European LeukemiaNet

When to change therapy?

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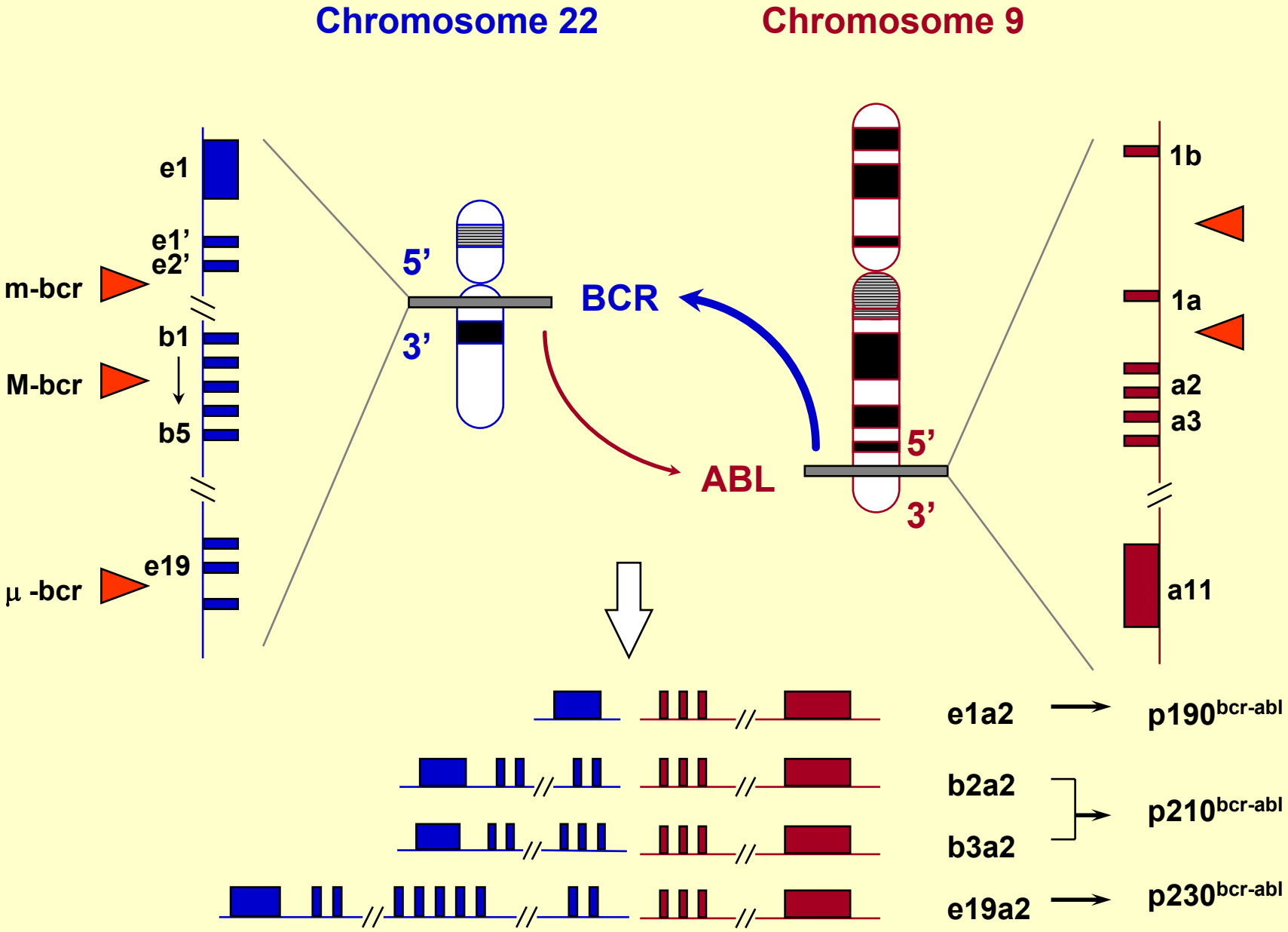
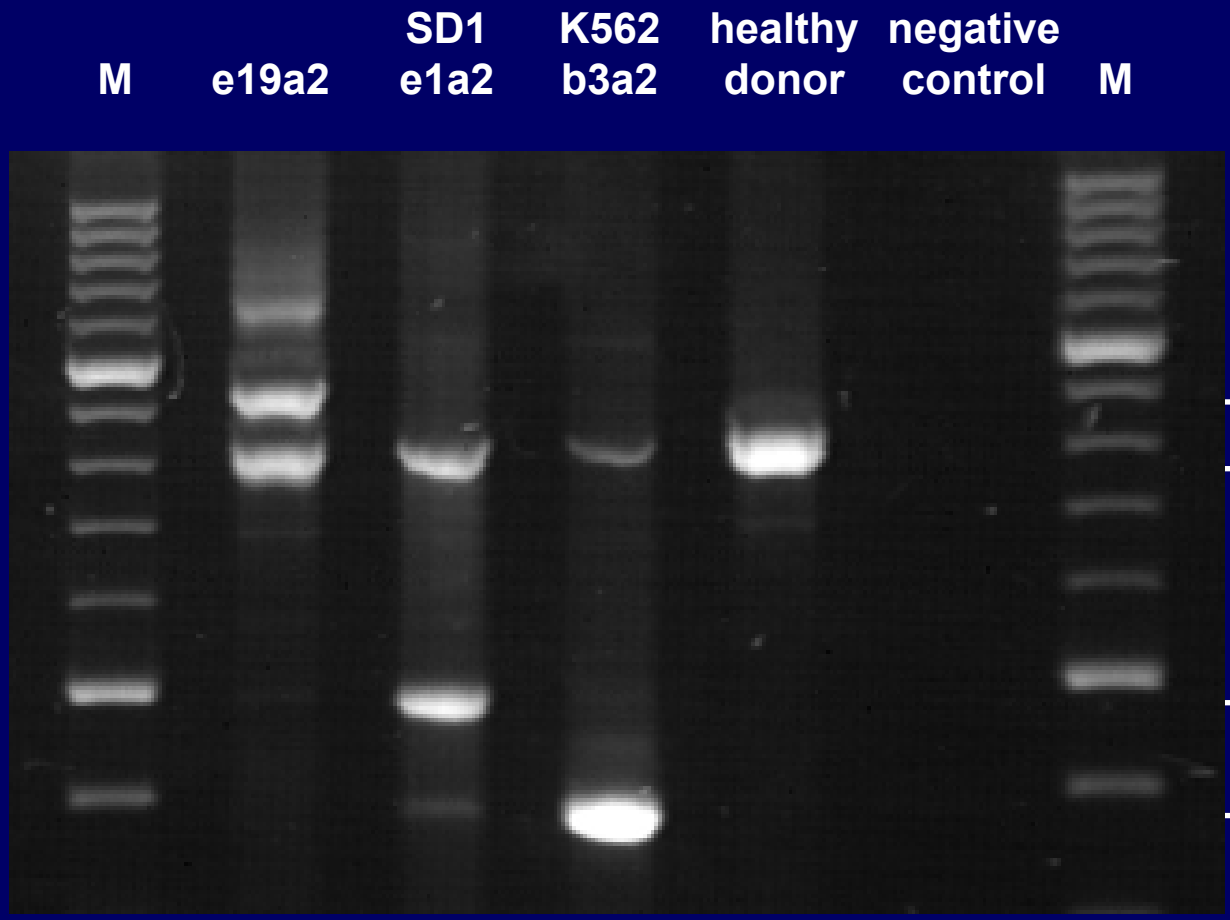
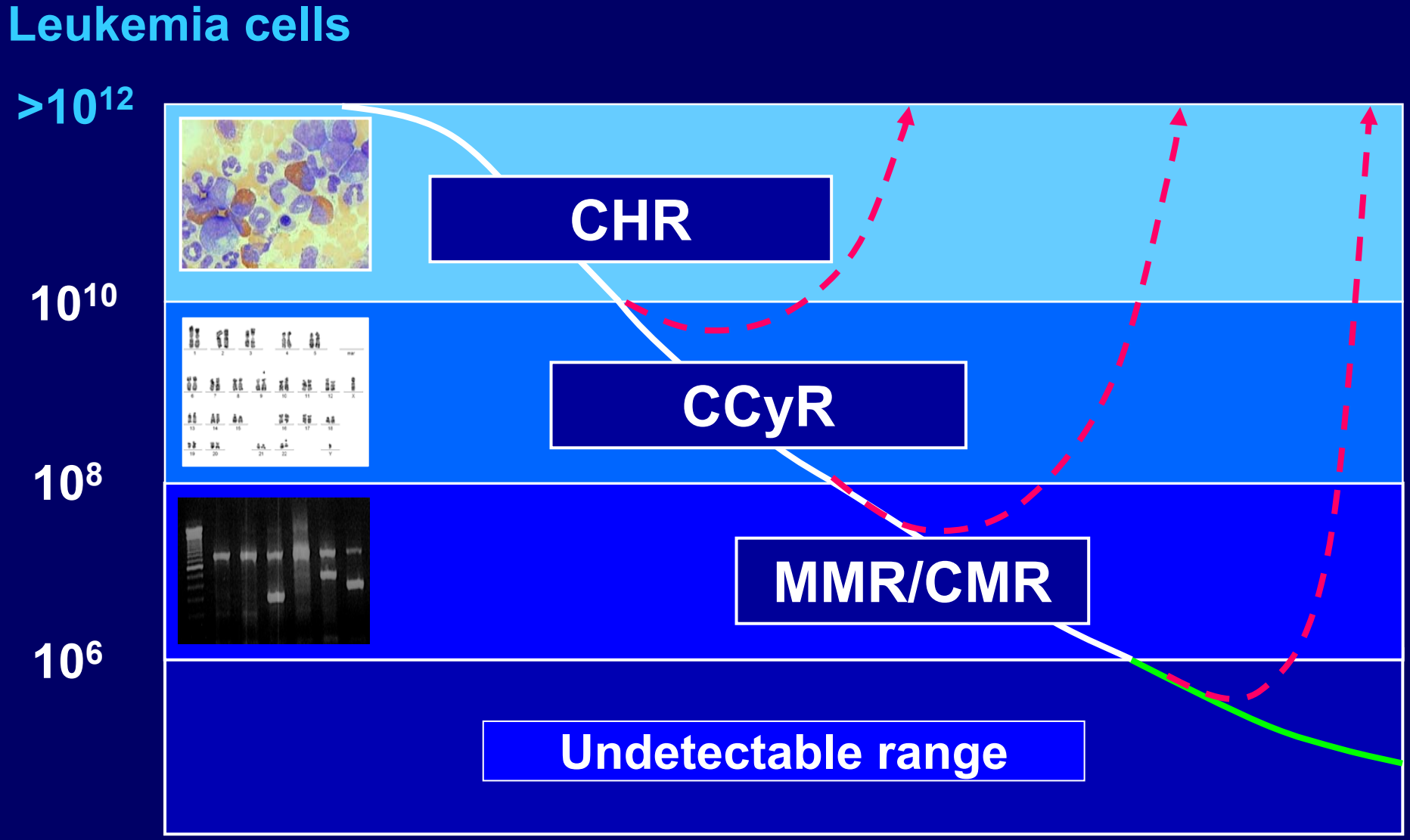

Chromosome 22
Chromosome 9
e1
e1'
e2'
m-bcr
b1
M-bcr
b5
e19
μ -bcr
5'
3'
BCR
ABL
5'
3'
1b
1a
a2
a3
a11
e1a2
p190bcr-abl
b2a2
b3a2
p210bcr-abl
e19a2
p230bcr-abl

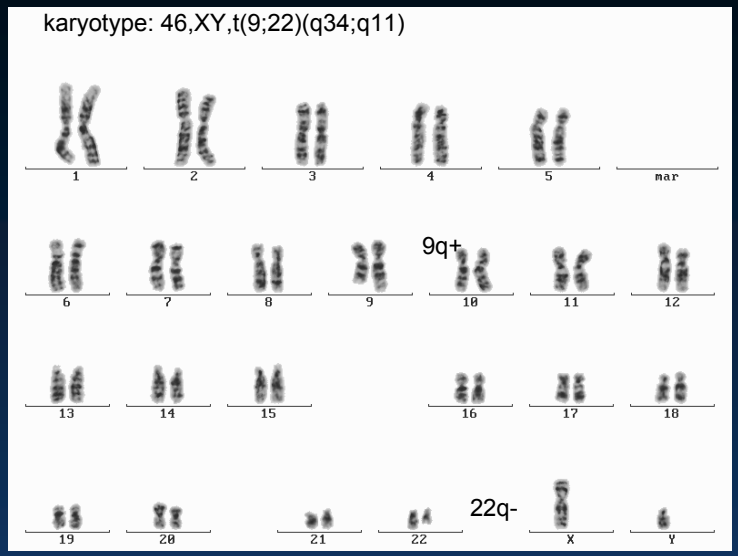
Detection of typical and rare BCR-ABL transcripts by multiplex PCR

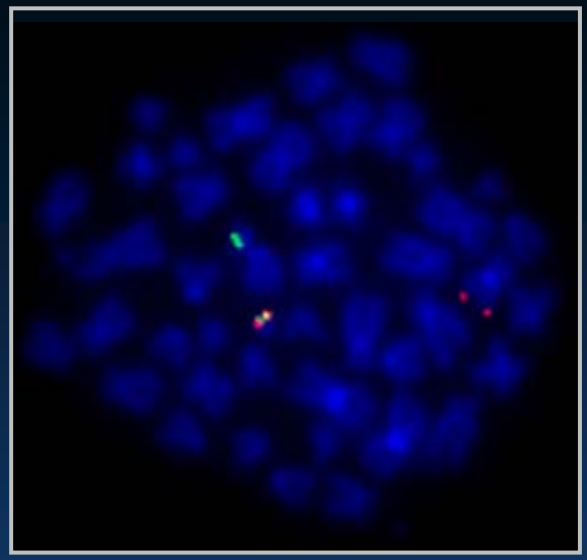


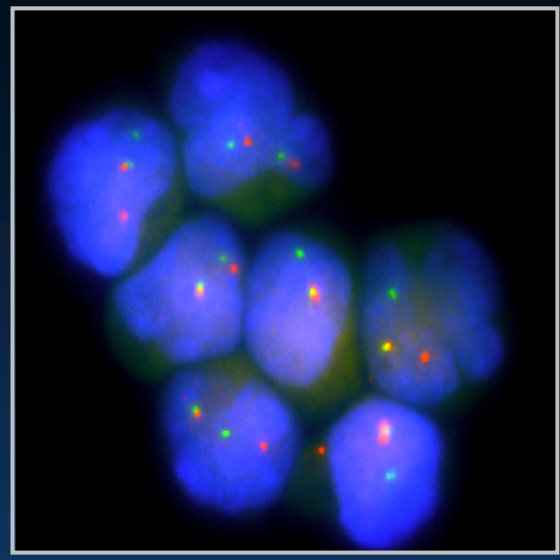
Cross et al *Leukemia 1994*

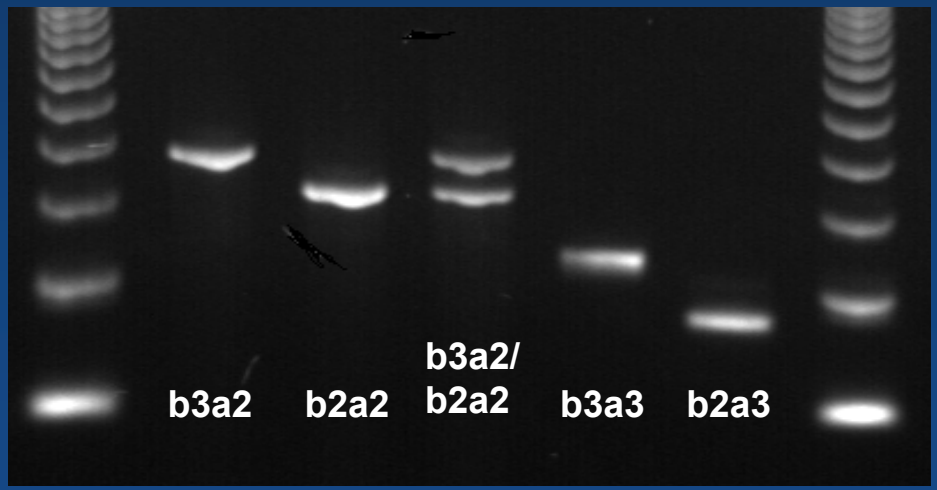
Goals of CML Therapy

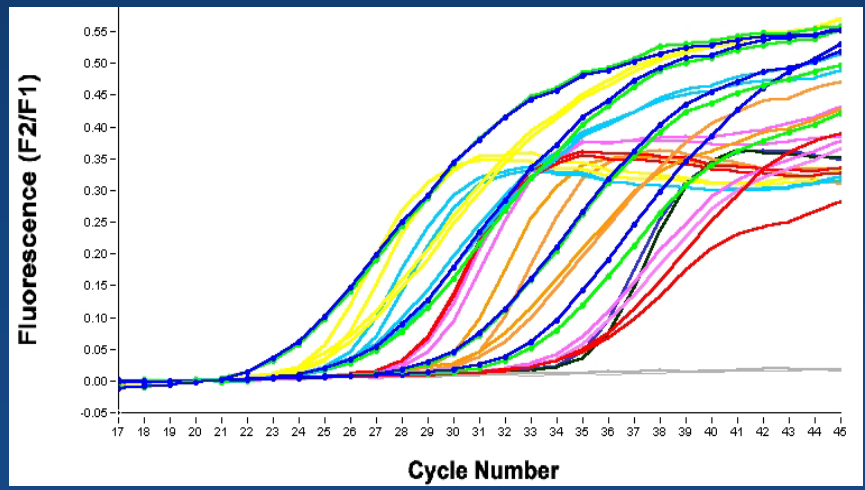



karyotype: 46,XY,t(9;22)(q34;q11)
9q+
22q-

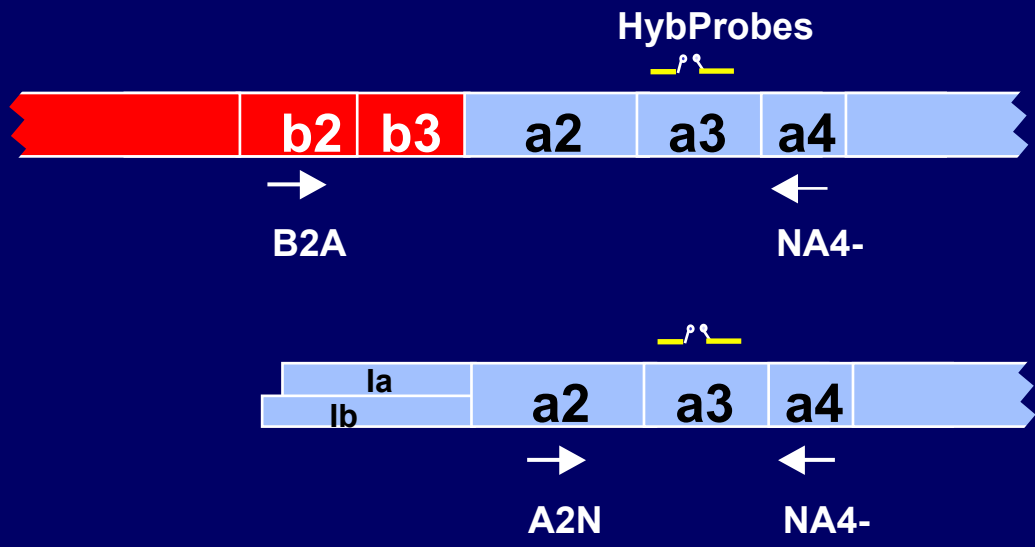





b3a2
b2a2
b3a2/
b2a2
b3a3
b2a3

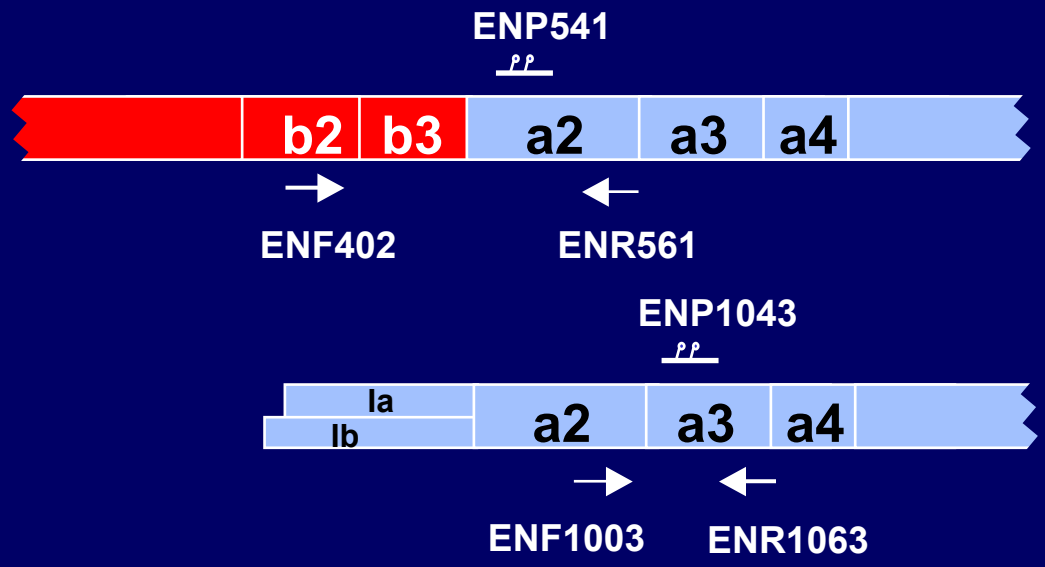

Fluorescence (F2/F1)
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
Cycle Number

LightCycler



Emig et al. *Leukemia.* 1999.

TaqMan

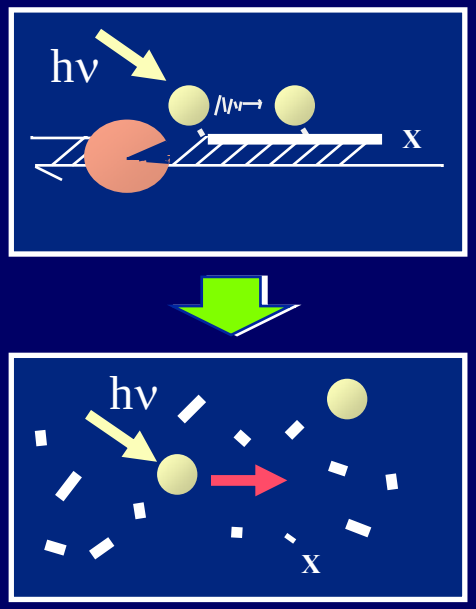


Gabert et al. *Leukemia. 2003*.

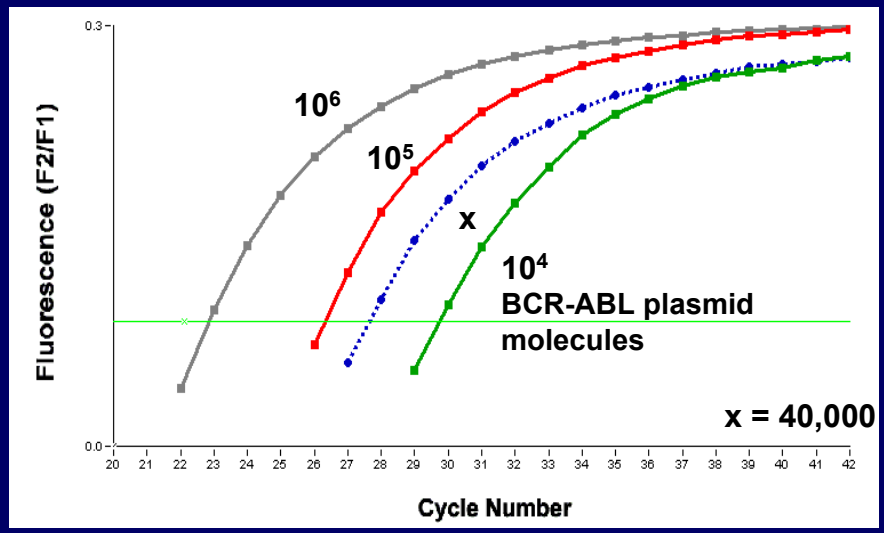
Real time quantitative RT-PCR

I. Hydrolysis Probes

Release from quenching by hydrolysis

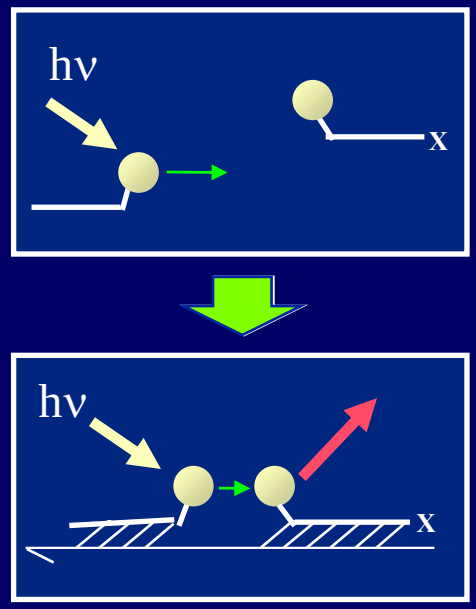


TaqMan™



II. Hybridization Probes

Increased resonance energy transfer by hybridization

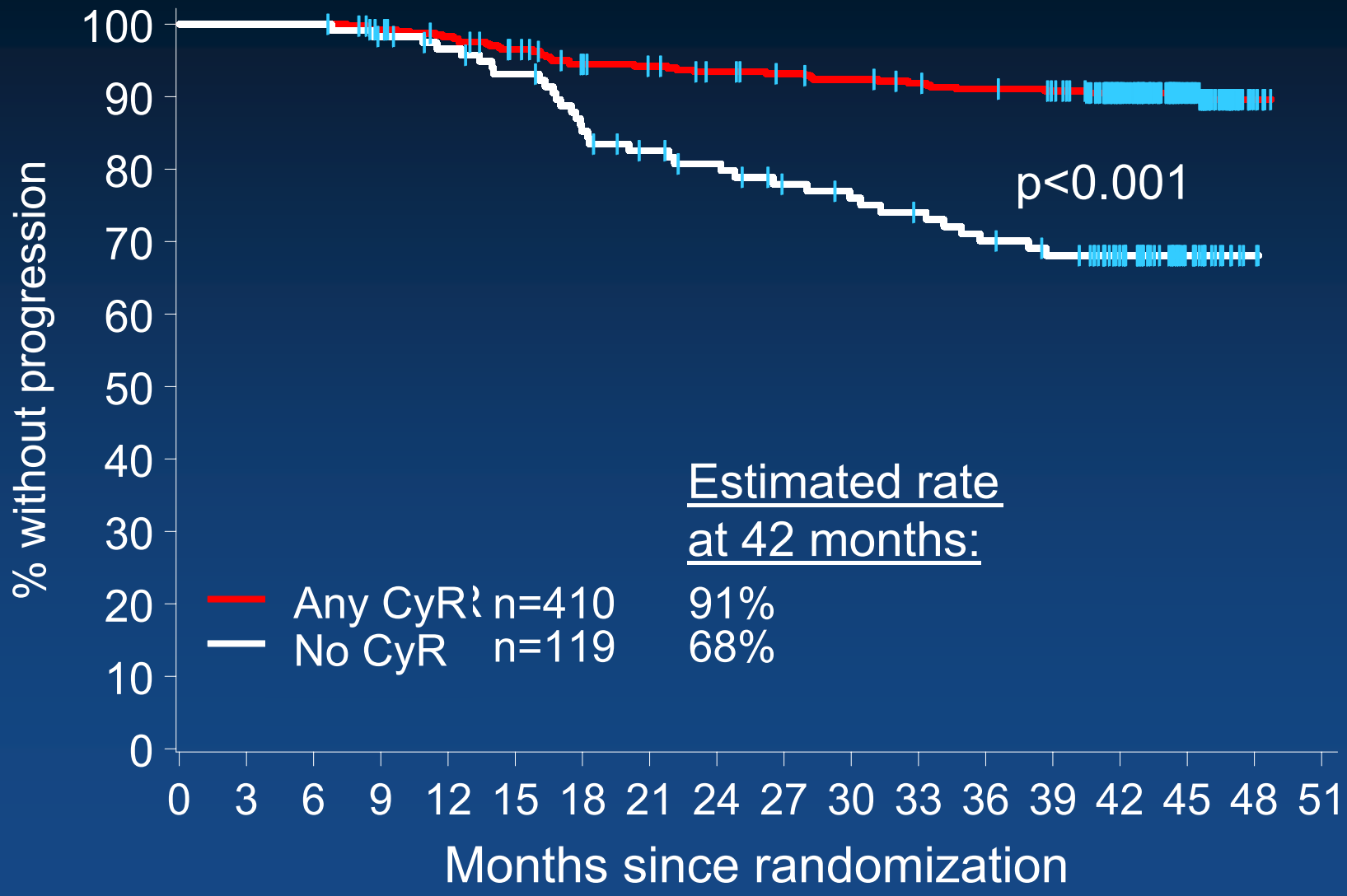


LightCycler™

Rationale for response monitoring

- Most patients in CP have a good response to imatinib
- Some patients, however, still progress
- Identify patients who will ultimately experience relapse
- Early identification of relapse or progression provides an opportunity for alternative therapy
- Identification of patients in stable remission after TKI withdrawal

Progression-free Survival on 1st line Imatinib by Cytogenetic Response at 6 Months

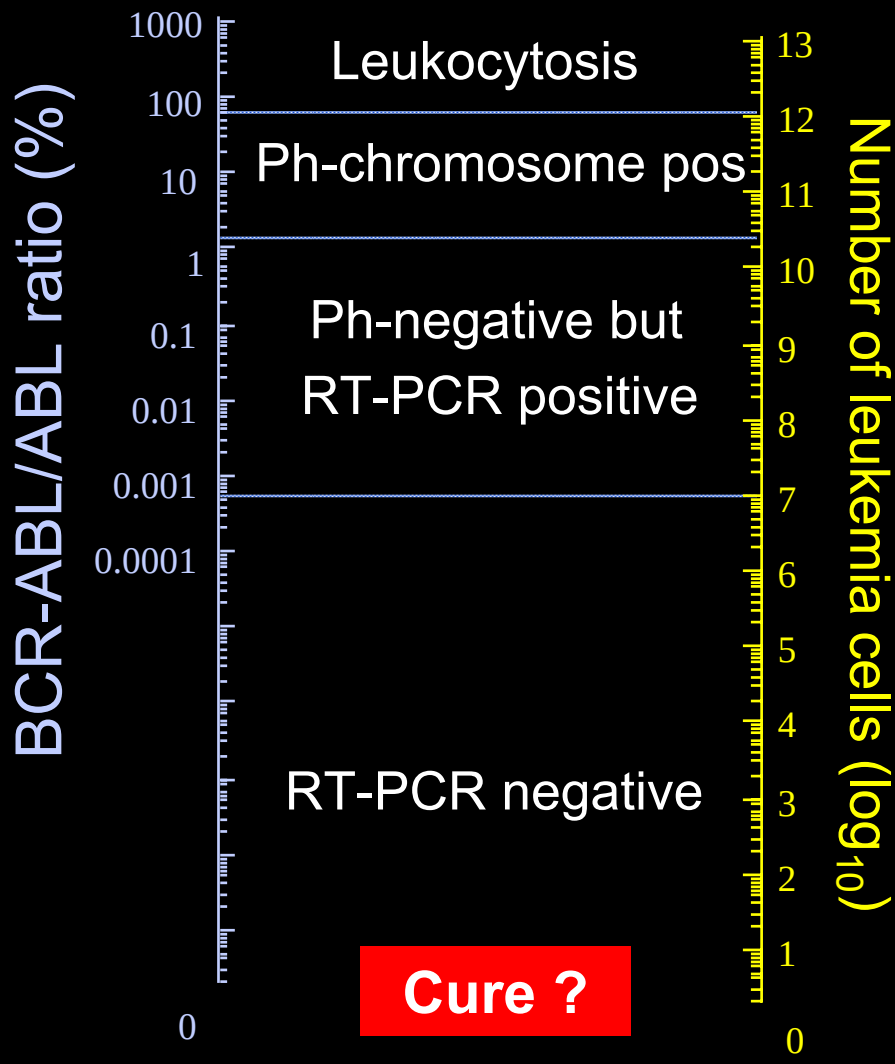


IRIS Study, Update ASH, 2004.

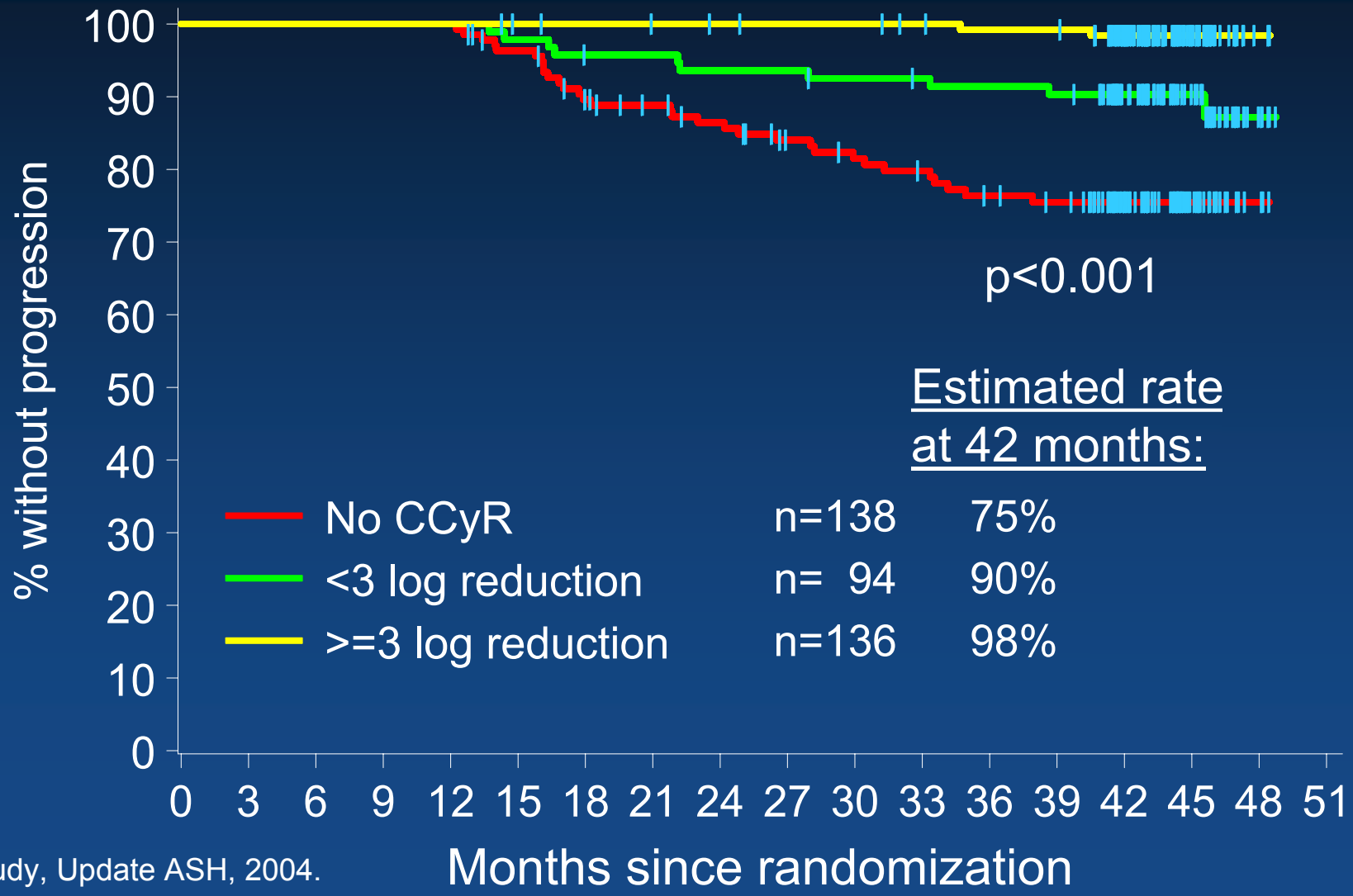
Ph chromosome and BCR-ABL transcript numbers as measures of 'residual' leukemia during treatment

(Copy numbers with Abl as control gene)

Decreasing residual leukemia

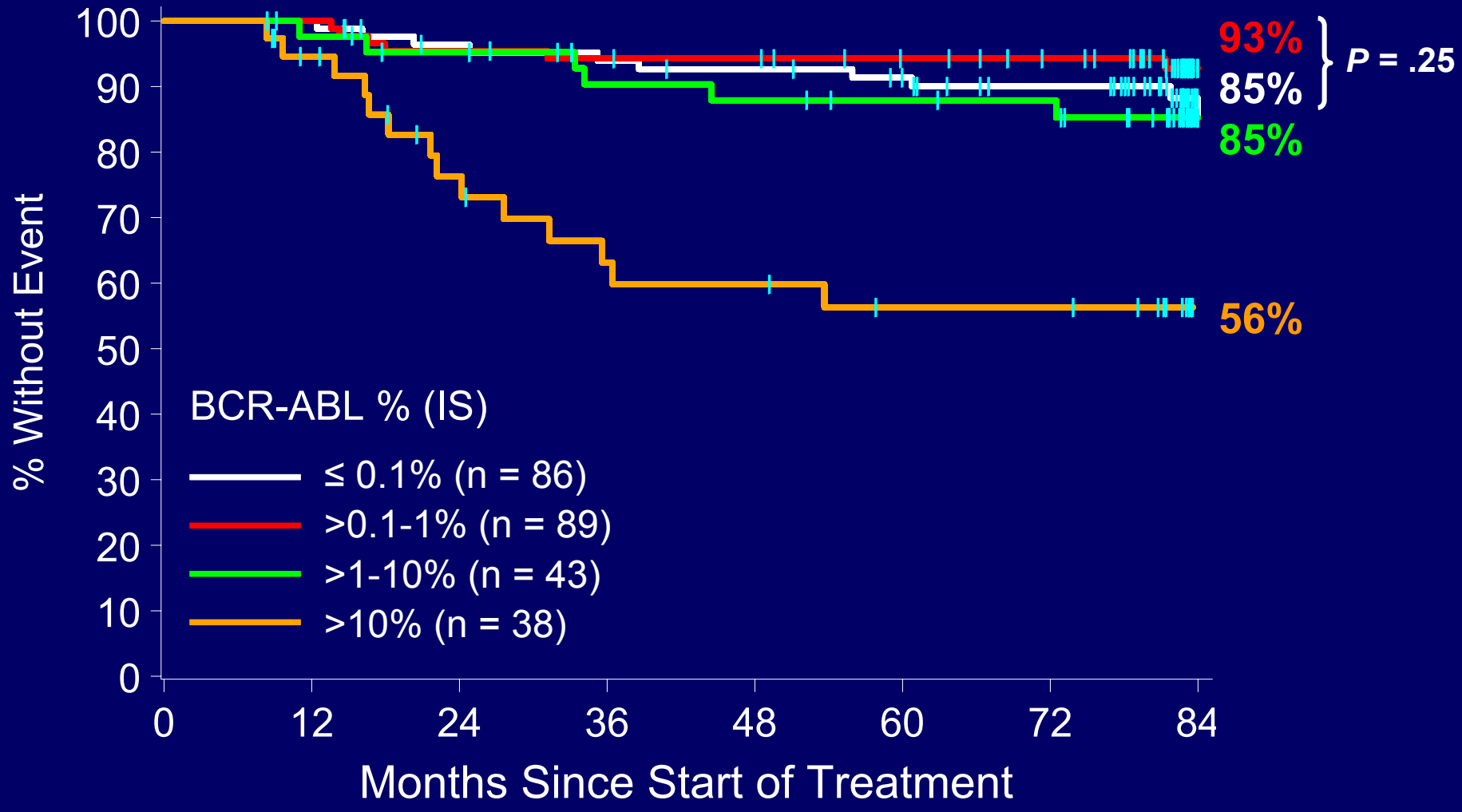


Progression-free Survival on 1st-line Imatinib by Molecular Response (MR) at 12 Months



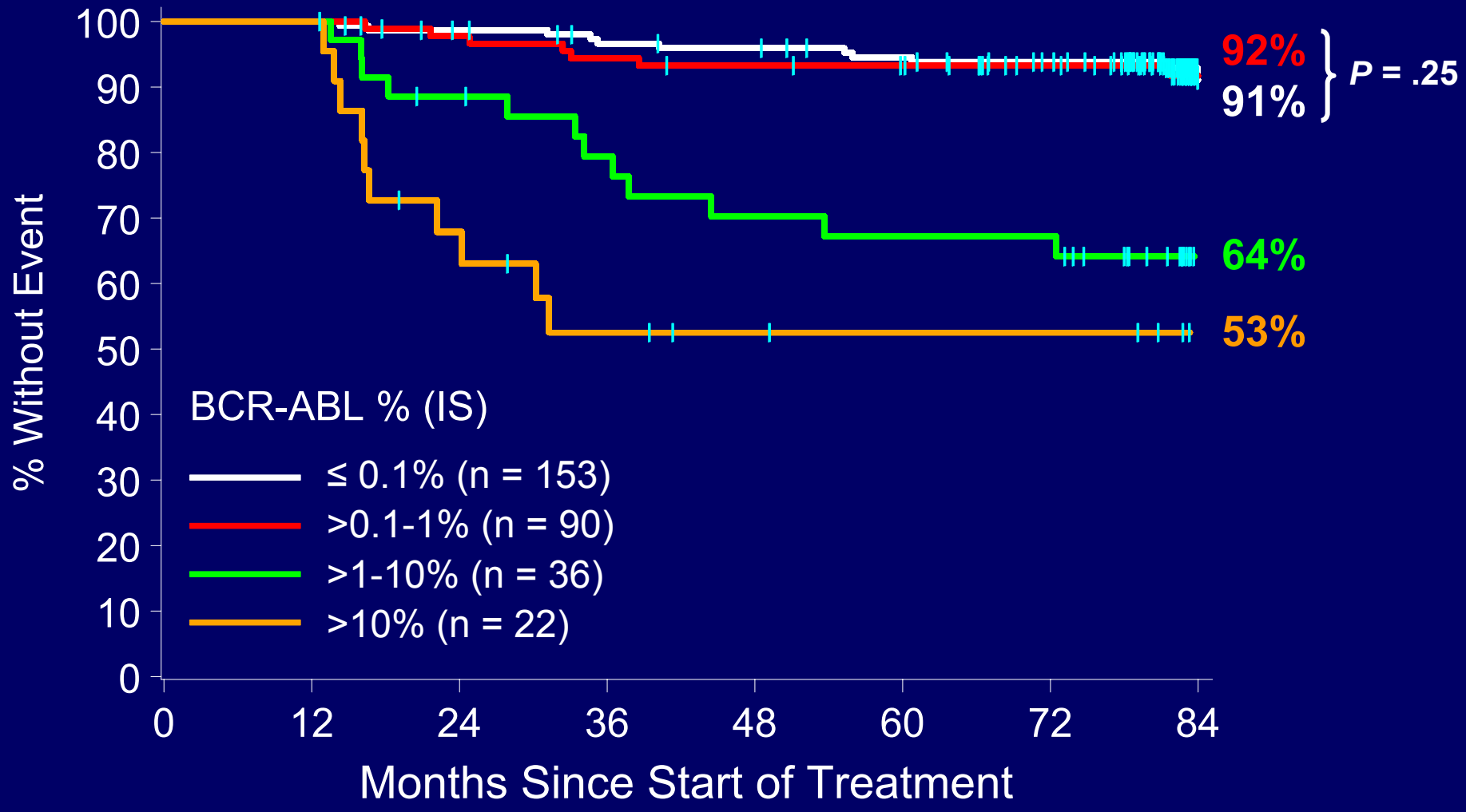
IRIS Study, Update ASH, 2004.

Imatinib:
EFS: 6-Month Landmark Analysis



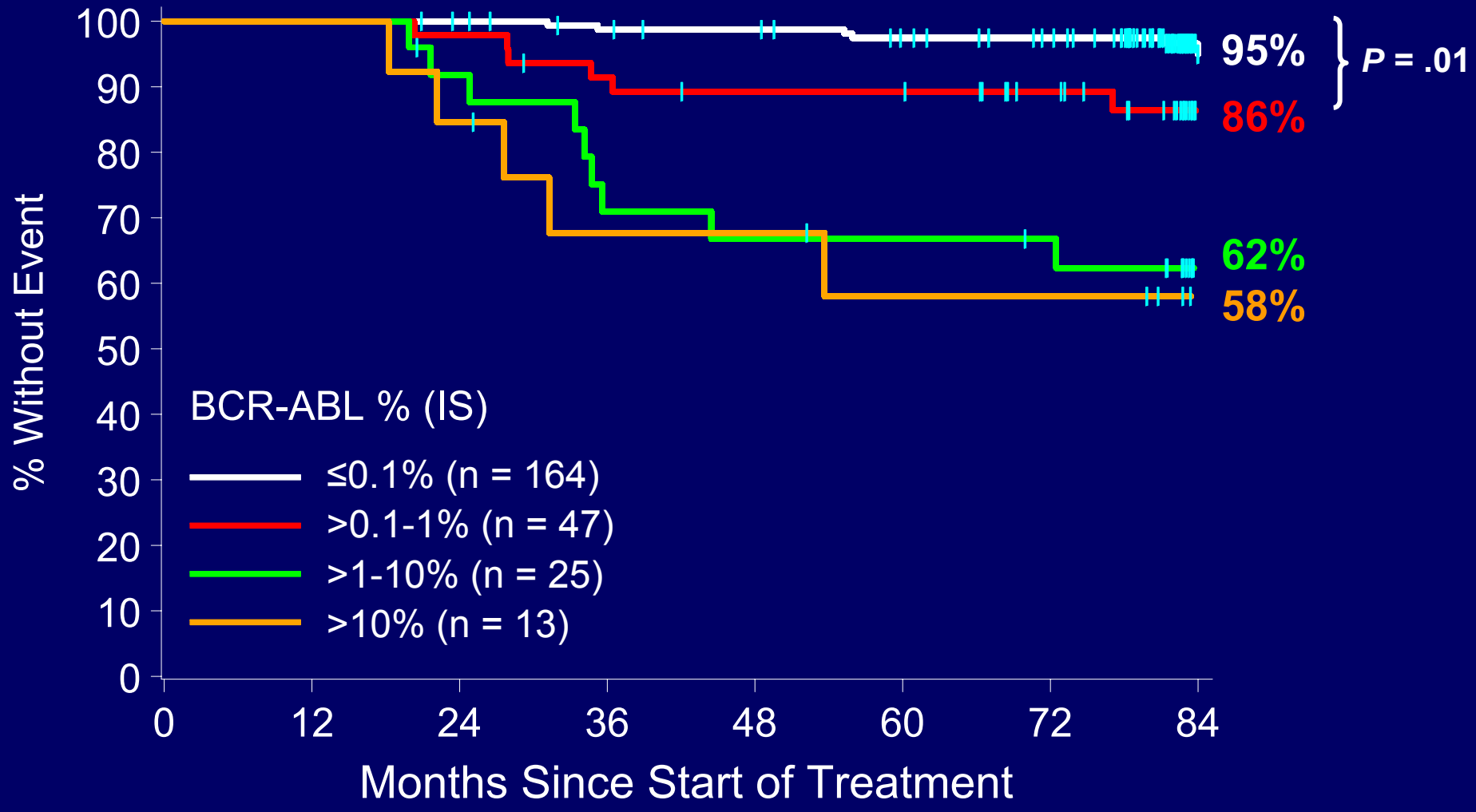
Hughes et al., ASH 2008

Imatinib: EFS: 12-Month Landmark Analysis



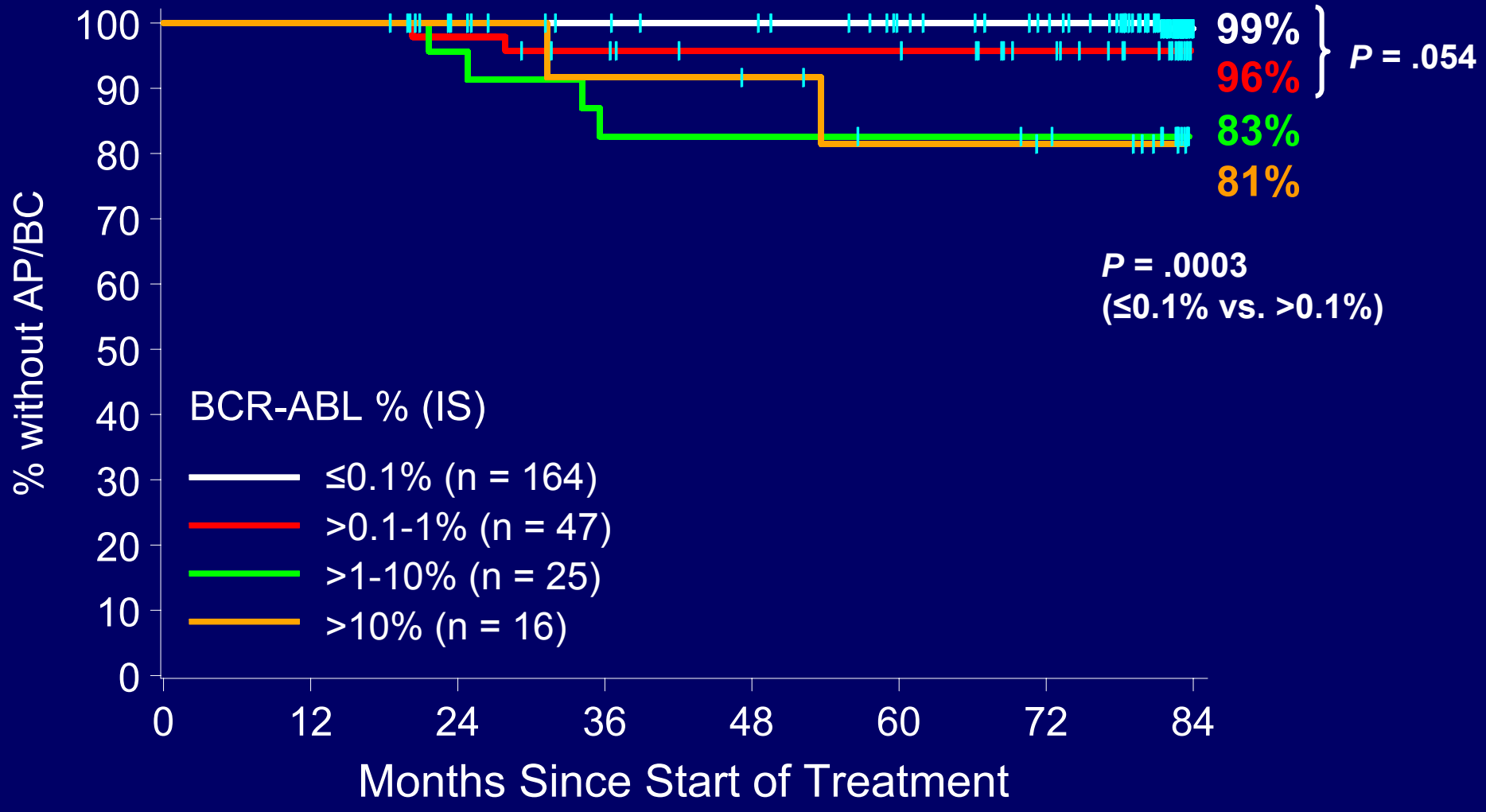
Hughes et al., ASH 2008

Imatinib: EFS: 18-Month Landmark Analysis



Hughes et al., ASH 2008

Imatinib: Progression to AP/BC - 18-Month Landmark Analysis



Hughes et al., ASH 2008

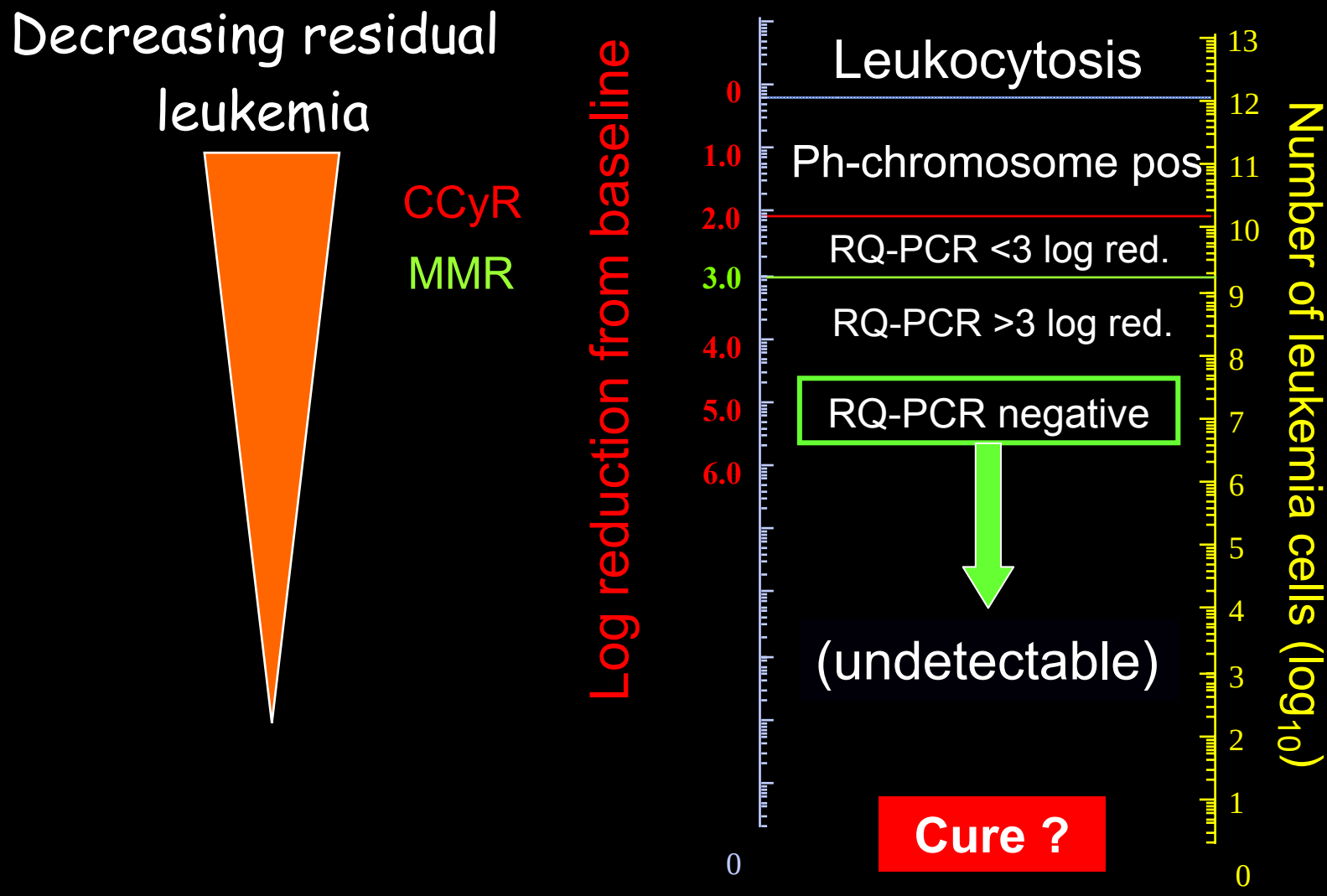
Criteria for Failure and Suboptimal Response to Imatinib

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

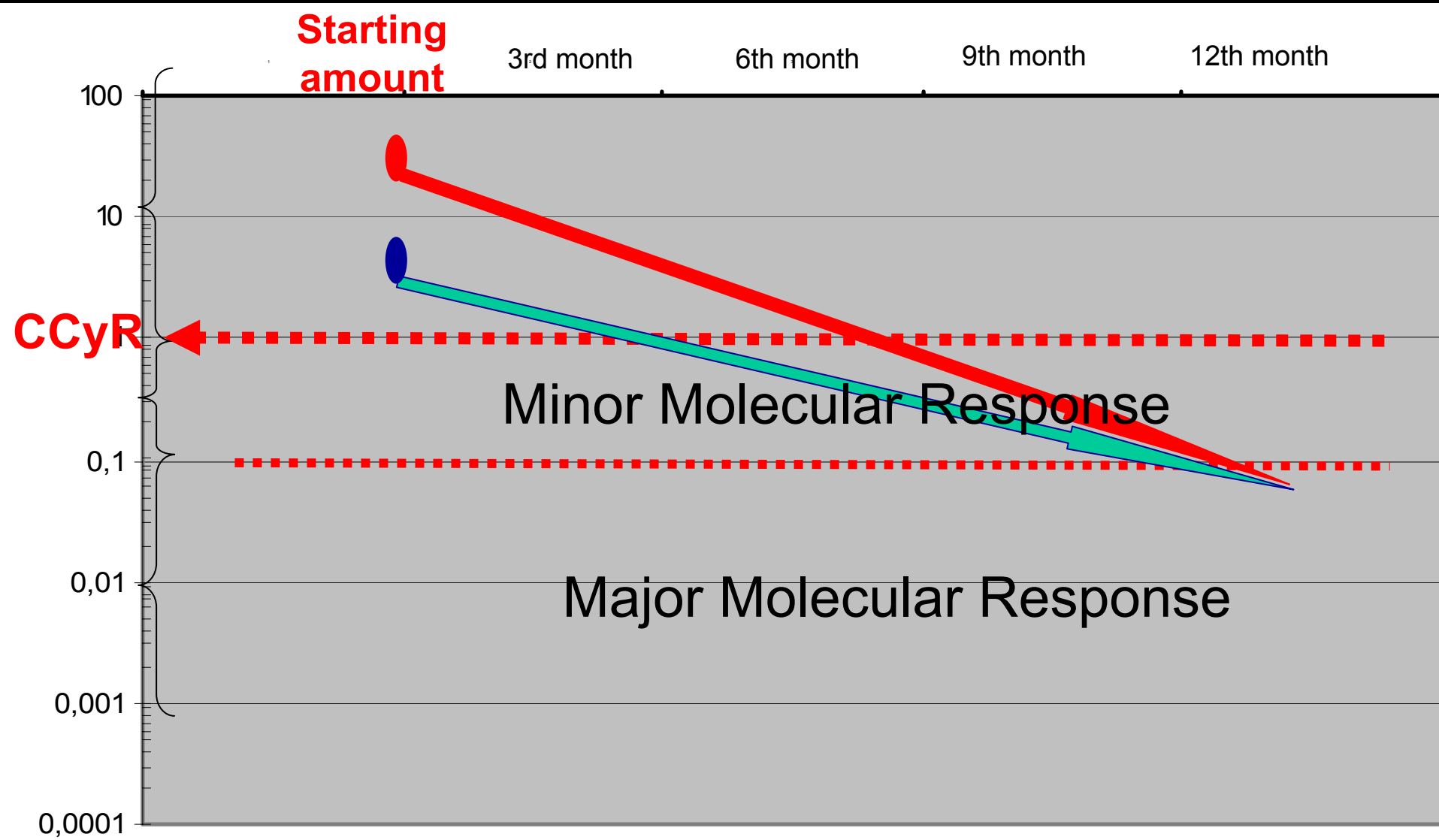
Baccarani et al. JCO 2009; 27: 6041-51

Ph chromosome and BCR-ABL transcript numbers as measures of 'residual' leukemia during treatment

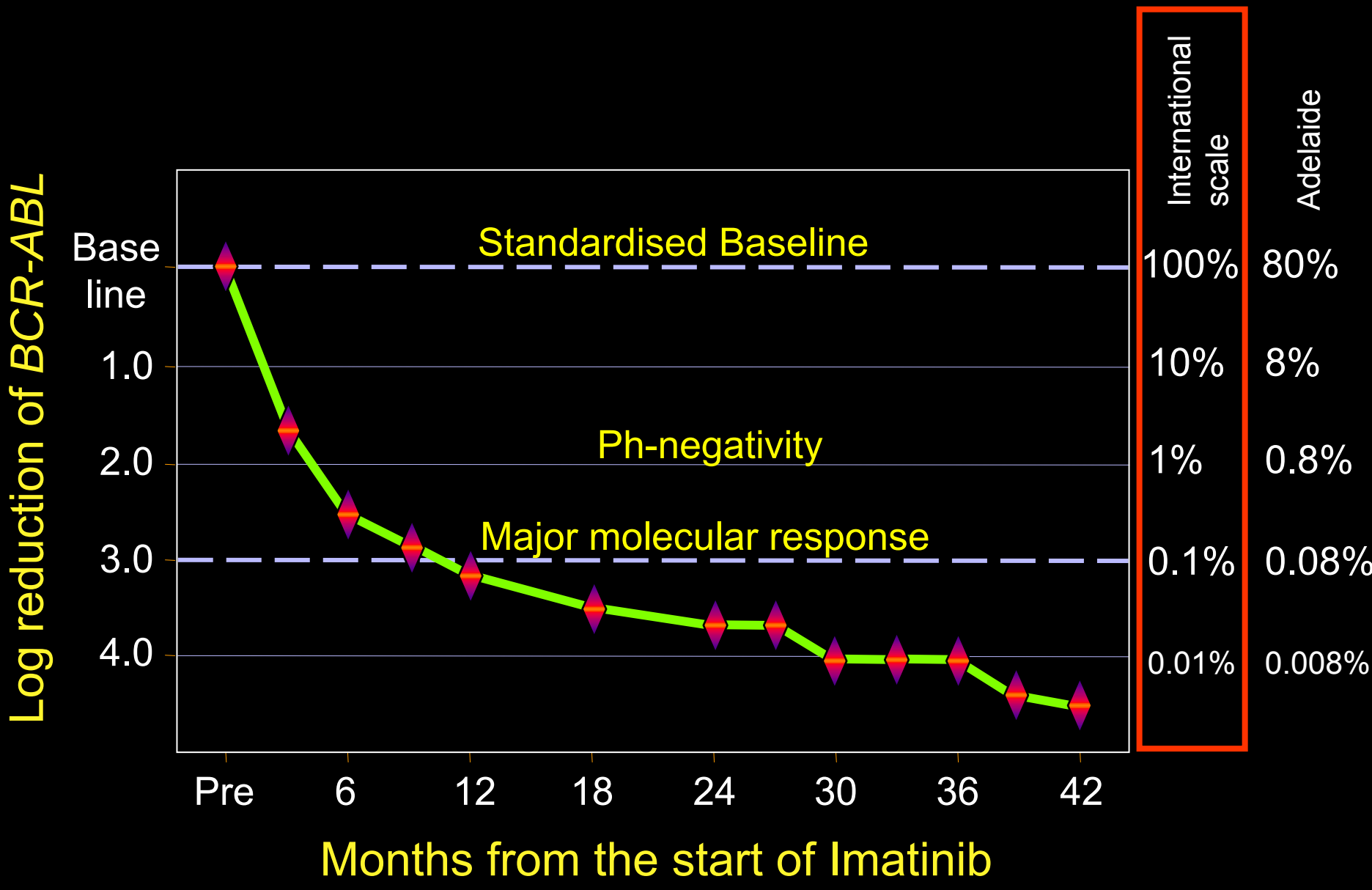
(Log reduction from 100% or log 0)



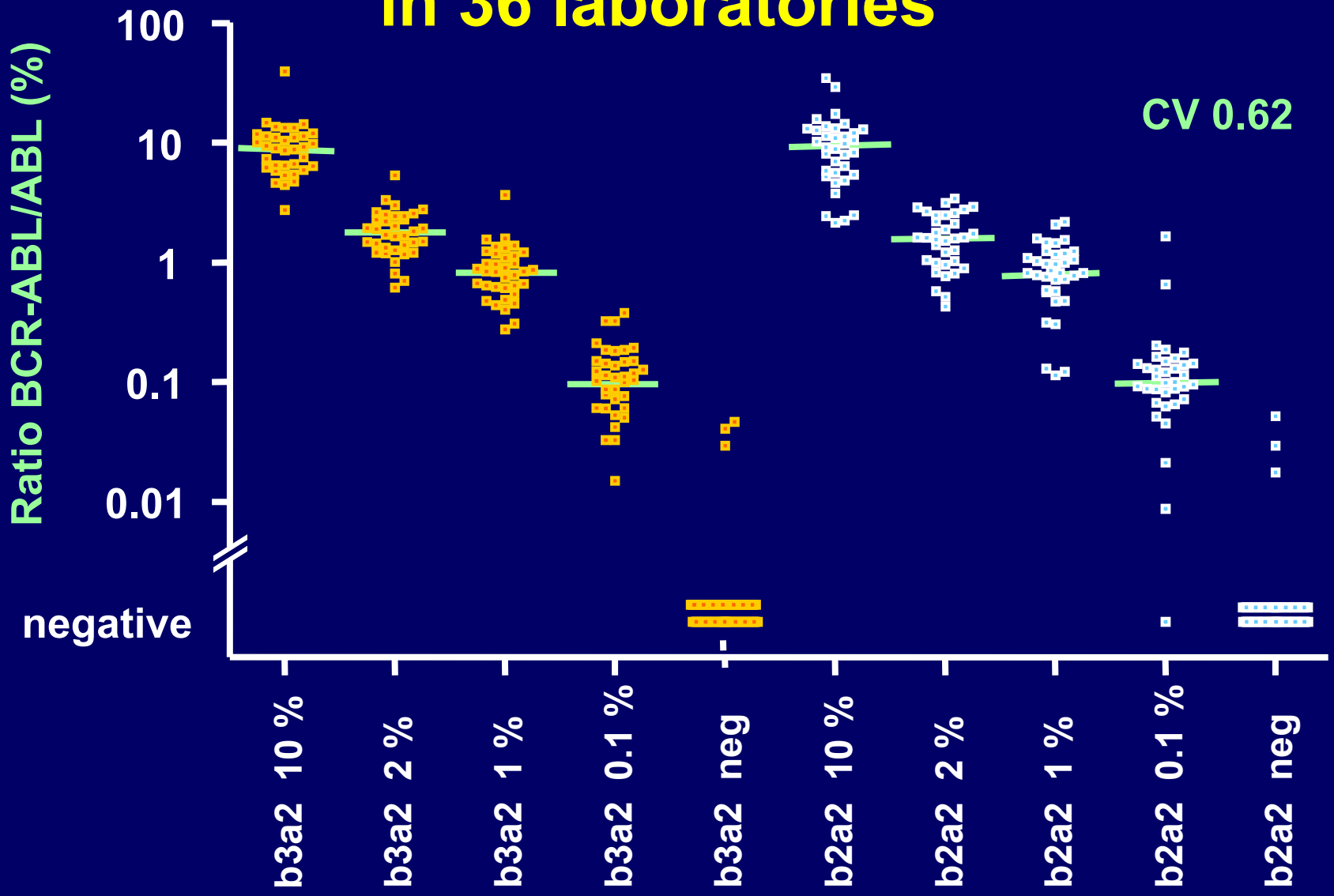
The evidence obtained with the IRIS study is that the absolute and not the relative amount is important!



Converting to International Scale

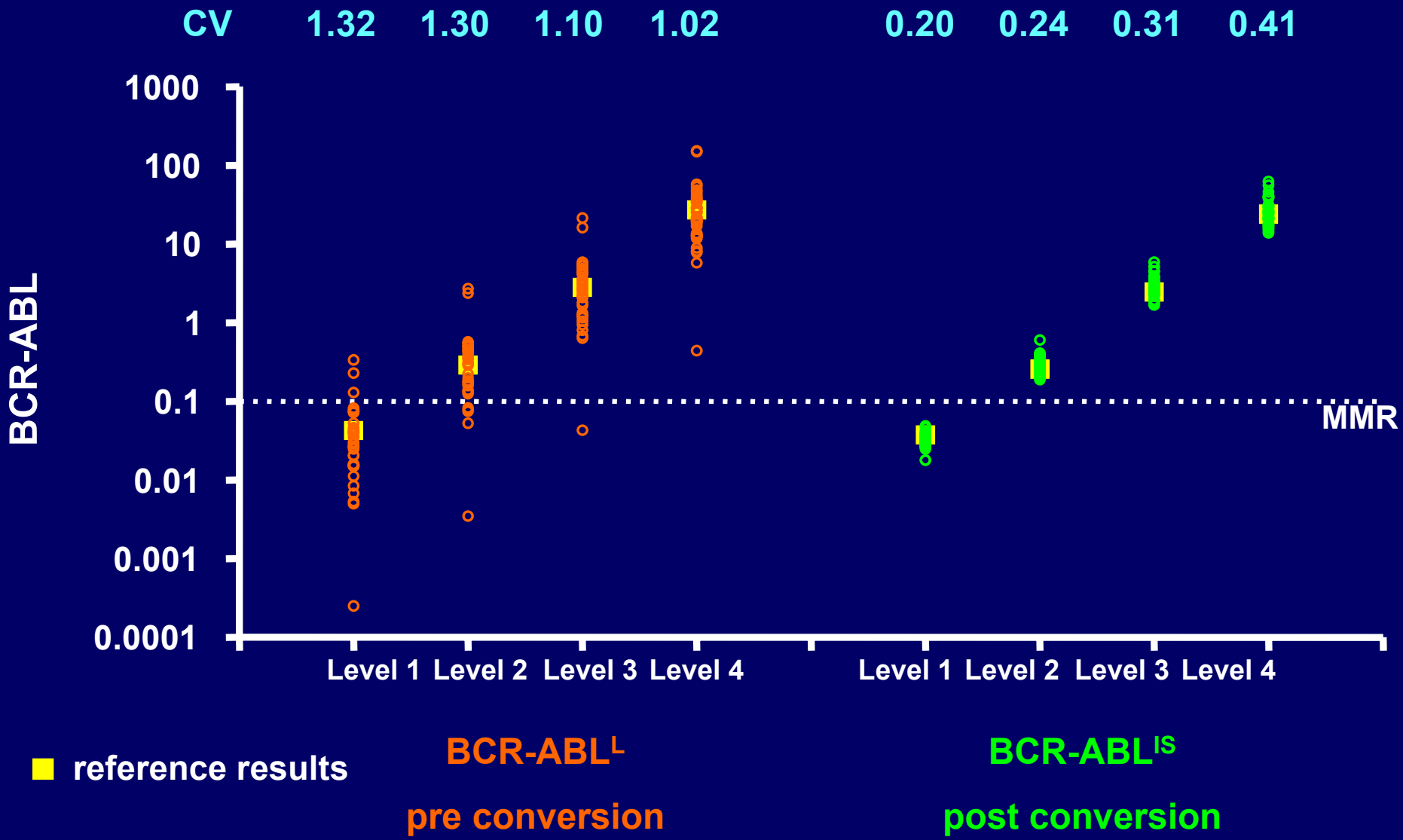


Variability of Ratios BCR-ABL/ABL (%) in 36 laboratories



Müller et al., *Leukemia* 2007

BCR-ABL levels in 58 labs pre and post conversion



Standardisation of *BCR-ABL* quantification in Europe

30 laboratories standardised

EUTOS for CML

European Treatment and Outcome Study

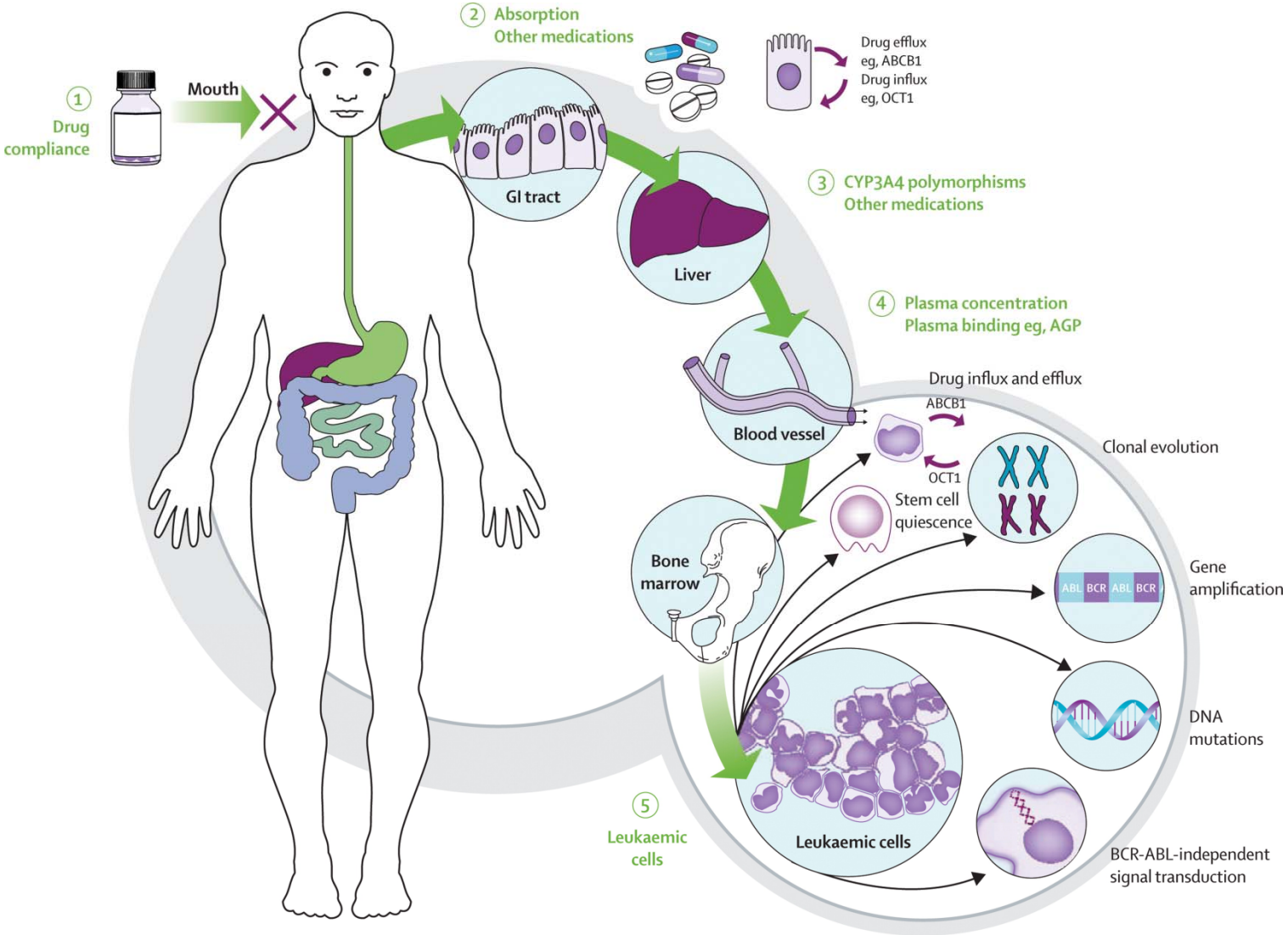
Countries with a ref lab with validated CF

Countries using a ref lab in a different country

Countries with a ref lab – validation pending

Israel

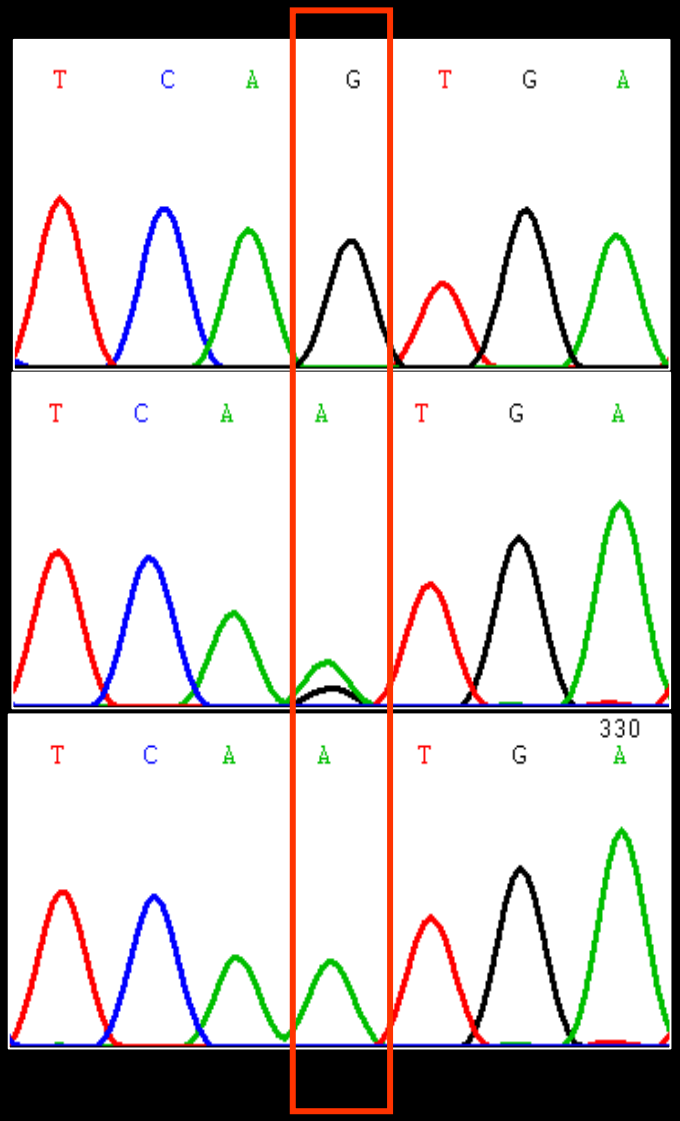
Why do patients fail imatinib?



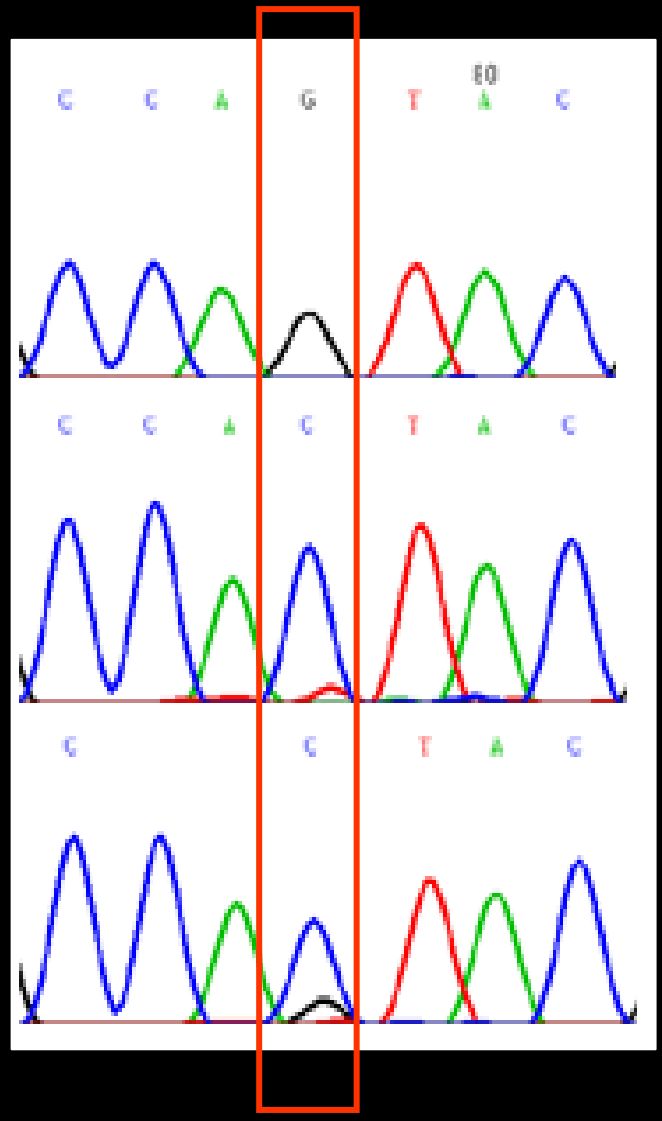
Apperley, Lancet Oncology 2007

Kinase domain mutations

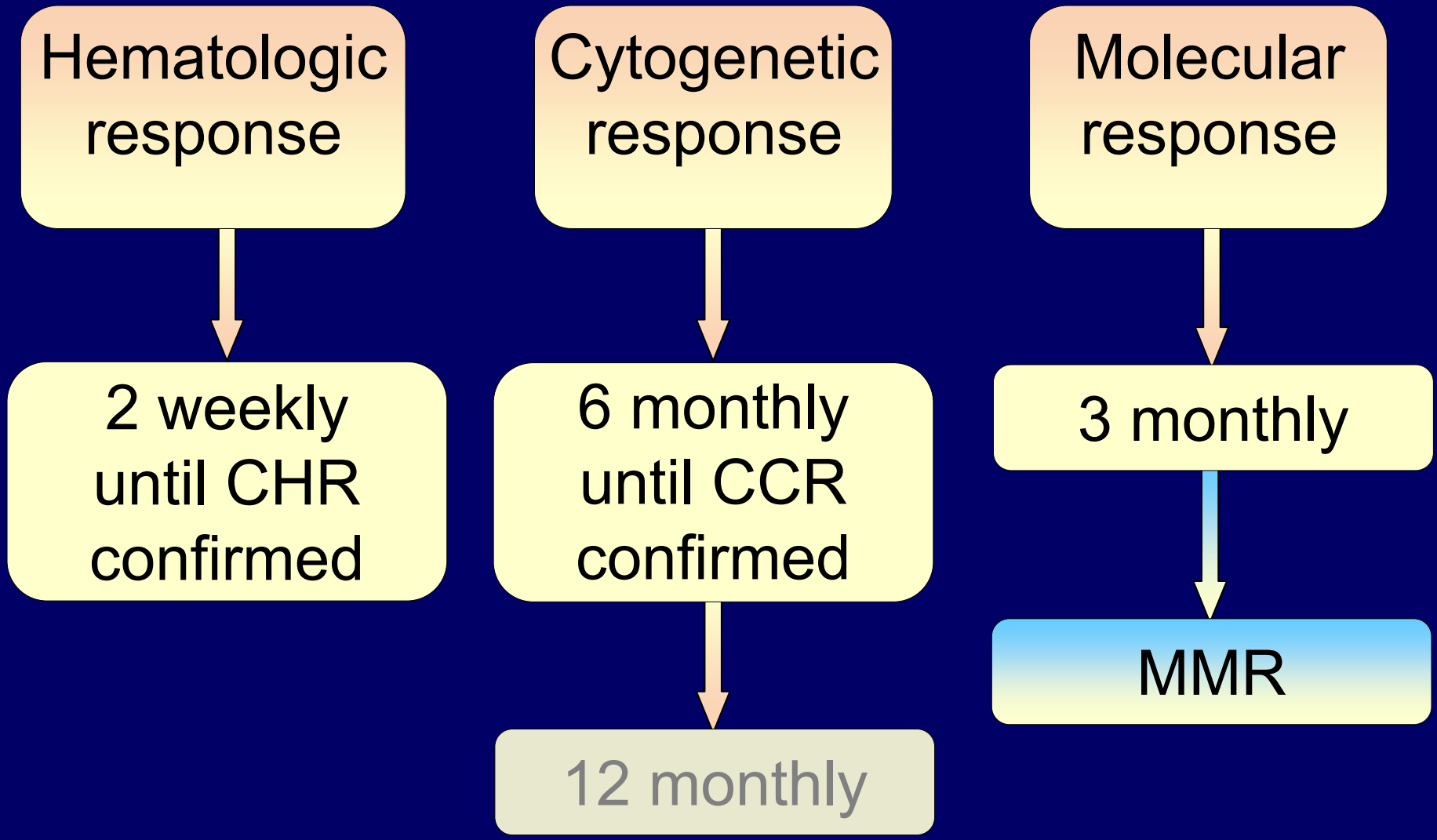
T315I (G→A)



Q252H (G→C)

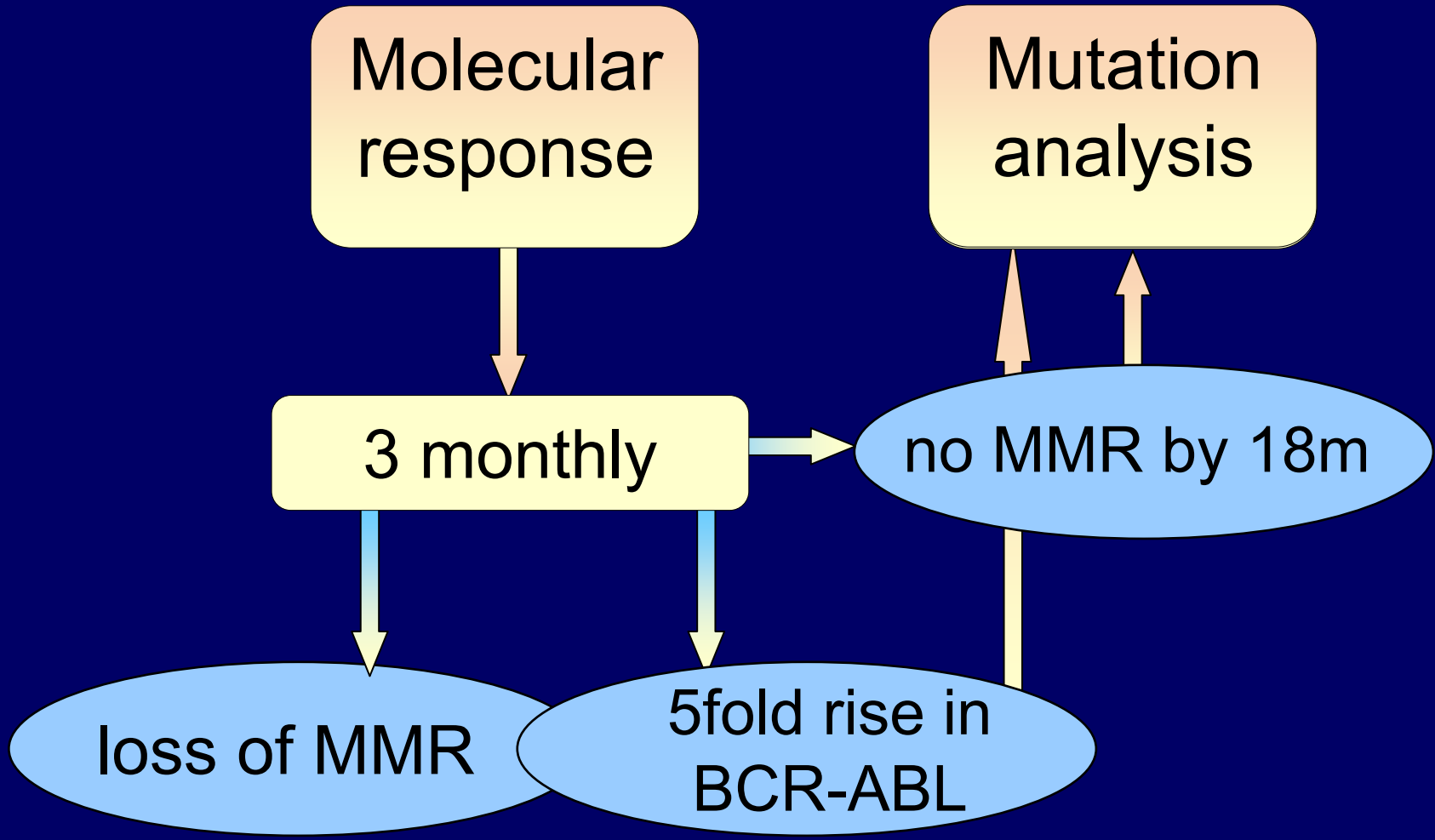


ELN Recommendations



Baccarani et al, Blood;2006;108;1809

ELN Recommendations



Baccarani et al, Blood;2006;108;1809

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