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Euregionales comprehensive Cancer Center Aachen (ECCA)

New Drugs in Hematology

Bologna, May 9th to May 11th, 2016

Bosutinib: innovation to CML treatment or "*just another 2nd generation TKI*" ?

Prof. Dr. med. Tim H Brümmendorf

Klinik für Hämatologie und Onkologie

Universitätsklinikum Aachen

ECCA Euregionales comprehensive Cancer Center Aachen

Challenges in Treatment of CML in 2016

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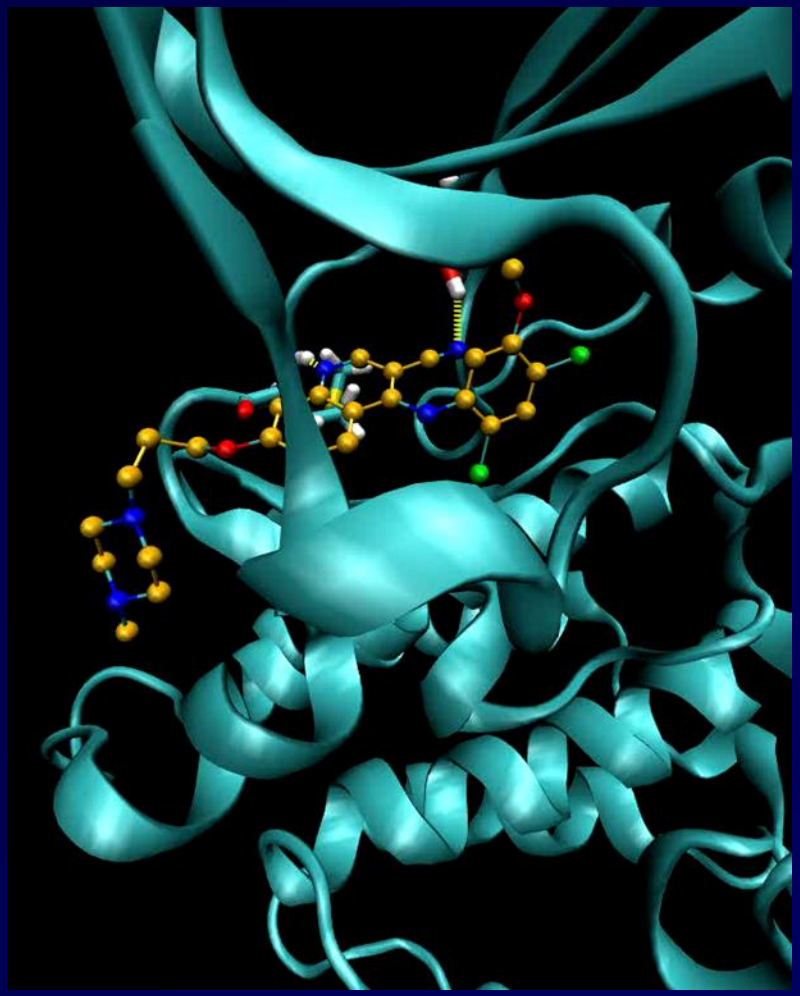
Background: Most patients with newly diagnosed CML are assumed to have a normal life-expectancy.

The challenges in CML treatment are focussed on

1. Offer the perspective of a **treatment-free remission** (cure ?) to as many as possible patients
2. Prevention of and (in case it happens) improved treatment of
   - **disease progression** to AP/BC and
   - development of **resistance** to TKI
3. Improvement of **tolerability** and **adherence** to TKI
4. **Eradiaction** of **leukemic stem cells** as a continued source of relapse/disease progression

Bosutinib: A Dual Inhibitor of Src and Abl Kinases



Puttini M, et al. *Cancer Res.* 2006;66(23):11314-11322.
Courtesy of Scapozza L and Shaheen A, University of Geneva, Switzerland.

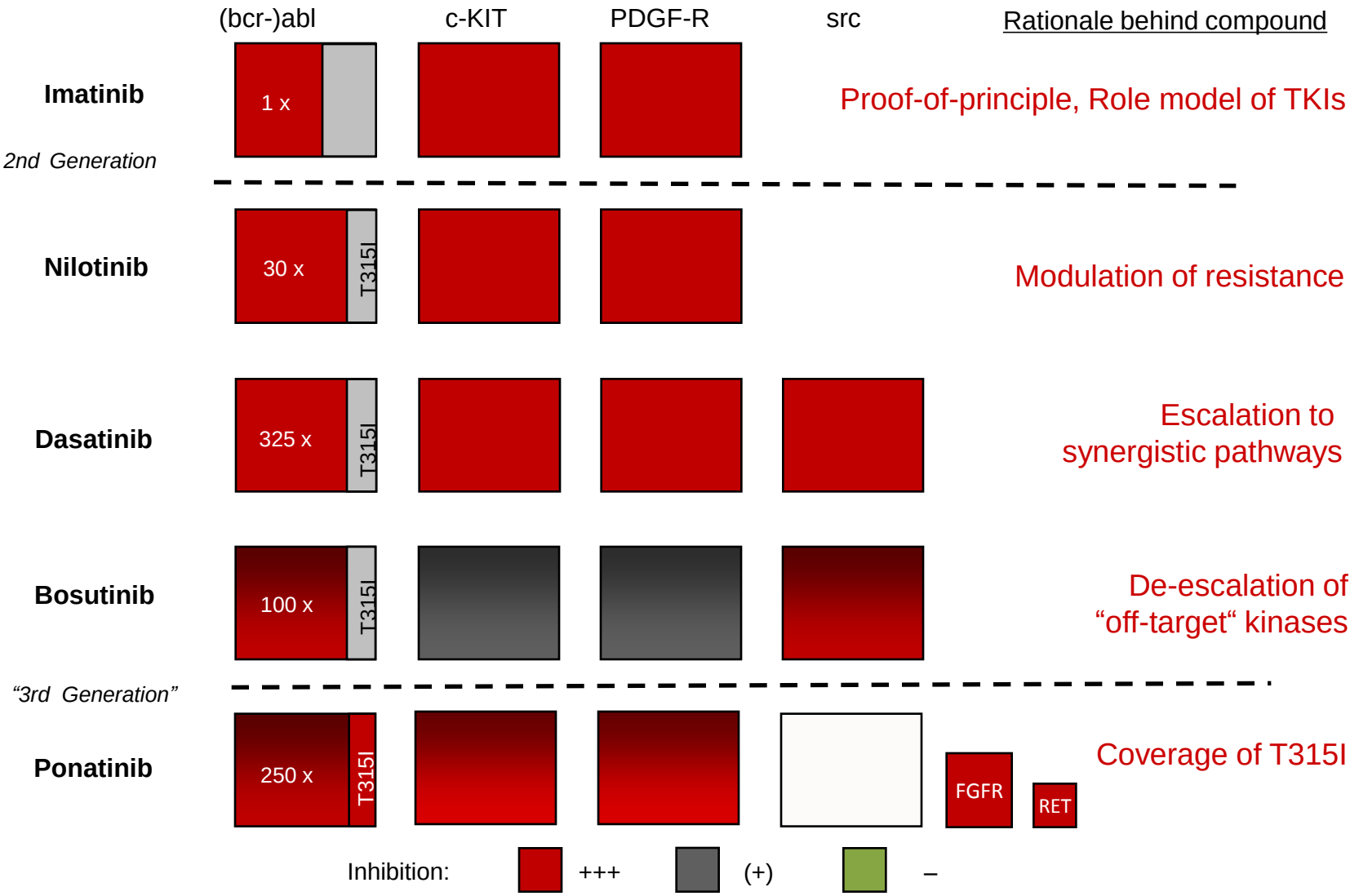
Src enzyme (ELISA) IC_{50} = 1.2 nM
Src enzyme (Lance) IC_{50} = 3.8 nM
Abl enzyme IC_{50} = 1.4 nM

K562 cell IC_{50} = 20 nM
KU812 cell IC_{50} = 4.3 nM

Once daily oral application !
independent of food !

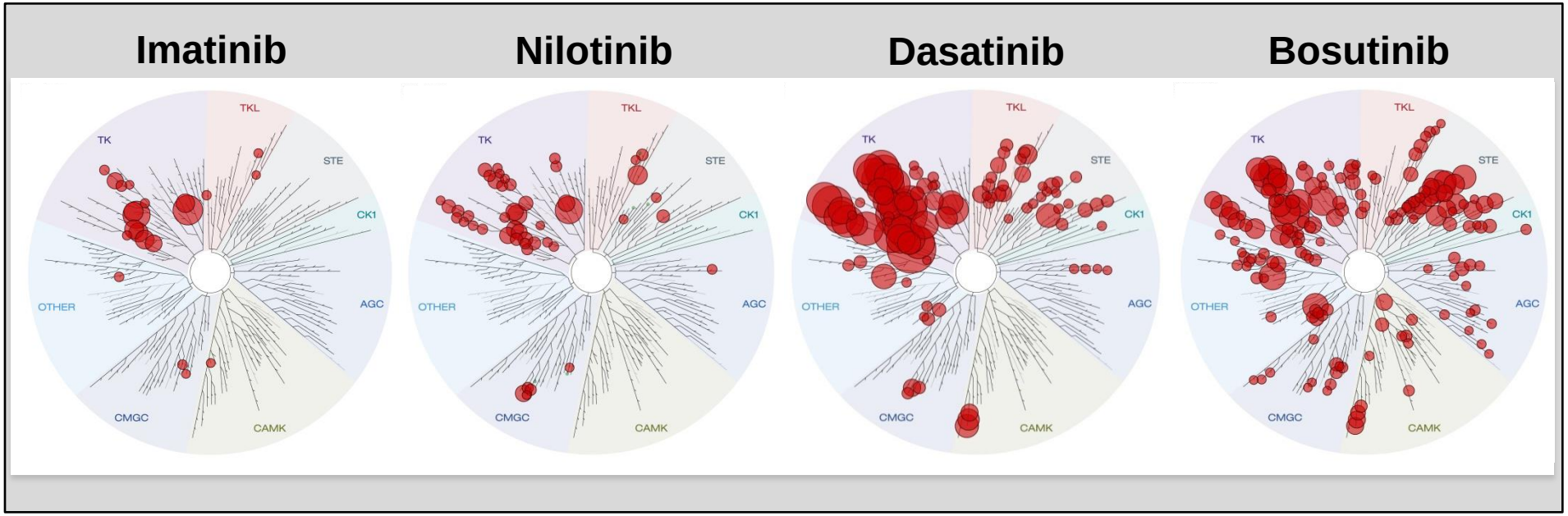
Boschelli DH, et al. *J Med Chem.* 2005;48(11):3891-3902.
Golas JM, et al. *Cancer Res.* 2003;63(2):375-381.
Golas JM, et al. *Cancer Res.* 2005;65(12):5358-5364.

Evolution of targeted therapy of CML: A simplified view



reviewed in: Balabanov, Braig and Brümmendorf ***Drug Discovery Today 2014****; 11:89-99*

Molecular Targets of 1st and 2nd generation TKIs



Balabanov, Braig and Brümmendorf ***Drug Discov Today Technol. (2014) 11:89-99***

Resistance spectrum of TKIs in CML

		IC50-fold increase (WT = 1)					
		Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib	DCC-2036
	Parental	10,8	38,3	568,3	38,4	570,0	13,1
	WT	1	1	1	1	1	1
P-loop	M244V	0,9	0,9	2,0	1,2	3,2	0,8
	L248R	14,6	22,9	12,5	30,2	6,2	0,4
	L248V	3,5	3,5	5,1	2,8	3,4	1,3
	G250E	6,9	4,3	4,4	4,6	6,0	3,0
	Q252H	1,4	0,8	3,1	2,6	6,1	2,1
	Y253F	3,6	1,0	1,6	3,2	3,7	2,3
	Y253H	8,7	0,6	2,6	36,8	2,6	2,7
	E255K	6,0	9,5	5,6	6,7	8,4	3,5
	E255V	17,0	5,5	3,4	10,3	12,9	2,1
C-helix	D276G	2,2	0,6	1,4	2,0	2,1	4,5
	E279K	3,6	1,0	1,6	2,0	3,0	6,5
	E292L	0,7	1,1	1,3	1,8	2,0	1,0
ATP binding region	V299L	1,5	26,1	8,7	1,3	0,6	0,3
	T315A	1,7	6,0	58,9	2,7	0,4	0,4
	T315I	17,5	45,4	75,0	39,4	3,0	0,7
	T315V	12,2	29,3	738,8	57,0	2,1	0,6
	F317L	2,6	2,4	4,5	2,2	0,7	1,1
	F317R	2,3	33,5	114,8	2,3	4,9	21,0
	F317V	0,4	11,5	21,3	0,5	2,3	6,6
SH2-contact	M343T	1,2	1,1	0,9	0,8	0,9	1,0
	M351T	1,8	0,7	0,9	0,4	1,2	2,2
Substrate binding region	F359I	6,0	2,9	3,0	16,3	2,9	0,7
	F359V	2,9	0,9	1,5	5,2	4,4	0,9
A-loop	L384M	1,3	0,5	2,2	2,3	2,2	0,9
	H396P	2,4	0,4	1,1	2,4	1,4	1,5
	H396R	3,9	0,8	1,6	3,1	5,9	0,7
C-terminal lobe	F486S	8,1	2,3	3,0	1,9	2,1	0,5
	L248R + F359I	11,7	39,3	13,7	96,2	17,7	1,0

Sensitive	≤2
Moderately resistant	2.1-4
Resistant	4.1-10
Highly resistant	>10

reviewed in: Gambacorti-Passerini et al. Am J. Hematol 2016; 91:67-75

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Study 200: Bosutinib in Previously Treated CML Patients

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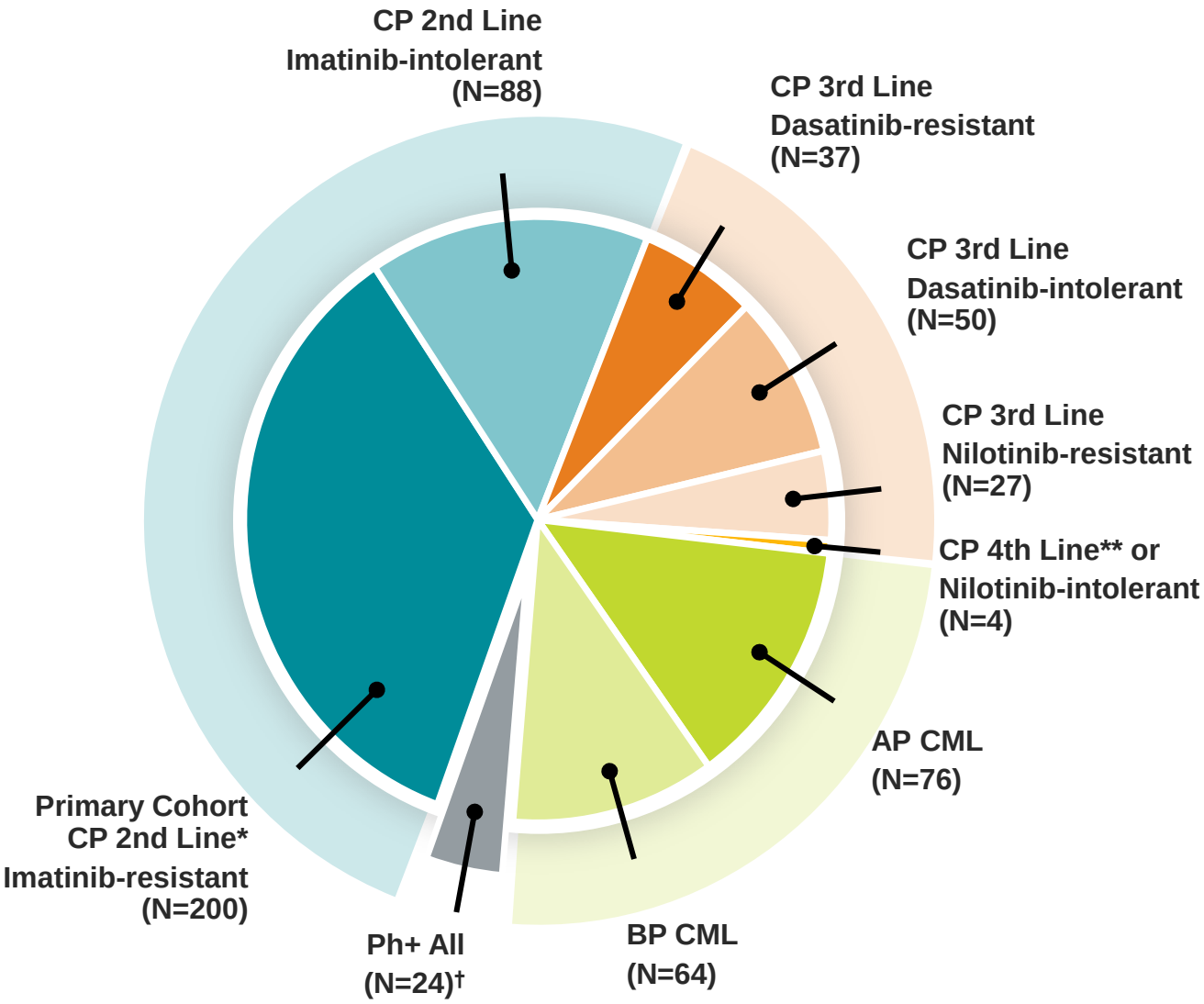
Study 200: Patient Cohorts (n=570) in 2nd+ line



1. Cortes JE, et al. Blood. 2011;118:4567-4576;
2. Khoury HJ, et al. Blood. 2012;119:3403-3412.

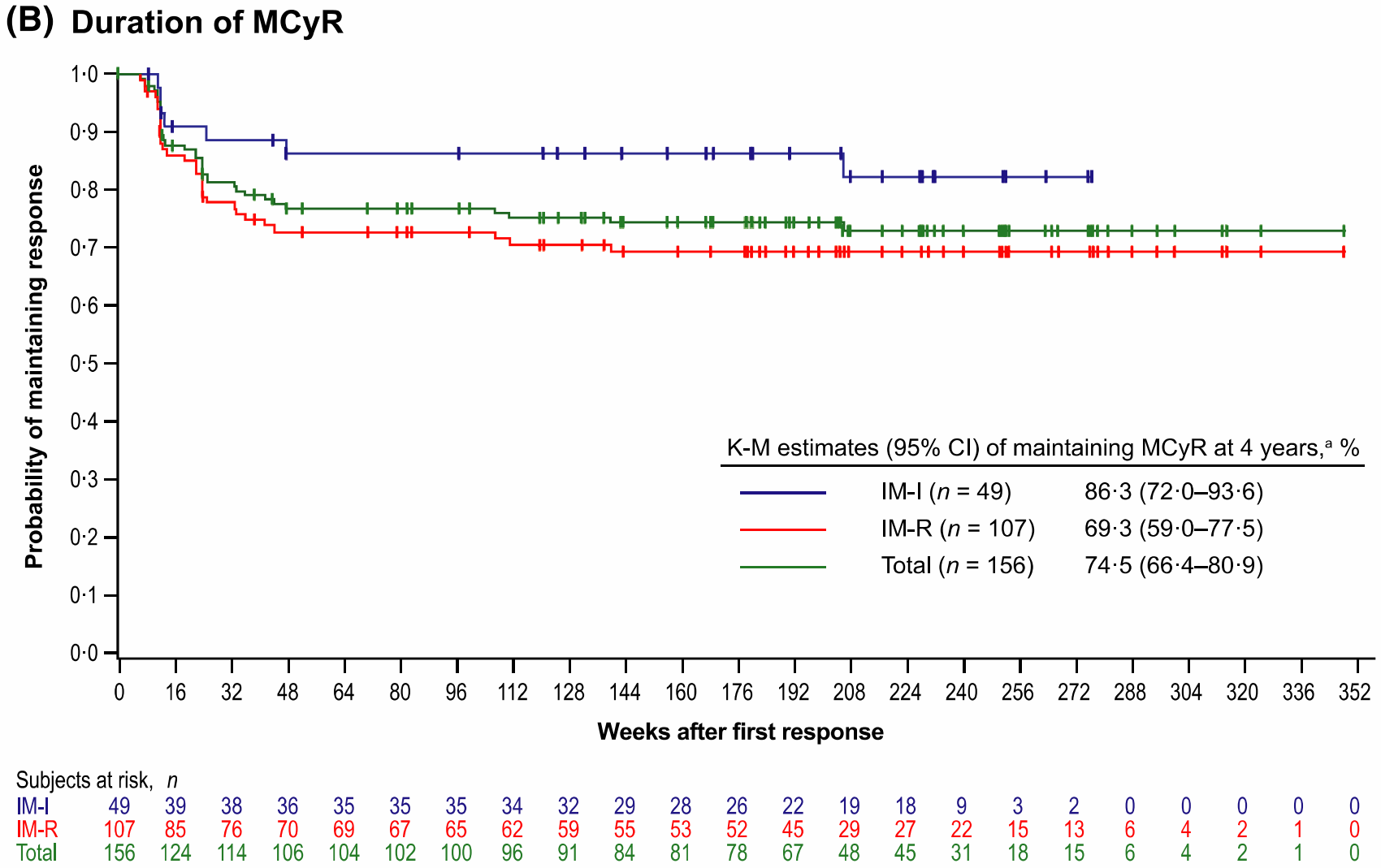
Second-Line CP Cohort (Bosutinib post IM)

Bosutinib-treated patients	Response					
	MCyR		CCyR		MMR	
	n	%	n	%	n	%
Total population	156/ 262	60	130/ 262	50	69/200	35
IM-R	107/ 182	59	88/182	48	45/132	34
IM-I	49/80	61	42/80	53	24/68	35

- Most MCyR responses were newly attained (54%) rather than maintained from baseline (6%), min. F/U 60 months

Brümmendorf, et al. *Blood*. 2014;124(21): Abstract 5544 (ASH 2014).

Duration of MCyR (Among Responders)



Brümmendorf et al. ***Br. J. Hematol*. 2016**;172:97-110

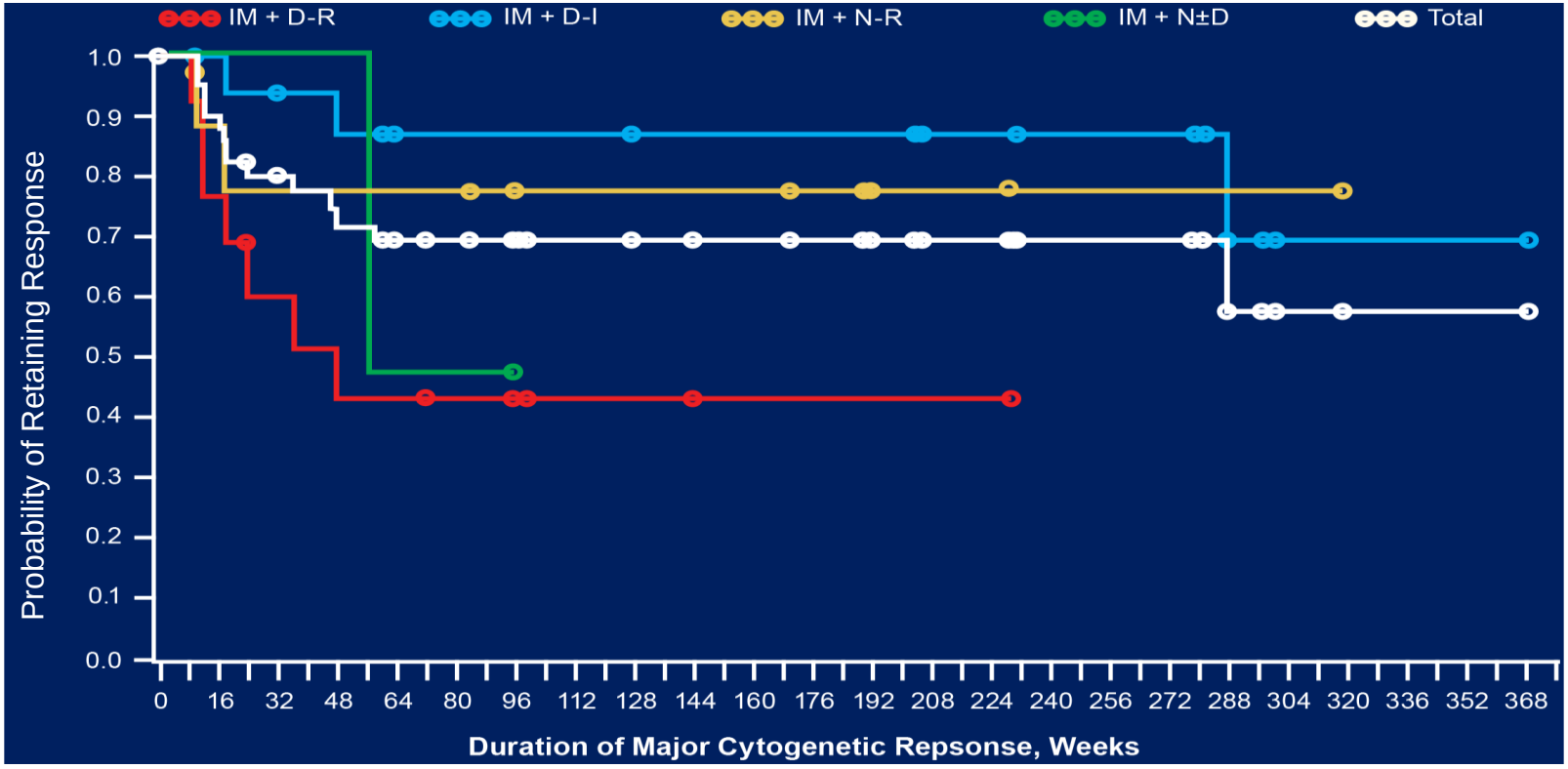
Bosutinib – Response Rates and Duration of Response (3rd+ line); min F/U 48 months

Bosutinib-treated Patients	Response			
	MCyR		CCyR	
	n	%	n	%
Total population	45/112	40	36/112	32
IM + DAS-R	14/39	36	8/39	21
IM + DAS-I	19/42	45	18/42	43
IM + NIL-R	10/26	38	8/26	31
IM + DAS +/- NIL	2/5	40	2/5	40

Most MCyR responses were newly attained (33%) rather than maintained from baseline (7%)

Gambacorti-Passerini, et al. *Blood*. 2014;124(21): Abstract 4559 (ASH 2014).

Duration of MCyR (Among Responders)



Cohort	n	K-M Estimate of Maintaining MCyR at 4 Y, % (95% CI)
Total	45	69 (52–81)
IM + D-R	14	43 (16–68)
IM + D-I	19	87 (57–97)
IM + N-R	10	78 (37–94)
IM + N±D	2	not reported

Gambacorti-Passerini, et al. *Blood*. 2014;124(21): Abstract 4559 (ASH 2014).

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Study 3000: Bosutinib in first line treatment of CML CP Patients

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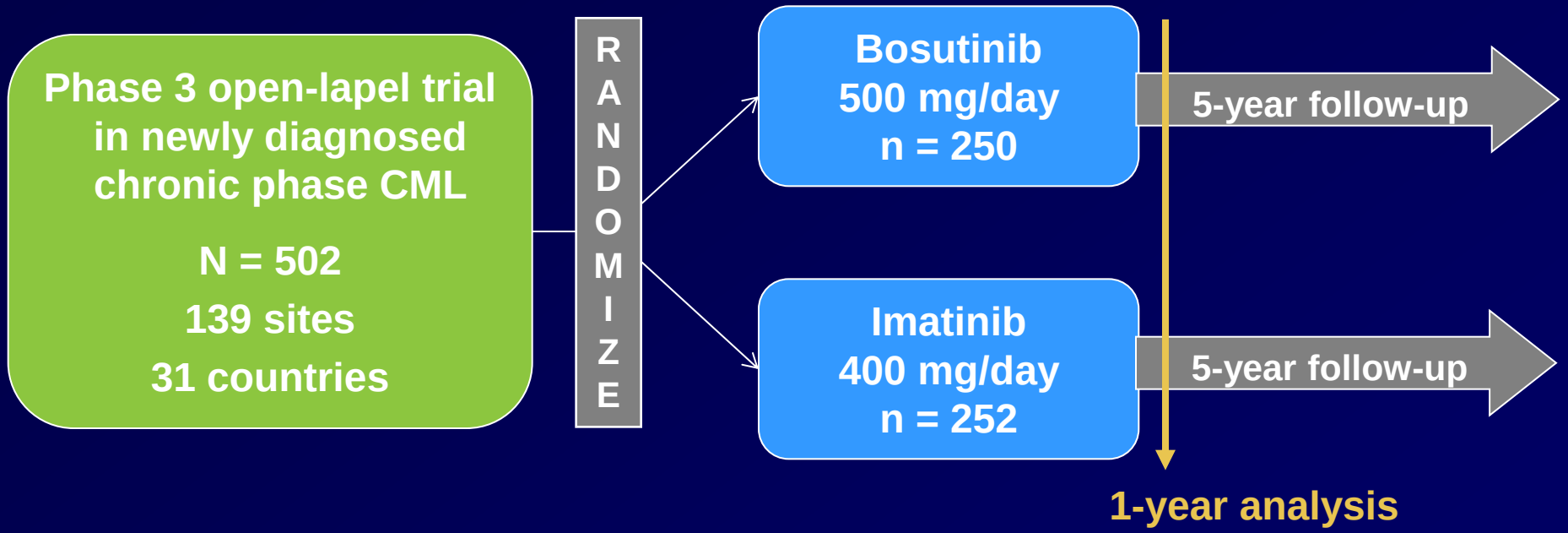
Bosutinib Efficacy and Safely in Newly Diagnosed CML (BELA): Study Design



- Primary endpoint: complete cytogenetic response (CCyR) rate at 12 mo
- Secondary endpoints:
  - Major molecular response (MMR) rate at 12 mo
  - Time to CCyR and MMR
  - Time to and rate of transformation to accelerated phase (AP) or blast phase (BP) CML
  - Safety and tolerability

Cumulative MMR: First line TKI studies in CML

Comparison of independent studies with differences in study design

MMR	12 Months	24 Months	36 Months
CML IV IM 400 / IM 800 / IM + IFN	31% / 55% / 35%	63% / 76% / 63%	79% / 82% / 71%
ENESTnd IM 400 / NIL 600 / NIL 800	27% / 51%* / 55%*	44% / 67%* / 71%*	53% / 70%* / 73%*
DASISION IM 400 / DAS 100	23% / 46%*	46% / 64%*	55% / 68%*
BELA IM 400 / BOS 500	32% / 47%*	52% / 67%*	52% / 61%* (30 Monate)

Hehlmann et al., 2011, J Clin Oncol, 29, 1634-42

Larson et al., 2012, Leukemia

Saglio et al., 2010, N Engl J Med, 362, 2251-9

Hochhaus et al., Abstract 6504, ASCO 2012

Gambacorti et al. ASCO 2011; Brümmendorf et al., ASH 2012

** p=<0,05*

Disease Progression: First line TKIs in CML

Comparison of independent studies with differences in study design

	Progression AP/BC	Progression (CML related)
CML IV (2 years) IM 400 / IM 800 / IM + IFN		4% / 6% / 5%
ENESTnd (3 years) IM 400 / NIL 600 / NIL 800	6,7% / 2,1%* / 3,2%*	
DASISION (3 years) (ITT) IM 400 / DAS 100	6,2% / 4,2%	
BELA (2 years) IM 400 / BOS 500	5% / 2%	

Hehlmann et al., 2011, J Clin Oncol, 29, 1634-42

Saglio et al., ASH 2011

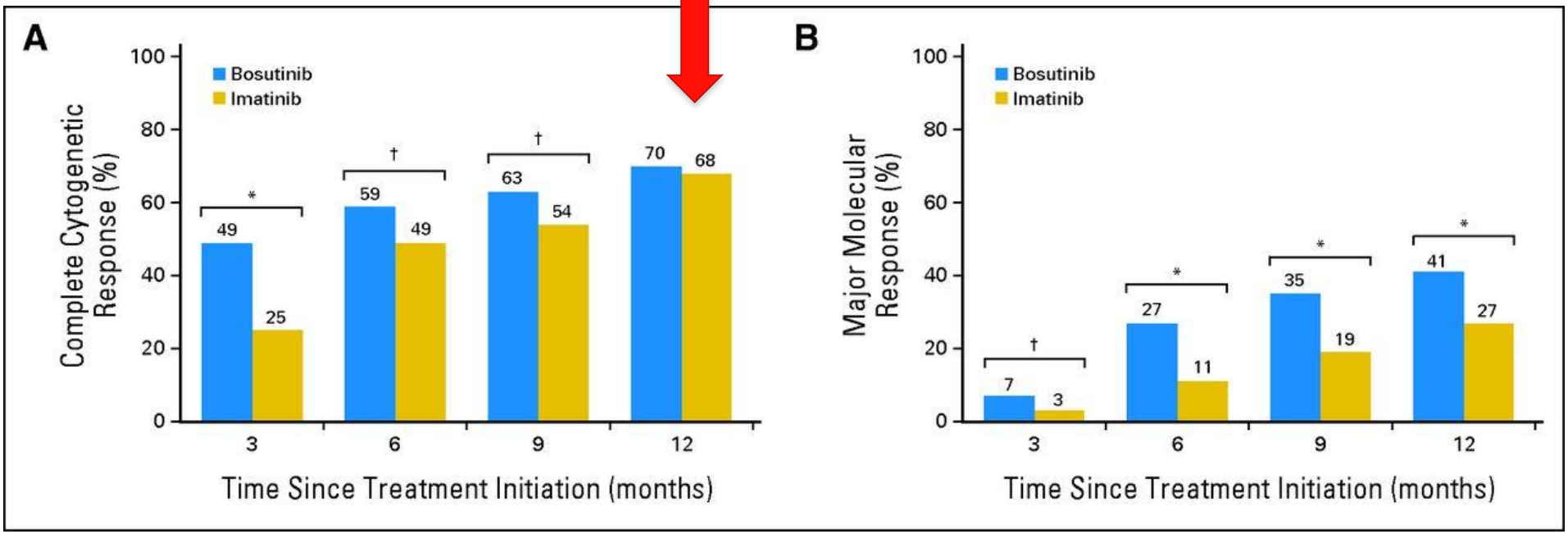
Hochhaus et al., Abstract 6504, ASCO 2012

Gambacorti-Passerini et al., ASCO 2011, Brümmendorf et al. ASH 2012

** p=<0,01*

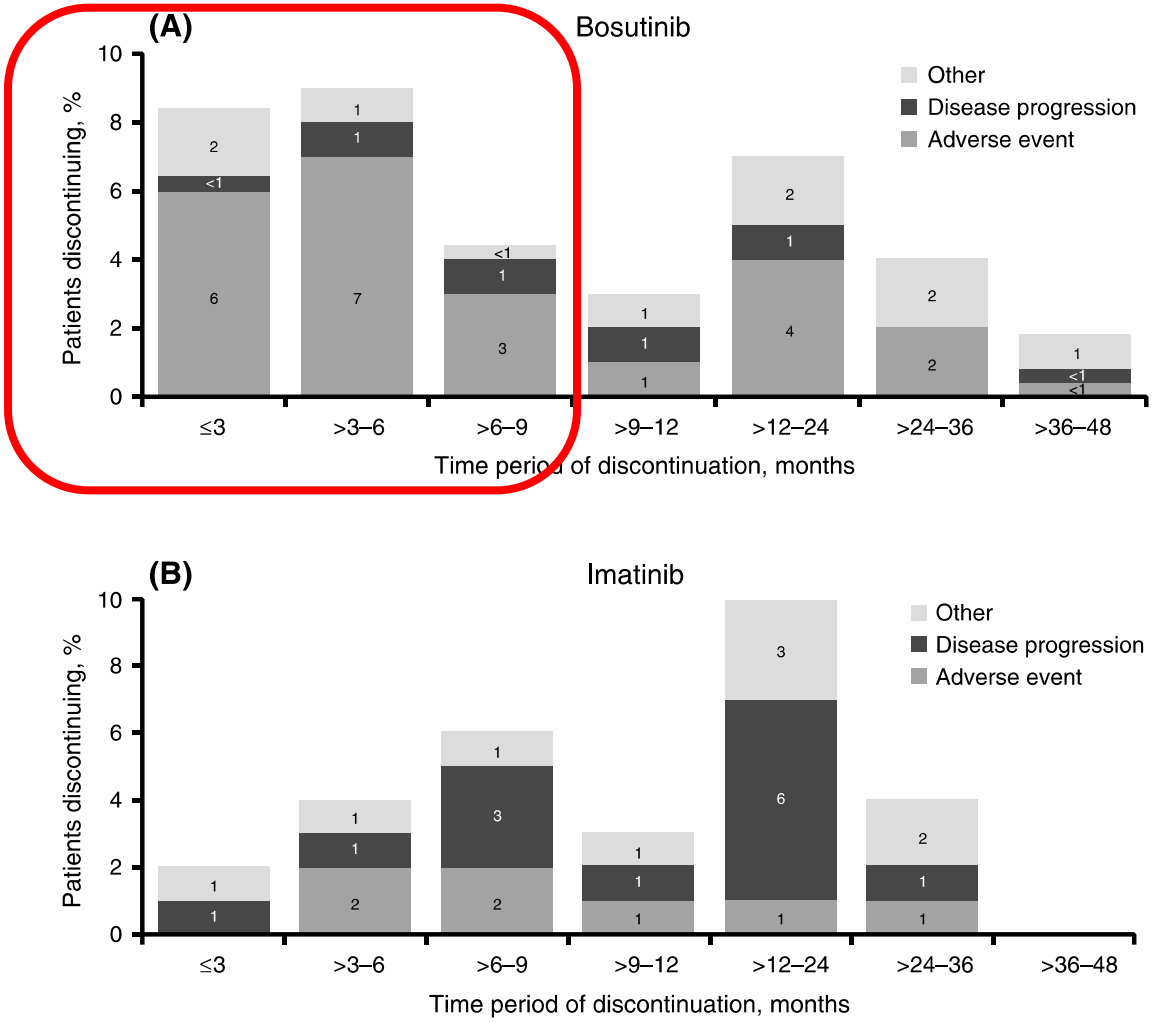
BELA Study (3000): CCyR and MCyR

Primary study endpoint



Jorge E. Cortes et al. ***J. Clin. Oncol. 2012;****30:3486-3492*

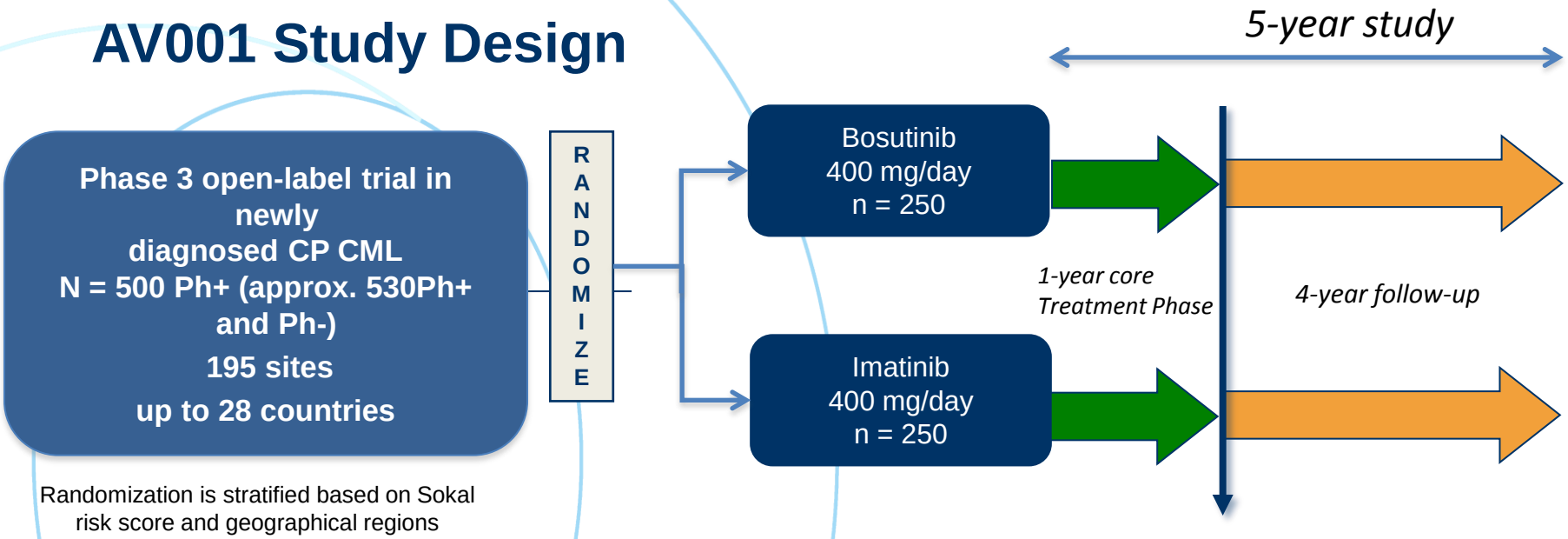
BELA Study: Reasons and kinetics of discontinuation



Brümmendorf et al. ***Br. J. Hematol*. 2015**;168:69-81

The BFORE Study

AV001 Study Design



Randomization is stratified based on Sokal risk score and geographical regions

- Key eligibility criteria: Chronic Phase - CP CML ≤6 months prior, no prior therapy (other than hydroxyurea or anagrelide)
- Primary endpoint: Major molecular response at 12 months (48 weeks)
- Key secondary endpoints
  - MMR by 18 months, duration of MMR, CCyR by 12 months, duration of CCyR, event-free survival (EFS), and overall survival (OS)

Lead investigators: ***Jorge Cortes, Houston (North America)***
Tim Brümmendorf, Aachen (Europe)

AVILLION

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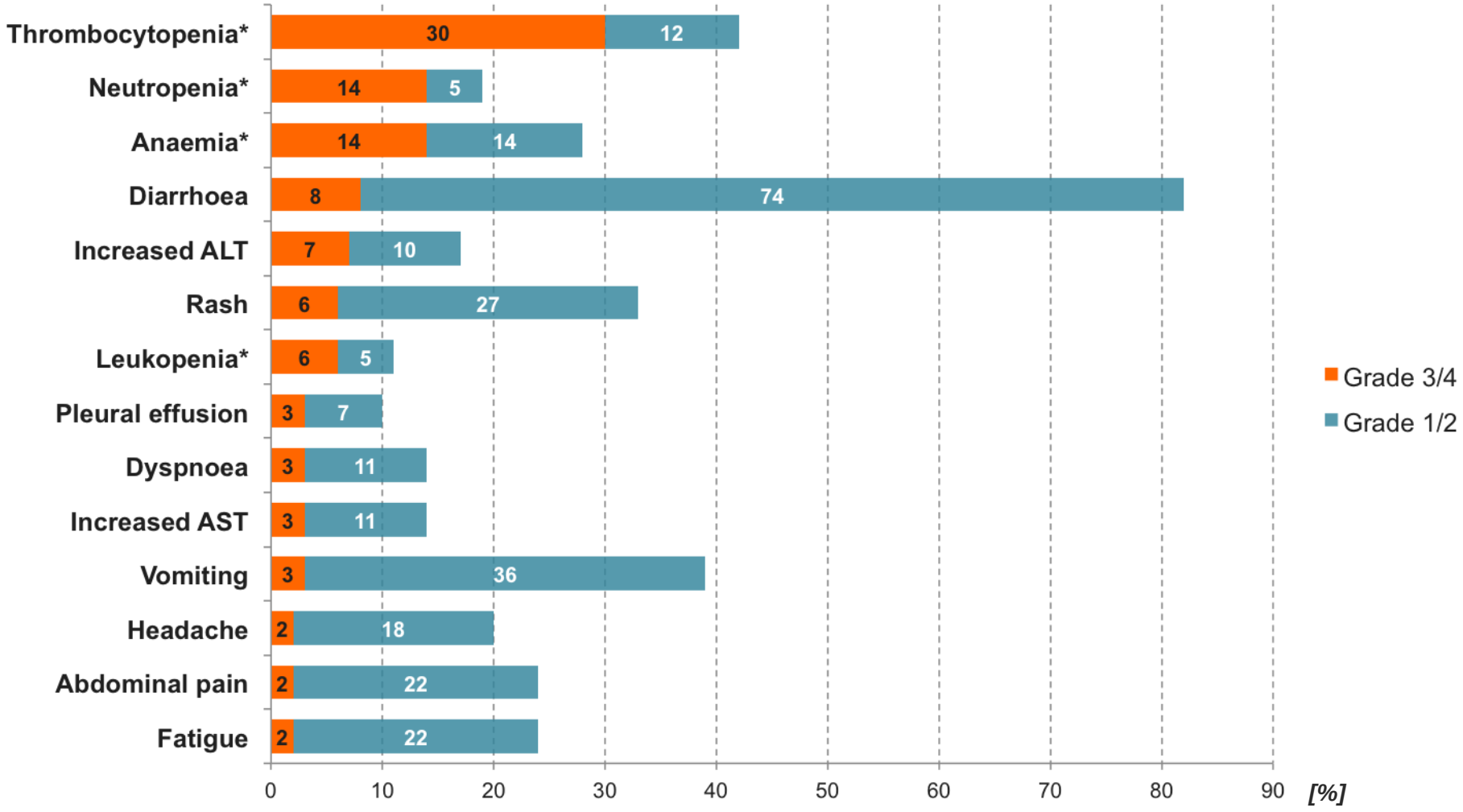
Bosutinib:
toxicity profile and specificities

ECCA Euregionales comprehensive Cancer Center Aachen

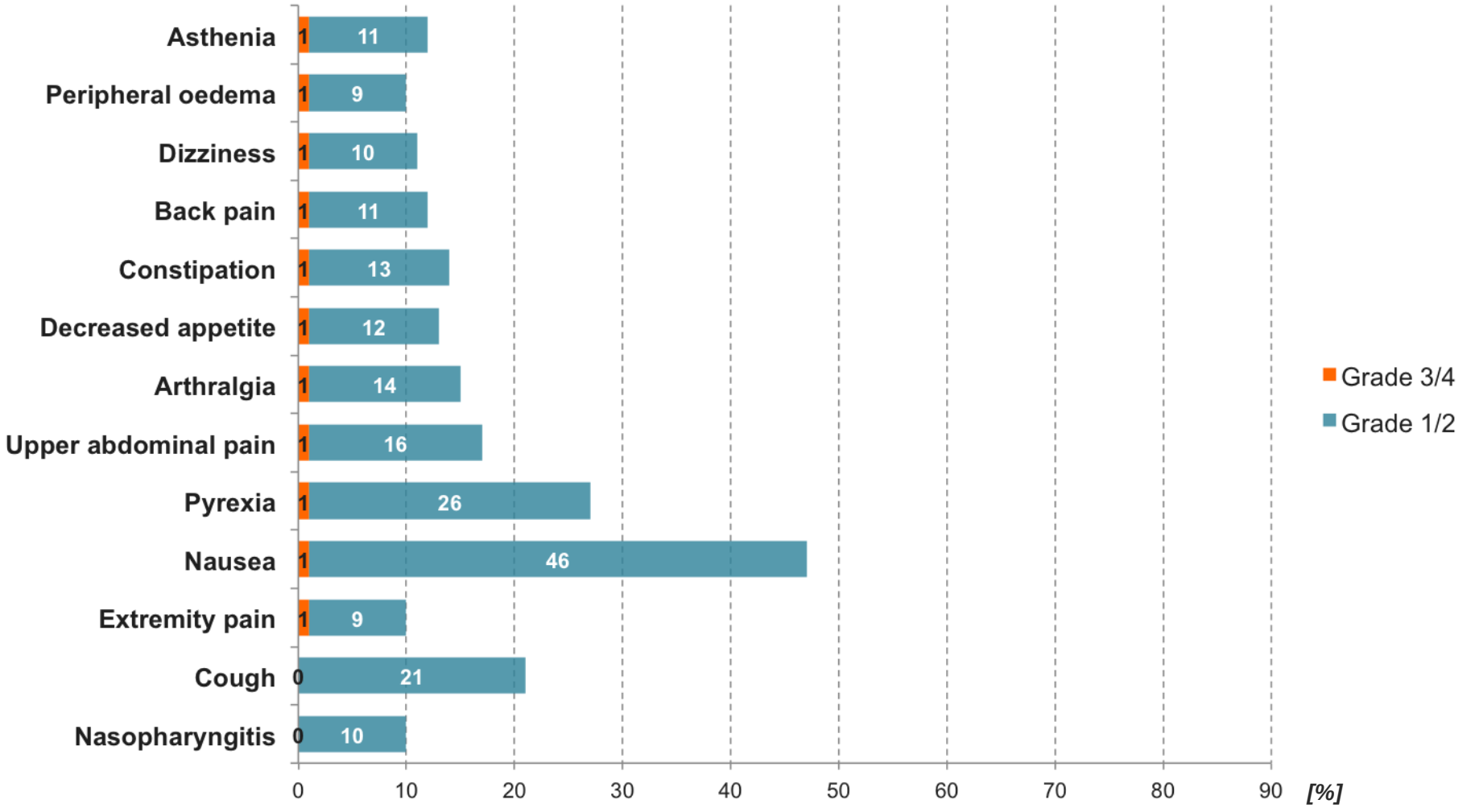
Study 200: Bosutinib AEs ≥10% Sorted by Grade 3/4 Events (n=570)



*Individual haematologic TEAEs were clustered with the related terms from investigations.

Kantarjian H, et al. *Blood.* 2014;123(9):1309-18.

Study 200: Bosutinib AEs ≥10% Sorted by Grade 3/4 Events (n=570)

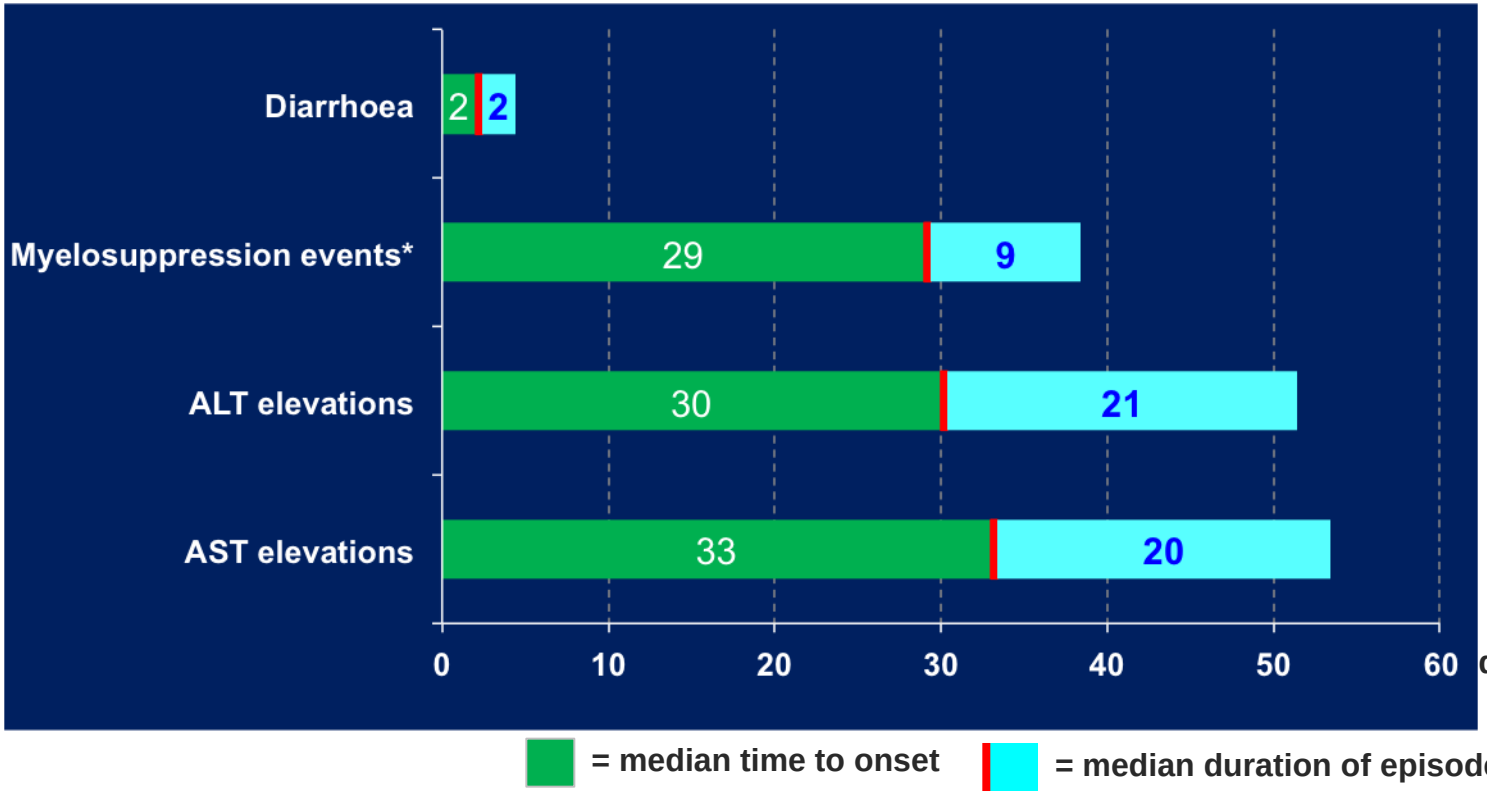


*Individual haematologic TEAEs were clustered with the related terms from investigations.

Kantarjian H, et al. *Blood.* 2014;123(9):1309-18.

Study 200: Onset and Duration of Selected AEs

Selected Grade ¾ Adverse Reactions for Bosutinib – Total CML Population [n=570]



Discontinuations During Trials

- Diarrhoea: 1% [6/570]
- Myelosuppression events*: 6% [33/570]
- ALT elevations: 2% [12/570]
- AST elevations: 1% [4/570]

***** Myelosuppression events include anaemia, hemoglobin decreased, neutropenia, neutrophil count decreased, thrombocytopenia, and platelet count decreased. Figure refers to grade 3/4 events (n=231)

Kantarjian H, et al. *Blood.* 2014;123(9):1309-18.

Multicenter, open-label single arm phase II study testing tolerability and efficacy of Bosutinib step-in dosing in Chronic Phase CML patients intolerant or refractory to previous Nilotinib or Dasatinib therapy

"**Bo**sutinib **D**ose **O**ptimization Study - **BODO**-Study" (CML-7)

Dominik Wolf und Tim Brümmendorf
Medizinische Universitäten Bonn und Aachen

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SZB Studienzentrum Bonn

universitäts klinikum bonn

CML. STUDIENGRUPPE DEUTSCHE

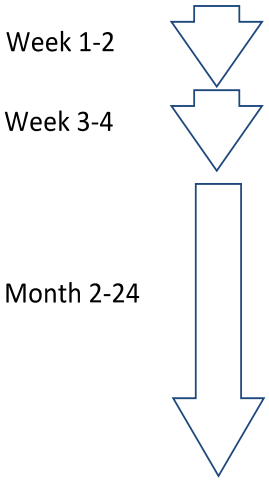
CML-7 (BODO) Study: Synopse

Patient population:

Nilotinib- OR Dasatinib-pretreated T315I and V299L negative CP-CML with

a) Treatment Failure ***OR***

b) Intolerance



Step-in phase

Core-phase

BODO (CML-7):
127 patients
20 German sites
(12 initiated)
2 year recruitment
First patient in:
5/2016 (Marburg)

Study lead:
Dominik Wolf (Bonn)
Tim Brümmendorf
(Aachen)

Primary Objective:
GI-Tolerability (rate of G2 to 4 GI-toxicity) at month 6

Secondary objectives:
Overall tolerability (all grade and G2 to G4) at month 6, 12 and 24
MMR, MR4, MR4.5 and CCyR rate at month 3, 6, 12, 18 and 24
QoL-measures
PFS/OS
Exploratory substudy endpoints

DEUTSCHE CML.STUDIENGRUPPE

Vascular TEAEs: (Exposure-Adjusted Rate and SOC Incidence)

	Phase 1/2 Study		BELA				Total	
	BOS (n=570)		BOS (n=248)		IM (n=251)		Pooled BOS (n=818)	
	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4
Exposure-adjusted vascular TEAE rate*	0.08	0.03	0.04	0.01	0.03	0.01	–	–
Any vascular TEAEs, %	15	6	12	2	10	2	14	5
Cardiovascular	4	2	2	1	2	<1	4	2
Cerebrovascular	2	1	1	<1	1	<1	2	1
Peripheral vascular	9	3	9	1	6	1	9	2

*Computed as the number of patients with events/total patient-year where total patient-year=sum of time to first TEAE for patients with cardiac TEAEs plus time on treatment for patients without cardiac TEAEs
TEAEs graded by NCI CTCAE v3.0; coded and classified by MedDRA (v≥15.0)

- Only 1 patient treated with BOS reported PAOD (considered by investigator unrelated to BOS)

PAOD=peripheral arterial occlusive disease; SOC=system organ class.

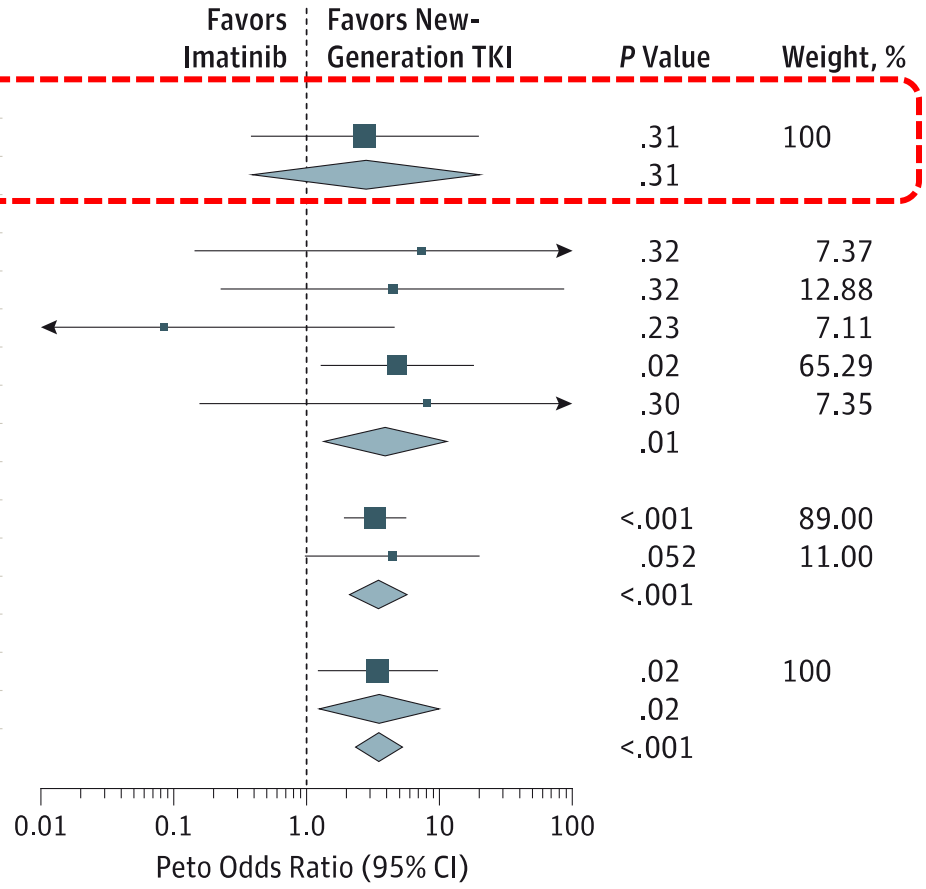
Cortes, et al. Vascular Toxicity with Bosutinib. ESH-iCMLf; 2014. Abstract 1782.

Metaanalysis comparing vascular toxicity in CML TKIs

Figure. Forest Plots of the Outcomes of Interest in Patients With Ph+ Leukemia Treated With New-Generation TKIs vs Imatinib

A Vascular occlusive events

Source	Peto Odds Ratio (95% CI)	*P* Value	Weight, %
Bosutinib			
NCT00574873-BELA	2.77 (0.39-19.77)	.31	100
Subtotal	2.77 (0.39-19.77)	.31	
Dasatinib			
NCT00070499	7.39 (0.15-372.38)	.32	7.37
NCT00103844-START-R	4.46 (0.23-86.51)	.32	12.88
NCT00320190	0.09 (0.00-4.61)	.23	7.11
NCT00481247-DASISION	4.86 (1.30-18.12)	.02	65.29
NCT00852566-NordCML006	8.09 (0.16-409.34)	.30	7.35
Subtotal	3.86 (1.33-11.18)	.01	
Nilotinib			
NCT00471497-ENESTnd	3.31 (1.95-5.61)	<.001	89.00
NCT00760877-ENESTcmr	4.45 (0.99-20.02)	.052	11.00
Subtotal	3.42 (2.07-5.63)	<.001	
Ponatinib			
NCT01650805-EPIC	3.47 (1.23-9.78)	.02	100
Subtotal	3.47 (1.23-9.78)	.02	
Overall	3.45 (2.30-5.18)	<.001	



Douxfils et al. ***JAMA Oncol. 2016****; Feb 4th*

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Summary

- Bosutinib is a 2nd generation TKI with a characteristic molecular profile
- Bosutinib has shown activity against a wide variety of resistance-confering mutations found in CML patients in 2nd+ line
- ***BELA trial*** using 500 mg Bosutinib first line has failed to reach primary endpoint (CyR rate @12 months), ***BFore study*** with Bosutinib @400 mg finished recruitment last summer
- side effect profile is ***distinct*** and partly differs from other 2nd generation TKIs
- GI toxicities are common, occur typically early under treatment and are often self-limiting (***run-in dosing concepts*** currently being investigated)
- no evidence exists so far indicating a significantly increased risk of cardiovascular or other ***irreversible*** toxicities compared to Imatinib

ECCA Euregionales comprehensive Cancer Center Aachen