

Breaking Free : **When and How to Stop TKIs in CML**

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Currently Available CML Therapies

Imatinib

- 1st gen TKI
- ATP-competitive
- 1st line

Nilotinib

- 2nd gen TKI
- ATP-competitive
- 1st, 2nd, 3+

Dasatinib

- 2nd gen TKI
- ATP-competitive
- 1st, 2nd, 3+

Ponatinib

- 3rd gen TKI
- ATP-competitive
- 2nd, 3+, T315I

Asciminib

- ABL myristoyl pocket
- STAMP inh
- 2nd, 3+, T315I

The Evolution of CML Tx

Treatment

• Hydroxyurea > IFN > TKIs

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Treatment

• Hydroxyurea > IFN > TKIs

Monitoring

• CBC > cytogenetic > FISH > PCR

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Endpoint

• CHR > MCyR > CCyR > MMR > MR4.5

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Goal

• symptoms control > survival > Transformation free > TFR

Currently CML Therapies Result

- 60% achieved MR 4.5 by 10 years
- CML-related mortality 0.5–1%
- 10-year blast phase progression 5–6%
- CML-specific 10-year survival rate 80–90%, approaching the general population
 - Long term treatment : side effects, drug adherence, quality of life

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“The goals of therapy evolves toward **quality of life and cost saving”**

Treatment Free Remission (TFR)

“The maintenance of a deep molecular response without the need for ongoing TKI therapy”

Important of TFR :

- Eradicate TKI side effects
- Improved quality of life (QoL)
- Ease the inconvenience of taking daily medication, drugs interaction
- Cost & reimbursement

Key to consider for TFR

Deep
Molecular
Response

Treatment
Duration

Patient
Selection

Monitoring

Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial

Susanne Saussele, Johan Richter*, Joelle Guilhot*, Franz X Gruber, Henrik Hjorth-Hansen, Antonio Almeida, Jeroen J W M Janssen, Jiri Mayer, Perttu Koskenvesa, Panayiotis Panayiotidis, Ulla Olsson-Strömberg, Joaquin Martinez-Lopez, Philippe Rousselot, Hanne Vestergaard, Hans Ehrencrona, Veli Kairisto, Katerina Machová Poláková, Martin C Müller, Satu Mustjoki, Marc G Berger, Alice Fabarius, Wolf-Karsten Hofmann, Andreas Hochhaus, Markus Pfirrmann†, Francois-Xavier Mahon†, on behalf of the EURO-SKI investigators‡ Lancet 2018*

Single-arm, prospective, open-label, no randomized trial

- ≥ 18 years, typical BCR-ABL1 transcript (e13a2, e14a2)
- 1st line, 2nd line (toxicity with 1st line)
- Treatment with any TKI or TKI as part of a combination Tx
- Minimum treatment duration 3 years
- Minimum duration of DMR 1 year
- At least 3 PCR showed DMR within a year

Primary endpoint

- Molecular relapse-free survival (loss of MMR or death)

Secondary endpoint

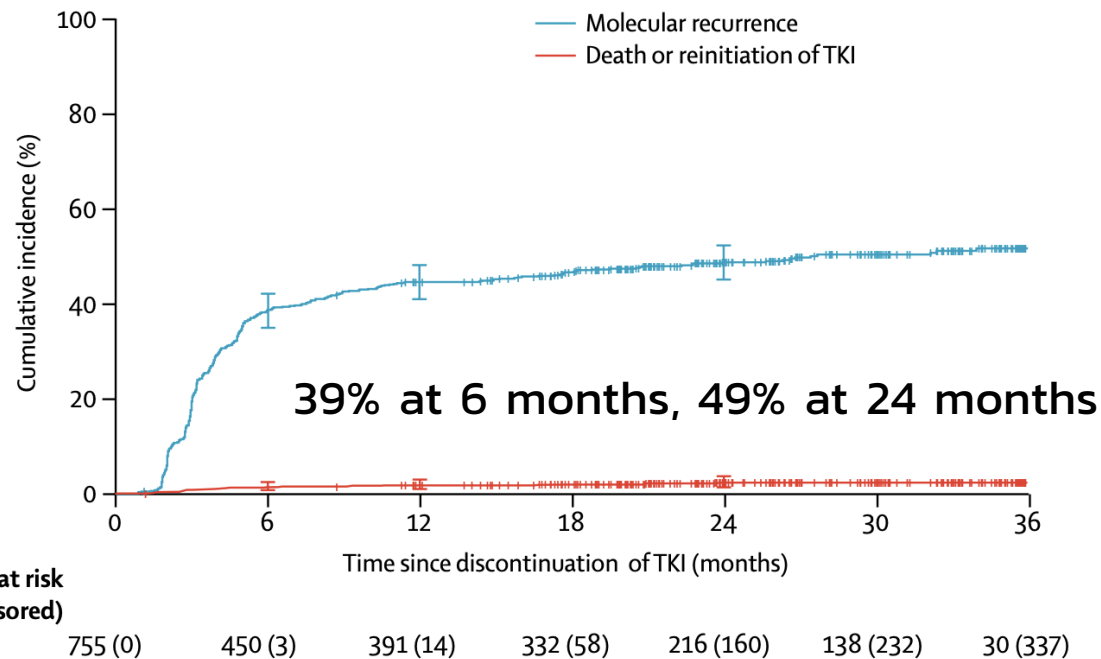
- Prognostic analysis of factors affecting maintenance of MMR at 6 months

- Exclude post AlloSCT, TKI failure, active concomitant malignancy

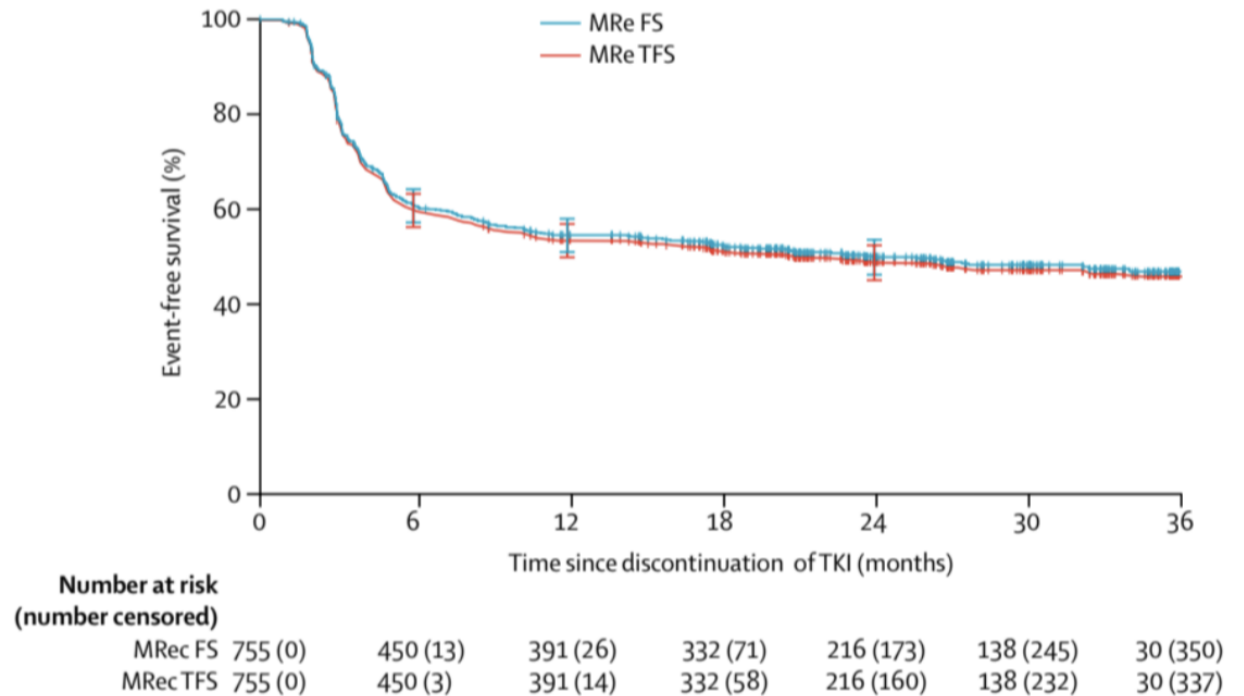
DMR : BCR-ABL $\leq 0.01\%$ or undetectable in sample of ABL1 $\geq 10,000$, GUS $\geq 24,000$

Result (EURO-SKI)

- 758 patients



Cumulative incidence of molecular recurrence after TKI discontinuation



MReFS and MReTFS after TKI discontinuation

Adverse Event

- Musculoskeletal pain
 - Bone, joint pain, arthralgia, myalgia, joint stiffness, lumbalgia, articular pain, muscle pain, neck pain, arthromyalgia, pain in both arms, pain in legs

Musculoskeletal pain		
	Grade 1-2	Grade 3
Total	263 (35%)	11 (1%)
During Treatment-free period	224 (30%0	9 (1%)

Clinical Study	TKI Therapy	Median Duration of TKI Therapy (years)	Relapse-Free Survival (RFS)	Number of Patients
STIM1 ¹³	Imatinib	4.9	38% at 60 mo	100
EURO-SKI ⁴	Any TKI	7.5	50% at 24 mo	755
LAST ⁶	Imatinib, Dasatinib, Nilotinib, or Bosutinib	6.9	65.5% at 3 y	172
DASFREE ⁸	Dasatinib	4.5, 3.8 ^a	46% at 2 y	84
ENESTfreedom ⁵	Nilotinib	3.6	52% at 48 wk	190
TWISTER ³	Imatinib	5.8	45% at 3.5 y	40
ENESTop ¹²	Second-line Nilotinib	4.1, 5.6 ^b	57.9% at 48 wk, 42.9% at 5 y	126

^a Median of 4.5 years in patients aged >65 years; median of 3.8 years in patients aged <65 years.

^b Median of 34.1 years in patients aged <53 years; median of 5.6 years in patients aged ≥53 years.

STIM : Etienne G, J clin Oncol 2017, **EURO-SKI** : Saussle S, Lancet Oncol. 2018, **LAST** : Atallah E, JAMA Oncol 2021, **DASFREE** Shah NP, Leuk Lymphoma 2020
ENESTfreedom : Hochhaus A, Leukemia. 2017, **TWISTER** : Ross DM, Blood 2013, **ENESTop** : Hughes TP, Leukemia 2021

Stop TKIs after 2nd line of Treatment

Leukemia (2021) 35:1631–1642

<https://doi.org/10.1038/s41375-021-01260-y>

ARTICLE



CHRONIC MYELOGENOUS LEUKEMIA

Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update

Timothy P. Hughes ¹ · Nelma Cristina D. Clementino² · Mikhail Fominykh ^{3,4} · Jeffrey H. Lipton⁵ · Anna G. Turkina ⁶ · Elena Beatriz Moiraghi⁷ · Franck E. Nicolini⁸ · Naoto Takahashi ⁹ · Tomasz Sacha ¹⁰ · Dong-Wook Kim ¹¹ · Rafik Fellague-Chebra¹² · Ranjan Tiwari¹³ · Catherine Bouard ¹² · Francois-Xavier Mahon¹⁴

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N 126

- Age $\geq$ 18 year
- Ph+ CML-CP, received $\geq$ 3 years TKI, include $>$ 4 wk of imatinib followed by $>$ 2 years of nilotinib
- Achieved MR4.5 ($BCR::ABL \leq 0.0032\%$) while on nilotinib (enter 1 year consolidation phase before stop)

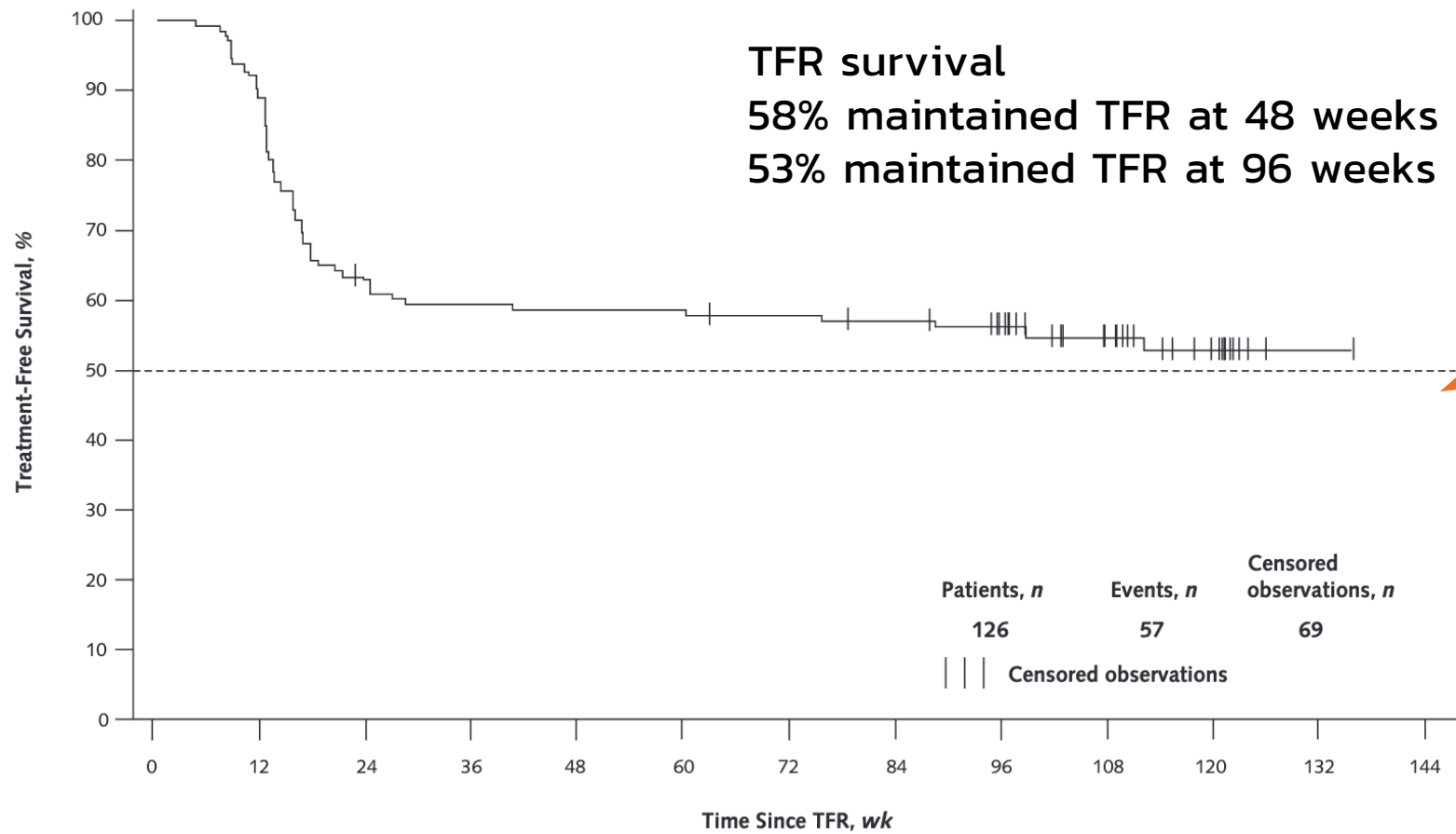
Reasons for switch from imatinib

- Intolerance 40%
- **Resistance 24%**
 - Resistance/treatment failure 13%
 - Suboptimal response 6%
 - Loss of HR 2%
 - Loss of CR 2%
 - Loss of MMR 1%
- Physician preference 36%

Primary endpoint

- Proportion of patients without loss of MMR, confirmed loss of MR4, treatment reinitiation within the first 48 weeks

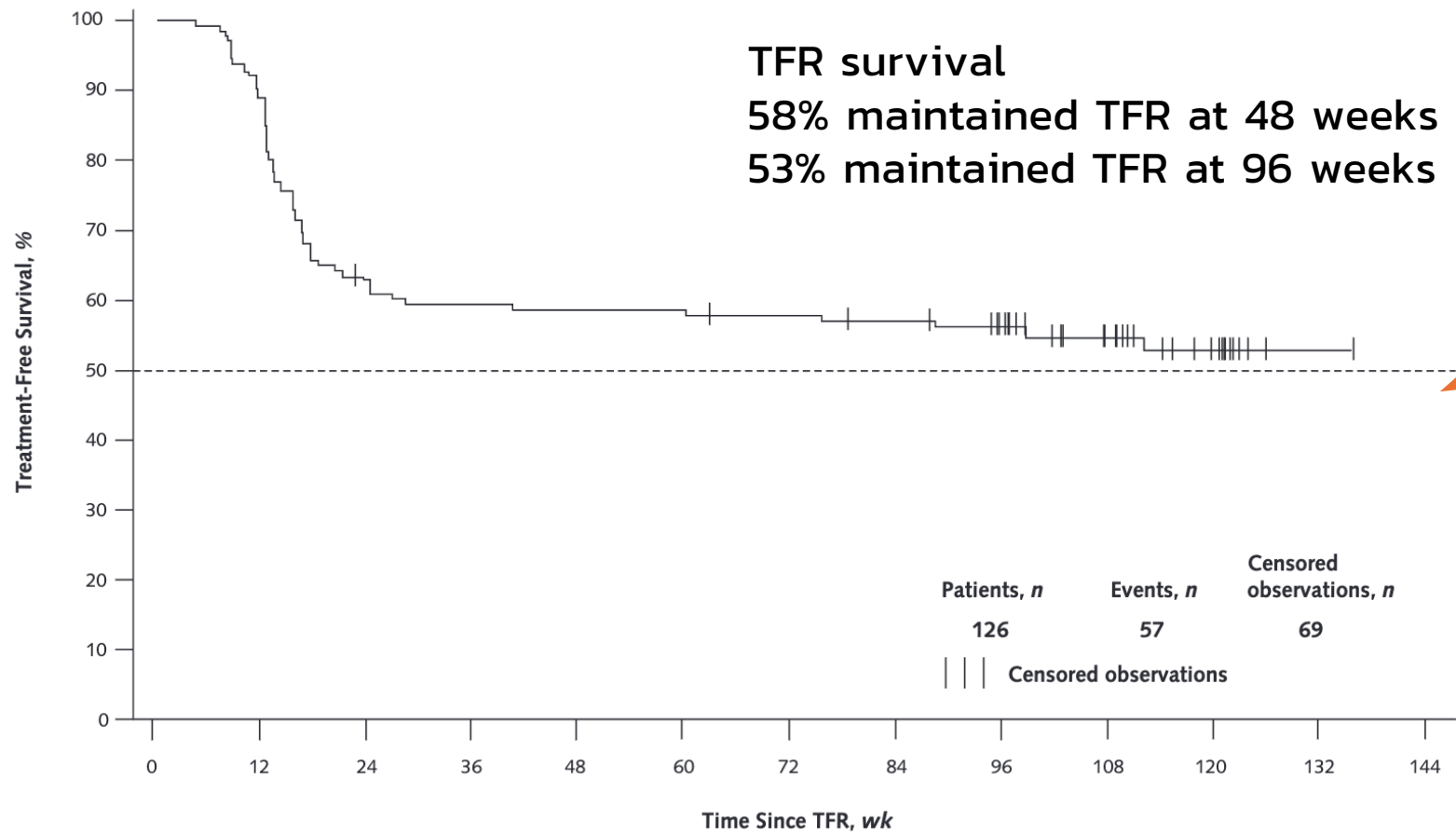
A



TFR seem achievable in patients with sustained MR4.5

Rate of TFR were similar in patients who switched to nilotinib because of intolerance, resistance

A



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Musculoskeletal pain most occurs 42%, most during the first 48 weeks after discontinuation

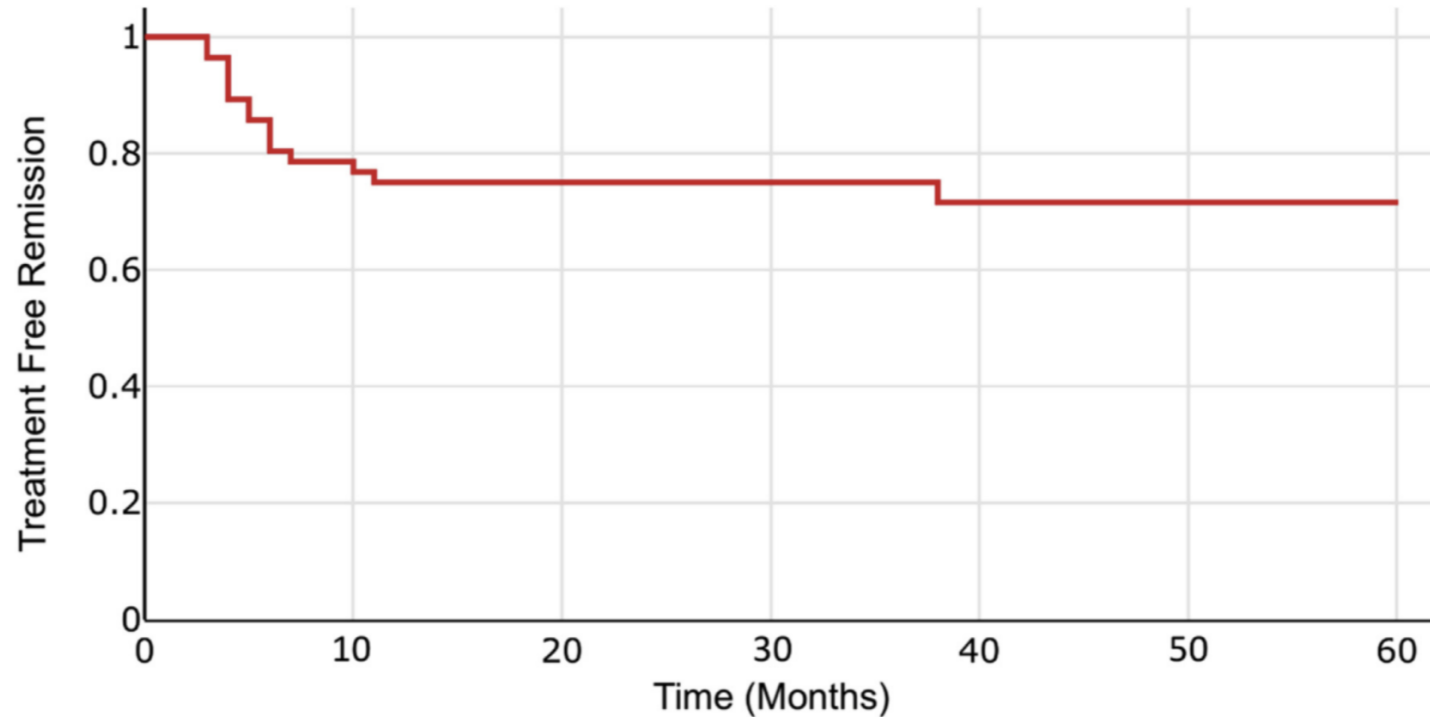
Discontinuation of Tyrosine Kinase Inhibitor Therapy and Treatment Free Remission (TFR) in Chronic Myeloid Leukemia: Successful Achievement of TFR in More Than Two-Third of Patients in a Real-World Practice

Aamer Aleem,¹ Naila A. Shaheen,^{2,3,4,5} Farjah Algahtani,¹ Ahmed Jamal,¹
Nora Alkhudair,⁶ Mashail Alghafis,¹ Zafar Iqbal,^{2,3,5,7} Hajar Wan Zuki Siti,^{2,3,4}
Abin Thomas,^{2,3,8} Bader Alahmari,^{2,3,4,5} Hind Salama,^{2,3,4,5} Giamal Gmati,^{2,3,4,5,9}
Mohsen Alzahrani,^{2,3,4,5} Ayman Alhejazi,^{2,3,4,5} Mansour Alfayez,^{10,11}
Abdullah Alrajhi,^{12,13} Mohammed A. Marei,¹⁰ Ahmed Alaskar^{3,4,5,6,7}

Parameter	Values (n = 55)
Female/Male	35/20
Age (y) at CML diagnosis, median (range)	40 (16-74)
Age at TKI stop, median (range)	48 (21-80)
Sokal score, n (%)	
Low	15 (27.3)
Intermediate	30 (54.5)
High	9 (16.4)
Not known	1 (1.8)
First-line TKI, n (%)	
Imatinib	48 (87.3)
Dasatinib	4 (7.3)
Nilotinib	3 (5.4)
Second-line TKI, n (%)	
None	29 (52.7)
Nilotinib	12 (22)
Dasatinib	8 (14.3)
Imatinib	6 (11)
Time (mo) to achieve initial MMR, median (IQR)	12 (3;24)
Total duration of TKI therapy (mo), median (IQR)	86 (60;132)
Duration of sustained DMR before TKI discontinuation, median (IQR)	66 (47;114)
Molecular response at discontinuation of TKI, n (%) CMR	55 (100)
Follow up after TKI discontinuation (mo), median (IQR)	34 (12;68)

TKI-discontinuation : Real World Data

- Median F/U 34 months



- 27.3% relapsed
- **Overall TFR 72.7%**
- Median time to relapse 5 months (3-38)

Risk Factors of Relapse

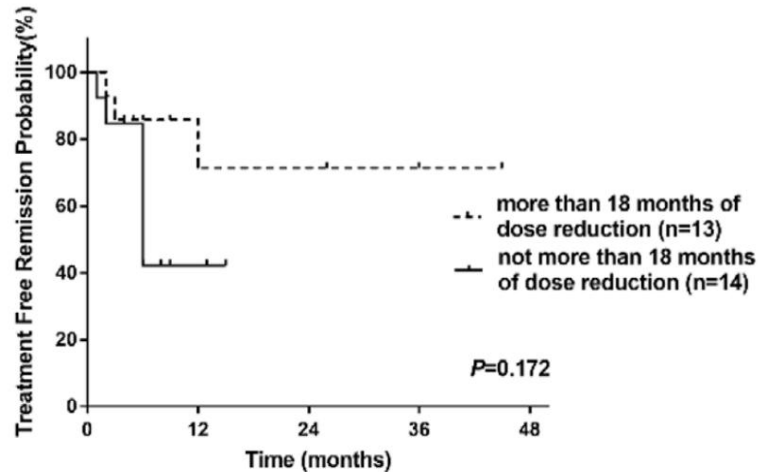
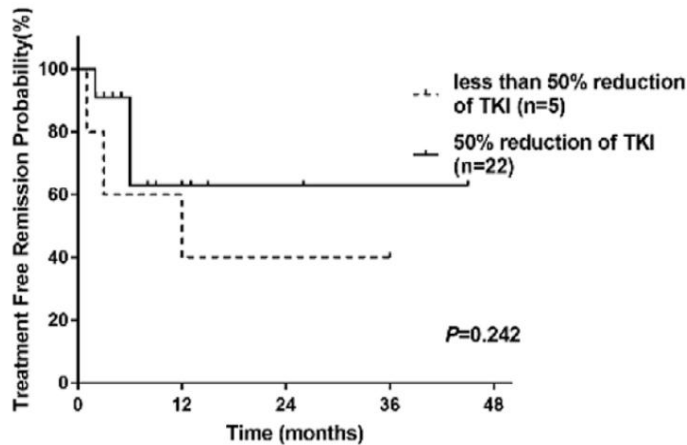
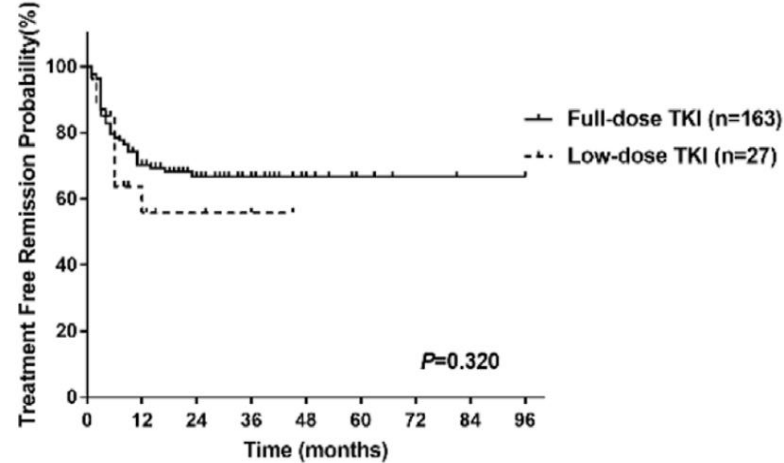
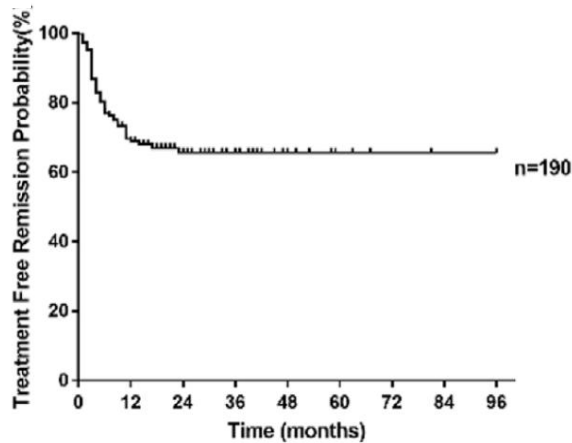
Parameter	Unadjusted Odds Ratio	95% Confidence Interval (lower limit- upper limit)	P-value
Age at diagnosis (≤ 40 years vs > 40 years)	1.48	0.45-4.89	.521
Gender (Male vs female))	0.51	0.15-1.72	.276
Sokal Score (low vs intermediate + high)	3.25	0.64-16.60	.238
Time to achieve MMR (≤ 12 months vs > 12 months)	1.55	0.45-5.25	.483
Total duration of TKI treatment till discontinuation (86 months or less)	1.20	0.37-3.97	.761
Duration of DMR (≥ 60 months vs < 60 months)	1.5	0.4-5.4	.494

Successful treatment discontinuation in CML patients with full-dose and low-dose TKI: Results from real-world practice

Yilin Chen^{1†}, Huifang Zhao^{2†}, Jingming Guo³, Jing Zou¹,
Wenjuan He¹, Danlei Han³, Fanjun Cheng^{1*}, Yanli Zhang^{2*} and
Weiming Li^{1*}

¹Department of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, ²Department of Hematology, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, Henan, China, ³Department of Hematology, Yichang Central People's Hospital & First Clinical Medical College of China Three Gorges University, Yichang, Hubei, China

- Retrospective study, **190 patients**, **27 patients experienced dose reduction** before discontinuation
- Median duration of TKI treatment 82 months, MR4 61 months



- TFR rate were not impaired in patients experiencing dose reduction before TKI discontinuation

TKI Withdrawal Syndrome

Musculoskeletal pain

- **30%** of the patients after TKI cessation
 - Gradually from 1-6 weeks
- After both 1st and 2nd generation TKIs
- Related with c-kit receptor and PDGF inhibition
- Usually mild symptoms (92% Gr 1-2), consider steroid in severe cases (8% Gr 3-4)
- 45% resolved spontaneously, 55% treated with NSAIDs or steroid

TKI discontinuation

NCCN Guideline V3 2025

General Considerations

- Discontinuation of TKI therapy appears to be safe in select patients with CML.
- Review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Patients need more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Should only be performed in patients who give consent after a thorough discussion of the potential risks and benefits.
- Outside of a clinical trial, discontinuation of TKI therapy should be considered only if **all** of the criteria are met.

Criteria for TKI discontinuation

NCCN Guideline V3 2025

- Age > 18 years
- CP-CML
- On approved TKI therapy for ≥ 3 years
- Stable MR4 ($BCR::ABL1 \leq 0.01\%$ for ≥ 2 years, on at least 4 tests, at least 3 months apart)
- Access to qPCR test that provides results within 2 weeks
- Molecular monitoring every 1-2 months x 6 months, every 2 month (7-12 months), every 3 months indefinitely

Molecular Monitoring after STOP TKI

- Monitor Real time PCR for *BCR:ABL*
 - Every month for 6 months
 - Every 2 months for 6 months
 - Every 3 months thereafter

Relapse After TKI Discontinuation

Definition

Study	Definition of molecular relapse	
STIM	Loss of MMR or increase BCR-ABL1	2 consecutive samples or MMR loss in any single sample
TWISTER	Loss of MMR or confirmed loss of MR4.5	
EURO-SKI	Loss of MMR	
A-STIM	Loss of MMR	

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Definition of Relapse : Loss of MMR in any single sample

Management of Molecular Relapses

- Consider resume TKI therapy at an efficient dose within 1 month after a molecular relapse (loss of MMR)
- Monitor *BCR::ABL1* every 3 months until MMR or DMR have been regained, then every 3-6 months
- Bone marrow karyotype and screening *BCR::ABL1* mutation are required in the absence of response to TKI

**Deep
Molecular
Response**

**Treatment
Duration**

- Tx with TKI $\geq$ 3 years
- DMR $\geq$ 2 years

**Patient
Selection**

Monitoring

- Every month for 6 months
- Every 2 months for 6 months
- Every 3 months thereafter

MR4

BCR::ABL IS $\leq$ 0.01% with 10,000 copies of ABL1

MR5

BCR::ABL IS $\leq$ 0.0032% with 32,000 copies of ABL1

High risk ??

Restart treatment if patient loss of MMR, resume TKI within 1 month

Conclusion

- Long-term TKI therapy can be associated with significant toxicity, symptom burden leading to a compromised quality of life
- Discontinuation of treatment is feasible in selected patient
- 40–60% of CP-CML with DMR can achieve durable TKF after TKI discontinuation
- Loss of MMR most frequently in the first 6 months after TKI discontinuation
- Discontinuation of treatment may save amounts of money, improve patients' QoL

Q & A

Persistent Challenges in CML

- ~40% change therapy by 5 yrs
- ~60% achieve MR4.5 by 10 yrs
- ~50% eligible for treatment discontinuation
- ~50% resume therapy after TFR
- Arterio-occlusive events with most TKIs
- Low-grade chronic AEs
- QoL

The Clinical Significance of Response to Therapy

Response	Translates into:
CCyR	Significantly improved survival
MMR	Improvement in EFS , possible longer duration CCyR
MR4.5	Possibility of considering treatment discontinuation