haematologica
Journal of the Ferrata Storti Foundation

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Received: November 13, 2025.
Accepted: June 10, 2026.

Citation: Carlo Gambacorti-Passerini, Tim H. Brümmendorf, Dong-Wook Kim, Yeow Tee Goh, Iryna Dyagil, Katia Pagnano, Arpad Batai, Anna G. Turkina, Eric Leip, Simon Purcell, Jocelyn Leone, Andrea Viqueira and Jorge E. Cortes. Second-line bosutinib for chronic phase chronic myeloid leukemia after imatinib: final, 10-year results of a phase I/II study.
Haematologica. 2026 June 18. doi: 10.3324/haematol.2025.300221 [Epub ahead of print]

Second-line bosutinib for chronic phase chronic myeloid leukemia after imatinib: final, 10-year results of a phase I/II study

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Data-sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Trial registration

ClinicalTrials.gov identifiers: NCT00261846 and NCT01903733

Acknowledgments

This study was sponsored by Pfizer. Andrea Viqueira is a former employee of Pfizer. Medical writing assistance funded by Pfizer according to Good Publication Practice guidelines was provided by Emily Balevich, PhD, and Simon R. Stones, PhD, CMPP (Engage Scientific Solutions) and Scott Battle, PhD, CMPP (Nucleus Global, an Inizio Company).

Funding

This study was sponsored by Pfizer.

Conflict of interest disclosures Carlo Gambacorti-Passerini reports consultancy with Bristol Myers Squibb; research funding from Pfizer; and honoraria from Pfizer. Tim H. Brümmendorf reports consultancy with Janssen, Merck, Novartis, and Pfizer; research funding from Novartis and Pfizer; and honoraria from Novartis and Pfizer. Dong-Wook Kim reports research funding from Pfizer. Yeow Tee Goh reports consultancy with Amgen, Antengene, EUSA Pharma, Gilead, Janssen, Pfizer, and Roche; research funding from Pfizer; and honoraria from AbbVie, Astellas Pharma, Bristol Myers Squibb, MSD, Novartis, and Takeda. Iryna Dyagil reports research funding from Pfizer. Katia Pagnano reports participation in advisory boards for AbbVie, Sandoz, Novartis, and Pfizer; and honoraria (lecture) from Pint Pharma, EMS, Novartis, Teva, and Pfizer. Arpad Batai and Anna G. Turkina report research funding from Pfizer. Eric Leip, Simon Purcell, and Jocelyn Leone report employment at and stock/equity ownership in Pfizer. Andrea Viqueira reports former employment at and stock/equity ownership in Pfizer. Jorge E. Cortes reports consultancy with Bio-Path Holdings Inc, BiolineRx, Bristol Myers Squibb, Daiichi Sankyo, Jazz Pharmaceuticals, Novartis, Pfizer, Sun Pharma, and Takeda; and research

funding from AbbVie, Amgen, Ascentage, Jazz Pharmaceuticals, Novartis, Pfizer, Sun Pharma, and Takeda.

Author contributions

EL, SP, JL and AV contributed to study conceptualization, data curation and formal analysis. CG-P, THB, D-WK, YTG, ID, KP, AB, AGT and JEC contributed to investigation. EL provided study validation. CG-P and JEC contributed to writing the original draft. All authors reviewed and edited the manuscript and approved the final version.

ABSTRACT

This is the final ≥10-year report of a phase I/II study and its extension study of second-line bosutinib for chronic phase chronic myeloid leukemia (CP-CML), representing the longest follow-up to date of any tyrosine kinase inhibitor after imatinib failure (*n*=284). Median (range) follow-up and treatment duration were 53.7 (0.5–171.6) and 25.6 (0.2–170.5) months, respectively. At the start of year 11, 19.4% of patients were receiving bosutinib; 13.4% were receiving bosutinib at study completion. The most common reasons for treatment discontinuation were lack of efficacy (disease progression/unsatisfactory response; 26.8%) and adverse events (26.1%). Cumulative rates of complete cytogenetic response, major molecular response, and MR^4 were 49.6%, 42.1%, and 37.1%, respectively. Kaplan–Meier probabilities of maintaining response at year 11 were 58.3%, 56.1%, and 55.7%, respectively. At year 11, cumulative incidence of on-treatment disease progression/death was 24.6%; 15 (5.3%) patients had on-treatment transformations to accelerated/blast phase (one after year 5). The Kaplan–Meier overall survival rate was 70.5%; 55 (19.4%) patients died on study (15 after year 5). At the start of year 11, 29/55 (52.7%) patients still on bosutinib were receiving ≥500 mg once daily. Thirteen patients had adverse events leading to discontinuation in year 6 or later. No new safety signals emerged. After ≥10 years, bosutinib demonstrated durable efficacy and acceptable safety as second-line treatment for CP-CML.

Trial registration: ClinicalTrials.gov identifiers: NCT00261846 and NCT01903733.

INTRODUCTION

Bosutinib is a potent, orally active Src/Abl tyrosine kinase inhibitor (TKI) indicated for the treatment of patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) resistant or intolerant to prior therapy and newly diagnosed Ph+ chronic phase (CP) CML (1-9). Bosutinib has demonstrated efficacy against many imatinib-resistant *BCR*::*ABL1* mutations and has a unique toxicity profile, which may relate to its minimal inhibitory activity against c-KIT and platelet-derived growth factor receptor (10-12).

Approval of bosutinib for patients with resistance or intolerance to prior therapy was based on results of an open-label, phase I/II study of bosutinib in Ph+ leukemias. Primary results demonstrated efficacy and acceptable safety in imatinib-resistant or -intolerant patients with CP-CML without other prior TKI exposure (2). Subsequent follow-up confirmed the durability of responses and no new safety signals in the second-line setting (3, 13-16). Despite the arrival of newer TKI agents, including asciminib shown to be superior to bosutinib in the third and subsequent lines (17, 18), bosutinib remains a clinically relevant treatment option for those intolerant to other TKIs (19) or with certain comorbidity considerations. This is the final efficacy and safety report of bosutinib in the second-line cohort of this phase I/II study and its extension study, which facilitated long-term continued therapy and/or follow-up. This analysis was based on ≥10 years' follow-up, representing the longest follow-up to date with any TKI after imatinib failure.

METHODS (current count: 491/500)

Study design

Design of the phase I/II study (recommended starting dose for part 2 was 500 mg once daily [QD]) (NCT00261846) has been described (2). The current analysis included patients with Ph+ CP-CML with imatinib as only prior TKI. After ≥5 years, patients could enroll in an extension study (NCT01903733), permitting long-term treatment and/or survival follow-up. Studies were conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent, and protocols were approved by relevant institutional review boards.

Assessments

Data from the phase I/II and extension studies were combined for the analyses; patients receiving ≥1 bosutinib dose in the phase I/II study were included.

Cytogenetic and major molecular response (MMR) assessments in the phase I/II study have been described (2) and are further described in the Supplementary Material. In the phase I/II study, molecular response was evaluated at a central laboratory but not on the International Scale (not available at study start). Molecular response was not evaluated for participants in China, India, Russia, and South Africa, as samples could not be exported. In the extension study, molecular assessments were performed locally.

Treatment-emergent adverse events (TEAEs) and TEAE clusters are defined in the Supplementary Material. Newly occurring TEAEs were those not previously reported for the same patient during a given year, defined as 48 weeks. Exposure-adjusted incidence rates were calculated as patients with TEAEs divided by total patient-years (sum of total time-to-first TEAE for patients with TEAEs plus total treatment duration for patients without TEAEs). Exposure-

adjusted incidence for vascular, cardiac, and hypertension TEAEs are presented in context with those observed in BFORE (7, 9) (phase III trial of bosutinib versus imatinib; both 400 mg QD for newly diagnosed CP-CML), and BELA (20) (phase III trial of bosutinib 500 mg QD versus imatinib 400 mg QD for newly diagnosed Ph+ CP-CML).

Estimated glomerular filtration rate (eGFR), QT interval corrected per Fridericia's formula (QTcF), and left ventricular ejection fraction (LVEF) are also presented.

Statistical methods

Response loss and time-to-event endpoints of overall survival (OS), time to disease progression/death (progression-free survival [PFS]), and duration of response (DOR) have been described (see (3) and Supplementary Methods). Outcomes were reported across ≥10 years as few events (eg, initial response, loss of response, death) occurred after year 10, although few patients remained at risk for certain time-to-event endpoints.

Baseline and on-treatment (time-dependent) patient characteristics were evaluated as potential prognostic factors using a backward-elimination, multivariable, cause-specific Cox regression model for DOR, proportional subdistribution hazards model for PFS, and Cox regression model for OS. Hazard ratios with 95% CIs excluding 1 were considered predictive of outcome; no adjustments for multiple comparisons were made. The backward-elimination criterion was 0.20 for all models. Hazard ratios with 95% CIs for treatment effect of bosutinib versus imatinib from a proportional subdistribution hazards model were also provided for BFORE/BELA exposure-adjusted TEAE data.

Extension study data for 13 patients in China were excluded due to regulatory requirements. See Supplementary Methods for further methodological details.

RESULTS

Patients and treatment

A total of 284 patients with Ph+ CP-CML treated with imatinib as only prior TKI (imatinib-resistant, *n*=195; imatinib-intolerant, *n*=89) were enrolled and treated in the phase I/II study (phase I, *n*=17; phase II, *n*=267; Figure 1) (2). Full demographics and baseline characteristics have been reported (3). Briefly, median (range) age was 53.5 (18.0–92.0) years, 149 (52.5%) patients were male, and 186 (65.5%) patients were White.

This final analysis was based on final database lock, 10 years after the last patient was enrolled. At phase I/II study closure, 89 patients were still receiving bosutinib. Ninety patients were enrolled in the extension study, of whom 69 were still receiving bosutinib and 21 were followed for survival only. Of 284 patients enrolled in the phase I/II study, 55 (19.4%) were still receiving on-study bosutinib at the start of year 11. Fifty-five (19.4%) completed the extension study: 38 (13.4%) were still receiving on-study bosutinib, and 17 (6.0%) were being followed for survival only at study completion. Time from first bosutinib dose to study completion was 134.7 months for the last enrolled patient. Median (range) follow-up was 53.7 (0.5–171.6) months, and median (range) treatment duration was 25.6 (0.2–170.5) months (Table 1). Overall, 226 (79.6%) patients discontinued treatment. The most common (≥10%) reasons for treatment discontinuation overall were lack of efficacy (disease progression/unsatisfactory response) in 26.8% of patients and AEs in 26.1% (Table 1). After year 5, treatment discontinuations were generally infrequent and occurred for heterogenous reasons, including lack of efficacy, death, AEs, or patient request (Figure S1.)

Of 55 (19.4%) patients still on treatment at the start of year 11, 29 (52.7%) were

receiving bosutinib ≥500 mg QD. The dose at the beginning of each year for patients still on treatment is shown in Figure 2. Among patients who discontinued treatment due to AEs, last non-zero dose prior to discontinuation was <500 mg in 62.2% of patients while it was ≥500 mg in 77.6% and 55.3% in those who discontinued due to lack of efficacy and any other reason, respectively. The last non-zero dose prior to discontinuation for those who discontinued during each year is shown in Figure S2. Median (range) dose intensity was 436.0 (87.4–599.2) mg/day (Table 1). Dose escalations to 600 mg QD were used in 37/273 (13.6%) patients who started on bosutinib at ≤500 mg; median time to first dose escalation was 288.0 days, and median cumulative duration of dose escalation was 358.0 days. Dose reductions due to AEs were required in 152 (53.5%) patients; median time to dose reduction was 53.0 days, and median cumulative duration of dose reduction was 411.5 days. Dose interruptions due to AEs occurred in 210 (73.9%) patients; median time to dose interruption was 30.0 days, and median cumulative duration of dose interruption was 28.0 days.

Efficacy

The cumulative major cytogenetic response (MCyR) and CCyR rates (attained or maintained) at any time were 59.9% and 49.6%, respectively, in 262 evaluable patients (Table S1). MCyR was achieved in 55.4% of 204 patients without a baseline MCyR, and CCyR was achieved in 47.2% of 246 patients without a baseline CCyR. Median DORs were not reached, and the probability of maintaining a response at year 11 was 62.1% for MCyR (Figure S3A) and 58.3% for CCyR (Figure S3B). The cumulative MMR and MR^4 rates were 42.1% and 37.1%, respectively, in 197 patients with evaluable molecular data (Table S1). MMR was achieved in 40.7% of 189 patients without a baseline MMR, and MR^4 was achieved in 35.8% of 190 patients without a baseline

MR^4. Median DORs were not reached, and the probability of maintaining a response at year 11 was 56.1% for MMR (Figure 3A) and 55.7% for MR^4 (Figure 3B); >50% of responders were censored prior to year 11. Most initial cytogenetic and molecular responses occurred by year 2 (Table S1). One patient first achieved CCyR, five first achieved MMR, and 14 first achieved MR^4 after year 5. Of 37 patients with a dose escalation to 600 mg QD, 31 (83.8%) had an improved response after escalation, including nine (24.3%) patients who attained CCyR after escalation.

Of 125 patients evaluated for *BCR*::*ABL1* kinase domain mutations before and at the end of bosutinib therapy, 28 had newly detectable mutations; eight occurred after year 5 (V299L in two patients and F359V, H295L, M244V, M351T, S348L and S410G in one patient each) (Table S2).

On-treatment transformation to accelerated phase/blast phase (AP/BP) occurred in 15 (5.3%) patients (imatinib-resistant, *n*=13 [6.7%]; imatinib-intolerant, *n*=2 [2.2%]). Most on-treatment transformations occurred in years 1 and 2, with only one occurring after year 5 (*n*=8 in year 1; *n*=5 in year 2; *n*=1 in year 3; *n*=1 in year 7). The cumulative incidence of on-treatment progression/death at year 11 was 24.6% (Figure 4A).

The median OS was not reached, and the Kaplan–Meier OS rate at year 11 was 70.5% (Figure 4B); >50.0% of patients were censored prior to year 7. A total of 55 (19.4%) patients died on study (15 after year 5): 30 (10.6%) due to disease progression, 16 (5.6%) due to AEs, five (1.8%) due to other causes, and four (1.4%) due to unknown cause. Sixteen (5.6%) deaths occurred within 30 days of the last bosutinib dose: five (1.8%) due to disease progression, 10 (3.5%) due to AEs, and one (0.4%) due to unknown cause. No deaths were considered treatment-related by the investigator.

Safety

Any-grade TEAEs occurred in 283 (99.6%) patients and grade 3/4 TEAEs occurred in 223 (78.5%) patients. A total of 79 (27.8%) patients had AEs leading to discontinuation across all treatment years, the most common (in ≥5 patients) being thrombocytopenia (*n*=17), neutropenia, and increased alanine aminotransferase (ALT; *n*=6 each) (Figure S4). Thirteen patients had AEs leading to discontinuation in year 6 or later, including pleural effusion (*n*=2), rash, pneumonia, pregnancy, cerebral infarction, subarachnoid hemorrhage/skull fracture/subdural hematoma, cerebrovascular accident, acute myocardial infarction, congestive cardiac failure, pulmonary hypertension, chronic kidney disease, and hypertensive cardiomyopathy (*n*=1 each).

Newly occurring TEAE clusters and TEAEs are listed by year in Table S3. The only newly occurring any-grade TEAE in >5 patients in any given year of years 6 to 11+ was hypertension, with seven patients developing hypertension in year 11+. The exposure-adjusted incidence rate of any-grade hypertension TEAEs was 0.032 per patient-year (Table S4). The exposure-adjusted incidence rates of any-grade cardiovascular, cerebrovascular, and peripheral vascular TEAEs were 0.014, 0.009, and 0.008, per patient-year, respectively (Table S4). In year 6 or later, new any-grade vascular events were reported in 12 patients (including two with grade 5 events), three of whom had history of vascular events. Cerebellar infarction and cerebral infarction (*n*=2 each) were the only newly occurring vascular TEAEs reported in >1 patient in years 6 to 11+ (Table S3). Two patients had grade 5 vascular events (acute myocardial infarction and subarachnoid hemorrhage) that occurred in year 6 or later; both events were considered to be unrelated to bosutinib per the investigator. Rates of cardiovascular, cerebrovascular, and peripheral vascular events across all study years were 5.6%, 3.5%, and 3.5%, respectively. Rates

of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia (risk factors for vascular disease) across all study years were 4.6%, 1.1%, and 2.1%, respectively.

The exposure-adjusted incidence rate of any-grade cardiac (excluding cardiovascular) TEAEs was 0.030 per patient-year (Table S4). In year 6 or later, new any-grade cardiac TEAEs were reported in 11 patients (including three with grade 5 events), two of whom had history of cardiac events. Congestive cardiac failure (*n*=4), bradycardia and atrial fibrillation (*n*=2 each) were the only newly occurring cardiac TEAEs reported in >1 patient in years 6 to 11+ (Table S3). Three patients had grade 5 cardiac events that occurred in year 6 or later (congestive cardiac failure [*n*=2] and acute cardiac failure); all three were considered unrelated to bosutinib by the investigator. One patient had a decline in LVEF from grade 1 at baseline to grade 3 (Table S5), and one patient had an increase in QTcF from grade 2 at baseline to grade 3 (Table S6); both events occurred prior to year 6.

Thirteen patients had newly occurring pleural effusion in year 6 or later (Table 2). Pleural effusion occurred in 36/284 (12.7%) patients by end of study, and three patients discontinued treatment due to pleural effusion across all treatment years (Figure S4). Pleural effusion occurred in 3/7 (42.9%), 9/62 (14.5%), 11/143 (7.7%), 21/277 (7.6%), and 2/37 (5.4%) patients on 200, 300, 400, 500, and 600 mg QD bosutinib doses, respectively. Five (1.8%) patients (three [1.1%] after year 5) had pulmonary hypertension, which led to treatment discontinuation in two (0.7%) patients. No patient had pulmonary arterial hypertension during the study.

The most common newly occurring liver events in year 6 or later were increased ALT (n=4) and aspartate aminotransferase (AST; *n*=3; Table 2). Newly occurring gastrointestinal events were diarrhea and vomiting (*n*=2 each).

Twenty-two patients had newly occurring renal TEAEs in year 6 or later; the most common newly occurring renal event in year 6 or later was increased blood creatinine (*n*=13; Table 2). Across all treatment years, 27 (9.5%) patients had a decline from baseline to KDIGO grade 4 eGFR, and seven (2.5%) patients had a decline to KDIGO grade 5 eGFR (Table S7); nine and three of these events, respectively, occurred after year 5.

Predictors of disease progression, death, and response loss

Baseline factors predictive of decreased PFS were Ph+ ratio (≥95% vs. ≤35%), prior imatinib resistance (versus intolerance), splenomegaly, and higher PB blasts (Figure S5). No on-treatment factors were identified as being predictive of PFS. Baseline factors predictive of decreased OS were age (≥65 vs. <65 years), Ph+ ratio (≥95% vs. ≤35%), and higher PB blasts (Figure S5**)**. The only on-treatment factor predictive of decreased OS was no MCyR by week 12.

Baseline Ph+ ratio (≥95% vs. ≤35%) and lower eosinophils were predictive of MCyR loss; Ph+ ratio (≥95% vs. ≤35%) and CP (late vs. early) were predictive of CCyR loss; and sex (female vs. male), Ph+ ratio (≤35% vs. >35–<95%), and higher baseline platelet count were predictive of MMR loss (Figure S6). No on-treatment factors were predictive of response loss.

DISCUSSION

In this final report of a phase I/II study and its extension study, bosutinib demonstrated durable efficacy and manageable long-term safety as second-line treatment in patients with CP-CML resistant/intolerant to imatinib after ≥10 years. At the start of year 11, 19.4% of patients were on bosutinib, and 13.4% were still receiving bosutinib at study completion. Cumulative response rates were high (MCyR, 59.9%; CCyR, 49.6%; MMR, 42.1%; MR^4, 37.1%) but showed only

modest increases from previous reports of this cohort, indicating most responses were attained in prior treatment years (2, 3, 13, 14). Although cross-study comparisons are limited owing to differences in methodology and length of follow-up, a few studies have also focused on patients with prior imatinib failure and with generally similar eligibility criteria and endpoints to those used in the present study. In these other studies, percentages of patients still receiving treatment (nilotinib, 31% at 4 years; dasatinib, 22% at 7 years) and cumulative response rates (nilotinib: MCyR, 59%; CCyR, 45%; dasatinib: MMR, 46%; MR^4, 29%) after long-term follow-up were similar to those reported here with longer-term bosutinib (21, 22). Responses with bosutinib were durable, although there was some decline since year 5; probabilities of maintaining MCyR, CCyR, MMR, and MR^4 were 62.1%, 58.3%, 56.1%, and 55.7% at year 11 compared with 70.7%, 69.7%, 74.1%, and 74.7% at year 5. Year 11 molecular rates had wide confidence intervals and were immature owing to shorter follow-up from initial response compared with initial cytogenetic response.

Estimated rates of on-treatment disease progression/death and transformations to AP/BP remained low. After year 5, there was one transformation to AP/BP CML and 15 deaths. Across the entire study, transformations were observed in 15 (5.3%) patients, similar to reports of long-term, second-line dasatinib (10/165 [6%]) and nilotinib (11/321 [3%]) (21, 23). As with these other TKIs, most transformations with bosutinib occurred in the first few years of treatment, with new events occurring rarely with longer-term treatment. The estimated 11-year OS rate was 70.5% versus 83.5% at year 5 (3); there were no treatment-related deaths. For comparison, 7-year OS was 65% for second-line dasatinib, and 4-year OS was 78% for second-line nilotinib (21, 22). Notably, over half of deaths (54.5%) in this analysis were CML-related. However, this

study was initiated in 2006, and the prognosis for patients entering second-line treatment has substantially improved since then.

Information on late-emerging AEs associated with second-line TKI treatment is of interest given the prolonged nature of TKI therapy and limited availability of long-term data. In the current study, TEAEs were generally manageable with dose modifications, and no new safety signals emerged after ≥10 years. AEs leading to discontinuation were most common during year 1 of treatment.

Vascular toxicity is a concern with long-term use of some second- and third-generation TKIs (24-30). However, prior analyses of bosutinib clinical trials, some of which included the current cohort, reported a low incidence of vascular events after ≥4 years in the first-line setting and ≥4 and ≥7 years in the later-line setting (9, 31, 32). The current analysis indicated these events remained infrequent in this cohort after ≥10 years, with low exposure-adjusted incidence rates of cardiac and vascular toxicities. Bosutinib is associated with a low incidence of hyperglycemia and hyperlipidemia (known risk factors for vascular disease) compared with nilotinib (30, 33, 34). Rates of these events were low in this cohort, and this may have contributed to the infrequency of vascular events.

Rates of cardiovascular, cerebrovascular, and peripheral vascular events were 5.6%, 3.5%, and 3.5%, respectively, in the present study. In comparison, cardiovascular ischemic (defined as myocardial infarction, angina pectoris, or coronary artery disease), cerebrovascular, and peripheral vascular events were reported in 4%, 3%, and 0%, respectively, of patients receiving second-line dasatinib 100 mg QD after 7 years (22). Ischemic heart disease, peripheral arterial occlusive disease, and ischemic cerebrovascular disease occurred in 7.9%, 6.5%, and 4.7%, respectively, of patients receiving nilotinib 300 mg twice daily and in 13.0%, 7.2%, and

7.6%, respectively, of patients receiving nilotinib 400 mg twice daily for newly diagnosed CP-CML after 10 years (vascular AEs were not reported for second-line nilotinib) (35). Cumulative rates of cardiovascular, cerebrovascular, and peripheral vascular arterial occlusive events in patients with CP-CML receiving ponatinib after prior therapy were 16%, 13%, and 14%, respectively, after 5 years (28). Although direct comparison of studies is complicated by differences in patient populations, definitions for types of events, and length of follow-up periods, the rates with bosutinib appear similar to those observed with dasatinib and numerically lower than those seen with nilotinib or ponatinib.

Bosutinib was associated with minimal effects on QTcF after ≥10 years, with only one (0.4%) patient having an on-treatment QTcF >500 ms. In comparison, four (1.2%) patients had QTcF >500 ms after 4 years in a study of second-line nilotinib (21, 36).

In the current study, the rate of pleural effusion, a toxicity primarily associated with dasatinib (29), was 12.7% and appeared to be lower than with second-line dasatinib (7-year rate, 28%) (22). These events were largely manageable, and most patients were able to remain on treatment, with only three discontinuations due to pleural effusion occurring across all treatment years. Additionally, five patients in this cohort experienced pulmonary hypertension, and no patients developed pulmonary arterial hypertension, a serious complication that has been observed in dasatinib-treated patients (37).

Newly occurring renal TEAEs were consistent with previous reports of the effect of bosutinib on renal function (38) and with the progressive increase in patient age. Careful monitoring of renal function during bosutinib treatment is indicated because reductions in eGFR are potentially reversible (1, 38), as has been reported with imatinib (39) where the increase in creatinine levels does not represent a decrease in renal filtration (40). Overall, the incidence of

newly occurring TEAEs in this and other clusters of interest was low after ≥10 years, but these data highlight the importance of close monitoring of patients on long-term therapy, especially those with pre-existing comorbidities.

In multivariable analyses, certain baseline factors were found to be predictive of outcomes. Notably, a higher percentage of Ph+ cells at baseline was predictive of decreased OS and PFS; this is consistent with prior findings of adverse clinical outcomes in patients with a high percentage of baseline Ph+ metaphases (5, 41). Other baseline factors predictive of decreased OS and/or PFS in this cohort included older age (≥65 vs. <65 years), higher PB blasts, splenomegaly, and prior imatinib resistance. The only on-treatment predictor of worse outcomes identified was no MCyR by week 12, which was predictive of decreased OS, consistent with previous studies of patients treated with second-generation TKIs following imatinib failure that identified no MCyR within 1 year as an adverse prognostic factor of survival outcomes (42, 43). A previous response to imatinib has also been identified as predictive of better outcomes in other studies (41, 44) but was not found to be prognostic in this cohort. There were no factors consistently identified to be predictive of response loss in this cohort.

Limitations of this study include the fact that not all patients who were still receiving bosutinib and/or had completed follow-up at the time of the phase I/II study closure were enrolled in the extension study. Twenty patients (7.0% of the total study population) still on treatment with bosutinib at the end of the phase I/II study and 103 (36.3%) who completed survival follow-up in the phase I/II study were not enrolled in the extension, leading to a potential selection bias.

Additionally, molecular assessments were not standardized as the International Scale was not available at the start of the study and molecular assessments were not performed in patients

enrolled in countries where samples could not be exported (30.6% of the total population). Despite these limitations, this analysis presents the longest follow-up to date of any TKI after imatinib failure and provides useful insights about the longer-term effect of TKIs.

In conclusion, bosutinib demonstrated durable efficacy and manageable toxicity after ≥10 years in patients with CP-CML resistant or intolerant to prior imatinib therapy and who remain on long-term treatment.

A plain language summary of this article can be found as Supplementary Information.

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TABLE 1 Treatment summary

	Imatinib-resistant (*n* = 195)	**Imatinib-intolerant (*n* = 89)**	**Total (*N* = 284)**
Duration of follow-up, median (range), months[a]	46.6 (0.5–171.6)	65.8 (0.6–159.6)	53.7 (0.5–171.6)
Duration of treatment, median (range), months[a]	27.6 (0.2–170.5)	24.2 (0.3–154.8)	25.6 (0.2–170.5)
Dose intensity, median (range), mg/day	461.0 (102.9–599.2)	361.8 (87.4–595.2)	436.0 (87.4–599.2)
≥1 dose reduction due to adverse events, *n* (%)	95 (48.7)	57 (64.0)	152 (53.5)
≥1 dose interruption due to adverse events *n* (%)	134 (68.7)	76 (85.4)	210 (73.9)
Dose escalation to 600 mg/day [b], *n*/*N* (%)	34/185 (18.4)	3/88 (3.4)	37/273 (13.6)
Treatment discontinuation at study completion, *n* (%)	149 (76.4)	77 (86.5)	226 (79.6)
Lack of efficacy (disease progression/unsatisfactory response)	64 (32.8)	12 (13.5)	76 (26.8)
Disease progression	45 (23.1)	8 (9.0)	53 (18.7)
Unsatisfactory response	19 (9.7)	4 (4.5)	23 (8.1)
Adverse event	35 (17.9)	39 (43.8)	74 (26.1)
Patient request[c]	19 (9.7	16 (18.0)	35 (12.3)
Death	9 (4.6)	4 (4.5)	13 (4.6)
Investigator request	7 (3.6)	1 (1.1)	8 (2.8)
Lost to follow-up	4 (2.1)	0	4 (1.4)
Global deterioration of health status	2 (1.0)	0	2 (0.7)
Other	9 (4.6)	5 (5.6)	14 (4.9)

[a]One month is defined as 30.4 days.

[b]Patients who started with 600 mg dose were excluded.

[c]Includes patient refused further follow-up and patient no longer willing to continue treatment for reasons other than adverse event.

TABLE 2 Any grade newly occurring renal, effusion, and liver TEAEs, by year

Cluster, *n* (%) MedDRA PT, *n* (%)	**Year 6** **(*n* = 115)**	**Year 7** **(*n* = 106)**	**Year 8** **(*n* = 84)**	**Year 9** **(*n* = 61)**	**Year 10** **(*n* = 58)**	**Year 11+** **(*n* = 55)**
Renal	2 (1.7)	5 (4.7)	4 (4.8)	3 (4.9)	0	8 (14.5)
Chronic kidney disease	0	0	0	0	0	2 (3.6)
Renal failure	0	0	0	0	0	1 (1.8)
Acute kidney injury	1 (0.9)	0	0	0	0	3 (5.5)
Increased blood creatinine	0	3 (2.8)	3 (3.6)	3 (4.9)	0	4 (7.3)
Anuria	1 (0.9)	0	0	0	0	0
Renal impairment	0	2 (1.9)	0	0	0	0
Decreased GFR	0	0	1 (1.2)	0	0	0
Renal injury	0	0	0	0	0	1 (1.8)
Effusion	5 (4.3)	4 (3.8)	4 (4.8)	2 (3.3)	1 (1.7)	4 (7.3)
Pleural effusion	4 (3.5)	2 (1.9)	2 (2.4)	2 (3.3)	1 (1.7)	2 (3.6)
Pericardial effusion	1 (0.9)	2 (1.9)	2 (2.4)	1 (1.6)	0	2 (3.6)
Liver	1 (0.9)	1 (0.9)	2 (2.4)	1 (1.6)	0	3 (5.5)
Increased AST	0	0	1 (1.2)	1 (1.6)	0	1 (1.8)
Increased blood alkaline phosphatase	0	0	0	1 (1.6)	0	0
Increased transaminases	1 (0.9)	0	0	0	0	0
Increased ALT	0	1 (0.9)	1 (1.2)	1 (1.6)	0	1 (1.8)
Increased blood bilirubin	0	0	1 (1.2)	0	0	1 (1.8)
Hepatic lesion	0	0	0	0	0	1 (1.8)

Note: Includes newly occurring TEAEs within clusters of interest in any given year (years 6 to 11+) of treatment in patients still on treatment at the start of each treatment year. Totals for patients with any TEAE in a cluster are not necessarily the sum of lower levels since patients may report two or more different TEAEs within the higher-level category.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TEAE, treatment-emergent adverse event.

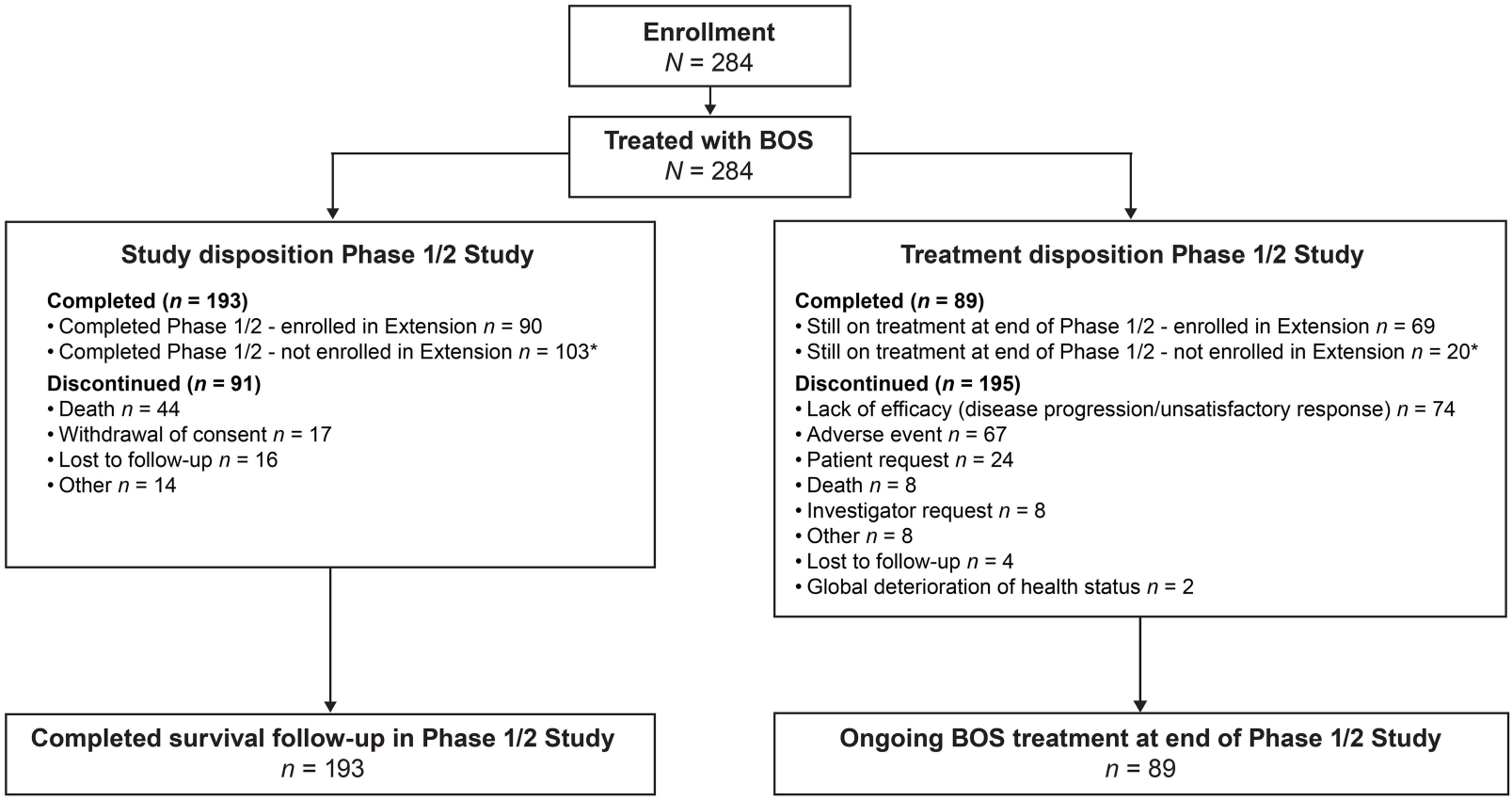
FIGURE LEGENDS

Figure 1 Disposition of patients. BOS, bosutinib.

Figure 2 Bosutinib dose by year for patients on treatment. QD, once daily.

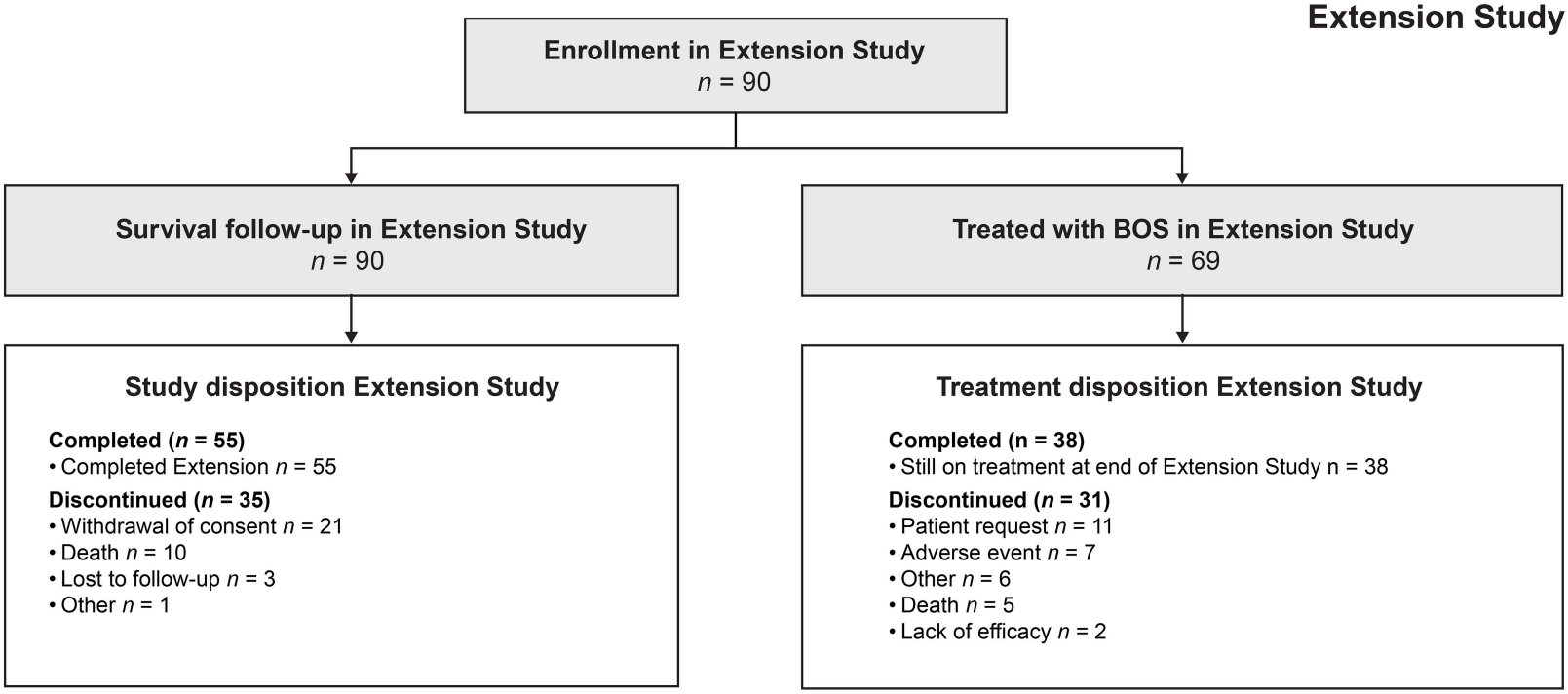
Figure 3 Duration of molecular response among responders: (A) MMR and (B) MR^4. CI, confidence interval; IM, imatinib; MMR, major molecular response.

Figure 4 Survival outcomes. (A) Cumulative incidence of disease progression/death and (B) Kaplan–Meier estimated OS. CI, confidence interval; IM, imatinib; OS, overall survival.

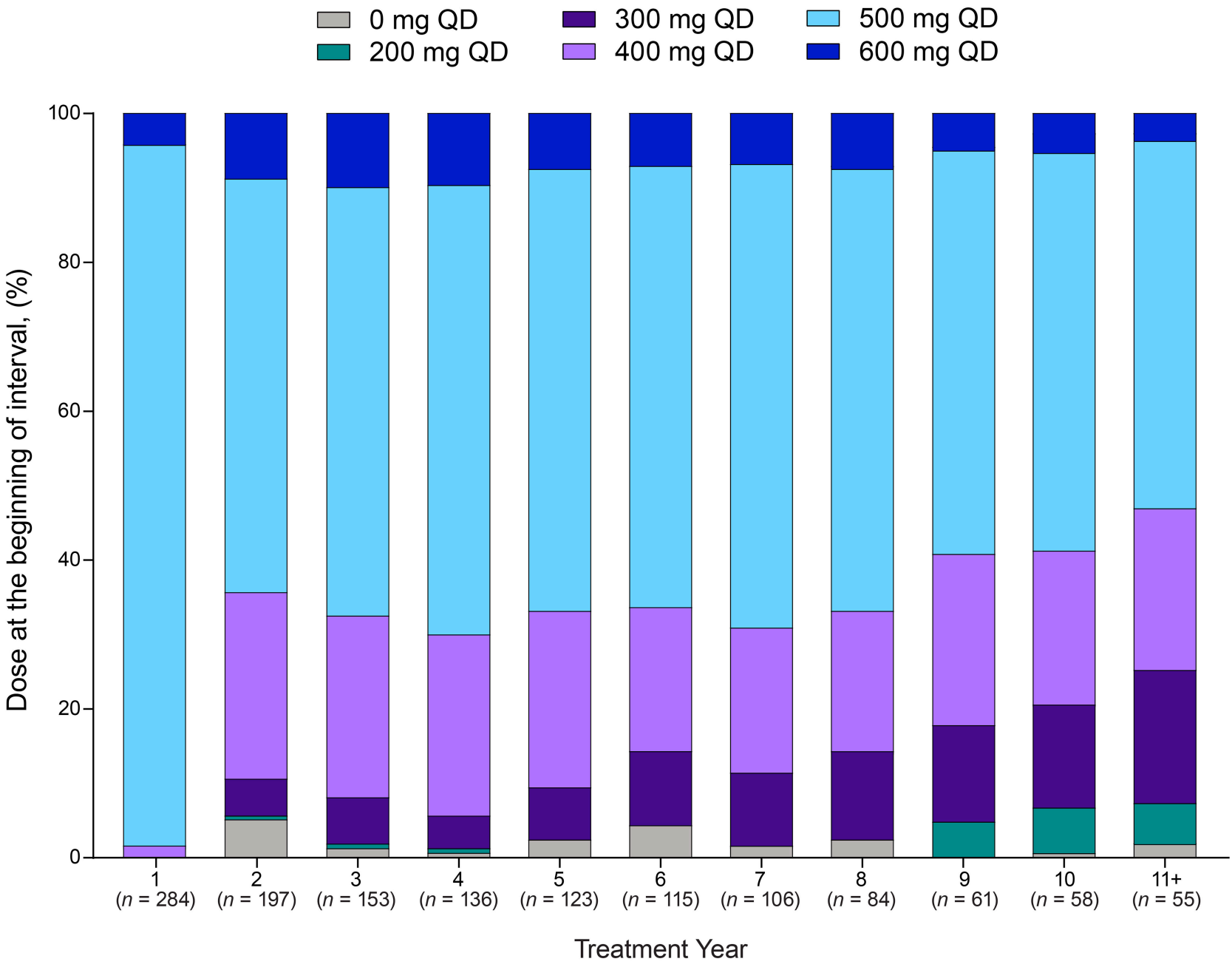


Phase 1/2 Study

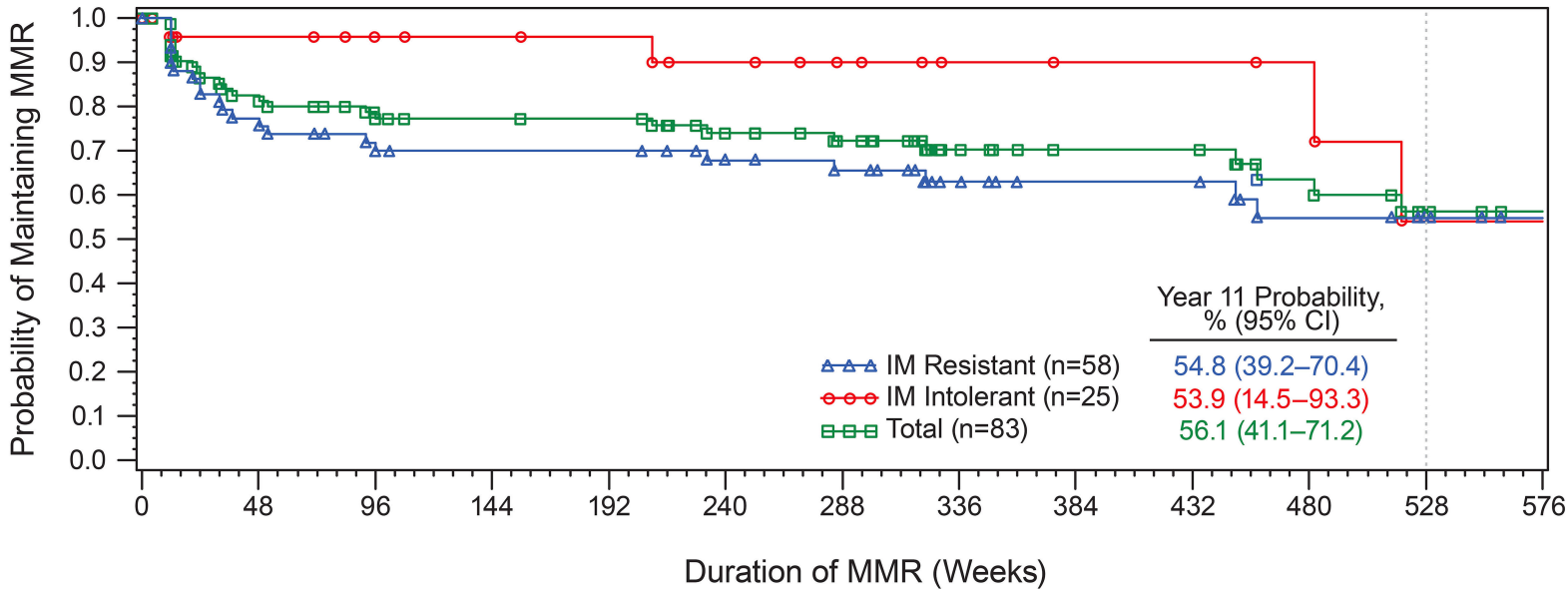
Extension Study



* 13 patients from China were enrolled in the Extension Study but the data was excluded due to regulatory requirements.


0 mg QD
200 mg QD
300 mg QD
400 mg QD
500 mg QD
600 mg QD
Dose at the beginning of interval, (%)
100
80
60
40
20
0
1 (n = 284)
2 (n = 197)
3 (n = 153)
4 (n = 136)
5 (n = 123)
6 (n = 115)
7 (n = 106)
8 (n = 84)
9 (n = 61)
10 (n = 58)
11+ (n = 55)
Treatment Year

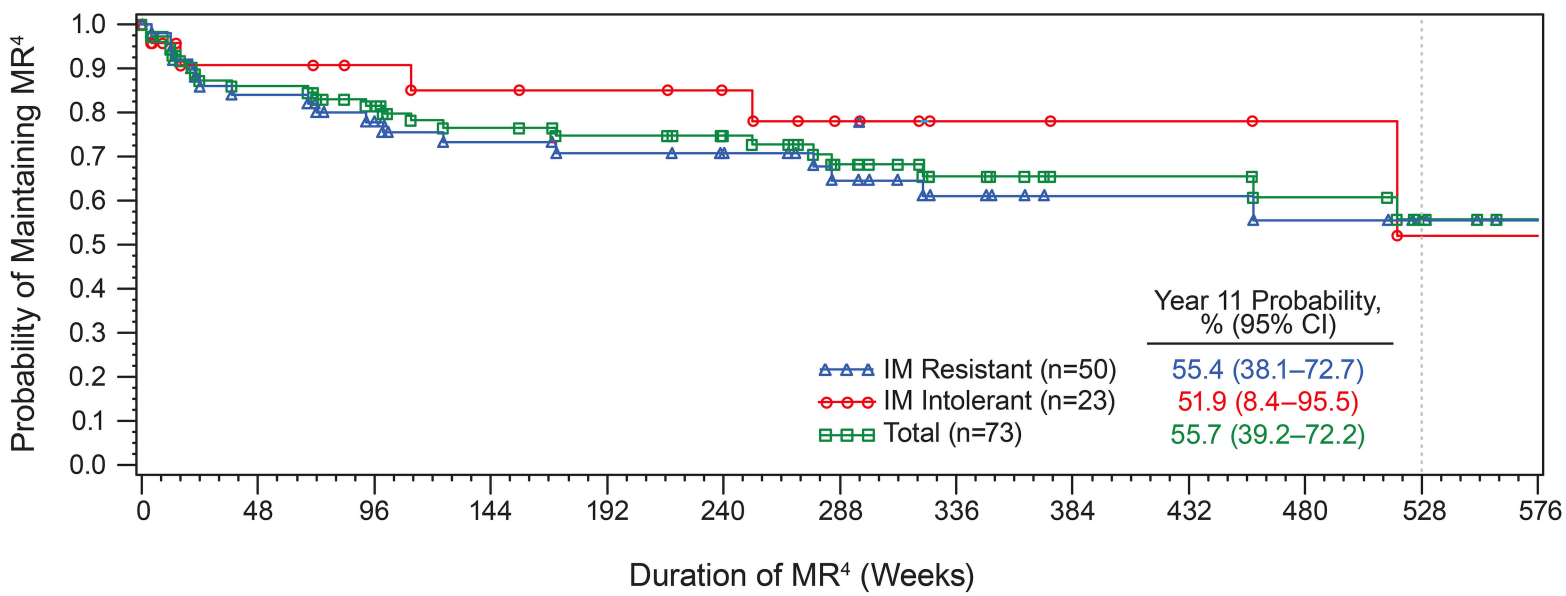
A.



Patients at Risk / Cumulative Event (*n*)

IM Resistant	58/0	43/13	38/17	36/17	36/17	32/18	29/19	21/20	17/20	17/20	13/22	10/22	7/22
IM Intolerant	25/0	21/1	18/1	17/1	16/1	14/2	11/2	7/2	6/2	6/2	5/2	3/4	3/4
Total	83/0	64/14	56/18	53/18	52/18	46/20	40/21	28/22	23/22	23/22	18/24	13/26	10/26

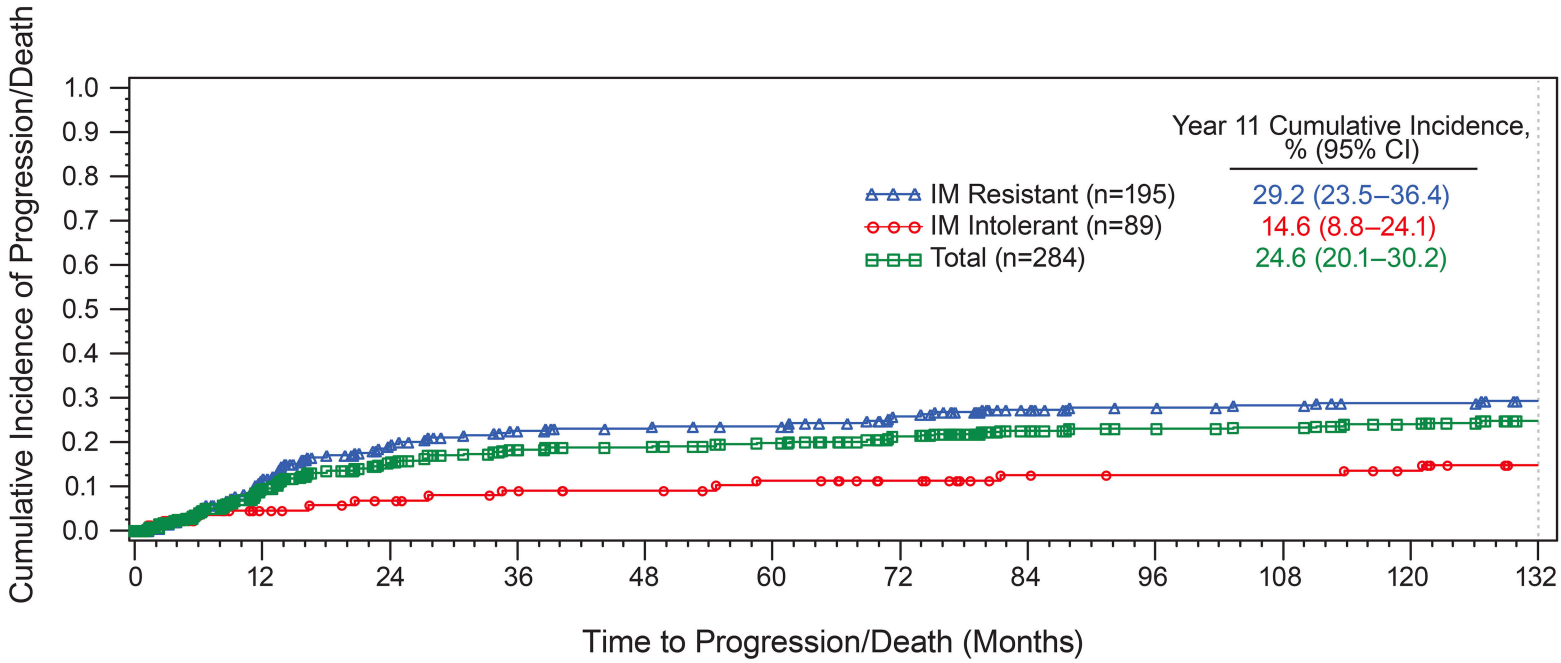
B.



Patients at Risk / Cumulative Event (*n*)

IM Resistant	50/0	42/8	36/11	31/13	29/14	26/14	21/16	15/17	11/17	11/17	10/18	7/18	4/18
IM Intolerant	23/0	18/2	16/2	15/3	14/3	12/3	9/4	5/4	4/4	4/4	3/4	2/5	2/5
Total	73/0	60/10	52/13	46/16	43/17	38/17	30/20	20/21	15/21	15/21	13/22	9/23	6/23

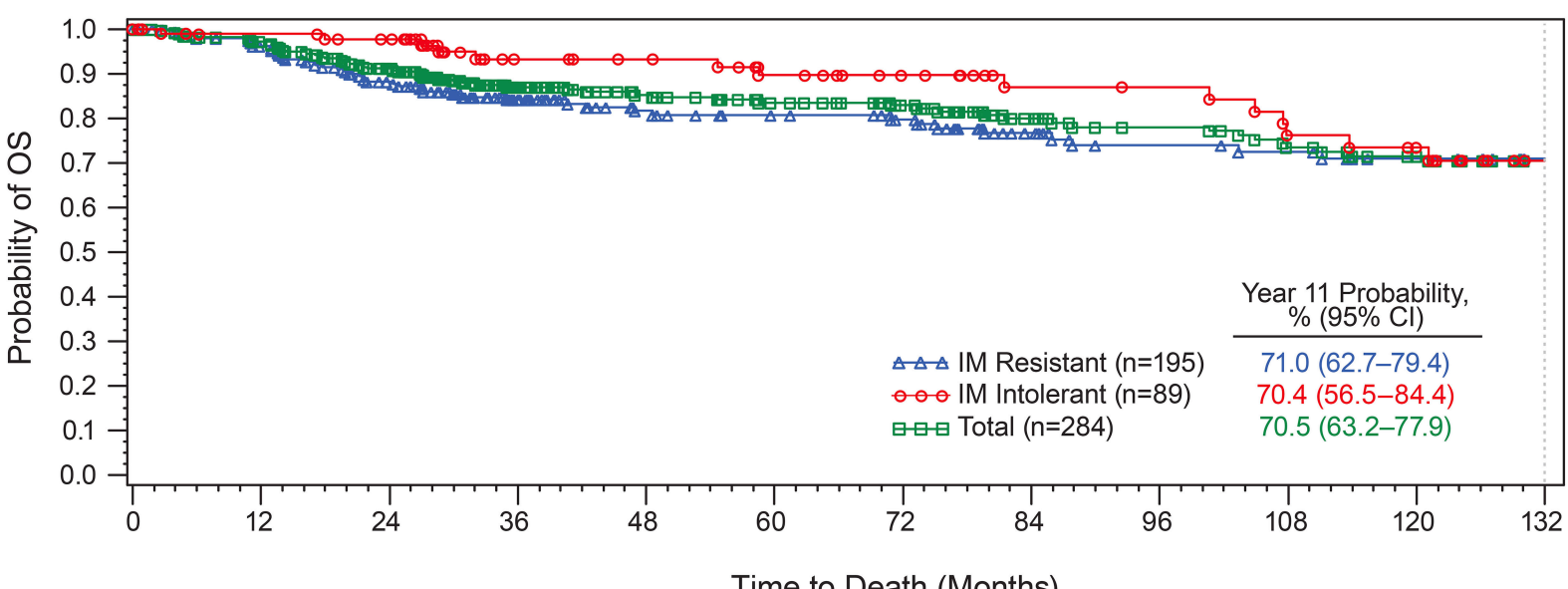
A.



Patients at Risk / Cumulative Event (*n*)

IM Resistant	195/0	136/22	103/37	91/44	85/45	81/46	69/50	51/53	43/54	40/55	36/56	30/57
IM Intolerant	89/0	51/4	45/6	40/8	37/8	33/10	27/10	18/11	16/11	16/11	13/12	7/13
Total	284/0	187/26	148/43	131/52	122/53	114/56	96/60	69/64	59/65	56/66	49/68	37/70

B.



Patients at Risk / Cumulative Event (*n*)

IM Resistant	195/0	182/7	159/22	120/29	94/32	87/33	81/34	61/37	53/39	51/40	46/41	40/41
IM Intolerant	89/0	84/1	80/2	56/5	53/5	47/7	41/7	33/8	32/8	28/12	25/13	15/14
Total	284/0	266/8	239/24	176/34	147/37	134/40	122/41	94/45	85/47	79/52	71/54	55/55

SUPPLEMENTARY MATERIAL

Second-line bosutinib for chronic phase chronic myeloid leukemia after imatinib: final, 10-year results of a phase I/II study

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METHODS

Additional efficacy methods

MR^4 was defined similarly to MMR but required *BCR*::*ABL1* ≤0.01%. In the extension study, complete cytogenetic response (CCyR) was imputed on a specific date if MMR was achieved and there was no valid cytogenetic assessment on that date. Evaluable patients for cytogenetic and molecular response had a valid baseline assessment for the respective endpoint. Mutation analysis was performed by direct sequencing using a peripheral blood (PB) sample collected prior to first dose and at treatment completion. In the phase 1/2 study, mutational analysis was performed centrally. In the extension study, mutational analysis was performed locally initially and at a central laboratory after Protocol Amendment 1.

Additional safety methods

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) increasing in severity from baseline or AEs starting during treatment or within 30 days of last bosutinib dose. Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v3.0). eGFR was calculated using Modification of Diet in Renal Disease method and graded per Kidney Disease: Improving Global Outcomes (KDIGO) functional stages. Cardiac, effusion, gastrointestinal, hypertension, liver, renal, and vascular TEAE clusters included prespecified Medical Dictionary for Regulatory Activities (v23.0) terms.

Treatment-emergent adverse event cluster definitions

Clusters of TEAEs included the following Medical Dictionary for Regulatory Activities (MedDRA; v23.0) terms:

- Cardiac: high level group terms (HLGTs) Cardiac arrhythmias and Heart failures; preferred terms (PTs) Cardiac death, Ejection fraction decreased, Sudden cardiac death, and Sudden death; standardized MedDRA query (narrow) Torsade de pointes/QT prolongation.
- Cytopenias:
    - Anemia: PTs Anemia and Hemoglobin decreased.
    - Neutropenia: PTs Neutropenia and Neutrophil count decreased.
    - Leukopenia: PTs Leukopenia and White blood cell count decreased.
    - Lymphopenia: PTs Lymphopenia and Lymphocyte count decreased.
    - Thrombocytopenia: PTs Thrombocytopenia and Platelet count decreased.
- Effusion: PTs Pleural effusion and Pericardial effusion.
- Gastrointestinal: PTs Diarrhea, Defecation urgency, Frequent bowel movements, Gastrointestinal hypermotility, Nausea, Regurgitation, Retching, Vomiting, and Vomiting projectile.
- Hypertension: HLGT Vascular hypertensive disorders; PTs Blood pressure abnormal, Blood pressure ambulatory abnormal, Blood pressure ambulatory increased, Blood pressure diastolic abnormal, Blood pressure diastolic increased, Blood pressure increased, Blood pressure systolic abnormal, and Blood pressure systolic increased.
- Liver: Sub-standardized MedDRA queries (Narrow) Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions; and Hepatitis, non-infectious; PTs Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Bilirubin conjugated abnormal, Bilirubin conjugated

increased, Blood alkaline phosphatase abnormal, Blood alkaline phosphatase increased, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Hepatic function abnormal, Hyperbilirubinemia, Hypertransaminasemia, Liver function test abnormal, Liver function test increased, Transaminases abnormal, and Transaminases increased.

- Renal: high level term (HLT) Renal failure and impairment; PTs Blood creatinine abnormal, Blood creatinine increased, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Glomerular filtration rate abnormal, and Glomerular filtration rate decreased.
- Vascular:
    - Cardiovascular: HLGT Coronary artery disorders; HLTs Arterial therapeutic procedures (excluding aortic), Vascular imaging procedures not elsewhere classified (NEC), and Vascular therapeutic procedures NEC; PT Transcatheter arterial chemoembolization.
    - Cerebrovascular: HLTs Central nervous hemorrhages and cerebrovascular accidents, Central nervous system vascular disorders NEC, and Transient cerebrovascular events.
    - Peripheral vascular: HLGTs Arteriosclerosis, stenosis, vascular insufficiency and necrosis, and Embolism and thrombosis; HLTs, Non-site specific vascular disorders NEC and Peripheral vascular disorders NEC (excluding the 2 PTs Flushing and Hot flush); PT Intestinal ischemia.

Additional statistical methods

Response loss was defined as confirmed loss of response (two consecutive nonresponse assessments ≥4 weeks apart), treatment discontinuation due to progressive disease or death, or death within 30 days of last dose. For complete cytogenetic response (CCyR), confirmed loss was defined as two consecutive assessments with >0 Ph+ metaphases or ≥1% positive cells from fluorescence in situ hybridization (FISH) ≥4 weeks apart. For major molecular response (MMR), confirmed loss was defined as two consecutive assessments ≥4 weeks apart with a <3-log (>0.1%) reduction in transcripts. Loss of MR^4 was defined similarly to loss of MMR but required <4-log (>0.01%) reduction in transcripts. Disease progression was defined as evolution from CP to accelerated phase or blast phase; doubling of white blood cell count over ≥1 month with a confirmed second count >$20x10^9$/L; or loss of confirmed complete hematologic response or major cytogenetic response (MCyR) with an increase of ≥30% in Ph+ metaphases. Time-to-event distributions were estimated using the Kaplan–Meier method (duration of response [DOR] and overall survival) or cumulative incidence adjusted for the competing risk of treatment discontinuation without an event (time to disease progression/death [progression-free survival]). Two-sided 95% confidence intervals (CIs) for response rates and Kaplan–Meier quartiles were determined using the exact binomial and Brookmeyer–Crowley linear transformations methods, respectively. Two-sided 95% CIs for the Kaplan–Meier estimates and the cumulative incidence yearly probability estimates were based on Greenwood's formula and the delta method using a log transformation, respectively.

Covariates for multivariable regression analysis

Prior response to imatinib was defined as the achievement of at least a minimal cytogenetic response (standard cytogenetic criteria: 66%–95% Ph+ cells from bone marrow or *BCR*::*ABL1*

from FISH). Determination of Ph+ ratio occurred during the screening visit within 14 days before registration of the patient in the study and required ≥20 metaphases for standard cytogenetics or ≥200 cells for FISH. Disease duration was defined as the time between the primary diagnosis and date of administration of first dose of bosutinib. Patients initiating imatinib treatment ≥6 months after diagnosis or who had received prior interferon therapy were considered to be in late chronic phase; other patients were considered to be in early chronic phase. Bosutinib-sensitive mutations are those resulting in half maximal inhibitory concentration (IC_{50}) ≤3-fold higher than wild type (*M244V, Q252H, Y253H, Y253F, D276G, E279K, E292L, F317L, M343T, M351T, F359I, F359V, L384M, H396P, H396R, G398R,* and *F486S*); insensitive mutations are those with IC_{50} values >3 to ≤10-fold higher than wild type (*L248V, G250E, E255V,* and *T315A*); highly insensitive mutations are those with IC_{50} values >10-fold higher than wild type (*L248R, L248R+F359I, E255K, V299L, T315I, T315V, F317R, F317V*); all other baseline mutations are considered as sensitivity unknown [1,2]. Patients with multiple mutations of different sensitivities were categorized by the following hierarchy: highly insensitive, insensitive, unknown sensitivity, then sensitive. Liver function test TEAEs included PTs Alanine aminotransferase increased, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood bilirubin increased, Hepatic enzyme increased, Hyperbilirubinemia, Liver function test abnormal, Liver function test increased, Transaminases increased. Thrombocytopenia TEAEs include PTs: Thrombocytopenia, Platelet count decreased.

SUPPLEMENTAL REFERENCES

1. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol 2009;27:469-471.

2. Redaelli S, Mologni L, Rostagno R, et al. Three novel patient-derived BCR/ABL mutants show different sensitivity to second and third generation tyrosine kinase inhibitors. Am J Hematol 2012;87:E125-128.

TABLE S1 Cumulative response rates by years 2, 5, and 10+ in evaluable patients

	Imatinib-resistant			**Imatinib-intolerant**			**Total**		
***n*/*N* (%)**	**(*n* = 195)**			**(*n* = 89)**			**(*N* = 284)**		
[95% CI]	**Year 2**	**Year 5**	**Year 10+**	**Year 2**	**Year 5**	**Year 10+**	**Year 2**	**Year 5**	**Year 10+**
All evaluable patients									
MCyR	102/182 (56.0)	106/182 (58.2)	108/182 (59.3)	49/80 (61.3)	49/80 (61.3)	49/80 (61.3)	151/262 (57.6)	155/262 (59.2)	157/262 (59.9)
	[48.5–63.4]	[50.7–65.5]	[51.8–66.5]	[49.7–71.9]	[49.7–71.9]	[49.7–71.9]	[51.4–63.7]	[52.9–65.2]	[53.7–65.9]
CCyR	78/182 (42.9)	87/182 (47.8)	88/182 (48.4)	41/80 (51.3)	42/80 (52.5)	42/80 (52.5)	119/262 (45.4)	129/262 (49.2)	130/262 (49.6)
	[35.6–50.4]	[40.4–55.3]	[40.9–55.9]	[39.8–62.6]	[41.0–63.8]	[41.0–63.8]	[39.3–51.7]	[43.0–55.5]	[43.4–55.8]
MMR	40/127 (31.5)	53/127 (41.7)	58/127 (45.7)	20/70 (28.6)	25/70 (35.7)	25/70 (35.7)	60/197 (30.5)	78/197 (39.6)	83/197 (42.1)
	[23.5–40.3]	[33.0–50.8]	[36.8–54.7]	[18.4–40.6]	[24.6–48.1]	[24.6–48.1]	[24.1–37.4]	[32.7–46.8]	[35.1–49.4]
MR[4]	31/127 (24.4)	37/127 (29.1)	50/127 (39.4)	19/70 (27.1)	22/70 (31.4)	23/70 (32.9)	50/197 (25.4)	59/197 (29.9)	73/197 (37.1)
	[17.2–32.8]	[21.4–37.9]	[30.8–48.4]	[17.2–39.1]	[20.9–43.6]	[22.1–45.1]	[19.5–32.1]	[23.6–36.9]	[30.3–44.2]
Patients without the respective baseline response									
MCyR	77/148 (52.0)	80/148 (54.1)	82/148 (55.4)	31/56 (55.4)	31/56 (55.4)	31/56 (55.4)	108/204 (52.9)	111/204 (54.4)	113/204 (55.4)
	[43.7–60.3]	[45.7–62.3]	[47.0–63.6]	[41.5–68.7]	[41.5–68.7]	[41.5–68.7]	[45.8–59.9]	[47.3–61.4]	[48.3–62.3]
CCyR	74/178 (41.6)	83/178 (46.6)	84/178 (47.2)	31/68 (45.6)	32/68 (47.1)	32/68 (47.1)	105/246 (42.7)	115/246 (46.7)	116/246 (47.2)
	[34.2–49.2]	[39.1–54.2]	[39.7–54.8]	[33.5–58.1]	[34.8–59.6]	[34.8–59.6]	[36.4–49.1]	[40.4–53.2]	[40.8–53.6]
MMR	40/126 (31.7)	53/126 (42.1)	58/126 (46.0)	14/63 (22.2)	19/63 (30.2)	19/63 (30.2)	54/189 (28.6)	72/189 (38.1)	77/189 (40.7)
	[23.7–40.6]	[33.3–51.2]	[37.1–55.1]	[12.7–34.5]	[19.2–43.0]	[19.2–43.0]	[22.2–35.6]	[31.1–45.4]	[33.7–48.1]
MR[4]	31/126 (24.6)	37/126 (29.4)	50/126 (39.7)	14/64 (21.9)	17/64 (26.6)	18/64 (28.1)	45/190 (23.7)	54/190 (28.4)	68/190 (35.8)
	[17.4–33.1]	[21.6–38.1]	[31.1–48.8]	[12.5–34.0]	[16.3–39.1]	[17.6–40.8]	[17.8–30.4]	[22.1–35.4]	[29.0–43.0]

CCyR, complete cytogenetic response; CI, confidence interval; MCyR, major cytogenetic response; MMR, major molecular response.

TABLE S2 New *BCR::ABL1* point mutations for patients who were still on-treatment at the start of Year 6

Mutation	**CP2L (N=115)**
Evaluable samples	45
Patients with emergent mutation, n (%)	8 (7.0)
Type of mutation, n (%)	
P-Loop	0 (0)
Non P-Loop	8 (100)
F359V	1 (12.5)
H295L	1 (12.5)
M244V	1 (12.5)
M351T	1 (12.5)
S348L	1 (12.5)
S410G	1 (12.5)
V299L	2 (25.0)

TABLE S3 Any grade newly occurring vascular, cardiac, hypertension, gastrointestinal, and other TEAEs, by year

Cluster, *n* (%) MedDRA PT, *n* (%)	**Year 6** **(*n* = 115)**	**Year 7** **(*n* = 106)**	**Year 8** **(*n* = 84)**	**Year 9** **(*n* = 61)**	**Year 10** **(*n* = 58)**	**Year 11+** **(*n* = 55)**
Vascular	2 (1.7)	0	3 (3.6)	3 (4.9)	1 (1.7)	6 (10.9)
Cardiovascular	1 (0.9)	0	0	1 (1.6)	0	2 (3.6)
Coronary artery disease	1 (0.9)	0	0	0	0	0
Myocardial ischemia	0	0	0	1 (1.6)	0	0
Acute coronary syndrome	0	0	0	0	0	1 (1.8)
Acute myocardial infarction	0	0	0	0	0	1 (1.8)
Cerebrovascular	1 (0.9)	0	2 (2.4)	2 (3.3)	1 (1.7)	1 (1.8)
Cerebellar infarction	1 (0.9)	0	0	0	1 (1.7)	0
Cerebrovascular disorder	1 (0.9)	0	0	0	0	0
Cerebral infarction	0	0	1 (1.2)	1 (1.6)	0	0
Subarachnoid hemorrhage	0	0	1 (1.2)	0	0	0
Cerebrovascular accident	0	0	0	1 (1.6)	0	0
Cerebral arteriosclerosis	0	0	0	0	0	1 (1.8)
Cerebral ischemia	0	0	0	0	0	1 (1.8)
Peripheral vascular	0	0	1 (1.2)	0	0	3 (5.5)
Ischemic necrosis	0	0	1 (1.2)	0	0	0
Blue toe syndrome	0	0	0	0	0	1 (1.8)
Deep vein thrombosis	0	0	0	0	0	1 (1.8)
Peripheral artery stenosis	0	0	0	0	0	1 (1.8)
Thrombophlebitis	0	0	0	0	0	1 (1.8)

Cluster, *n* (%) MedDRA PT, *n* (%)	**Year 6** **(*n* = 115)**	**Year 7** **(*n* = 106)**	**Year 8** **(*n* = 84)**	**Year 9** **(*n* = 61)**	**Year 10** **(*n* = *58)***	**Year 11+** **(*n* = 55)**
Thrombosis	0	0	0	0	0	1 (1.8)
Cardiac (excluding cardiovascular)	3 (2.6)	2 (1.9)	1 (1.2)	2 (3.3)	0	2 (3.6)
Congestive cardiac failure	1 (0.9)	2 (1.9)	0	0	0	1 (1.8)
Bradycardia	1 (0.9)	0	0	0	0	1 (1.8)
AV block complete	1 (0.9)	0	0	0	0	0
Chronic cardiac failure	1 (0.9)	0	0	0	0	0
Atrial fibrillation	0	0	0	2 (3.3)	0	0
Acute cardiac failure	0	0	1 (1.2)	0	0	0
Hypertension	0	2 (1.9)	0	0	2 (3.4)	7 (12.7)
Hypertension	0	2 (1.9)	0	0	1 (1.7)	7 (12.7)
Hypertensive crisis	0	0	0	0	1 (1.7)	0
Gastrointestinal	1 (0.9)	2 (1.9)	0	1 (1.6)	1 (1.7)	0
Nausea	0	1 (0.9)	0	0	0	0
Vomiting	1 (0.9)	0	0	0	1 (1.7)	0
Diarrhea	0	1 (0.9)	0	1 (1.6)	0	0
Other TEAEs						
Anemia	2 (1.7)	1 (0.9)	3 (3.6)	0	0	3 (5.5)
Cough	1 (0.9)	0	0	2 (3.3)	2 (3.4)	1 (1.8)
Fatigue	1 (0.9)	0	0	0	0	0
Increased lipase	1 (0.9)	1 (0.9)	0	2 (3.3)	0	2 (3.6)
Back pain	0	0	0	1 (1.6)	1 (1.7)	3 (5.5)

Cluster, *n* (%) MedDRA PT, *n* (%)	**Year 6** **(*n* = 115)**	**Year 7** **(*n* = 106)**	**Year 8** **(*n* = 84)**	**Year 9** **(*n* = 61)**	**Year 10** **(*n* = *58)***	**Year 11+** **(*n* = 55)**
Dyspnea	2 (1.7)	1 (0.9)	1 (1.2)	1 (1.6)	0	2 (3.6)
Abdominal pain	2 (1.7)	0	0	1 (1.6)	0	2 (3.6)
Constipation	1 (0.9)	4 (3.8)	1 (1.2)	0	1 (1.7)	0
Peripheral edema	1 (0.9)	3 (2.8)	1 (1.2)	0	1 (1.7)	2 (3.6)
Pneumonia	1 (0.9)	3 (2.8)	0	1 (1.6)	0	5 (9.1)
Increased blood creatine phosphokinase	0	1 (0.9)	1 (1.2)	0	0	2 (3.6)
Pyrexia	0	0	3 (3.6)	1 (1.6)	1 (1.7)	0
Arthralgia	3 (2.6)	4 (3.8)	0	3 (4.9)	1 (1.7)	2 (3.6)
Myalgia	2 (1.7)	1 (0.9)	0	2 (3.3)	0	0
Hyponatremia	0	1 (0.9)	0	0	0	2 (3.6)
Edema	0	0	0	1 (1.6)	0	2 (3.6)
Asthenia	2 (1.7)	1 (0.9)	0	2 (3.3)	0	1 (1.8)
Neck pain	2 (1.7)	0	1 (1.2)	2 (3.3)	0	0
Hyperglycemia	2 (1.7)	0	0	2 (3.3)	0	0
Cellulitis	1 (0.9)	1 (0.9)	0	0	1 (1.7)	2 (3.6)
Increased blood cholesterol	1 (0.9)	0	2 (2.4)	1 (1.6)	1 (1.7)	2 (3.6)
Bone pain	1 (0.9)	0	0	2 (3.3)	1 (1.7)	3 (5.5)
Pulmonary hypertension	1 (0.9)	0	0	0	0	2 (3.6)
Underdose	0	1 (0.9)	2 (2.4)	2 (3.3)	0	0
Increased amylase	0	1 (0.9)	0	2 (3.3)	0	1 (1.8)
Colitis	0	0	1 (1.2)	1 (1.6)	0	2 (3.6)

Cluster, *n* (%) MedDRA PT, *n* (%)	**Year 6** **(*n* = 115)**	**Year 7** **(*n* = 106)**	**Year 8** **(*n* = 84)**	**Year 9** **(*n* = 61)**	**Year 10** **(*n* = *58)***	**Year 11+** **(*n* = 55)**
Fall	0	0	1 (1.2)	1 (1.6)	0	2 (3.6)
Product dispensing error	0	0	0	2 (3.3)	0	0
Fluid retention	0	0	0	0	0	3 (5.5)
Anxiety	0	0	0	0	0	2 (3.6)
Peripheral neuropathy	0	0	0	0	0	2 (3.6)

Note: Includes newly occurring TEAEs within clusters of interest and newly occurring TEAEs reported in ≥3% of patients in any given year (years 6 to 11+) of treatment in patients still on treatment at the start of each treatment year. Totals for patients with any TEAE in a cluster are not necessarily the sum of lower levels since patients may report two or more different TEAEs within the higher-level category.

AV, atrioventricular; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TEAE, treatment-emergent adverse event.

TABLE S4 Yearly exposure-adjusted incidence rates of any-grade cardiac, hypertension, and vascular TEAEs

Exposure-adjusted incidence rate, per patient-year (95% CI)	**Second-line study[a]**	**BELA trial[b]**			**BFORE trial[c]**		
	Bosutinib 500 mg QD (*N* = 284)	**Bosutinib 500 mg QD (*N* = 248)**	**Imatinib 400 mg QD (*N* = 251)**	**HR[d] (95% CI)**	**Bosutinib 400 mg QD (*N* = 268)**	**Imatinib 400 mg QD (*N* = 265)**	**HR[d] (95% CI)**
Cardiac TEAEs	0.030 (0.020–0.042)	0.024 (0.015–0.037)	0.019 (0.010–0.031)	1.36 (0.70–2.65)	0.031 (0.020–0.046)	0.029 (0.018–0.043)	0.91 (0.47–1.74)
Hypertension TEAEs	0.032 (0.022–0.044)	0.027 (0.017–0.041)	0.018 (0.010–0.030)	1.51 (0.79–2.91)	0.034 (0.022–0.048)	0.037 (0.025–0.053)	0.95 (0.57–1.59)
Vascular TEAEs	0.027 (0.018–0.038)	0.017 (0.009–0.028)	0.011 (0.005–0.020)	1.48 (0.63–3.45)	0.023 (0.014–0.036)	0.011 (0.005–0.021)	2.23 (0.97–5.09)
Cardiovascular	0.014 (0.008–0.023)	0.008 (0.003–0.017)	0.006 (0.002–0.014)		0.015 (0.008–0.026)	0.001 (<0.001–0.007)	
Cerebrovascular	0.009 (0.004–0.016)	0.002 (<0.001–0.008)	0.002 (<0.001–0.009)		0.002 (<0.001–0.008)	0.004 (0.001–0.010)	
Peripheral vascular	0.008 (0.004–0.016)	0.006 (0.002–0.014)	0.002 (<0.001–0.009)		0.007 (0.002–0.015)	0.007 (0.003–0.016)	

[a]MedDRA v23.0 was used.

[b]Based on ≥5 years of follow-up from the final database snapshot in 2015; imatinib-treated patients were only followed for 4 years; cardiac and vascular rates and HRs have been reported (Brümmendorf T, et al. *Leukemia* 2022). MedDRA v18.0 was used.

[c]Based on 5 years of follow-up from the final database snapshot on June 12, 2020; cardiac and vascular exposure-adjusted rates and associated HRs have been reported (Brümmendorf T, et al. *Leukemia* 2022). MedDRA v23.0 was used.

[d]Based on a proportional subdistribution hazards model of TEAEs, adjusted for the competing risk of treatment discontinuation due to any reason. HRs with a 95% CI that excluded 1 were considered predictive of outcome, and no adjustments for multiple comparisons were made.

CI, confidence interval; HR, hazard ratio; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; TEAE, treatment-emergent adverse event.

TABLE S5 Changes in LVEF

		Maximum NCI CTCAE on-treatment grade					
***n* (%)**	**Baseline**	**Normal**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Missing**
Normal	149 (52.5)	100 (35.2)	19 (6.7)	1 (0.4)	0	0	29 (10.2)
Grade 1	60 (21.1)	18 (6.3)	29 (10.2)	2 (0.7)	1 (0.4)	0	10 (3.5)
Grade 2	5 (1.8)	0	1 (0.4)	3 (1.1)	0	0	1 (0.4)
Grade 3	3 (1.1)	0	0	0	2 (0.7)	0	1 (0.4)
Grade 4	0	0	0	0	0	0	0
Missing	67 (23.6)	13 (4.6)	8 (2.8)	3 (1.1)	1 (0.4)	0	42 (14.8)
Total	284 (100.0)	131 (46.1)	57 (20.1)	9 (3.2)	4 (1.4)	0	83 (29.2)

Grades are defined as: grade 1, <60 to 50%; grade 2, <50 to 40%; grade 3, <40 to 20%; grade 4, <20%.

CTCAE, Common Terminology Criteria for Adverse Events; LVEF, left ventricular ejection fraction; NCI, National Cancer Institute.

TABLE S6 Changes in QTcF.

		Maximum NCI CTCAE on-treatment grade			
***n* (%)**	**Baseline**	**Normal**	**Grade 1**	**Grade 2**	**Grade 3**
Normal	272 (95.8)	252 (88.7)	18 (6.3)	2 (0.7)	0
Grade 1	8 (2.8)	3 (1.1)	5 (1.8)	0	0
Grade 2	3 (1.1)	0	0	2 (0.7)	1 (0.4)
Grade 3	0	0	0	0	0
Missing	1 (0.4)	1 (0.4)	0	0	0
Total	284 (100.0)	256 (90.1)	23 (8.1)	4 (1.4)	1 (0.4)

Grades are defined as: normal, ≤450 ms; grade 1, >450 to 470 ms; grade 2, >470 to 500 ms or ≥60 ms change from baseline; grade 3, >500 ms.

CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; QTcF, QT interval corrected for heart rate according to Fridericia's formula.

TABLE S7 Changes in eGFR.

		Maximum KDIGO on-treatment grade					
***n* (%)**	**Baseline**	**Grade 1**	**Grade 2**	**Grade 3a**	**Grade 3b**	**Grade 4**	**Grade 5**
Grade 1	75 (26.4)	13 (4.6)	48 (16.9)	7 (2.5)	5 (1.8)	0	2 (0.7)
Grade 2	163 (57.4)	2 (0.7)	53 (18.7)	66 (23.2)	28 (9.9)	11 (3.9)	3 (1.1)
Grade 3a	33 (11.6)	0	2 (0.7)	10 (3.5)	14 (4.9)	7 (2.5)	0
Grade 3b	13 (4.6)	0	1 (0.4)	0	1 (0.4)	9 (3.2)	2 (0.7)
Grade 4	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0
Total	284 (100.0)	15 (5.3)	104 (36.6)	83 (29.2)	48 (16.9)	27 (9.5)	7 (2.5)

Note: GFR is estimated according to the MDRD method. eGFR = 175 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if patient is female) × 1.212 (if patient is Black or African American).

KDIGO kidney function grades: grade 1, ≥90 mL/min/1.73 m^2; grade 2, 60 to <90 mL/min/1.73 m^2; grade 3a, 45 to <60 mL/min/1.73 m^2; grade 3b, 30 to <45 mL/min/1.73 m^2; grade 4, 15 to <30 mL/min/1.73 m^2; grade 5, <15 mL/min/1.73 m^2.

eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; MDRD, Modification of Diet in Renal Disease.

Figure S1. Treatment discontinuations by year

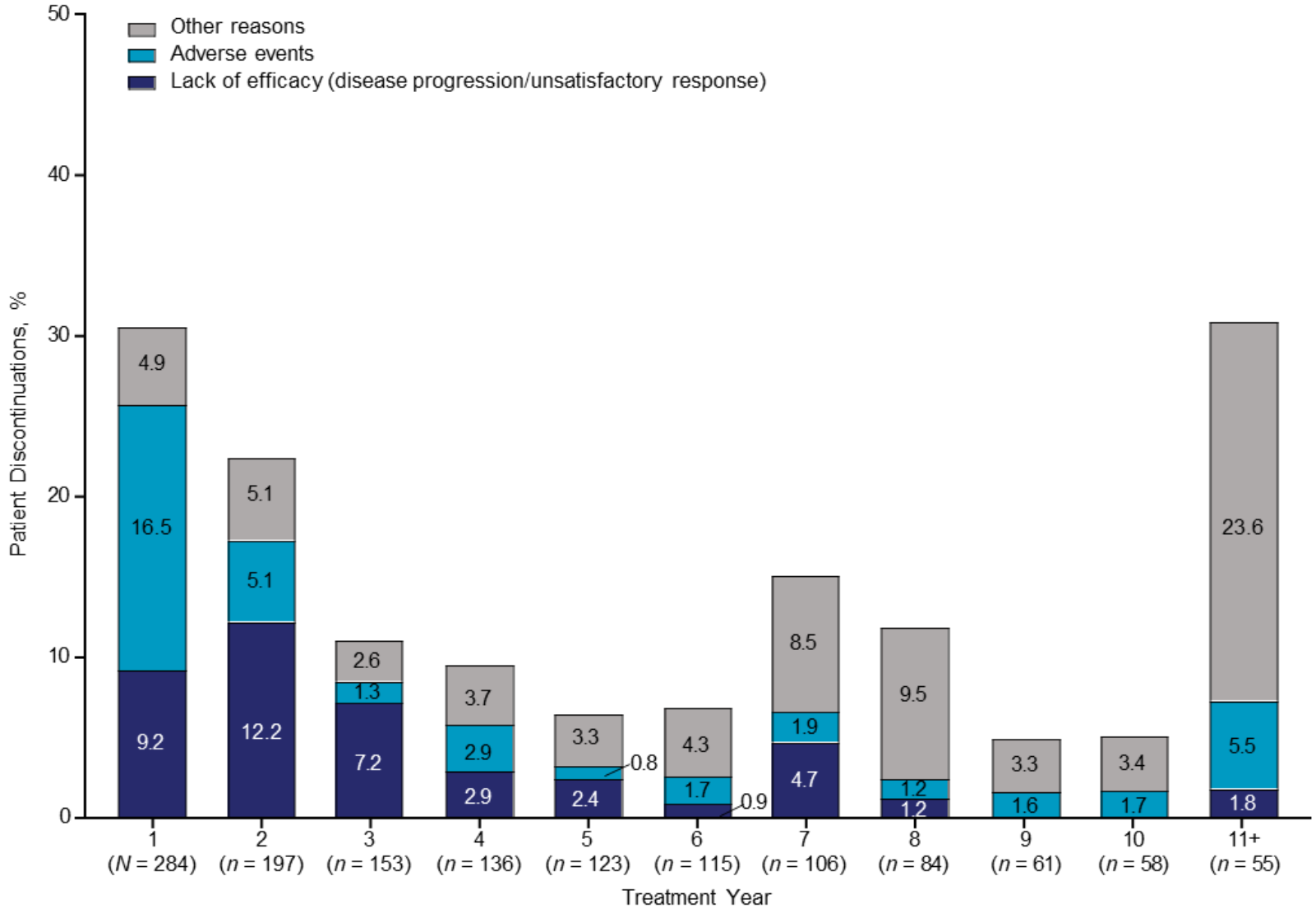
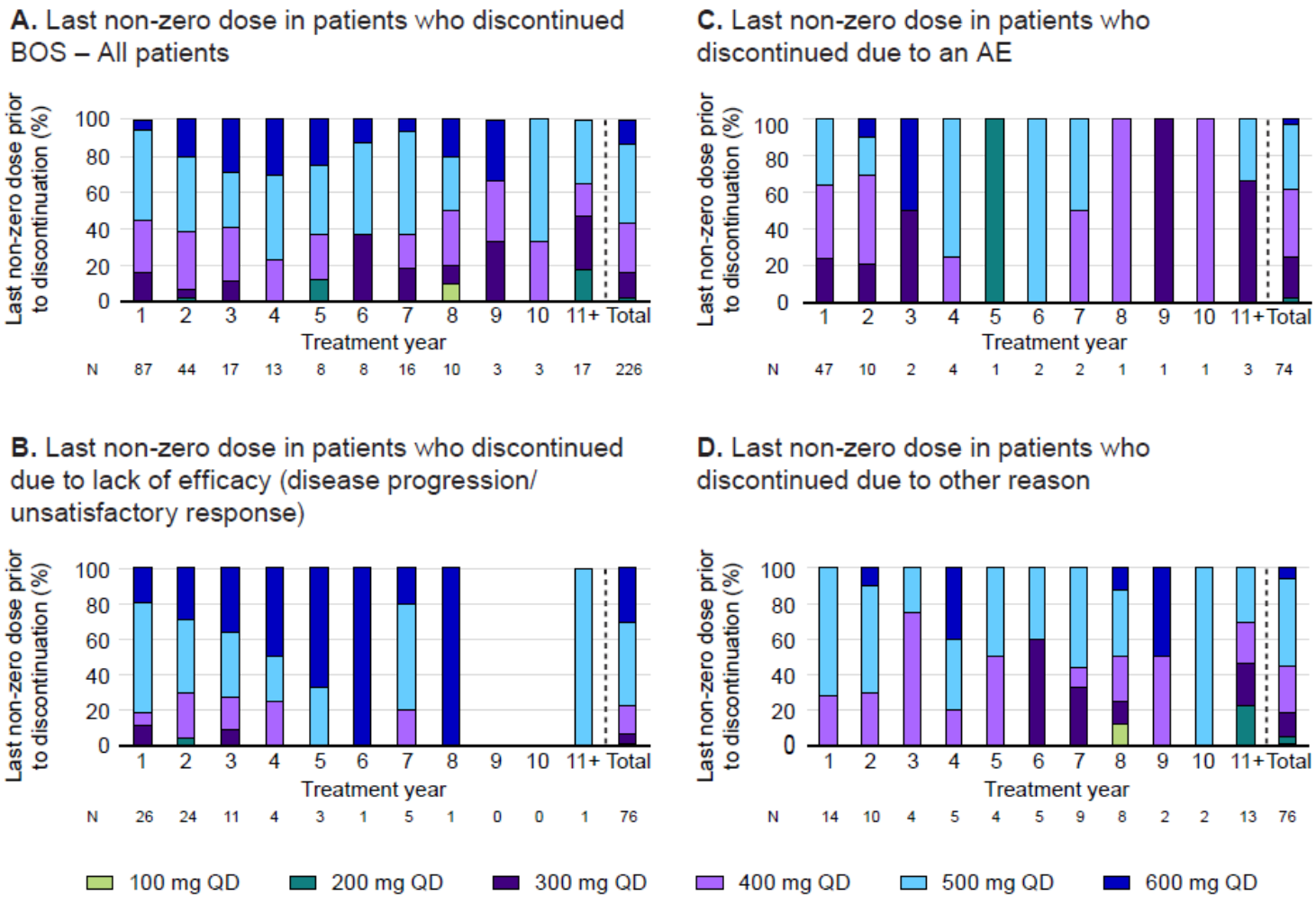
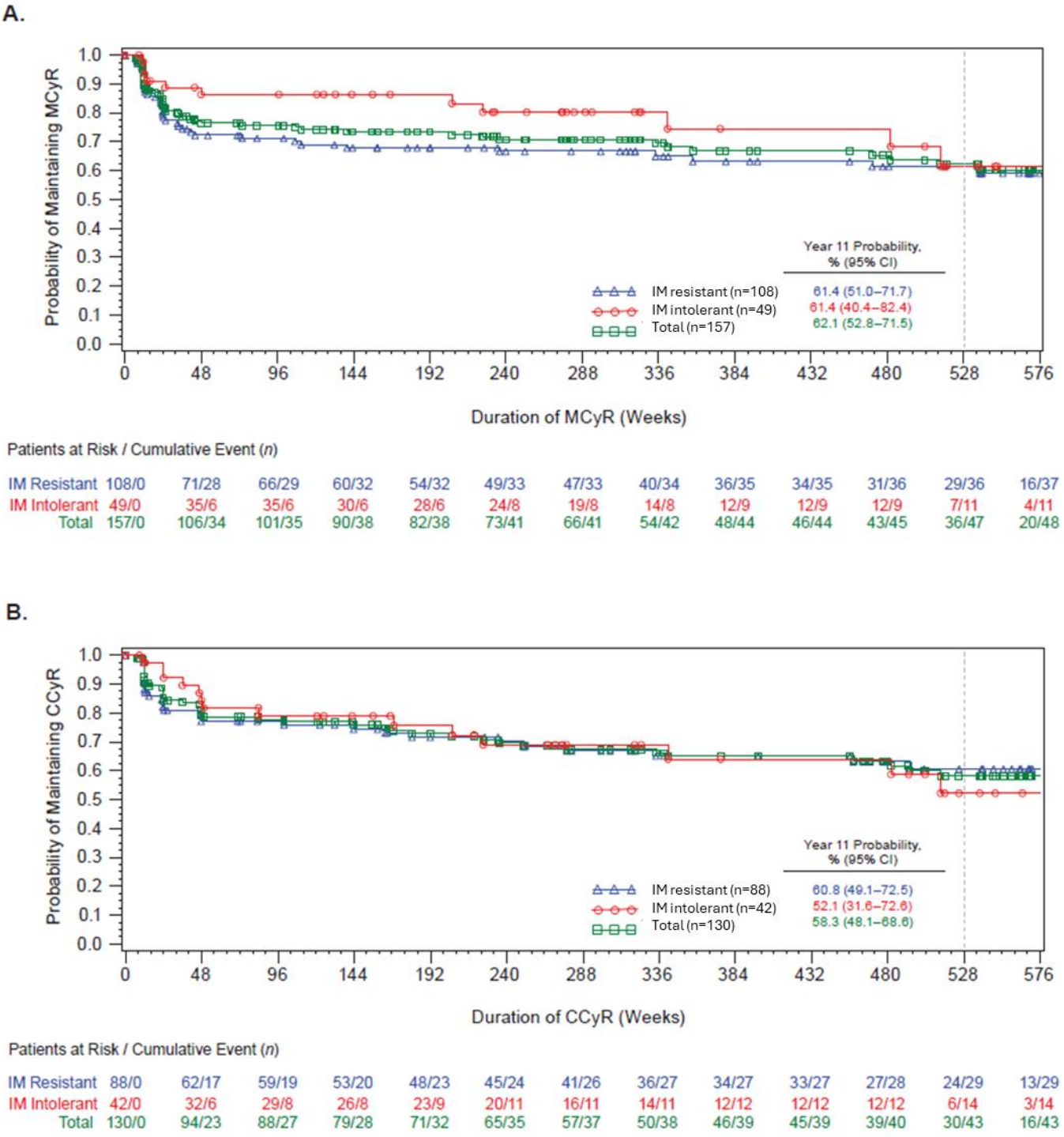


Figure S2 Last non-zero dose prior to discontinuation for those who discontinued during each year



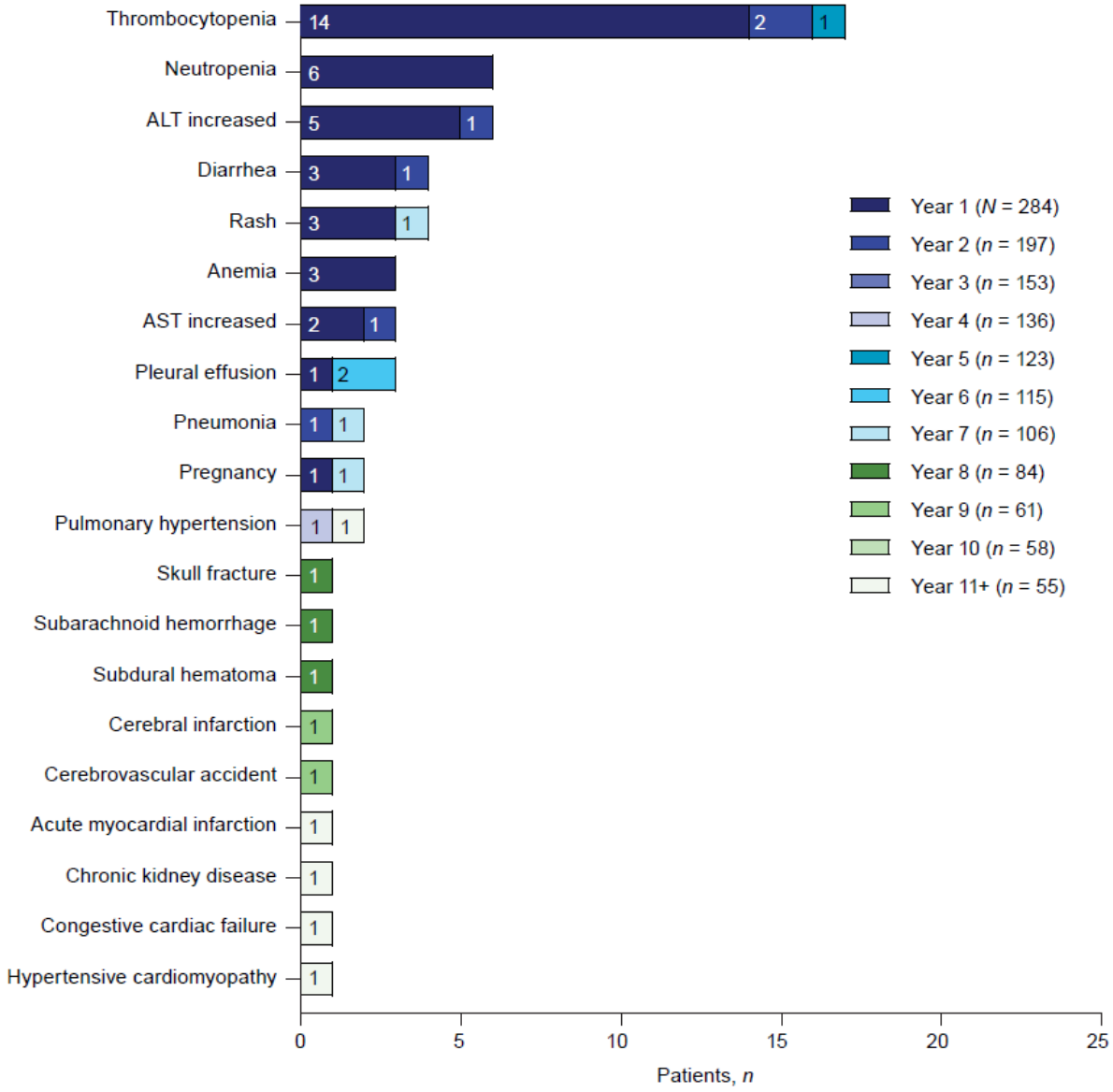
AE, adverse event; BOS, bosutinib; QD, once daily.

Figure S3. Duration of cytogenetic response among responders (A) MCyR and (B) CCyR



CCyR, complete cytogenetic response; CI, confidence interval; IM, imatinib; MCyR, major cytogenetic response.

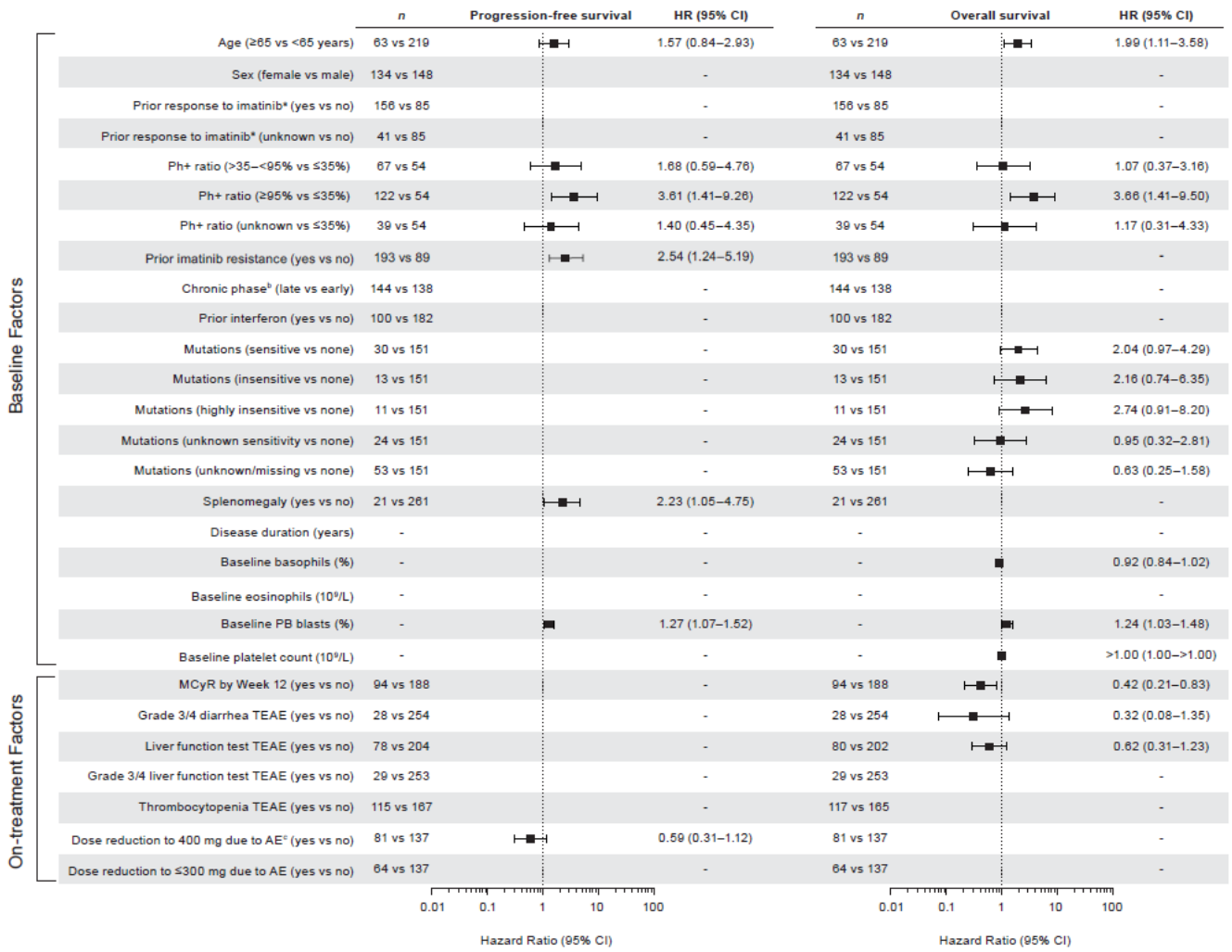
Figure S4. AEs leading to treatment discontinuation, by year



AEs leading to treatment discontinuation in years 5–11+ or in ≥1% of patients are shown.

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

Figure S5. Predictors of disease progression and death



The number of observations used in the analysis was N = 282.

HRs >1 favor the reference group.

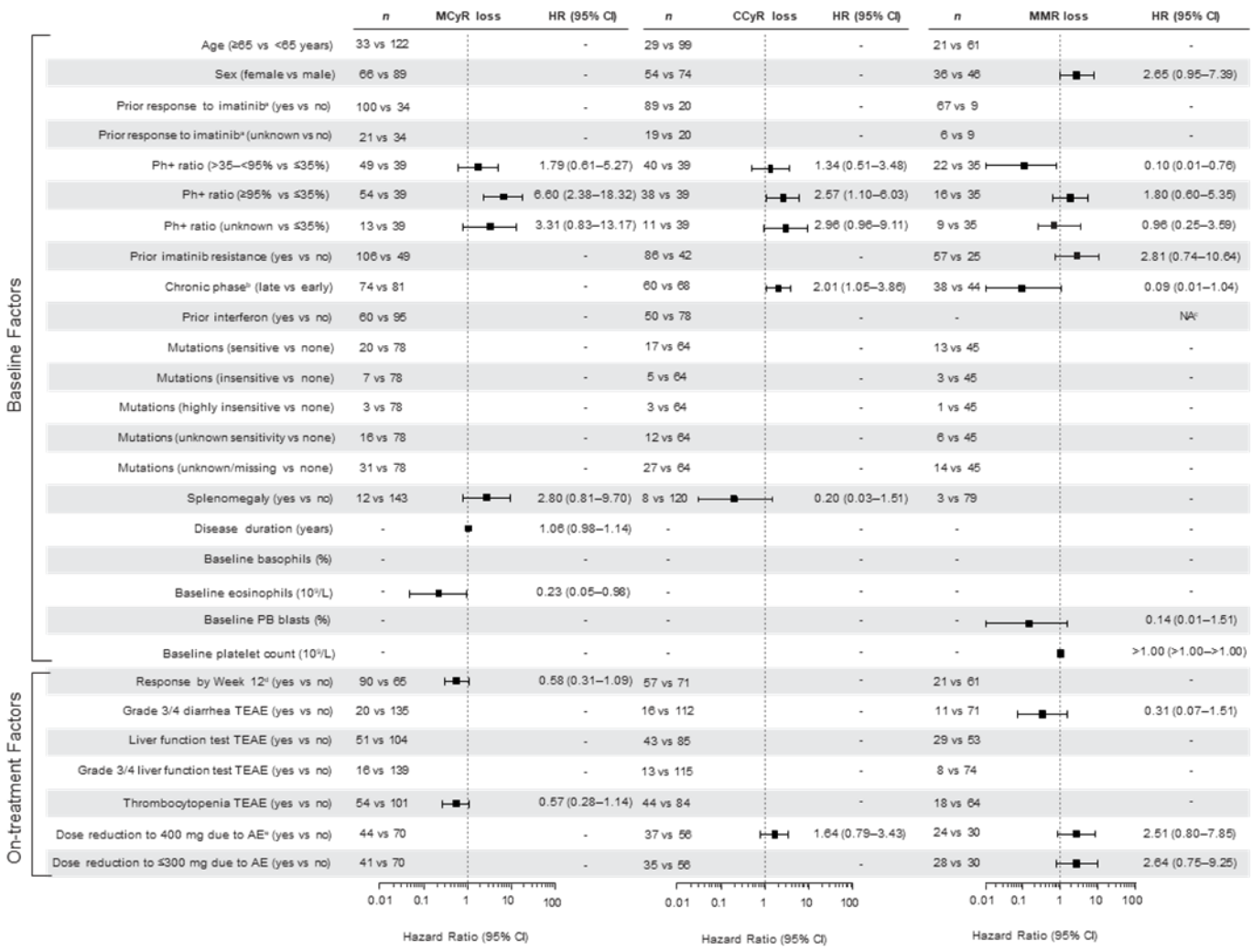
[a]Prior response was defined as achievement of at least a minimal cytogenetic response (standard cytogenetic criteria: 66–95% Ph+ cells from bone marrow or *BCR*::*ABL1* from FISH).

[b]Patients were considered to be in late chronic phase upon initiating imatinib if they had commenced imatinib treatment ≥6 months after diagnosis or had received prior interferon therapy; other patients were considered to be in early chronic phase.

[c]Includes patients whose dose was reduced to 400 mg once daily without reduction to 300 mg or less once daily.

AE, adverse event; CI, confidence interval; FISH, fluorescence in situ hybridization; HR, hazard ratio; MCyR, major cytogenetic response; PB, peripheral blood; PH+, Philadelphia chromosome-positive; TEAE, treatment-emergent adverse event.

Figure S6. Predictors of response loss



The number of observations used in the analysis for loss of MCyR, CCyR, and MMR was N = 155, N = 128, and N = 82, respectively.

HRs >1 favor the reference group.

[a]Prior response was defined as achievement of at least a minimal cytogenetic response (standard cytogenetic criteria: 66–95% Ph+ cells from bone marrow or *BCR*::*ABL1* from FISH).

[b]Patients were considered to be in late chronic phase upon initiating imatinib if they had commenced imatinib treatment ≥6 months after diagnosis or had received prior interferon therapy; other patients were considered to be in early chronic phase.

[c]Prior interferon was not included in the MMR analysis due to non-proportional hazards; however, it was not significant in the bivariate model.

[d]MCyR by Week 12 for MCyR analysis, CCyR by Week 12 for CCyR analysis, and MMR by Week 12 for MMR analysis.

[e]Includes patients whose dose was reduced to 400 mg once daily without reduction to 300 mg or less once daily.

AE, adverse event; CCyR, complete cytogenetic response; CI, confidence interval; FISH, fluorescence in situ hybridization; HR, hazard ratio; MCyR, major cytogenetic response; MMR, major molecular response; PH+, Philadelphia chromosome-positive; TEAE, treatment-emergent adverse event.

Plain Language Summary

Please note that this summary only contains information from the full scientific article:

View Scientific Article

Bosutinib treatment in people with chronic myeloid leukemia (CML) who had taken imatinib before: 10-year follow-up results

Bosutinib
<bo-SOO-tih-nib>

Chromosome
<KROH-muh-some>

Chronic myeloid leukemia
<KRAH-nik MY-eh-loyd loo-KEE-mee-uh>

Imatinib
<ih-MA-tih-nib>

Tyrosine kinase inhibitor
<TY-ruh-seen KY-nays in-HIH-bih-ter>

Date of summary: May 2025

Study number: NCT00261846; NCT01903733

Study start date: January 2006; August 2013

Study end date: August 2015; June 2020

The full title of this article: Second-line bosutinib for chronic phase chronic myeloid leukemia after imatinib: Final, 10-year results of a phase 1/2 study

Key takeaway

- **Bosutinib** treatment was effective after 10 years or more in people who had taken imatinib before for their chronic myeloid leukemia (CML).
- Long-term side effects were like those seen in earlier studies of **bosutinib**.

The purpose of this plain language summary is to help you to understand the findings from recent research.

- Bosutinib and imatinib are approved to treat the condition under study that is discussed in this summary.
- The results of this study may differ from those of other studies. Researchers should make treatment decisions based on all available evidence.

More information can be found in the scientific article of this study, which you can access here: View Scientific Article

Additional information

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https://www.clinicaltrials.gov/study/NCT00261846

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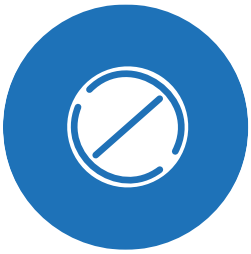
What did this study look at?

What is CML?

- CML is the shortened name for chronic myeloid leukemia. CML is a type of cancer that affects white blood cells.
  - Chronic means it tends to progress slowly over many years.
- CML is caused by the formation of an abnormal fusion gene called BCR-ABL1.
  - Genes are segments of DNA and are found in structures called chromosomes. They are found within each cell of the body.
    - DNA is a molecule in a person's cells that tells the cells how to work.
    - Chromosomes are bundles of DNA.
  - A fusion gene is formed when pieces of 2 different chromosomes break off and change places. They can cause of some types of cancer.
- The BCR-ABL1 gene is found in a chromosome called the Philadelphia chromosome.
  - The chromosome is present in some types of cancer cells and absent in healthy cells.

What is bosutinib?

- **Bosutinib** is a type of medicine known as a tyrosine kinase inhibitor (TKI).
  - Tyrosine kinases are proteins in the body that control how cells grow and divide.
  - The BCR-ABL1 gene makes a tyrosine kinase that is more active than normal.
    - This makes cancer cells grow faster than healthy cells.
  - **Bosutinib** works by blocking this more active tyrosine kinase in the cancer cells, causing those cells to die.
- People take **bosutinib** once a day by mouth with food.



What was the aim of this study?

- In this study, researchers looked at people with CML who had already taken a different TKI called imatinib before they took **bosutinib**.
- These people stopped their imatinib treatment because:
  - their CML was no longer responding (resistant) to treatment, or
  - they could no longer tolerate their treatment due to side effects (intolerant).
    - A side effect is something (expected or unexpected) that you feel was caused by a medicine or treatment you take.
- This summary looks at how effective **bosutinib** was after 10 years or more of follow-up. It also looks at what side effects people had while taking **bosutinib**.

Additional information

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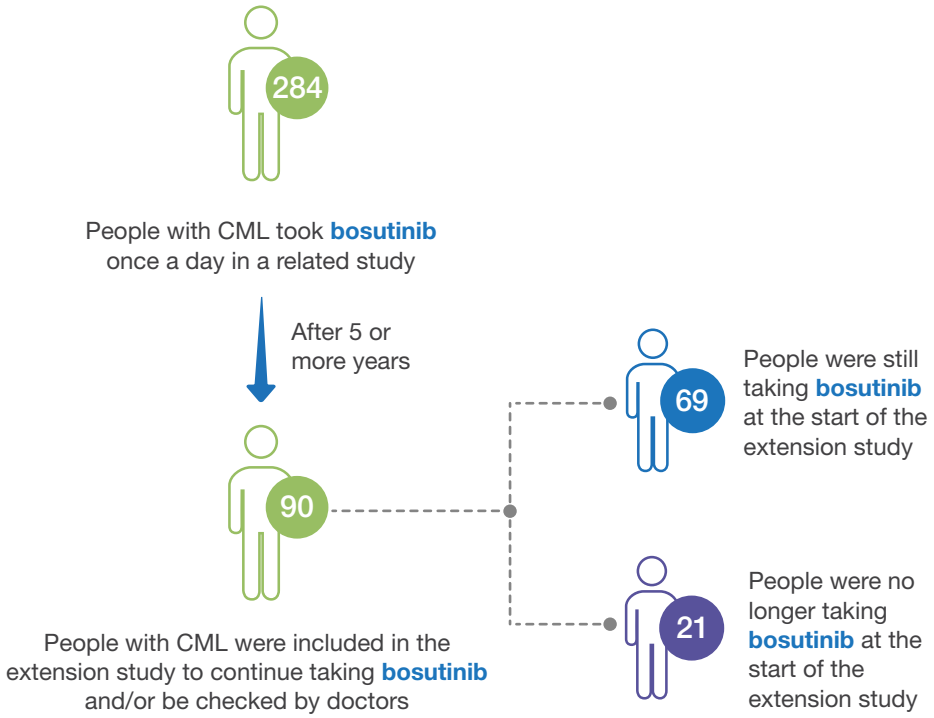
Where is this study in the medicine development timeline?

- This was an extension study. This is a type of clinical study where researchers collect more information about a medicine after the initial study is over.
- This study allowed some people who were included in a related **bosutinib** study to continue taking **bosutinib** and/or be checked by doctors for a long time.

Who took part in this study?



What were the results of this study?

19 in 100 people were still receiving **bosutinib** after 10 years

The most common primary reason why people stopped taking bosutinib was that their treatment did not work well enough or their CML got worse

27 in 100 people permanently stopped **bosutinib** treatment because their treatment did not work well enough or their CML got worse

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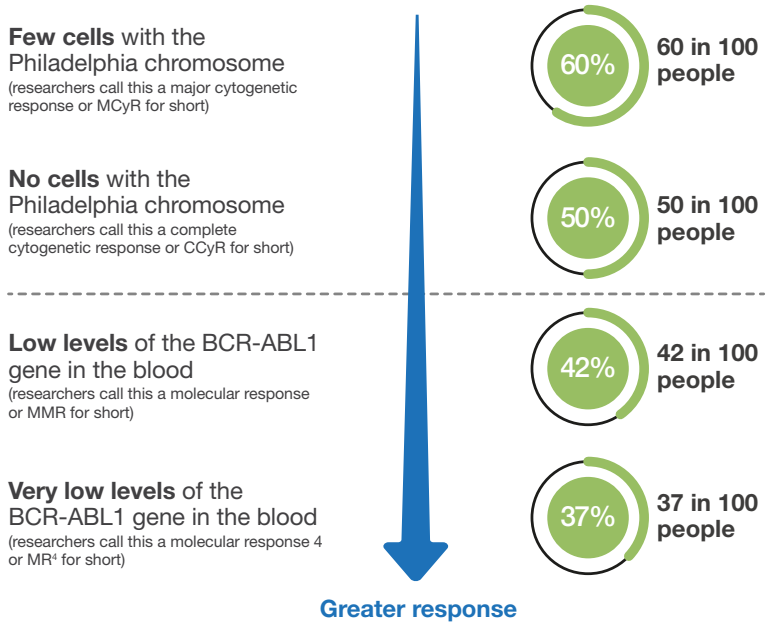
Effectiveness of bosutinib

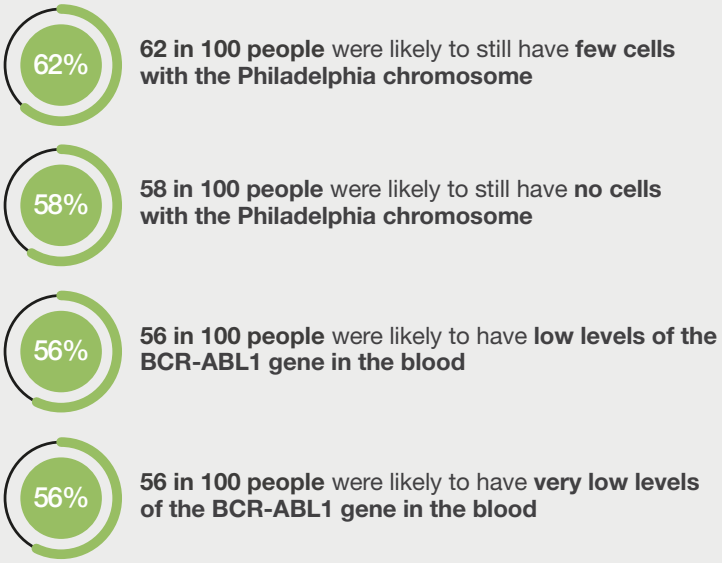
- Researchers looked at whether treatment with **bosutinib** lowered:
  - the number of cells with the Philadelphia chromosome in the bone marrow, and
  - the levels of the BCR-ABL1 gene in the blood.
- People who respond well to **bosutinib** treatment have fewer cells with the Philadelphia chromosome and lower BCR-ABL1 gene levels.

Following treatment with bosutinib, the proportion of people who had:



- Researchers looked at how likely people who responded well to **bosutinib** treatment were to continue to respond after 11 years.

Among people who had a response to bosutinib treatment:



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Researchers looked at how likely people were to live without their CML returning, and how likely they were to live overall. After 11 years:

25 in 100 people were likely to have their CML return, become worse, or die while taking **bosutinib**

71 in 100 people were likely to be alive

- Overall, 55 out of 284 people (19%) with CML died.
  - The researchers determined that 30 out of 284 people (11%) died because of their CML.
  - 16 out of 284 (6%) people died due to side effects.
    - No person died due to side effects caused by **bosutinib**.

Safety of bosutinib

- Most of the people who took part in this study had side effects while taking **bosutinib**.
- Some of these side effects were considered severe by the researchers.
  - A side effect is considered "severe" when it limits daily activities such as:
    - bathing and dressing,
    - is disabling or is medically significant,
    - or could be life-threatening, need hospital care, or cause lasting problems.

79 in 100 people had severe side effects

- Researchers looked at how many people:
  - had a side effect that caused them to permanently stop taking **bosutinib** (this might not always be the main reason why they stopped treatment) and,
  - what type of side effects they had before permanently stopping **bosutinib**.

28 in 100 people had a side effect which caused them to permanently stop taking **bosutinib**

- People were most likely to stop taking **bosutinib** during the first year of treatment

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Side effects that 5 or more people had before permanently stopping bosutinib treatment were:

Low levels of a type of blood cell called a platelet that helps blood to clot (also known as thrombocytopenia)

Low levels of a type of white blood cell called a neutrophil that helps the body fight infections (also known as neutropenia)

Increased levels of alanine aminotransferase in the blood (high levels of this protein may be a sign of liver damage)

What were the main conclusions reported by the researchers?

- This study showed that treatment with **bosutinib** continued to be effective after 10 years or more in people with CML who had already taken imatinib.
- The long-term side effects were generally manageable and consistent with what is already known about **bosutinib**.

Who sponsored this study?

This study was sponsored by Pfizer.

Pfizer Inc.

235 East 42nd Street NY, NY 10017

Phone (United States): +1 212-733-2323

Pfizer would like to thank all of the people who took part in this study.

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Scientific Article
Gambacorti-Passerini C, et al. Second-line bosutinib for chronic phase chronic myeloid leukemia after imatinib: Final, 10-year results of a phase 1/2 study. <full citation to be added>

Acknowledgements
Writing support for this summary was provided by Gemma Shay-Lowell, CMPP, PhD, at Engage Scientific Solutions Ltd, and was funded by Pfizer.