The changing treatment paradigm for patients with bladder cancer

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After decades of relative therapeutic standstill, the introduction of new treatment modalities including antibody-drug-conjugates, immune checkpoint inhibitors and targeted therapies are causing a dramatic change in the treatment paradigm for patients with bladder cancer. While the most profound impact of these new treatment modalities is currently seen in patients with advanced, or metastatic disease, these agents will likely also penetrate the treatment algorithms for earlier disease stages in the years to come. This article provides a brief overview of the contemporary, medical management of bladder cancer, with a particular focus on the innovative treatment modalities that have recently emerged for patients with locally advanced and metastatic disease. In doing so we assess how the recently updated treatment guidelines for bladder cancer formulated by the European Society of Medical Oncology (ESMO) and the European Urology Association (EAU) can be translated to clinical practice, taking into consideration the Belgium reimbursement landscape.

Introduction

Bladder cancer currently ranks 11th on the list of most common cancers worldwide, mounting to place 6 when only Europe is taken into consideration (1). Given the fact that bladder cancer comes with a specific set of suspect urinary symptoms early in the disease course (e.g., hematuria, changed urination frequency [pollakiuria], burning sensation during urination [dysuria], etc.), the majority of patients are diagnosed at an early stage, when the prognosis tends to be more favorable. For patients with carcinoma in situ (CIS), the 5-year relative survival rate is excellent at approximately 96%. This decreases to around 70% for patients with localized disease that remains confined to the bladder but may extend beyond the mucosa. In contrast, outcomes are significantly worse for those with regional lymph node involvement or distant metastases, with 5-year survival rates dropping to 37.5% and 6.4%, respectively (2).

Urothelial cells are the primary cell of origin in bladder cancer, with urothelial cancer accounting for 90-95% of all bladder cancer cases. The remaining 5-10% of cases consist of squamous cell carcinomas, adenocarcinomas and neuroendocrine carcinomas (3). Bladder cancer is predominantly a disease of the elderly, with a median age at diagnosis of about 75 years (3). Epidemiological studies have identified tobacco use as the most prominent risk factor for the development of bladder cancer, with smoking being linked to half of all bladder cancers (4). In addition, occupational exposure to certain chemicals (e.g., benzidine and β-naphthylamine) and drinking water contaminated with arsenic or pesticides also increase the risk for bladder cancer (5). Finally, bladder cancer is characterized by a strong male predominance, with a male to female ratio of approximately 4:1 (1).

Bladder cancer staging reflects the spread and depth of bladder wall invasion of the tumour (**Figure 1**). In 70-75% of the cases, the tumor is limited to the inner lining of the bladder without the involvement of deeper muscle layers. These tumors are referred to as non-muscle invasive bladder cancer (NMIBC) and can be further subdivided in Tis, Ta and T1 disease (6-8). A Tis tumor, or carcinoma in situ (CIS), refers to a flat tumor that is not extending into the bladder lumen. In addition, papillary tumors that do not invade the lamina propria are classified as Ta disease, whereas T1 tumors are papillary tumors that do invade the lamina propria.

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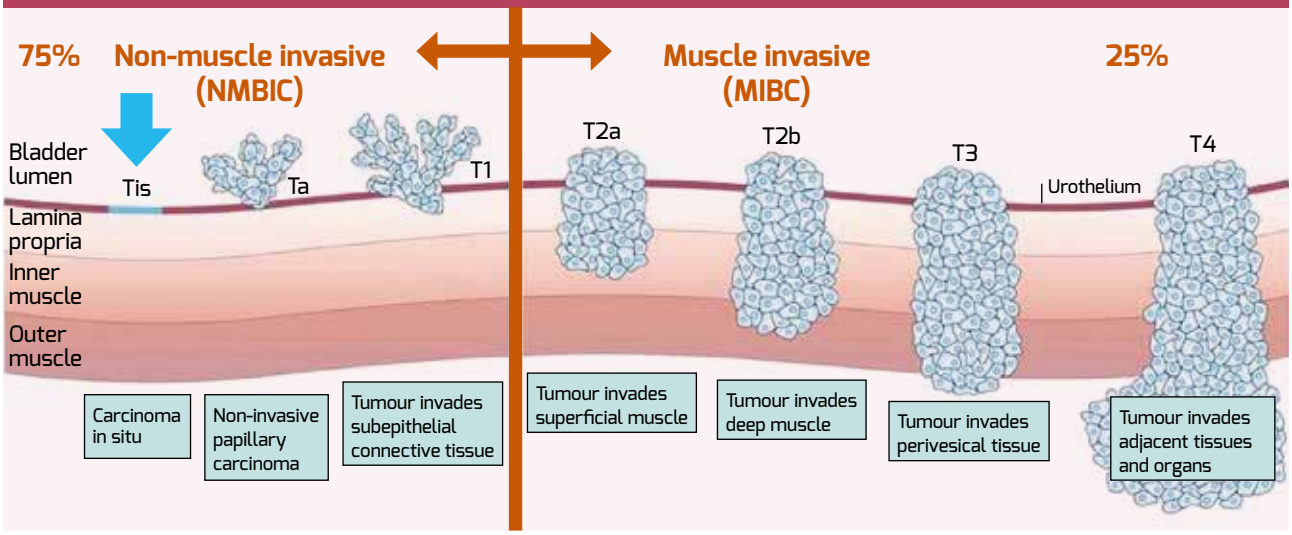
Figure 1: Staging of bladder cancer is based on the depth of tumor infiltration into the bladder wall (9).



Importantly, NMIBC Ta tumors have a much more benign disease course than T1 or Tis tumors, and the treatment of these subtypes is markedly different. When the disease has grown into the muscularis propria, the term muscle-invasive bladder cancer (MIBC) is used. Depending on the depth of bladder wall invasion, MIBC tumors are further classified as T2a, T2b, T3 and T4 disease.

In this article, we will review the contemporary, medical management of bladder cancer, with a particular focus on locally advanced and metastatic disease, an area in which the introduction of novel treatment modalities, such as antibody-drug conjugates (ADCs), immune checkpoint inhibitors (ICIs) and targeted therapies caused an important shift in the treatment paradigm.

NMIBC

All patients with a suspected bladder cancer should undergo a transurethral resection of bladder tumor (TURB), both as a diagnostic procedure and as an initial treatment. In specific cases, for example when there is doubt on the completeness of the initial TURB, when the specimen does not contain detrusor muscle, or when a T1 tumor is diagnosed, a second TURB is indicated (10). While these procedures theoretically allow a complete removal of a NMIBC, recurrences are common. To mitigate this recurrence risk, both the European Association of Urology (EAU) and the European Society of Medical Oncology (ESMO) recommend that all patients should receive some form of adjuvant therapy following a TURB (6, 10). This adjuvant therapy can consist of intravesical instillations with either chemotherapy or Bacillus Calmette-Guérin (BCG). The choice between these two options should be based on the recurrence risk of the individual patient (**Table 1**).

For patients with intermediate- or high-risk NMIBC, however, data indicate that BCG is associated with a significantly lower risk of disease recurrence than intravesical chemotherapy (11-13). Based on these results, maintenance therapy with intravesical BCG for 1-3 years became the universal standard of care for intermediate and high-risk NMIBC. For patients with very high-risk NMIBC, ESMO guidelines recommend an upfront radical cystectomy (RC) (10).

Unfortunately, a series of events has led to a global shortage of BCG, significantly impacting the management of patients with NMIBC. To address the issues posed by BCG shortage, the EAU proposed intravesical chemotherapy as a feasible alternative for

Table 1. Risk classification for NMIBC (6, 10).

Category	Characteristics
Low risk	Primary, solitary, Ta G1 (PUNLMP, LG), < 3cm, no CIS
Intermediate risk	All tumors not defined in the two adjacent categories (between the category of low and high risk)
High risk	Any of the following: - T1 tumour - G3,HG tumour - CIS - multiple, recurrent and large (> 3cm) Ta G1-G2/LG tumours (all features must be present)
Very high risk	- T1 G3/HG associated with concurrent bladder CIS - Multiple and/or large T1 G3/HG and/or recurrent T1 G3/HG, T1 G3/HG with CIS in the prostatic urethra - Some forms of variant histology of urothelial carcinoma, lymphovascular invasion

BCG immunotherapy in intermediate-risk NMIBC patients. For patients with high-risk NMIBC, however, full dose intravesical BCG for one to three years remains the preferred option (6). In addition, research efforts are culminating in the continuous development of alternative treatments to BCG for patients with NMIBC. This includes the use of TAR-200, an indwelling device that elutes intravesical gemcitabine over 3 weeks, and sequential intravesical instillations of gemcitabine and docetaxel. While these strategies have yielded promising early results (mainly in BCG-unresponsive NMIBC patients), data from phase III randomized studies confirming their non-inferiority to first-line BCG have not yet been reported (14, 15). In addition, several phase III studies are underway investigating combination therapy with an ICI and BCG in patients with BCG-naïve NMIBC.

For high-risk NMIBC patients who do not respond to BCG, a RC is currently the only recommended treatment option (6, 10). However, this treatment modality comes with a significant morbidity and has an important impact on quality of life, underscoring the need for new effective treatments for patients with high-risk NMIBC. In this respect, several studies are ongoing to evaluate the role of ICIs in this setting. For example, the single-arm, phase II KEYNOTE-57 study showed that pembrolizumab was associated with a complete response (CR) rate of 41% in BCG unresponsive NMIBC patients with Tis who were ineligible or unwilling to undergo a RC (16). Similarly, the randomized phase III POTOMAC recently showed that adding one year of durvalumab plus standard-of-care BCG induction and maintenance therapy induced a statistically significant and clinically meaningful improvement in disease-free survival (DFS) in patients with high-risk NMIBC compared to BCG induction and maintenance alone (17). For the moment, however, these options are not approved by the European Medicines Agency (EMA).

MIBC

Neoadjuvant therapy

The current standard of care for patients with a cT2-T4a N0 M0 tumor consists of a RC in combination with a pelvic lymph node dissection (PLND) (10, 18). However, when used on its own, this treatment strategy only results in a 5-year overall survival (OS) of approximately 50% of patients (19). To improve on this, several studies have successfully evaluated the effect of neoadjuvant chemotherapy prior to a RC. In a large meta-analysis, pooling the results of 15 randomized trials, 3-4 cycles of cisplatin-based neoadjuvant chemotherapy prior to a RC proved to be associated with an 8% absolute OS benefit at 5 years compared to RC alone (20).

Based on these findings, both ESMO and EAU have embraced neoadjuvant cisplatin-based chemotherapy as a standard of care for all cisplatin-eligible MIBC patients (10, 18). The usual neoadjuvant regimen in this setting consists of cisplatin plus gemcitabine (CG), even if the optimal number of cycle remains unknown (3 or 4 cycles of CG) (10, 18). The VESPER (GETUG-AFU V05) phase III trial evaluated the potential benefit of using a dose-dense regimen in order to increase the rate of pathological complete response (pCR), an established marker for a better patient outcome. In this trial, dose-dense MVAC (dd-MVAC) was associated with a higher pCR rate than GC alone (42% vs. 36%), along with an improved PFS and OS. However, dd-MVAC is more intensive, and requires careful patient selection. As with GC, the optimal number of dd-MVAC cycles in the neoadjuvant setting has not yet been clearly established. In fact, a large proportion of patients receiving dd-MVAC in VESPER did not reach the six planned courses of chemotherapy (21). ESMO and EAU do not specifically state whether dd-MVAC should be systematically implemented in the neoadjuvant strategy (10, 18).

More recently, studies have looked into the role of ICI in the neoadjuvant treatment of MIBC patients. The phase III NIAGARA trial randomized patients to either neoadjuvant durvalumab plus gemcitabine-cisplatin every 3 weeks for four cycles, followed by radical cystectomy and adjuvant durvalumab every 4 weeks for eight cycles (durvalumab group), or neoadjuvant gemcitabine–cisplatin followed by radical cystectomy alone (comparison group). The addition of durvalumab to neoadjuvant gemcitabine-cisplatin, followed by a RC and adjuvant durvalumab resulted in a significantly better OS (HR[95%CI]: 0.75 [0.59-0.93]) and event-free survival (EFS) (HR [95%CI]: 0.68 [0.56-0.82]) (22). In addition, two phase II studies have yielded promising results with a neoadjuvant ICI in cisplatin-ineligible MIBC patients (23, 24). While being very promising, ICI-based neoadjuvant therapies are currently not EMA approved and not included into the MIBC treatment guidelines formulated by the EAU and ESMO.

Adjuvant therapy

While there is strong consensus on the benefit of neoadjuvant therapy in patients with MIBC, the use of adjuvant therapy in this setting is more controversial (10, 18). To date, there are no randomized, controlled phase III data showing an OS benefit for the use of adjuvant cisplatin-based chemotherapy in this setting. In contrast, a meta-analysis of 9 studies including a total of 945 patients did show a significant benefit in OS (HR [95%CI]: 0.77 [0.59-0.99]) and DFS (HR [95%CI]:

0.66 [0.45-0.91]) with adjuvant chemotherapy (25). However, the studies included in this meta-analysis had important methodological flaws, limiting the validity of these results. To date, EAU and ESMO do not recommend the routine use of adjuvant cisplatin-based chemotherapy in MIBC (10, 18). However, the EAU does recommend adjuvant cisplatin-based combination chemotherapy in patients pT3/4 and/or pathological node-positive disease who did not receive neoadjuvant chemotherapy (18).

More recently, three different randomized, controlled phase III trials generated mixed results on the potential of an ICI as adjuvant treatment for MIBC. In fact, CheckMate 274 and AMBASSADOR, respectively evaluating nivolumab or pembrolizumab as adjuvant therapy for 12 months in high-risk MIBC patients, demonstrated a significant benefit in DFS (26, 27). In CheckMate 274, adjuvant nivolumab resulted in an improved the median DFS of 20.8 months as compared to 10.8 months with placebo. Among patients with a PD-L1 expression level of 1% or more, the percentage of patients who were disease-free at 6 months was reported at 74.5% with nivolumab as compared 55.7% with placebo (HR [98.72%CI]: 0.55 [0.35 to 0.85]; p< 0.001) (26). In contrast, the IMvigor010 study, evaluating adjuvant atezolizumab, failed to show a significant delay in disease recurrence with this strategy (28). Currently, nivolumab is the only ICI that is EMA approved as adjuvant treatment for patients with high-risk patients (pathological stage pT3, pT4a, or pN+) MIBC who underwent a RC and have a tumour cell PD-L1 expression ≥ 1% (tumor proportion score, TPS). While EAU guidelines recommend adjuvant nivolumab in this setting, ESMO is waiting for a demonstrated OS benefit to endorse this strategy (10, 18).

Trimodality bladder-preserving therapy

A bladder preserving, trimodality treatment (TMT) strategy in which TURB is combined with radiotherapy and chemotherapy can be a viable alternative for a RC in selected patients (10, 18). TMT can be considered in 2 clinical situations: for selected fit patients who refuse a cystectomy, and for older, less fit patients in whom a RC is not feasible (10, 18). When opting for a TMT in the first scenario, patient selection is of the utmost importance. In this respect, the ideal patient for this strategy has a small tumor for which a complete resection is likely feasible, without hydronephrosis, no prostatic urethra invasion and no diffuse CIS throughout the bladder (10, 18). The TMT criteria for patients who are unfit for a RC are less stringent, but extensive CIS and a poor bladder function should be considered as relative contraindications (18). Chemotherapy is a crucial element of a TMT strategy as it synergistically increases the efficacy of radiotherapy. This chemotherapy can consist of cisplatin, or mitomycin-C in combination with 5-FU. Gemcitabine (alone) may serve as an alternative for cisplatin-ineligible patients (29-31).

For the moment, there are no successfully completed randomized controlled trials comparing the outcome of TMT to that of a RC in patients with MIBC. However, several systematic reviews, meta-analyses, and multi-institutional propensity score matched and weighted analyses suggest comparable outcomes with both strategies in selected patients (32-34). Importantly, the management of patients who are candidates for TMT should be done in a multidisciplinary team setting and a close follow-up, including frequent cystoscopy with or without a salvage cystectomy, should be applied (18).

Metastatic bladder cancer

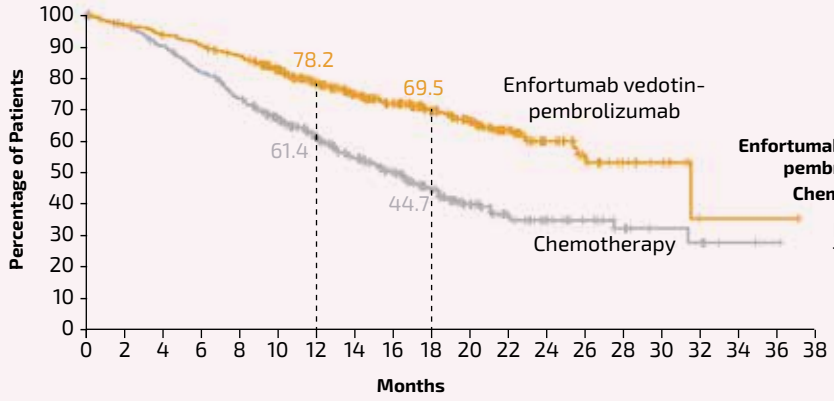
First line treatment

For several decades, the standard first line treatment for patients with metastatic bladder cancer consisted of cisplatin-based chemotherapy, with carboplatin-based chemotherapy as a more tolerable alternative for cisplatin-ineligible patients (10). In recent years, however, the results of three ICI-based clinical trials caused a dramatic shift in the first line treatment recommendations for patients with metastatic bladder cancer.

The first of these studies to be published was the JAVELIN Bladder 100 trial. In this study, 700 patients with advanced or metastatic UC who had not progressed after 4-6 cycles of front-line gemcitabine plus cisplatin/carboplatin were randomized to receive either best supportive care alone or best supportive care (BSC) plus maintenance avelumab. The median OS obtained with avelumab maintenance was 23.8 months, while patients in the control arm had a median OS of 15.0 months (HR [95%CI]: 0.76 [0.63-0.91]; p = 0.0036). This corresponds to a 24% reduced death risk with BSC plus avelumab maintenance compared to BSC alone. The use of maintenance avelumab led to immune related AEs in 29% (7% grade ≥ 3). However, this added toxicity did not have a detrimental effect on the quality of life of patients (35). Based on these results, maintenance therapy with avelumab was established as a standard of care for all patients with at least stable disease on first-line platinum-based chemotherapy (10). More recently, however, two studies again overturned this treatment paradigm.

In the phase III EV-302/KEYNOTE-A39 trial, 886 patients with previously untreated, locally advanced or metastatic urothelial cancer (UC) were randomly assigned to receive a combination of the

Figure 2: Overall survival in the EV-302/KEYNOTE-A39 trial (36).



	No. of events/ No. of patients	Median Overall Survival (95% CI) *mo*
Enfortumab vedotin-pembrolizumab	133/442	31.5 (25.4-NE)
Chemotherapy	226/444	16.1 (13.9-18.3)

Hazard ratio 0.47 (95 CI: 0.38-0.58)
Two-sided P < 0.001

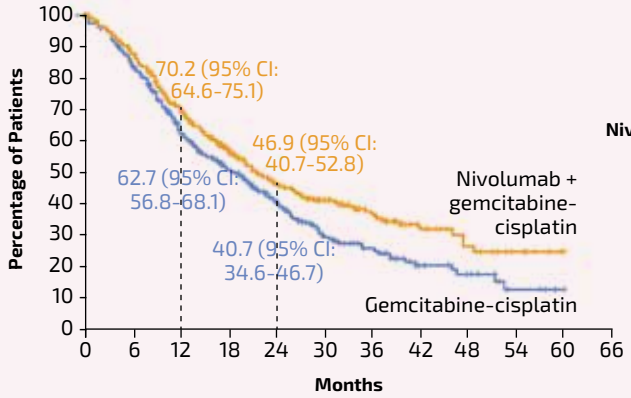
No. at Risk

Enfortumab vedotin-pembrolizumab	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

nectin-4 directed ADC enfortumab vedotin (EV) and pembrolizumab (EV Day 1 and 8 on a 21-day cycle and pembrolizumab every 3 weeks), or platinum-based chemotherapy (gemcitabine + cisplatin/carboplatin) (36). The median progression-free survival (PFS) with EV-pembrolizumab was reported at 12.5 months, which was almost twice as long as the 6.3-month median PFS seen in the control arm (HR [95%CI]: 0.45 [0.38-0.54]; p < 0.001). Importantly, this delayed disease progression also translated into a significant benefit in OS with a median OS of 31.5 and 16.1 months, respectively (HR [95%CI]: 0.47 [0.38-0.58]; p < 0.001), corresponding to a 53% reduced death risk with EV-pembrolizumab (**Figure 2**) (36). The PFS and OS advantage obtained with EV-pembrolizumab was seen across all investigated subgroups, irrespective of age, sex, performance status, the level of PD-L1 expression, cisplatin eligibility status, primary tumor location and the presence of visceral metastases. Interestingly, the clinical benefit obtained with EV-pembrolizumab did not come at the cost of a higher rate of grade ≥ 3 treatment-related adverse events (TRAEs) compared to platinum-based chemotherapy (55.9% vs. 69.5%). Grade ≥ 3 TRAEs of special interest in patients treated with EV-pembrolizumab included skin reactions (15.5%), peripheral neuropathy (6.8%), and hyperglycemia (6.1%). TRAEs resulted in treatment discontinuation in 35.0% of patients in the EV-pembrolizumab arm vs. 18.5% in patients treated with chemotherapy (36).

The phase III CheckMate 901 trial randomized 608 patients with cisplatin-eligible unresectable or metastatic UC to nivolumab + gemcitabine-cisplatin for up to 6 cycles, followed by nivolumab maintenance or gemcitabine-cisplatin alone. The study met both its primary endpoints by demonstrating a significantly better PFS (median 7.9 vs. 7.5 months; HR [95%CI]: 0.72 [0.59-0.88]) and OS (median: 21.7 vs. 18.9 months; HR [95%CI]: 0.78 [0.63-0.96]) (**Figure 3**) among patients treated

Figure 3: Overall survival in the CheckMate 901 study (37).



	No. of events/ No. of patients	Median Overall Survival (95% CI) *mo*
Nivolumab + gemcitabine-cisplatin	172/304	21.7 (18.6-26.4)
Gemcitabine-cisplatin	193/304	18.9 (14.7-22.4)

Hazard ratio for death: 0.78 (95% CI: 0.63-0.96)
P = 0.02

No. at Risk

Nivolumab + gemcitabine-cisplatin	304	264	196	142	97	69	48	25	15	7	2	0
Gemcitabine-cisplatin	304	242	166	122	82	49	33	17	13	4	1	0

with the nivolumab-gemcitabine-cisplatin. Furthermore, the nivolumab-based regimen also resulted in a significantly higher objective (57.6% vs. 43.1%) and complete (21,7% vs. 11.8%) response rate than gemcitabine-cisplatin alone (37). The addition of nivolumab to the treatment regimen did lead to an increase in the rate of grade ≥ 3 TRAEs compared to gemcitabine-cisplatin alone (61.8% vs. 51.7%) (37).

Based on the convincing results of EV-302/KEYNOTE-A39, both ESMO and EAU have endorsed the combination of EV and pembrolizumab as the standard of care first line treatment for patients with advanced or metastatic UC. This regimen may be offered in large majority of patients, including patients who are cisplatin- or carboplatin ineligible (18, 38). When this combination is not available, or contra-indicated (e.g., uncontrolled diabetes, grade ≥ 2 peripheral neuropathy, pre-existing significant skin disorders), EAU and ESMO guidelines recommend:

- cisplatin eligible patients should receive the combination of nivolumab and cisplatin-gemcitabine. Cisplatin-gemcitabine, followed by avelumab in patients without disease progression is an alternative option for these patients (18, 38);
- patients who are cisplatin-ineligible but carboplatin-eligible should receive the gemcitabine-carboplatin combination followed by avelumab maintenance in patients without disease progression (18, 38).

For patients with a contra-indication for an ICI, chemotherapy with gemcitabine in combination with cisplatin or carboplatin is still the preferred first line treatment (18). The use of single agent pembrolizumab or atezolizumab in the first line treatment of advanced/metastatic UC is limited. In the contemporary treatment landscape, this is only a reasonable option for patients who are unable to tolerate combination therapy, do not have a contra-indication for an ICI and have PD-L1 positive tumors. PD-L1 positivity for the use of pembrolizumab is defined by immunohistochemistry as a CPS of ≥ 10 using the Dako 22C33 platform, while for atezolizumab PD-L1 positivity is defined as ≥ 5% tumour-infiltrating immune cells using Ventana SP142 (18).

Second line treatment and beyond

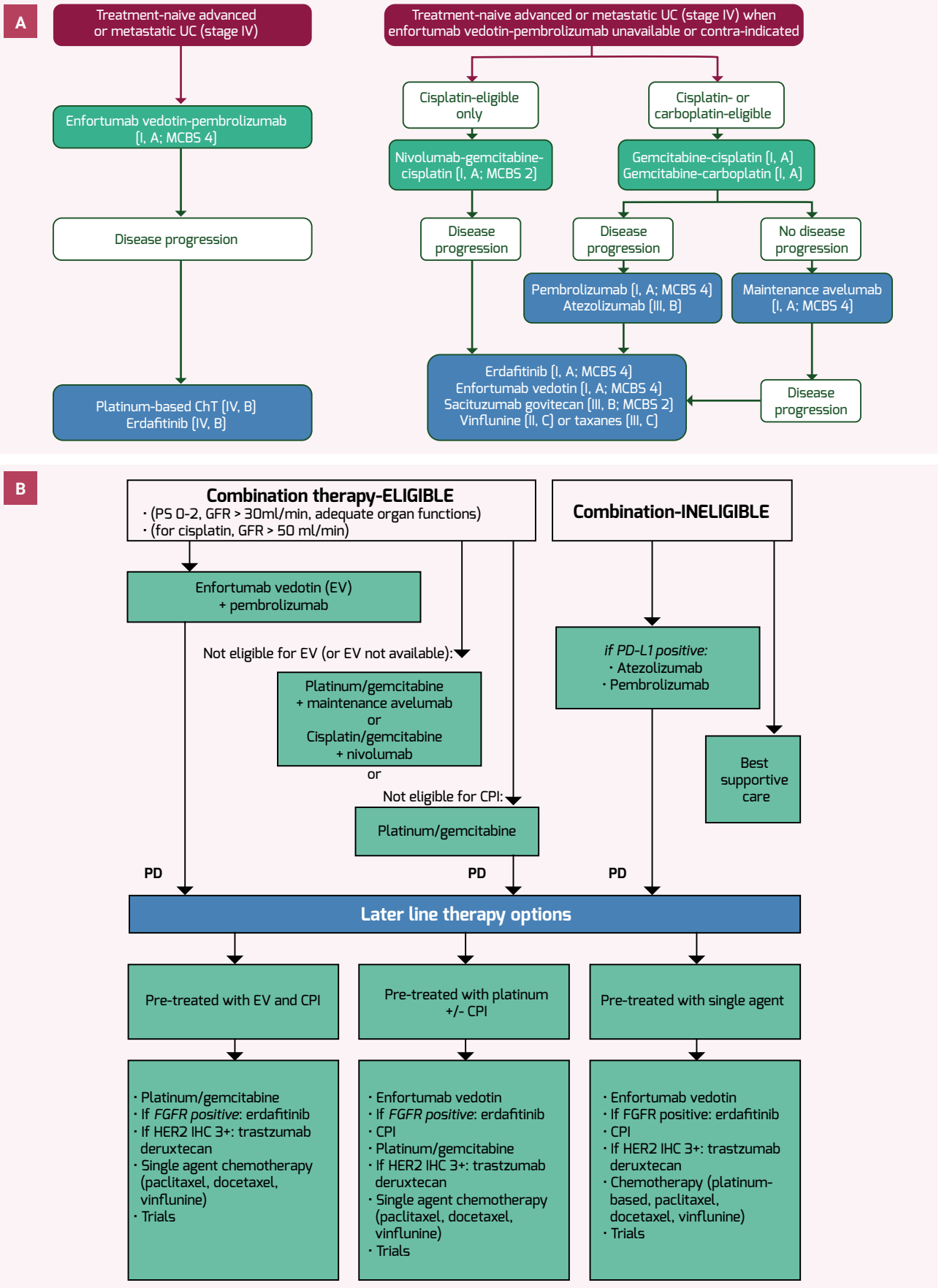
The treatment for patients with relapsed metastatic bladder cancer is mainly steered by the treatment that was given in 1st line.

For patients progressing on the EV-pembrolizumab combination, both EAU and ESMO recommend the use of platinum-based chemotherapy (10, 18, 38). For patients who received platinum-based chemotherapy, alone or in combination with an ICI (i.e., nivolumab or maintenance avelumab), the preferred second line treatment consists of EV monotherapy. The latter is based on the results of the randomized, phase III EV-301 study in which EV proved to be associated with a significantly better OS (median: 12.9 vs. 9 months; HR [95%CI]: 0.70 [0.56-0.89]; p = 0.001) and PFS (median: 5.55 vs. 3.71 months; HR [95%CI]: 0.62 [0.51-0.75]; p < 0.001) than single-agent chemotherapy (docetaxel, paclitaxel, or vinflunine) in patients with metastatic UC who previously received platinum-containing chemotherapy and a PD-(L)1 inhibitor (39).

For patients who did not receive an ICI as part of their 1st line treatment regimen, single-agent ICI therapy can be considered in 2nd line (18, 38). This recommendation is based on the phase III KEYNOTE-045 indicating a 3-year OS rate of 20.7% with pembrolizumab as compared to 11% with chemotherapy in metastatic UC patients who progressed after platinum-based chemotherapy (HR [95CI]: 0.71 [0.59-0.86]) (40). Also atezolizumab demonstrated a survival benefit over chemotherapy in this setting (2-year OS rate: 23% vs. 13%), but this difference did not meet the threshold for statistical significance in the IMvigor211 study (41). Given the stronger data for pembrolizumab compared to atezolizumab, both EAU and ESMO have a preference for pembrolizumab in this setting (10, 18).

Irrespective of the treatment in 1st line, EAU and ESMO recommend the pan-FGFR inhibitor erdafitinib as a treatment for patients harboring an actionable fibroblast growth factor receptor (FGFR) alterations (i.e., FGFR2/3 fusions, or FGFR3 mutations) and who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor (10, 18, 38). The clinical basis for this recommendation is formed by the phase III THOR study. In cohort 1 of this trial, erdafitinib was compared to chemotherapy (docetaxel or vinflunine) in patients with FGFR3/2-altered metastatic UC who progressed on two previous treatments, including an anti-ICI. In this cohort, erdafitinib was associated with a median OS of 12.1 months, which was significantly longer than the 7.8 months median OS seen with chemotherapy (HR [95%CI]: 0.64 [0.47-0.88]; p = 0.005) (42). In cohort 2 of the THOR study, 351 ICI-naïve, metastatic UC patients who received 1 prior line of therapy, erdafitinib did not show an OS benefit compared to pembrolizumab (median: 10.9 vs. 11.1 months; HR [95%CI]: 1.18 [0.92-1.51]). Furthermore, erdafitinib also came with a higher incidence of grade ≥ 3 AEs than pembrolizumab (64.7% vs. 50.9%) (43). Inspired by these findings, the EMA has restricted the use of erdafitinib to metastatic UC patients who were pre-treated with an ICI.

Figure 4: Most recent treatment guidelines for patients with metastatic bladder cancer formulated by ESMO (A) and the EAU (B) (18, 38).



CPI: checkpoint inhibitor; FGFR: fibroblast growth factor receptor; GFR: glomerular filtration rate; PD: programmed death; PD-L1: programmed death-ligand 1; PS: performance status

Also TROP-2 directed ADC sacituzumab govitecan (SG) emerged as a promising treatment in metastatic UC after failure of chemotherapy and an ICI. The clinical support for SG in this setting comes from the phase II TROPHY-U-01 study in which this agent was shown to induce an objective response in 28% of metastatic UC patients who were previously treated with chemotherapy and an ICI. The median PFS and OS with this agent were reported at 5.4 and 10.9 months, respectively (44). This inspired the ESMO guidelines to recommend the use of SG in this setting (38). However, this is not the case in the updated EAU guidelines (18) (**Figure 4**). Recently, the phase III TROPiCS-04 trial, which randomized patients who had progressed after platinum-based chemotherapy and ICI to SG or chemotherapy (physician's choice), did not meet its primary endpoint (median OS: 10.3 vs. 9.0 months; HR: 0.86; p = 0.087). This led to the withdrawal of SG in this setting (45).

For patients who have progressed on EV, ICI-based therapy and platinum-based chemotherapy, treatment options include participation in clinical trials, single-agent chemotherapy, or erdafitinib in patients with an actionable FGFR alteration. Best supportive care alone should only be considered in patients who are not a candidate for further cancer-specific systemic therapy (18).

Belgian reimbursements

Since patients with MIBC are a vulnerable population, only half will receive systemic treatment, and fewer than 20% of them will be able to undergo second-line therapy. Under these circumstances, the best available systemic treatment should be administered in the first line for eligible patients (46). While the updated EAU and ESMO treatment recommendations provide clear guidance on the preferred treatment strategy in patients with metastatic bladder cancer, specific reimbursement restrictions limit their implementation in Belgium. The main limitation in this respect lies in the fact that the first line combination of EV and pembrolizumab is currently not yet reimbursed. The reimbursement of this combination is expected later this year (2025), but for the moment EV is only reimbursed as monotherapy in metastatic UC patients who previously received platinum-based chemotherapy and an ICI. As a result, the standard 1st line treatment for metastatic UC patients according to both ESMO and the EAU is currently unavailable in Belgium. In contrast, the combination of nivolumab and gemcitabine-cisplatin is reimbursed, making this regimen a preferred option for cisplatin-eligible patients in Belgium. Maintenance therapy with avelumab after platinum-based chemotherapy is also available in Belgium, making this a good alternative for nivolumab + gemcitabine-cisplatin in cisplatin-eligible patients and a preferred 1st line treatment strategy in cisplatin-inelgible patients after carboplatin-gemcitabine. Finally, also the ICI pembrolizumab and atezolizumab are reimbursed in the 1st line treatment of metastatic UC, provided that the patient is ineligible for platinum-based chemotherapy and has a tumor with a sufficient level of PD-L1 expression.

In the 2nd line setting, pembrolizumab and atezolizumab are reimbursed for patients progressing on a first line treatment with platinum-based chemotherapy. While erdafitinib is currently not reimbursed in Belgium, access to this drug has been provided through a compassionate use program (CUP). Eligibility criteria for this CUP are: locally advanced unresectable or metastatic UC, the presence of a susceptible FGFR3 alteration and disease progression during or following at least one line of treatment with an anti-PD-(L)1 ICI in the metastatic setting.

Conclusions & future perspectives

After decades of relative therapeutic standstill, the introduction of ADCs, ICIs and to a lesser extent targeted therapies are causing a rapid change in the treatment paradigm for patients with bladder cancer. While the most profound impact of these new treatment modalities is currently seen in patients with advanced, or metastatic disease, these agents will likely also penetrate the treatment algorithms for earlier disease stages in the years to come.

In fact, CheckMate 274 and AMBASSADOR already demonstrated a significant benefit in DFS with adjuvant nivolumab and pembrolizumab in high-risk MIBC patients. Should this DFS benefit also translate into a significantly longer OS in this setting, it is to be expected that a growing number of patients with metastatic UC will have undergone pre-treatment with ICI. To date, however, the optimal choice of first-line treatment in metastatic setting after previous adjuvant ICI remains unknown. According to the EAU guidelines, the 1st line treatment choice for these ICI-exposed metastatic patients should be informed by the type of peri-operative therapy that was given and the time until relapse. If at least twelve months have passed since the end of the peri-operative treatment, these patients should be treated as ICI-naïve patients (18). Whether this is also the case for patients with a faster recurrence is subject to debate. As discussed earlier, studies with ICIs are also underway in NMIBC, both in combination with BCG in BCG-naïve patients and in BCG unresponsive patients.

Building on the success of EV in the metastatic UC setting, studies are also underway to evaluate this agent in earlier disease stages. For example, the EV-304/KEYNOTE-B15 trial is currently

comparing peri-operative therapy with EV-pembrolizumab to gemcitabine-cisplatin in cisplatin-eligible MIBC. In cisplatin-ineligible MIBC, KEYNOTE-905/EV-303 is comparing peri-operative pembrolizumab with or without EV to upfront RC + PLND. In addition, phase II trials are underway to evaluate induction therapy with EV-pembrolizumab followed by definitive radiotherapy in node positive MIBC patients who are unfit or unwilling to undergo a RC, while phase I studies are also evaluating the potential of intravesical EV in patients with NMIBC. If positive, the results of these studies will again cause a ripple effect on the treatment algorithm for patients with more advanced disease.

Another important area of research in UC consists of the identification of biomarkers. In this respect, the recognition of FGFR-alterations as a therapeutic target in metastatic UC represents an important breakthrough. Researchers have also looked into biomarkers that can predict a response to ICI in advanced bladder patients. Unfortunately, however, randomized controlled trials failed to confirm the predictive value of PD-L1 expression or a high tumor mutational burden in this setting (18, 22, 24, 28, 40). Other ICI biomarkers that are under evaluation include molecular subtypes, immune gene cell signatures, and the composition of the tumoral micro-environment. For the moment, however, none of these biomarkers are ready for clinical practice.

Finally, also evaluations of circulating tumor DNA will become increasingly important in the management of bladder cancer. In fact, studies have already established that ctDNA has prognostic potential in MIBC patients who received (neo)adjuvant chemotherapy and showed that it may serve as an early marker of disease progression (24, 28, 47-50). For the moment, ctDNA data are only informative and do not yet alter standard practice. For example, the detection of ctDNA during neoadjuvant therapy does not necessarily prompt treatment changes beyond updated imaging. Similarly, if ctDNA is undetectable after a RC, adjuvant nivolumab is still offered to patients meeting high-risk criteria. In the future, ctDNA is expected to play a more active role in clinical decision-making. For example, it could be used in the treatment selection at diagnosis or ctDNA dynamics may steer treatment adjustments during neoadjuvant therapy, escalating the treatment in non-responders and de-escalating it in patients with a good response. As such, ctDNA-guided treatment decision may in time lead to better outcomes and a better quality of life for patients (51).

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