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COMMENTARY

A Podcast Discussion on the Current Treatment Landscape for Renal Cell Carcinoma

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ABSTRACT

During the last 15 years, tremendous efforts have been made in the medical treatment of metastatic renal cell carcinoma (mRCC). Immune-oncological (IO) combinations are the current standard of care in the first-line setting of mRCC. Here, the current phase 3 trials CM214 (nivolumab/ipilimumab vs. sunitinib), KN426 (axitinib/pembrolizumab vs. sunitinib), Javelin-ren-101 (axitinib/avelumab vs. sunitinib), CM9ER (cabozantinib/nivolumab vs. sunitinib), and CLEAR (lenvatinib/pembrolizumab vs. sunitinib) were discussed. In the mentioned phase 3 trials, primary and secondary endpoints were discussed. Strengths and weaknesses of each trial were reflected in terms of overall survival, progression-free survival, objective remission, health quality of life, and safety. Reflecting on the data, as well as the current ESMO guidelines, we discuss choosing the appropriate medical treatment for patients' individualized treatment journey and relay the strength and weaknesses of each combination—starting with the appropriate first-line therapy.

Keywords: PD1/TKI; CPI-CPI; mRCC; Medical treatment; First line treatment

DIGITAL FEATURES

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TRANSCRIPT

LA: Thank you for joining us on this Adis podcast. Today's session was funded by an educational grant from Eisai. In this session we'll be discussing the current treatment landscape for renal cell carcinoma, and I'm joined by experts Dr. Philip Ivanyi and Dr. Viktor Grünwald. Thank you so much for being here and it would be really great to hear a bit about you both before we start the discussion.

VG: My name is Viktor Grünwald. I'm a medical oncologist by training and I work in a hybrid position, which I think is different from many other places, where I do work in urology but also in the medical oncology department and oversee the medical treatment for GU (genitourinary) cancer patients in the University Hospital of Essen, where we introduced this novel concept of an interdisciplinary professorship for GU cancers.

PI: Well, Viktor, that sounds great. I'm a little bit jealous about the position, but anyhow, my name is Philip Ivanyi. It's also a privilege being here and working in the very north of Germany in the University of Hannover. I'm also a medical oncologist and we have a little bit more broad spectra here, but one of the focuses is also GU kidney cancer setting and involvement in the trials. And to be honest, I have had the privilege of also being trained whilst I was a young guy (which I'm not anymore) by you Viktor, so I'm really happy about this discussion.

And so, let's go to the topic. And the first topic is the current landscape of treatment of kidney cancer and mainly the ESMO guidelines (the latest version) [1, 2]. And if I remember appropriately you have been involved in also editing and writing and recommending, and whatever is necessary, for doing such a guideline. And so can you give us a short summary?

VG: Well, Philipp, I think the kidney cancer landscape really evolved dramatically in recent years [3]. And I think it's not only that we have more options, it's also improving patients' lives and I think that's quite important. So how did we advance the field? I think something that was quite important is to understand that we do have different risk categories among our patients. Meaning that the prognosis really differs depending on the different group of patients. And that is something that Daniel Heng was originally [discussing], I think well Motzer did actually, but then Heng really brought it up to the targeted field [4]. So, where we had targeted therapies available, he optimized that prognostic score to the IMDC (International Metastatic Database Consortium) score [2]. That's what we use. And this is what's being used to select patients in the different trials and that's why we adopted this also to our clinic and how we make decisions. And I think it was very important at the time, being for single-agent treatments. But it became less important with the combinations because with the TKI (tyrosine kinase inhibitors)/IO (immune-oncological) combinations, meaning that we have tablets and immune agents that we combine, they're usually recommended across all risk groups. The question will be, you know, whether there will be a future purpose to dissect it a bit more to those risk groups. But for right now, we don't differentiate. And then there is the TKI-free IPI NIVO [ipilimumab and nivolumab] combination, which is a pure checkpoint inhibitor combination, and that is more bound in terms of its labor to those that have at least one risk factor, actually [5]. And I think that's something that is a bit different, and these are the recommendations as a mainstay or gold standard in first-line kidney cancer treatment. And I think something that is missing is the question, you know, do you always have to treat with combinations? I don't know, Philipp, how do you feel about it? Is that something you give to every single patient or is that something that you limit to certain subgroups of patients?

PI: Well, you know jumping directly deeply into the data, right? I mean that's a one-billion-

dollar question. All the trials you mentioned, and which are labeled in the ESMO guidelines (the combinations), the design of the trial is irrespective of the risk categorization. So, if we go to the data and look only to favorable risk patients, we have an exploratory or subgroup analyzed [1, 2, 6–19]. And what we can see there, those patients with favorable risk receiving a PD1 (programmed cell death protein 1)/TKI combination in this subgroup analyzed, they do not show any evidence of improved overall survival. But you have to be also fair, regarding the prognosis of those patients, we do have a low number of events. Although recently at ASCO GU we saw a very long follow-up from the CHECKMATE-9ER, so the combination of cabozantinib and nivolumab, and we have had a very long follow-up and I don't know what you feel [Viktor] but the curves have been completely similar [20]. Nonetheless, it's really a wondering question. According to overall survival evidence base, I think you have to do a combination. But on the other hand, if you have a 90-year-old patient, why should you aim for very a long-term overall survival, right? So it's a really tricky question.

VG: Yeah, yeah, I totally agree but I think it's quite important to settle this upfront and I think as you said, TKI single-agent therapy is still part of our clinical routine, but it applies to only a small fraction of patients. And what is pushing for that is really the lack of overall survival benefit. I think that's the major issue that is being discussed.

PI: Right.

VG: And I think you also said the major limitation is the data is not mature and I think that's something that is not frequently enough discussed. I mean, if you don't hit your median how can you be sure that with a 2- or 3-year observation time there's just no overall survivor benefit? And it cannot be said, I mean, the only fair summary is we don't know. Okay?

PI: Right. I agree.

VG: I think for me, that's quite important because there are different interpretations and the only mature data that we have available that it enhances is from CHECKMATE-214. So that investigated IPI + NIVO [ipilimumab + nivolumab] in first-line combination therapy, in first-line RCC (renal carcinoma). And there the median overall survive was about 70 months [19, 21, 22]. So it kind of tells you if you have 36 months of overall follow-up time, that is not sufficient in order to conclude that one drug is better than the other, or two drugs are better than one drug. And I think that is something that needs to be said. And then there is: What is the benefit that we can tell is real? And I think with the combinations, even in the good risk patients, you see more responses, you see better progression-free survival. And giving for the clinical outcomes in second line, I would say with NIVO second line, the PFS (progression-free survival) after 5 years' time is very low. You know, the PFS rate being patients that are without progression after 5 years' time, that's about 5% [23]. So I mean, having this all enhance, I think the sequential approach might not be optimal, I think you need an immuno agent upfront and until we have final OS data I'm compelled really to use combos in my patients. And I think something that you said is also right. In a 90-year-old or in the elderly or frail patients, do you need something that is more toxic and more efficacious? Or do we need something that is more gentle? And I think I totally agree. I mean, whatever we write in the guidelines, I think you have to break it down to the individual patient and the needs of the patients and does not mean that that's a blueprint and every single patient has to be treated like this. You always have to adapt this to the patient situation.

PI: Yes. Exactly, exactly. What we did now in a very fast manner, we jumped all over the data. And I think we have to be fair to some extent that once we're looking to the data we have, I mean, it's really a privilege having so many phase 3 trials showing clearly in the first-line setting an overall survival benefit. To be honest, once we started the business years ago [this is a] great development. Nonetheless, once we are thinking about treating the patient, and once we are thinking what might be the best, there's a very nice editorial once upon a time in *The New England Journal* [24]. I think it was written by Motzer (I'm not sure anymore) but who really did a nice dissect of the different distributions of the trials, right? So it's really hard to

say in which situation or at all which is the best. I guess it's really hard to argue because we have a different distribution of risk according to IMDC, which you mentioned, which is very important. We also do have in all these phase 3 trials different distributions of metastatic sites as well as the percentage of patients who received the nephrectomy, it's different. This might be either a distribution of the biological risk or might also reflect a different landscape of treatment, with decreasing numbers of nephrectomy. And ultimately, we also have a very strong range of time points of medium follow-up once we have the latest data. So, I think it's really always fair to look to the data and be aware. Although all the trials have had the same competitor, sunitinib, but all the trials do have different cohorts and it's really hard to compare the data. Would you agree in the main message? How do you feel about this one, Viktor?

VG: Yeah, I think there's a lot of heterogeneity between the trials and I think that is something that can be seen if you look for how sunitinib behaved in the trials, and it behaved differently depending on the trial, you know? Some are just having better efficacy, others behave poorly and it relates to the fraction of the patients that have favorable risk or poor risk and that are more or less sensitive to TKIs. I think that can be seen and we do see that the heterogeneous should not be compared. I think that that's important. Philipp, what about you? I mean about endpoints. We have all kinds of different topics that are being gathered in these clinical trials. So what about early and late endpoints? How do you really balance this and what is important for you?

PI: If you go to all the ESMO guidelines mentioned [in] trials; so the CHECKMATE-214, the KEYNOTE-426, the Javelin trial and the 9ER, and the CLEAR [5–7, 9, 12, 13, 16, 18, 19]. (*And we're not discussing novel trials, like the COSMIC trial, because we are looking to the current landscape of daily life.)* There's one thing to mention; until now, we do not have a report from the Javelin trial. So the axitinib compared with avelumab, the only PDL1 agent in this setting. We don't have any data about long-term overall survival, and according to statistics, this is the only trial which did not reach this endpoint, right? So this is worth to mention. If you look on the long run through the curve, this is highly speculative. It looks like the curve from the IMP (investigative medical product—here axitinib and avelumab, and sunitinib), that they are starting to separate but we didn't see any mature or significant overall survival. All the other trials reached an overall survival with a novel therapy (IO combinations); so the IO/IO on the one hand, the CTLA-4/PD1 inhibitor and all the other PD1 TKI combinations. And the hazard ratio, I think this is one important size, the hazard ratio is, let's say to some extent, nearly more or less the same, it's around 0.65. And this means all of those agents mentioned can improve their overall survival. And I think this is still a very important endpoint and I'm often looking to it. It's not always in the clinical context the most important one but I think it's what treatment decision, from the balance of all endpoints which I'm reflecting in day life, one of the very important ones. Would you agree…?

VG: Yeah, I totally agree. I think overall survival is a key endpoint, and what can be said is that all of these agents improve overall survival. All but one really reached significance, I'm speaking about statistics; for whatever reason Javelin did not do so.

PI: Yeah for whatever reason, right?

VG: I think it cannot be said why it didn't reach [significance] insofar as we don't have the final analysis. I think there are many variables that have to be taken into account in order to understand that and I think we're not quite there. Something I think that is important is the hazard ratios; they also migrate, I mean, what was reported after 18 months is not the same after 36 months. So, my interpretation is really, or let's put it in another context, I think with CHECKMATE-214 you do see very stable reports. The hazard ratio with each time point was pretty much the same. With the TKI/IO combinations, what you see is a strong punch in the initial reports, preventing early deaths and then you do see that the hazard migrates. It goes up basically. And so, I think the strongest benefit that you will have from the TKI/IO combination is really on one of the early time points or early outcomes and that's early deaths.

PI: Right you are. So let's focus on the second endpoint and I remember once we have had shared time here in Hannover, that we often discussed progression-free survival. Over the years, I changed my mind a little bit. What about you? What do you say? Furthermore, what is your impression from all those trials according to PFS and what is the clinical importance or is there any clinical importance? Or is it simply just a surrogate parameter for making trial design more efficient and faster?

VG: No, I think progression-free survival is an intermediate endpoint that is sufficient to tell you whether one drug performs better than another, or a combination, better than another single-agent drug or whatever. And I think that's something that we have to take into account. Of course, the gold standard—you ultimately want to improve overall survival. And I think that's important but still efficacy is also important as well because that's what patients experience. You know, if you start a therapy you would like to be successful, meaning that you have benefit. You're doing your first or second scan, you would like to see tumor control or tumor shrinkage to occur. And I think that's something that is represented by the progression-free survival curve and it gives you the certainty that, you know, that specific drug or combination performs better than another. And I think that's what you can read from the Kaplan–Meier curves for progression-free survival.

PI: And can you summarize for the audience in short, some typical issues and behavior of the combinations? We see here, three different things. This is at least my interpretation. The first thing is we see the IO/IO combination. What we can see here on the long run, the PFS curve, it looks a little bit like for NIVO-IPI that it achieves a plateau, which I always interpreted, and you can argue about this, if you reach some kind of a plateau in a PFS curve, this means no patient is progressing anymore [22]. And this might, you know, be the perspective of seeing also a plateau on the overall survival curve. And although the absolute number of PFS, is not the strongest, this is the only curve which is showing this kind of phenomenon. While the other PD1, the other combos, the PD1 TKI combos, they show high efficacy, according to the number, the median month of PFS, way higher than the combination of TKI/OI with some, again, some combinations which are having a third-generation TKI. It looks like that the PFS is a little bit stronger than the combination with the second-generation TKI [6, 7, 9, 13]. Would you agree?

VG: Well, I think there's some caveats to that. So first of all with the PFS curve, there are also censoring effects that take place and at the tail of the curve you just drop down to very few patients. So there's some uncertainty on what this really is. I think the benefit for IPI-NIVO is that we have more than just one trial where you do see the same pattern, that's one thing, and the other one is that we do have single-agent or other cohorts, you know, previously treated patients where you do see the same phenomenon. And I think there are long-term effects and durable effects that are associated with immunotherapy. And that's exactly what we have seen in CHECKMATE-214 and/or something else. I think that's a matter of debate and when you compare to the TKI IO business, they don't have the maturity to call it a tail. So if you have 26 months only of follow-up... you don't know whether that plateau may occur afterwards or it doesn't.

PI: Absolutely, yes.

VG: But when you look for absolute numbers at a given time point, they're very similar to what has been reported for CHECKMATE-214. So between IPI-NIVO and let's say AXI-PEM, the 3 years benchmark for progression-free survival is very similar, it's about 30%. And you know, it's first of all cross-trial comparison, different cohorts of patients and so on. I mean there are many, many points that make it difficult to compare. And I think we have to wait to draw definite conclusions between those different trials to see whether a plateau will occur in the other ones because they still have an immune component. The question will be, you know, what is IPI really distributing or adding to the backbone of the PD1 inhibitor? And so, I think what can be said is, the weak point of IPI-NIVO is the primary progression rate. It's as good or as poor as soon as sunitinib.

PI: It's good or it's poor. Yeah, I agree.

VG: And I mean, as soon as you add a TKI plus IO component, you just have immediate improvement of the primary progression. And that's why you have this big belly in the progression-free survival curve. So, meaning, that you have a lot of easy stabilization or tumor shrinkage, so more efficacy, and less progression. And, I think that's something. So, if you're in need of tumor control, TKI is always the choice.

PI: Right. Absolutely I agree. I mean I was really impressed over the years. You remember we were at ESMO 2018 and we saw the NIVO-IPI data first of all and we have been impressed, then it went on over the year of the Congress and then we saw the KEYNOTE and the Javelin trial and had been really impressed by the objective response rates and the CR (complete remission) rate [18, 19, 25]. And then ultimately, we saw 9ER and CLEAR which are also incredibly strong. I mean, for me personally, it's really one of the benchmarks where I'm thinking about giving a patient either IO/IO or giving them PD1 TKI combination. Is this a patient who needs remission, right? What is your impression about it? Are you only looking for radiological pictures or are you also looking for clinical symptoms or lab values? How would you define in this term? Because I mean, this is really a separation parameter and how to choose the first-line therapy objective response needs; how you define these terms of remission pressure? Or in one of the articles reviewed from the German word like kindergarten, it was written, it's zugzwang, so it's coming from chess [26]. So, in ultimate movement, which you have to do necessarily, how do you define zugzwang remission pressure in kidney culture?

VG: Yeah, I mean there are patients that are symptomatic where you just have to have the response because you know, otherwise they will progress and they won't be treated anymore because they go for best supportive care, for instance. And so, in that sense, I mean, that's what zugzwang really means. I mean, you have to score. Then you have to take your best bet. What's your best chance to be successful? And I think with the third-generation combinations that's probably the best bet. And with LEN (lenvatinib) + PEM (pembrolizumab), we have seen objective responses that are above 70%, and I think that's the strongest data that we have seen for efficacy [7]. So that we might go to that area for symptomatic patients, of course. But I think, I mean, with CHECKMATE-9ER, we have only also a very low primary progression rate. So I think that's also a very decent combo that can be used and chances are higher that you'll progress if you use IPI-NIVO.

PI: Absolutely I agree. It's overall response and the objective response, also very important to have those data in your mind once you're choosing a therapy. And you asked me the question at the beginning, I guess you remember, what about TKI monotherapy, right? And now, we go to a concept you worked on very early in kidney cancer, and it's the death of remission. We just reflected the CR rates, which is going up in LEN-PEM up to 16% overall, but all of those combinations if you compare to sunitinib do have good CR rates. Do you think it's really a good surrogate for reaching an early tumor shrinkage [27–29]? Reaching CR rates, really in particularly, for also, for the frail at risk group. Is this a surrogate for good overall survival would you say? Or is this more an intellectual concept?

VG: No, I think it's a good concept. And when you look into the clinical data for those trials patients with a CR do best, that's a fact I think. And the question is, do you need to have a complete remission? Or can you get away with a certain amount of tumor shrinkage that gives you more or less similar outcome in terms of overall survival [28]? And I think it can be said that you don't have to have complete response in order to derive major benefit from a particular treatment. And that's also true for sunitinib, it does not only apply for the combinations, you know. But the fraction of patients that benefit is just way higher when you do the combination that, you know, those patients that reach deep response compared to sunitinib. So you just improve chances basically by the combination and I think that's important and it really builds up the story that response is important. If you have a higher fraction of patients that respond, you know, that really adds up to the survival benefit that we see in the different trials. What about you? I

mean, it's always great to have complete response, isn't it? It cheers up the patients, it cheers up the physicians, so, it's a good thing to happen!

PI: In particular, when you're working as a medical oncologist, or all kinds of guys working in oncology, telling great news is not the most common phenomenon during the day life, right? But in fact, you're absolutely true. A patient is really happy after fighting and suffering. I mean, any kind of therapy, any kind of disease costs you a lot of energy, mental strength, and it's you know, altering your whole life. And once you can say you've reached CR I think that the impact on quality of life is really good. So, I agree, but as you said, also, if you look to other counts of diseases, it's also not always necessary reaching CR, right? It's also sometimes the question of risk and benefits and you don't need to go with every patient all in on the CR approach, right? And then we come to two different parameters of the trials. And let's argue again whether or not we have the same opinion on the topic and if it's relevant or not. I'm talking about the duration of response and let's do it more kind of basket of IO/IO compared to PD1 TKI. And there I think if you look to the data [is] a really important difference and I think it's also of clinical impact. The duration of response, of course this is also going along with treatment and follow-up, in NIVO-IPI is quite longer than in the PD1 TKI combination, although the percentage of patients reaching an objective response is lower. Do you think this an important parameter?

VG: Well, the durability of responses is important. And it's true, I mean after 5 years, it's about 56% durability of response in IPI-NIVO and it's less in the others reached the median. And as a matter of fact I think TKI-derived responses don't last as long and if you have, let's say, half of your responses are coming from the tablet you know, that's what happens. I mean, you just deteriorate on your duration of response. It does not mean that there isn't a fraction of patients that have a long-term response to the TKI IO combinations so, that's not necessarily the interpretation because you have different cohorts of patients. As you said.

PI: Okay, great. So ultimately, Viktor, it was really great having you here, having the discussion with you, and focusing on different aspect of all of the trials. I think what our audience now understand, if they had not at all understood it already, is that if you have carefully looked to all the data be aware of the trials and the cross-trial selection and the topic is finding the best therapy for the appropriate patient, I guess.

VG: Yeah, I think that's a very good summary. So, you know, the good thing about plethora is that you have a choice, and we are in a very luxurious position where we can choose between different treatments and to match it up to the corresponding patients in the best way. I think that's something that we can do and that's great.

PI: Thank you very much.

VG: Thank you.

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