549P Second line EGFR-inhibitors in RAS mutant metastatic colorectal cancer: The plasma RAS wild type "window of opportunity"

P. Gazzaniga[1], C. Raimondi[2], F. Urbano[3], E. Cortesi[3]

[1]*Molecular Medicine, Sapienza University of Rome, Rome, Italy,* [2]*Radiology, Oncology and Pathology, Sapienza Univeristy of Rome, Rome, Italy,* [3]*Radiology, Oncology and Pathology, Policlinico Umberto I, Rome, Italy*

Background: RAS mutations are found in 30-50% of metastatic colorectal cancer (mCRC) and determine the ineligibility for EGFR-targeted therapies. Recent studies have demonstrated that the analysis of circulating tumor DNA (ctDNA) is a surrogate of tumor biopsy for mutations detection. To date, studies have been focused on the appearance of RAS-mutant clones in patients with RAS-wild type mCRC, as biomarkers of anti-EGFR therapy resistance. We here describe a population of RAS mutant

mCRC who converted to wt -RAS status in blood over the course of first-line treatments. As proof of concept, the absence of any clinically relevant mutation of RAS genes in blood has been used as a therapeutically exploitable window. To this purpose five patients received second-line treatment with anti-EGFR, achieving a durable clinical benefit.

Methods: Blood samples from 20 patients with mutant RAS status were prospectively collected before initiating first- line therapies. RAS mutational status was assessed on tumor tissue and plasma samples at baseline. In all cases with plasma-tissue concordance at baseline (n. 15), RAS mutations were serially monitored every 3 months. Idylla^{TM}(Biocartis) was used to investigate RAS mutational profile from plasma. Specifically, Idylla^{TM} ctKRAS Mutation Assay and Idylla^{TM} ctNRAS/BRAF/EGFR Mutation Assay were used.

Results: 15 mCRC patients harboring any RAS mutation in tumor tissue and plasma at the time of diagnosis were serially monitored through plasma ctDNA analysis. Eleven patients (73%) switched to a wild- type RAS status in blood during the course of first line treatments. At disease progression in the first-line setting, 5 of them have received EGFR inhibitors as a second-line treatment, achieving a durable clinical benefit.

Conclusions: ctDNA analysis might reveal a therapeutically exploitable window of opportunity, characterized by the prevalence of wt -RAS clones, which can be converted in a clinically meaningful benefit for patients. Our planned KAIROS trial might determine whether the response to EGFR inhibition, in patients with RAS mutant cancers converted to RAS wild-type in course of treatments, might become the rule rather than the exception.

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