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SO-20 Prospective validation of Ang-2 and Tie-2 plasma levels as predictors of benefit from regorafenib in metastatic colorectal cancer patients: REGOLAND study

C. Antoniotti[1], F. Marmorino[1], A. Boccaccino[1], M. Antista[2], N. Zaffaroni[3], G. Zucchelli[1], A. Martinetti[3], E. Campi[3], D. Rossini[1], E. Sottotetti[3], B. Borelli[1], F. Corti[3], V. Conca[1], R. Moretto[4], M. Germani[1], A. Falcone[5], M. Giordano[6], G. Masi[7], F. Pietrantonio[2], C. Cremolini[8]

[1]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [2]Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; [3]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [4]Department of Oncology, University Hospital of Pisa, Pisa, Italy; [5]University of Pisa, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [6]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [7]University of Pisa, Pisa, Italy; [8]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy

Background: Regorafenib is a treatment option for refractory metastatic colorectal cancer (mCRC) patients. The identification of markers to predict or monitor the efficacy of regorafenib represents a key issue in this palliative setting. In a previous exploratory study, the early increase of Ang-2 plasma levels during treatment with regorafenib seemed to predict benefit from this agent and low baseline Ang-2 and Tie-2 plasma levels were associated with good prognosis. REGOLAND is a translational study, which aims to prospectively validate these retrospective findings.

Methods: Ang-2 and Tie-2 were assessed by ELISA on plasma samples collected at baseline (d1) and after 15 days (d15) of treatment in a cohort of mCRC patients receiving regorafenib, as per indication. To detect a HR for PFS of 0.50 in favour of the early increase (Δd15-d1) of Ang-2 levels, setting two-sided α=0.05 and β=0.10, 87 events were required according to Schoenfeld design. Comparisons among concentrations of each marker at d1 and d15 were performed by Wilcoxon test. d1 median cut-off values of Ang-2 and Tie-2 were adopted to discriminate patients with low versus high plasma levels and were analysed for their correlation with outcome.

Results: One hundred patients were included. Median PFS and OS were 2.5 and 6.7 months, respectively. As compared to d1, Tie-2 levels decreased at d15 (P=0.007), while no significant early modulation was reported for Ang-2. Patients with Ang-2 early increased levels (n=42) had a trend for a better outcome (HR for PFS: 0.72 [95% CI:0.48-1.08], P=0.095; HR for OS: 0.77 [95%CI:0.51-1.16], P=0.204) than those with Ang-2 early decreased levels (n=58). No difference was detected for d1 Tie-2 levels in terms of outcome, while d1 low levels of Ang-2 were associated with longer PFS (HR: l0.59 [95%CI:0.39-0.89], P=0.005) and OS (HR:0.62 [95%CI:0.41-0.94], P=0.017). In the multivariate model, the association of d1 Ang-2 levels with PFS was confirmed (HR:0.48 [95%CI:0.31-0.76], P=0.001), but not in OS (HR: 0.80 [95%CI:0.49-1.28], P=0.351).

Conclusions: This experience met to prospectively validate Ang-2 baseline levels as prognostic marker and its early modulation as a predictor of benefit from regorafenib in mCRC patients. Whether the early modulation of Ang-2 levels suggests that the successful Tie-2 inhibition by regorafenib leads to a compensatory increase in Ang-2 and correlates with anti-tumour activity deserves further investigation.

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