



REACH-2: first biomarker-based anti-angiogenic therapy in patients with advanced hepatocellular carcinoma

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Provenance and Peer Review: This article was commissioned by the editorial office, *Chinese Clinical Oncology*. The article did not undergo external peer review.

Comment on: Zhu AX, Kang YK, Yen CJ, *et al.* 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.

Submitted Dec 21, 2019. Accepted for publication Jan 06, 2020.

doi: 10.21037/cco.2020.01.04

View this article at: <http://dx.doi.org/10.21037/cco.2020.01.04>

Hepatocellular carcinoma (HCC) is known as a hypervascular tumor (1,2). Various angiogenic pathways are known to be deregulated and involved in HCC; diverse pro-angiogenic and anti-angiogenic factors establish complex networks to regulate tumor vasculature in HCC (2,3). Therefore, multiple anti-angiogenic therapies have been developed and approved to treat patients with advanced HCC over the last decade (1,4-8). Because the efficacy of anti-angiogenic therapies was modest and transient, there has been an intense effort to discover biomarkers that can select patients with more favorable responses, thereby optimizing the clinical benefit of anti-angiogenic therapy in HCC (9-12).

Recently, Zhu *et al.* suggested biomarker-based anti-angiogenic therapy in patients with HCC after sorafenib based on the results of a pivotal REACH-2 trial (8). This is the first positive trial with biomarker-based patient selection to open the personalized medicine era of advanced HCC (13).

The REACH-2 trial is a randomized, double-blind, phase III clinical trial comparing ramucirumab, an anti-VEGFR2 monoclonal antibody, versus placebo as a second-line treatment after first-line sorafenib treatment in patients with advanced HCC. In REACH-2 trial, patients with a baseline alpha-fetoprotein (AFP) ≥ 400 ng/mL were included based on the results of previous phase III REACH trial in which patients with high baseline AFP showed improvements in overall survival (OS) (14). All patients were treated with first-line sorafenib and Child-Pugh class

A. Stratification factors were geographic region, ECOG performance status, and macrovascular invasion. A total of 292 patients were randomized to either ramucirumab (n=197) or placebo group (n=95) in a 2:1 ratio. The primary endpoint of the trial was OS and the secondary endpoints were progression-free survival (PFS), time-to-progression (TTP), objective response rate (ORR), and safety profiles. Patients in the ramucirumab group were treated with intravenous injections of ramucirumab (8 mg/kg) on day 1 of 14-day cycle. Ramucirumab showed superior OS (median 8.5 *vs.* 7.3 months; HR 0.710; P=0.0199) and PFS (median 2.8 *vs.* 1.6 months; HR 0.452; P<0.001) (*Table 1*). Although disease control rate was significantly higher in the ramucirumab group (59.9% *vs.* 38.9%, P=0.0006), there were no significant changes in ORR (5% *vs.* 1%; P=0.1697), indicating ramucirumab, like other anti-angiogenic agents, is more suited to tumor stabilization than regression of HCC. Safety profiles showed consistent results with previous trials of ramucirumab. The most common adverse events related to ramucirumab were fatigue (27%), followed by peripheral edema (25%) and hypertension (25%). Overall, this study met its primary endpoint and demonstrated the efficacy of ramucirumab in patients with advanced HCC and AFP ≥ 400 ng/mL who had been previously treated with sorafenib. The pooled analysis of REACH (only patients with AFP ≥ 400 ng/mL) and REACH-2 trials also revealed consistent results (*Table 1*). When a total of 542 patients were analyzed, ramucirumab

Table 1 Summary of REACH-2 and pooled REACH/REACH-2 (AFP \geq 400 ng/mL)

	REACH-2		Pooled REACH and REACH-2 (AFP \geq 400 ng/mL)	
	Ramucirumab (n=197)	Placebo (n=95)	Ramucirumab (n=316)	Placebo (n=226)
Median OS	8.5 (7.0–10.6)	7.3 (5.4–9.1)	8.1 (6.9–9.3)	5.0 (4.3–6.1)
HR for OS (95% CI), P	0.710 (0.531–0.949), 0.0199		0.694 (0.571–0.842), 0.0002	
Median PFS	2.8 (2.8–4.1)	1.6 (1.5–2.7)	2.8 (2.7–2.8)	1.5 (1.5–2.0)
HR for PFS, P	0.452 (0.339–0.603), <0.0001		0.572 (0.472–0.694), <0.0001	

AFP, alpha-fetoprotein; OS, overall survival; PFS, progression-free survival.

treatment significantly increased OS by 3.1 months (median 8.1 *vs.* 5.0 months; HR =0.694, P=0.002). Moreover, it can improve ORR (5.4% *vs.* 0.9%; P =0.004) and PFS (median 2.8 *vs.* 1.5 months; P<0.0001).

Ramucirumab is a fully human monoclonal antibody against VEGFR2 and, thus, is expected to more selectively block VEGF/VEGFR2 signaling with less off-target effects than other multi-target anti-angiogenic tyrosine kinase inhibitors (TKIs) (8,15). In REACH-2 trial ramucirumab was well tolerated and the only grade \geq 3 adverse events that occurred in >5% of patients in ramucirumab group were hypertension and hyponatremia. Therefore, the duration of ramucirumab treatment was almost the same as the duration of PFS without significant interruptions. In contrast, oral VEGFR TKIs induce chronic toxicities, such as hand-foot syndrome and diarrhea, that result in dose reductions, treatment delays or discontinuation. Therefore, ramucirumab could be a better treatment option to patients who cannot tolerate oral VEGFR TKIs. And this could be especially true for East Asian patients with advanced HCC because they are known to be more susceptible to oral TKIs and have more frequent TKI-related toxicities, such as hand-foot syndrome, compared to patients of European ancestry (16).

AFP is a well-defined tumor marker in patients with HCC and approximately 50% of HCC patients have elevated baseline AFP (\geq 400 ng/mL) (17). The prognostic role of AFP has been evaluated in many prospective studies and a high AFP level at baseline was consistently associated with poor prognosis in patients with HCC (13). However, its biologic functions, especially regarding tumor angiogenesis, have not been well elucidated. Few studies have reported that AFP itself may act as a pro-angiogenic factor in a VEGF-dependent manner to promote robust angiogenesis within tumors (18–20). Silencing of AFP markedly reduces the amount of VEGF secreted from

HCC cells (17). Therefore, AFP may stimulate HCC cells to produce VEGF, which can promote tumor angiogenesis and establish a VEGF-rich tumor microenvironment that contributes to the aggressive phenotype of HCC. In supporting this hypothesis, elevated AFP levels correlated with high expression of VEGF-A, as well as its receptor, VEGFR2, in the tumor tissues of patients with HCC (21,22). However, because preclinical and clinical evidence is very limited at present, it is hard to conclude whether AFP itself is a direct proangiogenic factor that establish highly-angiogenic HCC or AFP is just an indirect surrogate marker for highly aggressive subtypes of HCC. Therefore, the biological role of AFP during HCC carcinogenesis and the characteristics of AFP-high HCCs need to be thoroughly elucidated in further studies.

In conclusion, Zhu *et al.* demonstrated that AFP-based patient selection is a valid strategy in patients with advanced HCC and ramucirumab will be a well-tolerated second-line therapy after sorafenib failure when baseline AFP \geq 400 ng/mL.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/cco.2020.01.04>). Dr. Chon has received consultancy and advisory fees from Bayer, Eisai, ONO, and MSD. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Chon HJ, Kim C. REACH-2: first biomarker-based anti-angiogenic therapy in patients with advanced hepatocellular carcinoma. *Chin Clin Oncol* 2020;9(4):58. doi: 10.21037/cco.2020.01.04