New treatment strategies for advanced-stage gastrointestinal stromal tumours

Lillian R. Klug, Homma M. Khosroyani, Jason D. Kent and Michael C. Heinrich ✉

Abstract | When gastrointestinal stromal tumour (GIST), the most common form of sarcoma, was first recognized as a distinct pathological entity in the 1990s, patients with advanced-stage disease had a very poor prognosis owing to a lack of effective medical therapies. The discovery of *KIT* mutations as the first and most prevalent drivers of GIST and the subsequent development of the first KIT tyrosine kinase inhibitor (TKI), imatinib, revolutionized the treatment of patients with this disease. We can now identify the driver mutation in 99% of patients with GIST via molecular diagnostic testing, and therapies have been developed to treat many, but not all, molecular subtypes of the disease. At present, seven drugs are approved by the FDA for the treatment of advanced-stage GIST (imatinib, sunitinib, regorafenib, ripretinib, avapritinib, larotrectinib and entrectinib), all of which are TKIs. Although these agents can be very effective for treating certain GIST subtypes, challenges remain and new therapeutic approaches are needed. In this Review, we discuss the molecular subtypes of GIST and the evolution of current treatments, as well as their therapeutic limitations. We also highlight emerging therapeutic approaches that might overcome clinical challenges through novel strategies predicated on the biological features of the distinct GIST molecular subtypes.

Gastrointestinal stromal tumour (GIST) is the most common type of soft-tissue sarcoma. The annual incidence of GIST ranges from 6 to 22 cases per million individuals worldwide, with an estimated 3,000–6,000 new diagnoses each year in the USA[1,2]. GIST has become a paradigm for the development of precision medicine treatment approaches owing to the elucidation of the oncogenic drivers that define different molecular subtypes of the disease[3]. Nearly 99% of GISTs have an identifiable driver alteration, and the presence of a particular driver imparts distinct molecular and biological features and guides treatment strategies using different approved targeted therapies[4] (FIGS 1 and 2). The vast majority of these driver alterations (around 85%) are activating mutations in either one of two closely related members of the type III receptor tyrosine kinase (RTK) family, KIT and PDGFRA (platelet-derived growth factor receptor alpha, also known as PDGFRα)[5–7]. Other molecular drivers of GIST include rare gene fusions involving different RTKs, mutations in components of oncogenic signalling pathways that are activated downstream of these RTKs, and loss-of-function alterations affecting subunits of the mitochondrial respiratory complex II, succinate dehydrogenase (SDH)[1,8,9]. We now have therapeutic approaches with which to treat the majority of advanced-stage GISTs (FIGS 1 and 2). However, some of the rarer molecular subtypes still lack effective treatments. Even with the available treatments, important clinical challenges remain. In this Review, we discuss the molecular subtypes and current treatment landscape of GIST, as well as the emerging novel therapies that exploit distinct strategies to target the unique biology and/or molecular features of the different GIST subtypes.

Portland VA Health Care System and Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA.

✉*e-mail: heinrich@ohsu.edu*

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Biology of GIST

GISTs can occur throughout the gastrointestinal tract, most frequently arising in the stomach (60–65%) and small intestine (20–35%); however, their specific molecular distribution and biology can differ between anatomical sites[1,3,4,8–13] (TABLE 1). Distinct molecular subtypes of GIST are defined broadly by individual driver alterations. The three major molecular subtypes — *KIT* mutant, *PDGFRA* mutant or SDH deficient — constitute nearly 95% of all GISTs. Various other rare molecular drivers account for the remaining cases of GIST, with only about 1% of GISTs lacking a known driver (FIG. 1).

Molecular subtypes

KIT-*mutant GIST.* In 1998, *KIT* mutations were the first driver mutation to be discovered in GISTs[7,14]. Occurring in around 70% of GISTs, these gain-of-function mutations

Key points

- All currently approved systemic therapies for GIST are tyrosine kinase inhibitors (TKIs); these agents can be used to treat the majority of patients with advanced-stage GIST.
- TKIs have limitations, particularly in the setting of advanced-stage disease, because of secondary intra-allelic mutations that confer drug resistance, but also because of the need for indefinite treatment to control quiescent, drug-persistent tumour cells.
- Understanding the underlying biology of the different molecular subtypes of GIST has presented new therapeutic approaches beyond TKIs.
- TKIs remain relevant for GISTs harbouring receptor tyrosine kinase mutations or fusions, but applying them in new, more strategic ways will benefit patients.

are found at only a few locations in the protein — the membrane-proximal extracellular domain (mutations involving exons 8 or 9), the intracellular juxtamembrane domain (encoded by exon 11) or the kinase domain (exons 13 or 17) — and cause constitutive, ligand-independent kinase activity by disrupting autoinhibitory regions of the RTK[15]. The most common primary *KIT* mutations affect the juxtamembrane domain; point mutations or indels (insertions and/or deletions) within *KIT* exon 11 drive around 60% of all GISTs[1,3,4,8–12,16,17]. GISTs with *KIT* exon 11 mutations can occur throughout the gastrointestinal tract, from the oesophagus to the rectum, but account for almost all cases arising in the proximal stomach[18] (TABLE 1). *KIT* exon 11-mutant GISTs, especially those with deletion mutations, typically have high mitotic rates and are associated with a high risk of recurrence and metastasis[19,20]. As discussed further below, GISTs with *KIT* exon 11 mutations are extremely sensitive to the KIT tyrosine kinase inhibitor (TKI) imatinib and account for the vast majority of patients with metastatic GIST who respond to this agent. The next-most-common primary *KIT* mutations involve the membrane-proximal extracellular region encoded by exon 9 (accounting for 9–10% of all GISTs). Almost all *KIT* exon 9-mutant GISTs arise in the small intestine, colon or rectum, with rare reports of such GISTs arising in the stomach[21] (TABLE 1). Finally, mutations in *KIT* exons 8, 13 or 17 are rare primary drivers, each accounting for ≤1% of GISTs[1,3,4,8–12,16,17]. These rare subtypes of *KIT*-mutant GIST usually arise in the intestines, approximately twice as often as in the stomach[22] (TABLE 1).

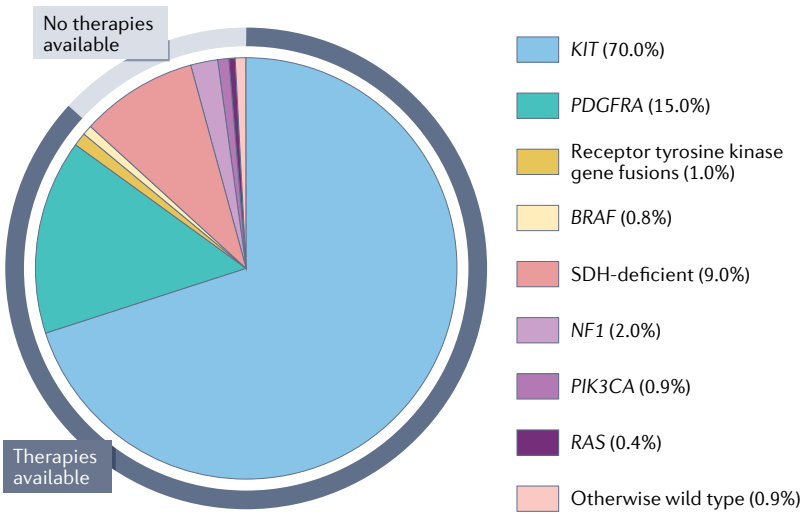

Fig. 1 | **Summary of GIST molecular subtypes.** The pie chart indicates the proportion of gastrointestinal stromal tumour (GIST) cases that is driven by each recurrent driver alteration associated with this disease. *KIT* and *PDGFRA* mutations account for approximately 85% of GISTs. Effective targeted therapies are now available for patients with GIST harbouring such alterations, as well as those with *BRAF* mutations or receptor tyrosine kinase gene fusions (predominantly involving *FGFR1* or *NTRK3*), encompassing about 88% of all advanced-stage GISTs (indicated by the black segment of the outer ring). The remaining 12% of GISTs are SDH deficient, *NF1*, *PIK3CA* or *RAS* mutant, or otherwise wild type, and lack effective therapies (indicated by the grey segment of the outer ring).

PDGFRA-mutant GIST. PDGFRA is an RTK that is highly homologous to KIT, both functionally and structurally. Accordingly, *PDGFRA* mutations occur in about 15% of all GISTs (FIG. 1) and are similar to those in *KIT*; however, distinctions between the two have important treatment implications. Like *KIT* mutations, *PDGFRA* mutations in GISTs are gain of function, disrupting autoinhibitory regions of the RTK and thereby resulting in ligand-independent activation[5,6]. *PDGFRA* mutations can also be either point mutations or indels, but the mutational frequencies at the various hotspots in *PDGFRA* are the opposite of those in *KIT*[1,3,4,8–12,16,17]. Whereas the majority of *KIT* mutations affect the juxtamembrane domain, mutations affecting this region of PDGFRA (encoded by *PDGFRA* exon 12) are rarely seen in GISTs, with a prevalence of approximately 1–2%. Conversely, the most common *PDGFRA* mutation, found in 9–10% of all primary GISTs, is a D842V point mutation within the kinase domain activation loop (encoded by exon 18)[5,6,23]. Notably, the *PDGFRA* D842V mutation is homologous to the *KIT* exon 17 D816V mutation found in the vast majority of patients with mastocytosis, although this particular *KIT* mutation has not been reliably reported as a primary mutation in GIST. Other primary *PDGFRA* alterations include diverse indels and point mutations in exon 18 (in around 5% of GISTs) and mutations affecting the ATP-binding pocket encoded by exon 14 (in 1%), which is homologous to *KIT* exon 13 (REF.[5]). Historically, the survival outcomes of patients with advanced-stage *PDGFRA*-mutant GIST have been poor because *PDGFRA*^{D842V}-mutant GIST is highly resistant to imatinib and other type II PDGFRA/KIT TKIs[5,24–26]. However, the development of avapritinib, a type I PDGFRA/KIT TKI, has now improved the outcomes of many patients with *PDGFRA*^{D842V}-mutant GIST, as discussed in more detail below. The majority of *PDGFRA*-mutant GISTs arise in the stomach or the omentum, with rare cases originating in the intestines or mesentery[27] (TABLE 1).

SDH-deficient GIST. SDH-deficient GIST constitutes the third-largest molecular subset, accounting for about 9% of all GISTs[1,3,4,8–13,16,17,28–30] (FIG. 1). These tumours have unique clinical and pathological features compared with most other GISTs, given that they usually occur in young adults, are almost exclusively gastric in origin (specifically arising in the distal stomach), often have an epithelioid rather than spindle cell morphology and frequently give rise to lymph node metastases[13,28,30] (TABLE 1). Across different series, 82–100% of patients with SDH-deficient GIST had an associated germline pathogenic mutation

in any one of the four genes encoding the SDH subunits: *SDHA, SDHB, SDHC* and *SDHD*[13,31,32]. Each of the four SDH complex genes are considered classical tumour suppressors, with tumours arising owing to inheritance of a germline loss-of-function allele followed by spontaneous somatic loss of heterozygosity of an *SDH* gene or, less often, a second independent somatic loss-of-function mutation in the originally wild-type allele of the same SDH subunit affected by a germline mutation[33,34]. Loss-of-function mutations in any of the SDH subunits lead to dysfunction and degradation of the whole complex, resulting in a loss of SDHB expression as assessed using immunohistochemistry, which can be used as a diagnostic marker[35]. The majority of GIST-associated SDH mutations occur in *SDHA*[13,36]. In addition to loss-of-function mutations, a minority of SDH-deficient GISTs arise through somatic hypermethylation of the *SDHC* promoter (around 0.5% of all GISTs), leading to loss of both SDHC expression and SDH enzymatic function[13,37,38]. Most SDH-deficient GISTs behave in an indolent fashion, with a clinical course measured in decades, although some are aggressive and are associated with rapidly progressive disease[13]. No therapies are specifically approved for SDH-deficient GIST.

Other molecular drivers of GIST. Beyond KIT, PDGFRA and SDH, a few other molecular drivers account for small subsets of GISTs. Loss of neurofibromin (NF1) accounts for about 2% of GISTs, and activating *BRAF* V600E mutations account for about 0.8% of GISTs[39–42] (FIG. 1). Both of these subtypes of GIST arise predominantly in the small intestine via excessive activation of the MEK–ERK signalling pathway (TABLE 1 and FIG. 2a). Treatment with BRAF inhibitors can be effective for patients with *BRAF*^{V600E}-mutant GIST[43]. On the basis of experience in treating *BRAF*-mutant melanoma, we speculate that combining a MEK inhibitor with a BRAF inhibitor might be even more effective for treating *BRAF*-mutant GIST[44]. GISTs with NF1 loss most often arise as a manifestation of classical neurofibromatosis type I, owing to a germline mutation in one *NF1* allele and subsequent somatic loss or inactivation of

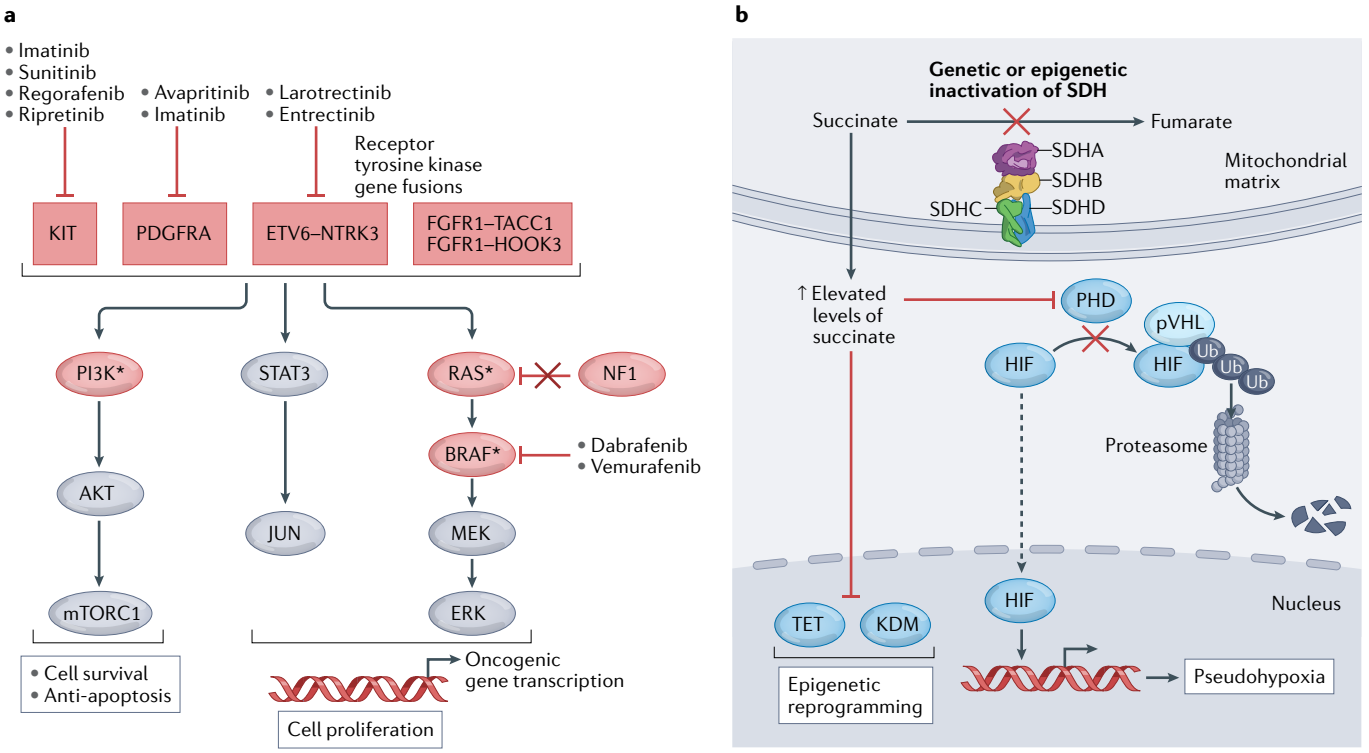

Fig. 2 | **GIST signalling pathways, drug targets and current systemic therapies. a** | The genetic alterations that drive gastrointestinal stromal tumours (GISTs) generally result in activation of signalling through the MEK–ERK (MAPK), JAK–STAT and PI3K–AKT pathways to prevent apoptosis and drive cell survival and proliferation. The components of these pathways and upstream receptor tyrosine kinases that are recurrently mutated in GIST are shown in red ovals and boxes, respectively; those indicated with an asterisk can also arise as secondary mutations after therapy. Gain-of-function (activating) mutations are found in positive signalling effectors, including KIT, PDGFRA, fusion proteins involving NTRK3 (TRKC) or FGFR1, as well as RAS, PI3Kα or BRAF. Loss-of-function (inactivating) mutations are found in tumour suppressors, such as neurofibromatosis-related protein NF1 (also known as neurofibromin). **b** | GIST can also be driven by deficiency of the mitochondrial respiratory complex II, succinate dehydrogenase (SDH), resulting from a genetic mutation in any one of the four SDH subunit genes (*SDHA*, *SDHB*, *SDHC* or *SDHD*) or, more rarely, from epigenetic inactivation of *SHDC* via promoter hypermethylation. Inactivation of the SDH complex results in an accumulation of succinate, which leads to competitive inhibition of α-ketoglutarate-dependent dioxygenases, including those of the hypoxia-inducible factor (HIF)-prolyl hydroxylase domain (PHD), ten-eleven translocation methylcytosine dioxygenase (TET), and lysine-specific histone demethylase (KDM) families. In turn, inhibition of PHDs leads to pseudohypoxia by preventing von Hippel–Lindau disease tumour suppressor (pVHL)-mediated ubiquitination and subsequent proteasomal degradation of HIF, while inhibition of the TET and KDM proteins results in increased methylation of DNA and histones, respectively, and thus broad epigenetic reprogramming. Ub, ubiquitin.

Table 1 | **GIST subtypes and their cellular and molecular features by anatomical location**

Proportion of GIST cases	Anatomical location	GIST subtype	Cell morphology	Cell of origin
60–65%	Proximal stomach	*KIT* exon 9 or 11 mutant	Spindle	ICC-IM or ICC-MY
	Distal stomach	*KIT* exon 8, 9, 11, 13 or 17 mutant	Spindle	ICC-IM or ICC-MY
		PDGFRA exon 12, 14 or 18 mutant	Epithelioid	Telocytes
		SDH deficient	Epithelioid	Unknown
20–35%	Small intestine	*KIT* exon 8, 9, 11, 13 or 17 mutant	Spindle	ICC-MY
		FGFR1 or *NTRK3* RTK fusion	Spindle	Unknown
		BRAF mutant	Spindle	ICC or SM
		NF1 mutant	Spindle	ICC-MY
3–5%	Colon or rectum	*KIT* exon 9 or 11 mutant	Spindle	ICC-IM or ICC-MY
		FGFR1 or *NTRK3* RTK fusion	Spindle	Unknown

GIST, gastrointestinal stromal tumour; ICC, interstitial cells of Cajal; ICC-IM, intramuscular ICC; ICC-MY: myenteric ICC; SDH, succinate dehydrogenase; SM, smooth muscle precursor; RTK, receptor tyrosine kinase.

the remaining functional allele. Such GISTs might also arise spontaneously as a result of somatic homozygous/biallelic or hemizygous loss-of-function mutations in *NF1*, although such tumours have actually been suggested to constitute unrecognized cases of neurofibromatosis type I[45,46]. Indeed, malignant GIST occurs in 5–10% of patients with neurofibromatosis type I, with up to 33% of patients having one or more occult GIST found during autopsy[47]. Neurofibromatosis-associated GISTs occur on average a decade or so earlier than sporadic GISTs, and affected individuals can have multiple, and in some cases, numerous, clinically occult primary GISTs[42]. Fortunately, many of these tumours have an indolent phenotype and clinical course[38,48], and in patients with multiple small tumours located throughout the small intestine, observation rather than radical resection might be indicated[39,42,49]. Currently, no known effective therapy exists for *NF1*-mutant GIST. In 2020, the MEK inhibitor selumetinib was approved for treatment of paediatric patients with neurofibromatosis type I who have symptomatic, inoperable plexiform neurofibromas[50]. This drug is now being evaluated in a phase II study involving patients with *NF1*-mutant GIST (NCT03109301). Of note, some *NF1*-mutant GISTs also express mutant forms of KIT, possibly as a secondary mutational event that further augments cell proliferation[51,52]. This hypothesis is supported by the observation that, in certain tumours, the mutant form of KIT seems to be expressed in some, but not all, cancer cells.

Most recently, gene-fusion proteins involving the RTKs NTRK3 or FGFR1 were discovered as the drivers of up to 1% of all GISTs (FIG. 1), usually among those arising in the small intestine or rectum[8] (TABLE 1). The fusion partners and nature of these translocations (including *ETV6–NTRK3* and *FGFR1–TACC1*) are similar to those found in other human cancers and result in constitutive signalling by the RTK component[53].

Other rare driver mutations involve *KRAS* or *PIK3CA*, and are each found in <1% of GISTs[8,17,54–56] (FIG. 1). Additionally, some GISTs harbouring *KRAS* or *PIK3CA* mutations also have an activating *KIT* mutation[54]. In these tumours, the *KIT* mutation is hypothesized to be the original oncogenic driver, with secondary subclonal mutation of *KRAS* or *PIK3CA*, sometimes in the setting of acquired resistance to KIT inhibitors[57–59]. This observation suggests that activation of RAS or PI3K downstream of mutant KIT provides a proliferative advantage.

Finally, overexpression of FGF4 owing to gene duplication has been reported as a potential cause of a minority of GISTs lacking any known driver mutations[60]. However, further studies are needed to validate this mechanism of GIST oncogenesis.

Cells of origin

Most GISTs arise from transformation of interstitial cells of Cajal (ICCs), located in the wall of the gastrointestinal tract, which function as pacemakers for peristaltic contractions[61]. At least four different classes of ICC have been identified, including myenteric ICCs (ICC-MY), intramuscular ICCs (ICC-IM), submucosal plexus ICCs (ICC-SMP) and deep mucosal plexus ICCs (ICC-DMP)[62,63]. Notably, the distribution of these ICC classes varies throughout the gut. For example, the stomach contains only ICC-MY and ICC-IM, while the large intestine contains these classes as well as ICC-SMP. By contrast, the small intestine lacks ICC-IM and ICC-SMP, but contains ICC-MY and ICC-DMP[63]. All four ICC subtypes express KIT, but only ICC-MY and ICC-IM can be transformed by *KIT* mutations[64].

Alternative cells of origin have been proposed for certain GIST subtypes. Telocytes were identified in 2005 as a ICC-like cell type with a $CD34^{+}PDGFRA^{+}$ immunophenotype in the gastrointestinal tract[48]. Moreover, hyperplasia of telocytes has been observed in rare families with germline *PDGFRA* mutations, analogous to ICC hyperplasia that occurs in individuals with germline *KIT* mutations[65]. These observations suggest that telocytes are the cell of origin for *PDGFRA*-mutant GISTs[48]. Whether transformed ICCs can also give rise to *PDGFRA*-mutant GISTs is unclear. In the case of *BRAF*-mutant GIST, findings in different animal models indicate that either ICCs or a smooth-muscle-derived cell type can serve as the cell of origin[66,67]. Currently, the exact cell(s) of origin for SDH-deficient GIST remains unknown.

Differences between these cells of origin are thought to underlie the clinical observation that certain molecular subtypes of GIST often arise at specific locations along the gastrointestinal tract (TABLE 1). For example, the vast majority of SDH-deficient and *PDGFRA*-mutant GISTs occur in the distal stomach; these two subtypes also share a distinctive epithelioid cell morphology[18,68]. By contrast, *KIT*-mutant GISTs predominate in the proximal stomach, but can be found throughout the gastrointestinal tract[18]. *NF1*-mutant and *KIT* exon 9-mutant GISTs arise almost exclusively in the small intestine.

Histologically, GISTs harbouring *KIT*, *NF1* or *BRAF* mutations are most commonly composed of spindle cells[1,3] (TABLE 1).

Pathobiology

In GISTs, RTK-activating mutations lead to ligand-independent kinase activation and increased signalling through downstream proliferative and survival pathways, including the PI3K–AKT, JAK–STAT and RAS–RAF–MEK–ERK (MAPK) cascades[3,6,69,70] (FIG. 2a). Rarely, mutations involving other effectors within these pathways, including PI3K, BRAF or RAS proteins, or their regulators, such as NF1 (a GTPase-activating protein that inactivates RAS), can also drive oncogenic signalling[8,40,71,72] (FIG. 2a).

SDH-deficient GIST is one molecular subtype that seems to deviate from this canonical RTK signalling-driven mechanism of tumorigenesis[73]. Loss of SDH activity owing to loss-of-function mutations in any of the *SDH* genes results in accumulation of its substrate, succinate, and a decrease in fumarate production[74–76] (FIG. 2b). Elevated succinate has been suggested to act as an oncometabolite that drives tumorigenesis in multiple ways, including inhibition of α-ketoglutarate-dependent dioxygenases, such as hypoxia-inducible factor (HIF)-prolyl hydroxylases, TET family methylcytosine dioxygenases and lysine-specific histone demethylases, which induces both pseudohypoxic HIF-1 signalling and DNA and histone hypermethylation phenotypes[77–79] (FIG. 2b).

Lessons learned from imatinib

Prior to the year 2000, no effective medical therapies were available for patients with advanced-stage GIST. GISTs have minimal sensitivity to the chemotherapy agents commonly used to treat other sarcomas. Historically, GISTs have also been considered to be resistant to external beam radiotherapy[80]. Although, more recent studies, including a single prospective phase II trial, have shown that radiotherapy can provide palliative disease stabilization in selected patients[81–83]. The only known effective GIST therapy at the turn of this century was surgery, which is performed with curative intent for patients with localized disease or to palliate patients with advanced-stage GIST through selective metastasectomy[84].

The discovery of activating *KIT* mutations in GIST in 1998 (REFS[7,14]) led to the hypothesis that KIT inhibitors might be effective for the treatment of this disease. At around this time, imatinib was identified as a potent KIT TKI, with activity against mutant forms of KIT, and had already undergone extensive clinical testing for the treatment of patients with chronic myeloid leukaemia[85]. Accordingly, imatinib was evaluated as a treatment for GIST in several phase II studies and subsequently in several large-cohort international randomized phase III trials[86–89]. In these studies, imatinib induced a high rate of clinical benefit (either a complete response, partial response or durable stable disease) ranging from 70–84%, with median progression-free-survival (PFS) durations in the range of 20 months[86–89]. These results lead to the 2001 FDA approval of imatinib for the treatment of metastatic GIST[90]. Notably, the median overall survival duration of patients with advanced-stage GIST is estimated to have increased from 12 months to 4–5 years with the use of imatinib, with 10-year overall survival estimates of 10–20%[84,91,92]. Imatinib is generally well tolerated, with many of the common adverse effects being mild or easily managed with standard supportive care measures; however, up to 5% of patients are intolerant of imatinib and require a change in therapy based on toxicity alone[93,94].

The success of imatinib had major effects on GIST therapy, drug development and research. Ultimately, the development of all currently approved systemic treatments for GIST, which are all TKIs, was sparked by the limitations of imatinib, particularly those related to primary (intrinsic) or secondary (acquired) resistance to this agent (FIG. 3). These limitations also provide a perspective from which to consider novel therapeutic approaches.

Molecular testing to optimize therapy

A notable finding in the early studies of imatinib was that not all GISTs responded uniformly. We now know that these variable outcomes can be almost entirely understood through molecular testing of the primary tumour. Most patients with GISTs lacking a *KIT* mutation had minimal to no clinical response to imatinib and generally had markedly inferior PFS and overall survival relative to patients with *KIT*-mutant GISTs[91,95,96]. Remarkably, even among patients with *KIT*-mutant GISTs, the likelihood and durability of the response to imatinib can be predicted based on the specific primary *KIT* mutation; patients with exon 11 mutations have superior outcomes to those with exon 9 mutations, especially when using standard-dose imatinib (400 mg total daily dose)[91,95,96]. These responses led to different dosing recommendations for patients, depending on the specific *KIT* mutation detected[97].

Further investigation of GISTs with primary resistance to imatinib (that is, those in patients with disease progression <6 months after starting treatment), ultimately led to the identification of the other molecular drivers of this disease, including the *PDGFRA* D842V mutations (although not all GISTs with *PDGFRA* mutations are imatinib-resistant). For decades, patients with GISTs harbouring the D842V mutation, the most common *PDGFRA* mutation, had no therapeutic options because this mutation confers resistance to imatinib. Therefore, the D842V variant of PDGFRA presented a key target for rational drug design[5,95]. Indeed, the development of the type I PDGFRA/KIT TKI avapritinib has provided patients with *PDGFRA*-mutant GIST with a promising treatment option[98,99]. In 2020, avapritinib was approved by the FDA specifically for patients with advanced-stage GIST harbouring a *PDGFRA* exon 18 mutation, including D842V mutations, based on data from the phase I NAVIGATOR trial that showed an objective response rate of 84% (7% complete responses), with 61% of responses lasting ≥6 months[100].

The remaining molecular subtypes of GIST (SDH deficient, *BRAF* mutant or RTK translocated) were also identified through studies in the imatinib-refractory, *KIT*/*PDGFRA*-wild type population, and the subsequent

development and application of mutation-specific treatments has been shown to benefit some patients. For example, patients with *BRAF*^{V600E}-mutant GIST have been successfully treated with dabrafenib[43], although this agent is not yet formally FDA approved for this indication. Moreover, the TRK TKIs larotrectinib and entrectinib are now FDA approved for the treatment of patients with solid tumours harbouring *NTRK* fusions, including GISTs, based in part on a 100% objective response rate and durable responses among patients with GIST in the histology-agnostic registrational studies[101,102]. Of note, the appropriate diagnosis of GIST with *NTRK* fusions is challenging, potentially requiring multiple techniques that can include fluorescence in situ hybridization (FISH), immunohistochemistry and RNA sequencing[103]. Treatment of SDH-deficient GISTs with imatinib is associated with a very low objective response rate (<5%), although the second-line TKI sunitinib has been reported to have modest activity in terms of disease stabilization, with a reported partial response rate of approximately 15%[13,104]. Notwithstanding, the treatment outcomes of patients with advanced-stage SDH-deficient GIST lag far behind those of patients with *KIT*-mutant GIST, emphasizing an unmet need for more effective therapies.

The variable, mutation-dependent responses to imatinib highlight just how crucial molecular testing and patient selection based on the detection of a specific molecular driver is for achieving clinical success. This paradigm has subsequently been applied to other therapies for GIST, beginning with the KIT TKIs sunitinib, regorafenib and ripretinib, but also avapritinib, larotrectinib and entrectinib, and will need to be considered in the development of any future novel therapeutic approaches.

Requirement for continuous treatment

Researchers and clinicians quickly recognized that continuous, long-term treatment with imatinib is required to achieve disease control because inhibition of KIT does not result in elimination of all GIST cells; some cells persist by entering a nonproliferative, quiescent state[105,106] (FIG. 3). These so-called persistent GIST cells can rapidly proliferate again when KIT inhibition is removed, as demonstrated in vitro and also clinically through randomized discontinuation trials in patients with long-term responses to imatinib[107,108]. Persistent GIST cells typically lack acquired genetic aberrations that might confer more permanent drug resistance, and despite being insensitive to TKIs while quiescent, these cells remain sensitive to imatinib should they re-enter the proliferative state[105,109]. Nevertheless, the quiescent cells are thought to provide a source of subclones that confer clinical resistance once they acquire secondary mutations.

Several clinical studies have investigated the benefit of adjuvant imatinib for various durations, revealing that longer treatment results in better outcomes[110]. Indeed, in patients with imatinib-sensitive GIST, the relapse rate is <2% per year during adjuvant imatinib treatment but increases substantially after imatinib therapy is stopped, probably owing to re-entry of quiescent cells into a proliferative state[111–113]. For example, about 10% of patients had recurrence during 3 years of continuous treatment with imatinib, but an additional 40% of patients relapsed after completing adjuvant therapy[111].

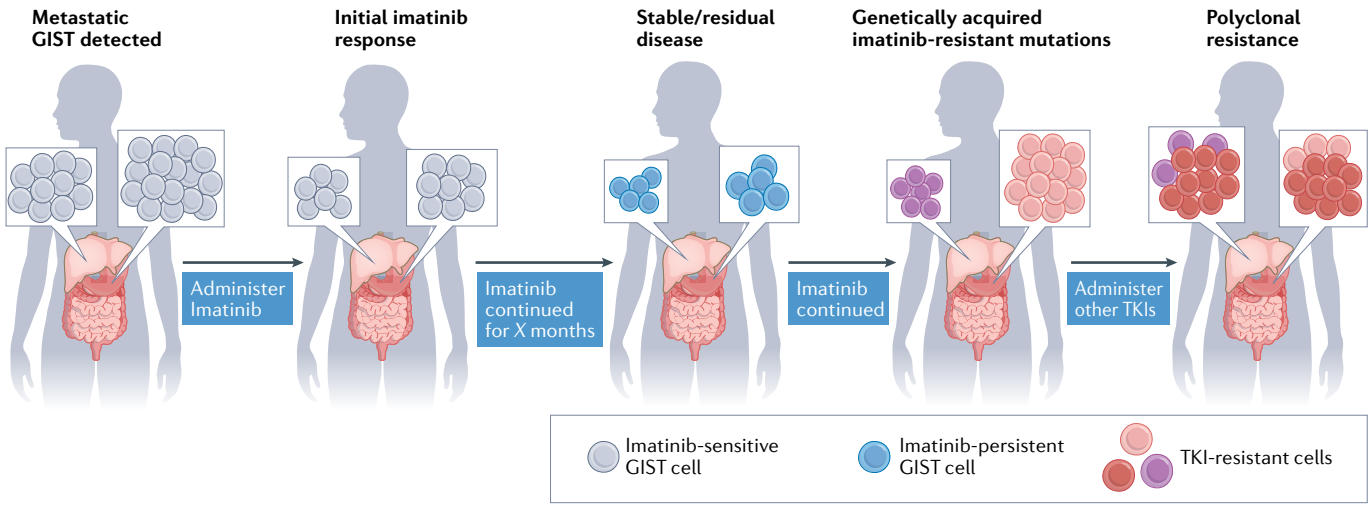

Fig. 3 | **Typical pattern of GIST response and evolution during TKI treatment.** Patients diagnosed with metastatic *KIT*-mutant gastrointestinal stromal tumour (GIST; lesions indicated by grey cells) are initially treated with the KIT-targeting tyrosine kinase inhibitor (TKI) imatinib. Typically, imatinib induces tumour shrinkage by inducing apoptosis of GIST cells; however, not all GIST cells are eradicated, with a fraction persisting throughout treatment by entering a non-proliferative, quiescent state (imatinib-persistent GIST cells, shown in blue). Some of these persistent GIST cells will eventually acquire genetic mutations that confer resistance to imatinib, leading to tumour outgrowth and disease progression (pink and purple cells). Other KIT TKIs can be administered sequentially to patients with GISTs harbouring resistance mutations. Nevertheless, genetically heterogeneous subclones can arise across tumour lesions (shown as pink, purple and red cells), leading to polyclonal resistance of the tumours to multiple TKIs. Both intertumour and intratumour heterogeneity can be found in patients with TKI-resistant GIST. Intertumour heterogeneity is illustrated by the presence of different imatinib-resistant subclones, either pink or purple, across the two lesions. In the rightmost panel, intratumour heterogeneity is also depicted by the co-existence within a single lesion of newly emergent red subclones together with the pink or purple cell population.

Secondary resistance mutations

Similar to what had already been observed for *BCR–ABL1* in studies of imatinib-refractory chronic myeloid leukaemia, secondary *KIT* mutations were identified as the main cause of imatinib resistance in *KIT*-mutant GISTs[114]. These mutations clustered in two regions of the KIT kinase domain: the ATP/drug-binding pocket (encoded by *KIT* exons 13 and 14) and the activation loop (exons 17 and 18)[115–119]. Rarely, drug resistance can arise owing to mutations in genes encoding downstream effectors, such as *PIK3CA* or *KRAS*, which promote activation of the cell proliferation and survival pathways[56,58] (FIG. 2a).

Independently of our emerging understanding of imatinib-resistance mechanisms, additional KIT inhibitors were generated, many of them through programmes aiming to develop multi-kinase inhibitors capable of also inhibiting PDGFR and/or VEGFR family members. Large-cohort randomized phase III studies of sunitinib[94] and regorafenib[120], both with placebo control arms, resulted in approval of these agents for second-line and third-line treatment of advanced-stage GIST, respectively. The median time to tumour progression was 27.3 weeks in patients receiving sunitinib after failure of imatinib, compared with 6.4 weeks in those receiving placebo (HR 0.33; $P<0.0001$)[94]. In the case of regorafenib used to treat patients after failure of prior imatinib and sunitinib, the median PFS duration was 4.8 months versus 0.9 months with placebo (HR 0.27; $P<0.0001$)[120]. Over time, the basis for the notably lower objective response rates and shorter PFS durations with these agents relative to imatinib became known: both sunitinib and regorafenib have activity against some, but not all, secondary imatinib-resistant mutations in *KIT*. This knowledge provided a molecular explanation for mixed tumour responses in an individual patient, whereby some lesions regress but at the same time anatomically distinct lesions progress, which defines the clinical entity of complex polyclonal resistance[121,122] (FIG. 3). Ultimately, understanding of the mechanisms of drug resistance in *KIT*-mutant GISTs resulted in the development of broad-spectrum KIT inhibitors, with activity against most, if not all, of the described resistance mutations. The success of this approach is exemplified by the development of ripretinib, a TKI that binds to a novel region of both the KIT and PDGFRA kinases, referred to as the switch control pocket[123]. In the randomized, double-blind phase III INVICTUS trial involving patients with advanced-stage GIST who had progression on at least imatinib, sunitinib and regorafenib, ripretinib resulted in an objective response rate of 9% versus 0% with placebo ($P=0.05$), a median PFS of 6.3 months versus 1.0 months (HR 0.15; $P<0.0001$) and median overall survival of 15.1 months versus 6.6 months (HR 0.36, 95% CI 0.21–0.62; *P* value not evaluated)[124,125]. These results formed the basis for the FDA approval of ripretinib for this indication in 2020 (REF.[125]).

Polyclonal TKI resistance, both within and across tumours, in patients with advanced-stage GIST continues to present a substantial clinical challenge when eventually none of the approved TKIs can control all lesions within a given patient (FIG. 3). Not only is polyclonal resistance recognized for *KIT*-mutant GIST, but has also been seen in patients with *PDGFRA*-mutant GIST treated with avapritinib, and will probably be a challenge in patients with *NTRK*-rearranged GIST treated with larotrectinib or entrectinib[126,127].

Novel strategies to treat GIST

The limitations of the therapies discussed above present opportunities for innovation to develop novel treatment strategies including those that utilize TKIs, both newly developed and currently available ones, as well as approaches that are entirely new to the field of GIST therapy (FIG. 4 and TABLE 2). Importantly, although not a novel strategy, developing new KIT and/or PDGFRA inhibitors that are capable of controlling a broader range of resistance mutations when used as single agents remains very clinically relevant for GIST (FIG. 4a). Currently, at least two novel KIT TKIs are entering clinical testing as single agents in patients with advanced-stage GIST: THE-630 (NCT05160168) and NB003 (formally known as AZD3229; NCT04936178) (TABLE 2). Both of these agents have potent in vitro activity against all reported secondary *KIT* mutations (with the possible exception of certain mutations involving codon 816)[128,129]. This spectrum of activity could theoretically overcome polyclonal resistance in patients with *KIT*-mutant GIST that has progressed after multiple prior lines of treatment with KIT TKIs. If promising clinical activity is identified in this population with advanced-stage, multidrug-resistant disease, additional studies will probably test the new agents in earlier lines of therapy and they could potentially replace the current standard-of-care TKIs. Nevertheless, additional compound mutations will eventually result in clinical drug resistance even to these new agents, similar to that observed with the latest generations of EGFR and ABL1 inhibitors[130–132].

Combination therapy using TKIs

The current KIT TKIs lack activity against all relevant drug-resistance mutations, which limits their effectiveness as single agents. However, each agent has a unique spectrum of activity against the different KIT variants; therefore, combination therapy is one way to potentially overcome the challenges of polyclonal resistance and/or drug-persistent cells in GISTs (FIG. 4a). Combinations of different KIT TKIs have been studied in vitro and in a few clinical studies. In a phase I study, Serrano et al.[133] investigated a novel strategy of alternating sunitinib and regorafenib to overcome polyclonal resistance involving different secondary *KIT* mutations in patients previously treated with at least imatinib, sunitinib and regorafenib. Unfortunately, this approach was unsuccessful, probably owing to overlapping toxicities of the two TKIs (gastrointestinal and hand–foot skin reaction) and difficulties in devising a tolerable and effective dosing scheme[133], although perhaps also because the patients all had tumours that had previously been exposed to, and thus might have developed resistance against, both drugs. More recently, bezuclastinib (previously known as CGT9486 and PLX9486), a type I inhibitor with potent activity against *KIT* exon 17 and 18 (activation

loop) resistance mutations, showed good tolerability and clinical activity when combined with sunitinib, a type II inhibitor that has potent activity against *KIT* exon 13 and 14 (ATP-binding pocket) resistance mutations, in patients with advanced-stage, TKI-refractory GIST[134]. On the basis of the promising data from this phase Ib/IIa trial, including a clinical benefit rate of 80% and a median PFS duration of 12.1 months[134], a randomized phase III trial comparing the combination treatment versus single-agent sunitinib for the treatment of imatinib-resistant, sunitinib-naive GIST is under way (NCT05208047) (TABLE 2).

As mentioned previously, primary KIT mutations in GISTs result in activation of the downstream MAPK, PI3K–AKT and JAK–STAT pathways (FIG. 2). MEK–ERK and PI3K–AKT are particularly crucial effectors of mutant KIT signalling, and evidence suggests that both pathways need to be inhibited to optimally decrease the proliferation and/or induce apoptosis of GIST cells[135,136]. The combination of imatinib with either a MEK inhibitor or a PI3K inhibitor has been tested in patients with advanced-stage GIST, usually in the setting of acquired resistance to imatinib (for example, NCT01735968, NCT01468688 and NCT01991379). To date, these studies have not provided any strong signs of efficacy[137,138], probably because in the setting of imatinib resistance these treatments no longer function as a combination therapy, but instead as MEK or PI3K inhibitor monotherapy. Given the activation of multiple pathways by unopposed KIT signalling in the setting of imatinib resistance, it is not surprising that inhibiting a single downstream pathway is not effective. More promising activity has been demonstrated in the setting of front-line treatment of advanced-stage GIST by combining imatinib and the MEK inhibitor binimetinib. In a phase II study (NCT01991379), this therapeutic strategy

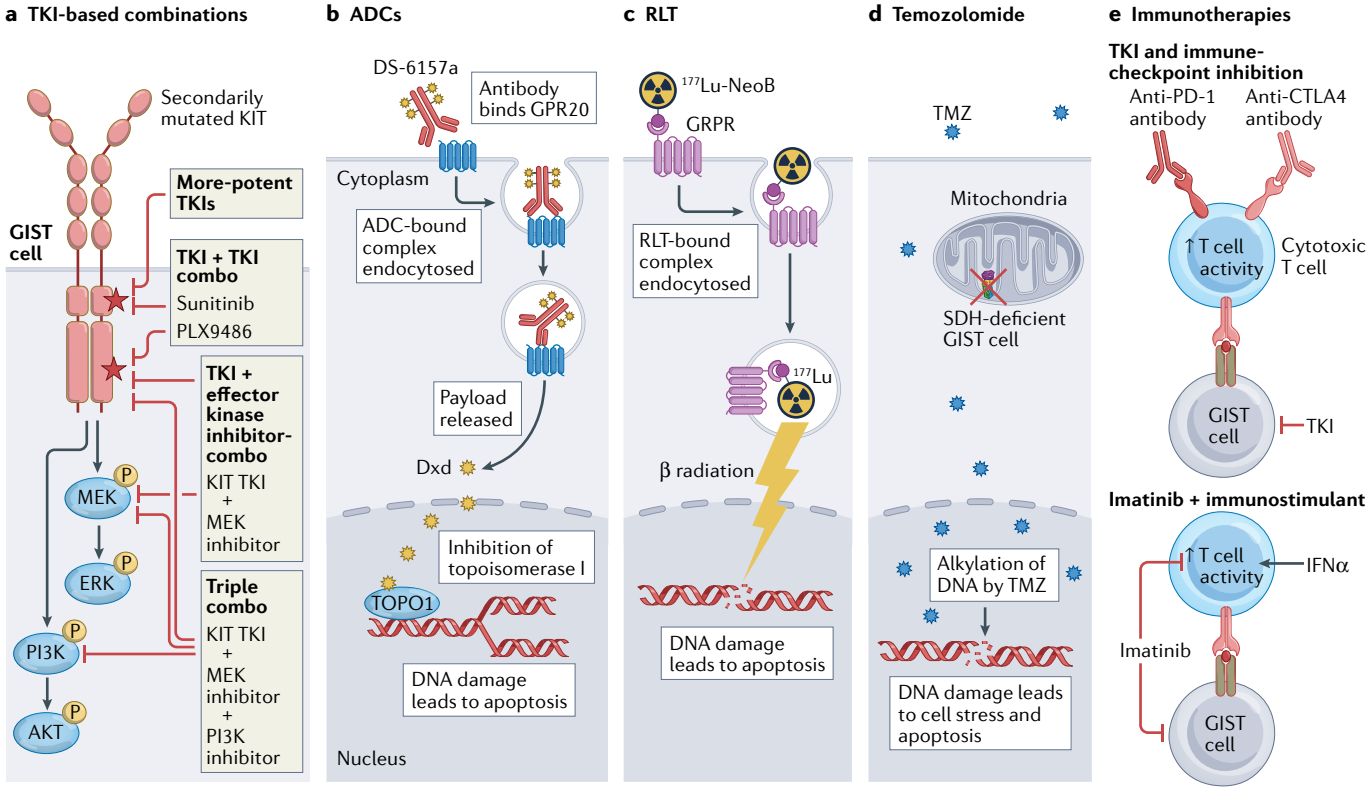

Fig. 4 | **New therapeutic approaches exploiting different elements of GIST biology. a** | Tyrosine kinase inhibitor (TKI)-based therapy remains relevant for the majority of patients with advanced-stage GIST, particularly those with *KIT*-mutant disease; however, new strategies are required to overcome treatment resistance and thereby improve outcomes, including the development of more-potent TKIs, or combinations of two TKIs or a TKI plus inhibitors of downstream effector kinases (such as MEK and/or PI3K). Many of these approaches might also be applicable in *PDGFRA*-mutant GIST if PDGFRA-specific TKIs, such as avapritinib, are utilized. **b** | The antibody–drug conjugate (ADC) DS-6157a combines an anti-G protein-coupled receptor 20 (GPR20) antibody and the DNA topoisomerase I (TOPO1) inhibitor deruxtecan (Dxd). Upon binding to GPR20, the receptor–ADC complex is endocytosed, with subsequent lysosomal degradation of the complex resulting in release of the Dxd payload, which in turn causes DNA damage and cell death. **c** | ^{177}Lu-NeoB is a radioligand therapy (RLT) consisting of the radioisotope ^{177}Lu conjugated via the chelating agent dodecanetetraacetic acid (DOTA) to a peptide antagonist of the gastrin-releasing peptide receptor (GRPR; also known as bombesin receptor subtype 2 or BB_2). Thus, this agent enables specific intracellular delivery of radiation to GRPR-expressing GIST cells, resulting in DNA damage and apoptosis. **d** | In an approach specific to SDH-deficient GIST cells, treatment with the alkylating agent temozolomide (TMZ) can cause irreparable DNA damage and cell death. This vulnerability is probably at least partially attributable to epigenetic silencing of 6-*O*-methylguanine-DNA methyltransferase (MGMT), which is involved in the repair of alkylated DNA, as a consequence of the metabolic alterations resulting from SDH deficiency in these cells. **e** | Various immuno-oncology approaches to the treatment of GIST have been proposed, including combining a TKI with PD-1 and/or CTLA4 immune-checkpoint inhibitors to simultaneously suppress GIST cells while stimulating antitumour T cells, or imatinib with an immunostimulant such as IFNα to prevent imatinib-related T cell inactivation.

Table 2 | **Predicted efficacy of novel treatment strategies against common subtypes of GISTs**

Treatment strategy	Novel treatment	Target	Predicted efficacy		
			KIT-mutant GIST	*PDGFRA*-mutant GIST	SDH-deficient GIST
TKI-based	THE-630 (NCT05160168)	KIT driver (all known primary and secondary variants)	✓	×	×
	NB003 (NCT04936178), formally known as AZD3229	KIT or PDGFRA driver	✓	✓	×
	Bezuclastinib (previously known as CGT9486 and PLX9486) + sunitinib (NCT05208047; REF.[134])	KIT driver	✓	✓	×
	TKI + MEKi (such as imatinib plus binimetinib; NCT01991379; REFS[137,139])	KIT or PDGFRA driver	✓	✓	×
	TKI + PI3Ki + MEKi (REF.[140])	KIT or PDGFRA driver	✓	✓	×
Antibody–drug conjugate	DS-6157a (NCT04276415)	GPR20	✓	✓	✓
Radioligand therapy	^{177}Lu-NeoB (NCT03872778)	GRPR (expression determined by ^{68}Ga-NeoB uptake)	✓	?	?
DNA damage repair	Temozolomide (NCT03556384; REF.[161])	SDH-deficient cells (negative for MGMT expression)	×	×	✓
Immuno-oncology	TKI + immune-checkpoint inhibitor (such as axitinib and avelumab; NCT04258956)	KIT or PDGFRA driver and PD-1 or PD-L1	✓	✓	×
	TKI + immunostimulant (such as IFNα[167])	KIT or PDGFRA driver and cytokine receptors	✓	✓	×

?, unknown; GIST, gastrointestinal stromal tumour; GPR20, G protein-coupled receptor 20; GRPR, gastrin-releasing peptide receptor (also known as bombesin receptor subtype 2 or BB_2); MEKi, MEK inhibitor; PI3Ki, PI3K inhibitor; SDH, succinate dehydrogenase; TKI, tyrosine kinase inhibitor.

produced an objective response rate of 69.0%, with a median PFS duration of 29.9 months[139]; however, in the absence of a randomized control arm, whether this approach is superior to front-line imatinib monotherapy is impossible to determine. Given the long PFS duration associated with single-agent frontline therapy of GIST, along with concerns about increased toxicity and financial costs, a study comparing imatinib with imatinib plus binimetinib in the first line is unlikely.

An alternative and potentially more feasible approach to combining downstream kinase inhibitors with imatinib would involve the use of short-term pulse combination therapy in order to eliminate drug-persistent GIST cells (FIG. 3). The results of an in vitro study by Gupta et al.[140] demonstrated that triplet therapy with imatinib plus a MEK inhibitor and a PI3K inhibitor can eliminate cells that persist during imatinib treatment. Triplet therapy would probably also be limited by toxicities, but might be clinically feasible using pulse treatments of limited duration, such as a cyclical treatment schedule. Further clinical studies are needed to determine the safety and potential efficacy of this treatment approach.

Antibody–drug conjugates

Antibody–drug conjugates (ADCs) are one of the most rapidly expanding therapeutic classes in clinical oncology. ADCs entered clinical studies in the 1980s, but initially failed to yield relevant clinical benefits[141]. However, continued improvements in this technology resulted in the first ADC approval in 2000, of gemtuzumab ozogamicin for acute myeloid leukaemia, followed by a second in 2011, brentuximab vedotin for Hodgkin lymphoma or anaplastic large cell lymphoma[141]. Currently, a total of 11 ADCs are FDA approved for the treatment of various cancers and dozens of new agents are currently in clinical studies[141]. ADCs consist of three elements: (1) a tumour-associated antigen-specific monoclonal antibody; (2) a chemical linker; and (3) a potent cytotoxic agent (also known as the 'payload')[142]. The monoclonal antibody element enables tumour-selective targeting, with the therapeutic index optimized through selection of an antigen with high levels of tumoural expression and minimal to no expression by nonmalignant cells[141]. Advances in the design and synthesis of ADCs have increased the drug-to-antibody ratio, thereby improving payload delivery to cells targeted by the monoclonal antibody[141]. Theoretically, the payload is only released after the ADC enters a cell by endocytosis and the linker is subsequently cleaved or degraded in the lysosome, thus minimizing systemic toxicity from the payload agent[142–144] (FIG. 4b).

In 2021, a report identified GPR20 as a novel GIST-specific target antigen for ADC treatment[145]. GPR20 is an orphan G protein-coupled receptor that was found to be strongly expressed in the vast majority of GISTs, regardless of molecular subtype, as well as in subsets of ICCs, but not in other nonmalignant tissues or types of sarcoma[145]. On the basis of these findings, DS-6157a was generated using a humanized anti-GPR20 antibody, a protease cleavable maleimide Gly-Gly-Phe-Gly tetrapeptide-based linker and an exatecan-derivative topoisomerase I inhibitor payload (deruxtecan)[145] (FIG. 4b). DS-6157a was shown to have antitumour activity against *KIT*-mutant GIST cells in vitro and in patient-derived xenograft models, regardless of the presence or absence of secondary

resistance mutations[145]. The favourable pharmacokinetic profiles, efficacy and safety and tolerability metrics in animal models have led to advancement of DS-6157a to a first-in-human phase I study in patients with advanced-stage GIST[145] (NCT04276415) (TABLE 2). The success of this approach will depend in part on GPR20 expression, and thus a diagnostic grade GPR20 immunohistochemistry assay will probably need to be developed.

Radioligand therapy

Radiolabelled peptides, also known as radioligand therapies (RLTs), have been developed for imaging and/or treatment of various cancers, leading to the birth of the field of theragnostics (or theranostics)[146]. For example, ^{68}Ga-DOTATATE and ^{177}Lu-DOTATATE are both FDA approved for imaging and treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours[146,147]. In addition, ^{177}Lu-PSMA-617 has been granted FDA priority review as a treatment for metastatic castration-resistant prostate cancer[148]. Several receptors expressed on GIST cells have been proposed as targets for RLT, including somatostatin receptors 1 and 2 (SST1/2) and the gastrin-releasing protein receptor (GRPR, also known as bombesin receptor subtype 2 or BB_2)[149–151] (FIG. 4c). Follow-up imaging studies have revealed that most GISTs do not express sufficient levels of SST1/2 for effective targeting[152,153], although a radiolabelled antagonist of GRPR known as NeoB (previously NeoBOMB1) continues to garner interest as a treatment of GIST. In patient-derived xenograft models of *KIT* exon 13-mutant GIST, ^{177}Lu-NeoB was found to localize to the tumours, with only minimal accumulation in nonmalignant tissues[154]. Notably, near-complete tumour regression and improved survival was noted in mice treated with a 400-pmol dose of ^{177}Lu-NeoB[154]. Imaging of patients with GIST using a ^{68}Ga-labelled version of NeoB revealed both interpatient and intrapatient tumour heterogeneity in GRPR expression, with some patients having uptake in 100% of tumours, but others having uptake in only some of the tumours[155], suggesting that imaging with this agent could be used for patient selection for treatment with ^{177}Lu-NeoB (TABLE 2). Currently, ^{177}Lu-NeoB is being tested in the phase I/II NeoRay study involving patients with advanced-stage breast or prostate cancer, GIST or glioblastoma (NCT03872778). In this study, patients are being imaged with ^{68}Ga-NeoB PET–CT and those with at least one measurable NeoB-avid lesion will be treated with a putative therapeutic dose of ^{177}Lu-NeoB.

Both the ADC and RLT approaches have the potential to overcome several limitations of the current kinase-directed therapies for GIST. First, target expression might be independent of kinase mutation status, as seems to be the case for GPR20[145]; therefore, these treatments might prove effective for GISTs with no proven effective therapies, including *NF1*-mutant or SDH-deficient GIST. Second, given that ADCs and RLTs have distinct mechanisms of action and are unlikely to have substantial overlapping toxicity with TKIs, each of these agents could potentially be combined to achieve an additive or synergistic effect. Finally, because these ADCs and RLTs act in a kinase-independent fashion, they might be effective against tumours with secondary resistance mechanisms, including both secondary kinase mutations and kinase-independent mechanisms of drug resistance.

Temozolomide for SDH-deficient GIST

SDH-deficient tumours in general have presented a persistent therapeutic challenge. Technically, the approved indications for imatinib, sunitinib, regorafenib and ripretinib include patients with SDH-deficient GIST, although it is clinically recognized that KIT/PDGFRA TKIs, with the possible exception of sunitinib, provide limited benefit for these patients[13,104]. Therefore, different therapeutic approaches are needed for SDH-deficient GIST, and exploiting the unique biology of this disease subtype is a possible strategy. Much has been learned about SDH-deficient GIST from the study of other SDH-deficient tumours, owing to their shared pathobiology. For example, SDH-deficient tumours are known to have functional defects in DNA damage repair pathways[156], prompting investigation of agents targeting DNA damage repair in these cancers. Additional studies in a small number of patients with *SDHB*-mutant paraganglioma have shown that treatment with the alkylating agent temozolomide often results in disease stabilization[157,158] (FIG. 4d). Lack of expression of the DNA dealkylating enzyme 6-*O*-methylguanine-DNA methyltransferase (MGMT), owing to promoter hypermethylation and resultant transcriptional silencing of *MGMT*, is predictive of a favourable response to temozolomide in patients with glioblastoma, an approved indication, as well as paraganglioma[157–159]. SDH-deficient GISTs have been shown to lack MGMT expression[160], and in vitro studies using novel patient-derived SDH-deficient GIST models provide evidence of the sensitivity of these tumour to temozolomide[161]. A phase II study of temozolomide in patients with advanced-stage SDH-deficient GIST is under way (NCT03556384), with promising preliminary results in five initial patients, including two partial responses and disease control in the three other patients[161] (TABLE 2).

Immunotherapeutic approaches

Immunotherapy approaches have impressive activity against advanced-stage tumours of certain histologies (such as melanoma, non-small-cell lung cancer and renal cell carcinoma). However, immune-checkpoint inhibitors, including anti-PD-1 antibodies as single agents or in combination with anti-CTLA4 antibodies, have thus far shown only modest activity in patients with GIST. For example, in a randomized phase II study of nivolumab versus nivolumab plus ipilimumab, the median PFS duration in the monotherapy arm was 11.7 weeks, and was only 8.3 weeks in the combination therapy arm[162]. Nonetheless, 3 of 35 patients across both arms had PFS durations >1.5 years, suggesting the feasibility of an immunotherapy approach for GIST if pre-treatment characteristics of such long-term responders could be identified and used to select patients for treatment[162]. Similar to these clinical findings, monotherapy with anti-PD-1 or anti-PD-L1

antibodies had no effect on tumour growth in a mouse model of GIST; however, addition of an anti-PD-1 antibody to imatinib markedly decreased tumour growth compared with single-agent imatinib[163]. Thus, the feasibility of combining TKIs with immunostimulatory agents needs to be tested in clinical studies. Indeed, the combination of the anti-PD-L1 antibody avelumab and KIT/PDGFRA TKI axitinib is currently being tested in the phase II AXAGIST study involving patients with advanced-stage GIST that has progressed after treatment with at least imatinib and sunitinib (NCT04258956) (TABLE 2 and FIG. 4e). One caveat is that these combination therapies depend upon effective KIT/PDGFRA inhibition, indicating the need to partner immunotherapeutic agents with broad-spectrum KIT/PDGFRA TKIs, probably earlier rather than later in the treatment paradigm. Thus, testing such combination therapies as part of first-line treatment of advanced-stage GIST might be warranted.

Notably, the microenvironment of *KIT*-mutant GIST is altered by KIT TKIs, with an initial augmented immune response owing to activation of $CD8^+$ T cells and dendritic cells[164,165]. With chronic imatinib therapy, however, the abundance of both intratumoral dendritic cells and $CD8^+$ T cells decreases, which dampens the immune response to tumour cells[165]. This blunted immune response partly reflects reduced type I interferon (IFN) production, which in turn leads to decreased $CD8^+$ T cell activity[166]. Restoration of type I IFN signalling through administration of IFNα could potentially reverse the chronic immune-inhibitory effects of imatinib (TABLE 2 and FIG. 4e), a concept previously tested with promising initial results in a small phase II study conducted in the early 2000s[167]. On the basis of our improved understanding of the GIST microenvironment, this approach should be further tested in a larger study. Another approach to reversing the immune-inhibitory effects of chronic KIT TKI therapy would be to use other cytokines and/or chemical stimulants, such as FLT3 ligand and the Toll-like receptor agonist polyinosinic:polycytidylic acid (poly I:C), to promote dendritic cell expansion and maturation[165].

Conclusions

For the past 5 years we have been able to identify the oncogenic driver event in 99% of patients with GIST, but our ability to target all driver mutations has lagged behind. The past few years have, nevertheless, yielded new strategies for targeting the drivers of GIST beyond KIT, providing effective therapies for approximately 80–90% of patients with advanced-stage GIST. However, the limitations of current TKI therapies pose challenges to long-term disease control, and some subtypes of GIST are inherently insensitive to such agents. Thus, alternative approaches will be required to manage advanced-stage GIST better, and as new therapies become available, the optimal treatment sequence will need to be continuously refined.

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Competing interests
M.C.H. has been a consultant for Blueprint Medicines, Deciphera Pharmaceuticals, Novartis and Theseus Pharmaceuticals, and has a patent for the treatment of GIST using imatinib that has been licensed by his institute to Novartis. The other authors declare no competing interests.

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