

Lenvatinib in Hepatocellular Carcinoma

An Expert Interview with Miguel Marcao

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Miguel Marcao

Miguel Marcao has been working in oncology for 22 years and is currently vice president at Eisai, in charge of commercial operations across Europe, the Middle East, Africa, Russia and Australia. Miguel has extensive experience in leadership of multicultural teams across Europe and a strong scientific background with a degree in chemical engineering and Masters in biotechnology.

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Liver cancer is the second leading cause of cancer-related death, and has limited treatment options and a poor prognosis.¹ Mortality owing to liver cancer has increased in the past 20 years, with a reported incidence of 841,080 cases per year.² Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancer cases.¹ Multiple single agent and combination therapies have been investigated for the treatment of HCC but failed to show clinical benefit.³ Recently, the European Commission granted marketing authorisation to the oral receptor tyrosine kinase inhibitor lenvatinib mesylate (Lenvima®; Eisai, Tokyo, Japan), for the first-line treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy. This is the first new first-line treatment option for advanced or unresectable HCC to be approved in Europe in 10 years. Approval was based on the results of the REFLECT study.⁴ In an expert interview, Miguel Marcao discusses the findings of this study and the next steps in the clinical development of lenvatinib for the treatment of HCC.

Q. Why is the treatment of unresectable hepatocellular carcinoma such an important unmet need?

Firstly, because there is a very high level of mortality in HCC; it is the second leading cause of cancer death globally, with 70,000 deaths per year in Europe and about 4,000–5,000 deaths in the UK alone depending on the source of the data.⁵ It is a disease with a very poor prognosis; every year in Europe 82,466 cases are diagnosed and there are 77,375 deaths.² Part of the reason for this is that, for the last 10 years, only one systemic therapy, sorafenib, has been available for the treatment of advanced HCC; therefore, treatment options are limited for these patients.

Q. Could you tell us a little about the rationale behind and objectives of the REFLECT clinical trial?

The REFLECT trial aimed to demonstrate non-inferiority of lenvatinib when compared with sorafenib, the leading reference treatment, in terms of overall survival.⁴ This has been the objective of many trials of other drugs for HCC in the last 10 years, but REFLECT is the first study that met the primary endpoint.

Q. What were the key findings of this study?

The primary endpoint of overall survival by statistical confirmation of non-inferiority against standard of care was met.⁴ Within the secondary endpoints, lenvatinib demonstrated benefit compared with sorafenib in the response rate, i.e., progression-free survival, time to progression and objective response rate. Lenvatinib also showed statistically significant superiority and clinically meaningful improvements in the secondary efficacy endpoints. Progression-free survival was around 7.4 months with lenvatinib, which is double that of

current treatment, and response rate was around 3.5 times higher with lenvatinib: 41% of patients experienced significant shrinkage of the tumour.⁴

Q. What was the safety profile of lenvatinib in this study?

The safety profile was consistent with that seen with lenvatinib in other indications and with other drugs in this class. The most common adverse events were observed in around 30% of patients. These were hypertension, diarrhoea, loss of appetite, fatigue and weight loss.⁴ We are experienced in managing these symptoms. The study found nothing surprising in terms of safety.

Q. What are the next steps in the clinical development of lenvatinib for unresectable hepatocellular carcinoma?

Currently we are in the early stages of an extensive clinical trial programme investigating the combination of lenvatinib with pembrolizumab, in partnership with Merck Sharp & Dohme (Hoddesdon, Hertfordshire, UK). Two ongoing phase III studies are investigating this combination in metastatic renal cell carcinoma (Clinicaltrials.gov Identifier: NCT02811861)⁶ and advanced endometrial carcinoma (Clinicaltrials.gov Identifier: NCT03517449).⁷ Depending on the data, this combination will be studied in phase III studies in other indications including HCC. □

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