O – 021 Ramucirumab in advanced hepatocellular carcinoma and elevated alpha-fetoprotein following sorafenib: outcomes by prior transarterial chemoembolisation from two randomised, double-blind, placebo-controlled phase 3 studies (REACH-2 and REACH)

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Introduction: Patients with localised hepatocellular carcinoma (HCC), preserved liver function, and good performance status (PS) commonly receive locoregional treatment with transarterial chemoembolisation (TACE) but have high rates of recurrence and require systemic therapy. REACH (NCT01140347) and REACH-2 (NCT02435433) studied ramucirumab (anti-VEGFR2 antibody) in patients with HCC following sorafenib, and REACH-2 only enrolled patients with baseline alpha-fetoprotein (AFP) $\geq$400 ng/mL. REACH-2 met its primary endpoint of overall survival for ramucirumab treatment compared to placebo. Here we present post-hoc analyses of outcomes by prior TACE treatment in the pooled population of patients from REACH-2 and REACH (AFP $\geq$400 ng/mL).

Methods: Patients with advanced HCC, Child-Pugh A, ECOG PS 0-1, with progression or intolerance to sorafenib, were randomised in REACH (1:1) or REACH-2 (2:1) to receive ramucirumab 8 mg/kg or placebo Q2W. Pooled individual patient data of REACH-2 and REACH patients with AFP $\geq$400 ng/mL were analysed (stratified by study) by prior TACE treatments (none, one, $\geq$1, $\geq$2). Overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method and the Cox proportional hazards model. Prior TACE subgroup-by-treatment interaction was tested using the Wald test from the Stratified Cox model.

Results: Baseline demographics and disease characteristics were similar between treatment arms in prior TACE (n = 302) and non-TACE (n = 240) patients. Overall, 179 (56.6%) patients in the ramucirumab arm and 123 (54.4%) in the placebo arm had received prior TACE, with a median of 1 treatment in both arms. In patients who received prior TACE, 65.6% received 1 treatment and 34.4% received $\geq$2 treatments. Regional differences were noted, with increased prevalence and frequency of prior TACE treatment in Asia compared to Western countries (75.2% Japan, 69.8% Asia [except Japan], 38.5% Western countries). Median duration of disease, defined as the time from initial diagnosis to randomisation, was 24 months in prior TACE and 11 months in non-TACE treated patients. Efficacy was similar between TACE and non-TACE subgroups (OS interaction p-value = 0.948). In patients who received prior TACE, ramucirumab treatment improved OS compared to placebo (median 8.2 vs 5.2 months; HR 0.687; 95% CI, 0.530-0.890) and PFS (median 2.8 vs 1.5 months; HR 0.557; 95% CI, 0.432-0.719). Similarly, in non-TACE patients, ramucirumab treatment also improved OS compared to placebo (median 7.7 vs 5.0 months; HR 0.705; 95% CI, 0.524-0.950) and PFS (median 2.8 vs 1.6 months; HR 0.583; 95%, CI 0.431-0.787). Analyses of OS and PFS hazard ratios by total number of TACE treatments (0, 1, $\geq$1, $\geq$2) all favored ramucirumab compared to placebo (OS HR range 0.656-0.766; PFS HR range 0.432-0.644). Hypertension was the most frequently reported Grade $\geq$3 treatment-emergent adverse event in patients who received ramucirumab compared to placebo in both prior TACE (12.3% vs 3.3%) and non-TACE (13.1% vs 4.0%) groups, respectively.

Conclusion: Ramucirumab improved OS and PFS for patients with advanced HCC and a baseline AFP $\geq$400 ng/mL, irrespective of prior TACE treatment. A consistent manageable safety profile was also observed irrespective of prior TACE.