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Treatment Discontinuation in Chronic Myeloid Leukemia

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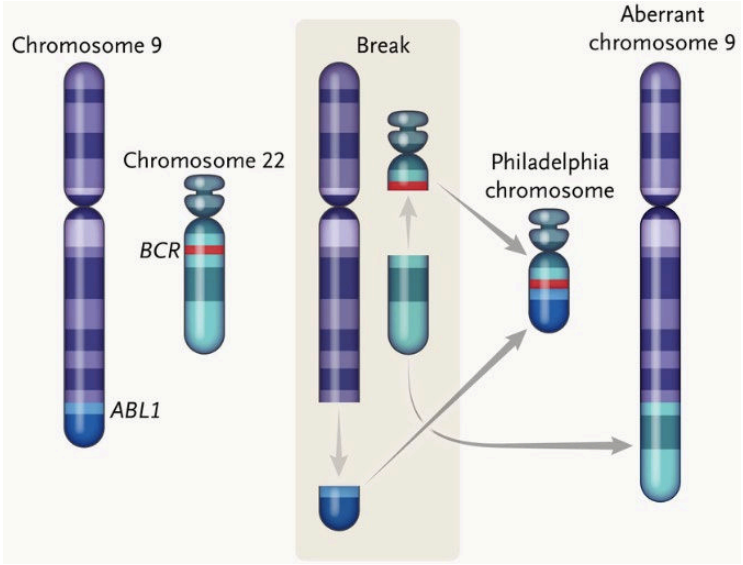
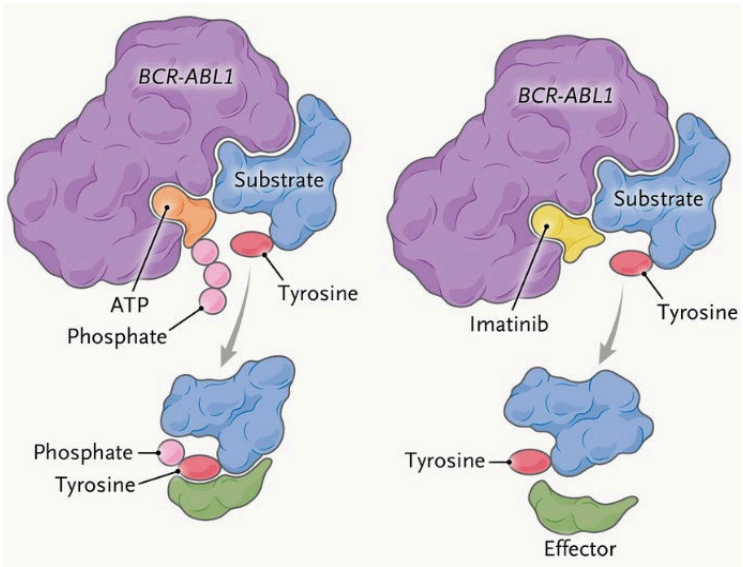
Conflicts of Interest

- Consulting/Honoraria: GSK, Cogent Biosciences, PharmaEssentia
- Research support: Incyte, Cogent Biosciences, Ascentage Pharma, Blueprint Medicines, Syntrix Biosystems

Chronic Myeloid Leukemia (CML)

- Myeloproliferative neoplasm defined by presence of the Philadelphia chromosome
- Accounts for 15-20% of adult leukemias
- Incidence of 1-2/100,000
- Prevalence in US estimated to reach 180,000 by 2050





Available Tyrosine Kinase Inhibitors (TKI) in 2023

Approved in frontline setting

1st Generation

- Imatinib

2nd Generation

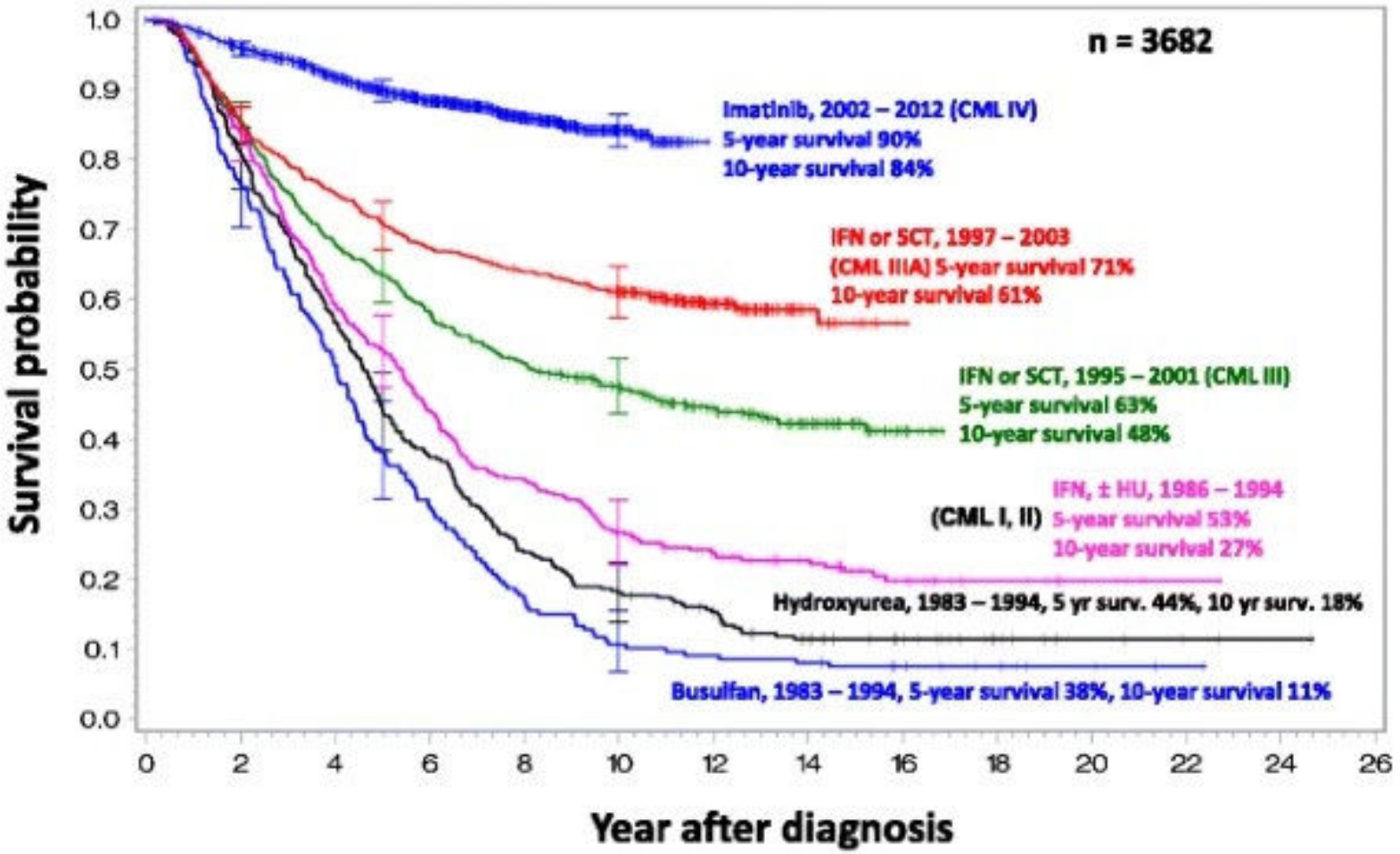
- Dasatinib
- Nilotinib
- Bosutinib

≥2 TKIs or T315I mutation

3rd Generation

- Ponatinib
- Asciminib
  - Approved 10/29/21

Tyrosine Kinase Inhibitors Have Dramatically Improved Outcomes in CML



Hehlmann R. *Ann Hematol* 2015; 94suppl 2: S103-5

Rationale for Treatment Discontinuation

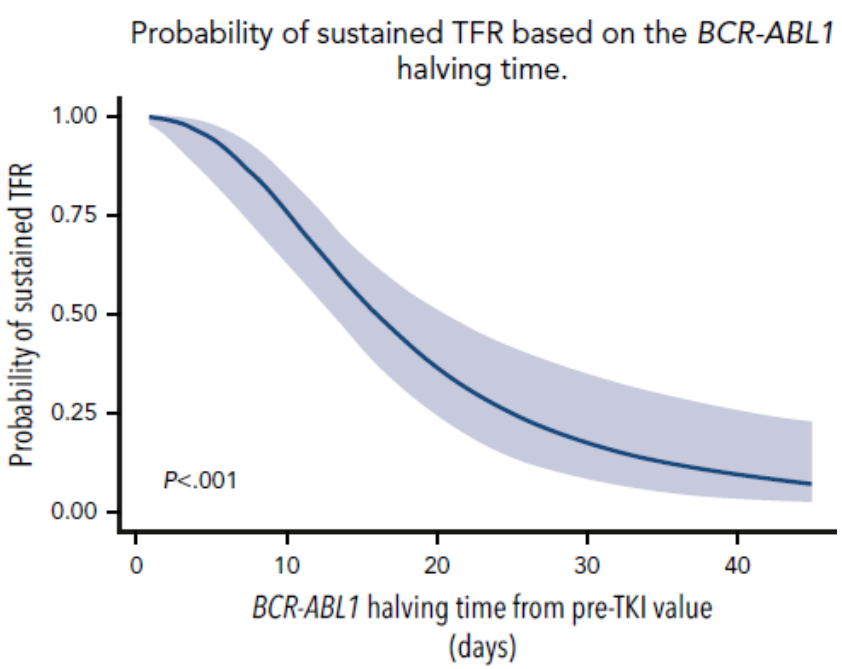
- Patients with CML now have a life expectancy approaching normal
- TKIs are associated with toxicities:
  - Serious adverse events (thrombotic events, effusions, pancreatitis, etc.)
  - Long-term toxicity (Cardiovascular, renal toxicity, etc.)
  - Low-grade, chronic toxicities affect quality of life
  - Financial toxicity
- Early clinical and anecdotal reports of patients remaining in remission off of TKI

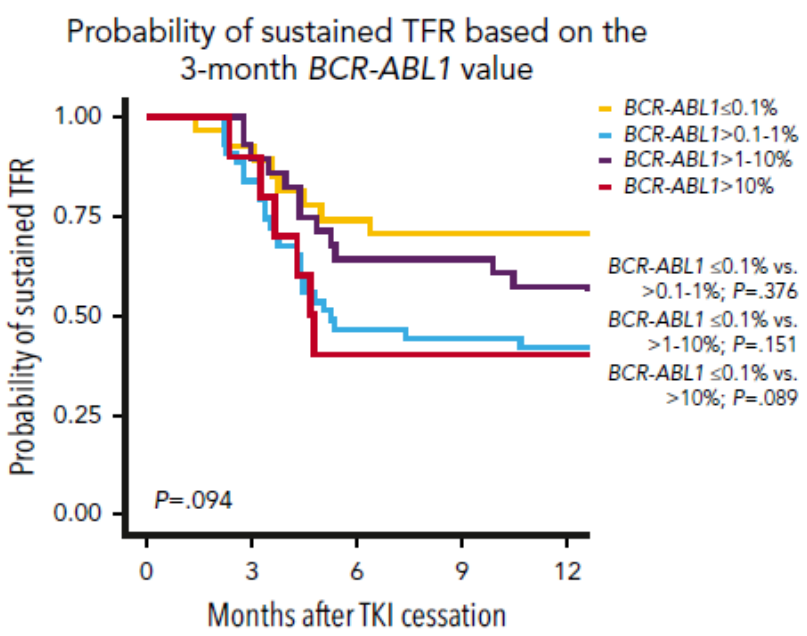
Key Treatment-Free Remission (TFR) Studies in CML

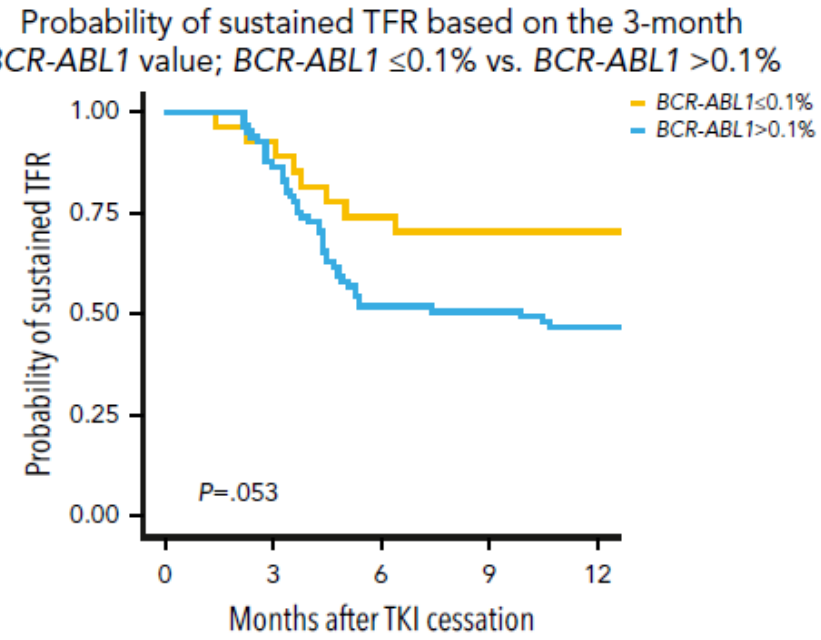
Study	TKI	Patients (N=)	Years on TKI	Molecular response	TFR success	Predictors of Success
EURO-SKI	94% Ima	758	3	DMR ≥ 1 year	46% at 3 years	Time on TKI, Duration of DMR
LAST	Any	172	3	DMR ≥ 2 years	60.8% (median follow up 41 mo)	Detectable BCR-ABL at d/c and at 3 months
DASFREE	Das	84	2	MR4.5 ≥ 1 yr	44% at 5 yrs	TKI duration, first line therapy, older age
ENESTfreedom	Nil	190	2 (+1 yr on study)	MR4.5 ≥ 1 yr	51.6% at 48 weeks 42% at 5 years	Sokal: low, stable MR4.5 at 1yr, TKI duration, Duration MR4.5
ENESTop	2nd Nil	126	3 (2 on Nil) +1 yr	MR4.5 ≥ 1 yr	57.9% at 48 weeks 42.9% at 5 years	Time in MR4.5
STIM1	Ima	100	3	Undetectable ≥ 2 years	38% at 5 years	Sokal score and TKI duration

Saussele S, et al. *Lancet Oncol* 2018; 19(6):747-757. Mahon FX, et al. (ASH 2021). Atallah, et al. *JAMA Oncol* 2021; 7(1):42-50. Shah N, et al. *Leuk Lymphoma* 2020; 61(3):650-659. Radich et al. *Leukemia* 2021; 35(1): 1344-1355 Etienne G, et al. *J Clin Oncol* 2017; 35: 298-305. Hughes T, et al. *Leukemia (*2021); 35:1631-1642

Early Response Kinetics Predict Success







Shanmuganathan N, et al. *Blood*2021; 137(9):1196-1207.

Consensus TFR Criteria & Monitoring

Criteria for TKI Discontinuation

- Age ≥18 years.
- CP-CML. No prior history of AP-CML or BP-CML.
- On approved TKI therapy for at least 3 years.[1,2]
- Prior evidence of quantifiable *BCR::ABL1* transcript.
- Stable molecular response (MR4; *BCR::ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[2]
- Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR::ABL1* ≤0.0032% IS) and that provides results within 2 weeks.
- Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; *BCR::ABL1* ≤0.1% IS).
- Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR::ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.

Table 8 Requirements for tyrosine kinase inhibitor discontinuation.

Mandatory:

- CML in first CP only (data are lacking outside this setting)
- Motivated patient with structured communication
- Access to high quality quantitative PCR using the International Scale (IS) with rapid turn-around of PCR test results
- Patient's agreement to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter.

Minimal (stop allowed):

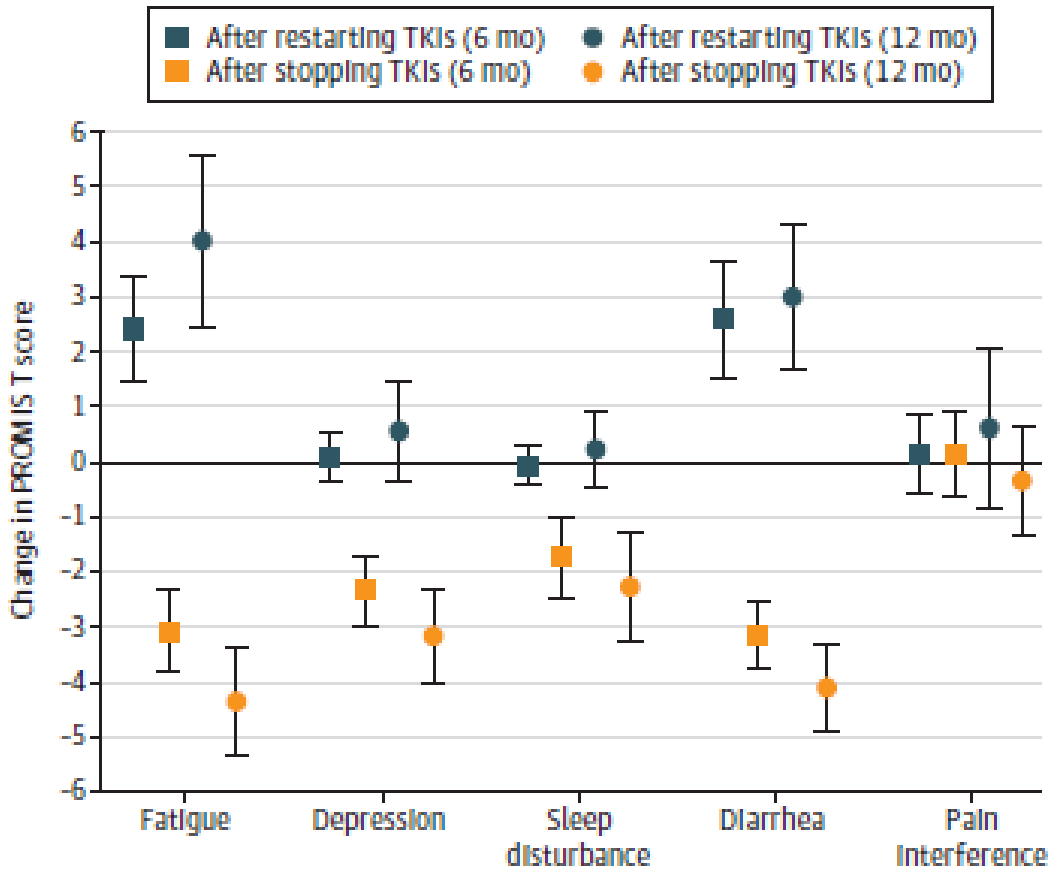
- First-line therapy or second-line if intolerance was the only reason for changing TKI
- Typical e13a2 or e14a2 BCR–ABL1 transcripts
- Duration of TKI therapy >5 years (>4 years for 2GTKI)
- Duration of DMR (MR^4 or better) >2 years
- No prior treatment failure

Optimal (stop recommended for consideration):

- Duration of TKI therapy >5 years
- Duration of DMR > 3 years if MR^4
- Duration of DMR > 2 years if $MR^{4.5}$

NCCN v2.2023. Hochhaus A, et al. *Leukemia* 2020; 34(4):966-984

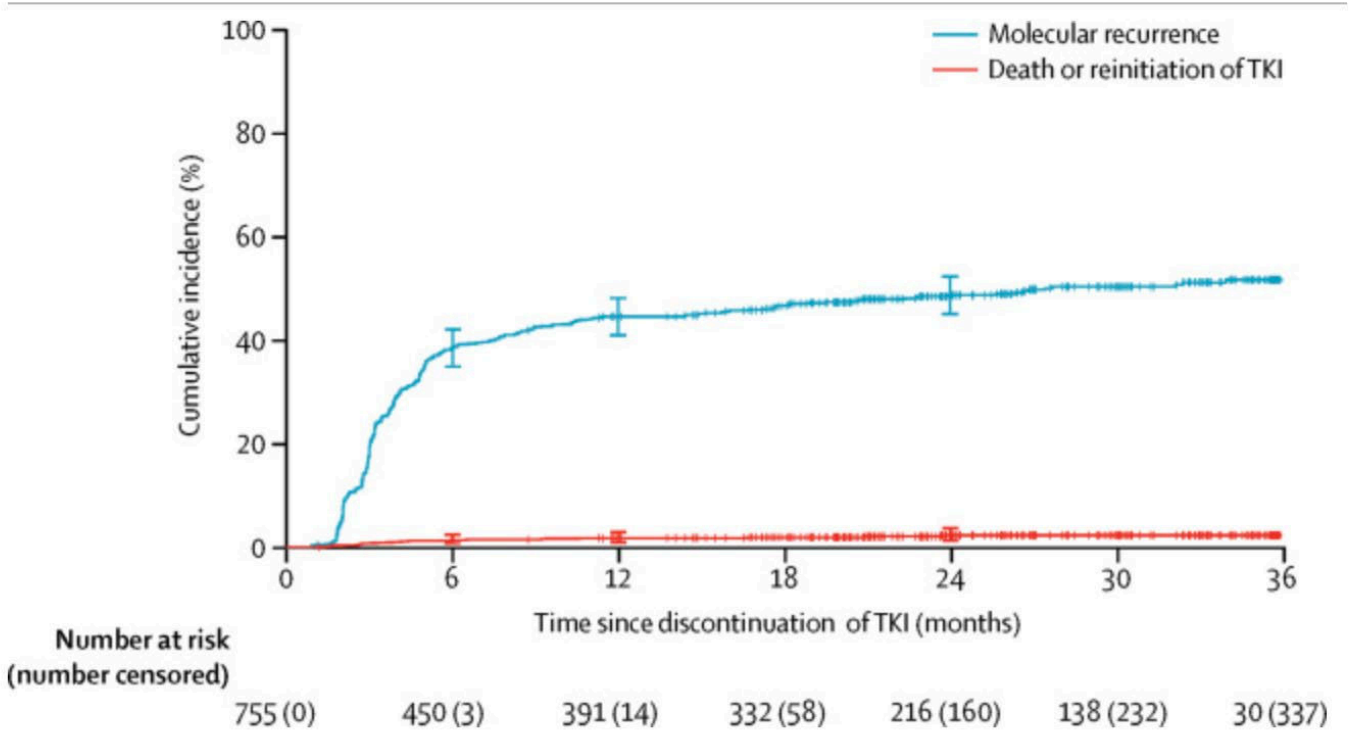
TFR is Associated with Improved Quality of Life and Decreased Cost

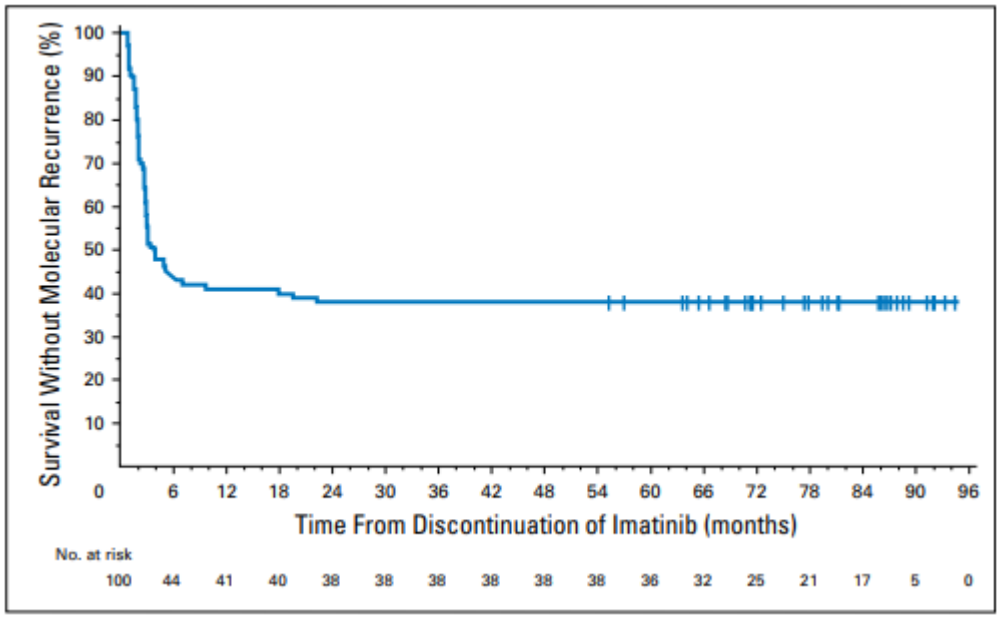


- Cost savings:
  - In Euro-ski: €22 million in 596 evaluable imatinib treated patients (at time of analysis)
  - French study: €56k per TFR period
  - Japanese study: $66k over 3 years per TFR
  - Lebanese study: ~$42k per patient on study (only half TFR eligible)

Atallah, et al. *JAMA Oncol* 2021; 7(1):42-50. Saussele S, et al. *Lancet Oncol* 2018; 19(6):747-757. Etienne G, et al. *Br J Haematol* 2020; 189(3):e97-e100. Yamazaki K, et al. *Cancer Sci* 2020; 111(7):2526-2535. Elias F, et al. *J Glob Oncol* 2019; 5:1-7

Molecular Relapse Occurs Early After Discontinuation





Saussele S, et al. *Lancet Oncol* 2018; 19(6):747-757. Etienne G, et al. *J Clin Oncol* 2017

Management and Outcomes After Molecular Relapse

- Reinitiate TKI immediately at loss of MMR, with monthly monitoring until MMR is achieved
- Median time to MMR <3 months

Study	TKI	Response to re-initiation	Accelerated/blast phase
EURO-SKI	94% Ima	86% MMR, 81% MR4 (short follow up)	None
LAST	Any	MR4 in 93.2%	Not reported
DASFREE	Das	100% MMR and MR4.5	None
ENESTfreedom	Nil	99% MMR, 92% MR4.5	None
ENESTop	2nd Nil	98% MMR, 93% MF4.5	None
STIM1	Ima	96.5% undetectable PCR	None
ENESTPath	2nd Nil	92% MMR at 3 months	Not reported

Saussele S, et al. *Lancet Oncol* 2018; 19(6):747-757. Mahon FX, et al. (ASH 2021). Atallah, et al. *JAMA Oncol* 2021; 7(1):42-50. Shah N, et al. *Leuk Lymphoma* 2020; 61(3):650-659. Radich et al. *Leukemia* 2021; 35(1): 1344-1355 Etienne G, et al. *J Clin Oncol* 2017; 35: 298-305. Rea D, et al. *ASH Annual Meeting* 2021

TKI Withdrawal Syndrome

- Up to 30% of patients, median of 1.8 months after stopping
- Musculoskeletal pains +/- pruritis
- Generally self-limited and will resolve, but may persist for several months
- Treatment:
  - NSAIDs
  - Anti-histamines
  - Corticosteroids if refractory/severe.
  - TKI resumption in severe cases

Increasing the Proportion of Eligible Patients and Success of TFR

- Estimates suggest ~ 20% of all CML patients ultimately achieve long-term TFR.
- As a key goal in CML therapy, methods are needed to increase proportion of patients achieving eligibility (and success of TFR):
  - 2nd generation TKIs
    - Rates of TFR eligibility ~30-40% with imatinib vs. 50-60% with 2G-TKI
  - Combination approaches
    - Ruxolitinib
    - Interferon
    - Multiple TKIs
    - Other non-BCR-ABL pathways, including immune therapies
  - 3rd generation and novel TKIs.

Kantarjian HM, et al. *Leukemia* 2021; 35(7):2142-43

ENESTPath Study: 2nd Line Nilotinib to Achieve TFR Eligibility After Imatinib

Figure 1: ENESTPath study design

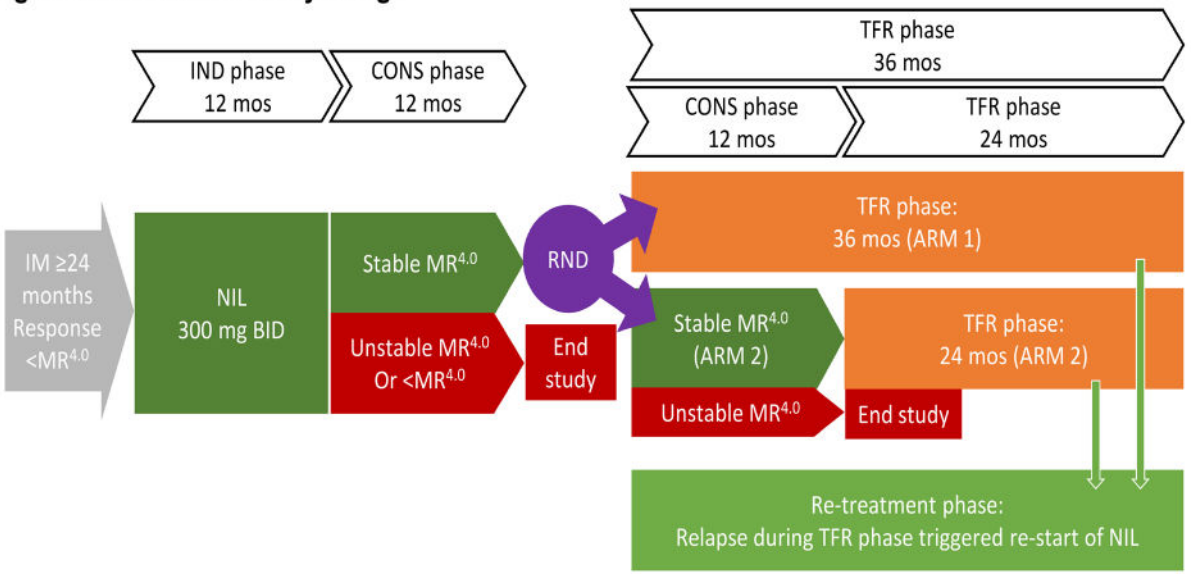
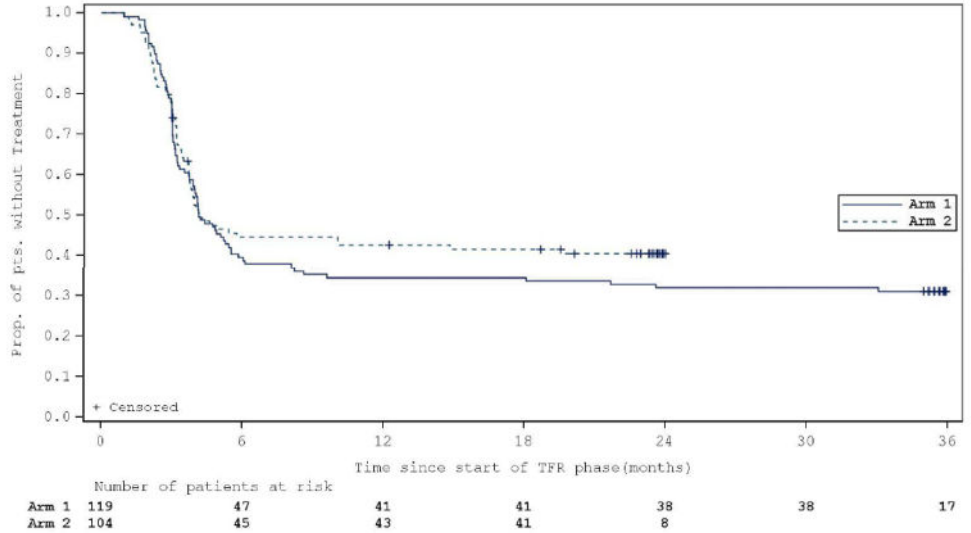


Figure 2: Kaplan-Meier analysis of TFS during the TFR phase (subset of FAS randomized patients entering the TFR phase)



Rea D, et al. *ASH Annual Meeting* 2021

Is Attempting TFR a Second Time Feasible?

	Number of patients	TFR (@months)	Notes
TRAD[20]	25	21% (6)	Patients restarted dasatinib after MMR loss with imatinib
RE-STIM[21]	70	35% (36)	TFR 72% *vs.* 36% for those who did *vs.* did not remain in DMR at 3 months with first attempt. 61 of 70 patients received the same TKI
Matsuki[22]	10	24% (24)	All patients on dasatinib.
Sweet	41	NR	Ongoing study, adding ruxolitinib (NCT03610971)
Rousselot	26	NR	Ongoing study, adding pioglitazone (NCT02889003)
Olsson-Strömberg	134	NR	Ongoing study, second attempt with dasatinib (NCT03573596)
Spanish	80	NR	Ongoing study, second attempt with ponatinib (NCT04160546)
ELN	200	NR	Ongoing study, second attempt with nilotinib (NCT02917720)

TFR: treatment-free remission; MMR: major molecular response; DMR: deep molecular remission; TKI: tyrosine kinase inhibitor; NR: not reported; ELN: European LeukemiaNet.

Atallah E, et al. *Haematologica* 2020. Legros L, et al. *ASH* 2019.

Conclusions

- TKIs have revolutionized treatment of CML, with long-term survival approaching normal life expectancy
- TKI use is associated with toxicity as well as significant cost
- Treatment-free remission has become a key treatment goal in CML
- Multiple studies have demonstrated success in eligible patients
  - ~45-50% achieve long-term TFR
- Measures to increase the number of eligible patients and rates of success are needed