Expert Perspectives: Q&A on Advances in Treatment Landscape of mRCC: Nicholas J. Vogelzang, MD, FASCO, FACP

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KCJ: Can you please provide your perspective about the currently evolving therapeutic landscape of metastatic renal cell carcinoma?

Dr. Vogelzang: The major phenomenon that we are all dealing in the kidney cancer space is the power of the immuno-oncology agents to effect complete responses. For the first-line therapy, physicians have f our FDA approved regimens to choose from: nivolumab/ipilimumab, pembrolizumab/axitinib, nivolumab/cabometyx, pembro/lenvantinib, and of course clinical trials. Nivolumab/ipilimumab combination has big advantages and performs dramatically well in eliminating the tumors in certain RCC patients. In some patients, complete response is attained fairly quickly within three months. Such complete responses are well documented both clinically and sometimes surgically by nephrectomy. Such highly impressive outcomes are driving a lot of physicians who are on the fence between nivolumab/ipilimumab versus pembrolizumab/axitinib to go with nivolumab and ipilimumab.

I am not denying that immunologic side effects can be daunting with the use of nivolumab/ipilimumab; certainly side effects could be severe or life threatening. But despite all, nivolumab/ipilimumab has an allure that is hard to match. The other combinations like pembro/axitinib, nivo/cabo and pembro/lenvantinib are competing, if you will, with nivolumab/ipilimumab for the first line space. The main draw back with the other 3 FDA approved regimens are the toxicities of their oral companion drugs (axitinib, cabometyx and lenvantinib). These drugs give chronic side effects over long periods of time eg. two to three years even with dose reductions.

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For good risk disease which is about 15% of subpopulation, a variety of approaches are used but generally Nivo/Ipi is not used. In this population, all three doublet regimens (including cabometyx) were superior to sunitinib. Since pembrolizumab/axitinib was the first regimen to show superiority to sunitinib in good risk patients and has been approved the longest, it is the most commonly used. Patients with very well differentiated clear cell subsets certainly need to be treated with tyrosine kinase inhibitors. Investigators Brian Rini and James Brugarolas have shown that this subset of tumors which can metastasize to the endocine organs (ie thyroid, pancreas, ovary etc) respond very poorly to immunological therapy, but respond well to TKIs. So we're beginning to get a flavor for the spectrum of disease. For the high grade sarcomatoid poor risk RCCs, almost everyone agrees should get nivolumab/ipilimumab. The good risk patients have more flexibility in treatment, patients can either go for TKI monotherapy or TKI/IO therapy. However, the large majority of kidney cancer patients fall into the intermediate group. Here, the debate is whether you give these people an IO/TKI doublet or nivolumab/ipilimumab.

Now, with highly effective regimens available, the role for nephrectomy may be increasing. With near complete responses in the lungs and/or other sites, a nephrectomy to remove residual disease makes clinical sense. With all disease removed or eliminated, therapy can realistically be discontinued. This has really been a fairly dramatic sea change compared to what we used to do with continuous sunitinib or pazopanib therapy, namely a rather long drawn out affair. The future is we can make the cancer go away fairly quickly with doublet therapy and surgical resection of all disease whenever feasible.

However, the question remains regarding which population will get the most from nivolumab/ipilimumab and the other doublet regimens? The way I read it is that the biomarkers for response are still to be determined. The best would be serum markers since tissue markers cannot be sequentially sampled.

Regarding therapeutic sequencing, the duration of response, degree of response and the type of toxicity from first line therapy determine which regimen is used in the 2nd line. There is also considerable debate about whether an IO agent should be continued into the 2nd /3rd line. For instance, if nivolumab/ipilumab was used as a 1st line therapy, should nivolumab/cabometyx combination or cabometyx monotherapy be given in the 2nd line? By the time patients get to 3rd or 4th line, IO agents have usually been dropped and patients revert to a sequence of TKI drugs; cabometyx, lenvantinib, axitinib, pazopanib, sorafenib etc. The role of nephrectomy still needs to be addressed if not done prior to systemic therapy. Overall, this whole field is still in flux with some new agents being introduced to the clinical practice, and some in the pipeline; IO and IO/TKI combinations, and HIF based targeting agents will require more studies and time to be validated and incorporated to the RCC treatment landscape.

KCJ: What are your expectations for evolving IO or TKI therapies under clinical trial pipeline getting integrated into the real world clinical practice?

Dr. Vogelzang: Currently, doublet therapies such as nivolumab/ipilimumab, pembrolizumab/axitinib, nivo/cabo and pembro/lenvantinib are getting incorporated in the mRCC landscape.

In addition, many other agents are currently being explored for their utility. For example, I've been working in a phase 1 trial involving macrogenics B7-H3 antibody which theoretically is able to be synergistic with pembrolizumab. Similarly other cytokines such as anti-IL8, anti-IL2 seem to be synergistic and are also being investigated in clinical research. First, they have to perform better as compared to standard regimens available in practice to prove that they have better efficacy and potentially less toxic. Remember, it took us almost 15 years to show that pembrolizumab/axitinib, nivo/cabo are better than sunitinib. So, my reaction to these new immunologic doublets is that they're going to have a big challenge. So I think we're not going to get the real world evidence for a while and they have to go through further clinical trials to assess their roles in clinical practice as compared to currently available standard regimens

KCJ: Recently, we come across favorable outcomes from belzutifan study which led to the FDA approval. What does the future hold for such therapies ?.

Dr. Vogelzang: Now that we have an RNA based approach to deliver HIF molecules, we can investigate it in patients who are in the third or the fourth line of treatment. If we see any glimmer of activity, we'll begin to compare it to those drugs that are in the second or third line. Overall, further clinical trials required us to assess the efficacy of HIF1/HIF2 inhibitor molecules against standard regimens such as cabometyx or lenvatinib at that level. But imagine doing the trial and HIF1/2 companies would then have to beat or at least be somewhat equivalent to axitinib. That's the path forward that I can see. That's going to take two or three years. Abstract: Close to 74,000 cases of renal cell carcinoma (RCC) are diagnosed each year in the United States. The past 2 decades have shown great developments in surgical techniques, targeted therapy and immunotherapy agents, and longer complete response rates. However, without a global cure, there is still room for further advancement in improving patient care in this space. To address some of the gaps restricting this progress, the Kidney Cancer Association brought together a group of 27 specialists across the areas of clinical care, research, industry, and advocacy at the inaugural "Think Tank: Coalition for a Cure" session. Topics addressed included screening, imaging, rarer RCC subtypes, combination drug therapy options, and patient response. This commentary summarizes the discussion of these topics and their respective clinical challenges, along with a proposal of projects for collaboration in overcoming those needs and making a greater impact on care for patients with RCC moving forward.

KCJ: What would you consider to be the greatest challenge for IO therapeutic regimens and how do you think we can overcome?

Dr. Vogelzang: The biggest challenge is to find out the reasons for immune resistance to IO agents. We already spent a lot of time investigating resistance to sunitinib like agents in the past. However, now sunitinib was supplanted by better drugs that came along. So, I think the balance of power, is not just about finding the resistance pathways to nivolumab/ipilimumab, but rather, finding the better third drug that will synergize with nivolumab/ipilimumab and bring that combo to a higher level. The best part is we already heading in that direction; nivolumab/ipilimumab versus nivolumab/ipilimumab/cabometyx trial is on the way.

KCJ: Moving on from the challenges we have now, what developments do you think are possible in the next five to 10 years ?

Dr. Vogelzang: I believe that, as I wrote in editorial many years ago when we had only three drugs for kidney cancer, we had an embarrassment of riches. Now we have 10 plus drugs, that's indeed an embarrassment of riches. As a matter of fact, we don't even quite know how best to sequence. Some of the newer things that I expect to happen will be EZH inhibitors and glutaminase inhibitors. But, there are other drugs are out there trying to find a home in renal cancer space. One of the other things that I'd like to see is developing therapies tailored for patients with renal dysfunction/real failure because they are not accounted for any clinical trial. So some savvy company may be able to figure out that that's an unmet medical need. For trials, I would imagine that that will be a niche that needs to be included. Likewise, we also need suitable therapies for rare subsets like non ccRCC subpopulation. There may be a carve out for some of these new drugs in non-clear cell RCC space.

KCJ: How do you think COVID-19 changes the treatment landscape in the future. What do you foresee ?

Dr. Vogelzang: There is an enormous investment in studying the immunologic underpinnings of cancers. They are currently directed towards vaccine development for COVID-19. I believe such vaccine development may have a large spin off for immunologic manipulation in kidney cancer patients. Given the hyper immune response in patients who are IO therapy, they may be already somewhat protected against COVID-19 infections. Right now, it sounds hypothetical. But I wouldn't be surprised if someone shows that renal cell carcinoma patients on pembrolizumab or nivolumab/ipilimumab have a lower rate of COVID infection rate than the general population. It could be an ancillary benefit to IO therapy. Even patients who were on nivolumab/ipilimumab or pembrolizumab in the distant past may be protected as well. So it's an interesting set of potentials that the COVID environment brings to us.