ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 2037–2045, 2018
doi:10.1093/annonc/mdy309
Published online 8 August 2018

REVIEW

Translational insights into gastrointestinal stromal tumor and current clinical advances

M. L. Hemming[1], M. C. Heinrich[2], S. Bauer[3] & S. George[1]*

[1]Department of Medical Oncology, Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston; [2]VA Health Care System and Knight Cancer Institute, Oregon Health and Science University, Oregon, USA; [3]Sarcoma Center, Western German Cancer Center and German Cancer Consortium (DKTK), Essen, Germany

*Correspondence to: Dr Suzanne George, Department of Medical Oncology, Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave Dana 1212, Boston, MA 02215, USA. Tel: +1-617-632-5204; Fax: +1-617-632-3408; E-mail: suzanne_george@dfci.harvard.edu

Gastrointestinal stromal tumor (GIST) is the most common soft tissue sarcoma of the gastrointestinal tract and, in the vast majority of cases, is characterized by activating mutations in *KIT* or, less commonly, *PDGFRA*. Mutations in these type III receptor tyrosine kinases (RTKs) account for over 85% of GIST cases, and the majority of *KIT* primary mutations respond to treatment with the tyrosine kinase inhibitor (TKI) imatinib. However, drug resistance develops over time, most commonly due to secondary kinase mutations. Sunitinib and regorafenib are approved for the treatment of imatinib-resistant GIST in the second and third lines, respectively. However, resistance to these agents also develops and new therapeutic options are needed. In addition, a small number of GISTs harbor primary activating mutations that are resistant to currently available TKIs, highlighting an additional unmet medical need. Several novel and selective TKIs that overcome known mechanisms of resistance in GIST have been developed and show promise in early clinical trials. Additional emerging targeted therapies in GIST include modulation of cellular signaling pathways downstream of KIT, antibodies targeting KIT and PDGFRA and immune checkpoint inhibitors. These advancements highlight the rapid evolution in the understanding of this malignancy and provide perspective on the encouraging horizon of current and forthcoming therapeutic strategies for GIST.

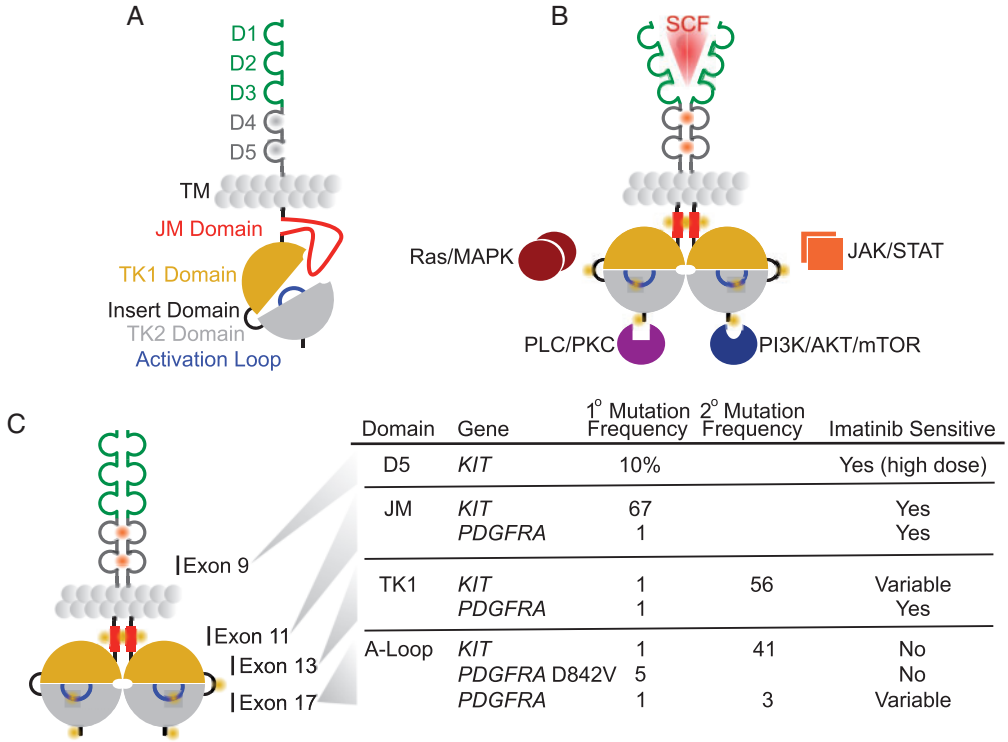
Key words: sarcoma, gastrointestinal stromal tumor, tyrosine kinase inhibitor

Introduction

Gastrointestinal stromal tumor (GIST) is among the most common soft tissue sarcomas, with an estimated annual incidence of up to 6000 cases in the USA [1], and population-based annual incidence rates of 0.78–1.1 cases per 100 000 [2, 3]. Their recognition as a pathologic entity distinct from smooth muscle and other gastrointestinal mesenchymal tumors came first from the identification of specific immunohistochemical markers, and subsequently the discovery of recurrent activating mutation in the type III receptor tyrosine kinases (RTKs) *KIT* and *PDGFRA* [4–7]. Due to similar morphologic and expression patterns, GIST has been hypothesized to arise from the transformation of interstitial cells of Cajal [8] or their cellular progenitors, which are pacemaker cells situated between enteric neurons and the smooth muscle of the gastrointestinal tract that regulate gut motility.

KIT is normally expressed in many tissues during development and is important for hematopoiesis, gut motility, gametogenesis, neurodevelopment, pigmentation, mast cell function and vascular endothelial formation [9]. Wild-type KIT is activated upon binding its ligand, stem cell factor (SCF), which induces receptor dimerization and subsequent conformational changes. These structural changes evict the inhibitory juxtamembrane (JM) domain from the split kinase domains. Activation of the kinase domains requires a conformational change in the activation loop (A-loop), enabling the kinase domains to bind ATP and phosphorylate target substrates. Phosphorylation of the KIT intracellular domain constructs docking sites for several mediators of signal transduction, stimulating signaling through the Ras/MAP kinase pathway, the JAK/STAT pathway, PLC/PKC and the PI3K/AKT/mTOR pathway (Figure 1A and B) [9].

Activating mutations in several domains within KIT and PDGFRA lead to dysregulated receptor signaling (Figures 1C and 2). Crystal structures of the KIT extracellular and kinase domains have shed light into how these mutations lead to aberrant receptor activity. Mutations in exon 9, which encodes the



Domain	Gene	1° Mutation Frequency	2° Mutation Frequency	Imatinib Sensitive
D5	*KIT*	10%		Yes (high dose)
JM	*KIT*	67		Yes
	PDGFRA	1		Yes
TK1	*KIT*	1	56	Variable
	PDGFRA	1		Yes
A-Loop	*KIT*	1	41	No
	PDGFRA D842V	5		No
	PDGFRA	1	3	Variable

Figure 1. Schematic of the KIT protein and activating mutations. (A) Diagram of KIT functional domains including the five immunoglobulin-like domains (D1–5), JM (red) domain, tyrosine kinase 1 (TK1, gold) domain, tyrosine kinase 2 (TK2, silver) domain and activation loop (A-loop, blue). (B) Upon binding the SCF ligand, wild-type KIT homodimerizes through homotypic interactions involving D4–D5, inducing conformational changes activating the kinase domains. Receptor phosphorylation and binding of adaptor proteins initiates downstream signaling through multiple pathways. (C) Locations of mutational hotspots in KIT and characteristics of associated GIST [1, 10, 11].

C-terminal portion of the ectodomain including the immunoglobulin-like D5 domain, lead to aberrant receptor activation through ligand-independent dimerization (Figure 2A) [12, 18]. Exon 11 encodes the JM domain of KIT, which stabilizes the autoinhibited kinase conformation with the A-loop in the 'DFG-Out' orientation ('DFG' indicates the first three amino acids of the A-loop: aspartate, phenylalanine and glycine) which sterically blocks the ATP-binding pocket (Figure 2B) [14]. Deletions, insertions or mutation of the JM domain produces a disinhibited and unregulated kinase domain, and represents the most common KIT activating mutation in GIST [19]. Mutation in exon 13, encoding the tyrosine kinase 1 (TK1) domain, and exon 17, encoding the TK2 domain, are rare in primary GIST tumors [20]. Mutations in exon 13 alter areas of TK1 important for contact with the JM domain and also with the ATP-binding-pocket and imatinib [21]. Exon 17 and 18 mutations lie within the A-loop, biasing the A-loop toward the 'DFG-in' conformation that excludes the inhibitory JM domain and permits ATP and substrate binding (Figure 2C and D) [10]. These structural insights into aberrant receptor activation in KIT and related tyrosine kinases has led to an understanding of drug resistance and significant advances in the development of kinase inhibitors which can bind to the active (type I inhibitors) or inactive (type II inhibitors) kinase states and other mechanisms of kinase inhibition [22]. As these mechanistic insights have evolved into novel therapeutic approaches currently being deployed, an appreciation of their therapeutic basis is important for modern oncology clinical practice.

In addition to GIST, activating KIT mutations have also been implicated in mastocytosis, seminoma, natural killer/T-cell lymphomas, acute myeloid leukemia, thymic carcinoma, melanoma and myeloproliferative disorders [23]. Germline activating *KIT* mutations are rare, with reported mutations involving exons 8, 9, 10, 11, 13 and 17. Affected individuals have variable phenotypes, with hyperpigmentation, gastrointestinal motility disorders and increased risk of cancers limited to GIST and mastocytosis [24]. Germline *PDGFRA* mutations resulting in familial GIST have also been reported [25].

Recently, the discovery of circulating tumor DNA has arisen as a method to detect, monitor response to therapy and identify resistance mutations in several cancer subtypes [26]. This methodology has been applied to GIST in the research setting and shown preliminary utility in diagnosis before tumor biopsy [27], in monitoring response to therapy [28] and in identifying tyrosine kinase inhibitor (TKI) resistance mutations [29]. Though not yet formally part of the standard diagnostic armamentarium, this approach is currently being evaluated in clinical trials as a surrogate marker for disease control and evolution of drug resistance mutations, with early results suggesting circulating tumor DNA may be a more sensitive and rapid indicator of disease response compared with imaging [30].

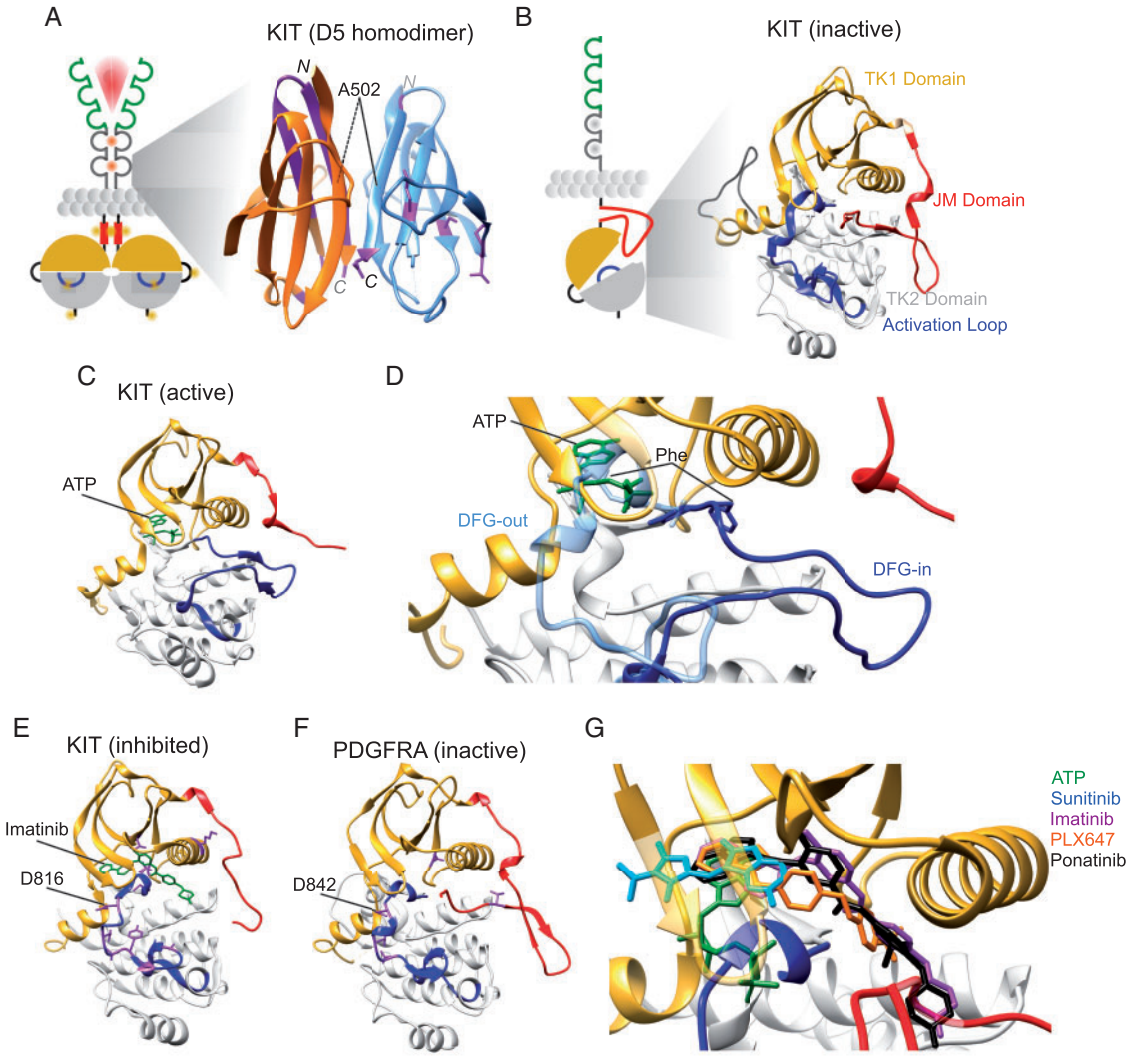


Figure 2. Structures of the KIT D5 and kinase domains and mechanisms of activation and inhibition. (A) Schematic and crystal structure of the KIT D5 homodimer [12], demonstrating surface interactions facilitating ectodomain dimerization. Position 502 is highlighted, which is at the dimer interface and a site commonly altered in exon 9 mutant GIST. Individual monomers are colored for distinction, with sites of indels on the left and point mutations on the right monomer indicated in purple. (B) Schematic and crystal structure of KIT in the inactive and (C) active [13] kinase states. The JM domain is colored in red, TK1 domain in gold, TK2 in silver and the A-loop in blue. ATP bound in the active state is in green. (D) Overlay of inactive and active KIT structures, demonstrating the DFG-out and DFG-in conformation of the A-loop. The DFG phenylalanine within the A-loop is highlighted, and in the DFG-out conformation sterically blocks the ATP-binding pocket. (E) Imatinib binding to wild-type KIT [14] stabilizes the kinase in the inactive, auto-inhibited state. (F) Kinase domain of PDGFRA in the inactive state [15]. In (E) and (F), activating mutation sites seen in GIST and the associated native amino acid side-chains are highlighted in purple. The most common A-loop mutation is labeled in both KIT and PDGFRA structures. (G) Expanded view of the KIT kinase domain with color-coded structures including ATP, imatinib, sunitinib [10], ponatinib [16] and PLX647 [17] that were merged on to sunitinib-bound KIT to obtain relative positions of each molecule. Structures were modified with UCSF Chimera software (http://www.rbvi.ucsf.edu/chimera).

Current therapy

Before targeted therapy, effective treatment options for GIST were limited to surgical resection, when feasible. Five-year survival for all patients diagnosed with GIST was 35%, and in those with metastatic disease at presentation or disease recurrence median survival was 12–19 months [31]. Shortly after the identification of activating *KIT* mutations in GIST, imatinib was found to selectively inhibit KIT signaling *in vitro* [32] and effectively treat metastatic tumors in patients with GIST [33]. In contrast to the prior dismal outlook for patients with metastatic or unresectable GIST, treatment with imatinib significantly prolongs survival, with approximately half of patients with metastatic disease surviving beyond 5 years [34]. Imatinib achieves disease control (in the form of complete or partial responses or stable disease) in ~80% of advanced KIT-expressing GIST, with median progression-free survival of 20–24 months [35] and 5-year overall survival of 69% in primary exon 11 mutant GIST, 49% in exon 9 mutant GIST and 40% in wild-type GIST treated with 400 mg imatinib [36]. Exon 9 mutant tumors have a higher response rate when treated at 800 mg imatinib daily [37]. Approximately

one-fourth of patients experience prolonged disease control on imatinib and subsequent lines of therapy [38].

The success of imatinib used in the metastatic setting has also led to interest in its use as a neoadjuvant and adjuvant therapy. Neoadjuvant imatinib is deployed with the goal of reducing operative morbidity, with treatment having demonstrated safety, efficacy in tumor size reduction and enabling less morbid surgery [39, 40]. For completely resected GIST tumors treated without neoadjuvant imatinib, select tumors at high risk of recurrence [41] may benefit from adjuvant imatinib [42]. For these high-risk patients, adjuvant imatinib has been shown to improve recurrence-free and overall survival, with 3 years of therapy being superior to one [43]. Importantly, treatment with adjuvant imatinib may not promote the development of imatinib-resistance mutations in patients with recurrent disease [44]. The benefit of longer durations of adjuvant treatment with imatinib is currently under investigation. In early reports, the single-arm PERSIST-5 trial (NCT00867113) is evaluating 5 years of adjuvant imatinib in GIST patients at high risk of recurrence. In this study, nearly half of patients discontinued imatinib early, and while most recurrences occurred following imatinib cessation, the single patient who recurred on adjuvant therapy had a PDGFRA D842V mutation [45]. Two additional trials underway (NCT02260505 and NCT02413736) are comparing 3 to up to 6 years of adjuvant imatinib. There may be additional opportunity to more accurately risk-stratify patients through molecular features of the tumor, both from the specific RTK mutation [46] as well as from an emerging understanding of GIST biology predictive of metastatic behavior [47].

Resistance to imatinib therapy occurs in the majority of patients, with risk increasing over time on therapy, and is commonly due to KIT mutations that render the kinase domain resistant to inhibitor therapy [48]. For progressing tumors with primary exon 11 mutations, the secondary kinase domain mutation evolves at a median of 27 months, which suggests either the generation of a secondary *KIT* mutation or competitive growth of a pre-existing but rare drug-resistant clone, although studies remain ongoing in this arena [49]. These secondary mutations commonly lie within either the ATP-binding pocket or A-loop domains in KIT and PDGFRA, biasing the kinase domain toward the active state and excluding the binding of standard TKIs (Figure 2E–G).

Amplification of *KIT* is not a common mechanism of disease progression or drug resistance [49, 50], although hemizygous *KIT* mutations following loss of the wild-type allele have been correlated with more aggressive disease [51]. Under effective treatment with KIT inhibition, tumor volume decreases as GIST cells undergo apoptosis and cell cycle arrest following withdrawal of trophic kinase signaling [52]. However, even following effective long-term treatment with TKIs, GIST tumor cells can remain viable but quiescent and may escape cell death through alterations in gene expression, transdifferentiation and autophagy [53, 54]. It remains incompletely understood how this subpopulation of tumor cells survives years of TKI therapy and later emerges with treatment resistant RTK mutations, and how this process can be therapeutically interrupted.

Following resistance to imatinib, subsequent lines of TKIs associated with more modest rates and durations of disease control have been developed. Second-line therapy with sunitinib has been found to prolong time to progression compared with placebo from 6.4 to 27.3 weeks [55]. Third-line therapy with regorafenib similarly prolongs progression-free survival from 0.9 to 4.8 months compared with placebo [56]. Compared with first-line imatinib, the more modest benefits conferred by these second- and third-line TKIs likely arises from the emergence of multiple unique drug-resistant KIT mutations within an individual tumor [49, 57]. Despite heterogeneity at the time of imatinib resistance, secondary KIT mutations occur in a nonrandom pattern, with mutations clustered in both the ATP binding pocket and the A-loop.

Other TKIs have been evaluated for advanced GIST, including pazopanib [58], ponatinib [16], sorafenib [59] and nilotinib [60], though results have been less supportive of their clinical development in imatinib-resistant GIST. Additional multi-targeted TKIs approved for the treatment of other malignancies are currently under clinical evaluation in imatinib-resistant GIST (e.g. NCT02216578), which may offer additional lines of therapy for this disease. All of these TKIs have overlapping contact sites within the ATP-binding pocket of KIT (Figure 2G), and their unique points of contact dictate the KIT mutations they are able to inhibit as well as their kinase selectivity and promiscuity.

PDGFRA-mutant GIST bears alterations in analogous functional domains of this related type III RTK, though the preponderance of PDGFRA activating mutations lie within the A-loop. Compared with KIT-mutant tumors, PDGFRA mutant tumors primarily have a gastric origin [61], epithelioid morphology [62] and appear to be less adept at metastasis [63–65]. Many PDGFRA mutations are sensitive to imatinib in the first-line setting, with the notable exceptions including the D842V mutation that is highly resistant to currently approved TKIs. The D842V mutation is the most common PDGFRA mutation and represents a clear unmet medical need [66]. KIT and PDGFRA mutations are mutually exclusive and drive a similar repertoire of signal transduction pathways [7]. Other less common oncogenic causes of GIST, making up less than 10% of total cases, include *NF1* loss of function mutations [67], SDH deficiency [68], *BRAF* mutation [69] and *NTRK* or *FGFR1* fusions [70, 71].

Novel tyrosine kinase inhibitors

Akin to other RTK-dependent malignancies, GIST can remain reliant upon kinase signaling even following years of effective treatment with TKIs [72, 73]. The liabilities of currently available TKIs are the development of secondary resistance mutations, which modify the structure of the kinase domain to prevent therapeutic KIT inhibition [74]. In imatinib-resistant GIST, sunitinib has been found to be most effective *in vitro* and in clinical experience at targeting secondary mutations involving the ATP-binding pocket encoded by exons 13 and 14 [75]. Evaluation of tissue biopsies following imatinib failure demonstrates the V654A ATP-binding pocket mutation as the most common site of imatinib resistance [76]. In contrast, in a phase II trial of regorafenib in GIST following failure of imatinib and sunitinib, pre- and postregorafenib treatment biopsies demonstrated inhibition of KIT protein phosphorylation in GIST tumors with A-loop mutations, primarily in exon 17 [77]. Though kinases other than KIT are inhibited by these TKIs and may contribute to their

clinical efficacy, these data suggest that later line inhibitors target a selective range of imatinib resistance mutations. The ability to pharmacologically target a spectrum of kinase-domain mutations has generated enthusiasm for the development of additional lines of TKIs, with specific inhibition of common resistance mutations in KIT and PDGFRA, several of which are currently under active clinical investigation.

Crenolanib is a novel inhibitor of type III RTKs in development for PDGFRA D842V mutant GIST, among other malignancies. It has been shown to potently and selectively inhibit many PDGFRA mutations found in GIST [78], and is currently in a phase III trial for PDGFRA D842V mutant GIST (NCT02847429). Early results from a phase II trial have been presented in preliminary form and suggest possible clinical activity. However, the spectrum of kinase inhibition is broad and suggests multiple targets in addition to PDGFRA [79].

Imatinib, sunitinib and regorafenib are type II kinase inhibitors, and as such preferentially bind to the inactive kinase conformation. As A-loop mutations bias the kinase domain toward the active state, these existing TKI are relatively less active in the setting of TKI resistance mutations seen in GIST. In search of a type I kinase inhibitor that can bind to the kinase domain in its active form, avapritinib (BLU-285) was developed [30]. This compound demonstrates type I binding characteristics, with consequential potent inhibition of KIT and PDGFRA A-loop mutants *in vitro* and in preclinical models that are superior to existing type II kinase inhibitors. Analogous to imatinib, avapritinib demonstrates a narrow range of kinase selectivity, potently inhibiting KIT and PDGFRA but few other kinases, and is more selective for mutant KIT than its wild-type counterpart. Avapritinib is currently under clinical investigation for advanced GIST (NCT02508532) and other KIT and PDGFRA D842V mutant tumors [80].

For KIT and many other kinases, activation requires conformational change in the A-loop that moves it away from the ATP- and substrate-binding pocket and into contact with a region called the 'switch pocket' or 'switch control', which stabilizes the active kinase conformation [81]. Disruption of this contact with a small molecule leads to destabilization of the active kinase and, unlike traditional TKIs, inhibits the kinase in a non-ATP-competitive manner (Figure 3). Switch pocket inhibitors have shown preclinical promise by inhibiting a variety of TKI-resistant mutations within the BCR-ABL1 kinase [82]. A KIT switch pocket inhibitor, DCC-2618, was developed with the goal of bypassing secondary kinase resistance mutations and has also entered clinical trials for GIST and other tumors (NCT02571036) [84].

Given the emergence of multiple distinct drug-resistance clones within an individual GIST patient [48, 57], the concept of combining multiple TKIs targeting a different spectrum of mutations has emerged. Two clinical trials utilizing this approach are under evaluation, either using the commercially available TKIs sunitinib and regorafenib (NCT02164240) or the novel TKI PLX9486 alone or in combination with PLX3397 or sunitinib (NCT02401815). Furthermore, the use of alternating TKIs in the first-line setting as a strategy to prevent the emergence of TKI-resistance is under evaluation (NCT02365441). Early results from these trials of novel kinase inhibitors, most notably avapritinib and DCC-2618 [85], have demonstrated encouraging preliminary evidence of disease control through the targeting of TKI resistance mutations, even in patients treated with multiple prior lines of TKIs.

Novel targeted therapies

Given the propensity of GIST to generate TKI-resistance mutations, targeting alternative steps in the KIT signaling pathway, affecting KIT protein maturation or immune-based therapies, are attractive antineoplastic strategies. Heat shock protein 90 (HSP90) is a protein chaperone that assists in the folding and intracellular transport of RTKs, among many other client proteins. As HSP90 contributes to many oncogenic pathways, the development of HSP90 inhibitors has drawn therapeutic interest in diverse malignancies [86]. HSP90 inhibitors in pre-clinical models have been shown to decrease KIT protein levels, induce cell-cycle arrest and apoptosis and decrease xenograft tumor growth [52, 87]. However, early clinical trials to date have shown modest effects in patients with TKI-refractory GIST [88–90]. As an alternative means of targeting HSP90, histone deacetylase inhibition has been found to lead to HSP90 acetylation and destabilize KIT *in vitro* [91], though this strategy has yet to reach clinical trial.

As an alternative means of destabilizing or deactivating KIT protein and enhancing immune response, treatment with KIT-directed monoclonal antibodies has been shown to decrease KIT cell-surface expression, enhance macrophage phagocytosis of GIST cells and decrease tumor xenograft growth [92]. A KIT-directed antibody is currently in early clinical trials (NCT02642016). The PDGFRA-directed antibody olaratumab has been found to block receptor phosphorylation and downstream signaling through PDGFRA and control xenograft growth [93] and may have effects both on tumor cells and the tumor microenvironment. Olaratumab in combination with doxorubicin has shown a benefit in overall survival in non-GIST soft tissue sarcoma [94], leading to its approval by the FDA. Considering the dependence upon mutant PDGFRA signaling in a subset of GIST, and expression of PDGFRA in many cases of KIT-mutant GIST, a phase II trial explored the use of olaratumab in GIST [95]. While there was no clear benefit in this study to patients with tumors bearing KIT mutations, of six patients with PDGFRA mutations half experienced prolonged stable disease at a rate higher than expected from historical controls. Additional investigation of olaratumab is warranted, possibly in combination with emerging TKIs, to further evaluate this finding.

KIT and PDGFRA signaling occurs through multiple signal transduction pathways, and inhibitors of these pathways are under clinical development [96]. In preclinical models, PI3K inhibition [97], AKT inhibition [98], MEK inhibition [99] and mTOR inhibition [100] have been found to inhibit KIT signaling and show promising effects *in vitro* and in xenograft models. However, early efforts translating these findings into clinical trials has not succeeded to date [101, 102], though additional trials are underway with novel agents (NCT01991379, NCT01735968 and NCT01468688). Signaling through fibroblast growth factor receptors (FGFRs) has been found to increase following KIT inhibition in GIST, resulting in drug resistance through alternative and complimentary signal transduction, and FGFR inhibition reduces GIST xenograft tumor growth [103, 104]. Clinical

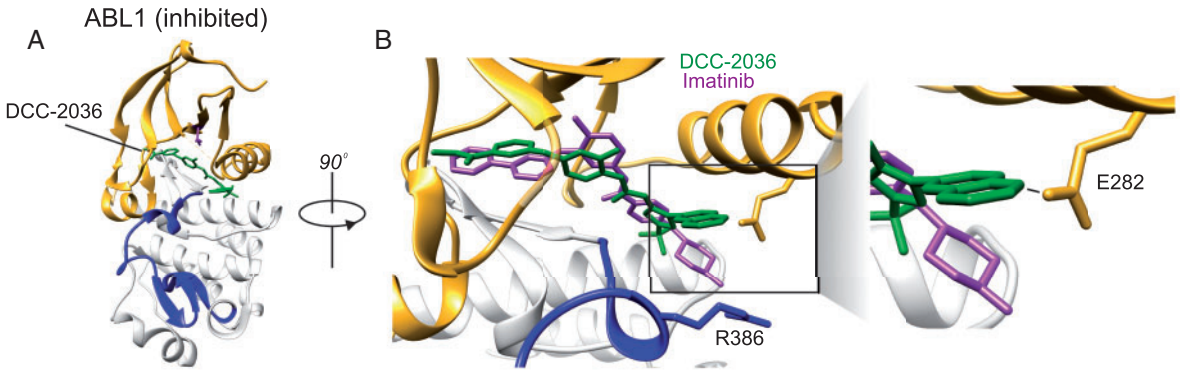


Figure 3. Switch pocket inhibition in the ABL1 kinase. (A) Structure of DCC-2036 bound to ABL1 [82]. The TK domain is colored in gold and silver, corresponding to the split kinase domain of KIT, and the A-loop in blue. The ABL1 T315I mutation is labeled in purple, which produces resistance to ATP-competitive inhibitors. (B) Structural overlay of imatinib [83] and DCC-2036 in the ABL1 kinase. DCC-2036 disrupts contact between the A-loop residue R386 and E282 within the switch pocket (expanded view in right panel), favoring the inactive kinase conformation.

evaluation of FGFR inhibitors is currently underway (NCT02257541). Though there has been substantial preclinical evidence in support of targeting downstream or alternative signaling mediators in GIST, these results have not yet translated into clinical impact. This lack of success to date may have several contributing factors, including compensatory activation of multiple alternative signaling cascades downstream of RTKs, alternative RTK-independent mechanisms of survival in advanced GIST where these novel therapies are initially tested or lack of pairing with an effective TKI.

There has been an evolving understanding of the tumor microenvironment and immune interactions in GIST. Immune cell infiltration into GIST tumors has been well documented, with unique immunologic features seen in localized and metastatic disease and as a consequence of TKI therapy [105, 106]. Imatinib has been found to have important roles in modulating intratumoral T cells to exert an antitumor response, which may in part work by preventing tumor cell production of the immune inhibitory enzyme indoleamine 2,3-dioxygenase (IDO) [107]. Combination treatment with imatinib and checkpoint inhibitors have shown superior effects to imatinib alone in pre-clinical models [107, 108], though efficacy of checkpoint blockade may depend on concurrent TKI treatment. These findings have broadened interest in studying immunotherapy in many forms for the treatment of GIST [109]. Efforts at utilizing immune checkpoint inhibition alone and in combination with TKI treatment are under early clinical evaluation in GIST (NCT02880020, NCT03291054, NCT02834013 and NCT02500797) [110].

Discussion

Conclusions

From its initial distinction from other sarcomas with similar histology, to the identification of activating *KIT* mutations and the development of targeted therapies, GIST is an outstanding example of scientific and medical progress in oncology. With prolonged TKI treatment, secondary KIT resistance mutations arise which present challenges to available therapies. Currently, multiple novel kinase inhibitors targeting KIT and PDGFRA resistance mutations through various mechanisms are in clinical trials, with encouraging preliminary results reported. Additional means of therapeutically targeting GIST under clinical investigation include anti-KIT antibodies, modulation of KIT protein maturation or signaling and immune-based therapies. The deep and maturing understanding of this disease, and the development of targeted agents based on its scientific understanding, generates enthusiasm for the future of GIST therapeutics and hope for those currently treating and suffering from this condition.

Funding

None declared.

Disclosure

Dr Heinrich performs consulting for Novartis, Blueprint Medicines, Deciphera Pharmaceuticals, Bayer, MolecularMD and Ariad Pharmaceuticals, provides expert testimony to Novartis and holds equity interest in MolecularMD. Dr Bauer performs consulting for Novartis, Blueprint Medicines, Deciphera Pharmaceuticals, Bayer and has received research funding from Novartis, Incyte and Blueprint Medicines. Dr George performs consulting for and received research funding from Blueprint Medicines and Deciphera Pharmaceuticals and has received research funding from Bayer, Pfizer and Novartis. All remaining authors have declared no conflicts of interest.

References

1. Corless CL, Heinrich MC. Molecular pathobiology of gastrointestinal stromal sarcomas. Annu Rev Pathol 2008; 3(1): 557–586.
2. Ducimetière F, Lurkin A, Ranchère-Vince D et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. PLoS One 2011; 6(8): e20294.

3. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomarkers Prev 2015; 24(1): 298–302.
4. Appelman HD. Morphology of gastrointestinal stromal tumors: historical perspectives. J Surg Oncol 2011; 104(8): 874–881.
5. Miettinen M, Virolainen M. Maarit-Sarlomo-Rikala. Gastrointestinal stromal tumors–value of CD34 antigen in their identification and separation from true leiomyomas and schwannomas. Am J Surg Pathol 1995; 19(2): 207–216.
6. Hirota S, Isozaki K, Moriyama Y et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998; 279(5350): 577–580.
7. Heinrich MC, Corless CL, Duensing A et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003; 299(5607): 708–710.
8. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998; 152(5): 1259–1269.
9. Lennartsson J, Rönnstrand L. Stem cell factor receptor/c-Kit: from basic science to clinical implications. Physiol Rev 2012; 92(4): 1619–1649.
10. Gajiwala KS, Wu JC, Christensen J et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci USA 2009; 106(5): 1542–1547.
11. Heinrich MC, Maki RG, Corless CL et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008; 26(33): 5352–5359.
12. Reshetnyak AV, Opatowsky Y, Boggon TJ et al. The strength and cooperativity of KIT ectodomain contacts determine normal ligand-dependent stimulation or oncogenic activation in cancer. Mol Cell 2015; 57(1): 191–201.
13. Mol CD, Lim KB, Sridhar V et al. Structure of a c-Kit product complex reveals the basis for kinase transactivation. J Biol Chem 2003; 278(34): 31461–31464.
14. Mol CD, Dougan DR, Schneider TR et al. Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. J Biol Chem 2004; 279(30): 31655–31663.
15. Liang L, Yan X-E, Yin Y, Yun C-H. Structural and biochemical studies of the PDGFRA kinase domain. Biochem Biophys Res Commun 2016; 477(4): 667–672.
16. Garner AP, Gozgit JM, Anjum R et al. Ponatinib inhibits polyclonal drug-resistant KIT oncoproteins and shows therapeutic potential in heavily pretreated gastrointestinal stromal tumor (GIST) patients. Clin Cancer Res 2014; 20(22): 5745–5755.
17. Zhang C, Ibrahim PN, Zhang J et al. Design and pharmacology of a highly specific dual FMS and KIT kinase inhibitor. Proc Natl Acad Sci USA 2013; 110(14): 5689–5694.
18. Hirota S, Nishida T, Isozaki K et al. Gain-of-function mutation at the extracellular domain of KIT in gastrointestinal stromal tumours. J Pathol 2001; 193(4): 505–510.
19. Szucs Z, Thway K, Fisher C et al. Molecular subtypes of gastrointestinal stromal tumors and their prognostic and therapeutic implications. Future Oncol 2017; 13: 93–103.
20. Lasota J, Corless CL, Heinrich MC et al. Clinicopathologic profile of gastrointestinal stromal tumors (GISTs) with primary KIT exon 13 or exon 17 mutations: a multicenter study on 54 cases. Mod Pathol 2008; 21(4): 476–484.
21. McAuliffe JC, Wang W-L, Pavan GM et al. Unlucky number 13? Differential effects of KIT exon 13 mutation in gastrointestinal stromal tumors. Mol Oncol 2008; 2(2): 161–163.
22. Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. Nat Rev Cancer 2009; 9(1): 28–39.
23. Ashman LK, Griffith R. Therapeutic targeting of c-KIT in cancer. Expert Opin Investig Drugs 2013; 22(1): 103–115.
24. Ke H, Kazi JU, Zhao H, Sun J. Germline mutations of KIT in gastrointestinal stromal tumor (GIST) and mastocytosis. Cell Biosci 2016; 6(1): 1–10.
25. Ricci R. Syndromic gastrointestinal stromal tumors. Hered Cancer Clin Pract 2016; 14: 1–15.
26. Diaz LA, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. J Clin Oncol 2014; 32(6): 579–586.
27. Kang G, Sohn BS, Pyo J-S et al. Detecting primary KIT mutations in presurgical plasma of patients with gastrointestinal stromal tumor. Mol Diagn Ther 2016; 20(4): 347–351.
28. Maier J, Lange T, Kerle I et al. Detection of mutant free circulating tumor DNA in the plasma of patients with gastrointestinal stromal tumor harboring activating mutations of CKIT or PDGFRA. Clin Cancer Res 2013; 19(17): 4854–4867.
29. Wada N, Kurokawa Y, Takahashi T et al. Detecting secondary C-KIT mutations in the peripheral blood of patients with imatinib-resistant gastrointestinal stromal tumor. Oncology 2016; 90(2): 112–117.
30. Evans EK, Gardino AK, Kim JL et al. A precision therapy against cancers driven by KIT/PDGFRA mutations. Sci Transl Med 2017; 9(414): eaao1690.
31. DeMatteo RP, Lewis JJ, Leung D et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231(1): 51–58.
32. Heinrich MC, Griffith DJ, Druker BJ et al. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 2000; 96(3): 925–932.
33. Demetri GD, Mehren von M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002; 347(7): 472–480.
34. Blanke CD, Demetri GD, Mehren von M et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008; 26(4): 620–625.
35. Verweij J, Casali PG, Zalcberg J et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004; 364(9440): 1127–1134.
36. Patrikidou A, Dômont J, Chabaud S et al. Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group. Eur J Cancer 2016; 52(C): 173–180.
37. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. JCO 2010; 28(7): 1247–1253.
38. Heinrich MC, Rankin C, Blanke CD et al. Correlation of long-term results of imatinib in advanced gastrointestinal stromal tumors with next-generation sequencing results. JAMA Oncol 2017; 3(7): 944.
39. Wilkinson MJ, Fitzgerald JEF, Strauss DC et al. Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. Br J Surg 2015; 102(8): 965–971.
40. Eisenberg BL, Harris J, Blanke CD et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 2009; 99(1): 42–47.
41. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23(2): 70–83.
42. DeMatteo RP, Ballman KV, Antonescu CR et al. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. Ann Surg 2013; 258(3): 422–429.
43. Joensuu H, Eriksson M, Hall KS, Hartmann JT. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012; 307(12): 1265–1272.
44. Casali PG, Le Cesne A, Poveda Velasco A et al. Time to definitive failure to the first tyrosine kinase inhibitor in localized GI Stromal tumors treated with imatinib as an adjuvant: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma

Group Intergroup Randomized Trial in Collaboration with the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. JCO 2015; 33(36): 4276–4283.
45. Raut CP, Espat NJ, Maki RG et al. Extended treatment with adjuvant imatinib (IM) for patients (pts) with high-risk primary gastrointestinal stromal tumor (GIST): the PERSIST-5 study. J Clin Oncol 2017; 35: 11009.
46. Joensuu H, Wardelmann E, Sihto H et al. Effect of KITand PDGFRAMutations on survival in patients with gastrointestinal stromal tumors treated with adjuvant imatinib. JAMA Oncol 2017; 3(5): 602–608.
47. Hemming ML, Lawlor MA, Zeid R et al. Gastrointestinal stromal tumor enhancers support a transcription factor network predictive of clinical outcome. Proc Natl Acad Sci USA 2018; 96: 201802079–201802010.
48. Wardelmann E, Merkelbach-Bruse S, Pauls K et al. Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. Clin Cancer Res 2006; 12(6): 1743–1749.
49. Antonescu CR, Besmer P, Guo T et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res 2005; 11(11): 4182–4190.
50. Tabone S, Théou N, Wozniak A et al. KIT overexpression and amplification in gastrointestinal stromal tumors (GISTs). Biochim Biophys Acta 2005; 1741(1–2): 165–172.
51. Chen LL, Holden JA, Choi H et al. Evolution from heterozygous to homozygous KIT mutation in gastrointestinal stromal tumor correlates with the mechanism of mitotic nondisjunction and significant tumor progression. Mod Pathol 2008; 21(7): 826–836.
52. Bauer S, Yu LK, Demetri GD, Fletcher JA. Heat shock protein 90 inhibition in imatinib-resistant gastrointestinal stromal tumor. Cancer Res 2006; 66(18): 9153–9161.
53. Agaram NP, Besmer P, Wong GC et al. Pathologic and molecular heterogeneity in imatinib-stable or imatinib-responsive gastrointestinal stromal tumors. Clin Cancer Res 2007; 13(1): 170–181.
54. Gupta A, Roy S, Lazar AJF et al. Autophagy inhibition and antimalarials promote cell death in gastrointestinal stromal tumor (GIST). Proc Natl Acad Sci USA 2010; 107(32): 14333–14338.
55. Demetri GD, Garrett CR, Schoffski P et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res 2012; 18(11): 3170–3179.
56. Demetri GD, Reichardt P, Kang Y-K et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381(9863): 295–302.
57. Liegl B, Kepten I, Le C et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST. J Pathol 2008; 216(1): 64–74.
58. Mir O, Cropet C, Toulmonde M, Le Cesne A. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. Lancet Oncol 2016; doi:10.1016/S1470-2045(16)00075-9.
59. Park SH, Ryu MH, Ryoo BY et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012; 30(6): 2377–2383.
60. Reichardt P, Blay JY, Gelderblom H et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol 2012; 23(7): 1680–1687.
61. Wasag B, Debiec-Rychter M, Pauwels P et al. Differential expression of KIT/PDGFRA mutant isoforms in epithelioid and mixed variants of gastrointestinal stromal tumors depends predominantly on the tumor site. Mod Pathol 2004; 17(8): 889–894.
62. Pauls K, Merkelbach-Bruse S, Thal D et al. PDGFRalpha- and c-kit-mutated gastrointestinal stromal tumours (GISTs) are characterized by distinctive histological and immunohistochemical features. Histopathology 2005; 46(2): 166–175.
63. Lasota J, Dansonka-Mieszkowska A, Sobin LH, Miettinen M. A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. Lab Invest 2004; 84(7): 874–883.
64. Capelli L, Petracci E, Quagliuolo V et al. Gastric GISTs: analysis of c-Kit, PDGFRA and BRAF mutations in relation to prognosis and clinical pathological characteristics of patients—a GIRCG study. Eur J Surg Oncol 2016; 42(8): 1206–1214.
65. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. Histopathology 2008; 53(3): 245–266.
66. Cassier PA, Fumagalli E, Rutkowski P et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Clin Cancer Res 2012; 18(16): 4458–4464.
67. Andersson J, Sihto H, Meis-Kindblom JM et al. NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. Am J Surg Pathol 2005; 29(9): 1170–1176.
68. Boikos SA, Pappo AS, Killian JK et al. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors. JAMA Oncol 2016; 2(7): 922–927.
69. Hostein I, Faur N, Primois C et al. BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol 2010; 133(1): 141–148.
70. Brenca M, Rossi S, Polano M et al. Transcriptome sequencing identifies ETV6-NTRK3 as a gene fusion involved in GIST. J Pathol 2015; 238: 543–549.
71. Shi E, Chmielecki J, Tang C-M et al. FGFR1 and NTRK3 actionable alterations in "Wild-Type" gastrointestinal stromal tumors. J Transl Med 2016; 14(1): 339–349.
72. Shaw AT, Friboulet L, Leshchiner I et al. Resensitization to crizotinib by the lorlatinib ALK resistance mutation L1198F. N Engl J Med 2016; 374(1): 54–61.
73. Cortes JE, Kim DW, Pinilla-Ibarz J et al. A phase 2 trial of ponatinib in Philadelphia chromosome–positive leukemias. N Engl J Med 2013; 369(19): 1783–1796.
74. Gramza AW, Corless CL, Heinrich MC. Resistance to tyrosine kinase inhibitors in gastrointestinal stromal tumors. Clin Cancer Res 2009; 15(24): 7510–7518.
75. Heinrich MC, Owzar K, Corless CL et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. JCO 2008; 26(33): 5360–5367.
76. Heinrich MC, Corless CL, Blanke CD et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006; 24(29): 4764–4774.
77. George S, Wang Q, Heinrich MC et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable gi stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. J Clin Oncol 2012; 30(19): 2401–2407.
78. Heinrich MC, Griffith D, McKinley A et al. Crenolanib inhibits the drug-resistant PDGFRA D842V mutation associated with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res 2012; 18(16): 4375–4384.
79. Galanis A, Ma H, Rajkhowa T et al. Crenolanib is a potent inhibitor of FLT3 with activity against resistance-conferring point mutants. Blood 2014; 123(1): 94–100.
80. Heinrich MC, Jones RL, Mehren MD, von M et al. Clinical activity of BLU-285 in advanced gastrointestinal stromal tumor (GIST). Am Soc Clin Oncol 2017; 35: 11011.
81. Kornev AP, Haste NM, Taylor SS, Eyck LFT. Surface comparison of active and inactive protein kinases identifies a conserved activation mechanism. Proc Natl Acad Sci USA 2006; 103(47): 17783–17788.
82. Chan WW, Wise SC, Kaufman MD et al. Conformational control inhibition of the BCR-ABL1 tyrosine kinase, including the Gatekeeper T315I

mutant, by the switch-control inhibitor DCC-2036. Cancer Cell 2011; 19(4): 556–568.
83. Nagar B, Bornmann WG, Pellicena P et al. Crystal structures of the kinase domain of c-Abl in complex with the small molecule inhibitors PD173955 and imatinib (STI-571). Cancer Res 2002; 62(15): 4236–4243.
84. Smith BD, Hood MM, Wise SC et al. DCC-2618 is a potent inhibitor of wild-type and mutant KIT, including refractory exon 17 D816 KIT mutations, and exhibits efficacy in refractory GIST and AML xenograft models. Am Assoc Cancer Res 2015; 75: 2690.
85. Rose S. BLU-285, DCC-2618 Show Activity against GIST. Cancer Discov. 2017; 7(2): 121.3–122.
86. Sidera K, Patsavoudi E. HSP90 inhibitors: current development and potential in cancer therapy. Recent Pat Anticancer Drug Discov 2014; 9(1): 1–20.
87. Smyth T, Van Looy T, Curry JE et al. The HSP90 inhibitor, AT13387, is effective against imatinib-sensitive and -resistant gastrointestinal stromal tumor models. Mol Cancer Ther 2012; 11(8): 1799–1808.
88. Demetri GD, Heinrich MC, Chmielowski B. An open-label phase II study of the Hsp90 inhibitor ganetespib (STA-9090) in patients (pts) with metastatic and/or unresectable GIST. J Clin Oncol 2011; 29: 10011.
89. Bendell JC, Bauer TM, Lamar R et al. A phase 2 study of the Hsp90 inhibitor AUY922 as treatment for patients with refractory gastrointestinal stromal tumors. Cancer Invest 2016; 34(6): 265–270.
90. Wagner AJ, Agulnik M, Heinrich MC et al. Dose-escalation study of a second-generation non-ansamycin HSP90 inhibitor, onalespib (AT13387), in combination with imatinib in patients with metastatic gastrointestinal stromal tumour. Eur J Cancer 2016; 61(C): 94–101.
91. Muhlenberg T, Zhang Y, Wagner AJ et al. Inhibitors of deacetylases suppress oncogenic KIT signaling, acetylate HSP90, and induce apoptosis in gastrointestinal stromal tumors. Cancer Res 2009; 69(17): 6941–6950.
92. Edris B, Willingham S, Weiskopf K et al. Anti-KIT monoclonal antibody inhibits imatinib-resistant gastrointestinal stromal tumor growth. OncoImmunology 2013; 2(6): e24452.
93. Loizos N, Xu Y, Huber J et al. Targeting the platelet-derived growth factor receptor alpha with a neutralizing human monoclonal antibody inhibits the growth of tumor xenografts: implications as a potential therapeutic target. Mol Cancer Ther 2005; 4(3): 369–379.
94. Tap WD, Jones RL, Van Tine BA et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016; 388(10043): 488–497.
95. Wagner AJ, Kindler H, Gelderblom H et al. A phase II study of a human anti-PDGFRα monoclonal antibody (olaratumab, IMC-3G3) in previously treated patients with metastatic gastrointestinal stromal tumors. Ann Oncol 2017; 28(3): 541–546.
96. Patel S. Exploring novel therapeutic targets in GIST: focus on the PI3K/Akt/mTOR pathway. Curr Oncol Rep 2013; 15(4): 386–395.
97. Van Looy T, Wozniak A, Floris G et al. Phosphoinositide 3-kinase inhibitors combined with imatinib in patient-derived xenograft models of gastrointestinal stromal tumors: rationale and efficacy. Clin Cancer Res 2014; 20(23): 6071–6082.
98. Zook P, Pathak HB, Belinsky M et al. Combination of imatinib mesylate and AKT inhibitor provides synergistic effects in preclinical study of gastrointestinal stromal tumor. Clin Cancer Res 2016; doi: 10.1158/1078-0432.CCR-16-0529.
99. Ran L, Sirota I, Cao Z et al. Combined inhibition of MAP kinase and KIT signaling synergistically destabilizes ETV1 and suppresses GIST tumor growth. Cancer Discov 2015; 5(3): 304–315.
100. Bauer S, Duensing A, Demetri GD, Fletcher JA. KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: pI3-kinase/AKT is a crucial survival pathway. Oncogene 2007; 26(54): 7560–7568.
101. Schoffski P, Reichardt P, Blay JY et al. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Ann Oncol 2010; 21(10): 1990–1998.
102. Conley AP, Araujo D, Ludwig J et al. A randomized phase II study of perifosine (P) plus imatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). J Clin Oncol 2009; 27(15S): 10563–10563.
103. Javidi-Sharifi N, Traer E, Martinez J et al. Crosstalk between KIT and FGFR3 promotes gastrointestinal stromal tumor cell growth and drug resistance. Cancer Res 2015; 75(5): 880–891.
104. Li F, Huynh H, Li X et al. FGFR-mediated reactivation of MAPK signaling attenuates antitumor effects of imatinib in gastrointestinal stromal tumors. Cancer Discov 2015; 5(4): 438–451.
105. van Dongen M, Savage NDL, Jordanova ES et al. Anti-inflammatory M2 type macrophages characterize metastasized and tyrosine kinase inhibitor-treated gastrointestinal stromal tumors. Int J Cancer 2010; 127: 899–909.
106. Menard C, Blay JY, Borg C et al. Natural killer cell IFN-levels predict long-term survival with imatinib mesylate therapy in gastrointestinal stromal tumor-bearing patients. Cancer Res 2009; 69(8): 3563–3569.
107. Balachandran VP, Cavnar MJ, Zeng S et al. Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido. Nat Med 2011; 17(9): 1094–1100.
108. Seifert AM, Zeng S, Zhang JQ et al. PD-1/PD-L1 blockade enhances T-cell activity and antitumor efficacy of imatinib in gastrointestinal stromal tumors. Clin Cancer Res 2017; 23(2): 454–465.
109. Tan Y, Trent JC, Wilky BA et al. Current status of immunotherapy for gastrointestinal stromal tumor. Cancer Gene Ther 2017; 24(3): 130–133.
110. D'Angelo SP, Shoushtari AN, Keohan ML et al. Combined KIT and CTLA-4 blockade in patients with refractory GIST and other advanced sarcomas: a phase Ib study of dasatinib plus ipilimumab. Clin Cancer Res 2016; doi:10.1158/1078-0432.CCR-16-2349.