European LeukemiaNet

Imatinib dose intensification, combination therapies

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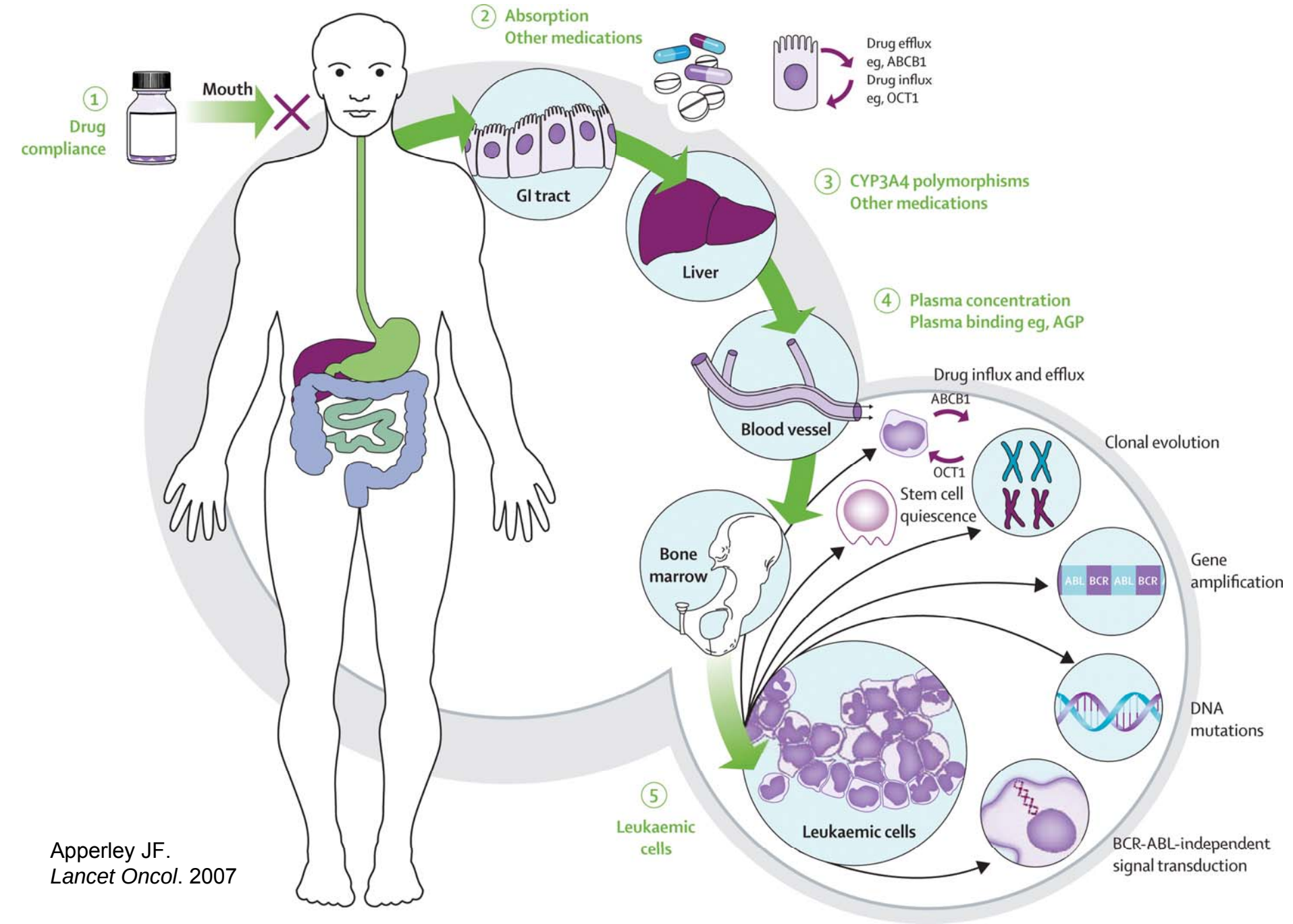
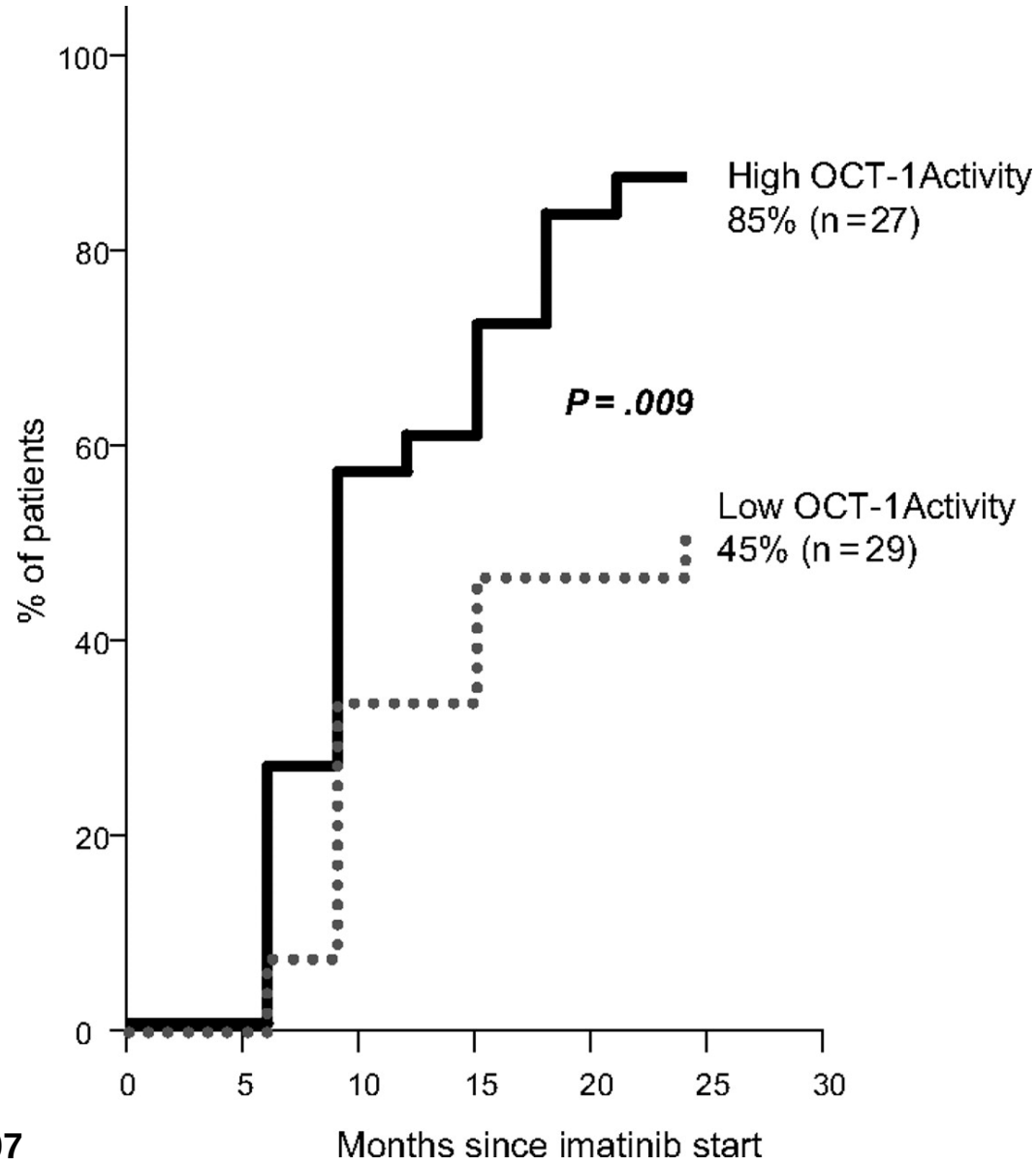


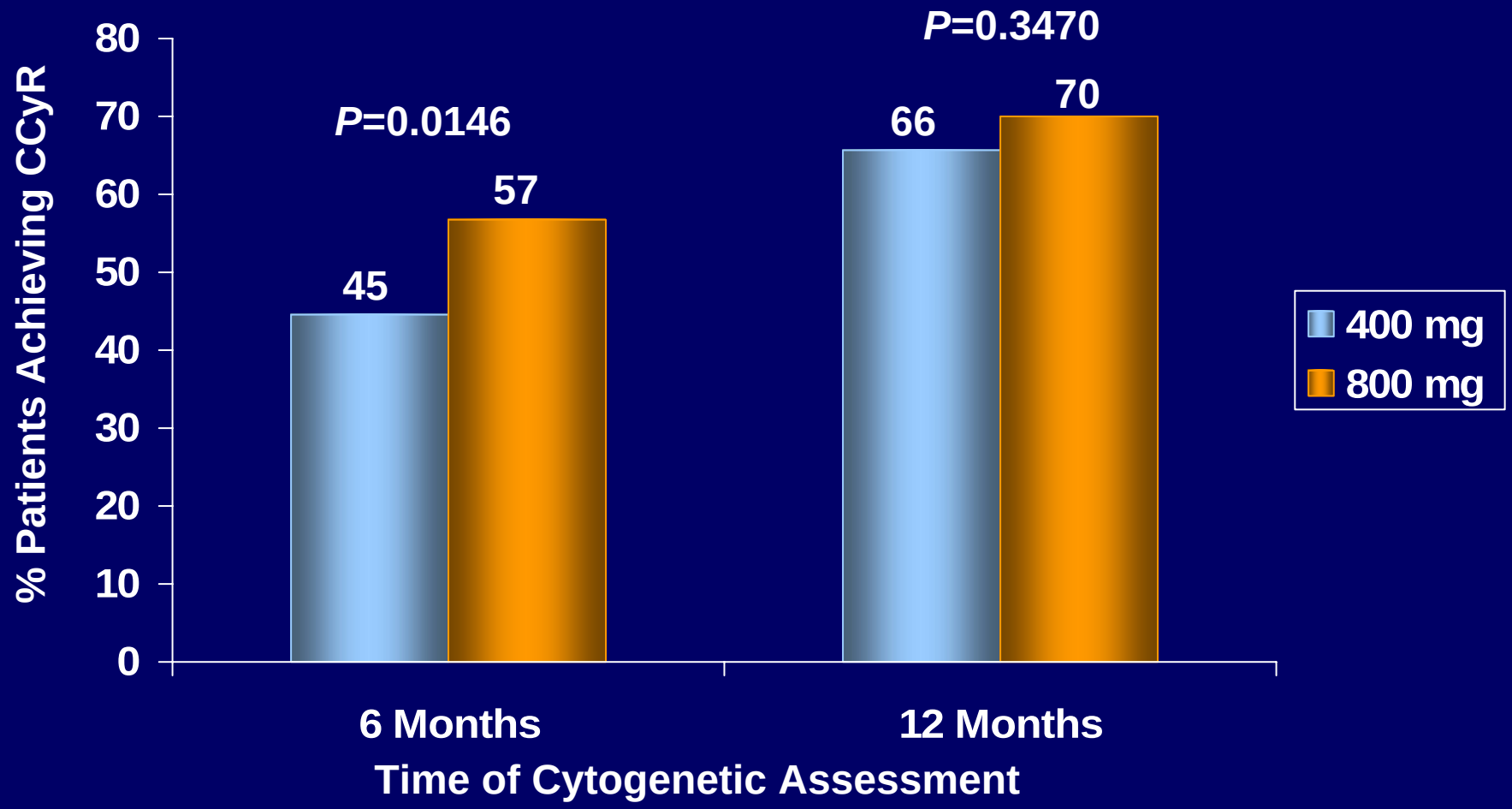
Apperley JF.
Lancet Oncol. 2007

High OCT-1 activity is associated with faster MMR in imatinib treated CML patients



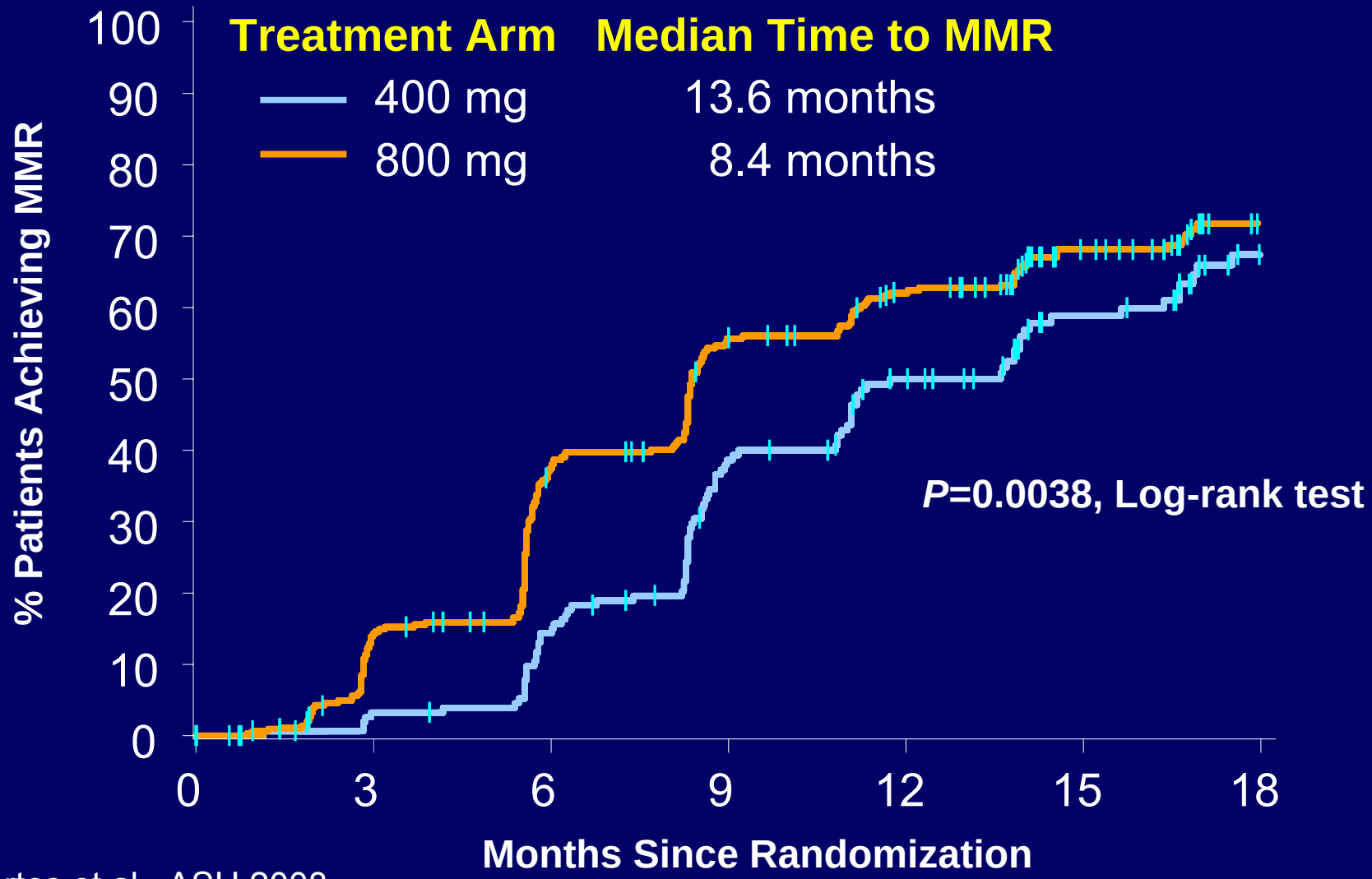
White DL et al. *Blood* 2007

Imatinib 400 mg vs 800 mg in CML-CP: Complete Cytogenetic Response Rates



Cortes et al., ASH 2008

Imatinib 400 mg vs 800 mg in CML-CP: Time to First MMR by Treatment Arm



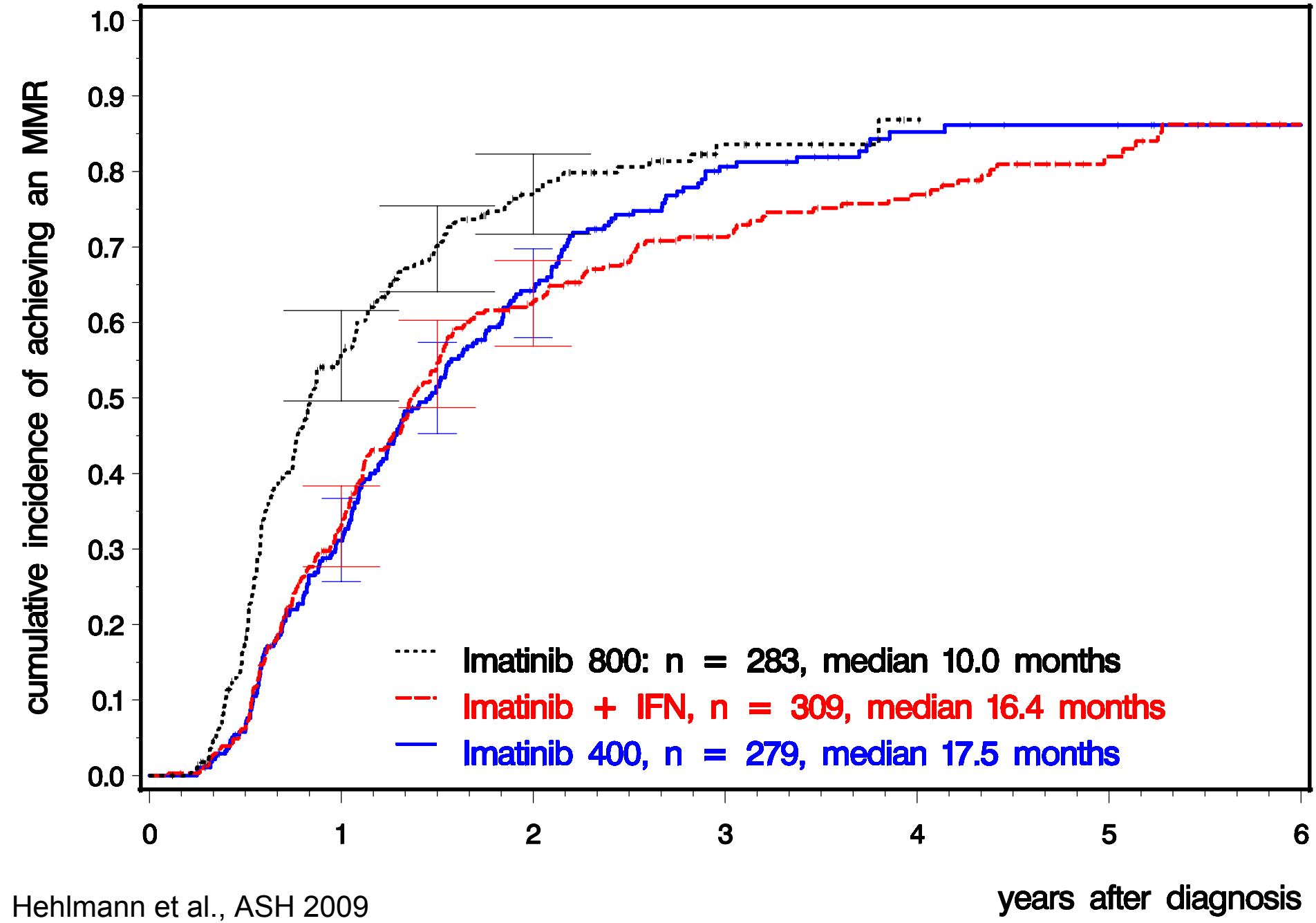
Cortes et al., ASH 2008

Imatinib 400 mg vs 800 mg in CML-CP: Patient Disposition at 12 Months

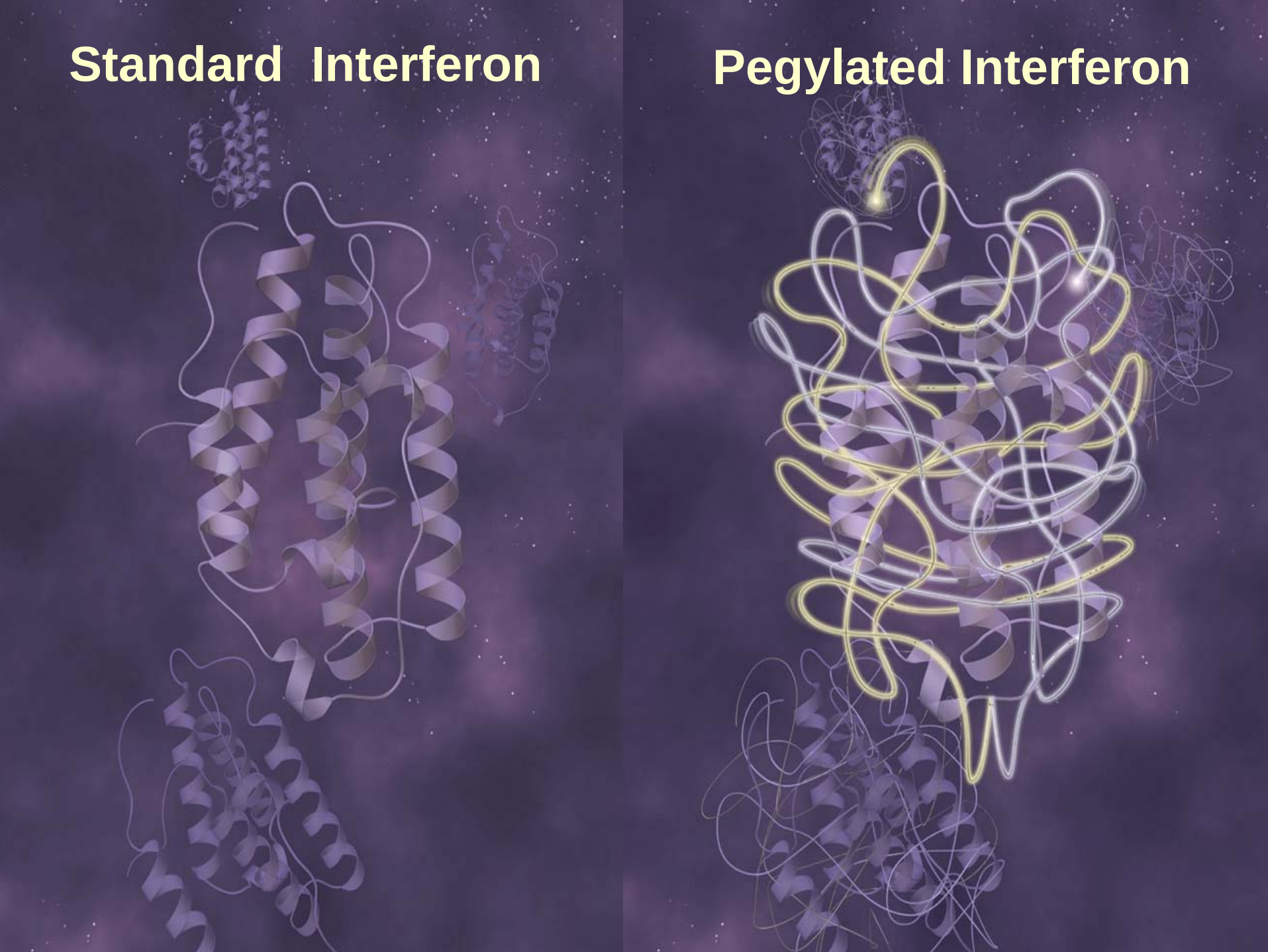
Disposition	No. (%)	
	400 mg N=157	800 mg N=319
Still on treatment	145 (92.4)	288 (90.3)
Discontinued treatment	12 (7.6)	31 (9.7)
Adverse events	2 (1.3)	18 (5.6)
Abnormal laboratory values	1 (0.6)	1 (0.3)
Unsatisfactory therapeutic effect	6 (3.8)	6 (1.9)
Protocol violation	2 (1.3)	1 (0.3)
Subject withdrew consent	0	2 (0.6)
Lost to follow-up	0	2 (0.6)
Administrative problems	1 (0.6)	1 (0.3)

Cortes et al., ASH 2008

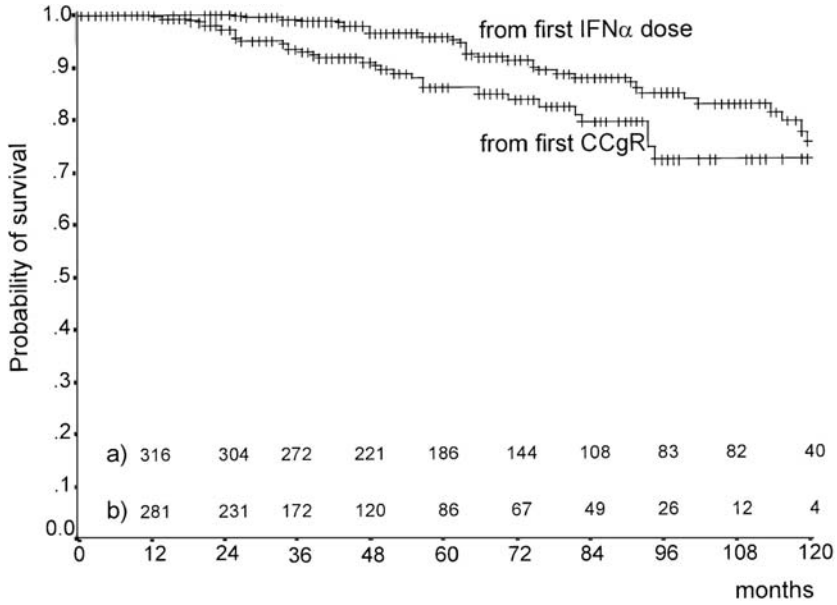
German CML IV Trial: Time to MMR by therapy

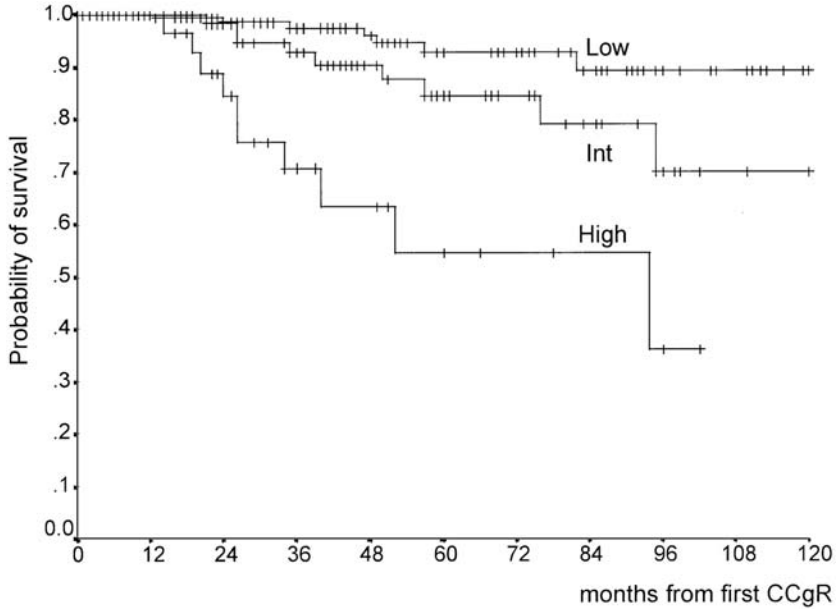


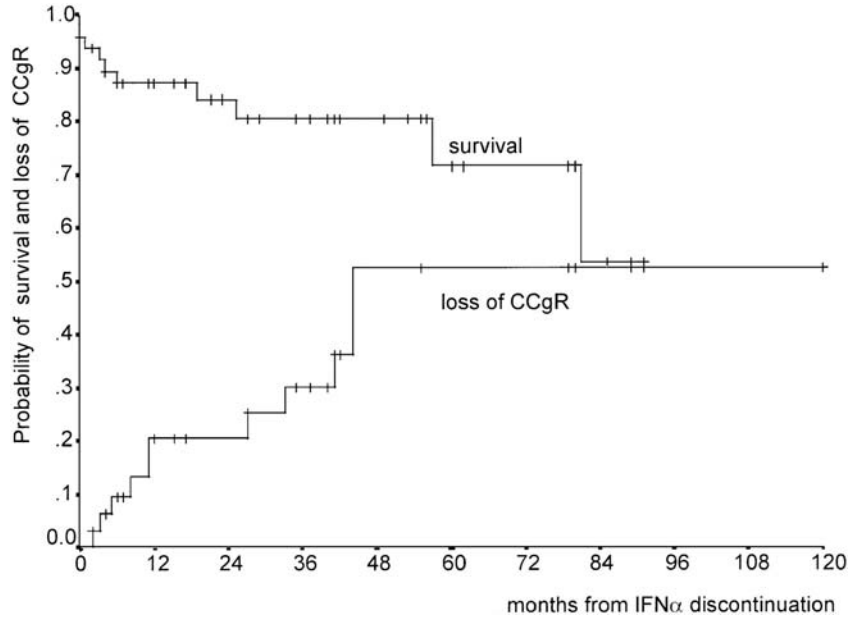
Hehlmann et al., ASH 2009


Standard Interferon
Pegylated Interferon

CCyR after IFN α therapy – EICML metaanalysis

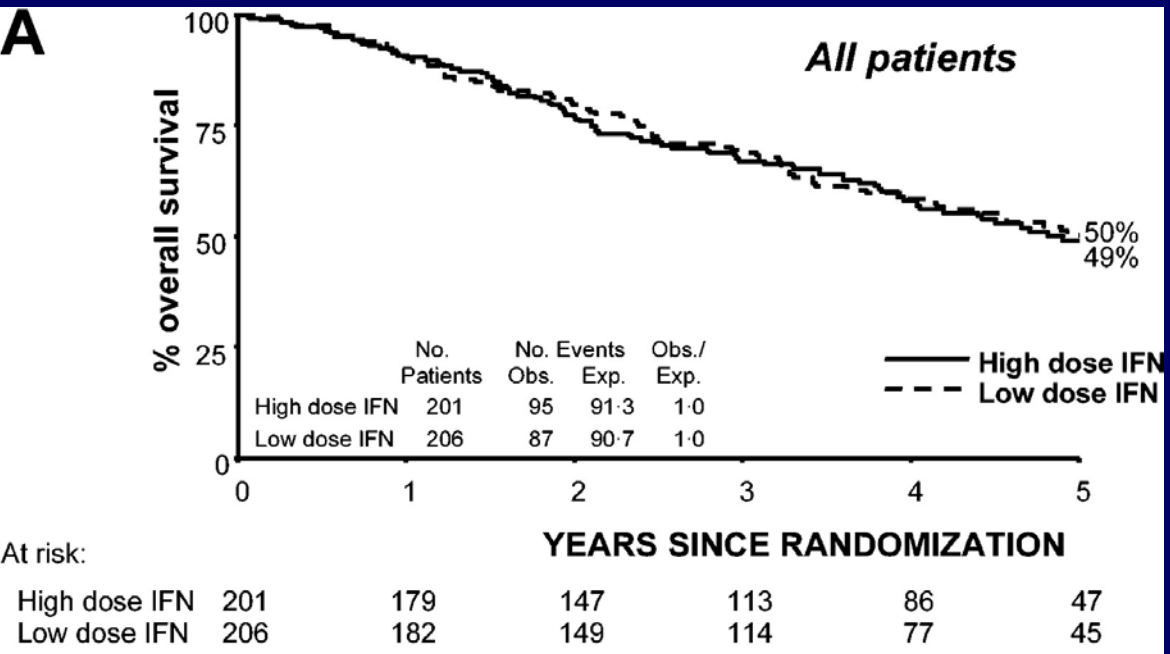


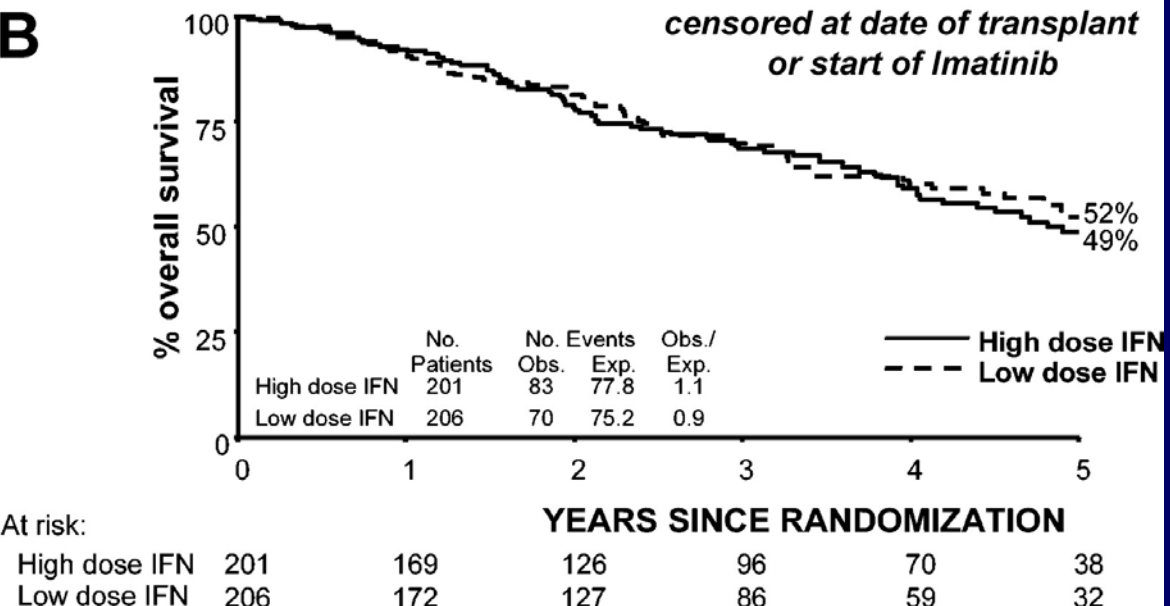




Bonifazi, F. et al. Blood 2001;98:3074-3081

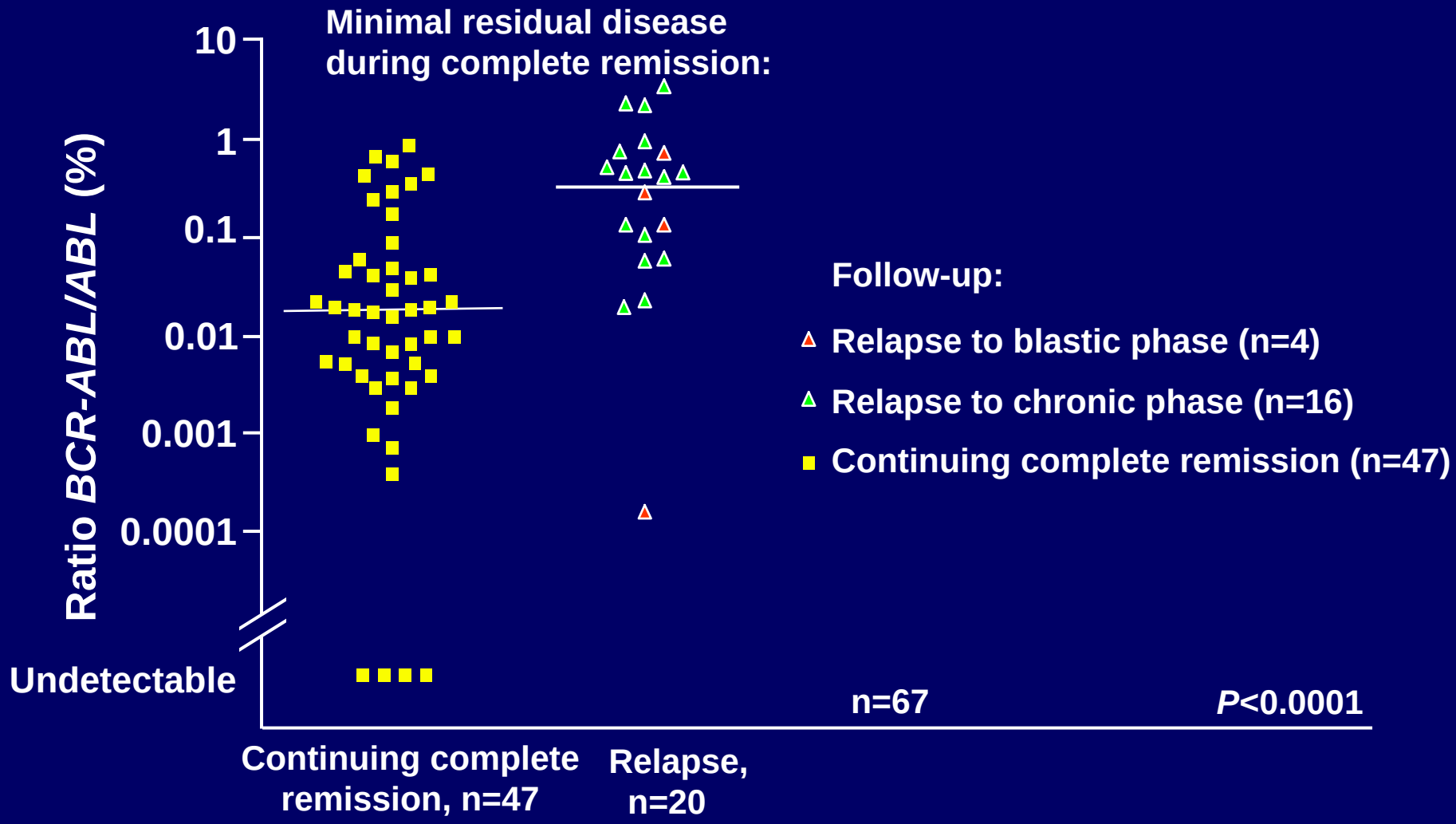
High vs. low dose IFN





Kluin-Nelemans et al. Blood 2004

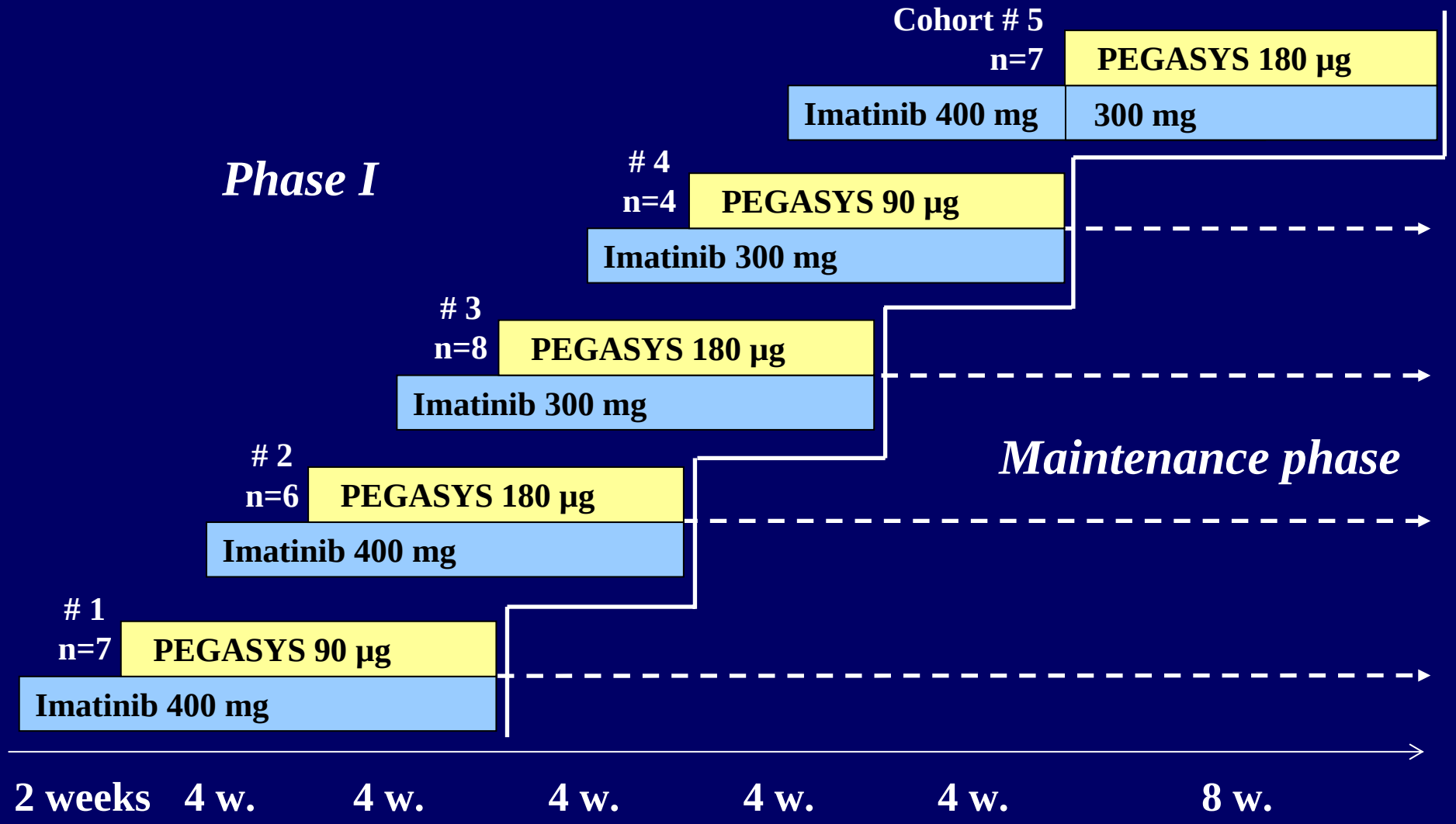
MRD Levels Predict Relapse After IFN-α Induced CCR



MRD = minimal residual disease; CCR = complete cytogenetic response.

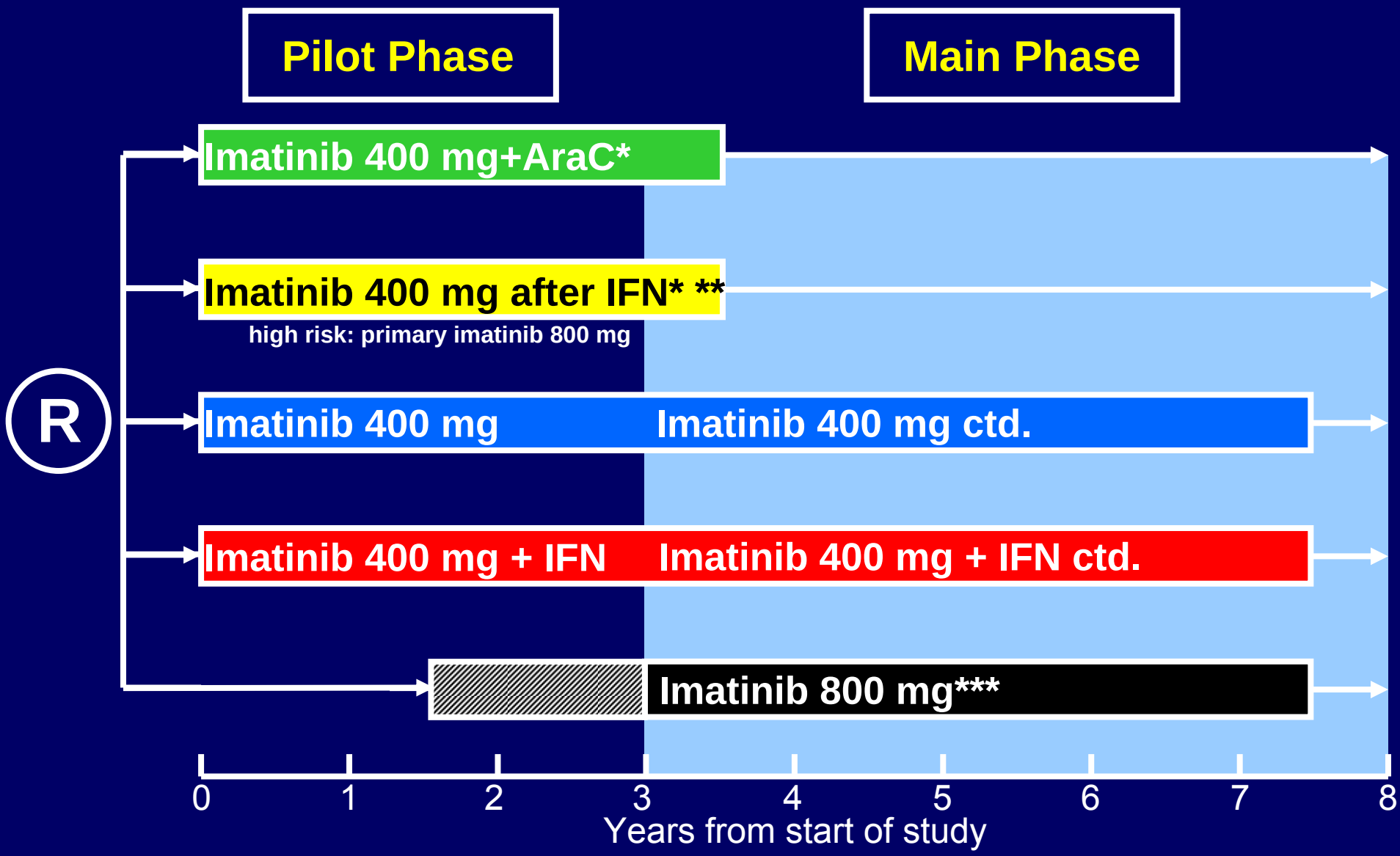
Hochhaus et al. *Blood*. 2000.

Phase I/II Imatinib + Pegasys combination study



Hochhaus et al., ASH 2005

Imatinib vs. combinations, high dose imatinib ± transplantation
CML Study IV, n=1400 (Hehlmann et al., ASH 2009)



* Recruitment terminated 7-11/2005; ** no high risk patients; *** Full recruitment started 7/2005

*Median dose per actual therapy day**

Imatinib 400 mg:	**400 mg/d (277-720 mg/d)**
Imatinib 400 mg+IFN:	**Imatinib: 400 mg/d (184-608 mg/d)** **IFN: 1.7 Mio I.U./d (0.4-6.0 Mio I.U./d)**
Imatinib 800 mg:	**646 mg/d (209-800 mg/d)**

*** IFN 3 days/week (imatinib+IFN)**

Hehlmann et al., ASH 2009

Adverse events

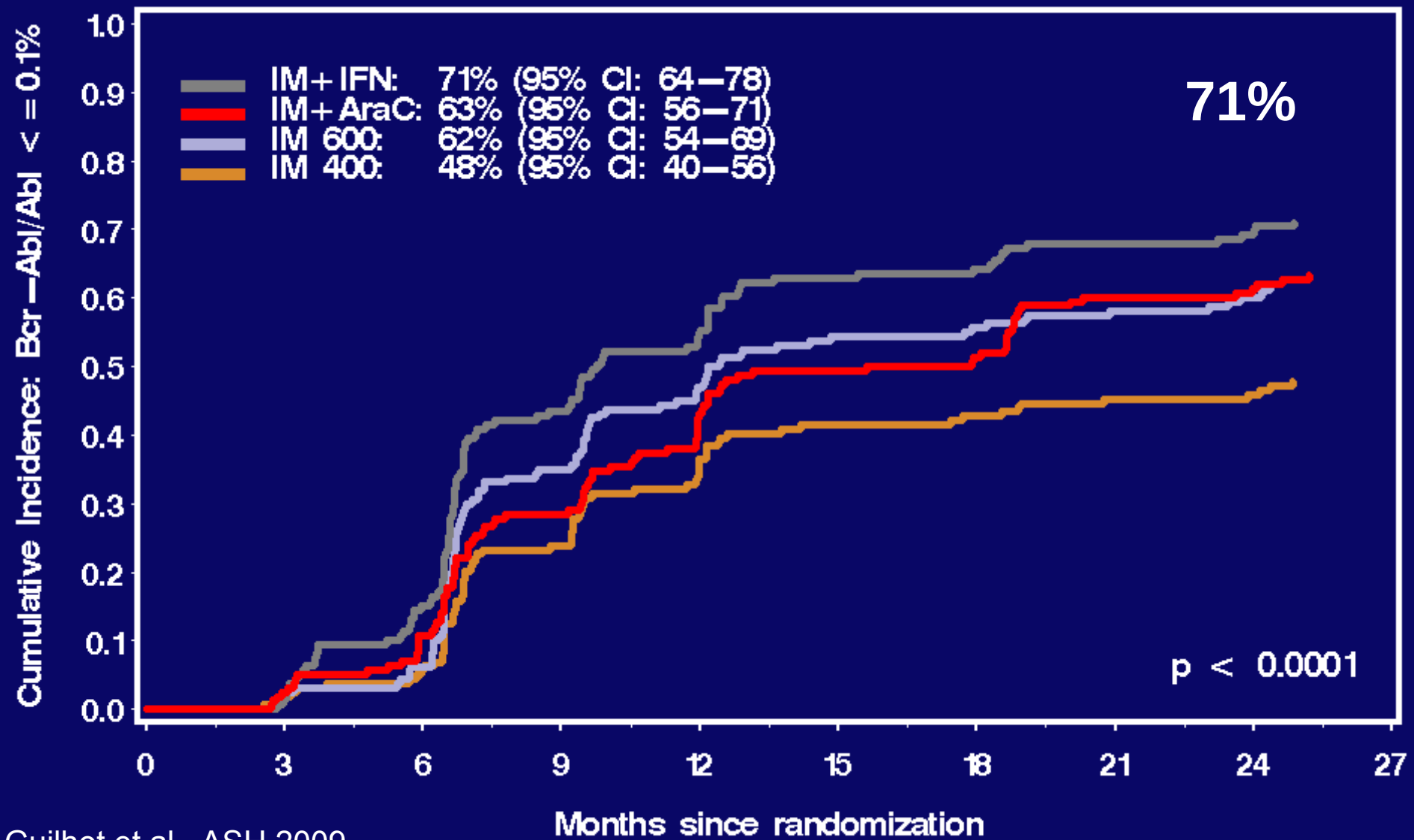
(WHO grade I-IV, total time of therapy)

	IM 800 mg n=240	IM 400 mg n=276	IM 400 mg + IFN n=280
Edema	33%	26%	20%
Myalgia	23%	20%	19%
Neurological AEs	12%	14%	21%
Gastrointestinal AEs	42%	29%	30%
Fatigue	15%	12%	19%

Hehlmann et al., ASH 2009

Major Molecular Responses at 24 months

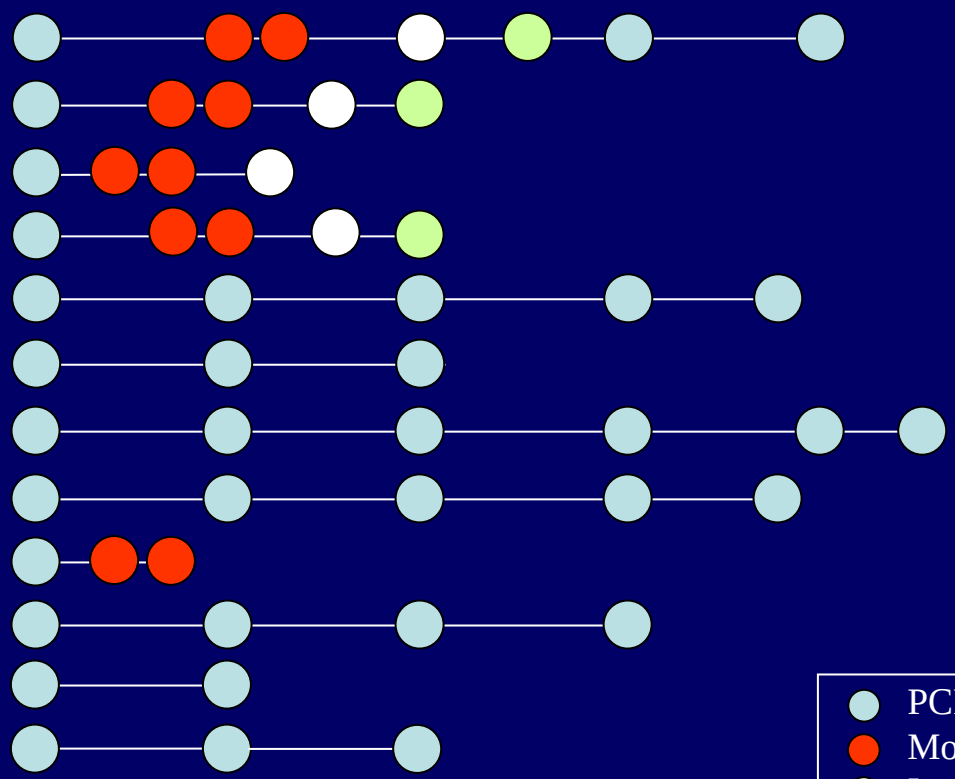
BCR-ABL/ABL ≤ 0.1% IS - 636 patients *(ITT)*



Guilhot et al., ASH 2009

Continuous molecular remission after imatinib withdrawal in case of IFN pretreatment

Pts	IFN (months)	Sokal
1	0	L
4	0	L
8	9	H
11	29	I
10	29	I
12	29	I
3	32	I
6	33	L
9	63	
2	67	L
7	71	L
5	153	I

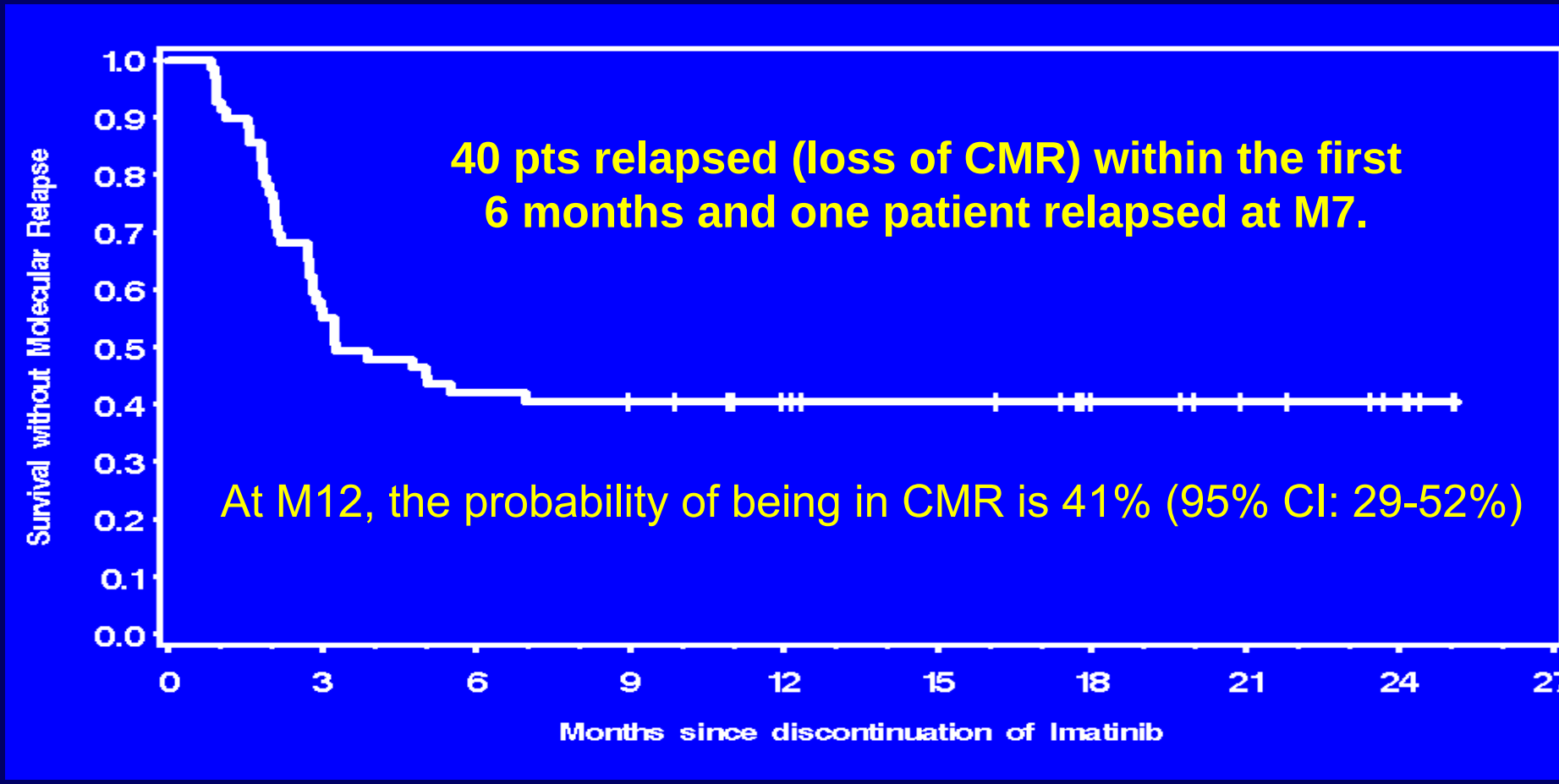


Rousselot et al. *Blood 2007*

STop IMatinib study

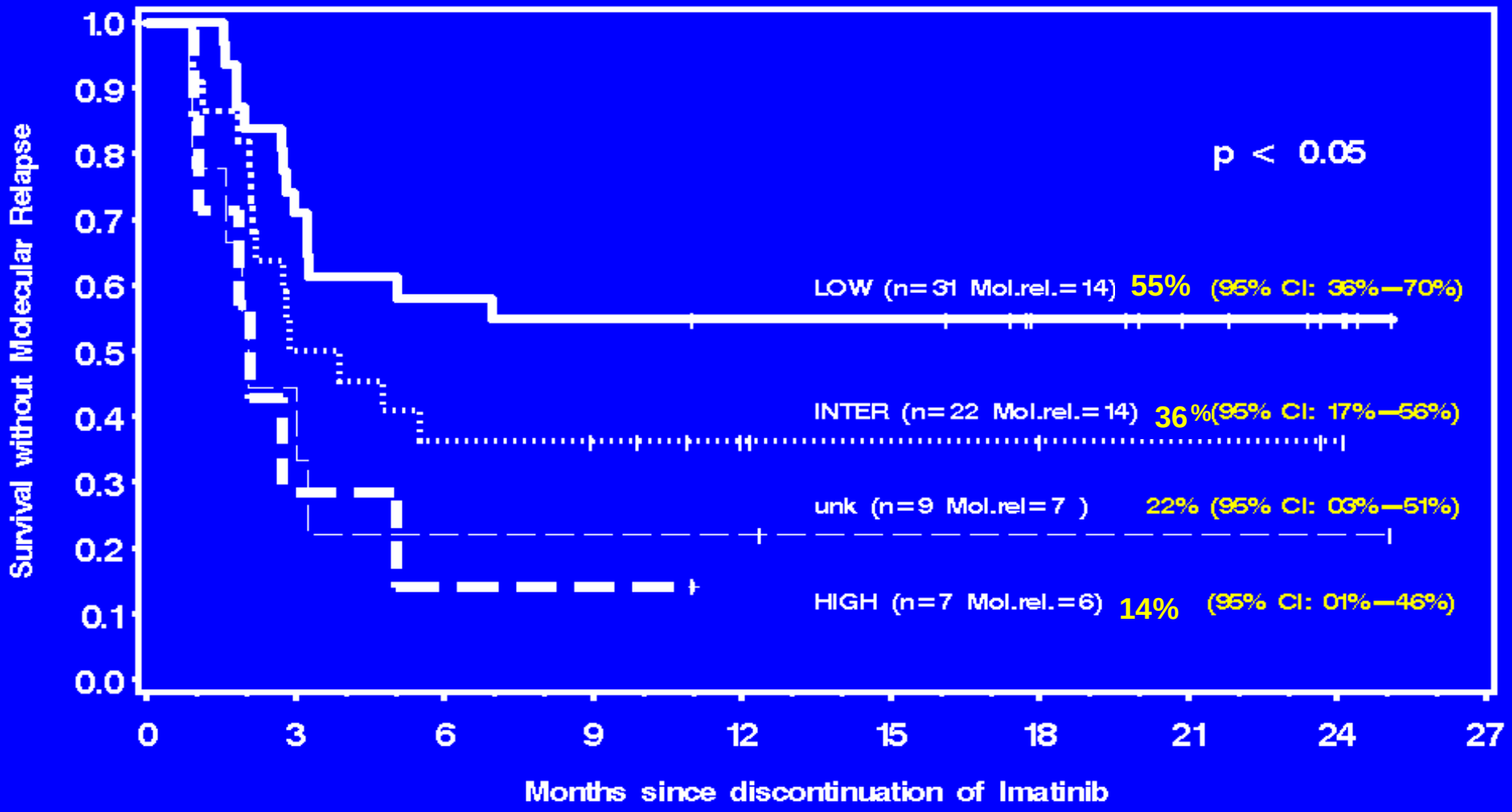
(MULTICENTER TRIAL ESTIMATING THE PERSISTANCE OF MOLECULAR REMISSION IN CML AFTER STOPPING IMATINIB)

(ClinicalTrials.gov number, NCT00478985 [ClinicalTrials.gov])



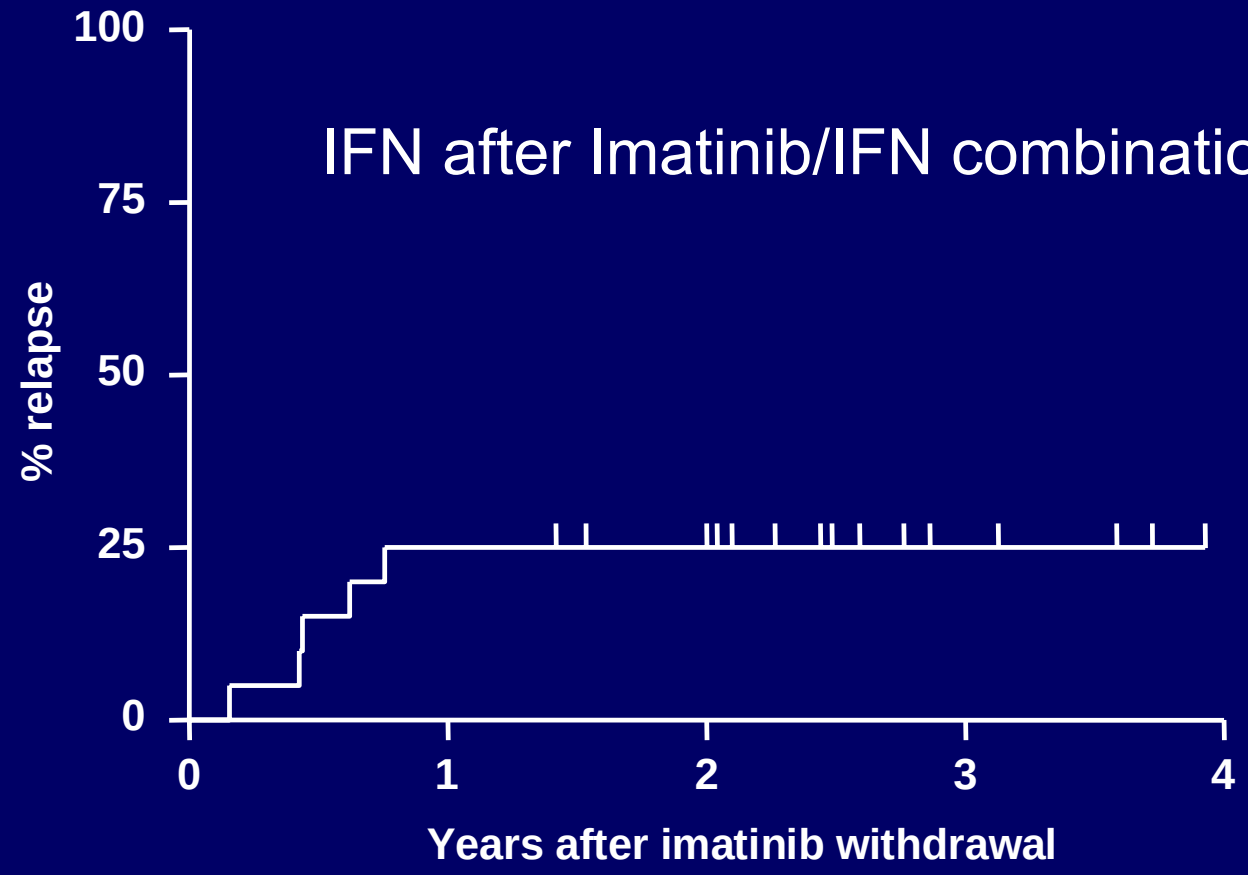
Mahon et al., ASH 2009

STIM Study: Results according to Sokal score



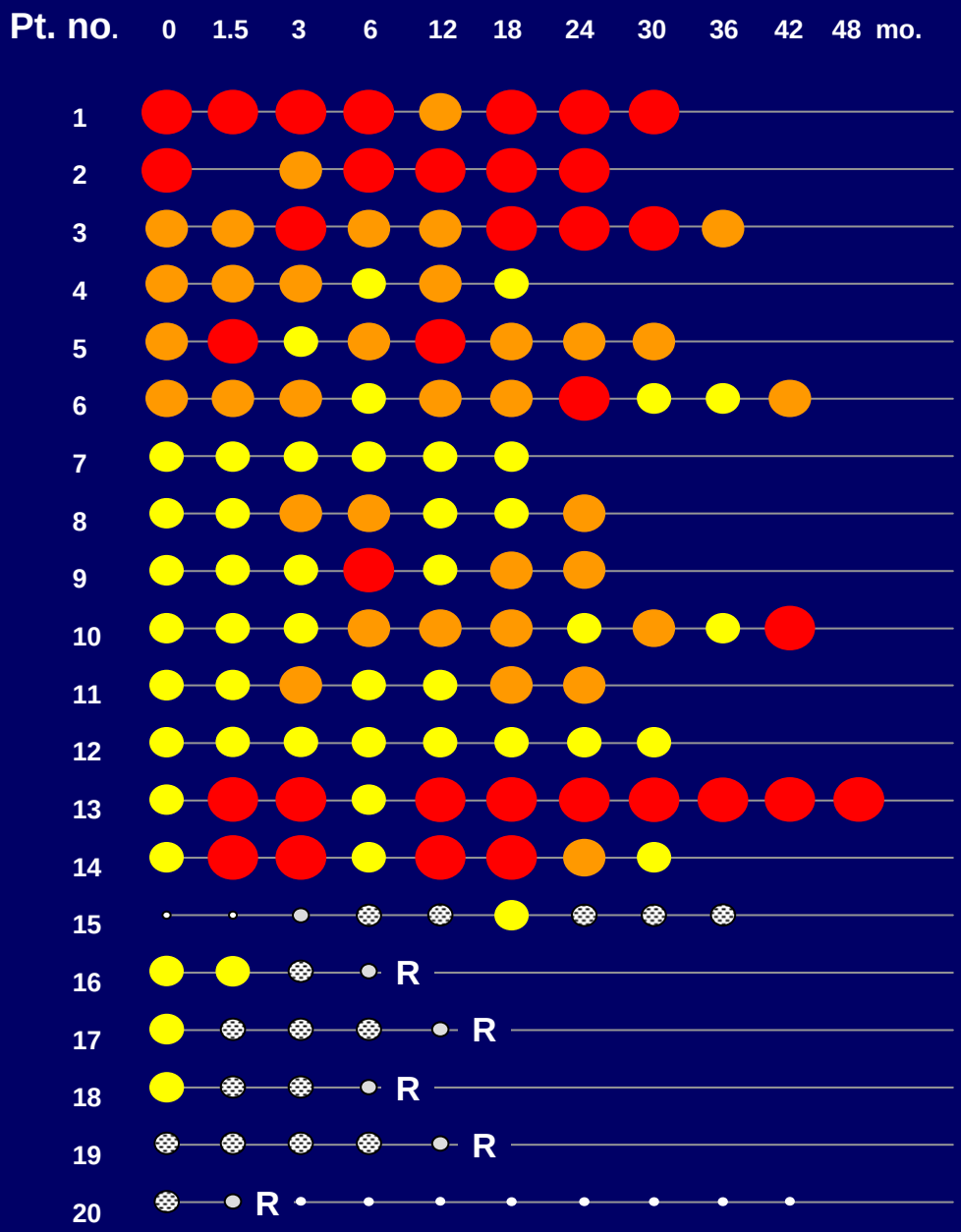
Mahon et al., Blood (ASH Annual Meeting Abstracts), Nov 2009; 114: 859

Stable remission on IFN maintenance therapy (n=20) after imatinib withdrawal



Burchert et al., JCO 2010

Level of residual disease at stop of imatinib and during IFN maintenance therapy



Complete molecular remission, CMR

BCR-ABL ≤0.01%

≤0.1%

≤1%

≤10% = Relapse, R

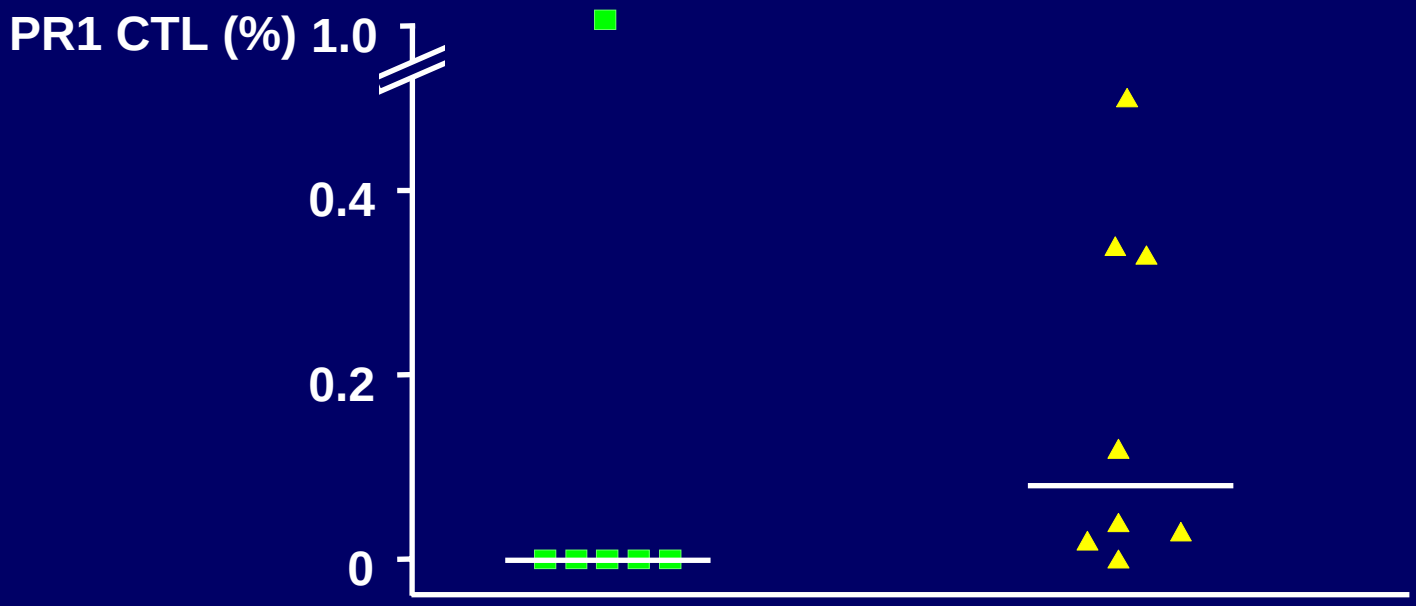
≥10%

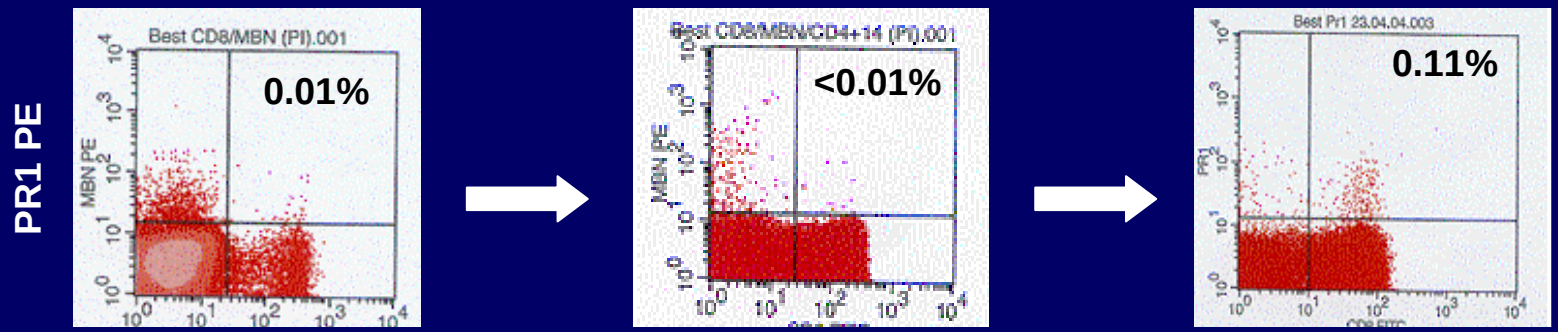
Burchert et al., JCO 2010

Increase of the proportion of PR1 cytotoxic T lymphocytes on IFN monotherapy.

n=9

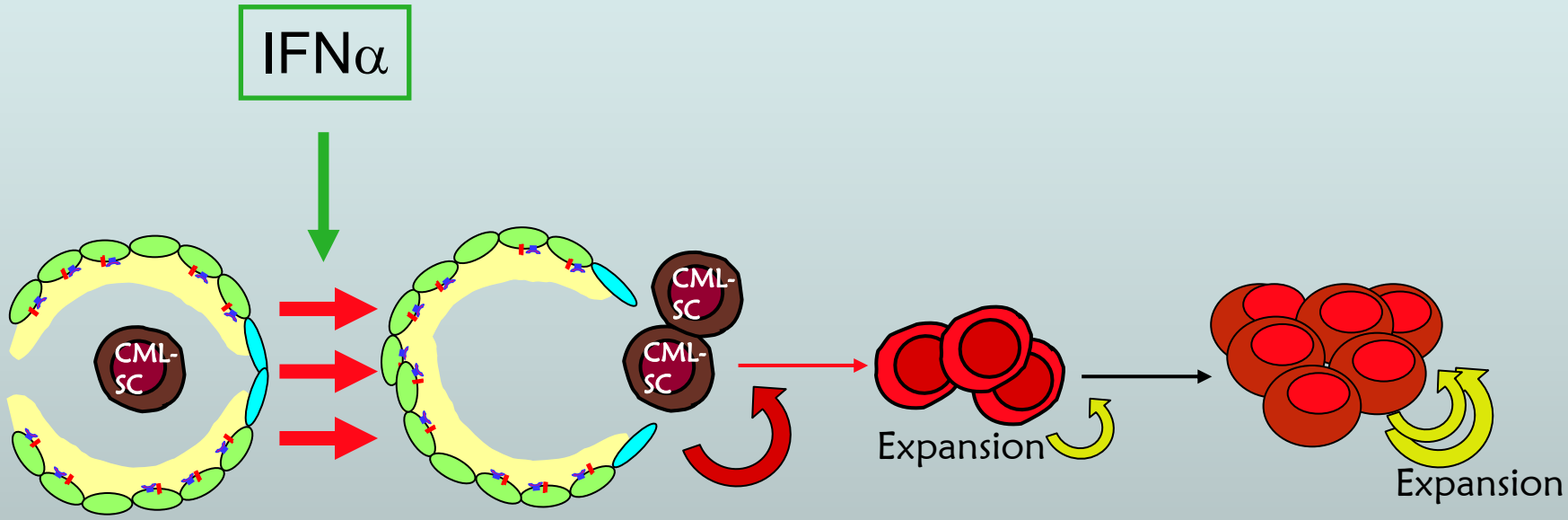
HLA A2+ patients





Burchert et al., JCO 2010

IFNα may also activate dormant CML stem cells making them sensitive to imatinib



Dormant CML-SCs are resistant to imatinib

Activated CML-SCs may be sensitive to imatinib

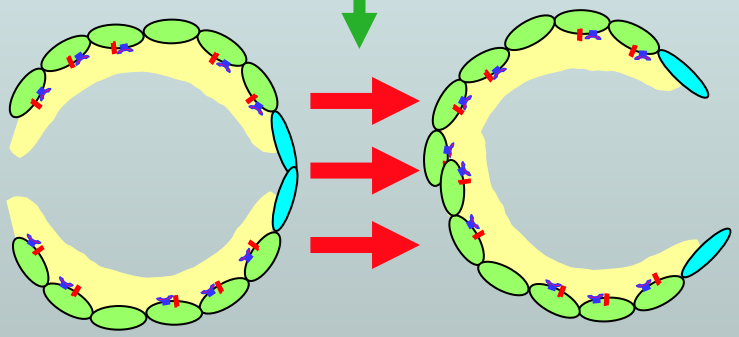
More differentiated CML cells are effectively eliminated by imatinib

M. Essers et al. Nature, 2009

IFNα may also activate dormant CML stem cells making them sensitive to imatinib

IFNα priming

Imatinib

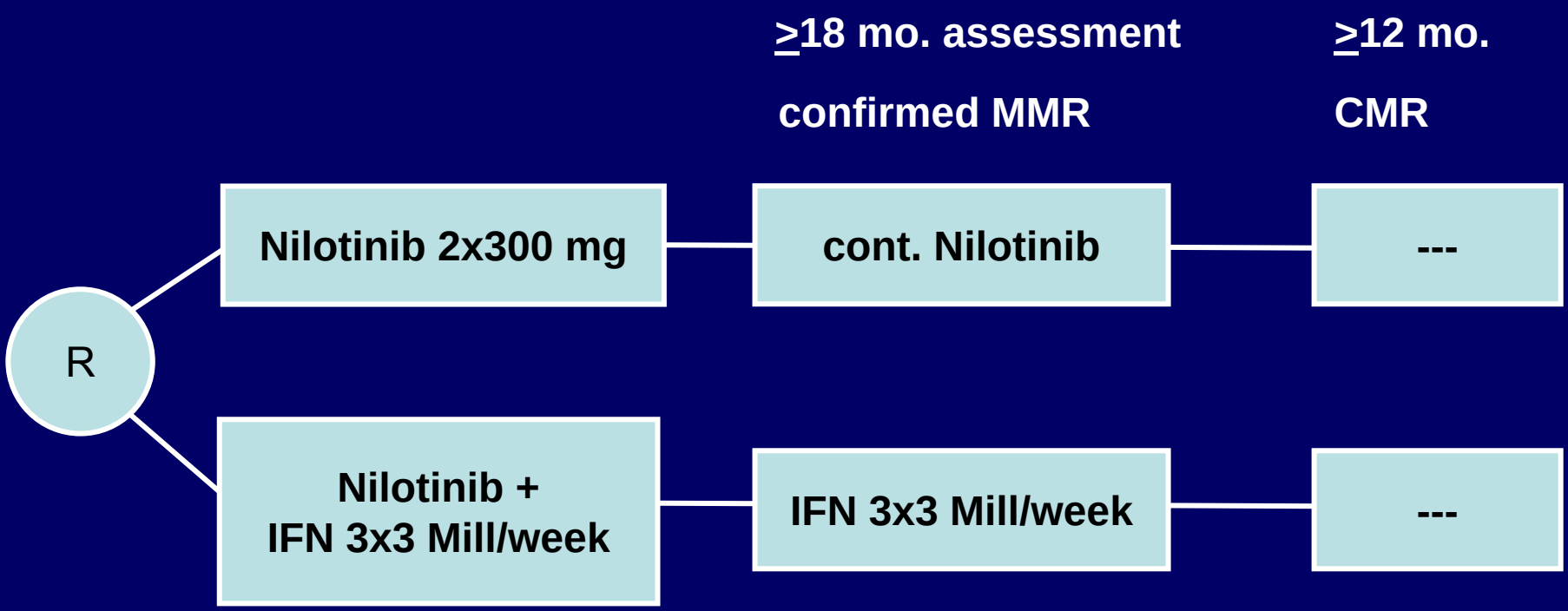


Long term cure ?

Dormant CML-SCs are resistant to imatinib	Activated CML-SCs may be sensitive to imatinib	More differentiated CML cells are effectively eliminated by imatinib

M. Essers et al. Nature, 2009

New German CML-Study V



Nilo dose acc. to
pilot phase

Nilo intolerance -> Imatinib
Nilo resistance -> Transplantation/Dasatinib
No MMR after 18 mo. -> Treatment cont.

Induction therapy **Maintenance therapy** **Cure?**

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