"This house believes there are good reasons NOT to stop CML treatment. It should only be done within clinical trials, or only in expert centers where frequent, best quality PCR is available."

In other words…

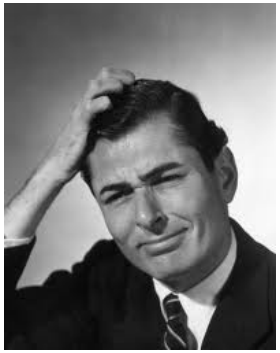
…there *are* good reasons to stop CML treatment. It can be done safely outside clinical trials, and in centers where frequent, best quality PCR isn't available."


Should
I stop?
Benefits
&
risks

History of TKI discontinuation

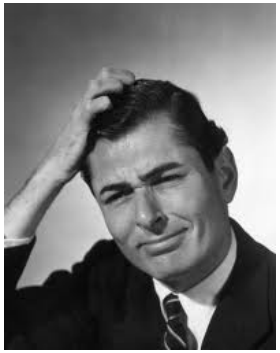
- First reports on imatinib discontinuation between 2004-2006
  - Patient request
  - Imatinib-related adverse events
  - Concomitant serious non-hematologic disease
  - Pregnancy
- Proof of concept in 2007: the STIM pilot study
  - Imatinib discontinuation after ≥2 years of "undetectable" *BCR-ABL1* transcripts
- First clinical trials in 2010: STIM and TWISTER
  - Imatinib discontinuation after ≥3 years of treatment and 2 years of MR4.5 (undetectable)
- Further confirmation in observational studies and trials
- Studies on new generation TKI discontinuation and optimization of discontinuation conditions currently ongoing

Mauro et al. Leuk Res 2004; 28S1: S71-S73.
Cortes et al. Blood 2004; 104; 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.



What I want to know?

- When can I stop?
- How many people ‘stay stopped’?
- Will I feel better/different?
- How long would it be before I knew whether I was going to relapse?
- If I relapse, will the drug work again?
- Is there any risk? Any chance I might die?



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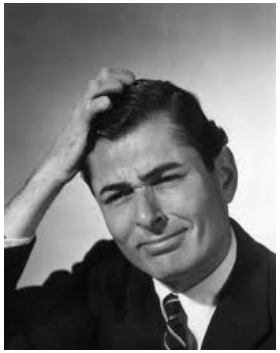
EUROSKI: Impact of time on TKI and duration of MR4 on risk of relapse

Interim analysis of 200 patients

Parameter	n	Relapses by 6 months (n)	Relapses by 6 months (%)	p
TKI duration < 8y	114	54	**47**	0.0030
TKI duration > 8y	86	23	**27**	
MR^4 duration < 5y	108	49	**45**	0.0305
MR^4 duration > 5y	92	28	**30**	

No loss of MMR n = 123 / Loss of MMR n = 77.
Median duration of TKI treatment: 8 years (3-13).
Median duration of MR^4: before TKI discontinuation: 5 years (1-12).

Mahon et al. Blood (ASH 2014); 124: abstract 151.



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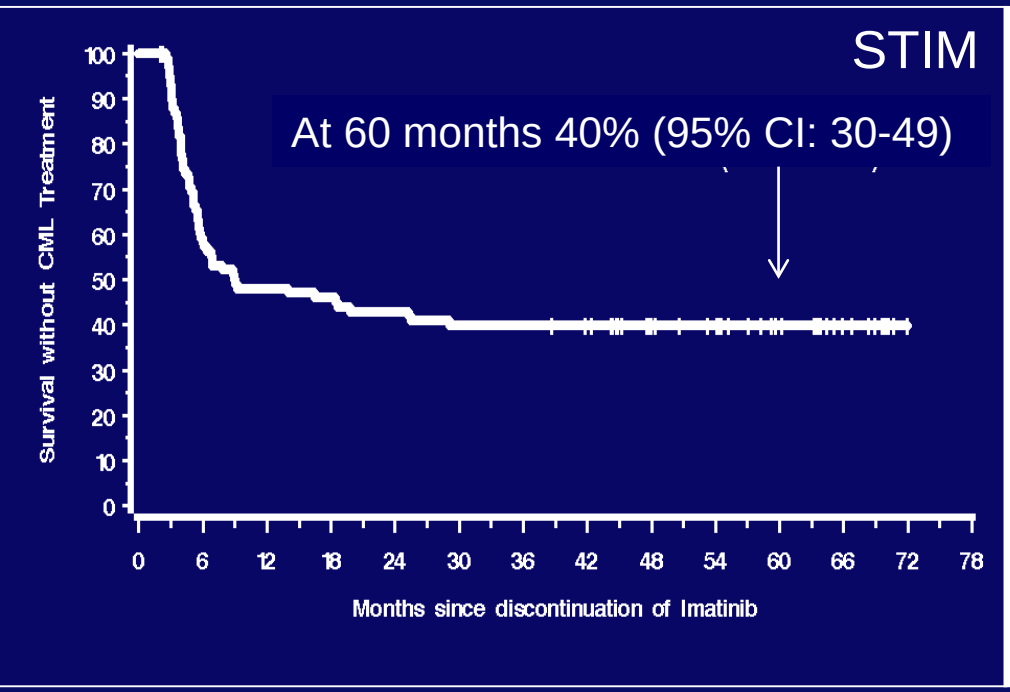
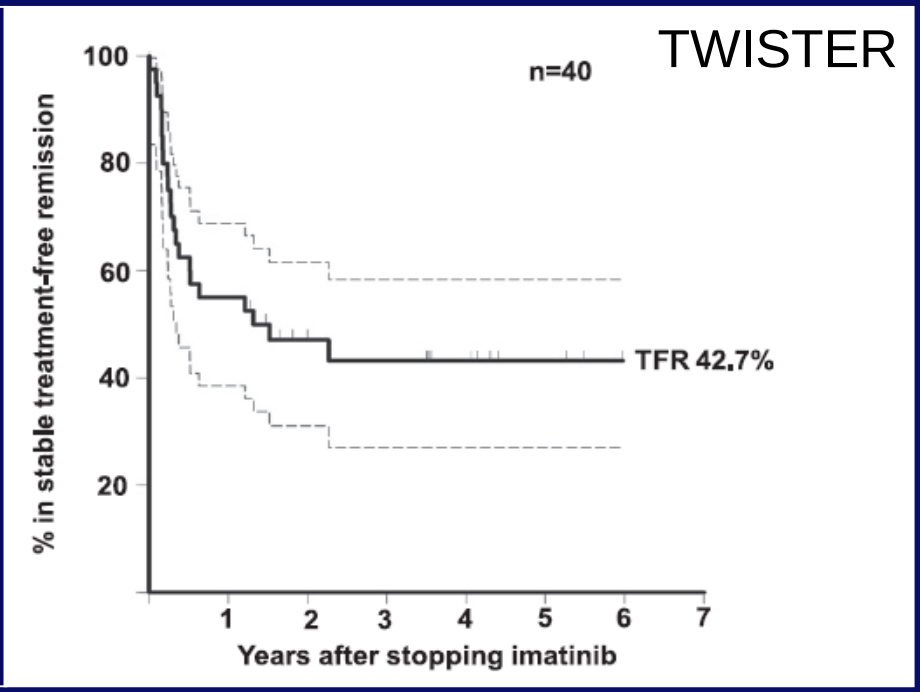
Treatment-free remission in STIM and TWISTER studies





Molecular relapse : detectable *BCR–ABL1* on 2 consecutive tests showing a significant increase.

Molecular relapse: any sample with loss of MMR or 2 consecutive positive samples at any value.

Mahon et al. Lancet Oncol. 2010; 11: 1029-1035.
Mahon et al. Blood 2013; 122: abstract 255.
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CORRESPONDENCE

Musculoskeletal Pain in Patients With Chronic Myeloid Leukemia After Discontinuation of Imatinib: A Tyrosine Kinase Inhibitor Withdrawal Syndrome?

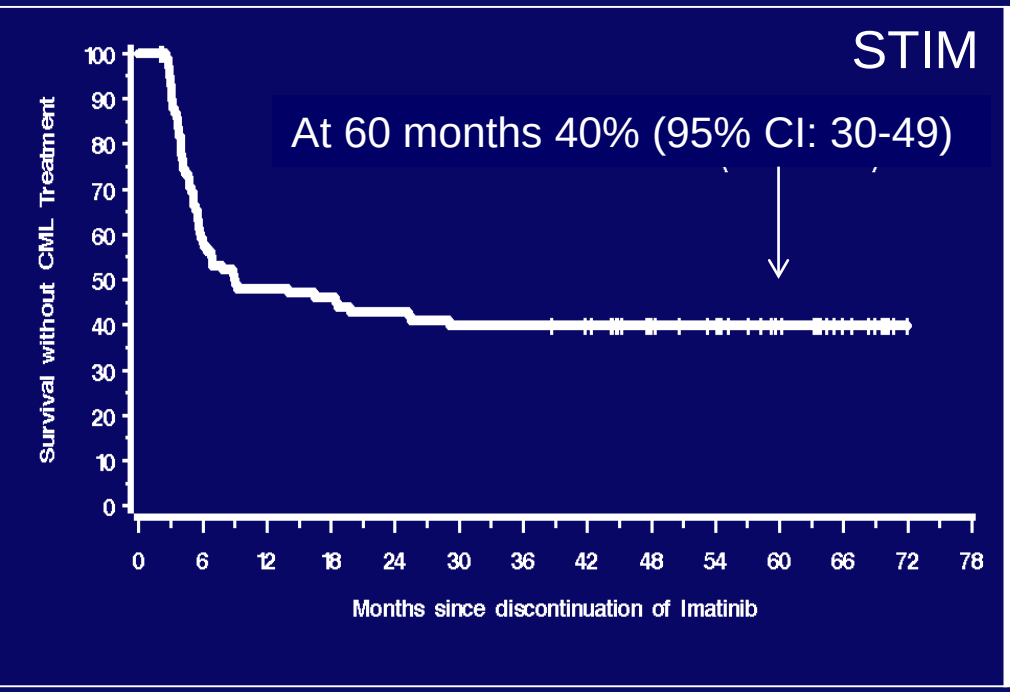
TO THE EDITOR: Rousselot et al[1] recently reported on the According to Stop Imatinib (A-STIM) study evaluating the persistence of major molecular response (MMR) in patients with chronic-phase chronic myeloid leukemia (CP CML) who had discontinued imatinib after prolonged deep molecular remission. They found that 61% of the patients were still in MMR and were treatment free after 36 months, whereas those who lost MMR and restarted tyrosine kinase inhibitor (TKI) therapy all regained MMR. They concluded that loss of MMR is a safe criterion for restarting therapy after TKI discontinuation. However, possible adverse effects derived from this therapeutic strategy were not mentioned in the report.

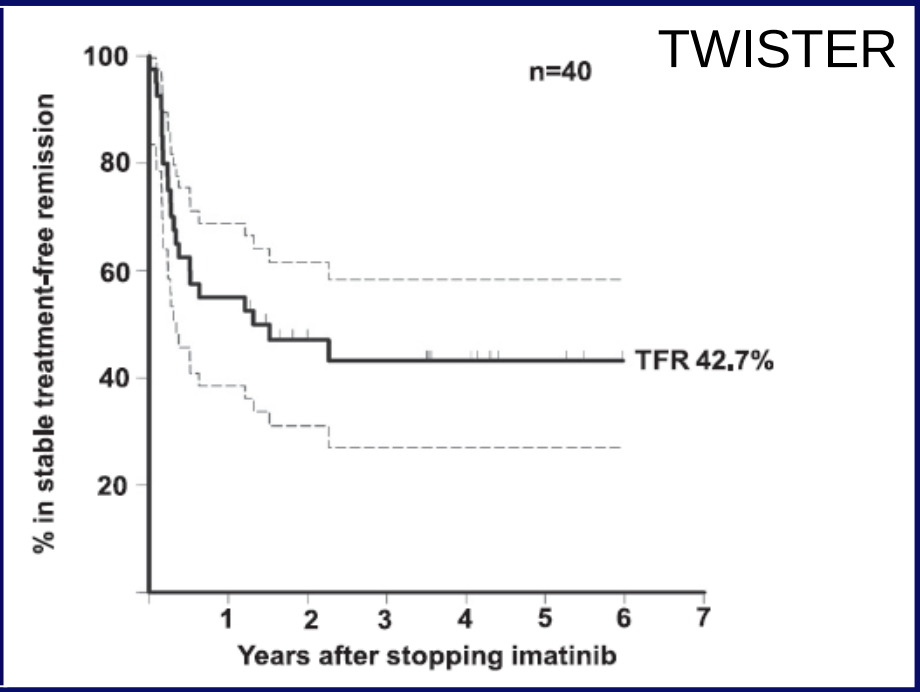
tory activity in three of eight investigated patients, but was normal in the others. Creatinine kinase and lactate dehydrogenase were normal in all patients analyzed, 14 and seven patients, respectively.

Although these adverse events were mild in seven individuals, only leading to use of nonprescription drugs (paracetamol or nonsteroidal anti-inflammatory drugs), eight patients were more severely afflicted, with manifestations that interfered with everyday activities. In five of these patients, corticosteroids were given (10 to 20 mg prednisolone per day), with tapering within weeks. All five patients demonstrated clear improvement within days, but in one patient, prednisolone could not be tapered without the reappearance of symptoms.

The rate of molecular relapse within the first 6 months after imatinib discontinuation did not differ between patients presenting with musculoskeletal adverse effects and those without (data not shown). Among these 15 patients, seven lost MMR and restarted imatinib, at which point six patients had persistent musculoskeletal symptoms. In all six patients, the symptoms completely resolved within 1 to 3 months after imatinib reinitiation. Among the remaining

Treatment-free remission in STIM and TWISTER studies





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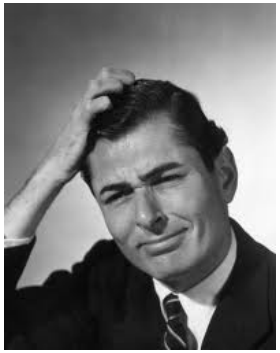

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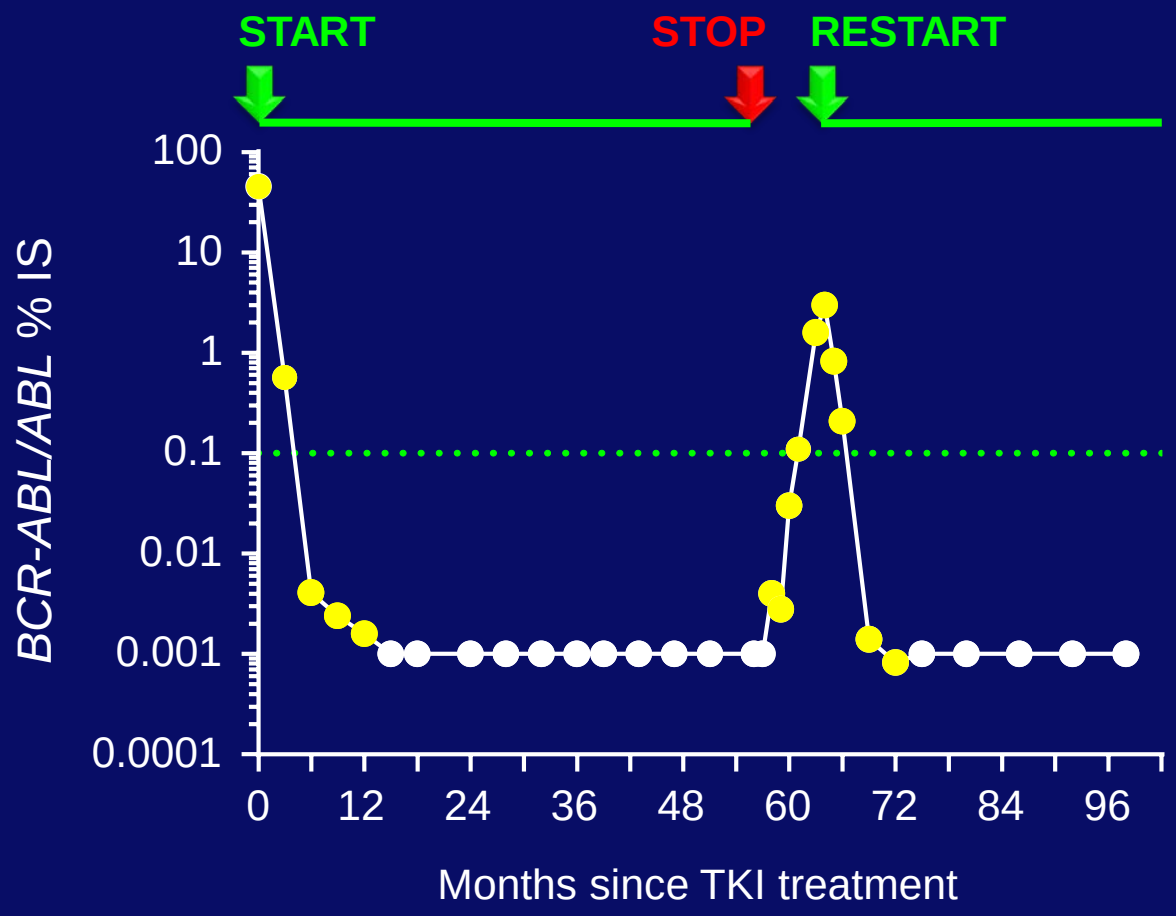
Safety of TKI discontinuation

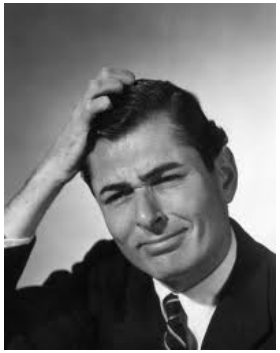


● Detectable *BCR-ABL* ● Undetectable *BCR-ABL* ≥ 32000 copies of *ABL*

D. Rea personal data
Patient enrolled in the STIM2 trial

Benefits…


Risks…



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It’s OK to stop now…