Podcast Episode Title: HCC Updates from ILCA and ESMO 2022

Brought to you by:

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Transcript

Matthias Pinter

Hello, everyone, on behalf of HCC CONNECT I want to welcome you to this podcast on systemic treatment in hepatocellular carcinoma, summarising key data presented and discussed at ILCA and ESMO 2022. My name is Matthias Pinter. I am a hepatologist at the Medical University of Vienna, and today I am joined by Jeroen Dekervel from Belgium. Maybe you want to say a few words about yourself?

Jeroen Dekervel

Hi. Good day, everybody. My name is Jeroen Dekervel. I'm a GI oncologist here in UZ Leuven in Belgium, focusing on all kinds of GI

tumours, but in research mainly on HCC. I'm really happy that we can discuss, together with you the results of the upcoming data in this field.

Matthias Pinter

So, as you know, there have been some new presentations of IO therapies over the last couple of months, and at this year's ILCA meeting the ILCA Committee proposed a new treatment algorithm based on these recent presentations of Phase 3 trials, and, according to their draft, atezolizumab and bevacizumab as well as the combination of durvalumab and tremelimumab represent the recommended first choices in first line.

And alternative options in frontline include the well-known TKIs, lenvatinib as well as sorafenib, and they also included a PD-L1 targeted monotherapy durvalumab, which showed non inferiority versus sorafenib in the HIMALAYA trial, which was presented earlier this year at ASCO GI.

Now the combination of camrelizumab, a PD-1 inhibitor plus rivoceranib, a TKI, as well as tislelizumab, a PD-1 targeted monotherapy, were also added as first options in first line. But this recommendation, however, was based on the press release reporting superiority over sorafenib for the combination regimen and non-inferiority for tislelizumab monotherapy.

The respective results of both trials were disclosed only later on at ESMO, and we will discuss these results shortly.

In second line after sorafenib they recommend regorafenib, cabozantinib, ramucirumab as well as pembrolizumab, which all have proven efficacy in sorafenib pre-treated patients as you know.

We have high-level evidence. We have positive Phase 3 trials for these agents. But keep in mind that for pembrolizumab the global trial was negative. But a second trial, a second Phase 3 trial, conducted in Asian countries, finally reached its primary endpoint.

Now sequencing after prior IO therapy, which is now the standard of care in systemic frontline treatment, and sequencing after lenvatinib is less clear because we do not have any data from Phase 3 trials here.

And therefore, the ILCA Committee, as well as other associations like ESMO, recommend more or less all approved TKIs as well as ramucirumab as per local availability. But obviously the level of evidence for this recommendation is low.

May I ask you, what is your standard of care at your institution? What is your preferred option in frontline?

Jeroen Dekervel

Thank you for the question. I mean what you just said, it all sounds very complex. We have so many agents right now. I think it's really important that we keep ourselves reminding where we come from. We come from a TKI era of course, the first systemic treatment options in advanced HCC. And we have had the TKI's now for many years, and then in a second time there was the immunotherapy that was coming first in monotherapy, and we know there is a subset of patients with HCC that responds to immunotherapy but it's a small subset, and in trials with all comers, they just were not positive. And then, of course, now we are in the era of the combination treatments with immunotherapy and TKIs, or VEGF antibodies.

And in this new era, of course, we have to look which treatments showed superiority in terms of overall survival compared to the standard of care, compared to the TKIs. And the TKIs, of course, mainly is sorafenib in most of the trials. And then we look at atezolizumab bevacizumab, which showed in the IMbrave150 a clear overall survival benefit.

So, for me, without any contraindications, and this is of course really important, it remains a question of good patient selection without any contraindications, atezolizumab bevacizumab is the standard of care.

There's another combination treatment that showed superiority in terms of overall survival, however, not yet approved by the EMA yet, and that's of course, the STRIDE regimen. One cycle of tremelimumab, followed by durvalumab, the PD-L1 inhibitor, every four weeks, and this is a good alternative option again showing superiority in terms of overall survival for those patients mainly that have, for example, contraindications for atezolizumab bevacizumab.

And then we still have the TKIs. The TKIs we know really well. We have learned to use them over the years, and they're still in terms of patient profile, a proportion of patients that is best helped with the TKI in first line.

So I think for me these are the options, atezolizumab bevacizumab for most of the patients, durvalumab tremelimumab for a selected number as well as TKIs for patients that cannot have immunotherapy.

Matthias Pinter

So I couldn't agree more. Atezolizumab/bevacizumab is certainly also the reference standard here in Austria as well. But you mentioned contraindications for the combination of atezolizumab and bevacizumab and that was also discussed during a session at the ILCA meeting. Maybe you want to talk about certain contraindications where you may prefer other treatment options in first line?

Jeroen Dekervel

In patients with liver cirrhosis, of course, we're always very concerned about bleeding risk, and in the IMbrave trial every patient had to have an EGD, an endoscopy to exclude esophageal varices, and if there were varices, of course they had to be treated along local standards, and this is still very important in clinical practice.

If you put these precautions in place, then the risk of bleeding is low. However, there are still some patients with liver cirrhosis where the bleeding risk is uncontrolled, and where we would rather not give an anti-VGF antibody like bevacizumab. So, these are patients that preferably get the STRIDE regimen, also patients with uncontrolled cardiovascular risk, or I remember some patients with wounds that would not heal. Of course these patients, they are not good candidates for bevacizumab and there the durvalumab tremelimumab combination is certainly an option.

And then, of course, we look also at the IO component of the combination, atezolizumab. Some patients cannot get immunotherapy,

at least patients with autoimmunity, and then I would say, rather uncontrolled autoimmunity, which means they are actively treated for, for example, autoimmune hepatitis with steroids or other immunosuppressants. These patients are not such good candidates for immunotherapy, and of course, the patients with HCC recurrence, post-liver transplantation, for example. So we know that immunotherapy induces rejection in the majority of patients after solid organ transplantation. You can discuss in the setting, for example, of a clinical trial, whether after kidney transplantation, it's, of course, weighing of benefits and risk, because you always have the dialysis as a back up option. But for liver transplantation this is not the case. And, of course, fulminant rejection will in fact, lead to more poor outcome for these patients so we really have to be careful there. I would say autoimmunity, if the autoimmunity is controlled, if this patient has, for example, a history of Crohn's disease, but it's untreated. If this patient has rheumatoid arthritis very well under control you might consider an IO combination with only one component of immunotherapy, such as a PD-L1 inhibitor. But probably there the double combination, durvalumab tremelimumab could lead to more flares of autoimmune disease, as we have seen also in the HIMALAYA trial where the need for steroids in that combination arm was higher than in the arm with durvalumab monotherapy.

Matthias Pinter

Yeah right, I couldn't agree more. So basically, to summarise that, contraindications for bevacizumab basically include uncontrolled hypertension, it includes recent cardiovascular events as well as patients who have a high bleeding risk for example, recurrent bleeding despite optimal management of varices.

And for IO therapy the most important contraindications include solid organ transplantation and severe autoimmune diseases that may be life-threatening if reactivated.

So, I’ve mentioned briefly before that at the ESMO meeting three Phase 3 trials were presented that tested new IO combinations or IO monotherapies in HCC. All of these trials were frontline trials, So they were testing these agents in systemic treatment naive patients. And I think it's time now to discuss these studies in more detail.

The first study that was presented was the so-called LEAP-002 study which tested the combination of lenvatinib plus pembrolizumab versus lenvatinib plus placebo, so it was a double-blind study, and it included only, as I mentioned before, systemic treatment naive patients that had well-preserved liver function and a good performance status, and one of the main exclusion criteria was invasion of the main portal vein.

The study was eagerly awaited. The phase 1b trial one looked pretty good that tested this combination, showed a response rate of almost 50% so high expectations. But unfortunately, the LEAP-002 study was a negative one, as the study failed to reach the pre-specified thresholds for superiority, for both primary endpoints of overall survival and progression free survival. And the certainly unexpected exceptional performance of the lenvatinib plus placebo arm, was probably the main reason for the failure of this trial. Showing a median overall survival that was probably the longest ever recorded for a TKI in HCC.

Maybe you want to present the second study that tested the combination of camrelizumab + rivoceranib and then we may discuss the differences between those trials and possible reasons for the different outcomes of these trials.

Jeroen Dekervel

Thank you. Indeed we saw three Phase 3 trials, and the trial, the late-breaking abstract thirty-five at ESMO was one, testing the combination of a PD-1 Inhibitor camrelizumab with the TKI which formerly was named apatinib, now rivoceranib. A TKI, of which we do not know, I would say, the potency in monotherapy right now in a good large Phase 3 trial. So, it's a little bit of a question mark what this TKI would give, together with a PD-1 inhibitor. Andthe control arm, was the standard of care, again, sorafenib so not lenvatinib like in the LEAP-002 but sorafenib. And again, first line treatment unresectable HCC, so the classic inclusion criteria that we see in all the Phase 3 trials, front-line treatment. Here the invasion of the main portal branch was allowed as an inclusion criteria, and this trial, in fact, was a positive trial, positive in terms of overall survival, the primary endpoint, was clearly longer with the combination of PD-1 rivoceranib compared to sorafenib.

So this is in fact now the only trial that we have that showed a benefit and overall survival frontline combination, PD-1 inhibition and the TKI. So the LEAP-002 was negative, and also the COSMIC-312 which was

presented last year, 2021, which was comparing atezolizumab and cabozantinib, another TKI, versus sorafenib. As you know this trial was positive for its primary endpoint of progression free survival but did not meet superiority in terms of overall survival, the most clinically relevant endpoint. So, this is really something that is new now, a combination of PD-1 inhibition and a TKI. I have to emphasize that this trial was mainly run in Asian countries, and of course this is a very specific population which might differ from the Western population in terms of etiology, for example of HCC which is, of course, more viral. And then also, the second thing I should mention about this trial is the safety data. Always interesting if you combine a immunotherapy with a TKI, the TKI of which we expect might be a little bit more toxic than a VEGF antibody. And indeed, here also we saw in the interventional arm we saw quite a high number of grade 3-4 adverse events. So, this is really something we have to look into more deeply, especially as apatinib or rivoceranib, this TKI is a little bit less well known in the community.

Matthias Pinter

Yeah. So, you mentioned that there were some differences between both trials. One of the main differences was probably the fact that the camrelizumab/rivoceranib trial mainly recruited patients from Asian countries, while the LEAP-002 trial was well-balanced in terms of geographical distribution of patients.

So that was one of the main differences but there were several other ones. We have mentioned that the inclusion and exclusion criteria are somewhat different. When we look at the study design, the LEAP-002 was a double-blind study, while camrelizumab/rivoceranib was an open label trial. So that may explain a very low rate of consent withdrawals in the lenvatinib/placebo arm of the LEAP-002 study compared to the relatively high rate in the sorafenib arm of the camrelizumab/rivoceranib trial. So that was one of the differences between both studies, and certainly the geographical distribution of patients. You mentioned that Asian patients mainly suffer from viral underlying liver disease etiologies, especially hepatitis B is very common in Asian countries. And we know from this trial, from subgroup analysis of this trial and other Phase 3 trials, that, especially the HBV population seems to benefit from IO therapy. That is also supported by the fact that pembrolizumab in second line failed in the global Phase 3 trial, but not in the Asian trial.

And the Chinese subgroup of the IMbrave150 trial also showed better outcomes than the overall cohort.

So, it seems that the Asian population does somewhat better, and that may have something to do with the underlying liver disease etiology. But that certainly deserves further research.

What we also have to acknowledge here is, however, that the IO arms in the LEAP-002 trial and the camrelizumab/rivoceranib trial showed quite similar outcomes in terms of efficacy, only the control arm performed different. And therefore again, I believe that the main reason for the failure of the LEAP-002 Trial was the outstanding performance of the lenvatinib control arm. What is your take on that?

Jeroen Dekervel

Of course it's unfortunate that's a negative trial, in the LEAP-002 we had put our hopes to it, to have an extra option first line, but I still think we can learn a lot from negative trials. It's indeed the case that the fact that the trial will be positive or negative, it does not depend only on the efficacy of the drug or the drug combination, there’s so much more that plays a role here. It's the inclusion criteria, so the population in the trial, it’s the control arm, the choice of the control arm, it's the statistical design, so here with the LEAP-002 with the co-primary endpoint. It's also the post protocol treatment, and if you look at the LEAP-002 trial of course the question is, the lenvatinib arm performed extraordinarily well, but why was that the case? It’s something that we also see, maybe to a lesser extent, although not really, in the control arms with sorafenib, as you know, back in the days the SHARP trial showed a modest improvement in overall survival with sorafenib. But if you look at the performance of the sorafenib control arm in all those Phase 3 trials where sorafenib was control, and you can see that at least a fifty percent increase in overall survival has been noted also with sorafenib. So this is not new, with lenvatinib we have seen, it's a little bit less, but of course this is due to the fact that lenvatinib was not frequently used as control arm in Phase 3 trials. So the difference is shocking almost in comparison with the REFLECT trial. But it might be not so surprising if we look at the evolution that sorafenib has gone through.

Also we have to look at post progression treatment. And there we see, of course, that about fifty percent of patients, about half of patients in the

lenvatinib arm of the LEAP-002 got another treatment. And about one in four got, in fact, immunotherapy as a second line. But these numbers compare very well to the IMbrave trial for example. And so it's not really that easy to just put it all on to the fact that this was a sequencing trial where lenvatinib in the control arm was used in first line for those patients, and then they got immunotherapy in the second line. No this is not the case for all the patients and does not explain all the differences, but it might contribute.

And then the question is, yes, what is the ideal partner for immunotherapy? We always thought that TKIs would be better in partnering with immunotherapy because they have more mechanisms of action, they're not only inhibiting VEGF receptor, but they also inhibit other kinases, and of course the toxicity profile is a downside of that. But we thought maybe this might also increase the potency of immunotherapy.

But maybe we have to come back a little bit from that. We have now two trials that show a very nice survival benefit with bevacizumab. It's the IMbrave150 but let's not forget the ORIENT-32 trial which was also a combination of PD-1 inhibition sintilimab with bevacizumab biosimilar, and also there we saw that the same effect, so anti-VEGF antibody seems to synergise, we're not sure yet but it seems to synergise, maybe a little bit more than certain TKIs. So this is also something that we need to take into account, and we need further pre-clinical and translational research.

And then I talked about the trial design. The co-primary endpoint here in the LEAP-002, of course you have to split the alpha, as we say, statistically, that means that, of course, the threshold to be statistically significant is higher for both endpoints overall survival and progression free survival. And this also might, of course, contribute to the statistical result of this trial, which was, in fact negative.

Matthias Pinter

So what we've learned over the last couple of months is that it seems that it is the combination treatment that is effective in HCC, it's the combination of IO therapy, and especially anti-VGF treatments. We have now a couple of positive Phase 3 trials. You mentioned IMbrave150, the ORIENT-32 trial and now the camrelizumab/rivoceranib trial. So we have three Phase 3 trials that showed improvements versus TKIs for these

combinations, while – you mentioned in the beginning – PD-(L)1 targeted monotherapy was not that impressive in Phase 3 trials in HCC so far, even though a proportion of patient still responds and shows very good long-term outcomes with PD-1 monotherapy.

Now at ESMO a third Phase 3 trial was presented, the RATIONALE-301 trial which tested another PD-1 monotherapy versus sorafenib as a first line treatment and compared tislelizumab versus sorafenib in systemic treatment naive patients with advanced HCC.

And tislelizumab finally demonstrated non-inferiority regarding OS versus sorafenib but it did not meet the criteria for superiority. Regarding other secondary endpoints like response rate and adverse events, tislelizumab showed similar overall response rates and toxicity profiles that were reported for other PD-L1 targeted monotherapies in HCC so far.

However, and that is something that is important here, similarly to the camrelizumab/rivoceranib trial, the majority of patients again came from Asia and Japan, and only around one forth came from the EU and US, and that certainly limits, in my opinion, the generalisability of the results. How do you interpret this new data on another PD-L1 targeted monotherapy?

Jeroen Dekervel

It's interesting to have confirmation, but it is as it is. I think it’s confirmation of what we already knew. There is, indeed, that signal of efficacy of this monotherapy in HCC. But it's not large enough to result really in a superiority in terms of overall survival in frontline. Durvalumab also showed its non-inferiority in the HIMALAYA trial, so of the monotherapy with PD-L1 inhibition, and now the trial with tislelizumab, the RATIONALE-301, confirms in fact, this finding. And for me it's really puzzling. I really struggle, Matthias, to find a good place, a good patient profile to match with these monotherapies, because, of course, we have atezolizumab bevacizumab, which is a monotherapy, well, it's a combination, but of course, one type of checkpoint inhibitor. And there, of course, this combination is contraindicated mostly for the bevacizumab toxicity.

And then, on the other hand, you have the STRIDE regimen, the combination of durvalumab tremelimumab, where, of course, patients

with autoimmunity are a little bit more at risk for side effects. So, I have two very good options with superiority. I don't really have a patient in mind right now that I think this would be really a good candidate for monotherapy. Because probably if they cannot get the durvalumab tremelimumab combination they can get the atezolizumab bevacizumab combination and the other way around. So, there I struggle still a little bit. I think these data are very good to know, and especially in the future if we would be able to really select those patients based on biomarkers that have these excellent outcomes with monotherapy PD-1 or PD-L1 inhibition. Well, of course, this data will come in hand. We will know a lot about the efficacy and toxicity from these trials, and we can use maybe a lesser intense regimen.

Matthias Pinter

Yeah, I couldn't agree more. I don't see a major role for PD-1 targeted monotherapy in frontline, because, as you mentioned, we have combination treatments that have shown higher efficacy. They have shown a superiority versus control arm. So, I don't see a large impact of these PD-1 monotherapies in frontline as well.

Now, with these new treatments, with this new Phase 3 trials that have been presented at ESMO we have to discuss how we should integrate all those new treatments in the treatment algorithm of HCC. I mentioned before there was a discussion and a presentation at ILCA where these new treatments were integrated in the treatment algorithm.

Certainly the LEAP-002 study, which was a negative study won't change clinical practice. But I think what the study demonstrated is that lenvatinib is very active, and probably the TKI with the highest activity in HCC. But again, I do not see a significant role for the combination treatment in HCC.

Now, what do you think about the camrelizumab/rivoceranib trial? Do you think that is something that will become a main first line option? Probably in Asia right? But do you think it will become a main option in Western countries?

Jeroen Dekervel

I think it's a potent combination, but I think the trial was not designed in that way that it will lead to approval here, for example, in Europe. We'll have to see. And of course, I have a little bit of questions about the tolerability of the regimen. I don't know it, so it's difficult to estimate that. But of course, if you have a combination like atezolizumab bevacizumab with very similar profile in terms of patients that are legible, then of course, this toxicity also should be kept in mind.

Matthias Pinter

Right. I agree. So less than twenty percent of the patients came from non-Asian countries. That is a limitation of this study, and you mentioned toxicity, that was also quite high. And given that we have atezolizumab/bevacizumab, which is equally effective, but has less toxicity, or at least – it's always hard to do these cross-study comparisons – but still I think the tolerability of atezolizumab/bevacizumab is better.

Therefore, I think it may become a standard treatment in Asian countries in first line but I don't see a main role for this combination in Western countries.

Jeroen Dekervel

And so you see that indeed the management of HCC which was already quite different in the West compared to the East will maybe further drift apart. And so you also have, for example, the hepatic arterial infusion. We did not talk about that but they have a huge experience on that in, for example, China and very nice results. And this is something in the West we do not use. So yeah, it's really a trend that we're seeing right now. Different patient population and also different treatment algorithm, East versus West.

Matthias Pinter

That's right. We have discussed that but just to mention it again. Tislelizumab as well mainly included patients from Asian countries. So I also do not see a main role for this treatment in Western countries, especially since we have durvalumab which showed non-inferiority

versus sorafenib in the HIMALAYA trial, and this study was better balanced in terms of geographical distribution of the patients included.

Jeroen Dekervel

So the question now Matthias is a little bit for the future. How do we continue? What are the next steps to do in this very, very innovative field that HCC is? What do you think? Where should our focus be right now?

Matthias Pinter

Well, I think when we look at phase 3 trials that are currently ongoing, we will have to adopt immunotherapy, probably in earlier stages of the disease, in early-stage HCC as an adjuvant treatment after resection and local ablation. There are a couple of studies investigating this approach and hopefully, we have data from Phase 3 trials within the next few months.

And the other group that may benefit from immunotherapies is the intermediate stage where TACE is the standard of care. But we have had studies, phase 3 trials that tested the combination of TACE plus systemic therapy. But these trials, most of them were negative. We had some interesting studies, like the TACTICS trial that defined progression a bit differently, and this trial indeed showed an improvement in progression free survival but failed to show superiority in terms of overall survival. So, there is some signs of efficacy for the combination of TACE plus systemic therapy but currently we do not have any valid phase 3 trials that really support the use of this combination.

There are several Phase 3 trials ongoing that are testing TACE plus IO therapy. And again, hopefully, we will have data soon, because I think that are some interesting combinations that are tested right now. Especially the concept behind combining TACE plus immunotherapy is a very good one, because by inducing tumour necrosis through TACE you have a high antigen load that leads to T-cell priming in the lymph nodes, and with immunotherapy you can enhance this immune response and probably induce higher response rates than with TACE alone, so a good concept. And I think we will have data on IO therapy in this earlier stages soon.

Jeroen Dekervel

Let me just also finish by making a case for the little bit forgotten populations within HCC. I think the first ones are the patients with the Child-Pugh B liver disease, because they're always excluded from the clinical trials, and maybe it's time now with more potent drugs that we specifically design a trial that is directed to those patients to see whether we can also improve their survival, and whether the toxicity, of course, is acceptable. I know we have some real-world data that’s very nice, but we do not have any prospective randomised data, and this is, I think, an unmet need.

And the second is, of course, right now we are seeing a benefit, I think, in forty to fifty percent of HCC patients treated with immunotherapy combinations. About twenty/twenty-five percent have a response and some more have a quite durable stable disease. But then there's still this very significant proportion of patients that are currently underserved with the combinations and we urgently need new strategies, of course new targets and new mechanisms to target their disease as well. So I think this is really something for the future.

Matthias Pinter

Thank you Jeroen. Now it is time to close this discussion. I really enjoyed our conversation. On behalf of HCC CONNECT I want to thank you all for listening. Bye bye.

Jeroen Dekervel

Thank you and bye.