1650

Efficacy of Bosutinib in Imatinib-Resistant vs Dasatinib/Nilotinib-Resistant Chronic Phase Chronic Myeloid Leukemia: Results From the Phase 4 BYOND Study

B Douglas Smith[1], Tim H Brümmendorf[2], Gail J Roboz[3], Carlo Gambacorti-Passerini[4], Aude Charbonnier[5], Andrea Viqueira[6], Eric Leip[7], Frank Giles[8], Thomas Ernst[9], Andreas Hochhaus[9], Gianantonio Rosti[10]

[1]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [2]Universitätsklinikum RWTH Aachen, Aachen, Germany; [3]Weill Cornell Medicine, New York, NY, USA; [4]University of Milano-Bicocca, Monza, Italy; [5]Institut Paoli Calmette, Marseille, France; [6]Pfizer SLU, Madrid, Spain; [7]Pfizer Inc, Cambridge, MA, USA; [8]Developmental Therapeutics Consortium, Chicago, IL, USA; [9]Jena University Hospital, Jena, Germany; [10]University Hospital, University of Bologna, Bologna, Italy

Objective

- To evaluate the efficacy of bosutinib in patients with CP Ph+ CML according to subgroups of resistance or intolerance to prior TKIs.

Conclusions

- High rates of cytogenetic and molecular responses were observed in patients with CP Ph+ CML who were resistant or intolerant to prior TKIs.
- Response rates were similar between patients with resistance to imatinib and patients who were intolerant to all prior TKIs. Despite the fact that patients in the dasatinib/nilotinib-resistant cohort were more heavily pretreated, responses were also seen in patients with resistance to second-generation TKIs, including patients achieving MR despite the shorter treatment duration.
- These results further support bosutinib use for patients with CP Ph+ CML and resistance/intolerance to prior TKIs.

Background

- In the phase 4 BYOND study in patients with chronic myeloid leukemia (CML) resistant/intolerant to prior tyrosine kinase inhibitors (TKIs), high rates of cytogenetic and molecular responses, including a large proportion of patients who achieved deep molecular response (MR)[4] and MR[4.5], were observed during treatment with bosutinib 500 mg once daily.[1]

Methods

- BYOND (NCT02228382) is an ongoing, phase 4, single-arm, open-label, study of bosutinib. Primary results were previously reported.[1]
- Patients were assigned to the following subgroups:
  - **Imatinib-resistant:** patients who were resistant only to imatinib, but not to nilotinib or dasatinib.
  - **Dasatinib/nilotinib-resistant:** patients who were resistant to ≥1 second-generation TKI (dasatinib- and/or nilotinib-resistant).
  - **TKI-intolerant:** patients with intolerance to all prior TKIs.
- The data cutoff date for these subgroup analyses was September 18, 2018. Data are reported at ≥1 year after last enrolled patient; 85 % of patients had a minimum follow-up of 2 years.
- For further details, please refer to the supplementary material that is downloadable using the QR code.

Results

- Of 163 patients who received bosutinib, 156 had chronic phase (CP) Philadelphia chromosome–positive (Ph+) CML: 52 had resistance only to imatinib, 31 had resistance to dasatinib and/or nilotinib, and 73 were intolerant to all prior TKIs.
- Patients in the dasatinib/nilotinib-resistant cohort were more pretreated than patients in the imatinib-resistant and TKI-intolerant cohorts (**Table 1** and **Table S1**).
- In all, 69.2 %, 41.9 %, and 53.4 % of imatinib-resistant, dasatinib/nilotinib-resistant, and TKI-intolerant patients, respectively, were still receiving treatment as of the data cutoff date; reasons for treatment discontinuation are shown in **Tables 2** and **S2**.
- Dose reductions and temporary discontinuations, respectively, occurred in 78.8 % and 75.0 % of imatinib-resistant, 64.5 % and 58.1 % of dasatinib/nilotinib-resistant, and 84.9 % and 84.9 % of TKI-intolerant patients.
- Both cohorts of patients resistant to therapy received higher doses of bosutinib than the cohort that was TKI-intolerant; patients in the dasatinib/nilotinib-resistant cohort had the highest dose intensity (**Table 2**).
  - At all time points, ~80 % of dasatinib/nilotinib-resistant patients and ~65 % of imatinib-resistant patients received ≥400 mg once daily (**Figure S1**).
- Across all evaluable patients, there was a substantial proportion of patients with CCyR, MMR, and deeper responses by 1 year (**Figures S2** and **S3**).
- In patients without baseline major cytogenetic response (MCyR) or complete cytogenetic response (CCyR), high rates of cumulative cytogenetic responses (≥50 %) by 1 year were observed (**Figure 1**).
- In patients without the respective baseline response, there was a substantial proportion of patients with major molecular response (MMR) or deeper responses by 1 year (**Figure 2**).
- Rates of MMR were 50.0 %, 42.9 % and 33.3 % in patients resistant to dasatinib only (n=16), patients resistant to nilotinib only (n=7) and patients resistant to both dasatinib and nilotinib (n=6), respectively.
- In patients without MMR at baseline, rates of MMR were 33.3 % each in patients resistant to dasatinib only (n=9), patients resistant to nilotinib only (n=6) and patients resistant to both dasatinib and nilotinib (n=6).

Table 1. Baseline Demographics and Characteristics

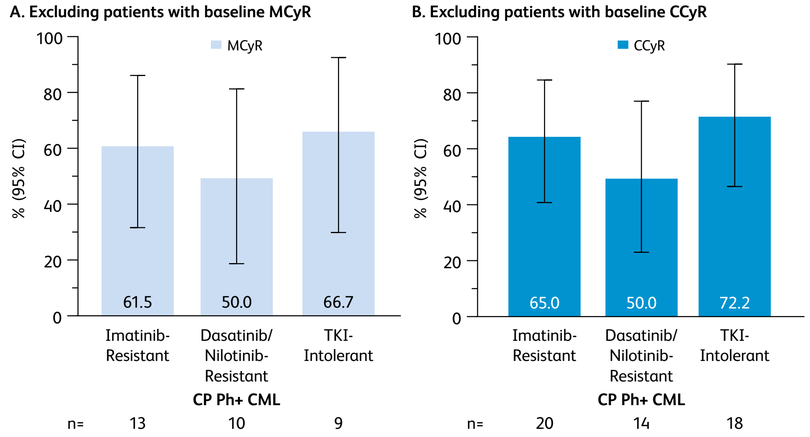
n (%)*	Imatinib-Resistant n=52	Dasatinib- and/or Nilotinib-Resistant n=31	TKI-Intolerant n=73
Male	34 (65.4)	17 (54.8)	30 (41.1)
Age, median (range), y	63.5 (33.0–85.0)	54.0 (20.0–85.0)	57.0 (25.0–89.0)
ECOG PS			
0	35 (67.3)	25 (80.6)	46 (63.0)
1	14 (26.9)	5 (16.1)	26 (35.6)
2	3 (5.8)	1 (3.2)	1 (1.4)
Number of prior TKIs			
1	13 (25.0)	4 (12.9)	29 (39.7)
2	23 (44.2)	12 (38.7)	26 (35.6)
3	16 (30.8)	15 (48.4)	18 (24.7)
Prior interferon alpha	3 (5.8)	5 (16.1)	3 (4.1)
Prior imatinib	52 (100.0)	23 (74.2)	66 (90.4)
Prior dasatinib	33 (63.5)	26 (83.9)	36 (49.3)
Prior nilotinib	22 (42.3)	24 (77.4)	33 (45.2)

* Except as noted.
ECOG PS=Eastern Cooperative Oncology Group performance status

Table 2: Treatment Summary

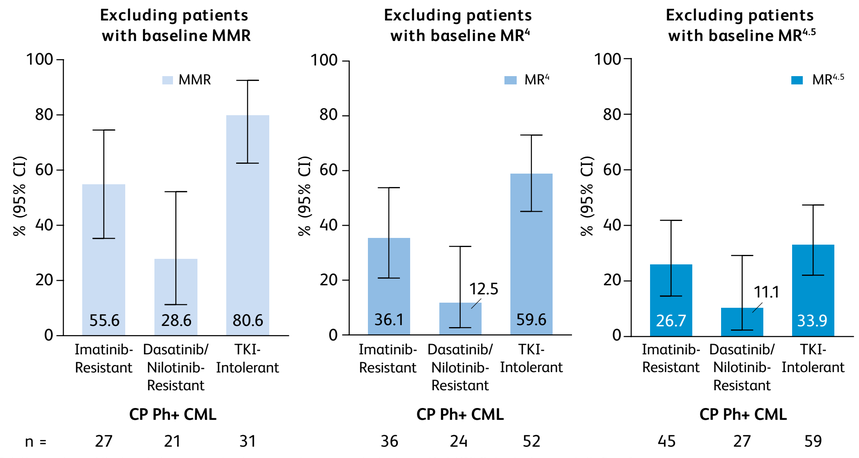
	Imatinib-resistant n=52	Dasatinib- and/or Nilotinib-resistant n=31	TKI-intolerant n=73
Duration of treatment, median (range), months	24.1 (0.2–42.2)	8.9 (0.9–41.6)	25.3 (0.4–41.9)
Dose intensity, median (range), mg/day	359.7 (125.0–500.0)	430.9 (194.6–560.6)	292.0 (79.7–500.0)
Discontinued treatment, n (%)	16 (30.8)	18 (58.1)	34 (46.6)
Adverse event	10 (19.2)	8 (25.8)	21 (28.8)
Insufficient clinical response	2 (3.8)	5 (16.1)	1 (1.4)
Other	4 (7.7)	5 (16.1)	11 (15.1)
Patient died	0	0	1 (1.4)

Figure 1: Summary of Cumulative Cytogenetic Response Rates by 1 Year, Excluding Patients With Baseline (A) MCyR and (B) CCyR, in Patients With CP Ph+ CML Resistant/Intolerant to Prior TKIs



Evaluable patients have a valid baseline cytogenetic assessment without the respective endpoint response at baseline. Associated 2-sided 95 % CI is based on the exact method by Clopper-Pearson.
CCyR=complete cytogenetic response; CI=confidence interval; CP Ph+ CML=chronic phase Philadelphia chromosome–positive chronic myeloid leukemia; MCyR=major cytogenetic response; TKI=tyrosine kinase inhibitor

Figure 2: Summary of Cumulative Molecular Response Rates by 1 Year, Excluding Patients With the Respective Baseline Response, in Patients With CP Ph+ CML Resistant/Intolerant to Prior TKIs



Evaluable patients have a valid baseline molecular assessment without the respective endpoint response at baseline. Associated 2-sided 95 % CI is based on the exact method by Clopper-Pearson.
MMR: *BCR-ABL1* IS ≤0.1 %. MR[4]: *BCR-ABL1* IS ≤0.01 %. MR[4.5]: *BCR-ABL1* IS ≤0.0032 %.
CI=confidence interval; CP Ph+ CML=chronic phase Philadelphia chromosome–positive chronic myeloid leukemia; IS=international scale; MMR=major molecular response; MR=molecular response; TKI=tyrosine kinase inhibitor

Plain Language Summary
Please scan this quick response (QR) code with your smartphone app to view a plain language summary.

Electronic Poster and Supplementary Material
Please scan this quick response (QR) code with your smartphone app to view an electronic version of this poster and supplementary material. If you don't have a smartphone, access the poster and supplementary material via the internet at: https://congress-download.pfizer.com/ash_2019_american_society_of_hematology_595_bosutinib_smith_1650.html

Reference: 1. Gambacorti-Passerini C, et al. J Clin Oncol 2019;37(15 suppl):7012.

Disclosures: BDS: honoraria for consulting (Novartis, Agios, Celgene, Jazz Pharmaceuticals, Pfizer). THB: consultancy (Pfizer, Novartis, Janssen, Merck, Takeda, Ariad) and research funding (Pfizer, Novartis). GJR: none to disclose. CG-P: consultancy (Bristol-Myers Squibb) and honoraria and research funding (Pfizer). AC: consultancy (Novartis, Pfizer, Incyte). AV and EL: employment (Pfizer). FG: employment (Actuate Therapeutics Inc), leadership, stock/other ownership and consultancy (Epigene Therapeutics Inc), expert testimony (Novartis). TE: research support (Pfizer, Novartis, Bristol-Myers Squibb, Incyte). AH: research funding (Pfizer, Novartis, Bristol-Myers Squibb, Incyte). GR: consultancy, honoraria, and membership on advisory committee or board of directors (Novartis, Pfizer, Incyte), and speakers bureau (Bristol-Myers Squibb).

Acknowledgments: The study was sponsored by Pfizer. Medical writing support was provided by Anne Marie McGonigal, PhD, of Engage Scientific Solutions, and funded by Pfizer.

Presented at the 61st American Society of Hematology (ASH) Annual Meeting & Exposition • December 7–10, 2019 • Orlando, Florida

Efficacy of Bosutinib in Imatinib-Resistant vs Dasatinib/Nilotinib-Resistant Chronic Phase Chronic Myeloid Leukemia: Results From the Phase 4 BYOND Study

B Douglas Smith[1], Tim H Brümmendorf[2], Gail J Roboz[3], Carlo Gambacorti-Passerini[4], Aude Charbonnier[5], Andrea Viqueira[6], Eric Leip[7], Frank Giles[8], Thomas Ernst[9], Andreas Hochhaus[9], Gianantonio Rosti[10]

[1]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [2]Universitätsklinikum RWTH Aachen, Aachen, Germany; [3]Weill Cornell Medicine, New York, NY, USA; [4]University of Milano-Bicocca, Monza, Italy; [5]Institut Paoli Calmette, Marseille, France; [6]Pfizer SLU, Madrid, Spain; [7]Pfizer Inc, Cambridge, MA, USA; [8]Developmental Therapeutics Consortium, Chicago, IL, USA; [9]Jena University Hospital, Jena, Germany; [10]University Hospital, University of Bologna, Bologna, Italy

Methods

STUDY DESIGN AND PATIENTS

- Briefly, patients were aged ≥18 years and had a cytogenetic or polymerase chain reaction-based diagnosis of Ph+ or *BCR-ABL1*+ if Ph-negative from initial diagnosis of CML, and prior treatment with ≥1 TKI for CML.
- Patients were administered bosutinib at a starting dose of 500 once daily QD. Dose modifications were permitted.

ENDPOINTS AND ANALYSES

- Key endpoints assessed in imatinib-resistant, dasatinib- and/or nilotinib-resistant, and TKI-intolerant subgroups:
  - Cumulative MCyR.
  - Cumulative CCyR.
  - Cumulative MMR (*BCR-ABL1* international scale [IS] ≤0.1 %), MR^4 (*BCR-ABL1* IS ≤0.01 %), and $MR^{4.5}$ (*BCR-ABL1* IS ≤0.0032 %).
  - Overall survival.
  - Transformation to accelerated phase (AP) or blast phase (BP) CML.
- All bosutinib-treated patients with Ph+ CML with a valid baseline efficacy assessment for the respective endpoint (evaluable population) were included in the molecular and cytogenetic efficacy analyses.
- Analyses of cytogenetic response were based on the data from local laboratory assessment, whereas MR was assessed at an independent central laboratory.
  - CCyR was imputed from MMR on a specific date if there was no valid cytogenetic assessment.

Results

TREATMENT

Table S1: Reasons for Prior TKI Discontinuation

n (%)	Imatinib-Resistant n=52	Dasatinib- and/or nilotinib-Resistant n=31	TKI-Intolerant n=73
Reasons for imatinib discontinuation			
Lack of efficacy	52 (100.0)	23 (74.2)	5 (6.8)
Intolerability	0	0	63 (86.3)
Other	0	0	3 (4.1)
Reasons for dasatinib discontinuation			
Lack of efficacy	2 (3.8)	24 (77.4)	1 (1.4)
Intolerability	32 (61.5)	3 (9.7)	35 (47.9)
Other	1 (1.9)	0	1 (1.4)
Reasons for nilotinib discontinuation			
Lack of efficacy	1 (1.9)	18 (58.1)	0
Intolerability	21 (40.4)	6 (19.4)	33 (45.2)
Other	2 (3.8)	3 (9.7)	0
TKIs discontinued due to intolerance			
0	13 (25.0)	19 (61.3)	0
1	23 (44.2)	12 (38.7)	29 (39.7)
2	16 (30.8)	0	26 (35.6)
3	0	0	18 (24.7)
TKIs discontinued due to resistance			
0	0	0	73 (100.0)
1	52 (100.0)	5 (16.1)	0
2	0	22 (71.0)	0
3	0	4 (12.9)	0

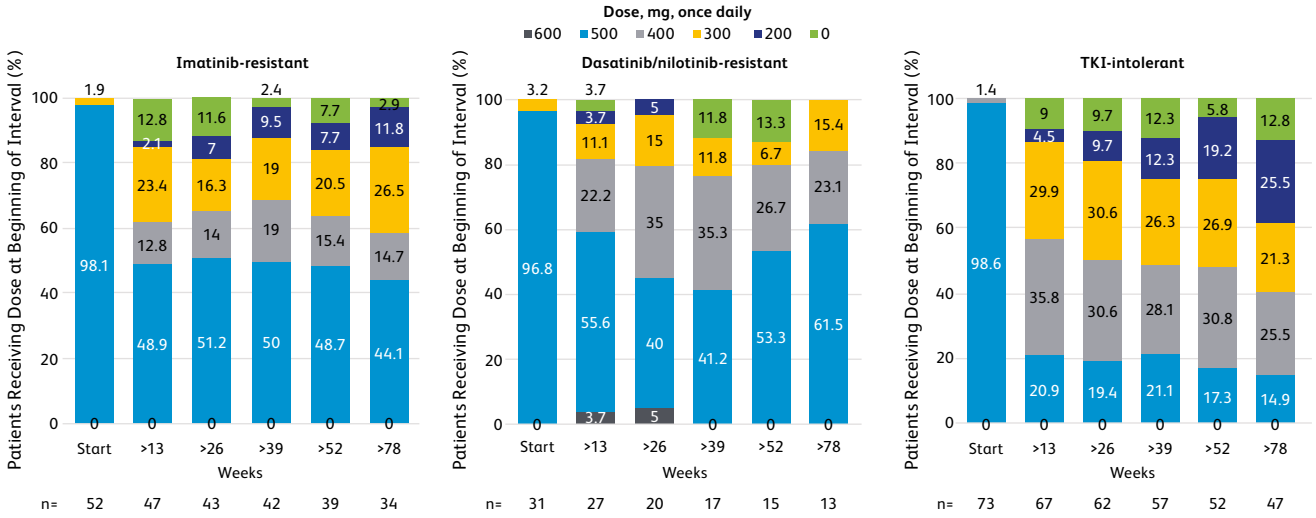
If a patient received >1 treatment regimen with imatinib, dasatinib, nilotinib or interferon alpha, the patient was only counted once for the respective treatment.
Patients with discontinuation reason as Other or those who discontinued due to both intolerability and lack of efficacy were categorized as TKI-intolerant.
TKI=tyrosine kinase inhibitor

CONTINUED

Table S2: Treatment Summary

	Imatinib-Resistant n=52	Dasatinib- and/or Nilotinib-Resistant n=31	TKI-Intolerant n=73
Treatment duration, median (range), mo	24.1 (0.2–42.2)	8.9 (0.9–41.6)	25.3 (0.4–41.9)
Dose intensity, median (range), mg/d	359.7 (125.0–500.0)	430.9 (194.6–560.6)	292.0 (79.7–500.0)
Discontinued treatment, n (%)	16 (30.8)	18 (58.1)	34 (46.6)
Adverse event	10 (19.2)	8 (25.8)	21 (28.8)
Insufficient clinical response	2 (3.8)	5 (16.1)	1 (1.4)
Patient died	0	0	1 (1.4)
Lost to follow-up	0	1 (3.2)	0
Noncompliance	0	1 (3.2)	4 (5.5)
Investigator declined further study participation	1 (1.9)	0	1 (1.4)
Other	1 (1.9)	1 (3.2)	2 (2.7)
Protocol violation	1 (1.9)	1 (3.2)	1 (1.4)
Patient request	1 (1.9)	1 (3.2)	3 (4.1)

Figure S1: Bosutinib Dose Over Time in Patients With CP Ph+ CML, According to Resistance or Intolerance to Prior TKIs

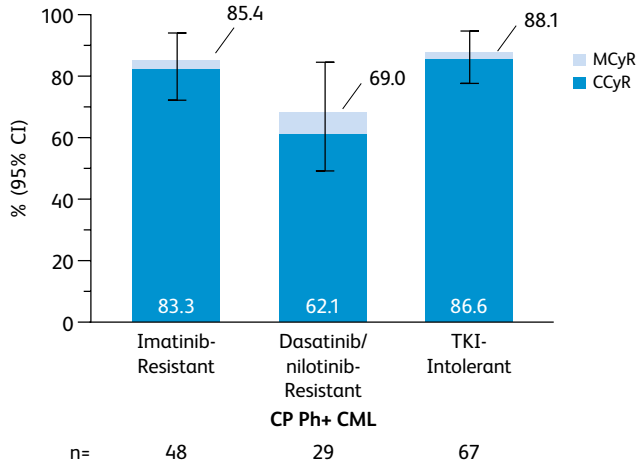


CP Ph+ CML=chronic phase Philadelphia chromosome–positive chronic myeloid leukemia; TKI=tyrosine kinase inhibitor

EFFICACY

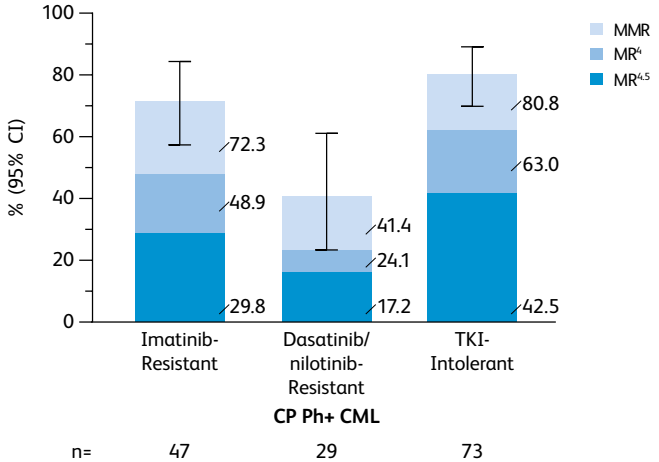
- In all patients evaluable for cytogenetic response, high rates of cumulative CCyR (≥60%) by 1 year were observed across subgroups (**Figure S2**).
- In all patients evaluable for molecular response, there was a substantial proportion of patients with MMR and deeper responses by 1 year (**Figure S3**).

Figure S2: Summary of Cumulative Cytogenetic Response Rates by 1 year in Patients With CP Ph+ CML Resistant/ Intolerant to Prior TKIs



Evaluable patients have a valid baseline assessment for the respective endpoint.
Associated 2-sided 95% CI (for MCyR only) is based on the exact method by Clopper-Pearson.
CCyR=complete cytogenetic response; CI=confidence interval; CP Ph+ CML=chronic phase Philadelphia chromosome–positive chronic myeloid leukemia; MCyR=major cytogenetic response; TKI=tyrosine kinase inhibitor

Figure S3: Summary of Cumulative Molecular Response Rates by 1 year in Patients With CP Ph+ CML Resistant/ Intolerant to Prior TKIs



Evaluable patients have a valid baseline assessment for the respective endpoint.
Associated 2-sided 95% CI (for MMR only) is based on the exact method by Clopper-Pearson.
MMR: *BCR-ABL1* IS ≤0.1%. MR4: *BCR-ABL1* IS ≤0.01%. MR4.5: *BCR-ABL1* IS ≤0.0032%.
CI=confidence interval; CP Ph+ CML=chronic phase Philadelphia chromosome–positive chronic myeloid leukemia; IS=international scale; MMR=major molecular response; MR=molecular response; TKI=tyrosine kinase inhibitor

CONTINUED

- Of 10 patients with CP Ph+ CML with mutations at baseline, 3 achieved MMR on treatment: 2 were imatinib-resistant and 1 was resistant to imatinib, dasatinib, and nilotinib (**Table S3**).
- One patient (see * in **Table S3)** who was imatinib-resistant/dasatinib-intolerant with a baseline *Y253F* mutation had an emergent *T315I* mutation.

Table S3: Response by Mutational Status

Treatment Line	Prior TKIs	Mutation	Best Response
2nd	Imatinib-resistant	*Y253F*	MMR
2nd	Imatinib-resistant	*A365V*	MMR
3rd*	Imatinib-resistant / dasatinib-intolerant	*Y253F*	Complete hematologic response
3rd	Imatinib-resistant / dasatinib-intolerant	*E453K*	No response
4th	Imatinib-resistant / dasatinib-resistant / nilotinib-resistant	*G250E*	Complete hematologic response
4th	Imatinib-resistant / dasatinib-intolerant / nilotinib-resistant	*G250E*	No response
4th	Imatinib-resistant / dasatinib-resistant / nilotinib-resistant	*E255K*	No response
4th	Imatinib-resistant / dasatinib-resistant / nilotinib-resistant	*E255V*	MMR
4th	Imatinib-resistant / dasatinib-resistant/intolerant / nilotinib-resistant/intolerant	*Q252H*	Complete hematologic response
4th	Imatinib-resistant / dasatinib-resistant / nilotinib-resistant	*L298V*	Complete hematologic response

Evaluable population.
Data cutoff date: September 18, 2018, ≥1 year after last enrolled patient.
MMR=major molecular response; TKI=tyrosine kinase inhibitor.

- No patient experienced on-treatment transformation to AP or BP CML, or discontinued treatment due to disease progression.
- Kaplan–Meier estimated overall survival rates (95 % confidence intervals) in imatinib-resistant, dasatinib/nilotinib-resistant, and TKI-intolerant patients, respectively, were 96.1 % (85.2–99.0), 100 % (100–100), and 98.6 % (90.5–99.8) at 1 year, and 96.1 % (85.2–99.0), 92.6 % (73.4–98.1), and 97.2 % (89.2–99.3) at 2 years; 3, 3, and 4 deaths occurred on study.

SAFETY

- In imatinib-resistant, dasatinib/nilotinib-resistant, and TKI-intolerant patients, respectively, 73.1 % , 64.5 % , and 78.1 % reported grade 3 or 4 treatment-emergent adverse event (**Table S4**).

Table S4. Summary of Adverse Events

TEAE, n (%)	Resistant to Imatinib Only n=52	Resistant to Dasatinib or Nilotinib n=31	Intolerant to All Prior TKI n=73
Any grade	52 (100.0)	31 (100.0)	72 (98.6)
Grade 3/4	38 (73.1)	20 (64.5)	57 (78.1)
Serious	14 (26.9)	8 (25.8)	32 (43.8)
Leading to treatment discontinuation	10 (19.2)	8 (25.8)	21 (28.8)
Leading to dose reduction	41 (78.8)	20 (64.5)	62 (84.9)
Leading to temporary stop	39 (75.0)	18 (58.1)	62 (84.9)
Leading to death	1 (1.9)	0 (0.0)	4 (5.5)

Data cut-off date: September 18, 2018, ≥1 year after last enrolled patient.
TEAEs were defined as any event increasing in severity from baseline or any new event starting during bosutinib therapy or within 28 days of the last dose of study drug. Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA version 21.1).
TEAE=treatment-emergent adverse event