# IMPROVING THE MANAGEMENT OF HCC:
## best practice and future directions

CME Accredited

ILCA 2019 – 13th Annual Conference
of the International Liver Cancer Association

Independent Satellite Symposium
Friday 20th September

## SCIENTIFIC SUMMARY

**Chaired by Dr Andrew Zhu**
With Dr Peter Galle and Dr Richard Finn


Andrew Zhu


Peter Galle


Richard Finn

Springer Healthcare IME

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## Educational grant

This activity is supported by an education grant from Eli Lilly and Company.

## Welcome message

Dear Colleagues,

Thank you for downloading this report from our independent satellite symposium "Improving the management of HCC: best practice and future directions" which took place at the 13th Annual Conference of the International Liver Cancer Association (ILCA).

The ILCA annual meeting is the leading scientific forum in the liver cancer field connecting hundreds of international participants from all related disciplines to exchange their knowledge and best practices in general sessions, symposia, workshops and networking sessions.

In this symposium we discussed the evolution of the landscape of hepatocellular carcinoma (HCC) treatment. We find ourselves in very exciting times when novel and emerging therapies may offer the possibility for individualized treatment in HCC. Our esteemed faculty looked at current standards of care determined by disease stage and progression rate, and how the characteristics of tumor microenvironment interactions can help with developing new treatment strategies in HCC.

We hope that your knowledge and understanding of this area will be enhanced by the information contained within this report and that you can utilise the learning in your daily practice.

Yours faithfully,

Andrew Zhu, Chair

## Faculty biographies

**Andrew Zhu (Chair)**
Professor of Medicine,
*Harvard Medical School, Massachusetts General Hospital Cancer Center, USA*

Dr Andrew Zhu is Professor of Medicine at Harvard Medical School and Director of Liver Cancer Research at Massachusetts General Hospital Cancer Center. His research focuses on developing therapies and biomarkers for hepatocellular carcinoma (HCC) and cholangiocarcinoma, and characterizing genetic mutations associated with these conditions to assess their impact on clinical outcomes and explore molecular mechanisms of drug resistance.

Dr Zhu has served as principal investigator in many clinical trials. He led early development of several molecularly targeted and immunotherapy agents in liver cancers, and studies into circulating and imaging biomarkers. He has received the V Foundation Translational Research Award, Lorenzo Cappussotti Award, and Jonathan Kraft Translational Award.

Dr Zhu is a founding board member of the International Liver Cancer Association, Fellow of American College of Physicians, and a member of ASCO and AACR. He serves on the Hepatobiliary Cancer Committee of the National Comprehensive Cancer Network, the Grants Selection Committee of ASCO, the Hepatobiliary Cancer Task Force of The NCI Gastrointestinal Cancer Steering Committee, the American Joint Committee on Cancer Hepatobiliary Task Force, the Hepatocellular Carcinoma Practice Guidelines Committee of the American Association for the Study of Liver Diseases, and the Clinical Advisory Board of The Cholangiocarcinoma Foundation.

**Peter Galle**
Director of Internal Medicine
*University Medical Center, Mainz, Germany*

After majoring in internal medicine, Dr Peter Galle received an MD from Marburg University and a PhD from Heidelberg University, where he was a postdoctoral fellow at the Centre for Molecular Biology. He completed his residency in internal medicine and gastroenterology at the University Hospital of Heidelberg and, in 1998, became Director of the Internal Medicine Department in Mainz. He was CEO of Mainz University Hospital from 2005–2008.

Dr Galle is a member of several societies, including the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (EASL). He has served as Executive Board Member and President of the International Liver Cancer Association, and Congress President of the German Society for Digestive Diseases. Dr Galle is 2020 President-elect of the German Association for the Study of the Liver.

Dr Galle's research has focused on apoptotic cell death in the liver, immune escape of tumor cells, and clinical and molecular aspects of HCC. He has published more than 500 peer-reviewed papers, and was awarded several prizes, including the prestigious Tannhauser award. Dr Galle chaired the panel updating the 2018 EASL Clinical Practice Guideline on HCC and has served as Co-editor for the Journal of Hepatology.

**Richard Finn**

Professor of Clinical Medicine

*Geffen School of Medicine, University of California Los Angeles (UCLA), USA*

Dr Richard Finn is a Professor of Clinical Medicine in the Department of Medicine, Division of Hematology/Oncology at the Geffen School of Medicine. He is also Director of the Signal Transduction and Therapeutics Program at the Jonsson Comprehensive Cancer Center, UCLA.

Dr Finn's research interests lie in the development of molecular targeted agents and biomarkers in liver and breast cancer, with a particular interest in identifying predictive markers of response to novel therapeutics. He has served as principal and sub-investigator in trials exploring the use of targeted therapies, and has led the approval of palbociclib, the first CDK 4/6 inhibitor in cancer medicine. Dr Finn's work has been widely published in respected journals, and he is a Senior Editor of Clinical Cancer Research and on the editorial boards of the Journal of Hepatology and Liver Cancer.

Dr Finn is a member of the American Society of Clinical Oncology, American Association of Cancer Research and the European Society of Medical Oncology and has presented at major meetings organised by such societies (ECCO / ESMO / ASCO / AACR). He is also the immediate past President of the International Liver Cancer Association.

# UPDATES IN HCC PATHOPHYSIOLOGY AND DIAGNOSIS

## Dr Peter Galle

Dr Galle began his presentation by stating that HCC represents an "unusual situation" at diagnosis. In contrast to any other solid tumor, in HCC it is possible to skip biopsy, with the exception of non-cirrhotic patients, in which biopsy is required. The reason why it is possible to rely on radiographic imaging is the peculiar vasculature of HCC; hyperperfusion abnormality is a key characteristic for diagnosis.

In addition, alpha fetoprotein (AFP) can support the diagnosis of HCC as a serological biomarker. Although there is no specific threshold to determine diagnosis, AFP has different roles in the management of HCC[1] (Figure 1).

| | |
|---|---|
| **Pathophysiology** | Correlation with molecular HCC classes |
| | Association between AFP high subclass and VEGF levels |
| **Clinical relevance** | AFP for defining patients at risk of HCC development (problem cut-off) |
| | AFP for surveillance in HCC |
| | AFP as a diagnostic tool in HCC |
| | AFP as prognostic factor:<br>· For candidates to resection/ablation<br>· As predictor of drop-out in waiting list<br>· As prognostic factor for HCC in LT/LDLT<br>· Prognostic factor in BCLC B treated with TACE<br>· AFP-based scores (in combination with other markers) |
| | Role of AFP as stratification factor in RCT |
| | Role of AFP as predictor of response to treatment |

**Figure 1**. The different uses of AFP as a serological biomarker for HCC. Galle, P, et al. *Liver Int* 2019; In press
AFP, alpha fetoprotein; BCLC, Barcelona clinic liver cancer staging system; HCC, hepatocellular carcinoma; LT, liver transplantation; LDLT, living donor liver transplantation; RCT, randomised controlled trial; TACE, transarterial chemoembolization; VEGF, vascular endothelial growth factor

Dr Galle gave some examples of the arguments against the use of biopsies, such as the possibility of a reliable diagnosis using noninvasive radiologic imaging and obtaining misleading results of small lesions with a diameter of 1–2 cm. Biopsies also have associated risks such as bleeding (particularly in cirrhosis patients)[2], possible injury of other organs, and needle track seeding[3].

## HCC biopsy in the future

These arguments were created almost two decades ago when there were no therapeutic options available, the presenter commented. By not using biopsies, the opportunity to find biomarkers for patient stratification is lost and "this, in the future, will be absolutely required in order to obtain an idea of who is responding to what therapy," he highlighted. Biopsy is also needed to find genetic variations which can be used for clinical characterization of HCC[4].

Dr Galle also described the importance of the signaling pathways involved in the pathophysiology of HCC, which could help to classify patients according to prognosis; there are with several pathways helping to define new therapeutic strategies targeted at these subgroups in HCC[5]. Nonetheless, at present, we can only treat HCC on a patient-by-patient basis due to the lack of oncogene addiction in this tumor type[6].

## Tumor microenvironment and immunotherapy

Dr Galle then explained the importance of the microenvironment surrounding the tumor which, through gene expression profiling, has been proven to be predictive of HCC patient survival and can make a difference with respect to prognosis[7]. Tumor cells are in close proximity with the large variety of cells included in their microenvironment; particularly important are the escape mechanisms that the tumor uses to avoid immune attachment. Immune checkpoint molecules have been shown to play a crucial role in the immune evasion of tumor cells[8] (Figure 2). "How does the tumor fight against T-cell attack; this is the hallmark of immune therapy," he remarked.

He explained that the majority of patients do not respond to immunotherapy. Furthermore, it has been suggested that roughly a quarter of nonresponsive HCC patients are characterized by an inflammatory signature, which might be predictive of outcome after immunotherapy[9]. In addition, the immune contexture of HCC correlates with survival as it has been shown that upregulation of T-cells and cytotoxic cells, and downregulation of T helper type 2 (Th2) cells and macrophages, produces an immune signature that can differentiate between patients with good and bad prognoses[10].

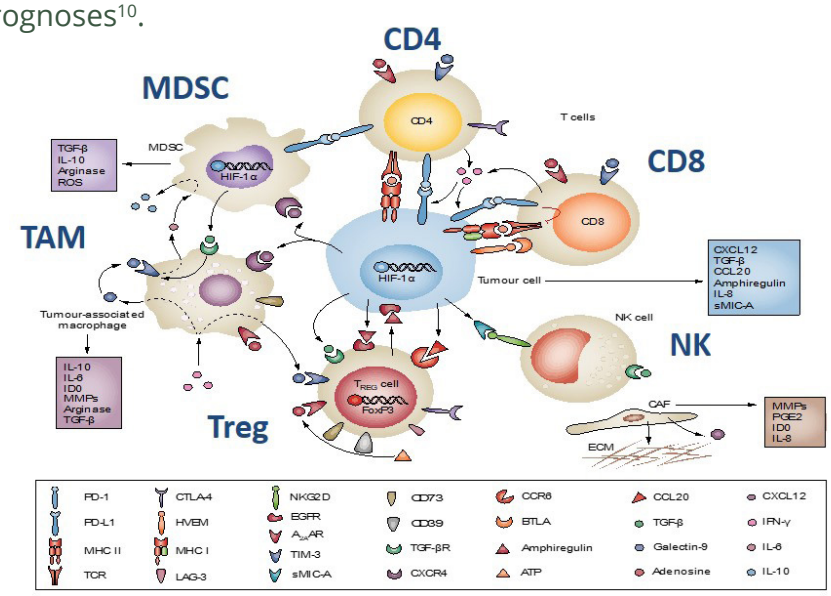


**Figure 2**. The tumor microenvironment of HCC inhibits immunogenic functions. Prieto, J, et al. *Nat Rev Gastroenterol Hepatol* 2015; 12: 681–700

## Conclusions

To close his presentation, Dr Galle advocated for the use of biopsies in the diagnosis of HCC to provide important histologic and epigenetic information on the tumor and its microenvironment. He also highlighted that HCC is characterized by molecular heterogeneity and activation of prognostic adverse signaling pathways; this molecular diversity requires individual treatment strategies for which biopsies are needed. In addition, he strongly emphasized the importance of the tumor microenvironment, particularly the immune cells which might, in the future, indicate which therapeutic strategy will be most effective.

Click here to view a clip from Dr Galle's presentation

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# OPTIMIZING SEQUENCING OF THERAPIES IN HCC

**Dr Andrew Zhu**

Dr Zhu opened his presentation stating that the treatment for HCC has changed from chemotherapy to targeted therapy and immune therapy, and at present a combination strategy is actively pursued. In the USA, there are seven approved drugs for the treatment of advanced HCC; five of these were approved based on data from phase III clinical trials: sorafenib[1] and lenvatinib[2] in the first line; and cabozantinib[3], regorafenib[4], and ramucirumab[5] in the second line. Clinical data from phase II studies led to accelerated approval of the two immunotherapy agents, nivolumab[6] and pembrolizumab[7], both in the secondline.

## TKI therapy in the first- and second-line

Dr Zhu focused on the clinical trials that led these agents to approval, starting with the SHARP and Asian-Pacific clinical trials, which resulted in regulatory approval for first-line sorafenib after demonstrating a visible improvement in overall survival (OS) compared with placebo[8,9]. Also in the first-line setting, the REFLECT trial demonstrated that lenvatinib was noninferior to sorafenib in OS but did not show superiority. Looking at secondary endpoints, both progression-free survival (PFS) and the overall response rate (ORR) were significantly in favor of lenvatinib[10].

In the second-line setting, Dr Zhu started by describing the RESORCE trial, which showed significantly better OS with regorafenib versus placebo in patients who had previously progressed on sorafenib therapy[11].

The next agent to be discussed was cabozantinib, with the CELESTIAL trial showing a significant OS benefit compared with placebo for patients who had progressed on sorafenib[12]. The REACH-2 study of ramucirumab in the second line for patients with a baseline AFP of at least 400 ng/mL also showed improved OS versus placebo[13].

## Immunotherapies in the first- and second-line

CheckMate 040 looked at nivolumab in patients with or without hepatitis C or B virus (HCV/HBV) infection and found a “durable response” across the subgroups, regardless of whether sorafenib had been used previously (Figure 1). These results led to an accelerated approval from the US Food and Drug Administration (FDA)[1,14]. Pembrolizumab also achieved a response in the KEYNOTE-224 clinical trial across different etiologies and achieved an accelerated approval for this indication by the FDA[7,15,16].

## What to choose?

Dr Zhu highlighted the challenge of how to select and sequence each agent in clinical practice and described some of the factors that might make this decision more difficult, such as lack of level 1 evidence, and reliable predictive biomarkers for immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs). In the end, the decision must be influenced by the safety profiles of each agent, the tumor burden and aggressiveness in individual patients, and the subgroup analyses in the phase III trial results.

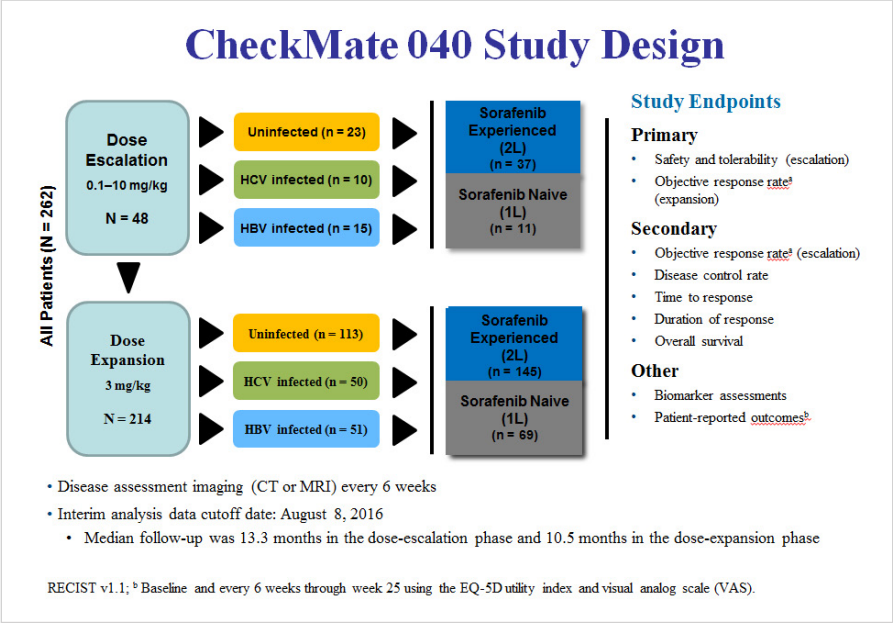


**Figure 1**. CheckMate 040 study design
Melero I, et al. *26th Conference of the Asian Pacific Association for the Study of the Liver* 2017
HCV: Hepatitis C; HBV: Hepatitis B

For first-line treatment, Dr Zhu noted that for sorafenib, there is extensive clinical experience with adverse events, management, and dosing adjustment and superior benefit for the HCV-positive subgroup. On the other hand, lenvatinib has achieved longer PFS and a higher ORR across patient subgroups.

For second-line, the selection of the treatment "is more challenging," stated Dr Zhu. Regorafenib is only suitable for patients who have tolerated prior sorafenib, while cabozantinib is suitable for patients with more than one line of prior treatment. Baseline AFP greater than 400 ng/mL can indicate the suitability of ramucirumab, while nivolumab or pembrolizumab should be considered for patients with a high tumor burden.

## Conclusions

To conclude, Dr Zhu remarked that targeted therapy and ICIs (in the USA) have become the standard of treatment for advanced HCC, but there is an unmet need to identify molecular biomarkers capable of predicting response to these agents. He closed his talk by saying that clinicians should make clinical decisions based on the safety profiles, tumor aggressiveness including AFP level, tumor burden, and other subgroup factors.

Click here to view a clip from Dr Zhu's presentation

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# THE EVOLVING LANDSCAPE OF HCC TREATMENT

**Dr Richard Finn**

Dr Finn opened his presentation by stating that "cancer is a rapidly changing space and at the moment we are in the phase of choosing where to go." While sorafenib and lenvatinib are the front-line options, and second-line treatment is supported by the data explained previously, more frequently there will be patients in need of third-line therapy or beyond. Dr Finn said that choosing the optimal sequence is going to be based on previous experience using the same drugs in other tumor types.

## Third-line and beyond – the challenges

The challenge associated with new drugs is where to place them, he explained. There are no second-line phase III studies because there is no suitable control arm. Another option for new agents is to trial them in the third line, but they may also be placed in the front-line in a combination regimen based on strong rational or used within a biomarker-selected population.

The presenter explained that, although there have been cases of accelerated approval based on phase II studies, phase III data are lacking.

In the case of pembrolizumab in the KEYNOTE-240 study for pembrolizumab versus best supportive care in the second line, Dr Finn remarked that although the p-value was 0.01 (not significant), PFS went from 2.8 to 3.0 months. The study showed pembrolizumab improved OS by over 3 months but again the p-value was 0.02 and not significant[1]. These results show that the drug is active with a response ratio of 17% according to the phase II study. The phase III CheckMate 459 also failed to demonstrate a significant PFS for nivolumab versus sorafenib for patients with newly diagnosed unresectable HCC[2].

## Combining TKI and immunotherapy approaches

Dr Finn then explained lenvatinib, a TKI approved in front-line with a complex mechanism of action highlighting the importance of fibroblast growth factor receptors (FGFR), this component is able to reverse resistance to anti-angiogenic drugs. There are some data on the combination of TKIs with ICIs which show significant activity.

For example, a phase Ib/II study of first-line lenvatinib plus pembrolizumab for unresectable HCC has achieved an ORR of 27%, Dr Finn said. While the mechanism behind this response is yet unclear, perhaps related to lenvatinib's effect on the tumor microenvironment, this combination is now being moved into a phase III study, he commented[3].

Another study presented at American Society of Clinical Oncology (ASCO) 2019 for regorafenib plus nivolumab in colorectal and gastric cancer suggested an ORR of around 40%, in patients who had not previously responded to single-agent nivolumab or another PD-1 inhibitor[4]. This leads to the idea of a synergy between TKIs and PD-1 inhibitors, Dr Finn said. Lenvatinib plus pembrolizumab were FDA approved recently in uterine cancer based on single-arm, phase II data[5].

In addition, the PD-1 inhibitor durvalumab and the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor tremelimumab have been evaluated in a phase I/II study of unresectable HCC showing response rates that are "not as robust as the TKI combinations," Dr Finn said. This has progressed to the HIMALAYA randomized study of the combination versus sorafenib in front-line[6,7]. Nivolumab plus the CTLA-4 inhibitor ipilimumab as a combination therapy has also shown response rates around 30% in advanced HCC patients who have previously received sorafenib, and this study will be moving into phase III[8].

Dr Finn referred then to bevacizumab plus atezolizumab data, which have been updated at ILCA 2019[9] and will be updated again at ESMO 2019[10]. He focused on the mechanism of action of bevacizumab, which modifies VEGF signaling; there has been evolving data suggesting that altering VEGF alters the immune microenvironment, producing a change in the balance between T-cells, suppressor cells, and activating cells (Figure 1) that may make tumors more sensitive to PD-L1 inhibition.

## Phase III front-line combinations

"ImBRAVE 150, in untreated patients with advanced HCC, showed very interesting overall response rates, 36% by independent review RECIST, 39% by modify RECIST; this speaks to the new benchmark that we are looking at for phase III studies with combinations in the 30% line," Dr Finn said. This combination appears to be tolerable with most toxicity from bevacizumab[11].

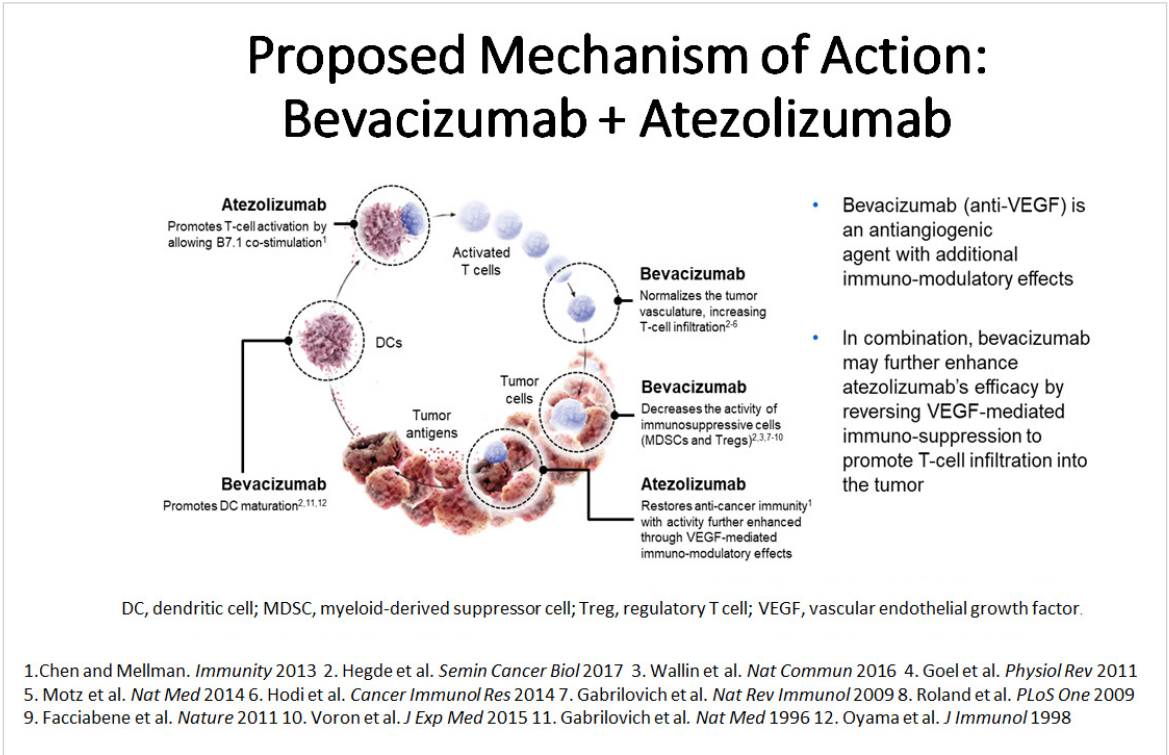


**Figure 1**. Proposed mechanism of action: bevacizumab + atezolizumab
Pishvaian MJ, et al. *Ann Oncol* 2018; **29** (8): LBA26

There are several other ongoing phase III front-line studies. The RATIONALE clinical trial is testing the noninferiority of the PD-1 inhibitor tislezizumab versus sorafenib[12]; LEAP 002 is comparing the combination of lenvatinib and pembrolizumab versus lenvatinib monotherapy[13]; HIMALAYA is testing the combination of durmalumab and tremelimumab versus sorafenib[14]; and the COSMIC trial is comparing cabozantinib and atezolizumab versus sorafenib[15].

## Conclusions

To conclude his presentation, Dr Finn remarked that level 1 evidence for ICIs is still needed, including the awaited results for nivolumab versus sorafenib in the front line and pembrolizumab versus placebo in the second line. He also stated that after nearly a decade of negative data, there has been four positive phase III studies of new drugs in advanced HCC that improve survival: lenvatinib, regorafenib, cabozantinib, and ramucirumab. However, these studies look at monotherapies while "the next step is combination therapy", Dr Finn said, and this should begin to focus on an approach to the second line.

Click here to view a clip from Dr Finn's presentation

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## PUTTING EVIDENCE INTO PRACTICE: CASE STUDIES AND PANEL DISCUSSION

**Dr Andrew Zhu, Dr Peter Galle and Dr Richard Finn**

**Case 1**: Dr Galle described an example of the diagnosis and the therapeutic flow in a given patient. He started by explaining the characteristics of the patient, a 46-year-old man with elevated liver enzymes. The patient presented with fatigue and pruritus. He was obese and has had insulin-dependent type 2 diabetes for 20 years, as well as arterial hypertension and hyperlipidemia. Biopsy confirmed a fatty liver and cirrhosis, which led the patient to undergo surveillance for liver cancer. After 1.5 years, the patient presented with HCC (Figure 1) and was recommended for transplantation and bridging with transarterial chemoembolization (TACE). Dr Galle showed an image of the explanted liver, which presented with some necrosis, TACE beads and still some remaining tumor tissue.

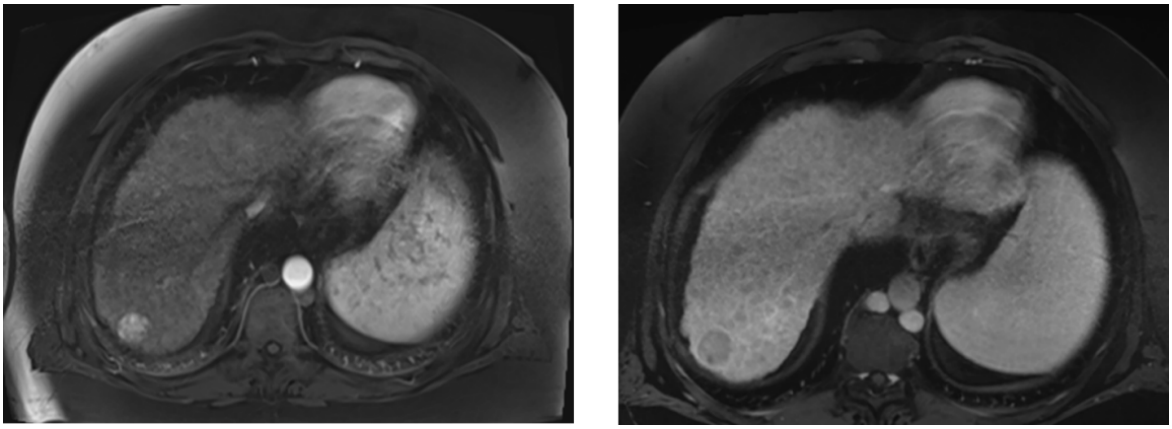

**Figure 1**. Surveillance – 18 months later

**Case 2**: Dr Finn described the patient as a 64-year-old man with a history of cirrhosis from HCV and alcohol. Initially presenting with abdominal pain and syncope, he was found to have hemoperitoneum from a peripheral 5 cm tumor that had ruptured and multi-focal HCC. The patient underwent urgent embolization and was presented for management. He eventually recovered Child Pugh A liver function and underwent repeat TACE but developed multiple new lesions after the procedure. He did not have extrahepatic spread or microvascular invasion.

Dr Zhu suggested that in the absence of an available clinical trial, this patient should be given sorafenib or lenvatinib, with a preference for sorafenib, as a safer choice with the earlier bleeding events of this patient. Dr Galle was in favor of systemic therapy but "theoretically this is still a patient that could go on with TACE," he added.

Dr Finn said the patient was started on sorafenib 200 mg twice a day in June 2016 and then titrated up to 400 mg twice a day without significant toxicity, despite a rising AFP during treatment from 3300 ng/mL to 4500 ng/mL, and then 5800 ng/ mL. Here he indicated that he does not usually make a decision based on AFP alone if the imaging is normal.

Dr Zhu agreed that he would not make a solid decision based on AFP level alone, but he would continue with imaging, with the expectation of progression.

With the patient progressing with sorafenib and a rising AFP, Dr Finn asked Dr Galle what would be his next step? From Dr Galle's point of view, "this would be the perfect patient for regorafenib based on the RESORCE trial[1], as this patient has tolerated sorafenib," he mentioned.

Agreeing with Dr Galle, Dr Finn also pointed out that cabozantinib could be also an appropriate choice, while nivolumab and pembrolizumab are both options in the USA, and also ramucirumab, which Dr Galle supported, saying that "one could take the high level of AFP as a direct open door for ramucirumab."

Dr Finn confirmed that this patient was given ramucirumab, in the context of REACH-2 study[2]. The patient had a rapid fall in AFP and imaging was consistent with the response, with the patient continuing on ramucirumab for 13 months until he developed a rising bilirubin (3.0 mg/dL) that meant he had to come off the study despite no imaging evidence of progressive disease.

The patient began regorafenib 80 mg/day, with an attempt to titrate up to 120 mg/day but the higher dose was not tolerated. The patient presented with fatigue and asthenia, as well as a falling bilirubin level and gradually rising AFP level. Dr Finn said. He remained on regorafenib for 4 months until radiographic progressive disease and a rising AFP, as well as ascites, edema and a worsening Child Pugh B score. In the final stage, the patient received nivolumab for 3 months with no clear benefit, his liver dysfunction continued to worsen and he was referred to a hospice.

**Case 3**: Dr Zhu shared the last case study of a 49-year-old man with history of HBV, alcohol-related compensated Child Pugh A cirrhosis, and biopsy-proven multifocal HCC. He underwent bland embolization twice (June 2017 and October 2017). There was evidence of recent rapid disease progression with markedly elevated AFP. His performance status was excellent and his laboratory results were all within normal range. The liver MRI showed multifocal HCC, predominantly in the right hepatic lobe, and enlarged upper abdominal lymph nodes.

Dr Zhu invited the faculty to discuss what treatment could be recommended in that case.

Dr Finn said that lenvatinib is the appropriate option. And Dr Galle agreed, pointing out that "it is a difficult decision and if you talk to colleagues presenting this case many would favor immuno oncology (IO) therapy because of good tolerability and if it is active it would be very active, but it is not [supported] by phase 3 studies. So you are stuck here: lenvatinib or nivolumab," he concluded.

Dr Zhu agreed with Dr Galle's recommendation for lenvatinib but noted that ICIs could be used as an alternative, or in combination if there was an available clinical trial.

Dr Zhu closed his case by stating that the patient achieved disease stabilization for 4 months and then progressed, an ICI was added and this treatment continued for 6–8 months before further disease progression.

## REFERENCES


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# SUMMARY AND CLOSE

The three faculty members have given the current landscape of treatments for advanced HCC and the future possibilities. Dr Zhu closed the session by saying that although there are still many challenges in this field and they don't have all the answers, continuing with this research will hopefully help bring more opportunities to the patients.

# IMPROVING THE MANAGEMENT OF HCC:
## best practice and future directions

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