Ramucirumab in patients with advanced hepatocellular carcinoma and elevated α-fetoprotein: Outcomes by treatment-emergent ascites

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Aim: The REACH and REACH-2 trials investigated ramucirumab versus placebo in patients with advanced hepatocellular carcinoma (HCC). Ascites is common in HCC and is associated with poorer outcomes. This exploratory, pooled meta-analysis of patients with baseline α-fetoprotein (AFP) ≥400 ng/ml investigated outcomes by treatment-emergent (TE) ascites in REACH and REACH-2.

Methods: A pooled meta-analysis of independent patient data for participants (N = 542) with baseline AFP ≥400 ng/ml (stratified by study) from REACH and REACH-2 was carried out. Overall survival (OS) and progression-free survival (PFS) were evaluated by Kaplan–Meier estimator, and OS further assessed by Cox models. The effect of TE ascites on OS was evaluated by multivariate Cox models.

Results: Treatment-emergent ascites developed in 66 patients (20.9%) in the ramucirumab group and 33 patients (14.8%) in the placebo group. When adjusted for treatment duration, the incidence rates per 100 patient-years of any grade TE ascites were 59.1 and 71.9 for the ramucirumab and placebo groups, respectively, and the incidence of grade ≥3 TE ascites were 13.4 and 19.6, respectively. Treatment-emergent ascites was associated with TE hypoalbuminemia (odds ratio 4.9; 95% confidence interval 2.5–9.3), but not TE proteinuria or hypertension. One patient discontinued ramucirumab treatment due to TE ascites. Ramucirumab treatment improved OS and PFS compared with placebo, irrespective of TE ascites.

Conclusions: When adjusted for treatment duration, the incidence of TE ascites was no higher in patients who received ramucirumab than in those who received placebo.
placebo. Ramucirumab was well tolerated and provided a survival benefit irrespective of the development of TE ascites.

**KEYWORDS**
ascites, hepatocellular carcinoma, ramucirumab, survival analysis

**INTRODUCTION**

The REACH and REACH-2 phase III studies investigated ramucirumab, a recombinant immunoglobulin G1 monoclonal antibody and VEGFR-2 antagonist, versus placebo in patients with advanced HCC following treatment with sorafenib. REACH 1, prior sorafenib therapy, and no clinically meaningful ascites were randomized (REACH 1:1; REACH-2 2:1) to ramucirumab 8 mg/kg or placebo every 2 weeks. Clinically meaningful ascites was defined as CTCAE version 4.0 grade ≥1 ascites resulting from cirrhosis. Patients who had been on a stable medical regimen for ≥3 months to manage ascites were included if they showed no evidence of ascites on clinical examination that would require further intervention.

The proportion of patients who achieved an objective response was assessed locally by investigators according to Response Evaluation Criteria in Solid Tumors version 1.1. Safety data were collected continuously and graded according to CTCAE version 4.0.

Both REACH and REACH-2 complied with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable local regulations. Ethics committees at all participating centers approved the protocol, and all patients provided written informed consent.

**Statistical analysis**

This exploratory, pooled meta-analysis of independent patient data (stratified by study) investigated outcomes for participants with baseline AFP ≥400 ng/ml in REACH and REACH-2 by TE ascites. Overall survival was evaluated by Kaplan–Meier estimator and Cox models. The prognosis of TE ascites in OS was evaluated by univariate and multivariate Cox models that were adjusted for ECOG PS, AFP, macrovascular invasion, and treatment. Progression-free survival was evaluated by Kaplan–Meier estimator and Cox proportional hazards model.

The ratios between odds (OR) of specific TEAEs in patients with and without TE ascites were calculated to evaluate the association between specific TEAEs and TE ascites. The p-values were derived from Fisher’s exact test.

An exposure-adjusted incidence rate was calculated for TE ascites to account for the observed difference in treatment duration between treatment groups using the following formula: incidence rate / 100 patient-years = n / patient-years × 100. The patient-years for each group was defined as the sum of individual patient treatment durations and converted to the unit of year.

**METHODS**

**Study design**

The study designs, patients, assessments, randomization and masking methods, procedures, and outcomes for REACH (NCT01140347) and REACH-2 (NCT02435433) have been published previously. In brief, REACH and REACH-2 were randomized, double-blind, multicenter, phase III studies that investigated ramucirumab versus placebo as second-line treatment in patients with advanced HCC following treatment with sorafenib. REACH-2 only enrolled patients with AFP ≥400 ng/mL.

Patients with HCC, a Child–Pugh classification of A, an ECOG PS ≤1, prior sorafenib therapy, and no clinically meaningful ascites were randomized (REACH 1:1; REACH-2 2:1) to ramucirumab 8 mg/kg or placebo every 2 weeks. Consistent with these findings, REACH-2 met its primary endpoint with ramucirumab demonstrating improved OS (HR 0.710; p = 0.0199) and PFS (HR 0.452; p < 0.0001) compared with placebo in patients with baseline AFP ≥400 ng/mL.

In both the REACH and REACH-2 studies, ramucirumab was well tolerated and the toxicity was manageable. In patients with cancer, ascites is most frequently managed by diuretics and abdominal paracentesis.

In patients with HCC, concomitant ascites is associated with poor outcomes. In a study of 2203 patients with HCC, ascites was shown to be associated with an increased risk of mortality of up to 80% to 94%. Furthermore, an association was shown between the severity of ascites and hyperbilirubinemia, hypoalbuminemia, hypoproteinemia, prothrombin time prolongation, and renal insufficiency. More severe ascites was also found to be associated with large tumor burden and vascular invasion. The objective of this study was to undertake an exploratory, pooled meta-analysis of outcomes for participants with baseline AFP ≥400 ng/ml in REACH and REACH-2 by TE ascites.
RESULTS

Characteristics of TE ascites

Treatment-emergent ascites developed in 66 patients (20.9%) in the ramucirumab group and 33 patients (14.8%) in the placebo group, and was predominantly grade 1 or 2 in severity. The median treatment duration was longer in the ramucirumab group versus the placebo group (patients with TE ascites, 14 vs. 8 weeks; patients without TE ascites, 10 vs. 6 weeks). In order to correct for the observed differences in treatment duration between the ramucirumab and placebo groups, treatment duration-adjusted incidence rates were calculated. When adjusted for treatment duration, the incidence rates per 100 patient-years of any grade TE ascites in the ramucirumab group versus placebo group were 59.1 versus 71.9, and the incidence rates per 100 patient-years of grade ≥3 TE ascites were 13.4 versus 19.6.

The onset, duration, and grading of TE ascites in patients in the ramucirumab and placebo groups are shown in Figure 1. The median time (IQR, Q1–Q3) to onset of TE ascites was 43 (29–100) versus 47 (29–77) days and duration of TE ascites was 13 (5–16) versus 18 (14–22) days in the ramucirumab versus placebo treatment groups, respectively. One patient discontinued ramucirumab due to TE ascites. The number of patients with ongoing TE ascites at the end of study treatment was 43 of 66 patients (65%) in the ramucirumab group and 17 of 33 patients (52%) in the placebo group.

The baseline patient demographics and disease characteristics were generally similar for patients with and patients without TE ascites despite the relatively small numbers of patients (Table 1). More patients with TE ascites had macrovascular invasion at baseline and a Child–Pugh score of A-6 compared with A-5. In those with TE ascites, more patients in the ramucirumab group were from Japan compared with the placebo group. Baseline characteristics associated with TE ascites were an albumin–bilirubin grade ≥2, a Child–Pugh score > A-5, the presence of macrovascular invasion, and an absence of extrahepatic spread (Table S1).

Management of TE ascites

The management of TE ascites was less intensive in the ramucirumab group compared with the placebo group (Table S2). Furosemide (18% in the ramucirumab group vs. 30% in the placebo group) and spironolactone (17% in the ramucirumab group vs. 24% in the placebo group) were the most common treatments, and paracentesis (15% in the ramucirumab group vs. 24% in the placebo group) was the most common procedure, for TE ascites. In both the ramucirumab and placebo groups, 12% of patients underwent two or more paracentesis procedures.

Treatment-emergent ascites as a prognostic factor

Univariate and multivariate Cox regression analyses in the pooled population of 542 patients showed that TE ascites trended as a negative prognostic factor for OS after adjustment for significant baseline prognostic factors (with TE ascites vs. without TE ascites: HR 1.27; 95% CI 0.99–1.62; Table S3).
**Outcomes by TE ascites**

Kaplan–Meier analyses showed that ramucirumab improved OS and PFS irrespective of the presence of TE ascites (Figure 2). In patients with TE ascites, median OS in the ramucirumab group versus placebo group was 6.7 versus 3.4 months (HR 0.30; 95% CI 0.18–0.49; p < 0.0001), and median PFS was 4.2 versus 2.0 months (HR 0.46; 95% CI 0.29–0.74; p = 0.0011). In patients without TE ascites, median OS in the ramucirumab group versus placebo group was 8.3 versus 5.9 months (HR 0.77; 95% CI 0.62–0.95; p = 0.0155), and median PFS was 2.7 versus 1.5 months (HR 0.62; 95% CI 0.50–0.77; p < 0.0001).

In patients with TE ascites, the ORR in the ramucirumab group versus placebo group was 9% versus 0% and the DCR was 70% versus 42%. In patients without TE ascites, the ORR in the
ramucirumab group versus placebo group was 4% versus 1% and the DCR was 53% versus 36%.

In patients with TE ascerts, the proportion of patients who received postdiscontinuation therapy in the ramucirumab group versus placebo group was 18% versus 6%. In patients without TE ascerts, the proportion of patients who received postdiscontinuation therapy in the ramucirumab group versus placebo group was 34% versus 30%.

**Treatment-emergent adverse events associated with TE ascerts**

Patients who experienced TE ascerts experienced other TEAEs more frequently than patients who did not have ascites, irrespective of the treatment group (Table 2). Overall, hypertension was the most common grade ≥3 TEAE experienced by patients in the
DISCUSSION

Ascites is commonly diagnosed in patients with HCC, and is likely caused by either progression of HCC over time or worsening of liver function during the natural course of underlying chronic liver disease. The incidence of TE ascites noted in our study is generally consistent with that observed in other studies of previously treated, advanced HCC. In the RESORCE study, TE ascites was reported by 16% of patients in both the regorafenib and placebo groups. In the CELESTIAL study, TE ascites was reported by 12% of patients in the cabozantinib group and 13% of patients in the placebo group. The number of patients with TE ascites was not reported in the KEYNOTE-240 study; however, TE ascites was reported as the most common reason for treatment discontinuation (4% of patients in the pembrolizumab group vs. 2% of patients in the placebo group). No TE ascites was reported in the CheckMate 040 study of nivolumab.

In this study, the exploratory analysis of patients with baseline AFP ≥400 ng/ml in the REACH and REACH-2 phase III studies showed that the incidence of TE ascites was higher for the ramucirumab group (20.9%) compared with the placebo group (14.8%). It has been suggested that therapeutic inhibition of VEGFR-2 with agents such as ramucirumab could increase hepatic sinusoidal pressure, and lead to increased portal vein pressure and hence TE ascites. Subsequent adjustment for treatment duration showed the incidence of TE ascites was no higher for ramucirumab than placebo. It is expected that events consistent with hepatic decompensation, such as ascites, will be captured more frequently in patients treated with ramucirumab compared with placebo due to the longer duration of therapy in patients deriving disease control from ramucirumab therapy. This presumption is supported by the analysis of time to onset of TE ascites, in which the upper IQR was 100 days in the ramucirumab group versus 77 days in the placebo group. Adjustment for treatment duration is considered useful for evaluating such events as it allows for appropriate comparison of frequency of events between treatment groups that are influenced by total time on study treatment. Baseline characteristics associated with TE ascites in the ramucirumab group included albumin–bilirubin grade ≥2, a Child–Pugh score >A-5, the presence of macrovascular invasion, and the absence of extrahepatic spread. Although most of these characteristics are typically associated with poor outcomes that might also be expected to increase risk of TE ascites, the absence of extrahepatic spread was a noteworthy exception in that this usually portends a better prognosis. However, patients with an absence of extrahepatic spread were also more likely to have macrovascular invasion compared to those with extrahepatic spread (43% vs. 32%), and macrovascular invasion was shown to be the strongest risk factor for development of TE ascites. Nonetheless, these patient numbers are small and exploratory, and so should be interpreted with caution.

Despite the higher overall incidence of ascites observed in patients receiving ramucirumab in this study, only one patient discontinued ramucirumab due to TE ascites. The duration and outcomes of TE ascites were comparable for patients receiving ramucirumab and placebo. Management of TE ascites appeared to be less intensive with ramucirumab versus placebo, however, these data should be interpreted with caution due to the small numbers of patients in each subgroup. Diuretics and paracentesis were the mainstays of treatment. This is consistent with how ascites is managed for patients with HCC, and indicates that ascites management is generally no different in patients receiving ramucirumab.

In patients with TE ascites, the HRs for OS and PFS (0.30 and 0.46, respectively) were smaller compared with patients without TE ascites (0.77 and 0.62, respectively). However, it is difficult to draw a conclusion from these HR data because patients in the ramucirumab group were more likely to be categorized as having TE ascites compared with patients in the placebo group as they had more time to develop ascites because they derived a longer survival benefit from treatment.

In conclusion, ramucirumab provided a survival benefit in patients irrespective of the development of TE ascites. In patients with TE ascites, ramucirumab was well tolerated and no new safety findings were observed.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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