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Neoadjuvant immunotherapy for muscle invasive urothelial bladder carcinoma: will it change current standards?

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***Abstract*:** Immunotherapy, in the form of immune checkpoint inhibitors (ICI), has shown activity in metastatic urothelial bladder carcinoma, resulting in the approval of several ICI agents in the first- and second-line settings. This has led to an increased interest in studying their efficacy in the neoadjuvant setting for muscle invasive disease – an area of significant unmet need. This non-systematic review will look at the evidence supporting the use of ICI in the neoadjuvant setting for this tumor, results of early-phase studies, ongoing trials, and possible future applications for these drugs.

Keywords: bladder cancer, immune checkpoint inhibitor, immunotherapy, muscle invasive, neoadjuvant

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Introduction

Bladder cancer is the most common malignancy involving the urinary system, accounting for 3% of all new cancer diagnoses worldwide, with around 550,000 new cases per year.[1] The predominant histologic type in developed countries is urothelial carcinoma (UC). Tumoral depth of invasion and detrusor invasiveness are the most significant variable for progression, recurrence, and survival. Radical cystectomy with bilateral pelvic lymphadenectomy is the preferred curative approach for fit patients with non-metastatic muscle invasive bladder cancer (MIBC). Even with this approach, 5-year survival rates are as low as 62.8% for pT2 and 38.9% for pT3-T4 tumors.[2] Neoadjuvant chemotherapy (NAC) has been shown to increase 10-year overall survival by 6%,[3] and thus current guidelines encourage the use of cisplatin-based combination therapy before surgery for eligible patients.[4,5] However, NAC has failed to gain wide adoption due to cisplatin ineligibility in up to 50% of cases, concerns for toxicity, and the potential delay of surgery in non-responders.

Rationale for immunotherapy in UC

UC is an immunogenic tumor, that has been treated with immunotherapy in the form of Bacillus Calmette–Guérin (BCG) instillation for decades in the setting of non-muscle invasive bladder cancer (NMIBC).[4] We know that immune cells, including CD8+ tumor-infiltrating cytotoxic T lymphocytes (TILs), are increased in these tumors.[6] They also present with one of the highest levels of DNA alterations in human cancers, just below melanoma and lung cancer, as shown by The Cancer Genome Atlas (TCGA).[7]

However, cancer cells have several ways to evade immune surveillance. One of the most important mechanisms is the expression of co-inhibitory factors such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and programmed death ligands 1 (PD-L1) and 2 (PD-L2). The receptor for the latter two factors, programmed cell death-1 (PD-1), is typically expressed in the surface of activated lymphocytes including CD8+, CD4+, and natural killer T cells. Binding of the ligand to PD-1 leads to the suppression of cytotoxic T cell functions, mostly by

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altering cytokine production, leading to decreased endogenous anti-tumor activity. Urothelial carcinomas can over-express PD-L1 in a significant number of patients.[8] As for CTLA-4, T-cell activation is a process that requires costimulatory signals such as the binding of CD28 on the T-cell to B7-1 (CD80) or B7-2 (CD86) on the antigen-presenting cell. CTLA-4 acts as a CD28 homolog with a higher binding affinity to B7 but, instead of activation, it leads to inhibition of the T-cell.

Thus, blocking the PD1/PD-L1/PD-L2 axis with monoclonal antibodies directed either against the PD-1 receptor with drugs such as pembrolizumab and nivolumab, or its ligands with atezolizumab, durvalumab or avelumab, can lead to increased antitumoral response. The same is true for anti-CTLA4 antibodies such as ipilimumab and tremelimumab.

Immunotherapy in advanced UC

PD-1/PD-L1 inhibitors in UC were first studied in patients with unresectable or metastatic disease. Significant activity was demonstrated for all the previously mentioned drugs.

Pembrolizumab was studied in first-line setting in 370 patients with an overall objective response rate (ORR) of 24% and complete response (CR) of 5%. Subgroup analysis using the PD-L1 combined positive score (CPS), defined as the percentage of cells (tumor cells, macrophages, or lymphocytes) expressing PD-L1 in a tumor biopsy, showed an ORR of 39% in those with CPS $>$ 10%, 20% for CPS between 1% and 10%, and 11% for those with CPS scores below 1%.[9]

Similarly, Atezolizumab was studied in 486 patients in the second-line setting, showing an overall ORR of 15%, while CR was reported in 5% of patients. Subgroup analysis by the percentage of PD-L1-positive immune cells in the tumor microenvironment IC0 ($<$1%), IC1 ($\geq$1% but $<$5%), and IC2/3 ($\geq$5%), showed an ORR of 8%, 10%, and 26% respectively.[10]

Additionally, in a phase I/II study including 191 patients, Durvalumab showed an ORR of 17.8%. The rate was 27.6% for patients with high PD-L1 expression (defined as $\geq$25% of either tumor cells or immune cells staining for PD-L1) and 5.1% for those with low or negative PD-L1 expression ($<$25% of both tumor cells and immune cells staining for PD-L1). CR for Durvalumab was seen in 3.7% of the overall studied population.[11]

Another immune checkpoint inhibitor (ICI), Nivolumab, was assessed in 265 patients in the second-line setting, after platinum-based chemotherapy, showing an overall ORR of 19.6% and CR in 2% of patients. Subgroup analysis by PD-L1 expression 5%, $>$1% and $<$1% indicated an ORR of 28.4%, 23.8% and 16.1%, respectively.[12]

Also, Avelumab was evaluated in 249 patients in the second-line setting, after at least one previous platinum-based chemotherapy, showing an ORR of 17% and CR in 4% of patients. Patients with PD-L1 expression of 5% or more had an ORR of 28%, while patients with less of 5% had an ORR of 14%.[13]

Currently, all five of the discussed agents are approved by the United States (US) Food and Drug Administration (FDA) for locally advanced or metastatic urothelial carcinoma in the second-line setting without the need of PD-L1 expression testing. Only pembrolizumab and atezolizumab have been approved in the first-line setting, but restricted to patients not eligible for any platinum-containing chemotherapy and who express PD-L1, with a cutoff of CPS $>$ 10% for pembrolizumab, and IC2/3 ($\geq$5%) for atezolizumab.

Neoadjuvant immunotherapy

Today, since ICI have shown significant activity in the advanced setting, they are being tested as neoadjuvant therapy for several tumor types, including melanoma, non-small cell lung cancer, and urothelial carcinoma. The concept of immunotherapy before resection has several theoretical advantages. Since the antigen load is higher prior to resection, we could expect a better priming of the immune system with the tumor in place, leading to increased eradication of residual metastatic disease. Neoadjuvant therapy also gives us the opportunity to analyze the pathological response and efficacy of therapy in that specific patient and tumor.

Mice models have shown improved efficacy of neoadjuvant compared with adjuvant immunotherapy.[14] Authors conclude this is probably due to both T cell numbers and IFN levels, as they

observed a strong increase in tumor-specific CD8+ T cells in blood and organs, which were capable of producing IFNγ and TNF, shortly after treatment with an anti-PD1 agent. Interestingly, they noted no survivors when IFNγ was neutralized, underscoring its importance regarding the efficacy of neoadjuvant therapy.

The current neoadjuvant scenario in UC

Historically, the standard of care for MIBC patients who are eligible has been platinum-based chemotherapy. For patients receiving three cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) in stage T2-T4aN0 muscle-invasive bladder, pathologic complete response (pCR), defined as the absence of viable tumor in the resection specimen, has been reported in 38% of cases. Some of the significant adverse events (AEs) for this chemotherapy regimen were grade 4 granulocytopenia (33%) and gastrointestinal toxicity, such as grade 3 nausea or vomiting, stomatitis, diarrhea, or constipation (17%).[15]

Gemcitabine plus cisplatin (GC) – the most widely used regimen in neoadjuvant MIBC – has not been studied prospectively in the neoadjuvant setting. However, retrospective results for 935 patients across 19 centers for patients with clinical cT2-4aN0M0 showed a pCR of 23.9% for GC, compared with 24.5% for MVAC, with no difference on multivariable analysis for these regimens.[16]

Immunotherapy as neoadjuvant agent for UC

In humans, three prospective studies have reported results for neoadjuvant ICI in muscle-invasive urothelial carcinoma.

In the PURE-01 study, 50 patients received pembrolizumab 200 mg every 3 weeks for three cycles before radical cystectomy.[17] Median age was 66 years and 82% of patients were male. Clinical stage was T2N0 for 42%, T3N0 for 54%, and T2-3N1 for 4% of the patients. The primary end point in the intention-to-treat population was pCR rate, which occurred in 41% of patients. A total of 25 patients (70%) had a positive baseline PD-L1 expression defined as CPS ⩾ 10% by immunohistochemistry (IHC; Dako 22C3 pharmDx assay). pCR in PD-L1(+) patients was achieved in 54% of the patients, while it was only 13% for PD-L1 negative patients. Median tumor mutation burden (TMB) for all patients was 11.4 mut/Mb and the authors reported a nonlinear association between TMB and pCR when using a 15 mutations/Mb cutoff. Moreover, no patient had disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) during treatment. Therapy was well tolerated, with only 6% of patients developing grade 3–4 adverse events by Common Terminology Criteria for Adverse Events (CTCAE) v.5.0, and only one patient required discontinuation of pembrolizumab, due to hepatic toxicity.

Another single arm phase II trial, ABACUS,[18] included 95 patients with T2-4N0M0 tumors who received two doses of single-drug atezolizumab (1200mg Q3w) prior to cystectomy. Median age was 73 years and T stage was T2, T3, T4 in 73%, 19%, and 8% of patients, respectively. The primary endpoint was pCR rate, which occurred in 31% (27/88) of patients, and 17% (3/18) in pT3/4 tumors. At baseline, 40% of patients were positive for PD-L1 expression, defined as ⩾5% of immune cells (ICs) staining (IHC, Ventana/Roche SP142 assay); pCR rate was 37% in PD-L1(+) and 24% in PD-L1(−) tumors. The baseline median TMB was 10.09 mutations per Mb, the group of patients with TMB above the median had a pCR rate of 31%, while patients with TMB below the median had a pCR of 27%. Radiological evaluation was performed in 30 patients, with 22% showing an objective response, and 16% showing progression during treatment by RECIST criteria. Treatment was generally well tolerated, with only 12% of patients presenting any grade 3/4 treatment-related AEs.

The only study so far looking into the efficacy of a dual immunotherapy strategy with an anti-PD1 plus an anti-CTLA4 agent has been published recently.[19] NABUCCO is a single-arm feasibility trial that included 24 patients with stage III UC who were cisplatin ineligible or refused cisplatin-based chemotherapy, to be treated with ipilimumab on day 1, nivolumab plus ipilimumab on day 22, and nivolumab alone on day 43, followed by surgery. Pathological complete response was achieved in 11 patients (46%) and 14 (58%) had no remaining invasive disease (pCR or pTisN0/pTaN0). Regarding toxicity, grade 3–4 immune-related adverse events occurred in 55% of patients.

Table 1. Overview of drug activity in the neoadjuvant setting for UC.

Study	Drug	Design	Patients	cTNM stage	cT2 (%)	cN+ (%)	pCR (%)	AE G3–4 (%)
PURE-01[17]	Pembrolizumab	Prospective phase II	50	T2-T3 N0-1 M0	42	4	41	6
ABACUS[18]	Atezolizumab	Prospective phase II	95	T2-T4 N0 M0	74	0	31	11
NABUCCO[19]	Nivolumab + Ipilimumab	Prospective phase II	24	T2-4a N1-3 M0	N/A	42	46	55
HCRN GU14-188[20]	GC + Pembrolizumab	Prospective phase Ib/II	43	T2-T4a N0 M0	43	0	44	30
BLASST-1[21]	GC + Nivolumab	Prospective Phase II	41	T2-T4a N0-1 M0	90	3	49	20
SWOG 8710 (INT-0080)[15]	MVAC	Prospective phase III	153	T2-T4a N0 M0	40	0	38	72
Zargar *et al.*[16]	MVAC	Retrospective	183	T2-T4a N0 M0	50	0	25	N/A
Zargar *et al.*[16]	GC	Retrospective	602	T2-T4a N0 M0	69	0	24	N/A

AE, adverse events; GC, gemcitabine plus cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; N/A, not available; TMN, tumour, node, metastasis; UC, urothelial carcinoma.

An overview of the results is provided in Table 1.

Immunotherapy plus chemotherapy as neoadjuvant agents for UC

Two phase II studies have reported results for the combination of an anti-PD1 agent with standard platinum-based chemotherapy.

BLASST-1 is an investigator initiated, single arm, phase II study that investigated the efficacy and safety of adding nivolumab to neoadjuvant gemcitabine and cisplatin in MIBC.[21] A total of 41 patients were enrolled, the median age was 66 years. A total of 90% of the cohort had cT2N0 disease. pCR was observed in 49% of patients, and 66% had no evidence of muscle-invasive disease at the time of surgery. Interestingly, there was no correlation between PD-L1 status and response: 10 of 15 patients (67%) with PD-L1–positive tumors had downstaging compared with 17 of 24 (71%) with PD-L1–negative tumors. Overall rate of grade 3–4 AEs was 20%, one patient developed Guillain Barre Syndrome after surgery, and no deaths were reported.

The second study, HCRN GU14-188,[20] evaluated the use of pembrolizumab added to neoadjuvant GC chemotherapy. The cohort included 43 patients with MIBC; median patient age was 65 years. Clinical staging for 36 patients whose disease stage was known at screening was cT2 for 17 patients, while 19 had cT3/T4 disease. Final results for the cisplatin-eligible arm show that pCR rate was 44.4% and downstaging to non-muscle invasive disease was 61.1%. Grade 3/4 hematologic AEs occurred in 60% of patients, and grade 3/4 nonhematologic AEs occurred in 30% of patients. One patient died due to mesenteric ischemia and was not considered to be related to study treatment.

Moving forward, four large stage III trials are looking into the efficacy of immunotherapy combined with chemotherapy for MIBC as neoadjuvant treatment (Table 2).

The ENERGIZE trial is currently comparing three different strategies: (A) GC followed by surgery, and no adjuvant treatment.[22] (B) GC plus Nivolumab followed by surgery and adjuvant Nivolumab. (C) GC plus Nivolumab and Linrodostat mesylate (BMS-986205) followed by surgery and adjuvant Nivolumab plus Linrodostat. This third arm incorporates an oral Indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor – Linrodostat – which has shown encouraging preliminary evidence of activity in metastatic UC.

Table 2. Ongoing phase III neoadjuvant studies including immunotherapy for MIBC.

Study	TNM stage	Treatments (neoadjuvant phase)	Treatments (adjuvant phase)	Estimated Enrollment	Primary endpoints	Start date	End date
ENERGIZE (NCT03661320)[22]	T2-T4aN0M0	Experimental: Gemcitabine + Cisplatin + Nivolumab +/– BMS-986205 (Linrodostat) Comparator: Gemcitabine + Cisplatin	Experimental: Nivolumab +/– BMS-986205 (Linrodostat) Comparator: None	1200 participants	pCR, EFS	October, 2018	2025
NIAGARA (NCT03732677)[23]	T2-T4aN0/ 1M0	Experimental: Gemcitabine + Cisplatin + Durvalumab Comparator: Gemcitabine + Cisplatin	Experimental: Durvalumab Comparator: None	1050 participants	pCR, EFS	November, 2018	2025
KEYNOTE-866 (NCT03924856)[24]	T2-T4aN0M0	Experimental: Gemcitabine + Cisplatin + Pembrolizumab Comparator: Gemcitabine + Cisplatin	Experimental: Pembrolizumab Comparator: None	790 participants	pCR, EFS	June, 2019	2023
KEYNOTE-905/ EV-303 [ClinicalTrials.gov identifier: NCT03924895][25]	T2-T4aN0M0 or T1-T4aN1M0	Experimental 1: Pembrolizumab Experimental 2: Pembrolizumab + enfortumab vedotin Comparator: None (study is for cisplatin-ineligible patients only)	Experimental 1: Pembrolizumab Experimental 2: Pembrolizumab + enfortumab vedotin Comparator: None	836 participants	pCR, EFS	July, 2019	2026

EFS, event-free survival; MIBC, muscle invasive bladder cancer; pCR, pathologic complete response.

The NIAGARA trial is studying the combination of durvalumab plus GC *versus* GC alone in the neoadjuvant setting, followed by radical cystectomy, and then durvalumab alone as adjuvant therapy.[23] This study is the only one so far including patients with N1 nodal stage.

Similarly, KEYNOTE-866 is comparing the combination of pembrolizumab plus GC *versus* GC alone in the neoadjuvant setting, followed by radical cystectomy, and then pembrolizumab alone as adjuvant treatment.[24]

KEYNOTE-905/EV-303 is the only ongoing phase III trial focusing on cisplatin-ineligible patients. It will compare three different strategies[25]: surgery alone, *versus* surgery with neoadjuvant/adjuvant pembrolizumab, *versus* surgery with neoadjuvant/adjuvant pembrolizumab plus enfortumab vedotin.

These trials described above show interesting similarities. They have all settled for Gemcitabine and Cisplatin as the chemotherapy backbone, instead of the more toxic but potentially more effective MVAC or ddMVAC. They also have similar primary endpoints: pCR and event-free survival (EFS), while 5-year overall survival has been incorporated as a secondary endpoint in all of them. Although promising, we must be aware of certain limitations for these trials. Since the chemotherapy agent used in these studies is GC (except for KEYNOTE-905/EV-303), they will not provide information for cisplatin-ineligible patients, which is a significant portion of MIBC patients. They are also including patients regardless of PD-L1 expression, which broadens the potential number of patients that could be treated if a drug receives approval, but benefit may be limited to PD-L1 (+) as we have seen in the metastatic setting. Therefore, scrutinous interpretation of the data emerging from these trials will be warranted when available, as well as careful consideration of both clinical toxicity and financial issues if these combinations are approved in the future.

Conclusion

There is a significant need for improved therapeutic strategies for MIBC. Immunotherapy, in the form of ICI, has proved its activity in the metastatic setting, and it is now being studied as perioperative therapy to improve clinical results, in combination with chemotherapy. This is not only occurring in the field of urology, but similar studies are also ongoing in several other tumor types including melanoma and lung cancer. Although

there is a strong rationale for the use of ICI in the neoadjuvant setting, there are also several limitations, including their high cost. The question of whether these promising agents or their combinations will change current standards is still under investigation. Early phase results show encouraging results, but we will need to wait for data arising from the large ongoing phase III trials before these agents can be recommended as the standard of care.

Conflict of interest statement

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References

1. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Ploussard G, Shariat SF, Dragomir A, *et al.* Conditional survival after radical cystectomy for bladder cancer: evidence for a patient changing risk profile over time. *Eur Urol* 2014; 66: 361–370.
3. International Collaboration of Trialists; Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group); European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol* 2011; 29: 2171–2177.
4. Alfred Witjes J, Lebret T, Compérat EM, *et al.* Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol* 2017; 71: 462–475.
5. National Comprehensive Cancer Network, Bladder Cancer, Version 6.2020, https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed 11 November 2020).
6. Sharma P, Shen Y, Wen S, *et al.* CD8 tumor-infiltrating lymphocytes are predictive of survival in muscle-invasive urothelial carcinoma. *Proc Natl Acad Sci USA* 2007; 104: 3967–3972.
7. Lawrence M, Stojanov P, Polak P, *et al.* Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* 2013; 499: 214–218.
8. Nakanishi J, Wada Y, Matsumoto K, *et al.* Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer Immunol Immunother* 2007; 56: 1173–1182.
9. Balar AV, Castellano D, O'Donnell PH, *et al.* First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2017; 18: 1483–1492.
10. Rosenberg JE, Hoffman-Censits J, Powles T, *et al.* Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016; 387: 1909–1920.
11. Powles T, O'Donnell PH, Massard C, *et al.* Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. *JAMA Oncol* 2017; 3: e172411.
12. Sharma P, Retz M, Siefker-Radtke A, *et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017; 18: 312–322.
13. Apolo AB, Ellerton JA, Infante JR, *et al.* Avelumab as second-line therapy for metastatic, platinum-treated urothelial carcinoma in the phase Ib JAVELIN solid tumor study: 2-year updated efficacy and safety analysis. *J Immunother Cancer* 2020; 8: e001246.
14. Liu J, Blake SJ, Yong MC, *et al.* Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. *Cancer Discov* 2016; 6: 1382–1399.
15. Grossman HB, Natale RB, Tangen CM, *et al.* Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003; 349: 859–866.

16. Zargar H, Espiritu PN, Fairey AS, *et al.* Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. *Eur Urol* 2015; 67: 241–249.

17. Necchi A, Anichini A, Raggi D, *et al.* Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. *J Clin Oncol* 2018; 36: 3353–3360.

18. Powles T, Kockx M, Rodriguez-Vida A, *et al.* Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. *Nat Med* 2019; 25: 1706–1714.

19. van Dijk N, Gil-Jimenez A, Silina K, *et al.* Preoperative ipilimumab plus nivolumab in locoregionally advanced urothelial cancer: the NABUCCO trial. *Nat Med* 2020; 26: 1839–1844.

20. Hoimes C, Adra N, Fleming M, *et al.* Phase Ib/II neoadjuvant (N-) pembrolizumab (P) and chemotherapy for locally advanced urothelial cancer (laUC): Final results from the cisplatin (C)- eligible cohort of HCRN GU14-188. *J Clin Oncol* 2020; 38(Suppl. 15): 5047.

21. Gupta S, Sonpavde G, Weight CJ, *et al.* Results from BLASST-1 (Bladder Cancer Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in muscle invasive bladder cancer (MIBC) undergoing cystectomy. *J Clin Oncol* 2020; 38(Suppl. 6): 439.

22. ClinicalTrials.gov. A study of chemo only versus chemo plus nivo with or without BMS-986205, followed by post- surgery therapy with Nivo or Nivo and BMS-986205 in patients with MIBC, https://clinicaltrials.gov/ct2/show/NCT03661320 https://ClinicalTrials.gov Identifier: NCT03661320 (accessed 11 November 2020).

23. ClinicalTrials.gov. Durvalumab+ gemcitabine/cisplatin (neoadjuvant treatment) and durvalumab (adjuvant treatment) in patients with MIBC (NIAGARA), https://clinicaltrials.gov/ct2/show/record/NCT03732677?view=record ClinicalTrials.gov Identifier: NCT03732677 (accessed 11 November 2020).

24. ClinicalTrials.gov. Perioperative pembrolizumab (MK-3475) plus neoadjuvant chemotherapy versus perioperative placebo plus neoadjuvant chemotherapy for cisplatin-eligible Muscle-Invasive Bladder Cancer (MIBC) (MK-3475-866/KEYNOTE-866). Available from: https://clinicaltrials.gov/ct2/show/NCT03924856 ClinicalTrials.gov Identifier: NCT03924856 (accessed 11 November 2020).

25. Galsky MD, Necchi A, Shore ND, *et al.* KEYNOTE-905/EV-303: perioperative pembrolizumab or pembrolizumab plus enfortumab vedotin (EV) and cystectomy compared to cystectomy alone in cisplatin-ineligible patients with muscle-invasive bladder cancer (MIBC). *J Clin Oncol* 2021; 39(Suppl. 6): TPS507.