Dasatinib

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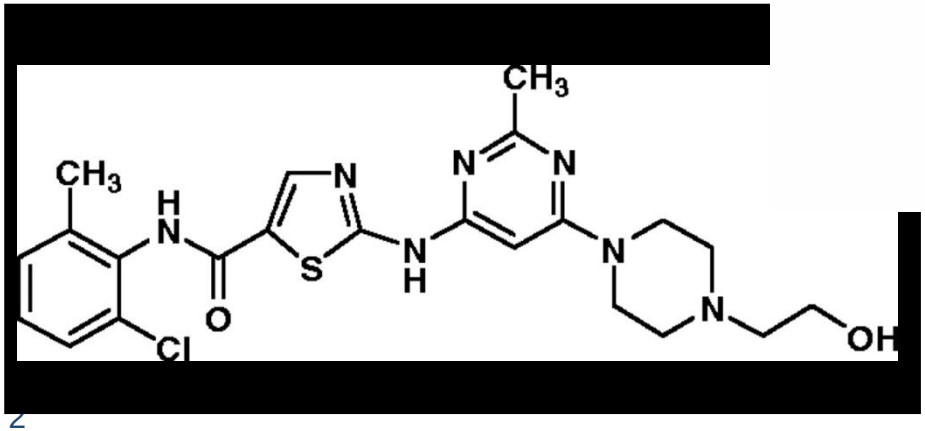
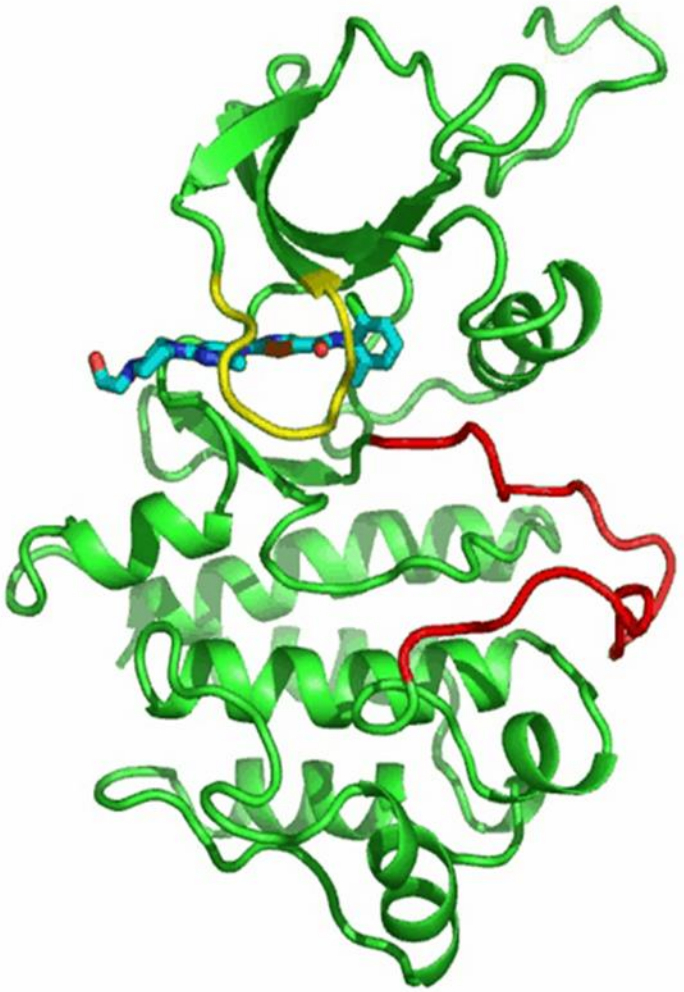
Dasatinib

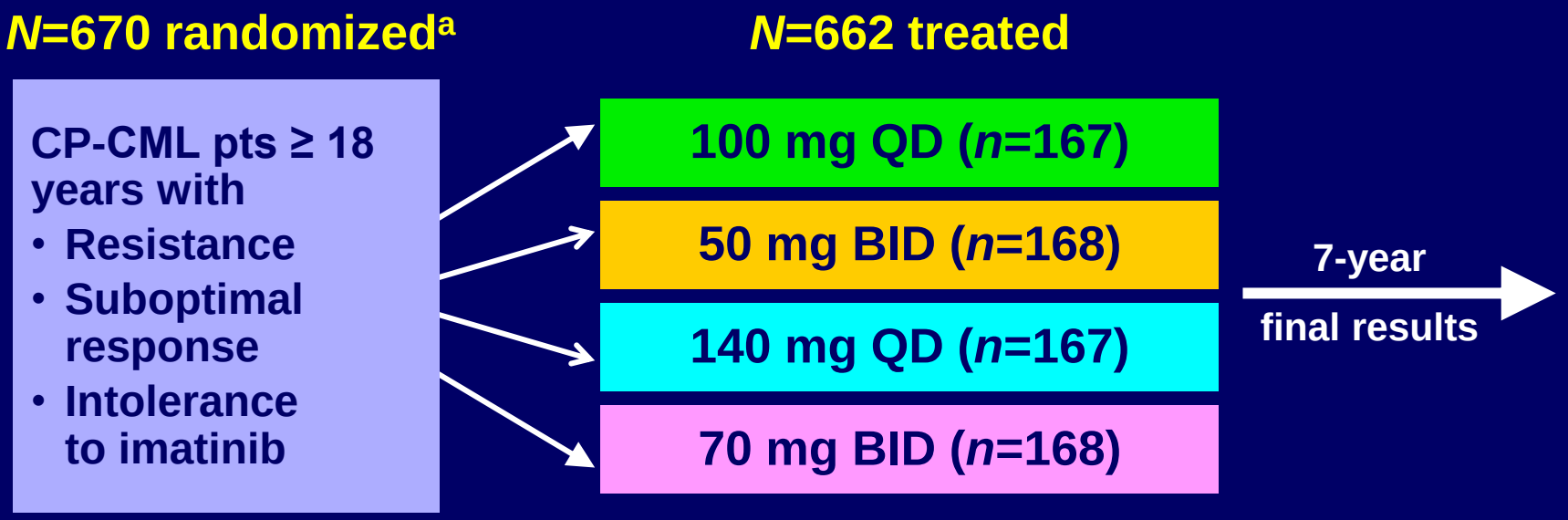
- Dasatinib 300 X more potent than imatinib *in vitro*
- Multitargeted (SRC, ABL, KIT and PDGFR)
- Active on most BCR – ABL Mutations resistant to imatinib





Druker et al, NEJM 2006;355:2408
O'Hare et al, Cancer Res 2005;65:4500
Kantarjian et al, Blood 2003 15;101:473

Figure 1. CA180-034 Study Design



- After 2 years, protocol allowed switching from BID to QD dosing
- Primary endpoint: To compare the MCyR rates of dasatinib when administered QD vs BID after a minimum follow-up of 6 months

Enrollment period: July 13, 2005 – March 13, 2006.
[a] Patients were stratified by imatinib resistance vs. imatinib intolerance.

Patient Demographics

Dasatinib Dose	100 mg QD (*n*=167)	50 mg BID (*n*=168)	140 mg QD (*n*=167)	70 mg BID (*n*=168)
Resistance to imatinib, n (%)	124 (74)	124 (74)	123 (74)	127 (76)
Primary	75 (45)	88 (52)	78 (47)	82 (49)
Acquired	49 (29)	36 (21)	45 (27)	45 (27)
Imatinib-resistant BCR-ABL mutation detected, n (%)	49 (34)	60 (41)	51 (37)	45 (31)
Patients with samples available	144	145	138	143
Other prior therapy, n (%)				
Interferon-α	87 (52)	87 (52)	93 (56)	82 (49)
Chemotherapy	39 (23)	52 (31)	41 (25)	43 (26)
Stem-cell transplantation	10 (6)	13 (8)	5 (3)	7 (4)

Shah NP et al. Am J Haematol, accepted for publication

Reason for Discontinuation

No. of patients who discontinued, (%)	Dasatinib Dose			
	100 mg QD (*n*=166)	50 mg BID (*n*=166)	140 mg QD[a] (*n*=163)	70 mg BID (*n*=167)
Protocol-defined progression[b]	35 (21)	29 (17)	42 (26)	27 (16)
Drug-related AE	39 (24)	45 (27)	45 (28)	51 (31)
AE unrelated to study drug	10 (6)	10 (6)	4 (2)	8 (5)
Investigator request	12 (7)	7 (4)	6 (4)	5 (3)
Patient request	14 (8)	18 (11)	19 (12)	16 (10)
Still in Therapy (Dasatinib 100mg)	53 (32)	57 (34)	47 (29)	59 (35)

[a] Reason for discontinuation was not reported in one patient in the 50 mg BID arm.

[b] Protocol-defined progression included increasing WBC count, loss of CHR or MCyR, ≥30% increase in Ph+ metaphases, or transformation to AP/BP.

[c] A majority of the patients discontinuing under "Other" were those switching to commercial supply due to planned study closure.

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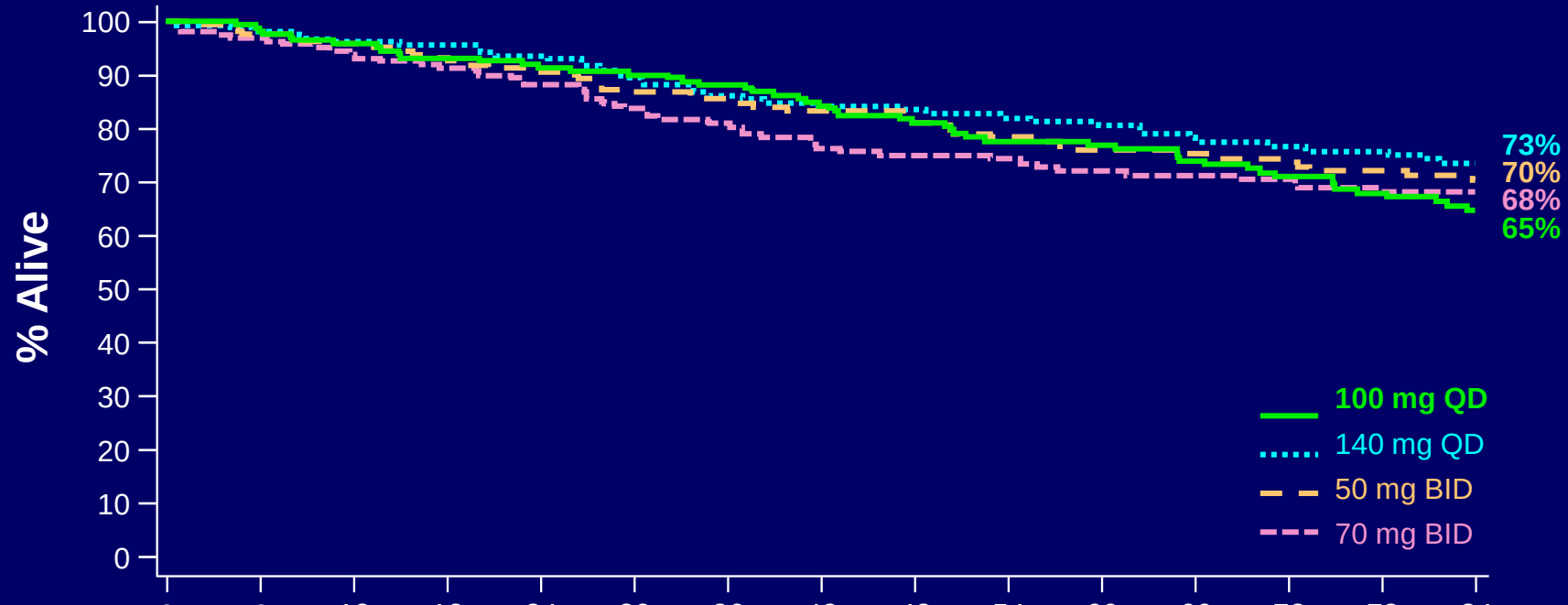
Efficacy Results

- **Over 7 years of follow-up, rates for MMR, PFS, and OS were similar across dose groups**

	100 mg QD (*n*=167)	50 mg BID (*n*=168)	140 mg QD (*n*=167)	70 mg BID (*n*=168)
MMR in assessed treated patients, n (%)	73 (46)	70 (44)	68 (44)	69 (46)
PFS at 7 yr, % (95% CI)	42 (33-51)	44 (35-53)	38 (30-47)	44 (35-52)
OS at 7 yr, % (95% CI)	65 (56-72)	70 (62-77)	73 (65-80)	68 (60-75)

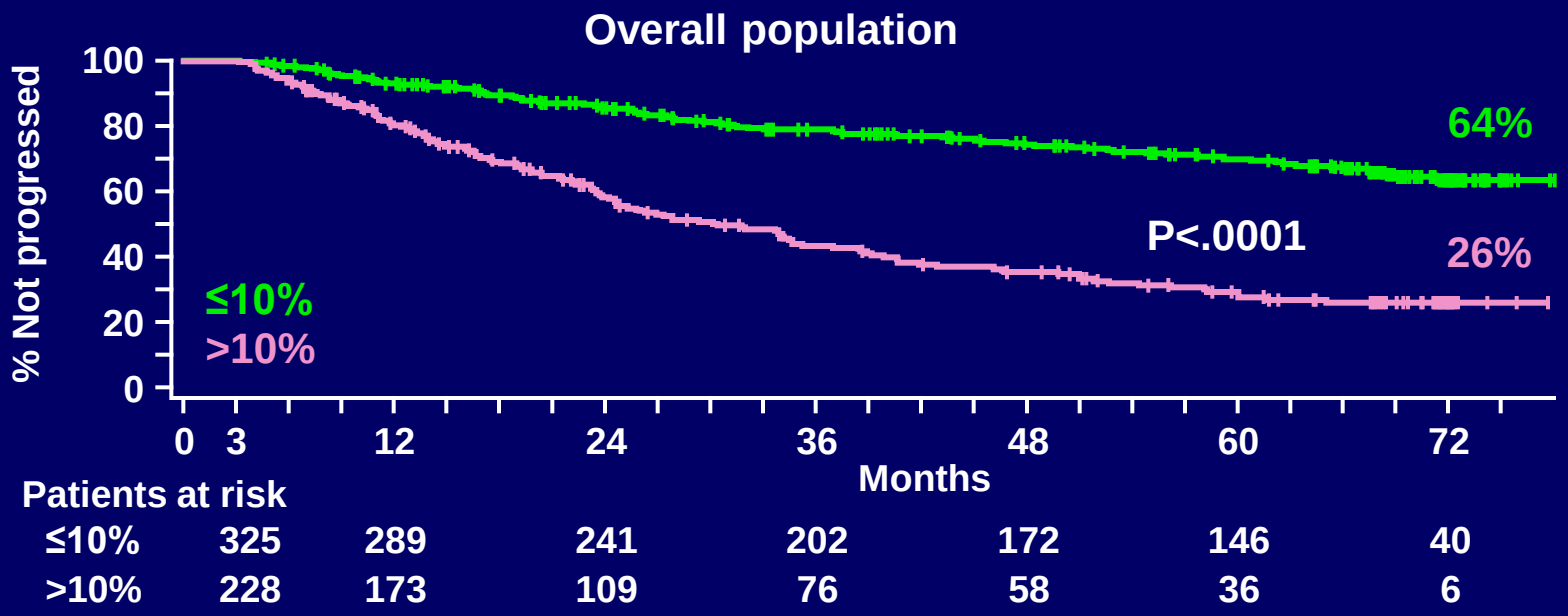
OS is Similar Across Dose Groups



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

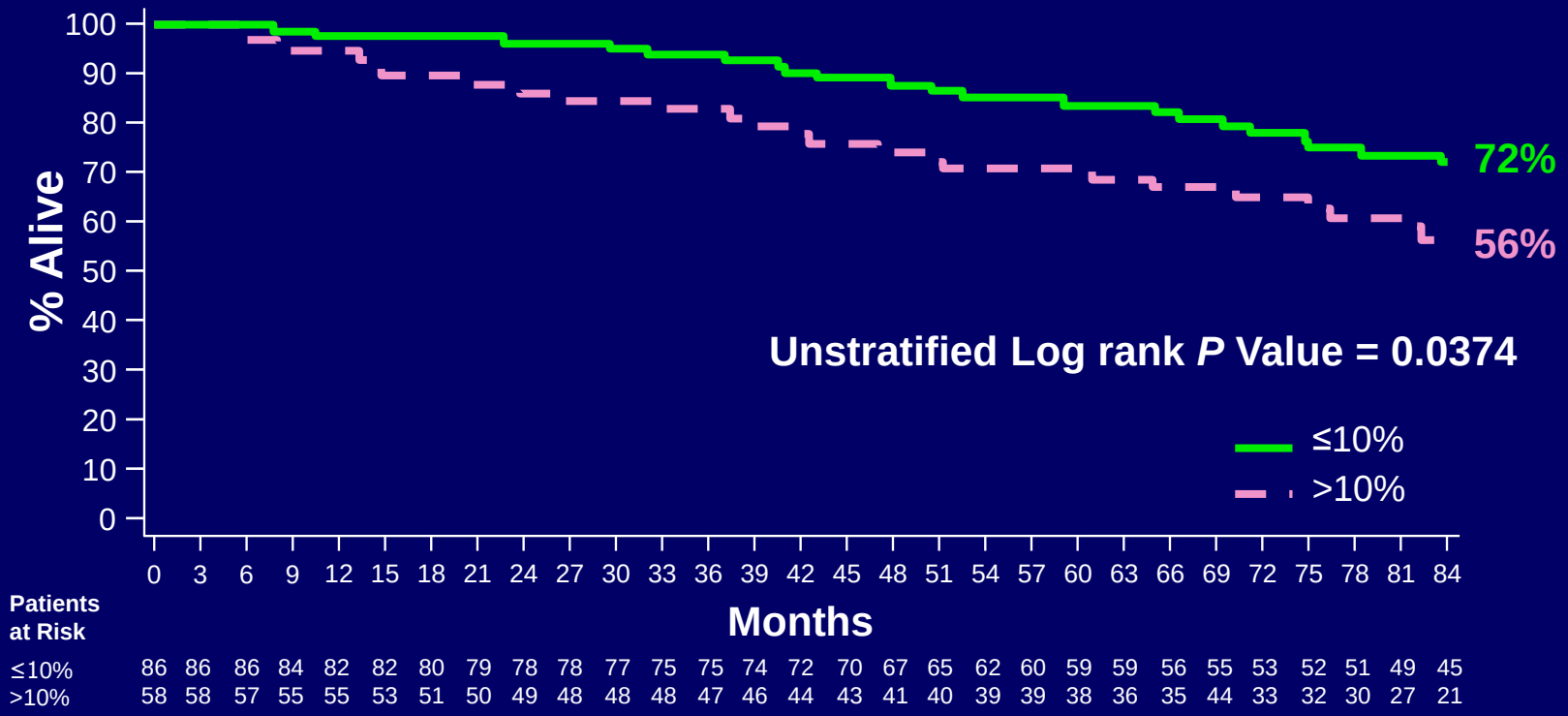
	Imatinib-resistant Patients	Imatinib-intolerant Patients	Overall
OS, % (95% CI)	63 (53–71)	70 (52–82)	65 (56–72)
PFS, % (95% CI)	39 (29–49)	51 (32–67)	42 (33–51)

Exploratory analysis: PFS by BCR-ABL level at 3 months



	≤10%	>10%
Imatinib-resistant, n	222	202
Rate of PFS, %	62	25
Imatinib-intolerant, n	103	26
Rate of PFS, %	68	30

OS by 3 Month BCR-ABL Level: 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)

Drug-related Pleural Effusion and Pulmonary Hypertension Over Time (Any Grade)

	Treated Patients (%)					
	100 mg QD (*n*=165)			Other Dose Groups (*n*=497)		
	2-year	5-year	7-year	2-year	5-year	7-year
Pleural effusion	23 (14)	40 (24)	46 (28)	118 (24)	158 (32)	174 (35)
Pulmonary hypertension	0 (0)	0 (0)	3 (2)	5 (1)	8 (2)	13 (3)
Pulmonary arterial hypertension	--	0 (0)	1 (<1)	--	0 (0)	0 (0)

Shah NP et al. Am J Haematol, accepted for publication

Arterial Ischemic Events Summary: All Treated Patients

	Number of Patients (%)					
	100 mg QD (*n*=165)			Other Dose Groups (*n*=497)		
	Any Grade	Grade 3/4	Grade 5	Any Grade	Grade 3/4	Grade 5
Subjects with any cardiovascular ischemic events[a]	7 (4)	4 (2)	0	20 (4)	11 (2)	1 (<1)
Myocardial infarction	3 (2)	3 (2)	0	4 (1)	3 (1)	1 (<1)
Angina pectoris	2 (1)	1 (1)	0	12 (2)	6 (1)	0
Coronary artery disease	2 (1)	0	0	1 (<1)	0	0

MedDRA Version 16.1.

[a] Patients may have more than one event within a class.

Shah NP et al. Am J Haematol, accepted for publication

DASISION (CA180-056)[a] Study Design

- Treatment-naïve CML-CP patients (N=519)
- 108 centers
- 26 countries
- Enrollment: September 2007–December 2008

Randomized [b]

- Dasatinib 100 mg QD (n=259)
- Imatinib 400 mg QD (n=260)

5-year final results

- Database lock of 24-Mar-2014
- Primary end point: confirmed CCyR by 12 months
  - 77% dasatinib vs. 66% imatinib (*P*=0.007)[1]

[a] Clinicaltrials.gov NCT00481247.

[b] Stratified by EURO (Hasford) risk score.

1. Kantarjian H et al. *N Engl J Med* 2010;362:2260–70.

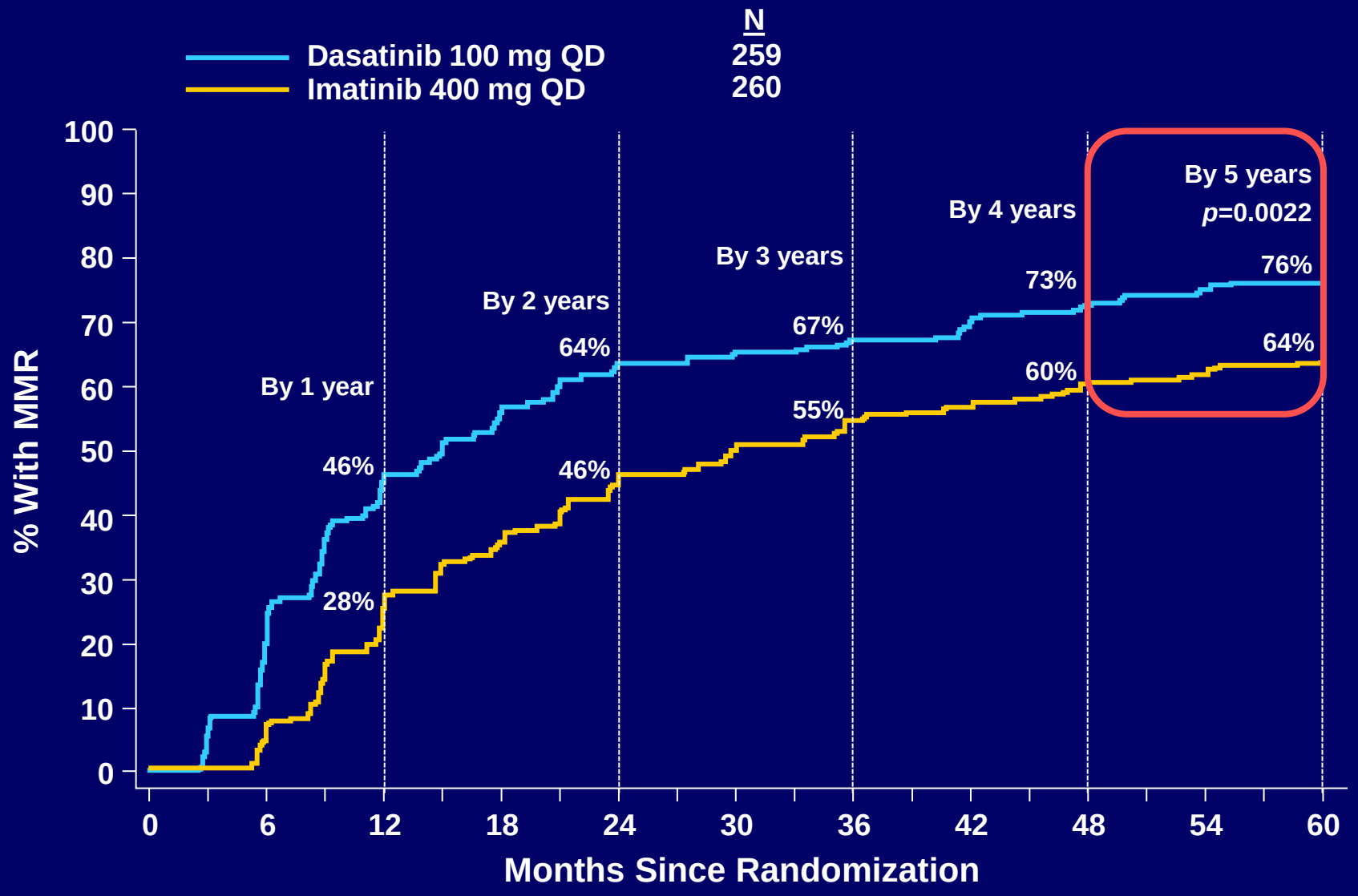
Patient Disposition at 5 Years

- At 5 years (study end), patients were transitioned to off-study therapy or remained on study therapy until local drug access was available

	Treated Patients, n (%)	
	Dasatinib 100 mg QD (n=258)	Imatinib 400 mg QD (n=258)
On initial therapy at study end	158 (61)	162 (63)
Discontinued		
Progression or treatment failure	28 (11)	36 (14)
AE related to study treatment [a]	42 (16)	17 (7)
AE unrelated to study treatment [a]	12 (5)	4 (2)
Poor/nonadherence	1 (<1)	7 (3)
Other	17 (7) [b]	31 (12) [c]

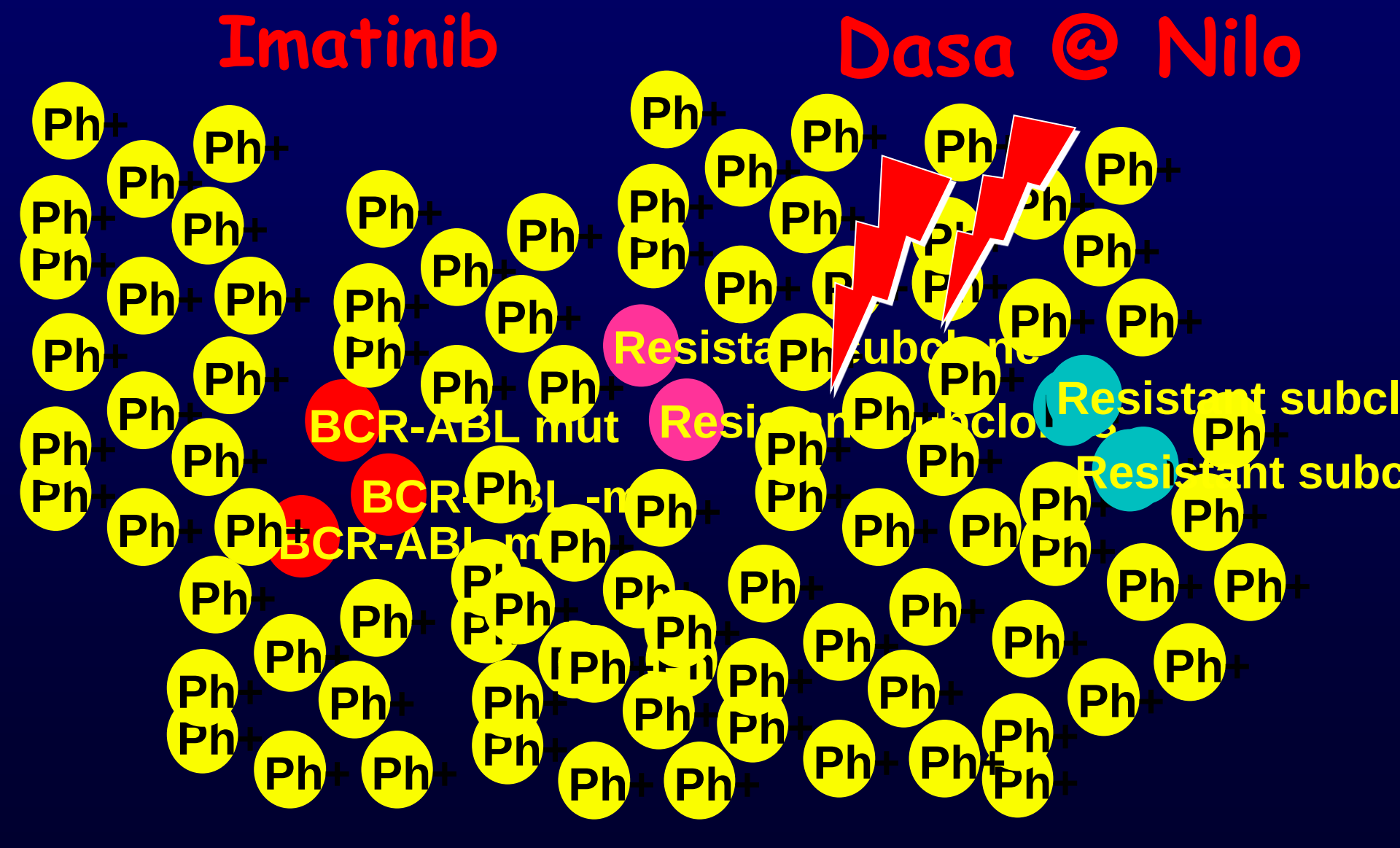
Cortes J et al., ASH 2014 and JCO in press

Cumulative MMR Rates Over Time

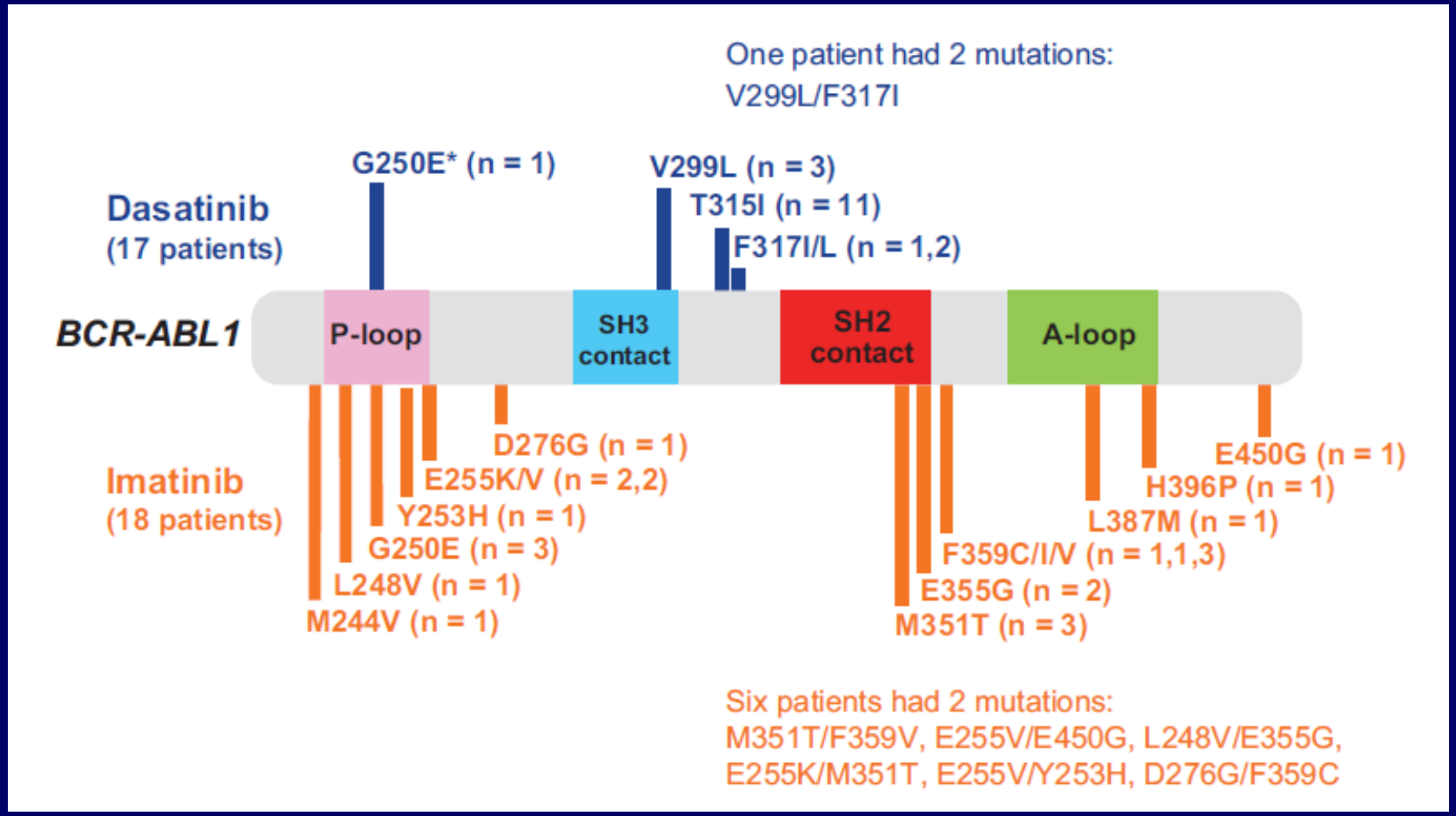


Cortes J et al., ASH 2014 and JCO in press

2nd gen TKIs achieve faster and deeper molecular responses than imatinib

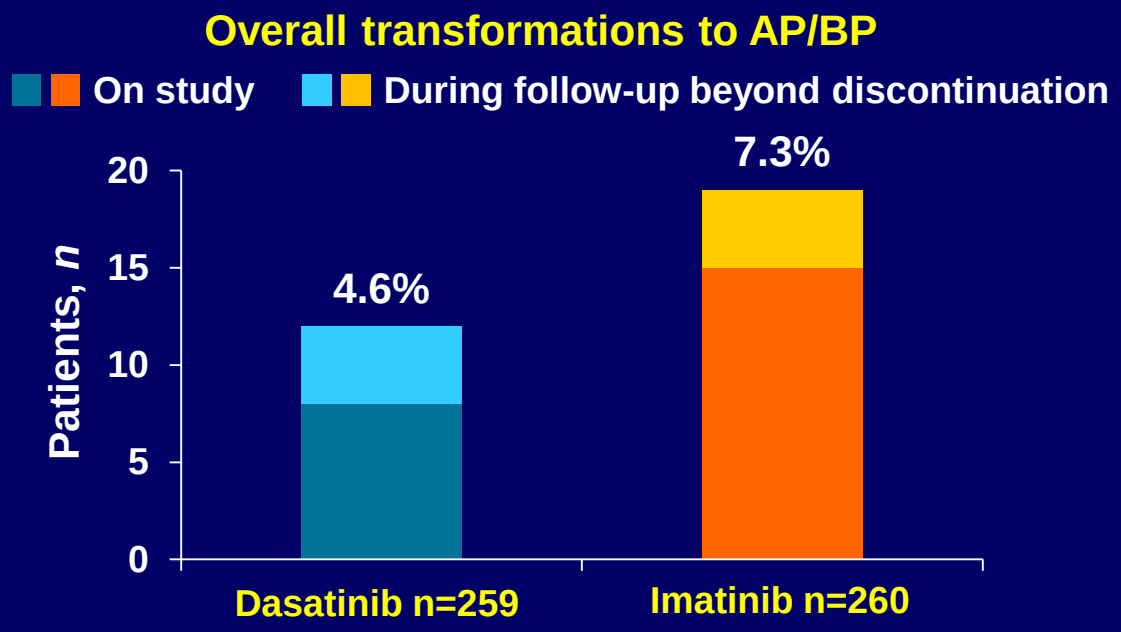


Distribution of mutations detected in DASISION trial by treatment arm and BCR-ABL1 location



Hughes T et al. Leukemia. 2015;29:1832-38

Transformation to AP/BP CML by 5 Years



	Dasatinib 100 mg QD (n=259)		Imatinib 400 mg QD (n=260)	
BCR-ABL at 3 Months [a]	≤10% n=198	>10% n=37	≤10% n=154	>10% n=85
Transformation to AP/BP [b], n (%)	6 (3)	5 (14)	5 (3)	13 (15)

- **One imatinib patient and no dasatinib patients transformed between 4 and 5 years**

[a] One dasatinib and one imatinib patient transformed but did not have 3-month molecular assessments.

[b] Including follow-up beyond discontinuation (intent to treat).

Cortes J et al., ASH 2014 and JCO in press

Overall Survival and Progression-Free Survival

	Dasatinib 100 mg QD (n=259)	Imatinib 400 mg QD (n=260)	Hazard ratio (95% CI)
Total number of deaths [a], n	26	26	–
Estimated 5-year OS [a], % (95% CI)	91 (87–94)	90 (85–93)	1.01 (0.58–1.73)
Estimated 5-year PFS [a], % (95% CI)	85 (80–89)	86 (80–89)	1.06 (0.68–1.66)

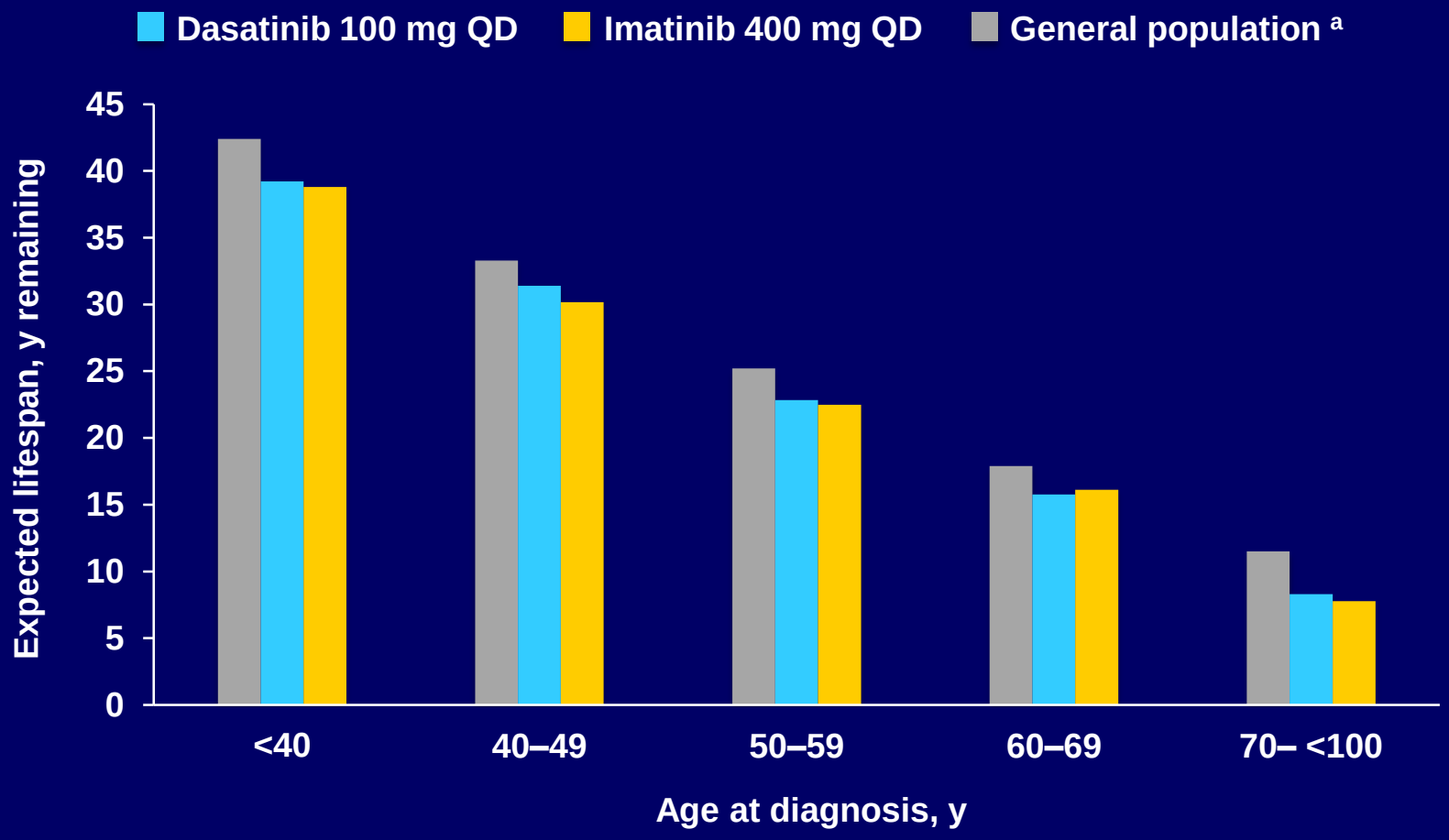
- **Causes of death were cardiovascular disease (2 dasatinib, 1 imatinib); disease progression (9 dasatinib, 17 imatinib); infection (11 dasatinib, 1 imatinib); other malignancy, septic shock and cardiac failure, multi-organ failure, and whole body swelling (1 each dasatinib); stem cell transplantation complications and unknown (2 each imatinib); severe chest pain, clinical deterioration and decrease in performance status, and fatal bleeding (1 each imatinib)**

[a] On-study treatment and in follow-up after discontinuation of randomized treatment.

CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Cortes J et al., ASH 2014 and JCO in press

Expected Survival by Age at Diagnosis

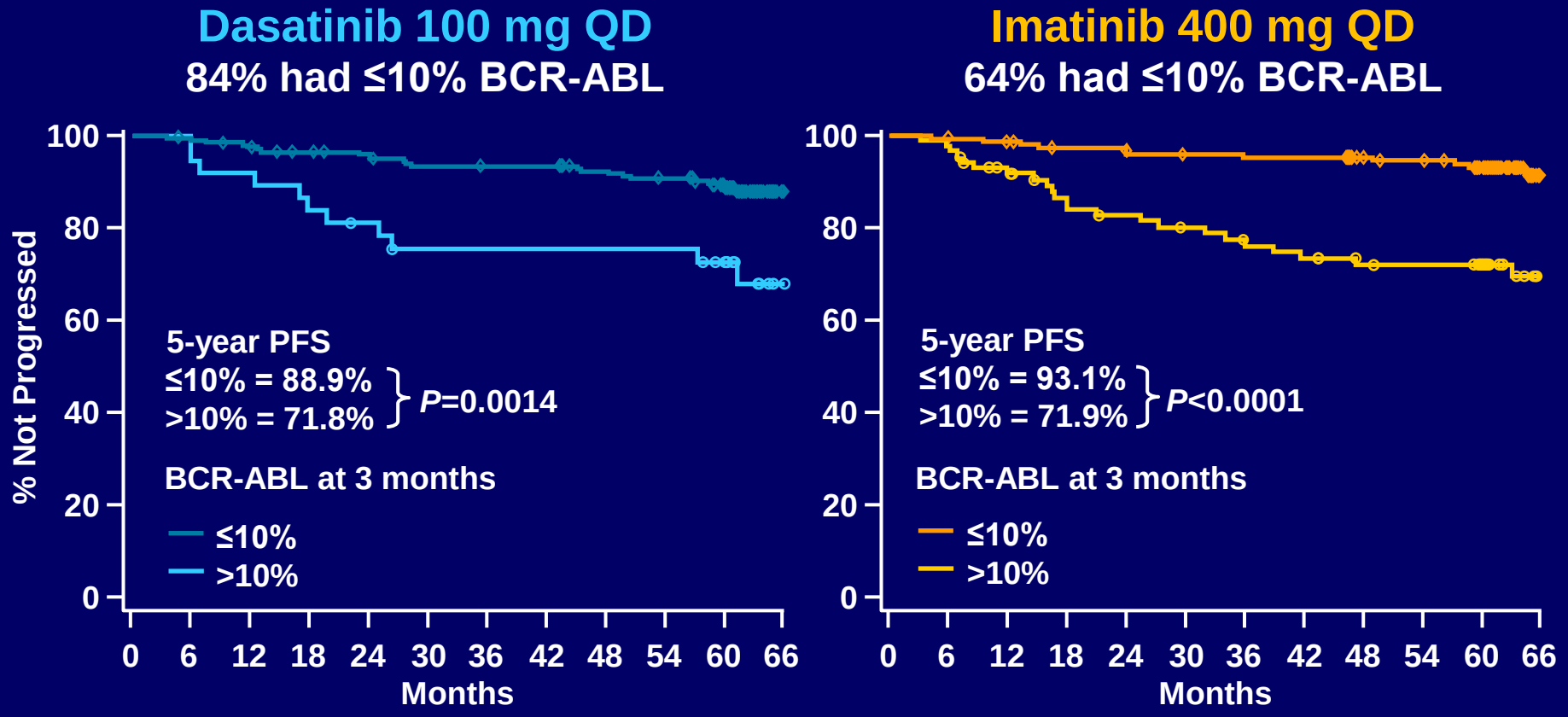


- Age-adjusted life expectancy for patients with CML-CP approaches that for patients without CML

[a] Expected lifespan estimates were adapted from: Ludwig H et al. *J Clin Oncol* 2010;28(9):1599–1605.

Cortes J et al., ASH 2014 and JCO in press

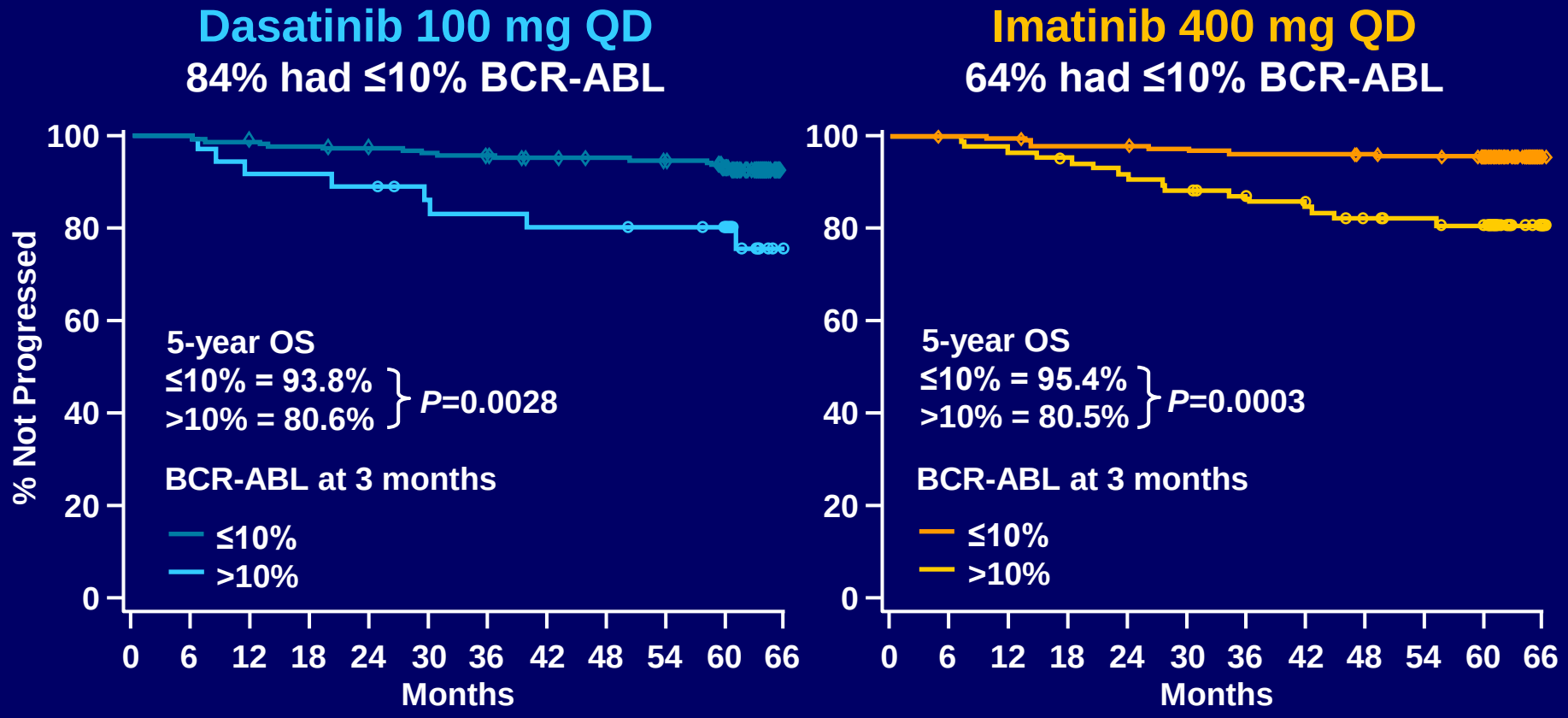
Estimated 5-year PFS [a,b] by Molecular Response at 3 Months



[a] On-study treatment and in follow-up after discontinuation of randomized treatment.

[b] Doubling of white blood cell count, loss of complete hematologic response, increase in Ph+ metaphases to >35%, transformation, or death from any cause.

Estimated 5-year OS [a] by Molecular Response at 3 Months



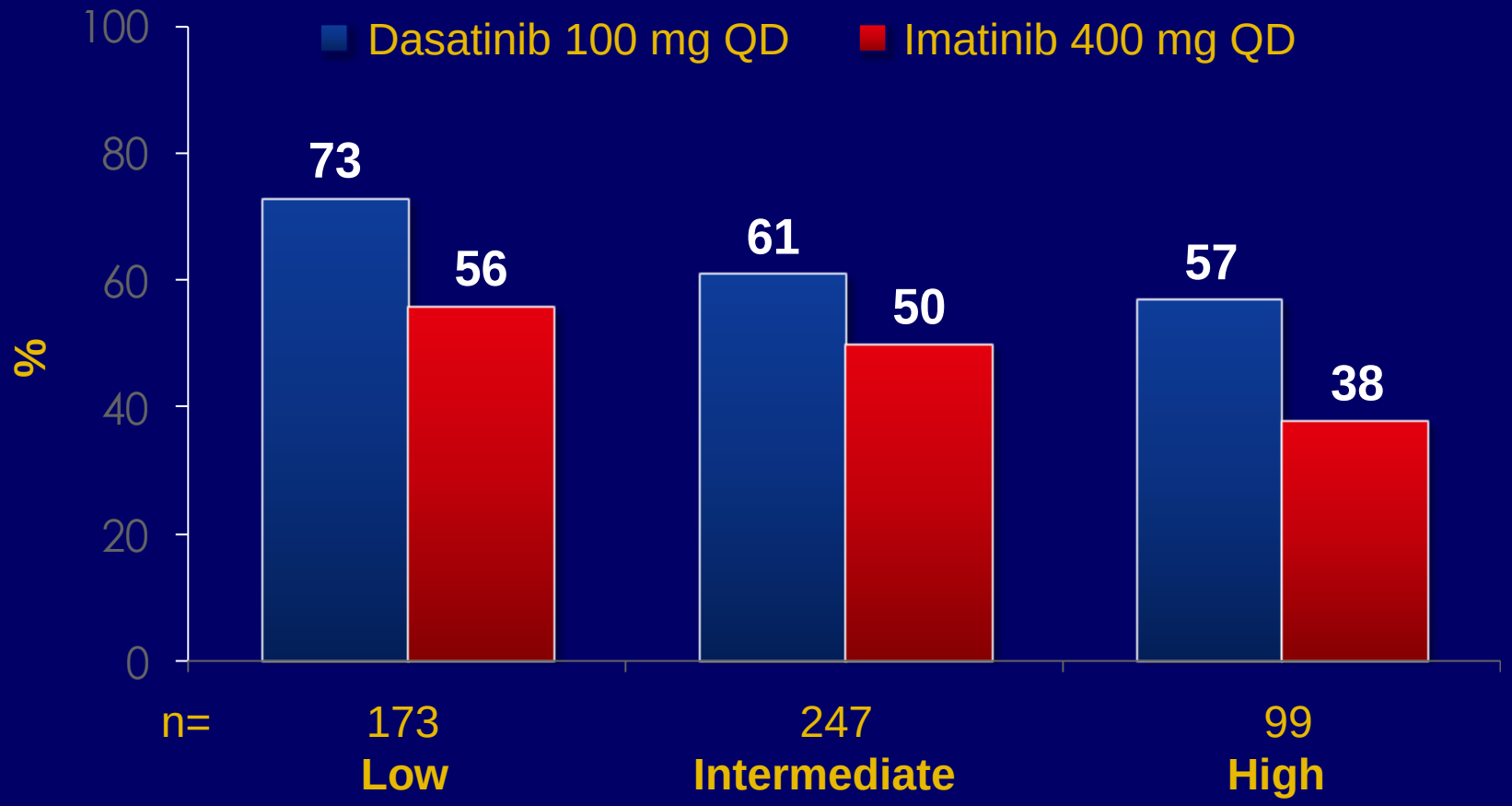
[a] On-study treatment and in follow-up after discontinuation of randomized treatment.

Best 5-Year Responses by Molecular Response at 3 Months

	Dasatinib 100 mg QD (n=259)		Imatinib 400 mg QD (n=260)	
BCR-ABL at 3 Months	≤10% (84%)	>10% (16%)	≤10% (64%)	>10% (36%)
CCyR, %	94	41	92	59
MMR, %	87	38	81	41
$MR^{4.5}$, %	54	5	48	12

MMR Rates at any Time by EURO/Hasford Risk Groups

DASISION 2-year Follow-up



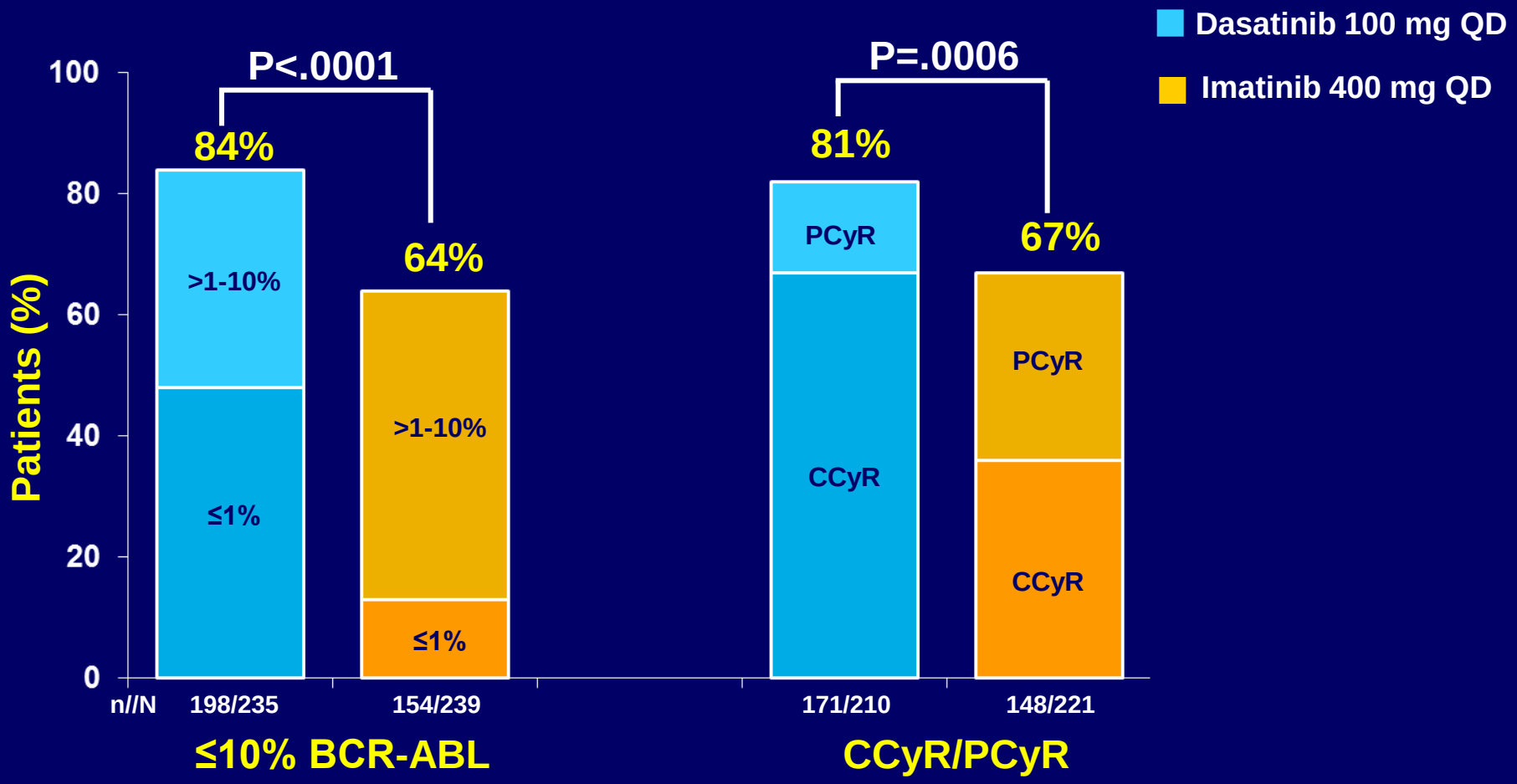
Kantarjian HM et al. Blood. 2012; 119: 1123-29

BCR-ABL1 Transcript Levels at 3 Months Are the only Requirement for Predicting Outcome for CML Patients Treated with TKIs

Outcome	RR for Transcript Level (Log) RR	*P*	Cutoff (%)	No. of Patients at Risk	8-Year Probability of the Outcome %	*P*
BCR-ABL1 transcript level at 3 months						
OS	0.161	< .001				< .001
Low risk			≤ 9.84	211	93.3	
High risk			> 9.84	68	56.9	
PFS	0.162	< .001				< .001
Low risk			≤ 9.54	208	92.8	
High risk			> 9.54	71	57.0	
EFS	0.102	< .001				< .001
Low risk			≤ 9.84	211	65.1	
High risk			> 9.84	66	6.9	
CCyR	5.17	< .001				< .001
Low risk			≤ 8.58	169	99.4	
High risk			> 8.58	79	21.7	
MMR	12.98	< .001				< .001
Low risk			≤ 2.81	141	82.5	
High risk			> 2.81	137	21.1	
CMR	10.95	< .001				< .001
Low risk			≤ 0.61	57	84.7	
High risk			> 0.61	222	1.5	

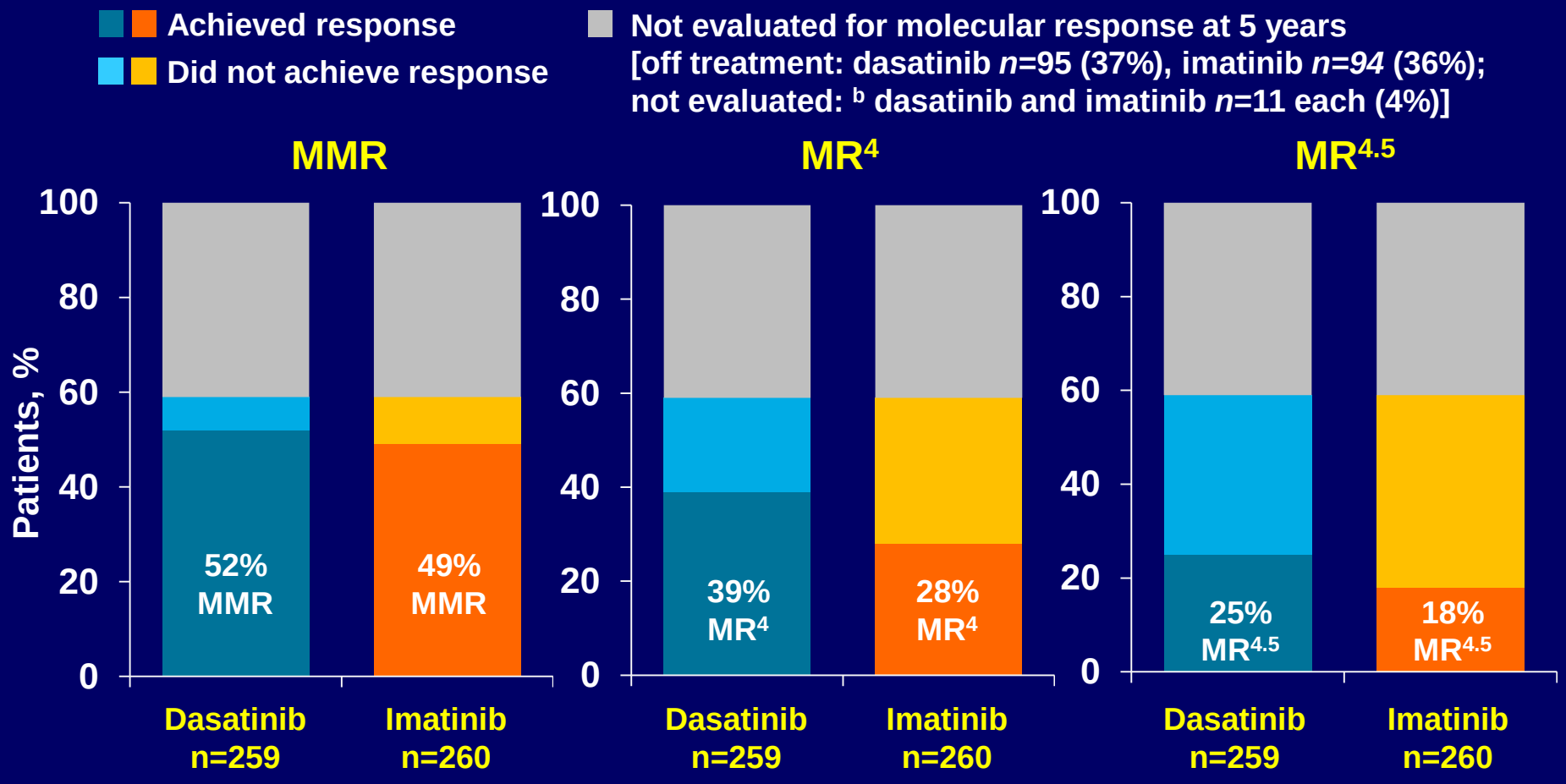
Marin D. et al. J Clin Oncol. 2012 Jan 20;30(3):232-8

Response at 3 Months



Saglio G. et al., ASH 2012

Molecular Responses at 5 Years [a]



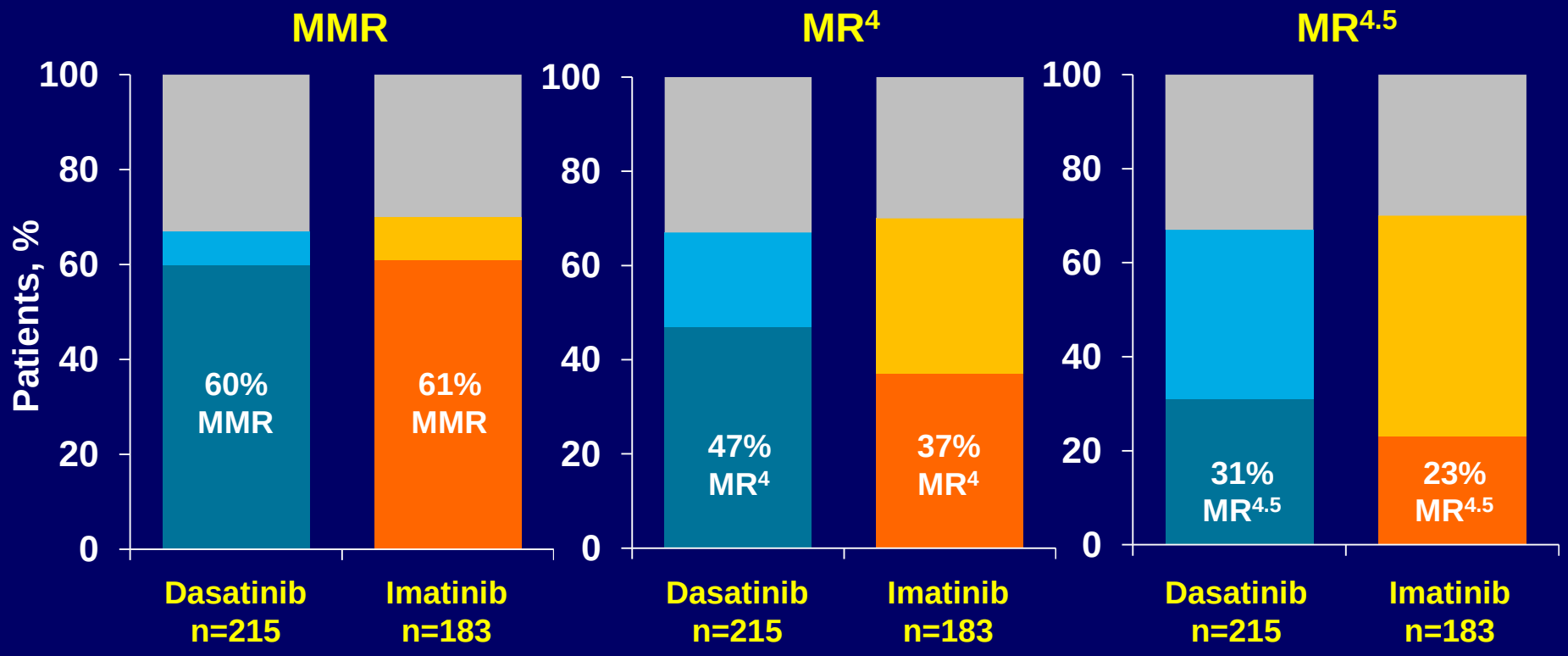
[a] 5 years ± 3 months.

[b] Patients on treatment with no sample analyzed at 5 years ± 3 months.

MR^4, BCR-ABL (IS) ≤0.01%.

Molecular Responses at 5 Years [a] for Patients With BCR-ABL ≤10% at 3 Months

Achieved response
Did not achieve response
Not evaluated for molecular response at 5 years [off treatment: dasatinib n=62 (29%), imatinib n=48 (26%); not evaluated: [b] dasatinib n=9 (4%), imatinib n=6 (3%)



[a] 5 years ± 3 months.

[b] Patients on treatment with no sample analyzed at 5 years ± 3 months.

Prerequisites for TKI Discontinuation

Stable and very low amount of residual disease:

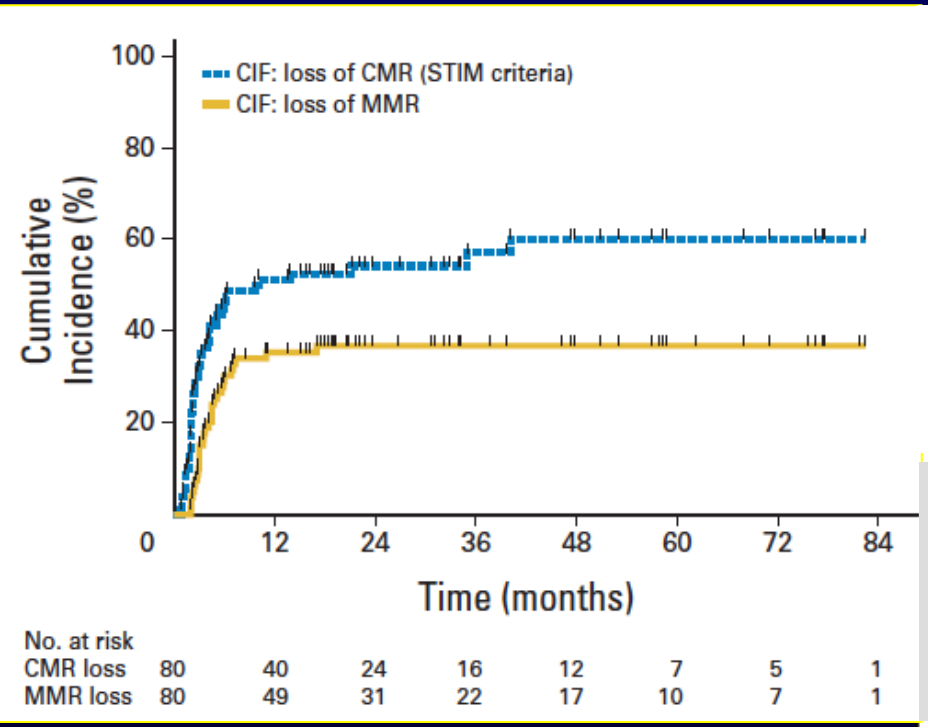
- ✓ **MR^4 (4 logs), $MR^{4.5}$ (4.5 logs) minimum**

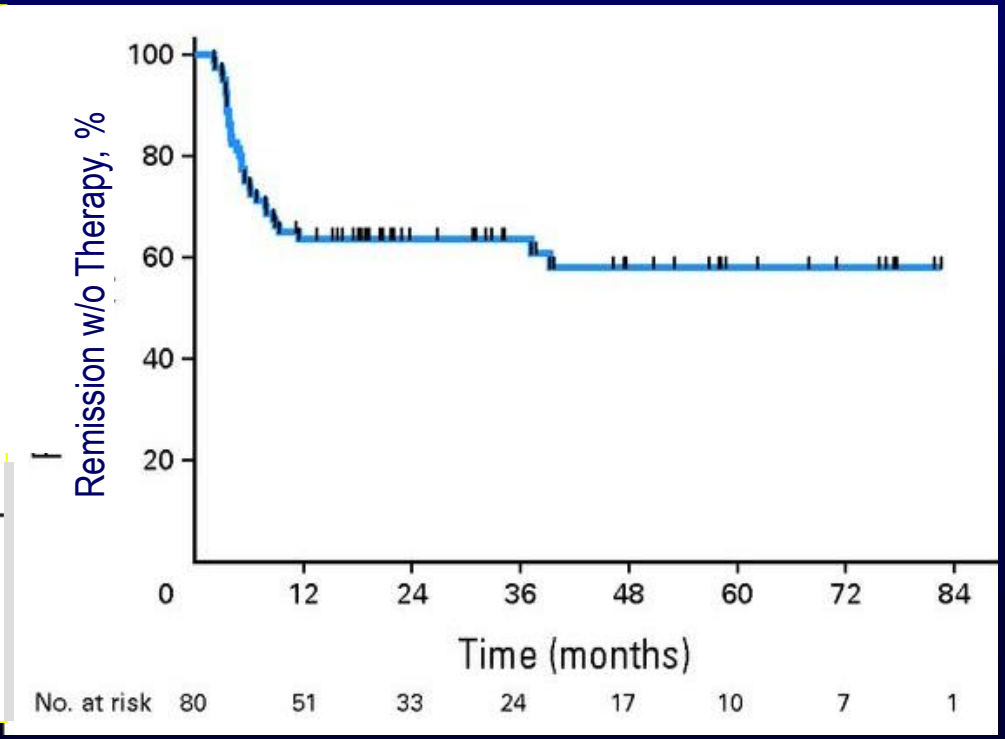
How long must response be acheived:

- ✓ **1 or 2 years?**

✓ **Only in Context of Investigational study?**

Molecular Recurrences and TFR After Imatinib Discontinuation in 100 Patients With CML

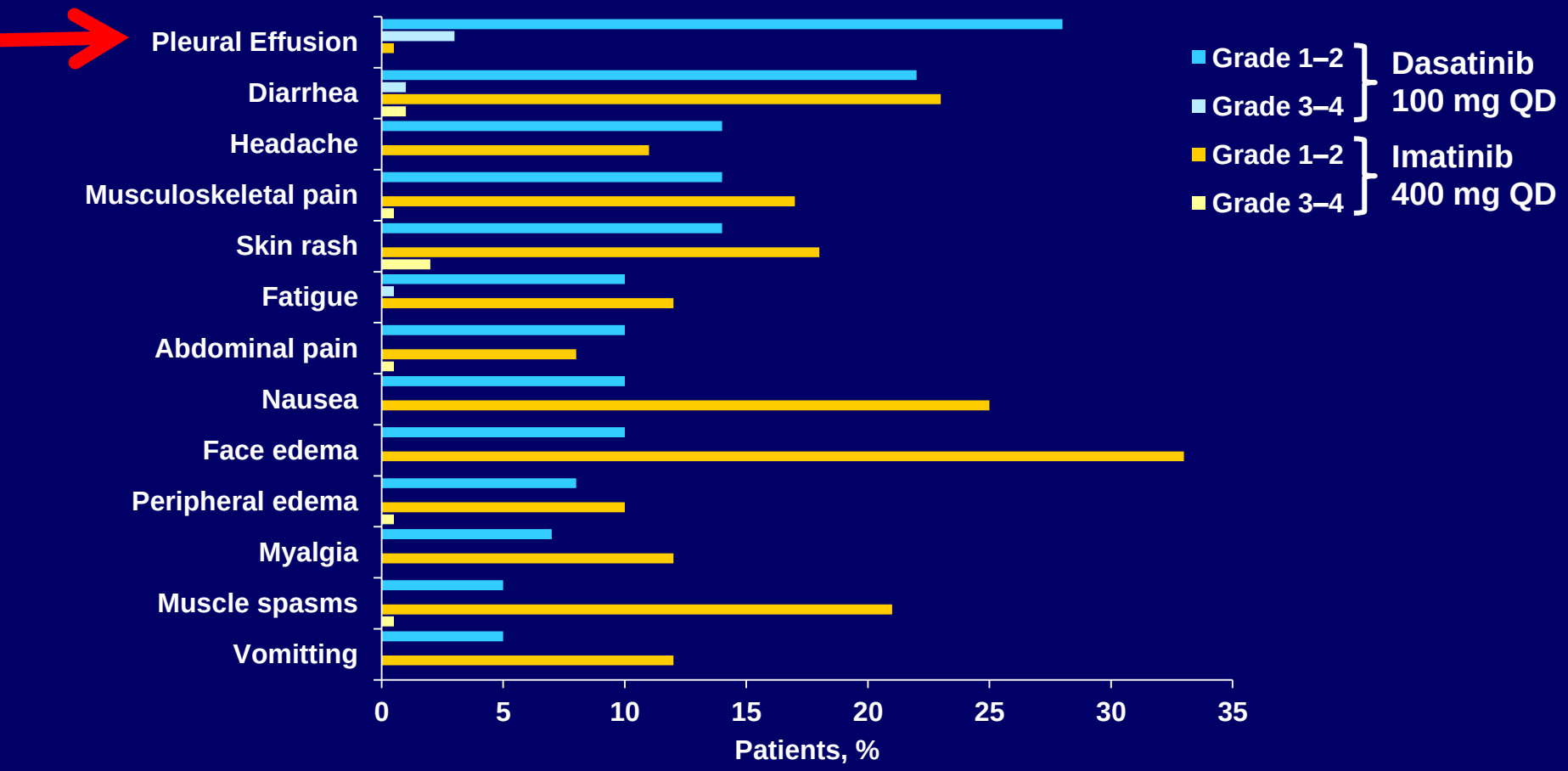




Rousselot P, et al. *J Clin Oncol*. 2014;32(5):424-430.

CIF, cumulative incidence function; TFR; treatment-free remission

On-study Drug-related Nonhematologic AEs (Frequency ≥10%)



- No grade 5 AEs were reported for the nonhematologic AEs listed here
- Pulmonary hypertension was reported in 14 patients in the dasatinib group and 1 patient in the imatinib group
  - No patients had pulmonary arterial hypertension per WHO definition

Characteristics and Management of Pleural Effusion

	Dasatinib 100 mg QD (n=258)
Total, n (%)	73 (28)
Grade 1–2	66 (260
Grade 3–4	7 (3)
Discontinuation due to pleural effusion, n (%)	15 (6)
Dose interruptions due to pleural effusion, n (%)	45 (61)
Dose reductions due to pleural effusion, n (%)	30 (41)
Median time to first grade 1–2 pleural effusion, weeks (range)	114 (4–299)
Median time to first grade 3–4 pleural effusion, weeks (range)	175 (114–274)

- 9 (12%) dasatinib-treated patients had therapeutic thoracentesis
- 9 out of 14 dasatinib-treated patients with pulmonary hypertension also had pleural effusion

Arterial Ischemic Events Regardless of Relationship to Study Therapy

	Treated patients, n (%)					
	Dasatinib 100 mg QD (n=258)			Imatinib 400 mg QD (n=258)		
	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5
Any ischemic event	12 (5)	7 (3)	2 (1)	6 (2)	3 (1)	1 (<1)
Cardiovascular[a]	10 (4)	5 (2)	2 (1)	4 (2)	2 (1)	1 (<1)
Transient ischemic attack	2 (1)	2 (1)	0	0	0	0
Peripheral Arterial Occlusive Disease	0	0	0	2 (1)	1 (<1)	0

[a]Includes myocardial infarction, angina pectoris, coronary artery disease, and acute coronary syndrome.

- Cardiovascular ischemic events occurred in 7 out of 10 patients within 1 year of dasatinib initiation

Dasatinib as first-line therapy

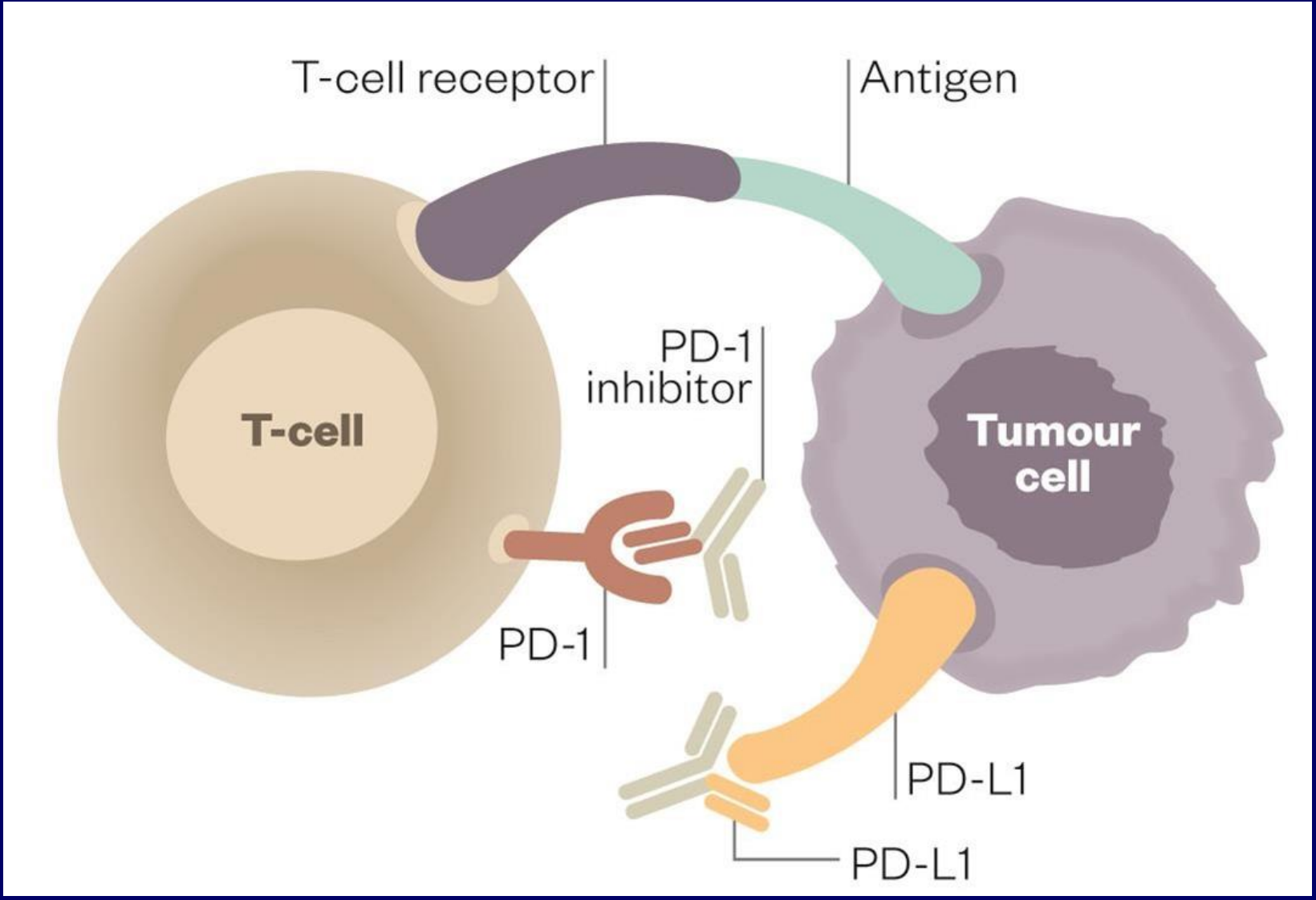
PRO

- Induces faster and deeper MRs (MMR, MR^4, $MR^{4.5}$)
- Reduces the number of patients failing EMR (<10% BCR-ABL at 3 months)
- Reduces the risk of progression and of CML related death
- Does it increase the TFR possibility (?)

CON

- Does not seem to improve substantially OS
- More expensive

DASATINIB and ……..?



Thank you!