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What is the Role for TKIs in RCC? Highlights from the 18th Annual Meeting of the SUO

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Here is your host, Dr. Barry Mennen

Dr. Mennen: I am Dr. Barry Mennen and I recently spoke with Dr. Vitaly Margulis at the 18th annual meeting of the society of urologic oncology in Washington, DC. Dr. Margulis is an Associate Professor of Urology at the University of Texas Southwestern Medical Center in Dallas. He is an expert surgeon, using minimally-invasive techniques to treat patients with soft-tissue tumors as well as kidney, bladder, and other genitourinary cancers. At SUO we talked about the ever-changing role of tyrosine kinase inhibitors (or TKIs) in the treatment of advanced renal cell carcinoma in light of the research findings that were presented at the meeting.
Although renal cell carcinoma (or RCC) accounts for only 2-3% of all adult cancers, for those who present with or progress to advanced RCC, which can be up to 65% of patients, the 5-year survival rate has never been above 10%.
TKIs are one of several types of preferred first-line therapies for relapsed or stage IV and surgically unresectable metastatic RCC. TKIs are a group of targeted cancer therapies that inhibit the production of VEGF, a growth factor that allows angiogenesis and tumorigenesis. TKIs and some of these other agents have also demonstrated effectiveness in the second-line setting. But this is a rapidly changing field. The emergence of immunotherapy, in the form of checkpoint inhibitors, is reshaping the landscape of treatment options, for advanced RCC and neo/adjuvant therapy for RCC. So, we expect to see some changes in the 2018 NCCN guidelines.

Now let's turn to our discussion.

Dr. Mennen: So happy to have you with us today, Dr. Margulis.

Dr. Margulis: Glad to be here.

Dr. Mennen: So, we are going to be talking about aspects of genitourinary cancer, specifically renal cell cancer right now. In the session on immunotherapy of genitourinary cancer, what new data are being presented for locally advanced and metastatic disease in renal cell carcinoma?

Dr. Margulis: Broadly speaking, it is a very exciting time for kidney cancer. Specifically, that has to do with our understanding of biology of kidney cancer that led to the development of drugs and a specific class of drugs known at checkpoint inhibitors that allow us to provide treatment to our patients with response rates that we have not seen before.

Dr. Mennen: Could you define checkpoint inhibitors a little better? Where do they check?

Dr. Margulis: That is a good question. Basically, what we have known is that kidney cancer, among other cancers, has a unique ability to turn off your immune system and it does it through very sneaky and different ways. Some of them have to do with having certain receptors on the tumor cells that basically deactivate our immune system – our white cells, and that turns off the immune response. So,

what we have learned is that we now have antibodies that can prevent that interaction and prevent these tumors from turning off our immune system, so our immune system stays on and can effectively – or more effectively – fight these cancers.

Dr. Mennen: Now, how do these data affect, if at all, future NCCN guidelines?

Dr. Margulis: So, the first, I would say, what I would call a revolution in kidney cancer occurred when we developed targeted therapy, specifically anti-angiogenic therapies, and these were the molecules, mostly taken orally, that would prevent tumors from growing new blood vessels. That happened roughly in the early 2000s and that led to development of multiple drugs that basically prevent the vasculature from growing.

Dr. Mennen: The VEGF.

Dr. Margulis: The VEGF – various other receptors, but the idea was to prevent angiogenesis. We know that kidney cancer is an extremely angiogenic tumor and so up until then, these targeted agents such as sunitinib, sorafenib, among others, pazopanib, became first-line therapy for patients with metastatic kidney cancer. Now what happened over the last few years with our understanding of immunobiology of kidney cancer is that now we have drugs that reactivate our immune system. Most recently, and this happened literally within the last year, there'd been a clinical trial which compared head-to-head in the first-line setting, a drug like Sutent, which is a checkpoint inhibitor and a combination of two different checkpoint inhibitors. The trial was CheckMate 214 and was presented a few months ago at the European Oncology Meeting, and the findings were staggering. What I mean by that is that the combination of checkpoint inhibitors outperformed our standard first-line options, which was a TKI, not only in terms of overall survival, progression-free survival and tumor response. So, not only did that happen, these drugs were actually better tolerated, and when we checked the patient's quality of life, pretty much, in every single quality of life domain, the patients did better while taking these checkpoint inhibitors. So, not only do we now have drugs that are more effective in the perspective of oncologic outcomes but also are less toxic.

Dr. Mennen: So, the guidelines seem to be behind the times, correct?

Dr. Margulis: Correct, yes. So, as you know, these checkpoint inhibitors are now approved in a second-line setting, but with these new trials emerging in a front-line setting, I think it is only a matter of time before these drugs will be approved in that setting as well.

Dr. Mennen: Now, what are we learning about the very important issue of predicting response?

Dr. Margulis: Well, that remains a million-dollar question. We know that only roughly 30-40% of patients treated with immune checkpoint inhibitors would actually have a response. Another 30-40% would have stable disease, and so there are a significant proportion of patients that do not respond to checkpoint inhibitors. In fact, in the pivotal CheckMate trial that I just mentioned, if you categorize patients as having a favorable prognostic risks versus intermediate and poor, patients with favorable prognostic risks actually did better with a TKI, and patients with an intermediate to poor risk actually performed better and had better oncologic outcomes with a checkpoint inhibitor. So, there is significant need in terms of prediction and our understanding of which patients should go on to which therapy. That is a very hot, obviously, topic in area of research.

Dr. Mennen: Now, what role will immunotherapy versus TKIs play in those with predicted good response versus those with predicted intermediate poor response, as you just were talking about and what is the takeaway?

Dr. Margulis: Right, so the takeaway is that we do not know. The data needs to mature a little bit. Right now, the preliminary signal from these trials seems to indicate that patients that are categorized as good risk in terms of their prognosis, they are going to live for a long time, they seem to actually be doing better with a TKI. In patients that have intermediate to poor prognosis will actually benefit from a checkpoint inhibitor, and I think if you want my opinion and looking into the future, I would imagine that that is how this is going to shake out.

Dr. Mennen: Now, are there any new developments in genetic testing for developing neoadjuvant or adjuvant treatments?

Dr. Margulis: Well, genetic testing, obviously, alludes to the whole theme of personalized medicine, and there are multiple laboratories around the country in every major academic center that has a program devoted to finding out and understanding how we can use genetics and genomics to predict which patient should be treated, how they should be treated, how they will respond, etcetera, etcetera. It is a very complex and rapidly advancing field. What is pertinent to checkpoint inhibitors right now? The clinical trials indicate that if we were to stain the tissue, the tumor tissue, for some of the markers predictive of immune infiltration such as PD-L1 staining, it seems to indicate that in patients who show higher proportion of PD-L1 staining they actually respond better to the checkpoint inhibitors; so higher immune infiltration, higher ligand staining and a better response to the drugs that target that.

Dr. Mennen: But that is a phenotypic.

Dr. Margulis: Correct.

Dr. Mennen: What about the genotypic – is there relation there?

Dr. Margulis: Correct, genes drive the phenotype and so that basically is a quick and indirect way to measure the genotype.

Dr. Mennen: I see.

Dr. Margulis: You are absolutely right. The next area that I think warrants discussion is using genetic sequencing and genetic profiling and that is, again, a very hot and rapidly evolving area of investigation and actually in this meeting, there was a presentation that documented that kidney tumors can be classified as angiogenic type, which would obviously be treated probably better by a TKI antiangiogenic drug or the immune-infiltrating type, which would be better treated by a checkpoint inhibitor.

Dr. Mennen: Now, what role do you see TKIs playing in neoadjuvant therapy based on what you have seen and heard at this meeting?

Dr. Margulis: I guess the better question that I would ask is what is the future of neoadjuvant therapy in kidney cancer? I think we have done several trials with TKIs, and TKIs, unfortunately, have more of a static profile. They may shrink the tumor, but very few complete responses were seen with these drugs, and so I think the TKIs can be used to shrink the tumor before surgery to make the surgery easier in highly complicated cases, but where it gets really interesting is with checkpoint inhibitors. The idea here is that if we can give an immune-stimulating drug while the primary tumor is still in place, i.e., in the neoadjuvant setting, you essentially have an in-situ vaccine, right, so you are stimulating your immune system, you have very high antigenic load, the tumor is still there and then you go in and remove the tumor and give additional checkpoint inhibition to continue this sort of treatment. So that seems to be very interesting and a very promising paradigm.
There is a clinical trial in this setting that basically gives neoadjuvant checkpoint inhibitor followed by surgery followed by additional checkpoint inhibition in patients that have high risk of not being cured by surgery alone.

Dr. Mennen: This certainly seems like a very exciting time in the area of kidney cancer. We have spoken about several things. You have given us your take on it. Is there any other area that you have seen here, or you think would be a very important communication point for our audience?

Dr. Margulis: Again, this is a very exciting time in kidney cancer, and I think this is where I will toot my urologic horn here in as much as that this is a really exciting time for clinical trials. I think we really need to come together as a community to enroll as many of these patients as possible, so we can establish and answer some of these questions that you have asked me.

Dr. Mennen: So, you are talking about the medical oncologist and the urologic oncologist.

Dr. Margulis: Correct. We need to play better. We need to play more, and I think this will all translate into better care for our patients.

Dr Mennen: Let's review some of the studies Dr. Margulis discussed.Dr. Margulis discussed the CheckMate 214 study, a landmark study comparing the safety and efficacy of sunitinib, a TKI, to combination therapy with nivolumab and ipilimumab, which are checkpoint inhibitors, in about 1000 patients with treatment-naïve advanced or metastatic clear cell renal carcinoma. The primary analysis focused on the roughly 800 intermediate- and poor-risk patients. However, there was also an intent-to-treat analysis, which included an additional 200 patients who were deemed favorable risk. Risk was determined by a number of factors including the Karnofsky performance status score, time from initial diagnosis to randomization, hemoglobin level, corrected serum calcium concentration, absolute neutrophil count, and platelet count.
The IMmotion 150 study of gene signatures was a phase 2, 3-arm study of about 100 patients in each arm, looking at the combination of PD-L1 blockade with atezolizumab and VEGF inhibition with the antibody bevacizumab, comparing it to single-agent atezolizumab and to the standard of care, sunitinib.
The primary endpoint was progression-free survival for all-comers in the intent-to-treat population and the results showed that there was no difference between the treatment groups. But, for the first time in kidney cancer clinical trials, PD-L1 expression on the tumor immune cells was analyzed and the results showed that response to the atezolizumab combinations improved with increased PD-L1 expression in the microenvironment. This was true for both PD-L1 expression of at least 1% and at least 5%.

As Dr. Margulis discussed, as part of the IMmotion trial, the patients' tumors and blood underwent a variety of different assays, including whole exome sequencing, immunohistochemistry, and RNA sequencing on almost all the tumors in this trial.
The RNA sequencing showed that tumors could be grouped into 3 subtypes based on their predominant gene expression. For example, tumors that had an angiogenic signature had high levels of VEGF-A, Immunogenic tumors expressed high levels of CD8 (indicating high levels of T effector cells). And the third group were tumors that might be somewhat immunosuppressed, that had a myeloid inflammation signature. The study investigators are now asking whether, based on these "gene signatures", might some tumor types respond better to certain types of therapies. Early results indicate that this may be the case, for example, that tumors with an angiogenic signature respond better to sunitinib alone than to atezolizumab alone.

Study investigators also are looking at whether these RNA signatures can predict response based on PD-L1 expression.

Next, we discussed treatment guidelines and future directions for treatment of advanced RCC.

Dr. Mennen: Are there any new updates in the guidelines on the management of small renal masses?

Dr. Margulis: As you know, this is also a very hot topic in a somewhat evolving field, and there were a few updates; I would say no major changes, but there were a few clarifications. Our number one topic had to do with the role of the biopsy and do we biopsy kidney tumors? Pretty much, any malignancy that gets treated, usually we get a biopsy first, establish a diagnosis and move on with treatment. Kidney cancer is unusual in that most of the kidney cancers are treated without a biopsy, so if we see a renal mass, we presume that it is kidney cancer and we render treatment, which is again not really how it is done in most other malignancies. There is an ongoing debate, "What should be the role of the kidney biopsy?" I think that the newest guidelines further clarify that really – because the majority of these tumors will end up being kidney cancer – there is no need for routine kidney biopsy except in unusual cases where we suspect metastasis to the kidney or where the diagnosis is not clear,
and in those cases, a biopsy could be acceptable, but as a routine practice, the guidelines actually, to some degree, discourage performing routine biopsies unless it is part of the clinical trial of some sort. The second clarification, really not a change, from the guidelines was utilization of nephron-sparing surgery, and again, the recommendation is that we should try to preserve as much kidney function by performing nephron-sparing surgery such as ablation or partial nephrectomy whenever possible; however, in situations where, and especially if there is no imperative indication for nephron sparing and the tumors are complex, there is nothing wrong with performing a radical surgery as not to increase the potential complications in these patients. There was a period of time in our field where the pendulum was swinging and went completely from performing radical nephrectomies in everybody to now, where there is a big push to try nephron-sparing in every single case, and I think we are realizing that in
some cases in complicated tumors and without imperative indication, we can actually compromise people's outcomes. The guidelines caution against that and they do recommend radical surgery in appropriate cases. Finally, there is section on ablation. Ablation is, again, also an evolving and a somewhat hot topic in our field. Ablation has to do with, instead of extirpating tumors surgically, utilizing either heat or cold, usually in a percutaneous fashion to kill the tumor, and the guidelines actually state now that ablation is acceptable treatment, and again, in appropriately-selected cases, usually older patients with smaller tumors, but it is actually a reasonable option.

Dr. Mennen: How does multidisciplinary management fit in to the use of TKIs as adjuvant therapy?

Dr. Margulis: The adjuvant therapy field – you know there are multiple trials and pretty much every agent that has been approved in a metastatic setting has been studied or is being studied in an adjuvant setting. The idea here is, you know, we operate on a lot of tumors. We know the hyperability of recurrence and we want to be able to minimize these recurrences. Can we give these patients after surgery some sort of therapy to prevent the cancer from recurring? And again, there are multiple trials, but most recently, there was a trial of sunitinib, also known as Sutent, that demonstrated a delay in progression in patients who got adjuvant treatment. So, patients that got the treatment recurred at a less frequent rate. Based on that trial, which was a randomized, phase three trial, observation versus Sutent in patients with high risk of recurrence, based on the findings of this trial, Sutent is now approved as first-line adjuvant therapy in kidney cancer, and so we are obligated to discuss this with our
patients. There are problems with the trial; there are controversies and one of the controversies has to do with the fact that even though sunitinib increases the time to recurrence or decreases the probability of recurrence, the overall survival in this trial was not any different. Patients seem to recur later, but their survival overall was not affected. So, we as clinicians and the patients have to discuss this data and make a shared, informed decision making as to whether this type of therapy is appropriate, but it is, again, exciting because now finally after probably, I would say, over 10-15 different clinical trials, that we have an agent that is approved in an adjuvant setting. One more thing that I would like to point out that with checkpoint inhibitors is that these agents are now being studied in an adjuvant setting as well. None of the data is mature, but the opportunity to increase your immune response to occult metastatic disease is very exciting and I am hoping that some of these trials will be positive. Not only are there single agent trials, there are trials of combination checkpoint inhibitors as well.

Dr. Mennen: What did we learn in today's state-of-the-art lecture on advanced renal cell carcinoma that we have not heard about yet?

Dr. Margulis: Again there is somewhat of a shifting landscape that has to do with our understanding of the biology of kidney cancer and some of the newer agents have been approved. When we talk about advanced kidney cancer, I think we need to understand that there are tumors that are at high risk for recurrence, but manageable by surgery alone, and there are patients with metastatic kidney cancer. I would sort of say that usually those patients are lumped in the same bucket, although I think they are quite different patients. The patients that have had operations surgically and are at high risk of recurrence, I think, again, the finding of the Sutent or sunitinib trial being positive so these patients now have an option for adjuvant therapy, but also in these patients, there are ongoing clinical trials where checkpoint inhibitors are studied. For patients with metastatic kidney cancer – this is probably the most rapidly shifting paradigm

based on, again, the recent clinical trials that have been presented at the European Oncology Meeting, there is now a combination checkpoint inhibitor trial that is shown to be superior to what used to be standard therapy with sunitinib or a TKI. I see that, again, the sands are shifting. I think the checkpoint inhibitors in combination most likely will move to be the first or become the first-line therapy for patients with metastatic kidney cancer. The hard question is when do we use what? When do we use the TKIs? When do we use the checkpoint inhibitors? I think some of the newer genetic profiling studies may help us answer that question. Finally, I want to say that from the surgical perspective, there are always the questions, "What should the role of surgery be?" Should we still be taking out the primary tumors when the cancer has already spread? The data seems to again over and over confirm that patients whose primary tumors have been removed tend to do better than patients whose tumors are left in situ.

Dr. Mennen: What have we learned in regard to current or ongoing clinical trials in regard to immunotherapy, TKIs, combination of, whether it is here or any other meetings that you have attended or heard of?

Dr. Margulis: Right, so this is where it gets really exciting for me at least and I have always felt that cancer is a very complicated phenomenon with multiple biologic pathways affected. It would only make sense that we maximize our therapeutic strategies by attacking cancer from different angles. So, case in point, as we have discussed earlier, we have had for over 10 years now, targeted therapies that attack the vascular pathway; the kidney cancer that prevents the kidney cancer from growing new blood vessels and growing an spreading and now we have the checkpoint inhibitors which reactivate our immune system to fight cancer better, and the question is, can we combine the agents from the individual class of drugs and also combine drugs that work by completely different mechanisms of action and see if we can leverage that benefit to our patients? The answer is, at least based on preliminary data, is very exciting.

Again, case in point is that – and the trial of combination of checkpoint inhibitors seems to perform very well, better than the individual checkpoint inhibitors alone. There are several ongoing clinical trials where the idea is to combine a TKI with a checkpoint inhibitor. It certainly makes biologic rationale since we are attacking different cancer pathways, but again the preliminary data of combination trials are ongoing. We do not have the final data, but interim analyses and early looks, which should be interpreted with a grain of caution, the preliminary data seems to indicate that combining the checkpoint inhibitors with targeted therapies such as sunitinib for example does provide cumulative action and improved outcomes. Again, the data is maturing. I think we will see more within the next two years, but this is very rapidly moving in an exciting field in kidney cancer.

Dr. Mennen: Any final thoughts as you are wrapping up the meeting here, the society meeting, what holds in the future, what is coming up?

Dr. Margulis: If I have to summarize the key points here, it is that surgery still has an important role in management of kidney cancer. I think the future of treatment will have to do with individualizing therapy based on most likely genetic profiling so we can look at an individual tumor, individual patient characteristics and say that you are best treated with targeted therapies versus a different patient treated by combination or checkpoint inhibitor. Finally, the role of individual therapy will have to do with attacking various biologic pathways in combination.

Dr. Mennen: To expand further on our discussion with Dr. Margulis, he began by mentioning some of the highlights of the recently updated AUA guidelines for the management of localized renal masses, as presented by Dr. Ithar Derweesh. The recommendations regarding renal mass biopsy were an important part of the guidelines and the guidelines now recommend RMB when a mass is suspected to be hematologic, metastatic, inflammatory, or infectious. When considering utility of renal mass biopsy, patients should be counseled regarding the rationale, positive and negative predictive values, and the potential risks of nondiagnostic rates of renal mass biopsy. This is generally a very safe procedure. Dr. Derweesh noted that the overall incidence of side effects or complications is about 1%. The sensitivity, specificity, and positive predictive values of RMB are in the upper 90s. The nondiagnostic rate is about 14%, which can be substantially reduced with a repeat biopsy. However, a nonmalignant biopsy may not accurately indicate whether the tumor is benign.

Regarding partial nephrectomy, Statement 14 indicates that physicians should prioritize partial nephrectomy for the management of clinical T1A renal masses when intervention is indicated. In this setting, partial nephrectomy minimizes the risk of chronic kidney disease progression and is associated with favorable oncologic outcomes, including excellent local control.

With respect to morbidity, partial nephrectomy can be associated with an increased risk of urologic complications, but most can be successfully managed with conservative approaches.

Statement 19, regarding radical nephrectomy, was also one of the key guidelines. It is shown here.

Statements 24-27 review thermal ablation. Specifically, physicians should consider thermal ablation as an alternate approach for the management of clinical T1A renal masses less than 3 cm in size. And for those who elect thermal ablation, a percutaneous technique is

preferred over a surgical approach to minimize morbidity. It should be noted that the meta-analysis on which these recommendations were based, demonstrated an increased risk of local recurrence or primary treatment failure after one treatment. However, as Dr. Derweesh noted, most of these types of local recurrence or primary treatment failures can be managed successfully and usually with a repeat ablation. This guideline was discussed further by Dr. Thomas Atwell at the SUO conference. He noted the importance of the AUA recommendation of renal mass biopsy prior to or concurrent with thermal ablation, especially as thermal ablation is translated to the more general population with renal tumors, particularly young patients. For those patients, a d efinitive pathology is important for both the patient and the provider to guide subsequent surveillance.

Dr. Margulis then discussed the results of the S-TRAC study, a randomized, double-blind phase 3 trial of 650 patients with high-risk, clear cell, renal carcinoma, who received either sunitinib or placebo, for 1 year as adjuvant therapy until disease recurrence. The primary endpoint was disease-free survival, according to blinded, independent review. The secondary endpoints were investigator-assessed disease-free survival, overall survival, and safety. You can see that the disease-free survival curves suggest a significant advantage to those who received a year of sunitinib compared to those who received placebo.
But the overall survival curves (a secondary endpoint) are overlapping, showing no benefit. So, as Dr. David McDermott noted when he discussed these data, this is a controversial area, and hopefully adjuvant immune therapy will offer a better advantage in future studies.
Dr. Margulis also discussed what Dr. Rana McKay presented in her State of the Art Lecture on the evolving management of renal cell carcinoma. She provided an overview of the recent studies of novel combinations of TKIs and immunotherapy.
Starting with the Atkins study, presented in 2016 at ESMO the combination of axitinib with pembrolizumab, a PDL—PD-1 targeting monoclonal antibody, was evaluated in a phase 1 trial, which had 52 patients with clear cell histology and no prior therapy. They reported an objective response rate of 71%. Choueiri and colleagues presented the data of axitinib and avelumab which is a PD-L1 targeting agent in a similarly designed trial, including clear cell patients with no prior therapy. The response rate was 58.2%. In this past ESMO from 2017, the results from a study of the combination of lenvatinib and pembrolizumab were presented. In the phase 2 portion of the trial, it restricted eligibility to clear cell patients having received no more than 2 lines of prior therapy and the response rate was 63%. And, finally, the combination of cabozantinib and nivolumab with or without ipilimumab was also presented at ESMO this past year. This trial included patients with all genito-urinary malignancies but there were only 2 patients with sarcomatoid RCC. The response rate was 33% in that study.

Overall, these early results suggest improved responses with combination therapy compared to monotherapy, as Dr. Margulis discussed.

This concludes our CME program covering highlights of the 18th annual meeting of the Society of Urologic Oncology meeting in Washington, D.C. with Dr. Vitaly Margulis. Thank you for participating.

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