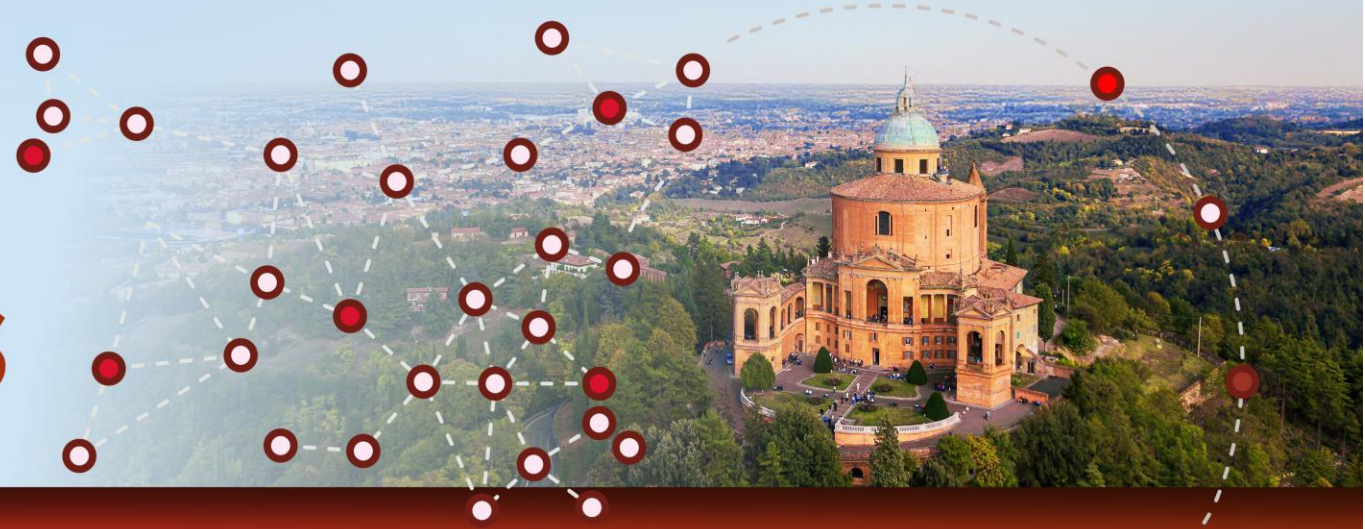
1ST INTERNATIONAL CONFERENCE ON

Ph+Leukemias



Bologna, Royal Hotel Carlton **September 29-30, 2025**

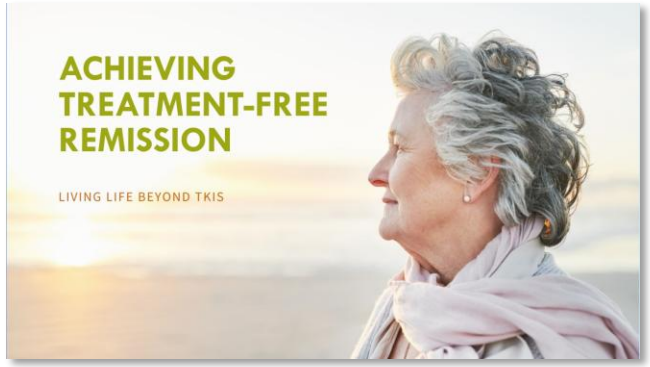
New challenges in treatment-free remission

Dr Franck E. NICOLINI

Hematology department

& INSERM U1052 CRCL

Centre Léon Bérard, Lyon, France



ELN Foundation European LeukemiaNet · FIM France Intergroupe Syndromes Myéloprolifératifs · fiolmc France Intergroupe de la Leucémie Myéloïde Chronique · Centre de Lutte contre le Cancer Léon Bérard · CRCL Centre de Recherche en Cancérologie de Lyon

Disclosures Dr Franck E. NICOLINI

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	x		x		x	X	
Incyte Biosciences	x		x		x	X	
Terns Pharmaceuticals						X	
GSK					X		
Kumquat Sciences			X				
BMS						x	

Treatment-Free Remission has entered routine practice

2025 European LeukemiaNet (ELN) Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Jane F Apperley[1,2], Dragana Milojkovic[2], Nicholas CP Cross[3], Henrik Hjorth-Hansen[4], Andreas Hochhaus[5] Hagop Kantarjian[6], Jeffrey Lipton[7], Hemant Malhotra[8], Dietger Niederwieser[9], Jerald Radich[10], Philippe Rousselot[11], Suzanne Saussele[12], Charles A Schiffer[13], Richard Silver[14], Simona Soverini[15], Leif Stenke[16], Anna Turkina[17], Luis Felipe Casado Montero[18], Fausto Castagnetti[19], Francisco Cervantes[20], Jorge Cortes[21], Richard Clark[22], Michael Deininger[23], Timothy P Hughes[24], Jeroen Janssen[25], Qian Jiang[26], Dong-Wook Kim[27], Richard A Larson[28], Francois X Mahon[29], Michael Mauro[30], Jiri Mayer[31], Franck E Nicolini[32], Fabrizio Pane[33], Delphine Rea[34], Johan Richter[35], Gianantonio Rosti[36], Giuseppe Saglio[37], Rudiger Hehlmann[38]

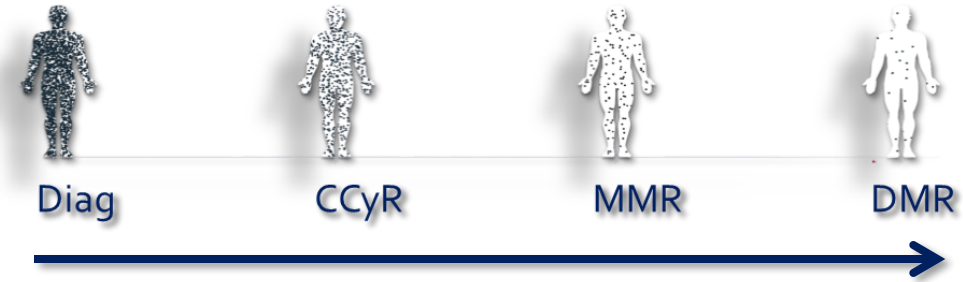
J. F. Apperley et al., Leukemia 2025

Treatment-Free Remission requirements

Requirements for tyrosine kinase inhibitor discontinuation in CP CML	
Mandatory:	CML in first CP only (data are lacking outside this setting).
	Motivated patient with structured communication.
	Access to high quality molecular monitoring using the International Scale (IS) with rapid turn-around of results. In case of atypical transcripts in laboratories with a high standard of quantification.
	Patient's agreement to more frequent monitoring after stopping treatment.
Minimal (stop allowed):	First-line therapy, second-line if the reasons for switch were intolerance or resistance due to a mutation sensitive to another TKI.
	Typical e13a2 or e14a2 *BCR::ABL1* transcripts. In case of atypical transcripts in laboratories with a high standard of quantification.
	Duration of TKI therapy >5 years (>4 years for 2G-TKI).
	Duration of DMR (MR^4 or better) >2 years.
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 $MR^{4.5}$.
Procedures after stop:	Molecular monitoring 6 to 8 weekly for the first 6 months, 2 monthly for months 6–12, and every 3–6 months thereafter. Monitoring should increase in frequency if there is an increase in *BCR::ABL1* transcript levels.
	Restart TKI-therapy if MMR is lost.
	If TKI-therapy is restarted monitor 4-6 weekly until MMR is regained and then every 3 months until MR^4 is regained.

J. F. Apperley et al., Leukemia 2025

TFR: Remaining questions and challenges

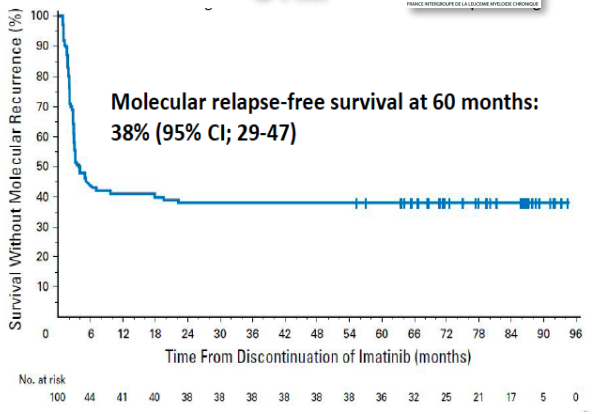


Obtain sustained DMR

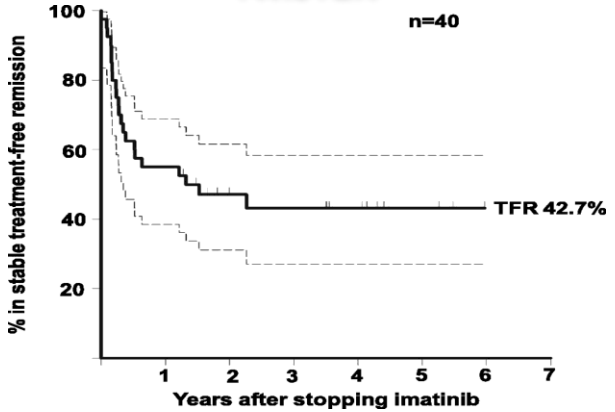
- How can we increase the access/success to TFR ?
- New tools to better select patients for TFR ?
- What are the very long term results of TFR ?
- TFR = No blast crises ?
- Are 2nd attempts (or more) possible ?
- Are TFR attempts possible for rare *BCR::ABL1* transcripts ?

How can we increase access to TFR (1) ?

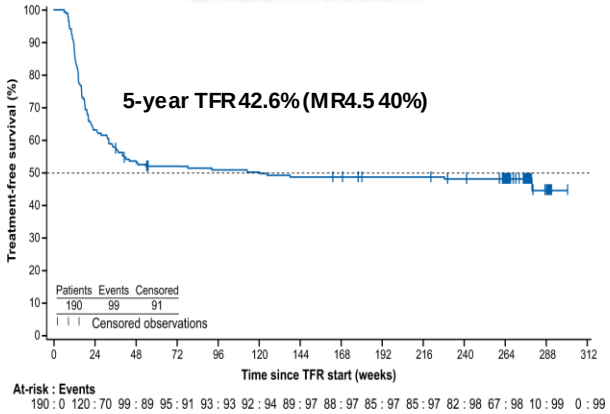
STIM[1]



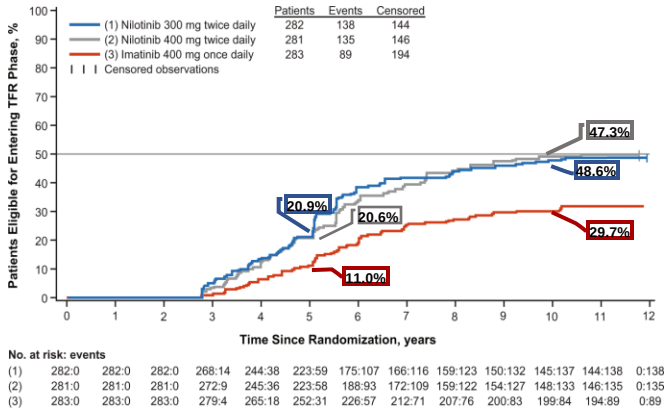
TWISTER[2]



ENESTfreedom[3]



ENESTnd[4]



BFORE[5]

- **2-year sustained MR4: bosutinib 32.5% vs imatinib 26.5% (OR 1.33 [95% CI, 0.92, 1.93])**

~47% eligible
X
~60% TFR
~28% Success

[1]Etienne et al. JCO 2017; 35: 298-305; [2]Ross et al. Blood 2013; 122: 515-22; [3]Radich et al. Leukemia 2021; 35: 1344-55; [4]Kantarjian et al. Leukemia 2021; 35: 440-53; [5]Brümmendorf TH, et al. Leukemia 2022; 36:1825–1833

Summary of Imatinib discontinuation data

Study	n[a]	Median duration of treatment with TKI	Qualifying DMR	Median duration of DMR	Definition of molecular relapse	Percentage (%) of patients in TFR
STIM[24,25]	100	50 months	UMRD for ≥2 years	35 months	Loss of UMRD[b]	38 at 60 months
TWISTER[26,27]	40	70 months	UMRD for ≥2 years	36 months	Loss of UMRD[c]	45 at 60 months
STIM2 (REF.[28])	218	79 months	UMRD for ≥2 years	39 months	Loss of UMRD[b]	50 at 24 months
DOMEST[29]	99	100 months	MR4.0 for ≥2 years	55 months	Loss of MR4.0	64 at 24 months
A-STIM[30]	80	79 months	UMRD for ≥2 years	41 months	Loss of UMRD[b] Loss of MMR	44 at 36 months 61 at 36 months
KID[38]	90	81 months	UMRD for ≥2 years	40 months	Loss of MMR	69 at 24 months
ISAV[32]	108	103 months	UMRD for ≥18 months	26 months	Loss of MMR	48 at 36 months
JALSG-STIM213 (REF.[33])	68	97 months	MR4.0 for ≥2 years	67 months	Loss of MMR	65 at 36 months
EURO-SKI[d] (REF.[34])	755	7.5 years	MR4.0 for ≥1 year	4.7 years	Loss of MMR	49 at 24 months
DESTINY[d] (REFS[35,36])	125	6.5 years	MR4.0 for ≥1 year	NR	Loss of MMR	72 at 36 months
	49	7.7 years	MMR for ≥1 year	5.5 years	Loss of MMR	36 at 36 months

Overall average is 54.2% at 24-60 months FU

Ross D, Hughes TP. Nature Reviews Clinical Oncology 2020

Summary of 2G-TKI discontinuation data

Study	n[a]	TKI and line of treatment	Median duration of treatment with TKI (total and second-generation TKI)	Qualifying DMR	Median duration of DMR	Definition of molecular relapse	Percentage (%) of patients in TFR
First-line DADI[39]	58	Dasatinib, first	40 months	MR4.0 for ≥1 years	23 months	Loss of MR4.0	55 at 12 months
DADI[40,41]	63	Dasatinib, second	82 months and 17 months	MR4.0 for ≥1 years	NR	Loss of MR4.0	44 at 36 months
D-STOP[42]	54	Dasatinib, first and second	92 months and NR	MR4.0 for ≥2 years	51 months	Loss of MR4.0	63 at 12 months
DASFREE[43]	84	Dasatinib, first and second	69 months and NR[b]	MR4.5 for ≥2 years	28 months	Loss of MMR	46 at 24 months
STOP 2G-TKI[44]	30 (each TKI)	Dasatinib and nilotinib, first and second	76 months and 39 months	UMRD for ≥2 years	29 months	Loss of MMR	54 at 48 months
STAT2 (REF.[45])	78	Nilotinib, second	99 months and 25 months	MR4.5 for ≥2 years	51 months	Loss of MR4.5	63 at 36 months
ENESTop[46]	126	Nilotinib, second	88 months and 53 months	MR4.5 for ≥1 years	32 months	Loss of MR4.0	53 at 96 weeks
ENESTfreedom[47,48]	190	Nilotinib, first	44 months	MR4.5 for ≥1 year	30 months	Loss of MMR	49 at 96 weeks

Ross D, Hughes TP. Nature Reviews Clinical Oncology 2020

Overall average is 53.4% at 12-48 months FU

Factors influencing recurrence after TKI cessation

Imatinib

- Imatinib duration (≥5years vs <5 years)*
- Imatinib duration (>8years vs <8 years)**
- Sokal score (Low vs High)*
- MR4 duration (>5 years vs <5 years)
- PB NK cells levels at cessation***
- *BCR::ABL1* Major transcript type (higher in e13a2 vs e14a2)
- High regulatory T cells and $CD86^{+}$ plasmacytoid dendritic cells

2G-TKI

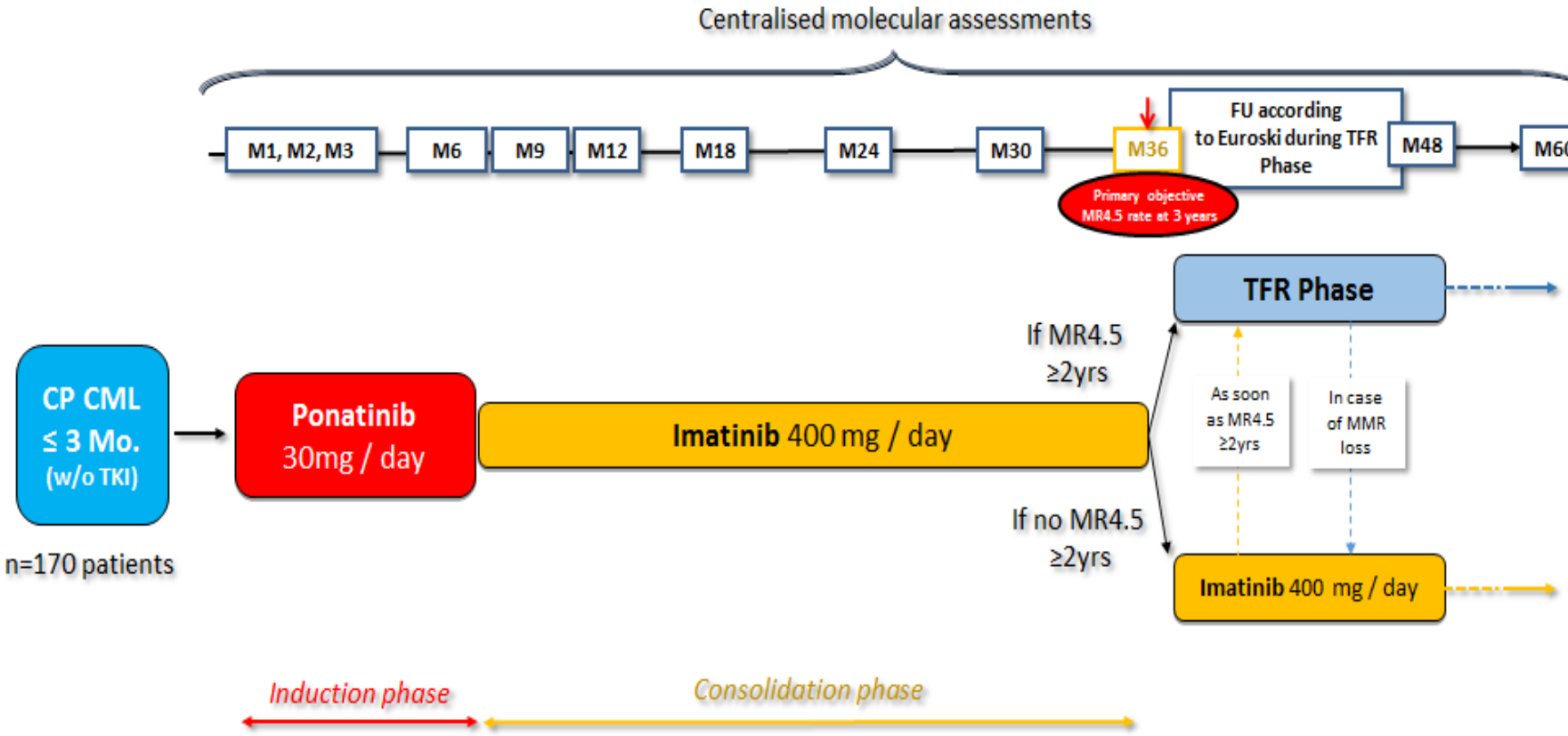
- Imatinib resistant/warning *vs* Imatinib-Intolerance
- *BCR::ABL1* levels M3 after cessation (>0.0032% vs ≤00032%)

- Design of the clinical trial

**Mahon F-X.. et al. Lancet Oncol. 2010*
***Saussele S. et al. Lancet Oncol 2018*
****Rea D. et al. Haematologica 2017*
Schutz C. et al. Leukemia 2018
Rea D. et al. Blood 2017
Ross D. Hughes T., Nature reviews Clin Oncol 2020

How can we increase access to TFR (2) ?

- Hit the disease harder at onset ?



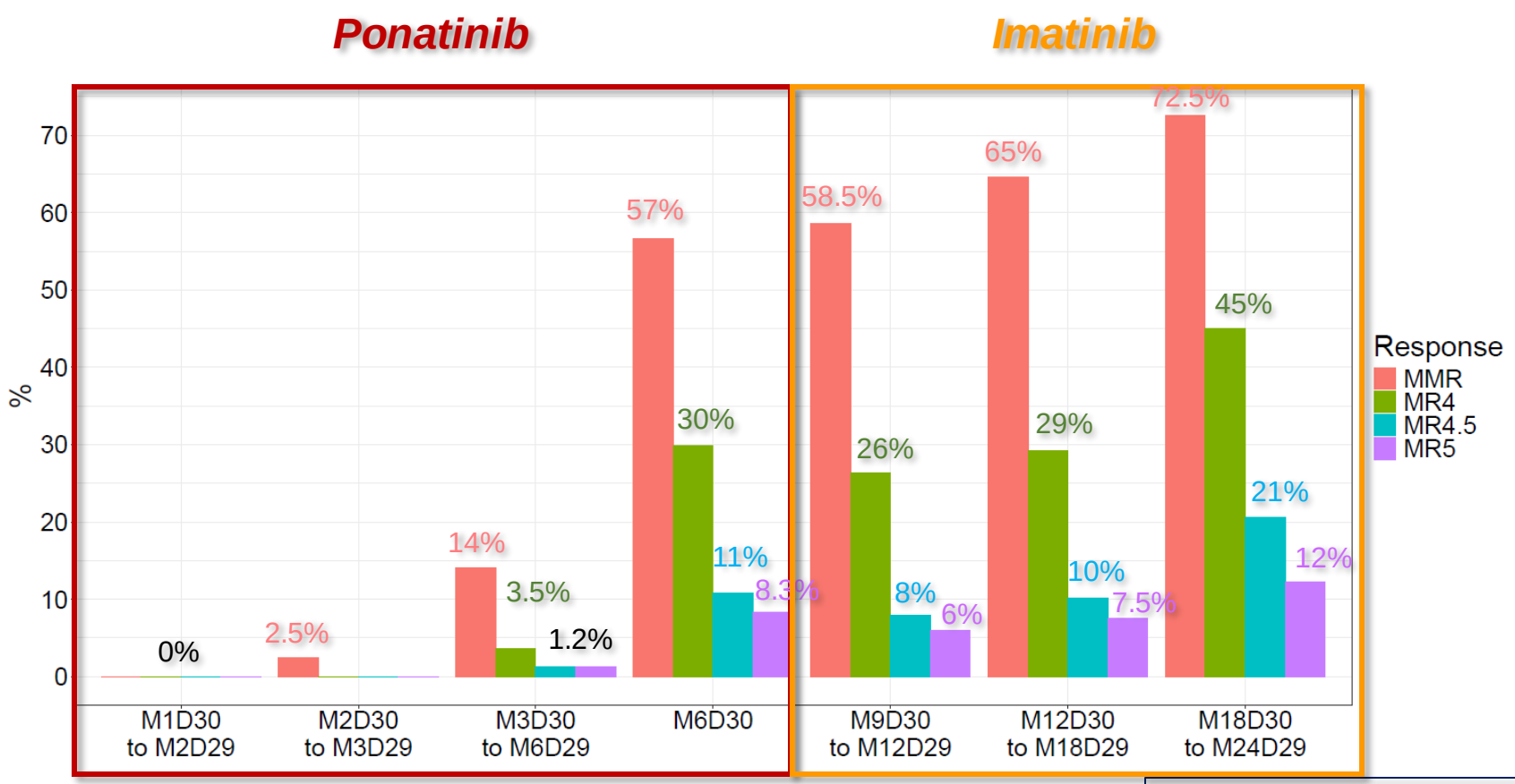
Nicolini FE et al.. ASH 2024

EudraCT Number: 2018-001789-41 - Sponsor ID: ET18000120
Clinical Trial: NCT04070443

How can we increase access to TFR (3) ?

Proportion of molecular response « at » time points

- Hit the disease harder at onset ?



- CHR @ M1: 147/158 (93%)
- Median halving time: 13.5 (11.5-17.5) days
- EMR rate: 158/163 (97%)
- CCyR rate* @ M3: 115/169 (70.5%)

Nicolini FE et al.. ASH 2024

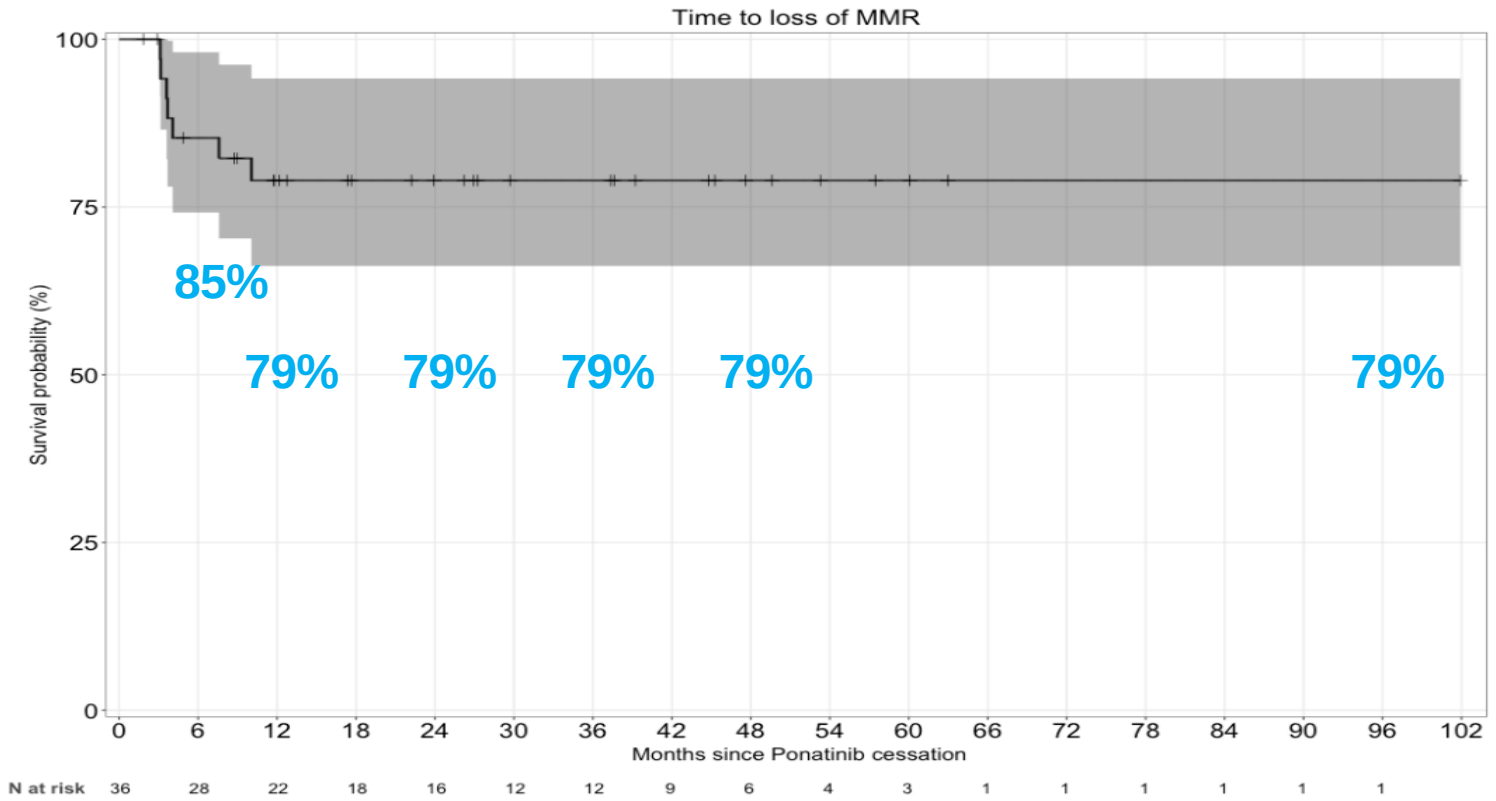
All *BCR:ABL1* assessments and molecular analyses were centralised in the Hematology lab, University hospital of Bordeaux
(Dr Stéphanie Dulucq, PharmD, PhD)

How can we increase the access to TFR (4) ?

- Hit the disease harder at later stages ?

- The median follow-up after Ponatinib cessation is 20 (8-41) months.

n=16 pts



Time to MMR loss.

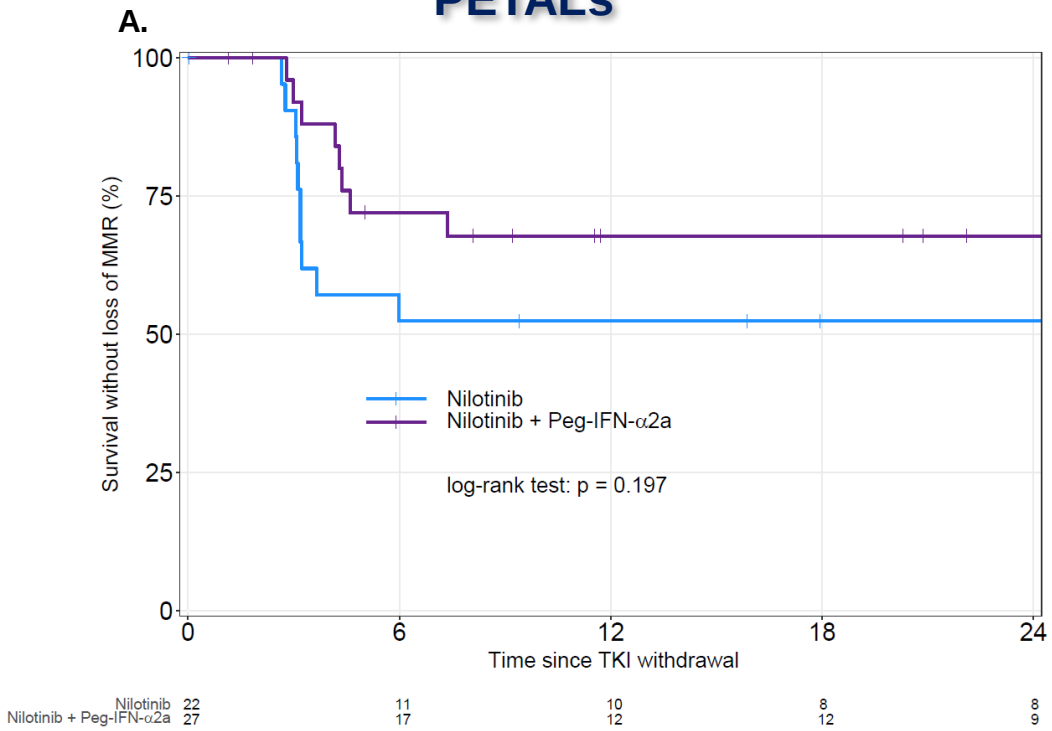
Gray zone represents 95% confidence interval

Nicolini FE, Fava C et al.. Ei CML 2024 & in preparation

How can we increase the access to TFR (5) ?

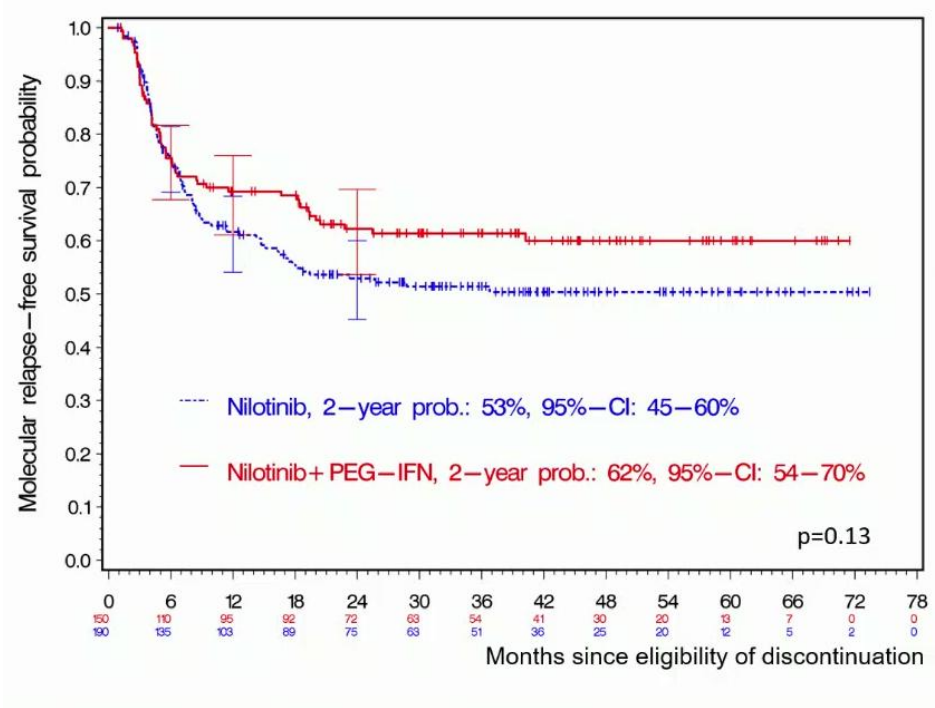
- Combine 2G-TKI (Nilotinib) with interferon ?

PETALs



n=200 pts

TIGER

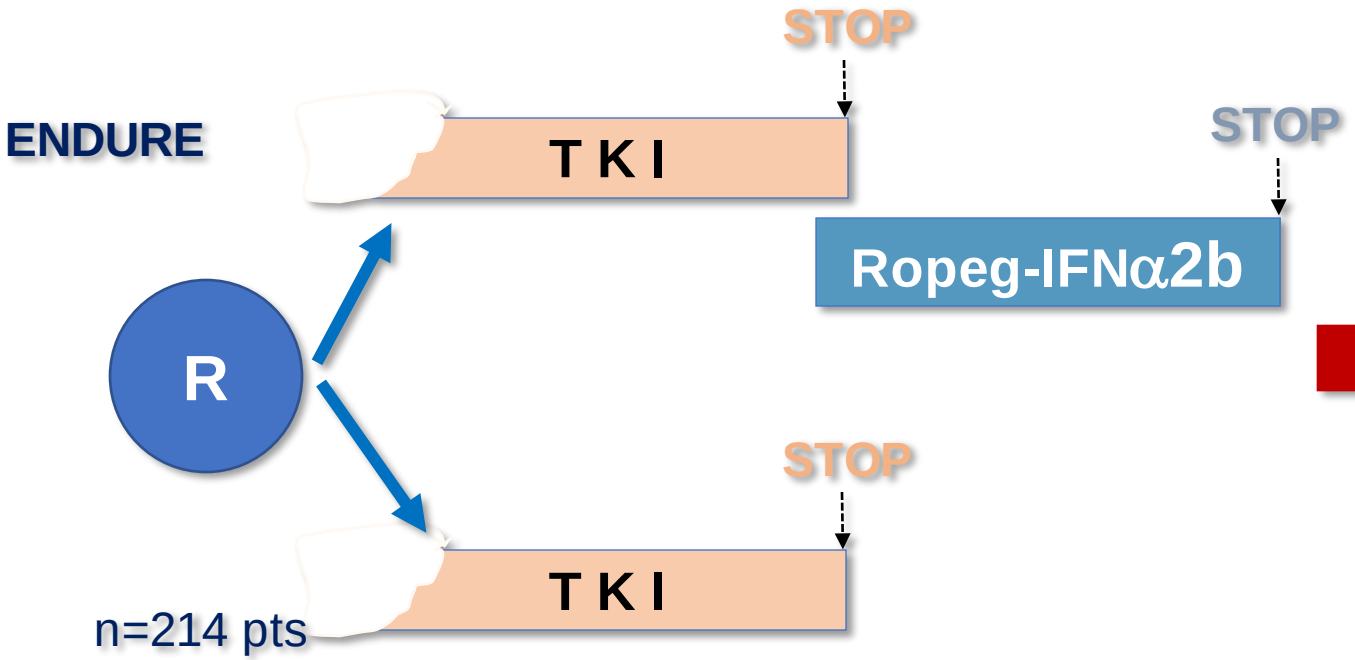


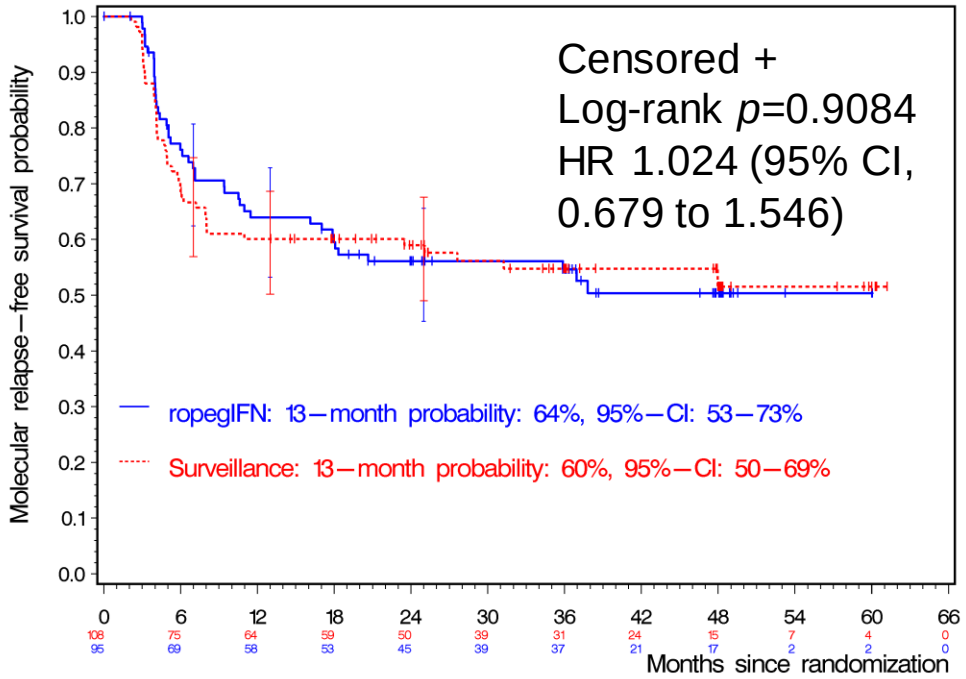
n=313 pts

Nicolini FE et al.. Submitted
Hochhaus A et al. EHA 2023

How can we increase the access to TFR (6) ?

- Combination of TKI followed by interferon ?





Burchert A et al.. Submitted

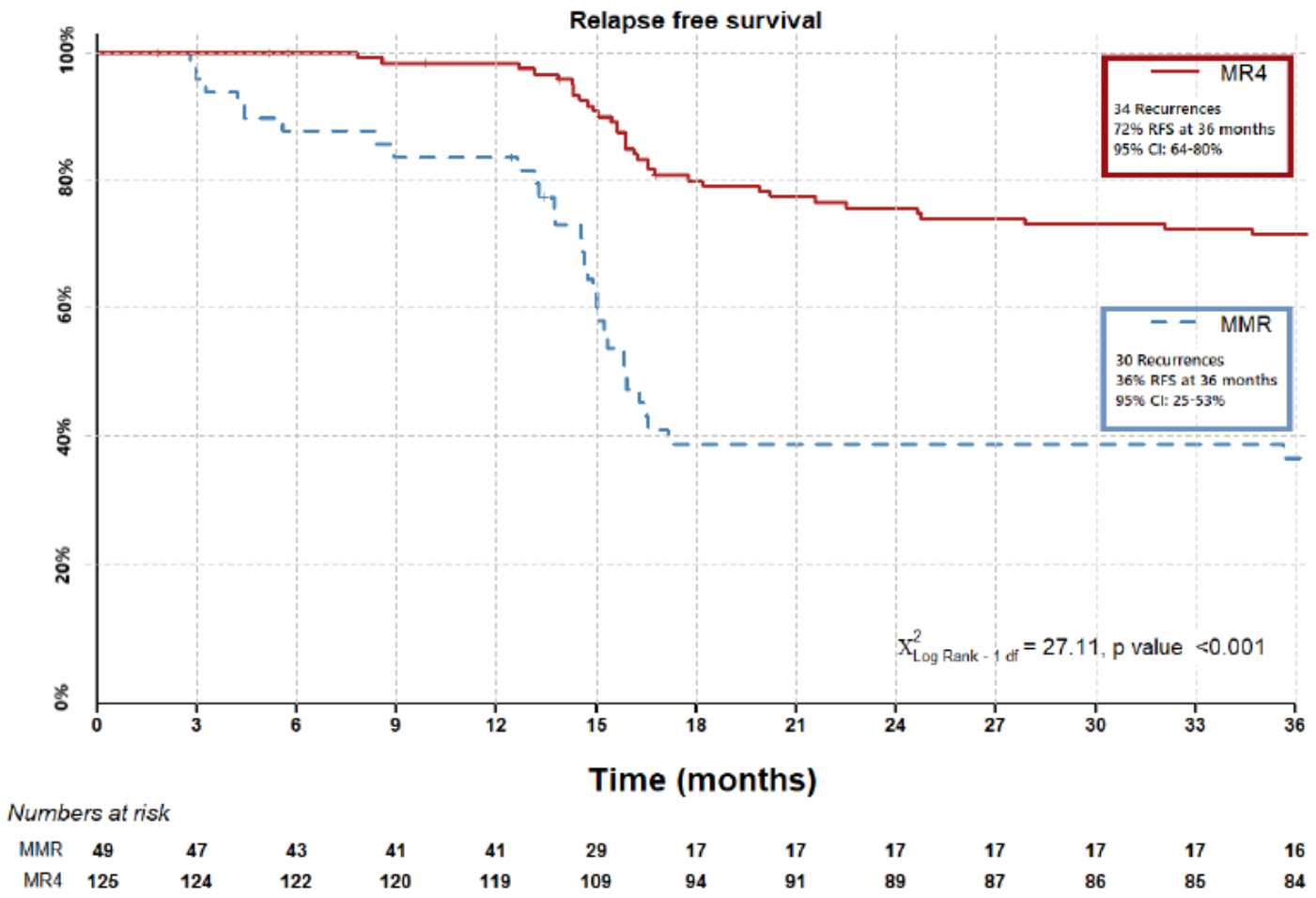
How can we increase the access to TFR (7) ?

- Decrease TKI by half 12 months prior to cessation ?

Destiny trial in UK

n=141 pts in stable MMR but not in MR4 at enrollment

n= 125 pts in MR4 at enrollment



Clark RE et al.. Lancet Haematol 2019

How can we increase the access to TFR (8) ?

- Decrease TKI by half 12 months prior to cessation ?

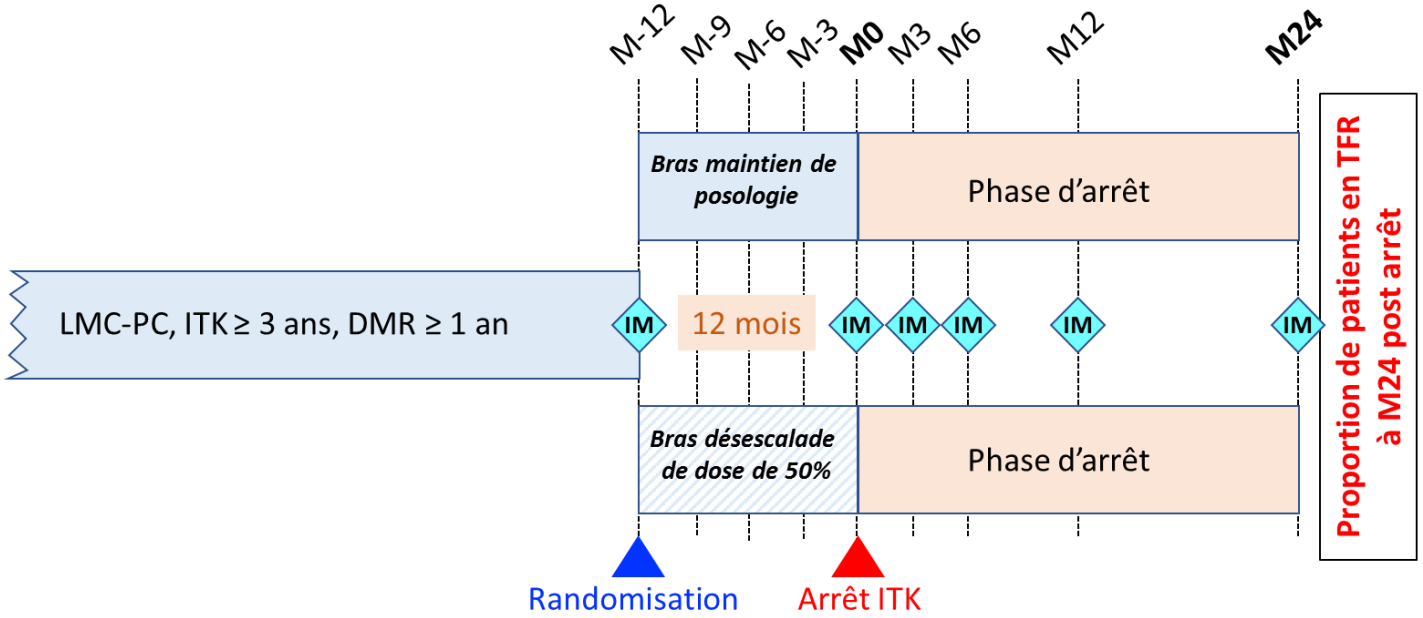
Investigateur coordonnateur :
Dr Emilie CAYSSIALS-CAYLUS

CHU Poitiers
CENTRE HOSPITALIER UNIVERSITAIRE

AITIK

Arrêt de traitement par **I**nhibiteur de **T**yros**I**ne **K**inase dans la leucémie myéloïde chronique et impact sur le système immunitaire : étude comparative randomisé de deux stratégies thérapeutiques

Diaporama MEP - AITIK Version 2 du 11/10/2023



Evaluation de la qualité de vie : M-12, M-6, M0, M3 et M6

Evaluation de la concentration résiduelle de l'ITK : M-12 et M0

IM **Immunomonitoring** ⟶ *Signature sanguine LT CD8 innés prédictive d'un succès d'arrêt*

Cayssials E et al.. Submitted ASH 2025

fiLMC
FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

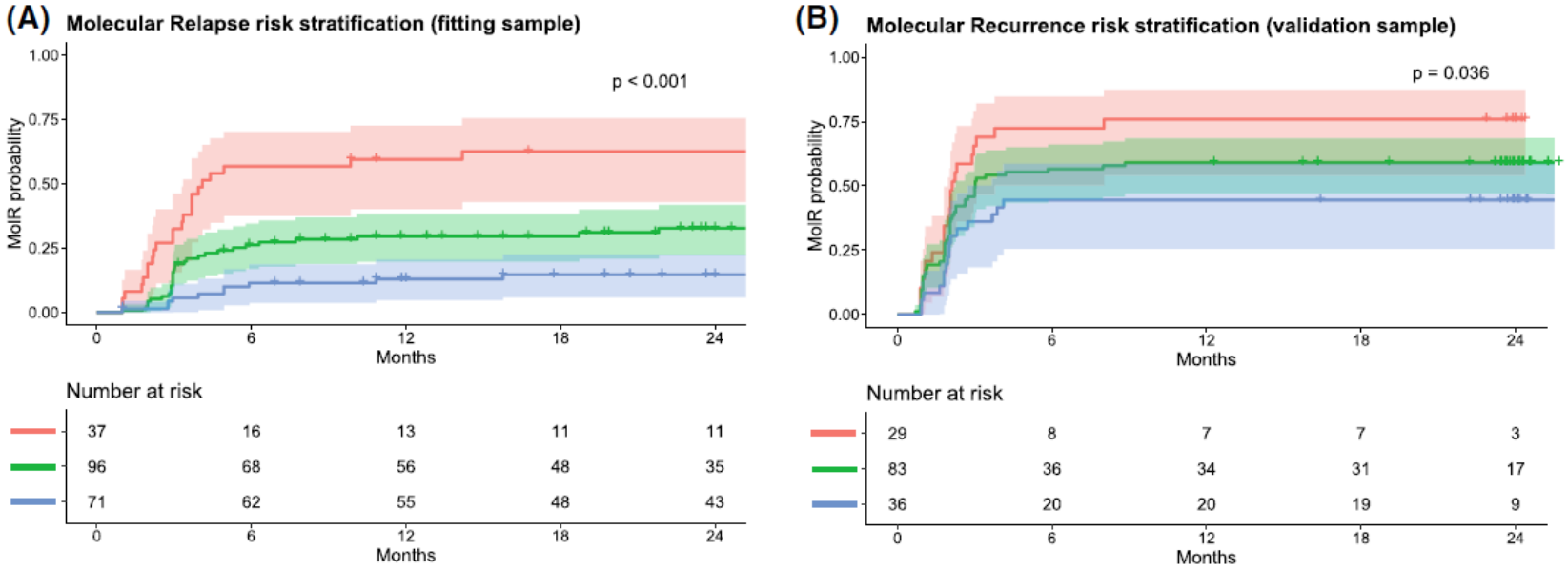
New tools to better select patients (1) ?

- Digital droplet PCR at cessation ?
  Meta-analysis MolR prediction with *BCR::ABL1* ddPCR

Depth of molecular response measured by *BCR::ABL1* ddPCR is a valuable and robust predictive parameter for successful TKI discontinuation

Molecular recurrence risk stratification model

Risk parameters	HR [95%CI]	Points	Score	
dPCR-high	2.327 [1.548-3.497]	+2	3-4	High
Treatment duration <6 years	1.278 [0.921-1.771]	+1	1-2	Intermediate
E13a2 transcript	1.480 [1.037-2.113]	+1	0	Low

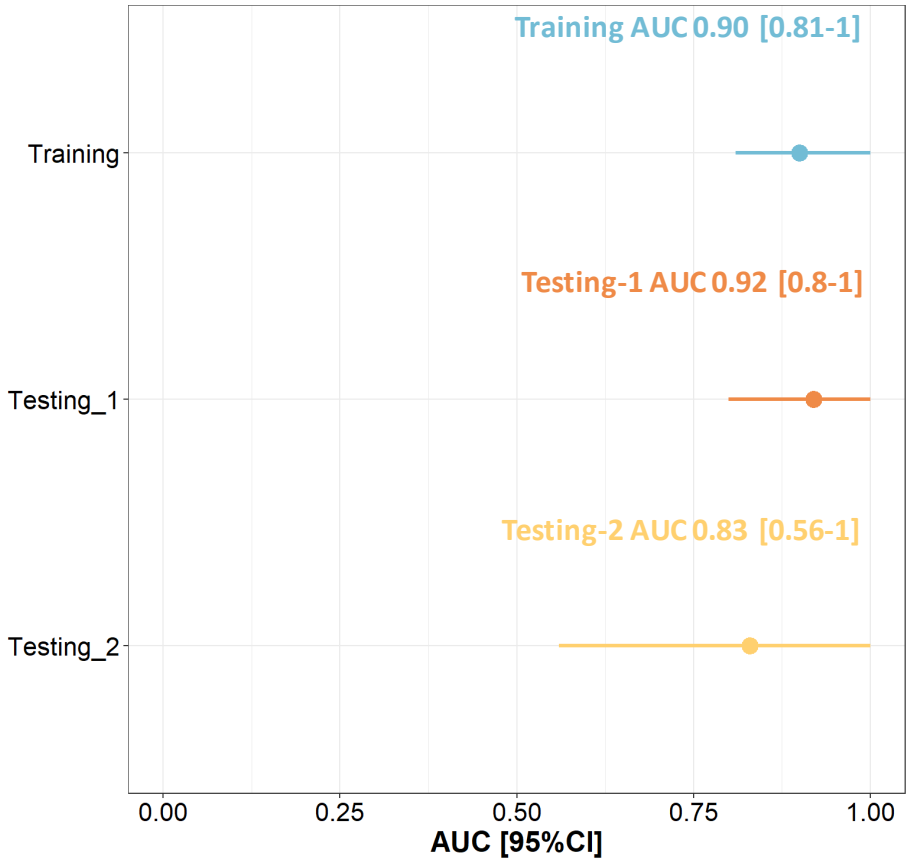


Cockerols C et al.. AJH 2024

New tools to better select patients (2): RNASeq at cessation ?

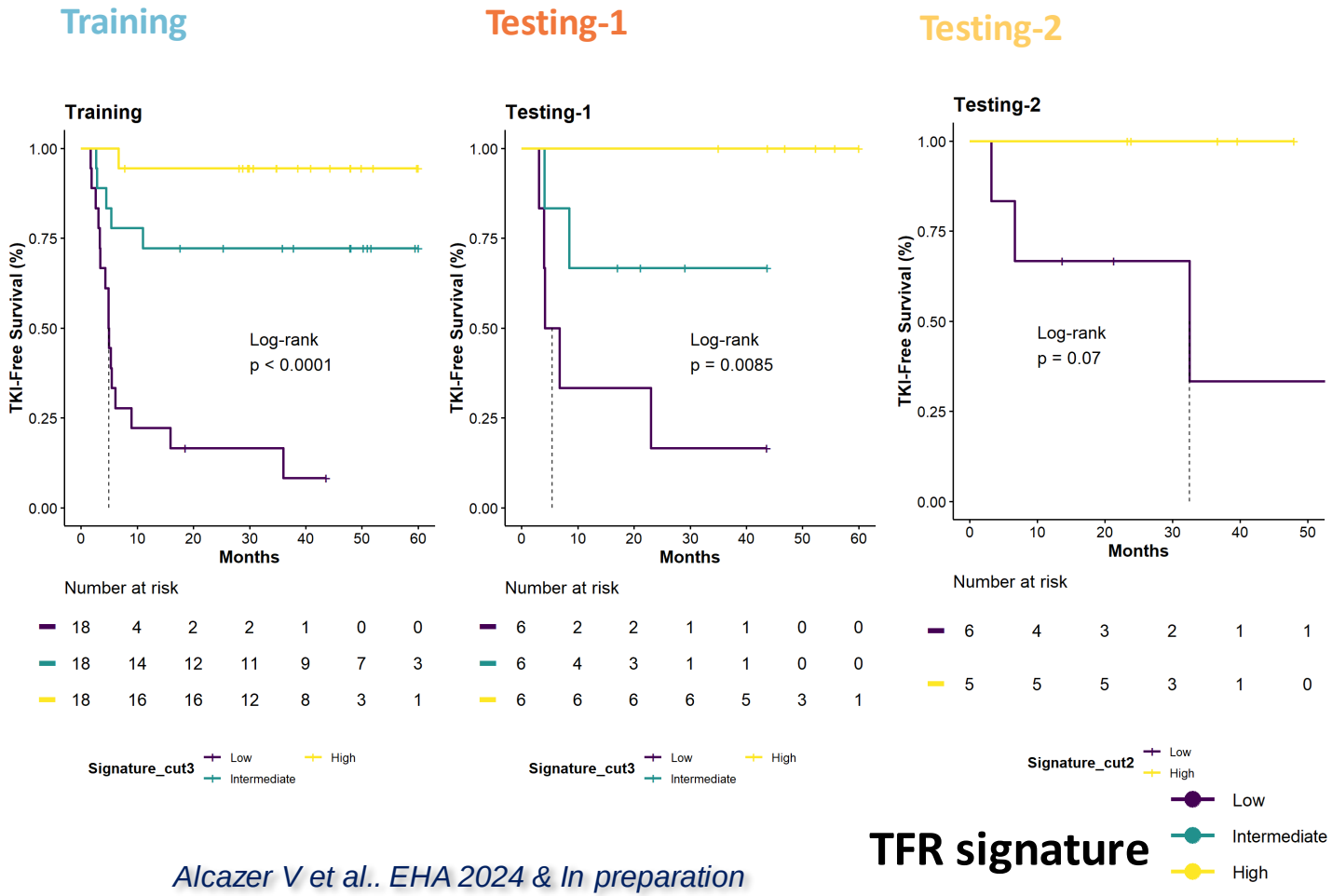
Binary outcome (TFR at 2 years: Yes *vs* No)

AUC [95%CI] of 27-gene signature



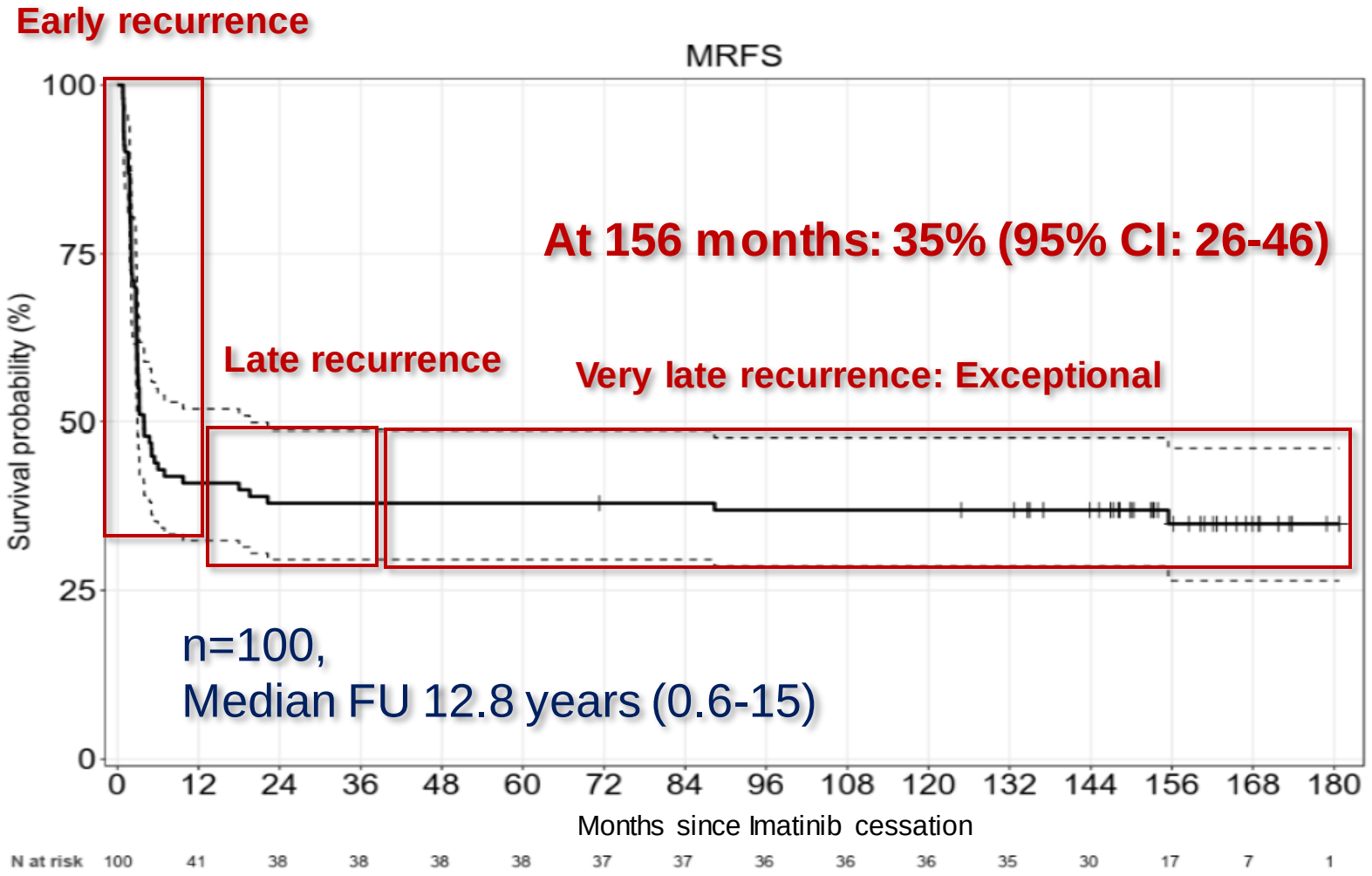
Time-dependent outcome (TFR along time)

27-gene signature cut at terciles / median value



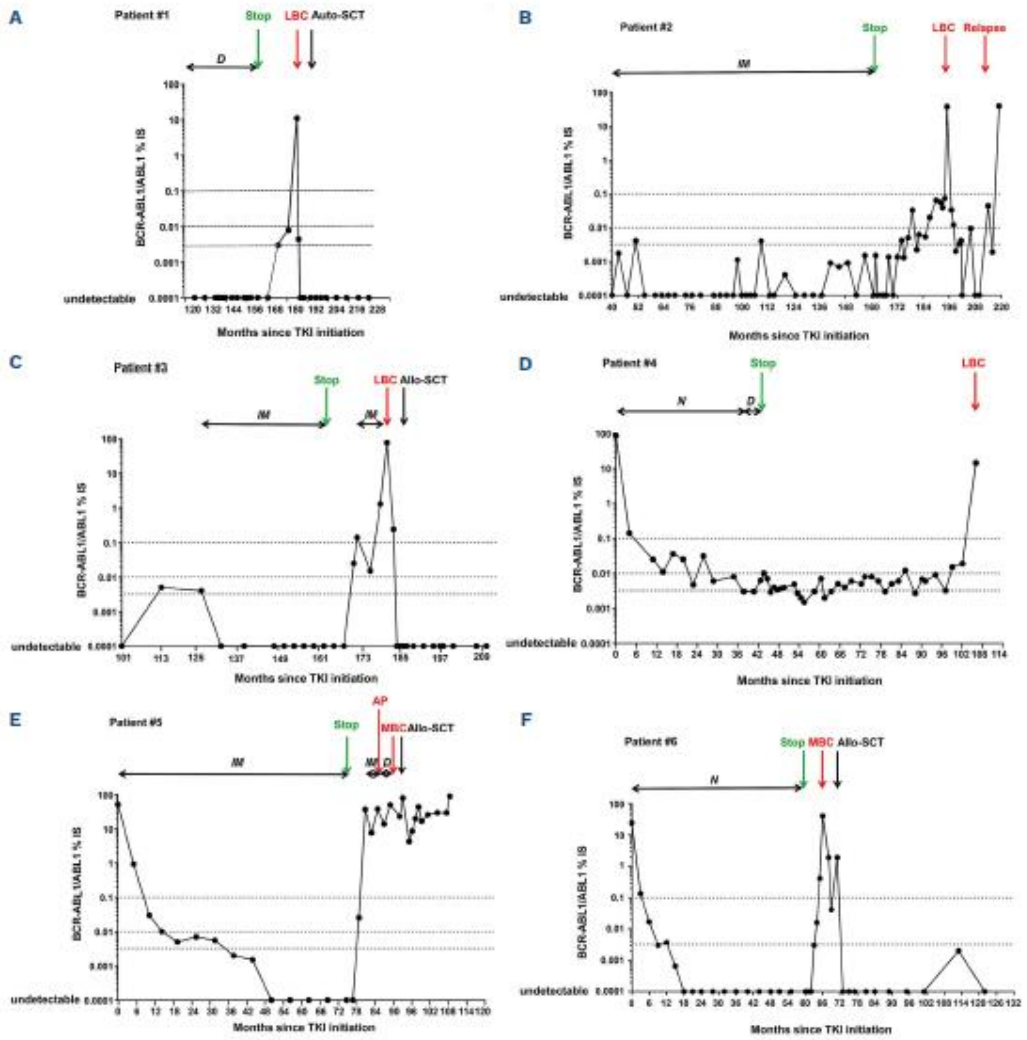
Alcazer V et al.. EHA 2024 & In preparation

What are the very long term results of TFR ? 2025 STIM 1 update



Mahon F-X. et al. Blood Neoplasia 2025 In press

TFR = No blast crises ?



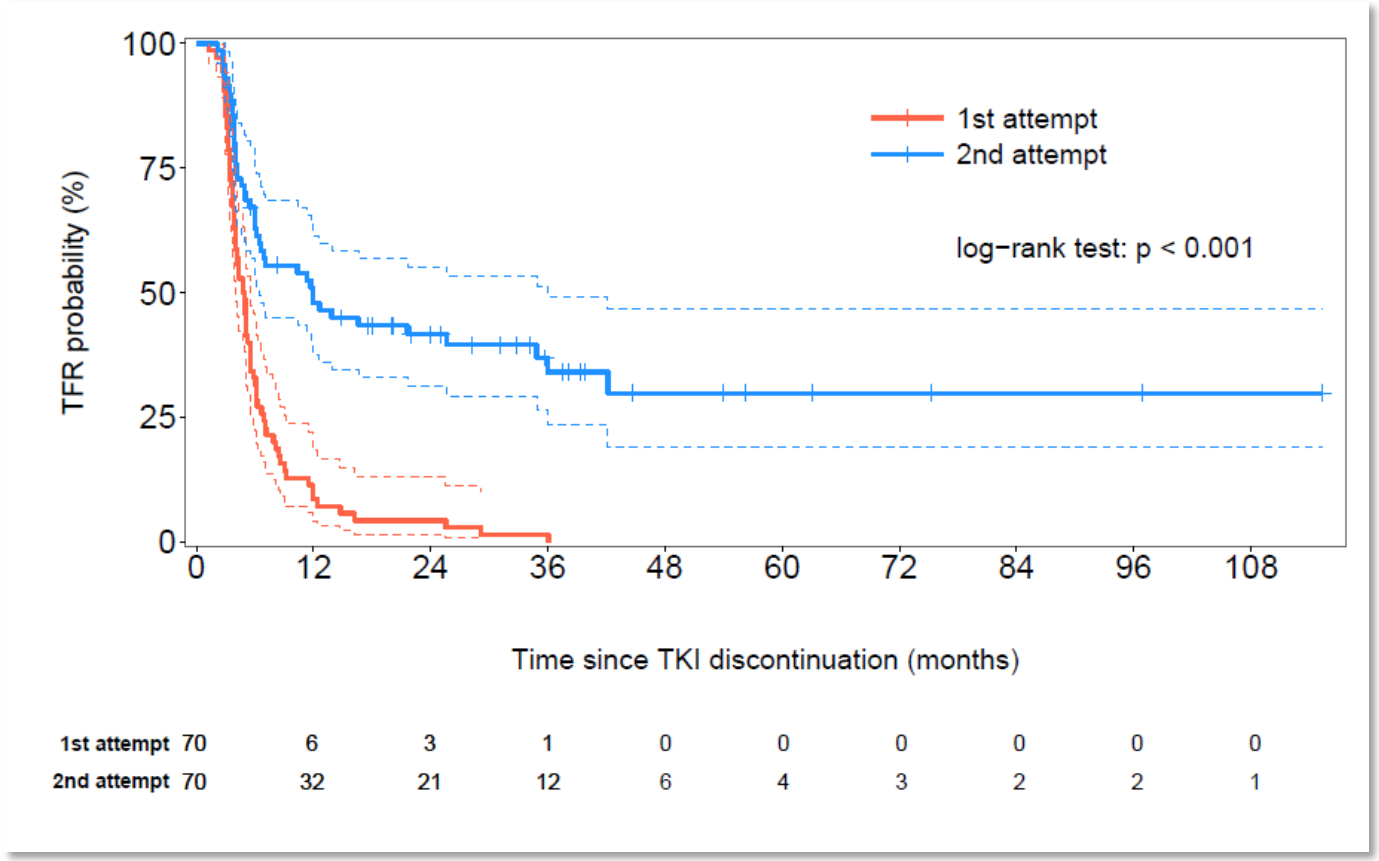
LETTER TO THE EDITOR

Onset of blast crisis in chronic myeloid leukemia patients in treatment-free remission

- 6 cases of BC (4 LBC, 2 MBC) during TFR procedure
- Rare event probably close to ~0.005%
- All pts had mutations or CNV in myeloid genes by NGS
- Recurrent EP300 (2 pts, 1 LBC, 1 MBC) and SETD2 genes (2 LBC)] mutations/deletions.

Dulucq S. et al. Haematologica 2022

Are second TFR attempts possible ?



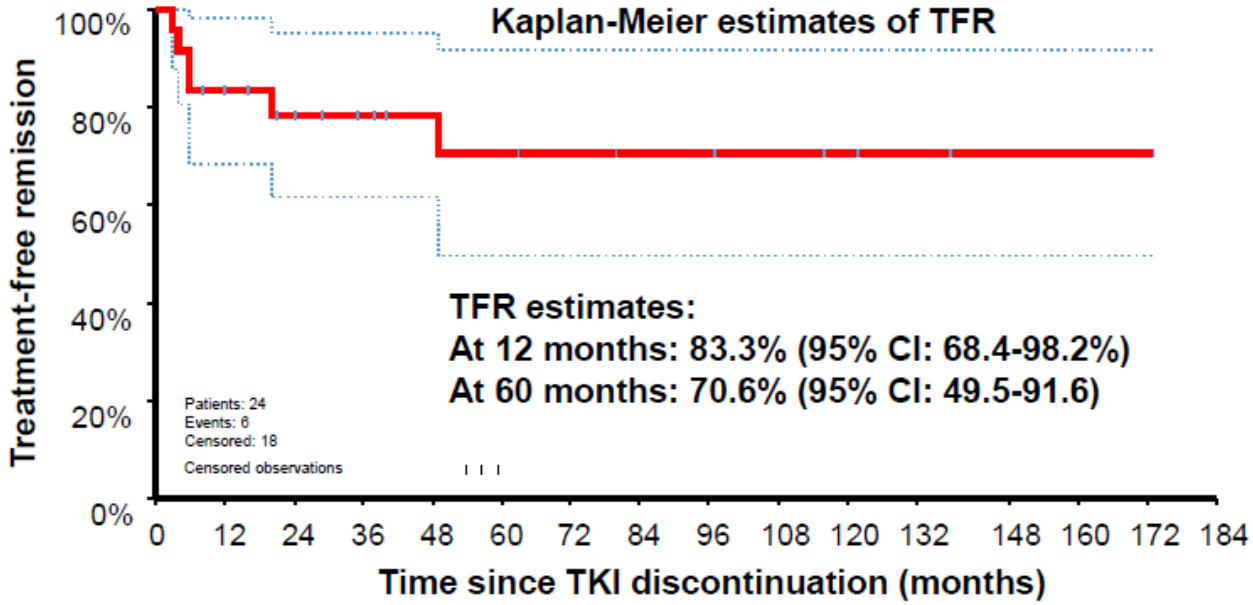
2nd attempt

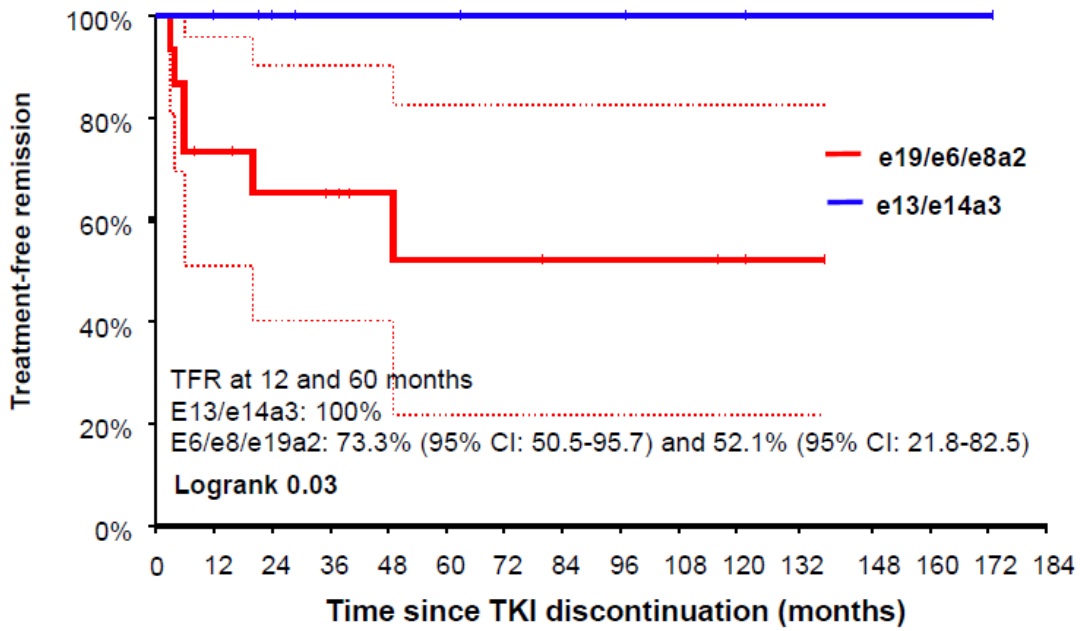
65.19% [95% CI 54.85−77.46] at 6 months
48.69% [95% CI 38.13−62.18] at 12 months
40.61% [95% CI 30.32−54.39] at 24 months

Legros L. et al. Cancer 2018

Are TFR attempts possible for rare *BCR::ABL1* transcripts ?

n=24 pts, e13/e14a3 in 37.5%, e19a2 in 37.5%, e6/e8a2 in 25% of pts on Imatinib.





Early relapses were sudden: 4 CHR loss including 1 acceleration. All were rescued.

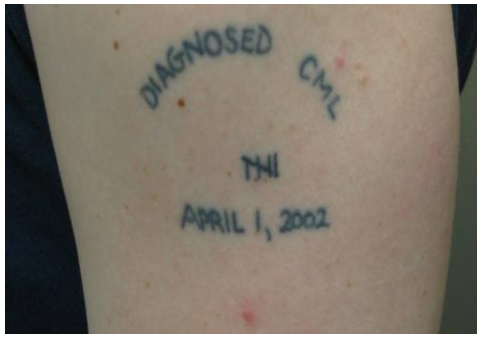
Johnson-Ansah H. et al. Leuk Res 2025 In press & SOHO 2025

General conclusions

- TFR attempts have entered now routine practice
- The longer time on TKI, the better
- Acurate and prolonged molecular follow-up is required
- Multiple efforts are ongoing in order to improve TFR success
- Better selection of patients should be done
- Clinical and biological factors of success have been described
- TFR is possible in patients with atypical *BCR::ABL1* transcripts
- Be aware that BC can occur in exceptional cases

Acknowledgements

CML patients



Pr F. Castagnetti
Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna

Mr D. Bartozzi ER Congressi