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KF1601, a dual inhibitor of BCR::ABL1 and FLT3, overcomes drug resistance in FLT3^{+} blast phase chronic myeloid leukemia

Hyun-Jin Kwon[1†], Ji Eun Shin[2†], Amir Khan[3†], So Yeon Park[2†], Jiyoung Kim[1], Jee-Young Lee[4], Doohyun Lee[4], Seungyeon Lee[4], Chun Young Im[4], Heegyum Moon[4], Ye Ri Han[5], Minori Tamai[6], Koshi Akahane[6,16], Takeshi Inukai[6,16], Wonhwa Lee[7], Hyelim Kim[8,12], Hong Nam Kim[8,13,14,15], Sung-Min Ahn[1,9*], Hyun Woo Park[2*] and Dong-Wook Kim[10,11*]

Abstract

Blast phase chronic myeloid leukemia (BP-CML) poses significant clinical challenges due to its drug resistance, resulting from BCR::ABL1-dependent mutations and BCR::ABL1-independent pathways. Previously, we reported that FLT3 pathway is activated in ~ 50% of BP-CML cases, indicating a potential avenue for therapeutic intervention via dual inhibition of BCR::ABL1 and FLT3. Here, we aimed to evaluate the efficacy of KF1601, a dual inhibitor of BCR::ABL1 and FLT3, in overcoming drug resistance in BP-CML while also comparing its thrombo-inflammatory responses with those of ponatinib, known to have severe cardiovascular adverse events in human. Our findings revealed that KF1601 effectively inhibited of BCR::ABL1 signaling pathway, even in the presence of the T315I mutation. KF1601 achieved complete tumor regression in K562 xenograft mouse models, and prolonged survival significantly in orthotopic mouse models. Furthermore, KF1601 effectively inhibited the FLT3 signaling pathway in imatinib-resistant K562 cells expressing FLT3 and TAZ, suppressing cell proliferation through dual inhibition of BCR::ABL1 and FLT3. These findings were corroborated using drug-resistant BP-CML cells from patients. In assessing thrombo-inflammatory responses using a murine thrombosis model, ponatinib induced severe responses, leading to carotid artery occlusion and extensive vessel wall damage. In contrast, in mice treated with KF1601, carotid arteries remained unoccluded, with vessel walls preserved intact. In summary, KF1601 demonstrated promising preclinical efficacy in overcoming resistance mechanisms, including the BCR::ABL1^{T315I} mutation, while also addressing FLT3 signaling implicated in BP-CML progression. Unlike existing therapies such as ponatinib, KF1601 offers a favorable safety profile, potentially minimizing the risk of life-threatening adverse effects.

Keywords KF1601, Chronic myeloid leukemia (CML), Chronic phase CML (CP-CML), Blast phase CML (BP-CML), Tyrosine kinase inhibitor (TKI), TKI resistance, FLT3, BCR::ABL1

†Hyun-Jin Kwon, Ji Eun Shin, Amir Khan and So Yeon Park contributed equally to this work.

*Correspondence:
Sung-Min Ahn
ahn@immunoforge.com
Hyun Woo Park
hwp003@yonsei.ac.kr
Dong-Wook Kim
dwkim@eulji.ac.kr
Full list of author information is available at the end of the article

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm, characterized by the fusion of the *ABL1* gene on chromosome 9 with the *BCR* gene on chromosome 22 [1]. This fusion results in the constitutive activation of the BCR::ABL1 tyrosine kinase, which drives aberrant cellular proliferation through downstream signaling pathways including RAS, MYC and STAT [2, 3]. Imatinib, the first generation tyrosine kinase inhibitor (TKI) targeting BCR::ABL1, has revolutionized CML treatment by significantly improving patients' outcome [4–10]. Nevertheless, there are two clinically important unmet needs.

Firstly, resistance to imatinib may arise from mutations in the BCR::ABL1 protein, hindering the binding of imatinib to its ATP-binding site [11, 12]. While second generation TKIs such as nilotinib, radotinib, dasatinib, and bosutinib have been developed to overcome imatinib resistance, certain mutations, such as BCR::ABL1^{T315I}, remain refractory to these therapies [12–17]. Ponatinib, a third-generation TKI, is efficacious against BCR::ABL1^{T315I}, but is associated with life-threatening side effects such as arterial obstruction (33%), thromboembolism (6%), and heart failure (9%) [18–25].

Secondly, blast phase (BP) CML presents a significant clinical challenge due to its resistance to TKIs and high relapse rates. BP-CML is an advanced stage of the disease, marked by the proliferation of immature, undifferentiated blast-like cells in the bone marrow and peripheral blood. While the advent of TKIs has reduced the progression rate to BP-CML from 5–20% to 1–5%, prognosis remains poor, with most patients succumbing within a year of onset [26]. For instance, in a BP-CML cohort treated with ponatinib, only 23% achieved a major cytological response within six months, and the median overall survival was just seven months, underscoring the limited efficacy of current therapies [18].

The progression to BP-CML involves multiple molecular mechanisms such as β-catenin and C-MYC upregulation, oxidative DNA damage leading to genomic instability, mutations such as T315I, and epigenetic reprogramming via the polycomb repressive complex [27]. Recently, we reported that FLT3-TAZ signaling is activated in approximately 50% of BP-CML cases conferring TKI resistance [28]. In acute myeloid leukemia, it has been reported that FLT3 increases β-catenin activity, contributing to self-renewal and leukemogenesis, and that FLT3-mediated STAT5 activation upregulates C-MYC, supporting malignant progression [29, 30]. Given that β-catenin and C-MYC are key players in BP-CML progression, FLT3 activation may contribute to disease advancement through these pathways, further supporting the rationale for targeting BCR::ABL1 and FLT3 together provides novel therapeutic opportunities for FLT3^{+} BP-CML patients.

In this study, we aimed to evaluate the efficacy of KF1601, a dual inhibitor of BCR::ABL1 and FLT3, in overcoming TKI resistance in BP-CML. Specifically, we investigated KF1601's efficacy in inhibiting drug-resistant mutant forms of BCR::ABL1, including BCR::ABL1^{T315I}, and its capacity to suppress FLT3 signaling and proliferation in drug-resistant BP-CML cells, expressing FLT3 and harboring BCR::ABL1. Additionally, we aimed to compare thrombo-inflammatory responses, associated with severe cardiovascular adverse events in human, of KF1601 and ponatinib.

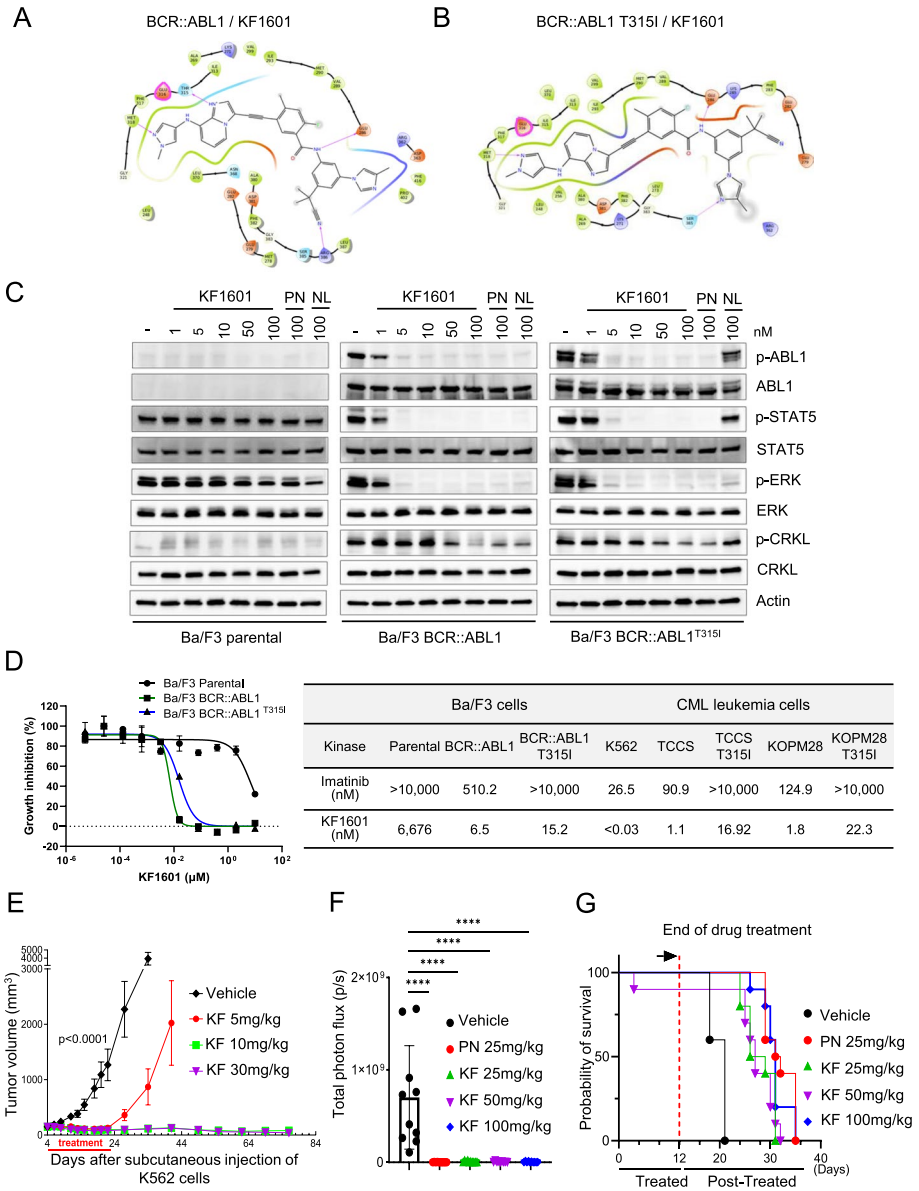
Results

KF1601 forms stable complexes with both native BCR::ABL1 and BCR::ABL1^{T315I}

KF1601 forms four hydrogen bonds with native BCR-ABL1 and three hydrogen bonds with BCR::ABL1^{T315I}. Specifically, the pyrazole ring consistently forms a hydrogen bond with the hinge site residue M318, while the amide nitrogen of KF1601 interacts with the E286 side chain. Moreover, in the native BCR:ABL1, the nitrile moiety of KF1601 forms a hydrogen bond with R386, whereas in the BCR::ABL1^{T315I}, the nitrogen atom of the indole ring forms a hydrogen bond with S385. Both interactions contribute to enhancing KF1601's stabilization within the ATP-binding pocket. While a hydrogen bond is formed between the nitrogen of the pyridine ring and the T315 side chain of native BCR::ABL1, this bond is absent in BCR::ABL1^{T315I}. The computational binding energy calculations revealed that BCR::ABL1^{T315I} exhibits a relatively higher binding energy (native BCR::ABL1 = −83.15 kcal/mole, BCR::ABL1^{T315I} = −62.43 kcal/mole). However, it is expected that KF1601's robust binding to BCR::ABL1^{T315I} with three hydrogen bonds will suffice for effective inhibition. In summary, molecular docking simulations demonstrated that KF1601 forms stable complexes with both native BCR::ABL1 and BCR::ABL1^{T315I} (Fig. 1A and B).

KF1601 inhibited the downstream signaling pathway of BCR::ABL1

We investigated the effects of KF1601 on the downstream signaling pathway of BCR::ABL1 in three different types of cells: 1) parental Ba/F3 cells; 2) Ba/F3 cells with native BCR::ABL1; and 3) Ba/F3 cells with BCR::ABL1^{T315I}. Ponatinib served as a positive control for BCR::ABL1^{T315I}, and nilotinib as a negative control [13, 24, 25]. KF1601 downregulated the phosphorylation of CRKL, an adaptor and the major substrate of BCR::ABL1 as well as that of STAT5 and ERK, critical mediators of oncogenic transcriptional events in CML, in Ba/F3 cells with



	Ba/F3 cells			CML leukemia cells				
Kinase	Parental	BCR::ABL1	BCR::ABL1 T315I	K562	TCCS	TCCS T315I	KOPM28	KOPM28 T315I
Imatinib (nM)	>10,000	510.2	>10,000	26.5	90.9	>10,000	124.9	>10,000
KF1601 (nM)	6,676	6.5	15.2	<0.03	1.1	16.92	1.8	22.3

Fig. 1 KF1601 forms stable complexes with BCR::ABL1 and BCR::ABL1^{T315I}, inhibiting downstream signaling pathways and demonstrating potent in vivo efficacy. **A** KF1601 forms four hydrogen bonds with native BCR::ABL1. **B** KF1601 forms three hydrogen bonds with BCR::ABL1^{T315I}. The magenta dashed lines represent hydrogen bond interactions. **C** Immunoblotting results shown in three panels: the left panel displays results from Ba/F3 parental cells, the middle panel displays results from Ba/F3 cells expressing native BCR::ABL1, and the right panel displays results from Ba/F3 cells expressing BCR::ABL1^{T315I}. Ponatinib served as a positive control for BCR::ABL1^{T315I}, and nilotinib as a negative control. KF1601 demonstrated dose-dependent inhibition of the downstream signaling pathway of BCR::ABL1 in both Ba/F3 cells expressing native BCR::ABL1 and Ba/F3 cells expressing BCR::ABL1^{T315I}. **D** Dose–response curves for KF1601 in Ba/F3 cell line and IC_{50} values of KF1601 and imatinib. Ba/F3: Ba/F3 parental cells; Ba/F3$^{BCR::ABL1}$: Ba/F3 cells expressing native BCR::ABL1; Ba/F3^{T315I}: Ba/F3 cells expressing BCR::ABL1^{T315I}; K562, TCCS, KOPM28: patient-derived CML cell lines with native BCR::ABL1; TCCS^{T315I} and KOPM28^{T315I}: sublines of TCCS and KOPM28 with BCR::ABL1^{T315I}. **E** Tumor growth inhibition in a CML xenograft mouse model using K562 human CML cells. Following cessation of KF1601 treatment, complete tumor regression was maintained in 3 out of 10 mice treated with 5 mg/kg of KF1601, and in all mice treated with either 10 mg/kg or 30 mg/kg of KF1601 until the end of the study. Each KF1601 treatment group was compared to the vehicle group based on the treatment day using GraphPad prism 10, with statistical significance ($p < 0.0001$). **F** Reduction in tumor burden in an orthotopic CML mouse model mice. The tumor burden in KF1601-treated groups was reduced by over 99% compared to that in the vehicle-treated group. **** $p < 0.0001$. **G** Post-treatment survival of orthotopic CML mice. In the KF1601-treated groups, the median survival time increased to 31–35 days, compared to 21 days in the vehicle-treated group. Curves were compared by Log-rank Mantel-Cox test (KF1601 25 mg/kg $p < 0.001$, Ponatinib 25 mg/kg, KF1601 50 mg/kg and KF1601 100 mg/kg $p < 0.0001$)

either native BCR::ABL1 or BCR::ABL1^{T315I} in a dosage-dependent manner. Nilotinib, a second-generation TKI, inhibited the downstream signaling pathway of native BCR::ABL1, but not that of BCR::ABL1^{T315I} (Fig. 1C).

Since CRKL phosphorylation is directly associated with the kinase activity of BCR::ABL1, we further investigated the effect of KF1601 on CRKL phosphorylation in four different cell lines: Ba/F3 cells expressing BCR::ABL1^{T315I}, and patient-derived CML cell lines including TCCS, TCCS^{T315I} and K562. Quantitative analysis of CRKL phosphorylation demonstrated that KF1601 is a potent inhibitor of both native BCR::ABL1 and BCR::ABL1^{T315I} (Fig. S1).

KF1601 inhibited the kinase activity of native and mutant forms of BCR::ABL1

We quantitatively assessed the inhibitory effect of KF1601 on the kinase activity of native and mutant forms of BCR::ABL1 through in vitro biochemical kinase assay. KF1601 inhibited the kinase activity of clinically important mutants of BCR::ABL1, including BCR::ABL1^{T315I} with IC_{50} values ranging between 0.76 and 10.9 nM (Table S1).

KF1601 inhibited the proliferation of murine Ba/F3 and human CML cell lines with either native BCR::ABL1 or BCR::ABL1 ^{T315I}

We investigated the inhibitory effect of KF1601 on cellular proliferation using three murine Ba/F3 cell lines (i.e., parental, Ba/F3 cells expressing either native BCR::ABL1 or BCR::ABL1^{T315I}) and five human CML cell lines (i.e., K562, TCCS, TCCS^{T315I}, KOPM28, and KOPM28^{T315I}). Figure 1D summarizes IC_{50} values of KF1601 and imatinib in these eight cell lines. Both KF1601 and imatinib strongly suppressed the proliferation of Ba/F3$^{BCR::ABL1}$, K562, TCCS, and KOPM28 harboring native BCR::ABL1. KF1601 strongly suppressed the proliferation of Ba/F3^{T315I}, TCCS^{T315I} and KOPM28^{T315I} harboring BCR::ABL1^{T315I}, while imatinib did not.

KF1601 achieved complete tumor regression and prolonged survival in a CML xenograft mouse model

We evaluated the efficacy of KF1601 in reducing tumor burden in a CML xenograft mouse model using K562 human CML cells. K562 tumor-bearing mice received oral doses of either vehicle ($N=10$) or KF1601 (5, 10, or 30 mg/kg, $N=10$ per group) once daily for 18 consecutive days. We measured tumor volume to assess tumor growth inhibition, and monitored survival for 8 weeks post-treatment. As depicted in Fig. 1F, tumor growth was entirely inhibited in all KF1601-treated groups. Following the cessation of KF1601 treatment, complete tumor regression was sustained in 3 out of 10 mice treated with 5 mg/kg of KF1601, and in all mice treated with either 10 mg/kg or 30 mg/kg of KF1601 for 8 weeks (i.e., until the end of the study).

KF1601 reduced tumor burden and prolonged survival in an orthotopic CML mouse model

We evaluated the efficacy of KF1601 in reducing tumor burden in an orthotopic CML mouse model. Ba/F3 cells, engineered to co-express BCR::ABL1^{T315I} and firefly luciferase, were intravenously injected into BALB/c nude mice. Three days post-injection, mice were randomly assigned to one of five treatment groups: vehicle (negative control), ponatinib (positive control), and three groups treated with varying doses of KF1601 (25, 50 and 100 mg/kg ($N=10$ per group). Proliferation of the Ba/F3 cells was monitored using in vivo bioluminescence imaging, revealing that the tumor burden in KF1601-treated groups was reduced by over 99% compared to that in the vehicle-treated group (Fig. 1F). A reduction of over 99% in tumor burden corresponds to complete cytogenetic response in human CML treatment [31].

Following the cessation of KF1601 treatment at day 12, we monitored the survival of the five treatment groups. As depicted in Fig. 1G, we observed a median survival time of 21 days for the vehicle-treated mice, while in the KF1601-treated groups, the median survival time increased to 31–35 days, demonstrating a significant survival benefit comparable to that of ponatinib.

KF1601 inhibited FLT3 and suppressed the proliferation of BP-CML cells

In our previous study, we established two CML cell line models to demonstrate the involvement of FLT3-TAZ signaling in TKI resistance in BP-CML: 1) K562 cells overexpressing FLT3 (K562-FLT3); 2) a subline of K562-FLT3 with imatinib resistance (K562-FLT3-IR). K562-FLT3 does not express TAZ and is not resistant to imatinib while K562-FLT3-IR expresses TAZ [28].

Utilizing the same cell line models (i.e., K562-FLT3 and K562-FLT3-IR), we investigated the efficacy of KF1601 in inhibiting FLT3 signaling, in comparison to that of ponatinib. KF1601 effectively suppressed FLT3-pSTAT3-TAZ signaling and BCR::ABL1 signaling in both K562-FLT3 and K562-FLT3-IR cells (Fig. 2A and B). Furthermore, KF1601 significantly suppressed the proliferation of both K562-FLT3 and K562-FLT3-IR cells (Fig. 2C-E).

To further evaluate the clinical relevance of our findings, We investigated the efficacy of KF1601 in bone marrow mononuclear cells (BMMCs) isolated from CML patients. Initially, we confirmed the up-regulation of FLT3 protein expression in BMMCs from BP-CML patients (i.e., 1588(BP) and 2084(BP)) compared

to those from chronic phase (CP) CML patients (2F-2I). As depicted in Fig. 2J and K, both imatinib and KF1601 exhibited minimal toxicity in PBMCs (PBMC1 and PBMC2) derived from healthy donors, even at high concentrations. However, while imatinib exhibited limited efficacy against BP-CML cells with FLT3 overexpression, KF1601 demonstrated dose-dependent inhibition of their proliferation. These results underscore the potential of KF1601 as a promising therapeutic agent for both prevention of resistance acquisition driven by FLT3 upregulation and treatment post-acquisition.

Evaluation of thrombo-inflammatory responses: KF1601 versus ponatinib in a murine thrombosis model

We compared the thrombo-inflammatory effects of KF1601 with ponatinib, a drug known for its potential to induce acute ischemic and other thrombo-inflammatory responses, using a murine thrombosis model. As illustrated in Fig. 2L, ponatinib triggered severe thrombo-inflammatory responses, leading to the occlusion of carotid arteries with extensive vessel wall damage. In contrast, in mice treated with KF1601, carotid arteries remained unoccluded, with the vessel walls preserved intact. To further evaluate thrombus size, thrombosis was induced in testicular arteries. The average size score of thrombi induced by KF1601 was 3.24, whereas that induced by ponatinib was 5.21. A size score of 3 indicates a medium-sized thrombus (measuring 75—150 × 75—150nm^2), while a size score of 5 indicates an extra-large thrombus (measuring 300 – 400 × 300 – 400 nm^2). In simpler terms, the size of thrombus induced by KF1601 was approximately one-tenth that induced by ponatinib (Fig. 2M).

Evaluation of KDR and platelet function inhibition: KF1601 versus ponatinib

KDR inhibition and platelet dysfunction are recognized contributors to thrombo-inflammatory responses. KDR inhibition triggers endothelial cell damage, culminating in thrombosis [32]. As depicted in Fig. 2N, ponatinib demonstrated a KDR inhibition potency tenfold greater than that of KF1601. In addition, we conducted kinome analyses to compare the overall selectivity of KF1601 and ponatinib. As summarized in Supplementary Table 2, KF1601 exhibited greater selectivity compared to ponatinib.

Platelet dysfunction in normal physiological conditions often results in platelet aggregation, promoting thrombosis. As summarized in Supplementary Table 3, ponatinib inhibited platelet function by more than 90% while KF1601 inhibited platelet function by approximately 25%, comparable to imatinib, a drug known for relatively low cardiovascular toxicity and arterial thrombotic event rate.

Discussion

In this study, we demonstrated the preclinical efficacy of KF1601, a novel dual inhibitor of BCR::ABL1 and FLT3, in addressing the unmet needs of CML treatment. KF1601 exhibited potent inhibitory activity against native BCR::ABL1 and clinically meaningful mutant forms, including BCR::ABL1^{T315I}. This broad spectrum of activity holds promise for overcoming resistance associated with BCR::ABL1 mutations, offering a potential therapeutic option for patients with refractory disease.

Importantly, our study also highlights the role of FLT3 pathway activation in promoting TKI resistance in BP-CML. Activation of FLT3 signaling has been implicated in promoting leukemic cell proliferation and survival, particularly in the context of BP-CML [33]. By targeting

(See figure on next page.)

Fig. 2 Effects of KF1601 on FLT3 signaling pathway and thrombo-inflammatory responses. **A** Immunoblotting analysis of FLT3 signaling pathway in K562-FLT3 cells treated with KF1601, ponatinib (Pona) for 4h. **B** Immunoblotting analysis of FLT3 signaling pathway in K562-FLT3-IR cells treated with KF1601, ponatinib for 17h. **C** Cell images of K562-FLT3 cells at day 4 post-treatment with compounds, and images of K562-FLT3-IR cells at day 6 post-treatment with compounds. **D** and **E** Cell viability measurement of K562-FLT3 cells at day 4 post-treatment with compounds (D), and that of K562-FLT3-IR cells at day 6 post-treatment with compounds (E). **F** and **G** Immunoblotting analysis of FLT3 protein in BMMCs from BP CML patients (1588(BP) and 2084(BP)). BMMCs from CP CML patients (1588(CP) and 903(CP)) were used as negative controls for FLT3 expression. **H** and **I** Immunofluorescence images of FLT3 expression (green) on the cell surface in 1588(BP) and 2084(BP) cells. 1332(CP) and 2084(CP) were used as negative controls for FLT3 expression. DAPI (blue) was used as a nuclear marker. **J** and **K** Cell viability measurement of PBMCs from normal donors and BMMCs from BP CML patients. PBMCs and BMMCs were subjected to treatment with either imatinib (J) or KF1601 (K) for 4 days. 2084 (BP) harbors BCR::ABL1 T315I mutation with a distinct FLT3 expression pattern (F); 1588 (BP) harbors BCR::ABL1 E255V mutation with a distinct FLT3 expression pattern (G). $n = 3$ per group. **L** The left panel illustrates the pivotal role of FLT3 in BP-CML progression and TKI resistance. The right panel illustrates potential of KF1601 may overcome TKI resistance by targeting mutant forms of BCR::ABL1 while also addressing the FLT3-mediated signaling pathways. **L** Thrombo-inflammatory responses in carotid arteries. Ponatinib induced occlusion of carotid arteries with extensive vessel wall damage. Conversely, in mice treated with KF1601, carotid arteries remained unoccluded, with the vessel walls preserved intact. **M** Evaluation of thrombus size in testicular arteries. The size of thrombus induced by KF1601 was approximately one-tenth that induced by ponatinib. **N** KDR inhibition. Ponatinib exhibited a KDR inhibition potency tenfold greater than that of KF1601

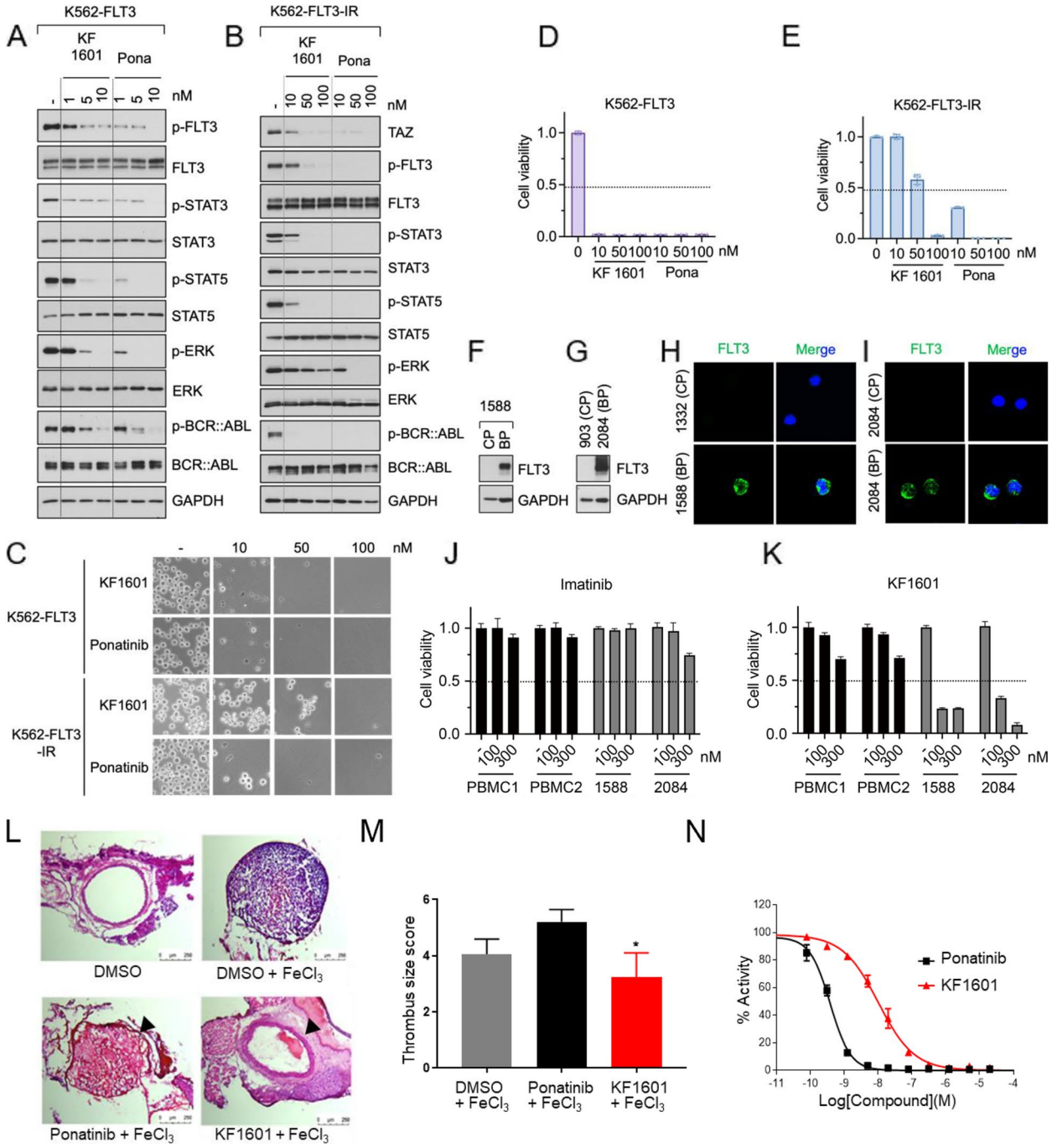


Fig. 2 (See legend on previous page.)

both BCR::ABL1 and FLT3, KF1601 demonstrated synergistic anti-leukemic effects, as evidenced by its ability to induce cell death in FLT3 + BCR::ABL1 TKI-resistant CML cells. These findings underscore the potential clinical utility of KF1601 in addressing the therapeutic challenges associated with BP-CML, where conventional TKIs may fall short. Also, as Copland [27] emphasized, due to poor outcomes of BP-CML, we need to focus on preventing the progression to BP-CML. The ability of KF1601 to concurrently inhibit both BCR::ABL1 and FLT3 signaling pathways has the potential to mitigate the development of BP-CML cells, offering a novel therapeutic strategy for preventing disease progression and improving patient outcomes.

While ponatinib demonstrated efficacy in inhibiting both BCR::ABL1 and FLT3, thereby potentially addressing the

therapeutic challenges associated with BP-CML, its clinical utility is hindered by significant limitations. The occurrence of life-threatening adverse effects, including arterial obstruction, thromboembolism, and heart failure, underscores the need for alternative treatment options [20]. In contrast, KF1601 presents a promising alternative with a favorable safety profile observed in preclinical studies. The ability of KF1601 to simultaneously target BCR::ABL1 and FLT3, coupled with its oral bioavailability and potential for reduced adverse effects, positions it as a compelling candidate for the management of BP-CML. Additionally, the development of KF1601 offers the possibility of addressing the unmet needs of CML patients resistant to first- and second-generation TKIs, including those harboring the BCR::ABL1^{T315I} mutation, without compromising on safety or efficacy. Further clinical investigation is warranted to validate the therapeutic benefits of KF1601 in BP-CML and to delineate its comparative advantages over existing treatment modalities, including ponatinib.

Conclusion

The emergence of TKI resistance and the clinical complexities associated with BP-CML underscore the urgent need for novel therapeutic approaches. KF1601, a dual inhibitor targeting both BCR::ABL1 and FLT3, demonstrates promising preclinical efficacy in overcoming resistance mechanisms, including the notorious BCR::ABL1^{T315I} mutation, while also addressing FLT3-mediated signaling implicated in BP-CML progression (Supplementary Fig. 2). Unlike existing therapies such as ponatinib, KF1601 offers a favorable safety profile, potentially minimizing the risk of life-threatening adverse effects. Future clinical studies are warranted to validate the therapeutic benefits of KF1601 in TKI-resistant chronic and blast phase CML.

Abbreviations

BCR::ABL1	*BCR::ABL1* Fusion gene (Breakpoint Cluster Region gene and ABL Proto-Oncogene 1)
FLT3	Fms Related Receptor Tyrosine Kinase 3
TAZ	Transcriptional coactivator with PDZ-binding motif
CML	Chronic myeloid leukemia
AML	Acute myeloid leukemia
TKI	Tyrosine kinase inhibitor
BMMCs	Bone marrow mononuclear cells
CP	Chronic phase
AP	Accelerated phase
BP	Blast phase
TKD	Tyrosine kinase domain

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12943-025-02292-z.

Additional file 1. Supplementary materials and methods

Additional file 2. Supplementary Figures and Tables

Additional file 3

Authors' contributions

HJK performed most experiments related to BCR::ABL1; JES and SYP performed most experiments related to FLT3 signaling. AK performed bioinformatics analysis and wrote the manuscript. JYK designed the animal experiments. JYL performed molecular modeling study. DHL, SYL, CYI, and YRH synthesized chemical compounds. HGM established Ba/F3 cell lines and performed cell-based experiments. WHL performed experiments related to thrombo-inflammatory responses. MT, KA and TI established and provided human CML cell lines with T315I mutation. SMA, HWP, and DWK conceived the project, provided leadership, and wrote the manuscript. All authors reviewed and edited the manuscript.

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Data availability

All data associated with this study are present in the paper or the Supplementary Materials.

Declarations

Ethics approval and consent to participate

All human samples were obtained from the Korea Leukemia Bank and the protocol was approved by the Institutional Review Board. Patient consent was obtained in accordance with the Declaration of Helsinki. Animal experiments were approved by Institutional *Animal* Care and Use Committee (IACUC), the preclinical research center, Daegu-Gyeongbuk Medical Innovation Foundation (Documentation KMEDI-22011801–01).

Consent for publication

Not applicable.

Competing interests

HJK, JYK, and SMA are employees of ImmunoForge, Inc., and KF1601 is a proprietary drug candidate of ImmunoForge, Inc. The remaining authors declare no conflict of interests.

Author details

[1]ImmunoForge, Co. Ltd, Seoul 08591, Republic of Korea. [2]Department of Biochemistry, College of Life Science and Biotechnology, Brain Korea 21 FOUR Program, Yonsei University, Seoul 03722, Republic of Korea. [3]Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. [4]Daegu-Gyeongbuk Medical Innovation Foundation, New Drug Development Center, Daegu 41061, Republic of Korea. [5]Department of Chemistry, College of Science and Technology, Duksung Women'S University, Seoul 01369, Republic of Korea. [6]Department of Pediatrics, University of Yamanashi, Chuo, Japan. [7]Department of Chemistry, Sungkyunkwan University, Suwon 16419, Republic of Korea. [8]Brain Science Institute, Korea, Institute of Science and Technology (KIST), Seoul, 02792, Republic of Korea. [9]Department of Genome Medicine and Science, College of Medicine, Gachon University, Incheon 21565, Republic of Korea. [10]Hematology Department, Eulji Medical Center, Eulji University, Uijeongbu-Si, Gyeonggi-Do, Republic of Korea. [11]Leukemia Omics Research Institute, Eulji University, Uijeongbu-si, Gyeonggi-Do, Republic of Korea. [12]Department of Biotechnology, Yonsei University, Seoul 03722, Republic of Korea. [13]Division of Bio-Medical Science and Technology (KIST School), Korea University of Science and Technology (UST), Seoul 02792, Republic of Korea. [14]School of Mechanical Engineering, Yonsei University, Seoul 03722, Republic of Korea. [15]Yonsei-KIST Convergence Research Institute, Yonsei University, Seoul 03722, Republic of Korea. [16]Global Leukemia Cell-Line Assembly Network, University of Yamanashi, Kofu City, Japan.

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