Sunitinib added to FOLFIRI versus FOLFIRI in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: a randomized, placebo-controlled phase II AIO trial with serum biomarker program.

As a multi-targeted anti-angiogenic receptor tyrosine kinase (RTK) inhibitor sunitinib (SUN) has been established for renal cancer and gastrointestinal stromal tumors. In advanced refractory esophagogastric cancer patients, monotherapy with SUN was associated with good tolerability but limited tumor response. This double-blind, placebo-controlled, multicenter, phase II clinical trial was conducted to evaluate the efficacy, safety and tolerability of SUN as an adjunct to second and third-line FOLFIRI (NCT01020630). Patients were randomized to receive 6-week cycles including FOLFIRI plus sodium folinate (Na-FOLFIRI) once every two weeks and SUN or placebo (PL) continuously for four weeks followed by a 2-week rest period. The primary study endpoint was progression-free survival (PFS). Preplanned serum analyses of VEGF-A, VEGF-D,
VEGFR2 and SDF-1 were performed retrospectively. Overall, 91 patients were randomized, 45 in each group (one patient withdrew). The main grade>=3 AEs were neutropenia and leucopenia, observed in 56 %/20 % and 27 %/16 % for FOLFIRI + SUN/FOLFIRI + PL, respectively. Median PFS was similar, 3.5 vs. 3.3 months (hazard ratio (HR) 1.11, 95 % CI 0.70-1.74, P = 0.66) for FOLFIRI + SUN vs. FOLFIRI + PL, respectively. For FOLFIRI + SUN, a trend towards longer median overall survival (OS) compared with placebo was observed (10.4 vs. 8.9 months, HR 0.82, 95 % CI 0.50-1.34, one-sided P = 0.21). In subgroup serum analyses, significant changes in VEGF-A (P = 0.017), VEGFR2 (P = 0.012) and VEGF-D (P< 0.001) serum levels were observed. Although sunitinib combined with FOLFIRI did not improve PFS and response in chemotherapy-resistant gastric cancer, a trend towards better OS was observed. Further biomarker-driven studies with other anti-angiogenic RTK inhibitors are warranted. This study was registered prospectively in the NCT Clinical Trials Registry (ClinicalTrials.gov) under NCT01020630 on November 23, 2009 after approval by the leading ethics committee of the Medical Association of Rhineland-Palatinate, Mainz, in coordination with the participating ethics committees (see Additional file 2) on September 16, 2009.