THE LANCET Haematology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Jain P, Kantarjian H, Alattar ML, et al. Long-term molecular and cytogenetic response and survival outcomes with imatinib 400 mg, imatinib 800 mg, dasatinib, and nilotinib in patients with chronic-phase chronic myeloid leukaemia: retrospective analysis of patient data from five clinical trials. *Lancet Haematol* 2015; **2:** e118–28.

Appendix

Supplemental figure 1 – Best response to therapy with TKI (overall and by TKI modality) – A) by complete cytogenetic response (CCyR) (0% Ph-positive metaphases) **B)** by partial cytogenetic response (PCyR) (1-35% Ph-positive metaphases) **C)** by major molecular response (MMR) (≤0.1% BCR-ABL-IS) and **D)** by molecular response (MR4.5) (≤0.0032% BCR-ABL-IS).

Supplemental figure 2 – Long term outcomes according to cytogenetic responses - complete cytogenetic response (CCyR), partial cytogenetic response (PCyR) and minimal cytogenetic response (min.) (>35% Ph-positive metaphases) **achieved by different TKI modalities (Imatinib 400, Imatinib 800, Dasatinib and Nilotinib) A)** Event free survival (EFS) **B)** Failure free survival (FFS) **C)** Transformation free survival (TFS) and **D)** Overall survival (OS).

Supplemental figure 3 - Long term outcomes according to major molecular response (MMR) achieved by different TKI modalities (Imatinib 400, Imatinib 800, Dasatinib and Nilotinib) A) Event free survival (EFS) **B)** Failure free survival (FFS) **C)** Transformation free survival (TFS) and **D)** Overall survival (OS).

Supplemental figure 4 – Event free survival (EFS) according to the type of response at 12 months - Major molecular response (MMR) (≤0.1% BCR-ABL-IS) vs Complete cytogenetic response (CCyR) with no MMR vs no MMR, no CCyR. Median survival was not reached in patients with CCyR no MMR, MMR and 30 months in patients without CCyR and/or MMR

Supplemental figure 5 – Rates of discontinuation among the TKI modalities according to the duration of therapy

Supplemental Tables -

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Table 9 – Summary of subsequent therapies after discontinuation of initial TKI modality

Table 1 – Summary of 95% confidence intervals of complete cytogenetic response (CCyR) and major molecular response (MMR) at different time points according to type of TKI modality.

	Imatinib 400	Imatinib 800	Dasatinib	Nilotinib
CCyR				
3	0.19-0.41	0.49-0.63	0.70-0.86	0.75-0.90
6	0.28-0.50	0.72-0.84	0.81-0.94	0.83-0.95
9	0.49-0.72	0.79-0.89	0.83-0.95	0.81-0.93
12	0.50-0.73	0.79-0.89	0.85-0.96	0.84-0.95
18	0.59-0.81	0.79-0.89	0.85-0.96	0.81-0.94
24	0.56-0.79	0.77-0.88	0.77-0.92	0.81-0.94
36	0.65-0.87	0.79-0.89	0.84-0.97	0.84-0.97
60	0.65-0.87	0.70-0.83	0.68-0.91	0.77-0.97
MMR				
3	0-0.06	0.32-0.46	0.40-0.59	0.47-0.66
6	0.01-0.13	0.58-0.71	0.57-0.75	0.57-0.75
9	0.22-0.45	0.69-0.81	0.62-0.80	0.60-0.77
12	0.26-0.49	0.70-0.82	0.63-0.80	0.71-0.87
18	0.55-0.78	0.69-0.82	0.68-0.85	0.74-0.90
24	0.52-0.76	0.72-0.84	0.73-0.89	0.74-0.89
36	0.51-0.76	0.75-0.87	0.76-0.92	0.78-0.93
60	0.61-0.84	0.75-0.87	0.65-0.90	0.77-0.97
MR4.5				
3	0-0.06	0.02-0.09	0.02-0.12	0.05-0.16
6	0.0001-0.08	0.18-0.30	0.15-0.31	0.21-0.38
9	0.02-0.15	0.26-0.39	0.15-0.31	0.23-0.42
12	0.10-0.30	0.25-0.39	0.28-0.47	0.30-0.49
18	0.20-0.42	0.31-0.45	0.36-0.56	0.34-0.54
24	0.23-0.47	0.34-0.48	0.49-0.69	0.44-0.64
36	0.25-0.40	0.46-0.60	0.52-0.74	0.51-0.72
60	0.25-0.51	0.60-0.74	0.45-0.74	0.65-0.90

Table 2 – Analysis of factors predictive of failure free survival (FFS) including the type of TKI modality.

	N	Events	Log-rank	HR	95% CI HR	P-value	5-year EFS
***Univariate**							
TKI Type							
Imatinib 400#	68	38	0.353				59
Imatinib 800	200	88		0.84	(0.57-1.24)	0.382	70
Dasatinib	105	23		0.61	(0.36-1.05)	0.075	76
Nilotinib	108	28		0.78	(0.46-1.30)	0.332	70
Sokal score							
Low	333	113	0.189				72
Intermediate	118	48		1.07	(0.76-1.50)	0.702	69
High	30	16		1.62	(0.96-2.74)	0.071	62
Age, years							
≤55	322	115	0.95				71
>55	159	62		0.99	(0.73-1.35)	0.950	69
Splenomegaly (≥10cm)							
No	445	157	0.022				71
Yes	36	20		1.71	(1.08-2.73)	0.023	57
Multivariate							
TKI Type							
Imatinib 400#	68	38					59
Imatinib 800	200	88		0.80	(0.54-1.19)	0.264	70
Dasatinib	105	23		0.61	(0.36-1.06)	0.079	76
Nilotinib	108	28		0.77	(0.46-1.28)	0.310	70
Splenomegaly (≥10cm)							
No	445	157					71
Yes	36	20		1.5	(0.94-2.64)	0.086	57

*White blood cell (WBC) count, Hemoglobin, platelet count, peripheral blood blasts, serum lactate dehydrogenase (LDH) are not significant (p=NS; data not shown), # Imatinib 400 is the reference for comparison with other 3 TKI modalities

Table 3 – Analysis of factors predictive of transformation free survival (TFS) including the type of TKI modality.

	N	Events	Log-rank	HR	95% CI HR	P-value	5-year EFS
***Univariate**							
TKI Type							
Imatinib 400#	68	10	0.078				87
Imatinib 800	200	14		0.45	(0.20-1.01)	0.053	94
Dasatinib	105	3		0.25	(0.07-0.93)	0.038	96
Nilotinib	108	8		0.72	(0.28-1.85)	0.493	88
Sokal score							
Low	333	18	0.119				94
Intermediate	118	13		1.82	(0.89-3.71)	0.101	90
High	30	4		2.41	(0.81-7.13)	0.112	87
Age, years							
≤55	322	20	0.307				93
>55	159	15		0.71	(0.36-1.38)	0.310	91
Splenomegaly (≥10cm)							
No	445	30	0.107				93
Yes	36	5		2.14	(0.83-5.51)	0.116	86
Multivariate							
TKI Type							
Imatinib 400#	68	10					87
Imatinib 800	200	14		0.39	(0.17-0.89)	0.025	94
Dasatinib	105	3		0.26	(0.07-0.96)	0.043	96
Nilotinib	108	8		0.63	(0.24-1.64)	0.345	88
Splenomegaly (≥10cm)							
No	445	30					93
Yes	36	5		1.67	(0.61-4.62)	0.320	86

*White blood cell (WBC) count, Hemoglobin, platelet count, peripheral blood blasts, serum lactate dehydrogenase (LDH) are not significant (p=NS; data not shown), # Imatinib 400 is the reference for comparison with other 3 TKI modalities

Table 4 – Analysis of factors predictive of overall survival (OS) including the type of TKI modality.

	N	Events	Log-rank	HR	95% CI HR	P-value	5-year EFS
***Univariate**							
TKI Type							
Imatinib 400[#]	68	13	0.497				89
Imatinib 800	200	30		0.82	(0.43-1.59)	0.563	93
Dasatinib	105	3		0.40	(0.11-1.45)	0.162	98
Nilotinib	108	7		1.01	(0.38-2.67)	0.981	89
Sokal score							
Low	333	27	0.034				94
Intermediate	118	19		1.6	(0.98-3.17)	0.059	91
High	30	7		2.53	(1.10-5.82)	0.029	89
Age, years							
≤55	322	22	0.00				95
>55	159	31		0.35	(0.20-0.60)	0.000	87
Splenomegaly (≥10cm)							
No	445	50	0.431				92
Yes	36	3		0.63	(0.20-2.02)	0.435	97
Multivariate							
TKI Type							
Imatinib 400[#]	68	13					89
Imatinib 800	200	30		0.72	(0.37-1.42)	0.351	93
Dasatinib	105	3		0.44	(0.12-1.62)	0.218	98
Nilotinib	108	7		0.81	(0.29-2.28)	0.689	89

*White blood cell (WBC) count, Hemoglobin, platelet count, peripheral blood blasts, serum lactate dehydrogenase (LDH) are not significant (p=NS; data not shown), # Imatinib 400 is the reference for comparison with other 3 TKI modalities

Table 5 –Multivariate analysis showing type of cytogenetic and/or molecular responses at 3, 6, and 12 months achieved with different TKI modalities are predictive of event free survival (EFS).

*Covariates	P-value	HR	95% C.I. for HR	
			Lower	Upper
3 months MCyR by TKI				
#Imatinib 400 + No MCyR				
Imatinib 400 + MCyR	0.009	0.31	0.13	0.75
****3TKI + No MCyR**	0.386	0.66	0.26	1.68
3TKI + MCyR	<0.001	0.19	0.09	0.37
6 months CCyR by TKI				
#Imatinib 400 + No CCyR				
Imatinib 400 + CCyR	0.013	0.21	0.06	0.73
****3TKI + No CCyR**	0.625	1.18	0.60	2.33
3TKI + CCyR	<0.001	0.20	0.11	0.36
12 months CCyR by TKI				
#Imatinib 400 + No CCyR				
Imatinib 400 + CCyR	<0.001	0.09	0.03	0.25
****3TKI + No CCyR**	0.628	1.18	0.60	2.33
3TKI + CCyR	<0.001	0.08	0.04	0.15
12 months MMR by TKI				
#Imatinib 400 + No MMR				
Imatinib 400 + MMR	0.029	0.23	0.06	0.86
****3TKI + No MMR**	0.666	0.83	0.36	1.93
3TKI + MMR	<0.001	0.20	0.09	0.43

C.I., confidence interval; WBC, white blood cells, 3 TKI (Imatinib 800, Dasatinib and Nilotinib), CCyR (complete cytogenetic response), MMR (major molecular response), * Age and splenomegaly were included in the model and were not significant (not shown), age was included as a priori, ** 3 TKI are combined since there were low numbers in categories of No CCyR for dasatinib and nilotinib, # Imatinib 400 with no CCyR or no MMR was used as a reference at all-time points.

Table 6 –Multivariate analysis showing type of cytogenetic and/or molecular responses at 3, 6, and 12 months achieved with different TKI modalities are predictive of failure free survival (FFS).

*Covariates	P-value	HR	95% C.I. for HR	
			Lower	Upper
3 months MCyR by TKI				
#Imatinib 400 + No MCyR				
Imatinib 400 + MCyR	<0.001	0.29	0.15	0.57
**3TKI + No MCyR	0.876	0.95	0.48	1.87
3TKI + MCyR	<0.001	0.27	0.15	0.47
6 months CCyR by TKI				
#Imatinib 400 + No CCyR				
Imatinib 400 + CCyR	0.019	0.43	0.21	0.87
**3TKI + No CCyR	0.183	1.44	0.84	2.45
3TKI + CCyR	<0.001	0.41	0.26	0.64
12 months CCyR by TKI				
#Imatinib 400 + No CCyR				
Imatinib 400 + CCyR	<0.001	0.09	0.05	0.19
**3TKI + No CCyR	0.232	1.41	0.80	2.46
3TKI + CCyR	<0.001	0.11	0.07	0.19
12 months MMR by TKI				
#Imatinib 400 + No MMR				
Imatinib 400 + MMR	0.022	0.35	0.14	0.86
**3TKI + No MMR	0.942	1.03	0.52	2.03
3TKI + MMR	0.003	0.39	0.21	0.72

C.I., confidence interval; WBC, white blood cells, 3 TKI (Imatinib 800, Dasatinib and Nilotinib), CCyR (complete cytogenetic response), MMR (major molecular response), * Age and splenomegaly were included in the model and were not significant (not shown), age was included as a priori, ** 3 TKI are combined since there were low numbers in categories of No CCyR for dasatinib and nilotinib, # Imatinib 400 with no CCyR or no MMR was used as a reference at all-time points.

Table 7 –Multivariate analysis showing type of cytogenetic and/or molecular responses at 3, 6, and 12 months achieved with different TKI modalities are predictive of transformation free survival (TFS).

*Covariates	P-value	HR	95% C.I. for HR	
			Lower	Upper
3 months MCyR by TKI				
#Imatinib 400 + No MCyR				
Imatinib 400 + MCyR	0.031	0.24	0.07	0.88
****3TKI + No MCyR**	0.098	0.25	0.05	1.29
3TKI + MCyR	<0.001	0.18	0.07	0.45
6 months CCyR by TKI				
#Imatinib 400 + No CCyR				
Imatinib 400 + CCyR	0.091	0.17	0.02	1.33
****3TKI + No CCyR**	0.286	0.54	0.17	1.68
3TKI + CCyR	<0.001	0.22	0.10	0.51
12 months CCyR by TKI				
#Imatinib 400 + No CCyR				
Imatinib 400 + CCyR	0.004	0.10	0.02	0.47
****3TKI + No CCyR**	0.551	0.72	0.24	2.13
3TKI + CCyR	<0.001	0.10	0.04	0.23
12 months MMR by TKI				
#Imatinib 400 + No MMR				
Imatinib 400 + MMR	0.142	0.19	0.02	1.75
****3TKI + No MMR**	0.240	0.44	0.11	1.74
3TKI + MMR	0.017	0.23	0.07	0.77

C.I., confidence interval; WBC, white blood cells, 3 TKI (Imatinib 800, Dasatinib and Nilotinib), CCyR (complete cytogenetic response), MMR (major molecular response), * Age and splenomegaly were included in the model and were not significant (not shown), age was included as a priori, ** 3 TKI are combined since there were low numbers in categories of No CCyR for dasatinib and nilotinib, # Imatinib 400 with no CCyR or no MMR was used as a reference at all-time points.

Table 8 –Multivariate analysis showing type of cytogenetic and/or molecular responses at 3, 6, and 12 months achieved with different TKI modalities are predictive of overall survival (OS).

*Covariates	P-value	HR	95% C.I. for HR	
			Lower	Upper
3 months MCyR by TKI				
#Imatinib 400 + No MCyR				
Imatinib 400 + MCyR	0.031	0.30	0.10	0.89
****3TKI + No MCyR**	0.140	0.38	0.10	1.38
3TKI + MCyR	0.006	0.31	0.14	0.72
6 months CCyR by TKI				
#Imatinib 400 + No CCyR				
Imatinib 400 + CCyR	0.599	0.73	0.22	2.38
****3TKI + No CCyR**	0.702	1.21	0.46	3.18
3TKI + CCyR	0.049	0.45	0.20	1.00
12 months CCyR by TKI				
#Imatinib 400 + No CCyR				
Imatinib 400 + CCyR	0.001	0.08	0.02	0.37
****3TKI + No CCyR**	0.229	0.56	0.21	1.45
3TKI + CCyR	<0.001	0.17	0.08	0.37
12 months MMR by TKI				
#Imatinib 400 + No MMR				
Imatinib 400 + MMR	0.948	0.91	0.06	14.73
****3TKI + No MMR**	0.117	5.40	0.66	44.54
3TKI + MMR	0.353	2.63	0.34	20.24

C.I., confidence interval; WBC, white blood cells, 3 TKI (Imatinib 800, Dasatinib and Nilotinib), CCyR (complete cytogenetic response), MMR (major molecular response), * Age and splenomegaly were included in the model and were not significant (not shown), age was included as a priori, ** 3 TKI are combined since there were low numbers in categories of No CCyR for dasatinib and nilotinib, # Imatinib 400 with no CCyR or no MMR was used as a reference at all-time points.

Table 9 – Summary of subsequent therapies after discontinuation or coming off of initial TKI modality

Type of TKI modality (n)	1 Subsequent TKI (n)	≥1 Subsequent TKI (n)	SCT and Others (n)
Imatinib 400 (n=17)	Dasatinib (3) Bosutinib (2) Imatinib 800 (1)	Imatinib 800 then Dasatinib (5) Nilotinib then Dasatinib (1) Dasatinib then Nilotinib (1)	SCT (4)
Imatinib 800 (n=47)	Imatinib 400 (8) Dasatinib (8) Nilotinib (7) Bosutinib (2)	Dasatinib then nilotinib then others (6) Imatinib 400 then Dasatinib (2) Nilotinib then Dasatinib (3) Chemotherapy with TKI then Dasatinib/Nilotinib (3) Bosutinib then Nilotinib (1)	SCT (4) Others (3) - Homoharringotonin, PR-1 vaccine, Imatinib 400 with Tipifarnib
Dasatinib (n=16)	Nilotinib (6) Ponatinib (2) Imatinib 800 (2)	Imatinib 400 then Nilotinib (1) Imatinib 400 then SCT (1) Nilotinib then Ponatinib/Bosutinib (2)	SCT (2)
Nilotinib (n=17)	Dasatinib (6) Imatinib 400 (3)	Chemotherapy with TKI then Dasatinib (3) Ponatinib then SCT (1) Dasatinib then Nilotinib (1) Imatinib 400 then Dasatinib (2)	Imatinib 400 with Ruxolitinib (1)

SCT- stem cell transplant, # - Some patient's received third line and fourth line TKI's or other investigational agents

Summary of inclusion and exclusion criteria of patients enrolled into prospective clinical trials of four TKI modalities.

Nilotinib - NCT00129740 – Protocol - 50048 (MDACC)

Inclusion Criteria:

1. Diagnosis of Ph-positive or Bcr-positive CML in early chronic phase CML (i.e., time from diagnosis 12 months). Except for hydroxyurea, patients must have received no or minimal prior therapy, defined as <1 month (30 days) of prior interferon-alpha (with or without cytarabine) and/or an FDA-approved TKI. Patients with de novo accelerated phase will be treated but analyzed separately.
2. Age ≥ 16 years (Age >18 years to participate in optional symptom burden assessment)
3. ECOG performance of 0-2.
4. Adequate end organ function, defined as the following: total bilirubin < 1.5 x ULN, SGPT < 2.5 x ULN, creatinine < 1.5 x ULN.
5. Patients must sign an informed consent indicating they are aware of the investigational nature of this study, in keeping with the policies of the hospital.
6. Reliable telephone access to receive calls from an interactive voice response system (IVR) (only applicable to patients who will participate in optional symptom burden assessment).

Exclusion Criteria:

1. NYHA cardiac class 3-4 heart disease as well as impaired cardiac function defined as: LVEF < 45% as determined by MUGA scan or electrocardiogram; Complete left bundle branch block; Use of cardiac pacemaker; ST depression of > 1 mm in 2 or more leads and/or T wave inversions in 2 or more continuous leads; Congenital long QT syndrome; History of, or presence of significant ventricular or atrial tachyarrhythmia's; Clinically significant resting bradycardia (< 50 bpm); QTc > 450 msec on screening ECG (using the QTcF formula);
2. (Continued from #1) Right bundle branch block plus left anterior hemi block, bivascular block; Myocardial infarction within 12 months prior to starting AMN107; Unstable angina diagnosed or treated within the past 12 months; Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).
3. Patients with active, uncontrolled psychiatric disorders including: psychosis, major depression, and bipolar disorders.
4. Female patients of childbearing potential must have negative pregnancy test within 7 days before initiation of study drug dosing. Postmenopausal women must be amenorrhea for at least 12 months to be considered of non-childbearing potential. Surgical sterilization is considered non-childbearing potential. Female patients of reproductive potential must agree to employ an effective method of birth control (hormonal or barrier) throughout the study and for up to 3 months following discontinuation of study drug.
5. Patients with severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, chronic renal disease, or active uncontrolled infection [persistent fever and worsening clinical condition]).
6. Patient with known chronic liver disease (i.e., chronic active hepatitis, and cirrhosis).
7. Patient with known diagnosis of human immunodeficiency virus (HIV) infection.
8. Patients in late chronic phase (i.e., time from diagnosis to treatment >12 months) or blastic phase are excluded. The definitions of CML phases are as follows: A. Early chronic phase: time from diagnosis to therapy < 12 months late chronic phase: time from diagnosis to therapy > 12 months'. Blastic phase: presence of 30% blasts or more in the peripheral blood or bone marrow. C. Accelerated phase CML: presence of any of the following features: * Peripheral or marrow blasts 15% or more.
9. (Cont. #8)Peripheral or marrow basophils 20% or more. *Thrombocytopenia < 100 x 10(9)/L unrelated to therapy. * Documented extramedullary blastic disease outside liver or spleen due to past causes D. Clonal evolution defined as the presence of additional chromosomal abnormalities other than the Ph chromosome is part of accelerated phase CML. Ph chromosome variants or complex Ph chromosome translocations are not considered to indicate disease acceleration.

Dasatinib - NCT00254423 – Protocol - 50422 (MDACC)

Inclusion Criteria:

1. Diagnosis of Ph-positive or Bcr-Abl positive CML in early chronic phase CML (i.e., time from diagnosis </= 12 months). Except for hydroxyurea, patients must have received no or minimal prior therapy, defined as <1 month of prior IFN-alpha (with or without ara-C) and/or imatinib
2. Continued from above #1: Clonal evolution defined as the presence of additional chromosomal abnormalities other than the Ph chromosome has been historically been included as a criterion for accelerated phase. However, patients with clonal evolution as the only criterion of accelerated phase have a significantly better prognosis, and when present at diagnosis may not impact the prognosis at all. Thus, patients with clonal evolution and no other criteria for accelerated phase will be eligible for this study
3. Age >/= 16 years (Age >18 years to participate in optional symptom burden assessment)
4. ECOG performance of 0-2
5. Adequate end organ function, defined as the following: total bilirubin <1.5 x ULN, SGPT <2.5x ULN, creatinine <1.5x ULN
6. Patients must sign an informed consent indicating they are aware of the investigational nature of this study, in keeping with the policies of the hospital.
7. Reliable telephone access to receive calls from an interactive voice response system (IVR) (only applicable to patients who will participate in optional symptom burden assessment)

Exclusion Criteria:

1. New York Heart Association (NYHA) cardiac class 3-4 heart disease
2. Cardiac Symptoms: Patients meeting the following criteria are not eligible unless cleared by Cardiology: Uncontrolled angina within 3 months; Diagnosed or suspected congenital long QT syndrome; Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes); Prolonged QTc interval on pre-entry electrocardiogram (> 450 msec) on both the Fridericia and Bazett's correction; Uncontrolled hypertension; History of significant bleeding disorder unrelated to cancer, including:
3. Cont: Diagnosed congenital bleeding disorders (von Willebrand's disease) Diagnosed acquired bleeding disorder w/in 1 year (acquired anti-factor VIII antibodies);Pts currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes including: quinidine, procainamide, disopyramide amiodarone, sotalol, ibutilide, dofetilide erythromycins, clarithromycin chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.
4. Patients with active, uncontrolled psychiatric disorders including: psychosis, major depression, and bipolar disorders
5. Women of pregnancy potential must practice an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Postmenopausal women must be amenorrhea for at least 12 months to be considered of non-childbearing potential.
6. Continued: Women must continue birth control for the duration of the trial and at least 3 months after the last dose of study drug; Pregnant or breast-feeding women are excluded; All WOCBP MUST have a negative pregnancy test prior to first receiving investigational product. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study.
7. Patients in late chronic phase (i.e., time from diagnosis to treatment >12 months), accelerated or blast phase are excluded.
8. The definitions of CML phases are as follows: a) Early chronic phase: time from diagnosis to therapy ≤12 months; Late chronic phase: time from diagnosis to therapy > 12 months, b) Blastic phase: presence of 30% blasts or more in the peripheral blood or bone marrow, c) Accelerated phase CML: presence of any of the following features: •Peripheral or marrow blasts 15% or more, •Peripheral or marrow basophils 20% or more, •Thrombocytopenia < 100 x 10^9/L unrelated to therapy, • Documented extramedullary blastic disease outside liver or spleen.

Imatinib 800 - - NCT00038649 – Protocol - 1151 (MDACC)

Inclusion Criteria:

1. Patients age 15 years or older with a diagnosis of Ph-positive or Bcr-positive CML in early chronic phase CML (diagnosis < 12 months). Except for hydroxyurea, patients must have received no or minimal prior therapy, defined as less than 1 month of prior IFN-a or ara-C.
2. ECOG performance of 0-2
3. Serum bilirubin less than 2 mg%, serum creatinine less than 2mg%
4. Women of pregnancy potential must practice contraception. Women and men must continue birth control for the duration of the trial and at least 3 months after the last dose of study drug.
5. Patients must sign an informed consent indicating they are aware of the investigational nature of this study, in keeping with the policies of the hospital.
6. The definitions of CML phases are as follows: a) early chronic phase: time from diagnosis to therapy < 12 months, late chronic phase: time from diagnosis to therapy > 12 months; b) blastic phase: presence of 30% blasts or more in the peripheral blood or bone marrow; c) accelerated phase CML: presence of any of the following features: peripheral or marrow blasts 15% or more, peripheral or marrow basophils 20% or more, thrombocytopenia <100 x 10(9)/L unrelated to therapy, documented extramedullary blastic disease outside liver or spleen due to past causes
7. The definitions of CML phases are as follows: clonal evolution defined as the presence of additional chromosomal abnormalities other than the Ph chromosome is part of accelerated phase CML. Ph chromosome variants or complex Ph chromosome translocations are not considered to indicate disease acceleration. We have recently found clonal evolution to have a variable prognostic impact and may be suppressed with IFN-a therapy. Hence these patients will be eligible if no other accelerated phase signs are present, and analyzed separately.
8. Inclusion of women and minorities: As per NIH policy, women and members of minorities will be included in this protocol as they are referred in the CML population. Their distribution is similar to the general referral profiles for CML: about 50% of CML patients are females and 25% to 30% are members of minorities. There are no exclusions of women or minorities based on the study objectives.

Exclusion Criteria:

1. NYHA class 3-4 heart disease
2. Psychiatric disability (psychosis)
3. Pregnant or lactating females
4. Patients in late chronic phase, accelerated phase or blastic phase are excluded.

Imatinib 800 - - NCT00050531 – Protocol - 2534 (MDACC)

Inclusion Criteria:

1. Patients with Ph-positive CML in early chronic phase CML who have received no or minimal prior therapy, (<1 month of prior IFN-alpha (with or without ara-C) and/or Gleevec).
2. ECOG performance of 0-2.
3. Adequate end organ function, defined as the following: total bilirubin < 1.5 x ULN, SGPT < 2.5 x ULN, creatinine < 1.5 x ULN
4. Signed informed consent.

Exclusion Criteria:

1. NYHA cardiac class 3-4 heart disease.
2. Psychiatric disability (psychosis)
3. Pregnant or lactating females
4. Late chronic phase, accelerated or blastic phase

Imatinib 400 - - NCT00048672 – Protocol - 1015 (MDACC)

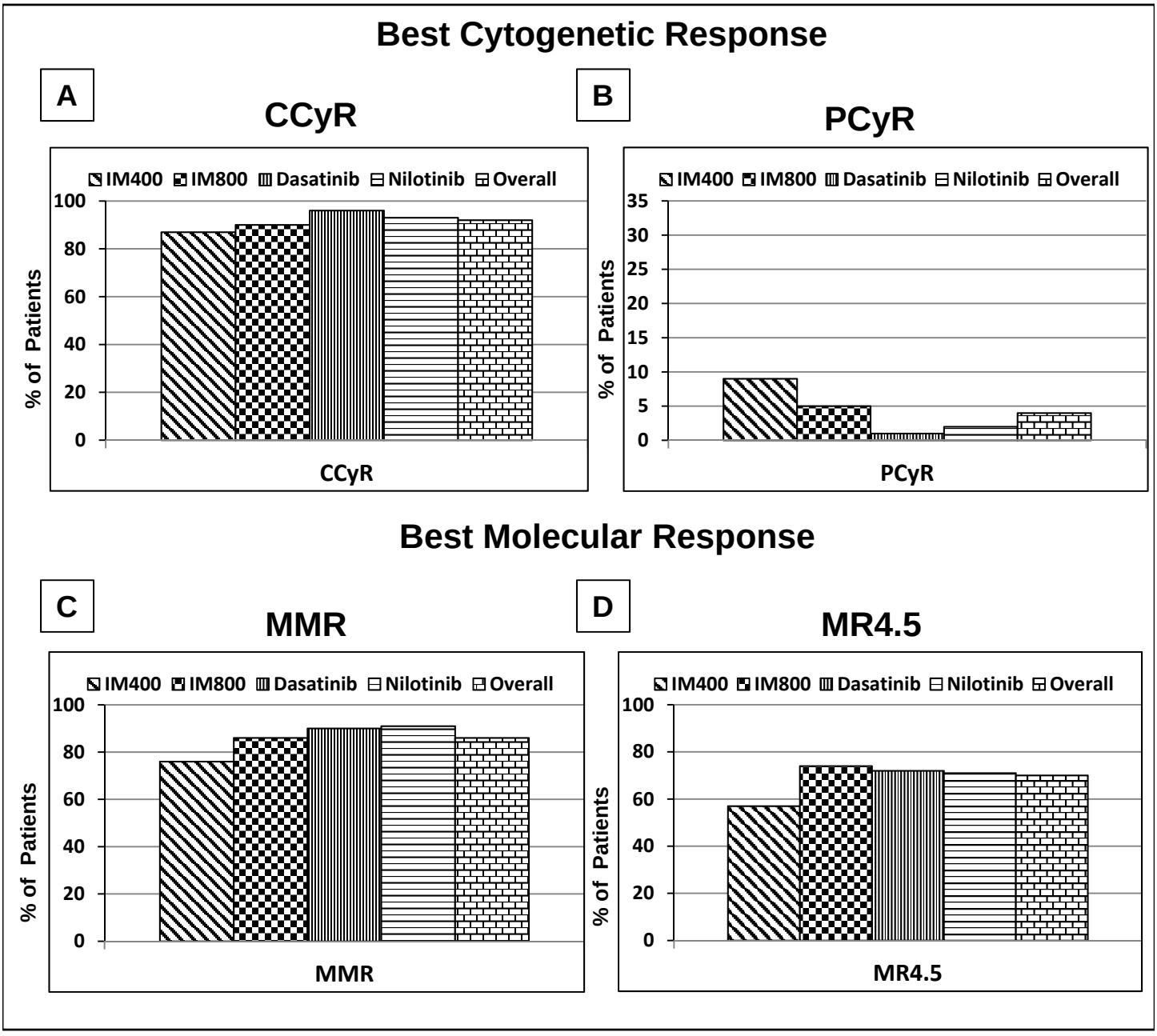
Inclusion Criteria:

1. Diagnosis of Philadelphia chromosome (Ph)- positive or breakpoint cluster region (bcr)-positive CML in early chronic (diagnosis < 12 months).
2. Age 15 years or above
3. Adequate renal, hepatic, cardiac and performance status (ECOG 0-2) - no psychiatric disability (psychosis)
4. Signed informed consent

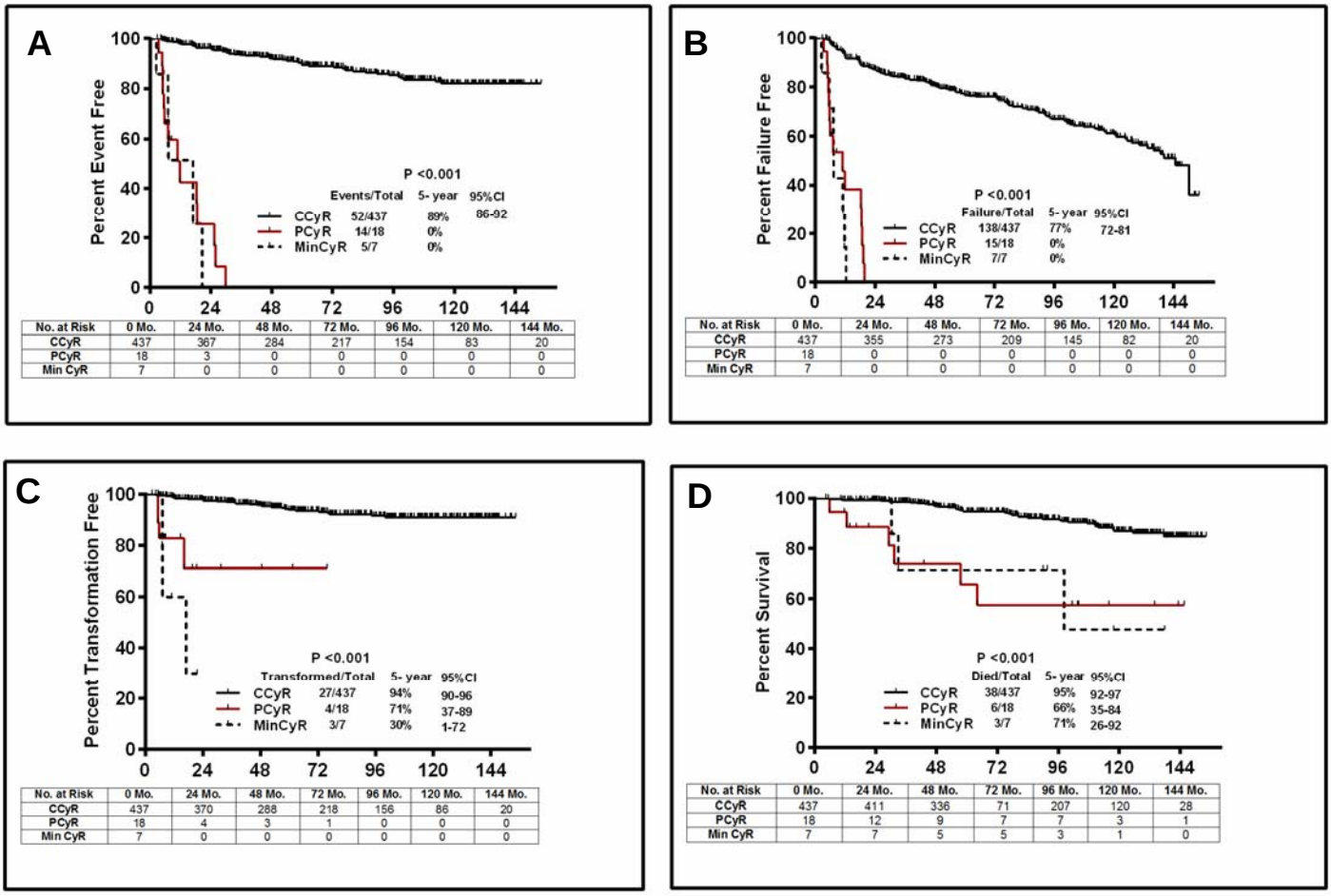
Exclusion Criteria:

1. Grade 3-4 cardiac
2. Psychiatric problem
3. Pregnant or lactating

Supplemental figure 1



Supplemental figure 2



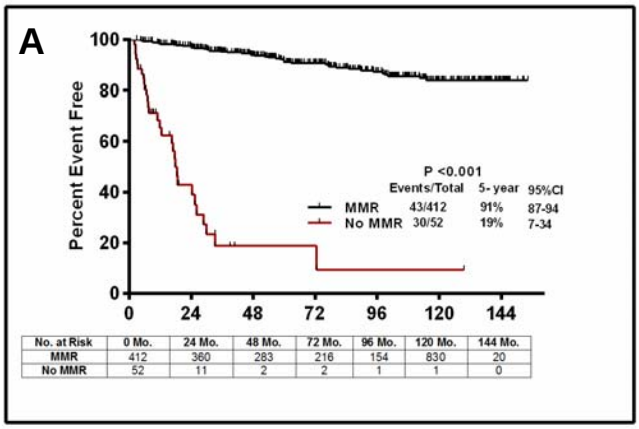
No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
CCyR	437	367	284	217	154	83	20
PCyR	18	3	0	0	0	0	0
Min CyR	7	0	0	0	0	0	0

No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
CCyR	437	355	273	209	145	82	20
PCyR	18	0	0	0	0	0	0
Min CyR	7	0	0	0	0	0	0

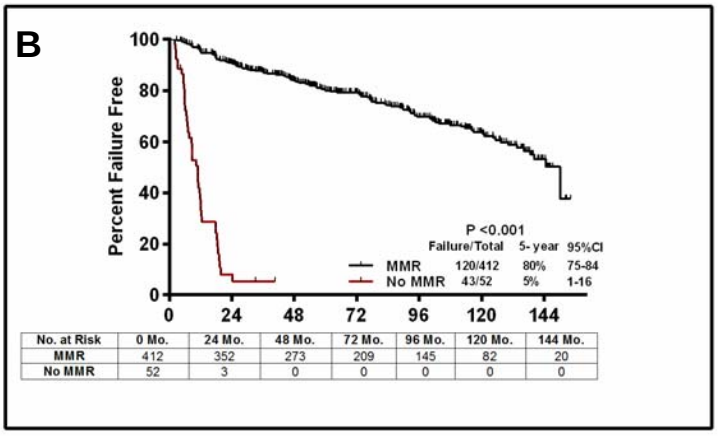
No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
CCyR	437	370	288	218	156	86	20
PCyR	18	4	3	1	0	0	0
Min CyR	7	0	0	0	0	0	0

No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
CCyR	437	411	336	71	207	120	28
PCyR	18	12	9	7	7	3	1
Min CyR	7	7	5	5	3	1	0

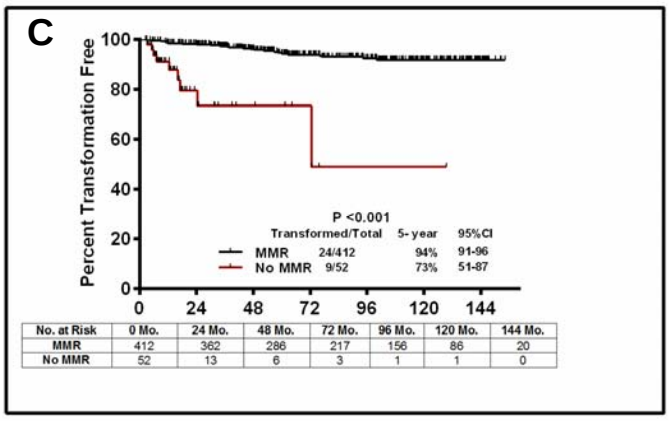
Supplemental Figure – 3 (A-D)



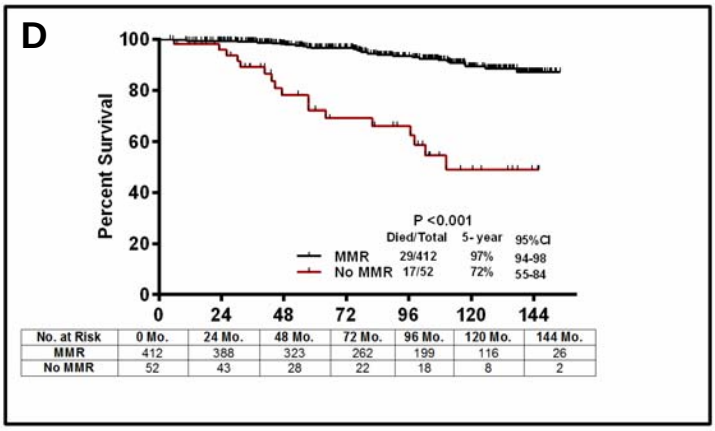
No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
MMR	412	360	283	216	154	830	20
No MMR	52	11	2	2	1	1	0



No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
MMR	412	352	273	209	145	82	20
No MMR	52	3	0	0	0	0	0

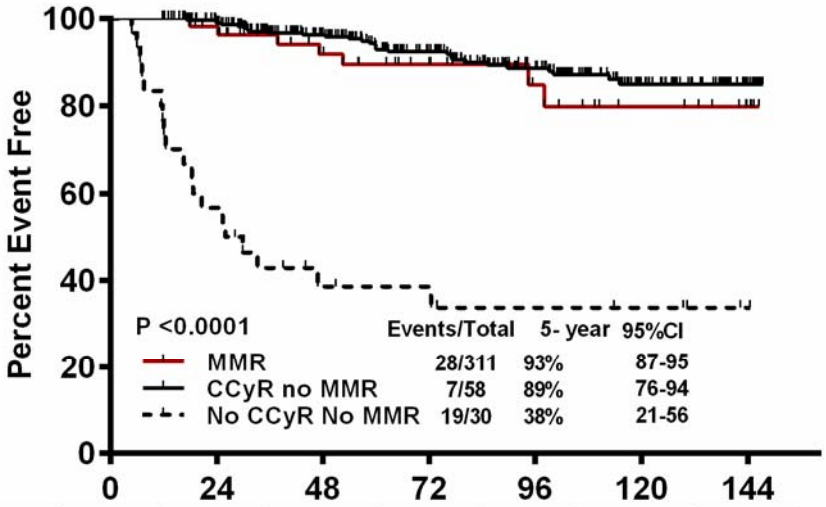


No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
MMR	412	362	286	217	156	86	20
No MMR	52	13	6	3	1	1	0



No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
MMR	412	388	323	262	199	116	26
No MMR	52	43	28	22	18	8	2

Supplemental Figure – 4



No. at Risk	0 Mo.	24 Mo.	48 Mo.	72 Mo.	96 Mo.	120 Mo.	144 Mo.
MMR	311	281	219	165	121	58	11
CCyR no MMR	58	52	40	32	17	10	4
No CCyR, NO MMR	30	18	10	8	4	3	1

Supplemental Figure – 5