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Optimizing Care for Patients with Advanced Hepatocellular Carcinoma: Current Standards and Future Directions with Immunotherapy

Announcer:
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Dr. Finn:
Recently, immunotherapy has revolutionized the management of hepatocellular carcinoma, or HCC. Particularly with combination therapies, identifying the right patients and understanding the sequencing of agents is crucial. How can you best utilize combination therapy to improve outcomes for your patients with HCC?

This is a CME on ReachMD, and I'm Dr. Richard Finn. Here with me today is Dr. Peter Galle.

Dr. Galle:
Hi, Richard, great to discuss with you.

Dr. Finn:
Thanks for joining me, Peter. Let's get started.

To set the stage for this chapterized course, let's discuss on the diagnosis of liver cancer and the impact of this diagnosis and staging on the management of our patients and their treatment. Now, we all know that liver cancer arises in the background of a sick liver most of the time. And imaging can give us a diagnosis, but increasingly, there's been some more thoughts given to making a biopsy, perhaps for biomarkers for better understanding tumor biology. What are your thoughts?

Dr. Galle:
Yeah, I think it's worthwhile looking backwards about 2 decades. At that time, indeed, guidelines recommended to diagnose HCC purely based on imaging, provided that there is a cirrhotic liver. That might have been correct at that time because there was basically no systemic therapy to choose from. But the issue was, if you don't do biopsy regularly in clinical routine, you also won't do it in clinical trials. And therefore, in the upcoming years, there were many successful and some non-successful trials, but they were not guided by biopsy, and there was no gain in knowledge about biomarkers of predictive quality.

What we have today are descriptive signatures, biomarker profiles, which are prognostic but not in any way controlled in a prospective way with respect to their predictive value. So what do we do today? And this is, I would say, a disaster if you compare it, for example, with pulmonary cancer. We decide basically on clinical trials. Tumor burden and liver function, they tell us what to do. So we do in the end an all-comer treatment. And that's something where, I believe, Richard, you agree on that, where we really need to get better.

Dr. Finn:
As we have more treatment options available, having some way to triage patients other than clinical parameters would be great, like we

do, as you mentioned, in lung cancer, based on biomarkers or breast cancer. What about alpha fetoprotein?

Dr. Galle:
It's a marker of prognostic value. If it's high; it's bad. It's a marker, which can be used to evaluate treatment response. Patients dropping an alpha fetoprotein, whatever you are doing, are giving you a message that what you are doing is probably working. But you can't choose from alpha fetoprotein with respect to therapy with one exception, and this is for the high-level alpha fetoprotein patients; it has been shown that they in particular benefit from a ramucirumab treatment. But this is the only exception where we use a, let's say, somewhat predictive quality of a biomarker.

Dr. Finn:
And now that we have combinations that are, I would argue, are highly active in liver cancer such as atezolizumab and bevacizumab, which is globally approved, many of us anticipate the combination of tremelimumab and durvalumab will eventually get approval. And still ipilimumab and nivolumab are in development in phase 3 and are approved second line in the United States. And then recently, we saw provocative data with lenvatinib and pembrolizumab.

Now when we look at the NCCN guidelines for selecting patients for systemic treatment, still, it looks like atezolizumab and bevacizumab is level one. But to the point on biomarkers, we have not been able to identify, like in other diseases, those patients who benefit best from that regimen as compared to perhaps a double CTLA-4 or IO [immunotherapy] regimen. What's also interesting in the NCCN guidelines is they still have nivolumab listed as an option for patients with Child-Pugh B. Can you comment on that, Peter?

Dr. Galle:
Yeah, well, I mean, Child-Pugh B is an under-investigated area. We have some sketchy data that in some patients you can do it, but in the end the more the liver function is impacted, the less likely it is an antitumor effect to become visible. That's the simple truth.

Probably immunotherapy is a good choice here because it's typically not coming at the expense of liver function. But again, it's just a proportion of these patients with poor liver function in the end benefiting. And again, a point where we would love to see a better distinction based on whatever marker.

Dr. Finn:
So in summary, a few of the takeaways is that, increasingly, a biopsy should be considered for patients with advanced liver cancer to help us understand the tumor biology a little better and to confirm the diagnosis. Still, LI-RADS [Liver Reporting & Data System] criteria can be used with high specificity for patients who meet those criteria to make the diagnosis of liver cancer. The NCCN guidelines still recommend that we approach patients [for first line] not based on a biomarker, but based on clinical characteristics, which include liver function as well as tumor burden. That is tumor outside the liver or invading the liver vasculature or just a large tumor burden within the liver. And that combination immunotherapy is a first-line choice. And at this time, that would be atezolizumab and bevacizumab, unless a patient has a contraindication.

Thank you. In Chapter 2, we'll be discussing the current role of immunotherapy in the treatment of HCC. Stay tuned.

Dr. Finn:
Welcome back. We just discussed the lack of biomarker assessments in HCC and the impact that has on treatment. Now we're going to delve into the current role of immunotherapy in the treatment of HCC.

Peter, can you explain how immunotherapy is currently used in the treatment of HCC? And then we can discuss some of the relevant data. What about, let's start with the rationale to use IO in liver cancer.

Dr. Galle:
Well, the immune system is a tightly controlled system. If it wouldn't be, we would explode. Full of T cells, full of inflammation. So you need to down-titrate the immune response, and there are physiological means to do that. But, and that's the issue, the tumor, not just HCC, other tumors as well, but in particular HCC, the tumor is smart, using exactly those control mechanism checkpoints to down-regulate T cells and to escape from tumor immune response.

So there is a theoretical background. And ever since in 2011, melanoma treatment became successful based on immunotherapy. We all have been eagerly waiting for what role that would play in hepatocellular carcinoma. And the reason why we were looking optimistically at the tumor is it's typically an inflammatory disease. There is lots of inflammation. The inflamed liver is cirrhotic. There are maybe viral replication. That is a good background for immunotherapy.

And then we saw the data. Particular most mature first-line treatment with IMbrave150, which you were the one who is number one in the author list of The New England Journal paper. I just looked it up; to date it has now 2,000 citations. That was a breakthrough. And I congratulate you. And as being part of it, what do you think is the role of IMbrave150?

Dr. Finn:
Yeah, so the IMbrave150 study really brought us into the modern age of liver cancer treatment, I think. We had seen that with single-agent IO, whether it be pembrolizumab or nivolumab, that these drugs did have activity in liver cancer, but really with response rates around 15% to 20% pretty consistently. And in randomized studies of single agents, we never were able to improve survival, which is the ultimate endpoint for our patients with advanced liver cancer.

This got us thinking that perhaps the way we're going to improve survival is essentially to improve these objective responses. And that led to the understanding that targeting the VEGF axis, in combination with the PD-1 or PD-L1 axis may be synergistic. And this was initially tested in a phase 1B study with bevacizumab and atezolizumab and showed objective response rates of 36%.

This was a pretty strong signal for us to go ahead and launch a global large phase 3 study known as IMbrave150. And this study met its endpoints in a very robust fashion. That is to say, we improved overall survival (OS) and progression-free survival (PFS) with hazard ratios of 0.58 and 0.59. And in updated data, we see that the median survival with atezo/bev is now just over 19 months.

Now, we have to balance that survival data with safety data. And importantly, this regimen appears to be very well tolerated. We know that bevacizumab can be associated with bleeding events, and therefore patients do need an upper endoscopy within 6 months of starting on trial. And if they have high-risk features, large varices, or varices that have recently been bled, those needs to be managed before being started with this regimen. However, it is very active. In the follow-up data, we have an objective response rate of 30%. It's incredibly gratifying now to use a regimen like this in patients.

Now, what do we do after progression on this? Right? What about the role of IO in the second-line setting or for patients who don't get IO in the frontline setting? What are the options for patients who wouldn't qualify for IMbrave 150?

Dr. Galle:
This has been addressed in several guidelines. However, it's basically opinion based because we definitely lack a thorough dataset on second-line options or alternatives to atezo/bev in case it can't be used.

In the setting of contraindications against, for example, bevacizumab and you want to go for kinase inhibitors, you can use the old standard, which would be sorafenib or lenvatinib. In these days, probably more recent, more frequently lenvatinib used. But again, in the second line, it's basically depending what is available, and there is not much data to give clearcut recommendations.

Dr. Finn:
Yeah, so we do have numerous drugs available that had been shown to improve survival in liver cancer in specific settings. The fact that, recently, the combination of atezo/bev has become frontline, I don't think means that we stop using the drugs that have been shown to improve survival in patients. Just like in other diseases, advances need to be incorporated in the context of what we know already and what we have available to treat the disease.

I think the impact of IO has been very significant. And even with single-agent IO, we've seen that patients do respond. And if we look at KEYNOTE-240, which was a second-line study of pembrolizumab versus placebo, this study just missed statistical significance. But we saw, again, single-agent IO is well tolerated in the second-line setting and provided an objective response rate of about 17%. And recently, we saw a companion study from Asia, KEYNOTE-394, which did meet its endpoint of improving survival. So for patients who might not be candidates for the doublet of atezo/bev in the frontline setting, these patients may receive lenvatinib, for example, in frontline, and a progression may be a candidate for single-agent IO, such as pembrolizumab [for patients with HCC who have previously been treated with sorafenib].

Peter, what do you see about the use of a regimen like ipilimumab and nivolumab in the second-line setting?

Dr. Galle:
You are privileged in that you have it based on accelerated approval in the US. We in Europe don't have access to this combination. But naturally, the combination out of CTLA-4 inhibition and PD-1 and PD-1 ligand inhibition is making sense, because it's really stepping in at different time points in the immune reaction and probably acts synergistically.

As we have seen from the durvalumab/tremelimumab data, the HIMALAYA trial, a similar sort of combination, that this combination is active. And we saw the earlier phase data of ipi/nivo, which were very promising, 30% response rates, and very long, I have to say, overall survival rates in second line. So these data are promising, and we will get the full results of ipi/nivo based on the CheckMate 9DW analysis and await these data eagerly. It might be very well another good option in the future.

But again, here, the more choices we have, we will have to choose wisely. And that would require biomarkers. They are coming back to the topic of our first presentation.

Dr. Finn:
Well, thank you very much, Peter, for your thoughts. I mean, so in takeaway, the field has changed rapidly. Immunotherapy has now become our frontline choice. And really the combination of atezolizumab and bevacizumab is the most active for patients who are candidates for that. But should they progress on this regimen, going back to sequencing the kinase inhibitors that we've used for the past decade would be appropriate. Or for patients who do not meet the criteria to receive a doublet in the frontline setting, sequential kinase inhibitors and perhaps even single-agent PD-1 inhibition at progression may be appropriate.

In Chapter 3, we'll be discussing recent and emerging treatments for HCC. Please stay tuned.

Dr. Finn:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Richard Finn, and here with me today is Dr. Peter Galle. We're discussing the role of immuno-oncology in the treatment of our patients with advanced hepatocellular carcinoma.

Welcome back. We just looked at the current role of immunotherapy in the treatment of HCC. Now let's shift gears and talk a bit about recent and emerging treatments.

Peter, recently at ESMO, we saw the results of a fair number of phase 3 studies in liver cancer. I presented the LEAP-002 data. What are your thoughts on that?

Dr. Galle:
Yeah, LEAP-002 was really a surprise. A negative trial with the best results shown ever. Overall survival of 21 months. The problem of LEAP-002 was that the control arm, and that was lenvatinib alone versus lenva plus pembro. Lenvatinib alone was performing exquisitely well, in a range unpredicted. We should recall in the REFLECT trial, we were in a range of about 13 months or so overall survival. And now that was elevated by almost half a year. So I mean, we have seen that over the time, in recent years, actually over the decades, typically, results have been gotten better, for various reasons and probably most relevant patient selection.

But it is really a pity, I have to say, that we have and what we believe active combination, but a negative trial.

And what we definitely should not forget, if we are now using first-line treatments, there is a lot going on with respect to post-study medication, obscuring any effect on overall survival. But honestly, I'm a bit puzzled. I would have expected in that sort of setting a difference in progression-free survival. Nevertheless, this was pretty much the same. Maybe you have a feeling on what that means, no change in PFS, a minor difference in OS, why?

Dr. Finn:
Yeah, this was disappointing, this finding. I mean, in many ways the treatment arm performed as expected. From the single-arm phase 1B study, we had a survival in the range of 21 months, which is what we saw in this phase 3 study. The objective response rate for the combination was 26%. There were no new safety signals. But as you mentioned, the control arm performed very well. And that likely is a reflection of a fair amount of crossover. Many patients who started on lenvatinib went on to receive IO at progression. And as we discussed before, single-agent IO is probably an active drug in sequence for these patients. And there are probably some other inclusion criteria and statistical design issues that limited its ability to show the OS improvement.

You know, this idea of not improving PFS also has been a challenge for some studies. Ultimately OS, I think, is the most important readout. I think the fact that we didn't have the most high-risk population in this study might have contributed to that. And that is to say we did not include patients who had main portal vein invasion, which is a poor prognostic group and probably benefits the most potentially from this dual IO, TKI, or VEGF approach.

RATIONALE-301 was also presented at ESMO. And this is an important study because it was the first phase 3 study that established a role for single-agent IO in the frontline setting. This study was a non-inferiority study of tislelizumab versus sorafenib, and was open label. And you know, unlike CheckMate 459, which looked at nivolumab versus sorafenib, whose results looked fairly similar, CheckMate 459 was designed to be superiority. But RATIONALE-301 was designed to be non-inferior. And by doing so, they did meet the statistical threshold to be non-inferior. Survival with tislelizumab, a PD-1 antibody, was in the 15-month range, which when we look at the confidence intervals, was not statistically superior to sorafenib, but the upper limit of the confidence interval was within the non-inferior threshold.

The study confirmed what we've seen with other single-agent PD-1 inhibitors. These drugs are very safe in patients with liver cancer, especially those with Child-Pugh A. And as we alluded to in Chapter 1, the NCCN guidelines still feels that for patients Child-Pugh B disease, single-agent PD-1 inhibitors may be considered just because they are tolerated and do have some activity. Their activity really seems the same regardless of underlying liver disease.

But in the context of RATIONALE-301 there were no new safety signals seen with these antibodies, specifically tislelizumab. The

immune-related adverse event rate is fairly low. And especially when we look at liver toxicity, again, fairly low. And it looks to be better tolerated than sorafenib.

There was also an arm in the HIMALAYA study presented earlier this year and published recently, of single-agent durvalumab versus sorafenib. And again, those results look very similar to RATIONALE-301, in that we have non-inferiority versus sorafenib.

At this point, we'll have to see how regulators approach these datasets. They do provide evidence for single-agent IO. However, the survival with single-agent IO is still inferior to what we've seen with a doublet such as atezolizumab and bevacizumab, given we are making cross-study comparisons.

Now another doublet was presented, which really was interesting data. Quite a bit of efficacy from the combination of apatinib, in combination with camrelizumab. Peter, are you familiar with this study?

Dr. Galle:
Yeah, I was impressed, I have to say. The difference, the separation of the curves, very impressive. And it's just another example of, in this setting, apatinib and anti-angiogenic TKI and checkpoint inhibitor are a very active combination. So it's basically coming with the same rationale as the IMbrave150, but here with different substances. So both with respect to OS, PFS, all on good hazard ratio levels, positive objective response rates, convincing. So I think this is definitely a trial where I would expect approval for the long-term run and addition to our armamentarium.

And, as you are aware, Richard, there's more to come. There will be CheckMate 9DW and other ongoing trials. So it will be a crowded scenario, and not everybody will survive. We have seen the COSMIC trial, where there was only a difference in PFS, but no OS difference. So that was investigating atezolizumab and cabozantinib. So not all these combinations work, but some do. And with IMbrave150, with HIMALAYA, with the camre plus apatinib combination, and maybe in RATIONALE, a single-agent, we really have added a lot to our armamentarium

Dr. Finn:
Yes, I agree. I mean, the camrelizumab and apatinib, now known as rivoceranib, really was an impressive dataset. You know, 22 months' survival with that combination versus 15 months with sorafenib, that improved objective response rates, really an objective response rate we saw of about [25%] with this combination. However, the study was done in mostly Asia, not a lot of enrollment from the West. I think was less than 20%. But also grade 3/4 adverse events, treatment-related adverse events was 80%. So we'll have to see how regulators approach these data. Certainly impressive efficacy, but also associated with probably more toxicity than we're used to seeing.

So a lot of exciting data at this year's ESMO. Some negative, some positive, some kind of in the middle. And at this point, we'll have to see how these new studies, as well as the HIMALAYA study which was presented and published this year, how these move through the regulatory network so that we can get them to our patients as soon as possible.

Thank you for being with us. In Chapter 4, we'll discuss regional considerations in testing and treatment of HCC. Please stay with us and we will be back with you soon. Stay tuned.

Dr. Finn:
Welcome back. We just reviewed recent and emerging treatments for HCC, and we're turning now to regional considerations in testing and treatment. I'm from the United States. Peter, you practice in Europe. How does your population of liver cancer patients maybe differ than mine and differ from our colleagues perhaps in Asia?

Dr. Galle:
Regional differences are of tremendous importance in hepatocellular carcinoma. It starts with a disease burden, which is much higher in Asia and in Africa. And then the ideology differs throughout the world. In Africa and Asia, it's basically hepatitis B and C driven; in the Western world, increasingly driven by a fatty liver disease either on an alcoholic background or as non-alcoholic fatty liver disease.

In addition, the availability of treatment options such as, for example, if we go to high-end liver transplantation, is very different. But even within Europe, we see a huge variety with respect to availability. Not all the, for example, all TKIs which have been used in the past in the treatment of HCC are available in all countries. So it makes definitely a difference, and we have been discussing that in many guidelines.

Guidelines give guidance, but in real life, and this is quite dependent on regional differences, availability, approval status, costs may be quite variable. In addition, what's adding to it is the different ways to treat liver disease. Here, we have patients which definitely frequently develop complications. And that is also not treated the same way throughout the world.

Dr. Finn:
Yeah, a common theme is that 90% of our patients with liver cancer have underlying liver disease.

Now, how these patients present in the clinic can be very variable. Those patient with hepatitis B are typically not as cirrhotic or decompensated as compared to those with Hep C, or NASH.

Now all our clinical studies to date have included all of these patients and studies. And really, how they respond to these drugs, regardless of etiology, seems to be pretty consistent. There are some questions about maybe viral-related disease behaves different than nonviral-related liver cancer. But I think at this point, that data has not reached primetime and is not ready to really influence our treatment decisions.

Also, how closely patients are followed for their liver disease before coming to attention will reflect to the fact, do they get screening for varices, upper endoscopies? That's a very important thing to look for, for our patients with underlying liver disease. And especially now, as we're using drugs like atezolizumab and bevacizumab, which require an upper endoscopy before starting treatment.

And again, the risk of bleeding is likely related to how cirrhotic they are, whether or not they have portal vein invasion and portal hypertension.

Well, Peter, this has certainly been a fascinating conversation. And I really appreciate always working with you. In this section, we did review the importance of considering underlying liver disease in our management of patients with liver cancer. It's important to have patients with hepatitis B on treatment for their hepatitis B, viral suppression. As well as hepatitis C is now curable, and it's important that those patients are treated. And increasingly, NASH is becoming a large unmet need for our cirrhotic and liver cancer population.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening. And thank you, Dr. Peter Galle, for joining me and for sharing all of your valuable insights. It was great speaking with you today. Thank you and goodnight.

Dr. Galle:
Thank you, Richard. It was a pleasure, as always, to discuss HCC with you. And thanks to our audience and goodnight.

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