KIT Exon 9-Mutated Gastrointestinal Stromal Tumours: Biology and Treatment

Andrea Napolitano^a Khin Thway^{a, b} Myles J. Smith^{a, b} Paul H. Huang^b
Robin L. Jones^{a, b}

^aSarcoma Unit, Royal Marsden NHS Foundation Trust, London, UK; ^bThe Institute of Cancer Research, London, UK

Keywords

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Abstract

Background: The majority of gastrointestinal stromal tumours (GISTs) harbour oncogenic mutations in the gene encoding for the tyrosine kinase (TK) KIT. The most common mutations are found in exon 11, followed by mutations in exon 9. The latter mutations are associated more frequently with GISTs in extra-gastric locations and with a more aggressive clinical behaviour. **Summary:** Here, we review the unique and often poorly recognized molecular, biological, and clinical characteristics that differentiate *KIT* exon 9-mutant GISTs from other GIST subtypes. In particular, *KIT* exon 9 mutations are associated to KIT mutants with retained sensitivity to stimulation by stem cell factor and localization to the cell membrane. Moreover, *KIT* exon 9-mutant GISTs display significant activation of KIT-independent oncogenic pathways. These characteristics may explain the limited activity of the TK inhibitor imatinib in the adjuvant setting in *KIT* exon 9-mutant GISTs, as well as their lower sensitivity to standard dose imatinib in the advanced setting. In contrast, the multi-TK inhibitor sunitinib displays better activity in *KIT* exon 9-mutant GISTs compared to others. **Key Messages:** *KIT*

exon 9-mutant GISTs represent a subtype of GIST distinct from other GISTs, including the more common *KIT* exon 11-mutant GISTs. A better understanding of the molecular biology and clinical behaviour of *KIT* exon 9-mutant GISTs may help identify more improved treatment options.

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Introduction

Gastrointestinal stromal tumours (GISTs) are the most common type of mesenchymal cancer, with an estimated global incidence of 10–15 cases per million individuals, with no clear gender differences. They are more frequently diagnosed in the sixth and seventh decade of life, although they have been reported in patients of all ages [1, 2]. They arise more commonly in the stomach (~60–65% of all cases) and small intestine (~25–30% of all cases); however, anatomic location in other areas of the gastrointestinal tract as well as more rarely in extra-gastrointestinal sites is possible [1–4]. Putative precursor lesions known as micro- and mini-GISTs have been identified and reported in up to 30% of elderly individuals [5–8]. They have similar biological characteristics to larger GISTs, but size, respectively, of <1 and 1–2 cm and indolent clinical behaviour [5–8].

GISTs are characterized by differentiation towards the interstitial cells of Cajal; these are mesenchymal cells located within the muscle layers of the alimentary tract serving as pacemaker cells [9, 10], and precursors of these have been believed to represent the histogenetic originators for GIST [9]. Most GISTs present pathogenic driver mutations in the genes *KIT* (60–70% of all cases) and *PDGFRA* (10–15%), respectively encoding the tyrosine kinase (TK) receptors KIT and platelet-derived growth factor receptor α [10]. When these molecular driver events are present, targeted therapies with TK inhibitors (TKIs) have shown a significantly larger benefit compared to traditional chemotherapy [11]. GISTs without mutations in *KIT* or *PDGFRA* can present several different alterations [12], in genes encoding for the subunits of the enzyme succinate dehydrogenase [12, 13], in Ras family genes such as *NF1* [14, 15] and *BRAF* [16], or very rare gene fusions [17, 18].

Within the larger group of *KIT*-mutated GISTs, different mutational hotspots have been reported. Primary activating mutations in the exon 11 of the *KIT* gene were first described in 1998 [19], and they are the most common, accounting for ~80% of all *KIT* mutations [1]. Two years later, duplication of six nucleotides encoding Ala-Tyr in exon 9 and missense mutations in exon 13 were recognized as rarer primary *KIT* mutations mutually exclusive with exon 11 mutations [20, 21]. They account, respectively, for ~10% and ~4% of all *KIT* mutations [1]. Other even rarer primary mutation sites include exons 17 [22] and 8 [23].

In the last decades, it has become increasingly clear that the natural history and responses to treatments of GIST patients is significantly influenced by the underlying genotype of the disease, and that GISTs with different *KIT* mutations should be considered separate molecular subtypes. In this review, we will summarize the most relevant structural aspects of the different *KIT* mutations reported in GIST patients and will focus our attention to the unique biological and clinical characteristics of exon 9-mutated (Ex9-) GISTs that separate them from the other *KIT*-mutated GISTs.

Pathophysiology of KIT Mutations in GIST

The TK KIT was described for the first time in 1987 as the human cellular homologue of the feline sarcoma viral oncogene *v-kit*. KIT is a transmembrane glycoprotein with ligand-induced TK activity, structurally related to the colony stimulating factor 1 receptor and PDGFRs [24,

25]. Its ligand stem cell factor (SCF) was identified in 1990 and it exists both as a membrane-bound and soluble form [26–31].

From a structural perspective, KIT is characterized by the presence of 5 extracellular immunoglobulin-like domains (D1-D5) responsible of ligand binding (D1-D3) and receptor dimerization (D4-D5); a single transmembrane helix; a cytosolic juxtamembrane (JM) domain; two kinase domains, TK1 and TK2, separated by a kinase insert domain, respectively including the ATP-binding pocket and the activation loop (A-loop); and a C-terminal tail. When considering the primary and secondary mutations reported in GISTs, exons 8 and 9 fall in the D5 domain, exon 11 corresponds to the JM domain, and exons 13/14 and 17/18, respectively, fall in the TK1 ABP and TK2 A-loop. Importantly, the TKI imatinib, the cardinal therapy for most *KIT*-mutated GIST patients in the advanced phase, binds the JM domain of the inactive form of KIT [32] (Fig. 1).

When KIT is in its monomeric inactive form, the JM domain binds to the TK1 domain as a pseudosubstrate, thus resulting in suppression of the kinase activity [32, 33]. Upon binding of SCF, dimerization of neighbouring KIT receptors is mediated by homotypic interactions at the D4-D5 interface. This is followed by asymmetric arrangements of the cytoplasmic region of the KIT dimers associated to transautophosphorylation [34–36] and final kinase activation [37].

Active KIT can induce several downstream signal transduction pathways mediating its effects on cell growth, differentiation, and apoptosis [10, 24]. Feedback loops result in inhibition of SCF-induced autophosphorylation [38] and in SCF-induced ubiquitination, internalization, and degradation of KIT [39].

Notably, different *KIT* mutations have different effects on the protein inactive and active structures, dimerization affinity, and cellular localization. *KIT* mutations arising in exon 11 – in correspondence of the JM domain – relieve the autoinhibitory constraint of the JM domain, and therefore, lead to constitutively activated ligand-independent KIT variants [36, 40]. These variants have negligible membrane localization, undergo constitutive ubiquitination, internalization, and degradation and have a short, ligand-independent half-life [40]. Conversely, mutations seen in *KIT* exon 9 lead for the most part to oncogenic KIT variants with increased dimerization affinity compared with the wild-type variant and elevated basal TK activity, “sensitized” for SCF stimulation (i.e., responding robustly at even low ligand concentrations) [36, 40]. These KIT variants maintain a partial localiza-

Fig. 1. *KIT* gene exons and corresponding KIT protein domains. KI, kinase insertion.

tion to the cell membrane; undergo ligand-induced ubiquitination, internalization, and degradation; and have a prolonged half-life in unstimulated cells [40].

The preferential cellular localization of different KIT mutants is particularly important. KIT variants unable to reach the cell membrane, retained in an immature form within the endoplasmic reticulum and Golgi, are in fact constantly activated, and this represents a crucial step of their oncogenic signalling [41–43].

Biology and Natural History of Ex9-GIST

The most common mutation in exon 9 is by far the duplication of the amino acids Ala502 and Tyr503. Additional rare mutations have been described [44, 45]. Given their poor characterization and lack of clear differenc-

es compared to the more common duplication, for the purposes of this review, we will consider all exon 9 mutations as a homogeneous group with biological, histopathological, and clinical characteristics distinct from other GISTs.

The structural and cellular characteristics of exon 9-mutated KIT suggest that the inhibitory activity of imatinib might be less effective in these mutants compared to variants carrying activating exon 11 mutations. This has been confirmed in vitro with isolated KIT mutant proteins and ex vivo using biopsies of Ex9-GIST patients showing primary resistance to the treatment with the standard dose of imatinib of 400 mg/day. In these samples, phosphorylation of KIT was not abrogated by the treatment, and persistent activation of the downstream AKT and MAPK pathways was observed [46]. Ex9-GISTs also differ from the exon 11-mutated (Ex11-) GISTs at the transcriptional level. In fact, a number of genes are differentially regulated based on the driver mutation. Among others, Ex9-GISTs overexpress mRNAs from the *SCF* gene, which leads to an autocrine proliferative loop, and from genes involved in the WNT pathway [47], which has been shown to contribute to GIST malignancy [48]. Together, these data suggest that Ex9-GISTs might rely to a lower extent than other *KIT*-mutated GISTs on ligand-independent oncogenic signalling originating from the mutated KIT protein.

From a histopathological perspective, Ex9-GISTs are almost universally composed of spindle cells, whereas ~30% of all GISTs present with epithelioid or mixed spindle/epithelioid cells [1, 49]. The absence of epithelioid elements, although characteristic, has not been fully explained so far and might be related to the different transcriptional programs observed in GISTs arising from different anatomical locations [50].

Clinically, approximately 85% of Ex9-GISTs arise in extra-gastric sites, with a high predilection for the small intestine. In fact, ~20–25% of all intestinal GISTs present an exon 9 mutation [45, 51]. Compared to most Ex11-GISTs, Ex9-GISTs have been associated to a more aggressive clinical behaviour [47], and they have been reported to metastasize, significantly, more often to the peritoneum than to the liver, when compared to *KIT*/*PGFRA* wild-type and Ex11-GISTs [45]. More recently, a direct prognostic impact of exon 9 mutations has been questioned in favour of a prognostic role of its extra-gastric localization, as intestinal GISTs are generally diagnosed when larger and present an average higher mitotic rate [45, 51, 52]. A large study on 451 primary localized GISTs originally suggested that the presence of specific driver

mutations has in fact an independent prognostic impact on the natural course of localized, untreated GIST, with Ex9-GISTs and Ex11-GISTs belonging to the same group, with the worst prognosis. When restricting the analysis to small intestinal GISTs, there were no differences in clinical behaviour between Ex9- and Ex11-GISTs, supporting the hypothesis of a prognostic impact of anatomic location over mutational status [53]. However, in a population-based series of more than 5,000 cases, GISTs arising in the duodenum and jejunum/ileum had similar prognosis to gastric GISTs when adjustment was made for other confounding variables, suggesting that the worse prognosis of patients with non-gastric GISTs depends on the poor outcomes of patients with colonic and extra-gastrointestinal GIST location [54]. Currently, mutational status is not included in the most common risk-stratification models, and the potential impact of Ex9-mutations in GISTs arising from specific anatomic location, such as colonic and extra-gastrointestinal sites, remains uncertain.

Ex9-GIST in the Adjuvant Setting

The most commonly used risk-stratification tools for localized GISTs incorporate primary mitotic count, tumour size, and tumour site [55, 56]. More recently, prognostic contour maps have been generated and validated, using mitotic count and tumour size as continuous variables, with the addition of tumour rupture [57]. These tools allow defining a subgroup of GIST patients with a risk of recurrence of 50% and more, which defines the high-risk population.

In completely resected high-risk *KIT*-mutated GISTs, the current standard treatment in the adjuvant setting is imatinib at a dose of 400 mg/day for 3 years [58]. This indication derives from a phase III randomized clinical trial comparing 3 years versus 1 year of adjuvant treatment, which showed longer relapse-free survival (RFS) rates in the 3-year arm. In particular, the 5-year RFS was 71.1% in the 3-year arm versus 52.3% in the 1-year arm [59]. In this trial, 14 and 12 Ex9-GIST patients were, respectively, enrolled in the 3-year and 1-year arms. Although the numbers were small, in this subgroup there was no significant difference in RFS in the 2 groups [60, 61]. Notably, two earlier randomized clinical trials had evaluated the role of 1 or 2 years of adjuvant imatinib [62, 63]. In the original trial with 1 year of adjuvant imatinib, 22 and 13 Ex9-GIST patients were, respectively, enrolled in the placebo and imatinib arms. Also in this case, no differences in terms

of RFS were observed between treatment arms in the Ex9-GIST subgroup of patients [64].

These data raise the question of whether imatinib at a dose of 400 mg/day represents an adequate standard for Ex9-GIST patients. A recent retrospective analysis on a small sample size suggested that imatinib at 400 mg/day in high-risk Ex9-GIST patients might be beneficial compared to no treatment [65]. Given the data supporting the use of 800 mg/day in patients with advanced Ex9-GISTs (see next paragraph), some expert clinicians, where local policies allow it, prefer to offer this dose in the adjuvant setting also. A recent retrospective evaluation of 185 Ex9-GIST patients treated in the adjuvant setting with either 400 mg/day ($n = 131$, 70.8%) or 800 mg/day ($n = 54$, 29.2%) showed that baseline characteristics between the two populations were partially unbalanced, suggesting a physician's bias in offering the higher dose to patients with a higher risk of relapse. When accounting for these confounders, a dose of 800 mg/day was not associated with longer RFS and other survival outcomes [66]. If confirmed, these results might suggest that presence of a macroscopic disease could be a necessary condition for the activity of high-dose imatinib in Ex9-GISTs. It could be speculated that the presence of macroscopic disease affects the extent and types of cell-to-cell interactions in the microenvironment, which is important in regulating proliferation of GIST cells [67, 68], as well as the local levels of SCF responsible for the paracrine activation of KIT [69]. Ultimately, prospective evaluation of the role and dose of imatinib (or alternative drugs borrowed from the advanced setting) as an adjuvant treatment for Ex9-GIST patients is needed.

Ex9-GIST in the Metastatic Setting

First Line: Imatinib

The efficacy of imatinib in GIST patients with advanced disease was first reported in 2001 [70]. In the same year, a phase I trial explored doses of imatinib ranging from 400 mg/day to 1,000 mg/day. The latter dose was associated with dose-limiting toxicities [71]. The following year, a randomized trial comparing 400 mg/day and 600 mg/day was reported. This study did not show any significant difference in progression-free survival (PFS) between the two doses, but 3 of the 9 patients that were escalated to the higher dose after having progressed on 400 mg/day showed a sustained partial response or stable disease [72], raising the possibility that imatinib dose might have a significant clinical impact. These earlier

studies noted the existence of patients with primary resistance to imatinib, but mutational information was not available to suggest any association.

To clarify the role of higher imatinib dose in the advanced setting, two large randomized clinical trials compared the PFS of advanced GIST patients treated with either 400 mg/day or 800 mg/day [73, 74]. The results of these 2 studies were jointly analysed in a meta-analysis including a total of 1,640 patients. Of these, 772 had mutational analysis available, and 91 had a *KIT* exon 9 mutation. This analysis showed that Ex9-GIST patients were the only subgroup deriving a significant benefit in PFS from the higher imatinib dose. Ex9-GIST patients also showed a higher response rate with 800 mg/day; however, no significant difference was observed in overall survival (OS) [75]. Based on these data, imatinib at a dose of 800 mg/day is considered a standard treatment in Ex9-GIST patients, where local and national policies allow it. Intra-patient dose escalation, i.e., starting treatment at 400 mg/day and offering 800 mg/day upon progression, also appears to be a feasible strategy [65]. Importantly, high-dose imatinib has been associated with a higher risk of toxicities, and continuation of the treatment is highly dependent on patients' compliance and supportive measures [76]. The evaluation of plasmatic levels of imatinib might be important in this setting to optimize the response while limiting toxicities [77].

Second Line: Sunitinib

For ~75% of Ex11-GIST patients, progression to first-line imatinib is associated with the development of secondary mutations in exon 11, in exons 13 and 14 (TK1 ABP), and in exons 17 and 18 (TK2 A-loop). On the other hand, secondary mutations in *KIT* are found only in ~20% of Ex9-GIST patients progressing to imatinib [78]. Upon progression to imatinib, the multi-targeted TKI sunitinib at the dose of 50 mg/day in a "4 weeks on/2 weeks off" schedule is the standard second-line, based on a positive phase III trial [79]. Notably, PFS and OS in the sunitinib group were, significantly, longer in patients with primary *KIT* exon 9 mutation or *KIT/PDGFR*A wild-type GIST (median PFS and OS, respectively, of ~19 months and 27–30 months) compared to patients with *KIT* exon 11 mutation (median PFS and OS, respectively, of ~5 and ~12 months) [78]. This association has been further confirmed in a large series of patients treated with sunitinib off trial in clinical practice [80].

The higher sensitivity to sunitinib of *KIT* exon 9 compared to exon 11 mutation has also been confirmed in in vitro assays. The efficacy of sunitinib is also preserved in

presence of secondary ABP mutations, but is lost in presence of A-loop mutations [78], possibly because these mutations stabilize the active conformation of *KIT*, which is inaccessible to both imatinib and sunitinib [81]. Resistance to sunitinib in Ex9-GIST was independently predicted to be more likely to occur due to A-loop mutations with in vitro mutagenesis assays [82]. This association has been confirmed in vivo, with ~50% of Ex9-GIST patients treated in fourth-line in which secondary mutations were identified via tissue biopsy or circulating DNA, presenting a secondary mutation in exon 17 of *KIT* [83].

Notably, in the INTRIGUE trial, the novel TKI ripretinib did not meet the primary endpoint of improved PFS compared with the standard of care sunitinib. In 327 patients with *KIT* exon 11 primary mutation, ripretinib demonstrated a median PFS of 8.3 months compared to 7.0 months for the sunitinib arm. In the overall intention-to-treat population (453 patients), ripretinib demonstrated a median PFS of 8.0 months compared to 8.3 months for the sunitinib arm. The full results of the trial are still awaited, but it might be possible that GIST patients with mutations other than *KIT* exon 11, including *KIT* exon 9, benefited from sunitinib more than ripretinib [84].

Third and Fourth Lines: Regorafenib and Ripretinib

The multi-TKI regorafenib has shown superiority over placebo in a randomized phase III trial in patients previously treated with imatinib and sunitinib. Patients with Ex9-GIST showed a similar benefit compared to patients with other *KIT* mutations or *KIT/PDGFR*A wild-type GISTs [85]. In vitro, regorafenib is active against most primary and secondary A-loop mutations, thus providing a rationale to the activity of this TKI in advanced GIST patients [86, 87].

A novel TKI, avapritinib, has also been recently tested in third line against regorafenib in the VOYAGER trial. Median PFS was not statistically different between the two arms. Unfortunately, no specific analyses were reported for Ex9-GIST patients, though it appears highly unlikely that avapritinib might be superior to regorafenib in this population [88].

Recently, ripretinib has shown significant clinical activity in the fourth-line setting [89], independently of *KIT* mutational status [83]. Ripretinib, contrary to all the other approved TKIs, does not bind to the inactive form of *KIT*, but act as a "switch-control" kinase inhibitor that forces the A-loop into an inactive conformation, thus inhibiting a broad range of primary and secondary *KIT* mutations [90]. Despite its broad activity, ~50% of the patients treated with ripretinib progressed within 6 months

of treatment, suggesting that additional mutations responsible for resistance to ripretinib rapidly develop in the context of advanced disease, and/or KIT-independent signalling pathways become even more important for tumour progression [91–93].

Beyond Standard Lines: Cabozantinib and TKI Rechallenge

In a recently published phase II trial, the TKI cabozantinib showed encouraging signs of activity in patients who had progressed on imatinib and sunitinib [94]. In this study, 4 patients with exon 9 mutations and 1 patient with simultaneous exon 9 and exon 17 mutations were enrolled. The latter patient achieved a radiological partial response as best response, while the former 4 patients achieved stable disease, suggesting that cabozantinib might have activity in Ex9-GIST patients.

In GIST patients with preserved performance status who have failed all available treatment, retrospective and prospective evidence suggest that rechallenge with imatinib or other TKIs might have some benefit [95, 96]. In the phase III trial RIGHT, imatinib rechallenge (400 mg/daily) was compared to placebo in patients who had previously benefited from imatinib, including a small subset of exon 9 patients. Results specifically achieved in this population are not available [96]. Given the particular sensitivity of Ex9-GIST patients to sunitinib, rechallenge with this agent could have a biological rationale, although only 2 case reports in exon 11-mutant GIST patients are available [97].

Conclusion and Future Perspectives

The duplication of the amino acids Ala502 and Tyr503 reshapes the KIT receptor at the molecular and cellular levels. GISTs harbouring this mutation are significantly different from the others for their biology, natural history, and response to first- and second-line TKIs. Given their relative rarity, Ex9-GISTs have never been investigated as a separate entity. However, preclinical and clinical data would recommend doing so. Unfortunately, the characterization of transcriptomic, proteomic, and immunological profiles unique to Ex9-GISTs are at an early stage, and currently, there are no therapeutic targets specific for Ex9-GISTs.

In consideration of the relative resistance of Ex9-GISTs to imatinib, the development of more selective KIT inhibitors also active against this mutation [98] might prove particularly significant, as they would probably

come without the common side effects of other multi-TKIs. A new potential approach might be also represented by the combination of two KIT inhibitors cotargeting the two complementary KIT active and inactive conformations, as recently done with the combination of PLX9486 with sunitinib [99].

Moreover, due to the distribution at the cell membrane of exon 9-mutated KIT, Ex9-GISTs might represent a better target for monoclonal antibodies targeting the extracellular region of KIT than those harbouring other mutants [40, 100]. The clinical development of KIT-targeting antibodies is however complicated by the risk of hypersensitivity reactions due to the physiological presence of the KIT receptor on mast cells [101].

A further strategy that is being investigated is the inhibition of heat shock proteins, in particular HSP90, which in turns inhibits oncogenic KIT signalling on the Golgi [102]. A recent clinical trial showed for the first time positive results with a HSP90 inhibitor in patients with refractory GIST [103]. Whether particular *KIT* mutants might be more sensitive to this compound remain to be ascertained.

Past research efforts have clarified the unique biological and clinical characteristics of Ex-9 GISTs as well as the therapeutic role of imatinib 800 mg/day and sunitinib as mainstay for the treatment of Ex-9 GISTs. Results addressing the response of Ex9-GIST to newer targeted therapies are eagerly awaited to refine our treatment algorithms. Despite our best efforts, a number of questions still remain partially or totally open: does exon 9 mutation carry any prognostic value in extra-gastric GISTs arising from specific anatomical locations? As neoadjuvant treatment is often offered to patients with GISTs arising from extra-gastric sites, might TKIs other than imatinib have a role in the neoadjuvant treatment of Ex9-GIST patients? What is the real efficacy of imatinib in the adjuvant treatment of Ex9-GIST patients? Are there any treatments more effective or better tolerated than imatinib 800 mg/day for Ex9-GIST patients with advanced/metastatic disease? Future translational and clinical studies will tackle these questions and lead in the future to a truly personalized management of Ex9-GIST patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.N. wrote the first draft of the manuscript. K.T., M.J.S., P.H.H., and R.L.J. critically reviewed it. All authors approved the final version.

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