Leucemia mieloide cronica la TFR: per chi pensarci, quando pensarci, come arrivarci e come gestirla

Dott.ssa Germana Beltrami
U.O. Ematologia e Terapie Cellulari
Ospedale Policlinico San Martino IRCCS

Disclosures

Germana Beltrami

Speakers bureau e Advisory board: Novartis, Incyte, Pfizer

Moving TFR into clinical practice:the first step

Criteria	Green	Yellow	Red
Institutional criteria met (per table 1)	Yes	-	No
Sokal score at diagnosis	Non-high	High	-
BCR-ABL transcript at diagnosis	Typical - B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to first line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	> 8 years	3–8 years	< 3 years
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0
Duration of deep molecular response monitored in a standardized laboratory	> 2 years	1–2 years	< 1 year

All green lights: strong recommendation to consider TKI withdrawal

Any yellow lights: only consider TKI withdrawal in high priority circumstances (e.g. significant toxicity or planned pregnancy)

Any red lights: TKI withdrawal not recommended except in clinical trial

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

Moving TFR into clinical practice: ELN 2020 requirements

Mandatory	Minimal requirements	Optimal requirements
Motivated patients	1° chronic phase only	TKI > 5 years
Access to RT-qPCR using the IS scale	1° line or 2° line (after intolerance) No prior failure or progression	Duration of DMR > 3 years if MR4
Rapid turnaround of results	e13-a2 or e14-a2 transcripts	Duration of DMR > 2 years if MR4.5
Patients agreement to frequent monitoring	TKI > 5 years (imatinib) or > 4 years ((2G-TKI) DMR (MR4 or better) > 2 years	

EURO-SKI final analysis

- 728 pts eligible for analysis
- Median age 51 years
- Median duration TKIs 7.6 years
- Median duration of MR4 4.7 years

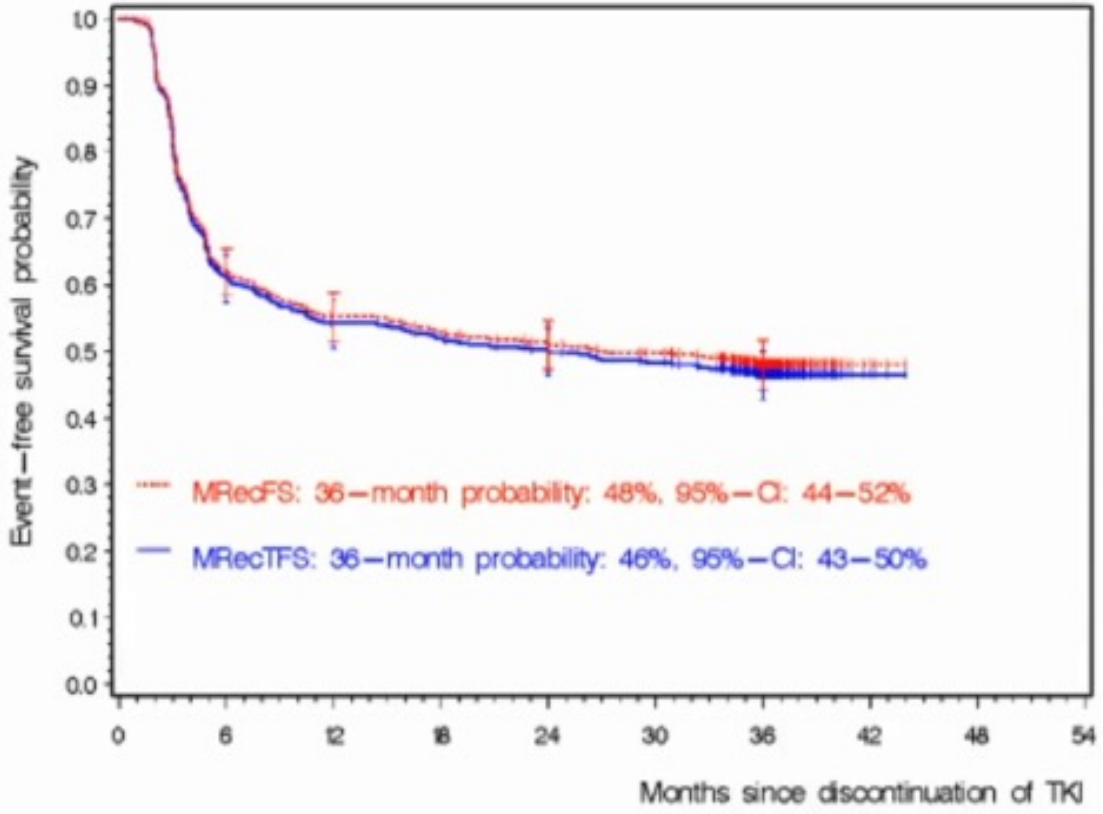
At 36 months

309 pts remained in MR3 (46%)

MRecFS: 48%

No blast crisis observed

Late relapses 15% (between 6-36 mos)



TFR: MDACC experience

297 pts attempt discontinuation

Median age 63 years

after 38 months, 18% of pts lost MR3 in a median time of 6 months

Median TFR a 3-y 69%

According to duration of MR4.5

-91% if sDMR of more than 72 months

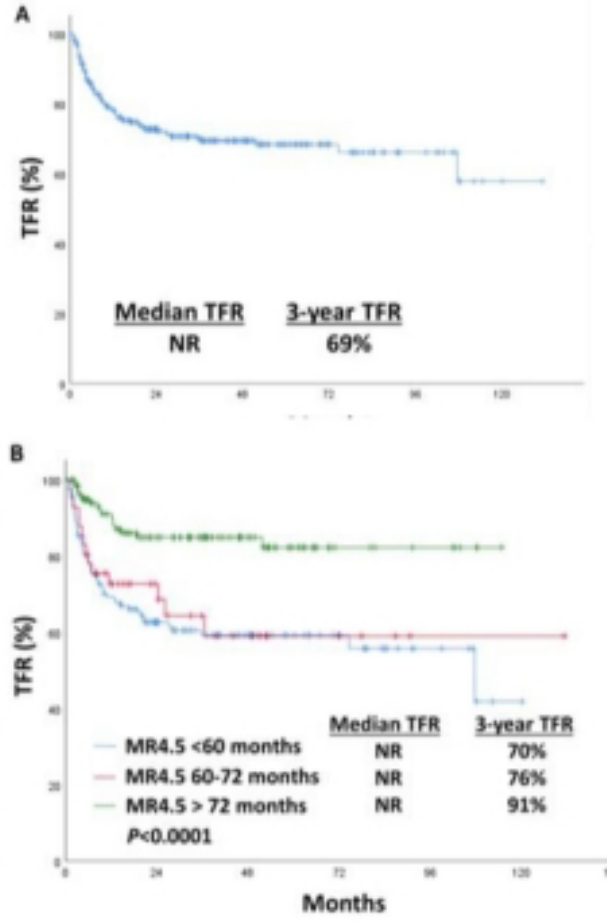
-76% if sDMR 60-72 months

-70% if sDMR less than 60 months

No differences based on type of TKI

sMR4.5 for more than 6 years correlate with low probability of loss of MR3 and MR4.5 after the discontinuation

Haddad et al ASH 2021 abstract 1480



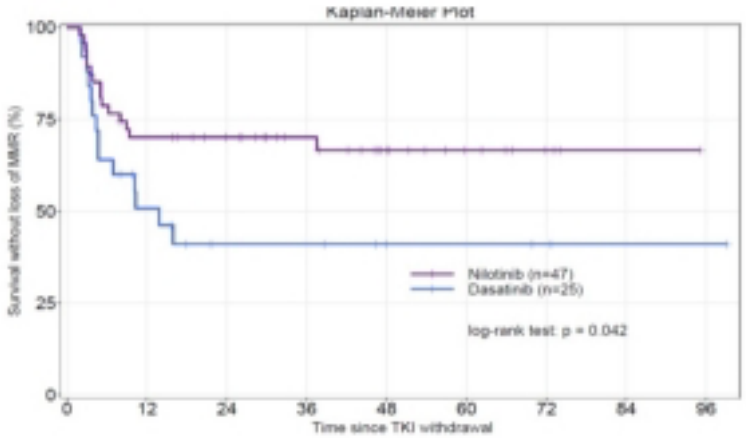
TFR: French experience (dasa vs nilo)

72 pts (47 nilotinib , 25 dasatinib)

The median time from TKI2 initiation to sustained MR4.5 was 19 (3.12-36) months in the Nilo group and 16 (6.3-39) months in the Dasa group (p=0.644).

The median survival of pts without loss of MMR was not reached in the Nilo group, and was 14 (4.73-NR) months in the Dasa group

Multivariate analysis identified the type of TKI2 as a significant factor impacting on TFR outcome [HR 2.11 (0.97-4.55], p=0.05].



Nicolini et al ASH 2021 abstract 2552

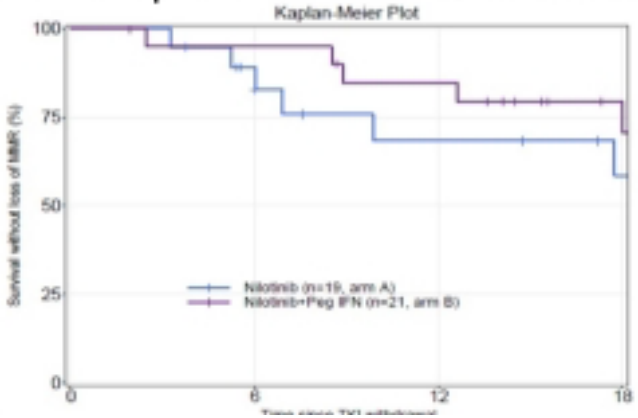
TFR: PETALS trial

Newly diagnosed CP CML pts ≤65 years, without vascular history were randomized 1:1 to get NIL 300 mg BID alone [M0 to M72 (unless TFR), arm A] *vs* Peg-IFN alone for 30 days (M-1→M0) 30 mg/wk, prior to NIL 300 mg BID + Peg-IFN 30 mg/wk 2 wks, upgraded to 45 mg/wk thereafter, for up to 2 y (M0 to M24, arm B) followed by NIL alone until M72 unless TFR

200 pts randomized

Overall cumulative incidence of MR4.5 was somewhat superior in arm B (54.6 [43.7-65.5] %) *vs* A (44 [31.5-54] %), p=0.05

The survival without loss of MMR looks superior in arm B over arm A, but did not reach statistical difference (p=0.445)



Nicolini et al ASH 2021 abstract 2553

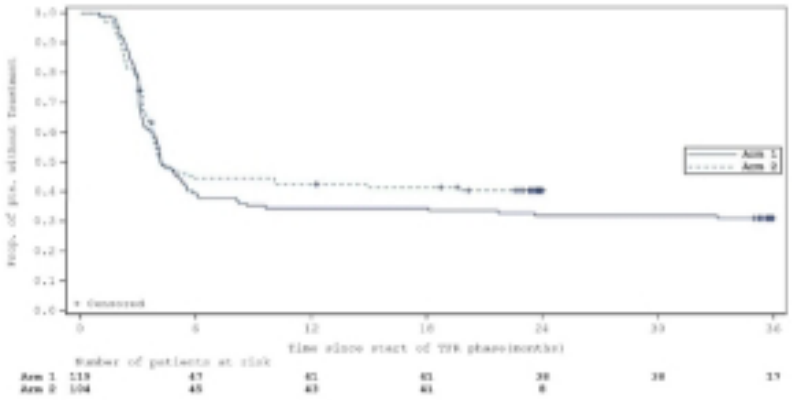
TFR: ENESTPath trial

620 pts enrolled. 238 randomized

Baseline characteristics well balanced between arm of TFR and arm in which nilotinib was continued for other 12 months

There was no significant difference in the primary endpoint of $MR^{4.0}$ rate at 12 mos of TFR between arms (Arm 1, 31.9% [95% CI: 23.7 - 41.1]; Arm 2, 37.5% [95% CI: 28.2 - 47.5]; P=0.383)

Median time to treatment-free survival event (TFS; defined as loss of MMR, confirmed loss of $MR^{4.0}$, re-start of NIL for any reason, progression to accelerated phase/blast crisis, or death from any cause) was 4.1 (95% CI: 3.7 - 5.5) mos in Arm 1 and 4.2 (95% CI: 3.7 - 19.7) in Arm 2 . No additional benefit in continuing nilotinib before TFR



Rea et al ASH 2021 abstract 635

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

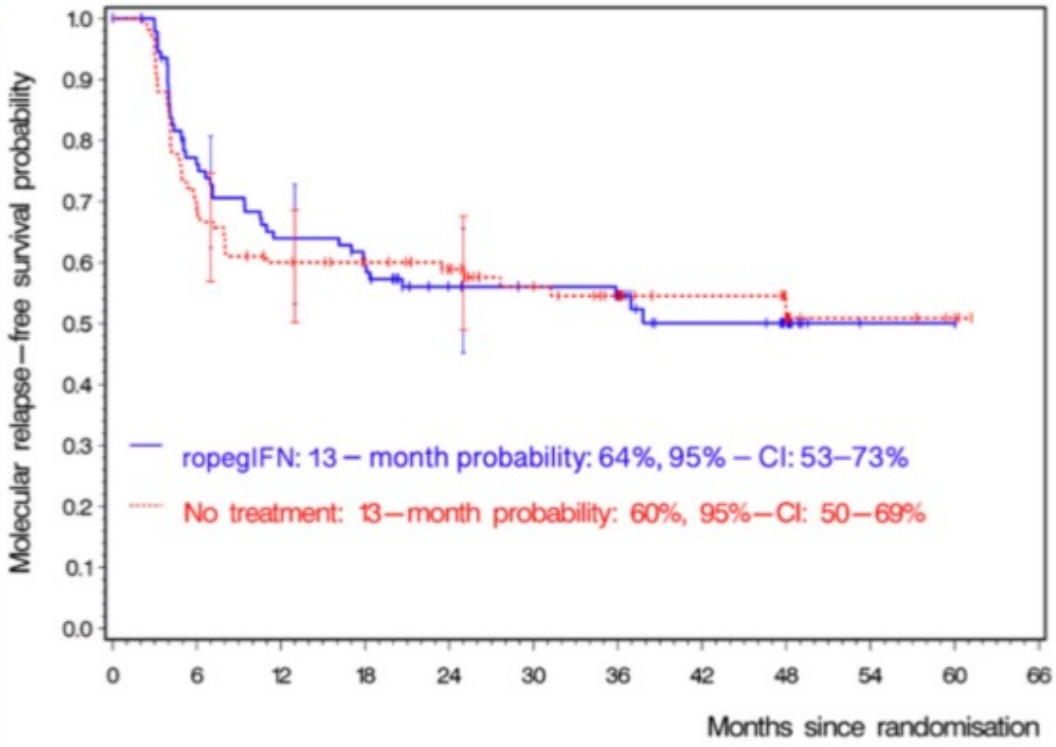
Preudhomme C et al. 2010, NEJM
Kantarjian H et al. 2012, Blood (data « by » 24 months and not « at » 24 months)
Kantarjian H et al. 2011, Lancet Oncol
Simonsson B et al. Blood 2011

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

Emerging strategies: the role of ropeg-IFN in TFR

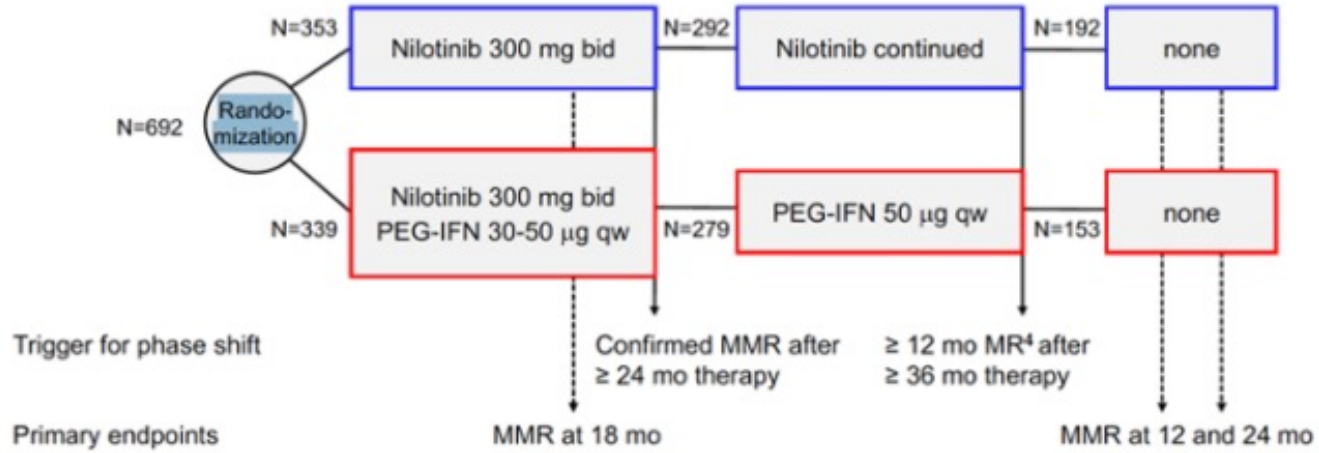
- Pts in stable DMR or in second TFR randomized to receive ropeg-IFN or no other treatment
- Primary endpoint the molecular relapse free survival
- 203 pts randomized
- In 80% of pts was the first attempt of TFR
- MRFS at 24 months was 56% for ropeg-IFN vs 59% for no treatment arm

- Ropeg-IFN maintenance after discontinuing TKI-monotherapy **does not increase** the proportion of patients, who persistently maintain at least an MMR. The German CML-V (TIGER) trial currently explores the impact of IFN maintenance on TFR when patients receive a combination of TKI plus IFN before TKI stop



Burchert et al ASH 2022; 622

TIGER trial: nilo vs nilo+peg-IFN



		Nilotinib	Nilotinib+peg-IFN	p
Treatment phase	MMR at 12 mos	76%	81%	0.035
	MMR at 18 mos	83%	88%	0.021
	MR4 at 18 mos	51%	64%	0.0018
Discontinuation phase	MMR at 12 mos	60%	69%	0.12
	MMR at 24 mos	48%	57%	0.13

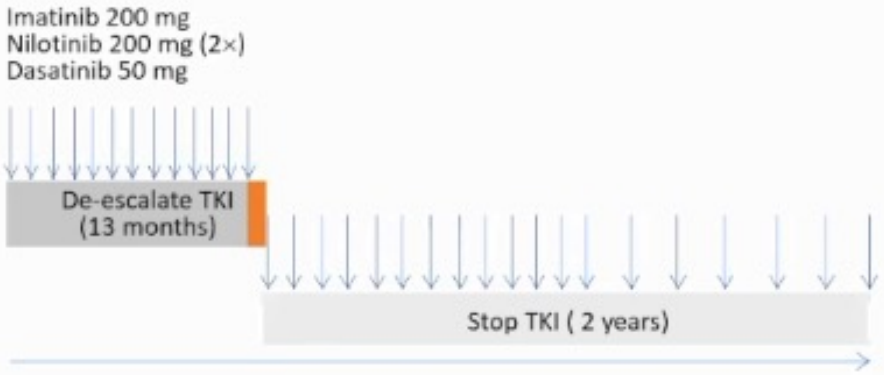
At 24 months, 22% in both arms were in TFR

Hochhaus et al EHA 2023; 1560

DESTINY: first example of dose optimization trial

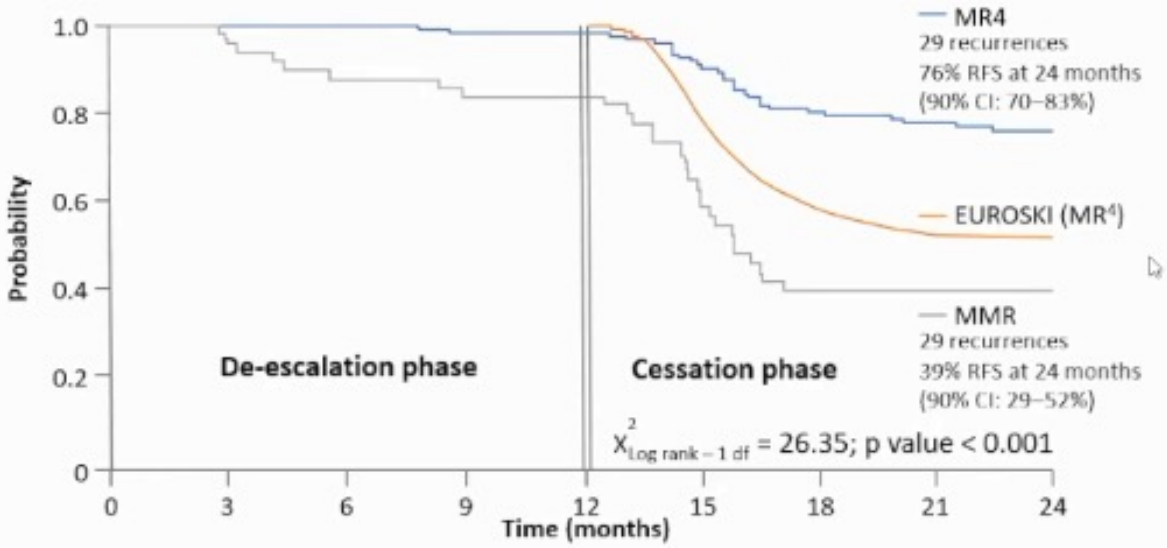
De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel

Half TKI dose



- **Treatment de-escalation maintains response and improves adverse events**

Recurrence-free survival



Clark RE, et al. Lancet Haematol. 2019;6(7):e375-e383.
Saussele S, et al. Lancet Oncol. 2018;19:747-57

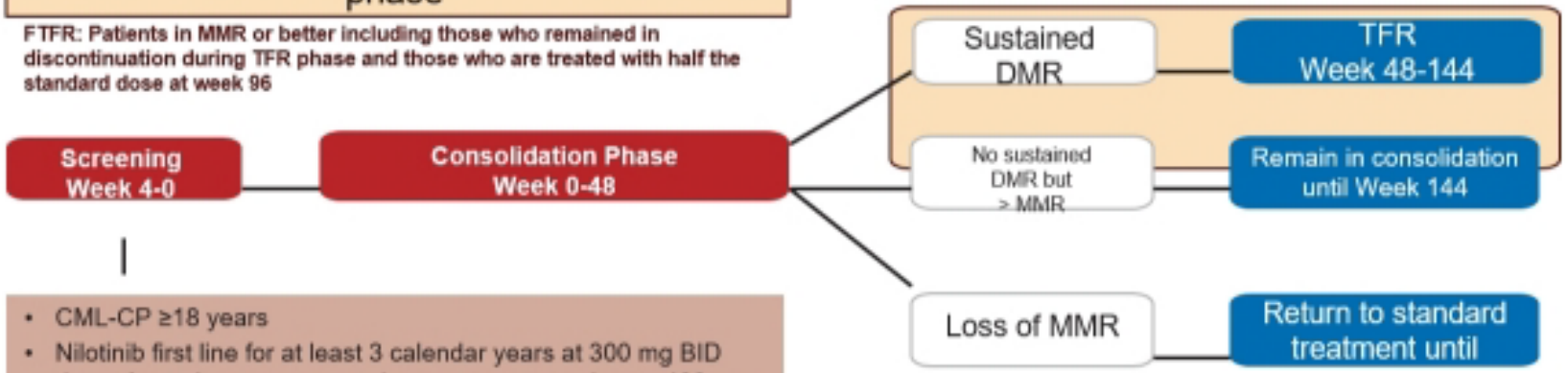
DANTE trial: first interim analysis

Primary endpoint: Percentage of patients in FTFR 96 weeks after the start of consolidation phase

FTFR: Patients in MMR or better including those who remained in discontinuation during TFR phase and those who are treated with half the standard dose at week 96

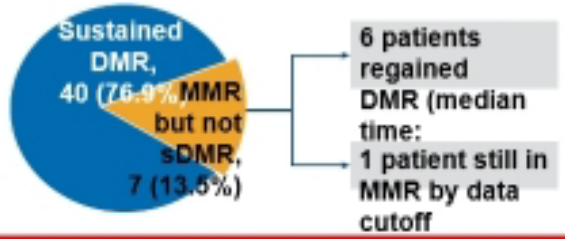
Patients with loss of MMR at any time will return to standard nilotinib regimen (300 mg BID) until end of (week 144).

FTFR: patients in MMR or better at week 96



- CML-CP ≥18 years
- Nilotinib first line for at least 3 calendar years at 300 mg BID dose. At study entry, an ongoing treatment at a dose ≥ 400 mg per day is allowed.
- Sustained DMR, defined as MR 4.0 in all of the last 4 BCR-ABL RQ-PCR assessments
- No prior TFR attempt or known atypical transcript
- ECOG performance status 0-2

Molecular response in 47 patients who completed Consolidation Phase



Breccia et al ASH 2021 abst 1474

DANTE: dose optimization trial for TFR

Primary endpoint: Percentage of patients in FTFR 96 weeks after the start of consolidation phase

FTFR: Patients in MMR or better including those who remained in discontinuation during TFR phase and those who are treated with half the standard dose at week 96

Screening Week 4-0 → **Consolidation Phase Week 0-48**

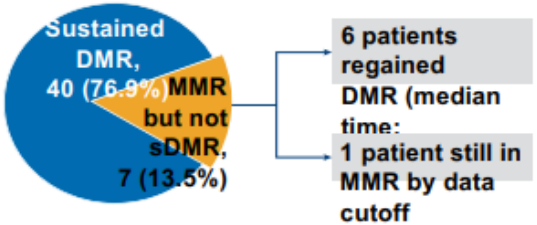
- CML-CP ≥18 years
- Nilotinib first line for at least 3 calendar years at 300 mg BID dose. At study entry, an ongoing treatment at a dose ≥ 400 mg per day is allowed.
- Sustained DMR, defined as MR 4.0 in all of the last 4 BCR-ABL RQ-PCR assessments
- No prior TFR attempt or known atypical transcript
- ECOG performance status 0-2

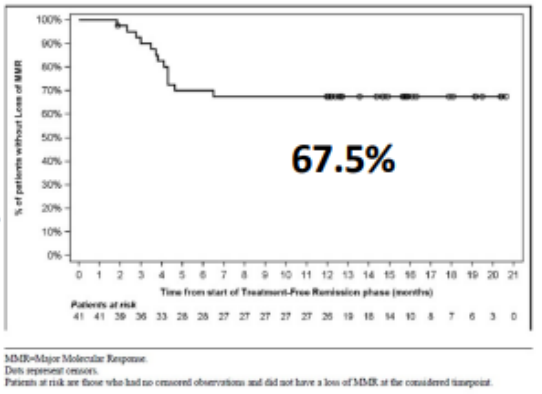
FTFR: patients in MMR or better at week 96

- Sustained DMR → TFR Week 48-144
- No sustained DMR but ≥ MMR → Remain in consolidation until Week 144
- Loss of MMR → Return to standard treatment until

Patients with loss of MMR at any time will return to standard nilotinib regimen (300 mg BID) until end of trial (week 144).

Molecular response in 47 patients who completed Consolidation Phase



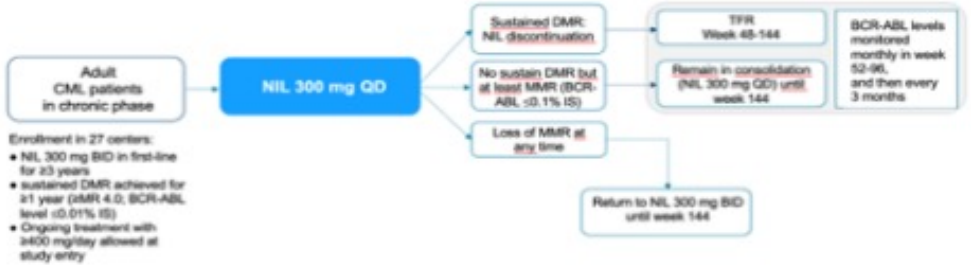


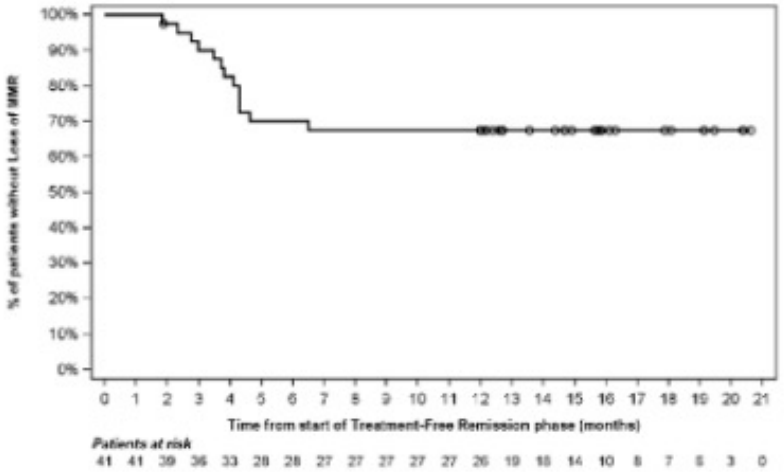
MMR=Major Molecular Response.
Dots represent censors.
Patients at risk are those who had no censored observations and did not have a loss of MMR at the considered timepoint.

Stagno et al, ASH 2022, 4326

Other ongoing de-escalation trials before TFR

DANTE trial





READIT 2020 Two de-escalation point at 6 and 12 months

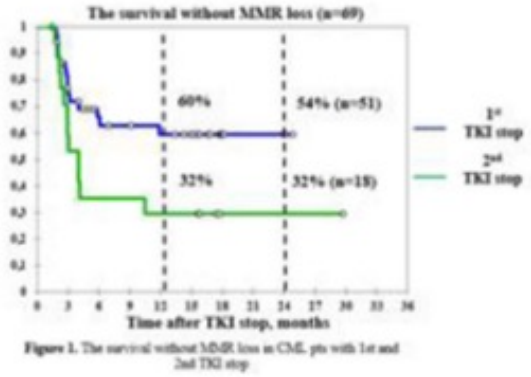


Figure 1. The survival without MMR loss in CML pts with 1st and 2nd TKI step

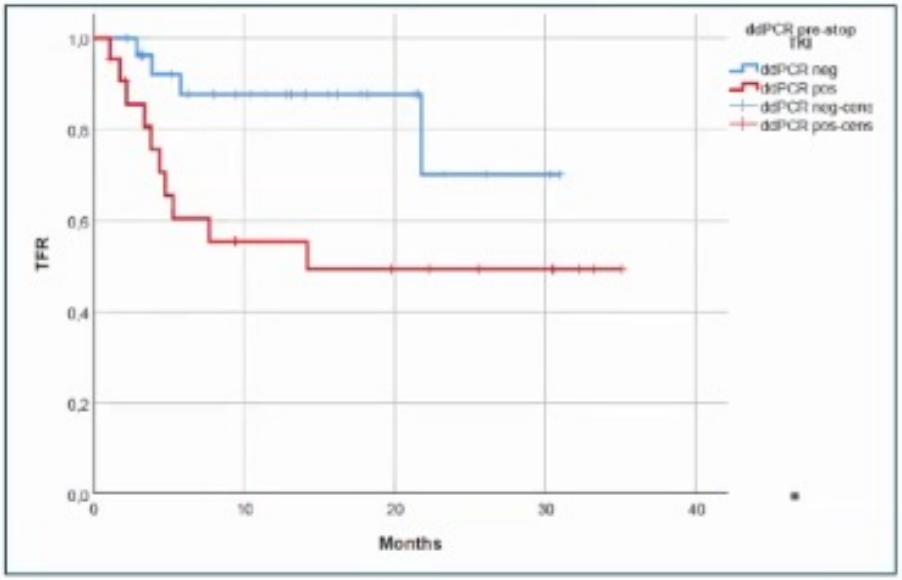
HALF trial: reduction to ½ dose and second step with TKI every other day

Stagno F. Blood 2022; 9614-9616 140: ; Gurianova et al EHA 2023, 2802

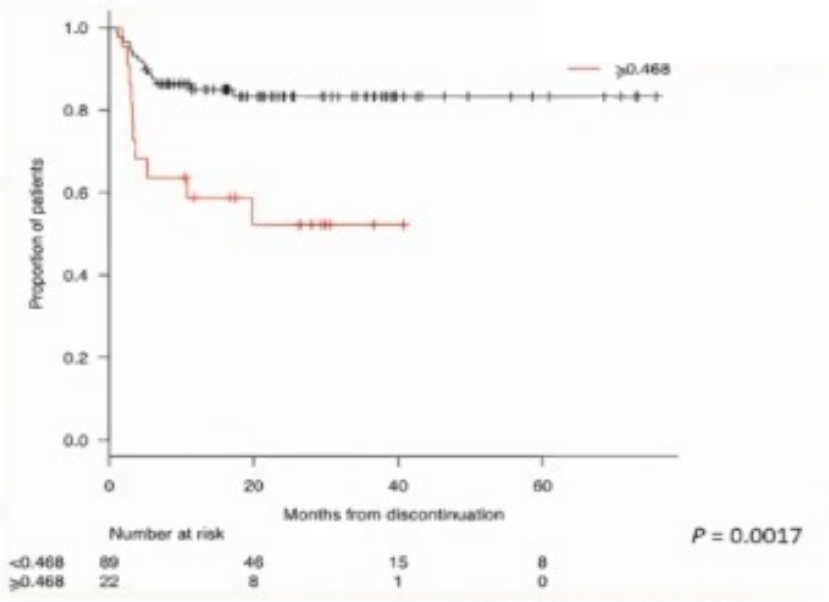
Prognostic indicators of sustained TFR

Factor category	Factor	Prognostic value
Patient	Age, sex	Inconsistent results
Disease	Prognostic scores at diagnosis	Inconsistent results
Treatment history and response to therapy	Depth of molecular response	Inconsistent results
	Type of TKI	Possible
	History of suboptimal response or resistance	**Yes**, decreased TFR probabilities
	IFN pre-treatment	**Yes** (in EURO-SKI trial, excluded as prognostic due to possible bias
	TKI treatment duration	**Yes**, imatinib better results after at least 5-6 years
	Deep molecular response duration	**Yes**, imatinib better results if at least 3 years in MR4

ddPCR as a possible predictive tool for TFR

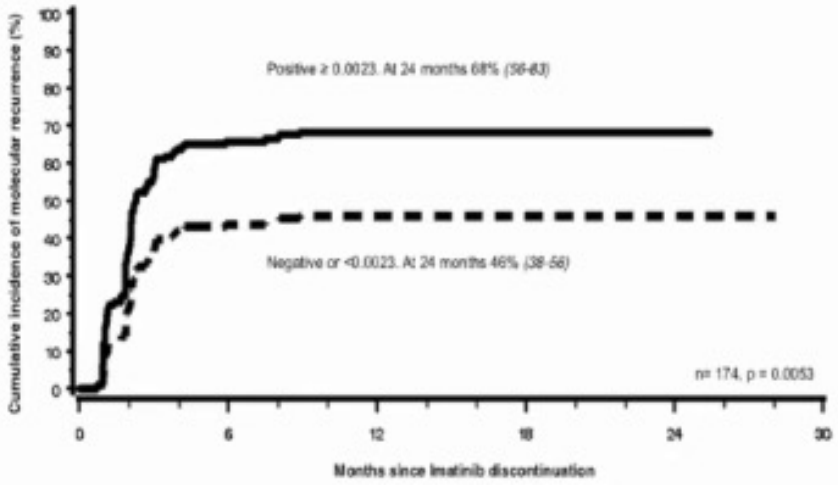


Colafigli G, Breccia et al Hematol Oncol 2019



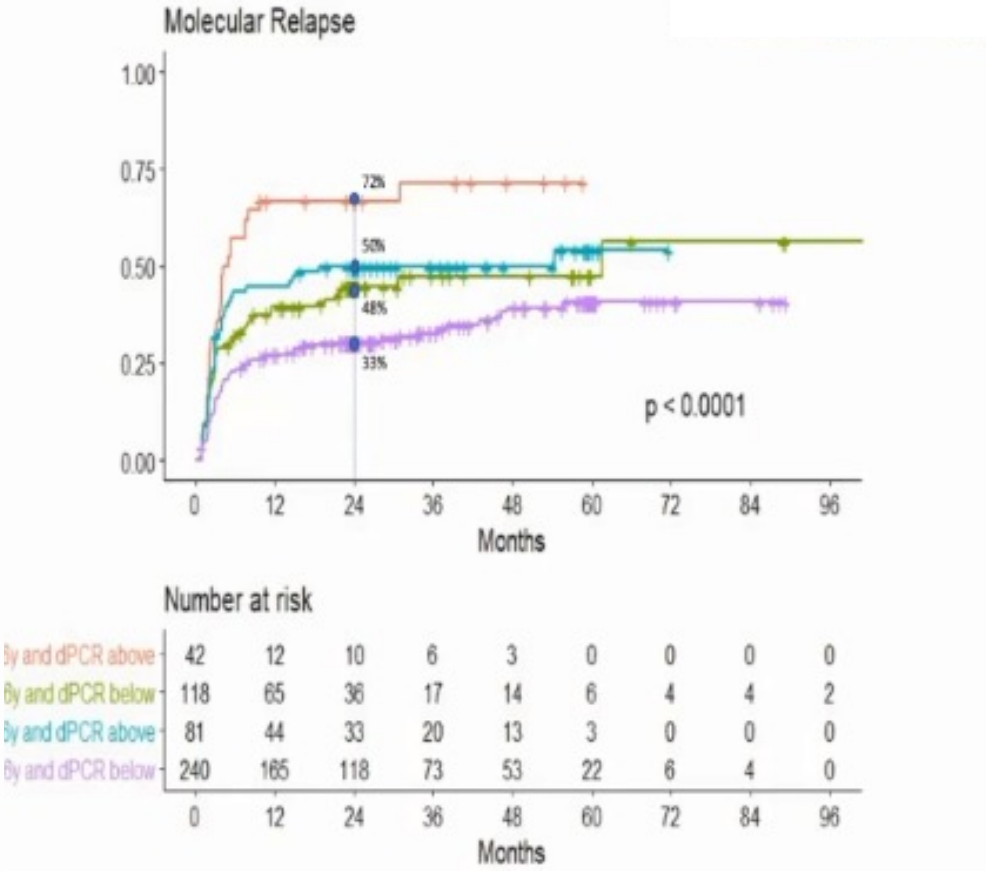
Bernardi et al Cancer Med 2019

Nicolini et al Clin Cancer Res 2019



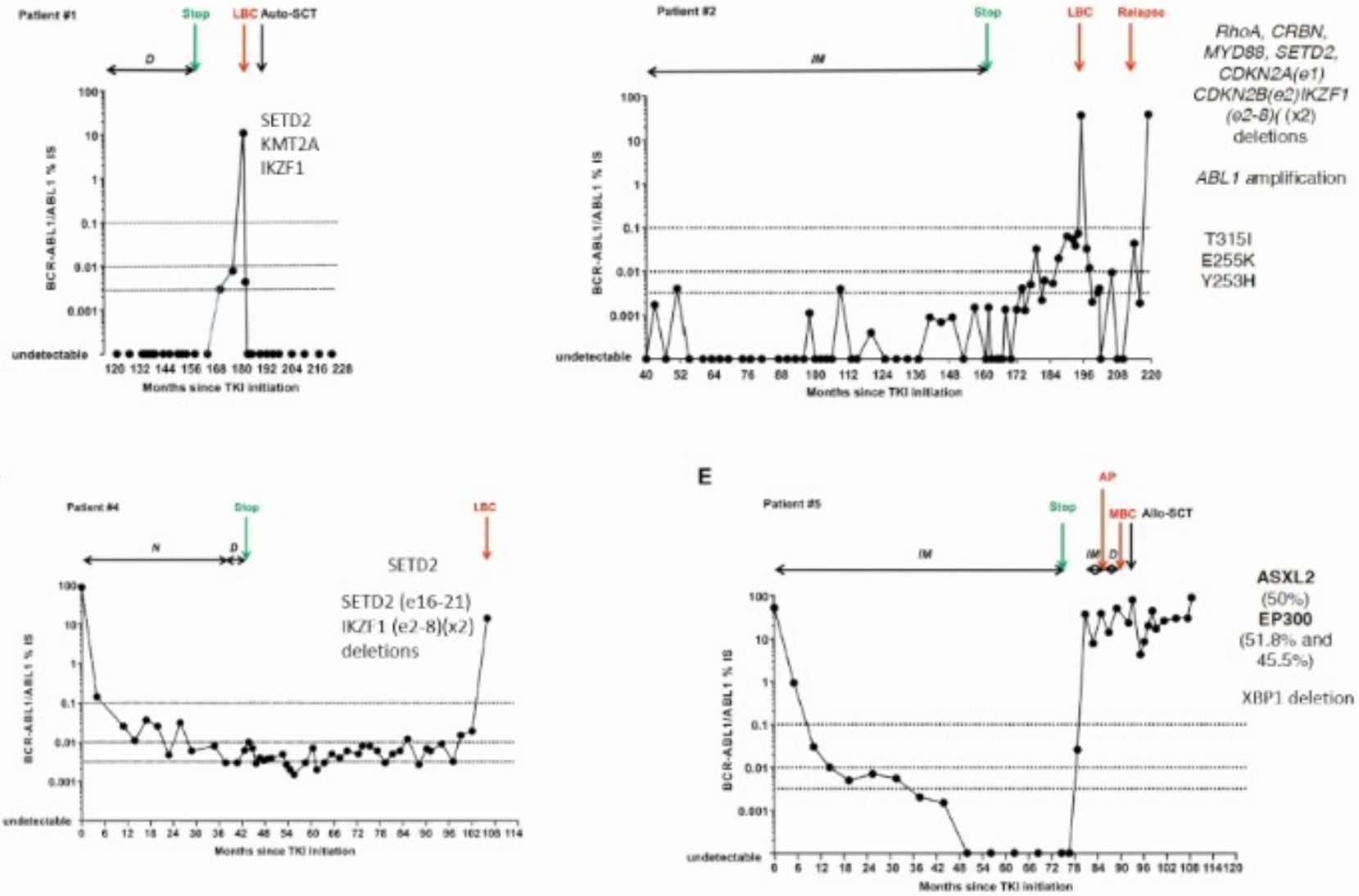
ddPCR and duration of treatment: a patient-level meta analysis

- Individual Patient Data Meta-Analysis (IPD-MA) combining data from different study cohorts in which *BCR-ABL1* was assessed by D-PCR prior to discontinuation
- The pooled dataset comprised **483 patients** of 5 different experiences
- A total of 205 patients (**42%) experienced MolR**. These patients had a significantly shorter treatment duration prior to TKI discontinuation (6,7 *vs* 7,9 years, p=0.006) and more often presented a *BCR-ABL1* D-PCR above the study-defined prediction cut-off (34% *vs* 19%, p<0.001).
- The probability of MolR at 24 months was 38% *versus* 58% for patients with a D-PCR *BCR-ABL1* below *versus* above the prediction cut-off (p <0.001).
- When stratifying into four groups based on the D-PCR result and treatment duration, **patients treated with a TKI for >6 years and low D-PCR result had the lowest MolR rate (33% at 24 months).**



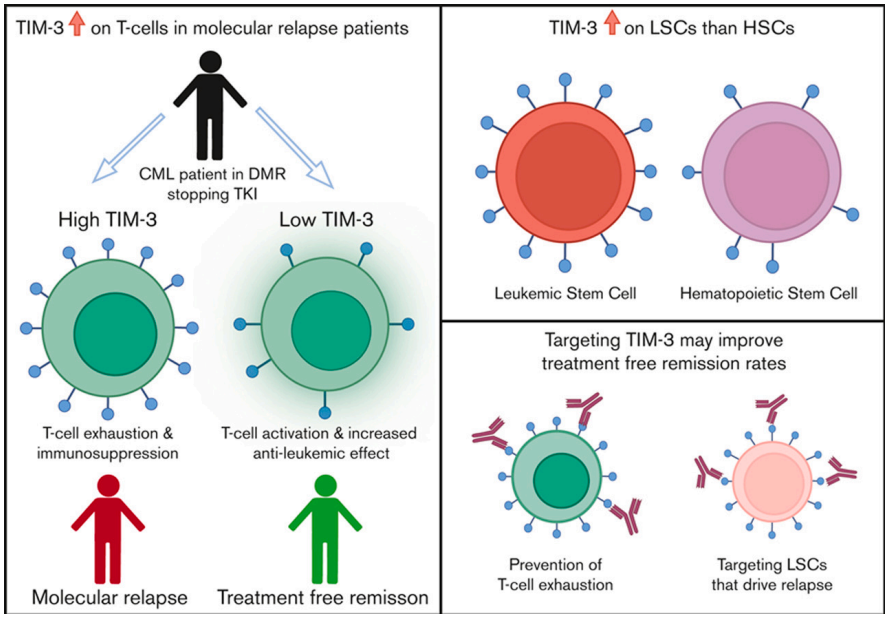
Kockerois et al, EHA 2022 and SIE 2022

Sudden BC after discontinuation: the need of good quality long term



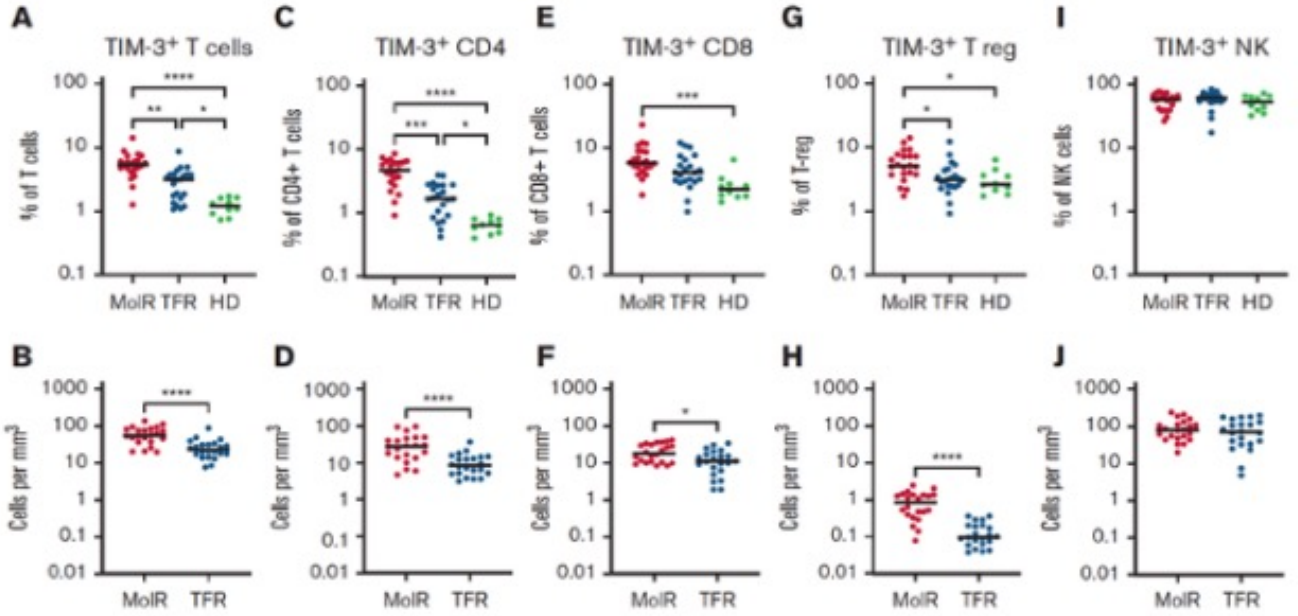
Dulucq et al, Haematologica 2022

Association of TIM-3 checkpoint receptor expression on T cells with treatment-free remission in chronic myeloid leukemia



Yazad D. Irani,Chung H. Kok,Jade Clarson,Naranie Shanmuganathan,Susan Branford,David T. Yeung,David M. Ross,Timothy P. Hughes,Agnes S. M. Yong,
Association of TIM-3 checkpoint receptor expression on T cells with treatment-free remission in chronic myeloid leukemia, Blood Adv, 2023,

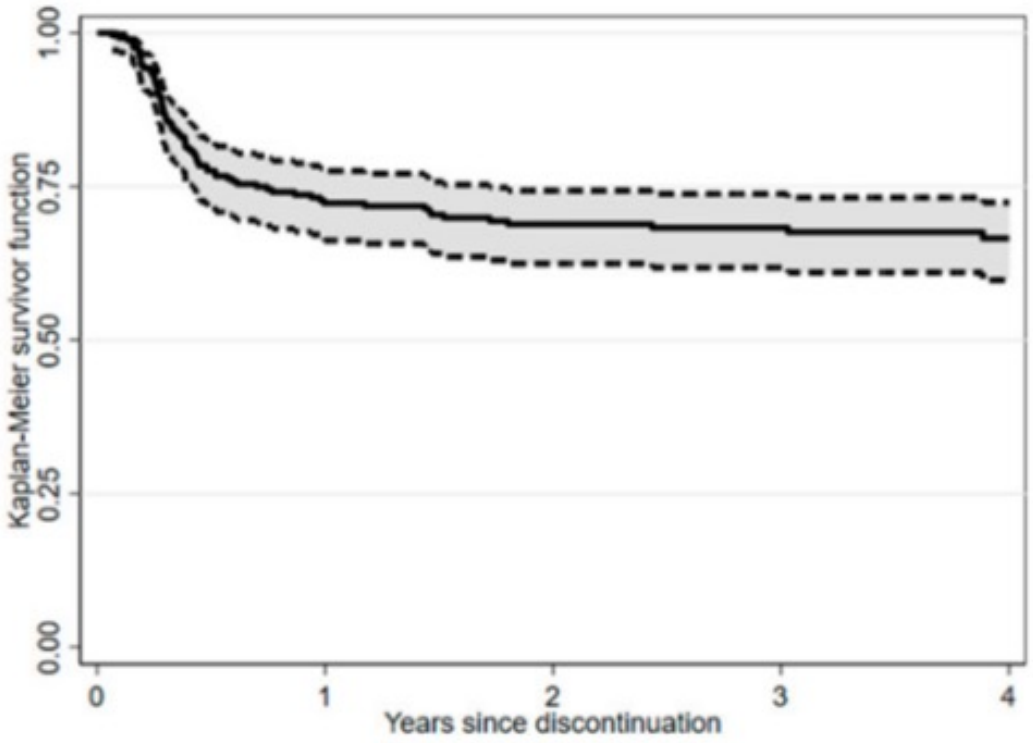
TIM-3 overexpressed in pts who relapsed after discontinuation



- 44 pts at the time of discontinuation: 22 relapsed
- Increased % of T-regs in patients who relapsed
- The immune checkpoint receptors PD-1, CTLA-4, LAG-3, and TIGIT on T or NK cells were not differentially expressed between the MolR and TFR groups
- TIM-3 was consistently upregulated on bulk T cells (CD3+) and T-cell subsets including, CD4+ T cells, CD8+ T cells, and T-regs, in patients who relapsed in comparison with those who maintained TFR after discontinuation.
- Increased TIM-3 expression on CML stem cells compared with normal hematopoietic stem cells.

Irani et al. Blood Adv 2022

TFR is not impaired by dose reduction in retrospective study



- 248 patients attempted TFR after dose reduction
- 172 (69.4%) were still in TFR after a median FU of 24.9 months

- TFR outcome was not influenced by gender, Sokal/ELTS score, prior IFN, number and last TKI received, DMR degree, or median TKI duration
- TFR was influenced by previous resistance to any TKI. A trend to better TFR was observed in patients with a long duration of therapy (> 6.8 years) and e14a2 type of transcript

Iurlo, et al. *Front Oncol 2023; 14: 1154377*

FASCINATION trial: asciminib and add-on with TKIs

- 144 newly diagnosed CP CML started with nilotinib 300 mg BID, dasatinib 100 mg QD and imatinib 400 mg
- 125 started the combination:
  - nilotinib + asciminib 20 mg BID (cohort 1) or
  - Nilotinib + asciminib 40 mg QD (cohort 2),
  - Dasatinib 100 mg +asciminib 80 mg QD (cohort 3)
  - Imatinib +asciminib 60 mg QD (cohort 4)
- Primary endpoint: rate of MR4 at 12 months
- Adverse events grade 3-4 in 37.6% of patients. 17% of total discontinuation due to toxicity

Cohort	TKI combination	No. pts recruited	No. pts eligible for molecular response at 12 months	MR4 rate at 12 months
1	nilo+asc 20 mg BID	30	28	32%
2	nilo+asc 40 mg BID	32	31	41.9%
3	dasa+asc 80 mg QD	32	27	33.3%
4	ima+asc 60 mg QD	31	28	42.9%

Ernst et al EHA 203; 2882

CONCLUSIONS

- Combination treatments as firstline strategy failed to improve the rate of TFR
- TFR as possible endpoint (need of identification of candidates)
- Still searching for new prognostic factors to predict a succesful discontinuation
- De-escalation strategy it seems the most promising approach before the discontinuation
- Future: studies designed for TFR
  - Combinations
  - Immnutherapy
  - Targeted therapies: quiescent cells

SOSPENSIONE DEL TRATTAMENTO CON INIBITORI DELLE TIROSIN KINASI IN PAZIENTI AFFETTI DA LEUCEMIA MIELOIDE CRONICA: ANALISI RETROSPETTIVA DI 442 PAZIENTI IN ITALIA

V. Bonuomo, P. Berchialla, E. Koumantakis, G. Rege-Cambrin, C. Elena, M. Bocchia, F. Castagnetti, T. Intermesoli, A. Iurlo, M.C. Miggiano, L. Luciano, E. Abruzzese, F. Lunghi, M. Breccia, B. Scappini, S. Crescenzi Leonetti, M. Annunziata, M. De Gobbi, D. Rapezzi, D. Luzi, S. Galimberti, F. Sorà, A.R. Scortechini, A. Maggi, M. Bonifacio, G. Beltrami, G. Caocci, L. Campiotti, F. Cavazzini, F. Stagno, C. Musolino, G. Pietrantuono, G. Saglio, D. Cilloni, C. Fava (Torino, Pavia, Siena, Bologna, Bergamo, Milano, Vicenza, Napoli, Roma, Firenze, Aversa, Cuneo, Terni, Pisa, Ancona, Taranto, Verona, Genova, Cagliari, Varese, Ferrara, Catania, Messina, Rionero in Vulture)

BACKGROUND

In the last 15 years different studies analyzed the outcome of patients with sustained deep molecular response (DMR) who discontinued tyrosine kinase inhibitors (TKIs), demonstrated that it is safe to discontinue treatment with tyrosine-kinase according to the current recommendations.

AIMS

To evaluate TFR in the setting of clinical practice for bringing out unmet clinical needs and optimizing already consolidated practices (atypical transcripts, >1 line of treatment, discontinuation in MMR, comparison between different treatment) and obtaining increasingly personalized treatment based on their disease profile.

METHODS

We proposed a retrospective and prospective observational study on patients with CML who discontinued TKIs in 36 centers in Italy.

National Comprehensive Cancer Network NCCN Clinical Practice Guidelines in Oncology 2024

Patient's characteristics:

- Median age was 60 yrs
- Sokal score was high in 18% of pts who discontinued a 2° gen TKI vs 9% of pts in 1° gen group
- 54% of pts discontinued Imatinib
- 45% of pts discontinued a 2° gen TKI
- 10% of pts carried an atypical transcript

	Overall (N=509)	I Generation (N=277)	II Generation (N=232)
Sex Male	271	153 /55,2%)	118 (50,9%)
Age at disc.	60 (48-71)	61 (50-70)	50 /47-71)
Sokal low	257 (53,9%)	157 (59,2%)	100 (47,2%)
Sokal interm.	158 (33,1%)	84 (31,7%)	74 (15%)
Sokal high	62 (13%9	24 (9,1%9)	38 (18%)
ELTS low	186 (73,8%)	112 (76,7%	74 (69,8%)
ELTS interm.	52 (20,6%)	29 (19,9%)	23 (21,7%)
ELTS high	14 (5,6%)	5 (3,4%)	9 (8,5%)
b2a2	115 (26,6%)	62 (25,8%)	53 (27,5%)
b3a2	308 (71,1%)	174 (72,5%)	134 (69,4%)
rare	10 (2,3%)	4 (1,7%)	6 (3,1%)
Last treat. before discontinuation			
Imatinib generator	249 (48,9%)		
Imatinib generics	25 (5,5%)		
Nilotinib	146 (28,7%)		
Dasatinib **Bosutinib**	81 (15,9%) 5 (1,0%)		

p-value<0.01

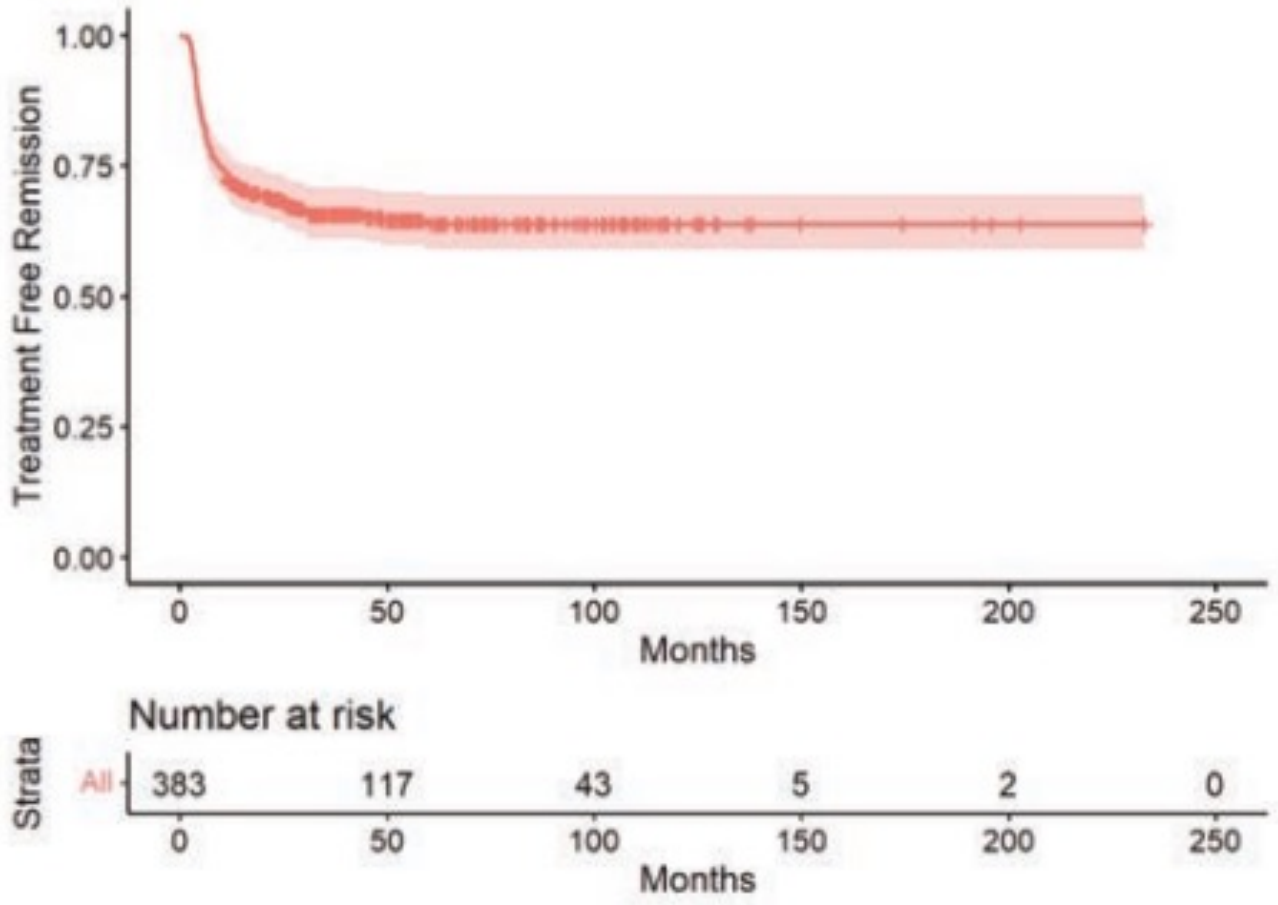
Patient's characteristics:

- No differences in terms of depth of MR at discontinuation time
- Duration of treatment was significally longer in pts who discontinued Imatinib vs 2° gen (110 vs 60 mo.)
- Time to attempt DMR was shorter in pts who discontinued 2° gen TKI and also the duration of DMR before discontinuation (time to DMR 23 vs 11 mo; duration of DMR 79 VS 47 mo)

	Overall (N=509)	I Generation (N=277)	II Generation (N=232)	P-value
	271	153 /55,2%)	118 (50,9%)	
MR at discontinuation				0.72
Minor of MMR	3 (0,6%)	1 (0,4%)	2 (0,9%)	
MMR	25 (5,2%)	11 (4,2%)	14 (6,4%)	
MR4	141 (29,1%)	79 (29,9%)	62 (28,2%)	
MR4.5	181 (37,4%)	97 (36,7%)	84 (38,2%)	
MR5	124 (27,7%)	76 (28,8%)	58 (26,4%)	
Duration of treatment	97 (68—126)	110 (79-144)	60 (42-80)	<0.01
Duration of last TKI	82 (55-121)	97 (71-122)	96 (65-135)	0.65
Time to DMR	17 (7-33)	23 (11-47)	11 (5-23)	<0.01
Duration of DMR	63 (39-94)	79 (54-103)	47 (31-68)	<0.01
Reason of discontinuation				
Toxiticy	99 (19,8%)	29 (10,5%)	70 (31,4%)	
Pregnancy	26 (5,2%)	13 (4,7%)	13 (5,8%)	
Shared decision	322 (64,5%)	195 (70,7%)	127 (57%)	
Other	52 (10,4%)	39 (14,1%)	13 (5,8%)	

Outcome by 10 years: KM analysis of TFR

- Median follow-up at the TKI restart was 21 months (range: 6-53)
- The probability of remaining in TFR in the first year after TKI discontinuation is around 75% (95%CI: 72%-80%), while decreases at 68% at 4 years (95%CI: 63%-72%)



CONCLUSIONS

- Discontinuation of salvage TKI in pts with a history of resistance, warning or lack of DMR is feasible. In our serie no pts progressed to AP/BP

- Discontinuation of 2° gen (unrespect of the line therapy) seems to be more successful than 1° gen discontinuation

- Whether ponatinib discontinuation may be more successful than 2° generation TKI discontinuation is an open question

- The Depht of molecular response still have a crucial role in prognosis (undetactable transcripts?)

- Such study should continue to collect more pts and increase results reliability