Video Title: <u>HCC treatment algorithm with systemic therapy based on the recently updated HCC guidelines</u>

<u>Supported with accompanying Infographic</u>

<u>Brought to you by:</u>
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Mahir Karababa (Moderator, Scientific Lead at COR2ED)
Welcome to the HCC CONNECT newsletter. Thank you for joining us. Today, we do have the privilege to be joined by two experts from the HCC CONNECT group. Professor Ruth He, medical oncologist at Georgetown University School of Medicine in the USA. Welcome, professor He.

Ruth He
Thank you for inviting me. It's a pleasure to be on the panel.

Mahir Karababa
Thank you.
And Professor Matthias Pinter, Medical hepatologist at Medical University of Vienna in Austria. Welcome, Professor Pinter.

Matthias Pinter
Hello everyone. I'm happy to be here today.

Mahir Karababa
Thank you. In this educational program, we are going to get insights from Professor He and Professor Pinter on the revised HCC guidelines and discuss mainly how to select systemic therapy options for advanced or unresectable HCC patients. Interestingly, we have the chance to confront the view from an oncologist and an hepatologist and get the insight from a US point of view and also a European point of view in this video. As we know today, immunotherapy combination Atezolizumab Bevacizumab is the new standard of care for advanced or unresectable HCC patients based on the IMbrave150 clinical trial results and various international guidelines on HCC have been revised accordingly in late 2020 and in 2021, such as NCCN, ASCO, ESMO, ILCA, AASLD, EASL.

It is worth to highlight that regarding the sequencing treatments so far, sorafenib in first line followed by regorafenib or cabozantinib, or ramucirumab as a second line remain, as well a standard of care because it's based on clinical trial results.
Most of the HCC International guidelines reflect the change in first line with the immunotherapy combination options and provide further guidance on first line with sorafenib and lenvatinib being now option treatment in first line setting when Atezo+ bev is not suitable. After progression with atezolizumab +bevacizumab, it seems that all the previous first line and second line systemic therapy could be proposed, according to the revised guidelines. However, we do believe that there is a need to define how to select the best systemic therapy treatment option based on the clinical characteristics of the patients and we would like to take the opportunity today to give some guidance to the audience on this matter. Professor Ruth He, I would like to start with you. What do we think about this statement that I just gave?

Ruth He
I agree with you. Now, with multiple approved treatment options and we have a lot of choice, we can pick different therapies for patients with advanced stage HCC. I think we want to also pick the right therapy for patients. And in the U.S., a lot of us follow NCCN guidelines, which is a National Comprehensive Cancer Network guideline, and there is also a new guideline from SITC: Society of Immunotherapy of Cancer that provides a lot of detailed information about immunotherapy for HCC. there are a lot of data on sorafenib, lenvatinib, it is very important to understand how to select the treatment for patients.

Mahir Karababa
Thank you, professor He, Professor Pinter. May I ask you the same question what do you think and which guidelines basically are you also following in your site?

Matthias Pinter
Yes. Well, I agree with your statement. So basically atezolizumab + bevacizumab is the new reference standard based on the IMbrave150 trial. That was actually a milestone with an improvement of almost six months in terms of overall survival compared to the previous standard of care sorafenib. So that is pretty clear. But what is less clear is treatment sequencing after first line atezolizumab + bevacizumab since we do not have data yet.

So current recommendations are not really based on evidence but rather on expert opinion, and both the EASL and ESMO guidelines. These are the guidelines that most Europeans probably follow. They recommend, as you said, the use of one of the approved TKI or ramucirumab as per off-label availability after atezolizumab + bevacizumab rather than sticking to a certain hierarchy.

Mahir Karababa
I see. Okay, great. Thank you, Professor Pinter. So just to start on this specific topic about the guidelines and the criteria. As a general question, which criteria will you take into consideration to select, let's say, the first line treatment option?

Professor He can I start with you? What would be your global approach and your global criteria that you would like to share with the audience today?

Ruth He
I think overall survival is always the most important endpoint. So, I would select a therapy for a patient based on the longest survival it can achieve, then followed by quality of life, followed by side effect profile.

Mahir Karababa
Thank you. Professor Pinter what would be your view as a hepatologist and from a European side?

Matthias Pinter
Yes, so I agree. I agree with Ruth. So that is basically what I look for when I decide whether to use this or another treatment, it's basically overall survival, that's the most important primary endpoint here. But other endpoints are also very important and that is safety of course, and quality of life is becoming more and more important in these trials. So that is also something that needs to be looked at.

Mahir Karababa
Great. Thank you. Thanks for your insights. I would like really now to start asking both of you if we do have HCC patients that are not suitable for the current standard of care as the first line setting, which is atezolizumab + bevacizumab. How would you select between the two available TKIs and approved TKIs: sorafenib and lenvatinib? Can I ask you, Professor He what will be your first, let's say criteria that you will look for to select between these two treatments for your patients that are not suitable for atezolizumab + bevacizumab?

Ruth He
If the HCC patient is not a candidate for bevacizumab and atezolizumab, Either Sorafenib or Lenvatinib will be selected to be the 1st line therapy. Look at the data from the REFLECT trial, lenvatinib is non-inferior to sorafenib on prolongation of overall survival in HCC patients. But if you look at the secondary endpoint of the study and the response rate of lenvatinib treatment is higher, at 44% per mRECIST, with doubled progression free survival in comparison to that of sorafenib treatment. If we are looking for a response to decrease the tumour-related symptoms, then I would select the one that has a higher response rate: lenvatinib. Then I would look at the safety profile to figure out which TKI would fit the patient.

Matthias Pinter
Let me just mention here, because I think it's important that we talk about those patients who are actually not eligible for atezolizumab + bevacizumab. And that is, I would say, it's around 10 to 20% of all HCC patients considered for systemic treatment. And these are mainly patients with a history of organ transplantation, mainly patients with recurrent HCC after liver transplantation. These are patients with severe autoimmune disease or also patients with a high and difficult to manage bleeding risk. So, for these patients, we would still prefer TKI over atezolizumab + bevacizumab apparently.
So regarding your question when choosing between sorafenib or lenvatinib in first line, as Ruth said, we have to look at the patient's comorbidities and we also have to look at the tumour characteristics. As Ruth mentioned, I would agree that in patients with a very high

tumour load, I would prefer lenvatinib because the likelihood of achieving a tumour shrinkage is really greater than with sorafenib. And lenvatinib also seems to work better in patients with extra hepatic metastases or a vascular invasion or high AFP at least when we look at the subgroup analysis from the REFLECT trial. On the other hand, sorafenib may be a better choice in patients with liver limited disease or HCV-related HCC. In patients with severe arterial hypertension, I may prefer sorafenib because hypertension is one of the most common side effects of lenvatinib. So basically, as Ruth said, we have to consider several factors that is comorbidities, that is the adverse event profile, and that is the tumour characteristics.

Mahir Karababa
Thank you. To summarize both of your view, so the efficacy is a critical, of course, criteria when you select your treatment, but obviously what will be the key element will be the comorbidity and the safety profile.

So, the clinical characteristics of your patients will be a key factor to select between lenvatinib and sorafenib. Based on, as you said, as you stated, Professor Pinter, hypertension without which is a known adverse common adverse event in the REFLECT trial, for example. And if I now think about the other criteria, is there other information that we can share with the audience to give them some guidance about this 20% of HCC patients that are not suitable for atezolizumab + bevacizumab?

Do you foresee any other criteria that you would use, like the preservation of the liver function? Are you looking at the ECOG performance status as well? Can you please elaborate a little bit more on that? May I ask you, Professor He, to start and give your view?

Ruth He
Yes. in patients with liver cancer, we always try to get a Child-Pugh score to evaluate the patient's liver reserve. Child-Pugh score is calculated based on three laboratory tests and two physical examinations. The three laboratory tests are albumin, bilirubin, and coagulation factors. The two physical examinations are ascites and encephalopathy. Child-Pugh score is strongly correlated with the survival of patients: patients with Child Pugh A score tend to do much better with longer survival. Patients with Child Pugh B score tend to do worse with shorter survival, while patients with Child Pugh C score have terminal liver dysfunction and limited survival. Child-Pugh A status is one of the inclusion criteria for most clinical trials. So, most treatments are approved for patients with Child Pugh A liver function. The GIDEON study had evaluated sorafenib in patients with Child Pugh B liver function. If a patient has moderately impaired liver function, I would select sorafenib, the one with more safety data in that patient group.

Mahir Karababa
Thank you. Professor Pinter, what is your view regarding the liver and the Child-Pugh scoring?

Matthias Pinter
So, I basically agree, so we have more safety data for sorafenib since it has been around for a little bit longer than lenvatinib. So, we know that it is also kind of safe in patients with

more advanced liver dysfunction. But I think it also depends on the cause of liver function impairment because if you have a severely impaired liver function because of advanced liver cirrhosis, the patient may not benefit from any treatment because not the tumour is the main problem here, but the advanced liver cirrhosis. On the other hand, if you have a liver function impairment due to a huge tumour load, I still would prefer lenvatinib may be in this setting because as we mentioned before, the likelihood of achieving a tumour shrinkage is better with lenvatinib.

So therefore, you might even improve liver function by inducing tumour shrinkage. So, it really depends on the individual patient. And what you also have to consider when talking about choosing lenvatinib or sorafenib, we also have to take into account that we have a very well-established line after first line sorafenib because the available drugs in previous, let's say, second line; ramucirumab, cabozantinib and regorafenib have been tested in sorafenib-pre-treated patients. But we do not have these data for lenvatinib. So, I personally don't believe that pre-treatment with sorafenib is basically a *conditio sine qua none* for ramucirumab, cabozantinib and regorafenib to be effective in HCC. But that could be a problem for reimbursements. Just to give you an example here in Europe, for example, here in Austria, that's where I come from. We have still liberal policies, which means that I can choose whichever treatment I want, as long as it is approved. In contrast, in Germany, they are strict, so they have really to stick to the drug label, which means that they actually can basically only choose ramucirumab, regorafenib or cabozantinib if they use sorafenib before.

Mahir Karababa
Can we state that because, as you said, we do have those clinical data, after patient pre-treated with sorafenib, with regorafenib, ramucirumab and cabozantinib, can we give at least this advice to our audience that this is the standard of care, and this is where we do have clinical data evidence? And if they are using sorafenib, most likely the next sequencing step should be with regorafenib or cabozantinib, or ramucirumab. Professor He, would you agree with that?

Ruth He
Yes. I don't think there is much cross-resistance among all the TKIs. I do believe that TKIs will work in different lines of therapy. Since sorafenib was the only approved systemic therapy for ten years, the current second line, third line treatment were tested post sorafenib progression, and post sorafenib treatment is indicated in approved indication. In the U.S., some insurance company will follow the approved indication strictly, 2nd line TKIs are not covered if patients have progressed through bevacizumab and atezolizumab treatment and if patient has not received sorafenib treatment. Most insurances are still relatively flexible of cover the TKI when patient progressed on bevacizumab and atezolizumab, not yet received sorafenib treatment.

Mahir Karababa
Thank you, Professor He. So, I do believe that we covered the first line selection for patients that are not suitable for atezolizumab and bevacizumab. I do believe that it's pretty, clear sorafenib lenvatinib selection based on efficacy, safety profile, knowing the common, the

most common adverse event and, also knowing which populations have been excluded from the REFLECT trial and the SHARP trial are also important criteria to take into account. So, let's move then to the key points. If a patient is eligible for atezolizumab bevacizumab as a first line, which, as you said, Professor Pinter, which would correspond around 80% of the HCC population. What will be your second line choice after progression? Professor Pinter, may I ask you first?

Matthias Pinter
In Vienna, we use sorafenib or lenvatinib as a second line treatment basically, and regorafenib, cabozantinib or ramucirumab in third line. So basically, the previous first line agents moved to second line and former second line agents moved to third line. But that is not really based on high level evidence. It's just a personal choice.

Mahir Karababa
OK, Professor He, do you have any view on that? What would you suggest or do after progression with atezolizumab bevacizumab as a second line?

Ruth He
I agree with Prof. Pinter. In addition, I also look at how long this patient has responded to bevacizumab + atezolizumab. And if they rapidly progressed on, then I would consider a TKI because those patients may have refractory disease to immunotherapy combination or immunotherapy. But if this patient had a very prolonged response to bevacizumab and atezolizumab, when patient later developed resistance, I would consider another immunotherapy combination. In the US, we have nivolumab + ipilimumab approved based on the Checkmate 040 study. If a patient has showed primary resistance to immunotherapy, for sure, I will consider another TKI. Usually, I will go and shift to the frontline TKI sorafenib or lenvatinib. And then followed by other TKIs.

Mahir Karababa
Thank you. Thank you, Professor He. I think it's a really, interesting point, this immunotherapy approach. And Professor Pinter, do you have any comment?

Matthias Pinter
Yes, I actually agree that this is a good approach. And you're lucky in the United States that you have another immunotherapy-based combination approved, we don't have that. So, our only immunotherapy-based regimen is atezolizumab + bevacizumab. We also didn't have nivolumab and pembrolizumab approved here in Europe in second line. It’s because, clearly the phase 3 trial data were negative. So, we don't have any immunotherapeutic options in second line available.

Mahir Karababa
Thank you, Professor Pinter. So, I can understand from both of you that after atezolizumab + bevacizumab, you are basically using the previous first line options becoming second line and the second line in the past becoming the third line.

I just would like to ask you as a last question regarding the sequencing is that do you see a place for the current second line, I'm talking about regorafenib, ramucirumab, cabozantinib? Do you think are they eligible as a second line after atezolizumab and bevacizumab? and if yes, which condition and why. Professor He can I start with you on this question?

Ruth He

Although there is no randomized phase III data evaluating these TKIs post bevacizumab and atezolizumab progression, Regorafenib, ramucirumab, cabozantinib can be used as 2nd line post bevacizumab and atezolizumab treatment for the following reasons: (1) the activities of TKI may be independent to the resistance to immunotherapy, therefore these TKIs likely provide benefit to patients who progressed on bevacizumab and atezolizumab, (2) no 2nd line therapy has been evaluated in patients who progressed on bevacizumab and atezolizumab treatment.

Mahir Karababa

Thank you. Professor Pinter?

Matthias Pinter

Yes. Well, I think you can do that. You can use these agents without having them treated with sorafenib before.

And, as I said before, I don't think it's a *conditio sine qua none* for these drugs to be effective in HCC. So, I think you can do that, and I think that is what most experts actually believe as well, because when you look at the guidelines, especially the ESMO guidelines, they allow the use of these agents even if patients haven't been treated with sorafenib before. So, I would consider that. But you know, and as I said before, we usually use lenvatinib and sorafenib, not because there is a lot of evidence here, but you know, you have to develop a certain strategy, a certain guidance for your institution, and that is just our approach.

Mahir Karababa

Thanks a lot. I think we covered most of the sequencing approaches and how to select the patients: what is the treatment option for the patients that are not eligible for atezolizumab bevacizumab. And we also cover now those patients that that are treated with atezolizumab and bevacizumab and understand what would be your sequencing strategy. So I would like just to finish this video by asking you what is your, let's say, take-home message you would like to share to the audience regarding all the revised guidelines and regarding all the data we have now and the treatment option we have on systemic therapy. Can I ask you first, professor He, to give us your take home message to the audience on that aspect?

Ruth He

Additional immune therapy combinations are being evaluated in HCC treatment. So, keep an eye on new approval and change of guidelines on HCC treatment. Secondly, HCC is a disease that requires the collaboration of multiple specialties. Thirdly, HCC patients are fighting two diseases: cancer and liver dysfunction, so aggressive treatment of liver disease will enable patient to receive more lines of systemic therapy So they can have better survival and outcome.

Mahir Karababa
Thank you, Professor He. Professor Pinter?

Matthias Pinter
So, yes, I couldn't agree more. It is a very complex disease, and I think what Ruth said is very important. The management should involve different specialties, mostly surgeons, hepatologists, oncologists, radiologists to manage these patients in a way that they can most benefit. And so basically the take home message from the guidelines is that we have a new reference standard with atezolizumab + bevacizumab. But we also have to keep in mind the main contraindications that I want to again point out here. And that is patients with a history of liver transplantation and patients with severe autoimmune disease. And we also should be aware that bevacizumab has a certain bleeding risk, and all patients should undergo endoscopy before being put on atezolizumab + bevacizumab. And if varices are present, they should be treated either with ligation or medically with beta blockers.

Mahir Karababa
Thank you very much. So, with this last take-home message, I would like to close this video. I wanted to thank Professor He and Professor Pinter for joining us today, for your valuable inputs on this discussion.

And for the audience, I also would like to inform them that infographic will be presented summarizing the discussion we had for the different type of HCC patient population. And with that, I want to thank and appreciate your time today.

Thank you very much and have a nice day.