A new era in treating patients with advanced HCC – 2nd line treatment selection and the right time to switch

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Tonke de Jong Welcome and thanks for listening to this podcast on treating patients with advanced HCC, where we are going to focus on second line treatment selection and the right time to switch. I'm Tonke de Jong and I'll be moderating today's podcast of COR2ED independent medical education.

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I'm honoured to introduce to you to today's two experts in the field of HCC, Prof. Dr Amit Singal, gastroenterologist and hepatologist and Prof. Dr Jeroen Dekervel, GI Oncologist. Could you please introduce yourself, Dr Singal?

Dr Amit Singal Yes. Thanks, Tonke. My name Amit Singal, Professor of Medicine, Chief of Hepatology and Medical Director of the Liver Cancer Program at UT Southwestern Medical Centre in Dallas, Texas, in the United States. I'm excited to be here today.

Tonke de Jong Thank you so much, Dr Singal. I'm happy to also welcome Dr Dekervel for this podcast. Welcome.

Dr Jeroen Dekervel Yeah. Hi. Good day. My name is Jeroen Dekervel. So, I'm a GI oncologist in UZ Leuven in Belgium, treating patients with HCC, among other GI tumour types. And thank you for having me because I think it's really a timely podcast, a really important topic, not so much evidence there. So I think it's important also that we share our experience with the listeners of this podcast so we can provide optimal treatment sequencing for our patients.

Tonke de Jong Yeah I definitely agree to that. Thank you, Dr Dekervel. Today's podcast episode is all about optimal treatment sequencing and the right time to switch to second line therapy. I know from earlier podcast episodes that there's a lot going on in the field of HCC over the past decade with the approval of many new systemic treatments for patients with HCC, which are often IO or IO based. And I think it would be a good idea to start with a short overview of the available first line treatments for patients with advanced HCC by looking into the data from key clinical trials. Could you please share this overview with us? Dr Singal.

Dr Amit Singal Yeah, Thanks, Tonke. You're right. It's been a very exciting time in terms of the landscape for advanced stage HCC. We had the first agent that was shown to have a survival benefit in the advanced stage setting with the SHARP trial that was published back in 2008. This showed the superiority of sorafenib versus placebo in the front-line setting, and this provided a median survival of around 10.7 months. I think all of us remember that when this came out, we thought we would have many more trials come out over the next few years that would show also a survival benefit. And instead, over the next decade, all we saw was one agent after another that failed to show superiority versus sorafenib.

This bad streak ended with the REFLECT trial, which was published in 2018. The REFLECT trial evaluated two different TKIs, lenvatinib versus sorafenib, in the frontline setting. And in brief what we saw is that lenvatinib had non-inferior survival compared to sorafenib, 13.6 versus 12.3 months, but had superior benefits in secondary outcomes, including better progression free survival as well as notably higher objective responses. Now both of these are tyrosine kinase inhibitors (TKIs), so they have overall class effects in terms of their AEs, although we see less hand foot skin reaction with lenvatinib and we see higher proportions of other AEs like hypertension, anorexia, weight loss. But both agents are otherwise very effective TKIs in the frontline setting.

Now after TKIs, we entered into an IO-based regimen era as you referenced. We started with single agent PD-1 inhibition, which failed to show a benefit compared to sorafenib in the frontline setting in CheckMate 459. Subsequently, we now have two combinations which show superior survival compared to sorafenib in the frontline setting. We have IMbrave150 which showed superiority of the combination atezolizumab and bevacizumab - so a PD-L1 inhibitor combined with a VEGF inhibitor compared to sorafenib. And this has really set the benchmark for median survival at this point - 19.2 months with the

combination of atezolizumab and bevacizumab compared to a median survival of 13.4 months with sorafenib. It also hit its co-primary endpoint of superior progression free survival, and we see objective responses in 30% of patients - really much better. And these are durable responses compared to what we've seen in the past.

Subsequently, we've seen the HIMALAYA trial showing superiority of durvalumab and tremelimumab versus sorafenib, 16.4 months versus 13.8 months, also showing improved objective responses in 20% of patients on the combination of durvalumab and tremelimumab, versus 5% compared to sorafenib. So, once again, superior survival and superior objective responses.

And both of these combinations are very well-tolerated. You have to take a look at immune related AEs and we have to consider bleeding risk with the combination of atezolizumab and bevacizumab, requiring an EGD within six months prior to starting that combination. But otherwise, these combinations really showing prolonged preservation of quality of life. And few AEs and once again very high survival in the frontline settings so resetting what we can expect with systemic therapy in the first line setting.

Tonke de Jong Thank you for that very clear overview Dr Singal. And now that we have this overview clear, I'm wondering what are second line therapies? Could you briefly review the trials that have been done in the second line and where do they currently sit in the treatment landscape, Dr Dekervel, from a European perspective?

Dr Jeroen Dekervel It's important to stress that that the development of the second line treatments dates back from the TKI era. So as Dr Singal nicely put, it was sorafenib at that time, standard of care, first line treatment and all the second line trials were done in a sorafenib pre-treated population. This is an important caveat in the current context with the IO based combinations as a preferred first line. Nevertheless, in Europe approved second line treatment options are regorafenib and regorafenib is also a TKI and was tested in the RESORCE trial, which demonstrated an improvement in overall survival compared to placebo in patients who tolerated and progressed on first line sorafenib. Then in the CELESTIAL trial, cabozantinib, another TKI, was tested, again showing improvements in overall survival compared to placebo in pre-treated, advanced HCC and finally, the VEGFR2 monoclonal antibody ramucirumab also improved survival in pre-treated patients with HCC, albeit restricted to those patients with a serum alpha-fetoprotein (AFP) level of more than 400 nanograms per mL.

So regorafenib, cabozantinib and ramucirumab are the approved options in second line in Europe, improving overall survival in this context. But we have to stress that this improvement is rather moderate I would say, with a median of about two months OS gain for all three drugs.

(Efficacy data from the aforementioned trials. RESORCE: median survival of 10·6 months [95% CI 9·1–12·1] for regorafenib versus 7·8 months [6·3–8·8] for placebo [HR 0·63, 95% CI 0·50–0·79; one-sided p<0·0001]. CELESTIAL: median overall survival 10.2 months for cabozantinib vs 8.0 months for placebo [HR 0.76, 95% CI 0.63-0.92; p = 0.0049]. REACH-2:

median overall survival of 8·5 months for ramucirumab [95% CI 7·0–10·6] vs 7·3 months [5·4–9·1] for placebo; [HR 0·710, 95% CI 0·531–0·949; p = 0·0199])

Tonke de Jong Given that you are from a different part of the world, Dr Singal, are the same treatments approved in the US?

Dr Amit Singal All three of those agents are approved in the US, regorafenib, cabozantinib, ramucirumab. I think another combination that we have approved in the second line setting is the combination of ipilimumab and nivolumab - a CTLA-4 and a PD-1 inhibitor in combination. This combination had accelerated approval based off Phase II data. So, in contrast to the other three which have been shown to have superior survival in large Phase III studies, this combination was really had approval based off of exciting Phase II data showing high responses. And this is still a combination that has approval and can be considered in some select situations.

Tonke de Jong You point out that those second line treatments have evolved and developed in the era of sorafenib. So I'm wondering, what are possible sequences in the therapy of patients with HCC now? As I understand that IO combinations are now standard of care in first line. So what's your view on the best second line treatment after atezolizumab plus bevacizumab or durvalumab plus tremelimumab? How do you apply the aforementioned data with these new first line therapies and what's the role of real world data here, Dr Singal?

Dr Amit Singal Yeah, at the end of the day, these agents were all evaluated after sorafenib; we're now forced to apply them after these new combinations, atezolizumab plus bevacizumab or durvalumab plus tremelimumab in the frontline setting because those are used in a majority of our first line setting patients at this point. Unfortunately, we're not going to go back and redo large Phase III trials after these new agents, and so we're forced to apply these data and depend on real world data at this point. What we've seen is that there are small case series for some of these agents after atezolizumab plus bevacizumab or durvalumab plus tremelimumab showing some tolerability as well as some effectiveness of agents like sorafenib or lenvatinib, cabozantinib, etc. after these patients who receive atezolizumab plus bevacizumab. I think there are fewer data after durvalumab plus tremelimumab because this is a newer combination that has just recently obtained FDA approval. But we anticipate seeing those data come out over the next several years as well.

We will hopefully see more and more robust data to come out and we can then start to draw maybe indirect comparisons even of what are the optimal second line therapies after these new agents. Short of those data being available, I think many of us are forced to depend on mechanisms of action. For example, you may have, IO and VEGF inhibition in the front line setting and you want to choose an agent that gives you unique mechanisms in the second line setting.

Tonke de Jong Would you use the same approach and thus the same sequences? Dr Dekervel.

Dr Jeroen Dekervel Yes. So, there are many important things here, I think, that Amit said. First of all, I think these real world data, we are waiting for them and of course we're looking forward to it. But I think it's important that we realise which questions we can answer with real world data and which questions cannot be answered using these data.

Real world data will give us, for example, an answer on the percentage of patients that can receive a second line or even a third line in the real world setting. And the first report suggests that this is about half of patients after first line, which is clearly less than most of other GI tumours, by the way. Real world data can also inform us on safety of using a treatment option that was initially developed in a first line setting and now used in later lines, but we do not expect major surprises here. What, in my opinion, is very hard to do with real world data is to compare effectiveness of different treatments. For example, a hard statement that option A is better than option B in second line, that will be very difficult to make using real world data because these analyses are always subjected to biases which are very difficult to completely correct for.

So that taken into account, I think also we have to look at the mechanism of action. This was already used as an argument. And also, for example, in Europe, we have to look at drug approvals by EMA. And so we have no immunotherapy option approved in later lines. So it's really a question of which TKI to give after a first line immunotherapy regimen. And there we have sorafenib lenvatinib all the options regorafenib, cabo... However, also local reimbursement and insurance criteria have to be taken into account. For example, here in Belgium, the reimbursement of lenvatinib is restricted to first line use only, while sorafenib can be given in second line. And another example is regorafenib is only reimbursed after progression under sorafenib. So you have to use sorafenib first in order to be able to give regorafenib. So this is just an example how the local context might shape the treatment sequence in HCC.

Tonke de Jong Yes, I think it's really useful to keep these realities in mind, right? I think we can conclude that we don't have good comparative data right now for second line after IO based treatments. When do you think we get these real world data and what would you suggest to do in the meantime, Dr Singal?

Dr Amit Singal Yeah, unfortunately it will take some time to get these real world data. We're starting to see real world data come out after atezolizumab plus bevacizumab, relatively small numbers, but those will grow over time. The combination of durvalumab plus tremelimumab, as I mentioned, just recently obtained FDA approval in the United States, and we're starting to see more usage at this time. But I think it's probably going to be two or three years before we see robust second line data really come around.

In part, that speaks to the effectiveness of our first line agents. And so unfortunately, in the meantime, we're dependent on expert opinion and mechanisms of action. And, not only are we trying to get second line, but we're trying to get third line, and so trying to think through what sequences will allow you to keep people on therapy the longest.

Our personal approach is to use is what we call a T-1 approach. So using atezolizumab plus bevacizumab or durvalumab plus tremelimumab in the front line setting, using our prior first line setting therapy, sorafenib, lenvatinib in the second line setting, and then saving our prior second line therapies to the third line. And I have to say most commonly, although not 100%, we will use a sequence that goes somewhat like atezolizumab plus bevacizumab or durvalumab plus tremelimumab in the front line, often choosing lenvatinib given the higher responses, higher progression free survival in the second line. And then we use cabozantinib often in the third line setting because you also in the CELESTIAL trial had 27% of patients who had third line use of cabozantinib. So you have some data for cabozantinib in the third line setting and so that's often a sequence we use. But I think short of real world data, we're forced to depend on these expert opinions and mechanisms of action.

Tonke de Jong Thank you Dr Singal. And based on what you just told me about the reimbursement realities in Belgium Dr Dekervel, I guess, or I'm assuming that for you it would be more of a TKI discussion?

Dr Jeroen Dekervel Yeah, for sure. And we as I said, we cannot use lenvatinib in second line. So we would go for a sorafenib-regorafenib sequence after an IO based regimen like durva and treme or atezo and bev in first line. So a slight difference is there. I think there's a lot of uncertainty. There's a lot of heterogeneity in the use of these agents, and this is also reflected by the guidelines, for example. So if you look at AASLD, ESMO and EASL, their recommendations of course cannot be strong and they are slightly different one from another in terms of recommendations regarding a second line. Some like ESMO, will say, well, we do not prefer one TKI above another for second line after an IO based combination, while others like AASLD will more be in favour of the T-1 approach that Amit just sketched in favour of using the first line options of the past now in second line and then go from there to third line.

Tonke de Jong Now that we know the possible treatment sequences I also need to know more about the right time to switch to the second line therapy. Dr Dekervel. Let's talk a bit more about progression while receiving first line therapy. How would you measure progression in a patient with advanced HCC?

Dr Jeroen Dekervel Measuring progression in advanced HCC can be challenging, I think even more challenging than in other, solid GI tumours. Of course we have radiologic assessment criteria such as RECIST and derivatives of RECIST, such as the modified RECIST criteria which were developed specifically for HCC taking into account tumour necrosis. We have the iRECIST criteria, specifically for treatment with immunotherapy. However, we have to be honest and say that these criteria are mostly used in the context of clinical trials and not always in clinical practice.

When assessing progression in HCC, I think we need to be aware of a few challenges. So first of all, lesions in my experience might not be that well delineated or well visible on a certain scan, on a certain modality, and sometimes it's good for an individual patient that we go and look for the optimal imaging modality to follow up this specific patient. And this can be three phase contrast CT, but this can also be an MRI or even sometimes a PET CT if that is

available. So that is the first thing: I think it's important to look for that modality that will allow us to follow up the patient in an optimal way. And then also in HCC, disease progression can be mixed with some lesions responding and others not, which can complicate, of course, the assessment and the final decision that you have to make based on the scan. And then the last point specifically for immunotherapy, especially in a first assessment, it can be challenging as well. Pseudo progression might occur, although I think it's quite rare in HCC or the response to treatment might be somewhat delayed and you have to wait.

So what I do when I'm in doubt is that I give the benefit of the doubt. So I continue the treatment if there is an unclear scan but with a shorter interval towards the next assessment, for example, six weeks, I think that's really helpful. And sometimes also AFP levels, alpha-fetoprotein levels, can contribute to the assessment. If there's a clear rise, for example, in alpha-fetoprotein level, I think that pseudo progression is very unlikely and it's probably real progression that we are seeing.

Tonke de Jong Thank you for this and also thank you for this elaborate answer on the different aspects of measuring progression on IO treatments for patients with HCC. I take it that measuring progression and disease control is definitely not as straightforward as one might think, and indeed quite a challenge. Do you have anything to add to these challenges and what does it all mean in terms of timing for second line therapy Dr Singal?

Dr Amit Singal Yeah, I agree with you on that. It's nice when you read it in a textbook and it looks very clean, but in clinical practice, it's often much more complicated than one would imagine. You have these strict cut-offs that were defined for RECIST and mRECIST. But oftentimes when you're seeing a patient in clinic and they have some small progression, but they don't quite meet these thresholds, the question is what do you do? What do you do when a patient has what appears to be stable disease on imaging but has marked elevations in their AFP levels, their tumour markers? And so these mixed responses can be very difficult to determine or actually then decide what to do in terms of clinical practice. That really ends up being a very sort of important discussion between myself or another provider and the patient to determine what the patient and you think is the best decision in those situations.

The other thing is you can have differential speeds of progression or response. And so, Jeroen also referenced this as well; you can have a patient who is stable at some time on an IO based regimen and then has progression a year later. And I think that's very different than somebody who has progression on their first imaging, two months into an IO based regimen. And when you have different therapies available in the second line setting, some IO based, ipi-nivo for example, and some TKI based. I think those different speeds of response may also contribute to the optimal choice of second line therapy. And I don't know if we know the answers for exactly what all these different things mean, but I do think that we understand that those tumours and those responses likely differ in the second line setting. I think these aspects are going to bear out more and more over time. And the final thing that I'd say is that we do know that there are data showing that type of progression differs. So if you have a tumour and there's local progression, local growth, that's different

than somebody who develops new intrahepatic disease and that's different than somebody who develops new extrahepatic disease. The prognoses for those differ over time. And when you take a look at the new BCLC staging system, they actually differentiate these types of progression because of the different prognoses. What we don't know is even though we know it's different prognosis, how does that determine subsequent therapy choices? That is an area of investigation that we need to still have.

Tonke de Jong May I ask you to share your view on liver function with regard to further treatment? Dr Singal.

Dr Amit Singal Yeah, You know Tonke, that's another important point. Jeroen already mentioned that this can be more complicated than other tumours, and I think I'm surprised we got this far into the podcast without mentioning liver function actually. HCC is a unique tumour in the sense that it's a tumour that happens within a diseased organ. So over 90% of patients have underlying chronic liver disease, if not cirrhosis. And when we think through treatment choices, whether in the first line or second line setting, you need to always consider liver dysfunction and patient performance status, etc. And so, one of the other areas that you can see in terms of clinical progression, even if it's not from a tumour perspective, is patients having increased liver dysfunction. We do have some data from the first line setting that patients who start as a Child-Pugh A and then progressed to a Child-Pugh B, so some signs of liver dysfunction. It's generally regarded as being safe to continue that first line therapy. Although when you think through and have somebody who needs second line therapy, most of our second line therapies have not been well evaluated in patients with liver dysfunction. And that is always something that needs to be considered when you're thinking of second line therapies, what is that patient's performance status? What is that patient's degree of liver dysfunction? Because those can have very important implications for the optimal second line therapy in that patient.

Tonke de Jong What's your view on this, Dr Dekervel?

Dr Jeroen Dekervel Yeah, I completely agree. And I don't have a lot to add here. I think indeed, that subtle decompensation can be first sign, a clinical sign of progression, and we need to take this into account. And it's very important in light of potential second line treatments. If we wait too long, if we ignore the fact that this patient is deteriorating in terms of liver function, then we might also come to a point where subsequent treatment is no longer possible. And this is true from the real world data. It is true for half of our patients in some settings. So it's really something that we should be vigilant about.

Tonke Yeah. Now that we talk about this and we know more about measuring progression and liver function. I'm wondering how you really make the decision to switch to second line therapy. Could you share your view on this, please Dr Singal?

Dr Amit Singal Yeah. Tonke, I think this is another case where when you read the textbook, there's it's very simple and clear, and there can be clear demarcations on when you should switch to second line therapy. And so maybe it's best to start there if you have radiologic progression. Then the idea here is you have failure of the first line therapy and you should

switch to second line therapy. Likewise, if you have a significant immune related AE or significant intolerance of the first line therapy, it's another indication to switch to the second line therapy. And those are clear textbook answers of when you should switch to second line therapy, because we have effective second line therapies which can offer an advantage to that patient.

However, in clinical practice, this can be difficult because there's a lot of excitement about these IO based regimens. They're very well-tolerated. When you talk to a patient and you talk about some of the TKIs, you talk about the potential benefits and you talk about the AE profile, oftentimes you get into a situation where the patient's like, “I don't understand. I understand I have some progression, but I'm tolerating it so well” and there's reluctance to switch to second line therapies.

So, you know, from the textbook, this can be quite simple. But I think that there's clearly a lot of enthusiasm from an IO perspective, and these are generally well tolerated. So it can be much more difficult in clinical practice to actually determine exactly the right time to switch when talking to your patients -. Jeroen, do you agree? What what's your impression and your sort of experience switching from first line to second line?

Dr Jeroen Dekervel Yeah, I completely agree that this is this is challenging and it's not like in the textbooks. I'm always weighing these two sides in my head. On the one hand, I do not want to stop the treatment too soon because we know that these new first line options can be potent and provide durable remission in a subset of patients. So we don't want to miss that option. Switching too early specifically in the context where response assessment can be challenging as we discussed, certainly at the first evaluation. But on the other hand, we do know that we have these second line options and I have patients, for example, that did remarkably better with a TKI compared to an IO combination. So that exists as well. So we do not want to miss that opportunity either. So this is everything we have to combine: the state of the disease on the imaging, the evolution of the general condition of the patient, which also includes the toxicity of the treatment, the liver function. And then, as you mentioned really nicely, the preference of the patient and how comfortable he or she feels in terms of switching treatment. But this is the integration that we have to make that is really the challenging part of the clinical decision process. But this is what we have to do on a daily basis.

Tonke de Jong Thank you so much. I think we can conclude, if you agree with me, that making the decision to switch to second line is easier to do in a hypothetical case than in clinical practice when you have the actual patient right in front of you. I would like to thank you both for sharing your view on when you actually switch to second line and also the challenges in doing so. I'm wondering what would be the main message for our listeners, Dr Dekervel?

Dr Jeroen Dekervel Well, I think I would have two main take home messages. I think it's important to know that there are approved second line systemic therapies for patients with HCC and they have been adopted by several treatment guidelines. They are potent and this is the first one. The second one is that the decision to switch to a second line treatment is

really an integration, an assessment of the performance status of the patient, the toxicity of the prior treatment, the evolution of the liver function and the state of the of the disease, the state of the HCC.

Tonke de Jong Would you have anything to add to these clinical messages Dr Singal?

Dr Amit Singal Yeah, I agree with both of those from Jeroen, and I think both of them are very important. I think the other thing that I would just add is that we have second line systemic therapies, but there is now multiple second line systemic therapies from which we have to choose. And we've already talked about the fact that there are no current robust data, but there is a need for real world data and there's a need for comparative effectiveness data. That would be my other point is there's a need for comparative effectiveness data to really determine the optimal second line therapy. And even beyond comparative effectiveness data, ideally, there's a need for biomarkers so we can move from a one size fits all to a world where we have precision oncology actually implemented in clinical practice.

Tonke de Jong Thank you both so much for sharing these important messages and for your experiences deciding the right time to switch to second line therapy for patients with advanced HCC. I have learned a lot and take with me that the systemic treatment landscape for patients with HCC is rapidly evolving, which makes it even a bigger challenge to define optimal sequencing for the patients who progressed on these novel therapies. Thank you both, Dr Singal and Dr Dekervel.

If you liked this episode, then please look for the other episode of this series where we discuss the treatment options for patients with advanced HCC who are not eligible for IO first line. You can find the COR2ED medical education channel on your preferred podcast platform. If you are interested in finding out more about HCC, then please visit COR2ED.com and select Oncology. If you like this podcast, then don't forget to rate this episode or inform your colleagues about it. Thank you for listening and see you next time.

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