Treatment free remission 2016

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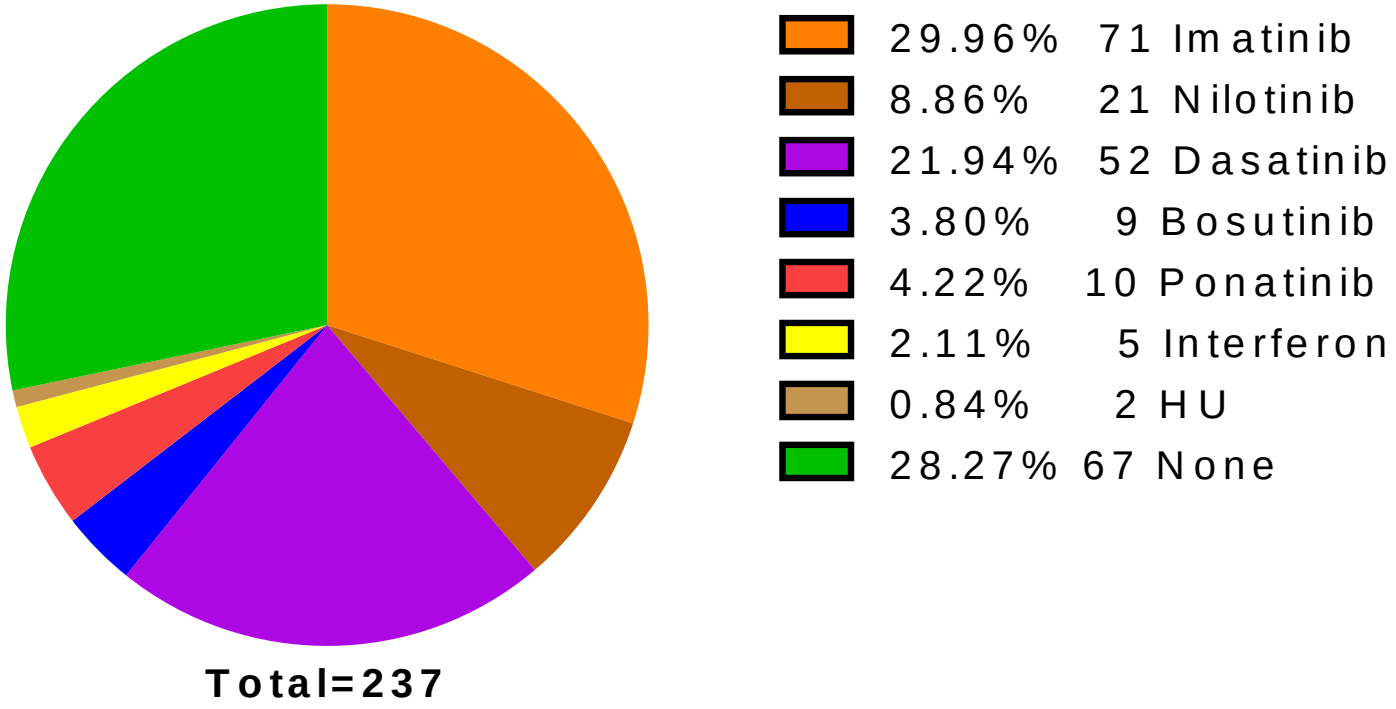
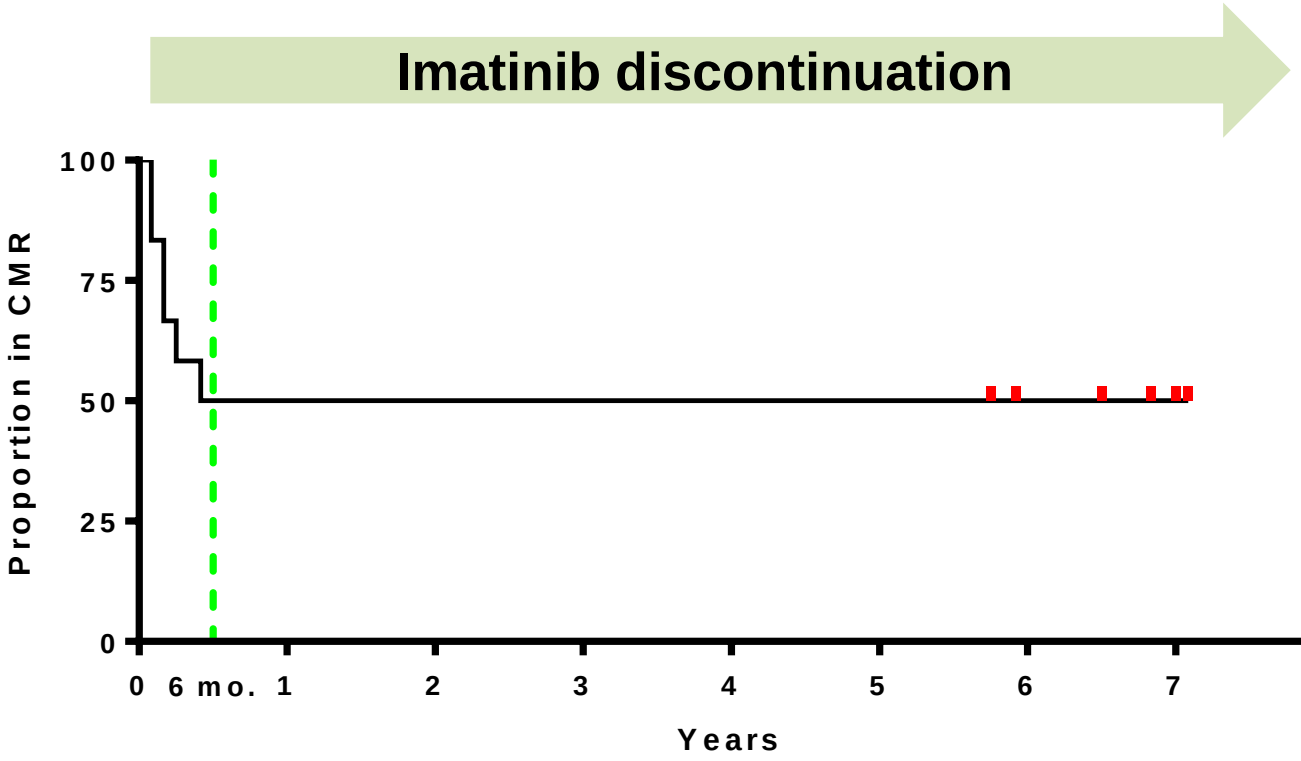
How many patients still on imatinib?

- Versailles cohort
  - 237 patients, 5 years from Dg or more, alive



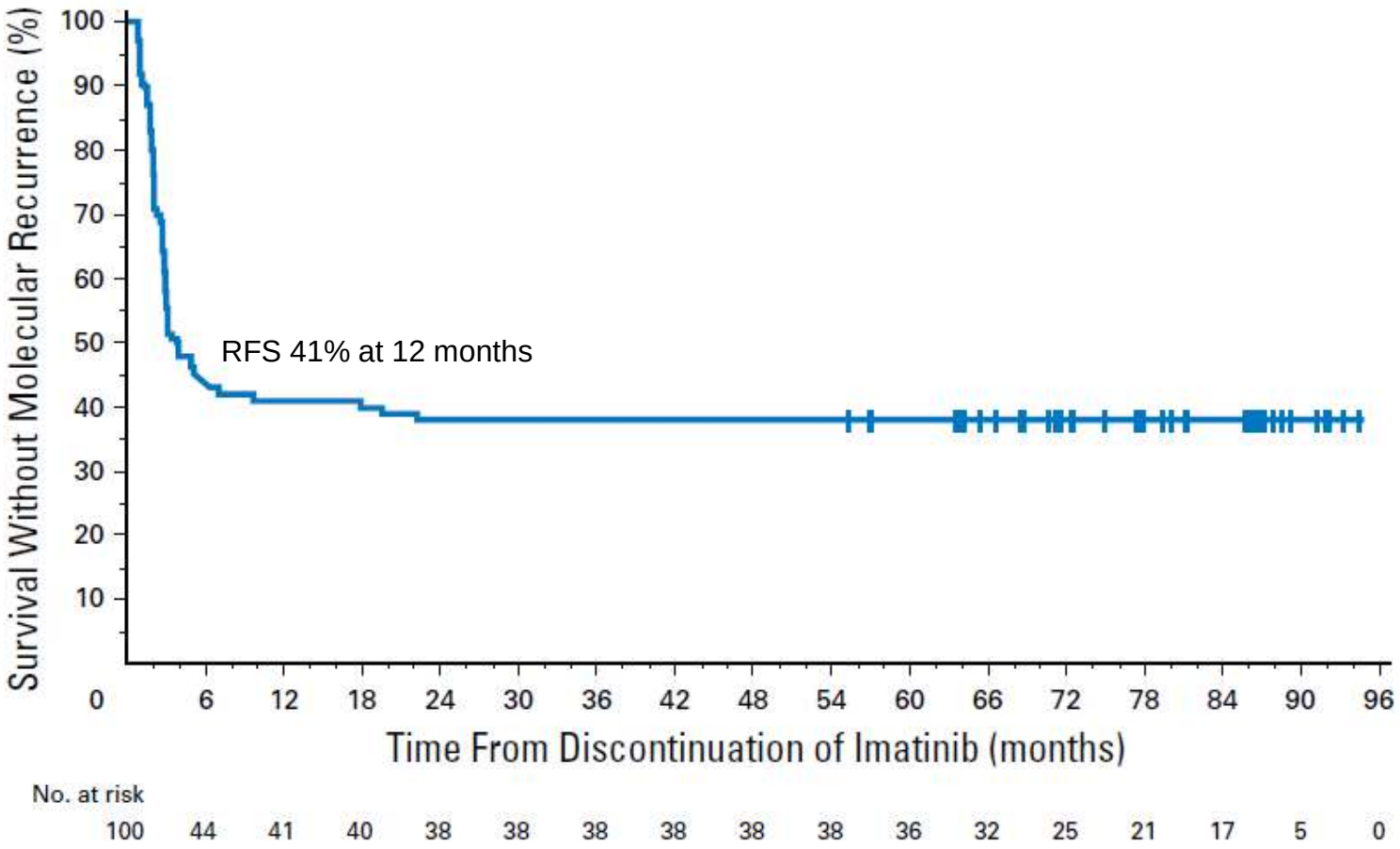
The Pilot Stop IMatinib (STIM) Study more than 6 Years Ago…

1. Twelve patients in long term CMR with imatinib : STOP imatinib
2. Definition of CMR : CMR 4.5 during 2 years
3. Definition of relapse : Two consecutive positive RQ-PCR
4. Six patients remain treatment free on the very long term



Rousselot P et al., *Blood*. 2007;109:58–60; and personal data.

The multicentric STIM study: an update



STIM1. Etienne G and Mahon FX, J Clin Oncol 2016.

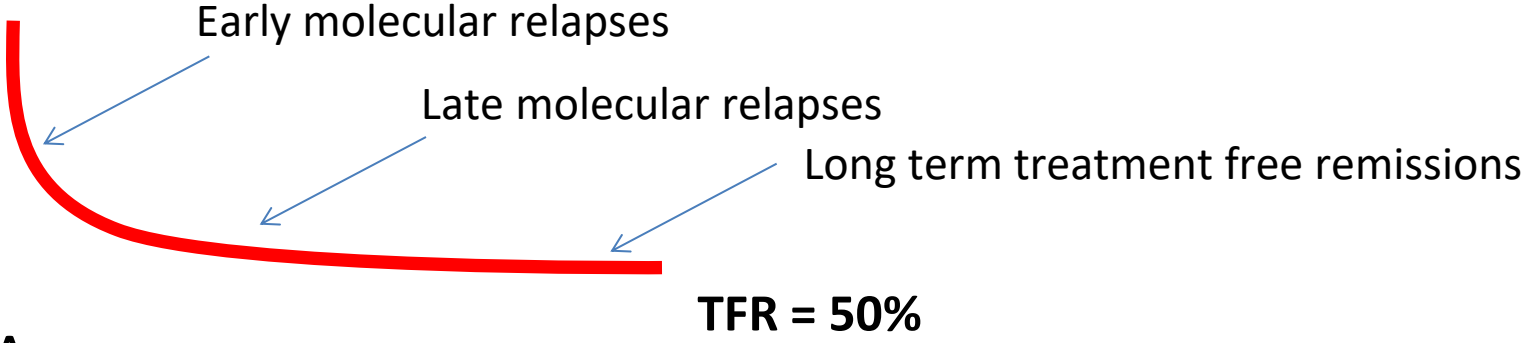
Other imatinib discontinuation studies

Study	Main inclusion criteria	Definition of relapse
TWISTER	Imatinib ≥ 3 years Undetectable MR4.5 ≥ 2 years	Detectable *BCR-ABL1* on 2 consecutive tests or MMR loss
STIM2 (Fi-LMC)	Imatinib ≥ 3 years Undetectable MR4.5 ≥ 2 years	At least 1 log increase in *BCR-ABL1* or MMR loss
KID	Imatinib ≥ 3 years Undetectable MR4.5 ≥ 2 years	MMR loss
ISAV	Imatinib ≥ 2 years Undetectable MR4 ≥ 18 months	Detectable *BCR-ABL1* on 2 consecutive tests and MMR loss
STIM123	Imatinib ≥ 3 years RM4.5 ≥ 2 years	MMR loss
EUROSKI	TKI ≥ 2 years MR4 ≥ 1 year	MMR loss

Ross et al. Blood. 2013;122(4):515-22.
Mahon et al. Blood (ASH 2013): abstract 654.
Lee et al. Haematologica. 2016;101(6):717-23.
Mori et al. Am J Hematol. 2015;90(10):910-4.
Takahashi et al. Blood (ASH 2015): abstract 4035.
Mahon et al. Blood (2016): abstract 787.

Results are reproducible

- > 1000 patients over the world
- All curves have a very similar shape



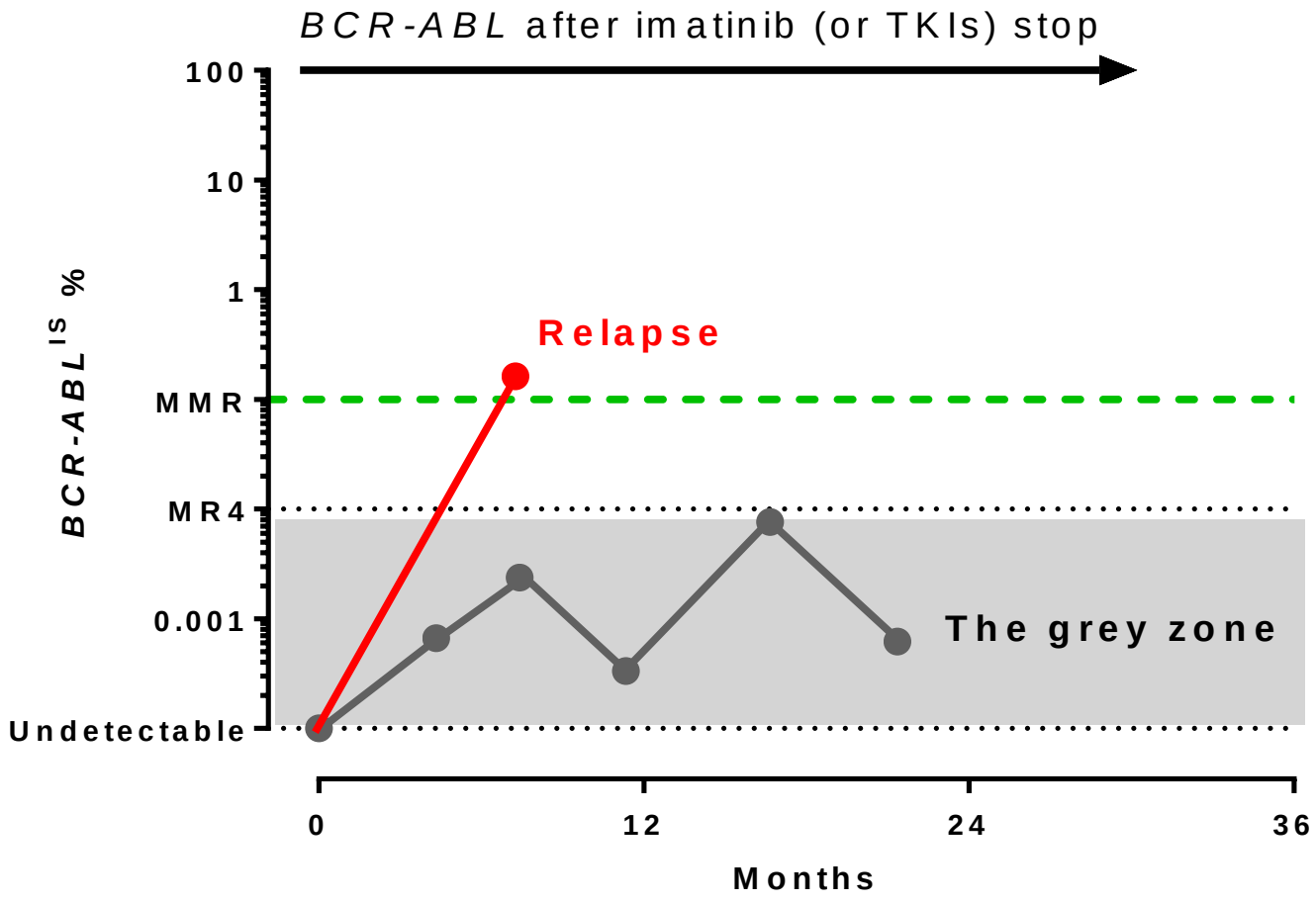
  - Across
    - Different studies
    - Different countries
  - Despite
    - Differences in eligibility criteria
    - Differences in molecular relapse criteria

Relapse criteria across studies

Criteria BCR-ABL IS %	PILOT	STIM	STIM2	TWISTER	JAPAN
≥ 0.1 at once (loss of MMR)	x	x	x	x	
≥ 0.01 at once					x
≥ 0.0032					
2 consecutives	x	x		x	
2 consecutives and 1 log increase			x		

Rousselot P et al., Blood. 2007;109:58–60.
Mahon FX, et al, Lancet Oncol. 2010; 11:1029-35.
Ross D, et al. *Blood*. 2013;122:515-522.
Yhim HY, et al. Leuk Res. 2012;36(6):689-693.
Takahashi N, et al. *Haematologica.* 2012;97:903-906.

MMR : a robust and reproducible criteria to define molecular relapse



ASTIM study
Molecular relapse criteria = MMR

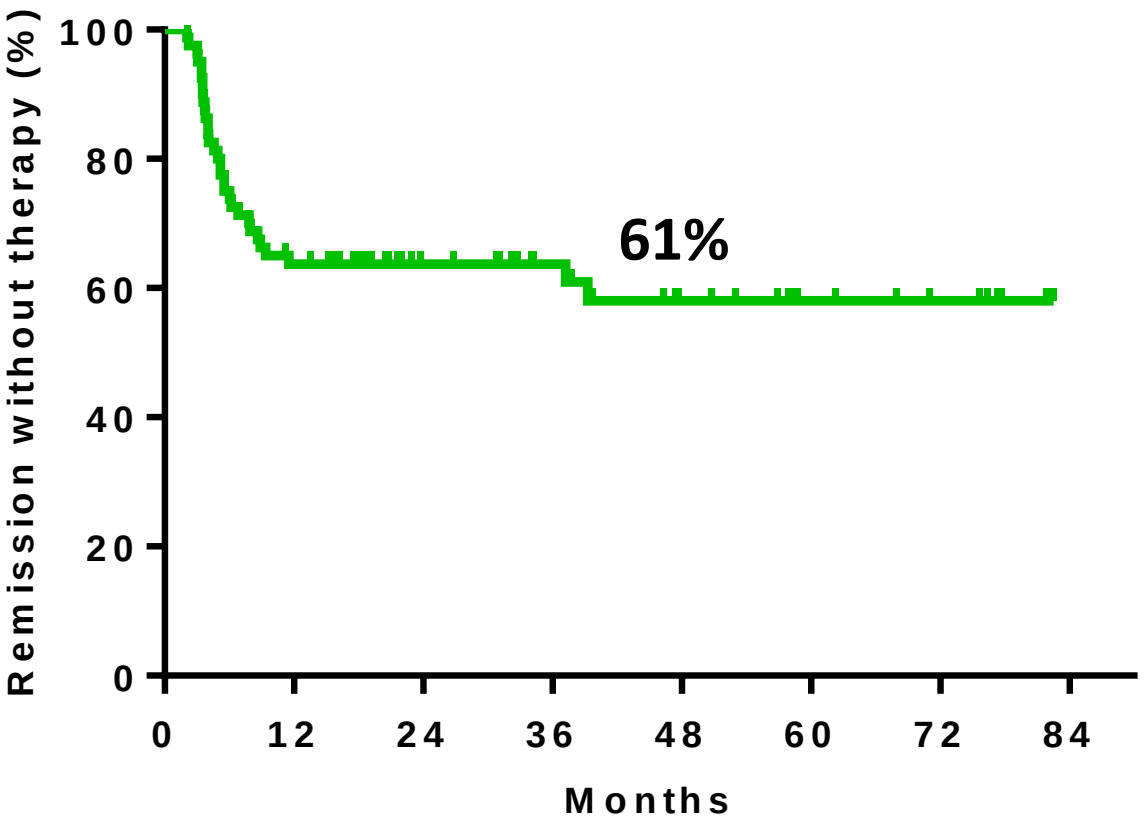
51 patients in TFS > 12 months and MMR after imatinib stop

Patients in MMR after imatinib discontinuation	Patients (%) (N=51)
Sustained BCR-ABL negativity	**23 (45%)**
Occasional BCR-ABL positivity	**12 (24%)**
BCR-ABL fluctuations (≥ 2 consecutive positive values)	**16 (31%)**

« STIM » results

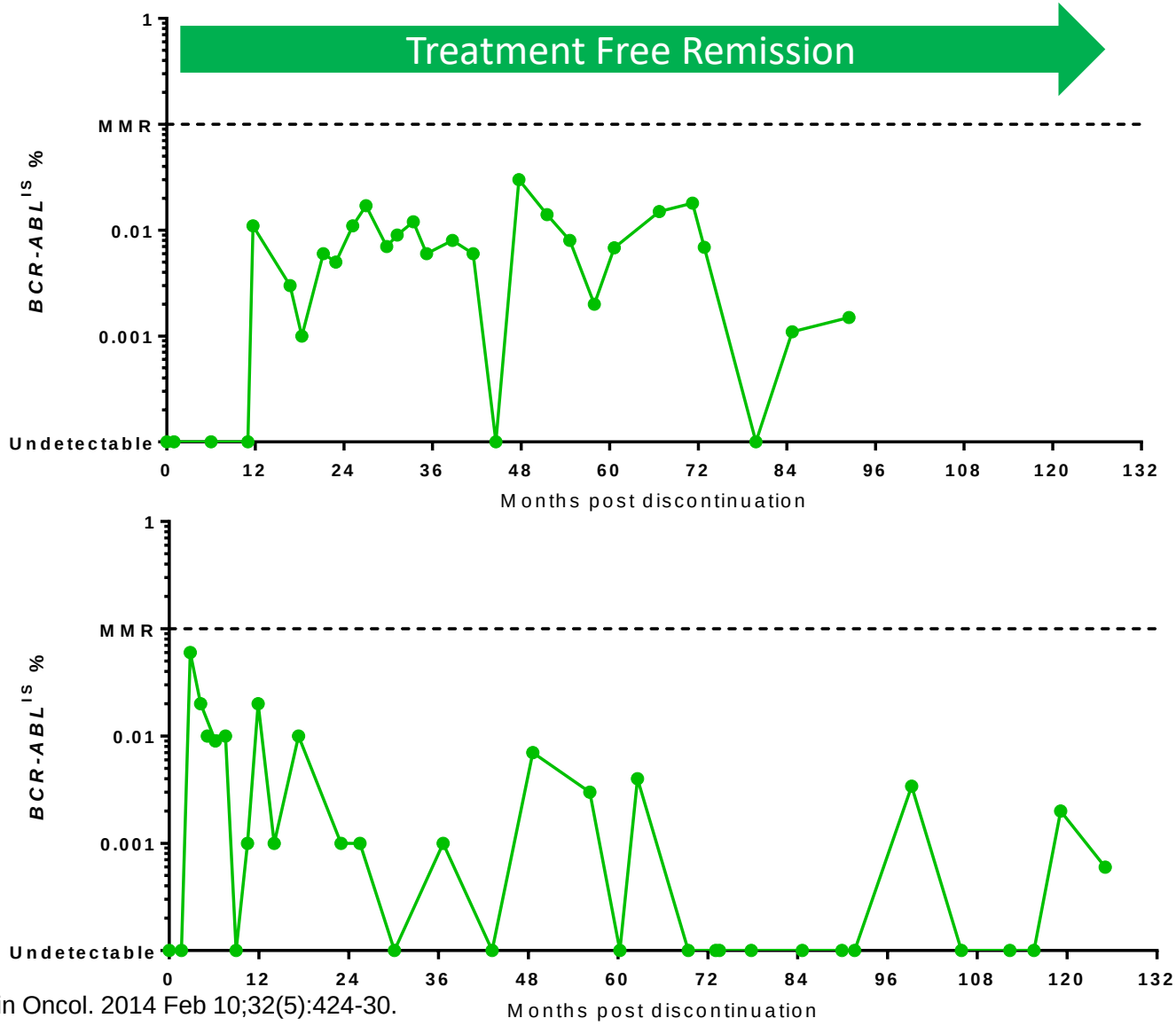
Rousselot et al. J Clin Oncol. 2014 Feb 10;32(5):424-

Treatment free remission (loss of MMR criteria)



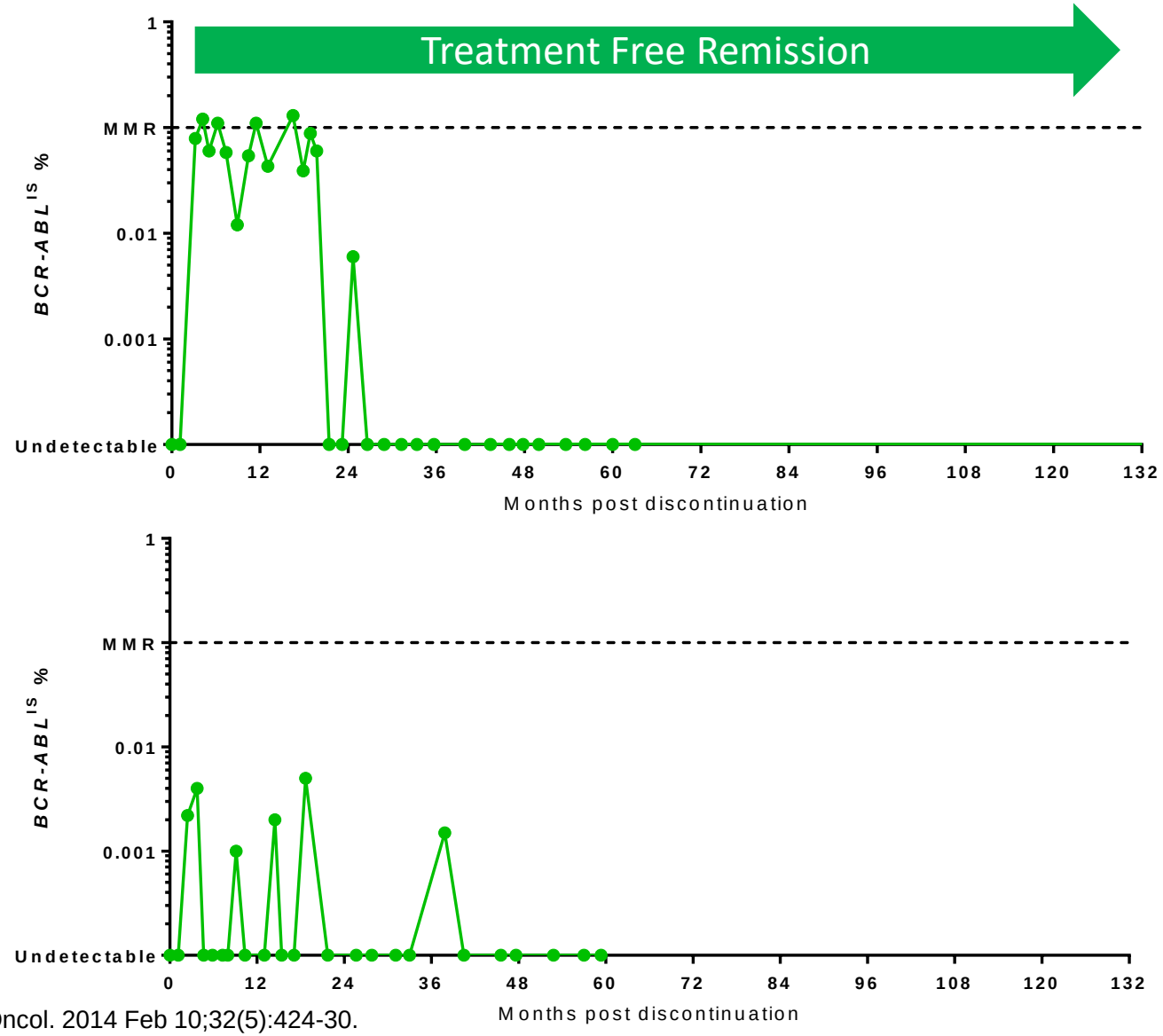
Rousselot et al. J Clin Oncol. 2014 Feb 10;32(5):424-30.

Fluctuations on the long term after IM discontinuation



Rousselot et al. J Clin Oncol. 2014 Feb 10;32(5):424-30.

Transient fluctuations after IM Stop



Rousselot et al. J Clin Oncol. 2014 Feb 10;32(5):424-30.

NK cells number are predictive of successful TFR in imatinib discontinuation studies

379 Disease Relapse After TKI Discontinuation In CML Is Related Both To Low Number and Impaired Function Of NK-Cells:Data From Euro-SKI

Program: Oral and Poster Abstracts
Type: Oral
Session: 632. Chronic Myeloid Leukemia: Therapy: Prognosis

Monday, December 9, 2013: 10:30 AM
E3 (located inside Hall E) (Ernest N. Morial Convention Center)

Mette Matilda Ilander, MSc[1*], *Ulla Olsson-Strömberg, MD, PhD*[2*], *Hanna Lähteenmäki, MSc*[1*], *Tiina Kasanen*[1*], *Perttu Koskenvesa, MD*[1*], *Stina Söderlund, MD*[2*], *Martin Hoglund, MD, PhD*[2], *Berit Markevärn, MD*[3*], *Anders Själander, MD, PhD*[4*], *Kourosh Lofti, MD, PhD*[5*], *Claes Malm, MD*[5*], *Anna Lubking, MD*[6*], *Marja Ekblom, MD, PhD*[6*], *Elena Holm, MD*[6*], *Mats Björeman, MD*[7*], *Sören Lehmann, MD, PhD*[8*], *Leif Stenke, MD, PhD*[8], *Lotta Ohm, MD*[8*], *Henrik Hjorth-Hansen, MD, PhD*[9], *Susanne Saussele, MD*[10*], *Francois-Xavier Mahon, MD, PhD*[11], *Kimmo Porkka, MD, PhD*[12*], *Johan Richter, MD, PhD*[6*] *and Satu Mustjoki, MD, PhD*[12]

856 Low Natural Killer (NK) Cell Counts and Functionality Are Associated With Molecular Relapse After Imatinib Discontinuation In Patients (pts) With Chronic Phase (CP)-Chronic Myeloid Leukemia (CML) With Undetectable *BCR-ABL* Transcripts For At Least 2 Years: Preliminary Results From Immunostim, On Behalf Of STIM Investigators

Program: Oral and Poster Abstracts
Type: Oral
Session: 631. Chronic Myeloid Leukemia: Biology and Pathophysiology, excluding Therapy: Biologic Factors Impacting on Alternative Therapeutic Strategies in Chronic Myeloid Leukemia

Tuesday, December 10, 2013: 8:15 AM
E3 (located inside Hall E) (Ernest N. Morial Convention Center)

Delphine Rea, MD, PhD[1*], *Nicolas Dulphy, PhD*[2*], *Guylaine Henry, Ing.*[2*], *Joelle Guilhot, Ph.D.*[3*], *Francois Guilhot, PhD*[4], *Franck E. Nicolini, MD PhD*[5], *Laurence Legros, MD, PhD*[6*], *Philippe Rousselot, MD, PhD*[7*], *Francois-Xavier Mahon*[8*] *and Antoine Toubert*[2,9*]

Participating countries of the EUROSKI Trial

Country	Number of sites	Number of patients
Czech Republic	6	64
Denmark	4	33
Finland	1	31
France	17	204
Germany	21	217
Greece	1	44
Netherlands	3	96
Norway	4	27
Portugal	1	27
Spain	1	9
Sweden	9	116
Total	**61**	**868**

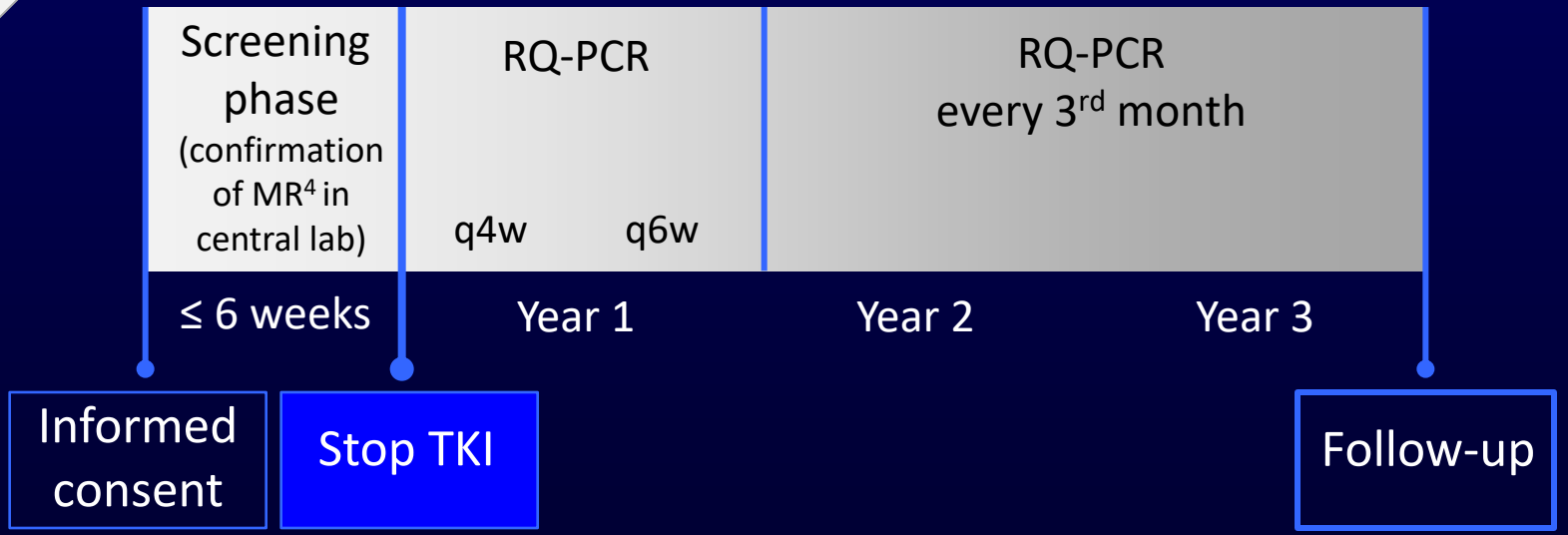
EURO-SKI design

Patients included between May 2012 and December 2014

TKI treatment ≥ 3 years

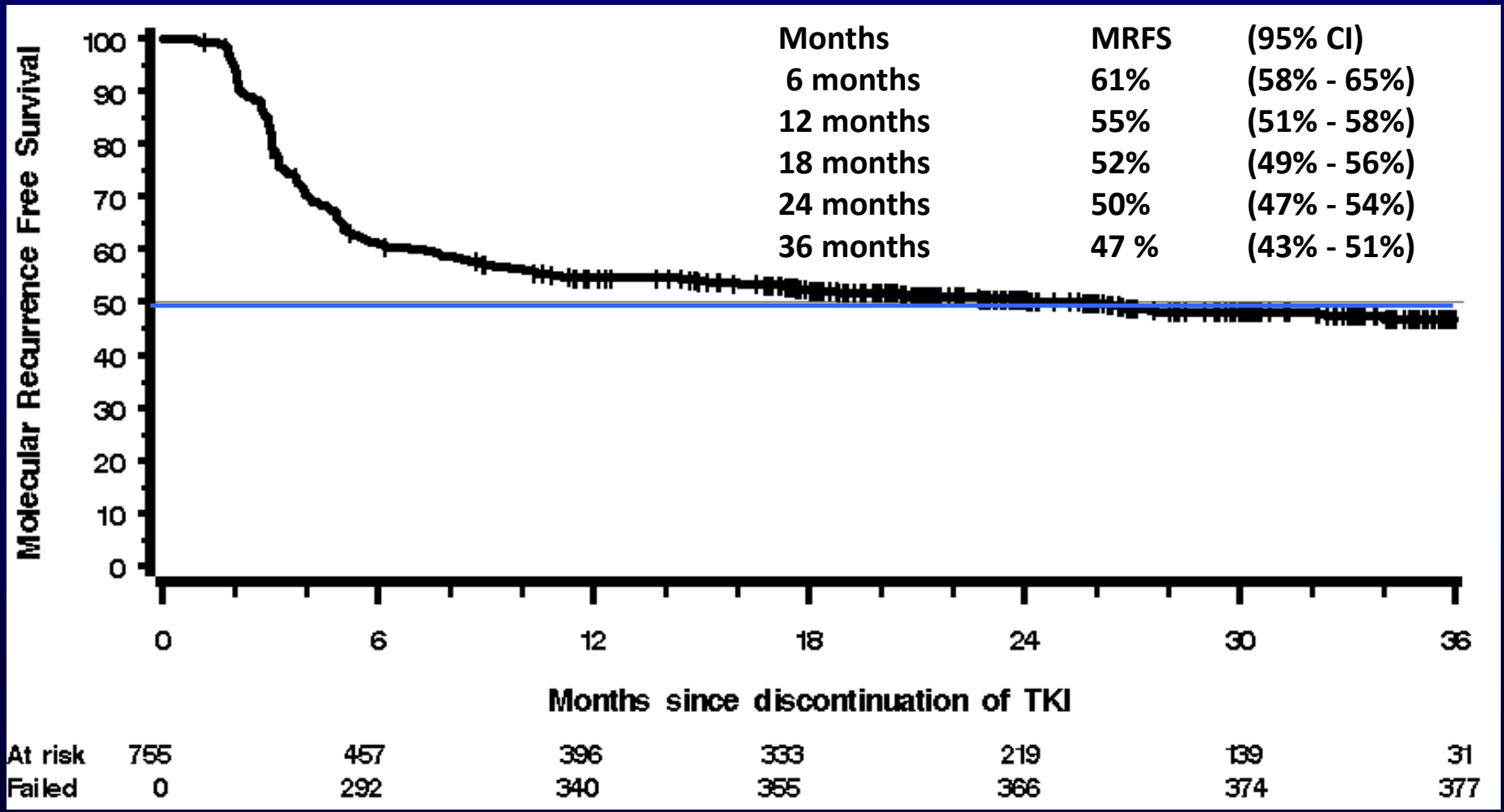
MR^4 ≥ 1 year

Molecular recurence defined as BCR-ABL >0.1% (loss of MMR) at one time point.



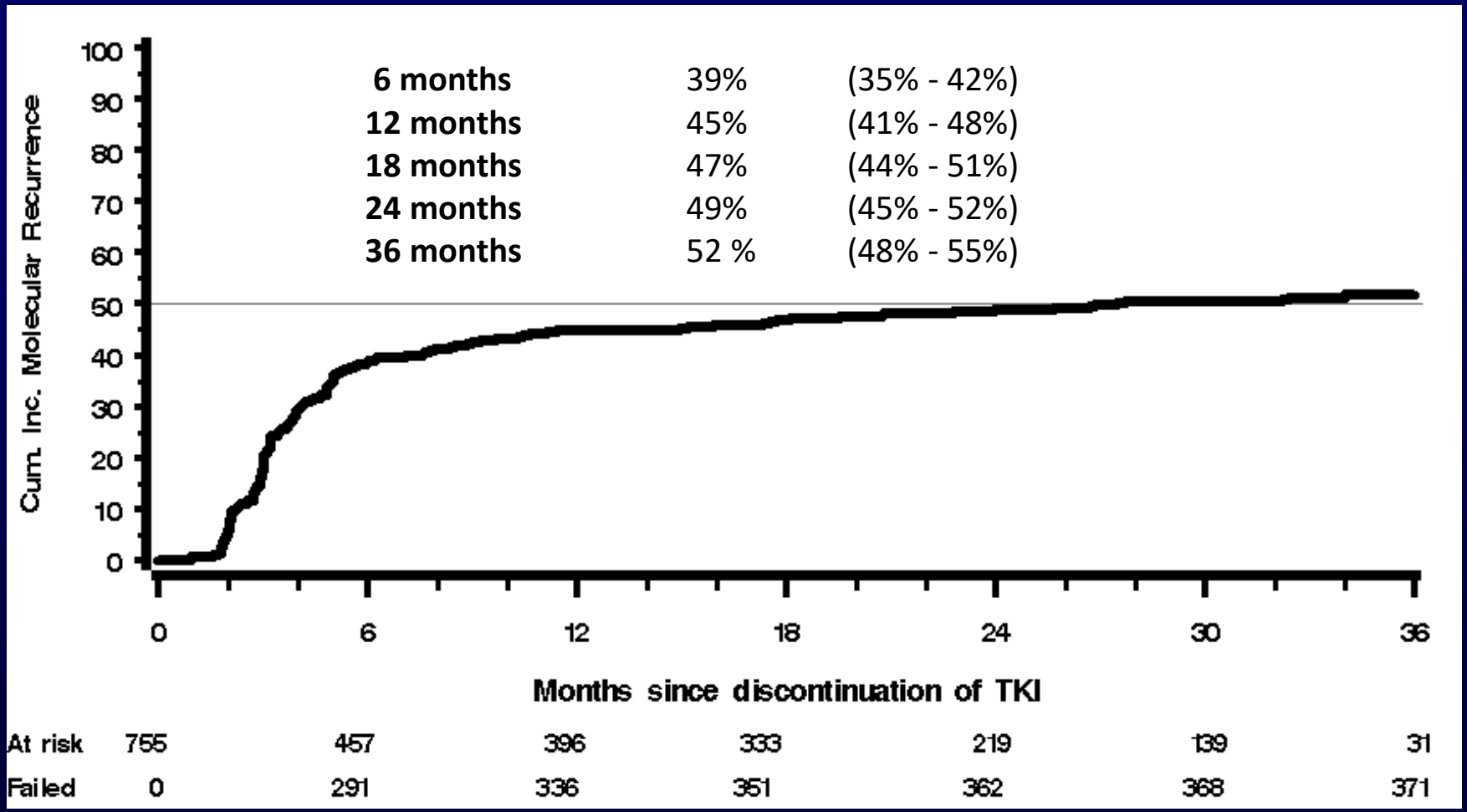
Clinicaltrials.gov. identifier NCT01596114.

Molecular recurrence-free survival (n=755)



Months	MRFS	(95% CI)
6 months	61%	(58% - 65%)
12 months	55%	(51% - 58%)
18 months	52%	(49% - 56%)
24 months	50%	(47% - 54%)
36 months	47 %	(43% - 51%)

Cumulative incidence of molecular recurrence



Facteurs prédictifs

Factors associated with successful imatinib discontinuation

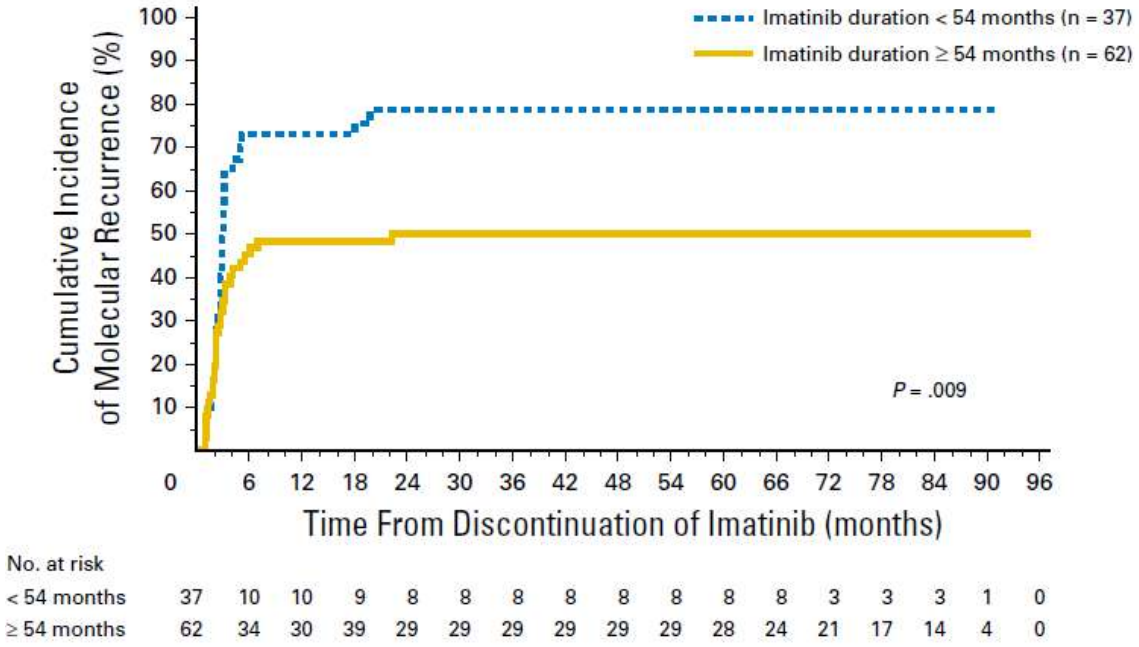
	Mahon et al	Ross et al	Yim, Lee et al	Takahashi et al
Age	Not significant	Not significant	Not reported	Not significant
Sex	Not significant	Not significant	Not reported	Not significant
Sokal score	Significant	Significant	Not reported	Not significant
Imatinib duration	Significant	Not significant	Not reported	Significant
IFN-a	Not significant	Significant	Not reported	Significant
Time to CMR	Not significant	Not significant	Significant	Not significant
Duration of CMR	Not significant	Not significant	Significant	Significant

Mahon FX, et al, Lancet Oncol. 2010; 11:1029-35.
Ross D, et al. *Blood*. 2013;122:515-522.
Yhim HY, et al. Leuk Res. 2012;36(6):689-693.
Takahashi N, et al. *Haematologica.* 2012;97:903-906.

Courtesy of N Takahashi, adapted

Rechutes moléculaires après arrêt de l'imatinib chez les patients en réponse moléculaire profonde

Etude STIM1



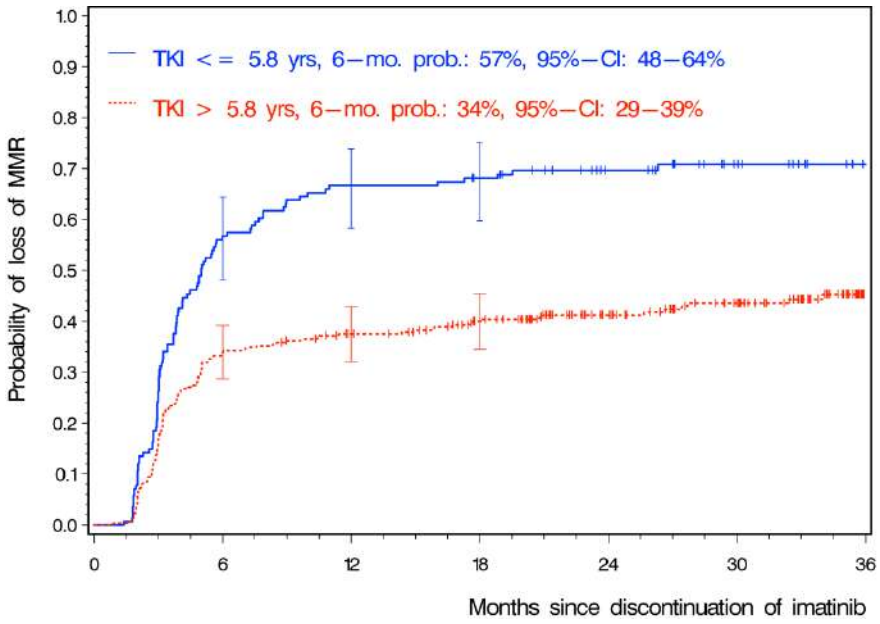
Importance de la durée du traitement avant arrêt (> ou < à 5 ans)

STIM1. Etienne G, et al. J Clin Oncol 2016.

EUROSKI: Factors associated with MRFS

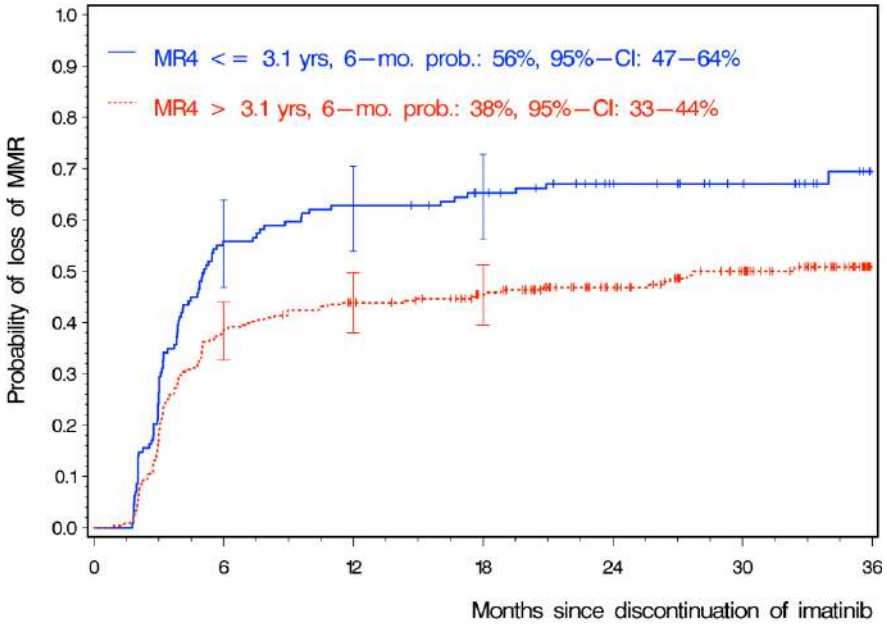
Univariate analysis

Duration of imatinib treatment



N=448

Duration of MR4 during imatinib



N=405

No difference in outcome between patients with an undetectable MR4.5 and those with a detectable MR4.5 at inclusion

Mahon FX et al. *Blood*. 2016:[abstract 787].
Pfirrmann M et al. *Blood*. 2016:[abstract 789].

Imatinib withdrawal syndrome

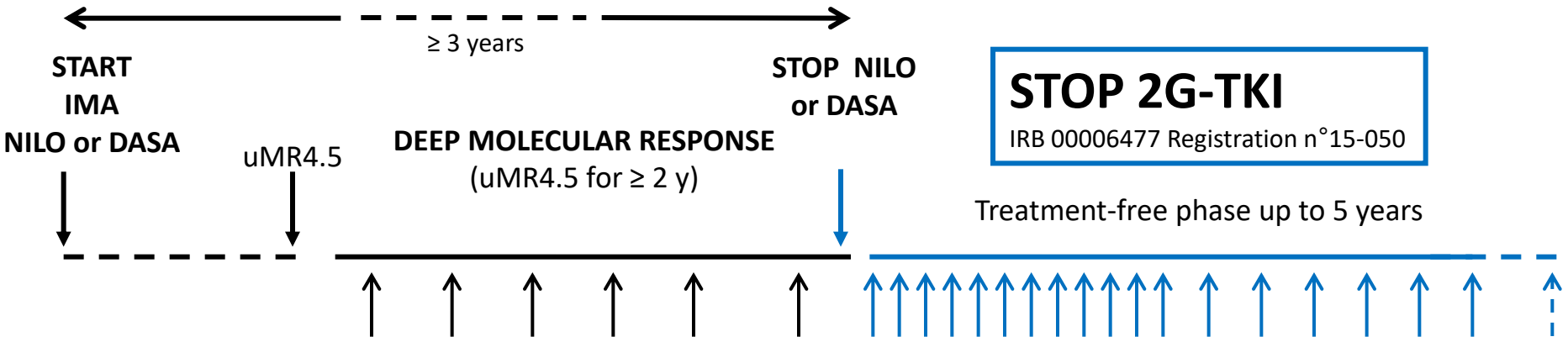
- First described by Richter et al.
  - 30%
  - Pain syndrome
    - Musculoskeletal pain
    - Joint pain
    - Arthralgia
    - Other
  - from 1 to 6 weeks after TKI discontinuation

Musculoskeletal pain in CML patients after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome?
J. Richter et al. J Clin Oncol. 2014 Sep 1;32(25):2821-3.

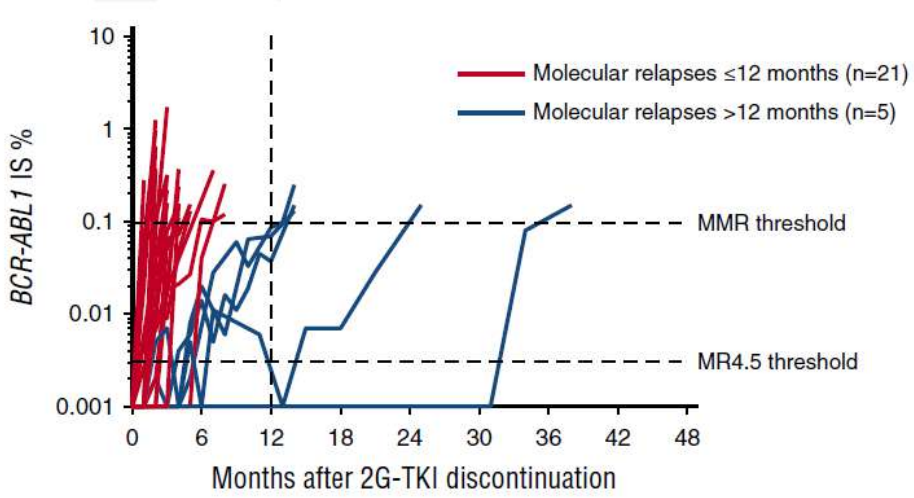
Tyrosine kinase inhibitor withdrawal syndrome: a matter of c-kit?
Response to Richter et al.
Ph. Rousselot et al. J Clin Oncol. 2014 Sep 1;32(25):2821-3.

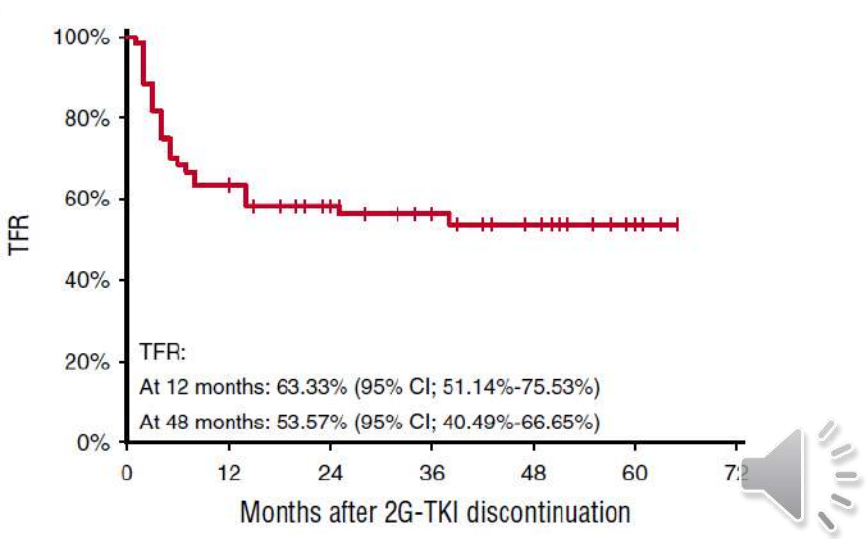
Arrêt des ITK 2G

STOP 2G-TKI study



Interim analysis:
60 patients included
Minimum follow-up of 12 months (median 47, range: 12-65)
Median duration of TKI: 76 months (36-153)

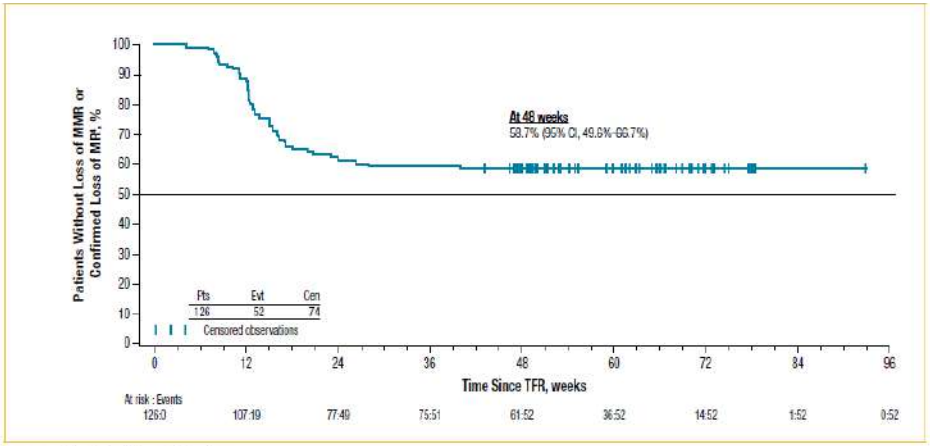




Rea et al. Blood. 2016 Dec 8. pii: blood-2016-09-742205. [Epub ahead of print]

ENESTop and ENESTfreedom

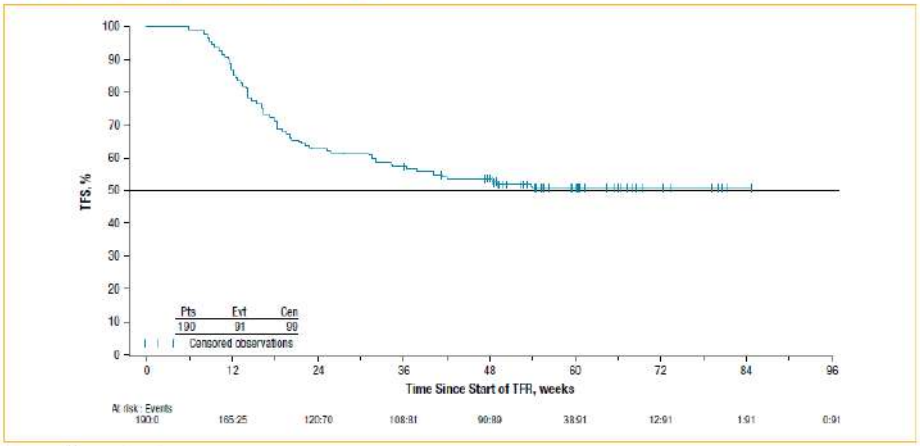
TFR at 48 weeks: 57.9% (95% CI, 48.8%-66.7%)



ENESTop:

126 patients in the treatment-free phase
Minimum follow-up 48 weeks
Median duration of TKI: 87.7 months (49-171)
Median duration of nilotinib: 53 months (37-109)
Relapse = loss of MMR or confirmed loss of MR4

TFR at 48 weeks: 51.6% (95% CI; 44.2-58.9)



Cen, censored; **Evt**, event; **Pt**, patient.
[a]TFS was 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.

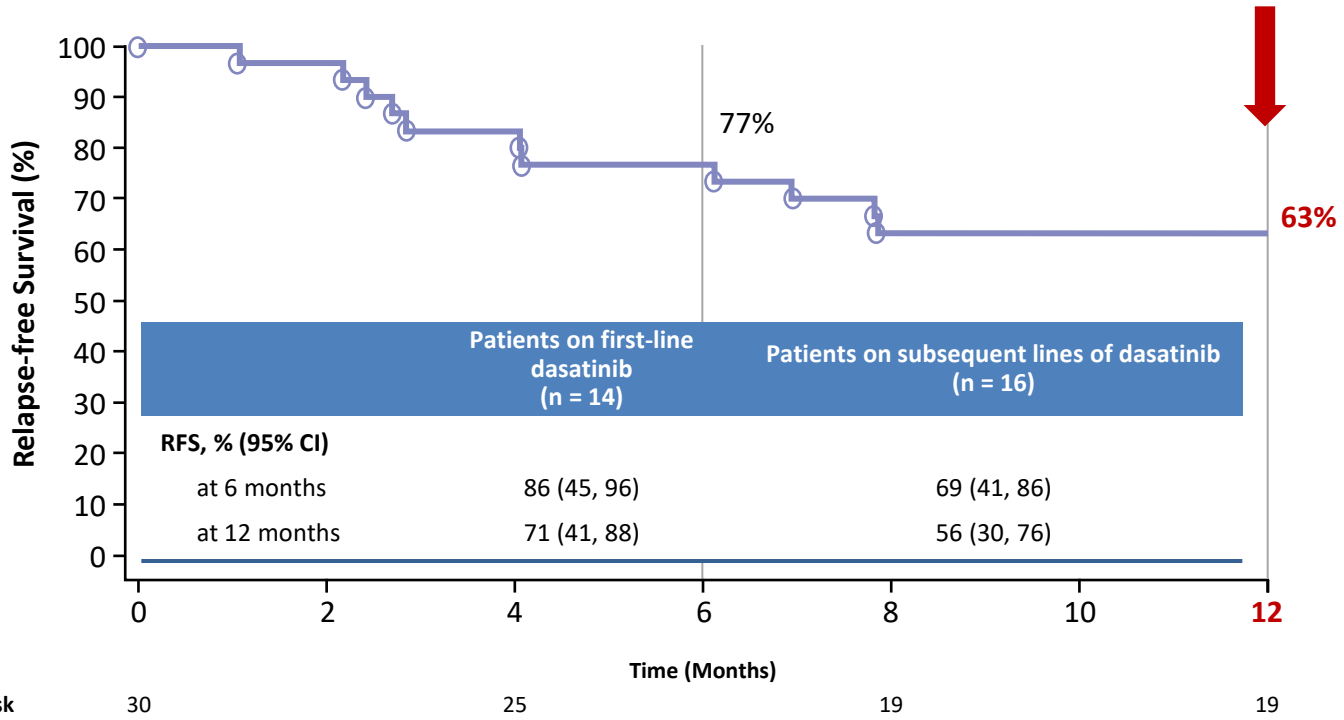
ENESTfreedom:

190 patients in the treatment-free phase
Median duration of nilotinib: 43.5 months (32.9-88.7)
Minimum follow-up 48 weeks
Relapse = loss of MMR

Hughes et al. Haematologica (EHA) 2016: abstract LB237.
Saglio et al. Haematologica (EHA) 2016: abstract LB618.

DASFREE - first interim analysis

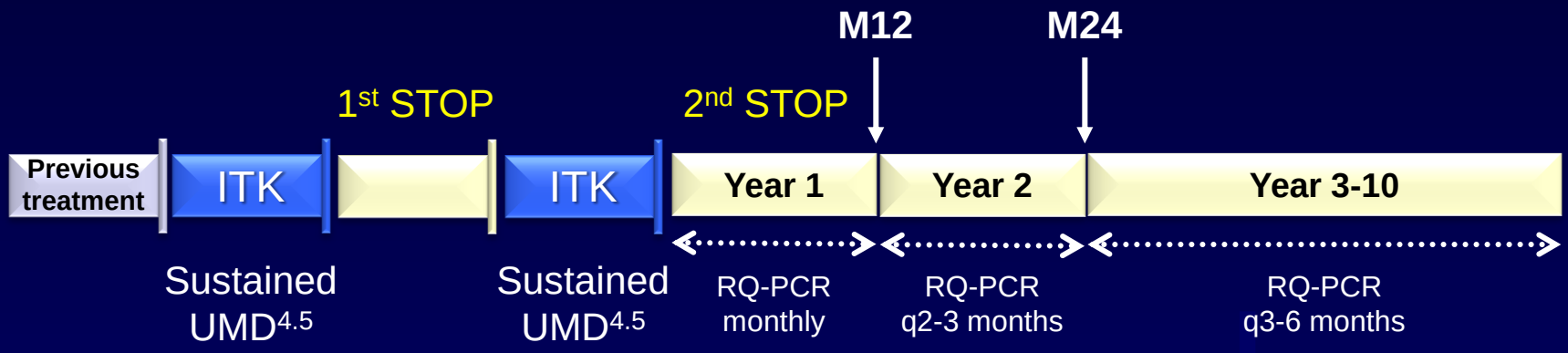
Interim analysis: 30 patients in MR4.5 ≥1 year who stopped dasatinib and had a follow-up of ≥1 year (over a total of 84 patients enrolled)
Relapse = loss of MMR



Shah et al. Blood (ASH) 2016: abstract 1895.

Study design and objective

- **Adult CP/AP-CML patients at diagnosis**
- **Failed a 1st TKI discontinuation (inside or outside clinical trials)**
- **Regained undetectable and sustained *BCR-ABL** (UMD4.5) after TKI re-challenge**



At 1st attempt of TKI discontinuation
Failure defined as TKI re-challenge for UMD** or MMR*** loss
At 2nd attempt of TKI discontinuation
Molecular Relapse defined as MMR loss

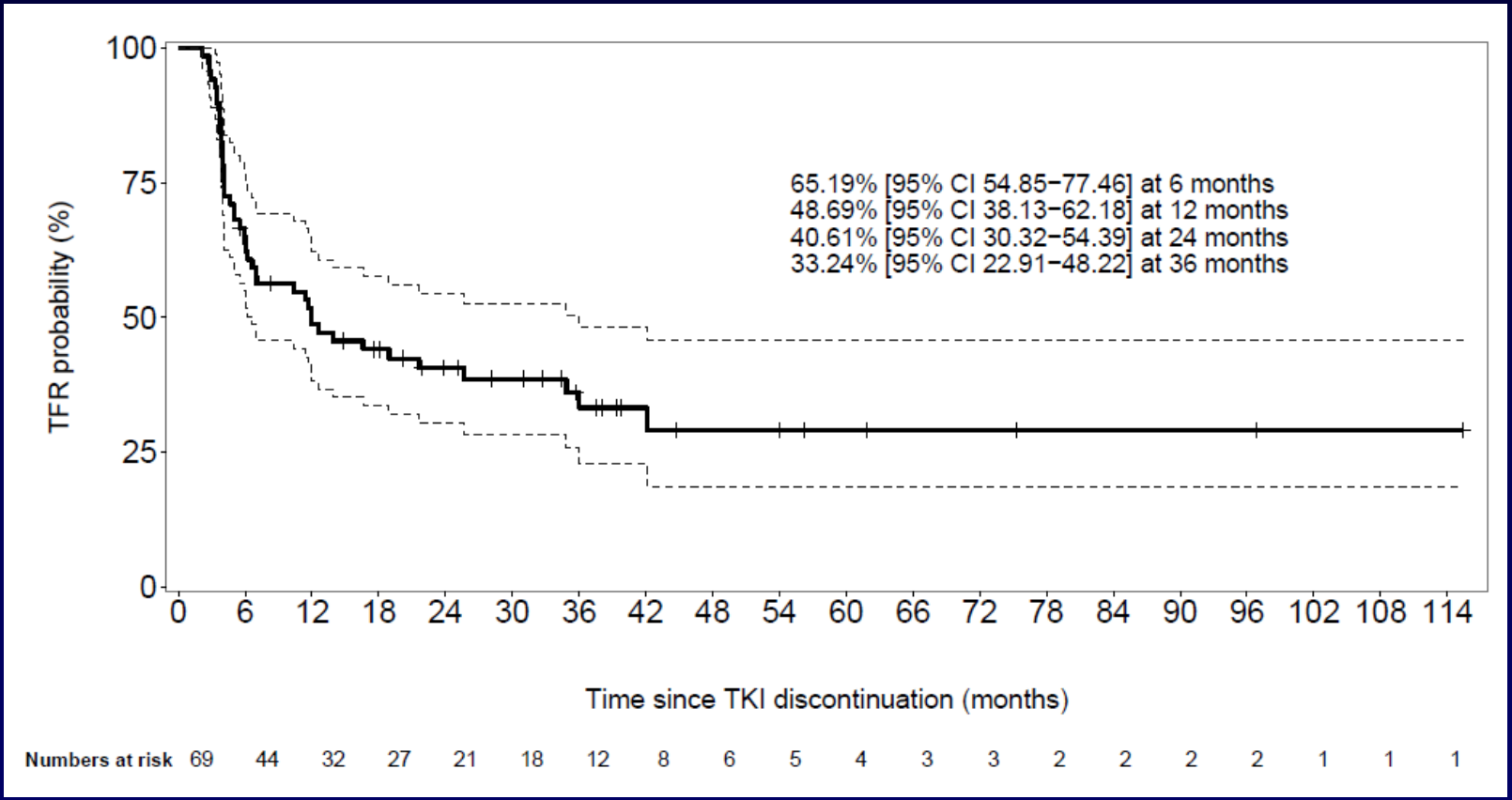
→ Primary objective: Treatment-Free Remission at 6, 12 and 24 months

**Molecular monitoring performed in local laboratories filling international standardization requirements. At least 20,000 x 2 copies of ABL control gene until 2012 then at least 32,000 copies (Cross et al. Leukemia 2015.)*
***UMD loss: at least one positivity of BCR–ABL transcript*
****MMR loss: BCR-ABL > 0.1% on the IS at one time point*

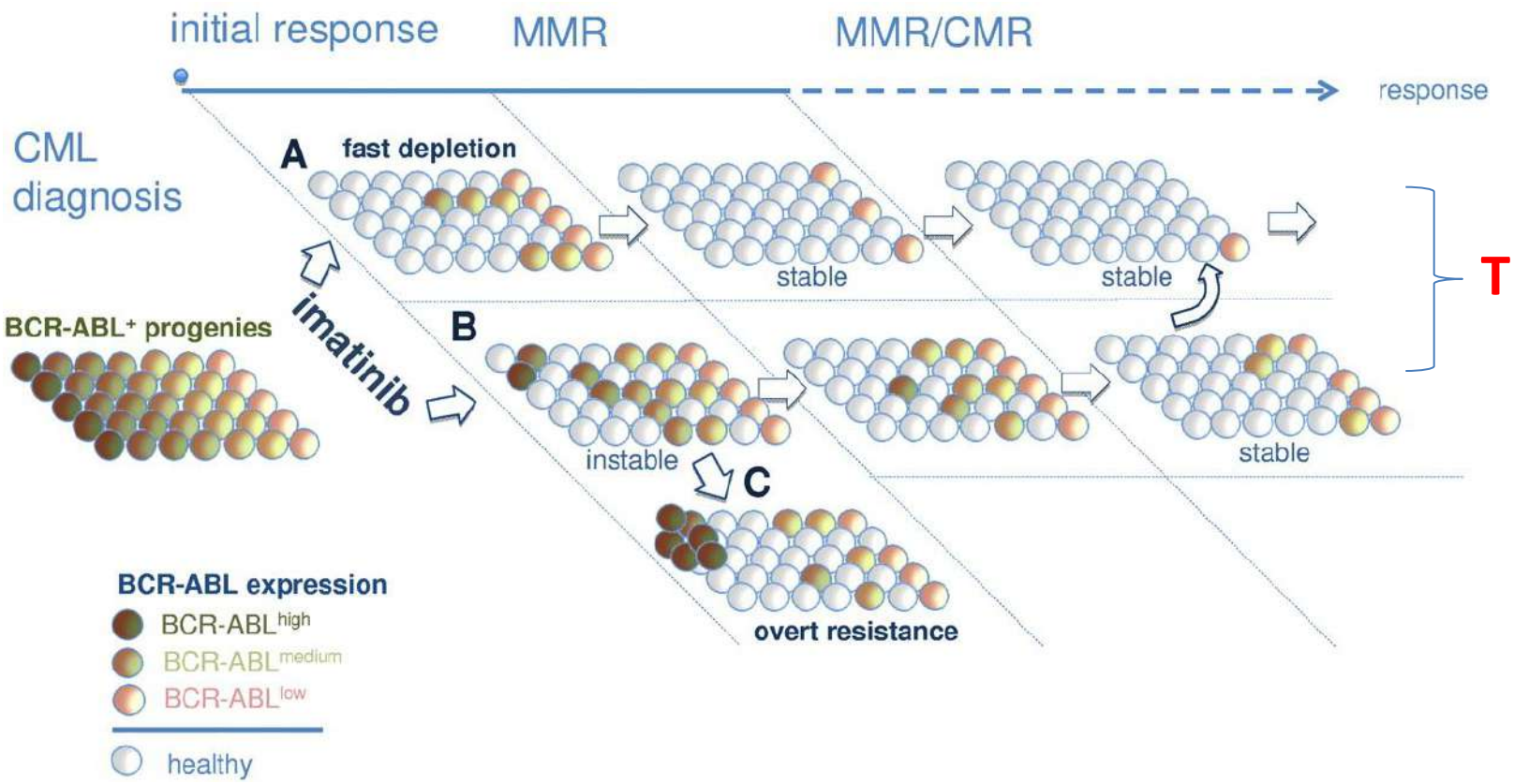
Legros L et al. Blood (ASH) 2016; Abstract 788

Treatment-Free Remission

Median follow-up 39 months (5-116)



Limitations of TKI monotherapy



TFS = 50%

adapted from Kumari A et al. Blood.2012;119(2):530-539.

Acknowledgments

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