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

Carlo Gambacorti-Passerini[1], Tim H Brümmendorf[2], Bjørn Tore Gjertsen[3], Camille Abboud[4], Gianantonio Rosti[5], Elisabetta Abruzzese[6], Pilar Giraldo-Castellano[7], Ulla Olsson-Stromberg[8], Eric Leip[9], Andrea Viqueira[10], Simon Purcell[11], Valentin Garcia-Gutierrez[12], Frank Giles[13], Fausto Castagnetti[14], Andreas Hochhaus[15]

[1]University of Milano-Bicocca, Monza, Italy; [2]Universitätsklinikum RWTH Aachen, Aachen, Germany; [3]Haukeland University Hospital, Helse Bergen, and University of Bergen, Bergen, Norway; [4]Washington University School of Medicine, St. Louis, MO, USA; [5]University Hospital, University of Bologna, Rome, Italy; [6]Hematology, S. Eugenio Hospital, Tor Vergata University, Rome, Italy; [7]CIBER Enfermedades Raras(CIBERER), Miguel Servet University Hospital, Zaragoza, Spain; [8]University of Uppsala and Department of Hematology, University Hospital, Uppsala, Sweden; [9]Pfizer Inc, Cambridge, MA, USA; [10]Pfizer SLU, Madrid, Spain; [11]Pfizer Ltd, London, UK; [12]Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain; [13]Developmental Therapeutics Consortium, Chicago, IL, USA; [14]S. Orsola-Malpighi University Hospital, University of Bologna, Bologna, Italy; [15]Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany

Objective

- **Examine efficacy and safety of bosutinib by age and comorbidities in patients with Ph+ CP CML resistant/intolerant to prior TKI therapy enrolled in the phase 4 BYOND study.**

Conclusions

- **Results demonstrate efficacy of bosutinib in patients with Ph+ CP CML resistant/intolerant to prior therapy across age groups and mCCI scores, with a substantial proportion of patients across age and mCCI groups achieving/maintaining molecular response.**
- **Older patients (aged ≥65 or ≥75 years) and those with high comorbidity burden (mCCI ≥4) showed a trend towards higher rates of TEAEs and were more likely to discontinue treatment due to AEs.**
- **Age and mCCI stratification may enable the identification of patients who are at higher risk of developing TEAEs and require more careful monitoring.**

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 Ph+ chronic phase (CP) CML.[1,2]
- High rates of cytogenetic and molecular responses were observed during treatment with bosutinib 500 mg once daily in the phase 4 BYOND study in patients with Ph+ CP CML who were resistant/intolerant to prior TKIs.[3]
- Increasing age and the presence of comorbidities may influence the outcomes of patients with CML treated with TKIs.[4-6]

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. Eligibility criteria and endpoints have been previously described.[3]
- Efficacy and safety outcomes are reported in patients with Ph+ CP CML by:
  - Age: ≥65 vs <65 years and ≥75 vs <75 years.
  - Comorbidities as assessed by Charlson Comorbidity Index score without the age component (mCCI)7: mCCI scores 2, 3, and ≥4.
- Results were based on ≥1 year of follow-up (data cut-off date: September 18, 2018).

Results

- A total of 156 patients with Ph+ CP CML received bosutinib (**Table 1**).
- At the data cut-off, 44.3 % vs 64.2 % of patients aged ≥65 vs <65 years; 39.3 % vs 60.2 % of patients aged ≥75 vs <75 years; and 62.0 %, 56.0 %, and 37.9 % of patients with mCCI scores of 2, 3, and ≥4, respectively, were still receiving bosutinib treatment. Reasons for permanent treatment discontinuation are shown in **Table 2** and **Table S1**.
- A substantial proportion of patients attained or maintained molecular response across age groups and mCCI scores (**Figure 1** and **Figures S1** and **S2**).
- No patient experienced on-treatment transformation to accelerated/blast phase CML.
- Grade 3/4 treatment-emergent adverse events (TEAEs) differed between groups; older patients (aged ≥65 and ≥75 years) and those with mCCI ≥4 had a higher rate of grade 3/4 TEAEs (**Figure 2**).
- Deaths occurred in 10 vs 0 patients ≥65 vs <65 years old and 4 vs 6 patients ≥75 vs <75 years old. Deaths occurred in 4, 3, and 3 patients with mCCI scores 2, 3, and ≥4, respectively.
- **Supplementary material can be accessed via the electronic QR code.**

Table 1: Demographics and Baseline Characteristics in Patients With Ph+ CP CML, by Age and Comorbidities

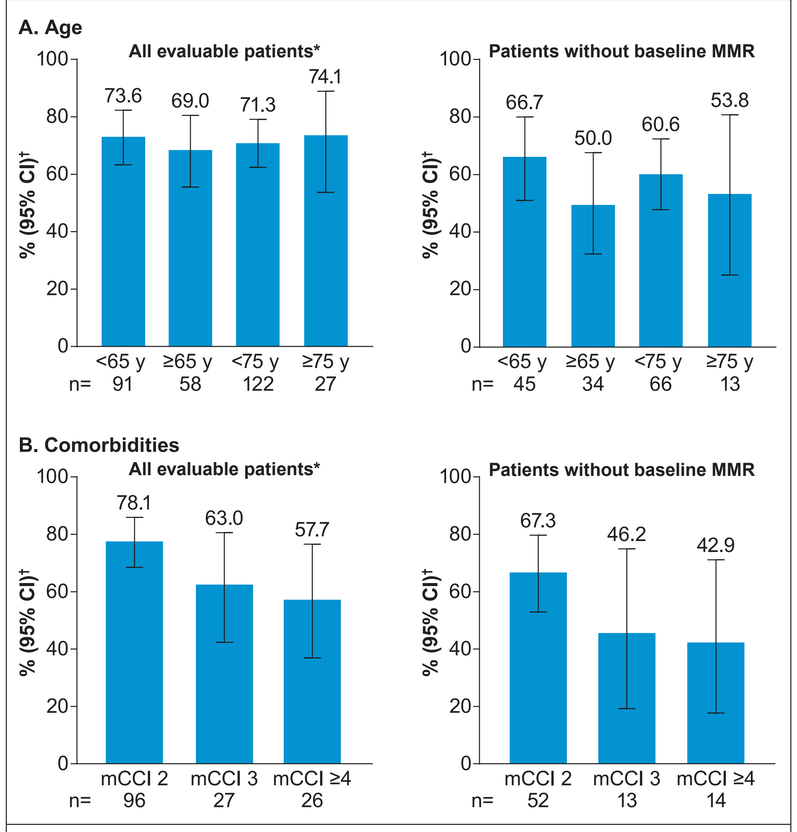
	By Age, years				By Comorbidities		
n (%)	<65 n=95 (60.9%)	≥65 n=61 (39.1%)	<75 n=128 (82.1%)	≥75 n=28 (17.9%)	mCCI 2 n=100 (64.1%)	mCCI 3 n=27 (17.3%)	mCCI ≥4 n=29 (18.6%)
Male	47 (49.5)	34 (55.7)	68 (53.1)	13 (46.4)	46 (46.0)	15 (55.6)	20 (69.0)
Age, median (range), y	51.0 (20.0–64.0)	74.0 (65.0–89.0)	56.0 (20.0–74.0)	78.0 (75.0–89.0)	53.5 (20.0–89.0)	67.0 (38.0–87.0)	70.0 (54.0–85.0)
ECOG PS							
0	70 (73.7)	36 (59.0)	93 (72.7)	13 (46.4)	74 (74.0)	15 (55.6)	17 (58.6)
1	22 (23.2)	23 (37.7)	31 (24.2)	14 (50.0)	23 (23.0)	11 (40.7)	11 (37.9)
2	3 (3.2)	2 (3.3)	4 (3.1)	1 (3.6)	3 (3.0)	1 (3.7)	1 (3.4)
No. of prior TKIs							
1	32 (33.7)	12 (19.7)	39 (30.5)	5 (17.9)	33 (33.0)	6 (22.2)	5 (17.2)
2	31 (32.6)	29 (47.5)	46 (35.9)	14 (50.0)	38 (38.0)	11 (40.7)	11 (37.9)
3	27 (28.4)	19 (31.1)	37 (28.9)	9 (32.1)	25 (25.0)	10 (37.0)	11 (37.9)
4	5 (5.3)	1 (1.6)	6 (4.7)	0	4 (4.0)	0	2 (6.9)
Prior IFN	8 (8.4)	3 (4.9)	10 (7.8)	1 (3.6)	6 (6.0)	3 (11.1)	2 (6.9)
Prior imatinib	81 (85.3)	60 (98.4)	113 (88.3)	28 (100.0)	88 (88.0)	25 (92.6)	28 (96.6)
Prior dasatinib	55 (57.9)	40 (65.6)	76 (59.4)	19 (67.9)	54 (54.0)	21 (77.8)	20 (69.0)
Prior nilotinib	51 (53.7)	28 (45.9)	67 (52.3)	12 (42.9)	52 (52.0)	9 (33.3)	18 (62.1)
Resistant to any prior TKI	50 (52.6)	33 (54.1)	71 (55.5)	12 (42.9)	53 (53.0)	16 (59.3)	14 (48.3)
Intolerant to all prior TKIs	45 (47.4)	28 (45.9)	57 (44.5)	16 (57.1)	47 (47.0)	11 (40.7)	15 (51.7)

Table 2: Treatment Summary in Patients With Ph+ CP CML, by Age and Comorbidities

	By Age, years				By Comorbidities		
	<65 n=95	≥65 n=61	<75 n=128	≥75 n=28	mCCI 2 n=100	mCCI 3 n=27	mCCI ≥4 n=29
Duration of Tx, median (range), months	24.2 (0.4–41.9)	22.5 (0.2–42.2)	23.8 (0.4–42.2)	23.1 (0.2–37.1)	24.1 (0.2–41.9)	23.6 (0.8–42.2)	17.8 (1.6–40.9)
Dose intensity, median (range), mg/day	342.9 (145.0–560.6)	304.5 (79.7–500.0)	340.4 (79.7–560.6)	264.7 (98.4–499.5)	343.6 (125.0–560.6)	299.1 (98.4–500.0)	303.6 (79.7–496.6)
Discontinued Tx, n (%)	34 (35.8)	34 (55.7)	51 (39.8)	17 (60.7)	38 (38.0)	12 (44.0)	18 (62.1)
Adverse event	19 (20.0)	20 (32.8)	29 (22.7)	10 (35.7)	22 (22.0)	7 (25.9)	10 (34.5)
Related to study Tx	18 (18.9)	12 (19.7)	25 (19.5)	5 (17.9)	16 (16.0)	5 (18.5)	9 (31.0)
Unrelated to study Tx	1 (1.1)	8 (13.1)	4 (3.1)	5 (17.9)	6 (6.0)	2 (7.4)	1 (3.4)
Insufficient clinical response	3 (3.2)	5 (8.2)	5 (3.9)	3 (10.7)	3 (3.0)	1 (3.7)	4 (13.8)
Other*	12 (12.6)	9 (14.8)	17 (13.2)	4 (14.3)	13 (13.0)	4 (14.8)	4 (13.8)

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

Figure 1: Cumulative MMR Rates in Patients With Ph+ CP CML, by (A) Age and (B) Comorbidities

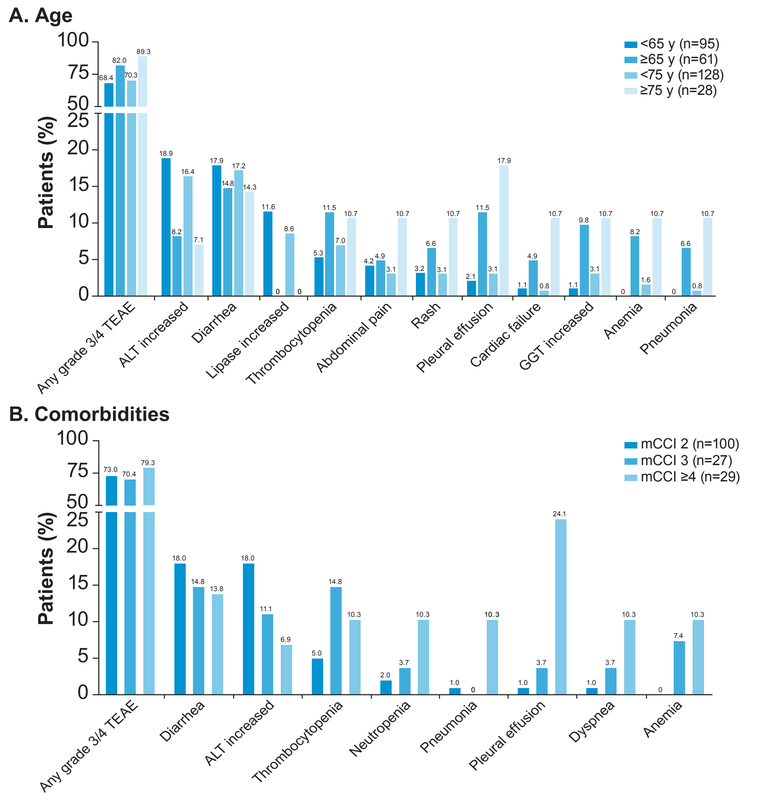


* Evaluable patients had valid baseline efficacy assessments for the respective endpoint.

† Associated 2-sided 95 % CI based on the exact method by Clopper-Pearson.

mCCI=Charlson Comorbidity Index without age component; MMR=major molecular response

Figure 2: Summary of Grade 3/4 TEAEs in Patients With Ph+ CP CML, by (A) Age and (B) Comorbidities*



* Includes TEAEs occurring in ≥10 % of patients in any subgroup.

ALT=alanine aminotransferase; mCCI=Charlson Comorbidity Index without age component; GGT=gamma-glutamyltransferase; TEAE=treatment-emergent adverse event

Electronic Poster and Supplementary Material

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