# Ramucirumab as Second-Line Treatment in Patients With Advanced Hepatocellular Carcinoma: Analysis of Patients With Elevated α-Fetoprotein From the Randomized Phase III REACH Study

## Abstract 232

Zhu AX, Ryoo B-Y, Yen C-J, Kudo M, Poon R, Pastorelli D, Blanc J-F, Chung HC, Baron AD, Pfiffer TEF, Okusaka T, Kubackova K, Trojan J, Sastre J, Chau I, Chang SC, Abada PB, Yang L, Hsu Y, Park JO

# Introduction

- Hepatocellular carcinoma (HCC) is the second most common cause of cancer death[1]
- After first-line sorafenib, no treatment has demonstrated a survival benefit in the second-line setting[2,3]
- The association of elevated baseline α-fetoprotein (AFP) levels with poor prognosis in HCC is well established[4]
- Ramucirumab inhibits VEGF- and VEGFR-2-mediated signaling and angiogenesis,[5] pathways important in HCC pathogenesis[6]
- REACH evaluated the safety and efficacy of ramucirumab in patients with advanced HCC following first-line therapy with sorafenib[7]
- Additional analyses were conducted to evaluate the relationship between baseline AFP and ramucirumab treatment effect

1. World Health Organization. Cancer Fact Sheet No. 297. 2014. Available at: www.who.int/mediacentre/factsheets/fs297/en/. Accessed. January 2015. 2. Llovet JM, et al. *J Clin Oncol.* 2013;31(28):3509-3516. 3. Zhu AX, et al. *JAMA* 2014;312(1):57-67. 4. Gomaa AI, et al. *World J Gastroenterol.* 2009;15(11):1301-1314. 5. Spratlin JL, et al. *J Clin Oncol.* 2010:28(5):780-787. 6. Zhu AX, et al. *Nat. Rev. Clin Oncol.* 2011;8(5):292-301. 7. Zhu AX, et al. *Ann Oncol.* 2014:25(suppl 5): Abstract LBA16.

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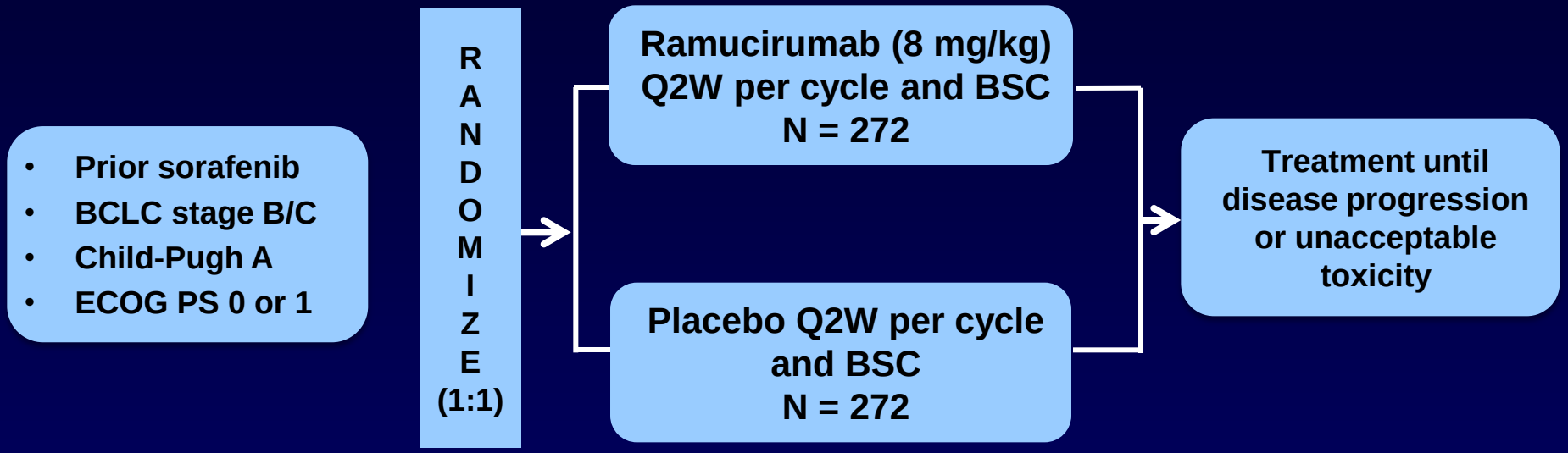
# REACH: Study Design




**Stratification factors:**

- Geographic Regions
  - North and South America
  - Europe
  - Asia
- Etiology of Liver Disease
  - Hepatitis B
  - Hepatitis C
  - Other etiologies

Primary endpoint: **Overall survival**

Secondary endpoints:
PFS, TTP, ORR, safety, patient-reported outcomes

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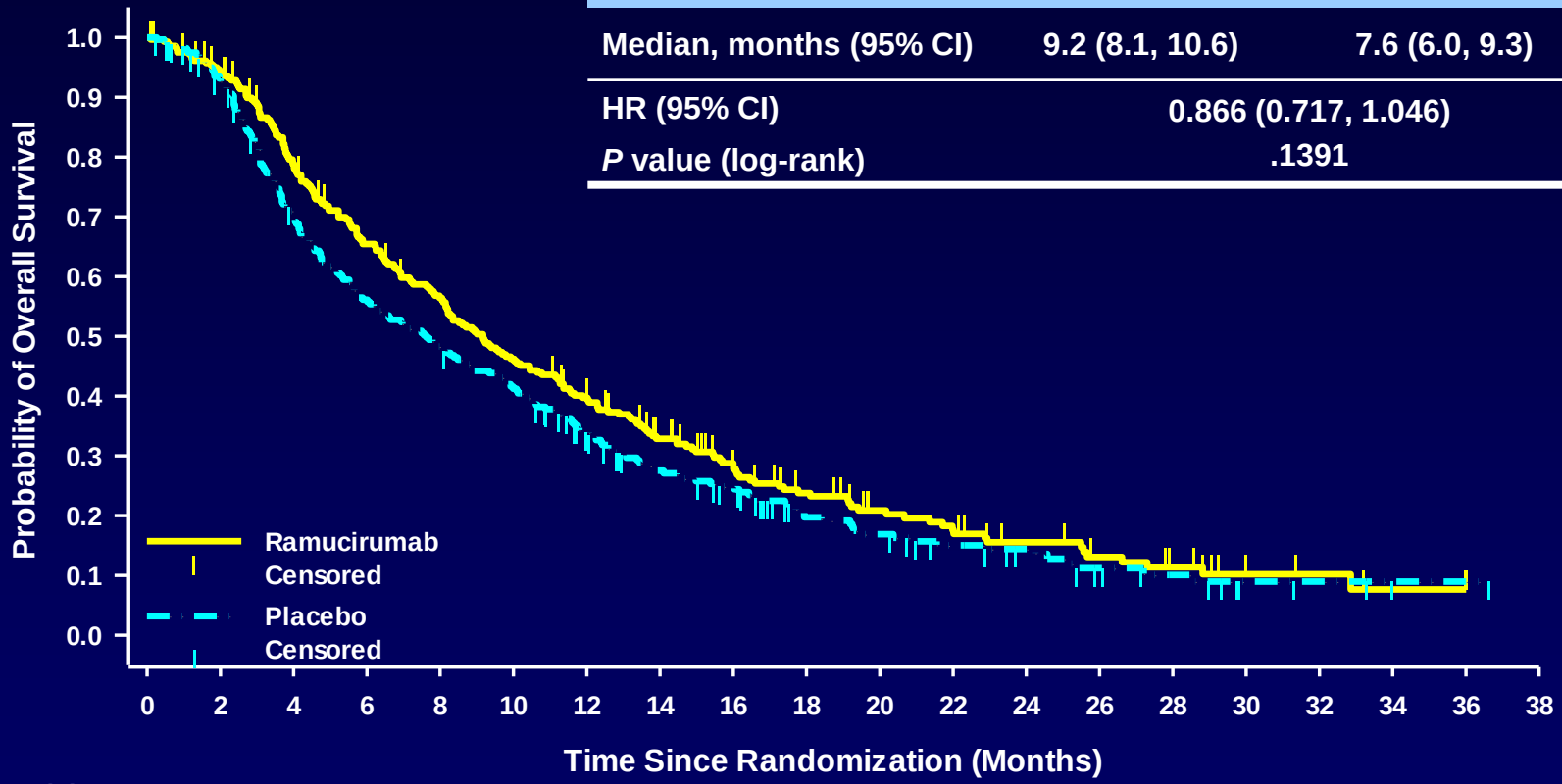
# Overall Survival of ITT Population

| | Ramucirumab | Placebo |
|---|---|---|
| Median, months (95% CI) | 9.2 (8.1, 10.6) | 7.6 (6.0, 9.3) |
| HR (95% CI) | 0.866 (0.717, 1.046) | |
| *P* value (log-rank) | .1391 | |




**Patients at risk**

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ramucirumab** | 283 | 261 | 214 | 175 | 149 | 122 | 101 | 78 | 61 | 43 | 32 | 27 | 20 | 15 | 11 | 5 | 4 | 2 | 1 |
| **Placebo** | 282 | 255 | 189 | 151 | 129 | 110 | 83 | 63 | 54 | 35 | 30 | 23 | 18 | 12 | 9 | 4 | 3 | 1 | 1 |

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat.

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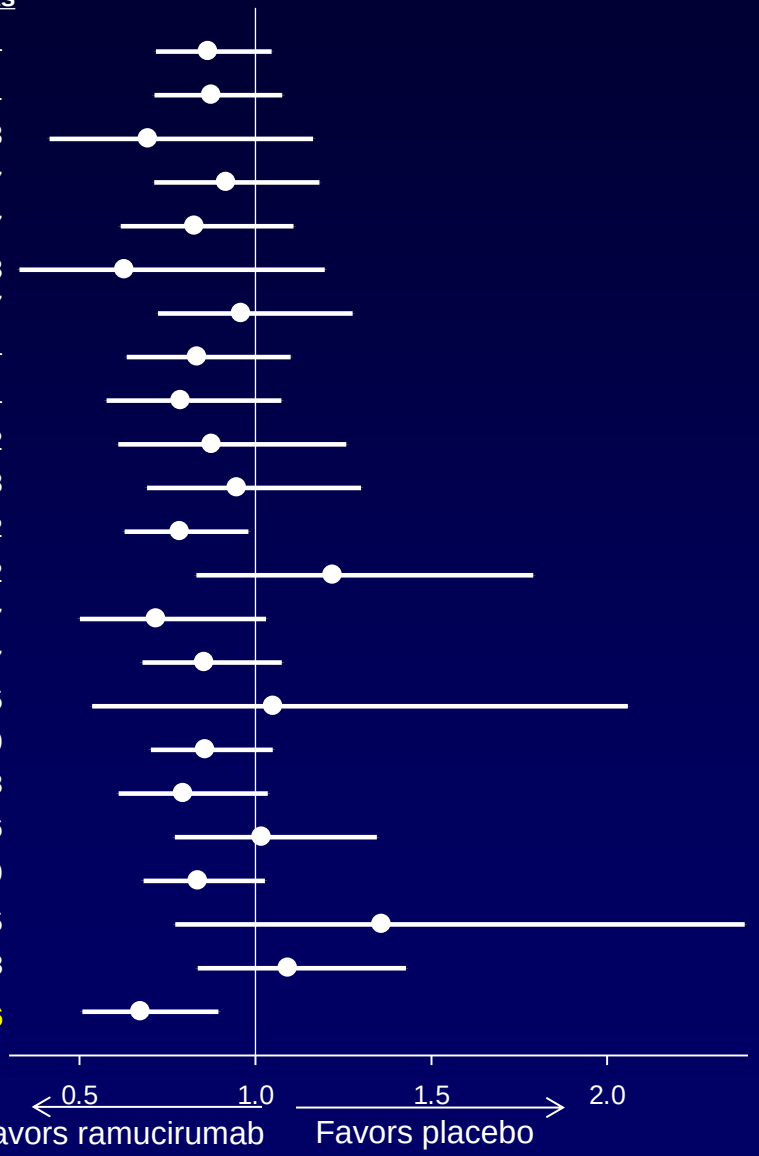
# Forest Plot of Overall Survival by Subgroup

| Category | Subgroup | Ramucirumab N | Ramucirumab # Events | Placebo N | Placebo # Events | HR (95% CI) |
|---|---|---|---|---|---|---|
| Overall | | 283 | 218 | 282 | 224 | 0.866 (0.717, 1.046) |
| Gender | Male | 236 | 182 | 242 | 191 | 0.875 (0.713, 1.076) |
| | Female | 47 | 36 | 40 | 33 | 0.695 (0.415, 1.164) |
| Age (years) | <65 | 150 | 124 | 162 | 127 | 0.917 (0.712, 1.182) |
| | ≥65 | 133 | 94 | 120 | 97 | 0.827 (0.617, 1.108) |
| Geographical region | N. & S. America | 32 | 17 | 33 | 23 | 0.628 (0.329, 1.197) |
| | Europe | 125 | 97 | 123 | 97 | 0.960 (0.723, 1.276) |
| | East Asia | 126 | 104 | 126 | 104 | 0.835 (0.634, 1.100) |
| Etiology of liver disease | Hepatitis B | 100 | 80 | 101 | 84 | 0.788 (0.577, 1.074) |
| | Hepatitis C | 77 | 58 | 77 | 62 | 0.876 (0.610, 1.258) |
| | Other | 106 | 80 | 104 | 78 | 0.948 (0.692, 1.300) |
| Extra-hepatic metastases | Yes | 207 | 157 | 200 | 162 | 0.785 (0.628, 0.980) |
| | No | 76 | 61 | 82 | 62 | 1.220 (0.832, 1.790) |
| Macrovascular invasion | Yes | 82 | 69 | 79 | 67 | 0.718 (0.501, 1.030) |
| | No | 201 | 149 | 203 | 157 | 0.855 (0.679, 1.075) |
| BCLC score | B | 33 | 25 | 34 | 25 | 1.051 (0.536, 2.059) |
| | C | 250 | 193 | 248 | 199 | 0.858 (0.703, 1.049) |
| ECOG PS | 0 | 159 | 115 | 153 | 118 | 0.795 (0.611, 1.035) |
| | 1 | 124 | 103 | 129 | 106 | 1.018 (0.771, 1.345) |
| Discont. of sorafenib | PD | 246 | 188 | 239 | 189 | 0.837 (0.682, 1.027) |
| | Toxicity | 37 | 30 | 43 | 35 | 1.359 (0.772, 2.391) |
| **Alpha-fetoprotein (ng/mL)*** | <400 | 160 | 116 | 150 | 108 | 1.093 (0.836, 1.428) |
| | **≥400** | **119** | **99** | **131** | **116** | **0.674 (0.508, 0.895)** |




*Interaction *P* value = .0272.

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# Baseline Characteristics

| | AFP ≥400 ng/mL | | AFP <400 ng/mL | |
|---|---|---|---|---|
| | Ramucirumab N = 119 n (%) | Placebo N = 131 n (%) | Ramucirumab N = 1 60 n (%) | Placebo N = 150 n (%) |
| **Baseline BCLC Score – Stage C** | 108 (90.8) | 122 (93.1) | 138 (86.3) | 125 (83.3) |
| **Primary tumor present** | 107 (89.9) | 117 (89.3) | 146 (91.3) | 134 (89.3) |
| **Number of metastatic sites** | | | | |
| **0-2** | 109 (91.6) | 116 (88.5) | 142 (88.8) | 138 (92.0) |
| **≥3** | 10 (8.4) | 15 (11.5) | 18 (11.3) | 12 (8.0) |
| **Etiology of liver disease** | | | | |
| **Hepatitis B** | 53 (44.5) | 66 (50.4) | 55 (34.4) | 41 (27.3) |
| **Hepatitis C** | 35 (29.4) | 28 (21.4) | 47 (29.4) | 48 (32.0) |
| **Other** | 46 (38.7) | 49 (37.4) | 77 (48.1) | 83 (55.3) |
| **Macrovascular invasion present** | 43 (36.1) | 44 (33.6) | 39 (24.4) | 35 (23.3) |
| **Extrahepatic spread present** | 85 (71.4) | 101 (77.1) | 118 (73.8) | 98 (65.3) |
| **Age <65 years** | 70 (58.8) | 84 (64.1) | 78 (48.8) | 77 (51.3) |
| **ECOG PS 0** | 60 (50.4) | 63 (48.1) | 97 (60.6) | 89 (59.3) |

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; N, number of patients; n, number of patients in category

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# Grade ≥3 Adverse Events of Special Interest

| | AFP ≥400 ng/mL | | AFP <400 ng/mL | |
|---|---|---|---|---|
| | Ramucirumab N = 119 n (%) | Placebo N = 128 n (%) | Ramucirumab N = 154 n (%) | Placebo N = 147 n (%) |
| Liver injury/failure† | 26 (21.8) | 39 (30.5) | 32 (20.8) | 26 (17.7) |
| Bleeding/hemorrhage† | 5 (4.2) | 12 (9.4) | 12 (7.8) | 9 (6.1) |
| Epistaxis | 0 | 0 | 0 | 0 |
| GI hemorrhage† | 4 (3.4) | 9 (7.0) | 7 (4.5) | 8 (5.4) |
| Hepatic hemorrhage† | 1 (0.8) | 2 (1.6) | 1 (0.6) | 0 |
| Pulmonary hemorrhage† | 0 | 1 (0.8) | 1 (0.6) | 1 (0.7) |
| Hypertension† | 15 (12.6) | 3 (2.3) | 19 (12.3) | 7 (4.8) |
| Proteinuria† | 0 | 0 | 6 (3.9) | 0 |
| Renal failure† | 1 (0.8) | 2 (1.6) | 5 (3.2) | 1 (0.7) |
| Infusion-related reaction† | 1 (0.8) | 0 | 2 (1.3) | 0 |
| Venous thromboembolic† | 1 (0.8) | 4 (3.1) | 1 (0.6) | 0 |
| Arterial thromboembolic† | 0 | 1 (0.8) | 0 | 0 |
| Congestive heart failure† | 0 | 0 | 0 | 1 (0.7) |

†Pooled adverse event terms; GI, gastrointestinal

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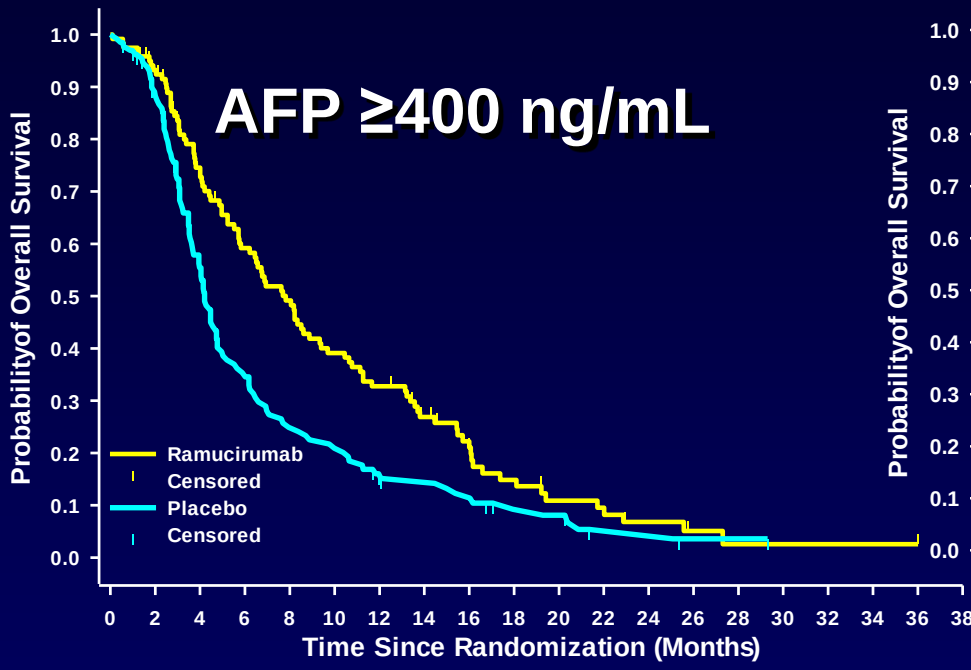
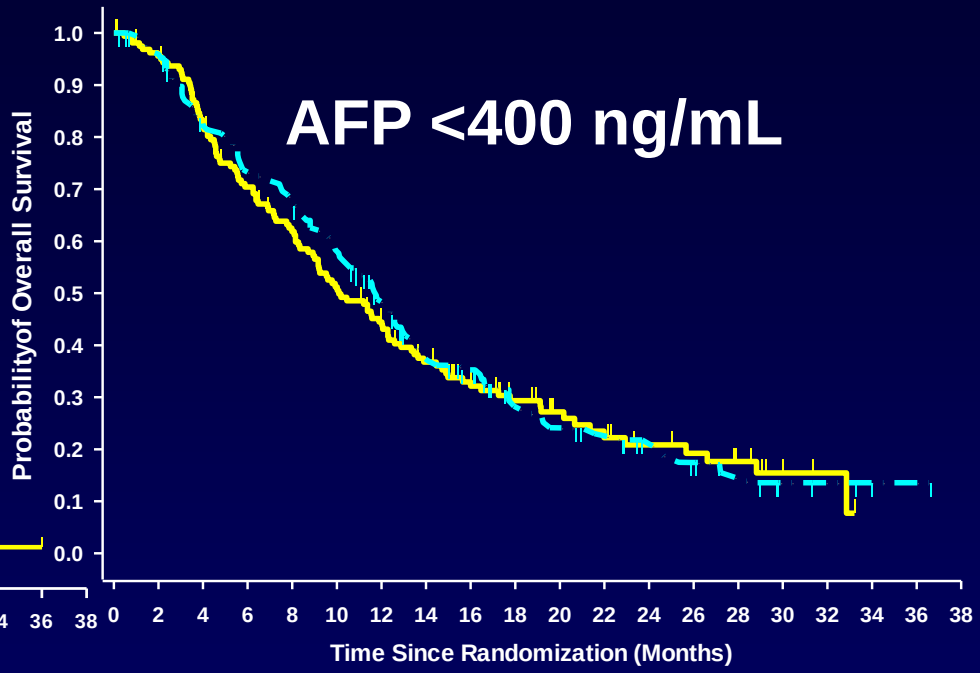
# Overall Survival in Patients With Baseline AFP ≥400 ng/mL or <400 ng/mL




| | Ramucirumab (N = 119) | Placebo (N = 131) |
|---|---|---|
| Median, months | 7.8 | 4.2 |
| (95% CI) | (5.8, 9.3) | (3.7, 4.8) |
| HR (95% CI) | 0.674 (0.508, 0.895) | |
| *P* value (log-rank) | .0059 | |

| | Ramucirumab (N = 160) | Placebo (N = 150) |
|---|---|---|
| Median, months | 10.1 | 11.8 |
| (95% CI) | (8.7, 12.3) | (9.9, 13.1) |
| HR (95% CI) | 1.093 (0.836, 1.428) | |
| *P* value (log-rank) | .5059 | |

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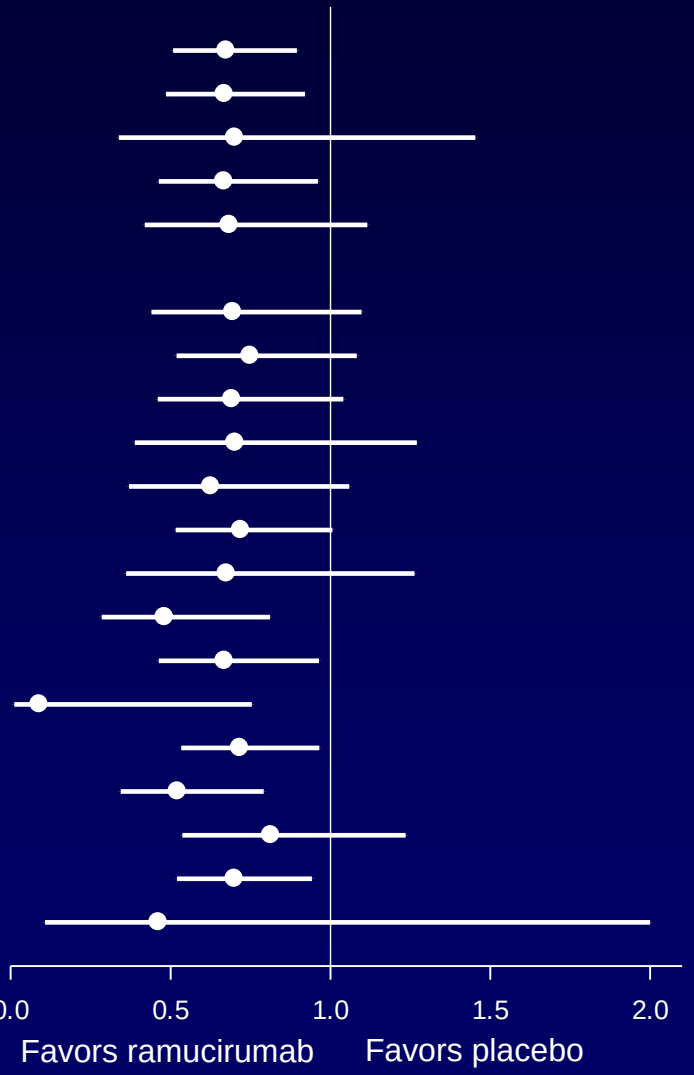
# Forest Plot of Overall Survival by Subgroup: Patients With Baseline AFP ≥400 ng/mL

| Category | Subgroup | Ramucirumab N | Ramucirumab # Events | Placebo N | Placebo # Events | HR (95% CI) |
|---|---|---|---|---|---|---|
| Overall | | 119 | 99 | 131 | 116 | 0.674 (0.508, 0.895) |
| Gender | Male | 92 | 77 | 110 | 98 | 0.669 (0.486, 0.920) |
| | Female | 27 | 22 | 21 | 18 | 0.701 (0.338, 1.453) |
| Age (years) | <65 | 70 | 61 | 84 | 74 | 0.667 (0.463, 0.961) |
| | ≥65 | 49 | 38 | 47 | 42 | 0.684 (0.419, 1.115) |
| Geographical region | N. & S. America* | 9 | 4 | 10 | 9 | — |
| | Europe | 44 | 36 | 48 | 44 | 0.695 (0.440, 1.097) |
| | East Asia | 66 | 59 | 73 | 63 | 0.749 (0.519, 1.082) |
| Etiology of liver disease | Hepatitis B | 50 | 46 | 63 | 56 | 0.692 (0.460, 1.040) |
| | Hepatitis C | 32 | 27 | 26 | 21 | 0.702 (0.388, 1.270) |
| | Other | 37 | 26 | 42 | 39 | 0.626 (0.370, 1.059) |
| Extra-hepatic metastases | Yes | 85 | 69 | 101 | 90 | 0.720 (0.516, 1.006) |
| | No | 34 | 30 | 30 | 26 | 0.675 (0.361, 1.263) |
| Macrovascular invasion | Yes | 43 | 39 | 44 | 39 | 0.481 (0.285, 0.811) |
| | No | 76 | 60 | 87 | 77 | 0.668 (0.463, 0.964) |
| BCLC score | B | 11 | 10 | 9 | 9 | 0.090 (0.011, 0.754) |
| | C | 108 | 89 | 122 | 107 | 0.717 (0.533, 0.965) |
| ECOG PS | 0 | 60 | 50 | 63 | 56 | 0.522 (0.344, 0.791) |
| | 1 | 59 | 49 | 68 | 60 | 0.814 (0.537, 1.235) |
| Discont. of sorafenib | PD | 108 | 89 | 122 | 107 | 0.700 (0.520, 0.942) |
| | Toxicity | 11 | 10 | 9 | 9 | 0.462 (0.107, 2.000) |




*Results cannot be calculated due to small number of events.

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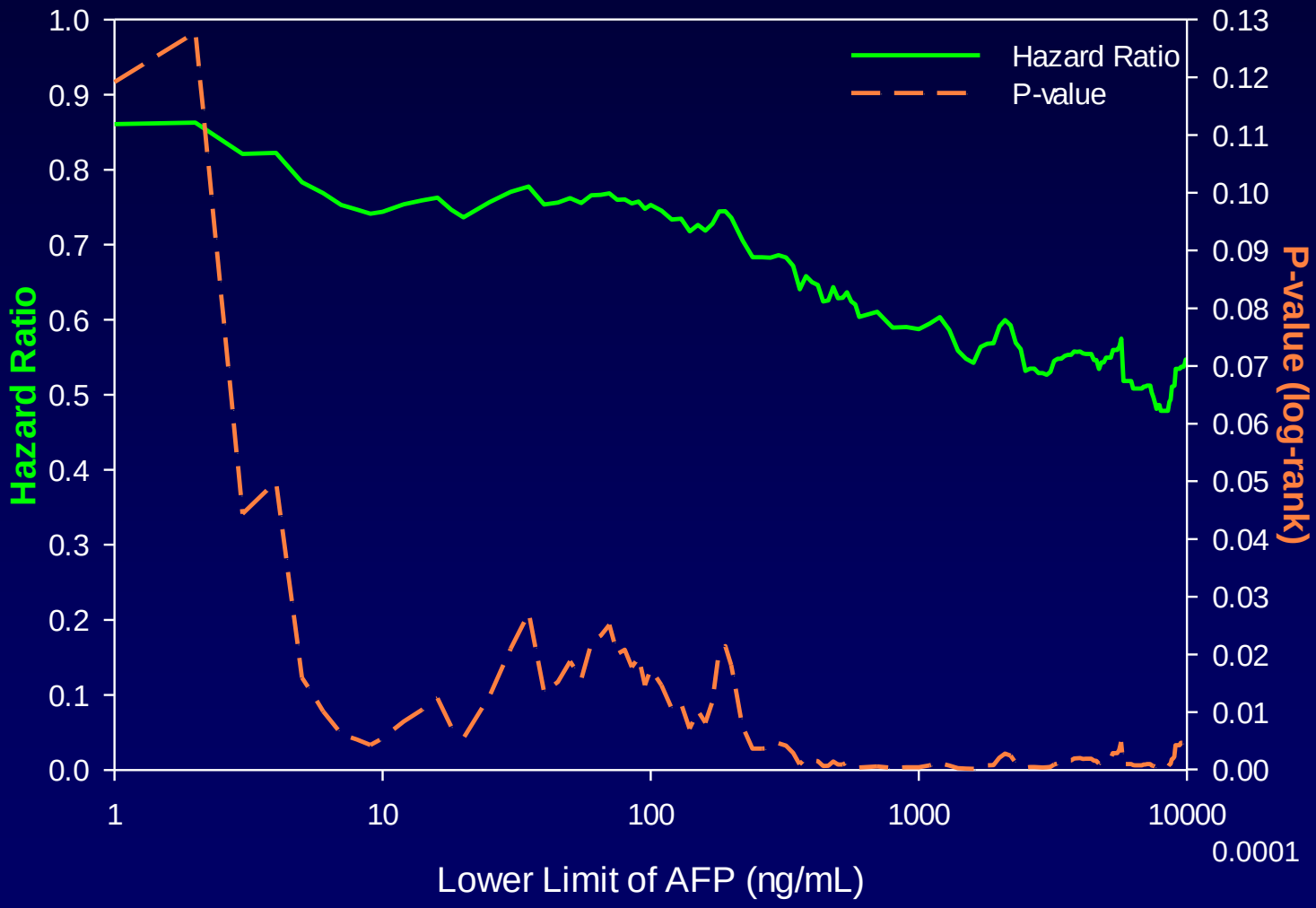
# Overall Survival Hazard Ratios and *P* Values by Threshold of Baseline AFP Level (Log-Scale)

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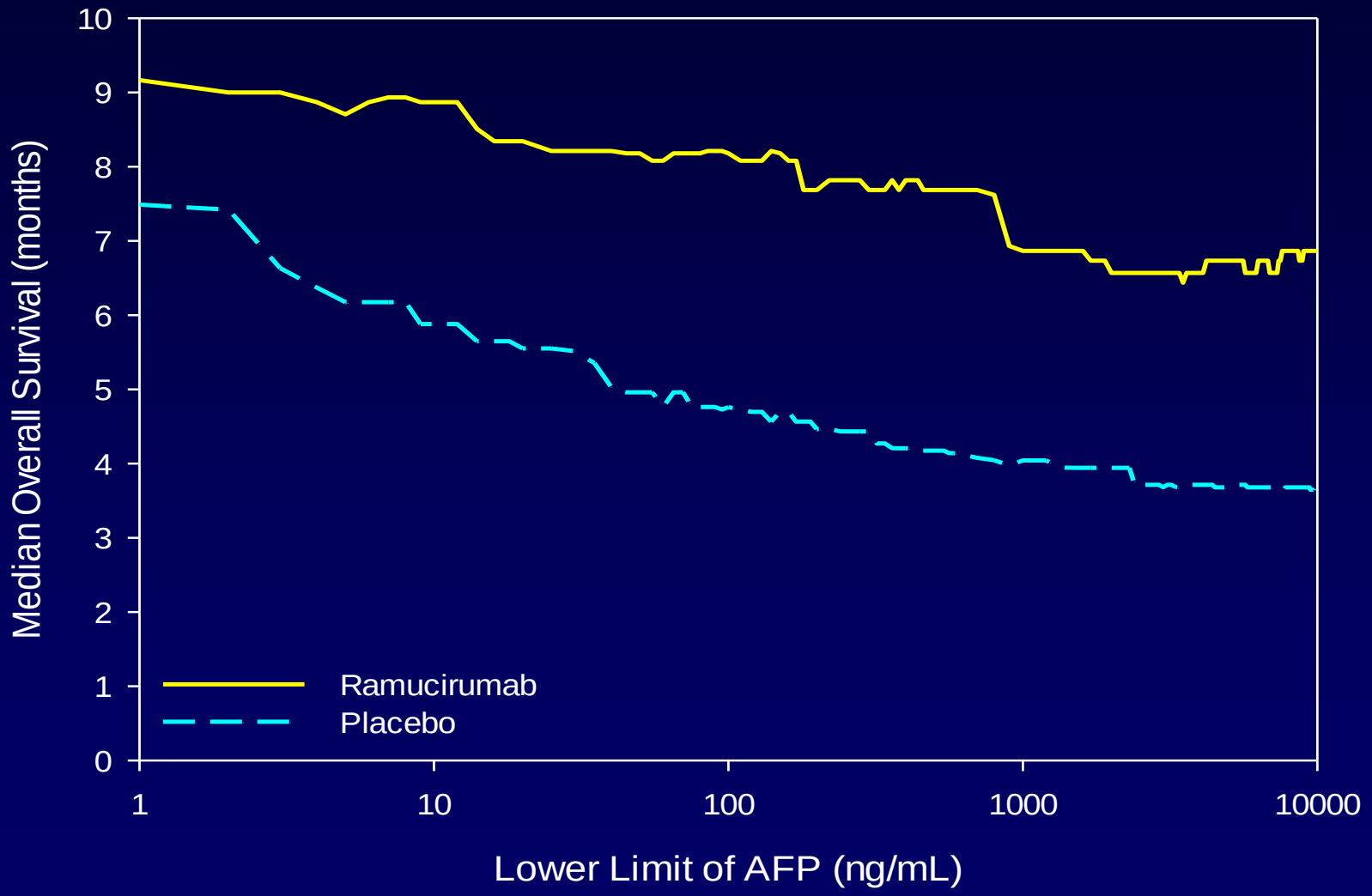
# Median Overall Survival by Threshold of Baseline AFP Level

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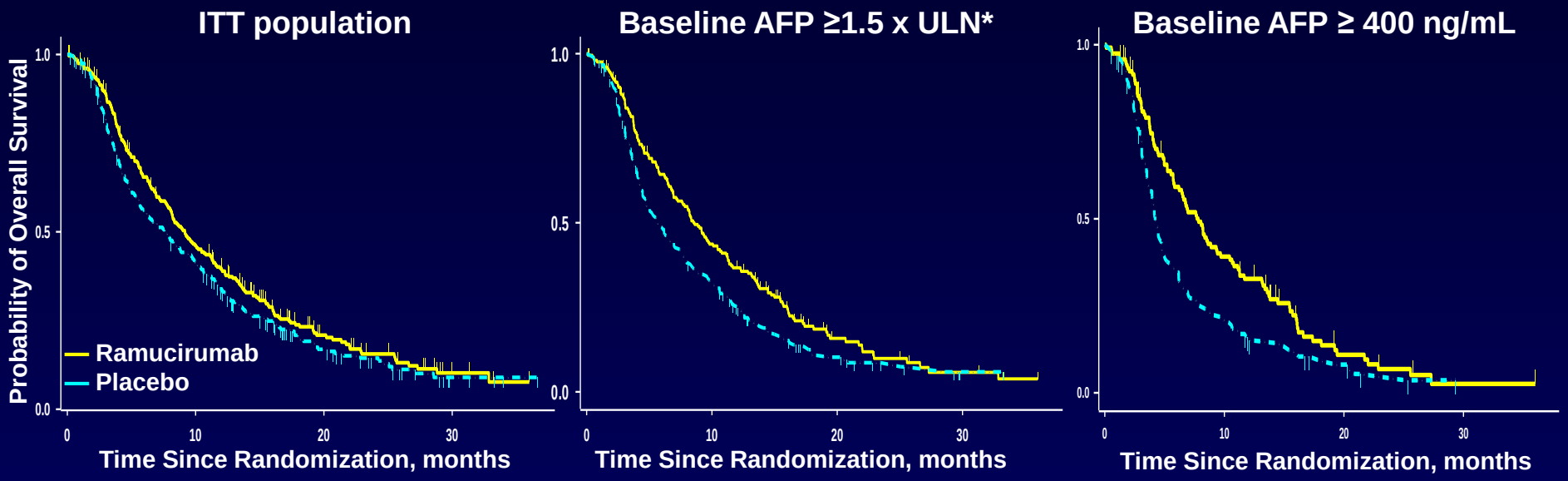
# OS Increases With Baseline AFP Threshold




| | Ramucirumab (N = 283) | Placebo (N = 282) | Ramucirumab (N = 205) | Placebo (N = 212) | Ramucirumab (N = 119) | Placebo (N = 131) |
|---|---|---|---|---|---|---|
| Median, months | 9.2 | 7.6 | 8.6 | 5.7 | 7.8 | 4.2 |
| (95% CI) | (8.1, 10.6) | (6.0, 9.3) | (7.2, 10.1) | (4.7, 7.0) | (5.8, 9.3) | (3.7, 4.8) |
| HR (95% CI) | 0.866 (0.717, 1.046) | | 0.749 (0.603, 0.930) | | 0.674 (0.508, 0.895) | |
| *P* value (log-rank) | .1391 | | .0088 | | .0059 | |

*ULN median was approximately 10 ng/mL

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# Conclusions

- Baseline AFP is identified as a potential marker for selecting patients who may benefit from ramucirumab
- A robust and clinically meaningful improvement in overall survival was observed in the population with elevated baseline AFP level (≥400 ng/mL), a population associated with poorer prognosis
- Ramucirumab was well tolerated and demonstrated an acceptable safety profile
- In a post-hoc analysis of REACH, ramucirumab treatment led to a greater reduction in the risk of death in patients with progressively higher baseline AFP values
- Further investigation of the relationship between baseline AFP level and angiogenesis inhibition is ongoing to better understand ramucirumab mechanism of action in HCC

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