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Studying Surveillance & Examining Frontline Treatment: A Look at Therapeutic Approaches for Advanced Cell Renal Carcinoma

Announcer Intro:
Welcome to *Project Oncology* on ReachMD, sponsored by Exelixis. Here's your host Dr. Paul Doghramji.

Dr. Doghramji:
This is *Project Oncology* on ReachMD. I'm Dr. Paul Doghramji and joining me today to examine approaches to frontline treatment for patients with advanced renal cell carcinoma is Dr. Rana McKay, a Medical Oncologist and Associate Professor of Medicine at the University of California, San Diego. Dr. McKay, welcome to the program.

Dr. McKay:
Thank you so much for having me, today. It's really a pleasure to be here.

Dr. Doghramji:
Well, to start us off, Dr. McKay, can you give us a high-level overview of the current treatment guidelines for patients with renal cell carcinoma? And can you also tell us what kind of role adjuvant therapy plays in these guidelines?

Dr. McKay:
Absolutely. The treatment landscape for advanced renal cell carcinoma has been rapidly evolving over the last five years. Historically, we used to treat patients with frontline single agent VEGF inhibition. Starting in 2018 with the results of the CheckMate214 study demonstrating that the combination of nivo + ipilimumab improved outcomes for patients with intermediate or poor risk disease, the landscape began to shift. And after that study was presented, there's been a series of IO/VEGF/TKI frontline trials for patients with advanced disease that have really changed the landscape. And now for most patients who present with metastatic disease, most are getting combination therapy, whether it be dual IO/IO or IO/VEGF.

Now, with regards to the adjuvant therapy landscape, this has been a continuing moving target, I should say. So, you know, historically the paradigm for testing drugs in the adjuvant space has been, well, let's evaluate their efficacy in the metastatic setting, those drugs demonstrate efficacy for patients with advanced disease, let's try to move them earlier on in the adjuvant context. There has been a series of studies that were conducted with adjuvant cytokines, interferon, interleukin, and in aggregate, all of those studies failed to demonstrate any significant improvement with regards to disease-free survival or overall survival.

Now, in the VEGF/TKI era, a series of studies were conducted, testing adjuvant, tyrosine kinase inhibitors, you know, looking at adjuvant sunitinib, adjuvant, sorafenib, pazopanib, there's been a series of trials that have been conducted and the data has been quite underwhelming. And two of the largest studies actually showed, mixed results. And in clinical practice, adjuvant TKI use is not generally implemented. So, the two large trials that I'm referencing is the ASSURE study and the S-TRAC study, the S-TRAC was positive for DFS with sunitinib, the ASSURE study was negative, you know, this agent is FDA approved in the U.S. for use, it's not approved for use in the AMA and so it's utilization has been pretty limited. And that's been the historic context of adjuvant therapy in the modern era. And I think that's about to change given the results that were recently presented at this year's ASCO, looking at adjuvant-based immunotherapy strategies for RCC, the KEYNOTE564 study demonstrating a benefit with regards to disease-free survival of pembrolizumab in the adjuvant setting.

Dr. Doghramji:
And how does our approach to treatment change for patients with advanced renal cell carcinoma?

Dr. McKay:

So, our treatment is changing given that most patients are now receiving frontline combination therapy as opposed to single agent VEGF inhibition, which, you know, prior to 2018 had really been the go-to standard of care. And so, you know, now most patients are getting, you know, combo-therapy. And some of the big questions are well, you know, which regimen do I select? and which patient should get which regiment? And, you know, right now we're using largely clinical parameters to help ask that answer that question. And hopefully in the future, we will evolve to also include biomarkers to help us you know, answer that question.

Dr. Doghramji:
So, let's focus on frontline local therapy for patients with advanced renal cell carcinoma. What treatment options are available?

Dr. McKay:
So, this is also another very interesting question and quite controversial in the field. So, historically, local therapy options predominantly in the form of a radical or a partial nephrectomy were offered up front to most patients. And the reason why that is 'cause there was a series of studies that were conducted in the cytokine era that demonstrated improvement in survival with patients who actually underwent nephrectomy. And again, the cytokine era, you know, this was a context when we didn't really have good therapies to treat patients who had advanced disease. And we adopted that practice in the TKI era until the results of two studies, CARMENA and SURTIME began to call into question, sort of, our approach for using for utilizing frontline up front nephrectomy. And I think the current practice has been that patient selection is huge for determining who should get, you know, surgery up front. Most patients now probably go on to start systemic therapy, get the systemic disease under control and then if it's under control and the patient is doing well, then offer cytoreductive nephrectomy at that point in time.

And there are a couple of trials that are currently ongoing looking at evaluating local therapy options for patients with advanced disease, the PROBE study is looking at the role of cytoreductive nephrectomy and the context of combination IO regimens and the CYTOSHRINK and SAMURAI trial will be looking at the role of radiation in this context.

Dr. Doghramji:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Paul Doghramji, and I'm speaking with Dr. Rana McKay about different treatment options for patients with advanced renal cell carcinoma. As we now know, Dr. McKay, the guidelines recommend starting treatment right away for patients with advanced renal cell carcinoma. But for asymptomatic patients, what role does surveillance play?

Dr. McKay:
Very good question. So, for patients who have favorable risk disease, who are presenting with low volume, low burden, metastatic disease, a handful of those patients can actually be monitored and don't necessarily need to initiate systemic treatment right at diagnosis of metastatic disease. There's been some studies that have been conducted by Dr. Rini and colleagues that have actually monitored patients, and implemented that active surveillance approach in the context of patients with advanced disease. And you can spare some patients the toxicity of up front, treatment without what is demonstrated to be a loss of efficacy when you do start treatment down the road. And so, I think that this certainly is a strategy for, you know, very select individuals who have very favorable features.

Dr. Doghramji:
And can you share some emerging clinical trial data on advanced renal cell carcinoma therapy? And how will this data impact our approach to frontline treatment?

Dr. McKay:
So, I think emerging clinical trial data, you know, as I stated, we've recently seen a series of IO/VEGF studies that have been recently reported out from KEYNOTE-426 which looked at pembro/axi the JAVELIN study which looked atavelumab/axitinib, we've got CheckMate 9ER which looked at nivolumab and cabozantinib, and just this past year presented at the genitourinary cancer symposium where the results of the CLEAR trial, which looked at pembrolizumab plus lenvatinib.

Now, there are gonna be a series of studies that are actually gonna be looking at triplicates in the frontline space the COSMIC-313 study will look at the combination of nivolumab, ipilimumab, and cabozantinib compared to nivolumab plus ipilimumab frontline.

Now, I think should adjuvant therapy be adjuvant immunotherapy be adopted and integrated into the clinical practice, it's absolutely gonna change what we do in the frontline and we're gonna need to develop studies that you know, answer the question of what's the best approach after somebody has received adjuvant therapy and then subsequently progressed.

But the field it's a really exciting time 'cause I think there's a lot of really interesting studies that are being developed. Our patients are living longer and living better and that's a really great thing.

Dr. Doghramji:

Lastly, Dr. McKay, what do oncologists need to keep in mind when considering treatment for patients with advanced renal cell carcinoma?

Dr. McKay:
I think the practice is changing for renal cell cancer. You know, lots of regimens are now you know, approved for use and there's more to come that'll be approved and I think being up-to-date on the data regarding the different regimens, the patients populations for which they seem to derive the most benefit, being cognizant of safety and toxicity profiles of these agents, I think is gonna be really critical.

Dr. Doghramji:
That's a great way to round out our discussion on this topic. I wanna thank my guest, Dr. Rana McKay for joining me to discuss frontline treatment approaches for patients with advanced renal cell carcinoma. Dr. McKay, it was great having you on the program.

Dr. McKay:
Thank you so much. It really was a pleasure.

Dr. Doghramji:
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Announcer Close:
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