Treatment-free remission after two-year consolidation therapy with nilotinib in patients with chronic myeloid leukemia: STAT2 trial in Japan

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 doi:10.3324/haematol.2018.194894

Received: April 4, 2018.

Accepted: June 28, 2018.

Pre-published: July 5, 2018.

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Supplemental data

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Supplemental methods

T/NK cell profiles and Natural killer cell activity in the treatment-free remission phase

Immuno-phenotypic examinations were performed by flow cytometry with a FACSCalibur system and CellQuest software, version 3.3 (Becton Dickinson, Franklin Lakes, NJ, USA). All antibodies were purchased from Becton Dickinson. The subsets of lymphocytes assessed were as follows: CD8+ T cells (CD3+ CD8+), natural killer (NK) cells (CD3– CD56+ and CD16+ CD56+), T-cell large granular lymphocytes (CD57+ CD3+), and NK-cell large granular lymphocytes (CD57+ CD56+). NK cells were isolated by magnetic selection using an NK isolation kit (Miltenyi Biotec K.K., Tokyo, Japan) from the mononuclear cells of peripheral blood 1 month into the TFR phase. Cytolytic activity was determined by performing standard 4-hour ^{51}Cr-release assays using NK-sensitive K562 cells. NK cell cytotoxicity testing was repeated three times, using K562 as target cells. Results were calculated and recorded as percentage of cells killed, as previously described (Mailliard RB, Son YI, Redlinger R, et al. Dendritic cells mediate NK cell help for Th1 and CTL responses: two-signal requirement for the induction of NK cell helper function. *J Immunol*. 2003;171(5):2366–2373).

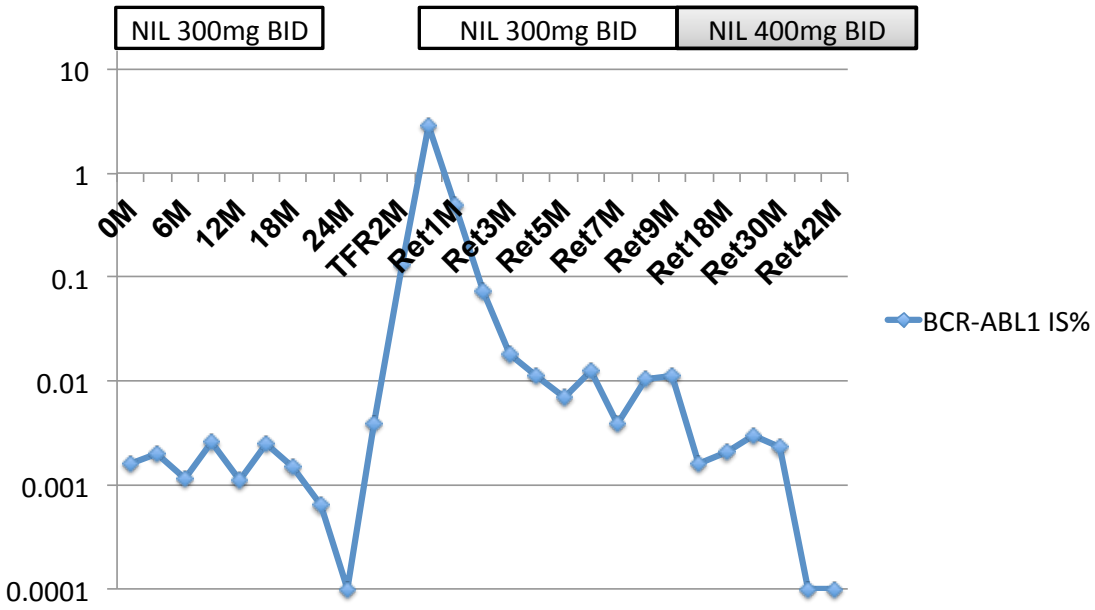
Statistical analysis

The planned sample size was calculated by estimating the minimum number of patients needed to reject the null hypothesis for the primary endpoint (TFR rate of ≤40% at 12 months). If 30% of enrolled patients did not qualify for the TFR phase, a minimum enrollment of 96 patients was required if the true TFR rate at 12 months was ≥60%. With the actual enrollment of 78 patients, the power increased to 99%, with all other assumptions being true.

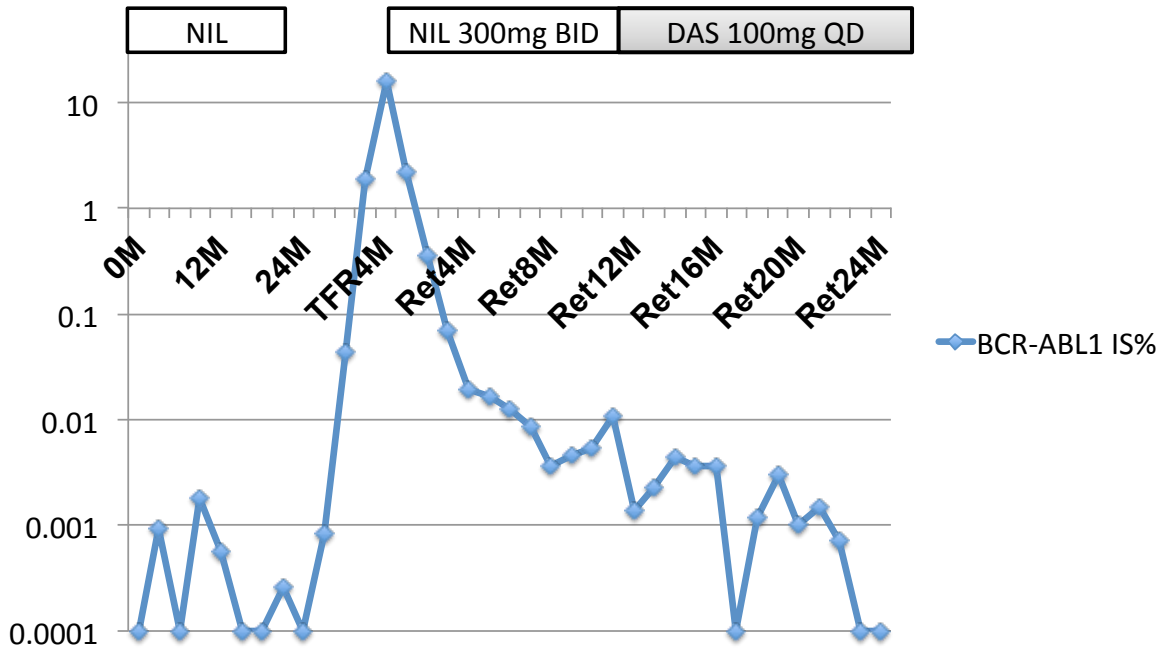
Statistical analyses were conducted with SPSS statistical software, version 17.0 (IBM Corp., Armonk, USA). Data were presented as number or median (range) and compared between groups using the chi-square test, Fisher's exact test, or the Wilcoxon test. The primary endpoint was presented as a percentage with 95% CI. The Kaplan-Meier method was used to summarize time-to-event endpoints. This analysis was also performed in patient subgroups according to baseline factors and clinical findings including TKI-WS and compared between groups using the log-rank test. Response to re-treatment after molecular recurrence was assessed by calculating the cumulative rates of regaining $MR^{4.5}$ and the time at which 50% of retreated patients regained $MR^{4.5}$. Analysis of baseline factors as predictors of TFR at 12 months was conducted via univariate or multivariate logistic regression analysis. Variables included age, height, body weight, comorbidity, initial platelet count, initial amount of peripheral blood blast cells, eosinophils or basophils, initial spleen size, Sokal score, Hasford score, European Treatment and Outcome Study score, prior interferon-α (IFN-α) treatment, imatinib duration, time-to-complete cytogenetic response by imatinib, time to MMR by imatinib, time to $MR^{4.5}$, positivity of molecular residual disease before TFR phase, nilotinib total dose, nilotinib treatment duration, nilotinib dose intensity, peripheral blood T/NK cell counts, and NK activity. A stepwise multivariate approach was used to identify the most important prognostic factors with a variable retention criterion of two-sided $P<0.05$.

The data presented herein are based on a cutoff date of 27 March 2018, at which time all patients who entered the TFR phase had either completed ≥36 months of TFR, entered the re-treatment phase, or discontinued the study.

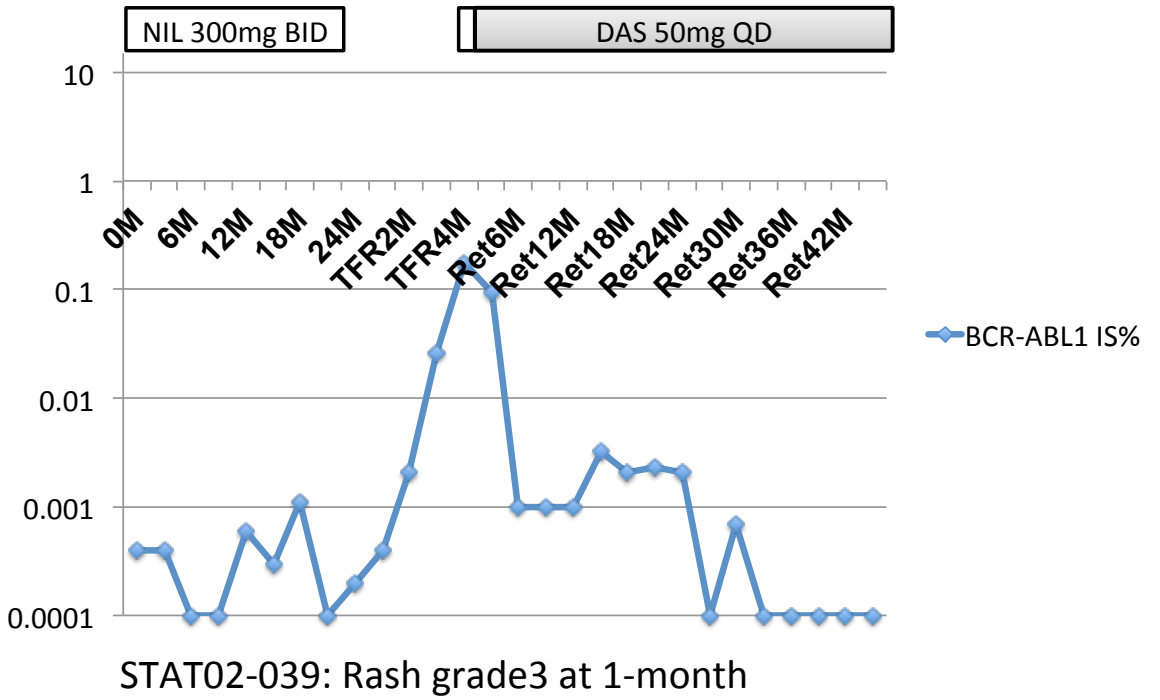
Supplemental figures

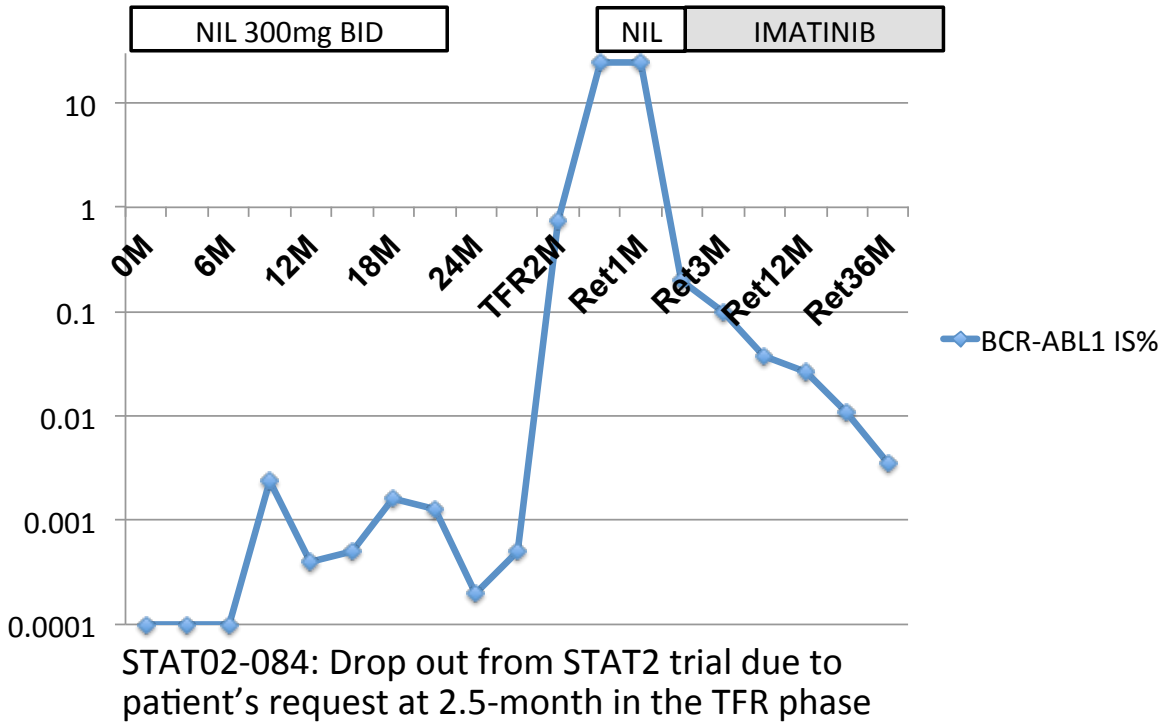


STAT02-075: an increasing IS (%) at 10-month



STAT02-079: an increasing IS (%) at 11-month





Supplemental Figure S1. The clinical course of four patients who discontinued treatment during the re-treatment phase. Y-axis indicates the percentage of *BCR-ABL1*^{IS} transcripts. NIL, nilotinib; BID, twice daily; DAS, dasatinib; QD once per day; TFR, treatment-free remission; Ret, re-treatment.

Table S1. Patients' background between subgroups based on prior TKI therapy (imatinib only and nilotinib following imatinib) before entering the STAT2 study

SAS (n=96)	Imatinib only (n=50)	Nilotinib following imatinib (n=40)	*P*-value
Age (years)	55.5 (25–78)	56.0 (20–83)	0.302
Sex (female)	16 (32.0)	16 (40.0)	0.431
Sokal risk			
Low	28 (58.3)	25 (62.5)	0.169
Intermediate	13 (27.1)	5 (12.5)	
High	7 (14.6)	10 (25.0)	
Prior IFN-α	7 (14.0)	8 (20.0)	0.415
TKI treatment duration (months)	86.0 (27–126)	71.5 (20–131)	0.436
Duration of imatinib (months)	86.0 (27–126)	62.0 (10–125)	0.037
Duration of nilotinib (months)	-	6.5 (0–34)	-
Reasons for switching to nilotinib			
Resistant	-	3 (7.5)	-
Intolerant		8 (20.0)	
Patients' request		29 (72.5)	
Time to MMR (months)	14.4 (4–103)	12.0 (2–95)	0.851
Time to $MR^{4.5}$ (months)	39.0 (8–112)	59.5 (5–127)	0.023

Data given as median (range) or n (%). SAS, safety analysis set; IFN-α, interferon-α; TKI, tyrosine kinase inhibitor; MMR, major molecular response; $MR^{4.5}$, 4.5-log reduction of *BCR-ABL1* transcripts by IS-PCR.

Table S2. Adverse events in the STAT2 trial

	Consolidation phase SAS (n=96)		TFR phase FAS (n=78)	
	All grades	Grade 3/4	All grades	Grade 3/4
Hematologic				
Anemia	25 (26.0)	0 (0)	4 (5.1)	0 (0)
Thrombocytopenia	3 (3.1)	0 (0)	0 (0)	0 (0)
Neutropenia	0 (0)	0 (0)	1 (1.3)	0 (0)
Non-Hematologic				
Headache	3 (3.1)	0 (0)	0 (0)	0 (0)
Rash	21 (21.9)	1 (1.0)	4 (5.1)	0 (0)
Nausea	6 (6.3)	0 (0)	1 (1.3)	0 (0)
Vomiting	4 (4.2)	1 (1.0)	0 (0)	0 (0)
Constipation	1 (1.0)	0 (0)	1 (1.3)	0 (0)
Fatigue	19 (19.8)	1 (1.0)	4 (5.1)	0 (0)
Myalgia	6 (6.3)	0 (0)	2 (2.6)	0 (0)
Arthralgia	0 (0)	0 (0)	8 (10.2)	0 (0)
Withdrawal syndrome	-	-	11 (14.1)	1 (1.3)
Total bilirubin elevated	34 (35.4)	1 (1.0)	1 (1.3)	0 (0)
AST elevated	20 (20.8)	2 (2.1)	5 (6.5)	0 (0)
ALT elevated	27 (28.1)	2 (2.1)	6 (7.7)	0 (0)
Total cholesterol elevated	3 (3.1)	0 (0)	2 (2.6)	0 (0)
Lipase elevated	2 (2.1)	1 (1.0)	0 (0)	0 (0)
Hyperglycemia	5 (5.2)	2 (2.1)	1 (1.3)	0 (0)
Creatinine increased	6 (6.3)	0 (0)	3 (3.8)	0 (0)
Body weight gain	3 (3.1)	0 (0)	3 (3.8)	0 (0)
Peripheral edema	6 (6.3)	0 (0)	1 (1.3)	0 (0)
Pleural effusion	3 (3.1)	0 (0)	0 (0)	0 (0)
Pericardial effusion	3 (3.1)	1 (1.0)	0 (0)	0 (0)
Hypertension	1 (1.0)	1 (1.0)	1 (1.3)	0 (0)
Vascular adverse events				
Ischemic heart disease	3 (3.1)	3 (3.1)	0 (0)	0 (0)
Cerebral infarction	3 (3.1)	0 (0)	0 (0)	0 (0)
Peripheral arterial occlusive disease	0 (0)	0 (0)	0 (0)	0 (0)
Total	55 (57.3)	14 (14.6)	30 (38.7)	2 (2.6)

Data given as n (%). SAS, safety analysis set; FAS, full analysis set; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TFR, treatment-free remission.