Switching from Imatinib to 2G TKI : When & how ?

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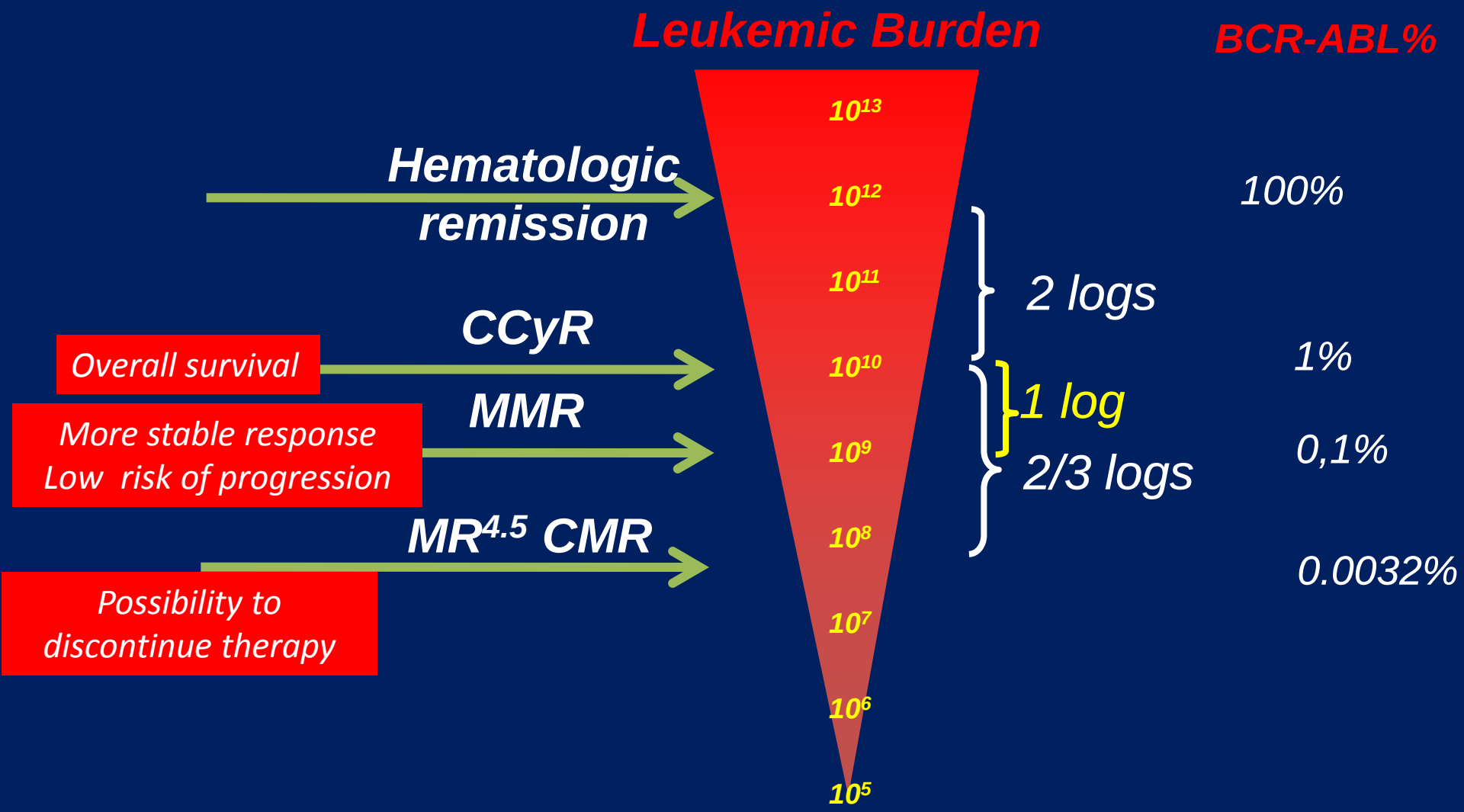
Parameters to evaluate response to imatinib

- *Degree of leukemic burden reduction*
- *Time to achieve it*

Monitoring Response in CML: Hierarchic Order Of Responses



Optimal Response to imatinib 400 mg per day

CHR within 3 months

Until the achievement of MMR (“safe haven”)
also a patient with an optimal response
can progress, but the risk is very low.

CCyR at 12 months

MMR at 18 months

ELN reccomendations 2009; Baccarani et al. JCO 2009

Criteria for Failure and Suboptimal Response to Imatinib

Time (mo)	SWITCH Failure	?? Suboptimal Response	Optimal
3	No CHR	No CG Response	<65% Ph+
6	No CHR >95% Ph+	≥35% Ph+	≤35% Ph+
12	≥35% Ph+	1-35% Ph+	0% Ph+
18	≥5% Ph+	No MMR	MMR
Any	Loss of CHR Loss of CCyR Mutation CE	Loss of MMR Mutation	Stable or improving MMR

Baccarani et al. JCO 2009; 27: 6041-51

ELN recommendations in case of failure, intolerance, or suboptimal response to imatinib

- For patients who experience imatinib failure … drug therapy should be changed to dasatinib or nilotinib. (The detection of some mutations may help to decide between dasatinib and nilotinib.)

- For instances of intolerance, the choices are dasatinib and nilotinib.

- For instances of suboptimal response to imatinib...there is no solid, confirmed evidence that a change in treatment will improve the response, but there are at least two other options - namely an increase of imatinib dose or a change to a 2nd-generation TKI.

ELN, Baccarani et al. J Clin Oncol. 2009; 27(35):6041-51.

Are all types of suboptimal response the same?

Probably not!

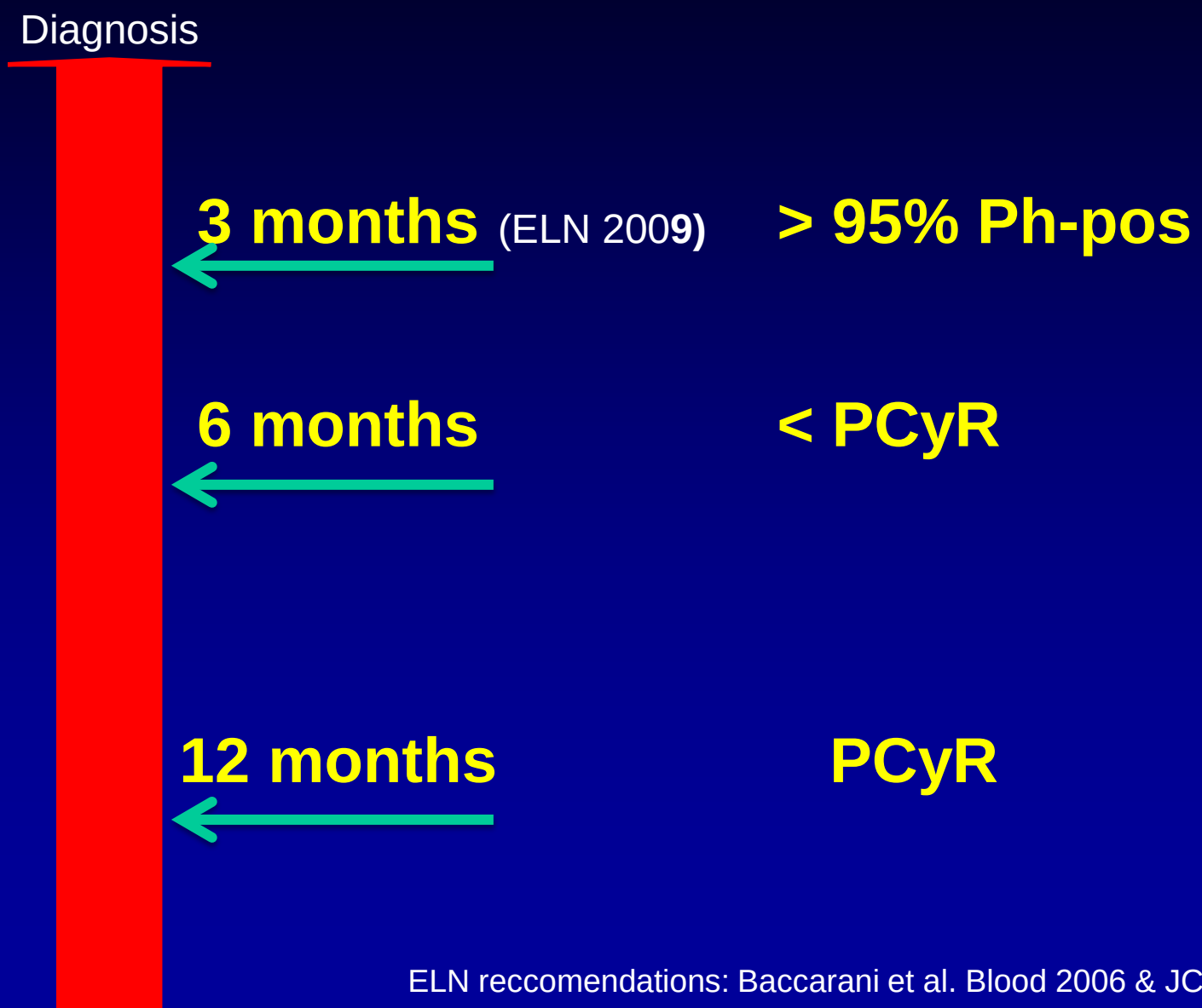
Cytogenetic and Molecular suboptimal responses are different

Cytogenetic Criteria for Suboptimal Responses to Imatinib 400 mg per day

Time (mo)	Response		
	Failure	Suboptimal	Optimal
3	No CHR	No CG Response	<65% Ph+
6	No CHR >95% Ph+	≥35% Ph+	≤35% Ph+
12	≥35% Ph+	1-35% Ph+	0% Ph+
18	≥5% Ph+	No MMR	MMR
Any	Loss of CHR Loss of CCgR Mutation CE	Loss of MMR Mutation	Stable or improving MMR

Baccarani et al. JCO 2009; 27: 6041-51

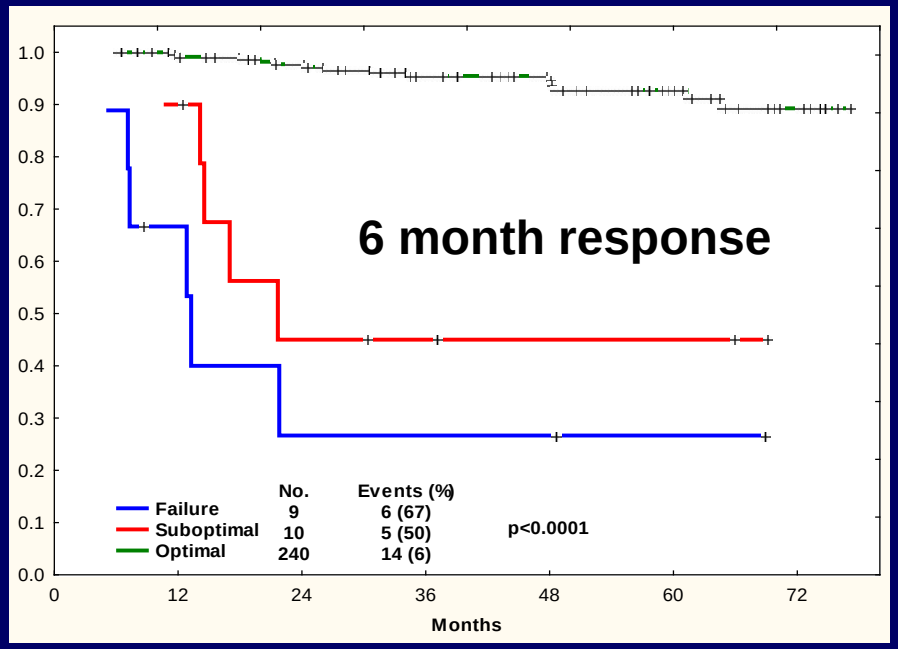
Cytogenetic monitoring ELN 2006

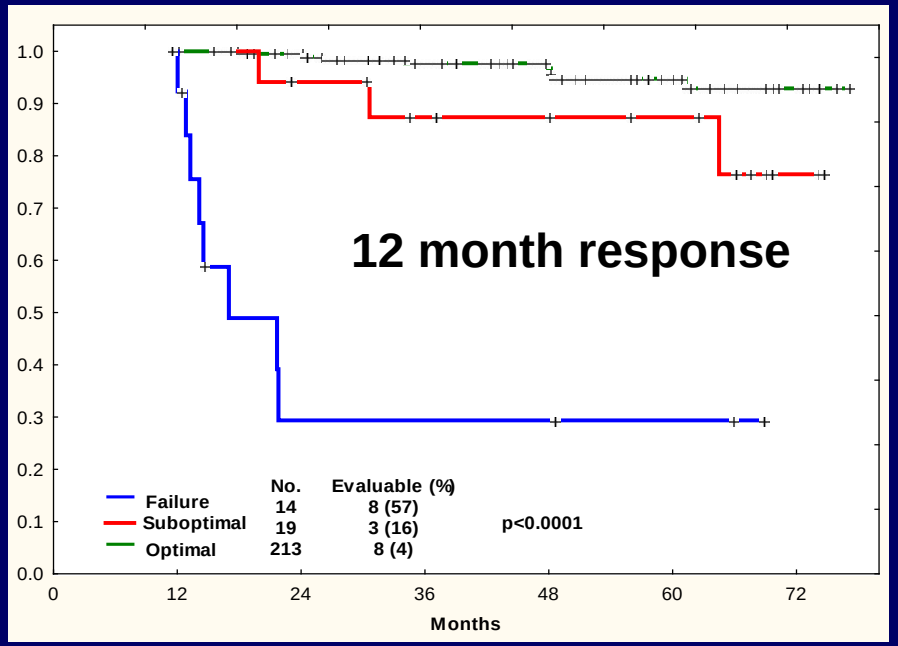


ELN reccomendations: Baccarani et al. Blood 2006 & JCO 2009

EFS by Response to Imatinib at 6 and 12 Months

- **281 pts; imatinib frontline (400 mg in 73, 800 mg in 208)**





Alvarado Y, et al. Blood 2007;110: Abstract 1932.

Suboptimal Response to Imatinib in CP CML (GIMEMA; n = 423)

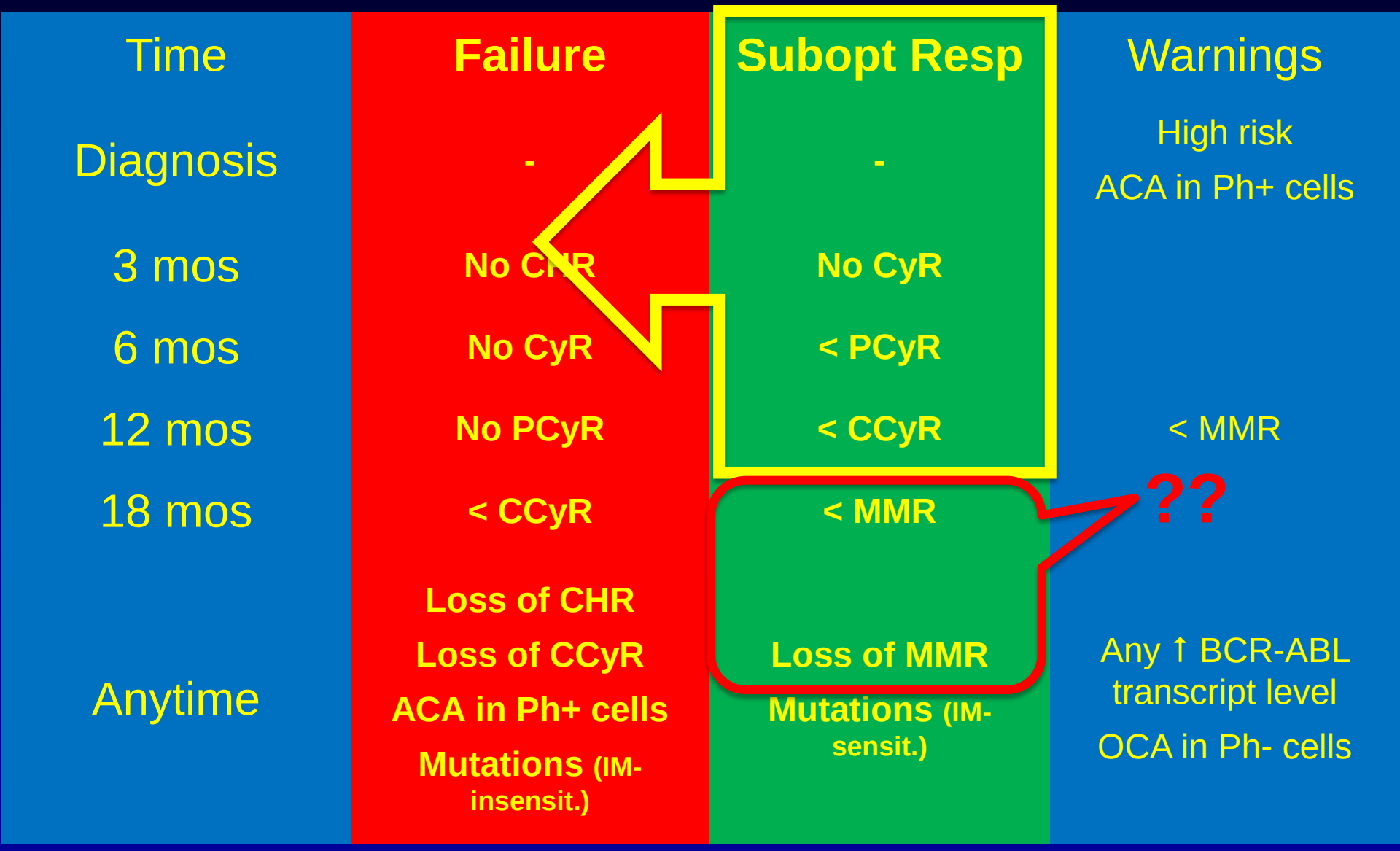
423 newly Dx pts Rx with IM 400 mg/D; median FU 41 mos

Subopt. Resp.		N	% EFS	% CCyR	% MMR
6 mos	No	341	90	98	93
	Yes	20	60	60	50
12 mos	No	323	94	100	96
	Yes	31	68	81	68

Castagnetti. Hematologica 2009;94 abstract 0528

Definition of Failure and Suboptimal Response

(ELN Recommendations, Baccarani et al., JCO 2009)



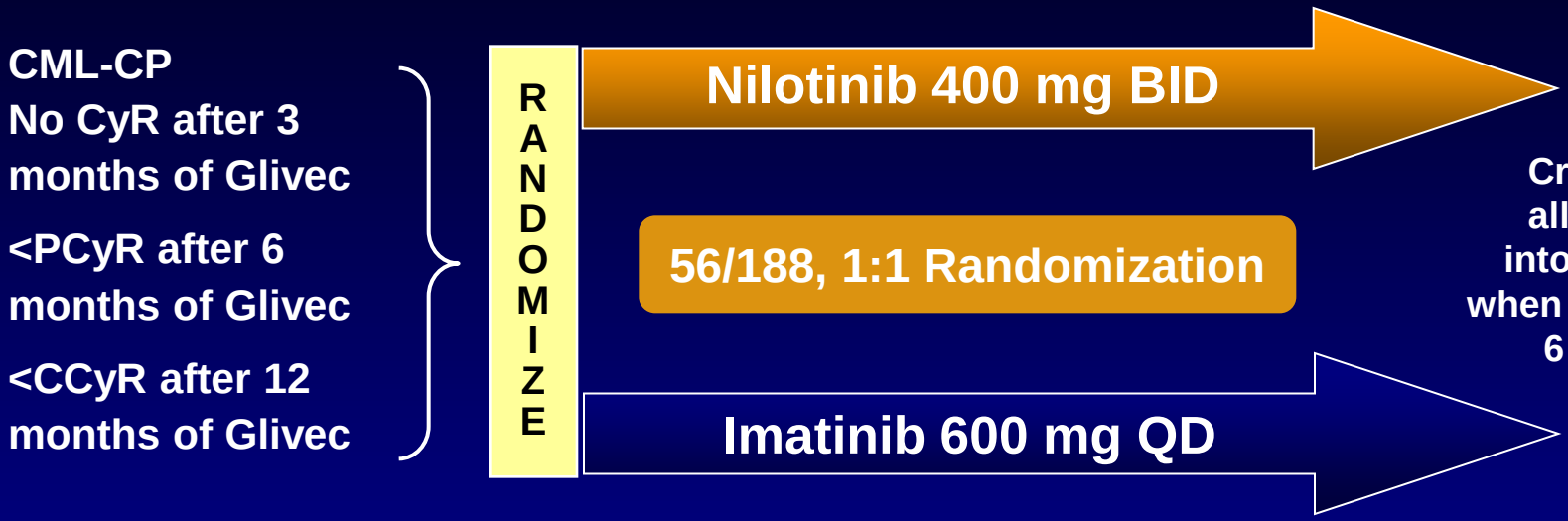
Which is the best way to react in suboptimal responders?

- Increasing Imatinib dosage?
- Switching directly to 2° gen TKIs?

Few data at the moment

for “suboptimal responders” only!

LASOR (2404): Study design



Study Design:	Phase III, randomized, open label
Primary Endpoint:	The rate of CCyR after 6 months on study
Enrollment:	On hold, will restart in March 2010, 56/188 (LATAM, Europe and EGM)
FPFV:	22-Jun-2010
Number of sites:	56/63 sites opened

Latin America, Europe, EGM; PI - Cortes, le Coutre

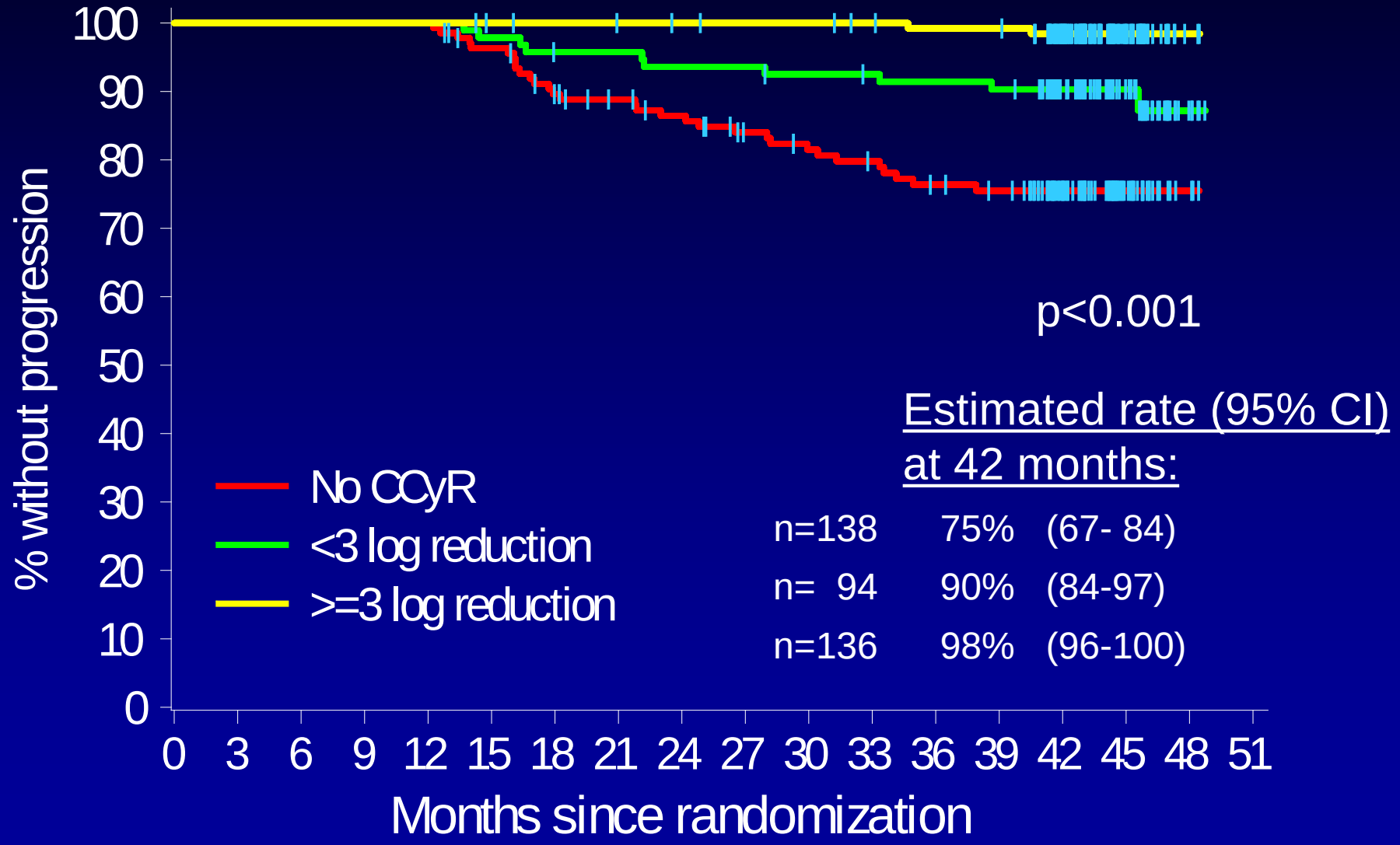
ClinicalTrials.gov Identifier: NCT00802841

Consideration

- If the results are so good with second generation TKIs for all patients from the beginning, why to deny at least an early switch to those who do not have an optimal response to imatinib?

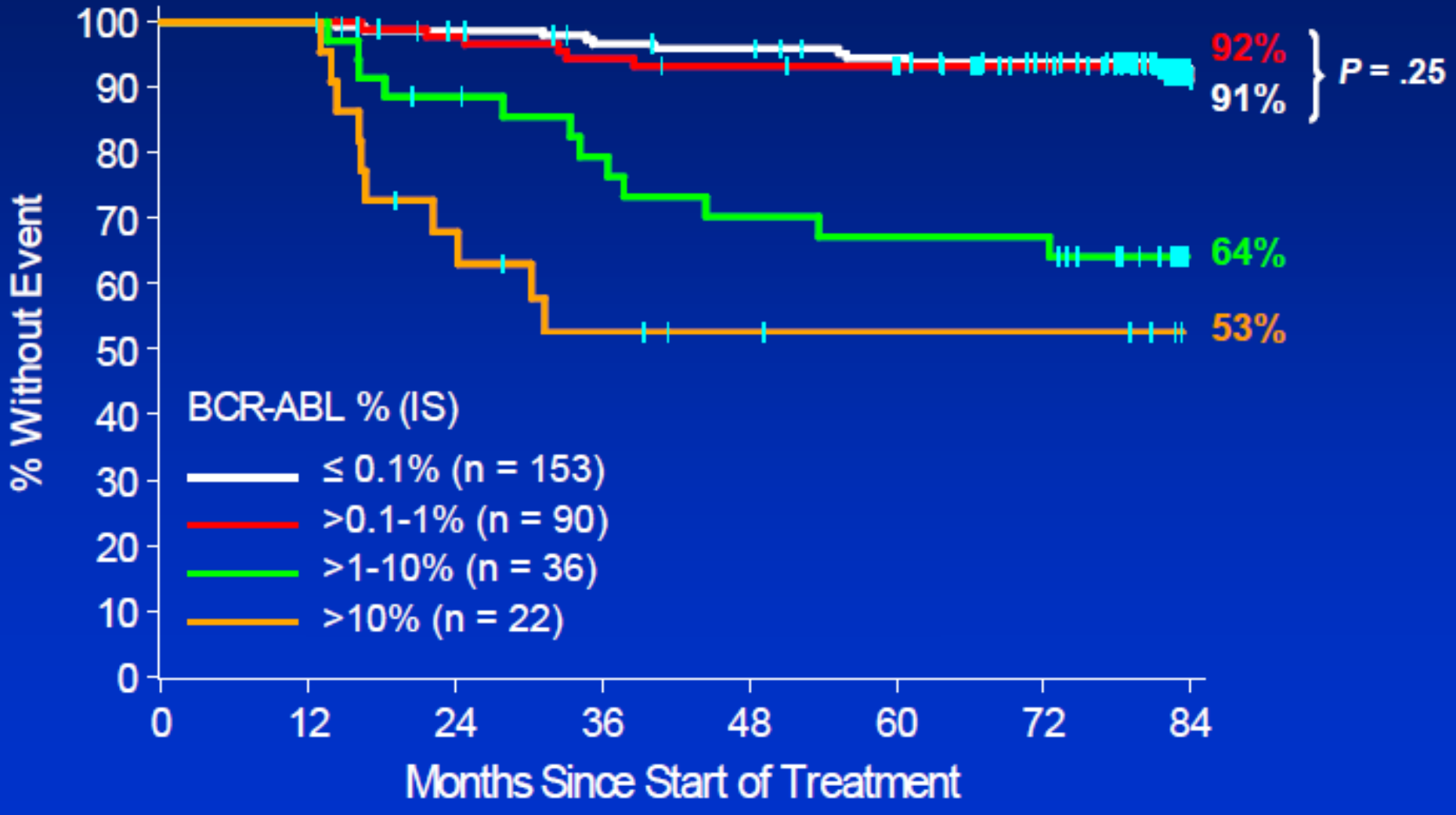
Is it important to achieve MMR in addition to CCyR?

IRIS, Progression-free Survival on First-line Imatinib by Molecular Response (MR) at 12 months



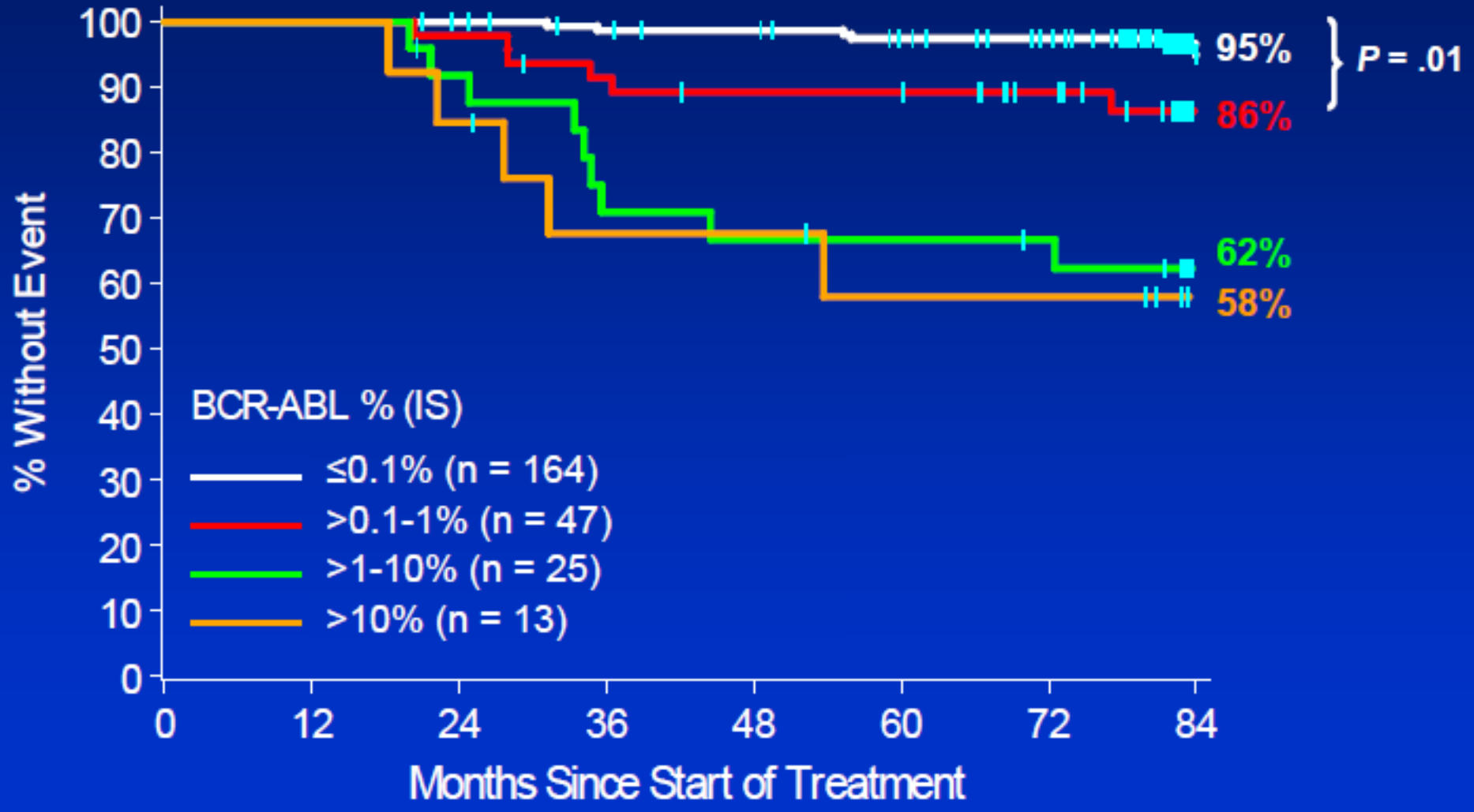
Hughes et al, NEJM 2003

EFS: 12-Month Landmark Analysis



Hughes et al ASH 2008

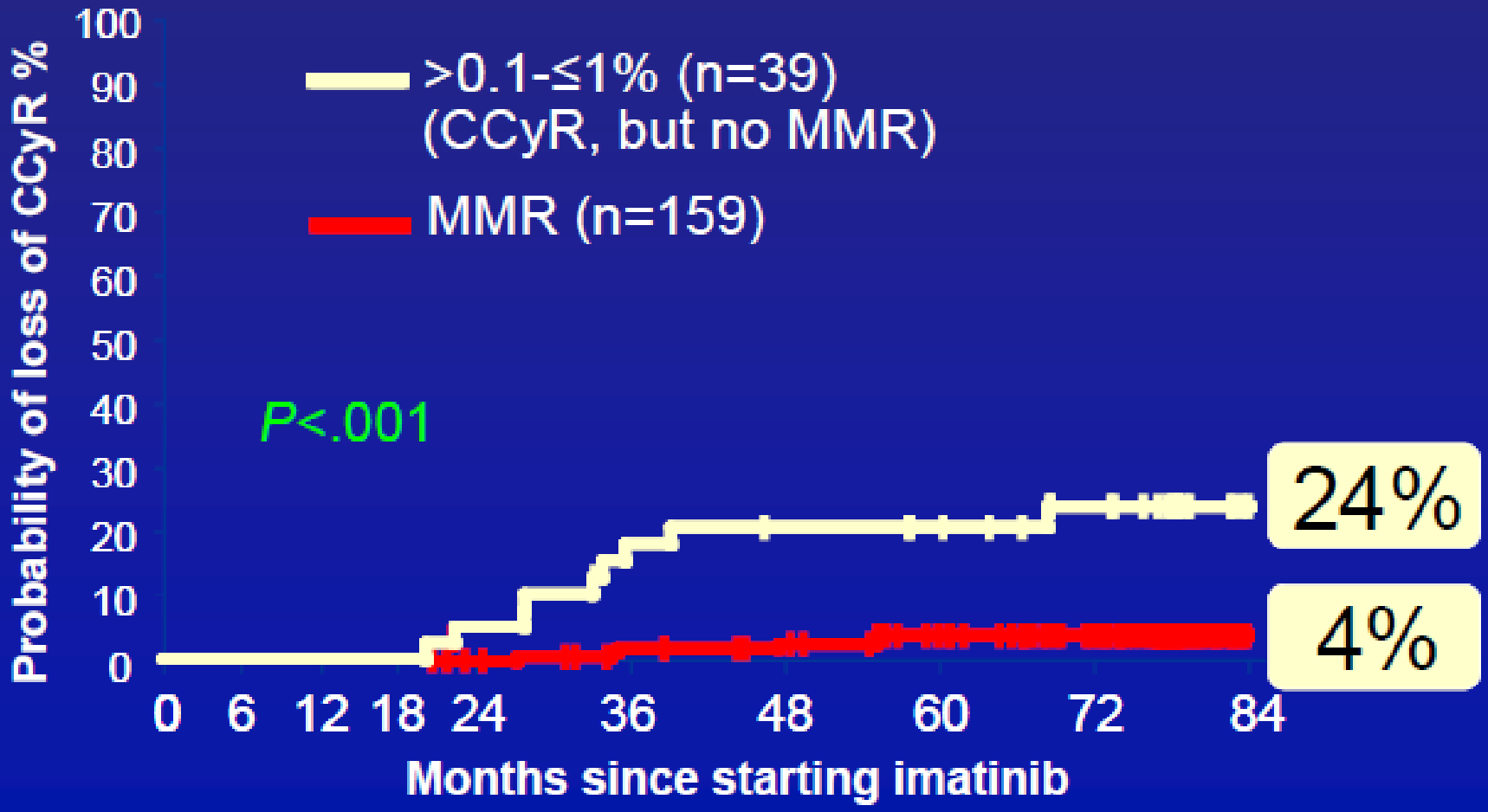
EFS: 18-Month Landmark Analysis



Hughes et al ASH 2008

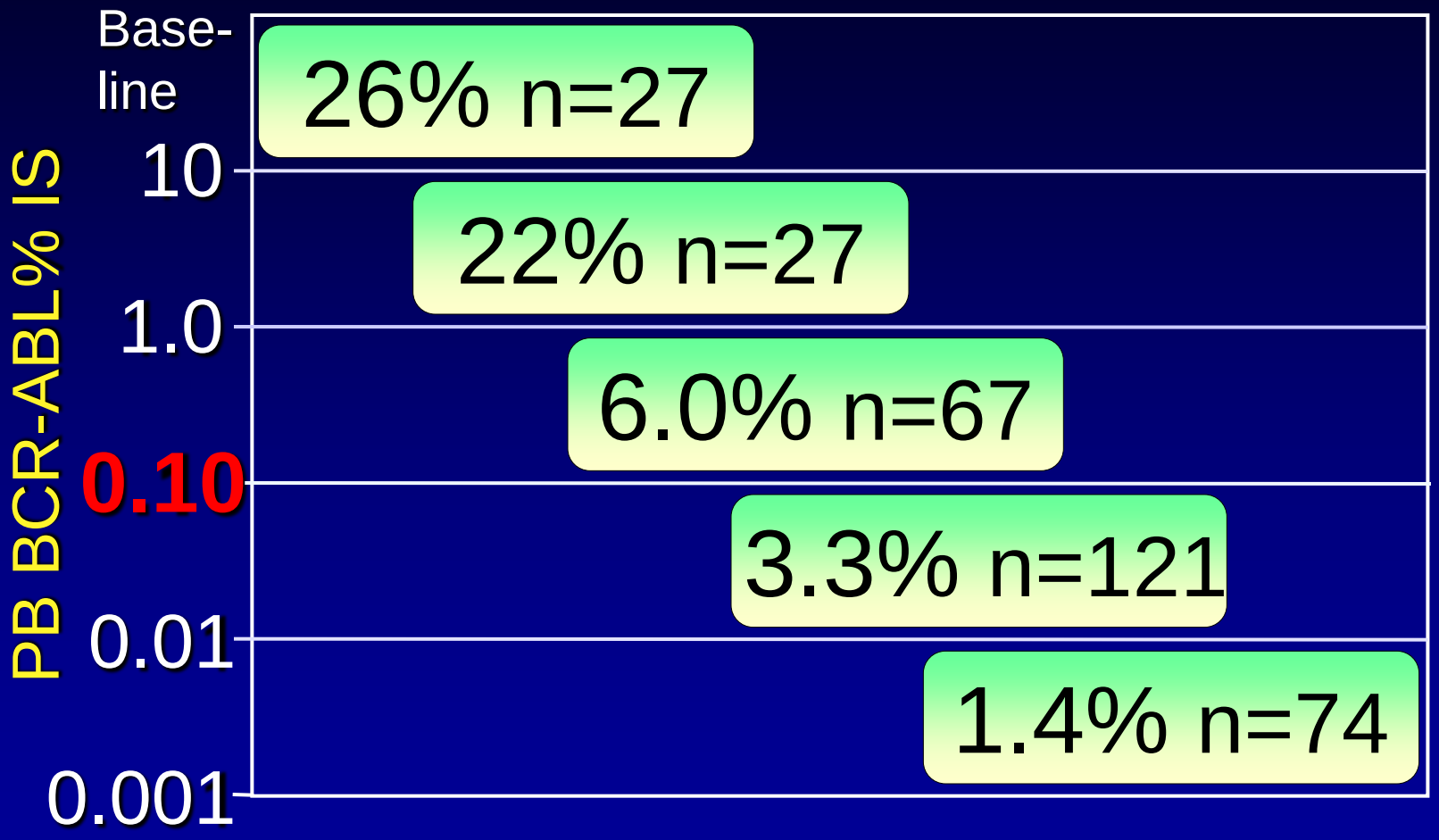
Loss of CCyR: 18-month landmark analysis

Sub-group analysis in the IRIS study



Adapted from Hughes et al. ASH Annual Meeting 2008; Oral Presentation 334.

Frequency of mutations according to the lowest BCR-ABL value in first 18 months



All newly diagnosed patients treated in trials of imatinib and tested in Adelaide, n=316

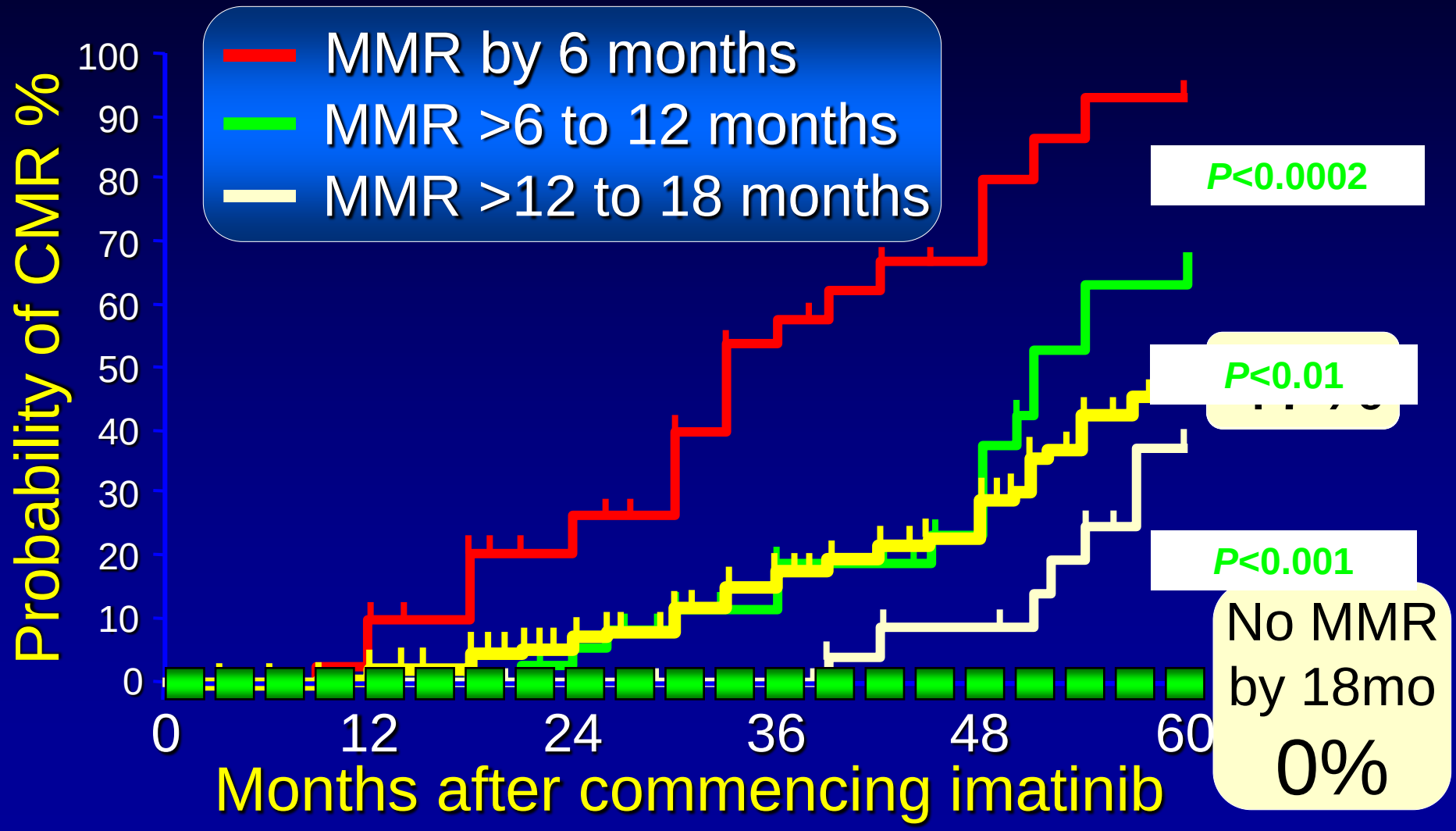
Courtesy Tim Hughes

MMR
“Safe Haven”

The current therapeutic strategy is to achieve higher rates of MMR, which is achieved with more potent inhibitors

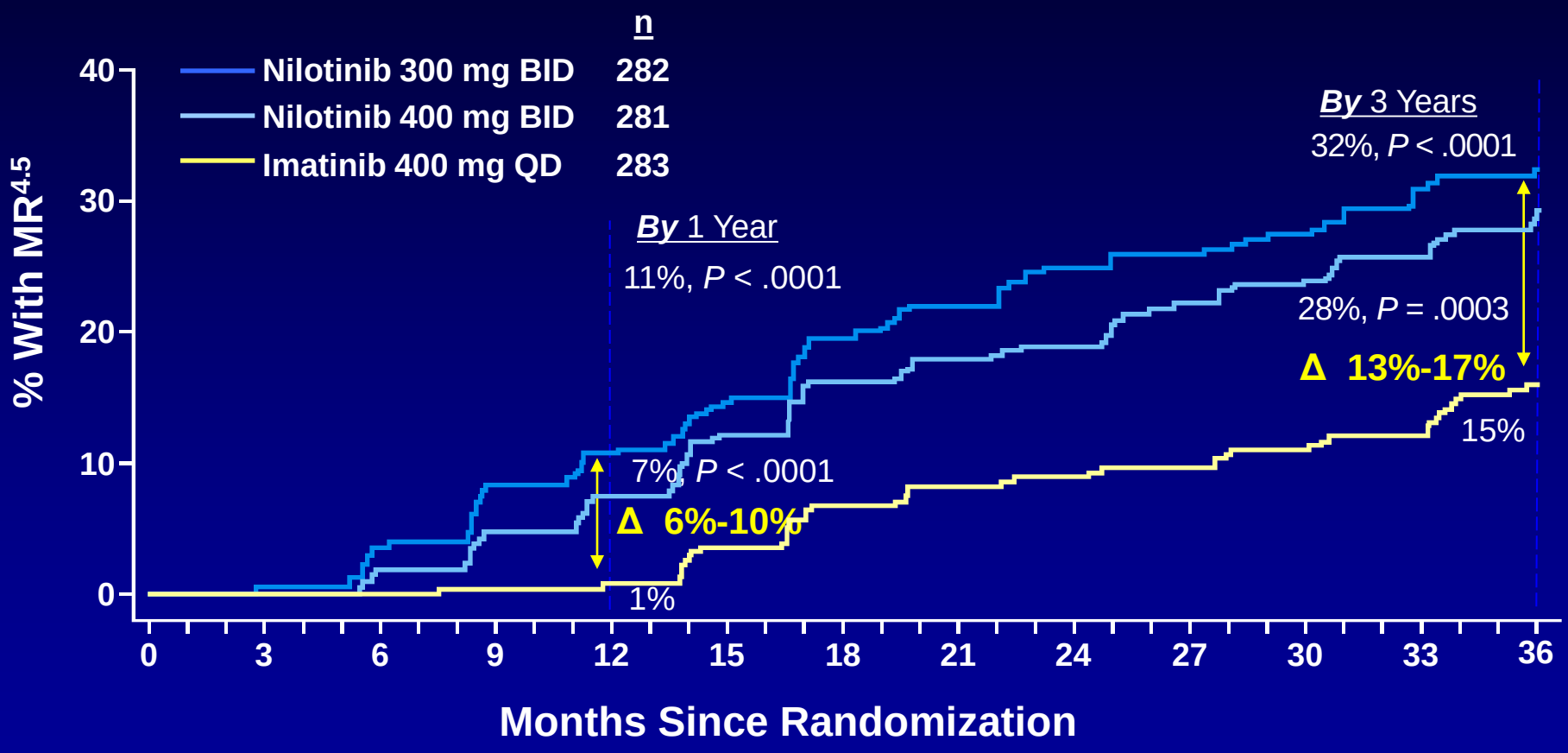
Probability of CMR by 60 months

181 de-novo patients 400/600 mg imatinib tested in Adelaide



Branford et al. Blood. 2008:112. Abstract 2113.

Cumulative Incidence of MR$^{4.5*}$ is higher with Nilotinib than with Imatinib



* Equivalent to BCR-ABL transcript levels of ≤ 0.0032% (IS).

Data cut-off: 27Jul2011.

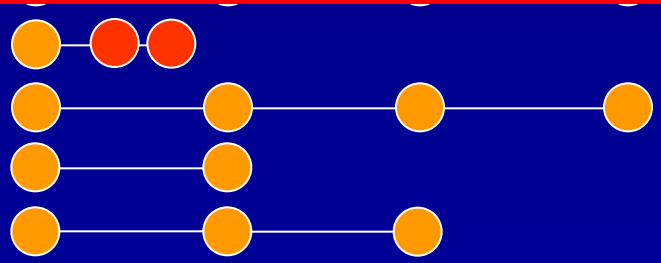
Saglio G, et al. *Blood*. 2011;118(21):208-209 [abstract 452].

CMR = cure?

Pts	IFN (months)	Sokal	M0	M3	M6	M12	M18	M24
2	67	L						
7	71	L						
5	153	I						

CMR, being prodromic to possible discontinuation without recurrence of the disease (cure), is gradually becoming the new therapeutic goal in CML.

A fast achievement of MMR is prognostic for achievement of CMR

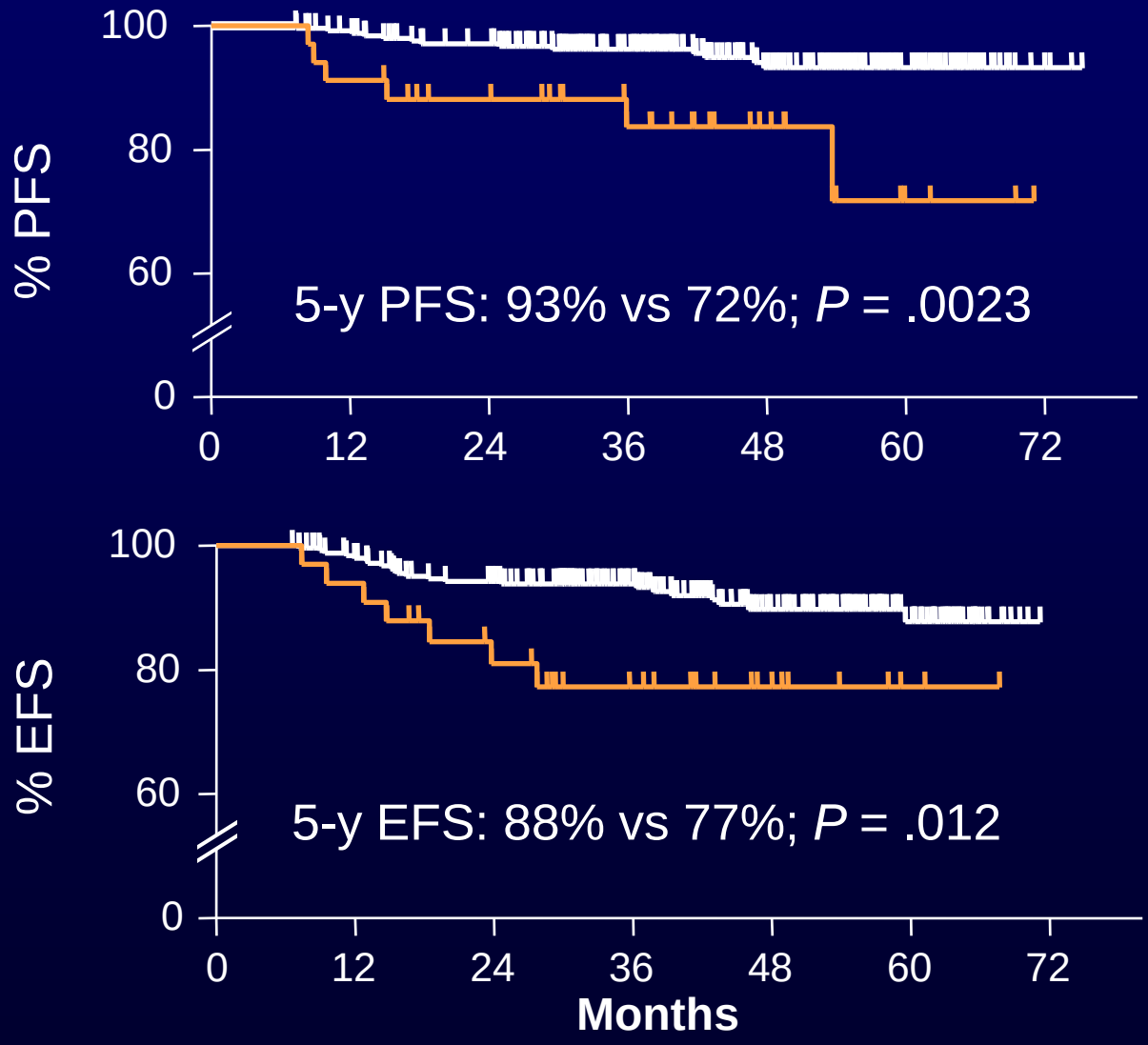


PCR negativity
Molecular relapse
Imatinib retreatment
Molecular response

Rousselot et al. *Blood 2007*

Is it important to achieve a fast response?

Degree of Molecular Response at Early Timepoints Predicts PFS and EFS



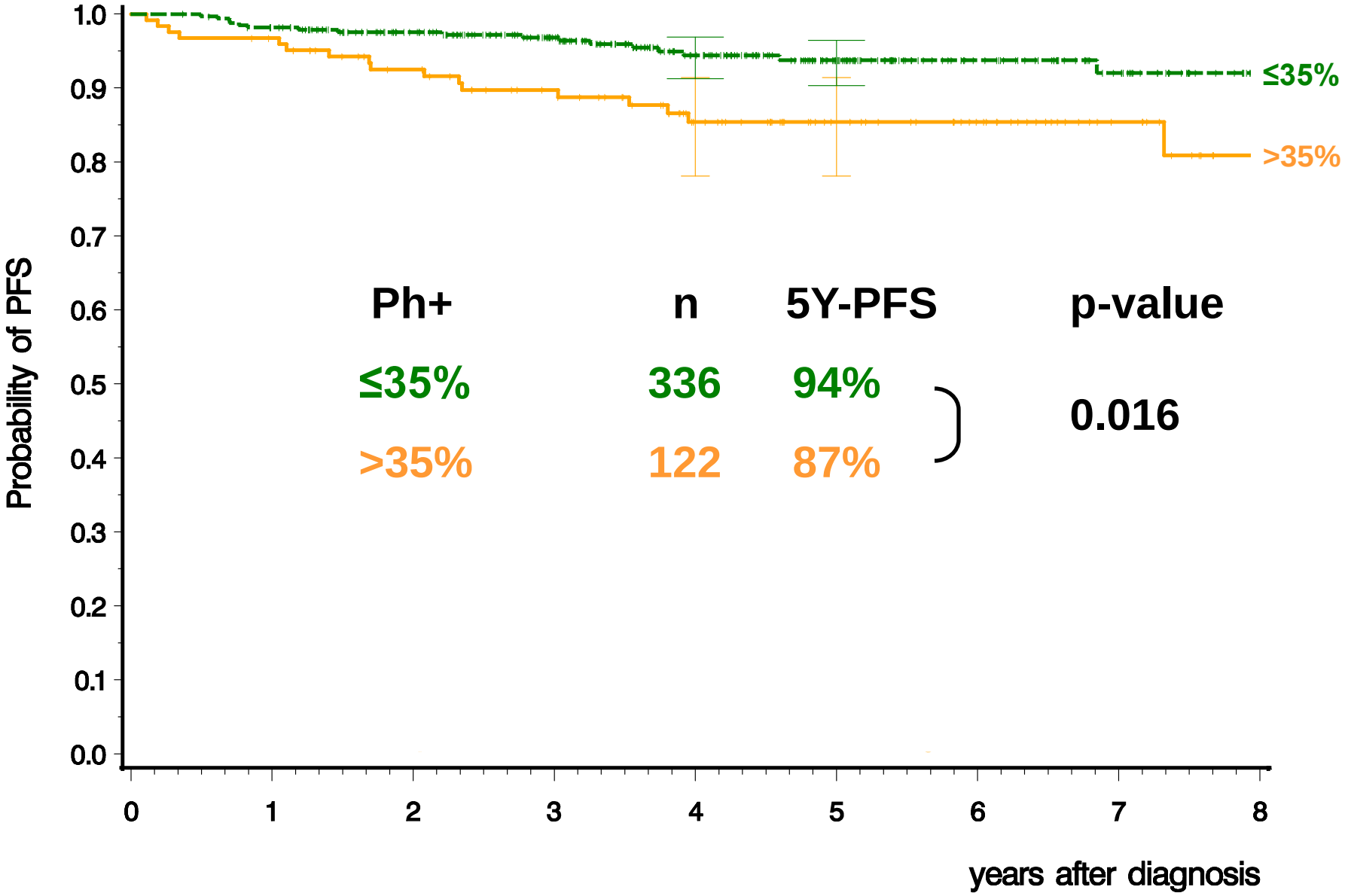
BCR-ABL% (IS)
at 3 months

< 10%
>10%

Patients randomized to imatinib-based therapies in the German CML Study IV

Hanfstein B et al. EHA 2011

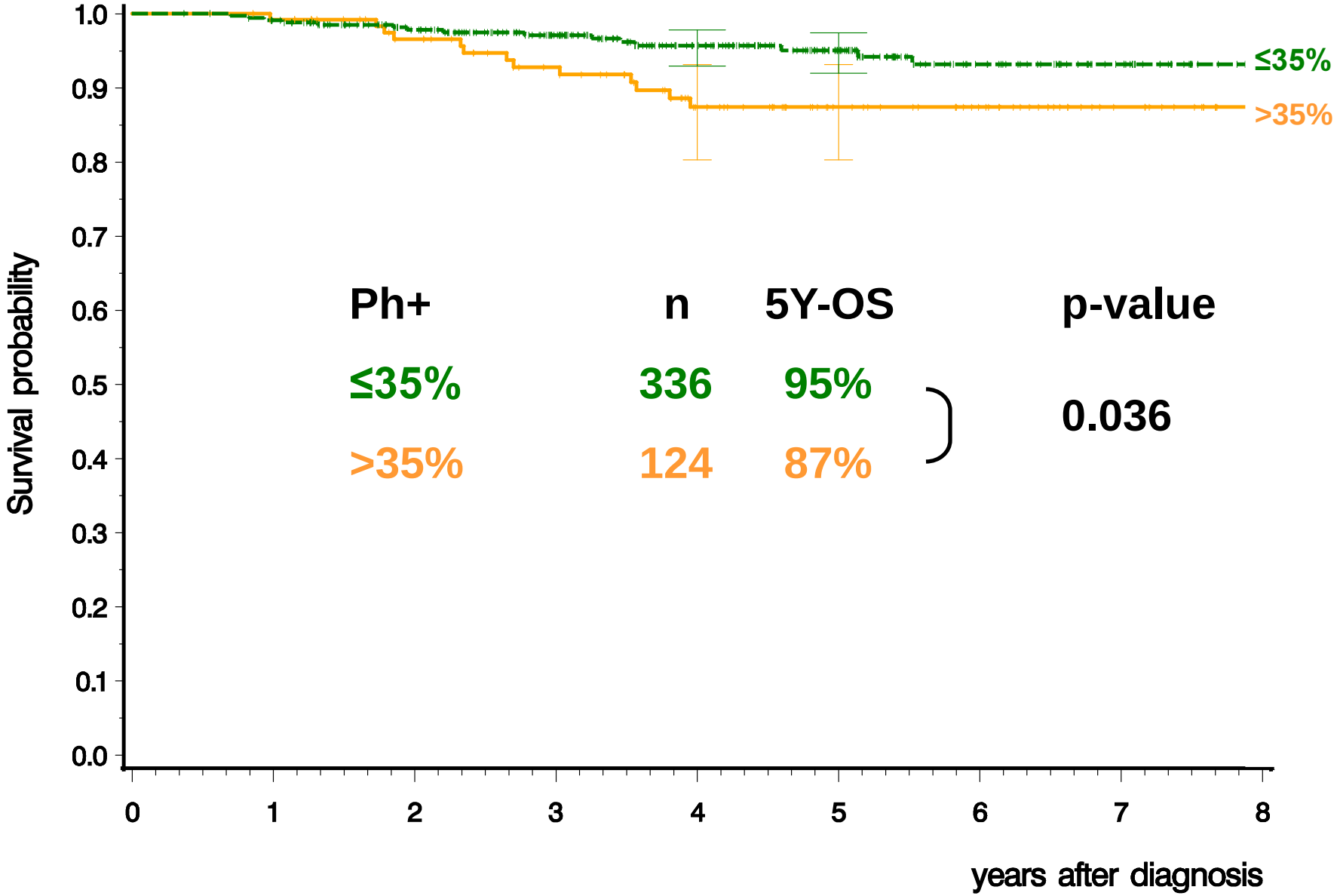
Progression-free Survival (PFS)
Ph+ at 3 months ≤35% vs. >35%



Ph+	n	5Y-PFS	p-value
≤35%	336	94%	0.016
>35%	122	87%	

Overall Survival (OS)

Ph+ at 3 months ≤35% vs. >35%

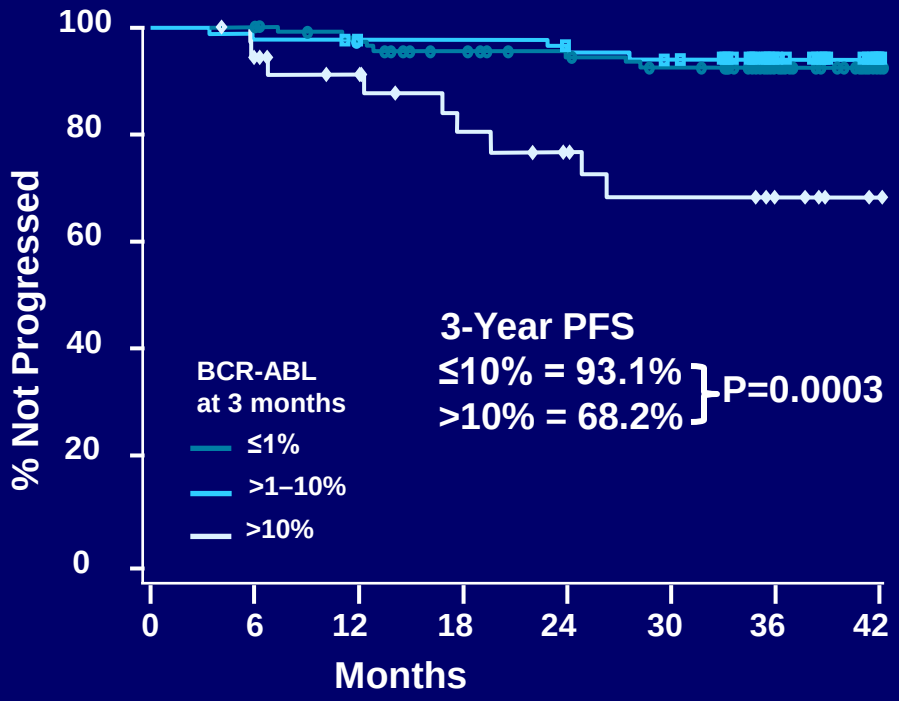


Ph+	n	5Y-OS	p-value
≤35%	336	95%	0.036
>35%	124	87%	

PFS According to BCR-ABL Level at 3 Months[a]

Dasatinib 100 mg QD

84% had ≤10% BCR-ABL

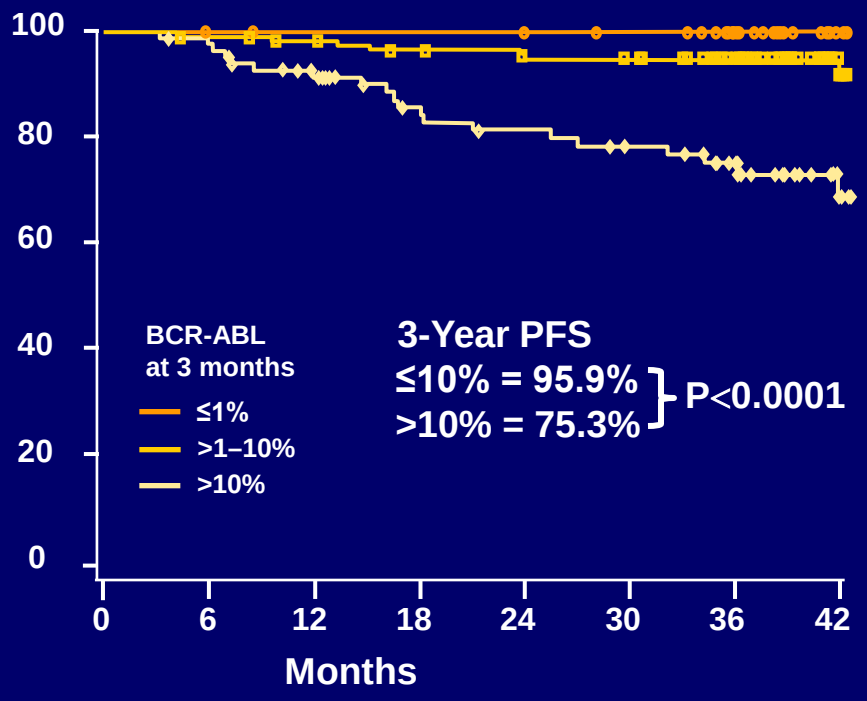


Subjects at risk

≤1%	112	112	105	98	93	89	60	24
>1-10%	85	83	81	81	79	75	52	21
>10%	36	33	28	22	19	16	11	6

Imatinib 400 mg QD

64% had ≤10% BCR-ABL



Subjects at risk

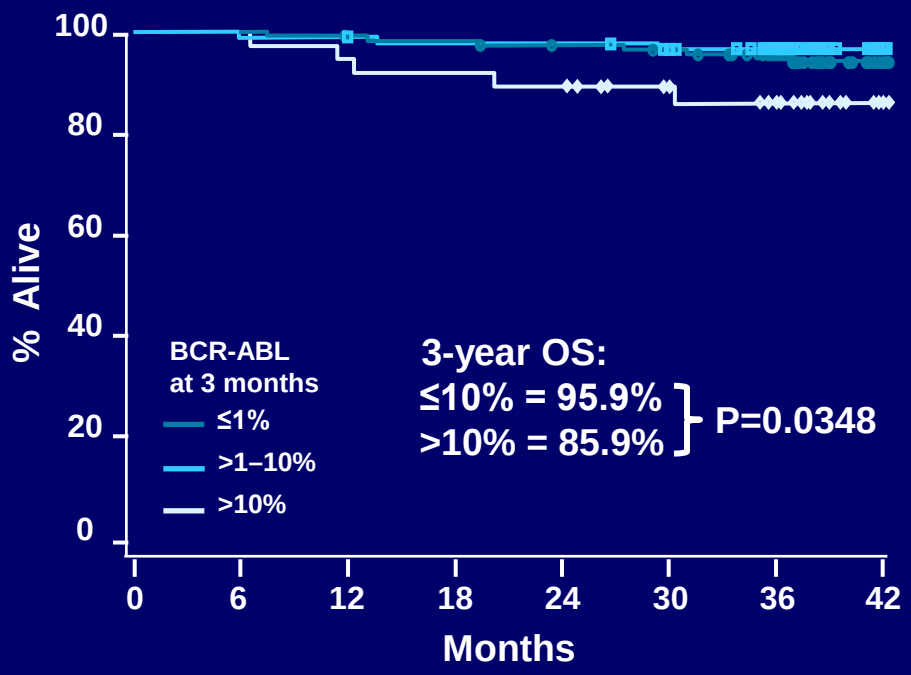
≤1%	32	31	30	30	29	28	20	7
>1-10%	121	119	116	112	108	106	76	25
>10%	84	81	71	59	56	51	37	13

[a]Calculated from total number of evaluable patients with PCR assessments at 3 months

OS According to BCR-ABL Level at 3 Months[a]

Dasatinib 100 mg QD

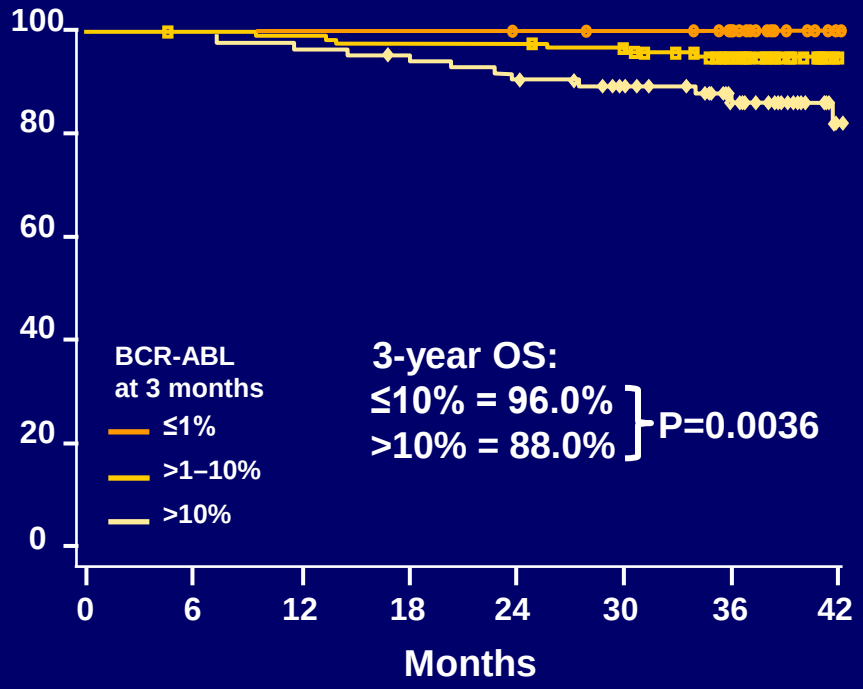
84% had ≤10% BCR-ABL



Subjects at risk								
≤1%	112	112	110	109	106	104	85	29
>1-10%	86	85	84	83	83	79	66	25
>10%	37	37	35	34	33	27	22	9

Imatinib 400 mg QD

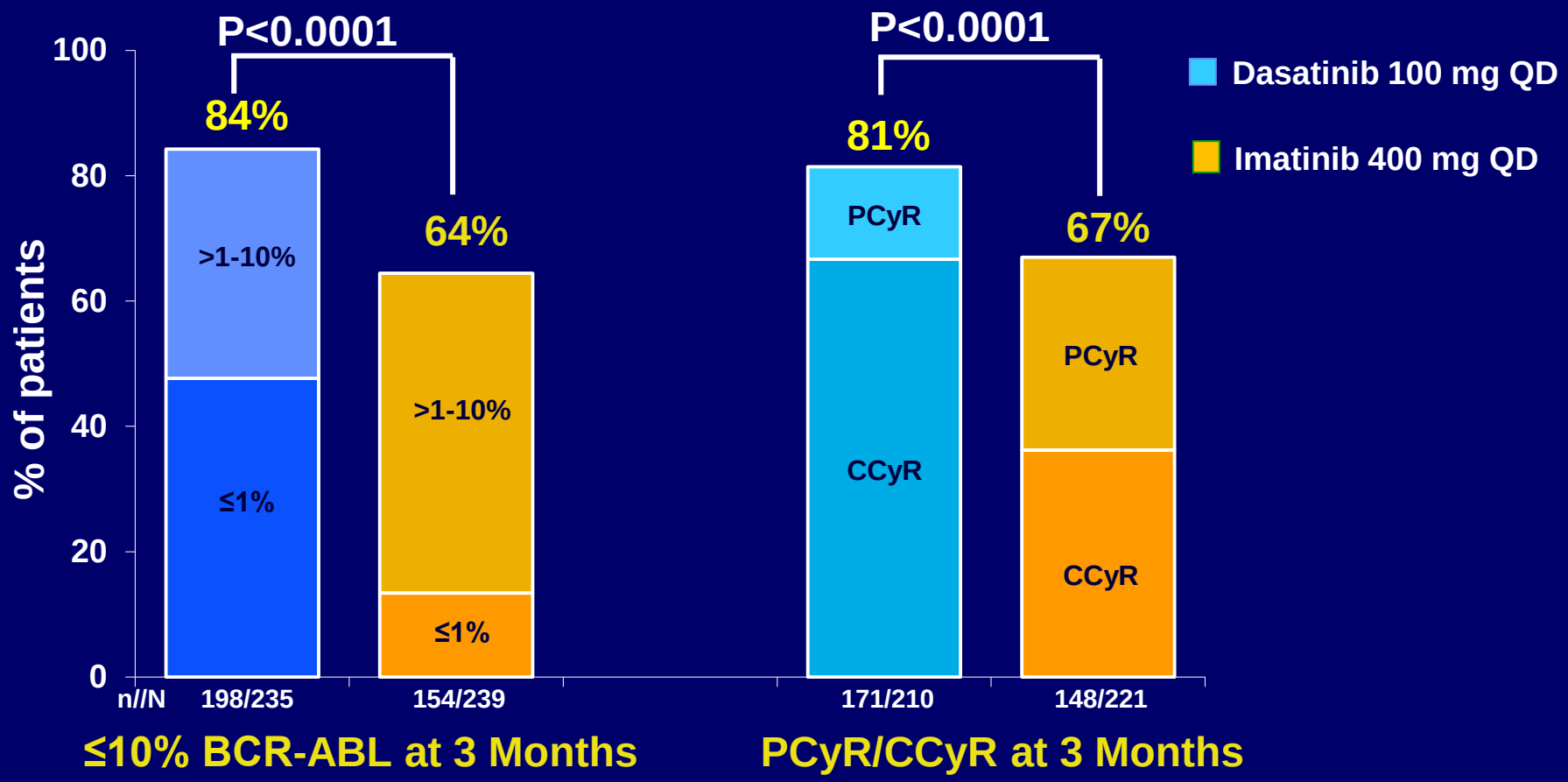
64% had ≤10% BCR-ABL



Subjects at risk								
≤1%	32	32	32	32	31	30	28	11
>1-10%	122	121	120	118	118	116	96	33
>10%	85	85	82	80	76	70	55	20

[a]Calculated from total number of evaluable patients with PCR assessments at 3 months

Molecular and Cytogenetic Response at 3 Months[a]



- BCR-ABL of <10% and ≤1% are not fully concordant with ≥PCyR and CCyR, respectively
  - 96% and 83% of dasatinib and imatinib pts with ≥PCyR had <10% BCR-ABL, respectively
  - 68% and 26% of dasatinib and imatinib pts with CCyR had ≤1% BCR-ABL, respectively

[a] Calculated from total number of evaluable patients with PCR assessments at 3 months

The response kinetics can tell us something

ENESTnd: 3-Month Landmark Analyses (Hochhaus A. et al. EHA 2012)

	Nilotinib 300 mg BID			Imatinib 400 mg QD		
BCR-ABL at 3 months	**≤ 1% N=145**	**>1– ≤10% N=89**	**>10% N=24**	**≤ 1% N=43**	**>1– ≤10% N=133**	**>10% N=88**
MMR	n=120	n=89	n=24	n=41	n=133	n=88
by 1 year (%)	76	40	4	71	31	2
by 2 years (%)	89	67	29	78	52	20
CMR$^{4.5}$	n=144	n=89	n=24	n=43	n=133	n=88
by 2 years (%)	40	12	4	33	8	0
by 3 years (%)	50	18	4	53	14	1

Evaluable patients (n) excluded patients with unevaluable/missing PCR assessments at 3 months, atypical transcripts at baseline, or patients who achieved response within 3 months

NCCN Guidelines Version 1.2013
Chronic Myelogenous Leukemia

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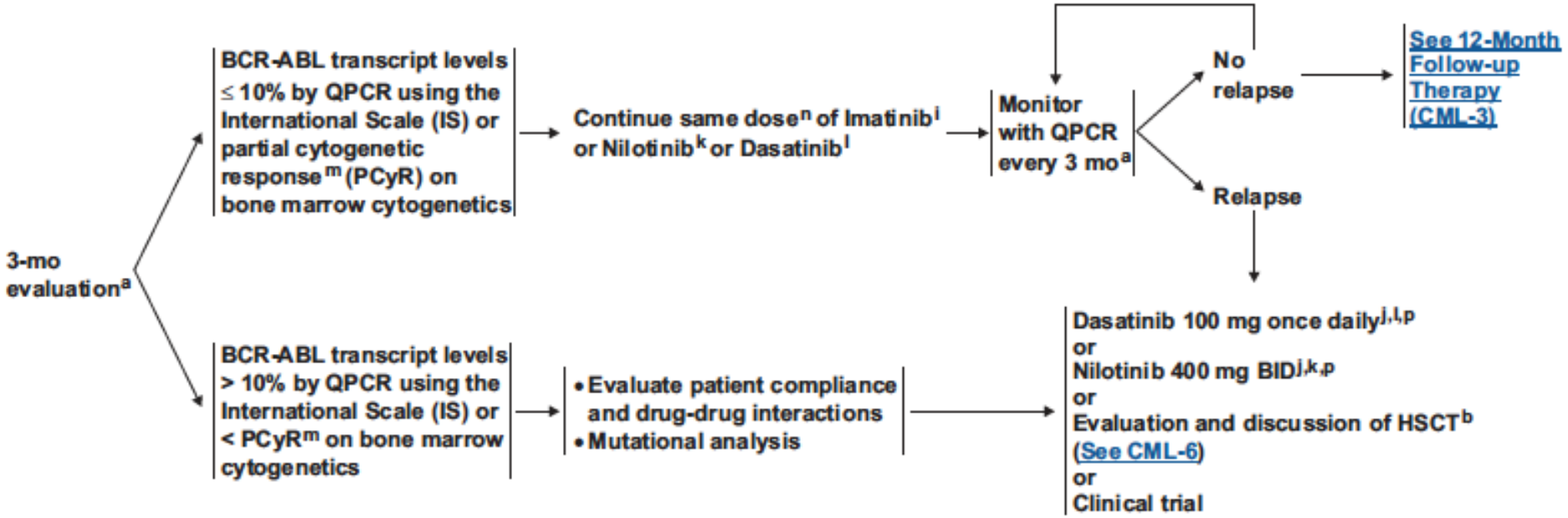
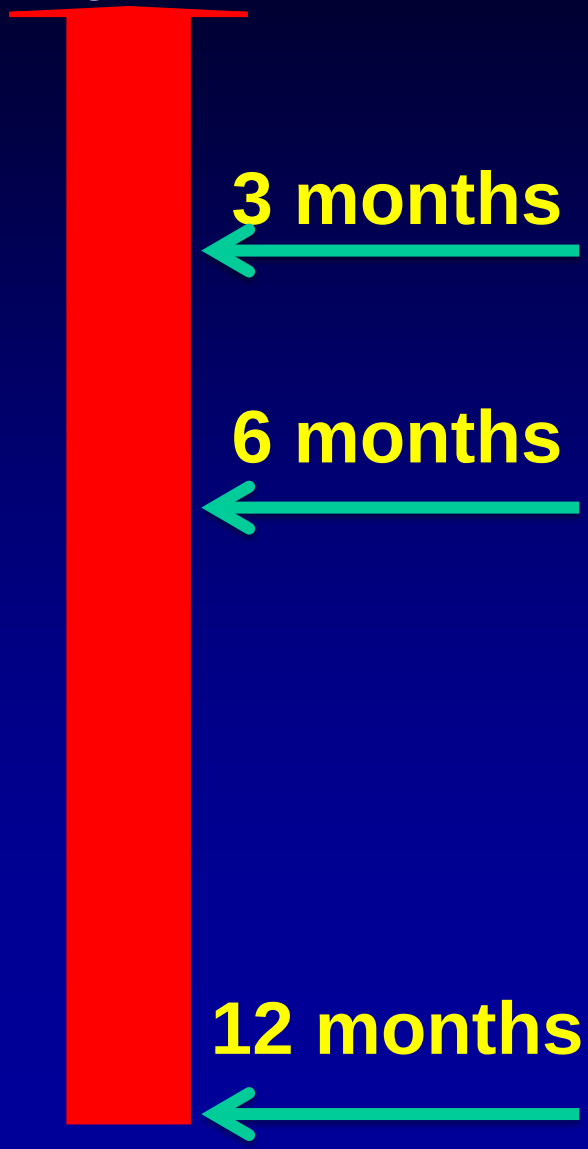
3 MONTH FOLLOW-UP THERAPY[a]



? ELN 2013 ?



Responders	Non responders
< PCyR or <10% BCR-ABL	> PCyR or >10% BCR-ABL
<CCyR or <1% BCR-ABL	>CCyR or >1% BCR-ABL
MMR / < 0,1% BCR-ABL	MMR / > 0,1% BCR-ABL

Thank you!