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Unresectable HCC: An Emerging Era of Combination Therapy – A Clinical Convergence®

Announcer:
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Dr. Richard Finn:
Hello, everyone, I'm Dr. Richard Finn, a Professor of Medicine at David Geffen School of Medicine at UCLA in Los Angeles, CA.

It's my pleasure to welcome you to the continuing education activity entitled *Stronger Together, An Emerging Era of Combination Regimens for Unresectable HCC, A Clinical Convergence*.

Joining me today for this activity are 2 colleagues and friends, Dr. Amit Singal, a hepatologist from the University of Texas Southwestern in Dallas and Dr. Mark Yarchoan, a medical oncologist from John Hopkins University in Baltimore, MD.

When we think about treating with systemic drugs in liver cancer, the backbone and the majority of drugs that are used today tend to target the VEGF pathway.

The majority of drugs are VEGF kinase inhibitors, so they hit the VEGF receptor, as well as other kinases. Ramucirumab, a monoclonal antibody to the VEGF receptor, is also approved. And more recently, we saw the approval of bevacizumab, an antibody to VEGF approved in combination with atezolizumab.

So, in 2008 we saw the approval of sorafenib based on the SHARP study. This was a hallmark study because for the first time we saw we could improve survival in advanced liver cancer with systemic treatment.

Here you see the SHARP study done in North America and Europe, and the Asia-Pacific companion study done in the Asia-Pacific region. And the hazard ratio for survival — 0.69, 0.68 — very comparable between the 2 studies. And we saw for the first time an improvement in OS from 8 months to just under 11 months with sorafenib.

Now importantly, the study concentrated on the Child-Pugh A population, like most Phase 3 studies. Sorafenib did not induce an objective response, really it improved survival by delaying progression, and it had a very predictable side-effect profile with the most common things being hand-foot skin syndrome, GI toxicity and diarrhea, fatigue, and anorexia.

Now, for over a decade sorafenib was the standard of care in front-line. That changed with the REFLECT study, which evaluated lenvatinib.

And you can see here lenvatinib is a very potent VEGF TKI, kinase inhibitor. More potent than sorafenib. And the FGFR family is also targeted very efficiently by lenvatinib, unlike sorafenib. And FGFs are felt to be important drivers for proliferation in liver cancer as well as mediating resistance to angiogenesis.

So the REFLECT study design is shown here. It was an open-label study, again taking patients who were Child-Pugh A, Barcelona

Stage B or C. This study had a unique exclusion criteria set in which they excluded patients who had 50% of their liver involved by tumor (so a very large tumor burden), or bile-duct invasion, as well as patients that had invasion of the main portal vein, so the extrahepatic portal vein. That was excluded not because we felt the drug would not be active in that group, but this study originated in Japan and the practice pattern there does not use systemic treatment for those patients, at least historically.

And lenvatinib was dosed by weight, something that's different about this kinase inhibitor against the others, and this was open-label versus sorafenib. The primary endpoint was overall survival.

Now, the study uniquely was powered to show superiority, but also non-inferiority. And it did meet this non-inferiority endpoint.

And here you see, lenvatinib had a survival of about 13.6 months, sorafenib 12.3 months. There was a hazard ratio of 0.92, but the upper limit of the confidence interval crossed 1. But 1.06 was still within the bound of the non-inferiority endpoint — that endpoint being 1.08. So based on this data, lenvatinib did get approval.

Now, lenvatinib did meet secondary endpoints and essentially doubled progression-free survival compared to sorafenib, 3.7 versus 7.4 months, by the modified RECIST criteria, which takes into account the enhancement, size of enhancing tumor in the liver.

And it also induced responses. And here, looking at independent review, both by modified RECIST and conventional RECIST, we see lenvatinib had response rates of 41% versus 19% by RECIST and sorafenib 12.4% versus 6.5% by RECIST.

So, now we had a kinase inhibitor that was non-inferior for OS but did meet important secondary endpoints. And also had some important toxicity differences.

Here, you can see lenvatinib has more hypertension — higher grade, and more frequent — however, it has less hand-foot syndrome as sorafenib, less frequent and less intense. Other toxicities tended to be the same, such as GI toxicity, anorexia, weight loss. But again, reflecting its VEGF component, more proteinuria with lenvatinib.

Now, there's been a lot of interest in the immune system in targeting cancer.

While this diagram is somewhat complex, I want to call our attention to the main drugs that have been approved in cancer medicine that are involved in regulating the immune system or interfering with it.

This includes antibodies, mostly that target the interaction between PD-L1 and PD-1, both on antigen-presenting cells and on tumor cells. This signaling between these molecules actually tells the immune system to ignore the tumor, and therefore by interrupting this signaling with antibodies we then allow the immune system to attack the tumor.

Also, on the priming side of the immune system, antibodies such as ipilimumab or tremelimumab — which interfere with CTLA-4 — are approved, and therefore again preventing the down-regulation of immune cells and allowing their priming.

So, the first data we have in liver cancer with one of the PD-1 antibodies was nivolumab. This came from the CheckMate 040 study from my colleague here in Los Angeles, Anthony El-Khoueiry, and this study led to the accelerated approval of nivolumab in second-line liver cancer.

That gave us a response rate of 15% with a median duration of response of over 16 months. And you can see that responses were seen across etiologies of liver cancer and further data showed that measuring PD-L1 expression also did not correlate with response.

Now the requirement for accelerated approval was to do a confirmatory study, and that was the CheckMate 459 study: an open-label study of nivolumab versus sorafenib in the front-line setting. The primary endpoint of the study was overall survival, again in Child-Pugh A patients.

Unfortunately, this was a negative study. Nivolumab had a survival of 16.4 months, the longest survival we've seen in liver cancer, [and] sorafenib about 15 months. Again, the longest survival we've seen with sorafenib in this population. However, the *P* value was .075. The upper limit of the confidence interval here was 1.02. Actually, this is even less than what we saw in the lenvatinib REFLECT study. However, this was a superiority study, not non-inferiority.

Now, progression-free survival was not significantly improved with nivolumab, and the challenge sometimes with immuno-oncology agents is that the median progression-free survival does not necessarily pick up what we see sometimes, which is a tail of the curve — a subset of patients who get a long-term benefit.

And this study confirmed actually what we saw in the Phase 2 study. A response rate of 15% with single-agent nivolumab versus 7% with sorafenib.

Now this drug still has accelerated approval and one of the reasons, maybe, that we did not reach the overall survival endpoint is that

many patients — and you see here, IO and investigational agents — about 30% of patients went on to receive other immuno-oncology agents in the sorafenib arm; an unintentional, so to speak, crossover.

However, nivolumab is very well tolerated. You can see here all-grade toxicities for nivolumab in blue. In red, sorafenib. All-grade are lighter, higher grades are darker. And you can see [that] by and large, the toxicity profile really does favor nivolumab.

So in order to improve on this response rate of 15% — to get a positive survival readout — we need to either identify a biomarker for these patients, or look at combinations.

So one of the combinations that looked very promising has been the combination of VEGF inhibition and PD-1 and PD-L1 inhibition. And our understanding of VEGF inhibition and how it affects the tumor has evolved, from not just affecting the vasculature — but by affecting the vasculature we can change the inflammatory milieu around the tumor, bring in antigen-presenting cells and CD8+ T-cells, which then with a drug like atezolizumab, can reverse the brakes on the immune system and allow a tumor attack.

This was tested in the IMbrave 150 study, which we published in the *New England Journal of Medicine* in May of this year, and this data led to the approval of atezo/bev for front-line liver cancer.

Again, a very standard design, advanced liver cancer, Child-Pugh A, randomized to atezo/bev given IV every 3 weeks, versus sorafenib. And this was an open-label study, 2 to 1 randomization.

It was very well-balanced and you can see here, balanced by all etiologies being represented, as well as the fact that this was a fairly high advanced cohort with over 70% of patients in each arm having macrovascular invasion or extrahepatic spread. And you can see here 80% of patients had Barcelona C disease [and] about 15% in each arm had intermediate disease — so Barcelona B [patients] that had progressed on TACE or were not candidates for TACE.

Also, patients on this study required an upper endoscopy to screen for varices within 6 months of starting. And you can see that it was well-balanced, about a quarter of patients in each arm had varices and here you see the numbers, 11% and 14% actually had them treated at baseline.

This is the primary endpoint of overall survival: a significant improvement in OS, with a hazard ratio of 0.58. The study was stopped at about 8½ months because of the early and maintained separation of the curve, so we don't have a median OS with atezo/bev. But needless to say, sorafenib performed as expected and this hazard ratio of 0.58 is the first time we saw an improvement in survival versus sorafenib since 2008.

And, unlike in CheckMate 459, we see that this combination actually improves PFS, 4.3 months to 6.8 months, [with a] hazard ratio of 0.59.

With this combination, looking at independent review of RECIST, 27% confirmed response rate versus 12% with sorafenib; 5½ percent of those patients were complete responses, so no evidence of disease with treatment.

Now, the regimen actually is very well tolerated. You can see all adverse events equal between arms, grade 3/4 events equal in between arms. Grade 5 events equal, if not a little higher with sorafenib. Serious adverse events were a little higher with atezo/bev, 38 versus 30%. However even with that in mind, only 7% of patients had to stop both atezo and bev, whereas in the sorafenib arm 10% of patients had to stop treatment because of an adverse event. Fifteen percent of patients had to drop either the atezo or bev, depending on the toxicity.

And when we look at toxicity, we can see that things again generally favor atezo/bev. The side effect profile is really similar to either drug alone, hypertension being more common with atezo/bev. Whereas [when] we look at other toxicities such as diarrhea, hand-foot skin syndrome, anorexia — these tend to occur more frequently with sorafenib and with higher intensity. Proteinuria — again, a sign of VEGF inhibition — more frequent with atezo/bev.

And here, looking at treatment-related adverse events, a very similar pattern. And really I think the way I would characterize this, is [that] things that the patient would generally notice and complain about occur more frequently in higher intensity with sorafenib.

Now, here we see the quality-of-life readout from this study, very favorable. [Deterioration of] quality of life was markedly delayed: sorafenib, a delay in 3.6 months, whereas with atezo/bev, 11.2 months.

And there's other combinations being looked at of VEGF receptor inhibitors, such as lenvatinib, in combination with pembrolizumab. Here we see an overall response rate of 36% in the single-arm study. And the toxicity from this regimen really looks again similar to single-agent lenvatinib or pembrolizumab.

Also being looked at now in front-line, but from a second-line Phase 2 study, tremelimumab and durvalumab, the CTLA-4 and PD-L1

antibody [combination] presented at ASCO recently, showed a response rate of 24% in the high-dosing cohort, and a survival of 18.7 months in second-line. And this is now being evaluated in front-line and Dr. Yarchoan will talk about another combination, ipilimumab and nivolumab, now being looked at in front-line.

So, if we look at ongoing studies, we have studies looking at TKIs — lenvatinib and pembrolizumab [(LEAP 002)] and COSMIC, which is atezolizumab and cabozantinib — and HIMALAYA, looking at durvalumab and tremelimumab, and in CheckMate 9-DW, which is nivolumab and ipi.

So, now I'll hand it over to my colleague Mark, who will talk us through some cases and data in second-line. Mark.

Dr. Mark Yarchoan:
Thanks for that introduction.

So, in the second-line setting we have 3 targeted therapies that all inhibit VEGF signaling. We have regorafenib, cabozantinib and ramucirumab. And then we have a number of immunotherapies as well. All of these therapies were approved in a second-line setting after prior treatment with sorafenib, which has made the second-line discussion much more challenging now that we have other options in the front-line setting.

Regorafenib, cabozantinib, and ramucirumab — all of them were approved on the basis of large Phase 3 trials that showed overall survival benefits over placebo. I wouldn't compare the hazard ratios of these 3 trials directly because the populations were actually a bit different. Importantly in the regorafenib trial, these were patients who tolerated sorafenib in the front-line setting.

The cabozantinib study was a little bit more permissive and it included patients who had been treated with either 1 or 2 prior therapies and it included patients who hadn't tolerated sorafenib, and it also showed an overall survival benefit.

I think ramucirumab is really our only drug in HCC that has an indication based on a biomarker. It's only approved for patients with an AFP over 400. And that's because, really, when an initial trial of ramucirumab was done, there was no benefit to ramucirumab in patients with an AFP less than 400. And so, the indication is strictly for patients with an AFP over 400.

And, a number of immunotherapies have been studied in the second-line setting. I want to review quickly our evidence for anti-PD-1 therapies. So, pembrolizumab and nivolumab were both approved in the second-line setting after prior sorafenib, based on single-arm Phase 2 data showing that these therapies were safe and have response rates in a range of 15 to 17%.

The approval was granted as long as the companies performed subsequent studies of these agents, and so pembrolizumab was in a Phase 3 trial versus placebo that was led by my colleague here, Dr. Rich Finn. And this was a negative study. The pembrolizumab was safe; safety and tolerability look similar to what was seen in the single-arm Phase 2 study. There clearly were responses, or a response rate of around 18% in the study.

And when we look at survival and progression-free survival, both of these endpoints — which were the co-primary endpoints of the study — definitely favored pembrolizumab with *P* value for overall survival of less than .05. But that did not meet the pre-specified primary endpoint for OS. And so this is a negative study, but it nonetheless remains an option for patients in the second-line setting after prior sorafenib.

And as you can see, there really were no subgroups that particularly benefitted from pembrolizumab in the study more than other subgroups. Everything trended in the right direction.

And then, I'll mention quickly that there's also the approval of nivolumab plus ipilimumab. So, nivolumab is an anti-PD-1 therapy, ipilimumab is a CTLA-4 inhibitor.

And the manufacturer in this case conducted a Phase 2 study where different doses of ipilimumab and nivolumab were studied. And in this Phase 2 study there really was the best survival for patients who received the high dose of ipilimumab: ipilimumab 3 and nivolumab 1. And the FDA actually granted accelerated approval of this combination. I think this is adding to the evidence that anti-CTLA-4 therapy has some role in HCC because the response rate here, 32%, is clearly higher than PD-1 as monotherapy, where the response rate is closer to 15%.

And whether this has a role after prior bevacizumab and atezolizumab is a matter of some debate. But there probably are some responders to this that don't respond to PD-1 or PD-L1 as monotherapy. As my colleague Dr. Finn mentioned earlier, this has now moved into a Phase 3 study in the front-line setting versus sorafenib.

Many patients, about 32%, had reductions in tumor volume. Really there didn't seem to be any difference whether patients were virally infected or not, or PD-L1 positive or not.

So, just to summarize our section, we have a default front-line option now, bevacizumab and atezolizumab, but multiple other therapies that are in investigation in the front-line setting. In the second-line, I think there are some people who would argue that there's still a role for our historical first-line treatment options, such as sorafenib or lenvatinib. Other people would argue that we really should be moving towards drugs that were studied in a second-line setting, even if none of them were studied after bevacizumab and atezolizumab.

I will now turn the talk over to my colleague, Dr. Amit Singal, who's going to talk about tailoring treatment options in HCC.

Dr. Amit Singal:
Thanks, Mark. So, as you heard, I'm really going to be trying to put this together in terms of how do we weigh all of these different treatment options that we've just heard about?

So just to summarize, we've really had a lot of progress over the last 5 years. Just thinking 5 years ago we had a single front-line agent in sorafenib, and you can see that we've had an explosion now of multiple options both in the first-line as well as in the second-line.

Now when we think of this, we really talked about a "one treatment fits all" approach. We think of these drugs and we say that we're going to put all patients in the front-line on a single therapy or taking a look at patients and putting them all through a second-line therapy. But this really doesn't get to the way that we think about our patients when we see them in front of us in clinic. And there's been a big push in the field in terms of a precision medicine initiative, ie, finding biomarkers that can really say that this person *should* receive this treatment because they are going to have the best treatment response on there.

Now, you heard from Mark that we have a single biomarker in AFP. But we don't have biomarkers that actually help us choose between therapies. And that's really one of the areas that we want to push forward as we think through the next several years.

Now, just taking a look at some of the targeted therapies that we have available — you can see them listed here, and you can see their mechanism of action. And, through here you can see that there are some subtle differences in terms of the receptors they hit. For example, the bevacizumab being a pure VEGF. You can see sorafenib hitting multiple pathways. And you heard from Rich where lenvatinib was a more potent agent and hit other pathways, so for example, it also acted upon the FGF receptor. And by taking a look at these different pathways, this may be able to give us some sense of patients in which these therapies could be used.

So for example, there is an exploratory analysis that takes a look at lenvatinib and takes a look at the FGF receptor, and those patients who had higher FGF receptor levels actually had a better response to lenvatinib.

And similarly, you can see cabozantinib has unique mechanisms of action in terms of c-Met and AXL but are not hit upon in terms of some of the other therapies.

Now while this is a nice theoretical phenomenon, this isn't something that we use in clinical practice, but at least gives us an idea of how we can move forward in terms of leveraging mechanism of action as we think through precision medicine initiatives.

Now when we think of other treatment response biomarkers, this is a nice review that talked about all of the different treatment response biomarkers that could be of interest and put them into 4 different buckets. And, you can see these categories can include, number 1, tumor and immunologic factors and the second category being tumor mutations, microsatellite instability. And as you'll hear, there's been incredible interest in tumor mutational burden, MSI-high status, which actually is an approval across different tumor types, but unfortunately tends to be rare in HCC.

Third bucket being circulating factors, including circulating immune cells, soluble factors such as TGF-ß, [and] extracellular vesicles. Once again, an area of interest.

And then of course, host factors: male sex, older age, [and] gut microbiome. Once again, something that we can't use in clinical practice, but something that is being evaluated at this time.

So, taking a look at PD-L1 expression because I think this is probably one that's been of the most interest, we can see that among 45 approvals through April 2019 across tumor type, PD-L1 status was predictive in just over one-quarter, and not predictive in just over one-half of different trials. And then not evaluated in about 15 to 20%.

And you can see when you take a look at this figure, there's heterogeneity in terms of this being a potential treatment response biomarker across different tumor types. And part of the reason why this may be the case is that there's actually heterogeneity, even when you take a look across studies, in terms of the thresholds, the types of cells expressing PD-L1 that have been evaluated, and the companion diagnostics. And so, there's different ways that this has been looked at across these different cancers.

However, when you take a look at HCC — you can see that actually this is done in a teal-color, and so has not been approved in HCC. So most of the studies actually have not shown that PD-L1 status is predictive in our current approved immunotherapies.

So given the fact that we don't have these more nuanced approaches, we've really been dependent on clinical factors, as we've been trying to think through different treatment selection factors.

And so, for example, when we think of targeted therapies and you think of the historic comparison between sorafenib and lenvatinib, we really are dependent on, for example, differences in terms of inclusion and exclusion criteria for the clinical trials. Once again, you heard from Rich that the REFLECT trial excluded patients with greater than 50% liver involvement, excluded patients with extrahepatic main portal vein invasion, and excluded patients with bile duct invasion, and so if you see some of those patients you may be more likely to use sorafenib. We've also heard some differences in terms of the AE profile between sorafenib and lenvatinib, and many of us use these differences when we are choosing between these 2 agents. And I think the other big difference that's highlighted in red here is that sorafenib actually has much more real-world effectiveness data behind it, and so we can use it in extended patient populations with some safety data, including patients with Child-Pugh B cirrhosis.

But these gross clinical features are truly how we've been deciding between the agents that have been available on market.

Likewise, I think we're going to have to use some of these clinical factors when we are thinking about atezolizumab and bevacizumab in the front-line setting.

When you think about the IMbrave 150 trial, here you can see the schematic, you can see some of the exclusion criteria that were listed, and you can see that patients with autoimmune disease, history of transplant, were excluded. Incompletely treated high-risk varices, these patients were excluded. Once again, you heard from Rich that all patients were required to undergo an EGD. And I think that this is one of the most important…selection factors as we use this treatment regimen in clinical practice, is this high risk of bleeding in the setting of bevacizumab. We know that cirrhosis is a high-risk state. We know bevacizumab can increase that risk. And so, this is really very important as we think of using this in our patients.

Likewise, we know that liver function is very important. The trial excluded patients with moderate-to-severe ascites; history of hepatic encephalopathy; and then finally, other risk factors for GI bleeding including chronic daily treatment with NSAIDS as well as significant thrombocytopenia with a platelet count less than 75,000. I think all of these factors were used in the clinical trial and I think have to at least be considered when we apply this in our clinical practice.

Now beyond that, one of the questions that I continue to see: Is there a difference in terms of viral etiology and does this need to be considered when we think about using atezolizumab and bevacizumab or other checkpoint inhibitors in clinical practice?

And, I think that this was a nice study that actually looked at this. And we see that when you take a look at patients who actually have hepatitis B, hepatitis C, or nonviral etiologies, we see no difference in terms of the immunologic background or the risk of actually having a response to immune checkpoint inhibitors. And likewise, when you take a look at the clinical trials, I think that this really is not a good treatment selection biomarker in terms of looking at response nor actually in terms of taking a look at AEs. And so really, I think viral status doesn't really play into our selection factors.

I'm going to next go to a patient case that I think highlights how we can think about applying atezolizumab and bevacizumab in our clinical practice.

So, this patient is a 56-year-old male, hepatitis C-related cirrhosis who was treated for their hepatitis C and achieved sustained virological response. Unfortunately, the patient was lost to follow-up, presented 2 years later symptomatically. But otherwise, feels healthy, good liver function, Child-Pugh A as you can see here, elevated alpha-fetoprotein. And unfortunately, the imaging shows multifocal bilobar HCC with the largest lesion being just under 10 centimeters and has vascular invasion. And so, given the fact that this patient has vascular invasion, fairly large multifocal bilobar disease, the patient was referred for systemic therapy.

And so, as we think of the next step here, this patient was referred to have an upper endoscopy and this is very important because this patient on upper endoscopy, despite having good liver function, was actually found to have large varices, red wale signs, and so really high risk of bleeding.

And so this is a patient where once again [we're] highlighting the fact that this is a very important selection biomarker clinically, and we would not use atezo/bev in this patient until the varices are eradicated, and this patient is [at] lower risk of bleeding. And so, this is probably someone that we would use instead one of our other targeted agents, whether that's sorafenib or lenvatinib, in the front-line setting.

Now, when we think of now moving away from this first-line setting into the second-line setting, once again you have heard from Mark that we have multiple agents approved in the second-line setting, all of these approved after sorafenib. But as you've heard, we've really shifted to atezolizumab and bevacizumab being the preferred front-line therapy in most patients with advanced HCC. And so, the question is, can we really apply all of these after atezo/bev being used in the front-line setting?

Now at least in my opinion, I've tried to color-code how I think of this after atezo and bev in the front-line setting. I think, once again, you acted upon the PD-1/PD-L1 axis with atezolizumab — and so it at least to me doesn't make sense to use single-agent PD-1 inhibition in the second-line setting, so nivo and pembro would fall much lower on my list. Otherwise, when you think of using bevacizumab — once again, you've acted on the VEGF axis as a single agent and so using ramucirumab acting upon the receptor, once again a lower likelihood of response at least theoretically. And then I put regorafenib also with a little bit of caution, because as you heard from Mark, regorafenib was really used in patients who tolerated sorafenib in the front-line setting as a safety marker. And so, at least in the way that we use it in clinical practice, we continue to use this in patients who have received prior sorafenib.

And so, at least the way that we approach this, is that we have used front-line and second-line agents otherwise in a big box that we can consider after atezo/bev, and so for most patients who have received atezo/bev, have progression or intolerance, we would consider sorafenib, lenvatinib, cabozantinib, or once again the IO doublet nivo and ipi as possible agents in the second-line setting.

Something else that we must consider as we use these immune checkpoint inhibitors — once again you've heard that these are very well tolerated, very good quality of life in most patients — however, it is important to remember that these can have immune-mediated adverse events. And you can see several of these listed here in the figure. And even though these are rare, they can be quite serious if and when they occur. And so it's important that we recognize these early, and we act upon them and either hold the immune checkpoint inhibitor or start steroids if and when needed.

The other thing that I'd say is that it's also very important for us to consider that these [agents] can have very important consequences if used in patients who have received any transplant, so let alone liver transplant but also kidney transplant, heart transplant, lung transplant, etcetera. These have been associated with high rates of graft loss and death in these patients and should not be considered in patients with a prior transplant.

So, in summary for this section, there is a strong desire and a need for biomarkers to help with patient selection, although unfortunately, this is an area of need. We don't really have anything right now. And so, we're really forced to rely on clinical characteristics and differences in clinical trial inclusion and exclusion criteria in the interim.

As you've already heard, atezo/bev has shown superior survival compared to TKI-based therapy, but once again careful patient selection is critical and TKI-based therapy does continue to play a role in some of these patients.

And then finally, we must continue to monitor patients on checkpoint inhibitor therapy for rare, albeit potentially serious adverse events, so we can act if and when necessary when these occur.

With that, I'm going to hand it back to my colleague, Dr. Mark Yarchoan to go through a clinical case to wrap up our session. Mark.

Dr. Yarchoan:
Thanks for that handoff. So, I'm going to present a case of a 70-year-old retired college professor named Bill from my clinic, who has no history of liver cirrhosis and is found to have abnormal liver enzymes on routine blood work. And tonight's a special night because Bill is actually able to join us here on our chat, so Bill, would you like to introduce yourself?

Bill:
Hi. I'm Bill. Patient One.

Dr. Yarchoan:
Bill, maybe you could just give us a sense, how did you actually find out that you had liver cancer?

Bill:
Actually, it was just pure luck. I had my annual physical and the doctor found raised levels of alkaline phosphatase and then from there went to ultrasound, CT scan, MRI, and finally the biopsy, which confirmed everything that was there. But lucky, I had no symptoms whatsoever.

Dr. Yarchoan:
Right. And, the scan on the right is from Bill's scan, as you can see, had an 8 centimeter by 6-centimeter mass in his liver. And, he had very good liver function. His bilirubin was normal. His synthetic function was excellent. His viral studies were negative. His AFP was within the normal range, which we know is a good prognostic feature in this cancer. And actually this was determined to be resectable and he underwent a resection for this cancer.

Bill, how was your experience with surgery and in particular how was your recovery from it?

Bill:

I'd never really been in the hospital before, so, I didn't know what to expect. I, at that time, I just thought that if you got liver cancer, well, that was basically the end and so you're going to operate, it wasn't a big deal. And, except I'd never been completely under before, I thought that might be my last view of the world. The recovery was not as bad as I thought. It was painful, but I remember thanking the doctors afterwards for feeling no pain and my wife said I kept on pressing that bedside button like crazy, which is probably why I didn't feel any pain. It took a couple of months to get back where I felt normal again. It was a big scar.

Dr. Yarchoan:
And unfortunately, your cancer came back after your surgery. This is your scan here on the right after surgery. The audience, you can see that there's a resection that happened. You can even see the surgical clips. And then, there's some areas, multiple regions of the liver, consistent with recurrence. Bill, how did you actually find out that your cancer had returned? Were you having symptoms at this point?

Bill:
It was through these scans.

Dr. Yarchoan:
Through the scans. Were you having symptoms at all or did you feel well at this point?

Bill:
No, I had no symptoms, no nothing. I went back and the surgeon said very disappointed, saying I didn't get it all, and then made a phone call. So, he was disappointed, too, he thought he had it.

Dr. Yarchoan:
And, if I recall this is about the time that we met, which now was November of 2018, is that right? And, you know, as the audience ...

Bill:
Correct, it was the same day that I found out.

Dr. Yarchoan:
I remember that day.

Bill:
That was exactly the same day I found out. He called over to you at 11. I saw you at 2.

Dr. Yarchoan:
Right. Today, if you were going to receive standard therapy, we likely would have offered you bevacizumab and atezolizumab as a front-line option, but, back then in 2018 our options were more limited and we discussed, if I remember, standard TKI therapy in the front-line setting or a clinical trial, which is what we opted for. Can you tell us a little bit about why you chose the clinical trial?

Bill:
Again, I sort of thought liver cancer was going to kill me anyway and I figured if I participated in this it might help someone else in the future by you doing the research that would help others. So, it really wasn't a choice. I remember looking at my wife and nodding and she nodded back and said yeah, go for it.

Dr. Yarchoan:
So, you enrolled in a Phase 3 trial called HIMALAYA, that was randomized, so one arm was sorafenib, which was the standard of care versus durvalumab, a PD-L1 immunotherapy versus durvalumab plus tremelimumab, which is anti-CTLA-4 as we learned about, and you were randomized to just the standard of care, after all the paperwork that we did. How did you feel about that decision?

Bill:
I remember you were disappointed, my wife was angry, and I was thinking, well, better than the placebo, but I didn't know what to expect either way, so I really wasn't that concerned. Like okay, I'm getting something that's supposed to be good. At that time, I wasn't even aware that there were that many treatment options available.

Dr. Yarchoan:
And, you went with the sorafenib as part of the trial and how did that treatment go? The pills that you were on at the time?

Bill:
Not very well. I remember reading the side effects and I had every one of them I think. It was not pleasant.

Dr. Yarchoan:

Okay. And unfortunately, even the first scan, if I recall, showed that the cancer was actually getting worse rather than stable or better. And so, at that point we discussed actually other options and again this was really back in very beginning of 2019, we didn't have all the options we have today. And we talked about starting immunotherapy with nivolumab and, tell me a little bit about what your thoughts were about starting immunotherapy. What were your concerns at the time?

Bill:
By that time, stuff was starting to come out about immunotherapy in general to treat lots of things and I always thought it was the idea you take stem cells, accelerate them, put them back in the body. And so, I started reading stuff about this. And said, this has really come a long way. I was really pleased and actually eager to get with it.

Dr. Yarchoan:
And, tell us a little bit about what happened next.

Bill:
I had no side effects from it at all and the tumors started getting smaller and smaller and smaller each scan I got. So, it was actually very exciting.

Dr. Yarchoan:
It was exciting for me as well. As our audience knows, the response rate to single-agent PD-1 is probably less than 20%, and to have a response is always a great thing. And in this case, Bill went on to actually have a complete response, which is even rarer, where he had complete regression of all the lesions that you see and his bone disease also completely regressed, although it's very hard to assess bony lesions because the bone doesn't always completely heal. And you've been on immunotherapy now since the beginning of 2019, is that right?

Bill:
I have been, yes.

Dr. Yarchoan:
That's great. And, my last question for you is, it's not every day that we get to hear from our patients this way, so what advice would you have for other physicians who are treating patients with liver cancer?

Bill:
I would advise them to have someone present at the appointments. And that's actually another way that the COVID has affected me. My wife, who happens to be a research librarian, was with me and took notes during the meetings. Because as a patient, when you would hear some of these words, like even initially, 'you've got cancer', your mind focuses on that and doesn't pay attention to some of the details you're getting. So she was there with me during this, taking notes as you know, asking lots of questions, because she knew a lot more about liver cancer than I did after she found out that I had it. So, having someone there serving as medical interpreter and advocate for you, I think is crucial. And I think that's true even during these COVID times because even now she can't go to my appointments, I know she'd love to be there. And sometimes I'd come home and I'd say, oh, that's right, I forgot to tell you this, I forgot to tell you this, because I wasn't paying strict attention to some of the things that were said, because sometimes the information is so compressed or so dense that you forget some of it. So, I would say that's a *very* important thing, is to have someone else there with you. And I think the doctor should sort of insist on that.

Dr. Yarchoan:
Yeah and we appreciate having your wife at those meetings — definitely helped with our conversations. I know she's been a great advocate for you the whole way. So, thanks for sharing your story with all of us.

Dr. Finn:
So, wow, what a special treat to have Bill with us. I think all of us who treat liver cancer patients are inspired by patients like yourself, and that's what has kept us going. You know, Bill, there were 10 years that all we had was sorafenib and it helped people, there's no doubt it's still an important drug in the management of patients. But when we see patients like you that have these dramatic responses, that's very inspiring and what drives us, I think, to keep looking for new things.

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