Review Article

# Systemic therapy in bladder cancer

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## ABSTRACT

Systemic chemotherapy is essential for the management of muscle-invasive bladder cancer (MIBC) and metastatic bladder cancer (BCa). Neoadjuvant chemotherapy is key to the management of MIBC with many cisplatin-based regimens. Adjuvant chemotherapy may be considered for selected patients who did not receive neoadjuvant therapy. Systemic chemotherapy with radiotherapy is a critical component of a trimodal bladder-preserving approach and is superior to radiotherapy alone. Cisplatin-based chemotherapy has been the mainstay for metastatic BCa. Immunotherapy in the form of checkpoint inhibitors is a promising new drug for the treatment of BCa. Molecular characterization of each individual BCa is likely to lead to a target-directed therapeutic revolution.

## INTRODUCTION

Bladder cancer (BCa) is the ninth most common cancer in India and worldwide,[1,2] with higher incidence in the USA (sixth most common cancer).[3] Incidence rates are consistently lower in women with diverging incidence trends with stabilizing or declining rates in men but increasing trends in women. The incidence is increasing globally as the use of tobacco products becomes more prevalent in developing nations.[4] The large majority of BCas are superficial although 30% invade past the bladder submucosa/mucosa and are defined as muscle-invasive bladder cancer (MIBC).[5] Muscle invasion is associated with a high risk of death from distant metastases. Despite radical cystectomy, half of patients with MIBC will develop metastatic disease within 2 years of diagnosis and usually succumb to their disease.[6] Despite strong evidence on the benefit of neoadjuvant chemotherapy (NACT) in MIBC, only 15%–20% of patients receive it.[7] Chemotherapy is also the foundation of treatment for unresectable and metastatic disease. This article reviews systemic chemotherapy in MIBC, bladder preservation, advanced and metastatic BCa. This article will also discuss exciting developments and future direction of systemic therapy for BCa.

## METHODS

A comprehensive search for articles was done on PubMed using key terms such as bladder cancer, metastatic BCa, systemic therapy, chemotherapy BCa, and NACT for MIBC.

### Neoadjuvant chemotherapy for muscle-invasive bladder cancer

NACT is recommended by most guidelines for MIBC but only 15%–20% of patients receive it.[7] This recommendation is based on two randomized controlled studies (RCTs) and two meta-analyses, showing improvement in pathologic response rate (PRR) and overall survival (OS).[8] Since pathologic stage at cystectomy correlates with OS, PRR has emerged as an end-point for neoadjuvant clinical trials.[8,9] The Southwest Oncology Group (SWOG) Trial randomized 317 patients with MIBC to neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) for three cycles each of 28 days plus cystectomy versus cystectomy alone.[8] The median survival in the NACT arm was 77 versus 46 months ($P$ = 0.06). In both groups, improved survival

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was associated with the absence of residual cancer in the cystectomy specimen with significantly more patients in the combination therapy group without residual disease (38% vs. 15%, $P < 0.001$). The BA06/European Organization for Research and Treatment of Cancer (EORTC) trial randomized 976 patients with MIBC to three cycles of neoadjuvant cisplatin, methotrexate, and vinblastine or no chemotherapy before cystectomy or full-dose external beam radiotherapy.[10] The NACT group had a 5.5% benefit in 3-year survival (55·5% vs. 50% $P = 0.075$), with a 6.5-month improvement in OS. Long-term follow-up showed an increase in 10-year survival of 6%, with a 16% reduction in risk of death at 10 years in the NACT arm (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.72–0.99; $P = 0.037$).[11] A 2005 updated meta-analysis that included 11 trials with 3005 patients demonstrated a 5% improvement in 5-year survival ($P = 0.003$) associated with platinum-based NACT.[12]

Currently, gemcitabine-cisplatin (GC) is the most widely used NACT regimen. Initially, the basis for this combination was a randomized study by von der Maase *et al*. in locally advanced or metastatic BCa, demonstrating similar efficacy but improved tolerability as compared to the MVAC regimen.[13,14] One prospective Phase 2 Brazilian study of 22 patients with MIBC getting GC NACT had 26% pathological complete response (pCR) rate.[15] Subsequently, Memorial Sloan-Kettering Cancer Center published their retrospective data with GC and MVAC showing similar proportion of tumors downstaged, disease-free survival (DFS), and minimal or no residual disease.[16] More retrospective international multicenter studies have also confirmed similar activity of the GC regimen as compared to MVAC as NACT in MIBC, achieving comparable pCR.[17,18]

To reduce time to cystectomy and improve pCR, dose-dense regimens have also been tried. In a Phase 2 trial, Choueiri *et al*. enrolled 39 patients for four cycles of dose-dense MVAC given every 2 weeks with growth factor support. The PRR (<pT1) was 49% with 10% patients experiencing grade 3–4 toxicities.[19] In another Phase 2 trial, Plimack *et al*. used three cycles of accelerated MVAC (dosed every 2 weeks) with a 53% <pT2 rate and median time to cystectomy 9.7 weeks.[20] In these studies 43% and 7% respectively of enrolled patients had N1disease. In the Choueiri study, 82% of the N1 patients had pN0 disease at the time of surgery, emphasizing importance of NACT in lymph node-positive patients. Another Phase 2 study added bevacizumab to dose-dense MVAC for NACT in MIBC, lymph node-negative patients with PRR rate to <pT1 in 45% without much added impact.[21] A trial evaluating three cycles of dose-dense GC in MIBC was closed early due to serious vascular adverse events even after modification of protocol requiring cardiac clearance. The regimen was active with a <pT2 rate of 45%.[22] In a second recent Phase 2 trial looking at six cycles of dose-dense GC with a decreased cisplatin dose, the regimen was well tolerated with 63% achieving PRR ≤ pT1 with a lack of deleterious DDR gene alterations seen in nonresponders.[23,24] A recently published two-step meta-analysis looked at 15 RCTs of NACT in MIBC, with second step analyzing 13 retrospective trials to compare MVAC with GC.[25] There was a significant OS benefit associated with cisplatin-based NACT (HR, 0.87; 95% CI, 0.79–0.96) without significant difference in pCR between MVAC and GC. GC was associated with a significantly reduced OS (HR, 1.26; 95% CI, 1.01–1.57), which persisted after excluding carboplatin data (HR, 1.31; 95% CI, 0.99–1.74); however, it lost significance. This study suggested NACT as a standard of care and MVAC as the regimen of choice. The SWOG is currently enrolling a multicenter trial of neoadjuvant GC versus dose-dense MVAC before cystectomy (NCT02177695) to evaluate the predictive capacity of a biomarker called the CO-eXpression ExtrapolatioN model, which uses preclinically derived gene expression signatures to predict response to different chemotherapy regimens.[26] Currently, patients with MIBC unable to receive cisplatin should participate in clinical trials or proceed to cystectomy without NACT as there are no established chemotherapy options with proven benefit [Table 1].

## Adjuvant chemotherapy

No randomized trials provide unequivocal support for the use of adjuvant chemotherapy (AC) as they are limited by poor accrual and conflicting results.[27-29] A 2005 meta-analysis analyzing 491 patients from six trials showed a HR for survival of 0.75 for AC (95% CI, 0.60–0.96), but was underpowered.[30] An updated meta-analysis in 2014 reviewed 945 patients included in nine RCTs found a similar benefit of AC (HR, 0.77; 95% CI, 0.59–0.99).[31] The Spanish Oncology Genitourinary Group enrolled 142 high-risk patients with MIBC postcystectomy and randomized them to four cycles of paclitaxel, gemcitabine, and cisplatin (PGC) or observation. The AC group had a significantly improved 5-year survival (60% vs. 31%, $P < 0.0009$).[32] The largest adjuvant Phase 3 trial EORTC 30994 recruited 284 of a planned 660 patients once again limited in power due to under accrual. Patients with high-risk MIBC (pT3–pT4 or node positive) were randomized to four cycles of AC (GC or MVAC or high-dose MVAC [HD-MVAC]) or deferred chemotherapy at relapse.[33] Early treatment significantly prolonged progression-free survival (PFS) (HR, 0.54; 95% CI, 0.4–0.73; $P < 0·0001$), with 5-year PFS of 47.6% versus 31.8% without significant improvement in 5-year OS (HR 0.78, 95% 0.56–1.08). A *post hoc* exploratory analysis revealed OS significantly improved in those without lymph node involvement at baseline (79.5% vs. 59%).

This does raise questions on what should be the extent of nodal dissection and that four cycles may be sufficient for

**Table 1: Neoadjuvant chemotherapy trials in metastatic breast cancer**

| Chemotherapy | Study | Type | *n* | Regimen | Control | OS (months)/pCR rates (percent) | *P* | Follow up |
|---|---|---|---|---|---|---|---|---|
| MVAC | Grossman *et al*. | RCT | 317 | MVAC | C | 77 Vs. 46 | 0.06 | 8.5 years |
| CMV | BA06/EORTC | RCT | 976 | CMV | C/RT | 44 Vs. 37.5 | 0.07 | 4 years |
| | BA06/EORTC long-term | RCT | 976 | CMV | C/RT | 10-year survival 36% Vs. 30% | 0.03 | 8 years |
| Platinum based | ABC meta-analysis (2005) | MET | 3005 | Platinum | C/RT | 5 years OS 45% Vs. 50% | 0.003 | NA |
| GC | Herchenhorn (2007) | Phase 2 | 22 | GC | None | pCR 26.7% | NA | NA |
| | Dash MSKCC (2008) | Ret | 42 | GC | None | pCR 26% | NA | NA |
| | Zagar (2015) | Ret | 935 | MVAC | GC | pCR GC 24.5% Vs. 23.9% | 0.2 | NA |
| DD MVAC | Choueiri (2014) | Phase 2 | 39 | DD-MVAC | None | pCR=26% | NA | 2 years |
| | Plimac (2014) | Phase 2 | 44 | DD-MVAC | None | pCR=38% | NA | NA |
| DD MVAC + bevacizumab | Siefker-Radtke (2014) | Phase 2 | 60 | DD-MVAC + bevacizumab | None | pCR=38% | NA | 21 months |
| DD GC | Plimac (2014) | Phase 2 | 32 | DD-GC | None | pCR=32% | NA | NA |
| | Balar (2016) | Phase 2 | 49 | DD-GC | None | pCR=18% | NA | NA |
| Meta-analysis | Yin (2016) | MET | 15 RCT | MVAC | G (C/Ca) | Cisplatin OS (HR 0.87) G (C/Ca) Vs. MVAC (HR 1.26) GC Vs. MVAC (HR 1.31) NS | Significant Significant NS | NA |

G=Gemcitabine, C=Cisplatin, Ca=Carboplatin, GC=Gemcitabine cisplatin, MVAC=Methotrexate, vinblastine, doxorubicin, cisplatin, CMV=Cisplatin methotrexate vinblastine, RCT=Randomized controlled trial, Met=Meta-analysis, Ret=Retrospective, pCR=Pathologic complete remission, NS=Not significant, DD=Dose-dense, NA=Not applicable or not available, C=Cystectomy, RT=Radiation, *n*=Number of patients, OS=Overall survival, HR=Hazard ratio, Vs.=Versus

node-negative patients but not for node-positive patients. An observational study from the National Cancer Data Base included 5653 patients with 1293 patients receiving AC and 4360 patients being observed.[34] They compared those that received AC with a propensity-score-matched control group that received cystectomy alone. AC was associated with improved survival (HR, 0.70; 95% CI, 0.64–0.76) as compared to observation. This was similar to an earlier large dataset that included 3947 patients and showed AC independently associated with improved OS, particularly those at highest risk for progression.[35]

Carboplatin, an alternative platinum agent, less nephrotoxic than cisplatin, does not seem to impact disease-specific survival although limited data exists.[36] In a Phase 3 trial, the use of adjuvant gemcitabine in cisplatin-ineligible patients resulted in insignificant higher rates of PFS and OS at 3 years. Currently, systemic platinum-based chemotherapy should be offered to patients with high-risk disease at cystectomy, including pT3–T4 or lymph node positive disease, after a discussion of risks and benefits with an acknowledgment of the limitations in data [Table 2].

## Chemotherapy in bladder preservation protocols for muscle-invasive bladder cancer

In appropriately selected patients, bladder preservation with trimodal therapy is a potential alternative to cystectomy for the treatment of MIBC. This approach combines radiotherapy, chemotherapy, and a complete transurethral resection of the bladder tumor. Earlier studies using cisplatin alone or in combination with fluorouracil (5-FU) and radiation have an average response rate (RR) around 75% with 5-year survival of 50%–60%, similar to cystectomy.[37-42] Cisplatin and paclitaxel have also been given with radiation, however, with additional adjuvant cisplatin and gemcitabine with 5-year OS of 50%.[43] Twice weekly gemcitabine in combination with radiotherapy has been used in a Phase 1 study with a reported 5-year bladder-intact survival of 62%, OS 76%.[44,45] A Phase 2 study NCT01495676 is recruiting for concurrent GC with radiation. The BC2001 is a Phase 3 RCT that compared radiotherapy alone to concurrent chemoradiotherapy with 5-FU and mitomycin C.[46] Around 30% of patients underwent NACT before enrollment. The chemotherapy group had a statistically significant improvement in 2-year locoregional DFS 67% versus 54% (HR, 0.68; 95% CI 0.48–0.96), with a trend toward improvement in OS at 5 years were 48% versus 35% (HR, 0.82; 95% CI, 0.63–1.09). Results are awaited from the closed Radiation Therapy Oncology Group trial NCT00777491 comparing cisplatin and 5-FU to gemcitabine in combination with radiation. Other alternatives to cisplatin that have been reported on include capecitabine, paclitaxel, and docetaxel[47-50] [Table 3].

## Chemotherapy for metastatic bladder cancer

### *First-line therapy*

MVAC is a standard first-line option based on RCTs demonstrating improved survival outcomes. In comparison to cisplatin alone, treatment with MVAC had significant improvement in overall response rate (ORR) 39% versus 12%, improved PFS 10 versus 4.3 months, and median OS 12.5 versus 8.2 months.[51] MVAC was also proven superior to cisplatin, cyclophosphamide, and adriamycin.[52] Toxicity with MVAC is of concern especially since many patients with BCa are elderly. Patients were randomly assigned to GC or MVAC with similar ORR, time to progression, OS (14 vs. 15 months), and similar 5-year survival 13%

**Table 2: Adjuvant chemotherapy**

| |
|---|
| PGC |
| GC |
| MVAC |
| DD MVAC |
| Gemcitabine |

PGC=Paclitaxel, gemcitabine, cisplatin, GC=Gemcitabine, cisplatin, MVAC=Methotrexate, vinblastine, doxorubicin, and cisplatin, DD=Dose-dense

**Table 3: Bladder preservation (chemotherapy with radiation)**

| |
|---|
| Cisplatin, 5-fluorouracil |
| Cisplatin, paclitaxel |
| 5-fluorouracil, mitomycin |
| Gemcitabine |

versus 15%.[13,14] This study was powered to show superiority and not equivalence. Gemcitabine was administered on days 1, 8, and 15 with 37% needing dose adjustment, most common being omission of day 15 dose. Hence, dosing of GC every 3 weeks with omission of the day 15 gemcitabine has become widely used after several studies have shown preserved efficacy with a decrease in rates of significant thrombocytopenia.[53,54] HD-MVAC with growth factor support has been compared to standard MVAC, with better ORR, PFS but similar OS.[55] HD-MVAC was associated with less frequent neutropenic fever (10% vs. 26%, $P < 0.001$), with a similar median survival (15.1 vs. 14.9 months).[56]

HD-MVAC or dose-dense MVAC has not been compared directly with GC in the metastatic setting. The EORTC Phase 3 trial of first-line GC with and without paclitaxel (PGC) enrolled 626 patients with advanced urothelial carcinoma (81% with primary BCa). PGC had a better ORR, trend toward better PFS and longer significant OS 16 versus 13 months (HR, 0.85; 95% CI, 0.72–1.02). There was an increased incidence of grade 3/4 adverse effects including neutropenia.[57] Bevacizumab in combination with GC first line in a Phase 2 trial with 43 patients had a median OS of 19 months.[58] This regimen is being evaluated in a Phase 3 randomized trial NCT00942331 that has finished accrual, but results are not yet available.

### *Cisplatin-ineligible patients*

Cisplatin-based combination therapy is consistently associated with better RR and improved survival outcomes as compared to carboplatin-based combinations.[59-61] Galsky *et al.* have proposed criteria for determination eligibility for cisplatin.[62] In candidates not eligible for cisplatin, the combination of carboplatin and gemcitabine is suggested. In the EORTC Trial, 238, chemotherapy-naive patients with impaired renal function were randomly assigned to gemcitabine plus carboplatin or combination of methotrexate, carboplatin, and vinblastine with similar median OS 9 versus 8.1 months but with less grade 3/4 toxicity.[63]

### *Non platinum-based regimens*

Regimens that combine gemcitabine with a taxane rather than a platinum have been evaluated. Paclitaxel and gemcitabine result in RR of 50%–70% and median survival of 13–16 months.[64-66] With this regimen, hematologic side effects are most common although severe pulmonary toxicity was reported in one series.[67] Two Phase 2 trials have reported outcomes with docetaxel, gemcitabine with RRs 33% and 52% and median OS 13 and 15 months.[68,69]

### *Second-line agents*

A number of chemotherapy drugs have single agent activity and none have been United States Food and Drug Administration (US-FDA) approved in the second line. Vinflunine is approved in Europe on a 2.6-month survival advantage over best supportive care.[70] Taxanes are the most commonly used single agents. Paclitaxel and docetaxel are associated with a modest ORR of 10%–30% and OS of 6–9 months.[71,72] A pooled analysis of trials on taxane-based salvage chemotherapy suggested a survival benefit with combination regimens, albeit with more toxicity.[73] In platinum refractory patients, nanoparticle albumin-bound (nab) paclitaxel achieved a remarkable ORR of 27.7% with 1 of 48 patients achieving a CR and was well tolerated.[74] Cabazitaxel in Phase 2 studies has shown 5% ORR but with increased toxicity and is currently being trialed as the second-line agent.[75] The initial Phase 2 study with pemetrexed reported a promising OS of 9.6 months;[76] however, more recent studies of pemetrexed reported a low ORR of 5%–8% with median PFS of 2.4 months.[77,78] Gemcitabine has been tested in three Phase 2 trials, with RR of up to 29%, median survival 9–13 months, and better median survival if administered in weekly for 3 weeks every 28 days.[79-81]

## Immunotherapy

Immunotherapy has emerged as the most encouraging class of agents in development for the treatment of metastatic BCa as second line agents. Tumor cells express receptors such as programmed death ligand-1 (PD-L1) and cytotoxic T-cell lymphocyte antigen (CTLA-4), which inhibit T-cell-mediated tumor cell killing through interaction with T cell receptors. Anti-PD-1 and anti-PD-L1 agents called immune checkpoint inhibitors have demonstrated exciting activity in many human cancers.

Atezolizumab is a PD-L1 inhibitor that was US-FDA approved in May 2016 for advanced urothelial cancer that has progressed during or after previous platinum-based chemotherapy either for metastatic or progressive disease < 12 months after adjuvant or neoadjuvant chemotherapy (NACT). The initial expanded Phase 1 study provided evidence of safety and efficacy.[82] An updated analysis revealed 55% of all patients showing a reduction in tumor burden by 50% in PD-L1-positive and 17% in PD-L1-negative patients, with a number of ongoing, durable responses.[83] These results were

expanded in a Phase 2 study involving a different cohort. Cohort 2 included patients with progressive platinum refractory disease, in which RR was 15%, and at 12-month follow-up, 84% responses were ongoing.[84] Fatigue was the most common adverse effect and immune-mediated adverse effects were seen in 5%. In the first cohort, atezolizumab was used first line in 119 patients in cisplatin-ineligible advanced or metastatic urothelial cancer. ORR was 24% with 7% CR with similar safety profile. There was no correlation with immunohistochemical (IHC) expression PDL1.[85] The Phase 3 trial of this agent in the metastatic, adjuvant, and neoadjuvant BCa is ongoing NCT02302807, NCT02450331, NCT02451423.

Pembrolizumab PD-1 antibody in the KEYNOTE-012 study showed encouraging results with 64% patients with decreased tumor burden, 28% ORR in PD-L1 positive metastatic BCa and a median OS of 12.7 months.[86] A Phase 3 second-line RCT NCT02256436 of pembrolizumab against standard cytotoxic chemotherapy in the second-line setting has recently completed accrual. It is also being tested in first-line metastatic setting for cisplatin-ineligible patients and in the neoadjuvant setting (NCT02335424, NCT02365766).

Nivolumab another anti-PD1 antibody is also being investigated in several cancers including BCa NCT02387996. The CTLA-4 inhibitor ipilimumab showed ORR 64% in metastatic BCa in combination with gemcitabine and cisplatin but with increased toxicity.[87] ALT-801, a biologic compound of interleukin-2 fused to a humanized soluble T-cell receptor directed against the p53-derived peptides expressed on tumor cells, has shown promising results.[88]

### Other novel agents

The Cancer Genome Atlas (GCA) comprehensive molecular characterization of 131 MIBC tumors found significant mutations in 32 genes with 69% of tumors identified as harboring potentially actionable targets including 42% with targets in the phosphatidylinositol-3-OH kinase/AKT/mammalian target of rapamycin (mTOR) pathway and 45% with targets (including ERBB2) in the RTK/MAPK pathway.[89] Even though 9% tumors have epidermal growth factor receptor (EGFR) amplifications, gefitinib, erlotinib, and cetuximab, have not demonstrated significant activity in unselected patients, erlotinib has a 55% downstaging effect as NACT.[90-93] Seven percent of CGA tumors had ERBB2 copy number alterations. Patients with advanced BCa human epidermal growth factor receptor 2 (HER2) overexpression as determined by HER2 IHC, gene amplification through fluorescence *in situ* hybridization, or elevated serum HER-2 neu were treated with a combination of trastuzumab, gemcitabine, carboplatin, and paclitaxel with 70% ORR with a median OS of 14.1 months.[94] This was an active regimen, but toxicity was high with two treatment-related deaths. Lapatinib, a dual HER2 and EGFR, has not shown much response in the metastatic either in second line or maintenance post first line.[95,96]

New agents targeting the fibroblast growth factor receptor pathway, altered in 70% of noninvasive BCa and 15% of MIBC tumors, are being studied.[97] The vascular endothelial growth factor (VEGF) pathway has also been evaluated. Sunitinib showed stable disease or regression in 43% in advanced, previously treated BCa with PFS of 2 months and OS of 6–7 months.[98] When used first line in cisplatin-ineligible metastatic BCa, it showed poor response with 50% stable disease, PFS of 4.8 months, and OS of 8.1 months.[99] Sorafenib in the advanced setting had similarly poor results.[100,101] Pazopanib in the relapse refractory disease had an ORR of 17% with 5% patients developing fistulas.[102] Ramucirumab, a monoclonal antibody directed against VEGF receptor 2, in a randomized Phase 2 trial with or without docetaxel, showed that the combination improved PFS (5.4 vs. 2.8 months, $P < 0.001$) with nonsignificant improvements in ORR (24% vs. 9%, $P = 0.088$) and median OS (10.4 vs. 9.2 months, $P = 0.20$).[103] The mTOR pathway is altered in 42% of tumors in the GCA, but the mTOR inhibitor everolimus evaluated in several trials is not very active.[104,105] There are reports of exceptional responses to everolimus (complete response lasting for 14 months) and whole genome sequencing identified specific mutations that lead to enhanced mTOR signaling and potential sensitivity to everolimus.[106]

Since there is a high frequency of retinoblastoma and cyclin-dependent kinase (CDK) pathway alterations in BCa, a Phase 2 trial of the CDK4/6 inhibitor palbociclib in second line is underway in molecularly selected patients with metastatic BCa (NCT02334527). A Phase 2 trial of eribulin a microtubulin modulator derived from the Black Pacific Sea sponge toxin was presented at the 2015 ASCO Annual Meeting. It was active with an ORR of 35% and median OS of 9.5 months in metastatic BCa.[107] Additional studies of eribulin are ongoing with gemcitabine in first line for locally advanced unresectable disease (NCT02178241) and alone in similar patients with renal dysfunction (NCT00365157) [Table 4].

## CONCLUSION

There is ongoing research and progress in advanced BCa management with immunotherapy at the forefront with recent US-FDA approval of one checkpoint inhibitor and many more such agents in the pipeline. There is increasing awareness of the survival benefit of NACT in MIBC. Select patients who do not receive NACT should get AC. In patients who opt for bladder preservation, the addition of chemotherapy is key to improved outcomes. With molecular characterization of an individual patient's BCa, practicing personalized medicine with highly targeted agent may become the norm.

**Table 4: Metastatic bladder cancer**

| |
|---|
| FIRST LINE |
| MVAC |
| GC |
| DD MVAC |
| PGC |
| Bevacizumab, gemcitabine, cisplatin |
| *Cisplatin ineligible* |
| Carboplatin, gemcitabine |
| *Nonplatinum* |
| Gemcitabine, paclitaxel |
| Docetaxel, gemcitabine |
| SECOND LINE |
| Atezolizumab: US-FDA approved in metastatic setup in second line |
| Vinflunine: Approved in Europe |
| Taxanes: Paclitaxel, docetaxel, cabazitaxel |
| Pemetrexed |
| Eribulin |
| Immunotherapy: pembroluzimab, nivolumab, ipilimumab |
| HER2: Trastuzumab, lapatanib |
| mTOR inhibitors: Everolimus |
| EGFR inhibitors: Erlotinib, gefitinib, cetuximab |
| VEGF: Bevacizumab, ramacirumab, sunitib, sorafenib, pazopanib |
| CDK4/6 inhibitor: Palbociclib |

PGC=Paclitaxel, gemcitabine, cisplatin, GC=Gemcitabine, cisplatin, MVAC=Methotrexate, vinblastine, doxorubicin, and cisplatin, VEGF=Vascular endothelial growth factor, mTOR=Mammalian target of rapamycin, HER2=Human epidermal growth factor receptor 2, US-FDA=United States Food and Drug Administration, EGFR=Epidermal growth factor receptor, DD=Dose-dense

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