Unsatisfactory treatment response: more imatinib or second-generation TK inhibitors?

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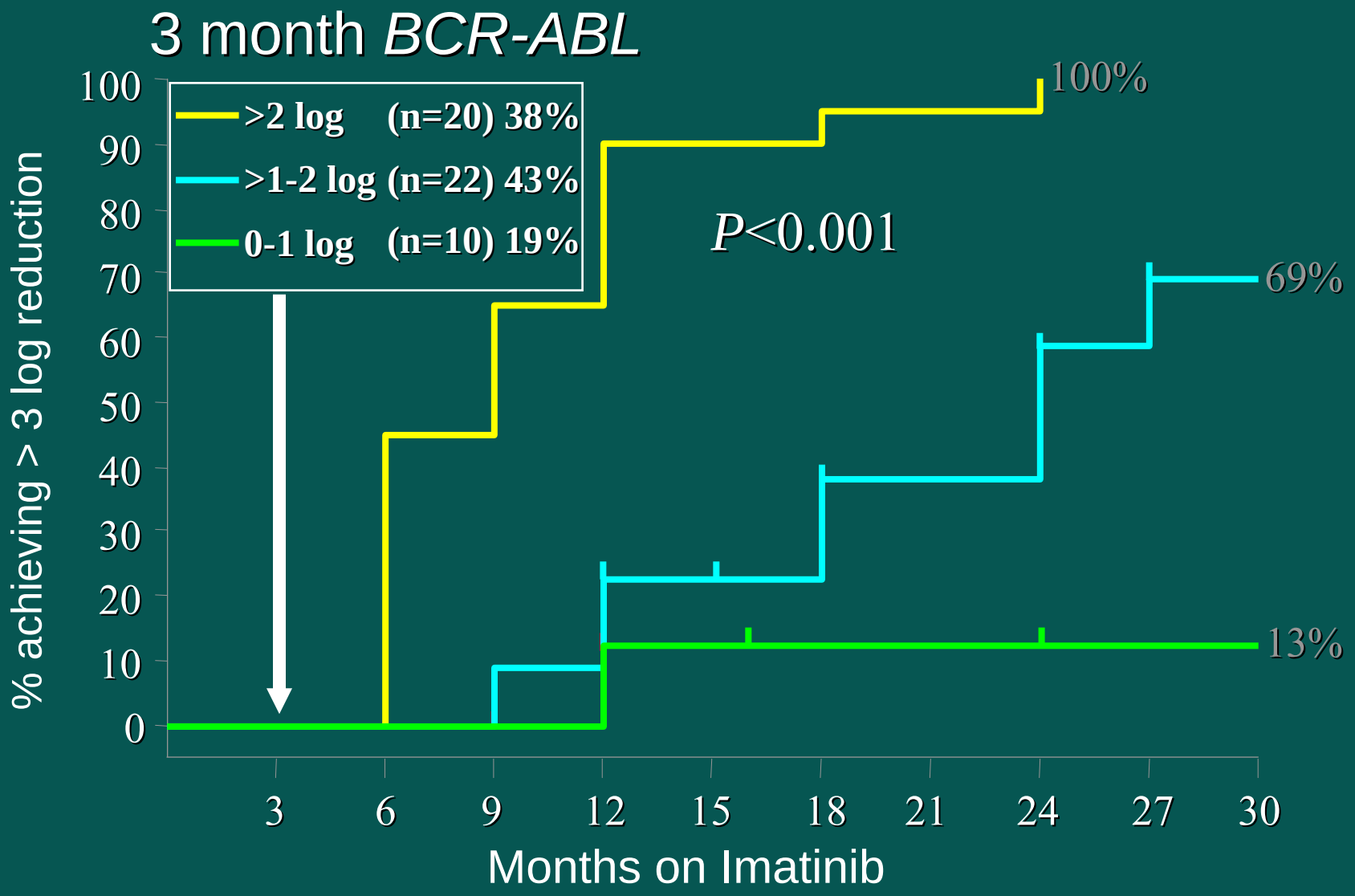
GIMEMA CML WP

EUTOS for CML

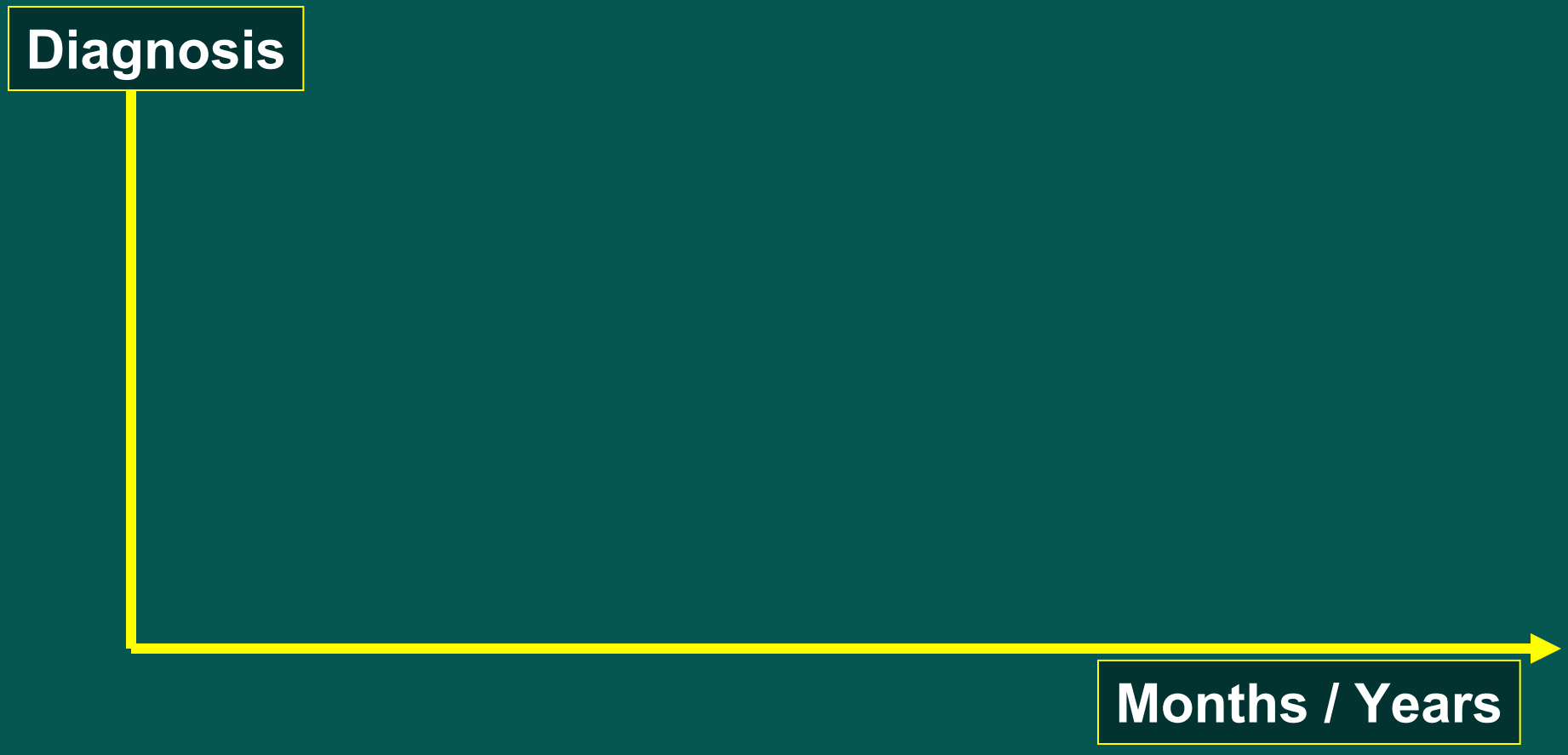
European Treatment and Outcome Study

IRIS trial: Probability of achieving MMR



Branford S & Hughes T., Blood Rev. 2006

Earlier the response, better the outcome



Consequences of treatment failure and suboptimal response

Time		
3 months	**Patient may still have a substantial benefit from continuing imatinib treatment at the current dose but the long-term outcome of the treatment would not likely be favorable... The patient may be eligible for other treatments**	**Continuing imatinib treatment at the current dose is no longer appropriate for these patients, who would likely benefit more from other treatments**
6 months		
12 months		
18 months		
Anytime		

Baccarani M, et al. *Blood* 2006;108(6):1809–1820.

Early cytogenetic response is a prognostic factor in the IRIS study

Months on treatment	Cytogenetic response	Probability of CCyR at 2 years (%)	Event-free survival at 42 months (%)
3	Partial	90	N/A
	Minor	60	N/A
	Minimal/none	50	N/A
6	Complete	N/A	95
	Partial	80	
	Minor/minimal	50	75
	None	15	
12	Complete	N/A	90
	Partial	50	
	Minor/minimal/none	<20	65

Baccarani M, et al. *Blood* 2006;108(6):1809–1820; Simonsson B, et al. *Blood* 2005;106:52a, Abstract 166; Guilhot F, et al. *Blood* 2004;104:10a, Abstract 21; Druker B, et al. *Blood* 2003;102:182a, Abstract 634.

What is a suboptimal responder?

- A typical “grey zone” where firm and homogenous suggestions for the management are difficult.
- We lack enough evidence-based information
- Many different conditions which deserve probably a single-patient-basis discussion

Prognostic significance of suboptimal response

blood

Prepublished online Aug 27, 2008;
doi:10.1182/blood-2008-06-162388

European LeukemiaNet criteria for failure or sub-optimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor

David Marin, Dragana Milojkovic, Eduardo Olavarria, Jamshid S Khorashad, Hugues de Lavallade, Alistair G Reid, Letizia Foroni, Katayoun Rezvani, Marco Bua, Francesco Dazzi, Jiri Pavlu, Matthias Klammer, Jaspal Kaeda, John M Goldman and Jane F Apperley

Median follow-up: 46 (13-93) months

Marin et al.		N	OS	PFS	CCgR
Suboptimal	No	154	96.0	91.4	97.2
at 6 mos	Yes	28	91.7	61.5	64.0
Suboptimal	No	120	98.4	96.1	100
at 12 mos	Yes	45	85.4	73.4	77.8

Suboptimal response: the GIMEMA experience

423 patients (ITT analysis):

- **CML 022**
- **CML 023**

Median follow-up: 41 (1-64) months

GIMEMA CML WP

GIMEMA		N	FFS	CCgR	MMR
Suboptimal at 6 mos	No	341	90	98	93
	Yes	20	60	60	50
Suboptimal at 12 mos	No	323	94	100	96
	Yes	31	68	81	68

The number of suboptimal responders may vary

	Hammersmith	GIMEMA
Suboptimal at 6 mos	15%	5%
Suboptimal at 12 mos	27%	9%

Baccarani M, et al. *Blood* 2006;108(6):1809–1820; Simonsson B, et al. *Blood* 2005;106:52a, Abstract 166; Guilhot F, et al. *Blood* 2004;104:10a, Abstract 21; Druker B, et al. *Blood* 2003;102:182a, Abstract 634.

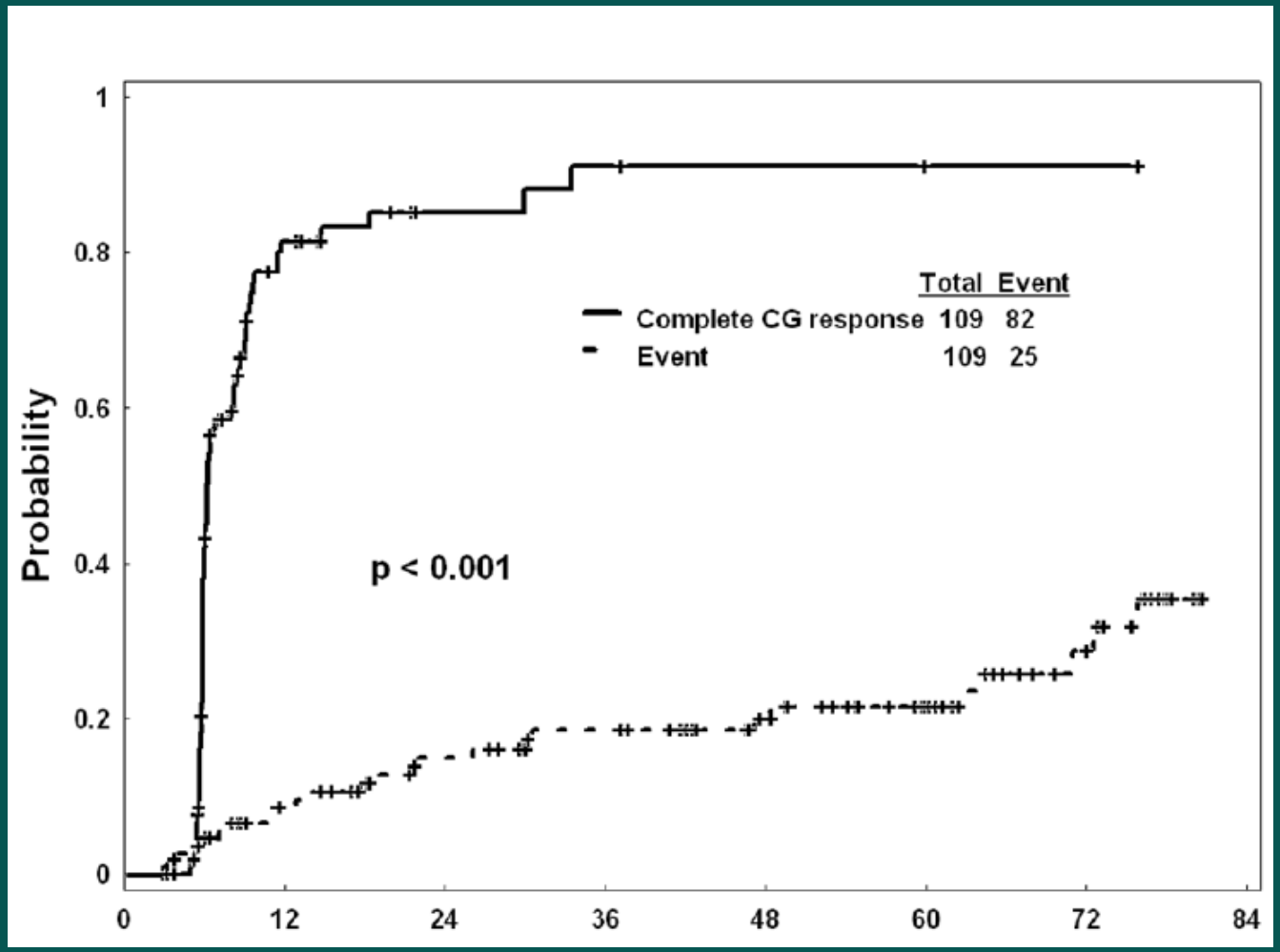
Time to CCyR and MolR and Risk of Disease Progression (*)

Months on treatment	No. (%) in CCyR	No. (%) not in CCyR	% eventually achieving outcome if not in CCyR at specified time		
			CCyR	MMR	Event
3	143 (56)	109 (43)	75	62	23
6	190 (79)	47 (20)	57	43	34
12	200 (85)	26 (12)	42	31	38
			p=0.002	p=0.004	p=0.16

258 ECP Pts, Imatinib 800 mg frontline 81%

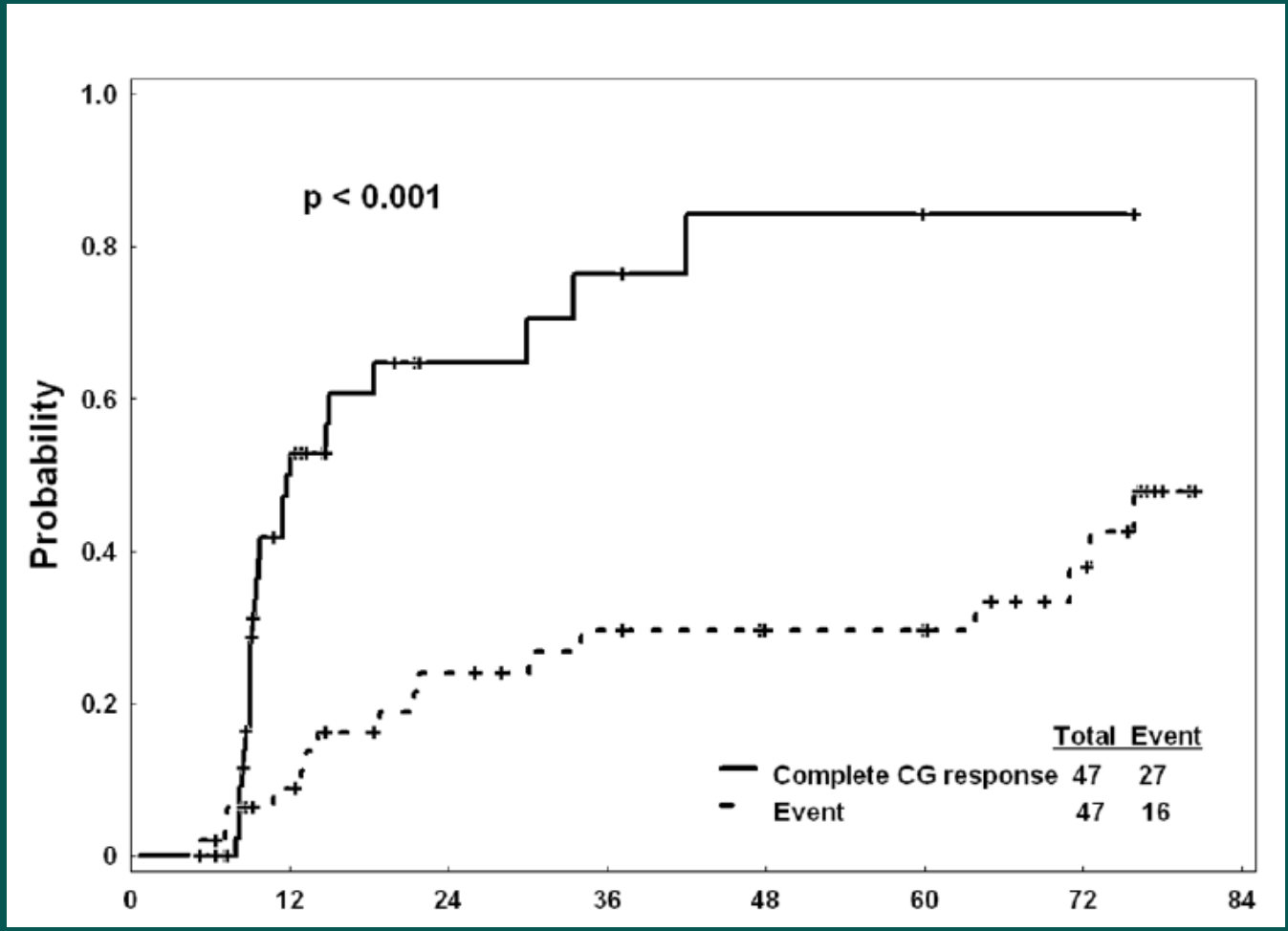
Quintas-Cardama et al, Blood FEP, Apr 15, 2009

Time to CCyR and Risk of Events (NOT in CCyR at 3 Months)



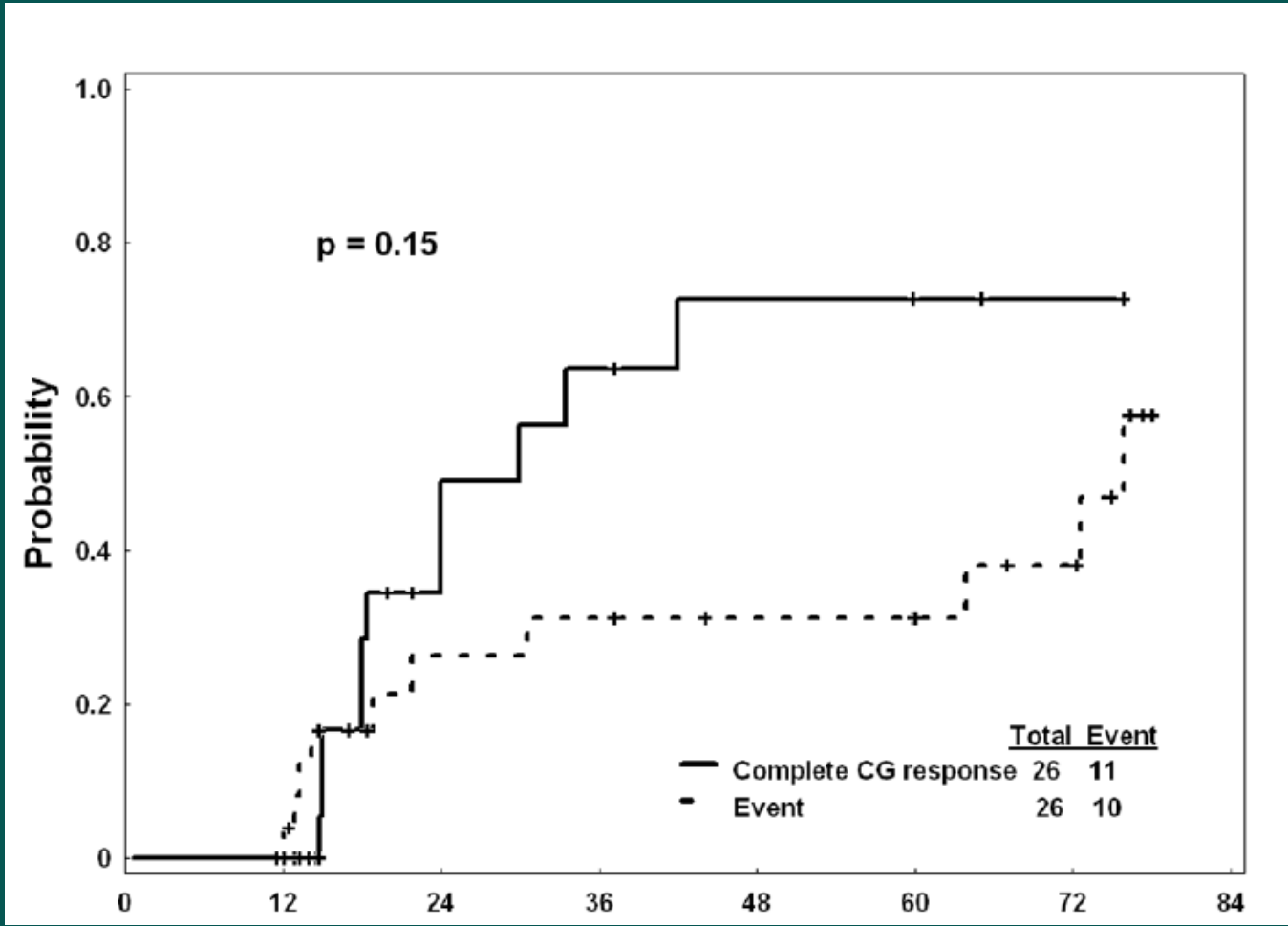
Quintas-Cardama et al, Blood FEP, Apr 15, 2009

Time to CCyR and Risk of Events (NOT in CCyR at 6 Months)



Quintas-Cardama et al, Blood FEP, Apr 15, 2009

Time to CCyR and Risk of Events (NOT in CCyR at 12 Months)



Quintas-Cardama et al, Blood FEP, Apr 15, 2009

IRIS TRIAL at 6 yrs
Sokal Risk and Outcome

SOKAL RISK	OS %	EFS %	PFS %
LOW	94	91	97
INTERMEDIATE	87	81	92
HIGH	76	67	82

All P values < 0.001

Hochhaus et al, Leukemia 2009

EVOLVING CONCEPTS IN THE MANAGEMENT OF CML: 2009 ELN RECOMMENDATIONS

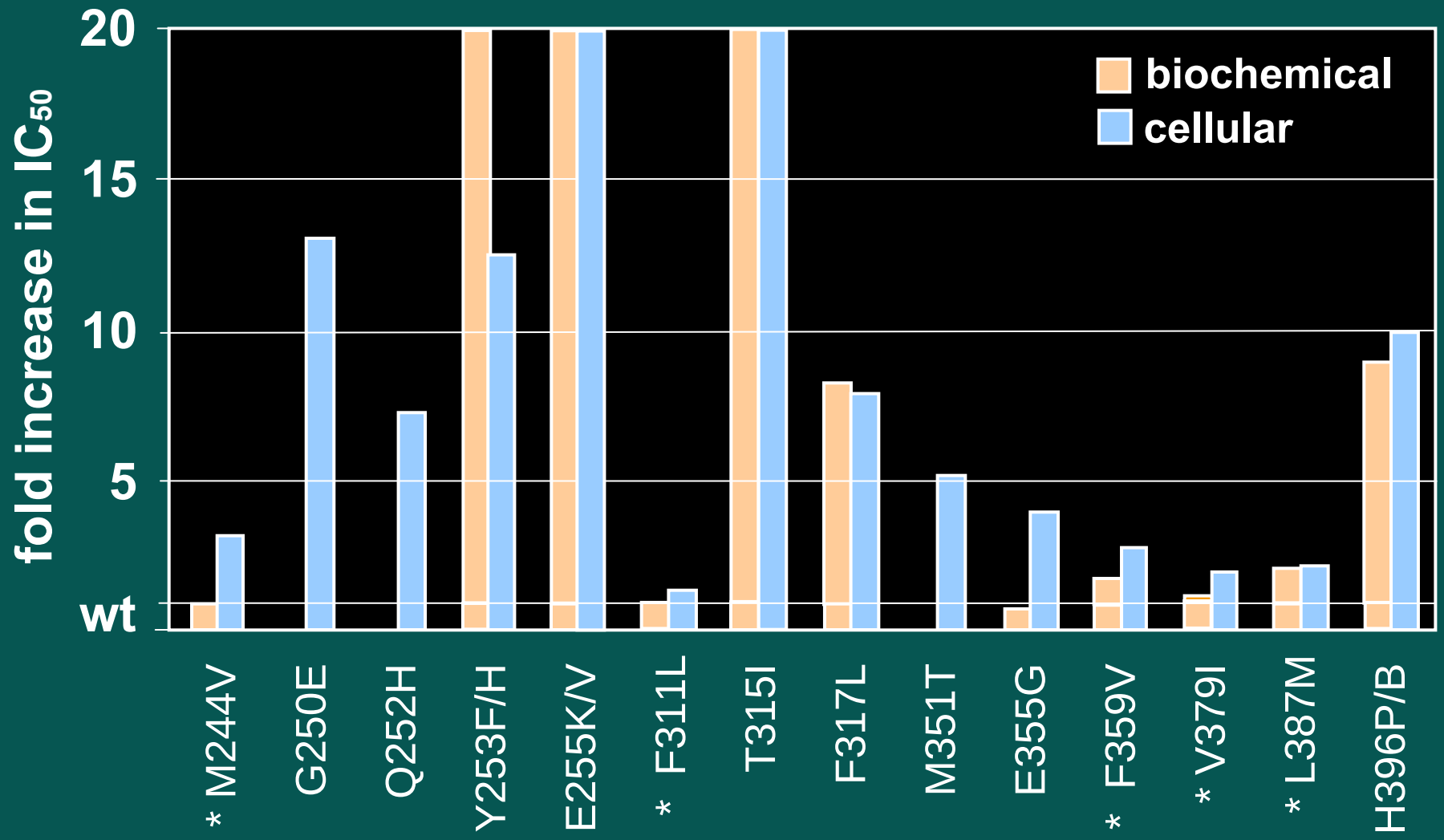
	OPTIMAL RESPONSE	SUBOPTIMAL RESPONSE	FAILURE	WARNINGS
BASELINE	**NA**	NA	NA	High risk ~~ACA in Ph+ cells~~ ~~Der(9) deletions~~
3 months	**CHR** **At least minor CgR** **(Ph+ ≤ 65%)**	**No CgR** **(Ph+ > 95%)**	**No CHR**	NA
6 months	**At least PCgR** **(Ph+ < 35%)**	No PCgR (Ph+ > 35%)	No CgR (Ph+ > 95%)	NA
12 months	**CCgR**	No CCgR (Ph+ ≥1%)	No PCgR (Ph+ > 35%)	No MMR
18 months	**MMR**	No MMR	No CCgR (Ph+ ≥1%)	NA
Any Time	**Stable response**	Loss of MMR Mutations (sensitive to IM)	Loss of CHR/CCgR Mutations (insensitive to IM) ACA in Ph+ cells	Any rise in transcripts level OCA in Ph- cells

Baccarani M and ELN CML panel, unpublished and provisional, 28.02.09

Rationale for High-Dose Imatinib Therapy

- Dose-response in preclinical models
- Phase I:
  - No MTD
  - Dose-response
- Responses to 800mg after failure to 400mg
- Accelerated phase 600 mg: improved response rate, survival and EFS
- Some mechanisms of resistance may be overcome by higher dose

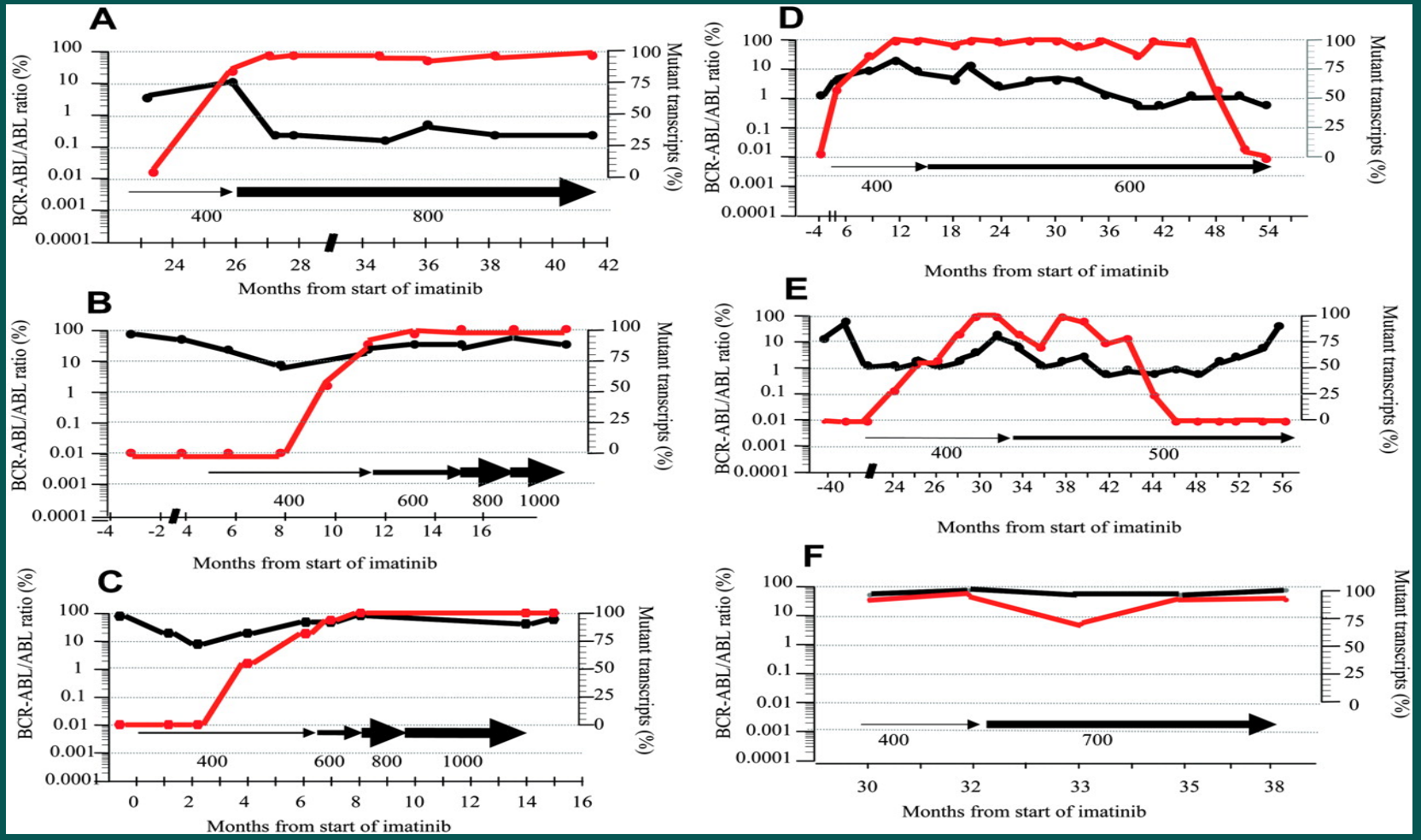
Increase of IC50 to Imatinib of Mutant BCR-ABL



Corbin et al., Blood 2003

Dose increase can sometimes be effective and sometimes not

6 patients who developed M244V while on imatinib



— BCR-ABL Transcripts
— Percentage of mutant clone

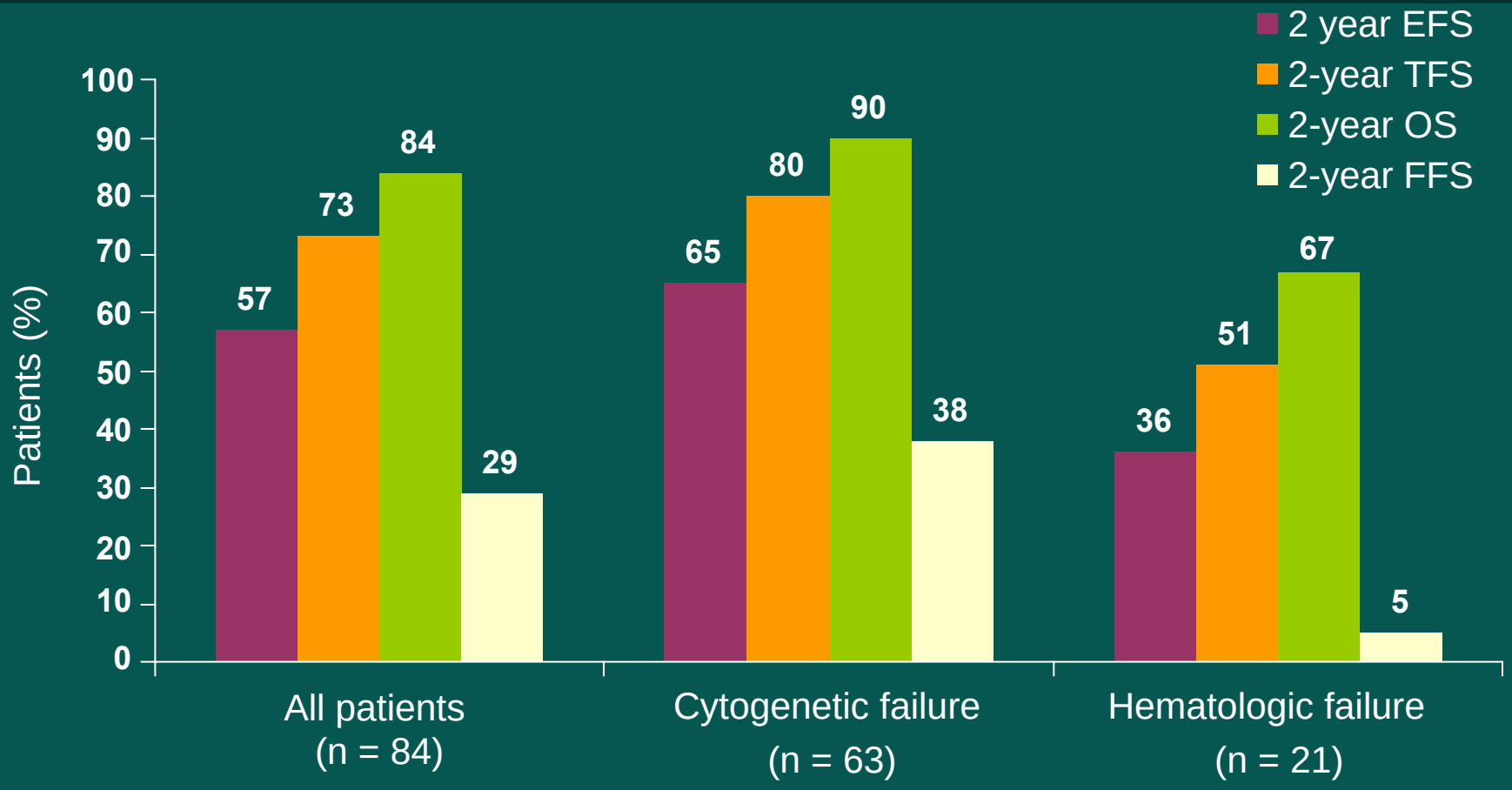
Anand et al. Blood. 2006; 108(8):2881-2.

Effect of Imatinib Dose Increase in Patients Resistant to Standard Dose

- MDACC (N=54)
  - Increase to 800 mg (n=47) or 600 mg (n=7)
  - Cytogenetic failure: MCyR 39%
  - Hematologic failure: CHR 45%, MCyR 5%
- Zonder et al. (N=16)
  - Increase to 800 mg (n=47) or 600 mg (n=7)
  - CHR 4/5, MCyR 38%
- Marin et al. (N=36)
  - Increase to 1000 mg (n=1), 800 mg (n=12), or 600 mg (n=23)
  - Improved CyR 39%, CCyR 19% (14% sustained)
  - Author suggests "there is little to be gained by increasing the imatinib dose for such patients"

Kantarjian et al. Blood. 2003; 101: 47
Zonder et al. Clin Cancer Res. 2003; 9: 2092
Marin et al. Blood. 2003; 102: 2702-3

MD Anderson analysis: long-term outcomes after dose escalation in patients with imatinib failure



EFS, event-free survival; TFS, transformation-free survival; OS, overall survival

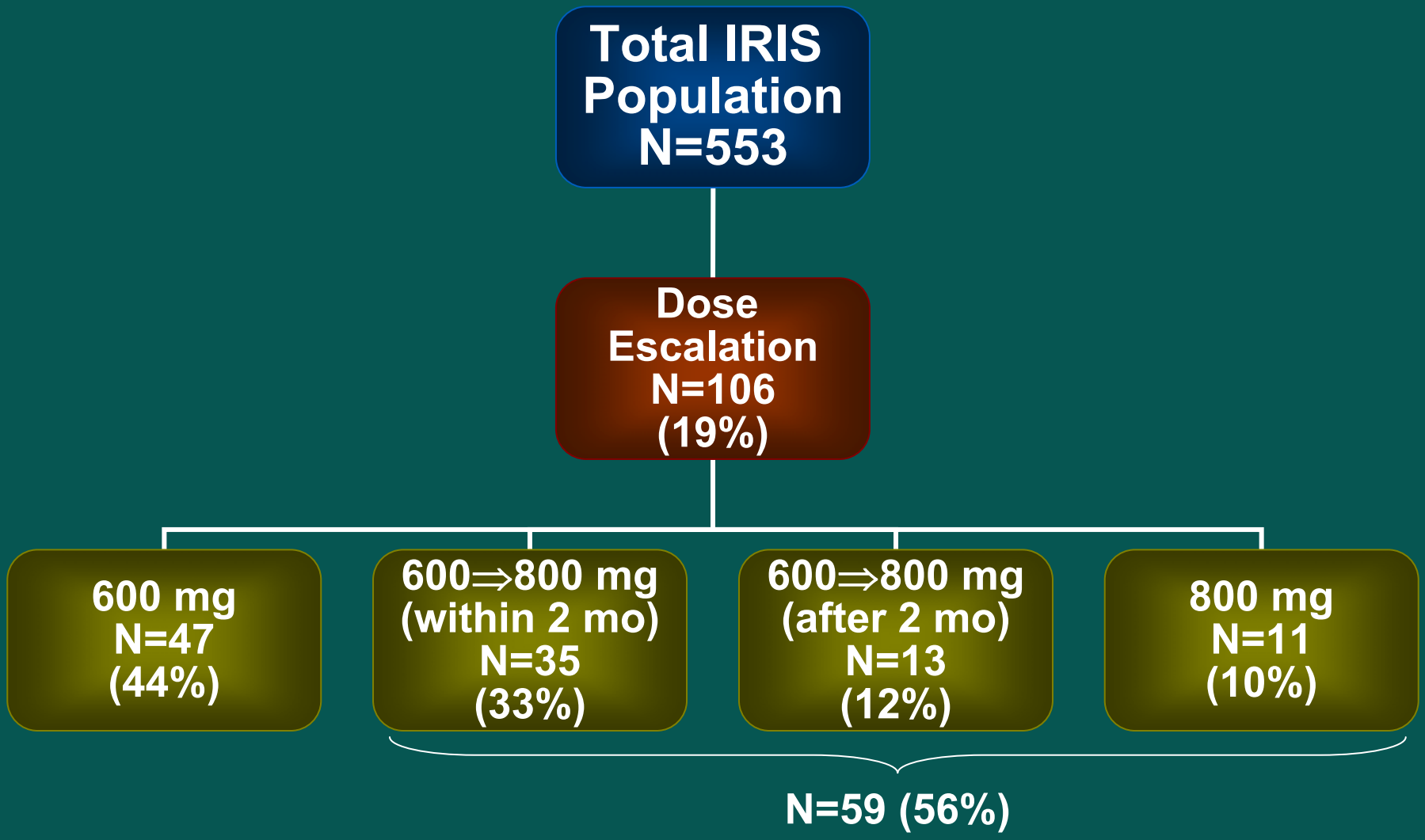
Jabbour et al. Blood 2008; Epub ahead of print

Retrospective analysis of the IRIS trial: dose escalation

- IRIS was not designed as a dose escalation study
- However, the IRIS protocol permitted stepwise dose escalation of imatinib when response criteria were not met
  - First to 600 mg/day, then 1 month later to 800 mg/day
- Two analyses were performed in patients who received ≥ 600 mg/day of imatinib
  - According to the IRIS protocol dose escalation guidelines
  - Retrospective review of the IRIS database classifying the reason for dose escalation as per the ELN criteria

Kantarjian et al. Cancer 2008; Epub ahead of print

Imatinib Dose Escalation: The IRIS Experience



Kantarjian et al. Cancer. 2009; 115: 551-60

IRIS- Dose Escalation: Criteria for Dose Escalation (N = 106)

Reasons per IRIS Protocol Criteria N = 39	n (%)
No CHR at 3 mo	7 (18)
No minor CyR at 12 mo	8 (21)
Loss of MCyR	**18 (44)**
Disease progression	6 (15)

Reasons per ELN Criteria N= 48	n (%)
3mo: Failure (no HR) or suboptimal response (<CHR)	7 (15)
6 mo: Failure (no CHR, no CyR)	1 (2)
12 mo: Suboptimal response (no CCyR)	4 (8)
12 mo: Failure (no MCyR)	**11 (23)**
18 mo: Failure (no CCyR)	**10 (21)**
Failure at any time: Loss of previous response*	15 (31)

*Confirmed loss of CHR, loss associated with progression to AP/BC, or loss of CCyR.
ELN, European LeukemiaNet;

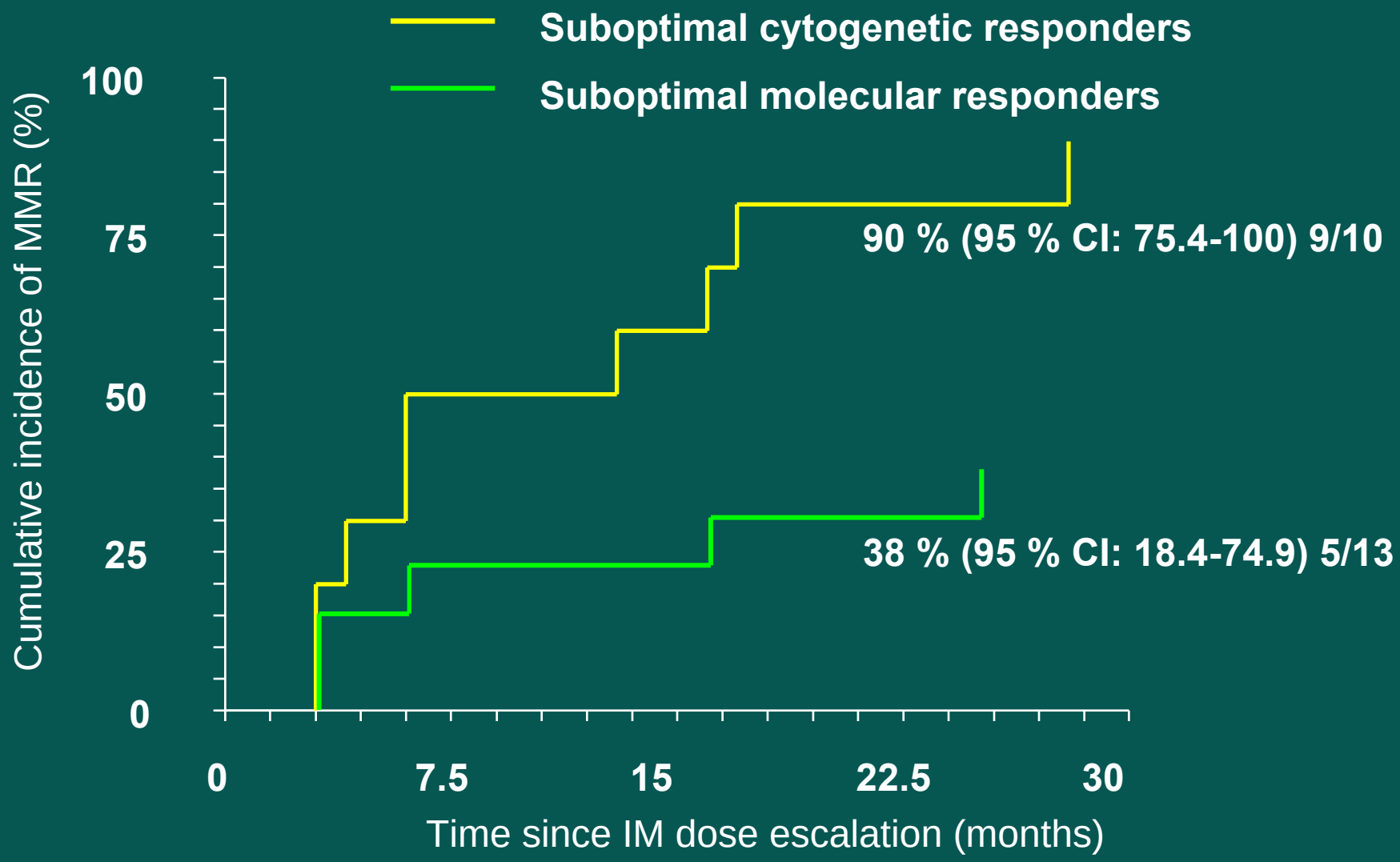
Kantarjian H. *et al*, Blood. 2007; 110, 11. Abstract 1047. ASH 2007 Poster Presentation

IRIS - Response to Imatinib Dose Escalation

Criteria for dose escalation	No.	No. (%)		
		Clinical response	MCyR	CCyR
IRIS	39	21 (54)	15 (38)	9 (23)
ELN	48	21 (44)	23 (48)	14 (30)

Kantarjian et al. Cancer. 2009; 115: 551-60

Imatinib Dose Escalation for 23 CML Patients in Primary Suboptimal Response to Imatinib



Rea D et al. Leukemia. 2009 Feb 26. [Epub ahead of print]

HI, GIANANTONIO, HAVE YOU ANY INFO ABOUT SECOND GENERATION TKIs?

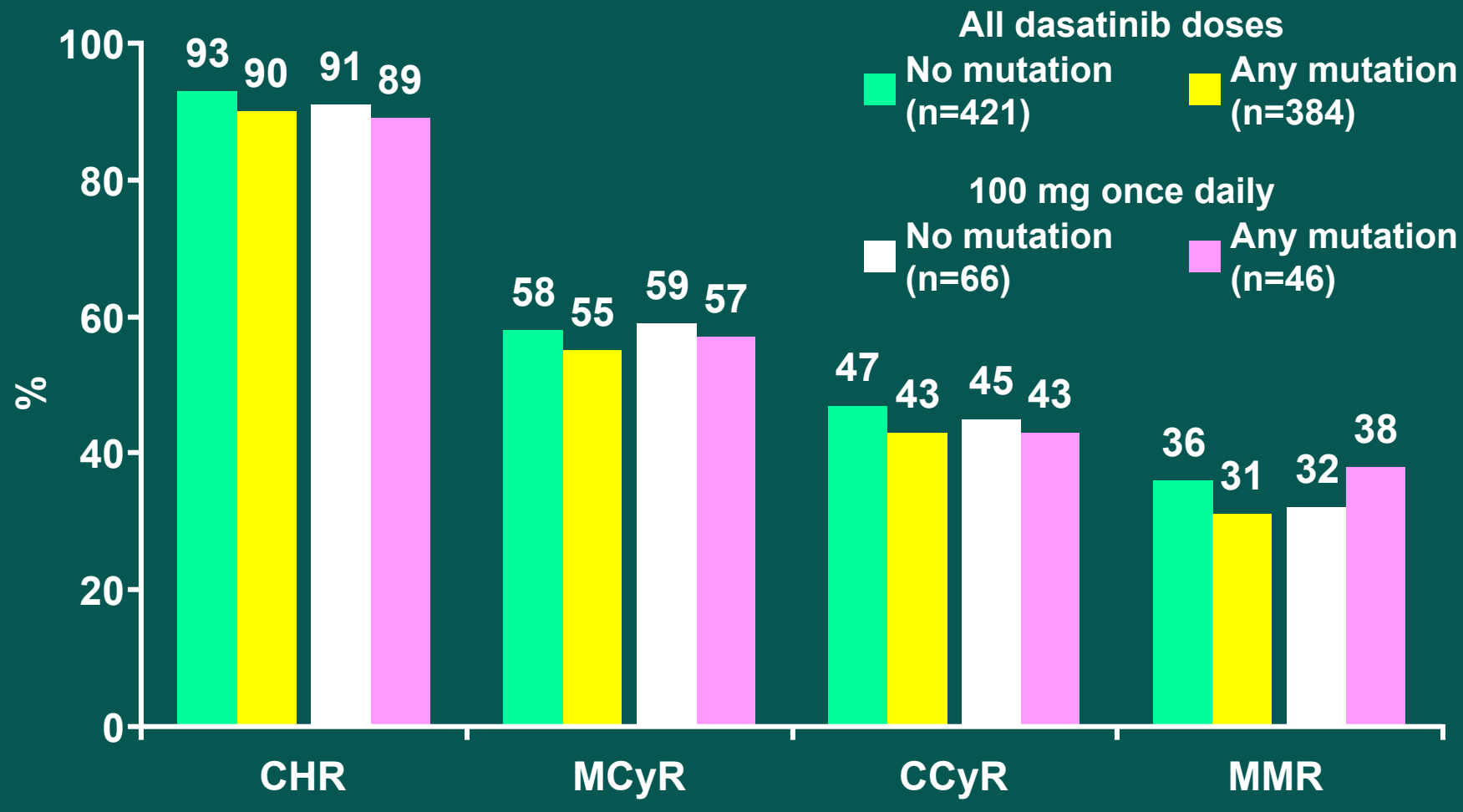
Nilotinib and dasatinib after imatinib failure (Median follow-up 15.2 months *)

	Nilotinib[1] (n. 321)	Dasatinib[2] (n. 387)
MCyR, %	58	59
CCyR, %	42	49
MCyR, % *	56	52
CCyR, % *	39	40
MMR, % * (at 12 months)	23	15
12-month overall survival, %	95	97

*** Resistant patients only**

*** 1.Kantarjian et al. EHA 2008. abs. 7010; 2. Guilhot et al. EHA 2007. abs. 0358**

Patients with resistance or suboptimal response to imatinib: Dasatinib response rates after ≥24 months



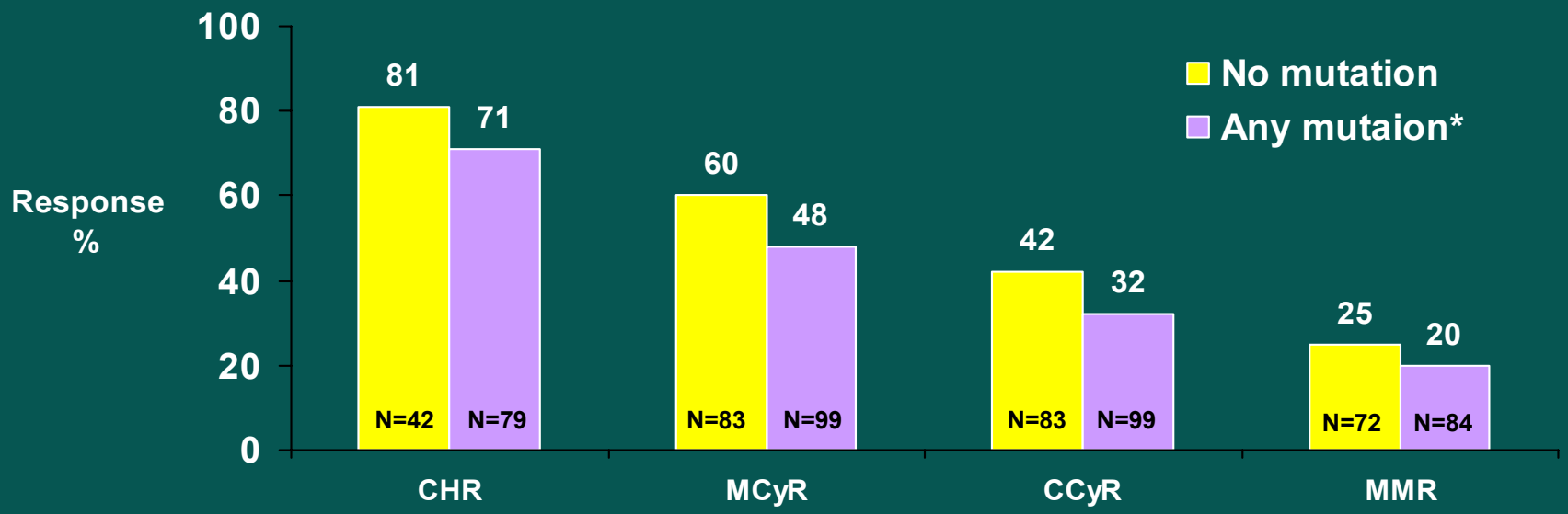
Overall MMR rate in patients with samples available

MMR = *BCR-ABL* ratio ≤0.1% on the international scale by RQ-PCR

Mutational Analysis in CML-CP

Nilotinib Efficacy in pts. with & without Baseline Mutation

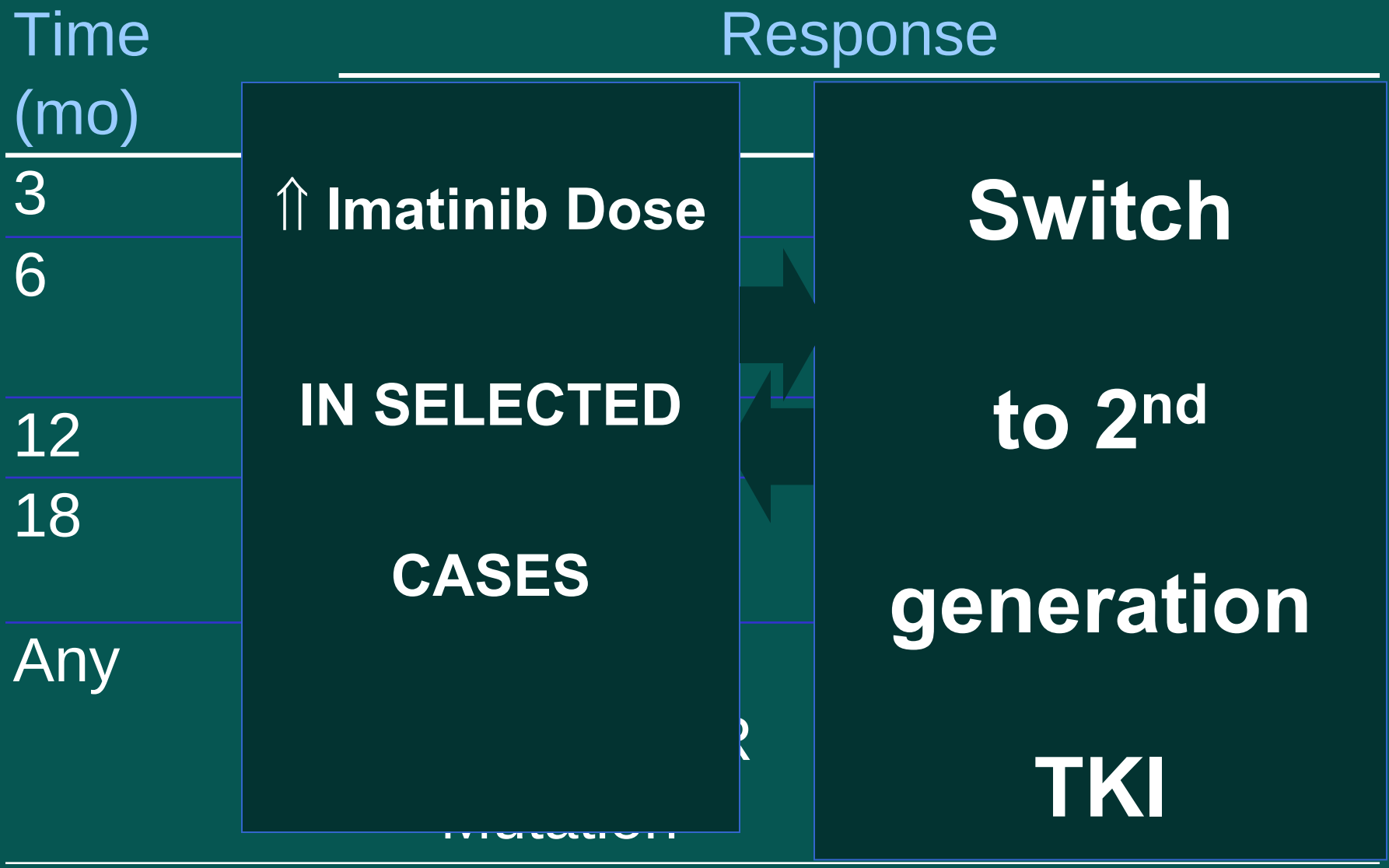
Best Responses by 12 Months in Imatinib-Resistant Patients with and without Baseline Mutations



* patients with T315I were excluded

Hughes et al. Blood. 2007;110(11):abstract # 320. Oral Presentation

To switch or not to switch….



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

THE SUBOPTIMAL RESPONDER IDEAL CANDIDATE TO IMATINIB DOSE INCREASE

- Suboptimal at (6) - 12 months
- Tolerating nicely 400 mg
- Without mutations
- Low imatinib blood levels
- Low OCT1 activity