Ponatinib vs. Imatinib as Frontline Treatment for Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia: A Matching Adjusted Indirect Comparison

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SUPPLEMENTAL MATERIALS

Supplemental Methods

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SUPPLEMENTAL METHODS

MAIC Matching Scenarios

Several MAIC models were investigated for each comparison. The base case models for the comparison of MDACC vs. GRAAPH-2005 and MDACC vs. NCT00038610 were based on scenario 2, whereas the base case model for the comparison of GIMEMA LAL1811 vs. CSI57ADE10 was based on scenario 3 **(Table S3**, **Table S4**, and **Table S5).** Sensitivity analyses were based on scenario 1 for MDACC vs. GRAAPH-2005 and MDACC vs. NCT00038610 and scenario 2 for GIMEMA LAL1811 vs. CSI57ADE10.

SUPPLEMENTAL RESULTS

Baseline Characteristics of the MAIC Populations

High Dose Eligible Population

MDACC vs. GRAAPH-2005

Population adjustment was conducted on clinically validated prognostic factors or effect modifiers (except sex) (**Table S8**). As the GRAAPH-2005 study enrolled patients aged <60 years, patients aged ≥60 years were excluded from the matching MDACC population to improve the overlap between the study populations. The GRAAPH-2005 study did not have an exclusion criterion for the ECOG PS, and at least one patient with ECOG >2 was enrolled in this study, whereas the MDACC study could only enroll patients with ECOG ≤2. However, this difference was not expected to lead to a substantial bias in the results of the comparative efficacy analyses. Two patients were missing BCR::ABL transcript information in the MDACC study. They were given 0 weights as they did not have active disease at baseline, but this was not expected to bias the analysis results.

MDACC vs. NCT00038610

Population adjustment was conducted on clinically validated prognostic factors or effect modifiers (except patient sex, platelet counts, lactate dehydrogenase levels, and hemoglobin levels) (**Table S9**). Both the MDACC and NCT00038610 studies could include patients who had been previously treated with chemotherapy.

The NCT00038610 study did not include patients who had received TKIs as part of their initial induction chemotherapy course, whereas the MDACC study allowed enrollment of patients who had previously received TKIs. The MDACC patients who had received TKIs were excluded

from the analysis to enable differentiation between the efficacies of ponatinib and imatinib analysis resulting in an imbalance between the weighted MDACC population and the NCT00038610 study population.

Nearly 0.9% of the weighted MDACC population had complete remission at baseline, as opposed to 16.7% of the NCT00038610 study population. However, as patients in complete remission at baseline have a better prognosis compared to those with active disease, this factor was included in the population adjustment to avoid biasing the results in favor of imatinib.

High Dose Non-Eligible Population

GIMEMA LAL1811 vs. CSI57ADE10

Population adjustment was based on the four factors highlighted as crucial by clinicians (i.e., age, ECOG, WBC count, and BCR::ABL transcript type) (**Table S10**). However, data on the ECOG was not available in the CSI57ADE10 study. The GIMEMA LAL1811 study enrolled patients aged >18 years while the CSI57ADE10 study enrolled patients aged >55 years. As there was at least one patient aged 54 years included in the CSI57ADE10 study, all patients who were aged ≤54 years in the GIMEMA LAL1811 study were excluded from the comparative efficacy analyses.

The BCR::ABL transcript was based mainly on bone marrow measurements in the GIMEMA LAL1811 study, with peripheral blood values used when bone marrow measurements were not available. Patients with missing data on BCR::ABL transcript type were excluded from the GIMEMA study, therefore, no adjustment was possible for this criterion. As there was some discrepancy in the data reported for the BCR::ABL transcript type in CSI57ADE10 study, the adjustment was made by matching the number of patients with p190 and p190/210 transcripts.

Adjustment on the proportion of patients with WBC ≥25 x 10^9/L was prioritized over those with missing WBC data.

Table S1. Summary of outcome definitions

Outcome	MDACC		GRAAPH-2005		NCT00038610		GIMEMA LAL1811		CSI57ADE10	
	Definition	**Available**	**Definition**	**Available**	**Definition**	**Available**	**Definition**	**Available**	**Definition**	**Available**
OS	OS is defined as the time from the first day of treatment to time of death from any cause.	Yes	NR	Yes	OS was calculated from the date of initiation of therapy until death.	Yes	OS was defined as the interval between the date of enrolment (date of steroid first dose) and the date of death due to any cause. The date of death was determined using the survival status eCRF. Participants who were lost-to-follow-up or still alive at the time of analysis were right-censored at the earlier date the participant was last known alive and the clinical data cut-off date for the analysis. The last known alive date was defined as the later of the last study visit and the date the participant was last known alive from the survival status eCRFs.	Yes	OS was calculated from the time of diagnosis.	Yes
EFS	EFS is the time from the first day of treatment until any failure (resistant disease, relapse, or death).	Yes	NR	Yes	NA	No	EFS was defined as the length of time from the date of enrolment (date of steroid first dose) to the date of the event. Event was defined as follows:	Yes	NA	No

							Failure of achieving of CHR at Week 6 Treatment discontinuation CHR lost Death by any cause			
DFS	DFS is the time from documented CR until relapse or death.	Yes	NA	No	DFS was calculated from the time of CR until relapse or death due to any cause. Relapse was defined by recurrence of more than 5% lymphoblasts in the bone marrow aspirate or by the presence of extramedullary disease after achieving CR	Yes	Not available	No	Remission duration and DFS were calculated from time of first documented complete remission to hematologic recurrence. Recurrence was defined by recurrence of bone marrow blasts to above 5% or of extramedullary involvement after a previously documented CR.	Yes
ORR	ORR is defined as the percentage of patients achieving complete remission and partial remission.	Yes	NA	No	NR	Yes	NA	No	NA	No
Complete remission	Complete remission: Normalization of the peripheral blood and bone marrow with: 5% or less blasts in normocellular	Yes	Hematologic CR was defined as <5% marrow blasts with adequate blood count recovery.		Complete response was defined as: 5% or less blasts in the bone marrow,	Yes	Complete hematologic response required all the following: Bone marrow with < 5% blast cells	Yes	CR was defined as: Less than 5% blasts in bone marrow Absolute neutrophils count	Yes

	or hypercellular marrow. Granulocyte count of 1 x 10^9/L or above. Platelet count of 100 x 10^9/L. Complete resolution of all sites of extramedullary disease required.				Granulocyte count of 1.0 × 10^9/L or over Platelet count of 100 × 10^9/L or over No extramedullary disease.		Peripheral blood differential with no blasts Polymorphonuclear leukocytes ≥ 1.5 × 10^9/L Platelet count ≥ 100 × 10^9/L No evidence of extramedullary involvement from leukemia		greater than 1 × 10^9/L Platelet counts greater than 100 × 10^9/L An incomplete CR required the same leukemic response as in a CR without complete recovery of peripheral blood counts.	
Molecular response	MCR: Same as for complete remission with RT-PCR negativity for BCR::ABL1 or with RT-PCR for BCR::ABL with 4 log reduction from baseline and/or ≤0.01%. MMolR was defined as BCR::ABL1 transcripts less than 0.1% by the international scale for patients with p210 transcripts and a 3-log reduction from baseline for patients with p190 transcripts, but not meeting criteria for CMR	Yes	MCR was defined as BCR::ABL1/ ABL ratio of ≤0.1% in the bone marrow, and MCR was defined by the absence of detectable MRD with a sensitivity of at least 0.01%.	No	MCR was defined by the attainment of RT-PCR negativity in patients with hematologic CR. MMolR was defined by RT-PCR for BCR::ABL transcript of less than 0.1%. CR duration was calculated from the time of CR until relapse.	Yes	Complete MCR if by RT-PCR the BCR::ABL: ABL ratio was <0.01, with a sensitivity of at least 30,000 molecules of ABL. MMolR if by RT-PCR the BCR::ABL: ABL ratio <0.10, with a sensitivity of at least 30,000 molecules of ABL.	Yes	A MCR required PCR negativity by RT-PCR of sufficient sensitivity, defined by at least 10^5 GAPDH plasmid equivalents in a sample, with confirmation by nested PCR.	Yes

Abbreviations: *BCR::ABL* a gene sequence found in an abnormal chromosome 22 of some people with certain forms of leukemia, *CHR* complete hematologic response, *CR* complete response, *DFS* disease-free survival, *eCRF* electronic case report form, *EFS* event-

free survival, *GAPDH* glyceraldehyde-3-phosphate dehydrogenase, *MCR* molecular complete remission, *MMolR* major molecular response, *MRD* minimal residue disease, *NA* not available, *NR* not reported, *ORR* overall response rate, *OS* overall survival, *PR* partial response, *RT-PCR* quantitative real-time polymerase chain reaction

Table S2. List of prognostic factors and effect modifiers in Ph+ ALL identified by clinical experts

	Availability in GRAAPH-2005	Availability in NCT00038610	Availability in CSI57ADE10
Age [a]	✓	✓	✓
ECOG PS [a]	✓	✓	×
Geographical region	×	×	×
CNS disease at baseline	✓	✓	✓
Testicular involvement	×	×	×
Race	×	×	×
Histology (CML in accelerated or blast phase)	×	×	×
Type of BCR::ABL transcript (m, M, p190, p210) [a]	✓	✓	✓
Response status at study entry	✓	✓	NA
WBC/blast counts at baseline [a]	✓	✓	✓
Cytogenetic risk groups (isolated Ph+, Ph+, diploid)	×	×	×
Deletion of 9p	×	×	×
Presence of +der (22)	×	×	×
Ikaros deletions and recurring lesions	×	×	×
BCR::ABL1 TKD	×	×	×
Additional chromosome aberrations	×	×	×
Pax5, pax5 plus	×	×	×

Abbreviations: *CNS* central nervous system, *CML* chronic myeloid leukemia, *ECOG* Eastern Cooperative Oncology Group, *NA* not applicable, *Ph+* Philadelphia chromosome-positive, *PS* performance status, *TKD* tyrosine kinase domain, *WBC* white blood cells

[a] Prognostic factors and effect modifiers identified by clinical experts and used in this study for population adjustment

Table S3. MAIC matching scenarios for MDACC vs. GRAAPH-2005

Scenario 1 All available baseline characteristics		Scenario 2 All available PFs and EMs		Scenario 3 Factors prioritized by clinical experts
Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
This model adjusted for all available baseline characteristics (patient age, patient sex, ECOG PS, CNS involvement, WBC count, BCR::ABL1 transcript type, prior TKI treatment, and response status at baseline).	This model adjusted for the same factors as model 1. However, the model performed a less granular population adjustment compared to model 1, and only retained an adjustment on grouped range of value (i.e., proportion of patients above a certain threshold value) instead of matching on both medians and grouped range of values.	This model adjusted for all factors that were highlighted as PFs or treatment-effect modifiers in Ph+ ALL. Patient sex was not included in the adjustment.	This model was based on model 3 but did not adjust for the baseline WBC count. The model was intended as a sensitivity analysis due to the large difference in the baseline WBC counts in the two studies.	This model only adjusted for the four factors prioritized by clinical experts (i.e., patient age, ECOG PS, WBC count, and BCR::ABL transcript type).
Convergence was reached but the ESS was small (15.54).	Convergence was reached and the ESS was small but satisfactory (19.75).	Convergence was reached and the ESS was satisfactory (24.36).	Convergence was reached and the ESS was high (46.58).	Convergence was reached and the ESS was only slightly higher than model 3 (25.5).
Despite being reported in GRAAPH-2005, no adjustment could be	This model was used in sensitivity analyses.	This model was used as the base case model.	This model was used in sensitivity analyses.	This model was not investigated further.

	carried out on BMI and ACAs as these were not available in the MDACC study.

Abbreviations: *ALL* acute lymphoblastic leukemia, *BMI* body mass index, *CNS* central nervous system, *ECOG* Eastern Cooperative Oncology Group, *EM* effect modifier, *ESS* effective sample size, *PF* prognostic factor, *Ph* Philadelphia chromosome, *PS* performance status, *TKI* tyrosine kinase inhibitor, *WBC* white blood cells

Table S4. MAIC matching scenarios for MDACC vs. NCT00038610

Scenario 1 All available baseline characteristics			Scenario 2 All available PFs and EMs		Scenario 3 Factors prioritized by clinical experts
Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
This model adjusted for all available baseline characteristics (patient age, patient sex, ECOG, WBC and platelet counts, hemoglobin level, LDH level, CNS involvement, BCR::ABL1 transcript type, and response status at baseline)	This model adjusted for the same factors as model 1 (excluding the proportion of patients with CR at the baseline; population adjustment on this factor was responsible for the drop in the ESS). This was a conservative approach as patients with active disease at baseline were expected to have better prognosis.	This model was based on model 2 but with less granularity (i.e., adjustments were applied only for percentages and not for both medians and percentages).	This model adjusted for all factors that were highlighted as being PFs or EMs in Ph+ ALL. Patient sex, platelet counts, hemoglobin levels and LDH levels were not included in the adjustment.	This model was based on model 4 and re-introduced an adjustment for patients with active disease at enrolment.	This model adjusted only on the four factors prioritized by clinical experts (i.e., patient age, ECOG PS, WBC count, and BCR::ABL transcript type).
Convergence was reached but the ESS was too small	Convergence was reached and the ESS was	Convergence was reached and the ESS was	Convergence was reached and the ESS was	Convergence was reached and the ESS was small but	Convergence was reached and the ESS was

for further analyses (11.65).	satisfactory (21.47).	satisfactory (31.56).	satisfactory (40.02).	satisfactory (19.54).	satisfactory (39.93).
No adjustment could be carried out on albumin levels and cytogenetics as these data were not available in the MDACC study.	This model was not considered further as model 3 achieved a higher ESS while adjusting for the same factors	This model was used in sensitivity analyses	This model was used as the base case model.	As one patient was given a high statistical weight that would have a large influence on the results, this model was not investigated further.	As the ESS was almost the same as in model 4, this model was not considered further.

Abbreviations: *ALL* acute lymphoblastic leukemia, *CNS* central nervous system, *CR* complete remission, *ECOG* Eastern Cooperative Oncology Group, *EM* effect modifier, *ESS* effective sample size, *LDH* lactate dehydrogenase, *PF* prognostic factor, *Ph* Philadelphia chromosome, *PS* performance status, *WBC* white blood cells

Table S5. MAIC matching scenarios for GIMEMA LAL1811 vs. CSI57ADE10

Scenario 1 All available baseline characteristics		Scenario 2 All available PFs and EMs		Scenario 3 Factors prioritized by clinical experts	
Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
This model adjusted for all available baseline characteristics (patient age, patient sex, CNS involvement, WBC and platelet counts, and BCR::ABL1 transcript type).	This model adjusted for the same factors as model 1 but did not adjust for the baseline WBC count (population adjustment on this factor was responsible for the drop in the ESS in model 1).	This model adjusted for all available factors that were highlighted as being PFs or EMs in Ph+ ALL.	This model was based on model 3 but did not adjust for the WBC count.	This model adjusted only on the four factors prioritized by clinical experts (i.e., patient age, ECOG PS, WBC, and BCR::ABL transcript type). The ECOG PS was not available in the CSI57ADE10 study.	This model adjusted for the same factors as model 5 but did not adjust for the WBC count at baseline (population adjustment on this factor was responsible for the drop in the ESS).
Convergence was reached but the ESS was too small for further analysis (5.93).	Convergence was reached and the ESS was satisfactory (16.05). This model was used in sensitivity analyses.	Convergence was reached but the ESS was too small for further analysis (7.67).	Convergence was reached and the ESS was satisfactory (22.12). This model was used in sensitivity analyses.	Convergence was reached and the ESS was satisfactory (16.65). This model was used as the base case model.	Convergence was reached and the ESS was satisfactory (31.09). This model was not investigated further as too few factors were included in the population adjustment.

Abbreviations: *ALL* acute lymphoblastic leukemia, *CNS* central nervous system, *ECOG* Eastern Cooperative Oncology Group, *EM* effect modifier, *ESS* effective sample size, *PF* prognostic factor, *Ph* Philadelphia chromosome, *PS* performance status, *WBC* white blood cells

Table S6. Summary of inclusion of imatinib studies conducted in HDT-SCT eligible patients in the MAIC

Study	Intervention	Included in the MAIC	Remarks
GRAAPH-2005 [1]	Induction with imatinib + reduced-intensity chemotherapy vs. induction with hyper-CVAD Induction followed by an imatinib + methotrexate + cytarabine cycle to bridge to stem cell transplantation. Up to 8 cycles of treatment alternating imatinib + hyper-CVAD with imatinib + methotrexate + cytarabine for patients not receiving transplant	Yes	MDACC patients 60 or below with active disease at baseline, not previously treated with TKI
NCT00038610 [2, 3] / AUS01 in the EMA EPAR / scientific discussion dossier of imatinib [4]	8 induction-consolidation courses of imatinib + hyper-CVAD alternated with imatinib + methotrexate + cytarabine	Yes	MDACC patients not previously treated with TKI
Wassmann, 2006 [5] / ADE04 in the EMA EPAR / scientific discussion dossier of imatinib [4]	Induction chemotherapy followed by continuous imatinib and a consolidation cycle before transplantation vs. induction chemotherapy with imatinib followed by continuous imatinib and a consolidation cycle before stem cell transplantation	No	Not a treatment of interest (induction without imatinib)
GIMEMA 0904 [6]	Induction imatinib + steroids, followed by one cycle of imatinib + chemotherapy consolidation before stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
Lim, 2015 [7]	Imatinib-based induction followed by up to 5 cycles of consolidation alternating imatinib + chemotherapy and treatment without imatinib	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)

Yanada, 2008 [8]	Imatinib-based induction followed by up to 8 cycles of consolidation alternating imatinib monotherapy and treatment without imatinib	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
GRAAPH-2003 [9, 10]	Induction chemotherapy without imatinib. Imatinib is introduced in the second phase of the induction for poor early responders. For good early responders, imatinib is given from consolidation, until stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
Lee, 2009 [11, 12]	Induction chemotherapy without imatinib followed by a second induction with imatinib monotherapy. A consolidation with chemotherapy then imatinib was planned to bridge to stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
JALSG Ph+ ALL208 [13]	Induction with imatinib + chemotherapy, followed by 8 cycles of consolidation with imatinib before stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
CSTI BES02 [14, 15]	Induction with imatinib + chemotherapy followed by 2 imatinib-based consolidation cycles followed by stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
UKALLXII / ECOG2993 [16]	Imatinib received after induction or co-administered with second phase of induction, before transplantation. Imatinib-based consolidation and maintenance for patients who cannot receive a stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
NILG protocol 09/00 [17]	Up to 8 cycles of imatinib + chemotherapy, before stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)

Lee, 2005 [18]	Imatinib-based induction followed by up to 8 cycles of consolidation-based imatinib chemotherapy, before stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
JALSG Ph+ ALL202 [19-21] / AJP01 in the EMA EPAR / scientific discussion dossier of imatinib [4]	Imatinib-based induction followed by up to 8 cycles of consolidation alternating imatinib + chemotherapy and treatment without imatinib, before stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)
PETHEMA-ALL-Ph-08 [14, 22, 23]	Induction with imatinib + chemotherapy followed by 2 imatinib-based consolidation cycles followed by stem cell transplantation	No	Not a treatment of interest (not from a GMALL protocol of hyper-CVAD)

Abbreviations: *ALL* acute lymphocytic leukemia, *CVAD* cyclophosphamide, vincristine, doxorubicin and dexamethasone, *EMA* European Medicines Agency, *EPAR* European public assessment report, *GMALL* German multicenter study group for adult acute lymphoblastic leukemia, *HDT-SCT*, high dose therapy and stem cell transplant, *MAIC* matching-adjusted indirect comparison, *Ph* Philadelphia chromosome, *TKI* tyrosine kinase inhibitor

Table S7. Summary of inclusion of imatinib studies conducted in HDT-SCT non-eligible patients in the MAIC

Study Name	Intervention	Included in the MAIC	Remarks
CSTI571ADE 10 [24] / ADE10 in the EMA EPAR / scientific discussion dossier of imatinib [4]	Imatinib induction followed by imatinib + age-adapted/ intrathecal chemotherapy consolidation	Yes	The chemotherapy-induction arm was not used in our analyses
GRAALL AFR09 [25] / AFR09 in EMA scientific discussion	Induction of chemotherapy without imatinib followed by consolidation with imatinib + steroids	No	Not a treatment of interest (imatinib not given continuously)
GIMEMA LAL0201-B study [26] / AIT04 in EMA scientific discussion	Imatinib + steroids followed by imatinib consolidation	No	Only age of patients at baseline was reported, which is insufficient to conduct a population-adjustment.

Abbreviations: *EMA* European Medicines Agency, *EPAR* European public assessment report, *HDT-SCT*, high dose therapy and stem cell transplant, *MAIC* matching adjusted indirect comparison

Table S8. Baseline characteristics of the MDACC study population, the weighted MDACC population, and the GRAAPH-2005 study population

	MDACC	MDACC weighted	GRAAPH-2005
Sample size	87	24.363	133
Age: ≥30 years	0.874	0.857	0.857
Age: ≥60 years	0.230	0.000	0.000
ECOG PS: 0–1	0.874	0.842	0.842
ECOG PS: unknown	0.000	0.000	0.023
CNS disease at baseline	0.069	0.023	0.023
WBC: $\geq 30 \times 10^9$/L	0.103	0.414	0.414
WBC: missing	0.023	0.000	0.000
BCR::ABL1 transcript: m or p190	0.724	0.722	0.722
BCR::ABL1 transcript: missing	0.023	0.000	0.010
Complete remission at start	0.207	0.000	0.000
Prior TKI	0.207	0.000	0.000

Abbreviations: *CNS* central nervous system, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *TKI* tyrosine kinase inhibitor, *WBC* white blood cells

All values (except sample size) indicate proportions

Table S9. Baseline characteristics of the MDACC study population, the weighted MDACC population, and the NCT00038610 study population

	MDACC	MDACC weighted	NCT00038610
Sample size	87	40.021	54
Median age (years)	46	51	51
ECOG PS: 0	0.253	0.130	0.130
CNS disease at baseline	0.069	0.130	0.130
WBC: $\geq 30 \times 10^9$/L	0.103	0.370	0.370
WBC: missing	0.023	0.000	0.000
BCR::ABL1 transcript: m or p190	0.724	0.667	0.667
BCR::ABL1 transcript: missing	0.023	0.000	0.000
Complete remission at start	0.207	0.009	0.167
Prior TKI	0.207	0.000	0.000

Abbreviations: *CNS* central nervous system, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *TKI* tyrosine kinase inhibitor, *WBC* white blood cells

All values (except sample size) indicate proportions

Table S10. Baseline characteristics of the GIMEMA LAL1811 study population, the weighted GIMEMA LAL1811 population, and the CSI57ADE10 study population

	GIMEMA	GIMEMA Weighted	CSI57ADE10
Sample size	44	16.65	28
Median age (years)	66.5	66	66
Age: <54 years	0.136	0.000	0.000
BCR::ABL1 transcript: p210	0.273	0.357	0.357
BCR::ABL1 transcript: p190/210	0.045	0.000	0.000
BCR::ABL1 transcript: missing	0.000	0.000	0.071
WBC: $\geq 25 \times 10^9$/L	0.159	0.50	0.50
WBC: missing	0.095	0.000	0.071

Abbreviations: *CNS* central nervous system, *TKI* tyrosine kinase inhibitor, *WBC* white blood cells

All values (except sample size) indicate proportions

Table S11. Relative efficacy estimates for ponatinib vs. imatinib

Outcome	MDACC vs. GRAAPH-2005		MDACC vs. NCT00038610		GIMEMA LAL1811 vs. CSI57ADE10	
	HR/OR [a] (95% CI)	p-value	HR/OR [a] (95% CI)	p-value	HR/OR [a] (95% CI)	p-value
EFS						
Unadjusted comparison	0.40 (0.26, 0.61)	<0.001	-	-	-	-
Population-adjusted comparison	0.42 (0.21, 0.83)	0.013	-		-	-
DFS						
Unadjusted comparison	-	-	0.55 (0.32, 0.92)	0.024	-	-
Population-adjusted comparison	-	-	0.50 (0.27, 0.93)	0.029	-	-
CHR [b]						
Unadjusted comparison	NE	NE	NE	NE	NE	NE
Population-adjusted comparison	NE	NE	NE	NE	NE	NE
Molecular response (MMolR + CMR)						
Unadjusted comparison	4.19 (1.77, 9.93)	0.001	2.18 (0.77, 6.15)	0.141	-	-
Population-adjusted comparison	5.24 (1.79, 15.37)	0.003	2.14 (0.55, 8.34)	0.274	-	-

Abbreviations: *CHR* complete hematologic response, *CI* confidence interval, *CMR* complete molecular response, *DFS* disease-free survival, *EFS* event-free survival, *HR* hazard ratio, *MMolR* massive molecular response, *MR* molecular response, *NE* not estimable, *OR* odds ratio, *OS*, overall survival

[a] HR for EFS and DFS; OR for molecular response

[b] Relative efficacy for CHR was not estimable because all ponatinib-treated patients achieved a CHR in the high-dose eligible population and all imatinib-treated patients had achieved a CHR in the high-dose non-eligible population. Ponatinib-treated patients achieving a CHR: 69 (100%) in the MDACC study and 42 (95.5%) in the GIMEMA LAL1811 study. Imatinib-treated patients achieving a CHR: 121 (91.0%) in the GRAAPH-2005 study; 42 (93.3%) in the NCT00038610 study; and 28 (100%) in the CSI57ADE10 study

Table S12. Sensitivity analysis for ponatinib vs. imatinib

	MDACC vs. GRAAPH-2005		MDACC vs. NCT00038610		GIMEMA LAL1811 vs. CSI57ADE10	
	HR/OR [a] (95% CI)	p-value	HR/OR [a] (95% CI)	p-value	HR/OR [a] (95% CI)	p-value
OS						
Unadjusted comparison	0.41 (0.25, 0.68)	<0.001	0.42 (0.24, 0.73) [b]	0.002 [b]	0.40 (0.20, 0.81)	0.011
			0.36 (0.20, 0.63) [c]	<0.001 [c]		
Population adjusted comparison (base case)	0.35 (0.17, 0.74)	0.006	0.35 (0.18, 0.70) [b]	0.003 [b]	0.24 (0.09, 0.64)	0.004
			0.30 (0.15, 0.59) [c]	0.001 [c]		
Population adjusted comparison (sensitivity: all factors)	0.36 (0.16, 0.82)	0.015	0.45 (0.22, 0.94) [b]	0.033 [b]	-	-
			0.39 (0.19, 0.80) [c]	0.010 [c]		
Population adjusted comparison (sensitivity: base case without adjusting for WBC)	0.52 (0.28, 0.95)	0.035	-	-	0.30 (0.11, 0.83)	0.020
Population adjusted comparison (sensitivity: all PFs and EMs except WBC)	-	-	-	-	0.44 (0.19, 1.03)	0.059

CMR						
Unadjusted comparison	12.34 (5.77, 26.41)	<0.001	4.93 (2.13, 11.39)	<0.001	7.65 (2.48, 23.64)	<0.001
Population adjusted comparison (base case)	12.11 (3.77, 38.87)	<0.001	5.65 (2.02, 15.76)	<0.001	6.20 (1.60, 24.00)	0.008
Population adjusted comparison (sensitivity: all factors)	11.21 (3.48, 36.06)	<0.001	5.95 (1.69, 20.99)	0.006	-	-
Population adjusted comparison (sensitivity: base case without adjusting for WBC)	11.82 (5.00, 27.94)	<0.001	-	-	8.54 (1.85, 39.43)	0.006
Population adjusted comparison (sensitivity: all PFs and EMs except WBC)	-	-	-	-	6.88 (1.76, 26.86)	0.006
EFS						
Unadjusted comparison	0.40 (0.26, 0.61)	<0.001	-	-	-	-
Population adjusted comparison (base case)	0.42 (0.21, 0.83)	0.013	-	-	-	-
Population adjusted comparison (sensitivity: all factors)	0.39 (0.18, 0.84)	0.016	-	-	-	-
Population adjusted	0.48 (0.28, 0.82)	0.007	-	-	-	-

comparison (sensitivity: base case without adjusting for WBC)						
Population adjusted comparison (sensitivity: all PFs and EMs except WBC)	-	-	-	-	-	-
DFS						
Unadjusted comparison	-	-	0.55 (0.32, 0.92)	0.024	-	-
Population adjusted comparison (base case)	-	-	0.50 (0.27, 0.93)	0.029	-	-
Population adjusted comparison (sensitivity: all factors)	-	-	0.64 (0.34, 1.22)	0.175	-	-
Population adjusted comparison (sensitivity: base case without adjusting for WBC)	-	-	-	-	-	-
Population adjusted comparison (sensitivity: all PFs and EMs except WBC)	-	-	-	-	-	-
CHR [d]	NE	NE	NE	NE	NE	NE
Molecular response (MMolR + CMR)						
Unadjusted comparison	4.19 (1.77, 9.93)	0.001	2.18 (0.77, 6.15)	0.141	-	-

Population adjusted comparison (base case)	5.24 (1.79, 15.37)	0.003	2.14 (0.55, 8.34)	0.274	-	-
Population adjusted comparison (sensitivity: all factors)	4.84 (1.32, 17.77)	0.018	1.86 (0.37, 9.41)	0.453	-	-
Population adjusted comparison (sensitivity: base case without adjusting for WBC)	3.85 (1.45, 10.23)	0.007	-	-	-	-
Population adjusted comparison (sensitivity: all PFs and EMs except WBC)	-	-	-	-	-	-

Abbreviations: *CHR* complete hematologic response, *CI* confidence interval, *CMR* complete molecular response, *DFS* disease-free survival, *EFS* event-free survival, *EM* effect modifier, *HR* hazard ratio, *MMolR* massive molecular response, *MR* molecular response, *NE* not estimable, *OR* odds ratio, *OS*, overall survival, *PF* prognostic factor, *WBC* white blood cells

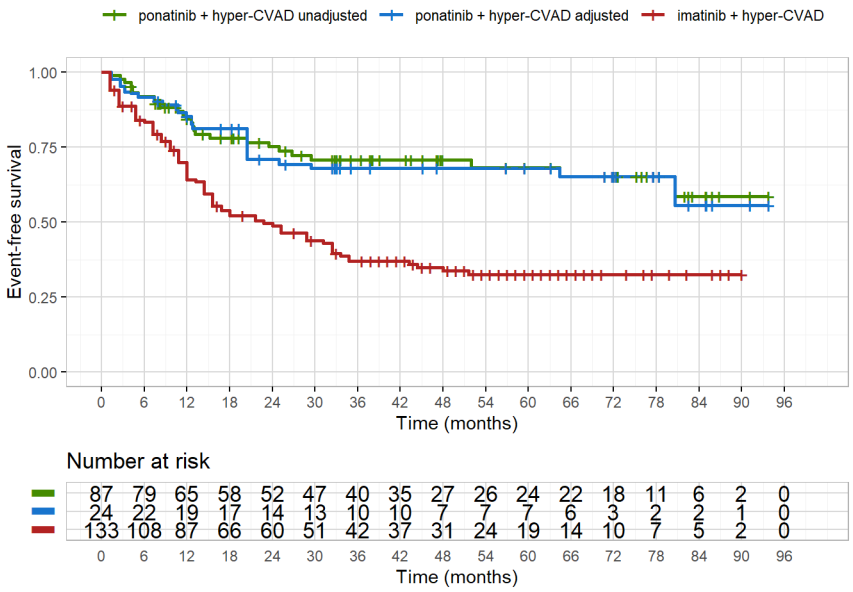
[a] HR for OS, EFS, and DFS; OR for CMR and molecular response

[b] HR with no censoring on stem cell transplantation

[c] HR with censoring on stem cell transplantation

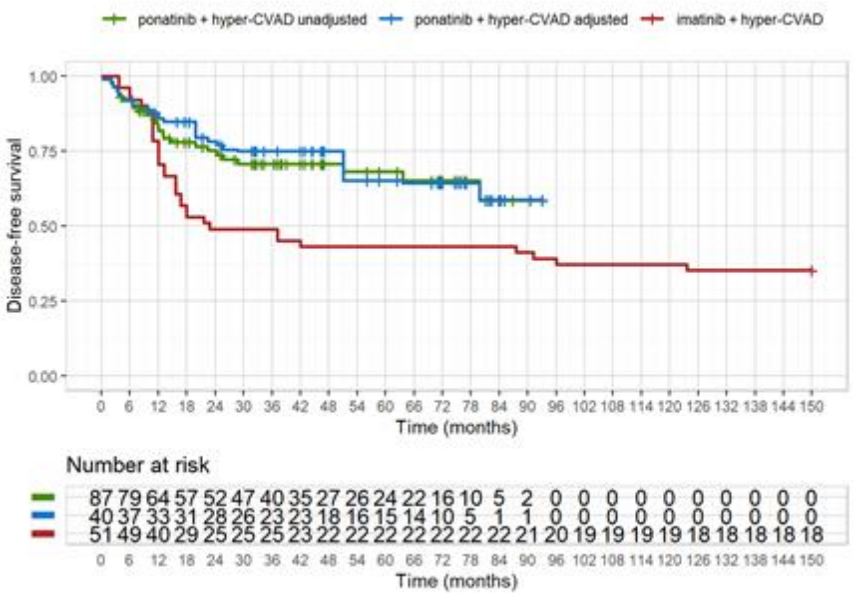
[d] Relative efficacy for CHR was not estimable because all ponatinib-treated patients achieved a CHR in the high-dose eligible population and all imatinib-treated patients had achieved a CHR in the high-dose non-eligible population.

Figure S1. Unadjusted and adjusted Kaplan-Meier curves for EFS (MDACC vs. GRAAPH-2005)



Abbreviations: *CVAD* cyclophosphamide, vincristine, doxorubicin, and dexamethasone, *EFS* event-free survival

Figure S2. Unadjusted and adjusted Kaplan-Meier curves for DFS (MDACC vs. NCT00038610)



Abbreviations: *CVAD* cyclophosphamide, vincristine, doxorubicin, and dexamethasone, *DFS* disease-free survival

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