SESSION III: Chronic myeloid leukemia

PONATINIB

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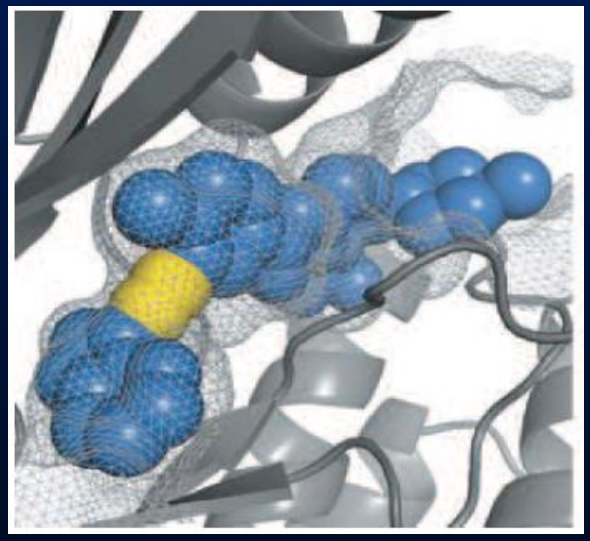
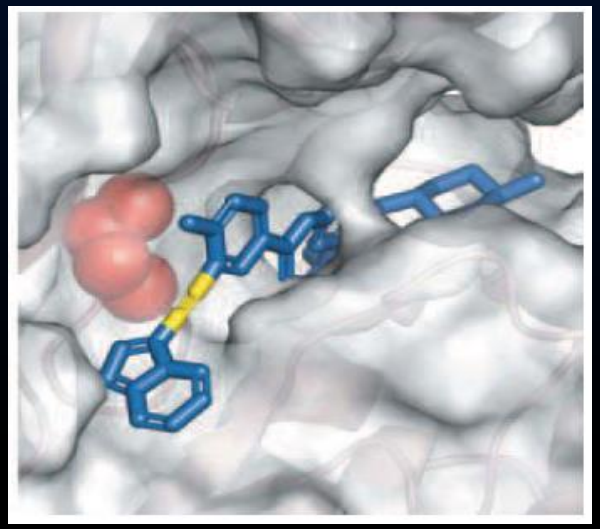
Ponatinib
A Pan-BCR-ABL Inhibitor

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Once-daily oral activity
- Half-life ≈ 22 hours
- Also targets other therapeutically relevant kinases:
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT





O'Hare T, et al. Cancer Cell. 2009;16:401-412

KINASE INHIBITION PROFILE OF AP24534 FOR NATIVE ABL, ABL T315I AND SELECTED KINASES

KINASE	IC 50 (nM)
ABL	0.37
ABL T315I	2.00
ABL, OTHER MUTANTS	0.30-0.44
LYN	0.24
cSRC	5.40
cKIT	12.50
VEGFR2	1.50
PDGFRa	1.10
FGFR1	2.20

O'Hare et al, Cancer Cell 2009;16:401-412

Phase 1 Study of Ponatinib Dose Selection for Phase 2

Safety* (all diagnoses)

Dose Cohort	N Patients treated	N Patients w/DLT	N Patients w/ Pancreatitis	% Patients w/ Pancreatitis
2 mg – 30 mg	31	0	3	10%
45 mg	**31**	**2**	**4**	**13%**
60 mg	19	6	4	21%

*Data for N=81 all treated patients.

Efficacy (CML CP patients only)

Dose Cohort	N Evaluable	N MCyR	% MCyR
30 mg	5	2	40%
45 mg	12	10	83%
60 mg	11	6	55%

- **45 mg once daily is the recommended phase 2 dose**

Cortes et al, ASH 2010 and NEJM 2012;367:2075-2088

Ponatinib PACE Study – Patient Population

	CP-CML n = 270*
Median [range] age, years	60 [18–94]
Median [range] time since diagnosis, years	7 [0.5–27]
Resistant to dasatinib or nilotinib, n/N (%)†	214/256 (84)
No mutation	138 (51)
Any mutation	132 (49)
T315I mutation	64 (24)
Median [range] follow-up, months	15.3 [0.1–25]

*Includes 3 CP-CML patients who were non-cohort assigned (post-imatinib, non-T315I), but treated.
†Denominator includes only patients who received prior dasatinib or nilotinib.

Cortes JE et al. *Blood*. 2012;120: Abstract 163.

Ponatinib PACE Study – Prior TKI Treatments

Prior TKI exposure, n (%)	CP-CML		Overall* N = 449
	R/I n = 203	T315I n = 64	
Imatinib only	0 (0)	10 (16)	21 (5)
Imatinib + (dasatinib OR nilotinib)†	74 (36)	31 (48)	172 (38)
Imatinib + dasatinib + nilotinib†	122 (60)	21 (33)	237 (53)
≥2 prior TKIs‡	199 (98)	53 (83)	417 (93)
≥3 prior TKIs‡	135 (67)	26 (41)	262 (58)

*Includes 5 patients (3 CP-CML, 2 AP-CML) who were non-cohort assigned (post-imatinib, non-T315I), but treated.
†Patients could have received other TKIs or anti-cancer therapy.
‡Includes approved and investigational agents.

Cortes JE et al. *Blood*. 2012;120: Abstract 163.

Ponatinib Phase II Study Responses to Therapy

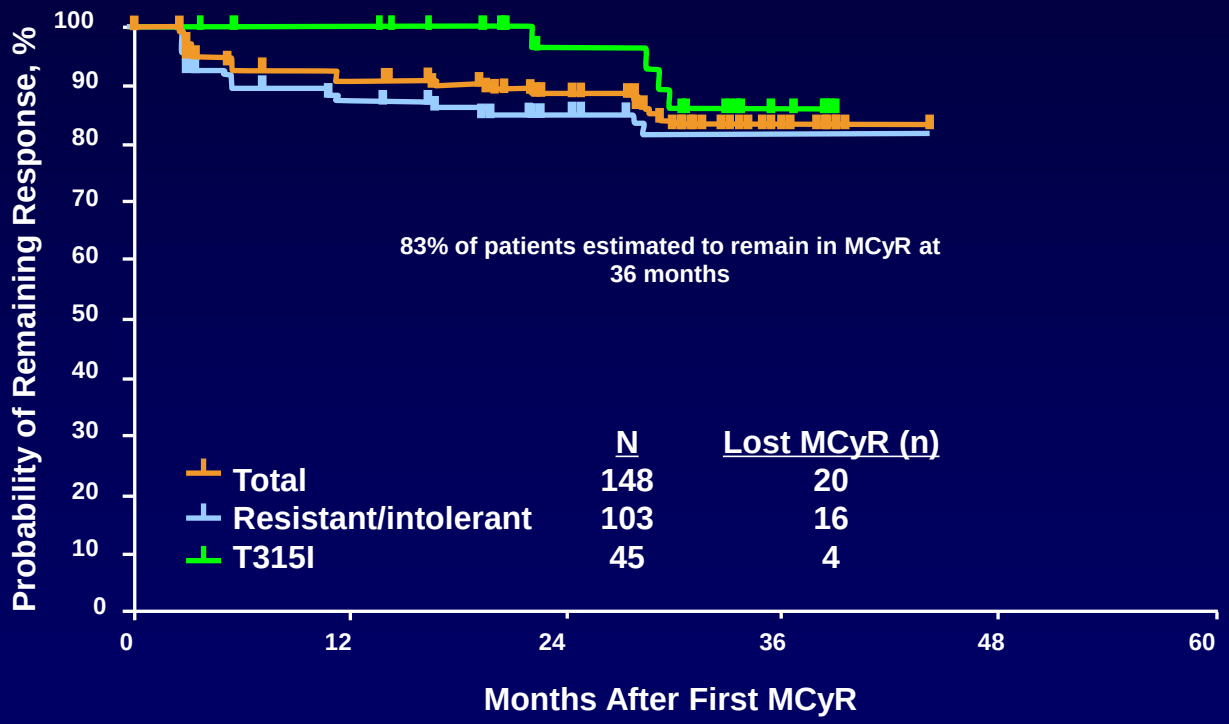
- Ponatinib 45 mg daily
- 93% ≥2 prior TKI, 58% ≥3 prior TKI
- Median follow-up 38.4 months (0.1-48.6 months)

	Percentage						
	CP-CML				AP-CML	BP-CML	Ph+ ALL
	MCyR	CCyR	MMR	$MR^{4.5}$	MaHR	MaHR	MaHR
R/I	55	48	33	19	62	32	50
T315I	72	70	58	34	61	29	36
Total**	59	53	39	22	61	31	41
Median mo to response	2.8	2.8	5.5	NR	0.7	1.0	0.7

Cortes J, et al. *Blood.* 2014;124: Abstract 3135. Kantarjian HM, et al. *J Clin Oncol.* 2014;21(5s): Abstract 7081.

Efficacy of Ponatinib in CP-CML

Duration of Response



- 83% estimated to maintain MCyR at 36 months

Cortes JE, et al. *Blood.* 2014;124: Abstract 3135.

Ponatinib – prescribing information

EU	CML and Ph+ ALL - Second line after dasatinib or nilotinib failure (when imatinib is not considered an appropriate treatment) - T315I mutation

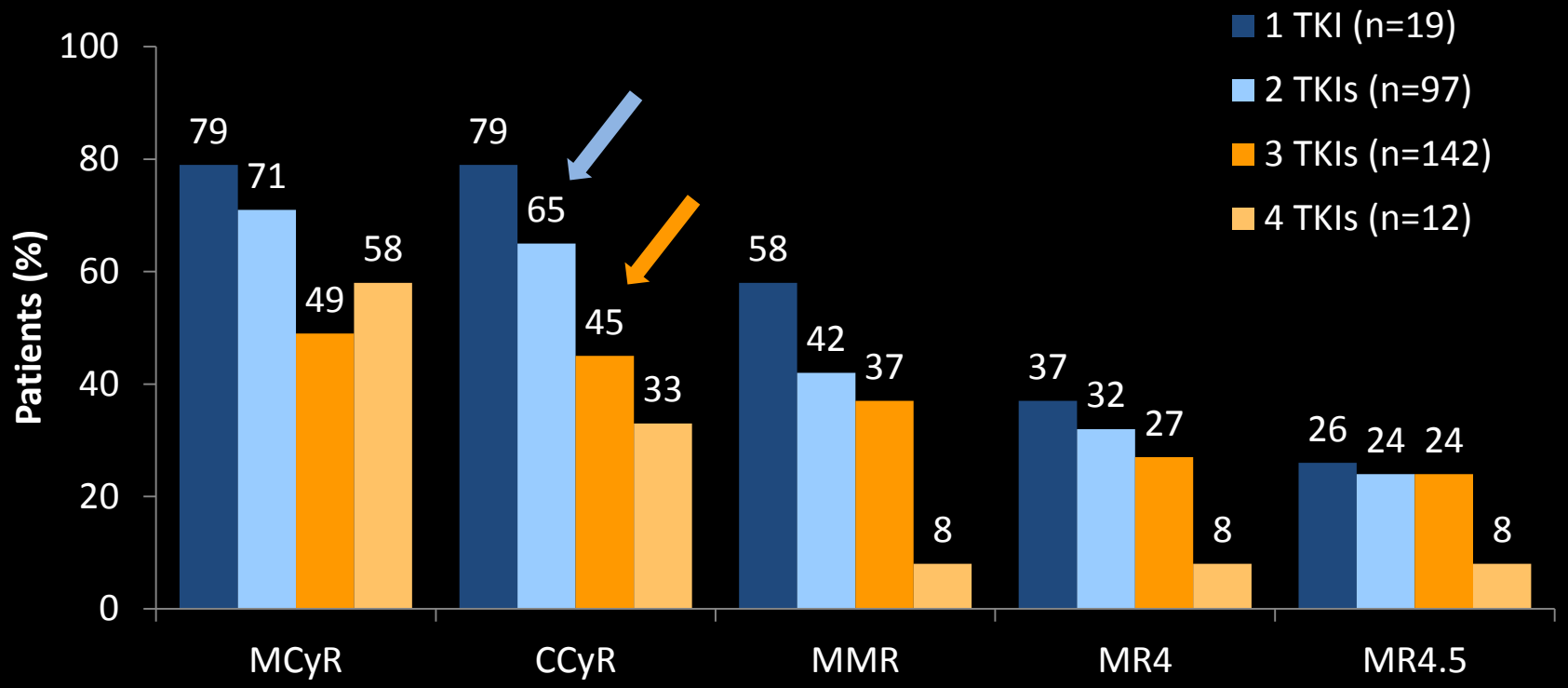
European LeukemiaNet 2013 Treatment Recommendations

First-line	Imatinib 400 x 1, nilotinib 300 x 2, or dasatinib 100 x 1
Second-line	
Intolerance	• Switch to another TKI, taking into account comorbidities and side effects
Failure	• Switch from imatinib to another TKI, taking into account mutations, comorbidities, and side effects • Switch from nilotinib to dasatinib, bosutinib, or ponatinib • Switch from dasatinib to nilotinib, bosutinib, or ponatinib • Allogeneic stem cell transplant
Third-line	• Switch to another TKI (ponatinib) • Allogeneic stem cell transplant • Experimental treatment

Blood 2013

Response to Ponatinib in CP-CML by Number of Prior TKIs: Response at Any Time (n=270)

> Rates of cytogenetic and molecular response to ponatinib were higher with fewer prior TKIs



MCyR, 0%–35% Ph+ metaphases; CCyR, 0% Ph+ metaphases; MMR, ≤0.1% BCR-ABL^{IS}; MR4, ≤0.01% BCR-ABL^{IS} or undetectable disease in cDNA with ≥10,000 ABL transcripts; MR4.5, ≤0.0032% BCR-ABL^{IS} or undetectable disease in cDNA with ≥32,000 ABL transcripts

Hochhaus et al ASH 2015

PACE: Response by Baseline Mutation Status

Mutation Status at Entry	MCyR n/N (%)	CCyR n/N (%)
CP – R/I Cohort		
Any mutations	30/66 (46)	24/66 (36)
No mutation	49/125 (39)	40/125 (32)
CP – T315I Cohort		
T315I only	19/29 (66)	15/29 (52)
T315I + additional mutation(s)	9/14 (64)	9/14 (64)

Cortes JE et al. *Blood*. 2012;120: Abstract 163.

Sequential TKI

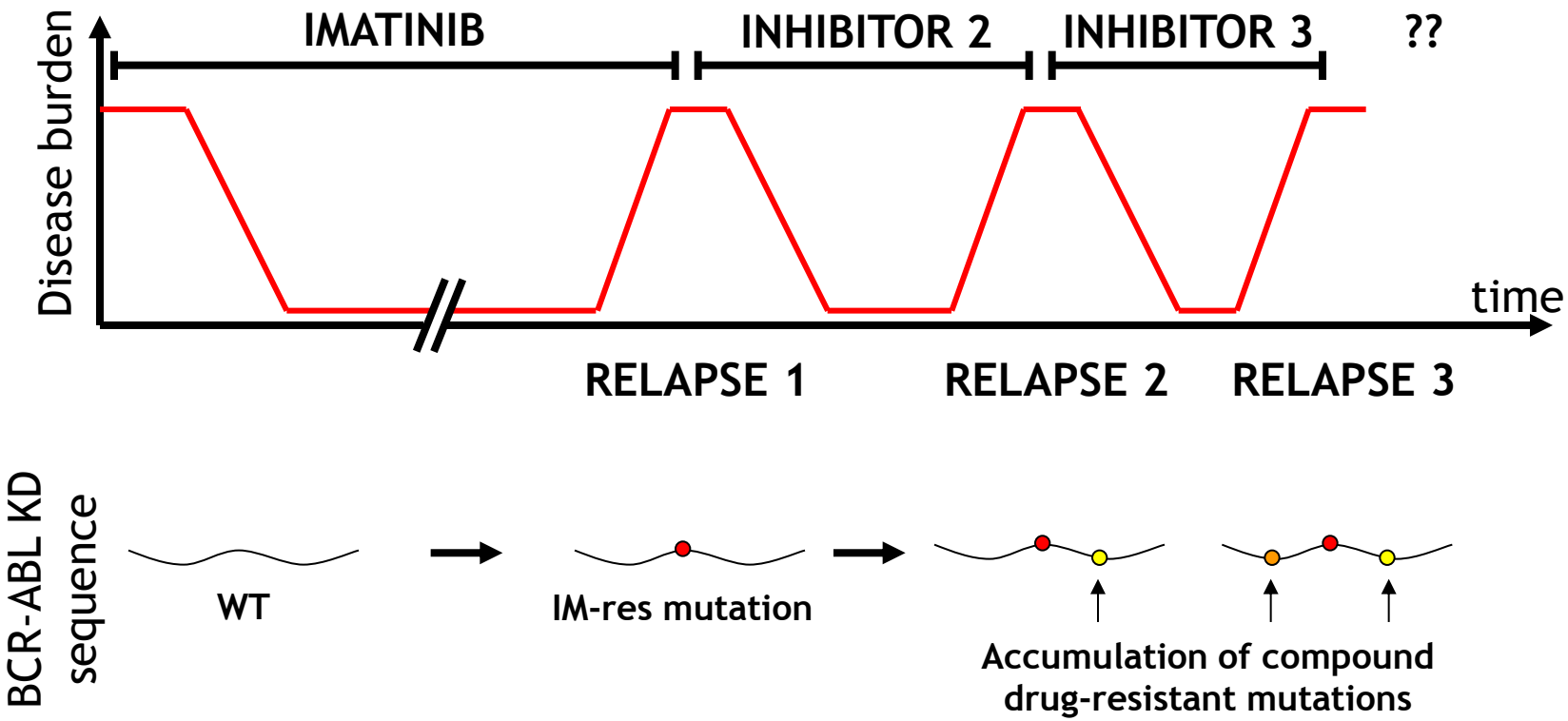
- **Non–head-to-head comparison of trials reporting results for CP-CML patients**

Study	Garg, et al 2009[1]	Rossi, et al[2]	Ibrahim, et al[3]	Giles, et al[4]	Khoury, et al[5]
Third-line treatment	Dasatinib or nilotinib	Dasatinib or nilotinib	Dasatinib or nilotinib	Nilotinib	Bosutinib
N	25 (CP)	66 (91% CP)	26 (CP)	37 (CP)	118 (CP)
CCyR, %	**24**	**15**	**35**	**24**	**24**
OS	Median NR, Median FFS 20 mos	Median 110 mos	30 mos, 47%	Median NR 18 mos, 86%	Median NR 24 mos, 83%

FFS=failure-free survival; NR=not reported.

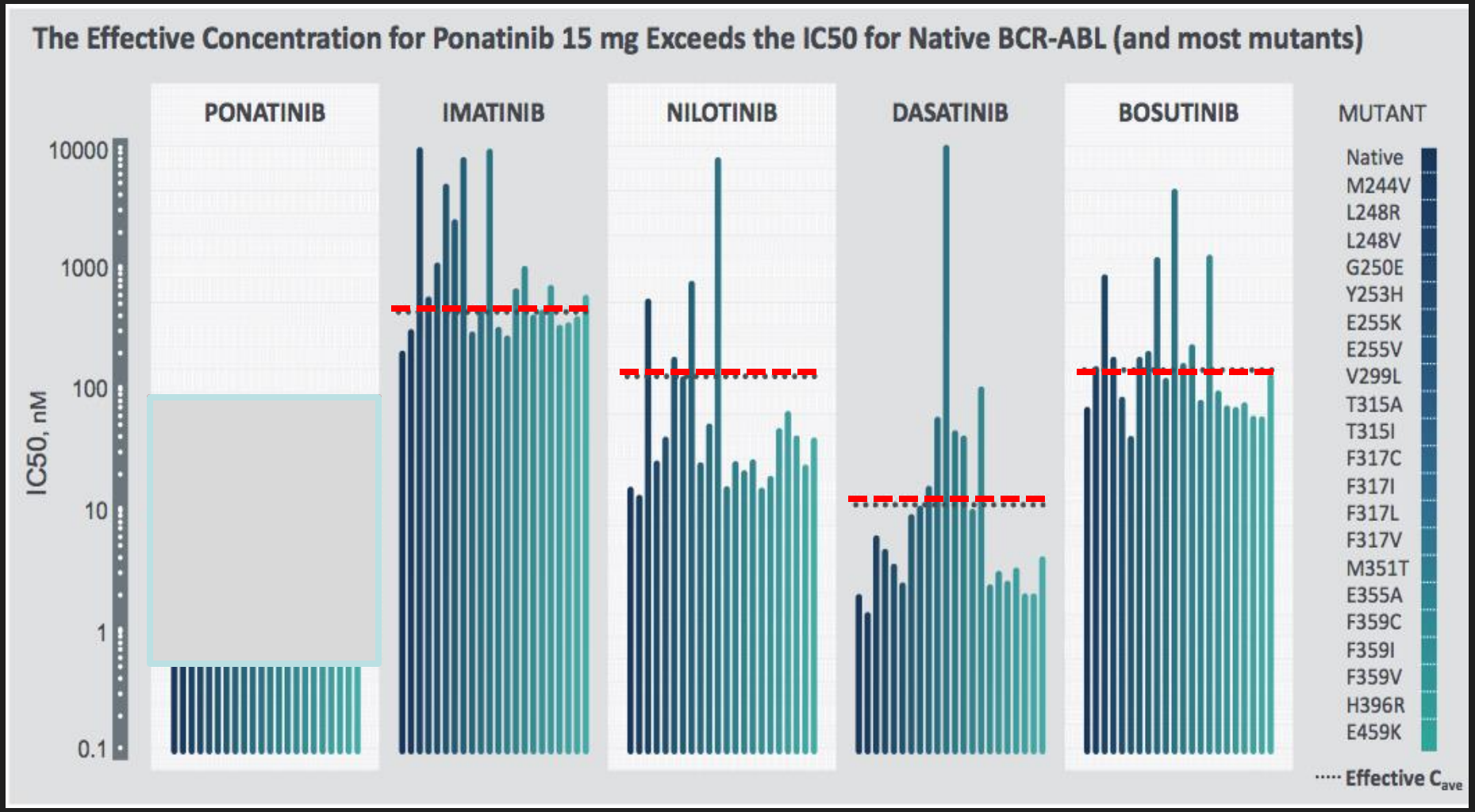
1. Garg RJ, et al. *Blood.* 2009;114:4361-4368. 2. Rossi AR, et al. Poster. ASH. 2010 (abstr 2294). 3. Ibrahim AR, et al. *Blood.* 2010;116:5497-5500. 4. Giles FJ, et al. *Leukemia.* 2010;24:1299-1301. 5. Khoury HJ, et al. *Blood.* 2012;119:3403-3412.

Sequential therapy with TKIs: the Ph+ clone knows how to find a way out



Modified from Shah et al, JCI 2007 Sep;117(9):2562-9.

Effective concentration of ponatinib



Gozgit, et al. *Blood.* 2013;122 (abstr 3992).

In Vitro Heat Map Based on Optimized Effective C_{ave}/IC_{50} Cutoffs

- In vitro IC_{50} values for imatinib, nilotinib, dasatinib, bosutinib, and ponatinib against 21 BCR-ABL mutants determined as described previously[1]
- Effective C_{ave} /IC_{50} values for each TKI/mutant were used to predict CCyR rates based on cutoffs generated in the nilotinib and dasatinib training set

Predicted Response Rate
0% CCyR
>0 to <25% CCyR
≥25% CCyR

✓ Indicates correct prediction
X Denotes incorrect prediction; symbol color indicates the correct category

In Vitro IC_{50} Values (nM) with CCyR Rate Prediction Overlaid					
BCR-ABL	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Native	201	15	2	71	3
M244V	287	12 ✓	2 ✓	147	3 ✓
L248R	10000	549	6	874	8
L248V	586	26	5 ✓	182	4
G250E	1087	41 ✓	4 ✓	85	5 ✓
Y253H	4908	179 X	3 ✓	40	5
E255K	2487	127 ✓	9 X	181	6 ✓
E255V	8322	784	11 X	214	16
V299L	295	24	16	1228	4 ✓
T315A	476	50	59	122	4
T315I	9773	8091 ✓	10000 ✓	4338	6 ✓
F317C	324	16	45	165	3
F317I	266	25	40	232	7
F317L	675	21 ✓	10 ✓	82	4 ✓
F317V	1023	26	104	1280	10
M351T	404	15 ✓	2 ✓	97	4
E355A	441	18	3	74	7
F359C	728	47	2 ✓	70	6
F359I	324	64	3 ✓	76	11
F359V	346	41 X	2 ✓	59	4 ✓
H396R	395	23 X	2 ✓	60	4 X
E459K	612	38	4 ✓	127	5

1. Gozgit MJ, et al. [Abstract 3992). Presented at the 55th ASH Annual Meeting and Exposition; December 7-10, 2013; New Orleans, LA, USA.

Rivera et al, ASH 2015

Incidence of Arterial and Venous Thrombotic Events

	Total (N = 449)		CP-CML (n = 270)	
	AE	SAE	AE	SAE
Cumulative exposure, patient-years	778.9		577.4	
ATEs, n (%)	99 (22)	78 (17)	74 (27)	60 (22)
Cardiovascular	52 (12)	37 (8)	36 (13)	28 (10)
Cerebrovascular	37 (8)	28 (6)	31 (11)	23 (9)
Peripheral vascular	37 (8)	27 (6)	28 (10)	20 (7)
Exposure-adjusted ATEs, number of patients w/events per 100 pt-yrs	12.7	10.0	12.8	10.4
VTEs, n (%)	24 (5)	20 (4)	12 (4)	10 (4)
Exposure-adjusted VTEs, number of patients with events per 100 pt-yrs	3.1	2.6	2.1	1.7

Cortes JE, et al. *Blood.* 2014;124: Abstract 3135.

Commonly Reported non-hematological adverse effects of TKIs in prospective Clinical Trials

	Imatinib [1[a], 8, 29[a], 34, 71, 15, 16[a]]		Dasatinib [10, 23, 36, 38, 66[a], 17]		Nilotinib [11, 24, 39, 40, 51, 18, 19]		Bosutinib [9, 25, 70, 20]		Ponatinib [21, 22, 37, 58[a], 55]	
Adverse event	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Cardiac (non-ischemic)	3–8 %	<1 %	2–5.8 %	–	<1–3 %	–	4–6 %	2 %	2–29 %	2–14 %
CHF	<1–[a]2 %	[a]<1 %	1–2 %	<1–2 %	NR	NR	NR	NR	7 %	4 %
Arrhythmia/rolonged QT	2–4 %	–	2 %	–	1–2 %	–	2 %	<1 %	2 %	2 %
Hypertension	<1–4 %	<1 %	NR	NR	NR	NR	6 %	2 %	9–68 %	2–39 %
	<1–2 %	<1 %	3–9 %	NR	2–15 %	NR	<1–3 %	<1–3 %	7–[a]24 %	7–14 %
Angina	[a]<1–11 %	<1 %	NR	NR	<1 %	–	NR	NR	16 %	–
CV/arterial ischemic event	<1[a]–2 %	<1 %	4–9 %	NR	3–6 %	3–6 %	<1 %	<1 %	4–13 %	4–8 %
PAOD	<1 %	NR	NR	NR	1.5–6 %	1–6 %	NR	NR	5–[a]7 %	2–6 %
Cerebrovascular	<1 %	NR	<1 %	NR	<1 %	<1 %	<1 %	NR	4–[a]7 %	2–4 %

J.J. Moslehi and Michael Deininger, JCO:33 (35), 2015

Flexibility of ponatinib

Risk Factors for Arteriovascular Events With Ponatinib

- 671 ponatinib-treated patients from phase I, II and III
- Median treatment duration: 224 days
- Median dose intensity: 37.2 mg/d

Covariate	Odds Ratio	*P* Value
Dose intensity	1.71	<.001
Hx of diabetes	1.60	.11
Hx of ischemic disease	2.64	<.001
Age	1.63	<.001
Log baseline platelets	1.36	.26
Log baseline neutrophils	1.04	.83
Number of prior TKI	1.20	.10
Time since diagnosis	1.58	.05

- Each 15-mg decrease in ponatinib dose intensity predicted 40% [illegible]

Knickerbocker R, et al. *Blood.* 2014;124: Abstract 4546.

PACE Trial: ATEs and VTEs

	CP-CML (N=270)		TOTAL (N=449)	
	AE, n (%)	SAE, n (%)	AE, n (%)	SAE, n (%)
Cumulative exposure, patient years	480.8		659.2	
Arterial thrombotic events (ATE)	61 (23)	44 (16)	86 (19)	61 (14)
Cardiovascular	27 (10)	20 (7)	43 (10)	29 (7)
Cerebrovascular	27 (10)	18 (7)	33 (7)	23 (5)
Peripheral vascular	23 (9)	14 (5)	31 (7)	19 (4)
Exposure-adjusted* incidence of ATEs	13	9	60	43
Venous thromboembolic events (VTE)	11 (4)	7 (3)	23 (5)	14 (3)
Exposure adjusted* incidence of VTEs	2	2	47	26

- Median time to onset of ATEs in CP-CML: 281 (8-952) days
- Median time to onset of VTEs in CP-CML: 604 (62-802) days

Kantarjian, et al. *J Clin Oncol.* 2014;32:5s (suppl; abstr 7081). ARIAD Pharmaceuticals, Inc. Data on File. 06 Jan 2014.

Impact of Prospective Dose Reductions

- The majority of patients who underwent dose reductions maintained their response 1 year post-reduction
  - 95% of patients in MCyR
  - 94% of patients in MMR

Cortes JE, et al. *Blood.* 2014;124: Abstract 3135.

PACE Trial

DOSE MODIFICATION WITHIN FIRST 12 MONTHS*

206/267 CP-CML patients=78%

DOSE MODIFICATION AT ANY TIME DURING TREATMENT

229/267 CP-CML patients=86%

MEDIAN TIME TO DOSE MODIFICATION: **29 days** (range 2-320)

DOSE REDUCTION†

At least 1 reduction, n (%)	172 (64)
>1 reduction, n (%)	74 (28)
Median time to first reduction, days (range)	64 (2-344)
Median time on reduced dose, days (range)	156 (1-362)

DOSE INTERRUPTION†

At least 1 interruption, n (%)	199 (75)
>1 interruption, n (%)	126 (47)
Median time to first interruption, days (range)	29 (3-320)
Median duration of interruption, days (range)	35 (3-309)

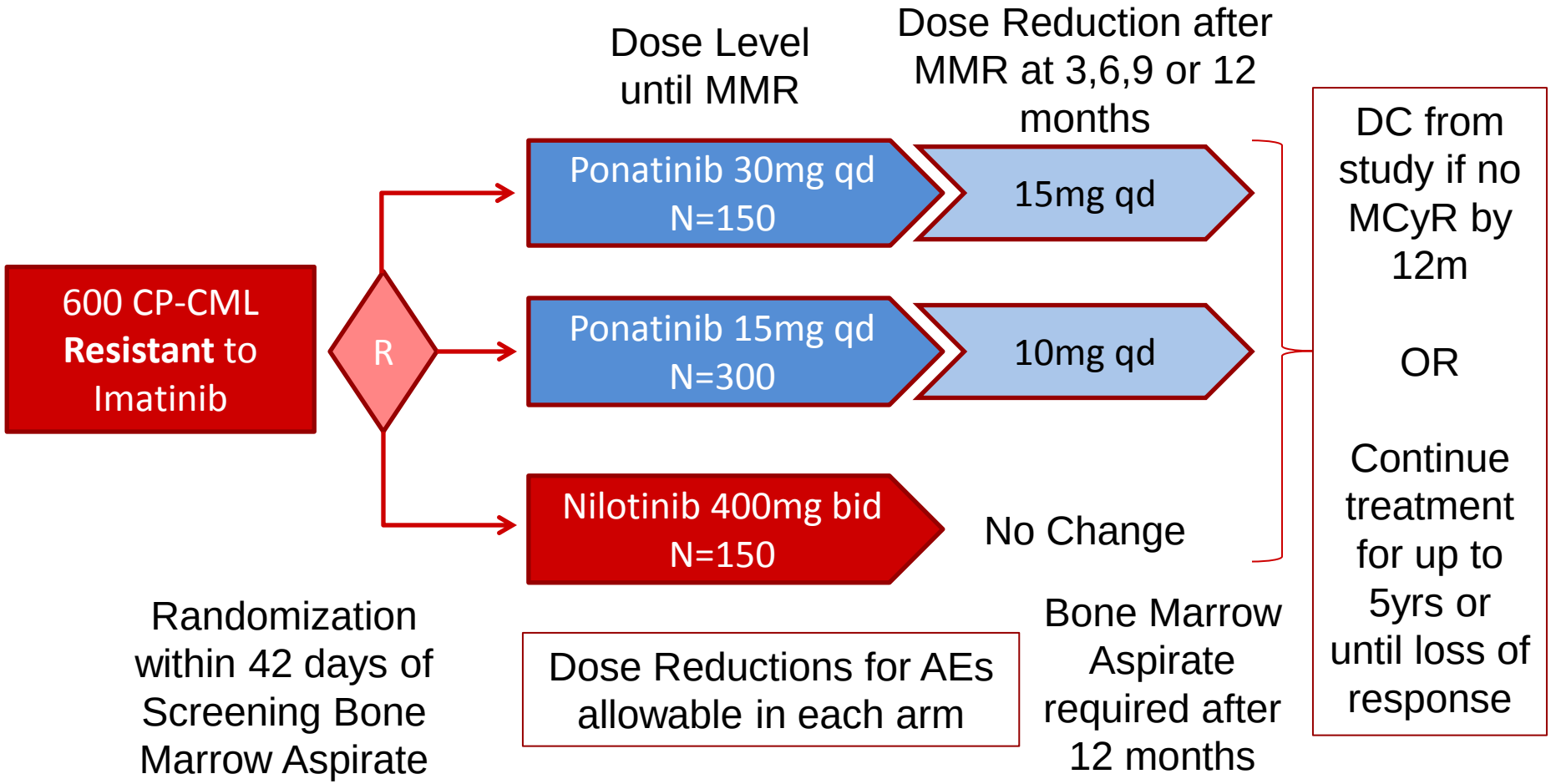
Hochhaus, et al. *J Clin Oncol*. 32:5s,2014 (suppl; abstr 7084).

Impact of Prospective Dose Reductions

- The majority of patients who underwent dose reductions maintained their response 1 year post-reduction
  - 95% of patients in MCyR
  - 94% of patients in MMR
- Similar maintenance of response was seen in patients who did not have dose reductions

Cortes JE, et al. *Blood.* 2014;124: Abstract 3135.

OPTIC-2L (AP24534-15-303)



OPUS Trial

Optimizing **P**onatinib **US**e A GIMEMA phase 2 study of the efficacy and risk profile of ponatinib, 30 mg once daily, in Chronic Myeloid Leukemia (CML) Chronic Phase (CP) patients resistant to imatinib.

Optimization of the dose at MMR

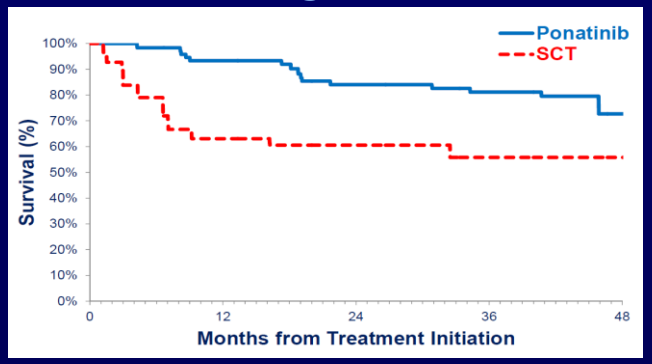
- ✓**The initial dose of ponatinib is 30 mg once daily**
- ✓**The MR is evaluated every 4 weeks.**
- ✓**At confirmed MMR > dose reduced to 15 mg daily**
- ✓**Than, QPCR every 12 weeks**
- ✓**BCR-ABL > 1% > dose back to 30 mg once daily**

Ponatinib or SCT for T315I CML

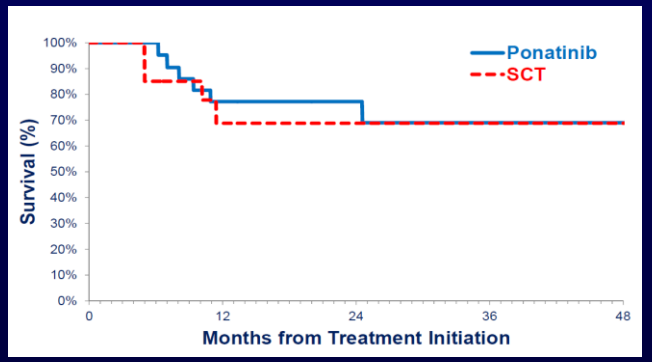
- Pts ≥18 yrs with CML *T315I* in any stage enrolled in PACE (n=449) or EBMT (1999-2010; n=222)
- Median age (yr): CP 53 vs 48; AP 55 vs 46; BP 47 vs 44; Ph+ ALL 55 vs 36

Disease group	Median survival (mo)	
	PACE	EBMT
CP	NR	103
AP	NR	56
BP	7	11
Ph+ ALL	7	32

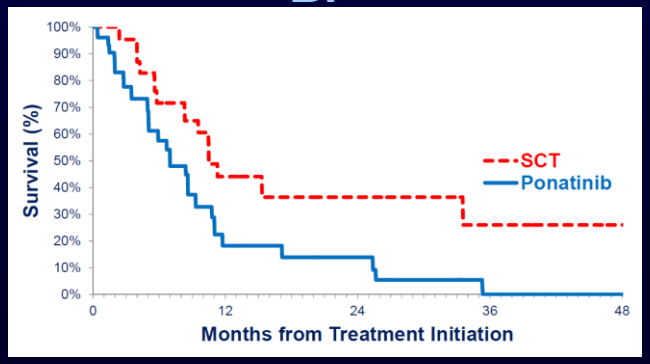
CP



AP



BP



Nicolini FE, et al. *Blood.* 2015;126: Abstract 480.

SESSION III: Chronic myeloid leukemia

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