Emerging perioperative therapeutic approaches in muscle invasive bladder cancer

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Abstract: Bladder cancer is a significant healthcare burden with more than 17,000 deaths in the United States in 2018. Patients who are diagnosed with muscle invasive bladder cancer (MIBC) have a high rate of micro-metastatic disease and have a much poorer prognosis compared with patients who have less advanced lesions. Historically, neoadjuvant administration of cisplatin-based therapy followed by surgery has been the mainstay of treatment. Unfortunately, of patients who come in with initially diagnosed MIBC, more than 50% are ineligible for traditional cisplatin-based therapy. Today, new modalities of treatment such as immune checkpoint inhibitors are beginning to radically improve outcomes in this population. The addition of immune checkpoint therapy to traditional chemotherapy appears to augment pathologic complete response rates in the bladder during surgery. Immunotherapy combinations also provide novel trimodality approaches with excellent outcomes in those pursuing non-surgical management. Pure immunotherapy approaches appear promising in the neoadjuvant and adjuvant setting, and the immune checkpoint inhibitor nivolumab is now approved in the adjuvant setting for high-risk patients. Antibody drug conjugates, such as enfortumab vedotin, and targeted therapies, such as infgratinib, are in trials in the perioperative setting. This review article summarizes the current evidence and likely future developments for the management of muscle invasive bladder cancer in 2022 and beyond.

Keywords: adjuvant therapy, bladder cancer, immunotherapy, neoadjuvant, urothelial carcinoma

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Introduction

Bladder cancer is the ninth most diagnosed malignancy in the United States. In 2018, there were an estimated 83,730 new cases and 17,200 deaths in the United States due to bladder cancer. Risk factors include older age, male sex, Caucasian race, personal/family history of bladder cancer, smoking, exposure to aromatic amines, aristolochic acid found in some dietary supplements, cyclophosphamide, or radiation. While a vast majority of bladder cancers are localized to the bladder and have not invaded through the bladder muscle, 25–30% of patients have muscle invasive bladder cancer (MIBC). MIBC is a very high-risk condition and without an intervention, almost 95% of patients would succumb to their disease within 5 years. Almost all bladder tumors evolve from urothelial epithelium, with a minority of cases comprising variants including adenocarcinoma, squamous cell carcinoma, plasmacytoid, or small cell differentiation. Historically, outcomes have been very poor in metastatic disease. Even with conventional cisplatin-based chemotherapy regimens, the 5-year survival rate had remained less than 10%. This compares with 5-year survival in the range of 96% in patients with non-muscle invasive disease, drops to 69% for localized disease, and reaches 37% with nodal involvement. Given these outcomes, novel therapies are needed for muscle invasive and metastatic urothelial tumors, and are the focus of ongoing research.
**Current standard of care in MIBC**

About 50% of patients with MIBC develop distant metastasis despite radical cystectomy and lymph node dissection, suggesting micro-metastatic disease exists even at the time of definitive management. As a result, systemic therapy plays a vital role in the treatment of MIBC. With recent advances in targeted therapy and immunotherapy, there is a potential of more effective and less toxic options in this space. Currently, neoadjuvant chemotherapeutic regimens are used to shrink the tumors before surgery and to hopefully eliminate micro-metastatic disease. This mode of treatment before the surgery makes the surgery less invasive, more effective and reduces recurrence.

Trimodality therapy is another effective bladder-sparing mechanism of tackling muscle invasive disease. Patients with MIBC typically receive a maximal transurethral resection of bladder tumor (TURBT) followed by a combination of a long course of radiation and chemotherapy, typically cisplatin based in combination with 5-fluorouracil, or paclitaxel in patients who have good renal function. Patients with poor renal function can receive a combination of 5-fluorouracil with mitomycin C or gemcitabine alone in particularly frail patients.

**Platinum-based neoadjuvant and adjuvant therapy**

Cisplatin-based neoadjuvant chemotherapy was first introduced in 1980s in MIBC. For example, Scher et al. treated 50 patients with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). The trial demonstrated a 33% complete pathological response (ypT0) rate with an additional 17% downstaged to less than muscle invasive disease (<ypT2). This was later confirmed in the large SWOG-8710 trial, which was conducted to see the difference in survival in patients getting cystectomy done versus neoadjuvant MVAC plus cystectomy in locally advanced bladder cancer. Overall, 375 patients were randomly assigned to receive three cycles of MVAC followed by radical cystectomy (RC) versus RC alone. Results showed a strong trend toward improved survival [hazard ratio (HR) 0.60, \( p = 0.02 \)] in patients who received MVAC. Because of the high incidence of adverse effects such as myelosuppression in patients taking MVAC, dose-dense MVAC (ddMVAC) was introduced which delivered the drug in two weekly cycles with growth factor support to abrogate this side effect. ddMVAC was well tolerated, with a ypT0 rate of 38% in one trial which included node-positive patients.

Numerous other trials were conducted in this space over the decades, some of which we have summarized below. Apart from MVAC, other regimens have also showed activity. The BA06 30894 trial is the largest study of neoadjuvant therapy to be completed to date. It included 976 patients and randomized them to either cisplatin, methotrexate, and vinblastine (CMV) or upfront surgery. Median follow-up was done for more than 8 years, improving 10-year survival from 30% to 36% \( (p = 0.037) \). In practice, the combination of gemcitabine and cisplatin (GC) has been used commonly as the regimen of choice for neoadjuvant therapy based on a comparative trial in the metastatic setting. Overall, 405 patients were recruited in this study and equally randomized between the two groups. Results were significant for a grade 5 adverse event rates of 1% versus 3% in GC and MVAC, respectively. Patients who received MVAC therapy also had an increased risk of neutropenic sepsis (12% versus 1%), alopecia (55% versus 11%), and mucositis (22% versus 1%) when compared with those who received GC therapy. Despite the added toxicity from MVAC, survival and progression-free survival (PFS) were similar, thus establishing GC as a comparable treatment. Evidence continues to mount for the benefit of neoadjuvant chemotherapy. A meta-analysis conducted in 3000 patients has shown a 5-year overall survival (OS) benefit of 5% and 14% reduction in risk of death with the addition of neoadjuvant chemotherapy. Hence, based on all available evidence, neoadjuvant cisplatin-based chemotherapy has become the standard of care and is recommended by the National Comprehensive Cancer Center Network (NCCN) as a Category 1 recommendation for patients.

Two recently presented trials have compared GC and ddMVAC in the neoadjuvant setting. The SWOG 1314 trial, also called the co-expression extrapolation (COXEN) study, was a neoadjuvant study designed to validate a COXEN score based on a combination of the patient’s gene expression profiling and in vitro data to predict if a specific patient would respond to neoadjuvant chemotherapy – either GC or ddMVAC with a signature specific to each regimen. The primary outcome of this study was a prespecified dichotomous COXEN score as predictor of pathologic
complete response (PCR) or pathologic downstaging at surgery. In this trial, 167 patients were randomized between GC and MVAC, representing a unique dataset. The results demonstrated that the COXEN score overall did not predict patients’ response to neoadjuvant therapy regimens. The odds ratio (OR) for ypT0 with the GC GEM score in GC-treated patients was 2.63 ($p=0.10$; 95% confidence interval (CI) 0.82–8.36) and for the ddMVAC COXEN score, the OR was 1.12 ($p=0.82$, 95% CI 0.42–2.95).

While a formal comparison of efficacy of GC and ddMVAC was not among the stated objectives, as the study was inadequately powered, it did provide an opportunity for a descriptive comparison of efficacy. Reported ypT0 rates between GC and ddMVAC were 32% versus 35%, respectively, and pathologic downstaging <ypT1 occurred in 15% versus 24%, respectively, resulting in CR + pathologic response (PR) rates of 50% for GC and 56% for ddMVAC. Intent to treat analysis failed to show a significant difference in OS or PFS for ddMVAC versus GC (for OS, HR 0.87, 95% CI 0.54–1.40, $p=0.57$; for PFS, HR 0.76, 95% CI 0.58–1.01, $p=0.055$). The authors of the study believed based on these findings that the estimates of PFS and OS appeared comparable.

In contrast to S1314, the GETUG/AFU V05 VESPER phase III randomized control study was designed and powered to compare the efficacy of ddMVAC or GC in the MIBC perioperative (predominantly neoadjuvant) setting. A total of 500 patients were randomized either to receive six cycles ddMVAC every 2 weeks or four cycles of GC every 4 weeks. This is one of the few trials to not only compare ddMVAC with GC but to also include patients with borderline renal function, thus including a group of patients traditionally called cisplatin ineligible, as we discuss later in this review. In the recently reported analysis after 40 months of follow-up, the trial narrowly failed to meet its endpoint of 3-year disease-free survival (DFS), (HR 0.77, 95% CI 0.57–1.02, $p=0.07$); however, it was statistically significant when not considering patients who did not eventually go on to receive therapy despite randomization, with 3-year PFS (66% versus 56%; HR 0.70, 95% CI 0.51–0.96, $p=0.025$) and OS (HR 0.66, 95% CI 0.47–0.92). In addition, ypT0 rates were higher with ddMVAC versus GC (42% versus 36%). In our opinion, the results of VESPER V05 are likely to shift clinical practice toward a higher utilization of ddMVAC as the regimen of choice in the perioperative setting. While we agree S1314 was not powered for the purpose of comparing regimens, the estimate of PFS, OS, and pathologic downstaging in totality does appear in favor of ddMVAC.

In contrast to neoadjuvant chemotherapy strategies, studies of adjuvant chemotherapy have been small and have had challenges with respect to accrual. The randomized EORTC 30,994 study of adjuvant chemotherapy showed an improved 5-year PFS benefit (48% versus 32%; HR 0.54, 95% CI 0.40–0.73), but failed to demonstrate an OS benefit (HR 0.78, 95% CI 0.56–1.08). Furthermore, in a large meta-analysis involving 940 patients across nine such studies of adjuvant platinum-based therapy, there appeared to be an OS (HR 0.77, 95% CI 0.59–0.99) and DFS (HR 0.66, 95% CI 0.45–0.91) benefit.

As such, adjuvant chemotherapy could be offered to patients who did not receive neoadjuvant therapy or are discovered at cystectomy to have high-risk disease (Table 1).

### Cisplatin ineligible patients

As indicated, cisplatin is the most effective chemotherapeutic currently known in bladder cancer. Unfortunately, cisplatin has multisystem toxicities, resulting in neuropathy, cardiac dysfunction, and hearing loss among other adverse events. Selecting appropriate patients is thus of utmost importance. A panel that consisted of 65 different oncologists from five different countries who are involved in the design and conduct of bladder cancer-specific clinical trials presented a working definition of cisplatin eligibility criteria that may be useful for categorizing patients with urothelial carcinoma. From the responses collected and analyzing the data from different studies, the panel recommended criteria that patients who possessed either of ECOG performance status of 2, creatinine clearance of less than 60 ml/min, Common Terminology Criteria for Adverse Events of at least grade 2 hearing loss; Common Terminology Criteria for Adverse Events of at least grade 2 neuropathy, and patients with NYHA Class III or greater cardiac failure were unlikely to be appropriate candidates for cisplatin. These are now the Galsky criteria for cisplatin ineligibility. Unfortunately, 50% of patients who present to clinic with MIBC are cisplatin-ineligible by this definition. For these patients, neoadjuvant therapy is unlikely to
Therapeutic advances in urology provide benefit, and standard of care is upfront cystectomy. However, the advent of immunotherapy has ushered in a new era of hope for these patients.

Immunotherapy and combination with chemotherapy in bladder cancer

While cisplatin-based chemotherapy remained the therapeutic backbone in the neoadjuvant setting and the metastatic disease, checkpoint blockers were explored initially in advanced and refractory patients and found to be efficacious, multiple immunotherapy agents being approved in quick succession. Approved immune checkpoint blockers since 2016 for metastatic bladder cancer include atezolizumab, pembrolizumab, avelumab, durvalumab, and nivolumab. Of these, atezolizumab was recently voluntarily withdrawn for post-platinum patients. Overall, most PD-1/PD-L1 blockers are associated with an overall response rate around 20–30%.

After these trials, other studies were initiated looking at the combination of immunotherapy and chemotherapy in the metastatic setting. The IMvigor 130 trial compared atezolizumab, atezolizumab with standard of care chemotherapy, and standard chemotherapy in three arms, and reported recently, showing an improvement in PFS when comparing chemoimmunotherapy and traditional chemotherapy (8.2 versus 6.3 months). There did not appear to be a survival difference at interim OS analysis (16 versus 13.4 months). Another similar trial was KEYNOTE-361 which tested the addition of pembrolizumab with chemotherapy, in contrast to IMvigor130, both PFS (8.3 versus 7.1 months) and OS (17 versus 14.3 months) also did not meet statistical significance. Other trials such as NILE will explore the combination of CTLA-4 blockers (tremelimumab) and PD-1 blockers (durvalumab) in combination with chemotherapy and are currently awaiting readout.

Neoadjuvant immunotherapy and chemoimmunotherapy trials

The addition of neoadjuvant immunotherapy to a chemotherapy backbone has a strong scientific

| Study            | Year | Phase | No. of patients | Intervention                          | Pathologic complete response (PCR) rate | OS                      |
|------------------|------|-------|-----------------|---------------------------------------|----------------------------------------|-------------------------|
| Malmstrom et al. | 1996 | III   | 325             | CA + RT + surgery versus RT + surgery |                                        | 5-year OS: 59% versus 51% (p = 0.1) |
| Sherif et al.    | 2002 | III   | 317             | CMV + surgery versus surgery          | 26.4% versus 11.5% (p = 0.001)          | 5-year OS: 53% versus 46% (p = 0.24) |
| BA06 30894       | 1999 | III   | 976             | CMV + surgery versus surgery          | 32.5% versus 12.3%                     | 10-year OS: 36% versus 30% (p = 0.037) |
| Grossman et al.  | 2003 | III   | 317             | MVAC + surgery versus surgery         | 38% versus 15% (p < 0.001)             | 5-year OS: 57% versus 43% (p = 0.06) |
| Choueiri et al.  | 2014 | II    | 39              | ddMVAC + surgery                      | 26%                                   | 2-year OS: 79%          |
| Plimack et al.   | 2014 | II    | 44              | ddMVAC + surgery                      | 38%                                   | 1.8-year OS: 83%        |
| Flaig et al. (COXEN) | 2019 | II    | 237             | GC versus dd-MVAC + surgery           | 30% (GC)                             | NR                      |
| Pfister et al. (VESPER) | 2021 | III   | 500             | GC versus dd-MVAC + surgery           | 42% (ddMVAC)                          | All pts [HR 0.74, 95% CI 0.55–1.00] ddMVAC [HR 0.66, 95% CI 0.47–0.92] |

CA, cisplatin, and doxorubicin; CMV, cisplatin, methotrexate, vinblastine; CR, complete response; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; NR, not reported; OS, overall survival; RT, radiotherapy.
rationale, CR rates, a surrogate for survival in localized bladder cancer is less than 20% in patients who cannot receive cisplatin, and even in patients with more robust performance status, appears to be less than 40%. Thus, the addition of a checkpoint inhibitor may improve local and distant control for these patients. Some initial data from chemoimmunotherapy combination trials are now available. The HCRN14-188 trial examined the combination of GC in combination with pembrolizumab or in combination with gemcitabine alone in patients who were cisplatin-ineligible. Initial results from the cisplatin-eligible cohort showed a ypT0 rate of 44.4%, pathologic downstaging to less than muscle invasive disease occurred in 53% of patients. There did not appear to be any correlation between the pathologic compete responses and PD-L1 status. As of report, the 2-year DFS approximated 66%. In the cisplatin-eligible arm of the trial, almost comparable responses for ypT0 (45%) and pathologic downstaging (52%) were notable given the much frail population and the exclusion of cisplatin. The KEYNOTE-866 trial will examine this combination in a randomized fashion. Another trial in a similar setting has been the BLASST-1 trial, where 41 patients with pT2-4, N0-1, M0 urothelial carcinoma were treated with a combination of gemcitabine, cisplatin, and nivolumab (360 mg Q3 weeks), followed by cystectomy. An excellent ypT0 rate of 49% was observed. Again, despite limited number of patients, no significant differences in PR were noted based on PD-L1 positivity (67% versus 71%). Several other neoadjuvant chemoimmunotherapy trials are underway as summarized in Table 2 below.

Checkpoint inhibitors also hold promise in improving outcomes with trimodality therapy. The PLUMMB trial was started in the United Kingdom as a safety study to combine three weekly pembrolizumab or in combination with gemcitabine and radiation therapy was recently reported by Balar et al, with better tolerance. Out of 48%, 19% required steroids, and the most common grade-3 immune-related toxicities were protein-losing enteropathy (2%) and polyneuropathy (2%). Almost 60% of patients were able to achieve a CR in the bladder, and a large majority (88%) had no disease progression at 1-year with an intact bladder. This modality is being further evaluated using large randomized controlled trials performed by the Southwest Oncology Group (SWOG 1806), and industry trials such as KEYNOTE-992. A summary of these trials is given below in Table 2.

Nonchemotherapy-based neoadjuvant and adjuvant trials

Immune checkpoint blockers now offer the attractive option of entirely chemotherapy-free neoadjuvant regimens, and very encouraging data are emerging in this niche. For example, the NABUCCO trial explored high-dose (3 mg/kg) ipilimumab only (cohort 1) or a combination of ipilimumab (3 versus 1 mg/kg) and nivolumab (cohort 2) prior to cystectomy in patients with pT3-4, N1-3, M0 bladder cancer. This represented overall a slightly more advanced population than some other trials in this space. Despite this, among 54 enrolled patients, a very encouraging ypT0N0 rate of 46% in cohort 1 and 43% in cohort 2 was notable. There appears to be a trend for the use of higher-dose ipilimumab in achieving CRs. However, high-dose ipilimumab was associated with a 33% rate of severe immune adverse events in this study. Single-agent immunotherapy has been explored in the PURE-01 and ABACUS trials. In the PURE-01 study, all muscle invasive patients cT2-4, N0, M0, irrespective of cisplatin eligibility, were offered neoadjuvant pembrolizumab prior to cystectomy. This trial included patients with variant predominant histology as well. A pathologic CR in the bladder was noted in 37% of patients. PD-L1 positivity and Tumor Mutation Burden (TMB) appeared to correlate with an improved probability of CR. Updated results from ABACUS, which had 95 cisplatin-ineligible patients receiving two cycles of atezolizumab prior to surgery, were significant for a ypT0N0 rate of 30%; although this improved to 37% in PD-L1-positive patients, no clear statistically significant association was noted. In addition to pure immunotherapy approaches, a combination of targeted therapies and antibody drug conjugates (ADCs) is also being investigated in the neoadjuvant setting. A recently reported trial of pembrolizumab in combination with an anti-angiogenic-targeted agent-soluble Ephrin B4 in metastatic disease was significant for an excellent CR rate of 24% in biomarker-positive patients. This combination is being investigated in the neoadjuvant setting. Similar trials combining other mechanisms are underway and will add to data in this space.
Finally, immunotherapy is being evaluated in patients who have completed traditional therapy for MIBC. In patients with high risk of recurrence after cystectomy – defined as who have residual muscle invasive disease or greater after traditional chemotherapy or those with >pT3 disease in those who could not undergo perioperative therapy, three large multicenter randomized trials have been performed. The checkmate 274 trial treated 353 patients, in a randomized fashion to nivolumab or placebo, with a primary endpoint of DFS in the intention to treat and PD-L1-positive population. DFS was significantly prolonged in those receiving therapy versus not (20.8 versus...
10.8 months, \( p < 0.001 \), and PD-L1 expression appeared to correlate with improved outcomes on therapy (Table 3).23

In contrast, the IMvigor010 trial reported negative results, 809 patients were randomized in this trial to adjuvant atezolizumab or observation, the trial was negative, with no statistically significant difference in DFS between intervention and observation (19.4 versus 16.6 months, \( p = 0.24 \)). In addition, serious adverse events were reported in 31%.24

There are important differences in these trials, such as the use of open-label design for IMvigor010 compared with the double-blinded placebo-controlled design for Checkmate-274, there appeared to be double the rate of treatment discontinuation in IMvigor010 versus Checkmate 274 (8.6 versus 3.6%), which introduces biases. Furthermore, the median DFS of 19.4 months with atezolizumab is comparable with 20.8 months with nivolumab, appearing to indicate that the observation arm performed quite well in the IMvigor010 study. Furthermore, despite the negative results, patients who had evidence of minimal residual disease (MRD) appeared to derive strong benefit from atezolizumab therapy; however, the study was not designed to assess this as a primary endpoint and a separate multicenter study IMvigor011 has been launched to examine this effect.

Importantly, both these studies appeared to show an improvement in treatment effect in patients treated with prior chemotherapy, and potential benefit in mixed pathologic variants of these tumors. As of 2021, Nivolumab is now FDA approved for the treatment of MIBC patients who appear to be at high risk of recurrence based on pathology at cystectomy. We believe the current data need careful discussion based on patient characteristics and treatment should be individualized.

**Discussion**

The approval of the checkpoint inhibitor atezolizumab in the treatment of urothelial carcinoma in 2016 was the first FDA-approved novel option for this disease in almost three decades. Since then, checkpoint inhibition therapy has revolutionized the treatment of metastatic bladder cancer, with a small but significant percentage of long-term responders despite metastatic disease. Incrementally, ADCs-targeting TROP-2 (Sacituzumab Govitecan) and Nectin-4 (enfortumab vedotin) have also been approved, in small molecule inhibitors of FGFR (Erdafitinib), other FGFR inhibitors, such as Infigratinib, are in clinical trials as described. These agents are now changing the landscape of therapy and outcomes in metastatic disease. Despite a better prognosis than metastatic disease, muscle invasive disease still has suboptimal outcomes, with a large proportion of patients having relapse and unfortunately succumbing to recurrent disease. The perioperative setting is thus an ideal opportunity to introduce these novel agents and improve long-term outcomes.

While efficacious, novel agents are not free of toxicity. Immune checkpoint inhibitors are associated with well-described adverse events ranging from rash, fatigue, nausea to steroid refractory colitis, hepatitis, pneumonitis, and irreversible endocrinopathies. ADCs such as Enfortumab have been extremely effective in relapsed metastatic settings; in the EV-201 trial cohort 2 of cisplatin-ineligible patients, Enfortumab resulted in overall response rates of more than 50% and CR rates of 20%, which appeared to be durable.25 However, treatment was associated with a high rate of dermatologic toxicity, diarrhea, and increased incidence of neuropathy. Similarly, Sacituzumab in the TROPHY-U-01 trial led to an overall response rate of 27% with decrease in tumor size in 77% of patients, but hematologic toxicities were prominent, 35% patients had grade 3 neutropenia, 18% had grade 3 leukopenia, and 18% had grade 3 anemia. Specifically, patients with pathogenic UGT1A1 variants run a very high risk of toxicity from this drug.26,27

With new developments, the traditional concept of cisplatin-ineligible patients having worse outcomes may change in the future; immunotherapy-only neoadjuvant trials such as PURE-01 and NABUCCO demonstrated pCR rates in the bladder and short-term DFS outcomes comparable with traditional chemotherapy in this much frailer population. Eventually these agents, which produce a long duration of response, would be expected to result in the greatest DFS and eventually OS benefit. Immunotherapies certainly possess these characteristics and the long-term follow-up data from these, and ongoing trials will be widely awaited. The combination of pembrolizumab with enfortumab vedotin, examined in the Phase Ib/II EV-103 trial, appears to be such a
| Study | Intervention | Setting | Phase/ randomization | Patients | Primary endpoints | Results | NCT number |
|-------|--------------|---------|----------------------|----------|-------------------|---------|------------|
| NABUCCO | 1: Ipilimumab (hd) versus 2: Ipilimumab (hd versus low dose) + nivolumab | Neoadjuvant, cisplatin-ineligible, stage III | Open-label, phase II, randomized | 54 | (Primary) Number of patients who undergo surgical resection at 12 weeks. PCR (ypT0) | 80% surgical resection. Cohort 1 (ypT0 46%) Cohort 2 (ypT0 43%) | NCT03387761 |
| ABACUS | Atezolizumab | Neoadjuvant, cisplatin-ineligible | Open-label, phase II, nonrandomized | 95 | PCR (ypT0) | ypT0 = 30% | NCT02662309 |
| PURE-01 | Pembrolizumab | Neoadjuvant, cisplatin-ineligible | Open-label, phase II, nonrandomized | 114 | PCR (ypT0) | ypT0 = 37% | NCT02736266 |
| CCC NCT02767921 | Ephrin B4 + pembrolizumab | Neoadjuvant, cisplatin-ineligible | Open-label, phase II, nonrandomized | TBD | Percentage of patients able to undergo surgery as planned | Currently accruing | NCT02767921 |
| KEYNOTE-905/ EV303 | Enfortumab + pembrolizumab | Neoadjuvant, cis-ineligible | Open-label, phase III, randomized | 836 | PCR (ypT0) EFS | Currently accruing | NCT03924895 |
| KEYNOTE-B15/ EV304 | Enfortumab vedotin + pembrolizumab versus SOC chemotherapy | Neoadjuvant, cis-ineligible | Open-label, phase III, randomized | 784 | PCR (ypT0) EFS | Currently accruing | NCT04700124 |
| HCRN GU18343 / ABATE | Cabozantinib + atezolizumab | Neoadjuvant | Open-label, phase II, nonrandomized | 42 | PCR (ypT0) | Currently accruing | NCT04289779 |
| BLASST-3 | Infigratinib | Neoadjuvant | Phase I, open label | 12 | ≥ 70% of patients receiving at least one dose of study treatment followed by completion of RC (feasibility) | Currently accruing | NCT04972253 |
| PEBBLE | Bintrafusp alfa | Neoadjuvant | Open-label, phase II, nonrandomized | 49 | PCR (ypT0) | Currently accruing | NCT04878250 |
| PROOF 302 | Infigratinib | Adjuvant | Quad-blind, placebo-controlled, phase III, randomized | 218 | DFS | Currently accruing | NCT04197986 |
| Checkmate 274 | Nivolumab | Adjuvant | Triple-blind, placebo-controlled, phase III, randomized | 709 | DFS | 6-month DFS (All) 74.9% versus 60.3% (PD1+) 74.5% versus 55.7% | NCT02632409 |
| Im vigor010 | Atezolizumab | Adjuvant | Open-label, phase III, randomized | 809 | DFS | mDFS 19.4 versus 16.6 months [0.89 [95% CI 0.74–1.08]; p = 0.24] | NCT02450331 |
| Im vigor011 | Atezolizumab (ctDNA + within 20 weeks of cystectomy)] | Adjuvant | Double-blind, placebo-controlled, phase III, randomized | 495 | DFS | Currently accruing | NCT04660344 |
| AMBASSADOR | Pembrolizumab | Adjuvant | Open-label, phase III, randomized | 739 | OS DFS | Completed accrual | NCT03244384 |
This relatively small trial, with around 45 metastatic patients, demonstrated an overall response rate of 73% in cisplatin-ineligible patients with more than 90% of patients experiencing tumor shrinkage. The median duration of response on the regimen appears to be more than 2 years. The EV-303/EV304 trials will provide more data on this combination in the neoadjuvant setting. As evidence evolves in this field, the upcoming challenges for clinicians will be to select those patients who are at the highest risk of relapse and thus with the most favorable risk reward for therapy, and after identification of these patients, an appropriate selection of therapeutic regimens likely to achieve the desired response.

The presence of residual muscle invasive disease after treatment with neoadjuvant therapy is an indicator for high risk of relapse. This criterion has been used for eligibility for patient selection in many adjuvant trials, including the recently reported checkmate 274 and IMvigor010. Yet, the results in these trials appear to be contradictory, at least on superficial examination. As mentioned prior, when considering a bespoke assay of circulating MRD, patients with negative MRD did not benefit from therapy (HR 1.14, \(p = 0.45\)) while those with positive MRD appeared to have a significant benefit (HR 0.58, \(p = 0.0005\)). MRD-positive patients had a median OS of 25.8 months on atezolizumab versus only 15.8 months on observation. These findings are of great interest in treatment selection and perhaps the reclassification of traditionally defined high-risk patients for relapse.

PD-L1 expression has long been explored as a potential marker for treatment benefit in patients; however, the results for this biomarker have been confounded in several studies due to the variation in measuring positivity, and possible prognostic in contrast to predictive role of utilized assays. Hence, while positive PD-1 expression appeared to be associated with an improved benefit with adjuvant nivolumab (HR 0.53) versus the intent-to-treat population (HR 0.70), this was not the case for atezolizumab with an HR of 1.01 (95% CI 0.75–1.35) in IC0/1% and 0.83 (95% CI 0.63–1.05) in IC2/3 patients. While nivolumab is now approved for adjuvant therapy, the randomized phase III multicenter AMBASSADOR study is thus eagerly awaited to provide much needed further clarity on the question of PD-1 directed therapy in an adjuvant setting.

The treatment of patients based on MRD may also become mainstream with the results of IMvigor010 and the upcoming IMvigor011 trial, this unique biomarker can be used in adaptive designs in the adjuvant setting as well. Finally, adjuvant data for targeted therapies, such as infiribatinib, remain to be read out. These exciting new developments augur a bright future for all locally advanced bladder cancer patients irrespective of cisplatin eligibility.

Declarations

Ethics approval and consent to participate

No patient related data were involved. IRB approval was not required or sought.

Consent for publication

Not applicable.

Author contributions

Goutham Patil: Data curation; Resources.

Arnab Basu: Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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