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REVIEW

Clinical Evaluation of Ramucirumab for the Treatment of Hepatocellular Carcinoma (HCC): Place in Therapy

Khalil Choucair[1]
Syed Kamran[1]
Anwaar Saeed[2]

[1]Department of Medicine, Kansas University School of Medicine, Wichita, KS, USA; [2]Department of Medicine, Division of Medical Oncology, Kansas University Cancer Center, Kansas City, KS, USA

Abstract: Hepatocellular carcinoma remains one of the leading causes of death from cancer worldwide as most cases are diagnosed at an advanced disease stage. Ramucirumab, a human anti-VEGFR-2 monoclonal antibody, is approved as a monotherapy for the treatment of patients with hepatocellular carcinoma and α-fetoprotein levels ≥400 ng/mL previously treated with sorafenib. As most patients present with an advanced disease, patients with α-fetoprotein levels ≥400 ng/mL have an aggressive disease and a poor prognosis, making ramucirumab an important treatment option for this subgroup of patients. This article provides a comprehensive review of the clinical efficacy of ramucirumab as highlighted in the two major trials that lead to its approval. We also briefly review the agent pharmacologic properties, as well as its safety and toxicity profile, before discussing certain limitations and challenges associated with ramucirumab use. Finally, we review completed and ongoing clinical trials and focus on those involving ramucirumab-based combinations, namely with immune therapy.

Keywords: hepatocellular carcinoma, ramucirumab, targeted therapy

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths worldwide.[1] Commonly asymptomatic in the early course of the disease, HCC is most diagnosed at an advanced stage, with a relatively poor prognosis and a five-year survival rate of 18%.[2] Most common risk factors for HCC include non-alcoholic fatty liver disease, alcohol abuse, hepatitis B or C virus infection, or any liver disease that causes cirrhosis.[2] Traditionally, high-risk regions included Japan and parts of China. However, recently the incidence of HCC has increased significantly in European regions and North America, and disproportionately in men ages 55–64 years.[3] The serum marker alpha-fetoprotein (AFP) is one of the most commonly used serum markers for diagnosis of HCC, and for monitoring treatment response; while elevated AFP levels are not specific to HCC, serum AFP levels >400 ng/mL in increased-risk patients are almost diagnostic for HCC.[4] In terms of prognostic markers, highly elevated AFP levels, vascular invasion, cirrhosis, and multinodular tumors are all predictive of poor outcomes.[5]

Many staging classification systems exist for HCC. A common system is the Barcelona Staging Classification (BCLC) which uses five stages based on the spread of the tumor, the vascularization, and the extent of the primary lesion.[6]

Correspondence: Anwaar Saeed
Department of Medicine, Division of Medical Oncology, Kansas University Cancer Center, 2650 Shawnee Mission Pkwy, Kansas City, KS, 66205, USA
Tel +1 913-588-3808
Email asaeed@kumc.edu

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Compared to the classical the Tumor/Node/Metastasis (TNM) system, it provides a more reliable prognostic tool for first-line treatment recommendation, with estimates ranging from three months to greater than five years.[7,8]

Treatment options for HCC are dictated by disease stage. The preferred treatments for HCC are surgical removal and transplantation which can be curative but are commonly not possible due to advanced disease at presentation. When surgical resection is not an option, treatment options are limited to either systemic therapy or liver-directed approaches including microwave or radiofrequency ablation, or embolization.[9] The choice of correct therapy can be decided using the Child-Turcotte-Pugh Classification, which classifies the severity of liver disease using the levels of ascites, bilirubin, albumin, prothrombin time, and encephalopathy. The most current guidelines favor the atezolizumab plus bevacizumab combination over sorafenib, a multi-tyrosine kinase inhibitor (TKI) that had so far been the standard first-line systemic therapy for patients with advanced HCC.[10,11] While regorafenib was considered the next-line therapy for patients with disease progression on sorafenib, the most recent National Comprehensive Cancer Network (NCCN) clinical guidelines have also supported the use of ramucirumab in the second-line setting for advanced HCC.[12]

Ramucirumab is a recombinant anti-VEGFR-2 monoclonal antibody that has been approved for treatment in patients with HCC who have failed sorafenib treatment and have an AFP level of ≥400ng/mL.[13] This article briefly summarizes the pharmacological properties of ramucirumab, provides a detailed review of its therapeutic efficacy and tolerability, and further explores ongoing ramucirumab-based trials and potential future treatment strategies.

Methods

A systematic review was conducted according to the PRISMA guidelines with the last search update performed on September 30, 2021. The search was conducted in PubMed as well as major conference proceedings (American Society of Clinical Oncology; European Society of Medical Oncology) using the following query terms: (hepatocellular cancer OR liver cancer OR HCC OR primary liver carcinoma) AND (ramucirumab OR cyramza) OR (angiogenesis inhibitors OR anti-VEGF OR anti-VEGFR). In addition, the clinical trials registry (clinicaltrials.gov) was searched to identify ongoing trials that have with so far unpublished reports. Studies were included if they ramucirumab as a monotherapy or in combination with any other agent in a clinical trial setting in patients with advanced HCC. Studies were excluded if they evaluated patients with localized HCC, if a study was a protocol-only publication without data or if it reported overlapping data. In the latter case, the study with the most recent and/or most comprehensive data was included. The initial search identified a total of 6406 studies. After review by title, abstract and full text review, 6 studies were included in the final review (Table 1). Furthermore, one additional ongoing and unpublished study was identified via clinicaltrials.gov.

Ramucirumab: Pharmacology

Ramucirumab is an IgG1 monoclonal antibody which binds to VEGFR-2 with affinity and acts as a competitive inhibitor of the receptor. This process inhibits downstream signaling pathways that are important for angiogenesis.[14] Ramucirumab also down-regulates the expression of VEGFR-2. While ramucirumab exerts its anti-angiogenic effects by uniquely and selectively targeting VEGFR-2, other TKIs with anti-angiogenic effects display inhibitory activity by targeting VEGFR-1, 2 and 3, as well as a wider range of receptors with kinase function (platelet-derived growth factor, RAF, follicular growth factor receptor, RET, KIT, MET and AXL).[15] During initial studies, it showed anti-angiogenic and anticancer properties along with a tolerable profile in advanced HCC.[16] In treatment studies for patients with solid tumors, ramucirumab's target trough level was set at >20ug/mL.[17] Body weight was found to be an important variable for ramucirumab pharmacokinetics. Initial doses ranged from 6–12mg/kg every 2–3 weeks. Saturation of ramucirumab clearance was seen at >8mg/kg, which would indicate that total VEGFR-2 blockage occurred at this dosage.[17] With this data, Phase 2 trials dosed ramucirumab in patients with HCC with 8mg/kg every two weeks. Steady state was obtained near 12 weeks of therapy.[14] In the US, dosage is 8mg/kg every two weeks via an intravenous infusion over 60 minutes, which can be reduced to 30 minutes if well tolerated.

Clinical Efficacy and Limitations of Ramucirumab

REACH and REACH-2 Trials

The first published study to examine the efficacy and safety of ramucirumab monotherapy in advanced HCC was

Table 1 Completed and Ongoing Trials Involving Ramucirumab in Hepatocellular Carcinoma

Study (NCT)	HCC Population (n)	Arm(s)	Primary Outcome(s)	Secondary Outcome(s)	Results
Zhu et al, 2013[12] (NCT00627042)	Unresectable, untreated HCC (42)	Ramucirumab	PFS	ORR, OS	**mPFS:** 4.0 months (95% CI: 2.6–5.7) ORR: 9.5% (95% CI: 2.7–22.6; 4/42 PR) **mOS:** 12.0 months (95% CI: 6.1–19.7)
Zhu et al, 2015[17] (NCT01140347)	Unresectable, 2nd line HCC (565)	1) Ramucirumab + BSC (283) 2) placebo + BSC (282)	OS	PFS, ORR	**mOS:** 9.2 months for Ramucirumab (95% CI: 8.0–10.6) vs 7.6 months for placebo (95% CI: 6.0–9.3); HR 0.87 (*P*=0.14) **mPFS:** 2.8 months for Ramucirumab (95% CI: 2.7–3.9) vs 2.1 months for placebo (95% CI:1.6–2.7) **ORR:** 7% (95% CI: 4.6—10.7) in the Ramucirumab group vs <1%; 95% CI: 0.2–2.5) in the placebo group.
Zhu et al, 2019[19] (NCT02435433)	Unresectable, 2nd line HCC with AFP ≥ 400 ng/mL (292)	1) Ramucirumab + BSC (197) 2) placebo + BSC (95)	OS	PFS, ORR	**mOS:** 8.5 months for Ramucirumab (95% CI: 7.0–10.6) vs 7.3 months for placebo (95% CI: 5.4–9.1); HR 0.710 (*P*=0.0199) **mPFS:** 2.8 months for Ramucirumab (95% CI: 2.8–4.1) vs 1.6 months for placebo (95% CI: 1.5–2.7); HR 0.452 (*P*<0.0001) **ORR:** 9/197 (Ramucirumab) vs 1/95 (placebo); *P*=0.1697
Lin et al, 2020[55] (NCT02069041)	Unresectable, untreated (1st line) HCC (8)	Ramucirumab + FOLFOX	SAEs	PK, ORR (CR or PR)	**SAEs:** 100% (8/8) **DCR:** (CR + PR): 62.5% **ORR:** 25.0%
Harding et al, 2019[56] (NCT0208220)	Advanced HCC (45)	Ramucirumab + emibetuzumab (anti-MET)	ORR (PR, CR)	PK, DCR, PFS	**ORR:** 6.7% **DCR:** 60% **mPFS:** 5.42 months (8.1 in high MET vs 2.8 in low MET expression)
Harding et al, 2021[57] (NCT01246986)	Unresectable, 2nd line HCC (8)	Ramucirumab + Galunisertib (anti-TGF-β)	SAEs	N/A	**SAEs:** 3/8 (37.5%)
NCT02572687	Unresectable, 2nd line HCC with AFP ≥1.5x ULN	Ramucirumab + Durvalumab	DLT	ORR, DCR, DoR, TTR, PFS, OS	N/A; ongoing trial

Abbreviations: NCT, National Clinical Trial Number; n, number of participants; HCC, Hepatocellular carcinoma; PFS, progression-free survival; ORR, Objective response rate; PR, Partial Response; OS, Overall survival; TRAEs, Treatment-related adverse events; m, median; 95% CI, 95% confidence interval; BSC, Best support care; HR, Hazard Ratio; AFP, Alpha-fetoprotein; PK, Pharmacokinetics; Cmax, maximum concentration; AUC, Area under the Curve; CR, Complete response; SAE, Serious Adverse Event (grade ≥3); NR, Not reported; N/A, not applicable; ULN, Upper limit of normal; DCR, Disease control rate; DLT, Dose-limit toxicity; DoR, Duration of Response; TTR, Time to first response.

a single-arm study involving untreated patients (n = 42) in the first-line setting.[18] Results revealed a median progression free survival (PFS) of 4.0 months (95% confidence interval-CI-: 2.6–5.7), an overall response rate (ORR) of 9.5% (95% CI: 2.7–22.6) with 4 patients exhibiting partial response, and a median overall survival (OS) of 12.0 months (95% CI: 6.1–197.7). Survival benefit was more pronounced in patients with Barcelona Clinic Liver Cancer (BCLC) stage C and Child-Pugh A cirrhosis. While prior attempts involving anti-angiogenic agents (such as bevacizumab) did not demonstrate efficacy in HCC, this was the first Phase II study to demonstrate effective anti-cancer activity of an anti-VEGF monotherapy agent with an acceptable safety profile. Of note, while sorafenib tyrosine kinase inhibitors VEGF receptors among other tyrosine kinases, this study was initiated prior to the approval of sorafenib for 1st line treatment of advanced HCC.

These positive results lead to the initiation of the Phase III REACH clinical trial[19] that evaluated ramucirumab + best supportive care (BSC), compared to placebo + BSC, in the second-line treatment of patients who previously received sorafenib. Despite manageable side effects, ramucirumab did not significantly improve median OS compared to placebo (9.2 vs 7.6 months) or median PFS (2.9 vs 2.1 months). Of note,

a trend toward survival benefit was observed only in patients with Child-Pugh A cirrhosis, similar to earlier observations.[20] However, a subgroup of analysis of patients with elevated of alpha-fetoprotein (AFP ≥ 400 ng/mL) revealed a significantly higher efficacy for ramucirumab (n = 119) compared to placebo (n = 131) with mOS of 7.8 months (vs 4.2 months; HR 0.67; $P < 0.001$), and a mPFS of 2.7 months (vs 1.5 months; HR: 0.70).[19,20] Subsequently, the efficacy of ramucirumab was specifically evaluated as a second-line treatment after sorafenib in patients with advanced HCC and AFP ≥ 400 ng/mL, in a phase III randomized clinical trial (REACH-2; NCT 02435433).[21] Overall, participants had an unfavorable prognosis as characterized by elevated AFP levels and by the high proportion of patients with extrahepatic disease (~75%). Median OS was 8.5 months in patient who received ramucirumab (vs 7.3 months in placebo; HR 0.71; $P = 0.0199$), and median PFS of 2.8 months for ramucirumab treatment arm (vs 1.6 months in placebo; HR 0.452; $P < 0.0001$). This survival benefit (OS and PFS) of ramucirumab was confirmed via pooled analysis of patients with AFP ≥ 400 ng/mL from REACH and REACH-2, with a mOS of 8.1 months (vs 5.0 months in placebo; HR 0.69; $P = 0.0002$) and mPFS of 2.8 months (vs 1.5 months for placebo; $P < 0.0001$).[22,23] Table 2 summarizes the survival benefit and effect on tumor response of ramucirumab in patients with an AFP ≥ 400 ng/mL. Based on these results, the US FDA approved ramucirumab for treatment of HCC patients with an AFP ≥ 400 ng/mL, who had previously been treated with sorafenib.[24]

Real-World Data

Since its FDA approval, several real-world studies have reported the therapeutic efficacy and safety of ramucirumab.[25–29] In a study by Kuzuya et al, 12 patients were treated with ramucirumab after lenvatinib failure with a reported disease control rate (DCR) of 80% at 6 weeks and a median time to progression of 3.1 months.[26] In a smaller study, 7 patients with unresectable HCC and AFP ≥ 400 ng/mL and previously treated with lenvatinib, received ramucirumab and achieved a DCR of 28.6% and a mPFS of 41 days.[27] A recent similar study with a larger sample size (n = 28) reported a DCR of 42.3% and a mPFS of 2.0 months following failure of lenvatinib.[28] In a study by Hatanaka et al exploring the role of albumin-bilirubin score in predicting outcome of ramucirumab for treatment of patients with advanced HCC, the treatment response of 16 patients was reported:[29] DCR ranged between 28.6% and 100%, mOS ranged between 3.0 months and 6.7 months, and mPFS ranged between 1.4 and 7.5 months (depending on albumin-bilirubin score).

Despite relatively small sample sizes, these studies revealed similar to better survival and response benefit in the real-world compared to data from REACH trials. This is of special significance given the marginal survival benefit reported in trial data, as well as the restricted patient population for whom ramucirumab is approved.

Ramucirumab Efficacy Across Patients' Subgroups (Table 3)

Serum Alpha-Fetoprotein Levels

Besides demonstrating the clinical efficacy of the first-angiogenic agent monotherapy in advanced HCC, the REACH-2 trial was also the first positive biomarker-driven study in this patient population based on AFP levels. Elevated AFP is associated with worse prognosis compared to the general population, and incremental changes in AFP levels at the

Table 2 Ramucirumab Efficacy in Patients with Advanced Hepatocellular Carcinoma and α-Fetoprotein Levels ≥400 ng/mL Treated Following Failure of First-Line Sorafenib: Data from Randomized, Double-Blind Phase 3 Trials

Study	Treatment (n)	OS		PFS		DCR	Reference
		Months	HR	Months	HR	(%)	
REACH[a]	Ramucirumab (119)	7.8	0.67*	2.7	0.70		17
	Placebo (131)	4.2		1.5			
REACH-2	Ramucirumab (197)	8.5	0.710*	2.8	0.452***	59.9**	18
	Placebo (95)	7.3		1.6		38.9	
Pooled analysis	Ramucirumab (316)	8.1	0.694**	2.8	0.572***	56.3***	18
	Placebo (226)	5.0		1.5		37.2	

Notes: [a]α-fetoprotein ≥ 400 ng/mL subgroup; *$P < 0.01$; **$P < 0.001$; *** $P < 0.0001$.
Abbreviations: OS, Overall survival; PFS, progression-free survival; DCR, Disease control rate; HR, Hazard Ratio.

Table 3 Summary of Subgroup Analyses of Pooled Data from REACH and REACH 2 for Patients with α-Fetoprotein Levels ≥400 ng/mL

Subgroup	Number		Ramucirumab vs Placebo			Rf
	RAM	PL	OS (Months; HR; 95% CI)	PFS (Months; HR; 95% CI)	DCR (%)	
Race						
Asian	168	123	8.1 vs 4.8 (0.73; 0.56–0.95)	2.7 vs 1.5 (0.58; 0.44–0.76)	53.6 vs 33.3	29
Non-Asian	148	103	8.0 vs 5.2 (0.65; 0.49–0.86)	3.1 vs 1.9 (0.55; 0.41–0.73)	59.5 vs 41.7	29
Japanese	61	40	10.8 vs 4.5 (0.56; 0.35–0.89)	3.9 vs 1.4 (0.34; 0.21–0.55)	67.2 vs 35.0	30
Age						31
< 65 years	171	131	8.2 vs 4.8 (0.72; 0.56–0.92)	2.7 vs 1.5 (0.62; 0.48–0.79)	N/A	
≥ 65 to < 75 years	93	37	7.6 vs 5.2 (0.59; 0.41–0.85)	2.8 vs 1.8 (0.55; 0.39–0.78)	N/A	
≥ 75 years	52	28	8.9 vs 6.3 (0.64; 0.39–1.1)	4.2 vs 1.6 (0.48; 0.29–0.78)	N/A	
HCC etiology						28
HBV	124	101	7.7 vs 4.5 (0.74; 0.55–0.99)	2.7 vs 1.4 (0.55; 0.41–0.74)	53.2 vs 28.7	
HCV	76	51	8.2 vs 5.5 (0.82; 0.55–1.23)	3.6 vs 2.7 (0.58; 0.39–0.88)	65.8 vs 52.9	
Other	116	74	8.5 vs 5.4 (0.56; 0.40–0.79)	2.8 vs 1.6 (0.57;0.41–0.79)	53.4 vs 37.8	
Liver disease stage						33
BCLC-stage B	30	22	13.7 vs 8.2 (0.43; 0.23–0.82)	4.2 vs 2.8 (0.33; 0.17;0.64)	80 vs 59	
BCLC-stage C	286	204	7.7 vs 4.8 (0.72; 0.59–0.89)	2.8 vs 1.5 (0.60; 0.49–0.74)	54 vs 35	
Prior TACE						34
Yes	179	123	8.2 vs 5.2 (0.69; 0.53–0.89)	2.8 vs 1.5 (0.56; 0.43–0.72)	56 vs 36	
No	137	103	7.7 vs 5.0 (0.71; 0.52–0.95)	2.8 vs 1.6 (0.58; 0.43–0.79)	56 vs 39	
Sorafenib discontinuation						35
Intolerance	42	28	10.2 vs 6.7 (0.59; 0.34–1.02)	4.4 vs 1.4 (0.32; 0.19–0.55)		
Disease progression	274	198	8.0 vs 4.7 (0.71; 0.58–0.88)	2.7 vs 1.6 (0.64; 0.52–0.79)		

Abbreviations: RAM, Ramucirumab; PL, placebo; OS, Overall survival; PFS, Progression-free survival; DCR, Disease control rate; HR, Hazard ratio; CI, confidence interval; N/A, not available; HBV, hepatitis B; HCV, hepatitis C; BCLC, Barcelona Clinic Liver Cancer staging; TACE, Transarterial chemoembolization; Rf, reference.

time of HCC diagnosis are significantly associated with increased mortality.[30,31] Additionally, serum AFP levels predict the risk of tumor recurrence following resection,[32] and levels ≥400 ng/mL consistently predict poorer prognosis.[33,34] This prognostic and predictive value of baseline AFP was further confirmed by a recent post-hoc analyses of clinical outcomes by AFP during, of both REACH and REACH-2 trials:[23] baseline AFP was confirmed as a continuous and dichotomous (≥400 vs <400 ng/mL) prognostic factor that was predictive of survival benefit with ramucirumab. Similarly, ramucirumab was favored in terms of time to AFP progression, and survival was longer in patients with an AFP response compared to those without it. This study consolidated the role of serum AFP levels as a selection criterion and biomarker of treatment response to ramucirumab.

HCC Etiology

The impact of HCC etiology on response to ramucirumab was evaluated in a meta-analysis of data from REACH/REACH-2 trials involving only patients with AFP ≥ 400 ng/mL.[35] Evaluated etiologies included: hepatitis B (HBV; n = 225), hepatitis C (HCV; n = 127) or other etiology (significant alcohol use, steatohepatitis, hemochromatosis, unknown etiology; n = 190). Although patients with chronic viral hepatitis were eligible in both studies, the impact of pre-treatment serum HBV DNA and HCV RNA on response to

ramucirumab was also evaluated. The study revealed no significant difference in treatment effect by etiology subgroup: mOS (ramucirumab vs placebo) was 7.7 vs 4.5 months (HR 0.74; 95% CI 0.55–0.99) for HBV, 8.2 vs 5.5 months (HR: 0.82; 95% CI 0.55–1.23) for HCV, and 8.5 vs 5.4 months (HR: 0.56; 95% CI 0.40–0.79) for other. Similar results were seen in terms of mPFS and disease DCR (Table 3). The safety profile of ramucirumab was also compared across subgroups: although similar overall safety profiles were observed across the different etiologies, worst outcomes were seen in patients with a detectable HBV viral load, with use of antiviral therapy showing benefit for survival, liver function and liver-specific adverse events, irrespective of the viral load.[35]

Other Subgroup Analyses

Two pooled exploratory subgroup analyses were done comparing ramucirumab treatment benefit in Asian vs non-Asian patients,[36] and in a subgroup of Japanese patients.[37] Benefits of ramucirumab were consistent with those of the overall population regardless of the race. Furthermore, ramucirumab treatment benefits were observed regardless of patient age,[38,39] liver disease stage,[40] prior transarterial chemoembolization (TACE),[41] and reason for sorafenib discontinuation.[42] These are summarized in Table 3.

Limitations of Ramucirumab Therapy

Despite the survival benefit of ramucirumab and its subsequent FDA approval for second-line therapy of patients with advanced HCC and AFP ≥ 400 ng/mL who received 1st line sorafenib, rates of disease progression remain significant for those who receive ramucirumab: 68.9% (vs 77.7% for placebo) in the REACH subgroup of patients with AFP ≥ 400 ng/mL, and 70% (vs 76.8% for placebo) in the REACH-2 trial.[19,21,43] Pooled analysis of 625 patients from both REACH and REACH-2 trials, who showed radiological progression examined possible association between patterns of progression (extrahepatic lesion, intra-hepatic lesion, extrahepatic growth or intrahepatic growth).[43] While ramucirumab provided an overall survival benefit across different progression patterns, OS was significantly reduced in patients with new extrahepatic lesions (HR 2.33 and 1.49 in REACH and REACH-2, respectively, and HR 1.75 in pooled analysis), conferring poor prognosis for post-progression survival.

Clinically, finding from both trials including rates of disease progression translate into a very modest absolute gain in medial survival of 1.2 months only, raising questions about the practical benefit, namely in light of associated costs and toxicity.[44] This marginal survival benefit was attributed to the fact that long median OS was also reached by the placebo group,[21] further raising questions about the interpretation of AFP and its prognostic value in patient selection for treatment for ramucirumab. Another challenge in translating the study findings into daily clinical practice pertains to the exclusion of patients at high risk of bleeding associated with liver disease (high-risk varices). Similarly, a clinical limitation of ramucirumab pertains to its selective approval for use in patients with Child-Pugh class A only, with no available safety data in patients with Child-Pugh B liver function to support its use in this patient's population.

On a molecular level, the relationship between AFP levels and tumor response remains poorly understood, and the interpretation of a potential relationship between elevated AFP levels (indicative of poor prognosis/advanced disease) and the tumor molecular biology that favors response to an anti-angiogenic agent like ramucirumab remains to be explored. Whether elevated AFP as surrogate markers of an advanced tumor could also reflect a higher immunogenicity remain to be explored and could potentially justify combining ramucirumab with immune therapies.[45]

Tolerability

The three main trials evaluating the use of intravenous ramucirumab (8 mg/kg, every 2 weeks) in patients with HCC, revealed acceptable tolerability and a manageable safety profile.[18,19,21] In the HCC population with current FDA indication to use ramucirumab (AFP ≥ 400 ng/mL), safety and tolerability data are available from the REACH-2 and the pooled analysis of REACH and REACH-2 (n = 316 for ramucirumab and n = 233 for placebo).[19,21]

In the pooled analysis, 9.5% of patients who received ramucirumab had a treatment-related adverse event (TRAE) compared to 3.6% in the placebo group. The most common TRAEs (of any grade) with ramucirumab included: nausea, fatigue, anorexia, peripheral edema, diarrhea, headache and abdominal pain. Most of these were mild/moderate TRAEs except for 2 patients who had grade ≥3 peripheral edema, 2 patients with grade ≥3 fatigues, and 1 patient with abdominal pain. In terms of treatment-emergent AEs, the only grade ≥3 events that occurred in ≥5% of patients treated with ramucirumab were hypertension (13% vs 4% in placebo) and hyponatremia (5% vs 2% in placebo).[19,21]

In REACH-2 (n = 197 for ramucirumab and n = 95 for placebo), TRAEs of any grade occurred in 11% of patients treated with ramucirumab, compared to 5% in placebo recipient.[21] Hepatic encephalopathy and dyspnea occurred only in the ramucirumab group. All-cause death rates (20% vs 17% for placebo), and on-treatment death due to AEs (3% in each group), were similar across both groups. In the ramucirumab group, 3 deaths (from acute kidney injury, hepatorenal syndrome, and renal failure) were deemed to be treatment-related. Compared to tyrosine kinase inhibitors such as sorafenib, ramucirumab showed a more favorable toxicity profile.[46] A detailed guide for the management of ramucirumab's most common treatment related side effects has already been published.[47]

As pre-specified by the study, treatment-related adverse events of special interest (AESIs) included: hypertension, proteinuria, bleeding/hemorrhage, liver injury/failure, and infusion-related reactions (IRRs) that occur within 24 hours of infusion.[21] In the pooled analysis, AESIs of any grade were more common with ramucirumab compared to placebo. In terms of grade ≥3 AESIs, hypertension occurred more frequently with ramucirumab (8.2% vs 1.3% in placebo), and liver injury or failure occurred in 4.7% and 4.5% of ramucirumab and placebo recipients. All other ASEIs occurred at similar frequency and in ≤2% in both groups. IRRs to ramucirumab were observed during or following the first of second infusion leading to the recommendation to pre-medicate with anti-histamine, dexamethasone and paracetamol prior to ramucirumab infusion, to decrease both incidence and severity of IRRs.[48] Other reported AESI related to ramucirumab included: gastrointestinal perforation, thromboembolic events, impaired wound health, posterior reversible encephalopathy syndrome, thyroid dysfunction, and embryo-fetal toxicity.[24,48] Whether the different adverse events of ramucirumab carry any significant prognostic significance remains unknown: in fact, multiple prior retrospective studies and post-hoc analyses of clinical trials of sorafenib in HCC suggested a prognostic significance of adverse events in terms of prolonged time to progression and longer OS.[49] These adverse events included dermatologic toxicities,[50,51] hypertension,[52] and diarrhea.[53,54] Given these reports, albeit retrospective, along with the similar toxicity profile, future studies ought to explore any potential correlation between ramucirumab associated toxicities and treatment response.

In terms of quality of life (QoL) and performance status (PS), analysis of patient-focused outcomes from REACH trial using the FACT Hepatobiliary Symptom Index (FHSI)-8 and the EuroQoL (EQ-5D), revealed a significantly reduced deterioration in FHSI-8 in patients with AFP 400 ng/mL who received ramucirumab compared to placebo.[55] Similarly, a trend towards a delay in symptomatic deterioration (using FHSI-8, $P = 0.054$ and PS, $P = 0.057$) in favor of ramucirumab. In the non-AFP selected population, ramucirumab was associated with no worsening of QoL compared to placebo.

Ramucirumab and Therapeutic Strategies for the Treatment of Hepatocellular Carcinoma

Ramucirumab and Current Management of HCC

Currently, ramucirumab is the only therapy specifically tested in a biomarker (AFP)-selected HCC population, with a recommendation only for patients with AFP ≥ 400 ng/mL.[11,42,43] Other available molecular targeted systemic therapies for advanced HCC include sorafenib, lenvatinib, regorafenib, and cabozantinib, all of which are multikinase inhibitors, and more recently the combination of atezolizumab and bevacizumab. While bevacizumab targets VEGF, ramucirumab is the only VEGF receptor (VEGFR-2) antagonist approved for HCC. Other therapies include immune checkpoint inhibitors: while nivolumab was originally indicated based on response data from a Phase 1/2 trial, recent Phase 3 trial data did not support the use of single-agent nivolumab in the second-line setting of advanced HCC that failed first-line sorafenib.[58] This is in contrast to the recent FDA accelerated approval of pembrolizumab monotherapy for patients with advanced HCC who received prior treatment with sorafenib, based on data from KEYNOTE-240 and KEYNOTE-394.[59]

Sorafenib had long been the standard first-line systemic therapy for patients with advanced HCC and well-reserved liver function, and those unsuitable for locoregional therapies.[11,42,43] However, the recent data from IMbrave 150 phase 3 trial showed that the combination of atezolizumab plus bevacizumab had significantly longer 12-month OS (67.2% vs 54.6%; HR 0.58, $P<0.001$) and median PFS (6.8 vs 4.3 months; HR 0.59; $P<0.001$) compared with sorafenib, making the combination the preferred first-line treatment of patients with advanced HCC.[60–62] Lenvatinib is another first-line option in these patients. Regorafenib had been the standard second-line

systemic therapy following progression on sorafenib, until recent guidelines also recommended cabozantinib and ramucirumab. Other recommended second-line regimens include nivolumab plus Ipilimumab combination, and pembrolizumab monotherapy.[12]

Ongoing Evaluation of Ramucirumab-Based Combinational Treatment Strategies

Combining targeted therapies designed to inhibit specific oncogenic pathways, such as ramucirumab, with systemic chemotherapy or immune checkpoint inhibitors has been an attractive strategy to harness and maximize anti-tumor effects with acceptable side effects.[63,64] For agents targeting VEGF or its receptors, the rationale is related to the potential of those agents to normalize tumor vasculature and contribute to increased T-cell infiltration, as well as promoting dendritic cell maturation and inhibition of immunosuppressive immune cells like regulatory T-cells and myeloid-derived suppressor cells.[65–67] There is thus good promise in combining VEGF-targeting therapies with anti-PD-1/PD-L1 therapy with considerable synergistic antitumor activity shown in Phase I to III, notably those involving bevacizumab (anti-VEGF antibody).[66] Clinically, for patients with advanced HCC bevacizumab administered in combination with atezolizumab significantly improved OS and PFS compared to sorafenib in the first-line setting (HR 0.58; 95% CI 0.42–0.79; $P < 0.001$).[60] The recent approval of atezolizumab in combination with bevacizumab in the first-line setting treatment of patients with advanced HCC thus opens the way for trials that evaluate ramucirumab in combination with checkpoint inhibitors.[68]

In fact, combination of ramucirumab with anti-PD1 pembrolizumab or with anti-PD-L1 durvalumab in previously treated advanced gastrointestinal cancers, non-small cell lung cancer, and urothelial carcinoma has shown a favorable anti-tumor activity with a manageable safety profile.[69–71] Currently, one ongoing trial in HCC specifically (NCT02572687) is evaluating combination ramucirumab with durvalumab in unresectable HCC with AFP 1.5x upper limit of normal who failed sorafenib (Table 1). The primary outcome of the study is dose-limiting toxicity with secondary outcomes including ORR, DCR, OS, PFS and duration of response.

Ramucirumab has also been evaluated in combination with chemotherapy: in a non-randomized, phase Ib trial, a safety cohort of 8 patients with unresectable, previously untreated HCC combination ramucirumab with FOLFOX chemotherapy revealed 62.5% disease control rate (complete and partial response) and a 25% overall response rate (including stable disease); however, 100% of patients exhibited serious adverse events (Table 1).[72]

Few studies have evaluated the feasibility of combining ramucirumab with other molecularly targeted agents in the treatment of HCC. In a phase Ib/II trial (NCT0208220) involving patients with advanced solid tumors, combination of emibetuzumab -a monoclonal antibody targeting MET- with ramucirumab was evaluated in a cohort of 45 patients with advanced HCC:[73] the study revealed no dose-limiting toxicities, and adverse events were mild or moderate. While the combination revealed partial response (5.2%) across different solid tumors (n = 97), the greatest antitumor activity was noted in HCC: ORR was 6.7% with 60% DCR and 5.42 months of PFS.[73] Interestingly, HCC patients with high MET expression showed improved PFS relative low MET expression (8.1 months vs 2.8 months respectively). Beyond the safety and potential efficacy of combined ramucirumab-based targeted therapy, the study highlighted the potential for signal-based treatment selection when combining therapies with ramucirumab. Another recently published phase Ib (NCT01246986) study investigated the combination of ramucirumab with galunisertib, an inhibitor of TGF-β receptor.[74] The rationale behind the combination is based upon the known interaction between VEGF and TGF-β pathways, which stimulates angiogenesis and suppress antitumor immune response in HCC. In this study, 8 patients with advanced HCC received the combination: while no dose-limiting toxicities were observed and the combination was overall well tolerated, the combination revealed very modest antitumor effect with 0% ORR and 12.5% DCR. Table 1 summarizes all completed and ongoing trial involving ramucirumab in patients with advanced HCC.

Conclusions and Prospects

Ramucirumab prolongs survival of advanced HCC in the second-line setting and has an overall tolerable and manageable safety profile. Currently, it is indicated only for patients with AFP ≥ 400 ng/mL. While survival advantage is pronounced in this molecular group, the biological relationship between higher level of AFP and this significant response to therapy remains not fully understood. Other considerations also remain to be addressed namely about the practical implications of a modest absolute gain of survival (median 1.2 months), and how to balance this

with the drugs cost and side effects. There is thus a need for further clinical data to assess the efficacy of ramucirumab in a broader patient population, and possibly within a combinatorial therapeutic approach. Similarly, clinical data is needed for a head-to-head comparison of ramucirumab and other agents in the second-line setting of advanced HCC. Future research ought to delineate safe and successful ramucirumab-based combinations such as other small targeted molecules and TKIs, as well as immune checkpoint inhibitors, including PD-1/PD-L1 inhibitors and others, especially in light of the recent approval of atezolizumab in combination with bevacizumab in the first-line setting treatment of patients with advanced HCC. The recently announced overall positive results from the HIMALAYA Phase 3 trial further highlights the potential impact of immune checkpoint inhibitors in the treatment of advanced HCC, whereby combination of a one priming dose of tremelimumab (CTLA-4 inhibitor) plus durvalumab demonstrated statistically significant and clinically meaningful OS benefit compared to sorafenib in the first-line treatment of patients with unresectable, treatment-naïve HCC.[75] From the perspective of ramucirumab, the upcoming likely approval of this regimen in the frontline setting will strengthen the position of ramucirumab as a viable later line option for patients with high AFP.

Abbreviations

HCC, Hepatocellular carcinoma; AFP, alpha-fetoprotein; BCLC, Barcelona Staging Classification; TNM, Tumor/Node/Metastasis; TKI, tyrosine kinase inhibitor; PFS, progression free survival; ORR, overall response rate; OS, overall survival; BSC, best supportive care; HBV, hepatitis B; HCV, hepatitis C; DCR, disease control rate; TACE, transarterial chemoembolization; TRAE, treatment-related adverse event; AESIs, adverse events of special interest; IRRs, infusion-related reactions; QoL, quality of life; PS, performance status; FHSI-8, FACT Hepatobiliary Symptom Index; EQ-5D, EuroQoL.

Author Contributions

AS and KC conceived and designed the structure of this manuscript. KC and SK reviewed the literature and collated data from major studies and clinical trials. KC and SK provided the initial draft of the manuscript, including the tables. AS, KC and SK revised the manuscript for important intellectual content. All authors contributed to data analysis, drafting and revising of the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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