New frontiers in the medical management of gastrointestinal stromal tumours

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Abstract: The tyrosine kinase inhibitor (TKI) imatinib has radically changed the natural history of KIT-driven gastrointestinal stromal tumours (GISTs). Approved second-line and third-line medical therapies are represented by the TKIs sunitinib and regorafenib, respectively. While imatinib remains the cardinal drug for patients with GISTs, novel therapies are being developed and clinically tested to overcome the mechanisms of resistance after treatments with the approved TKI, or to treat subsets of GISTs driven by rarer molecular events. Here, we review the therapy of GISTs, with a particular focus on the newest drugs in advanced phases of clinical testing that might soon change the current therapeutic algorithm.

Keywords: avapritinib, BLU-285, DCC-2618, gastrointestinal stromal tumours, GIST, imatinib, ripretinib

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Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms, with a global annual incidence of 10–15 cases per million.[1–3] GISTs arise from the interstitial cells of Cajal[4] primarily in the gastrointestinal (GI) tract, with the majority found in the stomach (60%),[3] although extra-GI sites of origin are possible.[5,6]

Pathologic diagnosis is based on morphologic features and ancillary techniques, such as immunohistochemistry and molecular biology. Over 95% of GISTs are strongly and diffusely positive for CD117 (c-KIT).[7] Several new immunohistochemistry (IHC) markers have been studied to improve the diagnostic accuracy, especially in KIT-negative GISTs. Among these, DOG1 (Discovered On Gist-1), a calcium-activated chloride channel, is a highly sensitive marker that can successfully identify most KIT-positive GISTs and up to one third of KIT-negative tumours.[8]

The most important prognostic factors determining the malignant potential of GISTs are tumour size (poor prognosis if >5 cm), mitotic count (expressed as the number of mitoses on a total area of 5 mm^2) and tumour site.[9,10] Recently, tumour rupture has been identified as an additional adverse prognostic factor.[11]

Molecular biology is an important tool because it may help to confirm the diagnosis and for its prognostic and predictive value in respect to disease sensitivity to targeted therapies. In most GISTs, activating mutations involving either *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) genes, can be found.[12] Approximately 60–85% of GISTs present *KIT* mutations. The most common affect exon 11, encoding for the juxtamembrane domain of the tyrosine kinase (TK) receptor. The main types of mutations are interstitial deletions, involving the initial portion of exon 11 (more often codons 557–559).[13,14] In 9–20% of cases, *KIT* mutation occurs in exon 9, which encodes for the extracellular domain.[15] This mutation is often associated with small bowel GISTs and to a greater malignant potential. Primary mutations of exons 13 and 17, encoding for KIT TK domains, have also been less frequently described.[16] About 5–10% of GISTs presents activating mutations of *PDGFRA*, which are usually associated with localized gastric tumours. The D842V mutation, in exon 18,

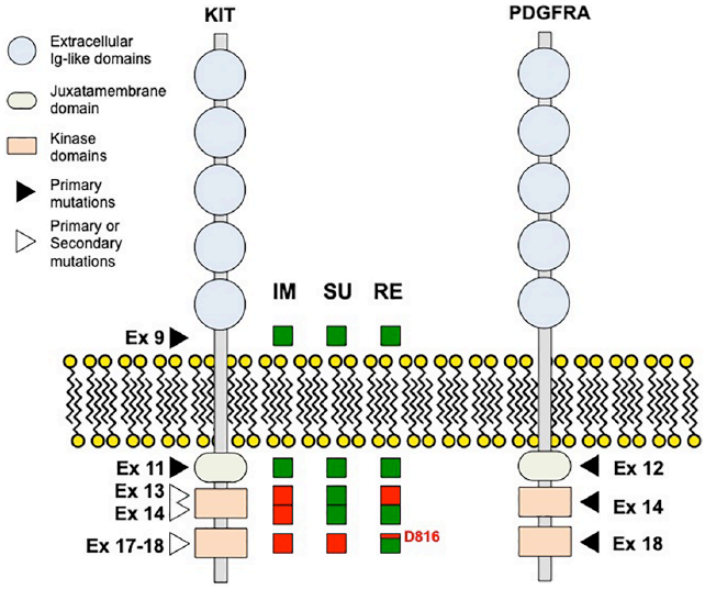

Figure 1. Schematic representation of *KIT* and *PDGFRA* mutations found in GISTs. Relative sensitivities of primary and secondary *KIT* mutations to approved TKIs are shown in coloured boxes (green = sensitive; red = resistant). Note that *KIT* mutations in D816 are associated with resistance to all approved agents.
GIST, gastrointestinal stromal tumours; *PDGFRA*, platelet-derived growth factor receptor α; TKI, tyrosine kinase inhibitor.

which encodes for the TK domain, is the most frequently observed (65–75%;[17] Figure 1).

GISTs represents one of the exceptional cases of solid tumours where the molecular biology is important to understand its medical therapy. Indeed, TK inhibitors (TKIs) are the standard therapy for *KIT*-mutated GISTs and will soon be the standard for *PDGFRA*-mutated ones, as well. In particular, the KIT inhibitor imatinib represented the first example of a TKI that radically changed the natural history of a solid tumour. Notably, the activity of TKIs largely depends on the specific mutations found in *KIT* and *PDFRA* genes. With the upcoming approval of novel and more active TKIs, the molecular profile will become more and more important for the selection of the best therapy.

Approximately 10% of adult and 85% of paediatric GISTs do not present a mutation in either gene, and are therefore defined as 'wildtype GISTs'. In these tumours, a number of genetic alterations have been described, including activating mutation of *BRAF*, inactivating mutations of *NF1* or in genes encoding components of the succinate dehydrogenase (SDH) enzymatic complex, and gene fusions involving the kinase NTRK3.[18–22] The spectrum of clinical behaviour of wildtype GISTs is variable, but slow progression is common, even in the metastatic setting.

Therapy of GISTs: current standards

Surgery

Localized setting. Surgery remains the mainstay of treatment for localized GISTs ⩾2 cm. The aim is a complete gross resection, with negative microscopic margins and intact pseudocapsule, to avoid tumour rupture and intraperitoneal dissemination.[23] Currently, there is no indication for routine lymphadenectomy.[24] In small GISTs (<2 cm in the widest dimension), complete surgical resection is recommended in symptomatic patients, while an endoscopic surveillance at 6–12 months intervals should be considered.[24,25]

Locally advanced and metastatic setting. Locally advanced primary GISTs deemed unresectable are currently treated with neoadjuvant imatinib, and surgery is offered to cases in which the medical therapy renders the GIST resectable. Surgery in metastatic or recurrent GISTs is more controversial and case selection is critical. It can be offered to patients whose disease is responding to imatinib or to those with limited focal progression, although impact on progression-free

survival (PFS) and overall survival (OS) are unknown. Palliative surgery can also be considered in symptomatic patients.[26]

Imatinib

GISTs are known to be refractory to conventional chemotherapy and radiation. Since 2001, with the identification of targetable *KIT* activating mutations in GISTs,[27] the introduction of TKIs has revolutionized the medical treatment of GISTs. Imatinib mesylate is a selective and potent drug inhibiting several TK receptors with a variable affinity, including KIT, the leukaemia-specific BCR-ABL chimera, and PDGFRs.[28,29]

Adjuvant setting. Even though complete gross resection is possible in 85% of patients with primary localized GISTs, at least 50% of them develop tumour recurrence. The postoperative approach is based on an assessment of the overall risk of recurrence.[24,30] Over time, prognostic factors have been identified to assess the risk of recurrence after surgery, and used to define risk categories.[9,31–35] Currently, the most widely used prognostication tool is the classification proposed by Joensuu and colleagues which considers tumour size, mitotic count, tumour site and tumour rupture as risk factors.[36]

In 2008, for the first time a recurrence-free survival (RFS) and OS benefit was shown from 1-year adjuvant imatinib at a dose of 400 mg/day in high-risk patients. This study also showed that *KIT* exon 11 mutations responded better to a standard dose of imatinib than *KIT* exon 9 mutations.[37] The following phase III trial led to imatinib approval in the adjuvant setting.[38] The Scandinavian-German SSG XVIII study, published in 2012, showed that postoperative imatinib administered for 3 years could improve both RFS and OS compared with 1 year in high-risk patients.[39]

The American PERSIST-5, a phase II, single-arm study, recently completed, is investigating the efficacy of 5 years of adjuvant imatinib in preventing relapse in high-risk patients harbouring sensitive mutations (ClinicalTrials.gov identifier: NCT00867113). Similarly, SSG XXII is a new intergroup phase III randomized study, comparing 3 years *versus* 5 years of adjuvant imatinib treatment in high-risk GISTs (ClinicalTrials.gov identifier: NCT02413736).

Currently, both European Society for Medical Oncology and National Comprehensive Cancer Network (NCCN) guidelines recommend 3 years of adjuvant treatment with imatinib in patients with a significant risk of relapse. Patients with *PDGFRA* D842V-mutated GISTs should not be treated with imatinib, due to its known resistance. Since no data suggest a benefit of the standard dose of imatinib in *KIT* exon 9-mutated GISTs and given the proven efficacy of a daily dose of 800 mg/day of imatinib in metastatic GISTs, in clinical practice the higher dose is preferred also in the adjuvant setting. The use of adjuvant imatinib in wildtype SDH-negative tumours is still controversial, while in *NF1*-related GISTs it should be avoided.

Neoadjuvant setting. In patients with large or poorly localized tumours requiring extensive surgery with significant morbidity or sacrifice of large amount of normal tissue, preoperative imatinib should be considered, given its good safety profile,[40–44] although no conclusive evidence from large phase III clinical trials is available. The most appropriate duration of preoperative imatinib is still controversial, with a preferred interval between 6 and 12 months before surgery, as the best response is usually expected in this frame.[45]

First-line metastatic disease. Imatinib represents the first-line standard treatment for unresectable, recurrent or metastatic disease. The standard dose of imatinib is 400 mg daily.[46,47] Importantly, an early interruption of imatinib is associated with a high risk of progression even in patients with a complete response, therefore the treatment should be continued until significant toxicity or disease progression.[48–50]

The assessment of tumour genotype is necessary, since it predicts different sensitivities to imatinib. *KIT* exon 11 mutations are associated with a better response to imatinib (400 mg daily), whereas *KIT* exon 9 mutations are less sensitive and may require a higher dose (800 mg daily), in order to achieve similar therapeutic results.[51–54] The *PDGFRA* exon 18 D842V mutation is resistant to imatinib, while other mutations of the same gene may be associated with variable sensitivity.[17] Wildtype GISTs are also thought to be less sensitive to imatinib.

Mechanisms of resistance to imatinib and disease progression. Primary resistance to imatinib (observed in 10% of patients) is defined as disease progression within 6 months of therapy. The most common causes are represented by *PDGFRA* D842V or *KIT* exon 9 (under standard

dose) mutations or wildtype subtypes. Secondary or acquired resistance, observed in initially responding or stable GISTs, is defined as disease progression after 6 months of therapy. The major mechanism is represented by the acquisition of secondary *KIT* mutations, as in KIT ATP-binding pocket (exons 13 and 14), which evade imatinib binding, and in KIT activation loops (exons 17 and 18), which enhance constitutive KIT activation[55] (Figure 1).

In advanced GISTs progressing during imatinib treatment, patient noncompliance and potential drug interactions with concomitant medications altering plasmatic levels of imatinib should be assessed. Moreover, responding tumours may show increase in size during early treatment with imatinib as a consequence of necrosis, myxoid degeneration or intra-tumoural haemorrhage, mimicking disease progression. Notably, the Choi criteria, which combine morphologic tumour volume response and changes in lesions density, show a higher sensitivity and specificity in the evaluation of treatment response compared with the widely used morphologic response evaluation criteria in solid tumors (RECIST).[56,57]

In patients with confirmed disease progression, additional treatment options may be considered before switching to a second-line therapy. In patients with limited progression, resistant lesions may be treated with surgical resection.[58,59] Another option to consider is dosage escalation of imatinib (to 800 mg per day), as a clinical benefit can be observed in about 30–35% of patients.[47,60]

Second-line and third-line TKIs

Sunitinib. Sunitinib malate is an oral multitargeted TKI, with activity against KIT, PDGFR, vascular endothelial growth factor receptor (VEGFR), RET and FMS-like TK receptor 3 (FLT-3). It represents the standard second-line treatment for imatinib-resistant or imatinib-intolerant patients based on a multicentre phase III trial showing a significant increase in the median time to progression compared with placebo.[61] An open-label phase II trial has shown efficacy of a continuous daily dose of sunitinib 37.5 mg, with a clinical benefit rate of 53%, a median PFS of 34 weeks and a median OS of 107 weeks.[62] Although the recommended schedule is 50 mg per day for 4 weeks followed by a 2 week rest, the continuous use of 37.5 mg daily has been approved in the United States and European Union as an alternative option in selected cases. The range of sunitinib-related adverse events is greater than those for imatinib, due to its wider spectrum of target inhibition. The most common side effects reported are fatigue, diarrhoea, hand-foot syndrome, hypertension and skin discoloration. As with imatinib, GIST genotypes relate to sunitinib responses: patients with primary *KIT* exon 9 mutations or wildtype tumours (for *KIT*/*PDGFRA* mutations) show a higher clinical benefit in terms of PFS and OS. Moreover, regarding secondary resistance, *KIT* mutations involving the ATP-binding pocket (exon 13 and 14) are thought to be more sensitive to sunitinib than those involving the activation loop domain (exon 17 and 18).[63]

Regorafenib. Regorafenib is an oral TKI active against several kinases involved in oncogenesis (KIT, PDGFR, RET, RAF1 and BRAF), in the regulation of angiogenesis (VEGFR1-3 and TIE2) and the tumour microenvironment [PDGFRs fibroblast growth factor receptors (FGFR)]. It represents the standard third-line treatment in patients with advanced GISTs after a randomized phase III trial which revealed a significant improvement in PFS compared with placebo.[64] The recommended dose of regorafenib is 160 mg taken once daily for 3 weeks followed by 1 week off therapy. The most common adverse events observed in patients receiving regorafenib are hypertension, hand-foot skin reaction and diarrhoea.

Beyond the approved lines

Despite the clear successes of TKIs in the treatment for advanced and metastatic GISTs, acquired resistance to all approved agents eventually occurs. In patients progressing after imatinib, sunitinib and regorafenib, enrolment in clinical trials should be considered.

Imatinib rechallenge

The reintroduction of previously tolerated and effective TKI therapy can be considered for palliation of symptoms in addition to best supportive care. The RIGHT trial, a randomized, double-blind, placebo-controlled, phase III study, showed efficacy and safety of imatinib rechallenge in patients after failure of at least imatinib and sunitinib.[65] Similarly, imatinib rechallenge after progression to sunitinib and regorafenib is associated with a potential clinical benefit.[66]

Sorafenib

Sorafenib is a pleotropic multi-TKI that has been used for advanced GISTs refractory to conventional treatments. Retrospective[67,68] as well as small prospective[69] experiences showed objective responses in about 5–10% of the patients and disease stabilization in more than half of them in the third-line and forth-line settings. Importantly, the activity of sorafenib on secondary *KIT* mutations usually associated with resistance to imatinib was also shown in preclinical models.[70]

Nilotinib

Nilotinib inhibits the TK activity of ABL1/BCR-ABL1, KIT, and PDGFRs. Nilotinib did not show superiority against imatinib in the first-line setting in a phase III clinical trial,[71] nor against best supportive care in GISTs following prior imatinib and sunitinib failure.[72] Nevertheless, a number of patients showed a significant response with different side-effect profiles from imatinib. Thus, nilotinib might still merit attention as an alternative to imatinib in patients with advanced GISTs who are intolerant to imatinib.

Pazopanib

Pazopanib is a multi-TKI that inhibits KIT, PDGFRs, and has particularly potent activity of VEGFRs, with proved activity in soft tissue sarcomas. A randomized phase II trial of pazopanib in GISTs in the third-line setting after treatment with imatinib and sunitinib showed disease control at 4 months in more than 40% of the patients treated with pazopanib.[73]

Novel therapies for advanced and metastatic GISTs

So far, the unique and most important breakthrough in the medical treatment of advanced and metastatic GISTs has been the successful use of imatinib to target pathogenic *KIT* mutants. Other TKIs, whether approved or not, showed efficacy in a more limited number of patients, and with a shorter average clinical benefit.

Novel molecules currently in late-stage clinical trials have the potential to be the next breakthroughs in the therapy of *KIT* and even more so, *PDGFRA*-mutated GISTs. Among these, particularly interesting data have been presented for ripretinib (formerly known as DCC-2618) and avapritinib (formerly known as BLU-285; Table 1). A list of selected ongoing phase II and III clinical trials is shown in Table 2.

Ripretinib (DCC-2618)

Ripretinib is a switch-control type II inhibitor of KIT, which arrests KIT in an inactive state, inhibiting the full spectrum of the mutations known to be present in patients with GISTs in exons 9, 11, 13, 14, 17, and 18, as well as an inhibitor of PDGFRα carrying exon 18 mutations, including the D842V mutation.[76]

The most recently updated results from the phase I clinical trial of ripretinib were presented at the CTOS Annual Meeting in 2018 in Rome, Italy.

A total of 178 patients with *KIT*-mutated GISTs have been treated so far. In the second-line setting, ripretinib showed an overall response rate (ORR) and disease control rate (DCR) at 3 months by RECIST respectively of 18% and 79%, with a median PFS of 42 weeks. In the third-line setting, ORR and DCR were respectively of 24% and 83%, with a PFS of 40 weeks. In the ⩾fourth-line setting, ORR, DCR were respectively of 9% and 66%, with a PFS of 24 weeks. Ripretinib showed good tolerability, which allowed for prolonged treatment duration in second-line and third-line settings.

Treatment emergent adverse events (TEAEs) associated with ripretinib were generally of grade 1 and 2. The most common grade 3 TEAEs was clinically asymptomatic lipase increase (11%). Out of 178 patients treated, 24 (14%) experienced dose reduction due to TEAEs and 19 (11%) experienced treatment discontinuations due to TEAEs.[74]

Ripretinib is being tested in a pivotal, randomized, placebo-controlled phase III study, INVICTUS (ClinicalTrials.gov identifier: NCT03353753), in the ⩾fourth-line population. In December 2018, a second phase III study, INTRIGUE (ClinicalTrials.gov identifier: NCT03673501), was announced in second-line patients with GISTs after imatinib failure against the standard therapy, sunitinib.

Avapritinib (BLU-285)

Avapritinib is a highly selective and potent a type I KIT/PDGFRα inhibitor that binds to the active protein kinase conformation, with biochemical activity against a wide range of primary and secondary mutations in the nanomolar range and confirmed activity

Table 1. ORR of ripretinib and avapritinib compared with other approved drugs.

Drug name	Line of treatment	ORR	Ref
Sunitinib	2	7%	Demetri and colleagues[61]
Regorafenib	3	5%	Demetri and colleagues[64]
Ripretinib	2	18%	George and colleagues[74]
Ripretinib	3	24%	George and colleagues[74]
Ripretinib	⩾4	9%	George and colleagues[74]
Avapritinib	3/4 regorafenib-naïve	26%	Heinrich and colleagues[75]
Avapritinib	⩾4	20%	Heinrich and colleagues[75]

ORR, overall response rate.

Table 2. Selected list of phase II and phase III clinical trials.

Drug name	Population	Line of treatment	Phase	ClinicalTrials.gov identifier
Avapritinib	KIT/PDGFRA-mutated	3rd/4th regorafenib-naïve	III	NCT03465722
Ripretinib	KIT/PDGFRA-mutated	2nd line	III	NCT03673501
Masitinib	KIT-positive (immunohistochemistry) imatinib-resistant/progressive	⩾2nd line	III	NCT01694277
Crenolanib	PDGFRA D842V-mutated	any	III	NCT02847429
Ponatinib	KIT/PDGFRA-mutated	2nd line (cohort A); after all approved lines (cohort B)	II	NCT03171389
Cabozantinib	KIT/PDGFRA-mutated	3rd line	II	NCT02216578
Regorafenib	KIT/PDGFRA wildtype GIST	1st line	II	NCT02638766
Temozolamide	SDH-mutant/deficient GIST	any	II	NCT03556384
Nivolumab ± ipilimumab	Imatinib-resistant/progressive	⩾2nd line	II	NCT02880020
Epadocast + Pembrolizumab	Imatinib-resistant/progressive	2nd to 5th line	II	NCT03291054

GIST, gastrointestinal stromal tumour.

in vitro in *KIT*-mutant cell lines and in an *in vivo* subcutaneous allograft mouse model.[77]

The updated results of the NAVIGATOR phase I trial were recently presented at the CTOS Annual Meeting in 2018. A total of four different populations of patients with GISTs were included in this trial: (1) GISTs in second-line; (2) GISTs in third/fourth-line regorafenib-naïve; (3) GISTs in fourth or more advanced lines; (4) *PDGFRA* D842V-mutated GISTs.

In the second-line, the reported ORR was 25%, but data on this cohort are still limited. In patients in third/fourth-line regorafenib-naïve setting, avapritinib was associated with an ORR of 26%

and a median duration of response (mDOR) of about 10 months. In the ⩾fourth-line setting, ORR was 20% with a mDOR of over 7 months. In these patients, the rare *PDGFRA* V654A and T670I mutations were associated with lower response rates, providing a strong rationale for genotype-selected therapy. In patients with GISTs with a *PDGFRA* D842V mutation, avapritinib caused tumour shrinkage in 98% of the cases, with an ORR of 84% (including 9% of complete radiological responses), an unprecedented result in a disease known to be resistant to imatinib.

Most TEAEs were grade 1 and 2, with manageable on-target toxicity. Nausea, vomiting, and peri-orbital oedema were the most common reported toxicities. Grade 3 anaemia was relatively frequent (25%). About 9% of the patients discontinued due to TEAEs.[74]

The phase III VOYAGER trial (ClinicalTrials.gov identifier: NCT03465722) is currently enrolling patients with GISTs who are known to have a *KIT* or *PDGFRA* mutation previously treated with imatinib and one or two other TKIs. Patients will be randomized to receive avapritinib *versus* regorafenib. The primary endpoint of this trial is PFS, with ORR, OS and quality-of-life measures as secondary endpoints.

Currently, no other clinical trials with avapritinib in other settings are planned or enrolling.

Masitinib

Masitinib is a highly selective oral TKI with comparable activity to imatinib against wildtype and mutant *KIT* (exons 9 and 11). After promising phase I data, masitinib activity was evaluated in a phase II trial in advanced imatinib-resistant GISTs against sunitinib. Masitinib met its noncomparative primary PFS endpoint, with a median PFS of 3.7 months.[78] A phase III trial investigating masitinib in imatinib-resistant/intolerant patients is currently ongoing (ClinicalTrials.gov identifier: NCT01694277).

Crenolanib

Crenolanib is a potent inhibitor of imatinib-resistant *PDGFRA* kinases associated with GISTs, including the *PDGFRA* D842V mutation that drives a subset of GISTs.[79] Clinical activity was observed in *PDGFRA*-mutated GISTs in a dose-escalating phase II trial, therefore a phase III was initiated specifically in patients with GISTs with D842V-mutated *PDGFRA* (ClinicalTrials.gov identifier: NCT02847429).

Ponatanib

Ponatinib is a TKI approved for imatinib-resistant BCR-ABL leukaemia, and has shown *in vitro* activity against a number of primary and secondary *KIT* mutations also in GIST models.[80] A phase II trial is currently evaluating its activity in patients with GISTs after prior failure or intolerability of imatinib (ClinicalTrials.gov identifier: NCT03171389).

Cabozantinib

Cabozantinib is a multi-TKI approved for the treatment of medullary thyroid cancer and as a second-line treatment for renal cell carcinoma. In preclinical models, cabozantinib showed antitumor activity in GISTs through inhibition of tumour growth, proliferation, and angiogenesis, in both imatinib-sensitive and imatinib-resistant models.[81] The clinical validity of cabozantinib is being explored in patients who have previously progressed on imatinib and sunitinib (ClinicalTrials.gov identifier: NCT02216578).

Other targeted therapies for rare mutations

A single case has been described of a patient carrying a GIST with *BRAF* mutations treated with the BRAF inhibitor dabrafenib, and it showed good disease control.[82]

Very recently, gene fusions involving the kinase NTRK3 have been identified in *KIT*/*PDGFRA*/*BRAF*-mutation negative, SDH-proficient GISTs.[21,22] Although rare, this subtype might greatly benefit from targeted therapy with tropomyosin receptor kinase (TRK) inhibitors.[83]

Targeted therapies for GISTs with inactivating mutations in *NF1* or SDH components appear to be further away in the development. *SDHB* mutations have been associated with a response to temozolomide in in patients with metastatic pheochromocytoma or paraganglioma,[84] and based on this a phase II trial is ongoing testing temozolomide in SDH-deficient GISTs (ClinicalTrials.gov identifier: NCT03556384).

Immunotherapy

Few trials are currently exploring a potential role for checkpoint inhibitors in TKIs-resistant GISTs

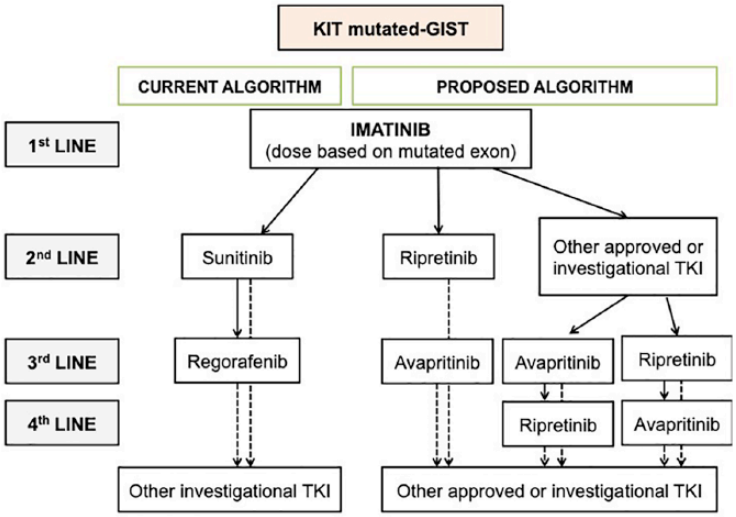

Figure 2. Novel potential treatment algorithm for locally advanced and metastatic *KIT*-mutated GISTs, compared with current one.
GIST, gastrointestinal stromal tumour.

(see Table 2), based on the presence of a diverse range of infiltrating inflammatory cells in GISTs.[85] Alternative forms of immunotherapy, such as the use of specific anti-*KIT* antibodies and of chimeric antigen receptor T-cells, are also at early stages of development.[85]

Discussion

A number of novel TKIs will soon be available for the treatment of advanced and metastatic GISTs after imatinib failure. Understanding the mechanisms of resistance to approved and novel TKIs will likely determine a genotype-driven therapeutic choice.

However, progression under imatinib is associated with the emergence of subclones harbouring multiple secondary *KIT* mutations.

The simultaneous evaluation of most *KIT* secondary mutations through re-biopsy of imatinib-progressive cases appears unpractical unless in the presence of oligo-progressive disease. The early identification of these mutations is an emerging medical need. Circulating tumour DNA sequencing could in theory act as a surrogate source to provide a comprehensive record of all secondary *KIT* mutations simultaneously present in a single patient, but it might not be sensitive enough for cases without large tumour burden.[86,87]

So-called 'wildtype' GISTs represent a small but significant fraction of GISTs, and recent efforts have identified additional drivers, such as *BRAF* and *SDHB* mutations and the *NTRK3* fusion gene. This effort has to continue to identify the yet unknown driver events in the remaining cases, in order to increase the likelihood of targeted therapies for this population. Accrual of these patients in specific clinical trials should be encouraged by clinicians. Nevertheless, the clinical approval of novel therapies for patients with wildtype GISTs still appears relatively distant in time.

Conclusions

The current algorithm for the medical management of *KIT*-driven GISTs has imatinib as the standard therapy in the neoadjuvant and adjuvant settings, as well as in the metastatic setting as a first-line treatment. A number of TKIs in clinical trials, in particular ripretinib and avapritinib, appear to be more effective than imatinib in unresectable or metastatic *PDGFRA*-driven GISTs. In this subset of patients, we therefore expect the fast approval of novel compounds.

In *KIT*-driven GISTs, imatinib is the standard therapy, and will likely continue to be for a long time. Instead, given the available results, ripretinib and avapritinib will probably soon change the second-line and third-line treatment after imatinib failure. A potential treatment algorithm is proposed in Figure 2. Importantly, caution is needed as these data derive from early-phase clinical trials, whereas sunitinib and regorafenib have shown their efficacy in a phase III trial. Examples of a

promising drug in phase I/II trials that did not confirm the results in larger trials are abundant, most notably the recent failure of olaratumab in soft tissue sarcomas.[88]

Nevertheless, as our understanding of the molecular biology of GISTs develops, novel rationally designed therapies are expected to cover also wildtype GISTs which currently represent a subset with very limited therapeutic options.

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Conflict of interest statement

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