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Systemic, perioperative management of muscle-invasive bladder cancer and future horizons

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Abstract

Many patients diagnosed with muscle-invasive bladder cancer (MIBC) will develop distant metastatic disease. Over the past three decades, perioperative cisplatin-based chemotherapy has been investigated for its ability to reduce the number of deaths from bladder cancer. Insufficient evidence is available to fully support the use of such chemotherapy in the adjuvant setting; however, neoadjuvant cisplatin-based combination chemotherapy has become a standard of care for eligible patients based on the improved disease-specific and overall survival demonstrated in two randomized phase III trials, compared with surgery alone. For patients with disease downstaging to non-MIBC at the time of radical cystectomy as a result of neoadjuvant chemotherapy, outcomes are outstanding, with 5-year overall survival of 80–90%. Nevertheless, the inability to define before treatment the patients who will and those who will not achieve such a response has impeded the achievement of better outcomes for patients with MIBC. High-throughput DNA and RNA profiling technologies might help to overcome this barrier and enable a more-personalized approach to the use of cytotoxic neoadjuvant chemotherapy. In the past 2 years, trial results have demonstrated the unprecedented ability of immune-checkpoint blockade to induce durable remissions in patients with metastatic disease that has progressed after chemotherapy; studies are now urgently needed to determine how best to incorporate this powerful therapeutic modality into the care of patients with MIBC. Herein, we review the evolution of chemotherapy and immunotherapy for muscle-invasive bladder cancer.

In the 1940s, Jewett and Strong¹ performed an exhaustive survey of 107 bladder cancer autopsies, and found that the incidence of extravesical extension and metastasis was low in patients with tumours confined to the submucosa, but high in those with tumours that had invaded the muscle layer. Over the ensuing decades, the hypothesis that invasion of the primary bladder tumour into the muscle layer reflects a distinct and lethal disease biology has been confirmed² (TABLE 1).

Each year, bladder cancer is diagnosed in approximately 430,000 patients worldwide, with urothelial carcinoma (also known as transitional-cell carcinoma) being the predominant

Author contributions

Both authors contributed substantially to all aspects of the preparation of the manuscript for publication.

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histological subtype in the USA and Europe³. Approximately 70% of patients with bladder cancer present with non-muscle-invasive disease (NMIBC) and have an excellent prognosis, with 5-year overall survival approaching 90%^{4,5} (TABLE 1). Most non-muscle-invasive tumours are low grade and harbour genetic mutations that result in constitutive activation of receptor tyrosine kinase (RTK)/RAS/PI3K signalling pathways^{6,7}. The remaining 20–40% of patients either present with muscle-invasive or advanced-stage disease (TABLE 1), or have disease progression after treatment of non-muscle-invasive disease; many of these patients have high-grade tumours driven by loss of tumour-suppressor genes (such as *TP53*, *RB1* and/or *PTEN*), which have a propensity for local and distant spread⁶. Once the disease becomes metastatic, 5-year overall survival is a dismal 6%⁵; therefore, treatment of muscle-invasive bladder cancer (MIBC; cT2–T4a, cN0M0) is an important opportunity to avoid metastasis and achieve cure.

Despite primary surgical management of MIBC with radical cystectomy and pelvic lymph-node dissection, up to 50% of patients will eventually develop tumours at distant sites, owing to pre-existing disseminated occult micrometastases^{8,9}. Thus, local and systemic therapies must be combined to improve outcomes. In this Review, we describe the evolution of the chemotherapy landscape in the perioperative treatment of MIBC. Neoadjuvant cisplatin-based chemotherapy has emerged as a standard of care^{10–13}, although many patients do not benefit from this approach^{14,15}. Therefore, we highlight advances in genomic profiling that might result in more-individualized treatment that could improve outcomes. Finally, the potential implications of novel immunotherapies for the future treatment of MIBC are considered.

Timing of perioperative chemotherapy

Theory versus practice.

Perioperative treatment encompasses the therapies given immediately before or after surgery. In theory, the administration of chemotherapy before (neoadjuvant) or after (adjuvant) definitive local therapy should be equally effective in eliminating micrometastases. Indeed, the findings of many large randomized trials of chemotherapy in patients with early stage breast cancer support this hypothesis^{16–18}. Nevertheless, upfront surgery can enable pathological confirmation of the extent of disease before systemic therapy. Of note, between 6% and 15% of patients with MIBC have been reported to achieve a pathological complete response (pCR) with transurethral resection of bladder tumour (TURBT) alone, and these patients have excellent outcomes without chemotherapy^{8,14,19,20}. Thus, the ability to use features associated with risk of disease recurrence in order to refine patient selection for treatments, and thereby prevent overtreatment or undertreatment of some patients, is a clear advantage of an adjuvant strategy over the neoadjuvant approach. In practice, however, many of the patients with MIBC who choose to undergo upfront surgery will never actually receive adjuvant chemotherapy. Bladder cancer is largely a disease of the elderly, with a median age at diagnosis of 73 years²¹, and radical cystectomy is a much more morbid procedure than the local therapies used in patients with early stage breast cancer. For example, the findings of a retrospective study in 1,142 consecutive patients who underwent radical cystectomy indicate that 30% of patients experience a grade 2–5 complication within

90 days of surgery that could delay the delivery of effective adjuvant chemotherapy²². Thus, the timing of perioperative therapy might be more critical in patients with MIBC than in those with breast cancer, and the proportion of patients with MIBC who receive chemotherapy might be increased using a neoadjuvant, rather than adjuvant, approach.

Poor accrual: the scourge of adjuvant therapy trials in MIBC.

Within the past 10 years, four randomized trials evaluating adjuvant chemotherapy for MIBC have been closed early owing to poor patient accrual^{23–26}, collectively achieving <50% of their enrolment target (TABLE 2). EORTC 30994 was the largest and most-recently published of these trials²⁶. In this trial²⁶, 284 patients with pT3–4 and/or lymph-node-positive disease were randomly assigned to receive one of three different chemotherapy regimens (either gemcitabine plus cisplatin; methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); or dose-dense MVAC (ddMVAC)), or the same regimens deferred until relapse. At a median follow-up duration of 7 years, the median overall survival in the immediate treatment group was 6.74 years (95% CI 3.85–not reached) versus 4.60 years (95% CI 2.15–6.25) in the deferred treatment group; however, the difference in overall survival favouring immediate use of chemotherapy did not reach statistical significance (adjusted hazard ratio (HR) 0.78, 95% CI 0.56–1.08; $P = 0.13$). Adjuvant chemotherapy did, however, significantly prolong progression-free survival (PFS): median PFS was 3.1 years with adjuvant therapy versus 0.99 years in the deferred chemotherapy group (HR 0.54, 95% CI 0.40–0.73; $P < 0.0001$). In contrast to earlier findings from a meta-analysis²⁷ and a retrospective study²⁸, the patients without lymph-node involvement included in the EORTC 30994 trial had a 5-year overall survival benefit from immediate treatment (HR 0.37, 95% CI 0.16–0.83; $P = 0.012$), whereas those with lymph-node involvement did not (HR 0.94, 95% CI 0.65–1.34; $P = 0.72$)²⁶. These findings raise the possibility that some patients without lymph-node involvement were classified as such owing to inadequate lymph-node sampling, and that subsequent chemotherapy compensated for undetected lymph-node involvement in these patients — an effect that was not needed in the lymph-node-positive group who underwent more-thorough lymph-node dissection.

Given the poor patient accrual and early closure of randomized trials, Galsky *et al.*²⁹ used data from the American College of Surgeons and American Cancer Society National Cancer Database (NCDB) to investigate the benefit associated with adjuvant chemotherapy in patients with pT3–4 and/or lymph-node-positive bladder cancer. A total of 5,653 patients treated between 2003–2006 were identified, of whom 23% had received adjuvant chemotherapy²⁹. The authors controlled for multiple factors associated with treatment selection, such as age, sex, pathological tumour stage, income, and insurance status, through the use of propensity scores, and found an improvement in overall survival with the use of adjuvant chemotherapy compared with no chemotherapy (HR 0.70, 95% CI 0.64–0.76)²⁹. The benefit of adjuvant chemotherapy was consistent when variables not captured in the NCDB, such as performance status, were accounted for through sensitivity analyses²⁹. The adjuvant chemotherapy regimens used, however, are not clearly defined in the NCDB, and information about disease recurrence or the timing of potential salvage chemotherapy in patients in the observation group is lacking. Furthermore, results of retrospective analyses are known to be subject to sources of bias and confounding, despite careful controlling for

imbalances, and cannot substitute for level 1 evidence, which can only be achieved through prospective randomized trials.

NACT: early lessons learned

The identification and confirmation of an effective NACT regimen for patients with MIBC required over two decades of investigation, with treatment regimens being extrapolated from the metastatic to the muscle-invasive-disease setting (TABLE 3 and TABLE 4, respectively). Pioneering work in the 1970s and early 1980s established the therapeutic activity of cisplatin in patients with urothelial bladder cancer, and led to its use as a cornerstone of combinatorial regimens for those with metastatic disease^{30–39}. After promising results of cisplatin-based combination therapies were demonstrated in patients with metastatic disease, the regimens were tested as neoadjuvant treatments in patients with MIBC. Many of the lessons learned during these early experiences remain relevant today.

Beware of clinical understaging in MIBC.

In 1988, Scher *et al.*⁴⁰ reported data from 50 patients who had received neoadjuvant treatment with 1–5 cycles of MVAC; of 30 patients who underwent radical cystectomy, 33% achieved a pCR and a further 17% had downstaged disease. Importantly, despite extensive re-evaluation using TURBT and other clinical staging procedures after NACT, a clinical and pathological staging discrepancy of 38% was observed in this study⁴⁰. Later trials and patient series have continued to report frequent clinical disease understaging using pre-chemotherapy and post-chemotherapy TURBT, and non-invasive imaging modalities^{41–45} (TABLE 5). Thus, at present, patients should proceed to radical cystectomy and bilateral pelvic lymph-node dissection, even if a clinical complete response is achieved with NACT. Indeed, at a consensus meeting held in 2012, a panel of bladder cancer experts stated that placing patients who have achieved a clinical complete response to NACT under observation only is “akin to playing Russian roulette” (REF. 46), and did not recommend the approach. Moreover, some centres have advocated using clinical factors to select patients for NACT⁴⁵, but the high discrepancy between clinical staging and actual pathological staging also raises important concerns regarding whether this strategy is appropriate.

Patients with lymph-node involvement during preoperative assessment have stage IV disease and should be treated accordingly.

Muscle-invasion alone reflects the capacity of a bladder tumour for distant spread, although lymph-node involvement is a more-definitive harbinger of systemic dissemination⁸. In the original trials of the MVAC regimen for the treatment of bladder cancer^{40,47}, patients with suspected lymph-node involvement were included in the metastatic disease cohorts; however, patients with metastases restricted to lymph nodes or soft-tissue sites can achieve long-term disease control if they experience a major response after six cycles of cisplatin-based combination therapy and then go on to have consolidation surgery, whereas such control of disease is rarely achieved in those who do not have a major response or in patients who have visceral metastases^{48–50}. An analysis of NCDB data, published by Galsky *et al.*⁵¹ in August 2016, revealed that treatment with perioperative chemotherapy and surgery was associated with better outcomes than either surgery or chemotherapy alone in patients with

bladder cancer and clinical evidence of regional lymph-node involvement. Chemotherapy for patients with clinical lymph-node involvement can, therefore, be followed by surgery, but should not be referred to as ‘neoadjuvant chemotherapy’ — which is defined as four cycles of chemotherapy for cT2–T4aN0M0 disease, rather than six cycles for nodal (N1-3) or metastatic (M1) disease. In the modern era, some data indicate that lymph-node metastases of 1–2 cm in diameter can be effectively evaluated with 2-[¹⁸F]fluoro-2-deoxy-D-glucose (¹⁸F-FDG)-PET-CT and, if necessary, CT-guided biopsy sampling⁵². Six cycles of cisplatin-based chemotherapy should remain the standard-of-care approach for patients with lymph-node involvement during preoperative assessment until compelling evidence from randomized clinical trials indicates that overall survival is equivalent with either a shorter duration of chemotherapy or a novel therapeutic approach.

Downstaging to NMIBC after NACT is an intermediate end point for survival.

Another important lesson learned from the early experience with cisplatin-based NACT is that improved overall survival is associated with not only a pCR, but also downstaging to NMIBC with no pathological lymph-node involvement (<pT2N0) at the time of radical cystectomy. In a retrospective analysis involving 147 patients with MIBC, Splinter *et al.*⁵³ reported that 41.5% of patients were downstaged to <pT2N0 after neoadjuvant treatment with MVAC. Notably, 5-year overall survival was 75% in this subgroup, compared with 20% among those with residual muscle-invasive tumours (>pT2) or lymph-node involvement at the time of surgery⁵³. Similarly, the findings of a retrospective analysis of a large, randomized trial demonstrated that patients with pathological MIBC and/or node-positive disease after neoadjuvant MVAC have dismal outcomes⁵⁴. The positive correlation between downstaging to <pT2N0 disease and improved overall survival has also been demonstrated in a retrospective case series⁵⁵ and a large meta-analysis⁵⁶. Indeed, phase II neoadjuvant trials with the <pT2N0 rate as an intermediate end point have been proposed as a model for accelerating drug development in MIBC^{57,58}.

Despite the fact that patients without downstaging to <pT2N0 after 12 weeks of cisplatin-based NACT have poor outcomes, no high-level evidence supports the use of additional adjuvant chemotherapy in this population. Nevertheless, one retrospective study in 37 patients with lymph-node involvement after NACT reported an improvement in disease-free survival (DFS) with a variety of different ‘adjuvant’ chemotherapy regimens⁵⁹. While hypothesis generating, this study did not demonstrate an overall survival benefit and the results must be confirmed in larger patient cohorts. As discussed in a later section of this Review, novel approaches with immune-checkpoint blockade might prove to be more effective than the use of cytotoxic chemotherapy in this setting.

The use of NACT does not affect the feasibility and safety of surgery.

The Nordic Cooperative Bladder Cancer Study Group conducted the first randomized phase III trials of cisplatin-based combination chemotherapy in patients with MIBC. In the Nordic Cystectomy Trial I⁶⁰, 325 patients were randomly assigned to receive either neoadjuvant cisplatin plus doxorubicin or no NACT before undergoing short-term radiotherapy followed by radical cystectomy (TABLE 4). In the Nordic Cystectomy Trial II⁶¹, the efficacy of cisplatin and methotrexate was compared with no pretreatment before radical cystectomy in

317 patients with MIBC. Neither trial demonstrated an improvement in overall survival with NACT, although the combined data from the Nordic trials helped alleviate concerns that NACT might negatively affect the ability to perform a radical cystectomy: radical cystectomy was performed in 86% of patients in the NACT arms and 87% of those in the control arms^{60,61}. The results of the subsequent large (n = 317), multi-institutional phase III SWOG-8710 trial¹⁴ also demonstrated that MVAC did not adversely affect a patient's chance of undergoing cystectomy, and the rate of surgical complications was not increased among the MVAC-treated patients versus those who did not receive NACT.

NACT improves survival in MIBC

Supportive level 1 evidence.

In the BA06 30894 trial^{62,63}, a multicentre study performed by an international collaboration of trialists, 976 patients were randomly assigned to receive either three cycles of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV), or no NACT before radical cystectomy and/or radiotherapy. In an updated analysis of this trial after a median follow-up duration of 8 years⁶³, neoadjuvant CMV was associated with an absolute improvement in 10-year survival from 30% to 36% (TABLE 4), with a corresponding 16% reduction in the risk of death (HR 0.84, 95% CI 0.72–0.99; $P = 0.037$).

In the pivotal SWOG-8710 randomized trial¹⁴, patients with MIBC received either radical cystectomy alone, or three cycles of MVAC followed by radical cystectomy (TABLE 4); disease-specific survival was inferior for the patients who received radical cystectomy alone versus those who received neoadjuvant MVAC (HR 1.66, 95% CI 1.22–2.45; $P = 0.002$)¹⁴. A trend toward inferior overall survival was also observed for the patients who underwent upfront surgery versus those treated with MVAC (5-year overall survival 45% versus 57%; HR 1.33, 95% CI 1.00–1.76; $P = 0.06$)¹⁴. In addition, the pCR rate was improved after neoadjuvant MVAC compared with surgery alone (38% versus 15%; $P < 0.001$)¹⁴. Consistent with prior reports⁵³, achieving a pCR to NACT was correlated with an excellent 5-year overall survival rate of 85% in the SWOG-8710 cohort¹⁴. Finally, for patients who did not have a pCR at the time of radical cystectomy, those who received neoadjuvant MVAC had a median overall survival that was not significantly different to that observed for those who received upfront radical cystectomy (3.8 years versus 2.4 years).

In 2005, an updated meta-analysis¹⁰ of data from 3,005 patients included in 11 clinical trials revealed a 5% absolute increase in 5-year overall survival and a 14% decreased risk of death (HR 0.86, 95% CI 0.77–0.95; $P = 0.003$) among patients with MIBC who received cisplatin-based NACT before local therapy compared with those who received the same local treatments only; this benefit was consistent across patient subgroups defined by age, sex, and clinical T or N category, and a significant DFS benefit of NACT was also observed (HR 0.78, 95% CI 0.71–0.86; $P < 0.0001$). At first glance, these findings could be interpreted as a small, incremental improvement in outcomes; however, a metaanalysis⁶⁴ of data from 17,723 women with early stage breast cancer that helped establish adjuvant chemotherapy as a standard of care showed a 7% survival benefit and a 15% decrease in breast-cancer-related mortality for women aged <50 years. Similarly, a pooled analysis⁶⁵ involving 3,302 patients with colon cancer helped establish 5-fluorouracil-based adjuvant therapy as a standard of

care based on a survival benefit of 7% at 5 years. Thus, the survival benefit of cisplatin-based NACT for patients with MIBC is comparable to that reported among patients with other tumour types in which perioperative chemotherapy is both statistically and clinically significant, and an accepted standard of care.

Level 1 evidence has not led to widespread implementation of NACT.

Despite the availability of level 1 evidence supporting its ability to improve survival, uptake of cisplatin-based NACT for the treatment of MIBC by the oncology and urology communities has been extremely slow. An analysis of NCDB data from 7,161 patients with American Joint Committee on Cancer (AJCC) stage III MIBC (TABLE 1) revealed that from 1998 to 2003, only 1.2% of patients received NACT⁶⁶. Subsequently, the publication of the SWOG-8710 trial results in 2003 might have led to a slight increase in the use of NACT, as evidenced by another NCDB evaluation involving 17,330 patients⁶⁷, among whom the use of NACT rose from 6% in 2003 to 13% in 2007. The most-recent analyses of the NCDB⁶⁸, published in 2015, revealed that the use of NACT for MIBC is increasing over time, with rates of 10.1% in 2006 rising to 20.9% in 2010, but nevertheless, remains low.

With the advent of novel chemotherapeutic agents and haematopoietic growth factor support, investigators have focused on developing NACT regimens with similar efficacy, but less toxicity than that of MVAC. Although not necessarily a 'real-world' estimate, findings of a surgical trial, reported in abstract form at the American Urological Association 2015 annual meeting⁶⁹, demonstrated that 187 out of the 381 patients involved (51%) had been treated with NACT. The favourable toxicity profile of modern chemotherapy regimens (as outlined in the following section) is one of the factors that could potentially explain this trend.

Improving on standard NACT with MVAC

Gemcitabine and cisplatin.

In a large randomized trial in patients with metastatic urothelial carcinoma^{70,71}, the combination of gemcitabine and cisplatin (GC) had similar efficacy and less toxicity than MVAC (TABLE 3), and thus the GC regimen became a standard-of-care treatment for this patient population. Dash *et al.*⁷² performed a retrospective, single-institution analysis of patients with MIBC who received either neoadjuvant GC or neoadjuvant MVAC before radical cystectomy. Among the 42 patients in the GC cohort, 39 (93%) received all four cycles of GC; 15 of these 39 patients (36%) had disease downstaging to <pT2N0 disease at the time of radical cystectomy and remained disease-free at a median follow-up duration of 30 months⁷². Similarly, 19 of the 54 MVAC-treated patients (35%) had <pT2N0 at the time of radical cystectomy⁷². The pCR rates for the GC-treated and MVAC-treated patients were also similar (26% and 28%, respectively).

In a retrospective assessment of 935 patients with MIBC who received NACT followed by radical cystectomy across 19 centres⁵⁶, the GC regimen was used in 602 patients (64.4%) and MVAC in 183 patients (19.6%). The <pT2N0 rates in the GC and MVAC cohorts were 44.8% and 43.7%, respectively⁵⁶; the pCR rate in the patients who received GC was 23.9%,

compared with 24.5% for those treated with MVAC ($P = 0.2$). The efficacies of GC and MVAC in the neoadjuvant setting have never been compared directly in a randomized trial, but the favourable toxicity profile of the GC regimen has nevertheless resulted in its adoption as a standard-of-care NACT endorsed by the National Comprehensive Cancer Network (NCCN)⁷³. This endorsement is supported by the aforementioned randomized study conducted in the metastatic setting⁷⁰ (TABLE 3), and data from retrospective studies^{56,72,74} — but not by level 1 evidence.

Dose-dense strategies.

The European Organisation for Research and Treatment of Cancer (EORTC) reported the first results of a phase III trial in which 263 patients with metastatic bladder cancer were randomly assigned to receive either ddMVAC plus granulocyte-colony-stimulating factor (G-CSF) in 2-week cycles, or standard MVAC chemotherapy in 4-week cycles⁷⁵. Use of the ddMVAC regimen seemed to be associated with less toxicity and greater clinical activity than treatment with MVAC⁷⁶ (TABLE 3). This finding resulted in ddMVAC being accepted as a standard of care for patients with metastatic bladder cancer⁷³.

In 2014, two single-arm, prospective studies evaluating neoadjuvant ddMVAC with G-CSF support in the treatment of patients with MIBC were reported simultaneously^{77,78}. Choueiri *et al.*⁷⁷ treated 39 patients with four cycles of ddMVAC, whereas Plimack *et al.*⁷⁸ evaluated three cycles of ddMVAC in 40 patients; the $\leq pT2N0$ rates at the time of surgery were 49% and 53%, respectively, and the pCR rates were 26% and 38%, respectively^{77,78}. Importantly, the dose-dense approach can decrease the time between the start of MVAC chemotherapy and the point of surgery, with a median time of 9.7 weeks reported in the study by Plimack *et al.*⁷⁸ (compared with 16–19 weeks for the standard regimens^{14,72}). The results of these two prospective trials^{77,78} (TABLE 4), as well as those from two retrospective studies^{79,80}, are promising; however, the authors of an editorial⁸¹, which accompanied the trial publications, identified issues regarding patient selection that might limit the generalizability of the results. For example, both trials included patients with N1 disease, therapy for whom, as previously discussed, cannot truly be considered ‘neoadjuvant’. Of note, a comparative effectiveness analysis of GC versus MVAC NACT has been performed across 28 international centres⁸², with 146 patients included in the GC cohort and 66 patients in the MVAC cohort, 51 (77%) of whom received ddMVAC; no statistically significant difference in the pCR rate or survival between the two cohorts was demonstrated after adjusting for propensity scores⁸².

Data from randomized clinical trials comparing GC and ddMVAC therapy are required to confirm the equivalence of these regimens, in terms of both efficacy and toxicity. In the ongoing SWOG 1314 trial⁸³, patients with MIBC are being randomly assigned to neoadjuvant GC or ddMVAC treatment arms in order to determine the utility of a gene-expression-based biomarker approach for predicting pCR, but the findings will also provide an estimate of comparative $\leq pT2N0$ rates. In addition, a multicentre phase III study is ongoing in France to compare six cycles of ddMVAC with four cycles of GC, using PFS as the primary end point. Unless the results of these trials strongly suggest that ddMVAC has

superior efficacy, neoadjuvant GC will probably remain the standard-of-care treatment for patients with MIBC owing to the more-favourable toxicity profile.

On the basis of the promising activity and toxicity profiles of dose-dense GC (ddGC) compared with that of ddMVAC reported in the metastatic setting⁸⁴ (TABLE 3), two prospective, multicentre phase II studies of neoadjuvant ddGC (2-week cycle) chemotherapy in patients with MIBC have been initiated and reported in abstract form^{85,86}. Plimack *et al.*⁸⁵ reported that, among the first 13 patients treated in one of these trials, two patients had a myocardial infarction resulting in congestive heart failure, one had a deep venous thrombosis (DVT), one had a pulmonary embolus, and one required coronary artery bypass grafting before surgical resection of the tumour⁸⁵. After a subsequent protocol amendment to require cardiac clearance before study entry, further vascular toxicity was seen, with one additional patient having a DVT and another having a stroke⁸⁵. The study was closed before reaching the enrolment target of 44 patients⁸⁵. Of the 31 patients who underwent radical cystectomy, 14 (45%) had <pT2N0 disease and 10 (32%) had a pCR⁸⁵. In the second, more-recent, trial, Balar *et al.*⁸⁶ excluded patients with any recent history of a cardiovascular event from the outset, used a higher dose of gemcitabine than that used by Plimack *et al.*⁸⁵ (2,500 mg/m² versus 1,200 mg/m²), and administered split-dose cisplatin (35 mg/m² on day 1 and 2) instead of the standard single dose (70 mg/m² on day 1). Of the 41 patients who underwent radical cystectomy in the study by Balar *et al.*⁸⁶, 26 (63.4%) had <pT2N0 disease and, importantly, the vascular toxicity was similar to that observed in neoadjuvant trials of standard-dose GC chemotherapy. In an intention-to-treat analysis (with patients who refused radical cystectomy counted as nonresponders), the <pT2N0 rate was 56.5%⁸⁶. The feasibility of drug delivery for ddGC was excellent: patients received a median of six cycles, and 80% received at least five cycles⁸⁶. Thus, the ddGC regimen used in the trial by Balar *et al.*⁸⁶ is a promising neoadjuvant strategy for appropriately selected patients with MIBC.

Non-cisplatin-based NACT.

Approximately 30–50% of patients with MIBC are ineligible for cisplatin-based NACT owing to ageing-related and disease-associated organ impairment⁸⁷ (BOX 1). The utility of non-cisplatin-based NACT in this population is controversial and is not supported by prospective evidence from randomized clinical trials. Findings indicate that carboplatin is inferior to cisplatin in the treatment of patients with metastatic disease^{88–90}; therefore, use of carboplatin before definitive therapy in the neoadjuvant setting would seem imprudent without strong supporting evidence. Single-arm, phase II trials with paclitaxel, carboplatin, and gemcitabine^{42,91}, as well as nab-paclitaxel, carboplatin, and gemcitabine⁹², have yielded pathological responses, but at rates less than those expected with the use of cisplatin-based chemotherapy and with higher incidences of haematological toxicity. Current guidelines suggest that non-cisplatin-based chemotherapy should only be considered when downstaging of surgically unresectable tumours is the primary objective¹³.

Hussain *et al.*⁹³ performed a small study to help address the barrier of renal insufficiency in patients with MIBC with a glomerular filtration rate <40 ml/min/1.73 m². In this study, split-dose cisplatin (35 mg/m²) and gemcitabine (1,000 mg/m²) were administered on days 1 and 8 of every 21-day cycle, for a maximum of four cycles. The regimen was well tolerated,

with no clinically significant decline in renal function reported⁹³. Determining the efficacy of the regimen based on the findings of this study is difficult, given the small sample size and the fact that pathological response rates at the time of radical cystectomy were not reported. Nevertheless, selective use of split-dose cisplatin might widen the spectrum of patients who are eligible for cisplatin-based chemotherapy.

Age alone is not a criterion for ineligibility to receive cisplatin, although many elderly patients will fall into this category. Given that the median patient age at diagnosis of bladder cancer is 73 years and individuals aged 75–84 years account for the largest percentage of new cases (30%)²¹, an urgent need exists for clinical trials and interventions to improve outcomes in this population⁹⁴. In addition to more-effective and less-toxic therapies, a coordinated multidisciplinary approach, geriatric assessment tools, and the incorporation of a geriatric oncologist can help identify patients with MIBC who are at an increased risk of chemotherapy-induced toxicity^{95–97}.

Predictors of response to NACT

The inability to predict responsiveness to cisplatin-based NACT is a major impediment to improving the outcomes of patients with MIBC. In a phase III trial of cisplatin-based adjuvant chemotherapy, investigators attempted to determine the utility of p53 positivity, assessed using immunohistochemistry, to predict response²⁴. Although p53 was not found to be prognostic, a high patient refusal rate, lower than expected event rate, and failures to receive the assigned therapy severely compromised the statistical power of the study²⁴. The current empirical treatment approach results in many patients receiving ineffective and potentially toxic chemotherapy; however, the molecular phenotyping made possible by improved high-throughput profiling technologies might lead to a much-needed shift toward individualized treatment.

Intrinsic subtypes.

Whole-genome profiling of RNA expression (the transcriptome) and the grouping of tumours into basal, luminal, and HER2-enriched sub-types has already had a major effect on the clinical management of patients with breast cancer^{98,99}. For example, NACT benefits primarily patients with basal-like or HER2-enriched tumours, and not those with luminal tumours^{100–102}.

Whole-genome RNA-expression profiling of more than 300 NMIBCs and MIBCs revealed intrinsic sub-types of bladder cancer that spanned the spectrum of cell differentiation^{103,104}. Additional investigations using mRNA-expression profiling demonstrated that MIBC can be grouped by differential expression of breast basal and luminal markers^{105,106}, and a p53-like subtype of ‘luminal’ MIBC has also been recognized¹⁰⁵. Using an RNA-sequencing platform (RNAseq), the TCGA investigators interrogated 131 MIBCs and also found that these tumours were enriched for breast basal and luminal markers¹⁰⁷. The TCGA researchers subdivided the luminal MIBCs into ‘cluster I’ (luminal, differentiated, with *FGFR3* aberrations and *CDKN2A* deletions) and ‘cluster II’ (luminal, less differentiated, with epithelial-to-mesenchymal transition (EMT)); cluster II corresponded with the aforementioned p53-like sub-type¹⁰⁸. The TCGA consortium also subdivided the basal

tumours into ‘cluster III’ (squamous) and ‘cluster IV’ (EMT and immune-infiltrated) subtypes. The results of an expanded TCGA analysis in an additional 281 patients were reported in abstract form at the 2016 Genitourinary Cancer Symposium and confirmed these four gene-expression-based MIBC subtypes¹⁰⁹.

Similar to observations in breast cancer, each of the intrinsic subtypes of MIBC seem to have distinct clinical characteristics and prognoses. For example, compared with those with basal MIBCs, patients with luminal MIBCs tend to have better clinical outcomes, with less-advanced-stage disease at presentation, but are also less chemoresponsive^{105,106}. A retrospective evaluation of patients treated with cisplatin-based NACT suggested that those with p53-like luminal MIBCs were chemo-resistant and less likely to be of stage < pT2N0 at the time of radical cystectomy than those with other tumour subtypes¹⁰⁵. Moreover, in a phase II trial evaluating neoadjuvant ddMVAC and bevacizumab, patients with basal tumours exhibited better 5-year overall survival rates compared with those with luminal and p53-like tumours (91%, 73%, and 36%, respectively)¹¹⁰. The findings were externally validated in a historical cohort of 49 patients treated with neoadjuvant MVAC, but the sample size was, nevertheless, small and heterogeneous, and no correlation between intrinsic subtype and pathological response at the time of surgery was reported. Thus, the predictive value of the intrinsic subtypes in MIBC requires additional confirmation.

Alterations in DNA-repair genes.

Cisplatin causes intrastrand and interstrand DNA crosslinks, which interfere with DNA replication and gene transcription; inability to repair this treatment-induced damage has been reported to increase tumour-cell sensitivity to cisplatin^{111,112}. Two groups have evaluated whether genomic alterations in DNA-repair pathways are predictive of responsiveness to cisplatin-based NACT in patients with MIBC^{113,114} (TABLE 6). Van Allen *et al.*¹¹³ found that inactivating mutations in the nucleotide excision repair (NER) gene *ERCC2* were significantly enriched in responders compared with nonresponders to cisplatin-based NACT ($P < 0.001$; $q < 0.007$); indeed, *ERCC2* was the only gene among a panel of 3,277 with possibly consequential somatic alterations that was significantly enriched in responders. Plimack *et al.*¹¹⁴ found that the presence of an alteration in one or more of the three DNA-repair-related genes, *ATM*, *RBI*, and *FANCC*, predicted a pathological response ($P < 0.001$ in the discovery cohort; $P = 0.033$ in the validation cohort).

The relationship between somatic alterations in DNA-repair genes and the intrinsic TCGA subtypes of MIBC has been explored^{108,114}. Plimack *et al.*¹¹⁴ evaluated 33 samples from the discovery group that had already been assigned to a TCGA subset and found that the *ATM/RBI/FANCC* signature did not correlate with the subset assignment. McConkey *et al.*¹⁰⁸ demonstrated that *ERCC2* mutations can be present in tumours from all four TCGA subgroups including, surprisingly, cluster II tumours — corresponding to the chemoresistant p53-like subtype. Thus, further explorations of whether *ERCC2*-mutated, p53-like luminal tumours are sensitive or resistant to cisplatin-based NACT will be revealing.

Prospective evaluation of genomic predictors.

As mentioned previously, SWOG 1314 is an ongoing clinical trial of GC versus ddMVAC NACT that was designed to prospectively evaluate the ability of a gene-expression profiling algorithm (COXEN) to predict pathological responses¹¹⁵. In this trial, gene-expression and microRNA-expression data, as well as patient samples for tissue microarray construction, are being collected before chemotherapy. The goal is to develop a rational and individualized treatment approach, in which patients who are unlikely to respond to NACT could be advised to undergo immediate radical cystectomy or to receive a novel treatment as part of a clinical trial. Alternatively, bladder-sparing approaches could be explored in patients who are predicted to be extremely sensitive to cisplatin.

Immune-checkpoint inhibitors

Despite the aforementioned advancements in the treatment of bladder cancer, the survival of patients with MIBC has not improved over the past 15 years, and no new drug has been approved in the USA in more than 20 years³. This therapeutic stalemate is not dissimilar to the state of treatment for metastatic melanoma in early 2011. Since 2011, however, the treatment armamentarium for metastatic melanoma has been bolstered by nine different drug approvals by the FDA, most of them immunotherapies. Bladder cancer was actually the first disease for which the FDA approved an immunotherapy: intravesical administration of bacillus Calmette-Guérin (BCG) was approved in 1990 for the treatment of NMIBC^{116,117}. More recently, antibodies targeting the programmed cell-death protein 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) pathway, which is an inhibitory immune checkpoint that regulates T-cell activity, have demonstrated robust evidence of therapeutic activity in patients with metastatic bladder cancer that has progressed despite treatment with platinum-based chemotherapy^{118–123} (TABLE 7).

Evidence from the metastatic setting.

Tumours can elude immune surveillance and elimination through expression of PD-L1, which binds to PD-1 on cytotoxic T cells, leading to cytotoxic T-cell deactivation and suppression of T-cell proliferation¹²⁴. Results of the single-arm, multicentre, phase II IMvigor 210 trial¹¹⁸ of the anti-PD-L1 antibody atezolizumab for the treatment of metastatic disease were published in May 2016. The reported objective response rate (ORR) among 311 patients was 15%, with 15 (5%) and 30 (10%) patients achieving complete and partial responses, respectively; at a minimum follow-up duration of 11.7 months, the median duration of response was not reached, with 38 of the 45 (84%) responders having a maintained response¹¹⁸. These findings led to the accelerated approval of this approach by the FDA in May 2016. The results of several single-arm, multicentre, phase I/II trials of other antibodies that target PD-1 or PD-L1 have also been reported^{119–123}, and are comparable to those of the IMvigor 210 study (TABLE 7). Importantly, in previously untreated, cisplatin-ineligible patients with metastatic disease, response rates to atezolizumab¹²⁵ and the anti-PD-1 antibody pembrolizumab¹²⁶ of 19.1% and 24%, respectively, have been demonstrated in two phase II trials. These response rates are lower than those seen historically with chemotherapy¹²⁷, although the durability of the responses (the median duration of response was not reached in either phase II study) suggests that

immunotherapy could soon become a first-line treatment option in this patient population. Given the strong evidence of clinical activity in the metastatic setting, a logical next step is to use these agents in the treatment of patients with MIBC; indeed, trials of this approach are underway (TABLE 8).

Moving immune-checkpoint inhibitors into the perioperative setting.

When a neoadjuvant treatment exists that improves overall survival, the FDA has recommended the use of an 'add-on strategy, in which the experimental therapy is given in conjunction with the standard-of-care therapy'¹²⁸. Indeed, combining anti-PD-1/PD-L1 immunotherapy with cisplatin-based NACT for the treatment of patients with MIBC is an attractive approach, given that both treatments have proven antitumour activity. Two urgent questions must be addressed, however. First, is synergy of the combination biologically plausible? Second, are predictive biomarkers available to identify the patients who are most likely to benefit?

Preclinical evidence is available both for and against a potential synergy between chemotherapy regimens and immune-checkpoint blockade. The effectiveness of GC in treating bladder cancer might derive from an ability to stimulate antitumour immune responses¹²⁹. For example, the gemcitabine included in this regimen can deplete regulatory T (T_{reg}) cells and myeloid-derived suppressor cells (MDSC), and enhances T-cell infiltration into tumours in animal models^{130–133}. Moreover, cisplatin has been shown to induce tumour-cell susceptibility to CD8⁺ cytotoxic T lymphocyte (CTL)-mediated killing¹³⁴. In addition, platinum-based chemotherapy has been shown to be mutagenic^{135,136}. Thus, cisplatin might increase the somatic mutational load in tumour cells and lead to the presentation of neoantigens, thereby enabling recognition of tumours by an immune system activated by PD-1/PD-L1 blockade. Conversely, the glucocorticoids given to attenuate chemotherapy-associated nausea and the nonspecific genotoxic effects of chemotherapy might hamper the antitumour immune response^{137,138}.

Clinical data from patients with non-small cell lung cancer (NSCLC) seem to support the safety and efficacy of combination treatment with an anti-PD-1/PD-L1 antibody and chemotherapy. For example, atezolizumab was investigated in combination with carboplatin and either paclitaxel, pemetrexed, or nab-paclitaxel in 37 patients with chemotherapy-naïve advanced-stage NSCLC¹³⁹, and the most frequent all-grade adverse events, regardless of attribution across arms, included those commonly associated with chemotherapy. One patient did experience grade 5 toxicity owing to candidaemia after prolonged neutropenia¹³⁹. Among the 30 patients available for evaluation of efficacy outcomes, the ORR across all arms was an impressive 67%¹³⁹. In a randomized phase II trial evaluating chemotherapy with or without pembrolizumab in 123 patients with advanced-stage NSCLC, chemotherapy with PD-1 blockade was tolerable and also resulted in a higher ORR than chemotherapy alone (55% versus 29%; $P = 0.0016$)¹⁴⁰.

Whenever possible, in neoadjuvant trials, investigators should take advantage of the availability of pretreatment and post-treatment tissue and blood samples to investigate mechanisms of response and resistance. In general, the duration of neoadjuvant treatment in such trials is limited, so as not to delay potentially curative surgery; however, biomarker

analysis in pretreatment and post-treatment tissue can provide valuable information, irrespective of pathological response rates. For example, Liakou *et al.*¹⁴¹ found that neoadjuvant administration of ipilimumab, an antibody that blocks the immune-checkpoint protein cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), led to markedly increased expression of inducible co-stimulator (ICOS) on CD4⁺ T cells present in the peripheral blood and tumour tissues of patients with cancer. The authors postulated that this finding could potentially be used as a biomarker to guide the dosing and scheduling of ipilimumab. Cisplatin-ineligible patients with MIBC, for whom no standard-of-care perioperative therapy exists, are an ideal target population for this type of investigative approach. The existence of a short-term intermediate end point in the form of pathological response at the time of radical cystectomy, combined with the ability to give a novel immunotherapy without confounding cisplatin-containing chemotherapy, makes the neoadjuvant setting an ideal platform for drug-development efforts focused on this patient population^{57,142}.

Predictive biomarkers.

Higher expression levels of PD-L1 are associated with increased ORRs to PD-1/PD-L1 blockade, although negative staining for this protein does not preclude durable and/or complete responses in patients with metastatic bladder cancer¹⁴³ (TABLE 7). Thus, an urgent need exists for the identification of biomarkers beyond PD-L1 expression that can help predict treatment outcomes. The authors of the IMvigor 210 trial of atezolizumab in metastatic urothelial carcinoma evaluated whether TCGA intrinsic sub-type and/or mutational load was predictive of a response to this agent¹¹⁸. Gene-expression analysis was used to classify the tumours of 195 patients as luminal ($n = 73$) or basal ($n = 122$) subtypes, which have unique PD-L1 and CD8⁺ T-effector-cell gene-expression profiles¹¹⁸. Responses to atezolizumab were observed across all TCGA disease subtypes, but occurred at a significantly higher rate in patients with the luminal cluster II disease subtype: ORR of 34% versus 10% for subtype I, 16% for subtype III, and 20% for subtype IV ($P = 0.0017$)¹¹⁸. Mutational load was estimated in the tumours from 150 patients by examination of a representative panel of 315 cancer-related genes, and was significantly increased in responders to treatment compared with nonresponders (12.4 per Mb versus 6.4 per Mb; $P < 0.0001$)¹¹⁸. The association between mutational load and response to atezolizumab was unrelated to TCGA disease subtype ($P = 0.22$). A biomarker integration tree proposed by the authors suggests that incorporation of information on TCGA gene-expression-based disease subtype, mutational load, and PD-L1 expression could improve the ability to predict a response to PD-L1 blockade. The value of a multibiomarker classifier merits further investigation in larger cohorts and in future studies of immunotherapy, including those planned in the setting of MIBC.

Bladder-sparing treatments for MIBC

Despite improvements in surgical techniques, radical cystectomy can lead to substantial morbidity, and not all patients are eligible or willing to undergo the procedure. Multimodality therapy incorporating maximal TURBT followed by radiotherapy combined with various forms of chemotherapy has emerged as an alternative, organ-preserving treatment strategy^{144,145}. Extensive discussion of this approach is outside the scope of this

Review, although such treatment can be offered to selected patients with MIBC and is associated with outcomes superior to those of radiotherapy alone^{13,146}. Future research efforts will focus on optimization of the treatment components, as well as the incorporation of predictive biomarkers and novel cytotoxic, targeted, and immunotherapeutic agents.

Conclusions

MIBC is an aggressive systemic disease that requires a multidisciplinary team to coordinate systemic and local treatments. Major strides in improving the outcomes of patients with this disease were made with the advent of cisplatin and cisplatin-based combination regimens three decades ago. Since then, two randomized trials and a meta-analysis of data from more than 3,000 patients with MIBC have established level 1 evidence for use of cisplatin-based NACT. Many patients with MIBC are, however, ineligible for cisplatin-based therapy and have no evidenced-based systemic treatment options available. In theory, adjuvant chemotherapy should be equally as effective as NACT, but in practice many patients experience postoperative complications, deterioration of performance status, or worsening renal function that can all preclude the safe and timely administration of chemotherapy. Adjuvant trials have failed to reach accrual targets and, although potentially compelling, data from retrospective analyses are not a replacement for prospective evidence from randomized clinical trials. Updated consensus guidelines recommend that clinicians have a detailed discussion with high-risk patients (those with pT3/4 and/or pN + disease) who did not receive preoperative treatment regarding the potential risks and benefits associated with adjuvant chemotherapy, and limitations of the available data on this approach¹³.

Incremental advances have been made over the past decade in improving the tolerability and effectiveness of systemic chemotherapy regimens; however, new molecular-profiling technologies and advances in immunotherapy are poised to dramatically reshape the therapeutic landscape for patients with MIBC. An improved understanding of the genomic makeup of MIBC, including somatic mutations in DNA-repair genes and intrinsic subtypes defined by unique gene-expression profiles, might enable a personalized approach to chemotherapy. Although outside the scope of this Review, the identification of driver mutations that can be targeted with selective inhibitors might also be of relevance to therapy for MIBC, as in other malignancies^{147,148}. Finally, blockade of the PD-1-PD-L1 axis might be a transformative approach in MIBC, by harnessing the power of antitumor immunity to obtain durable clinical benefit. Nevertheless, the future of immune-checkpoint blockade will probably involve combination-based approaches using established therapeutic modalities, novel immunotherapeutic strategies, or both. Coordinated efforts will be needed to determine the optimal therapeutic combinations and to apply both immune-profiling and genomic-profiling technologies to expand our predictive abilities beyond PD-L1 expression.

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Box 1 |**Criteria for cisplatin ineligibility**

Galsky *et al.*¹⁵ have established a consensus definition for cisplatin ineligibility in patients with bladder cancer based on at least one of the following criteria:

- Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2
- Impaired renal function: creatinine clearance rate (CrCl) <60 ml/min/1.73 m²
- Common Terminology Criteria for Adverse Events (CTCAE) version 4 grade ≥ 2 hearing loss
- CTCAE version 4 grade ≥ 2 neuropathy
- New York Heart Association class III heart failure

Key points

- High metastatic relapse rates after radical cystectomy indicate muscle-invasive bladder cancer (MIBC) is a systemic disease at diagnosis in many patients
- The use of adjuvant chemotherapy to decrease relapse rates after radical cystectomy is not supported by level 1 evidence, and the postoperative morbidity of patients often precludes such systemic treatment
- For eligible patients, the standard-of-care treatment approach for MIBC comprises cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy and bilateral pelvic lymph-node dissection
- Barriers to improved patient outcomes include inaccurate clinical staging before selecting curative treatment, slow uptake of neoadjuvant chemotherapy, and the lack of an effective non-cisplatin-based neoadjuvant treatment regimen
- Identification of genomic predictors of a response to chemotherapy might lead to a more-personalized approach to the treatment of patients with MIBC
- Immunotherapy will probably reshape the MIBC treatment landscape

Table 1 |Overview of bladder tumour staging, incidence, and outcomes^{4,5}

Clinical category	Depth of invasion	T stage	N stage	M stage	AJCC stage	Proportion of newly detected cases	5-Year OS
Non-muscle-invasive	Noninvasive papillary carcinoma	Ta	0	0	0a	~50%	~90%
	Carcinoma <i>in situ</i> : 'flat tumour'	Tis	0	0	Ois	~15%	
	Subepithelial connective tissue	T1	0	0	I	~5%	
Muscle-invasive	Muscularis propria	T2	0	0	II	~20%	~60%
	Perivesical tissue	T3	0	0	III		
	Local structures	T4	0	0	III		
	Prostatic stroma/uterus or vagina	T4a	0	0	III		
Advanced stage	Pelvic wall or abdominal wall	T4b	0	0	IV	~10%	5–30%
	Any depth	Any	1–3	0	IV		
		Any	Any	1	IV		

AJCC, American Joint Committee on Cancer; M, metastasis; N, lymph node; OS, overall survival; T, tumour.

Table 2 |

Randomized trials of adjuvant therapy for muscle-invasive bladder cancer

Study (year of publication)	TNM stage eligibility criteria (percentage of patients)	Planned enrolment (n)	Patients randomized (n)	Treatments (n)	Survival benefits demonstrated
Paz-Ares <i>et al.</i> ²³ (2010)	pT3–4N0 (44%) and/or anyTpN+(56%)	340	142	PCG (68) versus observation (74)	PCG improved DFS ($P<0.0001$), DSS ($P<0.0002$), and 5-year OS (60% versus 31%; $P<0.0009$) [*]
Stadler <i>et al.</i> ²⁴ (2011)	pT1–2N0M0 [‡]	190	114	MVAC (58) versus observation (56)	None [§] : DFS HR 0.78 ($P=0.62$)
Cognetti <i>et al.</i> ²⁵ (2012)	pT2N0–2 grade3, pT3–4N0–2, or anyTpN1–2	350	194	GC (102) versus observation (92)	None: 5-year DFS 37.2% versus 42.3% ($P=0.70$); 5-year OS 43.4% versus 53.7% ($P=0.24$)
Sternberg <i>et al.</i> ²⁶ (2015)	pT3–4N0 and/or anyTpN+	1,344/660 ^{//}	284	GC, MVAC, or ddMVAC (141) versus deferred chemotherapy at relapse (143)	DFS only: median DFS was 3.1 years versus 0.99 years (HR 0.54, $P<0.0001$), and 5-year DFS was 47.6% versus 31.8%; 5-year OS 54% versus 48%; 5-year DSS 39% versus 44% ($P=0.22$)

ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; DFS, disease-free survival; DSS, disease-specific survival; GC, gemcitabine and cisplatin; HR, hazard ratio; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; n, number of patients; OS, overall survival; PCG, paclitaxel, cisplatin, and gemcitabine.

^{*} Results presented only in abstract form.

[‡] All patients had tumours with 10% nuclear reactivity for p53 on immunohistochemical analysis.

[§] Trial was terminated early for futility.

^{//} Trial redesigned to reduce the target enrolment from 1,344 to 660 patients owing to poor patient accrual.

Table 3 |

Selected randomized clinical trial comparisons of chemotherapy for metastatic bladder cancer

Study (year of publication)	<i>n</i>	Interventions	Response rate (%)	Median OS (months)	Toxicity
Logothetis <i>et al.</i> ³⁶ (1990)	110	MVAC versus CISCA	65 versus 46; $P < 0.05$	15.5 versus 10.1; $P = 0.0003$	MVAC > CISCA
Loehrer <i>et al.</i> ³⁷ (1992)	269	MVAC versus cisplatin	39 versus 12; $P < 0.0001$	12.5 versus 8.2; $P = 0.0002$	MVAC > cisplatin
Mead <i>et al.</i> ³⁹ (1998)	214	CMV versus MV	46 versus 19 (P value not reported)	7.0 versus 4.5; $P = 0.0065$	CMV > MV
von der Maase <i>et al.</i> ^{70,71} (2000,2005)	405	GC versus MVAC	49 versus 46; $P = 0.51$	14.0 versus 15.2; $P = 0.66$	MVAC > GC
Sternberg <i>et al.</i> ^{75,76} (2001, 2006)	263	ddMVAC versus MVAC	72 versus 58; $P = 0.016$	15.1 versus 14.9 (P value not reported; 5-year OS was 21.8% versus 13.5%, $P = 0.04$)	MVAC > ddMVAC
Bamias <i>et al.</i> ⁸⁴ (2013)	130	ddGC versus ddMVAC	32 versus 27; $P = 0.67$	18 versus 19; $P = 0.98$	ddMVAC > ddGC

CISCA, cisplatin, cyclophosphamide, and doxorubicin; CMV, cisplatin, methotrexate, and vinblastine; ddGC, dose-dense gemcitabine and cisplatin; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine and cisplatin; MV, methotrexate and vinblastine; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; *n*, number of patients; OS, overall survival.

Table 4 |

Selected prospective clinical trials of neoadjuvant chemotherapy for MIBC

Study (year of publication)	n	Eligibility	Trial design	Intervention	Landmark OS
Martinez-Pineiro <i>et al.</i> ¹⁴⁹ (1995)	122	cT2–4aNx–2 [*]	Phase III	Cisplatin + surgery versus surgery	6.5-year OS: 35.5% versus 37.3% ($P = 0.95$)
Nordic Trial I: Malmström <i>et al.</i> ⁶⁰ (1996)	325	cT2–4aNx	Phase III	CA+RT+ surgery versus RT+ surgery	5-year OS: 59% versus 51% ($P = 0.1$)
Nordic Trial II: Sherif <i>et al.</i> ⁶¹ (2002)	317	cT2–4aNx	Phase III	CM + surgery versus surgery	5-year OS: 53% versus 46% ($P = 0.24$)
BA06 30894: international collaboration of trialists ^{62,63} (1999,2011)	976	cT2–4aN0	Phase III	CMV + surgery or RT versus surgery or RT	10-year OS: 36% versus 30% ($P = 0.037$)
SWOG-8710: Grossman <i>et al.</i> ¹⁴ (2003)	317	cT2–4aN0	Phase III	MVAC + surgery versus surgery	5-year OS: 57% versus 43% ($P = 0.06$)
Choueiri <i>et al.</i> ⁷⁷ (2014)	39	cT2–4aN0–1 [*]	Single-arm phase II	ddMVAC + surgery	2-year OS: 79%
Plimack <i>et al.</i> ⁷⁸ (2014)	40	cT2–4aN0–1 [*]	Single-arm phase II	ddMVAC + surgery	1.8-year OS: 83%

CA, cisplatin and doxorubicin; CM, cisplatin and methotrexate; CMV, cisplatin, methotrexate, and vinblastine; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; MIBC, muscle-invasive bladder cancer; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; n, number of patients; OS, overall survival; RT, radiotherapy.

^{*} Patients with lymph-node involvement are classified as having stage IV disease and not MIBC.

Table 5 |

Studies of clinical MIBC understaging rates

Study (year of publication)	<i>n</i>	Study type	Platinum-based NACT used	Proportion of patients upstaged at surgery
Scher <i>et al.</i> ⁴⁰ (1988)	50	Phase I/II trial	Yes	38%
Millikan <i>et al.</i> ⁴¹ (2001)	66	Phase III trial	No	61%
deVere White <i>et al.</i> ⁴² (2009)	10	Phase II trial	Yes	60%
Canter <i>et al.</i> ⁴³ (2011)	212	Case series	No	73.2%
Meijer <i>et al.</i> ⁴⁴ (2013)	125	Case series	Yes	37.5%
Culp <i>et al.</i> ⁴⁵ (2014)	199	Case series	No	49.2%

n, number of patients; NACT, neoadjuvant chemotherapy.

Table 6 |**Mutations in DNA-repair genes in predicting response to NACT**

Study characteristics	Van Allen <i>et al.</i> ¹¹³	Plimack <i>et al.</i> ¹¹⁴
Number of patients	50	<ul style="list-style-type: none"> Discovery cohort: 34 Validation cohort: 24
TNM stage selection criteria	pT2–T4cN0–IM0	pT2–T4cN0–IM0
Pathological response end points	pT0/pTis versus pT2	<ul style="list-style-type: none"> pT0pN0cM0 versus >pT0pN0cM0 pT1pN0cM0 versus >pT1pN0cM0
NACT	GC, ddMVAC, GC-sunitinib, or ddGC	ddMVAC and ddGC
DNA-profiling technique	WES	NGS of 287 cancer-related genes
Findings	<i>ERCC2</i> mutations enriched in responders to NACT compared with nonresponders ($P < 0.001$; $q < 0.007$), and associated with increased mutational load (15.5 versus 5.1 mutations per Mb; $P = 0.01$)	<i>ATM/RB1/FANCC</i> alterations predict response to NACT ($P < 0.001$ discovery; $P = 0.033$ validation)
Functional validation	<i>ERCC2</i> -deficient cell lines have increased sensitivity to cisplatin	NA

ddGC, dose-dense gemcitabine and cisplatin; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine and cisplatin; MIBC, muscle-invasive bladder cancer; NA, not applicable; NACT, neoadjuvant chemotherapy; NGS, next-generation sequencing; WES, whole-exome sequencing.

Table 7 |

Trials evaluating anti-PD-L1/PD-1 antibodies in patients with previously treated, metastatic urothelial cancer

	Rosenberg <i>et al.</i> ¹¹⁸	Plimack <i>et al.</i> ¹¹⁹	Apolo <i>et al.</i> ¹²⁰	Massard <i>et al.</i> ¹²¹	Sharma <i>et al.</i> ¹²²	Galsky <i>et al.</i> ¹²³
Phase	II	Ib	Ib	I/II	I/II	II
Therapeutic antibody evaluated	Atezolizumab	Pembrolizumab	Avelumab	Durvalumab	Nivolumab	Nivolumab
Antibody target	PD-L1	PD-1	PD-L1	PD-L1	PD-1	PD-1
Number of patients evaluable for response	310	29	44	42	78	265
Proportion of patients treated with 2 prior lines of therapy	42%	51.5%	52.3%	31%	66.6%	29.3%
Breakdown of PD-L1 scores/positivity* (proportion of patients)	<ul style="list-style-type: none"> IC 0/1: 68% IC 2/3: 23% 	PD-L1 *: 100%	PD-L1 *: 31.3%	PD-L1 *: 67%	PD-L1 *: 37.3%	PD-L1 *: 45.9%
ORR (RECIST v1.1)	15%	27.6%	15.9%	31%	24.4%	19.6%
CR rate (RECIST v1.1)	5%	10.3%	2.3%	Not reported	6.4%	2.3%
Median follow-up duration	11.7 months	15 months	3.5 months	6.5 months	9 months	7 months
Median DOR	Not yet reached	Not yet reached	Not yet reached	Not yet reached	Not yet reached	Not yet reached
Rate of grade 3–4 AEs	16%	15.2%	2.3%	4.9%	22%	17.8%

AEs, adverse events; CR, complete response; DOR, duration of response; IC, score based on percentage of PD-L1-positive tumour-infiltrating immune cells; ORR, objective response rate; PD-1, programmed cell-death protein 1; PD-L1, programmed cell death 1 ligand 1.

* Methodology of PD-L1 score ascertainment varied based on the study.

Table 8 |

Ongoing or planned trials of immune-checkpoint blockade for the treatment of MIBC

ClinicalTrials.gov trial identifier (trial name)	Phase	Patient population	Intervention
<i>Adjuvant</i>			
NCT02450331 (IMvigor010) ¹⁵⁰	III	±prior NACT	Atezolizumab (anti-PD-L1 antibody) versus observation
NCT02632409 (CheckMate 274) ¹⁵¹	III	± prior NACT	Nivolumab (anti-PD-1 antibody) versus placebo
<i>Neoadjuvant</i>			
NCT02690558 ¹⁵²	II	Cisplatin-eligible MIBC	GC + pembrolizumab (anti-PD-1 antibody)
Pending	II	Cisplatin-eligible MIBC	GC + atezolizumab
NCT02365766 ¹⁵³	I/II	Cisplatin-eligible/ineligible MIBC	GC + pembrolizumab, or G + pembrolizumab in platinum-ineligible patients
NCT02845323 ¹⁵⁴	II	Cisplatin-ineligible MIBC	Nivolumab ± urelumab (anti-CD137 antibody)
NCT02812420 ¹⁵⁵	II	Cisplatin-ineligible MIBC	Durvalumab (anti-PD-L1 antibody) + tremelimumab (anti-CTLA-4 antibody)

CD137, cluster of differentiation 137 (also known as 4-1BB and tumour necrosis factor receptor superfamily member 9); CTLA-4, cytotoxic T-lymphocyte-associated protein 4; G, gemcitabine; GC, gemcitabine plus cisplatin; MIBC, muscle-invasive bladder cancer; NACT, neoadjuvant chemotherapy; PD-1, programmed cell-death protein 1; PD-L1, programmed cell death 1 ligand 1.