CML HORIZONS
HYBRID MEETING 2024
Vilnius, Lithuania
24–26 May 2024

Predictors of Successful TFR - what have we learned - Drs‘ perspective

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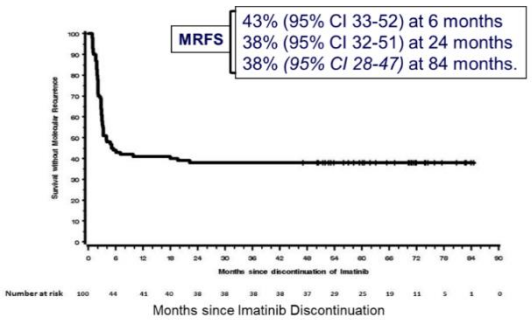
DEUTSCHE CML.ALLIANZ

TFR after Stop of First- and Second Generation TKI

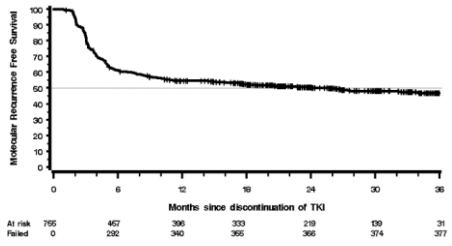
[1]Etienne et al. *J Clin Oncol* 2017;35:298, [2]Saussele et al. *Lancet Oncol* 2018;19:747-7. [3]Shah et al. *Blood* 2017;130,Suppl 1, 314], [4]Ross et al. EHA 2019, [5]Mahon et al. EHA 2019.

Imatinib

STIM (N=100)[1]



EURO-SKI (N=755)[2]



2ndG-TKI

DASFree (N=84)[3]

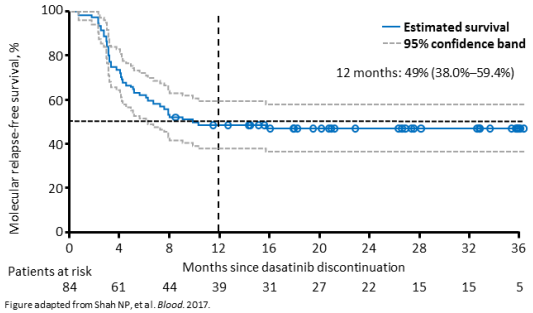
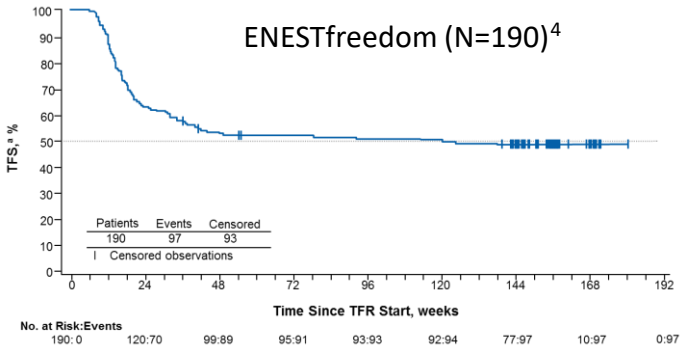
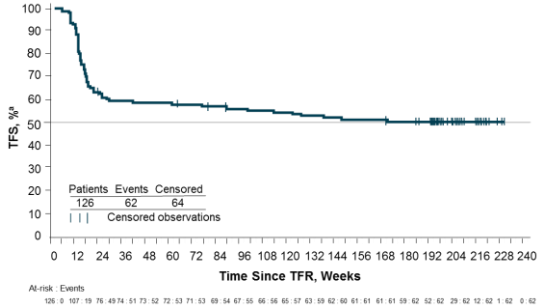


Figure adapted from Shah NP, et al. *Blood*. 2017.

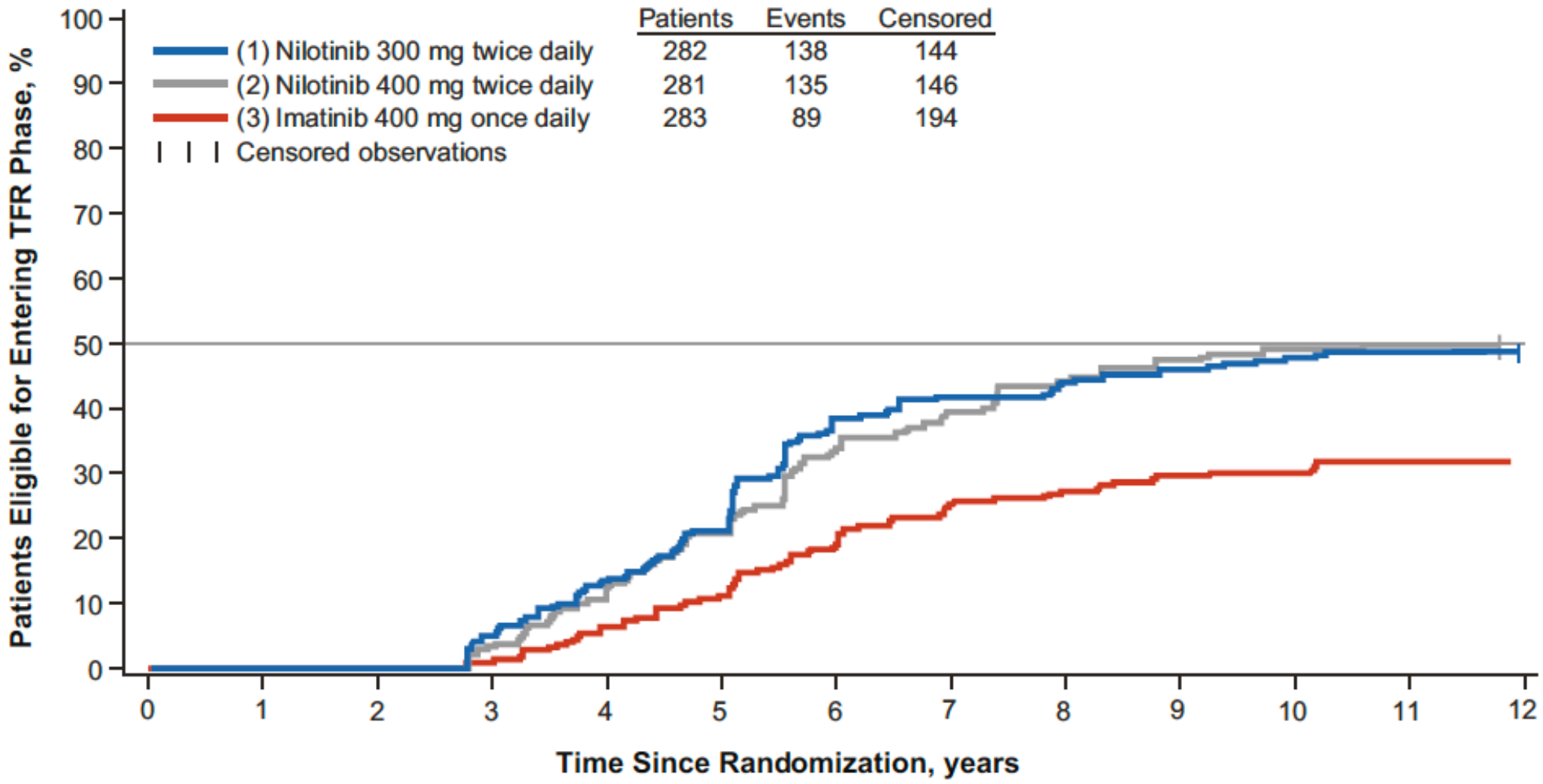
ENESTfreedom (N=190)[4]



ENESTop (N=126)[5]

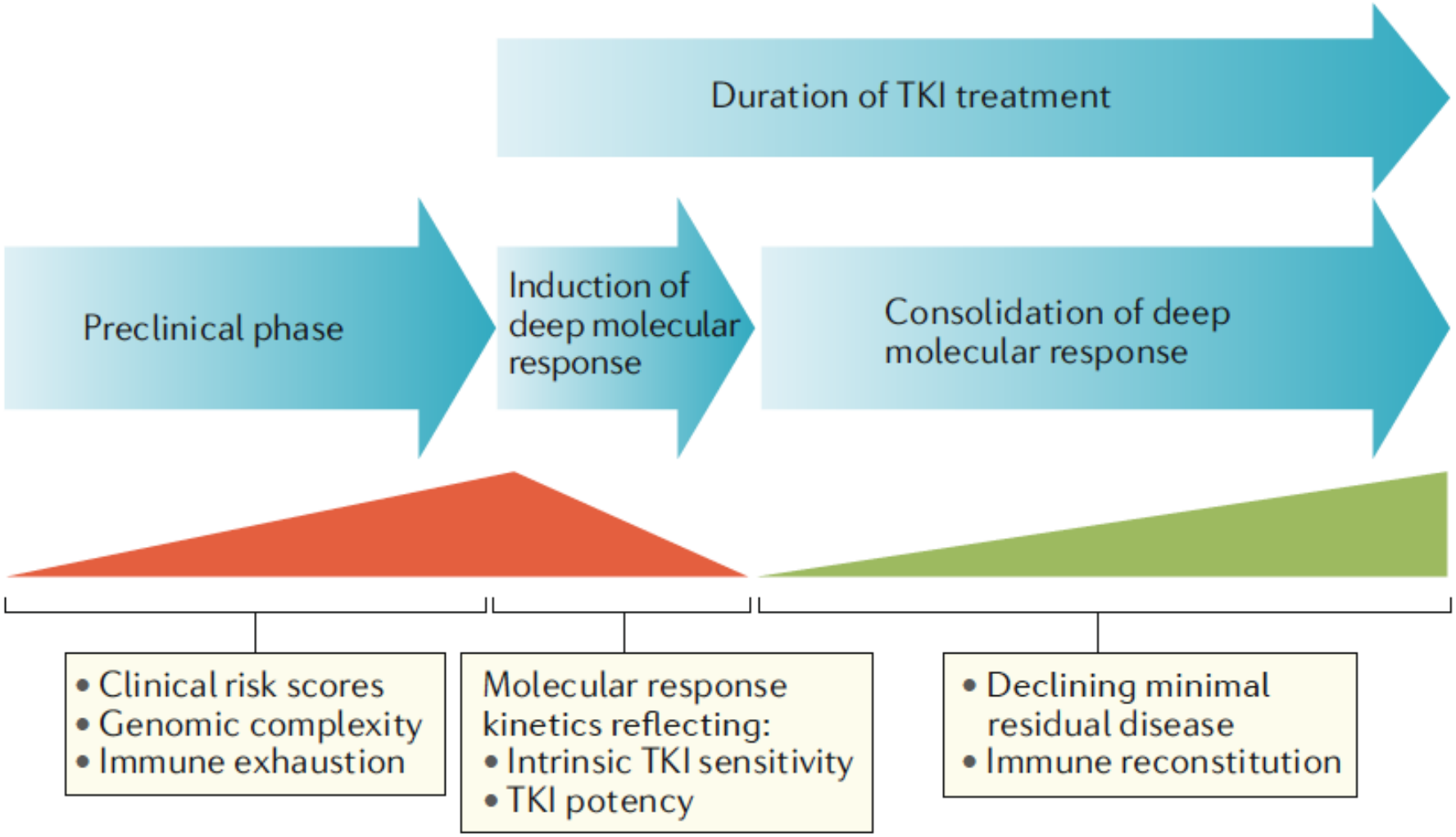


Cumulative rate of TFR eligibility (ENESTnd)



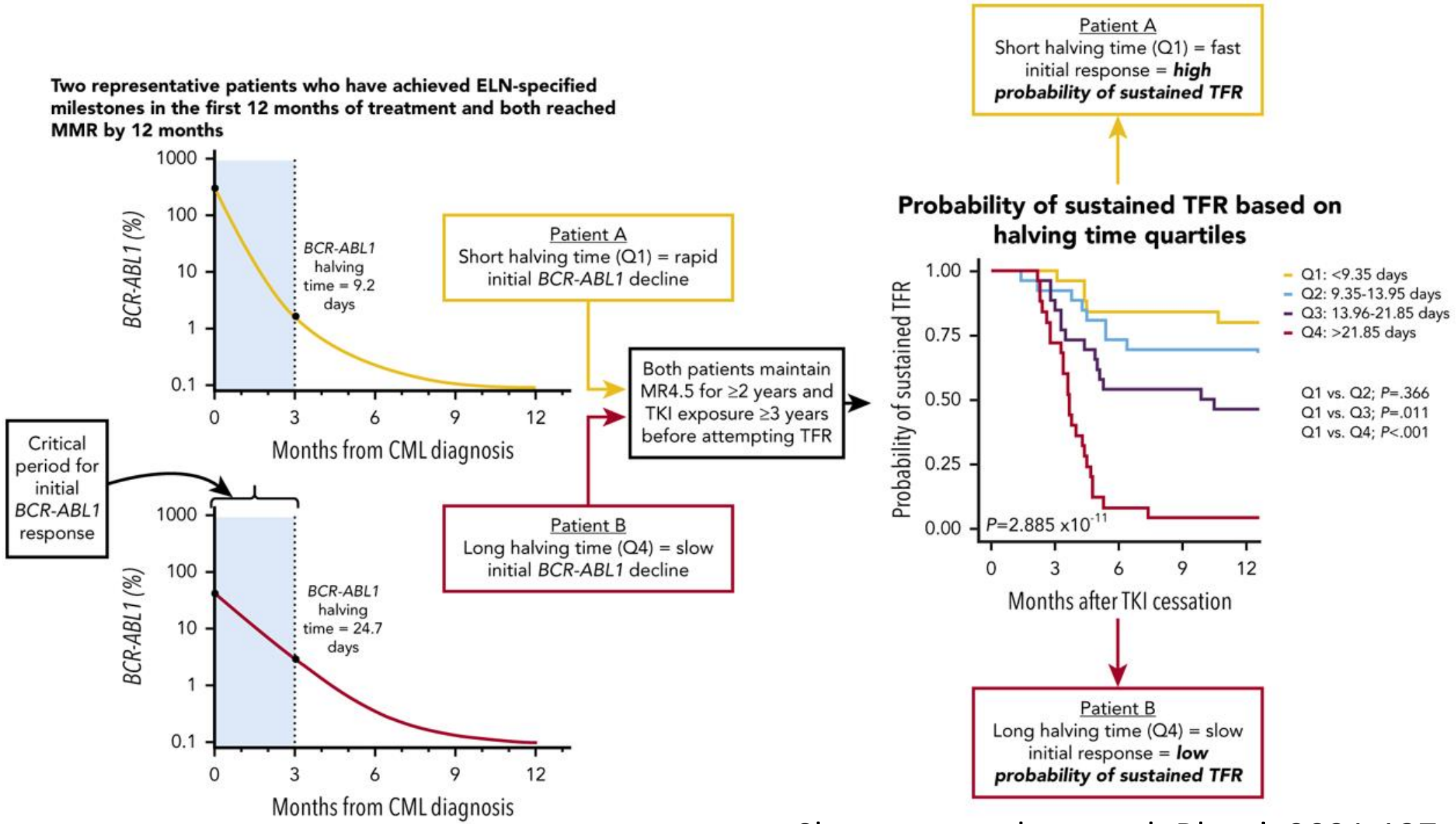
Kantarjian et al. Leukemia. 2021; 35:440-53

Hypothetical relationship between duration of treatment and outcomes of TFR



Ross & Hughes. Nat Rev Clin Oncol. 2020;17:493-503

Early BCR::ABL1 kinetics are predictive of subsequent TFR



Shanmuganathan et al. Blood. 2021;137:1196-207

ELN 2020 treatment milestones (First- and second line)

	Optimal	Warning	Failure
Baseline		High risk-ACA High risk ELTS score	
3 months	BCR::ABL1 ≤10%	BCR::ABL1 >10%	BCR::ABL1 >10%, if confirmed within 1-3 months
6 months	BCR::ABL1 ≤1%	BCR::ABL1 >1-10%	BCR::ABL1 >10%
12 months	BCR::ABL1 ≤0.1%	BCR::ABL1 >0.1-1%	BCR::ABL1 >1%
Any time	BCR::ABL1 ≤0.1%	BCR::ABL1 >0.1-1%, Loss of MMR	BCR::ABL1 >1%, Resistance mutations, High-risk ACA

For patients aiming at TFR, optimal response (at any time) is MR^4 (BCR::ABL1 ≤0.01%)

Leukemia 2020; 34:966

ELN European LeukemiaNet

The panel agrees that TFR is a new significant goal of CML management.
It recommends consideration of TFR in appropriate patients after careful discussion employing the concept of shared decision making.

Treatment may be changed to 2GTKI to improve the depth of response in selected patients in whom DMR has not been reached.

In special situations such as the motivated patient with a high priority for TFR, younger patients with low or intermediate risk disease or women who wish to become pregnant, a change to 2GTKI is recommended for consideration.

The vision for the next 5 years is that more CML patients will successfully achieve TFR and that it will be possible to talk more confidently about the curability of CML.

ELN recommendations 2020. Leukemia. 2020; 34:966-84

Requirements for tyrosine kinase inhibitor discontinuation

Mandatory:

- CML in first CP only
- Motivated patient with structured communication
- Access to high quality quantitative PCR using the International Scale (IS) with rapid turn-around of PCR test results
- Patient's agreement to more frequent monitoring after stopping treatment:
  Monthly for the first 6 months, every 2 months for months 6-12, and every 3 months thereafter.

Minimal (stop allowed):

- First-line therapy or second-line if intolerance was the only reason for changing TKI
- Typical e13a2 or e14a2 BCR::ABL1 transcripts
- Duration of TKI therapy >5 years (>4 years for 2GTKI)
- Duration of DMR (MR^4 or better) >2 years
- No prior treatment failure

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 $MR^{4.5}$

Leukemia 2020; 34:966-84

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Leukemia 2020; 34:966-84

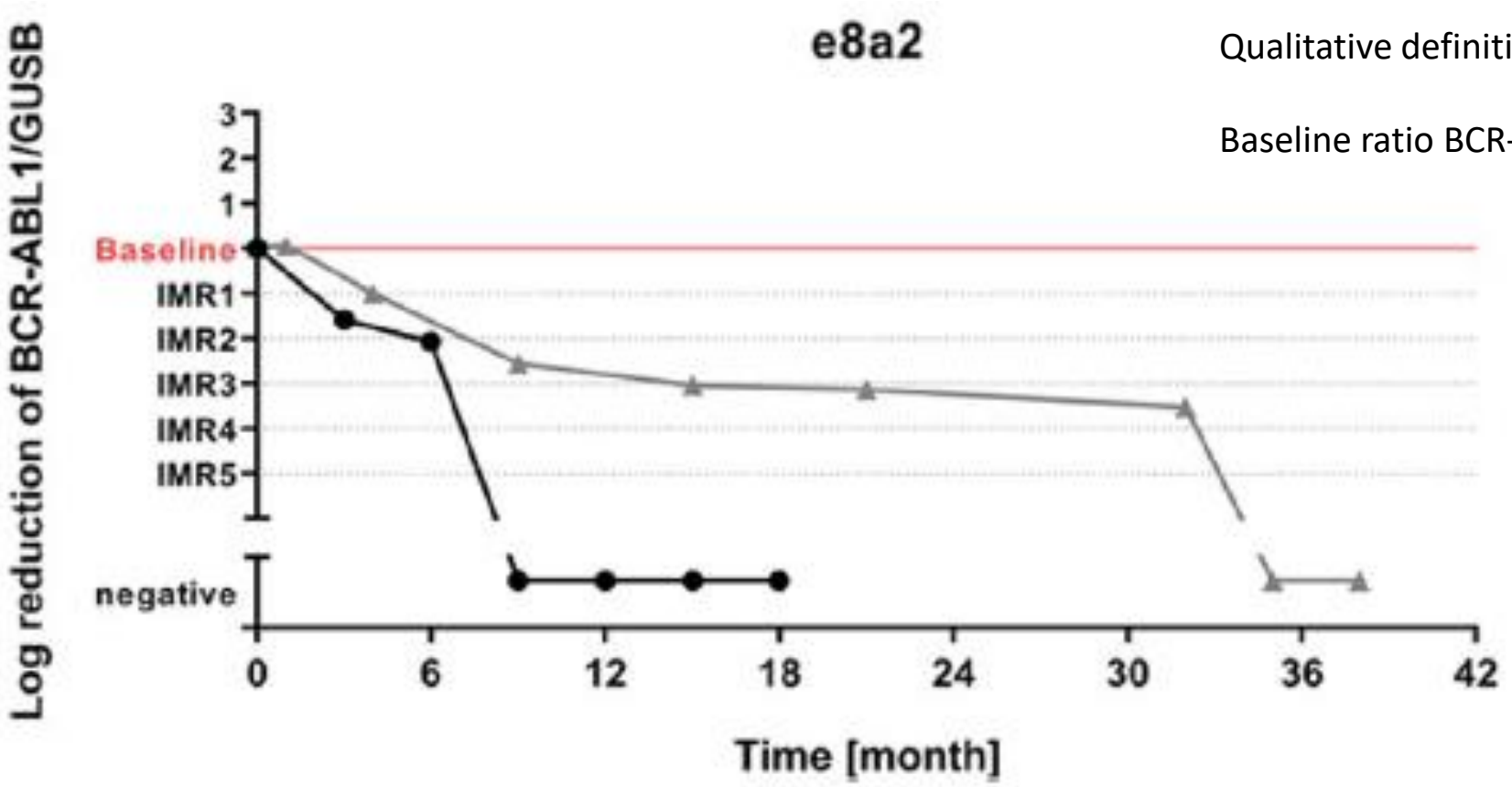
CASE REPORT:

32 y.o. male patient, e19a2 *BCR::ABL1* transcript, T315I mutation.

(CABL001X2101) Complete molecular remission on asciminib.

10/11	Dx. CML, CP/AP, e19a2 BCR::ABL1 transcript 46,XY,t(9;22)(q34;q11) Basophilia 21% ELTS intermediate risk
10/11	HU
11/11	Nilotinib ENEST1st study
2/12	„MMR“
8/12	PCR negative, 4 log sensitivity
2/14	loss of MMR
5/14	T315I mutation
6/14	Ponatinib 45 mg/d Hypertension, erectile dysfunction
9/14	Ponatinib 30 mg/d
10/14	„MMR“
4/15	Ponatinib + Peg-Intron
7/15	BCR::ABL1 0.01%, T315I mutation negative
8/15	Continuation of ponatinib ? Allo-SCT ?, asciminib phase I study Asciminib (phase 1)
1/16	Lipase elevated Grade 1 Asciminib dose reduction
10/15	PCR negative (5 log sensitivity)
....	
10/22	PCR negative (5 log sensitivity)
since 11/22	TFR; PCR negative (5 log sensitivity)

Proposal: “Individual molecular response (IMR)” for response assessment in patients with atypical transcripts



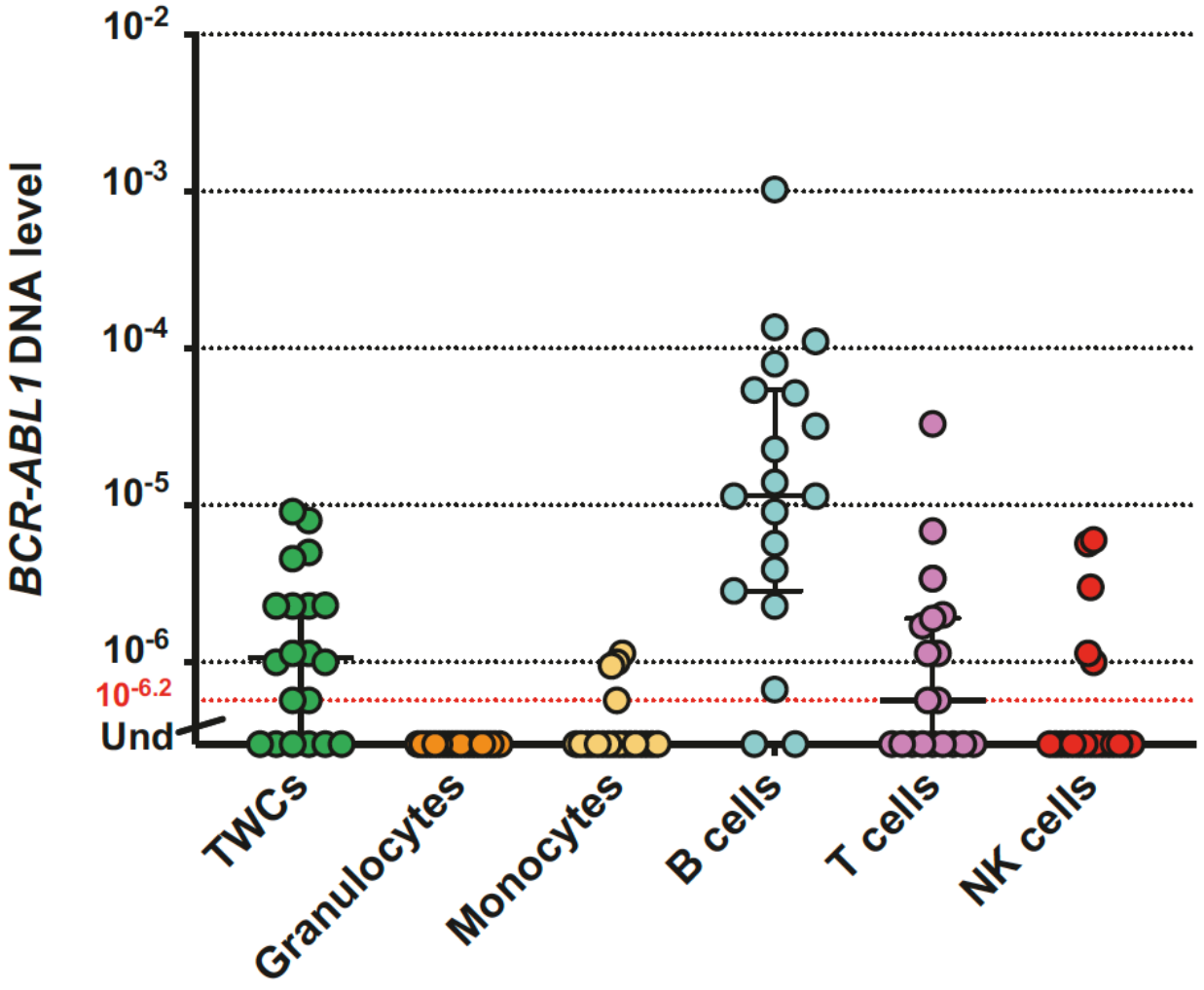
Requirements:

Qualitative definition of the BCR-ABL1 transcripts

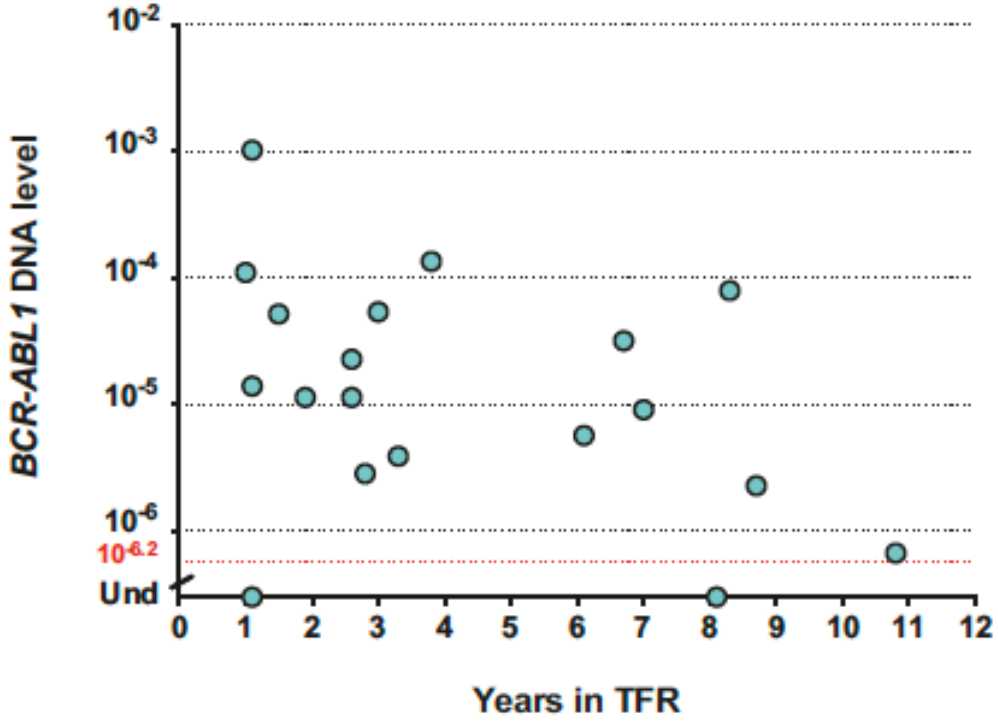
Baseline ratio BCR-ABL1/GUS

Schäfer et al. J Cancer Res Clin Oncol., 2021

Lineage of measurable residual disease in CML patients in TFR

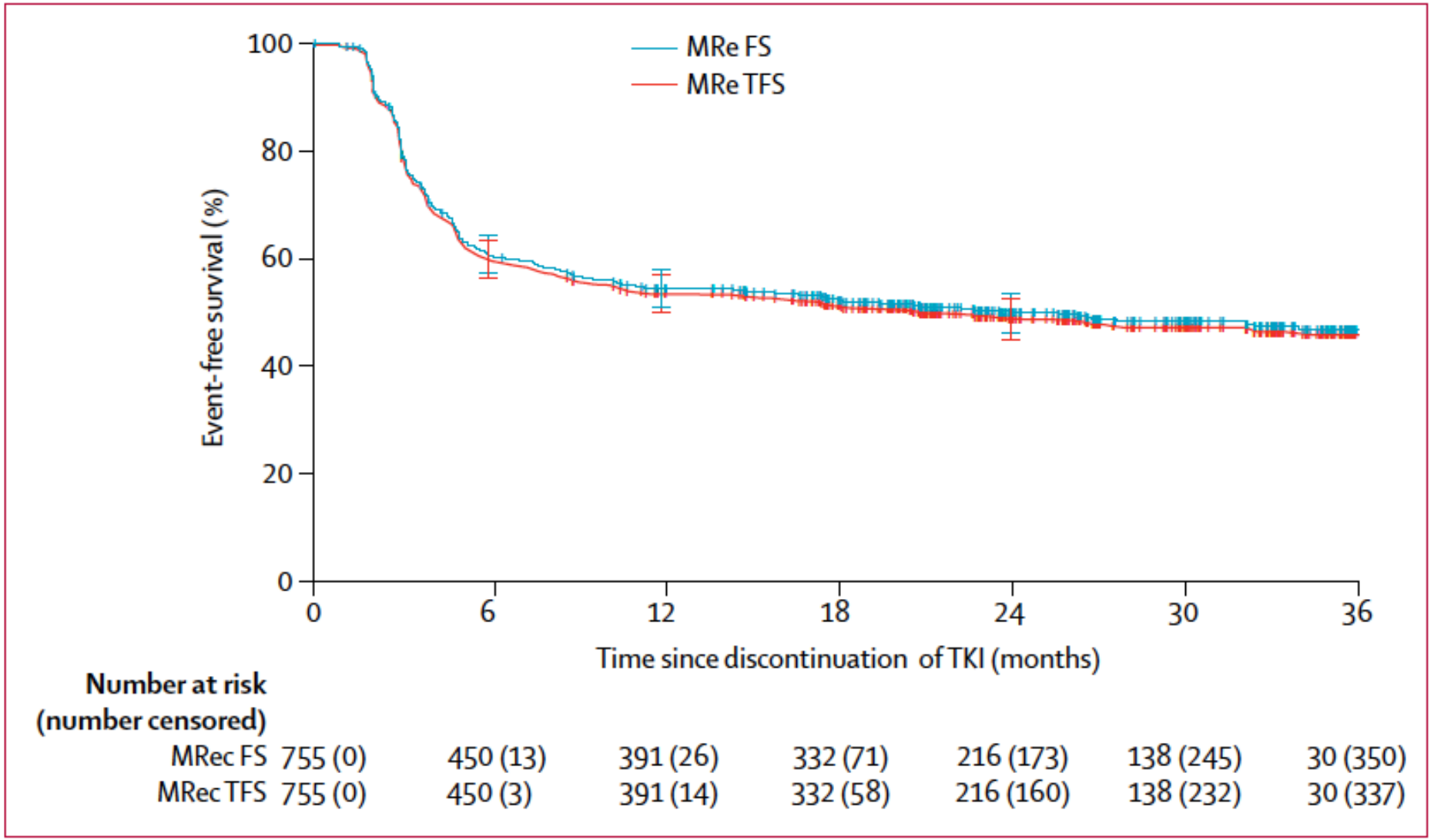


The proportion of total BCR::ABL1 pos.
B cells declines with increasing duration of TFR



Pagani et al. Leukemia. 2020;34:1952-61

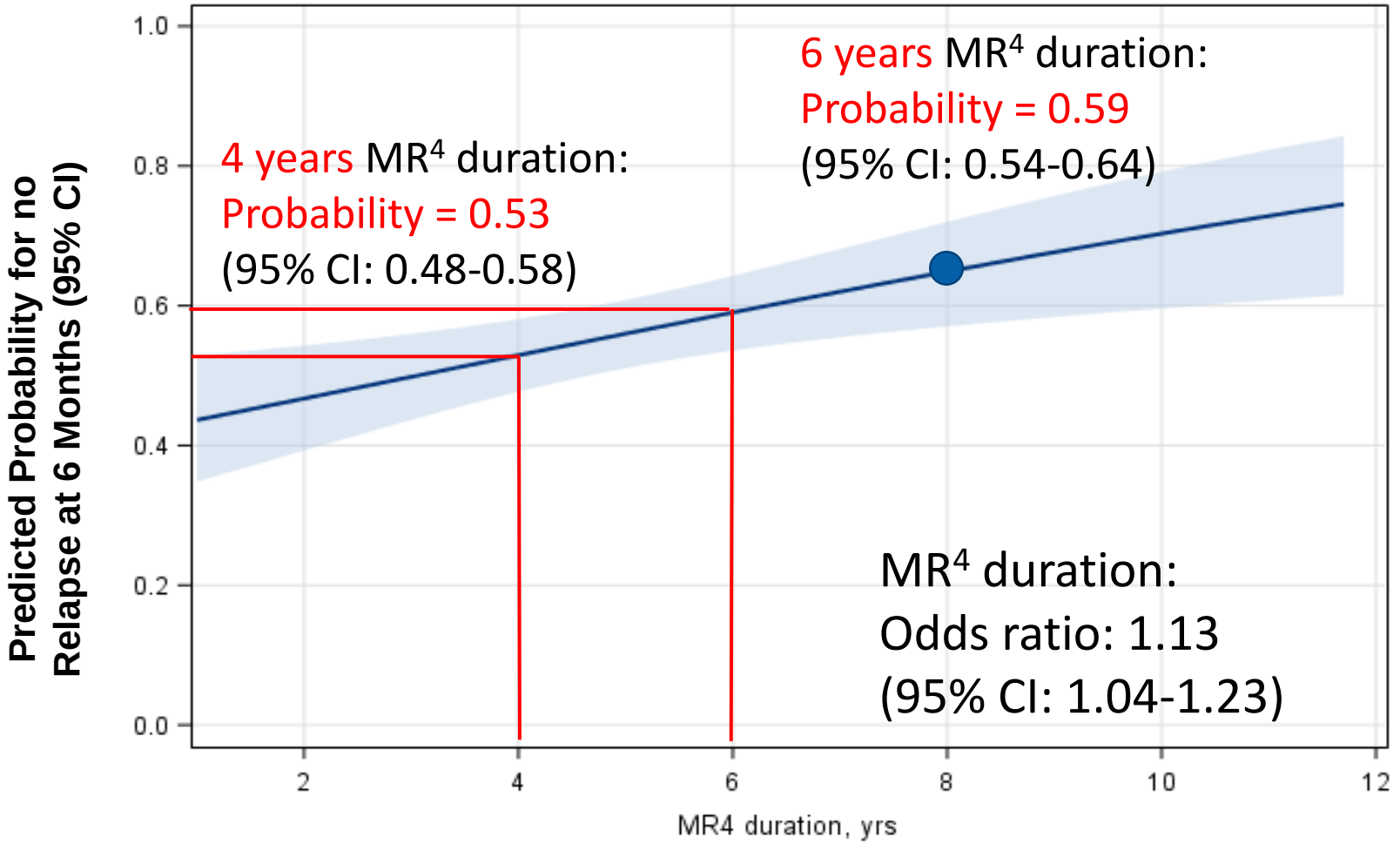
EURO-SKI: Treatment Free Survival (mainly Imatinib based)



Saussele et al. Lancet Oncol 2018

EURO-SKI: MR^4 duration and TFR probability

Absolute increase of probability of about 3% per year (n = 405)



Saussele et al. ASH 2017

EURO-SKI trial – background

European Stop Kinase Inhibitor (EURO-SKI) trial

- set up to deepen our knowledge on successful cessation of tyrosine kinase inhibitors (TKIs) in CML patients

  with stable deep molecular response
  (DMR: BCR::ABL1 transcripts ≤ 0.01% IS

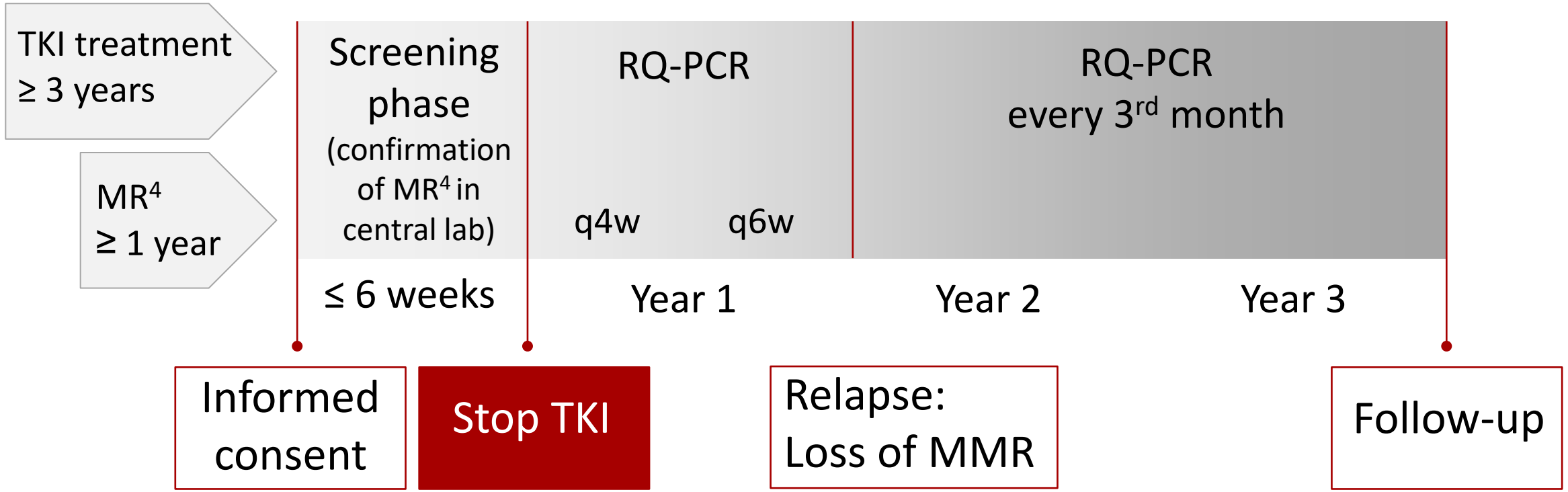
EURO-SKI trial – aims

- What fraction of patients remains in MMR after TKI stop?
- What is the optimal duration of TKI treatment before stop?
- What is the optimal duration of DMR before stop?
- **What are prognostic factors for remaining in molecular relapse-free survival 3 years after TKI-stop?**

Major inclusion / exclusion criteria

- Treatment for at least 3 years with TKI first line, or second line because of toxicity to first line
- Typical transcript (e13a2 and / or e14a2)
- DMR (BCR::ABL1 ≤ 0.01% on IS) for at least 1 year
- Information on treatment, response, age and sex available

Study outline



Patients included between May 2012 and December 2014

Candidate prognostic factors (n = 728)

Transcript type (all at major breakpoint), number (percent)		
e13a2	n = 576	139 (19.1)
e13a2 + e14a2 or e14a2		104 (14.3) and 323 (44.4)
e13a2 + other transcript type or exact type unknown		4 (0.6) and 158 (21.7)
Median percentage of blasts in pb at diagnosis (range)	n = 587	0 (0-18)
Median number of platelets at diagnosis, 10^9/L (range)	n = 615	435 (72-3050)
Median number of spleen size bcm at diagnosis, cm (range)	n = 652	0 (0-32)

Validation sample (STIM 2 trial)

- **STIM 2 sample** with 199 patients; within 36 months 5 losses to follow-up, 10 restarted TKI w/o loss of MMR
- Of remaining 184 patients, 83 events up to 36 months
- **MMR maintenance 45% (95% CI 38-52%)**
- In **EURO-SKI trial**, 300 events up to 36 months in n = 510
- **MMR maintenance 41% (95% CI 37-46%)**

MMR at 36 months, univariate models

Univariate Models	EURO-SKI				STIM2			
	n	OR	95% CI	p-value	n	OR	95% CI	p-value
Duration of TKI treatment (years)	510	**1.124**	1.046-1.207	**0.0014**	184	**1.192**	1.045-1.360	**0.0087**
DMR duration under TKI (years)	510	**1.102**	1.022-1.187	**0.0110**	184	**1.211**	1.041-1.410	**0.0134**
Blasts in peripheral blood (%)	413	**0.889**	0.809-0.976	**0.0137**	175	**0.760**	0.593-0.972	**0.0291**
Transcript, e14a2(+e13a2) vs. e13a2	392	**2.064**	1.243-3.427	**0.0051**	158	**2.378**	1.139-4.965	**0.0211**

- **Duration of treatment** and of **DMR under TKI** confirmed similar strong effects; **Blasts** confirmed
- **Transcript type** confirmed

Summary

Four prognostic factors

- **Duration of TKI treatment**,
- **DMR duration under TKI treatment**,
- **Transcript type**, and
- **Peripheral blasts at diagnosis**

confirmed by STIM 2 trial

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