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Clearing Up Non-Clear Cell Renal Cell Carcinoma Management

Dr. Sands:
Non-clear cell renal cell carcinoma is one of the rare diseases with limited treatment data. These are challenges for many practicing oncologists. But recent updates have radically changed the landscape.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and here to share the latest advances in non-clear cell renal cell carcinoma is Dr. Brad McGregor, the Clinical Director for the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute in Boston, Massachusetts. Dr. McGregor, it is a pleasure having you on the program today.

Dr. McGregor:
Thanks so much for having me.

Dr. Sands:
Dr. McGregor, to set the stage, can you tell us about some of the challenges associated with non-clear cell renal cell carcinoma?

Dr. McGregor:
For those patients living with metastatic clear cell disease with combination-based therapy over sunitinib, that would include drugs such as nivolumab/ipilimumab, pembrolizumab/axitinib, then more recently cabozantinib/nivolumab and lenvatinib/pembrolizumab. All these combinations are a marked improvement in not just progression-free survival, but overall survival in the frontline management of patients with advanced renal cell carcinoma.

But unfortunately, think about those patients with non-clear cell or variant cell carcinoma, which is still about 20% of kidney cancer. We haven't had that same degree of success. All these trials generally excluded patients with variant histology, require patients to have predominantly clear cell components and so we've had these great advances. We haven't seen those same degree of success in the management of non-clear cell disease. Until just this year, the only randomized data for the patients with non-clear cell renal cell carcinoma consisting that of ESPN and ASPEN trials which looked at sunitinib versus everolimus showing a benefit to sunitinib in that setting. So there's really been an opportunity to improve care for these patients.

Dr. Sands:
So now setting on that foundation that you've established of the challenges within this disease setting, can we talk a little bit, you mentioned one drug, but the current standard of management for non-clear cell renal cell carcinoma? Where do you see that today?

Dr. McGregor:
I think it's changing dramatically, which is fantastic. In the past couple years, we started seeing several phase 2 trials looking at management of patients with non-clear cell renal cell carcinoma showing very encouraging response rates. I think one of the more monumental trials was the PAPMET trial, which was presented by Dr. Paul at ASCO GU this past winter and was subsequently published in the *Lancet*, looking at those patients living with papillary renal cell carcinomas. This can actually just be met driven, but all

papillary, what was formally called type 2 as well as type 1. And these patients were randomized to receive cabozantinib or sunitinib. And what this very important trial showed was that with cabozantinib, there was an improvement in progression-free survival and objective response rate over sunitinib. And that's really probably established cabozantinib as a standard of care in those patients with papillary renal cell carcinoma.

I think that's fantastic. And I think what we've also seen with some of these studies is that similar to PAPMET looked specifically with those patients with papillary renal cell carcinoma maybe we should look even further. So there was another trial done by the NCI looking at the combination of bevacizumab with erlotinib. So there was some early phase 2 data demonstrating response. This would make standard trial looking at bevacizumab/erlotinib in those patients with papillary renal cell carcinoma but also specifically those with FH-deficient renal cell carcinoma, which is really an unmet need. And this trial showed remarkable activity for the combination of bevacizumab/erlotinib in those patients with FH-deficient renal cell carcinoma. The progression-free survival approaching two years, which is quite remarkable.

And so certainly what we see in there is that what works for type 1 papillary such as imatinib or cabozantinib or we've even seen data with Stavelin in the very potent met inhibitor may not work for a type 2 and certainly for things such as FH-deficient renal cell carcinoma, but novel combination such as bevacizumab/erlotinib may make sense in that situation.

Likewise, when we think about chromophobe renal cell carcinoma, a lot of the VEGF data has shown very poor response rates and if you look at any trial that looked at novel approaches, generally the cohort of patients that always do worse than the other varying histologies. But in a phase 2 trial done last year and published it this year looking at the combination of lenvatinib and everolimus was studied extensively in clear cell, in the CLEAR trial, for the first time ever we saw remarkable improvement in response in the chromophobe patients where four out of the nine patients actually had a response to the combination of lenvatinib and everolimus.

So to your point, I think that we're starting to appreciate that not all non-clear cell are the same. And a papillary behaves different from an FH-deficient, which behaves different from a chromophobe. We already know that varying histologies such as collecting duct or medullary respond better in response to chemotherapy and now we're seeing within the target therapy that each variant has a different approach.

Dr. Sands:
Yeah so that's a complicated amount of data that you're discussing and how that then leads to treatment, so maybe you can just take us through how the variant histology influences your decision making, maybe like an algorithm for how you would treat these different histologies?

Dr. McGregor:
I think we love to have a very specific algorithm, yet I think there is other exciting data looking at combination therapy. So we presented some data for atezolizumab and bevacizumab in patients with variant histology renal cell carcinoma showing a 26% response rate. Subsequently we did a phase 1 trial with cabozantinib/atezolizumab showed a 32% response rate. At ASCO just this year, Dr. Lee from Memorial presented phase 2 data looking at those patients with variant histology, there's two cohorts, and akin to what we've seen in other studies in the cohort 1, cohort 2 which included those patients with chromophobe, he didn't really see any response to the combination cabozantinib and nivolumab. But in cohort 1, those patients with unclassified or papillary translocation, he saw a response rate approaching 50% in this unmet need. So it certainly begs the question, these combinations that are approved in clear cell need to have a role in variant histology renal cell carcinoma.

So to the point of an algorithm, I do think that the histology certainly matters. And the first thing I'm going to look at to see are there patients who have a chemo-sensitive variant. So this is gonna be your collecting duct, your medullary, where we know that cytotoxic chemotherapy remains a critical part of the management of their disease. And then we'll look at the other varying histologies. And within that I think chromophobe is the most unique, in terms of its responses. And I think for chromophobe, I really do feel that lenvatinib and everolimus has a key role in the management.

We look at the rest of the different histologies. In general, I think cabozantinib has a great activity, not only in papillary, but in all variant histologies, based on a retrospective analysis that we did out of our group from multiple sites showing response rates over 20% in these patients. So cabozantinib right now I think would be one of the standards for non-clear cell renal cell carcinoma, potentially in combination with nivolumab, given the recent data presented by Dr. Lee from ASCO. Well that rare, FH-deficient, I do think about something like bevacizumab/erlotinib. But at the end of the day, I think a clinical trial is always going be really important because that's how we're gonna continue to advance care for these patients.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Brad McGregor about some of the recent developments in management of non-clear cell renal cell carcinoma.

Dr. McGregor, you had just mentioned atezolizumab, for example, as one of the immune checkpoint inhibitors, can you share with us some of the data around atezolizumab and maybe other checkpoint inhibitors specifically related to non-clear cell renal cell carcinoma?

Dr. McGregor:
Yeah. I think it's clear that while the responses probably are not as robust as they are in clear cell disease, checkpoint inhibition does have an important role in the management of certain variants of non-clear cell renal cell carcinoma. So again, the combination with atezolizumab with bevacizumab showed a response rate of 26% across histologies, including those patients even more chemo-sensitive disease have collecting duct or medullary. Then looking to combine atezolizumab with a better VEGF with cabozantinib with the multi-targeted therapy show response rate over 30% and that phase 1 data, certainly intriguing. And again, I think now we have data with cabo plus nivo.

We've also seen data for IO/IO combinations as well as IO alone. We've had data for pembrolizumab in the monotherapy setting for patients with treatment naïve non-clear cell renal cell carcinoma response rate just under 30%. And we saw data just this ASCO for nivolumab showing a response rate much less at around 15%, and when they looked to salvage ipilimumab for those patients who didn't respond, response rate was pretty poor at only 6%.

So I think the role of immune checkpoint blockade is certainly evolving in the management of variant histology renal cell carcinoma and further trials are gonna be necessary to establish the best role for it.

Dr. Sands:
So to that point about clinical trials, what are the clinical trials going on now or what are the ones coming that you're looking forward to seeing the results of? And anything that you specifically are working on as well within the field?

Dr. McGregor:
Yeah, I think I'm definitely excited about the trial that I'm presenting today and looking forward to what is to come. So I think one of the trials we're interested in is the SUNIFORECAST, so this is a trial, akin to the CheckMate 214 design in clear cell looking at nivo/ipi versus sunitinib in those patients with variant histology renal cell carcinoma. I think obviously given that data with cabo/nivo show a response rate close to 50%, that's quite intriguing. And given the encouraging signals in clear cell and ongoing COSMIC-313 looking at cabo/nivo/ipi versus nivo/ipi in clear cell, we actually designed a single arm phase 2 trial looking at the triplets, so cabozantinib with nivolumab and ipilimumab and those patients presenting with advanced renal cell carcinoma of variant histology that have the treatment naïve or progressed on one prior VEGF therapy, with the hope that this triplet therapy will really look to build upon the success we see with cabo/nivo and offer potentially a higher chance response that has potential for durability.

Dr. Sands:
So now just to put you on the spot, in a year, what do you think is gonna end up being a standard of care at that time?

Dr. McGregor:
So I think what we're gonna look at as we move forward is this pretentious idea of doing histology-directed therapy and we're gonna have different approaches that will work best for each histology. I've already seen some that in these small trials in the past year that really highlight that this is gonna be an important aspect.

But at the same time, I think these trials including all histologies are gonna be important because we're gonna do these trials and we're gonna see where the response is seen and is there a histology in that group that maybe responds well that we need to then take that trial and expand that histology to get better idea of how we can improve outcomes for our patients. So I hope that in the next year, we're gonna be talking about combination therapies and moving away from a point where we can design trials where sunitinib is no longer

going to be the standard of care as we think about randomization.

Dr. Sands:
Definitely exciting, as we get more into this personalized medicine pathways that we see now and more and more within oncology. It's exciting to see that, happening within non-clear cell renal cell carcinoma. And there's clearly a lot more to discuss in there, but that is the time that we have today.

I want to thank my guest, Dr. Brad McGregor, for joining me to discuss the recent advances in non-clear cell renal cell carcinoma. Dr. McGregor, lot of fun having you on the program today.

Dr. McGregor:
Thanks so much for having me. Enjoyed it.

Dr. Sands:
I'm Dr. Jacob Sands. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology, where you can Be Part of the Knowledge. Thanks for listening.