**Table S1. Completed and Active Bladder Cancer Clinical Trials that Evaluate Agents with Potential Modulatory Effects on Myeloid Derived Suppressor Cells**

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| --- | --- | --- | --- |
| **Clinical Trial** | | **Disease Setting** | **Comments** |
| **Chemotherapy combinations** |  |  |  |
| A Two-Dimensional Dose-Finding Study of Ixazomib in Combination With Gemcitabine and Doxorubicin, Followed by a Phase II Extension to Assess the Efficacy of This Combination in Metastatic, Surgically Unresectable Urothelial Cancer | NCT02420847 | Metastatic and locally advanced |  |
| Gemcitabine and Platinol Followed by Pemetrexed and Gemcitabine in Patients With Advanced or Metastatic Bladder Cancer | NCT00101842 | Metastatic and locally advanced |  |
| Docetaxel and Gemcitabine in Treating Patients With Progressive Regional or Metastatic Bladder Cancer | NCT00004223 | Metastatic and locally advanced, 2nd line | 17% ORR (5/29)109 |
| A Phase 2 Trial of ALIMTA (Pemetrexed) Plus Gemcitabine in Locally Advanced or Metastatic Transitional Cell Carcinoma of the Urothelium | NCT00034593 | Metastatic |  |
| JAVLOR Association Study in CDDP-unfit Patients With Advanced Transitional Cell Carcinoma: Gemcitabine Versus Carboplatin | NCT01599013 | Metastatic and locally advanced, cisplatin ineligible | Gemcitabine + Vinflunine: 44% ORR (15/34)  Gemcitabine + Carboplatin: 29% ORR (10/35)110 |
| First-Line Treatment of Advanced Bladder Cancer Randomized vs. Gemcitabine ± Vinflunine in Patients Ineligible to Receive Cisplatin-Based Therapy | NCT00389155 | Metastatic and locally advanced, cisplatin ineligible |  |
| Gemcitabine and Irinotecan in Treating Patients With Locally Advanced or Metastatic Bladder Cancer | NCT00089128 | Metastatic and locally advanced |  |
| Gemcitabine and Pazopanib in Chemotherapy Naive Patients With Advanced/Metastatic Urothelial Carcinoma Ineligible for Cisplatin-based Chemotherapy | NCT01622660 | Metastatic and locally advanced |  |
| Gemcitabine, Cisplatin, Plus Lenalidomide as First-line Therapy for Patients With Metastatic Urothelial Carcinoma | NCT01342172 | Metastatic and locally advanced, 1st line | 33% ORR (3/9) but regimen poorly tolerated111 |
| S0028, Gemcitabine and Paclitaxel in Treating Patients With Advanced or Recurrent Cancer of the Urinary Tract | NCT00022633 | Metastatic |  |
| Pemetrexed and Cisplatin in Advanced Urothelial Carcinoma (PECULIAR) | NCT01490437 | Metastatic and locally advanced, 1st line | 64% ORR (24/42); 14% OS112 |
| A Randomized Study Comparing Single Agent Gemcitabine Intravesical Therapy Versus Mitomycin C in Patients With Intermediate Risk Superficial Bladder Cancer | NCT00192049 | Non-muscle invasive bladder cancer |  |
| Four Cycles Versus Six Cycles of Cisplatin-based Chemotherapy in Metastatic Urothelial Carcinoma | NCT03296306 | Metastatic |  |
| Risk Adapted Treatment for Muscle Invasive Bladder Cancer After Neoadjuvant Accelerated MVAC | NCT02710734 | Neoadjuvant |  |
| Fluorouracil in Treating Patients With Recurrent or Metastatic Bladder Cancer | NCT00003175 | Metastatic | 15% ORR (7/46), median OS 6.5 mos113 |
| Fluorouracil, Leucovorin, Gemcitabine, and Cisplatin in Treating Patients With Metastatic or Unresectable Adenocarcinoma of the Urothelium or Urachal Remnant | NCT00082706 | Metastatic |  |
| Veliparib, Cisplatin, and Gemcitabine Hydrochloride in Treating Patients With Advanced Biliary, Pancreatic, Urothelial, or Non-Small Cell Lung Cancer | NCT01282333 | Metastatic |  |
| Larotaxel + Cisplatin Versus Gemcitabine + Cisplatin in First Line Treatment of Locally Advanced/Metastatic Urothelial Tract or Bladder Cancer | NCT00625664 | Metastatic and locally advanced |  |
| Trial of Paclitaxel Plus Gemcitabine and Cisplatin in Bladder Cancer | NCT02560038 | Metastatic and locally advanced | 100% ORR (3/3)114 |
| Gemcitabine, Paclitaxel, and Cisplatin in Treating Patients With Advanced Cancer of the Urothelium | NCT00310011 | Metastatic |  |
| Gemcitabine, Carboplatin, and Lenalidomide for Treatment of Advanced/Metastatic Urothelial Cancer and Other Solid Tumors | NCT01352962 | Metastatic and locally advanced, 2nd line |  |
| Gemcitabine Hydrochloride, Cisplatin, and AGS-003-BLD in Treating Patients With Muscle-Invasive Bladder Cancer Undergoing Surgery | NCT02944357 | Neoadjuvant |  |
| Methotrexate, Vinblastine, Doxorubicin and Cisplatin (MVAC) Followed by Gemcitabine Plus Cisplatin (GEM+CDDP) in Locally Advanced or Metastatic Bladder Cancer | NCT00635726 | Metastatic and locally advanced |  |
| Cisplatin, Paclitaxel, and Gemcitabine in Treating Patients With Progressive Unresectable Regional or Metastatic Bladder Cancer | NCT00006118 | Metastatic and locally advanced |  |
| Combination Chemotherapy in Treating Patients With Stage IV Locally Advanced or Metastatic Bladder Cancer | NCT00005086 | Metastatic and locally advanced bladder cancer |  |
| **PD-1, PD-L1, CTLA-4 Inhibitors** |  |  |  |
| A Study of Atezolizumab in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer (Cohort 2) | NCT02108652 | Metastatic and locally advanced, 2nd line | 23% ORR (27/119), 9% CR (11/119), median OS 15.9 mos115 |
| A Study of Atezolizumab in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer (Cohort 1) | NCT02951767 | Metastatic and locally advanced, cisplatin ineligible |  |
| A Study of Atezolizumab Compared With Chemotherapy in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer [IMvigor211] | NCT02302807 | Metastatic and locally advanced, 2nd line | Atezolizumab: median OS 11.1 mos (n=467)  Chemo: median OS 10.6 mos (n=464)116 |
| Testing the PD-1 Inhibitor Pembrolizumab as Maintenance Therapy After Initial Chemotherapy in Metastatic Bladder Cancer | NCT02500121 | Metastatic |  |
| Trial of Anti-PD-1 (Nivolumab) in Bladder Cancer Patients Recently Treated With Intravesical BCG Immunotherapy | NCT03106610 | Non-muscle invasive (cTis, cTa, cT1), BCG unresponsive |  |
| Assessment of Efficacy and Safety of Durvalumab Plus BCG Compared to the Standard Therapy With BCG in Non-muscle Invasive Bladder Cancer | NCT03528694 | Non-muscle invasive (cTis, cTa, cT1) |  |
| A Study Of Avelumab In Patients With Locally Advanced Or Metastatic Urothelial Cancer (JAVELIN Bladder 100) | NCT02603432 | Metastatic |  |
| Study of Atezolizumab as Monotherapy and in Combination With Platinum-Based Chemotherapy in Participants With Untreated Locally Advanced or Metastatic Urothelial Carcinoma | NCT02807636 | Metastatic and locally advanced | 23% ORR (27/119), 9% CR (11/119), median OS 15.9 mos115 |
| Study of Pembrolizumab (MK-3475) in Participants With Advanced Urothelial Cancer (MK-3475-052/KEYNOTE-52) | NCT02335424 | Metastatic and locally advanced, cisplatin ineligible |  |
| A Study of Pembrolizumab (MK-3475) Versus Paclitaxel, Docetaxel, or Vinflunine for Participants With Advanced Urothelial Cancer (MK-3475-045/KEYNOTE-045) | NCT02256436 | Metastatic and locally advanced, 2nd line | Pembrolizumab: median OS 10.3 mos (n=270)  Chemo: median OS 7.4 mos (n=272), p=0.0023 |
| Durvalumab Plus Tremelimumab With Concurrent Radiotherapy for Localized Muscle Invasive Bladder Cancer Treated With a Selective Bladder Preservation Approach | NCT03702179 | Localized muscle-invasive (cT2-4) |  |
| Radiation Therapy and Durvalumab With or Without Tremelimumab in Treating Participants With Unresectable, Locally Advanced, or Metastatic Bladder Cancer | NCT03601455 | Metastatic and locally advanced |  |
| Study Evaluating Neoadjuvant Pembrolizumab Monotherapy in Patients With Muscle-Invasive Bladder Cancer to Explore in Vivo the Mechanisms of Action of Pembrolizumab | NCT03212651 | Neoadjuvant |  |
| Pembrolizumab With Chemoradiotherapy as Treatment for Muscle Invasive Bladder Cancer | NCT02662062 | Neoadjuvant |  |
| Atezolizumab Given in Combination With a Personalized Vaccine in Patients With Urothelial Cancer | NCT03359239 | Metastatic and locally advanced |  |
| Cabozantinib Plus Pembrolizumab as First-Line Therapy for Cisplatin-Ineligible Advanced Urothelial Carcinoma | NCT03534804 | Metastatic |  |
| A Window of Opportunity Trial: Avelumab in Non-metastatic Muscle Invasive Bladder Cancer | NCT03498196 | Neoadjuvant |  |
| Evaluating Immune Therapy, Durvalumab (MEDI4736) With Tremelimumab for Metastatic, Non-transitional Cell Carcinoma of the Urinary Tract | NCT03430895 | Metastatic |  |
| Study of Durvalumab Given With Chemotherapy, Durvalumab in Combination With Tremelimumab Given With Chemotherapy, or Chemotherapy in Patients With Unresectable Urothelial Cancer | NCT03682068 | Metastatic and locally advanced |  |
| Pembrolizumab in Muscle Invasive/Metastatic Bladder Cancer | NCT02560636 | Metastatic and locally advanced |  |
| Radiation Therapy and Durvalumab, With or Without Tremelimumab, in Patients With Bladder Cancer | NCT03150836 | Metastatic and locally advanced |  |
| A Study of Two Dosing Schedules of Atezolizumab in Combination With Gemcitabine and Cisplatin as First-Line Treatment for Metastatic Bladder Cancer | NCT03093922 | Metastatic and locally advanced bladder cancer patients Eligible for cisplatin |  |
| First-line Gemcitabine/Cisplatin +/- Avelumab in Locally Advanced or Metastatic Bladder Carcinoma | NCT03324282 | Metastatic and locally advanced bladder cancer |  |
| A Phase II Study of Atezolizumab in Combination With Cisplatin + Gemcitabine Before Surgery to Remove the Bladder Cancer | NCT02989584 | Metastatic and locally advanced bladder cancer |  |
| **Other immunotherapies (checkpoint inhibitors, cellular therapies, monoclonal antibodies)** |  |  |  |
| Study Of OX40 Agonist PF-04518600 Alone And In Combination With 4-1BB Agonist PF-05082566 | NCT02315066 | Metastatic and locally advanced bladder cancer |  |
| Safety Study of MGD009 in B7-H3-expressing Tumors | NCT02628535 | Metastatic, multiple solid tumor types |  |
| A Study of Combinations of D-CIK Immunotherapy And Anti-PD-1 In Refractory Solid Tumors | NCT02886897 | Bladder Cancer, Hepatocellular carcinoma, Renal Cell carcinoma, Colorectal Cancer, NSCLC, Breast Cancer |  |
| Efficacy of Combination of Trastuzumab to Gemcitabine - Platinum Advanced or Metastatic Urothelial Carcinoma | NCT01828736 | Metastatic and locally advanced, HER2 positive | 13.3% of screened pts (75/563) were Her2+; Addition of trastuzumab to chemo not associated with PFS benefit 117 |
| Study of Gemcitabine and Cisplatin With or Without Cetuximab in Urothelial Cancer | NCT00645593 | Metastatic | Addition of cetuximab to chemotherapy not associated with PFS benefit118 |
| **VEGF/R inhibitors** |  |  |  |
| Gemcitabine Hydrochloride and Cisplatin With or Without Bevacizumab in Treating Patients With Advanced Urinary Tract Cancer | NCT00942331 | Metastatic |  |
| Randomized Study of Docetaxel +/- Vandetanib in Metastatic TCC | NCT00880334 | Metastatic, 2nd, 3rd, or 4th line | Addition of vandetanib to chemotherapy not associated with PFS benefit119 |
| Cisplatin, Gemcitabine and Bevacizumab in Combination for Metastatic Transitional Cell Cancer | NCT00234494 | Metastatic | 72% ORR (31/43)  19% (8/43) CR120 |
| Carboplatin and Gemcitabine Hydrochloride With or Without Vandetanib as First-Line Therapy in Treating Patients With Locally Advanced or Metastatic Urinary Tract Cancer | NCT01191892 | Metastatic and locally advanced |  |
| **mTOR inhibitors** |  |  |  |
| Secondary Prevention Trial of Rapamycin in Patients With Resected Non-muscle Invasive Bladder Cancer | NCT03298958 | Non muscle invasive bladder cancer |  |
| Gemcitabine Hydrochloride, Cisplatin, and Temsirolimus as First-Line Therapy in Treating Patients With Locally Advanced and/or Metastatic Transitional Cell Cancer of the Urothelium | NCT01090466 | Metastatic and locally advanced |  |
| Vaccine Therapy With or Without Sirolimus in Treating Patients With NY-ESO-1 Expressing Solid Tumors | NCT01522820 | Metastatic, other solid tumors |  |
| Trial of Gemcitabine, Carboplatin, and Sorafenib in Chemotherapy-naive Patients With Advanced/Metastatic Bladder Carcinoma | NCT00461851 | Metastatic and locally advanced | Median PFS 9.5 mos 114 |
| **FGFR inhibitors** |  |  |  |
| A Dose Escalation and Dose Expansion Study of PRN1371 in Adult Patients With Advanced Solid Tumors | NCT02608125 | Metastatic, other solid tumors |  |
| Dose Escalation Pan-FGFR (Fibroblast Growth Factor Receptor) Inhibitor (Rogaratinib) | NCT01976741 | Metastatic, other solid tumors |  |
| A Study of LY3076226 in Participants With Advanced or Metastatic Cancer | NCT02529553 | Metastatic |  |
| Dose Escalation, Expansion Study of Vofatamab (B-701) in Treatment of Locally Advanced or Metastatic Urothelial Cell Carcinoma | NCT02401542 | Metastatic and locally advanced |  |
| Phase 1B B-701 in Combination With Pembrolizumab in Metastatic Transitional Cell Carcinoma of the Urothelial Tract | NCT02925533 | Metastatic |  |
| Phase 1b/2 Study of Rogaratinib (BAY1163877) in Combination With Atezolizumab in Urothelial Carcinoma | NCT03473756 | Metastatic and locally advanced, cisplatin ineligible, FGFR positive |  |
| A Study of B-701 in Combination With Pembrolizumab in Treatment of Locally Advanced or Metastatic Urothelial Cell Carcinoma | NCT03123055 | Metastatic and locally advanced, 2nd line |  |
| **Tyrosine kinase inhibitors** |  |  |  |
| Sunitinib as Second-Line Therapy in Treating Patients With Locally Advanced or Metastatic Transitional Cell Cancer | NCT00792025 | Metastatic and locally advanced, 2nd line |  |
| Sunitinib in Treating Patients With Progressive Metastatic Transitional Cell Cancer of the Urothelium | NCT00397488 | Metastatic and locally advanced, 2nd line | 4% PR (3/71)  41% SD (29/71)114 |
| Sunitinib Malate in Treating Patients With Recurrent Transitional Cell Bladder Cancer | NCT01118351 | Non-muscle invasive (cTis, cTa, cT1), 2nd line |  |
| Activity Study of Sunitinib In Metastatic Pretreated Urothelial Cancer | NCT00818350 | Metastatic, 2nd line |  |
| Sunitinib Malate in Treating Patients With Locally Recurrent, Locally Advanced, Unresectable, or Metastatic Urinary Tract Cancer | NCT01118039 | Metastatic and locally advanced, cisplatin ineligible |  |
| Sorafenib in Treating Patients With Advanced or Metastatic Cancer of the Urinary Tract | NCT00112671 | Metastatic | 0% ORR (0/17)114 |
| Phase I Study With Sorafenib in Addition to Vinflunine in Metastatic Transitional Cell Carcinoma of the Urothelial Tract | NCT01844947 | Urothelial carcinoma anywhere in the urinary tract |  |
| Gemcitabine Hydrochloride, Cisplatin, and Sunitinib Malate as First-Line Therapy in Treating Patients With Locally Advanced And/or Metastatic Transitional Cell Carcinoma of the Urothelium (SUCCINCT) | NCT01089088 | Metastatic and locally advanced bladder cancer | 64% ORR (37/58); Median OS 12 mos121 |
| Gemcitabine, Cisplatin, and Sunitinib (GC-S) as Neoadjuvant Chemotherapy in Patients With Muscle-Invasive Bladder Cancer | NCT00847015 | Neoadjuvant | At radical cystectomy, 33% pT≤1 N0 (5/15); 6.7% pT0 N0 (1/15)114 |
| Study of the Combination of ACP-196 and Pembrolizumab in Subjects With Platinum Resistant Urothelial Bladder Cancer | NCT02351739 | Metastatic urothelial cancer |  |
| Gemcitabine and Split-dose Cisplatin (GC) Plus Sorafenib in Chemotherapy-naive Patients With Locally Advanced or Metastatic Urothelial Carcinoma | NCT00714948 | Metastatic and locally advanced |  |
| Phase II Gemcitabine + Cisplatin +/- Iressa Bladder CCT | NCT00246974 | Metastatic and locally advanced | 43% ORR (23/54); Median OS 15 mos122 |
| **HDAC inhibitors** |  |  |  |
| Phase I/Ib Study of Pembrolizumab With Vorinostat for Patients With Advanced Renal or Urothelial Cell Carcinoma | NCT02619253 | Metastatic |  |
| Bortezomib With Gemcitabine/Doxorubicin in Patients With Urothelial Cancer and Other Solid Tumors | NCT00479128 | Metastatic |  |
| Phase II Trial Of PS-341 (Bortezomib) In Patients With Previously Treated Advanced Urothelial Tract Transitional Cell Carcinoma | NCT00072150 | Metastatic | 0% ORR (0/25); Median OS 6 mos |
| Bortezomib in Treating Patients With Advanced or Metastatic Transitional Cell Cancer of the Bladder, Renal Pelvis, or Ureter | NCT00066352 | Metastatic and locally advanced | 0% ORR (0/21); Median OS 4 mos123 |
| Vorinostat in Treating Patients With Locally Recurrent or Metastatic Cancer of the Urothelium | NCT00363883 | Metastatic | Median PFS 1 month, Median OS 4 mos114 |
| Comparison of Standard of Care or Treatment on Protocol | NCT01010334 | Metastatic, other solid tumors |  |
| **TGFβ** |  |  |  |
| PF-03446962 in Relapsed or Refractory Urothelial Cancer | NCT01620970 | Metastatic, 2nd line | 0% ORR (0/14); Median OS 8 mos124 |
| **Intravesical Therapies** |  |  |  |
| Bacillus of Calmette and Guerin (BCG) Versus Gemcitabine For Intravesical Therapy In High Risk Superficial Bladder Cancer | NCT00696579 | Non-muscle invasive (cTis, cTa, cT1) | Gemcitabine: 53% recurrence rate (n=32)  BCG: 28% recurrence rate (n=32)125 |
| **Immuno-nutrition** |  |  |  |
| Influence of Immune Nutrition Diet on 90-Day Outcomes in Patients Undergoing Radical Cystectomy | NCT03147586 | Neoadjuvant |  |

**Table Abbreviations:**

PFS -- progression free survival

OS – overall survival

ORR – objective response rate

CR – complete response

PR – partial response

mos – months

chemo - chemotherapy

PD-1 – programmed cell death protein-1 (cell surface receptor, inhibitory immune checkpoint)

PD-L1- programmed death ligand-1 (cell surface ligand, inhibitory immune checkpoint)

OX40 – CD134 (cell surface receptor, stimulatory immune checkpoint)

B7-H3 – CD276 (cell surface receptor, inhibitory immune checkpoint)

mTOR – Mammalian Target of Rapamycin

FGFR – fibroblast growth receptor

5-FU – 5-Fluorouracile

BTK – Bruton’s Tyrosine Kinase

VEGF – Vascular Endothelial Growth Factor

TGFβ – Transforming Growth Factor Beta