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ORIGINAL ARTICLE

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

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Chronic myeloid leukemia (CML)-study IV was designed to explore whether treatment with imatinib (IM) at 400 mg/day (n = 400) 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) 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.

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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)[1,2] 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,[3,4] of comorbidities,[5] additional chromosomal aberrations[6,7] and deep molecular response.[8] CML-study IV has also shown that IM at 800 mg results in significantly earlier cytogenetic and molecular responses than IM400 mg.[3,8] Various

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observational and randomized studies have tried to improve IM-treatment by combination with IFN, cytarabine or a dose increase to 600 or 800 mg[9–16] 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 in combination with low-dose cytarabine 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 except with hydroxyurea or anagrelide, no consent, pregnancy, participation in another study, second neoplasia and serious illness that made per protocol participation a priori unlikely. Only low- and intermediate-risk patients were randomized to primary IFN and, during a pilot-phase of 3 years, only high-risk patients to IM800 mg/day. After 3 years, recruitment to IM plus cytarabine and IM after IFN-failure was terminated, and the IM800 mg/day arm started to include non-high-risk patients, too. Data lock was on 19 September 2016.

Initial treatment in all study arms except IM-after-IFN-failure was IM400 mg once daily. If no complete hematologic remission was reached after 2 months or no partial cytogenetic remission (PCyR) after 6 months, 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.[8] The IM-dose could be reduced according to tolerability.

Initial primary goal of CML-study IV were 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-survival (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 (× 10^9/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 (× 10^9/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 (0–14)	2 (0–16)	2 (0–20)
Basophils (%), median (range)	1526	3 (0–22)[a]	3 (0–20)	4 (0–21)	3 (0–17)	4 (0–26)	3 (0–26)
Blasts in blood (%), median (range)	1525	1 (0–17)[b]	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)	0 (0–20)	0 (0–19)	2 (0–30)	2 (0–38)
Euro score, n (%)	1527						
Low	—	142 (36)	150 (35)	55 (35)	48 (38)	159 (38)	554 (36)
Intermediate	—	205 (51)	226 (53)	81 (51)	79 (62)	202 (48)	793 (52)
High	—	51 (13)	49 (12)	22 (14)	1 (1)	57 (14)	180 (12)
Sokal score, n (%)	1513						
Low		140 (36)	164 (39)	62 (39)	51 (40)	153 (37)	570 (38)
Intermediate		155 (40)	164 (39)	53 (34)	58 (45)	152 (37)	582 (38)
High		97 (25)	92 (22)	42 (27)	19 (15)	111 (27)	361 (24)
EUTOS score, n (%)	1523						
Low		348 (88)	384 (90)	139 (88)	118 (92)	352 (85)	1341 (88)
High		49 (12)	44 (10)	19 (12)	10 (8)	60 (15)	182 (12)
ELTS score, n (%)	1521						
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 (46)	57 (46)	187 (45)	658 (44)
b2a2 and b3a2		54 (14)	55 (13)	29 (19)	24 (19)	61 (15)	223 (15)
Atypical transcripts		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-α; WBC, white blood cells. There were no significant differences between the treatment groups. [a]One patient with 66% basophils (basophil leukemia). [b]One 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.[6] Testing for residual *BCR-ABL1* transcripts[24,25] was done in two standardized and accredited laboratories with defined conversion factors for equivalence of tests (Mannheim and MLL Munich). Confirmed MR[4], MR[4.5] and MR[5] were defined as a reduction of residual *BCR-ABL1* transcripts of ⩾ 4, ⩾ 4.5 and ⩾ 5 logs compared with the standardized baseline in two consecutive analyses.[24,25] 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[4], ⩾ 32 000 for MR[4.5] and ⩾ 100 000 for MR[5].

Mutation analysis was performed according to the ELN recommendations.[26]

Sample size estimation

At first, differences in probability of MMR at 12 months were investigated.[3] 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.[27,28]

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[29] with regard to sex and individual age at diagnosis.[30] Cumulative incidences were calculated under consideration of competing risks[31] of death defined by accelerated phase, BC and death from any cause. Comparisons between cumulative incidences were performed by the Gray test[32] and prognostic impact of remissions determined by landmark analyses.[33] Besides 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.[34] 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
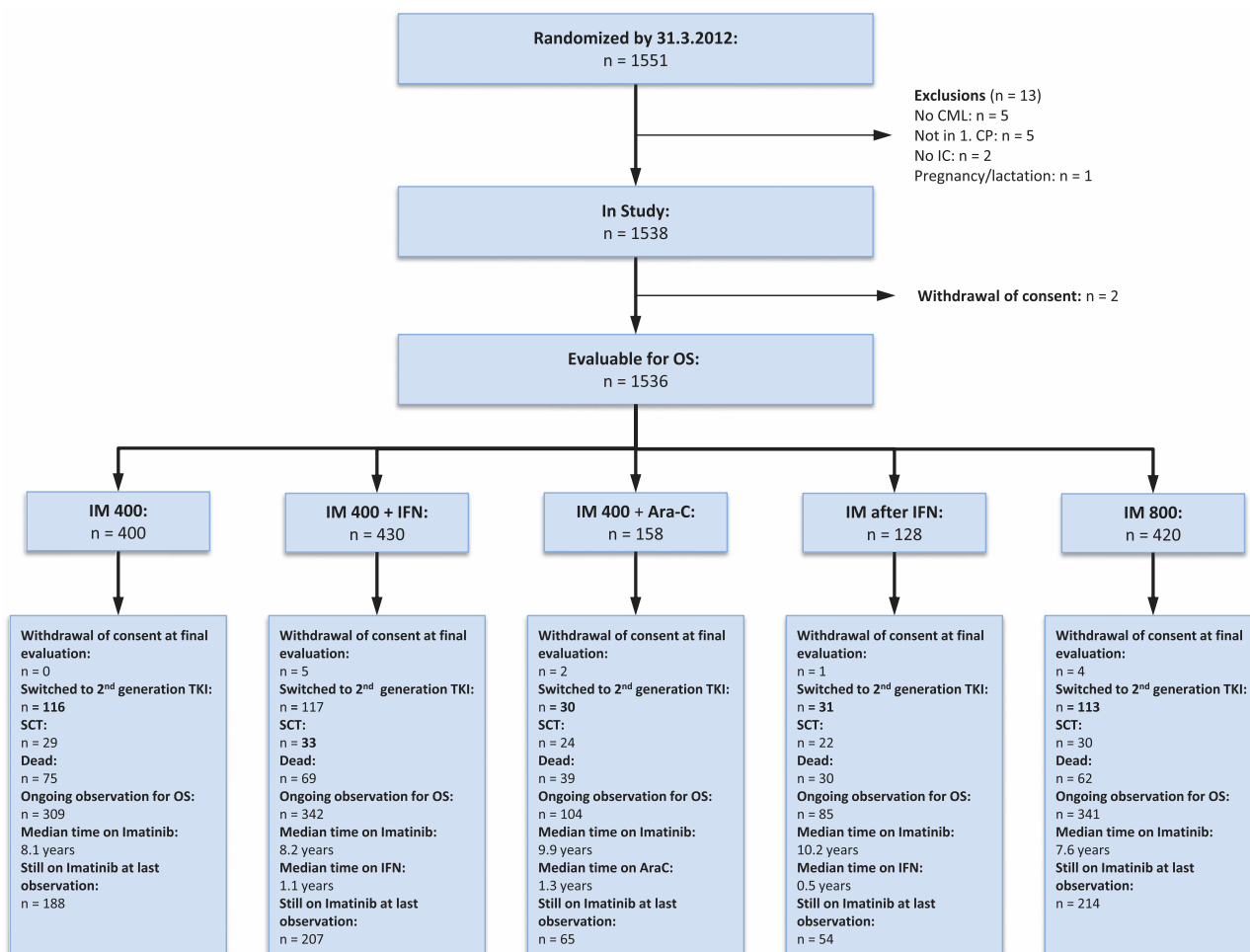

Figure 1. Flow diagram of all 1551 randomized patients. Ara-C, cytarabine; CP, chronic phase; IC, informed consent; IFN, interferon-α; IM, imatinib; OS, overall survival; SCT, stem cell transplantation; TKI, tyrosine kinase inhibitor.
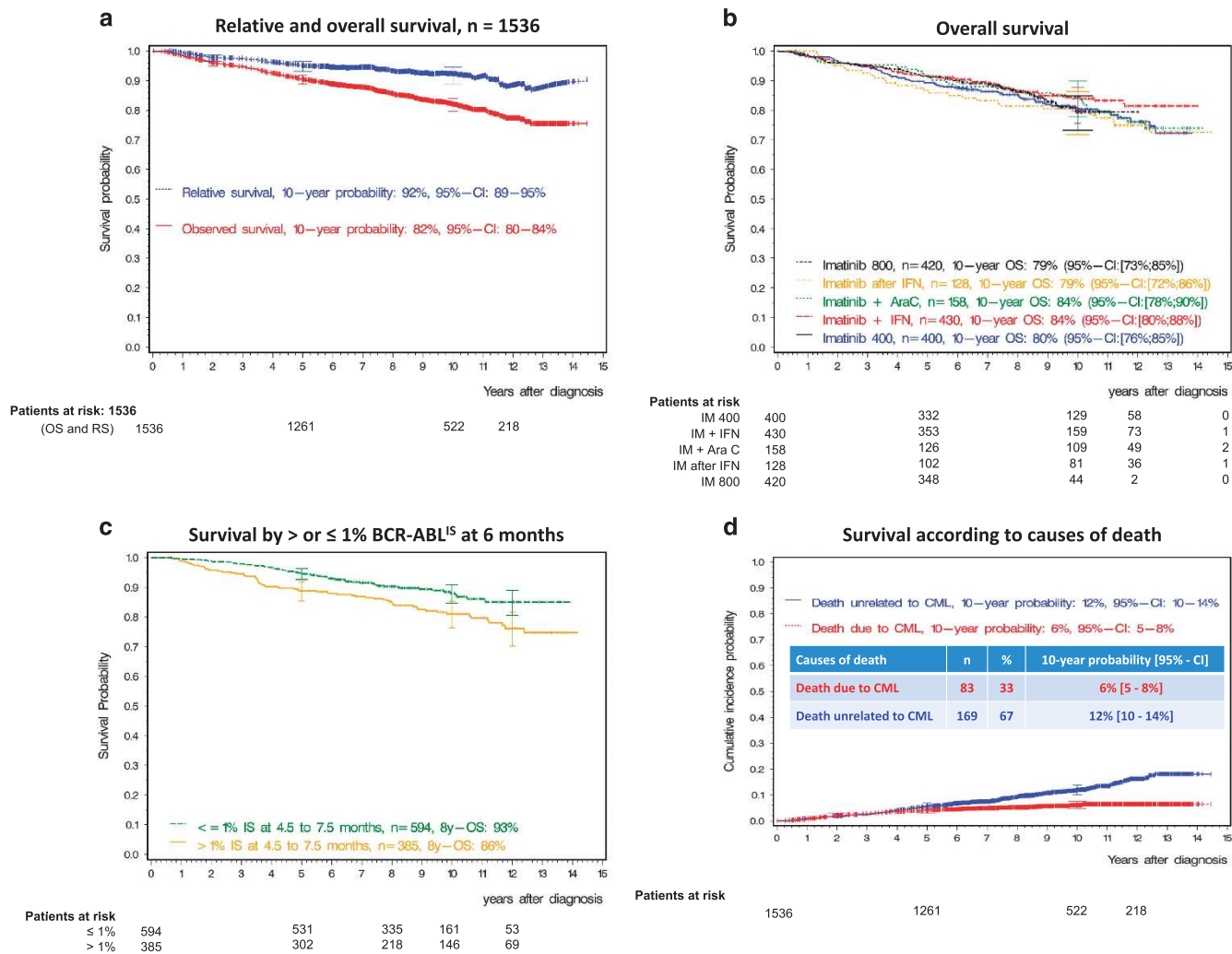
Figure 2. Long-term survival evaluation. (**a**) Overall survival and relative survival of all 1536 CML-patients. (**b**) Overall survival according to treatment groups over time. (**c**) Survival by landmark analysis at 6 months according to achieving and not achieving the milestone ⩽ 1% BCR-ABL1^{IS} at 6 months. The 594 responders have a significantly better survival and show a 10-year relative survival of 96%. The 385 non-responders include slow responders with very good prognosis and high-risk patients requiring attention to patients' and disease risk factors. (**d**) Survival according to causes of death defined as related or unrelated to CML. AraC, cytarabine; IFN, interferon-α; OS, overall survival; RS, relative survival; IM, imatinib.

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.

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, (Figure 2b). 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: 89; 95) (Figure 2a; 91% for IM400 mg, 94% for IM plus IFN, 94% for IM plus cytarabine, 93% 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
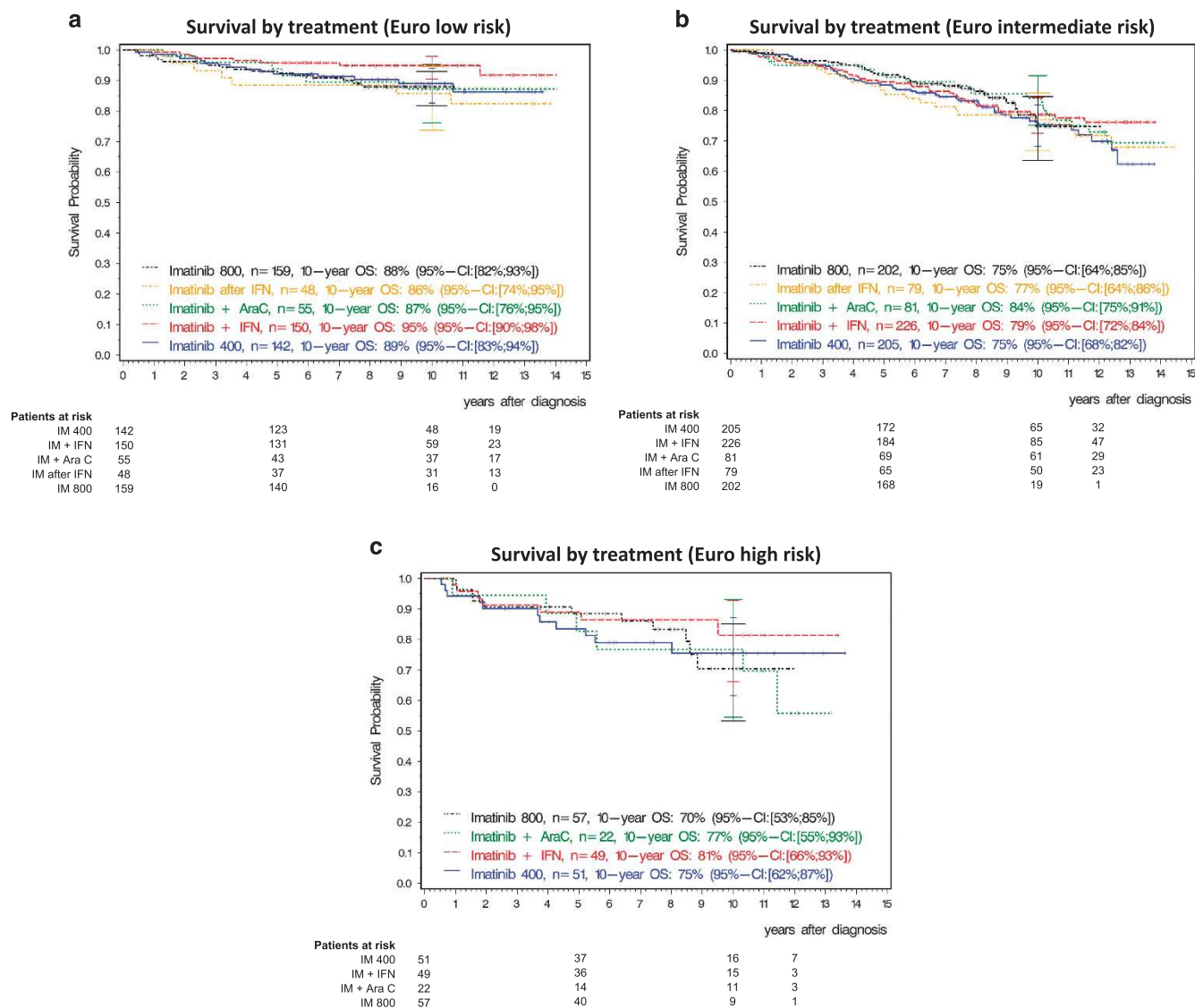
Figure 3. Overall survival by disease risk (Euro-score). (**a**) Low, (**b**) intermediate, (**c**) high. AraC, cytarabine; IFN, interferon-α; OS, overall survival; IM, imatinib.

Table 2. Causes of death

	IM 400 mg	IM+IFN	IM+cytaribine	IM after IFN-failure	IM 800 mg	Total
Total deaths (*n*)	75	69	39	30	62	275
Causes (n)						
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	0	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.

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)[a]	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. [a]Age considered by ELTS-score.

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.[23,35,36] 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.[23]

Multivariate analysis for impact on survival of variables at diagnosis: risk score, comorbidities, major-route additional chromosomal aberrations, smoking and treatment center (academic vs others) influenced survival significantly, but not gender, transcript-type or initial treatment selection (Table 3).

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
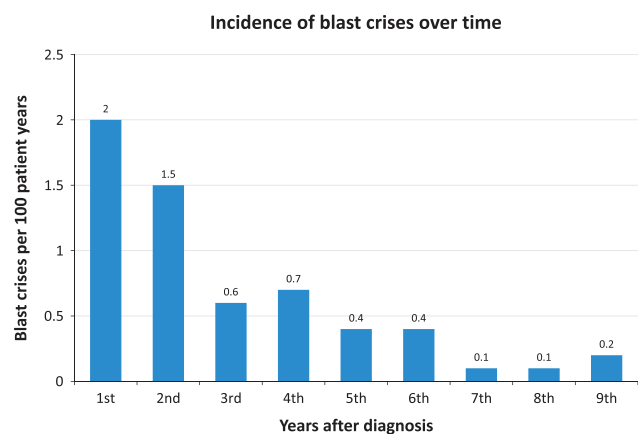

Incidence of blast crises over time

Figure 4. Incidence of blast crisis over time.

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;72.1)	108	90.1%	(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%	(63.0;72.2)	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;61.2)	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%	(38.9;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%	(22.5;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	48.5%	(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%	(0.08;4.5)	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;64.1)	98	68.6%	(63.3;73.3)	57	81.0%	(75.8;85.2)	2	
MR⁴·⁵															
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%	(0.09;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	70.6%	(62.5;77.3)	2	
MR⁵															
Imatinib 400	318	8.8	2.3%	(1.0 ;4.4)	290	16.5%	(12.5;21.1)	216	32.9%	(27.3;38.5)	146	53.5%	(46.5;60.0)	37	0.933
Imatinib + IFN	356	10.3	3.2%	(1.7 ;5.5)	316	18.6%	(14.6;23.1)	230	28.7%	(23.7;33.8)	173	48.9%	(42.3;55.1)	54	
Imatinib + AraC	124	9.0	0.0%	—	117	10.7%	(5.9;17.3)	95	21.3%	(14.1;29.4)	73	53.6%	(43.6;62.7)	34	
Imatinib after IFN	94	n.r.	0.0%	—	89	6.9%	(2.8;13.5)	70	20.8%	(12.9;30.0)	49	41.5%	(30.6;52.0)	22	
Imatinib 800	339	8.4	2.4%	(1.2;4.6)]	300	16.2%	(12.3;20.6)	216	31.5%	(26.2;36.9)	153	49.8%	(43.2;56.1)	8	

Abbreviations: CI, confidence interval;IFN, interferon-α;mo, months;n.r, not reached. Responses (confirmed) were defined as reductions of residual $BCR\text{-}ABL1$ 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 $BCR\text{-}ABL1$ transcripts, $BCR\text{-}ABL1^{IS} \leq 1\%$ was designated MR^2 equivalent to complete cytogenetic remission, $BCR\text{-}ABL1^{IS} \leq 0.1\%$ MR^3 or MMR, $BCR\text{-}ABL1^{IS} \leq 0.01\%$ MR^4, $BCR\text{-}ABL1^{IS} \leq 0.0032\%$ MR$^{4.5}$ and $BCR\text{-}ABL1^{IS} \leq 0.001\%$ MR^5. For a negative qRT-PCR, the number of $ABL1$ transcripts used for nested PCR had to be ≥ 10.000 for MR^4, ≥ 32.000 for MR$^{4.5}$ and ≥ 100.000 for MR^5.

equivalent to complete cytogenetic remission[37] ($\leqslant$1% *BCR-ABL1[IS]*) 91% (95% CI: 89; 94), of MMR 88% (95% CI: 86; 90), of MR[4] 83% (95% CI: 80; 85), and of MR[4.5] 70% (95% CI: 67; 73). The molecular responses according to treatment over time are shown in Table 4. Compared with IM400 mg, significantly faster responses were observed with IM800 mg for MR[2]-MR[4], but not for MR[5]. A faster response was observed with IM800 mg also for MR[4.5], but this was not significant ($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 $\leqslant$10% *BCR-ABL1[IS]* at 3 months ($n = 598$ of 873 (68.5%)), $\leqslant$1% *BCR-ABL1[IS]* (equivalent to complete cytogenetic remission) at 6 months ($n = 594$ of 979 (61%)), or $\leqslant$0.1% *BCR-ABL1[IS]* (MMR) at 12 months ($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[38] 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.[2] The study further demonstrates that with regard to survival none of the experimental treatments is superior to IM400 mg. Interestingly, the faster and earlier cytogenetic and molecular responses of the experimental arm IM800 mg[3,8] did not translate into longer survival. The lack of survival differences between treatment arms may be explained by relatively few events attributable to CML, considering an overall 10-year relative survival of 92%, matching well with the 10-year CML mortality of just 6% and pointing to the relevance of non-CML causes of mortality. Similar observations have been reported with 2G-TKI after median observation times of 5 years.[17,18]

CML-study IV was powered to detect an OS difference between the IM400 mg and IM800 mg arms of at least 5% 5 years after diagnosis, but due to survival probabilities of 89% and 92%, respectively, at 5 years, the difference was only 3%, and only 1% at 10 years. Any therapy aiming at improving survival above what is currently achieved with standard IM would have to further decrease the incidence and/or mortality of BC. The benefit of such therapy would have to be weighed against its toxicity.[18,39]

Patients that reached response milestones of $\leqslant$10% BCR-ABL1[IS] by 3 months, $\leqslant$1% by 6 months or $\leqslant$0.1% by 12 months had higher survival probabilities than those who did not—regardless of treatment. That this survival advantage was not detectable by analysis according to treatment group is probably due to the small survival difference (*ca*. 6% after 10 years) and the lower number of patients reaching milestones. Also the composition of the group not reaching the milestones has to be taken into account consisting of slow responders with very good survival as well as

higher proportions of high-risk patients and progressions to BC. Given the excellent overall prognosis of CML, considerably larger patient numbers than in this already large study are required to detect the expected small survival difference.

Survival as shown by multivariate analysis was influenced more by disease biology, patients' demographics and microeconomic elements than by initial treatment selection indicating that more attention has to be paid to non-CML factors in order to improve outcome of CML-patients. It is remarkable that a single tablet per day of a well tolerable drug reverses the course of a formerly uniformly fatal malignant disease and moves CML close to a potential cure. This is in line with reports of relapse-free survival following discontinuation of IM after deep and durable responses.[40] The 10-year deep molecular remission rates of 70–80% in this study indicate that the majority of IM-treated patients are candidates for treatment discontinuation.

Our experience with the two IFN-arms might provide useful information. Neither IFN-arm achieved a survival advantage over IM400 mg, but OS in the IM-after-IFN-failure arm, which resembles the IFN-arm of IRIS, was not inferior to that of the IM400 mg arm (with the limitation that no Euro-high-risk patients were randomized to IM-after-IFN). It is also noteworthy that the simultaneous application of IM and IFN may have an advantage, since, by intention to treat analysis, it showed a significantly better PFS than the consecutive application of IM after IFN-failure. As favorable response results on IM in combination with IFN were reported by others,[9,10] it appears worthwhile to further follow this line of treatment.

Four-hundred seven patients (26.5%) were switched to one or more other TKI. As switching was evenly distributed between treatment arms an influence on survival comparisons is unlikely. We cannot determine to what extent survival was improved by switching to 2G-TKI in this study, as this was not planned prospectively. Censoring at the time of switching, however, improved survival by about 3% across treatment arms indicating that predominantly poorer risk patients had been switched. Also progression was distributed evenly. Eighty-seven patients (5.8%) developed BC of whom 67 died in spite of multiple lines of therapy including intensive chemotherapy and transplantation.

In conclusion, the results show that monotherapy with IM400 mg achieved a survival not much different from that of the general population, and that survival with CML is currently more determined by patients' and disease factors than by initial treatment selection. More attention has to be paid to these factors in a personalized approach. Comorbidities should be addressed and smoking discouraged. Although improvements are also needed for the subgroups of refractory disease, more life-time can currently be gained by carefully addressing non-CML determinants of survival.

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