Inhibition of KIT Tyrosine Kinase Activity: Two Decades After the First Approval

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INTRODUCTION

In 2002, we published a review in *Journal of Clinical Oncology* examining the potential of KIT inhibition to treat advanced cancer.[1] At that time, imatinib was the first and only US Food and Drug Administration–approved kinase inhibitor and there were many unanswered questions (Table 1). Now, nearly 20 years later, there are five FDA-approved KIT-targeted kinase inhibitors, including imatinib. We have learned a great deal more about KIT and how mutations affect its function. We have also elucidated how specific secondary KIT mutations confer drug resistance in patients. This review will explore the journey of therapeutic KIT targeting that began with imatinib 20 years ago. We will discuss the basic research and clinical findings that informed the development of additional KIT inhibitors and how they were successfully integrated into patient care to combat resistance. We will make comparisons between the two malignancies that have been most significantly affected by KIT-targeted therapies, GI stromal tumor (GIST) and mast cell malignancies, to highlight the importance of genetic profiling in informing treatment success. Furthermore, we will discuss the lessons learned through the development of the five FDA-approved KIT targeted therapies (Table 2) and predictions for the future of the field.

HISTORICAL DEVELOPMENTS

Precision medicine, or targeted therapy, as a paradigm for cancer treatment is a relatively recent development. It began with the discovery that recurrent activating mutations in oncogenes can drive cancer development and sustain cell proliferation and survival. Chemical compounds were identified that have the ability to block the activity of mutant enzymes and thus reduce tumor viability, revolutionizing cancer treatment. The first, and most significant, of these compounds was imatinib (originally known as CGP57418B or STI-571), an inhibitor of BCR-ABL1, the oncogenic driver in chronic myeloid leukemia (CML).[2] After extensive testing in preclinical models, imatinib demonstrated both safety and efficacy in CML, moving quickly from phase I through III, as it surpassed the standard of care (interferon plus cytarabine).[3-5] Based on these studies, in 2001, imatinib set a new record for fastest FDA approval (Fig 1).

As the first successful targeted cancer therapy, imatinib opened the door for a new way of thinking about the treatment of cancers driven by distinct oncogenic mutations. At that time, evidence was building that *KIT* serves as an oncogene in several cancers and was therefore a logical therapeutic target. KIT, a member of the type III receptor tyrosine kinase (RTK) family, was originally discovered through the viral oncogene v-kit, encoded by the Harvey-Zuckerman-4 strain of the feline sarcoma virus.[6-8] Activating human KIT mutations were first identified in systemic mastocytosis (SM) cell lines and in humans with SM[9,10] (Fig 1). A few years later, Hirota et al reported activating KIT mutations in GI mesenchymal tumors that came to be known as GIST. Unlike BCR-ABL1, which is a fusion gene product, mutations in *KIT* were point mutations or small indels distributed throughout the kinase domain, and the location of mutations differed by tumor type.

From these early studies, it was apparent that KIT mutations are important in both SM and GIST, but there are important differences. It is now appreciated that > 80% of SM cases in adults have *KIT* mutations with the majority occurring in the activation loop (AL, *KIT* exon 17), the dominant being D816V (Fig 2). Rarely adult SM patients have mutations affecting the KIT extracellular (encoded by *KIT* exons 8 and 9), transmembrane (*KIT* exon 10), or juxtamembrane (JM, *KIT* exon 11) domains. Interestingly, these mutations are much more frequent in pediatric SM cases, of which 75% are KIT mutant.[11,12] In contrast, more than 70% of mutations in GIST involve the JM domain.[13-15] Mutations of the KIT extracellular domain and kinase domain (*KIT* exons 13 or 17) are found in a minority of GIST.[14,16,17] Notably, the D816V mutation typical of adult mast cell neoplasms has not been observed as a primary mutation in GIST, but other AL (*KIT* exon 17) mutations do rarely occur (Fig 2).[14,15,18]

The clinical success of imatinib in CML and the growing interest in targeting KIT led to efforts to identify a KIT inhibitor suitable for clinical testing. Originally, KIT was not an identified target of imatinib, but based on its activity against the homologous PDGFRA and PDGFRB RTKs, the ability of imatinib to inhibit ligand-activated KIT was investigated. This was the first example of drug repurposing to inhibit a target other than that for which it was originally designed. Imatinib was found to inhibit

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Accepted on February 25, 2021 and published at ascopubs.org/journal/jco on April 2, 2021: DOI https://doi.org/10.1200/JCO.20.03245

CONTEXT

Key Objective

Imatinib, the first kinase inhibitor for cancer treatment, was developed over 20 years ago. In that time, imatinib as a KIT-targeted therapy revolutionized the treatment of patients with KIT-driven malignancies, primarily GI stromal tumor and systemic mastocytosis, and led to the development of additional KIT inhibitors that have significantly improved patient outcomes. We explore the history of KIT-targeted therapies beginning with imatinib.

Knowledge Generated

Numerous lessons have been learned from the initial preclinical and clinical studies with imatinib and other KIT inhibitors. The clinical use of imatinib has also provided the basis to understand the molecular properties of KIT and its interactions with drugs, allowing for rational design of more successful KIT inhibitors.

Relevance

The development of imatinib, as well as later-line KIT-targeted kinase inhibitors, has transformed the way we treat GI stromal tumors and mast cell malignancies. Further understanding of KIT biology and resistance mechanisms will further inform and refine our treatment of KIT-driven diseases.

not only wild-type KIT with similar potency to the BCR-ABL1 and PDGFRA/B but also potently the KIT JM–mutant kinase activity, like those most commonly described in GIST.[19,20] No activity, however, was seen against KIT with compound JM + D816V mutations for reasons that were unknown at the time.[21,22] Further preclinical testing demonstrated that imatinib decreased proliferation and survival in the first KIT-mutant GIST cell line, indicating the oncogenic dependence of GIST cells on the kinase activity of mutated KIT.[23]

As the previous century ended, the stage was set for testing imatinib in GIST and mast cell neoplasms. The available preclinical data predicted that imatinib might be effective for treating GIST, which typically expresses imatinib-sensitive KIT JM mutations, but was unlikely to be effective against the majority of mast cell neoplasms that express the imatinib-resistant KIT D816V. In retrospect, these preclinical results not only were excellent predictors of the primary response outcomes in human studies of imatinib but also predicted how compound mutations in different parts of the kinase domain differentially affect kinase conformation and thus drug binding. As discussed below, the limitations of imatinib drove serial efforts to produce more potent KIT inhibitors for patients with GIST and SM.

IMATINIB, THE FIRST CLINICALLY EFFECTIVE KIT INHIBITOR

GIST Clinical Studies

The first clinical success with imatinib in GIST was seen in the treatment of a single patient with heavily chemotherapy

TABLE 1. Outstanding Questions 2000 Versus 2020

Topic	Outstanding Questions in 2000	Outstanding Questions in 2020
Treatment	What are the side effects of long-term imatinib treatment? What is the potential of KIT TKI for treating acute myelogenous leukemia, melanoma, germ cell tumors, and other cancers?[a] Are KIT overexpressing cancers treatable with KIT inhibitors?	What are the side effects of new type I and switch pocket KIT TKIs? Can combination treatments be developed? How to use KIT inhibitors in SM-AHN where there is a complex mutational landscape beyond KIT, which reflects the associated hematologic neoplasm?
KIT biology	How do somatic mutations activate KIT? Which KIT mutations are sensitive to imatinib?	Can agents that selectively degrade KIT be developed, thereby enabling mutation agnostic therapy? Is it possible for a single inhibitor to be effective against ATP binding pocket and AL mutations?
Resistance	What are the potential mechanisms of resistance to imatinib and how can they be overcome? How can we design new and better KIT inhibitors?	What are the resistance mechanisms to new type I and switch pocket KIT TKIs? With the use of multiple lines of KIT inhibitors, will tumors eventually become KIT-independent? Can mutation agnostic therapies be developed to control advanced disease?

Abbreviations: AL, activation loop; AML, acute myeloid leukemia; NCCN, National Comprehensive Cancer Network; SM, systemic mastocytosis; SM-AHN, SM with associated hematological neoplasm; TKI, tyrosine kinase inhibitor.

[a]Clinical testing of imatinib in other tumors with activating KIT mutations, including germ cell tumors, and rare subsets of melanoma and AML had disappointing results, with the exception of KIT-mutant melanoma, in which some activity of imatinib was noted.[50,133-143] NCCN guidelines suggest imatinib be considered as a second-line treatment of KIT-mutant melanoma, after progression or intolerance of a first-line immunotherapy regimen.[144]

TABLE 2. Summary of FDA-Approved KIT-Targeted Therapies

Drug Name (Alternative Name)	TKI Class	Original Targets	Approved GIST Indication	Approved SM Indication
Imatinib (STI-571)	Type II	BCR-ABL1	Patients with KIT (CD117)-positive unresectable and/or metastatic malignant GIST[38]	Adult patients with ASM without the D816V c-KIT mutation or with cKIT mutational status unknown[51]
Sunitinib	Type II	VEGFR and FLT3	GIST after disease progression on or intolerance to imatinib mesylate[145]	NA
Regorafenib	Type II	VEGFR	Locally advanced, unresectable, or metastatic GIST that has been previously treated with imatinib, mesylate, and sunitinib malate[146]	NA
Midostaurin (PKC412)	Type I	PKC	NA	ASM, SM-AHN, or MCL[116]
Ripretinib (DCC-2618)	Type II[a]	KIT	Indicated for the treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib[107]	NA
Avapritinib (BLU-285)	Type I	KIT/ PDGFRA	Not approved for KIT-mutant GIST, but approved for PDGFRA exon 18-mutant GIST[147]	NA[b]

Abbreviations: ASM, aggressive systemic mastocytosis; FDA, US Food and Drug Administration; GIST, GI stromal tumor; MCL, mast cell leukemia; NA, not available; SM, systemic mastocytosis; SM-AHN, SM with associated hematological neoplasm; TKI, tyrosine kinase inhibitor.

[a]Ripretinib is a type II inhibitor, but is not ATP-competitive.

[b]Approval of avapritinib for advanced SM (and possibly indolent SM) anticipated for 2021-2022 time frame.

pretreated, KIT JM–mutant GIST.[24] This small proof-of-concept trial was initiated amid concerns over drug absorption in patients with GIST, many of whom had undergone resection of the gut (stomach, small bowel, or colon), as well as drug metabolism, since these patients often had liver metastases and/or prior hepatic surgery.[25-27] Despite these concerns, the first patient's tumor showed a complete metabolic response and a 52% decrease in size after one month. Imatinib was well-tolerated, and the side effect profile was consistent with those reported in CML.[24] Based on these results, two randomized phase I-II studies were opened in the United States and Europe in 2000.[28-30] In both studies, the objective response rate (ORR) was approximately 67% and no new imatinib safety signals were noted.[27,31] Two large randomized phase III studies confirmed the efficacy of imatinib in GIST, with an ORR of approximately 50%, a median progression-free survival (PFS) of around 2 years, and a median overall survival (OS) of 4-5 years.[32-35] More recently, long-term follow-up of these phase III studies has estimated 10-year PFS and OS rates of 8% and 20%, respectively.[36,37] Imatinib was granted FDA approval for treatment of unresectable, recurrent, and/or metastatic GIST in February 2002, just nine months after its initial approval for CML[38] (Fig 1). Additional accelerated and subsequently regular approvals for the adjuvant treatment of patients following complete gross resection of GIST were granted in 2008 and 2012, respectively.[39]

Mastocytosis

Although the majority of KIT-mutant GIST have imatinib-sensitive mutations, the converse is true in SM. The D816V mutation is resistant, and only a small number of other KIT mutations are imatinib sensitive (Fig 2).[20,22,40-43] These preclinical observations were confirmed in the initial clinical studies in mastocytosis, where the majority of patients who had meaningful responses to imatinib were those with co-existent eosinophilia. Further analysis of these exceptional responders, as well as patients with hypereosinophilic syndrome without a diagnosis of SM, identified a chromosomal translocation producing the imatinib-sensitive FIP1L1-PDGFRA fusion kinase as the underlying molecular basis for response.[44,45] Based on these observations, in 2008, the WHO reclassified these cases as myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA, PDGFRB, FGFR1*, or *PCM-JAK2*.

In contrast, SM patients with the typical D816V had minimal or no response to imatinib, whereas the rare patients with imatinib-sensitive mutations involving *KIT* exons 8, 9, 10, or 17 were observed to have very good responses to imatinib.[46-50] In addition, some responses were noted in SM patients with no molecular analysis of *KIT* or *PDGFRA* mutations. In October 2006, the FDA approved imatinib for treatment of patients with aggressive SM whose disease had no detectable KIT D816V mutation or had an unknown *KIT* mutational status (Fig 1).[51] However, in retrospect, it is likely that many of these cases had imatinib-sensitive mutations that were not identified because of an incomplete spectrum of mutational analysis or insensitive technologies for detecting mutations in a background of normal cells.[12,52,53]

Lessons Learned From the Initial Experience in Treating KIT-Mutant Malignancies With Imatinib

Despite initial concerns that a potent KIT inhibitor might cause unacceptable short-term or long-term toxicities,

especially in terms of myelosuppression, the data from the initial imatinib studies in CML and GIST revealed an acceptable safety profile. Many patients have now been treated for more than a decade or two without any known long-term side effects. This important finding from the early imatinib studies generated interest in developing additional KIT kinase inhibitors.[36,54,55]

The results from the early imatinib studies in treating GIST and SM demonstrated a strong relationship between the underlying oncogenic mutation and drug response. In GIST, the best outcomes were seen with patients with KIT JM–mutant tumors.[56,57] Randomized phase III studies demonstrated that patients with *KIT* exon 9-mutant GIST respond better to high-dose imatinib (800 mg daily),

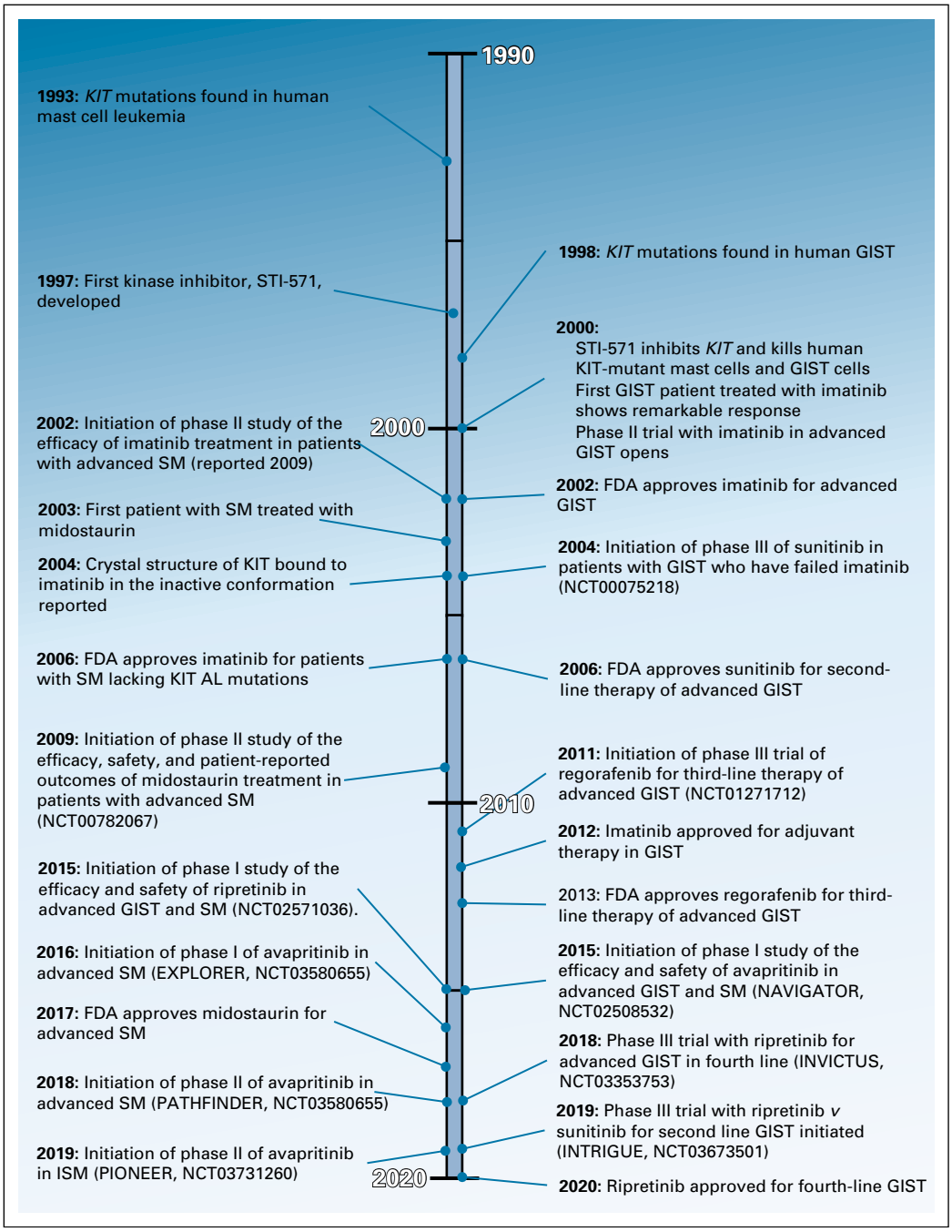

FIG 1. Significant milestones in KIT-targeted treatment (1990-2020). Events shown chronologically from top to bottom. Events relevant to mast cell disease shown on the left and those for GIST on the right. AL, activation loop; FDA, US Food and Drug Administration; GIST, GI stromal tumor; ISM, indolent systematic mastocytosis; SM, systemic mastocytosis.

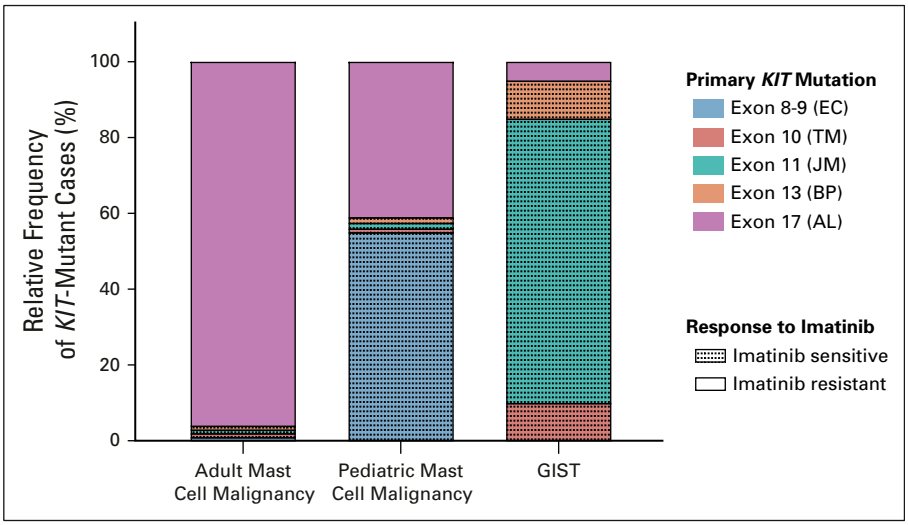

FIG 2. Frequency of activating primary *KIT* mutations observed in *KIT*-mutant GIST and mast cell malignancies. Relative frequency of *KIT* mutations seen in *KIT*-mutant cases only. *KIT* mutations are seen in > 80% of adult mast cell malignancies, 75% of pediatric mast cell malignancies, and 75%-80% of GIST; EC, TM, JM, BP, and AL. Dotted shading indicates mutations in tumors that typically respond to imatinib treatment. AL, activation loop; BP, binding pocket; EC, extracellular; GIST, GI stromal tumor; JM, juxtamembrane; TM, transmembrane.

whereas patients with KIT JM–mutant GIST had similar outcomes with standard (400 mg daily) or high doses.[32,58] Additionally, patients with GIST lacking KIT mutations rarely responded to imatinib, but analysis of the few responsive cases revealed imatinib-sensitive PDGFRA mutations as the basis for response.[57,59,60] However, the majority of PDGFRA-mutant GIST have an imatinib-resistant mutation, PDGFRA D842V, which is homologous to the KIT D816V mutation seen in SM.[59,60] Based on these observations, a molecular classification of GIST was proposed and has been used to guide therapy and also to focus discovery efforts on subsets of GIST lacking any definable oncogenic mutations[16,26] After two decades of research, the pathogenic cause of more than 99% cases of GIST can be identified and used to guide therapy.[61]

As noted above, imatinib was successfully repurposed from the BCR-ABL1 kinase inhibitor development program to target KIT. This paradigm has been extended in other diseases, where a kinase inhibitor used to target one particular kinase can be clinically expanded to homologous oncogenic kinases in the same or different diseases.[62,63] Adoption of imatinib as a KIT inhibitor helped lay the foundation for what has become a molecularly focused, histology agnostic approach to drug development.[64]

When imatinib was identified using high-throughput chemical compound screens, there were no crystal structures for ABL1 or KIT. When Schindler et al[65] reported the crystal structure of the ABL1 catalytic domain complexed with an imatinib analog, it was revealed that imatinib bound to the inactive conformation of ABL1 Subsequently, a similar mode of imatinib binding to the inactive KIT structure was reported (Fig 1).[66] Thus, imatinib is classified as a type II kinase inhibitor (binds to the inactive structure).[67] These results suggested that mutations of the AL that stabilize the active conformation of KIT would result in imatinib resistance, explaining the differential activity of imatinib against the typical GIST-associated KIT JM mutations (inactive conformation favored) versus the typical SM KIT D816V mutation (active conformation strongly favored).[68,69] Based on these and other considerations, structural biology-guided drug design became standard practice in drug development programs.[67,70-72]

Consistent with the observation that imatinib binds to the inactive KIT conformation, secondary mutations involving the KIT AL were discovered to be a common cause of acquired imatinib resistance in GIST. The other major class of secondary resistance mutations involves the KIT ATP (and imatinib) binding pocket (Fig 3).[73-78] Largely parallel to conclusions from the analysis of secondary ABL1 mutations in imatinib-resistant CML, these observations supported that KIT-mutant GIST remained strongly dependent upon KIT signaling.[79-82] This conclusion led to the hypothesis that imatinib-resistant GIST might be effectively treated using alternative KIT tyrosine kinase inhibitors (TKIs) that could overcome AL or ATP binding pocket mutations.

Development of Additional Type II Inhibitors for Imatinib-Resistant GIST

By the time resistance to imatinib was fully appreciated, many other kinase inhibitors had been created. The discovery that drug-resistant, KIT-mutant GIST remained KIT-dependent led to the development of salvage treatments for

imatinib-resistant GIST. The first of these to be tested clinically was sunitinib, originally known as SU11248 and developed as an inhibitor of FLT3, which is an RTK closely related to KIT.[77,83-85] Promising activity in a phase I-II study led to a randomized, double-blind, placebo-controlled, multicenter, international trial,[77,86,87] which led to the 2007 FDA approval of sunitinib for treatment of patients with GIST with disease progression or intolerance to imatinib.[88] A number of other repurposed KIT inhibitors were tested for treatment of imatinib-resistant GIST, including dasatinib, sorafenib, and nilotinib.[89-93] However, neither dasatinib nor sorafenib advanced to phase III studies (because of insufficient activity and competing kinase development programs, respectively). A phase III study to test the superiority of nilotinib versus imatinib for the front-line treatment of GIST was terminated early because of futility.[94] In contrast, another multitargeted kinase inhibitor with activity against KIT, regorafenib, was successfully tested in both a phase II and a placebo-controlled, double-blind, multicenter, international phase III study.[95,96] Despite the lack of a survival benefit in this or in the sunitinib study, real-world data from a large patient-reported registry strongly suggest that the availability of additional lines of therapy after front-line imatinib has improved OS for patients with advanced GIST during the 2000-2020 time period.[97]

The results of these studies showed the limitations of serial treatment with type II inhibitors, as the ORR decreased from around 50% with front-line imatinib to only 4.5% with third-line regorafenib. There was a corresponding decrease in median PFS, dropping from approximately 20-22 months with imatinib to 4.8 months with regorafenib.[26,34,35,37,87,96] These results are explained by in vitro studies showing that sunitinib is active against all secondary KIT ATP-binding pocket mutations (V654A and T670I), but has minimal activity against AL mutations (D816V, D820A, etc).[77,98] In contrast, regorafenib has limited activity against secondary KIT mutations located in the ATP binding pocket, but clinically useful activity against (some but not all) AL mutations.[98] Given the widespread heterogeneity of clones with different secondary mutations between lesions and within a given lesion,[99] it is likely that we are nearing the limits of what conventional type II inhibitors can deliver in the setting of advanced, drug-resistant GIST (Fig 3).

Attempts to Develop Type I KIT Inhibitors to Treat GIST

Based on the above observations, several type I inhibitors that target the active conformation of KIT have been tested for treatment of advanced GIST. Ponatinib, a TKI approved for treatment of CML and acute lymphoblastic leukemia, showed promising activity in vitro against secondary KIT AL mutations, but failed to demonstrate sufficient activity in a phase II study of drug-resistant GIST.[100] The results from this study have not been fully reported, but based on in vitro data, it is likely that ponatinib lacked sufficient potency against the common KIT V654A (ATP binding pocket) secondary mutation to produce meaningful disease control.[101]

More recently, a rationally designed type I KIT inhibitor, avapritinib (formerly BLU-285), has been clinically developed. This compound was designed by optimizing activity against the prototypical KIT AL mutation, D816V, an approach that differed from testing repurposed compounds against wild-type or KIT JM–mutant kinases. The end result of this screening approach yielded a compound with marked potency against all KIT AL mutations, including KIT D816V.[102-104] Avapritinib showed promising activity against drug-resistant KIT-mutant GIST in a phase I study, but overall clinical activity was limited by a lack of potency against KIT ATP binding pocket mutations.[105] Recently, the top-line data of a phase III randomized study of avapritinib versus regorafenib for patients with GIST who experience treatment failure during prior imatinib and sunitinib therapy were reported (VOYAGER, ClinicalTrials.gov identifier: NCT03465722). Unfortunately, avapritinib did not confer treatment benefit in terms of median PFS compared with regorafenib. However, it should be noted that avapritinib has strong clinical activity against the PDGFRA D842V mutation, homologous to KIT D816V, which is found as a primary mutation in 7%-10% of all primary GIST.[104,106] In January 2020, avapritinib was FDA-approved for treatment of GIST with a *PDGFRA* exon 18 mutation (Fig 1).[107]

Development of Type I KIT Inhibitors for Mastocytosis

The primary KIT AL mutation, D816V, in patients with SM presented an urgent clinical challenge that required the development of type I KIT inhibitors from the start. In vitro studies of the type I inhibitor dasatinib demonstrated activity against D816V-mutant KIT.[22,41] However, when this agent was tested in a phase II study of patients with indolent or advanced SM,[108] the ORR was 33% (11 of 33), and the only two complete responses were in patients whose disease lacked the KIT D816V mutation. The partial responses observed in the other nine patients were due to improved symptoms only, with no objective evidence of decreased neoplastic mast cell numbers using laboratory or pathology testing methods.

Subsequently, several new type I inhibitor therapies for treatment of KIT D816V+ advanced SM have shown substantial clinical activity. Midostaurin (formerly PKC412), a staurosporine derivative, emerged from a chemical screen of protein kinase C inhibitors and was later found to also inhibit VEGFRs, PDGFRs, KIT, and FLT3. Activity of midostaurin against KIT D816V was demonstrated in several preclinical models including cell lines and malignant mast cells isolated from patients with SM.[109-112] Much like during the development of imatinib to treat GIST, these preclinical observations led to the testing of midostaurin in a single patient with mast cell leukemia as part of a compassionate use protocol (Fig 1). This patient had evidence of a partial clinical and molecular response with an 80%

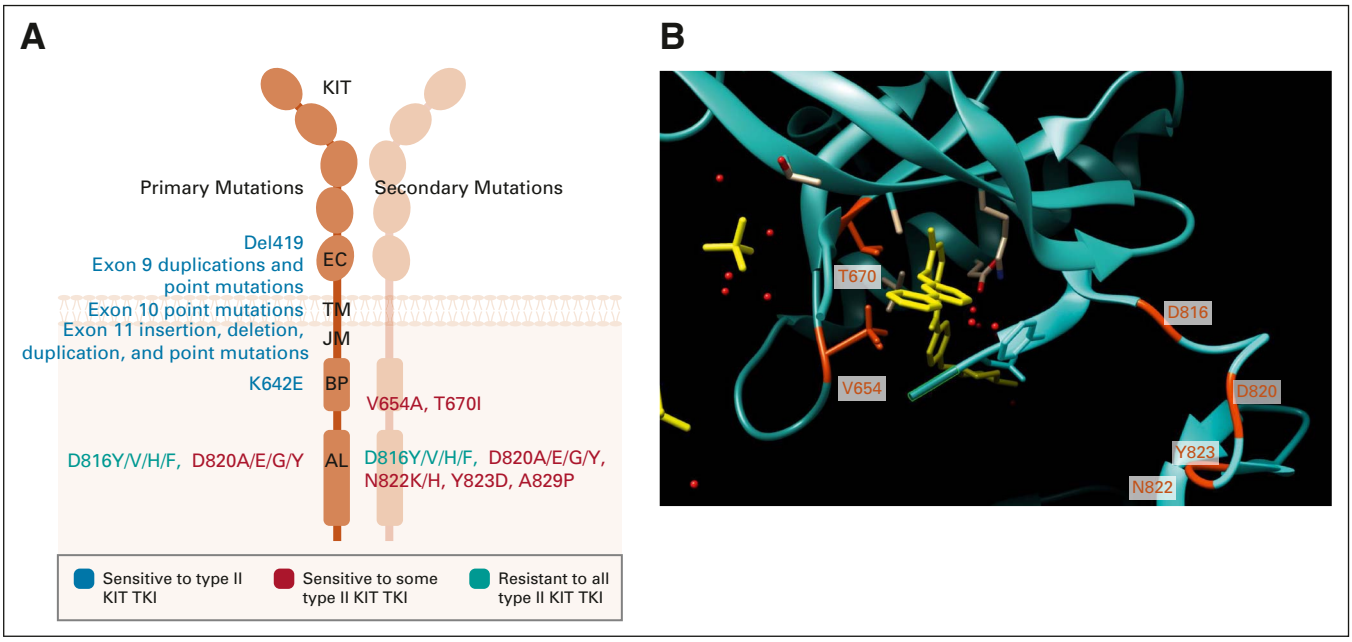

FIG 3. KIT primary mutations are largely sensitive to type II KIT TKIs, whereas KIT secondary mutations confer resistance. (A) Schematic of locations of primary and secondary KIT mutations observed in mast cell malignancies and GIST with their corresponding sensitivity to type II KIT TKIs. Created using BioRender. (B) Three-dimensional model of KIT (blue-green) in an inactive conformation bound to imatinib (yellow). Common secondary resistance mutation sites are highlighted in red-orange (T670 and V654 within the binding pocket) and in cyan (D816, D820, N822, and Y823 within the AL). Molecular graphics and analyses performed using UCSF Chimera, developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, with support from NIH P41-GM103311.[132] AL, activation loop; BP, binding pocket; EC, extracellular; GIST, GI stromal tumor; JM, juxtamembrane; TKI, tyrosine kinase inhibitor; TM, transmembrane.

decrease in the level of detectable KIT D816V in the peripheral blood.[113] Based in part on the results from this single patient treatment protocol, midostaurin was evaluated in two phase II studies, an open-label, international, multisite study and a study that reported patient outcomes with a 10-year median follow-up time.[114,115] Overall, midostaurin treatment was found to be well-tolerated and highly effective. The initial response rate of patients with SM to midostaurin was 60%-69%.[114,115] The median OS was 28.7 months, and the median PFS was 14.1 months.[115] Moreover, with a 10-year follow-up, little toxicity was observed.[114] Based on these results, the FDA approved midostaurin for treatment of advanced SM in 2017 (Fig 1).[116]

The novel type I inhibitor, avapritinib, also demonstrated promising in vitro and clinical activity against D816V-mutant mast cells. In the latest update from a phase I study (EXPLORER, ClinicalTrials.gov identifier: NCT02561988) of avapritinib in advanced SM, the ORR was 75%, with 70% reporting complete or partial responses.[117] Notably, avapritinib induced responses in patients regardless of prior midostaurin therapy, and these responses were rapid and long-lasting. In the phase I EXPLORER study, 25% of patients achieved a complete molecular response of the KIT D816V mutation using digital droplet PCR (sensitivity approximately 0.17%), a new response benchmark in the disease.[117,118] Avapritinib is undergoing further testing in a multicenter phase II study (PATHFINDER, ClinicalTrials.gov identifier: NCT03580655). Based on its activity in advanced SM and favorable side effect profile, avapritinib is also being examined in patients with indolent or smoldering SM whose symptoms are inadequately controlled by standard therapy (PIONEER, ClinicalTrials.gov identifier: NCT03731260).[119] This study includes a randomized, double-blind, placebo-controlled component. The clinical evidence to date suggests that avapritinib has a high potential to be approved as an additional therapy for SM, potentially for both advanced and indolent SM.

To date, clinical mechanisms of resistance to midostaurin or avapritinib in SM are not well-understood. In vitro studies of these agents have suggested that the previously described KIT V654A or T670I secondary mutations may result in midostaurin or avapritinib resistance.[103,120] Increased variant allele frequency of non-*KIT* mutations such as *K/NRAS, RUNX1, IDH2*, or *NPM1* has also been associated with clinical resistance to midostaurin.[121] In addition to the problems with emergence of drug-resistant mastocytosis clones, there still remains the challenge of how best to treat patients who have SM with an associated hematological neoplasm.[122]

Ripretinib, the Most Recently Approved KIT Inhibitor

Ripretinib (formerly DCC-2618) emerged from a program to develop novel inhibitors that bind to the switch control

region of kinases, rather than the ATP-binding pocket.[123-126] This discovery program used the known KIT structure to develop compounds that bind to the kinase switch pocket, therefore preventing the AL access to this region and thereby locking the kinase into the inactive state. In addition, ripretinib binds to the KIT AL to further secure it in the inactive state. Unlike all of the previously discussed inhibitors, ripretinib is not a competitive ATP inhibitor and thereby retains potency, even in the presence of physiological levels of ATP.[127] In preclinical studies, ripretinib had excellent potency against all tested KIT AL mutations and was also active, although less so, against KIT ATP–binding pocket mutations.[127]

Ripretinib was initially tested in a phase I study (ClinicalTrials.gov identifier: NCT02571036) that included patients with both GIST and advanced SM in which the recommended to phase II dose of 150 mg once daily was determined.[128] This novel inhibitor had a favorable safety and tolerability profile and was active in patients with GIST whose tumors were refractory to multiple previous TKIs (data about efficacy in SM are not yet reported). Ripretinib was further evaluated in a double-blind, randomized, placebo-controlled study (INVICTUS, ClinicalTrials.gov identifier: NCT03353753) of adult patients with GIST who had progression or intolerance during prior therapies, which included, at a minimum, imatinib, sunitinib, and regorafenib. Ripretinib was associated with 85% reduction in the risk of death or progression when compared with placebo and was associated with an acceptable safety profile.[129] Based on these results, the FDA approved ripretinib in May 2020 for the treatment of adult patients with advanced GIST who had received prior treatment with three or more kinase inhibitors, including imatinib.[130] Currently, the activity of ripretinib to treat patients earlier in their disease course is being tested in a global, randomized, open-label, phase III study comparing the safety and efficacy of ripretinib versus sunitinib in patients with advanced GIST following imatinib (INTRIGUE, ClinicalTrials.gov identifier: NCT03673501). The primary end point is PFS, and key secondary objectives include ORR and OS. Despite the impact of the COVID-19 pandemic, it is anticipated that accrual to this study will be completed in 2021.[131]

In conclusion, it has been two decades since the first KIT inhibitor was approved for treatment of a KIT-mutant disease. The very first kinase inhibitor approved as a cancer therapy, imatinib, has provided immense insights into how to manage the treatment of KIT-mutant neoplasms. At the time of its approval, we had little knowledge of either primary or secondary resistance mechanisms. We now understand the importance of molecular profiling of tumors to predict drug response as specific mutations, but not necessarily KIT overexpression or autocrine signaling, can confer sensitivity or resistance to KIT inhibitors.

In GIST, imatinib is still the first-line therapy for KIT-mutant patients, the majority of which present with imatinib-sensitive mutations (encoded in *KIT* exons 8, 9, 11, and 13). Secondary resistance because of intra-allelic *KIT* mutations emerging during imatinib treatment required the application of new drugs for second- and third-line treatment to combat imatinib resistance. Contrarily, the driving KIT mutation observed in the majority of SM, D816V, confers primary resistance to type II inhibitors like imatinib. For this reason, imatinib is not part of the treatment regimen for this form of SM, but other KIT inhibitors have been developed for this disease, such as midostaurin and avapritinib.

Early on, drug repurposing was the main approach to drug discovery. This approach led to the approval of three additional KIT inhibitors (sunitinib, regorafenib, and midostaurin) to treat GIST and SM. However, greater understanding of primary and secondary KIT mutations inspired more sophisticated approaches to rationally design KIT inhibitors with greater potency. Ripretinib and avapritinib are two such inhibitors that emerged from these KIT-focused drug development programs. There are now five FDA-approved inhibitors to treat KIT-mutant disease, with another, avapritinib, likely to be approved in the near future for KIT D816V+ SM (Table 2).

The overarching lesson learned from imatinib, beginning with BCR-ABL1 and translated to KIT, is that a detailed understanding of both the target and its mechanisms of drug escape is necessary to further advance the field. The introduction of each subsequent KIT inhibitor, first preclinically and then in clinical trials, provided further insight into how drug development should proceed. Preclinical studies have shown that the type I TKIs, avapritinib and midostaurin, will be thwarted by secondary KIT mutations just like imatinib, and this has been seen in early clinical data from patients treated with avapritinib, as discussed above. It is not yet clear if this will be the case with ripretinib, but it is likely, given that the PFS with this agent is only slightly more than 6 months. Thus, two decades on, the lessons from imatinib, the first kinase inhibitor, continue to be carried forward in the ongoing battle against kinase inhibitor resistance, leaving new outstanding questions for basic and clinical researchers to answer (Table 1).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.03245.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Inhibition of KIT Tyrosine Kinase Activity: Two Decades After the First Approval

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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No other potential conflicts of interest were reported.