Ramucirumab treatment in hepatocellular carcinoma

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Liver cancer is the sixth malignant tumor in incidence and the third in mortality worldwide with 781,631 deaths per year (1). Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. Chronic liver disease and cirrhosis are present in most of the patients developing HCC. Viral hepatitis, alcohol abuse and nonalcoholic steatohepatitis are the foremost liver injuries preceding HCC (2). The Barcelona Clinic Liver Cancer (BCLC) staging classification is one of the widely recognized algorithms to classify HCC patients in prognostic stages. BCLC staging classification is a useful tool to select the most appropriate treatment for each scenario (3). In global terms, systemic treatment in HCC offers approximately 12 months of median overall survival (OS) for advanced stage (BCLC-C) and for intermediate stage (BCLC-B) patients who are refractory to locoregional therapies. Since 2008 when the SHARP study was published, the multikinase inhibitor sorafenib was the only systemic treatment approved to treat advanced stage HCC patients (4). In the recent years, several drugs have demonstrated additional efficacy in randomized clinical trials for HCC. Lenvatinib has shown non-inferiority survival to sorafenib in the first-line setting (5). Moreover, regorafenib and cabozantinib have both demonstrated significantly better survival improvement compared with placebo in the second-line setting (6,7). *Table 1* summarizes the main positive phase III trials with systemic treatment for patients with advanced HCC. Ramucirumab is a human IgG1 monoclonal antibody that binds to the extracellular domain of VEGFR-2 (vascular endothelial growth factor receptor 2); blocks the interaction of this receptor and its ligands, mainly VEGF-A; and inhibits endothelial proliferation and migration through

the inhibition of downstream signalling pathways (10). Ramucirumab anticancer activity was firstly observed in a phase II trial with HCC patients treated in first-line. Median OS was 12 months with an acceptable toxicity profile (11). As a result, a randomized phase III trial was designed to confirm this activity. The REACH study randomized 565 HCC patients to receive ramucirumab or placebo in second-line after previous treatment with sorafenib (12). The characteristics of the patients included were: BCLC-C stage or BCLC-B after failure of locoregional therapies; Child-Pugh A liver disease and ECOG 0 or 1. The primary endpoint of OS improvement was not met, with a median survival of 9.2 months with ramucirumab and 7.6 months with placebo (HR 0.87; P=0.14). In the prespecified subgroup analysis, those patients with a baseline alpha-fetoprotein (AFP) concentration of 400 ng/mL or higher had a significantly improved survival with ramucirumab.

In this setting, to confirm the previous hypothesis, a new randomized trial was designed. Zhu *et al.* have recently reported in Lancet Oncology the results of the REACH-2 study, a randomized, doble-blind, placebo-controlled, phase III trial of second-line ramucirumab for HCC patients (9). The population of this study was similar of that in the REACH trial: BCLC-B or C stage disease; Child-Pugh class A liver disease; ECOG 0 or 1; and sorafenib intolerance or refractoriness. Nonetheless, only HCC patients with an elevated AFP of 400 ng/mL or higher could participate in the trial. The study met its primary endpoint achieving a statistically better OS with ramucirumab compared with placebo with a median survival of 8.5 versus 7.8 months (HR 0.71; P=0.0199) in the 292 randomized patients. Additionally, some of the secondary endpoints significantly

Table 1 Phase III trials with positive results in advanced HCC

Trial	Setting	Treatment arms	HR (OS)	P
SHARP (4)	1st line	Sorafenib *vs.* placebo	0.69	<0.001
REFLECT (5)	1st line	Lenvatinib *vs.* sorafenib	0.92	N.I.
IMbrave150 (8)	1st line	Atezolizumab + bevacizumab *vs.* sorafenib	0.58	0.0006
RESORCE (6)	2nd line	Regorafenib *vs.* placebo	0.63	<0.001
CELESTIAL (7)	2nd line	Cabozantinib *vs.* placebo	0.76	0.005
REACH-2 (9)	2nd line	Ramucirumab *vs.* placebo	0.71	0.02

HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; N.I., non-inferiority design.

favored ramucirumab treatment, such as progression-free survival (PFS), time to progression, time to deterioration by patient reported outcomes, and disease control rate. However, the objective response rate (ORR) with conventional RECIST criteria did not differ significantly between the treatment arms, 5% with ramucirumab and 1% with placebo. All the predefined subgroups of the study benefit from ramucirumab treatment, and it was well tolerated with manageable toxicities in comparison with the multi-kinase inhibitors commonly used in HCC. Finally, the authors performed a pooled analysis of REACH-2 and REACH trials including only those patients with an elevated AFP. Consistently, median OS was significantly improved in the ramucirumab group with 8.1 versus 5.0 months with placebo (HR 0.694; P=0.0002).

The identification of biomarkers to predict drug efficacy is crucial to optimize patient benefit. The REACH-2 authors conclusion remarks that it is the first positive phase III trial done in a biomarker-selected patient population with HCC (9). Nevertheless, AFP may act more like a prognostic biomarker than a predictive one in this setting (8). There are not validated biomarkers to predict the efficacy of ramucirumab or other antiangiogenic agents at this moment, but some reports have explored this issue. The expression of VEGFR-2 in tumor samples and the determination of VEGF-A/C/D and VEGFR-1/3 in serum; were not associated to ramucirumab efficacy in gastric cancer (13). High levels of plasma VEGF-D were associated with a survival improvement in patients with colon cancer treated with ramucirumab. No other trends were evident with tumor VEGFR-2 expression, levels of VEGF-A/C or VEGFR-1/2/3 in plasma (14). The placental growth factor (PlGF) gene overexpression was associated to shorter survival in gastric cancer patients, without any other association in the rest of genes analyzed (15). Another

interesting report explored the possibility to use a positron emission tomography of VEGFR-2 expression with a novel tracer (89Zr-labeled clinical VEGFR-2 antibody) in prostate cancer mice models. Additional research and prospective validation of new biomarkers are needed to predict ramucirumab treatment efficacy in clinical practice.

Furthermore, several attempts have been made to classify HCC in molecular subtypes. Hoshida *et al.* developed an initial classification for HCC with three subtypes: S1 with activation of the WNT pathway; S2 with increased proliferation, MYC/AKT activation and elevated AFP; and S3 with well-differentiated tumors. Elevated AFP and VEGF/VEGFR2 activation is present in S2 subtype, where an antiangiogenic treatment, like ramucirumab, may be beneficial for these HCC patients (16). On the other hand, the Cancer Genome Atlas (TCGA) research network classified HCC in three molecular subtypes: iClust1 with poor prognosis; iClust2 with lower grade tumors, CDKN2A silencing and TERT/CTNNB1 mutations; and iClust3 with chromosomal instability, 17p loss and P53 mutations. VEGF-A amplification was present in 11% and 14% of iClust2 and iClust3 respectively. The absence of VEGF-A amplification in iClust1 indicates that these patients may not benefit from antiangiogenic blockade. In addition, TCGA classification also identify a subgroup of tumors with infiltrating immune cells that may be suitable for immunotherapy (17).

It is worth to mention that all the comments above belong to a pre-immunotherapy era in HCC. In the ESMO Asia Congress, in November 2019, Cheng *et al.* presented the results of the IMbrave150 study (8). This trial randomized HCC patients to atezolizumab plus bevacizumab treatment versus sorafenib in the first-line setting. The study met the co-primary endpoints of OS (HR 0.58; P=0.0006) and PFS (HR 0.59; P<0.001).

ORR was also significantly higher with atezolizumab plus bevacizumab (27% versus 12%; P<0.0001) and safety was in line with the known profiles of safety of this combination. Consequently, the results of this trial will have an important impact in clinical practice and guidelines for first- and second-line treatment of HCC. Although not all HCC patients are good candidates for immunotherapy, in the near-future we will have uncertainty about the potential benefit of ramucirumab, regorafenib and cabozantinib after first-line treatment with atezolizumab plus bevacizumab. Further trials with immunotherapy agents are warranted, and antiangiogenic drugs like ramucirumab will be a good candidate to be combined with.

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Footnote

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References

1. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. (2018). Available online: https://gco.iarc.fr/today, accessed [7 Dec 2019].

2. Di Tommaso L, Spadaccini M, Donadon M, et al. Role of liver biopsy in hepatocellular carcinoma. World J Gastroenterol 2019;25:6041-52.

3. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.

4. Llovet JM, Ricci S, Mazzaferro V, et al. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.

5. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.

6. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.

7. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379:54-63.

8. Cheng A, Qin S, Ikeda M, et al. IMbrave150: Efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol 2019;30:ix183-ix202.

9. Zhu AX, Kang YK, Yen CJ, et al. REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282-96.

10. Roviello G, Sohbani N, Petrioli R, et al. Ramucirumab as a second line therapy for advanced HCC: a significant achievement or a wasted opportunity for personalised therapy? Invest New Drugs 2019;37:1274-88.

11. Zhu AX, Finn RS, Mulcahy M, et al. A phase II and biomarker study of ramucirumab, a human monoclonal antibody targeting the VEGF receptor-2, as first-line monotherapy in patients with advanced hepatocellular cancer. Clin Cancer Res 2013;19:6614-23.

12. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2015;16:859-70.

13. Fuchs CS, Tabernero J, Tomášek J, et al. Biomarker analyses in REGARD gastric/GEJ carcinoma patients treated with VEGFR2-targeted antibody ramucirumab. Br

J Cancer 2016;115:974-82.

14. Tabernero J, Hozak RR, Yoshino T, et al. Analysis of angiogenesis biomarkers for ramucirumab efficacy in patients with metastatic colorectal cancer from RAISE, a global, randomized, double-blind, phase III study. Ann Oncol 2018;29:602-9.

15. Natsume M, Shimura T, Iwasaki H, et al. Placental growth factor is a predictive biomarker for ramucirumab treatment in advanced gastric cancer. Cancer Chemother Pharmacol 2019;83:1037-46.

16. Hoshida Y, Nijman SM, Kobayashi M, et al. Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. Cancer Res 2009;69:7385-92.

17. Cancer Genome Atlas Research Network. Electronic address: wheeler@bcm.edu; Cancer Genome Atlas Research Network. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. Cell 2017;169:1327-41.e23.