'Deep dive' into biology of kidney tumors identifies markers of response to immunotherapy

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MSK medical oncologist Robert Motzer led a team of researchers to perform an analysis of kidney cancer tumors from nearly 900 people who were treated as part of a phase III clinical trial. Credit: Memorial Sloan Kettering Cancer Center

Treatments for kidney cancer have improved considerably over the past few decades. In 1988, when Memorial Sloan Kettering oncologist Robert Motzer started researching the disease, the average survival was less than one year. There were no approved therapies at the time besides surgery. By 2005, with the development of targeted drugs such as sunitinib (Sutent), survival nearly tripled. Today, with the addition of immunotherapy drugs to these regimens, people with kidney cancer are living even longer, and some even seem to be cured.

Despite this clear progress, it remains difficult to predict who will respond to these therapies, and what underlying biological factors influence these responses. To help answer these questions, an international team of investigators led by Dr. Motzer performed an in-depth study of kidney cancer tumors from nearly 900 people who were treated as part of a large, phase III clinical trial.

That trial compared two different treatments: a combination of avelumab (an anti-PD-L1 immunotherapy) and axitinib (a drug targeting tumor blood vessels), versus sunitinib (another blood vessel-targeting drug) given alone. People with advanced renal cell carcinoma who received the combination did better (in terms of the length of time their cancer shrunk or did not get worse) than people who received sunitinib alone. On the basis of these results, the US Food and Drug Administration approved the combination of avelumab (Bavencio) and axitinib (Inlyta) to treat kidney cancer in May 2019, establishing a new standard of care for this disease.

While that might seem like crossing the finish line, Dr. Motzer and his colleagues wanted to extract all the useful information they could out of the clinical trial data.

"Oftentimes, when a drug is approved, there's not really an effort on the part of pharmaceutical companies to understand the underlying biology

of tumors collected from patients treated on the pivotal trial," Dr. Motzer says. "With this study, which we conducted in partnership with Pfizer, we wanted to take a deep dive into the biology so that we could generate new avenues of research to keep the field moving forward."

The results of this deep dive—including identification of several novel biomarkers of response—were reported on September 7 in the journal *Nature Medicine*.

Beyond PD-1 and TMB

Among the variables the team analyzed were levels of a biomarker called PD-L1 (a common immunotherapy target) and the number of mutations present in the tumor (dubbed tumor mutation burden or TMB). Both these measures have been associated with improved responsiveness and better survival in other cancer types. Somewhat surprisingly, neither measure correlated to a better response to the immunotherapy and targeted therapy combination in this trial.

In addition to these well-known biomarkers, the scientists also looked for patterns of gene activity and specific genetic mutations that correlated with treatment response. Here, they found clear contenders.

In particular, they identified a set of 26 genes whose activity correlated with progression-free survival (PFS) in the combination arm of the trial. They dubbed this the "Renal 101 Immuno signature." They also identified mutations in 11 other genes that were associated with differences in PFS in the combination arm.

Likewise, in the sunitinib-only arm, the investigators found a specific pattern of gene activity that correlated with longer progression-free survival. Because the genes are mostly involved in generating new blood vessels, a process called angiogenesis, they dubbed this the "Renal 101

Angio signature."

By testing for these specific markers in tumors, doctors could potentially personalize treatments for patients based on whether they are more or less likely to respond. The gene signatures and mutations also provide scientists with new avenues of biological research to understand how these genes are contributing to the response.

"My priority right now as a clinical investigator in kidney cancer is to help facilitate this kind of collaborative translational research between clinicians and laboratory scientists so that we can identify why these new combinations are working and maybe develop even better treatments as a result," he says.

More information: Robert J. Motzer et al, Avelumab plus axitinib versus sunitinib in advanced renal cell carcinoma: biomarker analysis of the phase 3 JAVELIN Renal 101 trial, *Nature Medicine* (2020). DOI: 10.1038/s41591-020-1044-8

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