Clarifying the Checkpoint Inhibitor Treatment Options in Non-clear Cell RCC

To the Editor:

This spring, we launched a new papillary patient community that now has about 120 members and continues to grow. (For what it's worth, we also have a large chromophobe community and a recently launched unclassified renal cell carcinoma [RCC] community). As a rule, we don't create communities unless we're asked to do so, rather we let existing communities thrive and work within them to share information and provide support where we can.

This week, a caregiver in the papillary community mentioned that she was looking for a clinical trial involving ipi/nivo (ipilimumab/nivolumab) for her husband since "it wasn't approved for pRCC." When I explained to her that it was approved, she shared an article from the *Kidney Cancer Journal* stating clearly that it wasn't**.** [Liu ST, Wong K, Hui G, Kelley K, Pantuck AJ, Drakaki A. The classification and treatment of non-clear cell renal cell carcinoma. *Kidney Cancer Journal*. 2018;16:17-25.]

She was seeking help to get compassionate use. Upon further investigation, I found two other patients in other general RCC communities with the same reference.

My understanding of the label is that ipi/nivo is approved for kidney cancer and that there isn't a designation related to histology. I believe that's also true for nivolumab as monotherapy (and all other labels in kidney cancer for that matter).

Of course I understand that trials are conducted using predominantly clear cell patients and that navigating options for non-clear cell is difficult. I'm not making a case that every patient will benefit from checkpoint inhibitors - nor are we pushing this in any of the communities. But we're seeing more and more insurance denials these days and it's imperative that any messaging put out doesn't imply that FDA labeling excludes certain patients. Seventy percent of our patients are treated in the community setting. One article is all it takes to set things back and keep doctors from prescribing even in cases where patients might benefit.

Below is what is being shared - along with a link to the longer article.

"In general, the current treatment of choice for non-clear cell RCC is a vascular endothelial growth factor (VEGF) receptor inhibitor followed by a mammalian target of rapamycin (mTOR) inhibitor at the time of progression. Immunotherapy with checkpoint inhibitors is not yet FDA approved for non-clear cell RCC."

http://kidney-cancer-journal.com/liu_v16n1/

Perhaps the *Kidney Cancer Journal* could provide an update since the article was published prior to combination therapy approval? We could share that within our communities and dispel any concerns that checkpoint inhibitors aren't FDA approved in non-clear-cell RCC.

Any help you can provide is greatly appreciated!

Best,

Dena Battle
President, KCCURE

The authors' response:

We would like to thank Ms. Battle for pointing out the important fact that although there are currently no drugs with specific regulatory approval from the US FDA for non-clear cell RCC, all the targeted and immunotherapies approved in kidney cancer to date, including the recent approval of nivolumab and ipilimumab in combination, have been issued with the marketing indication for "advanced renal cell carcinoma."

These broad approvals, which encompass all sub-types of RCC, were issued regardless of the fact that the clinical studies leading to these approvals were conducted nearly exclusively in patients having clear cell predominant tumors, and often using risk stratification systems such as the one used by the IDMC which were developed nearly exclusively in clear cell patients. However, as we tried to point out in our review, RCC represents not one entity but rather a family of renal cortical tumors that arise in different cells of the kidney, have different underlying genetics and molecular biology, appear differently histologically, and which behave differently clinically.

It is not unreasonable to expect, therefore, that tumors with this many important differences might respond differently to "targeted" agents that have a mechanism of action directed to a specific molecular alteration. We would not advocate treating neuroendocrine and non-small cell carcinomas of the lung, for example, the same way simply because they both arose in the same organ, but rather ideally we would make treatment decisions based on evidence-based clinical data.

While we regret the impression left by our review article that currently patients with non-clear RCC tumors did not have access to approved drugs under the broad regulatory approval framework of the FDA, we would like to reiterate the need that we see for both industry and academia to do better for patients with non-clear histologies, both by developing agents that target the underlying biology of these tumors, and by doing the difficult studies to demonstrate the efficacy and safety of agents specifically in these challenging (since rare) patient populations.

To this end, we greatly anticipate the results of studies such as the now completely accrued BMS 920, which included patients with non-clear cell histology, and which will provide prospective data on the benefits of nivolumab/ipilimumab for non-clear cells tumors. Until then, however, the NCCN guidelines currently list checkpoint blockade as a systemic therapy option for non-clear cell histology, and, in the absence of other data in this treatment setting, it should be considered a reasonable treatment option offered to patients who have metastatic non-clear cell RCC.

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