GASTROINTESTINAL CANCER

Combination set to transform HCC therapy

> we have achieved something we had not been able to do for over a decade: improve OS in the first line-setting

Patients with unresectable hepatocellular carcinoma (HCC) typically receive frontline monotherapy with the multikinase inhibitors sorafenib or lenvatinib. These agents provide limited survival benefits and are associated with considerable toxicities and poor quality-of-life (QOL) outcomes. Immune-checkpoint inhibitors (ICIs) have also been tested as monotherapies in patients with HCC, with disappointing outcomes to date. Now the results of the phase III IMbrave150 trial show that the combination of an ICI with an anti-VEGFA antibody leads to promising activity in this setting.

In IMbrave150, patients with locally advanced, metastatic and/or unresectable HCC were randomly assigned to receive atezolizumab plus bevacizumab (combination therapy; $n = 336$) or sorafenib monotherapy ($n = 165$). The co-primary end points of this trial were overall survival (OS) and progression-free survival (PFS). At a median follow-up duration of 8.6 months, the hazard ratio (HR) for death in the combination therapy group versus the sorafenib group was 0.58 (95% CI 0.42–0.79; $P < 0.001$). OS estimates at 6 and 12 months were 84.8% and 67.2%, respectively, with combination therapy, and 72.2% and 54.6% with sorafenib. Median PFS durations were longer in patients receiving combination therapy than with sorafenib: 6.8 months versus 4.3 months (HR 0.59, 95% CI 0.47–0.76; $P < 0.001$). At 6 months, PFS was 54.5% and 37.2%, respectively. The OS and PFS benefits were consistent across clinically defined subgroups. The confirmed objective response rates were 27.3%, including complete responses (CRs) in 5.5%, with combination therapy and 11.9%, with no CRs, with sorafenib.

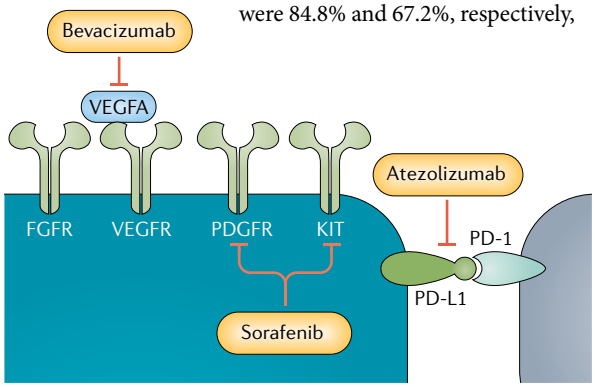
The median time to deterioration of patient-reported QOL, evaluated using the EORTC QLQ-C30 questionnaire, was longer for patients receiving combination therapy (11.2 months versus 3.6 months; HR 0.63, 95% CI 0.46–0.85). The incidence of adverse events (AEs) of any grade was similar in both groups: 98.2% and 98.7%. Serious AEs were more frequent with combination therapy (38.0% versus 30.8%), although the difference was not ≥2% for any AE. The most common grade 3–4 AE in patients receiving combination therapy was hypertension: 15.2% versus 12.2% with sorafenib. AEs led to treatment discontinuation in 15.5% of patients receiving combination therapy (with 7% discontinuing both treatments) and 10.3% of those receiving sorafenib.

"The results of IMbrave150 constitute an important milestone in our progress against this deadly disease. In addition, the favourable AE profile with this combination is really the icing on the cake," explains co-lead investigator Richard Finn. "This study represents a breakthrough comparable to the survival benefit of sorafenib over placebo presented in 2008," opines Josep Llovet, who was not involved in this study. He adds: "these results pose this combination as the first and only treatment superior to sorafenib so far, and thus, as the recommended standard first-line therapy for patients with HCC."

The results of IMbrave150 differ from those of previous clinical trials of ICIs in HCC. "The negative results of a trial comparing nivolumab with sorafenib in the first line of treatment and another comparing pembrolizumab with placebo in the second line represented an important drawback for the HCC community," states Llovet. "We know that single-agent ICIs are beneficial for a subset of patients, but the end points of randomized studies were not met," explains Finn, adding: "In this study, we have doubled the response rate of single-agent ICI. By doing so, we have achieved something we had not been able to do for over a decade: improve OS in the first line-setting."

The therapeutic activity of ICIs might be enhanced through combinations with other agents that promote antitumour immunity. In IMbrave150, this effect has been achieved with the incorporation of the anti-VEGFA antibody bevacizumab. Various combinations are currently being tested in phase III trials in the frontline setting. "Whether the combinations tested provide even better results will depend upon the capacity of specific kinase inhibitors and/or ICIs to transform immunologically 'cold' tumours into 'hot' tumours," Llovet concludes.

Diana Romero



Credit: Simon Bradbrook/Springer Nature Limited

ORIGINAL ARTICLE Finn, R. S. et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N. Engl. J. Med.* **382**, 1894–1905 (2020)