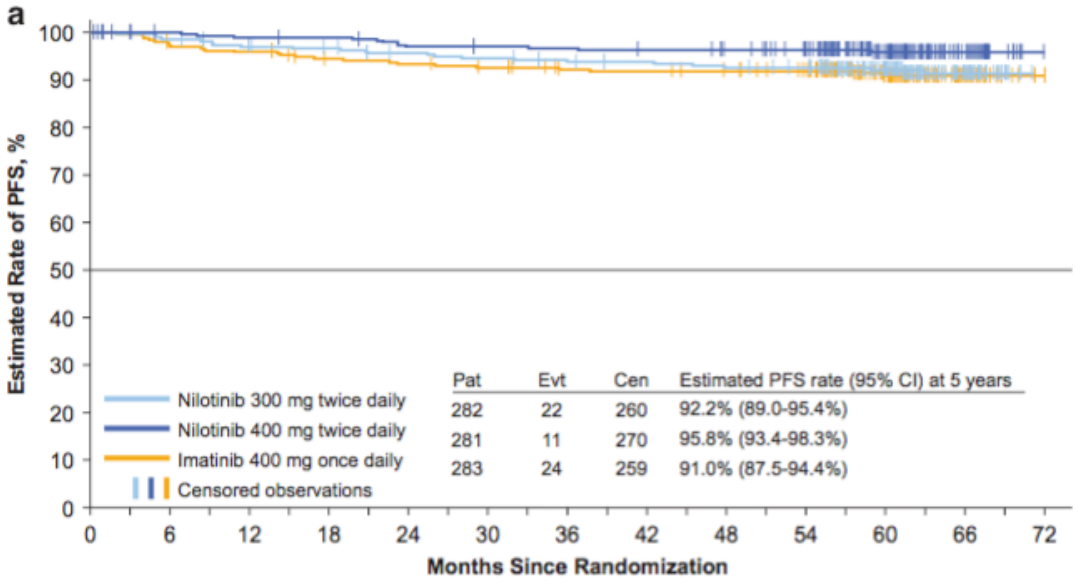
Regimi di trattamento chemotherapy-free

Nella Leucemia Mieloide Cronica

Gianantonio Rosti, MD

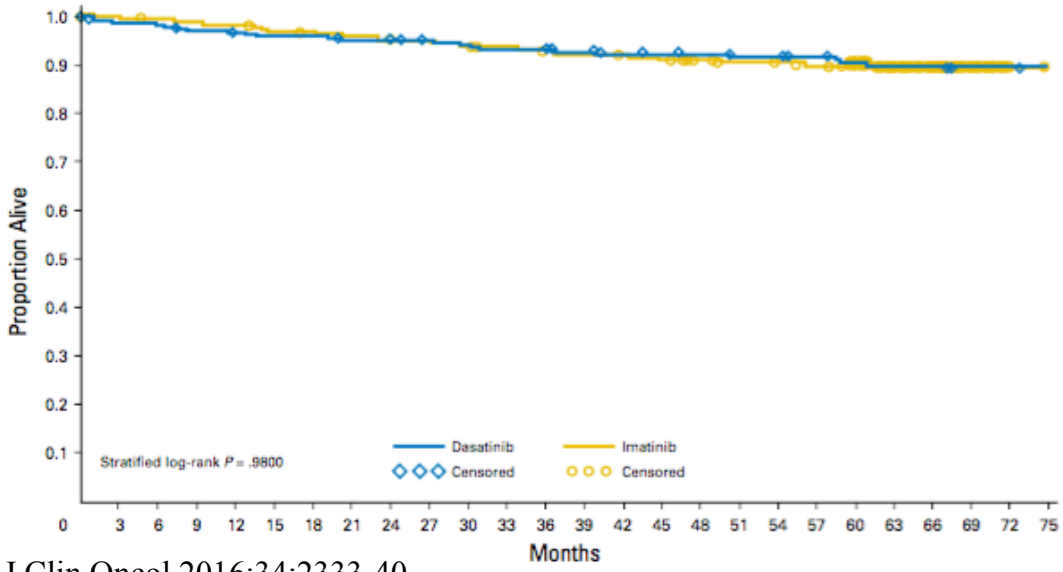
GIMEMA CML WP

5-years OS is similar in different trials



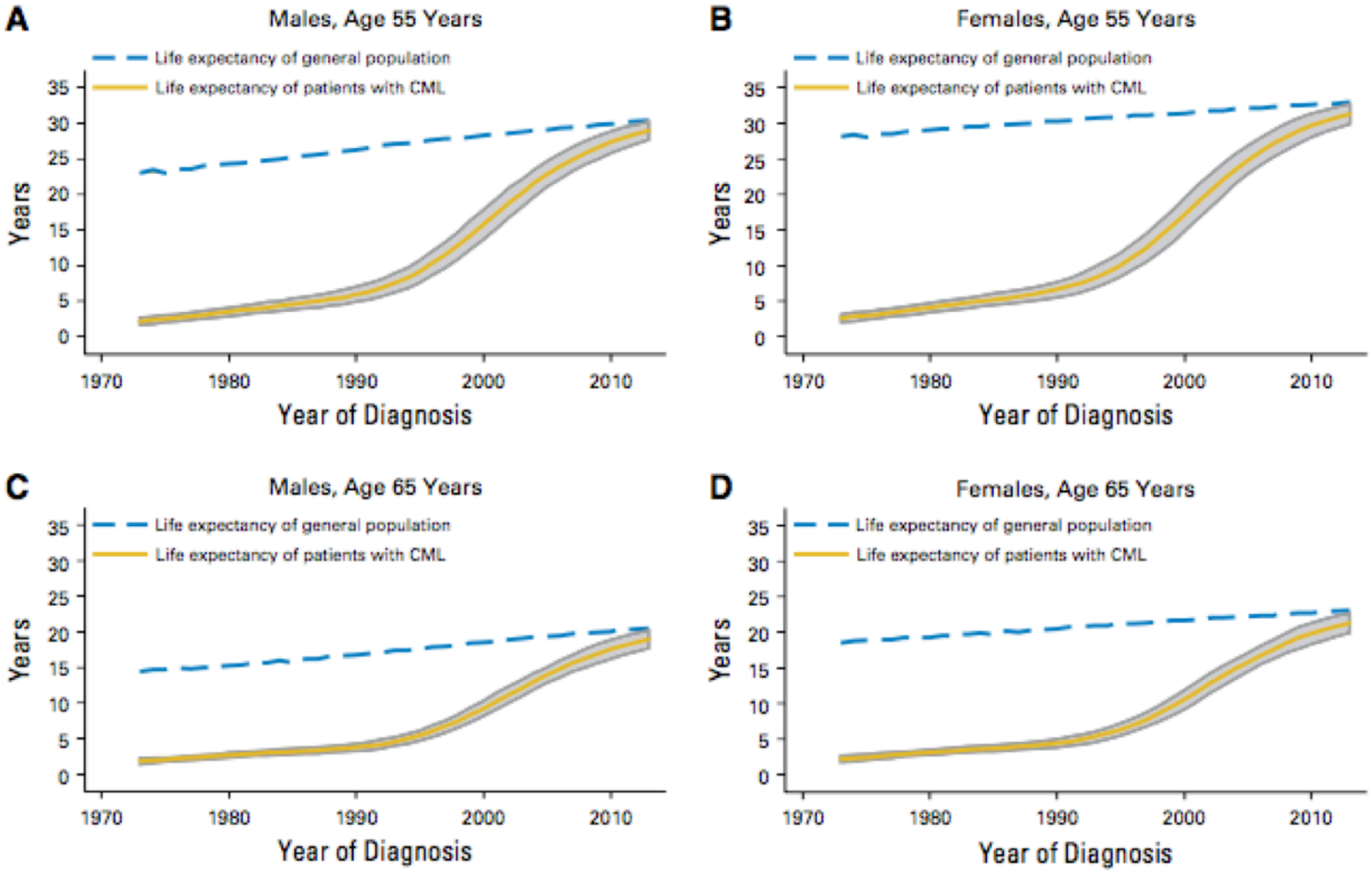
ENESTnd:
Nilotinib vs Imatinib

DASISION:
Dasatinib vs Imatinib



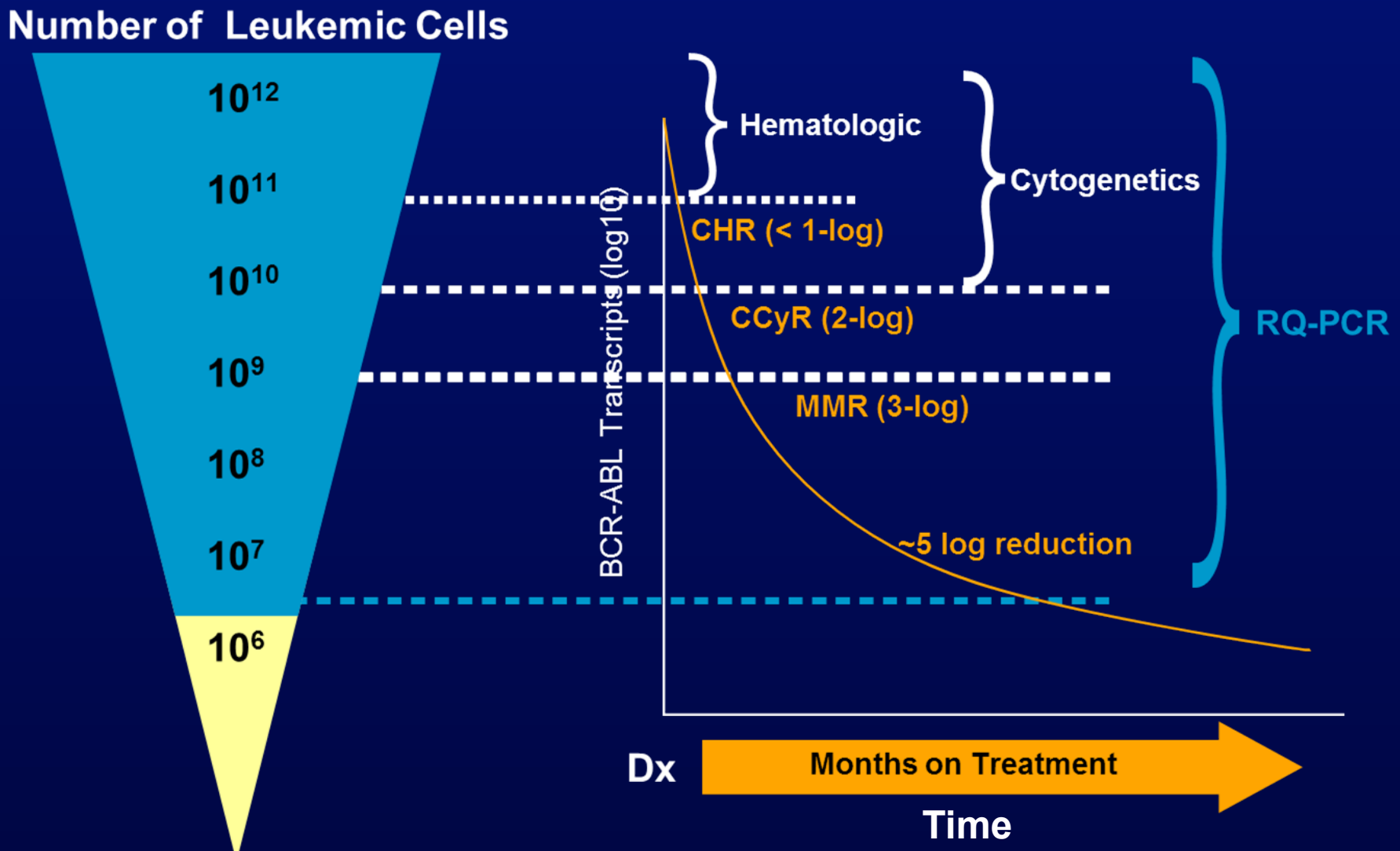
Hochhaus A et al, Leukemia 2016;30:1044-54; Cortes J et al, J Clin Oncol 2016;34:2333-40.

Expected survival of CML *vs* normal population



Bower H et al, J Clin Oncol 2016;34:2851-7.

Correlation Between Response and Disease Burden: Molecular Response



Baccarani M, et al. *J Clin Oncol*. 2009;27(35):6041-6051.
Radich JP. *Blood*. 2009;114:3376-3381.

History of imatinib discontinuation

- Case reports or series between 2004-2007:
  - **Patient request**
  - **Adverse events**
  - **Pregnancy**
  - STIM pilot series
- Pioneering “stop” trials:
  - STIM and TWISTER
- Feasibility confirmed in further trials or observational studies:
  - STIM 2, A-STIM, JALSG-STIM213, ISAV, KID, EUROSKI, HOVON 51

Mauro et al. Leuk Res 2004; 28S1: S71-S73.
Cortes et al. Blood 2004; 10: 2204-2205.
Ghanima et al. Eur J Haematol 2004; 72: 441-443.
Merante et al. Haematologica 2005; 90: 979-981.
Breccia et al. Leuk Res 2006; 30: 1577-1579.
Rousselot et al. Blood 2007; 109: 58-60.
Mahon et al. Lancet Oncol 2010; 11: 1029-1035.
Ross et al. Leukemia 2010; 24: 1719-1724.
Ross et al. Blood 2013; 122: 515-522.
Takahashi et al. Haematologica 2012; 97: 903-906.
Rousselot et al. JCO 2014; 32: 424-430.
Mori et al. Am J Hematol 2015; 90: 910-914.
Thielen et al. Eur J Cancer 2013; 49: 3242-3246.

Evolving Goals of Therapy
Discontinuation of TKIs in CML

Pro's	Con's
• Reducing off-target side effects which cause : - Impaired quality of life - Safety issues - Growth retardation in children - Teratogenicity • Positive effect on adherence? • Feeling "cured" of CML • Cost	• Not recommended in the absence of a deep and stable molecular response • Not recommended in absence of regular high quality molecular monitoring • Leukemic cell persistence despite TKI treatment[1-6]: -Risk of post discontinuation relapse or progression -Risk of resistance or progression upon reinstitution of the same TKI

1. Graham et al. Blood 2002; 99: 319-325
2. Copland et al. Blood 2006; 107: 4532-4539
3. Jorgensen et al. Blood 2007; 109: 4016-4019
4. Konig et al. Blood 2008; 111: 2329-2338
5. Corbin et al. JCI 2011; 121: 396-406
6. Hamilton et al. Blood 2012; 119: 1501-1510

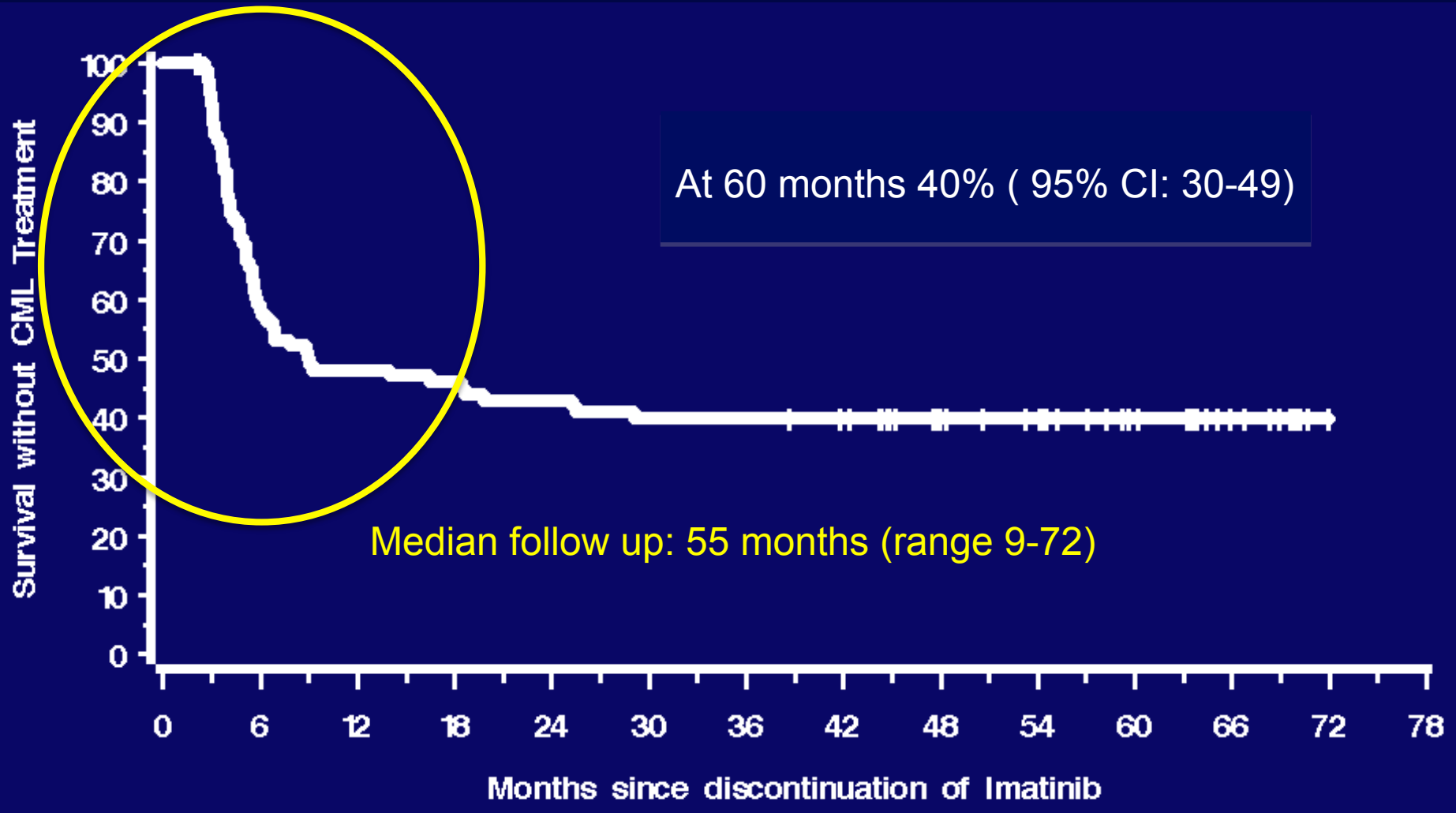
Imatinib discontinuation studies

Trial	N	Inclusion criteria	Relapse definition	TFR or RFS rate
A-STIM	80	**≥ 3 years of imatinib ≥ 2 years of CMR4.5**	MMR loss	64% (95% CI: 54-75) at 12 and 24 months 61% (95% CI: 51-73) at 36 months
JALSG-STIM213	68	**≥ 3 years of imatinib ≥ 2 years of MR4.5**	MMR loss	69.1% (95% CI: 58.1-80.1) at 12 months
KID	90 (non-transplant subgroup)	**≥ 3 years of imatinib ≥ 2 years of CMR4.5**	MMR loss	62.2% ± 5.1 at 12 months and 58.5% ± 5.2 at 24 months
ISAV	112	**≥ 2 years of imatinib ≥ 18 months of CMR4**	MMR loss	48.1% (95% CI: 38.4-58) at 36 months
EURO-SKI	200 (interim analysis, at least 6 months of follow-up)	**≥ 3 years of TKI ≥ 12 months of MR4**	MMR loss	56% (95% CI: 49-63) at 12 months

Mahon Rousselot et al. JCO 2014; 32: 424-430.
Takahashi et al. Blood (ASH 2015): abstract 4035.
Lee et al. Haematologica. 2016 Feb 17. pii: haematol.2015.139899.
Mori et al. Am J Hematol 2015; 90: 910-914.
Mahon et al. Blood (ASH 2014); 124: abstract 151.

DR

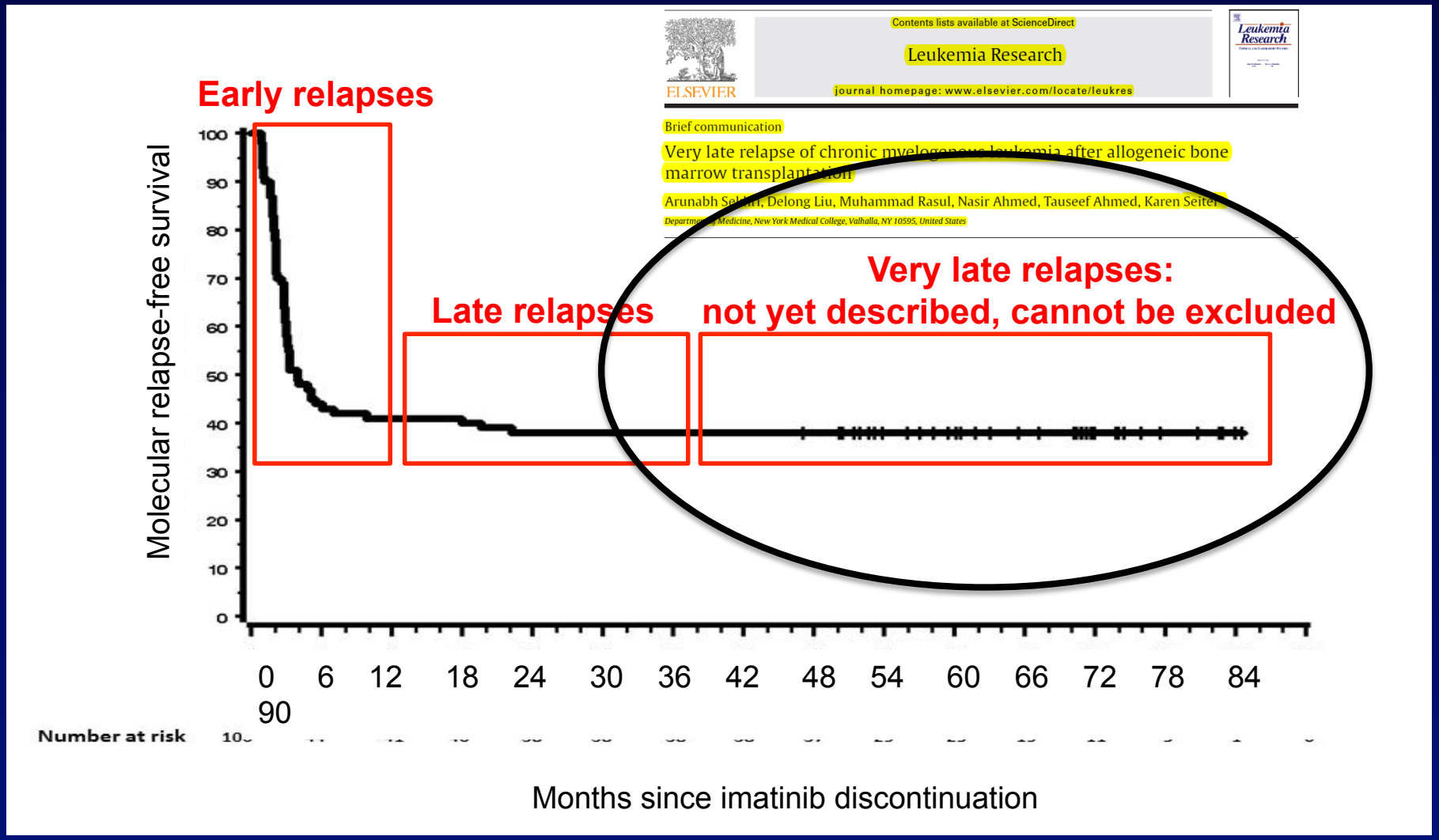
Treatment-free survival



Mahon, ASH 2013

DR

Imatinib-free remission:
Long-term follow-up



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Brief communication

Very late relapse of chronic myelogenous leukemia after allogeneic bone marrow transplantation

Arunabh Sehgal, Delong Liu, Muhammad Rasul, Nasir Ahmed, Tauseef Ahmed, Karen Seiter

Department of Medicine, New York Medical College, Valhalla, NY 10595, United States

Etienne et al. Blood (ASH) 2015; abstract 345.

DR

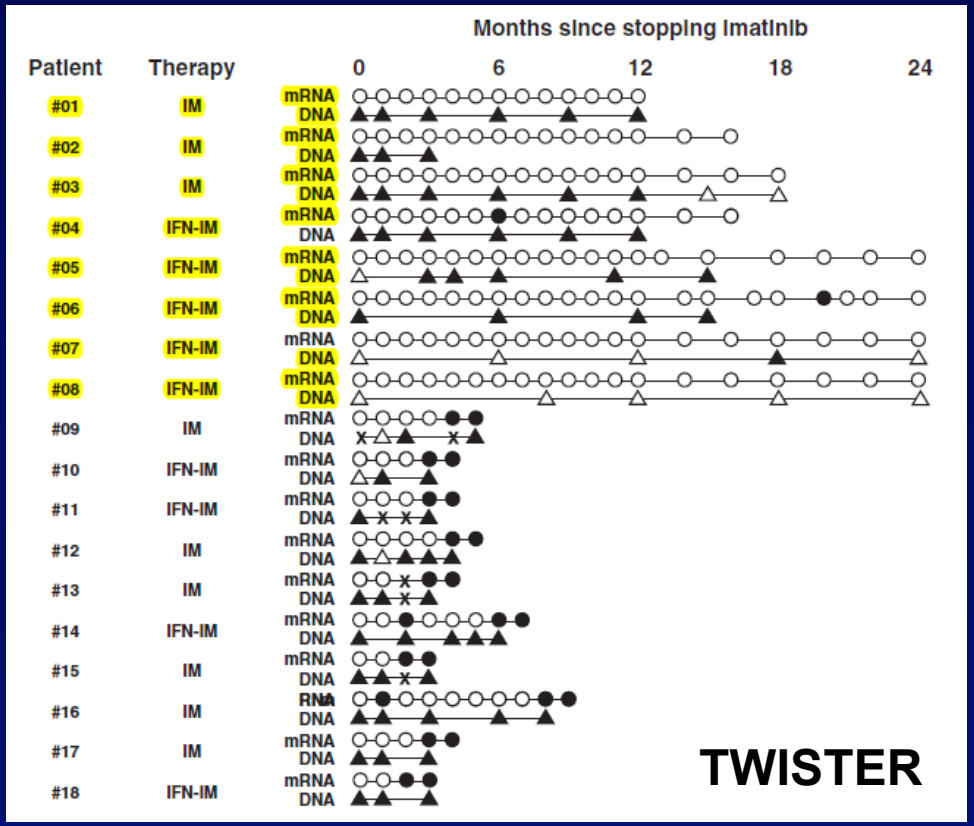
DEFINING CURE FOR CML

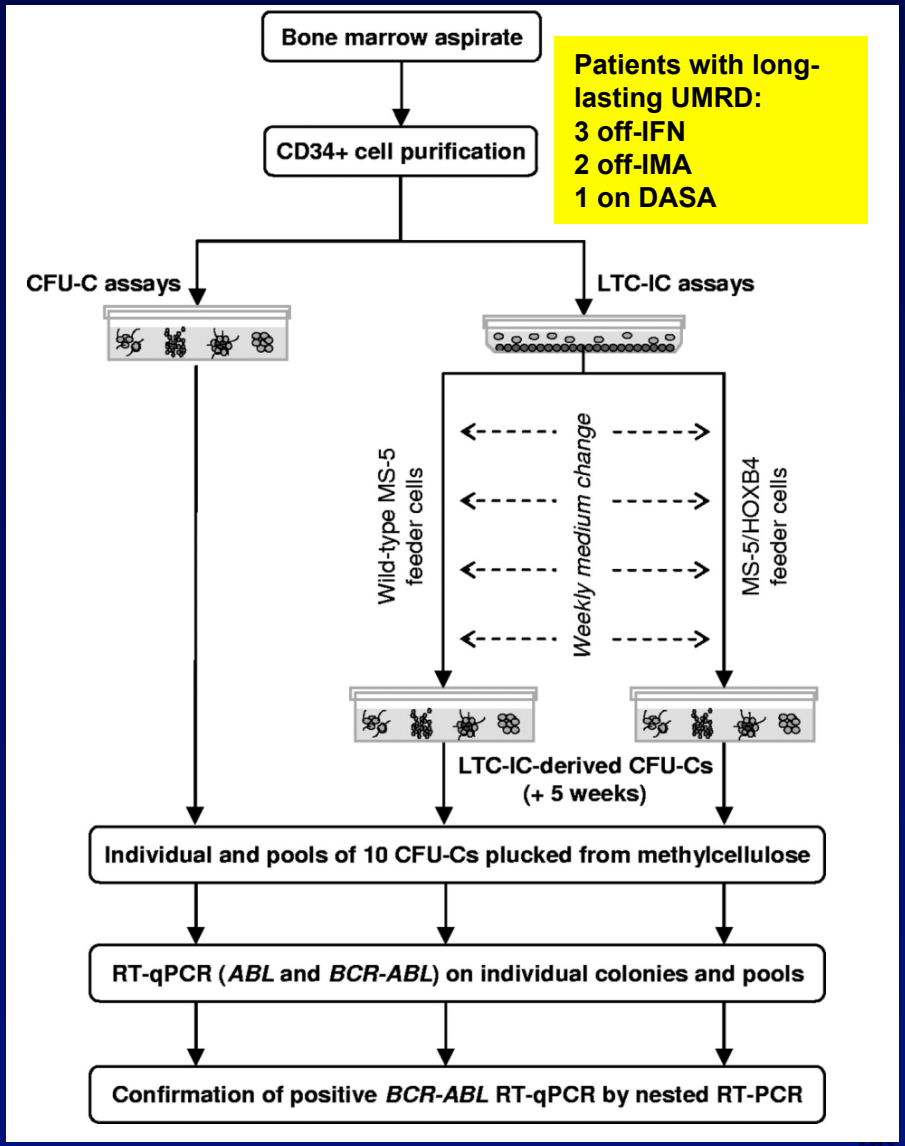
Levels of cure	Definition	Requirement
"Operational cure[1]"	No signs of CML and risk of advanced phase disease abolished	Sustained CCyR/MMR
"Functional cure[1,2]"	Long-term residual disease control without the need for ongoing therapy	At least a sustained MMR after discontinuation of therapy?
"Definitive cure"	Eradication of all leukemic cells preventing further recurrence of the disease	Undetectable *BCR-ABL* transcripts and genomic DNA (?)

[1]Goldman *et al.* Leuk Lymphoma 2006; 47: 1
[2]Radich *et al.* Blood 2001; 98; 1701

DR

Imatinib-free remission:
Despite LSC persistence

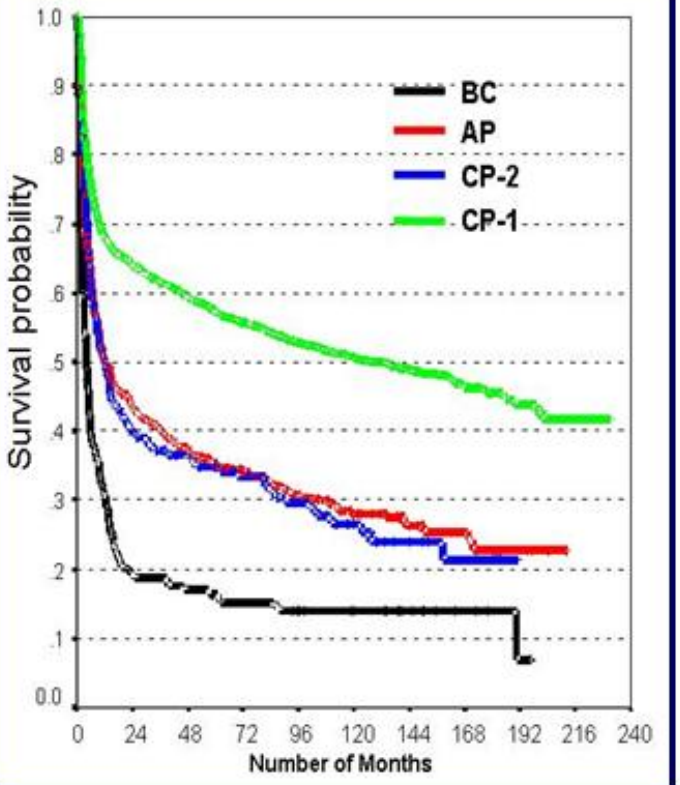




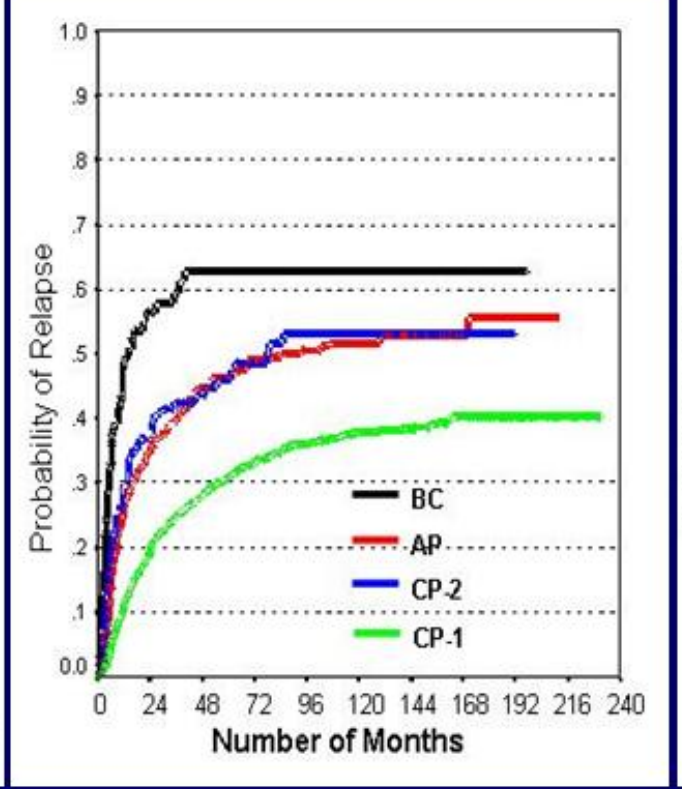
Ross et al. Leukemia 2010; 24: 1719-1724.
Chomel et al. Blood 2011; 118: 3657-3660.

Survival, Relapse and TRM in HCT for CML

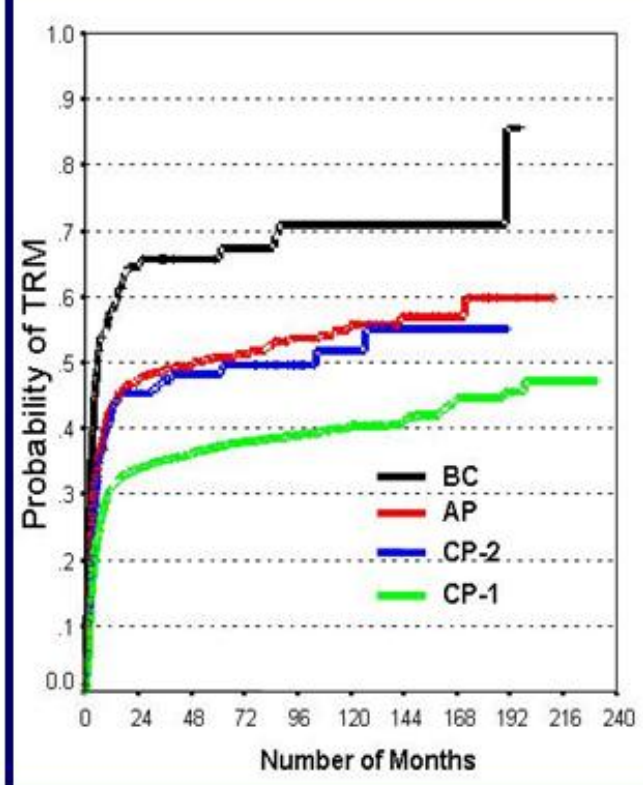
Survival



Relapse



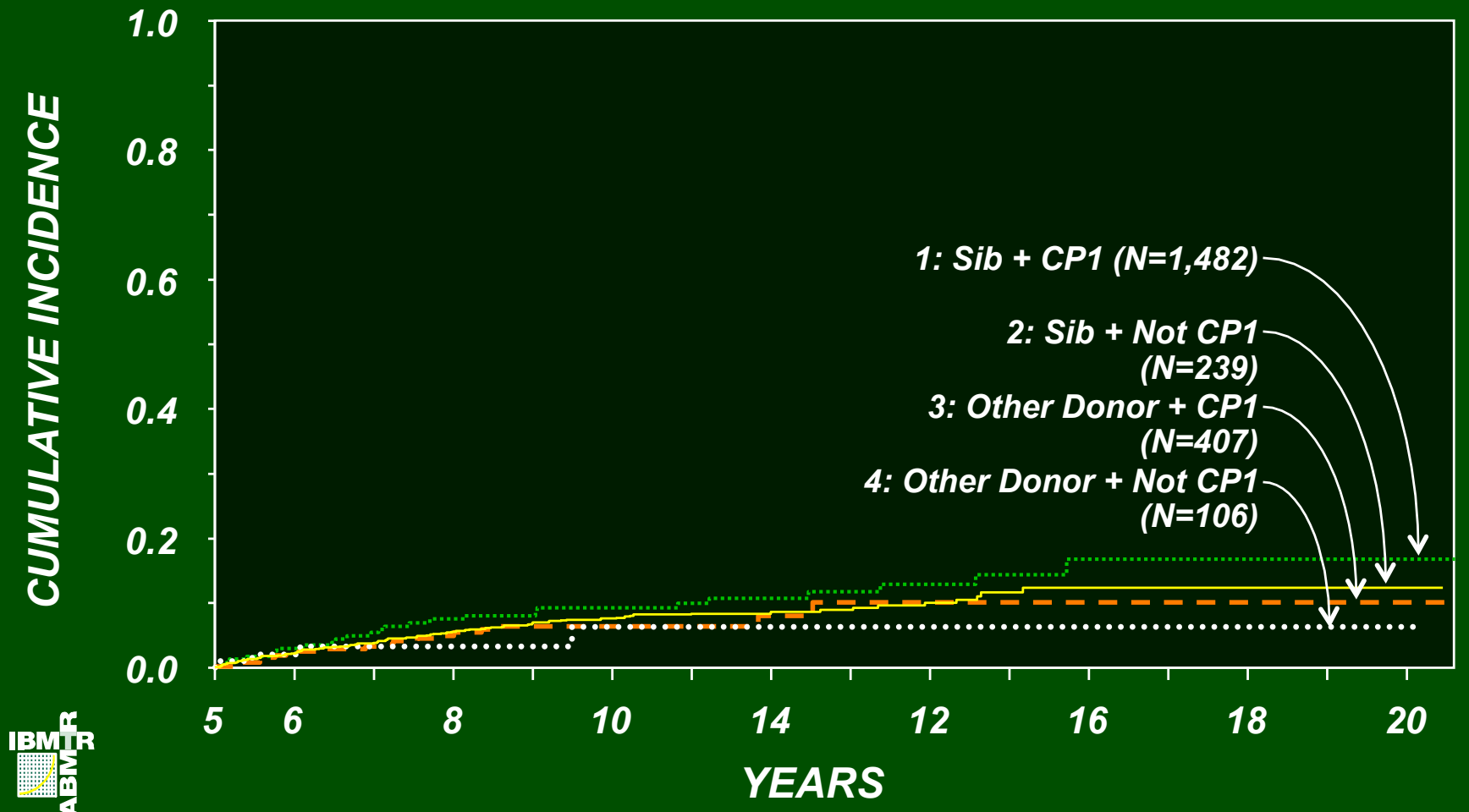
TRM



N=10,206 Patients

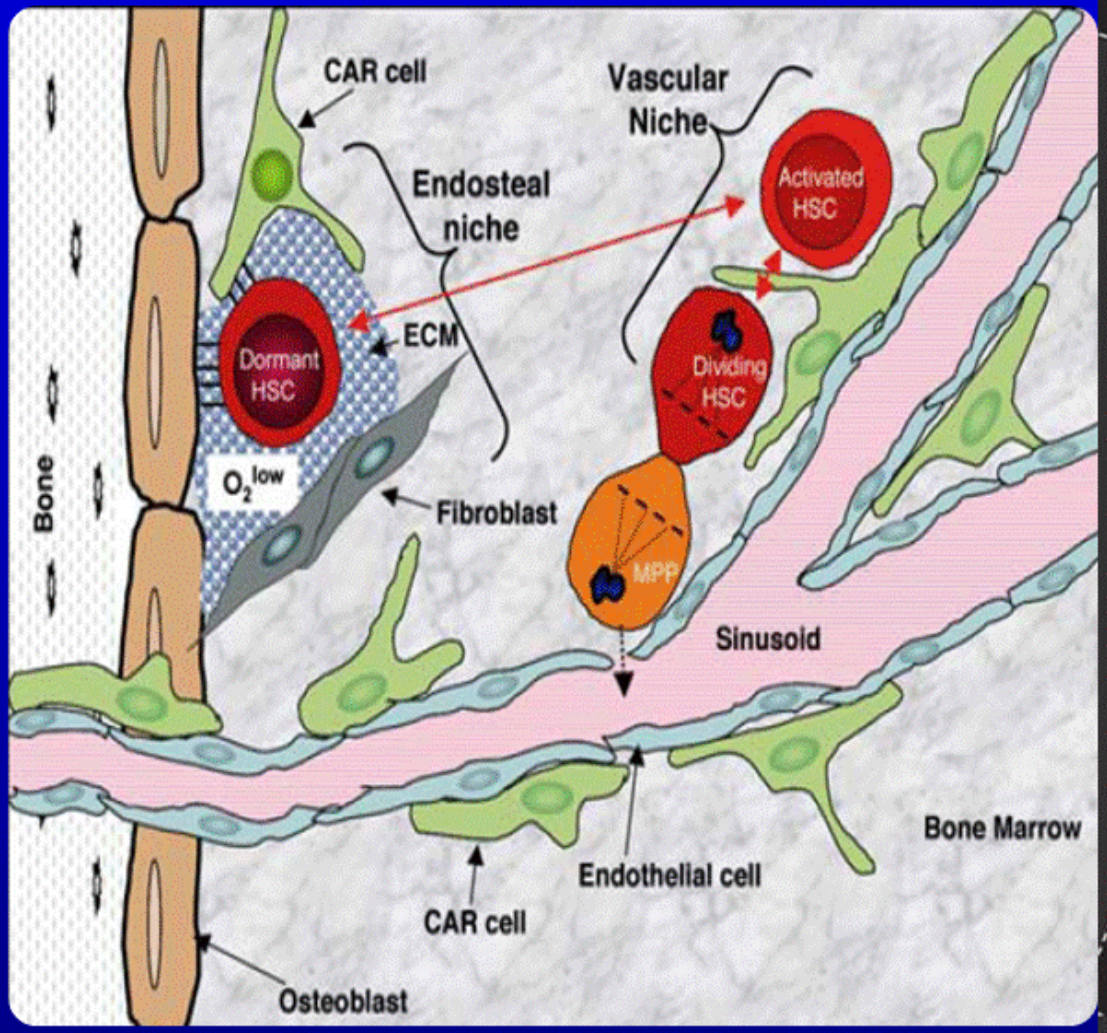
Courtesy of the EBMT

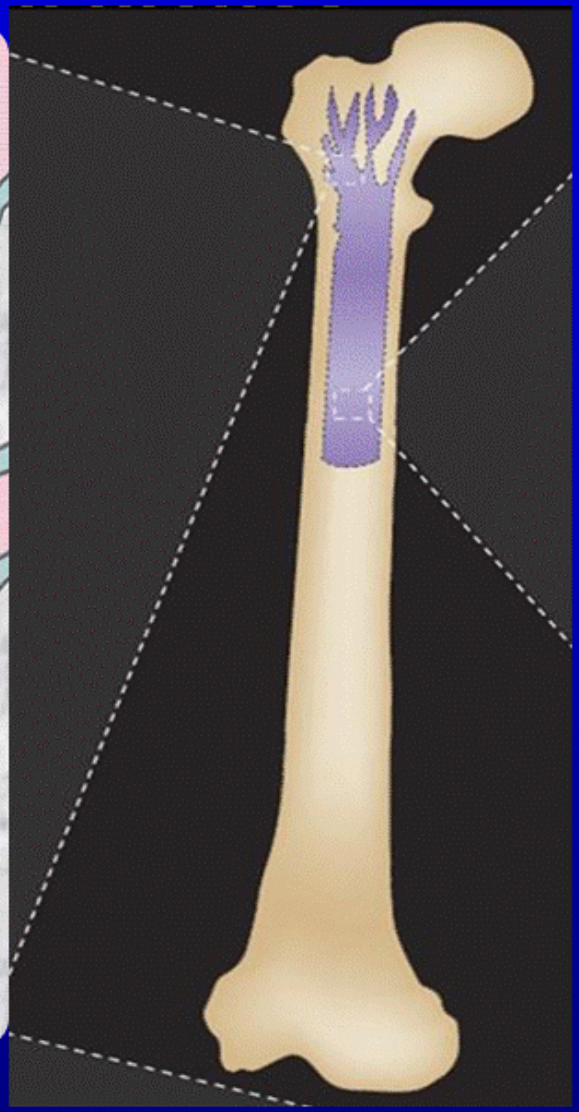
SUBSEQUENT RELAPSE AMONG PATIENTS ALIVE AND IN REMISSION 5 YEARS POST-BMT



IBMTR ABMTR

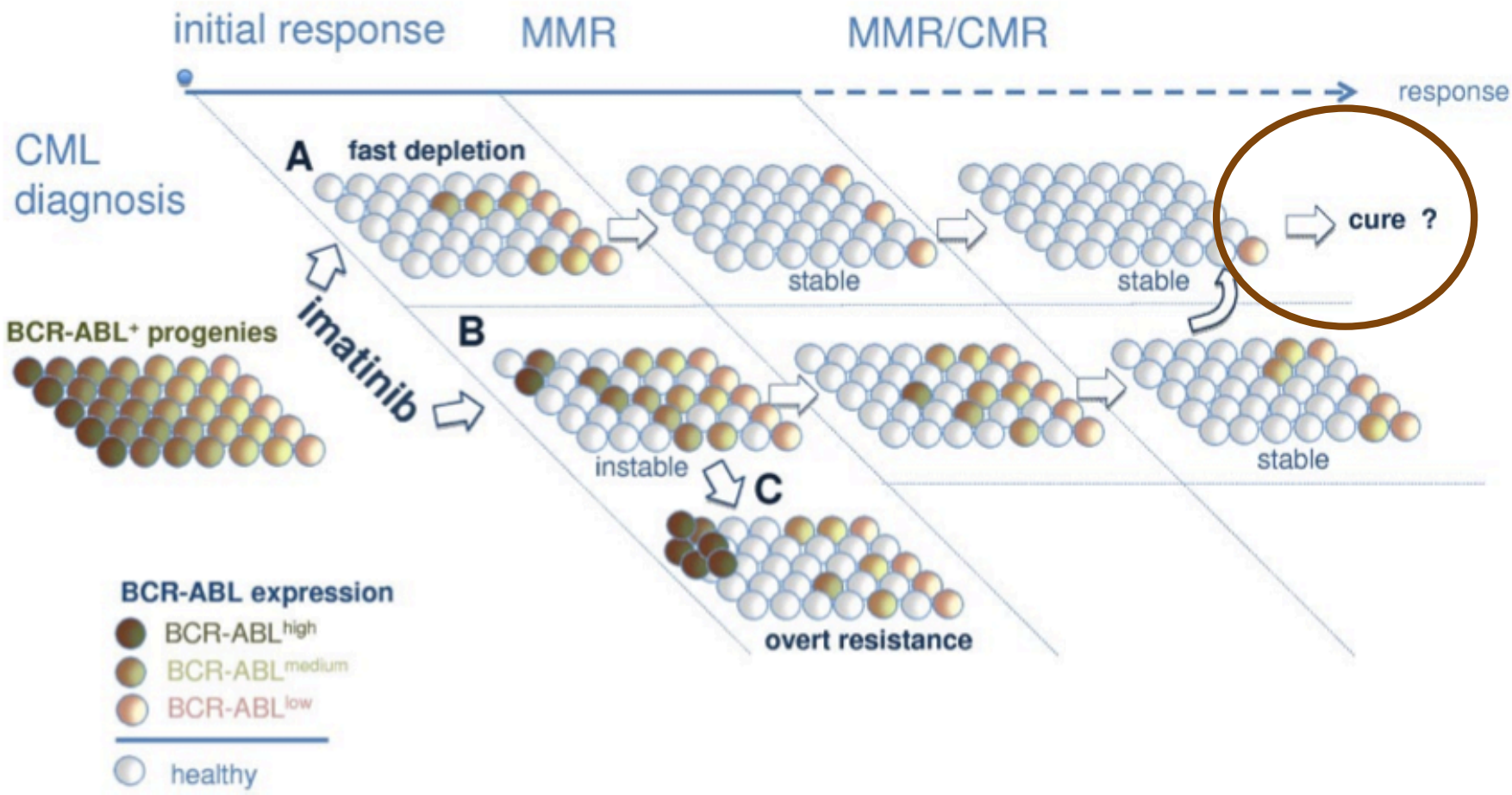
Hematopoietic stem cell niche





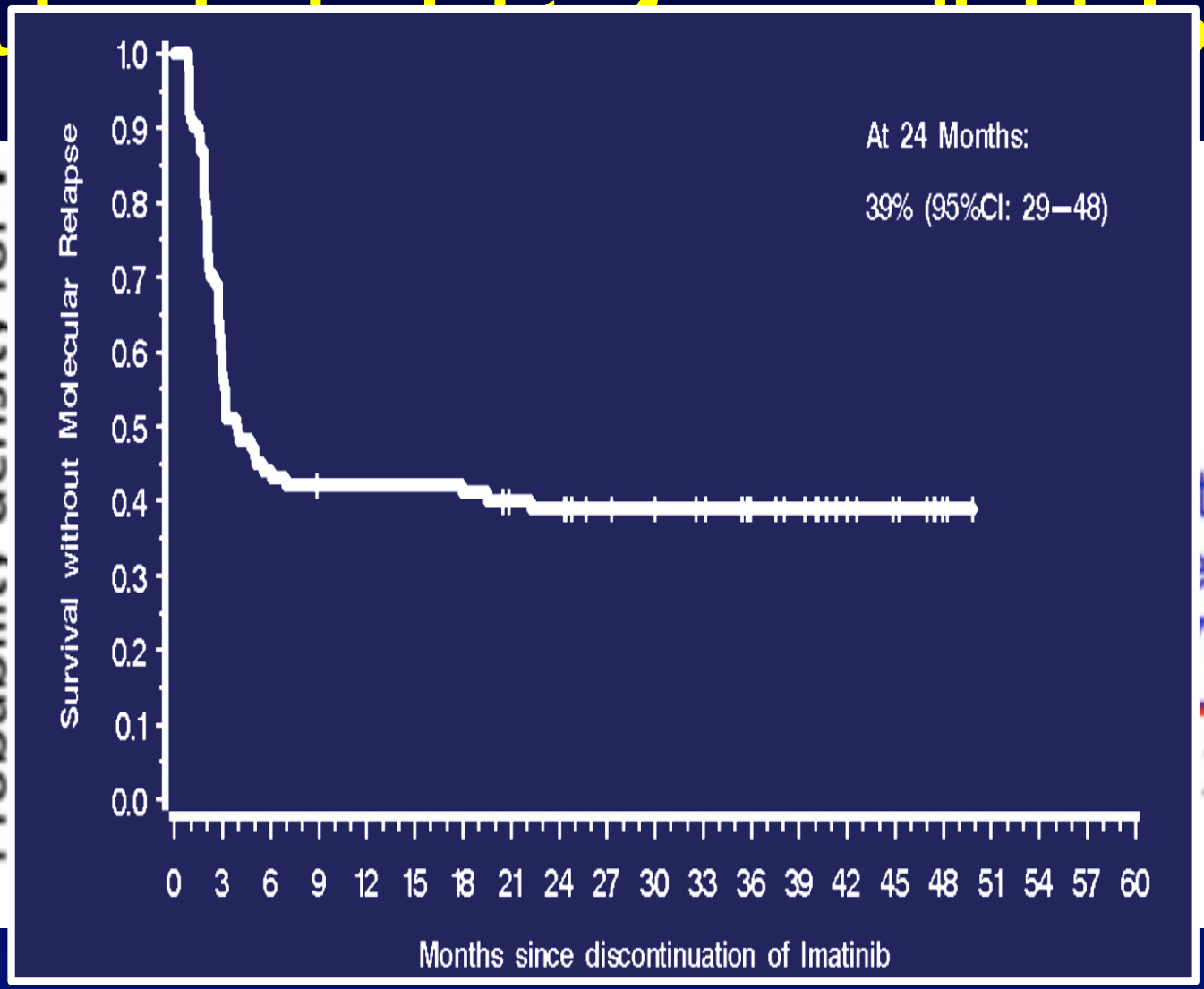
Wilson and Trumpp. Nat Rev Immunol. 2006; 6(2): 93-106.

Stem cell persistence is associated with low BCR-ABL expression



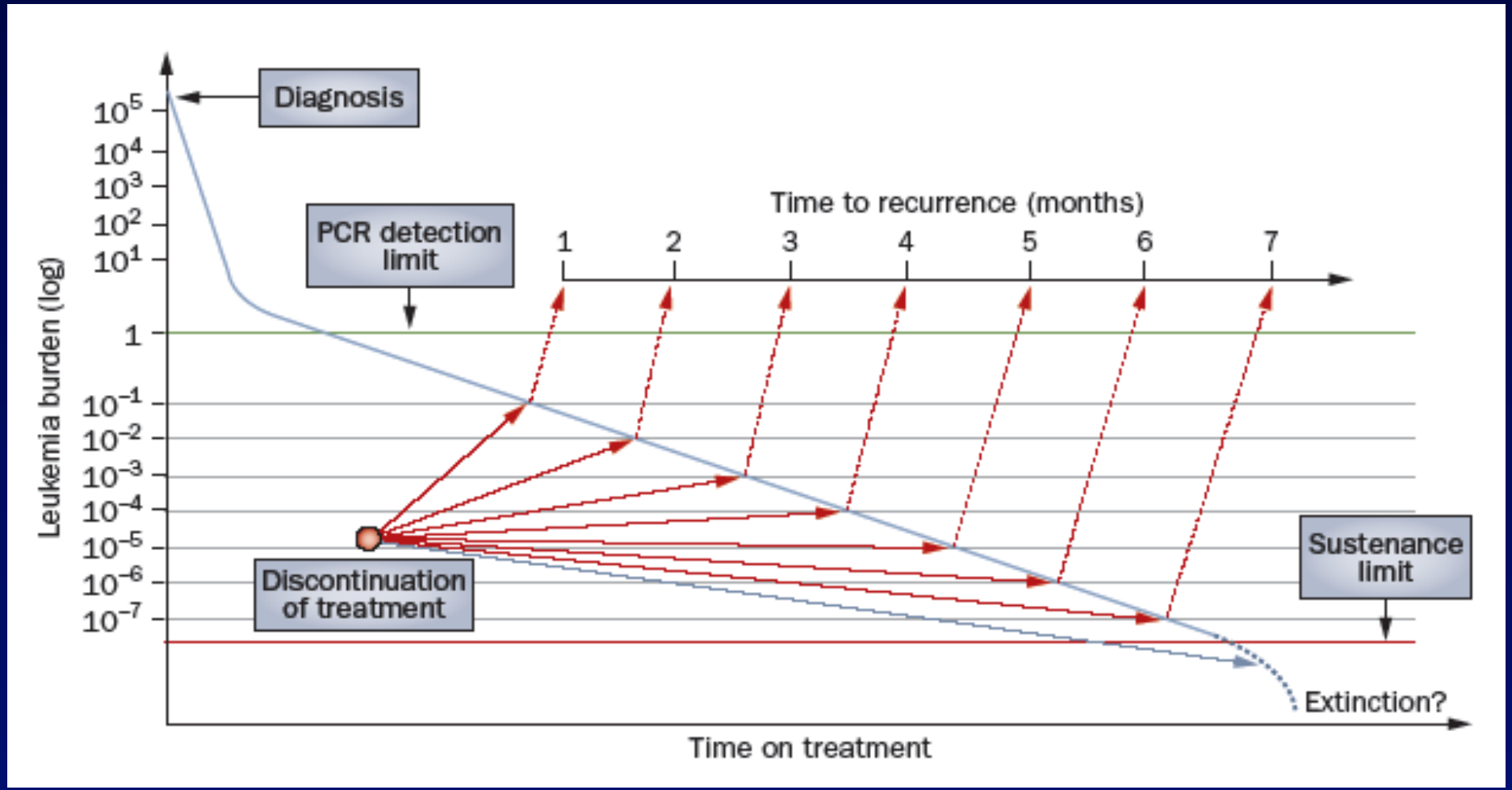
Kumari A et al, Blood. 2012 Jan 12;119(2):530-9.

Quantitative modeling of chronic myeloid leu[illegible]gy*



Tomas Radivoyevitch et al, Blood PEP February 21, 2012;

Hypothetical Model of CML persistence and recurrence versus extinction



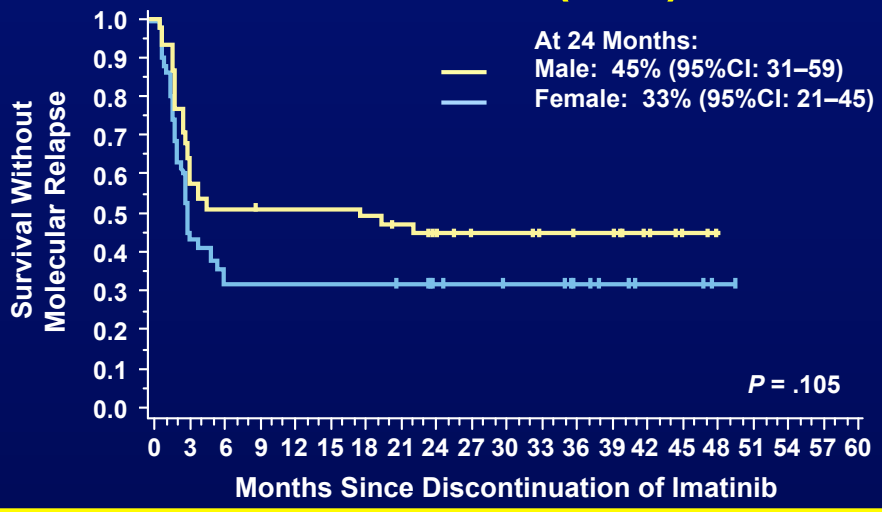
Deininger, M. *Nat. Rev. Clin. Oncol. advance online publication 1 February 2011;* doi:10.1038/nrclinonc.2011.17

DR

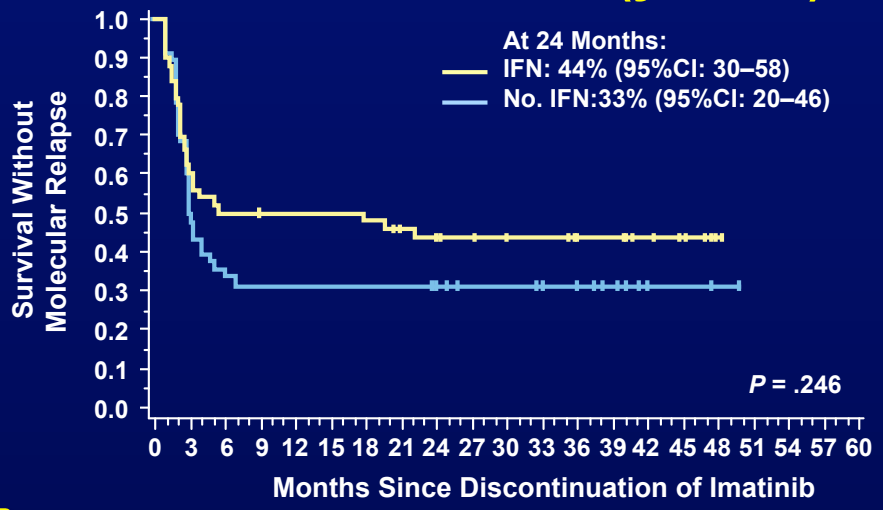
Can We Predict Which Patients Will Relapse?

Relapse-free Survival by Baseline Factor in STIM

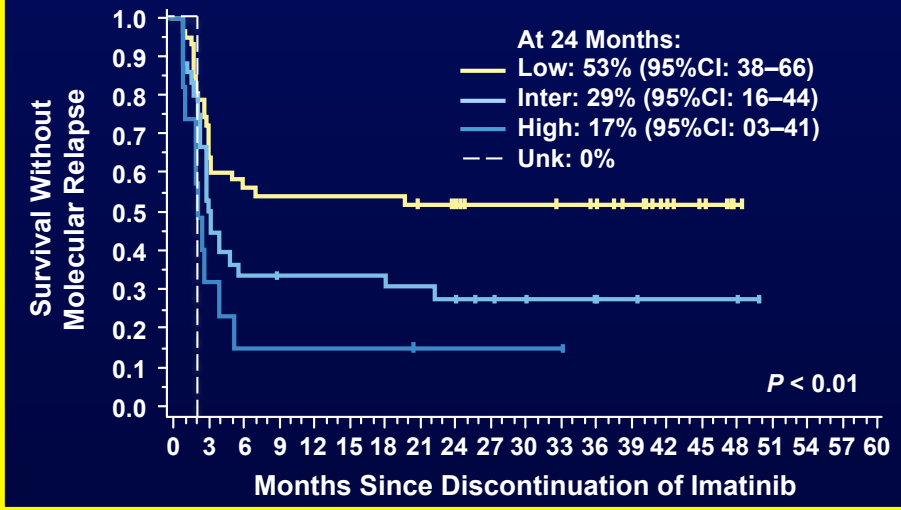
Gender (M/F)



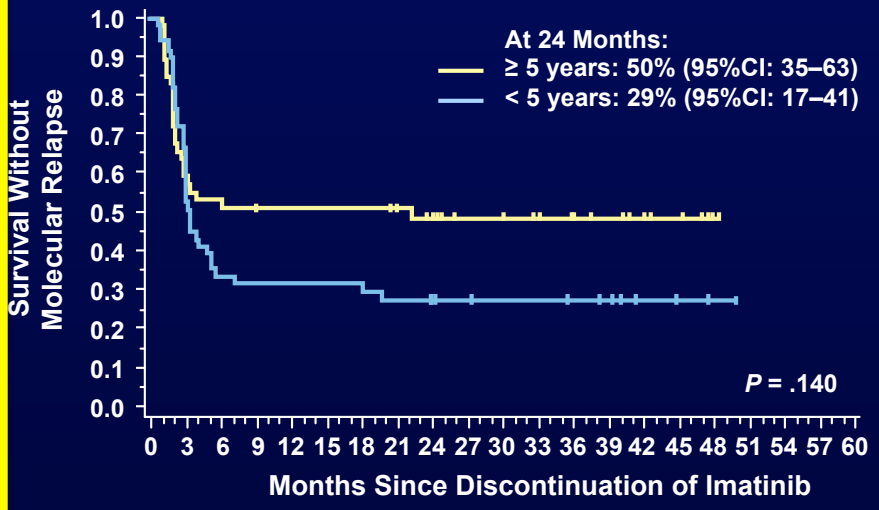
Previous IFN (yes/no)



Sokal risk (Low/Int/High)



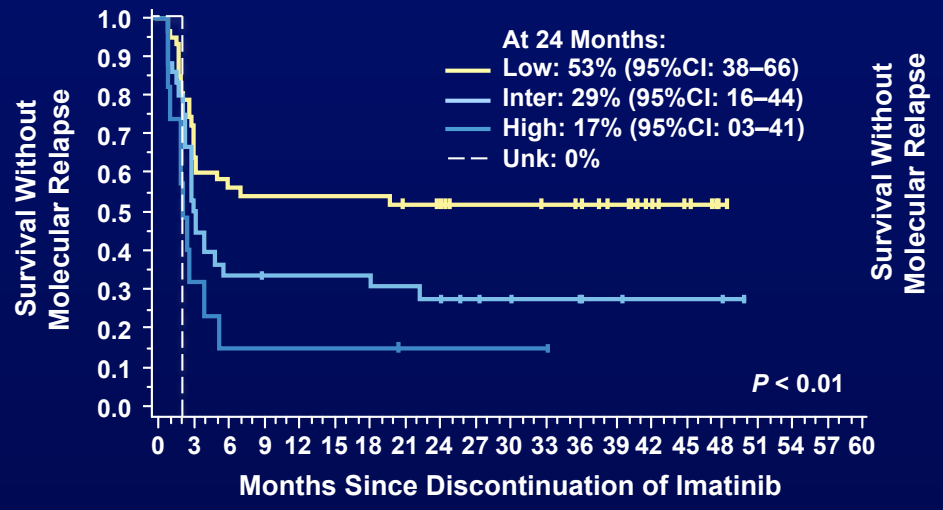
Imatinib duration (≥5 y/<5 y)



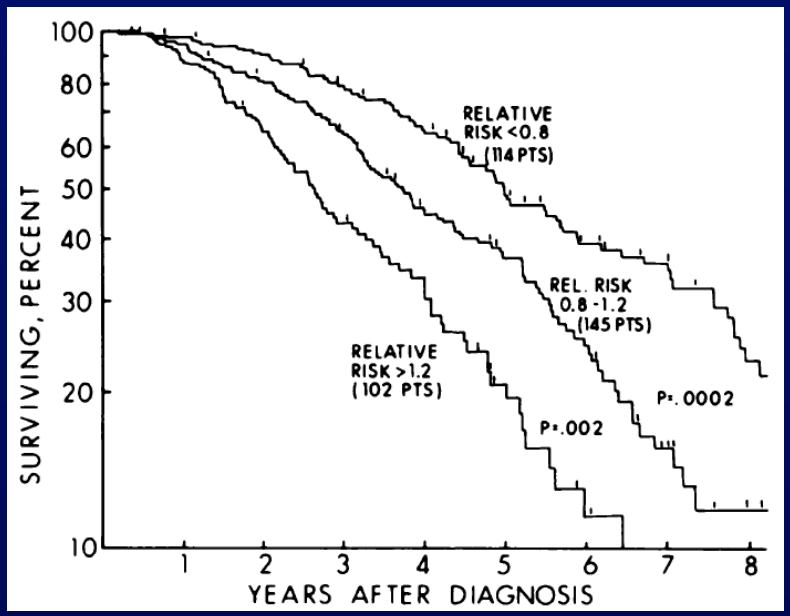
Mahon FX, et al. *Blood* 2011;118:abstract 603.

The same old story?

Sokal risk (Low/Int/High)

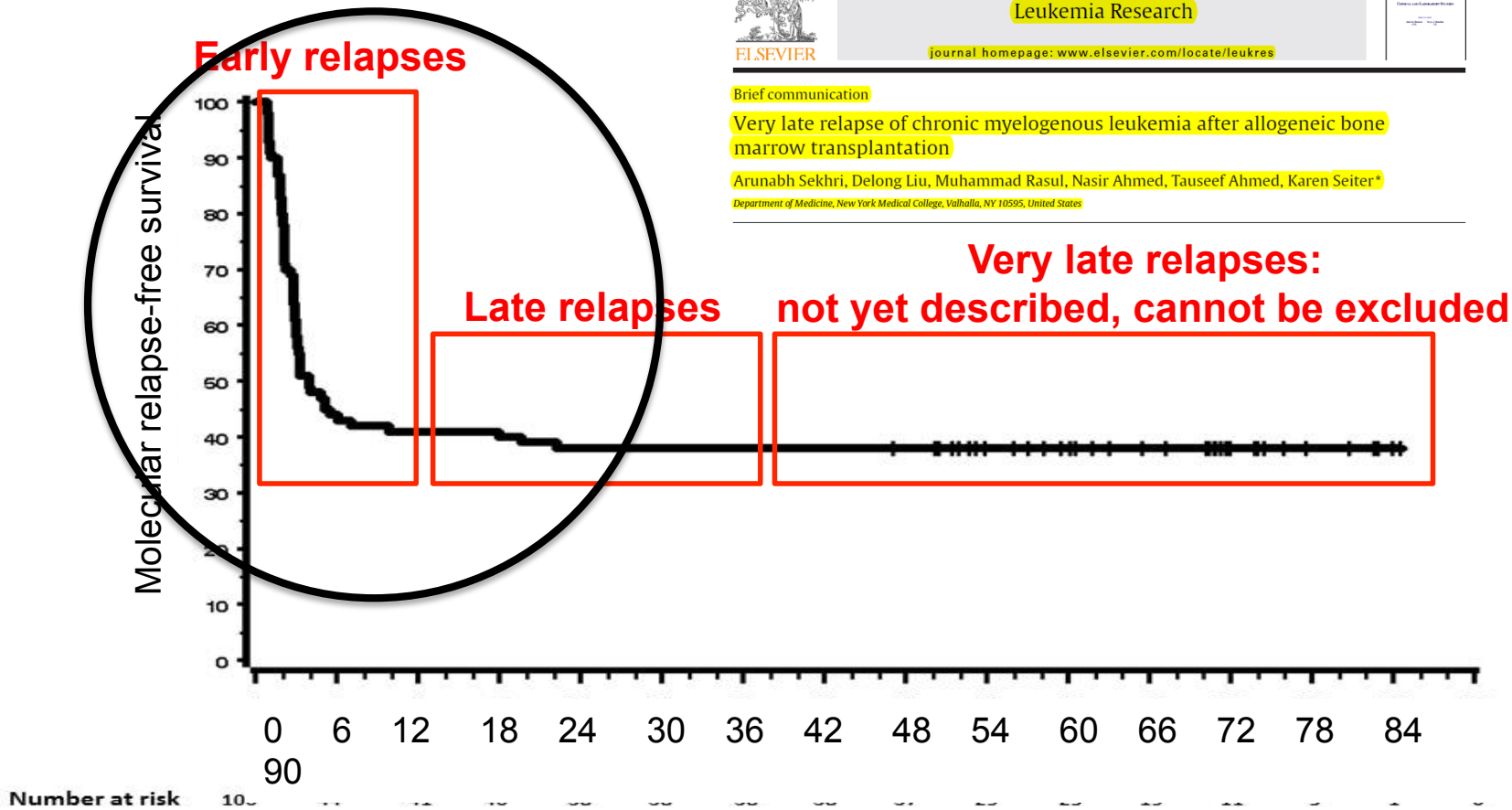


Mahon FX, et al. *Blood* 2011;118:abstract 603.



Sokal JE, et al. Blood 1984;63:789–799.

Imatinib-free remission:
Long-term follow-up



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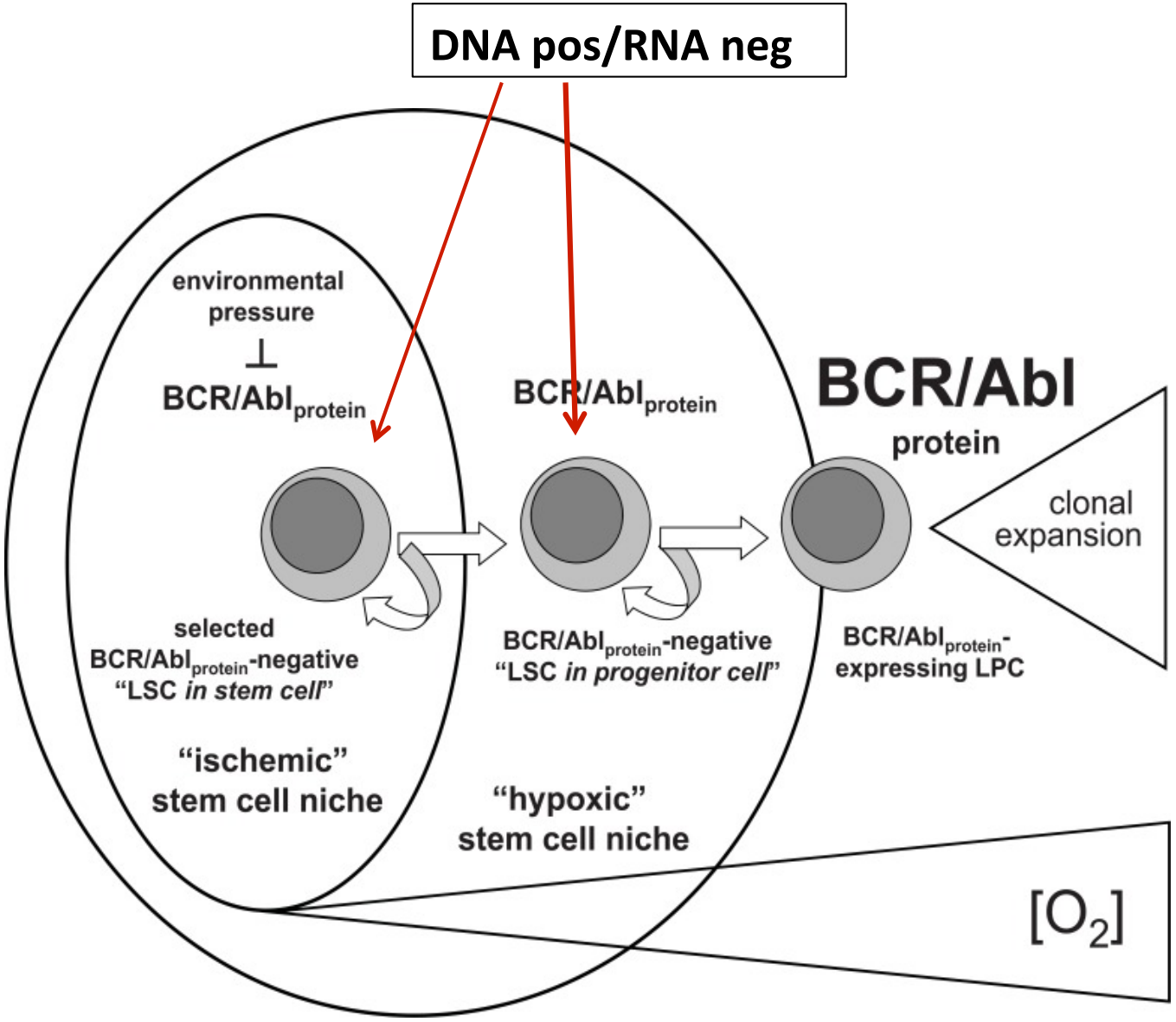
Very late relapse of chronic myelogenous leukemia after allogeneic bone marrow transplantation

Arunabh Sekhri, Delong Liu, Muhammad Rasul, Nasir Ahmed, Tauseef Ahmed, Karen Seiter*
Department of Medicine, New York Medical College, Valhalla, NY 10595, United States

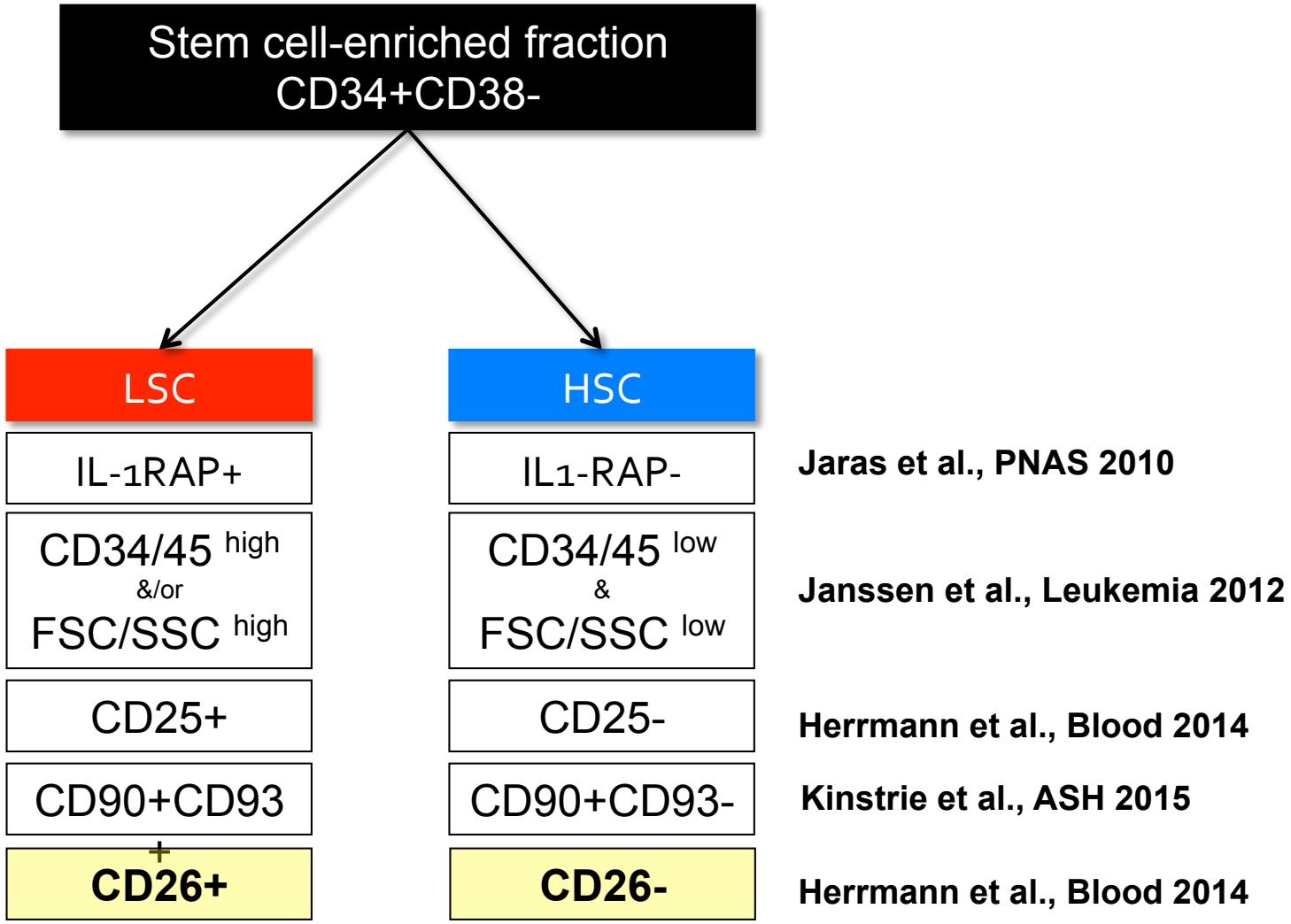
Etienne et al. Blood (ASH) 2015; abstract 345.

DR

THE DISTANCE BETWEEN
BCR-ABL QUANTITATION AND "THE FACE" OF RESIDUAL Ph+ SCs



Cipolleschi MG et al. Curr Pharm Des. 2013


Stem cell-enriched fraction
CD34+CD38-
LSC
HSC
IL-1RAP+
IL1-RAP-
Jaras et al., PNAS 2010
CD34/45 high
&/or
FSC/SSC high
CD34/45 low
&
FSC/SSC low
Janssen et al., Leukemia 2012
CD25+
CD25-
Herrmann et al., Blood 2014
CD90+CD93
CD90+CD93-
Kinstrie et al., ASH 2015
CD26+
CD26-
Herrmann et al., Blood 2014

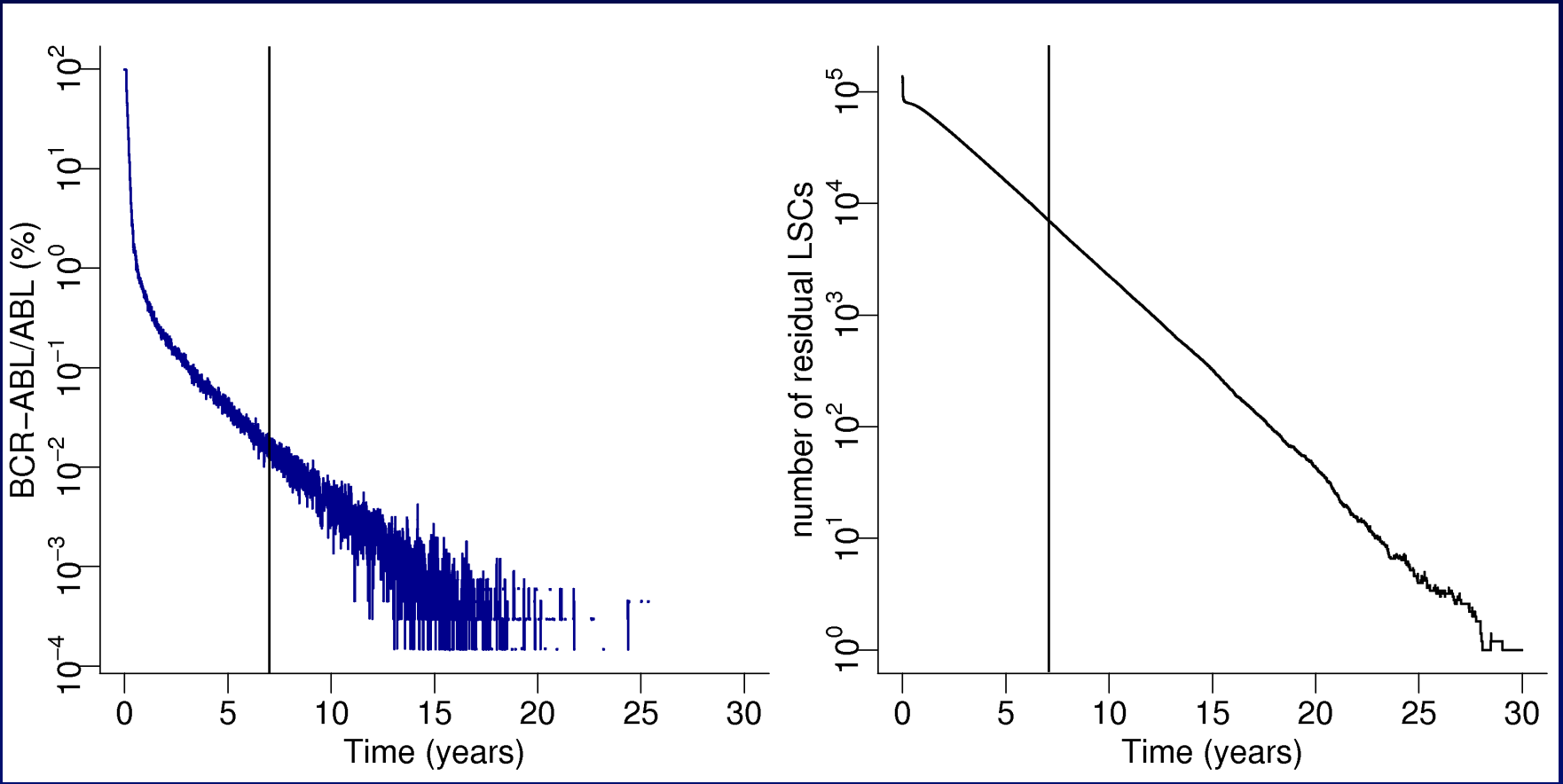
EUROSKI

Prognostic modeling (n=448, imatinib)

- Univariate analysis showed no significant association between molecular relapse-free survival at 6 months and age, gender, depth of molecular response ($MR^{4.5}$ vs. not in $MR^{4.5}$) or any variable parts of the Sokal, EURO, EUTOS or ELTS scores.
- However, treatment duration with imatinib and MR4 duration were significantly ($p<0.001$) correlated with MMR status at 6 months.
- **The odds ratio for treatment duration was 1.16 (95%-CI 1.08-1.25), meaning that one additional year of imatinib treatment increases the odds to stay in MMR at 6 months by 16%.**
- Molecular relapse-free survival at 6 months was 65.5% for imatinib treatment > 5.8 years and 42.6% for treatment ≤ 5.8 years. This cut-off was identified with the minimal p-value approach.

Long-Term Prediction

Prediction to response to imatinib



→ MRD eradication after about 30 years continuous therapy.

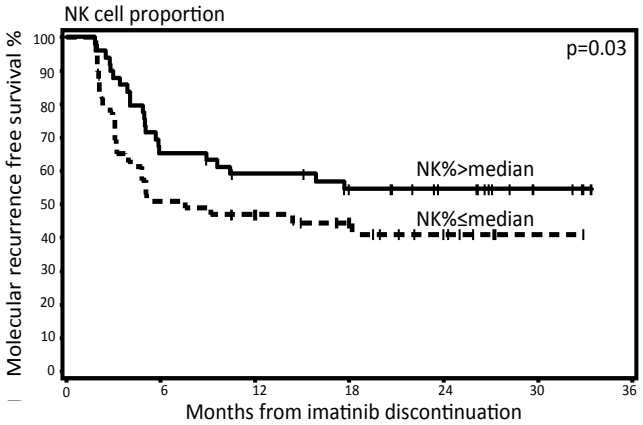
Ingo Roeder et al, Nat Med 2006

DR

Mature, adap+ve-like CD56DIM NK cells in chronic myeloid leukemia pa+ents in TFR

Ilander et al, Hematology Research Unit Helsinki, University of Helsinki, Finland

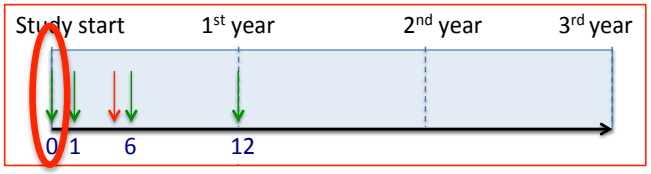
NK cell proportion in successful discontinuation



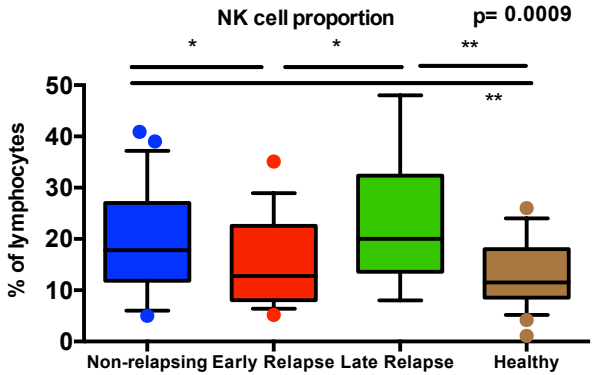
Non-relapsing= patients without treatment for over 12 months

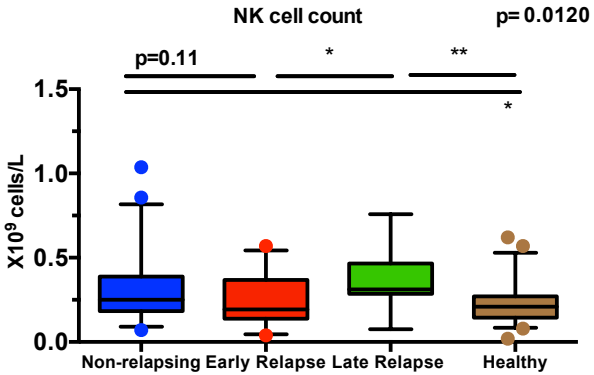
Early relapse= relapse before 6 months

Late relapse= relapse after 6 months



Non-relapsing patients have more NK cells





Ilander et al, ASH 2015

2nd Generation TKIs in Early CP

Outcome and Responses By 5 Years

	ENESTnd[1]		Dasision[2]	
Treatment	**Nilotinib**	**Imatinib**	**Imatinib**	**Dasatinib**
Patient N.	**282**	**283**	**260**	**259**
5-year PFS[&]	96.5%	94.7%	85.5%	85.4%
5-year OS^	93.6%	91.6%	89.6%	90.9%
MMR	77%	60%	64%	76%
MR$^{4.5}$	**54%**	**31%**	**33%**	**42%**

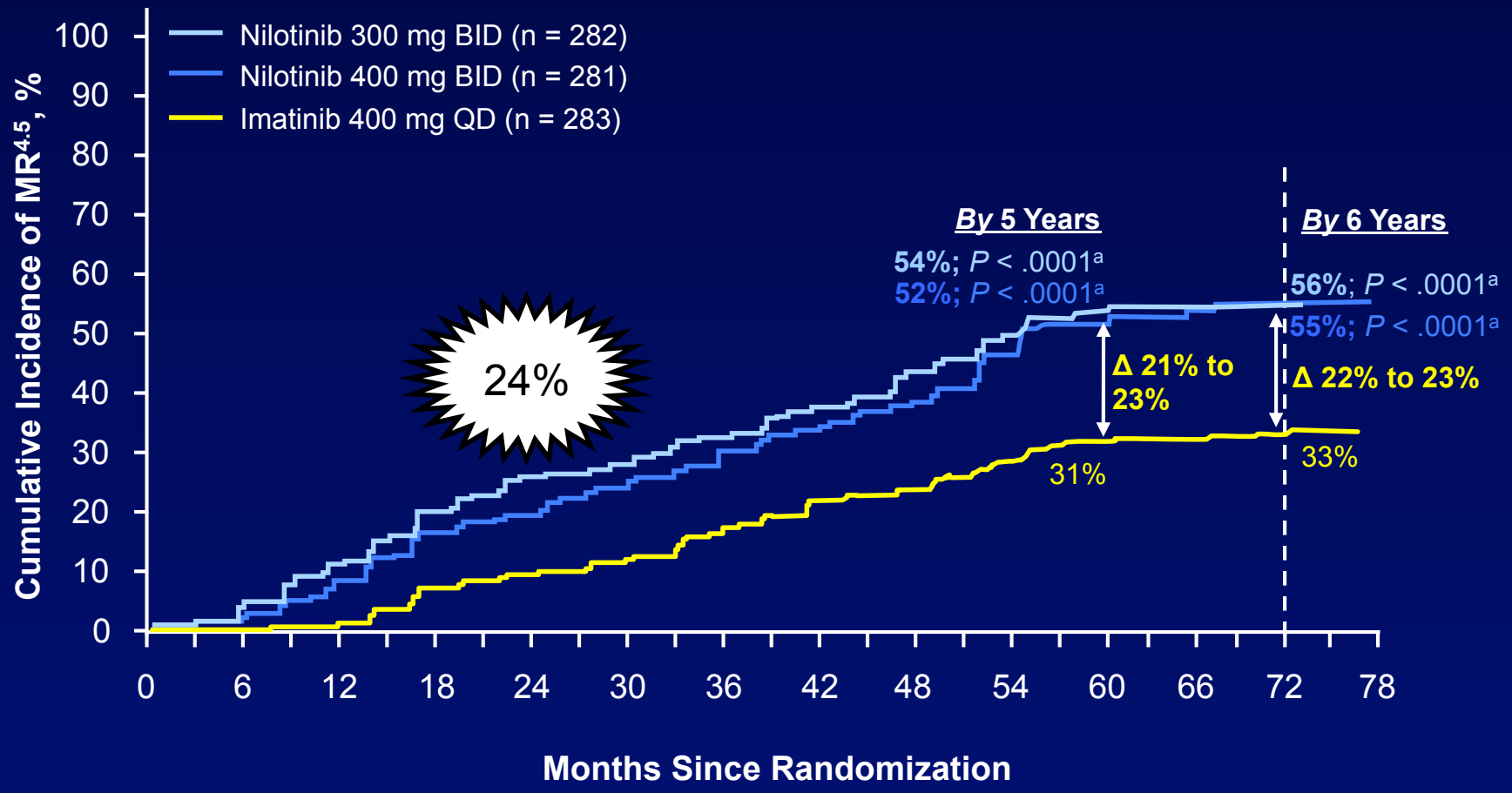
Note: Data from different studies, please interpret with care.

[&] ENESTnd: death from any cause or progression to AP/BC. DASISION: doubling of WBC count, loss of CHR, increase in Ph-positive metaphases to >35%, transformation, or death from any cause

^ ENESTnd Including events occurring on core or extension treatment or during f/u after treatment discontinuation; DASISION Total n. of deaths on-study treatment and in follow-up after discontinuation of randomized treatment.

[1] Hughes et al., EHA 2014 Abstract S677
[2] Cortes J. et al. ESH, iCMLf 2104

ENESTnd: cumulative incidence of MR4.5 by 6 years



KM-estimated median times to first $MR^{4.5}$ were:

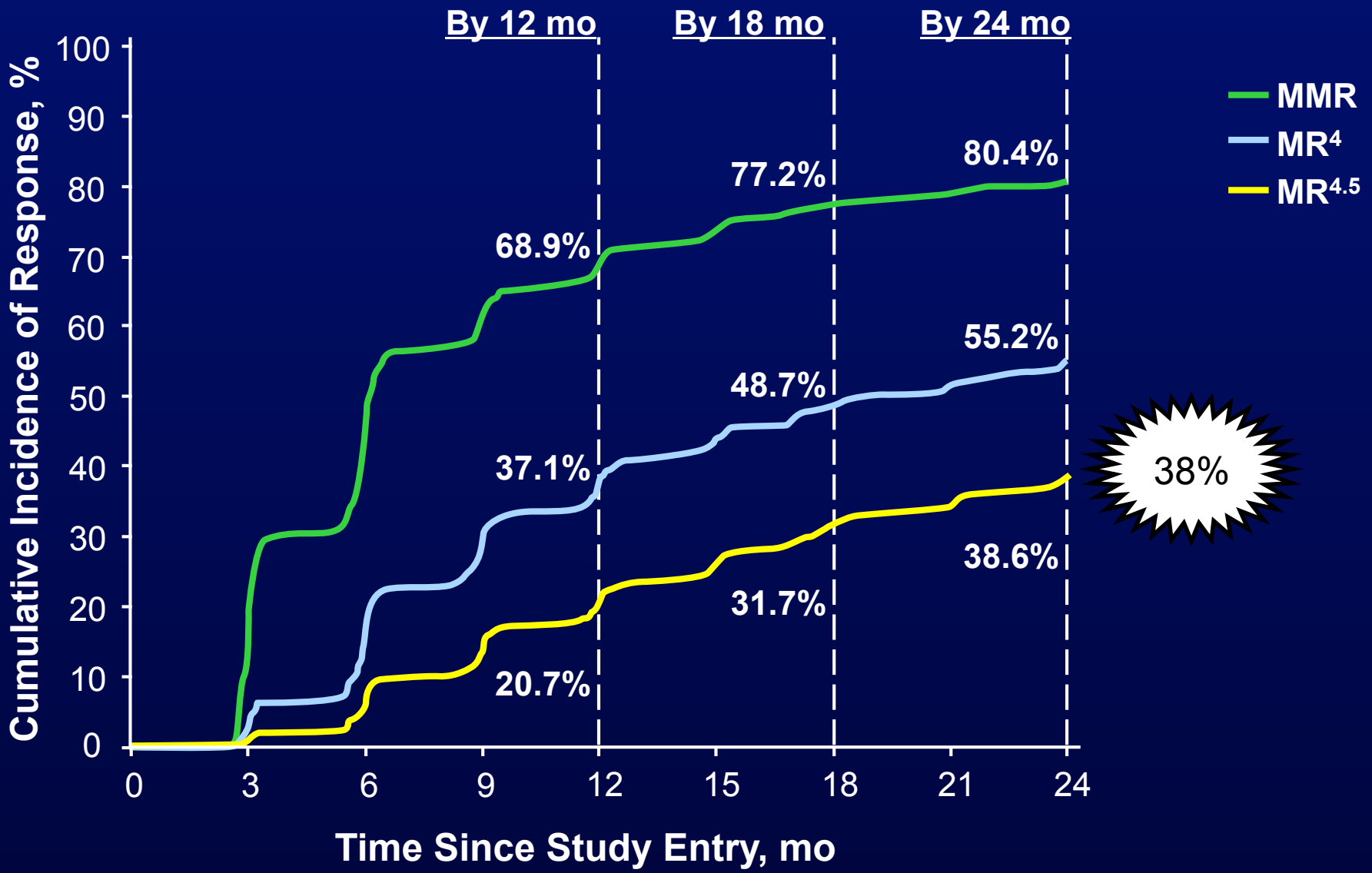
- Nilotinib 300 mg BID: 45.5 months (hazard ratio [HR] vs imatinib, 2.0387 [95% CI, 1.5807-2.6295]; nominal *P* < .0001)
- Nilotinib 400 mg BID: 49.8 months (HR vs imatinib, 1.7770 [95% CI,1.3780-2.2915]; nominal *P* < .0001)
- Imatinib 400 mg QD: 61.1 months

[a] *P* values are nominal.

Larson et al. *Blood*. 2014:[abstract 4541].

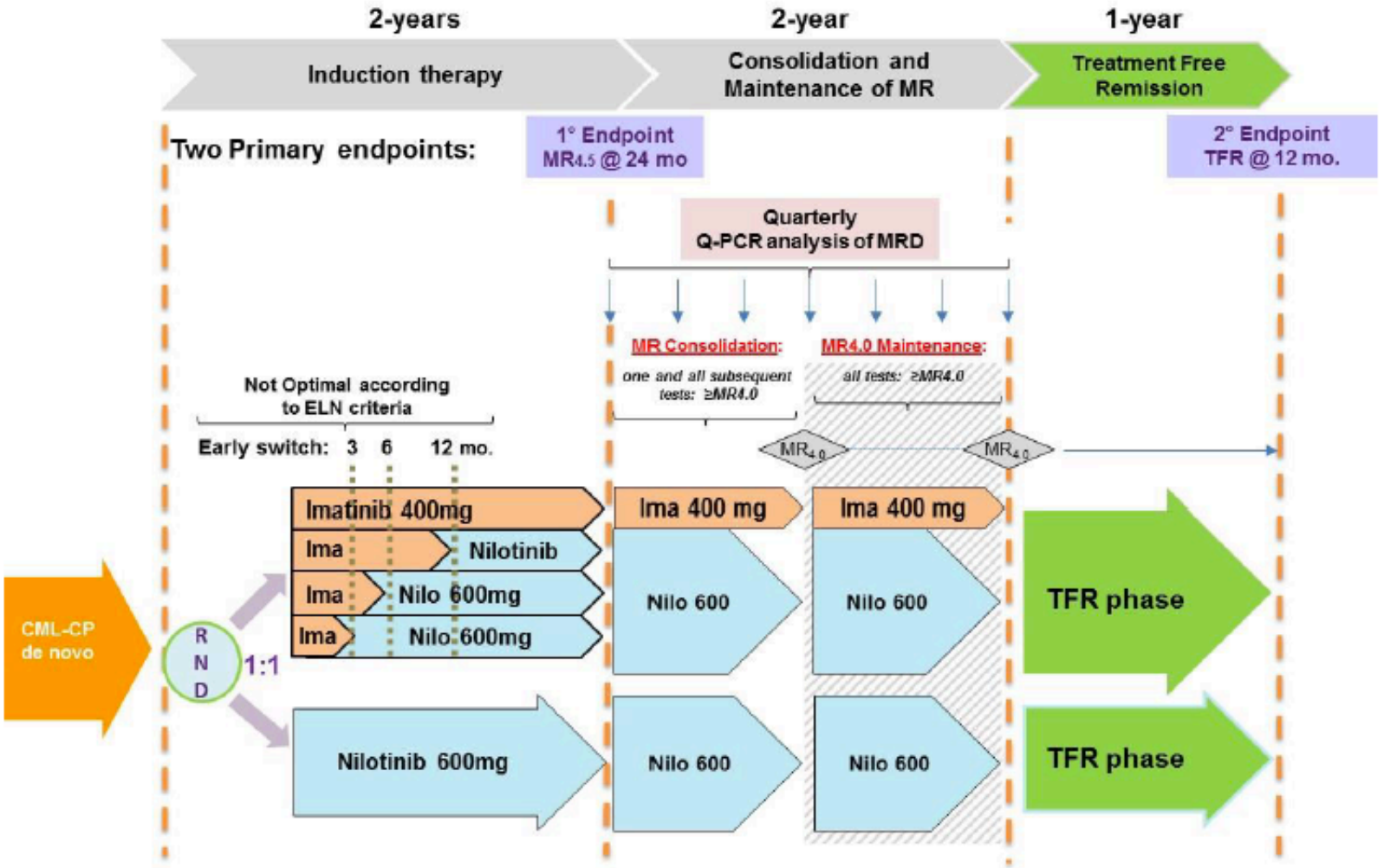
ENEST1st Final Analysis

Cumulative Incidence of MMR, MR^4, and $MR^{4.5}$



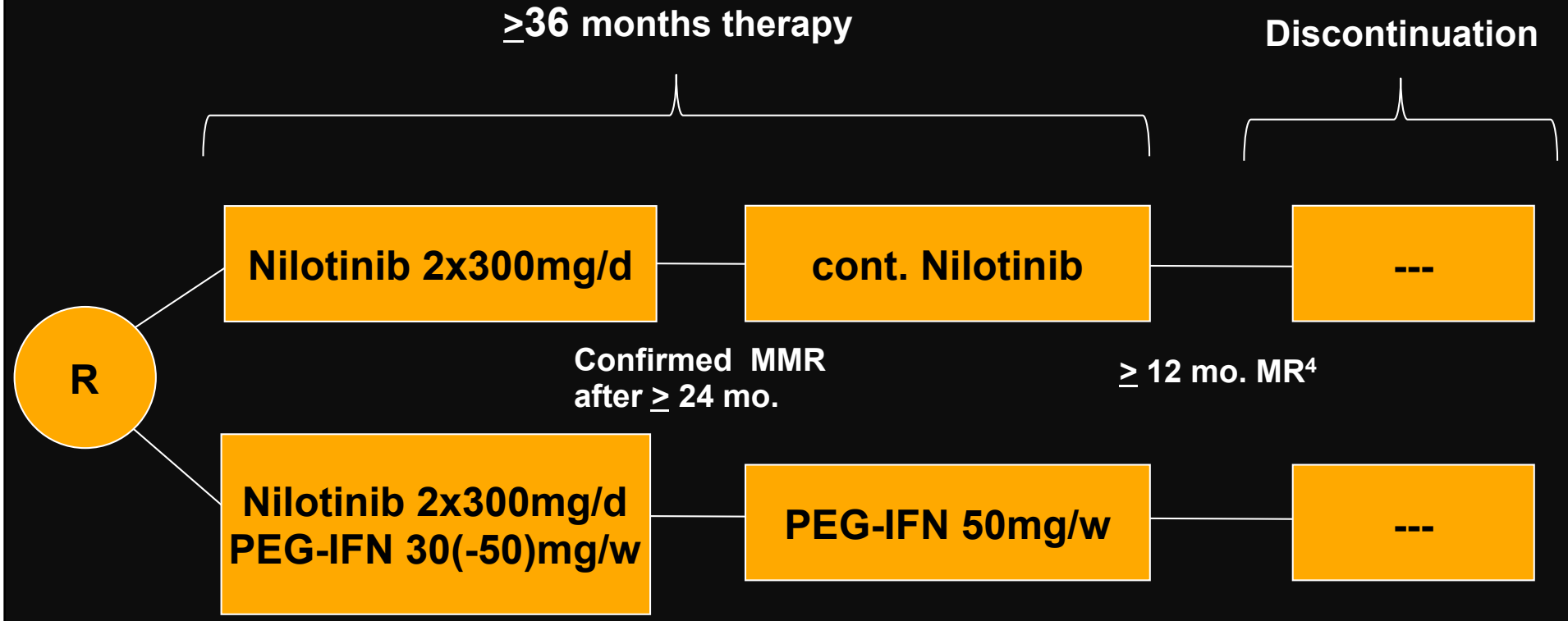
SUSTRENIM TRIAL

Sustained treatment-free remission in BCR-ABL+ chronic myeloid leukemia: a prospective study comparing Nilotinib versus Imatinib with switch to Nilotinib in absence of optimal response.



DR

TIGER (TKI + IFN in GERmany) TRIAL

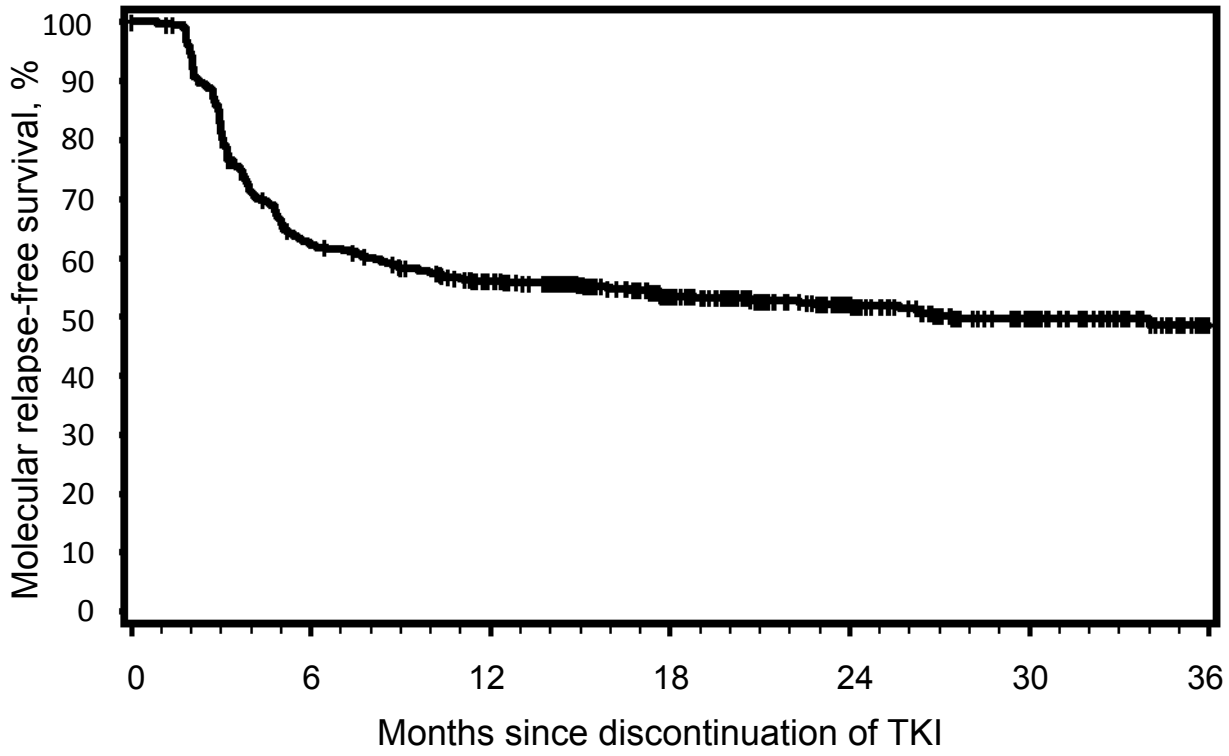


Nilotinib Intolerance → Imatinib
Nilotinib Resistance → Transplantation/Dasatinib
Suboptimal Response → Nilotinib 400 mg BID

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

PI A. Hocchaus

EUROSKI
Molecular relapse-free survival (n=750)



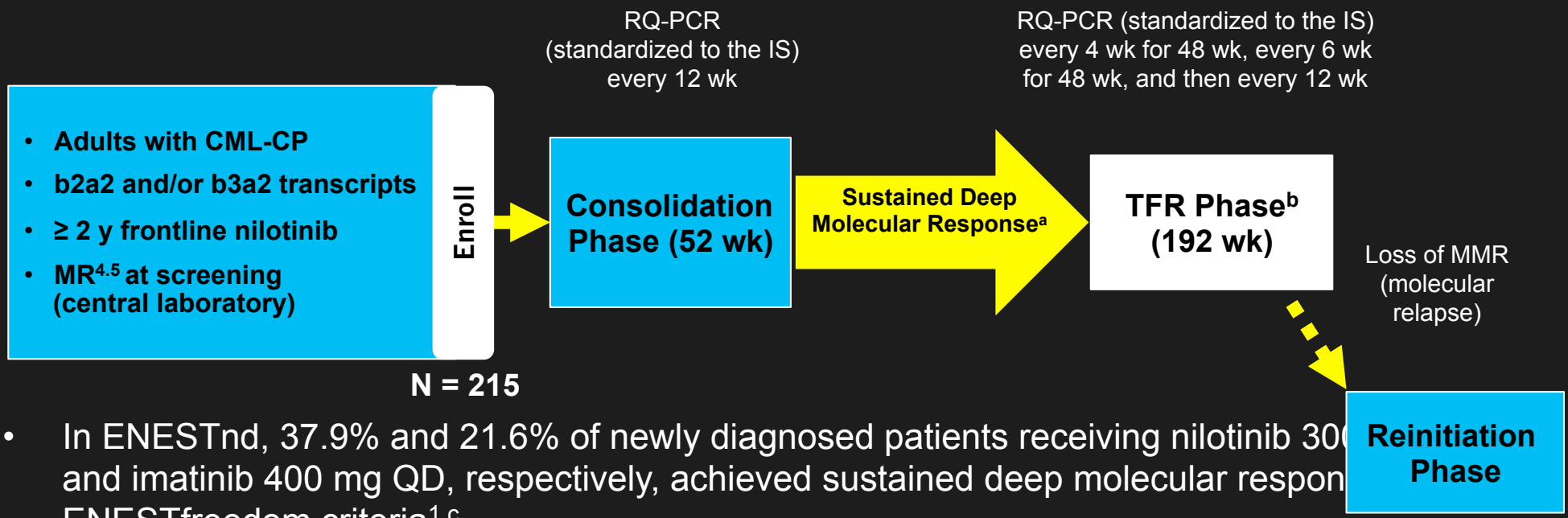
Month	MolRFS %	95%-CI
6	62	59-67
12	56	52-59
24	52	48-56
36	49	44-53

Events:
Molecular relapse n= 348
Death in remission n=5

For patients who resumed treatment, median time to restart was 4.1 months

Richter et al, EHA 2016

ENESTfreedom Study Design



- In ENESTnd, 37.9% and 21.6% of newly diagnosed patients receiving nilotinib 30(and imatinib 400 mg QD, respectively, achieved sustained deep molecular respon ENESTfreedom criteria[1,c]

[a] Defined as the following (in the last 4 quarterly PCR assessments): $MR^{4.5}$ in the last assessment, no assessment worse than MR^4, and ≤ 2 assessments between MR^4 and $MR^{4.5}$. [b] Post-treatment follow-up to continue up to 192 weeks after the last patient enters the TFR phase. [c] Defined as ≥ 3 years TKI therapy and ≥ 1 year sustained deep molecular response (after ≥ 2 years therapy).

BID, twice daily; CML-CP, chronic myeloid leukemia in chronic phase; RQ-PCR, real-time quantitative polymerase chain reaction.

1. Hochhaus A, et al. *Blood*. 2015;126 [abstract 2781].

Presented by: Prof Andreas Hochhaus

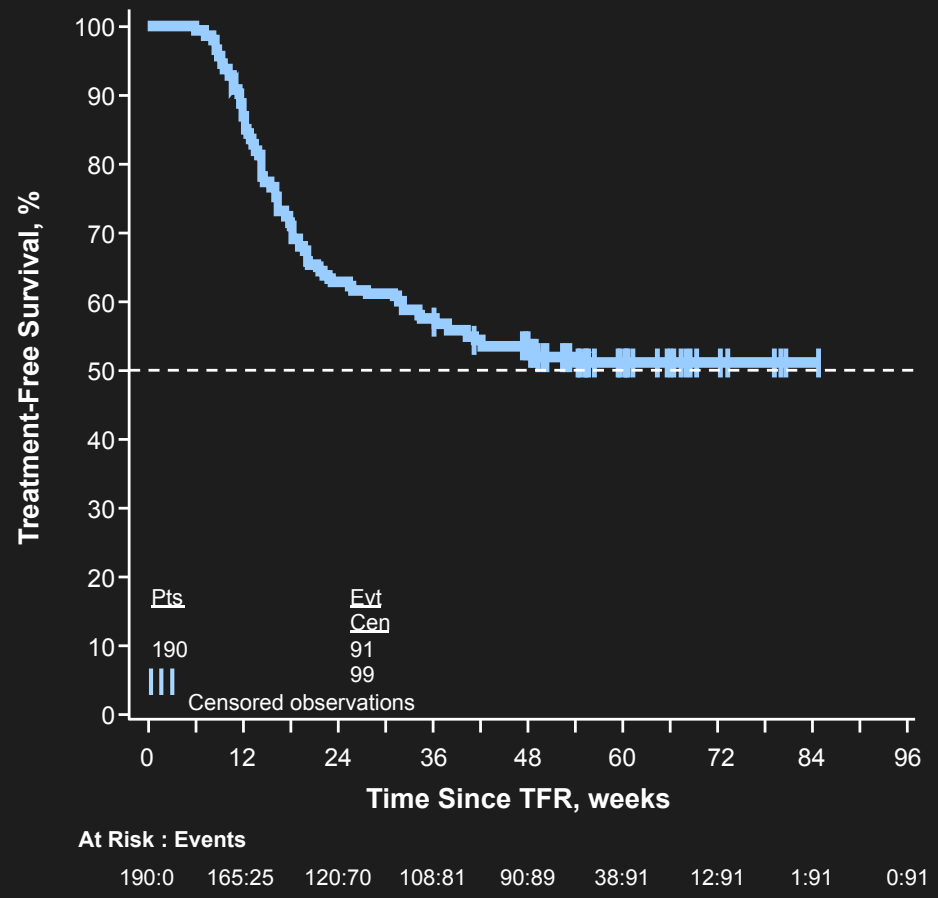
TFR Population Characteristics

	TFR Population (n = 190)
Median age at study entry (range), y	55 (21-86)
Median time from first $MR^{4.5}$ until study entry (range), mo	18.3 (0.3-70.9)
Median total nilotinib duration prior to TFR (range), mo	**43.5 (32.9-88.7)**
Median actual nilotinib dose intensity during consolidation phase (range), mg/d	600 (400-600)
Median follow-up in TFR phase, wk	49.4

Primary Endpoint and Treatment-Free Survival

- 98 of 190 patients (51.6%; 95% CI, 44.2-58.9%) remained in TFR after 48 weeks (primary endpoint)
- Statistical criterion for trial success was that the lower limit of the 95% CI of the observed primary endpoint be > 50%

Kaplan-Meier Estimated Treatment-Free Survival[a]



[a] Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause.

Presented by: Prof Andreas Hochhaus

Moving treatment-free remission into mainstream clinical practice in CML*

Criteria	Green	Yellow	Red
Institutional criteria met (per table 1)	Yes	-	No
Sokal score at diagnosis	Non-high	High	-
E			
C			
Response to first line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	> 8 years	3–8 years	< 3 years
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0
Duration of deep molecular response monitored in a standardized laboratory	> 2 years	1–2 years	< 1 year

All green lights: strong recommendation to consider TKI withdrawal

Any yellow lights: only consider TKI withdrawal in high priority circumstances (e.g. significant toxicity or planned pregnancy)

Any red lights: TKI withdrawal not recommended except in clinical trial

*** Hughes & Ross, Blood, 128:1; 17-23 (2016)**

Regimi di trattamento chemotherapy-free

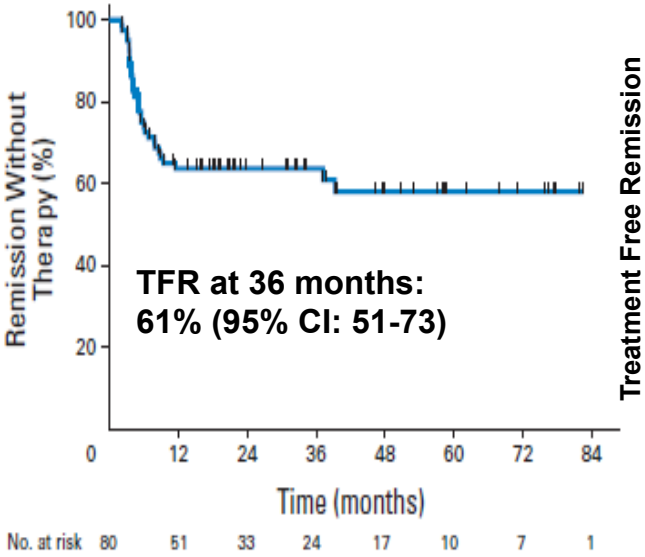
Nella Leucemia Mieloide Cronica

Gianantonio Rosti, MD

GIMEMA CML WP

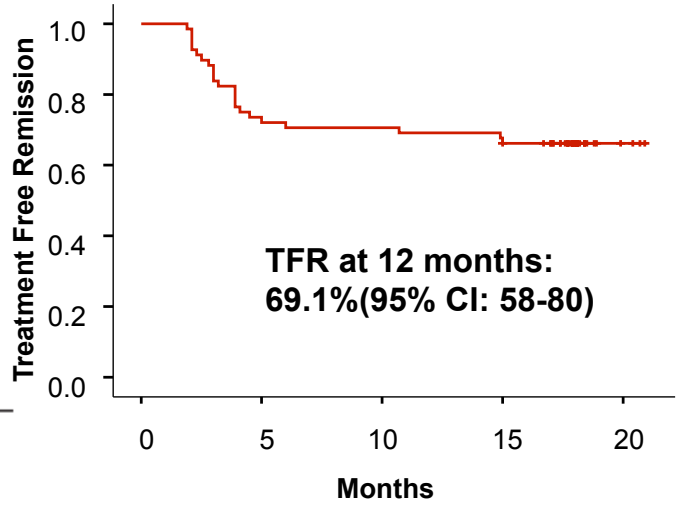
Imatinib-free remission:
A-STIM, JALSG-STIM213 and KID

A-STIM
- Imatinib ≥ 3 years
- CMR4.5 ≥ 2 years, occasional *BCR-ABL*+
- Relapse = loss of MMR



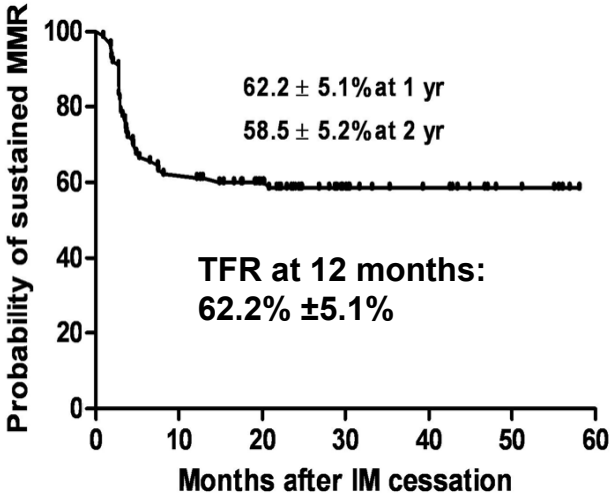
TFR at 36 months:
61% (95% CI: 51-73)

JALSG-STIM213
- Imatinib ≥ 3 years
- MR4.5 ≥ 2 years
- Relapse = loss of MMR



TFR at 12 months:
69.1%(95% CI: 58-80)

KID
- Imatinib ≥ 3 years
- CMR4.5 ≥ 2 years
- Relapse = loss of MMR



TFR at 12 months:
62.2% ±5.1%

Rousselot et al. JCO 2014; 32: 424-430.
Lee et al. Haematologica. 2016 Feb 17. pii: haematol.2015.139899. [Epub ahead of print]
Takahashi et al. Blood (ASH) 2015: abstract 4035.

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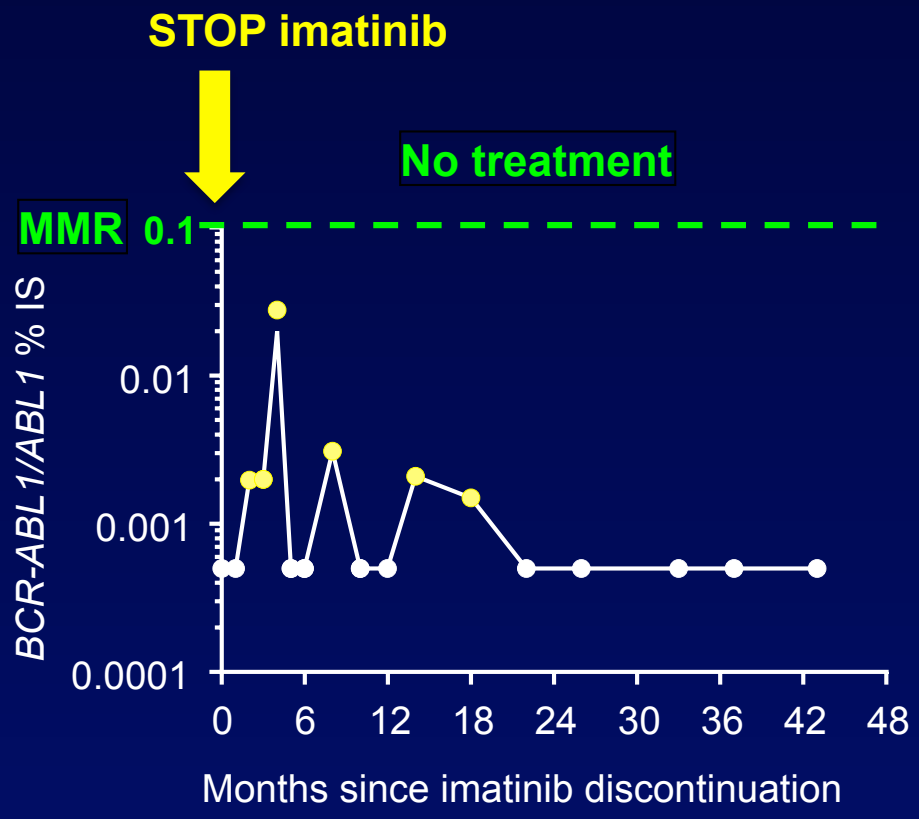
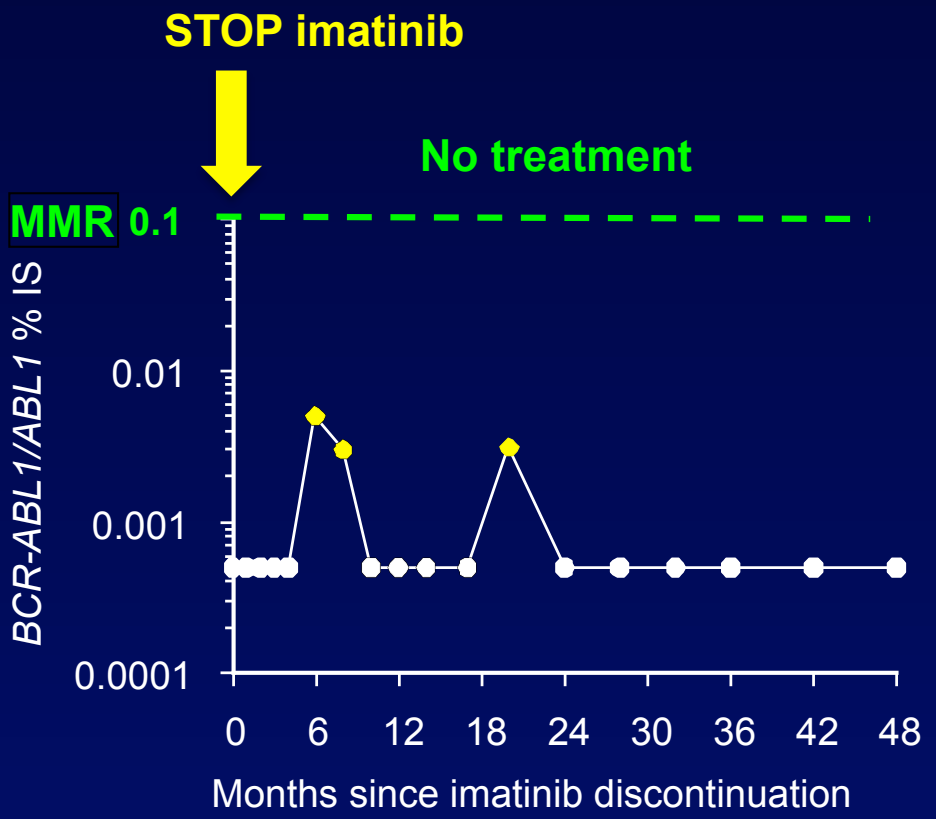




STIM: relapse
TWISTER: relapse
A-STIM: no relapse
JALSG-STIM123: no relapse

STIM: no relapse
TWISTER: relapse
A-STIM: no relapse
JALSG-STIM123: no relapse

● Detectable *BCR-ABL* ● Undetectable *BCR-ABL* ≥ 32000 copies of *ABL*

D. Rea personal data
Patients enrolled in imatinib discontinuation studies

DR

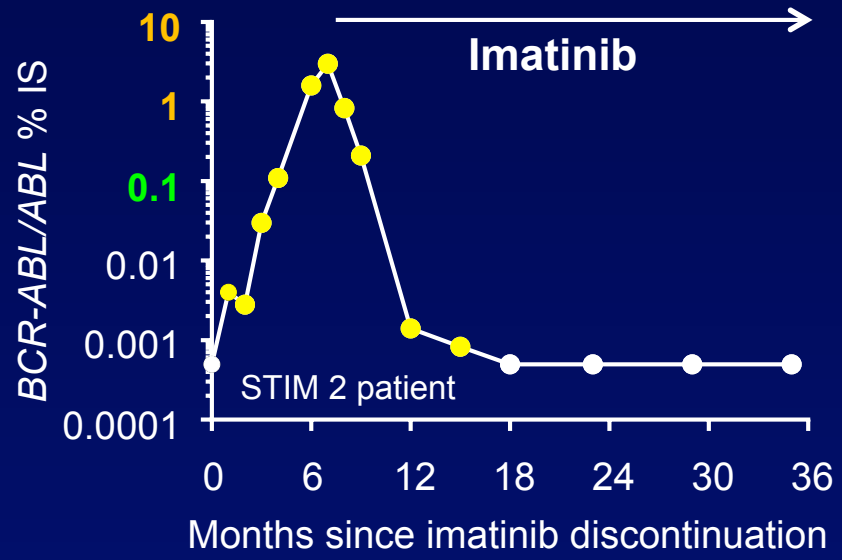
BCR-ABL transcripts in patients remaining in MMR

Patients in MMR without therapy (median follow-up 17 months: 7-37)	n=23
Always undetectable	7/23 (30.4%)
Occasionally detectable on 1 test	8/23 (34.8%)
Occasionally detectable on ≥ 2 consecutive tests	8/23 (34.8%)

Rea, ASH2013

Safety of imatinib discontinuation:
response to treatment resumption

- No case of imatinib resistance upon treatment resumption has been described in reported studies: MMR and deep molecular responses rapidly regained



- One case of acute lymphoblastic transformation in the A-STIM study, in a patient who had lost MMR after imatinib discontinuation but who had regained MMR after treatment reintroduction.

Mahon et al. Lancet Oncol 2010; 11: 1029-1035.
Ross et al. Blood 2013; 122: 515-522.
Mahon et al. Blood (ASH 2013): abstract 654.
Rousselot et al. JCO 2014; 32: 424-430.
Mahon et al. Blood (ASH 2014); 124: abstract 151.
Takahashi et al. Blood (ASH) 2015: abstract 4035.
Mori et al. Am J Hematol 2015; 90: 910-914.
Lee et al. Haematologica. 2016 Feb 17. [Epub ahead of print]

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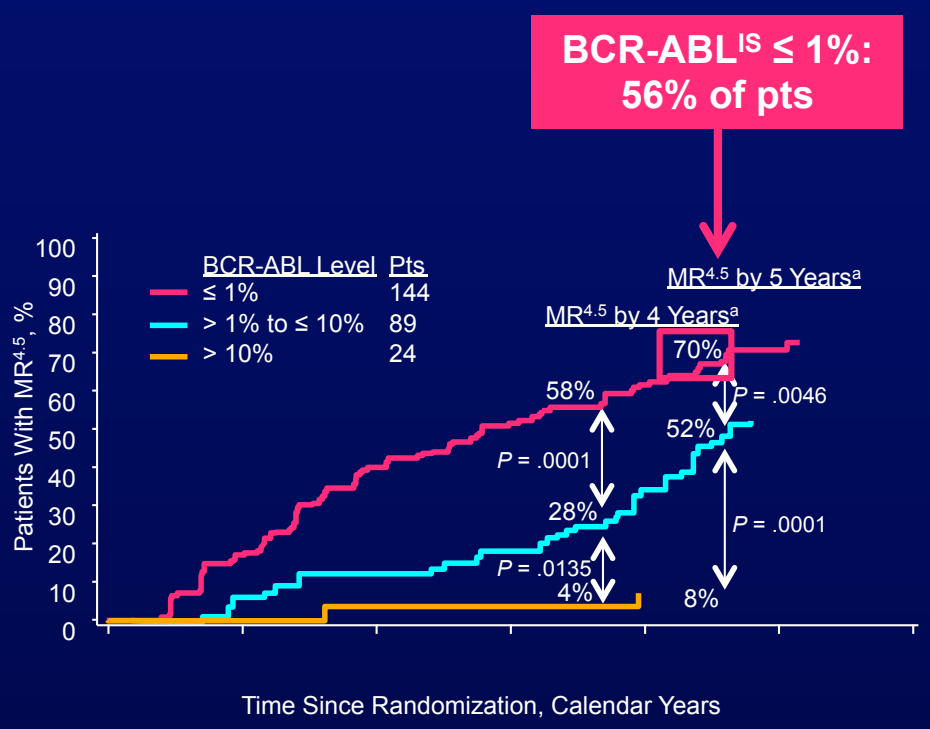
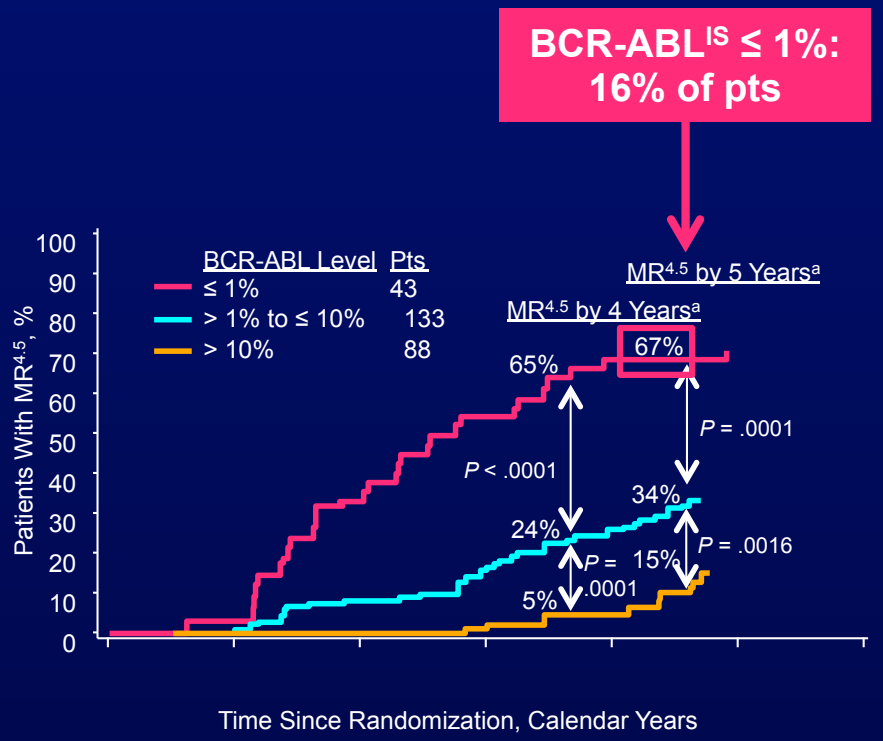
Proportion of Patients With MR$^{4.5}$ by BCR-ABL Levels at 3 Months

Nilotinib 300 mg BID



Imatinib 400 mg QD



- Patients with BCR-ABL ≤ 1% at 3 months have significantly higher rates of MR$^{4.5}$ by 5 years
- More patients achieve BCR-ABL ≤ 1% at 3 months on nilotinib 300 mg BID vs imatinib

[a] Cumulative response rates reported consider each year to consist of twelve 28-day cycles.

Saglio G, et al. *Blood*. 2013:[abstract 92].