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Targeted therapy in Advanced Bladder cancer- what have we learned?

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Synopsis

Urothelial carcinoma (UC) is the second most common genitourinary malignancy in the United States. In the metastatic setting, cisplatin-based chemotherapy results in a median overall survival (OS) of 12–15 months and remains the only standard of care for this disease. Despite advances in the treatment of other genitourinary malignancies, no novel therapies have been FDA-approved for UC in the last 20 years. To date, no clinical trials of targeted agents in UC have led to improvements in survival compared to cytotoxic therapy. The Cancer Genome Atlas (TCGA) has detected numerous potentially actionable genetic alterations in bladder cancer, providing a roadmap for the use of small molecule inhibitors in this disease. Additionally, the advancement of Next Generation sequencing technologies within the past five years has allowed for rapid, deep sequencing to define the molecular profile of tumors in real time. In this chapter, we outline representative trials of targeted therapies in UC and discuss the significance of genetic pre-selection in trial design as a method to optimize responses to these agents, thus hopefully expanding the armamentarium of treatment options against this lethal disease.

Keywords

Urothelial carcinoma; targeted therapy; small molecule inhibitors; Next Generation sequencing; angiogenesis; MAPK pathway; PI3K/Akt/mTOR pathway

Background

Urothelial carcinoma (UC) is the second most common genitourinary malignancy in the United States, with an estimated 74,690 new cases and 15,580 estimated deaths in 2014 [1]. For locally advanced or metastatic UC, first-line cisplatin-based chemotherapy results in an overall response rate (ORR) of 50–70%, a median progression-free survival (PFS) of 7–9 months and median OS of 12–15 months [2]. The doublet of gemcitabine plus cisplatin (GC)

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offers similar survival rates to the four drug regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) with a median survival of 14.0 months (95% CI 12.3-15.5 months) versus 15.2 months (95% CI 13.2-17.3 months), respectively. While these survival outcomes outstrip the estimated 6-month survival rates observed prior to these regimens, advances are indisputably needed [2]. The addition of paclitaxel to GC chemotherapy (PCG) improved response rates but did not show a significant improvement in median survival and resulted in increased toxicity [3], while the use of dose dense therapies have to date not resulted in improvements in OS.[4] These results, coupled with the success of targeted agents in other cancer types such as renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and chronic myelogenous leukemia, have driven the search to define a role for targeted therapies in advanced UC.

Genetic Alterations in UC

Sequencing of UC tumors initially identified two distinct mutation patterns which correlated with tumor grade. Low-grade papillary tumors were characterized primarily by oncogenic mutations in the Fibroblast Growth Factor Receptor 3 (*FGFR3*) (~70%), *HRAS* (30–40%), and *PIK3CA* (~10%) genes [5]. Conversely, invasive lesions harbored frequent loss of function alterations in tumor suppressor genes, including *TP53* and *RBI* [6, 7]. The bladder TCGA has since provided a more granular insight into the landscape of genetic alterations within muscle-invasive UC.[8] Despite a high mutation burden, many alterations can be organized into well known signaling pathways and canonical cellular functions against which inhibitors have been FDA approved in other cancer types or are currently under investigation in UC [9]. These primarily include the receptor tyrosine kinase (RTK) pathway, comprised of the EGFR family of receptors, FGFR3, and numerous others, as well as the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway. Additionally, UC is characterized by a high frequency of alterations within cell cycle regulatory genes, including *CDKN2A* deletion and *CCND1* amplification. Chromatin modifiers such as *KDM6A*, *KMT2D*, and *ARID1A* represent another class of genes commonly mutated in this disease. Finally, angiogenesis is thought to play a key role in UC growth and metastatic spread, and components of this signaling axis are also altered in UC. Most targeted therapy trials performed thus far in UC have investigated RTK and angiogenic signaling inhibitors as well as mTOR inhibitors, and these studies are the focus of the discussion below and outlined in Table 1.

Receptor Tyrosine Kinase Signaling Inhibitors

EGFR Signaling

Epidermal growth factor receptor (EGFR; ErbB1) is a 170-kDa transmembrane receptor tyrosine kinase (RTK) critically important for the regulation of cell proliferation, invasion and metastasis in preclinical models of UC [10]. Activation of the EGFR-TK stimulates both the MAPK and PI3K/Akt/mTOR signaling pathways. Additional members of the ErbB family of receptors also involved in mitogenic signaling via the MAPK pathway include HER2 and HER3. EGFR and HER2 have both been examined as potential targets in UC. In the bladder TCGA, comprised of untreated muscle-invasive specimens, MAPK pathway

alterations included EGFR amplification (9%), HER2 amplifications and mutations (9%), and HER3 mutations (6%).

Gefitinib—Gefitinib is an oral, selective EGFR tyrosine kinase inhibitor currently utilized in EGFR mutant NSCLC patients and has activity against EGFR-expressing UC cell lines [11]. Gefitinib was evaluated in a phase II trial in metastatic UC patients who failed one prior chemotherapeutic regimen. In the 31 patients enrolled, the median PFS was 2 months with one confirmed partial response (PR) [12]. Pre-treatment biopsies were required for retrospective evaluation of EGFR expression, although overexpression was not an inclusion criterion. The partial responder's tumor harbored 2+ EGFR expression; 8 of 15 patients showing primary progression also 2-3+ EGFR expression. No correlation was noted between EGFR staining and response; additionally, this study was designed prior to the observation that EGFR mutations correlate with gefitinib sensitivity in NSCLC.

The Cancer and Leukemia Group B conducted a multicenter phase II study (CALGB 90102) evaluating the addition of gefitinib (500 mg/day) to GC in untreated patients with advanced UC. [13] All patients received 6 cycles of GC plus gefitinib and those with objective responses or stable disease (SD) were continued on maintenance gefitinib until progression. An ORR of 42.6% was observed with 7 complete responses (CR) and 16 PRs. The median OS was 15.1 months; the median time to progression was 7.4 months. Grades 3-4 hematologic toxicity were seen in 22% patients (n=12). Non-hematological grade 3 toxicities included fatigue (20%), emesis (24%), diarrhea (14%) and rash (11%). Based on these results, the addition of gefitinib does not appear to improve response rate or survival compared to chemotherapy alone. Notably, patients were not screened for EGFR overexpression or mutation prior to trial enrollment.

Erlotinib—Erlotinib, another EGFR tyrosine kinase inhibitor, was tested in 20 patients with histologically confirmed muscle-invasive UC in the neoadjuvant setting for four weeks prior to radical cystectomy [14]. Seven patients (35%) with clinical T2 disease were downstaged to non-MIBC and 5 patients (25%) had no residual disease, comparing favorably to historical rates of <pT2 disease following transurethral resection and/or neoadjuvant chemotherapy, although the lack of a comparator arm in this study limits the ability to draw definitive conclusions. Treatment was well-tolerated with rash the most common side effect observed in 15 patients (75%). Five patients who achieved pT0 responses within the bladder exhibited the acneiform rash known to correlate with response to EGFR TK inhibition in NSCLC and colon cancers. While patients were not pre-selected based upon EGFR mutations or amplification, tumors are being retrospectively analyzed to define any molecular correlates with treatment response.

Lapatinib—Lapatinib, a dual tyrosine kinase inhibitor of EGFR and HER-2, was evaluated as second-line therapy in 59 platinum-refractory locally advanced or metastatic TCC patients with a primary endpoint of objective response rate >10%. [15] One patient achieved a PR; 18 (31%) patients displayed SD. Median time to disease progression and OS were 8.6 weeks and 17.9 weeks, respectively. Diarrhea, nausea, and vomiting were the most commonly reported toxicities. Seventeen of 19 patients who achieved SD or PR (89%) had EGFR and/or HER2 overexpressing tumors. The possible correlation between EGFR and

HER-2 expression and response to lapatinib therapy underscores the importance of prospective genetic sequencing as an eligibility criterion for targeted therapy studies.

Cetuximab—Cetuximab is an anti-EGFR monoclonal antibody FDA-approved for the treatment of head and neck as well as colorectal cancers.[16-18] A randomized phase II study gauged the efficacy of cetuximab with or without paclitaxel in patients with previously treated metastatic UC [19]. Patients received weekly cetuximab alone or weekly paclitaxel plus cetuximab. The single-agent cetuximab arm was terminated after 9 of the first 11 patients exhibited progression at 8 weeks. Median PFS and OS were 7.6 weeks and 17 weeks, respectively, and no objective responses were observed. In contrast, 28 patients were enrolled onto the combination arm with a median PFS and OS of 16.4 weeks and 42 weeks, respectively. The ORR was 25% (three CRs and four PRs). Notably, the most common treatment-related grade 3/4 adverse events were rash and hypomagnesemia. A comparator arm using single agent chemotherapy was not incorporated into this study. Additionally, patients who received perioperative chemotherapy but not first-line therapy in the metastatic setting were also enrolled. Finally, patients were not pre-selected based upon molecular predictors of response or resistance to cetuximab, such as EGFR overexpression or KRAS mutation, respectively.

A randomized phase II trial of GC with or without cetuximab was performed in advanced UC patients, with a primary endpoint of ORR. Patients were randomized in a 1:2 fashion to GC alone or GC with cetuximab [20]. Early in the study, gemcitabine was dose reduced by 20% to mitigate an observed increase in thromboembolic events with the 3-drug combination, resulting in decreased standard-of-care dose intensity. The ORR was 57.1% with GC and 61.4% with GC plus cetuximab. The median OS was 17.4 months with GC vs. 14.3 months with GC plus cetuximab (p=0.43). A higher rate of Grades 3-4 acneiform rash was seen with cetuximab.

Trastuzumab—HER-2 overexpression has been linked to shorter time to recurrence and is found in both primary and metastatic lesions in UC [21, 22]. Micropapillary histology, an aggressive variant characterized by poor survival, also harbors a high rate of *ERBB2* amplification [23]. In a retrospective analysis of 80 UC specimens derived from radical cystectomies, 28% exhibited HER2 2-3+ overexpression by IHC. In sixty of these specimens, matched metastatic samples were available and HER2 2-3+ overexpression was observed in both lymph node (63%) and distant (86%) metastatic deposits. Based upon these findings, a trial assessing the safety and efficacy of the humanized monoclonal anti-HER2 antibody trastuzumab in combination with carboplatin, gemcitabine, and paclitaxel in advanced UC patients was conducted, with cardiac toxicity as the primary endpoint [24]. HER2 overexpression by IHC, gene amplification by FISH, or elevated serum extracellular domain HER2 levels was a requirement for study participation. The median time to progression and OS were 9.3 and 14.1 months, respectively, and the ORR was 70%, with the majority of responses occurring in HER2 IHC 3+ or FISH-amplified patients. Since this was not a randomized trial, the impact of trastuzumab addition to chemotherapy could not be assessed. Additionally, the concordance between IHC overexpression and FISH

amplification seen in breast cancer was not observed in this sample set, suggesting that gene amplification does not necessarily correlate with protein levels in UC.

While the bladder TCGA identified HER-2 alterations in 9% of muscle-invasive specimens, the HER-2 mutation rate was higher than any other cancer type sequenced. Stemming from these data, neratinib, an irreversible HER2 TKI which has shown significant improvements in disease-free survival in HER2+ breast cancer, is currently being tested in UC through a novel basket trial design [25, 26]. Patients with EGFR mutations or amplifications as well as HER2 or HER3 mutations across multiple cancer types, including advanced UC, are being enrolled, with the primary objective of measuring 8 week ORR.

FGFR3 Signaling

Fibroblast growth factors (FGFs) are involved in a variety of cellular processes, such as proliferation, anti-apoptosis, and angiogenesis. FGFR3 is a particularly promising target for therapy in UC with an alteration rate of 16% in the bladder TCGA, including mutations (11%), amplifications (3%), and fusions (2%). Dovitinib, BGJ398, Ki23057, ponatinib, and AZD4547 are orally bioavailable FGFR inhibitors, which have demonstrated efficacy in preclinical models of UC [27].

Dovitinib—Dovitinib (TKI258), an oral multi-targeted receptor TKI of FGFR1-3, VEGFR, and others was assessed in 44 patients with metastatic UC with chemo-refractory UC at a dose of 500 mg/day on a 5-days-on/2-days-off schedule [28]. The study included both FGFR3 mutant and wild-type cases. None of the FGFR3-mutant patients responded; 1 PR was present in the wild-type cohort. The median PFS was 3 months in the mutant group and 1.8 months in the wild-type group. The drug was not carried into an expansion phase based upon these results. A phase I study of BGJ398, a pan-FGFR inhibitor, in patients with metastatic FGFR-altered cancers has shown promising results: 4 of 5 patients with FGFR3-mutant UC experienced tumor reductions (27%-48%), with hyperphosphatemia the most common adverse event noted [29].

Tumor Angiogenesis

Vascular endothelial growth factor (VEGF) is one of the key angiogenic factors that stimulate the formation of new blood vessels. [30] Heightened levels of VEGF and IL-8 correlate with higher stage and a worse disease-free survival in advanced UC [31-34]. Microvessel density (MVD), a surrogate for tumor angiogenesis, was linked to disease recurrence when measured in UC biopsy specimens, and MVD was an independent prognostic factor associated with both disease-free survival and OS in a multivariate analysis of 164 invasive UC specimens [35, 36]. These observations highlight the potential role for anti-angiogenic agents in UC, and the success of these compounds in other malignancies has driven further investigation in this disease.

Sunitinib

Sunitinib is a small molecule multi-targeted receptor TKI against VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and KIT, with activity in both *in vitro* and

in vivo UC models [37]. In 77 patients with advanced, previously treated UC, sunitinib was assessed in two patient cohorts by dose and schedule: cohort A patients received 50 mg daily on a 4-week-on and 2-week-off regimen while cohort B patients received 37.5 mg daily continuously. [38] Three patients in cohort A experienced a PR, and 1 in cohort B. Clinical regression or stable disease was observed in 33 of 77 patients (43%); the duration of regression ranged from 0.6 to 23.4 months. PFS (2.4 vs 2.3 months) and OS (7.1 vs 6.0 months) were comparable between cohorts A and B, respectively. Grades 3-4 toxicities were observed in 57 patients. Sunitinib did not achieve the threshold of 20% ORR (CR+PR) to be considered promising; however, antitumor responses were seen in some patients, indicating that anti-VEGF signaling may be therapeutically effective in a biomarker-guided context. Additionally, tumor necrosis resulted in decreased density of marker lesions but did not correlate with reduction in tumor diameter, implying that the Response Evaluation Criteria In Solid Tumors (RECIST) may not be the most accurate method to gauge responses to anti-angiogenic agents. In the metastatic and neoadjuvant (muscle invasive disease) settings, the combination of gemcitabine and cisplatin was assessed with sunitinib in two parallel phase II trials [39]. Both studies were limited by severe toxicity requiring premature closure.

Another multicenter trial evaluated sunitinib as first-line treatment in cisplatin-ineligible metastatic UC patients.[40] Of 38 patients, 3 (8%) evinced PRs and 19 (50%) exhibited stable disease. The median time to progression and OS were 4.8 months and 8.1 months, respectively, lower than the historical response rates observed with carboplatin-based chemotherapy. However, the 58% clinical benefit rate (PR+CR+SD) suggests activity in select patients. Notably, low pre-treatment IL-8 levels correlated with improved time to progression. Additionally, patients with >40 Hounsfield Unit enhancement within their tumors, a surrogate for high tumor vascularity, on baseline contrast-enhanced CT scans were likelier to benefit from sunitinib.

Sorafenib

Sorafenib, another oral multi-targeting receptor TKI against Raf and VEGFRs has also been evaluated in UC in two phase II trials: one in treatment-naïve metastatic disease and another in chemo-refractory patients. Neither study showed any objective responses [41, 42]. A randomized phase II trial in the first-line metastatic setting combined sorafenib or placebo with GC [43]. There were no significant differences in ORR or median PFS or OS between the 2 arms; diarrhea and hand-foot syndrome were more common with sorafenib therapy.

Pazopanib

Pazopanib is an oral multi-targeted receptor TKI against VEGFR-1, -2, and -3, PDGFR α and β , and KIT [44]. This drug was FDA approved for first-line treatment of clear cell RCC. A phase II study assessed the efficacy of pazopanib 800 mg daily in patients with chemo-refractory UC [45]. Twenty-one (51%) of 41 patients received pazopanib as third-line or further treatment and 24% had an ECOG performance status of 2. Seven patients had a confirmed PR (17.1%). The median PFS and OS were 2.6 and 4.7 months, respectively. Grade 3 toxicities were observed in 12 (29%) patients, including 2 cases each of gastrointestinal and vaginal fistulization; all 4 patients reinitiated therapy. One additional

patient died of a duodenal fistula [45]. Patients who developed fistulas also had bulky disease that responded significantly. On multivariate analysis, the presence of liver metastases, upper tract primary disease, and ECOG performance status were significantly associated with OS. When measured at 4 weeks post-treatment, IL-8 levels 87 pg/mL correlated with inferior OS (4.2 months vs. 6.7 months for patients whose 4 week IL-8 levels were <87 pg/mL). The study investigators postulate that elevations in IL-8 levels within 4 weeks of treatment may reflect a resistance mechanism to anti-angiogenic therapy, thereby serving as an early predictive marker of lack of efficacy.

Vandetanib

Vandetanib, a dual VEGFR and EGFR inhibitor, was assessed in a randomized, phase II study with docetaxel in advanced UC patients who had progressed on platinum-based chemotherapy [46]. 142 patients were randomly assigned to vandetanib 100 mg daily plus docetaxel or docetaxel plus placebo. The primary endpoint of this study was to compare PFS between the 2 arms. The median PFS was 2.56 months for docetaxel plus vandetanib vs. 1.58 months for docetaxel plus placebo with a HR of 1.02 (95% CI, 0.69 to 1.49; p=0.9). Response rates and OS were not different between the arms with a higher rate of toxicity in the combination arm including rash/photosensitivity (11% v 0%) and diarrhea (7% v 0%). When a validated prognostic model in patients who progressed on platinum-based chemotherapy comprising Hgb<10 g/dL, ECOG PS >0 and the presence of liver metastases was applied to the study population, all 3 parameters were significantly associated with a risk of death.[47]

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody against circulating VEGF and has displayed improvements in clinical outcomes when combined with chemotherapy in advanced RCC, NSCLC, colorectal cancer, and glioblastoma multiforme [48-53]. The Hoosier Oncology Group designed a phase II trial of GC plus bevacizumab (dosed at 15 mg/kg every 3 weeks) in chemotherapy-naïve patients with metastatic or unresectable UC [54]. After 8 cycles of combination therapy, bevacizumab was continued for a total of 12 months. Due to a higher than expected thromboembolic rate, gemcitabine was dose-reduced from 1,250 to 1,000 mg/m². DVT/PE events were subsequently significantly lower (8% after vs. 41% before dose reduction; p=0.023). Grades 3-4 hematologic toxicities included neutropenia, anemia, and thrombocytopenia. Non-hematologic grades 3-5 toxicities included hypertension (5%), proteinuria (2%), hemorrhage (7%), and cardiac toxicity (7%). Eight patients (19%) experienced a CR and 23 patients (53%) a PR. The median PFS and OS were 8.2 months and 19.1 months, respectively.

Bevacizumab was also evaluated in cisplatin-ineligible patients in a phase II study of gemcitabine, carboplatin, and bevacizumab 15 mg/kg every 3 weeks.[55] Patients received an initial dose of bevacizumab 10 mg/kg 2 weeks prior to the first dose of chemotherapy to enhance tumor penetration by cytotoxic agents. After a maximum of 6 cycles of chemotherapy, bevacizumab was continued for a total of 18 cycles as tolerated. The dose of carboplatin was reduced from an AUC of 5 to 4.5 after 13 patients were enrolled due to excess hematologic toxicities at the higher dose. An objective response was seen in 23

(49%) patients (three complete; 20 partial), and 11 (23%) had SD. The median PFS was 6.5 months. The most common grade 3-4 toxicity was neutropenia (31%) while thromboembolic events were the most common nonhematologic grade 3-4 toxicities (20%). The median OS was 13.9 months, superior to that of other studies of patients treated with carboplatin plus gemcitabine alone.

Additionally, 28 patients continued on maintenance bevacizumab after completing 6 cycles of chemotherapy, and 9 displayed shrinkage of target sites on monotherapy, suggesting that VEGF axis inhibition alone is effective in select patients.

Given these promising results, a phase III randomized trial (CALGB 90601) of GC with or without bevacizumab in the first-line metastatic setting is currently accruing.

PI3K/Akt/mTOR signaling

PI3K signaling results in activation of Akt, a central nexus within the cell that promotes growth and proliferation and inhibits apoptosis; *PIK3CA* activating mutations, *TSC1/2* mutations or deletions, and *AKT3* overexpression were detected in 42% of bladder TCGA samples. Akt upregulates mTOR, a serine-threonine kinase that forms 2 multi-protein complexes (mTORC1 and mTORC2) which regulate cell growth, motility, and proliferation [56]. In addition to Akt, mTOR activity is controlled by amino acid supply, hypoxia, and DNA damage; the mTOR inhibitor everolimus has been FDA approved in numerous cancer types, including RCC, pancreatic neuroendocrine tumors, and HER2-negative, hormone receptor-positive breast cancer.[57-59]

Everolimus

Initial in vitro studies demonstrated that mTOR blockade by everolimus inhibited proliferation, stimulated cell cycle arrest, and downregulated phosphorylated S6, a key effector of mTOR activity, within UC cell lines; these results were recapitulated in xenograft models. Based upon these preclinical findings, everolimus was explored further as a potential therapeutic agent in UC [60].

A multicenter phase II study assessed everolimus 10 mg daily in patients with advanced UC following prior platinum-based therapy [61]. The primary endpoint was 2 month disease control rate, defined as CR, PR, or SD. Of 37 evaluable patients, 2 patients experienced a PR and 8 patients SD, with a disease control rate of 27% at 8 weeks. The median PFS and OS were 61 days and 101 days, respectively [61]. Fatigue (27%) and thrombocytopenia (13%) were the most frequent grade 3-4 toxicities observed. Potential biomarkers of response to everolimus were examined, including plasma levels of angiopoietin-1, endoglin, and PDGF-AB (all angiogenesis regulating proteins). A statistically significant reduction in the level of these proteins was seen in patients with disease control as opposed to those with progressive disease. Loss of PTEN expression was observed in 57% of patients with progressive disease and in none of the patients who achieved disease control.

Another phase II study examined everolimus in 45 patients with advanced UC who had progressed on 1-4 prior lines of cytotoxic chemotherapy.[62] A median PFS of 2.6 (1.8-3.5)

months and a median OS of 8.3 (5.5-12.1) months were observed. In eight patients, treatment was stopped secondary to drug related toxicities; common grade 3-4 toxicities included hyperglycemia, hypophosphatemia, and fatigue. Six patients experienced everolimus-related pneumonitis. Notably, one patient experienced a durable CR to treatment lasting >26 months (ongoing). Whole genome sequencing of this patient's cystectomy specimen revealed alterations in TSC1 and NF2 which were predicted to result in premature truncation of both proteins. TSC1 and NF2 are negative regulators of the mTOR pathway, and inactivation of both proteins leads to enhanced mTOR signaling, suggesting that loss of both tumor suppressor proteins may have resulted in the depth and duration of response observed within this patient [63]. Exon capture sequencing of 13 additional patients on the study revealed 4 TSC1 alterations, 3 of which were present in patients with minor responses to therapy. This discovery reinforces the importance of the PI3K/AKT/mTOR signaling pathway as a potential target in UC and underscores the utility of prospective genotyping to identify those patients with pathway altered tumors most likely to respond to mTOR-directed therapies.

Additional Targets in UC

As mentioned before, cell cycle regulatory genes are frequently altered in UC, including CDKN2A (47% deletion) and CCND1 (10%, amplification). Tumors harboring these alterations may be amenable to cyclin dependent kinase inhibitors such as palbociclib or LEE001. Chromatin regulatory genes were altered in 76% of tumors in the bladder TCGA. While the biologic ramifications of such alterations have yet to be elucidated, evidence for the utility of histone deacetylase (HDAC) inhibitors in UC already exist: in one phase I trial of vorinostat in advanced solid tumor patients, 2 metastatic UC patients experienced responses lasting 6 and 7 months, respectively; in a second trial, 1 of 7 metastatic UC patients exhibited SD for 10 months.[64, 65] A trial of the HDAC inhibitor mocetinostat in advanced UC patients with *CREBBP* or *EP300* alterations is currently accruing.

Conclusions

Metastatic UC is a lethal disease and platinum-based chemotherapy remains the optimum first line therapy. While phase I and II trials of targeted agents have not displayed a significant improvement in survival or response when compared to cytotoxic therapy, a common theme has been the lack of genetic pre-selection of patients. A number of studies in other cancer types have shown that those patients whose tumors harbor a specific genetic target are most likely to respond to small molecule inhibitor treatments, with the requirement that the molecular target of these inhibitors is well-defined. With the advent of Next Generation sequencing technologies, both deep coverage exon capture sequencing and unbiased exome or genome sequencing, new trials of targeted agents are underway which incorporate the presence of specific genetic aberrations into enrollment criteria. Additionally, basket studies, in which a drug is tested across tumor types and enrollment is based principally upon the presence of specific genetic alterations within a gene or genes, represent a unique trial design to rapidly screen the efficacy of targeted agents and define the predictive capacity of the same aberration in different tumors. Finally, it should be noted that while novel sequencing technologies have unearthed a plenitude of somatic alterations in

UC, a better understanding of the functional consequences, relevance to tumorigenesis and drug sensitivity of many of these alterations (i.e., identifying the true drivers of oncogenesis) is still required and will hopefully inform clinical trials of targeted therapies for this disease in the future.

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Key Points

Clinical trials of targeted agents in UC have not displayed a significant improvement in response or outcome compared to chemotherapy

None of these trials have incorporated prospective sequencing to identify predictive biomarkers of response to therapy

Predictive biomarkers are crucial for identifying tumors most likely to obtain benefit from targeted agents

Basket clinical studies will allow targeted agents to be assessed across tumor types based upon the presence of a specific genetic biomarker

Table 1

Clinical trials of Targeted Agents in Urothelial Carcinoma

Targeted Therapy	No. of pts		Response Rate	Median PFS (months)	Median OS (months)
EGFR					
Gefitinib ¹²	31	Second Line	3%	2	3
Gefitinib ¹³	58	First line +GC	42.6%	7.4	15.1
Erlotinib ¹⁴	20	Neoadjuvant	60%	N/A	N/A
Cetuximab ¹⁹	28	Second Line +/- paclitaxel	25%	16.4 weeks	42 weeks
Cetuximab ²⁰	88	First Line +GC	57.1% (GC) vs. 61.4% (GC+ Ctx)	8.5 (GC) vs. 7.6 (GC + Ctx)	17.4 (GC) vs. 14.3 (GC + Ctx)
EGFR + Her2					
Lapatinib ¹⁵	59	Second Line	1.7%	8.6 weeks	17.9 weeks
Her2					
Trastuzumab ²⁴	44	First Line + PCaG	70%	9.3	14.1
FGFR3					
Dovitinib ²⁸	44	Second Line, FGFR3 wt and mut	3% (wt) 0% (mut)	1.8 (wt) 3 (mut)	NR
Angiogenesis					
Sunitinib ³⁸	77	Second Line A: 50 mg daily 4 wk on/2 wk off B: 37.5 mg daily	A: 7% B: 3%	A: 2.4 B: 2.3	A: 7.1 B: 6
Sunitinib ⁴⁰	38	First Line cisplatin ineligible	8%	4.8	8.1
Sorafenib ⁴¹	17	First Line	0%	1.9	5.9
Sorafenib ⁴²	22	Second Line	0%	2.2	6.8
Sorafenib ⁴³	40	First line +/- GC	52.5%	6.3	11.3
Pazopanib ⁴⁵	41	Second Line	17.1%	2.6	4.7
Bevacizumab ⁵⁴	43	First Line + GC	72%	8.2	19.1
Bevacizumab ⁵⁵	51	First Line + GCa	49%	6.5	13.9
mTOR					
Everolimus ⁶¹	37	Second Line	27%	61 days	101 days
Everolimus ⁶²	45	Second Line	6.7% **	2.6	8.3
VEGFR + EGFR					
Vandetanib ⁴⁶	142	Second Line +/- Docetaxel	7%	2.56	5.85

Data from Refs 12-15,19,20,24,28,38,40-43,45,46,54,55,61,62.

PFS: Progression-free survival; OS: Overall survival; EGFR Epidermal Growth Factor Receptor; GC: Gemcitabine + Cisplatin; Ctx: Cetuximab; PCaG: Paclitaxel + Carboplatin + Gemcitabine; FGFR3: Fibroblast Growth Factor Receptor-3; mut: mutant; wt: wild-type; NR: Not reported; GCa: Gemcitabine + Carboplatin; mTOR: mammalian target of rapamycin; VEGFR: Vascular Endothelial Growth Factor Receptor