ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA
DIAGNOSTICA E SPERIMENTALE

POLICLINICO DI
SANT'ORSOLA

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EMILIA-ROMAGNA
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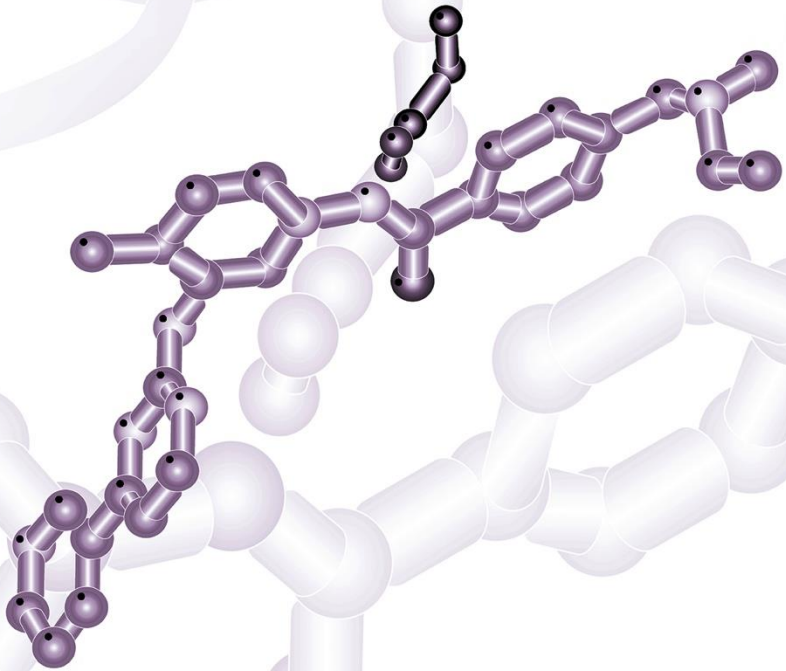

New Drugs in Hematology

President: Pier Luigi Zinzani

Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
May 18-20, 2022

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

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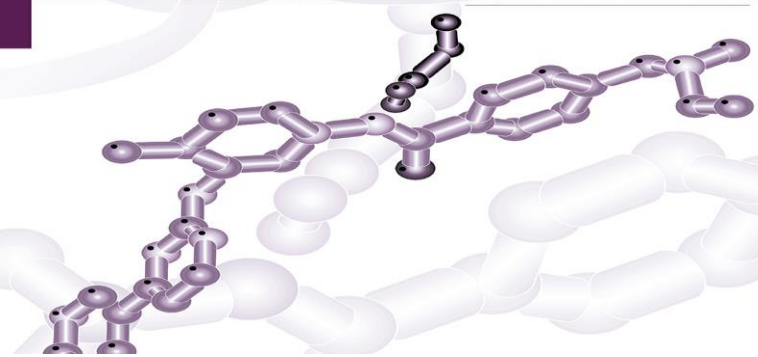

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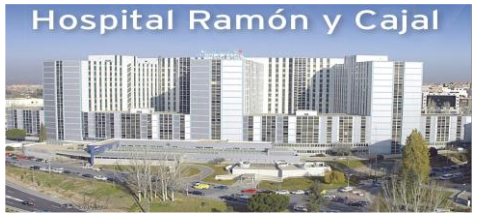
Bosutinib

Valentín García Gutiérrez
Hospital Universitario Ramón y Cajal
Instituto Ramón y Cajal de Investigación Sanitaria
Universidad de Alcala

ORGANIZA

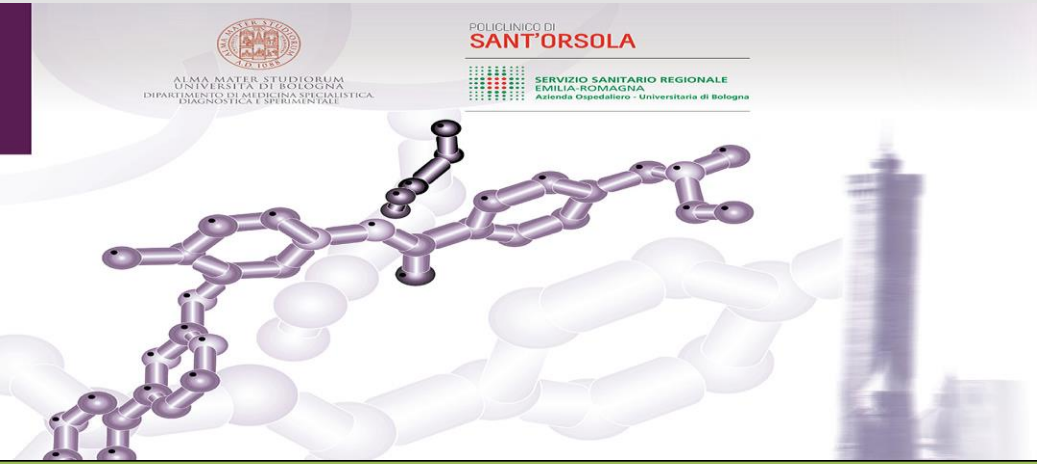
GE LMC

ZERO lmc



R y C

Fundación para la Investigación Biomédica
del Hospital Universitario Ramón y Cajal



New Drugs in Hematology

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Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	x		x		x	x	x
Pfizer	x		x		x	x	x
BMS/Celgene	x		x		x	x	x
Incyte	x		x		x	x	

During the presentation we will discuss about:

- What is bosutinib and when bosutinib could be used?
- When bosutinib should be used?
- How bosutinib should be used?

During the presentation we will discuss about:

- **What is bosutinib and when bosutinib could be used?**
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Bosutinib

- Dual TKI Scr-Bcr
- Minimal PDGFR and c-Kit inhibition

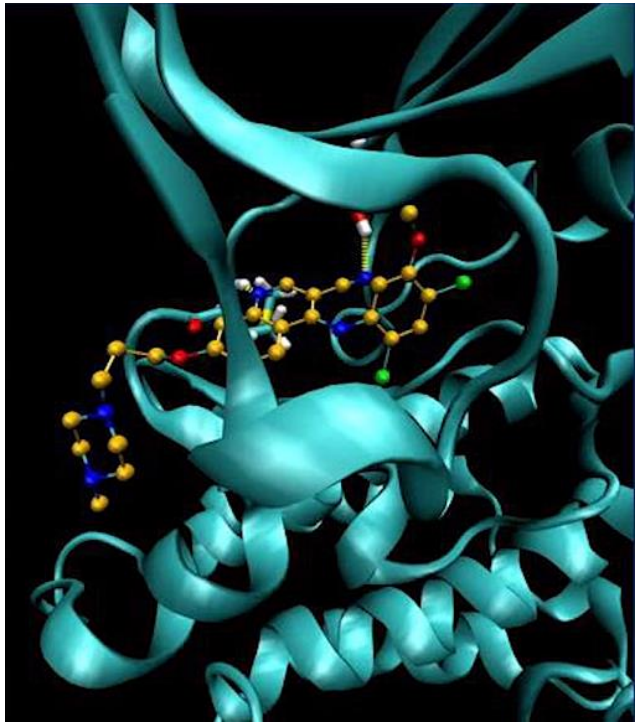

Table 1. Comparison of SKI-606 and imatinib on cell proliferation

Kinase	SKI-606 (nmol/L)	Imatinib (nmol/L)
	IC_{50} ± SE (no. repeats)	IC_{50} ± SE (no. repeats)
WT-Ba/F3 + IL-3	570 ± 350 (4)	5,660 ± 2,760 (3)
Bcr-Abl (K562)	20 ± 2 (2)	221 ± 20 (2)
Bcr-Abl (Lama84)	1 ± 0.3 (6)	86 ± 8 (11)
Bcr-Abl (KU812)	3 ± 1 (2)	51 ± 5 (2)
Bcr-Abl (KCL22)	5 ± 1 (2)	70.5 (1)
Bcr-Abl (K562R, imatinib resistant)	28 ± 3 (2)	3,190 (1)
Bcr-Abl (Lama84R, imatinib resistant)	35 (1)	735 ± 380 (2)
Bcr-Abl (KCL22R, imatinib resistant)	150 (1)	2,170 ± 460 (2)
p210 Bcr-Abl (Ba/F3)	13 ± 4 (6)	401 ± 70 (11)
D276G Bcr-Abl (Ba/F3)	25 ± 15 (2)	1147 ± 231 (4)
Y253F Bcr-Abl (Ba/F3)	40 ± 22 (3)	1,888 ± 979 (4)
E255K Bcr-Abl (Ba/F3)	394 (1)	3,174 ± 1,211 (2)
T315I Bcr-Abl (Ba/F3)	1,800 ± 850 (2)	>10,000 (1)
Tel-PDGFRβ (Ba/F3)	370 ± 180 (5)	3.4 ± 0.9 (5)
c-KIT exon 13 mutant (GIST882)	6,000 (1)	29.5 (1)
c-KIT G560V ($HMC1^{560}$)	950 ± 450(2)	19 (1)
(U937)	3,500 ± 850 (5)	>10,000 (4)

Cancer Res 2006; 66: (23). December 1, 2006

Current treatment options in CML

	First line	Second line (after imatinib)	Intolerance or resistance to 2GTKI
Approved	Imatinib 400 mg	Dasatinib 100 mg	Dasatinib 100 mg
	Nilotinib 300 mg BID	Nilotinib 400 mg BID	Nilotinib 400 mg BID
	Dasatinib 100 mg	Bosutinib 500 mg	Bosutinib 500 mg
	Bosutinib 400 mg	Ponatinib 45 mg*	Ponatinib 45 mg**
Pending approval			Asciminib

Bosutinib is approved for patients in whom imatinib, nilotinib, and dasatinib are not considered an adequate treatment option.
*Ponatinib is indicated after imatinib failure for patients harboring *T315I* mutation.
**Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

Baccarani M, et al. *Blood*. 2013;122(6):872-884; Hughes TP, et al. *Blood*. 2016;128:abstract 625; Cortes J, et al. *J Clin Oncol*. 2017;35(15 suppl):abstract 7051.

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Pending approval			Asciminib

Study 200:
- Phase I/II study (not First in Human)
- Pts in 2L and pts in 3/4L

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Bosutinib efficacy in 2L (after imatinib failure)

- 288 pt CML CP wit imatinib resistance (n=200) or intolerance (n=88)
- Bosutinib 500 mg orally daily
- Median follow-up 47 months

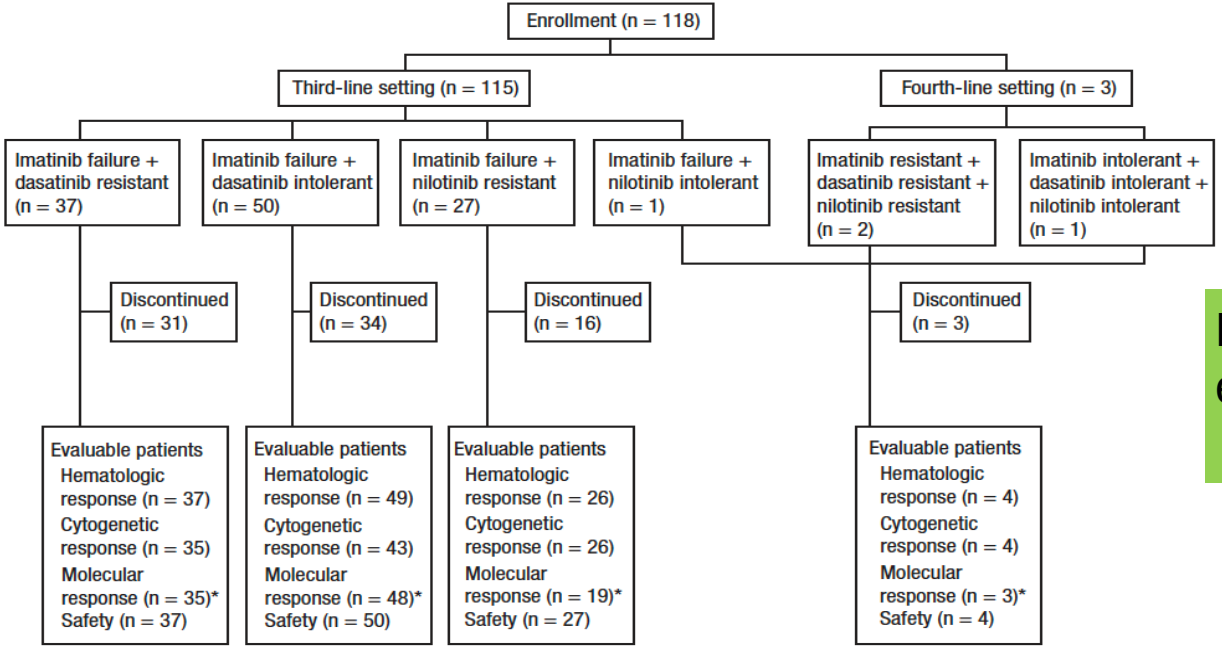
Response	Percentage	
	IM Resistant	IM Intolerant
CHR	86	84
MCyR	59	61
CCyR	48	52
MMR*	64	65
CMR*	49	61
2-yr PFS**	73	95
Discontinued therapy	60	62

- Median dose intensity: IM-resistant 485 mg/d, IM-intolerant : 394 mg/d

*Data from 2-yr follow-up among pts in CCyR; overall (all patients, 2-y) MMR 41%, CMR 34%
** 4-yr cumulative incidence of on-treatment progression or death 22% for resistant, 10% for intolerant

Gambacorti-Passerini et al. Haematologica 2018; 103: 1298-1307
Brummendorf et al. Br J Haematol 2016; 172: 97-110; Cortes et al. Blood 2011; 118: 4567-76

Bosutinib after imatinib and 2GTKI failure



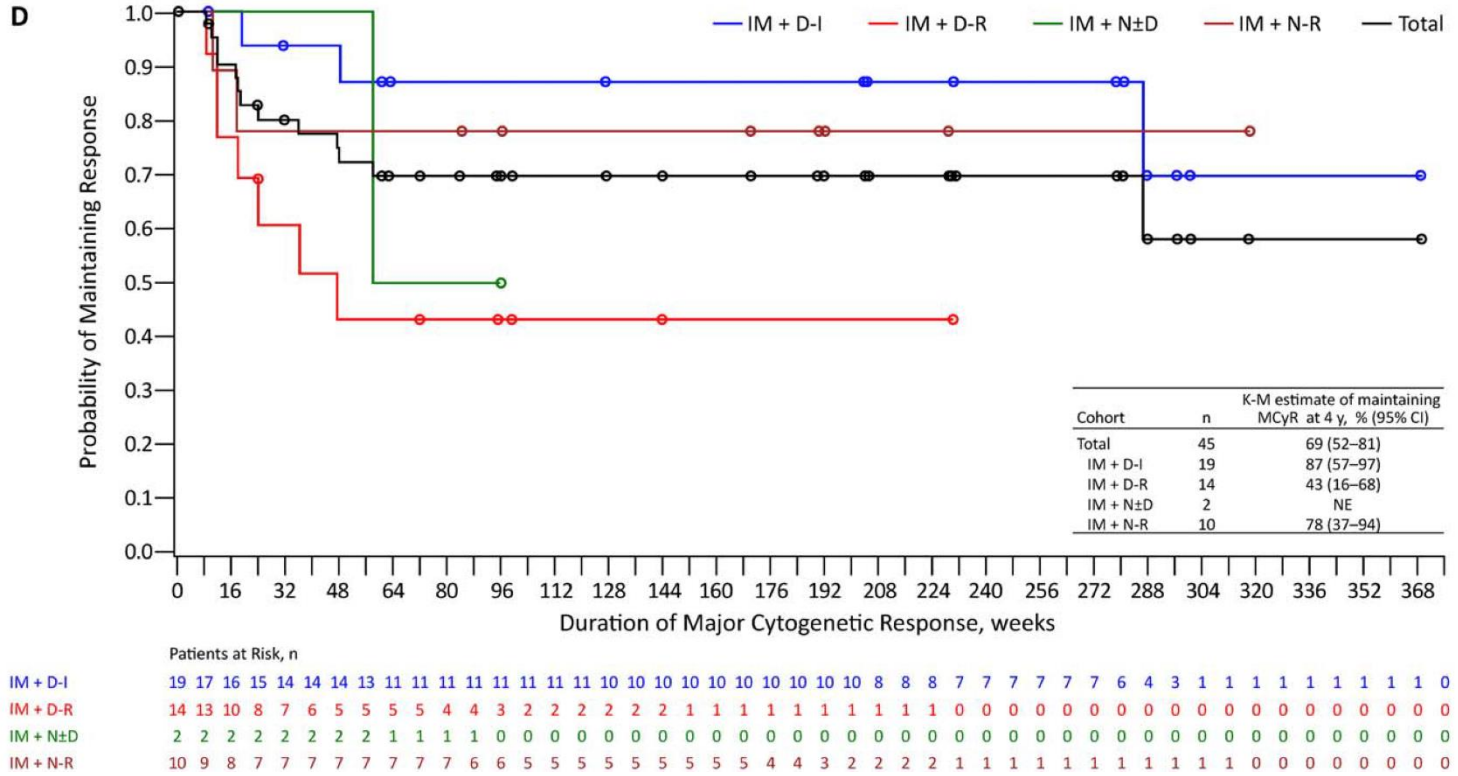
First clinical trial evaluating the use of 2GTKI in 2GTKI failure patients

Bosutinib after imatinib and 2GTKI failure

Table 3. Best cumulative response to bosutinib

Response, n (%)	IM + DAS resistant (n = 37)	IM + DAS intolerant (n = 50)	IM + NI resistant (n = 27)	IM + DAS ± NI (n = 4)*	Total (n = 118)
Median follow-up, mo (range)	20.0 (2.7-51.3)	34.5 (0.3-56.2)	23.0 (7.1-54.0)	34.5 (22.8-40.0)	28.5 (0.3-56.2)
Hematologic response†					
Evaluable patients	37	49	26	4	116
Complete response	23 (62)	39 (80)	20 (77)	3 (75)	85 (73)
Hematologic response among patients with no baseline CHR					
Evaluable patients	22	24	20	2	68
Cytogenetic response‡					
Evaluable patients	35	43	26	4	108
Major response	11 (31)	13 (30)	9 (35)	2 (50)	35 (32)
Complete response	5 (14)	12 (28)	7 (27)	2 (50)	26 (24)
Partial response	6 (17)	1 (2)	2 (8)	0	9 (8)
Minor response	0	4 (9)	2 (8)	0	6 (6)
Evaluable patients	35	48	19	3	105
Major response	1 (3)	12 (25)	2 (11)	1 (33)	16 (15)
Complete response	0	9 (19)	2 (11)	1 (33)	12 (11)

Long term response in patients treated with bosutinib after failure of imatinib and/or other 2GTKI



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	Bosutinib 400 mg	Ponatinib 45 mg*	Ponatinib 45 mg**
Pending approval			Asciminib

Two studies in 1L
- Bela study (Bosutinib 500mg)
- BFORE study (Bosutinib 400mg)

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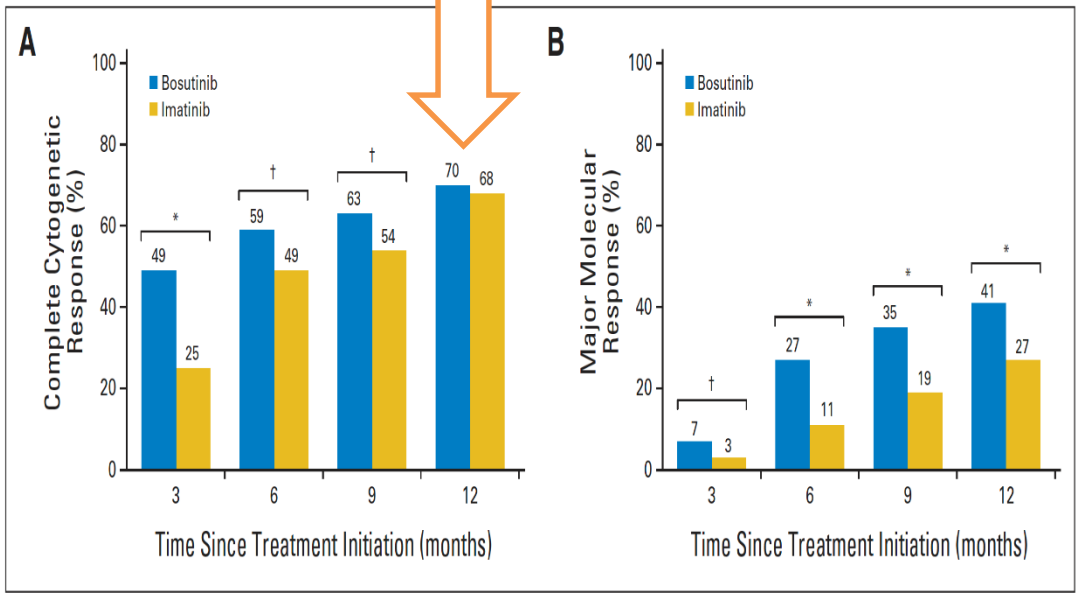
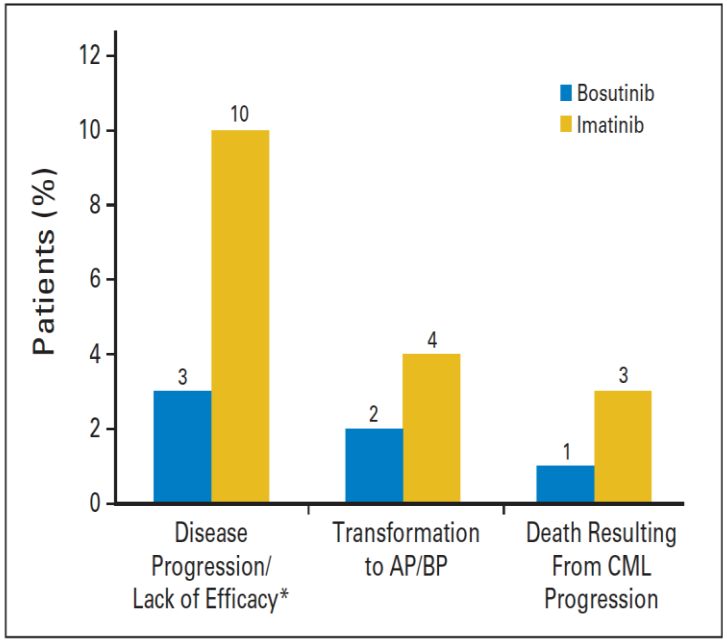
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Bosutinib Versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia: Results From the BELA Trial

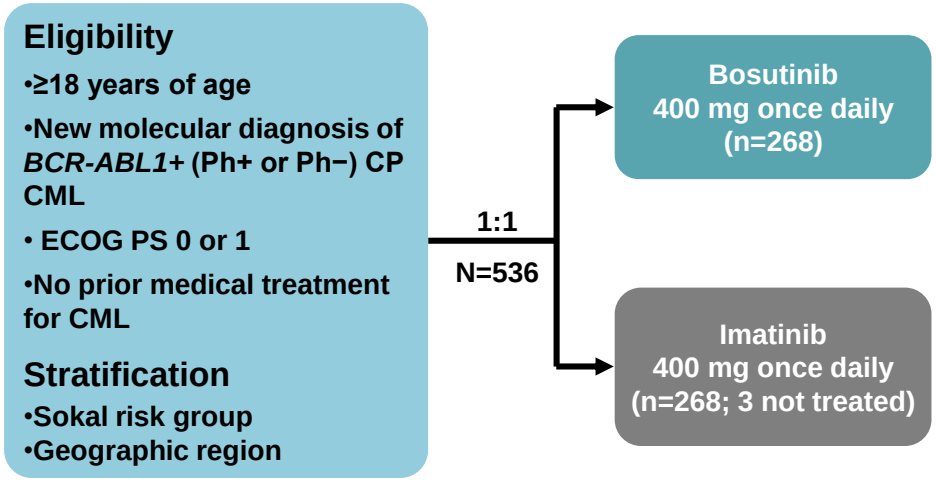
BELA study: Bosutinib "first try" in the 1st line





BFORE Study Design:

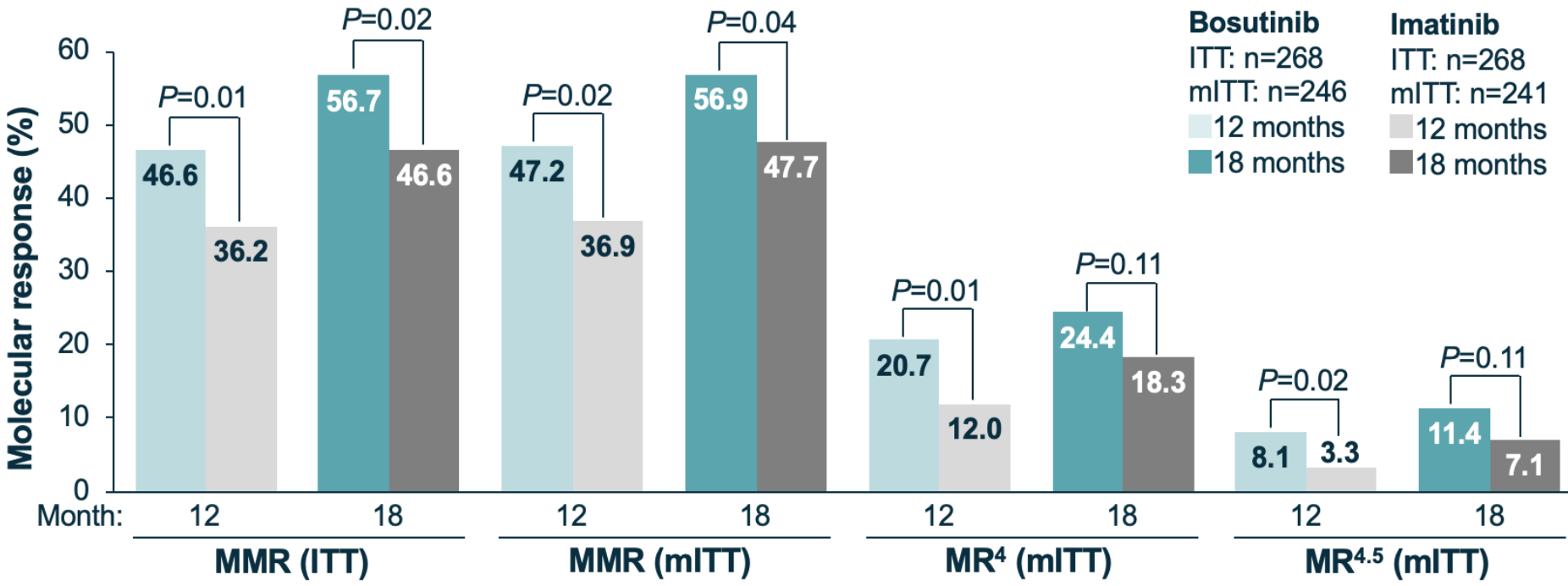
- BFORE (NCT02130557) is an ongoing (expected duration 5 years), multinational, randomized, open-label, two-arm, phase 3 study
- Prespecified primary endpoint:
  - MMR at 12 months in the mITT population
- mITT population: Ph+ patients with e13a2/e14a2 transcripts, excluding Ph− patients and those with unknown Ph status and/or *BCR-ABL* transcript type*
  - Bosutinib: n=246
  - Imatinib: n=241
- Current analysis based on ≥18 months of follow-up†



* 12 Ph– patients (ie, 0 of ≥10–99 metaphases at baseline; n=6 in each arm), 8 patients with atypical transcripts (n=3 in bosutinib arm; n=5 in imatinib arm), and 31 patients with unknown Ph status (n=13 in bosutinib arm; n=18 in imatinib arm [includes 2 patients also listed as having atypical transcripts]).

† All *P* values, except MMR at 12 months and CCyR by 12 months in the mITT population, are for descriptive purposes only; no adjustments for multiple comparisons.

CCyR=complete cytogenetic response; CML=chronic myeloid leukemia; CP=chronic phase; ECOG PS=Eastern Cooperative Oncology Group performance status; mITT=modified intent-to-treat; MMR=major molecular response; Ph=Philadelphia chromosome



CML=chronic myeloid leukemia; ITT=intent-to-treat; mITT=modified intent-to-treat; MR=molecular response; MMR=major molecular response

MR^4 (ITT), %	Bosutinib	Imatinib	*P*
12 mo	20.5	11.6	<0.01
18 mo	24.6	18.3	0.08

MR$^{4.5}$ (ITT), %	Bosutinib	Imatinib	*P*
12 mo	7.5	3.0	0.02
18 mo	11.9	8.2	0.16

Gambacorti-Passerini, ASH 2017

TEAEs of Special Interest (Any Grade), by Cluster

TEAE Cluster*	Bosutinib n=268	Imatinib n=265
Gastrointestinal	214 (79.9)	163 (61.5)
Myelosuppression	128 (47.8)	125 (47.2)
Liver	118 (44.0)	41 (15.5)
Rash	105 (39.2)	69 (26.0)
Musculoskeletal	95 (35.4)	158 (59.6)
Edema	42 (15.7)	115 (43.4)
Hypertension	28 (10.4)	29 (10.9)
Renal	28 (10.4)	26 (9.8)
Cardiac	26 (9.7)	23 (8.7)
Metabolic	24 (9.0)	21 (7.9)
Vascular	20 (7.5)	9 (3.4)
Effusion	16 (6.0)	6 (2.3)

* Frequency and characteristics of AEs of special interest were analyzed by selecting MedDRA system organ class high level group, high level and preferred terms and standardized MedDRA queries to generate TEAE clusters.

MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event

Tim H Brümmendorf. ASH 2020. PO

Grade ≥3 TEAEs* (Safety Population)

System organ class† preferred term	Bosutinib (n=268)	Imatinib (n=265)
Blood and lymphatic system disorders, n (%)	48 (17.9)	58 (21.9)
Thrombocytopenia	37 (13.8)	16 (6.0)
Neutropenia	19 (7.1)	34 (12.8)
Anemia	10 (3.7)	13 (4.9)
Leukopenia	3 (1.1)	10 (3.8)
Leukocytosis	2 (0.7)	7 (2.6)
Gastrointestinal disorders, n (%)	31 (11.6)	9 (3.4)
Diarrhea	22 (8.2)	2 (0.8)
Laboratory investigations, n (%)	91 (34.0)	35 (13.2)
Alanine aminotransferase increased	56 (20.9)	4 (1.5)
Lipase increased	28 (10.4)	12 (4.5)
Aspartate aminotransferase increased	27 (10.1)	5 (1.9)
Metabolism and nutrition disorders, n (%)	14 (5.2)	12 (4.5)
Hypophosphatemia	3 (1.1)	9 (3.4)

* Select all-causality adverse events occurring in ≥2% patients in either treatment arm.
† Medical Dictionary for Regulatory Activities v20.0; patients may report >1 adverse event at the level of preferred term within each system organ class.
CML=chronic myeloid leukemia; TEAE=treatment-emergent adverse event

During the presentation we will discuss about:

- What is bosutinib and when bosutinib could be used?
- **When bosutinib should be used?**
- How bosutinib should be used?

Bosulif

Therapeutic indication

Bosulif is indicated for the treatment of adult patients with:

- newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Clinical trials evaluating TKIs in 2GTKIs failure patients

Dasatinib	Nilotinib	Bosutinib	Ponatinib
None	Giles et al (37 pts dasatinib failure)	Study 200 (N 138pts)	Pace (274)
		BYOND study (163pts)	Optic (283 pts)

Giles F, et al. *Leukemia.* 2010;
Hochhaus A. Leukemia. 2020 Aug;34(8):2125-2137
Brümmendorf TH. Am J Hematol. 2016 Dec;91(12):1206-1214
Cortes J. Blood. 2021 Nov 25;138(21):2042-2050.
Cortes J. Blood. 2016 Feb 11;127(6):703-12..

Bosutinib later lines GELMC experience

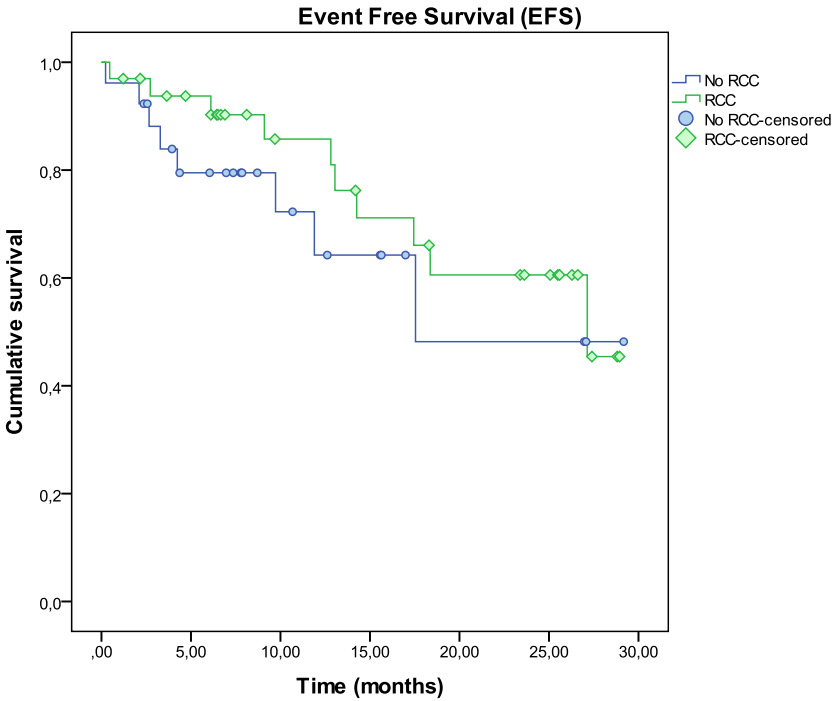
			IM+NI-I+DA-R (n = 4)	IM+NI-R+DA-R (n = 19)	IM+NI-I+DA-I (n = 32)	IM+NI-R+DA-I (n = 7)	Total (N = 61)
Median follow							13,47
Best responses to bosutinib, N (%)							61/61 (100)
							40/61 (65)
							25/61 (41)
							10/61 (16)
							7/28 (25)
	without previous responses	MMR	0/3 (0)	2/19 (10)	7/19 (38)	3/6 (50)	12/47 (25)
		MR.5	0/3 (0)	0/19 (0)	6/29 (20)	1/6 (16)	7/57 (12)

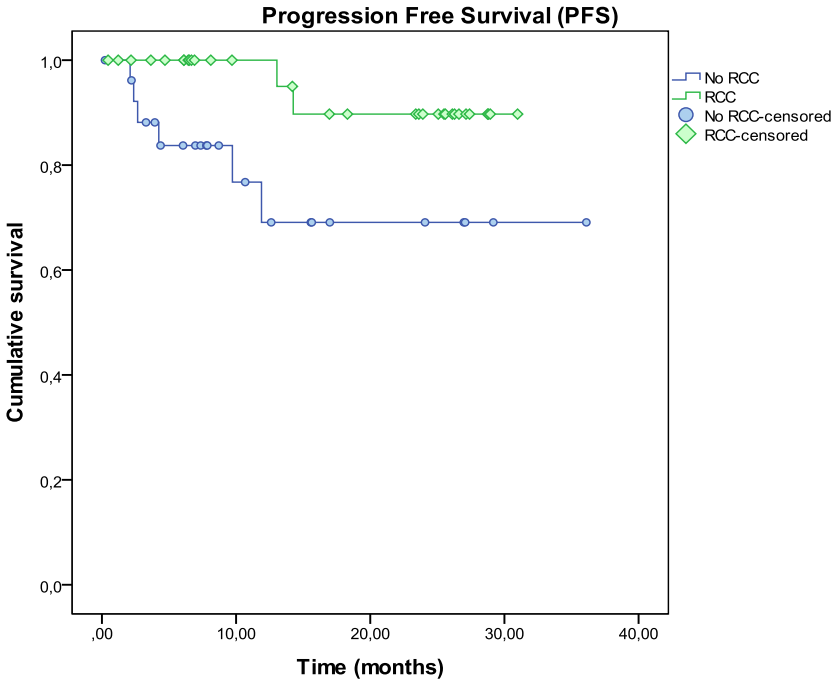
	Overall population, N (%)	Patients without previous responses, N (%)
CHR	100% (61/61)	NA
CCyR	65% (40/61)	25% (7/28)
MMR	41% (25/61)	25% (12/47)
MR4.5	16% (10/61)	12% (7/57)

CCyR probabilities 8% vs 44% for resistant and intolerant patients respectively

García-Gutiérrez V. Ann Hematol. 2019 Feb;98(2):321-330

EFS and PFS





García-Gutiérrez V. Ann Hematol. 2019 Feb;98(2):321-330

Phase IV BYOND study

Table 1: Demographics and Baseline Characteristics Across Patients With CP Ph+ CML

	Line of Treatment			
Characteristic, n (%)*	2nd n=46	3rd n=61	4th n=49	Total N=156
Male	23 (50.0)	37 (60.7)	21 (42.9)	81 (51.9)
Age, median (range), y	54.5 (20.0–89.0)	65.0 (28.0–85.0)	61.0 (21.0–85.0)	61.0 (20.0–89.0)
ECOG PS				
0	34 (73.9)	40 (65.6)	32 (65.3)	106 (67.9)
1	12 (26.1)	20 (32.8)	13 (26.5)	45 (28.8)
2	0	1 (1.6)	4 (8.2)	5 (3.2)
Number of prior therapies				
1	44 (95.7)	0	0	44 (28.2)
2	2 (4.3)	58 (95.1)	0	60 (38.5)
3	0	3 (4.9)	43 (87.8)	46 (29.5)
4	0	0	6 (12.2)	6 (3.8)
Prior IFN	2 (4.3)	3 (4.9)	6 (12.2)	11 (7.1)
Prior imatinib	35 (76.1)	57 (93.4)	49 (100)	141 (90.4)
Prior dasatinib	5 (10.9)	41 (67.2)	49 (100)	95 (60.9)
Prior nilotinib	6 (13.0)	24 (39.3)	49 (100)	79 (50.6)
Resistant to any prior TKI	17 (37.0)	35 (57.4)	31 (63.3)	83 (53.2)
Intolerant to all prior TKIs	29 (63.0)	26 (42.6)	18 (36.7)	73 (46.8)

* Except where indicated.

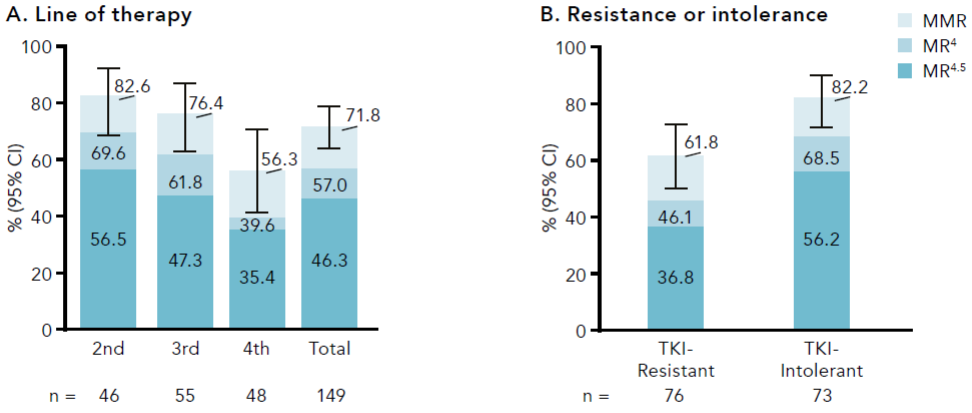
CML=chronic myeloid leukemia; CP=chronic phase; ECOG PS=Eastern Cooperative Oncology Group performance status; IFN=interferon; Ph+=Philadelphia chromosome–positive; TKI=tyrosine kinase inhibitor

Extraído de PS1176 EHA 2019

Hochhaus A. Leukemia. 2020 Aug;34(8):2125-2137

Treatment responses according to failure reasons (intolerance/resitance)

Figure 2: Summary of Cumulative Molecular Response Rates in Patients With CP Ph+ CML by (A) Line of Therapy and (B) Resistance or Intolerance to Prior TKIs*

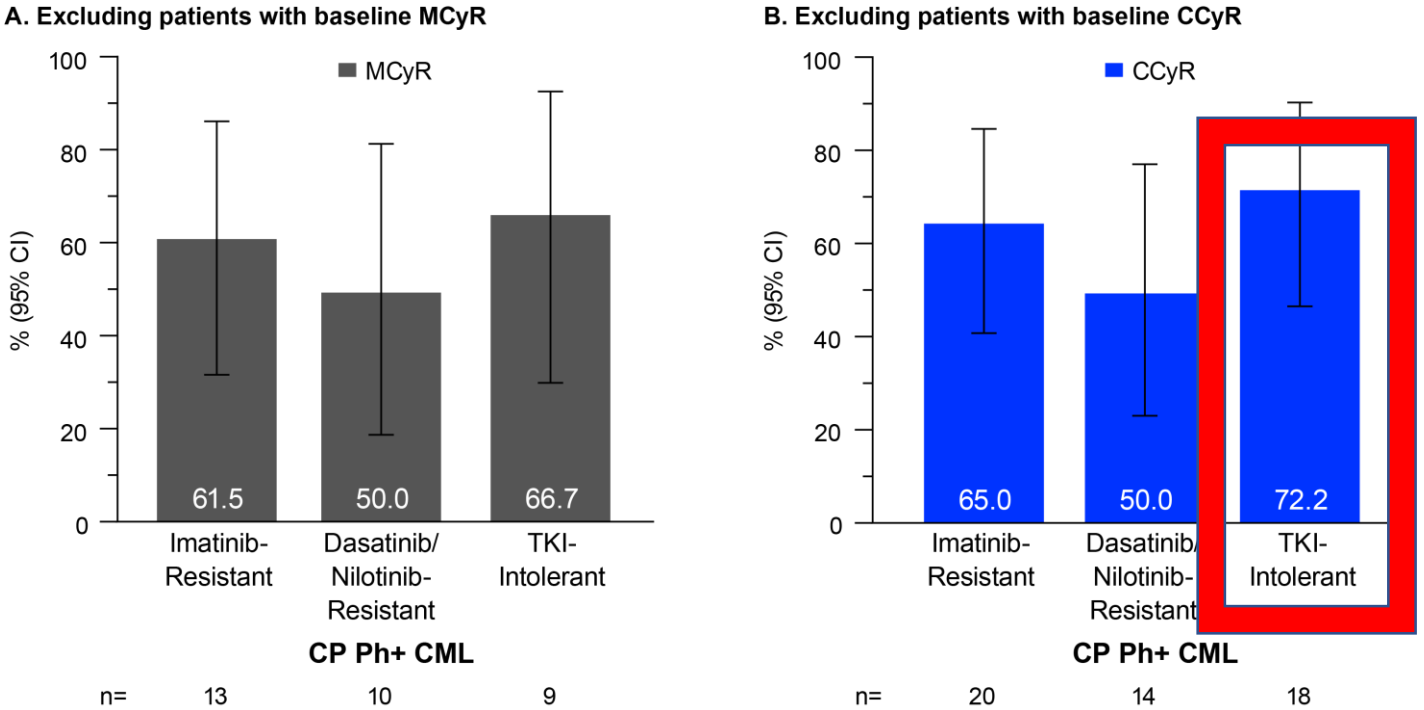


* Evaluable population. MMR (MR^3): ≤0.1% *BCR-ABL1* ratio on IS (≥3-log reduction from standardized baseline). MR^4: ≤0.01% *BCR-ABL1* ratio on IS (≥4-log reduction from standardized baseline). $MR^{4.5}$: ≤0.0032% *BCR-ABL1* ratio on IS (≥4.5-log reduction from standardized baseline).
Associated 2-sided 95% CI (for MMR only) based on the exact method by Clopper-Pearson.
CI=confidence interval; CML=chronic myeloid leukemia; CP=chronic phase; IS=international scale; MMR=major molecular response; MR=molecular response; Ph+=Philadelphia chromosome–positive; TKI=tyrosine kinase inhibitor

Hochhaus A et al. Presented at the EHA 2019 abstract #PS 1176

Hochhaus A. Leukemia. 2020 Aug;34(8):2125-2137

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

Creado de ASH 2019 #1650

2GTKIs second line (imatinib failure patients)

	Dasatinib 100 mg		Nilotinib 400 mg bid		Bosutinib 500 mg qd	
	Resistance	Intolerance	Resistance	Intolerance	Resistance	Intolerance
Follow up	24 months		24 months		24 months	
CCyR[a]	44%	67%	41%	51%	48%	52%
MMR[b]	37%		28%			
PFS[c]	80%		64%		79%	
OS[d]	91%		87%		92%	

[a] *Complete cytogenetic response.*
[b] *Major molecular response.*
[c] *Progression free survival.*
[d] *Overall survival.*

Extraído de V. García-Gutiérrez et al. Safety. Front. Oncol. 2019

Tasigna Nilotinib (Novartis), Sprycel Dasatinib (Bristol-Myers Squibb Pharma), Bosulif bosutinib, (Pfizer SLU)

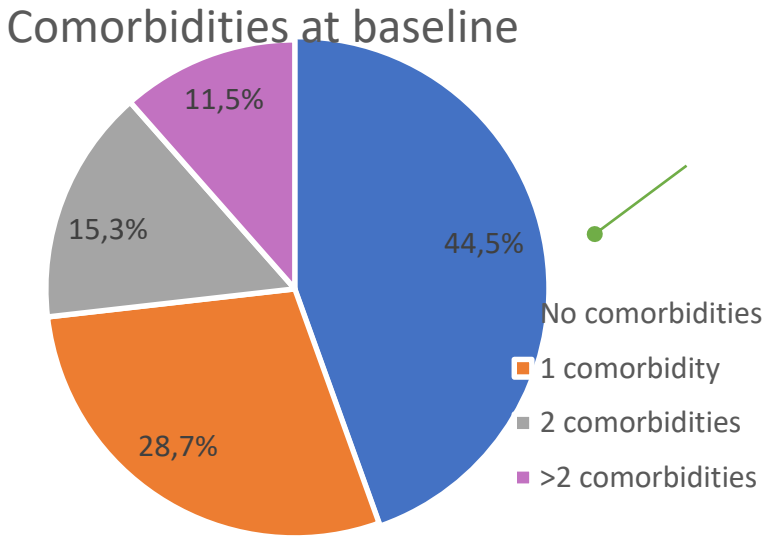
Data from different studies; should be interpreted with caution.

V. García-Gutiérrez et al. Safety. Front. Oncol. 2019,Shah NP, et al. *Haematologica.* 2010;95(2):232-240; Kantarjian H, et al. *Blood.* 2011;117(4):1141-1145; Cortes J, et al. *Blood.* 2011;118(17):4567-4576.

EUTOS STUDY: CML pts comorbidities

25.7%	**Hypertension**
17.2 %	**CV disorders**
9.5 %	Diabetes mellitus, all types
6.9 %	Neurological disorders
2.3 %	Behavior disorders
2.6 %	Chronic renal disease
2.2 %	Chronic liver disease
31.7 %	Other, or unspecified

(42%)



Hoffmann VS, et al. Leukemia. 2015;29:1336-1343;

Long term Cardiovascular toxicities with bosutinib

Patients with Newly Occurring TEAEs, n/N (%)	CP2L[a]	CP3L[b]	ADV[b]	Total
Cardiac cluster				
Year 5	5/123 (4.1)	0	1/17 (5.9)	6/169 (3.6)
Year 6	3/115 (2.6)	1/24 (4.2)	0	4/152 (2.6)
Year 7	2/106 (1.9)	1/19 (5.3)	0	3/136 (2.2)
Year 8	1/84 (1.2)	–	–	–
Vascular cluster				
Cardiovascular TEAEs				
Year 5	3/123 (2.4)	0	0	3/169 (1.8)
Year 6	1/115 (0.9)	0	1/13 (7.7)	2/152 (1.3)
Year 7	0	0	0	0
Year 8	0	–	–	–
Cerebrovascular TEAEs				
Year 5	1/123 (0.8)	0	0	1/169 (0.6)
Year 6	1/115 (0.9)	0	0	1/152 (0.7)
Year 7	0	0	0	0
Year 8	2/84 (2.4)	–	–	–
Peripheral vascular TEAEs				
Year 5	2/123 (1.6)	0	0	2/169 (1.2)
Year 6	0	0	0	0
Year 7	0	0	0	0
Year 8	1/84 (1.2)	–	–	–
Hypertension cluster				
Year 5	2/123 (1.6)	0	0	2/169 (1.2)
Year 6	0	0	0	0
Year 7	2/106 (1.9)	0	0	2/136 (1.5)
Year 8	0	–	–	–
Effusion cluster				
Year 5	4/123 (3.3)	1/29 (3.4)	1/17 (5.9)	6 /169 (3.6)
Year 6	5/115 (4.3)	1/24 (4.2)	0	6/152 (3.9)
Year 7	3/106 (2.8)	2/19 (10.5)	0	5/136 (3.7)
Year 8	4/84 (4.8)	–	–	–

Abbreviations: ADV, advanced phase/blast phase CML or Ph+ acute lymphocytic leukemia after at least imatinib; CML, chronic myeloid leukemia; CP2L, chronic phase Ph+ CML in 2nd line after imatinib; CP3L, chronic phase Ph+ CML in 3rd line after imatinib and dasatinib and/or nilotinib; Ph+, Philadelphia chromosome–positive; TEAE, treatment-emergent adverse event.

[a]8-year follow-up

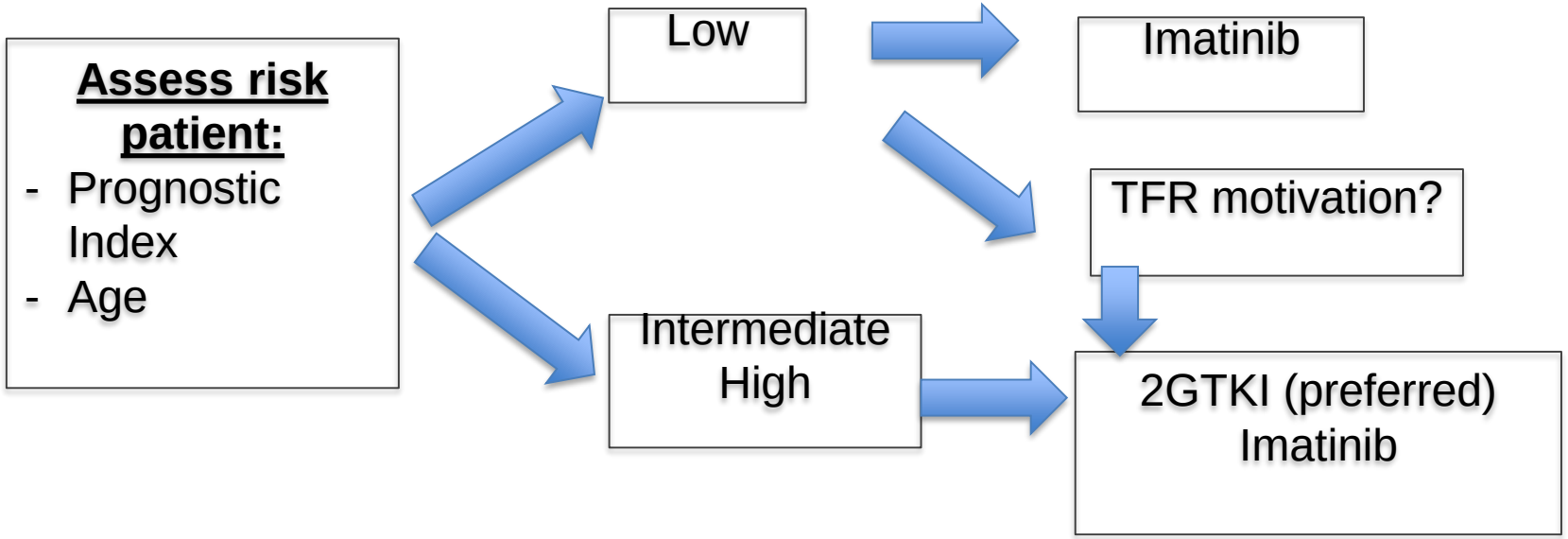
Eur J Haematol. 2021;106:808–82

Treatment recommendations based on pre-existing comorbidities

Parameter	TKI recommendations
Comorbidities	
Cardiac and vascular	• Bosutinib and imatinib are generally preferred • Treatment of existing comorbidities should be in line with current guidelines for that condition, and any potential drug-drug interactions considered • Introduce lifestyle changes, manage any risk factors, and correct serum electrolytes prior to initiating TKI treatment, and monitor throughout, e.g., smoking cessation, weight loss, exercise, or control of hypercholesterolemia, hypertension, or diabetes • Consider baseline ECG • Additional monitoring, e.g., ECG and blood pressure, throughout treatment is necessary for certain TKIs – bosutinib, dasatinib, nilotinib, and ponatinib
Pulmonary	• Bosutinib, imatinib, and nilotinib are generally preferred
Diabetes	• Bosutinib, dasatinib, and imatinib are generally preferred
Gastrointestinal	• Dasatinib and nilotinib are generally preferred
Renal	• Dasatinib and nilotinib are generally preferred
Hepatic	• Dasatinib and imatinib are generally preferred

Lipton et al. Blood reviews 2022

Treatment decision in CML First line patients



García-Gutiérrez et al. Frontiers in oncology 2019

During the presentation we will discuss about:

- What is bosutinib and when bosutinib could be used?
- When bosutinib should be used?
- **How bosutinib should be used?**

Table 1. Common Treatment-Emergent Adverse Events in Patients Treated With Bosutinib

	Phase III BELA study		Phase I/II study					
	First-line[a] (n = 248)		Second-line[b] (n = 286)		Third-/fourth-line[c] (n = 118)		Advanced[d] (n = 166)	
TEAE, %	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Common GI TEAEs								
Diarrhea	70	12	86	10	83	9	74	5
Vomiting	33	3	37	4	38	1	43	4
Nausea	32	1	46	1	48	1	48	2
Common skin TEAEs								
Rash	25	2	3(					
Common hematologic TEAEs								
Thrombocytopenia	28	13	4:					
Anemia	25	9	2:					
Neutropenia	13	8	1(					
Liver transaminase elevations								
Increased ALT	33	19	2:					
Increased AST	28	8	1:					

Table 5. Practical Recommendations for Clinical Management of and Patient Education Points for Common Bosutinib-Associated Adverse Events

Adverse event	Nonpharmacologic management/ monitoring	Pharmacologic management	Educational points
Diarrhea	**Assessment** *Signs of diarrhea* • Onset • Duration • Composition of stools • Frequency of episodes **Diet changes** Take bosutinib with food **Bosutinib dosing modifications** Grade 3/4[a] (i.e., increase of ≥ 7 stools/day over baseline/pretreatment): withhold bosutinib until recovery to grade ≤ 1, then resume at 400 mg qd	Early treatment with antidiarrheal agents: Over-the-counter and/or prescription (discontinue antidiarrheal medications after diarrhea resolution)	**Avoid** Lactose-containing products, alcohol, laxatives/stool softeners, spicy or fatty foods, and caffeine **Consider** Proactively starting antidiarrhea agent at treatment initiation and increase fluid intake using sports drinks to increase sodium and potassium

J Adv Pract Oncol. 2016 Mar;7(2):160-175

Does the 500mg dose fits for all patients?

Median	Resistance (28)	Intolerance (33)
Median follow up (months)	7,8	13,8
Median bosutinib dose (mg)	500	390
Interruptions (%)	46	45
Median age (years)	62	68
Discontinuations (%)	39%	31%

García-Gutiérrez V. Ann Hematol. 2019 Feb;98(2):321-330

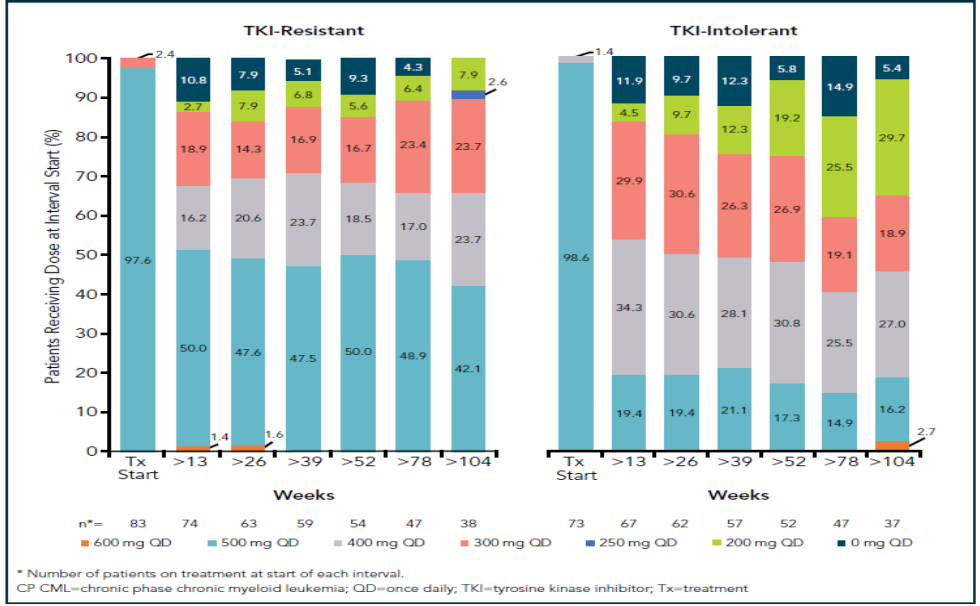
Second line

Table: Treatment Summary

	IM-R n=195	IM-I n=89	Total N=284
Follow-up duration, median (range), mo	47 (1–172)	66 (1–160)	54 (1–172)
Treatment duration, median (range), mo	28 (<1–170)	24 (<1–155)	26 (<1–170)
Dose intensity, median (range), mg/d	461 (103–599)	362 (87–595)	436 (87–599)
Total discontinued, n (%)	149 (76)	77 (87)	226 (80)
Objective progression or relapse	45 (23)	8 (9)	53 (19)
AE	35 (18)	39 (44)	74 (26)
Related to treatment	29 (15)	32 (36)	61 (22)
Unrelated to treatment	6 (3)	7 (8)	13 (5)
Unsatisfactory response – efficacy	19 (10)	4 (5)	23 (8)
Patient died	9 (5)	4 (5)	13 (5)
Lost to follow-up	4 (2)	0	4 (1)
Patient no longer willing to continue treatment*	7 (4)	4 (5)	11 (4)
Patient refused further follow-up	12 (6)	12 (14)	24 (9)
Investigator request	7 (4)	1 (1)	8 (3)
Global deterioration of health	2 (1)	0	2 (1)

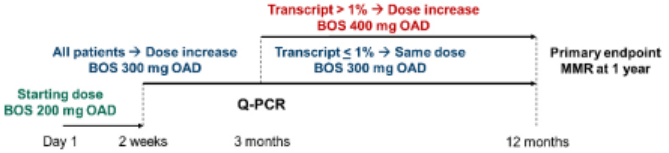
3rd and later lines

Figure 2: Bosutinib Dose Over Time in Patients With CP CML According to Resistance or Intolerance to Prior TKIs



* Number of patients on treatment at start of each interval.
CP CML=chronic phase chronic myeloid leukemia; QD=once daily; TKI=tyrosine kinase inhibitor; Tx=treatment

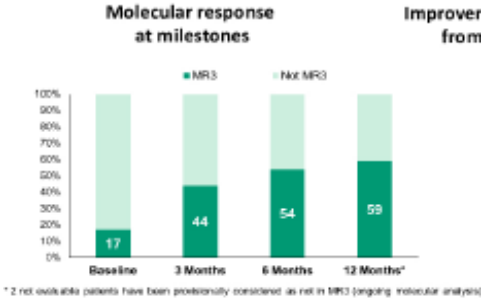
BEST study (2L pts >60yrs)

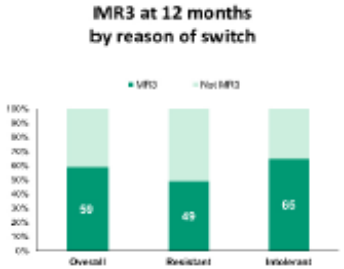


Patients (N = 63)

Median age (range), years	73 (60-90)
Age distribution	
• 60-69 years	29%
• 70-79 years	49%
• ≥ 80 years	22%
Sokal score	
• Low	19%
• Intermediate	49%
• High	32%
First-line treatment	
Imatinib - Nilotinib - Dasatinib	83% - 6% - 11%
Resistant / Inotolerant	37% - 63%
Median follow-up (range), months	13 (9-37)

Molecular response





Cumulative incidence
of molecular response

Non hematologic adverse events, maximum grade

Description	G2	G3	G4
Nausea/Vomiting	8%	-	-
Diarrhea	10%	8%	-
Abdominal pain	6%	-	-
AST/ALT increase	10%	10%	2%
Skin rash	13%	-	-
Infection	5%	3%	-
Bleeding	2%	2%	-
Renal failure	3%	3%	-
Myalgia	2%	-	-
Lipase increase	2%	2%	-

Acute coronary syndromes, 4 pts; pericarditis, 2 pts, peripheral arterial thrombosis, 1 pt

1. Castagnetti et al. Dose optimization of second line bosutinib in eldery CML patients: Final Results of the BEST Study. Poster EHA 2020

Conclusions

- What is bosutinib and when bosutinib could be used?:
  - BCR-ABL inhibitor approved in first and later lines in CML patients
- When bosutinib should be used?:
  - 2GTKIs failure: Intolerance
  - Imatinib failure: resistance and intolerance (main benefits CV safety profile)
  - First line: High risk patients (main benefit CV safety profile)
- How bosutinib should be used?:
  - First line: 500mg
  - Second an later lines:
    - Intolerance: lower doses (400mg or even lower starting doses)
    - Resitance: 500mg (lower doses in older pts?)

Thank you!!