# Immunotherapeutic Strategies for Advanced Renal Cell Carcinoma

**Brian I. Rini, MD:** Hello, and welcome to this educational activity, *Immunotherapeutic Strategies for Advanced Renal Cell Carcinoma*. I'm Brian Rini, professor of medicine at the Lerner College of Medicine and leader of the GU program in the Department of Hematology and Oncology at the Cleveland Clinic Taussig Cancer Institute in Cleveland, Ohio.

I'll first go over an overview of the approved immune checkpoint inhibitors for renal cell carcinoma (RCC).

I'll begin by reviewing immune recognition in the context of T cells and tumor cells. Tumor cells interact with various immune system cells, including importantly effector T cells. Effector T cells are the functional arm of the immune system, which are thought to mediate antitumor immunity. Other cells, including regulatory T cells and myeloid derived suppressor cells, may dampen the immune response; however, we'll focus on effector T cells.

There are many points of interaction between an effector T cell and a tumor cell, some of which are stimulatory to T cells; that is, they stimulate an anti-tumor T cell response, some of which are inhibitory.

Negative costimulatory signals or inhibitory signals, namely cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein ligand 1 (PD-1), serve as receptors interacting with their ligands that, when engaged, will dampen the immune response. In kidney and other cancers, a series of drugs have been developed to inhibit these inhibitory signals and therefore stimulate the immune system. And we'll now discuss those that are in advanced clinical development in kidney cancer.

The first drug to be approved as immunotherapy for kidney cancer was nivolumab in late November, 2015. Nivolumab, an anti–PD-1 used as monotherapy, was shown to extend survival in patients who had received prior antiangiogenic therapy, which has been our standard of care in this disease for over a decade. A little more than 1 year ago, nivolumab combined with a CTLA-4 inhibitor, ipilimumab, showed response rate and survival benefits in intermediate- and poor-risk front-line kidney cancer in the CheckMate 214 study that we'll talk about in more detail.

More recently, just in the past month or two, combinations of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs)—namely axitinib and either a PD-1 inhibitor, pembrolizumab, or a programmed cell death protein ligand 1 (PD-L1) inhibitor, avelumab—have been combined and showed very impressive clinical results in the front-line treatment of advanced RCC. We'll go over those results in more detail. So we now have 4 approved immunotherapy regimens in kidney cancer—one monotherapy and three doublet therapies.

The CheckMate 025 study led to the approval of nivolumab monotherapy. Patients with advanced clear cell RCC, who had received 1 or 2 prior VEGF targeted antiangiogenic therapies, received either nivolumab monotherapy or everolimus, an oral mechanistic target of rapamycin (mTOR) inhibitor, which had been commonly used in this refractory setting, and were randomized to either of those drugs with a primary endpoint of overall survival.

Nivolumab monotherapy extended overall survival by more than 6 months compared to everolimus. The hazard ratio was significant at 0.73. And the overall survival curves split early and stay split along their course, indicating a durable effect to this drug in this setting. This was the first large-scale signal that immunotherapy had life-extending properties in metastatic kidney cancer.

CheckMate 214 was the combination study I mentioned that followed the nivolumab monotherapy study. There were preliminary studies that looked at the activity of CTLA-4 inhibition in combination with PD-1 inhibition initially done in melanoma showing great activity. And then it was studied in RCC in the CheckMate 214 study, which was the registration phase 3 study that took patients with treatment-naïve kidney cancer and stratified them according to the IMDC prognostic risk scoring system developed for patients receiving VEGF-targeted therapy.

Then patients were randomized to this combination, which we commonly call ipilimumab/nivolumab (ipi/nivo), for up to 4 doses of combination, and received maintenance nivolumab monotherapy or the standard of care at the time, which was sunitinib 50 mg for 4 weeks on/2 weeks off. And sunitinib is the control arm for all the trials that I'll mention today of the novel combinations.

Just a word about the IMDC prognostic criteria, and this is important because we talk a lot about it in kidney cancer. These were developed over a decade ago by Danny Heng. It was derived entirely from kidney cancer patients who had received VEGF-targeted therapy, namely sunitinib but also pazopanib or a bevacizumab-based regimen. Six criteria were identified that defined how patients did on this therapy—2 clinical and 4 laboratory.

Patients with none of these adverse risk factors were favorable risk, 1 to 2 intermediate risk, and 3 to 6 poor risk. What these are really saying is that favorable risk patients, by definition, are VEGF-responsive patients. Intermediate-risk patients are somewhat VEGF responsive, and poor-risk patients probably aren't very VEGF responsive at all. So it's important to remember, as we apply these criteria now to immunotherapy-based regimens, where they were derived and it's important to understand them because we'll talk a lot about them as they relate to the CheckMate 214 data.

Updated data were presented at the GU symposium in 2019 of the 30-month follow-up for the CheckMate 214 data. This is overall survival broken down to intermediate and poor risk, which was the primary population of the study, showing an early split of the curves. There was  a significant advantage in favor of ipi/nivo in this primary risk group; the hazard ratio was 0.66, which was obviously significant, and the median was not reached yet.

If you look at favorable risk, however, it's a bit of a different story. A few things are notable. Number one, the median's not been reached in either arm, indicating that favorable risk patients do better regardless of type of therapy. That makes sense. The hazard ratio is above 1; and, although not significant, favors the sunitinib arm. This relates to previous information indicating that favorable-risk patients are the more VEGF-responsive phenotype of patients, so it is not surprising that they did well and, perhaps, even a bit better with sunitinib in this trial.

In intermediate- and poor-risk patients, there's a clear advantage to ipi/nivo, especially as you get farther out beyond the 1-year mark, with a notable 28% of patients still progression free at the 30-month follow-up. But in favorable risk, again, favoring sunitinib both at the median and in terms of hazard ratio, although nonsignificant. Clearly a trend in favor of sunitinib in this favorable-risk subset.

And then, finally, looking at response rate, in the three paired columns of the intention-to-treat population, intermediate/poor risk, or favorable risk. What's notable here is that the response rates—certainly to immunotherapy—in all risk groups showed that approximately 90% of the responses were durable with ipi/nivo, and that's what we expect with immunotherapy, less so with sunitinib. And certainly the complete response rate has favored the immunotherapy regimen over sunitinib throughout this dataset.

One remarkable subset that does particularly well is patients who have advanced kidney cancer with sarcomatoid features. Sarcomatoid is a growth pattern that occurs across histologic subtypes of kidney cancer; generally, it is more aggressive disease and generally less VEGF responsive. So, an unplanned subset analysis was done in this trial looking at the approximately 50 to 60 patients in each arm who had sarcomatoid features.

Results showed a very dramatic benefit in terms of complete response rate, 18 versus 0, as well as progression-free survival and overall survival advantages. And this is a theme that we'll see throughout these doublets—that sarcomatoid patients tend to be particularly susceptible to these immunotherapy-based regimens, as opposed to strictly VEGF therapy–based regimens. The biology behind this is not yet known but certainly deserves more investigation to understand why these patients are so immunoresponsive.

The next set of trials I'll talk about is a combination of VEGF-targeted therapy, again our standard in immunotherapy. VEGF turns off the immune system, dampens the immune response, and promotes cells that are immunosuppressive such as myeloid-derived suppressor cells and regulatory T cells. By inhibiting VEGF, you can reverse some of this VEGF-mediated immunosuppression and presumably allow immunotherapy to work better. And this, in part, was the rationale for some of these combinations, which I'll tell you about shortly.

The most prominent of these combinations recently reported and FDA approved was pembrolizumab plus axitinib (axi/pembro). This was called the KEYNOTE-426 study. This followed a small 50-patient phase 1/2 study, which showed tolerability and excellent clinical activity of this regimen. It then jumped to phase 3, similar in design to

the others, where patients with previously untreated kidney cancer were stratified by IMDC risk group and geographic region and then randomized equally to either pembrolizumab, which was given standardly every 3 weeks plus axitinib, which is a very potent small molecule VEGF receptor inhibitor given twice daily, or again, that standard sunitinib arm. This was an all-comers intention-to-treat population with dual endpoints of overall and progression-free survival.

The topline result, which was an impressive overall survival benefit with a hazard ratio of 0.53, was significant. The overall survival curves split early and seemed to be increasing throughout their course, noting the relatively short 12.8-month median follow-up in this trial with only about 15% to 20% of patients having an event, and the medians not reached; however, there was a difference in the 12- and 18-month survival of over 10%. This trial hit its survival endpoint at the very first interim analysis, and this was really the basis for its FDA approval.

For the progression-free survival from that KEYNOTE-426 trial, same story—about half the patients with an event, a 4-month difference in the median of 15.1 with axi/pembro versus 11.1 with sunitinib, and a hazard ratio of 0.69, which was significant.

An updated analysis presented at ASCO looked at depth of response. So one of the themes that has emerged throughout these immunotherapy-based regimens is looking at the complete response rate and durability of response. And one of the things that we haven't quite settled is who are the patients who are going to do really well long term. That's what we want to know when we're starting a patient on a regimen and as we get into the early parts of that regimen. Complete response is one measure of patients who are likely to do well; I mentioned 90% of complete responses on ipi/nivo maintained that at the 30-month minimum follow-up.

But my clinical sense is that there's an expanded group of patients who have very deep partial responses who are going to do quite well, in addition to the complete responses. You see different thresholds of depth of response looking at just the target lesions for axi/pembro versus sunitinib in this exploratory analysis; furthermore, 42% of patients had at least a 60% response, 17% had at least an 80% reduction in target lesions, etc. And really this was just descriptive trying to characterize these populations. The next

step, of course, will be to associate depth of response with outcome, and those analyses are ongoing.

Updated data presented at ASCO 2019 looks, again, at that interesting sarcomatoid subset. Also, about 50 patients per arm, as in CheckMate 214, again showing robust activity more than the VEGF-targeted monotherapy in the immune-based regimen with a remarkable 98% of patients with sarcomatoid features having decreases in their target lesions on axi/pembro. All of these sarcomatoid analyses are post hoc analyses and exploratory; none of them, to date, have had central pathology review. So, they are limited in terms of their value but clearly provide a hypothesis that sarcomatoid subsets are uniquely susceptible to this therapy.

The other main VEGF plus immunotherapy regimen is axitinib plus avelumab, which was studied in the JAVELIN 101 study. This included a very similar front-line renal cancer VEGF plus immunotherapy, axitinib plus avelumab, compared to standard sunitinib. This primary endpoint was in a PD-L1 subset of patients based on preliminary data from its early 50- to 60-patient study, which also showed a high level of activity.

This is one of the primary endpoints, that is progression-free survival, in the PD-L1 population, which showed an advantage over the immunotherapy-containing regimen with a hazard ratio of 0.61. And the medians that you see there are of about 14 versus 7 months.

Overall survival has a different signal than what we saw with axi/pembro for reasons that aren't entirely clear. Again, these are fairly immature data with only about 15% to 20% of events. The median is not reached with a hazard ratio of 0.78 that's not significant and curves that don't seem to separate as much. And so we'll have to follow this dataset further out to see if any survival signal emerges.

And now I'll talk about some novel combination approaches along the same lines and themes that I've mentioned already.

So there a lot of different trials—some of them completed, some of them ongoing. Just to go over in a bit of detail, so the atezolizumab plus bevacizumab was a series of 2 trials—one phase 2 and one phase 3—done in front-line kidney cancer that, in sum,

showed an advantage to the PD-L1 inhibitor plus bevacizumab, a VEGF ligand binding antibody in a PD-L1 defined population. The phase 3 trial did not show a survival benefit, so this regimen was not submitted for regulatory approval around the world as it waits for more mature survival data. Similarly, there's an atezolizumab plus cabozantinib, a small molecule VEGF and MET inhibitor, in a phase 1/2 study that's recruiting. There are two large phase 3 trials of nivolumab plus cabozantinib and pembrolizumab plus lenvatinib versus sunitinib that should be completing and reporting out within the next year or so and others that are just sort of starting up. They're all within the same theme of combining VEGF therapy and immunotherapy.

And then, notably, pembrolizumab monotherapy data in the KEYNOTE-427 study. This was a 2-cohort study not randomized with 2 cohorts—1 clear cell and 1 non-clear cell—that showed a high level of activity for mono-immunotherapy in this disease, with a 38% response rate in clear cell and 25% in non-clear cell with enhanced response rates in certain subsets such as PD-L1 positive in intermediate and poor risk. The role of mono-immunotherapy in kidney cancer is still being defined. I think most of us think that there's a subset of patients who could get away with immune monotherapy, which is very well tolerated and can provide durable responses. And then other patients—perhaps most patients—who probably need either CTLA-4 inhibition or VEGF inhibition on top of it. But that concept is still being sorted out, and hopefully further trials will provide light, and further translational data will provide light on which patient needs which therapy or at what intensity.

The phase 3 IMmotion151 combined atezolizumab with bevacizumab compared to standard sunitinib in the PD-L1 defined population, as mentioned. The topline result recently published showed a progression-free survival advantage for the immune combination group, 11.2 versus 7.7 months, a significant *P* value, and a hazard ratio of 0.74. As mentioned, overall survival has a hazard ratio of 0.93 so it is not significant. The data are relatively immature, although looking at the curves, it's not apparent that those curves are going to separate as time goes on. In fact, they may converge, perhaps because of some of the salvage immune therapy that the sunitinib group received.

I mentioned the KEYNOTE-427 study with 2 cohorts, A and B—that is clear cell and non-clear cell—who received pembrolizumab monotherapy. Just looking at response

rate, this was meant to be a complementary study to KEYNOTE-526, which was the axi/pembro study, to define the activity of pembrolizumab monotherapy. Because that was very much an unanswered question in kidney cancer, as I mentioned, certainly before this trial and even after a little bit.

In clear cell, there's a response rate of 38%. This is enriched in intermediate and poor risk up to 42%. In PD-L1 expressing, it's 50%. And you see complete responses are possible in 3% to 6% of patients depending on the subpopulation. So again, clearly activity, not as much of a high response rate as we've seen in the combination regimens. But again, important data to provide an anchor for what monotherapy shows and certainly something to build on as we think about applying these regimens thoughtfully to patients.

Cohort B was non-clear cell which, as you may know, is a mix of different histologies—papillary, chromophobe, and unclassified largely. There was a median progression-free survival of almost 9 months, and this is pretty similar to what's achieved with VEGF-targeted therapy but likely better tolerated. And so, how exactly to approach patients with non–clear cell RCC is still very much a work in progress. My personal opinion is that with these data, immunotherapy should be a front-line standard of care in these patients, and I would probably reserve VEGF therapy for salvage. Having said that, we don't have head-to-head data yet, and I still think clinical trials are probably the most appropriate initial therapy for this cohort of patients.

Ongoing trials include several different combinations. The top 2 are the most prominent and first to report out—other VEGF plus immunotherapy combinations. People expect these trial results to be positive. How they will integrate with established regimens such as ipi/nivo and axi/pembro is eagerly anticipated. How efficacious are they, how well tolerated are they, and are they going to provide advantages over what we have already? The COSMIC study is just starting, I believe, kind of combining everything together—ipi/nivo plus a VEGF agent, cabozantinib, compared to basically standard ipi/nivo. So a lot of therapy. Certainly there's a potential for toxicity. And again, I think the field needs to sort out which patients need monotherapy, which patients need doublet, and which patients potentially need triplet therapy, but that's likely going to take many years.

So let's talk a little bit about optimal selection and sequencing. I think right now, the regimens with proven overall survival advantages are ipi/nivo and axi/pembro. There's a lot of academic debate over which might be appropriate. I think most people agree in favorable risk patients, where ipi/nivo did not show advantages, that axi/pembro is appropriate. I think in intermediate and poor risk patients, there are arguments on both sides, and it's going to come down to ease of delivery and toxicity and doctor comfort with giving a regimen, etc. We just need more follow-up data for both these regimens, especially axi/pembro, to understand durability of response and how best to apply these regimens. The second bullet point I mentioned concerned combination therapy versus monotherapy, and I think it's very critical because kidney cancer patients can be elderly and have comorbidities. Again, looking at a clinical selection strategy or a biomarker selection strategy is important. Some of these studies are ongoing with no results to date. And the bottom bullet we don't really have data on, but people are asking "Do we need to really continue immunotherapy forever?" That is, if we generate an antitumor immune response, just like a childhood vaccination, that should persist. And I've certainly seen patients with persistent responses for months and now years off therapy. And how exactly do we study that systematically, how do we apply that in clinical practice? When patients have toxicity, it's easy; we have to stop therapy, and we often just watch them, and they often do well. In the absence of toxicity, though, deciding how long to continue therapy is certainly an academic question that I think we need to answer urgently for many reasons; toxicity probably chief among them.

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines), the most recent ones, indicate that immunotherapy fits in pretty much every treatment box. So, for favorable risk patients, axi/pembro is preferred; for poor and intermediate, both ipi/nivo and axi/pembro are category 1. In some of the other recommended regimens or subsequent therapy, immunotherapy is absolutely a standard of care in kidney cancer. My opinion is that every front-line patient should receive an immunotherapy-based regimen unless they have an absolute contraindication. The use of immunotherapy, in a salvage setting after prior immunotherapy, is totally unstudied. Whether this is going to be a backbone throughout therapy or just initial therapy remains to be determined.

Let's talk about adverse events and management, a very important part of delivering this therapy. The way I explain it to patients is that we're stirring up the immune system,

we are creating inflammation against tumors. Unfortunately, we also create inflammation against normal organs. This commonly includes rash, diarrhea, and hepatitis as the most common immune-related adverse events. Arthralgias and adverse effects on endocrine organs, such as the thyroid gland, are fairly common; however, any organ can be susceptible, including the heart. One percent of patients will have mild carditis which, unfortunately, is fatal about 50% of the time. We need to recognize that any organ can be affected, which calls for a high sense of vigilance for patients to call in with symptoms, for providers to be aware and bring patients in for laboratory tests or clinical examination, when needed. To admit patients, if they're sick, for IV steroids, and so on, is exceedingly important. I think the education around that has gotten better, certainly, over the past couple of years. And then, also, involving organ specialists, such as the gastrointestinal doctors for colitis or pulmonologists for pneumonitis—just for another layer of expertise. And often diagnostic testing is certainly indicated.

Nivolumab monotherapy is very well tolerated. You see grade 3 events for each individual only in the 1% or 2% range, and even any grade, really, no more than 10% or 15% with the exception of fatigue. So it's very well tolerated as monotherapy. When you add ipilimumab, you add a lot of activity but, unfortunately, you add a lot of toxicity as well. You will see a lot of any grade and certainly grade 3 events go up. And while any one toxicity for grade 3 is not that prominent, 46% of patients will have grade 3 events, and the majority of patients will require steroids with this combination. So again, the good and the bad of ipilimumab in this setting. Looking at VEGF inhibitors plus immunotherapy, we see diarrhea, thyroid dysfunction, fatigue, hand-foot syndrome, and so on. This trial had an increased incidence of transaminitis, with alanine aminotransferase and aspartate aminotransferase increase. That mechanistically is still being explored as to why that's the case because each of these drugs individually doesn't do it that much and requires monitoring every 3 weeks when the patient's getting pembrolizumab. I think one of the nice things about the current VEGF TKI regimens is that axitinib has a very short half-life, it's 4 to 6 hours. So 5 half-lives, which are commonly required for a drug to get out of the system, is about 1 day, it's about 24 hours. So if patients come in with any toxicity and you're not sure what drug it's from, simply withholding the axitinib, waiting 1 or 2 days, seeing what resolves, seeing if their laboratory values resolve or improve within 2 to 3 days is often a good way to approach these patients. If patients are very sick with toxicities, then they need to be admitted and probably need empiric steroids. However, most patients are not very sick and can be

managed as an outpatient with just a little bit of patience in dealing with them and withholding the TKI, axitinib in this case, you can often sort out which drug is causing what, allowing you to make the right choices in terms of continuing therapy or dose reducing, and so on. The other TKIs that have a longer half-life, which may be coming in these combos, it'll be a little bit of a different story, and we'll have to cross that bridge when we come to it. But the 2 axitinib-based regimens developed first have that short half-life of axitinib, which I think is an advantage when it comes to toxicity management. Similarly, the avelumab plus axitinib data had fairly similar numbers that we saw compared to the pembrolizumab-based axitinib regimen. But in general, I think both of these regimens are reasonably well tolerated in patients.

In terms of monitoring patients, there are many guidelines out there. These are NCCN Guidelines. There are SITC guidelines, ESMO guidelines, a lot of the major groups have guidelines in terms of both monitoring and specific toxicity management. And those should be posted on a clinic wall somewhere because they really are very good guidelines and very well thought out. But I think, you know, intensity of monitoring is important.  For baseline assessment, we generally will see people with every infusion. We want to see them, talk to them, make sure we understand their toxicities, that they're not downplaying any toxicities that we think need intervention. As patients get much farther out in therapy and are cruising, we don't necessarily have to have a provider visit. But certainly, early on—I would say at least for the first 6 months—we'll do that.

Further baseline assessment for specific organs includes a fairly standard set of laboratory tests. We don't commonly do organ-specific testing such as pulmonary function tests or cardiac examinations in the absence of some relevant history. Different institutions handle that differently. So again, I think it's developing a comfort level, within an institution, within a provider group, and also, involving the specialists at your institution for their recommendations and engagement in this process of taking care of these patients. General guidelines have been published about immune-mediated adverse events; however, one should recognize that the grading system for toxicity is very imperfect. And there are probably some grade 3 therapies, such as thyroid abnormalities, where you don't necessarily need to withhold therapy and don't need high-dose steroids. And some grade 2 abnormalities such as diarrhea or colitis that probably need more and higher-dose steroids. I wouldn't be a slave to exactly what the

grade is and what the number is but what you see in front of you with the patient—how are they doing, how sick are they? And then let that guide how intense the therapy needs to be.

In terms of patient and clinician communication, we read our patients the riot act when we're starting immunotherapy, making sure they understand that they can and should call us 24 hours a day with problems. An ONS immunotherapy wallet card is available, so if patients walk into an emergency department, the provider would know they're on immune therapy. I think, again, that awareness in emergency departments and primary care practices is increasing over time. That this is a special class, that these patients do need special care and sometimes immediate attention.

So in conclusion, immunotherapy-based regimens are now the initial standard of care in metastatic kidney cancer and certainly offer the best chance of achieving the patient goals of tumor burden control and living longer. Whether the dual immunotherapy or the VEGF plus immunotherapy regimens are better or most effectively achieve these goals is unknown; we need more follow-up data and more clinical trials. And the reality is they're both active regimens in this disease. Lastly, immune-mediated toxicity recognition and management is clearly a critical part of the optimal delivery of immunotherapy to best balance the benefit and risk of this very exciting class of medicines. Thank you for your attention.

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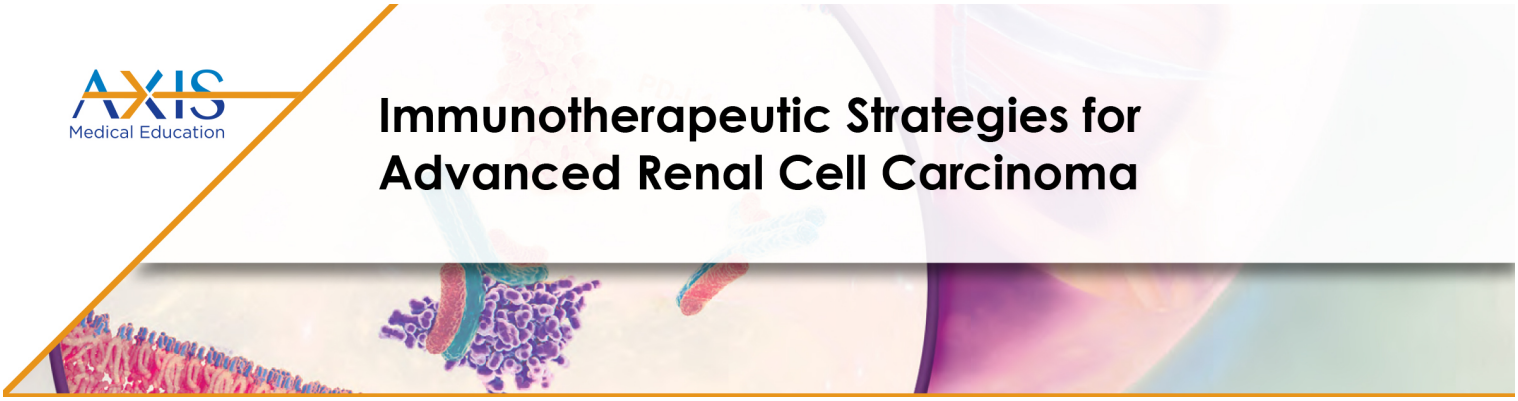

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