2017

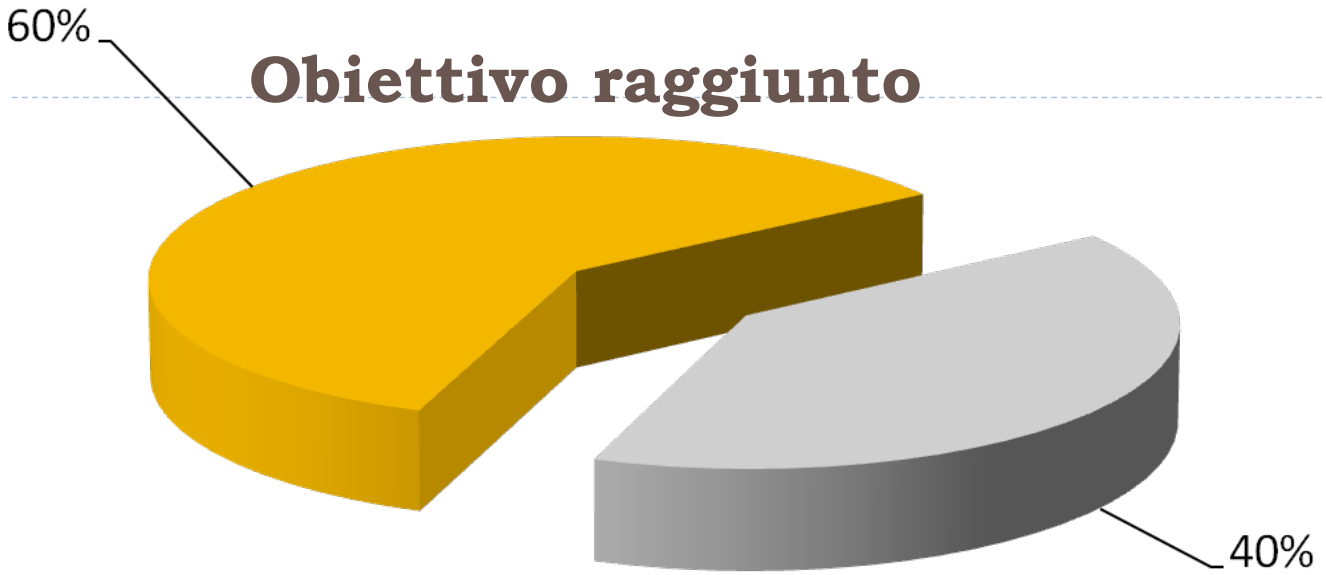
Cesena, 16 Settembre

Progetto Ematologia Romagna

Appunti di terapia

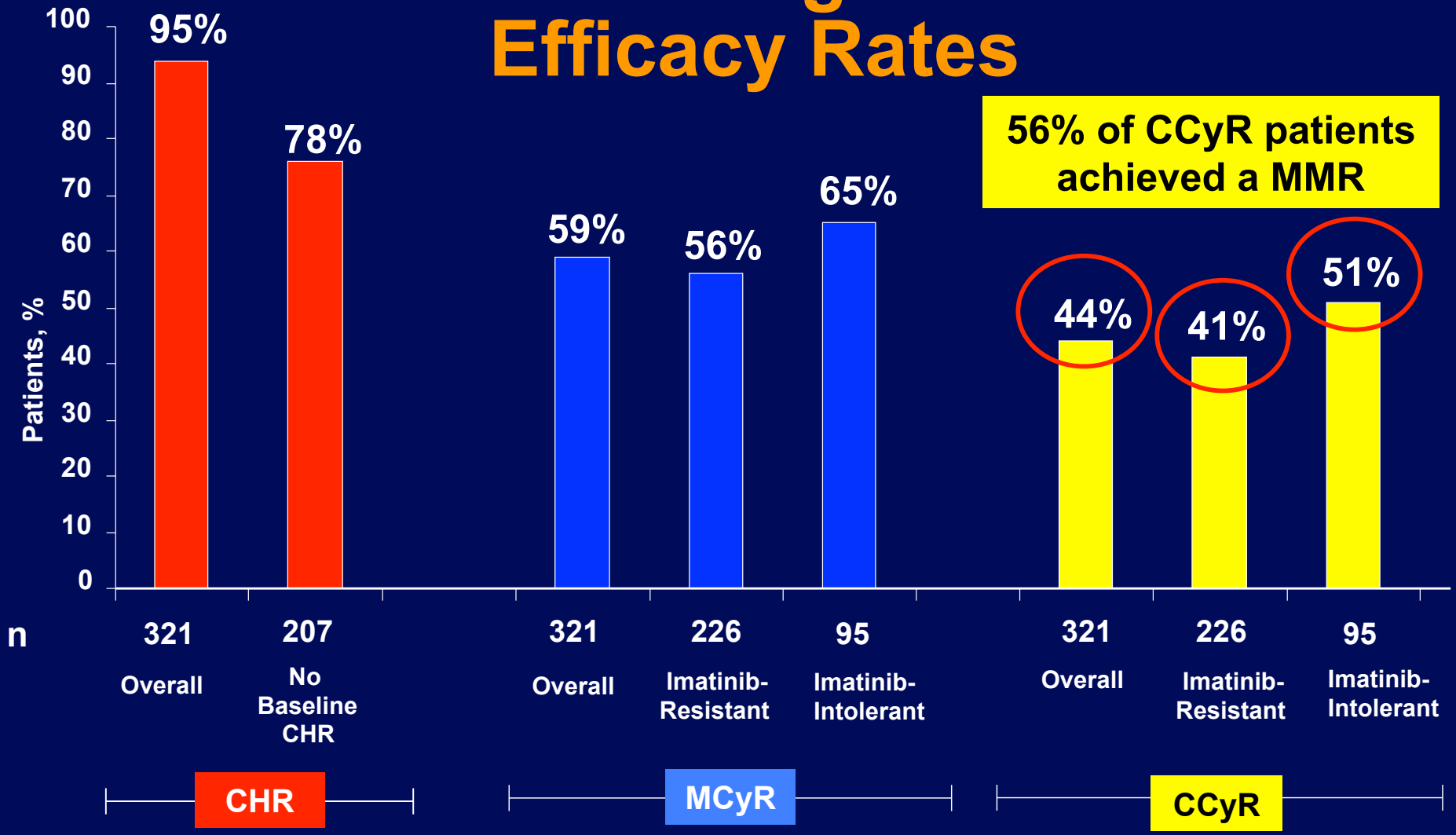
Mario Tiribelli

Imatinib front-line… va bene per tutti?



- 5% Intolleranza
- 18% Resistenza
- 17% Perdita risposta

Nilotinib 400 mg in CML-CP Efficacy Rates

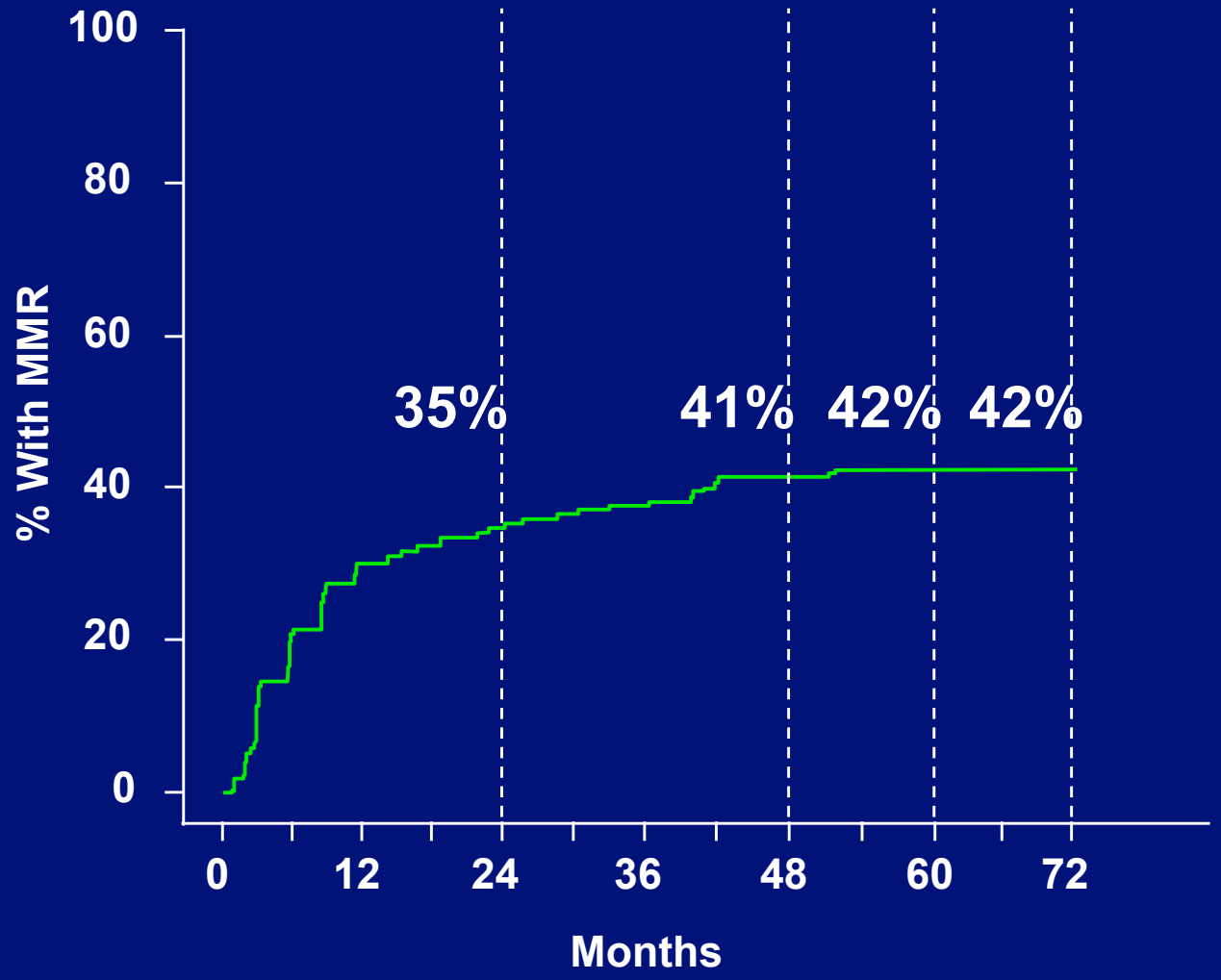


Patients with a minimum follow-up of 24 months

Kantarjian HM, et al. *J Clin Oncol.* 2009;27(15S): Abstract 7029.

6-years follow-up - CA180-034

Major Molecular Response (dasatinib 100 mg QD)

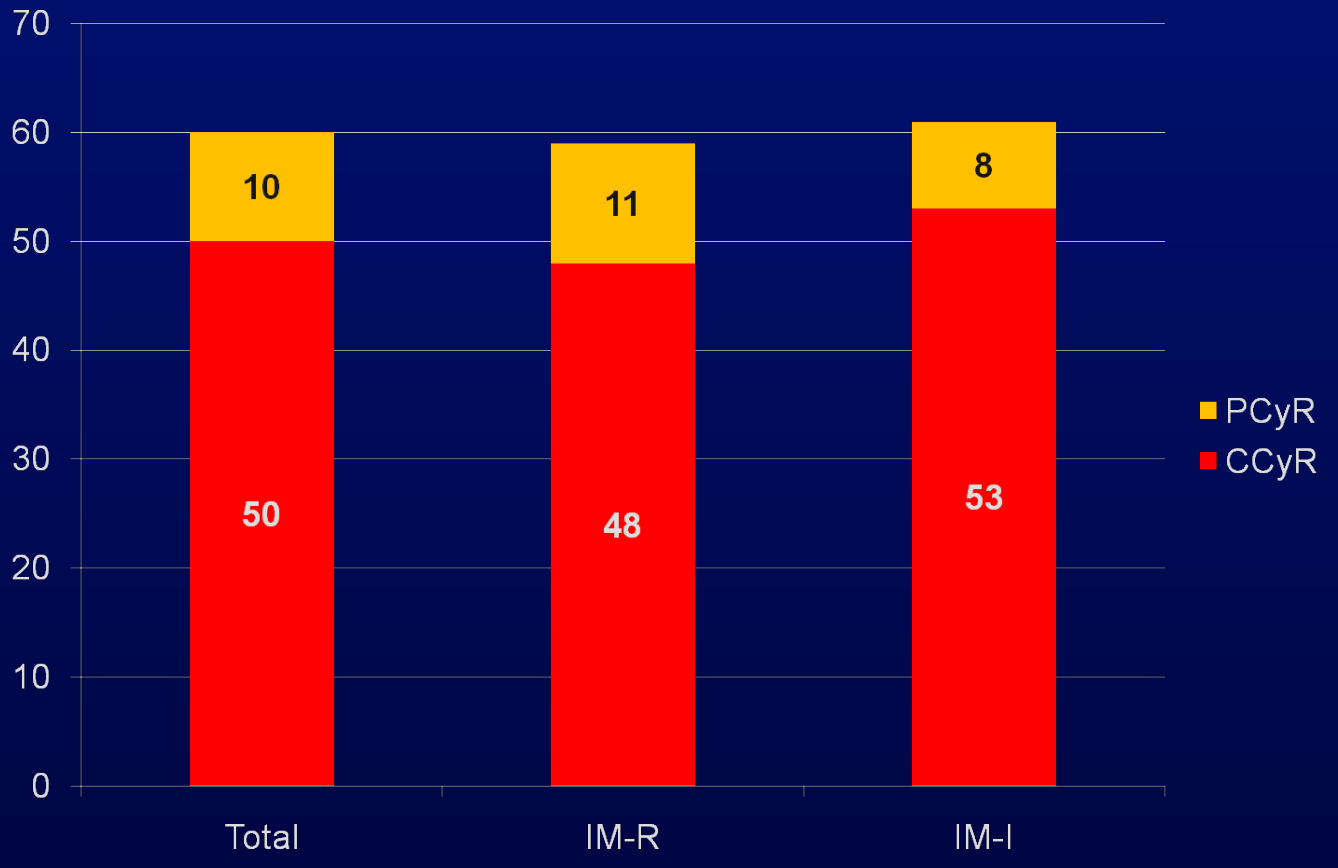


Shah N et al. ASCO 2012. Abs n. 6506

Protocol N. CA 180-034 (clinicaltrials.gov NCT00123474)

Bosutinib 2nd Line – Efficacy N = 262

262/284 patients were evaluable for cytogenetic response by 5 years



Responders: improvement from the baseline assessment or stable response
Evaluable patients: ≥1 bosutinib dose and valid baseline cytogenetic assessment

Lipton et al. *J Clin Oncol*. 2015; 33(suppl): Abstract 7076
Cortes et al. *Blood* 2011; 118 (17):4567-4577

Inibitori di seconda e terza generazione dopo intelleranza/resistenza a imatinib: efficacia

	DASATINIB	NILOTINIB	BOSUTINIB	PONATINIB*
CCyR	**50%**	**44%**	**48%**	**46%**
MMR	**37%**	**28%**	**35%**	**34%**
MR^4 / CMR	n.a.	n.a.	28%	15%
EFS a 2 anni	n.r.	53%	n.r.	n.r.
PFS a 2 anni	80%	64%	81%	80% (@ 1 anno)
OS a 2 anni	**94%**	**87%**	**91%**	**94% (@ 1 anno)**

*** pazienti con resistenza/intolleranza a più TKIs**

Shah N. et al, Haemotologica 2010;95:232-240. Kantarjian H. et al, Blood 2011;117:1141-1145. Cortes J.E. et al, Blood 2011;118:4567-4576. Cortes J.E. et al, N Engl J Med 2013;369:1785-1796.

Quanti pazienti rimangono in trattamento con TKI di seconda generazione?

Dasatinib IIa linea, F-U 72 mesi

Table 1. Patient disposition

	100 mg once daily (n = 165)	
	No.	%
On treatment	51	31
Reason for discontinuation		
Disease progression*	34	21
Study drug toxicity	34	21
Patient or investigator request	24	15
Adverse event unrelated to drug	7	4
Other†	15	9

≅30%

Shah et al. Blood. 2014;123:2317-2324

Nilotinib IIa linea, F-U 48 mesi

Table 1. Patient disposition

Disposition	*No. of Patients (%) (N = 321)*
Discontinued study	224 (69.8)
Disease progression	96 (29.9)
Adverse events	*66 (20.6)*
Drug-related	53 (16.5)
Subjects who withdrew consent	26 (8.1)
Abnormal test results	4 (1.2)
Death	4 (1.2)
Abnormal laboratory values	3 (0.93)
Lost to follow-up	3 (0.93)
Other[a]	22 (6.9)

[a]Includes administrative issues, protocol violations and not stated.

≅30%

Giles et al. Leukemia 2013;27:107–112

REAL LIFE COMPARISON OF DASATINIB AND NILOTINIB AS SECOND-LINE THERAPY AFTER IMATINIB FAILURE IN CHRONIC PHASE CML

Table 1. Patients' characteristics at diagnosis and at start of 2G-TKI			
	DAS (n = 95)	**NIL (n = 68)**	**p**
Age median, yrs (range)	58 (18-88)	54 (20-80)	0.43
Sex, M/F ratio	56 / 39	44 / 24	0.56
BCR-ABL: b_2a_2	38 (40%)	30 (44%)	0.72
b_3a_2	35 (37%)	19 (28%)	0.31
both	16 (17%)	7 (10%)	0.23
other/unknown	6 (6%)	12 (18%)	**0.04**
Sokal: Low	32 (34%)	31 (46%)	0.17
Intermediate	42 (44%)	27 (40%)	0.68
High	19 (20%)	9 (13%)	0.36
Unknown	2 (2%)	1 (1%)	1.00
EUTOS: Low	81 (85%)	59 (87%)	0-97
High	8 (9%)	4 (6%)	0.76
Unknown	6 (6%)	5 (7%)	1.00
IM therapy median, mo (range)	19 (1-113)	14 (1-149)	0.18
IM dose escalation	27 (28%)	9 (13%)	**0.03**
Hammersmith score (low/eval.)	57/83* (69%)	42/57* (74%)	0.65
Reason for 2G-TKI: 1^ resistance	47 (50%)	28 (41%)	0.37
2^ resistance	26 (27%)	7(10%)	**0.01**
intolerance	21(22%)	31 (46%)	**0.003**
other	1 (%)	2 (3%)	0.78

Tiribelli et al., EHA 2016

Results

Figure 1a (TTF)

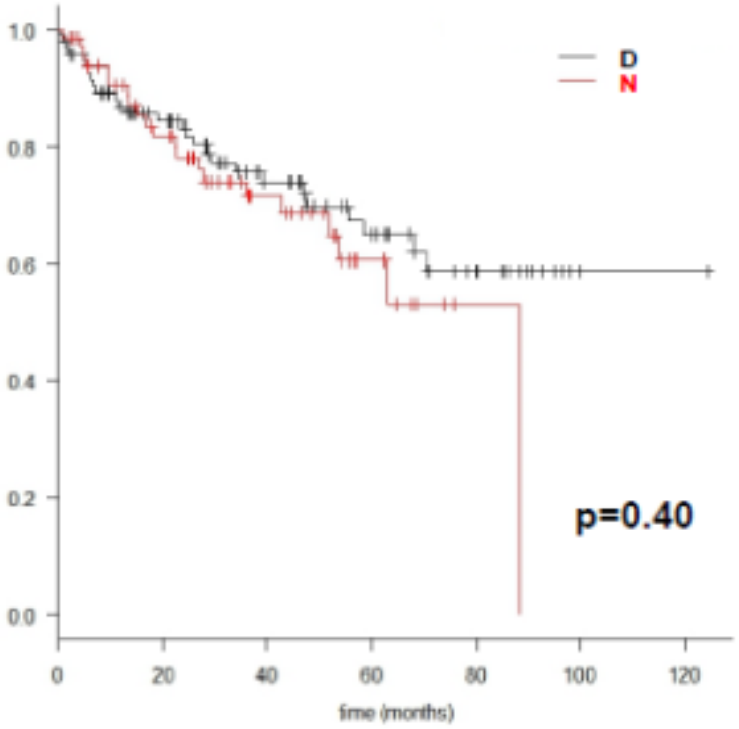
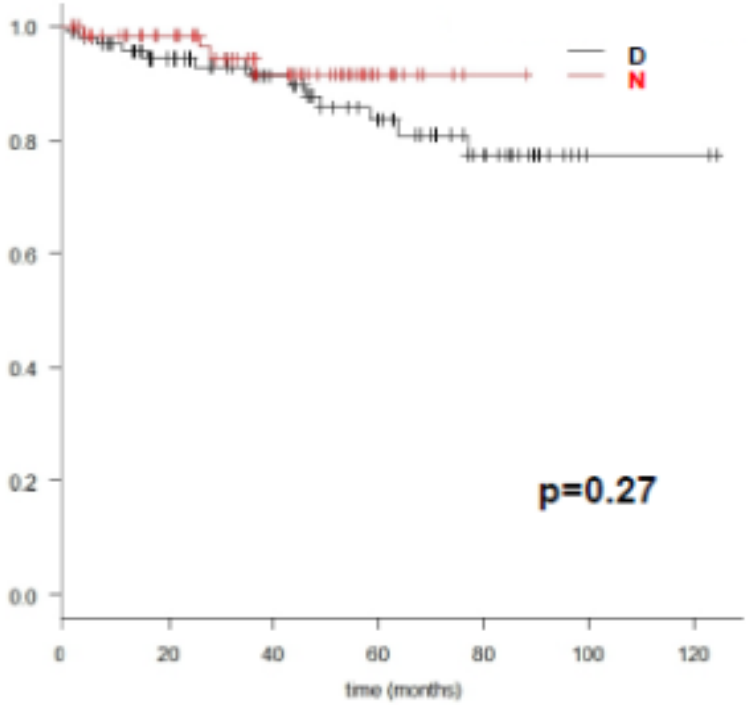


Figure 1b (PFS)



With the limits of a retrospective analysis, our data suggest similar efficacy of DAS and NIL after IM failure in CP-CML, with high rates of cytogenetic and molecular responses and excellent long-term survival.

Tiribelli et al., EHA 2016

TKIs for CML Therapy

Parameter	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
Target	Abl	Src & Abl	Abl	Src & Abl	Src & Abl
Standard dose	400 mg QD	100 mg QD	400 mg BID	500 mg QD	45 mg QD
IC50, Bcr-Abl1	260-679	0.8-1.8	10-25	42	0.5
IC50, c-Kit	99	18	209	10000	12
IC50, PDGFR	72	2.9	75	3.0	1.1
IC50, Src	>1000	0.1	>1000	3.0	5.4
IC50, VEGFR2	10000	NA	3720	NA	1.5
IC50, BTK	>5000	1.1	NA	2.5	849

Baccarani M et al Blood 2013;122(6):872-884.

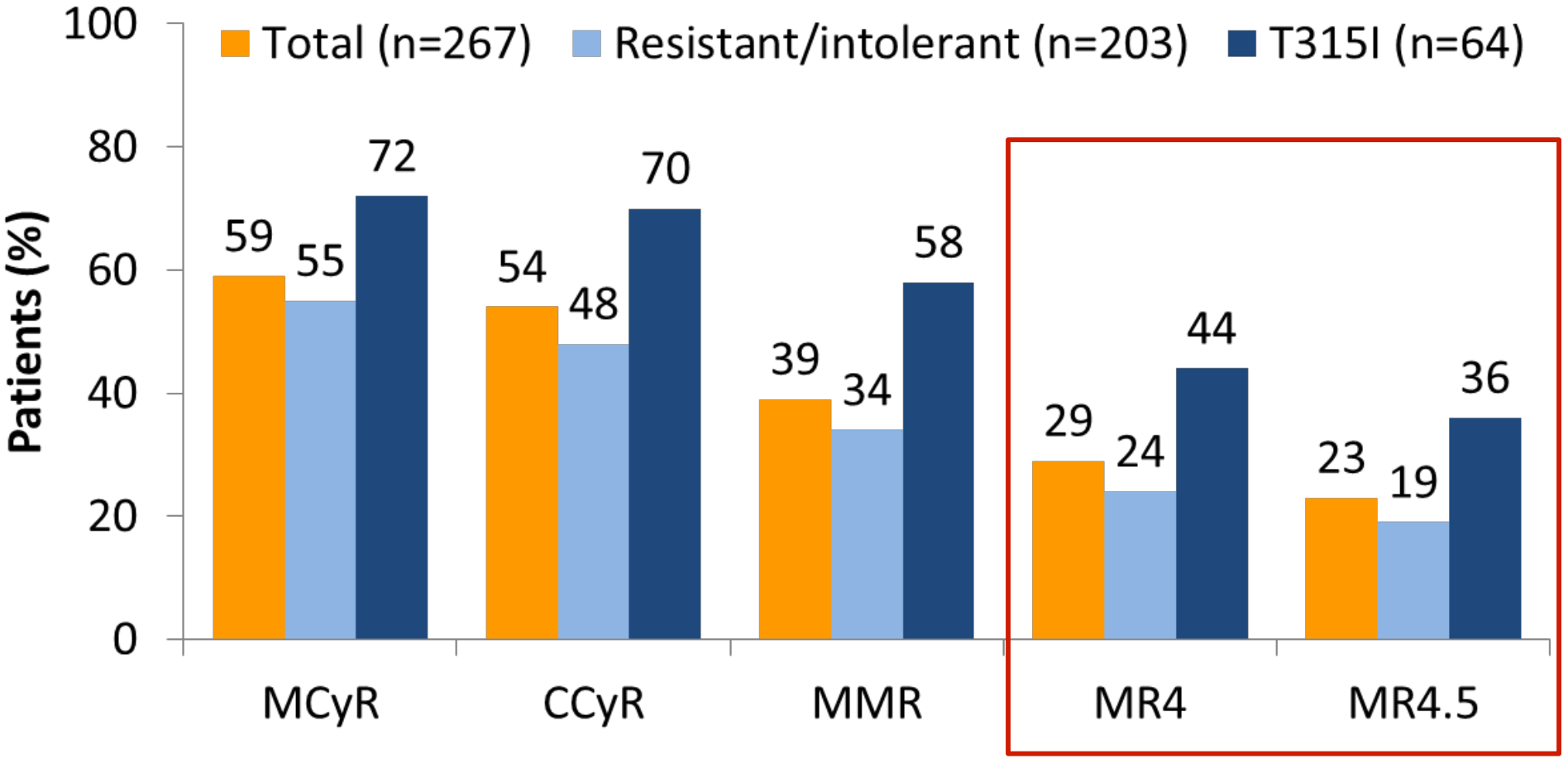
PACE trial - Patient characteristics

	CP-CML (n=270)	All (n=449)
Median age, years (range)	60 (18–94)	59 (18–94)
Prior TKI therapy,[a] n (%)		
1 TKI	18 (7)	31 (7)
2 TKIs	90 (33)	155 (35)
≥3 TKIs	162 (60)	263 (59)
R/I to dasatinib or nilotinib, n (%)		
Resistant	215 (80)	375 (84)
Intolerant only	39 (14)	49 (11)
Both resistant and intolerant	52 (19)	81 (18)
Mutation status, n (%)		
No mutation detected	138 (51)	198 (44)
T3151 mutation	64 (24)	128 (29)
Median follow-up, months (range)	48.2 (0.1–58.5)	37.3 (0.1–58.5)

Cortes et al, ASCO 2016

Data as of 3 August 2015

Response to Ponatinib at Any Time CP (N=270)

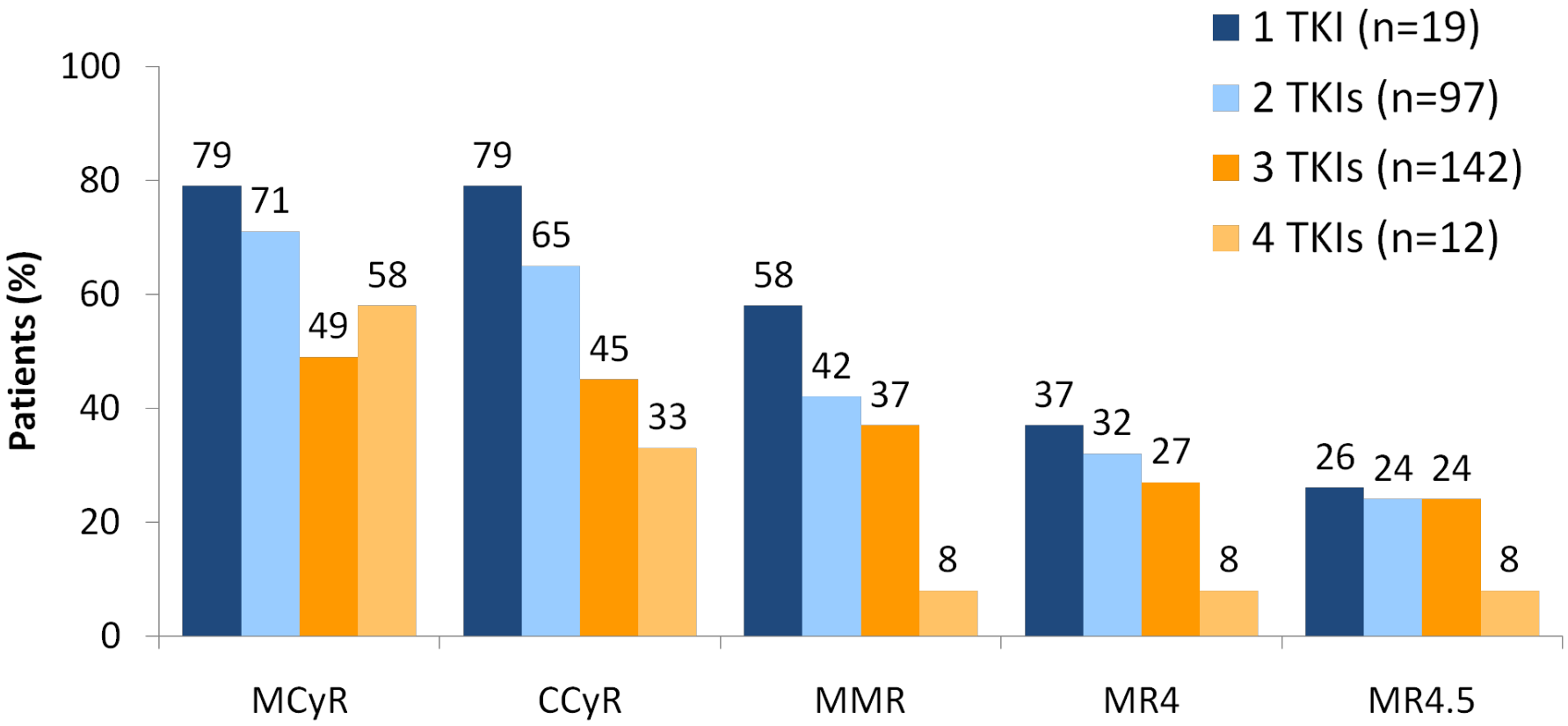


MR4 = 4-log molecular response (≤0.01% BCR-ABL^{IS}), MR$^{4.5}$ = 4.5-log molecular response (≤0.0032% BCR-ABL^{IS})

Cortes et al, ASCO 2016

Data as of 3 August 2015

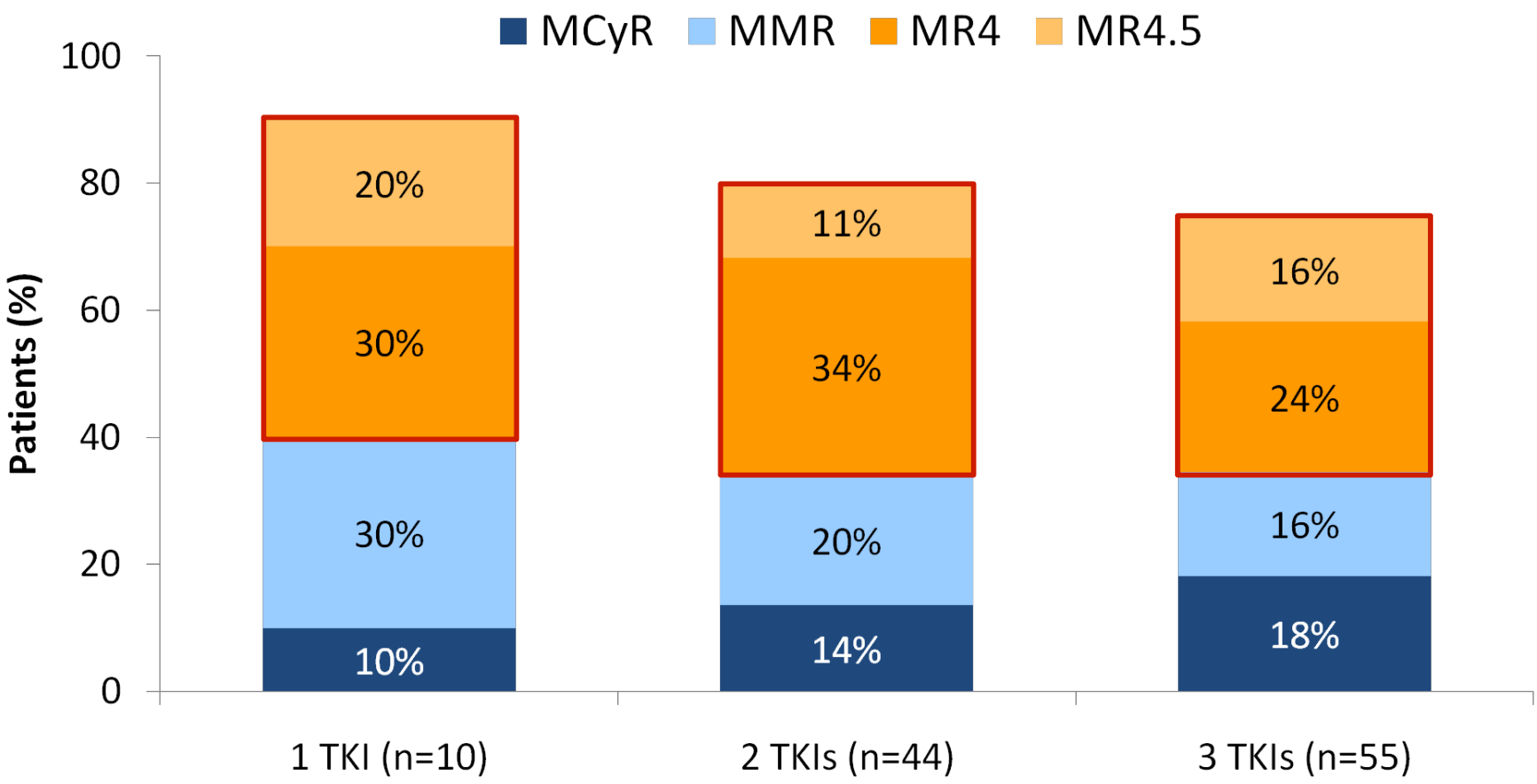
Response to Ponatinib in CP-CML (N=270) by Number of Prior TKIs: Response at Any Time



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

Current Response to Ponatinib in CP-CML by Number of Prior TKIs (Ongoing Patients=110)



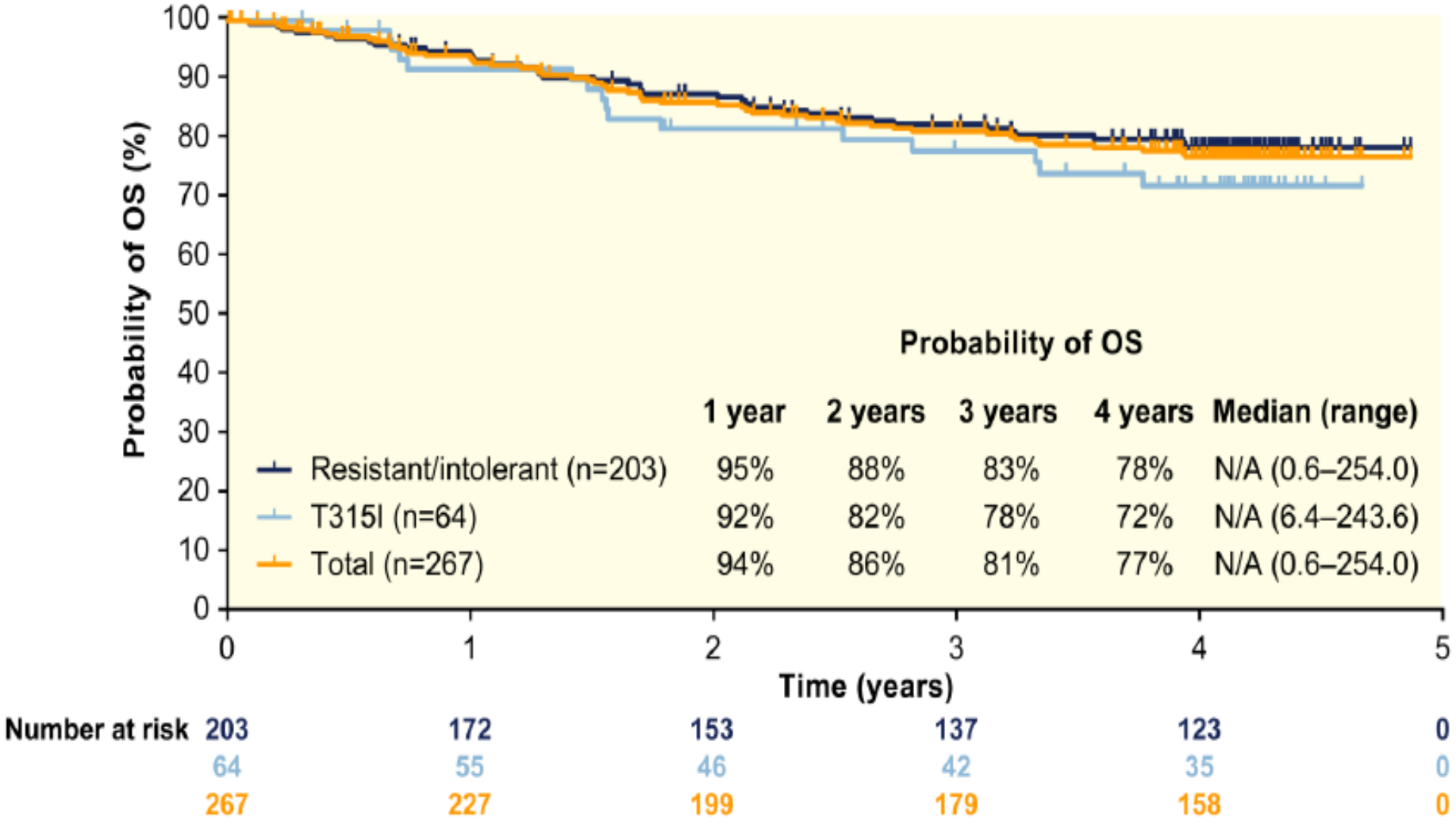
Hochhaus et al, ASH 2015

High response rates, regardless of mutation status

MUTATION STATUS AT ENTRY	PACE RESPONSE RATES: % (n/N)		
	MCyR	CCyR	MMR
No mutation detected	49 (66/136)	38 (52/136)	29 (40/136)
Any mutation	63 (83/131)	55 (72/131)	47 (62/131)
T315I only	74 (37/50)	68 (34/50)	60 (30/50)
Mutations other than T315I	57 (38/67)	45 (30/67)	37 (25/67)
Mutations in addition to T315I	57 (8/14)	57 (8/14)	50 (7/14)

- In preclinical and clinical studies, no single mutation has been identified that conferred resistance to ponatinib
- In post hoc analysis, T315I patients were younger, more recently diagnosed, had fewer prior TKIs, and a higher dose intensity of ponatinib compared with otherwise resistant/intolerant patients[2]
- Notable: In patients with no mutations, where mechanism of resistance is assumed to be non–BCR-ABL dependent, ponatinib has substantial activity

Estimated OS at 4 years CP (N=270)



Cortes et al, ASCO 2016

Data as of 3 August 2015

PACE trial
Most Common Treatment-Emergent AEs

- **The most common treatment-emergent AEs were**:
  - Skin-related AEs (including rash and dry skin)
  - Constitutional symptoms (including headache, fatigue, pyrexia, nausea, vomiting, and diarrhea)
  - Vascular (hypertension)
  - Pancreatic (increased lipase)
  - Myelosuppression (thrombocytopenia, neutropenia, and anemia)

- **The most common (≥10%) grade 3/4 AEs were:**
  - Thrombocytopenia, Neutropenia, Anemia
  - Increased lipase
  - Hypertension

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

Arterial and Venous Thrombotic Events

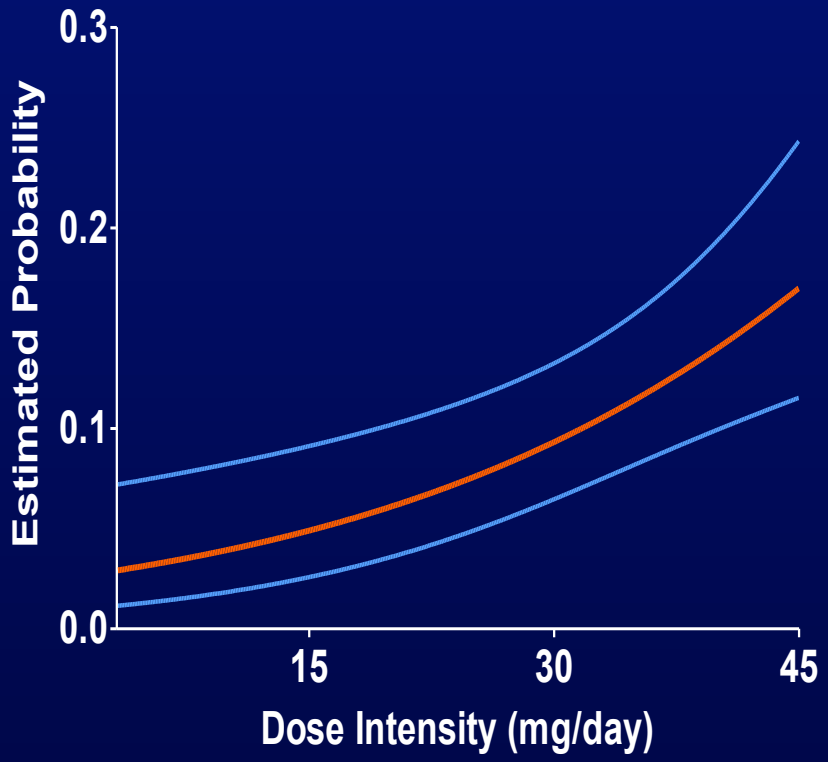
	Total (N = 449)		CP-CML (n = 270)	
	AE	SAE	AE	SAE
Cumulative exposure, patient-years	778.9		577.4	
ATEs, n (%)	99 (22)	78 (17)	74 (27)	60 (22)
Cardiovascular	52 (12)	37 (8)	36 (13)	28 (10)
Cerebrovascular	37 (8)	28 (6)	31 (11)	23 (9)
Peripheral vascular	37 (8)	27 (6)	28 (10)	20 (7)
Exposure-adjusted 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

Median time to onset for ATEs: 13.8 (0.3–44.0) months

Median time to onset for VTEs: 21.0 (2.0–31.4) months

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

Is risk-assessment feasible?
YES, identifiable risk factors



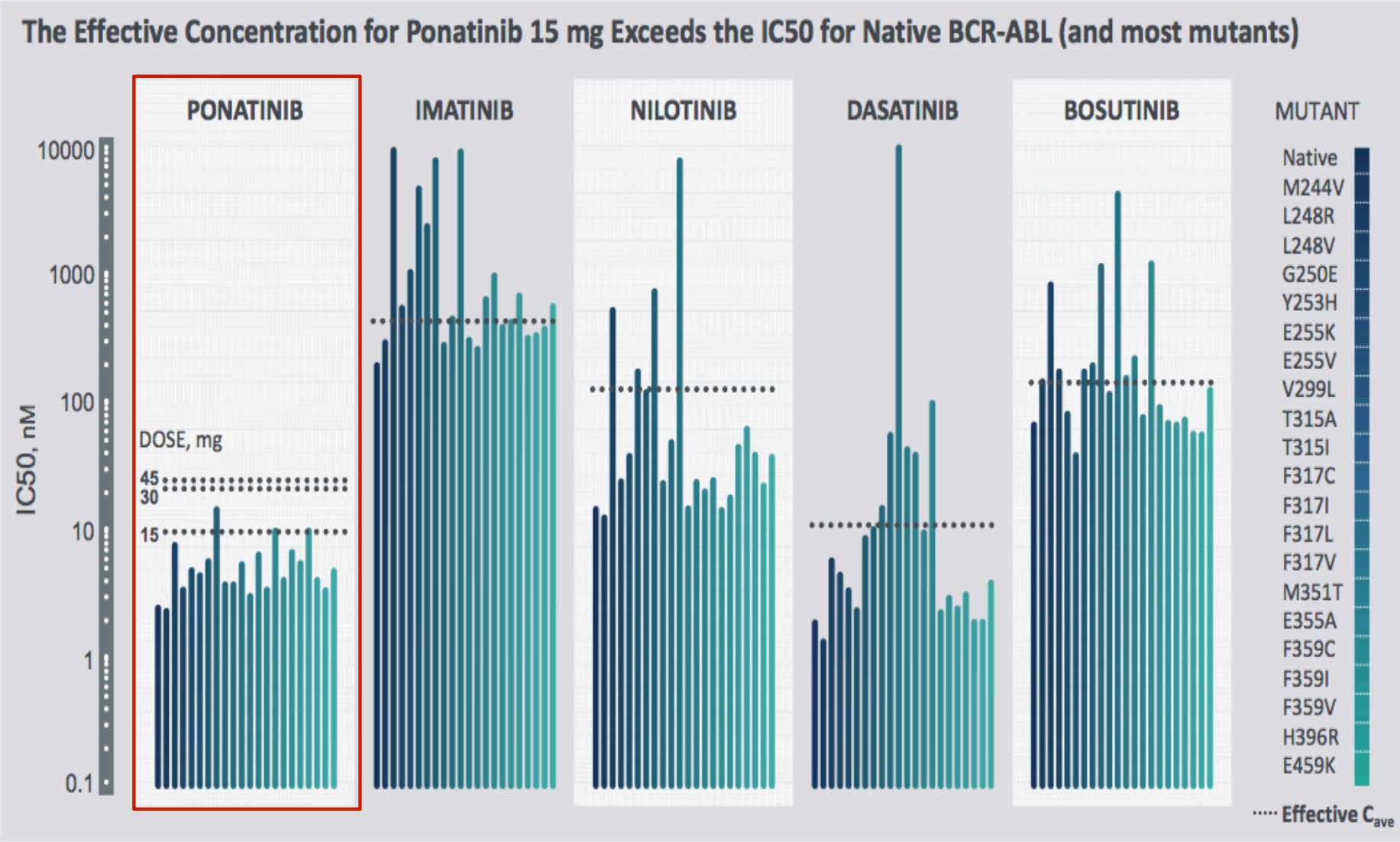
- **Risk factors significantly associated with arterial thrombotic AEs:**
  - Older age (p<0.0001)
  - History of diabetes (p=0.0003)
  - Higher dose intensity to time of first event (p=0.0009)
  - History of ischemia (p=0.0087)
  - Longer time since diagnosis (p=0.0228)
  - Higher baseline neutrophils (p=0.0276)
  - Higher baseline platelets (p=0.0466)

- **CV toxicity is dose-dependent: each 15 mg/day reduction in dose intensity results in a predicted reduction of ~40% in the risk of an arterial thrombotic event**
- **Other AEs with strong association with dose intensity: pancretitis and skin rash**

Data are similar for vascular occlusive events

Cortes et al. ASH 2013

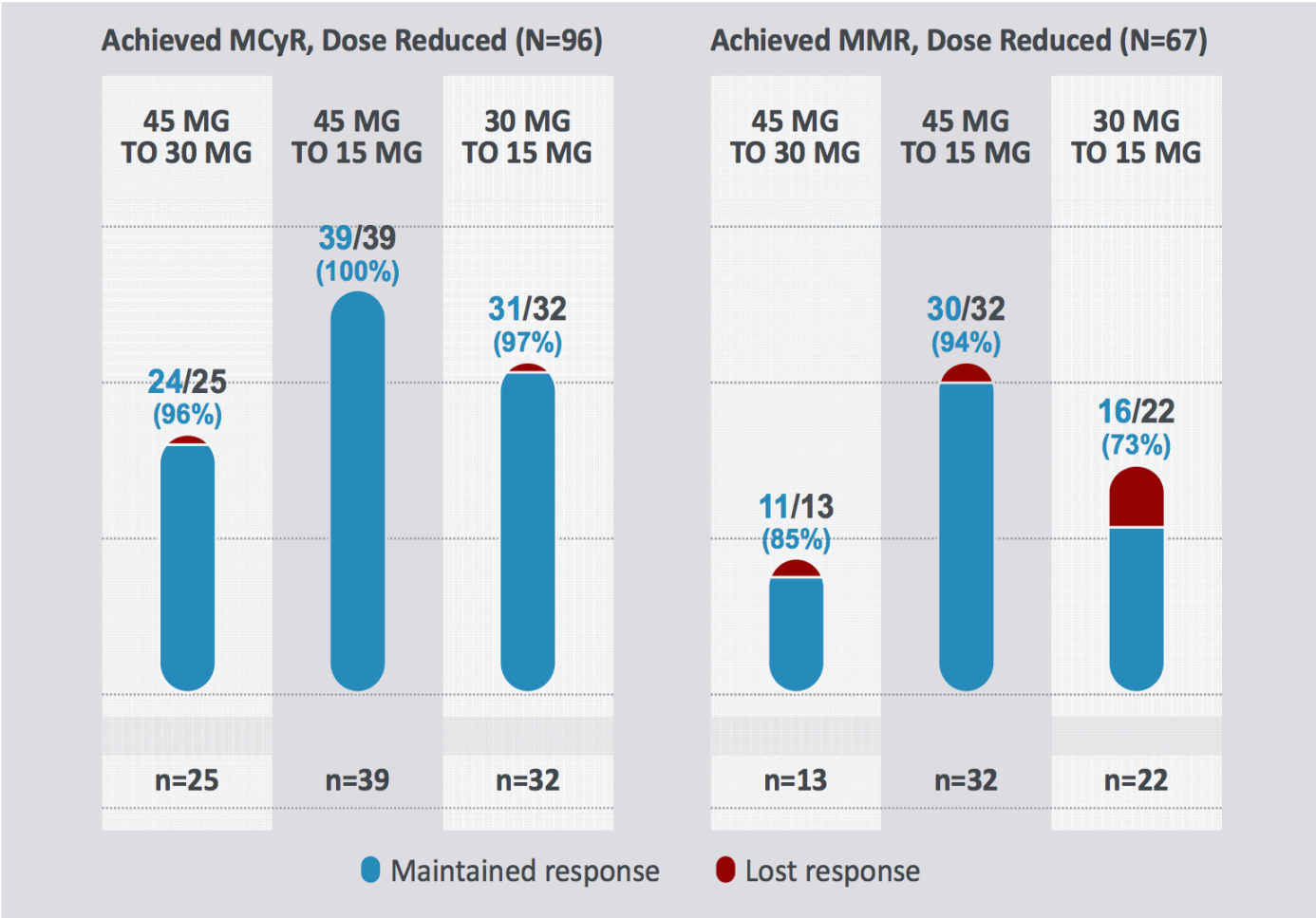
Actionability?
YES



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

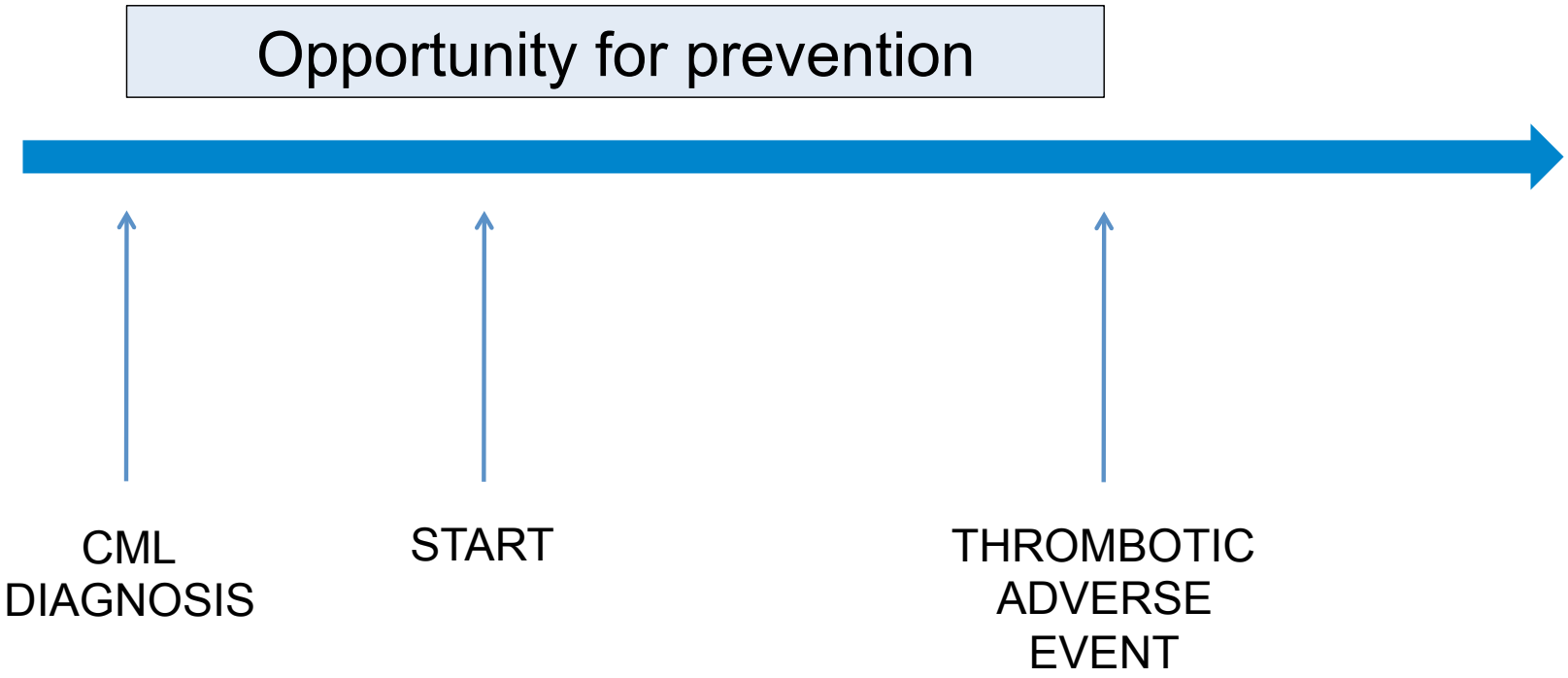
PACE: Stability of Responses after dose reduction

- The total number of CP-CML patients achieving MCyR was 149 (59%) and MMR was 103 (39%)
- Reductions to 15 mg were frequent and were effective in maintaining responses



Cortes et al, ASCO 2016

Time is a key factor



Ann Hematol
DOI 10.1007/s00277-016-2820-x

REVIEW ARTICLE

Identification, prevention and management of cardiovascular risk in chronic myeloid leukaemia patients candidate to ponatinib: an expert opinion

Massimo Breccia[1] · Patrizia Pregno[2] · Paolo Spallarossa[3] · Eleonora Arboscello[4] · Fabio Ciceri[5] · Mauro Giorgi[6] · Alberto Grossi[7] · Mario Mallardo[8] · Savina Nodari[9] · Stefano Ottolini[10] · Carla Sala[11] · Giovanni Tortorella[12] · Gianantonio Rosti[13] · Fabrizio Pane[14] · Giorgio Minotti[15] · Michele Baccarani[13]

Clinical and anamnestical evaluation at baseline

Laboratory and imaging tests (ECG, ABI, echocardiogram, other)

Prophylaxis (aspirin or clopidogrel, but there is no level of evidence)

Therapeutic targets (Blood pressure, Cholesterol, Diabetes, Lifestyle)

Monitoring (6 - 12 months)

Consider reducing the dose of Iclusig® to 15 mg for CP-CML patients who have achieved MCyR

OPUS Study - Optimizing Ponatinib USe

A GIMEMA phase 2 study of the efficacy and risk profile of ponatinib, 30 mg once daily, in CP CML resistant to imatinib.

Study design: dose optimization

Phase II, single arm, open-label, multicentre

- ✓ **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 once daily**
- ✓ Than, QPCR every 12 weeks
- ✓ **If BCR-ABL > 1%, dose back to 30 mg once daily**

ClinicalTrials.gov Identifier: NCT02398825
Study ID Numbers: CML1315 2015-001102-34

Thank you for attention!