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ABSTRACT

Genomics-driven, precision medicine has been adopted in virtually every tumour type and underlies the significant advances in cancer management to date. The paradigm shift from the indiscriminate use of chemotherapeutics, to strategies that harness our mechanistic knowledge of cancer biology has led to profound clinical benefit for patients, and will continue to mould present and future treatment approaches. In the realm of urothelial cancer, the present status of precision medicine includes a rich landscape that encompasses molecularly-matched therapy, predictive biomarkers that could help inform response to chemotherapy and immunotherapy, as well as novel strategies such as antibody drug conjugates that exploit the use of target proteins for enhanced tumour killing. Here, we present an overview on these clinically-impactful discoveries in urothelial cancer, discuss the limitations and challenges in the implementation of precision oncology, and offer our vision for its future.

INTRODUCTION

Precision medicine, known alternatively as personalised or stratified medicine, is a concept that permeates many disciplines of medicine.¹ Its application involves individualised management that is tailored to each patient's unique clinical characteristics, such as age, family history, medical comorbidities, performance status and immune competence.² Though precision medicine can be readily and broadly applied throughout the practice of medicine, oncological diseases are truly the front-runner candidate for genomics driven, tailored treatment.¹ Our growing knowledge on oncological driver mutations has supported the development of targeted drugs that interfere with pathways underscoring cancer biology.³

Although the successful practice of genomics-driven medicine is not without its challenges, we are poised to deliver more rational management options to many through the broader practice of precision oncology. As we better understand the molecular aspects of cancer, and their correlation with outcomes, we will be better placed to identify molecular biomarkers in individual patients that will guide treatment selection and management decisions.

Until recently, there was a paucity of therapeutic breakthroughs for the management of urothelial cancer. As with many

other tumour types, significant advances in genomic research have changed the state of play, heralding treatment options which harness the concept of precision medicine. The employment of personalised treatment strategies seems particularly apt in the management of urothelial cancer, a tumour characterised by its heterogeneity and high mutational burden.

As both discovery and translational research in urothelial cancer gathered momentum in recent years, the molecular insights gained^{4,5} have led to identification of targetable 'driver mutations' and both predictive and prognostic biomarkers that may be used in selecting optimal treatment options. Additionally, specific genetic alterations have been demonstrated to impact chemotherapy responsiveness, and potentially predict immunotherapy efficacy. Lastly, at the protein level, candidate cancer-specific proteins are being targeted by antibody–drug conjugates (ADCs).⁶

This review article will detail how precision oncology has taken many forms in urothelial cancer, ranging from molecularly matched treatments targeting driver mutations, to novel molecular biomarkers of treatment responsiveness, to fresh approaches targeting cancer-specific proteins.

MOLECULARLY MATCHED TREATMENT: TARGETING DRIVER MUTATIONS

Initiatives undertaken by the Cancer Genome Atlas (TCGA) Research Network to define the genomic profile of major human tumours have produced a laudable repository of landmark molecular insights.⁷ The publically accessible TCGA dataset encompasses over two petabytes of data outlining genomic alterations in 33 cancer types.⁸

Findings outlined in the 2014⁷ and 2017 TCGA reports⁹ on urothelial carcinoma have profoundly shaped our understanding on the genomic profile of this tumour type, and remains a vital source of reference for clinicians and laboratory researchers alike. Muscle invasive bladder cancer and non-muscle invasive bladder cancer were shown to harbour distinct molecular profiles.^{7–9} Genes

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with statistically significant levels of mutation in muscle-invasive samples include *TP53* (49%), *PIK3CA* (20%), *CDKN1A* (14%), *ERCC2* (12%), fibroblast growth factor receptor 3 (*FGFR3*) (12%) and *ERBB3* (11%).^{7–9} Several of the druggable genomic alterations highlighted in these studies have since been the subject of keen investigation in clinical trials (table 1). Of note, this landscape of mutations has stemmed from analyses performed on primary tumours, in non-metastatic settings. The 2014 TCGA initiative was undertaken on 131 biospecimens obtained from patients with non-metastatic muscle-invasive disease,⁷ while only a small fraction of tissue from the 2017 TCGA study were sourced from patients with metastatic disease (11 out of 412 patients).⁹

Targeting the FGFR pathway

The FGFR family incorporates four highly conserved receptor tyrosine kinases.¹⁰ Its signalling governs many key cellular mechanisms including proliferation, differentiation, migration, angiogenesis and tumourigenesis.¹⁰ Several intracellular pathways have been implicated in fibroblast growth factor (FGF)/FGFR signalling, including the Ras/Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK) and phosphoinositide 3-kinase (PI3K)-AKT pathways. FGFR receptor activation triggers complex intracrine, paracrine and exocrine actions that coordinate a host of physiological processes essential for development and metabolism.¹⁰

FGFR mutations are highly oncogenic in animal models, and are detected in a wide range of human cancers including urothelial cancer. In one landmark study, next generation sequencing was performed on 4853 solid tumour samples in order to characterise the oncological landscape of FGFR.¹¹ The robust results generated from this study provide an excellent overview of the spectrum of FGFR alterations detected in human cancers, with the most common abnormality being gene amplifications (66%), followed by gene mutations (26%) and gene rearrangements (8%).¹¹ In general, the frequencies of aberrations in different FGFR subfamilies were quantified as follows: *FGFR1* (49%), *FGFR3* (23%), *FGFR2* (19%), with *FGFR4* least commonly affected (7%).¹¹ A small proportion of patients harboured multiple aberrations (5%).¹¹ The 126 samples of urothelial carcinoma included in this dataset were not segregated by site, and incorporated urothelial cancers from the bladder, renal pelvis and ureter.¹¹ Activating mutations in *FGFR3*, including *S249C*, *R248C*, *Y373C*, *G370C* and *K650M*, featured most frequently among the urothelial tumour samples studied (15%).¹¹ *FGFR1* amplifications were seen in 7% of urothelial samples, gene fusions were detected in 6%, and 3% had *FGF3* amplifications.¹¹ Interestingly, three activating *FGFR3* mutations (*S249C*, *S248C* and *Y373C*) were even observed to transform cells in vitro.¹¹

Upper tract urothelial carcinomas exhibit distinct clinical features from urothelial carcinoma of the bladder, and are typically associated with late presentations and

a more aggressive course. The poorer outcomes of this cohort of patients speak to an unmet need for unique, upper tract-specific therapeutic strategies with good scientific rationale. Robinson *et al* undertook comprehensive genomic and transcriptomic analysis of 37 upper tract urothelial primary tumours in an attempt to define their key biological differences from urothelial carcinoma of the bladder.¹² Among the discoveries made were upregulation of *FGFR3*, a T-cell-depleted immune milieu, and a luminal-papillary signature in the majority of tumours.¹² The findings of outlier *FGFR3* messenger ribonucleic acid (messenger RNA) expression in 14/32 (43.7%) tumours have afforded deeper insights on FGFR signalling in upper tract urothelial carcinoma, and suggest that a strategy involving FGFR inhibition, in conjunction with programmed cell death protein 1 (PD-1)/PD-ligand 1 (PD-L1) inhibition for T-cell modulation in T-cell deplete phenotypes, can be applied to these tumours.¹²

Aberrant FGFR signalling in urothelial cancer has been the focus of intense investigation that has led to the development of an array of novel agents.^{13–15} Orally available FGFR tyrosine kinase inhibitors, including dovitinib, nintedanib and rogaratinib, have been the subject of several early-phase trials, demonstrating poor to modest activity in patients with urothelial cancer.^{14,16} In an unselected cohort of patients who progressed following first-line chemotherapy, dovitinib disappointingly showed limited activity.¹⁷ Another study investigated the use of debio 1347, a panFGFR inhibitor across 56 patients with a range of solid tumours.¹⁸ Preliminary responses have been seen in patients with cholangiocarcinoma, uterine, colon and urothelial cancer.¹⁸

The results of a global phase II study on erdafitinib has led to recent Food and Drug Administration (FDA) approval of this agent for patients with *FGFR2* and *FGFR3* altered urothelial cancer.^{19,20} In this trial (NCT02365597), 96 patients were treated with a median 5 cycles (8 mg/day of continuous erdafitinib in continuous 28 day cycles with potential uptitration to 9 mg/day), demonstrating 42% objective response rates (ORRs).²⁰ Patients who had progressed on prior immune checkpoint inhibitors experienced an exceptional ORR of 70%.²⁰ For the overall cohort, median progression-free survival (PFS) was 5.5 months and overall survival (OS) was 13.8 months.²⁰ The THOR study (NCT03390504), a phase III randomised, registration study of erdafitinib compared with vinflunine or docetaxel or pembrolizumab in patients with advanced urothelial cancer and selected FGFR gene aberrations, is currently open to recruitment. Patients who have received one or two prior lines of treatment including an anti-PD-(L) 1 agent (cohort 1) or one prior treatment not containing an anti-PD-(L) 1 agent (cohort 2) are eligible.

More recently, the use of Infigratinib (BGJ398), a FGFR 1–4 inhibitor, was examined in a group of 67 patients with *FGFR3*-altered urothelial cancer.²¹ Responses were seen in 25.4% of patients, while 64.2% of patients experienced disease control (complete response (CR), partial response (PR) and stable disease (SD)).²¹ Median PFS

Table 1 Key studies involving molecularly targeted therapy in metastatic urothelial cancer

Author	Agent	Target	Trial	Population	Patients (N)	Results	Clinical trial information
Loriot <i>et al</i> ²⁰	Erdafitinib	FGFR	Phase II	Patients with locally advanced and unresectable or metastatic urothelial carcinoma harbouring <i>FGFR3</i> mutation or <i>FGFR2/3</i> fusion	99	ORR 40%, median PFS 5.5 months, median OS 13.8 months	NCT02365597
Pal <i>et al</i> ²¹	Infigratinib	FGFR	Phase II	Patients with metastatic urothelial cancer harbouring <i>FGFR3</i> alterations including single-nucleotide polymorphisms and indels, rearrangement and amplification	67	ORR 25.4%, median PFS 3.75 months, median OS 7.75 months	
Necchi <i>et al</i> ²²	Vofatamab alone or in combination with docetaxel	FGFR	Phase I/IIb	Patients with locally advanced or metastatic urothelial cancer harbouring <i>FGFR3</i> mutation or fusion treated with platinum chemotherapy	55/300	OR seen in 7 patients (12.7%)	NCT02401542
Seront <i>et al</i> ³¹	BEZ235 (dactolisib)	PI3K and mTOR	Phase II	Patients with advanced or metastatic urothelial cancer who have progressed on first-line platinum-based chemotherapy	20	OR seen in one patient (5%), median PFS 1.8 months, median OS 3.8 months	NCT01856101
Munster <i>et al</i> ³²	GSK2126458 (omipalisib)	PI3K and mTOR	Phase I	Patients with advanced solid tumours	170 including 17 patients with bladder cancer	OR seen in 9 patients (5%)	NCT00972686
Iyer <i>et al</i> ³³	BKM120	PI3K	Phase II	Non-enriched cohort of patients with metastatic urothelial cancer who have progressed on up to 4 prior agents including platinum-based chemotherapy	15	OR seen in 1 patient, median PFS 2.77 months,	NCT01551030
Grivas <i>et al</i> ⁴¹	Mocetinostat	HDAC	Phase II	Patients with advanced or metastatic urothelial cancer harbouring inactivating mutations or deletions in acetyltransferase genes with progression following platinum-based chemotherapy	17	OR seen in 1 patient (11%), median PFS 57 days, median OS 3.5 months	NCT02236195
Choudhury <i>et al</i> ³⁸	Afatinib	ErbB	Phase II	Patients with advanced/metastatic urothelial cancer harbouring <i>ERBB2/ERBB3</i> aberrations with platinum-refractory disease	23	ORR 8.6%, 21.7% achieved 3 month PFS (primary endpoint), median PFS 1.4 months, median OS 5.3 months	NCT02780687
Powles <i>et al</i> ³⁹	Lapatinib or placebo	ErbB	Phase III	Patients with metastatic urothelial cancer who screened positive for <i>HER1/2</i> without progressive disease after 4–8 cycles of chemotherapy	446	Median PFS 4.5 and 5.1 months, respectively, for lapatinib and placebo, OS 12.6 months and 12 months, respectively, for lapatinib and placebo	

Continued

Table 1 Continued

Author	Agent	Target	Trial	Population	Patients (N)	Results	Clinical trial information
Rosenberg et al ⁷⁰	Enfortumab vedotin	Nectin-4	Phase II	Patients with metastatic urothelial cancer treated with platinum chemotherapy and anti-PD-1/L1 therapy	125	ORR 44%, median PFS 5.8 months, median OS 11.7 months	NCT03219333
Tagawa et al ^{78,79}	Sacituzumab	Trop-2	Phase II	Patients with advanced solid tumours	45 patients with metastatic urothelial cancer who progressed after ≥1 prior systemic therapy	ORR 31% in interim cohort 1 of 35 patients	NCT03547973

BKM120, Buparlisib; FGFR, fibroblast growth factor receptor; HDAC, histone deacetylase; HER1, human epidermal growth factor 1; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PD-1/L1, programmed cell death protein 1/ligand 1; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase.

and OS was estimated at 3.75 months (95% CI 3.09 to 5.39 months) and 7.75 months (95% CI 3.91 to 7.36 months), respectively.²¹ The majority of grade 3 or 4 toxicities were biochemical in nature and reversible.²¹

Vofatamab (B-701), a human monoclonal antibody against *FGFR3*, has been evaluated in the FIERCE-21 phase II trial as monotherapy, or in combination with docetaxel, as salvage treatment following disease progression on platinum-based chemotherapy and immune checkpoint inhibitors (NCT02401542).²² Interim analysis of 55 patients enrolled in FIERCE-21 has revealed an acceptable safety profile and efficacy in heavily pretreated patients.²² Thus far, responses have been observed in seven patients treated with vofatamab monotherapy or vofatamab with docetaxel.²² Other strategies involving FGF ligand traps and HSP-inhibitors targeting *FGFR3* signalling are also currently being investigated as potential therapeutic options.^{14,16}

Dose-dependent hyperphosphataemia, which occurs due to disturbances in renal phosphate homeostasis,²³ is well recognised as a pharmacodynamic biomarker of on-target FGFR inhibition.^{24,25} Where the use of concurrent phosphate binders has been necessary to manage the hyperphosphataemia, this has not impacted on the pharmacokinetics of FGFR inhibitors.²⁶

Targeting the PI3K pathway

The high prevalence of FGFR aberrations in urothelial cancer has prompted investigation into coaberrant genes that could be additionally harnessed as therapeutic targets. The signalling pathway defined by PI3K, AKT and mammalian target of rapamycin (mTOR) governs many fundamental hallmarks of cancer and promotes a microenvironment conducive to tumour growth. *PIK3CA* mutations are found frequently in colorectal (13%–28%), endometrial (24%–46%) and breast cancers (20%–32%).²⁷ In urothelial cancer, *PIK3CA* mutations have been identified in 20%–27% of cases.²⁷

Several classes of drugs that target the PI3K/AKT/mTOR network are currently under investigation, including pan class I PI3K inhibitors, isoform-specific PI3K inhibitors and pan-PI3K inhibitors/mTOR inhibitors.²⁸ Unfortunately, the toxicity of PI3K inhibitors observed in early-phase studies has posed a major challenge to their use, and has thus limited the therapeutic potential of these agents.²⁹ Here, grim realities relating to the intrinsic pharmacological properties of PI3K inhibitors have become apparent; the lack of a safe ‘therapeutic window’ has seen the emergence of mechanism-based toxicities before doses sufficient for cancer eradication.²⁸

Furthermore, while PI3K inhibitors were initially anticipated to be highly effective in the presence of ‘driver mutations’, early results have fallen short of expectations.^{29,30} Likely explanations include plasticity of compensatory mechanisms in response to PI3K inhibition, a non-exclusive ‘oncogene addiction’ to the PI3K/AKT/mTOR pathway suggested by mouse models,²⁸ and

acquired resistance following exposure to PI3K-targeting drugs.^{29,30}

In a phase II trial investigating BEZ235, a pan-class I PI3K and mTOR inhibitor, 1 PR (5%) and 2 instances of SD (10%) were demonstrated in a cohort of 20 patients with advanced or metastatic urothelial cancer.³¹ Three patients who were progression-free at 8 weeks did not harbour PI3K/AKT/mTOR activating mutations.³¹

In another study, the PI3K/mTOR dual inhibitor, GSK2126458, was evaluated in patients with solid tumours.³² Patients with bladder cancer comprised 10% of patients enrolled in this trial.³² In the expansion cohort of 84 patients, 6% of patients recorded prolonged OR or disease stabilisation, including one patient with bladder cancer who experienced ongoing PR beyond a duration of 4 years.³² Finally, a phase II study of buparlisib in patients with metastatic urothelial cancer treated with up to four prior agents revealed a median PFS of only 2.77 months (95% CI 1.83 to 3.71).³³ Results from two patients with identified PIK3CA mutations were more encouraging, with one patient demonstrating a 16-month PR and the other displaying SD for 3.7 months.³³ On the basis of this, an expansion cohort is recruiting patients with tumours enriched for activating PI3K/AKT/mTOR mutations (NCT01551030).³³

Rational combinations that manipulate the pharmacodynamics of different agents could overcome the aforementioned issues relating to toxicity and resistance.^{28,30} In a first-in-human study, an approach incorporating dual PI3K and FGFR inhibition with alpelisib and infigratinib, respectively, has been studied in 62 heavily pretreated patients with a range of tumour types, including urothelial cancer.³⁴ While this combination appeared feasible and did not confer prohibitive additive toxicity, there was no evidence of synergistic activity and it is unclear if this combination is helpful.³⁴

Targeting ErbB

While mutations involving the ErbB family occur relatively frequently in urothelial cancer, successful treatment options in this space are still lacking.¹⁶ Investigative efforts researching gefitinib (ZD1839) in chemotherapy-resistant metastatic urothelial cancer have yielded disappointing results.^{35,36} In the first-line setting, 58 patients were treated with cisplatin, gemcitabine and gefitinib with no significant improvements compared with historical outcomes for chemotherapy alone (ORR 42.6%, median time to progression 7.4 months, median OS 15.1 months).³⁵ In 31 patients treated with second-line gefitinib, median PFS was only 2 months, however, relatively high rates of grade 3–4 toxicities including cerebrovascular ischaemia (3%), raised creatinine (3%), diarrhoea (7%), fatigue (10%) and rash (13%) were seen.³⁶ The use of trastuzumab in combination with paclitaxel, carboplatin and gemcitabine in patients with human epidermal growth factor (HER) 2 positive urothelial cancer was associated with favourable response rates of 70%, however, results revealed higher than expected cardiotoxicity (22.7% had

grade 1–3 cardiac toxicity).³⁷ In preliminary results from a phase II trial of 23 patients involving afatinib, an oral tyrosine kinase inhibitor of the ErbB receptor family, encouraging activity was noted in those with HER2 and/or ERBB3 alterations, where five out of six patients achieved the primary endpoint of 3-month PFS, compared with none in the 15 patients without alterations ($p < 0.001$).³⁸ Those with HER2/ERBB3 alterations demonstrated a median time of progression/discontinuation of 6.6 months, superior to 1.4 months in patients without alterations ($p < 0.001$).³⁸ Disappointingly, however, a phase III, double-blind, randomised trial of maintenance lapatinib versus placebo after first-line chemotherapy in patients with HER1/2 positive urothelial cancer, did not show a significant difference in outcomes, even in patients with the strongest expression (3+) on immunohistochemistry (IHC).³⁹ Gene amplification demonstrated by fluorescence in situ hybridisation was only conducted in patients with equivocal positivity (1+ on IHC with 2 antibodies), and was exclusively negative in all.³⁹

Targeting chromatin remodelling genes

A host of chromatin regulatory genes, including *KDM6A*, *CREBBP*, *EP300* and *ARID1A*, is highly mutated in urothelial cancer.⁷ *EP300* and *CREBBP*, transcriptional coactivators with histone acetyltransferase (HAT) activity, are involved in many cellular processes. Dysregulated histone acetylation, via upregulation of histone deacetylases (HDACs) and inactivation of HATs, has been associated with cancer pathogenesis of many tumour types through suppression of tumour regulatory genes.⁴⁰ Although some success has been demonstrated with the use of HDAC inhibitors in the treatment of T-cell lymphoma,⁴⁰ a recent phase II trial (NCT02236195) involving the use of mocetinostat, an oral HDAC inhibitor, in patients with advanced urothelial cancer harbouring inactivating alterations of acetyltransferase genes, unfortunately failed to show activity in the second-line setting post platinum-based chemotherapy.⁴¹ From a total of 17 patients who were recruited into stage 1 of the trial, only one PR was seen among nine evaluable patients.⁴¹ These findings highlight the sobering challenges of translating in vitro findings into therapeutically significant outcomes. Ongoing trials (NCT02954991, NCT03220477 and NCT03565406) are investigating the use of mocetinostat in combination with checkpoint inhibitor immunotherapy in patients with advanced melanoma and lung cancer.

Targeting DNA damage repair response deficiency

The identification of loss-of-function mutations in *CHK1/2*, *RAD51*, *BRCA1/2*, *ATM*, *ATR*, *MDC1* and *FANCF* in urothelial tumour specimens^{7,9} provides good rationale for exploring the use of poly ADP ribose polymerase (PARP) inhibitors for advanced urothelial cancer. Two phase II trials employing olaparib monotherapy in patients with metastatic urothelial cancer harbouring somatic DNA damage repair response (DDR) alterations are currently open to recruitment (NCT03448718,

NCT03375307), while the ATLAS trial (NCT03397394) is aimed at evaluating the efficacy and safety of rucaparib monotherapy in unselected patients with metastatic urothelial cancer treated with 1–2 prior lines of systemic therapy. Lesions in DNA DDR genes have also been recognised to potentially predict response to platinum-based chemotherapy. These salient findings by Van Allen *et al* and Plimack *et al* will be discussed in later sections.

Pioneering an adaptive biomarker platform

BISCAY is a phase 1b umbrella study (NCT02546661) with an innovative design where patients are assigned to receive different targeted therapies on the basis of baseline next generation sequencing results.⁴² In this trial, those with *FGFR1/2/3* mutations or fusion are randomised to receive *FGFR* inhibitor AZD4547 monotherapy or AZD4547 in combination with durvalumab, while the patient cohort identified to have *ATM*, *BRCA1/2* or other homologous recombination repair gene defects are assigned PARP inhibitor olaparib and durvalumab.⁴² Additionally, patients identified to have rapamycin-insensitive companion of mTOR (*RICTOR*) or tuberous sclerosis 1/2 alterations are directed towards treatment with dual raptor-mTOR protein complex 1/ricor-mTOR protein complex 2 inhibitor vistusertib in combination with durvalumab.⁴² Lastly, those not found to have an identified biomarker-of-interest proceed to receive durvalumab monotherapy.⁴² Preliminary results have revealed activity in all arms of the study, with ORR ranging from 20% to 29%.⁴² In addition, two other trials are examining the use of PARP inhibitors combined with durvalumab in unselected patient cohorts, in the advanced (NCT03459846) and neoadjuvant setting (NCT03534492), respectively.

PREDICTIVE BIOMARKERS TO STANDARD THERAPIES

In muscle-invasive urothelial cancer, the standard of care remains neoadjuvant cisplatin-based chemotherapy, followed by radical cystectomy⁴³ or trimodality therapy (TMT) with optimal transurethral resection of bladder tumour (TURBT), followed by chemoradiotherapy.⁴⁴ In metastatic urothelial cancer, first-line systemic treatment remains platinum-based chemotherapy^{45,46}; alternatively, pembrolizumab⁴⁷ or atezolizumab⁴⁸ in cisplatin-ineligible patients, followed by second-line pembrolizumab in those who received first-line platinum-based cytotoxic agents.⁴⁹ However, the rapidly evolving treatment landscape suggests this standard will not remain for long. While molecularly matched treatments aimed at targeting driver mutations continue to be investigated as described above, a large component of precision oncology involves using predictive biomarkers to ensure the right treatment is given to the right patient at the right time; in this section, we review some of the biomarker work that will help us achieve this in urothelial cancer. Table 2 describes the pivotal trials involving predictors for response to standard therapies in urothelial cancer.

Predictive markers for platinum-based chemotherapy

The use of neoadjuvant platinum-based chemotherapy results in improved clinical outcomes in patients with muscle invasive bladder cancer. In the seminal Southwest Oncology Group-led study investigating the use of neoadjuvant chemotherapy, median survival among patients who underwent cystectomy alone was 46 months vs 77 months among patients who received neoadjuvant chemotherapy ($p=0.06$).⁵⁰ This clear survival advantage has subsequently been confirmed in several meta-analyses,^{51–53} and indisputably supports the use of neoadjuvant chemotherapy as standard of care in this setting. The strongest benefit is seen when neoadjuvant chemotherapy results in pathological downstaging to pT0, pTis or pTa at time of surgery.⁵⁰ Some data suggest that a proportion of patients who achieve pT0 are cured with chemotherapy alone, and may not need a radical cystectomy^{54,55}; subsequently, efforts to identify predictive markers of chemotherapy responsiveness have intensified.

Basal molecular subtype

Extensive work by multiple groups has defined key molecular subtypes of urothelial cancer, characterised by distinct gene signatures, varying expression of potential drug targets and differing chemotherapy sensitivity. Choi *et al* described intrinsic basal and luminal subtypes of urothelial cancer with gene signatures that were similar to breast cancer subtypes.⁵⁶ An additional subset of largely chemotherapy-resistant tumours, characterised by high levels of infiltrating stromal cells and an active p53 gene signature, have been classified as ‘p53-like’.⁵⁷ Basal subtypes are associated with a more aggressive disease course and a greater propensity to metastasize causing shorter survival.⁵⁶ However, basal tumours are also intrinsically chemotherapy sensitive, and patients with this tumour subtype often glean the most benefit from chemotherapy.^{56,58}

Additional work through the TCGA identified the basal-squamous subtype as featuring the strongest immune expression signature and predicted that this group was most likely to benefit from neoadjuvant chemotherapy in bladder-confined disease and immune checkpoint inhibitors in the metastatic setting.⁹ This study also showed that luminal-papillary urothelial cancers are associated with potentially actionable mutations in genes such as *FGFR*, *PIK3* and *ERBB2*, and also appear to have a better prognosis.⁹

The correlation between basal subtype and response to neoadjuvant chemotherapy was confirmed in a large multi-institutional cohort, where a marked benefit from neoadjuvant chemotherapy was observed in the basal group (3-year OS of 49.2% in those who did not receive neoadjuvant chemotherapy compared with 77.8% in those who did).⁵⁹ This study also confirmed the good prognosis linked to luminal subtype, as these patients fared the best, irrespective to the use of neoadjuvant chemotherapy. Among those with luminal features, patients who had responded to neoadjuvant chemotherapy had a 3-year OS

Table 2 Key studies involving predictors for response to standard therapies in urothelial cancer

Author	Predictive marker	Treatment	Population	Patients (N)	Results
Choi <i>et al</i> ⁵⁶	Molecular subtypes of urothelial cancer	Chemotherapy	Samples of fresh-frozen muscle invasive bladder cancers obtained by transurethral resection.	73	Discovery of specific panels of upregulated genes conferring classification of 3 molecular subtypes of muscle invasive bladder cancer (basal, luminal, p53-like) resembling subtypes of breast cancer.
The Cancer Genome Atlas (TCGA) Research Network ⁷	Molecular subtypes of urothelial cancer	Chemotherapy and molecularly targeted therapy	Samples from 19 tissue source sites, comprising chemotherapy-naïve, muscle-invasive, high-grade urothelial tumours (T2-T4a, Nx, Mx).	131	Statistically recurrent mutations in 32 genes, definition of 4 expression subtypes based on RNA sequencing.
Robertson <i>et al</i> ⁹	Molecular subtypes of urothelial cancer	Chemotherapy and molecularly targeted therapy	Samples from chemotherapy-naïve, invasive, high-grade urothelial tumours (T2-T4a, N0-3, M0-1).	412	Statistically recurrent mutations in 58 genes, identification of 5 expression subtypes that could inform response to different therapies.
Seiler <i>et al</i> ⁵⁹	Molecular subtypes of urothelial cancer	Chemotherapy	Pre-neoadjuvant chemotherapy transurethral resection specimens.	343	Development of a single-sample genomic subtyping classifier. Patients with basal subtype demonstrated the most prominent OS benefit after chemotherapy (3-year OS of 49.2% in those who did not receive neoadjuvant chemotherapy compared with 77.8% in those who did). Patients in the luminal subgroup did well, regardless of chemotherapy use.
Van Allen <i>et al</i> ⁶⁰	DNA repair gene, ERCC2	Chemotherapy	Patients with muscle invasive bladder cancer who received neoadjuvant chemotherapy, followed by cystectomy.	50	<i>ERCC2</i> mutations were enriched in chemotherapy responders (36% of cases; $p < 0.001$; binomial test). In vitro tests confirmed failed ability to rescue DNA damage in <i>ERCC2</i> mutated tumours.
Plimack <i>et al</i> ⁶²	DNA repair genes ATM, RB1, FANCC	Chemotherapy	Pre-treatment muscle invasive bladder cancer specimens prospectively collected from patients in two separate clinical trials.	Discovery cohort: 34 Validation cohort: 24	Discovery cohort: 87% of patients who had had a chemotherapy response showed alterations in one or more DNA repair genes, while none of the nonresponders (0%) had any relevant genetic abnormalities. P value for PFS and p value for OS association with <i>ATM/RB1/FANCC</i> were 0.0085 and 0.007 respectively. Validation cohort: Chemotherapy responders included 64% of patients with <i>ATM/RB1/FANCC</i> alterations, while the rate of genetic alterations was only 15% in non-responders. P value for PFS and OS association with <i>ATM/RB1/FANCC</i> were $p = 0.1018$ and $p = 0.0545$, respectively.
Liu <i>et al</i> ⁶¹	DNA repair gene, ERCC2	Chemotherapy	Pre-treatment muscle invasive bladder cancer specimens collected from patients from two clinical trials.	55	40% of chemotherapy responders vs 7% of non-responders had <i>ERCC2</i> alterations, OR 8.3.

Continued

Table 2 Continued

Author	Predictive marker	Treatment	Population	Patients (N)	Results
Choudhury <i>et al</i> ⁶⁵	DNA repair protein MRE11	Radiotherapy	Pre-treatment tumour specimens from patients with muscle invasive bladder cancer. Cohort A (1995–2000) and cohort B (2002–2005) were patients treated with radical radiotherapy. Patients from the cystectomy set were treated between 1995 and 2005.	Cohort A: 91 Cohort B: 93 Surgical cohort: 88	In the radiotherapy test (A) and validation cohorts (B), low MRE11 expression in tumour was linked to inferior CSS (43.1 vs 68.7%, $p=0.012$ in cohort A, 43% vs 71.2%, $p=0.020$ in cohort B). MRE11 expression was not associated with CSS in the cystectomy cohort. Patients with high MRE11 treated with radiotherapy demonstrated better CSS (69.9% v 53.8% in patients with high MRE11 who underwent cystectomy).
Laurberg <i>et al</i> ⁶⁶	DNA repair protein MRE11	Radiotherapy	Patients with T1-4a N0M0 urothelial carcinoma. Cohort A: patients undergoing radical cystectomy between 1980 and 2003. Cohort B: patients with accessible cystectomy tissue from 1992 to 2008. Cohort C: patients treated with radiotherapy (83% received concurrent chemotherapy).	Cohort A: 162 Cohort B: 273 Cohort C: 148	High MRE11 expression in patients who underwent radiotherapy was associated with long DSS ($p=0.005$). Findings were confirmed on multivariate analysis, $p<0.001$. There was no predictive value of MRE11 in the cystectomy cohort.
Rosenberg <i>et al</i> ⁷⁰	TCGA molecular expression, tumour mutational load, PD-L1 score	Checkpoint inhibitor	Patients with metastatic urothelial cancer who progressed after platinum-based chemotherapy.	315 patients were enrolled in this study. Gene expression analysis was performed in 195 specimens, mutational load was estimated in 150 specimens, PD-L1 analysis was conducted on 215 specimens.	Response to atezolizumab varied according to pre-specified immune cell subgroups as follows: IC0 (<1%), IC1 ($\geq 1\%$ but <5%), IC1/3 ($\geq 5\%$). ORR in the IC2/3 group was 26%, 18% in the IC 1/2/3 group, and 15% overall. Exploratory analyses demonstrated independent associations between TCGA subtypes and mutational load and response to atezolizumab.

CSS, cancer-specific survival; DSS, disease-specific survival; IC, immune cell; MRE11, meiotic recombination 11; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

of 95%, as opposed to 58% in non-responders ($p=0.002$).⁵⁹ While the data appear convincing that patients with basal subtype benefit most from neoadjuvant chemotherapy, the clinical utility of this is limited by the inability to assign molecular subtypes to individual patients in real time.⁵⁹ However, specific genetic mutations seen in the basal subtypes may have a predictive role.⁵⁹

DNA repair gene mutations

Two studies have demonstrated selected mutations in the DNA repair pathways that also confer platinum sensitivity. Van Allen *et al* sequenced pretreatment tumour and germline DNA sampled from 50 patients with muscle

invasive disease treated with neoadjuvant cisplatin-based chemotherapy and cystectomy.⁶⁰ This study demonstrated that the presence of mutations in *ERCC2* (important in the nucleotide excision repair pathway) was associated with cisplatin sensitivity, confirmed in an independent clinical validation study (40% of chemotherapy responders vs 7% of non-responders had *ERCC2* alterations, OR 8.3).⁶¹ In a series of in vitro experiments, they were able to provide a molecular explanation for this and demonstrated that *ERCC2* mutated tumours failed to rescue ultraviolet-induced DNA damage, suggesting that DNA damage caused by cisplatin in *ERCC2* mutated

urothelial cancers were more likely to result in apoptosis.⁶⁰

In another important body of work led by Plimack *et al*, alterations in a further trio of DNA repair genes, *ATM*, *RB1* and *FANCC*, also emerged as predictors for pathological response, PFS and OS.⁶² In the discovery group, 87% of patients who had had a chemotherapy response showed alterations in one or more DNA repair genes, while none of the non-responders (0%) recorded any relevant genetic abnormalities (87% specificity, 100% sensitivity, 100% positive predictive value, 90% negative predictive value, 94% accuracy).⁶² In the validation cohort, the frequencies of genetic alterations in *ATM*, *RB1* and *FANCC* were 64% in chemotherapy responders and 15% in non-responders.⁶² There were statistically significant associations between *ATM/RB1/FANCC* alterations with PFS ($p=0.0085$) and OS ($p=0.007$) in the discovery group, and a similar trend for benefit ($p=0.1018$ and $p=0.0545$ for PFS and OS, accordingly) in the validation group.⁶² Here, the defective DNA repair functions of these genes are once again hypothesised to be responsible for the chemosensitive response and clinical benefit manifested in responders.⁶²

While patients with *ERCC2/ATM/RB1/FANCC* gene alterations are likely to fall within the basal molecular subtype, it is inherently much easier to test for these individual gene mutations in individual patients than to conduct gene expression studies to determine which subtype they belong to. For this reason, given the extraordinary responses to cisplatin-based chemotherapy in these patients, bladder preservation strategies are currently being evaluated in patients who harbour mutations in these genes. This concept is being explored in three ongoing studies, two trials with neoadjuvant cisplatin-based chemotherapy alone, (the Risk Enabled Therapy After Initiating Neoadjuvant Chemotherapy for Bladder Cancer (RETAIN) trial (NCT02710734) and NCT03609216) and one trial with neoadjuvant cisplatin-based chemotherapy plus the PD-1 inhibitor, nivolumab (NCT03558087). In the RETAIN trial (NCT02710734), the mutational profile of tumour samples obtained from transurethral resection is used to stratify management following neoadjuvant accelerated methotrexate, vinblastine, doxorubicin and cisplatin. Here, the risk-adjusted options comprise active surveillance, standard of care intravesical therapy, chemoradiation or surgery. In the other chemotherapy-based trial (NCT03609216), patients with alterations in the DDR pathway with good clinical response ($<cT1$) to neoadjuvant dose-dense gemcitabine and cisplatin are offered the choice of bladder sparing surgery, while patients with $\geq cT1$ disease post neoadjuvant chemotherapy who do not harbour DDR mutations are offered radical cystectomy or chemoradiation. Finally, the trial using gemcitabine, cisplatin, plus nivolumab (NCT03558087) seeks to evaluate the safety and activity of this regimen in the neoadjuvant setting, but will also explore the link between a prespecified panel of genomic

alterations with pathological CR and 2-year metastasis-free survival in patients undergoing cystectomy.

Predictive markers for bladder sparing TMT

TMT, comprising maximum TURBT, followed by radiation with concurrent chemotherapy, is an alternative management strategy for muscle invasive bladder cancer that allows patients to retain their native bladder. However, a proportion of patients do require salvage radical cystectomy where there is an incomplete response to chemoradiation.⁶³

Subsequently, there is a need for reliable biomarkers that can determine which patients are best treated using TMT compared with radical cystectomy.⁶⁴ Traditional clinicopathological factors do not have sufficient discriminatory power. In view of this, some have sought to explore the role of meiotic recombination 11 homolog (MRE11). MRE11, a DNA nuclease involved in DNA damage repair, has been studied in patients treated with radiotherapy.^{65 66} While reduced amounts of other DNA repair proteins such as *ERCC1* have been observed to be linked with improved outcomes through impaired nucleotide excision repair mechanisms in the context of platinum cytotoxic therapy, low concentrations of MRE11 protein have somewhat unexpectedly been found to correlate with worse outcomes following radiotherapy-based treatment.^{65 66} In 86 patients treated with radical radiotherapy, reduced level of MRE11 expression in tumour was linked to inferior 3-year cancer-specific survival (CSS) (43.1% vs 68.7%, $p=0.012$).⁶⁵ Additionally, there were significantly better survival outcomes among patients with high MRE11 expression who had undergone radiotherapy compared with those with high MRE11 expression who had cystectomy (3-year CSS 69.9% vs 53.8%, $p=0.021$).⁶⁵ In a separate study, patients undergoing radical cystectomy were studied alongside patients who received radiotherapy.⁶⁶ Patients in the radiotherapy group were noted to have significant associations between high MRE11 expression and long disease-specific survival ($p=0.005$); however, once again, there was no predictive value of MRE11 seen in those who underwent cystectomy.⁶⁶ That the DNA damage response pathway is activated with the recruitment of the MRE11-RAD50 double strand break repair protein-nibrin 1 complex may provide the mechanistic reason for these findings. Failure of induction of the DNA damage signalling cascade following DNA damage may therefore be one of the causes of radioresistance.^{65 66}

Predictive markers for anti-PD-1/PD-L1 therapy

While pembrolizumab has demonstrated an OS benefit in metastatic urothelial cancer, it is still the minority that gain benefit, with an ORR of 21.1%.⁴⁹ Subsequently, ongoing research is aimed at identifying biomarkers of response to PD-1 and other checkpoint inhibitors. Initial efforts have been centred on grouping responders by PD-L1 expression, TCGA subtype and interferon-gamma signatures.⁶⁷ This approach has not yielded consistent associations, and has failed to identify clinically

relevant predictive factors for benefit.⁶⁸ The study of PD-L1 expression as a biomarker is ongoing, however, has been complicated by unstandardised assays and the lack of well-defined cutoffs.⁶⁹ In addition to microsatellite instability, a high tumour mutational burden is increasingly recognised to correlate with response to both cytotoxic T-lymphocyte-associated protein 4 and PD-1/L1 inhibition in wide-ranging tumour types.⁶⁹ In the realm of urothelial carcinoma, the link between tumour mutation load and response was elegantly established by Rosenberg *et al* in a phase II trial of second-line atezolizumab in patients who had progressed after platinum-based chemotherapy.⁷⁰ In this study, mutational load was found to be an independent predictive marker of response, separate from associations between molecular subtype and PD-L1 immune score.⁷⁰ Classification of patients using the TCGA approach revealed significantly higher ORR of 34% in patients with luminal cluster II, compared with 10% for subtype I, 16% for III and 20% for IV ($p=0.0102$).⁷⁰ PD-L1 thresholds were applied at 1% (immune cell (IC)0), $\geq 1\%$ but $<5\%$ (IC1), and $\geq 5\%$ (IC2/3).⁷⁰ Response evaluation criteria on solid tumours V.1.1 ORR were significantly improved for the prespecified IC cohorts as follows: IC2/3 26% including 11% CR, IC1/2/3 18% including 6% CR, all-comers 15% including 5%. A higher median mutational load was observed in responders (12.4/Mb) compared with non-responders (6.4/Mb) ($p<0.001$).⁷⁰ Moreover, a predictive model incorporating TCGA gene expression subtypes, mutational load and PD-L1 appeared to perform better (on a biomarker integration tree, strength of association of IC score alone was $p=0.0159$, gene expression subtype alone was $p=0.0102$, while the combination of three biomarkers was $p=2.14\times 10^{-4}$), highlighting the complex genomic, molecular and immunological factors that govern efficacy for checkpoint inhibitors.⁷⁰ For now, in urothelial cancer, no clinically applicable biomarkers exist to identify which patients will benefit from PD-1/L1 inhibition. The increasing number of patients treated with immune checkpoint therapy underscores the compelling need for reliable biomarkers to inform efficacy and help circumvent toxicity. Extensive study into this space continues.

NOVEL TARGETED APPROACHES

Antibody–drug conjugates

ADCs are a novel therapeutic strategy that uses antibodies as vehicles for the selective delivery of cytotoxics. The success of this approach has been well established in breast cancer, where ado-trastuzumab emtansine (TDM1) is used as standard care following progression on trastuzumab and lapatinib in patients with HER2-positive disease.⁷¹ In theory, ADCs are a molecularly matched therapy that unlike the targeted therapies described previously, do not target driver mutations, but rather, use an accessible target expressed on the cell surface. Generally, the use of ADCs should be limited to patients with cancers that express the target protein, such as HER2 for

TDM1. However, in urothelial cancer, the two most promising ADCs target proteins that are expressed in almost all urothelial cancers, and consequently do not require a companion diagnostic.

Enfortumab vedotin consists of an anti-nectin-4 monoclonal antibody linked to monomethyl auristatin E, a microtubule-disrupting cytotoxic agent. Nectin-4 is a cell adhesion molecule that is weakly to moderately expressed in normal tissue, such as skin, salivary gland, larynx, pituitary, testis and stomach.⁷² In a key study investigating nectin-4 expression, IHC analysis was performed in 2394 patient tumour samples spanning seven tumour types.⁷² Moderate to strong nectin-4 expression was present in 60% of bladder cancers.⁷² The distinction between nectin-4 expression in tumour and normal tissue suggests nectin-4 as a potential target for therapeutic manipulation.⁷² A phase I study noted expression of nectin-4 in up to 97% of metastatic bladder cancer samples.⁷³ Early results evaluating single agent enfortumab vedotin demonstrated encouraging activity in patients with heavily pretreated metastatic urothelial cancer, with ORR of up to 42%.⁷³ More recently, striking results from the EV-201 study published in the *Journal of Clinical Oncology* revealed an ORR of 44% including a 12% CR rate in patients with metastatic bladder cancer previously treated with PD-1/L1 therapy only or PD-1/L1 therapy and platinum-based chemotherapy.⁷⁴ And most recently, data regarding the combination of enfortumab vedotin and pembrolizumab resulted in an ORR of 71% in 45 patients (NCT03288545).⁷⁵ A randomised, open label, phase III trial, EV-301, investigating the use of enfortumab vedotin versus investigator's choice of docetaxel, paclitaxel or vinflunine in patients who have received previous platinum-containing chemotherapy and a checkpoint inhibitor, is currently open to recruitment (NCT03474107).

Sacituzumab govitecan is composed of a humanised anti-Trop-2 monoclonal antibody (hRS7) conjugated with a cytotoxic payload, SN-38, the active metabolite of irinotecan.⁷⁶ Trop-2 (tumour-associated calcium signal transducer 2, TACSTD2) is a glycoprotein is found in normal urothelium, and is expressed in up to 80% of urothelial carcinomas.⁷⁷ Overexpression of Trop-2 in many cancers, including breast cancer has been linked with a poor prognosis.⁷⁶ Sacituzumab has shown promise in platinum-refractory, heavily pretreated patients with urothelial carcinoma and merits ongoing evaluation as a potential therapeutic candidate.⁷⁸ The recently presented interim analysis of TROPHY-U-01 study (European Society for Medical Oncology 2019 Congress) has demonstrated 29% ORR in 35 patients (NCT03547973).⁷⁹

CONCLUSION

For decades, our simplistic armamentarium in the management of urothelial cancer yielded stagnant mortality rates. Recent prolific research efforts in the field of precision oncology have provided key insights

that have transformed the treatment paradigm, and will undoubtedly continue to expand our therapeutic options in the years to come. Increasingly, our biggest conundrum involves picking the right patient for the right treatment. From a rudimentary biological knowledge of the disease, advances in our molecular understanding of urothelial cancer have allowed us to adopt crucial finesse in our practice. With the right resources at hand, a contemporary management approach for patients with urothelial cancer could incorporate a review of biomarkers for platinum and PD-1/PD-L1 therapy responsiveness, interrogation of tumour for actionable mutations, followed by the application of molecularly matched treatments.

While this is a promising start, there is much more to be done to optimise the care of patients. Although tremendous progress has been made in the identification of many ‘druggable pathways’, it is increasingly evident that the correlation between molecular status and clinical efficacy of molecularly matched therapy is not absolute.⁸⁰ Moving forward, efforts should be directed towards further validation of existing biomarkers, evaluation of synergistic strategies to overcome resistance of single agent targeted therapies, and expanding investigation into new treatment approaches such as ADCs.⁸⁰

Adopting commonplace practice of precision oncology is not without hurdles. Key issues include contending with complex tumour heterogeneity and the emergence of selective pressures with treatment,⁸¹ teasing out functionally relevant molecular changes from a multitude of mutations identified through genomic profiling⁸² and reconciling the costs of a precision oncology workflow to healthcare systems.⁸¹

Despite the challenges faced so far, the application of precision oncology has brought about meaningful gains to patient outcomes. Where previously the treatment algorithm involved only chemotherapy, the notion of biomarker-driven care has become firmly entrenched in management of advanced lung cancer.⁸³ Widespread uptake of driver-mutation analysis, followed by the application of mechanistically designed drugs, such as erlotinib and crizotinib for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements, respectively, has revolutionised outcomes for many.⁸⁴ There are biological parallels between lung and bladder cancer; both smoking-related malignancies typically defined by a high mutational background. We envision an extension of the exemplary model of biomarker-personalised care currently practised in lung cancer to bladder cancer, where routine multiplex testing can be implemented to identify a panel of actionable mutations.

As the divide from bench-to-bedside is narrowed, and progress in basic cancer and clinical research continues with incredible momentum, we look forward to new treatment possibilities and improved prospects for patients with urothelial cancer.

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