Published OnlineFirst January 26, 2012; DOI: 10.1158/1078-0432.CCR-11-2230

Clinical Cancer Research

Predictive Biomarkers and Personalized Medicine

KRAS and BRAF Mutations Predict Primary Resistance to Imatinib in Gastrointestinal Stromal Tumors

Claudia Miranda[1], Martina Nucifora[4], Francesca Molinari[4], Elena Conca[2], Maria Chiara Anania[1], Andrea Bordoni[5], Piercarlo Saletti[6], Luca Mazzucchelli[4], Silvana Pilotti[2], Marco A. Pierotti[3], Elena Tamborini[2], Angela Greco[1], and Milo Frattini[4]

Abstract

Purpose: Gastrointestinal stromal tumors (GIST) are characterized by gain-of-function mutations in *KIT*/*PDGFRA* 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.

Experimental Design: Two independent naive GIST cohorts have been analyzed for *KIT*, *PDGFRA*, *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 naive GISTs carrying activating mutations in *KIT* or *PDGFRA* a concomitant activating mutation was detected in *KRAS* (5%) or *BRAF* (about 2%) genes. *In vitro* experiments showed that imatinib was able to switch off the mutated receptor KIT but not the downstream signaling triggered by RAS–RAF effectors.

Conclusions: These data suggest the activation of mitogen—activated protein kinase 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% to 4% of patients with GIST treated with imatinib, despite carrying KIT-sensitive mutations, do not respond to the treatment. *Clin Cancer Res; 18(6); 1769–76. ©2012 AACR.*