



Published in final edited form as:

*Cancer Treat Res Commun.* 2020 ; 25: 100179. doi:10.1016/j.ctarc.2020.100179.

## Emerging biomarkers in urothelial carcinoma: Challenges and opportunities

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### Abstract

Advanced urothelial carcinoma (UC) is a very important cause of cancer-related morbidity and mortality with, until recently, only a few available therapeutic options. The treatment landscape has dramatically changed in recent years with the introduction of immune checkpoint inhibitors and the development of novel targeted agents, such as erdafitinib, and antibody-drug conjugates, such as enfortumab vedotin. Cost-effective utilization of this rapidly expanding therapeutic armamentarium can be further optimized via the identification and validation of reliable prognostic and predictive biomarkers that inform prognostication and patient selection. In this review, we aim to summarize examples of recent developments in the rapidly expanding field of emerging biomarkers in UC, outlining challenges and opportunities.

### Keywords

Bladder; Biomarkers; DDR; Immunotherapy; NGS; Trial

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CRedit authorship contribution statement

**Nikolaos Andreatos:** Conceptualization, Investigation, Project administration, Methodology, Writing - original draft, Writing - review & editing. **Gopa Iyer:** Validation, Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Petros**

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

**Nikolaos Andreatos:** None.

**Gopa Iyer (unrelated to this work):** Mirati: Research funding and consulting; Janssen: Research funding; DeBio Pharm: Research funding; Novartis: Research funding; OncLive: Speaking fees.

**Petros Grivas (unrelated to this work, within 3 years):** consulting for AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Driver, EMD Serono, Exelixis, Foundation Medicine, GlaxoSmithKline, Genentech, Genzyme, Heron Therapeutics, Janssen, Merck, Mirati Therapeutics, Pfizer, Roche, Seattle Genetics, QED Therapeutics; participation in educational program for Bristol-Myers Squibb; institutional research funding from AstraZeneca, Bavarian Nordic, Bayer, Bristol-Myers Squibb, Clovis Oncology, Debiopharm, Genentech, Immunomedics, Kure It Cancer Research, Merck, Mirati Therapeutics, Oncogenex, Pfizer, QED Therapeutics.

## Introduction

Bladder cancer is prevalent in the United States, with 80,470 estimated cases in 2019 [1], 25% of which constitute muscle-invasive disease [2,3]. Urothelial carcinoma (UC) is the most common histology and can arise throughout the urinary tract [4]. Metastatic disease occurs *de novo* in 4% of cases, but more commonly follows initially localized disease and has poor prognosis [2,3,5,6]. First-line treatment consists of platinum-based chemotherapy (PBT) while salvage chemotherapy has limited benefit [7]. The introduction of immune checkpoint inhibitors (ICIs) has transformed this landscape; the Food and Drug Administration (FDA) has approved five ICIs in the platinum-refractory setting, two for cisplatin-unfit patients with high PD-L1 (hPD-L1) expression or platinum-unfit patients [7-9], and one for BCG-unresponsive *carcinoma in situ* (CIS) in patients unable/unwilling to undergo radical cystectomy [10,11]. The accelerated FDA approvals of erdafitinib (*FGFR* inhibitor) [12,13] and enfortumab vedotin [antibody-drug conjugate (ADC) against Nectin-4] [14,15] provide additional salvage options.

These advances are tempered by toxicity, cost, and limited data on patient selection and treatment sequencing [7,16]. While “prognostic” biomarkers have been identified, they cannot guide therapy selection, but only forecast anticipated outcomes, regardless of treatment [16-18]; biomarkers able to predict clinical benefit (“predictive”) are urgently needed [16]. Below we survey some key development in this exciting field, but space limitations preclude an exhaustive discussion. More details can be found in excellent reviews [16,19-21].

## Molecular classification of UC

Classification of UC into molecular subgroups is evolving. After a landmark publication from Lund University [22], leading to an immunohistochemistry-based (IHC) taxonomy in 2012 [23] (updated in 2018 [24]), groups from the University of North Carolina [25], MD Anderson [26,27], the Cancer Genome Atlas Research Network (TCGA) [28,29] and the Curie Institute [30] proposed independent classifications (Table 1). Most schemes recognize luminal and basal subtypes, with the latter demonstrating worse prognosis [31]. A neuronal subtype with even poorer prognosis was later incorporated and can be identified by a validated 84-gene panel [29,32,33]. Basal tumors appear to respond better to cisplatin-based neoadjuvant chemotherapy (NAC) [34,35] and luminal cluster II tumors to atezolizumab [36], suggesting that molecular subtypes may have predictive utility, upon further validation.

Discordance between classification schemes hinders their practical use, leading a multi-national consortium to formulate a consensus taxonomy, which recognizes six molecular types: luminal papillary (LumP), luminal unstable (LumU), luminal non-specified (LumNS), stroma-rich, basal/squamous and neuroendocrine-like [37]. LumP, stroma-rich and LumNS tumors have the best prognosis, LumU tumors fare worse, while basal/squamous and neuroendocrine-like tumors demonstrate the worst outcomes. Response to cisplatin-based NAC was prominent among LumNS and basal/squamous tumors, while LumNS, LumU and neuroendocrine-like tumors responded to atezolizumab. LumP tumors demonstrated *FGFR3*

alterations, LumU tumors *ErbB2* amplification, and basal/squamous tumors high *EGFR* expression, suggesting the potential of targeted inhibition.

## DNA damage response (DDR) gene mutations

Since DNA damage underlies the efficacy of PBT, alterations in the DDR pathway may enhance chemo-sensitivity [7,16,38]. Data on *ERCC1* and *ERCC2*, enzymes involved in nucleotide excision repair, shed light on this hypothesis [16,39,40]. Bellmunt et al. associated low *ERCC1* RNA expression with improved survival after PBT in advanced UC [41]; an IHC-based study demonstrated similar findings [42]. Reports from bladder-directed therapy cohorts demonstrated opposite results [43,44]. A trial of NAC with dose-dense (dd)MVAC showed no association between *ERCC1* expression and prognosis [45], while a meta-analysis associated high *ERCC1* expression with shorter progression-free survival (PFS), but not OS [46]. Loss-of-function *ERCC2* mutations have been associated with improved outcomes after PBT in clinical and pre-clinical settings [47-51]. Mutations in other DDR genes, (e.g. *ATM*, *FANCC*, *RB1*) correlate with response to cisplatin-based NAC [52], while *p53* mutations have been linked to both inferior [53-56] and improved outcomes [57] after chemotherapy. Notably the “*p53-like*” molecular subtype has been associated with resistance to NAC [26,58]. Counter-intuitively, *MRE11* (a protein involved in DNA double-strand break repair) expression correlated with improved outcomes following bladder-directed radiotherapy [59,60]. This paradox has been attributed to tumor DNA repair deficiency, with *MRE11* up-regulation signifying an ineffective adaptive response [40].

Given the plethora of putative biomarkers, comprehensive genomic assays may serve as better response predictors [51,61] and are increasingly integrated into clinical trials. The Alliance trial (NCT03609216) [62], assessing 3-year disease-free rates among individuals with DDR alterations and <cT1 response to dose-dense gemcitabine/cisplatin (GC) may help redefine discussions about indications for bladder preservation. The RETAIN trial investigates outcomes in patients with *ATM/RB1/FANCC/ERCC2* mutations and no residual disease after accelerated MVAC followed by active surveillance or bladder-directed therapy [63]. Mount Sinai investigators are assessing the impact of DDR gene mutations on outcomes of patients managed with neoadjuvant GC/nivolumab (with maintenance nivolumab allowed for up to 8 cycles) and radical cystectomy or surveillance [64]. The activity of PARP inhibitors in DDR-deficient tumors is also under investigation [65,66], but so far without promising results [67,68].

## Growth factors and kinase-mediated signaling

Constitutive activation of the *FGFR* pathway is common in UC, with a recent report identifying such aberrations in 33% of specimens [69], most frequently in upper-tract and non-muscle invasive disease [70,71]. Despite a small negative trial of the *FGFR* inhibitor dovitinib [72], erdafitinib, a pan-*FGFR* inhibitor demonstrated a response rate of 40% in the platinum-refractory setting [13] and received accelerated FDA approval for patients with activating *FGFR2/FGFR3* mutations/fusions in 2019 [12]. The ongoing THOR trial (NCT03390504) is comparing erdafitinib to chemotherapy or pembrolizumab [73]. BGJ398 (infigratinib) [74,75], AZD4547 [76], pemigatinib [77], rogaratinib [78], Debio1347 [79],

B701 [80] and MFGR1877S [81] are being evaluated in advanced disease, while a phase III trial (NCT04197986) will assess adjuvant infiratinib vs placebo after radical surgery [82]. Given the variable efficacy of these agents and the use of different assays and biomarkers in clinical trials, validation of predictive biomarkers for *FGFR* inhibitors is very challenging. Next-generation sequencing (NGS) of tumor tissue and cell-free circulating tumor (ct)DNA at baseline and after progression may help identify resistance mechanisms and guide therapy [74,83,84].

*VEGF* overexpression heralds poor prognosis in UC, suggesting the potential of angiogenesis inhibition [85-88]. The RANGE trial showed modest PFS gain (median 4.1 vs 2.8 months,  $p = 0.0002$ ), without significant OS benefit (median 9.4 vs 7.9 months,  $p = 0.25$ ), from the addition of ramucirumab to docetaxel in platinum-refractory disease [89]. The CALGB 90601 (Alliance) trial assessed bevacizumab/GC vs GC alone in the first-line setting and showed modest PFS (Hazard Ratio (HR): 0.77,  $p = 0.0074$ ) but not OS benefit (median 14.5 vs 14.3 months,  $p = 0.17$ ) [90]. Results with the anti-angiogenic kinase inhibitors sunitinib, sorafenib, pazopanib and vandetanib have been discouraging [91-98]. The combination of angiogenesis inhibitors with immunotherapy is being investigated, with promising signals for cabozantinib plus nivolumab/ipilimumab [99] pembrolizumab plus ramucirumab [100] or lenvatinib [101] and sitravatinib plus nivolumab [102]. A phase II trial (NCT03272217) evaluating atezolizumab/bevacizumab and a phase III trial comparing pembrolizumab/lenvatinib vs pembrolizumab/placebo (NCT03898180) in cisplatin-ineligible patients, among other trials, are ongoing [103,104].

*ErbB* pathway inhibition has produced variable results; *EGFR* blockade demonstrated minimal benefit [105,106] and trastuzumab-based *Her2/neu* inhibition showed potential [107] that was not confirmed on a subsequent trial [108]. Limited sample size and challenges with *Her2/neu* expression heterogeneity, assay concordance and standardization (known issues in breast cancer [109] but less studied in UC), may be responsible for this discrepancy. Interestingly, the MyPathway trial suggests that trastuzumab/pertuzumab can be active in advanced UC, while results from NCI-MATCH arm J are pending [110]. Additional anti-*Her2/neu* therapies are under investigation; a phase II study noted a response rate of 60.5% following RC48-ADC [111], while the DS-8201a/nivolumab combination is undergoing assessment (NCT03523572) [112]. Data on T-DM1 is needed, as the reported results of NCI-MATCH arm Q included no UC cases [113].

Broader inhibition of the *ErbB* family is another potential strategy, with lapatinib showing activity in tumors with *EGFR* or *Her2/neu* overexpression [114]; however, switch maintenance lapatinib after induction chemotherapy demonstrated no clinical benefit [115] and neratinib showed no significant activity in UC [116]. Afatinib, despite lacking activity in unselected patients and the four UC cases included in NCI-MATCH arm B [117], showed a promising signal in patients harboring *ErbB2/ErbB3* amplification/mutation in another trial [118]. Similarly, *PI3K/AKT/mTOR* pathway inhibition may hinge on patient selection, with durable response to everolimus noted in a patient with *TSC1* inactivating mutation, compared to suboptimal results in unselected cases [119,120]. Similar findings were reported with everolimus/pazopanib [121], suggesting the existence of rare, highly targetable

molecular profiles. Results from the NCI-Match ([NCT02465060](#)), TAPUR ([NCT02693535](#)) and the future Combo-Match trials will provide further guidance [122-124].

## Predicting immunotherapy response

ICIs are standard-of-care in platinum-refractory UC, and a first-line option for platinum-ineligible patients or cisplatin-ineligible patients with hPD-L1 tumor expression [7,8,16]. Pembrolizumab was also approved for BCG-unresponsive CIS in patients unwilling/unable to undergo radical cystectomy following the KEYNOTE-057 trial [10,11]. While rapid and durable responses following ICI administration occur, significant benefit is restricted to a minority of patients [125]. Given the cost and toxicity of ICIs, early identification of potential responders is desirable [126-129].

ICI response rates are associated with hPD-L1 tumor tissue expression in the platinum-refractory setting [36,130-134], but responses are not limited to the hPD-L1 group. While phase II trials of pembrolizumab or atezolizumab for cisplatin-ineligible patients in the first-line setting demonstrated responses across all PD-L1 subgroups [135,136], an interim analysis of the KEYNOTE-361 and IMvigor-130 phase III trials showed inferior survival with ICI monotherapy in patients whose tumors demonstrated low PD-L1 expression [137]. The FDA and the European Medicines Agency subsequently restricted pembrolizumab or atezolizumab in the first-line setting to cisplatin-ineligible patients with hPD-L1 tumor tissue expression based on a companion assay [the FDA also permits atezolizumab or pembrolizumab use in platinum-ineligible patients] [137,138]. Evidently, the association of tumor PD-L1 expression with outcomes is complex and confounded by disparities in employed assays and scoring systems [16,127]. Recently, the IMvigor-130 trial randomized patients to first-line PBT/atezolizumab (arm A), atezolizumab alone (arm B) or PBT/placebo (arm C) and suggested a non-significant trend towards longer OS in arm B vs arm C in the hPD-L1 subgroup analysis, but longer follow-up is needed [139]. It remains to be seen whether mature results from the IMvigor-130 [139], Key-note-361 [140] and Checkmate-901 [141] phase III trials, may result in a paradigm shift in UC similar to non-small cell lung cancer [142,143]. Interestingly, the DANUBE trial showed no OS benefit from either durvalumab in patients with hPD-L1 tumors or durvalumab/tremelimumab in “all-comers” with metastatic UC in the first-line setting compared to PBT [144]. However, the Javelin Bladder 100 trial which assessed switch maintenance avelumab following lack of progression on first-line PBT met OS endpoints in “all comers” and patients with hPD-L1 tumors [145]. Detailed data from these two trials are awaited.

Indicators of immune activation, such as infiltrating CD8 T-cells [36,146], increased T-effector gene [36] and *IFN-γ* expression [130] and high intra-tumoral T-cell clonality [147] are associated with ICI response. Conversely, *TGFβ* expression has been associated with worse outcomes possibly by hindering tumor infiltration by immune cells in the stroma [146,148,149]. Moreover, instability of the cancer genome seems relevant to neoantigen formation and immunogenicity [150,151], which may explain why biomarkers of genomic instability, such as high tumor mutational burden (TMB) [36,129,130,146], microsatellite instability [152] and DDR alterations [153,154] appear to correlate with ICI response.

Among non-UC bladder tumors, squamous cell carcinomas demonstrate high TMB and PD-L1 expression and may possibly benefit from ICIs [155].

The integration of the aforementioned biomarkers in a scoring system, (“immunogram” per van Dijk et al. [127,156]) may hold future promise. Two recent neoadjuvant single-agent ICI trials conducted such comprehensive biomarker assessment [157,158]. The ABACUS trial (2 doses of atezolizumab) demonstrated that CD8 T-cell infiltration and expression of an eight-gene transcriptional T-cell biomarker correlated with pathologic response, while *TGFβ* expression with resistance; PD-L1 expression, TMB and DDR gene mutations were not associated with pathologic response [157]. The PURE-01 trial (3 doses of pembrolizumab) reported that both higher PD-L1 expression and higher TMB correlated with pathologic response, while DDR gene mutations did not [158]. These discrepancies illustrate challenges in reproducibility, consistency and validation of emerging biomarkers. Novel technologies relying on RNA expression profiling may help identify robust signatures predictive of response to immunotherapy [159].

Discoveries on the impact of *IDO1* expression on immune response has led to the hypothesis that *IDO1* inhibition may facilitate response to ICIs [160]. Despite promising results from the Echo-202 study [161] and from a report assessing BMS-986205/nivolumab in a pre-treated cohort [162], recent data from patients with melanoma [163] and pancreatic carcinoma [164] question ICI/*IDO1* inhibitor combination therapy. Additional data from UC is anticipated [165,166].

## Evolving therapeutic targets

Nectin-4 is a cell adhesion molecule expressed in >90% of UC specimens [167,168]. An ADC targeting Nectin-4 (enfortumab vedotin) recently achieved a response rate of 44% with median PFS and OS of 5.8 and 11.7 months, respectively in a heavily pre-treated (PBT and ICI) cohort in the single-arm phase II EV-201 trial [14] and received accelerated FDA approval [15]; the EV-301 trial comparing enfortumab vedotin to salvage chemotherapy is ongoing (NCT03474107) [169]. Sacituzumab govitecan and ASG-15ME are other ADCs (anti-Trop-2 and anti-SLITRK6, respectively) with promising early activity [170,171]. Interim results from cohort 1 of the TROPHY-U-01 trial (sacituzumab govitecan following progression on PBT and ICI) are very encouraging with overall response rate of 29% in heavily pre-treated patients; follow-up data is pending [172].

Putative biomarkers of chromatin dysregulation in UC (e.g. *CREBBP/EP300* inactivating mutations or deletions) did not lead to significant efficacy of mocetinostat, a selective histone-deacetylase inhibitor, in a phase II trial in biomarker-selected patients with platinum-refractory advanced UC [173]. *EZH2* inhibitors, a novel class of epigenetic modifiers, are being tested in patients with *KDM6A/ARID1A* alterations [174-176].

## Biomarker analysis and utilization

Once biomarkers are validated, reliable laboratory identification constitutes the next challenge. ctDNA technology is promising in this respect, with potential roles in predicting outcomes, assessing treatment effect and identifying serially significant genomic alterations

[177,178]. Tissue-derived testing and ctDNA results may differ; the PREVAIL study (NCT03788746) is assessing the correlation of tissue vs blood-derived TMB among other biomarkers [178-180]. Additional assays focusing on whole transcriptome profiling are under development [34,181]. While NGS techniques are increasingly employed, data on their comparability, cost-effectiveness, and clinical utility is needed [182]. The role of mutant-allele fraction and bi-allelic status in predicting therapeutic response remains elusive. Expert review of somatic tumor testing can identify targets for approved therapies, biomarker-based trials, and trigger dedicated germline mutation testing [183], with germline mutations reported in up to 24% of patients with UC [184,185]. Importantly, somatic mutation testing is no substitute for germline testing.

Gene expression panels that integrate multiple underlying biomarkers are increasingly employed. The S1314 trial tested whether a gene expression score (COXEN) could predict response among patients treated with NAC (GC/ddMVAC). The GC-specific COXEN signature was prognostic in the whole cohort, but not predictive of response with no interaction between response to each regimen and COXEN score being noted [186]. Despite the negative result, the employed methodology can inform future trial designs and provide the setting for validation of other putative biomarkers.

## Conclusions

Therapeutic advances in UC necessitate the development of integral and integrated biomarkers to guide treatment allocation and stratification in clinical trials. The plethora of biomarkers and assays, limitations in funding and patients available for clinical trials, as well as variability in trial endpoints complicate this effort. Existing obstacles may only be surmounted by research coordination, assay standardization, establishment of biorepositories/registries and sophisticated trial designs. While the challenges are formidable, the promise of personalized therapy in UC has never been higher.

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**Table 1**

A selection of published molecular classification schemes for urothelial carcinoma.

Study	Year	Sample Size	Categories	Comments
Lindgren [22]	2010	144	-MS1 -MS2	-MS2 tumors characterized by genomic instability, p53 dysfunction
Sjodahl [23]	2012	308	-Urobasal A -Genomically unstable -Urobasal B -Squamous-cell like -Infiltrated	-Urobasal A/B strongly expressed FGFR3
Damrauer [25]	2014	262+49 (validation)	-Basal-like -Luminal	-Luminal with higher FGFR3/TSC1 expression, basal with RB1 loss -Claudin-low subtype in basal tumors; similar prognosis
Choi [26]	2014	73+57 (validation)	-Luminal -Basal -p53-like	-Luminal with FGFR3, ErbB expression -Basal with squamous features -p53 predicts chemo-resistance
TCGA [28]	2014	131	-Cluster I -Cluster II -Cluster III -Cluster IV	-High mutational burden across examined samples -76% of samples with altered chromatin regulation -Cluster I (papillary-like) with high FGFR3 expression -Cluster III noted to have mixed basal/squamous features
Rebouissou [30]	2014	383	-Non-basal-like -Basal-like	-Basal-like with EGFR signaling, squamous histologic features -FGFR3 expression equally distributed -Inhibition of EGFR effective against basal-like in experimental assessment
Robertson (TCGA) [29]	2017	412	-Luminal-papillary -Luminal-infiltrated -Luminal -Basal/squamous -Neuronal	-Luminal-papillary with FGFR3 signaling -Luminal-infiltrated and basal/squamous with immune signatures; former also with stromal signatures/p53 wild-type -Neuronal with loss of p53/RB1
Mo [27]	2018	Combination of TCGA 2017, MD Anderson and Lund datasets	Differentiated/Basal	-Basal with high CTLA4 and PD-L1 expression
Marzouka [24]	2018	426	-Uro (UroA-Prog, UroB, UroC, Uro-Inf) -Genomically unstable (GU, GU-Inf) -Basal-Squamous (BaSq, BaSq-Inf) -Mesenchymal-like -Small-cell/Neuroendocrine-like	-UroB worse prognosis than other Uro types -FGFR3 mutations noted in UroA-Prog and UroB, but not UroC -Remaining types with high mutational burden, DDR alterations
Kamoun [37]	2019	1750	-Luminal papillary (LumP) -Luminal non-specified (LumNS) -Luminal unstable (LumU) -Stroma-rich -Basal/Squamous (Ba/Sq) -Neuroendocrine-like (NE-like)	-NE-like worst prognosis -LumP with frequent FGFR3 overexpression -Ba/Sq with frequent EGFR overexpression and immune checkpoint markers -LumU with ErbB2 expression