

Optimizing CML Treatment in 2010

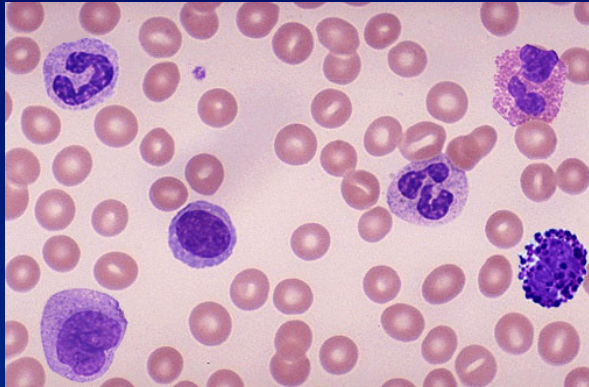
Michael O'Dwyer MD FRCPI FRCPath

Professor of Hematology

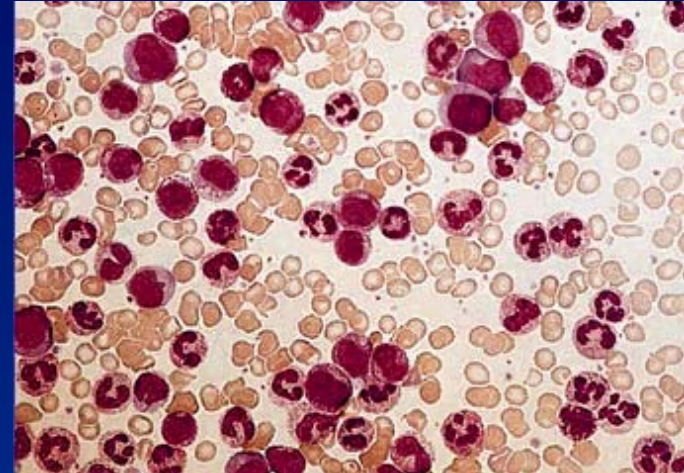
National University of Ireland, Galway

Ireland

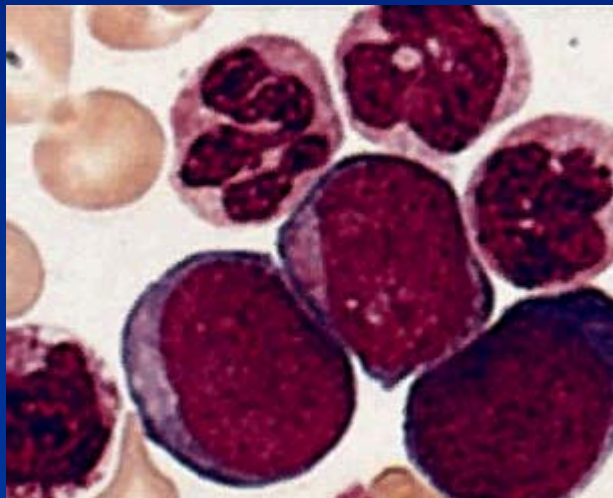
CML



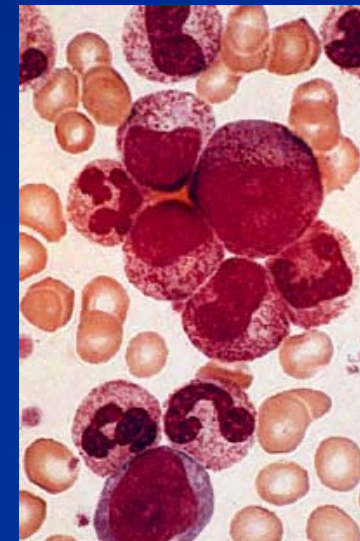
Normal Smear



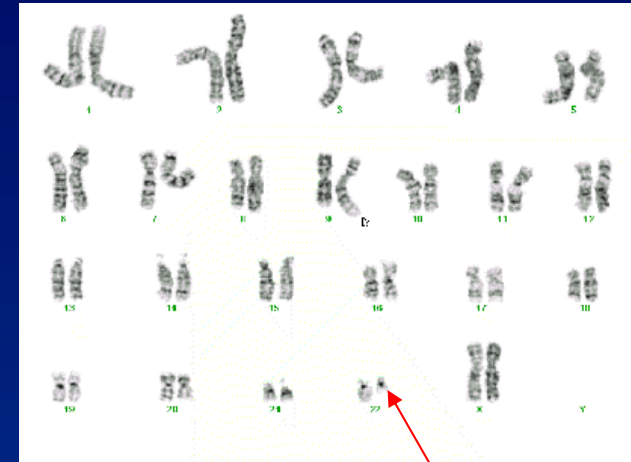
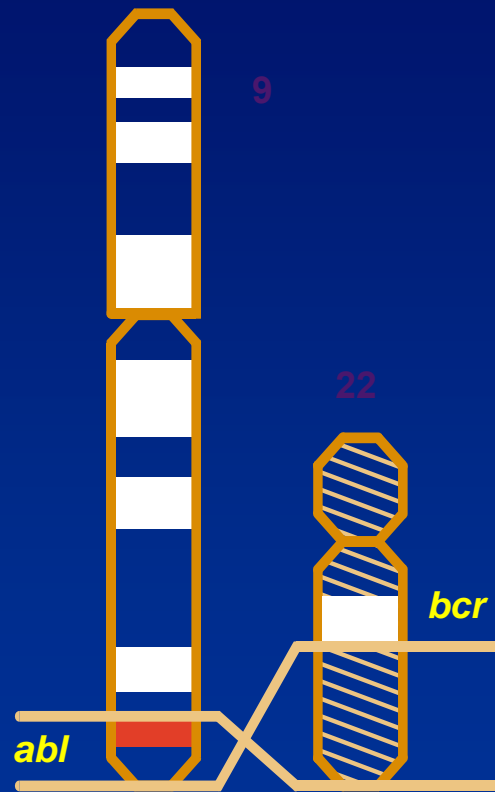
CML Chronic Phase



Blast Transformation



The Philadelphia Chromosome: t(9;22) Translocation and Bcr-Abl



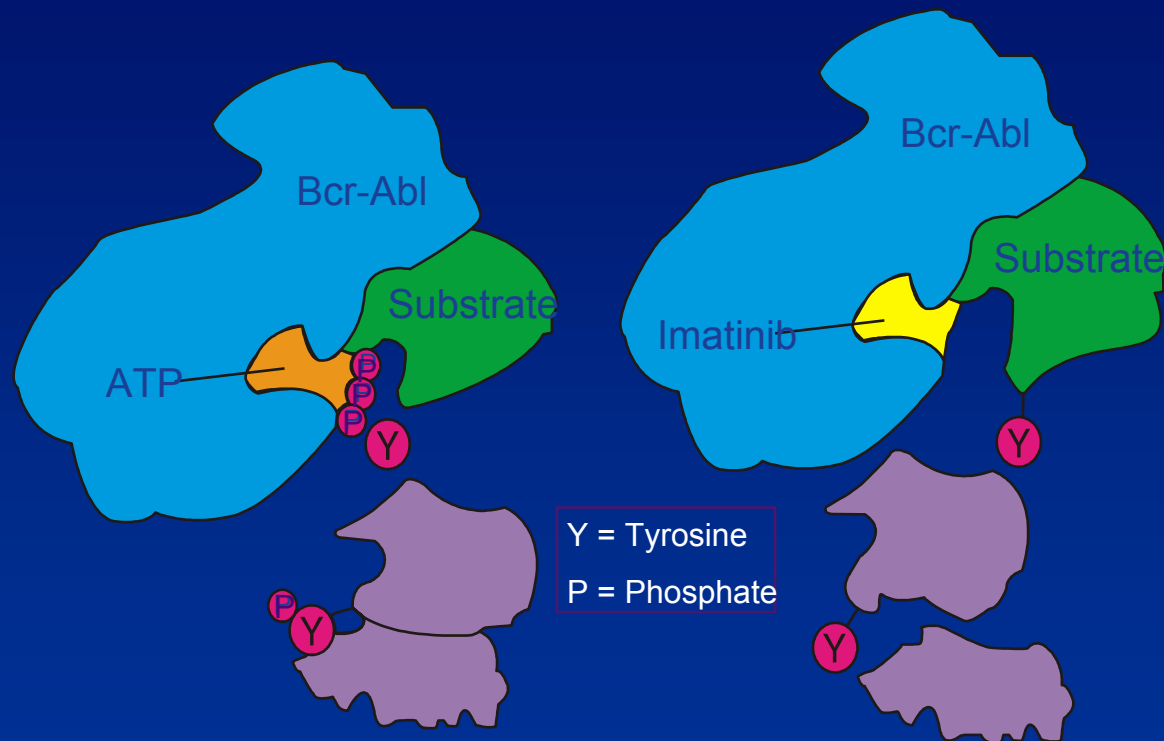
Ph



bcr-abl

FUSION PROTEIN
WITH TYROSINE
KINASE ACTIVITY

Mechanism of Action of Imatinib



Goldman JM. *Lancet*. 2000;355:1031-1032.

Outline of talk

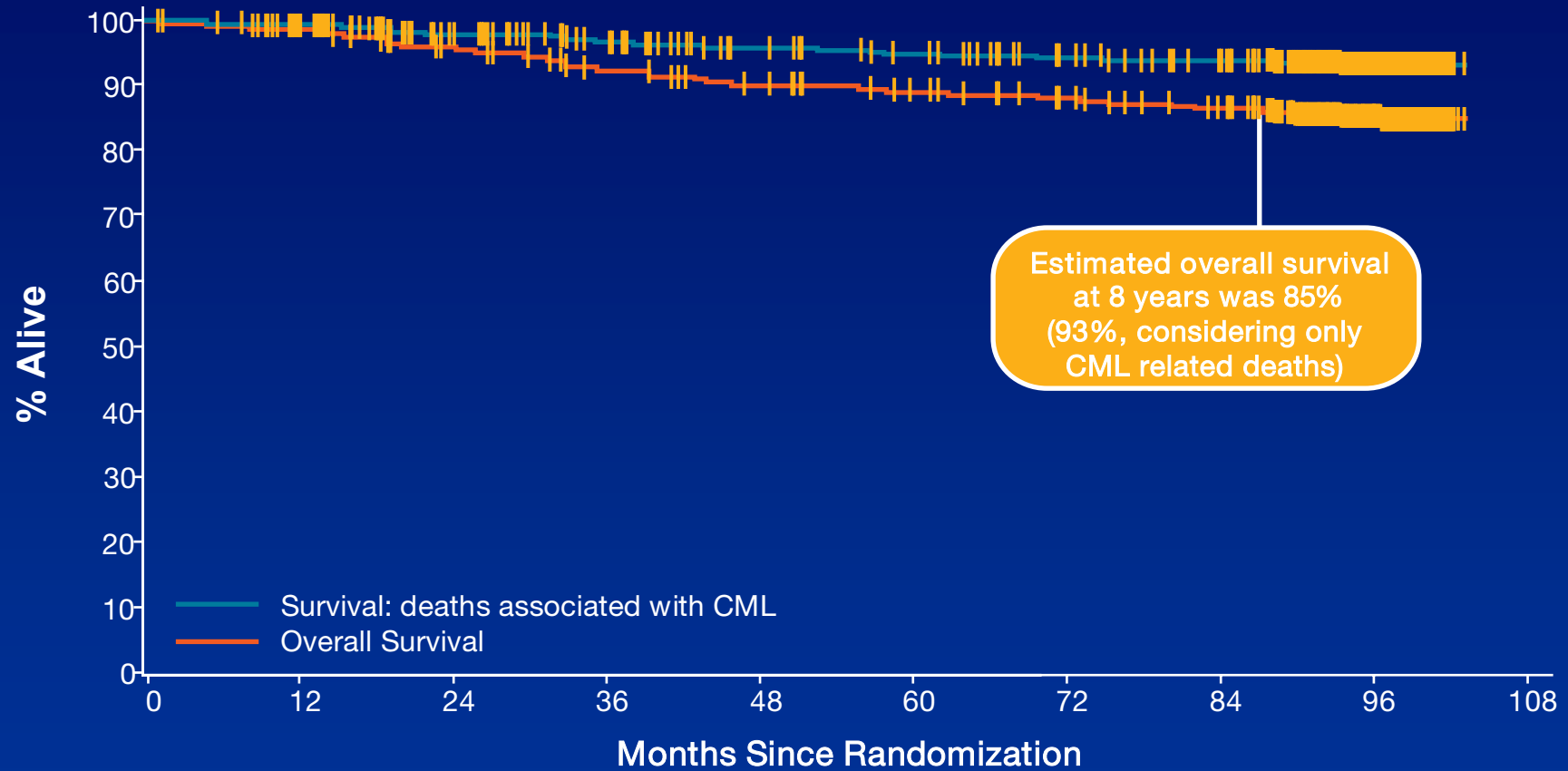
- **ELN Recommendations**
- **Management of Suboptimal Response and Failure**
 - Factors associated with suboptimal response/failure
 - Treatment options
- **Choice of Second line therapy**
 - Efficacy
 - Toxicity profile
- **Influence of specific factors on response to second line therapy**
 - Baseline disease status
 - Mutational status
- **Definitions of Suboptimal Response/Failure on 2nd Gen TKI's**
- **Frontline treatment of CML with 2nd Gen TKI's**

The Need for Revised Recommendations

- **We know more about imatinib therapy in CML:**
 - Long-term durability of response and
 - Long-term therapy well tolerated
 - We know more about the mechanisms and causes of resistance to imatinib
- **We know more about two potent new agents, nilotinib and dasatinib**

IRIS 8-Year Update

Results: Overall Survival (Intent-to-Treat) – Imatinib Arm



Treatment goals in CML

- **Complete hematological response, complete cytogenetic response (disappearance of Ph chromosome) and major molecular response (unable to detect 1 in 1000 CML cells by PCR for Bcr-Abl)**
- **Normal lifespan, normal quality of life**
- **Safe procreation**
- **100% survival and a normal quality of life**

Significance of Response Definitions - 2009

WARNING Requires a more stringent and careful monitoring.

FAILURE A patient who fails should receive a different treatment, whenever available and applicable.

SUBOPTIMAL The patient may still have a substantial long-term benefit from continuing a specific treatment, but the chances of an optimal outcome are reduced. Suboptimal responders may be eligible for alternative approaches, but the condition is transitory by nature.

OPTIMAL Based on current knowledge and expectation, results predict normal survival.

Response Definition - 2009

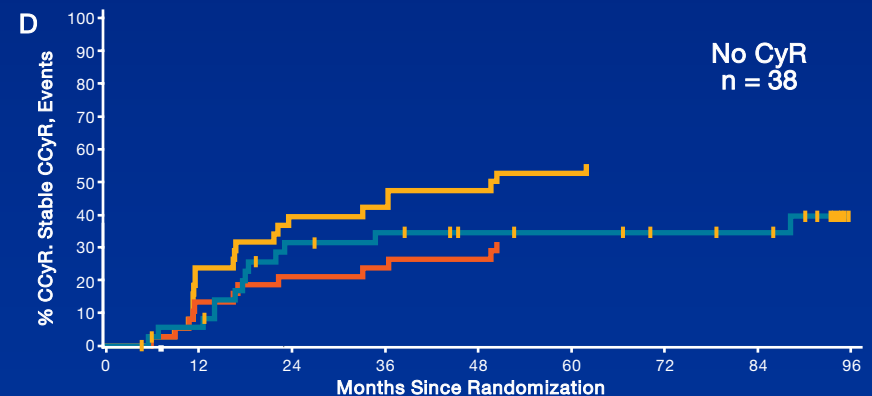
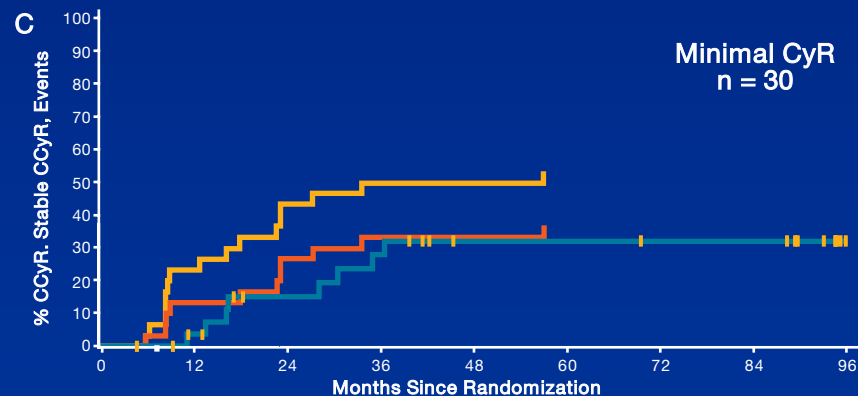
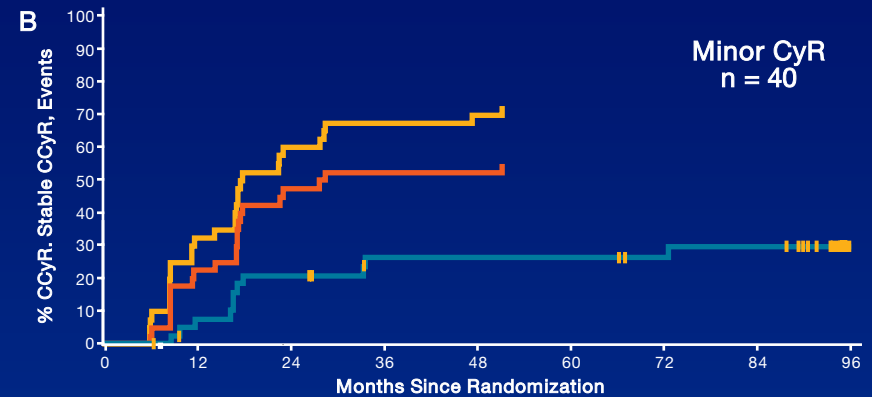
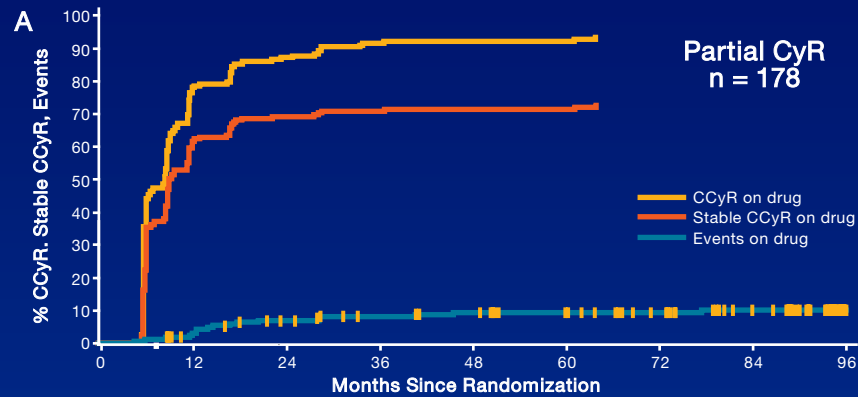
	OPTIMAL RESPONSE	SUBOPTIMAL RESPONSE	FAILURE	WARNINGS
BASELINE	NA	NA	NA	- High risk - CCA/Ph+
3 months	- CHR , and - At least minor CgR (Ph+ ≤ 65%)	- No CgR (Ph+ > 95%)	- Less than CHR	NA
6 months	- At least PCgR (Ph+ ≤ 35%)	- Less than PCgR (Ph+ > 35%)	- No CgR (Ph+ > 95%)	NA
12 months	- CCgR	- PCgR (Ph+ 1-35%)	- Less than PCgR (Ph+ > 35%)	- Less than MMoIR
18 months	- MMoIR	- Less than MMoIR	- Less than CCgR	NA
Any Time	- Stable or improving MMoIR	- Loss of MMoIR - Mutations*	- Loss of CHR - Loss of CCgR - Mutations** - CCA/Ph+	- Any rise in transcript levels - CCA/Ph-

Red indicates changes from 2006 recommendations

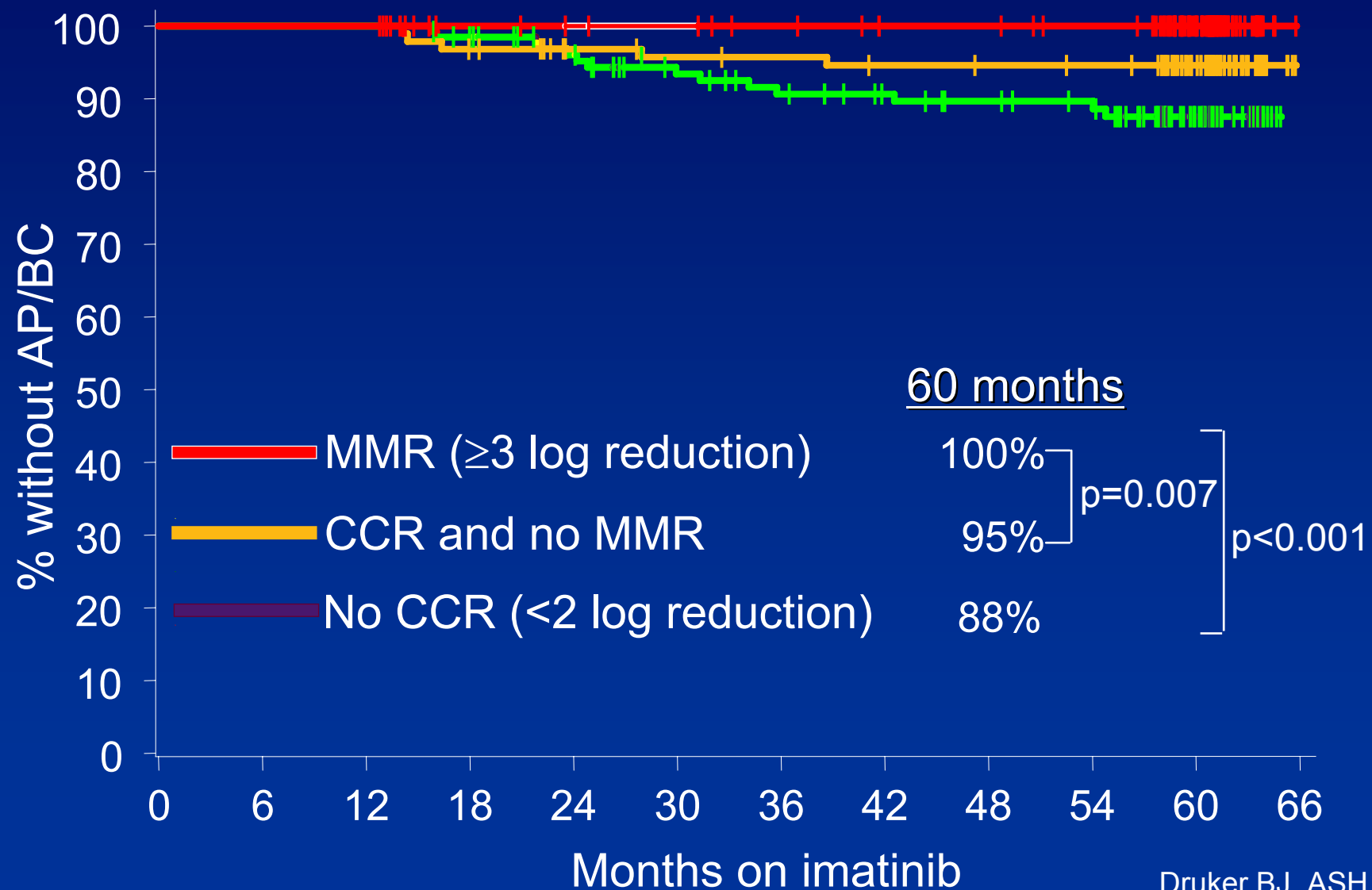
*Low level of insensitivity to Imatinib, ** Highly insensitive to imatinib

IRIS 8-Year Update

Results: Outcomes After Partial (A), Minor (B), Minimal (C), or No (D) Cytogenetic Response at 3 Months



Survival without AP/BC at 60 months by molecular response at 12 months



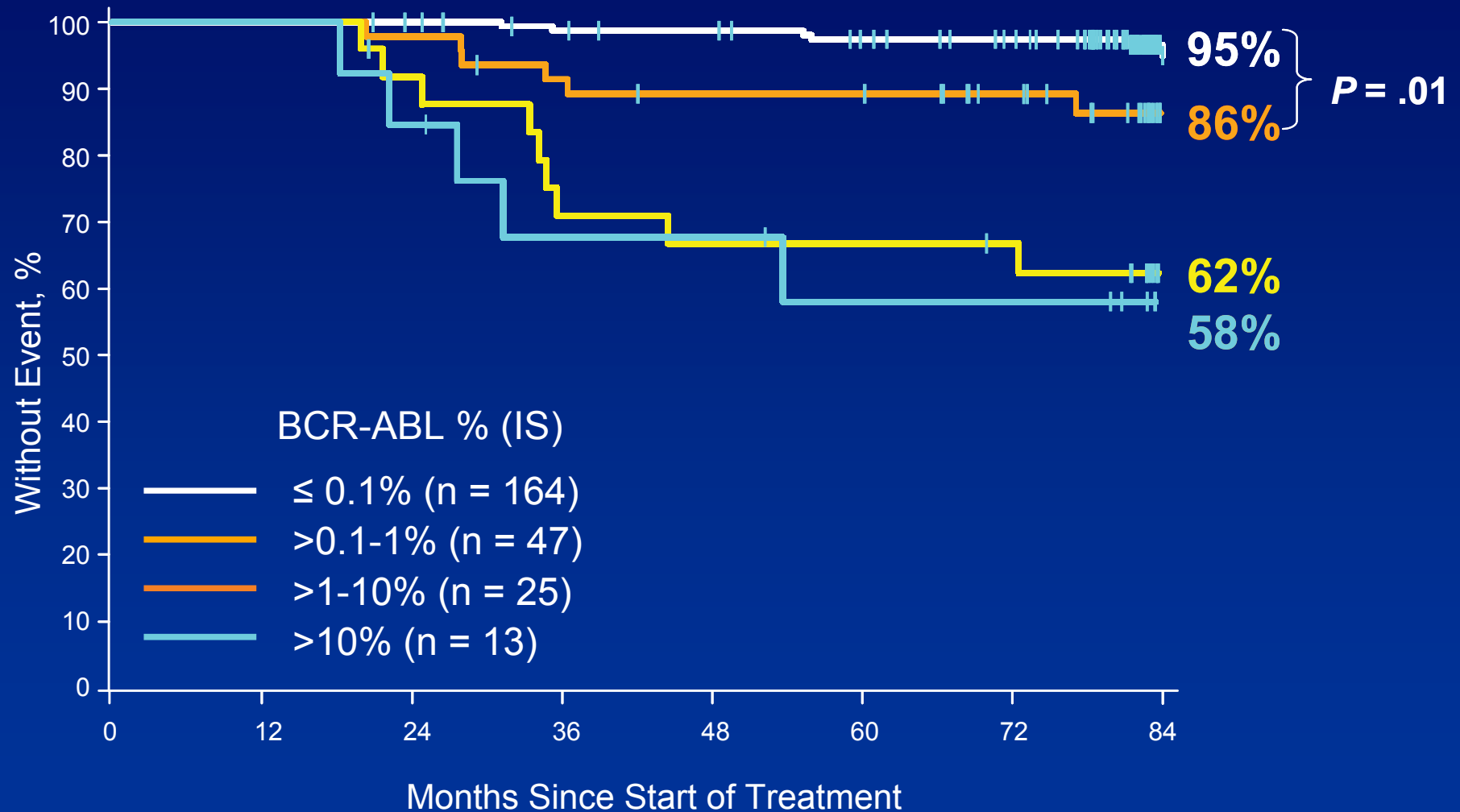
Slide 12

kro2

suggestion- took caps off words in middle of title

kroche, 08/10/2008

IRIS: Achievement of MMR by 18 Months Associated With Improved EFS



* MMR defined as BCR-ABL% (IS) ≤ 0.1.

EFS, event-free survival; MMR, major molecular response.

Hughes TP, et al. *Blood*. 2008;112:129-130 [abstract 334] (oral).

Potential Factors in Suboptimal Response/Failure

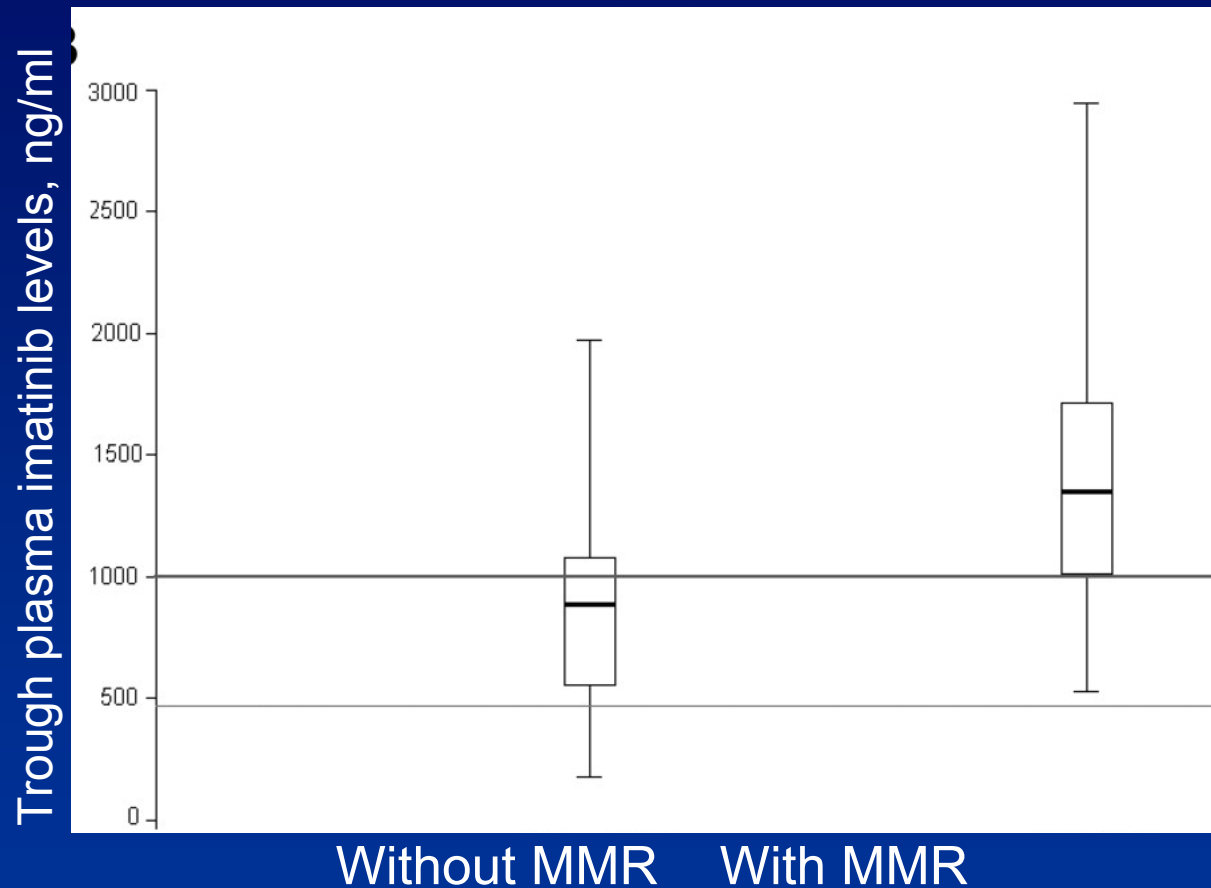
- Non-Compliance/poor adherence !
- Pharmacokinetics: inadequate plasma trough levels of imatinib
- kro3**
- Reduced uptake (low OCT1 expression) or increased efflux of imatinib (MDR1)
- Kinase domain mutations
- Bcr-Abl amplification
- Alternate signaling pathways
- Protein binding
- Stem Cell Quiescence

Slide 14

kro3

suggestion - remove the very end of the point but mention it in the talk
kroche, 08/10/2008

Trough imatinib plasma levels to achieve MMR



kro4

Exceeding plasma threshold of 1002 ng/ml is important for CCyR and MMR.

kro4

Changed font of reference, text, title

kroche, 08/10/2008

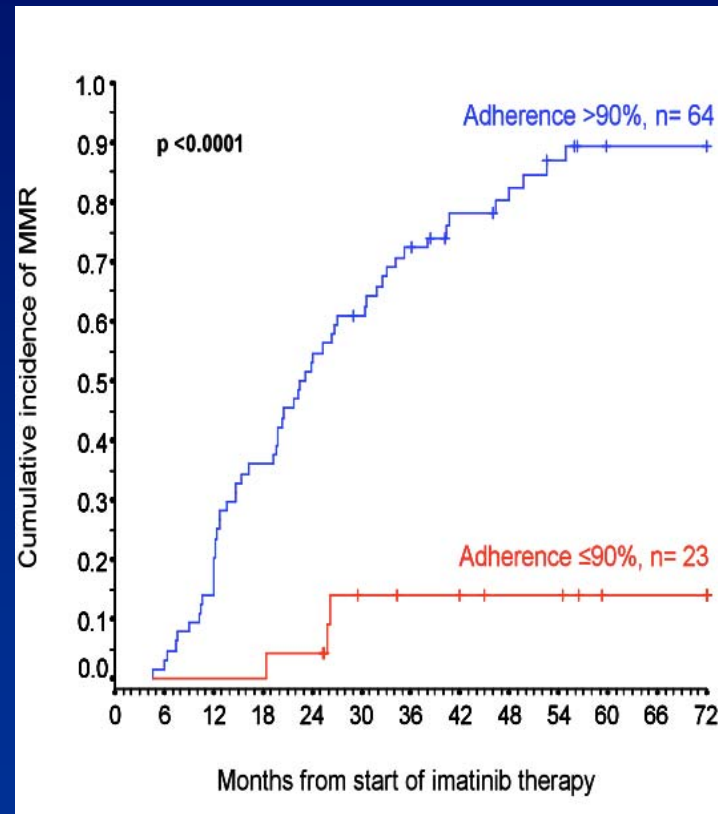
Clinical Situations Where Imatinib Blood Level Testing May Be Useful

- **Concern about non-adherence to therapy**
- **Suspicion that patient may be experiencing a drug-drug interaction**
- **Patient is not responding to therapy as well as you believe he or she should be**
- **Patient is experiencing side effects that are unusually severe for the dose level**

Long Term Adherence to Imatinib Critical for Achieving Molecular Responses in CML Patients



Microelectronic Monitoring Systems (MEMS) An electronic device fitted in the cap of a normal looking medication bottle records bottle opening. MEMS are considered as the 'gold standard' for adherence monitoring.



Median adherence rate was 97.6%. In 23 (26.4%) patients adherence was $\leq 90\%$ (median 76%) and in 12 (13.8%) $\leq 80\%$ (median 63%).

Suboptimal Response: Optimization of Response

- Consider potential for non-compliance, drug interactions, suboptimal dosing, mutations etc
- Blood level monitoring
- Mutation analysis
- Change of treatment

“For instances of suboptimal response, which is a transitory condition, there is no solid, confirmed evidence that a change in treatment will improve the response”

Sub-optimal response to imatinib

- Continue on same IM dose¹
- Test IM dose escalation¹

Evidence from a retrospective analysis of the IRIS study²

- 52% of patients achieved a clinical response 12 months after dose escalation as per IRIS criteria
- 44% of patients achieved a clinical response 12 months after dose escalation as per ELN criteria

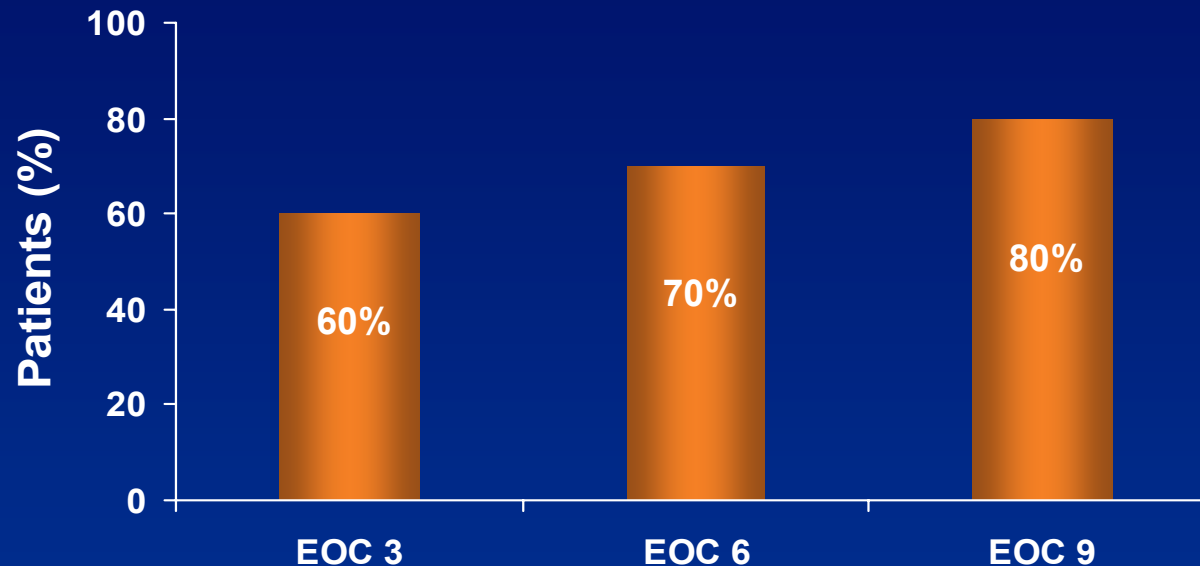
- Test dasatinib or nilotinib¹

1. Baccarani et. al., JCO 2009; 10.1200/JCO.2009.25.0779

2. Kantarjan et al, Cancer 2009; 115(3):551-560

ENABL: Nilotinib 300 mg BID in patients who demonstrate a suboptimal response to imatinib

Patients Achieving MMR During Nilotinib Treatment *



- 8 out of 10 (80%) evaluable patients achieved MMR on study, 6 after 3 months treatment, 1 after 4.5 months, and 1 after 9 months
- All patients (100%) maintained CCyR from baseline

*Cumulative Percentage of Evaluable Patients

Management of Resistance to Imatinib

- **2nd generation TKI (nilotinib or dasatinib)**
- **Allo SCT in patients who have progressed to AP/BC or in presence of T315I**

Second Line Therapy

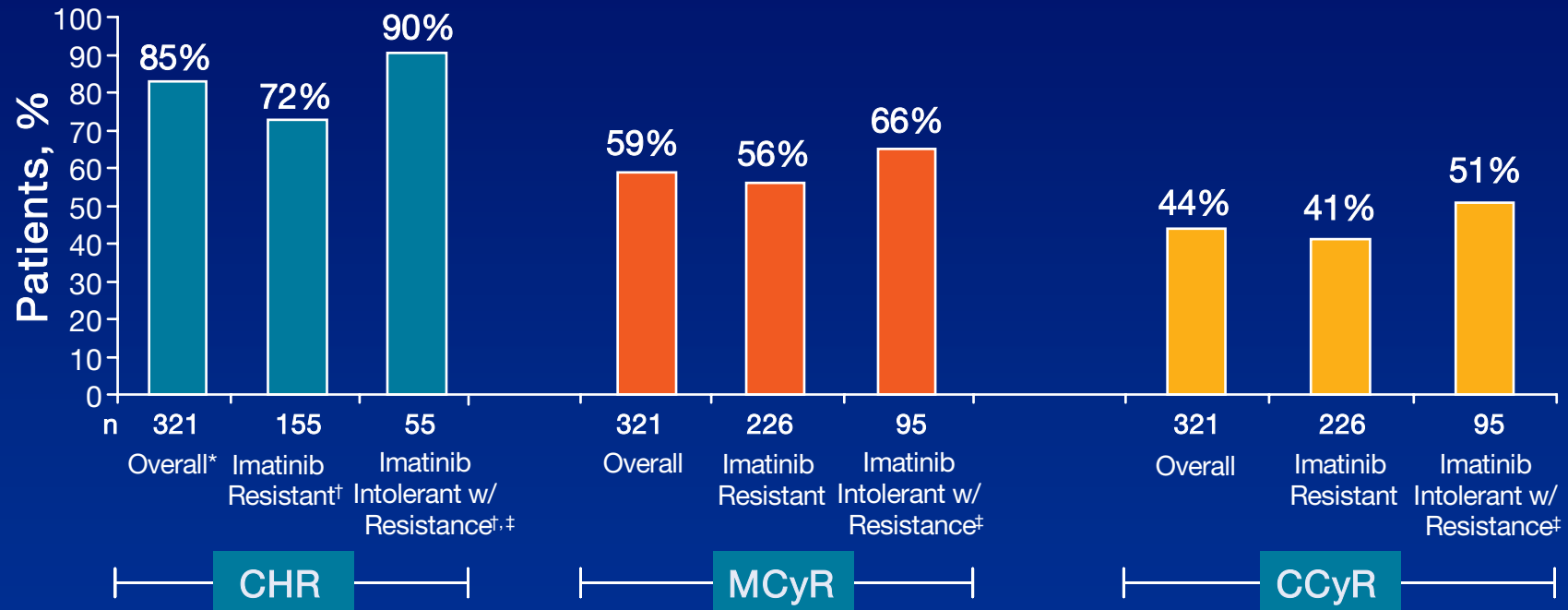
- **Reasons for changing from imatinib:**
 - Suboptimal response
 - Failure
 - Intolerance

Dasatinib or nilotinib as second-line?

- No randomized comparisons
- Different eligibility criteria for pivotal studies
- Comparable CHR, CCyR, MCyR, CyR duration, OS rates in all CML phases
- Different toxicities – type, incidence, severity, duration, onset, consequence
- Mutations clinically meaningful in 3-5% of patients

Phase 2 Study: CML-CP

Response in Patients With a Minimum Follow-Up of 24 Months (N = 321)



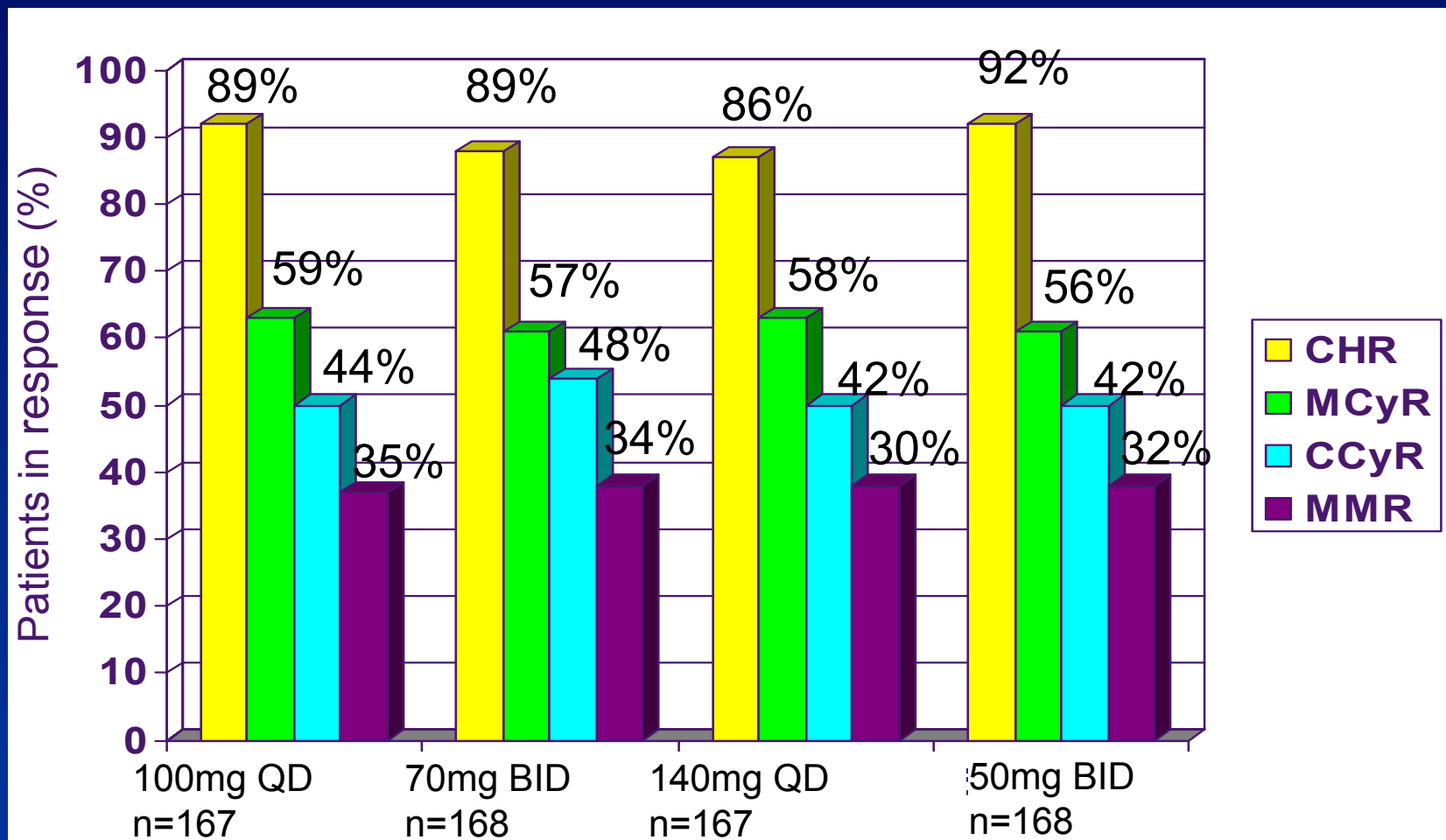
* Patients who achieved (without baseline CHR) or maintained CHR (had CHR at study entry).

† Patients with no CHR at baseline.

‡ See definition of imatinib-intolerant with resistance in the Methods sections.

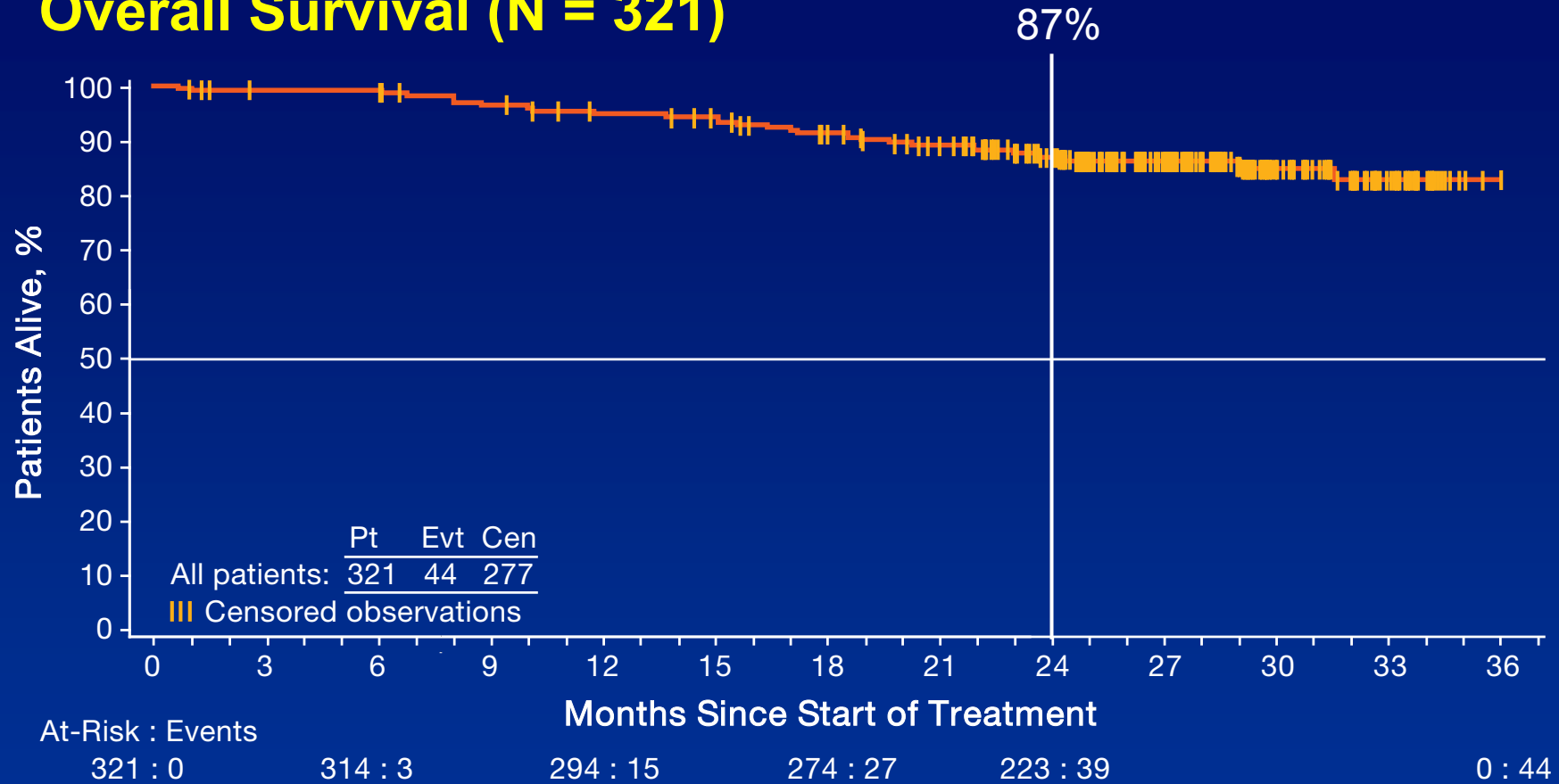
CCyR, complete cytogenetic response; CHR, complete hematologic response; MCyR, major cytogenetic response.

Dasatinib: CML-CP Response at minimum follow-up of 24 months



Dose of dasatinib

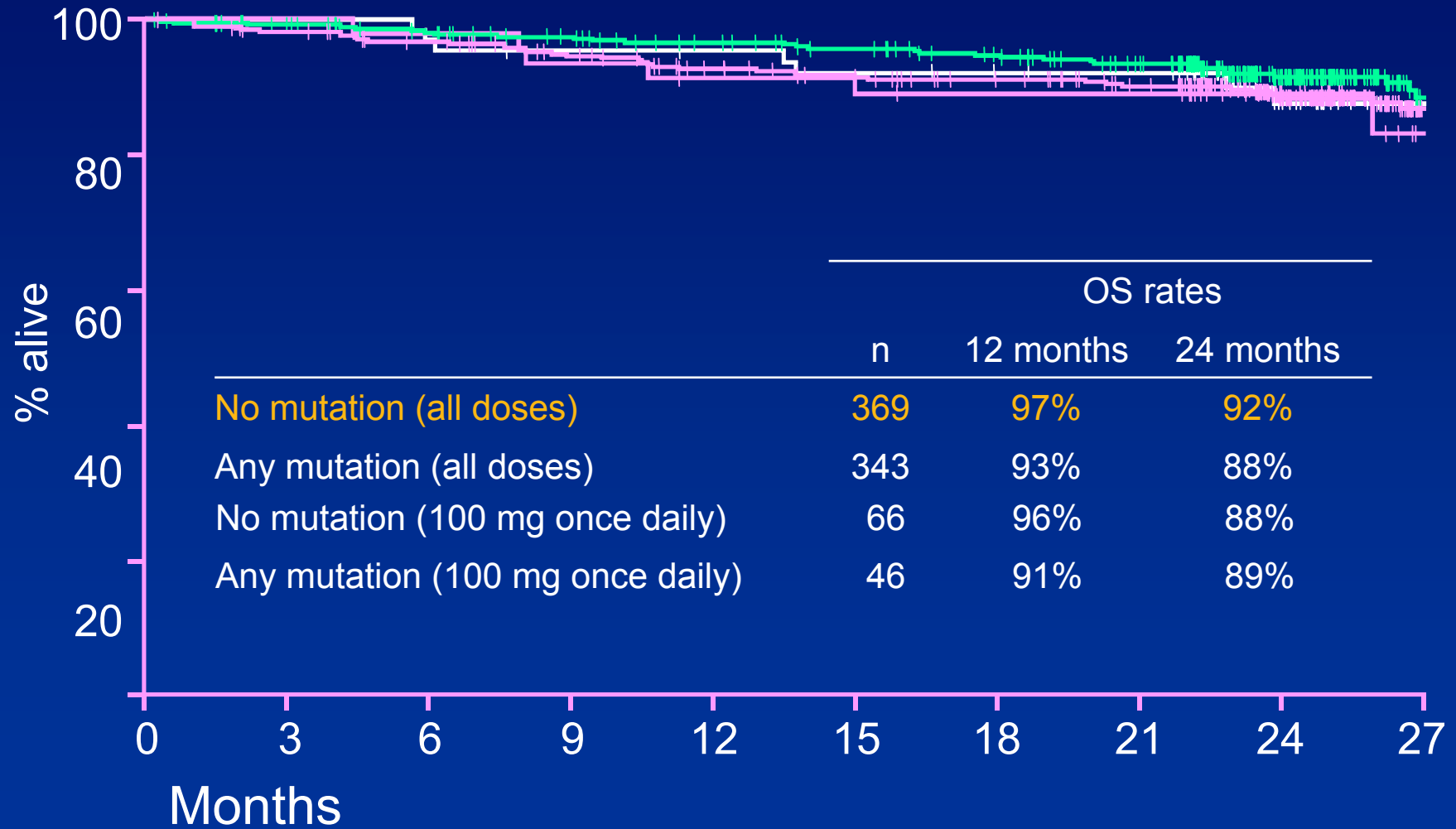
Phase 2 Study: CML-CP Overall Survival (N = 321)



Cen, censored; Evt, event; Pt, patient.

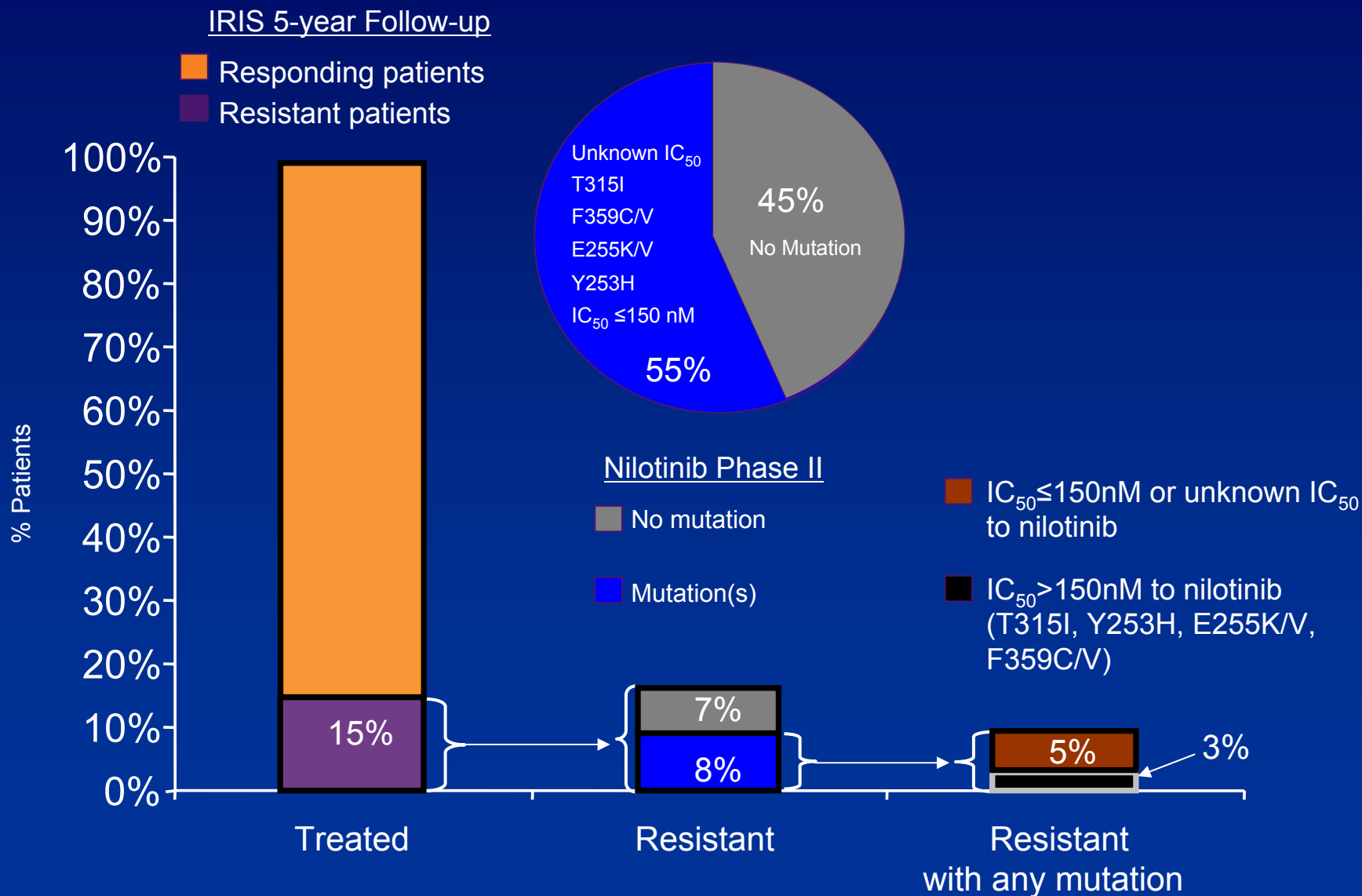
- Estimated OS rate at 24 months was 87%

Dasatinib in CML-CP: Survival

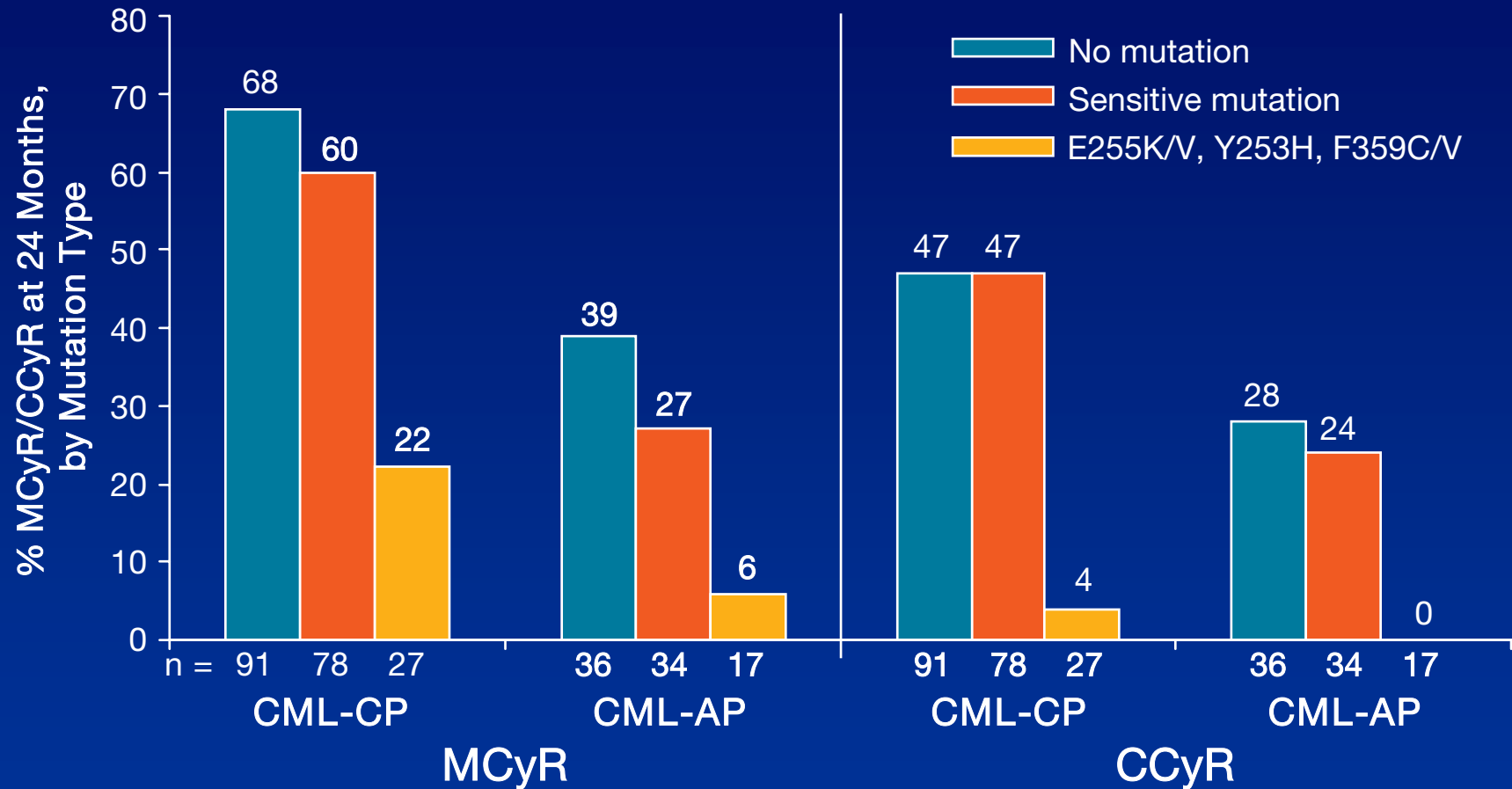


What impact do mutations have on response and EFS to 2nd line TKI's?

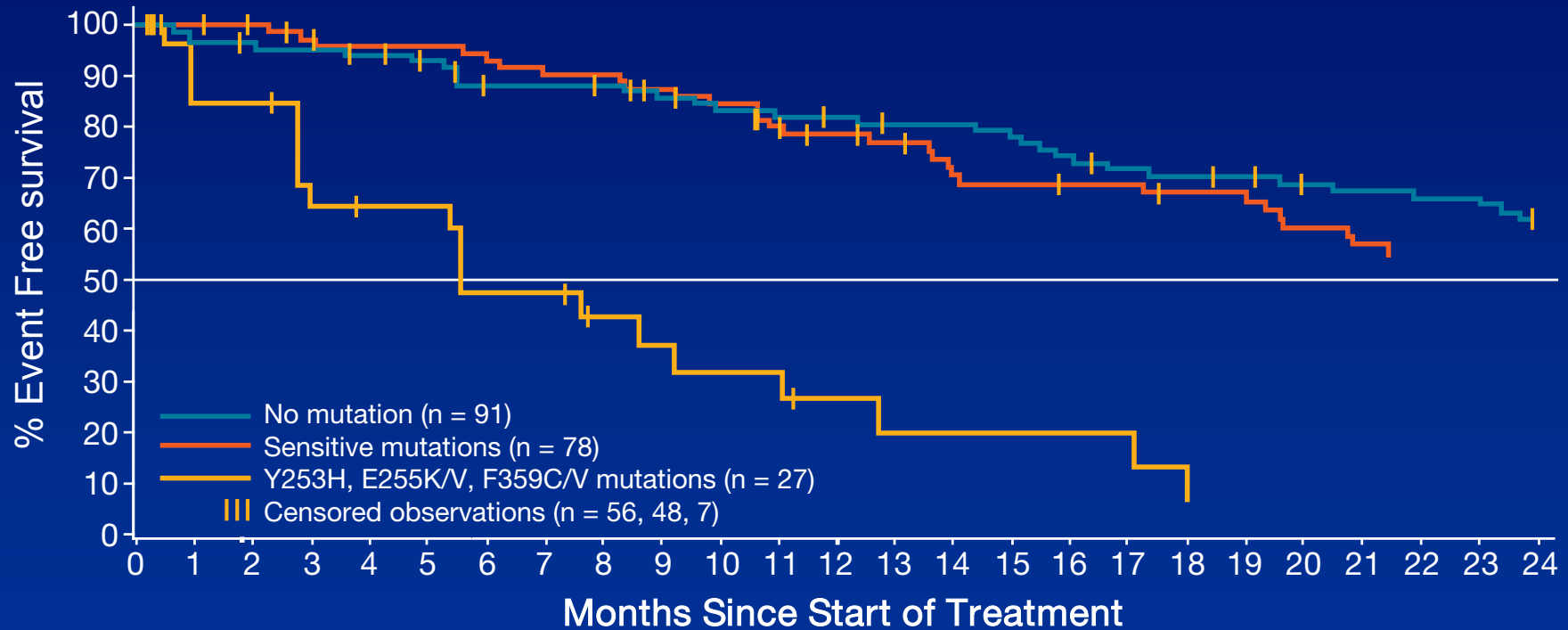
% Patients with mutations with $IC_{50} > 150nM$ to nilotinib



Cytogenetic Responses by 24 Months According to Mutation Type

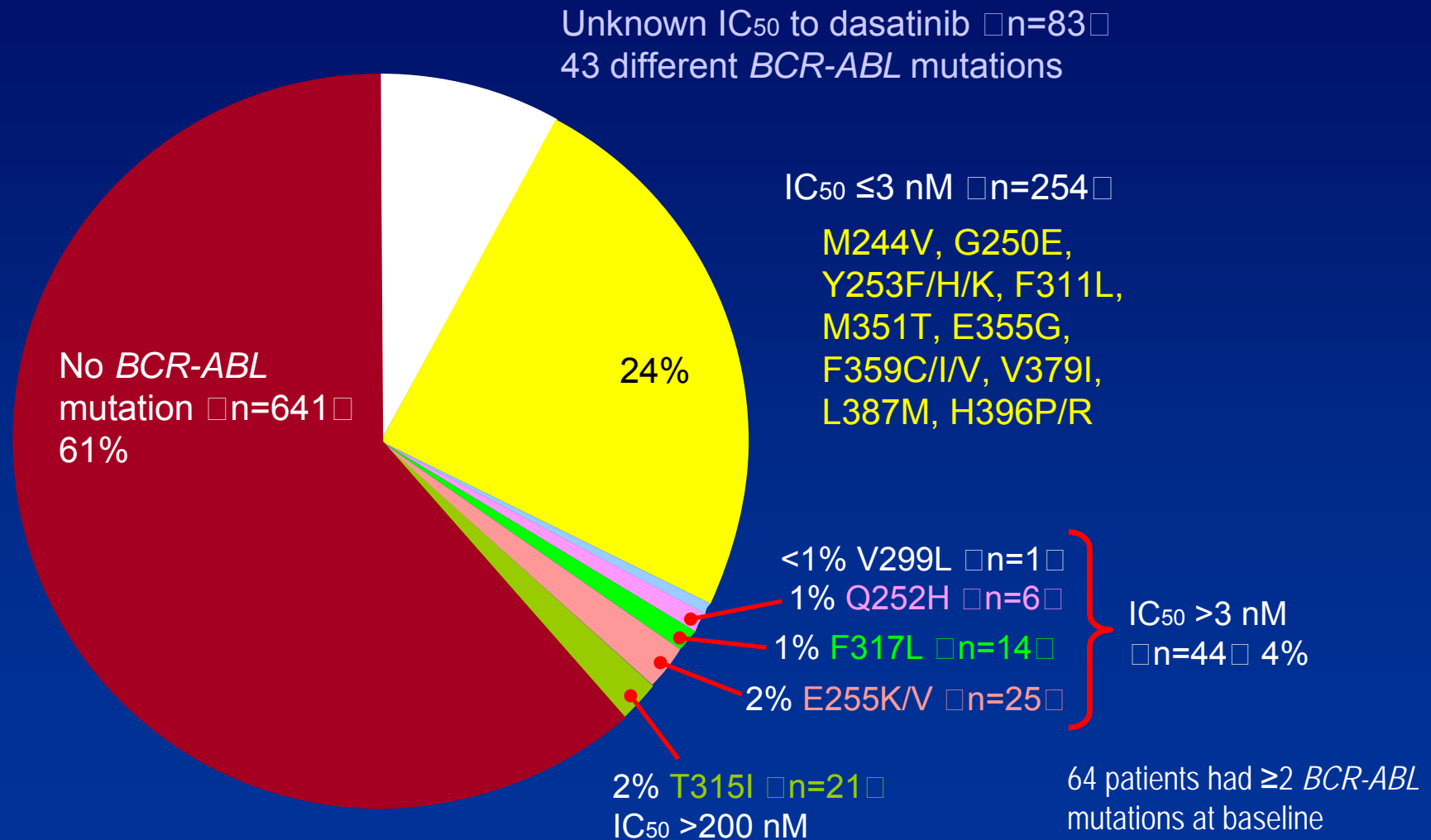


Event-free Survival in Patients With Imatinib-Resistant CML-CP According to Baseline Mutation Type



- At 24 months, event free survival was 62% in patients with no mutations, 55% patients with all other mutations (88%), and 7% in patients with the E255K/V, Y253H, or F359C/V mutation

Frequency of baseline *BCR-ABL* mutations by *in vitro* IC₅₀ to dasatinib



Mutational summary for nilotinib and dasatinib

	Nilotinib (2101 Study)	Dasatinib (Start-C molecular subset)
Specific mutations	E255K/V Y253F/H F359C/V	E255K/V F317L Q252H
12 mo CCyR (n/N)	0/26	1/10

Safety of 2nd Gen TKI's

Phase 2 Study: CML-CP

Most Frequent (> 10%) Drug-Related Nonhematologic Adverse Events (N = 321)

Adverse Event	All Grades (%)	Grades 3/4 (%)
Rash	31	2
Pruritus	26	< 1
Nausea	25	< 1
Fatigue	20	1
Headache	18	2
Diarrhea	12	2
Vomiting	13	< 1
Constipation	13	< 1

- **Severe nonhematologic adverse events were infrequent on nilotinib therapy**

Phase 2 Study: CML-CP

Biochemical Laboratory Abnormalities* (N = 321)

Laboratory Abnormality	Any Grade (%)	Grades 3/4 (%)
Lipase elevation	47	18
Hypophosphatemia	55	17
Hyperglycemia	70	12
Bilirubin elevation (total)	72	7
ALT elevation	69	4
AST elevation	55	3
Hypocalcemia	51	2
Creatinine	24	1
Hypomagnesemia	17	< 1

* Most frequent newly occurring or worsening, regardless of causality.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

What about toxicity in patients with prior imatinib intolerance?

Lack of Cross-Intolerance With Imatinib

- Cross-intolerance is minimal in patients with imatinib-intolerant CML-CP and CML-AP when treated with nilotinib
- Thrombocytopenia is the only imatinib-related AE that has led to nilotinib intolerance and discontinuation of therapy in some patients
- Nilotinib is an excellent therapeutic option for patients with prior intolerance to imatinib

Dasatinib / nilotinib cautions

- **QTc prolongation: Both – Baseline EKG, Close K⁺ and Mg⁺⁺ monitoring, Drug I/A**
- **Pancreatitis, diabetes: Nilotinib**
- **Hypertension, COPD, CCF, chest wall injury, asthma, pneumonia, GI bleeding, auto-immune disorders, aspirin: Dasatinib**

Kantarjian et al. *Blood* 2007; 110: 3540-3546.

Brave et al. *Clin Cancer Res.* 2008; 14(2): 352-359.

Palandri et al. *Haematologica* 2009; July 16 [Epub ahead of print].

Quintas-Cardama et al. *J Clin Oncol.* 2007; 25: 3908-3914.

Quintas-Cardama et al. *Blood* (ASH Annual Meeting Abstracts) 2007; 110: Abstracts 2941 & 2958.

Krusch et al. *Blood* (ASH Annual Meeting Abstracts) 2008; 112: Abstract 3200

Giles et al. *Leukemia.* 2009; May 28. [Epub ahead of print]. Review.

Can we identify who will do well with 2nd gen TKI's and how long does it take to find out?

Prognostic Factors Associated with Favorable PFS in Patients with Imatinib-Resistant /Intolerant CP-CML Treated with Nilotinib

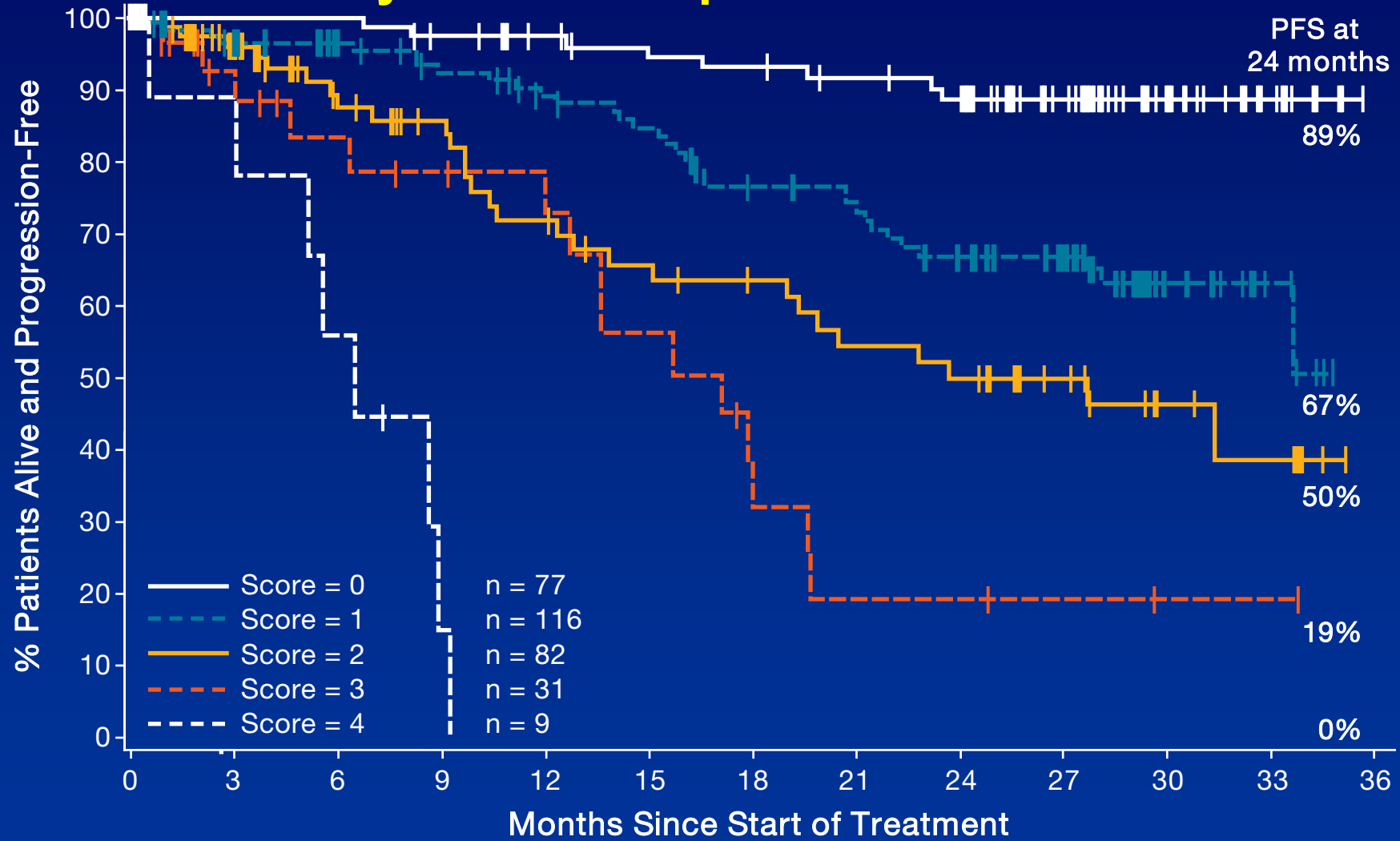
- Achievement of MCyR by 12 mos,
- Lack of baseline mutations with low sensitivity to nilotinib
- Baseline Hb > 120 g/L, and
- Baseline basophilia (< 4%)

Table 6. Kaplan-Meier Estimates of PFS in the Score Groups

Score	n	PFS at 24 Months (%)	95% CI
0	77	89	81-96
1	116	67	57-77
2	82	50	36-64
3	31	19	0.1-38
4	9	0	0

2101 Multivariate Analysis

Results: PFS by Score Groups



What constitutes suboptimal response and failure on 2nd gen TKI therapy?

Provisional definition of the response to Dasatinib and Nilotinib as 2nd Line Therapy of Imatinib –Resistant patients in Chronic Phase

	SUBOPTIMAL RESPONSE	FAILURE	WARNINGS
Baseline	NA	NA	Hematologic resistance to imatinib CCA-Ph+ (clonal progression) Mutations*
3 months	Minor CgR (Ph+ 36-65%)	No CgR (Ph+ >95%) New mutations*	Minimal CgR (Ph+ 66-95%)
6 months	PCgR (Ph+ 1-35%)	Minimal CgR (Ph+ 66-95%) New mutations*	Minor CgR (Ph+ 36-65%)
12 months	Less than MMoIR**	Less than PCgR (Ph+ >35%) New mutations*	

*BCR-ABL1 kinase domain mutations poorly sensitive to TKIs

**BCR-ABL1:ABL1, or other housekeeping genes, ≤0.1% on the international scale

Baccarani et. al., JCO 2009; 10.1200/JCO.2009.25.0779

Conclusions re 2nd line TKI's

- **Causes of secondary resistance to imatinib poorly understood and likely to be multifactorial**
- **In absence of mutations, response with both TKI's is equivalent to that seen in with mutations (with exception of minority of highly resistant cases)**
- **In patients without mutations no evidence that one TKI has superior efficacy to other**
- **Safety profile important consideration in choice of 2nd generation TKIs**

Treatment of Chronic Phase CML 2009 Recommendations

1 st Line all patients	imatinib 400mg daily
2 nd Line imatinib intolerant	dasatinib or nilotinib
2 nd Line imatinib suboptimal response	Continue imatinib at same dose, testing high dose imatinib, or dasatinib, or nilotinib
2 nd Line imatinib failure	Dasatinib or nilotinib In the case of progression to accelerated or blast phase or presence of the T3151 mutation: alloHSCT
3 rd Line dasatinib or nilotinib suboptimal response	Continue nilotinib or dasatinib; consider alloHSCT if warning features (prior hematologic resistance to imatinib, mutations) or EBMT risk score ≤ 2
3 rd Line dasatinib or nilotinib failure	alloHSCT

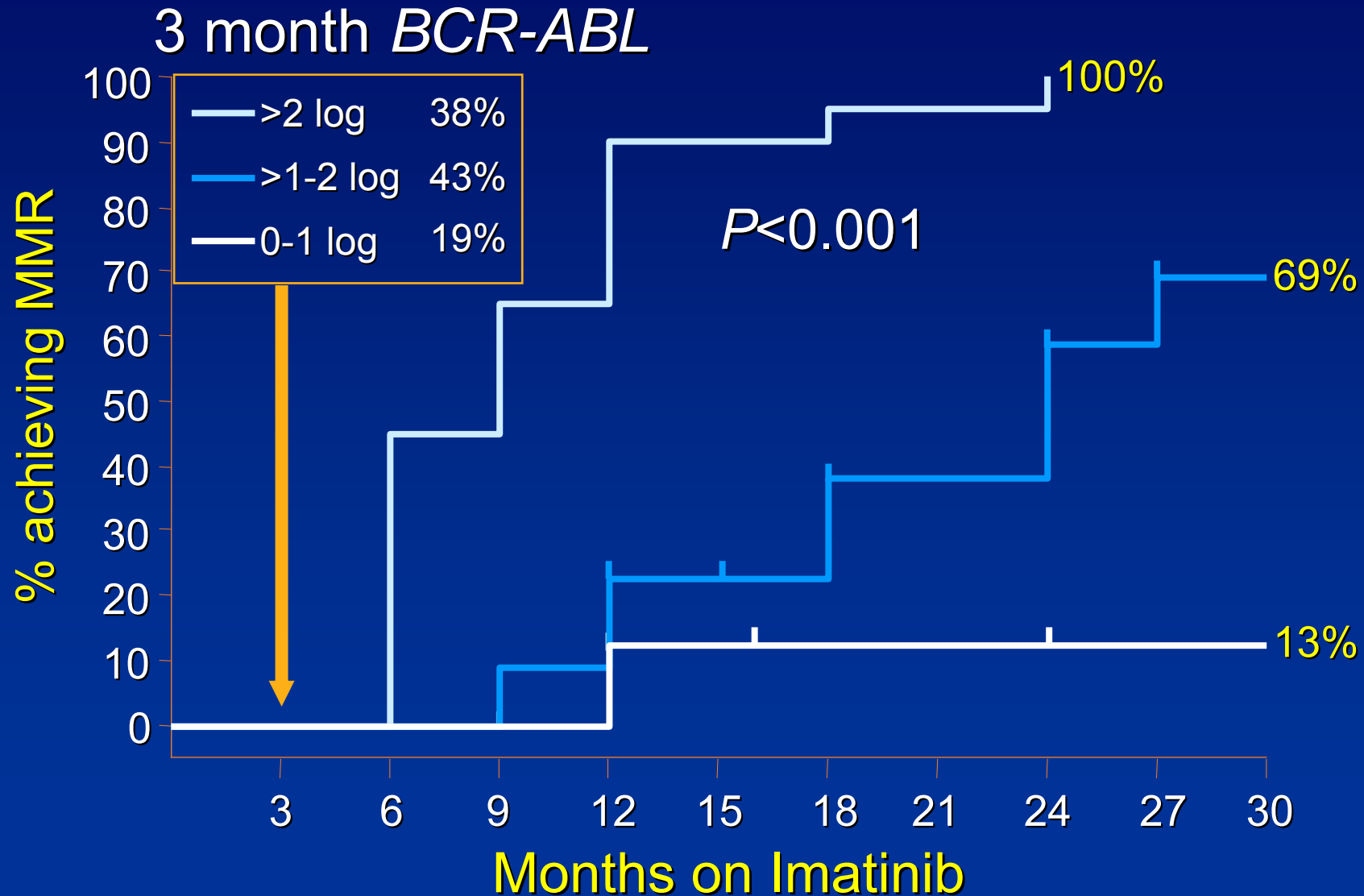
Nilotinib in Newly Diagnosed Patients With CML-CP

Annual Event Rates in Patients After Achievement of CCyR on First-line Imatinib

<u>Year after achieving CCyR</u>	<u>All events*</u>	<u>AP/BC</u>
1st	5.5%	2.1%
2nd	2.3%	0.8%
3rd	1.1%	0.3%
4th	0.4%	0%

* All deaths or loss of response including progression to AP/BC

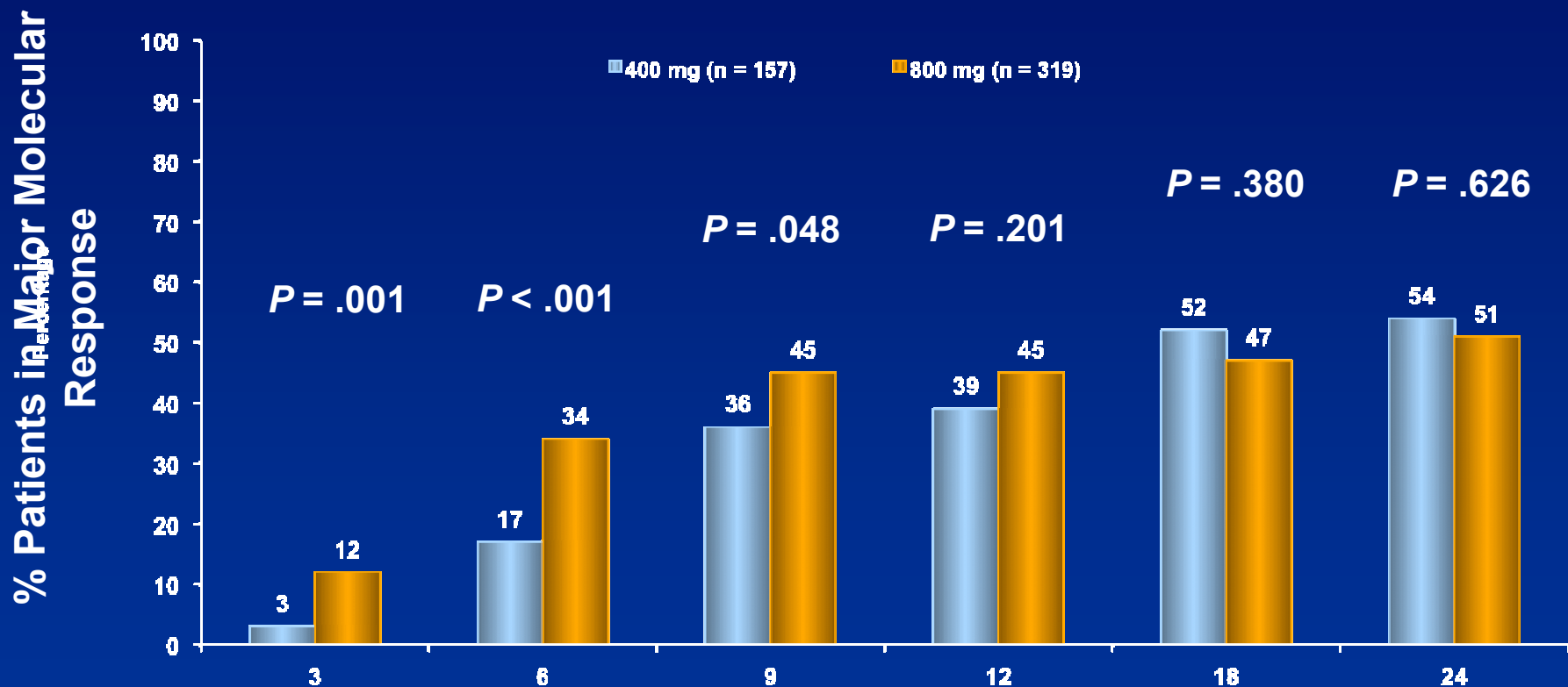
IRIS trial: Probability of achieving MMR



Early Optimization?

- **Could more intensive kinase inhibition early on improve long term outcome?**
- **Potential options**
 - high dose imatinib
 - 2nd generation TKI's e.g. Nilotinib, Dasatinib

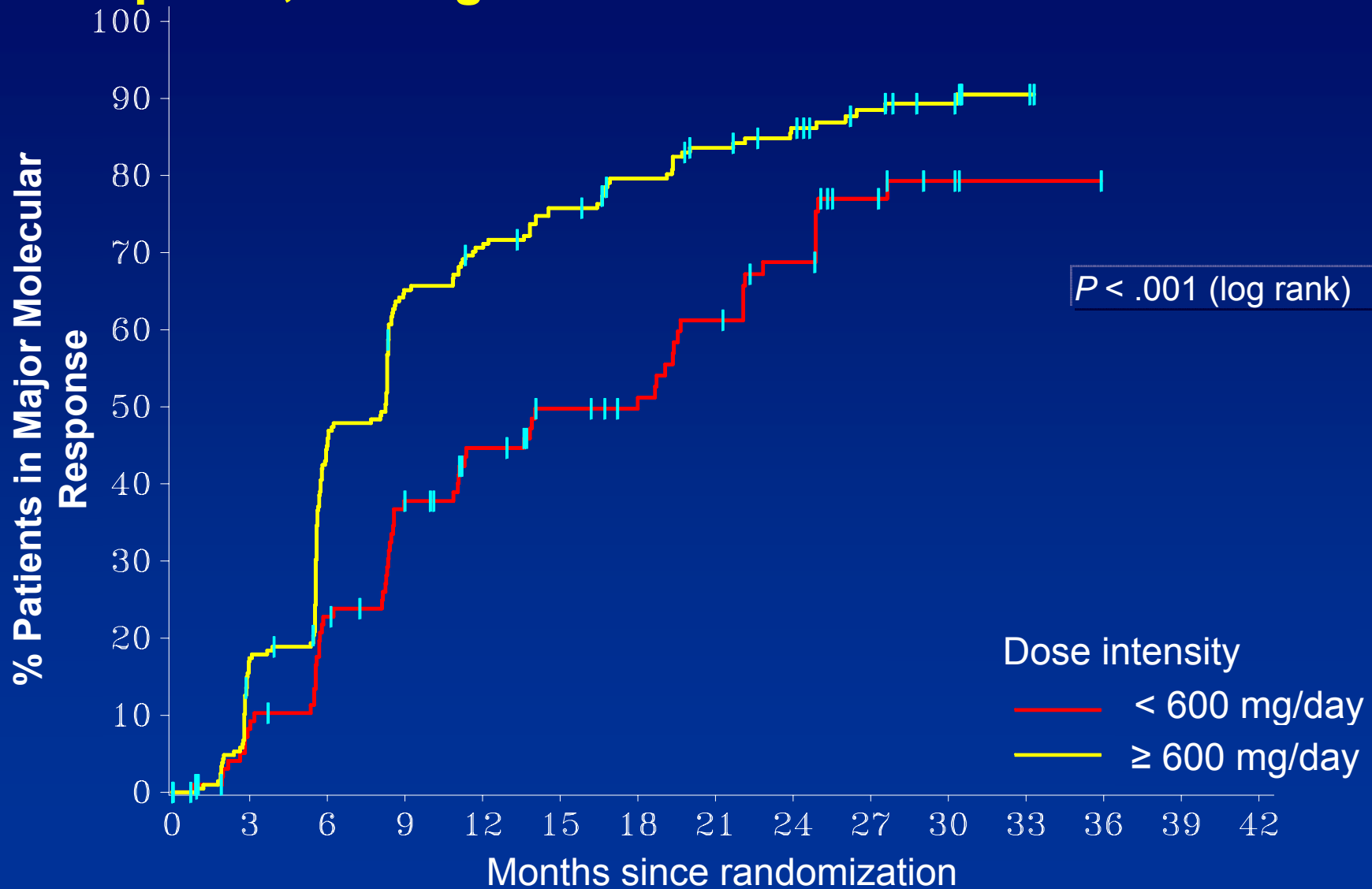
Observed Major Molecular Response Rates Over Time (Intention-to-Treat)



P values calculated by Fisher's exact test

Month

Impact of Dose Intensity* on Time to Molecular Response, 800 mg Arm



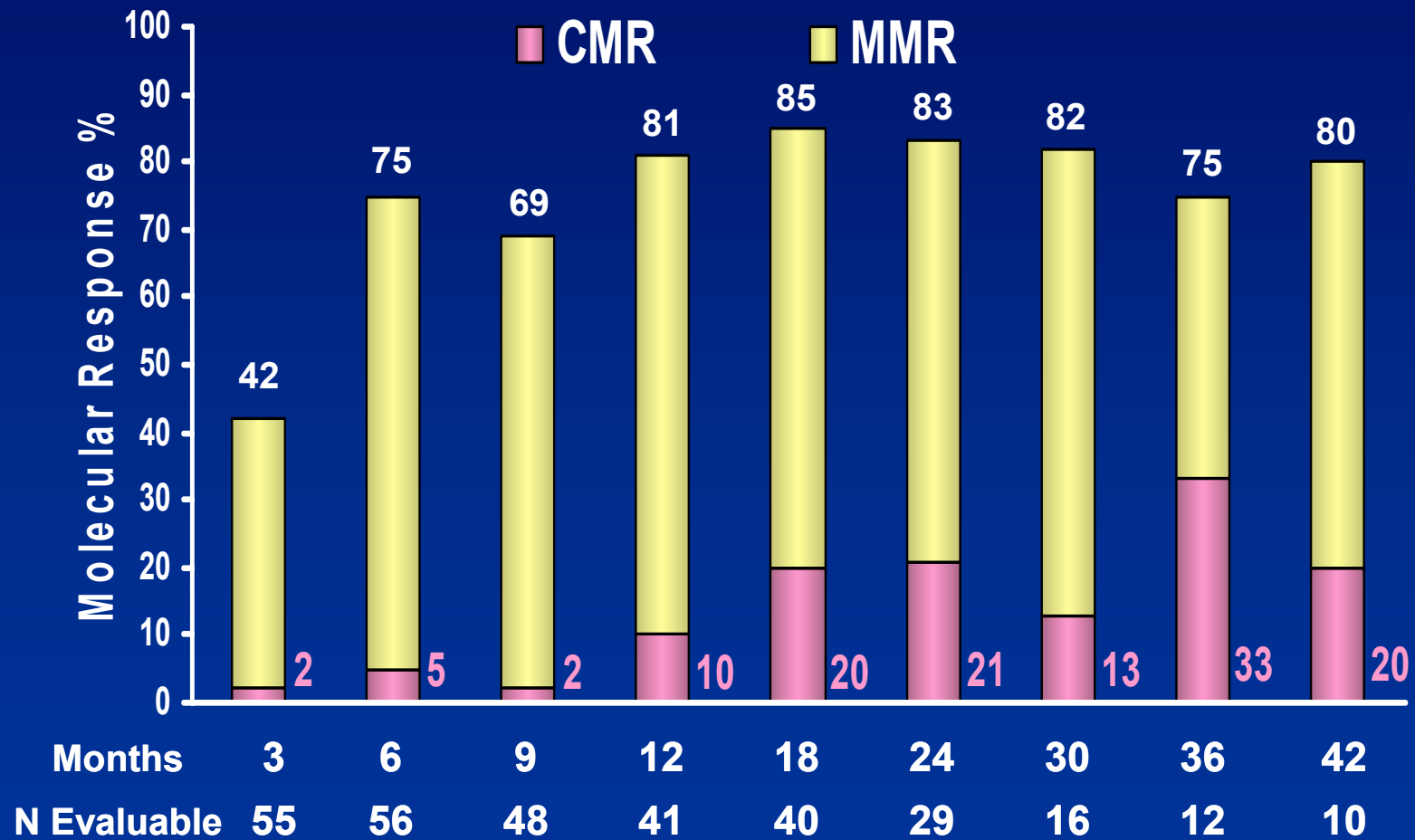
*Dose intensity (total amount of drug received divided by the number of days on treatment including days of zero dose) in the first 12 months

What About Nilotinib?

- **More potent Bcr-Abl Inhibition**
 - More rapid induction of CCyR and MMR?
 - Reduce genome instability and risk of mutations emerging?
 - Reduce early risk of progression?
 - Exhaust CML stem cell pool? => allow eventual treatment discontinuation?
- **More selective action**
 - Less side effects?

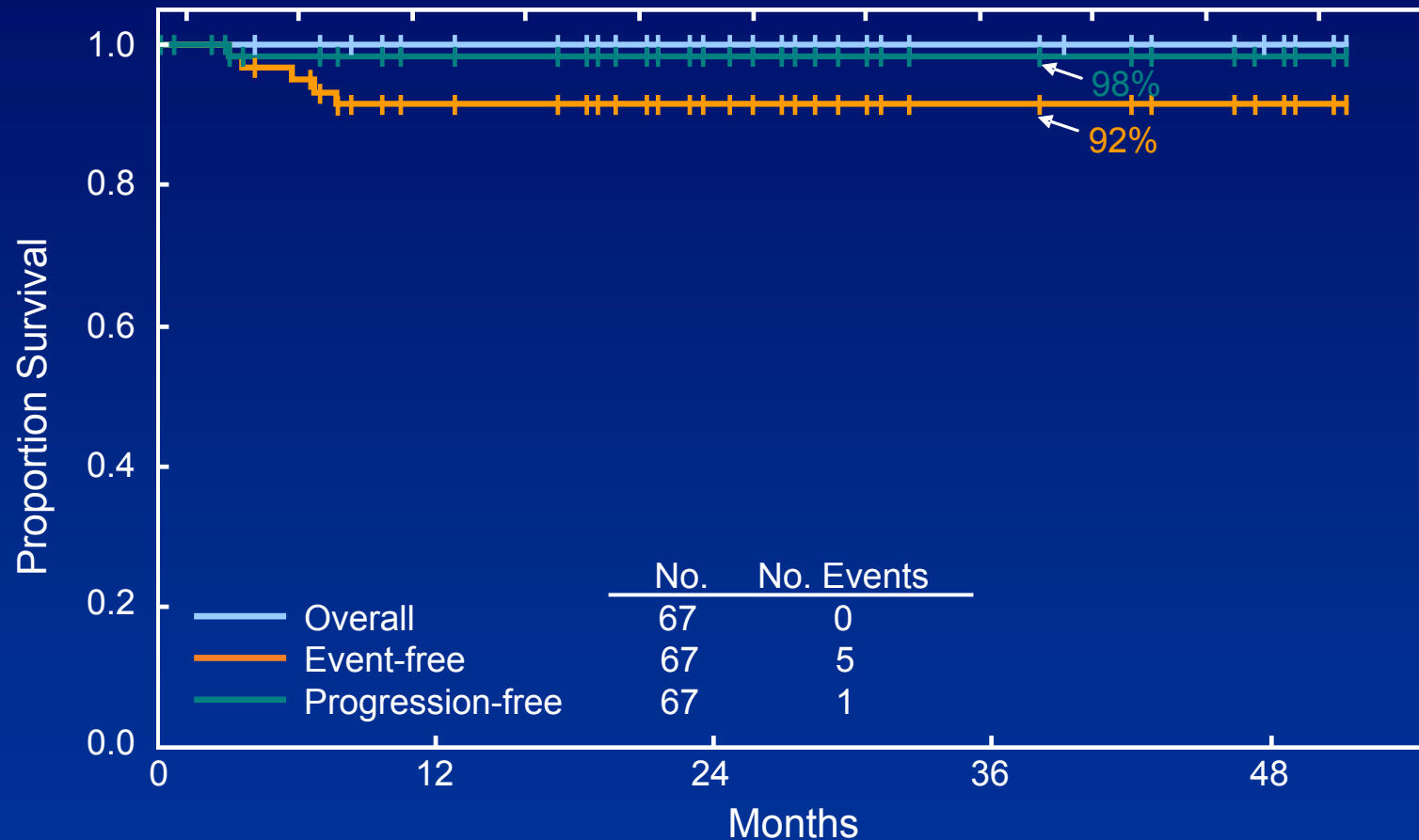
Nilotinib in Newly Diagnosed CML-CP (MDACC)

Molecular Response (ITT)



CMR, complete molecular response; MMR, major molecular response.

Nilotinib in Newly Diagnosed CML-CP (MDACC) Long-Term Outcome

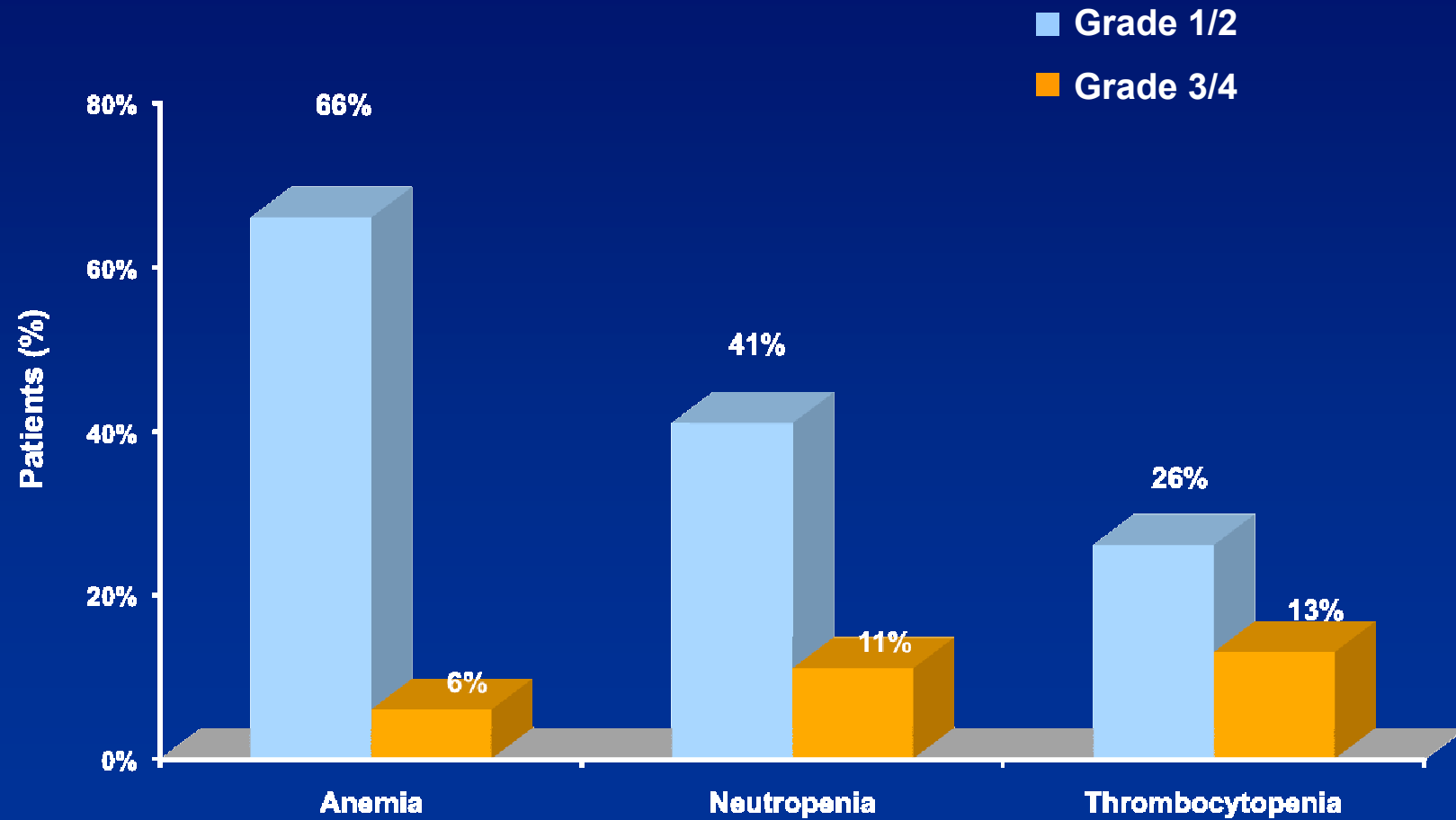


Definitions:

- Event: loss of CHR or MCyR, progression to AP/BC, death, or discontinuation due to toxicity
- Progression: transformation to AP/BC

Nilotinib in Newly Diagnosed CML-CP (MDACC)

Myelosuppression (n = 74)



Imatinib, Nilotinib and Dasatinib in Early CP CML

Complete Cytogenetic Response by Treatment

Response	Months	Percent CCyR		
		IM 400 N=50	Nilotinib* N=61	Dasatinib** N=71
CCyR	6	54	94	95
	12	65	95	94
	24	67	93	93
MMR	6	7	70	64
	12	34	71	74
	24	55	62	89
CMR	6	0	5	2
	12	5	10	6
	24	18	21	8

Primary endpoint

* Evaluable: 56 at 6 mo, 41 at 12 mo, 29 at 24 mo

** Evaluable: 63 at 6 mo, 50 at 12 mo, 36 at 24 mo

Nilotinib and Dasatinib Phase II studies in Early CP CML

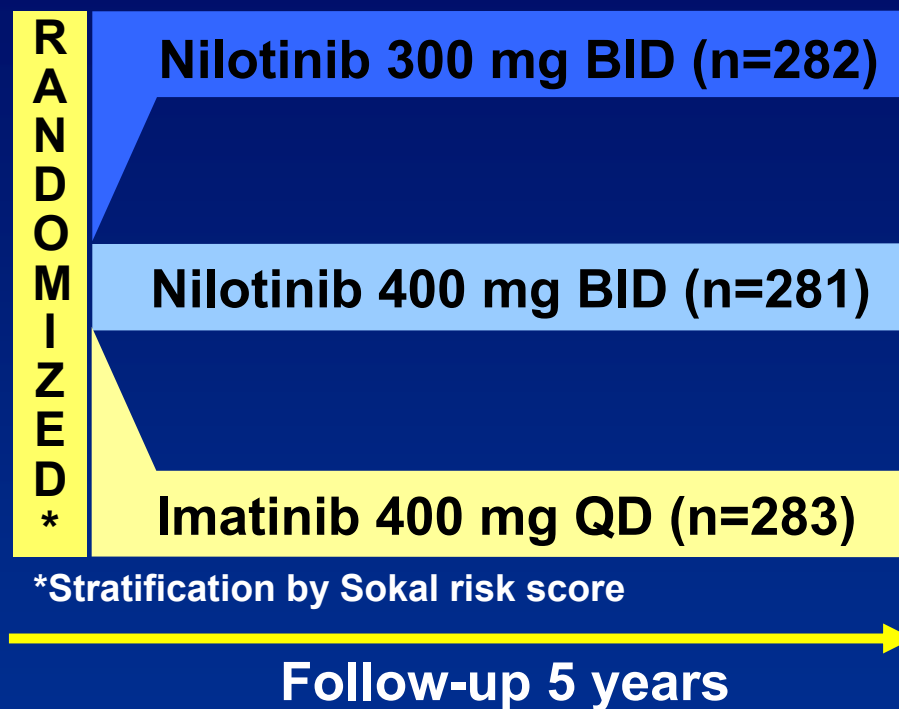
Conclusions

- **Both Nilotinib and Dasatinib induced rapid complete cytogenetic responses in most patients**
- **Cytogenetic responses faster than with standard dose imatinib**
- **Molecular response rate higher than with imatinib**
- **Nilotinib has a more favorable safety profile with less myelosuppression and lower risk of non hematologic AE's such as fatigue, musculoskeletal pain and pleural effusion**
- **Nilotinib 300mg BID may preserve efficacy of higher dose with even better tolerability**

Nilotinib in Newly Diagnosed CML-CP (ENESTnd)

Study Design

- N = 846
- 217 centers
- 35 countries



- **Primary endpoint:** MMR at 12 months
- **Secondary endpoint:** CCyR by 12 months
- **Other endpoints:** time to and duration of MMR and CCyR, EFS, PFS, time to AP/BC, OS

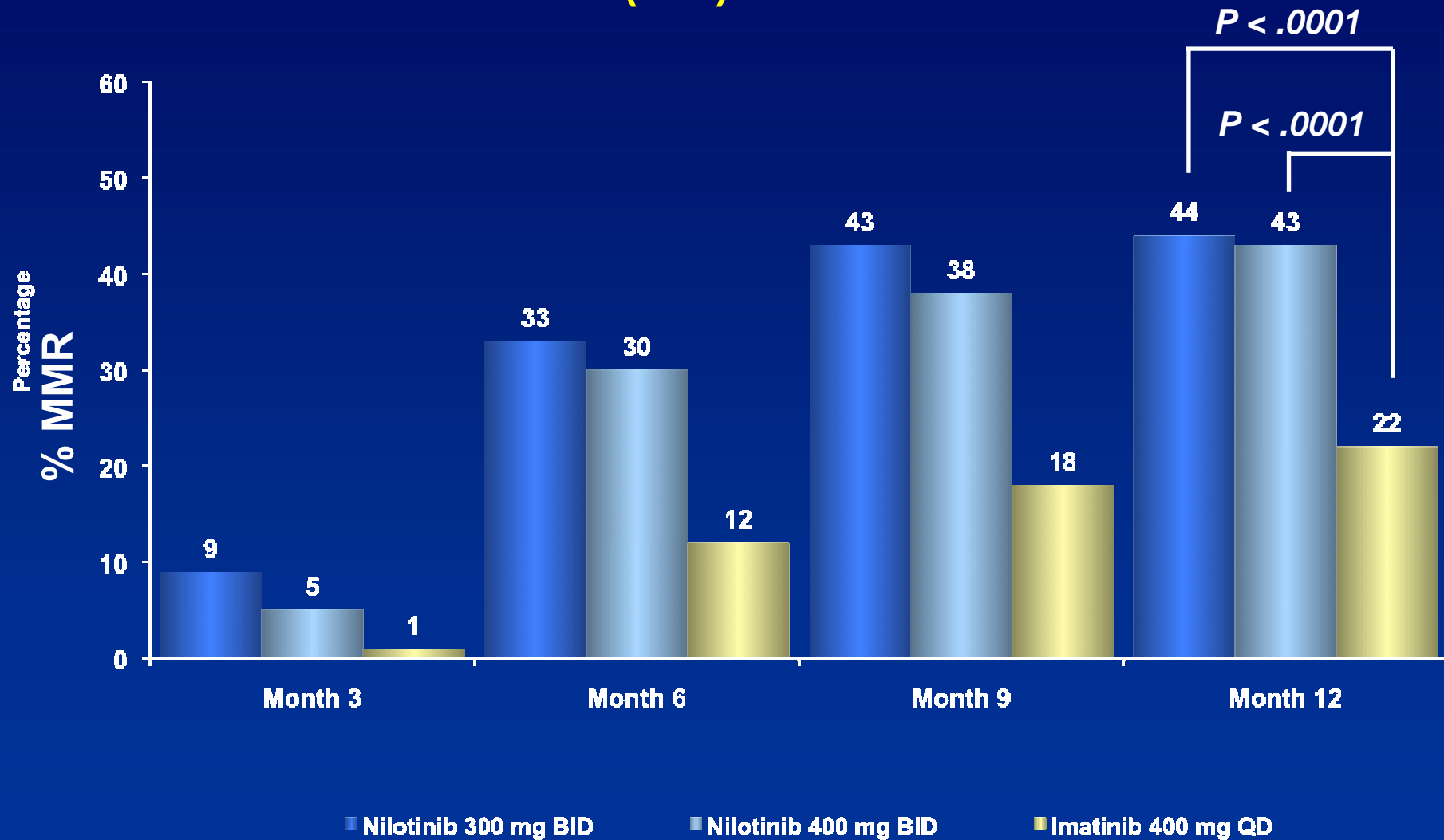
Nilotinib in Newly Diagnosed CML-CP (ENESTnd)

Demographics, Prior Treatment and Nilotinib Exposure

	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281	Imatinib 400 mg QD N = 283
Age, median (range)	47 (18-85)	47 (18-81)	46 (18-80)
Time since Dx, median (days)	31	31	28
Sokal risk, %			
Low	37	37	37
Intermediate	36	36	36
High	28	28	28
Prior Rx, %			
Hydroxyurea	77	75	71
Anagrelide	2	0	1
Imatinib (\leq 2 wks)	13	9	11
Duration of treatment, median (months)	13.8	13.8	13.8
Median dose intensity (mg/day)	592	779	400

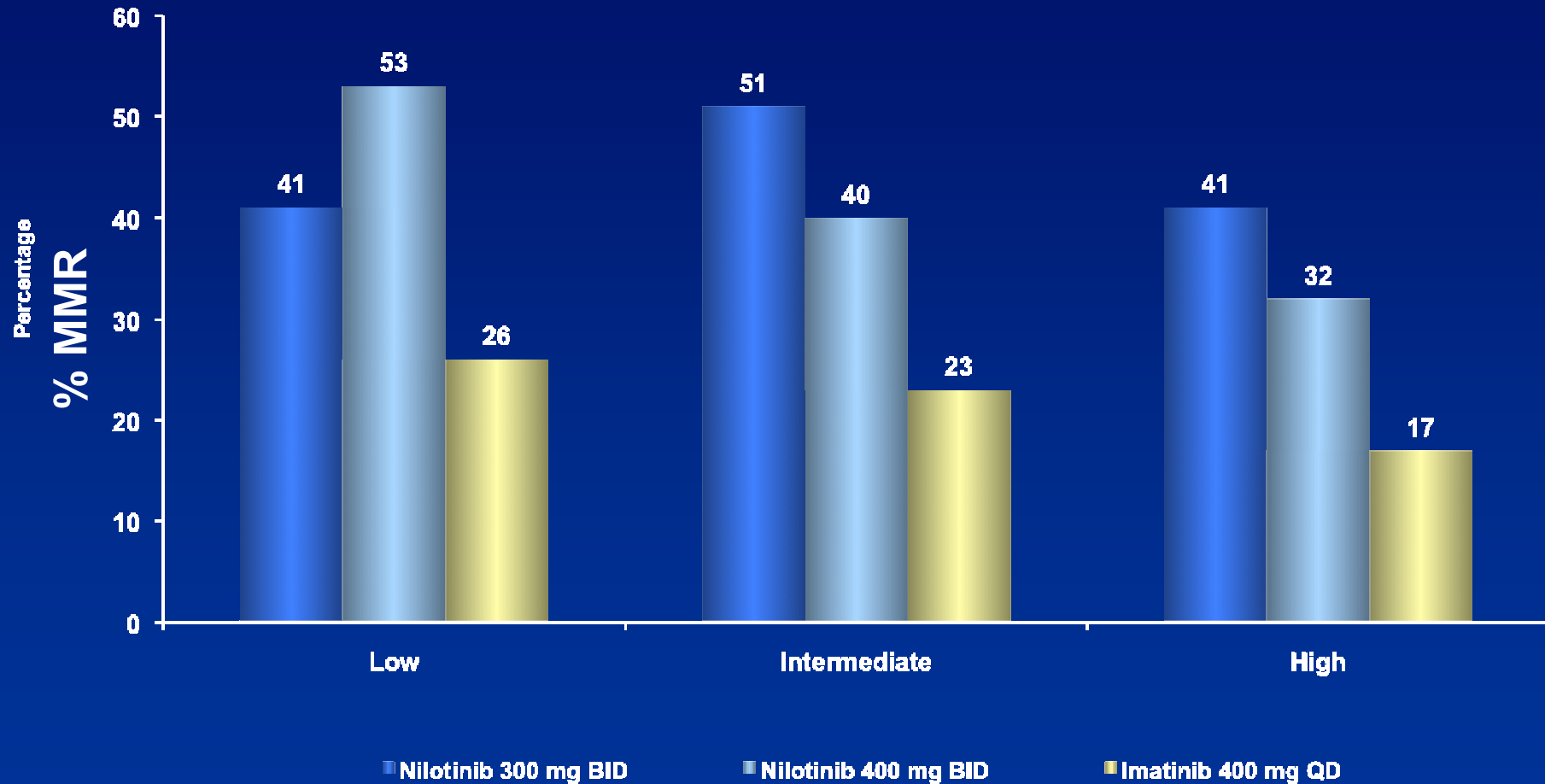
Nilotinib in Newly Diagnosed CML-CP (ENESTnd)

MMR Rates Over Time (ITT)

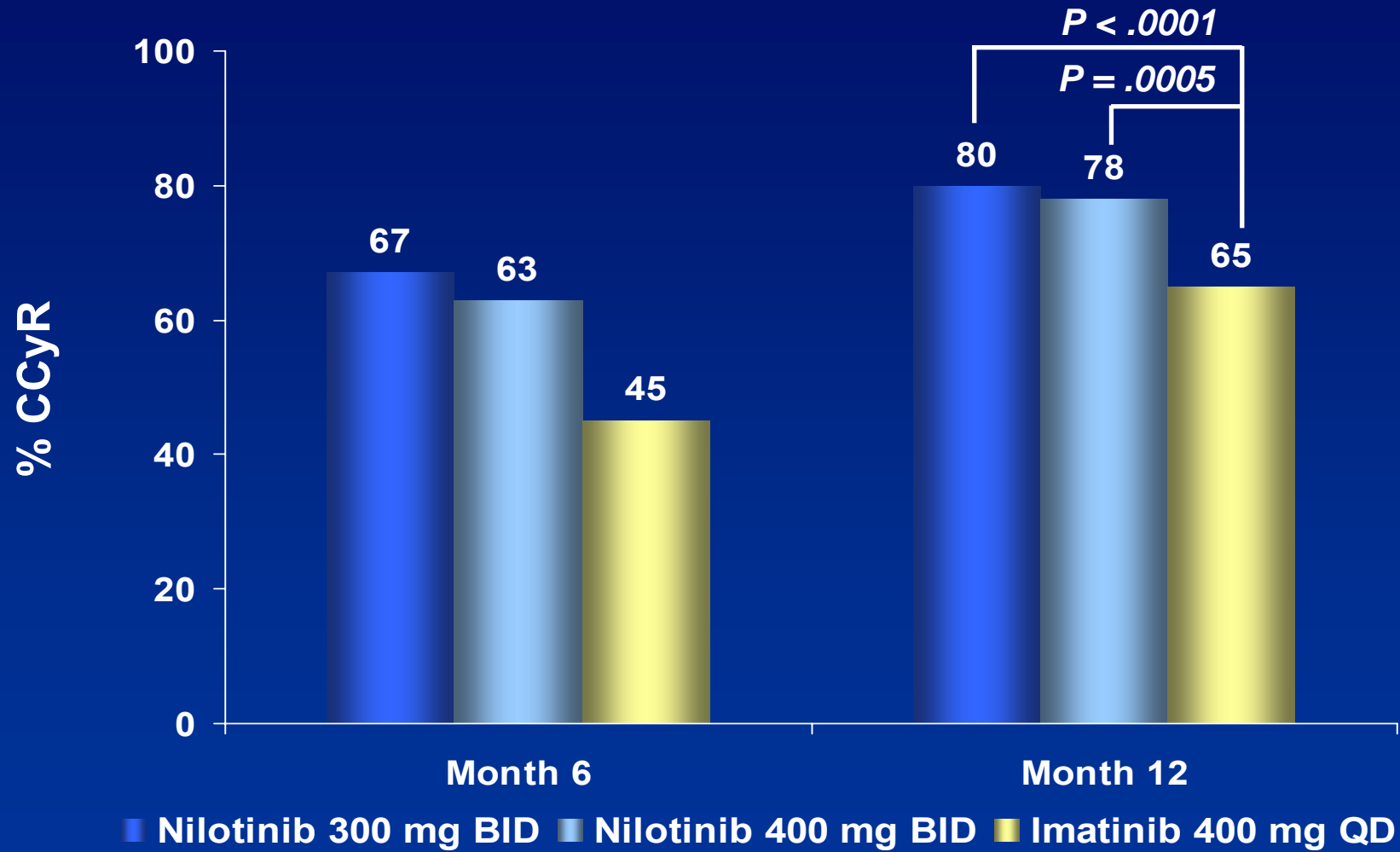


Nilotinib in Newly Diagnosed CML-CP (ENESTnd)

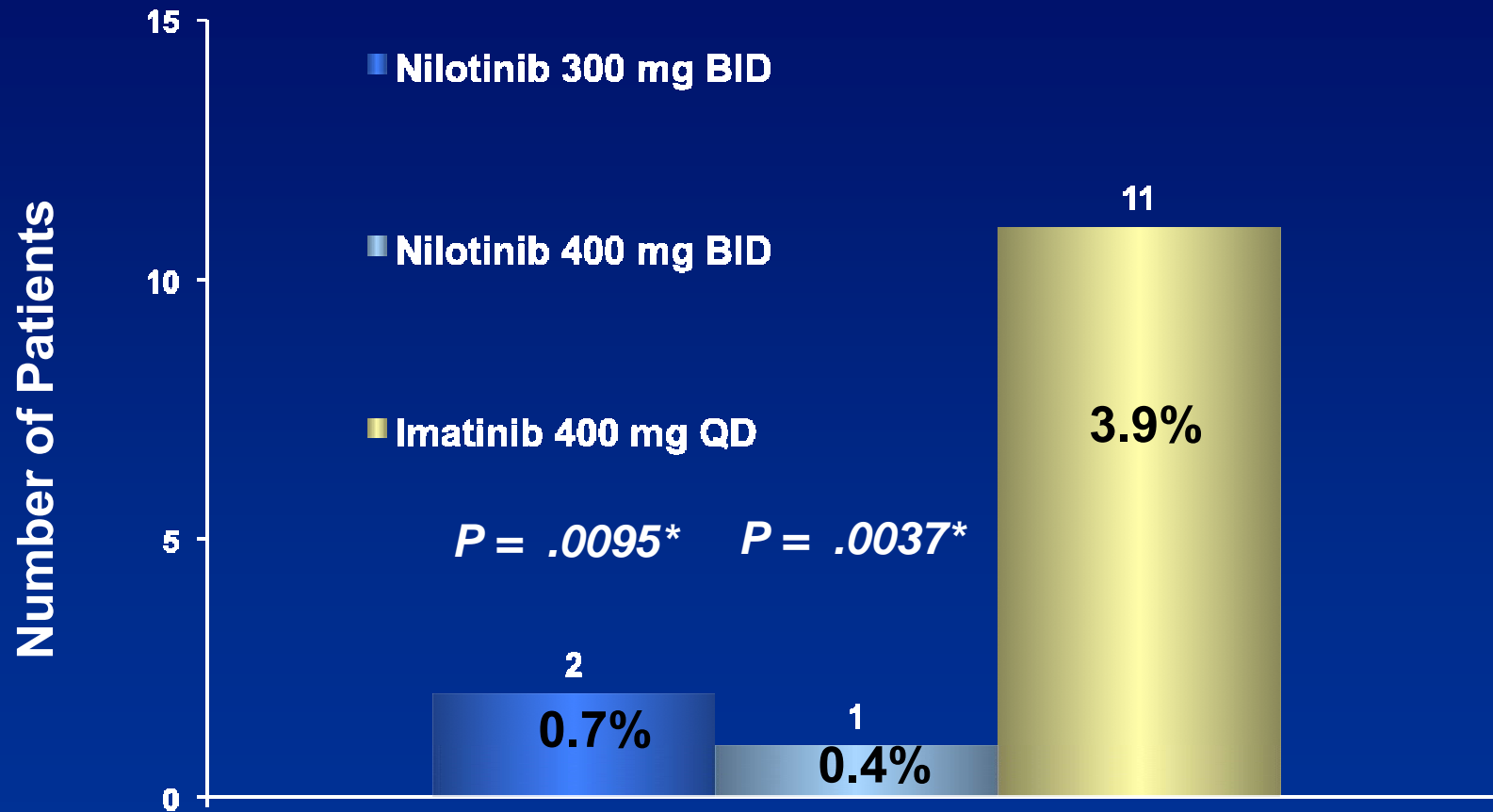
MMR Rates at 12 Months by Sokal Score



Nilotinib in Newly Diagnosed CML-CP (ENESTnd) CCyR Rates (ITT)



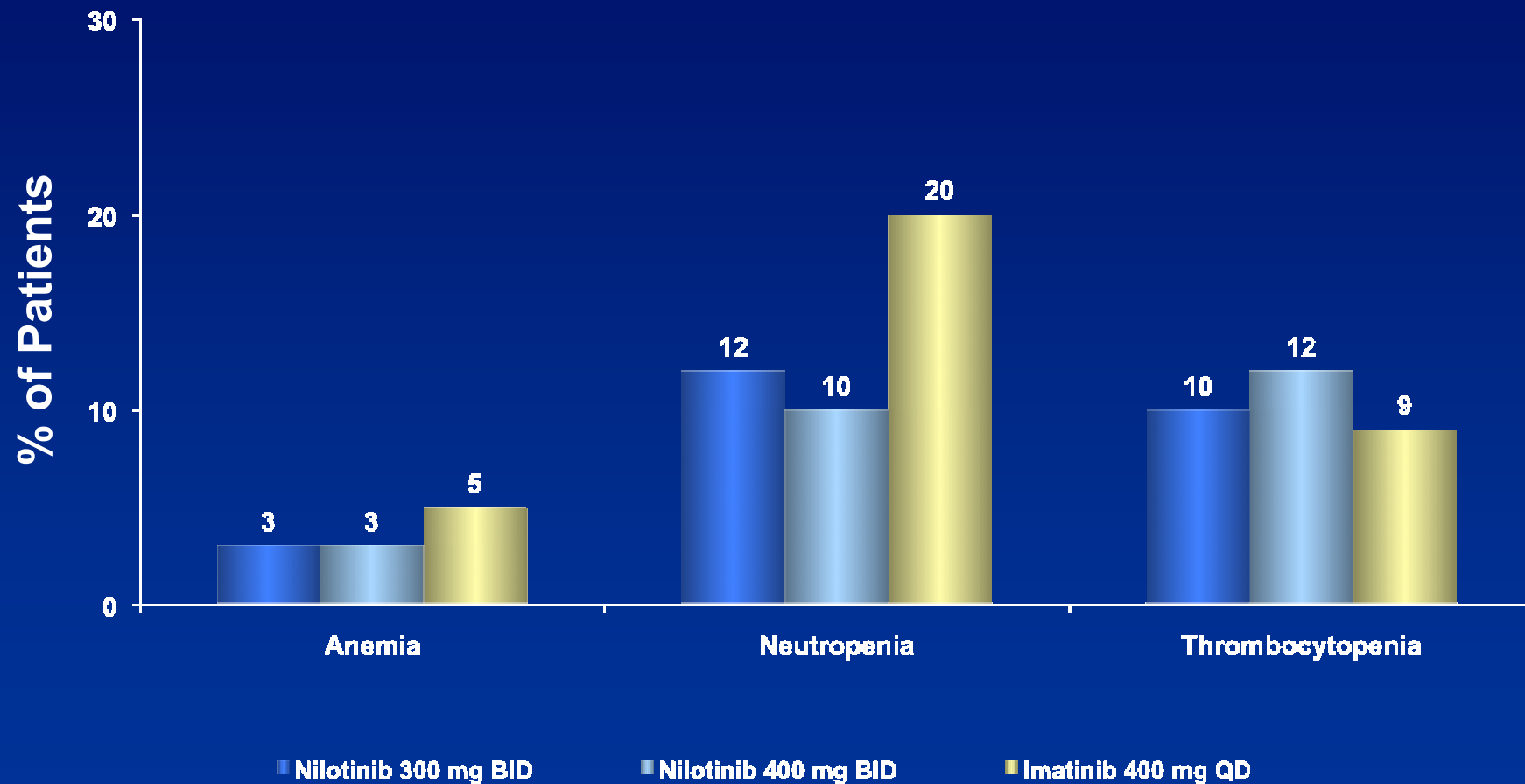
Nilotinib in Newly Diagnosed CML-CP (ENESTnd) Overall Progression to AP/BC (ITT)



- No patients who achieved MMR progressed to AP/BC
- 3 patients who achieved CCyR on imatinib progressed to AP/BC

* P-values are based on log-rank test stratified by Sokal risk group vs imatinib for time to AP/BC

Nilotinib in Newly Diagnosed CML-CP (ENESTnd) Grade 3/4 Myelosuppression



Nilotinib in Newly Diagnosed CML-CP (ENESTnd)

Study Drug-Related Adverse Events (≥ 10% in Any Group)

% of patients treated	Nilotinib 300 mg BID N = 279		Nilotinib 400 mg BID N = 277		Imatinib 400 mg QD N = 280	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	12	<1	20	1	31	0
Muscle spasms	7	0	6	<1	24	<1
Diarrhea	8	<1	7	0	21	1
Vomiting	5	0	9	1	14	0
Rash	31	<1	36	3	11	1
Myalgia	10	<1	10	0	10	0
Headache	14	1	21	1	8	0
Fatigue	11	0	9	<1	8	<1
Pruritus	15	<1	13	<1	5	0
Alopecia	8	0	13	0	4	0

Nilotinib in Newly Diagnosed CML-CP (ENESTnd)

Study Drug-Related Fluid Retention (All Grades)

% of patients treated	Nilotinib 300 mg BID N = 279	Nilotinib 400 mg BID N = 277	Imatinib 400 mg QD N = 280
Peripheral edema	5	5	14
Eyelid edema	<1	2	13
Periorbital edema	<1	<1	12
Facial edema	<1	2	8
Weight Gain	3	<1	6
Pericardial effusion	<1	0	<1
Pleural effusion	<1	0	0

- Grade 3/4 AEs were rarely observed in any treatment arm (<1%)

Nilotinib in Newly Diagnosed CML-CP (ENESTnd)

Laboratory Abnormalities (Grade 3/4)

% of pts treated	Nilotinib 300 mg BID N = 279	Nilotinib 400 mg BID N = 277	Imatinib 400 mg QD N = 280
Lipase ↑	6	6	3
Amylase ↑	<1	1	1
ALT ↑	4	9	3
AST ↑	1	3	1
Total bilirubin ↑	4	8	<1
Glucose ↑	6	4	0
Albumin ↓	0	0	0
Cholesterol ↑	0	<1	0
Phosphorous ↓	5	5	8
Alkaline phos. ↑	0	0	<1
Cholesterol ↓	0	<1	0
Creatinine ↑	0	0	<1
Calcium ↓	<1	<1	0

- One patient in the imatinib arm and one in the nilotinib 400 mg BID arm discontinued the study due to acute pancreatitis

Nilotinib in Newly Diagnosed CML-CP (ENESTnd)

Conclusions

- Nilotinib is superior to imatinib with significantly higher rates of MMR and CCyR, at both 300 mg BID and 400 mg BID
- Significantly fewer patients on nilotinib progressed compared with imatinib
- Nilotinib is superior to imatinib across all Sokal risk groups
- Nilotinib is generally well-tolerated
- Incidence of AEs leading to discontinuation was lowest in the nilotinib 300 mg BID arm
- Based on these results nilotinib may become the new standard of care in newly diagnosed CML

THANK YOU

Role of Allogeneic Stem Cell Transplantation*

AT DIAGNOSIS
(front-line)

In patients presenting in AP or BP. Pretreatment with a TKI recommended

IN CASE OF IMATINIB FAILURE

In patients who have already progressed to AP or BP. Pretreatment with a 2nd generation TKI is recommended

IN CASE OF FAILURE OR
SUBOPTIMAL RESPONSE TO 2ND
GENERATION TKIs
(3rd line)

In patients carrying the T315I mutation

In all eligible patients, depending on response (suboptimal or failure) and on EBMT risk score

*Standard (Myeloablative), from HLA-ID SIBS or matched unrelated donors (8/8 or 7/8 A,B,C,D, high resolution)

Baccarani et al. *Blood*, 2006; 108:1809-20