ANGIOGENESIS-RELATED CIRCULATING BIOMARKERS AND BENEFIT FROM SECOND-LINE TREATMENT WITH PACLITAXEL AND RAMUCIRUMAB IN ADVANCED GASTRIC CANCER

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Introduction: Ramucirumab plus paclitaxel is considered the standard of care in the second-line treatment of gastric carcinoma. However, prognostic and predictive factors to personalize treatment in molecularly-selected patients are still lacking. The aim of the present study was to evaluate relevant vascular endothelial growth factor (VEGF) family members, such as VEGF-A and VEGF-D, and circulating soluble VEGF receptor-2(sVEGFR-2) as putative mediators of resistance or response to ramucirumab administered with paclitaxel in pretreated metastatic gastric cancer patients.

Methods: Forty-one patients treated with ramucirumab and paclitaxel were prospectively enrolled. Plasma samples were collected at different time points (on days 1and 15of the first three cycles, at best radiologic response and at the time of disease progression). VEGF-A, VEGF-D and sVEGFR-2were analysed by ELISA. Correlations of biomarker baseline levels or dynamic changes with outcome measures were assessed. Progression-free survival (PFS) was the primary endpoint.

Results: VEGF-A and VEGF-D, but not sVEGFR-2, values significantly increased during treatment compared to baseline ($p<0.001$). A positive correlation between VEGF-A and sVEGFR-2at cycle 2was found ($p=0.045$). At univariate analysis, higher baseline levels of VEGF-A were associated with worse OS ($p=0.015$). Early increase of sVEGFR-2levels after the first treatment cycle was the only factor associated with longer PFS (6.6vs. 3.6months, $p=0.049$) and OS (18.6vs. 5.2months, $p=0.008$). Significance of sVEGFR-2early increase was retained at multivariate analysis for OS (HR 0.32; 95% CI 0.12-0.91; $p=0.032$).

Conclusions: Our results confirmed the prognostic role of baseline VEGF-A and identified the early increase of sVEGFR-2after 1cycle of treatment as a potential predictive biomarker of benefit from second-line ramucirumab plus paclitaxel in gastric cancer. Confirmation of these preliminary findings in larger cohorts is warranted. The study has been funded by ITT.

Keywords
Angiogenesis, biomarkers, gastric cancer, ramucirumab, sVEGFR-2, VEGF-A, VEGF-D