CML: Yesterday, Today and Tomorrow

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Five Years of Signal Transduction Inhibition – The Beginning

A Minute Chromosome in Human Chronic Granulocytic Leukemia

In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* **25**, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al.*, *Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years' duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

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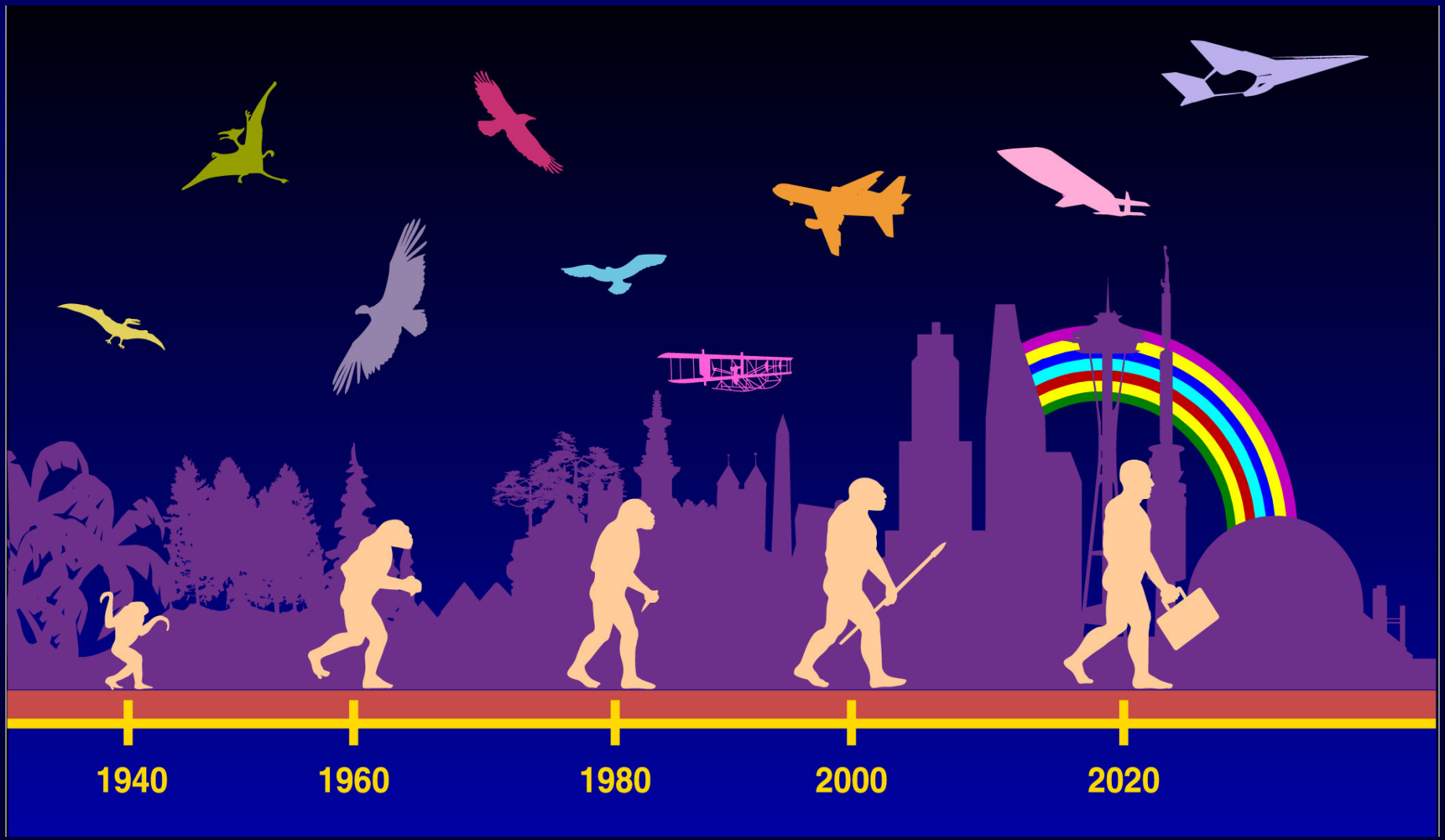
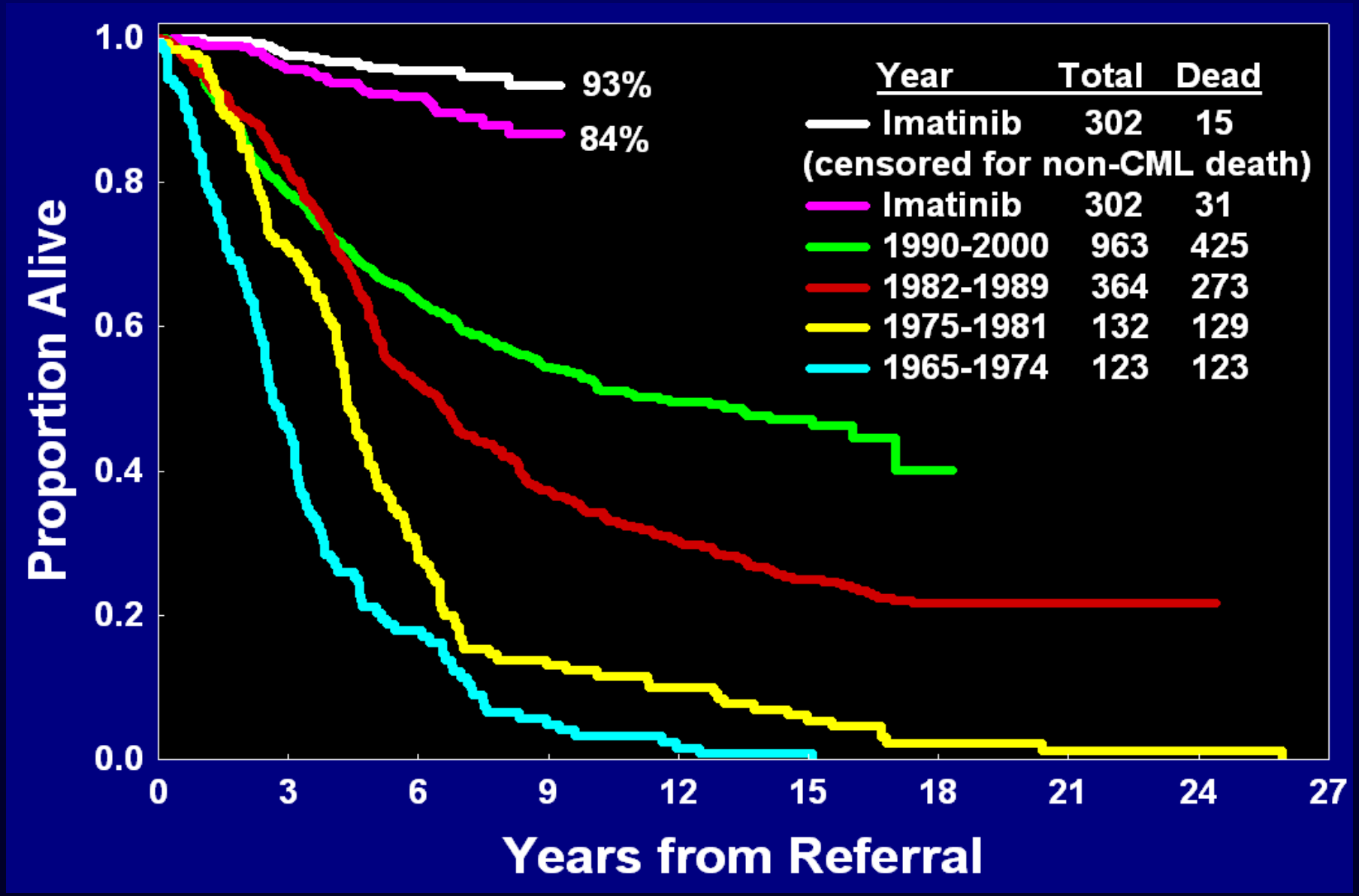
Nowell PC & Hungerford DA. Science 1960, 132: 1497

The Evolution of CML Therapy



Chemotherapy ⇒ SCT ⇒ IFN ⇒ TKI

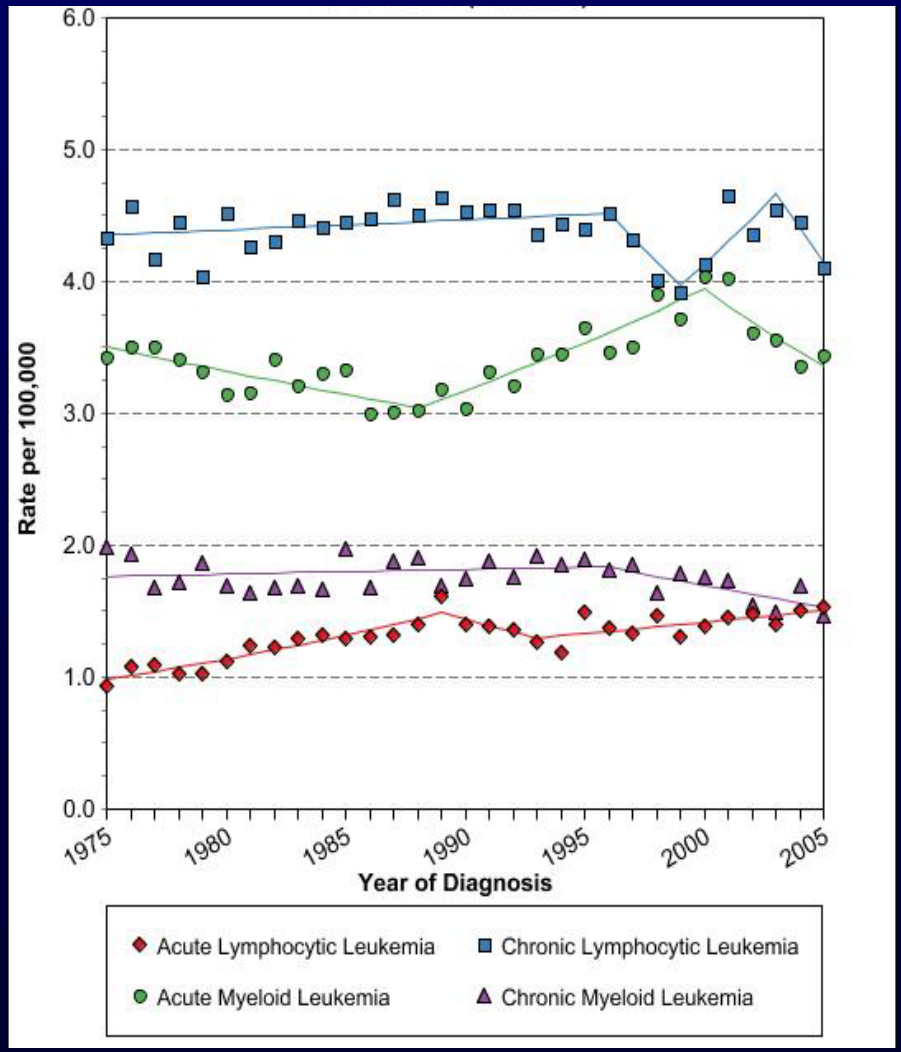
Survival in Early Chronic Phase CML



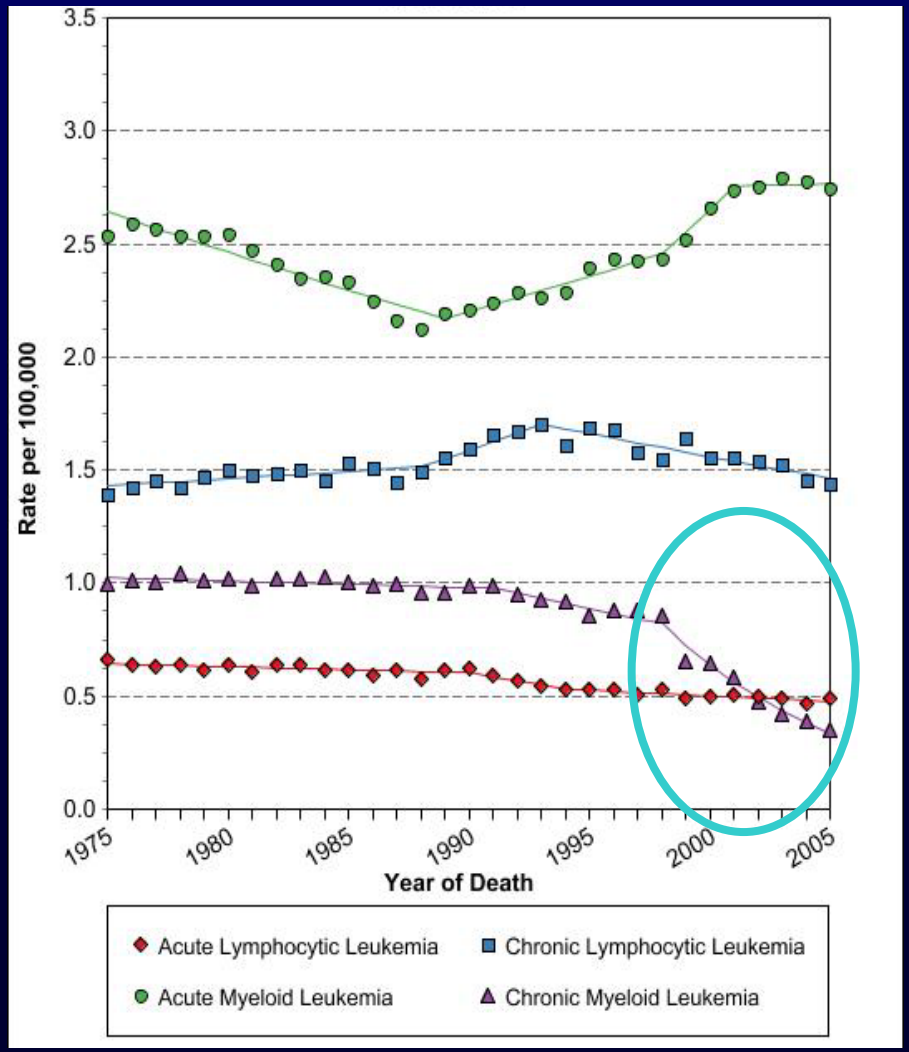
MDACC 2009

Incidence and Mortality of Leukemia SEER 1975-2005

Incidence

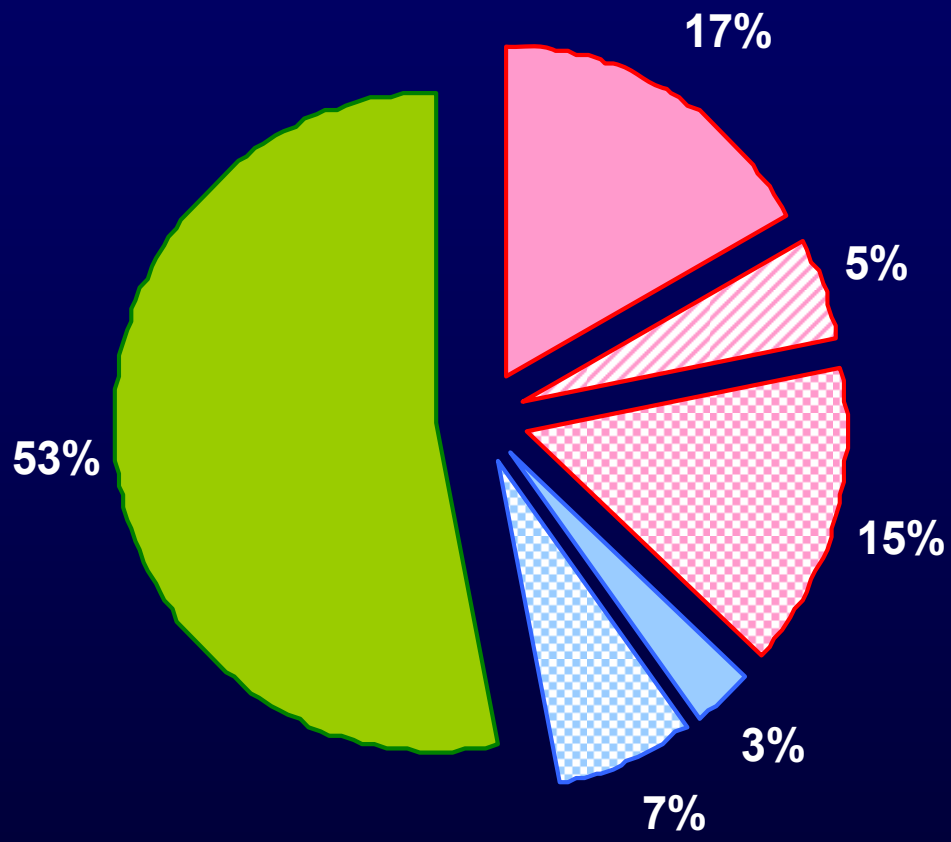


Mortality



SEER.CANCER.GOV (Accessed Oct 2009)

IRIS 8-Year Update



- No CCyR
- Lost CCyR
- CCyR Other
- Safety
- Lost-regained CCyR
- Sustained CCyR on study

Deininger et al; Blood 2009; 114: Abst# 1126

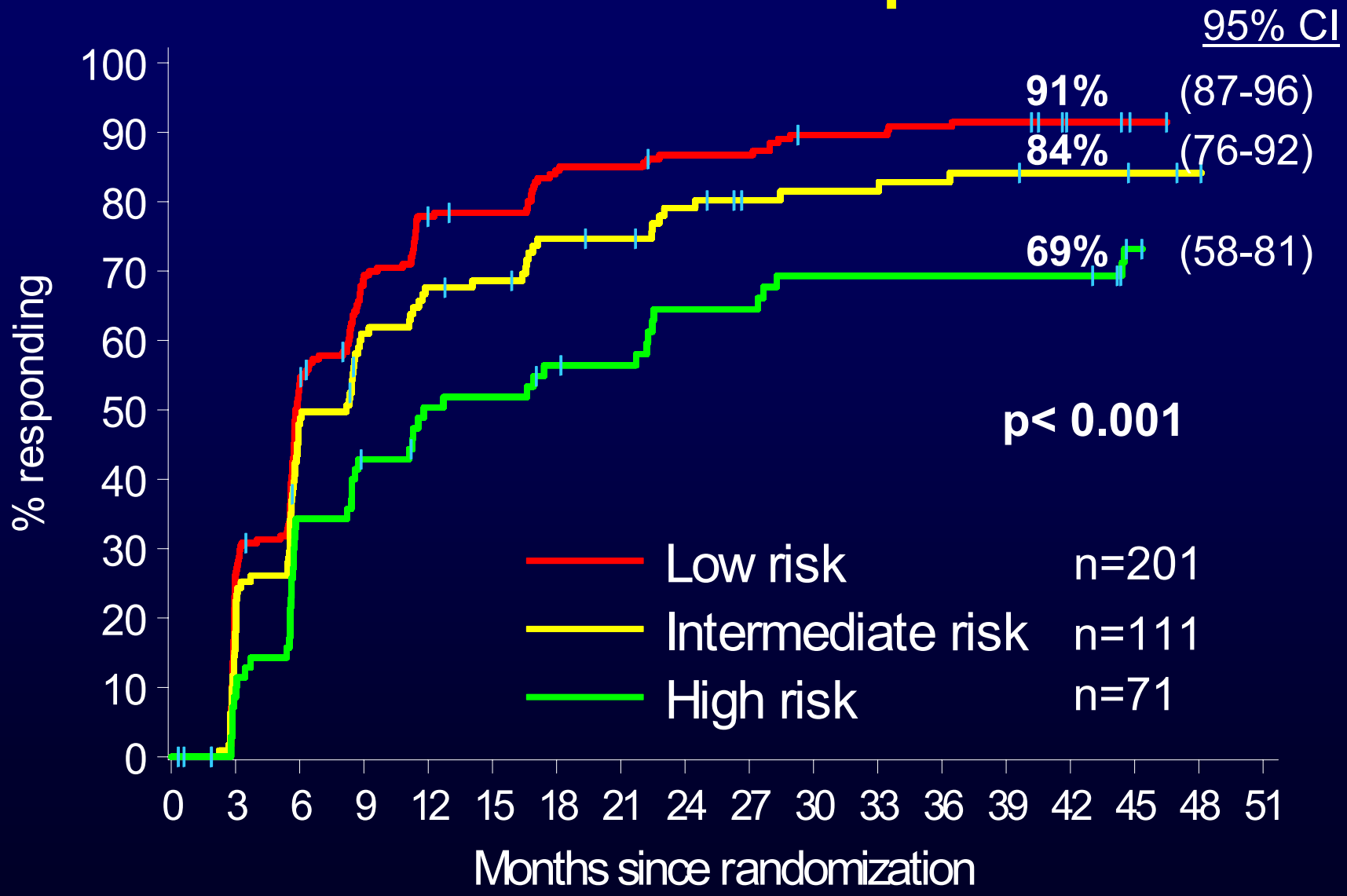
Predictors of Response

Similar Efficacy & Safety with 2nd Generation TKI in Older Pts

- Dasatinib
  - 97 pts age >60 yr
  - Dasatinib 140 mg/d (n=47) or 100 mg/d (n=44)
  - CCyR 48%, MMR 32%
  - Pleural effusion 25%, G3-4 myelosuppression 22% at 10mg/d
- Nilotinib
  - 452 pts age ≥60 yrs
  - CCyR 31%, 24mo PFS 81%
  - QTc >500msec 1%, G3-4 myelosuppression 14%

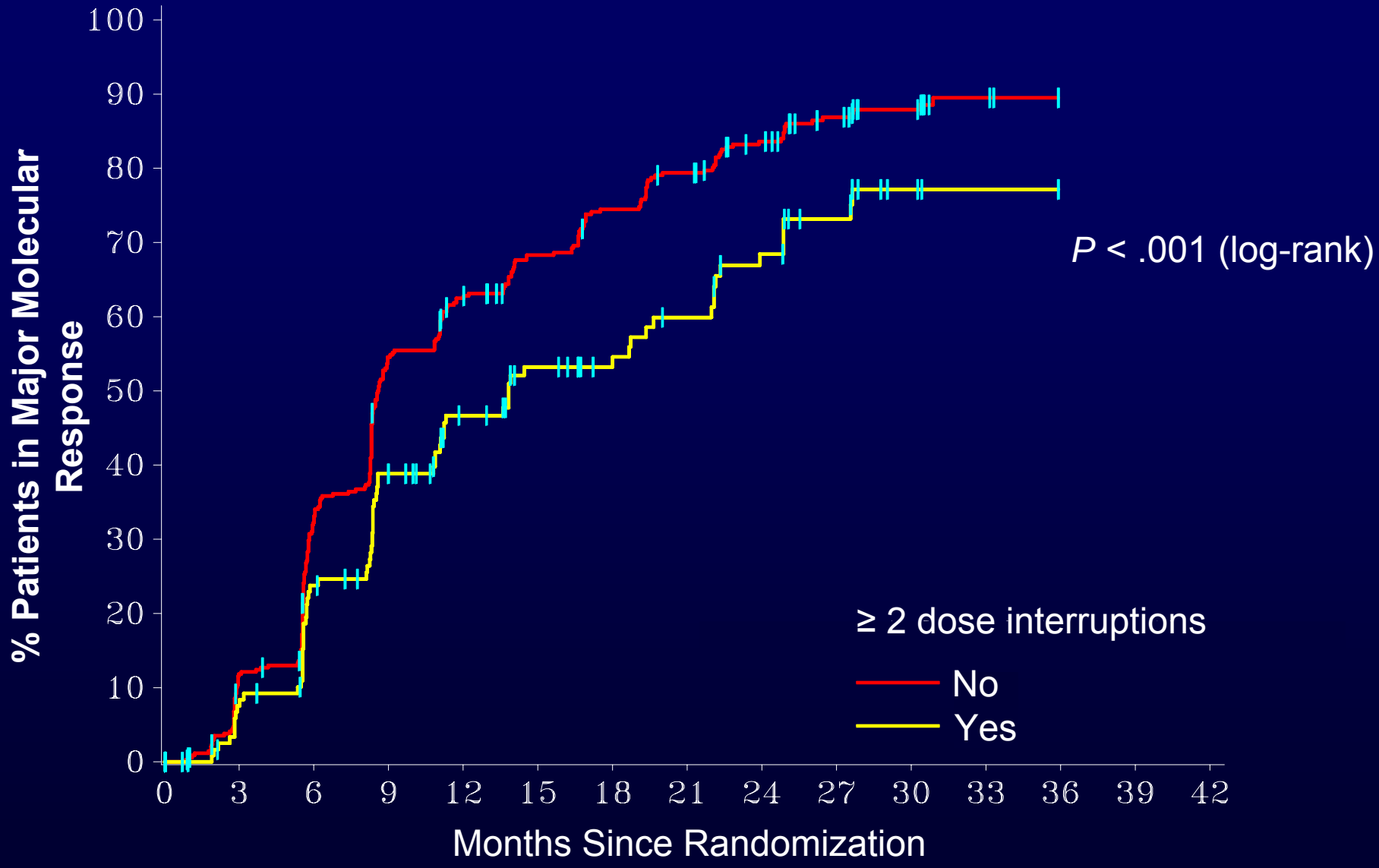
Le Coutre et al. ASH 2009; 114: Abst# 3286; Latagliata et al. Blood 2009; 114: Abst# 2211

Estimated CCyR to First-line Imatinib by Sokal Group



Druker et al. NEJM 2006; 355: 2408-17

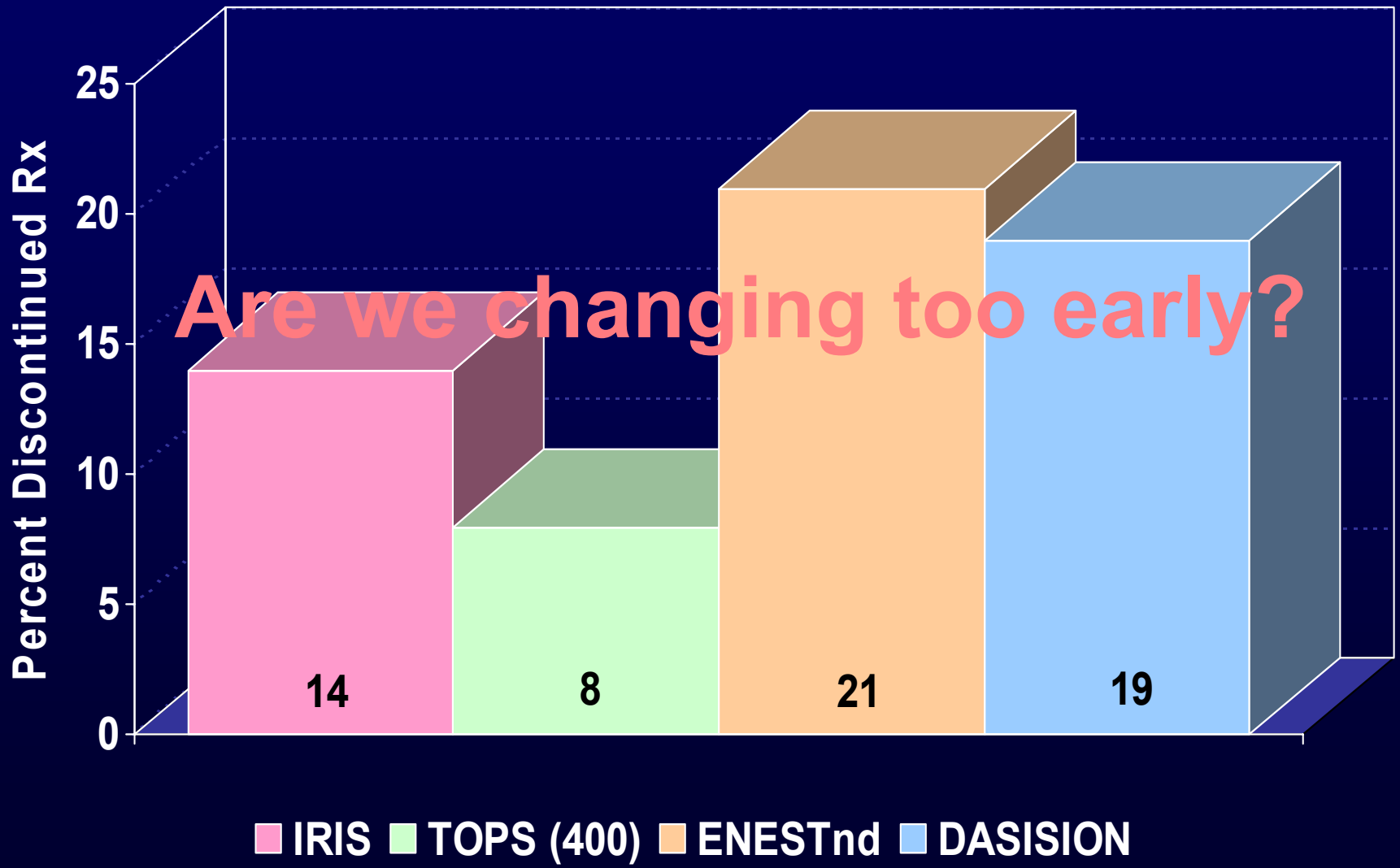
Time to MMR by Number of Dose Interruptions*, 400 and 800 mg Arms Combined



*Dose interruption > 5 days during first 12 months

Baccarani et al. Blood 114; Abst# 337

Imatinib Treatment Discontinuation First 12 Months



Significance of OCT-1 Activity in Response to Imatinib

- Transporter responsible for imatinib cell influx
- Not required for 2nd generation TKI

Outcome	Dose	Percentage		p value
		Low OCT1	High OCT1	
MMR	<600mg	27	92	0.021
	600mg	72	87	0.093
EFS	<600mg	27	67	0.018
	600mg	61	80	0.241
TFS	<600mg	73	100	0.048
	600mg	100	100	NS

White et al. Blood 2009; 114: Abst# 507

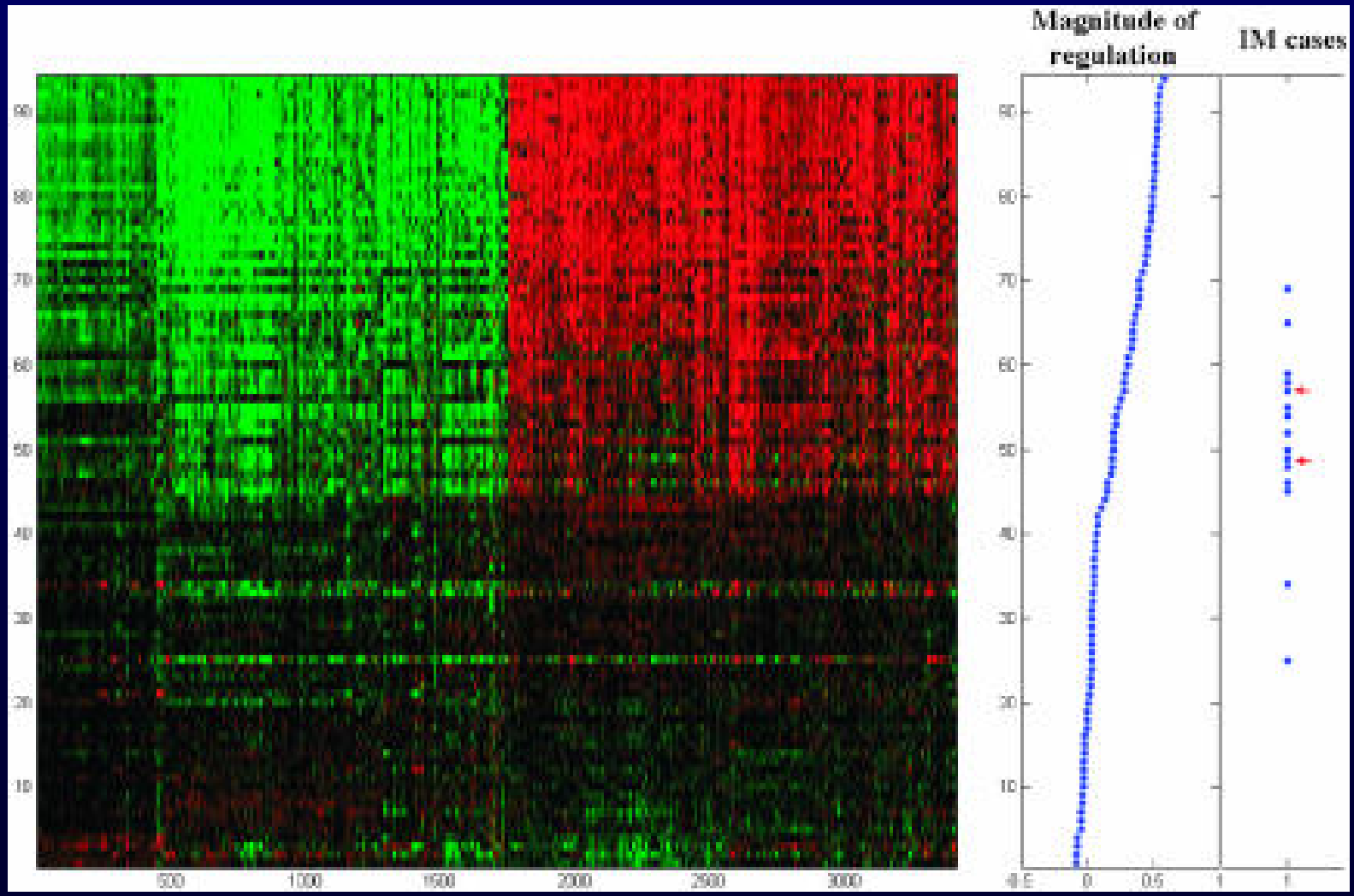
Predictive Factors of Outcome with 2nd Generation TKI

- 123 pts treated with dasatinib (n=78) or nilotinib (n=45) after imatinib failure
- Multivariate analysis for predictors of outcome
- Adverse factors: PS ≥ 1 and lack of CG response to imatinib

Risk factors	N (%)	Percentage		
		24-month		12-month
		EFS	OS	MCyR
0	59 (48)	78	95	64
1	48 (39)	49	85	36
2	5 (4)	20	40	20
p-value		0.001	0.002	0.007

Jabbour et al. Blood 2009; 114 (abst# 509)

Genetics of Disease Progression and Resistance to Therapy in CML



Radich et al. PNAS 2006; 103: 2794-9

Have we Reached Optimal Outcome with Frontline Therapy?

What Needs Improvement in Frontline Therapy of CML?

Outcome	Current	Relevance	"Improvability"
Survival[1]	85% @ 8 yr	++++	+
TFS[1]	92% @ 8 yr	++++	+
EFS[1]	81% @ 8 yr	+++	++
CCyR[1]	82%	+++	++
MMR[2]	87%	++	++(+)
CMR[2]	52%	+(+)	+++
Early response[3,4]	CCyR 65% @ 1 yr	+(+)(+)	+++(+)
Toxicity	"Low"	+++	-(+)

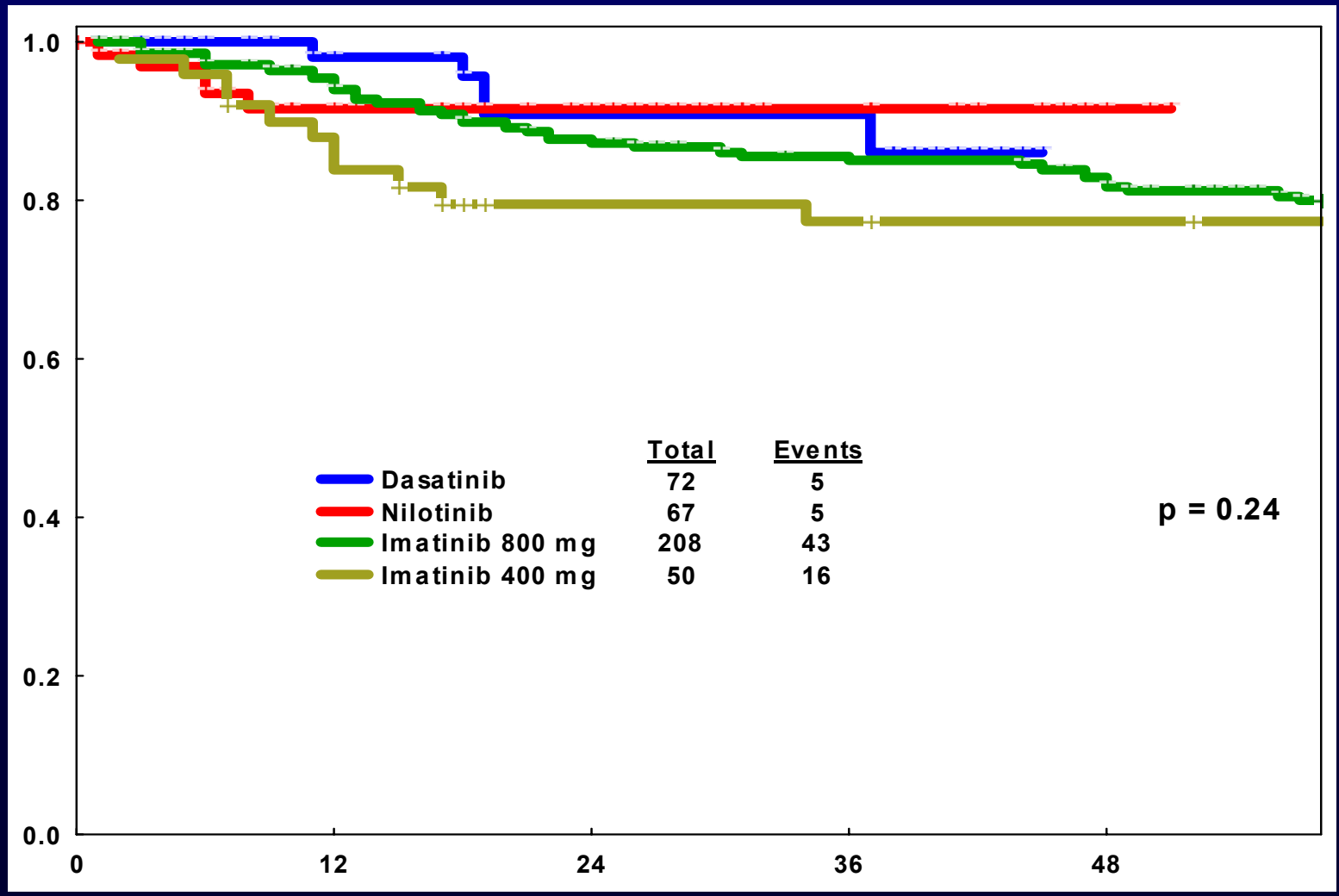
[1]Deininger et al; Blood 2009; 114: Abst# 1126; [2]Branford et al. Clin Cancer Res 2007; 13: 7080-5
[3]Quintas-Cardama et al. Blood 2009; 113: 6315-21; [4]Guilhot et al, Blood 2007; 110: Abst# 27

Complete Cytogenetic Response in Early CP CML by Treatment

Response	Mo.	Percent CCyR			
		IM 400 N=50	IM 800 N=205	Nilotinib N=61	Dasatinib N=71
CCyR	6	54	85	94	95
	12	65	89	95	94
	24	67	88	93	93
MMR	6	7	47	70	64
	12	34	58	71	74
	24	55	66	62	89
CMR	6	0	9	5	2
	12	5	12	10	6
	24	18	20	21	8

Cortes et al. Blood 2009; Abst# 338 & 341

Event-Free Survival by Treatment in ECP CML



Cortes et al. Blood 2009; Abst# 338 & 341

What Needs Improvement in Frontline Therapy of CML?

Outcome	Current	Relevance	"Improvability"
Survival[1]	86% @ 7y	++++	? +
TFS[1]	93% @ 7y	++++	(✓) +
EFS[1]	81% @ 7y	+++	? ++
CCyR[1]	82%	+++	✓ ✓ ++
MMR[2]	87%	++	✓ ++(+)
CMR[2]	52%	+(+)	? +++
Early response[3,4]	CCyR 65% @ 1 yr	+(+)(+)	✓ ✓ ✓ +++(+)
Toxicity	"Low"	+++	(✓) -(+)

[1]O'Brien et al; Blood 2008; 112: abst# 186; [2] Branford et al. Clin Cancer Res 2007; 13: 7080-5
[3] Quintas-Cardama et al. Blood 2009; 113: 6315-21; [4] Guilhot et al, Blood 2007; 110: Abst# 27

The Best Strategy

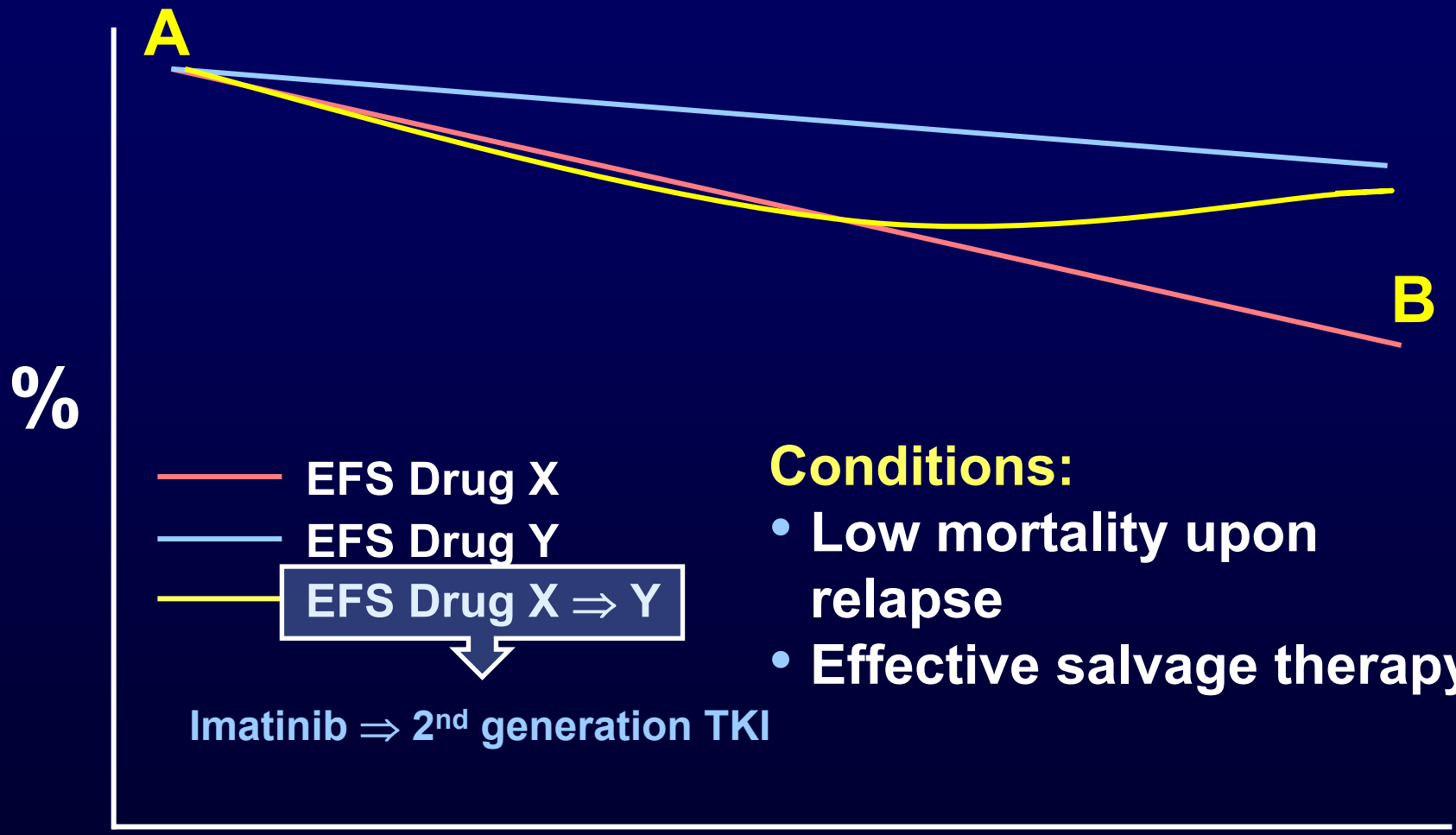
Improving Frontline Therapy in CML

- Standard-dose imatinib
- High-dose imatinib
- Imatinib-based combinations
- Second generation TKI
  - Dasatinib
  - Nilotinib
  - Bosutinib

Dasatinib, Nilotinib and Bosutinib in CML

Parameter	Dasatinib	Nilotinib	Bosutinib
Potency (fold vs IM)	325	30	20-50
Target	Src & Abl	Abl	Src & ABL
BCR-ABL binding	Active + Inactive	Inactive	Intermediate
Resistant mutations	T315I	T315I	T315I
Mutations with intermediate sensitivity	E255K/V, V299L, F317L	E255K/V, Y253F/H, Q252H, F359V	F317L, E255V/K
Standard dose (CP)	100mg QD	400mg BID	500mg QD
Grade 3-4 neutropenia & thrombocytopenia	33% / 22%	31% / 33%	12% / 21%
Other notable toxicities	Pleural effusion, bleeding	Bilirubin, lipase elevation	Diarrhea, rash
C-kit inhibition (vs imatinib)	Increased	Similar	None
PDGFR inhibition (vs imatinib)	Increased	Similar	None
Clinical activity	Highly active	Highly active	Highly active

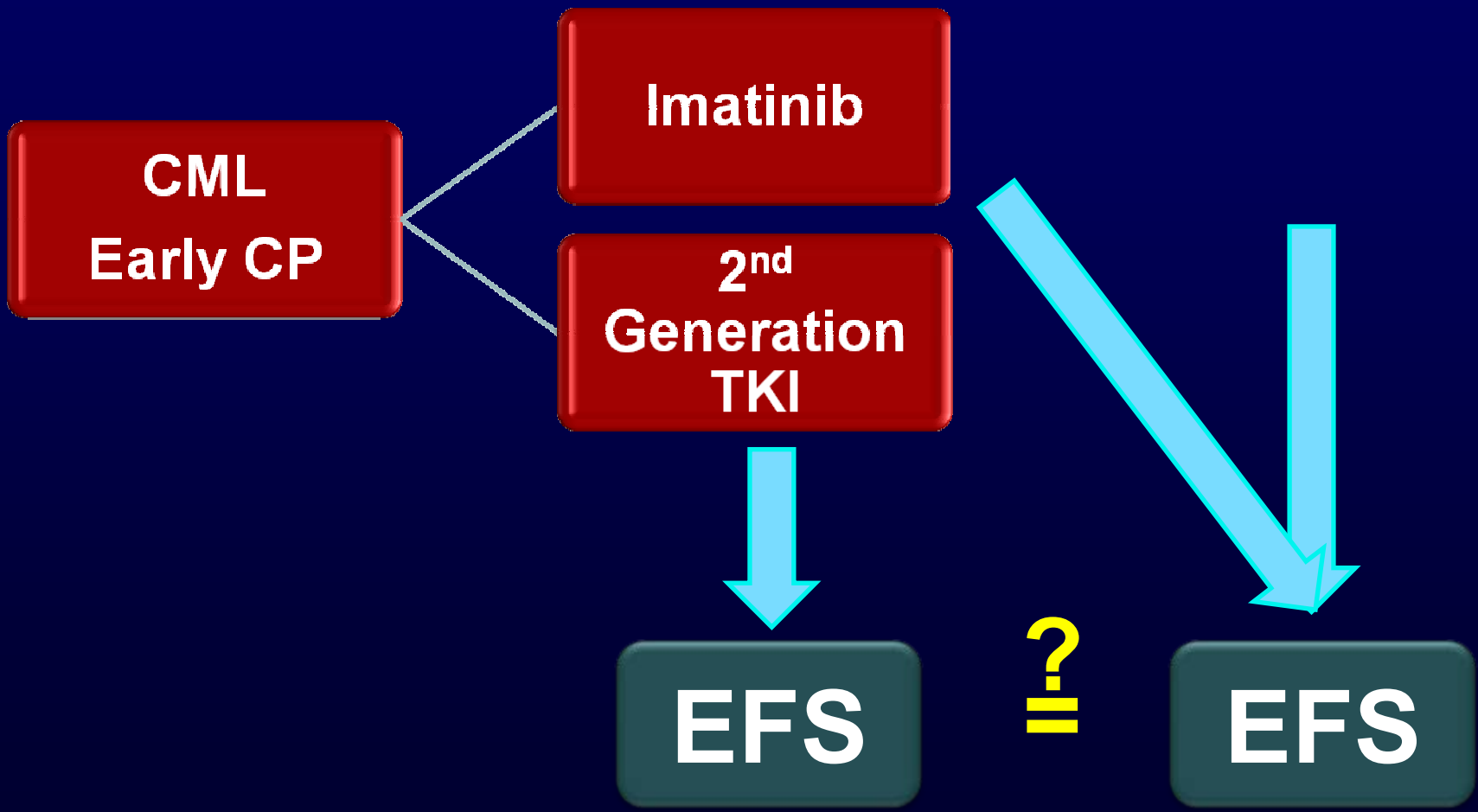
Frontline Therapy for CML
The Road from A to B



Conditions:

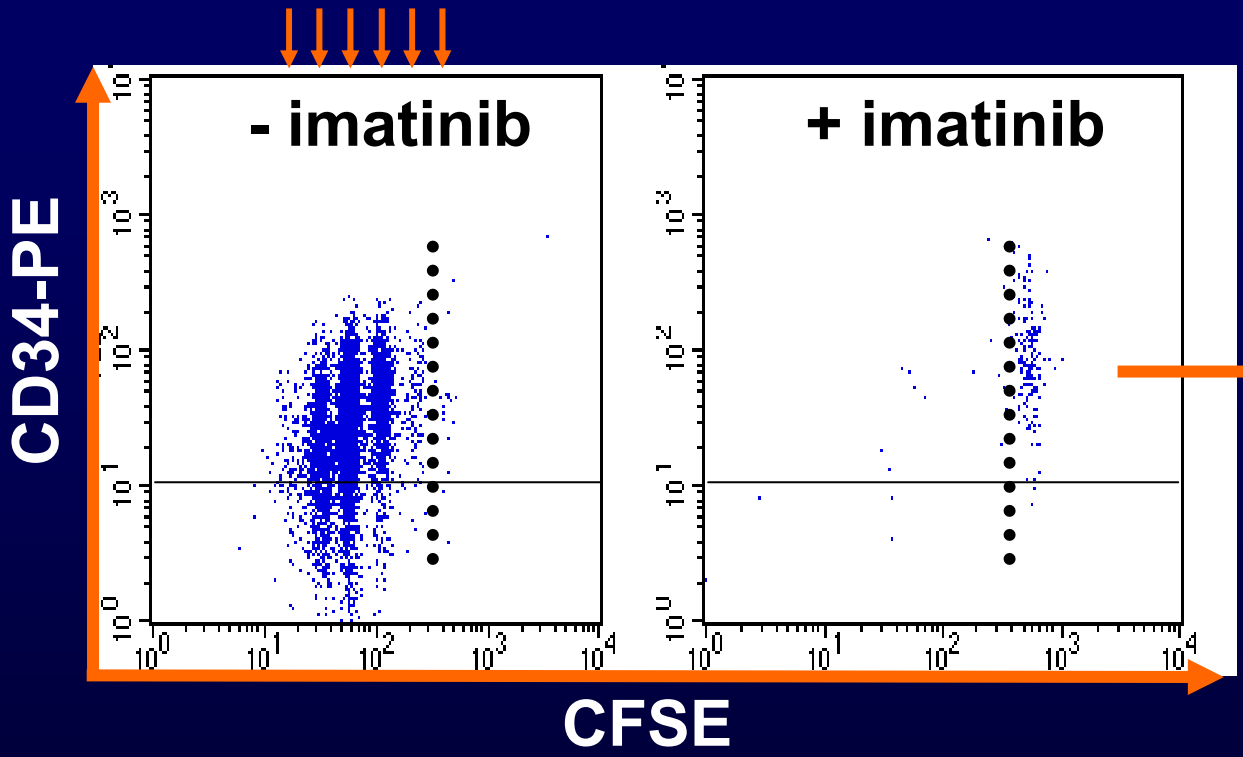
- Low mortality upon relapse
- Effective salvage therapy

The Optimal Frontline Strategy for CML



Cure

CML stem cells survive imatinib treatment *in vitro*



- Mechanisms of resistance of stem cells: ⇑ expression of BCR-ABL mRNA, protein and kinase activity; ⇑ expression of IL-3 and GM-CSF, ⇓ expression OCT1, ⇑ expression ABCB1 and ABCG2.

Graham et al, Blood 2002; 99: 319; Holtz et al, Blood 2002; 99: 3792
Jiang et al. Leukemia 2007; 21: 926-35

BCR-ABL Vaccine in CML (GIMEMA)

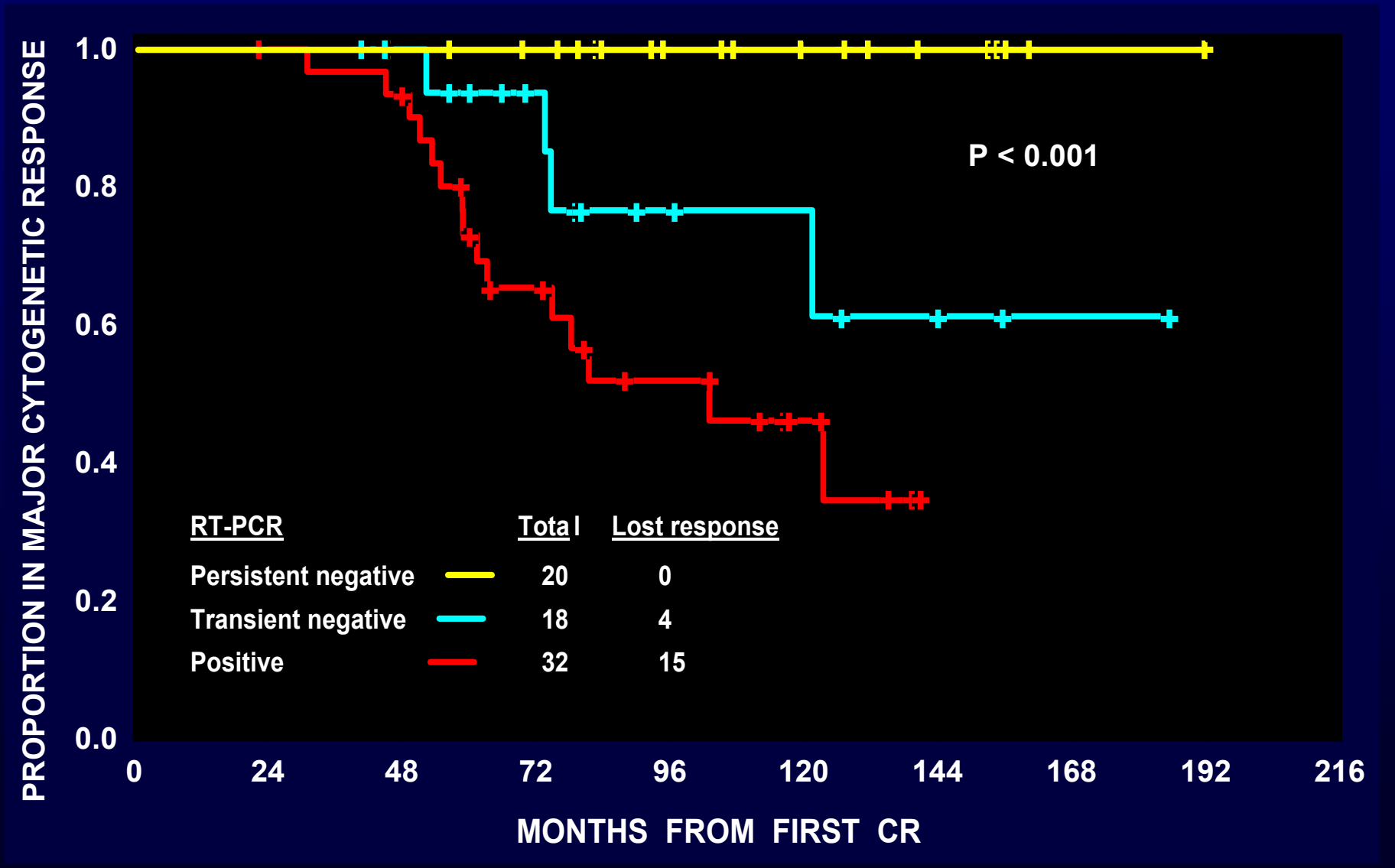
- CML VAX 100 (5 p210 b3a2 peptides) + GM-CSF
  - 6 vaccinations QOW, then Q mo x3, then Q 3 mos x2 (Boosts optional Q6 mo)
- 46 evaluable pts (≥18 mo on imatinib, CCyR, persistence molecular disease)
  - Median 55 mo imatinib therapy
  - 19 IM post IFN; 27 imatinib frontline
- ⇓ BCR-ABL/ABL ≥50% at 6 mo 51%
  - Undetectable at least once 41%

Bocchia et al. Blood 2009; 114:abst# 648

Strategies to Eliminate the CML Stem Cell

- New TKI
  - Combinations?
- Immune modulation
  - IFN, vaccines, CTLA4 monoclonal antibodies
- Alternative pathways
  - Hedgehog
- Other mechanisms
  - Omacetaxine

Molecular Response in Patients with Complete CG Response with IFN



Kantarjian et al. Cancer 2003; 97: 1033

Can we Cure CML with Imatinib?

What is cure?	Can we get?
"Normal" life expectancy	?
Prolonged survival	✓ ✓ ✓ ✓
+CCyR	✓ ✓ ✓ ✓
+Major molecular response	✓ ✓ ✓
+Complete molecular response	✓

“Operational” cure

Until death all is life.

Don Quixote

(Miguel de Cervantes Saavedra)

What is Next?

- Better frontline therapy
  - Lessen low-grade toxicity
  - Finite treatment
  - Improved results?
- Personalized therapy
  - Selecting patients for therapy
- Optimizing adherence
- Eradication of disease

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Questions?

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