Mutated KIT Tyrosine Kinase as a Novel Molecular Target in Acute Myeloid Leukemia

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Abstract: KIT is a type-III receptor tyrosine kinase that contributes to cell signaling in various cells. Since KIT is activated by overexpression or mutation and plays an important role in the development of some cancers, such as gastrointestinal stromal tumors and mast cell disease, molecular therapies targeting KIT mutations are being developed. In acute myeloid leukemia (AML), genome profiling via next-generation sequencing has shown that several genes that are mutated in patients with AML impact patients’ prognosis. Moreover, it was suggested that precision-medicine-based treatments from the HM-SCREEN-Japan-01 study, a genome profiling study for patients newly diagnosed with AML who are unsuitable for the standard first-line treatment (unfit) or have relapsed/refractory AML, and (3) new therapies targeting KIT mutations, such as tyrosine kinase inhibitors and heat shock protein 90 inhibitors. In this era when genome profiling via next-generation sequencing is becoming more common, KIT mutations are attractive novel molecular targets in AML.

Keywords: acute myeloid leukemia; genome profiling; KIT mutation; RUNX1-RUNXIT1; HSP90 inhibitor

1. Introduction

KIT is a type-III receptor tyrosine kinase that contributes to signal transduction in certain cells, such as hematopoietic stem cells, mast cells, and Cajal cells of the gastrointestinal tract [1]. KIT mutations have been reported in more than 90% of cases of mast cell tyrosine kinase and AML, and (3) new therapies targeting KIT mutations, such as tyrosine kinase inhibitors and heat shock protein 90 inhibitors. In this era when genome profiling via next-generation sequencing is becoming more common, KIT mutations are attractive novel molecular targets in AML.
factor (CBF) leukemia [7–11]. In AML, recent studies involving the genome profiling of AML via next-generation sequencing (NGS) showed that some mutated genes (e.g., ASXL1, NPM1, FLT3, TP53, CEBPA, and RUNX1) in patients with AML impacted the prognosis of these patients [12–14]. Moreover, recent clinical studies incorporating genomic data into treatment decisions, such as the BEAT AML trial [15], suggested that precision-medicine-based treatment using genomic data will improve treatment outcomes for AML. In this era when NGS genome profiling is becoming more common, KIT mutations are attracting attention as new molecular targets in AML.

2. Structure, Function, and Mutation of KIT

2.1. Structure and Function of KIT

The KIT gene is located on chromosome segment 4q11 in humans and is composed of 21 exons [3,16]. The structure of KIT consists of five immunoglobulin-like (Ig-like) domains (D1-D2-D3-D4-D5), a trans-membrane domain (TMD), a juxta-membrane domain (JMD), two kinase domains (KD), and a kinase insert that lies between the KDs [17] (Figure 1A). KIT is expressed on the cell surface and functions as a receptor. The first three Ig-like domains (D1-D3) bind the stem cell factor (SCF), and the two KIT monomers are adjacent to each other. After that, the interaction between D4-D4 and D5-D5 occurs between adjacent KIT monomers, and a stable homodimer is formed. It generates trans-phosphorylation in the JMD region, kinase insert region, KD, and COOH-terminal tail (Figure 1B) [3,18,19]. The signals transmitted by KIT activation are primarily mediated through the phosphatidylinositol 3-kinase (P13K) pathway [20,21], Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway [22–24], MAPK pathway [25–27], and the Src family kinase pathway [26,28] (Figure 1C). In the hematopoietic system, KIT is strongly expressed in hematopoietic stem cells and progenitor cells [29]. KIT plays an important role in the self-renewal potency of hematopoietic stem cells and differentiation into myeloid and lymphoid cells [30,31]. The expression of KIT is observed to decrease with the differentiation of hematopoietic cells [32]; however, it is highly expressed in mast cells [33].

![Figure 1](image_url)

Figure 1. (A) Schematic representation of the structure of KIT. (B) The homodimeric state of KIT brought about by SCF binding and stabilized by interactions between immunoglobulin-like domains. (C) Signaling pathways involving KIT. The MAPK pathway, JAK/STAT pathway, P13K pathway, and Src family kinase pathway are shown as orange, yellow, green, and blue lines, respectively.

2.2. Mutations of KIT in Cancer

Both the downregulation and upregulation of KIT signaling have been reported in human cancers. In many cancers, such as GIST, mast cytosis, and AML, the activa-
tion of KIT was detected through overexpression or mutation [34]. Moreover, the down-regulation of KIT signaling was detected in melanoma [35]. KIT mutations often occur in the membrane proximal immunoglobulin-like domain (exon 8 and exon 9), the JMD (exon 11), and the tyrosine kinase domain (exon 17) [36]. Mutations in the JMD of KIT have been described in GIST [37] and extranodal NK/T cell lymphoma (ENKL) [38]. Mutations in the tyrosine kinase domain of KIT are detected frequently in systemic mastocytosis (SM) [39,40], ENKL [38], and seminomas [41] (Table 1).

Table 1. Summary of KIT mutations in cancers.

| Site                        | Exon | Disease          | Description         |
|-----------------------------|------|------------------|---------------------|
| Immunoglobulin-like domain  | 8    | AML              | T417, Y418, D419    |
|                             | 9    | GIST             | A502                |
| Trans-membrane domain       | 10   | AML              | V530I               |
| Juxta-membrane domain       | 11   | GIST             | CD117, V559A, V559D, W557R, V560G |
| Kinase insert               | 13   | AML              | K642E               |
| Kinase domain               | 14   | AML              | K704, N705          |
| Kinase domain               | 15   | GIST             | S715                |
| Kinase domain               | 16   | AML              | 1748T, L773S        |
| Kinase domain               | 17   | AML              | D816V, D816Y, D816F, D816H, N822, V825I |
|                             |      | Germ cell tumor  | D816H, D816V        |
|                             |      | Mastocytosis     | D816V, D816Y, D816H, D820G |
|                             |      | ENKL             | V825A, D816N        |

Abbreviations: AML: acute myeloid leukemia, GIST: gastrointestinal stromal tumor, ENKL: extranodal NK/T cell lymphoma.

3. Prognosis of AML with KIT Mutations Treated with Conventional Chemotherapy

KIT mutations are detected in approximately 4–6% of adult patients with de novo AML [13,42] and 20–40% of adult patients with de novo CBF-AML [7–11]. Fan et al. reported that 256 patients (23%) had KIT mutations in 1123 children with CBF-AML [43]. Three mutational hot-spots (exon 8, exon 10–11, and exon 17) have been identified in the KIT gene [44–47] (Table 2). Of these, exon 17 has been recognized as the site of KIT mutations most strongly associated with poor prognosis in adult patients with de novo AML harboring RUNX1-RUNX1T1 [7,11,48,49]. Ishikawa et al. showed that KIT exon-17 mutations were associated with poor prognoses in patients with de novo AML with RUNX1-RUNX1T1 being treated with an HDAC regimen [49].

Table 2. Summary of KIT mutations in AML.

| Exon | Description          | Functional Impact             |
|------|----------------------|-------------------------------|
| 8    | T417, Y418, D419     | Hyper-reactivity to stem cell factor |
| 10–11| V530, V540, W557, V559, L576, ITD | Spontaneous dimer formation     |
| 17   | D816, D820, N822, Y823, V825 | Auto activation               |

Abbreviations: AML: acute myeloid leukemia.
Several reasons have been proposed for the poor prognosis in AML with RUNX1-RUNX1T1 harboring a KIT mutation. For instance, it has been reported that activated KIT cooperates with a C-terminal truncated variant of RUNX1T1 to expand the pool of human CD34+ hematopoietic progenitors and augment the DNA repair machinery, resulting in increased chemo-resistance [50]. Using an in vitro model, Omori et al. compared the cell-proliferative and anti-apoptotic activity of KIT-D816V and KIT-N822K, both of which have been shown to undergo autophosphorylation in the absence of growth factors. Cells harboring KIT-D816V exhibited the activation of the SRC kinase and JAK/STAT pathways and demonstrated greater cell-proliferative and anti-apoptotic ability than cells harboring KIT-N822K [51]. In another study, Tarlock et al. used a cell line harboring a KIT mutation in an in vitro functional analysis, confirming the results of a clinical study of pediatric CBF-AML [52]. Those authors showed that KIT exon-17 mutations resulted in aberrant KIT phosphorylation and were associated with worse clinical outcomes. They further reported that KIT exon-8 mutations have no functional or prognostic impact.

4. KIT Mutation in Unfit and Relapsed/Refractory AML: Results from the HM-SCREEN-Japan-01 Study

Hematologic Malignancy (HM)-SCREEN-Japan-01 (UMIN000035233) is a genome profiling study of patients newly diagnosed with adult AML who are unsuitable for the standard first-line treatment (unfit) or have relapsed/refractory (R/R) AML [53–55] (methods are described in Supplementary Materials). The objective of the present study was to evaluate the frequency and characteristics of cancer-related genomic alterations in patients with AML using a comprehensive genome profiling assay (FoundationOne® Heme (F1H)) and to determine the quality of specimens used in gene analysis. One hundred and eighty-two patients were recruited, and an F1H report was successfully obtained for one hundred and seventy-seven patients [53,55]. We show the subgroup analysis of the HM-SCREEN-Japan-01 dataset focusing on KIT mutations below.

4.1. Frequency of KIT Mutation in Unfit and R/R AML

Of the 177 patients who participated in the study, we identified 15 patients (8.5%) with a KIT mutation. Of the 15 AML patients with a KIT mutation, 6 were registered as unfit AML and 9 as R/R AML. In addition, a total of 17 patients with CBF leukemia (12 AML with RUNX1-RUNX1T1 gene fusion and 5 AML with CBFβ-MYH11 gene fusion) were confirmed via NGS analysis. Eight of the patients had both a KIT mutation and RUNX1-RUNX1T1; these individuals represented 53% of AML with KIT mutation cases and 67% of AML with RUNX1-RUNX1T1 cases. Two patients had both a KIT mutation and CBFβ-MYH11; these individuals represented 13% of AML with KIT mutation cases and 40% of AML with CBFβ-MYH11 cases. Five patients with non-CBF leukemia had a KIT mutation (Figure 2).

Our study showed a high frequency of KIT mutations in R/R or unfit CBF-AML patients compared with the previous studies targeting new-onset CBF-AML (Table 3). Patients’ characteristics and clinical outcomes are described in the Supplementary Materials.

| Author, Year | Disease Status | CBF Leukemia | RUNX1-RUNX1T1 | CBFβ-MYH11 |
|--------------|---------------|--------------|---------------|------------|
| Qin 2014     | Newly diagnosed | 37% (128/351) | 39% (99/253)  | 30% (29/98) |
| Allen 2013   | Newly diagnosed | 28% (100/354) | 23% (46/199)  | 35% (54/155) |
| Kim 2013     | Newly diagnosed | 26% (32/121)  | 27% (22/82)   | 35% (54/155) |
| Ishikawa 2019| Newly diagnosed | 34% (63/199)  | 32% (42/132)  | 31% (21/67)  |
| HM-SCREEN01  | R/R or Unfit   | 59% (10/17)   | 67% (8/12)    | 40% (2/5)   |

Abbreviations: CBF: core-binding factor, R/R: relapse/refractory.
The proportions of AML with RUNX1-RUNX1T1 among unfit and R/R patients harboring a KIT mutation were 19% (two of six) and 66% (six of nine), respectively. Other than KIT, the mutated gene detected most frequently was RAD21 (3/15, 20%). FLT3, TP53, and GATA2 mutations were found in two cases each (12%). The FLT3 mutations detected in patients 13 and 158 were FLT3-N676K and FLT3-D835H, respectively. The two cases with complex chromosomal abnormalities (patients 13 and 56) both harbored TP53 mutations. In R/R patients, mutations in tyrosine kinase-encoding genes other than KIT (e.g., FLT3 and JAK2) were not detected (Table 4).

4.3. Clinical Impact of KIT Mutation in Unfit and R/R AML

Our data also showed that AML with RUNX1-RUNX1T1 accounted for a very high proportion of unfit and R/R AML patients who had a KIT mutation. Notably, the proportion of AML with RUNX1-RUNX1T1 in R/R patients was 66%. Of the nine R/R patients, none harbored mutations in tyrosine kinase-encoding genes other than KIT, and the number of other gene mutations was similar in patients with and without RUNX1-RUNX1T1 (Figure 3B). Moreover, all of the KIT mutations detected in these nine R/R patients were located in exon 17 (typically encoding D816V/Y/F substitutions in the KIT protein). These data suggested that KIT mutations, especially those in exon 17, are related to a poor prognosis in AML with RUNX1-RUNX1T1, consistent with previous reports on the genetic profiling of R/R AML in patients with de novo AML [7,11,48,49,52].
Based on our analysis of all cases in HM-SCREEN-Japan-01, KIT mutations represented the predictor with the worst outcomes of all assessed gene mutations [53,55]. Most of the surviving patients had received allo-HSCT, regardless of whether they had been diagnosed with CBF or non-CBF leukemia in R/R cases (Supplementary Materials). However, CBF-AML is not currently indicated for transplantation after a first remission [14]. Indeed, there are unmet needs for these R/R patients, such as bridge therapy to transplantation.

In non-CBF leukemia with KIT mutation, three of five patients (Nos. 13, 56, and 111) had high-risk chromosomal abnormalities such as complex events or 3q abnormalities. An additional patient (No. 149) harbored t(3;3)(p25;q13), the source of which was unclear but might be related to the 3q abnormality. Although this subset of patients is small in number, these observations raise the interesting question of whether KIT mutations are associated with an elevated risk of chromosomal abnormality in non-CBF leukemia.

The results obtained from our study are limited by the small number of the KIT-mutated cases, and the results should be confirmed by increasing the total number of patients with AML including KIT-mutated AML. However, previous studies and our results suggested that the treatment strategies with conventional chemotherapy may not be able to overcome KIT-mutation-positive AML. Thus, new treatment agents targeting cancers with KIT mutations are needed.
Table 4. Summary of KIT mutations and chromosomal karyotypes.

| ID  | Category | Description | SNV          | VAF  | Other Mutations | Chromosomal Karyotype                  |
|-----|----------|-------------|--------------|------|-----------------|----------------------------------------|
| 13  | Unfit    | D816V       | 2447A > T    | 0.372| FLT3, KRAS, CEBPA, TP53 | Complex karyotype                      |
| 50  | Unfit    | D816V       | 2447A > T    | 0.123| RAD21, SPEN     | t(8;21)(q22;q22.1)                     |
| 56  | Unfit    | D816F       | 2446_2447GA > TT | 0.37 | TP53, CDKN2A, CDKN2B | Complex karyotype                      |
| 149 | Unfit    | D816V       | 2447A > T    | 0.344| ASXL1, DNMT3A, SETBP1, FANCD2, CASP8 | 46, XY, t(3;3)(p25;q13)                 |
| 158 | Unfit    | T417_D419 > Y | 1249_1255ACTTACG > T | 0.078| FLT3, NRAS      | inv(16)/t(16;16)                       |
| 160 | Unfit    | D816V N822K | 2447A > T    | 0.146| 2466T > G       | CSF3R, JAK1                            |
| 160 | R/R      | D816V       | 2447A > T    | 0.234| None            | t(8;21)(q22;q22.1)                     |
| 39  | R/R      | D816V       | 2447A > T    | 0.252| 2446G > T       | RAD21                                  |
| 45  | R/R      | D816V       | 2446G > T    | 0.923| CD36            | t(8;21)(q22;q22.1)                     |
| 76  | R/R      | D816V       | 2447A > T    | 0.932| NF1             | t(8;21)(q22;q22.1)                     |
| 94  | R/R      | D816V       | 2447A > T    | 0.459| RAD21, NPM1     | Normal                                 |
| 111 | R/R      | D816V       | 2447A > T    | 0.338| SETD2           | 3q Abnormality                         |
| 121 | R/R      | D816Y       | 2446G > T    | 0.021| CBL             | inv(16)/t(16;16)                       |
| 146 | R/R      | D816V       | 2447A > T    | 0.082| GATA2, HIST1H2BJ| t(8;21)(q22;q22.1)                     |
| 175 | R/R      | N822K       | 2446T > G    | 0.461| GATA2, PHF6, ATM| t(8;21)(q22;q22.1)                     |

Abbreviations: R/R: relapse/refractory, SNV: single-nucleotide variant, VAF: variant allele frequency.

5. Possible Role for Kinase Inhibitors in the Treatment of AML with KIT Mutation

Few specific inhibitors of KIT have been reported; however, several agents designed to target other RTKs such as FLT and ABL are expected to have utility for KIT mutations [56,57] (Table 5). Several drugs have been used in clinical trials in AML with KIT expression or KIT mutation.

Table 5. Summary of FDA-approved KIT-targeted therapies.

| Drug       | Primary Targets | FDA-Approved Disease                     |
|------------|-----------------|------------------------------------------|
| Imatinib   | BCR-ABL1        | CML, Ph+ALL, HES, GIST, SM, DFSP         |
| Dasatinib  | BCR-ABL1        | CML, PhALL                               |
| Sunitinib  | VEGFR and FLT3  | GIST, RCC, Pancreatic Cancer             |
| Regorafenib| VEGFR           | GIST, HCC, Colorectal Cancer             |
| Midostaurin| FLT3            | AML (FLT3 mutation), SM                  |
| Ripretinib | KIT             | GIST                                     |
| Avapritinib| KIT/ PDGFR      | GIST, SM                                 |

Abbreviations: FDA: US Food and Drug Administration, CML: chronic myeloid leukemia, PhALL: Philadelphia-positive acute lymphoblastic leukemia, HES: chronic eosinophilic leukemia with PDGFRα rearrangement, GIST: gastrointestinal stromal tumor, SM: systemic mastocytosis, DFSP: dermatofibrosarcoma protuberans, RCC: renal cell carcinoma, HCC: hepatocellular carcinoma.

Imatinib (IM), which inhibits ABL, KIT, and PDGFR, has been used in chronic myeloid leukemia, Philadelphia chromosome-positive acute lymphoblastic leukemia, and chronic eosinophilic leukemia with PDGFRα rearrangement. In a phase I study, a combination of cytarabine, daunorubicin, and IM was investigated in relapsed AML patients with KIT
expression [58]. The complete remission (CR)/CR with incomplete platelet recovery (CRp) rate was 57%. In addition, the phase I/II study evaluated IM combined with mitoxantrone, etoposide, and cytarabine therapy for patients with R/R KIT-positive AML [59]. The combination was well tolerated up to 400 mg/day IM. Of the 21 patients treated at this dose, 13 (62%) achieved CR. Low-dose cytarabine (LDAC) and IM were well tolerated in incompatible or R/R AML patients with KIT expression [60]. However, the combination of LDAC and IM was not shown to be effective compared to LDAC monotherapy. Recently, it was reported that IM as maintenance therapy after the completion of post-remission therapy may improve the outcome of newly diagnosed AML patients [61].

Dasatinib is a medication that is expected to target cancers harboring KIT mutations [52,62,63]. Tarlock et al. showed that cells with KIT exon-17 mutations exhibited in vitro sensitivity to dasatinib [52]. In other work, Malani et al. obtained drug response profiles for established AML cell lines and ex vivo samples from patients with AML by subjecting the cells to high-throughput drug sensitivity and resistance testing with 290 approved and investigational oncology compounds [63]. They suggested that the gene-expression-based upregulation of the KIT pathway may serve as a biomarker of dasatinib efficacy in AML. Indeed, several clinical studies have examined the use of dasatinib for the treatment of CBF leukemia with a KIT mutation. For instance, in single-arm studies by the Cancer and Leukemia Group B (CALGB), patients with CBF leukemia received combination treatment with dasatinib and chemotherapy including HDAC [64]. The results of that study showed that patients harboring tumors with a KIT mutation had disease-free survival and overall survival comparable to those observed for patients harboring tumors with wild-type KIT [64]. Separately, in the phase Ib/IIa study of the German–Austrian AML Study Group (AMLSG), dasatinib was added to intensive induction/consolidation chemotherapy and administered as a maintenance treatment for CBF leukemia [65]. The exploratory analysis of the KIT mutation in that trial showed that five of nine patients who exhibited KIT mutation in paired samples from the time of diagnosis and relapse had lost the variant at relapse, suggesting the possibility that dasatinib inhibited clones with KIT mutations.

Midostaurin is a first-generation FLT3 inhibitor that inhibits FLT3-ITD and TKD mutations [66]. It was reported that the KIT-D816V receptor expressed in Ba/F3 cells was sensitive to midostaurin [48]. A therapeutic effect of midostaurin is expected in KIT-D816V mutation-positive mastocytosis [67,68]. A phase II study (MIDOKIT study: NCT01830361) has been conducted to investigate the additional effect of midostaurin on the treatment of t(8;21) AML with KIT or FLT3-ITD mutations, and its results are awaited.

6. HSP90 Inhibitors for the Treatment of AML with KIT Mutation

Heat shock protein 90 (HSP90) is a molecular chaperone that plays an important role in mediating the correct folding and functionality of its client proteins in cells [69,70]. HSP90 is involved in the stabilization of the cancer-related proteins necessary for tumor development, including receptor tyrosine kinases, signal transducers, cell-cycle regulators, and transcription factors [71,72]. Therefore, HSP90 inhibitors have been developed and are undergoing clinical trials in various cancers. One mechanism of HSP90 inhibitors is blocking the binding of ATP, which induces the degradation of target proteins [71,73,74] (Figure 4). In AML, it has been reported that HSP90 inhibitors may suppress mutated FLT3, as well as the JAK-STAT and PI3K pathways [75–77]. Yu et al. reported that the inhibition of Hsp90 by 17-allylamino-17-demethoxygeldanamycin disrupted downstream signaling pathways of mutant KIT in a RUNX1-RUNX1T1 with a KIT-mutant cell line [78]. Tsujimura et al. examined the potency of the novel KIT inhibitor KI-328 against different types of mutant KIT kinases in AML. They reported that KI-328 showed little potency against D816V-KIT; however, they demonstrated that HSP90 inhibitors suppress the growth of D816V-KIT-expressing cells [79]. Although these reports suggested the effect of HSP90 inhibitors on AML, the clinical use of HSP90 inhibitors has been delayed, partly due to their association with adverse events such as hepatotoxicity and visual abnormalities [72,74].
AML other than CBF leukemia have also attracted attention. Current treatment strategies targeting KIT mutations as molecular targets for treating AML. KIT is a type-III receptor tyrosine kinase that contributes to signal transduction in many pathways, including the P13K, JAK/STAT, MAPK, and Src pathways, in various cells. The KIT mutation plays a central role in various malignant tumors such as GIST and SM, and it is attracting attention as an important molecular target. Treatment with tyrosine kinase inhibitors and HSP90 inhibitors is evolving for these diseases. In AML, it has been noted that the KIT mutation is associated with a poor prognosis in primary CBF leukemia. The HM-SCREEN01 study also showed that AML with RUNXI-RUNXIT1 accounted for a very high proportion of patients with R/R AML with KIT mutations, but this point needs to be confirmed in the future by increasing the study population. Furthermore, with the development of NGS in recent years, the pathological and clinical roles of KIT mutations in AML other than CBF leukemia have also attracted attention. Current treatment strategies may not be able to overcome KIT-mutation-positive AML, and the availability of new precision medicine strategies targeting KIT mutations is eagerly awaited in clinical practice.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms23094694/s1.

**Author Contributions:** Y.M. was the chief investigator in the trial; all authors were involved in patient accrual and data acquisition; S.K., S.C., D.A., Y.M. and A.G. were responsible for data analysis and interpretation; S.K., S.C., Y.M. and A.G. were responsible for the preparation and writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

**Figure 4.** HSP90 inhibitor treatment for leukemia (such as FLT3). By binding of the HsP90 inhibitor to the ATP/ADP pocket of Hsp90, the equilibrium state of Hsp90 becomes ADP dominant. This inhibits the function of chaperone complexes containing client proteins and promotes the degradation of client proteins.

Pimitesib (TAS-116), a highly selective inhibitor of HSP90 α and β, is a new agent that is attracting attention for the treatment of malignancies with KIT mutations. HSP90 regulates the conformation, function, and activation of several HSP90 client proteins, including KIT [80,81]. In a mouse model, pimitesib showed anti-tumor activities while minimizing the adverse effects (e.g., visual disturbances) observed with other HSP90 inhibitors [72]. Pimitesib prolonged progression-free survival in a phase III trial comparing the efficacy and safety of pimitesib to a placebo in patients with previously treated GIST [82]. Recently, it was reported that pimitesib exhibits anti-adult T-cell leukemia/lymphoma (ATL) effects in ex vivo and in vivo preclinical models [74]. In this study, pimitesib suppressed the growth of ATL-related cell lines and primary ATL cells ex vivo and tumors in ATL cell-xenografted mice.

**7. Conclusions**

Here, we discussed the potential of KIT mutations as molecular targets for treating AML. KIT is a type-III receptor tyrosine kinase that contributes to signal transduction in many pathways, including the P13K, JAK/STAT, MAPK, and Src pathways, in various cells. The KIT mutation plays a central role in various malignant tumors such as GIST and SM, and it is attracting attention as an important molecular target. Treatment with tyrosine kinase inhibitors and HSP90 inhibitors is evolving for these diseases. In AML, it has been noted that the KIT mutation is associated with a poor prognosis in primary CBF leukemia. The HM-SCREEN01 study also showed that AML with RUNXI-RUNXIT1 accounted for a very high proportion of patients with R/R AML with KIT mutations, but this point needs to be confirmed in the future by increasing the study population. Furthermore, with the development of NGS in recent years, the pathological and clinical roles of KIT mutations in AML other than CBF leukemia have also attracted attention. Current treatment strategies may not be able to overcome KIT-mutation-positive AML, and the availability of new precision medicine strategies targeting KIT mutations is eagerly awaited in clinical practice.
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