

# LACK OF RELATIONSHIP BETWEEN RESISTANCE TO IMATINIB OF MPM CELLS AND MUTATIONS WITHIN TYROSINE-KINASE RECEPTOR GENES

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Imatinib, a tyrosine-kinase inhibitor, selectively induces cytotoxicity and apoptosis in Malignant Pleural Mesothelioma (MPM) cell lines. However, in previous clinical trials where imatinib was administered as single agent it was observed a lack of therapeutic effectiveness on MPM patients. Among the targets of imatinib, PDGFR, c-KIT, and c-MET, are candidates with a hypothesized role in MPM. In other types of tumors, it has been shown that mutations in particular sites of tyrosine-kinase receptors domains are associated with chemo-resistance. In particular, in Gastro-Intestinal Stromal Tumors (GIST), the lack of responsiveness to Imatinib is due to mutations within exons 12, 14 and 18 of *PDGFR*, as well as in exons 13, 14 and 17 of *c-KIT*, and exon 18 of *c-MET*.

We undertook a genetic study aimed to ascertain whether mutations within *PDGFR*, *c-KIT* and *c-MET* could explain *in vitro* the lack of response to imatinib of MPM. We induced a long-term resistance to imatinib, in the MPM human cell line MERO-14, and the resistant clone was screened for mutations in the above mentioned genes. One imatinib-resistant clone derivative from the human MPM cell line REN was also screened. According to our observation, no mutations were found. This led to conclude that the lack of response to imatinib should not be ascribed to somatic mutations established in *PDGFR*, *c-KIT*, or *c-MET*.