

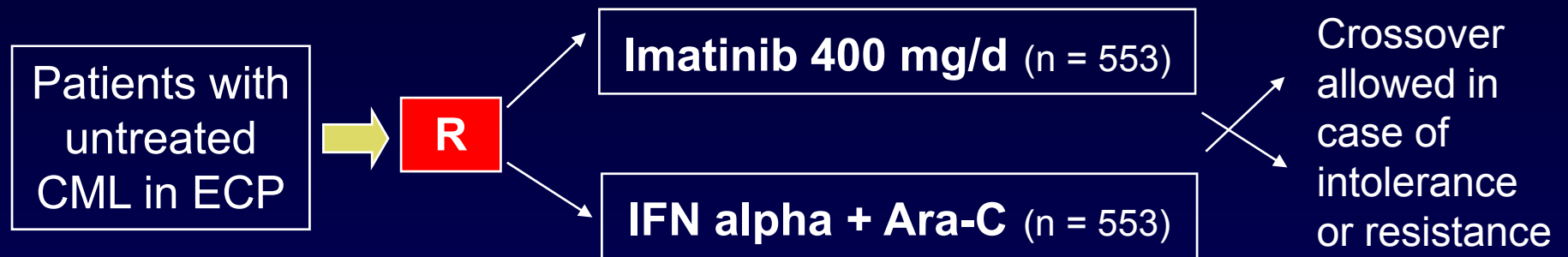
**Case #7**  
**Imatinib-Resistant Chronic**  
**Myelogenous Leukemia:**  
**Optimal Use of Tyrosine Kinase**  
**Inhibitors**

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## Disclosures for Julio Delgado, MD, PhD

Nothing to disclose

# IRIS: Study Design



## Primary endpoint

- Event-free survival (death, AP/BC, loss of CHR, loss of MCgR)

## Secondary endpoints

- Overall survival
- Rates of CHR and MCgR
- Safety and tolerability

# IRIS 6-Year Update: OS and EFS (Imatinib Arm)

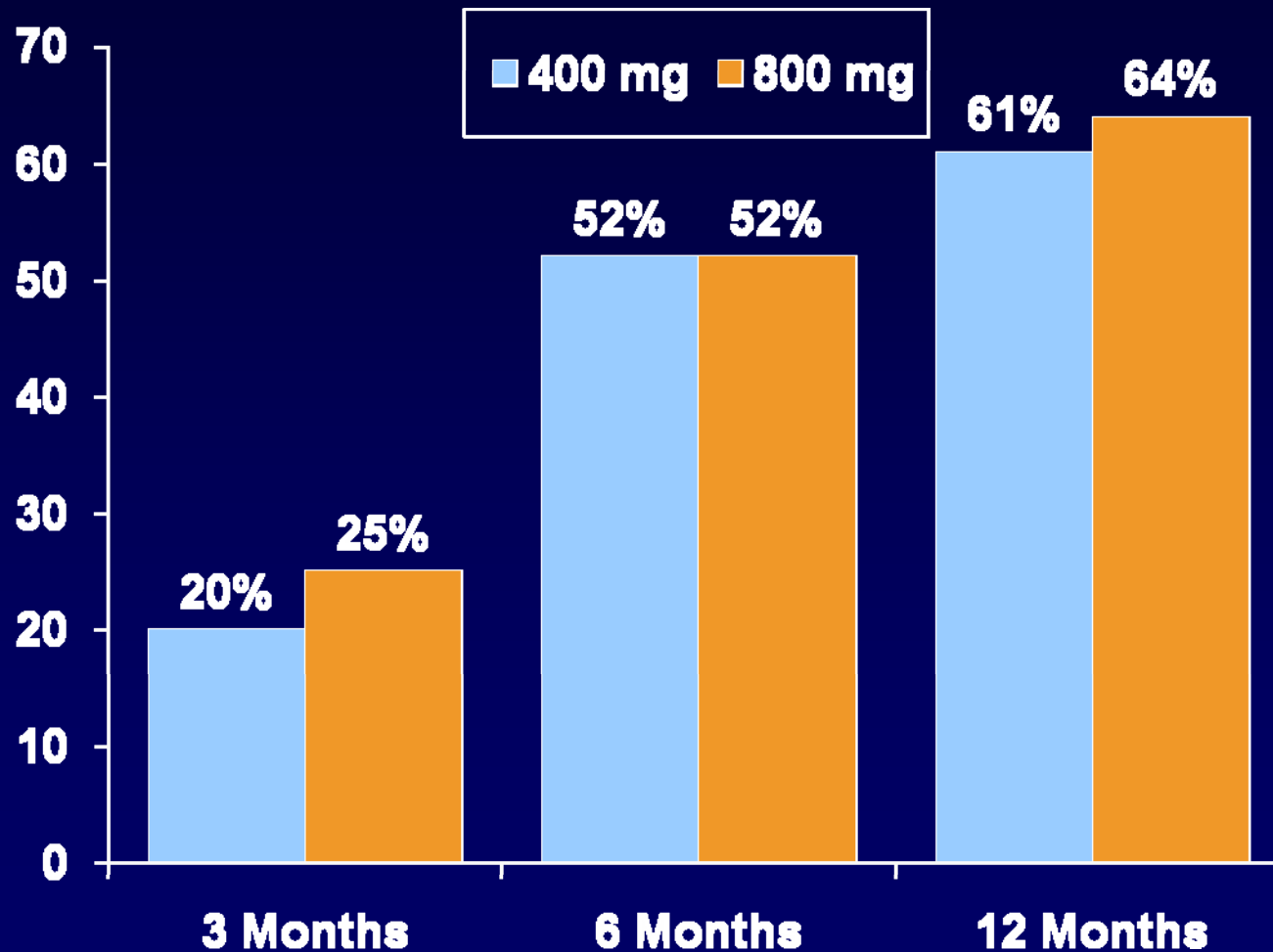
Sokal Risk	OS, %	EFS, %
Low	94	91
Intermediate	87	81
High	76	67

All *P* values <.001

Events:

- Loss of CHR
- Loss of MCgR
- AP/BC
- Death

# Imatinib 400 mg vs 800 mg in ECP, High Sokal Risk CCgR (ITT)



Baccarani M, et al. *Blood*. 2009;113(19):4497-4504.

*P* values >.10

# Treatment of CP-CML: 2009 ELN Recommendations

<b>1<sup>st</sup> line all patients</b>	<b>Imatinib 400 mg daily</b>
<b>2<sup>nd</sup> line imatinib intolerant</b>	<b>Dasatinib or nilotinib</b>
<b>2<sup>nd</sup> line imatinib suboptimal response</b>	<b>Continue imatinib at same dose, testing high dose imatinib, or dasatinib, or nilotinib</b>
<b>2<sup>nd</sup> line imatinib failure</b>	<b>Dasatinib or nilotinib In the case of progression to AP/BC or presence of the T3151 mutation: allogeneic HSCT</b>
<b>3<sup>rd</sup> line dasatinib or nilotinib suboptimal response</b>	<b>Continue nilotinib or dasatinib; consider allogeneic HSCT if warning features (prior hematologic resistance to imatinib, mutations) or EBMT risk score <math>\leq 2</math></b>
<b>3<sup>rd</sup> line dasatinib or nilotinib failure</b>	<b>Allogeneic HSCT</b>

# Monitoring the Response to Imatinib

Response	Description
Hematologic	Every 15 days until CHR is achieved, then at least every 3 months.
Cytogenetic	At 3 and 6 months, then every 6 months until CCgR is achieved, then every 12 months.
Molecular	Every 3 months until MMoIR is achieved, then at least every 6 months
Mutational analysis	In case of suboptimal response or failure; always before changing to other TKIs

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# Evaluation of Response to Imatinib

Months	Optimal	Suboptimal	Failure	Warning
0	NA	NA	NA	High Sokal risk, CCA
3	CHR + at least mCgR (<65%)	No CgR (>95%)	No CHR	NA
6	At least PCgR (<35%)	Less than PCgR (>35%)	No CgR (>95%)	NA
12	CCgR (0%)	<b>PCgR (1-35%)</b>	Less than PCgR (>35%)	No MMoIR
18	MMoIR	No MMoIR	Less than CCgR (>0%)	NA
Any time	Stable or improving	No MMoIR	Loss of CHR or CCgR, CCA	Increase in transcript levels

CCA: Clonal chromosome abnormalities

# Suboptimal Response to Imatinib: 2009 ELN Recommendations<sup>1</sup>

- **Continue on same imatinib dose**
- **Test imatinib dose escalation**  
Evidence from a retrospective analysis of the IRIS study,<sup>2</sup> where 52% of patients achieved a clinical response 12 months after dose escalation as per IRIS criteria (44% as per ELN criteria)
- **Test dasatinib or nilotinib**

# What about FISH?

“Interphase FISH cannot be used to assess a less than a complete response, but it can substitute for CBA to monitor the completeness of a CCgR.”

Baccarani M, et al. *J Clin Oncol*. 2009;27(35):6041-6051.

		MMoIR, n (%)	P
I-FISH and CBA	CCgR + <1% BCR-ABL nuclei	281 (66%)	.004
	CCgR + >1% BCR-ABL nuclei	43 (49%)	
I-FISH only	<1% BCR-ABL nuclei	284 (67%)	<.001
	>1% BCR-ABL nuclei	49 (52%)	

**“No cases of MMoIR were found among cases with >5% nuclei.”**

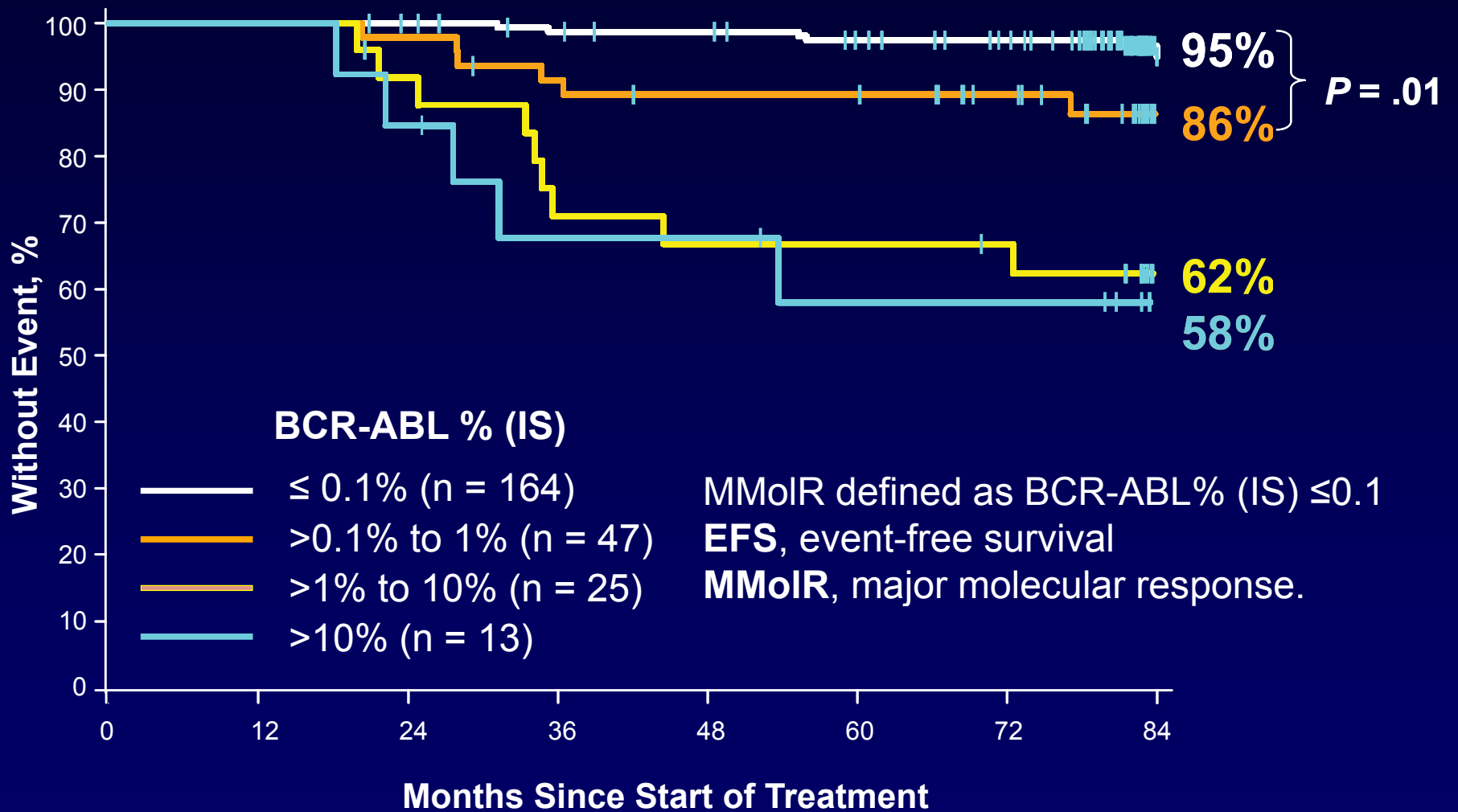
Testoni N, et al. *Blood*. 2009 114(24):4939-4943.

# Evaluation of Response to Imatinib

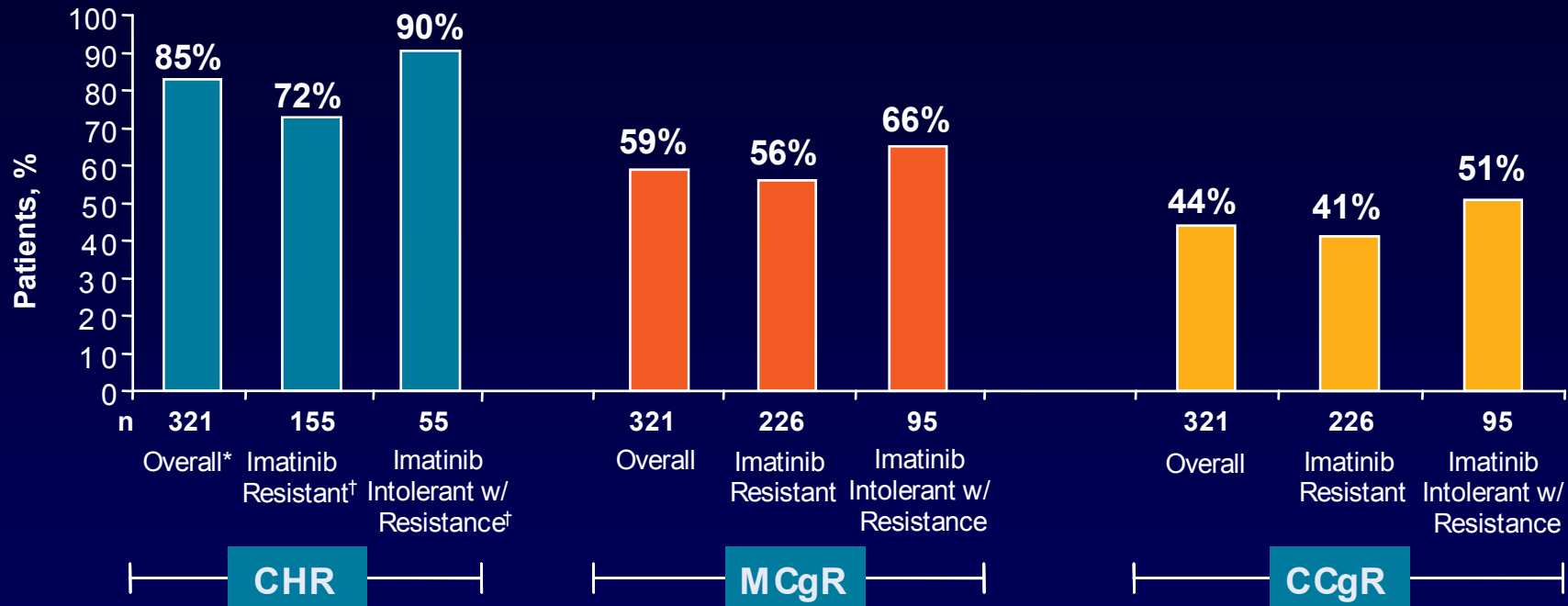
Months	Optimal	Suboptimal	Failure	Warning
0	NA	NA	NA	High Sokal risk, CCA
3	CHR + at least mCgR (<65%)	No CgR (>95%)	No CHR	NA
6	At least PCgR (<35%)	Less than PCgR (>35%)	No CgR (>95%)	NA
12	CCgR (0%)	PCgR (1-35%)	Less than PCgR (>35%)	No MMoIR
18	MMoIR	<b>No MMoIR</b>	Less than CCgR (>0%)	NA
Any time	Stable or improving	No MMoIR	Loss of CHR or CCgR, CCA	Increase in transcript levels

CCA: Clonal chromosome abnormalities

# IRIS: Achievement of MMoIR by 18 Months Associated With Improved EFS



# 2101: Outcome of Patients Receiving Second-Line Nilotinib (n = 321)

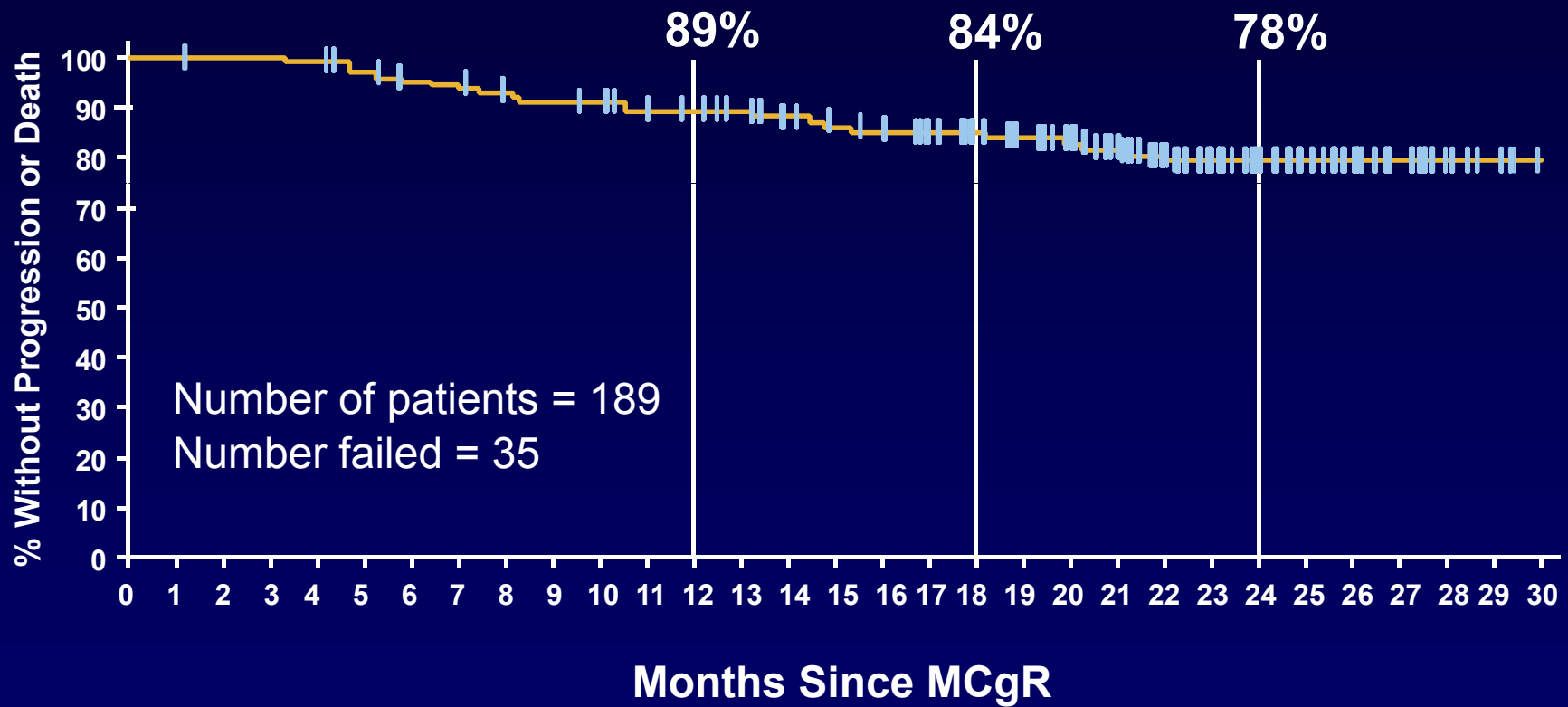


\* Patients who achieved (without baseline CHR) or maintained CHR (had CHR at study entry).

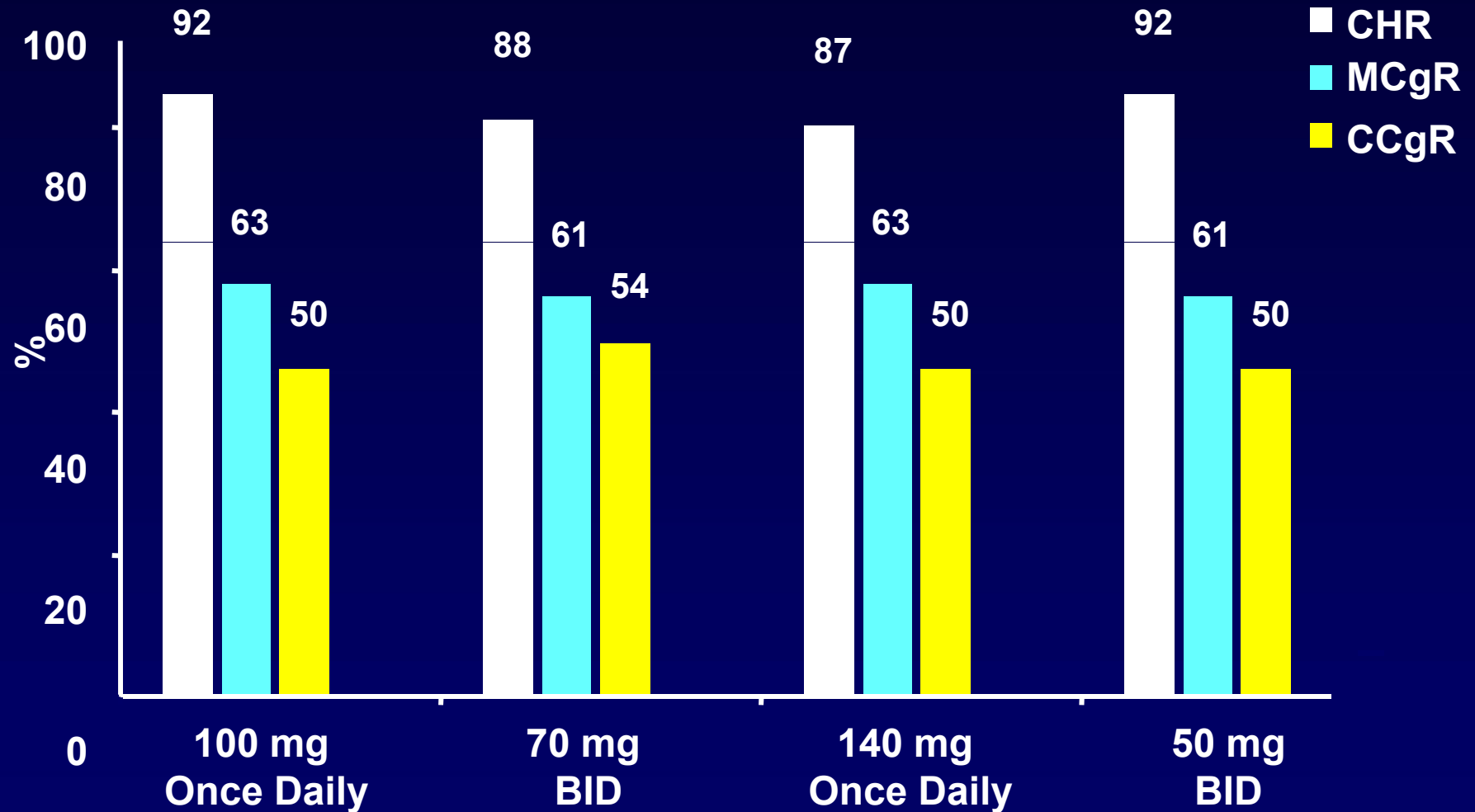
† Patients with no CHR at baseline

- Median time to CHR was **1.0 month** in patients without CHR at baseline
- Median time to MCgR was **2.8 months** (range, 0.9-28)
- Median time to CCgR was **3.3 months** (range, 0.9-27)

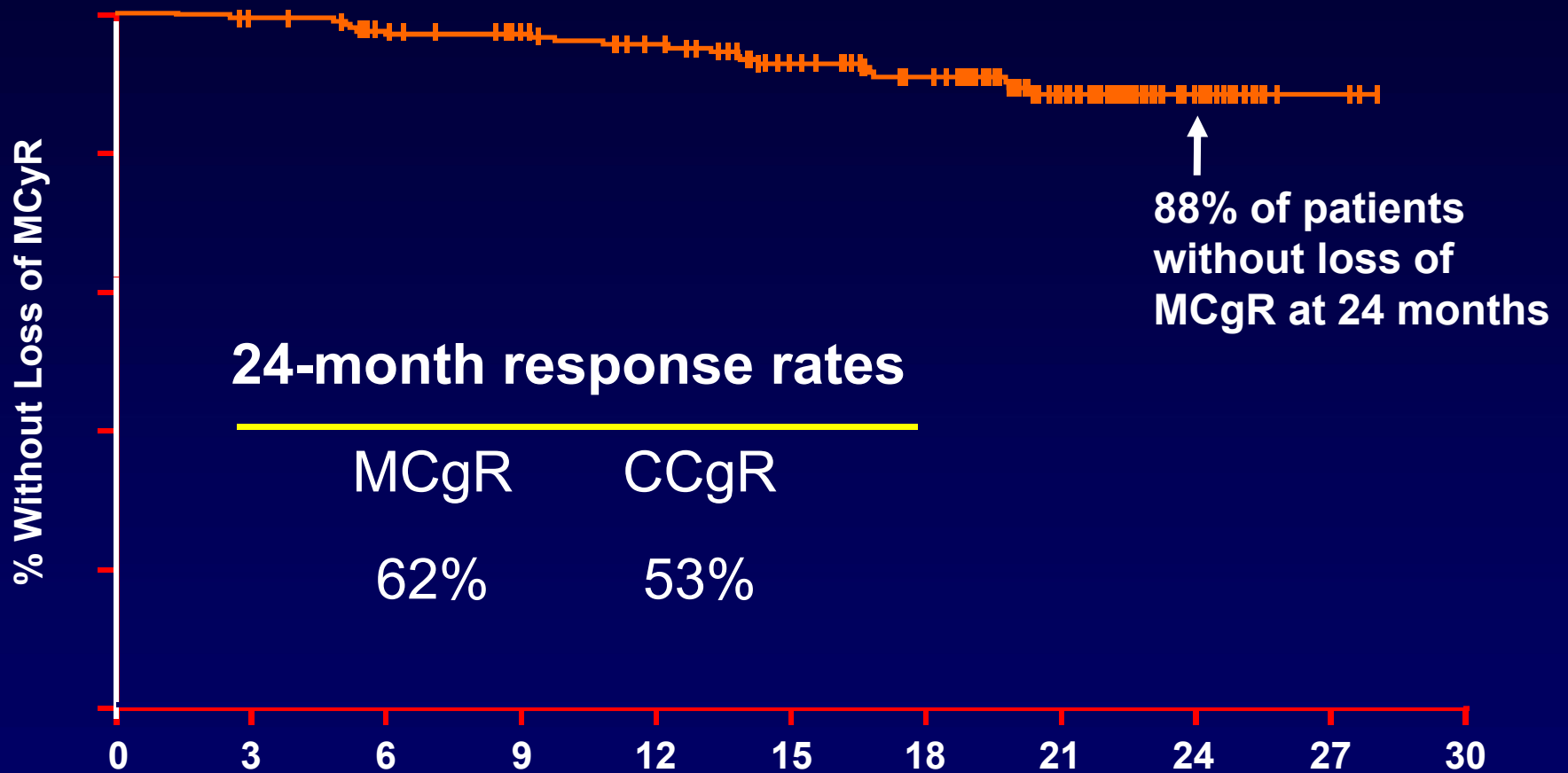
# 2101: Duration of MCgR



# CA180-034: Outcome of Patients Receiving Second-Line Dasatinib (n = 670)



# CA180-034: Duration of MCgR



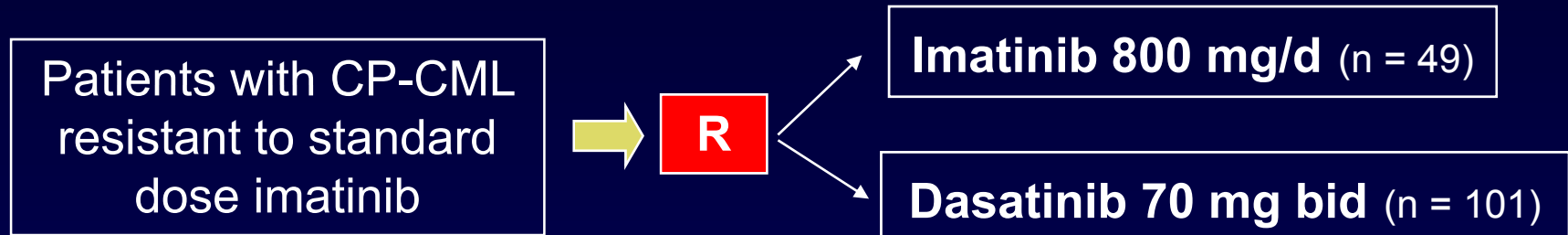
## Phase II Studies in CML-CP Adverse Events, %

	Dasatinib <sup>1</sup> (70 mg BID)		Nilotinib <sup>2</sup> (400 mg BID)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
<b>Myelotoxicity (thrombocytopenia &amp; neutropenia)</b>	-	<b>49-50</b>	-	<b>28-30</b>
<b>Pleural effusion (Peripheral Edema)</b>	<b>26</b> (29)	<b>9</b> (1)	<b>1</b> (6)	<b>1</b> (0)
<b>Bleeding</b>	<b>16</b>	<b>4</b>	<b>6</b>	<b>2</b>
<b>Hyperglycemia</b>	-	-	-	<b>13</b>
<b>Lipase elevation</b>	-	-	-	<b>15</b>

1. Stone RM, et al. *Blood*. 2007;110: Abstract 734.

2. Kantarjian HM, et al. *Blood*. 2007;110: Abstract 735.

# START-R: Study Design and Results



Minimum follow-up of 24 months

Study arm	CHR	MCgR	CCgR	MMoIR
Imatinib 800 mg/d	82%	33%	18%	12%
Dasatinib 70 mg bd	93%	53%	44%	29%

All *P* values <.05

# Mutations in the BCR-ABL Kinase Domain

## IC<sub>50</sub>-Fold Increase

	IM	DA	Nil	BO
WT	1	1	1	1
L248V	3.54	5.11	2.80	3.54
G250E	6.86	4.45	4.56	4.31
Q252H	1.39	3.05	2.64	0.81
Y253F	3.58	1.58	3.23	0.96
E255K	6.02	5.61	6.69	9.47
E255V	16.99	3.44	10.31	5.53
D276G	2.18	1.44	2.00	0.60
E279K	3.55	1.64	2.05	0.95
V299L	1.54	8.65	1.34	26.10
T315I	17.50	75.03	39.41	45.42
F317L	2.60	4.46	2.22	2.42
M351T	1.76	0.88	0.44	0.70
F359V	2.86	1.49	5.16	0.93
L384M	1.28	2.21	2.33	0.47
H396P	2.43	1.07	2.41	0.43
H396R	3.91	1.63	3.10	0.81
G398R	0.35	0.69	0.49	1.16
F486S	8.10	3.04	1.85	2.31

Sensitive	≤ 2
Mod. resistant	2.01–4
Resistant	4.01–10
Highly resistant	> 10

- 50% of patients with secondary imatinib resistance have mutations
- 61% of patients with >2-fold increase in BCR-ABL transcripts have mutations
- Absolute resistance to imatinib: T315I and E255V/K
- Poor response to dasatinib: T315I, F317L, V299L
- Poor response to nilotinib: T315I, Y253H, E255V/K, F359V

# Choice of Therapy for This Patient?

- Stop imatinib if the patient is carrying T315I or E255K/V mutations
- Switch to nilotinib in the absence of T315I, E255K/V, Y253H or F359C/V mutations, particularly if the patient is in CHR<sup>1</sup>
- Switch to dasatinib in the absence of T315I, F317L or V299L mutations
- Patients carrying the T315I mutation should be referred for allogeneic HSCT

# IRIS 8-Year Update

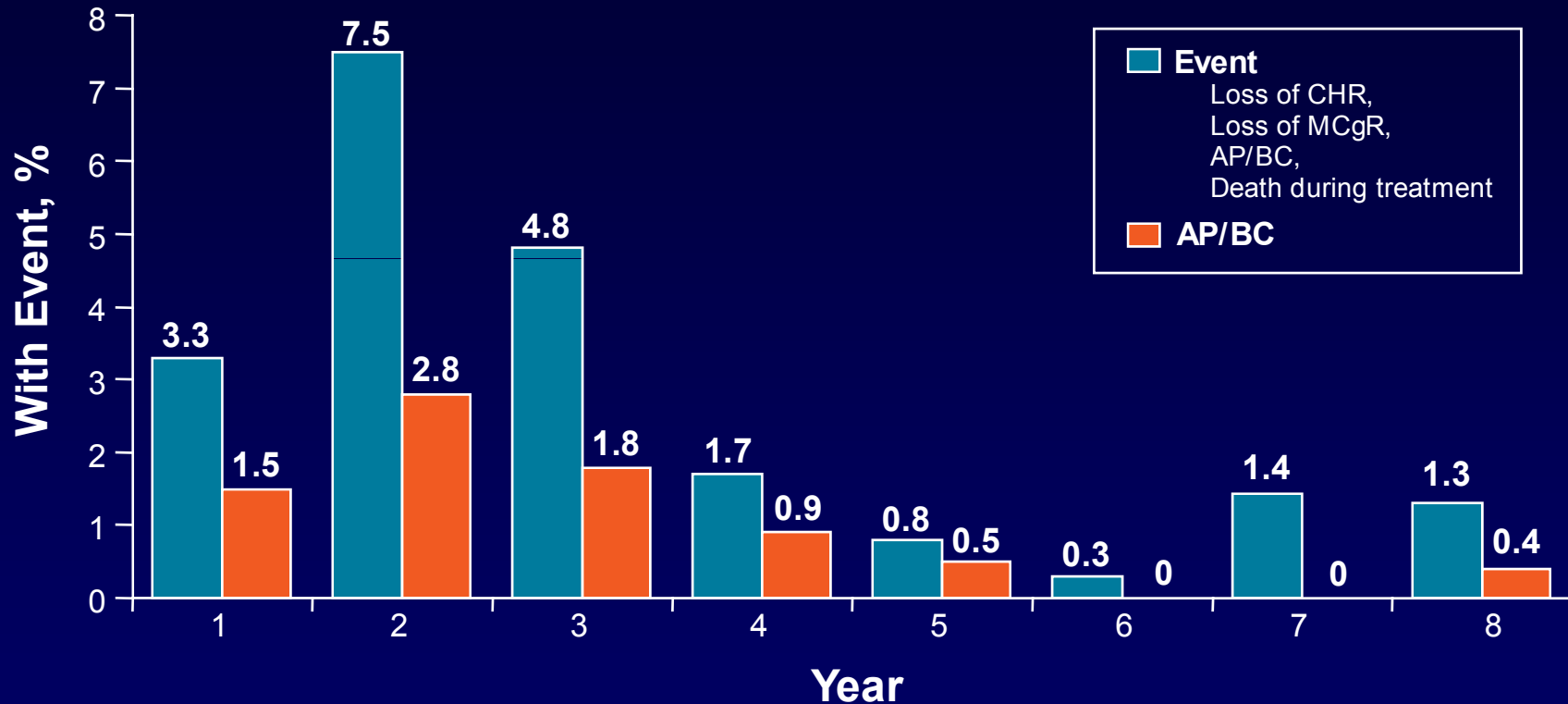
## Disposition of Patients Randomized to Imatinib (n = 553)

	n (%)
<b>Continued first-line imatinib</b>	<b>304 (55.0)</b>
<b>Discontinued first-line imatinib</b>	<b>249 (45.0)</b>
<b>AE(s)/abnormal laboratory value(s)</b>	<b>30 (5.4)</b>
<b>Unsatisfactory therapeutic effect</b>	<b>77 (13.9)</b>
<b>Death</b>	<b>16 (2.9)</b>
<b>Stem cell transplantation</b>	<b>16 (2.9)</b>
<b>Withdrawal of consent</b>	<b>44 (8.0)</b>
<b>No re-consent to amendment</b>	<b>19 (3.4)</b>
<b>Crossed over to IFN + ara-C arm*</b>	<b>14 (2.5)</b>
<b>Other reason†</b>	<b>33 (6.0)</b>

\* Due to intolerance (0.7%), no MCgR at 12 months or progression (1.8%).

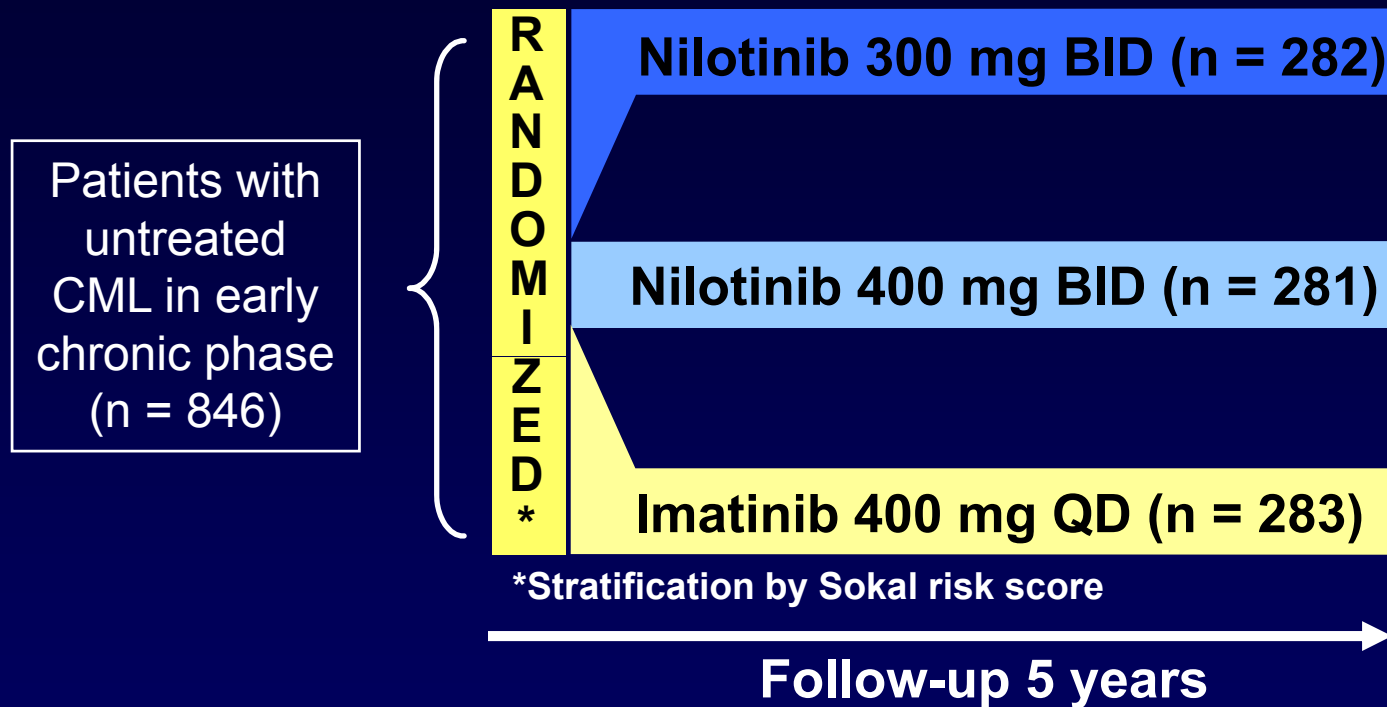
† Includes protocol violation, administrative problems, abnormal procedures, or lost to follow-up.

# IRIS 8-Year Update: Annual Event Rates



- Estimated EFS at 8 years = 81%
- Estimated rate of freedom from progression to AP/BC at 8 years = 92%

# ENESTnd Trial: Study Design

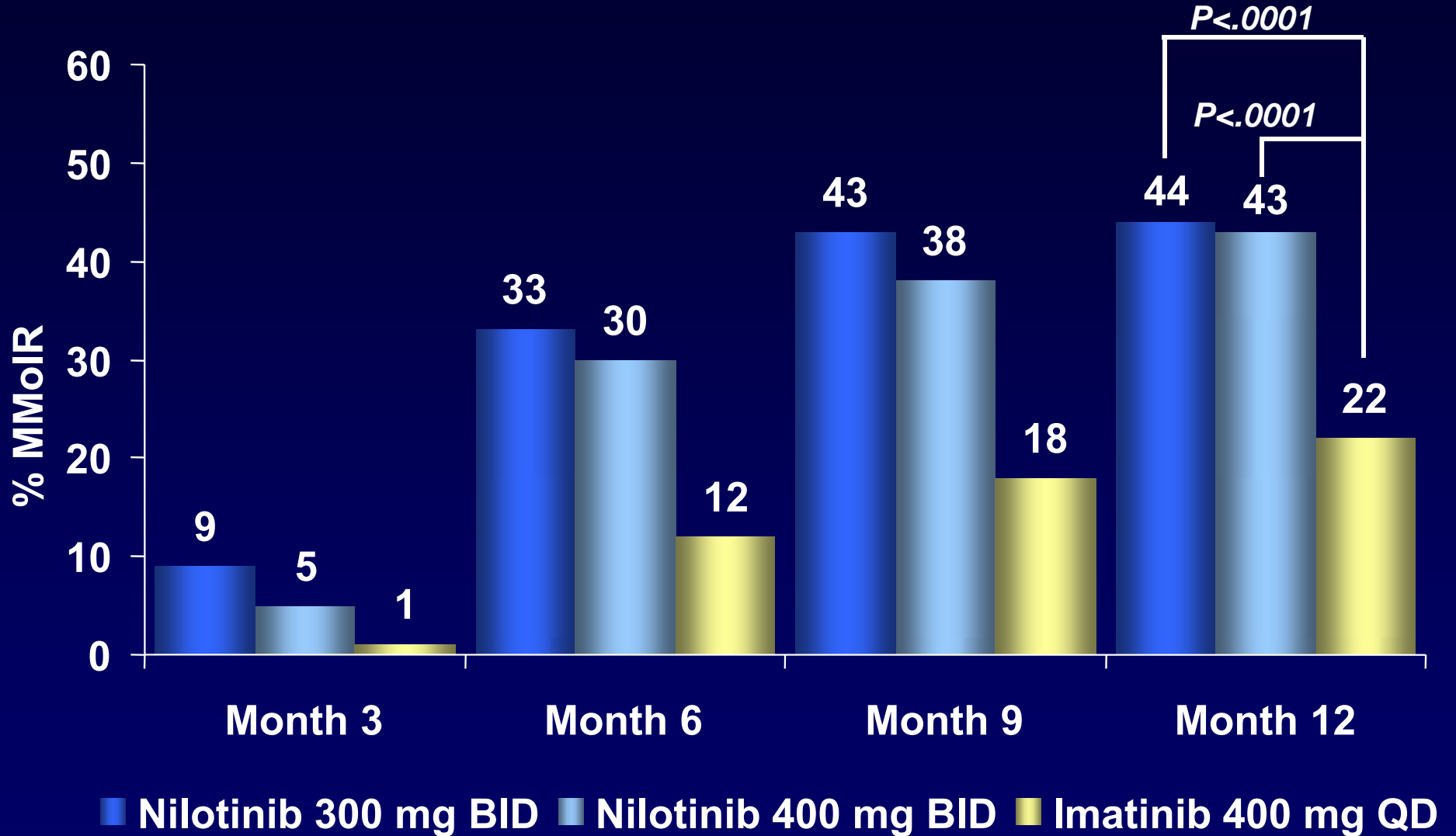


**Primary endpoint:** MMoIR at 12 months

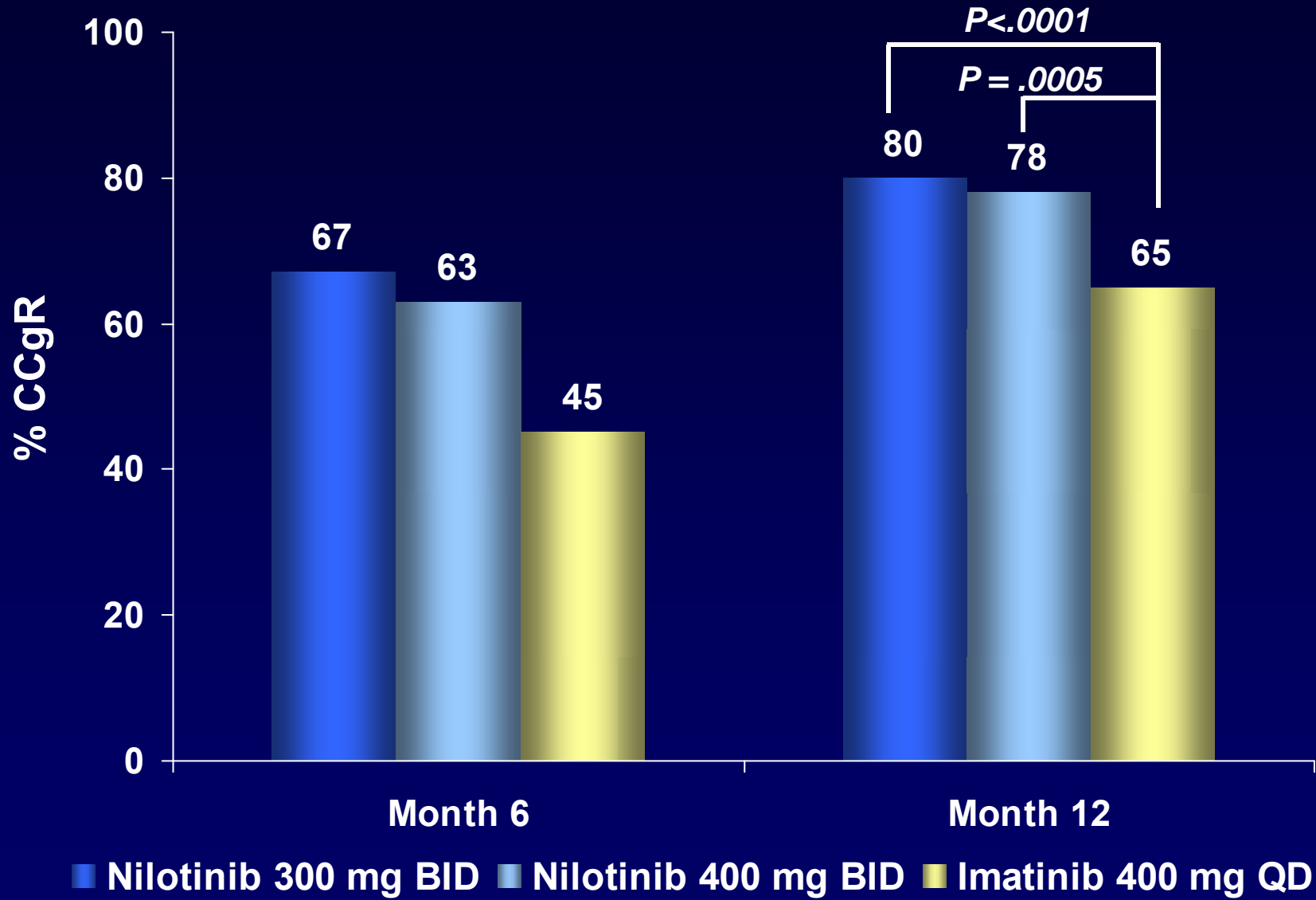
**Secondary endpoint:** CCgR by 12 months

**Other endpoints:** Time to and duration of MMoIR and CCgR, EFS, PFS, time to AP/BC, OS

# ENESTnd: Rate of MMoIR Over Time (ITT)

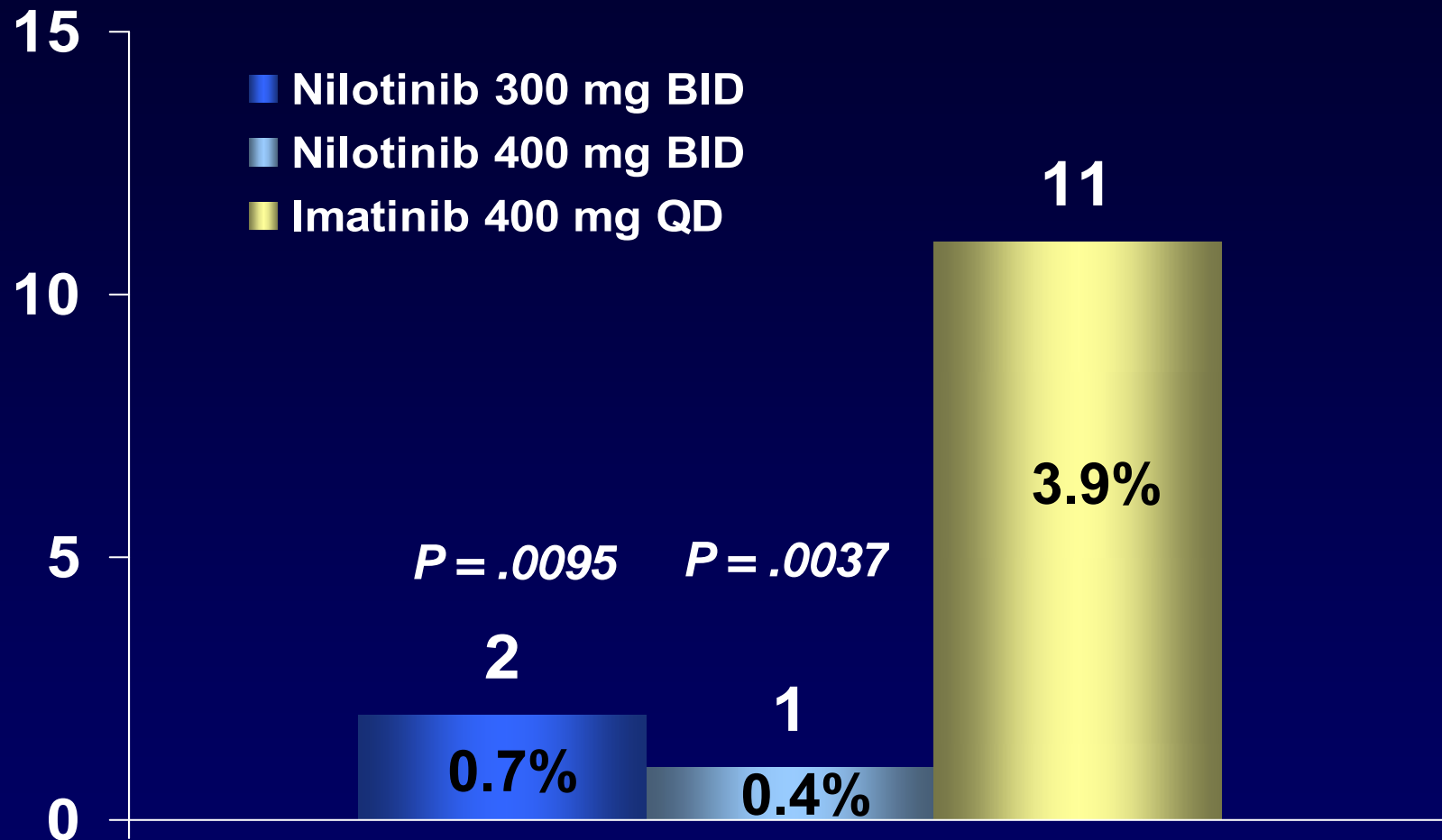


# ENESTnd: Rate of CCgR Over Time (ITT)



Saglio G, et al. *Blood*. 2009;114: Abstract LBA-1.

# ENESTnd: 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

# Conclusions

- **Imatinib remains the standard of care for ECP-CML, but this may change soon**
- **Appropriate monitoring is recommended in order to identify patients who may not benefit from long-term imatinib administration**
- **Second generation TKIs are effective in case of suboptimal response/failure or intolerance to imatinib**
- **Mutational analysis may allow for a rational selection of second line therapy**