LEUKEMIA2020-2021

April 26-27, 2021

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Patient management before and during treatment-free remission

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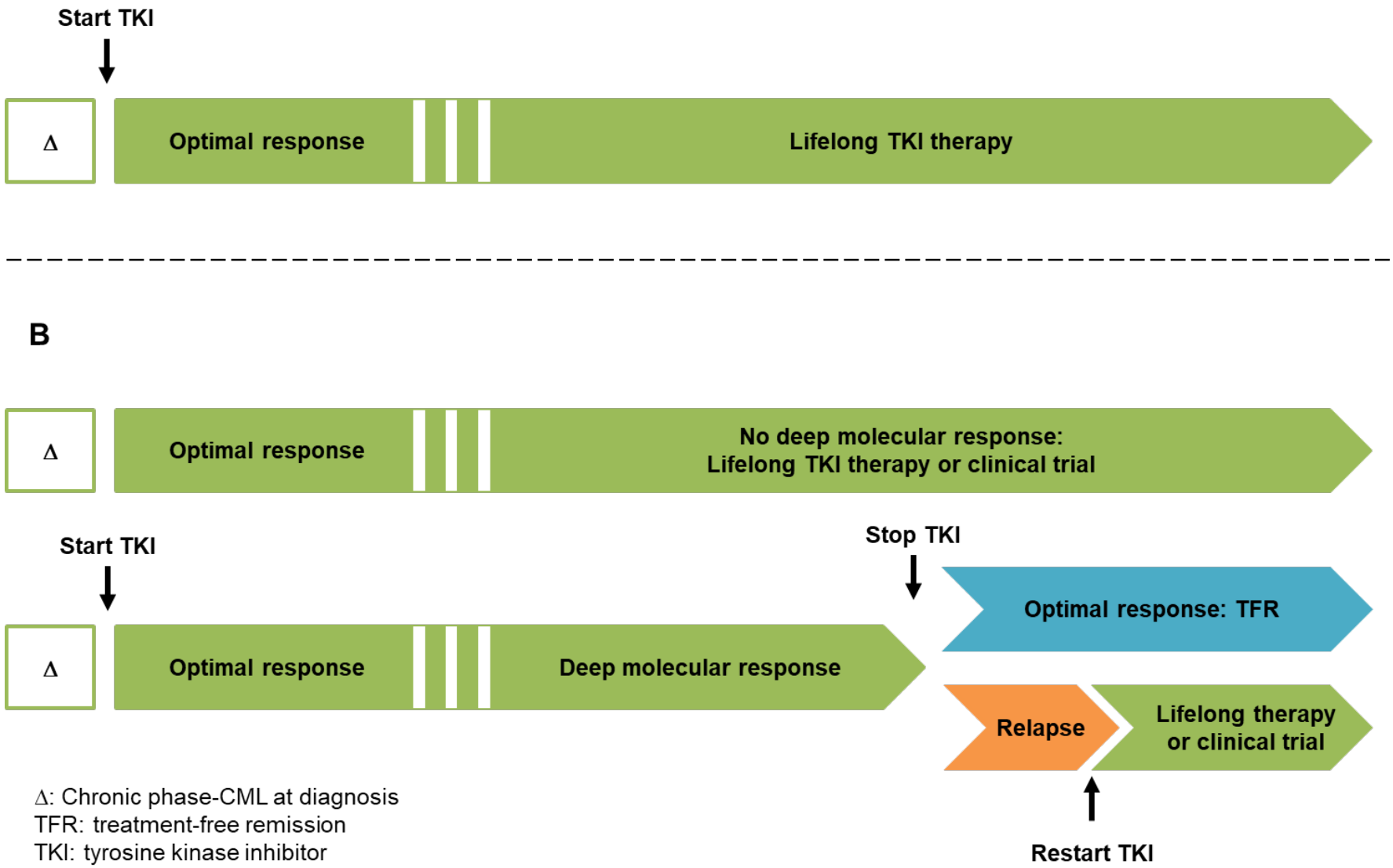
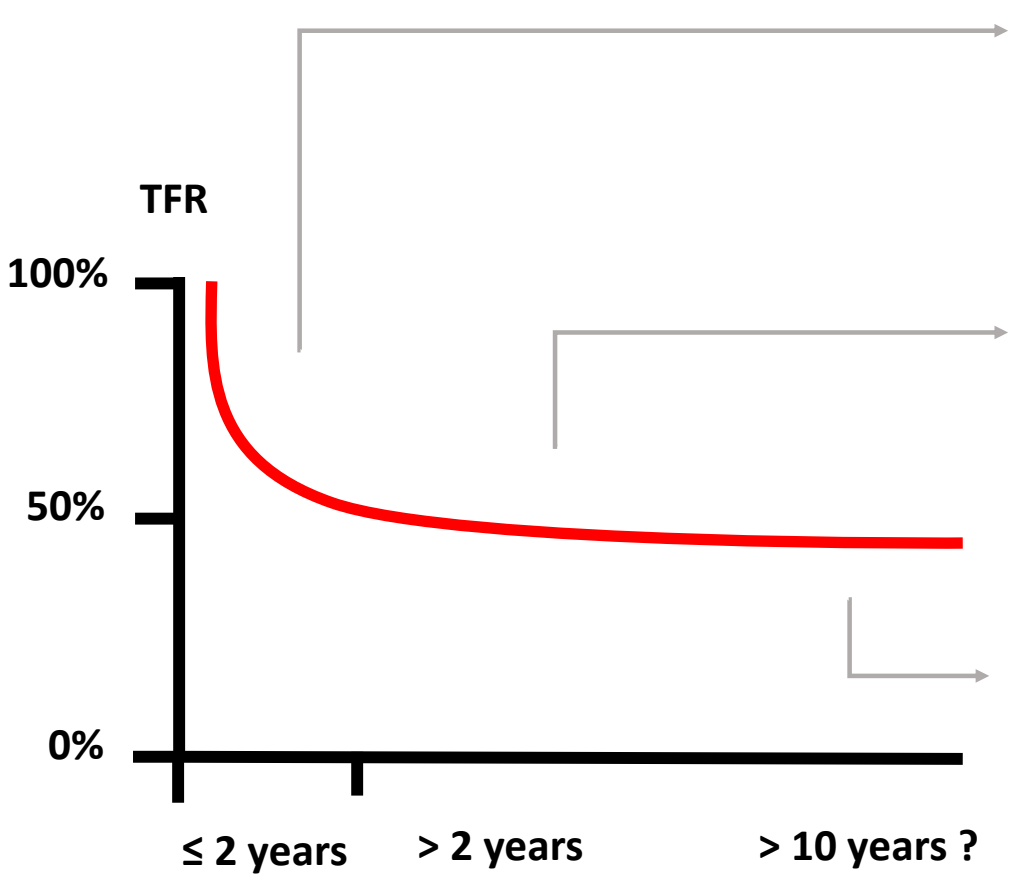
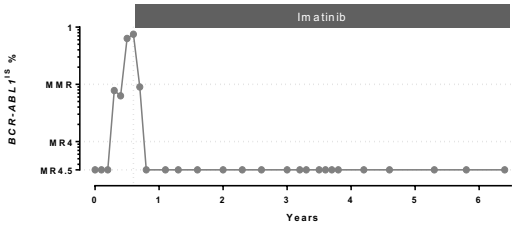


Δ: Chronic phase-CML at diagnosis
TFR: treatment-free remission
TKI: tyrosine kinase inhibitor

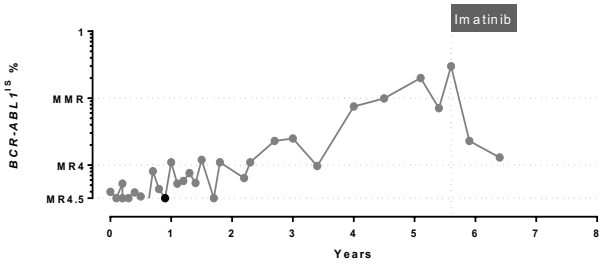
Molecular recurrences during treatment free remission (TFR) in CML patients



Early molecular recurrences **37%**



Late molecular recurrences **18%**



Long term treatment free remissions **45%**

Rousselot P, et al. Blood Adv. 2020 Jul 14;4(13):3034-3040

Eligibility of CML patients
Current recommendations forTFR

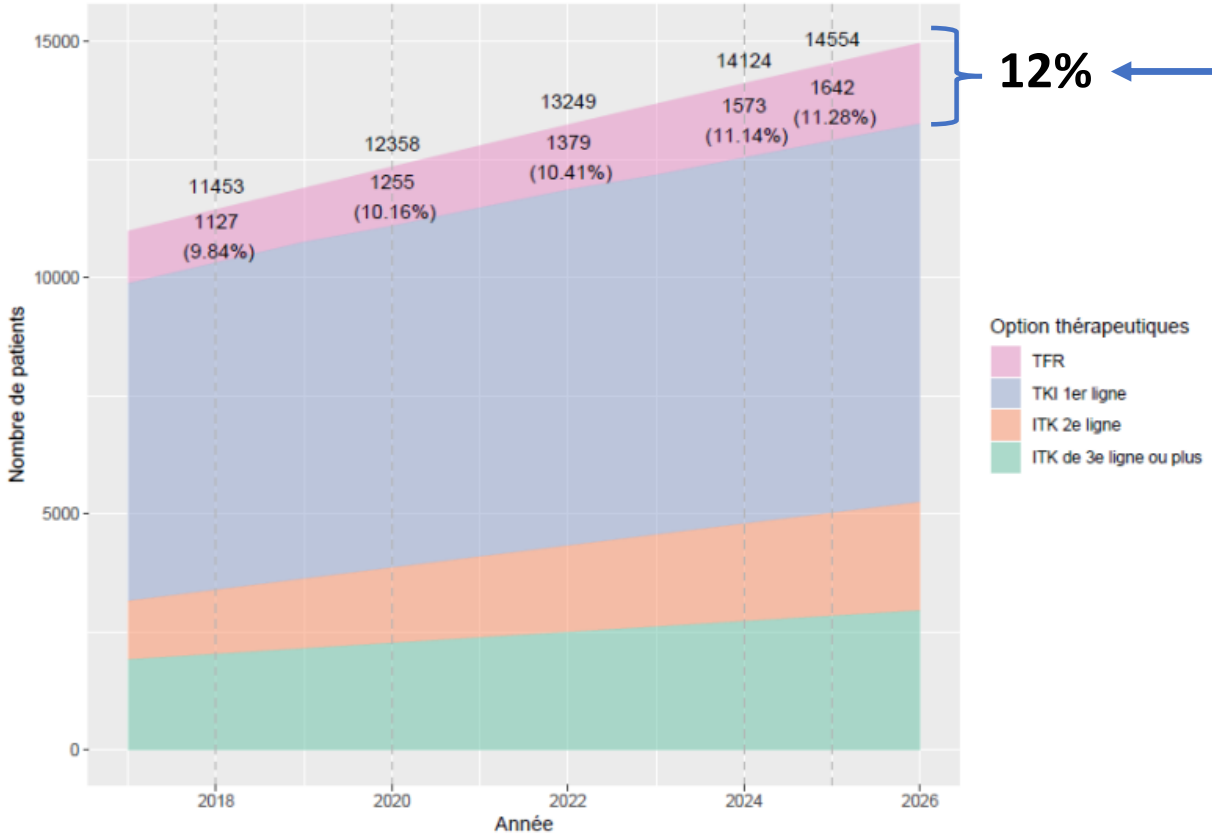
French CML groupe and ELN 2020

TFR eligibility criteria	FiLMC 2018[1]	ELN 2020[2]
Age	≥ 18 years	Not taken into account
CML phase	CP only	In first CP only 1st line or 2nd line if intolerance only
Pronostic score at diagnosis	Not taken into account	Not taken into account
BCR-ABL transcript	Typical (e13a2, e14a2 or e13a2 + e14a2)	Typical (e13a2, e14a2)
TKI treatment duration	≥ 5 years	> 5 years imatinib 4 years with a 2GTKI
Type of DMR	$RM^{4.5}$ at least	$MR^{4.0}$ or better
DMR duration	≥ 2 years	≥ 2 years with any TKI
Prior treatment history	No allogeneic HSCT, progression,resistance, suboptimal response, or warning	No prior treatment failure
Monitoring after treatment discontinuation	CBC and RT-PCR monthly until month 6, every 2 months from month 7 to 12, quarterly from month 13-24 Then every 3 to 6 months	Monitored monthly for the first 6 months, every 2 months for months 6-12, and every 3 months thereafter

1.Rea et al. Cancer 2018 ; 2. Hochhaus et al. Leukemia 2020

More patients eligible ?

Current senario : long term TFR rate



12%

Majority of patients on IMATINIB

Time to TFR : 5 years
Proportion of eligible patients 20%
TFR success rate : 40%

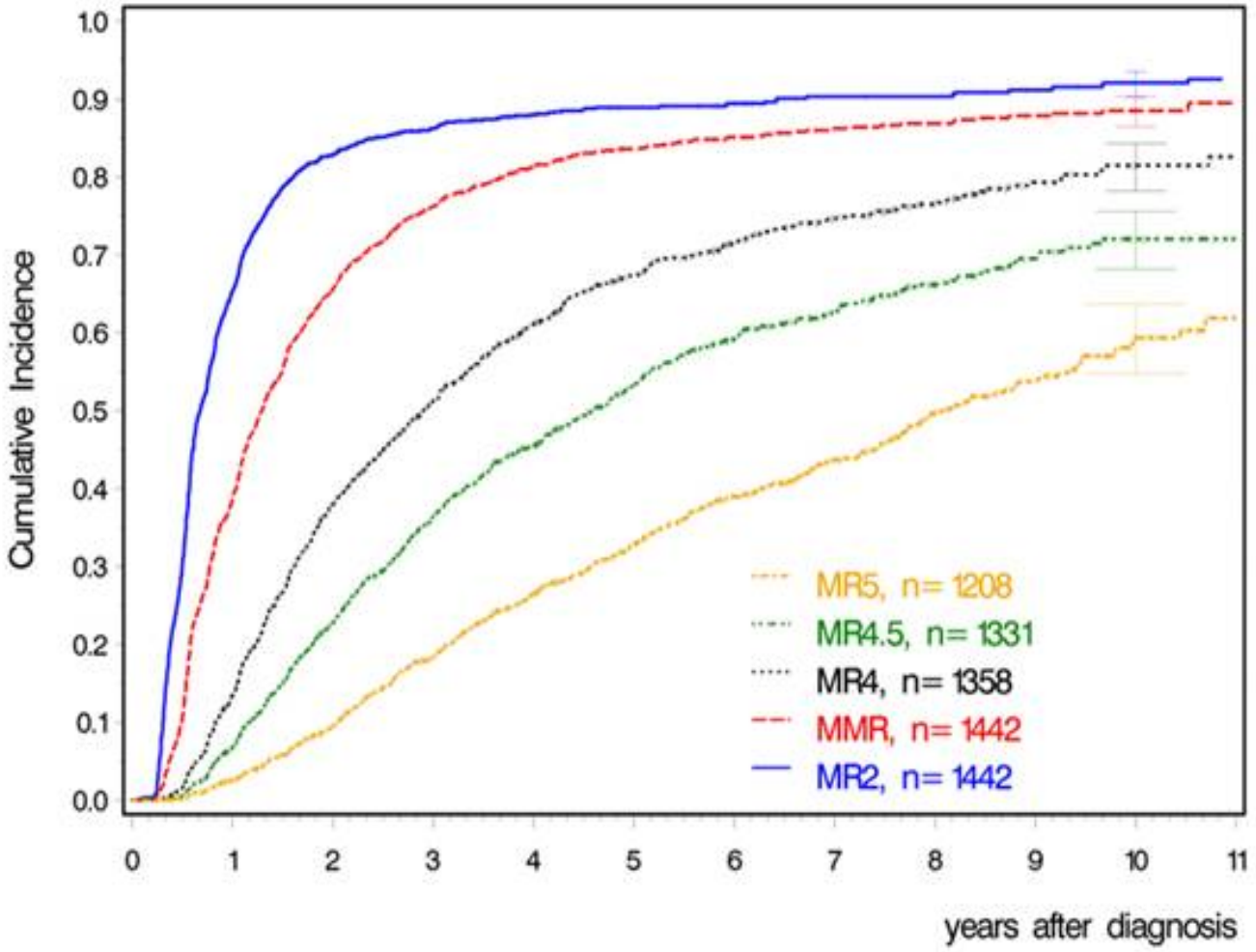
Successful TFR rate 12%

Majority of patients on 2GTKIs ?

Time to TFR : 3 years
Proportion of eligible patients 40%
TFR success rate : 60%

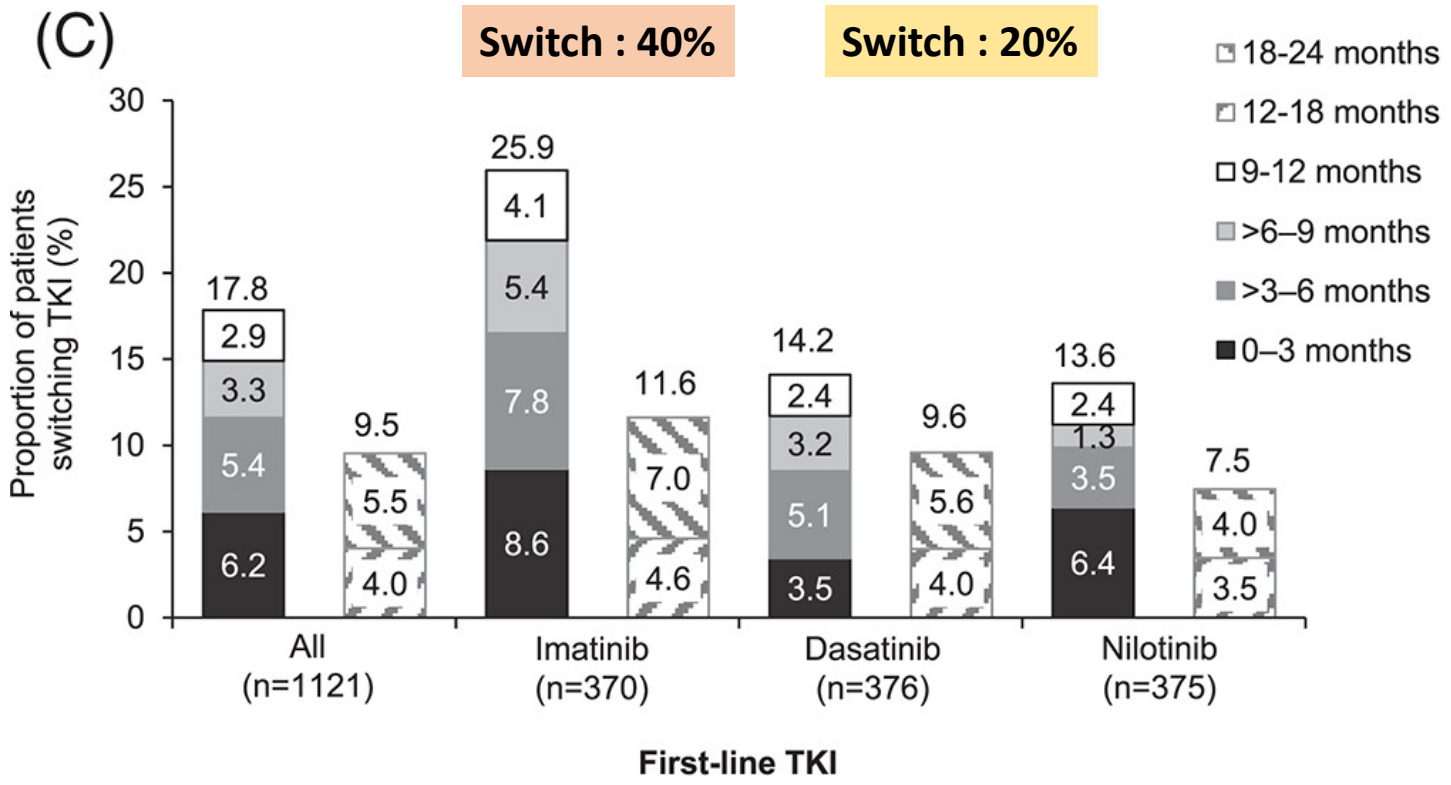
Successful TFR rate 20%

Kinetic of response : IM first line



Hehlmann et al., JCO 2013

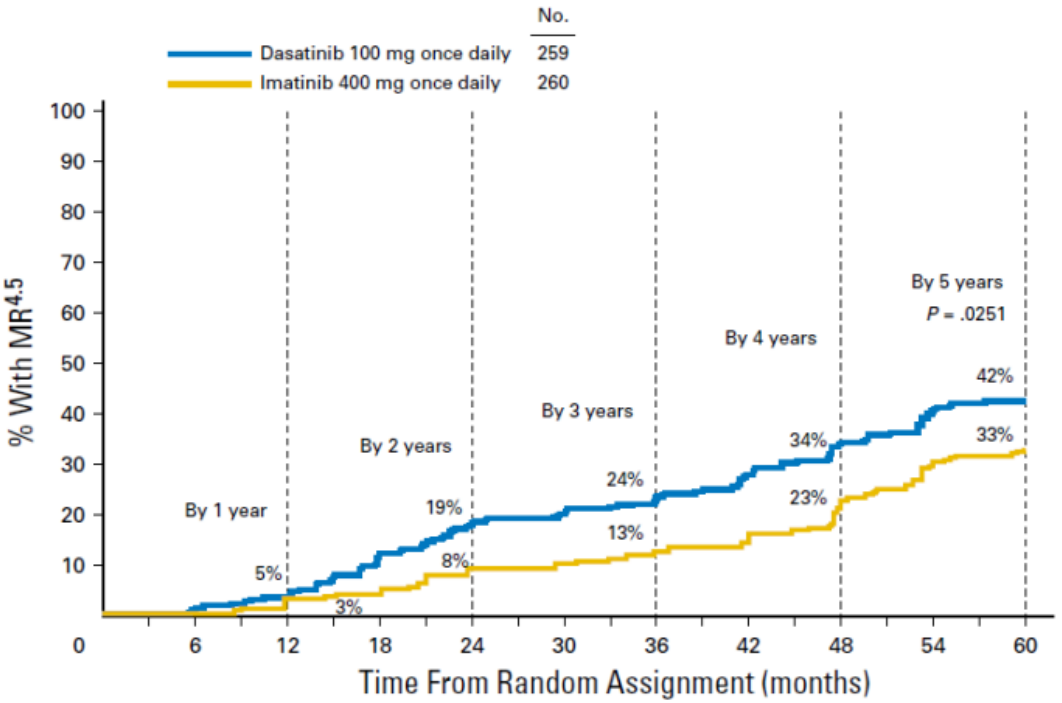
Tyrosine kinase inhibitor interruptions, discontinuations and switching in patients with chronic-phase chronic myeloid leukemia in routine clinical practice: SIMPLICITY



Tyrosine kinase inhibitor interruptions, discontinuations and switching in patients with chronic-phase chronic myeloid leukemia in routine clinical practice: SIMPLICITY, First published: 05 October 2018, DOI: (10.1002/ajh.25306)

MR4.5 with second generation TKI

Responses without switch



Cortes JE A et al. J Clin Oncol 2016.

Table 7 Cumulative incidence of deep molecular response (MR^4 and $MR^{4.5}$) with imatinib, nilotinib, and dasatinib by 5 and 10 years.

Study		5 years (%)	10 years (%)
CML-Study IV[a], [36, 37]	Imatinib MR^4	68	81
	Imatinib $MR^{4.5}$	53	72
ENESTnd[b], [41, 52]	Nilotinib MR^4	66	73
	Nilotinib $MR^{4.5}$	54	64
	Imatinib MR^4	42	56
	Imatinib $MR^{4.5}$	35	45
Dasision[c], [40]	Dasatinib $MR^{4.5}$	42	NA
	Imatinib $MR^{4.5}$	33	NA

DMR rates of these trials cannot be directly compared owing to different methods of trial evaluation.

NA not available.

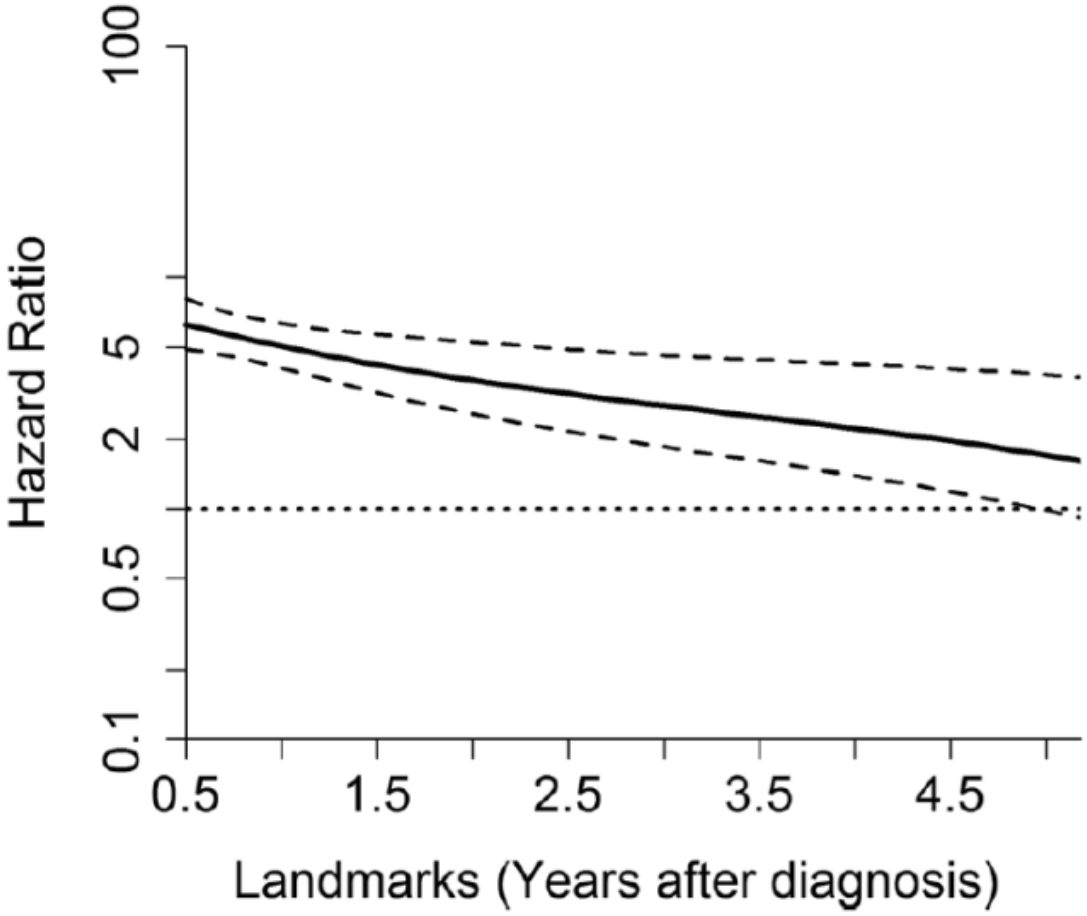
[a]Imatinib ($n = 1442$).

[b]Nilotinib 300 mg twice daily ($n = 282$), imatinib 400 mg daily ($n = 283$).

[c]Dasatinib 100 mg once daily ($n = 259$), imatinib 400 mg daily ($n = 260$).

Hochhaus A et al. Leukemia 2020.

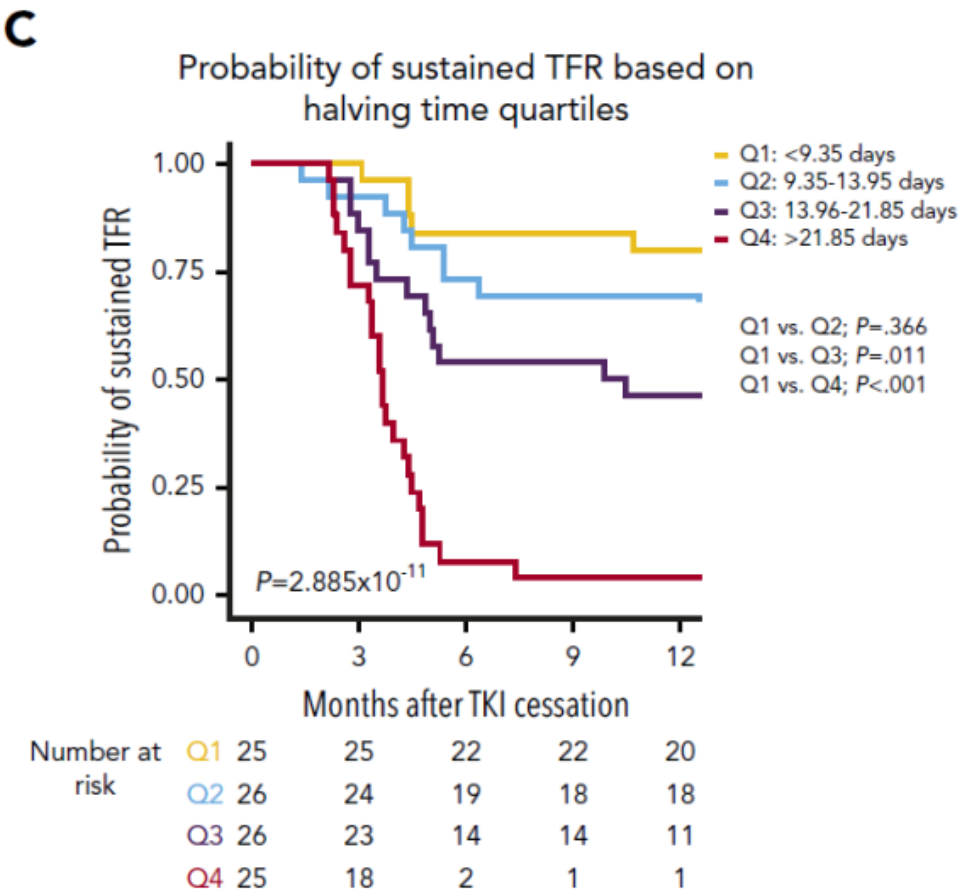
The time to MMR predicts MR4.5 probability



Saußele et al. Leukemia 2018.

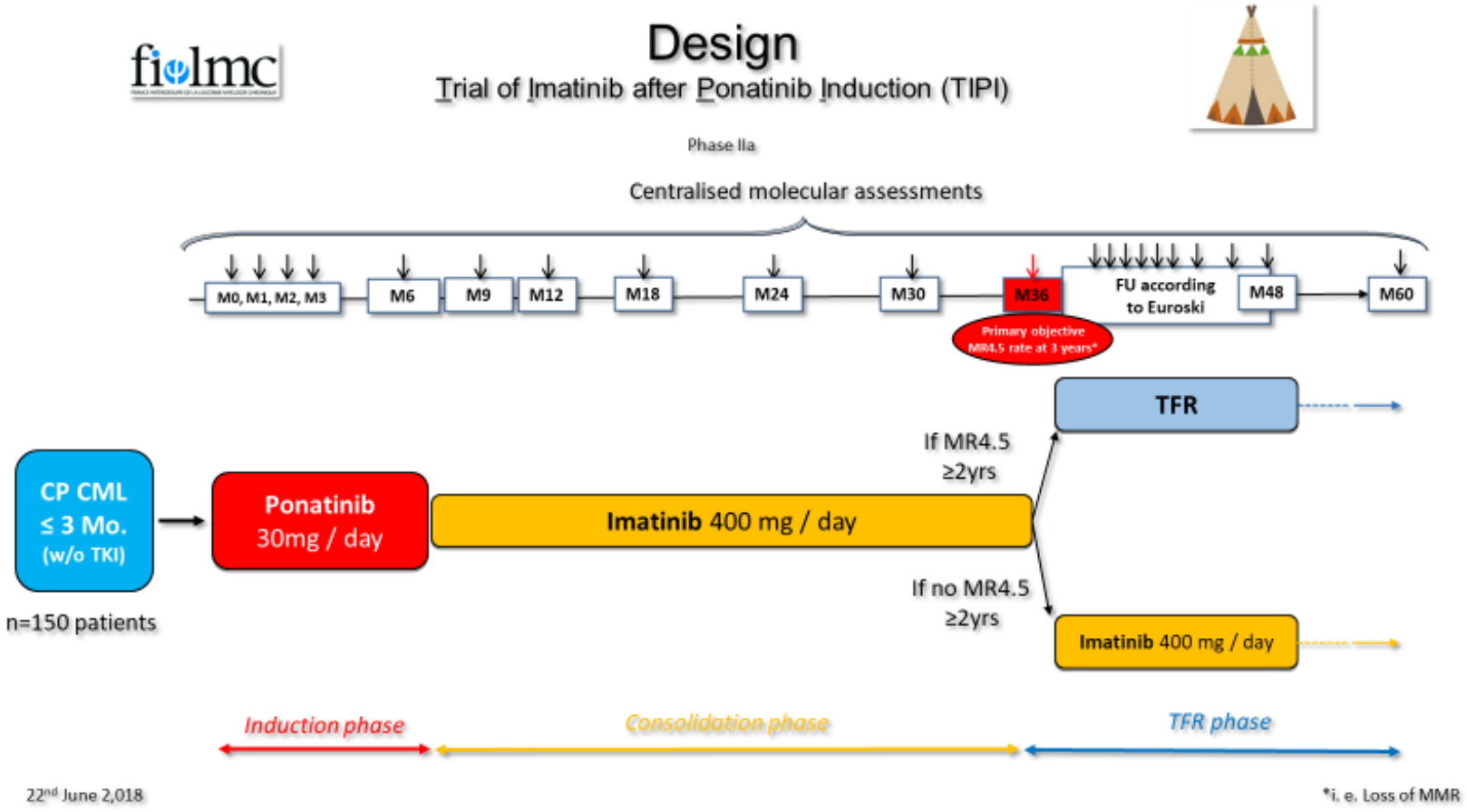
Early BCR-ABL1 kinetic and TFR

- Halving time reflect the kinetic of BCR-ABL decline
- Difficult to calculate (impossible with ABL as a reference gene)
- Median is 12 days
- First quartile is < 9.35 days : sustained TFR probability 80%
- Last quartiles is > 21.85 days : sustained TFR probability 4%



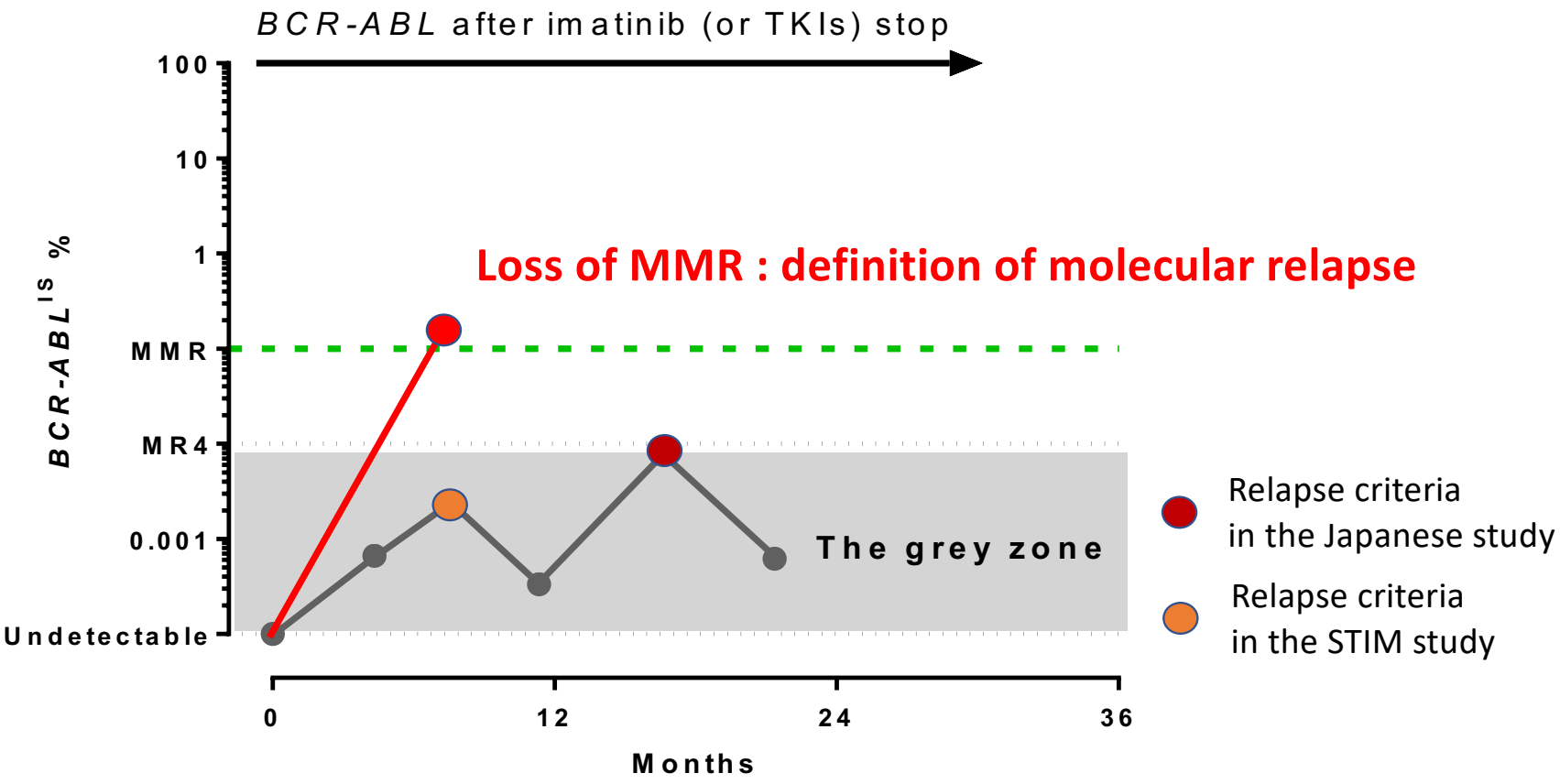
Shanmuganathan N et al. Blood. 2021;137(9):1196-1207)

Induction of a rapid BCR-ABL decline : TIPI trial



Less patients with molecular relapse ?

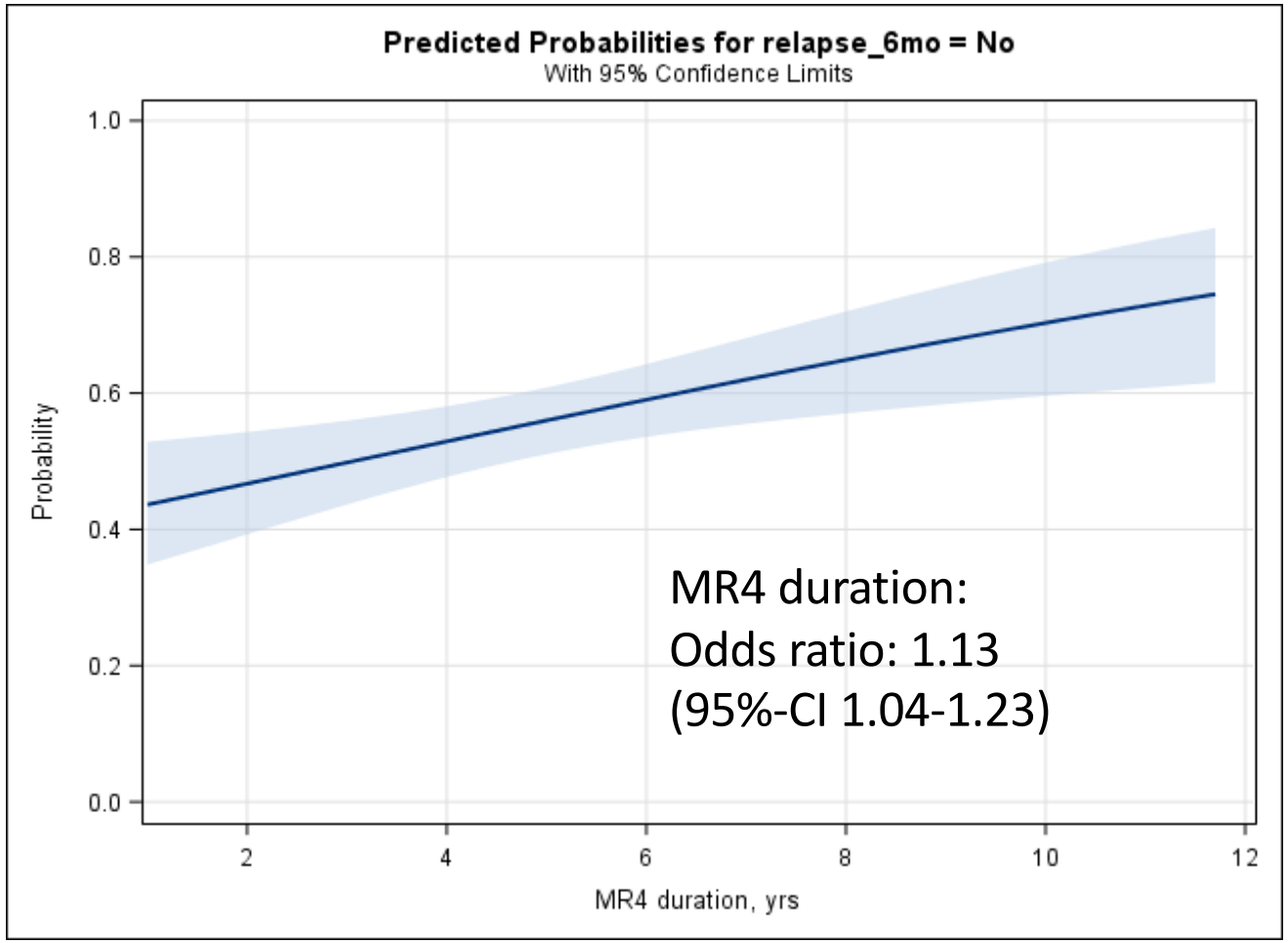
How to define a molecular recurrence ?



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

Study	Nb of patients	TKI type	TKI duration	Type and duration of deep response	Molecular relapse
STIM	100	Imatinib 1st line or post-IFN	≥3 years	MR4.5 with undetectable BCR-ABL1 ≥2 years	MMR loss or ≥1-log increase in BCR-ABL1
TWISTER	40	Imatinib 1st line or post-IFN	≥3 years	MR4.5 with undetectable BCR-ABL1 ≥2 years	MMR or confirmed MR4.5 loss
A-STIM	80	Imatinib 1st line or post-IFN	≥3 years	MR4.5 ≥2 years	MMR loss
JALSG-STIM123	68	Imatinib 1st line or post-IFN	>3 years	MR4.5 >2 years	MMR loss
KIDS	90	Imatinib 1st line or post-IFN	≥3 years	MR4.5 with undetectable BCR-ABL1 ≥2 years	MMR loss
ISAV	108	Imatinib 1st line or post-IFN	≥3 years	MR4 or MR4.5 with undetectable BCR-ABL1 ≥18 months	MMR loss
EURO-SKI	821	Imatinib 1st line or post -IFN, dasatinib or nilotinib ≥1st line, (no prior resistance)	≥3 years	MR4 ≥1 year	MMR loss

Predicted probabilities to be in MMR at 6 months depends on MR4 duration, n=405



EURO-SKI presented by FX Mahon at ASH 2016

Molecular responses of combined TKI to (Peg)IFN-α in CP CML 1st line

Efficacy comparison at 12/24 months in first-line therapies in the litterature

	SPIRIT		Nord CML II*	Dasision	Dasapeg*	Nord CML VII*	ENESTnd	Nilopeg*	PETALs*	TIGER
Treatments	IM 400	IM 400+Peg IFN-α2a	IM 400+Peg IFN-α2b	Dasa 100	Dasa 100 +PegIFN-α2b	Dasa 100 +PegIFN-α2b	Nilo 600	Nilo 600 +Peg IFN-α2a	Nilo 600 +Peg IFN-α2a	Nilo 600 +Peg IFN-α2b
Nb of pts (n)	159	160	56	259	61 >3 months	40	282	42	100	717
MMR	43%	64%	82%*	64%	73%*	84%*	71%	76%*	72.6%*	86.5%*
MR4	21%	38%	53%*	NA	39%*	46%*	39%	49%*	47.4%*	49%*
MR4.5	NA	NA	49%*	17%	31%*	27%*	25%	34%*	36.4%*	32.6%*
>MR4.5	NA	NA	36%*	NA	NA	NA	NA	23%	21%	NA

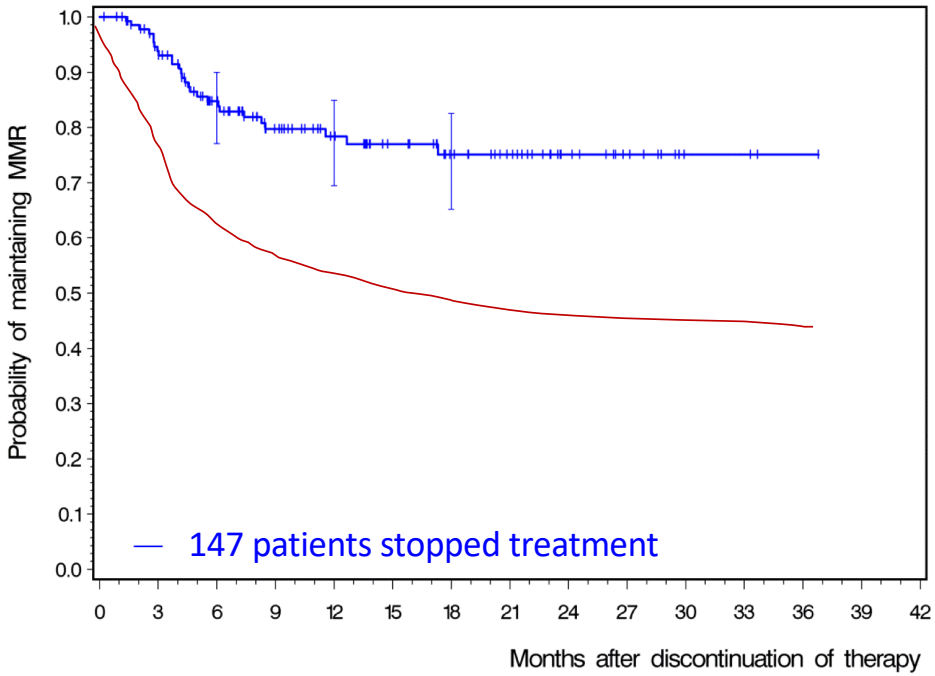
These are not randomised studies and should not be compared one by one.

* At 12 months

Preudhomme C et al. 2010, NEJM
Kantarjian H et al. 2012, Blood (data « by » 24 months and not « at » 24 months)
Kantarjian H et al. 2011, Lancet Oncol
Simonsson B et al. Blood 2011

Nicolini FE et al. 2015, Lancet Haematol
Roy L et al. ASH 2015
Hjörth-Hansen H et al. 2016, Leukemia
Nicolini FE et al. ASH 2019
Hochhaus et al. ASH 2019

Treatment free remission, TIGER study, n=147

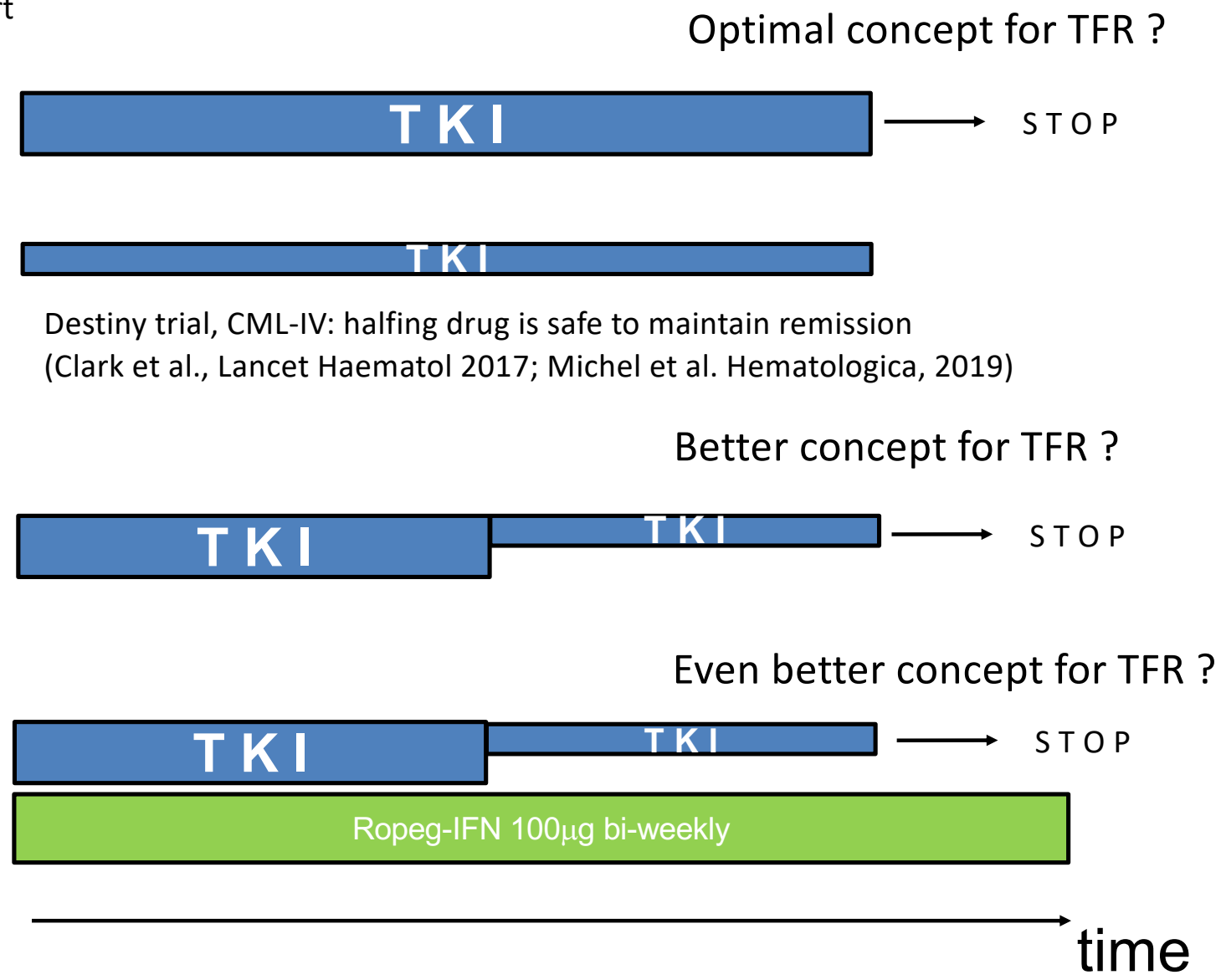


Probability of remaining in MMR:

after 6 mo:	85%
after 12 mo:	78%
after 18 mo.:	75%

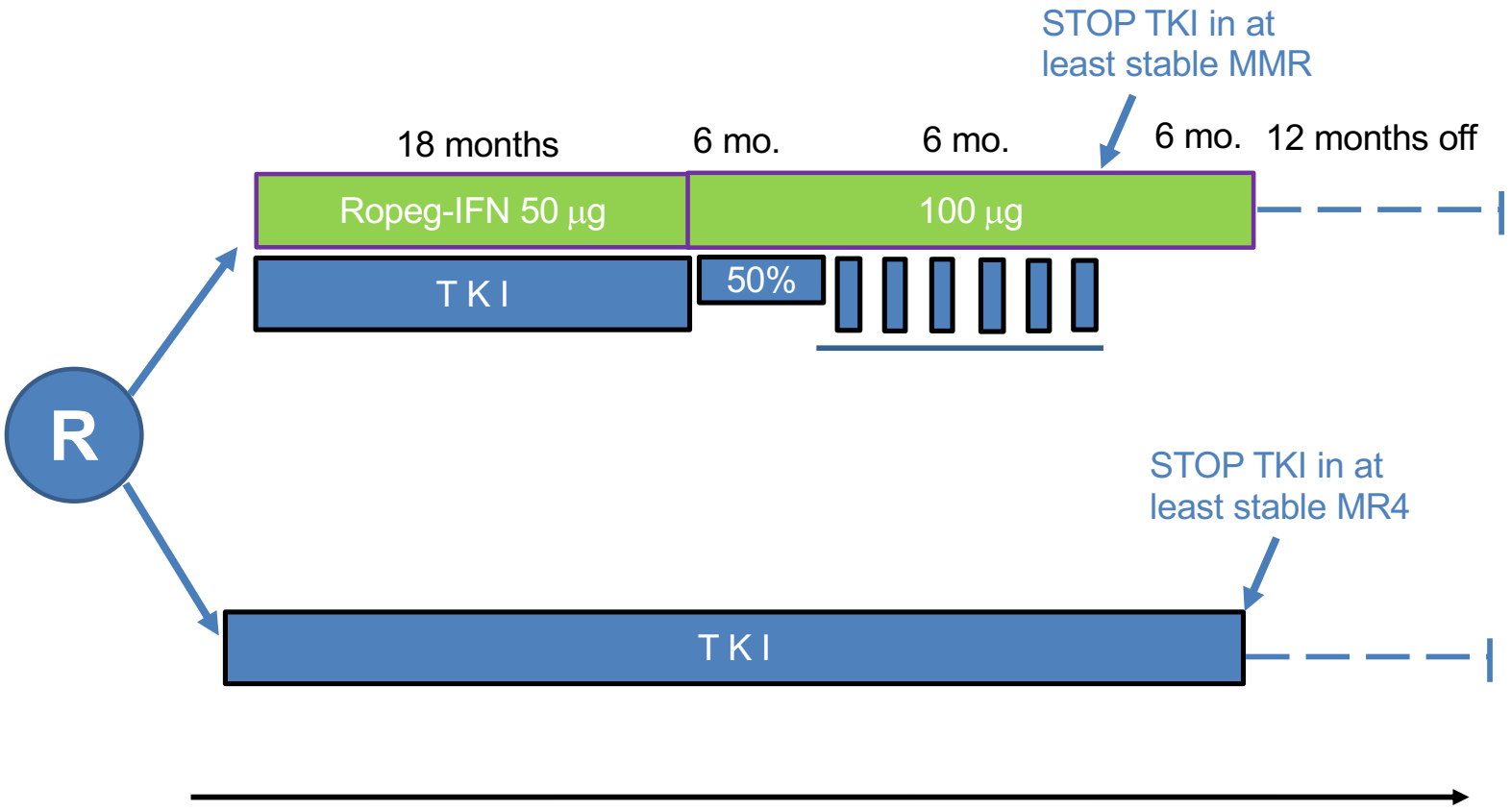
Hochhaus A et al., ASH 2018

Courtesy from A Burchert



Courtesy from A Burchert

CURE - CML study concept



Primary endpoint: TFR after 4 years
Secondary endpoints: MMR 18, 24, 36 months, MR4 36months

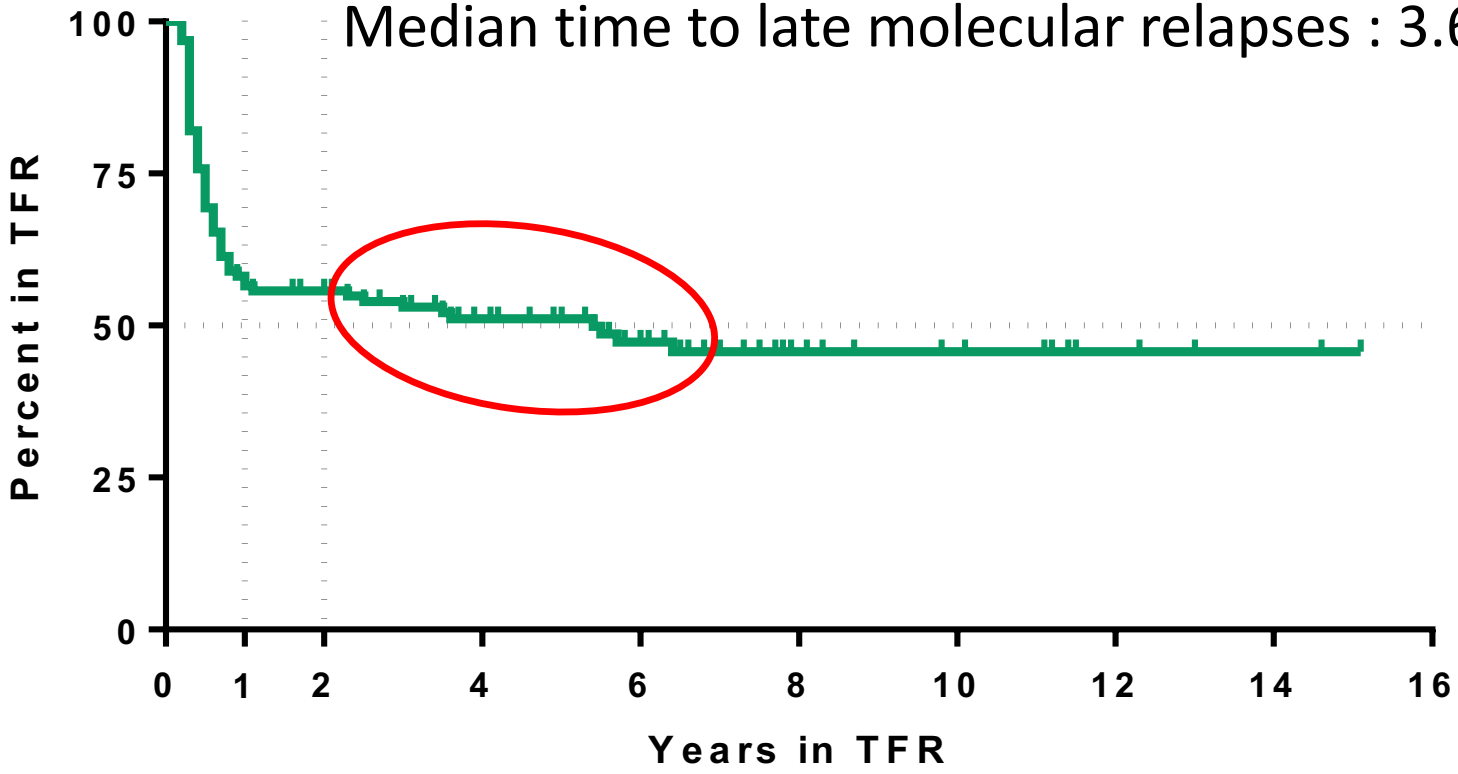
Late molecular reslapses

Late molecular relapses (> 2 years in TFR1)

128 patients in TFR, median follow-up in TFR 6.5y

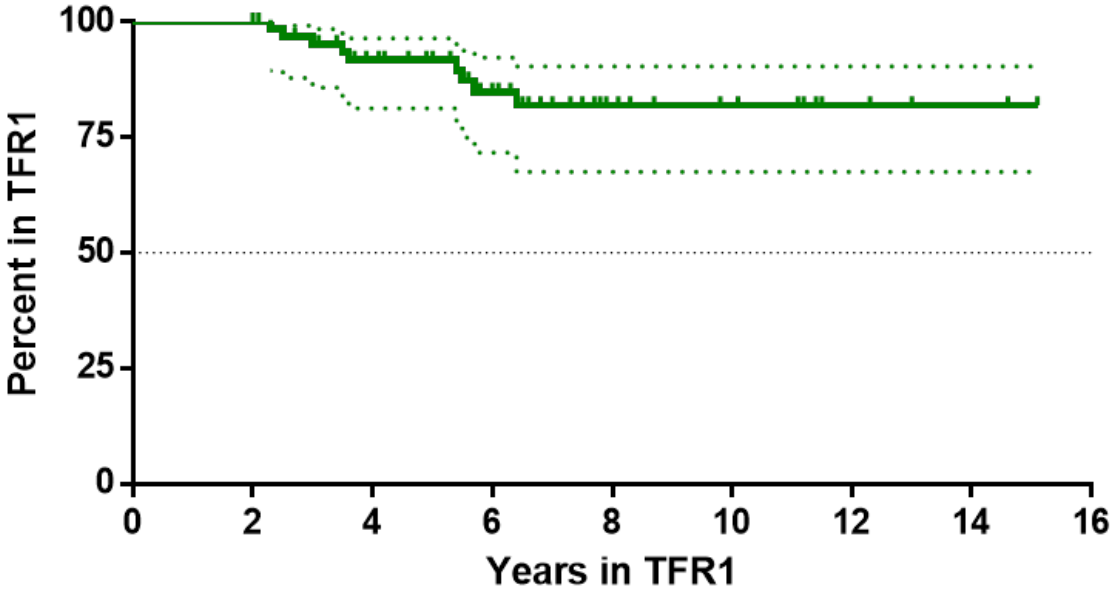
n=9 out 65 molecular relapses (**13.8%**)

Median time to late molecular relapses : 3.6 years (2.3-6.3)



Rousselot P, et al. Blood Adv. 2020 Jul 14;4(13):3034-3040

Landmark analysis at 2 years

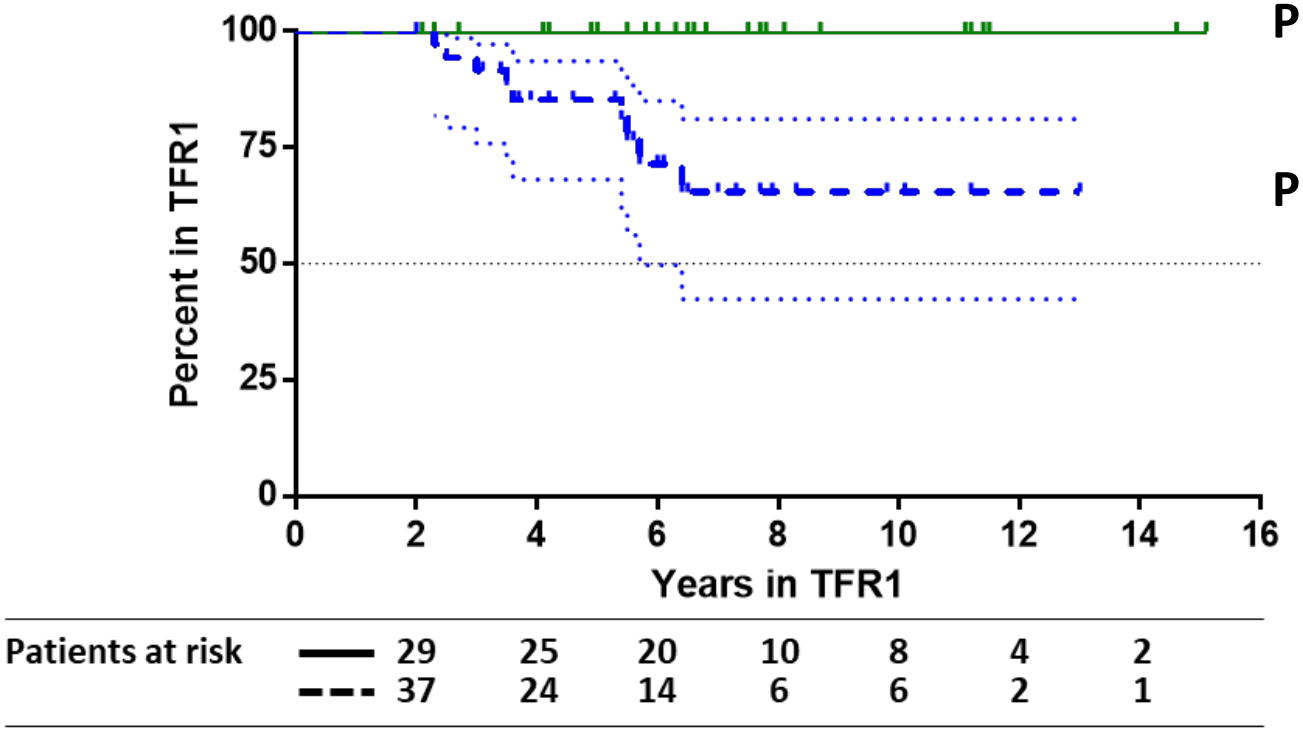


Patients at risk	66	49	34	16	12	6	3

Proportion in TFR1 : 81.9%

Rousselot P, et al. Blood Adv. 2020 Jul 14;4(13):3034-3040

Stable versus unstable molecular remission



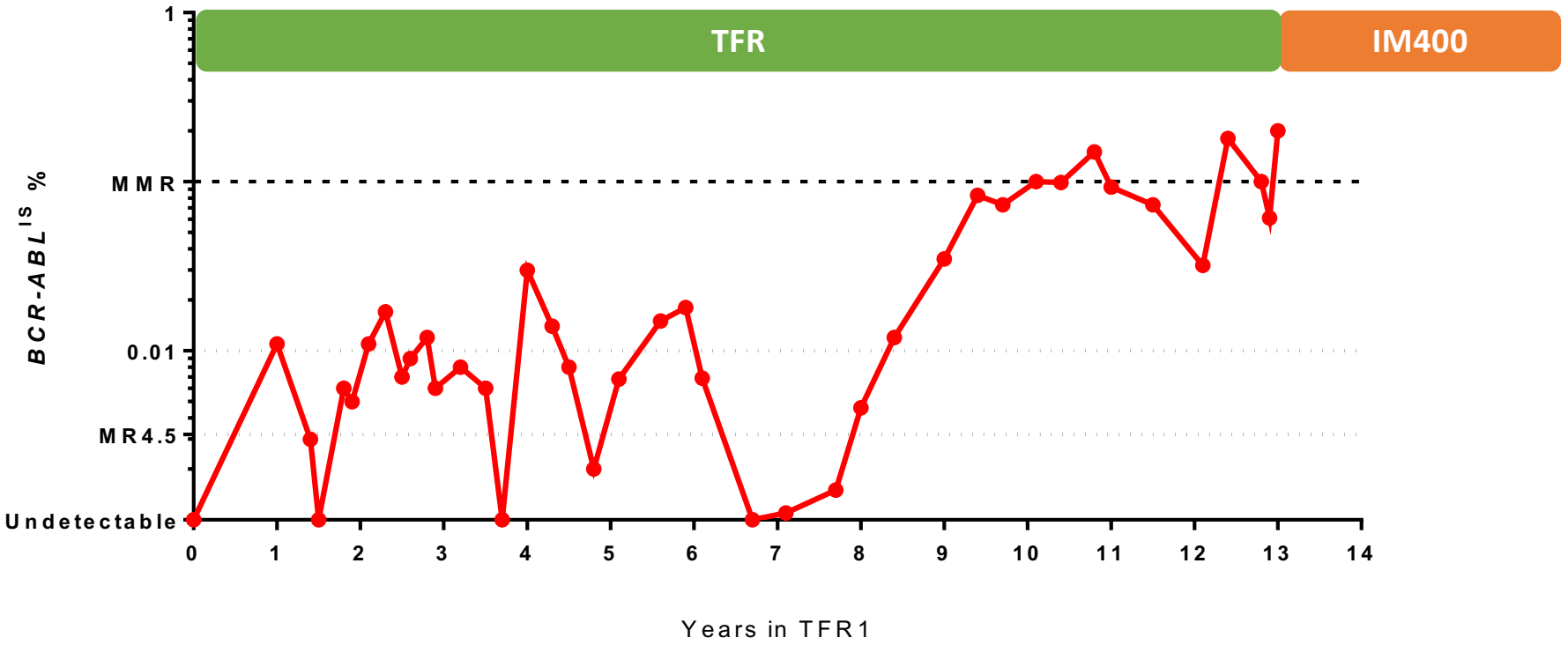
Proportion in TFR1 : 100%

Proportion in TFR1 : 65.4%

P = 0.02

Rousselot P, et al. Blood Adv. 2020 Jul 14;4(13):3034-3040

A very late molecular recurrence



Rousselot P, personal data

Conclusions

- Consensual eligibility criteria : the patient may also say NO
- Consensual relapse criteria
- It will be difficult to have more patients in TFR using TKI monotherapy
  - Try to induce a faster molecular response
  - Success rate higher ?

- Futur : studies designed for TFR
  - Combinations : interferon ?
  - New drugs
    - Immunotherapy
    - Targeted therapies : quiescent cells

Acknowledgments

S Prost
Y Ouzegdouh
F Relouzat
J Saliba
Ph Leboulch

C Chomienne
F Calvo

L Morisset
A Beulaygue
JP Beressi

Association Laurette Fugain
Information sur le don de plaquettes et aide à la recherche sur les maladies du sang

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