Bosutinib in the Treatment of CML

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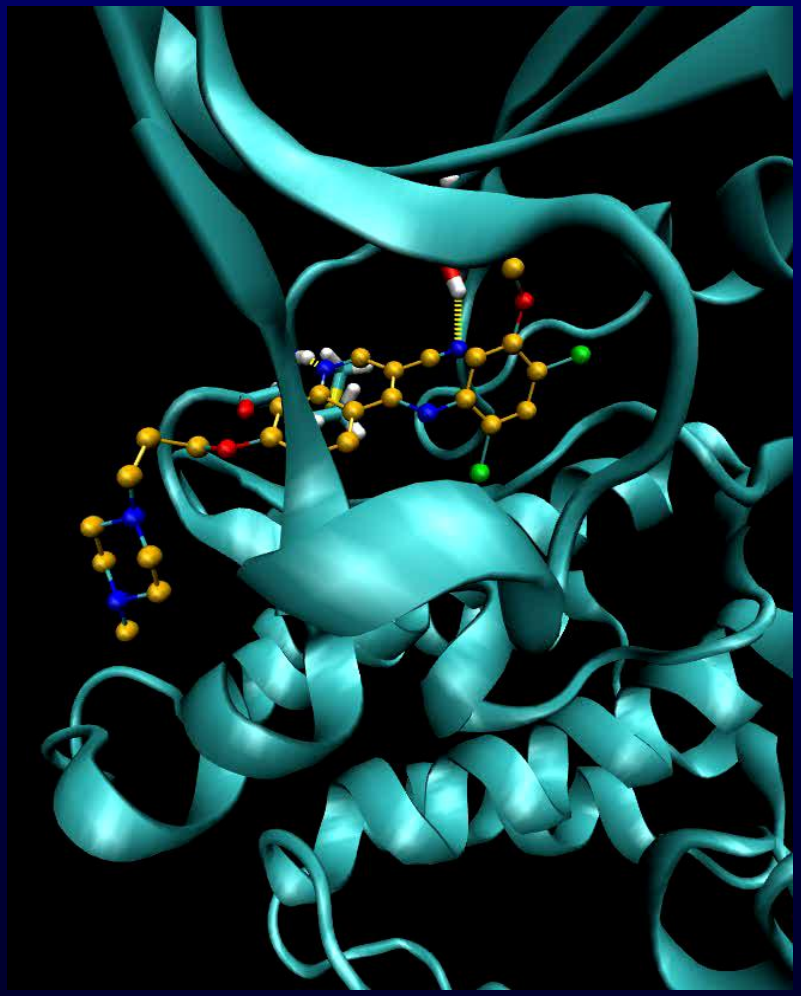
Bosulif® (bosutinib)

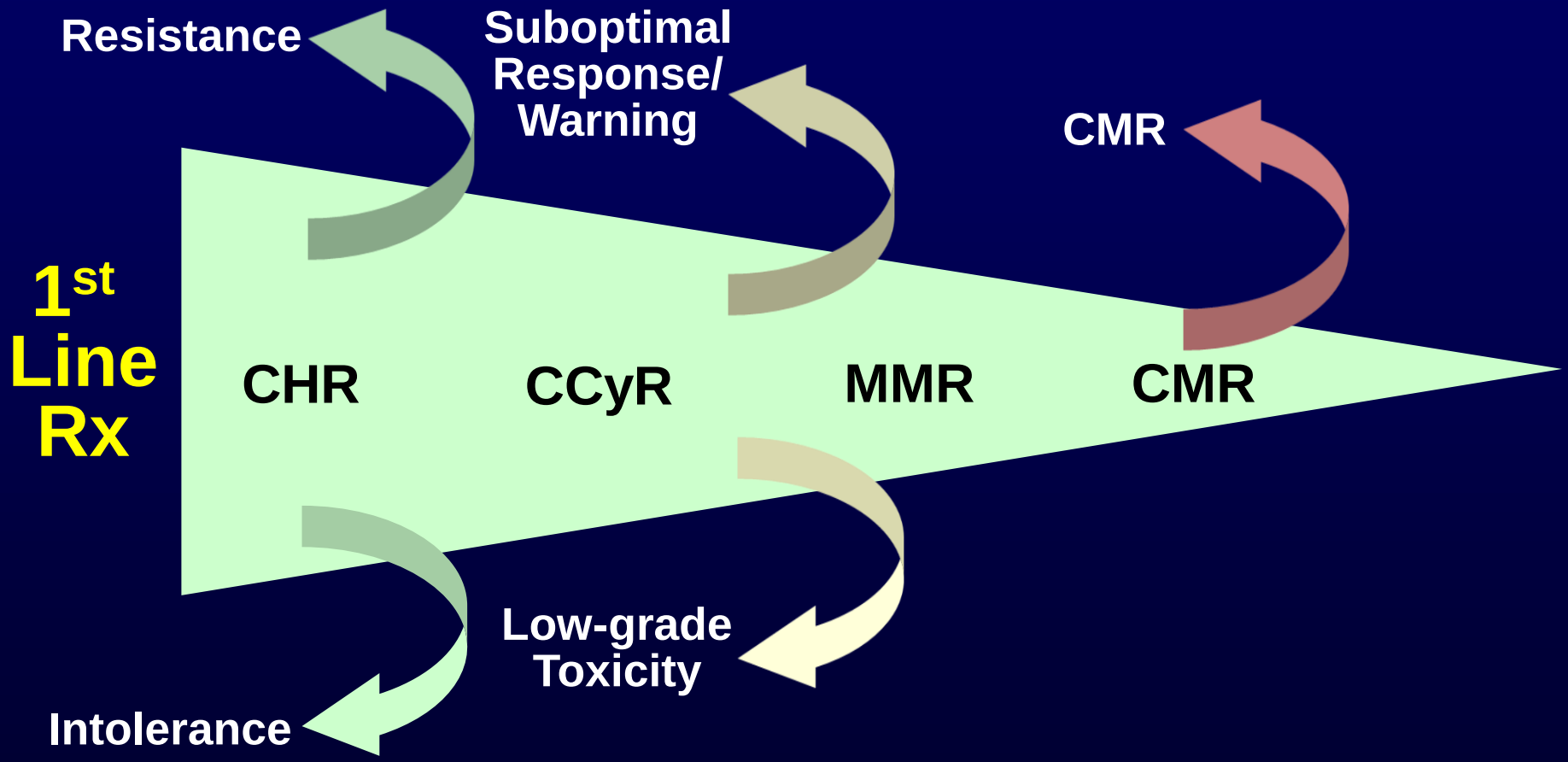


- Orally available, Bcr-Abl and Src inhibitor
  - ABL IC_{50} = 1.4 nM Src IC_{50} = 1.2–3.8 nM
  - C_{max} typically occur at 6 hours post dose
- Minimal PDGFR, c-KIT inhibition
- Drug disposition predominantly hepatic via CYP3A4 iso-enzyme; only 3% excreted in the urine
- Half-life: ≈33.8 hours
- Pharmacokinetics of bosutinib is linear between 200 to 800 mg
- Orally administered once daily with food
- Pre-clinical activity against most imatinib–resistant mutants of Bcr-Abl, with the exception of T315I and V299L

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

Boschelli DH, et al. *J Med Chem.* 2005;48(11):3891–3902.
Boschelli et al. *Eur J Cancer.* 2010;46(10):1781-1789.
Cortes et al. *Blood.* 2006;108. Abstract 168.
Golas JM, et al. *Cancer Res.* 2003;63(2):375–381.
Puttini M, et al. *Cancer Res.* 2006;66(23):11314–11322.
Data on file. Pfizer, Inc.

When Do We Change Therapy?

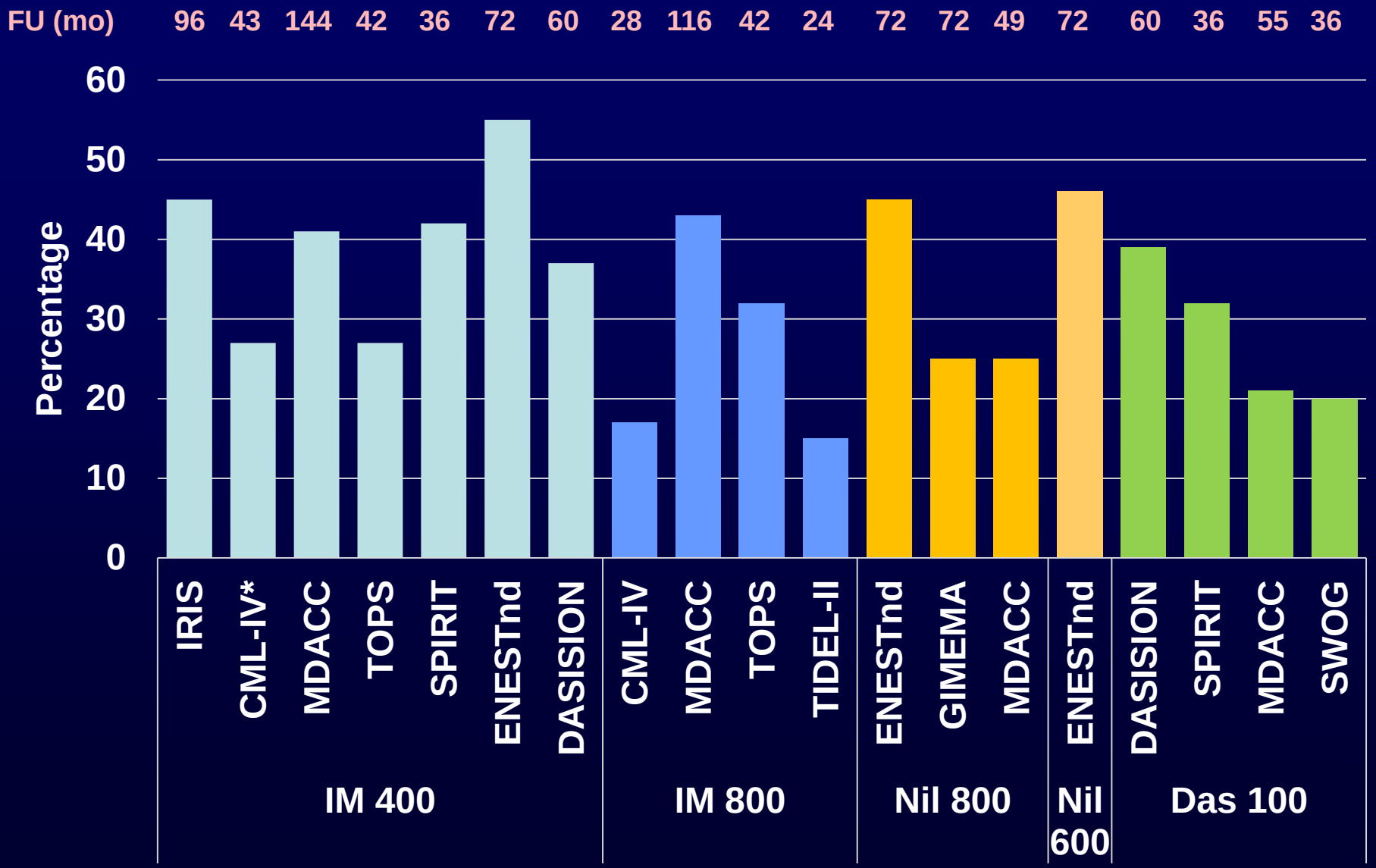


Criteria for Failure and Suboptimal Response to Imatinib – ELN 2013

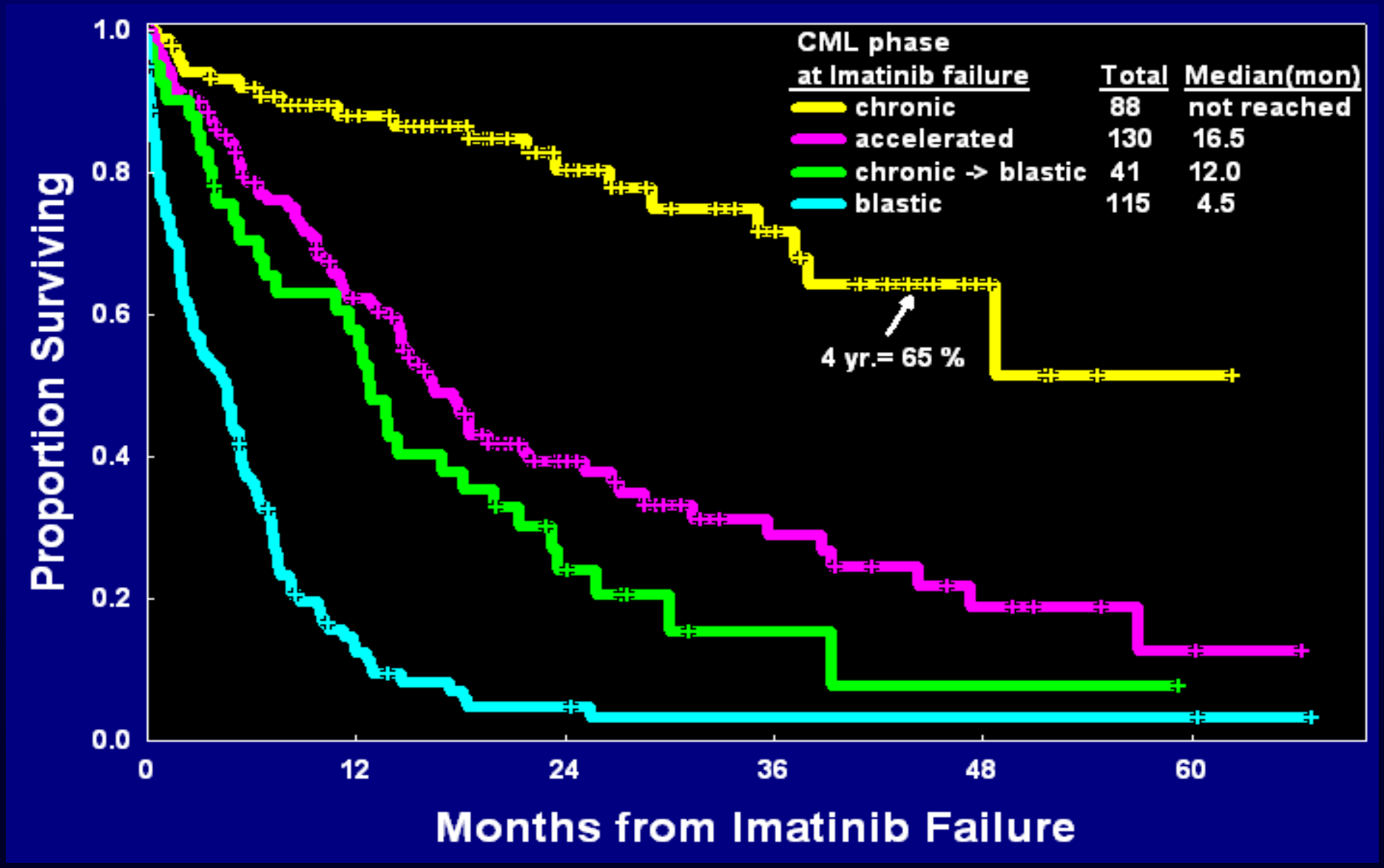
Time (mo)	Response		
	Failure	Warning	Optimal
3	No CHR, And/or Ph+ >95%	BCR-ABL >10%, and/or Ph+ 36-95%	BCR-ABL ≤10%, and/or Ph+ <35%
6	BCR-ABL >10% and/or Ph+ >35%	BCR-ABL 1-10%, and/or Ph+ 1-35%	BCR-ABL <1%, and/or Ph+ ≤35%
12	BCR-ABL >1% and/or Ph+ >0%	BCR-ABL >0.1-1%	BCR-ABL <0.1%
Any	Loss of CHR Loss of CCyR Confirmed loss of MMR Mutations CCA/Ph+	CCA/Ph- (-7, or 7q-)	BCR-ABL <0.1%

Baccarani et al. Blood 2013; 122: 872-84

Rates of Discontinuation by TKI – Long-Term



Survival Post Imatinib Failure by CML Phase



Kantarjian et al. Cancer 2007; 109: 1556-60

Approved Indications in CML (US)

	Frontline	Salvage	AP	BP
Imatinib[a]	**400 mg QD** **340 mg/m^2/d[d]**	**400 mg QD** (IFN failure)	**600 mg QD** (IFN failure)	**600 mg QD** (IFN failure)
Dasatinib[b]	**100 mg QD[e]**	**100 mg QD** (Resistance or intolerance prior Rx including imatinib)	**140 mg QD** (Resistance or intolerance prior Rx including imatinib)	**140 mg QD** (Resistance or intolerance prior Rx including imatinib)
Nilotinib[c]	**300 mg BID[e]**	**400 mg BID** (Resistance or intolerance prior Rx that included imatinib)	**400 mg BID** (Resistance or intolerance prior Rx that included imatinib)	**--**
Bosutinib[a]	**--**	**500 mg QD** (Resistance or intolerance prior Rx)	**500 mg QD** (Resistance or intolerance prior Rx)	**500 mg QD** (Resistance or intolerance prior Rx)
Ponatinib[b]	**--**	**45 mg QD** (Resistance or intolerance prior TKI)	**45 mg QD** (Resistance or intolerance prior TKI)	**45 mg QD** (Resistance or intolerance prior TKI)
Omacetaxine	**--**	**1.25 mg/m^2 SQ x14d Q28d (induction), then x7d Q28d** (Resistance or intolerance 2 TKI)	**1.25 mg/m^2 SQ x14d Q28d (induction), then x7d Q28d** (Resistance or intolerance 2 TKI)	**--**

[a] With food; [b] With or without food; [c] Avoid food 2 hrs before and 1 hr after; [d] Adult and pediatric, respectively; [e] Adults only

2G-TKI for Second Line Therapy in CML-CP

- 572 pts treated with 2G-TKI in CML-CP: for resistance (54%) or intolerance (45%)
- Median age 47 yrs (12-86); 51% female
- Median time from diagnosis to 2nd line TKI 32 mo (0-206 mo)
- 516 pts received TKI as frontline treatment and 105 had other prior therapies
- Treatment: dasatinib 338 (54%), nilotinib 194 (31%), bosutinib 40 (6%)
- MCyR 81%: CCyR 72%, PCyR 8%; MMR 75%
- Best molecular response: MMR 18%, MR4 6%, MR4.5 51%
- Mutations after 2G-TKI 70 (12%): T315I 22%, F317L 12%

2G-TKI for Second Line Therapy in CML-CP

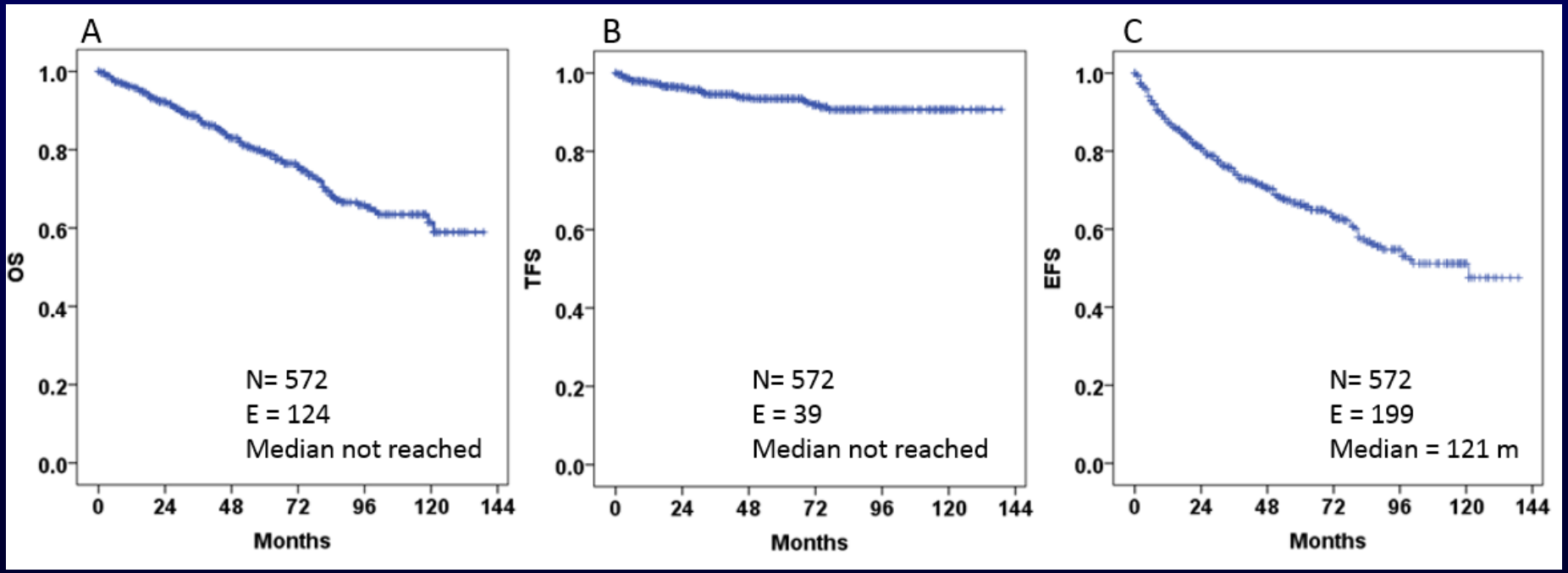
- 39 (7%) transformed to AP (n=26, 5%) or BP (n=13, 2%) while on 2G-TKI

		OS	TFS	EFS
Overall		66	91	55
Prior therapy	Frontline TKI	70	92	59
	Other prior Rx	49	83	38
	p value	<0.001	0.005	<0.001
Reason for change	Intolerance	79	95	74
	Resistance	58	87	42
	p value	<0.001	0.002	<0.001

- No difference in OS, TFS or EFS between dasatinib, nilotinib or bosutinib

2G-TKI for Second Line Therapy in CML-CP

OS TFS EFS



MDACC 2017

Difficult Choices

Pele

Maradona

Ivan Zamorano

Factors to Select 2nd Line TKI

- Efficacy
- Safety

- Co-morbidities
- Prior toxicity
- Schedule / convenience
- Availability
- Cost

Dasatinib in CML CP After Imatinib Failure

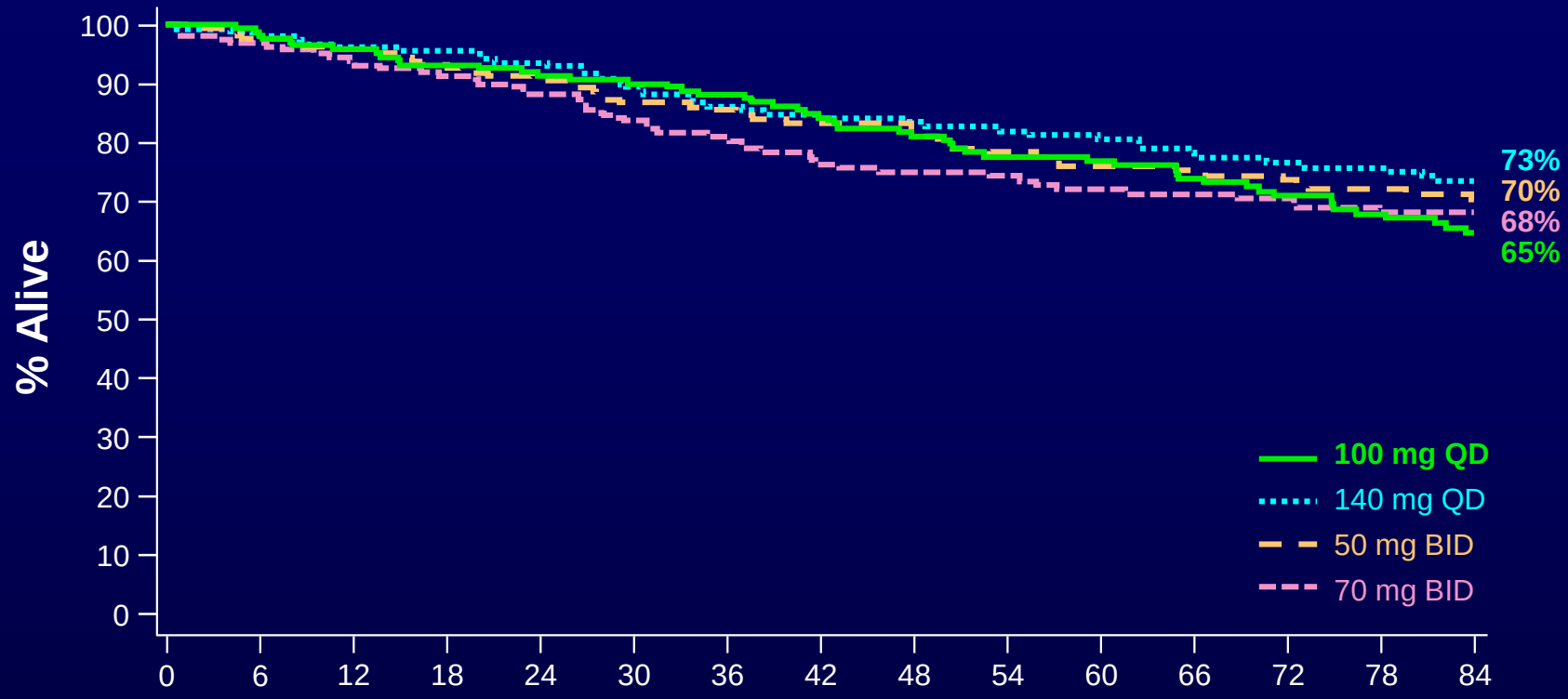
- 670 pts randomized to 4 dasatinib schedules
- 6-year follow-up

Outcome (100 mg/d)	Percent
MCyR / CCyR (within 2 yr)	63 / 50
MMR	46
IM Resistant	43
IM Intolerant	55
7-yr OS	65
7-yr PFS	42
Discontinued treatment	78

- Reason for discontinuation: AE 30% (related 24%, unrelated 6%), progression 21%, other 47%.
- Pleural effusion 28%, pulmonary hypertension 2%.

Shah et al. Am J Hematol 2016; 91: 869-74

Dasatinib Second Line - OS by Dose Schedule

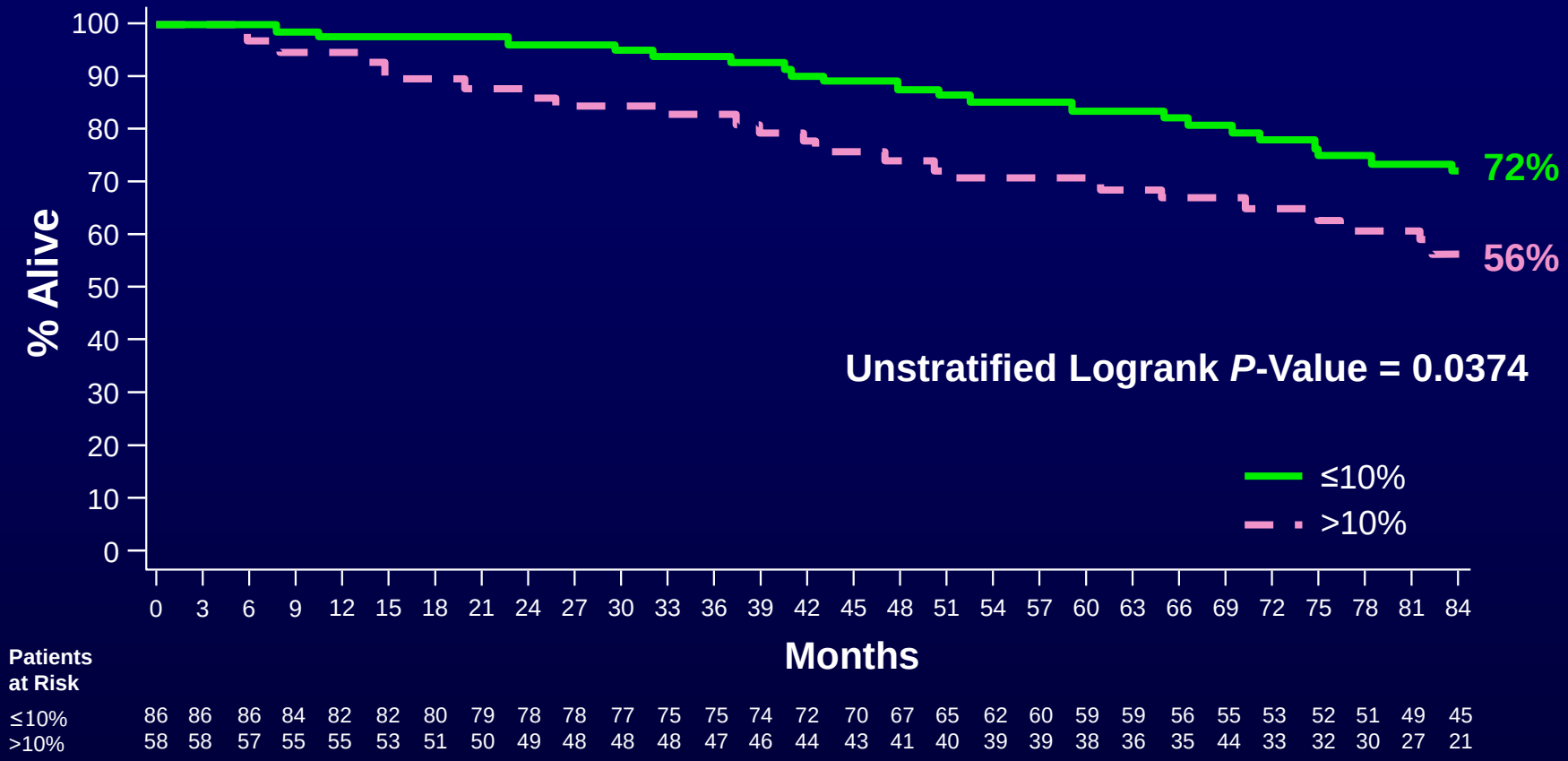


Patients at Risk															
100 mg QD	167	162	154	147	143	141	137	130	120	112	106	99	94	89	73
140 mg QD	167	154	150	147	141	132	126	120	118	114	106	101	97	94	76
50 mg BID	168	158	153	147	140	129	124	120	114	105	99	96	92	89	79
70 mg BID	168	157	150	142	136	129	123	113	106	104	95	92	89	83	74

	Imatinib-resistant Patients	Imatinib-intolerant Patients	Overall
OS, % (95% CI)	63 (53–71)	70 (52–82)	65 (56–72)
PFS, % (95% CI)	39 (29–49)	51 (32–67)	42 (33–51)

Shah et al. Am J Hematol 2016; 91: 869-74

OS by 3 Month BCR-ABL: Dasatinib 100 mg QD



	BCR-ABL ≤10% at 3 months (60%)	BCR-ABL >10% at 3 months (40%)
OS, % (95% CI)	72 (60–81)	56 (42–68)
PFS, % (95% CI)	56 (43–67)	21 (10–34)

Shah et al. Am J Hematol 2016; 91: 869-74

Nilotinib in CML CP Post Imatinib Failure

- 321 pts: imatinib resistant (71%) or intolerant (29%)
- Minimum 48 mo follow-up
- Nilotinib 400 mg PO BID

Outcome	Percent
MCyR / CCyR	59 / 45
Resistant*	56 / 41
Intolerant*	66 / 51
48-month OS	78
48-month PFS	57
Discontinued treatment	70

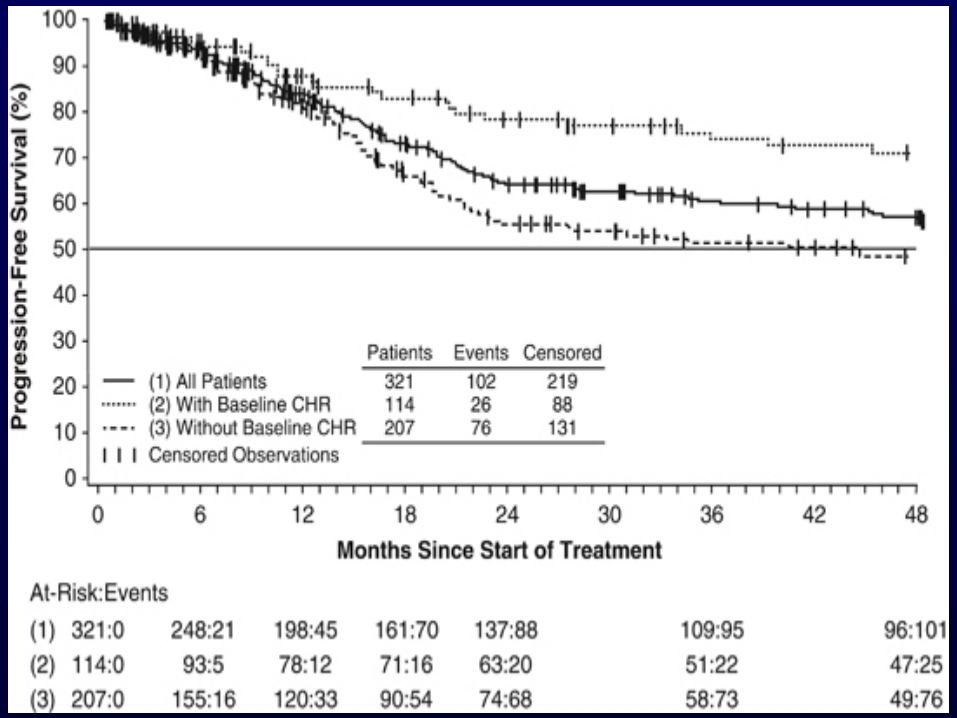
- Reason for discontinuation: progression 30%, AEs 21% (related 17%, unrelated 4%)
- AEs: Rash 31%, pruritus 26%, nausea 25%

* 24 mo data; no additional MCyR after 24 mo; 5 pts improved from MCyR to CCyR after 24 mo.

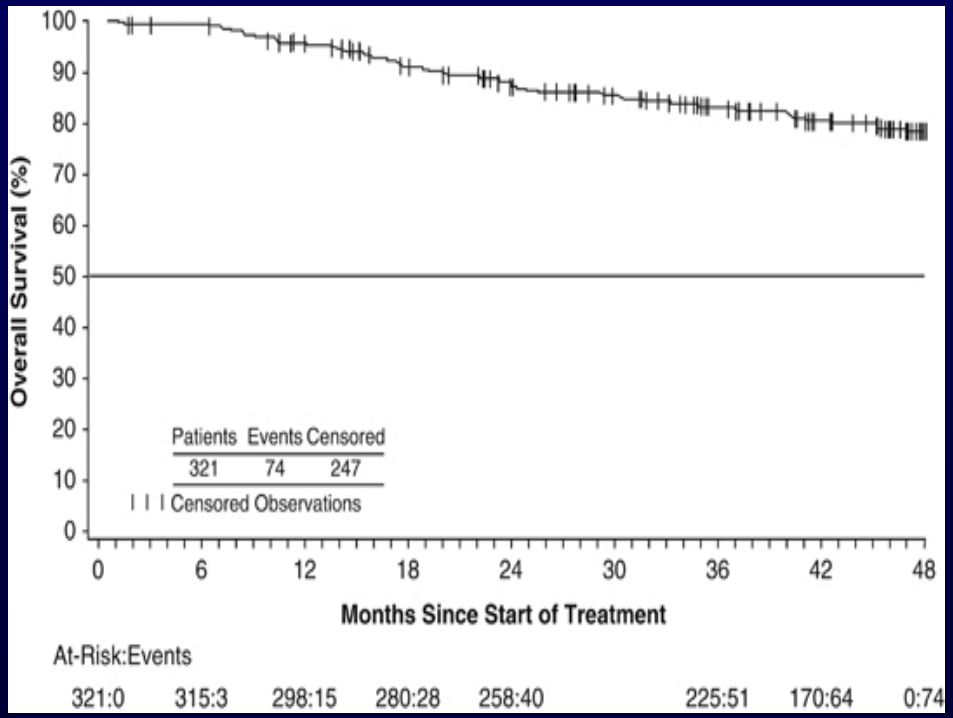
Kantarjian et al. Blood 2011; 117: 1141-5
Giles et al. Leukemia 2013; 27: 107-12

Long-Term Outcome With Nilotinib After Imatinib Failure

Progression-Free Survival



Overall Survival



Giles et al. Leukemia 2013; 27: 107-12

2nd-line Bosutinib in CP CML: 8-Year Update Efficacy Summary

- Phase 1/2 bosutinib 500 mg/d
- 284 pts: imatinib resistant 195, intolerant 89
- Median age 53 y (18-91 y), prior IFN 35%, SCT 3%

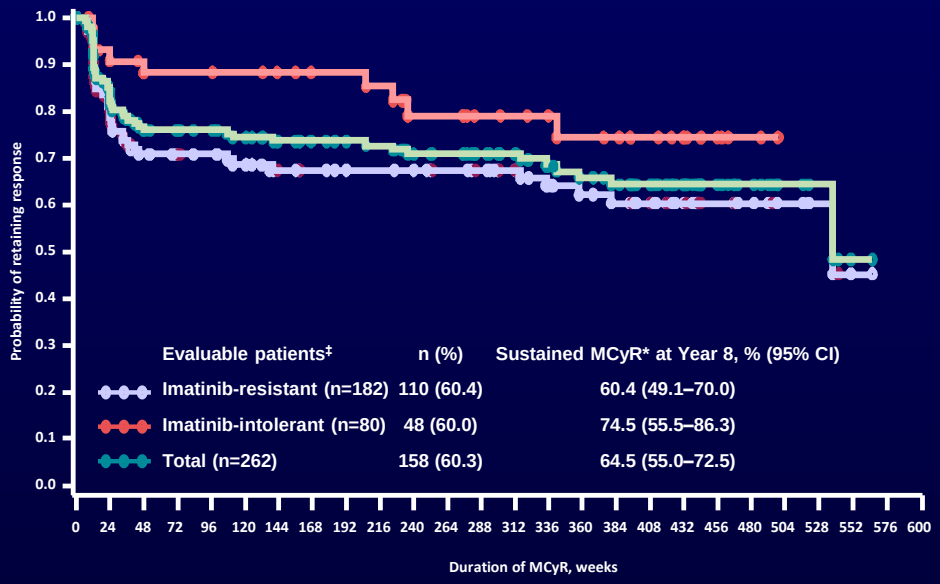
n (%)	Imatinib-resistant	Imatinib-intolerant	Total
Cytogenetic responses			
Evaluable patients†	182	80	262
MCyR	110 (60)	48 (60)	158 (60)
CCyR	89 (49)	41 (51)	130 (50)
Survival outcomes			
Cumulative incidence of progression‡ or death	57 (29)	10 (11)	67 (24)
Deaths	40 (21)	11 (12)	51 (18)

- New toxicities year 5-8: renal (14%), diarrhea 1 (0.8%), liver 7 (6%)
- Vascular events (per 100 pt/year): cardiovascular 0.008, cerebrovascular 0.005, peripheral vascular 0.001

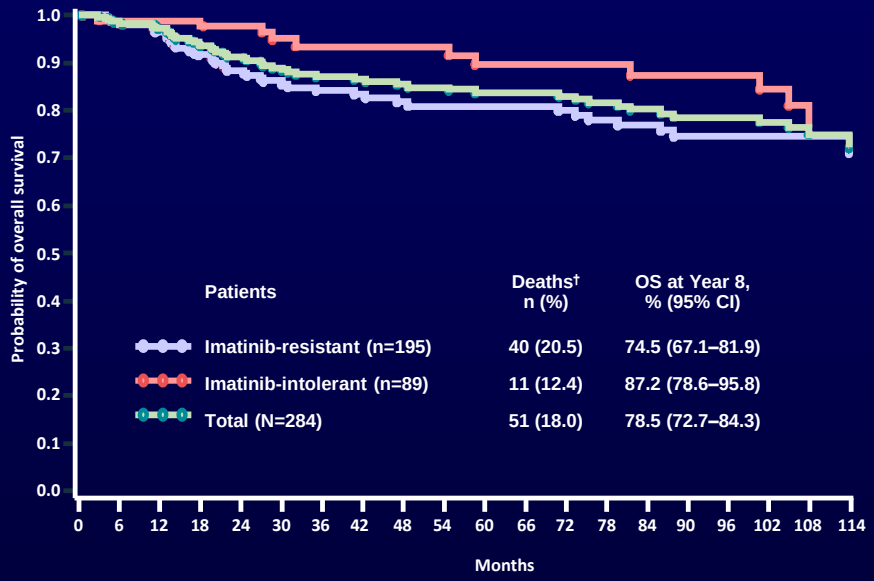
Gambacorti-Passerini et al. Am J Hematol 2018; 103: 1298-307;
Brummendorf et al. ASH 2017; abstract #900

2nd-line Bosutinib in CP CML: 8-Year Update MCyR Duration & Overall Survival

MCyR Duration



Overall Survival



- **No deaths assessed as treatment-related; 6 new deaths after the 5-year F/U**

- * Includes responses newly attained or maintained from baseline; 29.7% of patients had loss of response, PD, or death (imatinib-resistant: 34.5%; imatinib-intolerant: 18.8%). ‡ Received ≥1 dose of bosutinib and had a valid baseline cytogenetic assessment.
- † 13 deaths occurred within 30 days of the last bosutinib dose (imatinib-resistant patients: n=11; imatinib-intolerant patients: n=2).
- Most deaths were due to progressive disease (n=29 [10.2%]; imatinib-resistant patients: n=23 [11.8%]; imatinib-intolerant patients: n=6 [6.7%]) or AEs unrelated to study drug (n=16 [5.6%]; imatinib-resistant patients: n=14 [7.2%]; imatinib-intolerant patients: n=2 [2.2%]).

Gambacorti-Passerini et al. Am J Hematol 2018; 103: 1298-307;
Brummendorf et al. ASH 2017; abstract #900

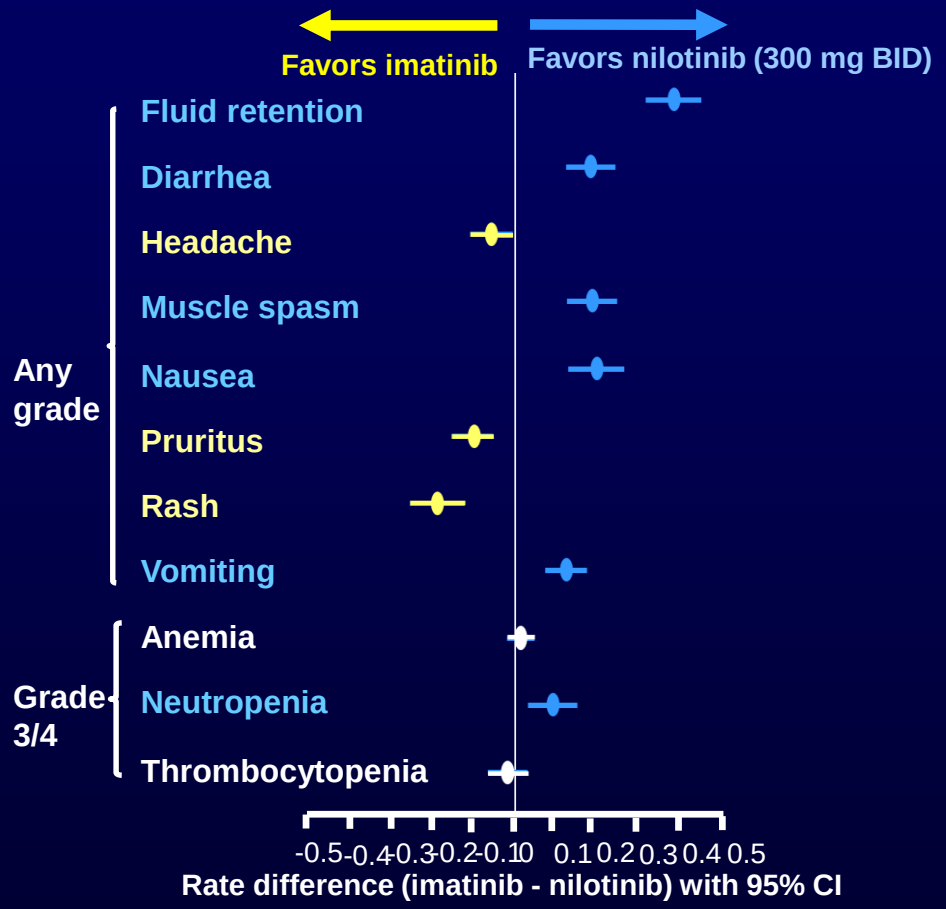
Study 200 Extended Follow-Up – CP-CML

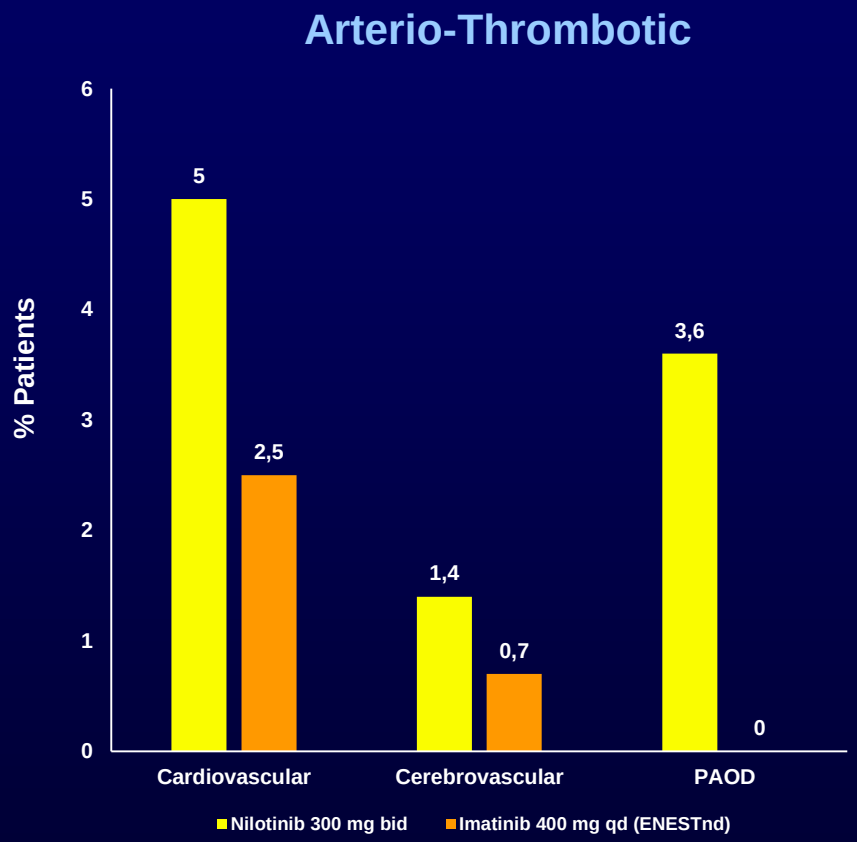
- **Follow-up: 2L CP-CML ≥48 months; 3L CP-CML ≥36 months**

	2L CP-CML			3L CP-CML
	IM-Resistant	IM-Intolerant	Total	Total
N	196	90	286	118
Evaluable	183	81	264	116
MCyR, %	59	61	59	40
CCyR	48	52	49	32

[1]Brummendorf et sl. Br J Haematol 2016; 172: 97-110; [2]Cortes et al. Am J Hematol 2016; 91: 1206-14

ENESTnd: Study Drug-Related Adverse Events and Grade 3/4 Myelosuppression

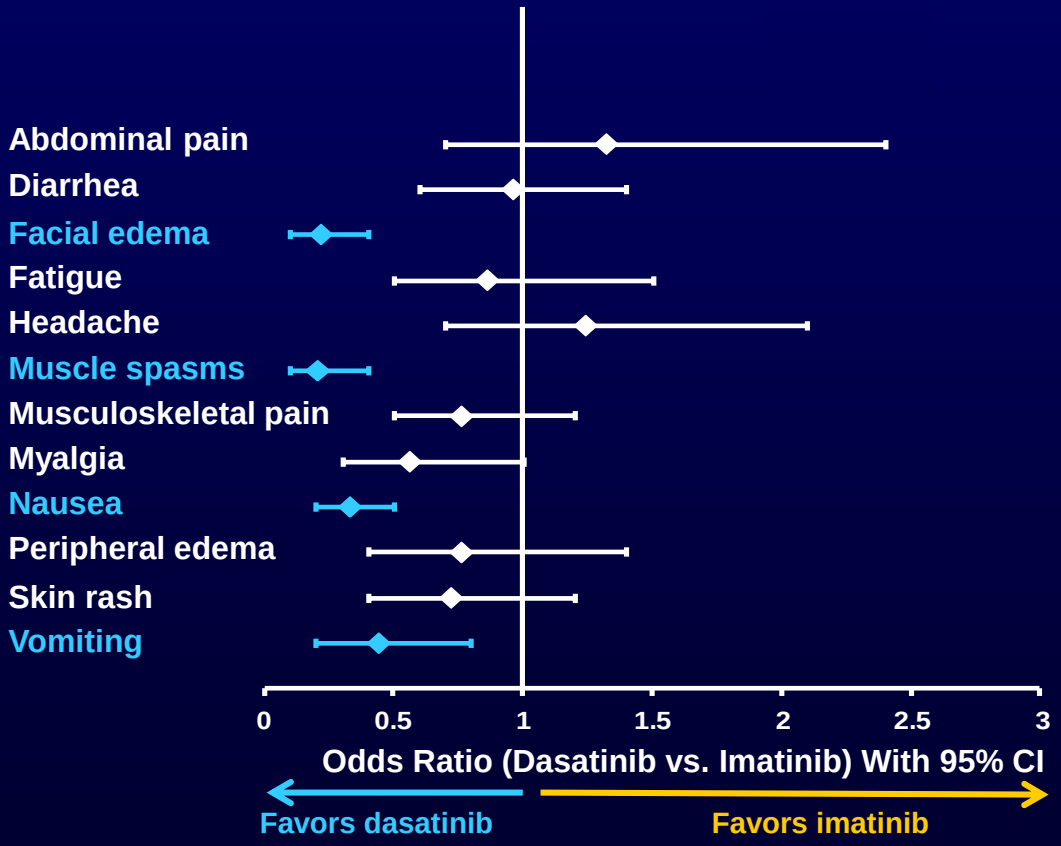


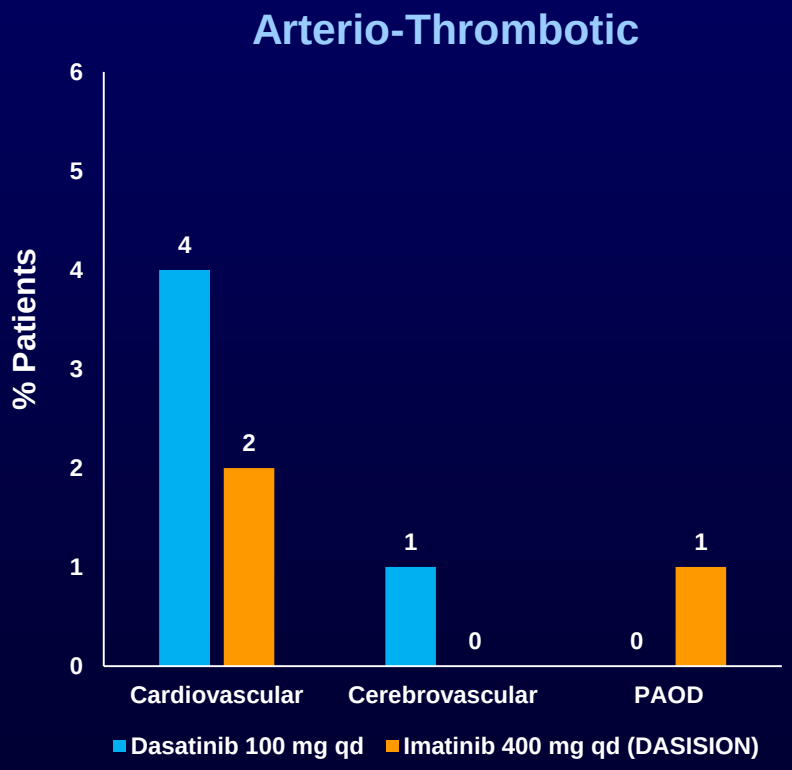


Hochhaus et al. Leukemia 2016; 30: 1044-54

DASISION - Drug-Related Non-Hematologic AEs

- **Pleural effusion: 73 (28%) patients on dasatinib, 2 (1%) on imatinib**
  - **Pulmonary hypertension (PH; based on ECHO): 12 patients on dasatinib and 1 on imatinib**
  - **Pulmonary arterial hypertension (PAH): not reported**
  - **Right heart catheterization in one patient ruled out PAH per WHO definition**



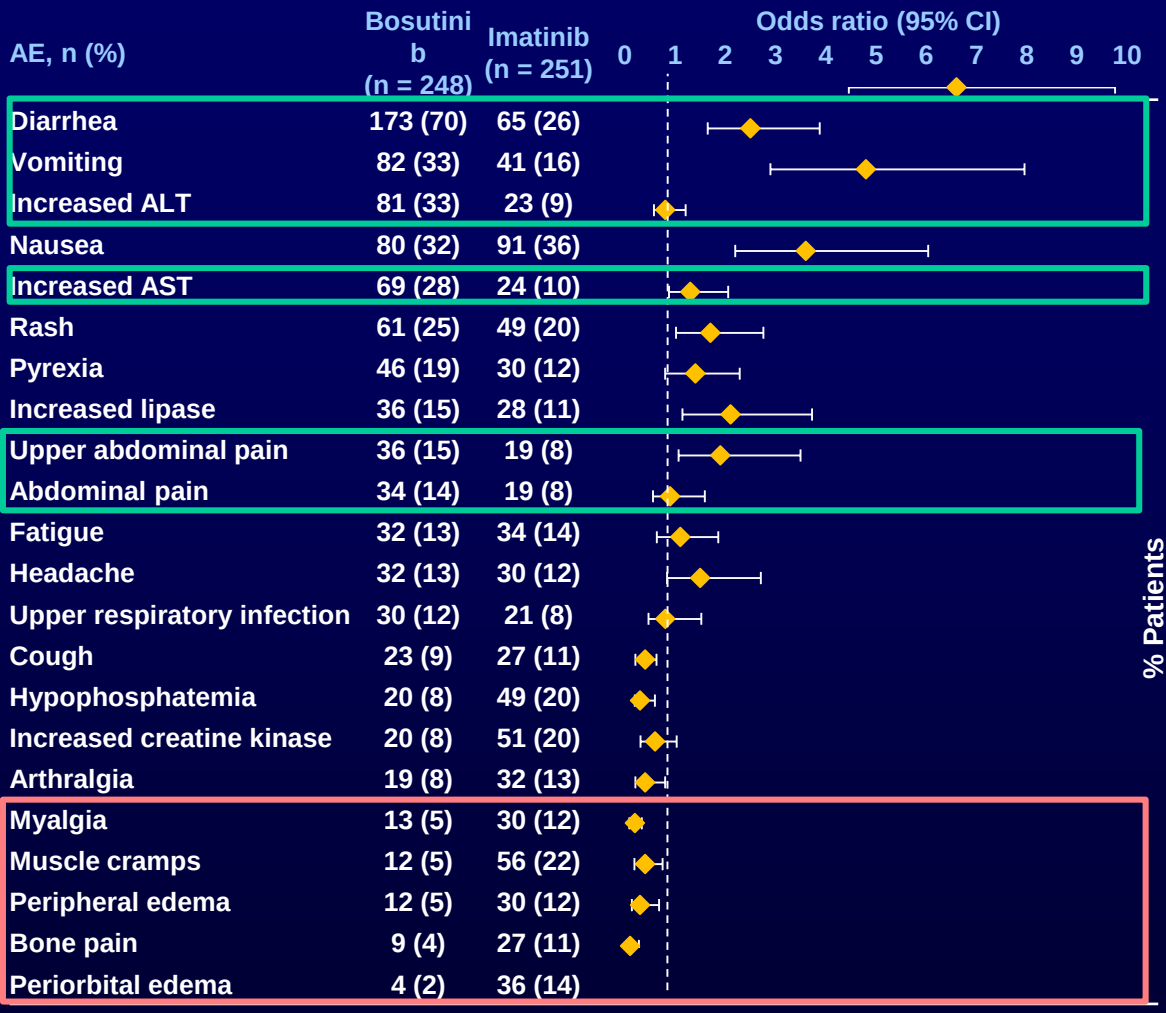


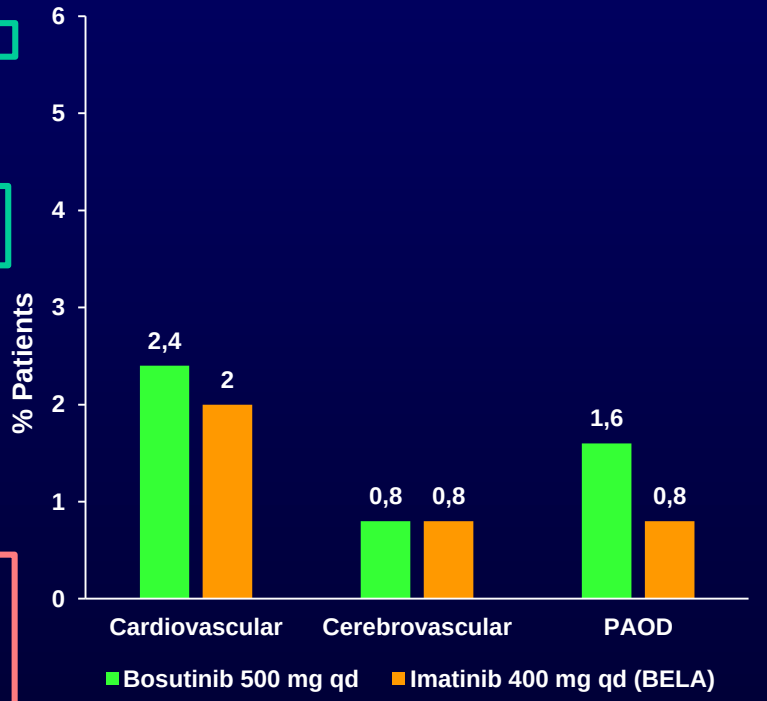
[a] Pleural effusion (28%) is not shown to allow adequate representation of other events.

Cortes et al. JCO 2016; 34: 2333-40

BELA: Treatment-Emergent AEs

AE, n (%)	Bosutinib (n = 248)	Imatinib (n = 251)
Diarrhea	173 (70)	65 (26)
Vomiting	82 (33)	41 (16)
Increased ALT	81 (33)	23 (9)
Nausea	80 (32)	91 (36)
Increased AST	69 (28)	24 (10)
Rash	61 (25)	49 (20)
Pyrexia	46 (19)	30 (12)
Increased lipase	36 (15)	28 (11)
Upper abdominal pain	36 (15)	19 (8)
Abdominal pain	34 (14)	19 (8)
Fatigue	32 (13)	34 (14)
Headache	32 (13)	30 (12)
Upper respiratory infection	30 (12)	21 (8)
Cough	23 (9)	27 (11)
Hypophosphatemia	20 (8)	49 (20)
Increased creatine kinase	20 (8)	51 (20)
Arthralgia	19 (8)	32 (13)
Myalgia	13 (5)	30 (12)
Muscle cramps	12 (5)	56 (22)
Peripheral edema	12 (5)	30 (12)
Bone pain	9 (4)	27 (11)
Periorbital edema	4 (2)	36 (14)





Selected AEs seen more frequently with bosutinib.
Selected AEs seen more frequently with imatinib.

Brummendorf et al. Br J Haematol 2015; 168: 69-81; Cortes JE, et al. Am J Hematol. 2016;91(6):606-616

Study 200 Extended Follow-Up – CP-CML

Parameter	2L CP-CML			3L CP-CML
	IM-R	IM-I	Total	Total
Rx duration, m	27 [0.2-83.4]	23.4 [0.3-77.6]	24.8 [0.2-83.4]	8.5 [0.2-78.1]
≥1 dose interruption 2º AE	66	83	72	66
≥1 dose reduction 2º AE	44	58	49	50
Dose escalation to 600 mg	18	3	13	18
Discontinuation	60	62	60	81
AE	15	38	22	25
Disease progression	21	10	18	21
Efficacy	10	3	8	19
Patient request	6	7	6	4
Death	2	1	2	5
Investigator request	1	1	1	3
Lost FU	2	0	1	2
Other	2	2	2	2

[1]Brummendorf et sl. Br J Haematol 2016; 172: 97-110; [2]Cortes et al. Am J Hematol 2016; 91: 1206-14

2nd Generation TKI in CML CP Post-Imatinib Resistance

Response	Percentage		
	Dasatinib†	Nilotinib‡	Bosutinib
FU (mo)	>24	>24	24*
CHR	89	77	86
MCyR	59	56	54
CCyR	44	41	41
24 mo PFS**	80%	64%	79%
24 mo OS**	91%	87%	92%

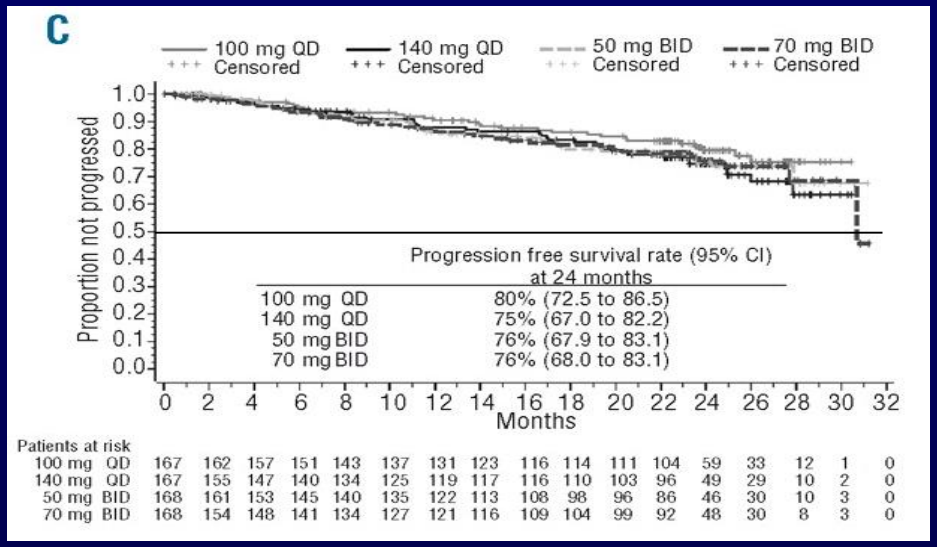
† 6-yr PFS 49%, OS 71%, TFS 76%
‡ 4-yr PFS 57%, OS 78%

* Median
** All patients

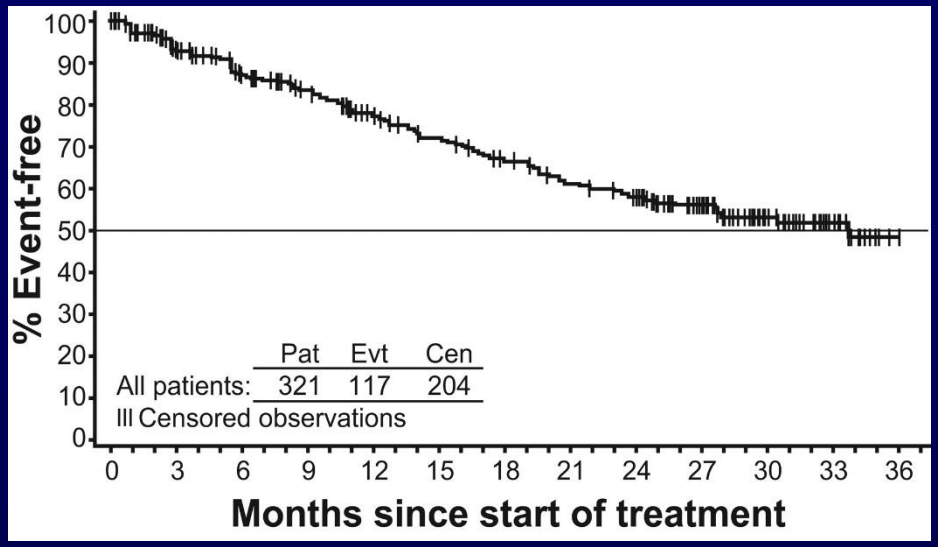
Shah et al. Haematologica 2010; 95: 232-40
Kantarjian et al. Blood 2011; 117: 1141-45
Cortes et al. Blood 2011; 118; 4567-76

PFS/EFS 2G-TKI in CML CP Post-Imatinib Failure

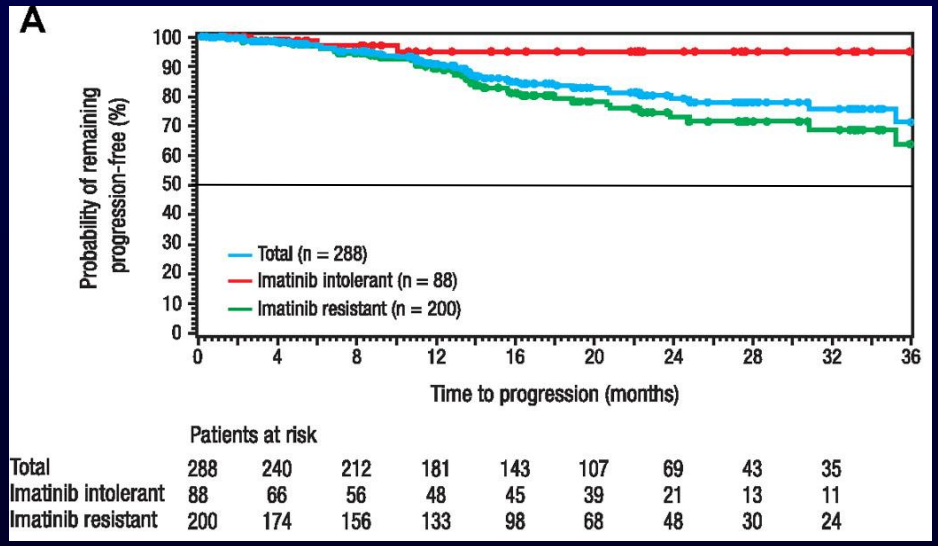
Dasatinib



Nilotinib



Bosutinib



Shah et al. Haematologica 2010; 95: 232-40; Kantarjian et al. Blood 2011; 117: 1141-45
Cortes et al. Blood 2011; 118; 4567-76

2nd Generation TKI in CML CP Post-Imatinib Intolerance

Response	Percentage		
	Dasatinib	Nilotinib	Bosutinib
CHR	100	NR	85
MCyR	77	66	49
CCyR	67	51	41

Shah et al. Haematologica 2010; 95: 232-40
Kantarjian et al. Blood 2011; 117: 1141-45
Cortes et al. Blood 2011; 118; 4567-76

Definition of Intolerance

- **Dasatinib:** grade 3 or worse toxicity (considered at least possibly related to imatinib at a dose of ≥400 mg/d) which led to discontinuation of therapy.
  - Pts in MCyR allowed (20% of all @ 100 mg/d)
- **Nilotinib:** any non-hematologic toxicity of grade 3 or higher severity, or of grade 2 or higher severity lasting more than 1 month or recurring more than 3 times despite dose reduction and maximal supportive care. The definition of intolerance also included hematologic toxicity of grade 4 severity persisting for more than 7 days.
  - Pts in MCyR not allowed
- **Bosutinib:** inability to take imatinib because of imatinib-related grade 4 hematologic toxicity lasting longer than 7 days; imatinib-related grade 3 or greater nonhematologic toxicity; persistent grade 2 toxicity not responding to dose reductions and medical management; or loss of previously attained response on lower-dose imatinib among patients with previous toxicity.
  - Pts in MCyR allowed

[1] Shah et al. JCO 2008; 26: 3204-3212; [2] Kantarjian et al. Blood 2007; 110: 3540-6; [3] Cortes et al. Blood 2011; 118: 4567-76

2nd Generation TKI in CML CP Post-Imatinib Failure – 2-yr Patient Disposition

Response	Percentage		
	Dasatinib	Nilotinib	Bosutinib
Discontinued	70	61	50
AEs	22	19	21
Disease progression	23	27	18*

* Includes “unsatisfactory response”

Shah et al. Haematologica 2010; 95: 232-40
Kantarjian et al. Blood 2011; 117: 1141-45
Cortes et al. Blood 2011; 118; 4567-76

2nd Line Bosutinib at MDACC

- 39 pts with 1 prior TKI (8 had prior IFN)
- Median age 45 y (range, 18 – 83 y), 59% females
- Prior TKI: resistance (n=27; 69%), intolerance (n= 12; 31%)
- MCyR 68%, MMR 56% (MR4.5 38%), 3-mo ≤10% 31%
- Median EFS 88 mo (95CI 57, 119), FFS 49 mo (95CI 11, 87), OS and TFS not reached
- 23 (59%) discontinued (15 resistance, 7 AEs, 1 pregnancy); 20 started 3rd TKI.

MDACC 2017

Bosutinib after Prior TKI at MDACC

- 68 CML-CP pts treated with bosutinib; median duration of therapy 24 mo (1 to 150)
- Median age 52 yrs (range, 24-87)
- 47 pts (69%) still receiving starting dose; 9 (10%) changed therapy due to side effects

Parameter	N (%)		
	1 prior TKI	2 prior TKI	≥3 prior TKI
MCyR	20 (59)	9 (27)	5 (14)
CCyR	13 (62)	6 (29)	2 (9)
MMR	12 (60)	6 (30)	2 (10)
MR4.5	10 (67)	4 (27)	1 (6)
Sustained MMR4.5	8 (67)	3 (25)	1 (8)

- 60 mo OS 96%, EFS 85%, , FFS 94%

MDACC 2018

Mechanisms of Resistance to Imatinib

- Bcr-Abl-Dependent
  - Mutations in Abl
  - Amplification/overexpression
  - Remigration of Bcr-Abl to cytoplasm
- Bcr-Abl-Independent
  - Decreased hOCT1 expression
  - Increased MDR expression
  - Increased alpha-1 acid glycoprotein
  - Overexpression of Src-related kinases
- Quiescent stem cells (Persistence)

LeCoutre Blood 95: 1758, 2000.Weisberg Blood 95: 3498, 2000
Mahon Blood 96: 1070, 2000. JNCI 92:1641, 2000. Vigneri Nature Medicine 7: 228, 2001

Sensitivity of Mutations to TKI

	IC50-fold increase (WT=1)			
	Imatinib	Bosutinib	Dasatinib	Nilotinib
WT	1	1	1	1
L248V	3.54	2.97	5.11	2.80
G250E	6.86	4.31	4.45	4.56
Q252H	1.39	0.31	3.05	2.64
Y253F	3.58	0.96	1.58	3.23
E255K	6.02	9.47	5.61	6.69
E255V	16.99	5.53	3.44	10.31
D276G	2.18	0.60	1.44	2.00
E279K	3.55	0.95	1.64	2.05
V299L	1.54	26.10	8.65	1.34
T315I	17.50	45.42	75.03	39.41
F317L	2.60	2.42	4.46	2.22
M351T	1.76	0.70	0.88	0.44
F359V	2.86	0.93	1.49	5.16
L384M	1.28	0.47	2.21	2.33
H396P	2.43	0.43	1.07	2.41
H396R	3.91	0.81	1.63	3.10
G398R	0.35	1.16	0.69	0.49
F486S	8.10	2.31	3.04	1.85

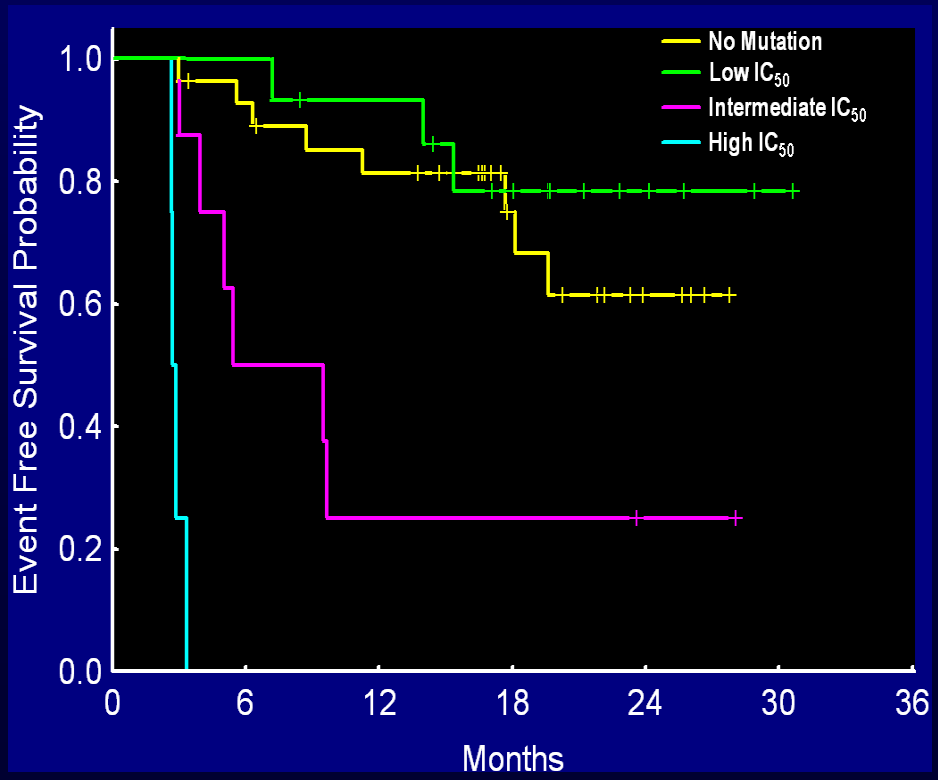
Highly Resistant / Resistant / Sensitive

Redaelli et al. JCO 2009; 27: 469-71

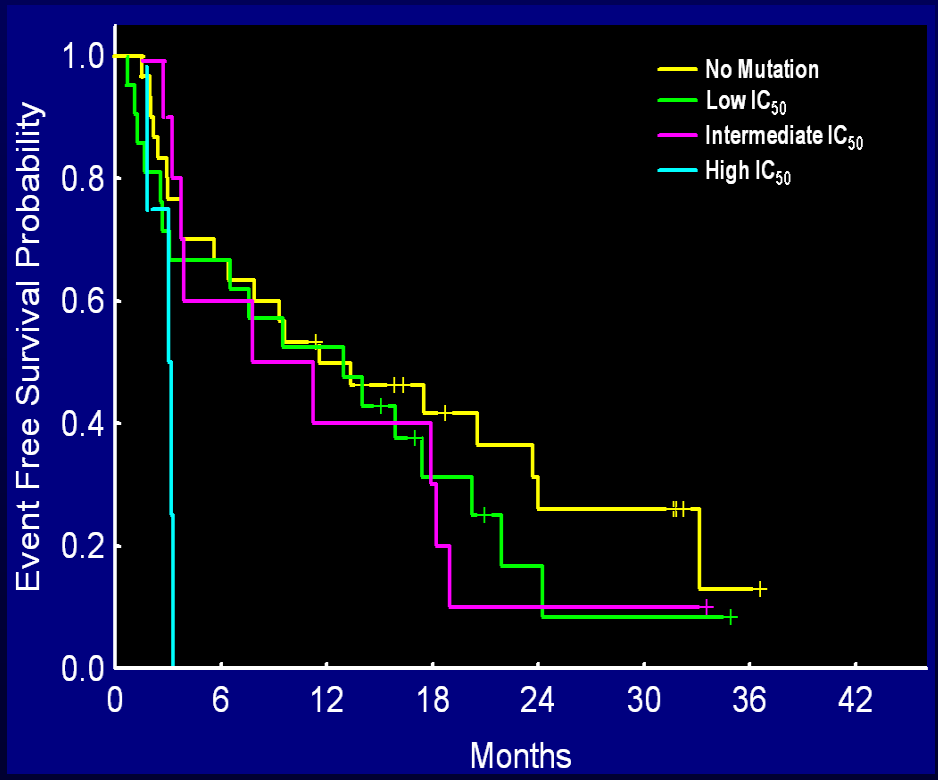
CCyR by Mutations in CML Treated with 2nd Generation TKI after IM Failure

- 86/169 (51%) pts treated had mutation
  - CP 30/59 (51%), AP 41/71 (58%), BP 15/39 (38%)
- IC50 for dasatinib, nilotinib predictive for response in CP and AP

Chronic Phase

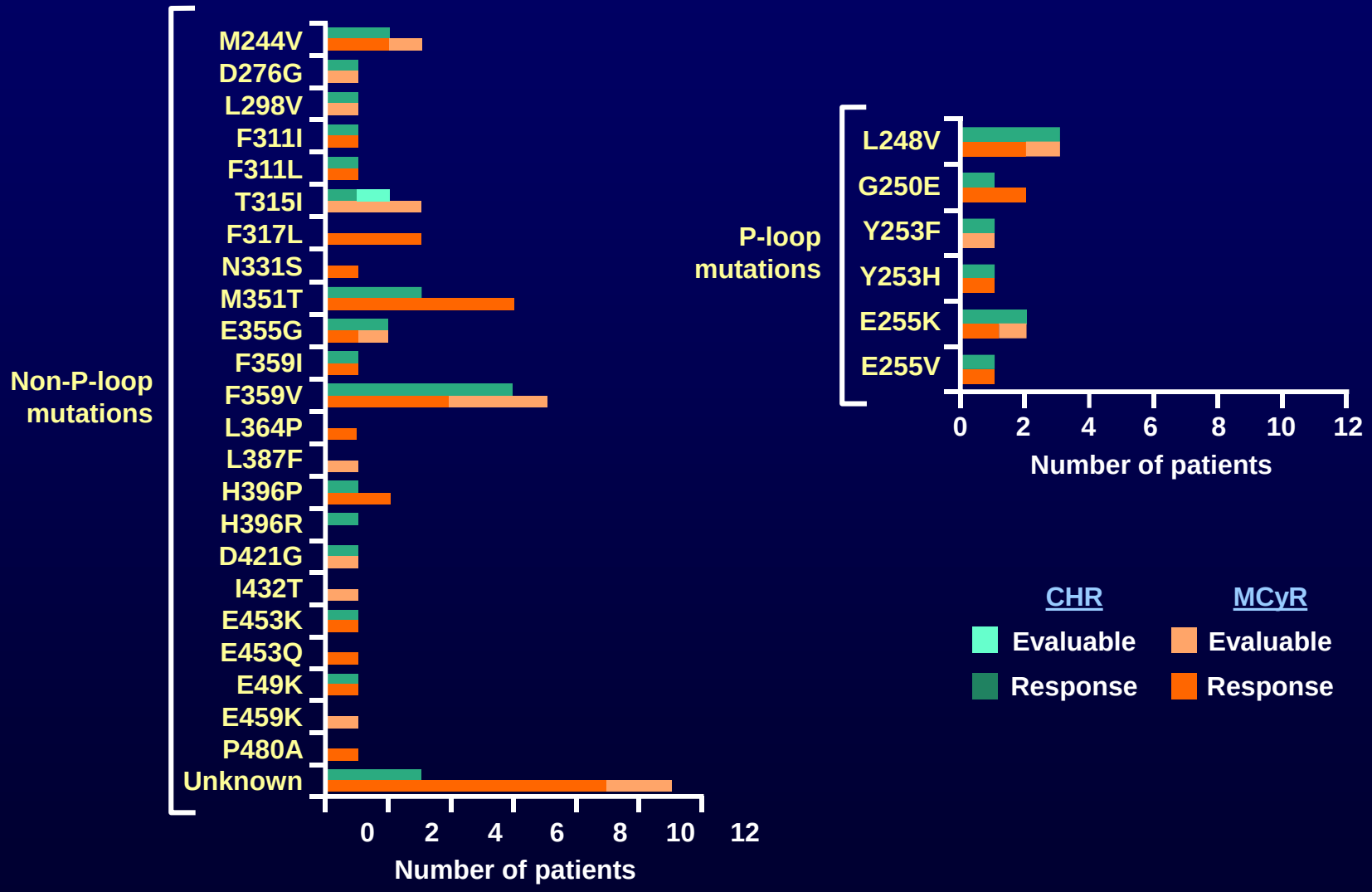


Accelerated Phase



Jabbour et al, Blood 2009; 114: 2037-43

Study 200 (2nd Line): Responses by Baseline Bcr-Abl Mutation Status



Cortes JE et al. *Blood.* 2011;118:4567–4576.

2nd-Generation TKI in CML CP Post- Imatinib Failure

Toxicity	Dasatinib	Nilotinib	Bosutinib
Pleural effusion	++	-	-
Liver	+	+	+
Transaminases	+	+	++
Bilirubin	-	++	-
Rash	+	+	++
Diarrhea	-	-	++
Lipase	- (+)	++	-
Glucose	-	++	-
Hypophosphatemia	++	++	+
Bleeding	+	-	-
QTc	++	++	-

Shah et al. Haematologica 2010; 95: 232-40; Kantarjian et al. Blood 2011; 117: 1141-45
Cortes et al. Blood 2011; 118; 4567-76

2nd-Generation TKI in CML CP Post- Imatinib Failure

Toxicity	Dasatinib	Nilotinib	Bosutinib
Anemia	13	11	13
Neutropenia	35	31	18
Thrombocytopenia	23	30	24

Shah et al. Haematologica 2010; 95: 232-40
Kantarjian et al. Blood 2011; 117: 1141-45
Cortes et al. Blood 2011; 118; 4567-76

2nd-Generation TKI in CML CP Post- Imatinib Failure – 2-yr Arterio-Thrombotic Events

Toxicity	Dasatinib	Nilotinib	Bosutinib
Cardiovascular	NR	NR	NR
Cerebrovascular	NR	NR	NR
Peripheral arterial	NR	NR	NR

Shah et al. Haematologica 2010; 95: 232-40
Kantarjian et al. Blood 2011; 117: 1141-45
Cortes et al. Blood 2011; 118; 4567-76

2nd-Generation TKI in CML CP Post- Imatinib Failure – 2-yr Arterio-Thrombotic Events

Toxicity	Dasatinib	Nilotinib	Bosutinib
Cardiovascular	4%	NR	4%
Cerebrovascular	3%	NR	2%
Peripheral arterial	0%	NR	2%
F/U	7 y	4 y	3 y

Terms reported:
Dasatinib: MI, angina, CAD (not reported for cerebro and peripheral)
Bosutinib: ~600

Shah et al. Haematologica 2010; 95: 232-40
Giles et al. Leukemia 2013; 27: 107-12
Cortes et al. Am J Heamtol 2016; 91: 606-16

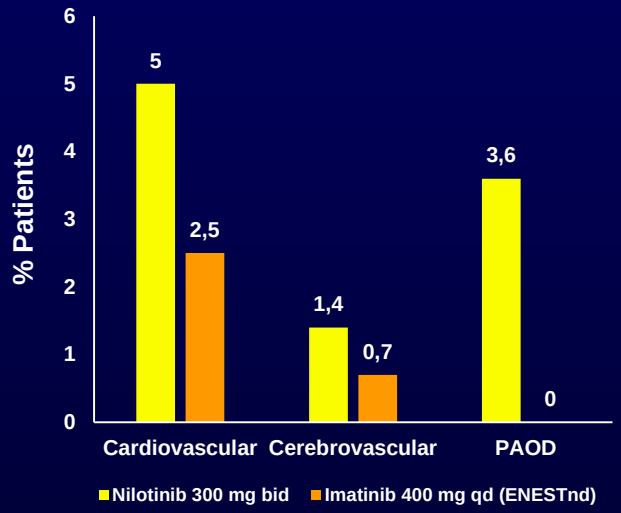
Arterio-Thrombotic Events with TKI

	Imatinib	Other TKI
ENESTnd	3	10-16
DASISION	2	5
BELA	4	5
EPIC	2	8
PACE*		27
Bosutinib Phase 2		6

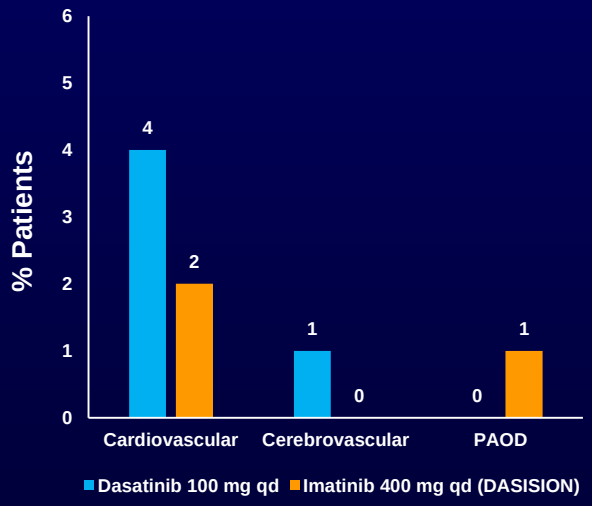
Larson et al. ASH 2014: Abstract #4541; Cortes et al, ASH 2014: Abstract #156; Lipton et al, ASH 2014: Abstract #519; Cortes et al. ASCO 2014: Abstract #7060

Ischemic Events by TKI From Randomized Trials

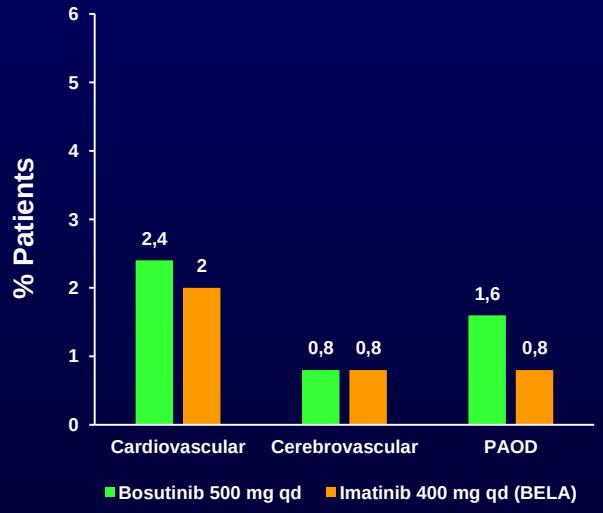
ENESTnd[1]



DASISION[2]



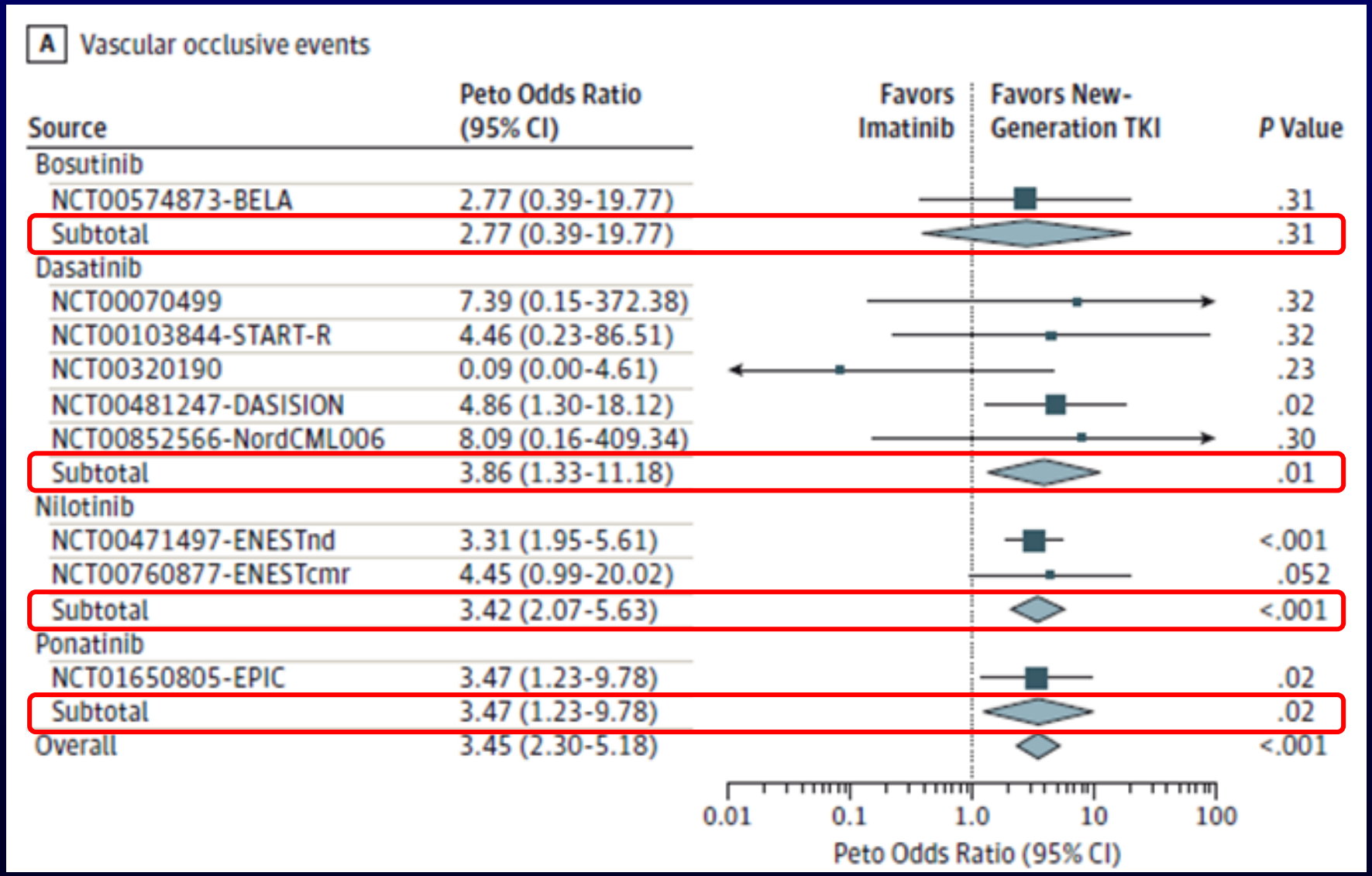
BELA[3*]



*** Median exposure 55 months (0.03-69.4)**

[1]Hochhaus et al. Leukemia 2016; 30: 1044-54; [2]Cortes et al. JCO 2016; 34: 2333-40; [3] Cortes JE, et al. Am J Hematol. 2016;91(6):606-616

Meta-analysis of Cardiovascular Events with TKI



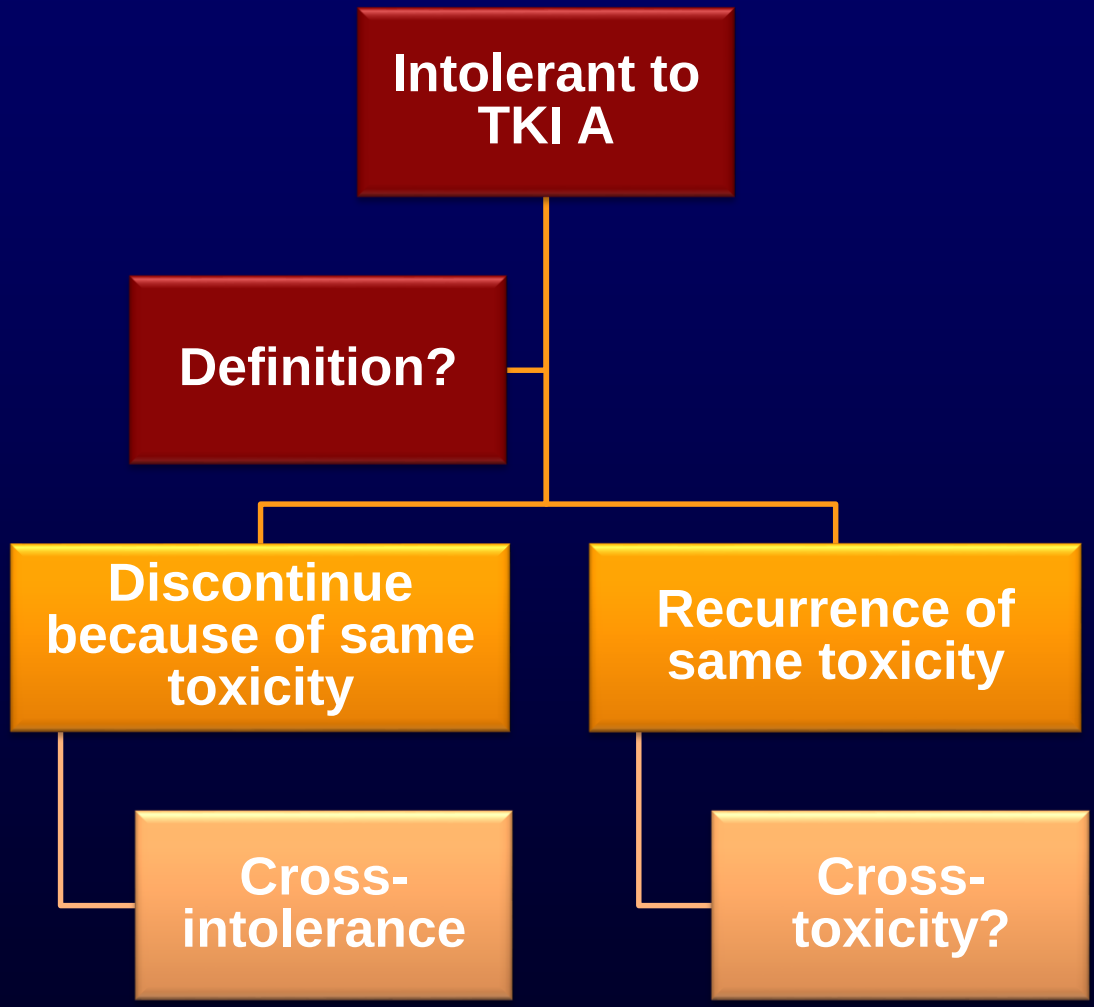
Douxfils et al. JAMA Oncology 2016 [Epub ahead of print]

Cross-Intolerance of TKI

	Discontinued due to same toxicity	Occurrence of same grade 3-4 toxicity
Dasatinib (n=43)	9 (21%) (8 the same, 1 different; not specified which one)	37 (86%)
Nilotinib (n=31)	7 (23%)	17 (55%) (+2 persistent grade 2, 61%)
Bosutinib (n=62)	10 (15%)	28 (45%)

Khoury et al. CLML 2016; 16: 341-6; Cortes et al. Blood 2011; 117: 5600-6; Cortes et al. iCMLf 2013

Cross-Intolerance vs Cross-Toxicity



Cross Intolerance of Bosutinib with Imatinib

Reason for Intolerance†	Intolerant to Prior IM, n	Same AE (Max G1/2) on BOS, n (%)‡	Same AE (Max G3/4) on BOS, n (%)‡	Dose Delay Due to Same AE, n (%)‡	Dose Reduction Due to Same AE, n (%)‡	Discontinued Due to Same AE, n (%)‡
Any AE	122§	37 (30)	39 (32)	38 (31)	19 (16)	20 (16)
Hematologic						
Thrombocytopenia	29	4 (14)	19 (66)	17 (59)	10 (35)	7 (24)
Neutropenia	19	1 (5)	6 (32)	6 (32)	2 (11)	3 (16)
Anemia	14	2 (14)	3 (21)	2 (14)	1 (7)	0
Bone marrow failure	7	2 (29)	5 (71)	3 (43)	2 (29)	4 (57)
Leukopenia	4	0	1 (25)	1 (25)	0	0
Nonhematologic						
Rash	18	8 (44)	2 (11)	4 (22)	0	1 (6)
Edema	12	5 (42)	0	0	0	0
Diarrhea	10	5 (50)	4 (40)	3 (30)	3 (30)	2 (20)
Fatigue	7	1 (14)	0	1 (14)	0	1 (14)
Vomiting	5	3 (60)	1 (20)	3 (60)	0	1 (20)
Myalgia	5	0	1 (20)	0	0	0
Fluid retention	4	1 (25)	0	0	0	0
Nausea	4	3 (75)	0	1 (25)	0	0

*Individual AEs leading to discontinuation from prior TKI therapy in ≥4 CP-CML patients.
†Intolerance is defined as permanent discontinuation due to G3/4 treatment-emergent AE.
‡Percentages are based on patients intolerant to prior TKI reporting AEs.
§Includes 87 CP 2L and 35 CP 3L patients (2 of the 89 CP 2L IM-intolerant patients did not report the AE that led to intolerance).

- There were no deaths on BOS due to the same AE that led to IM intolerance.

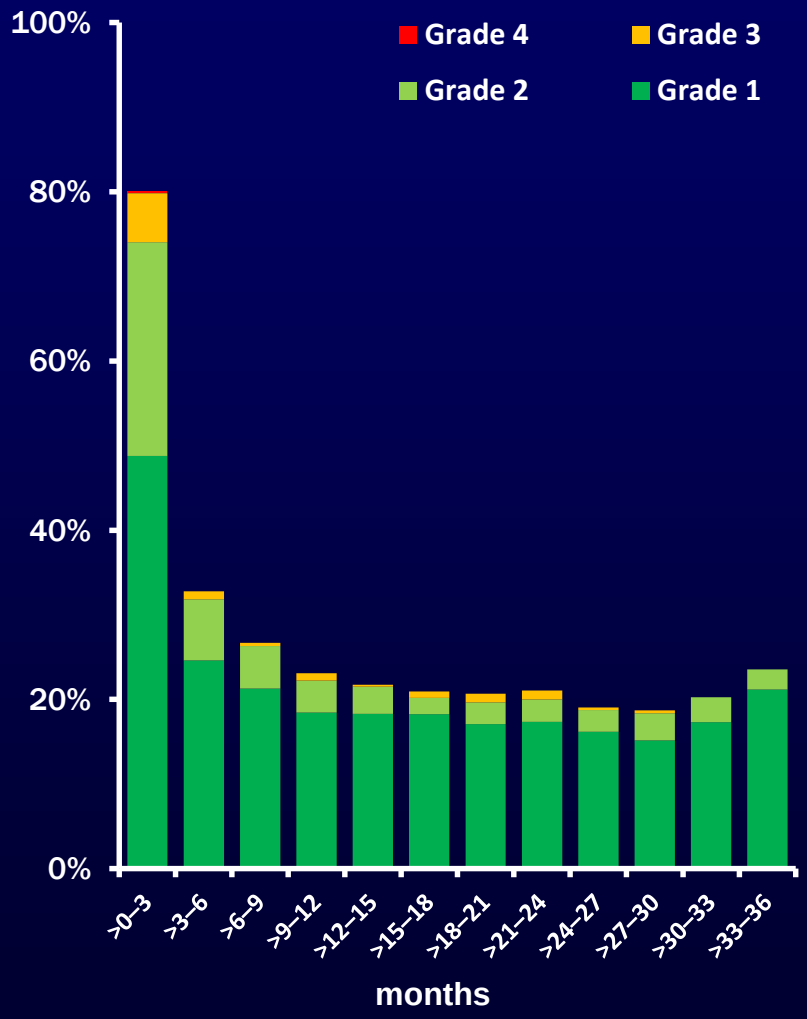
Cross Intolerance of Bosutinib with Dasatinib

Reason for Intolerance†	Intolerant to Prior DAS, n	Same AE (Max G1/2) on BOS, n (%)‡	Same AE (Max G3/4) on BOS, n (%)‡	Dose Delay Due to Same AE, n (%)‡	Dose Reduction Due to Same AE, n (%)‡	Discontinued Due to Same AE, n (%)‡
Any AE	50§	17 (34)	16 (32)	20 (40)	13 (26)	7 (14)
Hematologic						
Thrombocytopenia	8	0	8 (100)	8 (100)	7 (88)	4 (50)
Pancytopenia	5	0	0	0	0	0
Neutropenia	3	0	3 (100)	3 (100)	0	2 (67)
Bone marrow failure	3	1 (33)	2 (67)	2 (67)	2 (67)	1 (33)
Nonhematologic						
Pleural effusion	19	6 (32)	3 (16)	4 (21)	2 (11)	0
Headache	3	1 (33)	1 (33)	1 (33)	0	0
Rash	3	2 (67)	0	0	0	0
Cardiac failure	2	1 (50)	0	0	1 (50)	1 (50)
Bone pain	2	1 (50)	0	0	0	0
Diarrhea	2	2 (100)	0	0	0	0

*Individual AEs leading to discontinuation from prior TKI therapy in ≥4 CP-CML patients.
†Intolerance is defined as permanent discontinuation due to G3/4 treatment-emergent AE.
‡Percentages are based on patients intolerant to prior TKI reporting AEs.
§Includes 87 CP 2L and 35 CP 3L patients (2 of the 89 CP 2L IM-intolerant patients did not report the AE that led to intolerance).

- There were no deaths on BOS due to the same AE that led to IM intolerance.

Management of Diarrhea in the Overall Safety Population (N=570)



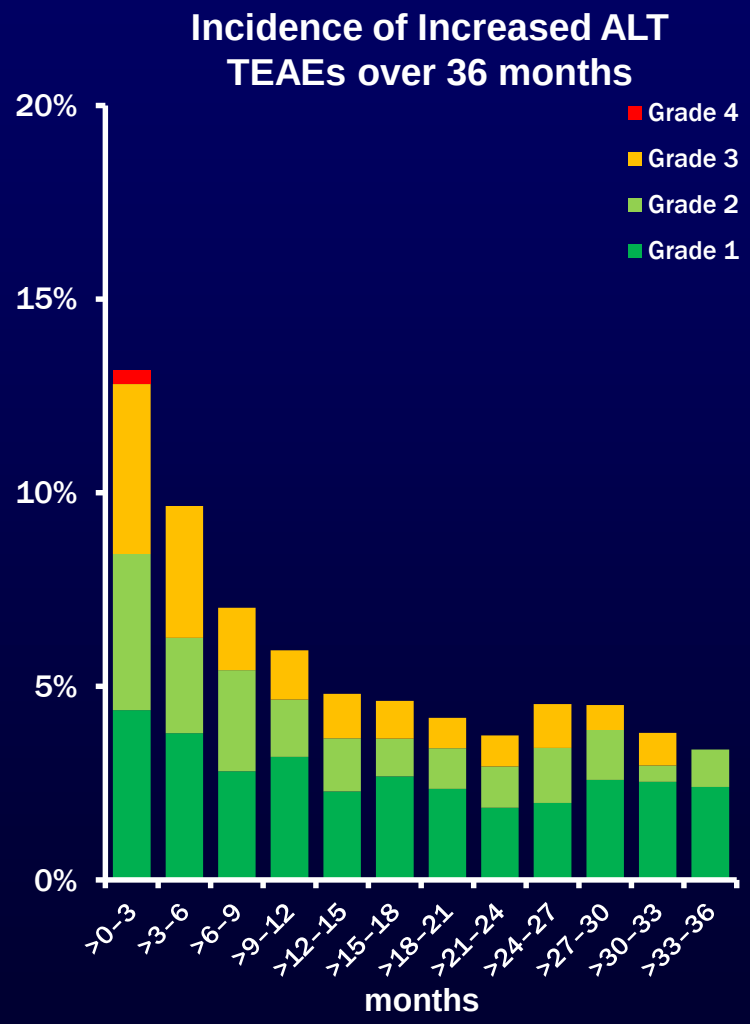
Diarrhea Management, n (%)	
Received dose reduction	26 (6)
Received dose interruption	63 (14)
Successful rechallenge[a]	59 (97)
Concomitant medication	305 (66)
Discontinuation due to diarrhea	7 (2%)

- Manageable with dose modifications and concomitant medication
- 57% of patients who received medication received loperamide; the median duration on anti-diarrheal was 3 days

[a] Successful rechallenge includes patients who did not experience subsequent diarrhea with bosutinib, n = 10 (17.5) or experienced subsequent diarrhea that did not lead to treatment discontinuation, n = 47 (82.5).

Kantarjian HM et al. Blood 2014; 123: 1309-18

Overall Safety Population Characteristics of ALT/AST Adverse Events



Safety Population (N=570)	ALT elevation	AST elevation
Subjects with TEAE	97 (17%)	80 (14%)
Discontinuation due to elevated ALT	10 (10%)	4 (5%)
Median time to onset (range)	29 days (6–841)	33 days (1–1400)
Median duration (range)	21 days (1–775)	20 (1–803)
Event resolved	83 (86%)	71 (89%)
Rechallenge	33 (87)	21 (78)
Succesfull	25 (76)	19 (91)

Kantarjian HM et al. Blood 2014; 123: 1309-18

Efficacy Following Reduction in Patients Who Reduced Bosutinib Dose to 400 mg/d

	CP2L (n=130)	CP3L (n=52)	ADV (n=47)	Total (n=229)
MCyR, n (%)				
Obtained after dose reduction	56 (43)	16 (31)	12 (26)	84 (37)
Maintained after dose reduction	15 (12)	4 (8)	10 (21)	29 (13)
Lost after dose reduction	4 (3)	1 (2)	1 (2)	6 (3)
OHR, n (%)				
Obtained after dose reduction	–	–	14 (30)	–
Maintained after dose reduction	–	–	10 (21)	–
Lost after dose reduction	–	–	2 (4)	–

CP2L – Chronic Phase Second Line; CP3L – Chronic Phase Third Line; ADV – Advanced; MCyR – Major Cytogenetic Response; OHR – Overall Hematologic Response.

Efficacy Following Reduction in Patients Who Reduced Bosutinib Dose to 300 mg/d

	CP2L (n=48)	CP3L (n=23)	ADV (n=21)	Total (n=92)
MCyR, n (%)				
Obtained after dose reduction	8 (17)	5 (22)	1 (5)	14 (15)
Maintained after dose reduction	14 (29)	4 (17)	5 (23)	23 (25)
Lost after dose reduction	4 (8)	1 (4)	2 (10)	7 (8)
OHR, n (%)				
Obtained after dose reduction	–	–	3 (14)	–
Maintained after dose reduction	–	–	4 (19)	–
Lost after dose reduction	–	–	5 (24)	–

CP2L – Chronic Phase Second Line; CP3L – Chronic Phase Third Line; ADV – Advanced; MCyR – Major Cytogenetic Response; OHR – Overall Hematologic Response.

Therapy Management Conclusions from the Overall Safety Population (N=570)

Diarrhea / Vomiting	Early onset, low grade, short duration, manageable with dose adjustments and/or standard of care treatment
Hepatotoxicity	One case in letrozole+bosutinib metastatic breast cancer study (overall rate in the bosutinib program <0.1% (1/1209 patients) No cases of irreversible liver failure Mild to moderate, early onset, reversible liver enzymes elevations
Myelo-suppression	Controllable with dose modifications and/or optimal medical management
Pleural Effusion	Uncommon, unless previously observed during prior dasatinib or imatinib
Cardiac Safety	Low risk of severe cardiac events; infrequent pericardial effusions, arrhythmias or vascular disorders QT prolongation or LVEF decreases were rare

Kantarjian HM et al. Blood 2014; 123: 1309-18

Response to Bosutinib 3rd Line Therapy

- Dual Src & Abl inhibitor, no effect over c-kit or PDGFR
- 114 pts who failed imatinib (600mg) & dasatinib or nilotinib

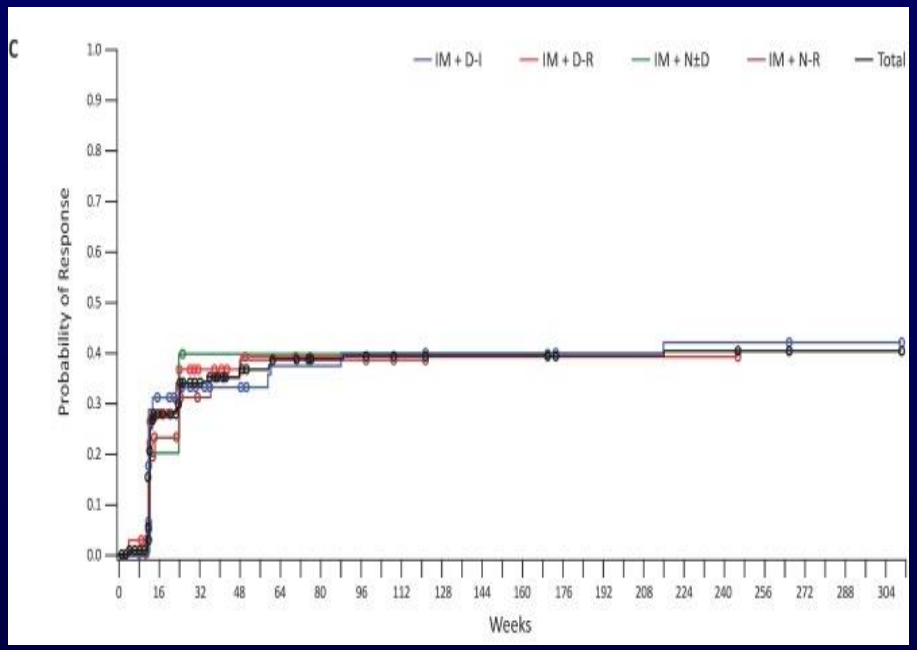
Response, %	IM + D resistant (n = 37)	IM + D intolerant (n = 50)	IM + NI resistant (n = 27)
CHR	68	76	76
MCyR	39	42	38
CCyR	22	40	31
PCyR	17	2	8
MMR	3	25	11
2-yr PFS	65	81	77

IM, imatinib; D, dasatinib; NI, nilotinib.

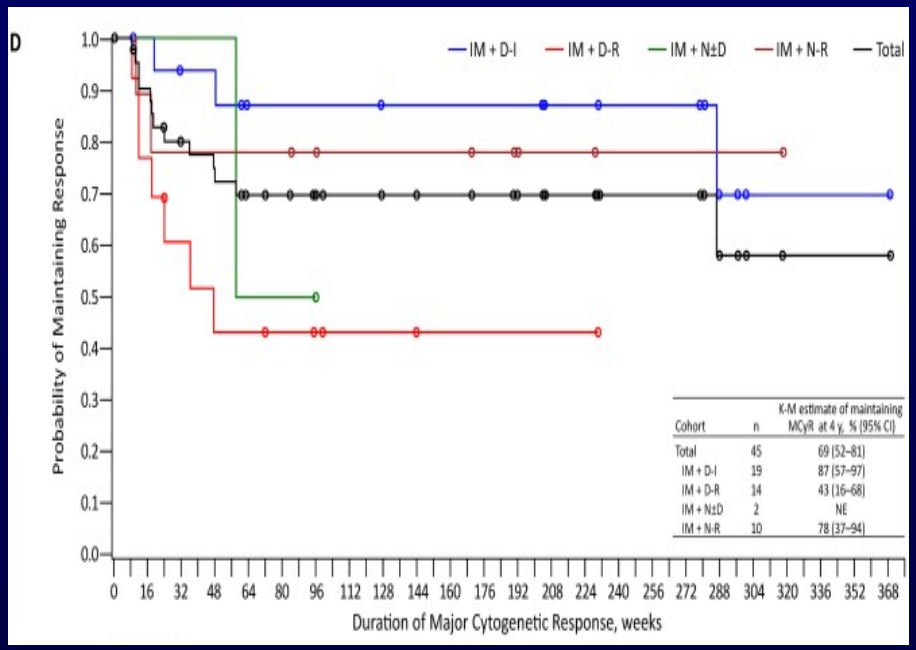
Cortes et al. Am J Hematol 2016; 91: 1206-14

Efficacy of Bosutinib After Imatinib And Dasatinib or Nilotinib

Cumulative Incidence of MCyR



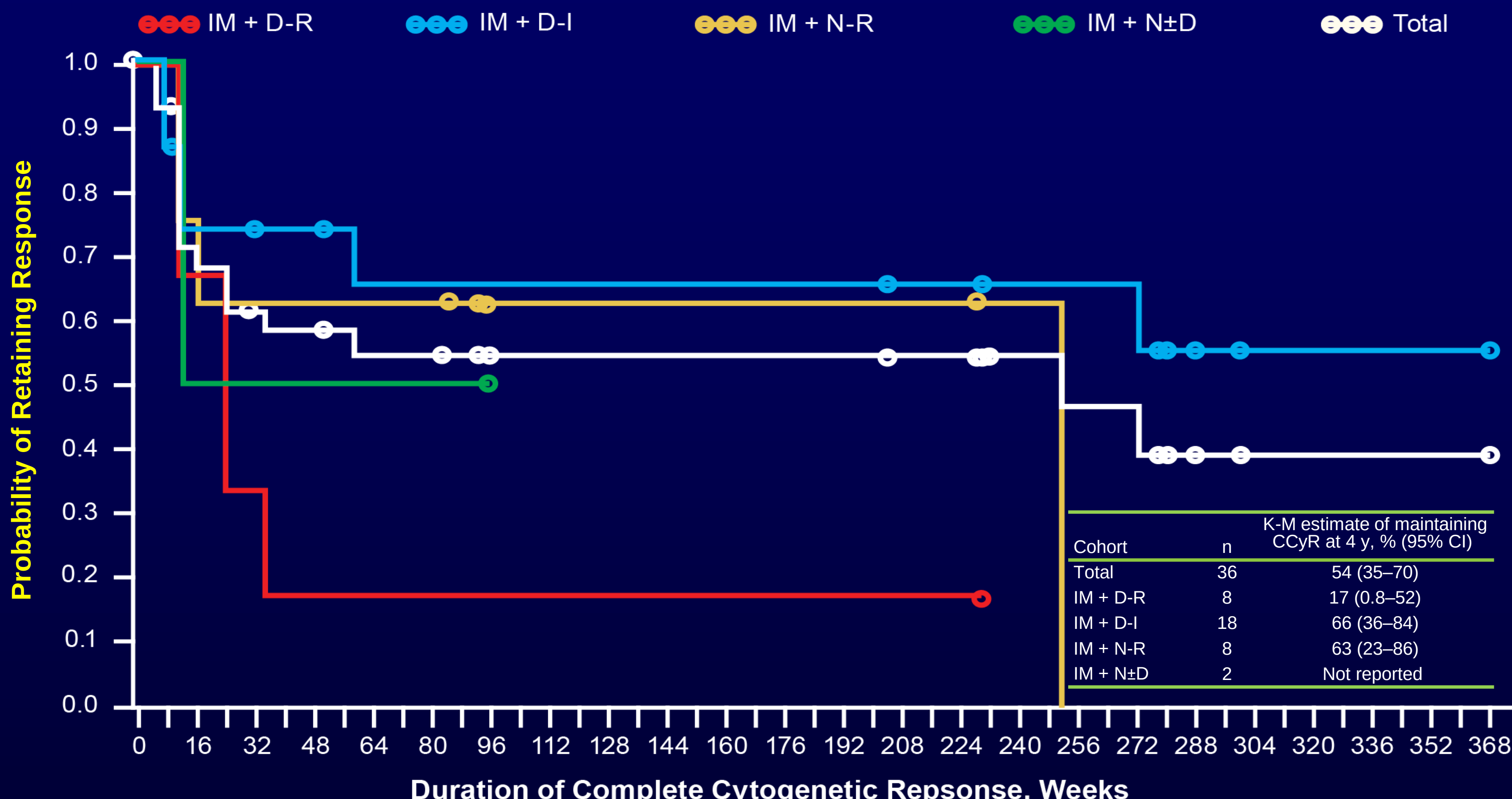
Duration of MCyR



- **Predictors of MCyR or CCyR: age <65 years; male; Ph+ ≤35%; prior interferon; and time from diagnosis to IM <6 mo.**
- **Predictors of inferior OS: No prior response to dasatinib or nilotinib.**
- **Predictors of PFS: Increased basophils.**

Cortes et al. Am J Hematol 2016; 91: 1206-14

Bosutinib 3rd Line Duration of CCyR



Cohort	n	K-M estimate of maintaining CCyR at 4 y, % (95% CI)
Total	36	54 (35–70)
IM + D-R	8	17 (0.8–52)
IM + D-I	18	66 (36–84)
IM + N-R	8	63 (23–86)
IM + N±D	2	Not reported

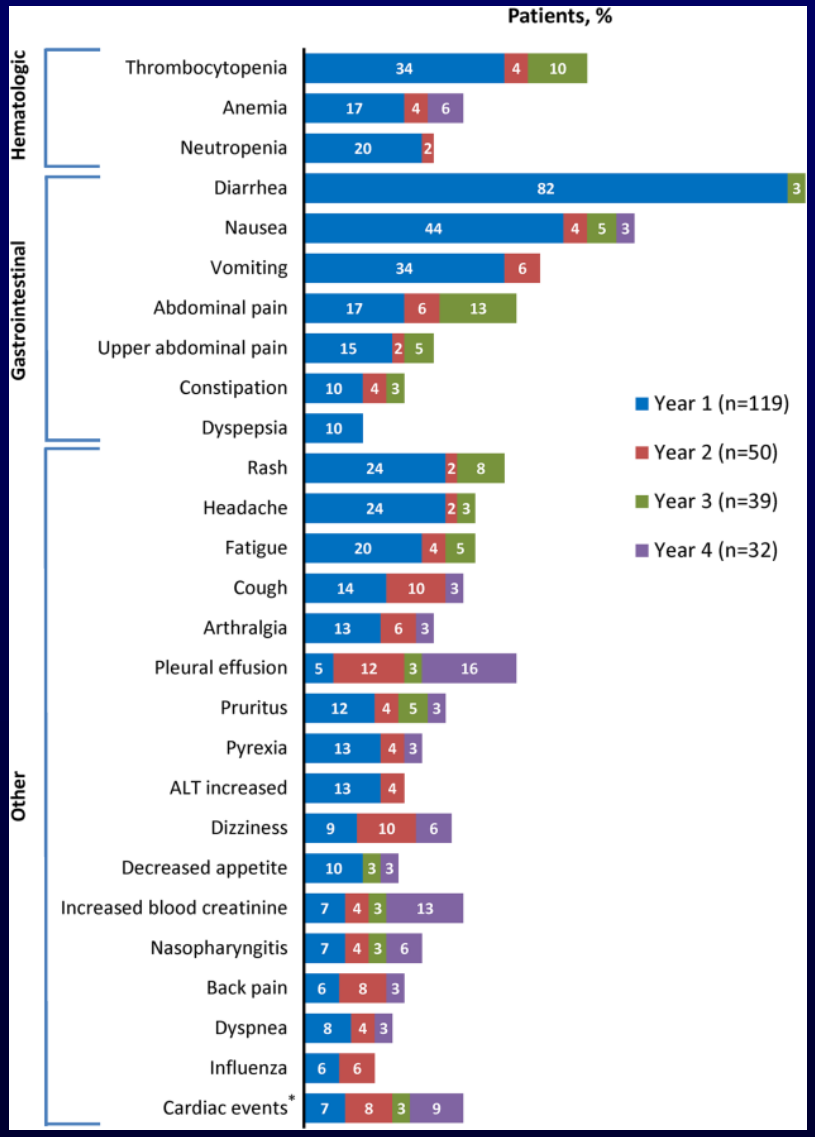
Subjects at risk, n

IM + D-R	8	6	4	4	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IM + D-I	18	14	11	11	10	10	10	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	7	7	7	6	6	6	6	6	6	4	3	2	1	1	1	1	1	1	1	1	1	0
IM + N-R	8	8	6	5	5	5	5	5	5	5	5	4	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IM + N±D	2	2	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	36	30	22	21	18	17	17	16	15	15	15	14	12	11	11	11	11	11	11	11	11	11	11	11	11	11	10	10	10	7	7	7	6	6	6	4	3	2	1	1	1	1	1	1	1	1	1	0

- **31% of responders still on-treatment at 4 years after initial response.**

Gambacorti-Passerini et al. ASH 2014; abstract 4559

Safety of Bosutinib After Imatinib And Dasatinib or Nilotinib by Year



Cortes et al. Am J Hematol 2016; 91: 1206-14

Study 200 (Advanced Disease): Clinical Responses

Response,[a] n (%)	Accelerated Phase		Blast Phase		Ph+ ALL
	Prior IM[b]	Other TKIs[c]	Prior IM[b]	Other TKIs[c]	
Hematologic response[d]					
Evaluable for response	43	29	34	26	22
MaHR	54	38	27	8	9
CHR	40	24	27	4	9
Cytogenetic response*					
Evaluable for response	46	26	30	24	20
MCyR	48	27	50	21	20
CCyR	35	23	37	17	20

[a]Patients were evaluable if they received at feast 1 dose of bosutinib, had a baseline and ≥1 post-baseline disease assessment for the corresponding endpoint, and did not enter the study in the best possible outcome for the corresponding endpoint

[b]Patients with prior imatinib therapy only

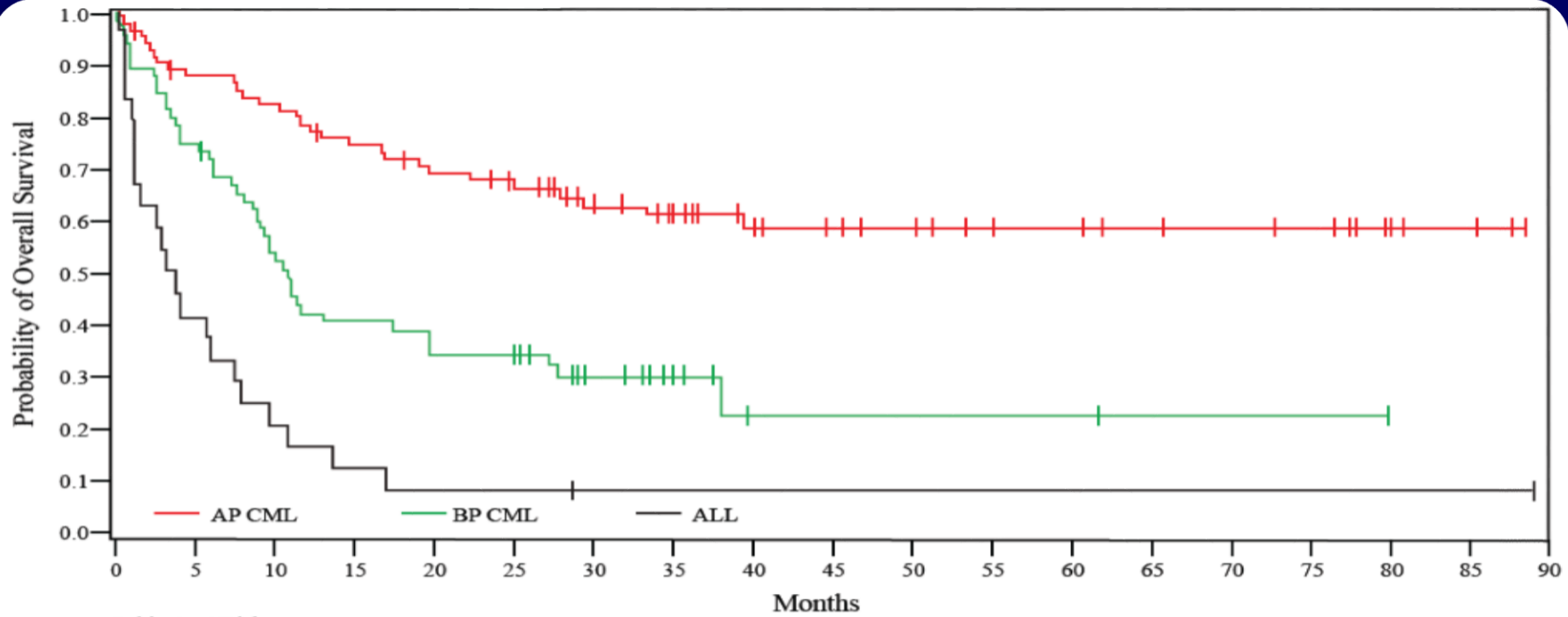
[c]Patients with prior other TKI therapies

[d]Includes patients with unconfirmed hematologic response, Median time to CHR was 23.4 weeks

* Median time to CyR was 24.0 weeks

Gambacorti-Passerini C et al. Am J Hematol 2015; 90: 755-68

Study 200 (Advanced Disease): Overall Survival



Subjects at Risk, n

AP CML	79	67	63	56	51	47	37	32	24	21	19	16	15	12	11	10	6	3	0
BP CML	64	47	33	25	21	20	13	7	2	2	2	2	2	1	1	1	0	0	0
ALL	24	10	5	3	2	2	1	1	1	1	1	1	1	1	1	1	1	1	0

	n	Median Duration of OS (95% CI), mo	Kaplan-Meier Estimate of OS (95% CI), %	
			Year 1	Year 2
AP CML				
2L	15	NR	81 (67–90)	66 (49–78)
≥3L	15	33.4 (14.6–NR)	73 (53–85)	45 (25–63)
Total	30	NR (33.4–NR)	78 (67–86)	59 (46–69)
BP CML				
2L	21	11.2 (9.4–NR)	44 (28–60)	28 (8–53)
≥3L	23	8.9 (4.1–17.4)	39 (22–57)	17 (6–33)
Total	44	10.9 (8.7–19.7)	42 (30–54)	23 (10–39)
ALL	22	3.6 (1.3–7.6)	17 (5–34)	8 (1–23)

Gambacorti-Passerini C et al. Am J Hematol 2015; 90: 755-68

Bosutinib After Prior TKI Failure

- Clinical efficacy after resistance or intolerance to 1 or more TKI
- Durable responses, adequate PFS and OS
- Very favorable safety profile
  - Early, manageable diarrhea, myelosuppression, liver toxicity
  - No cardiotoxicity
- Minimal cross intolerance with other TKI
- Dose adjustments maintain efficacy
- Excellent alternative to other TKI

Questions?

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