La terapia della LMC: è possibile guarire senza trapianto?

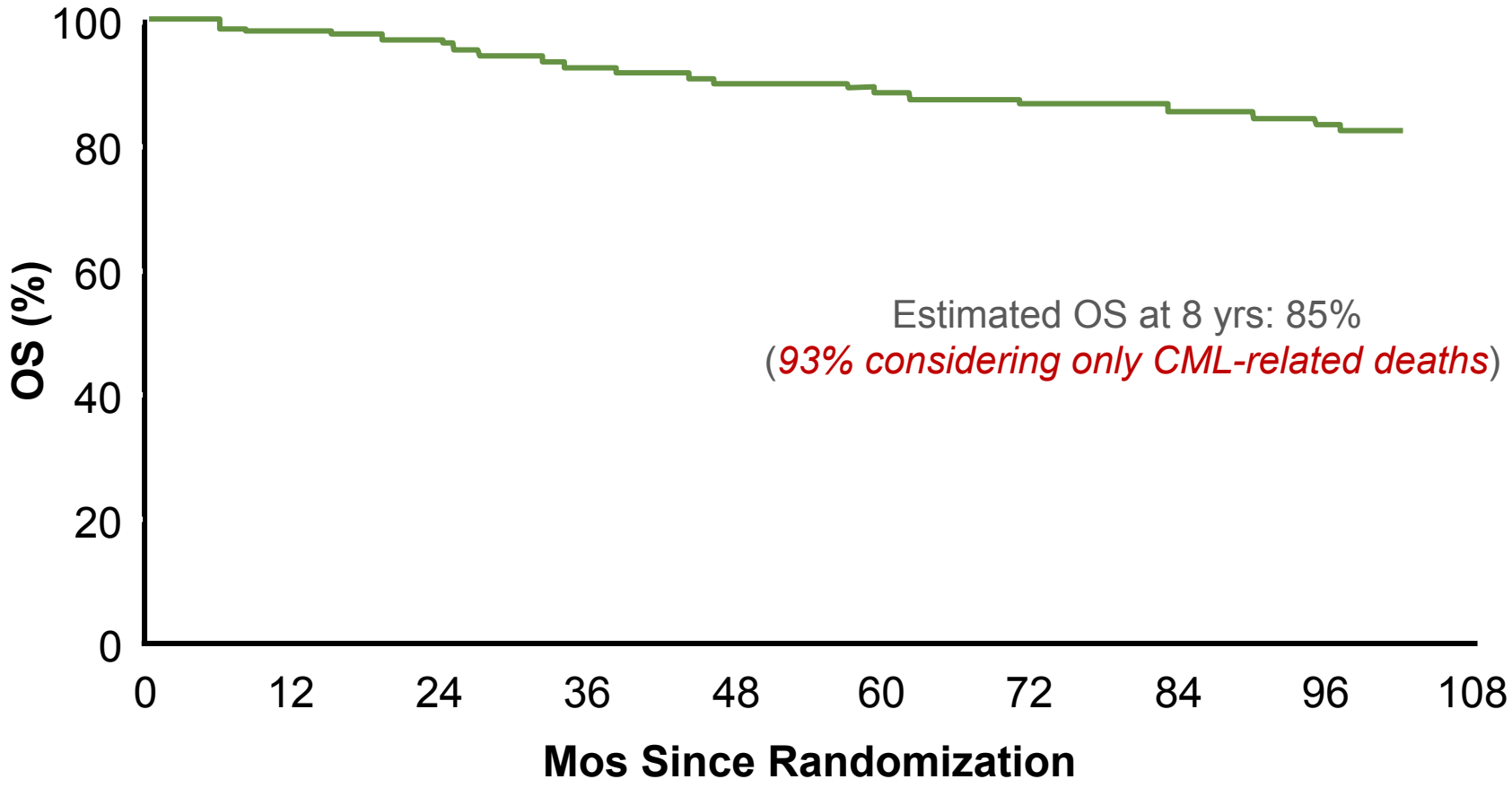
Fabrizio Pane

What could be the concept of "Cure" in CML?

- Sustained DMR ***with or without*** TKI therapy
- *And* 100% CML-related survival
- *And* QoL comparable to age-matched population

Medium-term Results of Imatinib Treatment in CML

IRIS Trial Update: the 8-Year Overall Survival



Overall outcome of TKI treatment in CML

ENESTnd + DASISION, 4 years data

	NILO+DASA	vs	IMATINIB	p
No. of pts	540		541	
Still on treatment	66%		61%	
Cum. prob. of MR 3.0	75%		58%	<0.001
Cum. prob of MR 4.5	40%		29%	<0.001
“Progression”#	6.8%		7.6%	
“PFS”	91%		91%	
AP/BP (transformation)	3.9%		7.4%	0.04
Death	6.3%		7.4%	
Overall survival	93%		92%	

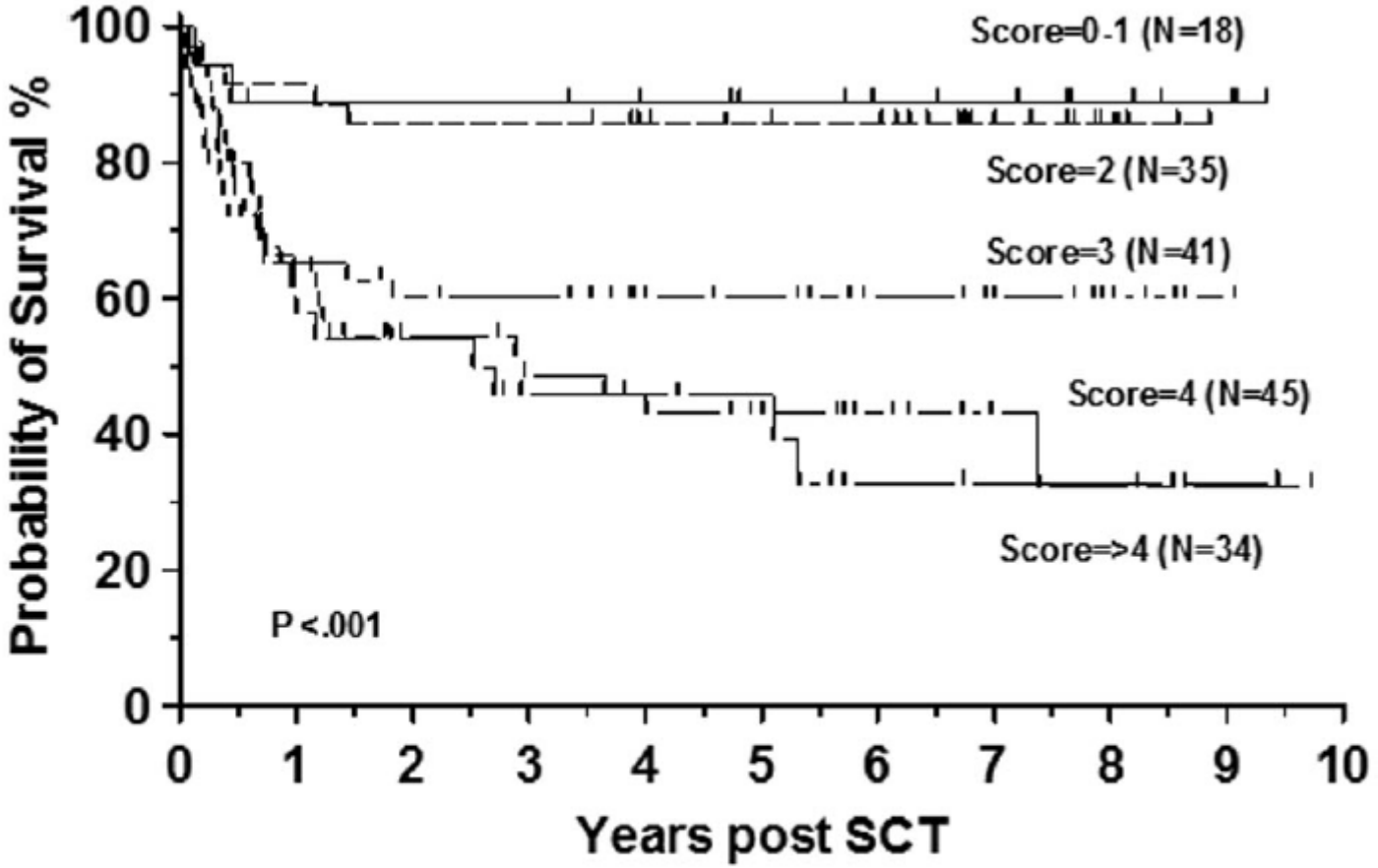
 # ENESTnd: AP, BP, death due to any cause at any time
DASISION: rising WBC count, loss of CHR, loss of MCyR, CCA/Ph+, AP, BP

TKI Side effects

- Heterogeneous pattern of the different TKIs
- Three general categories of side effects
  - Early onset, serious (grade 3/4) side effects
    - 10% of patients
    - Cause of early discontinuations
  - Minor (grade 1/2), mid / long term side effects
    - 50% of patients
    - Manageable but affect quality of life also leading to poor adherence
  - Off-target complications
    - Cardiovascular system, vessels, liver, pancreas, metabolism etc.
    - Incidence and seriousness not fully understood

Three decades of transplantation for CML

Survival of 173 patients allo-allografted from 2000 to 2010 stratified by EBMT risk score



Jirí Pavlu, Blood. 2011;117(3):755-763.

Donor lymphocyte infusion for relapsed CML after SCT

Table 4 Time-dependent covariate Cox regression model of survival after DLI

Parameters	*HR*	*95% CI*	P-*value*
No. GVHD	1		
GVHD overall effect	2.27	1.5 3.6	0.0001
Acute GVHD	2.25	1.4 3.7	0.001
Chronic GVHD[a]	1.10	0.6 1.9	0.75
GVHD within 45 days[b]	2.78	1.6 4.8	0.001
GVHD after 45 days	1.85	1.0 3.3	0.013
Other covariates			
Stage of disease at DLI			0.0001
Molecular relapse	1		
Cytogenetic relapse	1.1	0.5 2.5	
Hematological relapse	2.33	1.1 4.9	
Accelerated phase	10.94	4.9 24.7	
Blast crisis	35.43	15.2 82.4	
Time from BMT to DLI			
<2 years	1		
>2 years	0.69	0.4 1.1	0.12

Abbreviations: CI = confidence interval; DLI = donor lymphocyte infusion; HR = hazards ratio.
[a]chronic GVHD without prior acute GVHD.
[b]GVHD irrespective of clinical presentation.

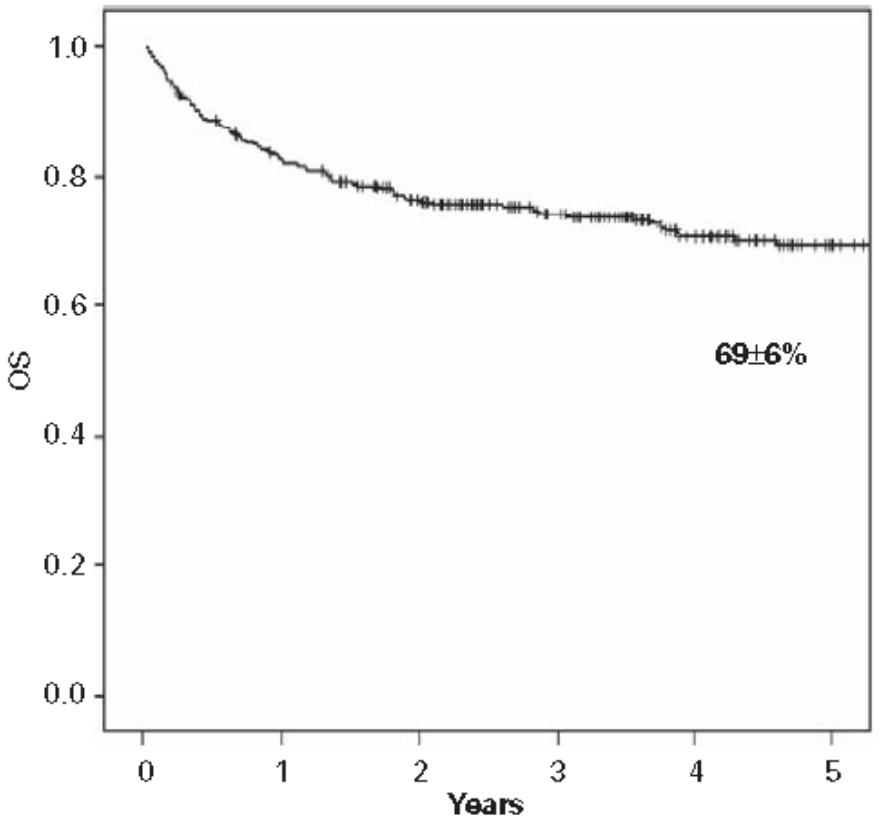


Figure 2 5-year OS after donor lymphocyte infusion of 69% (95% confidence interval 63 75%).

Relapse and Late Mortality in 5-Year Survivors of HSCT for CML in First CP

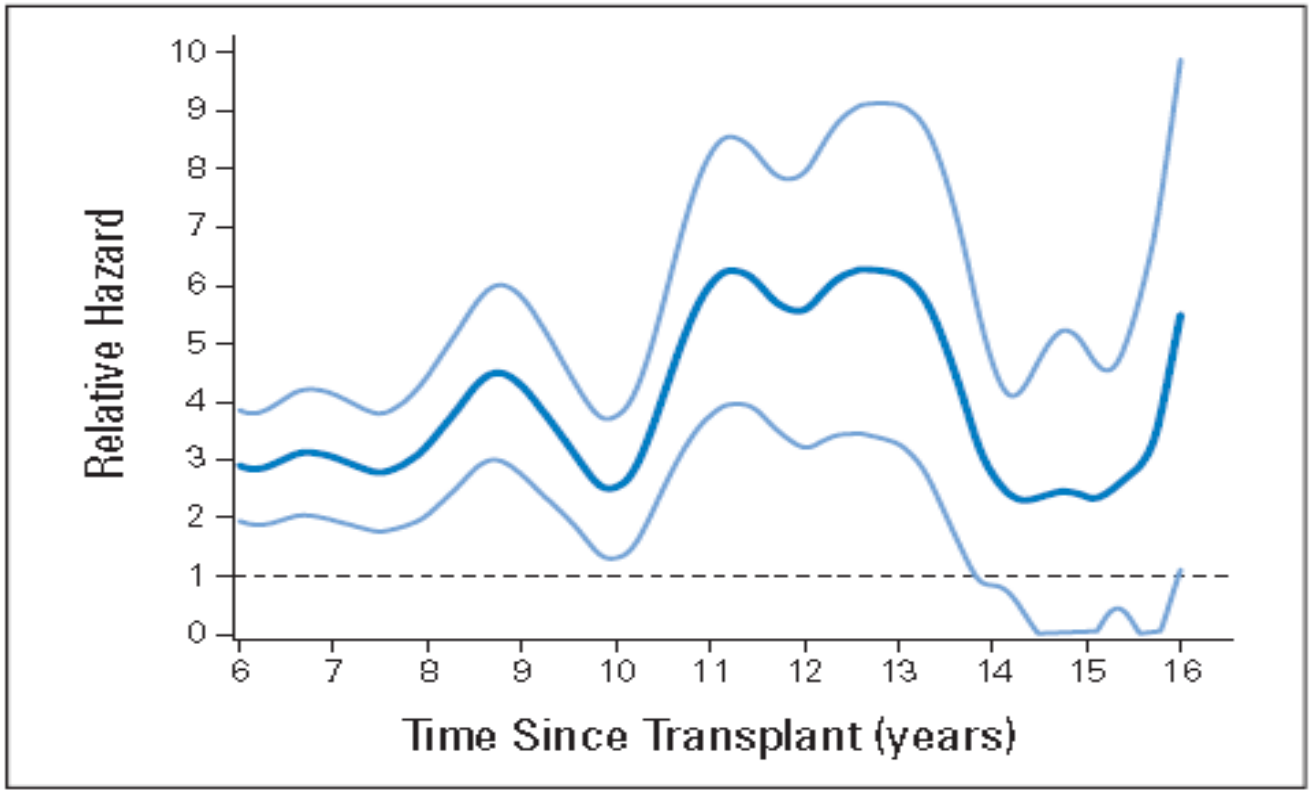


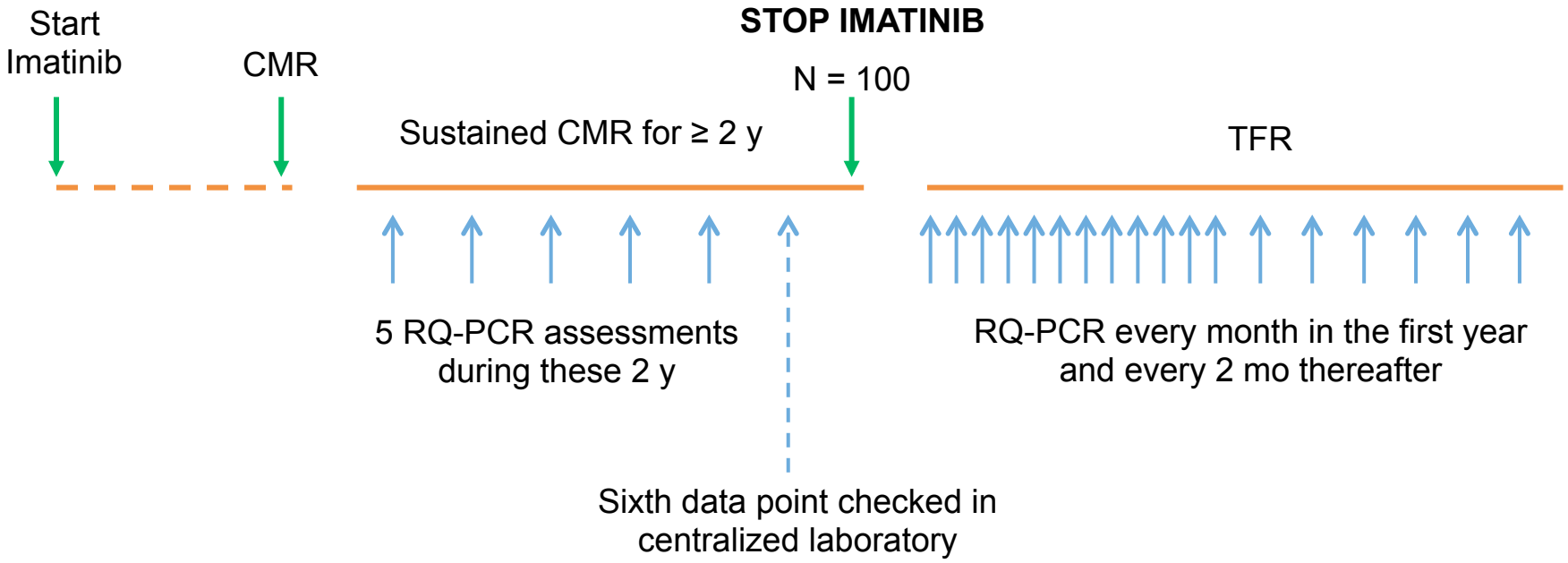
Fig 3. Relative excess mortality (dark blue line) compared with age-, sex-, and race- matched general population for patients surviving in remission for at least 5 years after myeloablative allogeneic hematopoietic cell transplant for chronic myeloid leukemia. A relative risk of 1 indicates that the mortality rate of the population of interest is similar to that of the general population. Light blue lines represent 95% CIs.

Goldman, J Clin Oncol, 2010, 28:1888-1895.

History of treatment discontinuation

- Successful discontinuation examples already in the IFN era
  - 22 of 44 patients in CCR stopped treatment successful (Bonifazi F. et al., Blood 2001)
  - 43% (of 15 patients) in CCR stopped treatment successful (Mahon FX. et al., JCO 2002)
  - 39 of 140 patients in CCR kept response without treatment for a median of 50 months (Kantarjian H. et al.,Cancer 2003)
- First case reports with TKI treatment already in 2004 (Mauro M. et al., Leuk Res 2004)
- Pilot study with 12 patients in 2007 (Rousselot P. et al., Blood)

STIM1 Study Design



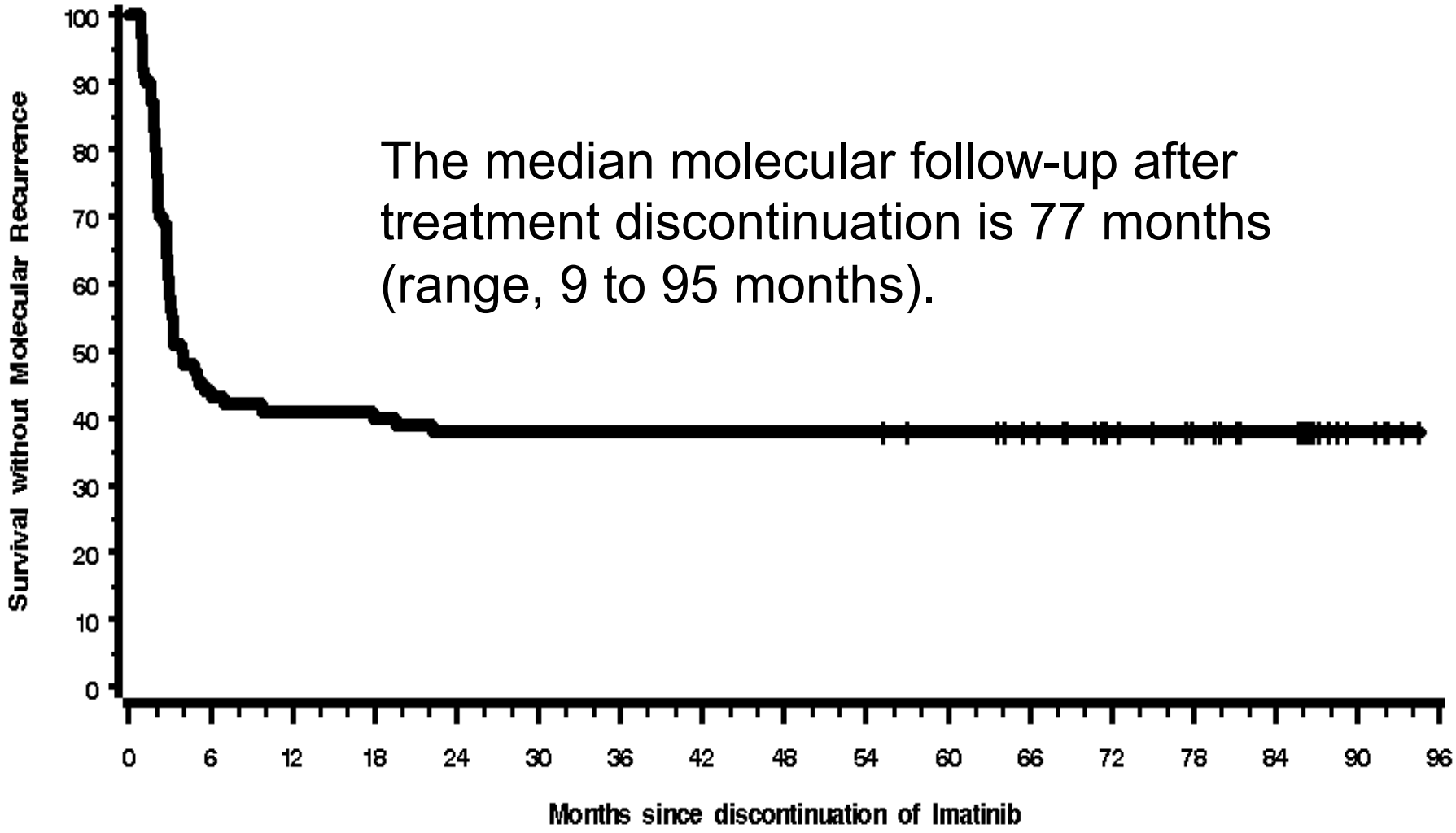
Response required to attempt TFR: Sustained CMR (no detectable *BCR-ABL1* for ≥ 2 consecutive years with ≥ 5 RQ-PCR assessments), confirmed in a central laboratory with a sensitivity of > 4.5 logs

Molecular relapse: Confirmed *BCR-ABL1* transcript positivity in 2 consecutive RQ-PCR assessments with a 1-log increase in the second assessment relative to the first, or loss of MMR in 1 assessment

CMR, complete molecular response; MMR, major molecular response (BCR-ABL1 ≤ 0.1% on the International Scale [IS]); RQ-PCR, real-time quantitative polymerase chain reaction; STIM1, Stop Imatinib 1 TFR study.

1. *Mahon FX, et al. Lancet Oncol. 2010;11:1029-1035.*
2. *Mahon FX, et al. Blood. 2013;122(21) [abstract 255].*
3. *Etienne G, et al. Blood. 2015;126(23) [abstract 345].*

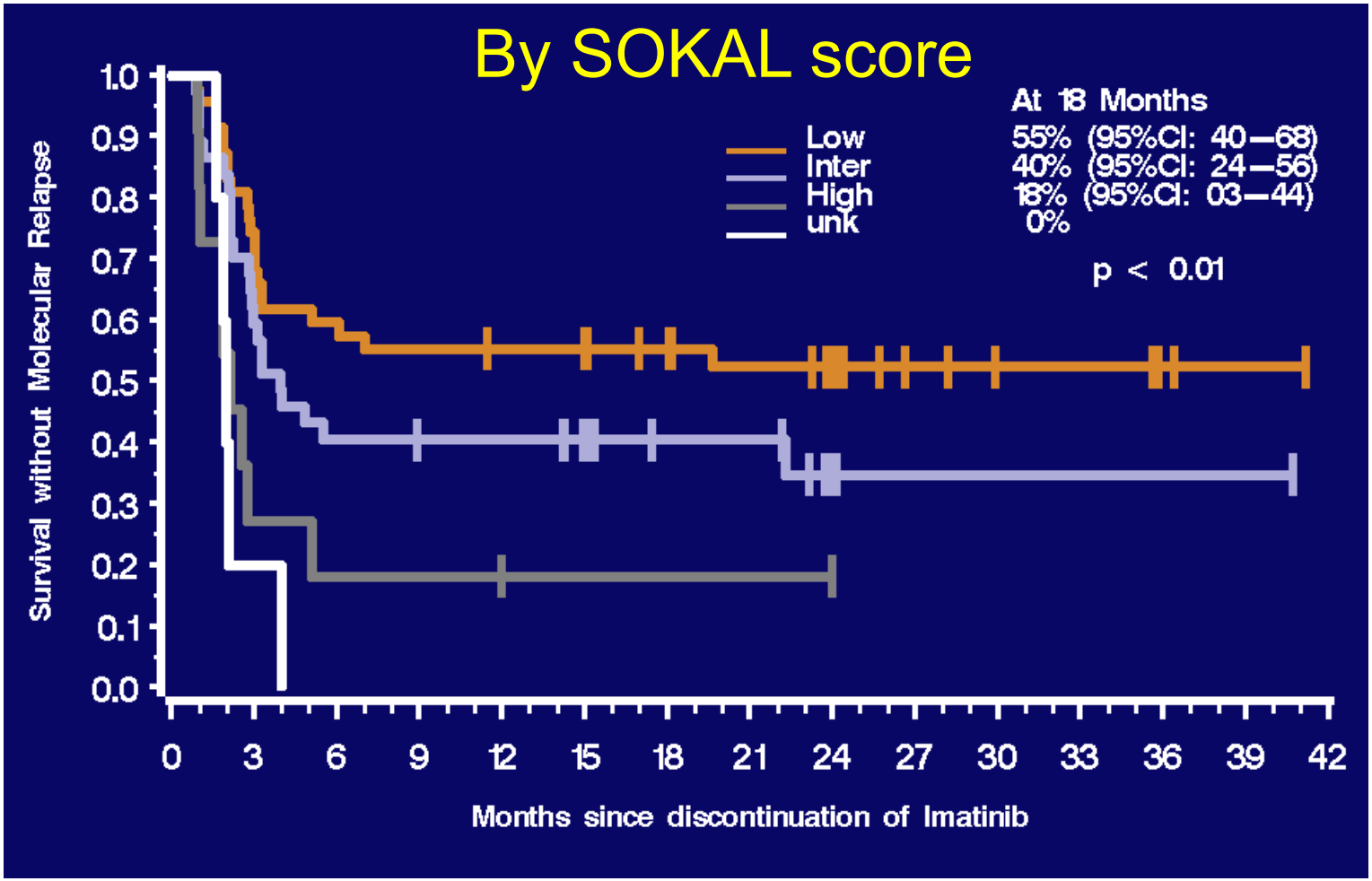
STIM 1: Molecular Recurrence-Free Survival (N = 100)



The median molecular follow-up after treatment discontinuation is 77 months (range, 9 to 95 months).

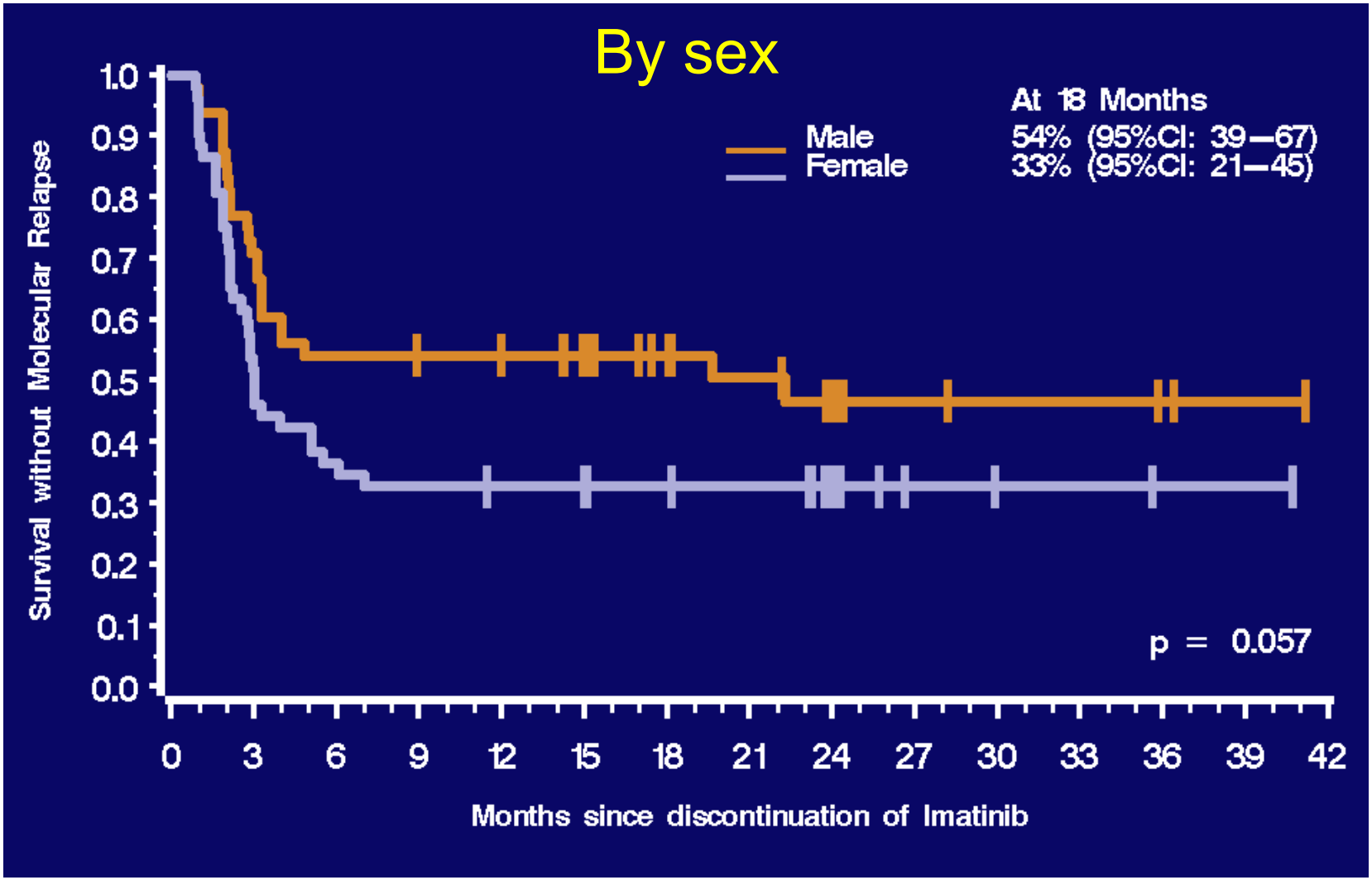
Etienne G, et al. ASH 2015. Abstract 345.

Kaplan-Meier probability of CMR after discontinuation of Imatinib in 100 CML patients

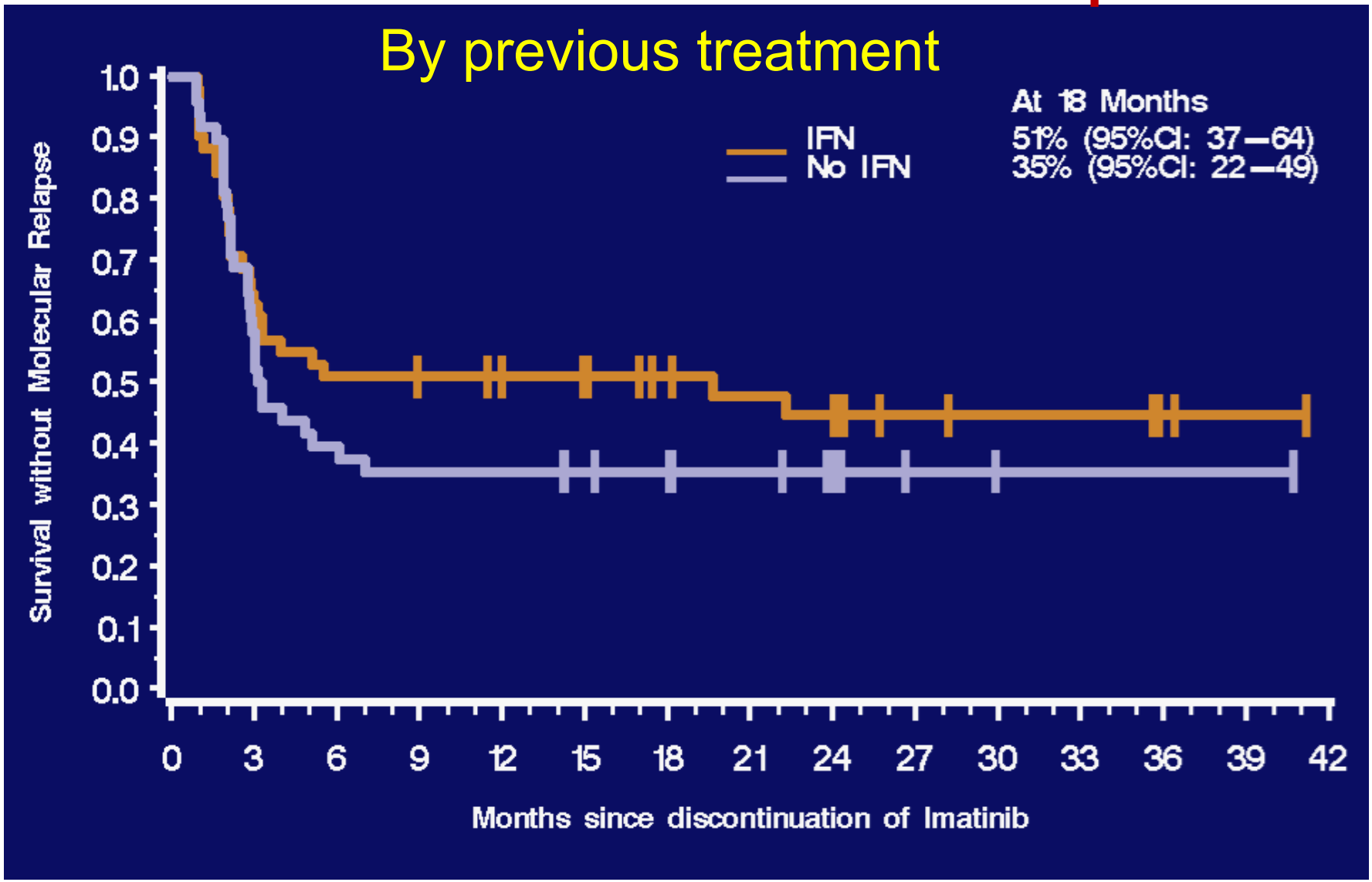


Among the 11 patients with high Sokal Risk score 9 relapsed

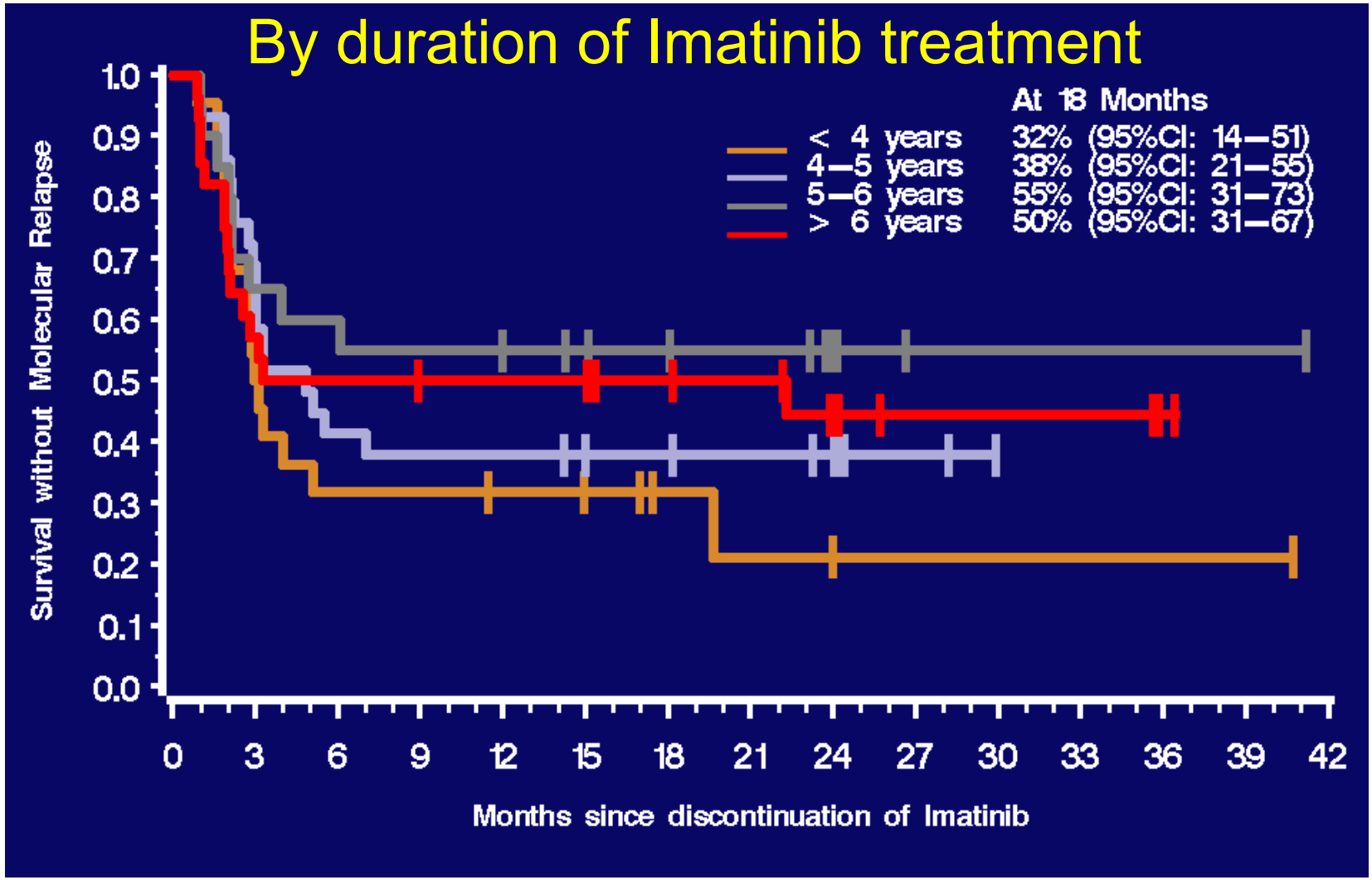
Kaplan-Meier probability of CMR after discontinuation of Imatinib in 100 CML patients



Kaplan-Meier probability of CMR after discontinuation of Imatinib in 100 CML patients



Kaplan-Meier probability of CMR after discontinuation of Imatinib in 100 CML patients



Imatinib discontinuation studies

Study	N	Treatment before discontinuation	Response Required to Stop Therapy	Definition of relapse	TFR (different FU)
STIM 1	100	IFN then Imatinib for 3 years	CMR	Loss of MMR or ≥1-log increase in BCR-ABL	39 %
STIM 2	200	Imatinib for ≥3 years	As for STIM	As for STIM	46 %
ALLG CML8	40	Imatinib for ≥3 years	UMRD 2 years	Loss of MMR or confirmed loss of $MR^{4.5}$	45 %
According to STIM	80	Imatinib for ≥3 years	As for STIM; occasional positive samples eligible	Loss of MMR	64 %
EUROSKI	868	Imatinib, Dasatinib, Nilotinib	MR^4 for ≥1year; TKI for ≥3 years	Loss of MMR	54 %
ISTAV	112	Imatinib	Undetectable PCR (3 PCRs)	Loss of MMR	52%
DESTINY	168	Imatinib, Dasatinib, Nilotinib	MR^4 and stable response under half standard dose for 12 months	Loss of MMR	In progress

2°-G TKI discontinuation studies

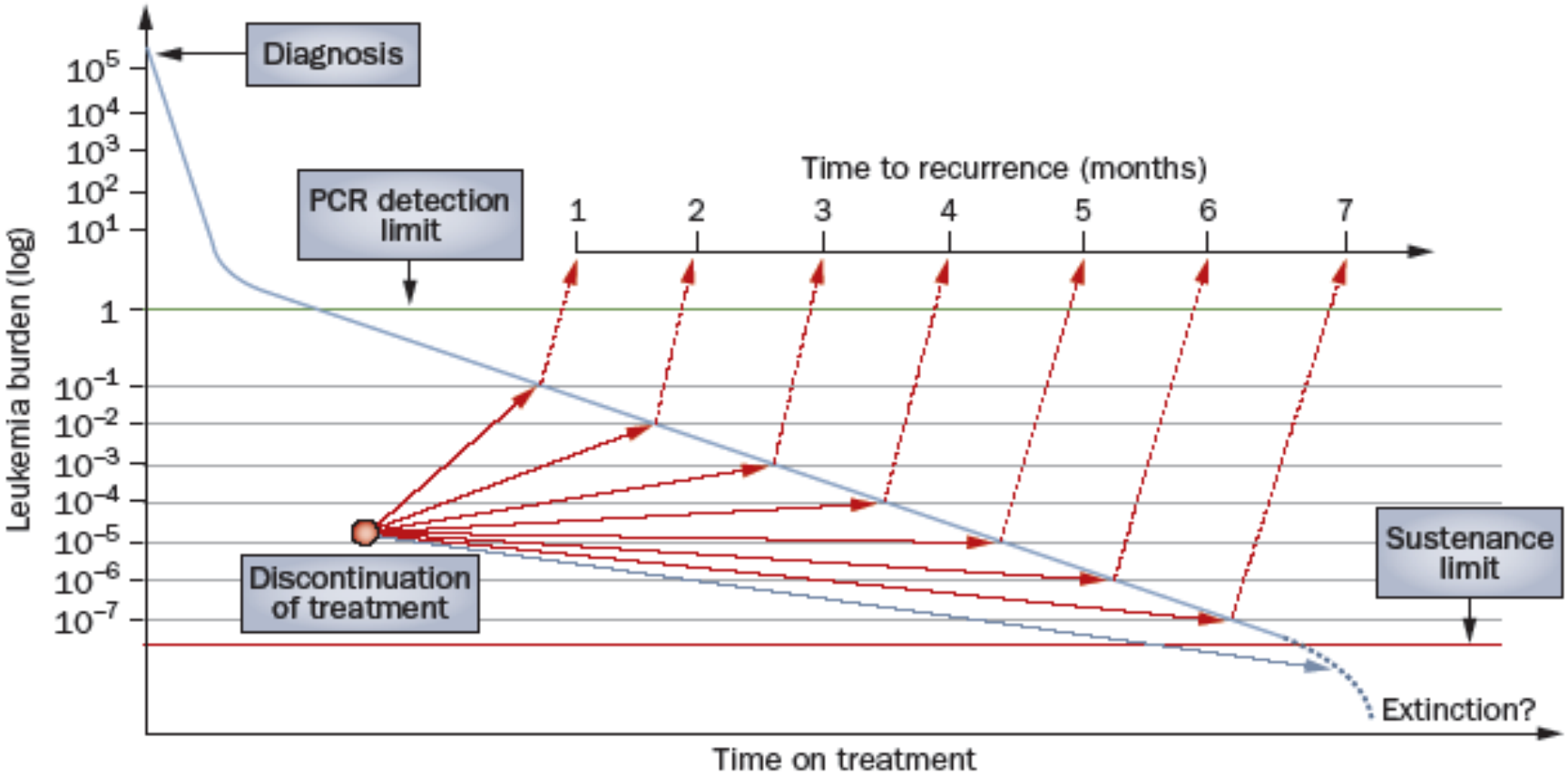
Study	N	Treatment before discontinuation	Response Required to Stop Therapy	Definition of relapse	TFR (different FU)
STOP 2G-TKI pilot	50	Nilotinib or Dasatinib	CMR for median 29 mo.	Loss of MMR	61%
ENEST freedom	175	Nilotinib	$MR^{4.5}$ for ≥1year	Loss of MMR	51.6%
ENESTop	117	Nilotinib	$MR^{4.5}$ for ≥1year	Confirmed loos of $MR^{4.0}$ or any loss of MMR	58.7%
ENESTpath	650	Nilotinib	Randomized $MR^{4.5}$ for ≥1year vs ≥2year	Confirmed loos of $MR^{4.0}$ or any loss of MMR	In progress
ENESTGoal	300	Nilotinib	$MR^{4.5}$ for ≥1year	Confirmed loos of $MR^{4.0}$ or any loss of MMR	In progress
DASFREE	75	Dasatinib	$MR^{4.5}$ for ≥1year	Loss of MMR	In progress
DADI	63	Dasatinib	DMR for ≥1year	Loss of MMR	48%

Deep Molecular Response

Issues relevant for a TFR trial

- Stability of response (sustained response)
  - Need for reproducibility at RQ-PCR low levels
    - NGS vs Digital PCR
- Sensitivity (4.5 vs 5.0 .. Better?)
  - Need for sensitive techniques
    - Digital PCR vs Genomic DNA PCR
- Quantitation of Ph+ Stem cells?

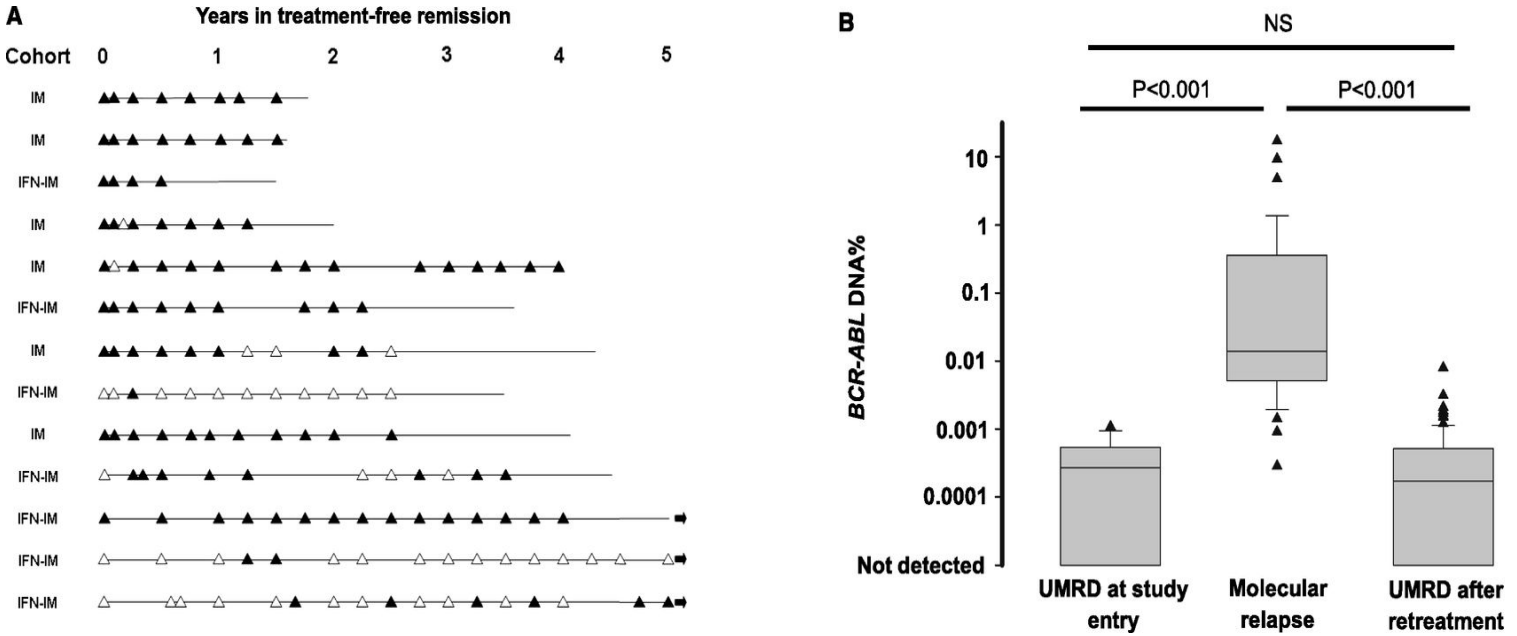
Hypothetical Model of CML persistence and recurrence versus extinction



The eradication of the leukemic clone may depend on inherent features of the disease or on the duration of therapy, or both.

Lessons learned from discontinuation trials

- Patients who discontinued treatment still have residual Ph positive cells left as indicated by genomic PCR data

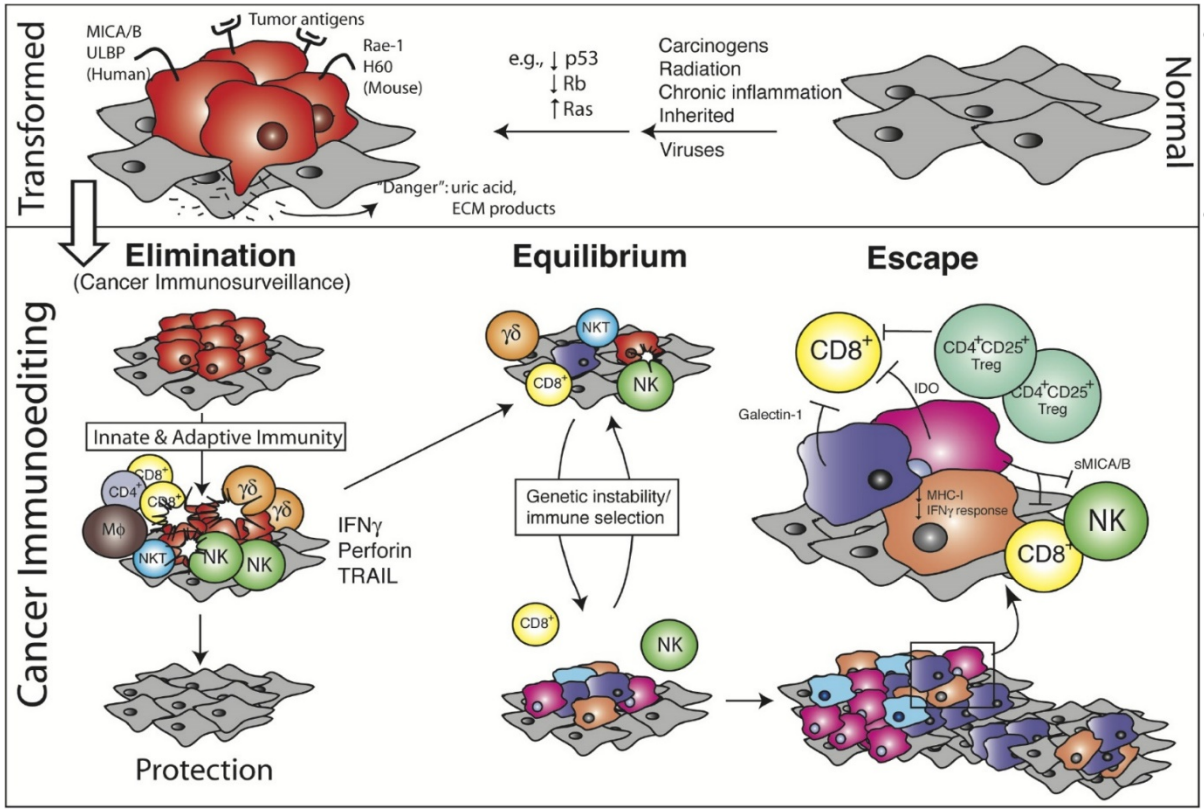


(*Ross et al Blood 2013*)

- Fluctuating levels of residual disease often observed in patients after treatment discontinuation

Does immune system play a role in CML control?

Cancer immunoediting

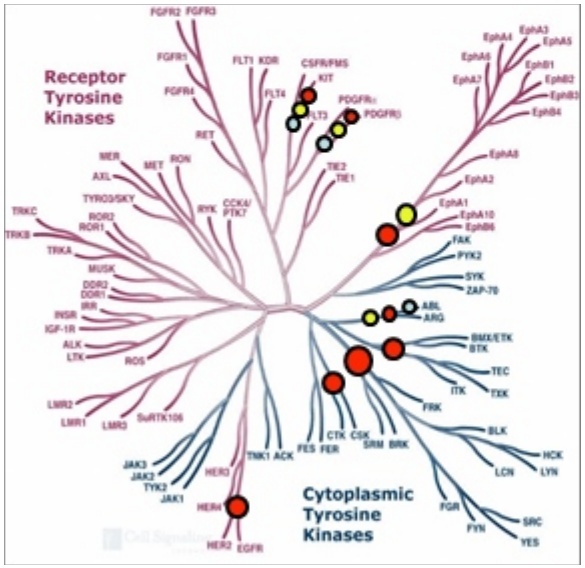


- Immune system dysfunctional (anergic) in many cancer types
- In CML:
  - Leukemia specific T- cells exhausted
  - High levels of PD1 on CD8 cells (Mumbrect et al, Blood 2009; Christiansson et al PlosOne 2013)
  - Quantitative and qualitative defects in NK-cells (Chen et al, Leukemia 2011)

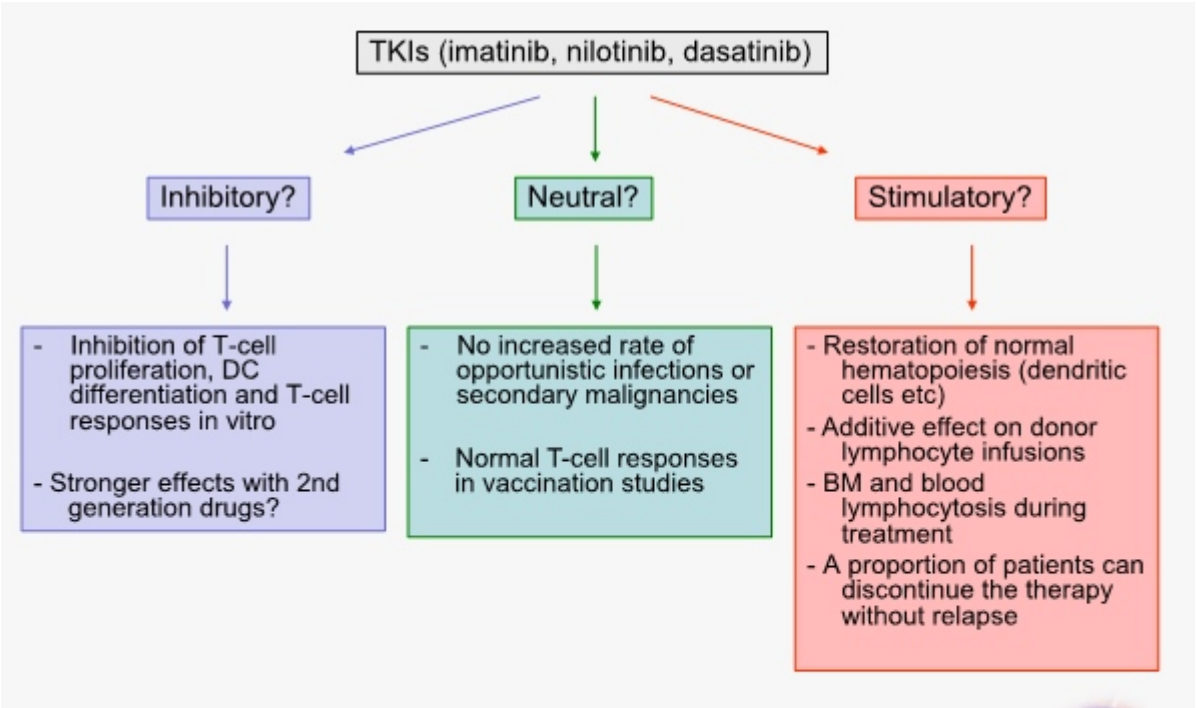
Can the function of immune system be restored in CML?

TKI Induced Immunomodulation

- Tyrosine kinase inhibitors are not entirely selective; effects on cells other than the malignant target cell
- Inhibition of functionally important kinases in normal cells
  - eg. 2nd generation TKI Dasatinib inhibits many kinases important in immune responses (T- and B-cell activation and proliferation)

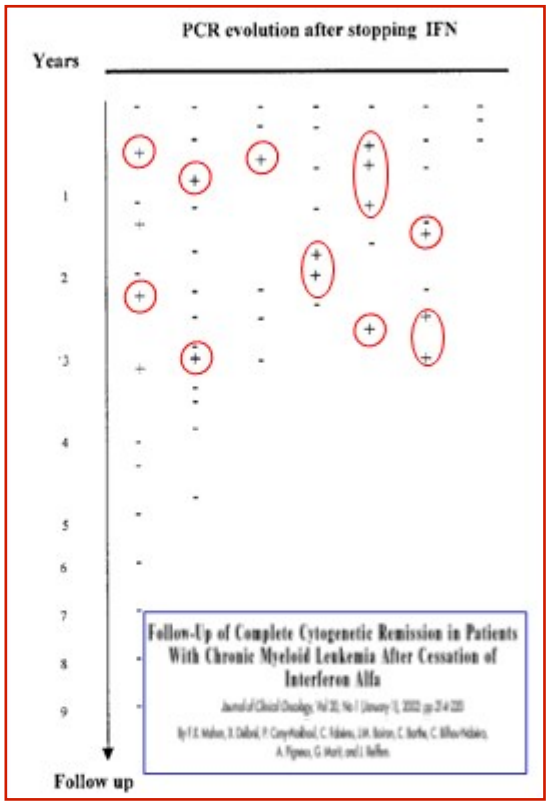


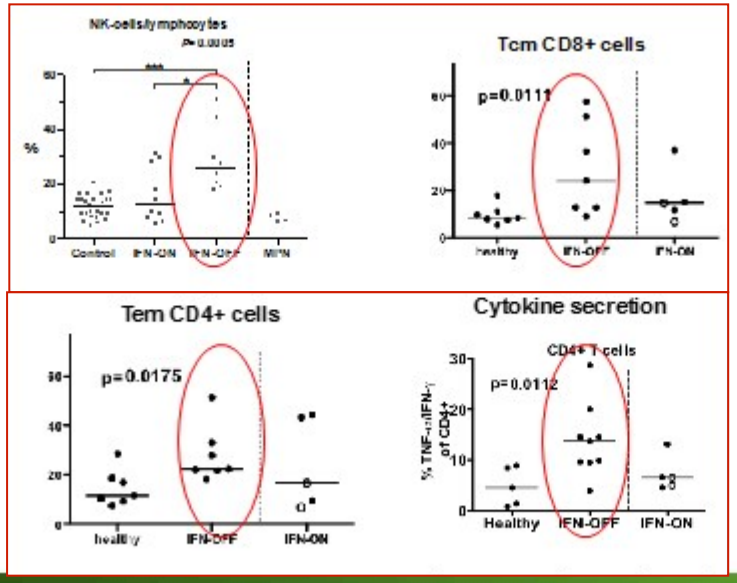
- Imatinib
- Nilotinib
- Dasatinib



Discontinuation of IFN monotherapy

- IFN discontinuation(IFN monotherapy)
  - Most patients have molecular evidence of MRD despite of successful discontinuation
  - Patients who have achieved good response to IFN-a and have been able to stop the therapy, have
    - Increase in **NK-cell number**
    - **Clonal γ/δ T-cells** and a unique cytokine profile
    - Increased **CD8+ central** and **CD4+ effector memory** pool and secretion **of Th1 inflammatory cytokines**





Kreutzman A et al., PloS ONE 2011;6(8):e23022
Ilander et al, PLoS One. 2014 Jan 31;9(1):e8n 94

Imunological studies in TKI stopping trials

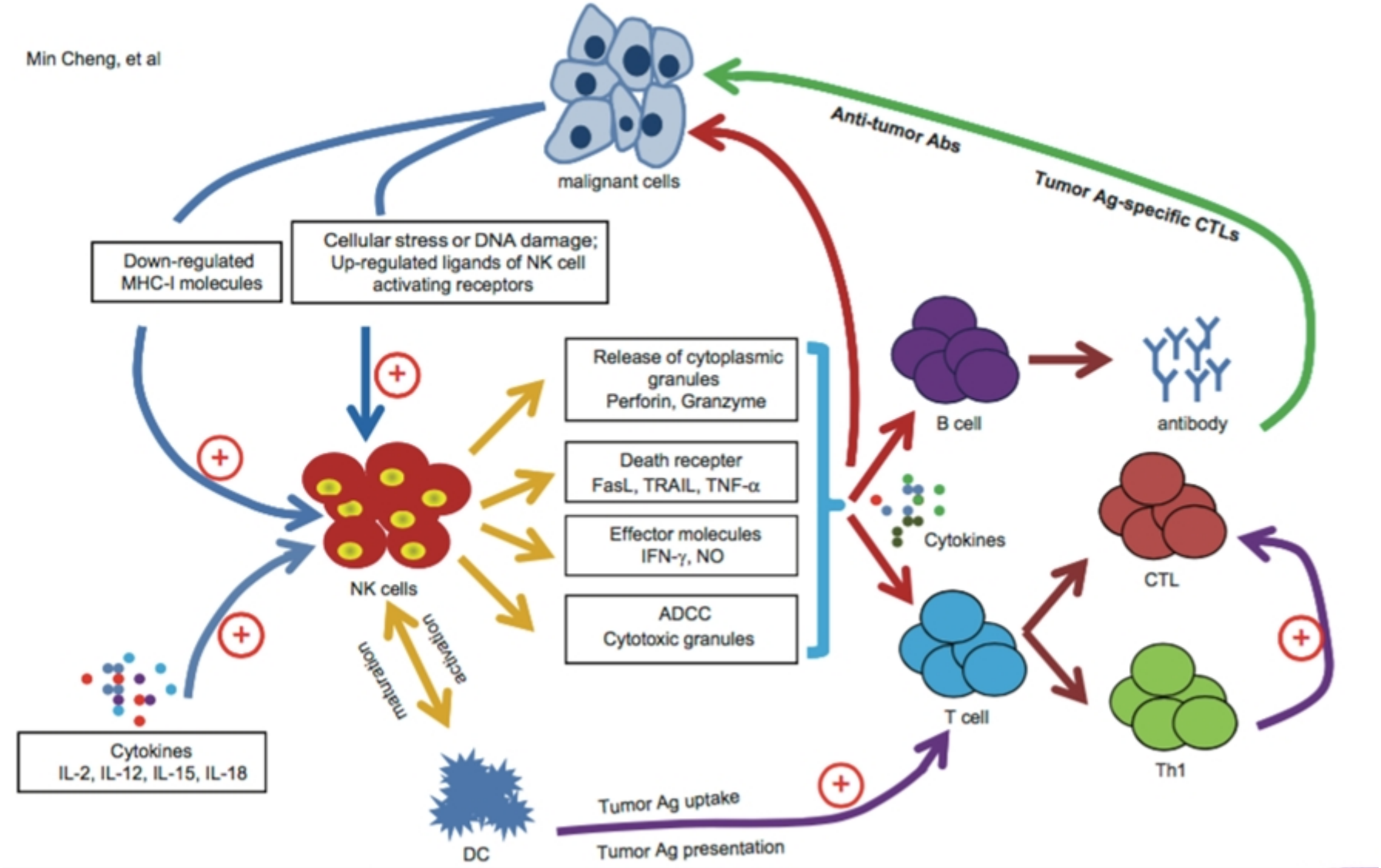
	STIM	DADI trial	EURO-SKI	ISAV	TRAD	STOP	Case series
TKI	Imatinib	2nd line dasatinib	Imatinib (small cohort of 2nd gen TKI treated)	Imatinib	Imatinib/dasatinib (2nd STOP)	Imatinib/ Imatinib+IFN	Imatinib
Study group	French (FiLMC)	Japanese CML study group	Nordic and German CML study groups	Italian	Canada	Nordic CML study group	Japanese/ Tokyo
Patient number in clinical study	100	88 (63)	>800	36	Ongoing	12	NA
Patient number in immunology	51	59	132 (50)/ 122	36	Ongoing	12	42 (10 patients stopped)
Analysis	Lymphocyte subsets and function	Lymphocyte subsets	Lymphocyte subsets and function, Dendritic cells	KIR (killer immunoglobulin receptor) genotype	Lymphocyte subsets and function	Lymphocyte subsets and function	Lymphocyte subsets
Publication	Rea et al, ASH 2013	Imagava et al, Lancet Haematol 2:e528-35, 2015	Ilander et al, ASH 2013-2015 Burchert et al. ASH 2015	Caocci et al, Exp Haematol 2015	NA	Koskenvesa et al. Eur J Haematol 2014	Mizoguchi et al, Cancer Sci 104:1146-53, 2013

Imunological studies in TKI stopping trials

	STIM	DADI trial	EURO-SKI	ISAV	STOP	Case series
TKI	Imatinib	2nd line dasatinib	Imatinib (small cohort of 2nd gen TKI treated	Imatinib	Imatinib/ Imatinib+IFN	Imatinib
Patient number in immunology	51	59	132 (50)/ 122	36	12	42 (10 patients stopped)
Analysis	Lymphocyte subsets and function	Lymphocyte subsets	Lymphocyte subsets and function (Nordic) DCs (German)	KIR (killer immunoglobulin receptor) genotype	Lymphocyte subsets and function	Lymphocyte subsets
Relapse criteria	MR4.5	MR4.0	MR3.0	MR4.5	MMR	CMR
Positive predictors	⇨ • High NK count • NK function impaired	⇨ • High NK count • High NK LGLs • Low Tregs	⇨ • High NK count • Low CD86 expression on DCs	KIR profile (KIR A haplotype)	⇨ • High NK count	⇨ • High NK count • Effector memory CD8+ T-cells

NK cells: Effector cells? Modulator of CTL or other effector immune cell response? Only a marker?

Role of NK cells in tumor immunology



Moving TFR into clinical practice in CML

Criteria	GREEN	YELLOW	RED
Institutional criteria met (per Table 1)	Yes	-	No
Sokal score at diagnosis	Non-high	High	-
BCR-ABL transcript at diagnosis	Typical - B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
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 TP, Ross DM. Blood 2016

Adverse events: TKI withdrawal syndrome?

- Musculoskeletal pain
- Joint pain
- Arthralgia
- Other

Musculoskeletal pain in CML patients after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome?
Richter J, et al. J Clin Oncol. 2014;32(25):2821-2823.

Tyrosine kinase inhibitor withdrawal syndrome: a matter of c-kit?
Response to Richter et al.
Rousselot P, et al. J Clin Oncol. 2014;32(25):2823-2825.

Musculoskeletal Syndrome

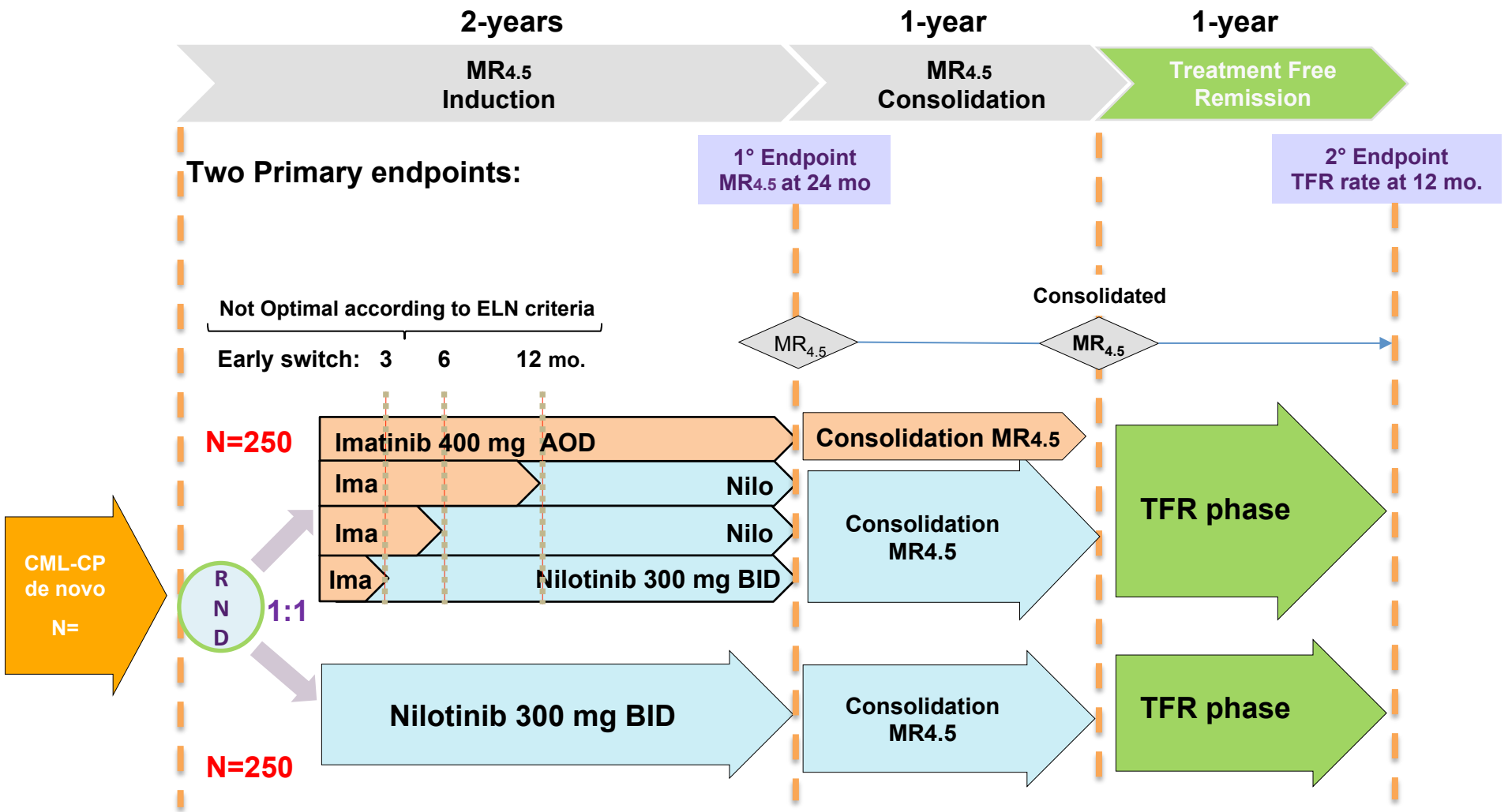
	Patients with AE grade 1-2	%	Patients with AE Grade 3	%	Total	%
Musculoskeletal symptoms*	226	29.7	9	1.2	235	30.9

*Musculoskeletal pain, bone and/or joint pain, arthralgia, muscle pain, myalgia, joint stiffness, lumbalgia, articular pain, muscular pain, neck pain, arthromyalgia, pain both arms, pain legs

Treatment free remission
Key issues remain under investigation

- Optimal frontline treatment strategy to achieve TFR
- Ideal duration of TKI therapy prior discontinuation
- Ideal depth and duration of molecular response
- Ideal criteria for reinitiating therapy
- Predictive factors for achieving deep molecular response
- Predictive factors for remaining in remission upon treatment discontinuation

Study Design



Conclusions

Is it possible to cure CML patients without Allo-SCT?

Yes, but….

- How many patients?
- Which treatment?
- QoL improvement?

Thank you for the attention!

fabrizio.pane@unina.it