Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants

Chronic myeloid leukemia (CML) study IV was designed to explore whether treatment with imatinib (IM) at 400 mg/day could be optimized by doubling the dose (n = 420), adding interferon (IFN) (n = 430) or cytarabine (n = 158) or using IM after IFN-failure (n = 128). From July 2002 to March 2012, 1551 newly diagnosed patients in chronic phase were randomized into a 5-arm study. The study was powered to detect a survival difference of 5% at 5 years. After a median observation time of 9.5 years, 10-year overall survival was 82%, 10-year progression-free survival was 80% and 10-year relative survival was 92%. Survival between IM400 mg and any experimental arm was not different. In a multivariate analysis, risk group, major-route chromosomal aberrations, comorbidities, smoking and treatment center (academic vs other) in combination influenced survival significantly, but not any form of treatment optimization. Patients reaching the molecular response milestones at 3, 6 and 12 months had a significant survival advantage. For responders, monotherapy with IM400 mg provides a close to normal life expectancy independent of the time to response. Survival is more determined by patients’ and disease factors than by initial treatment selection. Although improvements are also needed for refractory disease, more life-time can currently be gained by carefully addressing non-CML determinants of survival.

Leukemia (2017) 31, 2398–2406; doi:10.1038/leu.2017.253

INTRODUCTION

Chronic myeloid leukemia (CML) study IV was designed to explore whether treatment with imatinib (IM) at a dose of 400 mg/day as used in the International Randomized Study on Interferon (IFN) and STI571 (IRIS) could be improved by doubling the dose or by combining IM with IFN or cytarabine. Primary goals were the comparative response and long-term survival analyses of the experimental arms vs IM400 mg. Molecular monitoring of all patients was an integral part of the study from the beginning. The study has generated new insights in the relevance of molecular monitoring, of comorbidities, additional chromosomal aberrations and deep molecular response. CML-study IV has also shown that IM at 800 mg results in significantly earlier cytogenetic and molecular responses than IM400 mg. Various

1Medizinische Klinik, Medizinische Fakultät Mannheim, Universität Heidelberg, Mannheim, Germany; 2Medizinische Klinik II, Universität Heidelberg, Mannheim, Germany; 3Medizinische Klinik, Universitätsklinikum, Erlangen, Germany; 4Medizinische Klinik, Universität München, Munich, Germany; 5Klinik für innere Medizin, Universitätsklinikum, Marburg, Germany; 6Medizinische Klinik, Universitätsklinikum Eppendorf, Hamburg, Germany; 7Klinikum Schwabing, Munich, Germany; 8Universitätsklinik, Basel, Switzerland; 9Inselspital, Bern, Switzerland; 10RWTH, Aachen, Germany; 11MLU, Munich, Germany; 12Institut für Humangenetik, MHH, Hanover, Germany; 13Ev. Krankenhaus, Hannover, Germany; 14Medizinische Klinik und Poliklinik, Universitätsklinikum, Würzburg, Germany; 15Klinik für innere Medizin 3, Chemnitz, Germany; 16Medizinische Klinik V, Universität Heidelberg, Heidelberg, Germany; 17Onkologische Schwerpunktpraxis, Heilbronn, Germany; 18Medizinische Klinik 5, Klinikum Nürnberg-Nord, Nürnberg, Germany; 19Medizinische Abteilung 2, Universitätsklinikum, Tübingen, Germany; 20Klinik für Innere Medizin 3, Universität der Saarlandes, Homburg, Germany; 21Medizinische Klinik A, Universitätsklinikum, München, Germany; 22Onkologie Leer Unterems, Leer, Germany; 23Klinik für Innere Medizin 1, Universität der Saarlandes, Homburg, Germany; 24Klinik für Innere Medizin, Universität Innsbruck, Innsbruck, Austria; 25Klinik für Innere Medizin 1, Universität des Saarlandes, Homburg, Germany; 26Klinik für Innere Medizin, Universität Heidelberg, Mannheim, Germany; 27Klinik für Innere Medizin, Medizinische Fakultät Mannheim, Universität Heidelberg, Mannheim, Germany; 28Klinik und Poliklinik für Innere Medizin, Medizinische Fakultät, Mannheim, Germany; 29Medizinische Klinik 2, Klinikum der Universität Düsseldorf, Düsseldorf, Germany; 30Medizinische Klinik 3, Universitätsklinikum, Regensburg, Germany; 31St Marien-Hospital, Hagen, Germany; 32St Marien Hospital, Brno, Czech Republic; 33Klinik für Knochenmarktransplantation, Essen, Germany; 34Medizinische Klinik 3, Städtisches Klinikum, Karlsruhe, Germany; 35Klinik für Innere Medizin 3, Westpfalz-Klinikum, Kaiserslautern, Germany; 36Medizinische Klinik 2, Universitätsklinikum, Köln, Germany; 37Klinik für Hämatologie-Onkologische Schwerpunktpraxis, Würzburg, Germany; 38St Antonius-Hospital, Eschweiler, Germany; 39Klinik für Hämatologie, Medizinische Klinik 2, Universität Göttingen, Göttingen, Germany; 40Klinik für Hämatologie, Medizinische Klinik 1, Universität Heidelberg, Mannheim, Germany; 41Medizinische Klinik, Universitäatsmedizin, Göttingen, Germany; 42Klinik für Hämatologie, Medizinische Klinik 3, Universität, Bonn, Germany; 43St Marien-Krankenhaus, Siegen, Germany; 44Klinik für Hämatologie, Karolinska Institutet, Stockholm, Sweden; 45Klinik für Hämatologie, Medizinische Klinik 4, Universität, Hannover, Germany; 46Klinik für Hämatologie, Medizinische Klinik 1, Universität, Heidelberg, Germany; 47Klinik für Hämatologie und medizinische Onkologie, Medizinische Klinik, Universität Heidelberg, Mannheim, Germany; 48Klinik für Hämatologie, Medizinische Klinik 2, Universität Heidelberg, Mannheim, Germany; 49Klinik für Innere Medizin, Medizinische Klinik 3, Universität, Bonn, Germany; 50Klinik für Innere Medizin 1, Medizinische Klinik, Universität Heidelberg, Mannheim, Germany; 51Medizinische Klinik 2, Universitätsklinikum, Jena, Germany; 52Klinik für Hämatologie, Medizinische Klinik 1, Universität Heidelberg, Mannheim, Germany; 53Klinik für Innere Medizin 3, Universitätsklinikum, Jena, Germany; 54Klinik für Innere Medizin 2, Universitätsklinikum, Jena, Germany; 55Klinik für Hämatologie-Onkologische Schwerpunktpraxis, Bielefeld, Germany; and 56Klinik für Innere Medizin 2, Universitätsklinikum, Jena, Germany. Correspondence: Professor Dr R Hehlmann, ELN-Foundation, Im Langgewann 45, 69469 Weinheim, Germany.

E-mail: Hehlmann.ELN@gmail.com

Received 23 June 2017; accepted 4 July 2017; accepted article preview online 14 August 2017; advance online publication, 12 September 2017
observational and randomized studies have tried to improve IM-treatment by combination with IFN, cytarabine or a dose increase to 600 or 800 mg9–16 and have achieved earlier and deeper responses. In no instance a better survival was reported after median observation periods up to 3.5 years. Two studies have compared survival with IM400 mg and 2nd generation tyrosine kinase inhibitors (2G-TKI). After 5 years, 2G-TKI showed earlier and deeper responses than IM400 mg, but no survival advantage.17,18 CML-study IV was powered to detect a 5% survival difference after 5 years. We here report survival outcome after a median observation time of close to 10 years.

PATIENTS AND METHODS

Study design and treatment strategy have been published previously.3,8 In brief, newly diagnosed CML patients in chronic phase (CP) were randomized into a 5-arm study comparing IM400 mg/day vs IM400 mg/day in combination with IFN vs IM400 mg/day after IFN-failure vs IM800 mg/day. Recruitment was from July 2002 through March 2012. There was no upper age limit. Exclusion criteria were pretreatment cytogenetic risk, or a dose increase was permitted. If IM-treatment failed, stem-cell transplantation or risk-adapted drug treatment (hydroxyurea, cytarabine, intensive chemotherapy) was recommended - depending on type of mutation and degree of proliferation or progression. After availability, either dasatinib or nilotinib was recommended. Participation of IM-resistant or intolerant patients in the dasatinib and nilotinib phase II studies was permitted. The first patient was switched to 2G-TKI (dasatinib) on 30 March, 2005.

IFN, subcutaneous cytarabine and the full 800 mg/day dose were administered after a 6-week run-in period with IM 400 mg/day to avoid cytopenias.9 The IM-dose could be reduced according to tolerability.

Initial primary goal of CML-study IV was comparative response probabilities. Long-term primary goal was comparative survival (study protocol in the Supplementary Appendix). The strategy was to give more intensive treatment early since this has improved outcome.19

Definitions and end points

Definitions followed the ELN (European LeukemiaNet) recommendations.20,21 Risk assignment was made according to Euro-score.22 IFN-failure was defined as no complete hematologic remission after 6 months or not at least PCyR after 21 months, loss of complete hematologic remission or complete cytogenetic remission, or higher-grade AE. Overall survival (OS) was defined as the time between diagnosis and death resulting from any cause. Progression-free survival (PFS) considered the additional events accelerated phase and blast crisis (BC). Death unrelated to CML was defined as death without prior progression and unrelated to CML-therapy. Death due to CML was stratified according to the European treatment and outcome study (EUTOS)-long-term-surface (ELTS) score.23 All living patients were censored at the time of their last visit. When estimating the cumulative incidences of molecular remissions,

Table 1. Patients’ characteristics

| n | Imatinib 400 | Imatinib+IFN | Imatinib+AraC | Imatinib after IFN | Imatinib 800 | Total |
|---|-------------|-------------|--------------|-------------------|-------------|-------|
| Age (years), median (range) | 1538 | 53 (16–88) | 53 (16–83) | 52 (18–79) | 53 (18–87) | 51 (18–85) | 53 (16–88) |
| % Male | 1538 | 61% | 59% | 63% | 63% | 59% | 60% |
| % Smoker | 1326 | 21% | 16% | 21% | 20% | 20% | 19% |
| Karnofsky index (%), median (range) | 1394 | 100 (70–100) | 100 (50–100) | 100 (70–100) | 100 (70–100) | 100 (50–100) | 100 (50–100) |
| Hemoglobin (g/dl), median (range) | 1524 | 12.4 (4.9–17.5) | 12.2 (6.2–17.7) | 12.5 (6.7–15.9) | 12.9 (8.1–17.6) | 12.2 (4.7–19.1) | 12.3 (4.7–19.1) |
| WBC (× 10⁹/l), median (range) | 1531 | 77 (5.7–582) | 89 (2.8–630) | 58 (2.9–529) | 56 (3.2–456) | 79 (2.6–570) | 76 (2.6–630) |
| Platelets (× 10⁹/l), median (range) | 1533 | 382 (58–2419) | 343 (49–3020) | 403 (34–2799) | 390 (44–2205) | 386 (39–2716) | 374 (34–3020) |
| Eosinophils (%), median (range) | 1530 | 2 (0–20) | 2 (0–12) | 2 (0–14) | 2 (0–31) | 2 (0–16) | 2 (0–20) |
| Basophils (%), median (range) | 1526 | 3 (0–22) | 3 (0–20) | 4 (1–21) | 4 (0–21) | 3 (0–26) | 3 (0–26) |
| Blasts in blood (%), median (range) | 1525 | 1 (0–17) | 1 (0–16) | 1 (0–19) | 0 (0–16) | 1 (0–17) | 1 (0–19) |
| Spleen size (cm below costal margin), median (range) | 1529 | 2 (0–28) | 2 (0–38) | 2 (0–38) | 2 (0–38) | 2 (0–38) | 2 (0–38) |
| Euro score, n (%) | 1527 | 142 (36) | 150 (35) | 55 (35) | 48 (38) | 159 (38) | 554 (36) |
| Low | 205 (51) | 226 (53) | 81 (51) | 79 (62) | 202 (48) | 793 (52) |
| Intermediate | 51 (13) | 49 (12) | 22 (14) | 1 (1) | 57 (14) | 180 (12) |
| Sokal score, n (%) | 1513 | 140 (36) | 164 (39) | 62 (39) | 51 (40) | 153 (37) | 570 (38) |
| Low | 155 (40) | 164 (39) | 53 (34) | 58 (45) | 152 (37) | 582 (38) |
| Intermediate | 97 (25) | 92 (22) | 42 (27) | 19 (15) | 111 (27) | 361 (24) |
| High | 348 (88) | 384 (90) | 139 (88) | 118 (92) | 352 (85) | 1341 (88) |
| EUTOS score, n (%) | 1523 | 49 (12) | 44 (10) | 19 (12) | 10 (8) | 60 (15) | 182 (12) |
| Low | 212 (54) | 236 (55) | 106 (67) | 80 (62) | 235 (57) | 869 (57) |
| Intermediate | 123 (31) | 136 (32) | 35 (22) | 40 (31) | 116 (28) | 450 (30) |
| High | 60 (15) | 55 (13) | 17 (11) | 9 (7) | 61 (15) | 202 (13) |
| BCR-ABL1 transcript type, n (%) | 1506 | b2a2 | 147 (38) | 192 (46) | 54 (35) | 43 (34) | 160 (39) | 596 (40) |
| b3a2 | 178 (46) | 167 (40) | 69 (45) | 57 (46) | 187 (45) | 658 (44) |
| b2a2 and b3a2 | 54 (14) | 55 (13) | 29 (19) | 24 (19) | 61 (15) | 223 (15) |
| Atypical transcriptions | 10 (2) | 8 (1) | 3 (1) | 1 (1) | 7 (1) | 29 (1) |

Abbreviations: ELTS, European treatment and outcome study (EUTOS)-long-term survival; IFN, interferon-ı; WBC, white blood cells. There were no significant differences between the treatment groups. AOne patient with 66% basophils (basophil leukemia). BOne patient with ambivalent findings: 30% blasts in blood, 7% blasts in the marrow.
patients were censored when they received a 2G-TKI. No patient was removed from the study except at patient’s request (n = 14).

Cytogenetic and molecular analyses
Cytogenetic and molecular diagnostics were performed as described. Testing for residual BCR-ABL transcripts was done in two standardized and accredited laboratories with defined conversion factors for equivalence of tests (Mannheim and MLL Munich). Confirmed MR, MR and MR were defined as a reduction of residual BCR-ABL transcripts of > 4, > 4.5 and > 5 logs compared with the standardized baseline in two consecutive analyses. Testing was restricted to patients expressing b2a2 and/or b3a2 transcripts. For a negative quantitative reverse transcription polymerase chain reaction, the number of ABL1 transcripts used for nested PCR had to be > 10 000 for MR, > 32 000 for MR and > 100 000 for MR .

Mutation analysis was performed according to the ELN recommendations.

Sample size estimation
At first, differences in probability of MMR at 12 months were investigated. If the null hypothesis of equal probabilities could be rejected, OS differences between IM400 mg and IM800 mg were examined. Assuming an alpha = 0.05, a 5-year recruitment, and an additional 5-year follow-up, it would be possible to identify a survival difference with a power of at least 80%, if patients in the IM400 mg arm had a 5-year survival probability of 90% and in the IM800 mg arm of at least 95% or not more than 84%, and if n = 400 patients were randomized to each arm. Exponential distribution was assumed and survival probabilities were compared with the log-rank test.

Statistical analyses
OS and PFS were analyzed using Kaplan–Meier curves and log-rank tests. To estimate relative survival, OS probabilities were adjusted by survival probabilities of matched German population data from the Human Mortality Database for each year of diagnosis in CML-study IV with regard to sex and individual age at diagnosis. Cumulative incidences were calculated under consideration of competing risks of death defined by accelerated phase, BC and death from any cause. Comparisons between cumulative incidences were performed by the Gray test and prognostic impact of remissions determined by landmark analyses. The cumulative incidences of molecular responses, all analyses were by intention to treat. Level of significance was 0.05 two sided. For estimation of relative survival probabilities software R (version 3.0.3.3, GNU General Public License, R Foundation, Vienna, Austria) was applied. All other calculations were performed with SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Ethics
The protocol followed the Declaration of Helsinki and was approved by the ethics committees of the Medizinische Fakultät Mannheim and of participating centers. Written informed consent was obtained from all patients before randomization.

RESULTS
Patients
From July 2002 to March 2012, 1551 newly diagnosed CML patients in CP were randomized, 1536 were evaluable, 400 for IM400 mg, 430 for IM plus IFN, 158 for IM plus cytarabine, 128 for...
Patients were recruited by 210 centers in Germany, Switzerland and the Czech Republic. Patients’ characteristics are shown in Table 1. Median age was 53 years, 60% of patients were male. Euro score was low-risk in 36%, intermediate in 52% and high-risk in 12% of patients. In the arm IM plus IFN, IFN was added to IM400 mg for a median of 1.1 years. After 10 years, six patients still received IFN. In the IM after IFN-failure arm, the median time on IFN monotherapy was 0.5 years. After 10 years, one patient still continued in remission on IFN monotherapy. The median time on low-dose cytarabine was 1.3 years. The main reason for discontinuation of IFN and cytarabine was intolerance. In the IM800 mg arm, the dose could be reduced according to tolerability, the median IM-dose declined from a maximum of 645 mg/day in the 2nd quarter of year 1 to 400 (200–800) mg/day in year 4. The median dose in the IM400 mg arm was 400 (200–800) mg/day with a dose increase reported in 86 patients. Median observation time was 9.5 years (11.8 years for IM plus cytarabine and IM after IFN and 8.3 years for IM800 mg). The flow of patients in the five study arms is shown in Figure 1. At the last evaluation, at least 728 of 1181 patients under observation (62%) still received IM.

Survival
In all, 10-year OS of all patients was 82% (95% confidence interval (CI): 80; 84) (Figure 2a), 10-year PFS (95% CI: 78; 82) 80%. 10-year OS was 80% with IM400 mg, 84% with IM plus IFN, 84% with IM plus cytarabine, 79% with IM after IFN-failure and 79% with IM800 mg. In all, 10-year PFS was 80% with IM400 mg, 83% with IM plus IFN, 82% with IM plus cytarabine, 75% with IM after IFN and 77% with IM800 mg (Supplementary Figure 1). Adjusted for matched general population data, 10-year relative survival probability was 92% (95% CI: 90–94%) (Figure 2a; 91% for IM400 mg, 94% for IM plus IFN, 94% for IM plus cytarabine, 94% for IM after IFN and 87% for IM800 mg) and 96% (95% CI: 88; 99) for the 594 patients with BCR-ABL1 ≤ 1% (Figure 2c). Two-hundred seventy five patients died, 23 after stem cell transplantation in first CP. Of patients not transplanted in first CP, more deaths were unrelated to CML (n = 169, 67%) than due to CML (n = 83, 33%). The 10-year probability of death due to CML was 6%, of death unrelated to CML 12% (Figure 2d). In all, 10-year OS and PFS according to Euro score and treatment are shown in Supplementary Table 1. Whereas Euro low-risk patients had significantly better survival than higher-risk patients, survival with IM after IFN and 420 for IM800 mg. Patients were recruited by 210 centers in Germany, Switzerland and the Czech Republic. Patients’ characteristics are shown in Table 1. Median age was 53 years, 60% of patients were male. Euro score was low-risk in 36%, intermediate in 52% and high-risk in 12% of patients. In the arm IM plus IFN, IFN was added to IM400 mg for a median of 1.1 years. After 10 years, six patients still received IFN. In the IM after IFN-failure arm, the median time on IFN monotherapy was 0.5 years. After 10 years, one patient still continued in remission on IFN monotherapy. The median time on low-dose cytarabine was 1.3 years. The main reason for discontinuation of IFN and cytarabine was intolerance. In the IM800 mg arm, the dose could be reduced according to tolerability, the median IM-dose declined from a maximum of 645 mg/day in the 2nd quarter of year 1 to 400 (200–800) mg/day in year 4. The median dose in the IM400 mg arm was 400 (200–800) mg/day with a dose increase reported in 86 patients. Median observation time was 9.5 years (11.8 years for IM plus cytarabine and IM after IFN and 8.3 years for IM800 mg). The flow of patients in the five study arms is shown in Figure 1. At the last evaluation, at least 728 of 1181 patients under observation (62%) still received IM.
Figure 3. Overall survival by disease risk (Euro-score). (a) Low, (b) intermediate, (c) high. AraC, cytarabine; IFN, interferon-α; OS, overall survival; IM, imatinib.

Table 2. Causes of death

| Causes (n) | IM 400 mg | IM+IFN | IM+cytarbine | IM after IFN-failure | IM 800 mg | Total |
|------------|-----------|--------|--------------|----------------------|-----------|-------|
| Total deaths (n) | 75 | 69 | 39 | 30 | 62 | 275 |
| Progression to AP/BC | 17 | 15 | 9 | 6 | 20 | 67 |
| Transplantation related | 6 | 9 | 7 | 4 | 5 | 31 |
| Infection in CP | 7 | 6 | 1 | 2 | 4 | 20 |
| Secondary malignancy | 16 | 12 | 3 | 6 | 7 | 44 |
| Bleeding | 1 | 2 | 0 | 1 | 1 | 4 |
| Cardiopulmonary | 10 | 10 | 5 | 6 | 9 | 40 |
| Renal insufficiency | 2 | 1 | 1 | 1 | 2 | 7 |
| Thromboembolic/ischemic (not cardiac) | 1 | 1 | 2 | 1 | 3 | 8 |
| Suicide | 1 | 1 | 0 | 0 | 0 | 2 |
| Others | 3 | 4 | 2 | 1 | 2 | 12 |
| Unknown | 11 | 8 | 9 | 3 | 9 | 40 |

Abbreviations: AP, accelerated phase; BC, blast crisis; CP, chronic phase; IFN, interferon-α; IM, imatinib. n indicates number of patients.
any treatment was not significantly different from IM400 mg at any risk level (Figure 3) nor was a significant difference detectable by any other risk score. The non-CML causes of death correspond to those observed in the general population (Table 2). The cumulative incidences of death related and unrelated to CML were not different between the five treatment arms (Supplementary Figure 2), whether stratified for ELTS or not.

Multivariate analysis for impact on survival of variables at diagnosis: risk score, comorbidities, major-route additional chromosomal aberrations, smoking and treatment center (academic vs other) in Table 3.

Table 3. Multivariate analysis for impact on survival (n = 1252)

| Variable                                    | Regression coefficient | Standard error | P-value | Hazard ratio | Type-3-test |
|---------------------------------------------|------------------------|----------------|---------|--------------|-------------|
| Therapy                                     | IM-after-IFN-failure vs IM 400 | 0.288          | 0.254   | 0.256        | 1.334       | 0.676       |
|                                            | IM 800 vs IM 400       | 0.033          | 0.207   | 0.875        | 1.033       |             |
|                                            | IM+cytarabine vs IM 400| 0.157          | 0.244   | 0.519        | 1.170       |             |
|                                            | IM+IFN vs IM 400       | −0.069         | 0.199   | 0.727        | 0.933       |             |
| ELTS-score                                  | Low vs high risk       | −0.778         | 0.210   | <0.001       | 0.459       | <0.001      |
|                                            | Intermediate vs high risk | 0.061         | 0.208   | 0.770        | 1.062       |             |
| Treatment center                            | Academic center better than community hospital | 0.416 | 0.181 | 0.021        | 1.515       | 0.012       |
|                                            | Academic center better than private practice | 0.570 | 0.199 | 0.004        | 1.768       | 0.004       |
| Comorbidity (Charlson index)                | Per point (age not considered) | 0.417     | 0.050  | <0.001       | 1.518       | <0.001      |
| Gender                                      | Male vs female         | 0.181         | 0.154   | 0.240        | 1.199       | 0.240       |
| Transcript type                             | b2a2 vs b3a2           | 0.088         | 0.157   | 0.574        | 1.092       | 0.713       |
|                                            | b2a2+b3a2 vs b3a2      | 0.158         | 0.208   | 0.447        | 1.171       |             |
| Smoking habit                               | Smoker vs non-smoker   | 0.547         | 0.169   | 0.001        | 1.728       | 0.001       |
| Major-route ACA                             | Major-route ACA vs no major-route ACA at diagnosis | 1.814   | 0.392  | <0.001       | 6.137       | <0.001      |

Abbreviations: ACA, additional chromosomal aberration; ELTS, EUTOS-long-term survival; IM, imatinib, IFN, interferon-α. Also better education (bachelor vs no bachelor) had an impact (P < 0.001), but was not independent of smoking and selection of treatment center. *Age considered by ELTS-score.

Power
With n = 400 randomized to IM400 mg and n = 420 randomized to IM800 mg, an accrual time of 6.75 years across treatment arms and an additional follow-up of 4.25 years, the power would have been above 80% to observe OS differences, if the assumptions for the sample size estimation (see Methods) had been correct. In fact, survival probabilities at 5 years were 89% (95% CI: 86%; 92%) and 92% (95% CI: 88%; 94%), respectively. At 10 years, the difference in OS probability was only 1%. The hazard ratio of IM400 mg to IM800 mg was 1.091 (95% CI: 0.767; 1.550) instead of 2 or 0.61.

Switching to 2G-TKI
Four-hundred seven patients (26.5%) were switched to another TKI, mostly dasatinib or nilotinib, due to intolerance or resistance. Seven patients were switched to bosutinib, 5 to ponatinib, and 57 to more than one TKI. The median time to switching was 34 months. Switching was evenly distributed between treatment arms (Figure 1) arguing against an influence on comparative survival analyses. Censoring at the time of switching raised 10-year OS by 3% across treatment arms, indicating that predominantly poorer risk patients were switched.

Mutations and progressions
One-hundred ten of 541 analyzed patients (20.3%) had mutations of the BCR-ABL1-kinase domain, 70 (64%) had known resistance mutations (T315I (n = 33), E255K (n = 11), Y253H (n = 11), F359C (n = 8), G250E (n = 4) and F486S (n = 3)) and 73 (66%) were switched to 2G-TKI. More high-risk patients (31.5%) than low (16.9%) and intermediate risk patients (18.7%) had mutations. One-hundred fifteen patients fulfilled the criteria of progression to accelerated phase and BC, of which 89 had mutation analyses which were positive in 35 (39%). Eighty-seven patients progressed to BC. The 10-year cumulative incidence of BC was 5.8% (95% CI: 4.7%; 7.1%). Most BC occurred in the first two years, but some continued to occur later during the entire observation time (Figure 4). Median survival after BC was 7.9 months across all treatment arms. Thirty-eight patients had myeloid, 28 lymphoid BC, in 21 patients the type was mixed or unknown.

Transplantation
One-hundred thirty-eight patients were transplanted, 91 in first CP. Median age at transplantation was 41 (16–65) years, 94 (68%) were male. Eight-year survival after transplantation in first CP was 73%, of those transplanted not in first CP 38%.

Cytogenetic and molecular responses
By 10 years, the cumulative rates of complete cytogenetic remission were 77% (95% CI: 75; 79), of molecular response...
### Table 4. Molecular response by response depth and treatment over time

| BCR-ABL1 ≤ 1% | n | Median time to response (mo) | Year 1 | 95% CI | Patients at risk | Year 3 | 95% CI | Patients at risk | Year 5 | 95% CI | Patients at risk | Year 10 | 95% CI | Patients at risk | P-value IM 400 vs IM 800 |
|---------------|---|-------------------------------|--------|--------|-----------------|--------|--------|-----------------|--------|--------|-----------------|---------|--------|-----------------|--------------------------|
| Imatinib 400  | 372 | 7.9                           | 67.5%  | (62.4;72.7) | 108              | 91.1%  | (86.3;92.9) | 18               | 91.0%  | (87.3;93.6) | 12               | 94.6%  | (90.9;96.9) | 2                | 0.003                     |
| Imatinib + IFN| 405 | 7.9                           | 67.8%  | (63.2;72.7) | 111              | 83.9%  | (79.8;87.2) | 31               | 87.5%  | (83.7;90.5) | 16               | 91.2%  | (87.5;93.8) | 2                |                          |
| Imatinib + AraC| 150 | 11.0                          | 53.6%  | (45.2;61.6) | 59               | 87.6%  | (81.2;91.9) | 8                | 89.8%  | (84.0;93.6) | 3                | 91.0%  | (85.9;94.3) | 1                |                          |
| Imatinib after IFN | 122 | 18.6                          | 25.7%  | (18.3;33.7) | 85               | 67.6%  | (58.7;75.0) | 21               | 77.4%  | (69.6;83.5) | 6                | 80.9%  | (73.6;86.4) | 2                |                          |
| Imatinib 800  | 399 | 6.3                           | 77.6%  | (73.1;81.4) | 67               | 90.0%  | (86.3;92.7) | 7                | 90.0%  | (86.3;92.7) | 4                | 91.4%  | —            | 0                |                          |
| MMR           | Imatinib 400 | 372 | 14.9                          | 36.7%  | (31.8;41.7) | 216              | 80.6%  | (76.1;84.4) | 43               | 86.3%  | (82.3;89.5) | 19               | 92.2%  | (88.2;94.9) | 2                | 0.003                     |
| Imatinib + IFN| 405 | 13.5                          | 43.1%  | (38.4;48.7) | 198              | 76.3%  | (71.7;80.4) | 48               | 83.5%  | (79.0;87.1) | 20               | 87.9%  | (83.6;91.2) | 3                |                          |
| Imatinib + AraC| 150 | 17.8                          | 29.6%  | (22.3;37.2) | 93               | 79.6%  | (71.9;85.4) | 16               | 85.8%  | (79.1;90.5) | 4                | 87.2%  | (81.1;91.5) | 1                |                          |
| Imatinib after IFN | 122 | 29.9                          | 10.0%  | (5.5;16.2)  | 103              | 57.8%  | (48.6;65.9) | 31               | 69.1%  | (60.4;76.3) | 12               | 74.7%  | (66.6;81.1) | 3                |                          |
| Imatinib 800  | 399 | 10.3                          | 55.6%  | (50.5;60.4) | 147              | 83.2%  | (78.8;86.7) | 24               | 86.8%  | (82.7;90.0) | 11               | 89.1%  | (85.0;92.0) | 1                |                          |
| MR4           | Imatinib 400 | 353 | 36.7                          | 8.2%   | (5.6;11.4)   | 301              | 48.9%  | (43.0;53.9) | 133              | 65.7%  | (60.0;70.7) | 64               | 81.0%  | (75.4;85.5) | 8                | 0.033                     |
| Imatinib + IFN| 380 | 33.9                          | 16.4%  | (12.8;20.4) | 285              | 51.2%  | (45.8;56.4) | 130              | 67.4%  | (62.0;72.2) | 65               | 83.1%  | (77.9;87.2) | 11               |                          |
| Imatinib + AraC| 141 | 36.8                          | 5.9%   | (2.8;10.7)   | 123              | 49.4%  | (40.4;57.8) | 55               | 67.5%  | (58.5;75.0) | 27               | 85.5%  | (79.0;90.1) | 5                |                          |
| Imatinib after IFN | 113 | 56.6                          | 0.9%   | (0.0;8.4)    | 105              | 33.7%  | (24.9;42.6) | 55               | 54.0%  | (44.2;62.9) | 27               | 62.7%  | (52.6;71.2) | 11               |                          |
| Imatinib 800  | 376 | 26.2                          | 20.1%  | (16.1;24.3)  | 269              | 59.1%  | (53.7;64.8) | 98               | 88.3%  | (63.3;73.3) | 57               | 81.0%  | (75.8;85.2) | 2                |                          |
| MR5           | Imatinib 400 | 346 | 60.6                          | 4.8%   | (2.8;7.4)    | 308              | 34.6%  | (29.4;39.9) | 175              | 49.4%  | (43.6;54.9) | 109              | 67.2%  | (60.6;73.0) | 21               | 0.053                     |
| Imatinib + IFN| 376 | 54.2                          | 7.7%   | (5.3;10.8)   | 314              | 38.3%  | (33.1;43.4) | 175              | 53.8%  | (48.2;59.0) | 106              | 73.9%  | (68.1;78.8) | 24               |                          |
| Imatinib + AraC| 138 | 61.8                          | 3.8%   | (1.4;8.0)    | 124              | 31.1%  | (23.1;39.3) | 77               | 49.8%  | (40.6;58.4) | 47               | 69.6%  | (60.5;76.9) | 18               |                          |
| Imatinib after IFN | 105 | 74.5                          | 1.0%   | (0.0;4.8)    | 99               | 18.9%  | (11.8;27.3) | 66               | 45.5%  | (35.2;55.2) | 34               | 61.3%  | (50.5;70.5) | 12               |                          |
| Imatinib 800  | 373 | 44.6                          | 9.2%   | (6.5;12.4)   | 306              | 43.1%  | (37.8;48.4) | 150              | 58.4%  | (52.9;63.6) | 86               | 70.4%  | (62.5;77.3) | 2                |                          |

**Abbreviations:** CI, confidence interval; IFN, interferon-α; mo, month; n.r., not reached. Responses (confirmed) were defined as reductions of residual BCR-ABL1 transcripts of ≥ 2, 3, 4, 4.5 and 5 logs compared with the standardized baseline in two consecutive analyses. Testing was restricted to patients expressing b2a2 and/or b3a2 transcripts. In case of a positive quantitative reverse-transcription polymerase chain reaction (qRT-PCR) for BCR-ABL1 transcripts, BCR-ABL1IS ≤ 1% was designated MR2 equivalent to complete cytogenetic remission, BCR-ABL1IS ≤ 0.1% MR3 or MMR, BCR-ABL1IS ≤ 0.01% MR4, BCR-ABL1IS ≤ 0.0032% MR4.5 and BCR-ABL1IS ≤ 0.001% MR5. For a negative qRT-PCR, the number of ABL1 transcripts used for nested PCR had to be ≥ 10.000 for MR, ≥ 32.000 for MR4.5 and ≥ 100.000 for MR5.
equivalent to complete cytogenetic remission lower than 1% BCR-ABL1 (%), 91% (95% CI: 89; 94), of MMR 88% (95% CI: 86; 90), of MR2 83% (95% CI: 80; 85), and of MR4.5 70% (95% CI: 67; 73). The molecular responses according to treatment time are shown in Table 4. Compared with IM400 mg, significantly faster responses were observed with IM800 mg for MR3–MR4, but not for MR5. A faster response was observed with IM800 mg also for MR4.5, but this was not significant (P = 0.053). No patient who stopped IM in deep molecular remission or because of other reasons has died.

Survival by response milestones
One thousand-three hundred and eleven patients had molecular tests at response milestones. Patients who reached ≤10% BCR-ABL1 at 3 months (n = 598 of 873 (68.5%)), ≤1% BCR-ABL1 (equivalent to complete cytogenetic remission) at 6 months (n = 594 of 979 (61%)), or ≤0.1% BCR-ABL1 (MMR) at 12 months (n = 469 of 914 (54.7%)) had significantly better survival than those who did not regardless of therapy. Supplementary Table 2 summarizes survival and response according to milestones at 3, 6 and 12 months. Figure 2c shows the landmark analysis at 6 months across treatment groups with a survival difference of 6.4% after 10 years. When patients reaching and not reaching milestones were analyzed by therapy, the faster response with one therapy (IM800 mg) did not translate into a detectable survival advantage.

Safety
A detailed safety analysis showed frequent, but mostly mild adverse drug reactions. Over the last 3 years, no new safety concerns have evolved. No serious late toxicity was observed. Observation time is still short, late effects in cancer survivors may well appear decades later. Continuous monitoring of patients under TKI-treatment appears mandatory.

DISCUSSION
The data of this large randomized 5-arm treatment optimization study with the long median observation time of 9.5 years showed that high survival probabilities (82% at 10 years) can be achieved with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS. The study further demonstrates that with IM-based therapy. This corresponds well to the 83.3% survival after 10 years in IRIS.

CONFLICT OF INTEREST
R Hehlmann received research support from Novartis and honoraria from BMS, SS research support from Novartis, BMS, Ariad and Pfizer, MF honoraria from Novartis and BMS, SK honoraria from Novartis, GBM honoraria from Novartis, BMS and Pfizer, THB research support from Novartis, MCM grants and honoraria from Novartis, BMS, Ariad and Pfizer, AB honoraria from BMS, JM research support from Novartis and BMS, HL honoraria from Novartis, PF honoraria from Novartis, BMS, Pfizer and Ariad, CS honoraria from Novartis, AH research support from Novartis and honoraria from Novartis, BMS and Pfizer; all other authors reported no conflict of interest.

ACKNOWLEDGEMENTS
Supported by the German Government (BMBF 01GII070); Deutsche Krebshilfe (Nr. 106642); Deutsche José-Carreras Leukämiestiftung (DJKLS H09/f, H06/04v, H03/01, R05/23, AH06/01); European Union (LSHC-CT-2004–503216); Novartis Oncology, Nürnberg (Drs G Gerhard, S Schaffert, A Jacob and U Haus); Roche, Grenchen-Wyhlen; and Essex, Munich, Germany. We thank E Matzat, R Pleil-Lösch, I Stalljann, G Bartsch, C Sodan-Boyer, M Meckesheimer, U Böhm and J Hehlmann for assistance.
REFERENCES

1. O’Brien S, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003; 348: 994–1004.

2. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017; 376: 917–927.

3. Hehlmann R, Lauersek M, Jung-Munkwitz S, Leitner A, Mueller MC, Pfechts N et al. Tolerability-adapted imatinib 800mg/d versus 400mg/d versus 400mg/d plus interferon-alpha in newly diagnosed chronic myeloid leukemia. J Clin Oncol 2011; 29: 1634–1642.

4. Hanfstein B, Müller MC, Hehlmann R, Erben P, Lauersek M, Fabarius A et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). Leukemia 2012; 26: 2096–2102.

5. Saußele S, Krauss MP, Hehlmann R, Lauersek M, Proetel U, Kalmanti L et al. Impact of comorbidity on overall survival in patients with chronic myeloid leukemia: results of the randomized CML Study IV. Blood 2015; 126: 42–49.

6. Fabarius A, Leitner A, Hochhaus A, Muller MC, Hehlmann R, Haferlach C et al. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1511 patients from the randomized CML Study IV. Blood 2011; 118: 6760–6768.

7. Fabarius A, Kalmanti L, Dietz CT, Lauersek M, Rinaldetti S, Haferlach C et al. Impact of unbalanced minor route versus major route karyotypes at diagnosis on prognosis of CML. Ann Hematol 2015; 94: 2015–2024.

8. Hehlmann R, Müller MC, Lauersek M, Hanfstein B, Fabarius A, Schreiber A et al. Major molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. J Clin Oncol 2014; 32: 415–423.

9. Preudhomme C, Guilhot J, Nicolinì FE, Guerci-Bresler A, Rigal-Huguet F, Malosel F et al. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. N Engl J Med 2010; 363: 2511–2521.

10. Simonsson B, Gedde-Dahl T, Markvearn B, Remes K, Stentoft J, Almqvist A et al. Combination of pegylated IFN-alfa 2b with imatinib increases molecular response rates in patients with low- or intermediate-risk chronic myeloid leukemia. Blood 2011; 118: 3228–3235.

11. Baccarani M, Rosti G, Castagnetti F, Haznedaroglu I, Porrka K, Abruzzese E et al. Comparison of imatinib 400 mg and 800 mg daily in the front-line treatment of high-risk, Philadelphia-positive chronic myeloid leukemia: a European LeukemiaNet study. Blood 2009; 113: 4897–4904.

12. Cortes JE, Baccarani M, Guilhot F, Druker BJ, Branford S, Kim DW et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. J Clin Oncol 2010; 28: 424–430.

13. Baccarani M, Druker BJ, Branford S, Kim DW, Pane F, Mongay L et al. Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: final update from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study. Int J Hematol 2014; 99: 616–624.

14. Deininger MW, Kopecky KJ, Radich JP, Kamel-Reid S, Stock W, Paetza E et al. Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: results of the ENESTnd study, an intergroup randomized phase II trial in newly diagnosed chronic phase chronic myeloid leukemia. Br J Haematol 2014; 164: 223–232.

15. Hughes TP, Branford S, White HE, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia 2012; 26: 2172–2175.

16. Branford S, Fletcher L, Cross NCP, Müller MC, Saglio G, Hochhaus A, Kim D-W et al. Desirable performance characteristics for BCR-ABL measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. Blood 2008; 112: 3330–3338.

17. Sorveni S, Hochhaus A, Nicolinì FE, Gruber F, Lange T, Saglio G et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood 2011; 118: 1208–1215.

18. Dupont WD, PS power and sample size program available for free on the internet. Controlled Clin Trial 1997; 18: 274.

19. Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics 1982; 38: 163–170.

20. Shkolnikov V, Baberi M, Wilmorth J. The Human Mortality Database. http://www.mortality.org/.

21. Pfeffermann M, Lauersek M, Hoffmann VS, Hasford J. Prognostic scores for patients with chronic myeloid leukemia under particular consideration of competing causes of death, Ann Hematol 2015; 94: S209–S218.

22. Pfeffermann M, Hochhaus A, Lauersek M, Saußele S, Hehlmann R, Hasford J. Recommendations to meet statistical challenges arising from endpoints beyond overall survival in clinical trials on chronic myeloid leukemia. Leukemia 2011; 25: 1433–1438.

23. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988; 16: 1141–1154.

24. Andersen JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983; 1: 710–719.

25. Pohar M, Stare J. Relative survival analysis in R. Comput Methods Programs Biomed 2006; 81: 272–278.

26. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE et al. Prognostic discrimination in ‘good-risk’ chronic granulocytic leukemia. Blood 1984; 63: 789–799.

27. Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saußele S, Rosti G et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2050 patients with CML on imatinib treatment: the EUTOS score. Blood 2011; 118: 686–692.

28. Lauersek M, Hanfstein B, Haferlach C, Schnittert S, Pfeffermann M, Fabarius A et al. Equivalence of BCR-ABL transcript levels with complete cytogenetic remission in patients with chronic myeloid leukemia in chronic phase. J Cancer Res Clin Oncol 2014; 140: 1955–1969.

29. Kalmanti L, Saußele S, Lauersek M, Muller MC, Dietz CT, Heinrich L et al. Safety and efficacy of imatinib in CML over a period of 10 years: data from the randomized CML-study IV. Leukemia 2015; 29: 1123–1132.

30. Lipton JH, Chuah C, Guerci-Bresler A, Rosti G, Simpson D, Assouline S et al. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. Lancet Oncol 2016; 17: 612–621.

31. Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolinì F et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010; 11: 1029–1035.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2017

Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)