Podcast Episode Title: The use of VEGFR-TKIs monotherapy in the treatment of unresectable or advanced HCC in 1L setting: Who can benefit and guidance on implementation of dosing-strategies and pre-habilitation of patients for the prediction of efficacy and toxicities in clinical practice

Brought to you by;

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Dr Chan

Hello everyone, I'm Dr Steven Chan. I am a Professor from the Department of Clinical Oncology at the Chinese university of Hong Kong. Today, together with Dr Josep Llovet we are going to discuss a very interesting topic about the use of the VEGFR TKIs monotherapy in the treatment of unresectable or advanced HCC in the first-line setting. We will go into details of who can benefit, and also the current guidance on the implementation of the dosing strategies and the pre-habilitations of patients for the prediction of efficacy and toxicity in the clinical practice. My co-speaker is Professor Josep Llovet. I'll let him introduce himself. Dr Llovet, please.

Dr Llovet

Hi Stephen, I'm Josep M. Llovet. It's a pleasure to be here to participate in this podcast, I am the Director of the liver cancer program, Professor of medicine at Mount Sinai in New York, and Professor of medicine at the University of Barcelona.

Dr Chan

Thank you, Dr Llovet. The reason why we focus more on the VEGFR today, is because in the past sorafenib and also recently the TKI lenvatinib, all possess anti-angiogenic properties. And, we believe this is one of the main mechanisms, which can help halve the tumour, and also help treat the cancer of HCC. However, today we have also learned from a lot of preclinical, and also the recently published phase 3 IMbrave study, that sometimes when you combine the anti-angiogenic antibodies with the PD1 or the PD-L1 antibodies, there may also be some immunomodulatory effects, apart from the anti-angiogenesis. And this is probably one of the rationales for combining the atezolizumab and bevacizumab, which has now been accepted as the standard of care, for the first-line treatment for the advanced hepatocellular carcinoma. However, we know there's still a proportion of patients who may benefit from monotherapy TKI. Maybe I pass the microphone to Dr Llovet, to tell us more details; what patients, may benefit from monotherapy, instead of atezo-bev combinations.

Dr Llovet

Yes, thank you, Stephen. The proportion of patients that are currently receiving atezo-bev is not properly described in studies yet, but the estimate is that around 80% of the patients in frontline advanced HCC, and those in intermediate HCC progressing today are probably exposed to this combination. This may vary region by region, for instance, it may be a higher proportion, I would say in the western world, and then a lower proportion in Asia. So would a patient eventually receive other treatments, not atezo-bev in front-line. Or, in other words, which are the contraindications for atezo-bev in frontline?

Well, we know that these, let's say 20% of the patients that are not suitable, for atezo-bev in frontline may present contraindications. The first contraindication is liver transplantation. Certainly, using checkpoint inhibitors, in patients undergoing a liver transplantation has been reported to induce graft rejection, and is a risk. I would say that this is one of the contraindications that have more wider consensus. The second one, and it was stated in the paper, is that patients within six months prior to starting ateoz-bev, need to be explored for presence of esophageal and gastric varices by GI endoscopy. Those at a high risk of bleeding, either need to be treated, generally with banding for large varices, or need to be excluded. Because sometimes even with banding, wound healing might take between two to six weeks, and then you are postponing start of the treatment, so this may be a second contraindication, because it is well known that bevacizumab induces high risk of bleeding. The third area in which there is consensus is severe autoimmune disease. Here it has not been well established what severe means. Certainly, in some patients with hypothyroidism, for instance, that is properly controlled, some physicians feel comfortable treating those patients with checkpoint inhibitors. But, any case of severe autoimmune disease, particularly needless to say autoimmune hepatitis, are formal contraindications for atezo-bev.

Stephen, therefore having described the contraindications for this combination in frontline, who do you think can benefit from TKIs in frontline?

Dr Chan

So, the question is, what type of patients in our clinical practises, would most benefit from the TKI instead of atezo-bev, right? Is this your question?

Dr Llovet

Yes, exactly, so we know that in the frontline we have sorafenib and lenvatinib, accepted in guidelines and we can talk extensively about that. For those patients that are not candidates for atezo-bev, how would you select these patients to receive either sorafenib or lenvatinib in frontline?

Dr Chan

Yeah, you're right. Actually, I can go back to the literature on the monotherapy use of the sorafenib and the lenvatinib. For sorafenib we have two landmark papers, one is the SHARP study, led by Dr Llovet, published in New England Journal of Medicine, in 2008. Another is, we call it AP-SHARP, which is the phase 3 trial on the sorafenib versus placebo in advanced HCC in Asian populations, published in the Lancet in 2009 by Dr Ann-Lii Cheng. From these two studies we know that sorafenib have a better overall survival, and also the time to progression than the placebo. And then we know that in 2018, there's been another phase 3 clinical trial, we know as the REFLEX study, published by Dr Kudo in Lancet, which is a study comparing the lenvatinib head-to-head to sorafenib in the first-line setting. And in this study, it was found that the lenvatinib is non-inferior to sorafenib in the primary endpoints of the overall survival. But in the secondary efficacy endpoint, like the response rate, and also the time to progression, or progression-free survival, all showed favourable towards lenvatinib.

To me, one of the most remarkable findings is, the response rate with lenvatinib in the REFLEX study. According to the modified RECIST response, the response rate is over 40%. This is actually our highest response rate, as reported in the literature, even when you look at today's other PD1 or PD-L1 combinations. Even the atezo-bev combinations, the response rate is around close to 30%.

So, I would say, some people may think, monotherapy TKI may not be as effective as the atezo-bev combinations, but if you go to the literature, especially in terms of response rate, monotherapy lenvatinib is actually, quite impressive. So, if you ask me, and I think also a lot Asian doctors in Asian countries would be similar, patients who are not suitable or for some reason, could not be prescribed atezo-bev, then lenvatinib will be one of the popular choices. And I also know that the mechanism of action, may also play some role. Maybe, Dr Llovet, could you share something with us, about what's the difference between – in terms of mechanism of action, between sorafenib and lenvatinib, which may guide our treatment?

Dr Llovet

For sorafenib, as you know, and when we reported the paper in New England 2008, we were questioning is this a pure VEGF inhibitor or beyond that are there are other mechanisms. Certainly, sorafenib and also lenvatinib, I have to say, in the lingo of FDA, is a dirty molecule. This means that is a multi-kinase inhibitor blocking in the case of sorafenib around 40 kinases. Of course, VEGF receptor 2 particularly, is critical in HCC progression, and we know that, because in second line there is a drug, ramucirumab, that just blocks VEGF receptor 2 and leads to survival benefits, and this is a clean idea. But sorafenib is doing additional things, it is a blocking platelet-derived growth factor receptor, it is blocking RAF signalling, so there are several pathways that are abrogated with sorafenib.

Lenvatinib has an additional layer of complexity in my mind that is critical in the pathogenesis of HCC. Lenvatinib is blocking FGF receptor 1,2,3 and 4. And why is receptor 4 of FGF is critical - because we know that there is an oncogene in HCC that this FGF-19, and that this is the ligand of FGF receptor 4, that is overexpressed or highly expressed in 25% of the patients. Just by blocking with a TKI specific FGF receptor 4 you are achieving objective response of 15%, and we have published that in Cancer Discovery. Therefore the fact that lenvatinib is blocking all these kinases, not RAF, but all the other kinases, platelet derives, VEGF and on top of it, also key, but on top of if FGF receptor 1,2,3 and receptor 4, I think it's critical for the potency of the drug.

You were sharing before, how you could decide between sorafenib and lenvatinib, and it is true that sometimes to describe that in guidelines it's difficult in a sense that, it's not supported by a very high level of evidence; sometimes it's difficult to help to guide physicians. But it is true that the meta-analysis we published with the SHARP and Asia-pacific trial, with sorafenib, show that patients with hepatitis C virus infection respond better to sorafenib as well as patients with liver-only disease. Conversely, in the subgroup analysis of REFLECT study, it seems that lenvatinib responds particularly better in patients with hepatitis B virus related HCC, and patients with high tumour burden, or even patients with high AFP. I think that these are just some tips to navigate.

Another question, which I think that we can bring in here, because there is now a debate. So , I think throughout the guidelines of management, Stephen, there is no question that atezo-bev is the standard of care, however, in 20% of the patients, we should not give this treatment because of contraindications and then we'll have another frontline, lenvatinib or sorafenib. But a question that is emerging now is what happens with the sequencing after atezo-bev - what happens there, is my question. I understand that we are framing this discussion in the first-line setting, and this is an important thing, but also it is important in order to understand how we're using these drugs, even in patients progressing to atezo-bev, because, as you know, there has been a controversy and in some guidelines it is supported to respect the established hierarchy. So, progression to atezo-bev should receive lenvatinib, or sorafenib and this is in the guidelines of AASLD that we published in a Pathology 2021, the updated guidelines of EASL as well. But then in ASCO they say all TKIs are accepted, but we prefer sorafenib and lenvatinib, these are the GCO guidelines published at ASCO. I

think that the more appealing conversation occurred as a panellist of ESMO and we published that this year. In ESMO, there was a debate between those saying, ok, we need to respect the hierarchy therefore after atezo-bev we should recommend lenvatinib or sorafenib, and others that were saying no, there is no evidence for that. So, all drugs are equal there. And even, we had a vote there, and it is spelled out in the guidelines. So, that is some controversy that I wanted to bring here.

But I want you, Steve, if you can explain a bit, what's your view of these TKIs in frontline, in real world, in areas that are not particularly framed in the trials; particularly, I am curious about your opinion on Child Pugh B patients, particularly those B7 patients with known ascites that we see commonly, or sometimes ALBI-2 patients. So, what's your take on the use of these drugs, in let's say extended indications in real world; Could you share your experience with that?

Dr Chan

Yeah, thank you Josep. I would say, this is a really, great question, because of course in clinical trials, for example in the REFLEX study basically only patient with Child Pugh class A liver functions were recruited in the clinical trial, while all the patients with Child Pugh B were excluded. And therefore, sometimes we don't know the exact toxicity profile and the efficacy of lenvatinib or sorafenib in those populations.

But unfortunately, the real world, these are the group of patients, we are facing every day in the clinic. Patients with some degree of ascites, some possible hypertension, cirrhosis, ALBI grade 2 or even Child Pugh B7 or 8, so this is really important. And I think one of the things that can be addressed for these populations are by the real-world data. In fact, there'd be a number of real-world data published, and I think one of the most relevant one is a paper published by a Japanese colleague Maruta. S published in Liver Cancer in 2020. They reviewed the experience of lenvatinib. They deliberately looked at those patients with expanded indication from the REFLEX study i.e., those patients with Child Pugh B function, patients with main portal vein hypertension for example. They found that in the study the number are not huge for these populations. But in the study, they found in patients with Child Pugh B7, the tolerability and efficacy are also impressive which is quite similar to the Child Pugh class A.

But, of course, we need to interpret these with caution, because this is real world evidence, maybe those patients are highly selected patients, may be there's some reporting bias. But I think this is the best available evidence to help to guide us on how to use lenvatinib, if we really want to apply it to those patients who do not fulfil the REFLEX study. But I would make a caution that still in the initial phase 1/2 study, lenvatinib, is associated with toxicity, renal and hepatotoxicity in patients with poor liver function. Therefore, in the real world, when we really want to prescribe to our patients, we need to use it very cautiously probably with reduced dose and with close monitoring.

So, I think this is so far my experience. I would also like to point out that recently Dr Vogel also published that patients with a better liver function, patients with ALBI grade 1 actually were doing much better in terms of progression free survival, and overall survival, as compared to patients with ALBI grade 2, when they were receiving lenvatinib or even sorafenib in the REFLEX study, This highlighted an important point that we need to preserve the hepatic function of patients, we need to start the systemic therapy, if possible earlier and stop later after heavy treatment with TACE or some other local treatment. If the patient has bad liver function to start with, the outcome will be suboptimal, because they have worse hepatic functions, so I think this is my experience with those real-world data. So, Dr Llovet, I noticed that sometimes in the real world, some doctors prefer a lower dose of lenvatinib, without making reference to the body weight of the patients. What's your view on that, do you think is a good practice or do you think we should adhere to the recommendation of sponsor and also what do you think about if, finally, the patient required dose modifications?

Dr Llovet

Well, I have to say that I always recommend to stick to the dose that has been approved, according to the frame of the trial. I think that it is very important to try to adhere to the initial dose recommended by the physicians and the company when they ran the trial, because this is the dose that we know that is effective. I'm not saying that other doses cannot be effective and certainly now we will discuss about dose reductions and dose interruptions. But certainly, I would recommend for lenvatinib, as you know, 12 milligrams in patients with a weight above 60 kilos and 8 milligrams for patients below 60 kilos, which is very rare in the west. I have to say it's a very marginal proportion of patients, not so, for instance Japan where there's a higher proportion of patients there, that may adhere to this dose to start with. I think when we are analysing lenvatinib or even sorafenib in frontline, I think that we need to take into account three parameters:

The first parameter are the dose reductions.

The second parameter are particularly treatment related adverse events, leading to withdrawal, and these are two different things because if you have an adverse event, you have certainly to manage that, according to certain guidelines; For example, with sorafenib grade 1 was symptomatic treatment, grade 2, dose reduction, grade 3/4 dose interruption, and this is generally the rule applied in general for lenvatinib as well right.

So, what is the percentage of dose reductions, because dose reduction doesn't mean that there is a treatment failure. So, in reality, in all these trials, dose reductions are ranging between 30 to 40% of the cases and these patients actually are the body of the study that lead to differences in survival. So, the dose reductions are also providing a benefit, otherwise the trial would not be possible probably to keep superiority, imagine at the beginning with

sorafenib, for non-inferiority for lenvatinib compared to sorafenib. For lenvatinib I recall that those reductions are around 40% and the first step, if you got 12 milligrams is to move to 8 and then to move back to 4 if still something happens.

But my recommendation will be, okay, from 12 to 8 and then at one time point if the patient has recovered try to re-challenge 12, depending on the adverse events. The other thing is as I mentioned, treatment related adverse events leading to interruption, and here we have that for sorafenib generally, what has been reported in several trials, because, as you know, has been also the control arm for several trials. It's between 10 and 15% of the patients that should discontinue the drug generally as a result of greatly hand-foot skin reaction. In lenvatinib it's slightly less, it's around 9-10%, what has been reported. And, as you know, for atezo-bev that you cannot reduce the dose; then, the withdrawal has been around 16% in the trial, and even 7% of the patients should remove both treatment: atezo and bev.

So, this is somehow the figures that we need to keep in mind, also, there is a critical figure but it's out of the equation with these drugs, that are grade-5 related adverse events, so treatment related adverse events leading to death, that generally are 2% or less with these drugs.

So, in my mind, I think that this is somehow a way to frame it, I know because I have had several interactions particularly with Asian physicians, that they like sometimes to have a run-in period with four milligrams and then move up to 8 and 12. Can you brief us about that Stephen?

Dr Chan

Actually, I know, in real world, sometimes I especially, initially when the drugs were launched, sometimes clinicians were more cautious, so they sometimes prefer, you're right, start with a reduced dose for example for sorafenib 400 milligram qd, daily, or lenvatinib, 8 milligrams, even 4 milligrams, daily. On one hand, yes, this may be safer for the patient, but on the other hand, we understand that dose intensity is important for keeping the efficacy of the TKI, there are so many different subgroup analyses, showing that patients with higher dose intensity, actually tend to have a better outcome when treated with TKI.

So, nowadays, I think the phenomena has changed gradually. Initially 10 years ago when we started sorafenib everyone was afraid. Everyone says we see a lot of hand skin reaction but nowadays, you know a lot of physicians in Asia and I think the world's the same, tend to start with our full-dose now. The good thing is that you really subject the patient to the maximal recommended dosage. And as mentioned by Dr Llovet if the patient, has any problems, we can adjust the dose. Or even reduce the dose for a while, before allowing the patient to have a toxicity recovered to grade one. I think this is not treatment failure, it's just a personalisation of the dose according to the patient toxicity. You can start the patient with a low dose, you may lose the time period to treat the tumour, so I think this takes some time,

but with more experience with TKI, I think the phenomenon of so-called run-in phase is less observed nowadays in the world, including Asia.

So, Dr Llovet, what is your, the message you want to give to our audience; say what will happen next in 2022, or 2023, what do you think is the important findings or future studies or what the take home message you want to give to our audience?

Dr Llovet

Sure. Well first, I will give, if I can a very short summary of our discussion, I would say that in front line atezo-bev is the standard of care, but there are around 20%, or maybe more than that particular in Asia up to 30-40% of the patients that will not be exposed to atezo-bev, and in this situation, the frontline TKI are lenvatinib and sorafenib. The second thing is that these drugs even are currently considered by most of the guidelines in patients progressing to atezo-bev in second line. How to choose between sorafenib and lenvatinib, we have some tips based on subgroup analysis and meta-analysis. Generally, sorafenib was better in Hepatitis C and liver-only, eventually lenvatinib in high tumour burden, and aggressive tumours. Mechanism of action, there is clear overlap: VEGF, platelet derived, so on and so forth. Sorafenib is also targeting RAF signalling and lenvatinib is also targeting FGF receptor signalling, particularly receptor 4.

In terms of dosing, it is true that we recommend, starting with dose that is recommended, 12 milligrams for lenvatinib in patients, weighting more 60kg – 8 milligrams below 60kg. And for sorafenib 800 milligrams and then reduce the dose. That may happen in 30 to 40% of the patients according to adverse events; treatment withdrawal as a result of adverse events, occurring in 10-15% of the patients, this is what has been described.

Second part that you were asking, was the future. I think that we're in a very exciting times, not now but one year or two years ago, we were in the dawn of a new era; I remember when I presented the sorafenib trial at ASCO in 2007, that it was said, this is the dawn of a new era right, the date of the TKIs right. Now we're at the dawn of the era of the combination therapies, and we have atezo-bev, this is the first in class – we don't know if we'll be the best in class right, it could be the best in class, but hopefully at one time point there will be a combination that will be superior and all of us also will be happy for that.

There are several combinations ongoing, as you know, so the first combination certainly that we were involved, and we published that in JCO, is the lenvatinib-pembrolizumab phase 2 data, the phase 3 is the LEAP-002. Also, you have the COSMIC 312 with atezolizumab-cabozantinib. You have the CHECKMATE 9DW with nivolumab-ipilimumab with two I/Os that eventually will not, expand a lot the target population that may benefit but the response, may be deeper or more durable. You have the HIMALAYA trial also in the setting of a combination of I/Os with durvalumab/Tremelimumab and a lot of other trials; RATIONALE 301, we have several trials, so my impression, and this is only in advance, because I think that part of the business is also in early and intermediate. In early, there are four trials in Phase 3 that might become a standard of care if positive and will be a breakthrough because

we don't have adjuvant therapies after resection localisation, and in intermediate we have TACE for 15 years and we have been unable to improve the bar of survival, that is around 30 months for patients at intermediate stage, so these trials combining TACE , plus checkpoint inhibitors, TKIs, so we have the EMERALD-1, LEAP-012, the CHECKMATE 74W and RENOTACE and others, these trials also may improve the outcome of the patient, so I envision the future and near future in two or three years, very exciting in this field.

Dr Chan

Thank you, Dr Llovet. I fully agree with you to 2022 will be very exciting years for HCC, we have many combination trials to have a result, but don't forget about the monotherapy TKI. Even if you look at the sorafenib arm in the IMbrave study; in the past we have 6-8 months or 10 months, now, we have 14 months survival. And also, recently the COSMIC-312 study, we know that despite the progression free survival is better in the combination especially in the overall survival, interestingly, it seems, the combination is unable to beat the sorafenib arm easily, so I think in the future, certainly, the combination is the key but there's still a lot of patients who may not be suitable or be able to afford the combinations, maybe monotherapy TKI like lenvatinib or sorafenib has a role for our patients in daily clinical practices. So, thank you very much everyone for the attention.

Dr Llovet

Thank you