Supplementary material

Additional eligibility criteria information

Adequate hematological and organ function included but was not limited to a total bilirubin ≤ to the upper limit of normal value (ULN), AST and ALT ≤2.5 x ULN, or ≤5 x ULN if due to liver metastases, (CrCl) ≥50 mL/min and a urinary protein ≤1+ on dipstick or routine urinalysis in addition to adequate coagulation function defined as an INR ≤1.5 or PT ≤1.5 x ULN, and PPT ≤1.5 x ULN. Uncontrolled hypertension was defined as systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg despite standard medical management.

Dose modifications for treatment-related toxicities

Proteinuria

RELAY included patients with less than 1 gr of protein in their 24hr urine at baseline. During the study, patients were monitored for the development or worsening of proteinuria prior to every cycle by urine dipstick. If urine dipstick or routine urine analysis indicated proteinuria ≥2+, a quantitative 24-hour urine collection (to assess protein) must be obtained. The RELAY protocol included a detailed dosing algorithm for proteinuria, that considered both the degree of proteinuria and if the proteinuria was maintained over different cycles. Ramucirumab/placebo was to be permanently discontinued for proteinuria ≥2 g/24 hours sustained for 2 consecutive cycles or for proteinuria >3 g/24 hours or nephrotic syndrome.

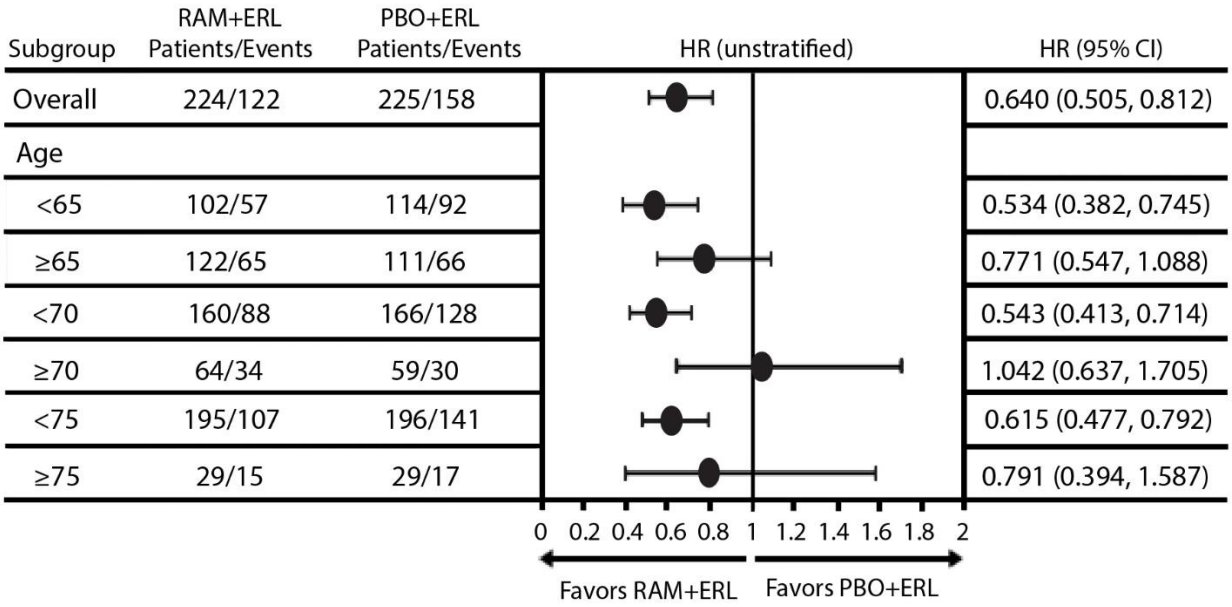
Hypertension
Hypertension is a known and manageable class effect of anti-angiogenic therapy. The RELAY protocol excluded patients with uncontrolled* hypertension despite medical management. During the study, blood pressure was to be monitored at every visit. In case of symptomatic hypertension, ramucirumab/placebo was to be temporarily withheld until BP was controlled and permanently discontinued for hypertension which could not be controlled with antihypertensive agents.

*Uncontrolled hypertension was defined as systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg despite standard medical management.

Bleeding
Bleeding is a known class effect of anti-angiogenic therapy. In the RELAY study, therefore, patients with an increased risk of bleeding were excluded, and the exclusion criteria included: concomitant use of NSAID´s or other antiplatelet agents within 7 days prior to first dose of study treatment, a prior history of bleeding or evidence of major blood vessel invasion.
During the study, patients were closely monitored with hematology collected every cycle and a coagulation profile every 4th cycle. Ramucirumab/placebo was to be permanently discontinued for Grade 3-4 bleeding.

Supplementary Figure

Supplementary Fig. 1: PFS results by age subgroup



CI = confidence intervals; ERL = erlotinib; HR = hazard ratio; PBO = placebo; RAM = ramucirumab