Bosutinib *versus* imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial

Tim H. Brümmendorf,[1,2] Jorge E. Cortes,[3] Cármino Antonio de Souza,[4] Francois Guilhot,[5] Ladan Duvillié,[6] Dmitri Pavlov,[7] Karïn Gogat,[6] Athena M. Countouriotis[8] and Carlo Gambacorti-Passerini[9]

[1]Universitätsklinikum Aachen, RWTH Aachen, Aachen, [2]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]University of Campinas, Campinas, SP, Brazil, [5]Inserm CIC 1402, CHU de Poitiers, Poitiers, [6]Pfizer Global Research and Development, Paris, France, [7]Pfizer, New York, NY, [8]Pfizer, La Jolla, CA, USA and [9]University of Milano-Bicocca, Monza, Italy

Summary

Bosutinib is an oral, dual SRC/ABL1 tyrosine kinase inhibitor for resistant/intolerant chronic myeloid leukaemia (CML). We assessed the efficacy and safety of bosutinib 500 mg/d ($n = 250$) *versus* imatinib 400 mg/d ($n = 252$) after >24 months from accrual completion in newly diagnosed chronic phase (CP)-CML (Bosutinib Efficacy and Safety in Newly Diagnosed CML trial [BELA]). Cumulative complete cytogenetic response (CCyR) rates by 24 months were similar (bosutinib, 79%; imatinib, 80%); cumulative major molecular response (MMR) rates were 59% for bosutinib and 49% for imatinib. Responses were durable; 151/197 vs. 172/204 and 125/153 vs. 117/131 responders remained on treatment and maintained CCyR and MMR, respectively. Since the 12-month primary analysis, no new accelerated-/blast-phase transformations occurred with bosutinib; four occurred with imatinib. Early response (*BCR-ABL1/ABL1* ≤ 10%, 3 months) was associated with better CCyR and MMR rates by 12 and 24 months (both arms). Gastrointestinal events and liver function test elevations were more common, and neutropenia, musculoskeletal events and oedema were less common with bosutinib. Discontinuations due to adverse events were more common with bosutinib *versus* imatinib (most commonly alanine aminotransferase elevation: 4% vs. <1%); most occurred within the first 12 months. Cardiovascular adverse events were similar in both arms. Bosutinib continues to demonstrate good efficacy and manageable tolerability in newly diagnosed CP-CML patients.

Keywords: bosutinib, tyrosine kinase inhibitor, chronic myeloid leukaemia, CML, BCR-ABL1.

Chronic myeloid leukaemia (CML) is characterized by a constitutively active BCR-ABL1 fusion protein produced by the Philadelphia chromosome (Ph) translocation (National Comprehensive Cancer Network®). Imatinib, a BCR-ABL1 tyrosine kinase inhibitor (TKI), is currently indicated as first-line treatment for Ph+ chronic-phase (CP)–CML (Druker *et al*, 2006; http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf; Hochhaus *et al*, 2009; O'Brien *et al*, 2003). However, the resistance or intolerance observed with imatinib (Deininger *et al*, 2003; Weisberg *et al*, 2007; Ramirez & DiPersio, 2008) prompted development of the second-generation TKIs, dasatinib and nilotinib, which have demonstrated efficacy in imatinib-resistant/intolerant (Kantarjian *et al*, 2006, 2009, 2011a; Hochhaus *et al*, 2008; Shah *et al*, 2008)

and newly diagnosed (Rosti *et al*, 2009; Cortes *et al*, 2010a,b; Kantarjian *et al*, 2011b, 2012) CP-CML patients.

Bosutinib (Bosulif®, Pfizer Labs, New York, NY, USA), an orally active, dual SRC/ABL1 TKI, has demonstrated more potent inhibitory activity against BCR-ABL1 than imatinib *in vitro* (Golas *et al*, 2003; Puttini *et al*, 2006) and minimal inhibitory activity against KIT and platelet-derived growth factor receptor (PDGFR) (Puttini *et al*, 2006; Remsing Rix *et al*, 2009), which are potentially associated with some toxicities reported for other BCR-ABL1 TKIs (Bartolovic *et al*, 2004; Puttini *et al*, 2006; Konig *et al*, 2008; Remsing Rix *et al*, 2009). In a phase 1/2 study, bosutinib demonstrated clinical activity and acceptable tolerability in patients with Ph+ CP, accelerated-phase (AP) and blast-phase (BP) CML

previously receiving imatinib only or imatinib plus dasatinib and/or nilotinib (Gambacorti-Passerini et al, 2010; Cortes et al, 2011; Khoury et al, 2012). Bosutinib is indicated for patients with Ph+ CML that is resistant or intolerant to prior therapy (http://labeling.pfizer.com/ShowLabeling.aspx?id=884).

The ongoing phase 3 Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial is comparing the efficacy and safety of bosutinib with imatinib in newly diagnosed CP CML (Cortes et al, 2012). At 12 months, bosutinib did not demonstrate a superior rate of complete cytogenetic response (CCyR; 70%) versus imatinib (68%; $P = 0.601$) (primary endpoint) but had a superior rate of major molecular response (MMR; 41%) versus imatinib (27%; $P < 0.001$), a key secondary endpoint. Bosutinib also demonstrated shorter median times to CCyR (12·9 vs. 24·6 weeks with imatinib) and MMR (37·1 vs. 72·3 weeks), a lower estimated probability of disease progression/lack of efficacy (3% vs. 10%) and lower estimated probability of on-treatment transformations to AP/BP CML (2% vs. 4%) at 12 months. The distinct safety profile of bosutinib was characterized by higher rates of gastrointestinal and liver-related events (primarily grade 1/2) but less frequent neutropenia, musculoskeletal events, and oedema. Treatment continues in this trial; long-term evaluation allows further assessment of the anticancer activity and tolerability of bosutinib in newly diagnosed CP-CML patients. The current analysis reports results from BELA up to a minimum of 2 years after completion of accrual.

Patients and methods

Patient eligibility

Eligibility criteria were previously described (Cortes et al, 2012) (see Table SI). Briefly, eligible patients (aged ≥18 years) had a cytogenetic diagnosis of Ph+ CP CML within 6 months of enrollment, an Eastern Cooperative Oncology Group performance status score of 0 or 1, adequate hepatic and renal function, and no prior antileukaemia treatment except ≤6 months of anagrelide or hydroxycarbamide.

Study design and treatment

Patients in the ongoing open-label, randomized, multinational phase 3 BELA trial (ClinicalTrials.gov Identifier: NCT00574873) were randomized 1:1 to bosutinib 500 mg/d or imatinib 400 mg/d and stratified by Sokal risk group and geographic region. Dose escalation to bosutinib 600 mg/d or imatinib 600 mg/d was permitted upon failure to achieve optimal response (2009 European LeukemiaNet criteria) (Baccarani et al, 2009) if no grade 3/4 or persistent grade 2 drug-related toxicity occurred. Treatment was discontinued if disease progression occurred.

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by an institutional review board at each study site before patient enrollment. Patients provided written informed consent before protocol procedures were performed.

Efficacy and safety assessments

The primary efficacy endpoint was CCyR at 12 months (Cortes et al, 2012). Secondary endpoints included MMR at 12 months, duration of CCyR, MMR and complete haematological response (CHR) and time to on-treatment transformation to AP/BP CML. Key longer-term and exploratory planned analyses included response by Sokal risk group; and comparisons by arm of rate and type of mutation, time to response, event-free survival (EFS) and overall survival (OS). Safety was assessed on an ongoing basis from time of consent (Cortes et al, 2012).

Cytogenetic assessments were conducted using bone marrow aspirates collected every 3 months during year 1 and every 6 months during year 2 of study treatment (Cortes et al, 2012). Molecular assessments were based on quantitative reverse transcriptase polymerase chain reaction for BCR-ABL1 in peripheral blood and conducted every 3 months during the first 2 years of study treatment. For assessment of MMR [transcript levels of BCR-ABL1 ≤ 0·1% on the International Scale (IS)], ≥3000 control genes (ABL1) were required; molecular response (MR) with a ≥ 4-log reduction in BCR-ABL1 IS (MR4; i.e., ≤0·01%) required ≥8100 control genes.

Progression to AP/BP CML was defined as meeting ≥1 criterion for either AP [15%–29% blasts, <15% blasts with ≥30% blasts + promyelocytes, ≥20% basophils (blood or bone marrow) or platelet counts <100 × 10^9/l (blood), unless related to therapy] or BP (≥30% blasts in blood, bone marrow, or extramedullary involvement other than liver or spleen). EFS was calculated from time of randomization to first on-treatment EFS event, including death from any cause, transformation to AP/BP CML, increased white blood cell count (WBC; doubling of WBC after ≥1 month with the second WBC >20 × 10^9/l and maintained for ≥2 weeks) without CHR, loss of CHR or loss of CCyR. Patients were censored at their last assessment if no EFS event occurred. OS was calculated from time of randomization until death from any cause or date of last follow-up contact.

Statistical analyses

The BELA trial had ≥90% power to detect a difference of 0·15 in CCyR rates at 1 year (improvement from 0·65 in the imatinib arm to 0·80 in the bosutinib arm) at the 0·025 one-sided significance level (P value <0·025, 1-sided) (Cortes et al, 2012). Strong control of the family-wide error rate was achieved by allowing analysis of the primary endpoint to serve as a gatekeeper for additional statistical testing. Because the study failed to achieve its primary objective, all presented

results are considered exploratory and descriptive. Response rates and associated 95% confidence intervals (CIs) were calculated for each treatment; statistical analysis was based on either a Cochran-Mantel-Haenszel (CMH) test (2-sided *P* value) or Fisher exact test (2-sided *P* value) with stratification by Sokal risk group (low, <0·8; intermediate, 0·8–1·2; high, >1·2) and geographic region. For time-to-event endpoints, distributions and medians were estimated using the Kaplan–Meier method or cumulative incidence in the competing risk setting (i.e., treatment failure and discontinuation of treatment without failure) as appropriate; associated 95% CIs for medians were obtained using Brookmeyer-Crowley methodology. Hazard ratios were estimated using a Cox proportional hazards model stratified by Sokal risk group and geographic region. A retrospective, exploratory landmark analysis was performed to evaluate long-term outcomes in patients with a *BCR-ABL1/ABL1* ratio ≤10% vs. >10% at 3 months using a cumulative rate of CCyR or MMR by 12 or 24 months or Kaplan–Meier method for EFS and OS. The findings from these retrospective analyses should be interpreted in the context of false-positive rate due to uncontrolled multiple comparisons done repeatedly over time and should be viewed as hypothesis-generating.

Efficacy analyses were performed on all randomized patients; for response analyses, patients who had missing data or discontinued before treatment response or failure were considered nonresponders. Safety analyses were performed on the safety population (all patients who received ≥1 dose of study drug).

Results

Patients and treatment

A total of 502 patients at 139 centres in 31 countries were randomized to bosutinib (*n* = 250) or imatinib (*n* = 252) between February 2008 and July 2009; 248 and 251 patients, respectively, received treatment (Cortes *et al*, 2012). Baseline characteristics were balanced across treatment arms [median age, 47–48 years (11%–12% of patients aged ≥65 years); 18% of patients in the high-risk Sokal category; Table I].

The duration from end of patient accrual to time of analysis (26 September, 2011) was >24 months. Median (range) duration of bosutinib and imatinib treatment at the time of this analysis was 27·5 (0·03–41·3) and 27·5 (0·5–38·8) months. Treatment dose was escalated to 600 mg/d because of lack of efficacy for 15 (6%) bosutinib-treated and 46 (18%) imatinib-treated patients.

At the time of analysis, 156/248 (63%) bosutinib-treated and 179/251 (71%) imatinib-treated patients were still receiving treatment. Reasons for discontinuation among bosutinib and imatinib patients, respectively, included adverse events (AEs, 24%; 7%), disease progression/lack of efficacy (4%; 13%), subject/investigator request (4%; 6%), death (1%; <1%), protocol violation (0%; 1%), failure to return (<1%;

Table I. Patient demographics and baseline disease characteristics.

Characteristic	Bosutinib (*n* = 250)	Imatinib (*n* = 252)
Median age (range), years	48 (19–91)	47 (18–89)
<65 years, *n* (%)	220 (88)	225 (89)
≥65 years, *n* (%)	30 (12)	27 (11)
Sex, male, *n* (%)	149 (60)	135 (54)
Race, *n* (%)		
White	160 (64)	164 (65)
Asian	65 (26)	57 (23)
Other	25 (10)	31 (12)
Median (range) time since diagnosis, days*	23 (0–183)	22 (0–241)
ECOG performance status, *n* (%)		
0	185 (74)	181 (72)
1	65 (26)	71 (28)
Sokal risk, (low/intermediate/high), %†	35/47/18	35/47/18
Geographic region, *n* (%)		
United States, Canada, Western Europe	65 (26)	66 (26)
Eastern Europe, Latin America	77 (31)	79 (31)
Other (e.g, India, Japan, Singapore)	108 (43)	107 (42)

ECOG, Eastern Cooperative Oncology Group.

*Range minimum is zero due to diagnosis of chronic myeloid leukaemia during the study screening period; range maximum is >6 months because of one patient who was considered a major protocol violator.

†Low Sokal risk corresponds to scores <0·8; intermediate risk corresponds to scores 0·8–1·2; high risk corresponds to scores >1·2.

0%), lost to follow-up (2%; 0%), and 'other' (1%; 2%). The majority of treatment discontinuations due to AEs in both arms occurred during the first 12 months (Fig 1). Among patients who discontinued bosutinib and imatinib, respectively, 37/92 (40%) and 17/72 (24%) were in CCyR at the time of discontinuation; 21/92 (23%) and 10/72 (14%) were in MMR (or better).

Efficacy

Among patients randomized to bosutinib (*n* = 250) or imatinib (*n* = 252) and included in the efficacy analysis, CCyR rates at 24 months were similar [58% and 65%; rate difference (95% CI), −8% (−16%, 1%)], as were cumulative CCyR rates by 24 months [79% and 80%; rate difference (95% CI), −1% (−8%, 6%)]. Among patients achieving CCyR at any time during the study, 151/197 and 172/204 responders remained on treatment and maintained CCyR at the time of analysis.

At 24 months, MMR rate was 47% for bosutinib and 41% for imatinib [rate difference (95% CI), 6% (−3%, 14%)], including 16% and 12% of patients achieving MR4 [rate
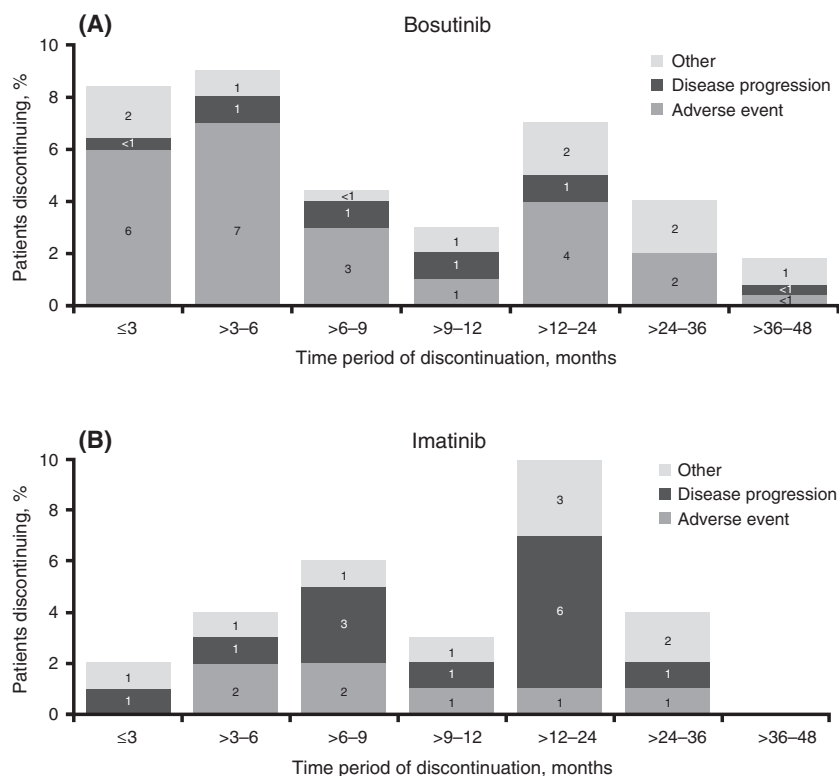
Fig 1. Reasons for discontinuation from (A) bosutinib and (B) imatinib treatment within time periods of up to 3, >3–6, >6–9, >9–12, >12–24, >24–36 and >36–48 months.

difference (95% CI), 4% (−2%, 10%)]. Cumulative MMR rate by 24 months was 59% with bosutinib and 49% with i-matinib [rate difference (95% CI), 10% (2%, 19%)]; 125/153 and 117/131 responders, respectively, were still on study treatment and retained MMR at the time of analysis. The median duration of MMR was not yet reached in either treatment arm.

Logistic regression was used to model the probability of response, with treatment, Sokal risk group, and treatment by Sokal risk group interaction included as predictors. The Wald test did not demonstrate a significant interaction between treatment and Sokal risk group for either CCyR or MMR at 24 months ($P = 0.366$ and $P = 0.164$, respectively). At 24 months, CCyR rates for bosutinib and imatinib, respectively, were 69% and 66% for the low-risk Sokal group, 55% and 70% for the intermediate-risk group and 47% and 51% for the high-risk group. MMR rates were 58% and 43% for the low-risk Sokal group, 42% and 42% for the intermediate-risk group, and 38% and 38% for the high-risk group. CCyR or MMR odds ratios for patients receiving bosutinib *versus* imatinib by Sokal risk group is shown in Fig 2.

Compared with the imatinib arm, numerically fewer patients receiving bosutinib discontinued treatment due to disease progression/lack of efficacy ($n = 10$ vs. $n = 33$), defined according to European LeukemiaNet recommendations (Baccarani *et al*, 2009) (including on-treatment transformation to AP/BP CML), and numerically fewer experienced on-treatment transformation to AP/BP CML ($n = 4$ vs. $n = 14$).

Since the 12-month primary analysis, no new on-treatment transformations to AP/BP CML occurred with bosutinib *versus* four with imatinib. Cumulative incidence estimates of AP/BP transformation by 24 months in the competing risk setting in the bosutinib and imatinib arms were 2% and 5% ($P = 0.019$ based on Gray's test for comparing cumulative incidence functions between treatment arms in the presence of competing risks of treatment discontinuation for any reason).

The Kaplan–Meier estimate of on-treatment EFS at 24 months was 92% [95% CI (87%, 95%)] for bosutinib *versus* 88% [95% CI (83%, 91%)] for imatinib, with median EFS not yet reached in either arm (Fig 3A). Estimates of EFS may be biased by early treatment discontinuations without an EFS event. Patients were not routinely followed for progression after treatment discontinuation; more patients discontinued treatment without progression in the bosutinib *versus* imatinib arm. Twelve (5%) and 34 (14%) patients discontinued treatment because of disease progression or death in the bosutinib and imatinib arms; 80 (32%) and 38 (15%) discontinued for other reasons (adverse events, patient request, investigator request, protocol violation, failure to return, lost to follow-up and other).

There were seven deaths in the bosutinib arm and 13 in the imatinib arm, representing an increase of three deaths in each treatment arm [all due to disease progression, except one imatinib patient (due to pneumonia)] since the 12-month primary analysis. Monitoring for survival continued after patients came off treatment; the Kaplan–Meier estimate

Fig 2. CCyR or MMR odds ratios for patients receiving bosutinib *versus* imatinib by Sokal risk-group. Black square = odds ratio; black error bars = 95% confidence interval; BOS, bosutinib; CCyR, complete cytogenetic response; CI, confidence interval; IM, imatinib; MMR, major molecular response; OR, odds ratio. *Low Sokal risk corresponds to scores <0·8; intermediate risk corresponds to scores 0·8–1·2; high risk corresponds to scores >1·2.
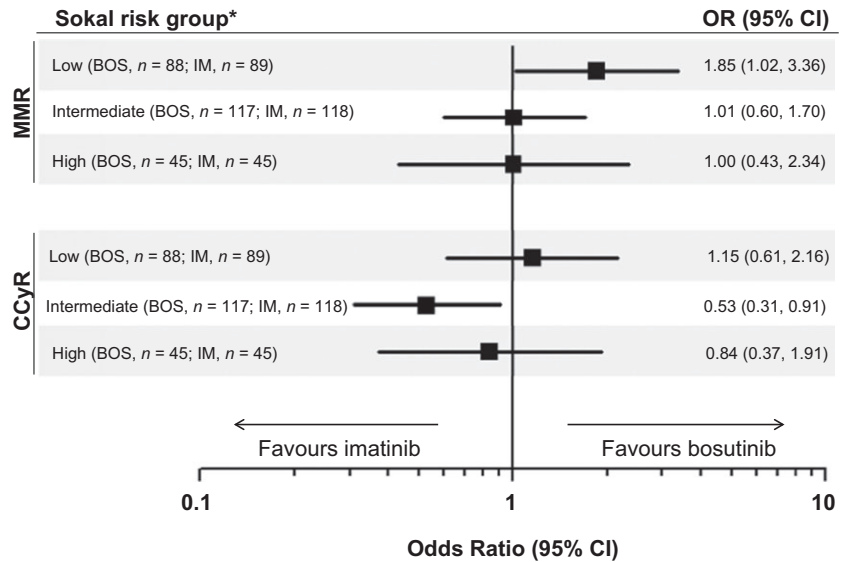
of 24-month survival was 97% [95% CI (94%, 99%)] for bosutinib and 95% [95% CI (91%, 97%)] for imatinib, with median OS not yet reached for either arm (Fig 3B). Most deaths (bosutinib, 5/7; imatinib, 9/13) occurred >28 d after treatment discontinuation. Deaths due to CML progression occurred in 6/7 patients receiving bosutinib and 10/13 patients receiving imatinib. Non–CML-related deaths (one patient each) included mesenteric embolia/intestinal necrosis (bosutinib), cardiovascular disease (imatinib), lung embolism (imatinib) and pneumonia (imatinib); none were considered related to study treatment by the investigator.

The CCyR and MMR rates appeared lower or similar for older (≥65 years) *versus* younger patients in both bosutinib (CCyR, 70% vs. 80%, respectively; MMR, 53% vs. 62%) and imatinib arms (CCyR, 78% vs. 81%; MMR, 48% vs. 52%), as was the proportion of patients retaining response at the time of analysis (Table SII).

In the retrospective landmark exploratory analysis, significantly more patients in the bosutinib *versus* imatinib arm had a *BCR-ABL1/ABL1* ratio ≤10% (IS) at 3 months [179/208 (86%) vs. 146/223 (66%), respectively; $P < 0·001$]. Cumulative CCyR and MMR rates by 12 and 24 months were higher among patients with a *BCR-ABL1/ABL1* ratio ≤10% vs. >10% at month 3 ($P < 0·001$ both treatment arms; Table II), as reflected in the time to CCyR and MMR curves (Fig 4A, B). OS and EFS appeared better among patients in the bosutinib arm with a *BCR-ABL1/ABL1* ratio ≤10% vs. >10% at month 3 ($P = 0·004$ for both endpoints). No significant difference was detected among imatinib patients, although in both arms the data are immature, with most of the patients without an event (Table II; Fig 4C).

Baseline *BCR-ABL1* sequencing data were available from 245 bosutinib and 246 imatinib patients. The majority of sequence variations detected at baseline in each treatment arm were polymorphisms (bosutinib, $n = 24/26$; imatinib, $n = 16/17$), the most common of which was E499E (bosuti-

nib, $n = 21$; imatinib, $n = 11$) in both arms. Additional polymorphisms included T83T (bosutinib, $n = 1$; imatinib, $n = 4$), K247R (bosutinib, $n = 1$; imatinib, $n = 1$) and T240T (bosutinib, $n = 1$). Three point mutations were identified at baseline: E197K (imatinib, $n = 1$), Y320C (bosutinib, $n = 1$), and R473Q (bosutinib, $n = 1$). Among patients with baseline *BCR-ABL1* sequence variations receiving bosutinib and imatinib, respectively, the cumulative CCyR rate by 24 months was 20/26 (77%) and 13/17 (76%); the cumulative MMR rate by 24 months was 13/26 (50%) and 8/17 (47%).

Sequencing data at discontinuation were available from 70/92 (76%) bosutinib and 55/72 (76%) imatinib patients, including 9/10 (90%) and 25/33 (76%) who discontinued because of progressive disease. At treatment discontinuation, emergent point mutations were less common among bosutinib [$n = 4$ (6%)] *versus* imatinib patients [$n = 10$ (18%); Table III]. One of the four patients in the bosutinib arm had achieved CCyR before detection of V299L mutation, and two experienced on-treatment transformation to AP/BP CML (one patient each with the E255K and T315I mutations). In the imatinib arm, three patients (one patient each with the M244V, G250E, and D276G/T277A/T315I mutations) had achieved CCyR before detection of their mutations at treatment discontinuation; one of these patients also achieved an MMR (G250E mutation); the patient with the M244V mutation subsequently lost CCyR while on treatment. Of the 10 imatinib patients with an emergent mutation, eight experienced disease progression/lack of efficacy while on treatment, including five who experienced transformation to AP/BP CML (Table III).

Safety and tolerability

Compared with imatinib, bosutinib was associated with higher incidences of some gastrointestinal events and alanine

(A)

Event-free survival

Patients at risk, n

Bosutinib	250	220	195	186	182	170	163	155	146	107	86	30	23	1	0
Imatinib	252	241	229	215	207	189	183	174	156	116	94	43	35	0	0

(B)

Overall survival

Patients at risk, n

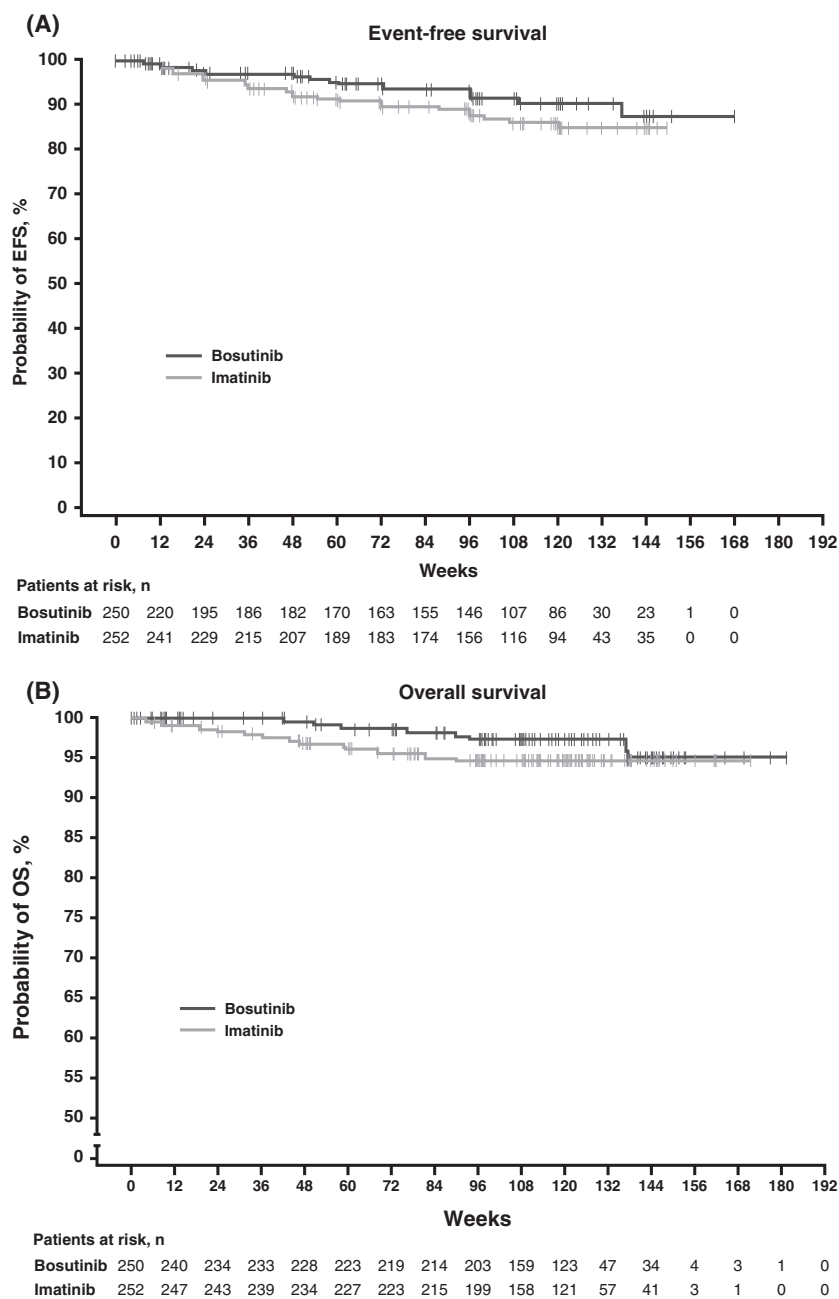|															
Bosutinib	250	240	234	233	228	223	219	214	203	159	123	47	34	4	3	1	0
Imatinib	252	247	243	239	234	227	223	215	199	158	121	57	41	3	1	0	0

Fig 3. (A) Event-free survival and (B) overall survival. EFS, event-free survival; overall survival (OS).

aminotransferase (ALT)/aspartate aminotransferase (AST) elevations and lower incidences of some musculoskeletal and oedema events, neutropenia, leucopenia, hypophosphataemia and blood creatinine phosphokinase elevations (Table IV).

Cardiovascular AEs were experienced by 25 (10%) bosutinib and 19 (8%) imatinib patients, including 7 (3%) and 1 (<1%) who experienced a grade ≥3 event. The most common cardiovascular AEs were hypertension (6% vs. 4%) and palpitations (2% vs. 2%). Cardiac failure occurred in 1 (<1%) bosutinib-treated patient and 2 (1%) imatinib-treated patients. No cases of myocardial infarction or peripheral arterial occlusive disease were reported. No statistically signif-

icant differences in cardiovascular AEs between the imatinib and bosutinib groups were evident.

The most common grade 3/4 treatment-emergent AE was diarrhoea (bosutinib, 12%; imatinib, 1%; Table IV). Diarrhoea of all grades typically occurred during the first month of bosutinib treatment, with a short median time to first event (3·0 vs. 43·0 d with imatinib) and a short median duration of event (3·0 vs. 5·5 d with imatinib). At the time of discontinuation, diarrhoea was reported in 27 patients receiving bosutinib (grade 1, *n* = 17; grade 2, *n* = 7; grade 3, *n* = 3) and six patients receiving imatinib (grade 1, *n* = 5; grade 2, *n* = 1). However, only one patient receiving imatinib discontinued

Table II. Landmark analysis of long-term outcomes (12 and 24 months) by early molecular response (*BCR-ABL1/ABL1* ratio ≤10% or >10% at 3 months).

	Bosutinib		Imatinib	
	BCR-ABL1/ABL1 Ratio IS		*BCR-ABL1/ABL1* Ratio IS	
	≤10%	>10%	≤10%	>10%
Evaluable patients,* *n* (%)	179/250 (72)	29/250 (12)	146/252 (58)	77/252 (31)
CCyR, *n* (%)				
By 12 months	170 (95)†	14 (48)	135 (93)†	42 (55)
By 24 months	172 (96)†	14 (48)	138 (95)†	50 (65)
MMR, *n* (%)				
By 12 months	100 (56)†	5 (17)	67 (46)†	4 (5)
By 24 months	132 (74)†	6 (21)	101 (69)†	13 (17)
EFS probability,‡ % (95% CI)	*P* = 0·004§		*P* = 0·331§	
12 months	97·1 (93·2, 98·8)	90·0 (66·3, 97·4)	95·8 (90·8, 98·1)	89·9 (80·0, 95·0)
24 months	93·2 (88·1, 96·2)	83·1 (56·6, 94·2)	91·8 (85·7, 95·4)	84·6 (73·3, 91·4)
OS probability,‡ % (95% CI)	*P* = 0·004§		*P* = 0·090§	
12 months	100·0 (NA, NA)	100·0 (NA, NA)	100·0 (NA, NA)	96·1 (88·3, 98·7)
24 months	98·9 (95·6, 99·7)	88·5 (69·0, 96·0)	98·6 (94·5, 99·6)	94·7 (86·5, 98·0)

CCyR, complete cytogenetic response (defined as described previously) (Cortes *et al*, 2012); EFS, event-free survival; IS, International Scale; MMR, major molecular response; NA, not attained; OS, overall survival.

*Evaluable patients had a valid molecular assessment at 3 months.

†*P* < 0·001 for *BCR-ABL1/ABL1* ratio ≤10% vs. >10% (Cochran-Mantel-Haenszel test for general association).

‡Kaplan–Meier probability estimates.

§*P* value based on stratified log rank test of time-to-event endpoint in patients with *BCR-ABL1/ABL1* ratio ≤10% vs. >10% at 3 months within each treatment arm.

treatment solely because of diarrhoea. Diarrhoea was typically treated with antidiarrhoeal medication (bosutinib, 69%; imatinib, 42%); additional management included temporary interruption (bosutinib, 23%; imatinib, 10%) or dose reduction (bosutinib, 8%; imatinib, 0%) of study treatment.

Consistent with the primary 12-month analysis (Cortes *et al*, 2012), the incidence of grade 3/4 laboratory abnormalities of neutropenia was lower with bosutinib (10%) *versus* imatinib (24%). Other frequently reported grade 3/4 haematological laboratory abnormalities included thrombocytopenia (14% vs. 15%) and anaemia (8% vs. 8%).

Grade 3/4 nonhaematological laboratory abnormalities of increased ALT (23% vs. 4%) and increased AST (12% vs. 4%) occurred more frequently with bosutinib than imatinib. ALT elevations (all grades) occurred with a median time to first event of 28·0 d (bosutinib) and 141·0 d (imatinib), with a median duration of 17·0 and 28·0 d, respectively. The time course of AST elevations was similar, with a median time to first event of 28·5 d (bosutinib) and 139·0 d (imatinib), with a median duration of 14·5 and 28·0 d, respectively. Concurrent medication and modification of study treatment (i.e., temporary interruption and/or dose reduction) were commonly used to manage ALT and AST elevations. No cases in the bosutinib arm led to hospitalization, were associated with permanent hepatic injury or liver-related deaths, or met Hy's law criteria [i.e., ALT or AST ≥3 × upper limit of normal (ULN) plus total bilirubin ≥2 × ULN, with near-normal alkaline phosphatase levels].

Other commonly reported (i.e., ≥5% of patients) grade 3/4 laboratory abnormalities included hypophosphataemia (6%, bosutinib; 20%, imatinib), increased creatine kinase (<1% vs. 7%), increased lipase (10% vs. 6%) and hypokalaemia (2% vs. 6%).

Overall, dose interruptions and reductions due to AEs occurred more frequently with bosutinib [*n* = 163 (66%) and *n* = 106 (43%)] *versus* imatinib [*n* = 112 (45%) and *n* = 52 [21%]]. However, dose modifications were more frequent during the first *versus* second 12 months on treatment in both the bosutinib (dose interruption, 59% vs. 27%; dose reduction, 38% vs. 10%) and imatinib (dose interruption, 40% vs. 18%; dose reduction, 17% vs. 5%) arms. Treatment discontinuations due to AEs were also more common with bosutinib [*n* = 62 (25%)] *versus* imatinib [*n* = 23 (9%)]. AEs most frequently leading to treatment discontinuation included increased ALT [bosutinib, *n* = 11 (4%); imatinib, *n* = 1 (<1%)], thrombocytopenia [bosutinib, *n* = 6 (2%); imatinib, *n* = 5 (2%)], neutropenia [bosutinib, *n* = 4 (2%); imatinib, *n* = 3 (1%)], vomiting [bosutinib, *n* = 4 (2%)], increased lipase [bosutinib, *n* = 3 (1%)] and pleural effusion [bosutinib, *n* = 3 (1%); the three patients with pleural effusion discontinued after 118, 176, and 409 d on treatment (all three pleural effusion events were considered treatment related by the investigators)].

The rates of common treatment-emergent AEs were generally similar or higher among older patients (Table SII). The rates of overall grade 3/4 treatment-emergent AEs, treatment
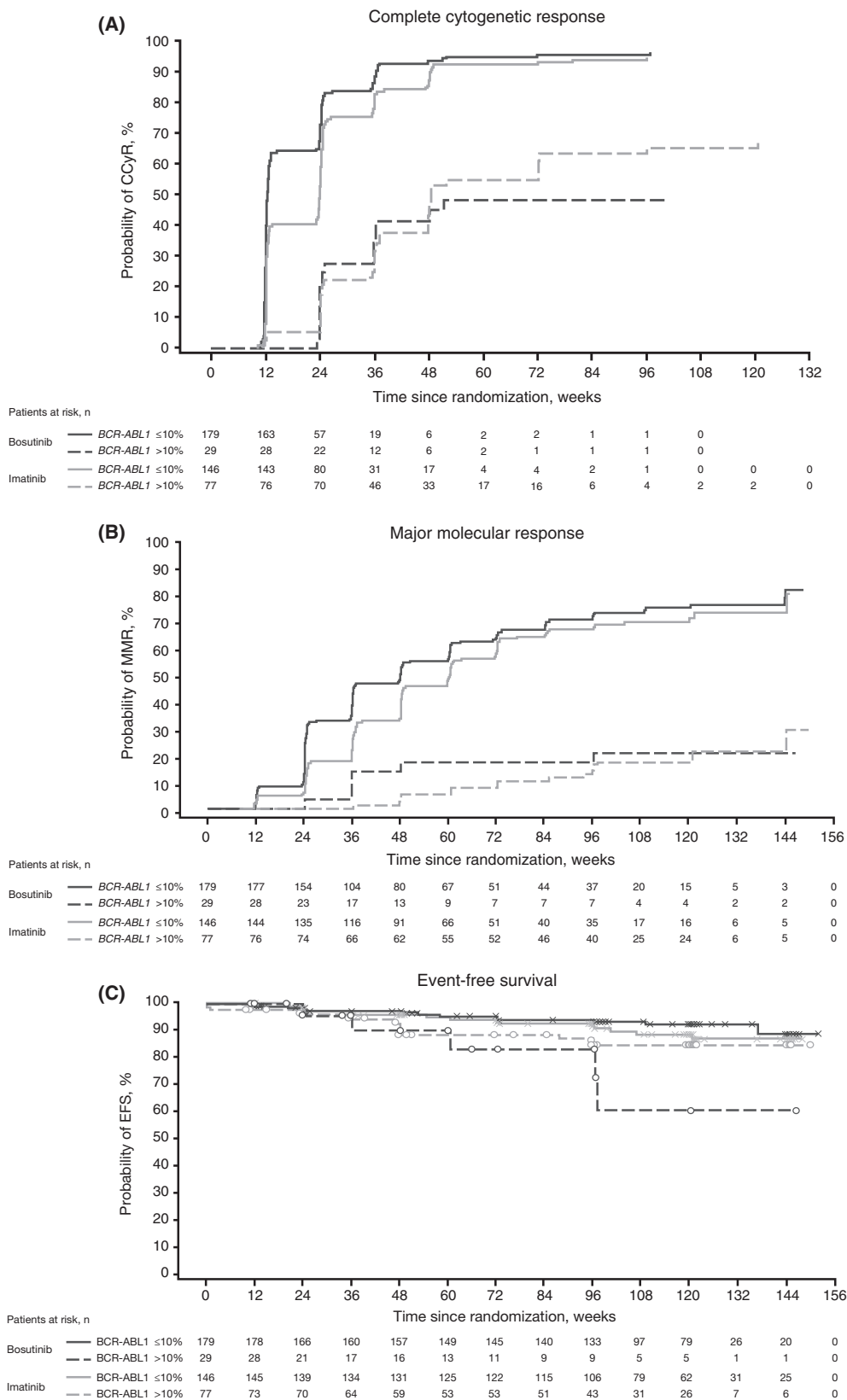
Fig 4. Time to (A) CCyR and (B) MMR, and (C) Kaplan–Meier estimate of on-treatment EFS among patients receiving bosutinib or imatinib with *BCR-ABL1/ABL1* ratio ≤10% vs. >10% at month 3 (landmark analysis). CCyR, complete cytogenetic response; EFS, event-free survival; MMR, major molecular response.

modifications and treatment discontinuations due to AEs were more frequent among older patients.

Discussion

In the previously reported 12-month analysis of data from the BELA trial, bosutinib did not demonstrate a superior rate of CCyR *versus* imatinib (primary endpoint). However, bosutinib was associated with faster achievement of CCyR; faster time to response; higher response rates at 3, 6 and 9 months and superiority in several secondary and exploratory endpoints, including achievement of MMR (Cortes *et al*, 2012). MMR is associated with approximately a 1-log deeper response than CCyR with respect to detection of *BCR-ABL1* levels and has been shown to predict longer duration of CCyR (Cortes *et al*, 2005; Iacobucci *et al*, 2006) and increased probability of progression-free survival (PFS) (Hughes *et al*, 2003) among CML patients. Deeper responses,

such as MMR and MR4, are clinically relevant because they are assumed to be associated with an increased chance of future durable treatment discontinuation without molecular relapse (Mahon *et al*, 2010). Consistent with the 12-month analysis, rates of MMR at 24 months and cumulative rates of MMR by 24 months were higher for bosutinib *versus* imatinib (59% vs. 49% cumulative MMR by 24 months). Notably, the proportion of patients with MMR was higher with bosutinib (47%) and imatinib (41%) at 24 months than in the primary 12-month analysis (41%; 27%) (Cortes *et al*, 2012); most responders (125/153 and 117/131, respectively) still retained MMR and were on study treatment as of this data snapshot.

Point mutations in the *BCR-ABL1* kinase domain were detected at treatment discontinuation in both treatment arms. Interestingly, whereas sequence variations (mostly representing polymorphisms) detected before treatment initiation occurred at similar frequency in both treatment arms,

Table III. Summary of patients with emergent *BCR-ABL1* mutations detected at treatment discontinuation.

Mutation	Sokal Risk Score Group*	Best response achieved	Reason for treatment discontinuation	Current status
Bosutinib arm				
E255K	Intermediate	Partial CyR; partial MR	Transformation to AP/BP CML after 140 d on treatment	Died because of disease progression 211 d after last study dose
T315I	Intermediate	Minimal CyR; complete MR	Transformation to AP/BP CML after 71 d on treatment	Died because of disease progression 315 d after last study dose
V299L	High	CCyR; partial MR	Emergence of mutation after 552 d on treatment	Alive, in the long-term follow-up phase of the study
T315I	High	Minimal CyR; partial MR	Emergence of mutation after 341 d on treatment	Alive, in the long-term follow-up phase of the study
Imatinib arm				
M244V	Low	CCyR; partial MR	Disease progression after 698 d on treatment	No information
M244V	Intermediate	Minor CyR; partial MR	Disease progression after 516 d on treatment	Alive, in the long-term follow-up phase of the study
G250E	Intermediate	CCyR; MMR	Patient request (BMT) after 533 d on treatment	Alive, in the long-term follow-up phase of the study
Y253H	Intermediate	No CyR; partial MR	Transformation to AP/BP CML after 379 d on treatment	Alive, in the long-term follow-up phase of the study
Q252H	Intermediate	No CyR; partial MR	Transformation to AP/BP CML after 98 d on treatment	Died because of disease progression 32 d after last study dose
G250E	Intermediate	Partial CyR; partial MR	Transformation to AP/BP CML after 378 d on treatment	Died because of an AE (pneumonia) unrelated to study treatment
E255K	High	Partial CyR; partial MR	Treatment failure after 588 d on treatment	Alive, in the long-term follow-up phase of the study
M244V/M351T	Low	No CyR; partial MR	Transformation to AP/BP CML after 78 d on treatment	No information
D276G/H396R	Intermediate	No CyR; partial MR	Transformation to AP/BP CML after 86 d on treatment	Alive, in the long-term follow-up phase of the study
D276G/T277A/ T315I	Low	CCyR; partial MR	Emergence of mutation after 340 d on treatment	Alive, in the long-term follow-up phase of the study

AE, adverse event; AP, accelerated phase; BMT, bone marrow transplant; BP, blast phase; CyR, cytogenetic response; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; MMR, major molecular response; MR, molecular response.

*Low corresponds to Sokal scores <0·8; intermediate corresponds to Sokal scores 0·8–1·2; high corresponds to Sokal scores >1·2.

Table IV. Treatment-emergent AEs reported for ≥10% of patients

AE,* n (%)	Bosutinib (n = 248)		Imatinib (n = 251)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Diarrhoea	173 (70)	29 (12)	62 (25)	2 (1)
Nausea	80 (32)	2 (1)	91 (36)	0
Vomiting	80 (32)	8 (3)	39 (16)	0
Increased ALT	79 (32)	45 (18)	21 (8)	7 (3)
Thrombocytopenia	69 (28)	31 (13)	70 (28)	34 (14)
Increased AST	66 (27)	20 (8)	22 (9)	8 (3)
Anemia	61 (25)	21 (8)	56 (22)	14 (6)
Rash	59 (24)	4 (2)	47 (19)	2 (1)
Pyrexia	45 (18)	3 (1)	31 (12)	3 (1)
Upper abdominal pain	35 (14)	0	18 (7)	0
Increased lipase	34 (14)	18 (7)	28 (11)	15 (6)
Abdominal pain	33 (13)	3 (1)	17 (7)	1 (<1)
Neutropenia	32 (13)	19 (8)	73 (29)	41 (16)
Headache	32 (13)	2 (1)	28 (11)	0
Fatigue	32 (13)	3 (1)	34 (14)	2 (1)
Upper respiratory tract infection	29 (12)	0	20 (8)	0
Leukopenia	23 (9)	7 (3)	54 (22)	14 (6)
Cough	23 (9)	0	27 (11)	0
Hypophosphataemia	19 (8)	3 (1)	45 (18)	25 (10)
Arthralgia	18 (7)	0	31 (12)	1 (<1)
Increased blood creatinine phosphokinase	17 (7)	1 (<1)	48 (19)	12 (5)
Myalgia	14 (6)	0	30 (12)	2 (1)
Muscle spasms	11 (4)	0	56 (22)	0
Bone pain	10 (4)	0	26 (10)	2 (1)
Peripheral oedema	9 (4)	0	28 (11)	0
Periorbital oedema	3 (1)	0	37 (15)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Grey shading indicates P value <0·05 based on Fisher exact test (2-tailed) for incidence (all grades) with bosutinib versus imatinib. Lighter grey shading indicates AEs more common with bosutinib; darker grey shading indicates AEs more common with imatinib.

*AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

these mutations appeared less often in bosutinib-treated [n = 4 (6%)] versus imatinib-treated [n = 10 (18%)] patients with sequencing data at discontinuation. A few patients in each treatment arm had achieved response before treatment discontinuation (and emergent mutation detection).

At 24 months, Kaplan–Meier estimates of the probability of EFS and OS remained high in the bosutinib and imatinib arms (92% and 88%, respectively, for EFS; 97% and 95% for OS), representing reductions of only 2–5% per treatment arm from the primary 12-month analysis (Cortes et al,

2012). Because of very low numbers of events in the present analysis, long-term endpoints are not yet mature. However, the observed estimates appear similar to 24-month estimates reported for the DASISION (DASatinib versus Imatinib Study In treatment-Naive CML patients) trial of dasatinib versus imatinib [92–94% for EFS (across treatment arms); 95% for OS] (Kantarjian et al, 2012) and the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients) trial of nilotinib versus imatinib (94–98% for EFS; 96–98% for OS) (Kantarjian et al, 2011b) in newly diagnosed CP-CML patients. As in the current BELA analysis, CML progression was the most common cause of death across treatment arms in DASISION (Kantarjian et al, 2012) and ENESTnd (Kantarjian et al, 2011b). Importantly, few (n = 4) on-treatment transformations to AP/BP CML occurred with bosutinib, with no new transformations reported since the primary 12-month analysis; in the imatinib arm, 14 patients experienced transformation, including four new transformations. In the German CML IV study of imatinib in patients with newly diagnosed CML, those who achieved MMR at 12 months had significantly improved PFS and OS at 3 years versus those who did not (Hehlmann et al, 2011). Longer-term evaluation in the present study will permit survival comparison.

A retrospective landmark analysis of this study indicates that a BCR-ABL1/ABL1 ratio ≤10% vs. >10% on the IS at month 3 is associated with a greater likelihood of achieving CCyR or MMR by 12 and 24 months. A similar trend was generally observed for EFS and OS among bosutinib patients, although the long-term endpoints are immature, as a majority of the patients did not have an event. In addition, a significantly higher proportion of patients achieved this important landmark at month 3 with bosutinib versus imatinib (86% vs. 66%; P < 0·001).

Bosutinib demonstrated acceptable toxicity in the current analysis, with an overall toxicity profile distinct from that of imatinib. Compared with imatinib, bosutinib was associated with higher rates of gastrointestinal events and ALT/AST elevations; both were mostly manageable with concomitant medication and/or dose modification. Although common with bosutinib, diarrhoea was typically of low severity, transient and occurred early during treatment; diarrhoea incidence (all grades) increased by only 2% since the primary 12-month analysis (Cortes et al, 2012). Similarly, the incidence of grade 3/4 ALT and AST laboratory abnormalities in the bosutinib arm were also little changed (1% increase for both), as was the associated number of treatment discontinuations (i.e., 9 of 11 patients discontinued because of ALT elevation). ALT and AST elevations were typically transient; no cases in the bosutinib arm met Hy's law criteria, led to hospitalization, or were associated with permanent hepatic injury or liver-related death. The incidence of certain toxicities, including musculoskeletal events, oedema/fluid retention and neutropenia, was also notably lower with bosutinib versus imatinib. The high incidence of oedema/fluid

retention with imatinib in the current analysis is unsurprising, as fluid retention/superficial oedema has previously been reported with imatinib treatment (http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf; Kantarjian *et al*, 2009, 2010; Saglio *et al*, 2010); pleural/pericardial effusions have been observed more commonly with dasatinib treatment (Talpaz *et al*, 2006; Hochhaus *et al*, 2007; Kantarjian *et al*, 2009, 2010; Quintas-Cardama *et al*, 2007; Shah *et al*, 2008; http://packageinserts.bms.com/pi/pi_sprycel.pdf). The lower incidence of grade 3/4 neutropenia with bosutinib *versus* imatinib may be at least partially due to the minimal inhibition of c-Kit by bosutinib relative to imatinib (Bartolovic *et al*, 2004; Puttini *et al*, 2006).

Although more bosutinib-treated (25%) *versus* imatinib-treated (9%) patients discontinued treatment because of an AE, the majority of these discontinuations occurred before the 12-month analysis (bosutinib, 19%; imatinib, 6%) (Cortes *et al*, 2012), consistent with observations with other TKIs for which most AEs occur early during treatment. Treatment discontinuation for any reason was also more common with bosutinib (37%) *versus* imatinib (29%), which could have biased observed efficacy outcomes.

Bosutinib demonstrated activity in both older and younger patients: although the frequency of certain toxicities and treatment discontinuations due to treatment-emergent AEs was higher among older patients, the safety profile of bosutinib remained manageable and distinct from that of imatinib regardless of age.

The current analysis of BELA, including data captured within a minimum of 24 months after the end of accrual, confirmed the efficacy and distinct but manageable tolerability profile of bosutinib in newly diagnosed CP CML previously observed in the primary 12-month analysis (Cortes *et al*, 2012). These findings were demonstrated in both older and younger patients. Patients with a *BCR-ABL1/ABL1* ratio ≤10% at month 3 had a greater likelihood of better long-term outcomes, underscoring the importance of deeper response monitoring. At treatment discontinuation, emergent *BCR/ABL1* kinase domain point mutations were less common with bosutinib *versus* imatinib. The higher rate of MMR with bosutinib *versus* imatinib previously observed in the primary 12-month analysis (Cortes *et al*, 2012) continues to be preserved in this 24-month follow-up, as was the high estimated probability of EFS. A low frequency of transformation to AP and BP CML and high estimated probability of OS were also observed. Further follow-up is warranted for a more thorough evaluation of survival.

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Author contributions

THB, JEC, CAD, FG, and CGP contributed substantially to the research design, acquisition, and interpretation of the data. LD, KG, and AMC contributed substantially to the research design and interpretation of the data. DP performed statistical analyses. All authors assisted in the writing and/or critical review of the manuscript, and all authors provided final approval of the manuscript for submission. THB has participated in advisory boards for and received honoraria from Pfizer, Ariad, BMS, and Novartis; received research funds from Novartis; and holds a patent on the combination of imatinib with hypusination inhibitors. FG has participated in advisory boards for Pfizer, BMS, and Novartis and has received honoraria from Novartis, BMS and Pfizer. JC received research support from Ariad, BMS, Novartis, Pfizer, and Teva, and is a consultant for Ariad, BMS, Pfizer, and Teva. LD and AMC are former employees of Pfizer. DP and KG are current employees of Pfizer. CAD has no conflicts of interest to disclose.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Study inclusion and exclusion criteria.

Table SII. Summary of results for older *versus* younger patients.

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