Published in final edited form as:

Curr Opin Oncol. 2014 May ; 26(3): 305–320. doi:10.1097/CCO.0000000000000064.

Targeted therapies in urothelial carcinoma

Monalisa Ghosh^a, Sam J. Brancato^b, Piyush K. Agarwal^b, Andrea B. Apolo^a

^aGenitourinary Malignancies Branch, National Institutes of Health, Bethesda, Maryland, USA

^bUrologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Purpose of review—Greater understanding of the biology and genetics of urothelial carcinoma is helping to identify and define the role of molecules and pathways appropriate for novel-targeted therapies. Here, we review the targeted therapies that have been reported or are in ongoing urothelial carcinoma clinical trials, and highlight molecular targets characterized in preclinical and clinical studies.

Recent findings—Trials in nonmuscle-invasive bladder cancer are evaluating the role of immunotherapy and agents targeting vascular endothelial growth factor (VEGF) or fibroblast growth factor receptor-3. In muscle-invasive bladder cancer, neoadjuvant studies have focused on combining VEGF agents with chemotherapy; adjuvant studies are testing vaccines and agents targeting the human epidermal growth factor receptor 2, p53, and Hsp27. In the first-line treatment of metastatic urothelial carcinoma, tubulin, cytotoxic T-lymphocyte antigen 4, Hsp27, and p53 are novel targets in clinical trials. The majority of targeted agents studied in urothelial carcinoma are in the second-line setting; new targets include CD105, polo-like kinase-1, phosphatidylinositol 3-kinases (PI3K), transforming growth factor β receptor/activin receptor-like kinase β , estrogen receptor, and the hepatocyte growth factor receptor (HGFR or MET).

Summary—Development of targeted therapies for urothelial carcinoma is still in early stages, consequently there have been no major therapeutic advances to date. However, greater understanding of urothelial carcinoma and solid tumor biology has resulted in a proliferation of clinical trials that could lead to significant advances in treatment strategies.

Keywords

epidermal growth factor receptor family; targeted therapy; tyrosine kinase inhibitors; urothelial carcinoma; vascular endothelial growth factor

Correspondence to Andrea B. Apolo, 10 Center Dr, Rm 12N226, MSC 1906, Bethesda, MD 20892, USA. Tel: +1 301 451 1984; andrea.apolo@nih.gov.

Conflicts of interest

The authors declare no conflicts of interest.

INTRODUCTION

In the United States in 2013, there were an estimated 72500 new cases of, and 15 210 deaths from, urothelial carcinoma. Although urothelial carcinoma is considered chemotherapy-sensitive, very few patients with metastatic disease are cured. Patients with a good prognosis can expect a median survival of 12–14 months [1]. Approximately 70–80% of urothelial carcinoma is nonmuscle-invasive bladder cancer (NMIBC); the remaining 20–30% is muscle-invasive bladder cancer (MIBC) or metastatic. Almost 70% of patients with NMIBC will have disease recurrence within 2 years of diagnosis. Chemotherapy regimens for MIBC and first-line metastatic urothelial carcinoma contain cisplatin, including methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), dose-dense MVAC, and gemcitabine and cisplatin. However, there is currently no standard second-line therapy for urothelial carcinoma [2,3,4]. Several trials evaluating single chemotherapy agents, such as docetaxel, pemetrexed, gemcitabine, and paclitaxel have shown response rates of 9–27%, with 2–3-month progression-free survival (PFS) and no improvement in overall survival (OS). Multidrug regimens have shown higher response rates, but no OS benefit [5–9].

A better understanding of the tumor biology and molecular patterns of urothelial carcinoma has led to clinical trials of several targeted therapies, including agents targeting angiogenesis, epidermal growth factor receptor (EGFR), and immunomodulatory agents. Research in immunotherapy and vaccines for urothelial carcinoma is in very early stages. Multiple tumor-associated antigens for vaccine targeting have been identified, but data on these agents are limited to safety, as their efficacy has not been demonstrated. Still, many targeted agents have been studied in all stages of urothelial carcinoma and many more are in ongoing clinical trials (Table 1).

TARGETED AGENTS IN NONMUSCLE-INVASIVE BLADDER CANCER

The current standard of care for patients with newly diagnosed high-grade NMIBC is transurethral resection, followed by intravesical Bacillus Calmette-Guerin (BCG) over 6 weeks, followed by maintenance therapy. BCG has an initial failure rate of approximately 35% in terms of disease recurrence or progression. For the 20–35% of patients who fail an initial induction of BCG, a second 6-week cycle of BCG may be beneficial. However, patients who fail two courses often proceed to radical cystectomy [10,11]. The majority of targeted therapies for NMIBC have been studied in patients who have failed intravesical BCG therapy.

Reported studies of targeted agents in nonmuscle-invasive bladder cancer

Several clinical trials using targeted therapy in NMIBC have been reported (Table 2a) [12,13,14,15]. Two were phase I dose-escalation studies using intravesical oportuzumab monatox [13] and TMX-101 [14]. Preliminary results from these trials show that the drugs are well tolerated, with no grade III–V adverse events. One phase II study was in patients who had failed BCG treatment and who were then treated with intravesical oportuzumab monatox targeting epithelial cell adhesion (EpCAM) [15]. A complete response was seen in 20 patients (44%) at the 3-month evaluation. In another phase II trial evaluating the use of intravesical apaziquone in the setting of intermediate-risk and high-risk

NMIBC, the observed recurrence rate at 1 year was 34.7% [12]. The clinical impact of these early-phase trials will require further investigation.

Ongoing studies of targeted agents in nonmuscle-invasive bladder cancer

Targeted agents being studied in high-grade NMIBC include sunitinib (VEGFR-1,2 inhibitor), lenalido-mide (immunomodulatory, antiangiogenic, and cytotoxic), recombinant melanoma-associated antigen (recMAGE)-A3 + AS-15 (vaccine MAGE), and rituximab (CD20 antibody) in combination with intravesical BCG (Table 2b) [16–29]. TMX-101 (toll-like receptor 7 agonist) is also being evaluated as a first-line intravesical therapy in patients with NMIBC with carcinoma *in situ*. Two clinical trials are evaluating apaziquone (cytotoxic) and DTA-H19/PEI (H19 transcription factor) in low-risk and intermediate-risk NMIBC, respectively. A phase 0 study is analyzing the use of valproic acid in the 4 weeks between tumor resection and initiation of intravesical therapy. Four ongoing trials in BCG-refractory patients are assessing ALT-801 (Altor Bioscience) [interleukin 2 (IL-2)/T-cell receptor fusion protein that targets p53] combined with intravesical gemcitabine, everolimus [mammalian target of rapamycin (mTOR) inhibitor] in combination with intravesical gemcitabine, recombinant adenovirus mediated interferon (antiangiogenic and immunomodulatory), and dovitinib [fibroblast growth factor receptor 3 (FGFR-3) inhibitor] in tumors positive for FGFR-3 mutation or overexpression. HS-410 (Heat Biologics) is a clone of live urothelial carcinoma cells from a single tumor source that continuously secretes gp96, a chaperone protein. In turn, gp96 chaperones tumor antigens to T cells designed to induce a pan-tumor antigen immune response mediated by T cells. This is now being evaluated in a phase I/II study. The National Cancer Institute has initiated a study with an induction course of intravesical BCG in combination with a ‘priming vaccine’ called PANVAC [PAN (all) VAC (vaccine)], a subcutaneous immunomodulatory vaccine, in patients who have failed prior BCG therapy. PANVAC is a poxviral cancer vaccine that has demonstrated therapeutic efficacy against a variety of carcinomas. PANVAC consists of a primary vaccination with a replication-competent recombinant vacciniavector, followed by multiple boosts with a replication-incompetent recombinant fowlpox (rF) vector. These vectors contain transgenes for both human T-cell costimulatory molecules and tumor-associated antigens against mucin 1 (MUC-1) [30,31] and (carcinoembryonic antigen) CEA [32]. MUC-1 and CEA are expressed in approximately 93 and 76% of high-grade bladder tumors, respectively.

TARGETED AGENTS IN MUSCLE-INVASIVE BLADDER CANCER

The primary therapy for MIBC is radical cystectomy and lymph node dissection. In randomized phase III trials, cisplatin-based neoadjuvant chemotherapy has demonstrated a survival benefit [33–35] over cystectomy alone [36,37] by increasing the rate at which MIBC tumors (stage T2–T4a) are downstaged to NMIBC tumors (< T2). Several targeted agents for MIBC have been reported and are currently under investigation (Table 3). Trials in the neoadjuvant setting have focused on combining VEGF agents with cisplatin-based chemotherapy. The data for adjuvant chemotherapy in MIBC are less compelling than for neoadjuvant chemotherapy, and there are limited data in the setting of persistent disease after cisplatin-based neoadjuvant chemotherapy, making the adjuvant setting ideal for novel-

targeted agents. Ongoing or planned adjuvant studies are testing several vaccines and agents targeting human epidermal growth factor receptor 2 (HER2), p53, and Hsp27.

Reported studies of targeted agents in muscle-invasive bladder cancer

Several clinical trials of targeted agents in MIBC have been reported (Table 3a and 3b) [38–43]. Two studies have used tyrosine kinase inhibitors (TKIs) as monotherapy in the neoadjuvant setting. Studies of erlotinib, which targets EGFR [44], and dasatinib, which targets breakpoint cluster region/abelson murine leukemia [45], reported pathologic response rates (RRs) to less than pT2 of 35 and 14%, respectively. Two studies used bevacizumab (VEGF inhibitor and monoclonal antibody) with chemotherapy. One of those studies used dose-dense MVAC and reported a pathologic RR (< pT2) of 53% [38]. Two studies used sunitinib with chemotherapy in the neoadjuvant setting. One study was stopped early due to excess toxicity. The second study did not report excess toxicity, although cisplatin was split between days 1 and 8. Nevertheless, this study was stopped early as well due to lack of interest from the sponsoring drug company [46].

Ongoing studies of targeted agents in muscle-invasive bladder cancer

The neoadjuvant setting is ideal for studying targeted therapy, as tissue can be analyzed for changes in protein expression and tumor morphology before and after treatment. Vaccine immunotherapy is a promising therapeutic approach for patients with MIBC, especially in the adjuvant setting wherein patients are at high risk of recurrence and have limited therapeutic choices after neoadjuvant chemotherapy. Agents being studied in the neoadjuvant and adjuvant settings are described in Table 3c and 3d [47,48,49■,50–59].

TARGETED AGENTS IN METASTATIC UROTHELIAL CARCINOMA

Although first-line treatment of metastatic urothelial carcinoma with cisplatin-based chemotherapy may have RRs as high as 70%, duration of response is short (median PFS is about 7 months) [60], highlighting the urgent need to improve treatment options in this setting. Multiple targeted agents used alone or in combination with chemotherapy have been studied in the first-line setting (Table 4a and 4b) [39,45,61,62■,63–69]. Cumulative toxicities in a patient population that is frail at baseline have limited the success of first-line combination studies with targeted agents, particularly TKIs. Nevertheless, there are many ongoing trials of targeted agents as first-line therapy with chemotherapy in metastatic bladder cancer for cisplatin eligible (Table 4c) [70–87] and cisplatin ineligible (Table 4d). In the second-line setting, vinflunine, a microtubule-inhibiting vinca alkaloid, has been extensively investigated and was approved as a second-line therapy by the European Medicines Agency based on a modest survival benefit compared with best supportive care (6.9 vs. 4.3 months, $P=0.04$) [88]. In the United States, where the majority of targeted agents are studied (Table 5), there is no approved second-line therapy for metastatic urothelial carcinoma.

Reported studies of targeted agents as first-line therapy in metastatic urothelial carcinoma

From 2007 to 2013, eight trials were reported using targeted agents in combination with chemotherapy for first-line treatment of metastatic urothelial carcinoma (Table 4a). The

agents studied included antiangiogenic agents (bevacizumab, sunitinib, and sorafenib) and EGFR-targeted agents (trastuzumab, gefitinib, and cetuximab). The addition of targeted agents to standard platinum-based regimens (with the exception of bevacizumab) has not demonstrated an improvement in OS compared with historical data. Three trials of targeted single agents as first-line treatment of metastatic urothelial carcinoma have been reported since 2010 (Table 4b). Single-agent sunitinib in cisplatin-ineligible patients and single-agent sorafenib had less than 10% RRs in the first-line setting [89,90]. Single-agent eribulin (microtubule inhibitor) reported a RR of 38% in the first-line setting [61].

Reported and ongoing studies of targeted agents as second-line therapy in metastatic urothelial carcinoma

Patients who progress after platinum-based combination therapy have urothelial carcinoma tumors that are often resistant to other available therapies. In these patients, tumor shrinkage with targeted single agents has been low in reported studies with the majority of RR of less than 10% (Table 5b) [89–105]. Similarly, the combination of targeted agents with chemotherapy has not shown significant improved RRs in this setting (Table 5a) [91–93]. A randomized phase II study of docetaxel and vandetanib (EGFR, VEGFR, and RET-TKI) compared with docetaxel alone did not show significant improvement in PFS, RR, or OS. Among 37 patients who crossed over to single-agent vandetanib, the overall RR was 3% [91]. A randomized phase II study of cetuximab (EGFR inhibitor) alone or in combination with paclitaxel reported a RR of 0% for cetuximab alone and 25% for the combination [92]. Even with the low activity of targeted agents reported in the second-line setting, the number of ongoing studies continues to rapidly grow (Table 5c and 5d) [53,106–118].

ANGIOGENESIS INHIBITION IN UROTHELIAL CARCINOMA

VEGF, one of the most important factors in angiogenesis, is increased in the tumor tissue, serum, and urine of patients with urothelial carcinoma and correlates with tumor stage and survival [9,119–121]. Higher levels of VEGF in the tumors and serum of patients with urothelial carcinoma correlate with worse prognosis and higher likelihood of disease recurrence. Angiogenesis inhibitors have been shown *in vitro* to be active in urothelial carcinoma cells. VEGF signaling occurs through binding of its receptors VEGFR1 (fms-like tyrosine kinase-1) and VEGFR2 (fetal liver kinase-1). In a preclinical study, six of 13 urothelial carcinoma cell lines examined expressed VEGFR2. Further analysis of the T24 urothelial carcinoma cell line revealed a functional autocrine loop involving VEGF and VEGFR2 [122]. One study revealed that VEGF and VEGFR1 expression was higher in NMIBC compared with MIBC specimens ($P < 0.001$), possibly due to a higher rate of cell growth in early stages of disease, whereas VEGFR2 was significantly higher in MIBC, as compared with NMIBC ($P < 0.001$) [123]. VEGFR inhibition has been shown to decrease proliferation and invasion of urothelial carcinoma cells, leading to the investigation of VEGF-targeted agents in urothelial carcinoma.

Bevacizumab in urothelial carcinoma

Phase II trials of bevacizumab in combination with chemotherapy have shown promising results in urothelial carcinoma compared with historical data. A phase II study of first-line

gemcitabine, cisplatin, and bevacizumab showed a RR of 72% and an OS of 19.1 months in metastatic urothelial carcinoma [45]. Another phase II study of first-line gemcitabine, carboplatin, and bevacizumab in cisplatin-ineligible patients with metastatic urothelial carcinoma showed a RR of 49% and an OS of 13.9 months [62]. This study compared survival in patients who received bevacizumab with gemcitabine and carboplatin to a contemporary control population that received gemcitabine and carboplatin alone during the same time the study was conducted. The study group that received bevacizumab had an OS of 13.9 vs. 10.3 months in the contemporary population that did not receive bevacizumab. A third phase II study of neoadjuvant dose-dense MVAC and bevacizumab in MIBC had a pathologic RR of 53% [38], which is higher than the pathologic RR reported with neoadjuvant MVAC. An ongoing study in MIBC of neoadjuvant gemcitabine and cisplatin with bevacizumab followed by adjuvant paclitaxel with bevacizumab has completed accrual [52]. An ongoing Cancer And Leukemia Group B/Alliance phase III study of first-line gemcitabine and cisplatin with or without bevacizumab in patients with meta-static urothelial carcinoma is nearing its anticipated accrual of 500 patients.

Sunitinib in urothelial carcinoma

Sunitinib, an oral multiple-receptor TKI approved for use in many types of solid tumors, was one of the first targeted agents to be studied in advanced urothelial carcinoma. Sunitinib targets VEGF receptors, stem cell factor receptor (KIT), platelet-derived growth factor receptor, RET, Fms-like tyrosine kinase 3, and colony-stimulating factor 1 receptor. It has been shown to be active against urothelial carcinoma cells *in vitro* and *in vivo* [124,125]. A phase II second-line study of 77 patients with urothelial carcinoma showed radiographic tumor regression and a clinical benefit (partial response and stable disease) of 43% with sunitinib [89]. However, subsequent studies of sunitinib, including a first-line combination study, two neoadjuvant combinations studies [39], and a maintenance study [46], showed low responses and high toxicity with combined sunitinib and chemotherapy. There is an ongoing study of sunitinib administered with BCG in high-grade NMIBC, but no ongoing studies in MIBC or metastatic urothelial carcinoma. However, there are multiple ongoing studies with other VEGF TKIs, including sorafenib, pazopanib, and cabozantinib in urothelial carcinoma.

Epidermal growth factor receptor/human epidermal growth factor receptor 2 in urothelial carcinoma

EGFR plays a significant role in mediating angiogenesis by regulating the activity of IL-8, VEGF, and basic fibroblast growth factor. Overexpression of EGFR leads to activation of the Ras signaling cascade, which leads to cell proliferation. Similar to VEGFR, EGFR is overexpressed in urothelial carcinoma and correlates with tumor stage, grade, prognosis, and survival [126]. Gefitinib, a selective EGFR inhibitor, was approved by the US Food and Drug Administration (FDA) for use in nonsmall cell lung cancer in 2003. Gefitinib has the potential to be effective in other solid tumors with increased EGFR expression, such as urothelial carcinoma. However, a phase II trial of gefitinib added to standard first-line gemcitabine and cisplatin showed no improvement in OS [127]. Gefitinib and lapatinib (dual TKI-targeting HER2/neu and EGFR) have been tested as single agents in the second-line

treatment of metastatic urothelial carcinoma, and both agents demonstrated RRs of less than 5% [97,98].

HER2/neu is the most studied of the four receptors in the EGFR family. HER2/neu regulates multiple processes, including cell proliferation. HER2/neu⁺ urothelial carcinoma patients have more advanced disease and more sites of metastasis [63]. HER2/neu⁺ patients with MIBC have a lower median OS than HER2/neu⁻ patients (33 vs. 50 months, respectively). However, results have been mixed, as a different study found that overexpression of HER2/neu in the primary tumor or any metastatic tumors was not predictive of survival [128]. A phase II study of trastuzumab (HER2/neu receptor-targeted monoclonal antibody), paclitaxel, carboplatin, and gemcitabine in HER2⁺ urothelial carcinoma showed an OS of 14.1 months [63]. Trastuzumab is being evaluated in combination with paclitaxel and radiotherapy for bladder conservation. Multiple ongoing trials are testing the HER2 axis in metastatic urothelial carcinoma, including a study of first-line lapatinib in combination with gemcitabine and cisplatin [70], a randomized phase II/III trial of second-line, single-agent lapatinib [106], a combination study of second-line lapatinib and docetaxel [107], and a vaccine study in HER2⁺ urothelial carcinoma [53].

NOVEL PATHWAYS AND AGENTS BEING STUDIED IN UROTHELIAL CARCINOMA

Multiple novel pathways and molecules that could potentially be targeted in urothelial carcinoma are being explored in preclinical and clinical studies; some of these include multiple receptor tyrosine kinases, MET, phosphatidylinositol 3-kinases (PI3K), heat shock proteins (HSPs), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and prostate stem cell antigen (PSCA).

Cabozantinib in urothelial carcinoma

Cabozantinib, an oral agent that primarily targets MET and VEGFR2, has been shown to prevent angiogenesis and invasive growth by inhibiting hepato-cyte growth factor (HGF)-induced MET signaling in urothelial carcinoma cell lines. MET, a proto-oncogene that encodes for the HGF receptor [129], is usually expressed by cells of epithelial origin. Activation of the MET receptor by HGF leads to down-stream activation of multiple cytokines involved in motility, matrix remodeling, angiogenesis, survival, and proliferation leading to invasive growth of cancer cells [130]. Soluble urinary MET levels are elevated in urothelial carcinoma and correlate with disease stage. Plasma HGF levels are frequently elevated in advanced urologic malignancies [131].

Urothelial carcinoma cell lines respond to HGF stimulation with increased activation of established intracellular signaling mediators [132]. HGF stimulation also increases invasion, growth rate, and anchorage-independent growth [133]. Cabozantinib reverses these HGF-driven activities and has shown activity in multiple solid tumors in phase I, II, and III clinical trials [134,135]. The efficacy of cabozantinib in advanced urothelial carcinoma is being studied for the first time in an ongoing phase II trial [136], wherein patients receive cabozantinib (60 mg/day) continuously in 28-day cycles. The study has three cohorts:

metastatic urothelial carcinoma with measurable disease, bone-only metastatic urothelial carcinoma, and metastatic rare histology of the bladder, urethra, ureter, or renal pelvis.

Buparlisib (BKM120) in advanced urothelial carcinoma

PI3Ks are enzymes involved in regulating multiple cellular functions, including growth, proliferation, motility, and differentiation. PI3K mutations are found in urothelial carcinoma, and this pathway is a potential therapeutic target. BKM120, a PI3K inhibitor, has shown activity in multiple solid tumors [137,138] and is currently undergoing phase III testing in breast cancer. There is also an ongoing phase II study of BKM120 in urothelial carcinoma [108], with the primary objective of PFS.

Apatorsen (OGX-427) in metastatic urothelial carcinoma

HSPs regulate the folding and unfolding of other proteins and are induced by exposure to elevated temperature or stress. OGX-427, an inhibitor of HSP27, inhibits apoptosis via cell death and proteo-toxic stress pathways [47]. Ongoing studies include a multicenter randomized phase II trial [71] of first-line OGX-427 and gemcitabine and cisplatin vs. placebo in advanced urothelial carcinoma, and a multicenter randomized phase II study of second-line OGX-427 and docetaxel vs. docetaxel alone [139].

Ipilimumab in metastatic urothelial carcinoma

Ipilimumab is an inhibitor of CTLA-4, a protein receptor on the surface of T cells that regulates T-cell activity by transmitting inhibitory signals. CD28, a costimulatory protein expressed on T cells, transmits stimulatory signals to T cells. Activation of T-cell receptors via CD28 leads to increased CTLA-4 expression. Ipilimumab interrupts the inhibitory process that prevents cytotoxic T lymphocytes from destroying tumor cells. By interrupting the inhibition of T cells mediated by CTLA-4, cytotoxic T lymphocytes are able to recognize and destroy tumor cells [72]. A multicenter phase II trial of ipilimumab with gemcitabine and cisplatin [140] is ongoing in patients with metastatic urothelial carcinoma. In this trial, patients with stable or responding disease continue ipilimumab maintenance therapy after completing six cycles of chemotherapy. There are also several ongoing checkpoint inhibitor phase I studies with bladder cancer expansion cohorts. These studies will help assess the activity of immune checkpoint blockade in metastatic urothelial carcinoma.

Prostate stem cell antigen as a therapeutic target in urothelial carcinoma

PSCA is a novel therapeutic target for urothelial carcinoma in carriers of the rs2294008-T allele [141]. A genetic variant (rs2294008) discovered by urothelial carcinoma genome-wide association studies is a strong predictor of PSCA protein expression in bladder tumors [142[■]]. Carriers of the T allele have been shown to be at higher risk of urothelial carcinoma [143], and urothelial carcinoma patients with the T allele have higher expression of PSCA mRNA and protein in tumors. The T allele predicts PSCA expression in tumors of all stages and tumor grades. Therefore, PSCA may be a promising therapeutic target, and genetic testing may be useful in selecting patients for treatment. An anti-PSCA monoclonal antibody is currently being tested in clinical trials [144,145].

THE FUTURE OF TARGETED THERAPIES FOR ADVANCED UROTHELIAL CARCINOMA

Targeted therapies currently being studied in advanced urothelial carcinoma have shown efficacy in other solid tumors. Cancer therapy continues to transition from cytotoxic to targeted therapies. There is a lot of genetic diversity and heterogeneity within tumor types, consequently, specific subsets of patients may have a greater benefit from targeted therapies. In addition, tumor cells can adapt to targeted therapies by developing resistance, usually through mutations in target enzymes and cell-death pathways, or by developing new methods of drug efflux. Therefore, researchers are developing even more selective targets, identified in individual tumors through genomic analysis.

The Bladder Cancer Analysis Working Group of The Cancer Genome Atlas (TCGA) analyzed 131 samples of MIBC and identified 32 significantly mutated genes, the most common of which were *P53* (49%), *MLL2* (27%), *ARID1A* (25%), *KDM6A* (24%), and *PIK3CA* (20%). The majority (69%) of tumors were found to harbor potential therapeutic targets with a mean and median somatic mutation rate per tumor of 7.7 and 5.5 per megabase, respectively. The analysis also showed that mutations in chromatin-modifying genes were enriched, and that the chromatin-modifying genes *MLL2*, *ARID1A*, and *KDM6A* were inactivated at high frequency in uro-thelial carcinoma. Significantly, *ERBB2* (Her-2/neu) was mutated or amplified in 9% of samples, suggesting a possible role for *ERBB2* as a therapeutic target in bladder cancer using similar treatment strategies that target *ERBB2* amplified breast cancers [146■].

Genomic sequencing studies may also be useful in the clinical setting by revealing new potential drug targets as well as mutations that may predict responsiveness to specific targeted therapies. A study that analyzed 97 high-grade bladder tumors identified several genomic alterations in molecular pathways that could be potential drug targets. In this study, 61% of the tumors analyzed had potential actionable drug targets due to mutations in the RTK-RAS-RAF and PI3K/AKT/mTOR pathways. Tumors with high burden of DNA copy number alterations were found to have more mutations in TP53 and RB1 [147■]. Another study analyzed 13 bladder cancer patients treated with everolimus, a mTOR-targeted agent. *TSC1* (tuberous sclerosis complex 1), which codes for TSC1 protein, a regulator of mTOR signaling, has been shown to be mutated in some bladder cancers [148]. In this study, two of three patients with nonsense mutations in *TSC1* gene had some degree of response to everolimus, one patient with missense mutation in *TSC1*, which is of unknown functional significance, had some tumor response to everolimus, and eight of nine patients with progressive disease were *TSC1* wild-type [149■].

The data obtained from these studies can help target therapies more specifically to tumors based on a large panel of mutational analysis and possibly predict responsiveness to targeted therapies based on the presence of specific mutations - a possible future direction for targeted therapy for urothelial carcinoma.

CONCLUSION

Targeting molecular aberrations has revolutionized the clinical management of multiple cancers. Significant progress has been made in the last few years in testing targeted agents in all stages of urothelial carcinoma, from NMIBC to advanced refractory metastatic urothelial carcinoma. However, clinical trial results of targeted therapies in urothelial carcinoma in unselected patient populations have been negative so far. Therefore, there have been no reported phase III studies nor FDA-approved targeted therapeutic agents for use in urothelial carcinoma. The focus of treatment for NMIBC in ongoing clinical trials is enhancing antitumor immunity with immunotherapeutic agents alone or with concurrent intravesical BCG therapy. Combination trials of TKIs and cytotoxic chemotherapy in MIBC and first-line metastatic urothelial carcinoma have reported significant toxicities. However, targeting angiogenesis via either the VEGF or mTOR pathways has demonstrated activity in a small number of urothelial carcinoma patients [148]. Studies of genomic alterations confirm that urothelial carcinoma is a heterogeneous disease driven by a large array of somatic mutations that may predict responsiveness to specific targeted therapies. In the future, improved understanding of the biology and genetics of urothelial carcinoma may lead to personalized therapies for specific molecular targets that will improve therapeutic outcomes.

Acknowledgements

The authors thank Bonnie L. Casey for editorial assistance in the production of this article.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ ■ of outstanding interest

1. Surveillance, Epidemiology, and End Results Program. [Accessed on 4 January 2014] <http://seer.cancer.gov/>.
2. Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. *J Clin Oncol* 2006; 24:5545–5551. [PubMed: 17158540]
3. Ortmann CA, Mazhar D. Second-line systemic therapy for metastatic urothelial carcinoma of the bladder. *Future Oncol* 2013; 9:1637–1651. [PubMed: 24156324] ■ This overview of the results of various studies of second-line systemic therapy in urothelial carcinoma is a good source of comparison for current studies of second-line-targeted agents.
4. Pectasides D, Pectasides M, Economopoulos T. Systemic chemotherapy in locally advanced and/or metastatic bladder cancer. *Cancer Treat Rev* 2006; 32:456–470.
5. Edeline J, Loriot Y, Culine S, et al. Accelerated MVAC chemotherapy in patients with advanced bladder cancer previously treated with a platinum-gemcitabine regimen. *Eur J Cancer* 2012; 48:1141–1146. [PubMed: 22364733]
6. Kaya AO, Coskun U, Ozkan M, et al. Paclitaxel plus doxorubicin chemotherapy as second-line therapy in patients with advanced urothelial carcinoma pretreated with platinum plus gemcitabine chemotherapy. *Onkologie* 2012; 35:576–580. [PubMed: 23038228]
7. Albers P, Park SI, Niegisch G, et al. Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged

- treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. *Ann Oncol* 2011; 22:288–294. [PubMed: 20682548]
8. Kouno T, Ando M, Yonemori K, et al. Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. *Eur Urol* 2007; 52:1115–1122. [PubMed: 17433855]
 9. Black PC, Agarwal PK, Dinney CP Targeted therapies in bladder cancer: an update. *Urol Oncol* 2007; 25:433–438. [PubMed: 17826665]
 10. Di Lorenzo G, Perdona S, Damiano R, et al. Gemcitabine versus bacille Calmette-Guerin after initial bacille Calmette-Guerin failure in nonmuscle-invasive bladder cancer: a multicenter prospective randomized trial. *Cancer* 2010; 116:1893–1900. [PubMed: 20162706]
 11. O'Donnell MA, Boehle A. Treatment options for BCG failures. *World J Urol* 2006; 24:481–487. [PubMed: 17021823]
 12. Hendricksen K, Cornel EB, de Reijke TM, et al. Phase 2 study of adjuvant intravesical instillations of apaziquone for high risk nonmuscle invasive bladder cancer. *J Urol* 2012; 187:1195–1199. [PubMed: 22335860]
 13. Kowalski M, Guindon J, Brazas L, et al. A phase II study of oportuzumab monatox: an immunotoxin therapy for patients with noninvasive urothelial carcinoma in situ previously treated with bacillus Calmette-Guerin. *J Urol* 2012; 188:1712–1718. [PubMed: 22998907]
 14. Falke J, Lammers RJ, Arentsen HC, et al. Results of a phase I dose escalation study of intravesical TMX-101 in patients with nonmuscle invasive bladder cancer. *J Urol* 2013; 189:2077–2082. [PubMed: 23206424] ■■■ This study of the novel and promising agent TMX-101, which is administered intravesically, is one of only three reported studies of targeted agents in NMIBC with good response and tolerability.
 15. Kowalski M, Entwistle J, Cizeau J, et al. A Phase I study of an intravesically administered immunotoxin targeting EpCAM for the treatment of nonmuscle-invasive bladder cancer in BCG-refractory and BCG-intolerant patients. *Drug Des Devel Ther* 2010; 4:313–320.
 16. Fishman MN, Thompson JA, Pennock GK, et al. Phase I trial of ALT-801, an interleukin-2/T-cell receptor fusion protein targeting p53 (aa264–272)/HLA-A*0201 complex, in patients with advanced malignancies. *Clin Cancer Res* 2011; 17:7765–7775. [PubMed: 21994418]
 17. Phase 2b, Trial of Intravesical DTA-H19/PEI in Patients With Intermediate-Risk Superficial Bladder Cancer. [Accessed on 4 January 2014]; <http://clinicaltrials.gov/ct2/show/NCT00595088>.
 18. Bacillus Calmette-Guerin Followed by Sunitinib for the Treatment of High Risk Non-muscle Invasive Lower Urinary Tract Urothelial Carcinoma (Sutent). [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT00794950>.
 19. RAD001 and Intravesical Gemcitabine in BCG-Refractory Primary or Secondary Carcinoma In Situ of the Bladder. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01259063>.
 20. Oral Lenalidomide and Intravesical BCG for Therapy of Bladder Cancer. [Accessed 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01373294>.
 21. Efficacy and Safety Study of Apaziquone vs. Placebo in Patients With Non-Muscle Invasive Bladder Cancer (NMIBC). [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01469221>.
 22. Intravesical Administration of INSTILADRIN (rAd-IFN With Syn3) in Patients With Bladder Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01687244>.
 23. A Study of ALT-801 in Patients With Bacillus Calmette-Guerin (BCG) Failure Non-Muscle Invasive Bladder Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01625260>.
 24. BCG Modulation of the recMAGE-A3 + AS15 ASCI Response in the Treatment of Non Muscle Invasive Bladder Cancer (NMIBC) Patients. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01498172>.
 25. Impact of Valproate on Angiogenesis and Histone Deacetylation in Bladder Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01738815>.
 26. Study With TMX-101 in Patients With Carcinoma In Situ (CIS) Bladder Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01731652>.

27. Dovitinib in BCG Refractory Urothelial Carcinoma With FGFR3 Mutations or Over-Expression. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01732107>.
28. A Phase 1/2 Study of HS-410 in Patients With High-Risk Non-Muscle Invasive Bladder Cancer After TURBT and BCG. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT02010203>.
29. Study of Bacillus Calmette-Guerin (BCG) Combined With PANVAC Versus BCG Alone in Adults With High Grade Non-Muscle Invasive Bladder Cancer Who Failed At Least 1 Course of BCG. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT02015104>.
30. Walsh MD, Hohn BG, Thong W, et al. Mucin expression by transitional cell carcinomas of the bladder. *Br J Urol* 1994; 73:256–262. [PubMed: 8162502]
31. Cardillo MR, Castagna G, Memeo L, et al. Epidermal growth factor receptor, MUC-1 and MUC-2 in bladder cancer. *J Exp Clin Cancer Res* 2000; 19:225–233. [PubMed: 10965823]
32. Goldenberg DM, Sharkey RM, Primus FJ Immunocytochemical detection of carcinoembryonic antigen in conventional histopathology specimens. *Cancer* 1978; 42:1546–1553. [PubMed: 361204]
33. 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. [PubMed: 12944571]
34. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet* 1999; 354:533–540. [PubMed: 10470696]
35. Griffiths G, Hall R, Sylvester R, et al. 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. [PubMed: 21502557]
36. Splinter TA, Scher HI, Denis L, et al. The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. European Organization for Research on Treatment of Cancer: Genitourinary Group. *J Urol* 1992; 147:606–608. [PubMed: 1538438]
37. Schultz PK, Herr HW, Zhang ZF, et al. Neoadjuvant chemotherapy for invasive bladder cancer: prognostic factors for survival of patients treated with M-VAC with 5-year follow-up. *J Clin Oncol* 1994; 12:1394–1401. [PubMed: 8021730]
38. Siefker-Radtke A, Kamat A, Corn PG, et al. Neoadjuvant chemotherapy with DD-MVAC and bevacizumab in high-risk urothelial cancer: results from a phase II trial at the M. D Anderson Cancer Center. *J Clin Oncol* 2012; 30 (Suppl 5); abstr 261.
39. Galsky MD, Hahn NM, Powles T, et al. Gemcitabine, cisplatin, and sunitinib for metastatic urothelial carcinoma and as preoperative therapy for muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2013; 11:175–181. [PubMed: 23228446]
40. Chaudhary UB, Golshayan AR, Brisendine AS, et al. Phase II trial of neoadjuvant cisplatin, gemcitabine, and bevacizumab followed by radical cystectomy (RC) in patients with muscle-invasive transitional cell carcinoma (TCC) of the bladder. *J Clin Oncol* 2011; 29 (Suppl 7); abstr 276.
41. Balar AV, Iyer G, Apolo AB, et al. Phase II trial of neoadjuvant gemcitabine (G) and cisplatin (C) with sunitinib in patients (pts) with muscle-invasive bladder cancer (MIBC). *J Clin Oncol* 2012; (Suppl); abstr 4581.
42. Pruthi RS, Nielsen M, Heathcote S, et al. A phase II trial of neoadjuvant erlotinib in patients with muscle-invasive bladder cancer undergoing radical cystectomy: clinical and pathological results. *BJU International* 2010; 106:349–354. [PubMed: 20089114]
43. Hahn NM, Daneshmand S, Posadas EM, et al. A phase II trial of neoadjuvant dasatinib (Neo-D) in muscle-invasive urothelial carcinoma of the bladder (miUCB): Hoosier Oncology Group GU07–122 trial. *J Clin Oncol* 2012; (Suppl); abstr 4586.
44. Pruthi RS, Nielsen M, Heathcote S, et al. A phase II trial of neoadjuvant erlotinib in patients with muscle-invasive bladder cancer undergoing radical cystectomy: clinical and pathological results. *BJU Int* 2010; 106:349–354. [PubMed: 20089114]

45. Hahn NM, Stadler WM, Zon RT, et al. Phase II trial of cisplatin, gemcitabine, and bevacizumab as first-line therapy for metastatic urothelial carcinoma: Hoosier Oncology Group GU 04–75. *J Clin Oncol* 2011; 29:1525–1530. [PubMed: 21422406]
46. Grivas P, Nanus DM, Stadler WM, et al. Randomized phase II trial of maintenance sunitinib versus placebo following response to chemotherapy (CT) for patients (pts) with advanced urothelial carcinoma (UC). *J Clin Oncol* 2012; 30 (Suppl 5); abstr 265.
47. Rexer H [First line therapy for local advanced or metastasized urothelial carcinoma: randomized double-blind phase II study to compare gemcitabin and cisplatin in combination with OGX-427 or placebo for advanced transitional cell carcinoma of the bladder (OGX-427 - AB 39/11 of the Working Group Urological Oncology)]. *Urologe A* 2011; 50:1617–1618. [PubMed: 22159705]
48. Morse MA, Bradley DA, Keler T, et al. CDX-1307: a novel vaccine under study as treatment for muscle-invasive bladder cancer. *Expert Rev Vaccines* 2011; 10:733–742. [PubMed: 21692696]
49. Disis ML, Dang Y, Coveler AL, et al. HER-2/neu vaccine-primed autologous T-cell infusions for the treatment of advanced stage HER-2/neu expressing cancers. *Cancer Immunol Immunother* 2013; 63:101–109. [PubMed: 24162107] ■ HER-2/neu expression in urothelial carcinoma offers another promising pathway to target, especially given the evolution of immunotherapy for solid tumors.
50. Marin AP, Arranz EE, Sanchez AR, et al. Role of anti-Her-2 therapy in bladder carcinoma. *J Cancer Res Clin Oncol* 2010; 136:1915–1920. [PubMed: 20213094]
51. Ulloa-Montoya F, Louahed J, Dizier B, et al. Predictive gene signature in MAGE-A3 antigen-specific cancer immunotherapy. *J Clin Oncol* 2013; 31:2388–2395. [PubMed: 23715562]
52. Cisplatin, Bevacizumab, and Gemcitabine Followed by Surgery, Bevacizu-mab, and Paclitaxel in Treating Patients With Locally Advanced Nonmetastatic Bladder Cancer That Can Be Removed By Surgery. [Accessed 4 January 2014] <http://clinicaltrials.gov/show/NCT00268450>.
53. Ad/HER2/Neu Dendritic Cell Cancer Vaccine Testing. [Accessed 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01730118?term=NCT01730118&rank=1>.
54. Paclitaxel and Radiation Therapy With or Without Trastuzumab in Treating Patients Who Have Undergone Surgery for Bladder Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT00238420>.
55. A Study of the CDX-1307 Vaccine Regimen in Patients With Newly Diagnosed Muscle-Invasive Bladder Cancer (The “N-ABLE” Study). [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01094496>.
56. A Study of ALT-801 in Combination With Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01326871>.
57. A Study for Treatment of Superficial Bladder Cancer Using OGX-427. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT00959868>.
58. DN24–02 asAdjuvantTherapy in Subjects With High RiskHER2+ Urothelial Carcinoma. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01353222>.
59. Clinical Study to Evaluate the Safety and Efficacy of recMAGE-A3 + AS-15 in Patients From Which the Bladder is Removed Due to Muscle Invasive Bladder Cancer (MAGNOLIA). [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01435356>.
60. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; 18:3068–3077. [PubMed: 11001674]
61. Synold T, Tsao-Wei D, Quinn D, et al. Phase I and pharmacokinetic (PK) study of eribulin (E7389) in patients (pts) with renal dysfunction (RD) and advanced urothelial cancer (UC):A California Cancer Consortium Trial. *J Clin Oncol* 2010; 28 (15s); abstr 2527.
62. Balar AV, Apolo AB, Ostrovnaya I, et al. Phase II study of gemcitabine, carboplatin, and bevacizumab in patients with advanced unresectable or metastatic urothelial cancer. *J Clin Oncol* 2013; 31:724–730. [PubMed: 23341513] ■■ This trial showed a good response rate and OS in cisplatin-ineligible urothelial carcinoma patients treated with combination therapy and bevacizumab.

63. Hussain MH, MacVicar GR, Petrylak DP, et al. Trastuzumab, paclitaxel, carboplatin, and gemcitabine in advanced human epidermal growth factor receptor-2/neu-positive urothelial carcinoma: results of a multicenter phase II National Cancer Institute trial. *J Clin Oncol* 2007; 25:2218–2224. [PubMed: 17538166]
64. Phillips GK, Halabi S, Sanford BL, et al. A phase II trial of cisplatin (C), gemcitabine (G) and gefitinib for advanced urothelial tract carcinoma: results of Cancer and Leukemia Group B (CALGB) 90102. *Ann Oncol* 2009; 20:1074–1079. [PubMed: 19168670]
65. Menhert JM, Mortazavi AM, Stein MN, et al. A phase II trial of gemcitabine (G), carboplatin (C), and sorafenib (S) in patients (pts) with transitional cell carcinoma (TCC): Preliminary safety and outcome. *J Clin Oncol* 2011; (Suppl 7); abstr 278.
66. Krega S, Rexer H, vom Dorp F, et al. Gemcitabine and cisplatin with or without sorafenib in urothelial carcinoma (AUO-AB 31/05). *J Clin Oncol* 2010; (Suppl); abstr 4574.
67. Grivas P, Agarwal N, Siefker-Radtke AO, et al. Randomized phase II trial of gemcitabine/cisplatin (GC) with or without cetuximab (CET) in patients (pts) with advanced urothelial carcinoma (UC). *J Clin Oncol* 2012; (Suppl); abstr 4506.
68. Bellmunt J, Gonzalez-Larriba JL, Prior C, et al. Phase II study of sunitinib as first-line treatment of urothelial cancer patients ineligible to receive cisplatin-based chemotherapy: baseline interleukin-8 and tumor contrast enhancement as potential predictive factors of activity. *Ann Oncol* 2011; 22:2646–2653. [PubMed: 21427062]
69. Sridhar SS, Winquist E, Eisen A, et al. A phase II trial of sorafenib in first-line metastatic urothelial cancer: a study of the PMH Phase II Consortium. *Invest New Drugs* 2011; 29:1045–1049. [PubMed: 20191303]
70. Carboplatin and Gemcitabine Hydrochloride With or Without Vandetanib as First-Line Therapy in Treating Patients With Locally Advanced or Metastatic Urinary Tract Cancer. [Accessed 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01191892?term=NCT01191892&rank=1>.
71. A Phase 2 Study Comparing Chemotherapy in Combination With OGX-427 or Placebo in Patients With Bladder Cancer. [Accessed 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01454089?term=NCT01454089&rank=1>.
72. Page DB, Postow MA, Callahan MK, Wolchok JD Checkpoint modulation in melanoma: an update on ipilimumab and future directions. *Curr Oncol Rep* 2013; 15:500–508. [PubMed: 23933888]
73. A Study of Herceptin (Trastuzumab) Combination Therapy in Patients With Metastatic Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT02006667>.
74. Efficacy of Combination of Trastuzumab to Gemcitabine - Platinum Advanced or Metastatic Urothelial Carcinoma (CVH-CT02). [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01828736>.
75. Gemcitabine Hydrochloride, Cisplatin, and Temsirolimus as First-Line Therapy in Treating Patients With Locally Advanced and/or Metastatic Transitional Cell Cancer of the Urothelium. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01090466>.
76. Lapatinib, Cisplatin, Gemcitabine as First-Line Therapy in Treating Patients With Locally Advanced or Metastatic Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT00623064>.
77. Gemcitabine Hydrochloride and Cisplatin With or Without Bevacizumab in Treating Patients With Advanced Urinary Tract Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT00942331>.
78. Eribulin Mesylate Administered in Combination With Gemcitabine Plus Cisplatin Versus Gemcitabine Plus Cisplatin Alone as First-Line Therapy for Locally Advanced or Metastatic Bladder Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01126749>.
79. PURO Panitumumab in Combination With Gemcitabine/Cisplatin in Advanced Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01374789>.
80. Cisplatin, Gemcitabine Hydrochloride, and Sorafenib Tosylate in Treating Patients With Transitional Cell Cancer of the Bladder. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01222676>.

81. Gemcitabine and Split-Dose Cisplatin Plus Everolimus (RAD001) in Patients With Advanced Solid Tumor Malignancies. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01182168>.
82. A Study of ALT-801 in Combination With Cisplatin and Gemcitabine in Muscle Invasive or Metastatic Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01326871>.
83. Phase I Study With Sorafenib in Addition to Vinflunine in Metastatic Transitional Cell Carcinoma of the Urothelial Tract (VINSOR). [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01844947>.
84. Trebananib (AMG 386) in Combination With Docetaxel for Advanced Urothelial Carcinoma. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01907308>.
85. First-line Everolimus +/- Paclitaxel for Cisplatin-ineligible Patients With Advanced Urothelial Carcinoma. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01215136>.
86. Gemcitabine, Carboplatin, and Lenalidomide for Treatment of Advanced/ Metastatic Urothelial Cancer and Other Solid Tumors. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01352962>.
87. Gemcitabine and Pazopanib in Chemotherapy Naïve Patients With Advanced/Metastatic Urothelial Carcinoma Ineligible for Cisplatin-based Chemotherapy. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01622660>.
88. Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009; 27:4454–4461. [PubMed: 19687335]
89. Gallagher DJ, Milowsky MI, Gerst SR, et al. Phase II study of sunitinib in patients with metastatic urothelial cancer. *J Clin Oncol* 2010; 28:1373–1379. [PubMed: 20142593]
90. Dreicer R, Li H, Stein M, et al. Phase 2 trial of sorafenib in patients with advanced urothelial cancer: a trial of the Eastern Cooperative Oncology Group. *Cancer* 2009; 115:4090–4095. [PubMed: 19536901]
91. Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. *J Clin Oncol* 2012; 30:507–512. [PubMed: 22184381]
92. Wong YN, Litwin S, Vaughn D, et al. Phase II trial of cetuximab with or without paclitaxel in patients with advanced urothelial tract carcinoma. *J Clin Oncol* 2012; 30:3545–3551. [PubMed: 22927525]
93. Theodore C, Geoffrois L, Vermorken JB, et al. Multicentre EORTC study 16997: feasibility and phase II trial of farnesyl transferase inhibitor and gemcitabine combination in salvage treatment of advanced urothelial tract cancers. *Eur J Cancer* 2005; 41:1150–1157. [PubMed: 15911238]
94. Gomez-Abuin G, Winkvist E, Stadler WM, et al. A phase II study of PS-341 (Bortezomib) in advanced or metastatic urothelial cancer. A trial of the Princess Margaret Hospital and University of Chicago phase II consortia. *Invest New Drugs* 2007; 25:181–185. [PubMed: 16983508]
95. Stadler WM, Vaughn DJ, Sonpavde G, et al. An open-label, single-arm, phase 2 trial of the polo-like kinase inhibitor volasertib (BI 6727) in patients with locally advanced or metastatic urothelial cancer. *Cancer* 2014; 120:976–982. [PubMed: 24339028]
96. Rosenberg JE, Halabi S, Sanford BL, et al. Phase II study of bortezomib in patients with previously treated advanced urothelial tract transitional cell carcinoma: cAIGB 90207. *Ann Oncol* 2008; 19:946–950. [PubMed: 18272914]
97. Wulfing C, Machiels JP, Richel DJ, et al. A single-arm, multicenter, open-label phase 2 study of lapatinib as the second-line treatment of patients with locally advanced or metastatic transitional cell carcinoma. *Cancer* 2009; 115:2881–2890. [PubMed: 19399906]
98. Petrylak DP, Tangen CM, Van Veldhuizen PJ Jr, et al. Results of the South-west Oncology Group phase II evaluation (study S0031) of ZD1839 for advanced transitional cell carcinoma of the urothelium. *BJU Int* 2010; 105:317–321. [PubMed: 19888985]
99. Twardowski P, Stadler WM, Frankel P, et al. Phase II study of Aflibercept (VEGF-Trap) in patients with recurrent or metastatic urothelial cancer, a California Cancer Consortium Trial. *Urology* 2010; 76:923–926. [PubMed: 20646741]

100. Cheung E, Quinn DI, Tsao-Wei D, et al. Phase II study of vorinostat (Suberoylanilide Hydroxamic Acid, SAHA) in patients with advanced transitional cell urothelial cancer (TCC) after platinum-based therapy: California Cancer Consortium/University of Pittsburgh NCI/CTEP-sponsored trial. *J Clin Oncol* 2008; 26 (15s); abstr 16058.
101. Milowsky MI, Iyer G, Regazzi AM, et al. Phase II study of everolimus in metastatic urothelial cancer. *BJU Int* 2013; 112:462–470. [PubMed: 23551593]
102. Pili R, Qin R, Flynn PJ, et al. Aphase II safety and efficacy study of the vascular endothelial growth factor receptor tyrosine kinase inhibitor pazopanib in patients with metastatic urothelial cancer. *Clin Genitourin Cancer* 2013; 11:477–483. [PubMed: 23891158]
103. Necchi A, Mariani L, Zaffaroni N, et al. Pazopanib in advanced and platinum-resistant urothelial cancer: an open-label, single group, phase 2 trial. *Lancet Oncol* 2012; 13:810–816. [PubMed: 22819172]
104. Lerner SP, Sternberg CN, Younes M, et al. Phase II trial of tamoxifen for progressive advanced urothelial carcinoma following prior chemotherapy. *J Clin Oncol* 2012; (Suppl); abstr e15003.
105. Milowsky MI, Dittrich C, Martinez ID, et al. Final results of a multicenter, open-label phase II trial of dovitinib (TKI258) in patients with advanced urothelial carcinoma with either mutated or nonmutated FGFR3. *J Clin Oncol* 2013; (Suppl 6); abstr 255.
106. A Double Blind Randomised Study of Lapatinib and Placebo in Metastatic TCC of the Urothelium (LaMB). [Accessed 4 January 2014] <http://clinical-trials.gov/show/NCT00949455>.
107. Docetaxel and Lapatinib in Metastatic Transitional Cell Carcinoma in Bladder. [Accessed 4 January 2014] <http://clinicaltrials.gov/show/NCT01382706>.
108. BKM120 in Metastatic Transitional Cell Carcinoma of the Urothelium. [Accessed: 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01551030?term=NCT01551030&rank=1>.
109. Study of Ramucirumab or IMC-18F1 With Docetaxel or Docetaxel Alone as Second-Line Therapy in Participants With Bladder, Urethra, Ureter, or Renal Pelvis Carcinoma. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01282463>.
110. Pazopanib and Vinflunine in Urothelial Cancer of the Bladder. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01265940>.
111. Phase 2 Study of Docetaxel +/- OGX-427 in Patients With Relapsed or Refractory Metastatic Bladder Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01780545>.
112. A Study of Herceptin (Trastuzumab) Monotherapy in Patients With Meta-static Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT02013765>.
113. Eribulin Mesylate in Treating Patients With Locally Advanced or Metastatic Cancer of the Urothelium and Kidney Dysfunction. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT00365157>.
114. A Phase I/II Trial of AEZS-108 in Urothelial Cancer Patients Who Failed Platinum-Chemotherapy. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01234519>.
115. TRC105 in Adults With Advanced/Metastatic Urothelial Carcinoma. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01328574>.
116. Cabozantinib for Advanced Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01688999>.
117. PF-03446962 in Relapsed or Refractory Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01620970>.
118. ASG-15ME is a Study of Escalating Doses of AGS15E Given as Mono-therapy in Subjects With Metastatic Urothelial Cancer. [Accessed on 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01963052>.
119. Bernardini S, Fauconnet S, Chabannes E, et al. Serum levels of vascular endothelial growth factor as a prognostic factor in bladder cancer. *J Urol* 2001; 166:1275–1279. [PubMed: 11547057]
120. Fauconnet S, Bernardini S, Lascombe I, et al. Expression analysis of VEGF-A and VEGF-B: relationship with clinicopathological parameters in bladder cancer. *Oncol Rep* 2009; 21:1495–1504. [PubMed: 19424629]
121. Bochner BH, Cote RJ, Weidner N, et al. Angiogenesis in bladder cancer: relationship between microvessel density and tumor prognosis. *J Natl Cancer Inst* 1995; 87:1603–1612. [PubMed: 7563203]

122. Wu W, Shu X, Hovsepyan H, et al. VEGF receptor expression and signaling in human bladder tumors. *Oncogene* 2003; 22:3361–3370. [PubMed: 12776187]
123. Kopparapu PK, Boorjian SA, Robinson BD, et al. Expression of VEGF and its receptors VEGFR1/VEGFR2 is associated with invasiveness of bladder cancer. *Anticancer Res* 2013; 33:2381–2390. [PubMed: 23749886] ■■■ This study shows that VEGF expression can be a useful indicator of the invasiveness of bladder cancer, and shows that the VEGF pathway is an important pathway to target.
124. Beekman KW, Bradley D, Hussain M. New molecular targets and novel agents in the treatment of advanced urothelial cancer. *Semin Oncol* 2007; 34:154–164. [PubMed: 17382799]
125. Sonpavde G, Jian W, Liu H, et al. Sunitinib malate is active against human urothelial carcinoma and enhances the activity of cisplatin in a preclinical model. *Urol Oncol* 2009; 27:391–399. [PubMed: 18534874]
126. Leibl S, Zigeuner R, Hutterer G, et al. EGFR expression in urothelial carcinoma of the upper urinary tract is associated with disease progression and metaplastic morphology. *APMIS* 2008; 116:27–32. [PubMed: 18254777]
127. Philips GK, Halabi S, Sanford BL, et al. A phase II trial of cisplatin (C), gemcitabine (G) and gefitinib for advanced urothelial tract carcinoma: results of Cancer and Leukemia Group B (CALGB) 90102. *Ann Oncol* 2009; 20:1074–1079. [PubMed: 19168670]
128. Jimenez RE, Hussain M, Bianco FJ Jr, et al. Her-2/neu overexpression in muscle-invasive urothelial carcinoma of the bladder: prognostic significance and comparative analysis in primary and metastatic tumors. *Clin Cancer Res* 2001; 7:2440–2447. [PubMed: 11489824]
129. Cecchi F, Rabe DC, Bottaro DP Targeting the HGF/Met signaling pathway in cancer therapy. *Expert Opin Ther Targets* 2012; 16:553–572. [PubMed: 22530990] ■■■ This review highlights the HGF/MET signaling pathway. Cabozantinib targets this pathway and is a promising agent under investigation in bladder cancer.
130. Sorbellini M, McNeil B, Cohen B, et al. Urinary met level as a novel biomarker for urothelial carcinoma of the bladder. *J Clin Oncol* 2011; 29 (Suppl 7); abstr 257.
131. Wang P, Nishitani MA, Tanimoto S, et al. Bladder cancer cell invasion is enhanced by cross-talk with fibroblasts through hepatocyte growth factor. *Urology* 2007; 69:780–784. [PubMed: 17445681]
132. Apolo AB, Lee Y, Cecchi F, et al. Preclinical and correlative studies of cabozantinib (XL184) in urothelial cancer (UC). *J Clin Oncol* 2013; 31 (Suppl); abstr 4543.
133. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther* 2011; 10:2298–2308. [PubMed: 21926191]
134. Bentzien F, Zuzow M, Heald N, et al. In vitro and in vivo activity of cabozantinib (XL184), an inhibitor of RET, MET, and VEGFR2, in a model of medullary thyroid cancer. *Thyroid* 2013; 23:1569–1577. [PubMed: 23705946]
135. Smith DC, Smith MR, Sweeney C, et al. Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. *J Clin Oncol* 2013; 31:412–419. [PubMed: 23169517]
136. Cabozantinib for Advanced Urothelial Cancer. [Accessed 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01688999?term=NC-T01688999&rank=1>.
137. Ren H, Chen M, Yue P, et al. The combination of RAD001 and NVP-BKM120 synergistically inhibits the growth of lung cancer in vitro and in vivo. *Cancer Lett* 2012; 325:139–146. [PubMed: 22781393]
138. Bendell JC, Rodon J, Burris HA, et al. Phase I, dose-escalation study of BKM120, an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. *J Clin Oncol* 2012; 30:282–290. [PubMed: 22162589]
139. Phase 2 Study of Docetaxel +/- OGX-427 in Patients with Relapsed or Refractory Metastatic Bladder Cancer. [Accessed 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01780545?term=ogx+docetaxel&rank=2>
140. First-Line Gemcitabine, Cisplatin + Ipilimumab for Metastatic Urothelial Carcinoma. [Accessed 4 January 2014] <http://clinicaltrials.gov/ct2/show/NCT01524991?term=NCT01524991&rank=1>.

141. Jachetti E, Mazzoleni S, Grioni M, et al. Prostate cancer stem cells are targets of both innate and adaptive immunity and elicit tumor-specific immune responses. *Oncoimmunology* 2013; 2:e24520.
142. Kohaar I, Porter-Gill P, Lenz P, et al. Genetic variant as a selection marker for antiprostate stem cell antigen immunotherapy of bladder cancer. *J Natl Cancer Inst* 2013; 105:69–73. [PubMed: 23266392] ■ This article describes PSCA as a novel potential target derived from genome-wide association studies analysis of urothelial carcinoma tumors.
143. Marra E, Uva P, Viti V, et al. Growth delay of human bladder cancer cells by prostate stem cell antigen downregulation is associated with activation of immune signaling pathways. *BMC Cancer* 2010; 10:129. [PubMed: 20374648]
144. Wolpin BM, O'Reilly EM, Ko Y J, et al. Global, multicenter, randomized, phase II trial of gemcitabine and gemcitabine plus AGS-1C4D4 in patients with previously untreated, metastatic pancreatic cancer. *Ann Oncol* 2013; 24:1792–1801. [PubMed: 23448807]
145. Antonarakis ES, Carducci MA, Eisenberger MA, et al. Phase I rapid dose-escalation study of AGS-1C4D4, a human anti-PSCA (prostate stem cell antigen) monoclonal antibody, in patients with castration-resistant prostate cancer: a PCCTC trial. *Cancer Chemother Pharmacol* 2012; 69:763–771. [PubMed: 22020316]
146. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature* 2014; 507:315–322. [PubMed: 24476821] ■■ This article is an integrated, comprehensive analysis of bladder cancer revealing recurrent mutations in 32 genes including nine new genetic mutations not reported as significantly mutated in any other cancer. Sixty-nine percent of the tumors revealed potential therapeutic targets.
147. Iyer G, Al-Ahmadie H, Schultz N, et al. Prevalence and co-occurrence of actionable genomic alterations in high-grade bladder cancer. *J Clin Oncol* 2013; 25:3133–3140. ■■ This study reveals multiple genomic alterations in a large percentage of analyzed bladder tumors that may be actionable drug targets and may predict response to targeted therapies.
148. Platt FM, Hurst CD, Taylor CF, et al. Spectrum of phosphatidylinositol 3-kinase pathway gene alterations in bladder cancer. *Clin Cancer Res* 2009; 15:6008. [PubMed: 19789314]
149. Iyer G, Hanrahan AJ, Milowsky MI, et al. Genome sequencing identifies a basis for everolimus sensitivity. *Science* 2012; 338:221. [PubMed: 22923433] ■ This study shows the efficacy of mTOR-targeted agent everolimus in a selected population based on genomic sequencing.

KEY POINTS

- A growing number of targeted agents are being studied in all stages of urothelial carcinoma, especially in the second-line setting.
- Clinical trials of targeted therapies for urothelial carcinoma in an unselected patient population have been negative so far, although agents targeting angiogenesis appear to have some activity in a small number of patients.
- For NMIBC, most ongoing trials are focusing on antitumor immunity using immunotherapeutic agents alone or with concurrent intravesical BCG.
- Combination trials of TKIs and cytotoxic chemotherapy in MIBC and first-line metastatic urothelial carcinoma have reported significant toxicities.
- Genomic studies reveal that urothelial carcinoma is a heterogeneous disease with a large number of somatic mutations that may provide targets for therapy and predict response to specific targeted agents.

Table 1.

Targeted agents studied in urothelial carcinoma

Agent	Target	Agent	Target
Angiogenesis inhibitors			
Aflibercept	VEGF, PDGF	Cetuximab	EGFR
Bevacizumab	VEGF	Erlotinib	EGFR
Cabozantinib	VEGFR/cMET	Gefitinib	EGFR
Everolimus	PI3K/Akt/mTOR	Lapatinib	HER2/EGFR
Lenalidomide	Apoptosis, antiangiogenesis, immune modulation	Trastuzumab	HER2
Pazopanib	VEGFR1/2/3, PDGFR a/b, c-Kit	Panitumumab	EGFR
PF-03446962	TGFb α /ALK1	Vandetanib	VEGFR, EGFR, RET
rAD-IFN/Syn3	Antiangiogenesis and immune modulation	Hormone-associated	
Ramucirumab			
Sorafenib	B-Raf, c-Raf, VEGFR-2/3, PDGFR-b	AEZS-108	LHRH linked to doxorubicin
Sunitinib	VEGFR-1/2, C-KIT, PDGFR a/b, FLT3, RET	Tamoxifen	ER-B
Temsirolimus	mTOR	Other targets	
TRC105	CD105		
Trebananib	Ang1, Ang2		
Immune therapy			
ALT-801	p53	Apaziquone	Mitomycin-C analogue, apoptosis
ASG-15ME	SLITRK6	BKM120	PI3K
CDX-1307	Dendritic-cell vaccine hCG-B	Bortezomib	Proteasome inhibitor
Dendritic-cell vaccine	Ad/HER2/neu	Dasatinib	BCR/ABL and Src
DN24-02	HER2 vaccine	Dovitinib	FGFR3
DTA-H19/PEI	DNA plasmid, DT-A gene, H19 transcription factors	Eribulin	Tubulin
HS-410	gp96-chaperoned peptides	Lonafamib	Farnesyl transferase
Ipilimumab	CTLA-4	OGX-427	HSP27
PANVAC	MUC-1, CEA	Oportuzumab monatox	EpCAM
recMAGE-A3 p AS15	MAGE-A3 vaccine	Valproic acid	Thrombospondin-1
Rituximab	CD20	Volasertib	Polo-like kinase 1
TMX-101	TLR-7	Vorinostat (SAHA)	SAHA: histone deacetylase

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

CTLA-4, cytotoxic T-lymphocyte antigen 4; DT-A, diphtheria toxin A; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; ER, estrogen receptor; FGFR, fibroblast growth factor receptor; hCG, human chorionic gonadotropin; HER, human epidermal growth factor receptor; HSP27, heat shock protein 27; LHRH, luteinizing hormone-releasing hormone; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinases; PR, progesterone receptor; SAHA, suberanilohydroxamic acid; SLITRK6, SLIT and TRK-like family member 6; TLR, toll-like receptor; VEGFR, vascular endothelial growth factor receptor

Table 2.

Reported and ongoing trials of targeted agents in nonmuscle-invasive bladder cancer

Table 2a. Reported trials of targeted agents in NMIBC

Author	Year	Agent	Target	Intravesical therapy	Study type	n	RR %
Kowalski [15]	2010	Oportuzumab monatox	EpCAM	None	Phase I	64	NR
Hendricksen [12]	2012	Apaziquone	Mitomycin-C analogue, apoptosis	Apaziquone	Phase II	53	NR
Falke [14]	2012	TMX-101	TLR-7	None	Phase I	16	NR
Kowalski [13]	2012	Oportuzumab monatox	EpCAM	None	Two-arm, phase II	46	44

Table 2b. Ongoing trials of targeted agents in nonmuscle-invasive bladder cancer

PI	Start year	Agent	Target	Intravesical therapy	Study type	Target enrollment	Clinicaltrials.gov ID
Lamm [17]	2008	DTA-H19/PEI	DNA plasmid, DT-A gene, H19 transcription factors	None	Phase IIb intermediate risk with prior intravesical induction	47	NCT00595088
Weizer [18]	2009	Sunitinib	VEGFR-1/2, C-KIT, PDGFR a/b, FLT3, RET	BCG	Phase II high grade	36	NCT00794950
Dalbagni [19]	2010	Everolimus	PI3K/Akt/mTOR	Gemcitabine	Phase I/II BCG failure	45	NCT01259063
Fishman [20]	2011	Lenalidomide	Apoptosis, antiangiogenesis, and immune modulation	BCG	Phase II with prior BCG induction	70	NCT01373294
Fishman [16]	2011	Rituximab	CD20	BCG	Phase II high grade	70	NCT01373294
Sun [21]	2011	Apaziquone	Mitomycin-C analogue, apoptosis	None	Randomized phase III low risk	658	NCT01469221
Dinney [22]	2012	rAD-IFN/Syn3	Antiangiogenesis and immune modulation	None	Randomized phase II high-grade BCG failure	40	NCT01687244
Rosser [23]	2012	ALT-801	p53	Gemcitabine	Phase Ib/II BCG failure	52	NCT01625260
Jichlinski [24]	2012	recMAGE-A3+AS-15	MAGE-A3 vaccine	BCG	Phase I high grade	24	NCT01498172
Shapiro [25]	2012	Valproic acid	Thrombospondin-1	BCG/MMC	Phase 0	50	NCT01738815
Lamm [26]	2013	TMX-101	TLR-7	None	Phase II with CIS	12	NCT01731652
Hahn [27]	2013	Dovitinib	FGFR3	None	Phase II BCG failure with FGFR3 mutation overexpression	50	NCT01732107
Steinberg [28]	2013	HS-410	gp96-chaperoned peptides	BCG	Phase I/II high grade with prior BCG induction phase I/II high grade with prior BCG induction	93	NCT02010203

Table 2a. Reported trials of targeted agents in NMIBC						
Author	Year	Agent	Target	Intravesical therapy	Study type	RR %
Agarwal [29]	2013	PANVAC	MUC-1, CEA	BCG	Randomized phase II BCG failure	NCT02015104

BCG, Bacillus Calmette-Guerin; CIS, carcinoma *in situ*; EpCAM, epithelial cell adhesion molecule; FGFR, fibroblast growth factor receptor; MMC, mitomycin C; mTOR, mammalian target of rapamycin; *n*, number of patients enrolled; NR, not reported; PDGFR, platelet-derived growth factor receptor; PI, principal investigator; RR, response rate; TLR, toll-like receptor; VEGFR, vascular endothelial growth factor receptor.

Table 3.

Reported and ongoing trials of targeted agents in muscle-invasive bladder cancer

Table 3a. Reported trials of targeted agents with chemotherapy in muscle-invasive bladder cancer						
Author	Year	Agent	Target	Chemotherapy	Study type	Path <T2 RR%
Chaudhary [40]	2011	Bevacizumab	VEGF	Gemcitabine and cisplatin	Phase II neoadjuvant	31
Siefker-Radtke [38]	2012	Bevacizumab	VEGF	Dose-dense MVAC	Phase II neoadjuvant	53
Balar [41]	2012	Sunitinib	VEGFR-1/2, C-KIT, PDGFR α/β , FLT3, RET	Gemcitabine and cisplatin	Phase II neoadjuvant	33
Galsky [39]	2013	Sunitinib	VEGFR-1/2, C-KIT, PDGFR α/β , FLT3, RET	Gemcitabine and cisplatin	Phase II neoadjuvant	22
Table 3b. Reported trials of targeted agents as single-agent therapy in muscle-invasive bladder cancer						
Author	Year	Agent	Target	Chemotherapy	Study type	Path <T2 RR%
Pruthi [42]	2010	Erlotinib	EGFR	None	Phase II neoadjuvant	35
Hahn [43]	2012	Dasatinib	BCR/ABL and Src	None	Phase II neoadjuvant	14
Table 3c. Ongoing trials of targeted agents with chemotherapy in muscle-invasive bladder cancer						
PI/group	Start Year	Agent	Target	Chemotherapy	Study type	Target enrollment
Michaelson RTOG [54]	2005	Trastuzumab	HER2	Paclitaxel and radiation	Phase I/II adjuvant	88
Kraft [52]	2005	Bevacizumab	VEGF	Neoadjuvant gemcitabine and cisplatin adjuvant paclitaxel	Phase II neoadjuvant and adjuvant	25
Bradley [55]	2010	CDX-1307	Dendritic-cell vaccine hCG-B	Gemcitabine and cisplatin	Phase II neoadjuvant and adjuvant	30
Wong [56]	2011	ALT-801	p53	Gemcitabine and cisplatin; gemcitabine alone	Phase Ib/II neoadjuvant or metastatic	76
Table 3d. Ongoing trials of targeted agents as single therapy in muscle-invasive bladder cancer						
PI/group	Start Year	Agent	Target	Chemotherapy	Study type	Target enrollment
So [57]	2009	OGX-427	Hsp27	None	Phase I neoadjuvant	36
Bajorin [58]	2011	DN24-02	HER-2 vaccine	None	Randomized phase II adjuvant	180
Mulders [59]	2011	recMAGE-A3pAS-15	MAGE-A3 vaccine	None	Randomized phase II adjuvant	273

Table 3a. Reported trials of targeted agents with chemotherapy in muscle-invasive bladder cancer						
Author	Year	Agent	Target	Chemotherapy	Study type	Path <T2 RR% NCT01730118
Wood [53]	2013	Dendritic-cell vaccine	Ad/HER2/neu	None	Phase I adjuvant	65

EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; *n*, number of patients enrolled; PI, principal investigator; RR, pathologic response rate to <pT2; VEGF, vascular endothelial growth factor.

Table 4.
Reported and ongoing trials of targeted agents as first-line therapy in metastatic bladder cancer

Table 4a. Reported trials of targeted agents with chemotherapy as first-line therapy in metastatic bladder cancer						
Author	Year	Agent	Target	Chemotherapy	Study type	RR% OS (months)
Hussain [63]	2007	Trastuzumab	HER2	Paclitaxel, gemcitabine, carboplatin	Phase II	44 70 14.1
Philips [64]	2009	Gefitinib	EGFR	Gemcitabine and cisplatin	Phase II	54 43 15.1
Hahn [45]	2011	Bevacizumab	VEGF	Gemcitabine and cisplatin	Phase II	43 72 19.1
Menhert [65]	2011	Sorafenib	B-Raf,c-Raf, VEGFR-2/3, PDGFR-b	Gemcitabine and cisplatin	Phase II	17 30 NR
Krege [66]	2011	Sorafenib	B-Raf,c-Raf, VEGFR-2/3, PDGFR-b	Gemcitabine and cisplatin	Phase II	40 53 11.3
Grivas [67]	2012	Cetuximab	EGFR	Gemcitabine and cisplatin + cetuximab; gemcitabine and cisplatin alone	Randomized phase II	88 57 14
Balar [62■]	2013	Bevacizumab	VEGF	Gemcitabine and carboplatin	Randomized phase II (1 : 2)	51 63 14
Galsky [39]	2013	Sunitinib	VEGFR-1/2, C-KIT, PDGFR a/b,FLT3, RET	Gemcitabine and cisplatin	Phase II	36 49 13.9
Table 4b. Reported trials of targeted agents as single-agent first-line therapy in metastatic bladder cancer						
Author	Year	Agent	Target	Chemotherapy	Study type	RR% OS (months)
Bellmunt [68]	2010	Sunitinib	VEGFR-1/2, C-KIT, PDGFR a/b, FLT3, RET	None	Phase II	38 8 8.1
Quinn [61]	2010	Eribulin	Tubulin	None	Phase II	37 38 9.4
Sridhar [69]	2011	Sorafenib	B-Raf,c-Raf, VEGFR-2/3, PDGFR-b	None	Phase II	17 0 5.9
Table 4c. Ongoing trials of targeted agents as first-line therapy with chemotherapy in metastatic bladder cancer						
PI/group	Start year	Agent	Target	Chemotherapy	Study type	Target enrollment Clinicaltrials.gov ID
Hoffman [73]	2001	Trastuzumab	HER2	Gemcitabine and cisplatin	Phase II	13 NCT02006667
Oudard [74]	2004	Trastuzumab	HER2	Gemcitabine and cisplatin or carboplatin	Randomized phase II	61 NCT01828736
Chester [75]	2008	Temsirolimus	mTOR	Gemcitabine and cisplatin	Phase I/II	99 NCT01090466
EORTC [76]	2008	Lapatinib	HER2/EGFR	Gemcitabine and cisplatin	Phase I	25 NCT00623064
Rosenberg [77]	2009	Bevacizumab	VEGF	Gemcitabine and cisplatin	Randomized phase III	500 NCT00942331
Eisai INC [78]	2010	Eribulin	Tubulin	Gemcitabine and cisplatin	Phase Ib/II	95 NCT01126749
Miller [79]	2010	Panitumumab	EGFR	Gemcitabine and cisplatin	Randomized phase II	124 NCT01374789
Salvioni [80]	2010	Sorafenib	B-Raf,c-Raf, VEGFR-2/3, PDGFR-b	Gemcitabine and cisplatin	Phase II	45 NCT01222676

Table 4c. Ongoing trials of targeted agents as first-line therapy with chemotherapy in metastatic bladder cancer

PI/group	Start year	Agent	Target	Chemotherapy	Study type	Target enrollment	Clinicaltrials.gov ID
Bajorin [81]	2010	Everolimus	PI3K/Akt/mTOR	Gencitabine and split-dose cisplatin	Phase I	30	NCT01182168
Petrylak [71]	2011	OGX-427	HSP27	Gencitabine and cisplatin	Randomized phase II	180	NCT01454089
Wong [82]	2011	ALT-801	p53	Gencitabine and cisplatin	Phase I/II	76	NCT01326871
Galsky [72]	2012	Ipilimumab	CTLA-4	Gencitabine and cisplatin	Phase II	36	NCT01524991
Ullen [83]	2012	Sorafenib	B-Raf, c-Raf, VEGFR-2/3, PDGFR- b	Vinflunine	Phase I	24	NCT01844947
Flag [84]	2013	Trebananib	Ang1, Ang2	Docetaxel	Phase II	38	NCT01907308

Table 4d. Ongoing trials of targeted agents for cisplatin-ineligible patients as first-line therapy in metastatic bladder cancer

PI/group	Start year	Agent	Target	Chemotherapy	Study type	Target enrollment	Clinicaltrials.gov ID
Oudard [74]	2004	Trastuzumab	HER2	Gencitabine and cisplatin or carboplatin ^a	Randomized phase II	61	NCT01828736
Jones [70]	2010	Lapatinib	HER2/EGFR	Gencitabine and carboplatin	Phase II	122	NCT01191892
Galsky [85]	2010	Everolimus	PI3K/Akt/mTOR	Paclitaxel	Phase II	68	NCT01215136
Apolo [86]	2011	Lenalidomide	Apoptosis, angiogenesis and immune modulation	Gencitabine and carboplatin	Phase I	42	NCT01352962
Bajorin [87]	2012	Pazopanib	VEGFR1/2/3, PDGFR a/b, c-Kit	Gencitabine	Phase II	45	NCT01622660

^aChemotherapy is gencitabine and cisplatin or gencitabine and carboplatin based on creatinine clearance.

EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; HER, human epidermal growth factor receptor; mTOR, mammalian target of rapamycin; n, number of patients enrolled; NR, not reported; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PI, principal investigator; RR, response rate; SLITRK6, SLIT and TRK-like family member 6; VEGFR, vascular endothelial growth factor receptor.

Table 5.
Reported and ongoing trials of targeted agents as second-line therapy in metastatic bladder cancer

Table 5a. Reported trials of targeted agents with chemotherapy as second-line therapy in metastatic bladder cancer						
Author	Year	Agent	Target	Chemotherapy	Study type	OS (months)
Theodore [93]	2005	Lonafarnib	Farnesyltransferase	Gemcitabine	Phase II	NR
Choueiri [91]	2012	Vandetanib	VEGFR, EGFR, RET	Docetaxel and vandetanib	Randomized phase II	5.56
				Docetaxel and placebo		7.39
Wong [92]	2012	Cetuximab	EGFR	Paclitaxel and cetuximab alone	Randomized phase II	10.5
						0
						1.3

Table 5b. Reported trials of targeted agents with single-agent second-line therapy in metastatic bladder cancer						
Author	Year	Agent	Target	Chemotherapy	Study type	OS (months)
Gomez-Abuin [94]	2007	Bortezomib	Proteasome inhibitor	None	Phase II	NR
Rosenberg [96]	2008	Bortezomib	Proteasome inhibitor	None	Phase II	5.7
Wulfing [97]	2009	Lapatinib	HER2/EGFR	None	Phase II	4.5
Petrylak [98]	2009	Gefitinib	EGFR	None	Phase II	3
Dreicer [90]	2009	Sorafenib	B-Raf, c-Raf, VEGFR-2/3, PDGFR- β	None	Phase II	6.8
Gallagher [89]	2010	Sunitinib	VEGFR-1/2, C-KIT, PDGFR a/b, FLT3, RET	None	Phase II	6.9
Twardowski [99]	2010	Aflibercept	VEGF, PDGF	None	Phase II	NR
Cheung [100]	2010	Vorinostat	SAHA: histone deacetylase	None	Phase II	4.3
Stadler [95]	2011	Volasertib	Polo-like kinase 1	None	Phase II	NR
Milowsky [101]	2011	Everolimus	PI3K/Akt/mTOR	None	Phase II	10.5
Pili [102]	2011	Pazopanib	VEGFR1/2/3, PDGFR a/b, c-Kit	None	Phase II	NR
Necchi [103]	2012	Pazopanib	VEGFR1/2/3, PDGFR a/b, c-Kit	None	Phase II	4.7
Lerner [104]	2012	Tamoxifen	ER-B	None	Phase II	NR
Milowsky [105]	2013	Dovitinib	FGFR3	None	Phase II	NR

Table 5c. Ongoing trials of targeted agents with chemotherapy as second-line therapy in metastatic bladder cancer				
PI/group	Start year	Agent	Target	Clinicaltrials.gov ID
Quinn [107]	2011	Lapatinib	HER2/EGFR	NCT01382706
ImClone [109]	2011	Ramucirumab	VEGFR2	NCT01282463
			Docetaxel	Target enrollment
			Phase II	40
			Three-arm randomized phase II	138

Table 5c. Ongoing trials of targeted agents with chemotherapy as second-line therapy in metastatic bladder cancer

PI/group	Start year	Agent	Target	Chemotherapy	Study type	Target enrollment	Clinicaltrials.gov ID
Otto [110]	2011	Pazopanib	VEGFR1/2/3, PDGFR a/b, c-Kit	Vinflunine	Phase I/II	NR	NCT01265940
Hahn [111]	2013	OGX-427	Hsp27	Docetaxel	Randomized phase II	200	NCT01780545

Table 5d. Ongoing trials of targeted agents as single-agent second-line therapy in metastatic bladder cancer

PI/group	Start year	Agent	Target	Chemotherapy	Study type	Target enrollment	Clinicaltrials.gov ID
Hoffman [112]	2001	Trastuzumab	HER2	None	Phase II	5	NCT02013765
Quinn [113]	2006	Eribulin	Tubulin	None	Phase I/II, renal dysfunction	82	NCT00365157
Fowles [106]	2009	Lapatinib	HER2/EGFR	None	Randomized phase II/III	204	NCT00949455
Fernandez [114]	2010	AEZS-108	LHRH linked to doxorubicin	None	Phase I/II	64	NCT01234519
Apolo [115]	2011	TRC105	CD 105	None	Phase II	45	NCT01328574
Bajorin [108]	2012	BKM120	PI3K	None	Phase II	35	NCT01551030
Apolo [116]	2012	Cabozantinib	VEGFR/cMET	None	Phase II	55	NCT01688999
Necchi [117]	2012	PF-03446962	TGFβR/ALK1	None	Phase II	45	NCT01620970
Wood [53]	2013	Dendritic-cell vaccine	Ad/HER2/neu	None	Phase I	65	NCT01730118
Agensys [118]	2013	ASG-15ME	SLITRK6	None	Phase I	45	NCT01963052

ALK1, activin receptor-like kinase 1; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FGFR, fibroblast growth factor receptor; HER, human epidermal growth factor receptor; mTOR, mammalian target of rapamycin; n, number of patients enrolled; NR, not reported; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PI, principal investigator; RR, response rate; SAHA, suberanilohydroxamic acid; TGFβR, transforming growth factor β receptor; VEGFR, vascular endothelial growth factor receptor.