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Stopping treatment – how much we understand about mechanisms to stop successfully today, and where are the limits?

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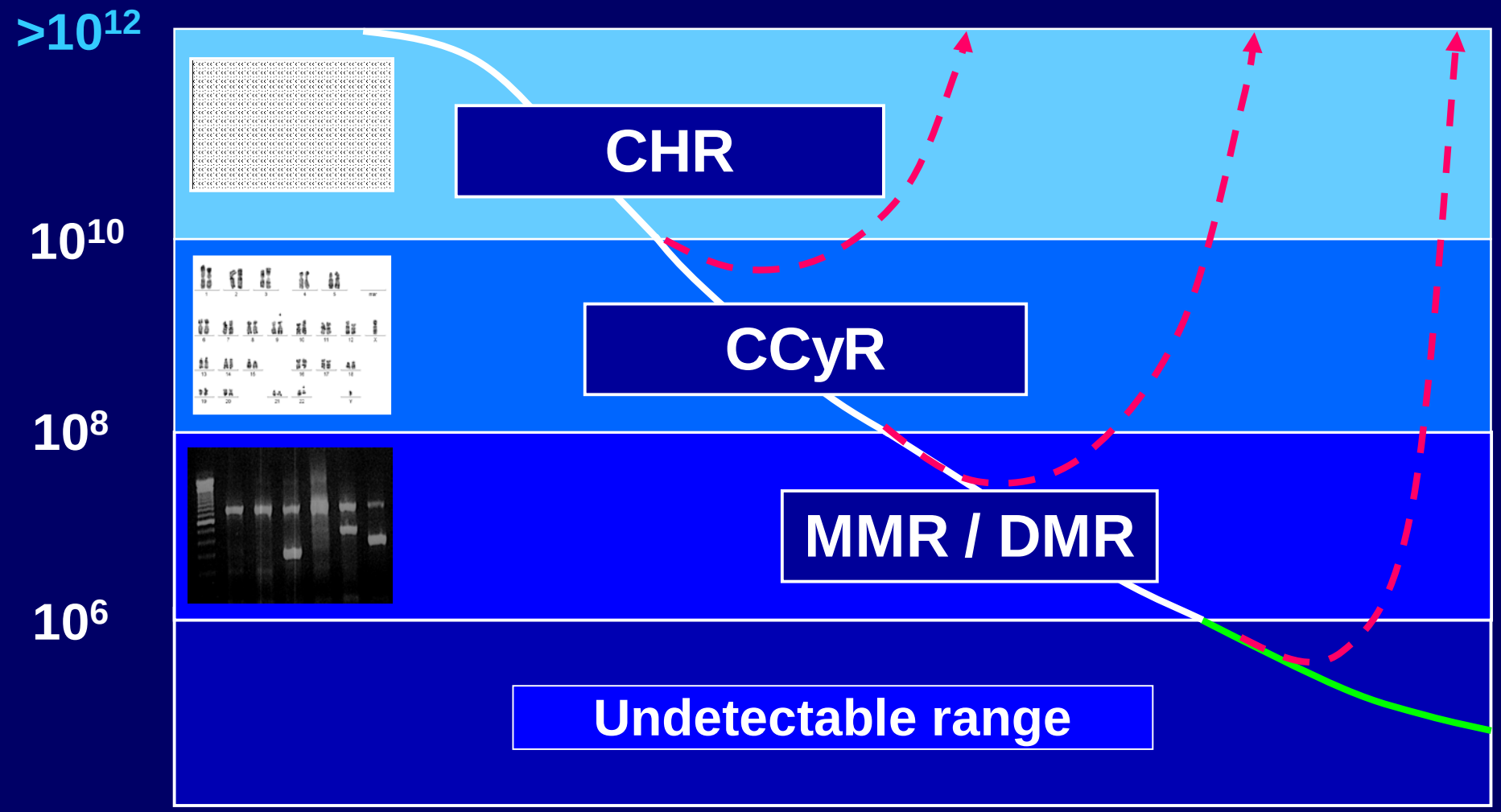
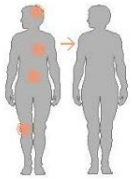
Frankfurt I 27.5.2017

Aims of CML Therapy



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]

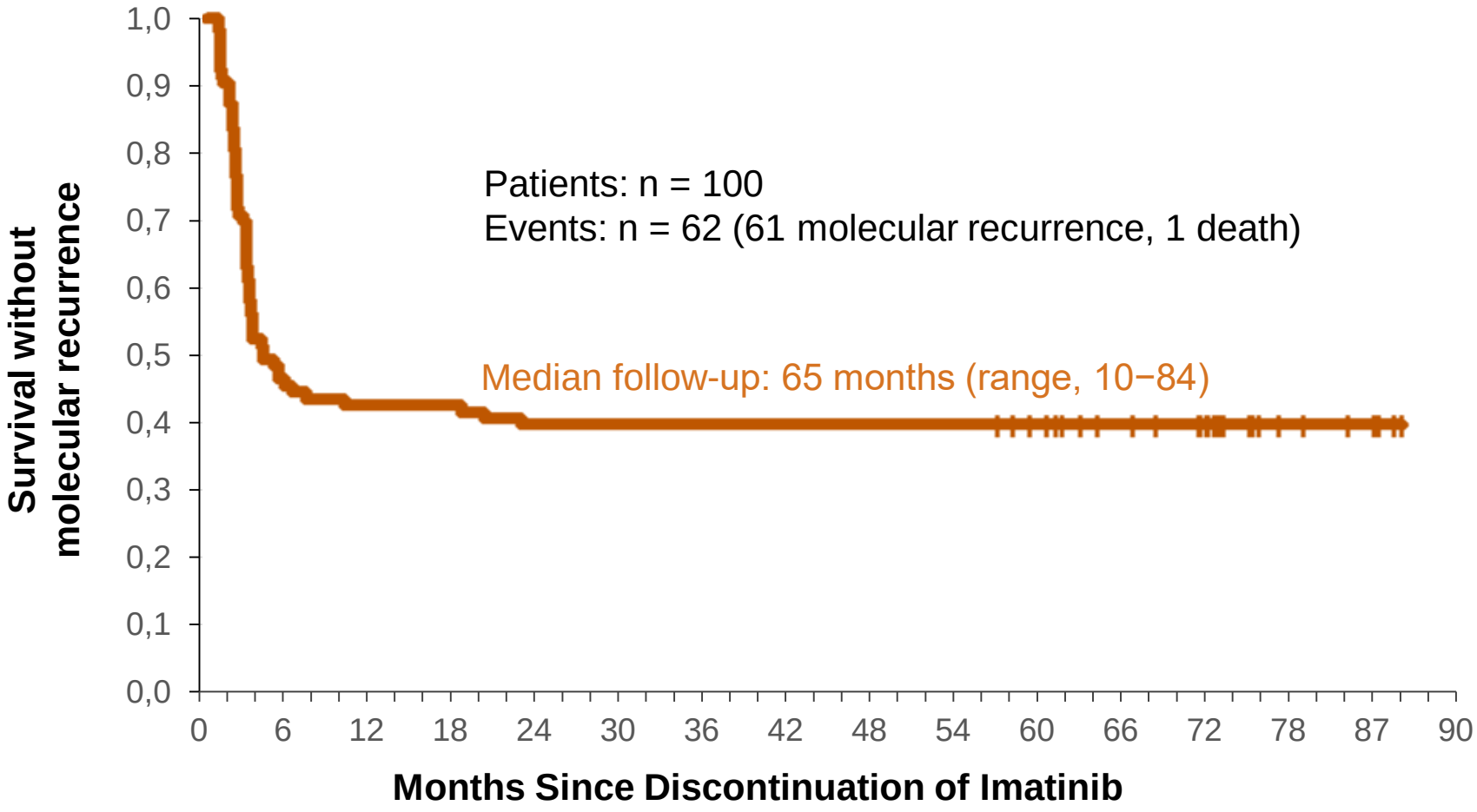
No TKI during pregnancy and nursing[6,7]

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 Pharma GmbH
7. Glivec® Prescription information; May 2016. Novartis Pharma GmbH
8. Bansal D et al., Pediatr Blood Cancer, 2012;59(3):481-4

STIM1: Patients With Sustained Deep Molecular Responses on Imatinib Can Maintain TFR

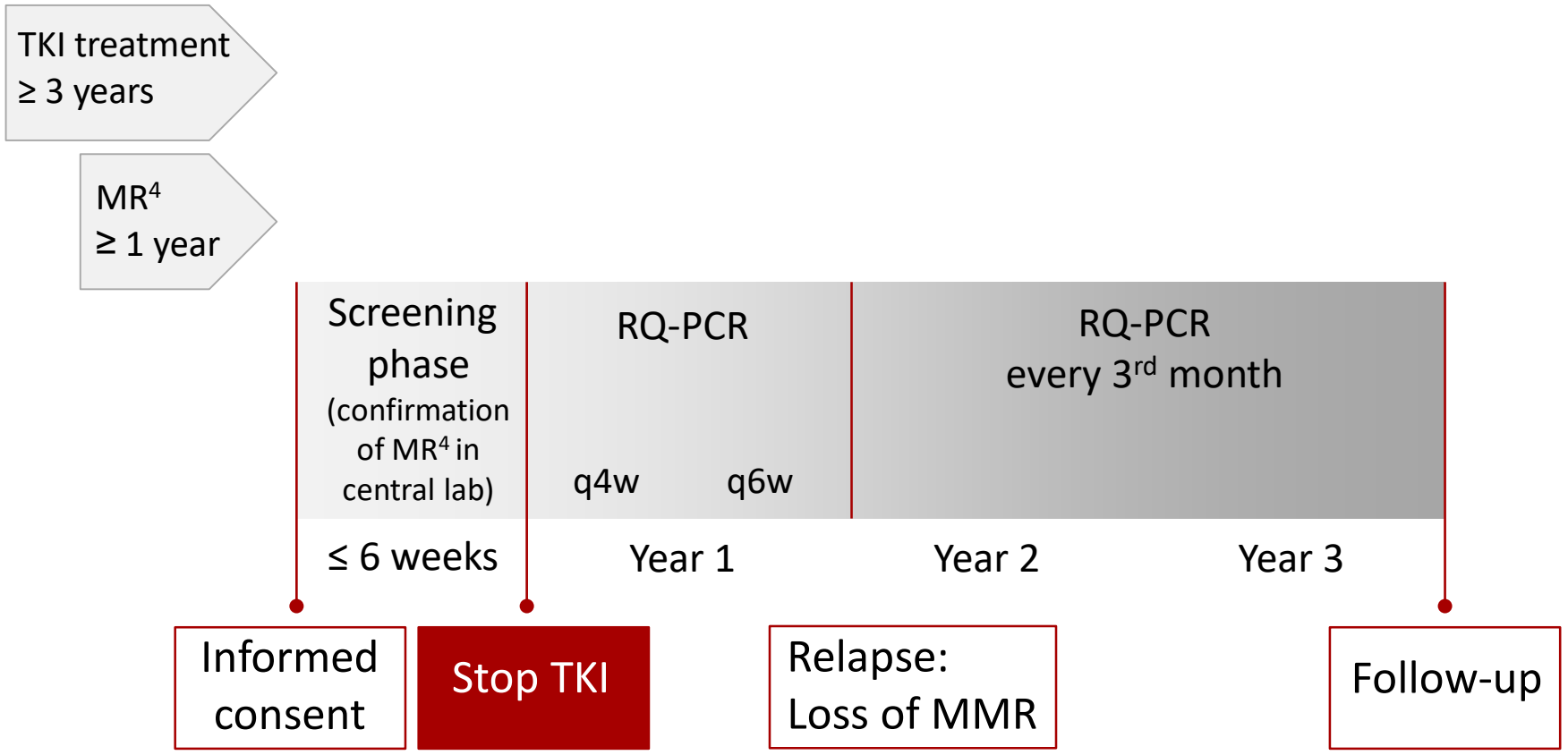


- After 6 months: 10% risk of molecular relapse at 24 months[2]

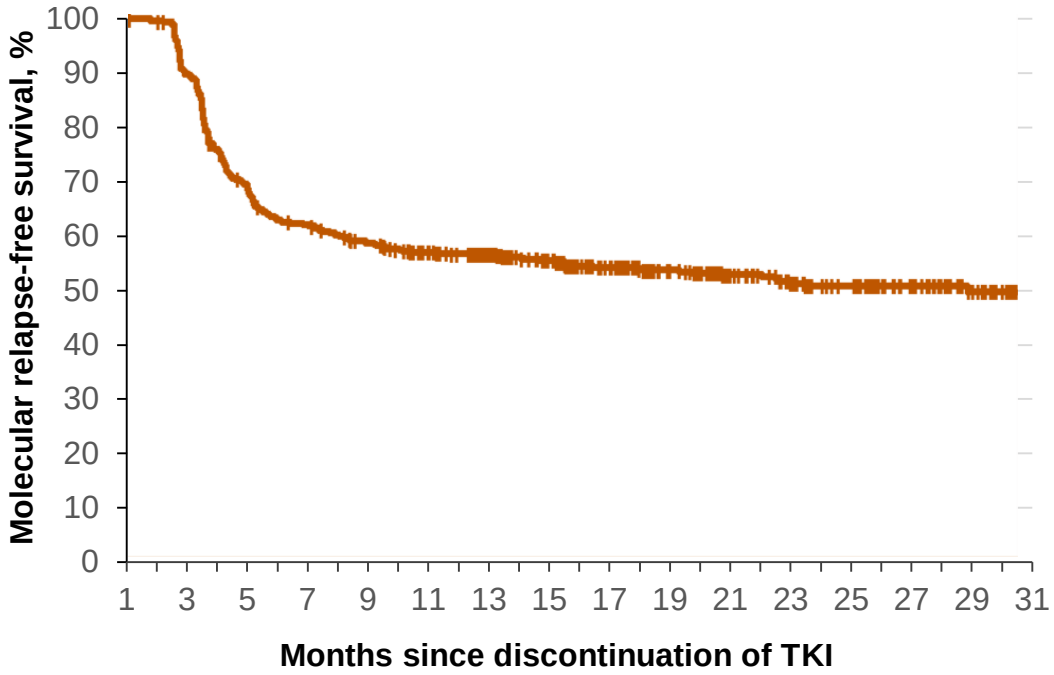
1. Mahon FX, et al. Blood. 2013;122(21) [abstract 255].
2. Etienne G, et al. Blood. 2015;126(23) [abstract 345].

EURO-SKI

Patients included between May 2012 and December 2014



EURO-SKI: Molecular 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

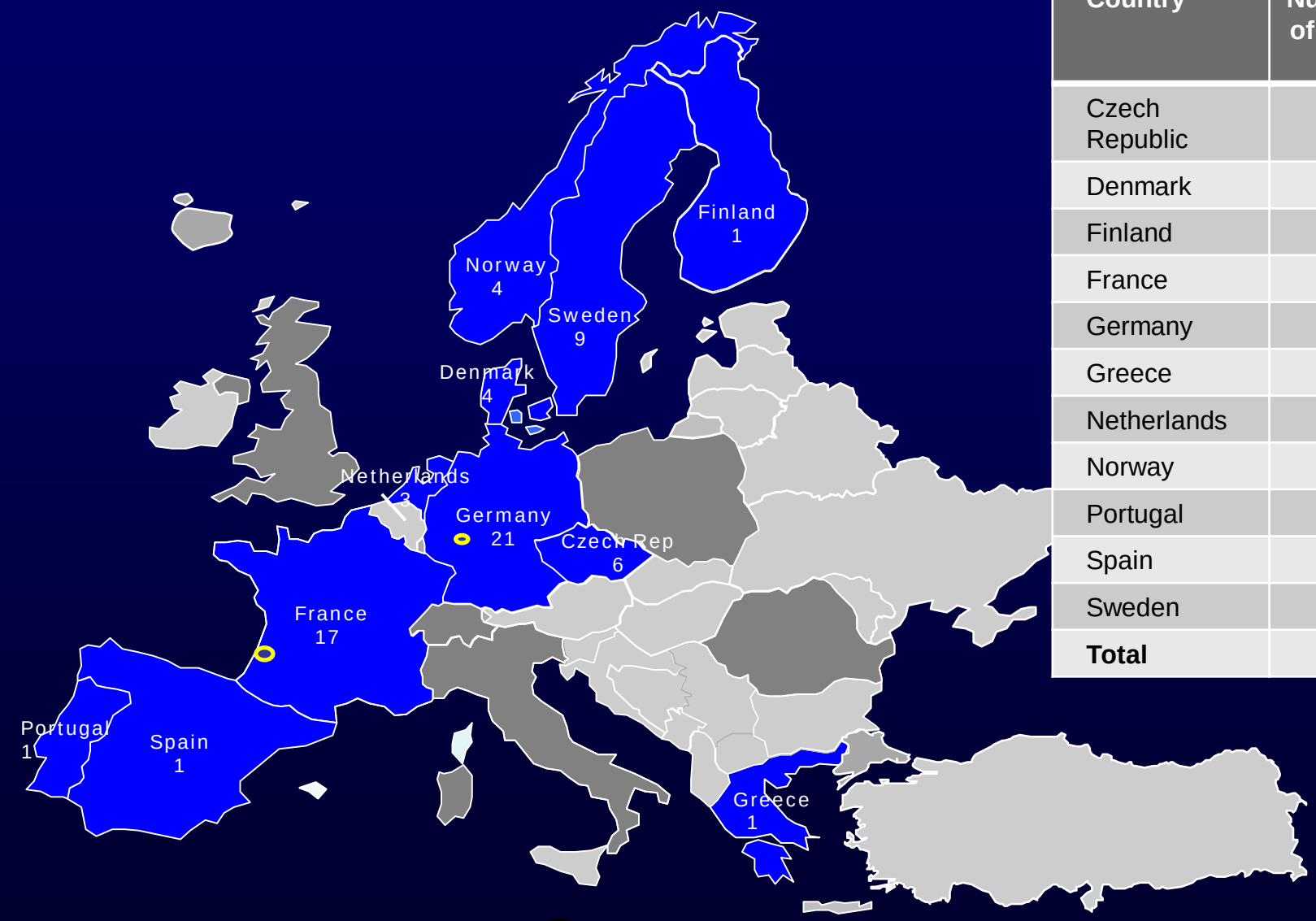
For patients who resumed treatment, median time to restart was 4.1 months

- 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]

Participating countries in EURO-SKI



Country	Number of sites	Number of patients
Czech Republic	6	64
Denmark	4	33
Finland	1	31
France	17	204
Germany	21	217
Greece	1	44
Netherlands	3	96
Norway	4	27
Portugal	1	27
Spain	1	9
Sweden	9	116
Total	**61**	**868**

Univariate analysis for relapse free survival at 6 months

Significant association

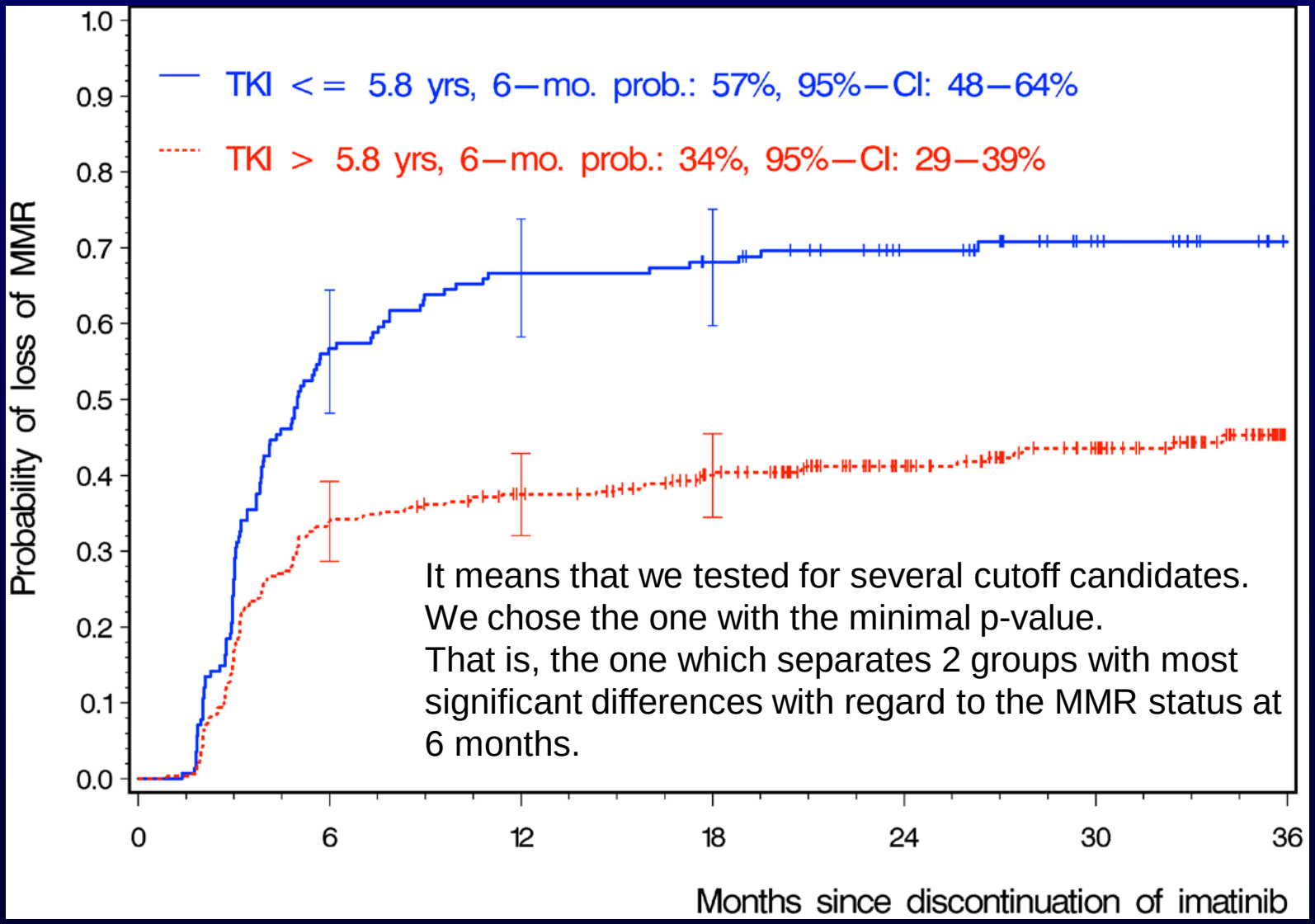
- Treatment duration with imatinib
- MR^4 duration
- Duration of IFN pre-treatment

No significant association

- Age
- Gender
- Depth of molecular response ($MR^{4.5}$ vs. not in $MR^{4.5}$)
- any variable part of the Sokal, EURO, EUTOS or ELTS scores

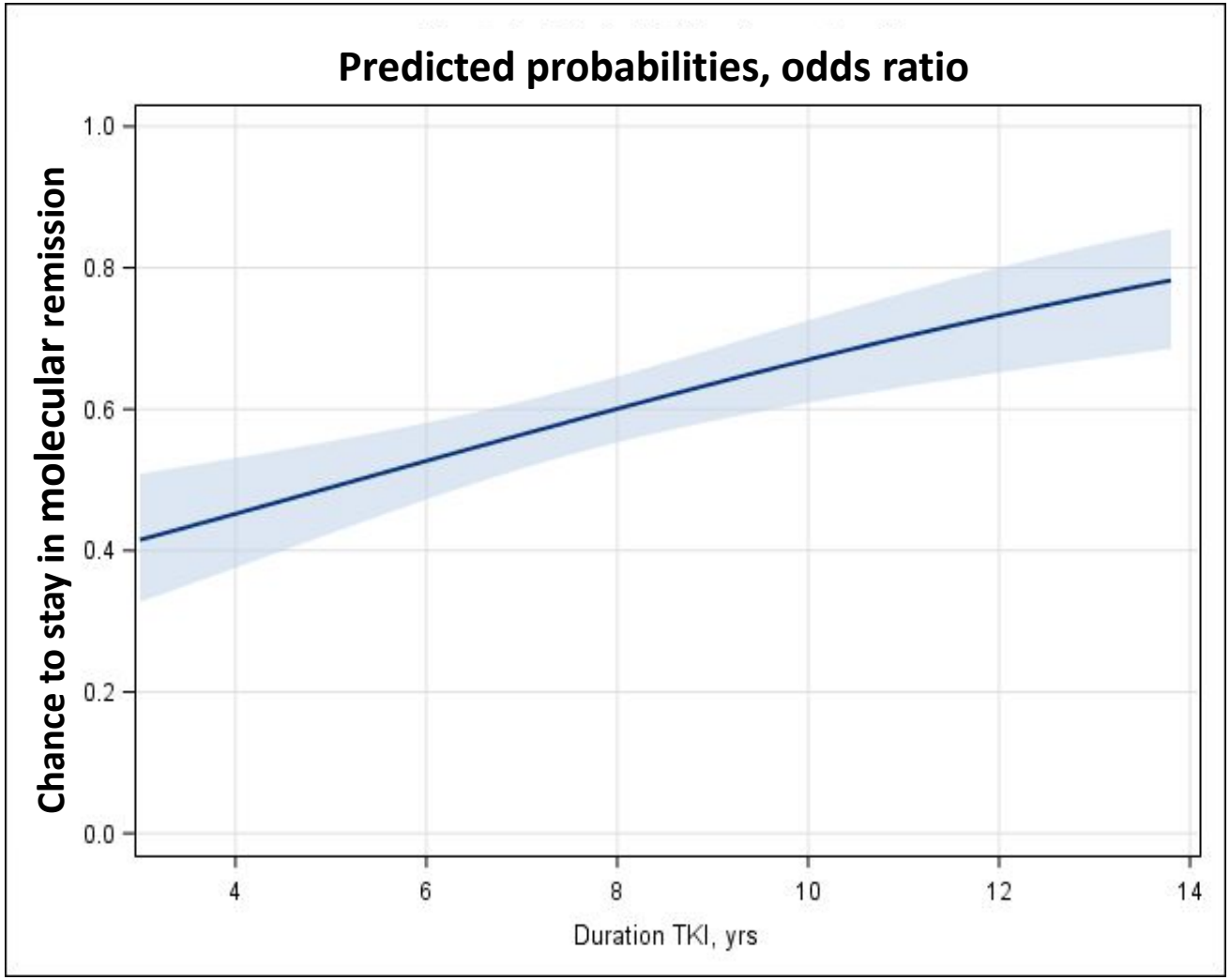
EURO-SKI presented by FX Mahon at ASH 2016

Treatment duration cut-off for loss of MMR at 6 months



EURO-SKI presented by FX Mahon at ASH 2016

Importance of treatment duration

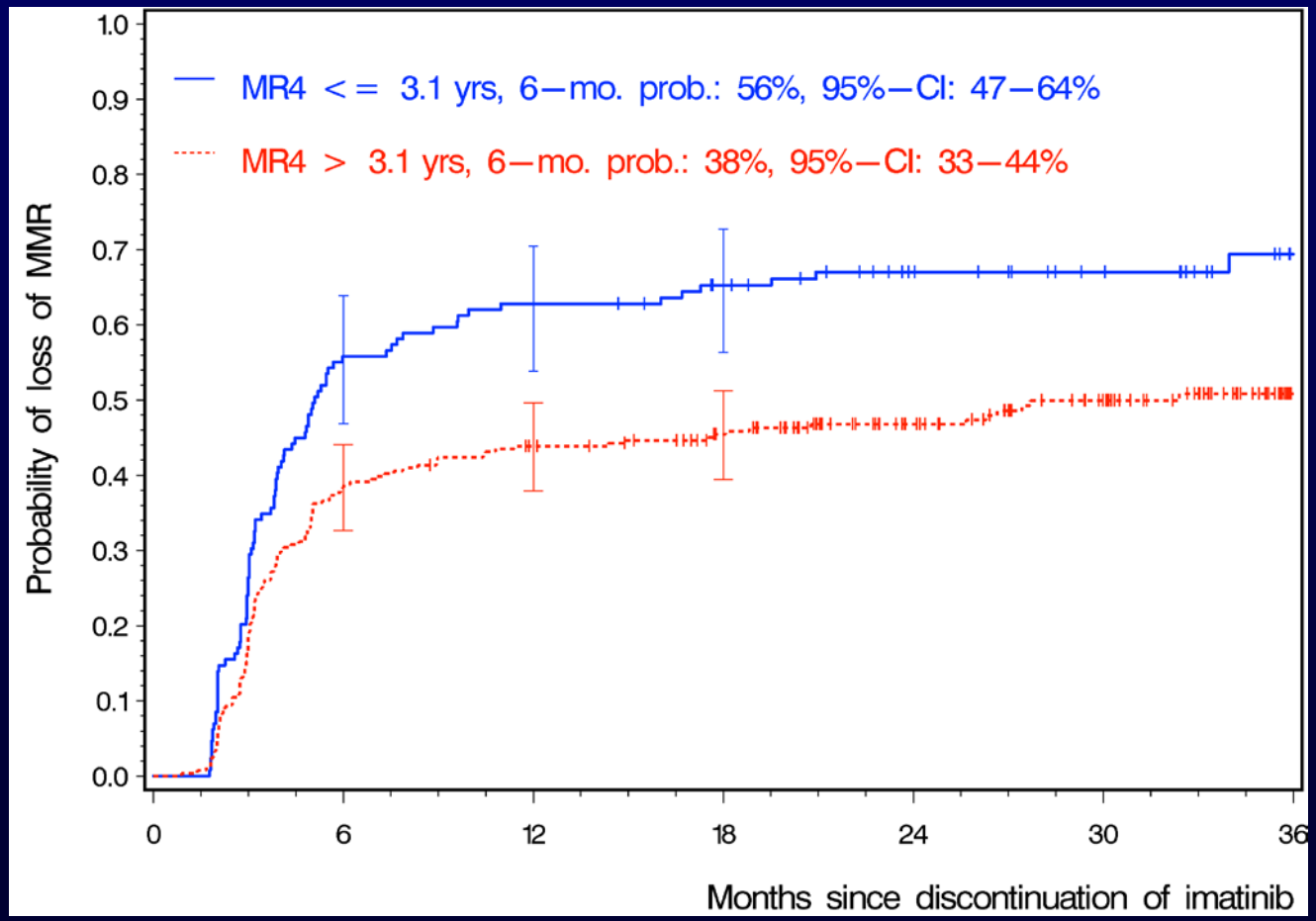


One additional year on TKI before stop increases the chance to stay in MMR at 6 months by **16%**.

Pfirrmann et al., ASH 2016

Duration of MR^4 vs. loss of MMR at 6 months

- Using the minimal p-value approach a 3.1 years cut-off was significant and chosen with respect to patient safety*



EURO-SKI presented by FX Mahon at ASH 2016

*20% of the patients in the smallest group

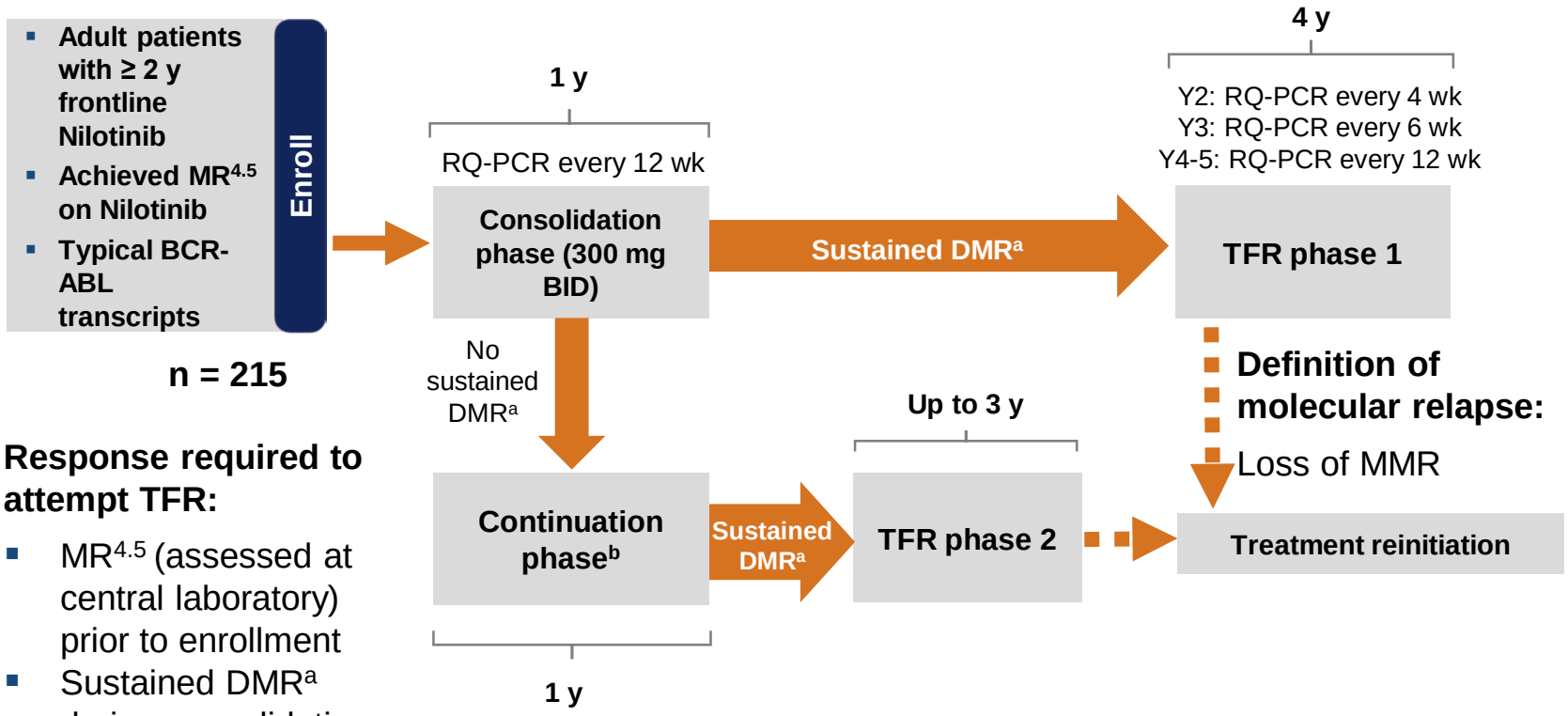
Adverse Events – Musculoskeletal symptoms

Previously a TKI withdrawal syndrome has been described in a sub cohort of patients in EURO-SKI (Richter et al. JCO 2014). This consists of newly emerging, but mostly transient, pain or discomfort from the musculoskeletal system. This has also been described in other cessation trials (Mori et al. Am. J. Hematol. 2015, Lee et al. Haematologica 2016).

	Patients with AE grade 1-2	%	Patients with AE Grade 3	%	Total	%
Musculoskeletal symptoms*	226	29.7	9	1.2	235	30.9

*Musculoskeletal pain, bone and/or joint pain, arthralgia, muscle pain, myalgia, joint stiffness, lumbalgia, articular pain, muscular pain, neck pain, arthromyalgia, pain both arms, pain legs

ENESTfreedom: Study Design



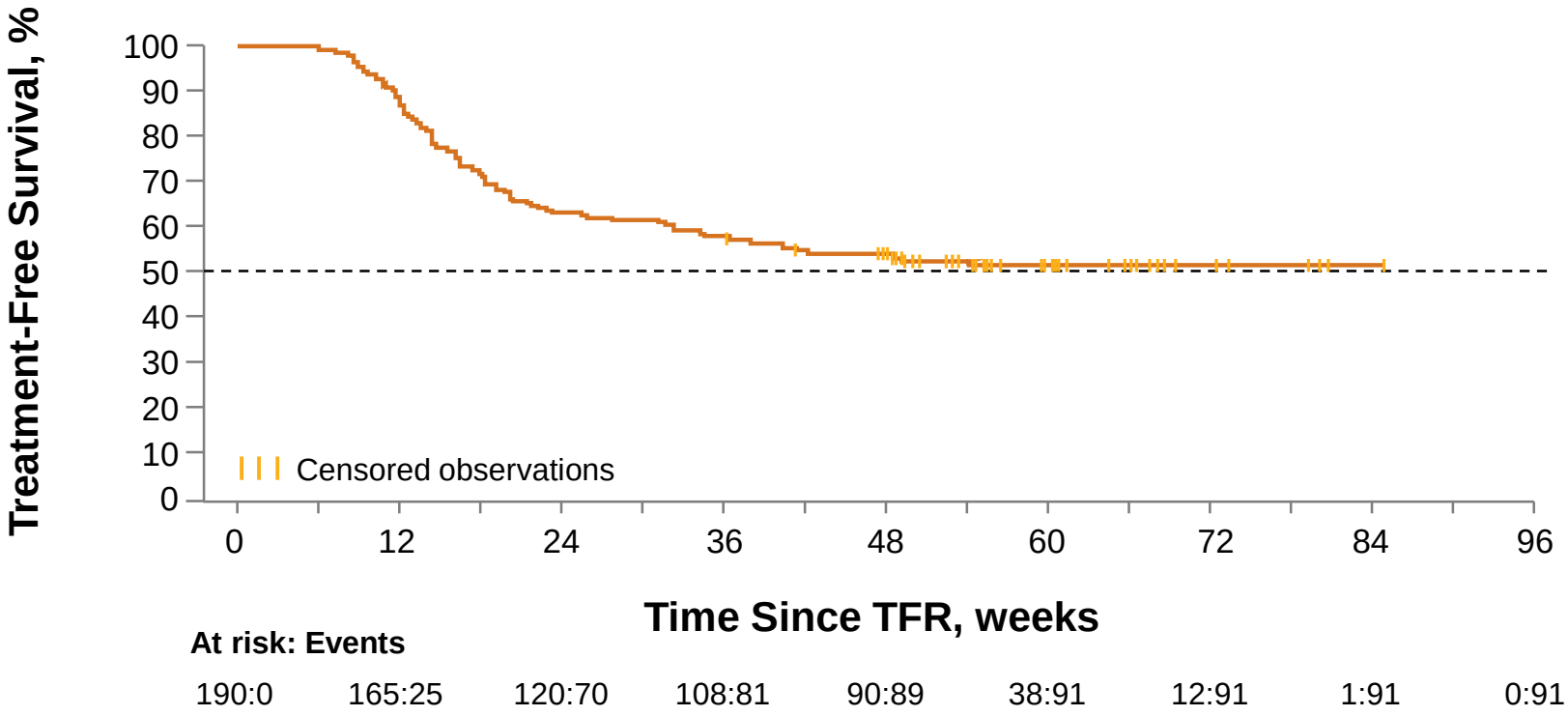
Response required to attempt TFR:

- MR4.5 (assessed at central laboratory) prior to enrollment
- Sustained DMR[a] during consolidation phase

DMR, deep molecular response; RQ-PCR, real-time quantitative polymerase chain reaction.
a Sustained DMR is defined as the following results from the last 4 quarterly performed PCR assessments: MR4.5 at last assessment, no assessment worse than MR4, no more than 2 assessments between MR4 and MR4.5.
b If no sustained DMR after this point, patients may continue to receive Nilotinib in the prolonged continuation phase until the end of the study.

Mahon FX, et al. J Clin Oncol. 2014;32(5s) [abstract TPS7124].

ENESTfreedom: Kaplan-Meier Estimated Treatment-Free Survival

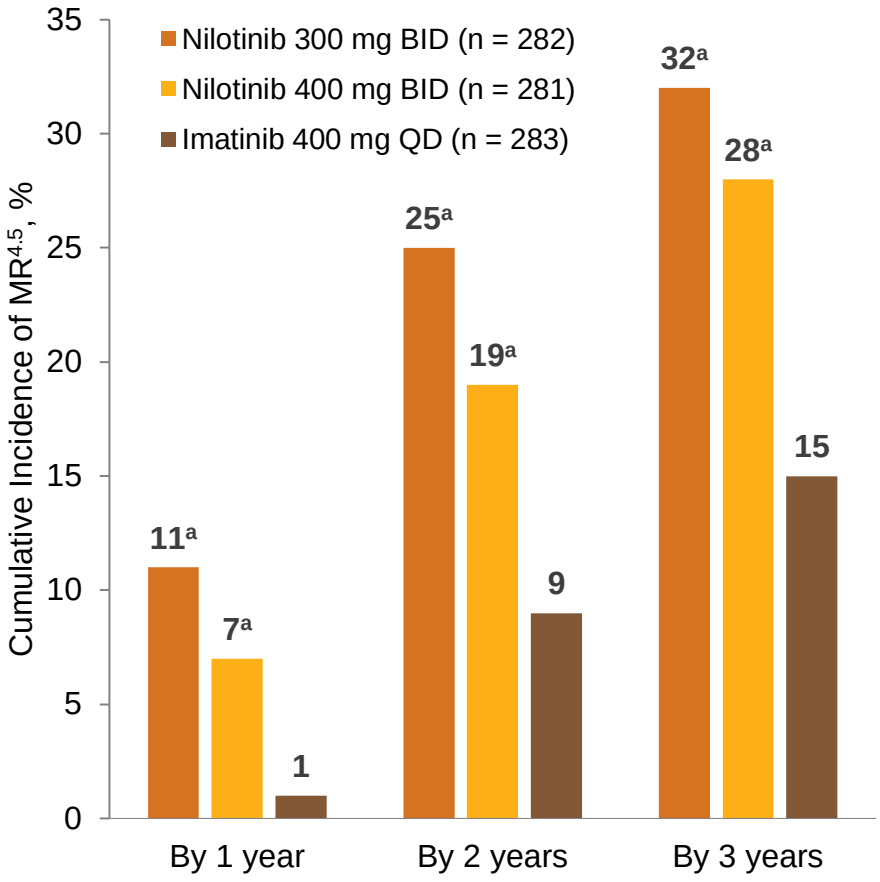


- 51.6% of patients (95% CI, 44.2%-58.9%) remained in TFR after 48 weeks (primary endpoint)

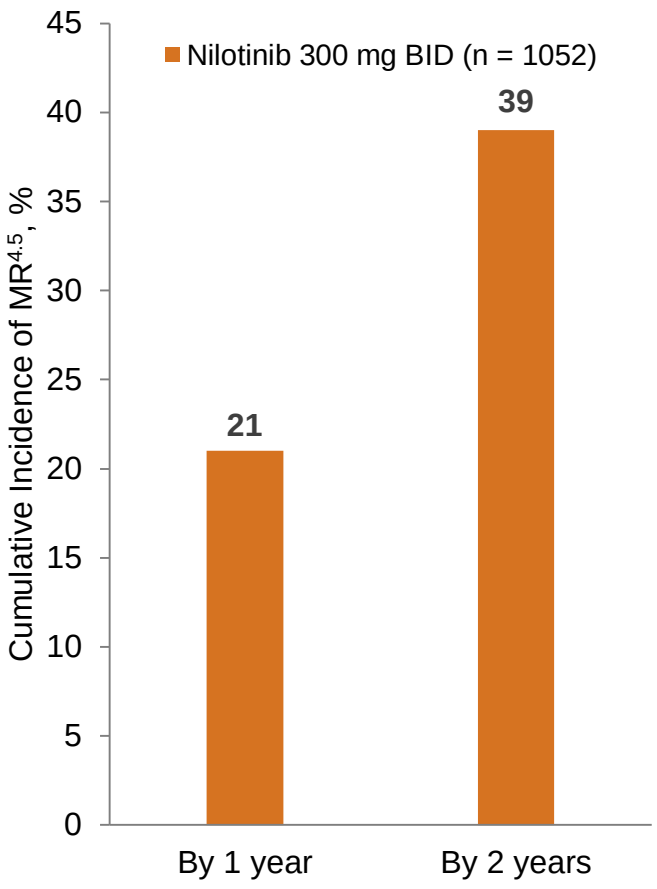
Hochhaus A, et al. J Clin Oncol. 2016;34 [abstract 7001].

Nilotinib Results in Higher Rates of MR$^{4.5}$ vs Imatinib

ENESTnd[1,2]



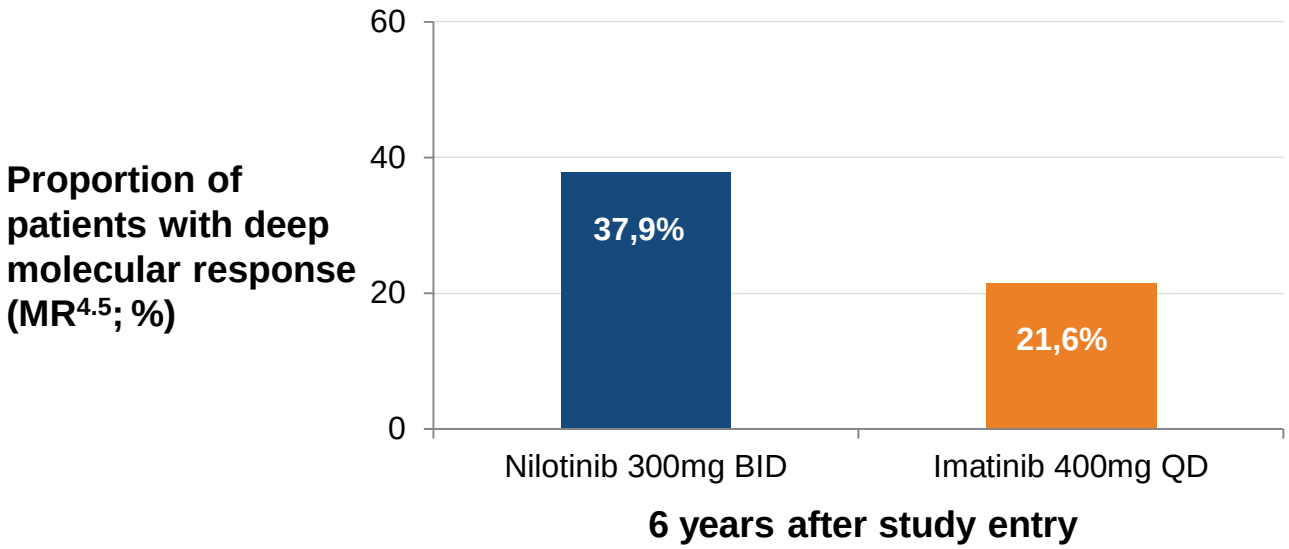
ENEST1st[3]



BID, twice daily; MR4.5, BCR-ABL1IS ≤ 0.0032%; ENESTnd, ENEST–Newly Diagnosed Patients; ; QD, once daily.
a Nominal P < 0.05 vs imatinib.

1. Kantarjian HM, et al. Lancet Oncol. 2011;12:841-851. 2. Larson RA, et al. Leukemia. 2012;26:2197-2203.
3. Hochhaus A, et al. Leukemia 2016;30:57-64 Blood.2013;122(21.

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

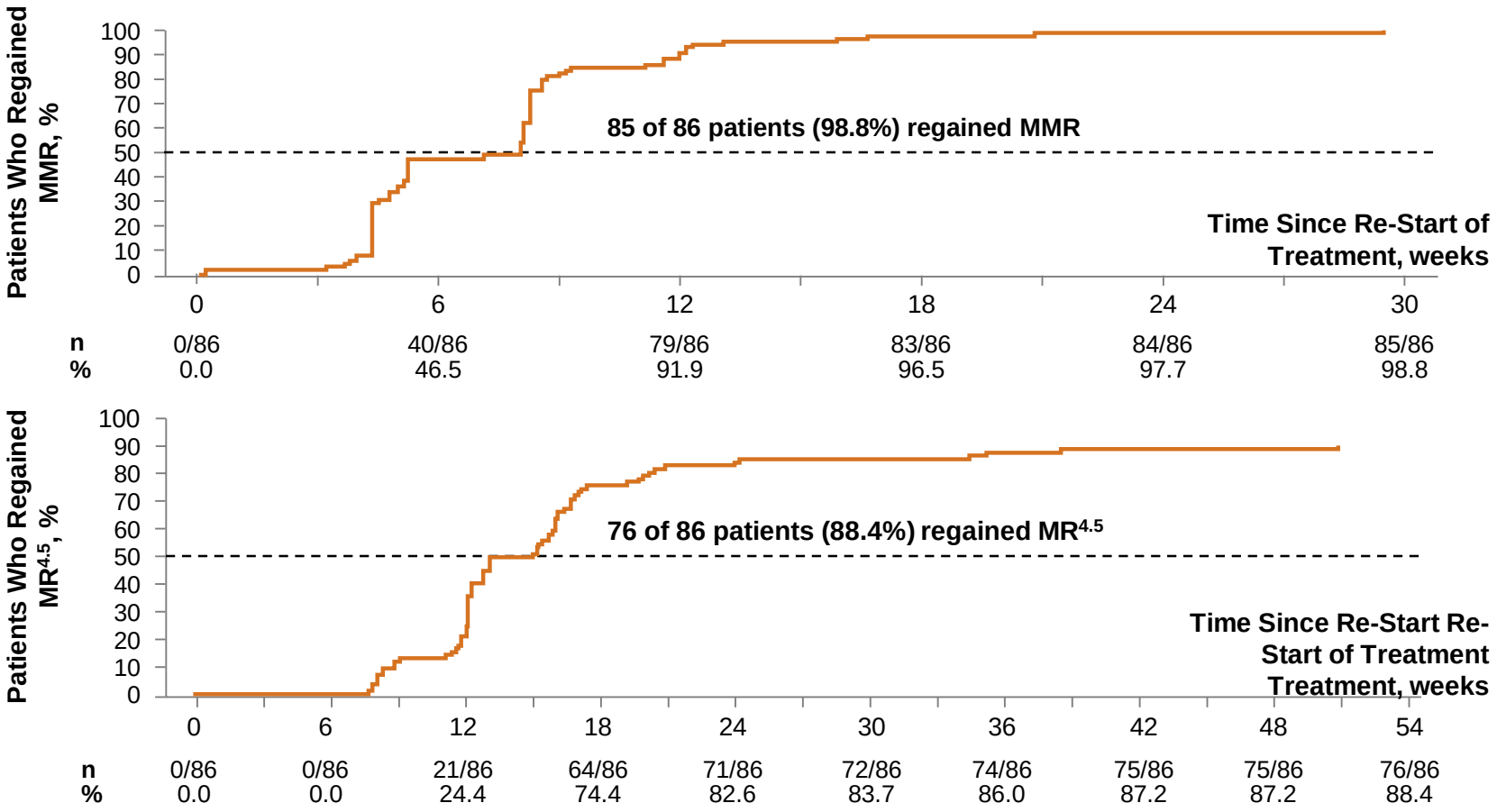
Sustained and deep molecular response in accordance to the ENESTfreedom protocol:

1. Achievement of a $MR^{4.5}$ or better in each RQ-PCR-based validation after ≥ 2 years of treatment with Nilotinib (Precondition for entering the consolidation phase).
2. After meeting the first requirement: sustained deep molecular response after ≥ 1 year. During this period, no RQ-PCR validation worse than MR^4 detected (≤ 2 validations between MR^4 und $MR^{4.5}$ and a final validation of $MR^{4.5}$ or better).

MR: deep molecular response; BID: twice per day; QD: once per day.

Modified after: A. Hochhaus *et al.*, "Impact of Treatment with Frontline Nilotinib (NIL) vs Imatinib (IM) on Sustained Deep Molecular Response (MR) in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP)," *Blood,* vol. 126, pp. 2781-2781, 2015; Abstract 2781.

ENESTfreedom: Response to Nilotinib Reinitiation



- 50% of all retreated patients achieved MMR and MR4.5 by week 7.9 and week 15.0 of treatment reinitiation, respectively

Hochhaus A, et al. J Clin Oncol. 2016;34 [abstract 7001].

ENESTfreedom: Clinically Notable Adverse Event Groups[a] (all grades)

Patients, n (%)	Consolidation Phase (n = 190)	TFR Phase (n = 190)
Musculoskeletal pain[b]	31 (16.3)	47 (24.7)
Fluid retention	4 (2.1)	8 (4.2)
Cerebrovascular events	4 (2.1)	5 (2.6)
Ischemic cerebrovascular events	1 (0.5)	2 (1.1)
Ischemic heart disease	2 (1.1)	0
Peripheral artery disease	1 (0.5)	2 (1.1)
Others	0	1 (0.5)
Rash	8 (4.2)	2 (1.1)
Pancreatitis	3 (1.6)	0

- Almost all AEs in the musculoskeletal pain grouping were grade 1/2 (1 patient in the consolidation phase and 2 patients in the TFR phases had grade 3/4 events)
- Comparable rates of „TKI Withdrawal Syndrome“ also reported in EURO-SKI[1]

a Each listed AE group includes a predefined set of individual AEs. Reported frequencies include all patients with ≥ 1 AE in the group.
b Defined as any of the following AEs: musculoskeletal pain, myalgia, pain in extremity, arthralgia, bone pain, and/or spinal pain.

Hochhaus A, et al. J Clin Oncol. 2016;34 [abstract 7001], 1. Richter et al, J Clin Oncol. 2016 [abstract S145]

Key Laboratory Abnormalities

	Consolidation Phase (n = 190)		TFR Phase (n = 190)	
Patients, n (%)	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Glucose ↑	74 (38.9)	1 (0.5)	36 (18.9)	1 (0.5)
ALT ↑	71 (37.4)	0	24 (12.6)	0
AST ↑	30 (15.8)	0	13 (6.8)	0
Bilirubin ↑	54 (28.4)	3 (1.6)	6 (3.2)	0
Lipase ↑	51 (26.8)	6 (3.2)	19 (10.0)	3 (1.6)

- There were no significant differences in hematologic abnormalities reported during the consolidation and TFR phases

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Molecular Monitoring → Key role in TFR

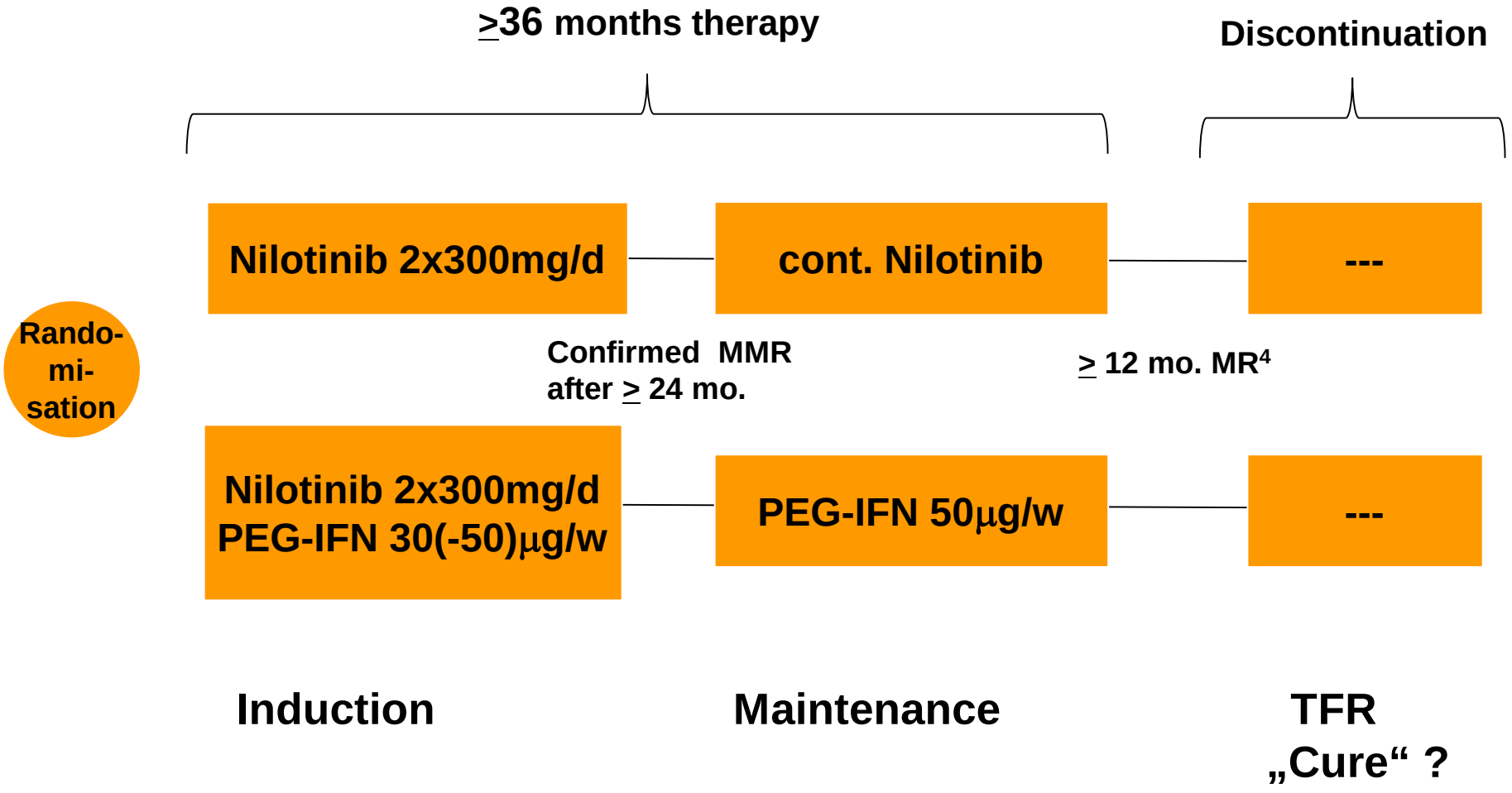
- Early and regular molecular monitoring during TKI-treatment:[1,2]
  - Assessment of prognosis
  - Validation of therapeutic response
  - Timely diagnosis of relapse or therapy resistance
  - Type of BCR-ABL transcript needs to be determined in advance
- Detection of a MR[4.5] as requirement for a possible discontinuation of TKI[3]
- Timely detection of a relapse for prompt reinitiation of TKI-Therapy
  - Highest risk of relapse within the first six months after discontinuation of treatment[4.5]
  - Recommended Monitoring[6]:
    - PCR every 4 weeks until month 6
    - PCR every 6 weeks from month 6 – 12
    - PCR every 12 weeks after month 12
- Standardized PCR-results are required as discontinuation of treatment is only safe in patients with a deep molecular response[3,4,5]

TFR: Treatment-free remission; TKI: Tyrosine Kinase Inhibitor; PCR: Polymerase Chain Reaction.

1. National Comprehensive Cancer Network (NCCN): Chronic Myelogenous Leukemia. Version I.2016; 2. Baccarani M et al. Blood. 2013;122:872–884; 3. Mahon FX. Ann Hematol. 2015;94(Suppl 2): S187–S193; 4. Etienne G, et al. ASH 2015, abstr. #345; 5. Mahon FX, et al. ASH 2014, abstr. #151; 6. Hochhaus A, et al. Deutsches Ärzteblatt – Perspektiven der Onkologie 1/2016

TIGER STUDY

TKI + Interferon trial initiated by the GERman CML Study Group)



TKI Discontinuation: A Novel Treatment Objective

- Multiple studies have consistently demonstrated the safety and feasibility of stopping treatment
- TKI discontinuation is an emerging goal of CML management and is happening right now
- Patient awareness of TFR has resulted in increasing need for who can appropriately discontinue TKI
- A sustained DMR and long-term TKI therapy seem to be necessary prior to attempting TFR

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,
achievement of $MR^{4.5}$,
and a stability of DMR (at least MR^4) for at least 2 years

PRELIMINARY

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