Monitoring and Management of Suboptimal Response to TKI Therapy in CML

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IRIS 7-Year Update Outcomes with Imatinib 400 mg/d

- 332 (60%) patients on imatinib on study
- Projected results at 7 years:
  - CCyR 87%
  - Event-free survival 81%
  - Transformation-free survival 93%
    - If MMR at 12 mo: 100%
    - If CCyR, no MMR: 98%
  - Survival 86% (94% CML-related)
  - Annual progression rates: 1.5%, 2.8%, 1.6%, 0.9%, 0.5%, 0%, 0.4%

O'Brien. Blood 112:abst 186, 2008

IRIS 7-Year Update
Outcome After Imatinib

- 40% of patients off-study
  - 8% due to safety reasons
  - 15% due to lack/loss of efficacy

  } OS 50% @ 5y

  - 17% due to other reasons

  } OS 85% @ 5y

- 60% (n=332) of patients on-study
  - 57% (n=317) in CCyR
  - 3% (n=15) not in CCyR

  } OS 86% @ 5y

O'Brien *et al*. ASH 2008

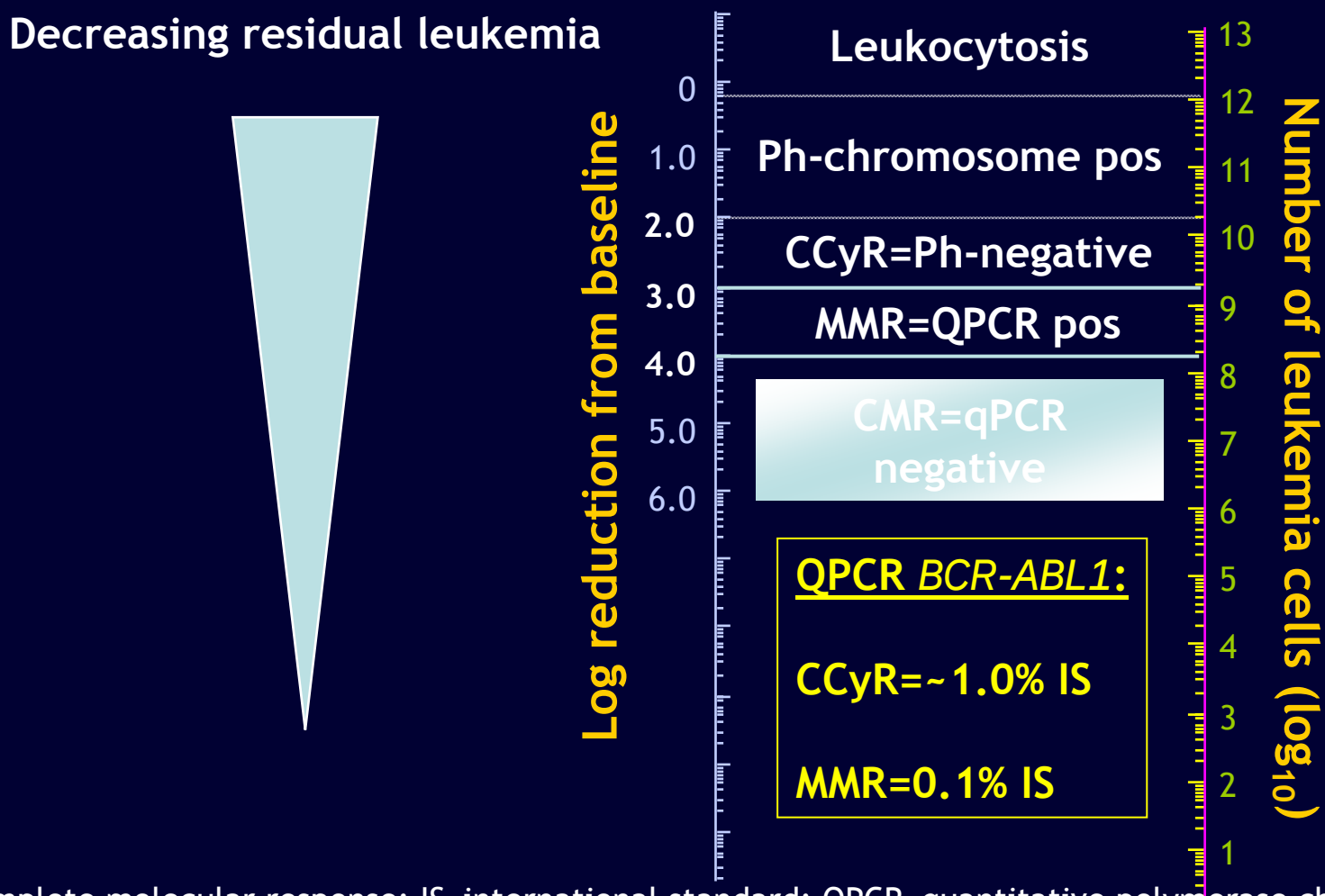
Monitoring Strategy

- Identify those who will do well with imatinib and need standard monitoring[1,2]
- IRIS trial identified CCyR at 12 months and MMR at 12 months as indicators of PFS[1,2]
- Identify those who will not do well and need more intense monitoring and changes in treatment: high Sokal score, poor absorption of imatinib (hOCT-1), low serum imatinib concentration, and inadequate response to imatinib[3-5]

hOCT-1=human organic cation transporter; PFS=progression-free survival.

1. O'Brien SG et al. *N Engl J Med.* 2003;348:994-1004; 2. Hughes TP et al. *N Engl J Med.* 2003;349:1423-1432;
3. Druker BJ et al. *N Engl J Med.* 2006;355:2408-2417; 4. White DL et al. *Blood.* 2007;110:4064-4072;
5. Larson RA et al. *Blood.* 2008;111:4022-2028.

Residual Disease: Cytogenetic Response and *BCR-ABL* Transcript Response



CMR=complete molecular response; IS=international standard; QPCR=quantitative polymerase chain reaction.

Goldman JM. *Blood*. 2007;110:2828-2837

Methods Used to Monitor CML Response

Parameter	Cytogenetics	FISH	QPCR
Sensitivity (% tumor)	5%-10%	1%-10%	0.001
Accuracy of measurement	15%	2%-5%	2-5 fold
Metaphases required	Yes	No	No
Marrow sample required	Yes	No	No
Equivalence of blood and bone marrow	NA	Yes	Yes
False (-)	Yes	Yes	Yes
False (+)	Rare	Yes, low	Yes, low
Detect other chromosomes	Yes	No	No
Detect del der 9	No	Yes	No

del der 9=deletion of derivative chromosome 9; FISH=fluorescence *in situ* hybridization

Kantarjian H et al. *Blood.* 2008;111:1774-1780

LeukemiaNet Guidelines for CML Response

Time	Failure	Suboptimal
3 months	No HR	No CHR
6 months	No CHR No CyR	>35% Ph^+
12 months	>35% Ph^+	>5% Ph^+
18 months	>5% Ph^+	No MMR
Anytime	Loss of CHR Loss of CCyR	Clonal evolution Loss of MMR

CHR=complete hematologic response; CCyR=complete cytogenetic response; CyR=cytogenetic response; HR=hematologic response; MMR=major molecular response.

Baccarani M et al. *Blood.* 2006;108:1809-1820.

LeukemiaNet Monitoring Recommendations

- CBC q 2 weeks until CyR, then q 3 months
- Marrow cytogenetics q 6 months until CyR and then annually
- QPCR for *BCR-ABL* q 3 months
- Mutational analysis if failure, suboptimal response, or transcript elevation

Baccarani M et al. *Blood.* 2006;108:1809-1820

PCR: Molecular Monitoring in CML

- QPCR results must be expressed as a ratio between *BCR-ABL1* and a housekeeping gene
- Characteristics of a houskeeping gene:
  - expression level broadly similar to that of *BCR-ABL* at diagnosis of CML
  - stability similar to *BCR-ABL1*
  - primers for the gene should be proven not to amplify sequences from genomic DNA such as pseudogenes
  - Similar levels of RNA stability are essential since delays in sample processing are common and marked changes in expression can occur very rapidly after blood collection
- *ABL1*, *GUS*, *BCR*, and *B2M* are suitable to correct for RNA quality/quantity variations
- *ABL1* is currently the most widely used control gene

Hughes et al. *Blood.* 2006;108:28-37

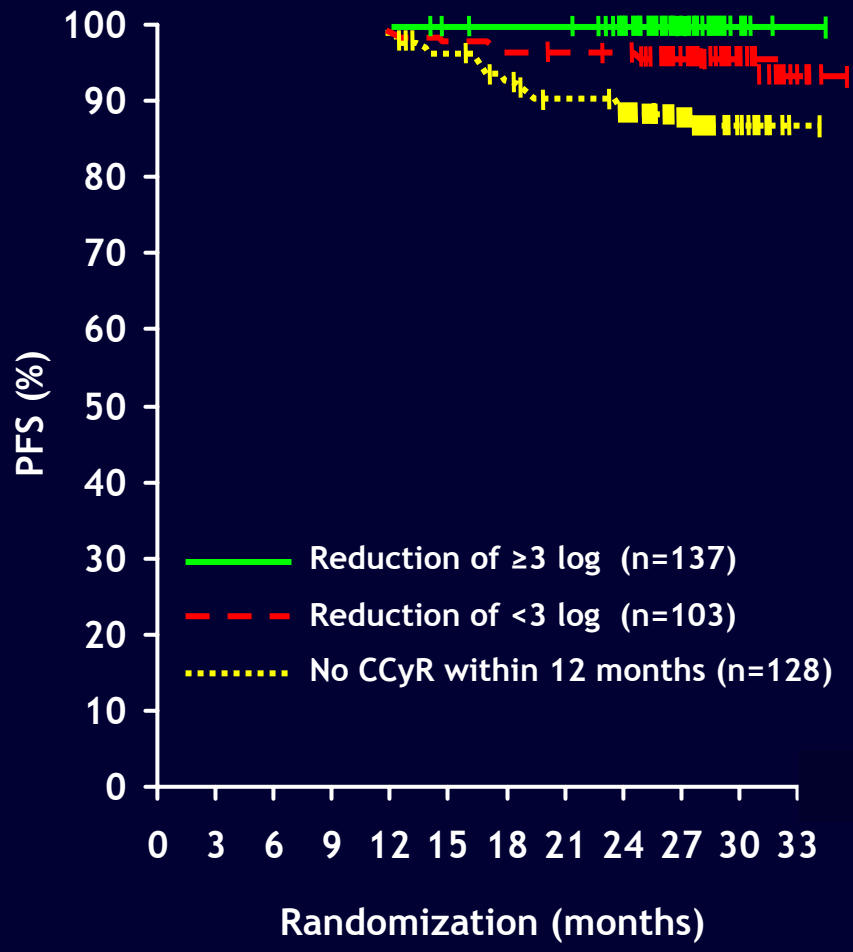
QPCR Influenced by Multiple Factors

- Collection and transportation are important
- Variable control genes used by different laboratories
- Cell number at the time of assay and quality of RNA extract are important
- Undetectable levels vary by method used
- Ideally convert local laboratory results to an International Standard: not yet implemented by most US commercial labs
- Methods using nonpatient standards may be possible in the near future

Hughes T et al. *Blood*. 2006;108:28-37; Müller MC et al. *Leukemia*. 2008;22:96-102.

PCR: Molecular Monitoring in CML

- IRIS trial molecular monitoring: early results
  - Evaluated CCyRs
  - Quantitative RT-PCR
  - Compared to median level of 30 untreated CML patients
  - Identified 1000-fold or 3-log reduction as a significant predictor of risk of progression
  - Defined MMR as 3-log reduction
  - Molecular monitoring became standard following this report



Hughes TP et al. *N Engl J Med*. 2003;349:1423-1432.

Value of Molecular Monitoring in CML

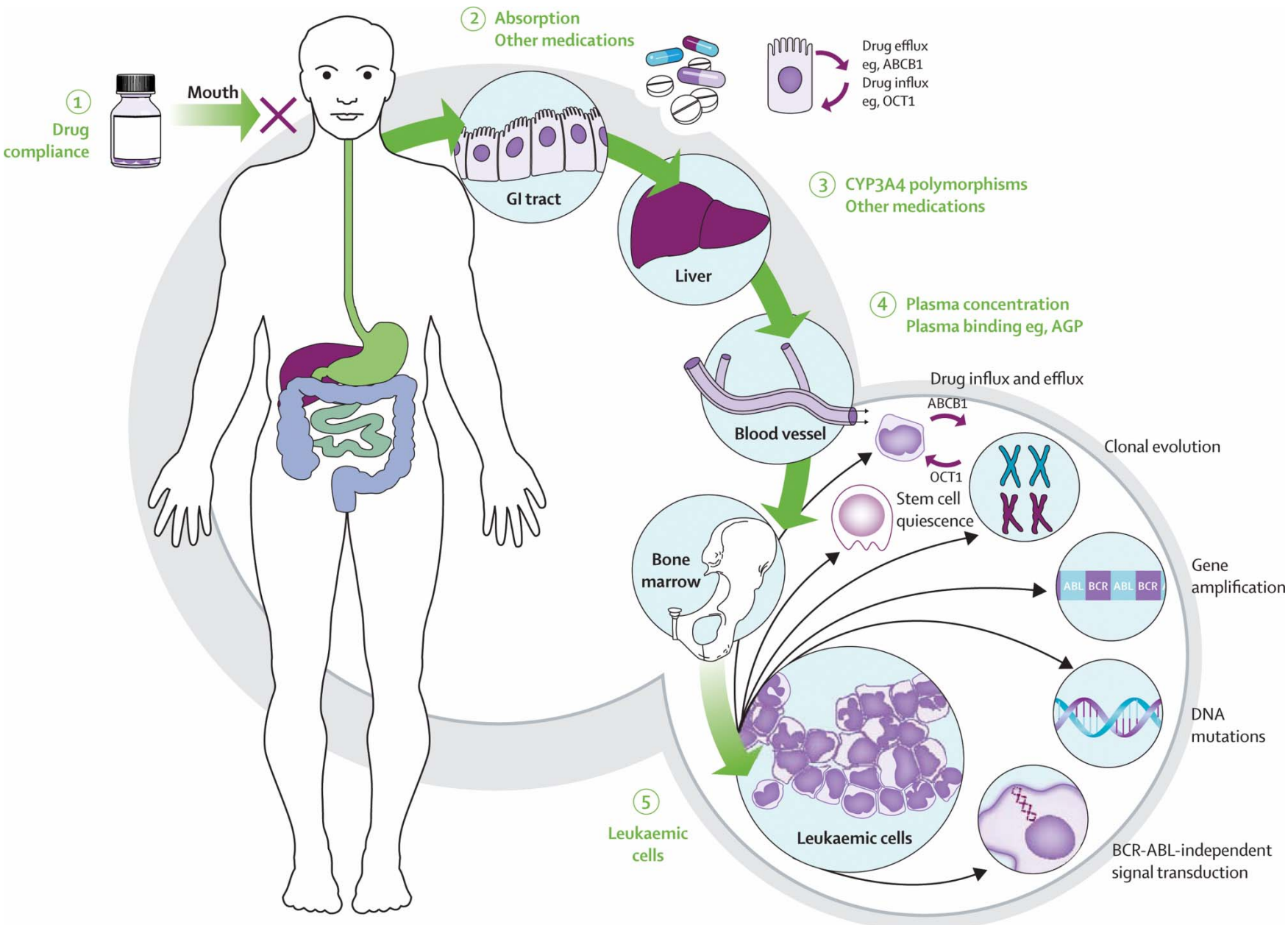
- CCyR + MMR at 18 months: 0% chance of progressing at 6 years[1]
- Level of molecular response associated with PFS[2]
- Early *BCR-ABL* transcript reduction may predict cytogenetic response[3,4]
- Use instead of cytogenetics or FISH to monitor response to TKI[5]
- Change therapy if the transcript levels rise[6]

1. Druker B et al. *N Engl J Med*. 2006;355-2408-2417;
2. Press RD et al. *Blood*. 2006;107:4250-4256;
3. Wang L et al. *Br J Haematol*. 2003;120:990-999; 4. Merx K et al. *Leukemia*. 2002;16:1579-1583;
5. Hughes T et al. *Blood*. 2006;108:28-37;
6. Wang L et al. *Haematologica*. 2006;91:235-239.

What Is a Significant Increase in *BCR-ABL1* Transcript Level That Would Prompt Change?

- Different results from different centers
  - Consecutive rises[1]
  - 2-fold rise[2]
  - 5-fold rise[3,4]
  - 10-fold rise[5]
- Changes may be more important at levels close to MMR 0.1%
- NCCN guideline: 1-log (10-fold) increase

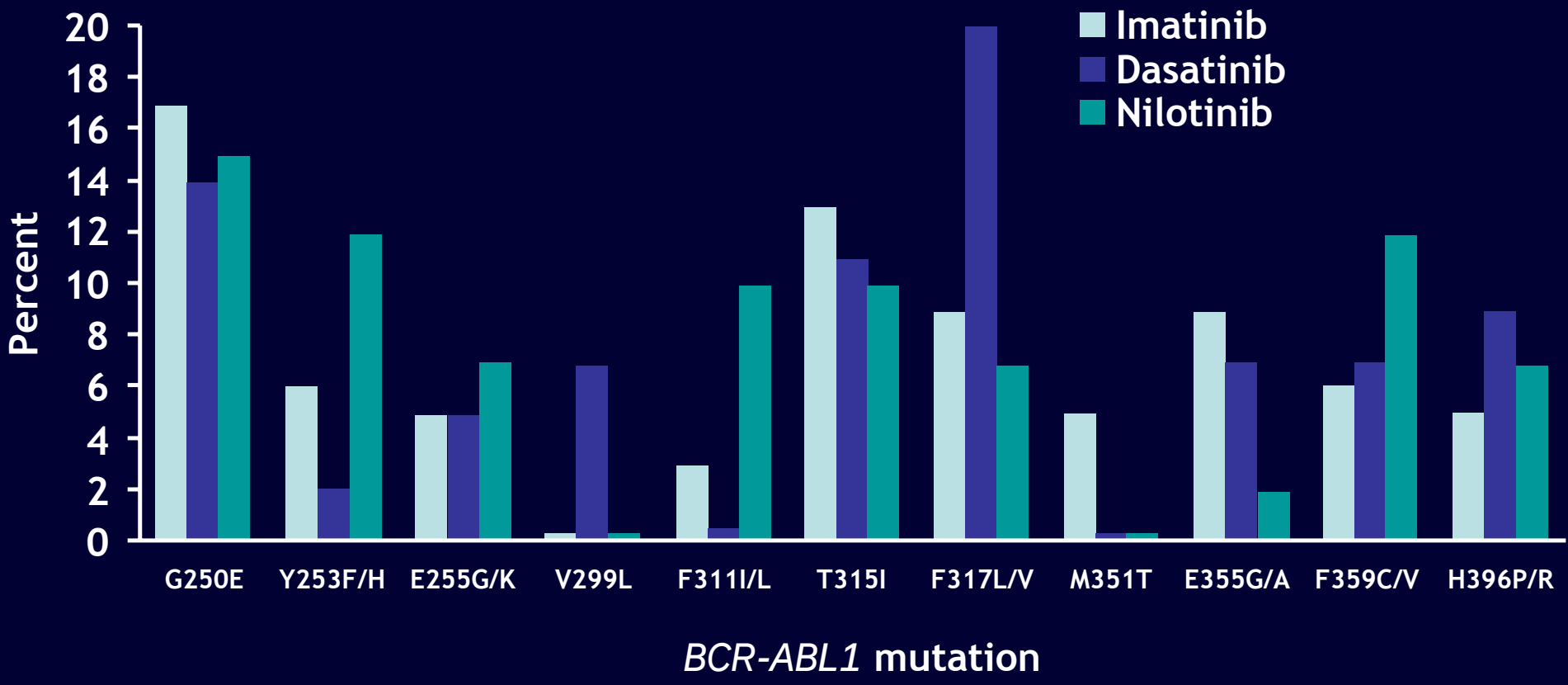
1. Wang L et al. *Haematologica*. 2006;91:235-239; 2. Branford S et al. *Blood*. 2004;104:2926-2932; 3. Baccarani M et al. *Blood*. 2006;108:1809-1820; 4. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp; 5. Cortes J et al. *Clin Cancer Res*. 2005;11:3425-3432.



ABCB1=ATP-binding competitor B1; AGP=alpha-1 acid glycoprotein;
CYP3A4=cytochrome P450 isoenzyme 4A; OCT1=organic cation transporter 1.

Apperley JF. *Lancet Oncol*. 2007;8:1018-1029.

Spectrum and Frequency of *BCR-ABL1* KD Mutations Detected After TKI Therapy



KD=kinase domain

Jabbour E et al. *Blood* 2006 (abstract 750)

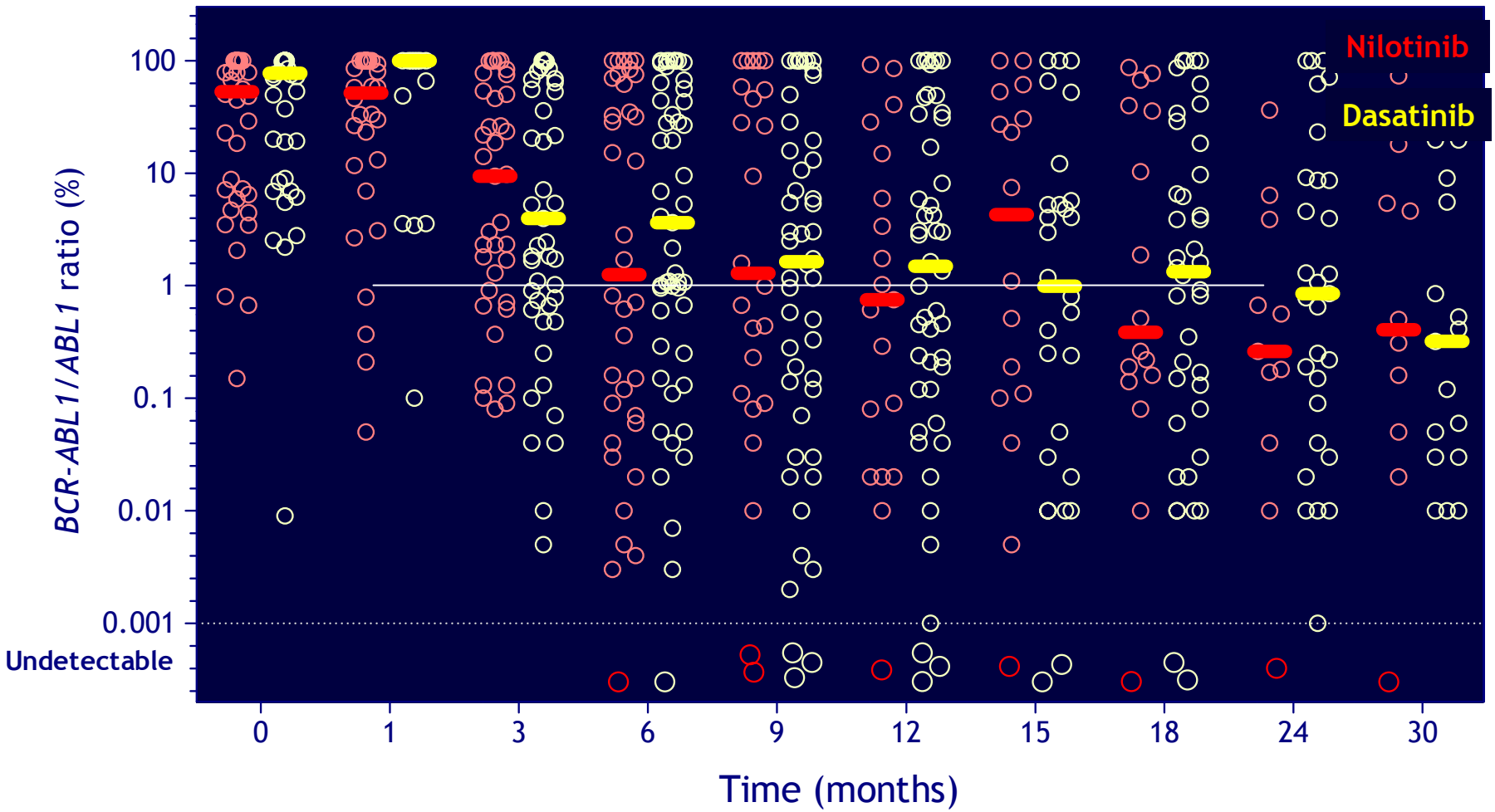
Imatinib vs SG ABL1 TKIs

	Imatinib	Dasatinib (BMS)	Bosutinib (SKI-606)	Nilotinib (AMN107)	INNO-406 (NS-187)
ABL1	X 1	X 300	X 30	X 20	X 55
active ABL1	-	+++	+++	-	+
inactive ABL1	+	+++	+++	++	++
PDGFR	+++	++	-	+	+
C-KIT	++	++	-	+	+/-
SRC	-	+++	++++	-	-
LYN	-	++	+++	-	+
CNS leukemia	-	+?	NA	-	Effective
Status	Approved	Approved	Phase 2-3	Approved	Phase 1-2

SG TKIs for Patients Resistant or Intolerant to Imatinib

TKI	CML Phase	No. of Patients	Response (%)			
			Cytogenetic			
			CHR	MCyR	CCyR	OS @ 24mo
Nilotinib	Chronic	321	77	55	42	91
	Accelerated	134	31	32	19	67
	BC	136	13	40	29	NA
	Ph^+ ALL	41	26	51	34	NA
Dasatinib	Chronic	387	91	62	53	94
	Accelerated	107	50	43	33	72
	Myeloid BC	116	26	34	27	26
	Lymphoid BC	6	29	52	46	20
Bosutinib	Chronic (resistant)	69	81	45	32	NA
	Chronic (intolerant)	33	82	51	40	NA

Molecular Response: Nilotinib vs Dasatinib 2nd line



Quintas-Cardama *et al*. Blood 112: ASH 2008

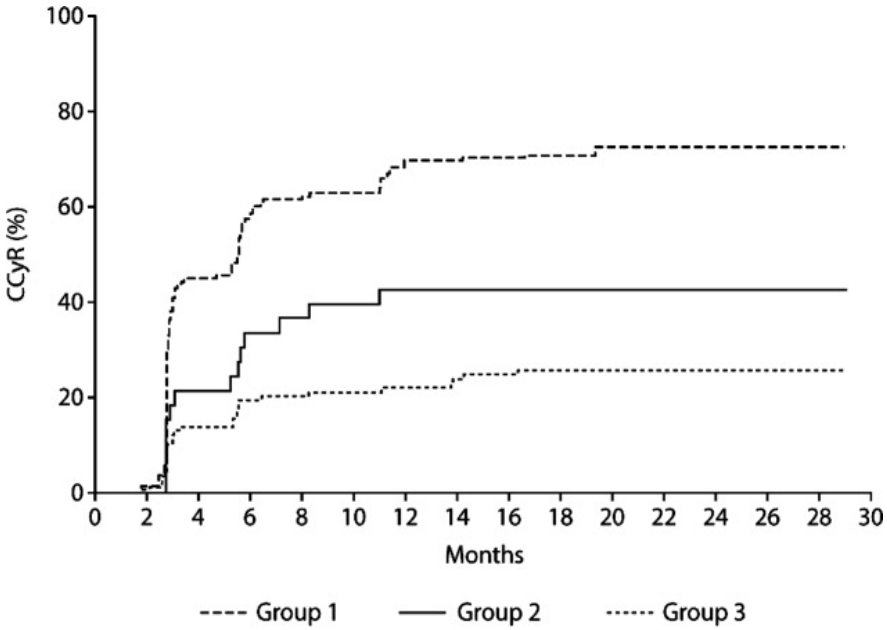
When Should Second Generation TKIs Be Started?

Dasatinib Early Intervention

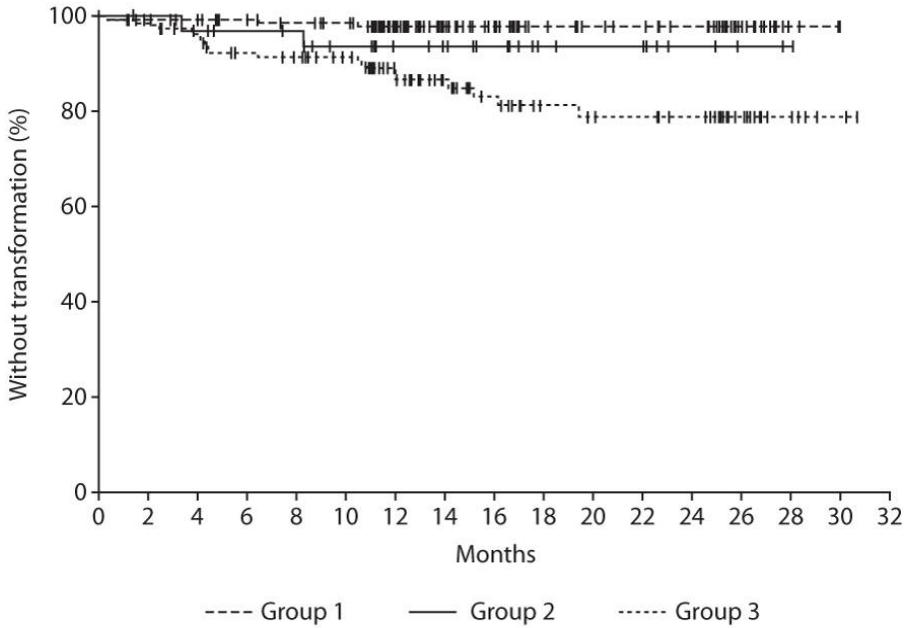
Variable	START-C (CA180-013)	START-R (CA180-017)	Optimization (CA180-034)
CML phase	CP	CP	CP
Median duration Rx (mo)	22.7	24.9	11.9
No. Pts with loss of response to IM	114	41	138
Loss of MCyR	47 (41)	19 (46)	85 (62)
Loss of CHR	50 (44)	20 (49)	39 (28)
Loss of CHR+MCyR	17 (15)	2 (5)	14 (10)
Median daily dose	112	128	100

Quintás-Cardama *et al* Cancer 2009

Dasatinib Early Intervention CCyR & TFS



Group	Responders/total
Group 1: loss of MCyR	108/151
Group 2: loss of MCyR and CHR	14/33
Group 3: loss of CHR	28/109



Group	Transformation/total	Median
Group 1: loss of MCyR	3/151	NR
Group 2: loss of MCyR and CHR	2/33	NR
Group 3: loss of CHR	17/109	NR

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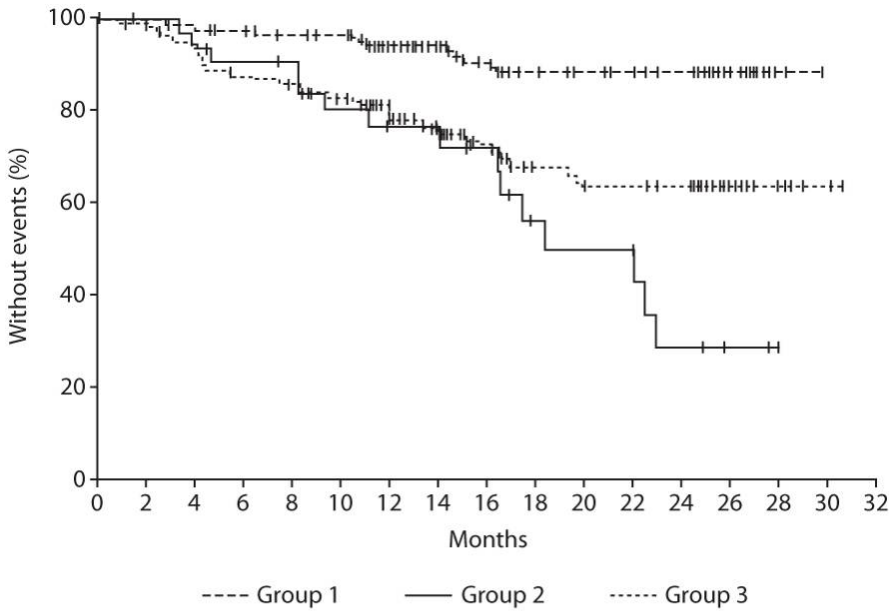
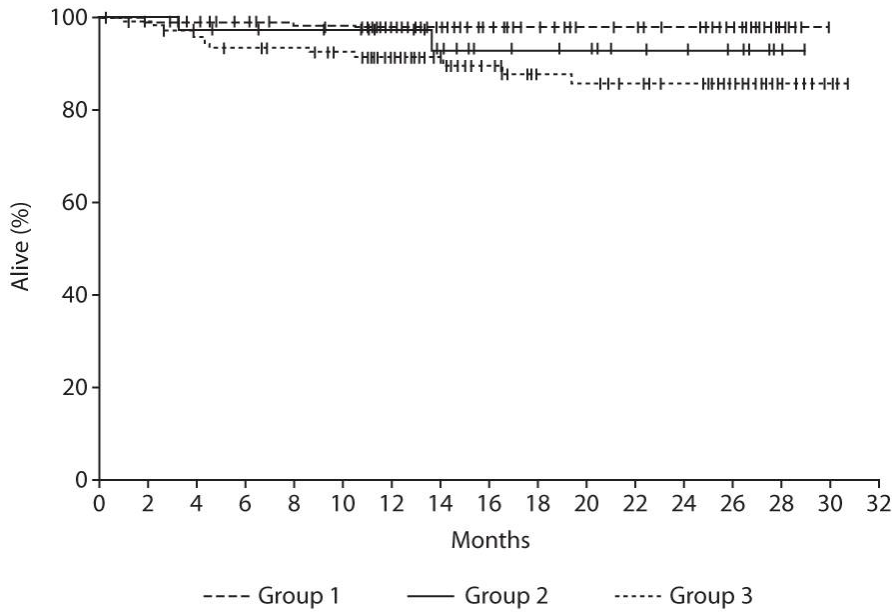
Dasatinib Early Intervention EFS & OS



Group	Events/total	Median
Group 1: loss of MCyR	12/151	NR
Group 2: loss of MCyR and CHR	15/33	18.5
Group 3: loss of CHR	31/109	NR



Group	Deaths/total	Median
Group 1: loss of MCyR	3/151	NR
Group 2: loss of MCyR and CHR	2/33	NR
Group 3: loss of CHR	12/109	NR

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Importance of Early Response to TKIs

Early Response with Imatinib in CML

- Response to imatinib improves over time
- Major CG response at 12, 18, or 24 months results in similar TFS rates

Druker *et al*. NEJM 2006; 355(23):2408-17

- PFS is similar in patients achieving a complete CG response before or after 12 months
  - Similar 4-year overall survival

Iacobucci *et al*. JCO 2006; 24(3):454-59

- EFS is equivalent regardless of the time at which CCyR is achieved

Guilhot et al. Blood 2007;110(11):(abstract 27)

Patient Characteristics (N=258)

Parameter	Category	No. Median	(%), or [range]
Age		48	[15-84]
% Ph+	>90	241	93
Clonal Evolution	Yes	7	3
Dose	400	50	19
	800	208	81
Sokal Risk Score	Low	165	64
	Intermediate	71	28
	High	22	8

Probability of CCyR and Progression if not in CCyR

Months on Rx	No. (%) not in CCyR	% Eventually achieving outcome if NOT in CCyR at specified time point		
		CCyR	MMR	Event*
3	109 (43)	75	62	23
6	47 (20)	57	43	34
9	26 (12)	42	31	38
p value		0.02	0.04	0.16

*Event: loss CHR, MCyR, doubling WBC, progression to AP/BP, death

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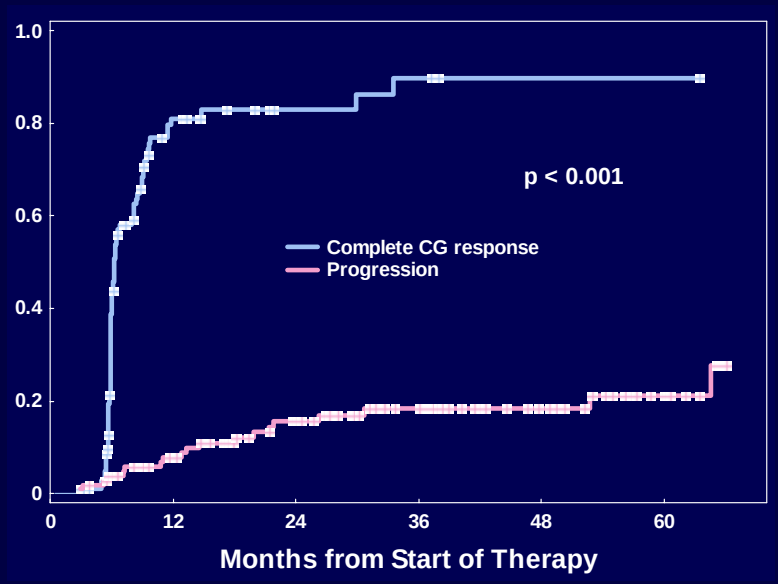
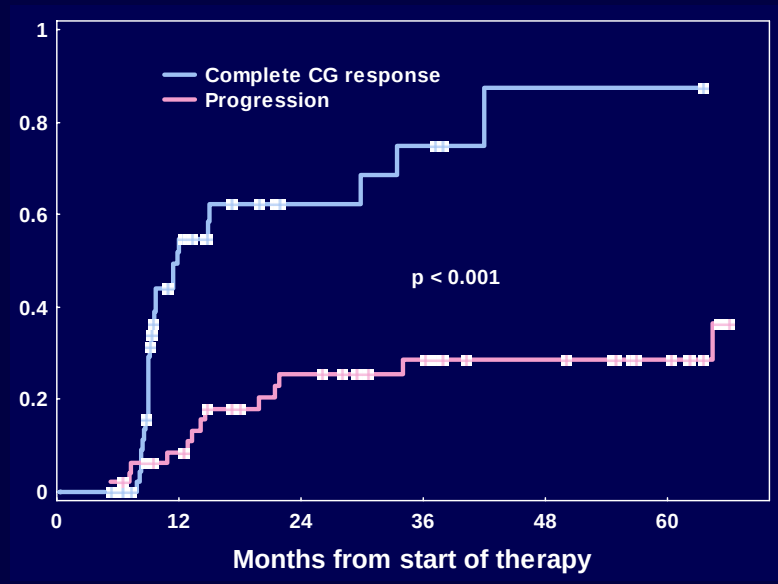
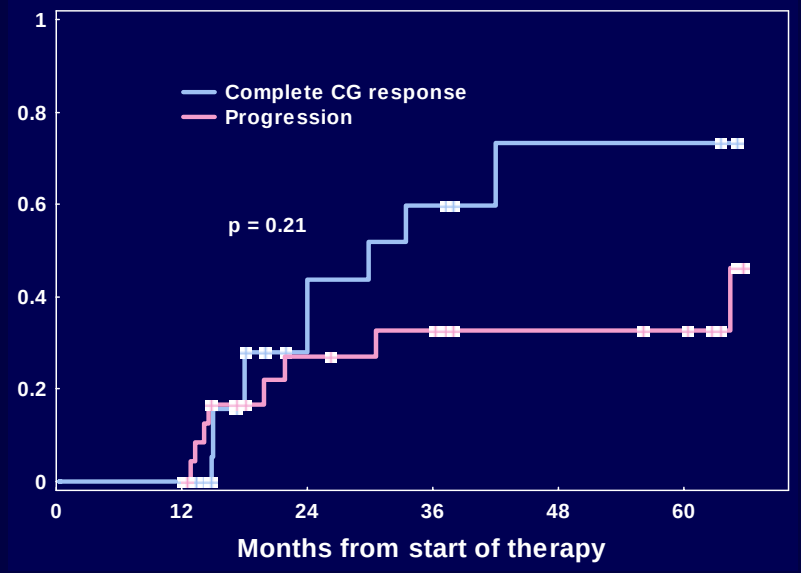
Probability of CCyR vs Progression if not in CCyR at 3, 6, or 12 months







Quintás-Cardama *et al* Blood 2009

Risk of Progression According to Molecular Response at 3 Months

Bcr-Abl/Abl (%)	No.	% eventually achieving					
		CCyR	*p*	MMR	*p*	Progression	*p*
≤0.1	24	96		100		4	
>0.1-1.0	63	98		84		3	
			<0.001		<0.001		0.05
>1.0-10.0	76	92		53		11	
>10.0	30	67		33		13	

Quintás-Cardama *et al* Blood 2009

Summary

- Failure to achieve a CCyR within 12 months of imatinib therapy is associated with higher rates of progression
- Risk discernible 3 months from imatinib start
- Early molecular responses improve outcome
- Strategies that render higher rates of early molecular response in frontline are desirable:
  - Interferon?
  - SG TKIs?

Imatinib vs Imatinib Combinations in CML ECP (SPIRIT Trial)

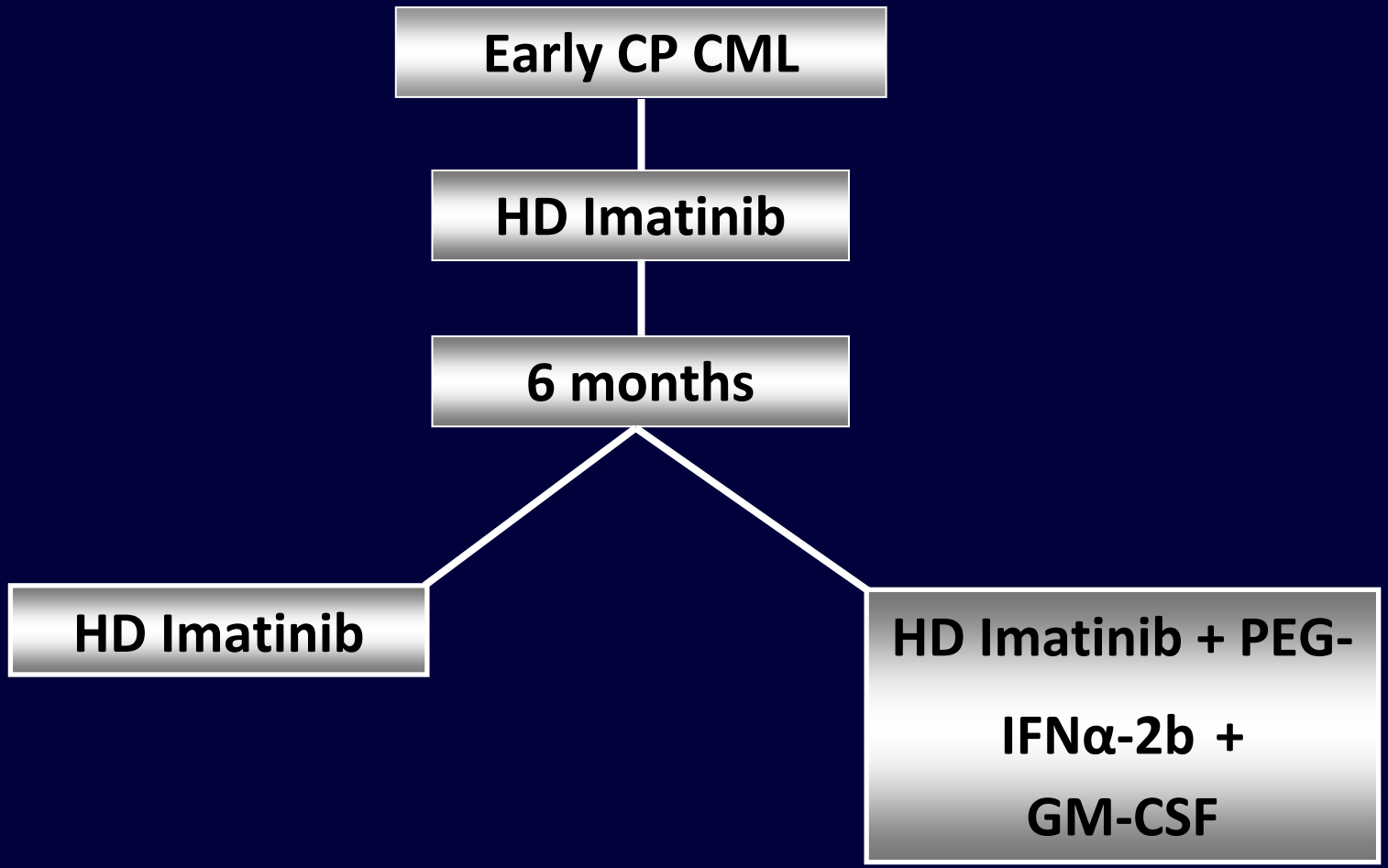
- 636 pts randomized to IM 400mg, IM 600mg, IM 400 + ara-C (20mgm^2/d, D15-28, 28-day cycles), IM 400 + PEG-IFNα (90 mcg/wk)
- Median FU: 36 months

		% Response			
		IM 400	IM 600	IM+AraC	IM+PEG-IFNα
6 mo	CCyR	48	67	55	56
	MMR	21	33	27	39
12 mo	CCyR	57	65	66	71
	MMR	40	52	51	61
	CMR	2	2	3	9

- Treatment discontinuation at 6 & 12 mo: IM+Ara-C 26% & 18%, PEG-IFNα 35% & 11%

Guilhot et al. Blood 2008 (abstract 183)

HDIM + PEG-IFNα-2b + GM-CSF



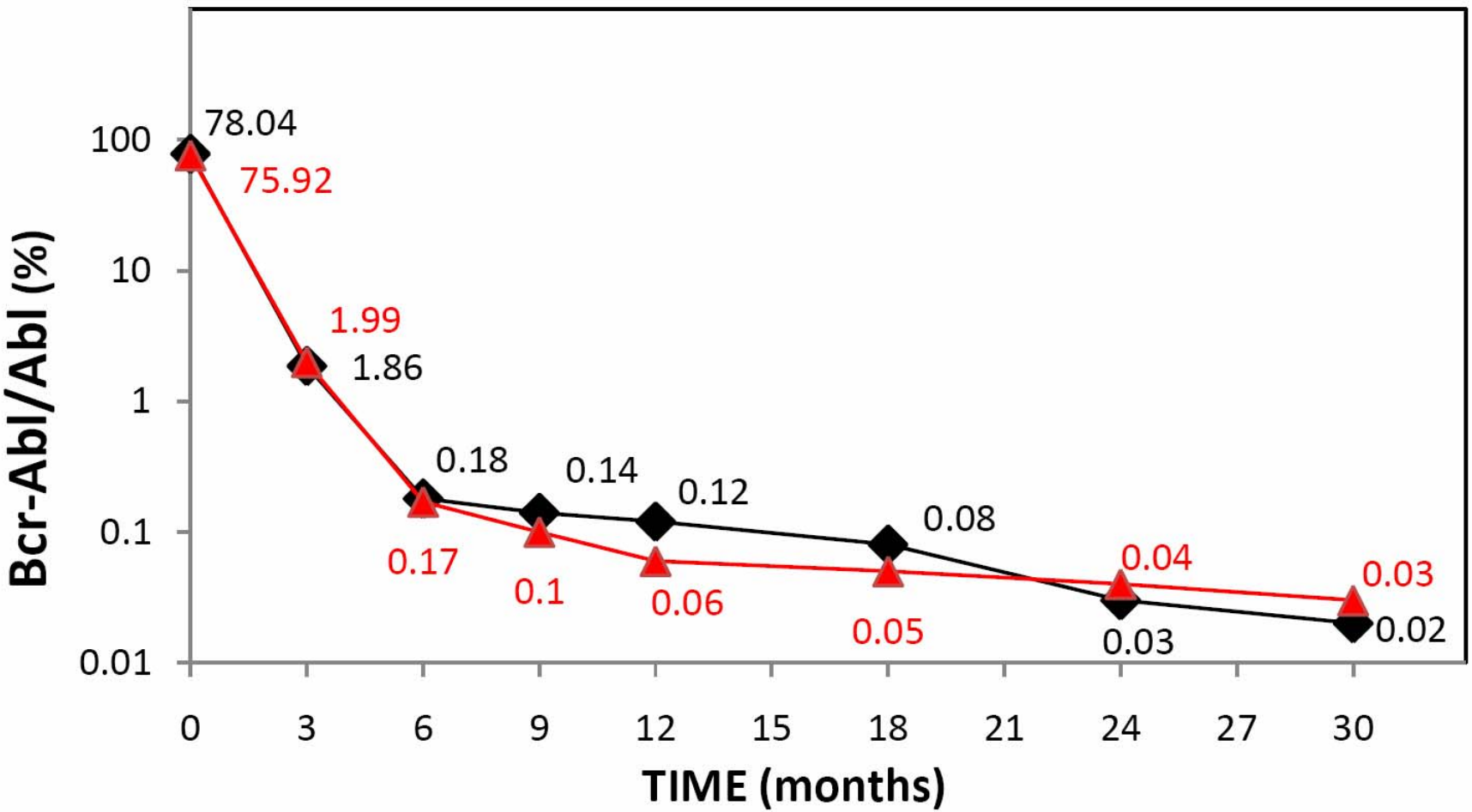
- Objective: Increase PCR negativity by 50% at 12 months

Cortes *et al* (submitted)

Patient Characteristics by Arm

Parameter		Median (range) or No (%) HDIM N=49	HDIM+PEG N=45
Age (y)		46 (19 – 73)	51 (19 – 79)
Hgb <12 g/dL		16 (33)	18 (40)
Plts >450 x 10^9/L		13 (27)	13 (29)
Spleen >0 cm		18 (37)	10 (22)
Pb blast >0%		23 (47)	22 (49)
Prior Imatinib		7 (14)	8 (18)
Sokal	Low	32 (65)	36 (80)
	Int	12 (24)	7 (16)
	High	5 (10)	2 (4)

HDIM ± PEG-IFNα-2b ± GM-CSF in CML CP: The MDACC Experience



Cortes *et al* (submitted)

Conclusions

1. Importance of close monitoring with CG and QPCR of patients with CML
2. Importance of detecting suboptimal responses to imatinib therapy
3. Importance of switching therapy from imatinib to a second generation TKI prior to loss of CHR

Leukemia Questions?

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