



EASL LCS22 Latest Data in Systemic Therapy for Liver Cancer

TRANSCRIPT

00:05 --> 00:58 Lorenza Rimassa

Hello everyone, my name is Lorenza Rimassa, I'm associate professor of medical oncology at Humanitas University and Humanitas Research Hospital in Milan, Italy. Today I have the pleasure of being here with Jens Marquardt professor of gastroenterology and hepatology at the University of Lubeck in Germany and today we are going to have a discussion about the session entitled Latest Data in Systemic Therapy for Liver Cancer that we had the pleasure to co-chair at the EASL Liver Cancer Summit 2022.

During this session speakers and panelists discussed some of the most relevant and hot topics in the field of systemic therapy for liver cancer, including hepatocellular carcinoma and cholangiocarcinoma. The first talk was on latest data and considerations for treatment sequencing in HCC, given by Maria Reig from the BCLC in Barcelona, Spain. Jens, would you like to comment on what has been presented and discussed on this topic by Maria?

01:19 --> 02:17 Jens Marquardt

Yes, absolutely, and many thanks for introducing me so kindly. I think it was a fantastic session and it gave a lot of food for thoughts for future clinical trial design, but also for the current problems that we are facing in HCC. Maria nicely recapitulated the results of the latest phase 3 trials, including COSMIC-312, HIMALAYA, ORIENT-32, but also KEYNOTE-394, and I think while reviewing all this data, it became apparently clear that currently the standard of care in advance stage HCC is an IO combination and I think that atezolizumab-bevacizumab with an overall survival of 19.2 months can be considered the standard of care, but Lorenza, how would you put this data in context of the latest phase 3 trials?

02:18 --> 02:58 Lorenza Rimassa

Ah, yes, thank you for the question. The point is that now we have and we will have in the near future different treatment options in first line so it will be good for the patient because we have more than one option, but we will have to decide which is the best treatment for each patient and this is really difficult because at least so far we don't have any biomarker to select patients and so it will be difficult to choose between atezolizumab plus bevacizumab or durvalumab plus tremelimumab or maybe also cabozantinib-atezolizumab or even the single agent tyrosine kinase inhibitors like sorafenib and lenvatinib or the single agent IO like durvalumab, based on the HIMALAYA trial.

02:59 --> 03:25 Lorenza Rimassa

So I think that we will have to consider the data we have based on the clinical trials but also not only the efficacy data but also the safety data, the quality of life, we have to consider patient preferences in the clinic, and we needed to generate more data, maybe from real world evidence, and we need to identify biomarkers that in the future will help us select the different treatments. And Maria also presented the updated BCLC staging system. What do you think of this, of the changes they implemented in the staging system?

03:26 --> 04:41 Jens Marquardt

I found this extremely intriguing, and I think in this new update in 2021 they really delineate the current standard of care and the transition from one stage to another. But this new update also indicates that there are selected patients that not necessarily need to be treated according to the old BCLC staging classification. For example, there are patients in the intermediate stage that have very large diffuse HCCs but limited to the liver, but those patients qualify for upfront systemic therapies so you can really select what treatment might be the best choice for your specific patient. And I think one of the key advantages of this new classification is also that it includes really decision-making tools and that it combines the evidence and the daily clinical practice that goes beyond the evidence from clinical trials. And what I found interesting is that she also... and we talked and discussed about patients that are unsuitable for the new first line and also subgroup analysis of Asian patients. What's your take on this aspect?

04:42 → 05:38 Lorenza Rimassa

Yeah, it's another important aspect, for patients who are not suitable for combination therapies, probably we have still to use a tyrosine kinase inhibitor as a single agent in first line. For instance, for patients who have contraindications for immuno oncology drugs due to prior liver transplant or autoimmune disorders or other contraindications. So tyrosine kinase inhibitors will still be used in clinical practice. And for results coming from Asian trials, it's difficult to translate the results from an Asian population to Western population because the patients are different. The etiology of the liver, the chronic liver disease is different: more HBV in Asian patients, more HCV or metabolic syndrome, non viral etiology in Western countries.

05:39 --> 06:30 Lorenza Rimassa

Maybe the prior locoregional treatments are different, so I think it's not so easy to use the data generated in Asian trials in Western patients. But as you mentioned we have a lot of new therapies and new things we have to think of, and to address, to identify the best treatment for our patients. And another important point that Maria addressed... when is the right time to move up from one line of treatment to the subsequent one? Does any progression have the same importance, the same role or do we, can we stay on, for instance first line beyond progression? There are some data also for atezolizumab beyond progression. So what are your thoughts on this aspect?

06:31 --> 07:53 Jens Marquardt

Yeah, I think this was a very intense discussion that we had on this topic during the session and the criteria to select a specific treatment for our patient was one of the key aspects that we were arguing and not even arguing, but recapitulating, and things that we have to consider when we select the patient and when we also select to change our sequence. So safety and response are extremely important, but the the selection or the switch of therapy goes beyond just radiological imaging. We also have to consider different clinical scenarios.

We have to consider the type of progression, we have to consider patient specific aspects including toxicity despite good response and of course also patient decision making and I think the trials that we have in phase 3, they are quite heterogeneous. We have different inclusion and exclusion criteria, probably most prominent portal vein invasion or main trunk portal vein invasion that has been excluded in HIMALAYA, but also in REFLECT trial but not in atezo-bev in IMbrave. And I think this really impacts the head-to-head comparison. What do you think about this?

07:54 → 08:42 Lorenza Rimassa

Yes, I totally agree with you Jens. In fact, if we look at the control arm of these trials and for all these trials the control arm was sorafenib, we can see that the results in the control arms are very different. So the population enrolled, the criteria of these trials were different, and so it's even more different. We all know that we cannot do cross trial comparisons, but we always do in the clinic. But this is a... Looking at the data in the control arm, looking at those data., it's clear that we cannot do cross trial comparisons

because the population enrolled in the different trials are different, we see different response rate, different overall survival, different progression-free survival with sorafenib in different trials.

08:43 --> 09:27 Lorenza Rimassa

So this is another aspect that makes more complex the current treatment scenario and so it's not that easy to select, again, to select one treatment or the other, and so we have to consider all the information we have to try to identify the best treatment for our patients and also for sequencing different treatments, we don't have clear data because we had sequences starting from sorafenib, sorafenib-regorafenib, sorafenib-cabozantinib, or even we have data after lenvatinib. But now if we start with atezolizumab plus bevacizumab, what is your preferred second option?

09:28 --> 09:57 Jens Marquardt

Yes, I completely agree. I think it's very very difficult. I think in daily practice we have no indication that we have to use sorafenib before we use the currently approved second-line therapies but I think in many countries we still have problems to skip sorafenib. This is for example the case in Germany as well. So the approval is based on sorafenib pre-therapy, so I think...

09:58 --> 10:52 Jens Marquardt

the main take of the session is that we now have several options which I think is absolutely fantastic for our patients. And now it's up to us to take the clinical decision and weigh the preferences with the data and see what the individual patient needs to, requires for his tumor. If there is an urge for response, we probably should rely on atezo-bev combination or potentially later on lenva-pembro that has a high objective response rate. But if there are other factors or patient preferences, like esophagus varices, we might rely on other combinations. So I think we now have many options, many questions and the future will tell us the answers.

10:53 --> 11:30 Lorenza Rimassa

Yeah, I totally agree with you Jens. And so we can move to the second talk of this amazing session. The second talk was given by Rachna Shroff from the University of Arizona Tucson in the US and was on latest data on cholangiocarcinoma. So we have talked about hepatocellular carcinoma and now cholangio. And what are the most important aspects discussed in this talk? And also I would like to mention that also Arndt Vogel from the Medical School of Hannover participated in this session and in the discussion. So...

11:31 --> 12:17 Jens Marquardt

Yeah, I think, I think he really had a very good impact on the discussion. In particular, given his prominent role in the FIGHT trial and he really is an expert on molecular precision oncology approaches in hepatobiliary cancers. So I think, Rachna's talk was really great and she highlighted the most important aspects of clinical developments in cholangiocarcinoma and I think what became extremely obvious in her talk is the fact how heterogeneous these cancers are, like we always put together intrahepatic, extrahepatic colangiocellular carcinomas and also gallbladder cancers, despite the fact that they are both phenotypically, but in particular, molecularly vastly different.

12:18 --> 12:38 Jens Marquardt

And this is probably the fact, the reason why over the last 10 to 12 years cholangiocellular carcinoma has been the domain for classical chemotherapy. Rachna also mentioned that there are developments in classical chemotherapy, right?

12:39 --> 13:49 Lorenza Rimassa

Yes, in fact as you mentioned, we had platin gemcitabine for more than 10 years but other chemotherapy regimens have been proved effective or are being tested, for instance in second line, we have the modified FOLFOX based on the ABC-06 trial and..., that is a standard care or the standard care after

cisplatin gemcitabine, but as Rachna mentioned there have been other trials, for instance, the research was to try to identify more effective chemotherapy regimens, adding a third drug, and we had the publication of the AMEBICA trial that tested FOLFIRINOX versus gemcitabine and cisplatin, but unfortunately no benefit was identified from FOLFIRINOX and so the standard of care in first line is still GemCis. But again, in terms of chemotherapy, there are positive, very promising phase 2 data adding nab-paclitaxel to GemCis and there is an ongoing phase 3 trial testing this triple combination versus the classical double combination.

13:50 --> 15:09 Lorenza Rimassa

And moving again to the second line, we have FOLFOX but very recently the NIFTY trial has been published, this is a Korean trial testing nal-IRI in combination with 5-fluorouracil in second line and the trial was positive. So at least in Asian patients, nal-IRI-fluorouracil can be another option in second line. And in the discussion we talked a lot about the possibility to use irinotecan versus nal-IRI, especially in countries where nal-IRI is not available. For instance, in Italy it is not available, and so I think we all agree that there is a possibility to use FOLFIRI in patients with cholangiocarcinoma in second line or in third line, in second line instead of FOLFOX or after FOLFOX if we consider only the chemotherapy regimen. But I said that cisplatin gemcitabine is still the standard of care in first line, but this is not completely true because at ASCO GI the TOPAZ-1 trial has been presented. Jens would you like to tell us something about the TOPAZ-1?

15:10 --> 15:39 Jens Marquardt

Yeah, I think this is a trial that we all awaited for long time after the first press release. I think in in November, December last year that the trial turned out positive and everybody was extremely eager to see the results. And basically this is a trial that is the first indication that the addition of immunotherapy to cytotoxic background can be beneficial in an all comer trial of cholangiocellular carcinoma and the trial is...

15:40 --> 16:43 Jens Marquardt

based on impressive data of a phase 2 trial that was conducted in Korea called the MEDITREME trial, where they had impressive objective response rate of around 70% for the combination of GemCis as well as durvalumab, and the TOPAZ trial is based on these, based on this trial and it used the classical ABC design of GemCis for 6 months in combination with durvalumab and durvalumab was continued until progression or toxicity. So here they used a combination of GemCis with the PD-L1 inhibitor durvalumab and the trial again included many Asian patients, roughly 50% were Asian and 50% were intrahepatic cholangios. And I think I mean, while the design and everything and basically also the results are intriguing, I think we all were a little bit disappointed about the OS. What do you think about it?

16:44 --> 17:37 Lorenza Rimassa

Yeah, I think, we were, we were so expecting this data that probably we expected more, but I think that the most important thing is, as you said, that we have for the first time, a new regimen that is more active than cisplatin-gemcitabine and it's the first demonstration in a phase 3 trial that immunotherapy can work in patients with cholangiocarcinoma because the prior phase 2 trial in previously treated patients like the KEYNOTE-158 results were not so so promising. So I I think yes, maybe we expected more because we would like to have more for our patients, but I think that the results are there and we will have a new option. And also it's important to mention that

17:38 --> 19:44 Lorenza Rimassa

Rachna presented very well also the characteristics of patients with cholangiocarcinomas. We know that not all patients and not all cholangiocarcinomas are the same. There are molecular alterations that characterize different subgroups of patients, and, for instance, for patients with FGFR2 gene fusions now we have drugs available in previously treated patients like pemigatinib in Europe and the US, and then

infigratinib in the US or for patients with IDH-1 mutations we can have ivosidenib. And also Rachna presented other molecular alterations or genetic mutations observed in patients with cholangio like BRAF mutation, and we can use for these patients the combination of dabrafenib and trametinib based on the ROAR trial, or for patients with HER2 alteration we can use the combination of trastuzumab plus pertuzumab and there is also other, there are also other trials ongoing, so I think that the field is rapidly changing.

18:47 --> 19:57 Lorenza Rimassa

There are so many new aspects that we have to study and to address, and there are new available options for our patients and we will have even more in the near future. One thing that is really important to me is, and a message, is that we have to offer to our patients molecular testing because we have talked about chemotherapy and immunotherapy, but targeted agents, molecular therapies are really important, so we have to offer our patients NGS or other molecular testing, so we have to define which drugs can be the best options for a specific patient and this is an important message for clinical practice, we have to test patients and we have to identify the genetic aberrations. So we have to, we will be able to prescribe or to include patients in clinical trials to test new molecular agents.

19:58 --> 21:37 Jens Marquardt

I think something that we discussed and this is, I mean, the data for the molecularly stratified trials are so convincing, I mean the overall survival rates, objective response rates, as well as PFS for all these different targeted therapies are so convincing and we have ongoing phase 3 trials that test these targeted strategies in first-line settings. So I think what became clear in our discussion and Arndt Vogel also agreed on that, it's very, very important to test molecularly as early as potentially possible and not wait until progression so the patient becomes ineligible.

21:38 --> 21:01 Lorenza Rimassa

Yeah, I totally agree. So the third talk, that was for the future, was given by Sandrine Favre from Paris in France, was entitled "What is coming in HCC and CCA", so the perfect talk to think of the future of our patients and so how will be the future for liver cancer?

21:02 --> 21:45 Jens Marquardt

I really liked the talk of Sandrine because she recapitulated results from IOs and put it in perspective of what we have now and where we go for the future. And she delineated very well how a patient looks like, that responds very well to the treatment, but as a note of caution, she also mentioned and showed results of patients that did not respond to immunotherapy and also raised the important question of toxicity, in particular the question of hyperprogression in response to immunotherapy. And what is your experience with hyperprogression?

21:46 --> 22:28 Lorenza Rimassa

This is a really important point, at least theoretically, because we can have patients who rapidly progress on immunotherapy. I don't know if we see so many hyperprogressions as described in other cancer types, but for sure we see some patients who rapidly progress on immunotherapy, and this is really important because for these patients we have to decide if we have to stop immunotherapy because they are really progressing on or if it is a real hyperprogression but maybe followed by, as we see in other cancer types, for instance, in Melanoma, followed by a response.

22:29 --> 23:43 Lorenza Rimassa

So this is a particularly difficult aspect, and we have to be very careful to avoid to go on with a treatment that is not effective, but we also have to avoid to stop it treatment that can be effective. So I think that the the CT can done after 6 or 8 weeks should be the standard of care, and if we see a kind of progression, we have to repeat a CT scan, maybe 4 weeks later and decide if you have to go on or to stop. And at the

same time, it's really important to manage the toxicity because these patients may respond well, may have an important benefit from immunotherapy, but as you mentioned, they can also have a toxicity, so it's important to balance the efficacy and the management of the toxicity, that is crucial to optimize the benefit of the treatment. And there are other aspects that Sandrine mentioned, for instance the combination of immunotherapy and locoregional therapy or moving immunotherapy in earlier stages.

23:44 --> 24:47 Jens Marquardt

I think this is a very important aspect that now with these new combinations of IO and whatever TKI or VEGF or, or even, immuno-immuno combinations, and the objective response rates of 20 to 30% really, the immunotherapy combinations, they move into earlier phases in adjuvant, but also potentially neoadjuvant setting and, and in particular there's new data coming with regards to intermediate stage and combination of immunotherapy and locoregional therapy, but also the ABC trial from Mainz compares the immunotherapy combinations with locoregional therapy. So I think there's many scenarios where this combination could enter the intermediate or even earlier stages of hepatocellular carcinomas.

24:48 --> 25:50 Lorenza Rimassa

Yes, and another important point for the future that Sandrine mentioned is that now we consider as immunotherapy PD-1, PD-L1, and CTLA-4, but we have other promising drugs that are being tested in early phase trials, for instance new drugs targeting IL-6 or TIGIT, TGF-beta and LAG-3 and other targets. So probably we will have more options in the future, and also in terms of new agents we have, we have bispecific antibodies that are targeting different targets. So... and also other important points are vaccination or CAR-T cell that are used in hematological cancers, but now we have some ongoing trials also in liver cancer. So there are several new options that are really really interesting, and if the data will be positive we will have even more options for our patients in the future.

25:51 --> 27:12 Lorenza Rimassa

So I think that the most important take home messages from Sandrine's talk, and also from this session are that we have now immunotherapy both in... in first line, both in HCC and in cholangiocarcinoma, and it's important to manage the toxicity and in both, especially in HCC, but there are some data also in cholangiocarcinoma we are, we have ongoing trials combining IO with locoregional therapy, or, as you have already said, moving IO in the adjuvant setting or already in the neoadjuvant setting, and for I did... this is especially true for HCC. And an important message, take home message for cholangiocarcinoma is that the personalized medicine probably will be the future, at least for a part of the patients, and we will have to identify new drugs and new targets, but also we will have to study the mechanisms of resistance to offer new treatments to patients who progress on targeted agents. So which are your take home messages or final?

27:13 --> 27:45 Jens Marquardt

I could not agree more. I think it's exciting times for patients with primary liver cancer and, as I said, there are a lot of new aspects, and a lot of new questions that couldn't be asked before. And I think the time will give us the answers. And I think HCC and also cholangio really are a prime field now for clinical trials, for development of new drugs, but also for biomarkers, as you said, for resistance, but also for prediction.

27:46 --> 27:52 Lorenza Rimassa

Totally agree, thank you so much Jens, and thank you all for listening. Bye.

27:52 --> 27:53 Jens Marquardt

Thank you very much. It was a pleasure.