Podcast Episode Title: <u>Key topics in HCC discussed at ASCO GI & EASL liver cancer summit 2022</u>

<u>Brought to you by:</u> Prof James Harding Gastrointestinal Oncology Service Department of Medicine Memorial Sloan Kettering Cancer Centre, New York, USA

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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 James Harding, Gastrointestinal Oncologist at Memorial Sloan Kettering Cancer Centre in the USA. Welcome Professor Harding.

James Harding

Thank you so much for having me.

Mahir Karababa

Thank you. In this episode, we are going to get insights from Professor Harding on the key abstracts and topic discussed at ASCO GI 2022 and EASL liver cancer summit 2022 in hepatocellular carcinoma.

So, first of all, from your point of view, Professor Harding, what were the key topics covered during these two congresses held this year on HCC.

James Harding

I have to say it was a very important year for ASCO GI in that we saw really wonderful data, continuing again focusing on treatment of advanced hepatocellular carcinoma.

I think the big study that everyone was anticipating and important to hear was the HIMALAYA study which evaluated dual immune checkpoint blockade inhibition in advanced HCC.

We also saw several other important studies at the meeting, highlighting two that evaluated various immune therapy combinations with tyrosine kinase inhibitors, namely the RENOBATE study and the GOING study.

At follow up meetings, we also had an excellent presentation by a colleague detailing how we should be sequencing these treatments, and this is what we'll try to cover today.

Mahir Karababa

Thank you, Professor Harding, so now I would like to ask you why did you select those topics, can you please elaborate more on the importance of those abstracts that you just introduced to us.

James Harding

Sure, so for the HIMALAYA study. This was a large multicentre open-label randomized phase three study of the anti-CTLA-4 antibody tremelimumab with the anti-PD-L1 antibody durvalumab in the frontline setting with patients with unresectable hepatocellular carcinoma.

In the history of clinical trials for I/O and HCC we've seen previously that single agent anti-PD-1 based therapy certainly had anti-tumour activity, but in an unselected patient population wasn't enough to demonstrate superiority over the historic standard of care, the tyrosine kinase inhibitor sorafenib. And so the question that HIMALAYA asked, was can we add a priming dose of an anti-CTLA-4 antibody tremelimumab to durvalumab and when we compare that to sorafenib in the frontline, can we actually improve overall survival. And, importantly the primary endpoint of the study of survival was met and survival was extended in patients receiving this priming dose of tremelimumab with continuous durvalumab versus sorafenib.

This study also found, because it included a durvalumab only arm, that durvalumab was non-inferior to sorafenib, it is not superior to it, but seemed equivalent in survival and hazard ratio. And so, this study really is the first study to demonstrate combination I/O with an anti-CTLA-4 antibody improving survival in this disease. The study was large, it included global enrolment, it's a heterogeneous group of patients that reflects a patient population that we would see in clinical practice restricted, of course, to Child-Pugh A and excluded large vein involvement, but nonetheless showed a favourable safety profile, a modest response rate and, in my opinion, represents another potential standard of care in the frontline setting.

The reason that I chose to discuss RENOBATE was particularly that there is another means of enhancing you know responses and outcome in the frontline and historically we've seen this with the IMbrave150 we're targeting VEGF with an anti-PDL-1/PD-1 antibody led to improved outcomes over sorafenib, so the idea of co-targeting VEGF appears to be important and that represents the other really standard of care at the present time. But a question that yet remains is if we target multiple signalling nodes that are involved in angiogenesis, namely VEGF receptor, platelet derived growth factor and others via multi-targeted tyrosine kinase inhibitors, can we also improve outcomes?

And RENOBATE was a small phase 1/2 study that looked at the combination of these two therapies, namely regorafenib and nivolumab. And as a study demonstrated a reasonable objective response rate of about 30%, a PFS that falls kind of into historic comparison of what we're seeing in ongoing Phase 3 studies right now, between five to seven months. The overall survival for that study was not reached, and so this, along with other data suggests that TKIs and immunotherapy may be important to improve outcomes. And this, you know, leads us to think about the prior studies of lenvatinib with pembrolizumab which also in Phase 1/2 studies have demonstrated promising outcomes and are now being assessed in the randomised Phase 3 study LEAP-02.

And so, this is why I kind of selected this study, although there were many important studies at ASCO, and we could easily talk about many others. This is really with an eye towards the future.

It also allows us to think about data not presented at the meeting, but the COSMIC-312 trial which looked at how does cabozantinib add to anti-PD/PDL-1 therapy and, in that study, we compared cabozantinib to sorafenib to cabozantinib plus atezolizumab. And that study met its primary endpoint of progression free survival, the co-primary endpoint of OS, at its interim was not met, but you know more data is required there. And then the final study that I highlighted was an investigator-initiated study called the GOING trial which looked at the sequence of TKIs starting in

the frontline, namely regorafenib, and then adding to this nivolumab. And this is an important question, because not all patients may receive upfront immunotherapy in the current time and it's unclear what the operating characteristics of immunotherapy are when added to an ongoing TKI. This study's primary objective was really to look at safety, tolerability, feasibility and it appeared, you know, safe and comparable to what we've seen.

Finally, you know, looking at the just the data review at the subsequent meetings, really begs the question of, we've had so much advance in the last you know five to six years in liver cancer, there are so many FDA approved drugs, many positive studies now, how do we position patients for treatment? What do we think about when we need to treat patients with this disease? And, I think for all medical oncologist and hepatologists it really does boil down to two major things. One is quality of life and lengthening of life and then secondarily the amount of tumour shrinkage and disease control, reduction in disease burden. And so, when we evaluate the data clearly in the frontline setting immunotherapy combinations are the standard of care for most patients, whether this is through an IMbrave regimen of atezolizumab plus bevacizumab or a HIMALAYA based regimen of priming tremelimumab with durvalumab. And for those patients who may have a contrindication to immunotherapy we certainly may consider tyrosine kinase inhibitors. And in patients that may not be fit for these but can tolerate I/O, single agent anti-PD-1 or PDL-1 blockade with durvalumab is certainly reasonable.

When we move to the second line there are a number of agents that are certainly approved. And these include cabozantinib, regorafenib, ramucirumab in AFP high patients. But importantly, these were only studied and demonstrated a survival advantage after failure of sorafenib. And so many of my colleagues will still utilise these agents in the second line, some will actually move them to the third line in favor of sorafenib or lenvatinib in the second line, pending you know, failure of an I/O based regimen. And so, you know the field is evolving rapidly, there are many, many new potential therapies and clinical trials will still be of critical importance to determine how do we best sequence these and ultimately how best to treat patients.

I think another complexity to it all is that, as this is a global disease with you know somewhere between 800,000 to 950,000 cases per year, we are seeing large Phase 3 studies happening all over the world. And because of that we're seeing sort of proof that these treatments work in different patient populations. So, for example, not at ASCO GI but certainly recent data of ORIENT-32 which looked at another anti-PD-1/PDL-1 antibody with bevacizumab biosimilar. So, a biologically similar concept to IMbrave150 in an Asian predominantly HBV subset also showed an improvement in overall survival and PFS. So, this study certainly confirms the importance of combination I/O in the frontline setting.

Mahir Karababa

Professor Harding thanks a lot for all these insights. So, I'd like to ask you a last question. In a few words what are you take home messages based on those results presented at these two congresses on HCC?

James Harding

The take home message for me is that the field of HCC is moving very rapidly. We are seeing important advances that are actually going to improve the quality of life and length of life for these patients. There's a tremendous pipeline of new drugs that are coming through and a number of important questions which include the sequencing of treatment, as well as moving these treatments to earlier stages of disease. I do think, to kind of paraphrase from the meeting, we're primed to

make a real difference in the field, and I really do look forward to the next two to five years with the outcomes of ongoing studies and many new novel therapies moving forward.

Mahir Karababa

I wanted to thank Professor James Harding for joining us today, for his valuable inputs and we appreciate your listening, thank you very much.

James Harding

Alright, thank you.