UNIVERSITÄTS KLINIKUM jena

Debate- Should TFR be a primary goal?

Yes.

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Hadera I Oct 2018

In hematology, adequate counseling is based on evidence and accurate data.

Which data should be discussed to select first line treatment in CML?

- ✓ Available options
- ✓ Chance of response
- ✓ Side effects
- ✓ Chance to live a normal life
- ✓ Costs
- ✓ Chance to discontinue therapy later

Objectives of Treatment Optimization

- ✓ Survival
- ✓ Progression free survival
- ✓ Quality of life
- ✓ Good tolerability
- ✓ Lack of severe long term adverse events
- ✓ Chance to achieve treatment free remission
- ✓ Cost-effective use of drugs

SPRYCEL™
dasatinib

Generika
drugstore

?

Bosulif™
bosutinib 500 mg tablets

Limitations in Therapy with Tyrosine Kinase Inhibitors

Disadvantages of TKI-Therapies

Occurrence of chronic low-grade adverse events[1,2,3]

- → Impaired Quality of Life
- → Risk of inadequate drug compliance and poorer clinical outcome

Age - increasing incidence of multimorbidity requires intake of several drugs, leading to a higher risk for medication interaction.[4,5]

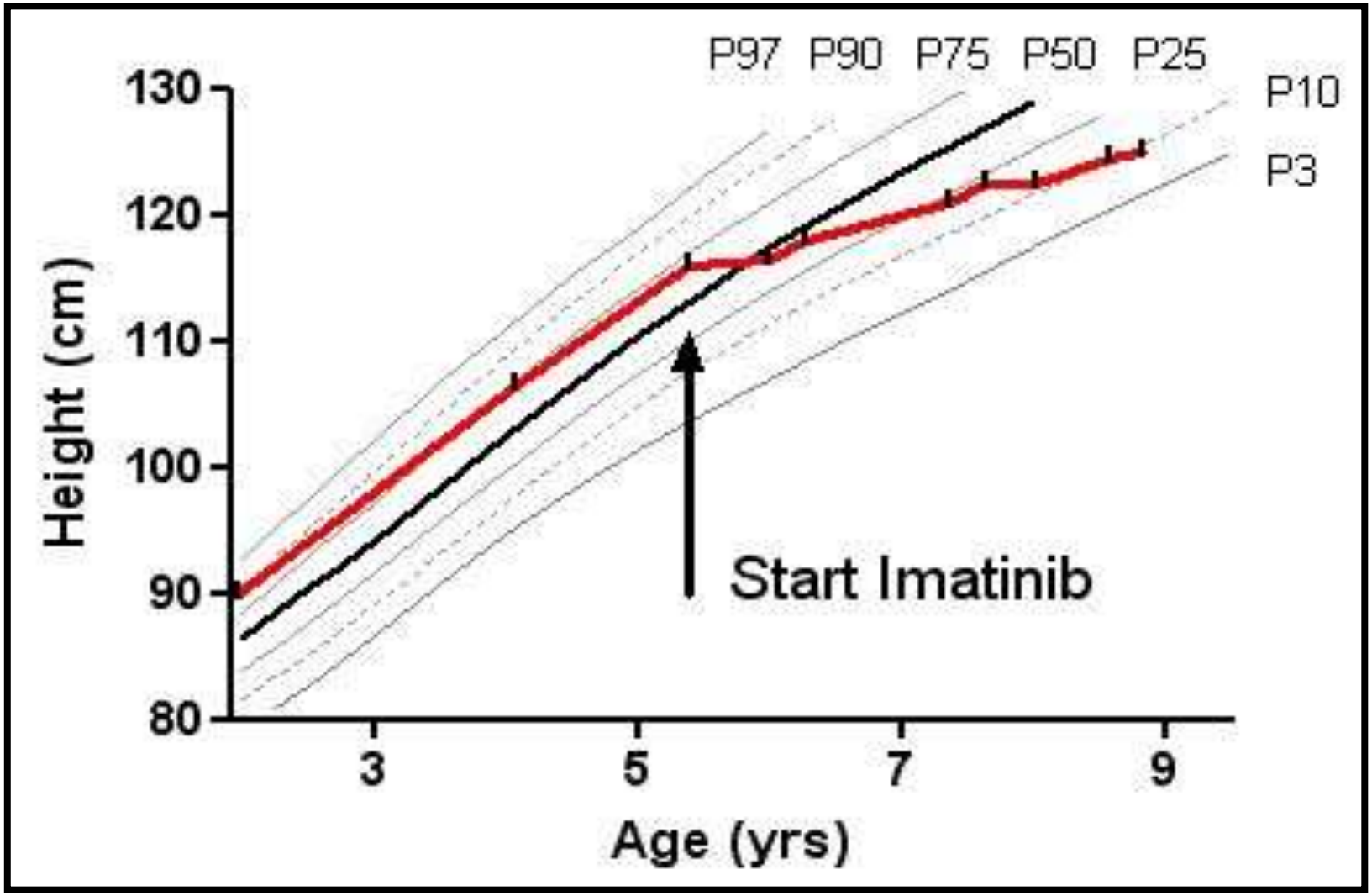
No TKI during pregnancy and nursing[6,7]

Negative impact on growth and development in children and adolescents under imatinib[8]

Lifelong CML-therapy[2] incl. cost implications

1. Eliasson L et al., Leuk Res, 2011;35(5):626-30
2. Noens L et al., Blood, 2009;13:5401–5411
3. Marin DJ et al., Clin Oncol, 2010;28:2381–2388
4. Akker M van den et al., J Clin Epidemiol, 1998;51:367–375
5. Akker M van den et al., Eur J Gen Pract, 1996;14:65–70
6. Tasigna® Prescription information; September 2015. Novartis
7. Glivec® Prescription information; May 2016. Novartis
8. Bansal D et al., Pediatr Blood Cancer, 2012;59(3):481-4

Growth retardation of children on imatinib therapy



Mariani S et al. Lancet, 2008

Schmid H et al. Haematologica, 2009

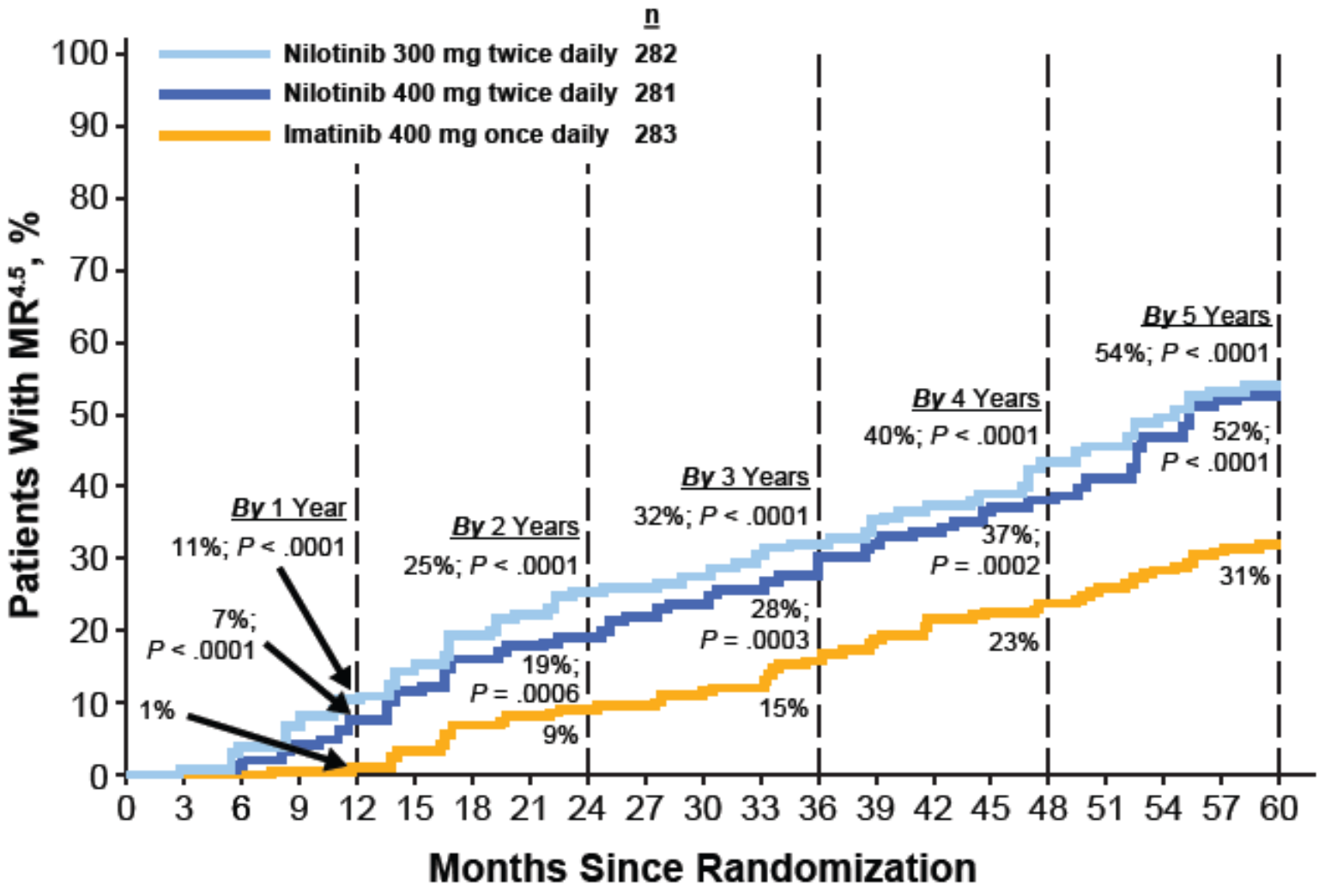
Kimoto T et al. Int J Haematol, 2009

Molecular response

	MMR by 5 years		$MR^{4.5}$		≤10% EMR, at 3 months	
DAS vs IM	76%	64%	42%	33%	84%	64%
NIL vs IM	77%	60%	54%	31%	91%	67%
	at 1 year					
BOS vs IM	47%	37%	8%	3%	75%	57%

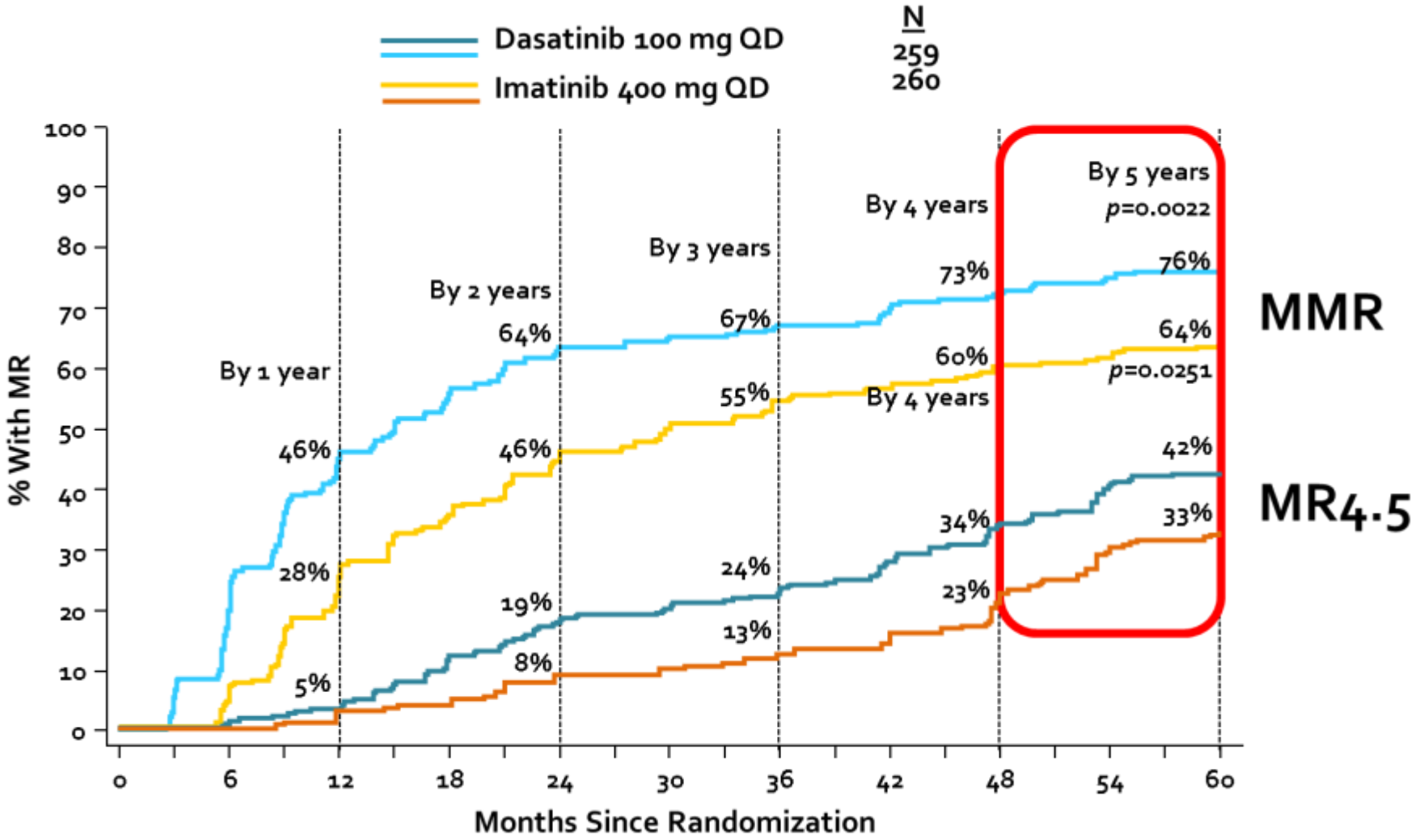
Hochhaus et al. ENESTnd. LEUKEMIA 2016
Cortes et al. DASISION. JCO 2016
Cortes et al. BFORE. ASCO 2017

Nilotinib vs Imatinib
$MR^{4.5}$ – on ENESTnd after 5 Years



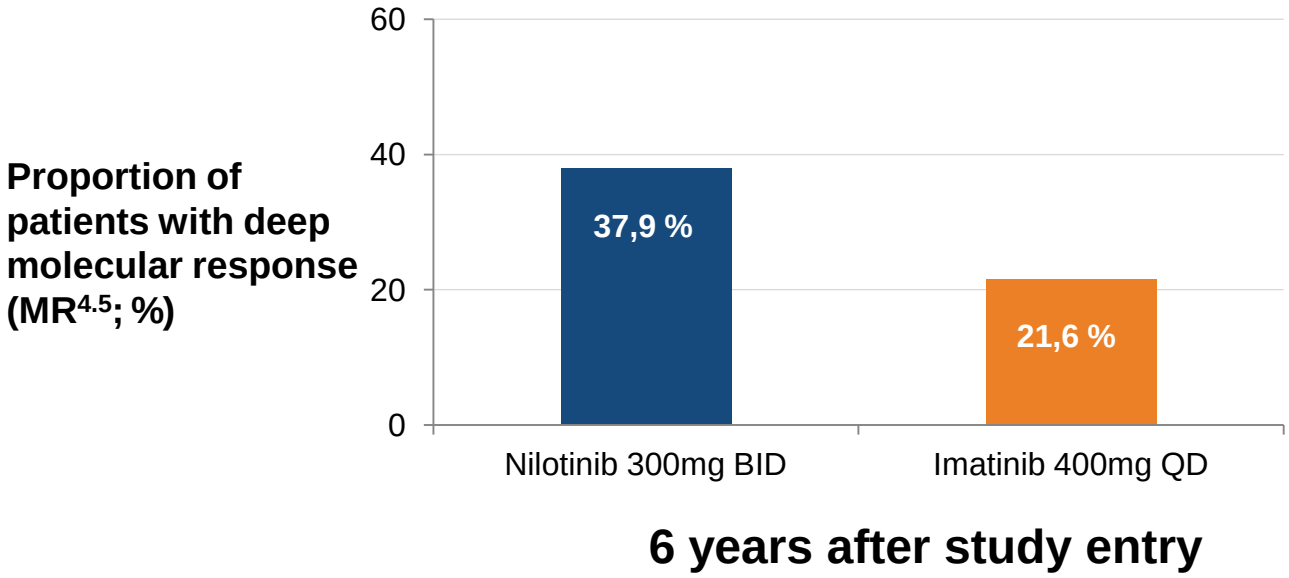
Hochhaus et al., Leukemia 2016

DASISION: Cumulative Molecular Response Rates Over 5 Yrs



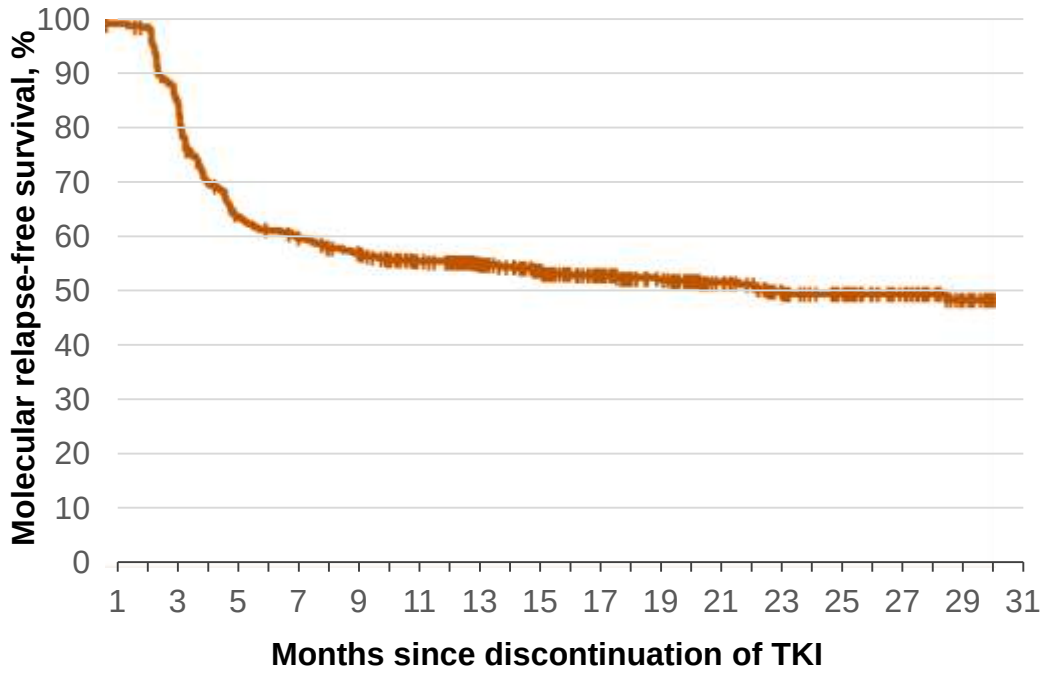
Cortes et al, J Clin Oncol 2016

Requirements for Treatment-Free Remission



- Deep and sustained molecular response: 37,9% in patients under Nilotinib vs. 21,6% under Imatinib
- This population met the requirements for TKI-discontinuation in accordance to the ENESTfreedom protocol

EURO-SKI: Relapse free survival (n = 750)



Month	MolRFS %	95%-CI
6	62	59-67
12	56	52-59
24	52	48-56
36	49	44-53

Events:
Molecular relapse n = 348
Death in remission n = 5

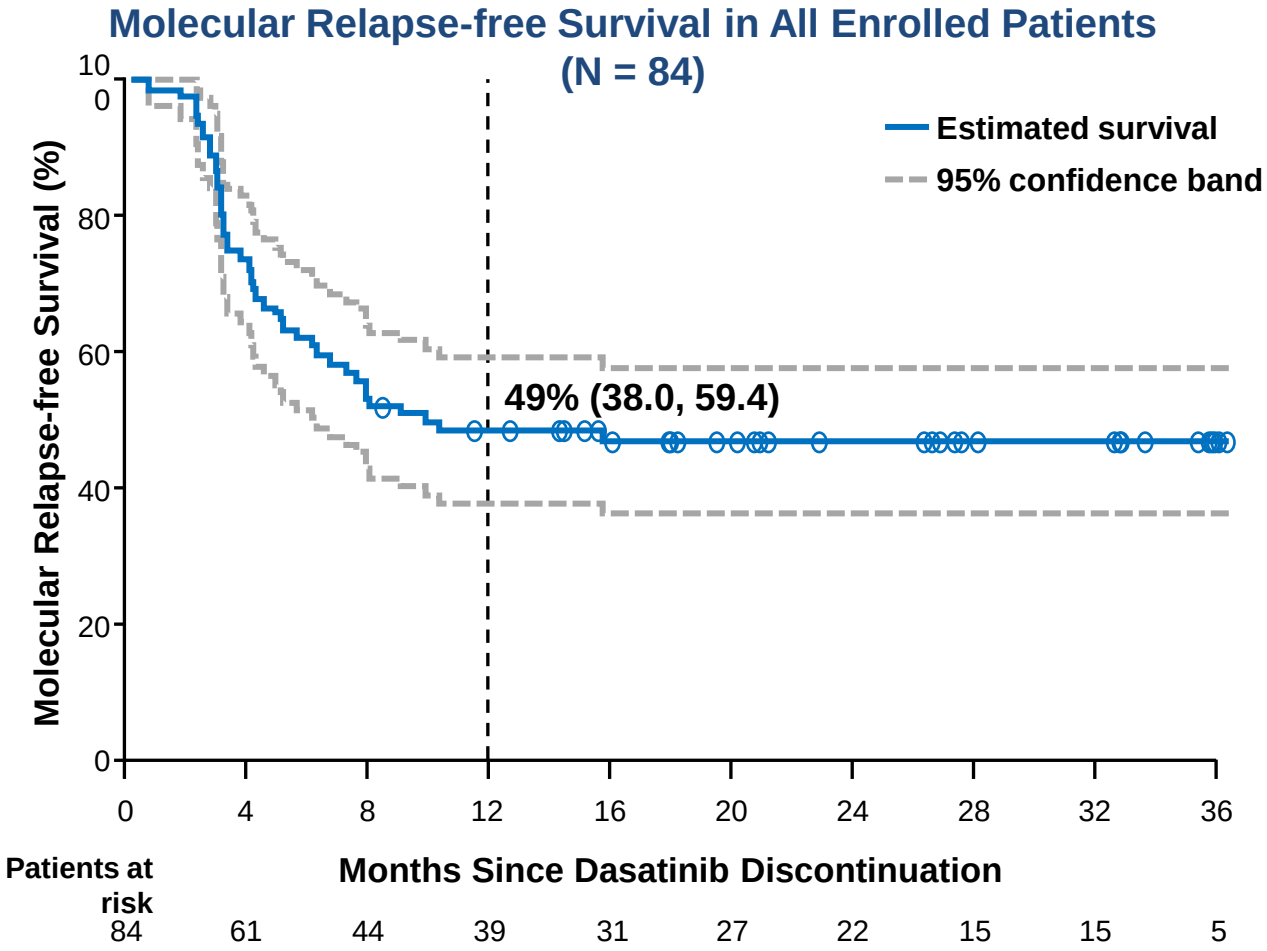
For patients who resumed treatment, median time to restart was 4.1 months

- Longer duration of imatinib-therapy (optimal ≥ 5.8 years) correlates to higher probability of relapse-free survival at 6 months.

EURO-SKI, European Stop TKI.

Richter et al. Haematologica 2016 [abstract S145]

Dasatinib: Molecular Relapse-free Survival



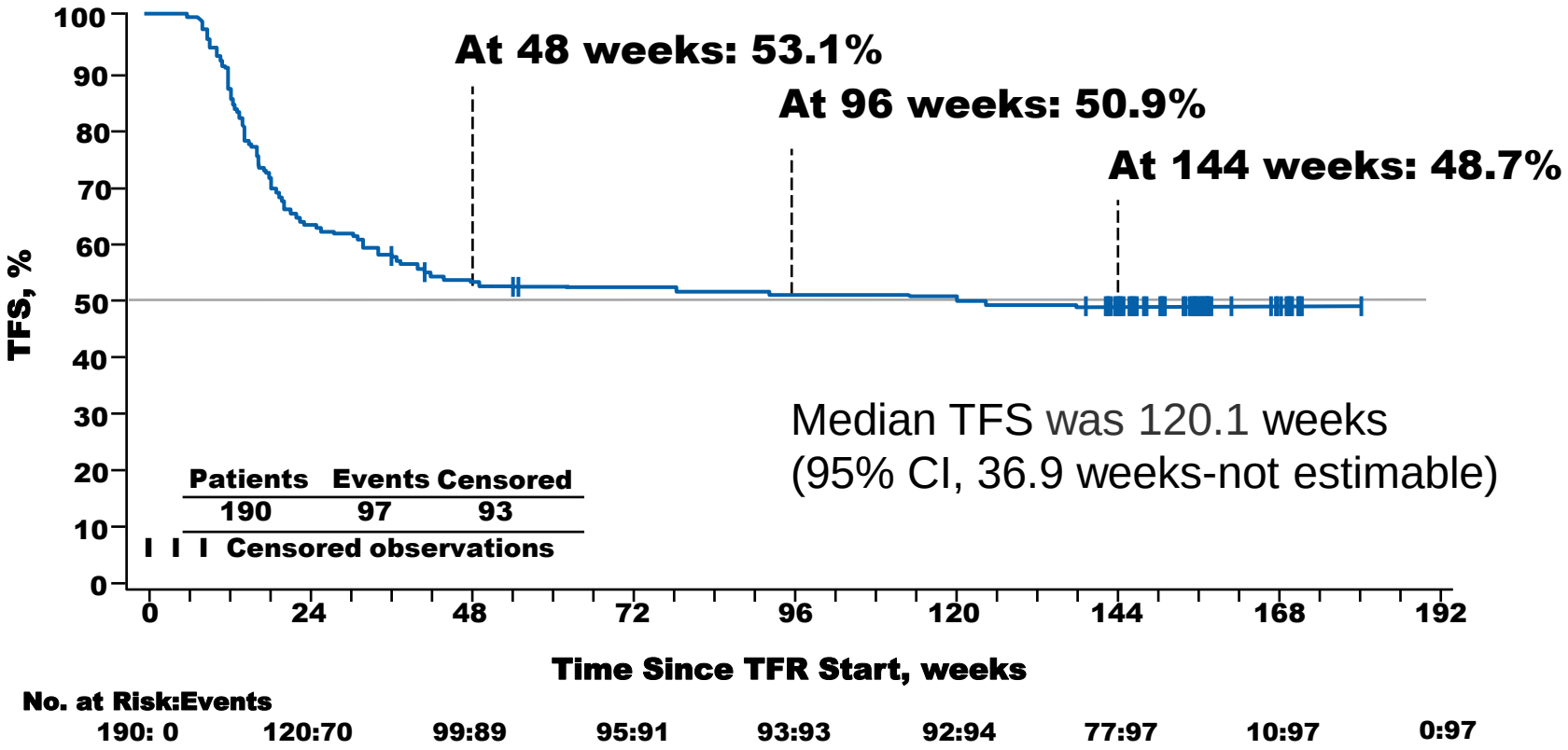
	MRFS, % (95% CI)
Patients on first-line dasatinib (n = 37)	54 (38.0, 70.1)
Patients on subsequent lines of dasatinib (n = 47)	45 (30.2, 58.7)
Resistant (n = 25)	44 (24.5, 63.5)
Intolerant (n = 18)	50 (26.9, 73.1)

- No patients lost CCyR or CHR; no transformation events or deaths were observed

Shah et al., ASH 2017

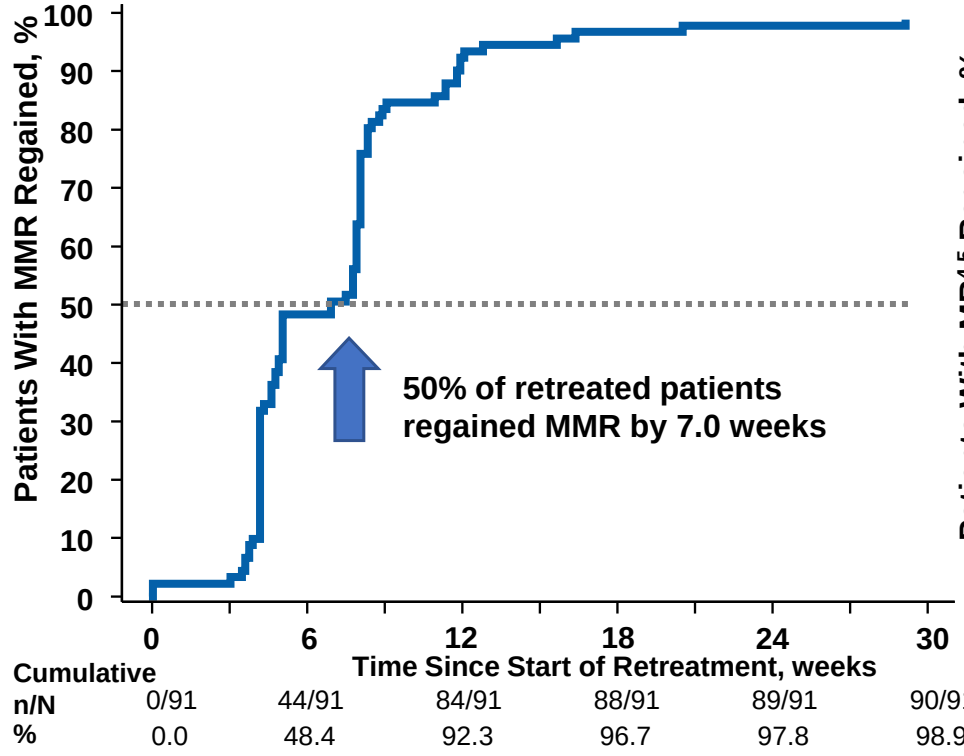
Nilotinib: Treatment Free Survival[a]

48-week TFR rate (primary endpoint): 51.6% (98/190)[b]



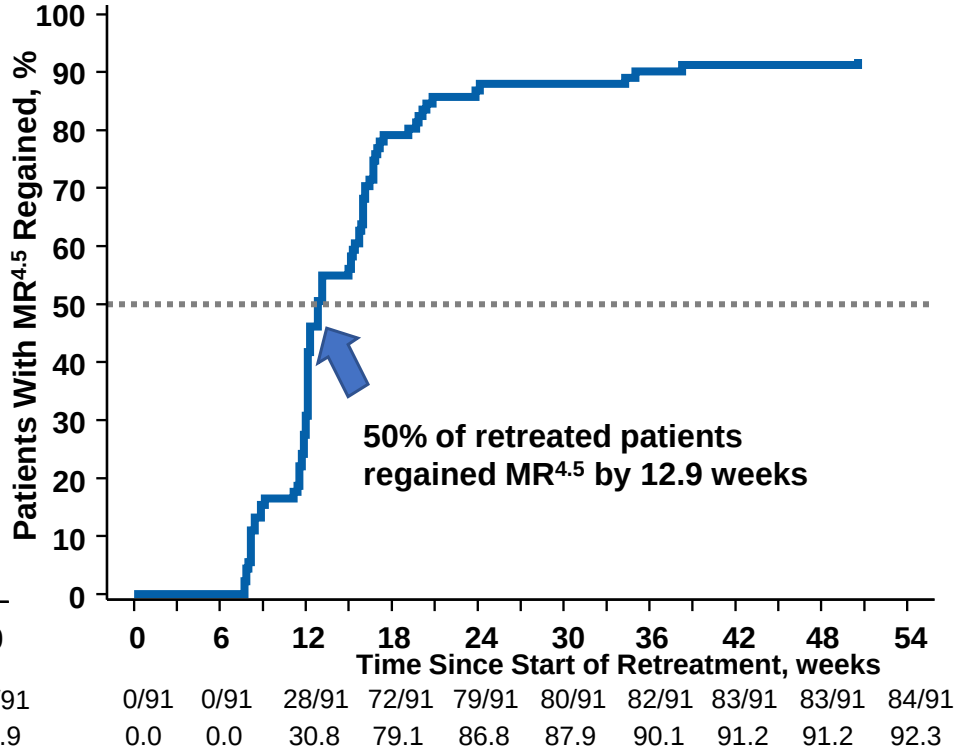
Cumulative Rate of MMR and MR$^{4.5}$ Regained in Nilotinib Reinitiation Phase

90/91 (98.9%) patients who restarted nilotinib regained MMR[a]



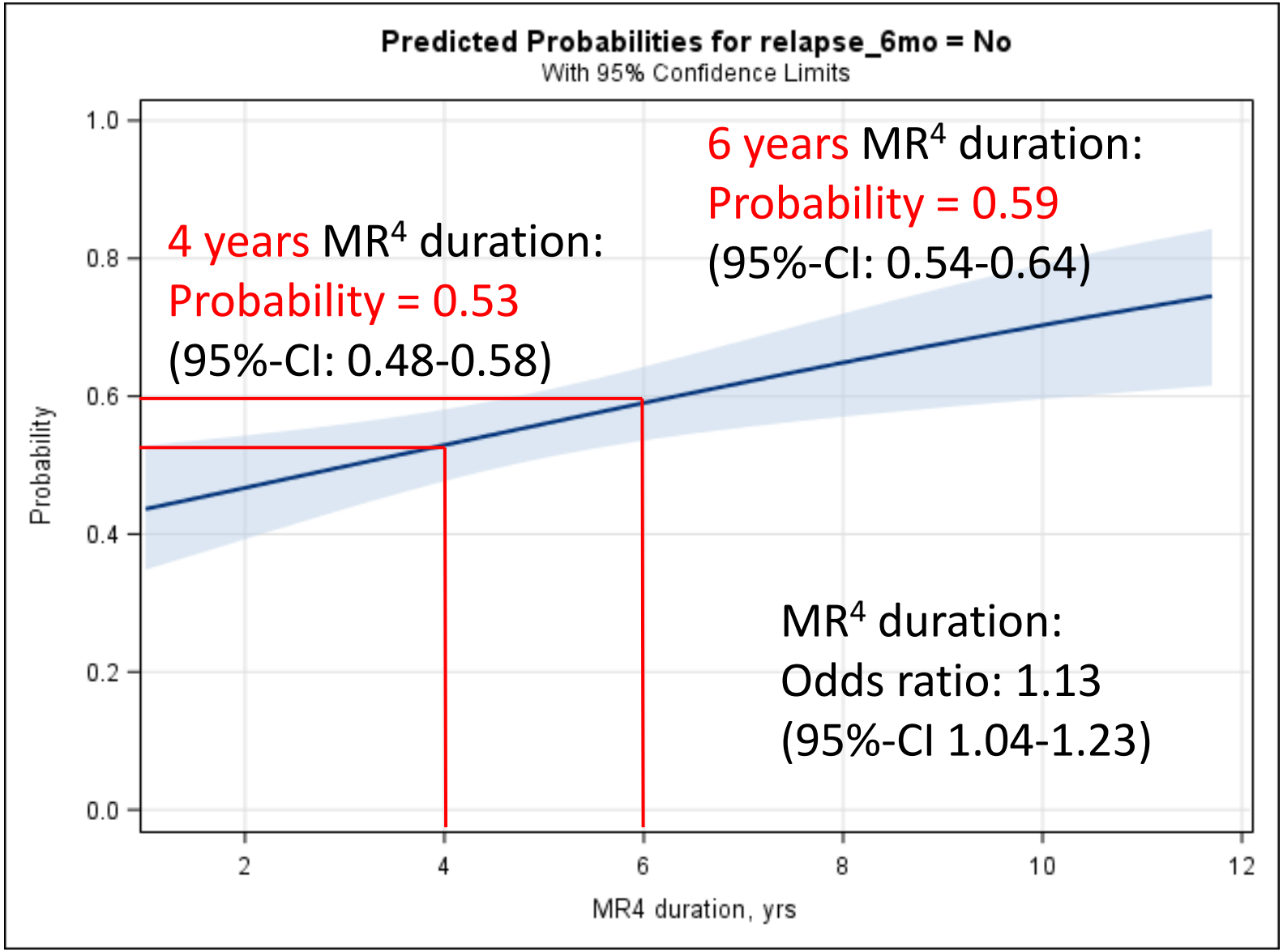
Cumulative n/N	0/91	44/91	84/91	88/91	89/91	90/91
%	0.0	48.4	92.3	96.7	97.8	98.9

84/91 (92.3%) patients who restarted nilotinib regained MR$^{4.5}$[b]



n/N	0/91	0/91	28/91	72/91	79/91	80/91	82/91	83/91	83/91	84/91
%	0.0	0.0	30.8	79.1	86.8	87.9	90.1	91.2	91.2	92.3

Duration of MR^4 most important parameter



Are we ready for routine stopping procedure?

Treatment discontinuation may be considered in individual patients, if proper, high-quality, and certified monitoring can be ensured.

Prerequisites for safe stopping are
institutional requirements for safe supervision,

- identification of typical BCR-ABL1 transcripts at diagnosis,
- at least 5 years of TKI therapy (for imatinib)
- achievement of $MR^{4.5}$,
- and a stability of DMR (at least MR^4) for at least 2 years

Less stringent criteria do not exclude successful TFR, but stability of TFR is improved with longer TKI therapy and longer DMR.

Standardized reporting of deep molecular response considering limits of detection and quantification

OPEN

Leukemia (2015), 1–5

www.nature.com/leu

REVIEW

Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia

NCP Cross[1,2], H White[1,2], D Colomer[3], H Ehrencrona[4], L Foroni[5], E Gottardi[6], T Lange[7], T Lion[8], KM Polakova[9], S Dulucq[10], G Martinelli[11], EO Leibundgut[12], N Pallisgaard[13], G Barbany[14], T Sacha[15], R Talmaci[16], B Izzo[17], G Saglio[6], F Pane[17,18], MC Müller[19] and A Hochhaus[20]

- Laboratory definition and recommendations
- Performance evaluation in Europe: can testing labs detect $MR^{4.5}$ consistently and reliably?

EUTOS for CML

European Treatment and Outcome Study


You Can
do it!