haematologica
Journal of the Ferrata Storti Foundation

Safety and efficacy of flumatinib as later-line therapy in patients with chronic myeloid leukemia

by Yunfan Yang, Yuntao Liu, Hui Sun, Li Meng, Hai Lin, Chunyan Chen, Jianda Hu, Xuliang Shen, Minghui Duan, Yanli Zhang, Dilinazi Abulaiti, Jinghua Wang, Hongqian Zhu, Luoming Hua, Qing Leng, Chun Zhang, Lili Sun, Weiming Li, Huanling Zhu, Bingcheng Liu, and Jianxiang Wang

Received: December 30, 2023.
Accepted: June 19, 2024.

Citation: Yunfan Yang, Yuntao Liu, Hui Sun, Li Meng, Hai Lin, Chunyan Chen, Jianda Hu, Xuliang Shen, Minghui Duan, Yanli Zhang, Dilinazi Abulaiti, Jinghua Wang, Hongqian Zhu, Luoming Hua, Qing Leng, Chun Zhang, Lili Sun, Weiming Li, Huanling Zhu, Bingcheng Liu, and Jianxiang Wang. Safety and efficacy of flumatinib as later-line therapy in patients with chronic myeloid leukemia.
Haematologica. 2024 June 27. doi: 10.3324/haematol.2023.284892 [Epub ahead of print]

Safety and efficacy of flumatinib as later-line therapy in patients with chronic myeloid leukemia

Running title: Flumatinib: Later-line therapy in patients with CML

Yunfan Yang[1*], Yuntao Liu[2*], Hui Sun[3*], Li Meng[4], Hai Lin[5], Chunyan Chen[6], Jianda Hu[7], Xuliang Shen[8], Minghui Duan[9], Yanli Zhang[10], Dilinazi Abulaiti[11], Jinghua Wang[12], Hongqian Zhu[13], Luoming Hua[14], Qing Leng[15], Chun Zhang[16], Lili Sun[17], Weiming Li[18#], Huanling Zhu[19#], Bingcheng Liu[2#], Jianxiang Wang[2]

[1]Department of Hematology, Institute of Hematology, West China Hospital of Sichuan University, Chengdu, Sichuan, China

[2]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China

[3]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

[4]Tongji Hospital Tongji Medical College of Huazhong University of Science &Technology, Wuhan, Hubei, China

[5]Department of Hematology, First Hospital of Jilin University, Changchun, Jilin, China

[6]Qilu Hospital of Shandong University, Jinan, Shandong, China

[7]Wilis F. Pierce Memorial Hospital, Fuzhou, Fujian, China

[8]Heping Hospital Affiliated to Changzhi Medical College, Changzhi, Shanxi, China

[9]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

[10]Henan Cancer Hospital, Zhengzhou, Henan, China

[11]Hematologic Disease Center, The First Affiliated Hospital of Xinjiang Medical University, Xinjiang Hematologic Disease Institute, Urumgi, Xinjiang, China

[12]The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China

[13]Department of Hematology, Guizhou Provincial People's Hospital, Guiyang, Guizhou, China

[14]Affiliated Hospital of Hebei University, Baoding, Hebei, China

[15]Anshan Central Hospital, Anshan, Liaoning, China

[16]The First Affiliated Hospital of Jiamusi University, Jiamusi, Heilongjiang, China

[17]The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China

[18]Xiehe Hospital Tongji Medical College of Huazhong University of Science &Technology, Wuhan, Hubei, China

[19]Department of Hematology, Institute of Hematology, West China Hospital of Sichuan University, Chengdu, Sichuan, China

***Co-first author**

#Corresponding authors:

Bingcheng Liu

State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China）

Email: liubingcheng@ihcams.ac.cn,

+8613602031023

Weiming Li

Xiehe Hospital Tongji Medical College of Huazhong University of Science &Technology, Wuhan, Hubei, China,

Email: lee937@126.com,

+8613098815546

Huanling Zhu

Department of Hematology, Institute of Hematology, West China Hospital of Sichuan University, Chengdu, Sichuan, China,

Email: zhuhuanling@scu.edu.cn,

+8618980601241

Author contribution:

Yunfan Yang: Data curation, Formal Analysis Yuntao Liu: Data curation, Formal Analysis Hui Sun: Data curation, Formal Analysis Li Meng: Data curation, Hai Lin: Data curation, Chunyan Chen: Data curation, Jianda Hu: Data curation, Xuliang Shen: Data curation, Minghui Duan: Data curation, Yanli Zhang: Data curation, Dilinazi Abulaiti: Data curation, Jinghua Wang: Data curation, Hongqian Zhu: Data curation, Luoming Hua: Data curation, Qing Leng: Data curation, Chun Zhang: Data curation, Lili Sun: Data curation, Weiming Li: Data curation, Formal Analysis, Conceptualization, Writing – original draft, Writing – review & editing Huanling Zhu: Data curation, Formal Analysis, Conceptualization, Writing – original draft, Writing – review & editing

Bingcheng Liu: Data curation, Formal Analysis, Conceptualization, Writing – original draft, Writing – review & editing Jianxiang Wang: Data curation, Writing – review & editing

Data sharing statement:

Data that support the results of this study are available from the corresponding author upon reasonable request

Clinical trial registration: NA

Funding: The work was supported by Science and Technology Project of Tianjin (grant no. 21JCQNJC01540). The authors would like to thank all doctors participating in this study.

Conflict of interest:

The authors declare no potential conflicts of interest.

Patient consent statement

This is a retrospective study, and the informed consent from patients was waived.

Permission to reproduce material from other sources

NA

Abstract

To evaluate the efficacy and safety of flumatinib in the later-line treatment of Chinese patients with Philadelphia chromosome-positive chronic-phase chronic myeloid leukemia (CP-CML previously treated with tyrosine kinase inhibitors (TKIs). Patients with CML-CP were evaluated for the probabilities of responses including complete hematologic response (CHR), cytogenetic response, and molecular response (MR) and adverse events (AEs) after the later-line flumatinib therapy. Of 336 enrolled patients with median age 50 years, median duration of treatment with flumatinib was 11.04 (2-25.23) months. Patients who achieved clinical responses at baseline showed maintenance of CHR, complete cytogenetic response (CCyR)/2-log molecular response (MR2), major molecular response (MMR), and 4-log molecular response or deep molecular response (MR4/DMR) in 100%, 98.9%, 98.6%, and 92.9% patients, respectively. CHR, CCyR/MR2, MMR, and MR4/DMR responses were achieved in 86.4%, 52.7%, 49.6%, and 23.5% patients respectively, which showed the lack of respective clinical responses at baseline. The patients without response at baseline, treated with flumatinib as 2L TKI, having no resistance to prior TKI or only resistance to imatinib, with response to last TKI, and with *BCR::ABL* ≤10% had higher CCyR/MR2, MMR, or MR4/DMR. The AEs observed during the later-line flumatinib treatment were tolerable and consistent with those reported with the first-line therapy. Flumatinib was effective and safe in patients who are resistant or intolerant to other TKIs. In particular, 2L flumatinib treatment induced high response rates and was more beneficial to patients without previous 2G TKI resistance, thus serving as a probable treatment option for these patients.

Keywords: *BCR::ABL1***,** Chronic myeloid leukemia, Flumatinib, Philadelphia chromosome, Tyrosine kinase inhibitors

Introduction

Tyrosine kinase inhibitors (TKIs) have improved the outcome of chronic-phase chronic myeloid leukemia (CML-CP) with a higher response rate and lower progression risk.[1,2] The relative survival of CML patients was 92% with TKI therapy.[3] The current evidence suggests that TKI therapy can be safely discontinued in patients after achieving deep molecular response (DMR) with subsequent follow-ups.[4]

The current paradigm for CML therapy has become sophisticated and complex, including the Food and Drug Administration–approved first-generation (1G) TKI imatinib; the second-generation (2G) TKIs, such as nilotinib, dasatinib, and bosutinib; and third-generation (3G) TKI ponatinib and STAMP (specifically targeting the ABL myristoyl pocket) inhibitor, asciminib.[1,5,6] In frontline therapy for patients with CML-CP, ~50% of patients treated with imatinib and ~30% to 40% of patients treated with 2G TKIs eventually require to change therapy in a span of 5 years because of the resistance or intolerance.[7,8] Only ~30% to 55% of patients treated with TKIs achieved a 4.5-log molecular response (MR4.5), leading to the discontinuation of TKI therapy.[9] Therefore, the National Comprehensive Cancer Network (NCCN) guidelines for Clinical Practice Guidelines in Oncology and European Leukemia Net (ELN) recommend the selection of first-line (1L) TKIs (1G or 2G) and subsequent TKI adjustments/switch on the basis of the risk level at initial diagnosis or follow-up, therapeutic goal, comorbidities, and milestone clinical response.[1,5]

Flumatinib mesylate, a 2G TKI, is a derivative of imatinib and has higher selectivity and potency toward *BCR::ABL1* kinase compared with imatinib.[10] Flumatinib was approved by the National Medical Products Administration in late 2019 for patients with newly diagnosed CML-CP.[11] In real-world clinical practice, flumatinib has been used as not only the 1L therapy but also later-line therapy on the basis of its substantial inhibitory effect against *BCR::ABL* kinase and tolerable side-effect profile, but there are no data on its real-world efficacy and safety in the large patient population.[12] In the recent phase 3 trial, flumatinib reported higher efficacy and a lower rate of side effects than imatinib in patients with newly diagnosed CML-CP.[13] The rate of early molecular response (EMR) at

3 months, the cumulative rate of major molecular response (MMR), and ≥4-log molecular responses (MR4) or better were significantly higher in the flumatinib group than in the imatinib group.[13]

The special pyridine group and a trifluoromethyl group in flumatinib strongly interacted with residues I293, L298, L354, and V379 in ABL kinase via hydrophobic interactions, causing an increase in potency of inhibition of *BCR::ABL1* kinase compared with imatinib and nilotinib. The in vitro studies showed that flumatinib has a high potency against mutant *BCR::ABL1* kinase, such as V299L, F317L, F317I, and M351T mutations.[10,14,15] Furthermore, an unpublished phase 1a study of flumatinib in patients with advanced CML showed that flumatinib had considerable antileukemic activity and acceptable tolerability. The results indicated the potential therapeutic efficacy of flumatinib in patients who were resistant to other TKIs.

Thus, the aim of this multicenter, retrospective, and observational study was to analyze the efficiency and safety of flumatinib in the later-line setting in patients with CML who were resistant or intolerant to the previous TKIs in real-world settings.

Methods

Study design and patients

This multicenter, retrospective, and observational study included adult patients with CML, aged ≥18 years, who were treated with flumatinib as second-line (2L) to fourth-line (4L) therapy between January 1, 2020 and January 21, 2022, across 18 centers in China. The patients with prior treatment with TKIs such as imatinib, nilotinib, dasatinib, and flumatinib were included in this study. Patients treated with flumatinib were replaced with other targeted drugs after the completion of the 1L flumatinib. After flumatinib was marketed, it was again used for treatment. As this is a real-world study, patients treated with all classes of TKIs were included. All patients were diagnosed and confirmed as Philadelphia chromosome-positive (Ph+) using conventional cytogenetic assessment and/or with *BCR::ABL1* transcript on the basis of the quantitative or qualitative polymerase chain reaction at diagnosis. The disease phase was defined according to the

ELN 2020 recommendations.[1]

Treatment procedure

The reason for changing the treatment to flumatinib was judged by the investigator and classified as resistant or intolerant to previous TKIs. Flumatinib was initially prescribed at a dose of 600 mg/day for most of the patients and modified by the clinician during the treatment according to the clinical practice.

Study endpoints

The primary outcome was to demonstrate the probabilities of responses including complete hematologic response (CHR), cytogenetic response, and molecular response (MR) after the later line of flumatinib. The secondary outcome was to assess adverse events (AEs).

Response evaluation

The treatment response such as CHR, cytogenetic response, and MR was judged by the investigator according to the ELN 2020 response criteria.[1] All the quantitative detection of *BCR::ABL1* transcript was performed in the laboratory with a certified international scale (IS). Patient's responses of MR4 or greater are referred to as DMR in this study. The mutation analysis of the ABL1 kinase domain was performed optionally on the basis of the decision of the investigators. The complete cytogenetic response (CCyR)/2-log molecular response (MR2) was defined as no Ph chromosome in ≥20 metaphases by conventional G-banding of chromosomes or *BCR::ABL1* transcript ≤1% on the IS. The AEs were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Ethical consideration

The study was approved by the Ethics Committee of Blood Diseases Hospital, Chinese Academy of Medical Sciences (ethics number: QTJC2021008-EC-1). The trial was conducted in accordance with the protocol and the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. This

is a retrospective study, and the informed consent from patients was waived.

Statistical analysis

Quantitative variables were expressed as median and range, whereas qualitative variables were expressed as number and percentage. Time-to-event variables, such as survival and cumulative rate of response, were estimated by the Kaplan-Meier method. The difference in time-to-event variables between groups was analyzed by the Log Rank test. All statistical analyses were performed using SPSS Version 21, statistical analysis software (IBM Corporation, NY, USA).

Results

Patients disposition and baseline clinical characteristics

Of 336 patients with CML included in this retrospective study, 190 (56.5%) males and 146 (43.4%) females with a median age of 50 (range: 18-87) years received flumatinib as the 2L or later-line treatment. The median time from enrollment to last follow-up was 11.4 months (2-25.46). The detailed disposition of the patients is shown in Supplementary Figure 1. At diagnosis, only 3 patients were included in the accelerated phase, whereas the remaining 333 patients were included in the chronic phase. All patients in the chronic phase received flumatinib treatment. Seven patients received 200 mg of flumatinib and 28 patients received 400 mg of flumatinib, a once-daily dose. All other patients were treated with higher flumatinib doses (600 mg once daily), with a median dosage of 600 mg/day. The treatment was switched from the previous TKI to flumatinib because of intolerance, non-optimal response, or to achieve a better response.

A total of 5 patients entered the 1L phase III clinical study of flumatinib compared with imatinib. After the experiment was designed according to the research plan, flumatinib was not available on the market, and hence, the administration was stopped and replaced with other TKI treatments. Four patients were replaced with imatinib and 1 patient was switched to nilotinib. Treatment with imatinib and nilotinib was found to be effective in all 5 patients with an optimal response even in the absence of treatment with flumatinib. After the launch of flumatinib, 5 patients were switched to flumatinib treatment again, 3

patients treated with imatinib were switched to flumatinib because of edema and 1 patient maintained MR4 during on imatinib treatment for pursuit of deeper molecular response to UMRD replacing flumatinib. One patient treated with nilotinib was changed to flumatinib again because of economic reasons. Of note, all the 5 patients did not develop AEs while taking flumatinib again.

The baseline clinical characteristics of the patients are presented in Table 1. Among the total patients, 220 patients had European Treatment and Outcome Study for CML (EUTOS) long-term survival (ELTS) information with 139 (63.2%), 49 (22.3%), 32 (14.5%) patients in low-ELTS, intermediate ELTS, and high-ELTS risk groups, respectively (Table 1). Out of the total 336 patients treated with flumatinib, ABL mutations were tested in 291 patients before initiating flumatinib. Among them, 14 (4.8%) patients had ABL mutations with 1 patient each showing E255K, V260A, E279K, M351T, Y253F, M351T/F359I, and Y253H/F317L double mutations; 2 patients each had Y253H and E459K mutations; and 3 patients had F317L mutation.

Among the total patients receiving flumatinib treatment, 199 (58.9%) patients received flumatinib as the 2L, followed by 100 (29.8%) and 37 (11%) patients receiving flumatinib as the third-line (3L) and 4L TKI, respectively. About 288 (85.7%) patients received imatinib as the 1L treatment, thus contributing to the maximum proportion, whereas 31, 12, and 5 patients received nilotinib, dasatinib, and flumatinib, respectively as 1L treatment. In total, 171 (50.9%) patients were not resistant to prior TKIs, whereas 97 (28.9%), 24 (7.1%), and 44 (13.1%) patients were resistant to imatinib, 2G TKI, and both imatinib and 2G TKIs, respectively. There were 121 (36%) and 90 (26.8%) patients with no response and warning response to the last prior TKI during the initiation of flumatinib treatment, respectively (Table 1).

In a total of 110 patients, different comorbidities were reported at baseline. The major complications were hypertension (*n*=27), diabetes mellitus (*n*=18), coronary heart disease (*n*=14), and cardiovascular or cerebrovascular embolic diseases (*n*=7).

Efficacy

The median duration of flumatinib treatment was 11.04 (2-25.23) months for overall

population. The reasons for treatment discontinuation included treatment failure (*n*=13), disease progression (*n*=4), intolerance (*n*=8), high cost (*n*=4), suboptimal response (*n*=6), loss of previous DMR (*n*=2), and non-CML death (*n*=1).

The cumulative response during flumatinib treatment is shown in Figure 1 and Table 2. The patients without evaluable data were considered without response. CHR and MR were not reported in 3 and 4 patients, respectively, during the flumatinib treatment because of lack of data. Most patients with a baseline response maintained the efficacy after flumatinib treatment. CHR was achieved in 38 (86.4%) patients without CHR at baseline after flumatinib therapy, 3 patients did not achieve CHR, and 3 patients were not eligible for CHR evaluation. After a median time of 9 months, 79 (52.7%) patients without CCyR/MR2 at baseline had achieved CCyR/MR2 following flumatinib therapy. Out of 262 patients without MMR at baseline, 130 (49.6%) patients had achieved MMR at a median of 11.3 months of flumatinib therapy and 4 patients were ineligible for MMR evaluation. DMR was achieved in 69 (23.5%) patients without DMR at baseline after flumatinib therapy (Table 2).

BCR::ABL1 transcript levels were detected in 322 patients after exposure to flumatinib for 3 months. Among 110/322 patients with transcript level >10% at baseline, 75 patients achieved EMR of $BCR::ABL1^{IS} \leq 10\%$.

Subgroup analysis

The probabilities of response from CHR to MR after the later-line flumatinib therapy were analyzed on the basis of clinical parameters which showed an association of flumatinib response with treatment lines, resistance to prior TKI, response to the last administered TKIs and their transcript expression levels, and mutation status at baseline (Table 2).

In patients without CHR at baseline, the 2L, 3L, and 4L flumatinib therapies induced CHR at similar rates. With higher lines of flumatinib treatment, cytogenetic response or MR was reduced and the median time to obtain these responses increased. (Table 2; Supplementary Figure 2). CCyR/MR2 was achieved after a median time of 6.2 and 12 months in the 2L and 3L flumatinib treatments, respectively. Similarly, the median time

for achieving MMR was 6.9 and 16.9 months for the 2L and 3L flumatinib treatments. The medium time was not reached for CCyR/MR2 and MMR in 4L treatment and for DMR in all groups.

The response to flumatinib therapy was also evaluated according to the patient history of resistance to prior TKIs as presented in Table 2. Most of the patients without CHR at baseline achieved CHR after exposure to flumatinib irrespective of the status of resistance to prior TKIs. Patients without CCyR/MR2 or MMR at baseline, those without previous resistance to prior TKIs had higher CCyR/MR2 or MMR rates than those with simple imatinib resistance, whereas patients with 2G resistance had lowest CCyR/MR2 or MMR rates. In the baseline population without DMR, only 4.5% of patients with 2G TKI resistance obtained DMR after flumatinib treatment. The rate of DMR was similar in patients with no previous resistance or with imatinib resistance only. The median time of attaining CCyR/MR2 in the patients with no resistance, those resistant to imatinib only, and those resistant to 2G TKI (only 2G/imatinib and 2G) was 3.8, 8.5, and 19.2 months, respectively, whereas the median time of attaining MMR in these patients was 6.2, 9.9, and 20.1 months, respectively (Table 2; Supplementary Figure 3).

Furthermore, we analyzed the impact of the response to the last TKI before replacing flumatinib on the subsequent efficacy of flumatinib treatment. According to the ELN 2020 criteria for the 2L TKI therapy, patients were categorized as failure, warning, and optimal groups. Patients who had not reached efficacy evaluation endpoints but replaced flumatinib treatment because of AE or for achieving better efficacy were included in the optimal group. As detailed in Table 2, most patients with response at baseline could maintain the CHR, CCyR/MR2, and MMR during the flumatinib therapy. The patients who were optimal to the last prior TKI had higher rates of CCyR/MR2, MMR, and DMR when compared with those with warning or failure response. The patients with optimal response to the last prior TKI also had a shorter median time to corresponding responses. The median time to CCyR/MR2, MMR, and DMR was 3.8 months, 6 months, and 15 months in patients with optimal response; 8.1 months, 8.1 months, and not reached in warning patients; 12 months, 19.2 months, and not reached in failure patients,

respectively.

The *BCR::ABL* transcript levels also affected the efficacy of flumatinib treatment. CHR at baseline was maintained in all 292 patients independent of baseline transcript levels during flumatinib treatment. With a median exposure of 11.04 months to flumatinib treatment, the patients with transcript ≤10% at baseline showed a higher probability of achieving CCyR/MR2 and MMR as compared with those with transcript >10%, whereas the probabilities to achieve DMR were similar in both groups (Table 2; Supplementary Figure 5). There were 12 patients with CCyR confirmed using traditional chromosome G-banding having transcript levels >10% at baseline, of whom, 11 patients maintained CCyR during flumatinib therapy, whereas MMR and DMR were achieved in 8 and 4 patients, respectively.

Fourteen patients had mutations at baseline and were treated with flumatinib. Out of the 4 patients having mutations in Y253H/Fm, 1 patient had F317L co-mutation, 2 patients had discontinued flumatinib because of failure or progression at 5 and 9.9 months, 1 patient had shifted to flumatinib from dasatinib because of pleural effusion (PE) and maintained DMR at the last follow-up with 8.9 months of flumatinib exposure. Although the patient with Y253H/F317L double mutation achieved CHR, there was no further improvement during exposure to flumatinib for 15.2 months. The only patient with E255Km treated with flumatinib as the 2L treatment maintained CHR with no improvement in MR during flumatinib treatment for 6.7 months. The only 1 patient with V260Am and resistant to nilotinib as well as without CHR at baseline shifted to the 2L flumatinib therapy for 6.2 months and achieved CHR but without EMR. The patient with E279Km and resistant to imatinib as well as without CHR at baseline achieved MMR within 7 months of flumatinib treatment. In total, 3 patients with F317Lm had a higher response to flumatinib. Of these patients, MR4 and MMR were achieved by 1 patient each. The patient with M315T/F359I co-mutation had progressed to the accelerated phase after 6.7 months of flumatinib treatment. The patient with M351Tm received flumatinib for 4.5 months and achieved EMR, whereas 2 patients with E459Km received flumatinib for 4 months and maintained CHR with stable *BCR::ABL* transcript levels.

Multivariate analysis showed the predictive factors along with their association with the achievement of CCyR, MMR, and DMR during the later-line flumatinib therapy. Of these factors, the only independent factor was the history of resistance to prior TKI treatment (Supplementary Table 1).

Safety

Overall, 204 patients had multiple AEs related to prior TKIs at baseline, and most of these AEs were improved after the flumatinib treatment. Supplementary Table 2 shows changes in >5% AEs during the last TKIs before the flumatinib treatment. Among imatinib-related AEs, only 1 patient each had sustained rash and itching, cytopenia, and gastrointestinal AEs without improvement after flumatinib therapy. Of 13 patients with cytopenia on nilotinib treatment, only five patients still had cytopenia without any improvement during flumatinib therapy. Eight patients with abnormal liver function related to nilotinib fully recovered after initiating flumatinib treatment. Of 9 patients with cardiac-related AEs during nilotinib treatment, two patients did not fully recover after the initiation of flumatinib treatment. Only 1 patient with PE did not recover after the discontinuation of dasatinib and showed sustained PE because of lung metastases during flumatinib treatment, which was not flumatinib-related AE. Among the 16 patients with cytopenia on dasatinib treatment, 8 patients achieved complete remission and 6 patients alleviated the symptoms after flumatinib treatment.

The AEs reported during flumatinib treatment are reported in Table 3. Of the total patients, there were 66 patients with hematological toxicities. Among these patients, hematological AEs persisted in 23 patients from the last prior TKIs before switching to flumatinib treatment, and 43 patients showed an incidence of new AEs after starting with flumatinib treatment. Apart from 1 patient with atrial fibrillation showing cerebral infarction during the flumatinib 3L treatment, no new cardio-cerebrovascular ischemic events were reported in this study.

Among the total patients, 8 patients discontinued the flumatinib therapy because of the incidence of AEs, including ≥grade 2 cytopenia (*n*=5), grade 3 rash (*n*=1), grade 3 diarrhea (*n*=1), and leg pain (*n*=1). Apart from 1 patient with chronic heart failure at

baseline who died of heart failure after flumatinib treatment, none of the patients with diverse complications had comorbidities deterioration leading to the discontinuation of flumatinib therapy.

Discussion

To the best of our knowledge, this is the first and largest global post-market real-world study of flumatinib to date in patients with CML resistant or intolerant to other TKIs. Previously published in vitro studies have reported an inhibitory action of flumatinib against ABL and ABL with mutations.[15] However, there are limited studies on the use of flumatinib in patients with CML having intolerance or resistance to other TKIs.[10,13,14]

In this retrospective study, flumatinib showed a promising efficacy and safety profile to be used as the later-line therapy in patients with CML-CP. Flumatinib was effectively used as the 2L, 3L, and 4L TKIs in patients resistant/intolerant to ≥1 TKI, including imatinib, nilotinib, and/or dasatinib. A significant improvement was observed in CHR and MR in patients receiving flumatinib treatment. The CCyR/MR2, MMR, and DMR increased to 78.3%, 60.4%, and 32.1% from 55.4%, 22%, and 12.5% at baseline, respectively. The earlier the shift to flumatinib treatment, the higher the response. In addition, benefiting population, with no previous resistance to the prior TKIs or simple imatinib resistance, had a higher response to flumatinib therapy.

In the present study, only 5% of the tested patients had an ABL mutation. In vitro studies have shown that flumatinib has an inhibitory effect on some mutated ABL, but it has not been confirmed by clinical studies. In real-world patients with ABL mutations, clinicians should refer to ELN, NCCN, or Chinese guidelines to recommend TKIs, among which flumatinib is not included. Therefore, more patients who are mutation-negative but resistant or intolerant to other TKIs choose flumatinib as later-line treatment.

The CCyR/MR2, MMR, and DMR rates reported for later-line treatment in this study were comparable to the previous studies. The studies have shown that nilotinib, dasatinib, and bosutinib as 2L treatments for CP patients who failed or intolerant to imatinib have CCyR 44% to 57% and MMR 28% to 38%[16–19], 3L treatment CCyR 17.1% to 32.4%,

MMR 15% to 21.1% [19–24], in addition to the BYOND study reporting higher cytogenetic and MR of bosutinib in the post-line treatment. The phase 4 BYOND study showed that bosutinib treated Ph+CP CML in patients with no corresponding efficacy at baseline, the CCyR, MMR, and MR4 rates obtained by bosutinib in 2L treatment were 75%, 76%, and 64.9% respectively, 68.4%, 64.3%, 52.6% and 47.1%, 38.5%, 29.7%, in 3L and 4L treatment, respectively. [25]

In the present study, flumatinib showed CCyR, MMR, and DMR rates of 61.2%, 56.4%, and 27.9%; 44.4%, 42.6%, and 21.7%; and 20%, 27.6%, and 3.1% in 2L, 3L, and 4L treatments, respectively, in patients without response at baseline. For accurately interpreting the difference of the response rates achieved with flumatinib compared with other 2G TKIs in later line as described above, the baseline characteristics were compared. We found that the major cytogenic response (MCyR; equal to *BCR::ABL* transcript ≤10%) at baseline was 63.1% in our study compared with 11%, 14% to 20%, and 77.8% observed in nilotinib, dasatinib, and BYOND studies, respectively. These data showed that flumatinib had comparable or non-inferior CCyR and MR to other 2G TKIs in patients with CML-CP as the later-line treatment.

Previous studies have shown that the use of other 2G drugs as a back-line treatment after failure of 2G drugs is not ideal, and 3G drugs ponatinib and STAMP show higher efficacy in patients after the failure of 2G TKIs. [6,26] Our study also showed that flumatinib has no obvious benefit for patients who failed other 2G TKIs. Since ponatinib and STAMP are not on the market in China, Chinese patients who have failed 2G TKIs should consider switching to 3G olverembatinib.[27]

AEs observed in the current study include hematological toxicity, diarrhea, creatinine elevation, and hepatic insufficiency, whereas FESTnd trial showed the presence of hematological AEs, diarrhea, and elevated levels of liver enzyme. In the current study, flumatinib treatment discontinuation was reported in 8 patients because of intolerance, whereas in the FESTnd study, flumatinib treatment discontinuation was reported because of abnormalities in liver function, thrombocytopenia, and aminotransferase elevation in 10.2%, 3.5%, and 3.1% of patients, respectively.[13] The present study has reported a lower

incidence of AEs during the flumatinib treatment as compared with the FESTnd trial that can be partially because of the retrospective nature of this study, thereby causing underrepresentation of flumatinib-related AEs. Although there was a lower incidence of flumatinib-related AEs in this study, the safety profile of flumatinib was consistent with that reported in the FESTnd study. An improvement in terms of incidence and severity of AEs related to prior TKIs was observed after switching to flumatinib treatment, which revealed no significant cross-intolerance between flumatinib and other TKIs such as imatinib, nilotinib, or dasatinib.

According to the ELN 2020 guidelines, dasatinib has been contraindicated in patients with respiratory failure and pleuropulmonary or pericardial disease because of the higher incidence of pulmonary toxicities.[1] The toxicity profile of flumatinib from the current study and FESTnd trial indicated that it would be safe for patients with pleuropulmonary disease. The frequent occurrence of glycolipid abnormalities was observed in patients treated with nilotinib or ponatinib, thereby leading to ischemic vascular events.[28] Therefore, the history of coronary heart disease, cerebrovascular accidents, and peripheral arterio-occlusive disease were recommended to be a strong contraindication along with increased risk of vascular AEs in patients with hypertension, hypercholesterolemia, and diabetes mellitus by the ELN 2020 guidelines in patients treated with nilotinib.[1] No vascular events were reported during flumatinib therapy in the present study as well as the FESTnd trial. [13] Thus, although these findings suggest that flumatinib treatment does not increase the risk of vascular events, further validation may be warranted given the relatively short duration of the present study (median duration of treatment:11.04 months).

Previous studies have reported a decline in renal function associated with long-term exposure to bosutinib or imatinib.[29,30] This retrospective study has reported an incidence of increased creatinine levels with grade 1 severity in 18 (5.36%) patients, of which 5 patients showed an incidence of comorbidities such as hypertension, hyperuricemia, or diabetes, thus elevating the possibility of the damage of kidney, yet no patients discontinued flumatinib. However, detailed studies are still required to evaluate the

deterioration of renal function during prolonged flumatinib treatment.

There are a few limitations associated with the present study. As the current study was retrospective in nature, the grading of AEs lacked accuracy, as the AEs were evaluated on the basis of the improvements including reduced severity and complete relief after treatment with flumatinib or other TKIs according to the clinical records.

Conclusion

Flumatinib induces high rates of CCyR and MMR or DMR in CML-CP patients as a later-line treatment, especially in patients with no previous TKI failure or only imatinib failure. The incidence of AEs during flumatinib treatment was tolerable and comparable with the AEs reported in the previous studies. Therefore, the present study showed that the treatment with flumatinib in patients who were resistant or intolerant to prior TKIs was reasonable.

References

1. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-984.

2. Welch HG, Kramer BS, Black WC. Epidemiologic Signatures in Cancer. N Engl J Med. 2019;381(14):1378-1386.

3. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM-L. Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. J Clin Oncol. 2016;34(24):2851-2857.

4. Breccia M, Efficace F, Colafigli G, et al. Tyrosine kinase inhibitor discontinuation in the management of chronic myeloid leukemia: a critical review of the current practice. Expert Rev Hematol. 2020;13(12):1311-1318.

5. Deininger MW, Shah NP, Altman JK, et al. Chronic Myeloid Leukemia, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(10):1385-1415.

6. Eşkazan AE. Asciminib in chronic myeloid leukemia: many questions still remain to be answered. Blood Cancer J. 2021;11(4):81.

7. Gambacorti-Passerini C, Aroldi A, Cordani N, Piazza R. Chronic myeloid leukemia: Second-line drugs of choice. Am J Hematol. 2016;91(1):67-75.

8. Cortes J, Lang F. Third-line therapy for chronic myeloid leukemia: current status and future directions. J Hematol Oncol. 2021;14(1):44.

9. Cortes J, Rea D, Lipton JH. Treatment-free remission with first- and second-generation tyrosine kinase inhibitors. Am J Hemato. 2019;94(3):346-357.

10. Luo H, Quan H, Xie C, Xu Y, Fu L, Lou L. HH-GV-678, a novel selective inhibitor of Bcr-Abl, outperforms imatinib and effectively overrides imatinib resistance. Leukemia. 2010;24(10):1807-1809.

11. Wang W, Sun Q. Novel targeted drugs approved by the NMPA and FDA in 2019. Signal Transduct Target Ther. 2020;5(1):65.

12. Zou X, Yang Z, Wang Y, Li W. A patient of chronic myeloid leukemia with BCR::ABL1 F317L mutation successfully treated with flumatinib. J Clin Intern Med. 2022;39(10):682-683.

13. Zhang L, Meng L, Liu B, et al. Flumatinib versus Imatinib for Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: A Phase III, Randomized, Open-label, Multi-center FESTnd Study. Clin Cancer Res. 2021;27(1):70-77.

14. Zhao J, Quan H, Xu Y, Kong X, Jin L, Lou L. Flumatinib, a selective inhibitor of

BCR-ABL/PDGFR/KIT, effectively overcomes drug resistance of certain KIT mutants. Cancer Sci. 2014;105(1):117-125.

15. Yang M, Xi Q, Jia W, Wang X. Structure-based analysis and biological characterization of imatinib derivatives reveal insights towards the inhibition of wild-type BCR-ABL and its mutants. Bioorg Med Chem Lett. 2019;29(24):126758.

16. Huang X, Jiang Q, Hu J, et al. Four-year follow-up of patients with imatinib-resistant or intolerant chronic myeloid leukemia receiving dasatinib: efficacy and safety. Front Med. 2019;13(3):344-353.

17. Kantarjian HM, Giles FJ, Bhalla KN, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood. 2011;117(4):1141-1145.

18. Shah NP, Guilhot F, Cortes JE, et al. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. Blood. 2014;123(15):2317-2324.

19. Cortes J, Quintas-Cardama A, Jabbour E, et al. The clinical significance of achieving different levels of cytogenetic response in patients with chronic phase chronic myeloid leukemia after failure to front-line therapy: is complete cytogenetic response the only desirable endpoint? Clin Lymphoma Myeloma Leuk. 2011;11(5):421-426.

20. Giles FJ, Abruzzese E, Rosti G, et al. Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy. Leukemia. 2010;24(7):1299-1301.

21. Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. Blood. 2009;114(20):4361-4368.

22. Ibrahim AR, Paliompeis C, Bua M, et al. Efficacy of tyrosine kinase inhibitors (TKIs) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy. Blood. 2010;116(25):5497-5500.

23. Russo Rossi A, Breccia M, Abruzzese E, et al. Outcome of 82 chronic myeloid leukemia patients treated with nilotinib or dasatinib after failure of two prior tyrosine kinase inhibitors. Haematologica. 2013;98(3):399-403.

24. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012;119(15):3403-3412.

25. Hochhaus A, Gambacorti-Passerini C, Abboud C, et al. Bosutinib for pretreated patients with chronic phase chronic myeloid leukemia: primary results of the phase 4 BYOND study. Leukemia. 2020;34(8):2125-2137.

26. Kantarjian HM, Jabbour E, Deininger M, et al. Ponatinib after failure of SECOND□GENERATION

tyrosine kinase inhibitor in resistant CHRONIC□PHASE chronic myeloid leukemia. Am J Hematol. 2022;97(11):1419-1426.

27. Jiang Q, Li Z, Qin Y, et al. Olverembatinib (HQP1351), a well-tolerated and effective tyrosine kinase inhibitor for patients with T315I-mutated chronic myeloid leukemia: results of an open-label, multicenter phase 1/2 trial. J Hematol Oncol. 2022;15(1):113.

28. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021;35(2):440-453.

29. Sakurai M, Kikuchi T, Karigane D, et al. Renal dysfunction and anemia associated with long-term imatinib treatment in patients with chronic myelogenous leukemia. Int J Hematol. 2019;109(3):292-298.

30. Cortes JE, Gambacorti-Passerini C, Kim D-W, et al. Effects of Bosutinib Treatment on Renal Function in Patients With Philadelphia Chromosome-Positive Leukemias. Clin Lymphoma Myeloma Leuk. 2017;17(10):684-695.

Tables:

Table 1: Baseline characteristics

	2nd line N=199	**3rd line N=100**	**4th line N=37**	**Total N=336**
Male, n (%)	117 (58.8)	55 (55%)	18 (48.6)	190 (56.5)
Median age, year (range)	52 (17-87)	47 (21-79)	48 (25-77)	50 (17-87)
Median time from diagnosis to flumatinib, months (range)	15 (0.4-375.3)	50.6 (3-246)	104.9 (9-461.8)	32 (0.4-461.8)
Median time from first TKI to flumatinib, months (range)	14.5 (0.4-185.3)	45.7 (3-163.6)	71.5 (9.2-197.8)	29.5 (0.4-197.8)
ELTS group, n (%)	N=150	N=56	N=14	Total N=220
ELTS low	97 (64.7)	34 (60.7)	8 (57.1)	139 (63.2)
ELTS intermediate	35 (23.3)	12 (21.4)	2 (14.3)	49 (22.3)
ELTS high	18 (12)	10 (17.9)	4 (28.6)	32 (14.5)
Prior TKI				
Imatinib	165	97	36	198
Dasatinib	9	72	35	116
Nilotinib	25	26	34	85
Flumatinib	0	5		5
Bosutinib	0	0	1	1
Resistant to prior TKI, n (%)				
Imatinib	68 (34.2)	25 (25)	4 (10.8)	97 (28.9)
2G TKI	15 (7.5)	6 (6)	3 (8.1)	24 (7.1)
1G and 2G TKI	0	21 (21)	23 (62.2)	44 (13.1)
Response to last TKI, n (%)				
Failure	80 (40.2)	21 (21)	20 (54.1)	121 (36)

Warning	49 (24.6)	32 (32)	9 (24.3)	90 (26.8)
Response at baseline, n (%)				
CHR	172 (86.4)	89 (89)	31 (83.8)	292 (86.9)
MR1	114 (57.3)	78 (78)	20 (54.1)	212 (63.1)
MR2	96 (48.2)	73 (73)	17 (45.9)	186 (55.4)
MMR	34 (17.1)	32 (32)	8 (21.6)	74 (22.)
MR4 or DMR	20 (10.1)	17 (17)	5 (13.5)	42 (12.5)

All values represented in terms of n/N; Abbreviations: CHR, complete hematologic response; ELTS, European Treatment and Outcome Study for chronic myeloid leukemia long-term survival; 1G, first generation; 2G, second generation; MR1, 1-log molecular response; MR2, 2-log molecular response; DMR, deep molecular response; MMR, major molecular response; n, number of affected patients; N, total number of patients; TKI, tyrosine kinase inhibitor

Table 2: Response during flumatinib treatment

	CHR		CCyR/MR2		MMR		MR4 or better (DMR)	
	With n (%)	**Without n (%)**	**With n (%)**	**Without n (%)**	**With n (%)**	**Without n (%)**	**With n (%)**	**Without n (%)**
Baseline, N	292	44	186	150	74	262	42	294
Best response	292/292 (100)	38/44 (86.4)	184/186 (98.9)	79/150 (52.7)	73/74 (98.6)	130/262 (49.6)	39/42 (92.9)	69/294 (23.5)
Flumatinib treatment line								
2L, N=199	172/172 (100)	22/27 (81.5)	94/96 (97.9)	63/103 (61.2)	34/34 (100)	93/165 (56.4)	19/20 (95)	50/179 (27.9)
3L, N=100	89/89 (100)	10/11 (90.9)	73/73 (100)	12/27 (44.4)	32/32 (100)	29/68 (42.6)	17/17 (100)	18/83 (21.7)
4L, N=37	31/31 (100)	6/6 (100)	17/17 (100)	4/20 (20)	7/8 (87.5)	8/29 (27.6)	3/5 (60)	1/32 (3.1)
P	0.058	0.488	0.376	**0.000**	0.261	**0.000**	0.376	**0.000**
Whether resistant (R) to prior TKI (R to 2G TKI including R to only 2G or R to both imatinib and 2G)								
No resistant N=171	162/162 (100)	9/9 (100)	134/135 (99.3)	28/36 (77.8)	62/62 (100)	71/109 (65.1)	34/36 (94.4)	39/135 (28.9)
R to imatinib N=97	80/80 (100)	13/17 (76.5)	36/36 (100)	34/61 (55.7)	11/11 (100)	43/86 (50)	5/5 (100)	27/92 (29.3)
R to 2G TKI N=68	50/50 (100)	16/18 (88.9)	14/15 (93.3)	18/53 (32.1)	0/1	16/67 (23.9)	0/1	3/67 (4.5)
P	0.092	0.371	0.121	**0.000**	**0.039**	**0.000**	0.096	**0.000**
Response to last TKI (O=Optimal, W= Warning, F= Failure)								
O, N=125	118/118 (100)	7/7 (100)	96/97 (99)	22/28 (78.6)	73/74 (98.6)	36/51 (70.6)	39/42 (92.9)	31/83 (37.3)
W, N=90	85/85 (100)	4/5 (80)	68/68 (100)	12/22 (54.5)		48/90 (53.3)		17/90 (18.9)
F, N=121	89/89 (100)	27/32 (84.4)	20/21 (95.2)	45/100 (45)		46/121 (38)		21/121 (17.4)
P	0.441	0.481	0.132	**0.001**		**0.000**		**0.001**
Baseline transcript level								
≤10% N=213	211/211 (100)	2/2 (100)	173/174 (99.4)	27/39 (69.2)	73/74 (98.6)	80/139 (57.6)	39/42 (92.9)	42/171 (24.6)
>10% =123	81/81 (100)	36/42 (85.7)	11/12 (84.6)	52/111 (46.8)		50/123 (40.7)		27/123 (22)

P	0.318	**0.004**	0.148	**0.005**		**0.004**		0.446
Mutation status at baseline								
No mutation N=277	246/246 (100)	25/31 (80.6)	157/157 (100)	71/120 (59.2)	64/65 (98.5)	115/211 (54.5)	35/37(94.6)	65/240 (27.1)
Mutation N=14	9/9 (100)	5/5 (100)	2/3 (66.7)	2/11 (18.2)	0/1	3/13 (23.1)	1/1 (100)	1/13 (7.7)
Total N=291	255/255 (100)	30/36 (83.8)	159/160 (99.4)	73/131 (55.7)	64/66(97)	118/224 (52.7)	36/38 (94.7)	66/253 (26.1)
P	0.91	0.292	0.1	0.053	0.861	0.169	0.665	0.268

All values represented in terms of n/N; Abbreviations: CHR, complete hematologic response; CCYR/MR2, complete cytogenetic response/2-log molecular response; DMR, deep molecular response; F, failure; 2G, second generation; 2L, second line; 3L, third line; 4L, fourth line; MMR, major molecular response; MR4, 4-log molecular response; n, number of affected patients; N, total number of patients; O, optimal; R, resistance; TKI, tyrosine kinase inhibitor; W, warning

Table 3: Adverse events on flumatinib therapy

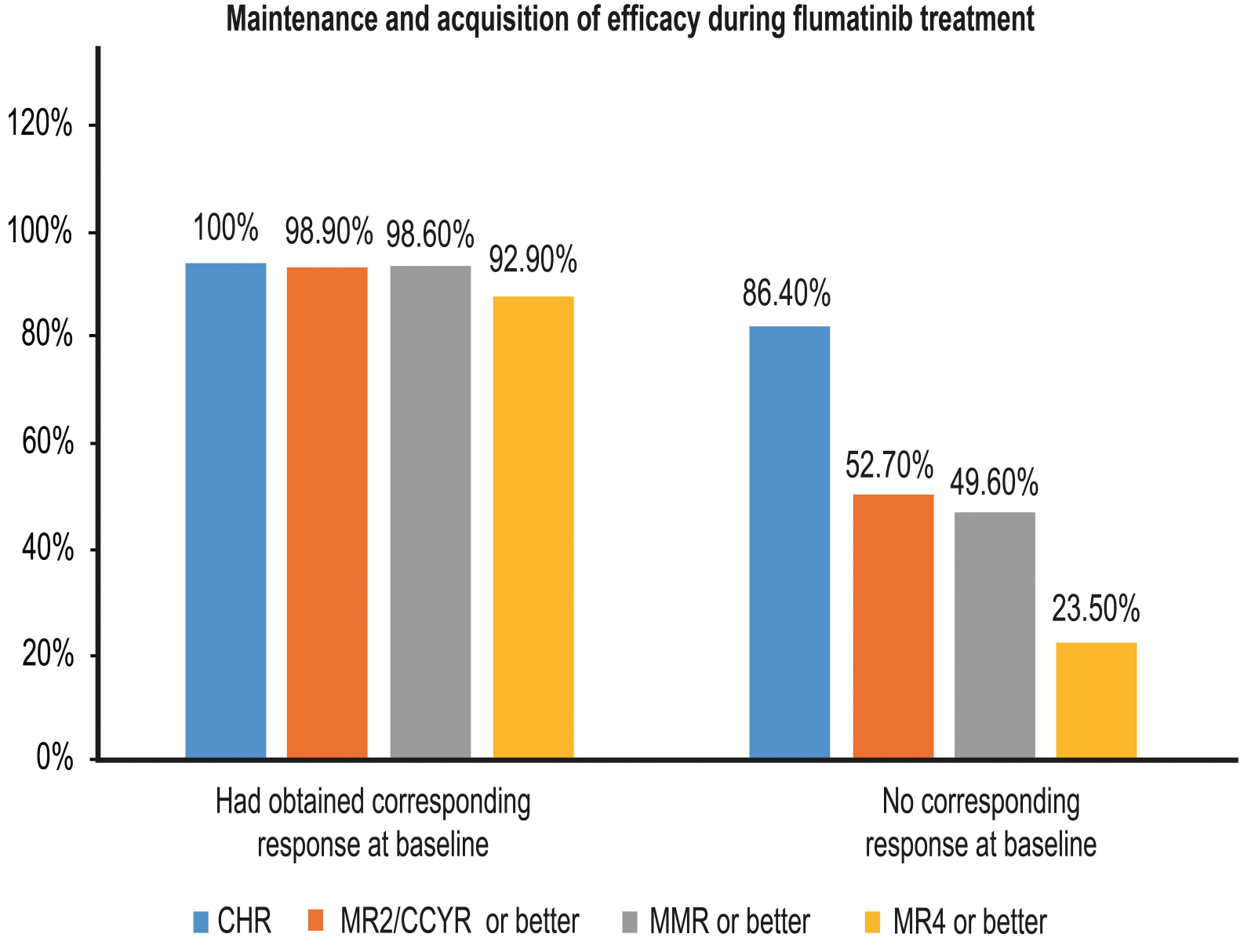
	All N=336	**Grade 3-4 N =336**
Hematological AEs, n (%)	66 (19.3)	
Thrombocytopenia	52 (15.5)	23 (6.8)
Leukocytopenia	18 (5.4)	8 (2.4)
Anemia	28 (8.3)	5 (1.5)
Nonhematological AEs, n (%)		
Gastrointestinal	60 (17.86)	0 (0.0)
Diarrhea	41 (12.20)	3 (0.89)
Nausea	8 (2.38)	0 (0.0)
Vomit	5 (1.49)	0 (0.0)
Constipate	4 (1.19)	0 (0.0)
Abdominal pain	2 (0.60)	0 (0.0)
Esophagitis	2 (0.60)	0 (0.0)
Rash	20 (6)	1 (0.3)
Pruritus	3 (0.89)	0 (0.0)
Skeletal muscle and joint pain	10 (2.98)	0 (0.0)
Headache and dizziness	5 (1.49)	0 (0.0)
Sub -acute thyroiditis	4 (1.19)	0 (0.0)
Hyperthyroidism	3 (0.89)	0 (0.0)
Arrhythmia	3 (0.89)	0 (0.0)
Facial edema	2 (0.60)	0 (0.0)
Paresthesia	2 (0.60)	0 (0.0)
Cerebral infarction	1 (0.30)	0 (0.0)
Fatigue	1 (0.30)	0 (0.0)
menstrual disturbance	1 (0.30)	0 (0.0)
Peripheral neuritis	1 (0.30)	0 (0.0)
Liver enzymes elevation	7 (2.1)	0 (0.0)
Increased bilirubin	4 (1.19)	0 (0.0)
Creatinine elevation	18 (5.36)	0 (0.0)
Elevated uric acid	2 (0.6)	0 (0.0)

All values represented in terms of N (%) which denotes number of affected patients; Abbreviations: AE, adverse event; N, number of affected patients; %, percentage

Figure legends:

Figure 1: The hematologic, cytogenetic and molecular response after flumatinib treatment

Abbreviations: CHR, complete hematologic response; MMR, major molecular response; MR2/CCYR, 2-log molecular response/complete cytogenetic response; MR4, 4-log molecular response


Maintenance and acquisition of efficacy during flumatinib treatment
120%
100%
80%
60%
40%
20%
0%
100%
98.90%
98.60%
92.90%
86.40%
52.70%
49.60%
23.50%
Had obtained corresponding response at baseline
No corresponding response at baseline
CHR
MR2/CCYR or better
MMR or better
MR4 or better

Supplementary file

Title: Safety and efficacy of flumatinib as later-line therapy in patients with chronic myeloid leukemia

Supplementary Table 1: Potential predictive factors of cumulative response to later-line flumatinib treatment by multivariate Cox analysis

	CCyR/MR2		**MMR**		**DMR**	
Resistance	**HR**	**P Value**	**HR**	**P Value**	**HR**	**P Value**
No vs to IM	0.709 (0.469-1.07)	0.102	0.541 (0.346-0.845)	**0.007**	0.721 (0.378-1.374)	0.32
No vs to 2G TKI	0.409 (0.236—0.708)	**0.001**	0.189 (0.091-0.392)	**0.000**	0.074 (0.01-0.543)	**0.01**
To IM vs to 2G TKI	0.577 (0.33-1.008)	0.053	0.349 (0.163-0.745)	**0.006**	0.103 (0.013-0.791)	**0.029**

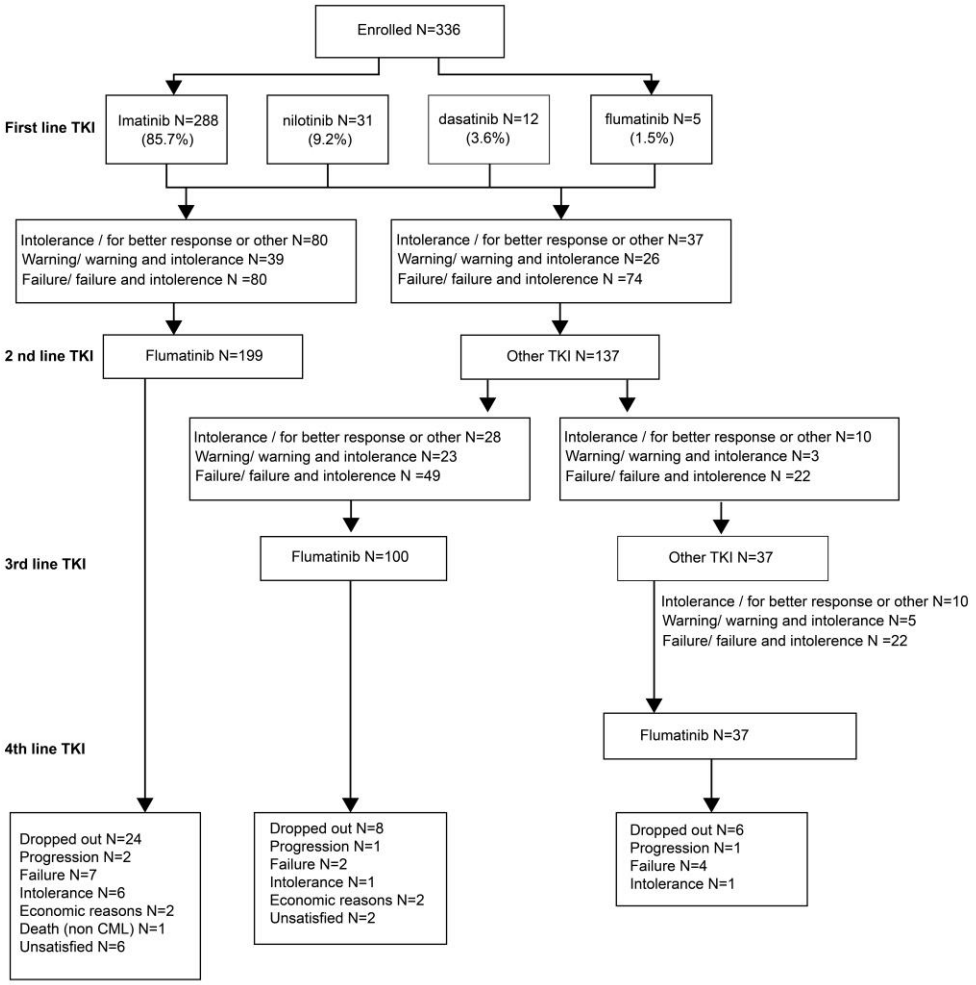
Abbreviations: CCyR, complete cytogenic response; DMR, deep molecular response; 2G, second generation; HR; hazard ratio; IM, imatinib; MMR, major molecular response; TKI, tyrosine kinase inhibitor

Supplementary Table 2: Patients with change of AE >5% in last TKI prior to flumatinib

AEs	Imatinib N=175		Nilotinib N=66		Dasatinib N=95	
	All n	Improved n	All n	Improved n	All n	Improved n
Cytopenia	19	18	13	8	16	14
Gastrointestinal	12	11	0	0	5	5
Edema	42	42	0	0	0	0
Rash and itch	22	21	7	7	0	0
Abnormality of liver function	0	0	8	8	0	0
Cardiac-related AE (not effusion)	0	0	9	7	0	0
Pericardial effusion	0	0	0	0	4	4
Pleural effusion	0	0	0	0	38	37
PAH	0	0	0	0	9	9

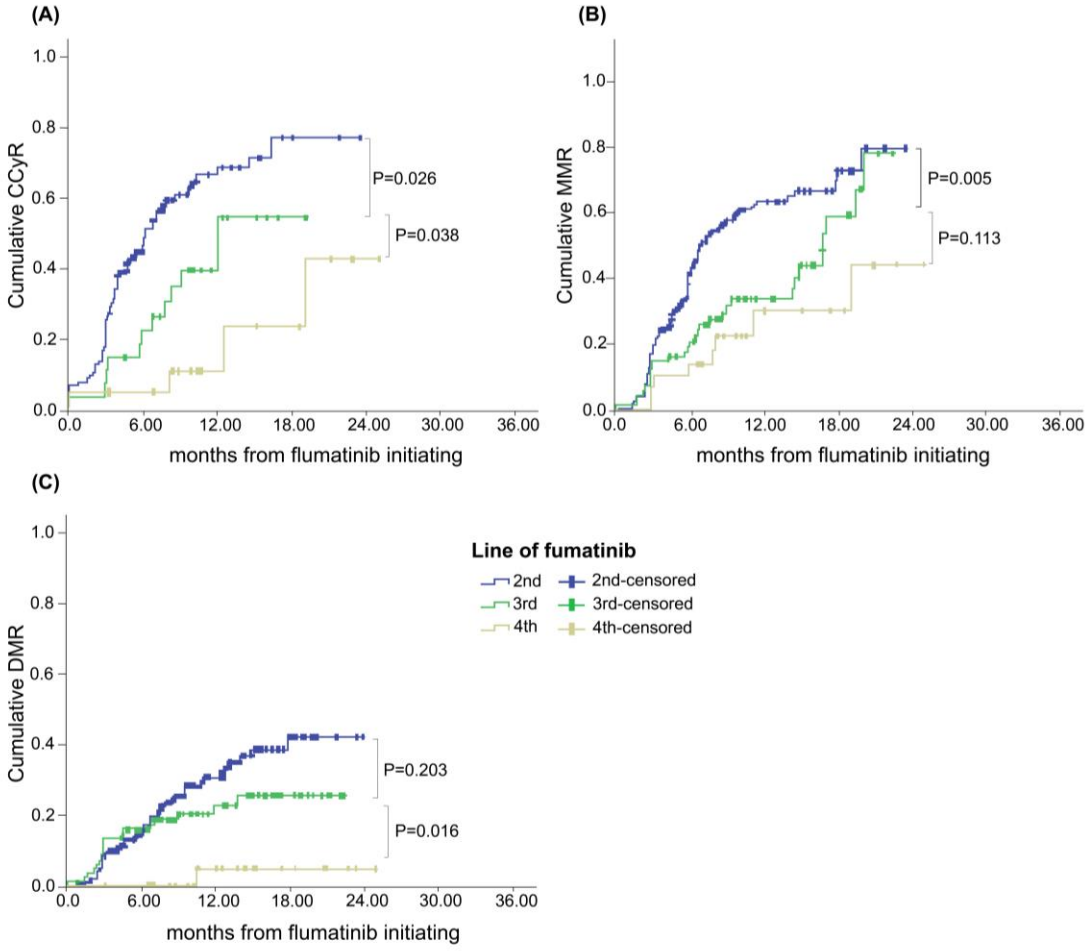
All values represented in terms of n which is number of affected patients
Abbreviations: AE, adverse event; N, total number of patients; n, number of patients presenting with particular AE; PAH, pulmonary arterial hypertension; TKI, tyrosine kinase inhibitor

Supplementary Figure 1: Patient disposition



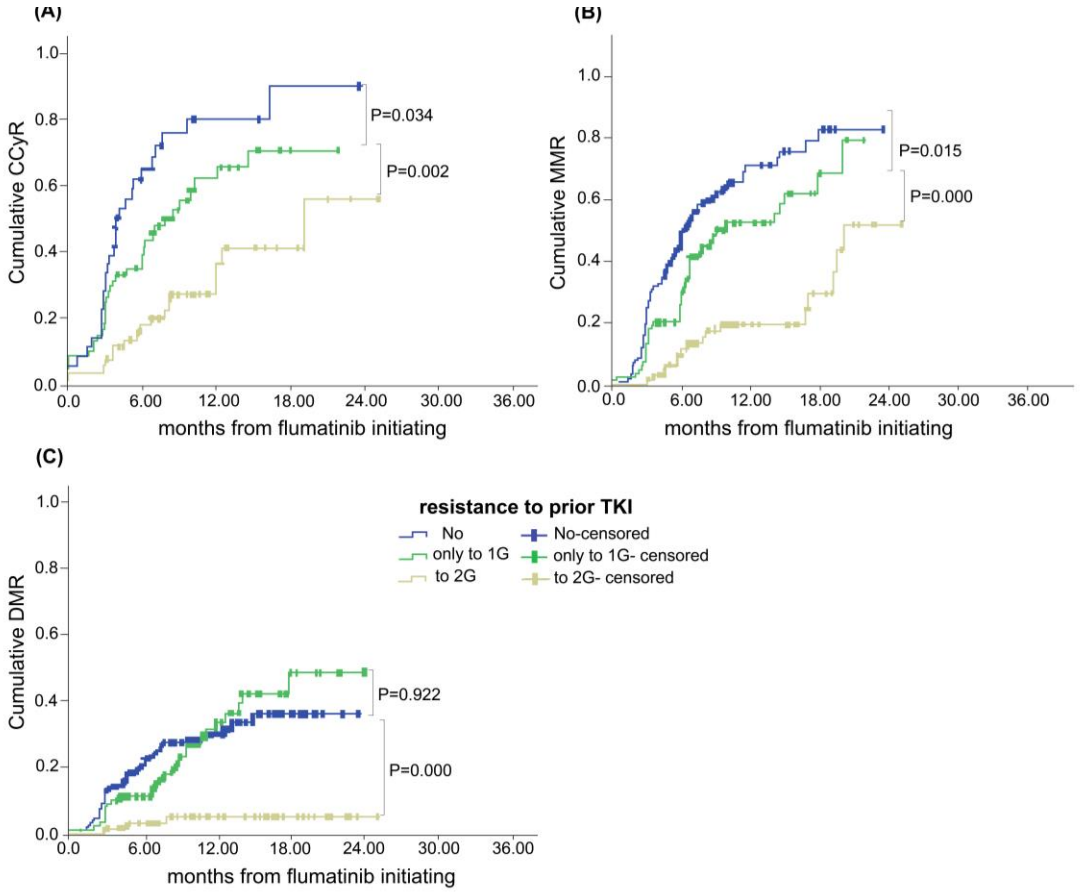
Abbreviations: CML, chronic myeloid leukemia; N, number of patients; TKI, tyrosine kinase inhibitor

Supplementary Figure 2: The cumulative response of CCyR (A), MMR (B) and DMR (C) over time in the patients without corresponding response at baseline according to the line of flumatinib treatment.



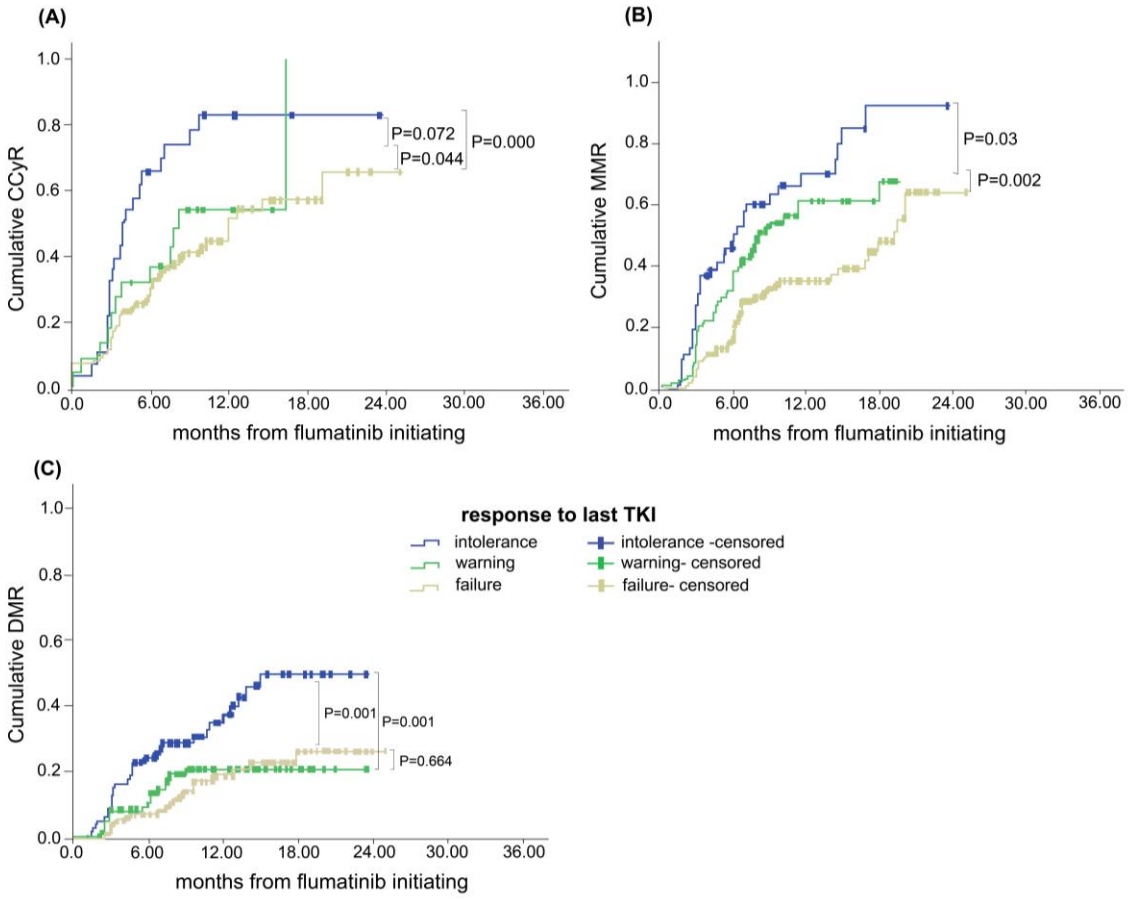
Abbreviations: CCyR, complete cytogenic response; DMR, deep molecular response; MMR, major molecular response

Supplementary Figure 3: The cumulative response of CCyR (A), MMR (B), DMR (C) over time in the patients without corresponding response at base line according to the status of resistance to prior TKIs illustrated



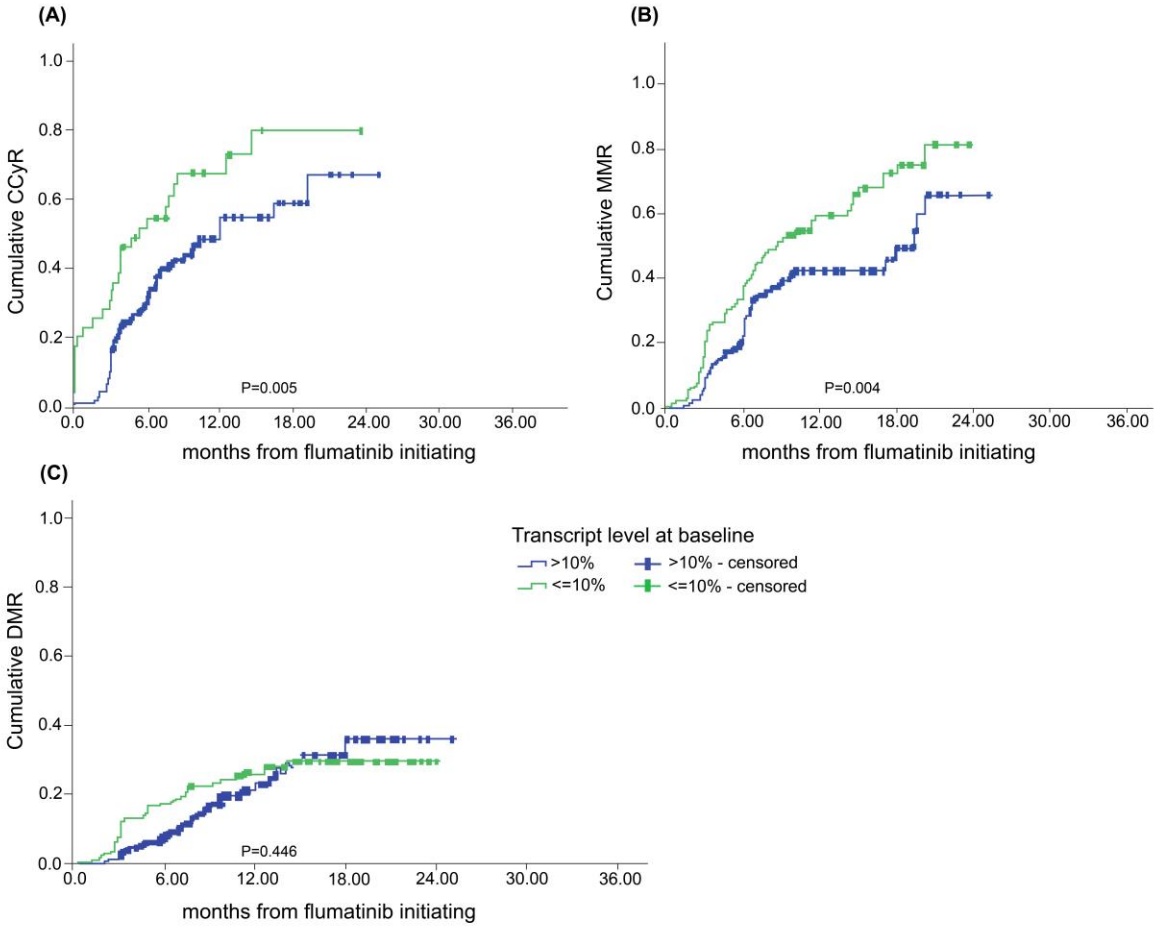
Abbreviations: CCyR, complete cytogenic response; DMR, deep molecular response; 1G, first-generation; 2G, second-generation; MMR, major molecular response; TKI, tyrosine kinase inhibitor

Supplementary Figure 4: The cumulative response of CCyR(A), MMR(B) and DMR (C) over time in the patients without corresponding response at base line according to the status of response to last TKI illustrated.



Abbreviations: CCyR, complete cytogenic response; DMR, deep molecular response; MMR, major molecular response; TKI, tyrosine kinase inhibitor

Supplementary Figure 5: The cumulative response of CCyR (A), MMR (B) and DMR (C) over time in the patients without corresponding response at base line according to the transcript level at baseline illustrated



Abbreviations: CCyR, complete cytogenic response; DMR, deep molecular response; MMR, major molecular response