# CCR 20th Anniversary Commentary: A Genetic Mechanism of Imatinib Resistance in Gastrointestinal Stromal Tumor—Where Are We a Decade Later?

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In the June 1, 2005, issue of *Clinical Cancer Research*, Antonescu and colleagues defined second-site *KIT* mutations in gastrointestinal stromal tumor (GIST) as the leading mechanism of acquired resistance to imatinib. Secondary mutations were detectable mainly in *KIT* exon 11 mutant GISTs after prolonged initial clinical responses. These findings played a critical role in designing the next generation of tyrosine kinase inhibitors. *Clin Cancer Res; 21(15); 3363–5. ©2015 AACR.*

*See related article by Antonescu et al., Clin Cancer Res 2005; 11(11) June 1, 2005;4182–90*

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Gastrointestinal stromal tumor (GIST) represents one of the most prevalent sarcoma subtypes and is the most common mesenchymal neoplasm of the gastrointestinal tract. Most GISTs harbor activating oncogenic "driver" mutations in the receptor tyrosine kinase (RTK) *KIT*, or, less frequently, platelet-derived growth factor receptor alpha (*PDGFRA*). Among GISTs with wild-type *KIT* and *PDGFRA*, the majority possess loss-of-function defects in the mitochondrial succinate dehydrogenase (SDH) complex, a component of the Krebs cycle. Imatinib mesylate inhibits KIT and PDGFRA kinase activity and represents the first-line drug for the treatment of unresectable and advanced GISTs, achieving a partial response or stable disease in about 80% of patients with metastatic disease (1). *KIT* mutation status has a significant impact on treatment response, with GIST now a leading paradigm for genotype-driven targeted therapy. Patients with GIST containing a *KIT* exon 11 mutation have a partial response rate of 84% compared with 0% among patients without a *KIT* or *PDGFRA* mutation (2). Despite a high initial overall disease control rate, within 2 to 3 years of treatment the majority of patients develop imatinib resistance (3), which remains the biggest challenge in the clinical management of GIST.

The mechanisms of imatinib resistance in GIST are complex and heterogeneous and based on the primary genotype and duration of clinical response to the drug. About 15% to 20% of patients exhibit primary or early resistance to imatinib (continuous growth or growth within 6 months of therapy), including those with *BRAF*, *RAS*, or *NF1* mutations or SDHB deficiency. Our study showed that secondary *KIT* mutations are rare in primary and early resistance, but are found in 50% to 67% of patients with secondary (i.e., acquired) resistance (3, 4). Most second-site *KIT* mutations are identified in GISTs with a mutant *KIT* exon 11 genotype, and these patients generally experience prolonged clinical responses. Thus, secondary mutations are found in 73% to 86% of imatinib-resistant patients harboring *KIT* exon 11 primary mutations, compared with only 19% to 33% of patients with *KIT* exon 9 mutations (3, 5, 6). Our study highlighted that the pattern of second-site mutations in the setting of acquired imatinib resistance was exclusively substitutions, distributed between the first and the second KIT kinase domains, which almost never occur in untreated GISTs. Notably, the primary and secondary mutations were always located on the same allele. Consistent with a secondary clonal evolution, the primary mutation was detectable in all metastases from an individual patient.

Two possible mechanisms have been proposed to explain how acquired resistance to imatinib therapy may develop. First, second-site mutations may specifically interfere with imatinib binding without affecting the overall KIT kinase conformation, as happens with the T670I gatekeeper mutation (exon 14) that disrupts an important H-bond to imatinib. The other explanation is that activation loop mutations (exon 17) specifically stabilize the active conformation of the KIT kinase and prevent imatinib binding, which occurs only in the inactive conformation.

Regardless of the primary genotype or whether resistance is primary or secondary, most resistant tumors remain addicted to the initial driver oncogene and show reactivation of KIT phosphorylation. The fact that resistance occurs at the level of KIT and not by additional mutations in downstream components or other signaling pathways is the most stunning illustration of the specificity of oncogene addiction and underscores the unique role of KIT as a therapeutic target in these tumors. In addition, our study ruled out the possibility of *KIT* gene amplification as a common mechanism of oncogene reactivation in imatinib-resistant GIST with or without second-site mutations. We also found that KIT activation, as measured by phosphorylation, was heterogeneous and did not correlate with histologic or clinical response to

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imatinib; surprisingly, most nonresistant GISTs showed reactivation or persistent activation of KIT protein by Western blotting. KIT activation was also variable in the subset of patients with second-site mutations, with uneven phospho-KIT expression among patients with similar primary and secondary genotypes or within different nodules of individual patients, regardless of the type of second-site mutation. Additional complexity for targeting imatinib-resistant GIST results from the intratumor and intertumor heterogeneity of secondary *KIT* mutations. Long-term imatinib therapy can lead to polyclonal acquired resistance, whereby different tumor nodules acquire different secondary mutations and progress independently (7). This genetic complexity of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable clinical benefit, with mutations located in the activation loop (exons 17/18) being particularly problematic. In contrast, patients with wild-type/SDH-deficient GIST have transient benefit or no clinical benefit from imatinib, and the progressing tumors consistently lack acquired mutations.

Up to one third of GIST patients with acquired resistance lack secondary mutations, although most show reactivation of the KIT oncoprotein. Several alternative mechanisms responsible for drug failure after an initial clinical response have been proposed. First, potential feedback mechanisms triggered by chronic KIT inhibition have been implicated, with either upregulation of the SRC/integrin axis (8) or MET (9). In these circumstances, combination therapies including dasatinib and cabozantinib, respectively, might have greater clinical efficacy. A positive feedback circuit was also demonstrated by MAPK kinase activation downstream of KIT that stabilizes ETV1 protein, which subsequently upregulates KIT expression (10). In addition, cross-talk mechanisms between KIT and other RTKs, for example FGFR3, were implicated in promoting GIST growth and drug resistance by activating the MAPK pathway (11). It is likely that compensatory signaling partially explains why oncogene-addicted tumors, such as GIST, do not regress completely after pharmacologic inhibition of the oncogenic driver. Insufficient oncoprotein inhibition by currently available drugs remains a constant concern, as KIT phosphorylation is rarely completely abolished even in responsive tumors, as shown in our initial study. One possibility recently suggested is impaired drug delivery due to the fibrotic stroma replacing the treated tumors (12).

A small subset of tumors fail imatinib through KIT-independent mechanisms. In this category, tumors typically lose KIT expression and undergo a phenotypic change to an undifferentiated sarcoma (i.e., dedifferentiated GIST), with aberrant expression of epithelial and muscle markers. At the molecular level, the KIT-negative dedifferentiated component shows loss of heterozygosity at the KIT locus (13). Less commonly, an RTK switch has been documented, such as loss of KIT and gain of AXL (14).

Sunitinib malate, a multitargeted TKI that inhibits KIT, PDGFR, and VEGFR, is the FDA-approved second-line therapy for patients who are intolerant to imatinib or have imatinib-resistant disease. Sunitinib was associated with a median time to progression of 27 weeks and a response rate of 7% (4). The clinical benefit of sunitinib is also genotype dependent, with GIST patients harboring a *KIT* exon 9 mutation being the most sensitive. Sunitinib resistance in GIST shares similar pathogenetic mechanisms identified in imatinib failure, with acquisition of secondary mutations in the activation domain after an initial benefit from the drug (15). Importantly, *KIT* exon 13 and 14 mutations were not detected in progressing tumors, as sunitinib is known to be efficacious with ATP-pocket second-site mutations (15). More recently, the FDA approved regorafenib as a third-line treatment for GIST based on a 17-week improvement in progression-free survival over placebo and a response rate of 4.5% (16). The limited efficacy of TKIs in the second-line and third-line settings clearly indicates that GISTs that progress on imatinib develop a generalized resistance to this class of inhibitors.

Ten years after the initial description of the leading mechanism of imatinib resistance in GIST, there is still a need to understand the different mechanisms of resistance to TKIs, identify the shared dependence and vulnerabilities of the genetically and clinically heterogeneous imatinib-resistant GISTs, and develop novel therapies. The need is particularly acute for patients with SDH-deficient GIST, for whom there is no effective treatment.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** C.R. Antonescu, R.P. DeMatteo
**Writing, review, and/or revision of the manuscript:** C.R. Antonescu, R.P. DeMatteo

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