Advances in diagnosis and treatment of bladder cancer

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ABSTRACT
Bladder cancer remains a leading cause of cancer death worldwide and is associated with substantial impacts on patient quality of life, morbidity, mortality, and cost to the healthcare system. Gross hematuria frequently precedes the diagnosis of bladder cancer. Non-muscle-invasive bladder cancer (NMIBC) is managed initially with transurethral resection of a bladder tumor (TURBT), followed by a risk stratified approach to adjuvant intravesical therapy (IVe), and is associated with an overall survival of 90%. However, cure rates remain lower for muscle invasive bladder cancer (MIBC) owing to a variety of factors. NMIBC and MIBC groupings are heterogeneous and have unique pathological and molecular characteristics. Indeed, The Cancer Genome Atlas project identified genetic drivers and luminal and basal molecular subtypes of MIBC with distinct treatment responses. For NMIBC, IVe immunotherapy (primarily BCG) is the gold standard treatment for high grade and high risk NMIBC to reduce or prevent both recurrence and progression after initial TURBT; novel trials incorporate immune checkpoint inhibitors. IVe gene therapy and combination IVe chemotherapy have recently been completed, with promising results. For localized MIBC, essential goals are improving care and reducing morbidity following cystectomy or bladder preserving strategies. In metastatic disease, advances in understanding of the genomic landscape and tumor microenvironment have led to the implementation of immune checkpoint inhibitors, targeted treatments, and antibody-drug conjugates. Defining better selection criteria to identify the patients most likely to benefit from a specific treatment is an urgent need.

Introduction
Bladder cancer was the fourth leading cancer in men in 2023, representing 6% of estimated new cancers and 4% of cancer related deaths.1 2 At initial presentation, 70-75% of patients have non-muscle-invasive bladder cancer (NMIBC), 20-25% have muscle invasive bladder cancer (MIBC), and 5% have metastatic disease. About 90% of bladder cancer cases are urothelial cell carcinoma; the remainder are mostly squamous cell carcinoma, adenocarcinoma, or neuroendocrine carcinoma.3 8 Carcinoma in situ represents about 10% of NMIBC.3 4 6 NMIBC frequently recurs or progresses with five year rates of 31-78% and 1-45%, respectively. Within NMIBC, low grade non-invasive Ta urothelial carcinomas frequently recur, but progression is rare. By contrast, carcinoma in situ (all of which is high grade) can progress at a five year rate of 50%. Importantly, untreated patients with carcinoma in situ can progress to MIBC at a 40-80% rate within five years. For patients with high grade T1 bladder cancer, five year recurrence, progression, and cancer specific survival are 42%, 21%, and 87%, respectively.4 6 9 These rates of progression among high grade NMIBC underscore the need for risk stratified intravesical therapy (IVe) and vigilant surveillance.

Overall survival in patients after cystectomy correlates with pathologic stage, and about 30% of patients can experience recurrence at a median of 12 months after cystectomy.1 3-15 Unfortunately, the five year overall survival of patients with distant metastasis remains low.13 Relevant clinicopathologic factors include the number and size of tumors, presurgical recurrence rates, T stage, presence of carcinoma in situ, and histologic grade and nodal status.3 5 10 12 14 16-24 While platinum based chemotherapy remains an important component of treatment for patients with metastatic disease, emerging novel treatments, including approved antibody-drug conjugates and targeted treatments, have represented a paradigm shift in managing metastatic bladder cancer.4 9 15 25-32 Immune checkpoint inhibitors remain helpful in these patients, particularly those with high tumor
mutation load and expression of programmed death ligand 1 (PDL1) (tumor mutational burden (TMB)high/PDL1+). A new generation of targeted treatments related to FGFR3 alterations and the tumor cells’ expression of nectin-4 and trophoblast cell surface antigen 2 (TROP2) have been rapidly incorporated into clinical practice.14, 25-27 31 32 35

This review discusses new treatment and diagnostic options for bladder cancer, including the completion of transurethral resection of a bladder tumor (TURBT), cystectomy and bladder preservation strategies, cisplatin based chemotherapy, systemic immunotherapy, and other recently introduced targeted treatments that represent a paradigm shift in both localized and metastatic disease, and which are behind the improvements achieved in quality of life of the patients. The role of enhanced diagnostic methods, including narrow band and blue light cystoscopy, urine related molecular biomarkers, and imaging methods, is also revisited. This review is intended to assist health professionals and scientists to understand the current management of patients with bladder cancer.

Sources and selection criteria
We searched PubMed and Embase using the terms “bladder cancer”, “bladder cancer and molecular pathogenesis”, “bladder cancer epidemiology”, “bladder cancer therapy”, “bladder cancer molecular subtypes”, “bladder cancer diagnosis”, “bladder cancer recurrence”, “bladder cancer progression”, “NMIBC”, “metastatic bladder cancer”, “bladder cancer chemotherapy”, “bladder cancer targeted therapy”, and “bladder cancer immunotherapy”. All English language studies published within the past 10 years (between 1 September 2013 and 1 September 2023) were considered. Studies were prioritized for discussion based on their level of evidence (randomized controlled trials, systematic reviews, and meta-analyses were preferred), their pursuit of mechanistic insights, and their time of publication (more recent studies were preferred). We also identified references from relevant review articles, as well as from the similar items section of the United States National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology clinical practice guidelines, and the European Association of Urology clinical practice guidelines. We screened and reviewed more than 300 articles in the preparation of this manuscript. We excluded articles published in non-peer-reviewed journals, case reports, and case series.

Epidemiology
Bladder cancer is common worldwide and poses a significant public health challenge. GLOBOCAN data from 2020 revealed an incidence of 573 000 new bladder cancer cases and 213 000 deaths worldwide in 2020. The five year prevalence worldwide in 2020 was 1 721 000 cases. Over three quarters of new bladder cancer cases occurred in men. Male to female ratios of age standardized rate for incidence (per 100 000 people) vary by region from 6:1 to 2:1.36 37 GLOBOCAN world maps of bladder cancer incidence and mortality rates are shown in figure 1 and figure 2. Bladder cancer is a complex disease with known risk factors.8 Smoking is the most common risk factor, and many patients with bladder cancer are active smokers at the time of diagnosis.8 38 Use of smokeless tobacco products is also associated with an increased risk of bladder cancer. Environmental risk factors for bladder cancer include occupational exposure (rubber, diesel, painting dyes, oils, cleaning solvents, coal) and drinking water contaminated with arsenic or pesticides. Therefore, reducing exposure to toxic chemicals in the workplace through appropriate protective equipment and avoiding consumption of contaminated drinking water can decrease the risk of bladder cancer. Exposure to specific chemotherapy or radiation protocols (ie, pelvic radiation, cyclophosphamide) can contribute to iatrogenic bladder cancer. In this clinical context, bladder cancer can have a latency period of many years, as is the case of patients with chronic urinary tract irritation, or inflammation in those with long term indwelling catheters, who are at risk for bladder cancer owing to frequently associated urinary tract infections.8

Interventions such as cessation of smoking (including tobacco consumption), reducing occupational toxic exposure, and improving the quality of water, together with increasing fruit and vegetable consumption, good hydration, and reduced consumption of processed meat and red meat, could be associated with a reduced risk of bladder cancer, but also can improve overall health and oncologic outcomes during bladder cancer treatment.8

Pathophysiology and molecular steps
Bladder cancer develops via two distinct pathways, giving rise to NMIBC and MIBC.16 39 The two subtypes have unique clinical and pathological features and different molecular characteristics. Alterations common in NMIBC, including deletion of chromosome 9 and point mutation in FGFR3, are evident in hyperplastic precursors and papillary NMIBC, suggesting a clonal relation between the precursor and bladder cancer.20 39 By contrast, MIBCAs require the inactivation of one or more tumor suppressor genes, such as TP53, RB1, and PTEN, and tumor development is preceded by the appearance of flat urothelial dysplasia and carcinoma in situ; interestingly, these lesions share molecular features with high grade and invasive bladder carcinomas (fig 3).16 18 20 39

Non-muscle-invasive bladder cancer
At the molecular level, most cases of NMIBC are genomically stable, with frequent chromosome 9 deletion occurring in about 50% of these tumors. The CDKN2A locus (9p21) encodes p16 and p14ARF, which are negative regulators of the RB pathway and p53 pathway, respectively. Chromosome 9 loss also implicates TSC1, a tumor
suppressor that regulates mammalian target of rapamycin (mTOR) signaling. Additional deletions of chromosome arms 10q, 11p, 11q, 17p, 18q, 19p, and 19q have been described in up to 20% of cases. Most cases of NMIBC are characterized by activating point mutations or chromosomal translocation in FGFR3. The fusion proteins resulting from these translocations function as oncogenes. Activating mutations in the RAS gene family members have also been found in NMIBC; these mutations and FGFR3 mutations are mutually exclusive.

Activation of the RAS-MAPK pathway can contribute to about 80% of NMIBC. Activating mutations in PIK3CA are also common in NMIBC, and frequently occur with FGFR3 mutations. Inactivated tumor suppressor genes include TSC1 (9q34), mutated in about 15% of cases, and, less frequently, mutations in TSC2. The TSC1/TSC2 complex regulates the mTOR branch of the PI3K pathway; loss of one copy or mutation of TSC1 in many of these tumors suggests that upregulated mTOR signaling is an important feature of NMIBC. Whole exome sequencing additionally identified inactivating mutations in genes encoding chromatin modifying proteins, including KDM6A, CREBBP, EP300, and ARID1A, thus indicating that epigenetic alterations are likely to play a major role in shaping the phenotype of these tumors.

Muscle invasive bladder cancer
Common alterations in MIBC include loss of function of key tumor suppressors, leading to escape from cell cycle checkpoints and dysregulation of major signaling pathways. TP53 and RB1 are frequently mutated, and regulators of their pathways are also altered (ie, amplification of MDM2 and E2F3 and homozygous deletion of CDKN2A). Hemizygous deletion, homozygous deletion, and low expression of PTEN are also common. Other mutations in gene encoding components of the PI3K pathway include those in TSC1, AKT1, and PIK3CA (at lower frequencies than in NMIBC). The upstream pathway activator ERBB2/HER2 is amplified, mutated, or overexpressed in a subset of cases, particularly in the micropapillary subtype.

Although FGFR3 mutations are less frequent in MIBC than in NMIBC, up to 40% of MIBCs show upregulated expression. Activation of FGFR1 can induce epithelial-mesenchymal transition, whereby cells acquire migratory and invasive properties, and might have a potential role in MIBC metastasis. RAS mutations and mutational inactivation of NOTCH pathway genes also contribute to MAPK pathway activation.

Epigenetic changes also play a significant role in MIBC development; genome wide analysis has indicated the importance of both DNA methylation and histone methylation in gene silencing.
differences in DNA methylation exist between NMIBC and MIBC, with common hypomethylation in non-CpG islands in NMIBC, and widespread promoter hypermethylation in MIBC. Tumors with HER2 mutations show a good response to neoadjuvant chemotherapy, and the response to cisplatin based chemotherapy is related to mutations in ERCC2. Regarding cisplatin based neoadjuvant chemotherapy and pathological response and survival of patients, the non-luminal molecular subtype is reported to be associated with improved survival compared with the luminal subtype.

Subtypes of bladder cancer
Bladder represents a morphologically and genomically heterogeneous disease with a wide spectrum of histological subtype and associated molecular alterations. The conventional urothelial carcinoma is the most common type, but a diversity of morphological appearances can be displayed. The World Health Organization fifth edition reclassified the histologic subtypes of urothelial carcinoma as follows: infiltrating urothelial carcinoma with divergent differentiation; nested, including large nested; micropapillary; lymphoepithelioma-like; plasmacytoid/signet ring cell/diffuse; sarcomatoid; giant cell; poorly differentiated; lipid rich; and clear cell. Some subtypes display specific molecular alterations. For example, plasmacytoid urothelial carcinoma is an aggressive subtype typically presenting at an advanced stage. This subtype shares immunohistochemistry and molecular alterations with conventional urothelial carcinoma, such as staining for KRT7, p63, GATA3, and uroplakins, along with genetic mutations in TP53, RB1, KMT2D, and ARID1A. However, the development of these tumors is additionally driven by loss of function mutations in CDH1 and promoter hypermethylation of CDH1. Of note, by contrast to the germline CDH1 mutations seen in diffuse hereditary gastric cancers and a subset of lobular breast cancer, no germline CDH1 mutations were identified in plasmacytoid subtype.

Micropapillary urothelial carcinoma represents another rare but aggressive subtype of bladder carcinoma. Many clinicians advise an early cystectomy in these tumors, even in the absence of invasion into the muscularis propria layer. This tumor is commonly associated with higher rates of ERBB2 alterations, more commonly amplifications than mutations.

Small cell/neuroendocrine carcinoma of the bladder is a rare subtype of bladder cancer morphologically identical to its counterpart in the lung, and similarly it commonly harbors combined alterations in both TP53 and RB1. Furthermore, other alterations have also been detected, including TERT promoter mutations and truncating alterations...
within chromatin-remodeling genes such as **CREBBP**, **EP300**, **ARID1A**, **KMT2D**, and **APOBEC**.

Sarcomatoid urothelial carcinoma is another extremely rare aggressive tumor subtype comprising about 0.3% of all primary urinary bladder tumors; it carries an overall dismal prognosis. At a molecular level, this tumor type is enriched with mutations in **TP53**, **RB1**, and **PIK3CA**, and is associated with the dysregulation of the epithelial–mesenchymal transition pathway.

**Clinical presentation, diagnosis, and risk stratification**

Most patients are diagnosed because of painless gross hematuria; the incidence of bladder cancer is 10-20% in patients presenting with gross hematuria and 2-5% in populations with microscopic hematuria.1 Bladder cancer can also be suspected if the patient presents with non-specific lower urinary tract symptoms associated with irritative voiding, namely increased urinary urgency, frequency, and dysuria.1 These symptoms are more frequent in patients with carcinoma in situ than with papillary Ta/T1 tumors, and should prompt urological assessment. Urinary tract infection needs to be ruled out, since it can mimic and/or coexist with bladder cancer.1 3 5 6

Evaluation of patients suspected of having bladder cancer is performed using cystoscopy. Cystoscopy remains the gold standard procedure for the initial diagnosis of bladder cancer. Any abnormal finding, such as reddish flat, papillary, or solid lesions, requires pathological evaluation, because inflammatory and other benign conditions can mimic bladder cancer. Cystoscopic detection of carcinoma in situ can be enhanced by fluorescence cystoscopy or narrow band imaging, both of which can be performed with flexible endoscopic equipment in the office.1 3 5-7 These technologies improve the differentiation of tumorous lesions from normal tissue by taking advantage of the increased metabolic activity (blue light) and vessel architecture (narrow band) in cancer tissues and they have higher specificity for bladder cancers than traditional cystoscopy.

Blue light fluorescence cystoscopy uses hexaminolevulinate hydrochloride (a photosensitizing heme precursor instilled one hour before cystoscopy) to detect the pathological accumulation of fluorescent porphyrin products in bladder cancer cells. The technique improves diagnosis and decreases short term and long term recurrence.1 3 However, limitations include the excessive cost of the equipment and a high false positive rate. Enhanced endoscopic technologies, such as blue light fluorescence cystoscopy or narrow band imaging, should be used when available to increase the detection rate of additional papillary and flat lesions and ensure complete tumor resection.

**Bipolar electrocautery** is another new technology that uses less energy and voltage than the standard monopolar cautery of the TURBT loop, because the circuit does not pass through the patient.5 6 47 48 Histopathologic material can be obtained by transurethral biopsy or resection of the entire area. Often, urine cytology is performed as an adjunct measure to detect bladder cancer in the setting of known or suspected high grade cancers and is usually followed by cystoscopy.
Currently, urine cytology is reported following the Paris system, which emphasizes reporting high grade urothelial carcinoma as the main diagnostic category, followed by suspicious for high grade urothelial carcinoma, atypical urothelial cells, and negative for high grade urothelial carcinoma categories. The average diagnostic rate following these categories is 79%, 55%, 24%, and 20%, respectively. Low grade urothelial neoplasia is an additional category to summarize cytologic changes suggesting low grade malignancy, including urothelial papilloma, papillary urothelial neoplasia of low malignant potential, and low grade urothelial carcinoma. In addition to urine cytology, several Food and Drug Administration approved molecular biomarkers (including NMP22 BC, NMP22 BladderChek, BTA Stat, BTA TRAK, UroVysion, and uCyt+/ImmunoCyt) have been variably applied to diagnose primary or recurrent bladder cancer. Some of the barriers to adoption and guideline endorsement associated with these urinary biomarkers in routine clinical practice include trial design (hematuria vs bladder cancer, low event rates, variable primary outcomes, etc), as well as low sensitivity and specificity.

Bladder cancer prognosis and management depend on bladder cancer histopathology (NMIBC or MIBC). Histopathology is one of most reliable determining factors of tumor biology to inform management. Although prognostication cannot be exact, the depth of tumor infiltration into the bladder wall can provide an adequate risk stratification (fig 4). Low grade versus high grade stratification is most relevant in NMIBC; all MIBCs are considered high grade. Tumors that do not invade the lamina propria are classified as Ta according to the tumor, node, metastases (TNM) classification system. Tumors invading the lamina propria are classified as stage T1, characterized by adverse tumor behavior. Tumors penetrating the bladder detrusor muscle and beyond are highly aggressive.

Imaging studies of the upper urinary tract (to evaluate the renal collecting system) and the ureter are essential to evaluate patients with hematuria and to assess for upper tract urothelial tumors. While moderate to large bladder tumors can be visualized on contrast imaging, it plays a minor part of role in the detection of bladder cancer. CT (computed tomography) and MRI (magnetic resonance imaging) urography are the imaging studies of choice and are associated with improved diagnostic accuracy over ultrasonography. CT or MRI is mandated in patients with confirmed MIBC to complete staging and to assess potential for distant spread. Bladder lumen provides risk stratification for non-muscle-invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). Tumors that do not invade the lamina propria are classified as Ta or Tis according to the tumor, node, metastases (TNM) classification system. Tumors invading the lamina propria are classified as stage T1 and show adverse tumor behavior. Tumors penetrating the bladder detrusor muscle (T2) and beyond (T3 and T4) are highly aggressive (A). Low grade versus high grade stratification is most relevant in NMIBC, with two different grading schemes in use (WHO 1973 and 2004) and a hybrid three tier system incorporating features from WHO 1973 and 2004; all MIBCs are considered high grade (B). PUNLMP=papillary urothelial neoplasm of low malignant potential.
To diagnose distant metastases, a sensitivity of 48-87% and specificity of 90-97%, respectively, have been reported for FDG PET (fluorodeoxyglucose-positron emission tomography)/CT in patients with MIBC.

TURBT is the mainstay of clinical diagnosis of bladder cancer to assess histologic grade, variant histology (histological subtype), and extent of invasion. TURBT has both a diagnostic and treatment role and can be a good and potentially curative treatment depending on the pathological features of the tumor. Small tumors can be resected en bloc with the electrified wire loop of the resectoscope, whereas larger tumors are resected in multiple fragments. En bloc resection can be accomplished with some newer laser technology but is still relatively limited.

Patients with NMIBC can be stratified into three risk groups according to the number of tumors, tumor size, recurrence rate, tumor stage, presence of carcinoma in situ, and tumor grade, as well as the role of the prostatic urethra to guide treatment after initial TURBT (table 1). Patients with low risk disease are often treated with the initial TURBT if all disease was visibly resected, but remain under close surveillance owing to the risk of recurrence. Although surveillance protocols have been recommended, at a minimum, cystoscopy should be performed three months postoperatively, 12 months postoperatively, and then at decreasing frequencies for up to five years. Tumor recurrences can also be treated with TURBT or in office fulguration (heat ablation) for smaller lesions. Understanding the biology of bladder cancer at the initial TURBT in patients with high risk disease is critical; the probability of upstaging a patient with T1 disease to T2 is up to 20%, even if muscle was present in the resected tissue, and up to 40% if muscle was not present. Furthermore, even if the tumor is accurately staged at initial TURBT, the probability of an incomplete resection resulting from factors such as multiplicity, tumor size, and location is 50%.

Accurate staging is of outmost importance in bladder cancer to determine the appropriate treatment after initial TURBT. Thus, a repeat TURBT is recommended within 2-6 weeks in patients with a known incompletely resected tumor or with tumors invading the lamina propria (T1), and should be considered in high grade non-invasive disease (except carcinoma in situ alone) to improve staging accuracy and increase recurrence free survival. Thus, repeating TURBT after newly diagnosed T1 bladder cancer improves recurrence free and progression free survival at five years by 25% and 14%, respectively. Repeat TURBT is also recommended in patients with NMIBC variant who are being considered for bladder sparing regimens.

### Treatment

Various guidelines on managing bladder cancer are available, including from the European Association of Urology, the American Urological Association, the Society of Urologic Oncology, and the NCCN. Although broadly concordant, these recommendations have essential differences due to the varying evidence underpinning them. In general, NMIBCs are frequently managed with endoscopic resection and risk based intravesical adjuvant treatment (tables 2-4). By contrast, MIBCs are managed with more aggressive treatments, including neoadjuvant or adjuvant systemic chemotherapy in combination with radical cystectomy or trimodal treatment, which includes TURBT, radiation treatment and chemotherapy (tables 5 and 6).

### Treatment of non-muscle-invasive bladder cancer

In patients with intermediate and high risk diseases, adjuvant intravesical immunotherapy is the treatment of choice. BCG can decrease the recurrence and progression of bladder cancer. Adjuvant BCG must include maintenance treatment for one year in intermediate risk disease and up to three years (if tolerable) for high risk disease to achieve maximal efficacy.

Patients with persistent or worsening disease after an appropriate treatment course with BCG and those who experience disease relapse while on maintenance treatment are deemed BCG unresponsive. Radical cystectomy is the most oncologically effective treatment for these patients who are fit for surgery, although consideration can be given to bladder preservation strategies, including IVe chemotherapy, IVe gene therapy (nadofaragene firadenovec), device assisted intravesical treatment, and clinical trials.

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**Table 1 | American Urological Association/Society of Urologic Oncology risk stratification for NMIBC**

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
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<tbody>
<tr>
<td>PUNLMP</td>
<td>Low grade urothelial carcinoma</td>
<td>High grade urothelial carcinoma</td>
</tr>
<tr>
<td>Low grade urothelial carcinoma</td>
<td>• Recurrence within one year, LGTa</td>
<td>• T1</td>
</tr>
<tr>
<td>• Ta and &lt;3 cm, and solitary</td>
<td>• Solitary LGTa &gt;3 cm</td>
<td>• Any recurrent, HGTa</td>
</tr>
<tr>
<td></td>
<td>• LGTa, multifocal</td>
<td>• HGTa &gt;3 cm (or multifocal)</td>
</tr>
<tr>
<td></td>
<td>• LGTa</td>
<td>• Any CIS</td>
</tr>
<tr>
<td>High grade urothelial carcinoma</td>
<td>• BCG failure in HG patient*</td>
<td>• Any variant histology*</td>
</tr>
<tr>
<td></td>
<td>• Ta &gt;3 cm solitary</td>
<td>• *Any HG prostatic urethral involvement</td>
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</tbody>
</table>

BCG=Bacillus Calmette-Guérin; CIS=carcinoma in situ; HG=high grade; LG=low grade; NMIBC=non-muscle invasive bladder cancer; PUNLMP=papillary urothelial neoplasm of low malignant potential; Ta=non-invasive bladder cancer; T1=lamina propria invasive bladder cancer.

*Features associated with very high risk disease.
Table 2 | Initial management per NMIBC risk groups49 50
<table>
<thead>
<tr>
<th>Risk group</th>
<th>Initial management</th>
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<tbody>
<tr>
<td>Low</td>
<td>Surveillance</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intravesical treatment (preferred) or surveillance</td>
</tr>
<tr>
<td>High</td>
<td>BCG naive</td>
</tr>
<tr>
<td></td>
<td>- Very high risk features: cystectomy (preferred) or BCG</td>
</tr>
<tr>
<td></td>
<td>- No very high risk features: BCG (preferred, category 1) or cystectomy</td>
</tr>
<tr>
<td></td>
<td>- BCG unresponsive or BCG intolerant</td>
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<tr>
<td></td>
<td>- Cystectomy (preferred) or intravesical chemotherapy or pembrolizumab (selected patients) or nadofaragene firadenovec</td>
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Table 3 | European Association of Urology risk groups for NMIBC and recommended treatment51
<table>
<thead>
<tr>
<th>Low risk</th>
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</thead>
<tbody>
<tr>
<td>- A primary, single, Ta LG/G1 tumor &lt; 3 cm in diameter without CIS in a patient &lt; 70 yr</td>
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<tr>
<td>- A primary LG/G1 tumor with at most one of the following additional clinical risk factors (age &gt;70 years, multiple tumors, and tumor diameter &gt; 3 cm)</td>
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<tr>
<td>- Recommended treatment: Offer one immediate instillation of intravesical chemotherapy after TURBT</td>
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<tr>
<td>Intermediate</td>
<td></td>
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<tr>
<td>- Patients without CIS who are not included in either the low risk, high risk, or very high risk groups</td>
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<tr>
<td>- Recommended treatment: For all patients, either one year full dose BCG treatment (induction plus three weekly instillations at 3, 6, and 12 months) or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient’s risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. Offer one immediate chemotherapy instillation to patients with small papillary recurrences detected more than one year after previous TURBT.</td>
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<tr>
<td>High risk</td>
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<tr>
<td>- All T1 HG/G3 without CIS, except those included in the very high risk group</td>
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</tr>
<tr>
<td>- All CIS patients, except those included in the very high risk group</td>
<td></td>
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<tr>
<td>- Ta LG/G2 or T1 G1, no CIS with all three risk factors (age &gt;70 yr, multiple tumors, and tumor diameter &gt; 3 cm)</td>
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<tr>
<td>- T1 HG/G3 or T1 LG, no CIS with at least two risk factors (two of: age &gt;70 yr, multiple tumors, and tumor diameter &gt; 3 cm)</td>
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<tr>
<td>- T1 G2 no CIS with at least one risk factor (one of: age &gt;70 yr, multiple tumors, and tumor diameter &gt; 3 cm)</td>
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<tr>
<td>- Recommended treatment: Offer intravesical full dose BCG instillations for 1-3 years or RC.</td>
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</tr>
<tr>
<td>Very high risk</td>
<td></td>
</tr>
<tr>
<td>- Ta HG/G3 and CIS with all three risk factors (age &gt;70 yr, multiple tumors, and tumor diameter &gt; 3 cm)</td>
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</tr>
<tr>
<td>- T1 G2 and CIS with at least two risk factors (two of: age &gt;70 yr, multiple tumors, and tumor diameter &gt; 3 cm)</td>
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</tr>
<tr>
<td>- T1 HG/G3 and CIS with at least one risk factor (one of: age &gt; 70 years, multiple tumors, and tumor diameter &gt; 3 cm)</td>
<td></td>
</tr>
<tr>
<td>- T1 HG/G3 no CIS with all 3 risk factors (age &gt; 70 yr, multiple tumors, and tumor diameter &gt;3 cm)</td>
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</tr>
<tr>
<td>- Recommended treatment: Consider RC and offer intravesical full dose BCG instillations for 1-3 years to those who refuse or are unfit for RC.</td>
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Following TURBT, a single dose of intravesical treatment with chemotherapeutic agents (gemcitabine, mitomycin or doxorubicin in the US, as well as epirubicin or pirarubicin in Europe) within 24 hours can decrease recurrence by 40% at one year and 15% at five years. Intravesical chemotherapy should be considered in patients immediately following TURBT (or within 24 hours post resection) with low grade papillary lesions if no contraindications are present, including clinical concern bladder perforation during TURBT.6 14 44

Off label combination intravesical chemotherapy (eg, with gemcitabine/docetaxel) is a viable alternative to BCG for some intermediate and high risk NMIBC patients and can also be used in the BCG unresponsive setting. In addition, pembrolizumab was approved by the FDA for BCG unresponsive carcinoma in situ with or without papillary disease in patients who refuse or are ineligible for radical cystectomy. Valrubicin is also approved in the BCG failure setting, although its inability to provide long term benefit coupled with high cost have relegated

Additional clinical risk factors are age >70 years, multiple tumors, and tumor diameter >3 cm; CIS, PUNLMP; and LG combined into one LG category owing to similar prognostic data. LG and HG (low and high grade) according to 2004/2022 WHO grading system; G1, G2, and G3 (grade 1-2-3) according to 1973 WHO grading system; patients with carcinoma in situ in the prostatic urethra, lymphoepithelial inxion, and micropapillary, plasmacytoid, sarcomatoid, or neuroendocrine variant histology should all be included in the very high risk group.

BCG=Bacillus Calmette-Guérin; NMIBC=non-muscle invasive bladder cancer; TURBT=transurethral resection of bladder tumor.
it to historical mention, as have other more effective agents, such as nadofarogene firadenovec (approved by the FDA).

The SunRISe-1 trial (TAR 200), recently reported an intravesical therapy delivering gemcitabine versus gemcitabine plus a PDL1 inhibitor.3 6  TAR 200 is an optimized drug intravesical delivery system that delivers drugs to the bladder while minimizing systemic toxicity. This trial has reported on the TAR 200 monotherapy arm in carcinoma in situ, with a 76% complete response rate for carcinoma in situ patients.1 3-6 These favorable outcomes, observed in BCG unresponsive NMIBC, have led to an FDA breakthrough therapy designation.3-6 The results of the BOND-003 trial using CG0070, a conditionally replicative adenovirus that selectively targets and destroys bladder cancer cells, have been reported.3-6

In the BOND-003 trial, BCG-unresponsive, high risk NMIBC with carcinoma in situ with or without concomitant high grade Ta or T1 papillary disease had an approximately 75% complete remission at six months. These results have led to both fast track and breakthrough therapy designation intended to accelerate path to FDA submission.7

Combination chemotherapy with gemcitabine and docetaxel has also been shown to be effective in the BCG unresponsive space. Preliminary studies highlight its potential in enhancing therapeutic efficacy and mitigating resistance mechanisms in both high risk BCG naive and BCG unresponsive disease.8 9 In addition, the Quilt-3.032 study represents another important trial in the management of BCG unresponsive disease.10 The Quilt trial investigates the synergy between immune checkpoint inhibitors and targeted therapies in this disease state. BCG unresponsive bladder carcinoma in situ with or without Ta/T1 papillary disease was treated with intravesical nogapendekin alfa inbakicept (NAI) plus BCG (cohort A). The complete response rate for the BCG unresponsive NMIBC carcinoma in situ cohort treated with NAI plus BCG was 71% at any time, and 45% and 33% at 12 and 18 months, respectively. Thus, combining NAI with BCG resulted in a significant improvement in response.

### Table 4 | Disease progression probability at 1, 5, and 10 years for the European Association of Urology NMIBC risk groups

<table>
<thead>
<tr>
<th>European Association of Urology NMIBC risk groups</th>
<th>Probability of progression, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporating low versus high grade (WHO 2004)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.06 (0.01 to 0.43)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.93 (0.49 to 1.7)</td>
</tr>
<tr>
<td>High</td>
<td>3.7 (2.3 to 5.9)</td>
</tr>
<tr>
<td>Very high</td>
<td>10 (10 to 18)</td>
</tr>
<tr>
<td>Incorporating with WHO 1973</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.12 (0.02 to 0.82)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.57 (0.21 to 1.5)</td>
</tr>
<tr>
<td>High</td>
<td>3.0 (1.5 to 6.3)</td>
</tr>
<tr>
<td>Very high</td>
<td>44 (30 to 61)</td>
</tr>
</tbody>
</table>

CI=confidence interval, WHO=World Health Organization. *This table does not include patients with variant histology, lymphovascular invasion, carcinoma in situ in the prostatic urethra, or primary or recurrent carcinoma in situ.

### Table 5 | First line systemic treatment for locally advanced or metastatic disease (stage IV)

<table>
<thead>
<tr>
<th>Cisplatin eligible</th>
<th>Preferred regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemcitabine and cisplatin* (category 1) followed by avelumab maintenance treatment (category 1) only if no progression on first line platinum containing chemotherapy</td>
</tr>
<tr>
<td></td>
<td>ddMVAC* with growth factor support (category 1) followed by avelumab maintenance treatment (category 1) only if no progression on first line platinum containing chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cisplatin eligible</th>
<th>Preferred regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemcitabine and carboplatin* followed by avelumab maintenance treatment if no progression on first line platinum containing chemotherapy (category 1)</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum containing chemotherapy)</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab and enfortumab vedotin</td>
</tr>
</tbody>
</table>

Other recommended regimes

- Gemcitabine
- Gemcitabine and paclitaxel
- Atezolizumab (only for patients whose tumors express PDL1 by immunohistochemistry)

Useful under certain circumstances

- Ifosfamide, doxorubicin, and gemcitabine (for patients with good kidney function and good performance status)
- Atezolizumab (only for patients who are not eligible for any platinum containing chemotherapy regardless of PDL1 expression) (category 3)

ddMVAC=dose dense methotrexate, vinblastine, doxorubicin, cisplatin; PDL1=programmed death ligand 1

*Platinum based chemotherapy is typically given for six cycles if tolerated and no disease progression, and at least four cycles before maintenance avelumab.
STATE OF THE ART REVIEW

The vagina and urethra in women. Increasing salpingo-oophorectomy and partial resection of prostatectomy in men, and hysterectomy, bilateral node negative patients, along with discovery lymphadenectomy with more accurate staging of with eLND. The Will Rogers effect of extended of lymph nodes that should be removed and the remains regarding the treatment role of extended treated with surgery alone. Nonetheless, debate among patients with low volume nodal involvement shown in patients, with some long term survivors important staging information. The oncologic benefit component of radical cystectomy that includes reduced blood loss and reduced length of hospital showing equivalent oncological outcomes for both robotic assisted laparoscopic techniques. Studies including radical cystectomy, performed using number of minimally invasive surgeries is growing, traditionally performed with an open technique, the patient selection. Although radical cystectomy is sparing radical cystectomy in men, with appropriate preserving radical cystectomy in women and prostate attention has been directed toward pelvic organ metastasis remains a gold standard treatment of muscle invasive bladder cancer.

Treatment of muscle invasive bladder cancer
Radical cystectomy remains a gold standard treatment for patients with resectable MIBC (T2-4a, N0/1-x, M0). Radical cystectomy typically includes radical prostatectomy in men, and hysterectomy, bilateral salpingo-oophorectomy and partial resection of the vagina and urethra in women. Increasing attention has been directed toward pelvic organ preserving radical cystectomy in women and prostate sparing radical cystectomy in men, with appropriate patient selection. Although radical cystectomy is traditionally performed with an open technique, the number of minimally invasive surgeries is growing, including radical cystectomy, performed using robotic assisted laparoscopic techniques. Studies showing equivalent oncological outcomes for both types of surgery are available, with the benefits of reduced blood loss and reduced length of hospital stay using minimally invasive surgeries.

Pelvic lymphadenectomy is also an important component of radical cystectomy that includes important staging information. The oncologic benefit of bilateral pelvic lymphadenectomy has been shown in patients, with some long term survivors among patients with low volume nodal involvement treated with surgery alone. Nonetheless, debate remains regarding the treatment role of extended lymphadenectomy (eLND) templates, the number of lymph nodes that should be removed and the trade-off for potentially higher morbidity associated with eLND. The Will Rogers effect of extended lymphadenectomy with more accurate staging of truly node negative patients, along with discovery of some low volume lymph node positive patients, could result in improved outcomes through more accurate staging, and therefore not be related to improved cancer control. The phase 3 trial SWOG S1011, which randomized 592 patients with muscle invasive bladder cancer (cT2-4a N0-2) in a 1:1 ratio to extended or standard lymph node dissection, showed no improvement in disease free or overall survival with extended versus standard lymphadenectomy and extended lymphadenectomy was associated with greater morbidity and perioperative mortality. Despite a median of 41 lymph nodes removed in the extended lymph node dissection arm versus 25 in the standard lymph node dissection arm, the hazard ratio for disease free survival comparing extended dissection with standard dissection was 1.10 (95% confidence interval 0.87 to 1.42; one sided log rank p=0.82) and the hazard ratio for overall survival was 1.15 (0.89 to 1.48; 0.87). The rate of lymph node metastasis was also similar between arms, with 26% and 24% in the extended and standard dissection arms, respectively. In the extended dissection arm, grade 3 to 4 adverse events occurred in 16% of cases, compared with 8% in the standard arm.

Following radical cystectomy and lymph node dissection, a urinary diversion is required. Almost all forms of urinary diversion use a short segment (15 cm) of the ileum or colon. Urinary diversions are generally segmented into continent and conduit diversions. Conduit or incontinent urinary diversion uses a small segment of ileum or colon that is anastomosed to the ureters, and then brought out to the skin in the formation of stoma. Cutaneous ureterostomies are the simplest form of urinary diversion; however, they are associated with a significant rate of stenosis and urinary tract infection, so they are only used in morbid patients in whom the quickest procedure is required. Continent urinary diversion involves orthotopic connection to the naïve urethra such as a neobladder, which creates a spherical, adequate volume and low pressure reservoir made from detubularized and folded bowel to the urethra; therefore, it has the advantaged of using a naturally situated reservoir. By contrast, continent cutaneous diversion uses a small channel of intestine brought out to the skin. Continent cutaneous diversions

<table>
<thead>
<tr>
<th>Preferred regimen</th>
<th>Pembrolizumab (category 1 post platinum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative preferred regimens</td>
<td>Immune checkpoint inhibitor:</td>
</tr>
<tr>
<td></td>
<td>• Nivolumab</td>
</tr>
<tr>
<td></td>
<td>• Avelumab</td>
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<tr>
<td></td>
<td>• Erdafitinib</td>
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<tr>
<td></td>
<td>Enfortumab vedotin</td>
</tr>
<tr>
<td>Other recommended regimens</td>
<td>Paclitaxel or docetaxel</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab and enfortumab vedotin (category 2B)</td>
</tr>
<tr>
<td>Useful in certain circumstances based on previous medical treatment</td>
<td>Ifosfamide, doxorubicin, and gemcitabine Gemcitabine and paclitaxel Gemcitabine and cisplatin ddMVAC with growth factor support</td>
</tr>
</tbody>
</table>

ddMVAC=dose dense methotrexate, vinblastine, doxorubicin, cisplatin.
are low pressure detubularized bowel reservoirs connected to skin for self-catheterization, the most commonly performed of which is the Indiana pouch. The Indiana pouch can be performed on patients who wish to avoid a stoma but are not candidates or are unwilling for orthotopic neobladder. Patient selection based on clinical and oncologic factors is the key to successful urinary diversion and health related quality of life.

Great strides have been made concerning recovery after radical cystectomy resulting from implementing specific enhanced recovery after surgery (ERAS) protocols. Preoperatively, these pathways encourage immunonutrition, avoidance of a bowel preparation (to avoid dehydration) except in situations where the colon will be opened or used, fluid hydration, and the use of drug treatments (such as alvimopan, an opioid antagonist that aids recovery of bowel function after bowel surgery).\(^5\) Intraoperatively, ERAS protocols minimize fluid resuscitation and encourage the removal of any nasogastric tubes. Postoperatively, the protocols encourage early ambulation, early feeding (typically with a regular diet by the second postoperative day), and the substitution and minimization of opioid pain treatments for non-narcotic alternatives, such as ketorolac, acetaminophen, and tramadol. Such ERAS protocols have resulted in a reduction in the length of hospital stay and faster convalescence.\(^6,7\)

Following radical cystectomy, survival outcomes largely depend on final pathological staging. The 10 year recurrence free survival for patients without lymph node involvement is 86% for pT0 tumors, 76% for T1–pT3a, 61% for T3b, and 45% for T4, but drops to 34% regardless of the stage when lymph nodes are involved. Advanced and metastatic bladder cancer remains a lethal disease. Indeed, despite radical cystectomy with seemingly good oncological outcomes, including patients with organ confined disease and negative margins and lymph nodes, many still experience recurrence, prompting the consideration of adjuvant treatments.\(^8\)

The iROC trial (NCT03049410) randomized 338 participants with non-metastatic bladder cancer from nine sites in the UK. Follow-up was conducted at 90 days, six months, and 12 months, with final follow-up in September 2021. It found that among patients with non-metastatic bladder cancer undergoing radical cystectomy, treatment with robot assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy significantly increased days alive and days out of the hospital at 90 days.\(^9\)

Radical cystectomy is also indicated to treat BCG failure for high grade T1 disease and high grade T1 disease with unfavorable pathologic characteristics. These characteristics are multifocal tumors, T1b, tumors within a diverticulum, associated carcinoma in situ, residual T1 disease on repeat TURBT, lymphovascular invasion, and micropapillary variant.\(^1\)

Neoadjuvant chemotherapy
Dose dense methotrexate, vinblastine, Adriamycin, cisplatin (ddMVAC) and gemcitabine plus cisplatin are accepted neoadjuvant regimens for MIBC (cT2–T4a, N0–N1).\(^10\) The role of neoadjuvant chemotherapy before radical cystectomy to help improve survival has been investigated in several clinical trials, and provides a 5% absolute survival advantage at five years with cisplatin based treatment, and a 22% relative improvement in disease free survival.\(^11\) Use of four cycles of gemcitabine-cisplatin in lieu of traditional MVAC was initially accepted in the neoadjuvant setting, by extrapolation from randomized data in the metastatic setting showing similar efficacy and less toxicity with gemcitabine plus cisplatin.\(^12\) However, the phase 3 GETUG-AFU V05-VESPER trial subsequently showed superior progression free survival at three years with six cycles of neoadjuvant ddMVAC compared with four cycles of gemcitabine plus cisplatin.\(^13\)

The trial randomized 500 patients with muscle invasive bladder cancer to either six cycles of ddMVAC versus four cycles of gemcitabine plus cisplatin in either the neoadjuvant or adjuvant setting. Notably, 437 (88%) of the patients on the trial received neoadjuvant treatment. The study did not meet its primary endpoint of three year progression free survival, with a three year progression free survival rate of 64% versus 56% among patients treated with ddMVAC versus gemcitabine plus cisplatin, respectively (hazard ratio 0.77, 95% confidence interval 0.57 to 1.02, p=0.066). However, ddMVAC was associated with a longer time to progression, with a hazard ratio of 0.68 (95% confidence interval 0.50 to 0.93, p=0.014) and in the neoadjuvant group, progression free survival at three years was significantly higher in the ddMVAC arm at 66% versus 56% with gemcitabine plus cisplatin (0.7, 0.51 to 0.96, 0.025). Moreover, overall survival and disease specific survival were both higher at five years in the ddMVAC arm, at 64% versus 56% for overall survival (0.77, 0.58 to 1.03, 0.078), and 72% versus 59% for disease specific survival (0.63, 0.46-0.86, 0.004). Among the patients treated in the neoadjuvant setting, five year overall survival for patients treated with ddMVAC was 66% versus 57% compared with gemcitabine plus cisplatin (0.71, 0.52 to 0.97, 0.032) while five year disease specific survival was 75% versus 60%, respectively (0.56, 0.39 to 0.80, 0.001). Results in the adjuvant group were limited in statistical power due to the small sample size of only 56 patients. While findings from the GETUG/AFU V05 VESPER trial have led many experts to favor ddMVAC for neoadjuvant treatment, gemcitabine-cisplatin remains an accepted alternative, especially for patients who are unable to tolerate the greater toxicity of ddMVAC. For example, in the GETUG/AFU V05 VESPER trial, grade ≤3 asthenia and gastrointestinal disorders were both more frequently observed with ddMVAC compared with gemcitabine plus cisplatin (p<0.001 and p=0.003, respectively).
Thus, in patients with MIBC (particularly those with clinical ≥T2N0 disease), neoadjuvant chemotherapy should be given if they can tolerate a cisplatin based regimen. However, comorbidities such as renal insufficiency make up to 50% of patients with bladder cancer ineligible for cisplatin based treatment. Conventionally, consensus criteria for cisplatin eligibility developed for the metastatic setting by Galsky et al recommend a creatinine clearance of ≥60 mL/minute, though some experts recommend consideration of curative intent cisplatin based chemotherapy for MIBC with creatinine clearance as low as ≥40 mL/minute. If cisplatin based chemotherapy is administered for management of MIBC for patients with creatinine clearance of 40-60 mg/m², cisplatin is typically given with split dosing of 35 mg/m² over two separate days per cycle instead of the conventional dose of 70 mg/m² on a single day to improve tolerability. If cisplatin based chemotherapy cannot be tolerated, patients should proceed directly to radical cystectomy, though ongoing investigations into neoadjuvant immune checkpoint blockade and antibody drug conjugates might result in additional neoadjuvant options for cisplatin ineligible patients in the future.

Adjuvant chemotherapy
The role of adjuvant treatment following radical cystectomy remains uncertain, probably owing to the limitations of available studies. Early evidence suggests that adjuvant radiotherapy might have a role in patients with adverse pathological features (pathological ≥T3 disease, lymph node involvement or positive margins) on radical cystectomy. No single randomized trial has shown a significant difference in survival with adjuvant chemotherapy, likely due in part to poor accrual to these studies. However, a meta-analysis of 1183 patients from 10 randomized trials showed an 18% relative decrease in the risk of death with adjuvant cisplatin based chemotherapy compared with surgery alone, representing a 6% absolute improvement in survival at five years. A 29% relative improvement in recurrence free survival was also identified, representing an absolute benefit of 11%. As a result, NCCN guidelines recommend consideration of cisplatin based adjuvant chemotherapy for patients with pathologic ≥T3 and/or node positive disease at time of cystectomy for patients who are fit enough for cisplatin based treatment and who did not receive neoadjuvant cisplatin based chemotherapy before surgery.

Adjuvant immune checkpoint inhibitors
The CheckMate 274 phase 3 trial compared one year of adjuvant nivolumab with placebo after R0 radical resection of high risk muscle invasive urothelial carcinoma. The definition of high risk depended on whether patients had received neoadjuvant cisplatin based chemotherapy before radical surgery. For patients who had not received neoadjuvant cisplatin based chemotherapy, high risk was defined as pT3-T4a, or pN+. For patients who had received neoadjuvant cisplatin, high risk was defined as ypT2-T4a or ypN positive. The trial randomized 353 patients to receive nivolumab and 356 to receive placebo and met the coprimary endpoints of significant improvements of disease free survival with nivolumab in all comers (hazard ratio 0.71, 95% confidence interval 0.58 to 0.86) and the PDL1 high (0.52, 0.37 to 0.72) populations. The median disease free survival in the intention-to-treat population was 22 months with nivolumab and 10.9 months with placebo. By contrast, the phase 3 trial that evaluated adjuvant atezolizumab (IMvigor 010) did not meet its primary endpoint for disease free survival in the overall or PDL1 high population. Findings from a third randomized phase 3 adjuvant study of pembrolizumab (AMBASSADOR) have yet to be reported, although a press release indicated that this trial met its primary endpoint for disease free survival. The results of CheckMate 274 led to the FDA approving adjuvant nivolumab in August 2021 for patients with urothelial carcinoma of the bladder or upper tract at an increased risk of recurrence (≥ypT2 and/or node positive after neoadjuvant chemotherapy, or ≥pT3 and/or node positive without neoadjuvant chemotherapy). By contrast, the European Medicines Agency has only approved adjuvant nivolumab for patients with PDL1 positive disease, defined as PDL1 expression on 1% or more of tumor cells. Overall survival data for CheckMate 274 are awaited.

Bladder preservation strategy with trimodality treatment
Various bladder sparing options have been explored that could benefit very carefully selected patients. Radical TURBT is an aggressive endoscopic resection procedure to remove all visible disease (while taking care not to cause a perforation); cautery (either monopolar or bipolar) is used to ablate tissue as deeply as possible, to destroy as much tumor as safely possible. Radical TURBT as a standalone treatment approach can have a longlasting effect on survival, but should only be considered for patients who are ineligible or who decline radical cystectomy or chemoradiation. Survival data of 133 patients revealed good cancer specific survival (76.7%) and progression free survival with bladder preservation (57.8%) at 15 years. However, complete tumor resection (confirmed by a negative biopsy of the tumor bed) is crucial for this type of management. Partial cystectomy can be cautiously considered for select patients with a small (<3 cm) solitary tumor, no associated carcinoma in situ, tumors in a bladder diverticulum, and those not involving the bladder trigone.

Trimodality treatment combines radical TURBT with concomitant radio sensitizing chemotherapy and external beam radiotherapy. This strategy can result in five year cancer specific survival rates of 50-82%; however, 25-30% of patients require salvage cystectomy due to failure to respond to treatment.

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Importantly, trimodality treatment severely limits the likelihood of future orthotopic neobladder diversion should salvage radical cystectomy be required, a limitation that must be discussed when counseling patients.\textsuperscript{66-69} Another study recently reported similar oncological outcomes between radical cystectomy and trimodality treatment for select patients with MIBC.\textsuperscript{70}

Given the preclinical evidence supporting the combination of immune checkpoint inhibitors with radiotherapy, and the activity of immune checkpoint inhibitors in advanced bladder cancer, studies incorporating immune checkpoint inhibitors into bladder preserving trimodality treatment are under way, such as SWOG 1806 and KEYNOTE-992.\textsuperscript{7,14}

Bladder sparing approaches for MIBC with TURBT plus systemic treatment that omit bladder radiation have also been investigated; however, such approaches require further evidence of safety and efficacy in clinical trials before implementation in standard clinical practice (NCT03609216).\textsuperscript{71,72}

**Treatment of metastatic bladder cancer**

Outside of the US, cisplatin based chemotherapy remains the gold standard treatment for metastatic urothelial carcinoma.\textsuperscript{3,4,40-48,73} Nevertheless, nearly all patients with a partial or complete response to treatment ultimately progress and die of the disease. Resistance to chemotherapy owing to treatment related selection of the sensitive subclones will be developed for most patients. Thus, long term survival for metastatic bladder cancer remains low. Notably, patients who relapse within 12 months of completing neoadjuvant or adjuvant cisplatin based chemotherapy are typically considered platinum refractory, and are treated with second line treatment options instead of repeat platinum based chemotherapy. Notably, cisplatin based chemotherapy is now being supplanted as first line therapy for metastatic bladder cancer by the antibody-drug conjugate enfortumab vedotin in combination with the anti-programmed-cell-death-protein 1 (PD1) checkpoint inhibitor pembrolizumab,\textsuperscript{74} as detailed in a later section of this review titled “Antibody-drug conjugates”.

Although cisplatin based chemotherapy remains the starting option for first line fit patients in most of the world, new treatment options have recently emerged. In recent years, multiple immune checkpoint inhibitors targeting PD1 or PD-L1 have been approved by the FDA for metastatic bladder cancer. This treatment is indicated as first line for platinum ineligible patients, maintenance after achieving response or stable disease with first line platinum based chemotherapy, and second line for those who experience progression after platinum based chemotherapy regimens.\textsuperscript{16,33} Immune checkpoint inhibitors targeting PD1 or PD-L1 have already substantially improved the outcomes of patients with many types of cancer, although only 20-40\% of patients with advanced bladder cancer experience significant benefit from these new treatments.\textsuperscript{75,76} For example, maintenance avelumab (an anti-PDL1 checkpoint inhibitor) after first line platinum based chemotherapy significantly prolonged overall survival among patients with locally advanced or metastatic urothelial carcinoma that had not progressed with frontline chemotherapy.\textsuperscript{77} In the phase 3 JAVELIN Bladder 100 trial, 700 patients who had not progressed after 4-6 cycles of frontline gemcitabine plus cisplatin or carboplatin were randomized in a 1:1 ratio to receive either best supportive care alone or best supportive care plus maintenance avelumab until disease progression, death, intolerable side effects, or other criterion for withdrawal. Overall survival favored the avelumab arm, with a hazard ratio of 0.76 (95\% confidence interval 0.63 to 0.91, \(p=0.0036\)) and median overall survival of 23.8 months with maintenance avelumab (95\% confidence interval 19.9 to 28.8) versus 15.0 months with best supportive care alone (95\% confidence interval 13.5 to 18.2). Progression free survival was also prolonged with avelumab versus best supportive care alone, with median progression free survival of 5.5 months (95\% confidence interval 4.2 to 7.2) versus 2.1 months (95\% confidence interval 1.9 to 3.0), respectively (hazard ratio 0.54, 95\% confidence interval 0.46 to 0.64, \(p<0.0001\)).\textsuperscript{78}

More recently, the addition of the anti-PD1 checkpoint inhibitor nivolumab to first line gemcitabine cisplatin chemotherapy was shown to confer an overall survival advantage compared with gemcitabine cisplatin alone.\textsuperscript{78} This was shown by the international phase 3 trial CheckMate 901, wherein 608 patients with previously untreated unresectable or metastatic urothelial carcinoma were randomized to receive gemcitabine plus cisplatin alone versus gemcitabine with nivolumab. With a median follow-up of 33.6 months, median overall survival with the regimen containing nivolumab was 21.7 months compared with 18.9 months, with a hazard ratio for death of 0.78 (95\% confidence interval 0.63 to 0.96, \(p=0.02\)). Progression free survival also favored the nivolumab arm, with a hazard ratio of 0.72 (0.59 to 0.88, 0.001) and median progression free survival of 7.9 months versus 7.6 months without nivolumab. The objective response rate of with versus without nivolumab was 57.6\% versus 43.1\%, respectively, and the complete response rates were 21.7\% and 11.8\%, respectively. Grade 3 or higher adverse events occurred in 61.8\% of patients who received the nivolumab containing regimen, versus 51.7\% of patients who received chemotherapy alone. Given the results of CheckMate 901, regulatory approval of gemcitabine cisplatin plus nivolumab as an option for the first line treatment of metastatic bladder cancer is anticipated in the near future.\textsuperscript{78,79}

PD-L1 testing, quantified using immunohistochemistry assays, is currently the most widely validated, used, and accepted biomarker to guide the selection of patients to receive treatment with anti-PD1 or anti-PDL1 antibodies. However, many challenges remain in the clinical use of these assays, including the necessity of using different
Targeted tyrosine kinase inhibitors

Although many agents are being investigated, erdafitinib, a pan-FGFR inhibitor, is the only tyrosine kinase inhibitor currently approved by the FDA for treating advanced or metastatic urothelial carcinoma. To be eligible for erdafitinib treatment, patients must have progressed during or after platinum containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum based chemotherapy, and have tumors harboring a susceptible FGFR2/3 alterations (fusions or mutations). About 20% of patients with metastatic urothelial carcinoma harbor FGFR alterations that can be targeted with FGFR inhibition. Erdafitinib has shown higher response rates than second line chemotherapy, and improves overall survival compared with chemotherapy for platinum and immunotherapy refractory disease. In cohort 1 of the phase 3 THOR study, 266 patients with susceptible FGFR2/3 alterations who had progressed after one or two lines of systemic treatment, including an anti-PDL1 agent, were randomized 1:1 to receive either erdafitinib or investigator’s choice of chemotherapy (docetaxel or vinflunine). With a median follow-up of 15.9 months, THOR met its primary endpoint, with a significant improvement in overall survival with erdafitinib compared with chemotherapy. Median overall survival was 12.1 months with erdafitinib versus 7.8 months with chemotherapy (hazard ratio 0.64, 95% confidence interval 0.47 to 0.88, p=0.0050). Erdafitinib also achieved longer progression free survival and a higher objective response rate than chemotherapy, with median progression free survival of 5.6 versus 2.7 months (0.58, 0.44 to 0.78, 0.0002), and objective response in 46% versus 12% of patients, respectively (relative risk 3.94, 95% confidence interval 2.37 to 6.57, p<0.001). About 20% of patients with metastatic urothelial carcinoma harbor FGFR alterations that can be targeted with FGFR inhibition. Treatment with erdafitinib can be limited by its unique side effect profile, including, but not limited to, risk of hyperphosphatemia, hand-foot syndrome, and central serous retinopathy.

Notably, erdafitinib failed to show superiority over pembrolizumab monotherapy in cohort 2 of the phase 3 THOR trial. In this cohort, 351 pretreated, PDL1 naïve patients with advanced or metastatic urothelial cancer with select FGFR alterations were randomized in a 1:1 ratio to receive erdafitinib daily versus pembrolizumab. With a median follow-up of 33 months, median overall survival with erdafitinib and pembrolizumab was 10.9 and 11.1 months, respectively, with a hazard ratio of 1.18 (95% confidence interval 0.92 to 1.51, p=0.18). Progression free survival with erdafitinib and pembrolizumab was 4.4 and 2.7 months, respectively (hazard ratio 0.88, 95% confidence interval 0.70 to 1.10). Objective response rate with erdafitinib was 40.0% compared with only 21.6% with pembrolizumab (relative risk 1.85, 95% confidence interval 1.32 to 2.59), but the median duration of response with erdafitinib was only 4.3 months compared with 14.4 months with pembrolizumab. Moreover, grade 3 or higher adverse events occurred in 64.7% of patients receiving erdafitinib compared with only 50.9% of patients receiving pembrolizumab.

Antibody-drug conjugates

Antibody-drug conjugates have begun to revolutionize the management of urothelial cancer. Antibody-drug conjugates use monoclonal antibodies to target proteins overexpressed on the surface of tumor cells (thereby limiting toxicity to normal tissue). The antibodies are linked to highly cytotoxic payloads. Enfortumab vedotin is a nectin-4 directed antibody-drug conjugate linked to the potent microtubule inhibitor monomethyl auristatine E. Enfortumab vedotin was approved to treat locally advanced or metastatic urothelial cancer patients who have previously been treated with platinum containing chemotherapy or PD1 or PDL1 checkpoint inhibitors, as well as those ineligible for cisplatin containing chemotherapy and who have previously received one or more lines of treatment. While usually tolerable compared with cisplatin based treatment, enfortumab vedotin has a unique toxicity profile of its own, including neuropathy, ocular disorders, occasionally severe hyperglycemia, and rash, which can be fatal in very rare cases. Efficacy of enfortumab vedotin monotherapy was established by the phase 3 trial EV-301, which randomized 608 patients with locally advanced or metastatic urothelial carcinoma in a ratio of 1:1 to enfortumab vedotin versus investigator’s choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). Patients in this trial had previously received a platinum containing chemotherapy regimen and had disease progression during or after PDL1 immune checkpoint treatment. Long term outcomes of EV-301 with 24 months of follow-up showed a significant overall survival advantage with enfortumab vedotin, with median overall survival of 12.9 months versus 8.9 months with chemotherapy (hazard ratio 0.70, 95% confidence interval 0.58 to 0.85, one sided p=0.00015). Enfortumab vedotin also resulted in longer progression free survival, with a median progression free survival of 5.6 months versus 3.7 months with chemotherapy (0.63, 0.53 to 0.76, 0.00001). In late 2023, the combination of enfortumab vedotin with the anti-PD1 immune checkpoint inhibitor pembrolizumab also received FDA approval as a treatment for locally advanced or metastatic urothelial cancer, either in the first line or post platinum containing chemotherapy.
The response rates for enfortumab vedotin plus pembrolizumab were 28% and 34%, respectively.91-93 In the U-01 (NCT03547973) trial, with early data reporting, enfortumab vedotin plus pembrolizumab compared with platinum chemotherapy resulted in an approximate doubling of median progression free survival (12.5 v 6.3 months) and overall survival (31.5 v 16.1 months). Compared with platinum chemotherapy, enfortumab vedotin plus pembrolizumab resulted in a hazard ratio for progression free survival of 0.45 (95% confidence interval 0.38 to 0.54, p<0.00001) and a hazard ratio for overall survival of 0.47 (0.38 to 0.58, 0.00001). The confirmed objective response rate for enfortumab vedotin plus pembrolizumab was 67.7%, compared with 44.4% with platinum chemotherapy (p<0.00001). Grade 3 or higher treatment related adverse events occurred in 55.9% of patients receiving enfortumab vedotin plus pembrolizumab, compared with 69.5% of patients receiving chemotherapy. The most common of these adverse events with enfortumab vedotin plus pembrolizumab were mucopapular rash in 7.7% of patients, hyperglycemia in 5.0%, and neutropenia in 4.8%. The most common grade 3 or higher treatment related adverse events of special interest for enfortumab vedotin were skin reactions (15.5%) and peripheral neuropathy (6.8%), while the most common for pembrolizumab were severe skin reactions (11.8%). In the context of metastatic bladder cancer, the combination of enfortumab vedotin plus pembrolizumab is the first cisplatin free regimen to show a survival advantage over cisplatin based regimens.

Sacituzumab govitecan also belongs to the antibody-drug conjugate family and targets the TROP2, conjugated by a linker to the payload SN-38, the active form of the topoisomerase inhibitor irinotecan. It has been analyzed as a single agent, 38, the active form of the topoisomerase inhibitor TROP2, conjugated by a linker to the payload SN-antibody-drug conjugate family and targets the skin reactions (11.8%). In the context of metastatic bladder cancer, the combination of enfortumab vedotin plus pembrolizumab compared with platinum chemotherapy resulted in an approximate doubling of median progression free survival (12.5 v 6.3 months) and overall survival (31.5 v 16.1 months). Compared with platinum chemotherapy, enfortumab vedotin plus pembrolizumab resulted in a hazard ratio for progression free survival of 0.45 (95% confidence interval 0.38 to 0.54, p<0.00001) and a hazard ratio for overall survival of 0.47 (0.38 to 0.58, 0.00001). The confirmed objective response rate for enfortumab vedotin plus pembrolizumab was 67.7%, compared with 44.4% with platinum chemotherapy (p<0.00001). Grade 3 or higher treatment related adverse events occurred in 55.9% of patients receiving enfortumab vedotin plus pembrolizumab, compared with 69.5% of patients receiving chemotherapy. The most common of these adverse events with enfortumab vedotin plus pembrolizumab were mucopapular rash in 7.7% of patients, hyperglycemia in 5.0%, and neutropenia in 4.8%. The most common grade 3 or higher treatment related adverse events of special interest for enfortumab vedotin were skin reactions (15.5%) and peripheral neuropathy (6.8%), while the most common for pembrolizumab were severe skin reactions (11.8%). In the context of metastatic bladder cancer, the combination of enfortumab vedotin plus pembrolizumab is the first cisplatin free regimen to show a survival advantage over cisplatin based regimens.

Sacituzumab govitecan received accelerated FDA approval as a single agent for the treatment of locally advanced or metastatic urothelial cancer for patients who previously received a platinum containing chemotherapy and either a PD1 or PDL1 inhibitor.94 A phase 3 trial to confirm sacituzumab govitecan’s single agent activity in advanced urothelial cancer, TROPICS-04 (NCT04527991) is ongoing.12,23 27 28 The toxicity profile of sacituzumab govitecan is similar to that of irontecan, and includes gastrointestinal side effects, alopecia, and neutropenia; sacituzumab govitecan is often given with growth factor support for prophylaxis against febrile neutropenia.

Prognostic and predictive biomarkers

Several molecular classifications of bladder cancer were reported over the last decade and further summarized on the so called consensus subtypes (table 7, fig 5). Whether or not if molecular subtyping of bladder cancer has implications for prognosis and treatment remains controversial.16 42 46 95 Available data, mostly derived from MIBC, typically show that patients with basal tumors are more likely to be women with locally advanced or metastatic disease, and achieve more significant benefits from chemotherapy and immunotherapy than surgery alone.42 Patients with non-luminal tumors benefited the most from neoadjuvant chemotherapy, while the luminal subtype molecular group might have the best overall survival and lowest rate of upstaging compared with other tumors, with or without administration of systemic treatment; therefore, patients with luminal tumors experienced minimal survival benefit of neoadjuvant chemotherapy.16 24 42 43 96-99 Furthermore, molecular subtypes determined by global gene expression have shown no association with cancer specific survival according to either the consensus molecular subtypes or the Lund classification, in a large population based series of patients treated with cystectomy.95 In another study, clinical parameters outperformed molecular subtypes for predicting the outcome of MIBC patients using multiple cohorts and different subtyping classifications.100 Currently, molecular taxonomy of bladder cancer remains in the hypothesis generating phase data phase, with no implication in clinical practice.

Currently, the consensus molecular classification of bladder cancer revealed an agreement on six molecular categories: luminal papillary, luminal non-specified, luminal unstable, stroma rich, basal-squamous, and neuroendocrine-like.

Moreover, the use of biomarkers to predict the response to cisplatin based chemotherapy remains investigational, with no clinical application at present. However, some studies emphasize the detection of ERCC1 (excision repair cross complementation group 1) protein that heterodimerizes with ERCC4 to form an endonuclease complex.101 102 This participates in the excision of the damaged DNA. Lower ERCC1 levels (mRNA expression or immunohistochemistry) are correlated with cisplatin sensitivity in MIBC and
metastatic bladder cancer, with improved outcomes in these patients. Conversely, ERCC1 overexpression is associated with worse overall survival in metastatic bladder cancer. Furthermore, ERCC2 mutations are associated with pathologic complete response, improved overall survival to neoadjuvant cisplatin based chemotherapy in MIBC, and improved responses in metastatic bladder cancer.\(^1\)\(^9\)\(^1\)\(^0\)

Immune checkpoint inhibitors have emerged as a treatment option for metastatic urothelial carcinoma. Immune checkpoint inhibitors are used as both first line and second line treatments for patients with metastatic urothelial carcinoma and maintenance following first line chemotherapy. Immune checkpoint inhibitors achieve a durable response in a subset of these patients.

Table 7 | Reported characteristics of the molecular subtypes of MIBC cancer and their treatment implications

<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>Luminal papillary (24%)</th>
<th>Luminal non-specified (8%)</th>
<th>Luminal unstable (15%)</th>
<th>Stroma rich (15%)</th>
<th>Basal squamous (35%)</th>
<th>Neuroendocrine-like (3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GATA3, FOXA1, FGFR3, CK20, Uroplakin 2</td>
<td>GATA3, FOXA1, FGFR3, CK20, Uroplakin 2</td>
<td>GATA3, FOXA1, FGFR3, CK20, Uroplakin 2</td>
<td>Vimentin, desmin, SMA</td>
<td>CK5/6, CK14, Desmoglein 3, STAT3</td>
<td>Insulin, Synaptophysin, Chromogranin, CD56</td>
<td></td>
</tr>
</tbody>
</table>

Potential targeting therapy

<table>
<thead>
<tr>
<th>Low risk, FGFR3 inhibitors, low sensitivity to NAC</th>
<th>Response to ICI, low sensitivity to NAC</th>
<th>Not specified</th>
<th>Response to ICI, EGFR inhibitors, cisplatin NAC</th>
<th>Response to ICI, combined chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund Uro A</td>
<td>Lund Uro C</td>
<td>Lund pathologically unstable</td>
<td>Lund mesenchymal-like</td>
<td>Lund basal-squamous and basal-squamous infiltrated/ Urolithin B</td>
</tr>
<tr>
<td>MDA luminal papillary</td>
<td>MDA p53-like and luminal TCGA luminal UNC luminal</td>
<td>MDA luminal TCGA luminal UNC luminal</td>
<td>MDA p53-like TCGA basal-squamous UNC basal</td>
<td>MDA basal TCGA basal-squamous UNC basal</td>
</tr>
</tbody>
</table>

Additional terminology

- Lund Uro A
- MDA luminal TCGA luminal papillary
- UNC luminal
- Lund Uro C
- MDA p53-like and luminal TCGA luminal UNC luminal
- Lund pathologically unstable MDA luminal TCGA luminal UNC luminal
- Lund mesenchymal-like MDA p53-like TCGA basal-squamous UNC basal
- Lund basal-squamous and basal-squamous infiltrated/ Urolithin B MDA basal TCGA basal-squamous UNC basal
- Lund small cell/ NE-like TCGA neuronal, UNC basal

Activated mutations (m), amplifications (a), fusions (f), deletions (d)

ICI=immune checkpoint inhibitors; MDA=MD Anderson Cancer Center; MIBC=muscle invasive bladder cancer; NAC=neoadjuvant chemotherapy; NE=neuroendocrine; TCGA=The Cancer Genome Atlas; TMB=tumor mutation burden; UNC=University of North Carolina.

* Some of the proposed categories in other classifications present overlapping features with limited correspondence between them.

Fig 5 | High throughput tumor profiling allowed the identification of novel molecular subtypes in both NMIBC and MIBC, resulting in diverse classification schemes. MDA=MD Anderson Cancer Center; MIBC=muscle invasive bladder cancer; TCGA=The Cancer Genome Atlas; UNC=University of North Carolina.
Across the field of oncology, FDA approved biomarkers for immune checkpoint inhibitor based treatment include PD1/L1 expression, tumor mutation burden, and microsatellite instability. However, while each of these biomarkers can enrich for response to immune checkpoint inhibitor in bladder cancer, none of the FDA approved indications for immune checkpoint inhibitor in urothelial cancer requires these biomarkers for clinical decision making given the biomarkers’ insufficient predictive accuracy in bladder cancer. In Europe, PD1/L1 expression is used to guide eligibility for immune checkpoint inhibitor in certain settings, such as eligibility for adjuvant nivolumab. When investigated by immunohistochemistry, PD1/L1 is typically expressed in 20-30% of urothelial carcinomas. The use of four different assays to assess PD1/L1 scores is behind the observed discrepancies and criticism regarding PD1/L1 expression in practice. Detecting 22C3, 28-8, and SP263 assays by immunohistochemistry might provide interchangeable results when evaluating their expression in urothelial carcinomas. However, limitations with the positive and negative predictive values associated with different assays to determine PD1/L1 make it unlikely that it could be a single biomarker to guide immune checkpoint inhibitor treatment of urothelial carcinoma. Studies have evaluated PD1/L1 expression, using algorithms powered by artificial intelligence to solve these problems. Overall, AI was able to identify more cases with PD1/L1 expressing tumor cells across different tumor types, and identified improved survival in patients whose tumors were scored using AI powered algorithms. AI might solve some interpretative challenges related to PD1/L1 detection and could soon be standardized.

The role of biomarker testing to guide immune checkpoint inhibitor remains uncertain, because PD1/PD-L1 as a single biomarker to predict immune checkpoint inhibitor response might not be sufficient. Several other potential biomarkers for immune checkpoint inhibitor treatment in metastatic urothelial carcinoma have been investigated. Transforming growth factor β (TGFβ) enriched stroma is a frequent finding in metastatic urothelial carcinoma unresponsive to immune checkpoint inhibitor agents and, therefore, is considered a biomarker of poor response to PD1/L1 blockade.

In recent years, much attention has been given to tumor mutation burden, a surrogate marker of neoantigen production and immunogenicity in TMB-high tumors. Tumor mutation burden is a clinically relevant biomarker to guide immune checkpoint inhibitor treatment for urothelial carcinoma at a metastatic stage. If treated with an immune checkpoint inhibitor, PD1/L1+/TMB-high urothelial tumors usually achieve the best responses. However, the variability and technological challenges in the tumor mutation burden determination limit its broader application in real world practice.

Microsatellite instability is associated with higher sensitivity to immune checkpoint inhibitor based treatment. Microsatellite instability and DNA mismatch repair mutations impair the activity of genes, leading to a higher tumor mutation burden and a higher sensitivity to immune checkpoint inhibitor. Mismatch repair defects can identify responders to immune checkpoint inhibitor, and this is independent of their tissue of origin. Unfortunately, the low prevalence of mismatch repair/microsatellite instability alterations in bladder cancer limits microsatellite instability and mismatch repair applicability in practice.

Bladder cancer is enriched for both nectin-4 and TROP2, surface cell targets of sacituzumab govitecan and enfortumab vedotin, respectively. Notably, emerging data suggest that nectin-4 expression could ultimately prove helpful in predicting sensitivity to

### Table 8 | Approved targeted treatment

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Targeted treatment</th>
<th>Clinical trial</th>
<th>Patient eligibility</th>
<th>Study arm and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR3</td>
<td>Erdafitinib</td>
<td>BLC2001</td>
<td>Advanced UC and progression on previous platinum based chemotherapy, with or without previous immunotherapy and with FGFR alterations (mutations/fusions)</td>
<td>Phase 2 single arm study ORR: 40% median PFS: 5.5 months Median OS: 13.8 months Adverse events: stomatitis, hyponatremia, hyperphosphatemia</td>
</tr>
<tr>
<td>Nectin-4</td>
<td>Enfortumab vedotin (an antibody targeting nectin-4 linked to a microtubule inhibitor conjugate)</td>
<td>EV-201</td>
<td>Locally advanced or metastatic disease ineligible for cisplatin, not having received previous platinum based chemotherapy, and previously treated with either a PD1 or a PD1 inhibitor; no biomarker assay needed</td>
<td>Phase 2 single arm study ORR: 52% Adverse events: neutropenia, rash, pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EV-301</td>
<td>Locally advanced unresectable or metastatic UC (including those with squamous differentiation or mixed cell types) previously treated with platinum based chemotherapy and PD1/PD-L1 inhibitor; no biomarker assay needed</td>
<td>Enfortumab vedotin or investigator’s choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). Significant improvement in Median OS: 13 v 9 months, Median PFS: 6 v 4 months ORR: 41% v 18% Adverse events: rash, peripheral neuropathy, hyperglycemia</td>
</tr>
<tr>
<td>TROP2</td>
<td>Sacituzumab govitecan (antibody-drug conjugate that targets TROP2, and is coupled with SN-38, an active metabolite of irinotecan)</td>
<td>TROPHY-U-01</td>
<td>Advanced UC previously treated with platinum based chemotherapy or immunotherapy; no biomarker assay needed</td>
<td>Single arm phase 2 study ORR: 27%; median PFS: 5 months Median OS: 11 months Adverse events: neutropenia, anemia, thrombocytopenia</td>
</tr>
</tbody>
</table>

**ORR=objective response rate; OS=overall survival; PD1/L1=programmed death ligand 1; PFS=progression free survival; TROP2=trophoblast cell surface antigen 2; UC=urothelial carcinoma.**
enfortumab vedotin.\textsuperscript{106} Currently, however, no FDA approved companion diagnostic biomarkers assess nectin-4 and TROP2 expression, and their detection is not currently required in practice because the treatment application is clinically guided (table 8).

Minimally invasive approaches to detect residual disease after surgery are needed to identify cancer patients at risk for metastasis. Circulating tumor DNA (ctDNA) holds promise as a biomarker for minimal residual disease detection. A panel based or personalized approach is frequently used. Predefined genes are analyzed in the former approach, and in the latter, mutations from the primary tumor are used to compose a personalized panel to identify the same mutations in plasma. Recent data from bladder cancer were obtained tracking up to 16 mutations in the adjuvant setting for patients who received atezolizumab versus placebo.

Outcomes in 581 patients who had undergone surgery and were evaluable for ctDNA from a randomized phase 3 trial of adjuvant atezolizumab versus observation in operable urothelial cancer (IMvigor010, NCT02450331) were reported. This trial did not reach its efficacy endpoint in the intention-to-treat population. Testing for ctDNA at the beginning of treatment (cycle 1 day 1) identified 214 (37%) patients who were positive for ctDNA and who had poor prognosis (observation arm hazard ratio 6.3, 95% confidence interval 4.45 to 8.92, p<0.0001). Notably, improved disease free survival and overall survival were reported in the atezolizumab arm compared with the observation arm (disease free survival hazard ratio 0.58, 95% confidence interval 0.43 to 0.79, p=0.0024; overall survival 0.59, 0.41 to 0.86) for patients who were positive for ctDNA. Non-relapse after atezolizumab was related to basal-squamous and immune response gene signatures, whereas relapse was related to stromal TGFβ and angiogenesis gene signatures.\textsuperscript{5, 29, 42}

Detection of postoperative ctDNA to guide patient selection for adjuvant treatment with atezolizumab is now undergoing prospective validation in a phase 3 trial (NCT04660344).

Although still investigational, preliminary data support the notion that studies derived from AI and machine learning will become relevant soon. Important areas of study include AI enhanced cystoscopy, AI enhanced radiology, and AI enhanced histopathologic diagnosis, as well as molecular subtyping analysis.\textsuperscript{108}

AI enhanced cystoscopy assessment attempts to fill the gap caused by inter-observer variability, and to reduce the risk of misdiagnosis, especially when equivocal findings are detected during routine cystoscopy. Data from recently reported studies show promising results in accuracy; however, AI needs to be improved before the application can be used in clinical daily practice.\textsuperscript{109}

**Emerging and novel treatments**

Nadofaragene firadenovec is an FDA approved IVe gene treatment showing great promise to treat BCG unresponsive NMIBC, while vicinium (oportuzumab monatox-qrs), and hyperthermic chemotherapy are also in various phases of the approval process.\textsuperscript{107} The immune cell activating interleukin 15 super agonist NA, also known as N-803, might act synergistically with BCG to elicit durable complete responses in BCG unresponsive NMIBC. In this open label multicenter study, patients with BCG unresponsive bladder carcinoma in situ with or without Ta/T1 papillary disease were treated with intravesical NAI plus BCG (cohort A) or NAI alone (cohort C). Patients with BCG unresponsive high grade Ta/T1 papillary NMIBC also received NAI plus BCG (cohort B). The study concluded that in patients with BCG unresponsive bladder carcinoma in situ and papillary NMIBC treated with BCG and the novel agent NAI, complete response was achieved with a persistence of effect, cystectomy avoidance, and 100% bladder cancer specific survival at 24 months. The study is ongoing, with an estimated target enrollment of 200 participants.\textsuperscript{110}

Novel antibody-drug conjugates have also begun to show promise as potential new treatment options for metastatic bladder cancer. Such antibody-drug conjugates include the HER2 targeted agents trastuzumab deruxtecan and disitamab vedotin. Trastuzumab deruxtecan, which is already used for the treatment of other tumor types such as metastatic breast cancer,\textsuperscript{111} carries a potent topoisomerase inhibitor payload. The single arm phase 2 trial DESTINY-PanTumor02 of trastuzumab monotherapy for multiple solid tumor types included 41 patients with HER2 overexpressing bladder cancer, in which trastuzumab deruxtecan achieved an objective response rate of 39.05 (95% confidence interval 24.2 to 55.5).\textsuperscript{112} In the phase 1b trial DS8201-AU105, trastuzumab deruxtecan was combined with the anti-PD checkpoint inhibitor nivolumab. Thirty-four patients with platinum treated advanced or metastatic HER2 expressing urothelial carcinoma received trastuzumab deruxtecan plus nivolumab. The combination regimen resulted in an objective response rate of 36.7%, with a median duration of response of 31.1 months (95% confidence interval 4.1 months to not estimable). Median progression free survival was 6.9 months (2.7 to 14.4) and median overall survival was 11.0 months (7.2 to not estimable).

Disitamab vedotin is a HER2 directed antibody-drug conjugate with the same microtubule inhibitor payload as enfortumab vedotin. In a combined analysis of two single arm phase 2 trials (RC48-C005 and RC48-C009) of 107 total patients with HER2 positive locally advanced or metastatic urothelial cancer, disitamab vedotin achieved an objective response rate of 50.5% (95% confidence interval 40.6 to 60.3).\textsuperscript{113} Grade 3 or higher treatment related adverse events occurred in 54.2% of patients, including peripheral neuropathy in 18.7% and neutropenia in 12.1%. In a phase 1b/2 study, 41 patients with locally advanced or metastatic urothelial cancer were treated with disitamab vedotin.
plus the anti-PD1 checkpoint inhibitor toripalimab. This combination achieved a confirmed objective response rate of 73.2% (95% confidence interval 57.1% to 85.8%). Patients with HER2 1+ and 0 expression by immunohistochemistry achieved response rates of 64.3% and 33.3%, respectively.118

Many other emerging treatment options remain under investigation for bladder cancer, including soluble EphB4-human serum albumin,115 bicycle conjugates,116 and FGFR3 specific inhibitors.117 Results of such ongoing developments are eagerly awaited.

Guidelines
Currently, researchers rely on risk stratification (low, intermediate, or high) for NMIBC, based on AUA/SUO 2020 update (table 1), which has also been adopted by the NCCN in their Guidelines for Bladder Cancer V.3.2023 (table 2).46 47 49 European Association of Urology risk groups for NMIBC (table 3) defining four categories (low, intermediate, high, and very high) are more frequently used by European urologists, and are gaining acceptance worldwide for their better definition of the probability of progression by pathologic grading according to WHO 2004 (low v high grade NMIBC) or WHO 1973 (grade 1, grade 2, or grade 3), since both grading systems are in use worldwide (table 4).66 47 49 In the US, the management of locally advanced and metastatic bladder cancer mostly relies on the NCCN Guidelines for Bladder Cancer V.3.2023 (tables 5 and 6) for first and second line systemic treatment and management worldwide.66

Conclusion
NMIBC is managed initially with TURBT, followed by a risk stratified approach to adjuvant IVe, and is associated with a 90% overall survival. By contrast, cure rates remain lower for MIBC. Tumor heterogeneity with unique pathological and molecular characteristics is behind the observed differences of NMIBC and MIBC groupings. For NMIBC, IVe immunotherapy (primarily BCG) remains a gold standard treatment for high risk disease to reduce or prevent both recurrence and progression after initial TURBT; recently completed novel trials have incorporated immune checkpoint inhibitors, IVe gene treatment, and combination IVe chemotherapy, with promising results in reducing recurrence and progression to MIBC.

For localized MIBC, improving care and reducing morbidity following cystectomy or bladder preserving strategies are essential goals. In metastatic disease, advances in understanding of the genomic landscape and tumor microenvironment have led to the implementation of immune checkpoint inhibitors, targeted treatments, and antibody-drug conjugates, thus enhancing the clinical landscape at an aggressive state of the disease. Cisplatin based chemotherapy is receiving much attention nowadays, alone or in combination with systemic immunotherapy and other recently introduced targeted treatments. These novel strategies, which are behind the improved quality of life of the patients, represent a paradigm shift in the management of both localized and metastatic disease. The role of enhanced diagnostic methods including narrow band and blue light cystoscopy to better differentiate neoplastic from

QUESTIONS FOR FUTURE RESEARCH
- What are the biomarkers to improve the detection of aggressive NMIBC progressing under standard treatments (BCG)?
- How can the non-invasive detection of bladder cancer recurrences using molecular urine biomarkers be improved?
- What are the biomarkers that predict improved treatment responses in locally advanced and metastatic bladder cancer (eg, PDL1, PD1, CTLA4, FGFR3, nectin-4, TROP2, molecular subtypes)?
- Can the immune microenvironment be modulated to better potentiate treatments for bladder cancer?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE
Two patients with NMIBC or locally advanced bladder cancer, who were practicing physicians, assisted in answering questions about what problems concern them as bladder cancer survivors. The patients raised concerns around accuracy of urinary molecular methods in detecting tumor recurrence and novel treatments in metastatic bladder cancer.

GLOSSARY OF ABBREVIATIONS
- BCG: Bacillus Calmette-Guérin
- CT: computed tomography
- ctDNA: circulating tumor DNA
- ddMVAC: dose dense methotrexate, vinblastine, adriamycin, cisplatin
- ECOG: Eastern Cooperative Oncology Group
- eLND: extended lymphadenectomy
- ERAS: enhanced recovery after surgery
- ERCC: excision repair cross complementation group
- FDA: Food and Drug Administration
- IVe: intravesical therapy
- MIBC: muscle invasive bladder cancer
- MRI: magnetic resonance imaging
- mTOR: mammalian target of rapamycin
- NAI: nogapendekin alfa inabikcept
- NCCN: National Comprehensive Cancer Network
- NMIBC: non-muscle-invasive bladder cancer
- P01: programmed cell death protein 1
- PDL1: programmed death ligand 1
- TGFβ: transforming growth factor β
- TMB: tumor mutational burden
- TNM: tumor, node, metastases
- TROP2: trophoblast cell surface antigen 2
- TURBT: transurethral resection of a bladder tumor

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normal tissues, urine related molecular biomarkers, imaging methods and potential application of AI are also revisited. Developing better selection criteria to identify the patients most likely to benefit from a specific treatment is an urgent need.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: None.

Contributors: All authors substantially contributed to conception and analysis of the manuscript, drafted the manuscript and revised it critically for important intellectual content; approved the final version to be published; and take responsibility for the accuracy and integrity of the manuscript.

Provenance and peer review: Commissioned; externally peer reviewed.

of patients with metastatic urothelial carcinoma who are unfit for lymphadenectomy performed at time of radical cystectomy for invasive bladder cancer molecular subtypes predict differential response to intravesical Bacillus Calmette-Guérin. Sci Transl Med 2017;9:394.e394. doi:10.1126/scitranslmed.aab4118


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87 Food and Drug Administration. FDA grants accelerated approval to enfortumab vedotin-evp with pembrolizumab for locally advanced or metastatic urothelial carcinoma. 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-enfortumab-vedotin-evp-pembrolizumab-loCALLy-advanced-or-metastatic


