I fattori prognostici della durata della TFR

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Thousands of patients have discontinued TKIs in "interventional" protocols

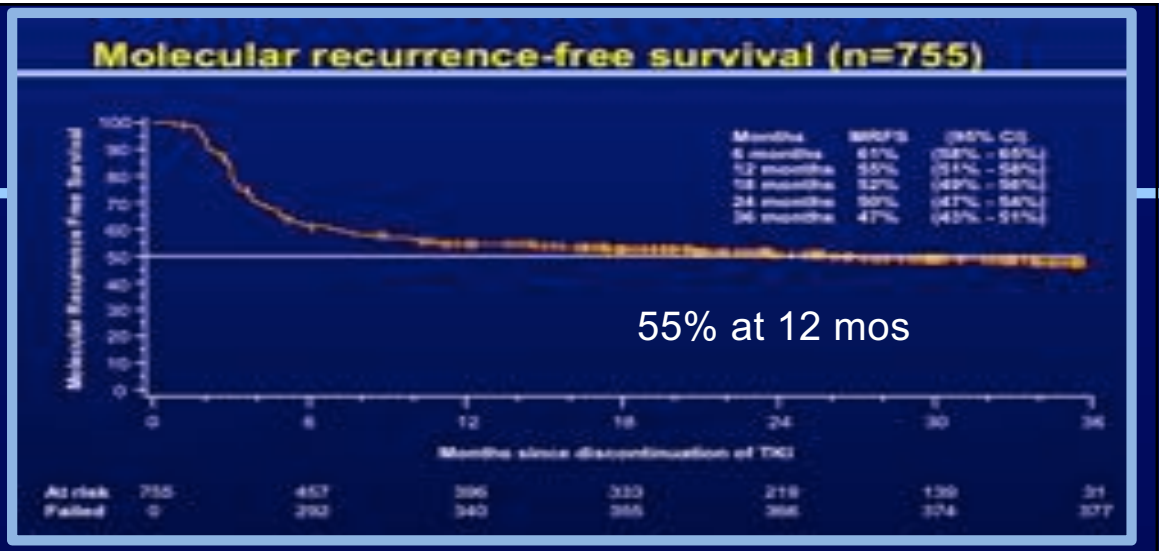
Only two cases of progression have been reported!

EURO-SKI design

N=755

TKI treatment
≥ 3 years

MR^4
≥ 1 year



Screening phase (confirmation of MR^4 in central lab)	RQ-PCR	RQ-PCR every 3rd month
	q4w q6w	
≤ 6 weeks	Year 1	Year 2 Year 3

Informed consent → Stop TKI → Follow-up

Molecular recurrence defined as BCR-ABL >0.1%
(loss of MMR) at one time point

Saussele, et al; Lancet Oncology 2018

Patient characteristics

	Patients included N = 755
Sex, Female %	47.9
Age at diagnosis, median years (range)	52 (11–86)
Age at stopping, median years (range)	61 (20–90)
Duration of TKI treatment, years (range)	**8 (3–14)**
Duration of MR4 before stopping TKI, years (range)	**5 (1–13)**
High risk, % EUTOS Sokal	 8 17.5

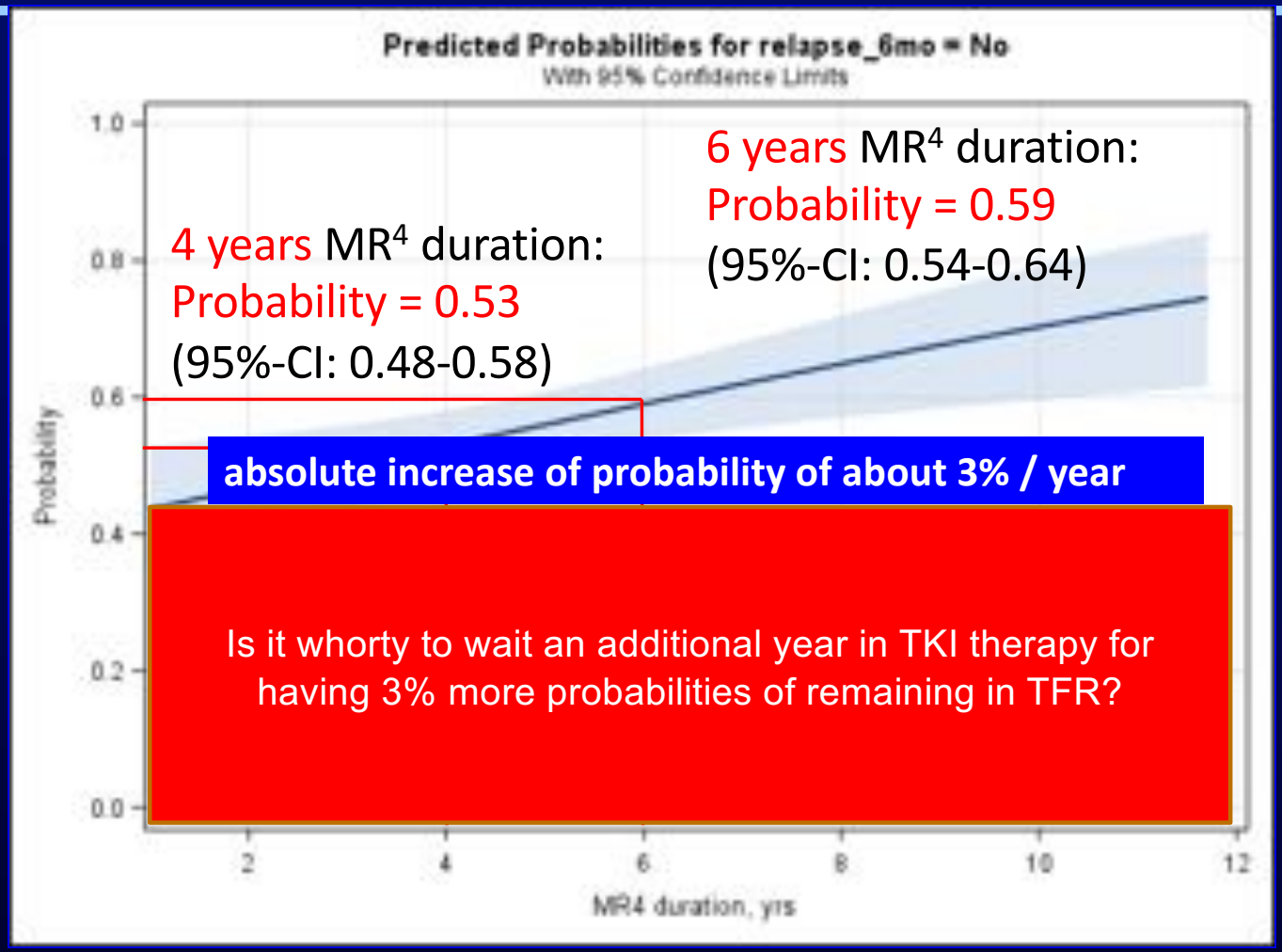
Saussele et al., Lancet Oncology 2018

Variables recorded at TKI discontinuation

	Odds ratio (95% CI)	p value
Age at stop of TKI (years)†	1·09 (0·95–1·26)	0·21
Interferon pre-treatment	..	0·0013
No	..	..
Yes	2·50 (1·43–4·36)	..
Duration of interferon pre-treatment (years)	1·38 (1·12–1·69)	0·0022
Duration of TKI treatment (years)	1·16 (1·08–1·25)	<0·0001
DMR duration while receiving TKI (years)	1·16 (1·08–1·25)	0·00011
Time of TKI treatment before DMR (years)	1·02 (0·93–1·13)	0·66

Saussele et al., Lancet Oncology 2018

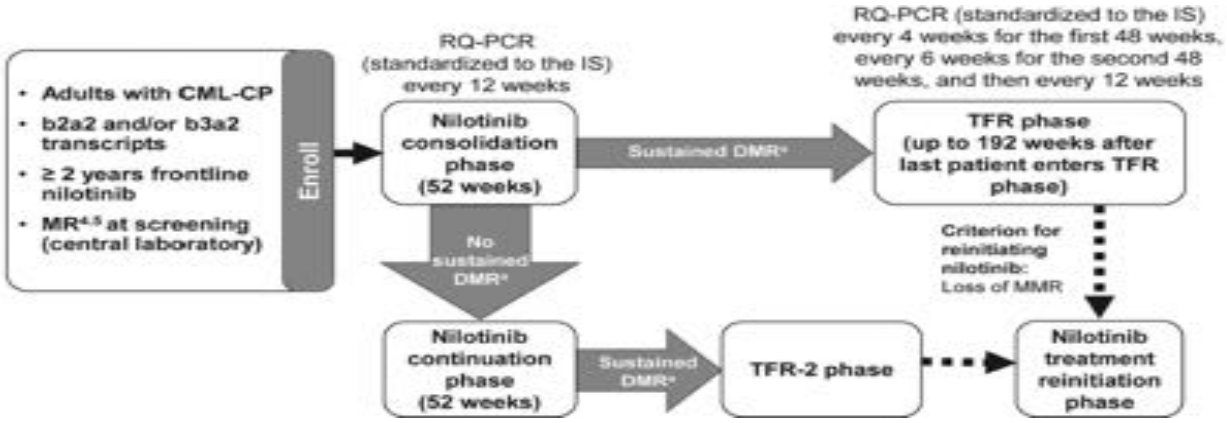
MR^4 duration, n = 405



ORIGINAL ARTICLE

Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study

A Hochhaus[1], T Masszi[2], FJ Giles[3], JP Radich[4], DM Ross[5], MT Gómez Casares[6], A Hellmann[7], J Stentoft[8], E Conneally[9], V García-Gutiérrez[10], N Gattermann[11], W Wiktor-Jedrzejczak[12], PD le Coutre[13], B Martino[14], S Saussele[15], HD Menssen[16], W Deng[17], N Krunic[18], V Bedoucha[16] and G Saglio[19]



N=190

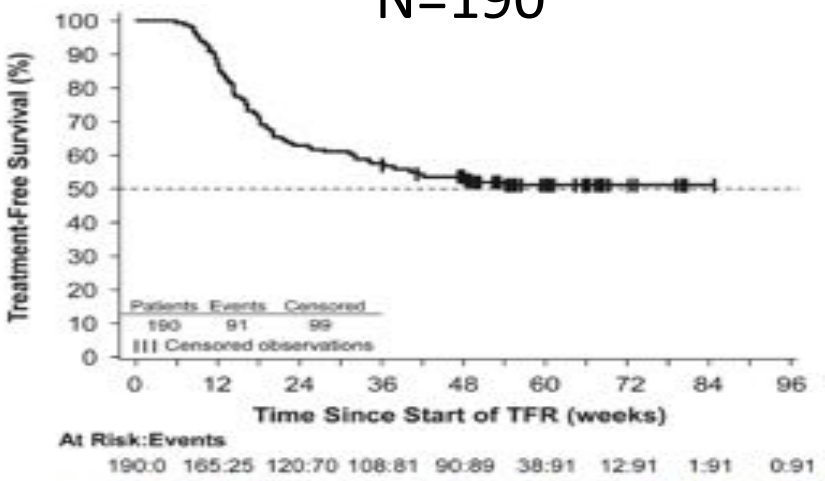


Figure 3. Kaplan–Meier estimate of TFS among all patients who entered the TFR phase. TFS was defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to AP/BC or death because of any cause.

In ENESTfreedom, 51.6% (95% CI, 44.2–58.9) of patients remained in remission at 48 weeks after stopping nilotinib.

The importance of TIME

	EuroSKI	ENESTfreedom
TKI	Mainly IM	NIL
Median TKI duration	7.5 years	3.6 years
Deep MR	$MR^{4.0}$	$MR^{4.5}$
Median DMR duration	4.7 years	1.5 years
2-year TFR rate	50%	52%

Mahon F, et al, ASH 2016; abstract 787;
Hochhaus A, et al, Leukemia 2017; 31:1525–1531.
IM, imatinib; NIL, nilotinib.

Is "***real life***" comparable with clinical studies? (safety/efficacy)

Observational study of chronic myeloid leukemia Italian patients who discontinued tyrosine kinase inhibitors in clinical practice

Fava C, et al. Haematologica 2019

Results

293 patients discontinued TKIs between June 2003 and February 2016

	Overall (n=293)	2nd generation (n=82)	Imatinib (n=211)
Reasons for Stop (%)			
Pt agreement	182 (62)	47 (57)	135 (64)
Toxicity	58 (20)	30 (37)	28 (13.5)
ISAV	34 (12)	0 (0)	34 (16)
Pregnancy	17 (6)	5 (6)	12 (6)
CHT for 2nd tum	1 (0)	0 (0)	1 (0.5)

Fava C, et al. Haematologica 2019

Results

- Median age at diagnosis: 49 years (IQR 38–60)
- Sex: 161 male, 132 female
- Sokal risk (263 patients): 59% low, 30% intermediate, 11% high
- At 3 months of last TKI
  - 34% of pts were in MR3,
  - 40% were in CCyR/ < 1%
  - 25% were in PCyR/ < 10%
- 211 patients on imatinib
- 82 patients with 2G TKIs
  - Nilotinib (n=58)
  - Dasatinib (n=23)
  - Bosutinib (n=1)
- Line of treatment:
  - 162 patients (55%) first line
  - 117 patients (40%) second line
  - 13 patients (4.5%) third line
  - One patient fourth line

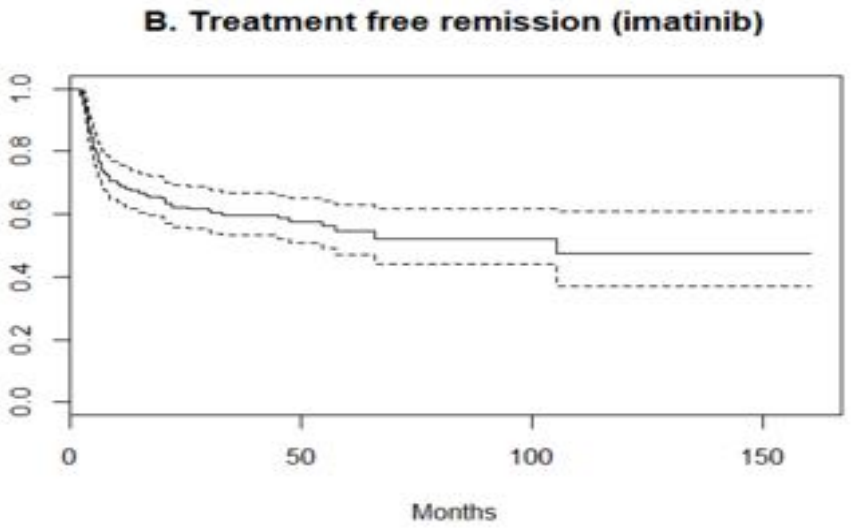
Fava C, et al. Haematologica 2019

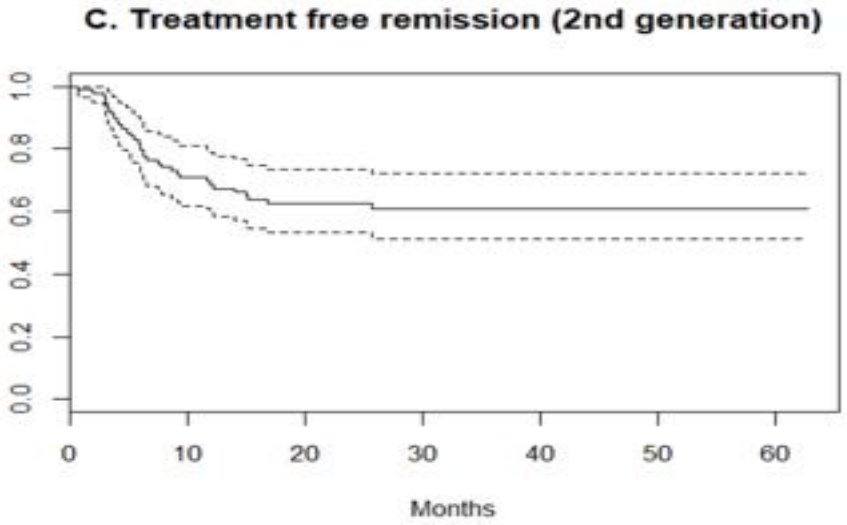
Results

Definition of DMR[4] at stop	Overall (n=293)
MR4	101 (35%)
MR4.5	90 (31%)
MR5	53 (18%)
Undetectable	46 (16%)

	Imatinib	II Gen	Overall	
Duration of last TKI, mos (median [IQR])	96 [62, 120]	50 [32, 66]	77 [54, 111]	<0.001
Duration of treatment with any TKIs, mos (median [IQR])	96 [62, 120]	73 [51, 96]	87 [59, 117]	0.002
Duration of total treatment, mos (median [IQR])	104 [73, 142]	76 [52, 109]	98 [65, 133]	<0.001
Time to DMR, mos (median [IQR])	24 [12, 52]	13 [6, 26]	21 [10, 42]	<0.001
Duration of DMR, mos (median [IQR])	53 [33, 82]	36 [25, 46]	46 [30, 73]	<0.001

Fava C, et al. Haematologica 2019.





	Time	No at risk	No of events	TFR	95%CI	
Overall	12	203	90	69,3%	64,2%	74,8%
Imatinib	12	143	68	67,8%	61,8%	74,4%
	26	102	12	61,4%	55,1%	68,4%
	42	66	2	60,0%	53,6%	67,2%
2nd generation	12	60	22	73,2%	64,2%	83,4%
	26	32	5	66,9%	57,4%	77,9%

Fava C, et al. Haematologica 2019.

A Retrospective Analysis about Frequency of Monitoring in Italian Chronic Myeloid Leukemia Patients after Discontinuation

- 227 chronic phase CML pts
- Median follow-up since TFR was 2 ys
- 55 pts (78%) lost MMR during the first six mos
- Every patient had a mean of 8 appointments for molecular evaluation
- In the first 6 mos the visits occurred with a mean interval of 1.5 mos
- Between mos 7-12 molecular evaluations were performed every 2 mos
- During the second yr of discontinuation every 3 mos

Dragani et al Poster ASH2020

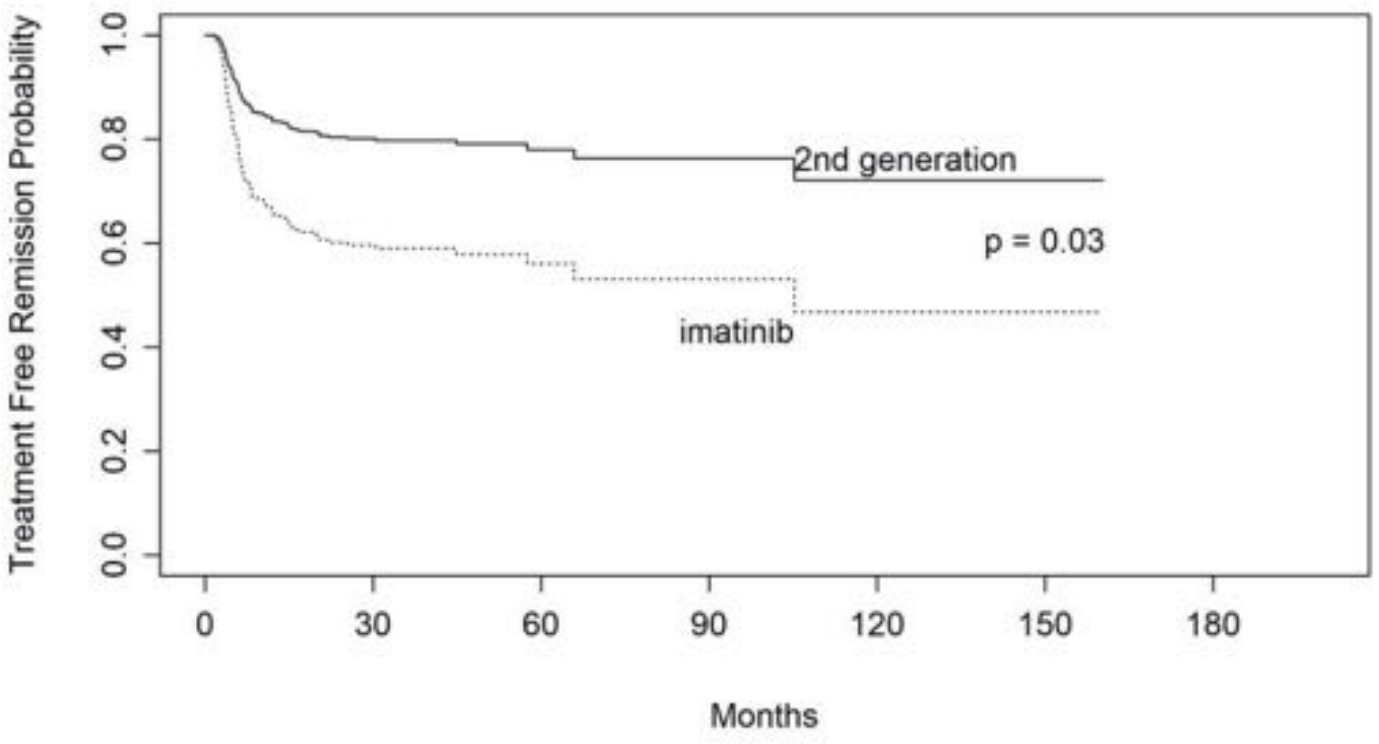
Prognostic Factors for TFR

Multivariate Cox regression analysis for restarting therapy. Figures reported are hazard ratios (HRs) and 95% confidence intervals (95%CI).

	HR	95%CI		p-value
Age at discontinuation (10 yrs difference)	0.84	0.73	0.97	0.02
Sokal score				
Intermediate vs low	0.92	0.54	1.57	0.76
High vs low	2.07	1.16	3.71	0.01
Line of therapy: 2nd vs 1st line	0.80	0.50	1.30	0.37
2nd generation TKIs vs imatinib	0.43	0.20	0.91	0.03
Duration of total therapy (1 yr increase) in patients treated with imatinib	1.00	0.94	1.07	0.90
Duration of total therapy (1 yr increase) in patients treated with 2nd generation TKIs	0.78	0.65	0.93	0.01

Fava C, et al. Haematologica 2019.

TKI-TFR curves adjusted for age at discontinuation, Sokal score, line of therapy and duration of therapy.



Fava C, et al. Haematologica 2019.

Conclusions

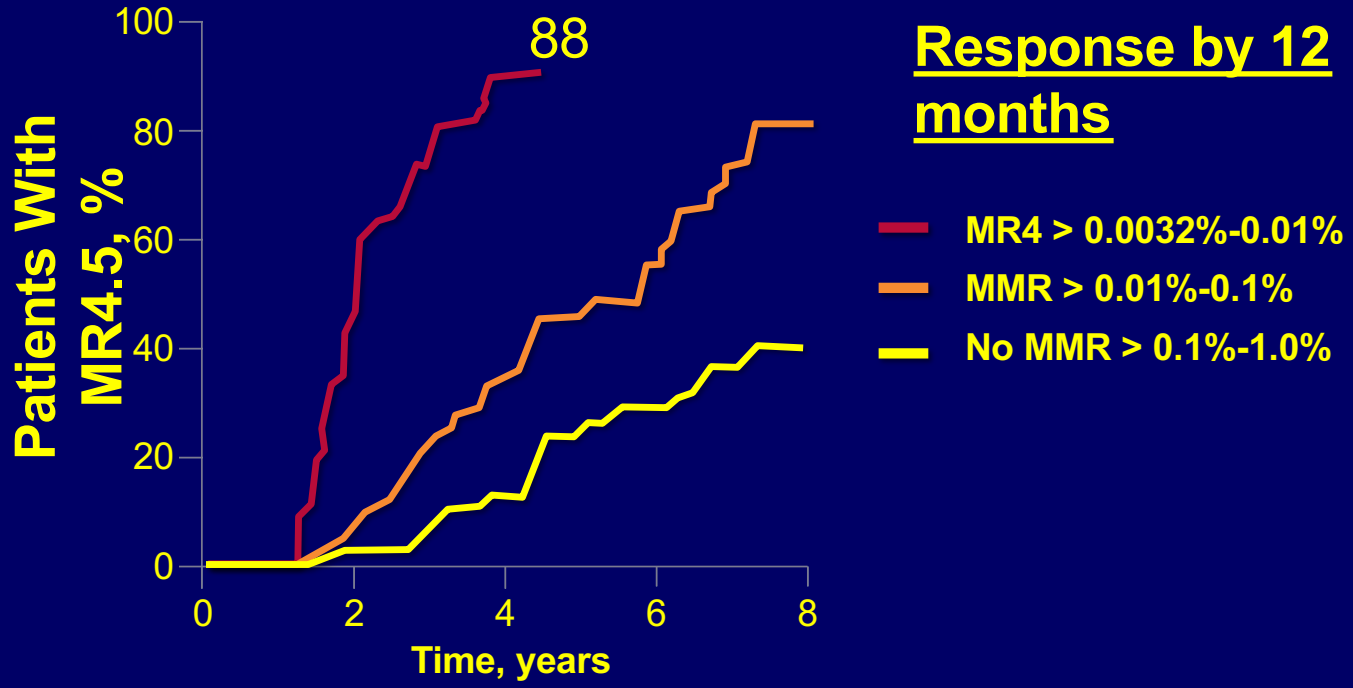
- Our experience, aligned to the literature, confirms that treatment discontinuation is feasible and safe for CML patients treated with TKIs
- No progressions or CML-related death occurred among our patients
- Patients who were retreated regained at least MMR
- At multivariate analysis, factors associated with TFR were older age, low vs high Sokal risk, treatment with 2nd generation TKIs (with an estimated 57% relative risk reduction) and treatment duration in patients treated with 2nd generation TKIs
- High quality molecular monitoring as obtained in the Labnet network Is needed for safe discontinuation

The most important criteria is probably represented by the depth and the duration of the Deep Molecular Response and……

by the time to DMR achievement

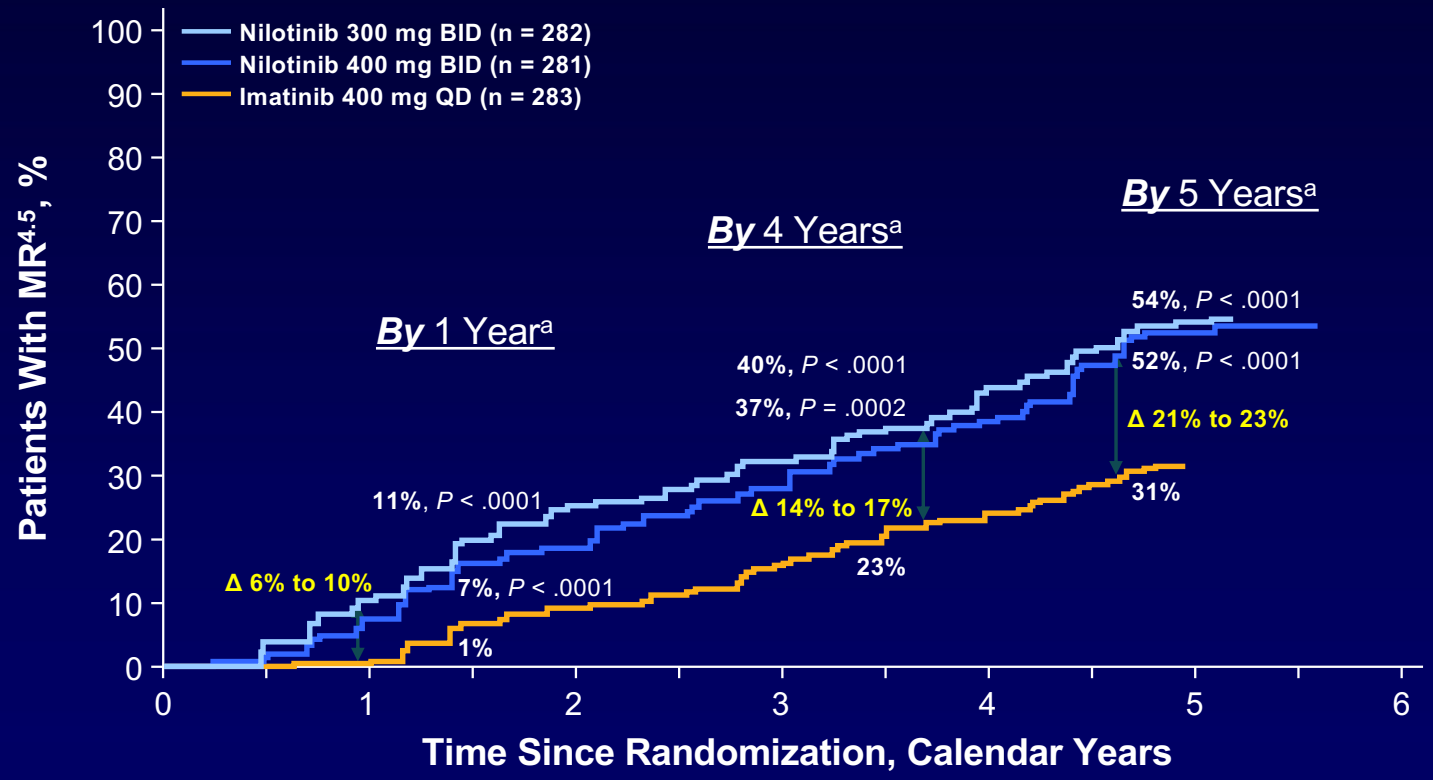
MMR at 12 Months Is Associated With Increased Long-Term Probability of Reaching MR4.5

Impact of Response to Imatinib by 12 Months on 8-Year Incidence of MR4.5 (N = 528)



Branford S, et al. *Haematologica*. 2015;100(s1) [abstract S490].

Cumulative Incidence of MR$^{4.5}$

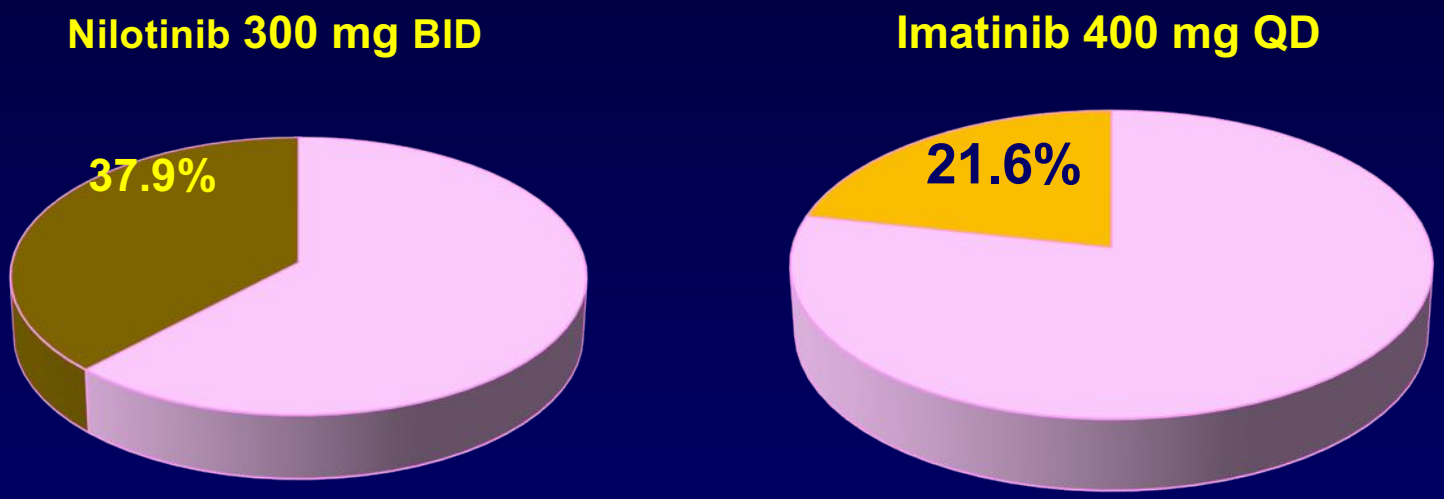


MR$^{4.5}$, molecular response ≥ 4.5-logs (*BCR-ABL*^{IS} ≤ 0.0032%).

[a] Cumulative response rates reported consider each year to consist of twelve 28-day cycles.

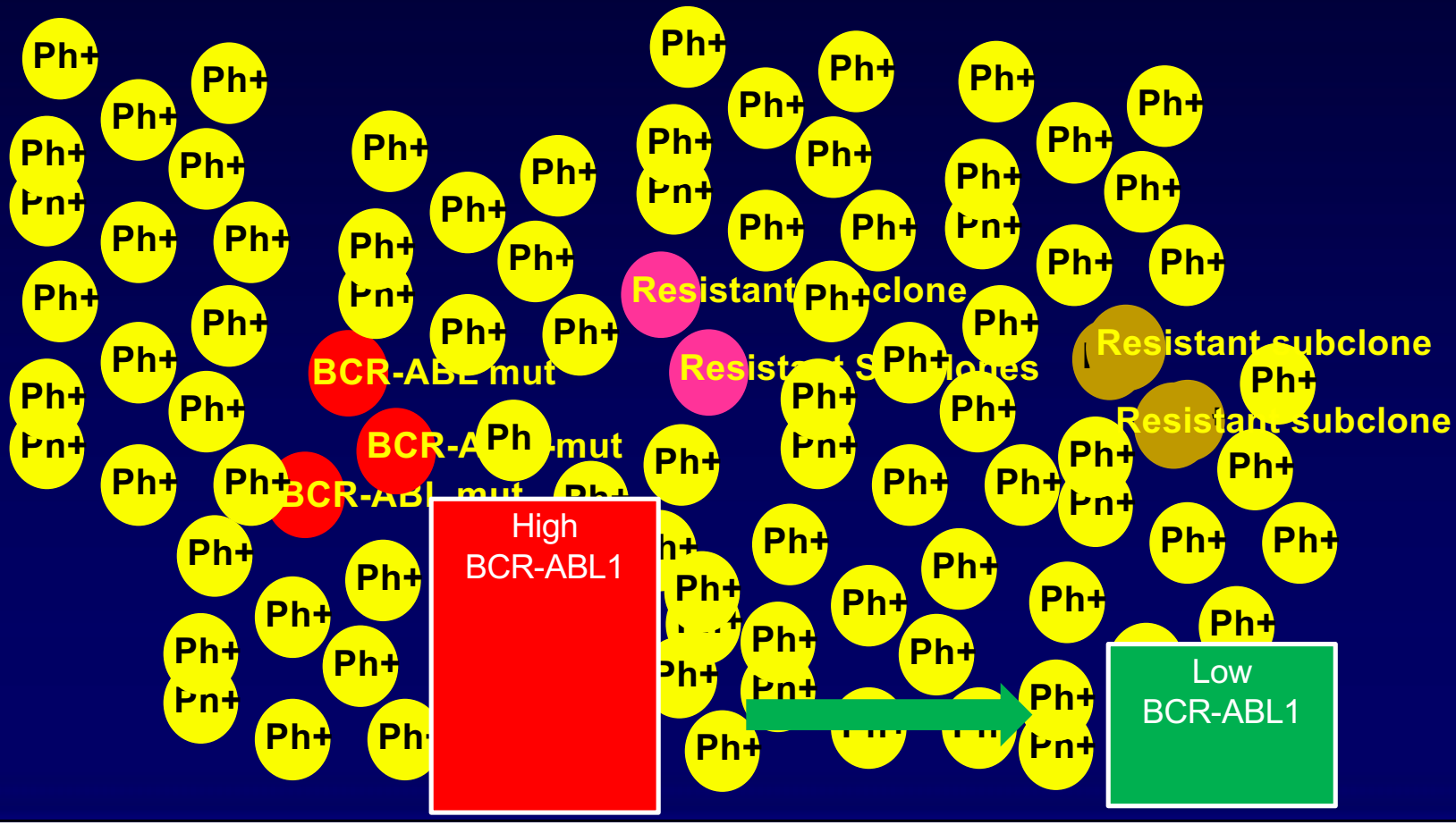
Hochhaus A.et al, Leukemia 2016

Patients who met stringent criteria for attempting TFR in the ENESTnd study

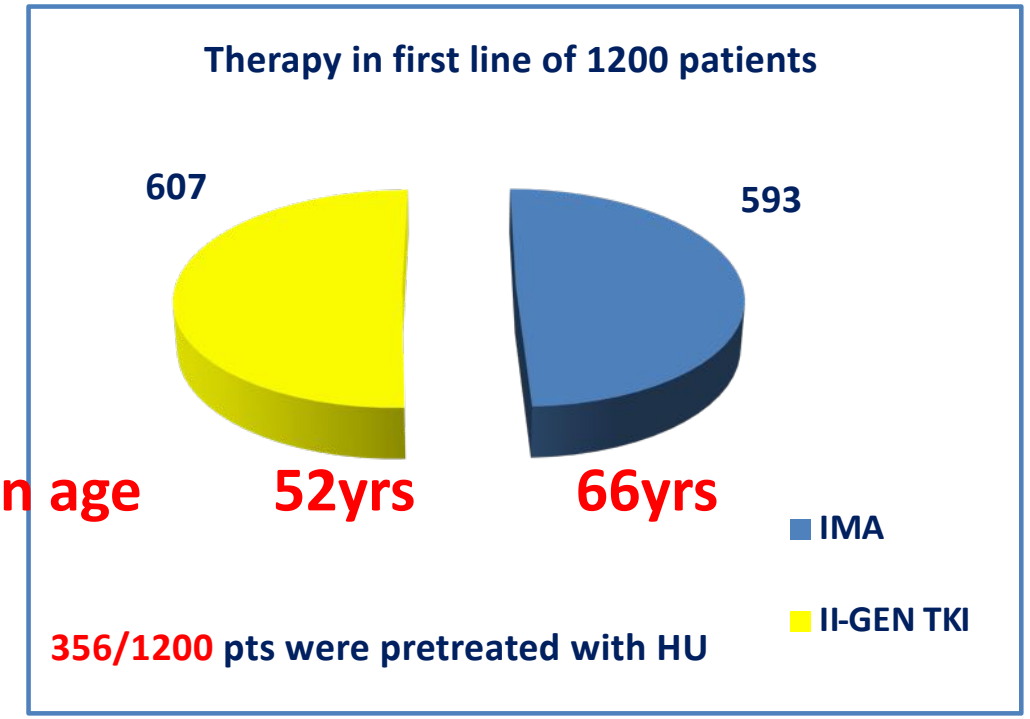


Hochhaus A. et al, ASH 2015

Possible biological basis: the patients who respond faster have less subclonal complexity



CML-IT-MOS
Analysis of TKI used in first line Therapy



Specchia G. et al., ASH 2018

ELN 2020?

Milestones	**Failure**	**Optimal for OS***	**Optimal for TFR****
3 Months	BCR-ABL > 10% If confirmed#	BCR-ABL≤10%	BCR-ABL≤10%
6 Months	BCR-ABL > 10%	BCR-ABL ≤ 10%	BCR-ABL ≤1%
12 months	BCR-ABL > 1%	BCR-ABL ≤ 1%	BCR-ABL ≤0.1%
24 months	BCR-ABL > 0.1%		BCR-ABL ≤0.01%
Anytime	Relapse, Loss of MMR		

Hughes' and Saglio' suggestion

Thanks to doctors, biologist and patients…

List will never be complete!

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