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Review

Genito-urinary genomics and emerging biomarkers for immunomodulatory cancer treatment

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ABSTRACT

Immunotherapy is gradually becoming a key factor in the therapeutic algorithm for patients with genito-urinary (GU) cancers at different stages of disease. Robust and reliable biomarkers are crucial for an appropriate inclusion of patients in clinical trials and for a reliable patient selection for treatments with immunomodulatory drugs. The increasing knowledge on the genomic landscape of GU cancers supports stratification of patients for targeted therapies. This review focusses on emerging biomarkers and the role of genomics in predicting clinical benefit to immunomodulatory agents in GU cancers. Based on cancer incidences and available data we restricted this overview to bladder, prostate and renal cancer.

1. Introduction

The exponential increase in knowledge on cancer genomics is changing the diagnostic and therapeutic approach of genito-urinary (GU) cancers. It gradually becomes clear that the genomic signatures of individual cancers may account for different prognosis and therapeutic decisions. Although clinically available targeted therapies based on genomic alterations in GU cancers are still limited, more insight is being gained in the different genomic subgroups per cancer type and this knowledge is likely to lead us to clinically prognostic and therapeutic relevance.

Immunotherapy is an upcoming and promising approach in the treatment of GU malignancies and several immunotherapeutic drugs have been approved by the Food and Drug Administration (FDA) and European Commission recently [1]. The availability of reliable biomarkers for immunomodulatory drugs is crucial to get an optimal patient selection, to limit drug-related side-effects [2] and to gain cost-efficiency [3].

An intriguing field related to cancer genomics and immunotherapy is the relationship among the genomic landscape of the tumour, mutational load, and benefit from treatment. It has been shown that the genomic landscape of a tumour affects the clinical benefit provided by immunomodulatory agents [4,5], and several possible underlying mechanisms, such as the role of neoantigen load in driving T cell responses [6], the presence of mutant tumour antigen-specific T cells [7], the association between somatic mutations associated with immune infiltrates [8] and tumour-intrinsic resistance to cytolytic activity have been elucidated [9].

In this review, we tried to give an overview of recent evolutions in GU cancer genomics and immunomodulatory therapies, with a focus on emerging biomarkers and the role of genomics in predicting clinical benefit to immunomodulatory agents. We think that in this context it is

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essential to define the concepts 'prognostic' and 'predictive' biomarkers. A prognostic biomarker informs about a likely cancer outcome (e.g., disease recurrence, disease progression, death) independent of treatment received, while a biomarker is predictive if the treatment effect (experimental compared with control) is different for biomarker-positive patients compared with biomarker-negative patients [10]. Biomarkers cover a range of possible biologic entities. In this review, we have tried to focus most on tissue-based biomarkers, ranging from protein to genomic level. Blood-based biomarkers, like immune cell ratios, cell-free DNA… are only briefly discussed. Based on cancer incidences and available data we restricted this overview to bladder, prostate and renal cancer.

2. Urothelial carcinoma

Bladder cancer (BC) is the ninth most common cancer worldwide [11,12]. Histopathology is still the mainstay in diagnosis, but in recent years, literature has shown evidence for the existence of several subtypes based on molecular characteristics. The classic histopathological distinction between non-muscle-invasive BC (NMIBC – pTa, pT1, carcinoma in situ [CIS]) and muscle-invasive BC (MIBC – ≥pT2) is reflected by parallel genomic subgroups. Earlier work showed that urothelial carcinomas (UC) arise and progress along two different pathways [13–16]. The majority of UC (70–80%) are low-grade papillary NMBIC, and harbour frequent mutations in the HRAS and FGFR3 genes [13–16]. The minor part of UC are characterised as high grade invasive tumours, which either originate from flat CIS or from progression in the low-grade pathway, and with the presence of frequent alterations in the tumour suppressor TP53, retinoblastoma (RB) and gene cyclin-dependent kinase inhibitor 2A (CDKN2A) genes [13–16].

Most of genomic studies have focused on MIBC. Comprehensive classification schemes for MIBC have been proposed by separate groups, at Lund University (Lund) [17], MD Anderson (MDA) [18], University of North Caroline (UNC) [19] and the Cancer Genome Atlas Project Consortium (TCGA) [20]. Several differences are present between the individual classification systems, based on cohort stage composition and basic questions posed by the respective investigators, but recent work has shown considerable overlap between the different classifiers [21–23]. At present we can distinguish 2 main subgroups in MIBC: basal and luminal tumours [17–19,22,24]. The basal or squamous-like subgroup (TCGA cluster III) is characterised by overexpression of basal markers such as K5 and K14 and downregulation of urothelial differentiation markers e.g. K20 and FOXA1 [19,20,22,25]. Another basal subgroup is the claudin-low subtype (TCGA cluster IV) characterized by epithelial-to-mesenchymal (EMT) transition [17,19,20,22,26]. The luminal MIBC group can be divided in 2 subgroups: urothelial-like UC (TCGA cluster I) and genomic unstable/infiltrated/p53-like UC (TCGA cluster II) [17,19,20,22]. Urothelial-like UC are characterised by urothelial differentiation and harbour alterations in the FGFR3-pathway [17,19,20,22]. The genomic unstable (GU) group has expression of urothelial differentiation markers, amplification of PPARG, GATA-3 and ERBB2, but is not related to the FGFR3-pathway [17,19–22]. A recent update of the TCGA subtypes resulted in a luminal group, a luminal immune group, a basal group and an immune undifferentiated group [27]. Both immune-related groups were characterised by high expression of immune genes and variable expression of EMT-genes [27]. In general, basal subtypes have the worst prognosis but a better response to neo-adjuvant chemotherapy (NAC), whereas the genomic unstable or p53-like UC are more chemo-resistant [28,29]. The MDA group showed that immunohistochemical expressions of only two markers, luminal (GATA3) and basal (KRT5/6), were sufficient to identify the molecular subtypes of UC with over 90% accuracy [30]. On a recent consensus-meeting on molecular taxonomy for UC, the attendees found a robust consensus on 2 different molecular subtypes: a basal/squamous-like subgroup (proposed acronym: BASQ) to designate the tumours displaying the KRT5/6$^+$ KRT14$^+$ FOXA1$^-$ GATA3$^-$

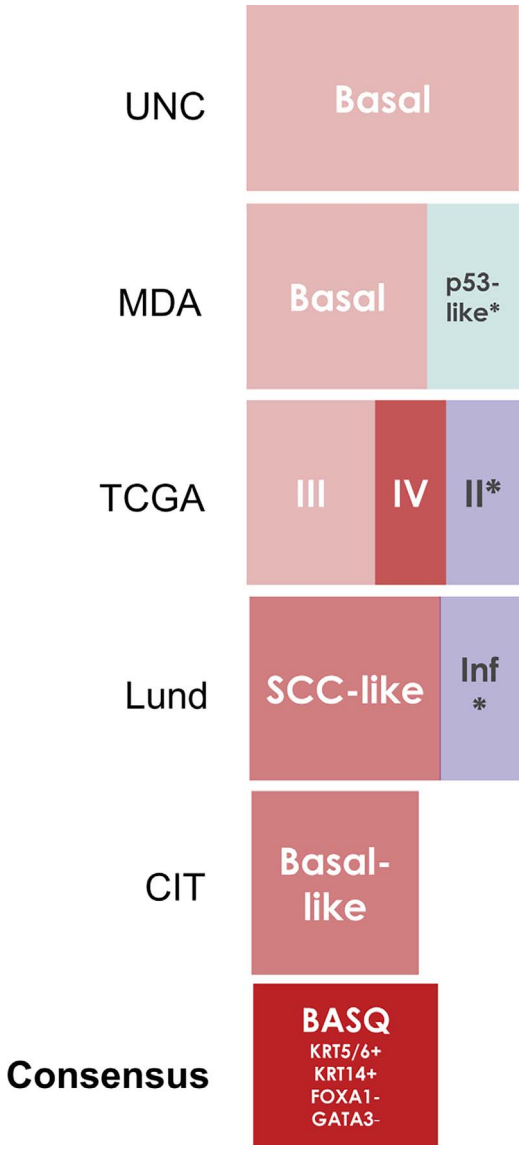

Fig. 1. Comparison of the proposed UC molecular classifications as they relate to the Basal-Squamous-like (BASQ) consensus group. The subtypes labelled with red background are overlapping among classifications, and comprise tumors that will be assigned to the BASQ subtype. Tumor subclasses in other colours (p53-like, TCGA, II, Infiltrated) comprise tumours that also express markers typical of urothelial differentiation to a variable extent. In red, the consensus definition of the BASQ subtype. Adapted with permission from reference [32].

phenotype and a differentiated subgroup correlating with the urobasal A tumours from the Lund classification [31,32] (see also Fig. 1). It was concluded that for the other subtypes more integrated work is needed to determine and validate their robustness [31,32]. Interestingly, similar subclassifications of NMIBC into three major classes with basal- and luminal-like characteristics and different clinical outcomes have recently been reported [33].

The presence of UC in Lynch syndrome (LS), a common genetic disease previously known as hereditary nonpolyposis colorectal cancer (HNPCC), has been largely underappreciated [34]. LS is a cancer-predisposing syndrome characterised by the autosomal dominant inheritance of a heterozygous germline mutation in one of the mismatch repair (MMR) genes [35]. Patients with LS are at increased lifetime risk to develop UC of the upper urinary tract [36,37] and the bladder [38]. UC in patients with LS are predominantly linked to MSH2 mutations [38–40]. Optimal screening for upper tract UC is still under debate and recommendations range from minimal to extensive surveillance [41]. A

higher awareness is recommended in younger patients and those with history of other common LS-associated neoplasms [34,40]; screening might be indicated in individuals with MSH2 mutations [38]. HNPCC-like upper tract UC have been reported to have greater benefit from adjuvant chemotherapy than sporadic tumours [42].

Platinum-based combination chemotherapy remains the standard first-line treatment for patients with metastatic UC with an overall survival of 9–15 months [43]. In the second-line setting, many drugs have been tested, but none have become established as a standard of care because of a low frequency of response. Interestingly, intravesical application of the immunomodulator Bacillus Calmette-Guérin (BCG) has been the standard therapy for selected patients with superficial UC for many years [44], although the exact working mechanism of BCG therapy in UC is still under debate [45]. The progressive understanding of the complex regulatory mechanisms that govern cellular immunity has led to the development of several novel agents and strategies, most notably immune checkpoint inhibitors (ICI). The best-known immune checkpoints in bladder are the programmed cell death 1 receptor (PD-1) and its ligands, PD-L1 and PD-L2; and several drugs targeting PD-1/PDL-1 showed significant therapeutic response in metastatic UC. This has led to the FDA-approval of several ICI drugs in recent months. The anti-PD-L1 drugs atezolizumab, durvalumab and avelumab have been approved by the FDA for the treatment in second line of patients with locally advanced or metastatic UC [46–48]. Based on the results from the Checkmate 275 and KEYNOTE-045 trials respectively, the anti-PD-1 drugs nivolumab and pembrolizumab obtained FDA-approval as second line treatments for locally advanced or metastatic UC [49,50]. Based on data from the KEYNOTE-52 and IMvigor210 studies respectively, pembrolizumab and atezolizumab have been approved by the FDA as first-line treatments in patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy [51,52]. Promising results have also been shown in a small patient cohort with the anti-CTLA-4 drug ipilimumab [53], and larger clinical trials are currently being conducted.

Several biomarkers have been explored to predict the response to specific immunomodulatory drugs, and most of studies has focussed on PD-L1. In a study with atezolizumab in second line for advanced UC, higher levels of PD-L1 expression on immune cells (IC) but not on tumour cells (TC) were associated with a higher response rate to and with a longer overall survival (OS) [46,54]. However, a study with atezolizumab in first line showed no significant enrichment of response by PD-L1 expression [52]. Data from trials with the anti-PD-L1 drug durvalumab showed highest responses in the PD-L1 high group (≥25% TC or IC expression) [47,55]. In the Checkmate 275 trial with nivolumab, responses were seen irrespective of PD-L1 TC expression, but IC expression was not assessed [49,56]. In the KEYNOTE-045 study with pembrolizumab in first line, responses were seen regardless of PD-L1 status [50], while more recent data from the KEYNOTE-052 study with pembrolizumab in second line showed a higher ORR in patients with a combined positive score (CPS, TC and IC PD-L1 expression) [57]. Updated data from the Javelin study showed durable responses to avelumab irrespective of tumour PD-L1 expression status [58]. (See Table 1 for an overview of the role for PD-L1 as biomarker for FDA-approved ICI drug for GU cancers). Moreover, several studies have reported on PD-L1 as a poor prognostic factor in UC [59]. In addition to PD-L1 expression on IC, response to atezolizumab was strongly related to mutational load [46,52]. This association was independent of the association between PD-L1 IC score and therapy response and reinforces the notion that the many mutations that occur in cancer create novel epitopes against which protective T-cell responses are directed [46,52]. In line with these findings, similar durable responses to ICI drugs have been reported in patients with MMR-deficient UC and UC with DNA damage repair and response (DDR) gene alterations [60,61]. Recent data from an exploratory study of the Checkmate-275 trial suggests that tumor mutational load may enrich for response to nivolumab in metastatic UC [62].

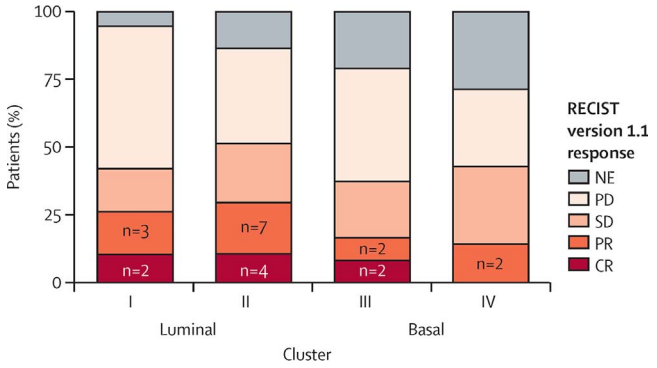

Fig. 2. Response as a function of TCGA subtype. Responses were seen across all subtypes and were most frequent with the luminal II subtype. RECIST: Response Evaluation Criteria in Solid Tumours. NE: not estimable. PD: progressive disease. SD: stable disease. PR: partial response. CR: complete response. Adapted with permission from reference [52].

The molecular subtypes identified by the TCGA analysis were also associated with response to atezolizumab, suggesting that in addition to PD-L1 expression, subtypes differed in their underlying immune biology [46,52]. Highest response rates were noticed in TCGA cluster II (Fig. 2) [46,52], although PD-L1 IC prevalence was highest in the basal subtype (TCGA cluster III) [46]. Others have reported highest expression of immune gene signatures and immune checkpoint molecules in the claudin-low subgroup (corresponding to TCGA cluster IV) [26]. A recent update on the TCGA-clusters showed high immune gene expression in the luminal immune group (former cluster II) [27], which seems to correlate with the clinical benefit of anti-PD-L1 therapy in TCGA cluster II [46,52]. PD-L1 expression in TCGA basal clusters was high on both IC and TC, suggesting that other immunosuppressive factors exist in the basal subtypes that prevent effective T-cell activation with inhibition of the PD-L1/-PD-1 pathway [46]. Another TCGA-analysis showed a relatively high frequency of putative resistance mutations in the antigen presentation pathway and in the interferon signalling pathway in UC compared to other cancers [63]. It becomes clear that although PD-L1 IC status was clearly associated with response to atezolizumab,

Table 1
Table summarizing the data on PD-L1 as a tissue biomarker for the current FDA-approved ICI drugs for GU cancers. An additional column summarizes drug-associated predictive genomics. CPS: combined positive score, IC: immune cells, TC: tumour cells, UC: urothelial carcinoma.

Cancer type	Treatment line	Target	Drug	Predictive value for PD-L1	Antibody Clone	Predictive Genomics
UC (advanced/metastatic)	2nd	Anti-PD-L1	Atezolizumab	≥5% IC [46]	SP142 (Ventana)	TCGA cluster II and mutational load [46]
UC (advanced/metastatic)	1st	Anti-PD-L1	Atezolizumab	Not found [52]	SP142 (Ventana)	TCGA cluster II and mutational load [52]
UC (advanced/metastatic)	2nd	Anti-PD-1	Nivolumab	Not found [49]	28.8 (Dako)	Mutational load? [49,62]
UC (advanced/metastatic)	2nd	Anti-PD-1	Pembrolizumab	Not found [50]	22C3 (Dako)	Unknown [50]
UC (advanced/metastatic)	1st	Anti-PD-1	Pembrolizumab	> 10% CPS [57]	22C3 (Dako)	Unknown [57]
UC (advanced/metastatic)	2nd	Anti-PD-L1	Avelumab	Not found [58]	73-10 (Dako)	Unknown
UC (advanced/metastatic)	2nd	Anti-PD-L1	Durvalumab	≥25% TC/IC [47]	SP263 (Ventana)	Unknown [47]
RCC (advanced/metastatic)	2nd	Anti-PD-1	Nivolumab	Not found [88]	28.8 (Dako)	ccRCC- subgroups? [76]

incorporation of TCGA gene expression subtype, mutational load, or both of these novel biomarkers into a model based on PD-L1 IC staining significantly improved the association with response [46,52]. Noteworthy, if the clinical and molecular correlations are further validated, cisplatin-based chemotherapy and atezolizumab may produce clinical benefit in complementary populations of patients (basal subgroup/cluster IV and GU subgroup/cluster II, respectively) [21].

3. Renal cancer

Renal cell carcinoma (RCC) is the most common kidney cancer and third leading cause of death among urological tumours[64]. About 30% of RCC patients present as widely disseminated, while 25–30% of localized cases progress to metastasis after resection [65,66]. Major subtypes of RCC include clear cell, papillary, and chromophobe, which represent 65%, 20%, and 5% of all RCC cases, respectively [67]. Several genomic changes have been found in clear cell RCC (ccRCC), most notably in oncogenic metabolism and epigenetic reprogramming [68–70]. Common genetic changes include alterations in genes controlling cellular oxygen sensing (e.g. VHL) and the maintenance of chromatin states (e.g. PBRM1) [68,69]. TCGA analysis of a ccRCC cohort found similar genomic changes and reported recurrent alterations in the PI(3)K/AKT pathway and several epigenetic changes in DNA methylation [71]. Molecular stratification of ccRCC revealed 2 different subtypes: clear cell type A (ccA) and B (ccB), with ccA patients having a markedly better prognosis [72,73]. A second TCGA study focussed on papillary RCC (pRCC) and found that type 1 and type 2 pRCC are distinctly different diseases based on molecular features and that type 2 pRCC is a heterogeneous disease with at least 3 different subgroups [74]. A third TCGA project focussed on the chromophobe RCC (ChRCC) and found gene expression changes related to mitochondrial function and recurrent structural breakpoints within TERT promoter region [75]. Recently, a multilevel molecular characterisation of the 3 TCGA RCC databases revealed nine major genomic RCC subtypes [76]. Overlapping and subtype-specific genomic changes were observed, and good correlation with histology was reported. RCC are not considered to belong to the HNPCC spectrum, but in sporadic RCC loss of MMR proteins is frequently observed, especially of MLH1 and MSH2 [77–81]. MMR gene alterations have been reported as underlying mechanisms [82,83], but others did not detect microsatellite instability (MSI) caused by either promoter hypermethylation or alteration of the coding region of MMR studied genes [79,81]. The diminished MMR protein expression has been linked to RCC subtypes and might contribute to the respective different biological behaviour [84].

For more than 20 years, immunotherapy using interleukin-2 (IL-2) or interferon (IFN) has been a primary treatment for patients with metastatic RCC [85]. Treatment of advanced RCC (aRCC) has improved significantly with the introduction and regulatory approval of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin (mTOR) inhibitors [86]. However some RCC tumours are inherently resistant to TKIs and most, if not all, acquire resistance over time, limiting overall clinical benefit and underscoring the need for new therapeutic strategies [87]. ICI has marked a new era in the treatment of RCC. The anti-PD1 drug nivolumab has been the first ICI drug to obtain approval by the FDA and European Commission for the treatment of aRCC, and showed a significant OS benefit in patients with aRCC whose disease has progressed following antiangiogenic therapy, compared with a comparator agent (everolimus) [66]. Several other ICI compounds are currently under investigation for the treatment of aRCC, alone or in combination with TKIs or other drugs [87,89,90].

Biomarker research to select RCC patients eligible for ICI has mainly focussed on the PD1-PD-L1 axis. Low-to-no expression of PD-L1 on IC and TC correlated with a trend toward lower response (progression-free survival [PFS] and OS) to the anti-PD-L1 drug atezolizumab compared with moderate to high PD-L1 expression levels [91]. Updated analyses confirmed the association between high PD-L1 expression and improved OS with atezolizumab treatment [87]. For the anti-PD1 drug nivolumab, early data suggested a positive correlation between PD-L1 expression on TC and objective response [92–94]. Data from the Checkmate 025 trial showed that higher levels of PD-L1 expression are associated with poorer survival in RCC, but did not support PD-L1 as a marker of treatment benefit in RCC; a benefit was observed with nivolumab irrespective of PD-L1 expression [88]. Furthermore, PD-L1 seems to be a dynamic biomarker since prior exposure to VEGF and mTOR inhibitors modulates its expression [95,96]. Notably, a significant number of patients with PD-L1$^+$ RCC do not respond to PD-1 pathway blockade, suggesting that additional intratumoral factors may influence treatment outcomes [95,96]. Based on recent data, PD-L1 could be a prognostic biomarker for the adverse clinicopathologic features of RCC but may not be discriminant enough to be a predictive biomarker [95,97,98]. Furthermore it was found that PD-L1 staining is almost exclusively observed in the high-grade component of a tumour and additionally a discordant expression of PD-L1 between primary tumours and their metastases was detected in approximately 20% of cases [99]. Similar heterogeneity has been observed between primary and metastatic tumour based on molecular analysis [100]. Other possible biomarkers like PD-L2 and CTLA4 are reported in literature, but without straightforward predictive value until now [87]. Increased amounts of CD3+/CD8+ tumour-infiltrating T-cells have been reported after nivolumab treatment, but further research is needed to determine the biomarker-potential [101].

Recent data from a gene expression study on a small cohort of PD-L1$^+$ RCC patients treated with nivolumab identified a metabolic gene profile in the non-responding subgroup and overexpression of immunologic factors in the responding subgroup [102]. Increasing mutational burden and neoantigen formation have been associated with increased responsiveness to ICI in several other malignancies and recent data showed increased frequency of genomic alterations in RCC post-VEGFR therapy [103]. These findings might explain the observed benefit of nivolumab post-VEGFR therapy and seem to correlate with the observation of diminished response rates to nivolumab monotherapy in front line studies [101]. A multilevel molecular analysis on the integrated TCGA RCC database showed relatively high expression of several genes representing targets for immunotherapy in ccRCC-associated molecular subtypes compared to other RCC subtypes, with additional differences within the several clear cell-enriched RCC genomic subtypes [76]. The data also suggested greater levels of IC infiltrates within ccRCC relative to other RCC types [76]. TCGA data suggest an intriguing hypothesis that clear cell-enriched RCC genomic subtypes would be most responsive to targeted immune checkpoints [76] (see also Fig. 3).

4. Prostate cancer

Multiple studies have identified recurrent somatic mutations, copy number alterations, and oncogenic structural DNA rearrangements in primary prostate cancer (PC). Roughly half of all PC contain a fusion of ETS-family transcription factor genes with androgen-responsive promoters [104–106], and the most common fusion links the *TMPRSS2* androgen-responsive promoter and the transcription factor gene ERG [105,106]. Alterations in PI3K and p53 signalling are common in ETS positive cancers, while deletions of CHD1 and overexpression of SPINK1 are specific to ETS negative cancers [107]. A TCGA paper suggested seven subtypes in primary PC based on the type of ETS-family gene fusion or mutations in SPOP, FoxA1 and IDH1 [108]. A study on metastatic PC showed similar subtypes, although many differences with primary PC were found, especially a higher amount of copy number alterations and mutations [109]. Earlier work reported that frequent PTEN alterations are associated with unfavourable clinical outcome [110–112]. Several other studies have confirmed the correlation of ETS re-arrangements with PTEN inactivation as synergistic steps in the

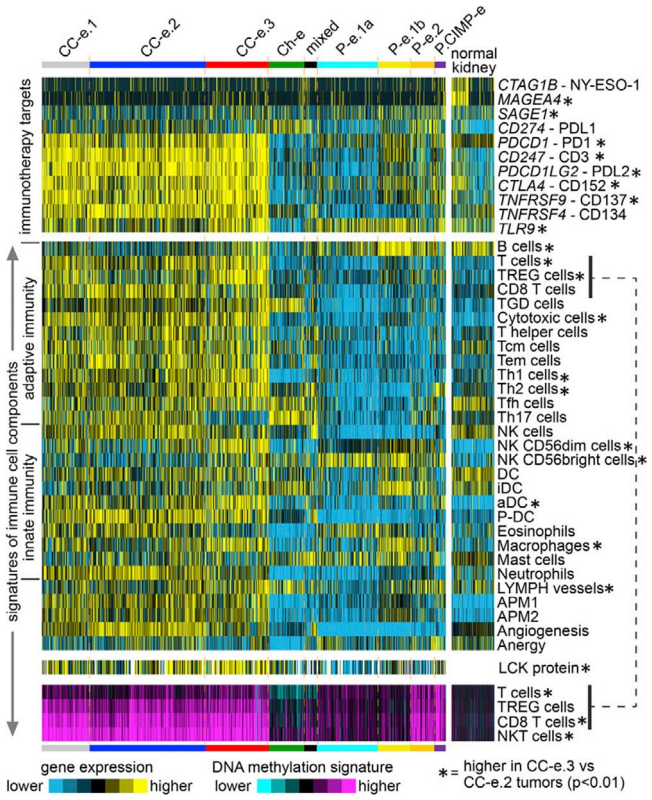

Fig. 3. Heatmaps of differential expression across RCC cases for genes encoding immunotherapeutic targets (top), gene expression-based signatures of immune cell infiltrates (middle), and DNA methylation-based signatures of T cell infiltrates (bottom). Asterisk indicates features significantly higher in CC-e.3 versus CC-e.2 tumours. CC: clear cell subgroups, Ch: chromophobe subgroup, P: papillary subgroups, TREG cells: regulatory T cells, TGD cells: T gamma delta cells, Tcm cells: T central memory cells, Tem cells: T effector memory cells, Tfh cells: T follicular helper cells, NK cells: natural killer cells, DC: dendritic cells, iDC: immature DCs, aDC: activated DCs, P-DC: plasmacytoid DCs, APM1/APM2: antigen presentation on MHC class I/class II, respectively. Adapted with permission from reference [76] and https://creativecommons.org/licenses/by/4.0/.

development of PC [104,113]. The molecular differences between primary and metastatic PC become particularly evident when related to the androgen receptor (AR). Some men will develop metastatic PC and receive primary androgen deprivation therapy (ADT). However, nearly all men with metastatic PC develop resistance to primary ADT, a state known as metastatic castration-resistant prostate cancer (mCRPC) [109]. High frequencies in AR alterations have been reported in mCRPC [109,114,115], and the genomic evolution of AR-aberrations from initial tumorigenesis to the development of mCRPC has been studied [116,117]. Recent data showed that when excluding AR aberrations, 65% of mCRPC have a potentially actionable aberration, including mutations in the BRCA1/2, PI3K, RAS and MEK-pathways [109]. Complex biologic events like chromoplexy (complex DNA rearrangements) and hypoxia have been reported as additional drivers of PC progression [118,119]. Like for other cancer types, amplification of c-MYC has been reported in primary PC, the frequency of which increased further in metastatic PC [120]. While its interplay with the AR axis has been documented at the molecular level [121], the clinical actionability of c-MYC remains limited. Several studies reported altered expression of MMR genes including MLH1, MSH2, MSH6 and PMS2 in PC [122–125]. However, the clinical significance of these alterations remains unclear. Some studies reported associations between loss of MMR gene expression and adverse PC features, whereas others suggested a link between MMR gene overexpression and PC development or poor patient prognosis [125].

ADT is the mainstay of systemic treatment for PC, and has been shown to have immunomodulatory effects, triggering an influx of CD4+ and CD8+ TILs [126,127]. Traditionally, PC has not been associated with a florid immune response and the potential of PC to respond to immunotherapy is still questioned [128]. Nevertheless, several immunotherapeutic approaches are under study. Sipuleucel-T, an autologous dendritic cell vaccine, became the first cancer vaccine to receive FDA approval in 2010 for the treatment of mCRPC [129], but the ideal clinical indications are still under discussion [130]. PROSTVAC, a recombinant vaccine virus encoding the human PSA, has shown a longer median OS in a randomized phase II trial and is currently enrolled in a randomized phase III trial [131,132]. Whole-cell vaccines (e.g., granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells vaccine; GVAX) are also under study [133,134]. Trials of ICI in PC have been largely disappointing [92,135,136]; however a small phase II trial of pembrolizumab in enzalutamide-resistant PC showed objective clinical responses, suggesting that ICI might be effective under certain conditions [137]. Similar encouraging results have been reported with ipilimumab [138,139], and a recent study suggested the presence of another compensatory inhibitory pathway (VISTA) in PC after ipilimumab therapy [140]. Several trials combining vaccines and ICI to further activate the immune response are ongoing [141–144]. Other types of immunotherapy are currently in early study phases. Chimeric antigen receptor (CAR) T cell therapy directed against prostate stem cell- (PSCA) or/and prostate specific membrane antigen (PSMA) has a promising potential as a novel immunotherapeutic treatment for PC, but solid clinical trials are needed to confirm its expected benefits [145,146].

Robust data on biomarkers for immunotherapy in PC are still limited. Blood-based biomarkers have been frequently studied in PC vaccine studies for their biomarker potential. In a phase III trial with Sipuleucel-T, a positive correlation between the amount of antigen presenting cells and OS has been reported [147]. Data from a phase II study with PROSTVAC and from a phase I study with PROSTVAC in combination with ipilimumab showed trends towards associations between longer OS and certain IC subsets respectively after and before immunotherapy [143,148]. Another study showed that the use of a peripheral immunoscore, based on immune cell subsets in the peripheral blood, revealed statistically significant differences in PFS in PC patients receiving radionuclide plus PROSTVAC [149]. A trial combining whole vaccine therapy with ipilimumab showed a correlation between low pre-treatment levels of PD1+/CD4+ IC and longer OS [150], whereas high pre-related expression of CTLA-4+/CD4+ T cells was found to be a dominant predictor for survival after GVAX/ipilimumab therapy [151,152]. There are some reports on the predictive value of cytokines, e.g. in a phase I trial with the AE37 peptide vaccination in PC, in which TGF-β and IFN-γ have been reported as biomarkers for assessing vaccine efficacy both in terms of immunologic and clinical responses [153]. Until now only prognostic value has been reported for the PD-L1/PD-1 axis in PC. High TC PD-L1 and IC PD-1 expressions have been reported as negative independent prognostic factors for BCR-free survival in PC [154,155], and recent data showed a similar independent prognostic value for methylation of PD-1/PD-L1 to predict BCR-free survival [156,157].

A possible relation between mutational burden and response to immunotherapy has been suggested by some authors, but no scientific data are yet available to support this hypothesis in PC [137]. Previous data suggested that loss of PTEN, a common event in PC, is potentially associated with PD-L1 expression [158], but a more recent study reported opposite data, arguing against innate immune resistance in PC [159]. A pilot study reported an increased OS after AE37 vaccination in PC patients expressing the HLA-DRB1*11 or HLA-A*24 alleles or both, suggesting a prognostic and predictive impact for these alleles [160].

5. Discussion

As outlined in the overview, several possible biomarkers to stratify patients for immunotherapy are currently under research, although

only some of them seem to have real predictive potential. Here we want to focus briefly on 2 biologic components that gained strong attention as promising biomarkers: PD-L1 and MMR-deficiency/mutational load.

5.1. PD-L1 IHC in GU cancers

Much of the therapeutic focus of immunomodulatory drugs in GU cancers has been on the PD-1/PD-L1 axis, and therefore PD-L1 could be promising as a biomarker. However, despite the rapid clinical implementation of several anti PD-1/PD-L1 drugs, we are still facing many obstacles to reach a robust and reliable implementation of PD-L1 into clinical practice. As shown in Table 1, data from clinical trials show conflicting values for PD-L1 as a predictive biomarker to different anti-PD-1/PD-L1 drugs in GU cancers.

Several technical and biochemical issues are involved to explain this ambiguity. Differences in anti-PD-L1 antibody-clones, staining assays, tissue characteristics and scoring systems are amongst the major technical obstacles to overcome [161]. The knowledge that PD-L1 expression is not binary, but instead shows a continuum with significant intra-tumour heterogeneity and therapy-induced changes, might even represent a bigger challenge for being a robust biomarker [140,161]. The recent report on the presence of compensatory inhibitory pathways (VISTA) in the setting of immunotherapy in metastatic PC further underlines the complexity to predict the therapeutic response based on a single biomarker like PD-L1 [140].

Recent concordance studies on non-small cell lung cancer (NSCLC) have shown only minimal differences in staining patterns between most of the different validated and commercially available anti-PD-L1 antibody clones [161–165]. These findings are encouraging, although clinical cross-validation data between the different assays are not available yet. High concordances between the different assays and between the pathologists within a single assay were only found for PD-L1 scoring in tumour cells (TC) and not in immune cells (IC) [162,163]. Related to GU cancers this could be a critical point since PD-L1 expression in IC is used as a companion biomarker for some FDA-approved anti-PD-L1 drugs (see Table 1).

5.2. MMR-deficiency and mutational load in GU cancers

As addressed earlier in this review, MMR-deficiency is more and more recognised as an important biologic event in GU cancers. MMR-deficiency can occur in patients with LS (HNPCC) and in patients with sporadic MMR-deficient tumours [166]. MMR-deficient tumours exhibit a remarkably high rate of mutations (high mutational load), which can result in the formation of neo-antigens, hypothesised to enhance the antitumor immune response [167]. Furthermore MMR-deficient tumours strongly express several immune checkpoint ligands, which indicates that their active immune microenvironment is counterbalanced by immune inhibitory signals that resist tumour elimination [168]. Recent data showing a better clinical response to the anti-PD-1 drug pembrolizumab in MMR-deficient patients, support the hypothesis that MMR-deficient tumours respond better to anti-PD-1 therapy than do MMR-proficient tumours [169].

In GU cancers, data on the relation between MMR-status and response to immunotherapy are still emerging, although recent studies showed durable responses to immunotherapy in patients with MMR-deficient UC and UC with DDR gene alterations [60,61]. Based on the promising results in patients with MMR-deficient cancers, FDA has recently approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic MMR-deficient solid tumors, irrespective of the original tumors localization. In this context, MMR-deficient/MSI-H solid GU tumors could be candidates for anti PD-1 treatment. The reality will however be more complex: several clinical trials have shown that some MMR-deficient tumors do not respond to immunotherapy, while mutations in other genes have also been linked to high mutational load and upregulation of immune checkpoints [167,170]. From a methodological point of view, there is an ongoing discussion and evolution in literature concerning the techniques to get reliable data on mutational load and MSI in a context of cost-efficiency and optimal logistics. Whole exome sequencing (WES), T-cell receptor (TCR) sequencing and targeted next generation sequencing (NGS) can be used to assess mutational load [171] and promising data on new platforms to detect MSI (e.g. MSISensor and MANTIS) have recently been published [172]. The detection of MMR-deficient tumors and the selection of those patients that will really benefit from immunotherapy remains an ongoing and challenging task.

6. Conclusions

Immunotherapy is gradually becoming a key factor in the therapeutic algorithm for patients with GU cancers at different stages of disease. The increasing knowledge on the genomic landscape of GU cancers supports stratification of patients for targeted therapies. Robust and reliable biomarkers are crucial in this process, but recent scientific insights indicate that a single biomarker for patient selection may not be feasible, given that immune responses are dynamic and evolve over time. Biomarker development for ICI drugs will require integration of multiple biologic components like PD-L1 expression, TILs, mutational load, …; and new methodological approaches like immunoscore [173,174], radiographic markers, liquid biomarkers,… are likely to enter the biomarker-field [175]. Large-scale biomarker-driven prospective trials with consensus methodologies on biomarker assessment and scoring are needed to reach clinical validation of different biomarkers, needed for a reliable single-patient appointment to the appropriate immunotherapy. A global collaboration and open interaction between researchers, healthcare-providers and pharma-businesses across clinical disciplines is vital to reach these goals. To that extent, the US National Cancer Institute (NCI) has recently introduced important initiatives that encourage multidisciplinary approaches and public–private partnerships [175]. In concusion, the better understanding of solid tumour genomics shows that also for GU cancers combining targeted therapy with checkpoint inhibitors has the potential to improve cancer outcomes, and that reliable biomarkers will be crucial for a stringent patient selection in trials of targeted and checkpoint inhibitor drugs [176,177].

Compliance with ethical standards

The authors adhere to institutional ethical standards.

Conflicts of interest

The authors declare that they have no conflict of interest.

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