Podcast Episode Title: Highlights from ILCA and ESMO 2021 in HCC

Brought to you by; Prof. Matthias Pinter MD, PhD. Division of Gastroenterology & Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

Please note:
HCC CONNECT podcasts are designed to be heard. If you are able, we encourage you to listen to the audio, which includes emotion and emphasis that is not so easily understood from the words on the page. Transcripts are edited for readability. Please check the corresponding audio before quoting in print.

This HCC CONNECT programme is supported through an independent educational grant from Bayer.

The views expressed within this podcast are the personal opinions of the authors. They do not necessarily represent the views of the author's academic institution, or the rest of the HCC CONNECT group.

Mahir Karababa (Moderator, Scientific Lead at COR2ED)

Welcome to the HCC CONNECT podcast, thank you for joining us. Today, we do have the privilege to be joined by Professor Matthias Pinter, medical hepatologist from the medical University of Vienna in Austria. Welcome Dr Pinter.

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

Mahir Karababa
In this episode Professor Pinter will share some insights from key abstracts and topics discussed at ILCA 2021 and ESMO 2021 in hepatocellular carcinoma. Professor Pinter, first of all, from your point of view, what were the key topics covered during these two virtual congresses this year on HCC?

Matthias Pinter
Well at ILCA, the main topics included discussions about treatment options in first-line systemic therapy since we have a new standard of care with an immunotherapy-based regimen. But there are still some patients who may receive a TKI in first-line instead.

And in this regard, we heard real world data on TKI's from HCC patients usually excluded from clinical trials, such as patients with impaired liver function, for example.
And finally, another important question was how to proceed with immunotherapy in HCC, in particular the rationale for triplet immunotherapy combination was discussed.

And at ESMO there were data presented on atezolizumab and bevacizumab, the new reference standards of care in systemic front-line HCC treatment and another interesting

topic was the combination of TACE with immune checkpoint blockade in intermediate stage HCC.

Mahir Karababa
Which data related to the systemic therapy, would you consider the most interesting in advanced HCC in the first-line setting?

Matthias Pinter
Well, there were two studies discussed at ESMO on the combination of atezolizumab plus bevacizumab. Doctor Kudo presented updated efficacy and safety data on patients without macrovascular invasion and extrahepatic metastasis from the IMbrave150 study and they reported similar safety and relative OS benefits compared to the intention to treat cohort, while the survival in absolute numbers was longer in these less advanced tumours.

And a study from Korea reported real world data on atezolizumab plus bevacizumab in around 120 patients with HCC in Child-Pugh class A. The efficacy and safety in their cohort were comparable with the results from the IMbrave150 phase 3 trial. So, this data further support the efficacy and safety atezolizumab and bevacizumab, in front-line HCC.

However, only a subset of patients achieves prolonged response from this combination therapy and therefore further improvements are necessary, and this could be triplet ICI based combination therapy.
At ILCA, Dr Kelly discussed the rationale for triplet combination therapy, which is either to augment or prolong response by targeting primary and acquired mechanisms of resistance called synergy or actually to achieve an additive benefit by targeting independent pathways to increase the chance of an anti tumour effect.

Several ongoing phase 1 and 2 trials are currently testing triple combination in HCC and one important question in this regard is whether to use all agents, at the same time or sequentially.

Mahir Karababa
Thank you, Professor Pinter. So we know that the immunotherapy combination with atezolizumab and bevacizumab is now the standard of care. But is there still a role for the monotherapy TKI in first-line setting?

Matthias Pinter
Well, not all patients can receive atezolizumab plus bevacizumab due to contraindications, and this was discussed in another session at ILCA. So around 15 to 20% of HCC patients are not ideal candidates for atezolizumab and bevacizumab, and these are mainly patients with HCC recurrence after liver transplantations, patients with severe autoimmune disease, or those with a high bleeding risk. Therefore, these patients should still receive a TKI in first-line.
And during this session, they discussed recent real-world evidence on lenvatinib from two retrospective cohorts: one from the United States and one from Japan. In contrast to the REFLECT trial, these cohorts included Child-Pugh B and even some Child-Pugh C patients, and also patients who received lenvatinib in further lines, meaning in second or third line.

The main takeaways from this data were higher response rates, even in Child-Pugh B patients in the safety profile, similar to that of that REFLECT trial. However, they also pointed out that it may be safer to start cautiously in Child-Pugh B patients, probably with a lower dose and monitor these patients more closely. They also concluded during this session that TKIs work best in patients with very well-preserved liver function and highlighted the importance of switching from local-regional, to systemic therapy when liver function is still preserved.

In another session at ILCA, real world data on sorafenib and regorafenib in special populations that are usually excluded from clinical trials were discussed. The main takeaways from this session were that sorafenib, in the sequence sorafenib, regorafenib were safe and effective in patients with HCC recurrence of the liver transplantation. They also reviewed data on Child-Pugh B patients from real world observational studies. The main conclusions here were that sorafenib was safe, even though Child-Pugh B patients had a shorter survival compared to Child-Pugh A patients by nature.

They also discussed the higher bleeding risk with atezolizumab and bevacizumab, the importance of endoscopic evaluation prior to treatment start, and they suggested to use alternative treatments in patients with high-risk of bleeding when prophylactic bleeding management is difficult. Another issue is the missing prospective data on second-line treatment after first-line immunotherapy. And in this regard, they discussed retrospective real-world data on regorafenib after I/O therapy, showing no new safety signals, and a similar benefit compared with patients who had no prior I/O exposure suggesting basically that regorafenib is a valuable option in this setting.

Finally, a bit of topic, as it concerns the second-line setting. Dr Kudo presented updated results from the REFINE trial at ILCA, a phase 4 observational study on regorafenib in real-world. In over 1000 patients they actually confirmed the safety and efficacy data of regorafenib from the RESORCE trial. But compared to the phase 3 trial, the REFINE included a much broader patient population, for example, they included patients with more advanced liver function impairment, or patients with an ECOG performance status of two or higher.

So thereby, they basically confirmed that regorafenib was not only safe and effective within a very selected clinical trial population, but also in the real-life setting.

Mahir Karababa
Predictive and prognostic biomarkers are critical, as we know. So were there any promising investigations presented in that field in these two virtual congresses?

Matthias Pinter
Well, regarding biomarkers and prognostic factors, there were several abstracts presented at ESMO and ILCA. Let's start with ILCA; Doctor Rich investigated the prevalence of cachexia in HCC patients in a retrospective cohort study of around 600 patients with HCC across all BCLC stages. They found cachexia in more than 20% of the patients, with higher prevalence

in more advanced tumour stages and, interestingly, these patients were less likely to receive HCC treatment and they had a worse survival.

Another interesting study was presented by Dr Zeng at ILCA. The study focused on immune profiling of resected HCCs using deep-learning on histological slides, where deep-learning actually predicted the activation of 6 gene signatures related to response to immunotherapy and survival. And another abstract from ESMO reported that a deep-learning model was able to predict relapse-free survival and again from histological slides, in patients who underwent a liver transplantation for HCC. So these studies highlight the potential of artificial intelligence which may become a very useful tool in the near future.

Another study discussed at ESMO retrospectively investigated AFP in over 500 patients treated with the TKI regorafenib. They identified baseline AFP equal or above 400 as well as an AFP decrease of 20% during treatment, as independent prognostic factors for OS and progression-free survival. And this again highlights AFP being a surrogate marker for more aggressive tumour biology and an important prognostic factor in HCC.

Finally, I want to share data from a retrospective multicentre study of HCC patients treated with immune checkpoint blockers presented by David Pinato at ILCA. They showed that treatment related adverse events of grade 2 or higher were associated with improved response and survival. And these data were also confirmed in an independent FDA clinical trial data set. So, this data can help in patient counselling, in particular, they can help to motivate patients to stay on treatment, despite experiencing some adverse events.

Mahir Karababa
Thank you so much, Professor Pinter. Is there anything else you would like to share with us in the field of HCC?

Matthias Pinter
Well, there are three more studies that I want to mention here.

The first one was presented by Dr Nault at ILCA. They retrospectively compared multibipolar radiofrequency ablation and liver resection in a large cohort of HCC patients within the Milan criteria. They found that multibipolar radiofrequency ablation was associated with a similar oncological outcome in tumours smaller than three centimetres, but not in tumours larger than three centimetres. However, radiofrequency ablation was associated with less morbidity and based on these data they propose the treatment algorithm for singular as well as multi-focal tumours which could be quite helpful in clinical practice.

Dr Haber presented data from a systematic review and meta-analysis of randomised control trials, showing that immunotherapy is more effective in patients with viral etiology than in patients suffering from non-viral liver diseases. So, there's growing evidence suggesting that the underlying etiology may affect the efficacy of immunotherapy and thus it may be important to use disease etiology as a stratification factor in future immunotherapy trials.

And finally, Dr Vogel presented data from a phase 2 study, including 49 patients with intermediate stage HCC who were treated with TACE, in combination with nivolumab, with

an objective response rate of around 70%, the study finally met its primary endpoint and the authors concluded that the results support further evaluation of this combination in HCC.

Mahir Karababa
What is the impact of all the data we discussed on clinical practice, is there anything we need to change when treating patients with HCC?

Matthias Pinter
Well, overall, there were no data presented at these meetings that will ultimately change current guidelines, but still there was important information that may be valuable to help physicians in daily clinical decision making.

Mahir Karababa
I wanted to thank Professor Matthias Pinter for joining us today for his valuable inputs and we appreciate your listening, thank you very much.

Matthias Pinter
Thank you very much, I hope you enjoyed the podcast.