2786 Safety and Efficacy of Bosutinib in Fourth Line Therapy of Chronic Myeloid Leukemia Patients

Chronic Myeloid Leukemia: Therapy
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Valentín García-Gutiérrez1*, Dragana Milojkovic2*, **María Luisa Martín Mateos3*,** Simone Claudiani4*, **Concepcion Boque, PhD5*, Luis Felipe Casado6*, Gloria González7*, Antonio Jiménez8*, Alejandra Martinez Trillos9*, Isabel Mata Vázquez10*, Ángel Ramírez Payer11*, Alberto Álvarez Larran12*, Elena Amutio Díez13*, Abelardo Bárez García, MD14*, Guiomar Bautista Carrascosa15*, Sabela Bobillo Varela16*, Beatriz Cuevas Ruiz17*, Mª Ángeles Fernández Fernández18*, María del Carmen García Garay19*, Pilar Giraldo, MD, PhD20,21, Jose María Guinea de Castro22*, Natalia De Las Heras Rodríguez, MD23*, Nuria Hernanz Soler24*, Ana Iglesias Pérez25*, José Luis López Lorenzo26*, Josep Maria Martí Tutusaus, MD, PhD27*, Rolando Omar Vallansot28*, Fernando Ortega Rivas29*, Jose Manuel Puerta30*, Maria Jose Ramírez Sánchez31*, Esperanza Romero Picos32*, Mario Andrés Romo Collada18*, Ana Rosell Mas33*, Silvana Saavedra Gerosa34*, Ana Sebrango Sadia35*, José Tallón Pérez36*, Sandra Valencia37* and Juan Luis Steegmann, MD38**

1Hospital Universitario Ramón y Cajal, Madrid, Spain
2The Hammersmith Hospital, Imperial College, London, United Kingdom
3Servicio de Hematología. Hospital San Pedro de Alcántara. Servicio Extremeño de Salud, Cáceres, Spain
4Haematology, Hammersmith Hospital (Imperial College Healthcare NHS Trust), London, United Kingdom
5Insitute Cotele d'Oncologie, Barcelona, Spain
6Servicio de Hematologíay Hematoterapia, Hospital Virgen de la Salud, Toledo., Toledo, Spain
7Hospital Universitario de Canarias, Tenerife, Spain
8Hospital Universitario Carlos Haya, Málaga, Spain
9Hospital Clinic, Barcelona, Spain
10Hospital Costa del Sol, Málaga, Spain
11Hospital Universitario Central de Asturias, Oviedo, Spain
12Hospital del Mar, Barcelona, Spain
13Hospital de Cruces, Vizcaya, Spain
14Department of Hematology, Hospital Nuestra Señora de Sonsoles, Avila, Spain
15Hospital Universitario Puerta de Hierro, Majadahonda, Spain
16Hospital Vall d'Hebron, Barcelona, Spain
17Hospital Universitario de Burgos, Burgos, Spain
18Hospital Meixoeiro, Vigo, Spain
19Hospital Santa Lucia, cartagena, Spain
20Haematology, Miguel Servet University Hospital, Zaragoza, Spain
21ISS, CIBERER, Zaragoza, Spain
22Hospital de Txagorritxu, Vitoria, Spain
23Complejo Hospitalario de Leon, Leon, Spain
24Hospital Virgen de la Candelaria, Santa Cruz de Tenerife, Spain
25Hospital Universitario de Cruces, Bilbao, Spain
26Fundación Jiménez Díaz, Madrid, Spain

27Hospital Mútua de Terrassa, Terrassa, Spain
28Hospital Universitari Joan XXIII, Tarragona, Spain
29Servicio de Hematología., Hospital de Palencia, Palencia, Spain
30Unidad de Gestión Clínica Hematología y Hemoterapia, Hospital Universitario Virgen de las Nieves, Granada, Spain
31Department of Hematology, Hospital de Jerez de la Frontera, Jerez de la Frontera. Cádiz, Spain
32Hospital Arquitecto Marcide, Ferrol, Spain
33Hospital Virgen de la Victoria, Málaga, Spain
34Hospital Santa Creu i Sant Pau, Barcelona, Spain
35Hospital de Torrejón, Madrid, Spain
36Hospital de Jaén, Jaén, Spain
37Hospital de Segovia, Segovia, Spain
38Instituto de Investigación Sanitaria, Hospital Universitario de la Princesa, Madrid, Spain

BACKGROUND: Despite the excellent prognostic of chronic myeloid leukemia (CML) patients since the introduction of tyrosine kinase inhibitors (TKIs), approximately 50% of patients that are treated with TKIs will discontinue first line treatment due to lack of efficacy or intolerance. Once patients need a second line treatment, a considerable proportion of patients will need third or even fourth line therapy during further evolution. At this moment, there is a lack of data about real benefit of this group of patients. We have recently published our experience of 30 CML patients treated with bosutinib in 4th line. We present an update of the study where we have increased the number of patients, and the follow-up. The aim of this study is to present safety and efficacy data CML chronic phase patients treated with bosutinib in 4thline.

METHODS: We have collected data from 59 CML patients treated with bosutinib in 4thline after resistance or intolerance to IM, NI and DA. 51 patients have been treated under the Spanish compassionate use program (36 centers) and 10 patients were treated in a single institution from United Kingdom. Median age of patients at diagnosis was 53 years. The percentage of low, intermediate and high risk Sokal groups were 47%, 37% and 16%. Median time TKIs exposure before bosutinib was 9 years. The most common indication (30/59) was intolerant to DA and NI. Patients' dispositions and main line characteristics are shown in table 1.

RESULTS: Median follow-up was 14.3 months. All patients started bosutinib at 500mg/d, median dose of was 450mg/d. Overall probabilities to either achieve or maintain previous response were 96% (57/59), 62% (37/59), 40% (24/59) and 17% (10/59) for complete hematological response (CHR), complete cytogenetic response (CCyR), major molecular response (MMR) and MR4.5 respectively. However, probabilities to obtain responses (in patients without response evaluated at baseline) were 27% (7/26), 26% (12/45) and 12% (7/55) for CCyR, MMR and MR4.5. As expected, probabilities to obtain CCyR were lower for patients resistant to DA and NI patients than for patients intolerant to DA and NI (8% VS 44%). Event free survival (EFS) and progression free survival (PFS) probabilities were 50% and 83% by 27 month. Treatment was discontinued in 20/58 (34%), most frequent reasons being adverse events 9/59(15%), lack of efficacy 5/59 (8.5%), disease progression 2/59 (3.4%) and death 1/59 (1.7%). Two patients discontinued due to stem cell transplantation. The adverse events that led to treatment discontinuation were pleural effusion (3), diarrhea (2), rash, renal impairment, auricular fibrillation and liver enzyme elevation one patient each. Overall,

bosutinib was well tolerated. Grade 3-4 hematological toxicities were 3%, 6% and 6% for anemia, thromboctytopenia and neutropenia. Most common non hematological side effects were diarrhea (39%, nauseas 13% and liver alterations 14% and pleural effusion 14%.

CONCLUSIONS: Little is known about the therapeutic role of Bosutinib in 4th line. The series presented here is, to our knowledge, the largest being presented. Bosutinib seems to be an appropriate treatment option for patients resistant or intolerant to three prior TKIs.

Table 1

			IM+NI-I+DA-R (N=4)	**IM+NI-R+DA-R (N=18)**	**IM+NI-I+DA-I (N=30)**	**IM+NI-R+DA-I (N=7)**	**Total (N=59)**
Sex, N (%) Male			2 (50)	11 (61.1)	16 (53.3)	2 (28.6)	**31 (52.5)**
Median age of diagnosis, yr (range)			57.32 (50-64)	49.19 (23-73)	54.95 (21-89)	48.87 (26-68)	**53.15 (21-89)**
Median age of Bosutinib initiation, yr (range)			69.13 (61-70)	62.27 (39-79)	64.85 (25-90)	64.79(35-74)	**63.7 (25-9)**
Median follow up, months (range)			18.5(7.8-34.1)	8.4(1.22-36.1)	16.3(0.5-34.7)	23.4(3.3-28.9)	**14.3(0.7-36.1)**
SOKAL Index at diagnosis, N (%)	High		2(50.0)	4 (23.5)	1 (4.3)	1 (20)	**8 (16.3)**
	Intermediate		1 (25.0)	5 (29.4)	10(43.5)	2 (40)	**18 (36.7)**
	Low		1 (25.0)	8 (47.1)	12 (52.2)	2 (40)	**23 (46.9)**
Median Time from first TKI to BOS, (yr, range)			10.3 (4.8-11.9)	9.3 (2.0-11.4)	8.8 (0.7-13.6)	8.2 (5.1-12.3)	**8.8 (0.7-13.6)**
Median duration of prior therapy, months (range)		**Imatinib**	38.8 (11.8-69.8)	32.6 (6.3-96.8)	26.2 (1.6-102.6)	23.1 (8.3-66.8)	**28.8 (1.6-102.6)**
		Dasatinib	21.5 (12.6-75)	21.8 (7.7-69)	31.4 (0.4-87.1)	23.7 (10.3-53.6)	**23.44 (0.4-87.1)**
		Nilotinib	19.1 (2.1-46.2)	16.7 (5-65.6)	8.9 (0.2-58.5)	30.9 (6.9-49.3)	**14.3 (0.2-65.6)**

BOS: bosutinib, IM, imatinib; DA, dasatinib; NI, nilotinib, I: Intolerance, R: Resistant, Yr: year

Disclosures: García-Gutiérrez: Ariad: Consultancy ; Pfizer: Consultancy , Honoraria ; BMS: Consultancy , Honoraria ; Novartis: Consultancy , Honoraria . Milojkovic: Novartis: Consultancy, Honoraria ; Pfizer: Consultancy , Honoraria ; Ariad: Consultancy , Honoraria ; BMS: Consultancy, Honoraria . Boque: Novartis: Honoraria ; BMS: Honoraria ; Celgene: Honoraria. Casado: Novartis: Honoraria , Research Funding ; BMS: Honoraria , Research Funding ; Pfizer: Honoraria, Research Funding ; Roche: Honoraria , Research Funding . Jiménez: Pfizer: Consultancy, Honoraria . Giraldo: Pfizer: Consultancy. Steegmann: Novartis: Consultancy, Honoraria , Research Funding , Speakers Bureau ; BMS: Consultancy , Honoraria , Research Funding , Speakers Bureau ; Pfizer: Consultancy , Honoraria , Research Funding , Speakers Bureau ; Ariad: Consultancy , Honoraria , Research Funding , Speakers Bureau .