-risk NMIBC and for patients with ≤1 recurrence/year and European Organization for Research and Treatment of Cancer (EORTC) recurrence score <5 (LE 1, strong recommendation). SIC should be discussed even when further adjuvant intravesical chemotherapy is planned (LE 2, weak recommendation)
- The benefit of SIC in patients with high-risk NMIBC is unclear when intravesical BCG is planned as adjuvant treatment (LE 3).
- SIC should not be administered after extensive resection or when bladder perforation is suspected (LE 3, strong recommendation)[11].

### c) Adjuvant intravesical chemotherapy

- Patients with intermediate-risk NMIBC should be considered for adjuvant induction intravesical chemotherapy (LE 1, strong recommendation) with

subsequent maintenance for up to one year (LE 3, weak recommendation), or induction BCG with maintenance therapy (refer to statement #30).

- Sub-stratification of intermediate-risk patients with recurrent LG Ta NMIBC can be used to guide adjuvant treatment decisions (LE 3, weak recommendation). For this purpose, four factors should be considered: number of tumors, size (≥3 cm), time to recurrence (<1 year), and frequency of recurrence (>1/year).
    - Patients with low-intermediate-risk NMIBC (0 factors) may be treated similarly to low-risk patients, with SIC alone (LE 3, weak recommendation).
    - Patients with high-intermediate-risk NMIBC (≥3 factors) may be treated as high-risk patients with induction and maintenance BCG (LE 3, weak recommendation).
- Patients who develop recurrence during intravesical chemotherapy may be offered induction followed by maintenance BCG (LE 3, weak recommendation).
- Although intravesical chemotherapy through device-assisted therapy has shown promising results in small, randomized controlled trials, further studies are needed to validate its routine clinical use[11].

#### d) Adjuvant intravesical BCG

- In patients with high-risk NMIBC, BCG therapy with induction (weekly instillations for six weeks) followed by three-year maintenance (weekly instillations for three weeks at three, six, 12, 18, 24, 30, and 36 months) is the standard of care for reducing disease recurrence and progression rates (LE 1, strong recommendation).
- When BCG is administered for intermediate-risk NMIBC, induction (weekly instillations for six weeks) followed by one-year maintenance (weekly instillations for three weeks at three, six, and 12 months) is recommended (LE 1, strong recommendation).
- RC with pelvic lymph node dissection is the standard of care for BCG-unresponsive bladder cancer in surgically fit patients (LE 3, strong recommendation). For patients with BCG-unresponsive CIS or HG Ta, a second-line bladder-preserving therapy can be considered before RC (LE 3, weak recommendation).
- Promising efficacy has been reported with intravenous pembrolizumab, intravesical oportuzumab monatox, nadofaragene firadenovec, and BCG plus N-803. These should be considered as potential options in patients with BCG-

unresponsive CIS who are unfit for or refuse to undergo RC (LE 2, weak recommendation).

- Alternative options, such as sequential intravesical gemcitabine/docetaxel (induction plus maintenance), may be considered for patients with BCG-unresponsive disease who are unfit for or refuse to undergo RC (LE 3, weak recommendation). Additional alternatives may also include other combination intravesical therapy (e.g., sequential gemcitabine/mitomycin-C, BCG + interferon if available) or single-agent intravesical therapy (mitomycin-C, epirubicin, docetaxel, gemcitabine) (LE 3, weak recommendation).
- Clinical trials may be considered for BCG-unresponsive patients who are unfit for or refuse to undergo RC[11].

#### e) Treatment adjustments only if BCG shortage

- For patients with intermediate-risk NMIBC during BCG shortage, intravesical chemotherapy is recommended as the first-line option. If BCG is planned as a second-line therapy for this population, induction might be administered with reduced dosing (one-half or one-third dose) and maintenance can be omitted (LE 3, weak recommendation).
- For patients with high-risk NMIBC, full BCG schedule (induction followed by maintenance) is recommended (LE 1, strong recommendation). Only during BCG shortage, when full dose is not possible due to limited supply, dose reduction to one-half or one-third might be considered, while maintenance can be reduced to one year (LE 3, weak recommendation).
- When BCG is unavailable, single-agent chemotherapy (e.g., mitomycin-C, gemcitabine) or sequential combination of intravesical chemotherapy (e.g., gemcitabine/docetaxel) is recommended with induction followed by monthly maintenance for up to one year (LE 3, weak recommendation)[11].

#### f) Timely cystectomy

- Upfront RC should be considered for patients with large-volume, diffuse, endoscopically unresectable NMIBC (LE 3, strong recommendation).
- Upfront RC should be offered to patients with HG T1 disease with additional adverse tumor pathological features, including: variant histology (e.g., micropapillary, plasmacytoid, sarcomatoid), extensive invasion of the lamina propria or invasion into or beyond the muscularis metastatic urothelial carcinomaosa (T1b/c), presence of LVI, concomitant CIS in the bladder or prostatic urethra, multiple and large (≥3 cm) tumors, or persistent HG T1 upon re-staging TURBT (LE 3, strong recommendation)[11].

### 1.2.5 Canadian Urological Association (CUA)/Genitourinary Medical Oncologists of Canada (GUMOC): Consensus Statement for Management of Unresectable Locally Advanced and Metastatic Urothelial Carcinoma (2019) Guideline on the Management of Muscle-Invasive Bladder Cancer

#### a) Eligibility for cisplatin-based chemotherapy

- Routine eligibility for cisplatin chemotherapy includes all of:
    1. creatinine clearance >60 ml/min;
    2. Eastern Cooperative Oncology Group (ECOG) performance status of <1;
    3. absence of hearing loss >Gr 2 (Common Terminology Criteria for Adverse Events [CTCAE]);
    4. absence of neuropathy >Gr 2 (CTCAE); and
    5. absence of New York Heart Association (NYHA) grade III/IV heart failure.
- In select cases, eligibility criteria may be extended to patients with a glomerular filtration rate (GFR) of 45–60 ml/min and/or ECOG 2 performance status. Administering split-dose cisplatin is an option for these patients[12].

#### b) First-line systemic therapy

- Patient eligible for cisplatin-based chemotherapy[12]
    - In patients suitable for cisplatin-based chemotherapy, the preferred routine regimen is gemcitabine/cisplatin (GC).
    - Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (DD-MVAC) with growth factor support may be considered in select cases where a more aggressive treatment approach is being considered.
- Patient ineligible for cisplatin-based chemotherapy[12]
    - In patients ineligible for cisplatin-based chemotherapy, the preferred regimen is gemcitabine / carboplatin (GC).
    - In patients not suitable for combination chemotherapy, single agent gemcitabine, paclitaxel or docetaxel is recommended.
    - Immunotherapy is not routinely recommended in the first line setting for cisplatin-ineligible patients.

### c) Second-line systemic therapy

- In patients who have progressive disease during or after platinum-based chemotherapy, pembrolizumab is the preferred regimen (if available) [12].
- Where pembrolizumab is unavailable or a patient is ineligible, single-agent paclitaxel or docetaxel is preferred for the majority of patients[12].
- Re-treatment with a platinum-based regimen is a reasonable option in a patient who has disease progression following a prolonged (>6–12-month) initial response to platinum-based chemotherapy[12].

### d) The role of PD-L1 testing in selecting patients for immunotherapy

- In the second-line setting, PD-L1 testing by IHC should not be used to select patients for immunotherapy[12].

### e) Management of cT4b and/or cN1–3 urothelial carcinoma of the bladder

- Patients with clinically staged T4b or N1–3 urothelial carcinoma of the bladder should be discussed in a multidisciplinary forum, including an experienced urologist/uro-oncologist, and radiation oncologist.
- Patients with cT4b and/or cN1–3 urothelial carcinoma of the bladder can be cured using multimodality treatment.
- In suitable patients, the preferred approach is to commence systemic chemotherapy with 4–6 cycles of platinum-based chemotherapy as per first-line systemic therapy.
- Depending on response to initial chemotherapy, consolidation with either radical cystectomy (RC) and pelvic lymph node dissection (PLND) or radical radiotherapy (± concurrent chemotherapy) can be administered[12].

### f) The role of aggressive surgical/radiotherapeutic management in oligometastatic disease

- Routine practice of metastasectomy/localized treatment to metastatic disease in patients with oligometastatic or limited metastatic disease is not recommended. However, such treatment may be appropriate in selected cases (see discussion).
- In metastatic urothelial carcinoma of the bladder, the routine practice of RC or HDRT (± chemotherapy) to the primary is not recommended. However, such treatment may be appropriate in selected cases (see discussion).
- The decision to treat oligometastatic disease with local therapies should be made in a multidisciplinary context with involvement of an experienced

medical oncologist, uro-oncologist, and radiation oncologist where appropriate[12].

## 1.3 European Guidelines

### 1.3.1 European Society for Medical Oncology (ESMO) Bladder Cancer Clinical Practice Guideline for Diagnosis, Treatment, and Follow-up (2021)

The European Society for Medical Oncology (ESMO) released in 2021 clinical practice guidelines for diagnosis, treatment, and follow up of bladder cancer. The key recommendations of the guideline are outlined in the following sections[13]:

#### a) Diagnosis and pathology/Molecular biology

The diagnosis and pathology recommendations for bladder cancer according to the ESMO guidelines are shown in table 12[13].

**Table 12.** Diagnosis and Pathology Recommendations for Bladder Cancer (ESMO Guidelines)

| Recommendations | Strength |
|---|---|
| ***Diagnosis and pathology*** | |
| ▪ Painless hematuria is the most common presenting symptom in bladder cancer and should in all cases be investigated. | IV,A |
| ▪ The diagnosis of bladder cancer is based on cystoscopic examination of the bladder and histological evaluation of tissue obtained either with cold-cup biopsy or TURBT. Complete resection of all tumor tissue should be achieved when possible. Muscle tissue should be included in the biopsies, except when a Ta/LG is expected. | IV,A |
| ▪ Cross-sectional upper tract imaging (CT/MRI urography) is recommended to screen for synchronous UTUC, in cases of HG bladder cancer. | IV,B |
| ▪ Pathological diagnosis should be made according to the latest WHO classification. | IV,A |
| ▪ In addition to stage and grade, presence, and percentage of variant histology, lymphovascular invasion and presence of detrusor muscle should be reported. | IV,A |

| | |
|---|---|
| ▪ Urine cytology can facilitate the diagnosis of HG UC but cannot be used as the primary method of histological diagnosis. The Paris system should be used for reporting. | IV,B |
| ▪ Molecular diagnostics such as The Cancer Genome Atlas (TCGA) classification and PD-L1 status are not required for all tumors. | IV,C |

### b) Staging and Risk assessment

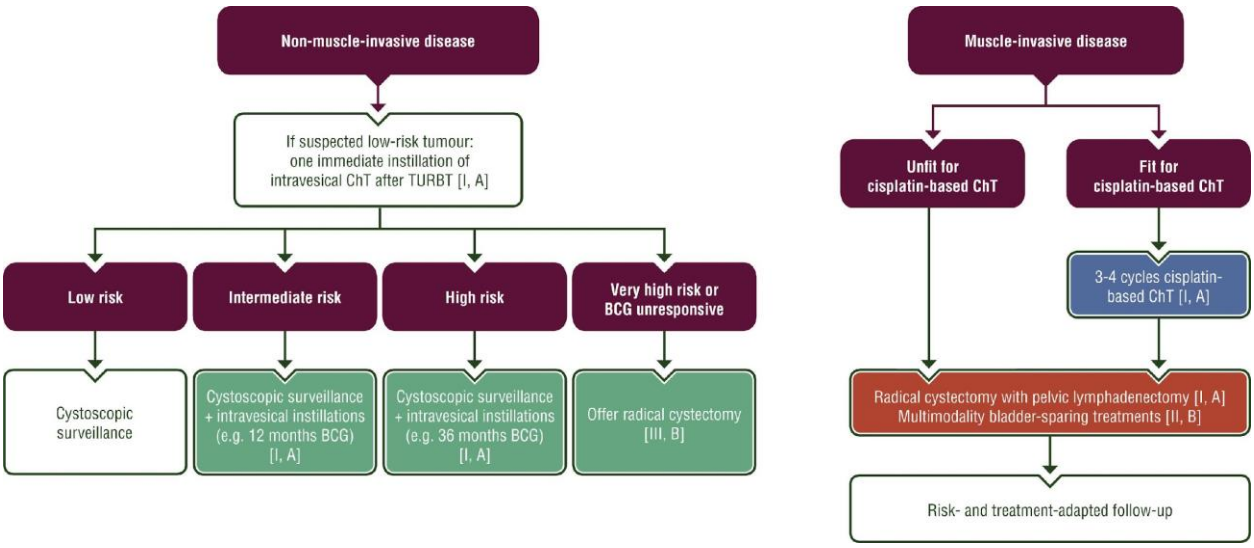
The staging and risk assessment recommendations for bladder cancer according to the ESMO guidelines are shown in table 13[13].

**Table 13.** Staging and Risk Assessment Recommendations for Bladder Cancer (ESMO Guidelines)

| Recommendations | Strength |
|---|---|
| ***Staging and Risk Assessment*** | |
| ▪ Patients with NMIBC are classified into four risk categories based on tumor characteristics (low risk, intermediate risk, high risk and very-high-risk), which constitutes the basis for treatment and follow-up recommendations. | IV,B |
| ▪ In patients with invasive disease (T1), regional and distant staging should be carried out with further imaging studies such as contrast-enhanced CT of chest-abdomen-pelvis or MRI of abdomen/pelvis combined with chest CT. | IV,B |
| ▪ FDG-PET-CT may aid in the detection of LN and distant metastases, but no clear consensus was reached. | IV,C |

### c) Treatment

A proposed algorithm for the management of patients with confirmed bladder cancer is shown in figure 1[13].




Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

BCG, bacillus Calmette-Guerin; ChT, chemotherapy; TURBT, transurethral resection of the bladder tumor.

***Figure 1.*** *Management of patients with histopathologically confirmed bladder cancer. Retrieved from Powles T, Bellmunt J, Comperat E, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment, and follow-up. Ann Oncol. 2022;33(3):244-258. doi:10.1016/j.annonc.2021.11.012.*

### c.1. Management of local/locoregional disease

The treatment recommendations for patients with local/locoregional bladder cancer according to the ESMO guidelines are shown in table 14[13].

**Table 14.** Treatment Recommendations for Patients with Local/Locoregional Bladder Cancer (ESMO Guidelines)

| Recommendations | Strength |
|---|---|
| ***Treatment of NMIBC*** | |
| ▪ Treatment of NMIBC should follow a risk-stratified approach with TURBT and intravesical chemotherapy or BCG in intermediate- and high-risk patients. | I,A |
| ▪ Subsets of patients with very-high-risk disease should be offered RC. RC should be carried out in CIS or HG T1 that are unresponsive to BCG due to the high risk of progression. | III,B |
| ▪ In patients who are BCG-unresponsive and -ineligible for or refuse cystectomy, pembrolizumab or nadofaragene firadenovec can be considered; however, more robust data are required before | III,C<br>IV,C |

| | |
|---|---|
| stronger recommendations can be made for these and other bladder-sparing approaches in BCG-unresponsive disease [III, C]. A multidisciplinary approach is required for these patients [IV, C]. | |
| ***Treatment of MIBC*** | |
| ▪ Multidisciplinary care via tumor board discussions and/or directed consultations with a medical oncologist, radiation oncologist and urologist is recommended for the optimal management of bladder cancer. | IV,B |
| ▪ RC with standard PLND is the standard treatment of MIBC T2-T4a, N0 M0. | I,A |
| ▪ Patients with radiological suspicious node-positive disease (cN1) can be considered for surgery but should be considered for preoperative platinum-based chemotherapy. | IV,B |
| ▪ Organ-preservation therapy with RT, as part of multimodal schema for MIBC, is a reasonable option for patients seeking an alternative to RC and an option for those who are medically unfit for surgery. | II,B |
| ▪ Contemporary organ-preservation protocols should utilize a tri-modality combination of TURBT, RT and chemotherapy. | II,B |
| ▪ Palliative RT can be offered for palliation (bleeding, pain). | III,C |
| ▪ Adjuvant RT (with or without radiosensitizing chemotherapy) is not standard treatment of patients with MIBC. | III,C |
| ▪ Three to four cycles of cisplatin-based neoadjuvant chemotherapy should be given for MIBC [I, A]. Cross-sectional imaging should occur after chemotherapy before RC [IV, B]. | I,A<br>IV,B |
| ▪ There is weak evidence to support the use of adjuvant cisplatin-based chemotherapy in patients who did not receive neoadjuvant therapy. Neoadjuvant chemotherapy is preferred. | II,B |
| ▪ Inconsistent results exist for adjuvant immune checkpoint inhibitors in urothelial carcinoma [I, A]. An overall survival advantage is needed before it can be recommended as standard therapy [I, D]. | I,A<br>I,D |

### c.2. Management of Advanced/Metastatic Disease

The treatment recommendations for patients with advanced or metastatic bladder cancer according to the ESMO guidelines are shown in table 15[13].

**Table 15.** Treatment Recommendations for Patients with Advanced or Metastatic Bladder Cancer (ESMO Guidelines)

| Recommendations | Strength |
|---|---|
| ***Treatment of advanced or metastatic urothelial carcinoma in patients fit enough to tolerate cisplatin-based combination chemotherapy*** | |
| ▪ Cisplatin-based chemotherapy [I, A] followed by maintenance avelumab in those tumors not progressing on chemotherapy is the standard of care [I, A; ESMO-MCBS v1.1 score: 4]. | I,A |
| ***Treatment of advanced or metastatic urothelial carcinoma in patients not eligible for cisplatin-based combination chemotherapy*** | |
| ▪ Gemcitabine/carboplatin [II, B] followed by maintenance avelumab (in those tumors not progressing on chemotherapy) for those not eligible for cisplatin-based therapy is the standard of care [I, A]. | II,B<br>I,A |
| ▪ Atezolizumab or pembrolizumab are alternatives for patients with PD-L1 biomarker-positive tumors who are not eligible for cisplatin-based combination chemotherapy. The level of evidence, however, is weaker than for chemotherapy followed by maintenance avelumab and this approach requires careful consideration. | III,B |
| ***Treatment of relapsed advanced or metastatic urothelial carcinoma*** | |
| ▪ Pembrolizumab has the most robust data for treatment in the setting of progression of disease after platinum-based chemotherapy [I, A; ESMO-MCBS v1.1 score: 4]. Other ICIs such as atezolizumab can be given with less robust evidence [II, B-III, C]. | |
| ▪ Erdafitinib is an alternative to ICIs in tumors with FGFR alterations. This has weaker levels of evidence than pembrolizumab. | III,B |
| ▪ Chemotherapy can be considered instead of best supportive care when other options are not available (vinflunine [II, C]; taxanes [III, C]). | |
| ***Treatment of tumors that relapse after first-line single-agent immunotherapy*** | |
| ▪ Randomized data are lacking in immunotherapy refractory disease. Enfortumab vedotin [III, B; ESMO-MCBS v1.1 score: 4] or platinum-based chemotherapy [IV, B] should be given. | |
| ***Treatment of Chemotherapy and immunotherapy-relapsed disease*** | |
| ▪ Enfortumab vedotin is recommended as standard treatment in this population [I, A; ESMO-MCBS v1.1 score: 4]. | I,A |

| | |
|---|---|
| ▪ Erdafitinib is an alternative in patients with FGFR alterations with a weaker level of evidence. | III,B |
| ▪ Chemotherapy can be considered instead of best supportive care, if clinically appropriate. | IV,B |
| ▪ Retreatment with chemotherapy for those patients that relapse after all other treatment options can be considered.<br>▪ Single agent taxane therapy or vinflunine can be considered. | IV,C |
| ***Treatment of upper urinary tract urothelial carcinoma*** | |
| ▪ Kidney-sparing management should be offered to low-risk upper urinary tract urothelial carcinoma and radical nephro-ureterectomy with bladder cuff excision for high-risk upper urinary tract urothelial carcinoma. | II,B |
| ▪ Systemic therapy recommendations for advanced upper urinary tract urothelial carcinoma should follow those for advanced bladder cancer. | IV,B |
| ▪ There is evidence to support the use of adjuvant cisplatin-based chemotherapy based on the POUT data and the OS meta-analysis for cisplatin-based treatment of urothelial carcinoma. | II,C |

### d) Follow-up, Long-Term Implications, and Survivorship

The follow-up, long-term implications, and survivorship recommendations for patients with bladder cancer according to the ESMO guidelines are shown in table 16[13].

**Table 16.** Follow-up, Long-Term Implications, and Survivorship Recommendations (ESMO Guidelines)

| Recommendations | Strength |
|---|---|
| ***Follow-up, Long-Term Implications, and Survivorship*** | |
| ▪ Follow-up for NMIBC requires regular cystoscopic examination according to the patient's risk category. | IV,A |
| ▪ Follow-up after curative therapy for MIBC requires cross-sectional imaging for 5 years. This should include 3-4 monthly imaging for the first 2 years. Bladder-sparing approaches also require regular cystoscopy. | IV,B |
| ▪ Follow-up during and after systemic therapy for advanced UC should focus on regular cross-sectional imaging of the chest, abdomen and pelvis and other target lesions. | IV,B |

### 1.3.2 European Association of Urology (EAU) Guidelines on Non-Muscle-Invasive Bladder Cancer (2023)

The European Association of Urology (EAU) released in 2023 an update on the guidelines of both muscle-invasive and metastatic bladder cancer, and non-muscle-invasive bladder cancer (TAT1 and CIS)[14]. The key treatment recommendations of the guideline are outlined in table 17[14].

**Table 17.** Management Recommendations for Bladder Cancer (EAU Guideline)

| Recommendations | Strength |
|---|---|
| ***Neoadjuvant therapy*** | |
| ▪ If eligible for cisplatin-based chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with muscle-invasive bladder cancer (T2-T4a, cN0 M0). | Strong |
| ▪ Do not offer neoadjuvant chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy. | Strong |
| ▪ Only offer neoadjuvant immunotherapy to patients within a clinical trial setting. | Strong |
| ***Pre- and post-operative radiotherapy in muscle-invasive bladder cancer*** | |
| ▪ Do not offer pre-operative radiotherapy (RT) for operable MIBC since it will only result in down-staging but will not improve survival. | Strong |
| ▪ Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned. | Strong |
| ▪ Consider offering adjuvant RT in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins). | Weak |
| ***Radical cystectomy and urinary diversion*** | |
| ▪ Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality unless the patient receives neoadjuvant chemotherapy. Strong Perform at least 10, and preferably > 20, RCs per hospital/per year. | Strong |
| ▪ Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon. | Strong |
| ▪ Do not offer an orthotopic bladder substitute diversion to patients who have an invasive tumor in the urethra or at the level of urethral dissection. | Strong |

| | |
|---|---|
| ▪ Only offer sexual-preserving techniques to eligible men very motivated to preserve their sexual function. | Strong |
| ▪ Select men for sexual-preserving techniques based on organ-confined disease; absence of any kind of tumor at the level of the prostate, prostatic urethra or bladder neck. | Strong |
| ▪ Offer sexual-preserving techniques to eligible women to preserve their sexual function. Weak Select women for sexual-preserving techniques based on: • absence of tumor in the area to be preserved to avoid positive soft tissue margins; • absence of pT4 urothelial carcinoma. | Strong |
| ▪ Do not offer preoperative bowel preparation. | Strong |
| ▪ Employ 'Fast track' measurements to reduce the time to bowel recovery. | Strong |
| ▪ Offer pharmacological venous thromboembolism prophylaxis, such as low molecular weight heparin, to RC patients, starting the first day post-surgery, for a period of at least 4 weeks. | Strong |
| ▪ Offer RC to patients with T2–T4a, N0M0 disease or very high-risk non-MIBC. | Strong |
| ▪ Perform a lymph node dissection as an integral part of RC. | Strong |
| ***Laparoscopic/ robotic-assisted laparoscopic cystectomy*** | |
| ▪ Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure. | Strong |
| ▪ Select experienced centers, not specific techniques, both for RARC and ORC. | Strong |
| ***Bladder-sparing treatments for localized disease*** | |
| ▪ Do not offer transurethral resection of bladder tumor alone as a curative treatment option as most patients will not benefit. | Strong |
| ▪ Do not offer radiotherapy alone as primary therapy for localized bladder cancer. | Strong |
| ▪ Do not offer chemotherapy alone as primary therapy for localized bladder cancer. | Strong |
| ▪ Offer surgical intervention or trimodality bladder-preserving treatments (TMT) to appropriate candidates as primary curative therapeutic approaches since they are more effective than radiotherapy alone. | Strong |

| | |
|---|---|
| ▪ Offer TMT as an alternative to selected, well informed, and compliant patients, especially for whom radical cystectomy is not an option or not acceptable. | Strong |
| ***Adjuvant Chemotherapy*** | |
| ▪ Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given. | Strong |
| ▪ Discuss immunotherapy with nivolumab with selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy | Strong |
| ***Metastatic Disease*** | |
| ***First-line treatment for platinum fit patients*** | |
| ▪ Use cisplatin-containing combination chemotherapy with GC or HD-MVAC. | Strong |
| ▪ In patients unfit for cisplatin but fit for carboplatin, use the combination of carboplatin and gemcitabine. | Strong |
| ▪ In patients achieving stable disease, or better, after first-line platinum-based chemotherapy, use maintenance treatment with PD-L1 inhibitor avelumab | Strong |
| ***First-line treatment in patients unfit for platinum-based chemotherapy*** | |
| ▪ Consider checkpoint inhibitors pembrolizumab or atezolizumab in case of high PD-1 expression | Weak |
| ***First-line treatment for platinum fit patients*** | |
| ▪ Use cisplatin-containing combination chemotherapy with GC or HD-MVAC. | Strong |
| ▪ In patients unfit for cisplatin but fit for carboplatin, use the combination of carboplatin and gemcitabine. | Strong |
| ▪ In patients achieving stable disease, or better, after first-line platinum-based chemotherapy, use maintenance treatment with PD-L1 inhibitor avelumab. | Strong |
| ***Second-line treatment*** | |
| ▪ Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease | Strong |
| ***First-line treatment for platinum fit patients*** | |

| | |
|---|---|
| ▪ Offer antibody drug conjugate enfortumab vedotin as monotherapy to patients with advanced or metastatic urothelial carcinoma pre-treated with platinum and immunotherapy. | Strong |
| ▪ Offer treatment in clinical trials testing novel drugs (e.g. sacituzumab govitecan); or in case of patients with FGFR3 alterations, FGFR tyrosine kinase inhibitors. | Strong |
| ▪ Evaluate for FGFR2/3 genetic alterations for the potential use of erdafitinib in patients with locally-advanced or metastatic urothelial carcinoma who have progressed following platinum-containing chemotherapy (including within 12 months of neoadjuvant- or adjuvant platinum-containing chemotherapy) | Weak |

The treatment algorithms for the management of early stage and metastatic bladder cancer according to the EAU guidelines are illustrated in figures 2 and 3[14].

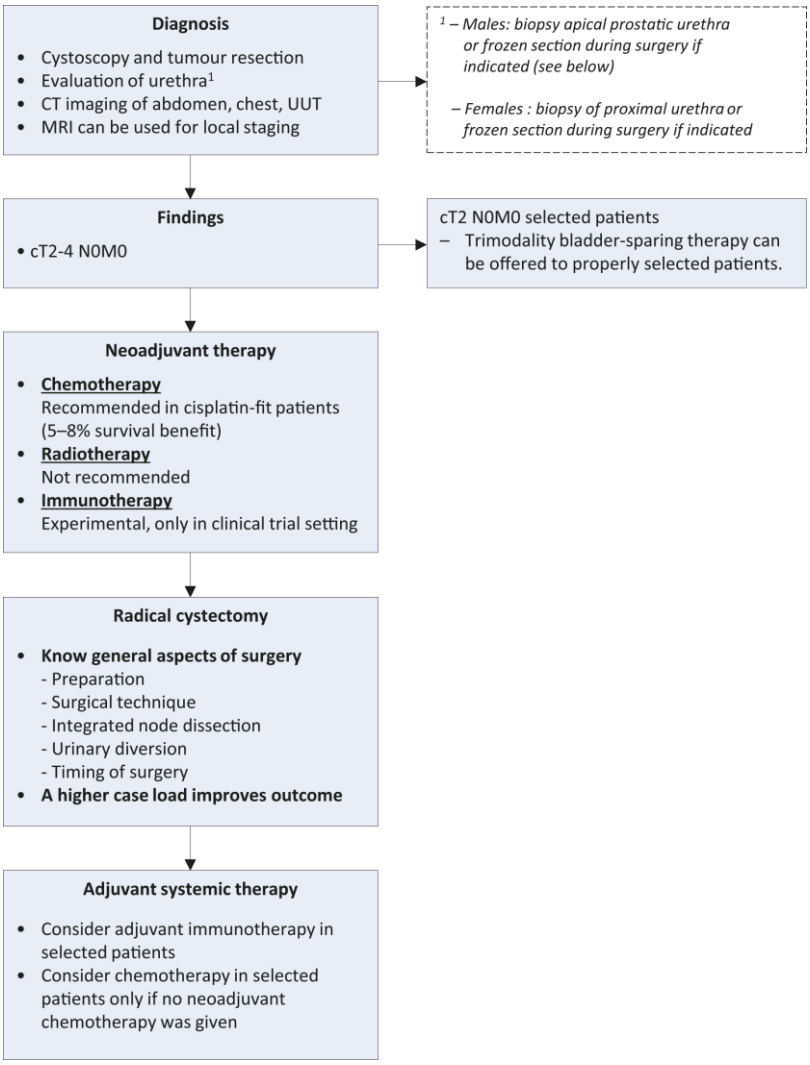



***Figure 2.*** *Flow chart for the management of T2–T4a N0M0 urothelial bladder cancer (EAU guideline). Retrieved from Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol. 2021;79(1):82-104. doi:10.1016/j.eururo.2020.03.055.*

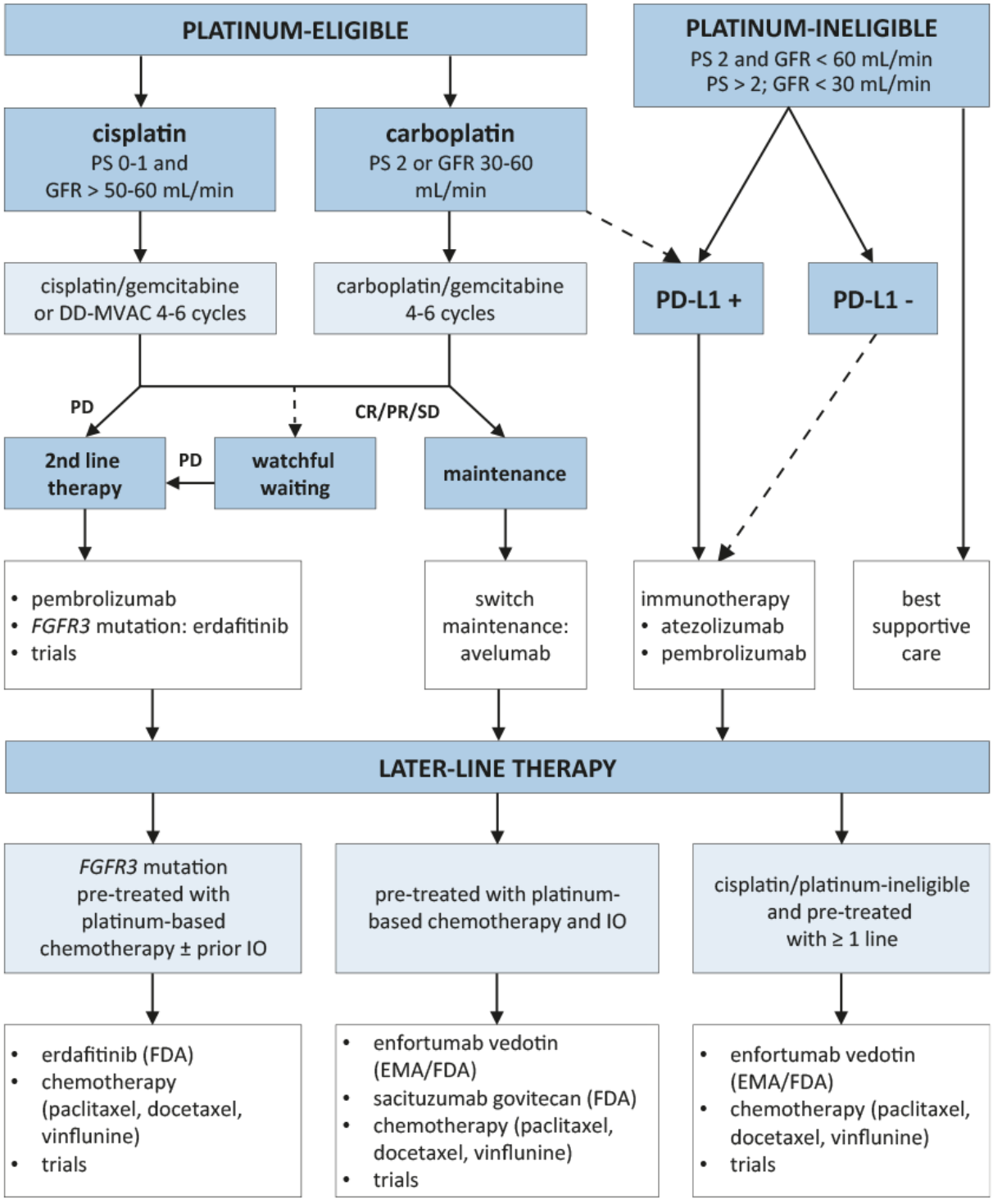



***Figure 3.*** *Flow chart for the management of metastatic urothelial cancer (EAU guideline). Retrieved from Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol. 2021;79(1):82-104. doi:10.1016/j.eururo.2020.03.055.*

## 1.4 International Guidelines

### 1.4.1 Japanese Urological Association (JUA) Clinical Practice Guidelines for Bladder Cancer (2019)

The Japanese Urological Association (JUA) released in 2019 an update on the 2015 clinical practice guidelines for bladder cancer. The bladder cancer treatment algorithm in the 2019 JUA guideline is illustrated in figure 4[43]:

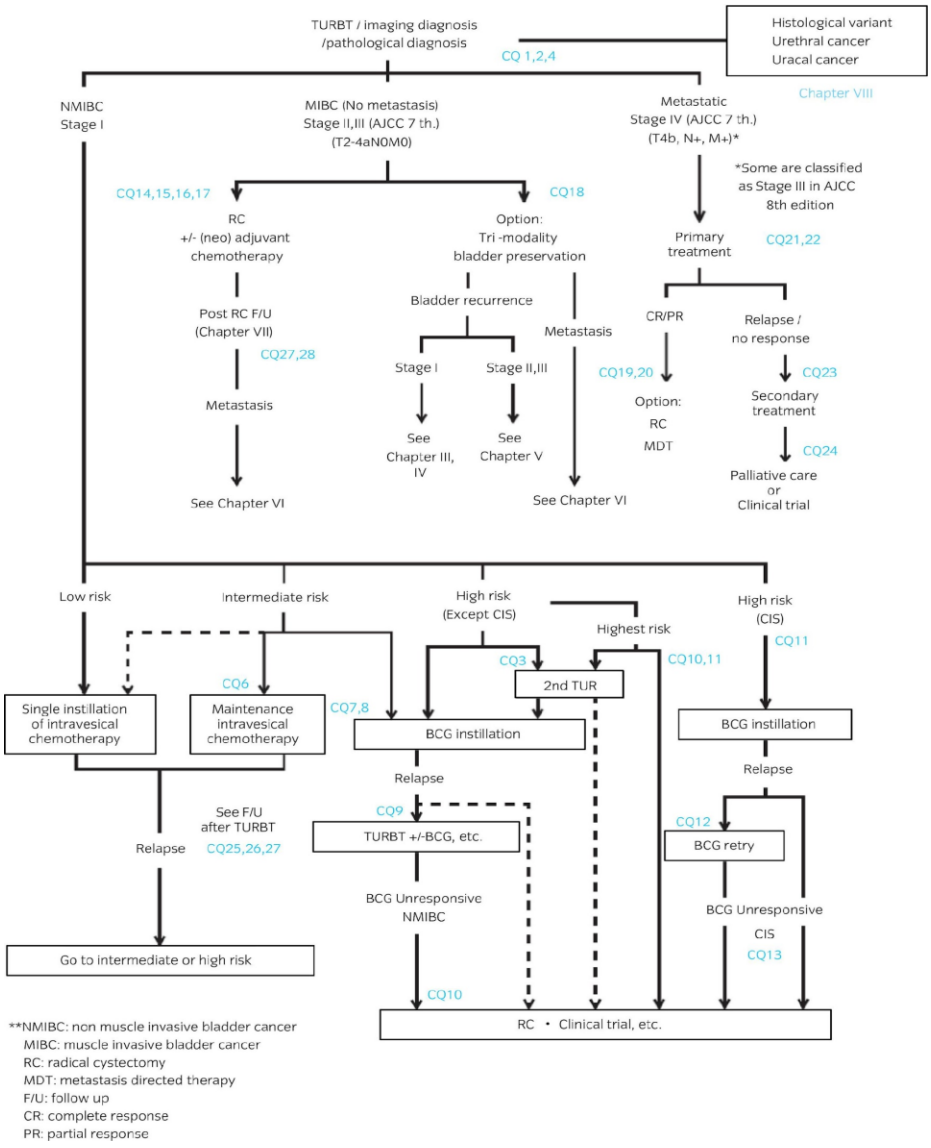



***Figure 4.*** *Bladder cancer treatment algorithm; JUA Clinical Practice Guidelines for Bladder Cancer 2019. Retrieved from Matsumoto H, Shiraishi K, Azuma H, et al. Clinical Practice Guidelines for Bladder Cancer 2019 update by the Japanese Urological Association: Summary of the revision. Int J Urol. 2020;27(9):702-709. doi:10.1111/iju.14281.*

The major points of change in the 2019 version are[43]:

1. Introduction of the new reference assessment system.
2. Modification of the risk classification for non-muscle-invasive bladder cancer:
    - Patients with NMIBC are divided into low, intermediate, high, and highest risk, and prevention of recurrence and progression after TURBT is carried out. Compared with the 2015 risk classification, the intermediate-risk group was reorganized, and the concept of BCG unresponsive disease was introduced into the high-risk group. Additionally, in accordance with overseas guidelines, a highest risk group was added (table 18)[43].

**Table 18.** Risk Classification of Non-MIBC (JUA Guideline)

| Risk Group | Definition |
|---|---|
| Low-risk group | The group meets all factors: single tumor, initial diagnosis, <3 cm, Ta, low grade, without concurrent CIS |
| Intermediate-risk group | The group meets other than low and high risk |
| High-risk group | The group contains any of the following factors: T1, high grade, CIS (including concurrent CIS) |
| Highest-risk group | The group is further defined as a highest-risk group that includes the following factors:<br>1. T1 high grade with any of the following factors<br>o Concomitant bladder CIS or prostatic urethral CIS<br>o Frequent or recurrent or ≥3 cm<br>o Variant histology or LVI<br>2. BCG-unresponsive NMIBC/CIS |

*Those that satisfy all factors; namely, relapses, multiple occurrences, Ta, low grade, ≥3 cm, are classified as high risk in EAU guidelines.*

3. Addition of clinical questions for the new tumor-visible techniques in non-muscle-invasive bladder cancer.
4. Inclusion of minimally invasive surgeries for muscle-invasive bladder cancer and **immune checkpoint inhibitors for locally advanced/metastatic muscle-invasive bladder cancer**[43].
    - Although gemcitabine plus cisplatin therapy is strongly recommended as the first-line treatment for patients with metastatic or unresectable MIBC, there were no established regimens for second-line systemic

treatment, and outcomes were unsatisfactory for many years. However, in a randomized controlled trial (KEYNOTE-045) of pembrolizumab versus other chemotherapy drugs in locally advanced or metastatic bladder cancer that recurred or progressed after first-line chemotherapy, the median overall survival was 10.3 months and 7.4 months in the patient groups receiving pembrolizumab and other chemotherapy, respectively. The primary endpoint showed superiority in the pembrolizumab-treated group[43].

- There was a strong push stating that "pembrolizumab is recommended for bladder cancer that has recurred or progressed after first-line platinum combination chemotherapy or has recurred or metastasized prior to or within 12 months after completion of neoadjuvant or adjuvant platinum combination chemotherapy (recommendation level 1, certainty of evidence A)." However, the efficacy of immune checkpoint inhibitors is limited to their overall response rate (21.1% in intention-to-treat population and 20.0% in Japanese patients), and the absence of effective third-line treatments is an ongoing issue[43].
- Additionally, in select patients, multimodality bladder-sparing treatment that is a combination of TUR plus chemotherapy plus radiotherapy can be considered[43].
- The recommendation for multimodality bladder-sparing therapy was "to consider this as a treatment option for select patients" (recommendation level 2, certainty of evidence C). Although patients for whom radical cystectomy is not indicated because of underlying diseases, such as the elderly, those with hepatic/respiratory/cardiac insufficiency or instances wherein the patient does not wish to undergo the procedure, there is a need to decide the treatment after obtaining sufficient informed consent[43].

5. Overview chapter of the histological variant of urothelial cancer and rare cancers of the bladder.
6. Recommendation of follow up in non-muscle-invasive bladder cancer and muscle-invasive bladder cancer.

### 1.4.2 Chinese Guidelines for Diagnosis and Treatment of Urothelial Carcinoma of Bladder (2018)

The National Health Commission of the People's Republic of China released in 2018 the Chinese guidelines for diagnosis and treatment of urothelial carcinoma of the bladder. The key treatment recommendations of the guideline are outlined in the following sections[44]:

### a) Treatment of NMIBC (Ta, T1 and Tis)

- **TURBT is the essential step in the treatment of NMIBC**: There are two objectives for TURBT, one is to remove all visible tumors, and the other is to remove the tumor tissue for pathological evaluation. The specimen should contain the bladder muscle layer and all visible tumors[44].
    - The efficacy of **transurethral bladder tumor laser surgery** is similar to TURBT.
    - **Photodynamic therapy** (PDT) is a treatment that combines laser and photosensitizer with a cystoscope. Singlet oxygen generated by action of laser will degenerate and necrotize tumor cells after the tumor cells taking up the photosensitizer. PDT is suitable for patients with bladder carcinoma in situ, repeated recurrence, intolerance of surgery, and failure of BCG intravesical therapy. The exact curative effect remains to be confirmed by multi-center clinical studies with large sample size.
    - Isolated solitary tumors with adequate margins and intradiverticular tumors with no carcinoma in situ in randomized biopsy are indications of **partial cystectomy**. Pelvic lymphadenectomy is recommended simultaneously when performing partial cystectomy.
    - **Radical cystectomy** is recommended for NMIBC patients with the following high-risk conditions: multiple and recurrent high-grade tumors, high-grade T1 tumors; high-grade tumors with carcinoma in situ, lymphatic vessel infiltration, micropapillary tumors or failure of BCG intravesical therapy. Concurrent chemoradiotherapy or TURBT + BCG intravesical therapy could be applied for patients who do not accept cystectomy[44].
- **Postoperative intravesical therapy for TURBT:**
    - **Intravesical chemotherapy is recommended for all NMIBC patients** to prevent planting of tumor cells within 24 h after surgery (immediate intravesical chemotherapy). However, patients with bladder perforation during TURBT or severe hematuria after surgery is prohibited[44].
    - The protocol of intravesical chemotherapy consists of **intravesical instillation of chemotherapeutic agent once a week for 4–8 weeks** (induction intravesical therapy) in 2–4 weeks after TURBT, and intravesical instillation with the same chemotherapeutic agent once a month for six to twelve months (maintenance intravesical therapy) [44].
    - Intravesical protocol was formulated based on the recurrence risk grouping[44]:

1. Patients with **low-risk** NMIBC: **immediate intravesical chemotherapy** should be performed, but *induction and maintenance therapy is not recommended*;
2. Patients with intermediate-risk NMIBC, it is generally recommended that **all immediate induction and maintenance intravesical therapy be performed**, and intravesical therapy with chemotherapeutic agent or BCG in induction and *maintenance phase may be optional*;
3. Patients with high-risk NMIBC, after **immediate intravesical chemotherapy, induction, and maintenance intravesical therapy with BCG is recommended in 2–4 weeks postoperatively**.

- Commonly used intravesical chemotherapy agents include pirarubicin (usually 30–50 mg each time), epirubicin (usually 50–80 mg), doxorubicin (usually 30–50 mg each time), hydroxycamptothecin (usually 10–20 mg each time), mitomycin (usually 20–60 mg each time), and gemcitabine (usually 1,000 mg each time) [44].
- In patients with high-risk NMIBC, intravesical therapy with **BCG** is usually performed with 60–120 mg of BCG dissolved in 50–60 mL normal saline, which should retain in bladder for about 2 h each time, and once a week for 6 weeks to induce immune response. In order to maintain and strengthen the efficacy of BCG, installation should be conducted once a week for 3 weeks on month 3, 6, 12, 18, 24 and 36 for 1 to 3 years (at least 1 year). For intermediate-risk NMIBC, 1/3 standard dose is recommended[44].

### b) Treatment of MIBC

- Treatments of patients with MIBC include radical cystectomy, partial cystectomy, neoadjuvant + radical cystectomy/radical cystectomy + adjuvant chemotherapy and bladder preserving comprehensive treatments[44].
- Neoadjuvant chemotherapy:
  - **Neoadjuvant chemotherapy combined with radical cystectomy is recommended for patients with cT2–T4a**[44].
  - **Adjuvant chemotherapy** is recommended for patients with pT3–pT4 or with lymph node metastasis. Without enough convincing evidence, then carboplatin-based chemotherapy could not be recommended for patients who couldn't cisplatin. An immediate radical cystectomy would be recommended for these patients[44].

- For patients with mild renal impairment, Fractional administration of cisplatin-based therapy (e.g., 35 mg/m$^2$ d 1, 2 or d 1, 8) may be considered. Although the program is safer, the relative efficacy is uncertain[44].

- **Neoadjuvant RT** for MIBC with a dose of 45–50 Gy results in pathologically complete response about 9%–34%[44].

### c) Treatment of metastatic urothelial carcinoma of bladder

- The main treatment approaches for metastatic urothelial carcinoma of bladder include systemic chemotherapy, chemotherapy combined with RT or RT alone[44].
- **Cisplatin-based combination chemotherapy** is the most important chemotherapy regimen for metastatic urothelial carcinoma of bladder[44].
- Urothelial cancerous cells are proved to be sensitive to chemotherapeutic agents such as platinum, gemcitabine, doxorubicin and paclitaxel[44].
- The **common first-line chemotherapy protocols include GC, DD-MVAC (modified MVAC enhancement regimen), MVAC, CMV** etc. The overall response rate can reach 50% for patients with metastatic disease while treated with platinum-containing combined chemotherapy[44].
- Multiple retrospective studies have confirmed that **resection of oligometastasis** in patients with metastatic bladder urothelial carcinoma is beneficial to prolong survival, especially in patients with good response to chemotherapy, isolated metastases, lung metastases or positive lymph node[44].
- Currently, **PD-1/PD-L1 immune checkpoint inhibitors** are main immunotherapy medicines, which include Atezolizumab, Durvalumab, Avelumab, Pembrolizumab and Nivolumab. These immune checkpoint inhibitors can serve as **second-line treatment** when patients with metastatic disease fail with platinum-based chemotherapy. Atezolizumab and Pembrolizumab can also be used as first-line treatment for those who could not tolerate platinum-based chemotherapy[44].

## 1.4.3 Society for Immunotherapy of Cancer (SITC) Clinical Practice Guideline of Immunotherapy for the Treatment of Urothelial Cancer (2021)

The Society for Immunotherapy of Cancer (SITC) released in 2021 clinical practice guidelines on immunotherapy for the treatment of urothelial cancer. The key treatment recommendations of the guideline are outlined in the following sections[15]:

### a) Diagnostic tests and biomarkers for urothelial cancer immunotherapy

- Currently, the evidence does not support routine use of biomarkers to guide BCG therapy in NMIBC. Cystoscopy (with biopsy/transurethral resection (TUR) of bladder tumor as needed), urine cytology, and periodic upper tract imaging should be used to detect recurrence.
- PD-L1 expression by IHC should be used to guide therapy in patients with metastatic urothelial carcinoma who are cisplatin-ineligible but eligible for carboplatin. Patients with PD-L1 negative tumors should receive carboplatin-based combination chemotherapy in this setting, while those with PD-L1 positive tumors can receive either immune checkpoint blockade or carboplatin-based chemotherapy (LE: 2). Clinical trial data otherwise does not currently support the use of PD-L1 expression to select patients with platinum-refractory disease for therapy.
- MSI-H/dMMR testing should be considered in patients with upper tract and bladder urothelial cancer, especially for patients of younger age and/ or with relevant personal or family history to rule out Lynch syndrome, which has implications for genetic counseling (LE: 3). The presence of MSI should not change the use of ICIs in advanced urothelial[15].

### d) Non-muscle invasive bladder cancer

- BCG is recommended for all eligible patients with high-risk NMIBC (including cases with CIS or papillary tumors) (LE: 1).
- BCG is also recommended for patients with intermediate-risk NMIBC. However, due to global shortages of BCG, and when BCG is unavailable, the panel recommends intravesical chemotherapy as the first-line therapy for intermediate-risk NMIBC (LE: 1).
- If patients experience recurrence of intermediate-risk NMIBC after a course of intravesical chemotherapy, the panel recommends BCG as second-line intravesical therapy (LE: 1).
- BCG is not recommended for the treatment of patients with low-risk NMIBC (LE: 1).
- BCG should not be administered to patients with active infection or gross hematuria, but BCG may be administered to patients experiencing asymptomatic bacteriuria.
- Best supportive measures should be employed to ensure that patients receive a full, adequate course of BCG.
- Pembrolizumab is approved for the treatment of high-risk BCG-unresponsive CIS with or without papillary tumors (LE: 2)[15].

### e) Muscle invasive bladder cancer

- The full results of CheckMate 274 are eagerly awaited to guide the potential use of immunotherapy in the adjuvant setting. Active investigation is ongoing into various neoadjuvant and adjuvant strategies, either as single agents or in combination with chemotherapy, radiotherapy, or novel agents[15].

### f) Advanced/Metastatic Urothelial Carcinoma

- The first-line standard of care for metastatic urothelial carcinoma is platinum-based chemotherapy. Atezolizumab or pembrolizumab can also be considered as first-line therapy for cisplatin-ineligible patients harboring PD-L1- positive tumors based on a companion assay, or for patients who cannot receive carboplatin (the latter in US only) (LE: 2). Combination ICI and chemotherapy treatment are not currently recommended for this setting.
- In patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy, avelumab maintenance therapy improves OS (LE: 2).
- Pembrolizumab is recommended for the treatment of patients with platinum-refractory metastatic urothelial carcinoma based on a significant OS benefit in a randomized phase III trial (LE: 2). Avelumab and nivolumab also have approvals in this setting[15].

### g) Patient Support and Quality of Life

- Urothelial cancer-specific outcome measures for BCG and ICI treatments should be developed, validated, and utilized as tools for patient navigation.
- ICI-specific measures should address a range of treatment protocols and QOL, including ICI alone, combinations with chemotherapy and/or radiation, or any other combination of therapies. Such measures should recognize the often-lengthy nature of bladder cancer treatment and surveillance, along with the potential for adverse effects to occur after the period of initial treatment.
- Practical patient information and education resources are needed for both BCG and ICI treatment. As more patients are treated with ICIs, written and digital educational materials are needed. Patient information resources in written and digital formats are available from bladder cancer and medical education organizations, in addition to materials provided by the providing clinic.
- There is now an opportunity to develop, study, and deploy digital/mobile technologies to increase patient awareness and reporting of BCG- and ICI-related AEs. Innovation in patient-provider communication and application of

technology to PRO/QOL communication could affect patient care for initial and follow-up of patients with urothelial cancer[15].

## 1.5 Systematic Reviews/Meta-analysis

A detailed search of PubMed and Cochrane databases for systematic reviews and meta-analysis on bladder management didn't yield any result more recent than the detailed previous guidelines. This is probably due to the fact that the treatment guidelines for bladder cancer are constantly being updated with the many clinical trials and treatment alternatives emerging in the market.

# Section 2.0 Drug Therapy

## 2.1 Alkylating agents

### 2.1.1 Carboplatin

**Table 19.** Carboplatin Drug Information

| Scientific Name<br>Carboplatin[45] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Carboplatin (Ebewe, Hospira), Cartinum |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, Carboplatin Ebewe, 2001; Cartinum, 2019; Carboplatin Hospira, 2020 |
| **FDA approved / off label** | Yes, 1989 |
| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2005 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Alkylating agent |
| **SFDA Registration Number (New)** | Carboplatin Ebewe:<br>2-355-01 (150mg); 3-355-01 (450mg)<br>Carboplatin Hospira:<br>15-5287-20 (150mg); 16-5287-20 (450mg)<br>Cartinum:<br>21-5223-19 (150mg); 22-5223-19 (450mg) |
| **ATC Code** | L01XA02 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | Target AUC 5 on day 1 every 3 weeks (in combination with gemcitabine) for 6 cycles unless disease progression or unacceptable toxicity occurred; may continue beyond 6 cycles if clinical benefit |
| **Dose (Pediatrics)** | N/A |

| | |
|---|---|
| **Adjustment** | Renal Impairment (Adult):<br>Dose determination with Calvert formula uses GFR and, therefore, inherently adjusts for kidney dysfunction. |
| **Prescribing edits*** | MD, ST, PE, CU, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | To be used with gemcitabine; To be used with antiemetics |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6 |
| **ST (Step Therapy)** | First and second-line treatment for locally advanced/metastatic bladder cancer in patients who are not eligible for cisplatin |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6 |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Decreased serum Ca, K, Mg, gastrointestinal pain, nausea and vomiting, anemia, leukopenia, thrombocytopenia, increased liver enzymes, asthenia, pain, decreased creatinine clearance<br>- Most serious: Ototoxicity, anemia, leukopenia, thrombocytopenia |
| **Drug Interactions*** | - Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene |

| | |
|---|---|
| | Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | Older adults |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy.<br>Causes harm to fetus, advice women on this treatment on the potential risks |
| **Lactation** | Carboplatin is present in breast milk. Breastfeeding is not recommended. |
| **Contraindications** | History of severe allergic reaction to carboplatin, cisplatin, other platinum-containing formulations, or any component of the formulation; should not be used in patients with severe bone marrow depression or significant bleeding |
| **Monitoring Requirements** | CBC (with differential and platelet count), serum electrolytes, serum creatinine and BUN, CrCl, LFTs; audiology evaluations (children <6 months of age); signs/symptoms of hypersensitivity reactions. |
| **Precautions** | - Bone marrow suppression<br>- GI toxicity<br>- Hepatic function abnormality<br>- Hypersensitivity<br>- Neurotoxicity<br>- Ototoxicity<br>- Renal toxicity<br>- Vision loss |

| | |
|---|---|
| **Black Box Warning** | - Experienced physician<br>- Bone marrow suppression<br>- Vomiting<br>- Hypersensitivity reactions |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for carboplatin in bladder cancer. This is probably because carboplatin use is limited to select patients who are not eligible for cisplatin-containing regimens. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Carboplatin**

Carboplatin is a first and second-line treatment option for locally advanced/metastatic bladder cancer in patients who are not eligible for cisplatin, in combination with gemcitabine.

There is no data issued by HTA bodies regarding its use.

### 2.1.2 Cisplatin

**Table 20.** Cisplatin Drug Information

| Scientific Name<br>Cisplatin[46] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Cisplatin (Ebewe, Hospira), Cipalin, Tinplat |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, Cisplatin Ebewe, 2001; Cisplatin Jazeera Pharmaceutical Industries (JPI), 2018; Cisplatin Hospira, 2019; Tinplat, 2019 |
| **FDA approved / off label** | Yes, 1978 |
| **EMEA approved / off label** | Yes, 1996 |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2004 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |

| | |
|---|---|
| **Drug Sub-class** | Alkylating agent |
| **SFDA Registration Number (New)** | Cisplatin Ebewe:<br>409222579 (10mg); 0409222580 (50mg)<br>Cipalin:<br>288-334-18 (10mg); 289-334-18 (25mg); 290-334-18 (50mg)<br>Cisplatin Hospira: 4-5287-19 (50mg)<br>Tinplat:<br>29-5223-19 (10mg); 30-5223-19 (50mg) |
| **ATC Code** | L01XA01 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | **Dose-dense MVAC**: 70 mg/m$^2$ on day 2 every 14 days until disease progression or unacceptable toxicity (with growth factor support).<br>**GC**: 70 mg/m$^2$ on day 2 every 28 days (in combination with gemcitabine) for up to 6 cycles. Split-dose cisplatin may be an option in select patients.<br>**MVAC**: 70 mg/m$^2$ on day 2 every 28 days until disease progression or unacceptable toxicity.<br>**Paclitaxel/cisplatin/gemcitabine** (PCG): 70 mg/m$^2$ on day 1 every 3 weeks for up to 6 cycles or until disease progression or unacceptable toxicity.<br>**CMV**: 100 mg/m$^2$ on day 1 every 21 days (in combination with methotrexate, vinblastine, and leucovorin) for 3 cycles |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult):<br>- CrCl ≥60 mL/mine: IV: No adjustment<br>- CrCl 50 to <60 mL/min: IV: 75% of the dose<br>- CrCl 40 to <50 mL/minute: IV: 50% of the dose |

| | |
|---|---|
| | - CrCl <40 mL/minute: Not recommended<br>- Hemodialysis/PD: Poorly dialyzable due to rapid and high degree of protein binding: 50% of the dose after dialysis<br>- CRRT/PIRRT: Use is not recommended<br>- Nephrotoxicity during treatment: Patients that develop AKI (SCr >2 times baseline) may require discontinuation of therapy |
| **Prescribing edits*** | MD, ST, PE, CU, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | To be used in combination with other chemotherapy agents; To be used with antiemetics, hyperhydration, and G-CSF support (in ddMVAC protocol) |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Total dose per cycle not to exceed 120 $mg/m^2$ |
| **ST (Step Therapy)** | First, second and later-line treatment of early stage MIBC and locally advanced/metastatic bladder cancer |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | Total dose per cycle not to exceed 120 $mg/m^2$ |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Neurotoxicity, nausea and vomiting, nephrotoxicity, anemia, leukopenia, thrombocytopenia, increased liver enzymes, ototoxicity |

| | |
|---|---|
| | - Most serious: Neurotoxicity, anemia, leukopenia, thrombocytopenia, hearing loss |
| **Drug Interactions*** | - Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | Renal Impairment |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy.<br>Causes harm to fetus, advice women on this treatment on the potential risks |
| **Lactation** | Cisplatin is present in breast milk. Breastfeeding is not recommended. |
| **Contraindications** | Severe hypersensitivity to cisplatin or any component of the formulation |
| **Monitoring Requirements** | Blood counts, serum creatinine, BUN, CrCl, and serum electrolytes<br>Neurological examination, consider audiometric and vestibular testing<br>Monitor closely for signs/symptoms of infection, hypersensitivity reactions, neuropathy, ocular toxicity, tumor lysis syndrome, and secondary malignancies |
| **Precautions** | - Bone marrow suppression |

| | |
|---|---|
| | - Extravasation<br>- GI toxicity<br>- Hypersensitivity<br>- Nephrotoxicity<br>- Neurotoxicity<br>- Ocular toxicity<br>- Ototoxicity<br>- Secondary malignancies<br>- Tumor lysis syndrome |
| **Black Box Warning** | - Myelosuppression<br>- Nausea and vomiting<br>- Nephrotoxicity<br>- Peripheral neuropathy |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for cisplatin in bladder cancer. This is probably because cisplatin is a long-standing standard of care for bladder cancer with a proven record of efficacy and safety. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Cisplatin**

Cisplatin is a first-line agent in the treatment of muscle-invasive bladder cancer in combination with methotrexate, vinblastine, and doxorubicin (ddMVAC) (preferred protocol for neoadjuvant/adjuvant therapy in early-stage disease and locally advanced/metastatic disease), or with gemcitabine (preferred protocol in locally advanced/metastatic disease). It is also used as a radiosensitizing agent used alone or in combination with 5-FU or paclitaxel in the first line setting of MIBC in select patients. Cisplatin can also be used in the second and subsequent-line setting of locally advanced/metastatic bladder cancer, part of the ddMVAC or GC regimens.

There is no data issued by HTA bodies regarding its use.

### 2.1.3 Ifosfamide

**Table 21.** Ifosfamide Drug Information

| Scientific Name<br>Ifosfamide[47] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Holoxan |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, Holoxan 1987 |
| **FDA approved / off label** | Yes, 1988 |
| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2004 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Alkylating agent (Nitrogen mustard) |
| **SFDA Registration Number (New)** | 38-15-87 (Holoxan 500 mg)<br>39-16-87 (Holoxan 1g)<br>40-16-87 (Holoxan 2g) |
| **ATC Code** | L01AA06 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Powder for concentrate for solution for infusion |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | 1,500 mg/m$^2$/day for 5 days every 3 weeks (with mesna) until disease progression |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult):<br>- CrCl ≥50 mL/min: No adjustment necessary<br>- CrCl <50 mL/min: Use is not recommended<br>- Hemodialysis: Use is not recommended<br>Hepatic Impairment (Adult):<br>- Bilirubin >3 mg/dL: Administer 25% of dose |

| | |
|---|---|
| **Prescribing Edits*** | MD, ST, CU, PE, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | To be used in combination with doxorubicin and gemcitabine; To be used with antiemetics; To be used with MESNA |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum daily dose 3000 mg/$m^2$ |
| **ST (Step Therapy)** | First, second, and subsequent line treatment of locally advanced/metastatic bladder cancer in patients ineligible for (or who relapsed on) cisplatin-containing therapy |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 3000 mg/$m^2$ |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Alopecia, nausea and vomiting, gross hematuria, hematuria, bone marrow depression, central nervous system toxicity (including neurotoxicity: aphasia, ataxia, cerebellar syndrome, coma, encephalopathy, extrapyramidal reaction, hallucination, motor dysfunction, muscle spasm, myoclonus, peripheral neuropathy, psychotic reaction, seizure, tremor)<br>- Most serious: Encephalopathy, febrile neutropenia, infection |
| **Drug Interactions*** | - Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, |

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|---|---|
| | Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | Older adults, pediatrics |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy.<br>Fetal growth retardation and neonatal anemia have been reported with exposure to ifosfamide |
| **Lactation** | Ifosfamide is present in breast milk. Breastfeeding is not recommended during ifosfamide treatment |
| **Contraindications** | Known hypersensitivity to ifosfamide or any component of the formulation; urinary outflow obstruction |
| **Monitoring Requirements** | CBC with differential, urine output, urinalysis (for erythrocytes prior to each dose), liver function, and renal function tests<br>Monitor for signs/symptoms of neurotoxicity, pulmonary toxicity, urotoxicity/hemorrhagic cystitis, and secondary malignancies |
| **Precautions** | - Bone marrow suppression<br>- Cardiotoxicity<br>- CNS Toxicity<br>- Hemorrhagic cystitis<br>- Hepatic effects<br>- Hypersensitivity |

| | |
|---|---|
| | - Infection<br>- Pulmonary Toxicity<br>- Renal toxicity<br>- Secondary malignancies<br>- Wound healing<br>- Radiation therapy: Use with caution |
| **Black Box Warning** | - Bone marrow suppression<br>- CNS toxicity<br>- Hemorrhagic cystitis<br>- Nephrotoxicity |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for ifosfamide in bladder cancer. This is probably because ifosfamide is only used as a later-line treatment option in patients with relapsed disease. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Ifosfamide**

In bladder cancer, ifosfamide is a first and second, and later line agent in the treatment of locally advanced/metastatic disease in patients who are not eligible (or who received in the first-line setting) for platinum-containing therapy, in combination with doxorubicin/gemcitabine.

There is no data issued by HTA bodies regarding its use.

## 2.2 Antimicrotubular Agents

### 2.2.1 Docetaxel

**Table 22.** Docetaxel Drug Information

| Scientific Name<br>Docetaxel[48] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Docetaxel Ebewe; Docetaxel SPC; Docadex; Taxotere; Docetaxel Accord; Tadoxel; Docetaxel Venus |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, 2017 |

| | |
|---|---|
| **FDA approved / off label** | Yes, 1998 |
| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2005 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Antimicrotubule, Taxane derivative |
| **SFDA Registration Number (New)** | Docetaxel Ebewe 10 mg/mL:<br>56-355-17 (80 mg); 55-355-17 (20 mg)<br>Docetaxel SPC 20 mg/mL: 5-5171-18 (80mg)<br>Docadex 20 mg/mL:<br>8-5251-20 (80mg); 2-5251-19 (20mg)<br>Taxotere 20 mg/mL:<br>1-5079-20 (20mg); 2-5079-20 (80mg); 3-5079-20 (160mg)<br>Docetaxel Accord 20 mg/mL:<br>2-5579-21 (20mg); 3-5579-21 (80mg); 4-5579-21 (160mg)<br>Tadoxel 20 mg/mL:<br>0206210761 (20mg); 0206210762 (80mg)<br>Docetaxel Venus 20 mg/mL :<br>2405233720 (20mg); 2405233721 (80mg) |
| **ATC Code** | L01CD |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | **Bladder cancer, advanced or metastatic**: 100 mg/m$^2$ every 3 weeks until disease progression or unacceptable toxicity or 35 mg/m$^2$ on days 1 and 8 of a 21-day cycle (in combination with gemcitabine and cisplatin) for at least 6 cycles or until disease progression or unacceptable toxicity. |

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| | **Bladder cancer, non–muscle invasive, refractory:**<br>*Single-agent docetaxel:* **Intravesicular instillation:** 75 mg per 100 mL NS; retain for 2 hours once weekly for 6 weeks during induction, followed 3 months later by 75 mg per 100 mL NS once a month for up to 9 maintenance treatments.<br>*Docetaxel/gemcitabine:* **Intravesical instillation:** 37.5 mg per 50 mL NS; retain for 1 to 2 hours once weekly (gemcitabine is administered and dwelled for 1 to 1.5 hours, followed by docetaxel) for 6 weeks during induction, followed by once-monthly maintenance treatments for up to 24 months. |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Hepatic Impairment (Adult):<br>- AST/ALT >2.5 to ≤5 times ULN and alkaline phosphatase ≤2.5 times ULN: Administer 80% of dose.<br>- AST/ALT >1.5 to ≤5 times ULN and alkaline phosphatase >2.5 to ≤5 times ULN: Administer 80% of dose.<br>- AST/ALT >5 times ULN and /or alkaline phosphatase >5 times ULN: Discontinue docetaxel. |
| **Prescribing edits*** | MD, ST, PE, CU, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | To be used with antiemetics |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Daily dose not to exceed 75 mg/$m^2$ |
| **ST (Step Therapy)** | Second and later-line treatment of locally advanced/metastatic bladder cancer in patients who previously received cisplatin and/or checkpoint inhibitor therapy. |

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|---|---|
| | First-line treatment of MIBC in combination with RT in select patients |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 75 $mg/m^2$ |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Alopecia, dermatological reactions, nails diseases, fluid retention, diarrhea, nausea and vomiting, anemia, leukopenia, neutropenia, thrombocytopenia, increased AST/ALT, hypersensitivity, infection, central nervous system toxicity, asthenia, myalgia, fever, pulmonary disease<br>- Most serious: Febrile neutropenia |
| **Drug Interactions*** | - Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: Anthracyclines, Coccidioides immitis Skin Test, COVID-19 Vaccine, CYP3A4 Inhibitors (Strong), Deferiprone, Denosumab, Dronedarone, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Platinum Derivatives, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, |

| | |
|---|---|
| | Sipuleucel-T, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy |
| **Lactation** | It is not known if docetaxel is present in breast milk. Breastfeeding is not recommended during treatment and for 1 week after the last docetaxel dose. |
| **Contraindications** | History of severe hypersensitivity to docetaxel or any component of the formulation; severe hypersensitivity to other medications containing polysorbate 80; neutrophil count <1,500/$mm^3$. |
| **Monitoring Requirements** | - CBC with differential, LFTs (bilirubin, ALT, AST, alkaline phosphatase), renal function.<br>- Pregnancy status<br>- Monitor for hypersensitivity reactions<br>- Monitor for signs/symptoms of neurosensory symptoms, GI toxicity, cutaneous reactions or severe skin toxicity, visual impairment, fluid retention, epiphora, canalicular stenosis, tumor lysis syndrome, and second primary malignancies.<br>- Prompt comprehensive ophthalmic exam if vision impairment occurs. |
| **Precautions** | - Bone marrow suppression<br>- Cutaneous reactions<br>- Extravasation<br>- Fluid retention<br>- GI toxicity<br>- Hypersensitivity<br>- Neurosensory symptoms<br>- Ocular adverse effects<br>- Secondary malignancies<br>- Tumor lysis syndrome<br>- Weakness |

| | |
|---|---|
| **Black Box Warning** | - Increased mortality<br>- Hepatic impairment<br>- Neutropenia<br>- Hypersensitivity<br>- Fluid retention |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for docetaxel in bladder cancer. This is probably because docetaxel is a later-line option in advanced disease in patients not eligible for cisplatin-containing therapy. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Docetaxel**

Docetaxel is a second and later-line agent in the treatment of locally advanced/metastatic bladder cancer in patients who previously received cisplatin and/or checkpoint inhibitor therapy. It is also used as a radiosensitizing agent in the first line setting of MIBC. There is no data issued by HTA bodies regarding its use.

### 2.2.2 Paclitaxel

**Table 23.** Paclitaxel Drug Information

| Scientific Name<br>Paclitaxel[49] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Anzatax, Ebetaxel, Rotub |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, Anzatax 1998; Ebetaxel 2006; Rotub 2018 |
| **FDA approved / off label** | Yes, 1998 |
| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2005 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Antimicrotubule, Taxane derivative |
| **SFDA Registration Number (New)** | Anzatax: |

| | |
|---|---|
| | 4-5669-22 (30 mg); 5-5669-22 (150 mg)<br>Ebetaxel:<br>33-355-06 (300mg); 34-355-06 (150mg); 35-355-06 (100mg); 33-355-06 (30mg)<br>Rotub:<br>1-5190-18 (30mg); 2-5190-18 (100mg); 3-5190-18 (150mg); 4-5190-18 (300mg) |
| **ATC Code** | L01CD01 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | *Paclitaxel/gemcitabine regimens:* 150 mg/m$^2$ every 2 weeks **or** 200 mg/m$^2$ over 1 hour every 3 weeks for 6 cycles **or** 175 mg/m$^2$ over 3 hours once every 3 weeks for a maximum of 6 cycles.<br>*Paclitaxel/cisplatin/gemcitabine (PCG) regimen:* 80 mg/m$^2$ on days 1 and 8 every 3 weeks for up to 6 cycles or until disease progression or unacceptable toxicity.<br>*Single-agent paclitaxel:* 80 mg/m$^2$ once weekly until disease progression or unacceptable toxicity.<br>*Chemoradiation (muscle invasive bladder cancer)*:<br>**Induction**: 50 mg/m$^2$ on days 1, 8, and 15 (in combination with cisplatin and radiation), followed by consolidation chemoradiation (in patients who achieved a complete response) of 50 mg/m$^2$ on days 1 and 8 (in combination with cisplatin and radiation).<br>**Adjuvant chemotherapy** (following chemoradiation and surgery): 50 mg/m$^2$ on days 1 and 8 (in combination with gemcitabine and cisplatin) every 3 weeks for 4 cycles. |

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|---|---|
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Hepatic Impairment (Adult):<br>24-hour infusion:<br>- Transaminases <2 times upper limit of normal (ULN) and bilirubin level ≤1.5 mg/dL: 135 mg/m$^2$<br>- Transaminases 2 to <10 times ULN and bilirubin level ≤1.5 mg/dL: 100 mg/m$^2$<br>- Transaminases <10 times ULN and bilirubin level 1.6 to 7.5 mg/dL: 50 mg/m$^2$<br>- Transaminases ≥10 times ULN or bilirubin level >7.5 mg/dL: Avoid use<br>3-hour infusion:<br>- Transaminases <10 times ULN and bilirubin level ≤1.25 times ULN: 175 mg/m$^2$<br>- Transaminases <10 times ULN and bilirubin level 1.26 to 2 times ULN: 135 mg/m$^2$<br>- Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN: 90 mg/m$^2$<br>- Transaminases ≥10 times ULN or bilirubin level >5 times ULN: Avoid use |
| **Prescribing edits*** | AGE, MD, ST, PE, CU, QL |
| **AGE (Age Edit)** | Not used in pediatrics |
| **CU (Concurrent Use)** | To be used as a single agent or in combination with chemotherapy (gemcitabine or cisplatin)<br>To be used with antiemetics |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Daily dose not to exceed 250 mg/m$^2$ |
| **ST (Step Therapy)** | First-line treatment of locally advanced/metastatic bladder cancer in |

| | |
|---|---|
| | patients not eligible to cisplatin-containing therapy<br>Second and later-line treatment of locally advanced/metastatic bladder cancer in patients who previously received cisplatin and/or checkpoint inhibitor therapy.<br>First-line treatment of MIBC in combination with RT in select patients |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 250 $mg/m^2$ |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: ECG abnormality, edema, hypotension, alopecia, diarrhea, nausea and vomiting, stomatitis, anemia, hemorrhage, leukopenia, neutropenia, thrombocytopenia, increased AST/ALT, hypersensitivity, infection, injection-site reaction, asthenia peripheral neuropathy, arthralgia), myalgia, fever<br>- Most serious: Bradycardia, cardiac arrhythmia, encephalopathy, tonic-clonic seizure, hemorrhage, leukopenia, neutropenia |
| **Drug Interactions*** | - Risk X: Abrocitinib, Atazanavir, Baricitinib, BCG Products, Brivudine, Bromperidol, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) |

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|---|---|
| | - Risk D: Amifostine, Anthracyclines, Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Obinutuzumab Palifermin, Platinum Derivatives, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | Older adults, Hepatic impairment |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy |
| **Lactation** | Paclitaxel is present in breast milk. Breastfeeding is not recommended during paclitaxel treatment |
| **Contraindications** | Hypersensitivity to paclitaxel, polyoxyl 35/polyoxyethylated castor oil (Cremophor EL), or any component of the formulation<br>Treatment of solid tumors in patients with baseline neutrophil counts <1,500/$mm^3$; treatment of Kaposi sarcoma in patients with baseline neutrophil counts <1,000/$mm^3$. |
| **Monitoring Requirements** | CBC with differential and platelet count (frequently), liver and kidney function<br>Monitor for hypersensitivity reactions, vital signs (frequently during the first hour of infusion), and continuous cardiac monitoring (patients with conduction abnormalities).<br>Monitor for signs/symptoms of peripheral neuropathy. Monitor infusion site during infusion. |
| **Precautions** | - Cardiovascular effects<br>- Extravasation<br>- Hepatic impairment |
| **Black Box Warning** | - Experienced physician |

| | |
|---|---|
| | - Hypersensitivity<br>- Bone marrow suppression |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for paclitaxel in bladder cancer. This is probably because paclitaxel is not widely used in bladder cancers, and rather considered a later-line option in patients not eligible to (or who received) cisplatin-containing therapy. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Paclitaxel**

Paclitaxel is a first-line treatment alternative (in combination with gemcitabine) for patients with locally advanced/metastatic bladder cancer who are not eligible for cisplatin-containing therapy. Paclitaxel is also a second and later-line agent in the treatment of locally advanced/metastatic bladder cancer in patients who previously received cisplatin and/or checkpoint inhibitor therapy (as a single agent or in combination with gemcitabine). It is also used as a radiosensitizing agent in the first line setting of MIBC (as a single agent or in combination with cisplatin).

There is no data issued by HTA bodies regarding its use.

### 2.2.3 Vinblastine

**Table 24.** Vinblastine Drug Information

| Scientific Name<br>Vinblastine[50] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Vinblastine sulfate |
| **SFDA approved Indication** | Yes, Vinblastine sulfate, 2020 |
| **FDA approved / off label** | Yes, 1962 |
| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2004 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Antimicrotubule, Vinca Alkaloid |
| **SFDA Registration Number (New)** | 18-5287-20 |
| **ATC Code** | L01CA01 |

| | |
|---|---|
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | **Dose-dense MVAC:** 3 mg/m$^2$ on day 1 or 2 every 14 days (with growth factor support) for 3-4 cycles (neoadjuvant), or 6 cycles, or until disease progression or unacceptable toxicity (locally advanced/metastatic)<br>**MVAC regimen**: 3 mg/m$^2$ on days 2, 15, and 22 every 28 days for 3 (neoadjuvant) or 6 (locally advanced/metastatic) cycles.<br>**CMV regimen**: 4 mg/m$^2$ on days 1 and 8 every 21 days for 3 cycles |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Hepatic Impairment (Adult):<br>- Serum bilirubin 1.5 to 3 mg/dL or transaminases 2 to 3 times ULN: Administer 50% of dose<br>- Serum bilirubin >3 times ULN: Avoid use. |
| **Prescribing edits*** | CU, MD, QL, PE |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | To be used with other chemotherapy agents (methotrexate/doxorubicin/cisplatin); To be used with antiemetics and G-CSF support (in ddMVAC protocol) |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Daily dose not to exceed 3 mg/m$^2$ |
| **ST (Step Therapy)** | First, second, and later line treatment of muscle invasive, locally advanced, or metastatic bladder cancer |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |

| | |
|---|---|
| **Maximum Daily Dose Adults*** | 3 $mg/m^2$ |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety**<br>High alert medication: NOT for intrathecal use: For IV use only. Administration by other routes may result in death. ISMP strongly recommends dispensing vinblastine in a minibag and NOT in a syringe | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Anemia, bone marrow depression, granulocytopenia, hemolytic uremic syndrome, leukopenia, constipation, alopecia, jaw pain, ostealgia, malaise, tumor pain, hypertension<br>- Most serious: neurotoxicity, thrombotic thrombocytopenic purpura |
| **Drug Interactions*** | - Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy<br>Women who are pregnant or become pregnant must be advised of the potential hazard to the fetus |

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|---|---|
| **Lactation** | It is not known if vinblastine is present in breast milk. A decision should be made to discontinue vinblastine or breastfeeding, taking into account the importance of treatment to the mother |
| **Contraindications** | Significant granulocytopenia (unless as a result of condition being treated); bacterial infection |
| **Monitoring Requirements** | CBC with differential and platelet count, serum uric acid, hepatic function tests. Monitor for signs/symptoms of infections (particularly if WBC <2,000/mm3). Monitor infusion site. |
| **Precautions** | - Bone marrow suppression<br>- Extravasation<br>- Gastrointestinal toxicity<br>- Neurotoxicity<br>- Pulmonary toxicity<br>- Ischemic heart disease: Use with caution |
| **Black Box Warning** | - Experienced physician<br>- Extravasation<br>- Appropriate administration |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for vinblastine in bladder cancer. This is probably because vinblastine is a long-standing standard of care for bladder cancer with a proven record of efficacy and safety. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Vinblastine**

Vinblastine is a first-line agent in the treatment of muscle-invasive bladder cancer in combination with methotrexate, doxorubicin, and cisplatin (ddMVAC) (preferred protocol for neoadjuvant/adjuvant therapy in early-stage disease and locally advanced/metastatic disease). Vinblastine can also be used in the second and subsequent-line setting of locally advanced/metastatic bladder cancer, part of the ddMVAC regimen.

There is no data issued by HTA bodies regarding its use.

## 2.3 Antimetabolites

### 2.3.1 5-Fluorouracil (5-FU)

**Table 25.** 5-Fluorouracil Drug Information

| Scientific Name<br>5-Fluorouracil[51] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Fluorouracil (Hospira); Fluorouracil Ebewe; Floryl |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, 1997 |
| **FDA approved / off label** | Yes, 1962 |
| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2004 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Antimetabolite (Pyrimidine Analog) |
| **SFDA Registration Number (New)** | Fluorouracil Hospira: 22-237-97 (500mg)<br>Fluorouracil Ebewe:<br>16-355-01 (500mg); 18-355-01 (1g)<br>42-355-07 (5g)<br>Floryl:<br>15-5223-19 (5g); 16-5223-19 (1g);<br>17-5223-19 (500mg); 18-5223-19 (250mg) |
| **ATC Code** | L01BC02 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | MIBC: 500 mg/m$^2$/day continuous infusion during radiation therapy fractions 1 to 5 and 16 to 20 (total dose/each 5-day course is 2,500 mg/m$^2$; in combination with mitomycin and radiation therapy) |

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| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal/Hepatic Impairment (Adult): There are no dosage adjustments provided in the manufacturer's labeling; use with caution. |
| **Prescribing edits*** | MD, ST, PE, CU, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | To be used with concurrent RT and Mitomycin C; To be used with antiemetics |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Daily dose not to exceed 1000 mg/m$^2$ |
| **ST (Step Therapy)** | First and second-line treatment of MIBC in select patients as a radiosensitizing agent |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | Daily dose not to exceed 1000 mg/m$^2$ |
| **Maximum Daily Dose Pediatrics*** | Daily dose not to exceed 1000 mg/m$^2$ |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia, neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever<br>- Most serious: hemolytic-uremic syndrome |
| **Drug Interactions*** | - Risk X: Abrocitinib, Allopurinol, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Nadofaragene |

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| | Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy |
| **Lactation** | It is not known if fluorouracil is present in breast milk. The manufacturer recommends a decision be made to discontinue breastfeeding or to discontinue fluorouracil, taking into account the importance of treatment to the breastfeeding patient. |
| **Contraindications** | N/A |
| **Monitoring Requirements** | CBC with differential and platelet count, renal function tests, LFTs, INR, and prothrombin time (in patients receiving concomitant coumarin-derivative anticoagulants).<br>Monitor for signs/symptoms of palmar-plantar erythrodysesthesia syndrome, cardiotoxicity, CNS toxicity, stomatitis, diarrhea, and hyperammonemic encephalopathy.<br>Promptly evaluate any symptoms suggestive of cardiotoxicity. Consider monitoring ECG in patients on |

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| | concomitant QT prolonging medications. |
| **Precautions** | - Bone marrow suppression<br>- Cardiotoxicity<br>- GI toxicity<br>- Hand-foot syndrome<br>- Hyperammonemic encephalopathy<br>- Neurotoxicity<br>- Dihydropyrimidine dehydrogenase deficiency<br>- Warfarin |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for 5-FU in bladder cancer. This is probably because 5-FU's use is limited to patients undergoing RT (which is not the preferred standard of care). Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – 5-FU**

In bladder cancer, 5-FU is used in the first line setting of MIBC in combination with RT and Mitomycin C as a radiosensitizing agent (preferred option in this setting).

There is no data issued by HTA bodies regarding its use.

### 2.3.2 Gemcitabine

**Table 26.** Gemcitabine Drug Information

| Scientific Name<br>Gemcitabine[52] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Gemcitabine Ebewe, Citabol, Gemcitabine Jazeera, Gemzar, Citarox, Gebtin, Gemcitabine Glenmark, Gemcitabine BOS |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, 2011 |
| **FDA approved / off label** | Yes, 1998 |

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| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2006 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Antimetabolite (Pyrimidine Analog) |
| **SFDA Registration Number (New)** | Gemcitabine Ebewe:<br>48-355-11 (1g); 50-355-11 (200mg)<br>Citabol: 3-796-15 (1g); 4-796-15 (200mg)<br>Gemcitabine Jazeera:<br>0712222984 (200mg); 0712222985 (1g)<br>Gemzar:1-5396-19 (200mg)<br>Citarox: 1-5251-19 (200mg); 10-5251-20 (1g)<br>Gebtin: 72-5286-20 (1g); 73-5286-20 (200mg)<br>Gemcitabine Glenmark:<br>1-5438-20 (200mg); 2-5438-20 (1000mg)<br>Gemcitabine BOS: 0301221548 (1g) |
| **ATC Code** | L01BC05 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Powder for concentrate for solution for injection |
| **Route of Administration** | Intravenous, Intravesical instillation |
| **Dose (Adult) [DDD]*** | *Advanced or metastatic:* 1,000 mg/m$^2$ over 30 to 60 minutes days 1, 8, and 15; repeat cycle every 28 days (in combination with cisplatin or carboplatin or paclitaxel/cisplatin [PCG]) for up to 6 cycles or until disease progression or unacceptable toxicity<br>*Transitional cell carcinoma (refractory):* **Intravesical instillation:** 2,000 mg (in 100 mL NS; retain for 1 hour) twice weekly for 3 weeks; repeat cycle every 4 weeks for at least 2 cycles |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult): |

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| | - CrCl ≥30 mL/min: No adjustment necessary<br>- CrCl <30 mL/min: No adjustment necessary. However, increased risk of hematologic toxicity<br>- Hemodialysis/ PD/CRRT/ PIRRT: No dosage adjustment necessary<br>Hepatic Impairment (Adult):<br>- Transaminases elevated (with normal bilirubin or total bilirubin <1.6 mg/dL): No dosage adjustment necessary<br>- Serum bilirubin >1.6 mg/dL: Use initial dose of 800 mg/m$^2$; may escalate if tolerated<br>- Total bilirubin ≥1.6 mg/dL: May begin with 80% of the usual gemcitabine dose and increase the dose if tolerated |
| **Prescribing edits*** | MD, ST, PE, CU, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | Can be used as a single agent or in combination with chemotherapy (cisplatin or ifosfamide/doxorubicin)<br>To be used with antiemetics |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum dose per day 1000 mg/m$^2$ |
| **ST (Step Therapy)** | First-line treatment of NMIBC (intravesical therapy)<br>First, second and later-line treatment of early stage MIBC and locally advanced/metastatic bladder cancer |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 1000 mg/m$^2$ |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |

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|---|---|
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia, neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever<br>- Most serious: hemolytic-uremic syndrome |
| **Drug Interactions*** | - Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | Older adults, radiation therapy recipients |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy |
| **Lactation** | It is not known if gemcitabine is present in breast milk. Breastfeeding is not recommended during treatment and for at least 1 week after the last gemcitabine dose. |
| **Contraindications** | Known hypersensitivity to gemcitabine or any component of the formulation |

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| **Monitoring Requirements** | CBC with differential and platelet count; LFTs, renal function, electrolytes, Pulmonary function<br>Monitor for signs/symptoms of capillary leak syndrome, hemolytic uremic syndrome, hepatotoxicity, hypersensitivity, posterior reversible encephalopathy syndrome, and pulmonary toxicity. |
| **Precautions** | - Bone marrow suppression<br>- Capillary leak syndrome<br>- Hemolytic uremic syndrome<br>- Hepatotoxicity<br>- Hypersensitivity<br>- Posterior reversible encephalopathy syndrome<br>- Pulmonary toxicity |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for gemcitabine in bladder cancer. This is probably because gemcitabine is a long time well-established standard of care in disease management. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Gemcitabine**

Gemcitabine is a first line treatment for non-muscle invasive bladder cancer, as an intravesical therapy post TURBT then for a 6-weeks induction therapy course (preferred agent).

Gemcitabine is a first-line agent in the treatment of muscle-invasive bladder cancer in combination with cisplatin (GC: preferred protocol in locally advanced/metastatic disease) or in combination with doxorubicin/ifosfamide in locally advanced/metastatic disease in patients ineligible for cisplatin. It is also used as a radiosensitizing agent (low-dose gemcitabine) in the first-line setting of MIBC in select patients. Gemcitabine can also be used in the second-line setting of locally advanced/metastatic bladder cancer, part of the GC regimen or part of the

ifosfamide/doxorubicin/gemcitabine protocol in patients ineligible (or who previously received) platinum-containing therapy.

There is no data issued by HTA bodies regarding its use.

### 2.3.3 Methotrexate (MTX)

**Table 27.** Methotrexate Drug Information

| Scientific Name<br>Methotrexate[53] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Methotrexate (Pfizer), Methotrexate Ebewe, Methotrexate Hospira, Mexat, Metoject, Mizotra |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, 1997 |
| **FDA approved / off label** | Yes, 1972 |
| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2008 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Antimetabolite (Antifolate) |
| **SFDA Registration Number (New)** | MTX (Pfizer): 25mg/mL<br>8-5287-20 (50mg); 7-5287-20 (500mg)<br>MTX (Ebewe): 100 mg/mL<br>9-355-01 (500mg); 10-355-01 (5g);<br>12-355-01 (1g)<br>MTX (Ebewe) 10mg/mL: 8-355-01 (50mg)<br>MTX Hospira: 100mg/mL: 27-237-97 (1g)<br>Mexat: 25mg/mL<br>2-5223-18 (50mg); 3-5223-18 (500mg);<br>4-5223-18 (1g)<br>Metoject: 50mg/mL pre-filled syringe<br>1511222900; 1511222901; 1511222902;<br>1511222903 (50mg); 9-463-19<br>Mizotra: (25mg/mL)<br>1509211053 (50mg) |
| **ATC Code** | L01BC05 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |

| Drug Information | |
|---|---|
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | **Dose-dense MVAC**: 30 mg/m$^2$ on day 1 every 14 days (with growth factor support) for 3-4 cycles (neoadjuvant), or 6 cycles, or until disease progression or unacceptable toxicity (locally advanced/metastatic)<br>**MVAC regimen**: 30 mg/m$^2$ on days 1, 15, and 22 every 28 days for 3 (neoadjuvant) or 6 (locally advanced/metastatic) cycles.<br>**CMV:** 30 mg/m$^2$ on days 1 and 8 every 21 days for 3 cycles |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult):<br>- CrCl >50 mL/minute: No dose adjustment necessary.<br>- CrCl 10 to 50 mL/minute: Administer 50% of dose.<br>- CrCl <10 mL/minute: Avoid use.<br>- Hemodialysis/PD: Cases of methotrexate toxicity (including death) have been reported, even at low methotrexate doses. Avoid use<br>- CRRT: Administer 50% of the dose<br>Hepatic Impairment (Adult/Pediatric):<br>- Bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose.<br>- Bilirubin >5 mg/dL: Avoid use.<br>- Hepatotoxicity during treatment: Withhold, consider a reduced dose, or discontinue methotrexate as appropriate.<br>Renal Impairment (Pediatric):<br>*Refer to specific protocols* |
| **Prescribing edits*** | MD, ST, PE, CU, QL |

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| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | To be used in combination with other chemotherapy agents (ddMVAC protocol)<br>To be used with antiemetics and G-CSF support (in ddMVAC protocol)<br>To be used with Folinic acid rescue, hyperhydration, and urine alkalinization (for high dose protocol, not applicable in bladder cancer) |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum dose 20 g per day (or per cycle) |
| **ST (Step Therapy)** | First, second and later-line treatment of early stage MIBC and locally advanced/metastatic bladder cancer |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | Maximum dose day (or per cycle 20 g) |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Diarrhea, nausea, oral metastatic urothelial carcinomaosal ulcer, vomiting, hepatic cirrhosis, increased liver enzymes, dizziness, fatigue, headache, cough<br>- Most serious: erythema multiforme, erythroderma, Stevens-Johnson syndrome, toxic epidermal necrolysis, life-threatening gastro-intestinal events, severe bone marrow depression with agranulocytosis, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, and thrombocytopenia, hepatic fibrosis, hepatic cirrhosis, life-threatening or |

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| | fatal infections, nephrotoxicity, encephalopathy, chronic interstitial pneumonitis |
| **Drug Interactions*** | - Risk X: Abrocitinib, Allopurinol, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category X |
| **Lactation** | Methotrexate and 7-hydroxymethotrexate are present in breast milk. Breastfeeding should be discontinued during treatment and for 1 week after the final methotrexate dose. |
| **Contraindications** | History of severe hypersensitivity to methotrexate or any component of the formulation; breastfeeding. |
| **Monitoring Requirements** | - CBC with differential and platelets, serum creatinine, BUN, LFTs |

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| | - Fluid and electrolyte status in patients with impaired methotrexate elimination; chest x-ray<br>- Pulmonary function test (if methotrexate-induced lung disease suspected)<br>- Monitor carefully for toxicities in patients with ascites, pleural effusion, decreased folate stores, renal impairment, and/or hepatic impairment |
| **Precautions** | - Infections<br>- Renal impairment<br>- Concurrent drug therapy issues: Nonsteroidal anti-inflammatory drugs, Proton Pump Inhibitors, Vaccines, Vitamins<br>- Benzyl alcohol and derivatives<br>- Administration schedules<br>- Intrathecal safety |
| **Black Box Warning** | - Intrathecal and high-dose therapy (use preservative-free formulations)<br>- Hypersensitivity<br>- Appropriate use<br>- Pregnancy<br>- Bone marrow suppression<br>- Renal impairment<br>- Hepatotoxicity<br>- Pneumonitis<br>- GI toxicity<br>- Secondary malignancy<br>- Tumor lysis syndrome<br>- Dermatologic toxicity<br>- Opportunistic infections<br>- Radiotherapy<br>- Experienced physician |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for methotrexate in bladder cancer. This is probably because methotrexate is a long-standing standard of care for bladder cancer with a proven record of efficacy and safety. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Methotrexate**

Methotrexate is a first-line agent in the treatment of muscle-invasive bladder cancer in combination with vinblastine, doxorubicin, and cisplatin (ddMVAC) (preferred protocol for neoadjuvant/adjuvant therapy in early stage disease and locally advanced/metastatic disease). Methotrexate can also be used in the second and subsequent-line setting of locally advanced/metastatic bladder cancer, part of the ddMVAC regimens.

There is no data issued by HTA bodies regarding its use.

## 2.4 Immune Checkpoint Inhibitors (ICIs)

### 2.4.1 Atezolizumab

**Table 28.** Atezolizumab Drug Information

| Scientific Name<br>Atezolizumab[54] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Tecentriq |
| **SFDA Classification** | Prescription |
| **SFDA Approved Indication** | Yes; 2017 |
| **FDA approved/off label** | Yes; May 2020 |
| **EMEA approved/off label** | Yes; November 2020 |
| **MHRA approved/off label** | Yes; date not available |
| **PMDA approved/off label** | Yes, 2022 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent, monoclonal antibody |
| **Drug Sub-Class** | Immune Checkpoint Inhibitor (PDL-1 Inhibitor) |
| **SFDA Registration Number (New)** | 285-24-17 |
| **ATC Code** | L01XC32 |

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| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution for injection |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | 1200 mg every 3 weeks |
| **Adjustment** | Renal impairment prior to treatment:<br>No dosage adjustment<br>Renal impairment during treatment:<br>• Grade 2/3: withhold and resume after resolution to grade 0/1<br>• Grade 4: permanently discontinue<br>Hepatic impairment prior to treatment:<br>No dosage adjustment<br>Hepatic impairment during treatment:<br>If no tumor involvement of the liver:<br>• AST/ALT increase to 3 up to 8 times ULN or total bilirubin increase by 1.5 up to 3 times ULN: withhold<br>• AST/ALT increase to more than 8 times ULN or total bilirubin increase by more than 3 times ULN: permanently discontinue<br>If tumor involvement of the liver:<br>• Baseline AST/ALT 1 up to 3 times ULN and increase to 5 up to 10 times ULN, or baseline AST/ALT 3 up to 5 times ULN and increase to 8 up to 10 times ULN: withhold and resume after resolution to grade 0/1<br>• AST/ALT increase to more than 10 times ULN or total bilirubin increase to more than 3 times ULN: permanently discontinue<br>Immune-mediated adverse reactions:<br>• Withhold atezolizumab for grade 3 immune-mediated adverse reactions, and resume after resolution to grade 0/1<br>• Permanently for grade 4 or recurrent grade 3 adverse reactions |

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| **Dosage Form** | Solution for injection |
| **Prescribing edits*** | MD, ST, PE, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | N/A |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum daily dose 1200 mg |
| **ST (Step Therapy)** | First-line treatment of locally advanced/metastatic UC in patients who are ineligible for cisplatin and whose tumors have a PD-L1 expression ≥ 5% (less preferred alternative) |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 1200 mg |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: increased ALTs, increased alkaline phosphatase, thrombocytopenia, leukopenia, anemia, hyperkalemia, hyponatremia, hypocalcemia<br>- Most serious: immune-mediated adverse reactions |
| **Drug Interactions*** | - Acetaminophen, antibiotics, corticosteroids, inhibitors of the proton pump: may diminish the therapeutic effect of anti-PD-L1 (risk C)<br>- Ketoconazole: hepatotoxic effect enhanced by anti-PD-L1 (risk C)<br>- Desmopressin: hyponatremic effect enhanced by anti-PD-L1 (risk C) |
| **Special Population** | N/A |
| **Pregnancy** | There is no data on the use of atezolizumab in pregnancy. Based on the mechanism of action, it can cause |

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| | fetal harm when administered to pregnant women. |
| **Lactation** | The potential for absorption and harm to the infant is unknown. It is advised not to breastfeed during treatment and for at least 5 months after the last dose. |
| **Contraindications** | Known hypersensitivity to the product or its components |
| **Monitoring Requirements** | At baseline and periodically during treatment:<br>- LFTs (AST/ALT/bilirubin)<br>- Serum creatinine<br>- Thyroid function<br>- Serum glucose<br>- CBC with differential<br>Pregnancy status<br>Signs and symptoms of immune-mediated adverse reactions<br>HBV screening prior to initiation (do not delay treatment for screening results) |
| **Precautions** | - Immune-mediated adverse reactions<br>- Cardiovascular toxicity<br>- Dermatologic toxicity<br>- Endocrinopathies (adrenal insufficiency, diabetes mellitus, thyroid disorders)<br>- Gastrointestinal adverse effects<br>- Hepatotoxicity<br>- Nephrotoxicity<br>- Infusion-related reactions<br>- Ocular toxicity<br>- Pulmonary toxicity |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

The table below lists the National Institute for Health and Care Excellence (**NICE**) and the Institute for Quality and Efficiency in Health Care (**IQWIG**) HTA review and recommendations of atezolizumab in urothelial carcinoma treatment options.

**Table 29.** Atezolizumab HTA Recommendations

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Atezolizumab | NICE[17,18] | 10/2021: Atezolizumab is **recommended**, within its marketing authorization, as an option for **untreated locally advanced or metastatic urothelial cancer** in adults whose tumors express **PD-L1 at a level of 5% or more** and when **cisplatin-containing chemotherapy is unsuitable**.<br>- Atezolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life (atezolizumab extends life by at least 3 months).<br>- The cost-effectiveness estimates are likely to be within what NICE considers an acceptable use of NHS resources. So, atezolizumab is recommended.<br>- The most plausible incremental cost-effectiveness ratios are below £50,000 per quality-adjusted life year.<br>06/2018: Atezolizumab is **recommended** as an option for treating **locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy**, only if atezolizumab is stopped at **2 years** of uninterrupted treatment or earlier if the disease progresses<br>- Treatment options for people whose disease has progressed after platinum-containing chemotherapy include docetaxel, paclitaxel or best supportive care.<br>- Evidence from 2 clinical trials (IMvigor210, IMvigor211), one of which compares atezolizumab directly with chemotherapy, suggests that atezolizumab is an effective |

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| | | treatment. According to clinical experts, the trial results compare favorably with their experience of current treatments for the disease.<br>- Atezolizumab **meets NICE's criteria to be considered a life-extending treatment** at the end of life.<br>- Although there are uncertainties in the economic model, the most plausible **cost effectiveness estimates for atezolizumab compared with taxanes are within the range NICE considers an acceptable use** of NHS resources. |
| Atezolizumab | IQWIG[19,20] | 03/2019: **Added benefit not proven** of atezolizumab versus chemotherapy in adult patients with locally advanced or metastatic urothelial carcinoma for whom cisplatin-containing chemotherapy is unsuitable and whose tumors have a PD-L1 expression ≥ 5%.<br>- The company identified no randomized controlled trials of direct comparison on the comparison of atezolizumab versus the appropriate comparator. The company identified 6 studies and used one arm from each of these studies for the benefit assessment. All studies investigated patients for whom cisplatin-based treatment is unsuitable according to the inclusion criteria of the studies.<br>- **The incomplete data situation allowed no adequate comparison between atezolizumab and carboplatin + gemcitabine**. In addition, conclusions on the added benefit based on a comparison of individual arms of different studies can only be drawn in the presence of very large effects due to the high uncertainty of results. There were no such effects for the relevant outcomes on overall survival, symptoms, health-related quality of life, as well as overall |

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| | | rates of AEs, SAEs, discontinuation due to AEs, and severe.<br>- **The preliminary results of the ongoing randomized controlled trial IMvigor130, which resulted in the restriction in the approval, support this assessment**.<br>12/2017: **Hint of considerable added benefit** of atezolizumab versus chemotherapy (vinflunine or platinum-based chemotherapy) in adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy.<br>- One relevant study (IMvigor211) was available for the benefit assessment.<br>- The IMvigor211 study was a randomized, open-label, active-controlled parallel-group study on the comparison of treatment with atezolizumab versus chemotherapy with vinflunine, paclitaxel or docetaxel. The study included adults who had received at least one prior platinum-containing chemotherapy for advanced or metastatic urothelial carcinoma.<br>- **There was no statistically significant difference between the treatment groups for the outcome "overall survival".** There was no hint of an added benefit of atezolizumab in comparison with vinflunine; an added benefit is therefore not proven.<br>- There were statistically significant differences in favor of atezolizumab for each of the outcomes "severe adverse events" and "discontinuation due to adverse events". This resulted in a **hint of lesser harm of atezolizumab** in comparison with vinflunine for each of the 3 outcomes. |

**Conclusion Statement – Atezolizumab**

The manufacturing company voluntarily withdrew the U.S indication of atezolizumab in the indication of urothelial carcinoma in accordance with the requirements of the FDA's Accelerated Approval Program following the results of the phase III IMvigor 130 trial. In that trial, atezolizumab plus chemotherapy did not meet the co-primary endpoint of overall survival compared with chemotherapy alone. NCCN still mentions atezolizumab as **a less preferred treatment option in the first-line setting of locally advanced/metastatic UC in patients who are ineligible for cisplatin and whose tumors have a PD-L1 expression ≥ 5%**.

In Europe, the European Medicine Agency (EMA) still maintains the indication for atezolizumab as a second-line agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior platinum containing chemotherapy, or as a first-line agent in patients who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥ 5%. It is therefore mentioned in the ESMO and EAU guidelines as a less preferred treatment option in this setting.

The **use of atezolizumab in the second-line setting after platinum therapy is endorsed by both NICE (for a 2 year use) and IQWIG for patients who have a PD-L1 expression of ≥ 5%**. IQWIG however states an **"added benefit not proven"** of atezolizumab in the **first-line setting** of locally advanced or metastatic disease versus chemotherapy, which aligns with international guidelines recommendations who only mention atezolizumab as a less preferred option in the second-line setting in patients with a PD-L1 expression of ≥ 5%.

### 2.4.2 Avelumab

**Table 30.** Avelumab Drug Information

| Scientific Name<br>Avelumab[55] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Bavencio |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, 2021 |
| **FDA approved / off label** | Yes, 2014 |
| **EMEA approved / off label** | Yes, 2015 |
| **MHRA approved / off label** | Yes, date not available |
| **PMDA approved / off label** | Yes, 2016 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent, monoclonal antibody |

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| **Drug Sub-class** | Immune Checkpoint Inhibitor (PDL-1 Inhibitor) |
| **SFDA Registration Number (New)** | 1506210790 |
| **ATC Code** | N/A |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | **Urothelial carcinoma, locally advanced or metastatic** (first-line maintenance therapy or for therapy of progressive disease): 800 mg once every 2 weeks until disease progression or unacceptable toxicity. |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult):<br>*Kidney impairment **prior** to treatment initiation:* No adjustment necessary<br>*Kidney toxicity **during** treatment:*<br>*Immune-mediated nephritis with kidney dysfunction:*<br>- Grade 2 or grade 3 serum creatinine elevation: Withhold pembrolizumab; resume after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no complete or partial response within 12 weeks of last dose.<br>- Grade 4 serum creatinine elevation: Permanently discontinue pembrolizumab.<br>Hepatic Impairment (Adult):<br>*Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment.<br>*Hepatic impairment **during** treatment initiation* |

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| | ● Immune-mediated hepatitis without tumor involvement of the liver:<br>- AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper.<br>- AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently.<br>● Immune-mediated hepatitis with tumor involvement of the liver:<br>- If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper.<br>- AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue pembrolizumab permanently. |
| **Prescribing edits*** | MD, ST, PE, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | N/A |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum daily dose 800 mg |
| **ST (Step Therapy)** | First-line maintenance treatment of locally advanced/metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy.<br>Second-line treatment of locally advanced/metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or |

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| | have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 800 mg |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Cardiac arrhythmia, peripheral edema, pruritus, skin rash, vitiligo, decreased serum bicarbonate, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperthyroidism, hypertriglyceridemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, decreased serum albumin, hypophosphatemia, hyponatremia, weight loss, abdominal pain, constipation, decreased appetite, diarrhea, nausea, vomiting, dysuria, anemia, leukopenia, neutropenia, hyperbilirubinemia, increased liver enzymes, infection, fatigue, peripheral neuropathy, arthralgia, asthenia, myalgia, increased serum creatinine, cough, dyspnea, fever.<br>- Most serious: Acute myocardial infarction, cardiac tamponade, facial edema, ischemic heart disease, immune-mediated myocarditis, pericarditis, adrenocortical insufficiency, diabetic ketoacidosis, Immune-mediated colitis, immune thrombocytopenia, immune-mediated hepatitis and nephritis, uveitis. |

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| **Drug Interactions*** | - Risk X: Thalidomide (Enhanced toxicity of thalidomide).<br>- Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs)<br>- Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Axitinib, Ketoconazole (Enhanced hepatotoxic effect). |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy |
| **Lactation** | It is not known if pembrolizumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 4 months after the last pembrolizumab dose. |
| **Contraindications** | N/A |
| **Monitoring Requirements** | - PD-L1 expression<br>- Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose<br>- Pregnancy status<br>- Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis, rash/dermatologic toxicity, ocular disorders, encephalitis<br>- Monitor for signs/symptoms of infusion-related reactions |
| **Precautions** | - Adverse reactions (immune mediated) |

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| | - Infusion-related reactions<br>- Auto-immune disorders<br>- Hematopoietic stem cell transplant<br>- Multiple myeloma<br>- Myasthenia gravis |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

### Health Technology Assessment (HTA)

The table below lists the Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), Canadian Agency for Drugs and Technologies in Health (**CADTH**), Institute for Quality and Efficiency in Health Care (**IQWIG**), and Pharmaceutical Benefits Advisory Committee (PBAC) HTA review and recommendations of avelumab in urothelial carcinoma treatment options.

**Table 31.** Avelumab HTA Recommendations

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Avelumab | HAS[21] | 03/2021: **Favorable opinion for reimbursement** as monotherapy for the **first-line maintenance treatment** of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free **following platinum-based chemotherapy**.<br>- Therapeutic improvement compared to supportive care.<br>- Moderate clinical added value (CAV III) compared to supportive care.<br>- Superiority of avelumab, as monotherapy, compared to supportive care, in terms of overall survival (HR=0.69 [CI%: 0.54-0.92], with an individual estimate of an absolute improvement of 7.1 months, deemed clinically relevant), in an open-label, randomized phase 3 study and,<br>- Substantial medical need in the absence of alternatives in this indication<br>- Despite: The onset of grade ≥ 3 adverse events in one in two patients; A mainly immunological toxicity and infusion-related reactions; The lack of demonstrated impact on quality of life. |
| Avelumab | NICE[22] | 11/2022: **Avelumab is recommended** as an option for **maintenance treatment of locally advanced or** |

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| | | **metastatic urothelial cancer that has not progressed after platinum-based chemotherapy** in adults, only if it is stopped at **5 years** of uninterrupted treatment or earlier if the disease progresses.<br>- There are no maintenance treatments routinely available for locally advanced or metastatic urothelial cancer that has responded to platinum-based chemotherapy.<br>- The clinical effectiveness evidence for avelumab came from 1 phase 3, randomized, open- label, parallel, 2-arm study (JAVELIN Bladder 100 trial).<br>- There was a 31% reduction in the risk of death in patients who received avelumab compared with patients who had best supportive care alone (median 14.3 months; 95% CI 12.9 to 17.9 months; [HR] 0.69; 95% CI 0.556 to 0.863; p=0.001). There was also a statistically significant improvement in overall survival for people with PD-L1 positive tumors.<br>- There was a statistically significant improvement in progression-free survival for all patients having avelumab compared with best supportive care (median 3.7 months; 95% CI 3.5 to 5.5 months).<br>- Avelumab meets NICE's criteria to be considered a life-extending treatment at the end of life.<br>- The most likely cost-effectiveness estimates are within what NICE usually considers an acceptable use of NHS resources for end-of-life treatments.<br>- The ICER with a 5-year stopping rule and 1 year treatment effect cap is within the range usually considered cost effective for end-of-life treatments. The company's base case with a 2-year stopping rule and treatment effect cap at 3 years resulted in an ICER of less than £50,000 per QALY gained. |
| Avelumab | CADTH[23] | 03/2021: pERC **conditionally recommends reimbursement of avelumab** (Bavencio) plus best supportive care (BSC) for the first-line **maintenance treatment** of patients with histologically confirmed, **unresectable, locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based** induction chemotherapy if the following conditions are met: · cost-effectiveness is |

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| | | improved to an acceptable level · feasibility of adoption (budget impact) is addressed.<br>- pERC made this recommendation because it was satisfied that **there is a net clinical benefit of avelumab plus BSC compared to BSC only** based on statistically significant and clinically meaningful improvements in overall survival (OS), progression-free survival (PFS), a manageable toxicity profile, and no apparent detriment in quality of life.<br>- pERC concluded that avelumab in combination with BSC **is not considered cost-effective** at the submitted price versus BSC alone. This is driven largely by the high cost of avelumab. CADTH's reanalysis of the sponsor's budget impact analysis suggests that the budget impact of introducing avelumab to the market is substantial and significantly underestimated by the sponsor.<br>- The incremental cost-effectiveness ratio (ICER) for avelumab with BSC versus BSC alone was $278,373 per QALY. At a willingness-to-pay threshold of $50,000 per QALY, **a price reduction of at least 83% is required for avelumab with BSC to be cost-effective**. |
| Avelumab | IQWIG[24] | 05/2021: There is an **indication of minor added benefit** of avelumab in comparison with best supportive care (BSC) for adults with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy.<br>- The first data cut-off (21 October 2019) showed a statistically significant difference between the treatment groups in favor of avelumab + BSC for the outcome "overall survival". The data of the second data cut-off of 19 January 2020 confirmed this result. This resulted in an indication of an added benefit of avelumab + BSC in comparison with BSC.<br>- There was no statistically significant difference between the treatment arms for the outcome of "serious adverse events". This resulted in no hint of greater or lesser harm from avelumab + BSC in |

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| | | comparison with BSC; greater or lesser harm is therefore not proven. |
| Avelumab | PBAC[25] | 03/2022: **Recommended** for the maintenance treatment of locally advanced (Stage III) or metastatic (Stage IV) urothelial carcinoma in patients whose disease has not progressed following first-line platinum-based chemotherapy:<br>- Avelumab provides for some patients a significant improvement in overall survival over best supportive care.<br>- It would be acceptably cost-effective at the price proposed by the sponsor with a risk sharing arrangement incorporating expenditure caps based on a mean avelumab treatment duration of an agreed number of months. |

**Conclusion Statement – Avelumab**

In bladder cancer, avelumab is a first-line agent used in the maintenance treatment of locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy. It is also a second-line agent used in the treatment of locally advanced or metastatic urothelial carcinoma in previously treated patients who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

**Avelumab** is used as a **maintenance therapy for locally advanced/metastatic urothelial carcinoma after completing platinum chemotherapy is endorsed by all HTA organisms HAS, NICE, CADTH, IQWIG, and PBAC**. All confirm the net clinical benefit of avelumab maintenance versus BSC in terms of OS, PFS, and QoL. While NICE recommends a 5-year maximal duration of treatment to be within the range of the cost-effective use of healthcare resources, CADTH recommends a price reduction of at least 83% for it to be cost-effective.

### 2.4.3 Nivolumab

**Table 32.** Nivolumab Drug Information

| Scientific Name<br>Nivolumab[56] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Opdivo |
| **SFDA Classification** | Prescription |

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|---|---|
| **SFDA approved Indication** | Yes, 2015 |
| **FDA approved / off label** | Yes, 2014 |
| **EMEA approved / off label** | Yes, 2015 |
| **MHRA approved / off label** | Yes, date not available |
| **PMDA approved / off label** | Yes, 2015 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent, monoclonal antibody |
| **Drug Sub-class** | Immune Checkpoint Inhibitor (PD-1 Inhibitor) |
| **SFDA Registration Number (New)** | 2-960-15 (40 mg); 3-960-15 (100 mg) |
| **ATC Code** | L01XC17 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | **Urothelial carcinoma, adjuvant therapy following resection:** 240 **mg** once every 2 weeks **or** 480 **mg** once every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year. **Urothelial carcinoma, locally advanced or metastatic:** 240 **mg** once every 2 weeks **or** 480 **mg** once every 4 weeks until disease progression or unacceptable toxicity. |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult): *Kidney impairment **prior** to treatment initiation:* No adjustment necessary *Kidney toxicity **during** treatment: Immune-mediated nephritis with kidney dysfunction:* - Grade 2 or grade 3 serum creatinine elevation: Withhold nivolumab; resume nivolumab after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. |

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| | Permanently discontinue if no complete or partial response within 12 weeks of last nivolumab dose.<br>- Grade 4 serum creatinine elevation: Permanently discontinue nivolumab.<br>Hepatic Impairment (Adult):<br>*Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment.<br>*Hepatic impairment **during** treatment initiation*<br>● Immune-mediated hepatitis without tumor involvement of the liver:<br>- AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold nivolumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper.<br>- AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently.<br>● Immune-mediated hepatitis with tumor involvement of the liver:<br>- If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold nivolumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper.<br>- AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue nivolumab permanently. |
| **Prescribing edits*** | MD, ST, PE, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | N/A |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |

| | |
|---|---|
| **QL (Quantity Limit)** | Maximum daily dose 480 mg |
| **ST (Step Therapy)** | First-line adjuvant treatment of urothelial carcinoma in patients who are at high risk of recurrence after undergoing radical resection.<br>Second-line treatment of locally advanced/metastatic urothelial carcinoma in patients with disease progression during or following a platinum-containing therapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing therapy. |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 480 mg |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Edema, hypertension, pruritus, skin rash, vitiligo, hypercalcemia, hyperglycemia, hyperkalemia, hyperthyroidism, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, increased serum albumin, weight loss, abdominal pain, decreased appetite, diarrhea, increased serum amylase, increased serum lipase, nausea, vomiting, anemia, leukopenia, , neutropenia, hepatitis, antibody development, dizziness, headache, arthralgia, asthenia, increased serum creatinine, cough, dyspnea, fever.<br>- Most serious: Acute coronary syndrome, vasculitis, immune-mediated myocarditis, pericarditis, Stevens-Johnson syndrome, toxic epidermal necrolysis, |

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| | hypothyroidism, hyperthyroidism, adrenocortical insufficiency, hypophysitis, type 1 diabetes mellitus, Immune-mediated colitis, immune thrombocytopenia, autoimmune hemolytic anemia, acquired blood coagulation disorder (hemophilia), disseminated intravascular coagulation, immune-mediated hepatitis and nephritis, uveitis, cerebral hemorrhage, myasthenia gravis, reversible posterior leukoencephalopathy syndrome, pneumonitis |
| **Drug Interactions*** | - Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs)<br>- Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Ketoconazole (Enhanced hepatotoxic effect). |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy |
| **Lactation** | It is not known if nivolumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 5 months after the last nivolumab dose. |
| **Contraindications** | N/A |
| **Monitoring Requirements** | - PD-L1 expression<br>- Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose<br>- Pregnancy status<br>- Monitor closely for signs/symptoms of immune-mediated adverse |

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|---|---|
| | reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis, rash/dermatologic toxicity, ocular disorders, encephalitis<br>- Monitor for signs/symptoms of infusion-related reactions |
| **Precautions** | - Adverse reactions (immune mediated)<br>- Infusion-related reactions<br>- Auto-immune disorders<br>- Hematopoietic stem cell transplant<br>- Multiple myeloma<br>- Myasthenia gravis |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

The table below lists the Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), Canadian Agency for Drugs and Technologies in Health (**CADTH**), Institute for Quality and Efficiency in Health Care (**IQWIG**), and Pharmaceutical Benefits Advisory Committee (PBAC) HTA review and recommendations of nivolumab in urothelial carcinoma treatment options.

**Table 33.** Nivolumab HTA Recommendations

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Nivolumab | HAS[26] | 10/2022: **Favorable opinion** in the restricted indication only: as a monotherapy in the **adjuvant treatment of adult patients with muscle-invasive urothelial carcinoma at high risk of recurrence** after complete removal, whose tumor cells express **PD-L1 at a threshold of ≥ 1%**: who received neoadjuvant chemotherapy; or who did not receive neoadjuvant chemotherapy and were ineligible for and/or refused cisplatin-based adjuvant chemotherapy.<br>- Substantial clinical benefit in this restricted indication only<br>- Minor clinical added value (CAV IV) |

| | | |
|---|---|---|
| | | - Gain in disease-free survival compared to surveillance alone in a randomized double-blind study (median not attained (95% CI: 21.19; N.A) in the nivolumab group versus 8.41 months (95% CI: 5.59; 21.19) in the placebo group, HR: 0.55 (98.72% CI: 0.35; 0.85), p = 0.0005),<br>- Inability to draw conclusions about overall survival due to the immaturity of the data on this criterion.<br>- Toxicity profile marked by the occurrence of adverse events of grades ≥ 3 in almost every other patient. |
| Nivolumab | NICE[27-28] | 08/2022: **Nivolumab is recommended** as an option for the **adjuvant treatment of muscle-invasive urothelial cancer that is at high risk of recurrence** after radical resection in adults whose tumors **express PD-L1 at a level of 1% or more when platinum-based chemotherapy is not suitable**.<br>- Clinical trial evidence from Checkmate 274 shows that adjuvant treatment with nivolumab reduces the risk of cancer recurrence compared with placebo. Median disease-free survival was not reached in the nivolumab arm (95% confidence interval [CI], 22.1 months to not estimable), versus 8.4 months (95% CI, 5.6 months to 20.0 months) with placebo.<br>- However, it was not certain to what extent a benefit in disease-free survival translates into a benefit in overall survival.<br>- The committee was not presented with any cost-effectiveness analyses comparing nivolumab with platinum-based chemotherapy. It therefore considered that the cost-effectiveness results were only relevant to situations when platinum-based chemotherapy was not suitable.<br>- **Nivolumab is cost effective only when adjuvant platinum-based chemotherapy is unsuitable**.<br>- The company's base-case incremental cost-effectiveness ratio (ICER) for nivolumab was £11,361 per quality-adjusted life year (QALY) gained compared with best supportive care. |

| | | |
|---|---|---|
| | | 07/2018: **Nivolumab is not recommended**, within its marketing authorization, for treating **locally advanced unresectable or metastatic urothelial carcinoma in adults who have had platinum-containing therapy**.<br>- Paclitaxel, docetaxel, and best supportive care are relevant comparators for people who have had platinum-containing chemotherapy.<br>- The CheckMate trials provide efficacy estimates for nivolumab, but no randomized controlled trial evidence is available.<br>- The application of a 2-year treatment stopping rule reduced costs associated with nivolumab but the effect on long-term efficacy is unknown.<br>- The company's deterministic revised base-case ICERs are £28,263 per QALY gained compared with docetaxel and £23,497 per QALY gained compared with paclitaxel, both with a 2-year treatment stopping rule applied for nivolumab.<br>- The committee agreed that the most plausible incremental cost-effectiveness ratios (ICERs) were somewhere between £58,791 per quality-adjusted life year (QALY) gained (compared with paclitaxel) and £78,869 per QALY gained (compared with docetaxel), **above what NICE normally considers to be acceptable for end-of-life treatments**.<br>- Nivolumab meets the criteria for end-of-life treatments |
| Nivolumab | CADTH[29] | 08/2022: The CADTH pCODR Expert Review Committee (pERC) recommends that nivolumab be **reimbursed** as a **monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma** (UC) who are at **high risk of recurrence** after undergoing radical resection of UC, only if the conditions below are met:<br>- Pathologic evidence of UC at high risk of recurrence based on pathologic staging of radical surgery tissue in patients who have either:<br>● Received cisplatin-based neoadjuvant chemotherapy (ypT2- pT4a or ypN+) or<br>● Not received neoadjuvant cisplatin chemotherapy (pT3- pT4a or pN+) and are |

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| | | ineligible for adjuvant therapy with cisplatin chemotherapy or<br>● Not received neoadjuvant cisplatin chemotherapy (pT3- pT4a or pN+) and are eligible for adjuvant cisplatin-based chemotherapy but decline to take it.<br>- Evidence of no recurrence confirmed before initiating therapy.<br>- Muscle-invasive UC at disease diagnosis.<br>Evidence from the CheckMate-274 trial demonstrated that adjuvant treatment with nivolumab resulted in a **statistically and clinically significant improvement in disease free survival** in patients with characteristics listed in this condition.<br>The ICER for nivolumab is uncertain. In patients who had received neoadjuvant chemotherapy or were not able to receive adjuvant chemotherapy, the **ICER for nivolumab was $112,386 per QALY when compared with observation**. A **price reduction of at least 56%** would be required for nivolumab to be able to achieve an ICER of $50,000 per QALY compared to observation.<br>At the submitted price, the budget impact of nivolumab is expected to be greater than **$40 million in each of years 1, 2, and 3**. The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates. |
| Nivolumab | IQWIG[30] | 07/2022: **Added benefit not proven** of nivolumab **in comparison with platinum-containing chemotherapy** in adult patients with muscle-invasive urothelial carcinoma with tumor cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are eligible for cisplatin-containing therapy for adjuvant treatment.<br>**Hint of minor benefit versus watchful waiting** in patients who are not eligible for cisplatin-containing therapy. |
| Nivolumab | PBAC[31] | 03/2022: **Not recommended** for the **adjuvant treatment** of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection |

| | | |
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| | | - The PBAC considered that, while a small improvement in disease free survival (DFS) was demonstrated with nivolumab compared to placebo in the overall trial population, there was a strong suggestion that a benefit was observed only in patients who had received prior neoadjuvant platinum-based chemotherapy.<br>- The PBAC also noted the impact of nivolumab as adjuvant treatment on overall survival (OS) was unknown.<br>- The PBAC considered that the incremental cost-effectiveness ratio (ICER) was uncertain and likely underestimated, and that revisions to the structure and inputs for the economic model are required. |

**Conclusion Statement – Nivolumab**

In bladder cancer, nivolumab is a first-line agent for the adjuvant treatment of urothelial carcinoma in adults who are at high risk of recurrence after undergoing radical resection. It is also a second-line agent for the treatment of locally advanced or metastatic urothelial carcinoma in adults with disease progression during or following a platinum-containing therapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing therapy.

**Nivolumab** use as an **adjuvant treatment of MIBC** for patients at **high risk of recurrence** post complete resection has a **favorable opinion from HAS** (substantial added benefit, minor clinical added value), **NICE (only if platinum-based chemotherapy is unsuitable)**, and **CADTH** (only in high-risk patients). IQWIG recommendation aligns with CADTH, stating a **"hint of added benefit" only when platinum chemotherapy is not possible**, while the "added benefit is not proven" for patients eligible for platinum-containing chemotherapy. PBAC doesn't recommend the use of nivolumab in this adjuvant setting. In the **second-line setting** of locally advanced/metastatic urothelial carcinoma, only **NICE** has issued a guidance, stating that nivolumab is **not recommended** post platinum-containing therapy; the **ICER for nivolumab was outside what NICE considered a cost-effective use of NHS resources**.

### 2.4.4 Pembrolizumab

**Table 34.** Pembrolizumab Drug Information

| Scientific Name<br>Pembrolizumab[57] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Keytruda |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, 2017 |
| **FDA approved / off label** | Yes, 2014 |
| **EMEA approved / off label** | Yes, 2015 |
| **MHRA approved / off label** | Yes, date not available |
| **PMDA approved / off label** | Yes, 2016 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent, monoclonal antibody |
| **Drug Sub-class** | Immune Checkpoint Inhibitor (PD-1 Inhibitor) |
| **SFDA Registration Number (New)** | 2501233168 |
| **ATC Code** | L01XC |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | 200 mg once every 3 weeks **or** 400 mg once every 6 weeks until disease progression, unacceptable toxicity, or (in patients without disease progression) for up to 24 months |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult):<br>*Kidney impairment **prior** to treatment initiation:* No adjustment necessary<br>*Kidney toxicity **during** treatment:*<br>*Immune-mediated nephritis with kidney dysfunction:*<br>- Grade 2 or grade 3 serum creatinine elevation: Withhold pembrolizumab; resume after complete or partial (to |

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| | grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no complete or partial response within 12 weeks of last dose.<br>- Grade 4 serum creatinine elevation: Permanently discontinue pembrolizumab.<br>Hepatic Impairment (Adult):<br>*Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment.<br>*Hepatic impairment **during** treatment initiation*<br>● Immune-mediated hepatitis without tumor involvement of the liver:<br>- AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper.<br>- AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently.<br>● Immune-mediated hepatitis with tumor involvement of the liver:<br>- If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper.<br>- AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue pembrolizumab permanently. |
| **Prescribing edits*** | MD, CU, ST, PE, QL |
| **AGE (Age Edit)** | N/A |

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| **CU (Concurrent Use)** | Can be used as a single agent or in combination with enfortumab vedotin |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum daily dose 400 mg |
| **ST (Step Therapy)** | First-line treatment of locally advanced/metastatic urothelial carcinoma in patients not eligible for platinum-containing chemotherapy.<br>Second-line treatment of locally advanced/metastatic urothelial carcinoma in patients with disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.<br>Second-line treatment for the management of BCG-unresponsive, high-risk, NMIBC who are ineligible for or have elected not to undergo cystectomy. |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 400 mg |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Cardiac arrhythmia, peripheral edema, pruritus, skin rash, vitiligo, decreased serum bicarbonate, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperthyroidism, hypertriglyceridemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, decreased serum albumin, hypophosphatemia, hyponatremia, weight loss, abdominal pain, |

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| | constipation, decreased appetite, diarrhea, nausea, vomiting, dysuria, anemia, leukopenia, neutropenia, hyperbilirubinemia, increased liver enzymes, infection, fatigue, peripheral neuropathy, arthralgia, asthenia, myalgia, increased serum creatinine, cough, dyspnea, fever.<br>- Most serious: Acute myocardial infarction, cardiac tamponade, facial edema, ischemic heart disease, immune-mediated myocarditis, pericarditis, adrenocortical insufficiency, diabetic ketoacidosis, Immune-mediated colitis, immune thrombocytopenia, immune-mediated hepatitis and nephritis, uveitis. |
| **Drug Interactions*** | - Risk X: Thalidomide (Enhanced toxicity of thalidomide).<br>- Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs)<br>- Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Axitinib, Ketoconazole (Enhanced hepatotoxic effect). |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy |
| **Lactation** | It is not known if pembrolizumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 4 months after the last pembrolizumab dose. |
| **Contraindications** | N/A |

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| **Monitoring Requirements** | - PD-L1 expression<br>- Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose<br>- Pregnancy status<br>- Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis, rash/dermatologic toxicity, ocular disorders, encephalitis<br>- Monitor for signs/symptoms of infusion-related reactions |
| **Precautions** | - Adverse reactions (immune mediated)<br>- Infusion-related reactions<br>- Auto-immune disorders<br>- Hematopoietic stem cell transplant<br>- Multiple myeloma<br>- Myasthenia gravis |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

The table below lists the Haute Autorité de Santé **(HAS)**, National Institute for Health and Care Excellence (**NICE**), Canadian Agency for Drugs and Technologies in Health (**CADTH**), Institute for Quality and Efficiency in Health Care (**IQWIG**), and Pharmaceutical Benefits Advisory Committee (PBAC) HTA review and recommendations of pembrolizumab in urothelial carcinoma treatment options.

**Table 35.** Pembrolizumab HTA Recommendations

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Pembrolizumab | HAS[32] | 02/2018: **High clinical benefit** for the monotherapy treatment of adults with **locally advanced or metastatic urothelial cancer having received prior platinum salt-based chemotherapy** urothelial cancer and **minor clinical added value** |

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| | | compared to chemotherapy in terms of overall survival.<br>- Its superiority over chemotherapy has been established: **absolute gain in median overall survival of 2.9 months** in favor of pembrolizumab.<br>● A randomized, open-label phase III study compared pembrolizumab (n=270) to a chemotherapy regimen chosen by the investigator (paclitaxel, docetaxel or vinflunine, n=272) in 542 patients with locally advanced or metastatic urothelial cancer having received prior platinum salt-based chemotherapy.<br>● In the second intermediate analysis (median follow-up of 14.1 months), the median overall survival (primary endpoint) was 10.3 months in the pembrolizumab group and 7.4 months in the chemotherapy group, i.e. an absolute gain of 2.9 months in favor of pembrolizumab (HR=0.73 95% CI [0.59; 0.91], p= 0.002). The study did not demonstrate any statistically significant difference between the groups in respect of progression-free survival (co-primary endpoint).<br>● The safety profile appeared to be superior with pembrolizumab than with chemotherapy particularly in terms of incidence of adverse effects of grades ≥ 3 (52.3% in the pembrolizumab group and 62.7% in the chemotherapy group).<br>- **It is the preferred therapeutic option over chemotherapy for second- and third-line treatments for these patients**.<br>- However, pembrolizumab increases the risk of death in the first two months of treatment compared to chemotherapy. |
| Pembrolizumab | NICE[33] | 04/2021: **Pembrolizumab is not recommended**, within its marketing authorization, for treating |

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| | | **locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy**.<br>- Paclitaxel, docetaxel, and best supportive care are the relevant comparators for this appraisal.<br>- Clinical trial evidence in KEYNOTE-045 shows that pembrolizumab **significantly improves overall survival** compared with docetaxel and paclitaxel but does not appear to improve progression-free survival.<br>- Pembrolizumab **meets NICE's criteria to be considered a life-extending treatment at the end of life**.<br>- Based on the available evidence, a **3-year duration** of treatment effect from the start of pembrolizumab is plausible. A 3-year to 5-year duration of treatment effect from the start of pembrolizumab treatment could be plausible.<br>- The most likely cost-effectiveness estimate for pembrolizumab is uncertain. This is because it is not clear which model of overall survival is most appropriate or how long the treatment benefit of pembrolizumab should continue. Even when pembrolizumab is offered with its agreed discount, the **most plausible cost-effectiveness estimate remains higher than what NICE normally considers acceptable for end-of-life treatments**. Therefore, pembrolizumab is not recommended.<br>- The most plausible ICER for pembrolizumab compared with docetaxel and paclitaxel is likely to be over £50,000 per QALY gained which is above the range that NICE normally considers a cost-effective use of NHS resources for a life-extending treatment at the end of life. |
| Pembrolizumab | CADTH[33,34] | 10/2019: pERC **does not recommend the reimbursement** of pembrolizumab (Keytruda) for **the first line treatment** of adult patients with **locally advanced or metastatic urothelial carcinoma** who are not eligible for cisplatin-containing chemotherapy and whose tumors |

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| | | express programmed death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 10) as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status (first-line treatment).<br>- While pERC acknowledged that there is an unmet need for effective treatments in this setting, the Committee concluded that **there was considerable uncertainty in the magnitude of clinical benefit of pembrolizumab** compared with appropriate comparators with regard to outcomes important to decision-making such as OS, PFS, and quality of life (QoL), given the limitations in the evidence from the available phase II clinical trial.<br>- pERC agreed that pembrolizumab aligned with patient values in that it has manageable side effects, has the potential to maintain QoL, and offers an additional treatment choice.<br>- pERC **could not draw a conclusion on the cost-effectiveness of pembrolizumab** compared with gemcitabine plus carboplatin or single-drug chemotherapy due to the uncertainty surrounding the incremental survival benefits used in the economic model.<br><br>03/2018: pERC **recommends the reimbursement** of pembrolizumab (Keytruda) for **the treatment** of patients with **locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy**, **conditional of cost-effectiveness being improved** to an acceptable **level** (second-line treatment).<br>- pERC made this recommendation because it was satisfied that **there is a net clinical benefit with pembrolizumab** compared with chemotherapy, based on a clinical meaningful improvement in OS, an |

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| | | acceptable toxicity profile, and high unmet need for effective treatments, while maintaining QoL.<br>- However, pERC noted that **at the submitted price, pembrolizumab could not be considered cost-effective compared with chemotherapy**. The potential budget impact of pembrolizumab may be underestimated and could be substantial. |
| Pembrolizumab | IQWIG[35] | 06/2021: There is an **indication of considerable added benefit** of pembrolizumab in comparison with chemotherapy added by physician in locally advanced or metastatic urothelial carcinoma in **adults who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a CPS ≥ 10** (first-line treatment).<br>- The overall consideration showed both positive and negative effects for pembrolizumab versus chemotherapy specified by the physician.<br>- No statistically significant difference between the treatment groups was shown for the outcome "overall survival".<br>- The advantages arise in particular in the outcome category “serious/severe AEs” due to an indication of lesser harm with the extent: “major”.<br>- There is an indication of a considerable added benefit of pembrolizumab in comparison with chemotherapy specified by the physician for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-based therapy and **whose tumors express PD-L1 with a CPS ≥ 10**.<br><br>01/2018: Patients with locally advanced or metastatic urothelial carcinoma **after pretreatment with a platinum-based** |

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| | | **chemotherapy** (second-line setting): **indication of considerable added benefit**. |
| Pembrolizumab | PBAC[36] | 11/2022: **Not recommended** for locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer<br>- The PBAC did not advise that its previous recommendation regarding the risk sharing arrangement (RSA) subsidization caps and rebate level for pembrolizumab for locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer be amended. |

**Conclusion Statement – Pembrolizumab**

In bladder cancer, pembrolizumab is a first-line agent for the treatment of locally advanced or metastatic urothelial carcinoma in patients who are not eligible for any platinum-containing chemotherapy as a single agent (preferred) or in combination with enfortumab vedotin. It is also a second-line agent for the treatment of locally advanced or metastatic urothelial cancer in patients with disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy as a single agent (preferred choice) or in combination with enfortumab vedotin.

Pembrolizumab is also a second-line treatment option (as a single-agent) for the management of Bacillus Calmette-Guérin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors in patients who are ineligible for or have elected not to undergo cystectomy.

**Pembrolizumab** use in the **second-line setting** of locally advanced/metastatic urothelial carcinoma **after first-line platinum therapy is endorsed by HAS** (high clinical benefit; **preferred therapeutic option over chemotherapy**) and **IQWIG** which aligns with international recommendations, while NICE doesn't support its reimbursement in this setting (for cost-effectiveness considerations). The NICE considers that while pembrolizumab **meets the criteria to be considered a life-extending treatment at the end of life**., the most plausible ICER for pembrolizumab compared with docetaxel and paclitaxel is likely to be over £50,000 per QALY gained **which is above the range that NICE normally considers a cost-effective use of NHS resources** for a life-extending treatment at the end of life. **CADTH** on the other hand recommends the reimbursement of pembrolizumab in this second-line setting, **under the condition of cost-effectiveness being improved**.

For pembrolizumab in the first-line setting, IQWIG confirms an **indication of considerable added benefit** in comparison with chemotherapy in locally advanced or metastatic urothelial carcinoma in **adults who are not eligible for cisplatin-**

**containing chemotherapy and whose tumors express PD-L1 with a CPS ≥ 10**. On the other hand, CADTH doesn't recommend the use of pembrolizumab in this first-line setting, stating that there was **considerable uncertainty in the magnitude of clinical benefit of pembrolizumab**, and that a conclusion of cost-effectiveness couldn't be drawn. PBAC as well states that pembrolizumab is not recommended for locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer.

## 2.5 Topoisomerase Inhibitors

### 2.5.1 Doxorubicin

**Table 36.** Doxorubicin Drug Information

| Scientific Name<br>Doxorubicin[58] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Doxorubicin (Ebewe, Accord), Adriablastina |
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes, 2004 |
| **FDA approved / off label** | Yes, 1974 |
| **EMEA approved / off label** | Yes, not mentioned |
| **MHRA approved / off label** | Yes, not mentioned |
| **PMDA approved / off label** | Yes, 2004 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Anthracycline; Topoisomerase II inhibitor |
| **SFDA Registration Number (New)** | Doxorubicin Ebewe:<br>4-355-01 (10mg); 5-355-01 (50mg);<br>39-355-07 (100mg)<br>Doxorubicin Accord:<br>5-5223-18 (10mg); 6-5223-18 (50mg)<br>Adriablastina:<br>6-5669-22 (10mg); 7-5669-22 (50mg) |
| **ATC Code** | L01DB01 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Solution |
| **Route of Administration** | Intravenous |

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| **Dose (Adult) [DDD]*** | **Dose-dense MVAC**: 30 mg/m$^2$ on day 1 or on day 2 every 14 days (with growth factor support) for 3-4 cycles (neoadjuvant), or 6 cycles, or until disease progression or unacceptable toxicity (locally advanced/metastatic)<br>**MVAC regimen**: 30 mg/m$^2$ on day 2 every 28 days for 3 (neoadjuvant) or 6 (locally advanced/metastatic) cycles.<br>*Small cell carcinoma of the bladder:*<br>25 mg/m$^2$ on days 1 to 3 every 21 days (in combination with ifosfamide, mesna, and growth factor support; IA cycle); IA cycle alternates with etoposide and cisplatin (EP cycle) for a total of 4 cycles (2 cycles of IA and 2 cycles of EP) |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult):<br>- CrCl <10 mL/minute: No need for adjustment<br>- Hemodialysis: Consider administering 75% of the original dose<br>Hepatic Impairment (Adult):<br>- Serum bilirubin 1.2 to 3 mg/dL: Administer 50% of dose.<br>- Serum bilirubin 3.1 to 5 mg/dL: Administer 25% of dose.<br>- Severe hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL): Use is contraindicated. |
| **Prescribing edits*** | MD, ST, PE, CU, QL |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | To be used concurrently with chemotherapy<br>To be used with antiemetics and G-CSF support (in ddMVAC protocol) |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |

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| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Cumulative lifetime limit: 400 mg/m$^2$ |
| **ST (Step Therapy)** | First, second, and later line treatment of muscle invasive, locally advanced, or metastatic bladder cancer |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | Cumulative lifetime limit: 400 mg/m$^2$ |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| Main Adverse Drug Reactions **(Most common and most serious)** | - Most common: Acute cardiotoxicity, malaise, alopecia, discoloration of sweat, pruritus, skin photosensitivity, skin rash, urticaria, amenorrhea, dehydration, hyperuricemia, abdominal pain, anorexia, diarrhea, discoloration of saliva, gastrointestinal ulcer, metastatic urothelial carcinomaositis, nausea, vomiting, urine discoloration, infertility, leukopenia, neutropenia, anemia, thrombocytopenia, weakness, discoloration of tears<br>- Most serious: Acute cardiotoxicity (Atrioventricular block, bradycardia, bundle branch block, ECG abnormality, extrasystoles, nonspecific ST or T wave changes on ECG, sinus tachycardia, supraventricular tachycardia, tachyarrhythmia, ventricular tachycardia), Delayed cardiotoxicity (cardiac failure, decreased left ventricular ejection fraction, myocarditis, pericarditis) |
| **Drug Interactions*** | - Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, CYP2D6 Inhibitors/Inducers, Deucravacitinib, Dipyrone, Fexinidazole, |

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| | Filgotinib, Lasmiditan, Nadofaragen, Natalizumab, Pacritinib, P-glycoprotein/ABCB1 Inducers/Inhibitors, Pimecrolimus, Ritlecitinib, Ruxolitinib (Topical), Sparsentan, Tacrolimus (Topical), Talimogene Laherparepvec, Taurursodiol, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: Ado-Trastuzumab Emtansine, COVID-19 Vaccine, Deferiprone, Denosumab, Erdafitinib, Influenza Virus Vaccines, Fam-Trastuzumab Deruxtecan, Leflunomide, Lenograstim, Lipegfilgrastim, Margetuximab, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Trastuzumab, Vaccines (Inactivated/Non-Replicating), Zidovudine |
| **Special Population** | Pediatrics, Radiation recipients |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy.<br>Causes harm to fetus, advice women on this treatment on the potential risks |
| **Lactation** | Doxorubicin and its metabolites are present in breast milk. The manufacturer does not recommend breastfeeding during doxorubicin therapy and for 10 days after the last doxorubicin dose. |
| **Contraindications** | Severe hypersensitivity to doxorubicin or any component of the formulation; recent myocardial infarction (within past 4 to 6 weeks), severe myocardial insufficiency; severe persistent drug-induced myelosuppression; severe |

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| | hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL). |
| **Monitoring Requirements** | - Cumulative (lifetime) anthracycline/doxorubicin dose<br>- CBC with differential and platelet count<br>- LFTs (bilirubin, ALT/AST, alkaline phosphatase; renal function (creatinine), serum uric acid, and electrolytes (calcium, potassium, phosphate)<br>- Assess cardiac function: ECG, left ventricular ejection fraction increase the frequency of assessments as the cumulative dose exceeds 300 $mg/m^2$)<br>- Pregnancy status prior to use<br>- Monitor hydration status and for signs/symptoms of tumor lysis syndrome and secondary malignancies<br>- Monitor infusion site |
| **Precautions** | - Bone marrow suppression<br>- Cardiomyopathy<br>- Extravasation: Vesicant<br>- Secondary malignancy<br>- Tumor lysis syndrome<br>- Hepatic impairment:<br>- Special populations<br>- Pediatric<br>- Radiation recipients<br>- Formulations (conventional vs liposomal) |
| **Black Box Warning** | - Cardiomyopathy<br>- Extravasation<br>- Secondary malignancy<br>- Immunosuppression |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for doxorubicin in bladder cancer. This is probably because doxorubicin is a long-standing standard of care for bladder cancer with a proven record of efficacy and safety. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

**Conclusion Statement – Doxorubicin**

Doxorubicin is a first-line agent in the treatment of muscle-invasive bladder cancer in combination with methotrexate, vinblastine, and cisplatin (ddMVAC) (preferred protocol for neoadjuvant/adjuvant therapy in early stage disease and locally advanced/metastatic disease). Doxorubicin can also be used in the second and subsequent-line setting of locally advanced/metastatic bladder cancer, part of the ddMVAC regimen.

Doxorubicin is also a first and second, and later line agent in the treatment of locally advanced/metastatic bladder cancer in patients who are not eligible (or who received in the first-line setting) for platinum-containing therapy, in combination with ifosfamide/gemcitabine.

There is no data issued by HTA bodies regarding its use.

## 2.6 Miscellaneous

### 2.6.1 Bacillus Calmette-Guerin (BCG)

**Table 37.** Bacillus Calmette-Guerin (BCG) Drug Information

| Scientific Name<br>Bacillus Calmette-Guerin (BCG) [59] | |
|---|---|
| **Trade Name(s) on Saudi Market** | BCG CULTURE AJV |
| **SFDA Classification** | Prescription |
| **SFDA Approved Indication** | Yes, 2022 |
| **FDA approved/off label** | Yes, not mentioned |
| **EMEA approved/off label** | Yes, not mentioned |
| **MHRA approved/off label** | Yes, not mentioned |
| **PMDA approved/off label** | Yes, 2010 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic Agent |
| **Drug Sub-Class** | Biological Response Modulator |

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| **SFDA Registration Number (New)** | 2706222262 |
| **ATC Code** | L03AX03 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Powder for bladder irrigation |
| **Route of Administration** | Intravesicular |
| **Dose (Adult) [DDD]*** | Induction: Intravesicular: One dose (~50 mg or 1 vial) instilled into the bladder (retain for 2 hours) once weekly for 6 weeks beginning 7 to 14 days after biopsy (may repeat cycle 1 time if tumor remission not achieved), followed by maintenance therapy of ~50 mg (one vial) approximately once a month for at least 6 to 12 months. |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Hepatic Impairment (Adult):<br>- Mild to moderate (Child-Pugh class A and B) impairment: No dosage adjustment is necessary.<br>- Severe impairment (Child-Pugh class C): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). |
| **Prescribing edits*** | AGE, MD, ST, PE, QL |
| **AGE (Age Edit)** | Not used in the pediatric population |
| **CU (Concurrent Use)** | N/A |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum daily dose: 50 mg |
| **ST (Step Therapy)** | Intravesical BCG is a first-line agent in the management of non-muscle invasive bladder cancer after TURBT, preferred for patients with high-risk features. |
| **EU (Emergency Use Only)** | N/A |

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| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 50 mg |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| Main Adverse Drug Reactions<br>**(Most common and most serious)** | • Most common: Bladder mucosa irritation (bladder irritability), dysuria, hematuria, urinary frequency, urinary urgency, pain, flu-like symptoms, fever<br>• Most serious: Cardiac disorder, hepatitis |
| **Drug Interactions*** | Risk X: Antibiotics, corticosteroids, Hexaminolevulinate, Immunosuppressants, Methotrexate, Myelosuppressive agents, Teplizumab, Ustekinumab |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category C |
| **Lactation** | It is not known if BCG (intravesical) is present in breast milk.<br>A decision should be made to discontinue breastfeeding or avoid use of BCG (intravesical), taking into account the importance of BCG (intravesical) to the patient. |
| **Contraindications** | Immunosuppressed patients or persons with congenital or acquired immune deficiencies whether due to concurrent diseases, cancer therapy, or immunosuppressive therapy (eg, corticosteroids); Tuberculosis disease (active TB); concurrent febrile illness, urinary tract infection, or gross hematuria; recent (TICE BCG: <7 to 14 days) biopsy, transurethral resection, or traumatic catheterization |
| **Monitoring Requirements** | - PPD test prior to initiation<br>- Intravesical treatment: Monitor for signs/symptoms of toxicity/infection following every treatment. Signs |

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| | that antituberculous therapy may be needed: Flu-like symptoms ≥72 hours, fever ≥101.3°F, systemic symptoms which worsen with each treatment, persistently abnormal liver function tests, prostatitis, epididymitis or orchitis of >2 to 3 day duration |
| **Precautions** | - BCG reaction: Febrile episodes with flu-like symptoms lasting >72 hours; fever ≥39.5°C (103°F); pneumonitis; hepatitis; organ dysfunction outside of the GU tract with granulomatous inflammation; clinical signs of sepsis<br>- Bladder irritation<br>- Disseminated infections |
| **Black Box Warning** | - Biohazard agent<br>- Disseminated infections |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for intravesical BCG in bladder cancer, probably because it has always been a long-standing standard of care with a proven record of efficacy and safety.

**Conclusion Statement – BCG**

In bladder cancer, intravesical BCG is a first-line agent in the management of non-muscle invasive bladder cancer after TURBT, preferred for patients with high-risk features. There is no data issued by HTA bodies regarding its use in this setting.

### 2.6.2 Enfortumab Vedotin

**Table 38.** Enfortumab Vedotin Drug Information

| SCIENTIFIC NAME<br>Enfortumab vedotin[60] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Padcev |
| **SFDA Classification** | Prescription |
| **SFDA Approved Indication** | No |
| **FDA approved/off label** | Yes, 2019 |
| **EMEA approved/off label** | Yes, 2022 |
| **MHRA approved/off label** | Yes, 2021 |
| **PMDA approved/off label** | Yes, 2021 |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-Class** | Antibody Drug Conjugate; Anti-Nectin-4 |
| **SFDA Registration Number (New)** | 57-4-14 |
| **ATC Code** | L01XE21 |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Powder for solution for injection |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]*** | **Urothelial cancer, locally advanced or metastatic, combination therapy: IV:** 1.25 mg/kg (maximum dose: 125 mg) on days 1 and 8 every 21 days (in combination with pembrolizumab) until disease progression or unacceptable toxicity<br>**Urothelial cancer, locally advanced or metastatic, single-agent treatment: IV:** 1.25 mg/kg (maximum dose: 125 mg) on days 1, 8, and 15 every 28 days until disease progression or unacceptable toxicity |
| **Adjustment** | Hepatic Impairment (Adults):<br>**Mild impairment** (total bilirubin 1 to 1.5 times ULN and any AST, or total bilirubin |

| | |
|---|---|
| | ≤ ULN and AST > ULN): No dosage adjustment necessary.<br>**Moderate to severe impairment** (total bilirubin >1.5 times ULN and any AST): Avoid enfortumab vedotin use.<br>Pre-existing severe impairment (total bilirubin >3 times ULN): Use is not recommended |
| **Maximum Daily Dose Adults*** | 125 mg |
| **Prescribing Edits*** | AGE, CU, MD, ST, PE, PA |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | Can be used as a single agent or in combination with pembrolizumab |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum daily dose 125 mg |
| **ST (Step Therapy)** | First-line treatment of locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin-containing chemotherapy (in combination with pembrolizumab).<br>Second and subsequent-line treatment (as a single agent) for locally advanced or metastatic urothelial cancer in patient who have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, or who are ineligible for cisplatin-containing chemotherapy and have previously received 1 or more prior lines of therapy. |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 125 mg |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Alopecia, maculopapular rash, pruritus, skin rash, xeroderma, decreased serum |

| | |
|---|---|
| | phosphate and potassium, hyperglycemia, weight loss, abdominal pain, constipation, decreased appetite, diarrhea, dysgeusia, increased lipase, nausea, urinary tract infections, anemia, decreased neutrophils, hemorrhage, lymphocytopenia, fatigue, peripheral neuropathy, blurred vision, dry eye syndrome, increased serum creatinine, fever<br>- Most severe: bone marrow suppression, febrile neutropenia, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, diabetic ketoacidosis, pneumonitis/interstitial lung disease |
| **Drug Interactions*** | Risk C: Antidiabetics, CYP450 Inducers/Inhibitors (decreased/increased serum concentration of enfortumab vedotin), Efgartigimod Alfa, Rozanolixizumab |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category D |
| **Lactation** | It is not known if enfortumab vedotin is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during treatment and for 3 weeks after the last dose. |
| **Contraindications** | N/A |
| **Monitoring Requirements** | - CBC with differential, blood glucose, and LFTs<br>- Pregnancy status<br>- Monitor for symptoms of new or worsening peripheral neuropathy, ocular disorders, and/or dermatologic toxicity. |

| | |
|---|---|
| | - Monitor for signs/symptoms of pneumonitis or interstitial lung disease.<br>- Consider ophthalmologic evaluation for ocular symptoms that do not resolve.<br>- Monitor infusion site during infusion for possible extravasation |
| **Precautions** | - Extravasation: May be an irritant.<br>- Hepatic impairment |
| **Black Box Warning** | Dermatologic toxicity |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

The table below lists the Canadian Agency for Drugs and Technologies in Health (**CADTH**), Institute for Quality and Efficiency in Health Care (**IQWIG**), and Pharmaceutical Benefits Advisory Committee (PBAC) HTA review and recommendations of enfortumab vedotin in urothelial carcinoma treatment options.

**Table 39.** Enfortumab Vedotin HTA Recommendations

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Enfortumab Vedotin | CADTH[39] | 01/2022: The CADTH pERC recommends that enfortumab vedotin be **reimbursed** for the treatment of adult patients with **unresectable, locally advanced or metastatic UC** who have **previously received a platinum-containing chemotherapy and PD-1 or PD-L1 inhibitor therapy**<br>- Evidence from Study EV-301 demonstrated that enfortumab vedotin resulted in significant improvements in OS, PFS, and ORR in patients with locally advanced or metastatic UC who had previously been treated with a platinum-containing chemotherapy in the neoadjuvant or adjuvant, locally advanced or metastatic setting, as well as a PD-1 or PD-L1 inhibitor in the locally advanced or metastatic setting.<br>- The **ICER for enfortumab vedotin is $506,439 when compared with taxanes**. A **price reduction of 93%** would be required for enfortumab vedotin |

| | | |
|---|---|---|
| | | to be able to achieve an ICER of $50,000 per QALY compared to a taxane.<br>- At the submitted price, the **budget impact** of enfortumab vedotin is expected to be **greater than $40 million in year 3** and the overall 3-year budget impact would be **$99 million**. |
| Enfortumab vedotin | IQWIG[40] | 08/2022: There is a **hint of minor added benefit** of enfortumab vedotin in comparison with vinflunine or cisplatin/gemcitabine chemotherapy for adults with locally advanced or metastatic urothelial carcinoma **who have received prior platinum-containing chemotherapy and a PD1 or PD-L1 inhibitor and for whom chemotherapy is suitable**.<br>- **Added benefit not proven** in comparison with BSC for adults with locally advanced or metastatic urothelial carcinoma **who have received prior platinum-containing chemotherapy and a PD1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable**. |
| Enfortumab vedotin | PBAC[41] | 03/2023: **Recommended** for the treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer who have progressed on or after a platinum-containing chemotherapy regimen and either a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor.<br>- The PBAC was satisfied that enfortumab vedotin provides, for some patients, a significant improvement in efficacy over docetaxel or paclitaxel, administered as single agents.<br>- The PBAC considered that the sponsor had addressed the outstanding issues identified at the November 2022 meeting via the proposed price reduction and the proposed Special Revenue Arrangement (SRA). |

**Conclusion Statement – Enfortumab vedotin**

In bladder cancer, enfortumab vedotin can be used in combination with pembrolizumab in the first-line setting of locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin-containing chemotherapy. It is also a second and subsequent-line treatment option (as a single agent) for locally

advanced or metastatic urothelial cancer in patient who have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, or who are ineligible for cisplatin-containing chemotherapy and have previously received 1 or more prior lines of therapy.

CADTH, IQWIG, and PBAC **support** the use of enfortumab vedotin in the **third and later-line setting of unresectable, locally advanced or metastatic urothelial carcinoma** in patients who have **previously received a platinum-containing chemotherapy** and a **PD-1 inhibitor or PD-L1 inhibitor therapy**. For CADTH, while the drug results in improvement is OS, PFS, and response rate, a **price reduction of 93%** would be required for enfortumab vedotin to be able to achieve an ICER of $50,000 per QALY compared to a taxane. For IQWIG, while enfortumab vedotin provides a **hint of minor added benefit** in comparison with vinflunine or cisplatin/gemcitabine chemotherapy, they state that the **added benefit is not proven** in comparison with best supportive care.

### 2.6.3 Sacituzumab Govitecan

**Table 40.** Sacituzumab Govitecan Drug Information

| Scientific Name<br>Sacituzumab govitecan[61] | |
|---|---|
| **Trade Name(s) on Saudi Market** | Trodelvy |
| **SFDA Classification** | Prescription |
| **SFDA Approved Indication** | Yes, 2023 |
| **FDA approved/off label** | Yes, 2020 |
| **EMEA approved/off label** | Yes, 2021 |
| **MHRA approved/off label** | Yes, not mentioned |
| **PMDA approved/off label** | No |
| **Indication (ICD-10)** | C67 |
| **Drug Class** | Antineoplastic Agent |
| **Drug Sub-Class** | Antibody Drug Conjugate; Anti-Trop-2 |
| **SFDA Registration Number (New)** | 2601233183 |
| **ATC Code** | N/A |
| **Pharmacological Class (ASHP)** | 10:00 – Antineoplastic Agents |
| **Drug Information** | |
| **Dosage Form** | Powder for concentrate for solution for injection |
| **Route of Administration** | Intravenous |

| | |
|---|---|
| **Dose (Adult) [DDD]*** | 10 mg/kg on days 1 and 8 of a 21-day treatment cycle (maximum: 10 mg/kg/dose); continue until disease progression or unacceptable toxicity |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Renal Impairment (Adult):<br>- CrCl >30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling; however, renal elimination of SN-38 (small molecule moiety of sacituzumab govitecan) is minimal.<br>- CrCl ≤30 mL/minute; End-Stage Renal Disease: There are no dosage adjustments provided in the manufacturer's labeling (no data are available).<br>Hepatic Impairment (Adult):<br>- Total bilirubin ≤ ULN with AST > ULN **or** bilirubin >1 to 1.5 times ULN with any AST: No initial dosage adjustment necessary.<br>- Total bilirubin >1.5 times ULN, **or** AST and ALT >3 times ULN without liver metastases, **or** AST and ALT >5 times ULN with liver metastases: There are no dosage adjustments provided in the manufacturer's labeling (no initial dosage recommendation can be made). |
| **Prescribing edits*** | AGE, CU, MD, ST, PE, QL |
| **AGE (Age Edit)** | Not used in the pediatric population |
| **CU (Concurrent Use)** | To be used with antiemetics, antihistamine, and appropriate hydration with electrolytes |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum daily dose: 10 mg/kg |

| | |
|---|---|
| **ST (Step Therapy)** | Third and subsequent line treatment of locally advanced or metastatic urothelial cancer in patients who have previously received platinum-containing chemotherapy and either PD-1 or PD-L1 therapy. |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | Part of a treatment protocol |
| **Maximum Daily Dose Adults*** | 10 mg/kg |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Safety** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Edema, alopecia, pruritus, skin rash, xeroderma, decreased: serum albumin, glucose, phosphate, magnesium; severe dehydration, increase lactate dehydrogenase, increased potassium, weight loss, increased serum glucose, abdominal pain, constipation, decreased appetite, diarrhea, dysgeusia, stomatitis, hematuria, urinary tract infection, decreased blood counts, increased hepatic enzymes, hypersensitivity, infection, dizziness, fatigue, headache, arthralgia, acute kidney injury, cough, dyspnea, respiratory infections, fever<br>- Most serious: Bone marrow suppression, gastro-intestinal toxicity, hypersensitivity |
| **Drug Interactions*** | - Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Irinotecan products, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, |

| | |
|---|---|
| | Tofacitinib, Upadacitinib, Vaccines (Live)<br>- Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating) |
| **Special Population** | Older age |
| **Pregnancy** | Pregnancy Category D |
| **Lactation** | It is not known if sacituzumab govitecan or SN-38 are present in breast milk. Breastfeeding is not recommended by the manufacturer during therapy and for 1 month after the last sacituzumab govitecan dose. |
| **Contraindications** | Severe hypersensitivity to sacituzumab govitecan or any component of the formulation. |
| **Monitoring Requirements** | - Blood counts prior to dose on days 1 and 8 of each cycle and as clinically necessary (especially in patients known to be homozygous or heterozygous for UGT1A1*28).<br>- Pregnancy status<br>- Monitor for neutropenic fever, hypersensitivity reactions, and infusion-related reactions<br>- Monitor for diarrhea, nausea, and vomiting, as well as a clinical indication for additional antiemetics and/or supportive measures<br>- Closely monitor for adverse reactions in patients with known reduced UGT1A1 activity. |
| **Precautions** | - Older age<br>- Polysorbate 80<br>- Reduced UGT1A1 activity |

| | |
|---|---|
| **Black Box Warning** | - Diarrhea<br>- Neutropenia |
| **REMS*** | N/A |

**Health Technology Assessment (HTA)**

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for intravesical Sacituzumab govitecan in bladder cancer; a NICE guidance is currently under development in this setting.

**Conclusion Statement – Sacituzumab Govitecan**

Sacituzumab govitecan is used in the third and subsequent-line setting of locally advanced or metastatic urothelial carcinoma in patients who have previously received platinum-containing chemotherapy and either programmed death receptor-1 or programmed death-ligand 1 inhibitor.

# Section 3.0 Key Recommendations Synthesis

## A. Non-Muscle Invasive Bladder Cancer (NMIBC)

Primary tumors without muscle invasion (Ta and T1 lesions) are generally managed initially with **TURBT**[8-15].

- A **single instillation of intravesical chemotherapy** is recommended to be administered within 24 hours of surgery (ideally within 6 hours) [8-15].
- **Gemcitabine** (Recommendation Level A, Evidence Level II) and **mitomycin** (Recommendation Level A, Evidence Level II) are the preferred agents for intravesical chemotherapy in this setting[8-15].
- The subsequent management of NMIBC will be based on the American Urological Association/ Society of Urologic Oncology (AUA/SUO) risk stratification[10] (Table 1) with the caution that an individual patient within each of the risk groups may have specific features that can influence care decisions[8,10].

**Table 1.** AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer. Adapted from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol. 2016;196(4):1021-1029. doi:10.1016/j.juro.2016.06.049

| Low Risk | Intermediate Risk | High Risk |
|---|---|---|
| ▪ Papillary urothelial neoplasm of low malignant potential<br>▪ Low grade urothelial carcinoma<br>- Ta and<br>- ≤3 cm and<br>- Solitary | ▪ Low grade urothelial carcinoma<br>- T1 or<br>- >3 cm or<br>- Multifocal or Recurrence within 1 year<br>▪ High grade urothelial carcinoma<br>- Ta and<br>- ≤3 cm and<br>- Solitary | ▪ High grade urothelial carcinoma<br>- CIS or<br>- T1 or<br>- >3 cm or<br>- Multifocal<br>▪ Very high-risk features (any):<br>- BCG unresponsive<br>- Variant histologies<br>- Lymphovascular invasion<br>- Prostatic urethral invasion |

### A.1. Patients with low-risk NMBC:

- The risk of recurrence or progression is low following TURBT and no further treatment is necessary, although a single instillation of intravesical chemotherapy immediately post-TURBT can be helpful in reducing the risk of recurrence.
- An appropriate surveillance schedule is recommended for early detection of disease recurrence. If the initial follow-up surveillance cystoscopy is negative within 4 months of TURBT, the next cystoscopy is recommended 6 to 9 months later and then yearly for up to 5 years[8-15].

### A.2. Patients with intermediate-risk NMBC:

- After TURBT and immediate intravesical chemotherapy, **a 6-week induction course of intravesical therapy** is recommended[8-15].
- **Gemcitabine** (Recommendation Level A, Evidence Level I) and **mitomycin** (Recommendation Level A, Evidence Level I) are the preferred agents for **induction intravesical chemotherapy**[8-15].
- **Gemcitabine** is preferred over **mitomycin** based on toxicity profiles and lower cost. In addition, in systematic reviews and meta-analyses, gemcitabine has shown superior efficacy compared to mitomycin, in that it demonstrated reduced rates of recurrence and progression[8].
- Intravesical **Bacillus-Calmette-Guerin (BCG)** is also an option for adjuvant intravesical chemotherapy. The availability of BCG should be considered in decision-making as it may be prioritized for treatment of higher risk disease[8-15].

### A.3. Patients with high-risk NMBC:

- High-risk NMIBC has a relatively high risk for recurrence and progression towards more invasiveness.
- Treatment options for high-risk NMIBC depend on whether the tumor has previously been shown to be unresponsive or intolerant to BCG.
- For BCG-naïve NMIBC, the options are **cystectomy** or **BCG**. When *very high-risk features* are present, **cystectomy** is preferred because of the high risk for progression to a more advanced stage, while **BCG** is preferred when these are *not present*.
- **BCG** is the preferred treatment recommendation for **BCG-naïve, high-risk NMIBC without very-high-risk features** (Recommendation Level A, Evidence Level I) [8-15].
- There are concerns regarding potentially severe local and systemic side effects and the inconsistent availability of BCG.

- All patients are at risk for recurrence both in the bladder and elsewhere in the urothelium, and **long-term surveillance is required** following initial therapy. For intermediate and high-risk NMIBC, follow-up is recommended with a urinary cytology and cystoscopy at 3- to 6-month intervals for the first 2 years, and at longer intervals as appropriate thereafter. Imaging of the upper tract should be considered every 1 to 2 years for high-risk tumors[8-15].
- Post-treatment of Recurrent or Persistent Disease:
    - ***Patients with Positive Cystoscopy***: Patients under surveillance after initial TURBT, who show a documented recurrence by positive cystoscopy, should undergo another TURBT to reclassify the AUA/SUO risk group. Patients should be treated and followed as indicated based on the risk of their recurrent disease[8-15].
    - ***Patients with Positive Cytology***: In patients without a documented recurrence but with initial positive cytology and negative cystoscopy and imaging, it may be appropriate to repeat the cytology test within 3 months.
        - If subsequent cytology tests are positive, selected mapping biopsies including transurethral resection of the prostate (TURP) may be considered. In addition, the upper tract must be evaluated and ureteroscopy may be considered for detecting tumors of the upper tract. If available, enhanced cystoscopy should be considered[8-15].
        - If the selected mapping **biopsy of the bladder is positive**, then the recommendation is to administer **intravesical BCG** followed by **maintenance BCG (preferred)** if a complete response is seen[8-15].
            - For tumors that are unresponsive to BCG or for persistent or recurrent disease post-BCG treatment, the subsequent management options include **cystectomy**, changing the intravesical agent, or participation in a clinical trial.
            - **Pembrolizumab** is also an option for patients with BCG-unresponsive, high-risk, NMIBC with Tis, with or without papillary tumors, who are ineligible for or have elected not to undergo cystectomy, although the data are currently not mature enough to determine if pembrolizumab can be considered curative in this setting[8-15].
            - Nadofaragene firadenovec-vncg is indicated for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS (with or without papillary) (Recommendation Level A, Evidence Level II) and may also be considered for patients with BCG-unresponsive, high-risk, NMIBC with high-grade papillary

Ta/T1 only tumors without CIS (Recommendation Level A, Evidence Level II)[8].

- Non-cystectomy candidates with recurrent or persistent cTa or cT1 disease may also consider concurrent **chemoradiotherapy** as an option[8].
- For patients with disease that does not respond or shows an incomplete response to treatment following a change in intravesical agent, subsequent management is cystectomy[8].

- If the bladder, prostate, and upper tract continue to show negative results on further evaluation, additional follow-up is indicated after 3 months, then at longer intervals. If BCG was given previously, maintenance BCG may be considered.

## B. Muscle-Invasive Bladder Cancer (MIBC)

**Radical cystectomy** with urinary diversion is the **treatment of choice** for patients with muscle invasive disease[8-15].

### B.1. Treatment of Stage II and IIIA Tumors

- **Neoadjuvant chemotherapy** – **Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy** improves overall survival (OS) and is the standard of care (Recommendation Level A, Evidence Level I) [8-15].
  - **ddMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles** is the preferred regimen for neoadjuvant chemotherapy (Recommendation Level A, Evidence Level II) [8-15].
  - **GC (gemcitabine/cisplatin)** is another alternative for neoadjuvant chemotherapy (Recommendation Level A, Evidence Level II) [8-15].
  - Partial cystectomy along with neoadjuvant cisplatin-based chemotherapy can be considered for stage II (cT2, N0) disease with a single tumor in a suitable location and no presence of Tis. Partial cystectomy is not an option for patients with stage III disease.

- **Adjuvant therapy** – Patients who receive initial treatment with definitive surgery and are at high risk for recurrence based on pathologic staging or those who have residual muscle-invasive cancer after neoadjuvant chemotherapy and cystectomy may be candidates for adjuvant therapy (Recommendation Level A, Evidence Level II) [8-15].
  - Available systemic agents include cisplatin-based chemotherapy **(ddMVAC with growth factor support for 3-6 cycles [preferred]; GC)** and **immunotherapy (nivolumab)** (Recommendation Level A, Evidence Level II) [8-15].

- If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered.
- If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered.
- Adjuvant RT is another option for patients with tumors that are T3–4, or with positive nodes or margins, following surgery (Recommendation Level B, Evidence Level II) [8-15].

- **Trimodality therapy (TMT)** – For patients unable or unwilling to undergo radical cystectomy with urinary diversion for muscle invasive urothelial bladder cancer, trimodality therapy (TMT) incorporating complete TURBT combined with radiation therapy (RT) plus chemotherapy may offer an alternative bladder-sparing approach[8-15].
  - Based on clinical practice and strength of the data, the following **radiosensitizing regimens** are preferred for organ-preserving chemoradiation: **5-FU plus mitomycin C** or **cisplatin** alone (Recommendation Level A, Evidence Level II). **Cisplatin plus 5-FU**, **cisplatin plus paclitaxel**, or **low-dose gemcitabine** may be considered as alternative regimens (Recommendation Level A, Evidence Level II) [8-15].
  - After a complete TURBT, 60 to 66 Gy of external beam RT (EBRT) is administered. Two doses of concurrent radiosensitizing chemotherapy may be given at weeks 1 and 4 (although weekly schedules are possible as well). Alternatively, an induction dose of 40 to 45 Gy radiotherapy may be given following complete TURBT[8-15].

- In patients with **extensive comorbid disease** or poor performance status who are non-cystectomy candidates, treatment options include concurrent **chemoradiation** (preferred) (Recommendation Level A, Evidence Level I) or **radiotherapy** alone[8-15].
  - TURBT is another option for patients with stage II disease who are non-cystectomy candidates.
  - The overall tumor status should be reassessed 2 to 3 months after treatment. If no tumor is evident, the patient should be observed. If tumor is observed, systemic therapy, concurrent chemoradiotherapy or radiotherapy alone (if no prior radiotherapy), TURBT with or without intravesical therapy, or best supportive care may be given.

### B.2. Treatment of Stage IIIB Tumors

- Primary treatment for stage IIIB (cT1–T4a, N2–3) disease can include either **down staging systemic therapy** or **concurrent chemoradiotherapy** (with the agents mentioned in the previous section) [8-15].
- Subsequent disease management depends on the response to primary treatment[8-15].
  - Patients who received downstaging systemic therapy and had a complete disease response may then be subsequently treated with cystectomy or chemoradiotherapy or may be observed until disease relapse.
    - Patients who received downstaging systemic therapy and showed a partial response may be treated with cystectomy or chemoradiotherapy (for persistent disease confined to the bladder) or treated as metastatic disease with additional lines of systemic therapy (for distant disease).
    - Patients who had disease progression following primary downstaging systemic therapy may be treated as with metastatic disease, with additional lines of systemic therapy.
  - Patients with complete disease response following concurrent chemoradiotherapy should be observed until disease relapse.
    - Disease with partial responses to concurrent chemoradiotherapy may be subsequently treated with surgical consolidation (for residual disease confined to the bladder), consideration of intravesical BCG (for Tis, Ta, or T1 residual disease), or treated as metastatic disease with systemic therapy (for remaining disease outside the bladder).
    - Progression following concurrent chemoradiotherapy may be treated as metastatic disease with systemic therapy.

### B.3. Treatment of Stage IVA Tumors

- For patients with stage IVA disease, treatment options differ depending on the presence of distant metastasis (M0 vs. M1a).
- Primary treatment recommendations for **patients with M0 disease** include **systemic therapy** or **concurrent chemoradiotherapy** followed by evaluation with cystoscopy, EUA, TURBT, and imaging of the abdomen and pelvis[8-15].
  - If no evidence of tumor is present after primary treatment, the patient may be treated with consolidation systemic therapy or adjuvant treatment with chemoradiotherapy may be initiated if the patient did not receive prior radiotherapy.
  - In general, stage IVA disease is considered unresectable. However, in patients with disease that responds to treatment, cystectomy may be an option if the tumor becomes technically resectable.

- If residual disease is noted on evaluation after primary therapy, systemic therapy or cystectomy is recommended. Systemic therapy may include targeted therapy, chemoradiotherapy (if no prior radiotherapy), or chemotherapy.

- **Patients with M1a disease** should receive **systemic therapy** as primary treatment[8-15].
  - Those select patients with metastatic disease treated with curative intent should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic imaging.
  - If a complete response is noted following primary treatment of metastatic disease, consolidative local therapy with concurrent chemoradiotherapy or cystectomy may be considered in select cases.
  - If the disease remains stable or progresses following primary therapy, these patients should follow treatment for metastatic disease.

### B.4. Follow-up

- Follow-up after a cystectomy should include urine cytology, liver function tests, creatinine, and electrolytes. Imaging of the chest, upper tract abdomen, and pelvis should be conducted at intervals based on the risk of recurrence. Patients should be monitored annually for vitamin B12 deficiency if a continent urinary diversion was created.
- Additionally, continued monitoring of the urothelium with cystoscopy and urinary cytologies with or without mapping biopsy is a routine part of the management of all cases in which the bladder is preserved[8-15].

### B.5. Recurrent or Persistent Disease

- Metastatic or local recurrence of muscle invasive disease may be managed with **cystectomy**, **systemic therapy**, or **palliative TURBT** and **best supportive care**[8-15].
- Subsequent-line therapy for metastatic disease or local recurrence includes systemic therapy, chemoradiotherapy (if no previous RT), or RT.
- **Chemotherapy** is sometimes combined with **palliative radiation** to treat metastases or pelvic recurrence after cystectomy. However, concurrent chemotherapy is inappropriate if high-dose radiation (>3 Gy fractions) is used[8-15].
  - The radiosensitizing chemotherapy regimens remain controversial in this setting. Possible options include cisplatin (Recommendation Level A, Evidence Level II); docetaxel or paclitaxel (Recommendation Level B, Evidence Level II); 5-FU with or without mitomycin C (Recommendation Level B, Evidence Level II); capecitabine (Recommendation Level C, Evidence Level III); and low-dose gemcitabine (Recommendation Level B, Evidence Level II) [8-15].

- Radiotherapy alone can also be considered as a subsequent-line therapy for patients with metastatic disease or local recurrence following cystectomy, especially in selected cases with regional-only recurrence or with clinical symptoms.

### C. Metastatic (Stage IVB) Bladder Cancer

- For patients with advanced unresectable and metastatic urothelial carcinoma, treatment options include **platinum-based chemotherapy**, **checkpoint inhibitor immunotherapy**, and **targeted therapies**[8-15].
- Patients with metastatic urothelial carcinoma who are **eligible for a cisplatin-containing regimen** should receive either **GC (gemcitabine/cisplatin)** or **ddMVAC (dose dense methotrexate/vinblastine/doxorubicin, cisplatin)** with growth factor support as first-line therapy (Recommendation Level A, Evidence Level I) [8-15].
  - A patient who is ineligible for cisplatin, but eligible for **carboplatin**, should preferentially receive gemcitabine in combination with carboplatin first line (Recommendation Level A, Evidence Level I) [8-15].
  - If there is no progression on a first-line platinum-containing chemotherapy, **avelumab maintenance therapy is preferred** (Recommendation Level A, Evidence Level I) [8-15].
- For patients with metastatic urothelial carcinoma who are **ineligible for a cisplatin-containing chemotherapy**:
  - **Pembrolizumab** is a **preferred first-line option for patients who are not eligible for any platinum-containing chemotherapy** or **who have disease progression within 12 months** of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Recommendation Level A, Evidence Level II) [8-15].
  - **Atezolizumab** is another, **non-preferred first-line treatment option** for patients who are not eligible for cisplatin-containing chemotherapy and **whose tumors express PD-L1** (Recommendation Level B, Evidence Level II) or in patients who are not eligible for any platinum-containing chemotherapy **regardless of PD-L1 expression** (Recommendation Level C, Evidence Level III) [8-15].
  - Several chemotherapy regimens, including **gemcitabine**, alone or in combination with **paclitaxel**, or the combination of **ifosfamide, doxorubicin, and gemcitabine** may also be appropriate first-line treatment options for some patients (Recommendation Level A, Evidence Level II) [8-15].
- The available **second-line options depend on what was given as the first line**.
  - If a platinum-based chemotherapy was given first-line, **pembrolizumab** (Recommendation Level A, Evidence Level I), **nivolumab**, **avelumab**,

**erdafitinib** (if eligible based on FGFR3 or FGFR2 genetic alterations), or **enfortumab vedotin** are preferred second-line treatment options (Recommendation Level A, Evidence Level II). These recommendations also pertain to patients who receive a non-platinum chemotherapy first-line[8-15].

- If progression-free survival was more than **1 year** following treatment with a platinum-containing regimen, **retreatment with platinum** may be considered[8-15].
- If a **checkpoint inhibitor was given first-line**, preferred second-line options include **enfortumab vedotin** or **gemcitabine/carboplatin** for those who are cisplatin-ineligible or **GC** or **ddMVAC** with growth factor support for those who are cisplatin-eligible (Recommendation Level A, Evidence Level II). Other regimens may also be appropriate in the second-line setting[8-15].

- For **subsequent therapy**, after treatment with a platinum-based therapy and a checkpoint inhibitor, if the patient is eligible for these, the preferred regimens are **enfortumab vedotin** (Recommendation Level A, Evidence Level I) or **erdafitinib**, if eligible based on FGFR3/FGFR2 testing results. A number of chemotherapy regimens and the antibody-drug conjugate, **sacituzumab govitecan**, are also recommended options in this setting (Recommendation Level A, Evidence Level II) [8-15]. Vinflunine is approved in Europe for second-line treatment of urothelial cancer based on one phase III trial that showed a survival benefit over best supportive care. However, vinflunine is not approved in the United States[12].

### D. HTA Recommendations

Recommendations were issued by different Health Technology Assessment (HTA) bodies on the use of the immunotherapy agents and enfortumab vedotin in urothelial carcinoma. The key recommendations are outlined below:

- **Avelumab** use as a **maintenance therapy for locally advanced/metastatic urothelial carcinoma after completing platinum chemotherapy is endorsed by all HTA organisms HAS, NICE, CADTH, IQWIG, and PBAC**. All confirm the net clinical benefit of avelumab maintenance versus BSC in terms of OS, PFS, and QoL. While NICE recommends a 5-year maximal duration of treatment to be within the range of the cost-effective use of healthcare resources, CADTH recommends a price reduction of at least 83% for it to be cost-effective.
- **Nivolumab** use as an **adjuvant treatment of MIBC** for patients at **high risk of recurrence** post complete resection has a **favorable opinion from HAS** (substantial added benefit, minor clinical added value), **NICE (only if platinum-based chemotherapy is unsuitable)**, and **CADTH** (only in high-risk

patients). IQWIG recommendation aligns with CADTH, stating a **"hint of added benefit" only when platinum chemotherapy is not possible**, while the "added benefit is not proven" for patients eligible for platinum-containing chemotherapy. PBAC doesn't recommend the use of nivolumab in this adjuvant setting. In the **second-line setting** of locally advanced/metastatic urothelial carcinoma, only **NICE** has issued a guidance, stating that nivolumab is **not recommended** post platinum-containing therapy; the **ICER for nivolumab was outside what NICE considered a cost-effective use of NHS resources**.

- **Pembrolizumab** use in the **second-line setting** of locally advanced/metastatic urothelial carcinoma **after first-line platinum therapy is endorsed by HAS** (high clinical benefit; **preferred therapeutic option over chemotherapy**) and **IQWIG** which aligns with international recommendations, while NICE doesn't support its reimbursement in this setting (for cost-effectiveness considerations). The NICE considers that while pembrolizumab **meets the criteria to be considered a life-extending treatment at the end of life**., the most plausible ICER for pembrolizumab compared with docetaxel and paclitaxel is likely to be over £50,000 per QALY gained **which is above the range that NICE normally considers a cost-effective use of NHS resources** for a life-extending treatment at the end of life. **CADTH** on the other hand recommends the reimbursement of pembrolizumab in this second-line setting, **under the condition of cost-effectiveness being improved**.
- For pembrolizumab in the first-line setting, IQWIG confirms an **indication of considerable added benefit** in comparison with chemotherapy in locally advanced or metastatic urothelial carcinoma in **adults who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a CPS ≥ 10**. On the other hand, CADTH doesn't recommend the use of pembrolizumab in this first-line setting, stating that there was **considerable uncertainty in the magnitude of clinical benefit of pembrolizumab**, and that a conclusion of cost-effectiveness couldn't be drawn. PBAC as well states that pembrolizumab is not recommended for locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer.
- In Europe, **atezolizumab** still has the EMA approval as a second-line agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior platinum containing chemotherapy, or as a first-line agent in patients who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥ 5%. **Its use in the second-line setting after platinum therapy is endorsed by both NICE (for a 2 year use) and IQWIG for patients who have a PD-L1 expression of ≥ 5%**. IQWIG however states an

**“added benefit not proven”** of atezolizumab in the **first-line setting** of locally advanced or metastatic disease versus chemotherapy, which aligns with international guidelines recommendations who only mention atezolizumab as a less preferred option in the second-line setting in patients with a PD-L1 expression of ≥ 5%.

- For **enfortumab vedotin**, CADTH, IQWIG, and PBAC support its use in the **third and later-line setting of unresectable, locally advanced or metastatic urothelial carcinoma** in patients who have **previously received a platinum-containing chemotherapy** and a **PD-1 inhibitor or PD-L1 inhibitor therapy**. For CADTH, while the drug results in improvement is OS, PFS, and response rate, a **price reduction of 93%** would be required for enfortumab vedotin to be able to achieve an ICER of $50,000 per QALY compared to a taxane. For IQWIG, while enfortumab vedotin provides a **hint of minor added benefit** in comparison with vinflunine or cisplatin/gemcitabine chemotherapy, they state that the **added benefit is not proven** in comparison with best supportive care.

## Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of bladder cancer.

These recommendations should be used to support and not supplant decisions in individual patient management.

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# Section 6.0 Appendices

## Appendix A. Prescribing Edits Definition

**1. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)**

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

| Prescribing edits Tools | Description |
|---|---|
| **AGE (Age Edit):** | Coverage may depend on patient age |
| **CU (Concurrent Use Edit):** | Coverage may depend upon concurrent use of another drug |
| **G (Gender Edit):** | Coverage may depend on patient gender |
| **MD (Physician Specialty Edit):** | Coverage may depend on prescribing physician's specialty or board certification |
| **PA (Prior Authorization):** | Requires specific physician request process |
| **QL (Quantity Limit):** | Coverage may be limited to specific quantities per prescription and/or time period |
| **ST (Step Therapy):** | Coverage may depend on previous use of another Drug |
| **EU (Emergency use only):** | This drug status on Formulary is only for Emergency use. |
| **PE (Protocol edit)** | Use of drug is dependent on protocol combination, doses and sequence of therapy |

Examples:

**Age edit:** Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.

**Concurrent Use Edit**: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.

**Gender Edit**: Exemestane in Endometriosis should be used only by Females.

**Physician Specialty Edit**: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.

**Prior Authorization**: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

**Quantity Limit**: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose
**Step Therapy**: Aripiprazole in Social Anxiety: should be used as third line after:
First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin
**Emergency use only**: Furosemide IV form in Hypertension is used only in emergency settings.
**Protocol edit**: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

**2. Adult and Pediatric Quantity Limit?**

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.
If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

**3. What information is available in the notes?**

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

**4. Drug interactions**

1. A: No known interaction
2. B: No action needed
3. C: Monitor therapy
4. D: Consider therapy modification
5. X: Avoid combination

**5. Defined Daily Dose**

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

**6. REMS**

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

## Appendix B. Level of Evidence Description

1. **Level of Evidence Adopted:**

| **Grade of research**[1] | |
|---|---|
| **A** | Strongly recommend; Good evidence |
| **B** | Recommend; At least fair evidence |
| **C** | No recommendation for or against; Balance of benefits and harms too close to justify a recommendation |
| **D** | Recommend against; Fair evidence is ineffective, or harm outweighs the benefit |
| **E** | Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined. |
| **Level of evidence** | |
| **Level I** | Meta-analysis of multiple studies |
| **Level II** | Experimental studies |
| **Level III** | Well-designed, quasi-experimental studies |
| **Level IV** | Well-designed, non-experimental studies |
| **Level V** | Case reports and clinical examples |

## Appendix C. PubMed Search Methodology Terms

The following is the result of the PubMed search conducted for Bladder Cancer guideline search:

| Query | Sort By | Filters | Search Details | Results |
|---|---|---|---|---|
| **(((((Urinary Bladder Neoplasms[MeSH Major Topic]) OR (Urinary Bladder Neoplasms[Title/Abstract])) OR (Non-Muscle Invasive Bladder Neoplasms[Title/Abstract])) OR (Non-Muscle Invasive Bladder Neoplasms[MeSH Major Topic])) OR (bladder cancer[MeSH Major Topic])) OR (bladder cancer[Title/Abstract])** | | Guideline, in the last 5 years | ("urinary bladder neoplasms"[MeSH Major Topic] OR "urinary bladder neoplasms"[Title/Abstract] OR "non muscle invasive bladder neoplasms"[Title/Abstract] OR "non muscle invasive bladder neoplasms"[MeSH Major Topic] OR "urinary bladder neoplasms"[MeSH Major Topic] OR "bladder cancer"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter])) | 26 |

## Appendix D. Treatment Algorithms

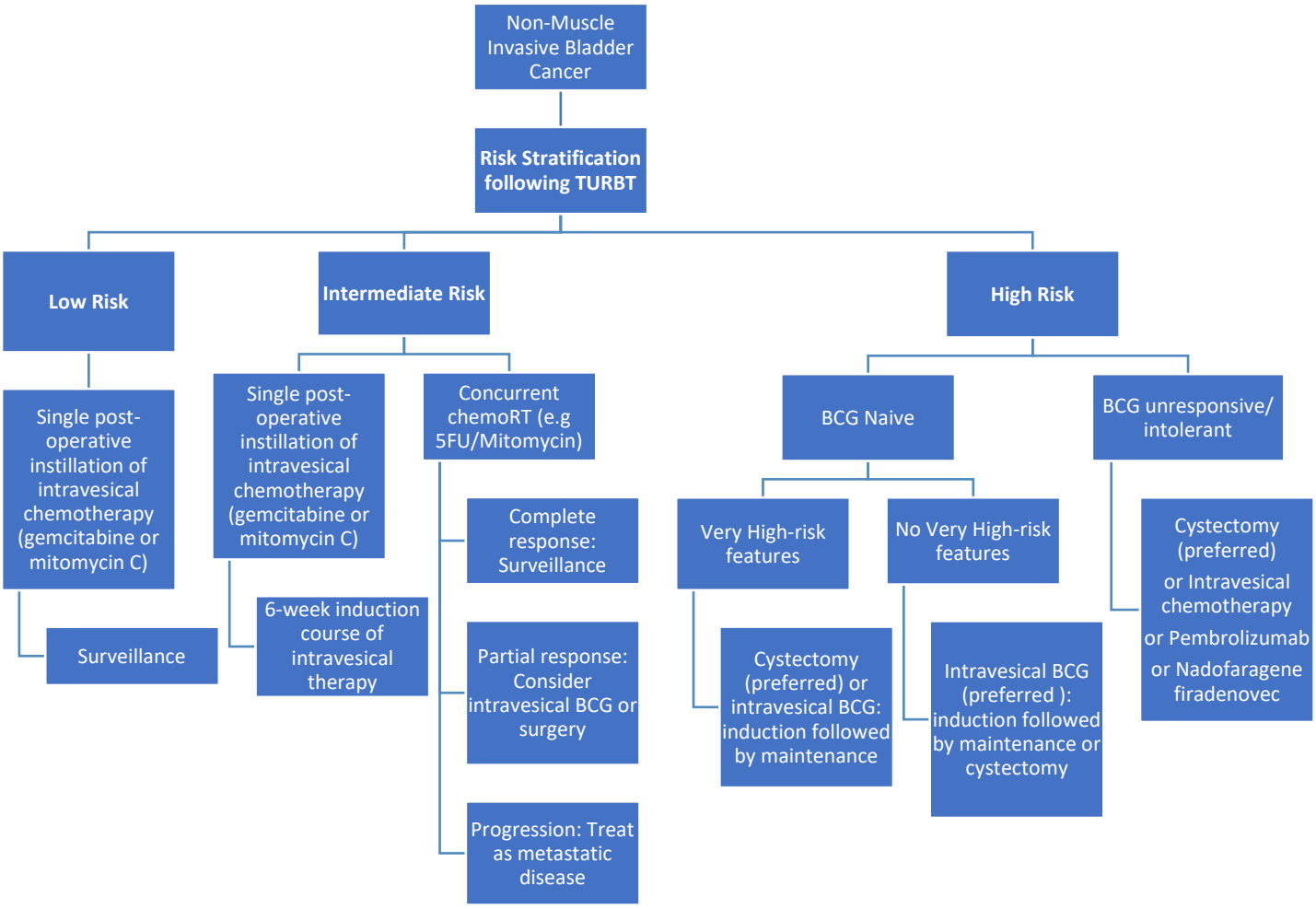


***Figure 5.*** *Management of Non-Muscle Invasive Bladder Cancer*

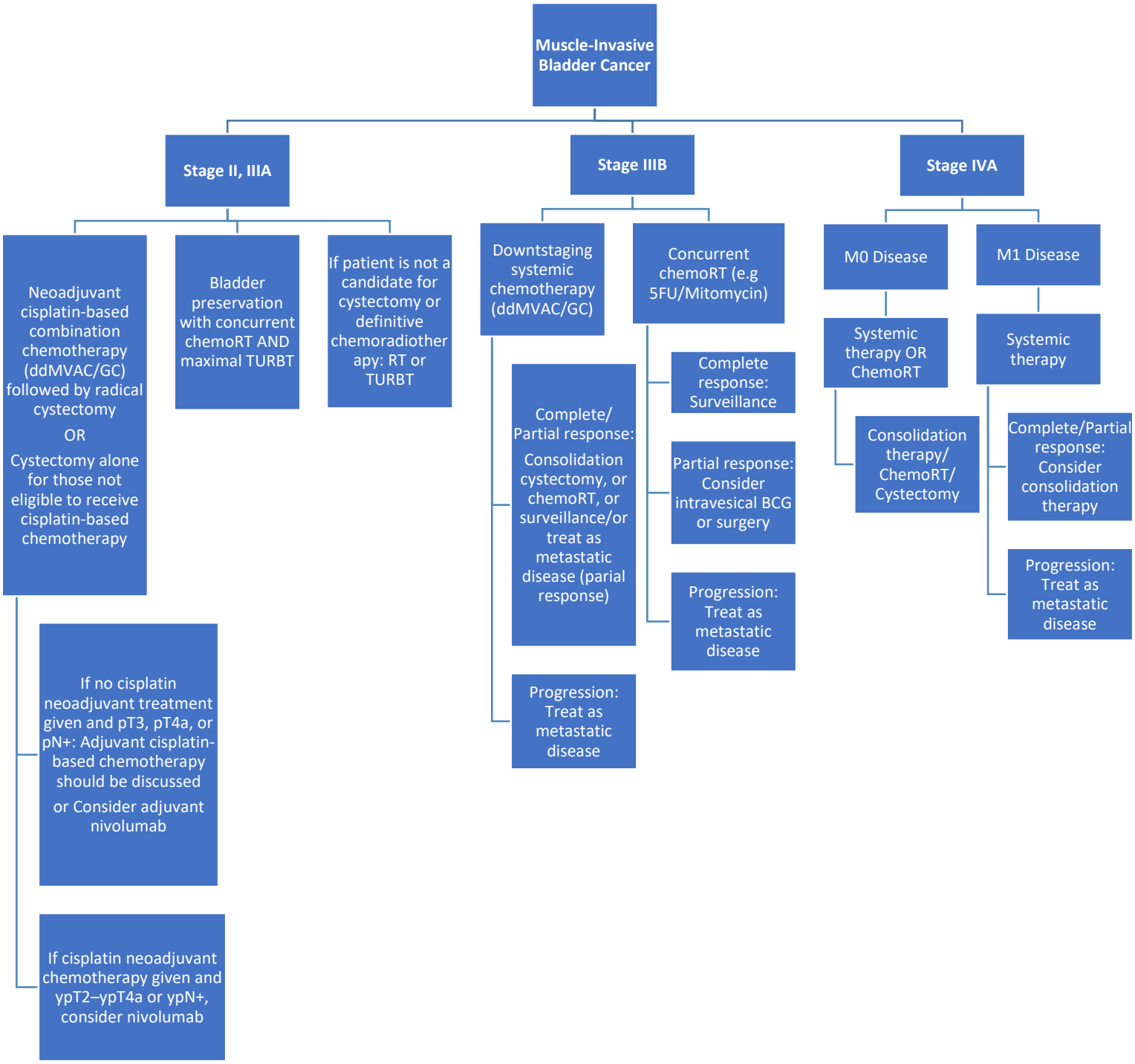


***Figure 6.*** *Management of Muscle-Invasive Bladder Cancer*

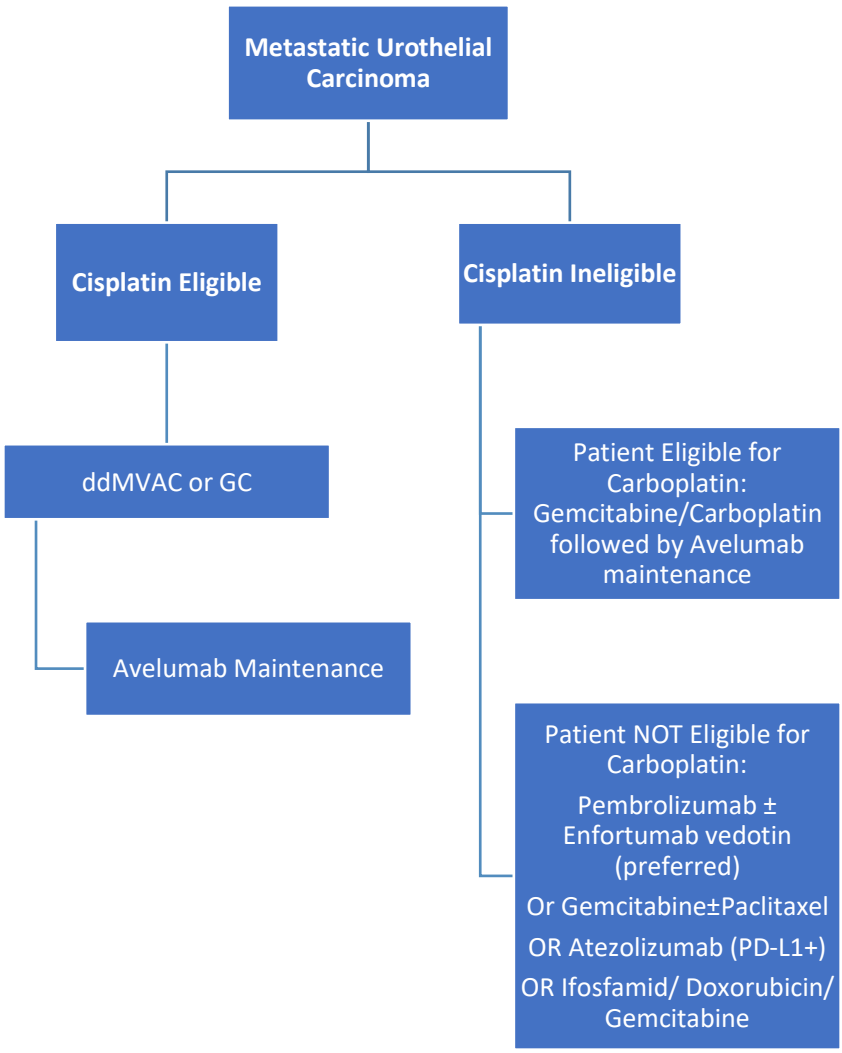


***Figure 7.*** *Management of Metastatic Urothelial Carcinoma*

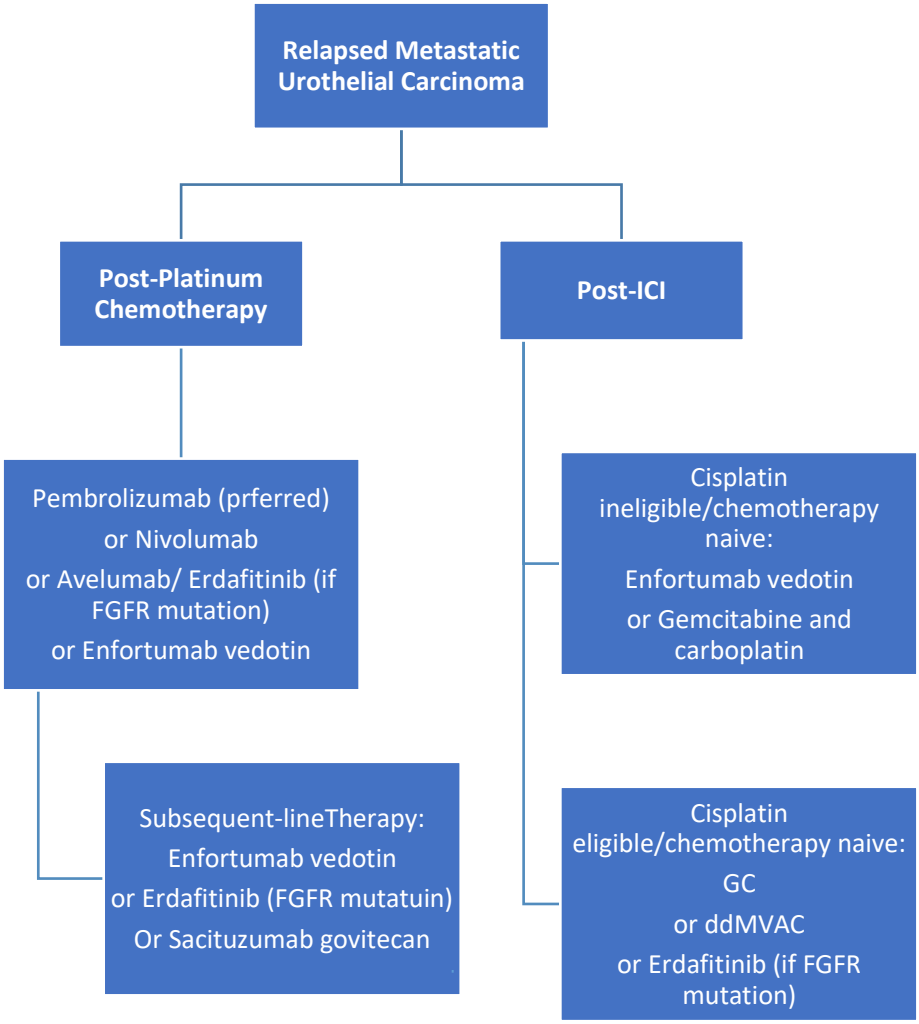


***Figure 8.*** *Management of Relapsed Metastatic Urothelial Carcinoma*