

Biomarkers for Renal Cell and Urothelial Carcinoma

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Abstract

Although current and emerging treatment regimens are gaining traction in renal cell carcinoma (RCC) and bladder cancer, experts admit that the development of biomarkers to identify patients who will best respond to these treatments is still in a state of flux.

In a presentation at the New York GU™: 9th Annual Interdisciplinary Prostate Cancer Congress® and other Genitourinary Malignancies conference, Sumanta K. Pal, MD, co-director of the Kidney Cancer Program at City of Hope, discusses the state of biomarker development in the field of genitourinary malignancies.

AJHO interviewed Dr Pal after his presentation. Dr Pal and colleagues provided additional commentary after the interview, which is included in this article.

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physiological domains of kidney cancer, including vascular and inflammatory genes. This gene score was validated across both Cleveland Clinic and a French-derived cohort. It predicts risk of metastasis. If you have a patient with localized kidney cancer, you can estimate of their risk score for developing metastases down the line.

For the medical oncologist, it's a little trickier. We do have some emerging biomarkers. For instance, if you're running mutational panels, there are certain alterations that may potentially predispose a response to VEGF-directed therapies, while others may potentially predict response to mTOR-directed therapies.

For VEGF, we think that there are alterations in the gene *KDM5C*, which may potentially lend itself to extended clinical benefit for a VEGF inhibitor. There has also been some great research from Dr Toni Choueiri and colleagues from Dana-Farber Cancer Institute suggesting that, if you have mutations in mTOR such as *TSC1* or *TSC2*, these are genes that are related to the mTOR pathway that may potentially predict response to agents such as everolimus or temsirolimus.

What is the evidence for PD-L1 as a biomarker in RCC or bladder cancer?

Certainly, PD-L1 plays a role in bladder cancer responsiveness to various immune-based treatments, including PD-1/PD-L1 inhibitors. Thus far, the data are most soundly attributed to atezolizumab, where we know the response rates are concordant. For instance, 3+ staining is intense staining for PD-L1, while 1+ staining is low staining for PD-L1.

We don't quite have an accurate estimate of whether or not those patients who lack PD-L1 expression will have zero response to immunotherapy. There is still a story to be told there. That's where other surrogates, such as mutational load, could potentially come in handy.

In general, why does it seem that many promising biomarkers are stuck in the discovery phase of research and not progressing to clinical phases?

There is a desire on the part of pharmaceutical companies, on the part of investigators, and on the part of patients to get drugs sent to the clinic quickly. I certainly wouldn't disagree

What is taking place in the field of renal cell carcinoma and bladder cancer?

Pal: In kidney cancer, there are some caveats to the way that we treat the disease. For instance, we use targeted therapies—drugs that affect VEGF and mTOR—but we really don't use biomarkers to apply these therapies. It is very different from lung cancer or colon cancer. How might we get there?

Bladder cancer is a very different landscape compared with kidney cancer. In contrast to kidney cancer, where we have had 10 drug approvals over the past decade, we really are still stuck with cisplatin-based chemotherapy in bladder cancer. We are very little beyond that.

What biomarkers are available in kidney cancer? What ones are in development?

For the practicing urologist, it is a little bit different. Right now, there are some biomarkers that are at their disposal. There is an Oncotype-like test available for kidney cancer, which uses a 16-gene recurrence score. These genes straddle various patho-

with that enthusiasm. It is clinically important that we segue drugs from the lab to the clinic very quickly.

One of the challenges observed in RCC, where we have a multitude of different targeted therapies and now immunotherapies, is we don't quite know how to apply them.

If we were to turn back the clock a couple of years, perhaps a more sensible way to design these trials would be to embed a lot of biomarker-based research. Then, we can better understand how we can select these patients who will have a better response to nivolumab over cabozantinib and vice versa.

What should the next steps entail?

The real key is, as time goes on, we're going to have to focus our efforts on embedding biomarkers prospectively in clinical trials for genitourinary oncology. We have not done a great job of this to date.

There are certainly some great examples of trials that have incorporated biomarkers early on. However, we need to really employ biomarkers in prospective fashion and stratify patients based on the presence or absence of PD-L1 or specific genes, for example, which can produce a predicted response to therapy. Unless we do that, we will never really have an understanding of which patient will benefit the most from any given therapy.

Additional Commentary

For the past decade, urothelial carcinoma (UC) and renal cell carcinoma (RCC) have shared space at international meetings, listed under the collective heading of non-prostate genitourinary cancers. Despite this grouping, the treatment of the two diseases has been quite disparate. Metastatic RCC (mRCC) has enjoyed some success, with multiple targeted therapies approved from 2005 and onwards.¹ In contrast, metastatic UC (mUC) has been a barren treatment landscape, limited primarily to moderately effective cytotoxic therapies. Several recent changes, however, unify the diseases. Late last year, nivolumab (a programmed death-1 [PD-1] inhibitor) was approved for mRCC on the basis of positive phase III data.² Within the past several weeks, atezolizumab, a distinct immunotherapy that inhibits programmed death-ligand 1 (PD-L1), was approved for mUC.³ Thus, checkpoint inhibition now plays a key role in management of both tumor types.

Another unifying feature of mRCC and mUC is an emerging understanding of the genomics of both diseases. In mRCC, findings from the investigators at The Cancer Genome Atlas have been published across all 3 major histologic subtypes of disease (clear cell, papillary, and chromophobe).^{4,6} Furthermore, other investigators have pooled together collections of rare subtypes (eg, collecting duct and sarcomatoid RCC) to gain a better understanding of their underlying biology using genomic profiling.^{7,8} In the setting of clear cell mRCC, frequent mutations are noted in the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway.⁴ Interestingly, studies assessing

dual PI3K and mammalian target of rapamycin (mTOR) inhibition have not shown substantial benefit with this approach over mTOR inhibition alone.⁹ However, these studies have not been enriched with patients who possess relevant alterations in the mTOR signaling pathway. Recently, Kwiatowski et al reported results from a multi-institutional study assessing "extreme responders" to mTOR inhibition—the study identified that alterations in *TSC1*, *TSC2*, and *MTOR* could identify those patients who derived the greatest clinical benefit from these agents.¹⁰ There may also be selected mutations that predispose patients to gain more substantial benefit from VEGF-directed therapies. Using a series of mRCC patients who received comprehensive genomic profiling (CGP) as a part of routine clinical care, we confirmed that patients with alterations in *KDM5C* alterations had prolonged durations of therapy with VEGF-directed agents.¹¹ These findings are supported from correlative studies accompanying the prospective RECORD-3 clinical trial, a study juxtaposing sunitinib and everolimus in the frontline setting with crossover.¹²

In bladder cancer, use of molecular profiling in a CLIA-certified laboratory is now supported by National Comprehensive Cancer Network (NCCN) guidelines for patients with advanced disease.¹³ The results from genomic profiling can be applied in numerous ways, although the ideal avenue is through referral to clinical trials. Our work in a population of patients with advanced UC identified alterations in *FGFR3* and *ERBB2* occurring at approximately 20% and 15%, respectively.¹⁴ Recently, several studies have shown promising results with the strategy of *FGFR3* inhibition in bladder cancer. In a cohort of 44 patients treated with BGJ398, an orally available specific inhibitor of *FGFR3*, a response rate of 35% was identified with a complete response occurring in a patient with bone metastases.¹⁵ For patients bearing an *ERBB2* or *ERBB3* alteration, early data suggest that there may be significant activity with afatinib.¹⁶ Although less frequent, alterations along the mTOR signaling pathway may also point to salient therapies in patients with mUC. Early data supported the activity of everolimus in the setting of *TSC1* alteration; our group and others have reported similar anecdotal findings.^{17,18}

The data outlined herein suggest many potential applications of genomic profiling to identify relevant therapies in the context of mUC and mRCC. Future work may go beyond simply tethering a specific alteration to a single therapy—rather, derivatives from genomic profiling such as mutational load could point to patients who may benefit from immunotherapy.¹⁹ This observation was made in the pivotal phase II assessment of atezolizumab leading to FDA approval.³ Several small, preliminary datasets provide conflicting data regarding the association of mutational load to nivolumab response in mRCC—future work will be necessary to clarify these findings.^{20,21} Other novel genomic profiling techniques may take advantage of biospecimens beyond the tumor. For instance, our group has recent-

ly reported results of stool bacteriomic profiling in a cohort of patients with mRCC who received VEGF-directed therapies.²² These studies suggest that stool flora may predispose to VEGF-tyrosine kinase inhibitor (TKI)-related diarrhea. Stool bacteriomic profiling represents one of many novel platforms available for molecular profiling. As genomic technologies expand in depth and scope, so too will the extent of their clinical application.

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