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KRAS and BRAF mutations predict primary resistance to Imatinib in gastrointestinal stromal tumors (GIST)

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Background. Gastrointestinal stromal tumors (GIST) are characterized by gain-of-function mutations in KIT/PDGFR α genes leading to a constitutive receptor activation which is well counteracted by Imatinib. However, cases in which Imatinib as first line treatment has no effects are reported (primary resistance). Our purpose is to investigate alterations in downstream effectors, not reported so far in mutated GIST, possibly explaining the primary resistance to targeted treatments.

Methods. Experimental design. Two independent naïve GIST cohorts have been analyzed for KIT, PDGFR α , KRAS and BRAF mutations by direct sequencing. Cell lines expressing a constitutively activated and Imatinib responding KIT, alone or in combination with activated KRAS and BRAF, were produced and treated with Imatinib. KIT receptor and its downstream effectors were analyzed by direct Western blotting.

Results. In naïve GISTs carrying activating mutations in KIT or PDGFR α a concomitant activating mutation was detected in KRAS (5%) or BRAF (about 2%) genes. In vitro experiments demonstrated that Imatinib was able to switch off the mutated receptor KIT but not the downstream signalling triggered by RAS-RAF effectors.

Conclusions. These data suggest the activation of MAPK pathway as a possible novel mechanism of primary resistance to Imatinib in GISTs and could explain the survival curves obtained from several clinical studies where 2–4% of GIST patients treated with Imatinib, despite carrying KIT sensitive mutations, do not respond to the treatment.