Supplementary material for Chuah CT, et al. Efficacy and safety of dasatinib versus imatinib in the East Asian subpopulation of the DASISION trial of newly diagnosed chronic myeloid leukemia in chronic phase. Leuk Lymphoma 2014;55:2093–2100.

Supplementary methods

Includes a more detailed description of DASISION study design and procedures, efficacy assessments and mutation analyses.

Supplementary results

Includes data showing similarities in East Asian versus non-East Asian patients, including baseline characteristics, treatment parameters, cytogenetic and molecular response, progression to AP/BP, PFS, OS, mutational analyses and rates of non-hematologic AEs.

Supplementary Methods

Study Design and Patients

As described previously [1], the DASISION trial included adults with Philadelphia chromosome-positive (Ph+) CML-CP diagnosed within 3 months who had received no previous treatment for CML (excluding anagrelide or hydroxyurea) and had adequate hepatic and renal function were eligible. Key exclusion criteria included serious, uncontrolled medical disorders or active infections, uncontrolled or serious cardiovascular conditions, corrected QT interval >450 msec, history of bleeding disorders unrelated to CML, previous or concurrent cancer, previous chemotherapy for peripheral stem cell mobilization, and baseline pleural effusion.

Patients were stratified according to Hasford risk score and randomly assigned (1:1) to receive oral dasatinib 100 mg QD (with or without food) or imatinib 400 mg QD (with food). Treatment was discontinued due to protocol-defined disease progression, unacceptable toxicity, patient/investigator decision, or pregnancy. In both arms, treatment interruptions or dose reductions were permitted for managing AEs and dose escalations were permitted for patients with a suboptimal response according to the ELN 2006 definition [2].

Efficacy Assessments

CCyR was defined as the absence of Ph+ metaphases as determined by G-banding in ≥ 20 cells in metaphase per bone marrow sample. Molecular responses were assessed by quantitative reverse-transcriptase polymerase chain reaction (PCR) assay and converted to the International Scale (IS). MMR was defined as a BCR-ABL1 transcript level in peripheral blood of IS $\leq 0.1\%$, (i.e., ≥ 3-log reduction in BCR-ABL1 transcript level from the standardized baseline). The most sensitive measure of BCR-ABL1 available in the trial was reduction to a level of IS $\leq 0.0032\%$ (i.e., ≥ 4.5-log reduction in BCR-ABL1 transcript level from the standardized baseline—sometimes termed complete molecular response). Progression was defined in the DASISION trial as doubling of white blood cell count to more than 20×10^9 per liter in the absence of complete hematologic response (CHR), loss of CHR, increase in Ph+ bone marrow metaphases to more than 35%, transformation to AP/BP CML, or death from any cause. Definition of PFS in the DASISION trial is similar to definition of event-free survival in the IRIS trial [3].

BCR-ABL1 Mutational Analysis

As previously described, BCR-ABL1 mutational analysis by direct sequencing was required following discontinuation of study therapy for any reason (samples obtained within 45 days before or after discontinuation were tested). Molecular and mutational assessments were performed at a centralized laboratory (MolecularMD, Portland, OR) [4].

References

[1] Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010; 362:2260–2270.

[2] Baccarani M, Saglio G, Goldman J, et al. European LeukemiaNet: Evolving concepts in the management of chronic myeloid leukemia. Recommendations from an expert panel on behalf of the European Leukemia Net. Blood 2006; 108:1809–1820.

[3] Druker BJ, Guilhot F, O'Brien SG, et al; and the IRIS Investigators. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006; 355:2408–2417.

[4] Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood 2012, 119;1123–1129

Supplementary Results

Treatment

Median duration of treatment with dasatinib and imatinib was 24.8 and 24.9 months for East Asian patients and 25.7 and 24.7 months for non-East Asian patients, respectively. Median doses administered to the East Asian and non-East Asian cohorts were 98.0 mg/day and 100.0 mg/day of dasatinib and 398.5 mg/day and 400.0 mg/day of imatinib.

Efficacy

Rates of CCyR and MMR were higher with dasatinib compared with imatinib at each time point assessed (Figures 1A and B) for East Asian and non-East Asian patients. By 24 months, the rate of BCR-ABL1 transcript reduction to $\leq 0.0032\%$ ($MR^{4.5}$) was higher for dasatinib compared with imatinib for each subpopulation (Figure 1C).

In an analysis of BCR-ABL1 kinetics in the East Asian subpopulation, a more rapid decline of BCR-ABL1 transcript levels was observed in the dasatinib versus imatinib arm (Figures 1D and E). Median BCR-ABL1 ratios, expressed as percent on the IS, for patients receiving dasatinib or imatinib at 12 months was 0.1% vs. 0.3%, and this decreased to 0.04% vs. 0.06% at 24 months, respectively. At 3 months a greater proportion of patients receiving dasatinib had achieved BCR-ABL1 transcript levels of $\leq 10\%$ compared with patients receiving imatinib.

Median time to CCyR was shorter with dasatinib versus imatinib among East Asian patients (3.1 vs. 5.6 months) and non-East Asian patients (3.7 vs. 6.1 months). Among East Asian patients, irrespective of response, median time to MMR was shorter for dasatinib (11.8 months), compared with imatinib (28.2 months). For non-East Asian patients, the median time to MMR was 16.7 months for dasatinib and has not yet been reached for imatinib.

In the East Asian subpopulation four patients (3.7%) transformed to AP/BP CML on study and during follow-up after discontinuation (three receiving dasatinib and one receiving imatinib). None of the four patients achieved MMR. One patient had a high Hasford risk score (dasatinib arm) and three patients had intermediate scores. Among non-East Asian patients, 20 (4.9%) transformed to AP/BP CML on study and during follow-up after discontinuation (6 receiving dasatinib and 14 receiving imatinib). At 24 months for East Asian patients receiving dasatinib versus imatinib, rates of PFS were 98.2% vs. 97.9%, and rates of OS were 98.3% vs. 97.9%, respectively. For non-East Asian patients receiving dasatinib versus imatinib, 24-month PFS rates were 92.4% vs. 90.8% and OS rates were 94.4% vs. 94.6%, respectively.

BCR-ABL1 Mutational Analyses

Overall in DASISION, 59 (23%) and 64 (25%) patients discontinued dasatinib and imatinib treatment, respectively, by 24 months. Of patients who discontinued study therapy, 44/59 subjects in the dasatinib arm and 49/64 subjects in the imatinib arm had a BCR-ABL1 mutation assay performed. BCR-ABL1 mutations were detected in 10 dasatinib patients and in 10 imatinib patients. For all patients who had mutations identified, the reason for discontinuation was treatment failure or disease progression. Three patients with BCR-ABL1 mutations were East Asian, two receiving dasatinib and one receiving imatinib.

All three of the East Asian patients with mutations achieved CHR, as did most of the non-East Asian patients with mutations (15/17). In each arm 4/10 patients with mutations had no cytogenetic response and 4/10 had at least a partial cytogenetic response (PCyR). Of the three East Asian patients with mutations, one each had CCyR (dasatinib), PCyR (dasatinib), and no CyR (imatinib). The two patients receiving dasatinib discontinued treatment following protocol-defined progression and the patient receiving imatinib discontinued treatment following treatment failure. Of the 17 non-East Asian patients with BCR-ABL1 mutations reported, reasons for discontinuation were similar: protocol-defined progression (6 and 7 for dasatinib and imatinib, respectively); treatment failure (1 and 2); and loss of CCyR (not defined as progression or failure, 1 and 0).

Safety

Of nonhematologic AEs occurring in $\geq 10\%$ of patients, overall fluid retention, superficial edema, rash, gastrointestinal AEs (nausea, vomiting, and diarrhea), fatigue, and myalgia (includes myalgia, muscle spasms, and musculoskeletal pain) in East Asian patients showed a trend for higher rates with imatinib, whereas pleural effusion and headache were more common with dasatinib (Supplementary Table III and Figure 2). Among non-East Asian patients, similar trends for nonhematologic AEs were observed, except for diarrhea and headache, where incidence was similar for dasatinib- and imatinib-treated patients.

At 24 months, for both East Asian and non-East Asian subpopulations, AE rates showing the greatest differences between treatment arms were fluid-related (all grades) (Supplementary Table III). In the East Asian subpopulation, overall fluid retention occurred at higher rates in patients receiving imatinib compared with dasatinib (64.6% vs. 39.0%), with superficial edema in 35.4% vs. 16.9%, respectively. Pleural effusion only occurred in dasatinib-treated patients (23.7%). In the East Asian subpopulation, pleural effusion events were grade 1 in 5.1% and grade 2 in 18.6% of patients In the non-East Asian population, pleural effusion events were grade 1 in 3% and grade 2 in 6.5% of patients.

For nonhematologic AEs occurring in $\geq 10\%$ of patients, increments in AE rates between 12 and 24 months were similar for East Asian and non-East Asian patients. The majority of increments were $< 5\%$, indicating that most AEs occur during the first 12 months (Figure 2). A larger sample size would be required to detect differences between the two populations.

Supplementary Table I. Clinical studies used in population pharmacokinetic model.

Study	Population	Design	Dasatinib dosing regimen(s)	Na	PK sampling scheduleb
CA180002 (NCT00064233)	CML (-CP, -AP, -BP), or Ph+ ALL resistant to imatinib	Phase 1, open-label, multicenter, dose-escalation study	15, 30, 50, 75, 105, 140, and 180 mg once daily (5 days on, 2 days off weekly dosing), 25, 35, 50, 70, 90, and 120 mg twice daily (5 days on, 2 days off weekly or continuous dosing)	83	Once daily (5 days on, 2 days off weekly dosing) Cycle 1, days 1, 5, and 26: pre-dose; 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 24 h (all days); 48 and 72 h (days 5 and 26 only) Twice daily (5 days on, 2 days off weekly dosing) Cycle 1, days 1, 5, and 26: predose; 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h (all days); 5 h (days 1 and 5 only); 24, 48, and 72 h (days 5 and 26 only) Twice daily (continuous daily dosing) Cycle 1, days 1 and 5, and Cycle 2, day 1: predose; 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h (all days); 5 h (Cycle 1, day 1 only); 24, 48, and 72 h (Cycle 1, day 8, and Cycle 2, day 1 only)
CA180005 (START-A; NCT00101647)	CML-AP resistant/intolerant to imatinib	Phase 2, open-label, multicenter study	70 mg twice daily	41	First 15 treated patients Cycle 1, days 1 and 8: predose; 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 h All subsequently treated patients Cycle 1, day 8: predose; between 0.5 and 3 h
CA180006 (START-B; NCT00101816)	CML-BP (myeloid) resistant/ intolerant to imatinib	Phase 2, open-label, multicenter study	70 mg twice daily	29	First 15 treated patients Cycle 1, days 1 and 8: predose; 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 h All subsequently treated patients Cycle 1, day 8: predose; between 0.5 and 3 h
CA180013 (START-C; NCT00101660)	CML-CP resistant/intolerant to imatinib	Phase 2, open-label, multicenter study	70 mg twice daily	144	Cycle 1, day 8: predose; between 0.5 h and 3 h; between 5 and 8 h; between 12 h and the next dose
CA180015 (START-L; NCT00101595)	CML-BP (lymphoid) or Ph+ ALL resistant/intolerant to imatinib	Phase 2, open-label, multicenter study	70 mg twice daily	39	Cycle 1, day 8: predose; between 0.5 and 3 h
CA180017 (START-R; NCT00103844)	CML-CP resistant to imatinib	Phase 2, open-label, randomized, multicenter study	70 mg twice daily	78	Cycle 1, day 8: predose; between 0.5 and 3 h; between 5 and 8 h; between 12 h and the next dose
CA180034 (NCT00123474)	CML-CP resistant/intolerant to imatinib	Phase 3, open-label, randomized two-by-two, multicenter, dose optimization study	100 or 140 mg once daily, or 50 or 70 mg twice daily	567	Day 15: predose; between 1 and 3 h; between 5 and 8 h Day 29: predose
CA180056 (DASISION; NCT00481247)	Newly-diagnosed CML-CP	Phase 3, open-label, randomized, multicenter study	100 mg once daily	235	Day 1: 0.5, 6, and 8 h Day 15: predose; 2 and 6 h Day 29: predose; 0.5 and 2 h

[a]Patients with PK samples included in the analysis.
[b]Nominal time from previous dasatinib dose.
ALL, acute lymphoblastic leukemia; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase; Ph+; Philadelphia chromosome-positive; PK, pharmacokinetic.

Supplementary Table II. Demographic and baseline disease characteristics of East Asian and non-East Asian subpopulations.

	East Asian patients ($n = 108$)		Non-East Asian patients ($n = 411$)	
	Dasatinib ($n = 60$)	Imatinib ($n = 48$)	Dasatinib ($n = 199$)	Imatinib ($n = 212$)
Age, years				
Median (range)	50.0 (21.0–80.0)	45.5 (18.0–77.0)	45.0 (18.0–84.0)	49 (19.0–78.0)
Sex, *n* (%)				
Female	25 (41.7)	18 (37.5)	90 (45.2)	79 (37.3)
Male	35 (58.3)	30 (62.5)	109 (54.8)	133 (62.7)
ECOG performance status, *n* (%)				
0	50 (83.3)	37 (77.1)	163 (81.9)	168 (79.2)
1	10 (16.7)	11 (22.9)	36 (18.1)	42 (19.8)
2	0	0	0	2 (0.9)
Hasford risk score, *n* (%)				
Low	23 (38.3)	25 (52.1)	63 (31.7)	62 (29.2)
Intermediate	32 (53.3)	20 (41.7)	92 (46.2)	103 (48.6)
High	5 (8.3)	3 (6.3)	44 (22.1)	47 (22.2)
Body weight, kg				
Median (range)	62.0 (43.0–93.0)	62.8 (44.0–107.0)	67.0 (40.0–146.0)	67.6 (38.0–113.7)
Body surface area, m^2				
Median (range)	1.7 (1.3–2.1)	1.7 (1.4–2.3)	1.8 (1.3–2.8)	1.8 (1.2–2.4)
Time from diagnosis to randomization, mo				
Median (range)	1.1 (0.16–3.61)	1.1 (0.23–3.29)	1.0 (0.03–9.72)	1.0 (0.10–8.02)
White cell count, $\times 10^9$/L				
Median (range)	16.3 (2.5–239.6)	20.4 (2.8–219.5)	32.5 (2.7–493.0)	24.3 (1.4–475.0)
Platelet count, $\times 10^9$/L				
Median (range)	438.0 (103.0–1880.0)	432.0 (100.0–1896.0)	450.0 (58.0–1800.0)	381.0 (29.0–2930.0)
Peripheral blood blasts, %				
Median (range)	0.0 (0.0–9.0)	0.0 (0.0–6.0)	1.0 (0.0–10.0)	1.0 (0.0–11.0)
Bone marrow blasts, %				
Median (range)	1.5 (0.0–8.0)	2.0 (0.0–8.0)	2.0 (0.0–14.0)	2.0 (0.0–12.0)
Previous therapy for CML, *n* (%)				
Hydroxyurea	38 (63.3)	34 (70.8)	151 (75.9)	156 (73.6)
Anagrelide	4 (6.7)	1 (2.1)	4 (2.0)	2 (0.9)

Supplementary Table III. Drug-related adverse events and biochemical abnormalities occurring by 24 months.

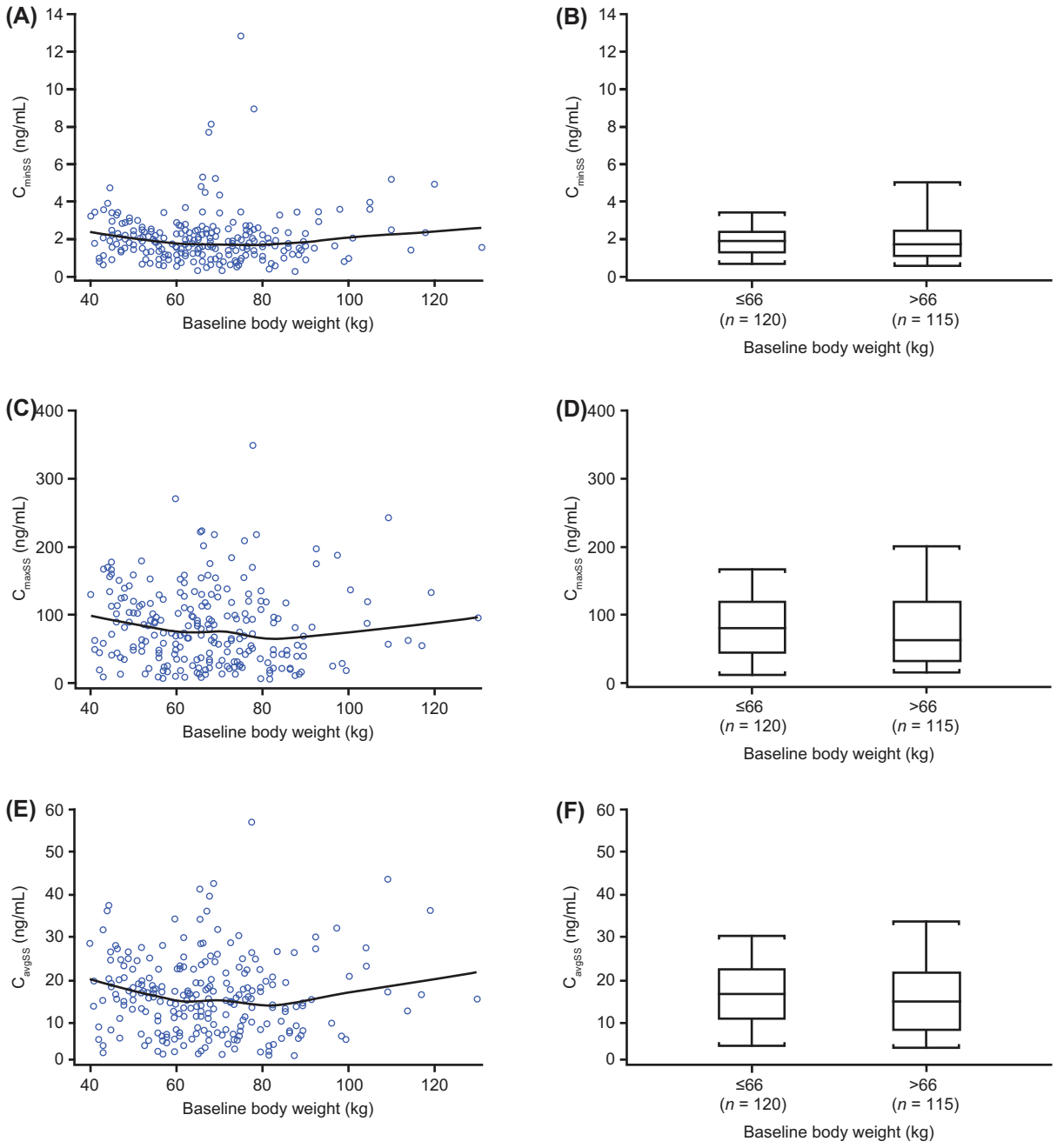
	East Asian patients ($n = 107$)				Non-East Asian patients ($n = 409$)			
	Dasatinib ($n = 59$)		Imatinib ($n = 48$)		Dasatinib ($n = 199$)		Imatinib ($n = 210$)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Nonhematologic[a], *n* (%)								
Fluid retention[b]	23 (39.0)	1 (1.7)	31 (64.6)	0	36 (18.1)	1 (0.5)	79 (37.6)	2 (1.0)
Superficial edema	10 (16.9)	0	17 (35.4)	0	17 (8.5)	0	74 (35.2)	1 (0.5)
Pleural effusion	14 (23.7)	0	0	0	19 (9.5)	0	0	0
Rash	14 (23.7)	0	18 (37.5)	0	14 (7.0)	0	24 (11.4)	3 (1.4)
Diarrhea	10 (16.9)	0	9 (18.8)	2 (4.2)	39 (19.6)	1 (0.5)	41 (19.5)	0
Nausea	7 (11.9)	0	15 (31.3)	0	19 (9.5)	0	42 (20.0)	0
Vomiting	1 (1.7)	0	3 (6.3)	0	11 (5.5)	0	23 (11.0)	0
Headache	9 (15.3)	0	0	0	24 (12.1)	0	28 (13.3)	0
Fatigue	7 (11.9)	0	7 (14.6)	0	14 (7.0)	1 (0.5)	20 (9.5)	0
Myalgia[c]	12 (20.3)	0	21 (43.8)	0	40 (20.1)	0	77 (36.7)	2 (1.0)
	Grade 3/4		Grade 3/4		Grade 3/4		Grade 3/4	
Hematologic, *n* (%)								
Neutropenia	21 (35.6)		19 (39.6)		39 (19.6)		34 (16.2)	
Thrombocytopenia	17 (28.8)		7 (14.6)		33 (16.6)		22 (10.5)	
Anemia	7 (11.9)		4 (8.3)		21 (10.6)		15 (7.1)	
Biochemical abnormalities, *n* (%)								
Elevated total bilirubin	0		0		3 (1.5)		0	
Elevated ALT	0		0		1 (0.5)		3 (1.4)	
Elevated AST	0		0		1 (0.5)		2 (1.0)	
Elevated creatinine	0		0		1 (0.5)		2 (1.0)	
Elevated uric acid	0		0		4 (2.0)		2 (1.0)	
Elevated alkaline phosphatase	0		0		1 (0.5)		0	
Decreased phosphate	8 (13.6)		12 (25.0)		7 (3.5)		50 (23.8)	
Decreased potassium	0		2 (4.2)		0		4 (1.9)	
Decreased calcium	6 (10.2)		1 (2.1)		2 (1.0)		4 (1.9)	
Decreased sodium	0		0		2 (1.0)		2 (1.0)	
Decreased magnesium	0		0		1 (0.5)		2 (1.0)	

[a]Occurring in ≥ 10% of patients.
[b]Includes superficial edema, pleural effusion, and other fluid-related AEs (congestive heart failure/cardiac dysfunction, generalized edema, pericardial effusion, pulmonary edema, pulmonary hypertension).
[c]Includes myalgia, muscle spasms and musculoskeletal pain.
ALT, alanine transaminase; AST, aspartate aminotransferase.

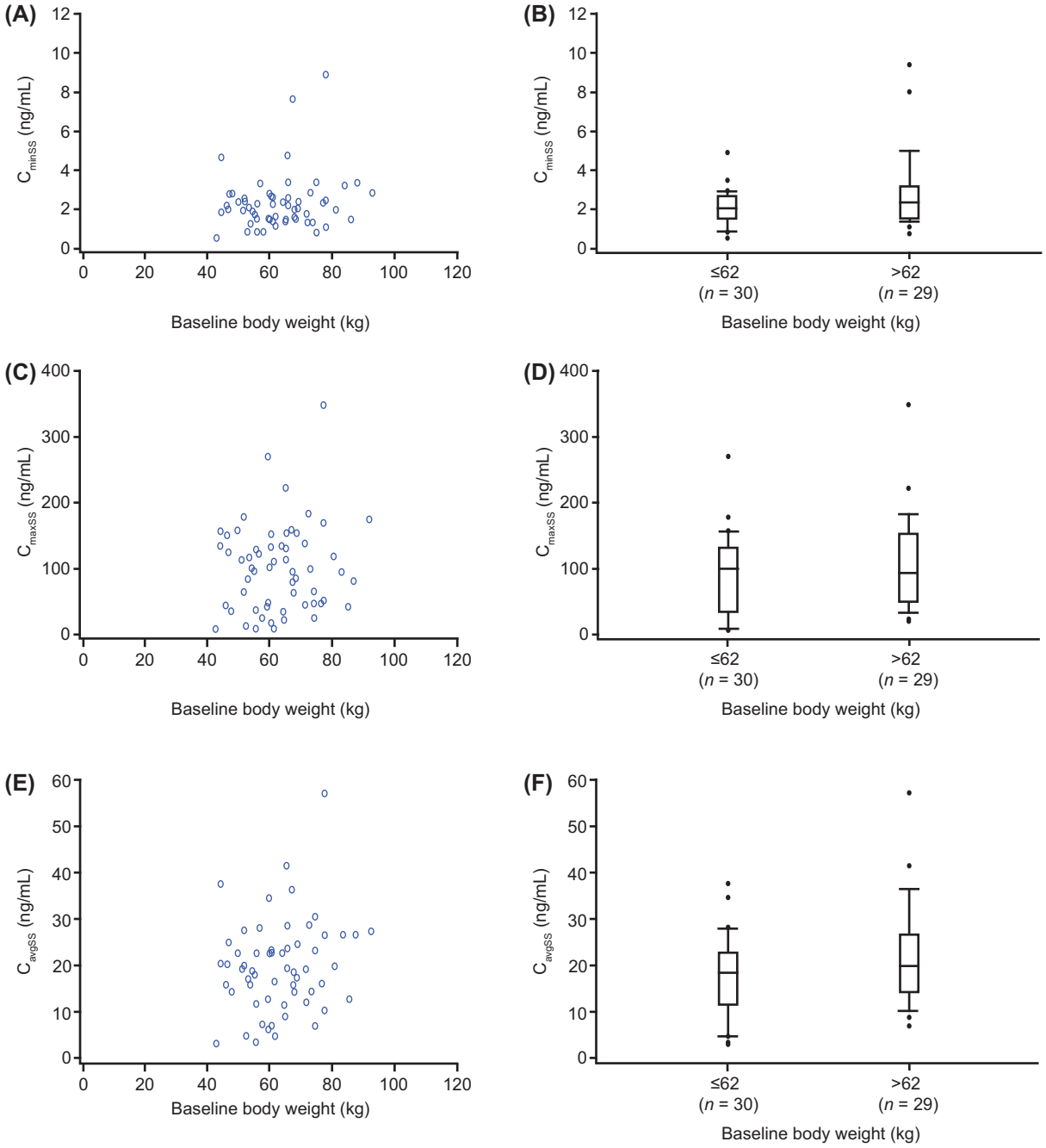
Supplementary Table IV. Summary of dasatinib pharmacokinetics parameters in East Asian and non-East Asian patients.

Dasatinib-treated patients	C_{maxSS}, ng/mL geometric mean (CV %)	C_{minSS}, ng/mL geometric mean (CV %)	AUC_{SS}, ng.h/mL geometric mean (CV %)	$T_{1/2}$, h Mean
East Asian ($n = 59$)	76.9 (65.7)	2.11 (77.9)	411 (50.2)	6.07
Non-East Asian ($n = 176$)	57.4 (68.5)	1.54 (60.4)	313 (54.7)	5.96

AUC, area under the curve; C_{max}, maximum plasma concentration; C_{minSS}, trough plasma concentration; CV, 50% coefficient of variation; $T_{1/2}$, plasma elimination half-life.



Supplementary Figure 1. Dasatinib exposure as a function of body weight for East Asian and non-East Asian patients. Steady-state exposure and body weight are plotted for each subject (blue dots), along with locally smoothed line to show trend (A, C and E). For subjects grouped by body weight (≤ 66 kg, > 66 kg), B, D and F show distributions of dasatinib steady-state exposure: median (horizontal line), interquartile range (25th–75th percentiles, box) and 9th and 95th percentiles (whiskers). Results are shown for three measures of exposure, C_{minSS} (A and B), C_{maxSS} (C and D) and C_{avgSS} (E and F).



Supplementary Figure 2. Dasatinib exposure as a function of body weight for East Asian patients. Steady-state exposure and body weight are plotted for each subject (blue dots in A, C and E). For subjects grouped by body weight (≤ 62 kg, > 62 kg), B, D and F show distributions of dasatinib steady-state exposure: median (horizontal line), interquartile range (25th–75th percentiles, box) and 9th and 95th percentiles (whiskers). Results are shown for three measures of exposure, C_{minSS} (A and B), C_{maxSS} (C and D) and C_{avgSS} (E and F).