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**AMACR GENE AMPLIFICATION AND PROTEIN OVEREXPRESSION IN PRIMARY IMATINIB-NAÏVE GASTROINTESTINAL INTESTINAL STROMAL TUMORS**

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**Background:** An integrative molecular and functional approach was aimed to identify amplified oncogenes on 5p and to validate the relevance of AMACR amplification and overexpression in gastrointestinal stromal tumors (GIST).

**Methods:** GIST samples and cell lines were analyzed for DNA imbalances by array-based genomic profiling and quantified for AMACR mRNA expression. AMACR-specific FISH and immunohistochemistry were both informative in 350 independent primary GISTs, including 213 with confirmed KIT and PDGFRA genotypes. GIST cells were stably silenced against AMACR to assess its oncogenic functions.

**Results:** 5p gains were differentially overrepresented in high-risk GISTs with 3 major amplicons, including one encompassing the mRNA-upregulated AMACR gene. Despite no amplification in 52% of AMACR-overexpressing GISTs, amplification (20%) and overexpression (38%) were strongly related to each other (p < 0.001). Apart from the associations with unfavorable genotypes, amplification and overexpression were strongly related to epithelioid histology, larger size, increased mitoses, and higher risk levels (all p < 0.003) and independently predictive of decreased disease-free survival (overexpression, p < 0.001; amplification, p = 0.020). Concomitant with downregulated cyclin D1, cyclin E, and CDK4, AMACR knockdown suppressed cell proliferation and induced G1-phase arrest but did not affect apoptosis in GIST cells.

**Conclusion:** AMACR amplification is a mechanism driving increased mRNA and protein expression to confer aggressiveness on GISTs through heightened cell proliferation.