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Early Release Paper

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High dose imatinib improves cytogenetic and molecular remissions in *pretreated* Ph$^+$/BCR-ABL$^+$ CML chronic phase patients: first results from the randomized CELSG Phase III CML 11 "ISTAHIT" Study

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Abstract

Background. Imatinib 400 mg/day is the standard treatment for patients with chronic phase CML. Recent reports suggested higher and more rapid cytogenetic and molecular responses with higher doses of imatinib.

Design and Methods. This prospective international, multicentre randomized phase III study randomized 227 patients with pre-treated Ph^+/BCR-ABL^+ CML either into a standard dose (SD) imatinib arm A (400 mg/day) or a high dose (HD) imatinib arm B (800 mg/day for 6 months followed by 400 mg/day as maintenance). In this planned interim analysis haematologic, cytogenetic and molecular responses as well as toxicity were evaluated.

Results. HD imatinib led to higher rates of major (MCyR) and complete cytogenetic responses (CCyR) at 3 months (MCyR: 21% versus 37%, p=0.01; CCyR: 6% versus 25%, p<0.001) and at 6 months (MCyR: 34% versus 54%, p=0.009; CCyR: 20% versus 44%, p<0.001). This was paralleled by a significantly higher major molecular response (MMR) rate at 6 months in the imatinib HD arm B (11.8% versus 30.4%; p=0.003). At 12 months, rates of MCyR (the primary endpoint) were comparable between both arms (57% versus 59%). In contrast to non-haematological toxicities, grade 3/4 haematological toxicities were more common in the HD arm B. Cumulative CCyR rates were higher in patients without dose reduction in the HD arm B (61%) compared to patients with no dose reduction in arm A (36%, p=0.014).

Conclusions. This is the first randomized phase III trial in pre-treated CP-CML patients demonstrating improvement in MCyR, CCyR and MMR rates with HD imatinib therapy.

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Introduction

Based on the impressive results of the IRIS study comparing imatinib 400 mg per day with Interferon alpha (IFN-α) plus low dose cytarabine in newly diagnosed Ph+/BCR-ABL+ CML patients in CP (1,2), imatinib 400 mg once daily became the first line standard treatment for these patients. Recently published seven year follow-up data revealed that frontline therapy with imatinib 400 mg per day is capable of inducing durable cytogenetic and molecular responses. The estimated seven year overall survival (OS) of patients on imatinib is 86% with only 6% CML-related deaths (3). The initial phase I study revealed a clear dose-response relationship, and the maximal tolerated dose was not reached (4). Moreover, higher doses of imatinib were able to improve or restore remissions that were not achieved with 400 mg (5). Recently conducted phase II studies performed both in CP-CML patients in second line after IFN- α failure (6) or in newly diagnosed CP-CML patients (7,8) suggest that a more aggressive dosing schedule (i.e. 800mg/day) induces higher and more rapid cytogenetic and molecular responses. Early good responses have further been shown to be associated with a better long-term progression-free survival (PFS) (2,9,10,11,12). Higher imatinib doses were generally well tolerated with the exception of myelosuppression, that caused dose reductions in 36% of the patients after six months of therapy in newly diagnosed CML patients (7). We have therefore initiated a prospective international, multicentre randomized phase III study in which we compared imatinib 400 mg/day with imatinib 800 mg/day for a six month induction period followed by 400 mg/day imatinib as "maintenance". This study was performed in a cohort of patients at high risk for acceleration including pretreated, but imatinib-naive CML patients in late CP who had not achieved a major cytogenetic remission (MCyR) at the time of enrollment into the study. The data presented are the results of a planned interim analysis that was performed on all patients after half of the patients had been treated for 12 months since randomisation.

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Design and Methods

Study design

This multicentre randomized phase III study was performed in 13 centres of seven different countries including Austria, Bulgaria, Latvia, Lithuania, Macedonia, Ukraine and Serbia. Eligibility criteria included patients ≥18 years of age with CML in late CP pre-treated for at least 12 months with no MCyR at study entry. Pre-treatment with tyrosine kinase inhibitors was not allowed. Patients intolerant to INF-a (defined by non-haematological toxicity grade 3/4 persisting for more than 2 weeks) were allowed to be included. A WHO status 0-2 was required, as well as an adequate organ function, determined as the following: total bilirubin < 1.5 x ULN, SGOT and SGPT < 2.5 x ULN, creatinine < 1.5 x ULN, ANC > 1.5 x 10^9/L, and platelets > 100 x 10^9/L. Exclusion criteria were uncontrolled clinical disorder and positive HIV serology. Moreover, women who were pregnant, breast feeding, or premenopausal without a negative pregnancy test before start of the study as well as patients in accelerated phase (AP) or blastic crisis (BC) were excluded. All patients provided written informed consent in accordance with the Declaration of Helsinki. The trial was reviewed and ethically approved at all participating centres and was registered at ClinicalTrials.gov, a service of the NIH with the gov.Identifier: NCT00327262. The trial was operated by the Central European Leukaemia Study Group (CELSG), and data were collected and processed by the CELSG trial centre at the Medical University of Innsbruck (MUI). A total of 227 patients were enrolled between February 2004 and December 2006. Baseline patient characteristics including pre-treatments are summarised in Table 1.

Treatment and dose modifications

Patients were randomized at a 1:1 ratio either into the standard dose (SD) arm A (400 mg/day; 24 months) or the experimental high dose (HD) arm B. In the HD arm B imatinib was administered for 6 months at 800mg/day (2 x 400 mg) followed by 18 months of 400 mg/day. Dose modifications due to toxicity were planned if patients experienced a grade 2 non-haematologic toxicity. In this case, the study drug had to be withheld until the toxicity resolved to ≤ grade 1 and was then resumed at the same daily dose. If the grade 2 toxicity recurred, imatinib had to be withheld until toxicity has resolved to ≤ grade 1, and the daily dose was then reduced to 300 mg once daily for patients in arm A or to 600 mg for patients in arm B. If grade 2 toxicity recurred after dose reduction to 600 mg in arm B, the dose was further decreased to 400 mg and if grade 2 toxicity recurred the dose was further decreased to 300 mg. In case of recurring grade 2 toxicity with 300 mg the patient went off study. If the patient experienced grade 3/4 toxicity, the study drug was withheld until the toxicity had resolved to ≤ grade 1 and the daily dose was then reduced to 300 mg for patients in arm A or to 600 mg for patients in arm B. If grade 3/4 toxicity recurred in arm B, imatinib was withheld until toxicity had resolved to ≤ grade 1, and the dose was further decreased to 400 mg and to 300 mg, if grade 3/4 toxicity recurred with 400 mg.

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If patients experienced grade 3/4 haematological toxicity, (i.e. ANC < 1 x 10^9/L or a platelet count < 50 x 10^9/L), imatinib was withheld until toxicity had resolved to ≤ grade 2. If the toxicity resolved within two weeks, imatinib treatment was resumed at the same dose. If the grade 3/4 toxicity recurred or persisted for > 2 weeks, imatinib was withheld and then recommenced at the dose of 300 mg once daily in arm A and to 600 mg in arm B. If grade 3/4 toxicity recurred the dose was further decreased to 400 mg and to 300 mg if grade 3/4 toxicity recurred with 400 mg. In case of recurring grade 3/4 toxicity with 300 mg/day the patient went off study. No dose reductions were performed for grade 3/4 anaemia. If the patient developed anaemia, s/he received red blood transfusions or recombinant human erythropoietin at the discretion of the investigator. Patients who progressed to AP or BC went off study.

End points

The primary end point for evaluation in the study was the proportion of patients who achieved a MCyR after 12 months of therapy. Secondary end-points were the achievement of CCyR and molecular responses as well as tolerability of standard versus high-dose imatinib.

Definition of response and response monitoring

Blood counts, biochemistry and clinical evaluations were performed at baseline and at 1.5, 3, 6, 12, 18 and 24 months, respectively. Haematologic responses were analyzed due to the criteria established by the ELN (13). Bone marrow morphology, cytogenetic analyses and quantitative real-time PCR from peripheral blood (PB) were performed at baseline, 1.5, 3, 6, 12 and 24 months, respectively. Cytogenetic responses were assessed locally, whereas molecular monitoring was done centrally at the ELN-certified reference laboratory at the Children's Cancer Research Institute (CCRI)/LabDia Labordiagnostik in Vienna, Austria. For molecular monitoring, PB was collected in four Paxgene RNA-stabilisation tubes (PreAnalytiX, Hombrechtikon, Switzerland), each containing 2.5 ml PB. The tubes were stored locally at -20 °C until shipment on dry ice every 3-6 months to the CCRI/LabDia. The extraction of total RNA was performed using the PAXgene Blood RNA kit (PreAnalytiX, Hombrechtikon, Switzerland) according to the manufacturer's instructions. Reverse transcription and real-time PCR analyses were carried out as described elsewhere (14). Quantitative analysis of BCR-ABL expression was performed in relation to the ABL gene. Assessment of the molecular response was performed on the basis of the international scale (IS) (15,16,17).

Statistical Analyses

This paper presents an interim analysis of a multi-centre, randomized, open-labeled, 2-arm, parallel group, phase III clinical trial comparing standard dose imatinib with high dose imatinib in treated CML patients. Demographic characteristics, diagnosis, extent of cancer, disease history, toxicity, adverse events and medication administered were summarised applying Fisher`s exact test, chi-square test, t-test or Mann-Whitney U test, as appropriate. Response rates at different time-points were summarised using contingency table analyses and compared between treatment groups using Fisher`s exact test. According to the protocol for this interim analysis, p-values <0.005 were considered to indicate statistical significance. All tests were performed two-sided. Event-free and

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progression-free survival (EFS, PFS) were compared applying the Kaplan-Meier estimator together with the log-rank test. The following were considered events: death from any course during treatment, progression to AP or BC, loss of a complete hematologic response, loss of a major cytogenetic response.

Results

Patient characteristics

A total of 243 patients were screened and finally 227 patients were randomized. The median follow-up at the time of the interim analysis was 12.75 months (range: 3-24 months). Distribution of age, sex and median duration of CML before study entry were not significantly different between both treatment arms (Table 1). Almost all patients had received hydroxyurea during the course of the disease (96%). Other pretreatments included interferons (72%), busulfan (17%) and "others" (26%; mainly AraC +/- additional drug).

Remission rates

Rates of complete haematological responses did not significantly differ between the 2 arms at 1.5, 3, 6 and 12 months, respectively (54% arm A and 59% arm B at 3 months, 92% arm A and 85% arm B at 6 months, 82% arm A and 90% arm B at 12 months). In contrast, more patients achieved a MCyR and a CCyR at 3 months (MCyR: 21% arm A, 37% arm B, p=0.01; CCyR: 6% arm A, 25% arm B, p<0.001) and 6 months (MCyR: 34% arm A, 54% arm B, p=0.009; CCyR: 20% arm A, 44% arm B, p<0.001), respectively (Figures 1 A and 1B). At 12 months, following dose reduction of imatinib to 400 mg/day for "maintenance" at month 6 in the HD arm B, the rates of MCyR (the primary endpoint of the study) were comparable (59% arm A, 57% arm B). Nevertheless, there was still a tendency towards higher rates of CCyR (37% arm A, 48% arm B, p=0.29) in the HD arm B, but at the time of the interim analysis these values did not reach statistical significance. The median BCR-ABL^{IS} values at 3 and 6 months (Figure 2) were in agreement with the significantly better cytogenetic response rates during the high-dose imatinib induction phase. The proportion of patients who achieved MMR was significantly higher at 6 months in the high dose arm B (Figure 1C). PFS and EFS were not significantly different at the time of the interim analysis (PFS: 97.3% arm A, 93.9% arm B, p=0.191; EFS: 93.8% arm A, 85.1% arm B, p=0.027; Figure 3). After the first 6 months of therapy, loss of response was common. Notably, loss of MCyR and CCyR was less frequent in the HD arm B (53.5% and 54.3%, respectively) compared to the SD arm A (72.4% and 82.4%, respectively; p=0.14 and p=0.07).

Toxicity and cumulative median doses

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Grade 3 and 4 non-haematological toxicities were low and did not differ statistically significant between the 2 treatment arms (Table 2). In contrast, grade 3/4 haematological toxicities were more common in the HD arm B (anaemia: 2% arm A, 14% arm B, p=0.02; leukopenia: 24% arm A, 46% arm B, p=0.02; thrombocytopenia: 15% arm A, 39% arm B; p=0.003; Table 2). In spite of higher rates of grade 3/4 leukopenia in the HD arm B, grade 3/4 infections were low and not statistically different between both treatment arms. The cumulative median dose of imatinib during the first 6 months was 400 mg in the standard arm A and 767 mg in the experimental HD arm B.

Correlation between the administered dose and response rates

A higher proportion of patients (65.1%) remained on the initial 400 mg dose of imatinib in arm A as compared to the HD arm B where only 45.6% remained on the initial 800 mg dose (p=0.009). Cumulative rates of MCyR of patients without dose reduction/interruption during the first 6 months were higher in the HD arm B (71%) as compared to arm A (59%, p=0.232). Moreover, cumulative rates of CCyR were superior in patients without dose reduction/interruption in the HD arm B (61%) as compared to the patients without dose reduction/interruption in arm A (36%, p=0.014; Table 3). In addition, within the HD arm B the cumulative rates of CCyR were better (61%) for patients with no dose reduction/interruption compared to patients in the HD arm B with a dose reduction/interruption (34.9%, p=0.017; Table 3). Interestingly, the CCyR rates of patients without dose reduction/interruption in the standard arm A (35.7%) are comparable with the CCyR rates of patients not able to maintain high dose imatinib therapy in the experimental arm B (34.9%).

Discussion

The results presented here are the first published phase III data from a randomized multi-centre study in pre-treated CP-CML patients comparing the standard dose of 400 mg/day imatinib with high doses of imatinib (i.e. 800 mg/day). It is also noteworthy that the majority of patients included in this trial were late CP-CML patients who already received various lines of previous therapies, thus representing a high-risk population. In addition, patients were not allowed to be in MCyR at study entry. Moreover, as these analyses represent data from the planned interim analysis, we primarily focused on interesting biological events (i.e. differences in achieving cytogenetic and molecular responses at different time points). Moreover, survival data (EFS, PFS) are reported as well, but should be considered with caution, as only limited numbers of patients were evaluable after 12 months of therapy (i.e. a total of 54 patients at 18 months, 1 patient at 24 months). Our data clearly show that better cytogenetic and molecular responses can be achieved earlier with higher doses of imatinib. This might be of importance because a delayed achievement of cytogenetic and molecular response was reported to

be associated with an increased risk of progression (1,10,18). The primary endpoint of the study (i.e. the achievement of a significantly higher MCyR rate at 12 months in the HD arm B), however, was not achieved. Of note, at 12 months, only half of the patients were analysed so far, suggesting that the statistical power may be limited to detect statistically significant differences between both treatment arms. Moreover, CCyR rates at 12 months show a clear tendency in favour for the higher imatinib dose, despite of the fact that at this time point imatinib was already reduced to the "maintenance dose" of 400 mg/day for 6 months in the HD arm B. In contrast to previous studies (1,2,3,6,8) loss of responses was common in this high risk patient population. Interestingly and in favour of the higher imatinib dose a lower proportion of patients in the in the HD arm B lost MCyR and CCyR after the first 6 months of therapy. One might speculate that these late CP-CML patients might have benefited from a continuous treatment with HD imatinib. The reasons for choosing the concept of 6 months high-dose imatinib at 800 mg/day followed by 400 mg/day as "maintenance" were a "hit hard and early" concept and concerns of haematotoxicity in the long term with HD imatinib, when considering the inclusion of heavily pre-treated patients in late CP-CML.

There are 2 additional reports on phase III trials comparing the same 2 different doses of imatinib in chronic phase CML patients (18,19). Both trials were, however, performed with newly diagnosed CML patients and both have chosen a concept of continuous high dose (i.e. 800 mg) imatinib application during the whole study period.

In line with our observation of a faster response to HD imatinib, the tyrosine kinase inhibitor optimization and selectivity (TOPS) study showed significantly improved CCyR and MMR rates during the first 6 months of therapy and a trend towards better cytogenetic and molecular remissions (MMR) at 12 months in favour of the 800 mg per day schedule (18). The primary endpoint (MMR at 12 months) was, however, not different between the different dosing schedules. A prospective trial of the European Leukemia Net (ELN) presented by Baccarani and co-workers (19) included only newly diagnosed CML patients with a high risk Sokal score (20). Interestingly, this study failed to demonstrate significant differences in terms of cytogenetic and molecular remissions, even at early time points. The primary endpoint of this study (the achievement of a significantly improvement of the CCyR rate at 12 months) was not attained. In contrast to these findings, a sub-analysis of high risk Sokal patients in the TOPS trial revealed an increased rate of patients in MMR at 12 months in the HD arm, which, however, did not reach statistical significance. (18)

In terms of toxicity, it is noteworthy that in the ISTAHIT study the higher dosing of imatinib (800mg/day) appears to be generally well tolerated although dose reductions or interruptions were more frequent in the HD arm B as compared to the SD arm A. It was interesting to notice that the patients that were capable to take the intended high dose of 800 mg per day over a 6 month period had improved CCyR rates compared to both, the patients who were intended to take the 400 mg per day as well as the patients that reduced the dose in the HD arm B. This observation highlights the possibly more efficient anti-leukaemic activity of HD imatinib supporting the idea that the anti-tumor activity of imatinib appears indeed to be dose-dependent. However, our data as well as the findings

from the TOPS and the ELN trial suggest that in the long-term the absolute anti-leukemic effect (i.e. the depth of the response) under HD imatinib might not be increased.

In conclusion, this is the first randomized phase III trial in late CP-CML patients showing that in comparison to continuous SD imatinib, induction with HD imatinib (i.e. 800 mg per day) induces more rapid and higher cytogenetic and molecular response rates. HD imatinib is tolerable even in this heavily pre-treated late CP-CML patient population. Despite higher grade 3 and 4 haematotoxic side effects in the HD treatment arm, relevant infectious or bleeding complications were not seen. Whether the earlier and better responses will lead to a reduced appearance of BCR-ABL mutations, a reduced number of events on the long-run (leading to reduced rates of progression into AP and BC) and subsequently to an improved overall survival remains to be determined. Our study is of particular relevance for those countries currently not having access to imatinib but with a future prospective in getting approval of imatinib in the near future.

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ALP, TL performed consultancies for BMS. A.B. performed expert testimonies.

Authorship and Disclosures

ALP, DW, DF TL, MK, FR and GG designed the study, performed research and wrote the manuscript; ID, ZM, AB, LG, SL, SG, LG, AS, DP, NT, RG and RO performed research and reviewed the manuscript. HU performed statistical analyses and reviewed the manuscript.

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Table 1. Patient characteristics including pre-treatments.

	Arm A (400 mg)	**Arm B (800/400 mg)**
Male	42.5 %	46.6 %
Female	57.5 %	53.5 %
Age (Mean)	46.5 ± 12.3*	45.5 ± 13.4*
Age (Median)	46.3 (20.2 – 68.2)§	46.6 (18.4 – 76.4)§
CML duration before Study Entry (Mean)	38.2 months (mo)	33.6 mo
CML duration before Study Entry (Median)	27 mo (2-199)§	26 mo (1-192)§
Pretreatments:		
Hydroxyurea	97% (109)#	96% (109)#
Interferons	70% (79)	74% (84)
Busulfan	20% (23)	14% (15)
Others (mainly AraC ± additional drug)	24% (27)	27% (31)

**SD* §*Range* #*Numbers*

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Table 2. WHO Grade 3 and 4 haematological toxicities during the first 6 months of treatment and WHO Grade 3 and 4 non-haematological toxicities reported until to the time of the interim analysis; *p=0.02; §p=0.003.

	400 (ARM A)	**400/800 (ARM B)**
Anemia	2 % (2/86)	14 % (11/80)*
Leukopenia	24 % (21/86)	46 % (37/80)*
Thrombopenia	15 % (13/86)	39 % (31/80)§
Infections	2 % (2/113)	3 % (3/114)
Liver	1 % (1/113)	2 % (2/114)
Fluid Retention	< 1 % (0/113)	< 1 % (0/114)
Gastrointestinal	< 1 % (0/113)	< 1 % (0/114)
Muscle	< 1 % (0/113)	3 % (3/114)
Renal	3 % (3/113)	3 % (3/114)
Cardia	< 1 % (0/113)	< 1 % (0/114)
Neurologic	< 1 % (0/113)	1 % (1/114)
Pulmonary	< 1 % (0/113)	< 1 % (0/114)
Others	< 1 % (0/113)	7 % (8/114)

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Table 3. Comparison of the cumulative CCyR rate if the intended dose of imatinib (i.e. 400 mg in arm A and 800 mg in arm B) was either continuously taken or if dose interruptions or dose reductions were performed.

	Cumulative Achievement of CCyR		
Therapy within first 6 months	**Arm A (400mg)**	**Arm B (800mg)**	
	p=0.014		
No change	20/56 (35.7%)	25/41 (61.0%)	p=0.017
Interruption/Dose reduction	6/25 (24.0%)	15/43 (34.9%)	
Discontinued	0/3 (<33%)	0/6 (<17%)	

In the case of toxicity in arm A, the dose was reduced to 300 mg, otherwise patients went off study. In the HD arm B, 35% of the patients that had to be dose reduced received 600 mg/day, 63% 400 mg/day and 2% 300 mg/day.

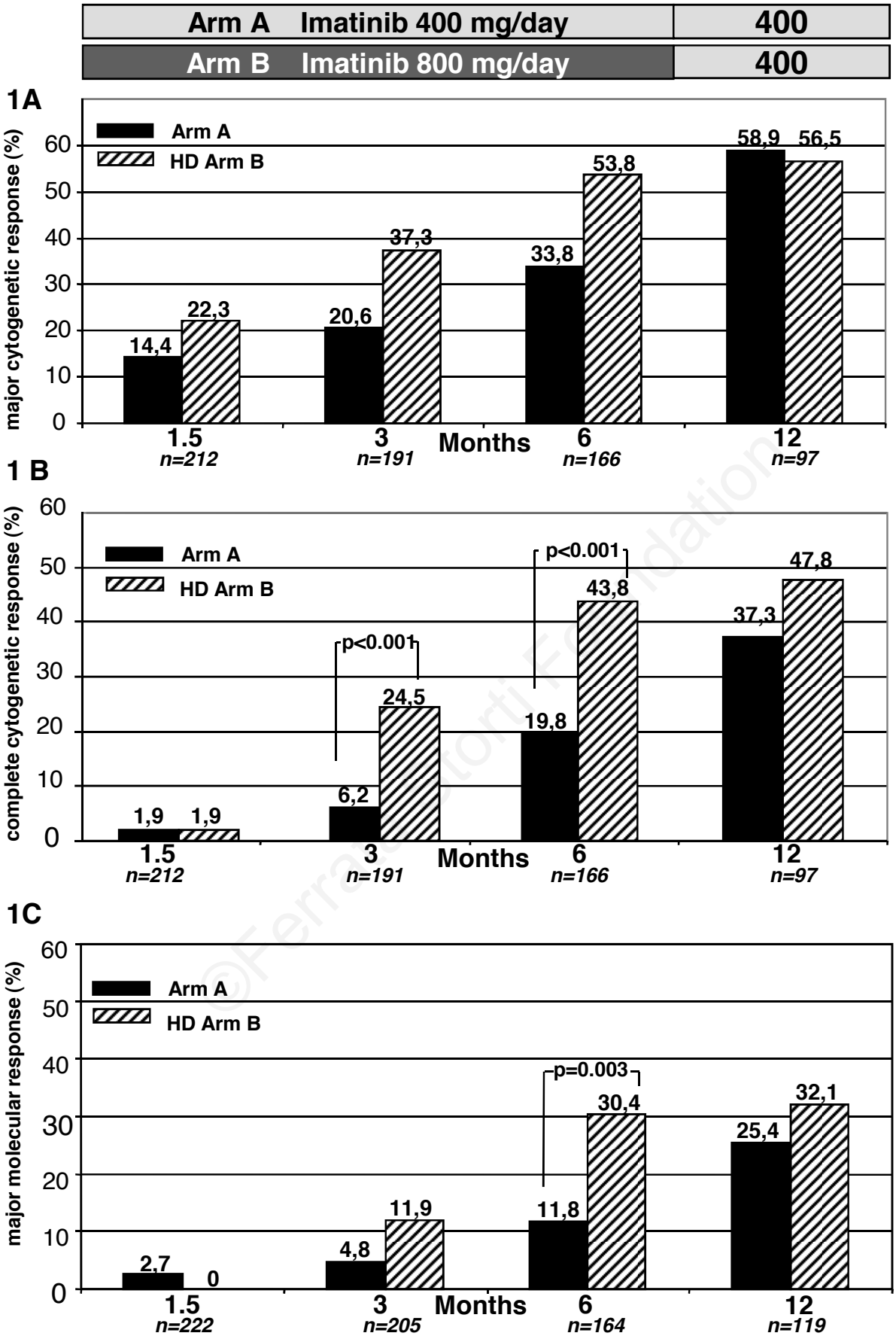

Figure 1 (A-C): MCyR (Fig. 1A), CCyR (Fig. 1B) and MMR (Fig. 1C) rates analysed at 1.5, 3, 6 and 12 months after randomisation

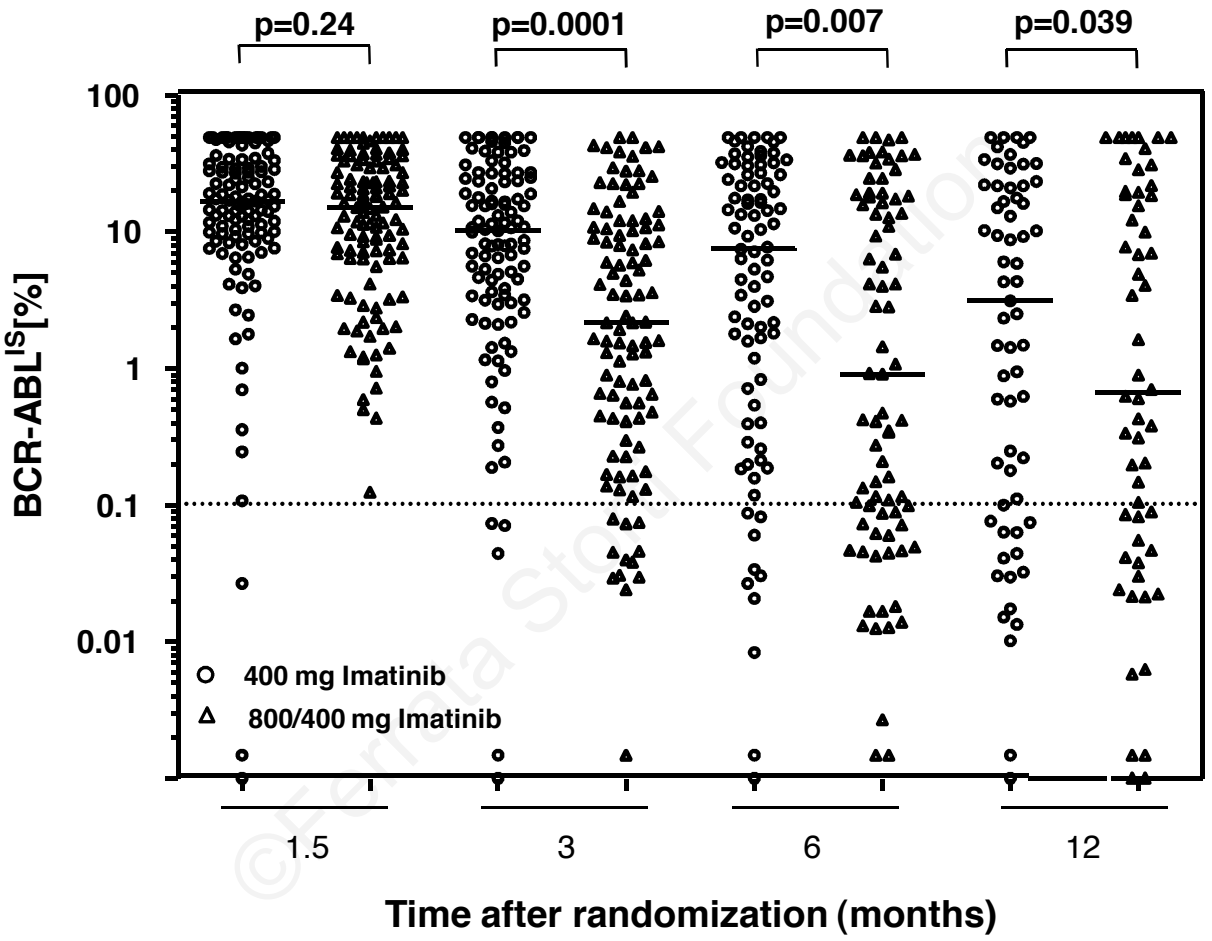

Figure 2: Molecular response (BCR-ABL^{IS}) at different time points after randomisation. Each symbol represents an individual patient at the respective time-point. Horizontal bars represent the median values for each study arm at the respective time points. The indicated p-values reflect the differences between median molecular responses observed in individual treatment arms at defined time points. The dashed line at 0.1% represents the cut-off value for definition of a MMR.

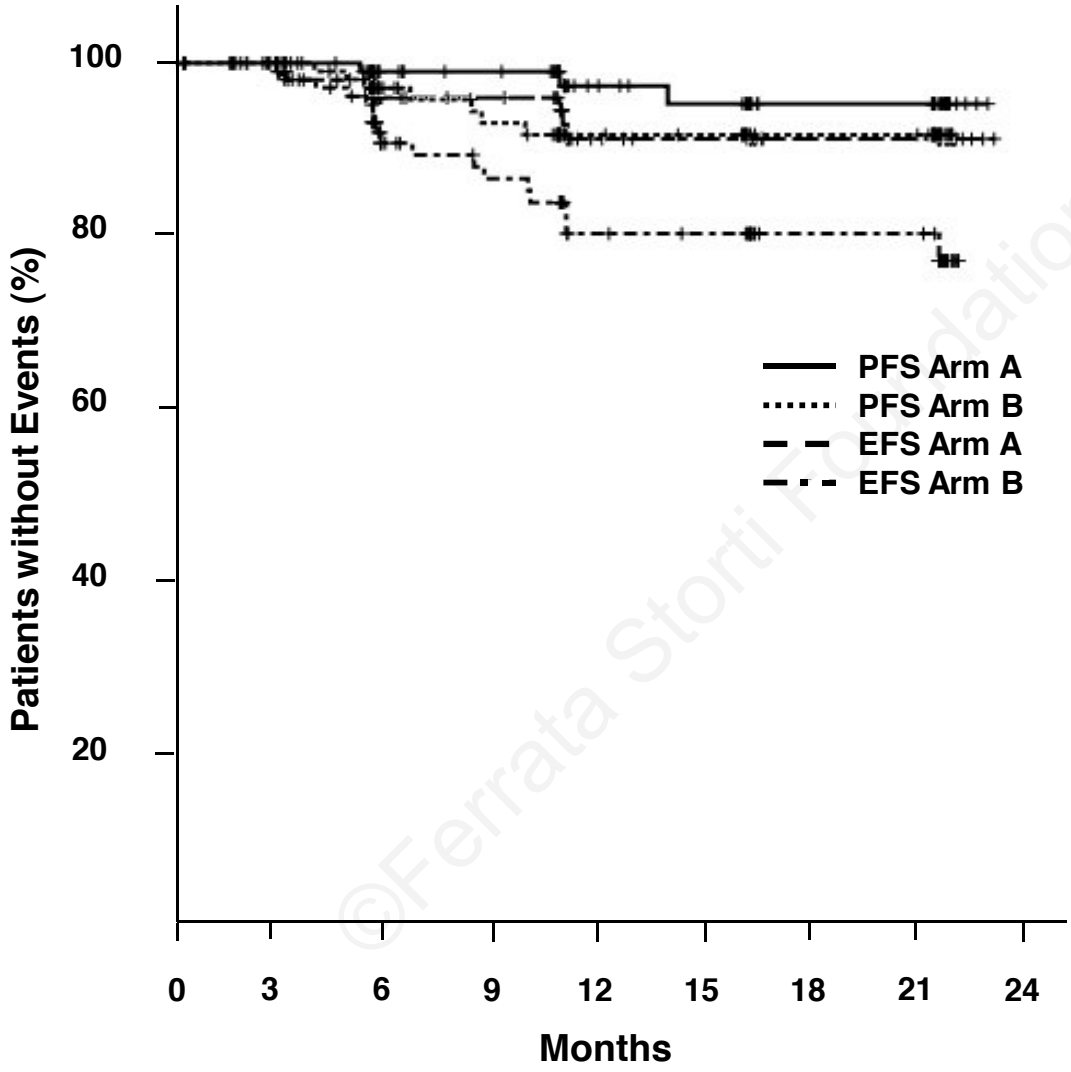

Figure 3: Kaplan-Meier estimates of the rates of event-free survival and progression to the accelerated phase or blast crisis for patients in arm A and arm B

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