Ramucirumab for patients with advanced hepatocellular carcinoma and elevated alpha fetoprotein following a non-sorafenib based systemic therapy: interim results from an expansion cohort of the Phase 3 REACH-2 study

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INTRODUCTION

- Liver cancer is the sixth most common cancer and the fourth most common cause of cancer death worldwide with hepatocellular carcinoma (HCC) representing approximately 90% of primary liver cancers.[1-3]
- Ramucirumab (an IgG1 VEGFR-2 antagonist) is the first and only treatment approved in a biomarker-selected population with advanced HCC and AFP ≥400 ng/mL, following sorafenib.
- Global approval of ramucirumab in HCC was based on evidence from the Phase 3 REACH (NCT01140347) and REACH-2 (NCT02435433) trials.[4-5]
- Like most other contemporary trials, REACH and REACH-2 did not include patients who received systemic therapy other than sorafenib, which was the only treatment with demonstrated OS benefit when the trials were designed.

AIM

- This global open-label expansion (OLE) cohort of REACH-2 was initiated to study ramucirumab in patients with advanced HCC and baseline alpha-fetoprotein (AFP) ≥400 ng/mL following non-sorafenib-based systemic therapy. Here we present data from an interim analysis of this cohort.

METHODS

Key Inclusion Criteria

- Diagnosis of HCC (histological or radiological imaging confirmation)
- BCLC stage C or B that is refractory or not amenable to locoregional therapy
- At least 1 untreated target lesion (RECIST 1.1)
- Child-Pugh Class A
- ECOG PS score of 0 or 1
- Baseline AFP ≥400 ng/mL
- Adequate hematologic and biochemical parameters
- Patient received 1-2 prior systemic therapy regimen, other than sorafenib or chemotherapy
- Patients with liver transplant are eligible

Key Exclusion Criteria

- Uncontrolled hypertension
- Esophageal or gastric varices requiring treatment
- Prior sorafenib
- Hepatic locoregional therapy or major surgery within 28 days
- Arterial thrombotic event within 6 months
- Therapeutic anticoagulation or chronic antiplatelet agents including NSAIDs
- History of or current hepatic encephalopathy (any grade) or ascites grade ≥2
- Patients who received prior immunotherapy and experienced:
  - Any clinically significant Grade ≥3 irAE
  - Any grade neurologic, ocular, pneumonitis, cardiomyopathy, or hepatitis irAE
  - Required steroids or other immunosuppressive agents at the time of enrollment

Red text represents newly added amendments to original REACH-2 protocol specific to the OLE addenda

RESULTS

Table 1. Baseline Demographics and Disease Characteristics

n (%)	Ramucirumab N=24
Gender, male	23 (95.8)
Age, years, median	62
ECOG PS 0	12 (50.0)
Country of Origin	
United States	9 (37.5)
Germany	5 (20.8)
Hong Kong	5 (20.8)
Taiwan	4 (16.7)
Switzerland	1 (4.2)
Child-Pugh Score A-5	16 (66.7)
ALBI grade 1	16 (66.7)
Barcelona Clinic Liver Cancer stage C	22 (91.7)
Macrovascular invasion present	12 (50.0)
Extrahepatic spread present	18 (75.0)
Discontinuation of prior systemic therapy due to progression	21 (87.5)
Median alpha-fetoprotein (IQR), ng/mL	2094 (854-7981)
Etiology of liver disease, n (%)	
Hepatitis B virus	11 (45.8)
Hepatitis C virus	9 (37.5)
Significant alcohol use	2 (8.3)
Steatohepatitis (NASH, Fatty Liver)	3 (12.5)
Hemochromatosis	1 (4.2)
Other	1 (4.2)

Table 2. Prior Systemic Therapies

n (%)	Ramucirumab N=24
Lenvatinib	8 (33)
Nivolumab	6 (25)
Atezolizumab + Bevacizumab	3 (13)
Lenvatinib + Pembrolizumab	2 (8)
Durvalumab	2 (8)
Durvalumab + Tremelimumab	1 (4)
Lenvatinib + Nivolumab	1 (4)
Pembrolizumab	1 (4)
Tepotinib	1 (4)
DKK1 mAb (DKN-01)	1 (4)

Table 3. Treatment-Emergent Adverse Events

TEAEs in ≥12.5% Preferred Terms, n (%)	Ramucirumab N=24 Any Grade	Grade 3/4
Patients with ≥1 TEAE	22 (91.7)	14 (58.3)
Proteinuria	9 (37.5)	3 (12.5)
Hypertension	7 (29.2)	4 (16.7)
Diarrhea	5 (20.8)	0
Fatigue	5 (20.8)	0
Ascites	4 (16.7)	1 (4.2)
Nausea	4 (16.7)	0
Abdominal distension	3 (12.5)	0
Decreased appetite	3 (12.5)	0
Hyponatremia	3 (12.5)	2 (8.3)
Edema	3 (12.5)	0
Pneumonia	3 (12.5)	3 (12.5)
Vomiting	3 (12.5)	0

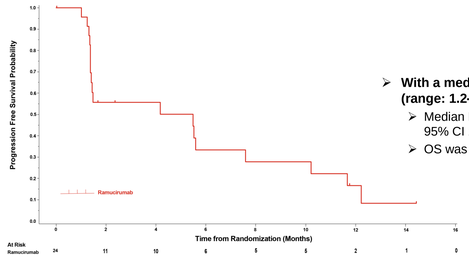
Adverse events were graded according to the CTCAE (version 4.0). TEAE: Treatment-emergent adverse events. No deaths due to AEs occurred on therapy or within 30 days of treatment discontinuation.

Table 4. Adverse Events of Special Interest

AESI Preferred Terms, n (%)	Ramucirumab N=24 Any Grade	Grade 3*
Patients with ≥1 Treatment Emergent AESI	12 (50.0)	8 (33.3)
Proteinuria	9 (37.5)	3 (12.5)
Hypertension	7 (29.2)	4 (16.7)
Bleeding/Haemorrhagic Events	6 (25.0)	3 (12.5)
Epistaxis	2 (8.3)	0
Contusion	1 (4.2)	0
Gastric Varices Haemorrhage	1 (4.2)	1 (4.2)
Gastrointestinal Haemorrhage	1 (4.2)	1 (4.2)
Gingival Bleeding	1 (4.2)	0
Haemarthrosis	1 (4.2)	0
Haematuria	1 (4.2)	1 (4.2)
Liver Injury / Liver Failure	6 (25.0)	5 (20.8)
Ascites	4 (16.7)	1 (4.2)
Jaundice	1 (4.2)	0
Oesophageal Varices	1 (4.2)	1 (4.2)
Increased Aspartate Aminotransferase	1 (4.2)	1 (4.2)
Increased Blood Bilirubin	1 (4.2)	0
Congestive Heart Failure	1 (4.2)	0
Ejection Fraction Decreased	1 (4.2)	0
Thrombotic Microangiopathy	1 (4.2)	0

Adverse events were graded according to the CTCAE (version 4.0). AESI: Adverse Events of Special Interests. AESIs were predefined per the protocol and based on the known safety profile of ramucirumab.
*No Grade 4 or 5 AESIs occurred during study treatment.

Figure 3. Progression-Free Survival and Best Overall Response



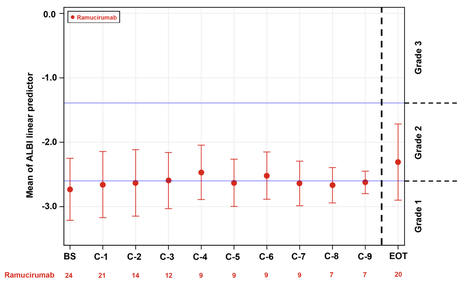
- **With a median follow-up of 6.5 months (range: 1.2–20.7):**
  - Median PFS was 5.5 months (18 events; 95% CI 1.3–7.5)
  - OS was not mature with only 10 events

Table 5. Best Overall Response

n (%)	Ramucirumab N=24
Best Overall Response	
Complete Response	0 (0)
Partial Response	4 (16.7)*
Stable Disease	9 (37.5)
Progressive Disease (PD)	10 (41.7)
Objective PD	10 (41.7)
Non-Evaluable	1 (4.2)
Overall Response Rate	4 (16.7)
Disease Control Rate	13 (54.2)

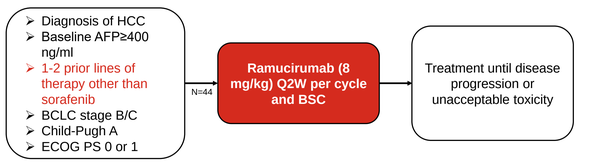
*All response assessments were done locally by investigators according to RECIST (version 1.1). *Prior therapy for patients with partial response: nivolumab (n=3), durvalumab + tremelimumab (n=1).*

Figure 4. Effect of Study Treatment on ALBI Score/Grade



- To evaluate liver function throughout the treatment period, albumin and bilirubin were measured (baseline and prior to each cycle) and the ALBI score and grade were calculated.
- Compared to baseline values, ALBI score was preserved during study treatment.

Figure 1. Study Design

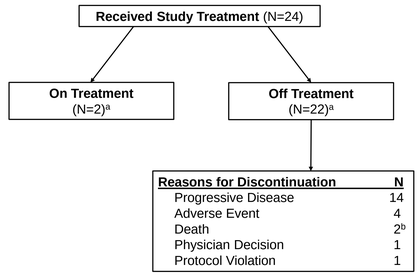


- **Primary endpoint:** Safety
- **Secondary endpoints:** OS, PFS (RECIST v1.1), TTP ORR, PK, patient-reported outcomes, immunogenicity

Analysis of single-arm Open-Label Expansion Cohort will be independent of Main Cohort. The final analysis of the primary and secondary endpoints will occur after all patients enrolled in the OLE cohort have completed at least 3 cycles of ramucirumab or discontinued for any reason.

Abbreviations: AFP= alpha-fetoprotein; BCLC= Barcelona Clinic Liver Cancer; BSC= best supportive care; ECOG PS= Eastern Cooperative Oncology Group Performance Status; ORR= objective response rate; OS= overall survival; PFS= progression-free survival; PK= pharmacokinetics; Q2W= every 2 weeks; TTP= time-to-progression

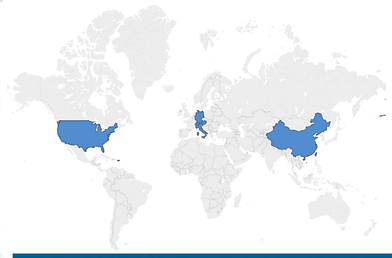
Figure 2. Patient Disposition



[a]*At the time of data cut-off on 2020-01-31.*
[b]*Primary Cause of Death: Study Disease.*

- **Median Duration of Therapy, weeks, (IQR):** 10.5 (6.00-31.86)
- **Median of Cycles Received (IQR):** 5 (3.00-14.50)
- **Median Relative Dose Intensity, % (IQR):** 98.17 (91.75-100.48)

CONCLUSIONS



- At this interim analysis, the safety and efficacy profile of ramucirumab following a non-sorafenib-based systemic therapy was consistent with that observed in patients who received prior sorafenib in the ITT population of REACH-2.[5]
- This global open-label OLE cohort of REACH-2 is enrolling (ClinicalTrials.gov: NCT02435433).

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