Final Study Results of the Phase III Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056)

Abstract #152

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Introduction

- **The second-generation TKI dasatinib is a standard first-line therapy for patients with CML-CP[1]**
- **Patients with newly diagnosed CML-CP treated with dasatinib at 100 mg QD in DASISION (compared with imatinib) demonstrated[1-4]**
  - **Improved rates of confirmed complete cytogenetic response**
  - **Faster rates of molecular response**
  - **An acceptable safety profile**
- **Final analysis from DASISION evaluating long-term efficacy and safety outcomes are presented**
  - **Minimum of 5 years of follow-up since randomization**
  - **Last patient first visit: 24-Nov-2008**

CML-CP, chronic phase chronic myeloid leukemia; DASISION (CA180-056): NCT00481247.

1. SPRYCEL (dasatinib) [prescribing information]. Princeton, New Jersey: Bristol-Myers Squibb Company; 2013. www.sprycel.com/index.aspx2. Accessed December 8, 2014. 2. Kantarjian H, *et al. N Engl J Med.* 2010;362:2260-2270. 3. Kantarjian HM, et al. *Blood.* 2012;119(5):1123-1129. 4. Jabbour E, et al. *Blood.* 2014;123(4):494-500.

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DASISION (CA180-056) Study Design

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

Randomized[a]

- 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* = .007)[1]

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

1. Kantarjian H, et al. *N Engl J Med.* 2010;362:2260-2270.

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Methods

- **Treatment failure: No hematologic response at 3 months, no CHR or cytogenetic response at 6 months, no PCyR at 12 months, no CCyR at 18 months, or progression at any time[1]**
- **Progression: Doubling of white blood cell count, loss of CHR, increase in Ph+ metaphases >35%, transformation to AP/BP, or death from any cause**
- **Progression and survival data collected at least annually after discontinuation in patients who agreed to continued follow-up**
- **Retrospective exploratory landmark analyses are presented**
- **Mutations were assessed at discontinuation of study treatment for any reason in patients that had sufficient BCR-ABL cDNA for amplification**
- ***P* values for secondary analyses are descriptive and not adjusted for multiple comparisons**

AP/BP, accelerated phase/blast phase; CHR, complete hematologic response; PCyR, partial cytogenetic response

1. Baccarani M, et al. *Blood.* 2006;108:1809-1820.

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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]

[a]As defined by investigator. [b] Includes withdrawal of consent and patient request (4 each), insufficient molecular response (3), pregnancy (2), and lost to follow-up, loss of CCyR, increased BCR-ABL, and relocation to the US (1 each).[c] Includes patient request (10), no molecular response/loss of molecular response (4), withdrawal of consent and suboptimal response (3 each), lost to follow-up, insufficient cytogenetic response, and investigator request (2 each), and pregnancy, recurrence of blasts in bone marrow, no CMR, no MMR, and appearance of mutation (1 each)

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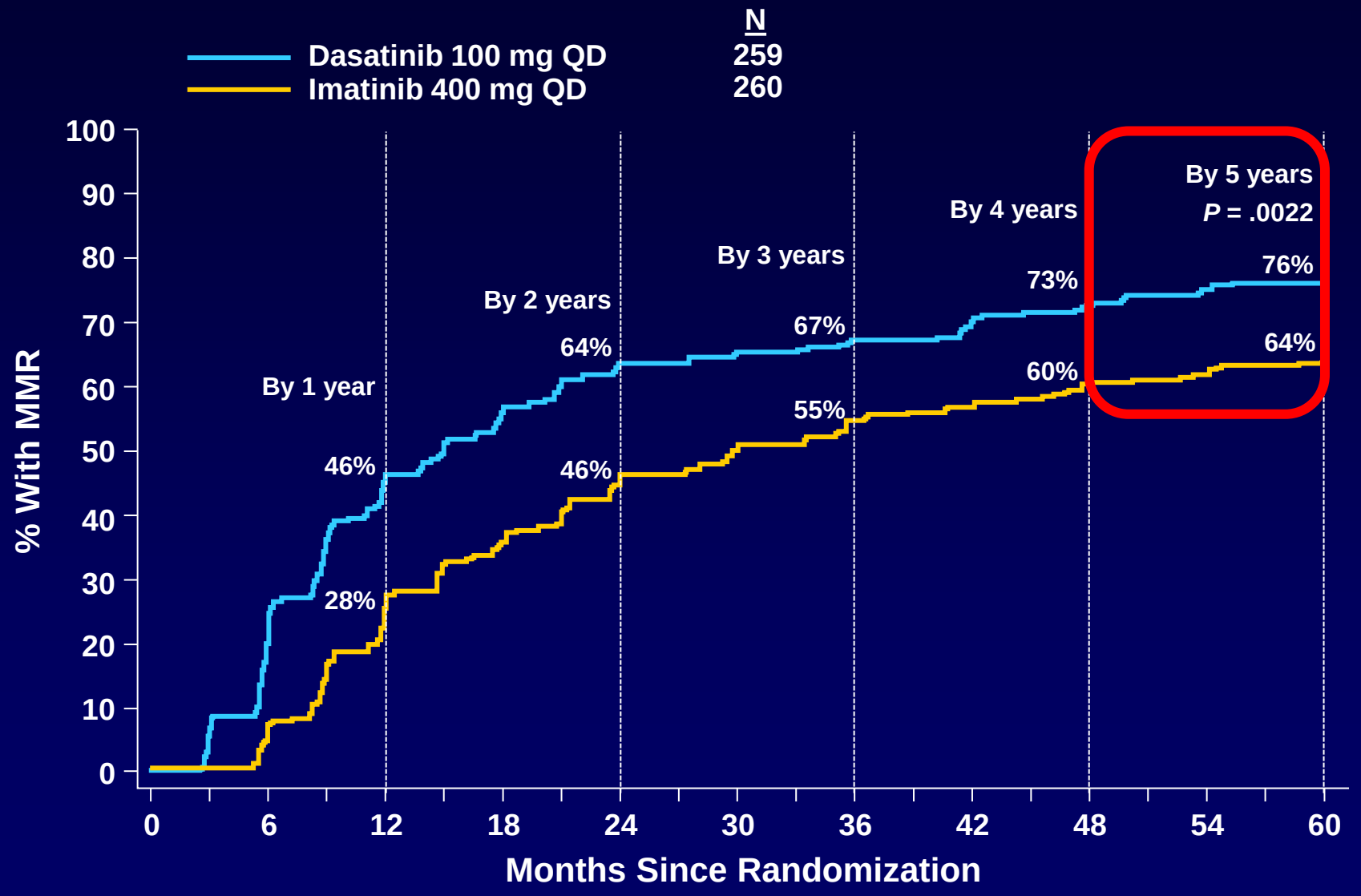
Cumulative MMR Rates Over Time



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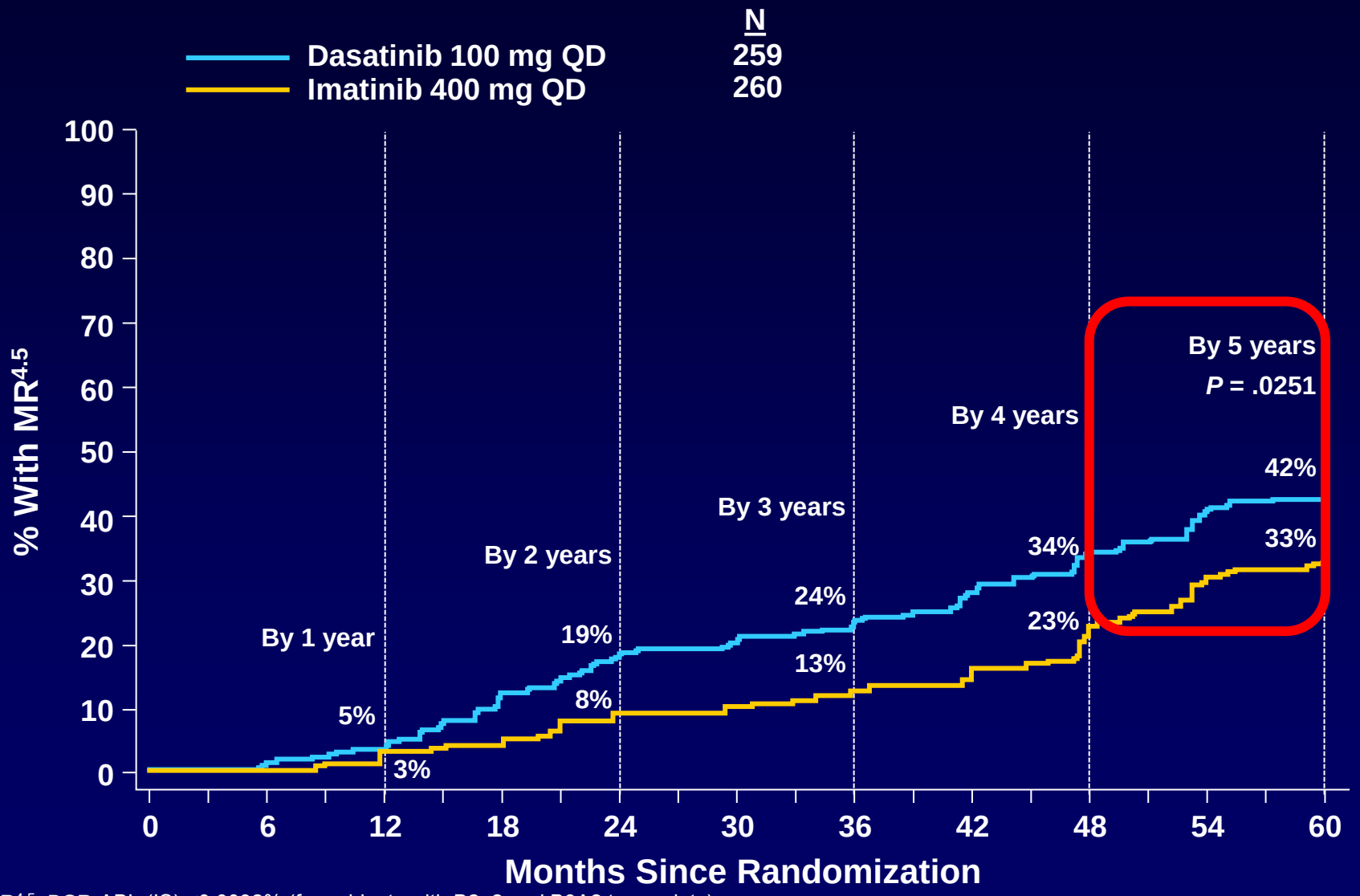
Cumulative MR$^{4.5}$ Rates Over Time



MR$^{4.5}$, BCR-ABL (IS) ≤0.0032% (for subjects with B2a2 and B3A2 transcripts)

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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, n	26	26	–
Estimated 5-year OS, % (95% CI)	91 (87–94)	90 (85–93)	1.01 (0.58–1.73)
Estimated 5-year PFS, % (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)

On-study treatment and in follow-up after discontinuation of randomized treatment. CI, confidence interval; OS, overall survival; PFS, progression-free survival

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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

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5-Year Outcomes 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%)	*P* value	≤10% (64%)	>10% (36%)	*P* value
Estimated 5-year OS, %	94	81	.0028	95	81	.0003
Estimated 5-year PFS, %	89	72	.0014	93	72	<.0001
Estimated 5-year TFS, %	97	83	.0004	97	80	<.0001

On-study treatment and in follow-up after discontinuation of randomized treatment

TFS, transformation-free survival

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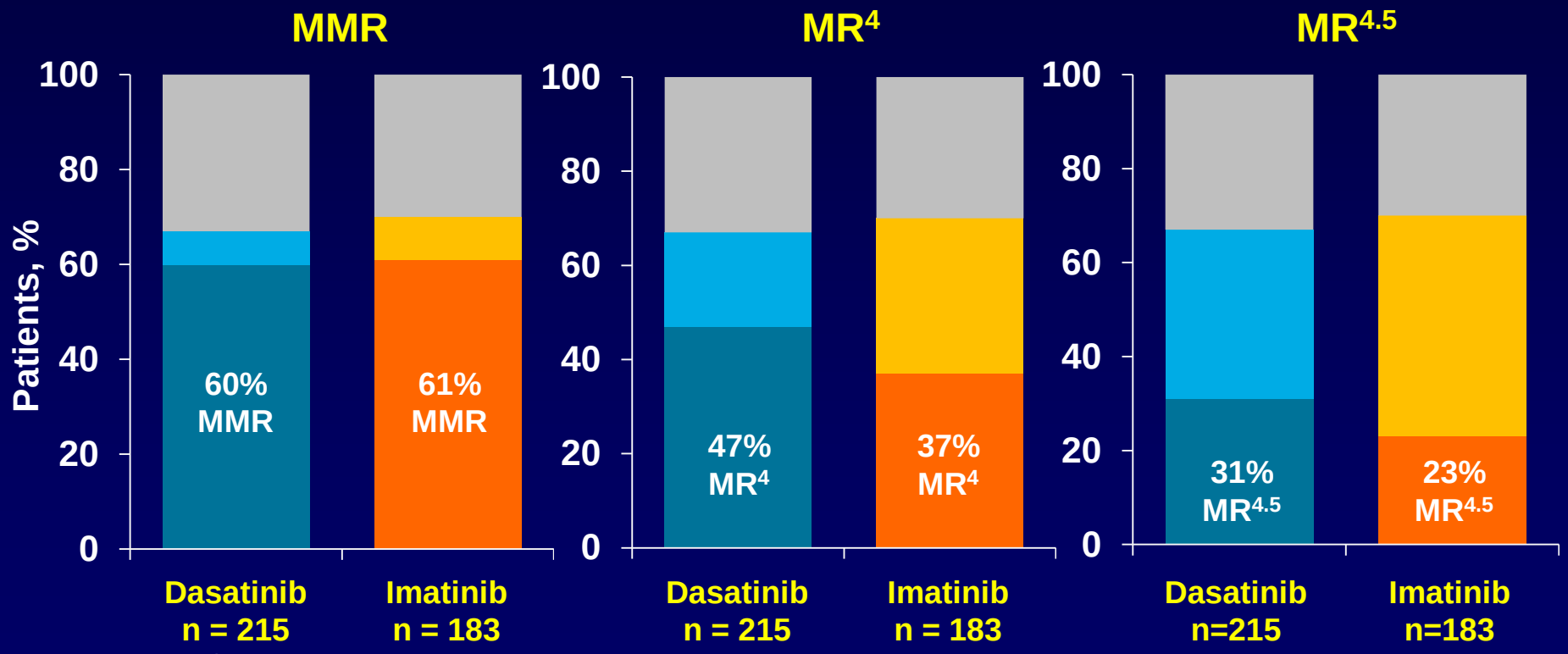
Molecular Responses at 5 Years for Patients With BCR-ABL ≤10% at 3 Months

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[a]: dasatinib n = 9 (4%), imatinib n = 6 (3%)



5 years ± 3 months

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

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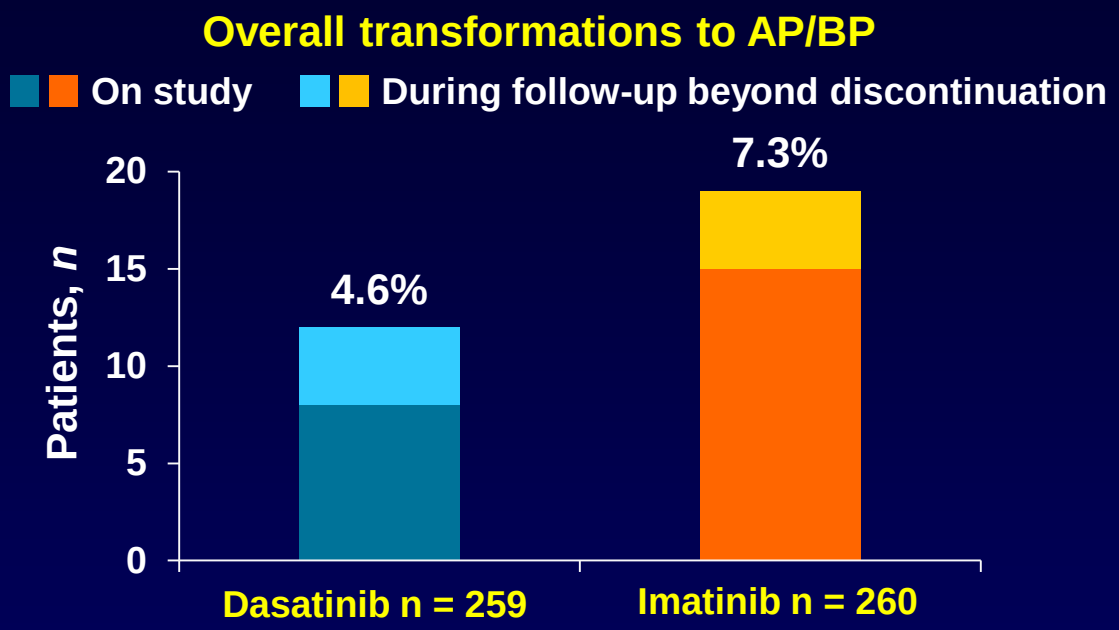
Transformation to AP/BP CML by 5 Years



	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).

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BCR-ABL Mutations at Time of Discontinuation

	Dasatinib (n = 259)			Imatinib (n = 260)		
	Progression n = 18	Treatment failure n = 10	Other n = 173	Progression n = 23	Treatment failure n = 14	Other n = 180
Mutation analysis attempted, n (%)	18 (100)	9 (90)	173 (100)	21 (91)	13 (93)	180 (100)
Mutation, n	10	3	2	10	4	5
No mutation, n	8	5	24	11	8	37

- Mutations were tested in all subjects at study discontinuation. Amplification was unsuccessful in 148 dasatinib- and 139 imatinib-treated patients
- The majority of the patients who had mutations identified discontinued study for progression or treatment failure
- Mutations identified in dasatinib-treated patients: T315I (8), V299L (5), and F317I/L (3)
- Mutations identified in imatinib-treated patients: F359C/I/V (4), G250E (3), M244V, E255K/V, D276G, F317L, E355G, and H396P/R (2 each), and L248V, Y253H, L387M, and E450G (1 each)

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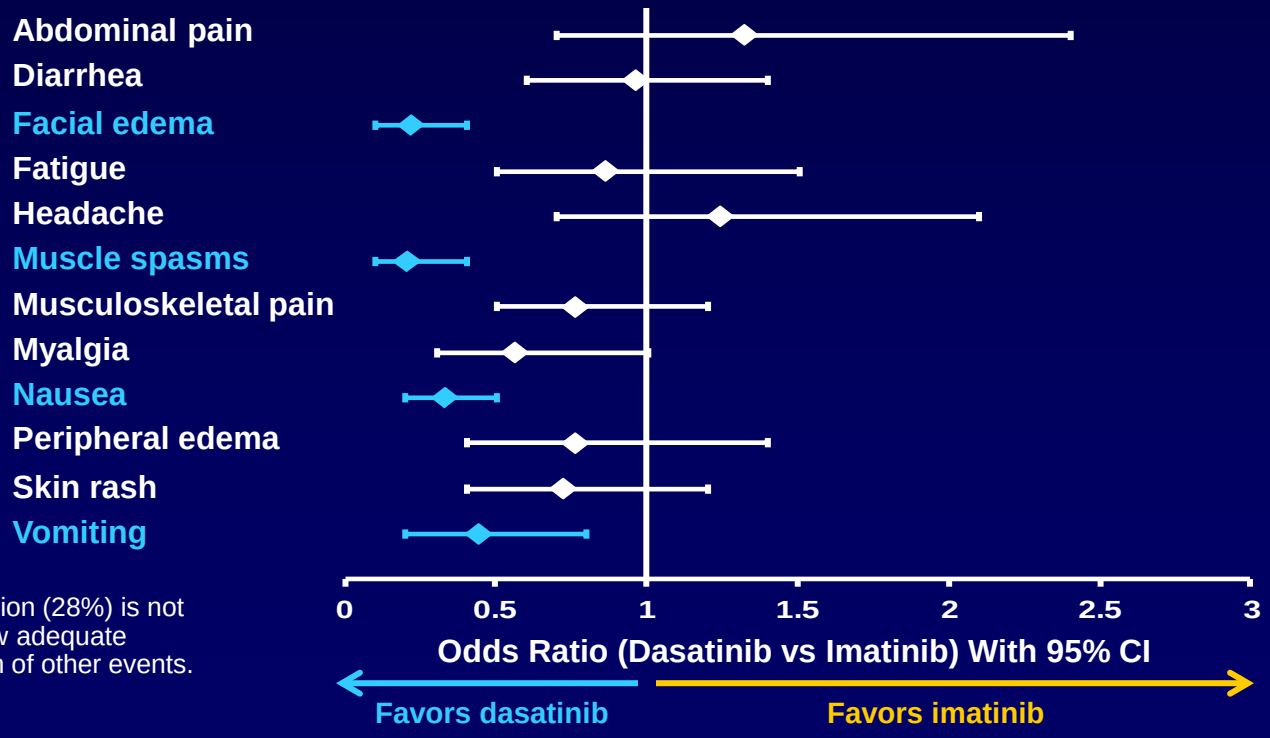
Key On-Study Drug-Related Nonhematologic AEs

- Pleural effusion: 73 (28%) patients on dasatinib and 2 (1%) on imatinib
  - Pulmonary hypertension (PH; on the basis of echocardiography): 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
- AEs reported in ≥10% of patients [a] (no grade 5):



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

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Characteristics and Management of Pleural Effusion

	n (%)
Total	73 (28)
Grade 1-2	66 (26)
Grade 3-4	7 (3)
Discontinuation due to pleural effusion	15 (6)
Dose interruptions due to pleural effusion	45 (62)
Median duration of dose interruption, d (range)	14 (2-63)
Dose reductions due to pleural effusion	30 (41)
Median duration of dose reduction, d (range)	50 (7-751)
Median time to first grade 1-2 pleural effusion, wk (range)	114 (4-299)

- At 5 years, 46 out of 73 patients had recurrent pleural effusions
- Although 62% of patients with pleural effusion had dose interruption (median, 14 d), this did not impair the ability of patients to obtain a response
  - Of patients with pleural effusion, 96% had cCCyR, 82% had MMR, and 50% had $MR^{4.5}$

cCCyR, confirmed complete cytogenetic response

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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

- 7 of 10 cardiovascular ischemic events occurred within 1 year of dasatinib initiation
- Most dasatinib patients restarted therapy without a recurrent event

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

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Conclusions

- DASISION final 5-year study results confirm that, compared with imatinib, patients treated with dasatinib had:
  - Faster times to response
  - Higher cumulative rates of molecular responses
  - Fewer transformations to AP/BP
- PFS and OS rates were similar between treatment arms
  - Given OS rates of ~90% at 5 years in DASISION, a larger population over a longer period of time would likely be required to show a survival difference between dasatinib and imatinib
- Achievement of BCR-ABL ≤10% at 3 months is associated with significantly higher PFS and OS by 5 years
- Safety profile remains consistent, with no new safety signals identified
  - Pleural effusion occurred throughout 5 years but did not impair the ability of patients to obtain a response
  - Arterial ischemic events were uncommon

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