The role of c-MET inhibitors in advanced hepatocellular carcinoma: now and future

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Comment on: Rimassa L, Assenat E, Peck-Radosavljevic M, *et al.* Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study. Lancet Oncol 2018;19:682-93.

Hepatocarcinogenesis is a complex biological process associated with several genetic and epigenetic alterations (1). Multiple molecular signaling pathways are critically involved in HCC carcinogenesis, such as Ras mitogen-activated protein kinase (Ras/Raf/MAPK), receptor tyrosine, phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), Wnt/β-catenin, Janus kinase-signal transducer activator of transcription factor (JAK/STAT), Hedgehog (HH) and Hippo (2). At present, systemic treatment approved for patients with advanced HCC are multitargeted drugs, including sorafenib, lenvatinib, regorafenib and cabozantinib, the immune checkpoint inhibitors (ICI) nivolumab and pembrolizumab, and the monoclonal VEGFR2 antibody ramucirumab (3-9).

The receptor tyrosine kinase MET and its cognate ligand hepatocyte growth factor (HGF) play an important role in tumor pathobiology, including tumor growth, survival, neo-angiogenesis, invasion, and dissemination (10,11). MET exon 14 (METex14) alterations occur in up to 4% non-small cell lung cancer (NSCLC) cases. FDA approval is expected for the novel oral selective MET inhibitors capmatinib and tepotinib, which are well tolerated with rapid and sustained effects on METex14-positive NSCLC (12). However, to date, no selective single targeted drugs have been effective for HCC. Cabozantinib, a non-selective MET inhibitor that also targets VEGFR2, AXL, and RET, has been shown to improve median overall survival about 2.2-month compared with placebo in patients with advanced HCC who had received prior therapy with sorafenib (5).

In a study of the use of tivantinib, a putative MET inhibitor, for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC) (13), overall survival was not improved with tivantinib compared to placebo [8.4 *vs.* 9.1 months, tivantinib *vs.* placebo; hazard ratio (HR) 0.97; P=0.81]. This randomized, double-blind, placebo-controlled, phase III study evaluated the efficacy and safety of oral tivantinib (120 mg twice daily) compared with placebo in patients with advanced MET-high HCC (staining intensity score of ≥2 in ≥50% tumor cells) who had failed with previous sorafenib therapy (*Table 1*). The METIV-HCC study is the first phase III trial using a biomarker during screening, such that only patients with MET-high HCC were enrolled. Although this could be looked upon as a good example of patient-oriented individualized therapy, the results did not support MET inhibition as an effective treatment for patients with HCC. Biopsy specimens were required to confirm the biomarker during screening, resulting in delayed treatment and a high rate of screening failure at the time of randomization. As a result, patients with rapid disease progression may have dropped out during the enrollment period while patients with less aggressive disease were included. This may explain the longer overall survival in the placebo group compared to the phase II study group. To date, the MET inhibitory role of tivantinib has yet to be validated because MET inhibition with tivantinib was not evaluated during the METIV-HCC study. Tivantinib is a putative MET inhibitor that may suppress the viability of cancer cells through microtubule inhibition, irrespective of MET activation (15-17), a finding supported by the observation of neutropenia of

Table 1 Trials of c-MET inhibitors for advanced HCC

Trial	Abou-Alfa et al. (5)	Rimass et al. (13)	Decaens et al. (14)
	CELESTIAL	METIV-HCC	
Phase	III	III	II
Primary endpoint	OS	OS	PFS
Number of patients	707	340	49
Arm (experimental/control)	Cabozantinib/placebo	Tivantinib/placebo	Tepotinib/none
Prior systemic treatment	Sorafenib	Sorafenib	Sorafenib
ORR (%)	4/1	0/0	8.2
PFS (months)	5.2/1.9	2.1/2.0	3.4
PFS, HR (95% CI)	0.44 (0.36–0.52)	0.96 (0.75–1.22)	2.8-4.2
OS (months)	10.2/8.0	8.4/9.1	5.6
OS, HR (95% CI)	0.76 (0.63–0.92)	0.97 (0.75–1.25)	5.1-8.2
%AE ≥ grade 3	68/36	56/55	28.6

HCC, hepatocellular carcinoma; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; AE, adverse events; ORR, objective response rate.

grade 3 or higher associated with tivantinib exposure in clinical trials (18). Therefore, the failure of tivantinib to improve overall survival in the METIV-HCC trial does not necessarily signify that MET inhibition was not effective as targeted therapy for HCC. Selective MET inhibitors, such as capmatinib and tepotinib, may be effective for HCC, similar to NSCLC, although further research is required to establish their efficacy. In a phase II trial with tepotinib, a selective MET inhibitor in patients with advanced Met-high HCC and previous sorafenib treatment, 31/49 (63.3%) cases were progression-free at 12 weeks. Although the phase II data with c-MET inhibitors are encouraging, phase III studies are not expected due to their relatively modest effects and limited patient population pool (14). Another potential explanation for the negative result obtained in this phase III trial is that MET expression might not be the only factor determining resistance to sorafenib, and that inhibition of another pathway, such as the VEGF pathway, might be necessary to exert the full oncogenic effect. As mentioned above, positive results were obtained in a phase III trial of cabozantinib, a multitargeted inhibitor, which may support this hypothesis.

In general, targeting the VEGF signaling pathway with small-molecule tyrosine kinase inhibitors (TKIs) has improved the clinical outcomes of patients with advanced HCC. However, improvements have been modest, with

median OS between 10.7 and 13.6 months (4,9). More recently, ICI therapies have been evaluated as a potential new strategy for HCC. While single-agent ICIs have not met the requisite endpoints in phase III studies (7), promising results are reported with drug combinations. In a phase Ib study of atezolizumab [1,200 mg once every 3 weeks (q3w)] combined with the anti-VEGF targeting antibody, bevacizumab, among 68 efficacy-evaluable subjects with a median survival follow-up of over 18 weeks, objective response rates were confirmed in 68 patients (34%) regardless of HCC etiology, geographic region, baseline alpha-fetoprotein (AFP) level or presence of metastasis. The median PFS was 14.9 months (95% CI, 8.1–not estimable). The median estimates for duration of response (DOR), time to progression (TTP) and OS were not yet attained at data cutoff in Jul 2018. Treatment-related Grade 3 or 4 adverse events (AEs) were recorded in 17 subjects (25%), most commonly hypertension [n=8 (12%)]. No Grade 5 AEs were observed. The high response rates indicate that the atezolizumab-bevacizumab combination exerts synergistic activity compared to early single-agent therapy with atezolizumab or bevacizumab alone in treatment-naïve advanced HCC (19). Based on these encouraging results, a phase III study comparing the efficacy of atezolizumab in combination with bevacizumab vs. sorafenib in unresectable HCC patients that have received no prior systemic therapy

is ongoing. Primary analysis disclosed an HR for overall survival of 0.58 (95% CI, 0.42–0.79; P<0.001) and an HR for PFS of 0.59 (95% CI, 0.47–0.76; P<0.001) for atezolizumab combined with bevacizumab *vs.* sorafenib with a median follow-up of 8.6 months. No new safety signals were identified. The observed improvements in OS and PFS support the utility of the combination therapy as an effective novel strategy for HCC (20).

Targets of cabozantinib are also implicated in promoting tumor immune suppression, including members of the TAM family of receptor tyrosine kinases TYRO3, MER, and AXL. Preclinical (21) and clinical studies on circulating immune suppressive cells and immune effector cells in cancer patients (22) suggest that cabozantinib promotes an immune-permissive environment that may present an opportunity for synergistic effects with ICIs. For instance, in a phase Ib study (NCT03170960) currently evaluating a combination of cabozantinib [40 and 60 mg orally once daily (qd)] and atezolizumab (1,200 mg IV q3w) in multiple tumor cohorts, confirmed ORR was 70% with 1 complete response (CR) and 6 PRs, along with no Grade 4 or 5 AEs. Based on the favorable safety profile and preliminary efficacy data, a phase III study evaluating the safety and efficacy of cabozantinib combined with atezolizumab versus standard-of-care sorafenib in subjects with advanced HCC with no previous exposure to systemic anticancer therapy is ongoing (23).

We are yet to establish whether combination of tivantinib or tepotinib with ICI can exert a synergistic effect as in the case of anti-angiogenesis agents. In a recent report (24), the expression of PD ligand 1 (PDL1) was enhanced and co-cultured T cells was inactivated when MET inhibitors exposed to liver cancer cell lines. Notably, however, tumor growth was suppressed and survival was prolonged with combination of anti-PD1 compared with anti-PD1 or MET inhibitors alone. These results highlight the possibility that treatment of HCC with a combination of c-MET inhibitors and ICI could effectively induce synergistic therapeutic effects without anti-angiogenetic activity. Future research efforts should focus on optimizing the antitumor effects of c-MET inhibitors.

Acknowledgments

Footnote

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