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Efficacy and Safety of Bosutinib by Charlson Comorbidity Index in Previously Treated Patients With Chronic Myeloid Leukemia: Results From the Phase 4 BYOND Study

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Objective

- To examine efficacy and safety of bosutinib by CCI score in patients with CP Ph+ CML resistant/intolerant to prior TKI therapy enrolled in the phase 4 BYOND study.

Conclusions

- Results demonstrate efficacy of bosutinib in patients with CP Ph+ CML resistant/intolerant to prior therapy across CCI scores, with a substantial proportion of patients across CCI groups achieving/maintaining molecular response.
- Patients with higher CCI scores (≥6) had a different pattern of TEAEs and higher rate of grade 3/4 TEAEs, and were more likely to discontinue treatment due to AEs and die due to reasons other than CML.
- CCI stratification may enable the identification of patients who are at higher risk of developing TEAEs (related and unrelated to study drug) and require more careful monitoring.

Plain Language Summary
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Electronic Poster and Supplementary Materials
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References: **1.** Bosulif® (bosutinib) prescribing information. Pfizer Inc; 2017. **2.** Bosulif® (bosutinib) summary of product characteristics. European Medicines Agency; 2018. **3.** Hoffman VS, et al. Leukemia 2015;29:1336-43. **4.** Saussele S, et al. Blood 2015;126:42-49. **5.** Gambacorti-Passerini C, et al. American Society of Clinical Oncology (ASCO), May 31–June 4 , 2019; Chicago, IL. **6.** Charlson M, et al. J Clin Epidemiol 1994;47:1241-51.

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Background

- Bosutinib is a tyrosine kinase inhibitor (TKI) approved for the treatment of Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) resistant/intolerant to prior therapy and newly diagnosed chronic phase (CP) Ph+ CML.[1,2]
- The presence of comorbidities may influence outcomes with TKI treatment for CML.
  - More than 50 % of patients with CML have ≥1 comorbidity at diagnosis.[3]
  - A prior analysis indicated survival of patients with CML treated with the TKI imatinib is determined more by comorbidities than by CML itself.[4]

Methods

- BYOND (NCT02228382) is an ongoing, phase 4, single-arm, open-label study examining the safety and efficacy of bosutinib (starting dose 500 mg once daily) in patients with CML resistant/intolerant to prior TKI treatment as a post-authorization commitment to the European Medicines Agency. Eligibility criteria and endpoints have been described.[5]
- Charlson Comorbidity Index (CCI) scores were derived from baseline data and patients were grouped by CCI scores 2–3, 4–5, and ≥6.
- Results were based on ≥1 year of follow-up (data cutoff date: September 18, 2018).
- For further details, please refer to the supplementary material that is downloadable using the QR code.

Results

- A total of 156 patients with Ph+ CP CML received bosutinib (**Table 1**).
- At the data cutoff date, 61.9 %, 68.7 %, and 43.9 % of patients with CCI 2–3, 4–5, and ≥6, respectively, were still receiving bosutinib. Reasons for permanent treatment discontinuation are shown in **Tables 2** and **S1**.
- A substantial proportion of patients attained or maintained molecular response across CCI scores (**Figure 1**).
- No patient in any CCI group progressed to accelerated/blast phase CML while on treatment.
- Any grade dyspnea, pleural effusion, blood creatinine increased, fatigue, and anemia were more common (>10 % difference) and diarrhea, nausea, and headache less common among patients with CCI ≥6 compared with patients with CCI 2–3 and/or 4–5 (**Table S2**).
- Grade 3/4 treatment-emergent adverse events (TEAEs) differed between groups; patients with CCI ≥6 had a higher overall rate of grade 3/4 TEAEs (**Figure 2**).
- Most common adverse events (AEs) leading to discontinuation for CCI 2–3, 4–5, and ≥6, respectively, were increased alanine and aspartate aminotransferase (7.1 % each), increased alanine aminotransferase (8.3 %), and pleural effusion (3.0 %; **Table S3**).
- A total of 10 deaths occurred (n=0, 1, and 9 for CCI 2–3, 4–5, and ≥6); 8 deaths were due to AEs unrelated to bosutinib, 1 was CML-related, and 1 was of unknown cause (**Table S4**).

Table 1: Demographics and Baseline Characteristics, by CCI score

n (%)*	CCI 2–3 n=42 (26.9%)	CCI 4–5 n=48 (30.8%)	CCI ≥6 n=66 (42.3%)	Total N=156
Male	18 (42.9)	26 (54.2)	37 (56.1)	81 (51.9)
Age, median (range), y	42.0 (20.0–50.0)	57.0 (45.0–69.0)	73.0 (54.0–89.0)	61.0 (20.0–89.0)
ECOG PS				
0	36 (85.7)	33 (68.8)	37 (56.1)	106 (67.9)
1	4 (9.5)	14 (29.2)	27 (40.9)	45 (28.8)
2	2 (4.8)	1 (2.1)	2 (3.0)	5 (3.2)
Number of prior TKIs				
1	19 (45.2)	14 (29.2)	13 (19.7)	46 (29.5)
2	13 (31.0)	18 (37.5)	30 (45.5)	61 (39.1)
3	10 (23.8)	16 (33.3)	23 (34.8)	49 (31.4)
Prior imatinib	31 (73.8)	46 (95.8)	64 (97.0)	141 (90.4)
Prior dasatinib	21 (50.0)	28 (58.3)	46 (69.7)	95 (60.9)
Prior nilotinib	23 (54.8)	24 (50.0)	32 (48.5)	79 (50.6)
Prior IFN	2 (4.8)	5 (10.4)	4 (6.1)	11 (7.1)
Resistant to any prior TKI	22 (52.4)	27 (56.3)	34 (51.5)	83 (53.2)
Intolerant to all prior TKIs	20 (47.6)	21 (43.8)	32 (48.5)	73 (46.8)

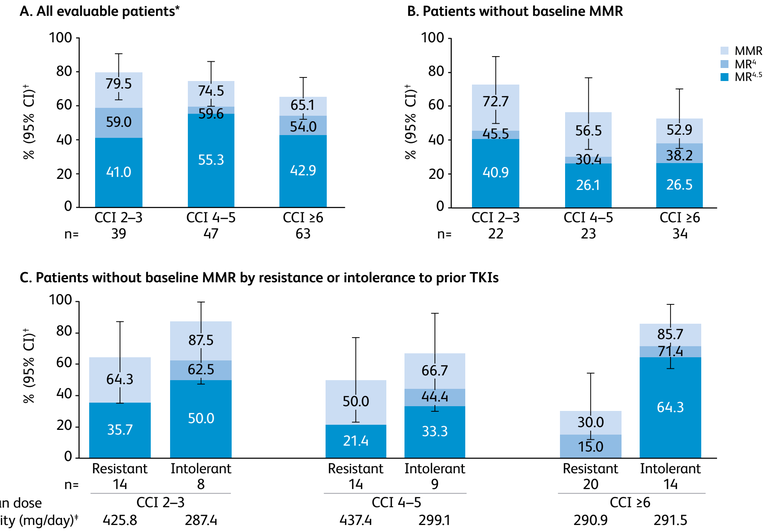
* Unless otherwise noted.
CCI=Charlson Comorbidity Index; ECOG PS=Eastern Cooperative Oncology performance status; IFN=interferon; TKI=tyrosine kinase inhibitor

Table 2: Treatment Summary, by CCI Score

	CCI 2–3 n=42	CCI 4–5 n=48	CCI ≥6 n=66
Treatment duration, median (range), mo	28.9 (0.4–41.9)	23.9 (0.9–41.9)	20.1 (0.2–42.2)
Dose intensity, median (range), mg/day	366.7 (153.9–560.6)	385.3 (145.0–500.0)	291.5 (79.7–500.0)
Total discontinued, n (%)	16 (38.1)	15 (31.3)	37 (56.1)
AE	8 (19.0)	10 (20.8)	21 (31.8)
Related to study treatment	8 (19.0)	8 (16.7)	14 (21.2)
Unrelated to study treatment	0	2 (4.2)	7 (10.6)
Insufficient clinical response	1 (2.4)	1 (2.1)	6 (9.1)
Other*	7 (16.7)	4 (8.3)	10 (15.2)

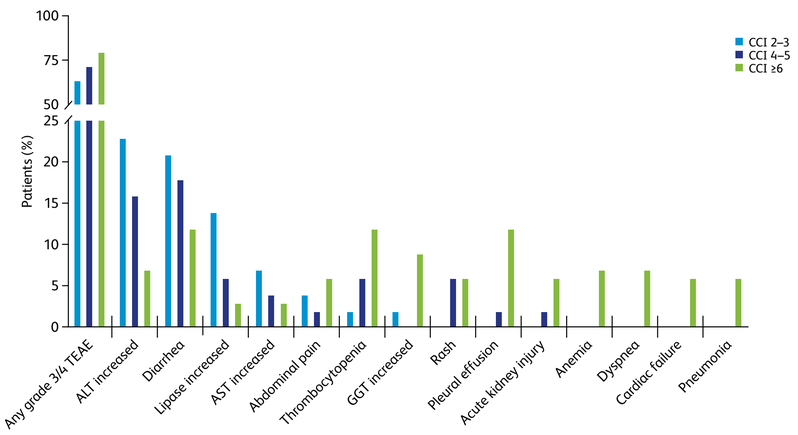
* Includes noncompliance, investigator declined further study participation, patient refusal to continue treatment for reason other than AE, protocol violation, lost to follow-up, death, and other.
AE=adverse event; CCI=Charlson Comorbidity Index

Figure 1: Cumulative Molecular Response Rates in (A) All Evaluable Patients, (B) Patients Without Baseline MMR, and (C) Patients Without Baseline MMR by Resistance or Intolerance to Prior TKIs



* Evaluable patients had valid baseline efficacy assessments for the respective endpoint.
† Associated 2-sided 95 % CI (for MMR only) based on the exact method by Clopper-Pearson.
‡ Dose intensity is for all treated patients (not only for those without MMR at baseline).
CCI=Charlson Comorbidity Index; CI=confidence interval; MMR=major molecular response; MR=molecular response; TKI=tyrosine kinase inhibitor

Figure 2: Summary of Grade 3/4 TEAEs, by CCI Score*



* Includes TEAEs occurring in ≥5 % of patients in any CCI group.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; CCI=Charlson Comorbidity Index; GGT=gamma-glutamyltransferase; TEAE=treatment-emergent adverse event

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Methods

ANALYSIS OF COMORBIDITIES

- Comorbidities were analyzed using the CCI, a validated measure of the influence of comorbid conditions and age on mortality.[6]
  - Relevant comorbid conditions are weighted from 1 to 6 points.
  - Each decade of age over 40 years adds 1 point.

Results

PATIENTS AND TREATMENT

Table S1: Treatment Summary, by CCI Score

	CCI 2–3 n=42	CCI 4–5 n=48	CCI ≥6 n=66
Treatment duration, median (range), mo	28.9 (0.4–41.9)	23.9 (0.9–41.9)	20.1 (0.2–42.2)
Dose intensity, median (range), mg/day	366.7 (153.9–560.6)	385.3 (145.0–500.0)	291.5 (79.7–500.0)
Total discontinued, n (%)	16 (38.1)	15 (31.3)	37 (56.1)
AE	8 (19.0)	10 (20.8)	21 (31.8)
Related to study treatment	8 (19.0)	8 (16.7)	14 (21.2)
Unrelated to study treatment	0	2 (4.2)	7 (10.6)
Noncompliance	2 (4.8)	0	3 (4.5)
Investigator declined further study participation	2 (4.8)	0	0
Patient refusal to continue treatment*	1 (2.4)	2 (4.2)	2 (3.0)
Insufficient clinical response	1 (2.4)	1 (2.1)	6 (9.1)
Other	1 (2.4)	1 (2.1)	2 (3.0)
Protocol violation	1 (2.4)	0	2 (3.0)
Lost to follow-up	0	1 (2.1)	0
Patient died	0	0	1 (1.5)

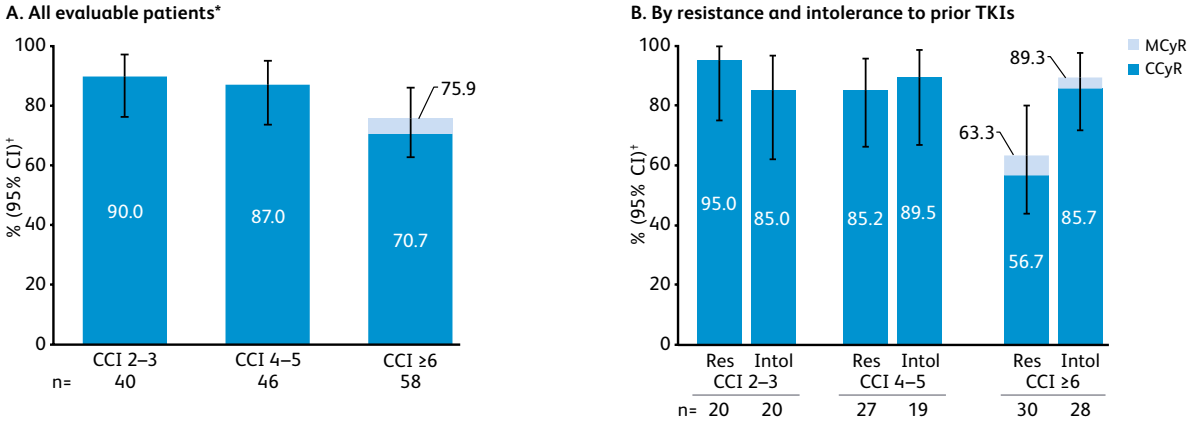
* For reason other than AE.
AE=adverse event; CCI=Charlson Comorbidity Index

CONTINUED

EFFICACY

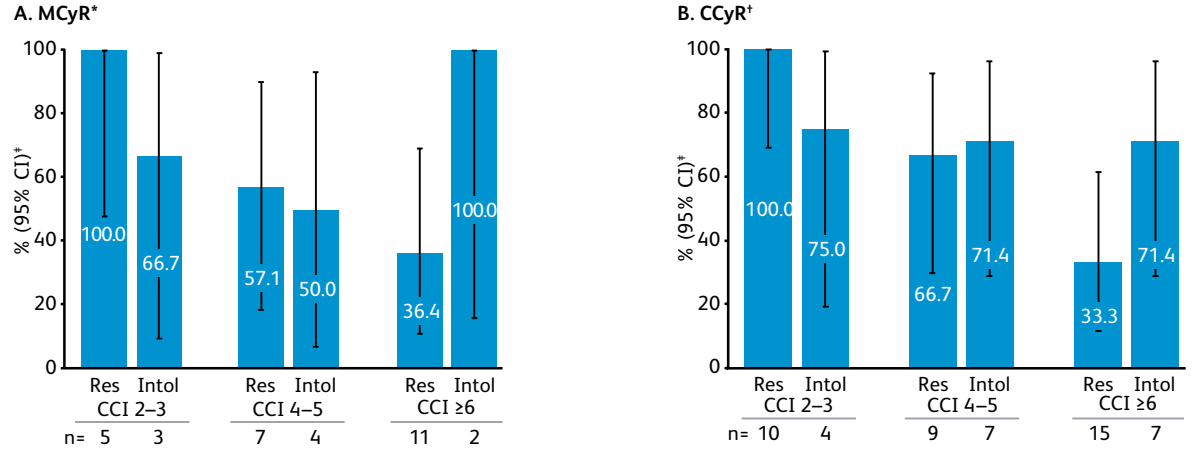
- Cytogenetic response rates were high across CCI groups (**Figures S1 and S2**).

Figure S1: Cumulative Cytogenetic Response Rates in (A) All Evaluable Patients and (B) by Resistance or Intolerance to Prior TKI Therapy



* Evaluable patients had a valid baseline efficacy assessment for the respective endpoint.
† Associated 2-sided CI (for MCyR only) based on the exact method by Clopper- Pearson.
CCI=Charlson Comorbidity Index; CCyR=complete cytogenetic response; CI=confidence interval; Intol=intolerant; MCyR=major cytogenetic response; MR=molecular response; Res=resistant; TKI=tyrosine kinase inhibitor

Figure S2: Cumulative Rates of (A) MCyR and (B) CCyR in Patients Without a Baseline Response, by Resistance or Intolerance to Prior TKI Therapy



Evaluable patients had a valid baseline efficacy assessment for the respective endpoint.
* In evaluable patients without baseline MCyR.
† In evaluable patients without baseline CCyR.
‡ Associated 2-sided 95% CI based on the exact method by Clopper–Pearson.
CCI=Charlson Comorbidity Index; CCyR=complete cytogenetic response; CI=confidence interval; Intol=intolerant; MCyR=major cytogenetic response; Res=resistant; TKI=tyrosine kinase inhibitor

SAFETY

- TEAEs differed among CCI groups (**Table S2**).

Table S2: Summary of Any Grade TEAEs, by CCI Score

TEAE, n (%)*	CCI 2–3 n=42	CCI 4–5 n=48	CCI ≥6 n=66
Any adverse event	42 (100.0)	47 (97.9)	66 (100.0)
Diarrhea	39 (92.9)	44 (91.7)	54 (81.8)
Nausea	20 (47.6)	21 (43.8)	23 (34.8)
Headache	19 (45.2)	11 (22.9)	13 (19.7)
Vomiting	17 (40.5)	13 (27.1)	22 (33.3)
Abdominal pain	15 (35.7)	10 (20.8)	19 (28.8)
ALT increased	13 (31.0)	12 (25.0)	17 (25.8)
Upper abdominal pain	12 (28.6)	9 (18.8)	14 (21.2)
Fatigue	11 (26.2)	8 (16.7)	18 (27.3)
AST increased	11 (26.2)	7 (14.6)	14 (21.2)
Dyspnea	7 (16.7)	4 (8.3)	23 (34.8)
Pleural effusion	2 (4.8)	3 (6.3)	21 (31.8)
Blood creatinine increased	1 (2.4)	5 (10.4)	17 (25.8)
Anemia	1 (2.4)	3 (6.3)	19 (28.8)

* Includes TEAEs occurring in ≥25% of patients in any CCI group.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; CCI=Charlson Comorbidity Index; TEAE=treatment-emergent adverse event.

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Table S3: AEs Leading to Treatment Discontinuation, by CCI Group

AE, n (%)*	CCI 2–3 n=42	CCI 4–5 n=48	CCI ≥6 n=66
Any AE	8 (19.0)	10 (20.8)	21 (31.8)
ALT increased	3 (7.1)	4 (8.3)	1 (1.5)
AST increased	3 (7.1)	1 (2.1)	0
Nausea	1 (2.4)	1 (2.1)	1 (1.5)
Pulmonary hypertension	1 (2.4)	1 (2.1)	0
Diarrhea	1 (2.4)	0	1 (1.5)
Neutropenia	1 (2.4)	0	1 (1.5)
Rash	1 (2.4)	0	1 (1.5)
Fatigue	1 (2.4)	0	0
Vomiting	0	2 (4.2)	0
Brain neoplasm	0	1 (2.1)	0
Decreased appetite	0	1 (2.1)	0
Rash maculo-papular	0	1 (2.1)	0
Rash papular	0	1 (2.1)	0
Subdural hematoma	0	1 (2.1)	0
Pleural effusion	0	0	2 (3.0)
Acute kidney injury	0	0	1 (1.5)
Anaplastic large-cell lymphoma	0	0	1 (1.5)
Anemia	0	0	1 (1.5)
Cardiac failure	0	0	1 (1.5)
Cardiogenic shock	0	0	1 (1.5)
Dyspnea	0	0	1 (1.5)
Edema peripheral	0	0	1 (1.5)
Fluid retention	0	0	1 (1.5)
Ileus	0	0	1 (1.5)
Lipase increased	0	0	1 (1.5)
Pancreatitis	0	0	1 (1.5)
Pericardial effusion	0	0	1 (1.5)
Peripheral ischemia	0	0	1 (1.5)
Pneumonia	0	0	1 (1.5)
Prostate cancer	0	0	1 (1.5)
Pseudomembranous colitis	0	0	1 (1.5)
Syncope	0	0	1 (1.5)
Ventricular dysfunction	0	0	1 (1.5)

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CCI=Charlson Comorbidity Index

Table S4: Summary of Deaths, by CCI Score

n (%)	CCI 2–3 n=42	CCI 4–5 n=48	CCI ≥6 n=66
Total deaths	0	1 (2.1)	9 (13.6)
AE unrelated to study drug	0	1 (2.1)	7 (10.6)
AE related to study drug	0	0	0
Disease under study	0	0	1 (1.5)*
Unknown	0	0	1 (1.5)
Deaths within 28 days of last dose	0	0	5 (7.6)
AE unrelated to study drug	0	0	4 (6.1)
AE related to study drug	0	0	0
Disease under study	0	0	1 (1.5)
Unknown	0	0	0

* Patient died due to cardiogenic shock and had several baseline conditions, including pleural effusion, that contributed to the outcome. The investigator's assessment was that the patient's death was CML-related, although the patient did not progress to AP/BP CML.
AE=adverse event; AP/BP=accelerated/blast phase; CCI=Charlson Comorbidity Index; CML=chronic myeloid leukemia