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REVIEW

# c-Kit Receptors as a Therapeutic Target in Cancer: Current Insights

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**Abstract:** c-Kit is a type III receptor tyrosine kinase (RTK) that has an essential role in various biological functions including gametogenesis, melanogenesis, hematopoiesis, cell survival, and apoptosis. c-KIT aberrations, either overexpression or loss-of-function mutations, have been implicated in the pathogenesis and development of many cancers, including gastrointestinal stromal tumors, mastocytosis, acute myeloid leukemia, breast, thyroid, and colorectal cancer, making c-KIT an attractive molecular target for the treatment of cancers. Therefore, a lot of effort has been put into investigating the utility of tyrosine kinase inhibitors for the management of c-KIT mutated tumors. This review of the literature illustrates the role of c-KIT mutations in many cancers, aiming to provide insights into the role of TKIs as a therapeutic option for cancer patients with c-KIT aberrations. In conclusion, c-KIT is implicated in different types of cancer, and it could be a successful molecular target; however, proper detection of the underlying mutation type is required before starting the appropriate personalized therapy.

**Keywords:** c-KIT, SCF, cancer, RTKs, TKIs, therapy

## Introduction

c-Kit is a classical proto-oncogene that encodes receptor tyrosine kinases (RTKs), which is expressed in nearly all tissues in the body.[1] RTKs respond to stem cell factor (SCF), which is crucial for the self-renewal potency, differentiation, and maintenance of stem cells and many other progenitor cells.[2] Hence, c-KIT has an essential role in many vital functions in the human body, including fertility, homeostasis, hematopoiesis, and melanogenesis.[3] The RTK is formed of three distinct domains: an extracellular ligand-binding domain, a hydrophobic transmembrane domain, and the cytoplasmic or intracellular domain, with conserved tyrosine kinase activity,[4] The intracellular domain consists of a juxtamembrane region, a tyrosine kinase (TK) domain, and a flexible carboxy-terminal (C-terminal) tail.[1,4]

Activation of the RTK occurs following binding to its receptor-specific ligands, which results in dimerization of the extracellular domain. This conformational change leads to trans-autophosphorylation of the tyrosine residue in the juxtamembrane domain, with the release of ADP, and subsequent autophosphorylation of the activation loop and the C-terminal tail.[5–7] This results in the activation of downstream signaling pathways, including the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), Src kinase, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways.[8] The PI3K/AKT pathway has an important role in maintaining cell survival, proliferation, regulation of the actin cytoskeleton, and avoidance of apoptosis,[9] while the MAPK/ERK pathway is essential for the regulation of gene transcription and cell proliferation.[10] Activation of the JAK/STAT pathway results in the stimulation of different gene promoters required for cell proliferation, differentiation, and apoptosis.[11,12] The Src kinase pathway is essential for many cellular biological functions, such as cell survival, proliferation, motility, and angiogenesis.[13] Therefore, dysregulation of c-Kit function, caused by either overexpression or mutations, leads to the development and progression of various human cancers, including gastrointestinal stromal tumors (GISTs), mastocytosis (MC), acute myeloid leukemia (AML), seminomas, and

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some types of melanoma.[14–18] The constitutive activation of RTKs in human cancers occurs as a result of gain-of-functions mutations, genomic amplification, chromosomal rearrangement, and/or autocrine activation.[19] On the other hand, c-Kit loss-of-function mutations have been observed in tumors such as melanoma, thyroid carcinoma (TC), and breast cancer (BC).[20–22]

The two main approaches that are commonly used for targeting and treating c-KIT mutated tumors are small molecule inhibitors and monoclonal antibodies (mAbs). Regarding small molecule inhibitors, imatinib mesylate was the first tyrosine kinase inhibitor (TKI) to be developed and approved for the treatment of hematological malignancies with aberrant TK activity.[23] It was then approved as the first-line treatment for patients with advanced metastatic GIST.[24] Subsequently, other TKIs were developed, including sunitinib, sorafenib, dasatinib, regorafenib, ripretinib, avapritinib, nilotinib, amuvatinib, and tivozanib, which were used to target c-KIT in various tumors in which c-KIT is the main driver oncogene.[25]

Regarding mAbs, they are used to target or inhibit dysregulated c-Kit to overcome the resistance developed in certain wild-type or mutant c-Kit-positive cancer treated with TKIs.[26] Moreover, antibody–drug conjugates (ADCs) were designed by conjugating mAbs with different therapeutic agents such as chemotherapeutic drugs, TKIs, or immune checkpoint inhibitors (ICIs). These ADCs could be a successful modality that is able to induce a potent cytotoxic effect on cancer cells while reducing toxicity to normal tissues, and therefore, improving patient survival and outcomes.[27]

In the current review, we aim to illustrate the role of c-KIT mutations in the development and progression of cancer from a clinical point of view. We also evaluate the therapeutic efficacy of TKIs in different types of tumor, including GIST, AML, melanoma, BC, TC, renal cell carcinoma (RCC), colorectal cancer (CRC), seminoma, germ cell tumors (GCTs), and lung cancer (Table 1). This was performed by investigating the exact role of c-KIT aberrations in each type of cancer individually. Each type has its specific pathogenesis and therefore the role of c-kit varies according to the type of the tumor. In addition, this review discusses the therapeutic significance and limitations of each TKI recommended for the aforementioned cancer types. This will help to open up avenues for more research on c-KIT as a molecular target for different cancer types when used alone or in combination with other treatment strategies.

## Gastrointestinal Stromal Tumors (GISTs)

Gastrointestinal stromal tumors (GISTs) are the main malignant mesenchymal neoplasm originating from the gastrointestinal tract.[93] The c-KIT activation mutation is the most common mutation detected in the GIST, accounting for 75–80% of cases, followed by the platelet-derived growth factor receptor alpha (PDGFRA) mutation, which represents nearly 10–15%.[94–96] Mutations in the KIT gene were mainly identified in the intracellular juxtamembrane domain at exon 11 (67%), followed by the extracellular dimerization domain at exon 9 (10%), the ATP-binding domain at exons 13 and 14 (1%), and the activation loop at exon 17 (1%), which leads to the expression of a truncated c-KIT/CD117 protein. Mutations in the PDGFRA gene were detected in exons 18 (6% of all GISTs), 12 (0.7% of GISTs), and 14 (0.1% of GISTs).[95,97–99] Activation of RTKs results in increased cellular proliferation, differentiation, and migration, and consequently carcinogenesis through activating downstream signaling pathways such as AKT, STAT1, STAT3, MAPK, S6K, PI3K/mTOR, and ETV1.[100,101] Therefore, efforts have been made over the past two decades to control GIST by blocking c-KIT signaling through small molecule inhibitors or monoclonal antibodies. Accordingly, GIST is a successful classical model for mutational targeted therapy, where molecular genotyping has become an essential step for managing GIST patients.[102]

Imatinib mesylate is a derivative of 2-phenyaminopyrimidine that acts as a small molecule inhibitor targeting RTKs. It is considered the first-line treatment for GIST patients with c-KIT or PDGFRA mutations. It inhibits the autophosphorylation and activation of those RTKs through binding to the ATP binding sites on CD117 and PDGFRA, resulting in signal transduction suppression.[1,103] It was approved for the treatment of GIST patients in 2001, where it could be used in the preoperative and in adjuvant setting.[104,105] Moreover, it was found to improve the progression-free survival (PFS) after 5 years of continuous imatinib treatment in 30% of metastatic GIST patients, and after 10 years in 7–9% of the patients.[106,107] Unfortunately, although it can achieve a remarkable clinical outcome in most GIST patients, 70–90% of these patients still develop imatinib resistance and disease relapse within 20–24 months.[102,106,108] Many studies have demonstrated that the sensitivity of GIST cells to imatinib is primarily dependent upon the underlying genotype of the

**Table 1** c-KIT Mutations and the Clinical Significance of Some TKIs in Different Types of Cancer

| Type of Tumor | Types of c-KIT Mutation | TKIs | Clinical Significance | Approval |
|---|---|---|---|---|
| Gastrointestinal stromal tumors (GISTs) | Gain-of-function mutation in exons 11, 9, 13, 14, and 17 | Imatinib mesylate | Binds to the ATP binding sites on CD117 and PDGFRA, resulting in signal transduction suppression | Approved by FDA in 2001 |
| | | Sunitinib | Effective for patients with exon 13/14 secondary c-kit mutations | Approved by FDA in 2006 |
| | | Regorafenib | Effective choice for patients with secondary exon 13/14 or exon 17/18 mutations | Approved by FDA in 2013 |
| | | Ripretinib | Blocks the two switch sites present in the juxtamembrane domain (exon 11) and in the activation loop (exons 17 and 18) | Approved by FDA in 2020 |
| | | Avapritinib | Effective for the activation loop mutants, which are encoded by exon 17 | Approved by FDA in 2020 |
| | | Pimitespib | HSP90 inhibitor[28] | Approved in Japan in 2022 |
| Leukemias | Gain-of-function mutation in exons 8 and 17 | Imatinib mesylate | Used as a maintenance therapy after the completion of post-remission therapy[29] | Approved by FDA in 2001 |
| | | Dasatinib | Effective in c-KIT-mutated CBF-AML[30] | Approved by FDA for Ph+ CML |
| | | Radotinib | Anti-leukemic therapy for c-KIT-positive AML patients[31] | Approved by FDA in 2012 |
| | | Pimitespib | HSP90 inhibitor[32] | |
| Melanoma | Loss-of-function mutations.[20,33] Activation mutations in exons 11, 13, 9, and 17[34–38] | Imatinib, nilotinib, dasatinib sunitinib, sorafenib, masitinib[39] | Research was conducted on the combination of TKIs with other therapeutic modalities[40–43] | |
| Breast cancer (BC) | Loss-of-function mutations.[22,44,45] Activation mutations in TNBC and adenoid cystic carcinoma[46–53] | Lapatinib | Approved for HER2-positive BC, as it also targets EGFRs[53,54] | Approved by FDA in 2007 |
| | | Nilotinib | A potent drug for TNBC treatment[53] | |
| Colorectal carcinoma (CRC) | Activation mutations in the consensus molecular subtype 4 (CMS4) subtype[55] | Bufalin | Blocks the C-Kit/Slug signaling axis[56] | Approved by Chinese FDA |

(*Continued*)


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**Table 1** (Continued).

| Type of Tumor | Types of c-KIT Mutation | TKIs | Clinical Significance | Approval |
|---|---|---|---|---|
| | | Imatinib | Mitigates the aggressive behavior of CRC-CMS4, and induces genes responsible for CMS-switching[57–60] | |
| Renal cell carcinoma (RCC) | Activation mutations[61–65] | Sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib | Considered the standard of care in patients with advanced RCC[66–69] | |
| Mastocytosis (MC) | Missense mutations affecting exons 17, 18, 11, 8, and 9[5,70–72] | Imatinib | | Approved by US FDA for systemic MC[73] |
| | | Midostaurin | Multikinase/KIT inhibitor against D816V mutant MC[74] | Approved by FDA, EMA, and AIFA[7,75] |
| | | Avapritinib | Small molecule kinase inhibitor of the activation-loop mutations of c-KIT including KIT D816V[74] | Approved by FDA and EMA[74] |
| | | Ripretinib | Type II switch pocket control inhibitor of c-KIT exon 17[76] | Under trial (NCT02571036)[76] |
| Germ cell tumors (GCTs) | Activation mutations in exons 11, and 17 | Imatinib | Effective treatment for CNS germinoma patients who were resistant to standard chemotherapy and have c-Kit mutations[77] | |
| Thyroid cancer (TC) | Downregulated in papillary, follicular, anaplastic, poorly differentiated, and differentiated TC[78–82] | Motesanib, lenvatinib, sorafenib, pazopanib, sunitinib, cabozantinib, anlotinib[83–90] | All are able to inhibit cell proliferation and angiogenesis by blocking VEGFR, FGFR, PDGFR, and c-Kit[90] | Sorafenib and cabozantinib approved by FDA for TC |
| Lung cancer | c-KIT protein overexpression | Anlotinib | | Approved by Chinese FDA[91] |
| | | Combined anti-c-Kit ADC plus anti-PD-L1 therapy[92] | Could exhibit potential therapeutic efficacy against SCLC[92] | |

**Abbreviations**: ACC, Adenoid cyctic carcinoma; AIFA, Agenzia Italiana del Farmaco; AML, acute myeloid leukemia; CBF, core-binding factor; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; HSP90, heat shock protein-90; PDGFR, platelet-derived growth factor receptor; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; VEGFR, vascular endothelial growth factor receptor.

tumor cell population, as patients with c-KIT exon 11 mutations are more clinically responsive to imatinib therapy compared to those with c-KIT exon 9 mutations.[109,110] Other studies proposed that the failure of imatinib therapy is mostly due to acquiring secondary mutations, resulting in the reactivation of c-KIT or PDGFRA downstream signaling pathways and, consequently, preventing optimal binding of imatinib. Such mutations usually develop in c-KIT exons 13 and 14, which code for the ATP-binding pocket, and in exons 17 and 18, which code for the activation loop of the kinase domain.[96,111] The secondary mutations that have evolved in PDGFRA are detected in exons 13, 14, and 15, which encode the ATP-binding pocket.[112] On the other hand, it is not clear whether these secondary mutations are originally present in the tumor cell population and become clinically obvious as a result of positive selection caused by imatinib therapy, or are de novo mutations acquired during treatment.[102]

Two other TKIs that have been approved for imatinib-resistant cases are sunitinib and regorafenib. They are considered the second and the third lines, respectively, for the treatment of patients with advanced GIST, where they have a broad activity against secondary c-kit mutations.[102,113] Sunitinib is more effective for patients with exon 13/14 secondary c-kit mutations compared to those with exon 17/18 secondary c-kit mutations,[108,111] while regorafenib is an effective choice for patients whose tumors harbor secondary exon 13/14 or exon 17/18 mutations.[114]

Another TKI that was approved by the US FDA in 2020, based on the positive results obtained from the INVICTUS trial, is ripretinib. It was recommended for advanced or metastatic GIST patients who were resistant to three or more kinase inhibitors including imatinib.[115] It hinders the conformational shift from the inactive to the active state of the RTKs by blocking the two switch sites present in the juxtamembrane domain (exon 11) and in the activation loop (exons 17 and 18).[116] Therefore, it keeps the c-KIT in an inactive state regardless of the type of mutations, whether primary or secondary, thus allowing for suppression of a wide range of KIT oncoproteins.[76] Although it was found that ripretinib achieved the same results regarding the overall response rate (ORR) and the mean progression-free survival (mPFS) rate as the other TKIs after imatinib failure, ripretinib is considered the preferred drug when combined with the other TKIs owing to its efficiency and its acceptable toxicity profile.[115]

Avapritinib is a small molecule inhibitor targeting RTKs that was approved in 2020 by the FDA for the treatment of GIST patients.[117] Unlike the other TKIs, avapritinib is a potent type I inhibitor as it efficiently binds to the active form of the c-KIT at subnanomolar concentrations. It specifically targets the activation loop mutants, which are encoded by exon 17.[118]

## Leukemia

c-KIT mutation is frequently detected in 60–80% of AML patients. It has also been identified in 33.3–45% of AML with inv (16), and in 12.8–46.8% of AML M2 with t(8;21).[119] Fan et al found that c-KIT mutations represented 23% of pediatric AML with core-binding factor (CBF).[120] The most common type of c-KIT mutation in AML is a gain of function, which is found in the juxtamembrane domain (Val560Gly) and in the second part of the kinase domain (sp816Val).[121] It is predominantly hyperactivation, formed of in-frame insertions or deletions in the extracellular domain involved in c-KIT dimerization, which is mainly present in exon 8, or missense mutations that affect the activation loop in the c-KIT TK domain, which is found in exon 17.[122] Many studies have highlighted the critical role of c-KIT expression in the proliferation, differentiation, and activation of hematopoietic progenitor cells.[31,123,124] Accordingly, it was found that c-KIT is associated significantly with poor survival, increased incidence of relapse, and unfavorable outcomes of AML patients, especially in those with CBF-AML.[31,125,126] Moreover, it had been reported that c-KIT exon 17 mutations are associated significantly with worse outcomes in adult de novo AML patients with RUNX1-RUNX1T1.[127–129]

Genetic markers underlying AML carcinogenesis are considered to be useful prognostic markers, and they could be potential therapeutic targets for AML. However, most AML patients respond initially to induction therapy and then they show resistance or relapses.[130] The RTKs are approved for various cancers with mutated c-KIT; however, their role in AML has not been well established.[33] Imatinib is used for the inhibition of ABL, KIT, and PDGFR in the treatment of chronic myeloid leukemia, Philadelphia chromosome-positive acute lymphoblastic leukemia, and chronic eosinophilic leukemia with PDGFRα rearrangement.[33] Several clinical trials have been performed to assess the utility of RTKs in c-KIT mutated AML.[29–31,131,132] Advani et al reported that imatinib can improve the outcome of newly diagnosed AML patients when it is used as a maintenance therapy after the completion of post-remission therapy.[29] Moreover, Kampa-Schittenhelm et al reported that dasatinib has an anti-leukemic effect on KIT-mutated CBF-AML.[30] Similarly, Heo et al

demonstrated that dasatinib and radotinib induce AML cell death by targeting c-KIT both in vivo and in vitro. Therefore, dasatinib and radotinib could have a potential role in anti-leukemic therapy for c-KIT-positive AML patients.[31]

Another line of AML therapy that has been developed is the heat shock protein-90 (HSP90) inhibitor. HSP90 is a molecular chaperone that regulates the function and folding of various client proteins, including c-KIT.[133] Pimitespib (TAS-116) is a HSP90 highly selective inhibitor that was proved by Honma et al, in the phase 3 CHAPTER-GIST-301 trial, to improve the PFS of GIST patients who were resistant to imatinib, sunitinib, and regorafenib.[28] Similarly, Ikebe et al proposed that pimitespib showed anti-adult T-cell leukemia/lymphoma (ATL) activity in ATL-related cell lines, in primary ATL cells ex vivo, and in tumors developed in ATL cell-xenografted mice.[32] Hence, HSP90 inhibitors in combination with TKIs could be a successful line of treatment in AML.[134]

## Melanoma

Melanoma is an aggressive type of skin cancer.[39] c-KIT mutations are identified in 3–9.5% of all melanoma cases, which is mutually exclusive of B-Raf proto-oncogene serine/threonine kinase (BRAF) and neuroblastoma rat sarcoma viral oncogene homolog (NRAS) mutations.[39,135,136] The most common c-KIT mutations detected are constitutive activating mutations, in nearly 70% of cases, comprising 39% of mucosal melanomas, 36% of acral melanoma, and 28% of chronically sun-damaged melanoma.[1] These mutations include a lysine to-proline mutation at codon 576 (L576P) in exon 11 and a methionine-to-glutamic mutation at codon 642 (K642E) in exon 13, which lead to stimulation of the down-signaling MAPK and PI3K/AKT pathways.[1,34,35] Other mutations were also found in exons 9 and 17.[36] In addition, c-KIT overexpression was detected in melanoma cases by immunohistochemical analysis, especially in those with ocular melanoma (36–91%).[37,38] In this context, Lukenda et al reported a significant association between c-KIT overexpression and shorter overall and disease-free survival in patients with choroidal and ciliary body melanoma.[137] Although most of the c-KIT alteration melanomas showed activated mutations, other studies reported a loss of c-KIT expression with tumor progression.[20,138] Accordingly, the role of c-KIT mutation in melanoma is controversial, with proper detection of the mutation type being required before starting the appropriate personalized therapy. Regarding the treatment modalities of melanomas, TKIs are one of the molecular-targeted options that provide efficacy against c-KIT mutated melanomas, especially the metastatic type. However, the emergence of resistance is common when it is used as a monotherapy for a prolonged period.[139,140] This resistance could be explained by secondary mutations, leading to the expression of various oncogenic proteins, or by the development of epithelial–mesenchymal transition.[141] Therefore, several clinical trials have worked on combining TKIs such as imatinib, nilotinib, dasatinib, sunitinib, sorafenib, and masitinib together with other modalities of treatment.[39] Some of these clinical trials combined imatinib with anti-PD-1 (pembrolizumab) immunotherapy, which improved the outcomes of the patients.[40] Other studies investigated the possibility of combining TKIs and immunotherapies targeting key protein elements involved in the oncogenic RAS/RAF/MAPK or PI3K/AKT pathways. This resulted in improved outcomes and prolonged PFS in patients with metastatic melanoma.[41,42] Moreover, Delyon et al[43] proposed the potential of combining JAK/STAT inhibitors and c-KIT inhibitors (nilotinib) for the treatment of melanoma, which could improve patients' response to nilotinib. Overall, melanoma patients with c-KIT mutations could benefit from combining c-KIT inhibitors and immunotherapy, which may be a successful treatment option for these patients in the future.

## Breast Cancer (BC)

The role of c-KIT mutation in BC is still a controversial issue, as some research has reported that most BC cases showed loss of c-KIT expression.[22,44] This loss of c-KIT function is considered the main deriving factor for malignant transformation due to c-kit gene promoter DNA hypermethylation.[45] In contrast, other types of breast cancer, such as adenoid cystic carcinoma (ACC), showed increased c-KIT expression in about 90% of cases, especially those with tubular and cribriform carcinomas of the breast.[46–48] Similarly, it had been found that c-KIT was significantly over-expressed in 20–89% of triple-negative breast cancers (TNBCs), which could provide a useful molecular target for this aggressive type of BC.[49–52] Moreover, López-Mejía et al[53] found that c-Kit overexpression in TNBC results in increasing cell migration and metastasis through the activation of STAT3, Akt, and ERK1/2 pathways. They proposed that TNBC cells expressing functional c-Kit are more sensitive to nilotinib than the other available TKIs. Therefore, nilotinib could

be considered a potent drug for TNBC treatment.[53] In addition, Funkhouser et al reported a significant association between c-KIT missense mutations (p.M541L) and elevated serum levels of galectins in patients with metastatic disease.[142] On the other hand, Vahdatinia et al concluded that c-KIT mutation is a rare event in BC (0.32%) and that the c-KIT-altered BC patients showed high-grade tumors with poor outcomes.[143] Many TKIs are commercially available for blocking c-KIT functions, such as imatinib, sorafenib, sunitinib, nilotinib, and dasatinib; however, the only approved TKI for treating BC patients is lapatinib, especially for those with HER2-positive BC, as it also targets epidermal growth factor receptors (EGFRs).[53,54]

## Colorectal Carcinoma (CRC)

The role of c-KIT mutations in CRC is not yet well understood. It has been reported that c-KIT hyperexpression is detected in approximately 50% of CRC tissues.[144,145] Moreover, c-KIT expression is significantly associated with the most aggressive subtype, the consensus molecular subtype 4 (CMS4), which has a high rate of disease recurrence and shows poor response to treatment.[55] Bellone et al found that c-KIT is highly expressed in the premalignant and malignant tissues of colonic lesions, where it is associated with unfavorable outcomes of the patients.[146] In a study performed by Küçükköse et al, c-KIT expression was found to increase the aggressiveness of the colonic tumor cells through the inhibition of SMAD2, which resulted in the stimulation of transforming growth factor-β (TGFβ) expression.[57] Another study, by Ma et al, demonstrated that c-KIT could promote CRC progression through the activation of the ERK1/2-ELK1 pathway, resulting in increased carcinoembryonic antigen (CEA) expression.[55] Therefore, they suggested TKIs as a therapeutic option for the treatment of CRC patients with CMS4 subtype.[55,58] In addition, Wang et al reported that the SCF/c-kit-JNK/AP-1 signaling pathway could maintain tumorigenesis in CRC by stimulating claudin-3 expression.[147] Similarly, Li et al reported that SCF/c-KIT signaling was significantly activated in mucinous colorectal adenocarcinoma (MCA), where it induced mucus secretion by goblet cells through the activation of PKCδ-MARCKS.[148] Hence, it could provide a new targeted marker for MCA treatment.[148] Many published studies have confirmed the supportive role of c-KIT in colonic cancer stem cells (CSCs), as it promotes migration, invasiveness, and EMT.[56,149] In this context, Ding et al proposed that bufalin has anti-stemness activity by blocking the C-Kit/Slug signaling axis, and therefore it could be a potent treatment for CRC patients.[56] Although c-KIT has been reported in many recently published studies to have an important role in CRC carcinogenesis, imatinib has not yet been approved for the treatment of CRC cases.[59] Accordingly, many clinical trials have been performed to assess the therapeutic effect of imatinib on CRC-CMS4. They revealed that imatinib could mitigate the aggressive behavior of CRC-CMS4, and it induces genes responsible for CMS switching, resulting in improvals in patient survival and outcomes.[57–60] Therefore, c-KIT targeting therapy could be a useful strategy for CRC-CMS4 management.[60]

## Renal Cell Carcinoma (RCC)

Several studies have reported that c-KIT protein is significantly overexpressed in renal tumor cells in comparison to its normal counterpart, especially in chromophobe RCC and renal oncocytoma subtypes, using immunohistochemical staining.[61–65] It was less frequently present in renal angiomyolipomas, papillary RCC, and clear-cell RCC.[61–63,65] Regarding the c-KIT mRNA expression analysis, Huo et al demonstrated that c-KIT mRNA was significantly over-expressed in chromophobe RCC and renal oncocytoma compared to the other RCC subtypes, using cDNA expression microarrays.[61] Moreover, Lin et al performed mutational analyses of the c-kit gene in different subtypes of RCC. They reported that no mutation was detected in exons 9, 11, 13, or 17 in RCC subtypes, apart from papillary RCC, which showed point mutations in 94% (17/18) of the cases.[73] Similarly, Zimpfer et al demonstrated that c-KIT was significantly overexpressed in chromophobe RCC and renal oncocytoma without c-kit mutations.[64] Ergün et al, in a study on the possible association between RCC and truncated KIT (tr-KIT), which is an alternative variant of c-KIT protein, proposed that the tr-KIT/c-KIT expression ratio was upregulated in RCC tissues, including clear cell, papillary, and chromophobe RCC. Added to that, the increased tr-KIT/c-KIT ratio was associated significantly with a more aggressive clinical course and inferior patient outcomes.[150]

Regarding the treatment options for RCC, vascular endothelial growth factor receptors (VEGFRs) and the TKIs sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib were considered the standard of care in patients

with advanced RCC. However, most patients showed disease relapse and drug resistance later.[66–69] Many clinical trials have investigated the combination of TKIs and immune checkpoint inhibitors, including nivolumab, ipilimumab, and pembrolizumab, which showed longer overall survival, better clinical prognosis, and more favorable patient outcomes.[151–153]

## Mastocytosis MC)

MC is a neoplastic proliferation of abnormal mast cells which infiltrate different organs. It can present in children as a cutaneous lesion, which undergoes spontaneous regression at puberty, whereas it commonly presents in adults as a more aggressive systemic MC that can lead to multiorgan failure.[154,155] More than 90% of systemic MC in adults is associated with c-KIT missense mutations affecting exon 17, codon 816, in which aspartate is substituted by valine (KIT D816V).[5] This mutation (KIT D816V) renders c-KIT 586-fold more active than the native c-KIT, which is responsible for imatinib resistance and a poor clinical prognosis.[70,71] Similarly, the D816V mutation is detected in 42% of children with systemic MC.[16] Other less frequent types of c-KIT mutation that occur in systemic MC and are imatinib sensitive include those occurring in exons 17 and 18 (eg D820G or N822I/K), exon 10 (eg F522C), exon 11 (eg V560G/I), exon 8 (eg deletion of codon 419), and/or exon 9 (deletion of codon p.A502_Y503dup).[72] Therefore, the treatment of MC is highly individualized according to the type of mutation detected.[154] Patients who have the KIT D816V mutation, which is the most common oncogenic driver for MC, usually experience primary resistance to the TKIs imatinib and masitinib.[156,157] Similarly, nilotinib and dasatinib have low clinical significance for these patients.[158,159] Imatinib is currently approved by the US FDA for patients with systemic MC who are negative for KIT D816V, have unknown KIT mutation status, or have the previously mentioned imatinib-sensitive KIT mutations.[160] Midostaurin is a multikinase/KIT inhibitor that confers a suppressive activity against D816V mutant MC.[74] It is approved by the FDA, the European Medicines Agency (EMA), and Agenzia Italiana del Farmaco (AIFA) as a targeted therapy for the treatment of patients with advanced systemic MC, indolent systemic MC, and severe MC mediator-release symptoms (MCMRS).[7,75] It is also approved as a first-line treatment for patients with mast cell leukemia (MCL), or as a maintenance therapy after allogeneic stem cell transplantation (ASCT).[161] Another available drug that is approved by the FDA and EMA for the treatment of advanced systemic MC is avapritinib.[74] Avapritinib is a small molecule kinase inhibitor of the activation-loop mutations of c-KIT, including KIT D816V.[74] Another investigational drug that is now under trial (NCT02571036) for the treatment of MC is ripretinib (DCC-2618), which is a type II switch pocket control inhibitor of c-KIT exon 17.[76]

## Germ Cell Tumors (GCTs)

c-KIT mutations have also been detected in human GCTs. Regarding testicular germ cell tumors (TGCTs), the incidence of c-KIT mutation is ten-fold higher in seminoma (20–25%) than in non-seminoma TGCTs.[162,163] The most common c-KIT alteration in seminoma is the activating c-KIT mutation, in 10–40% of cases, which present in exons 11 and 17. About two-thirds of seminoma cases have missense point mutations in exon 17, mainly at codon 816, where X is either valine [V] or histidine [H].[5,164–166] In addition, McIntyre et al reported that amplification of chromosome 4q12, containing the c-KIT gene, in TGCT was associated with the progression to the seminoma subtype.[164] Notably, activating c-KIT mutations have also been found in other tumors having the same histological features as testicular seminoma, including mediastinal seminomas, intracranial germinomas, and ovarian dysgerminomas.[167,168] c-KIT mutations have been detected in approximately half of pure ovarian dysgerminoma cases, where all are located in exon 17.[169] Moreover, Hersmus et al proposed that c-KIT mutations could have a role in disorders of sex development (DSD).[169] It had been reported that c-KIT protein overexpression using immunohistochemistry was also significantly found in ovarian dysgerminoma, which represents about 87% of cases of ovarian dysgerminoma. However, there was no significant correlation between c-KIT protein overexpression and c-kit mutations in the assessed cases.[170,171] In this context, Stemberger-Papic et al reported that c-KIT overexpression in patients with primary ovarian high-grade serous carcinoma was associated significantly with shorter disease-free survival and peritoneal metastasis.[172] On the other hand, Gao et al assessed c-KIT expression in intracranial GCTs and reported that c-KIT protein expression was found in 59.1% of patients, whereas c-KIT mutations were found in only 5.9% of CNS germinoma cases. This mutation was present in exon 11 at codon 557–558 WK (tryptophan-lysine).[77] They concluded that imatinib could be an effective treatment for CNS

germinoma patients who are resistant to standard chemotherapy and exhibit c Kit mutations.[77] Taken together, these studies show that c-KIT could be a potential prognostic marker and therapeutic target for patients with GCTs.

## Thyroid Cancer (TC)

It had been reported that c-KIT has an important role in the differentiation and growth of the thyroid epithelium.[21,173] Hence, several studies have investigated the impact of c-KIT mutations on the development of different histological types of TC.[21,78–80,173,174] They proposed that c-KIT was strongly downregulated in papillary,[81] follicular,[82] anaplastic,[78] poorly differentiated,[79] as well as differentiated TC,[80] in comparison to benign thyroid nodules. Moreover, Tomei et al demonstrated that assessment of c-KIT expression in thyroid fine-needle aspiration cytology (FNAC) smears could improve the diagnostic accuracy of the cytological analysis of TC.[81] Therefore, several studies were performed to investigate the usefulness of TKIs as a systemic therapy for radioactive iodine-refractory TC. Such TKIs include motesanib diphosphate,[83] lenvatinib,[84,85] sorafenib,[86] pazopanib,[87] sunitinib,[88] cabozantinib,[89] and anlotinib,[90] which are able to inhibit cell proliferation and angiogenesis by blocking VEGFR, FGFR, PDGFR, and c-Kit.[90] However, there are still some limitations regarding the administration of TKIs in TC, such as secondary resistance or the escape phenomenon, which may occur after a certain period of administration.[84]

## Lung Cancer

c-KIT is reported to be overexpressed in about 70% of small cell lung cancer (SCLC) cases, by immunohistochemical staining, without c-KIT mutation being detected.[175–177] Also, it was reported to be overexpressed in 46.9% of advanced non-small cell lung cancer (NSCLC) cases with ALK fusion.[178,179] However, the prognostic significance of c-KIT aberrations in lung cancer is still a debatable issue. This discrepancy could be explained by the variability in the type of the sample assessed, the tumor stage, the immunohistochemistry technique, and associated other genetic mutations.[1] In this regard, Yang et al demonstrated that c-Kit activation is a good predictor for crizotinib efficacy. They also concluded that c-KIT is a useful prognostic marker, as it is associated with shorter overall survival rates in patients with advanced-stage ALK fusion NSCLC.[178] Although c-KIT protein overexpression was found significantly in lung cancer patients, imatinib did not achieve valuable therapeutic efficacy in patients with SCLC.[180–182] Anlotinib is a tyrosine multikinase inhibitor that has been approved by the Chinese FDA for the treatment of advanced NSCLC.[91] Currently, anlotinib is being investigated as a treatment option for SCLC, CRC, and soft tissue sarcoma.[183,184] In addition, Kim et al developed a combination treatment using anti-c-Kit ADC plus anti-PD-L1 therapy (4C9-DM1) that exhibits a potential therapeutic efficacy against SCLC.[92]

## Conclusions

c-KIT has a crucial role in the pathogenesis and development of many cancers; however, its role is not well known yet, especially in certain tumors including breast cancer, melanoma, mastocytosis, thyroid cancer, germ cell tumors, and renal cell carcinoma. The role of c-KIT is still controversial as it varies according to the type of the tumor, as either gain or loss of function. Hence, TKIs are considered an important line of treatment in such c-KIT mutated tumors. However, attention should be directed toward proper detection of the underlying c-KIT mutational type and localization using advanced techniques such as next-generation sequencing. This will allow for better designing a personalized therapy according to the underlying mutations, and consequently maximize the benefit, which will be reflected in the prognosis and outcomes of the patients. Research is now being directed toward combination therapy including TKIs and other therapeutic modalities, such as immunotherapy or checkpoint inhibitors. Moreover, HSP90 is evolving for the treatment of AML patients in combination with TKIs. In summary, c-KIT is still a hot topic for more research on its diagnostic, prognostic, and therapeutic role. Therefore, more efforts should be made to achieve the proper management of cancer patients.

## Disclosure

All authors declare that there are no possible conflicts of interest.

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