

# Update on hepatocellular carcinoma from the 2018 Gastrointestinal Cancer Symposium (ASCO GI)

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**Abstract :** At the 2018 Gastrointestinal Cancer Symposium, sponsored by the American Society of Clinical Oncology, significant advances in the management of hepatocellular carcinoma (HCC) were announced. In intermediate-stage disease (Barcelona Clinic Liver Cancer stage B), interest in combining transarterial chemoembolization and sorafenib has been reignited as a consequence of the TACTICS trial. In advanced-stage disease (BCLC C), external-beam radiotherapy combined with transarterial chemoembolization proved to be superior to sorafenib in patients with portal vein thrombosis according to the START trial. Also, in patients with advanced-stage HCC, the CELESTIAL trial demonstrated survival benefits for patients undergoing treatment with cabozantinib in the second-line setting. Lastly, recent data on the activity of pembrolizumab in patients with HCC highlight the role of immunotherapy in the management of this disease in the years to come.

**Keywords:** hepatocellular, carcinoma, liver, cancer, meeting, highlights, ASCO

## Introduction

The 2018 Gastrointestinal Cancer Symposium (ASCO GI) was held in San Francisco (CA, USA) from January 18th through January 20th. In this meeting, breakthrough developments in the management of hepatocellular carcinoma (HCC) have been announced. In the intermediate-stage disease (BCLC B), the role of antiangiogenic therapy during transarterial chemoembolization (TACE) was revisited. In patients with HCC and portal vein thrombosis (BCLC C), the combination of external-beam radiotherapy and TACE proved to be more effective than sorafenib. Lastly, in advanced-stage HCC (BCLC C), cabozantinib was associated with improved survival outcomes when compared to placebo in the second-line setting, and pembrolizumab reinforced the activity of immune checkpoint inhibitors in HCC. In this report, we summarize the findings of the studies concerning HCC presented in the abstract section of the 2018 ASCO GI.

## TACE plus sorafenib in unresectable HCC – TACTICS trial (abstract number 206)

There is a strong biological rationale for combining TACE and sorafenib in patients with intermediate-stage HCC. Despite the fact that previous trials, including Japan–Korea post-TACE,<sup>1</sup> SPACE,<sup>2</sup> and TACE 2,<sup>3</sup> have portrayed disappointing results of TACE plus sorafenib in this setting, significant issues have been raised about these studies, and the proper role of sorafenib in intermediate-stage HCC remains elusive. To further explore the part played by sorafenib in this scenario, Kudo et al<sup>4</sup> (Kindai University Faculty of Medicine, Osaka, Japan) presented the results of a randomized Phase II

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trial comparing TACE plus sorafenib with TACE in patients with unresectable HCC – the TACTICS trial.

Eligible patients included those with unresectable HCC, Child–Pugh score  $\leq 7$ , up to two previous TACE treatments, and up to ten hepatic nodules. The study was carried out exclusively in Japan, and conventional lipiodol TACE was used on demand in this trial. Sorafenib was to be given at the dose of 400 mg daily with subsequent dose escalation to 400 mg twice daily upon adequate tolerance after the first TACE. The co-primary endpoints of the study were progression-free survival and overall survival. One hundred fifty-six patients were randomized to either TACE plus sorafenib ( $n=80$ ) or conventional TACE ( $n=76$ ). The patient population consisted mainly of patients with ECOG performance status 0, Child–Pugh score 5, and intermediate-stage HCC. Hepatitis C virus infection was the most common cause of underlying chronic liver disease, and most of the patients were TACE-naïve. Sorafenib was given for a median of 38.7 weeks (mean: 57.1 weeks) and the median dose of the drug was 355.2 mg/d (mean: 353.6 mg/d).

According to the data presented at the meeting, the combination of TACE plus sorafenib was associated with improved progression-free survival (hazard ratio [HR] =0.59, 95% CI: 0.41–0.87;  $P=0.006$ ). Median progression-free survival interval in the TACE plus sorafenib arm was almost twice as high as in the TACE arm (25.2 vs 13.5 months). Moreover, time to unTACEable progression (HR =0.57, 95% CI: 0.36–0.92;  $P=0.02$ ) and time to progression (HR =0.54, 95% CI: 0.35–0.83;  $P=0.005$ ) also favored the combined treatment. At the time of the presentation, overall survival data was considered to be immature, as the target number of survival events had not as yet been reached. Importantly, the toxicity profile of the combined treatment was considered mild, with differences related to the adverse event profile of sorafenib.

Altogether, the data from the TACTICS trial reassures the safety of the TACE plus sorafenib combination. While we await the results of the overall survival analysis, data on progression-free survival seem promising. By comparing the results of this trial with the findings of previous ones, it seems that a longer duration of sorafenib and a less restrictive TACE schedule might be key factors in the success of this approach.<sup>4</sup>

### External-beam radiotherapy plus TACE in patients with PVT – START trial (abstract number 210)

Based on randomized clinical trials, the proper management of patients with portal vein thrombosis (PVT) com-

plicating HCC (advanced-stage disease) entails the use of sorafenib.<sup>5,6</sup> Nevertheless, in this setting, the disease is still confined to the liver and local approaches might offer an opportunity to halt hepatic disease progression and possibly improve survival outcomes. To test this concept, Yoon et al<sup>7</sup> (Asan Medican Center, Seoul, Korea) have conducted a randomized Phase II trial comparing external-beam radiotherapy plus TACE to sorafenib in patients with HCC and PVT.

Patients were included if they had Child–Pugh A hepatic function, ECOG 0–1, a first diagnosis of HCC with major vascular invasion, and at least one measurable lesion according to RECIST 1.1. The primary endpoint of the study was progression-free survival rate at 12 weeks. Ninety patients were randomized to treatment with external-beam radiotherapy plus TACE ( $n=45$ ) or sorafenib at standard dose ( $n=45$ ). Hepatitis B virus infection was the predominant cause of chronic liver disease in this population. Most patients had multinodular disease, and 60% of patients presented unilateral portal vein involvement.

Progression-free survival strongly favored treatment with radiotherapy plus TACE over sorafenib. Progression-free survival rates at 12 months were 86.7% and 34.3% for radiotherapy plus TACE and sorafenib, respectively. Likewise, external-beam radiation plus TACE was associated with improved median progression-free survival (30.0 vs 11.3 weeks,  $P<0.001$ ). Additionally, overall response rate (33.3% vs 2.2%,  $P<0.001$ ) and median time to progression (31.0 vs 11.7 weeks,  $P<0.001$ ) also favored the combined treatment approach. Importantly, radiotherapy plus TACE was shown to provide improved median overall survival over sorafenib in this setting (55.0 vs 43 months,  $P=0.04$ ). All the benefit came at no extra toxicity, as there were no significant differences in grades 3 or higher toxicities or in severe side effects between the two treatment arms.

As a result, based on this small randomized trial, the combination of external-beam radiotherapy and TACE provides improved outcomes to patients with HCC and PVT when compared to sorafenib. Treatment was very well tolerated, and this study highlights the need to further assess the role of local therapies in patients with HCC and PVT.<sup>7</sup>

### Cabozantinib after sorafenib in advanced-stage HCC – CELESTIAL trial (abstract number 207)

Until very recently, the only data from a randomized controlled trial supporting treatment for advanced HCC after

sorafenib failure stemmed from the RESORCE trial.<sup>8</sup> In this study, regorafenib was shown to improve progression-free survival and overall survival over placebo. Cabozantinib, an oral tyrosine kinase inhibitor with activity against VEGF receptors, MET, and AXL, has shown significant activity against HCC in a Phase II trial.<sup>9</sup> In the 2018 ASCO GI, Abou-Alfa et al<sup>10</sup> (Memorial Sloan Kettering Cancer Center, New York, NY, USA) have expanded the options for treatment of sorafenib-resistant advanced HCC when cabozantinib demonstrated superior outcomes when compared to placebo in the CELESTIAL Phase III trial.<sup>10</sup>

Patients were included if they had HCC not amenable to curative treatment, Child–Pugh A liver function, ECOG 0–1, and prior treatment with sorafenib. The study's primary outcome was overall survival. Seven hundred and seven patients were randomized at the 2:1 ratio to cabozantinib 60 mg daily (n=470) vs placebo (n=237). The trial included patients from the Asia-Pacific region, North America, and Europe, and almost 80% of patients presented extrahepatic disease at the start of trial. All patients had been previously treated with sorafenib, with a median total duration of sorafenib treatment of around 5 months.

In primary outcome analysis, cabozantinib was associated with increased overall survival (HR =0.76, 95% CI: 0.63–0.92;  $P=0.005$ ). Median overall survival times were 10.2 and 8.0 months for patients treated with cabozantinib and placebo, respectively. Overall survival benefits seemed even more impressive when patients treated previously only with sorafenib were analyzed. Progression-free survival was also improved with cabozantinib (HR =0.44, 95% CI: 0.36–0.52;  $P<0.001$ ). Median progression-free survival times were 5.2 and 1.9 months for patients treated with cabozantinib and placebo, respectively. All that benefit came as a result of disease stabilization, as only 4% of patients in the cabozantinib arm displayed objective responses according to RECIST 1.1. Nevertheless, there was a significant increase in the number of patients experiencing disease stabilization in the cabozantinib arm when compared to the placebo arm (60% vs 33%).

These results came at the expense of significant toxicity, as has been previously shown with regorafenib. Rates of dose reduction (62%) and permanent drug discontinuation due to treatment-related adverse events (16%) were in the ranges reported in the regorafenib arm of the RESORCE trial. Similarly, 68% of patients in the cabozantinib arm experienced at least one grade 3–4 adverse event (vs 38% in the placebo arm), and six patients in the cabozantinib arm died as a consequence of treatment (vs one patient in the placebo arm).

These data point to different possibilities in the management of sorafenib-resistant HCC. Now, randomized controlled trials have shown significant activity of regorafenib and cabozantinib in this setting. So far, these drugs have shown similar activity and toxicity profiles. That raises the question about the adequate sequencing of these drugs after sorafenib failure, and further studies are needed to answer this question.<sup>10</sup>

## Pembrolizumab in advanced-stage HCC – KEYNOTE-224 (abstract number 209)

Due to inflammatory milieu inherent to the process leading to the development of chronic hepatic disease and hepatic carcinogenesis, the use of drugs that aim to boost the immune system against HCC is very sound. Previous studies using the anti-PD-1 checkpoint inhibitor nivolumab (CheckMate 040)<sup>11</sup> and the anti-PD-L1 checkpoint inhibitor durvalumab<sup>12</sup> have demonstrated significant activity of these drugs in HCC. To build up on this, Zhu et al<sup>13</sup> (Massachusetts General Hospital Cancer Center, Boston, MA, USA) presented the data of patients with HCC treated with pembrolizumab in the KEYNOTE-224 Phase II trial. Once again, immunotherapy has shown compelling activity in the treatment of HCC.

In this study, patients with pathologically confirmed HCC, ECOG 0–1, Child–Pugh hepatic function A, and intermediate- or advanced-stage disease were enrolled. Patients also had to experience progression on sorafenib or intolerance to this drug. The study's primary outcome was overall response rate according to RECIST 1.1. All patients were treated with pembrolizumab 200 mg intravenous every 3 weeks. One hundred and four patients received at least one dose of pembrolizumab. Most patients had ECOG 0 and advanced-stage HCC as a result of extrahepatic spread. Also, 80% of patients had experienced disease progression on sorafenib previously.

Seventeen patients (16.9%) experienced objective response to treatment according to RECIST 1.1, and the disease control rate (sum of objective response rate and stable disease rate) was 61.5%. There was no difference in tumor response to pembrolizumab according to the etiology of the underlying liver disease. When treatment achieved disease response, it did so after a median of 2.1 months, and response to pembrolizumab lasted for a median of 8.2 months. Median progression-free survival was 4.8 months, and median overall survival had not as yet been reached at the time of the presentation. Grade 3 or higher toxicities were observed in 25% of patients, but permanent treatment discontinuation occurred in only 6.7% of patients. Also, no viral infection flares were observed.

The results of the KEYNOTE-224 reiterate the promising activity of anti-PD-1/anti-PD-L1 immune checkpoint inhibitors against HCC. Also, a favorable toxicity profile has been demonstrated, and so work is now being conducted to better select those more prone to experience benefit from these treatments and to assess the role of immunotherapy early in the management of advanced HCC.<sup>13</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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