UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

CML: 2017

Role of combination treatments, Interferon and immunotherapy in CML

Andreas Burchert

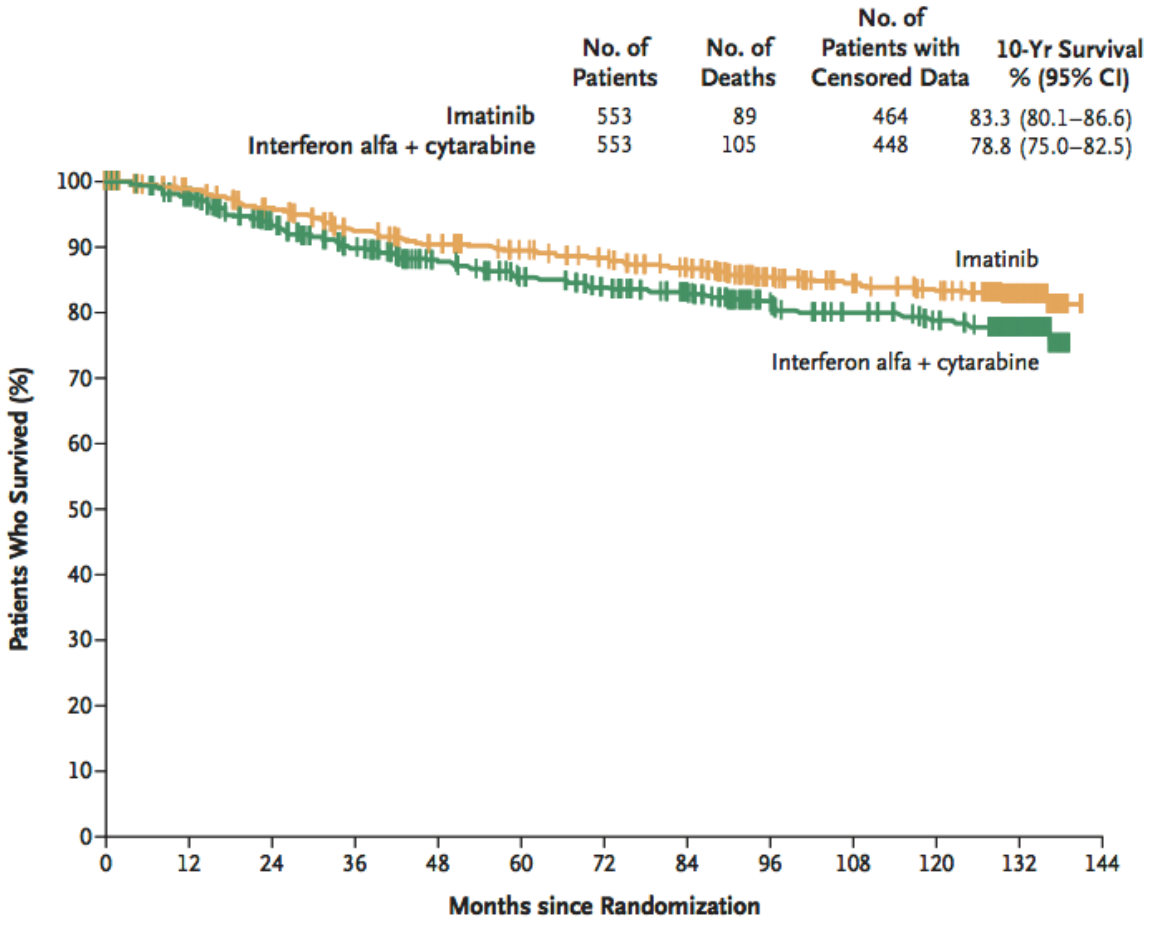
Philipps Universität Marburg
Universitätsklinikum Gießen und Marburg
GmbH

Key Developments that will Change the Treatment Landscape Over the Next 5 Years?

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

1. **therapy failure / early progression**
2. **side effects / toxicities**
3. **discontinuation / cure**

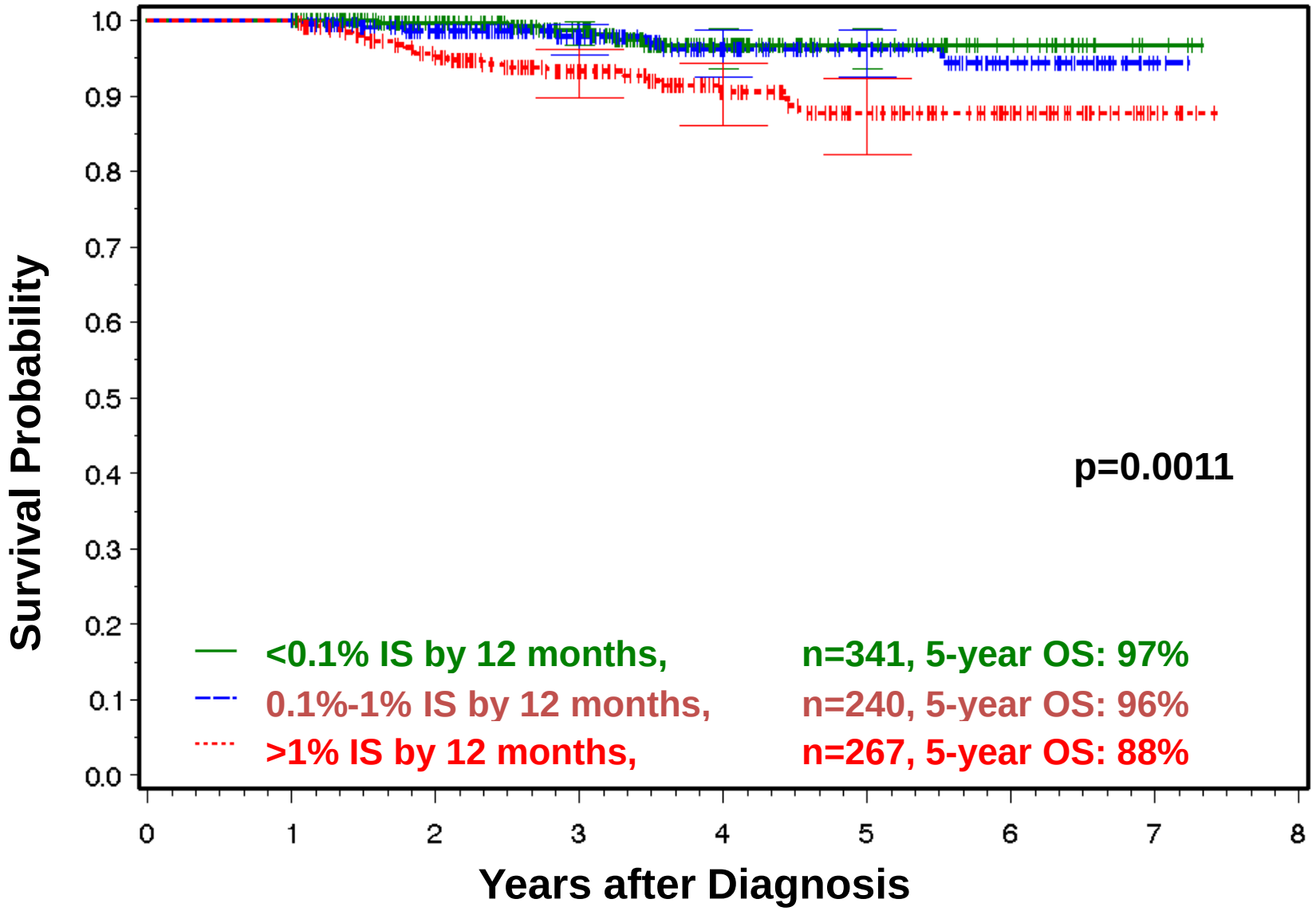
Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia.



Hochhaus, A., et al. (2017). Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *The New England Journal of Medicine*, *376*(10), 917–927.

Molecular response at 12 months predicts overall survival (CML-IV)

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

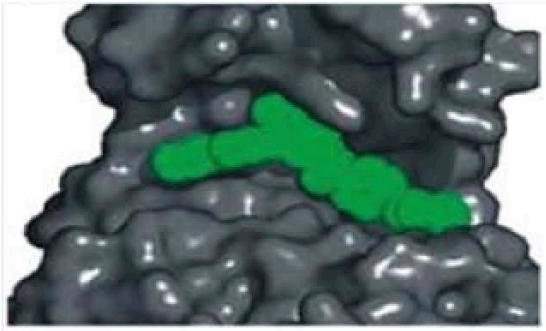
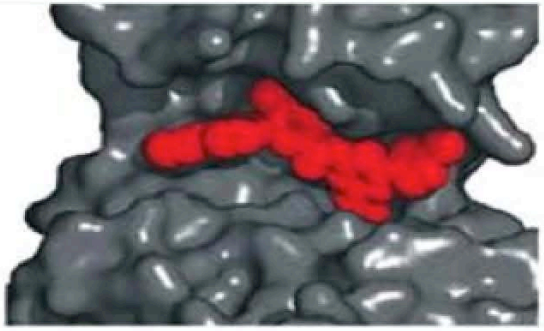
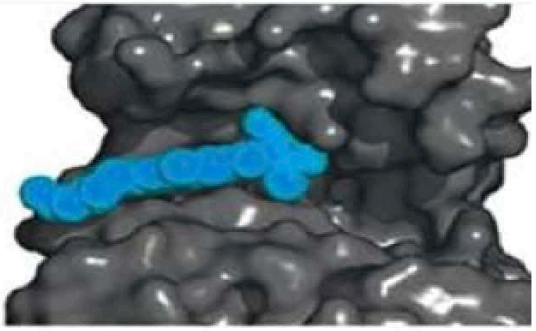


Hehlmann et al., J Clin Oncol 2011

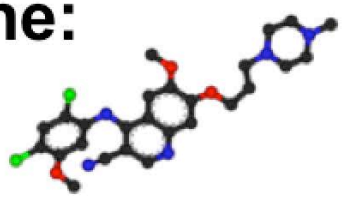
Kinase inhibitors in CML

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

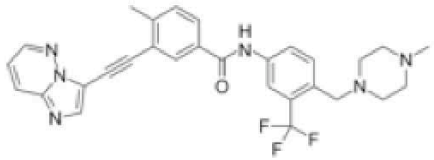
First Line:

Imatinib	Nilotinib	Dasatinib
		
400mg QD	300mg BD	100mg QD

≥ 2nd Line:



Bosutinib



Ponatinib

Allo-Tx
INF-α
HU
Omacetazine
Experimental

Imatinib generics .....

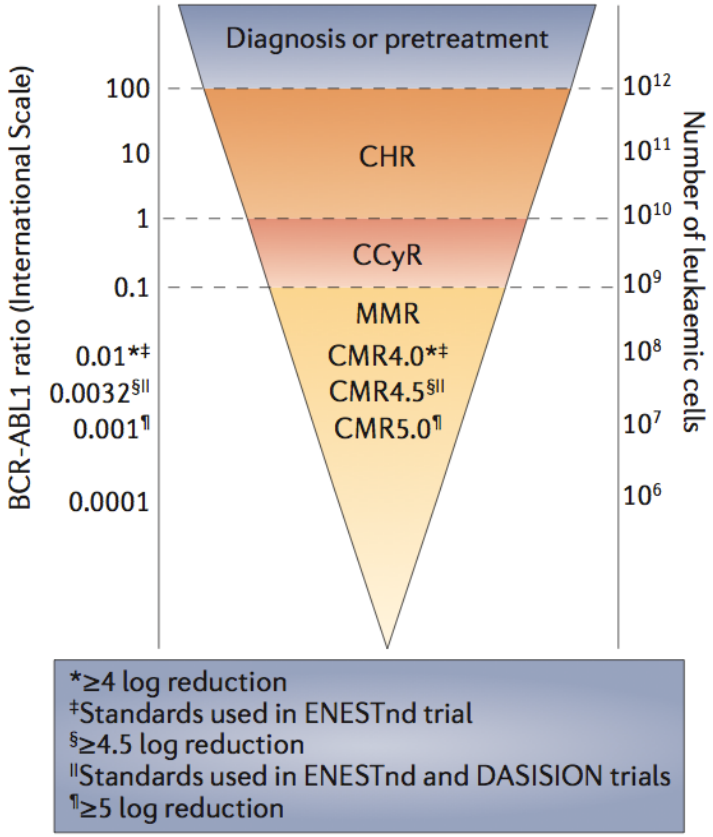
Key Developments that will Change the Treatment Landscape Over the Next 5 Years?

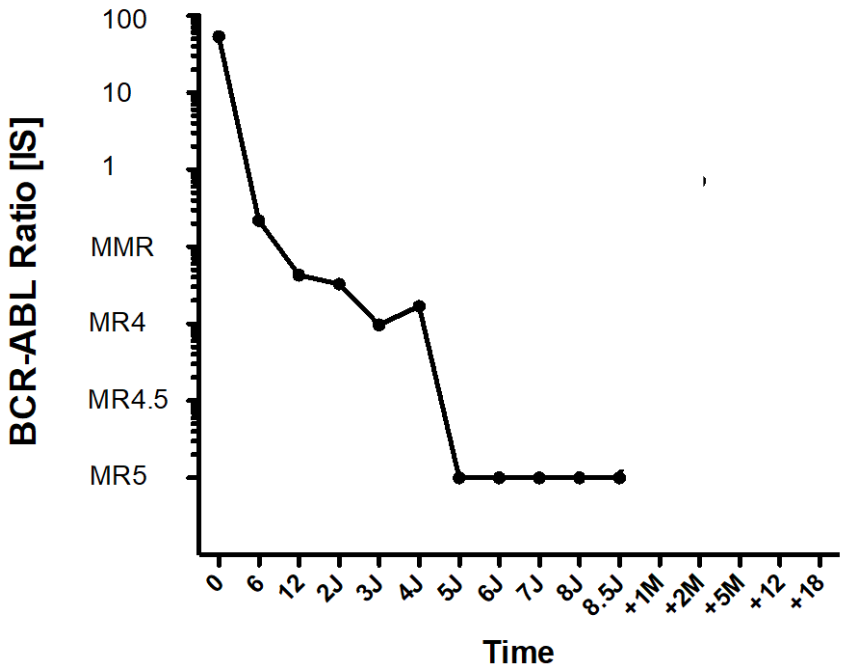
UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

1. therapy failure / early progression
2. **side effects / toxicities**
3. discontinuation / cure

8.5 years Imatinib

Remission „depth“ in CML





O´Hare, Nat. Rev Cancer 2012

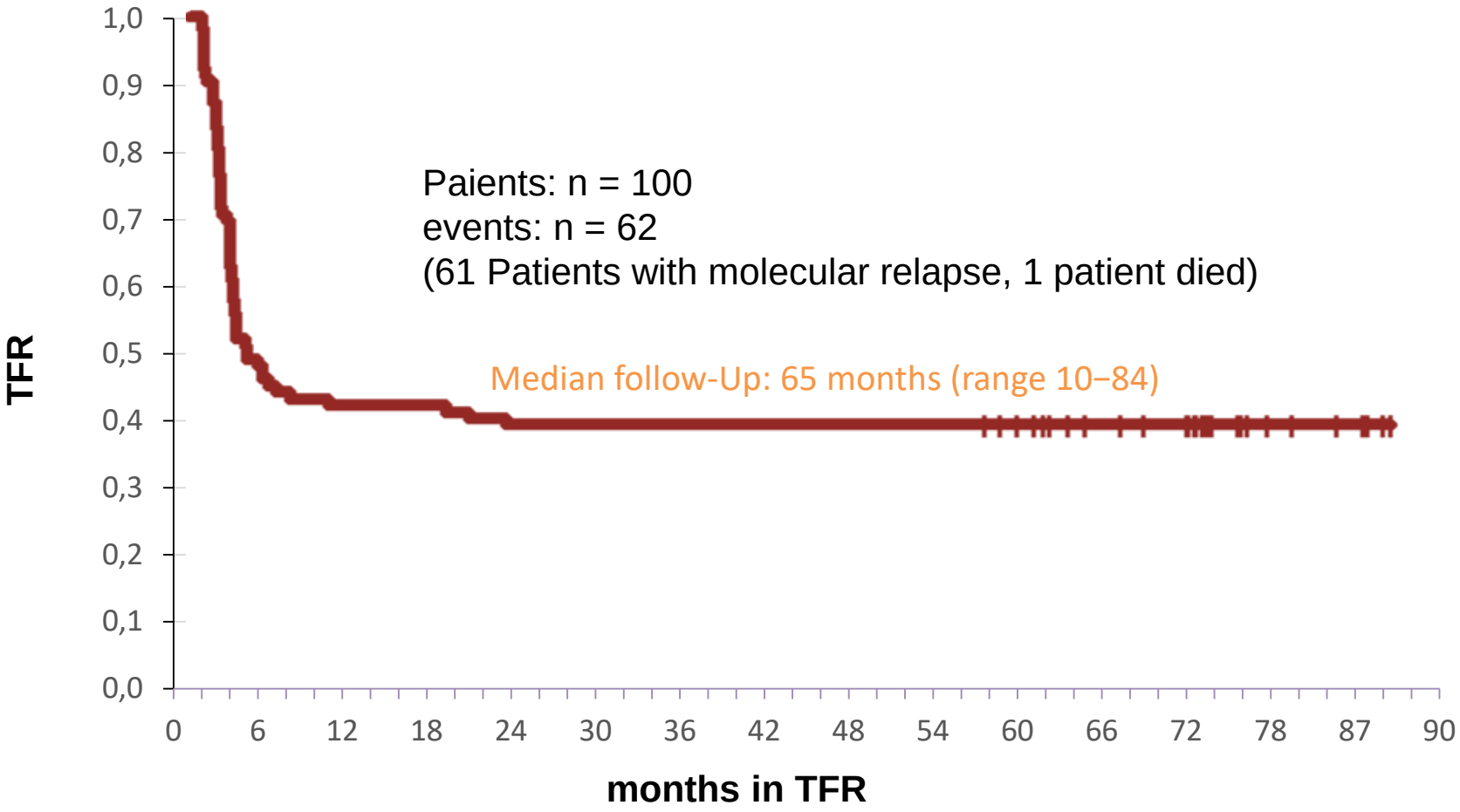
Key Developments that will Change the Treatment Landscape Over the Next 5 Years?

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

1. therapy failure / early progression
2. side effects / toxicities
3. **discontinuation / cure**

STIM1: Patients with undetectable BCR-ABL levels discontinued imatinib and maintained remission

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG



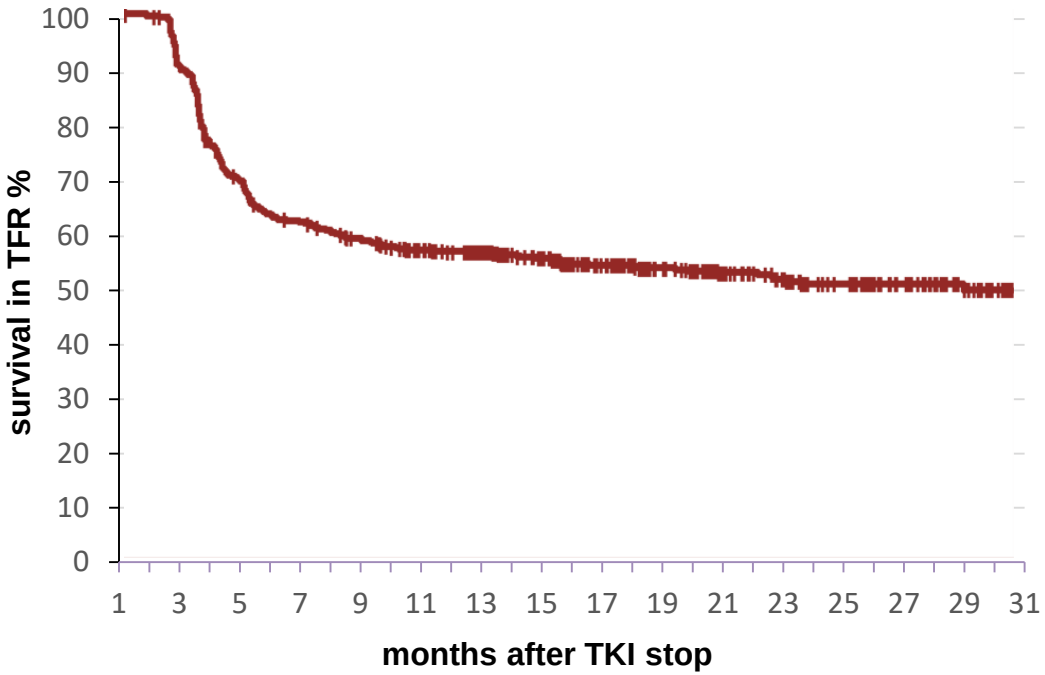
- maintained TFR @ 6 months: 10% risk of molecular relapse @ 24 months

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

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

- Who is a candidate ?

EURO-SKI: Survival in TFR (n = 750)



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

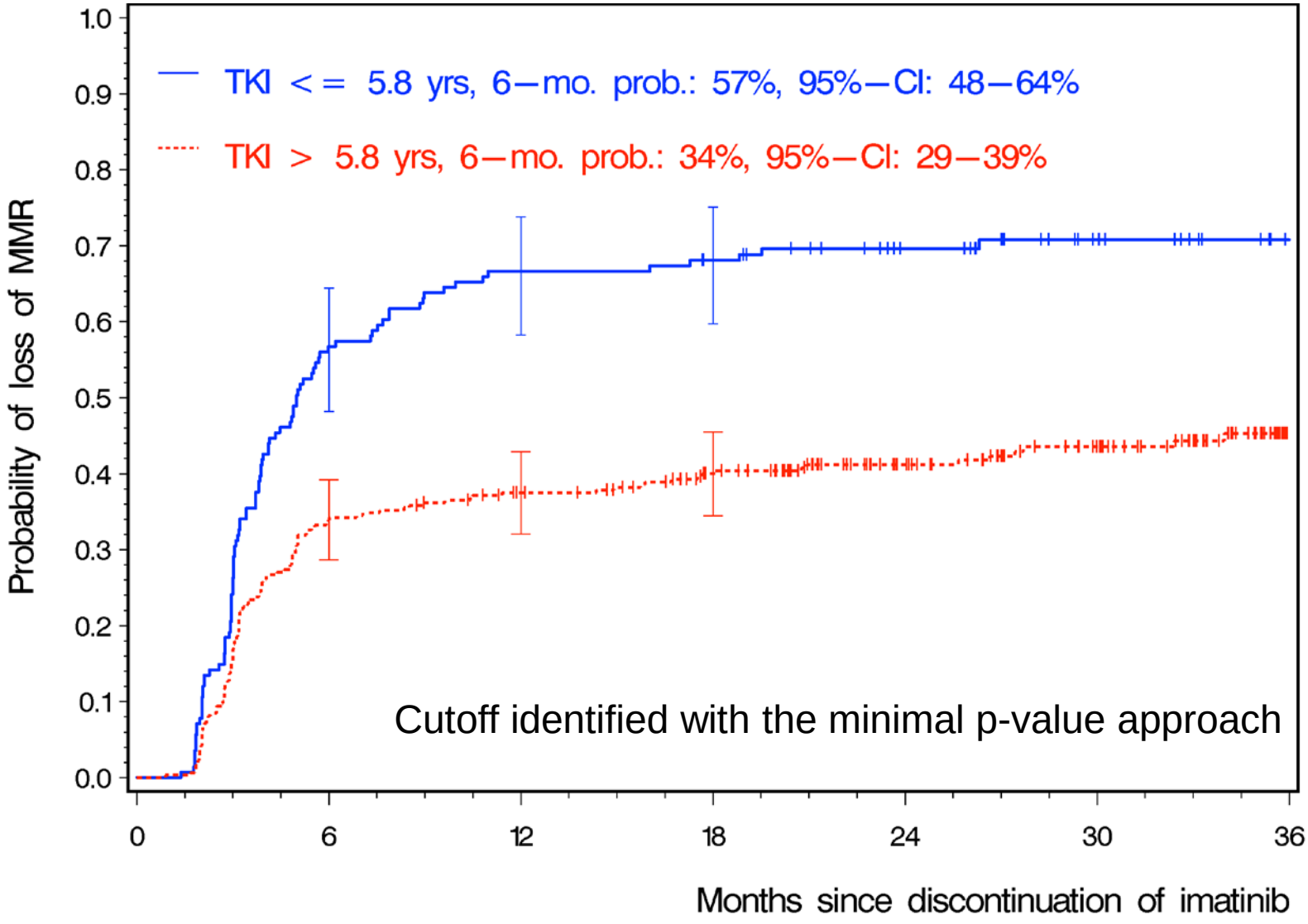
Events:
Molecular relapse (>0.1% IS, loss of MMR: n = 348
Deaths in remission: 5

Median time to re-treatment: 4,1 months

Richter et al, Haematologica 2016; [abstract S145]

Treatment duration cut-off for loss of MMR at 6 mo.: 5.8 years of imatinib

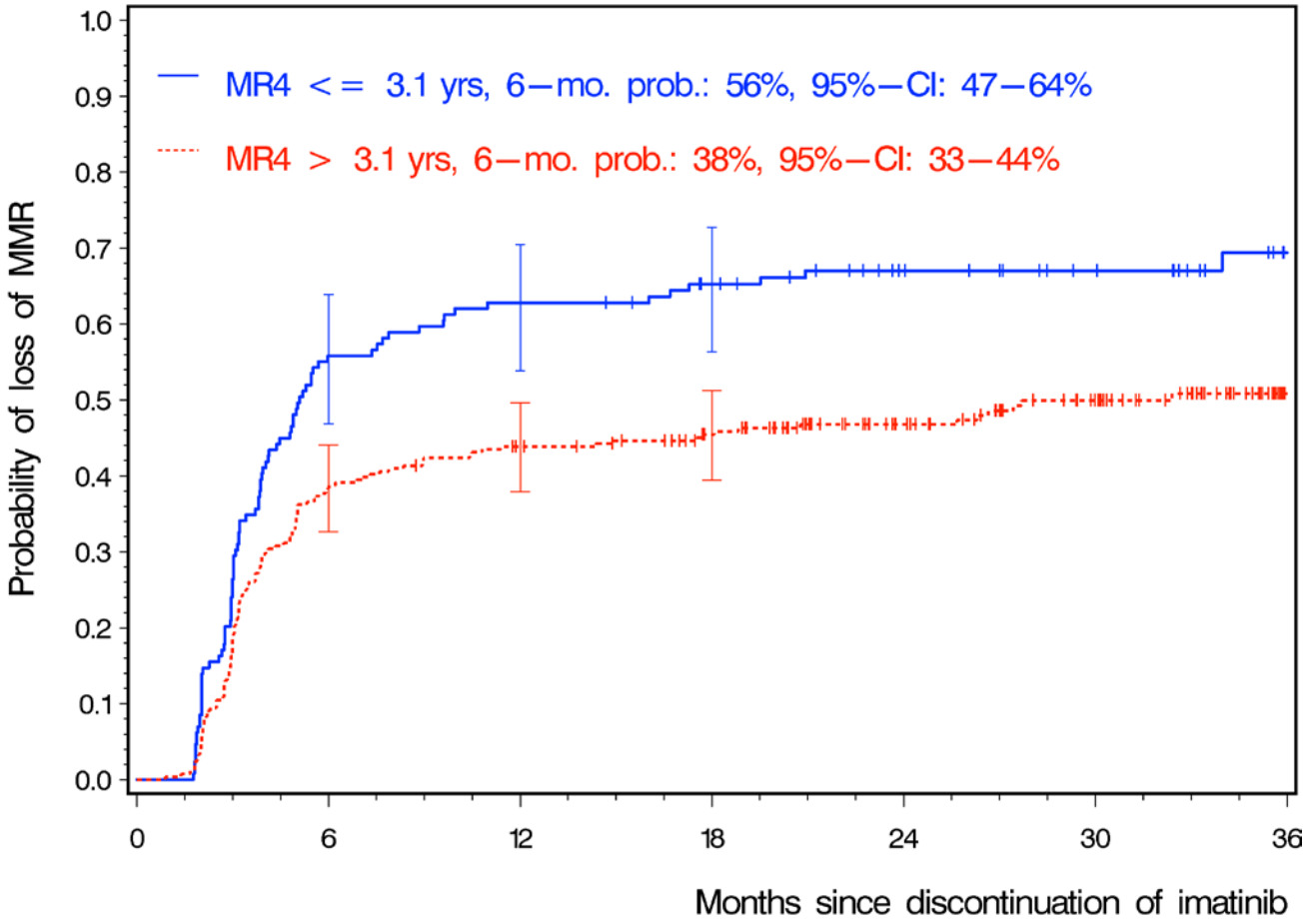
UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG



EURO-SKI presented by FX Mahon at ASH 2016

Prognostic modeling (n=405, imatinib)

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

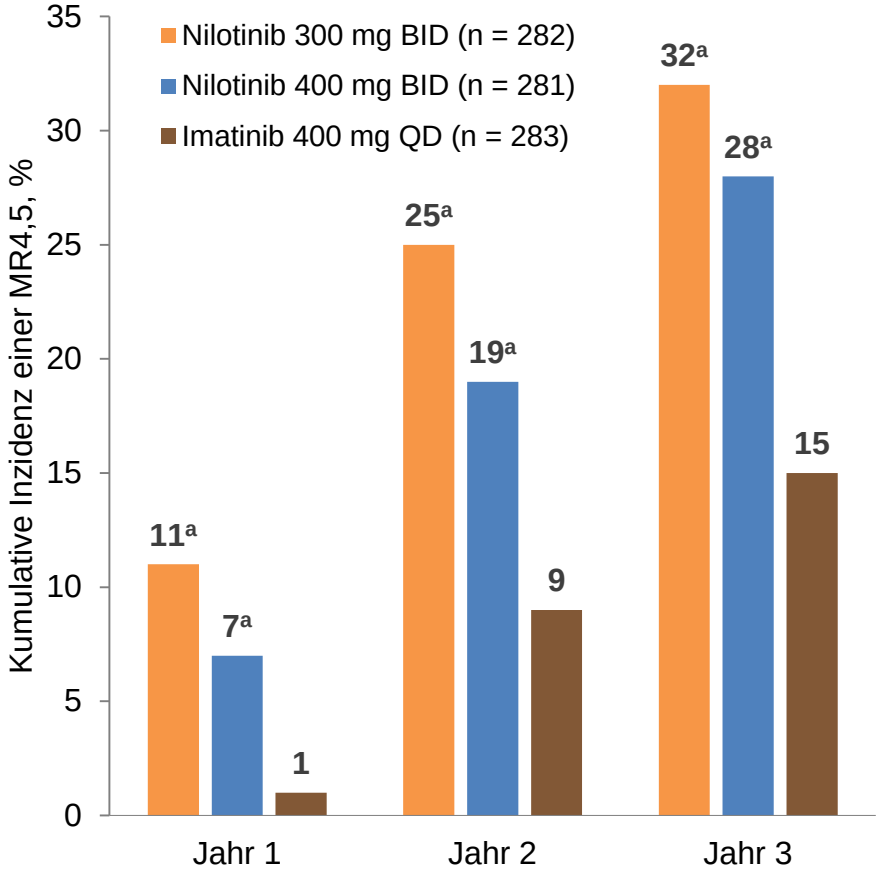


*20% of the patients in the smallest group

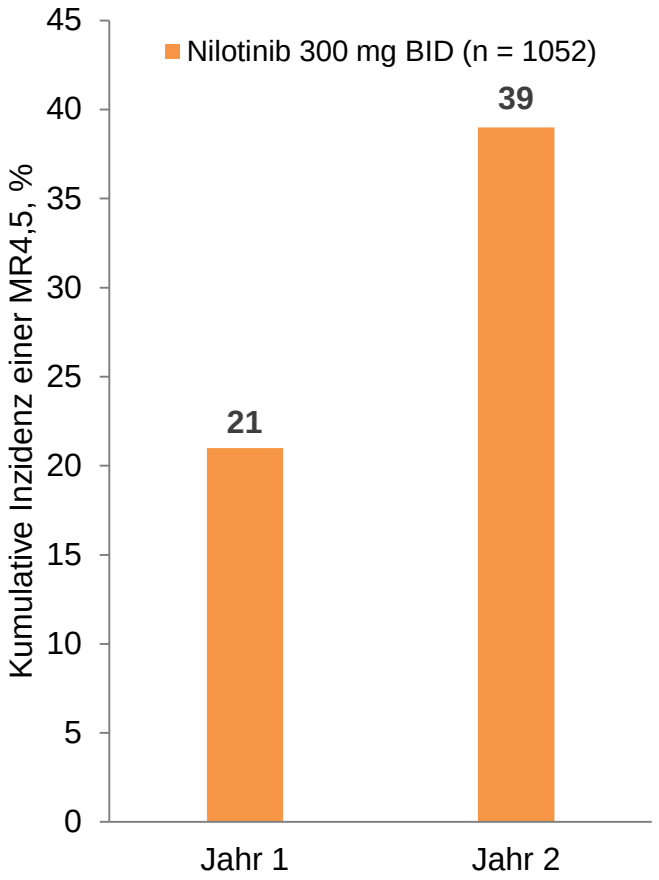
EURO-SKI presented by FX Mahon at ASH 2016

Higher rates of MR$^{4.5}$ within first 3 years with nilotinib compared to Imatinib

ENESTnd[1,2]



ENEST1st[3]



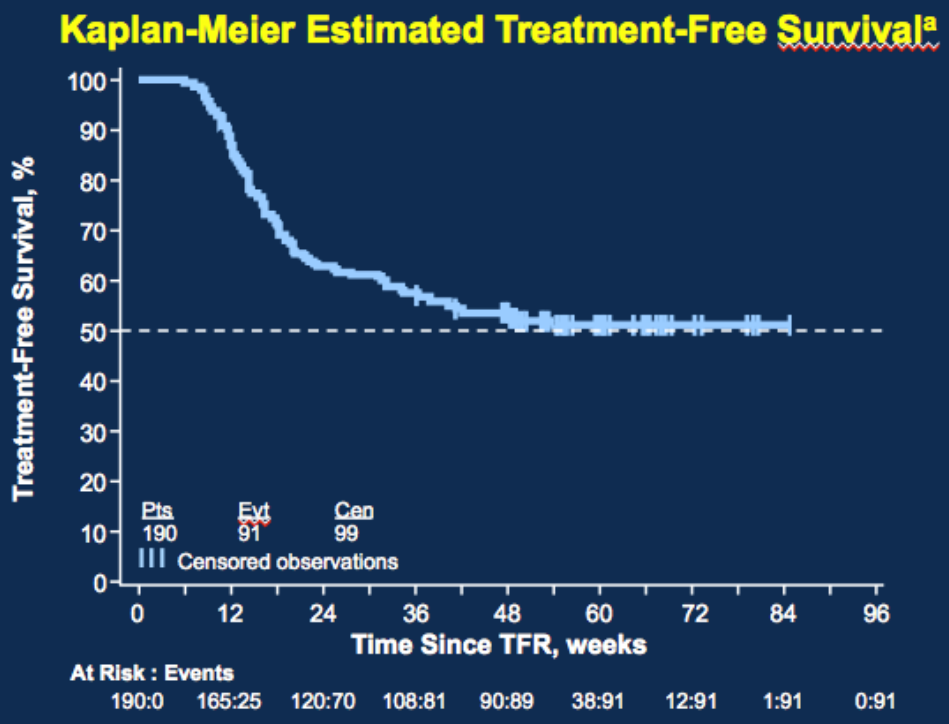
BID, zweimal täglich; MR^{4,5}, BCR-ABL1(IS) ≤ 0,0032%; ENESTnd, ENEST–Newly Diagnosed Patients; ; QD, einmal täglich.
a Nominal p < 0,05 vs. Imatinib.

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.

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

Primary Endpoint and Treatment-Free Survival

- 98 of 190 patients (51.6%; 95% CI, 44.2-58.9%) remained in TFR after 48 weeks (primary endpoint)
- Statistical criterion for trial success was that the lower limit of the 95% CI of the observed primary endpoint be > 50%



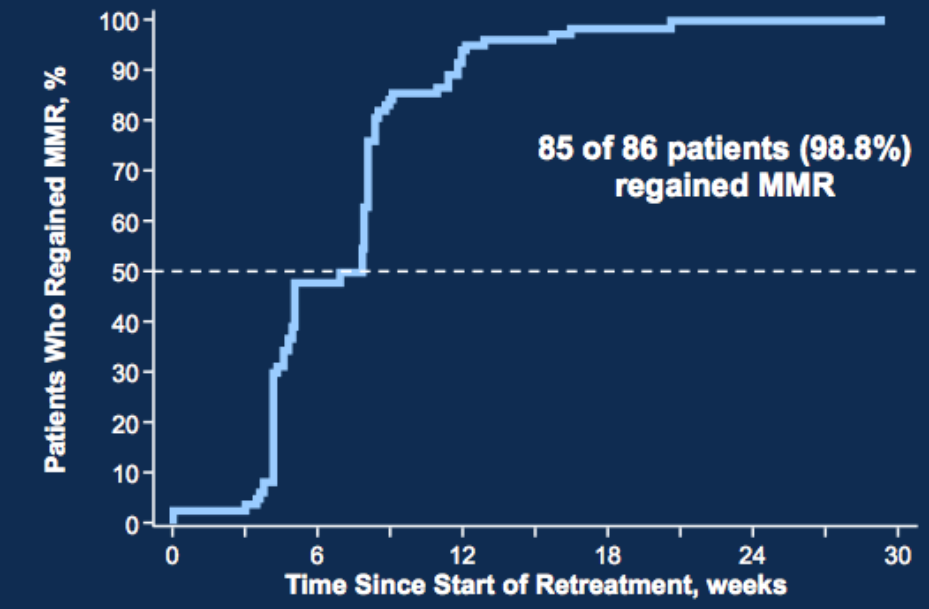
[a] Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause.

Slides are the property of the author. Permission required for reuse.

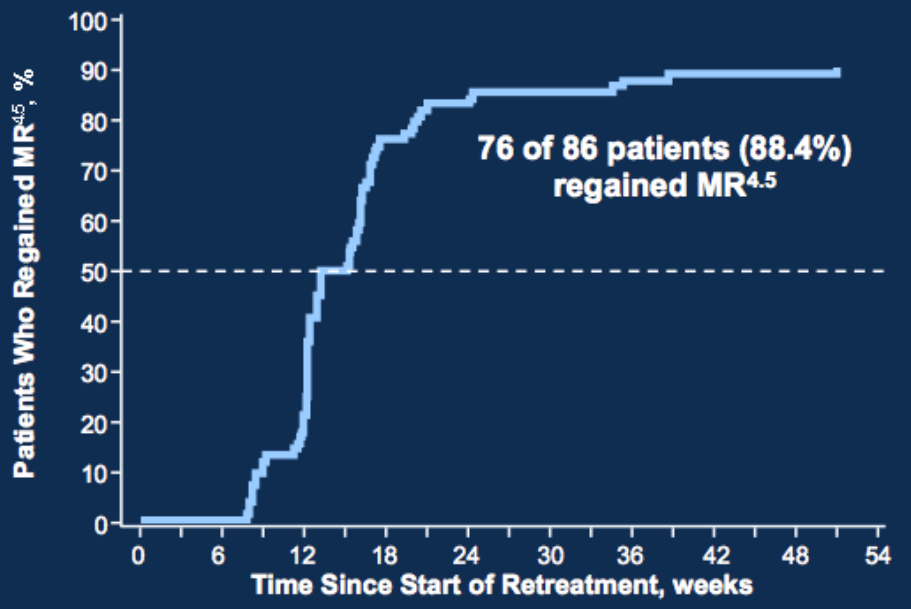
Hochhaus A, et al. Leukemia 2017

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

Response to Nilotinib Reinitiation



Cumulative/n	0/86	40/86	79/86	83/86	84/86	85/86
Cumulative %	0.0	46.5	91.9	96.5	97.7	98.8



Cumulative/n	0/86	0/86	21/86	64/86	71/86	72/86	74/86	75/86	75/86	76/86
Cumulative %	0.0	0.0	24.4	74.4	82.6	83.7	86.0	87.2	87.2	88.4

- By week 7.9 and week 15.0 of treatment reinitiation, 50% of all retreated patients already achieved MMR and $MR^{4.5}$, respectively

PRESENTED AT: ASCO ANNUAL MEETING '16

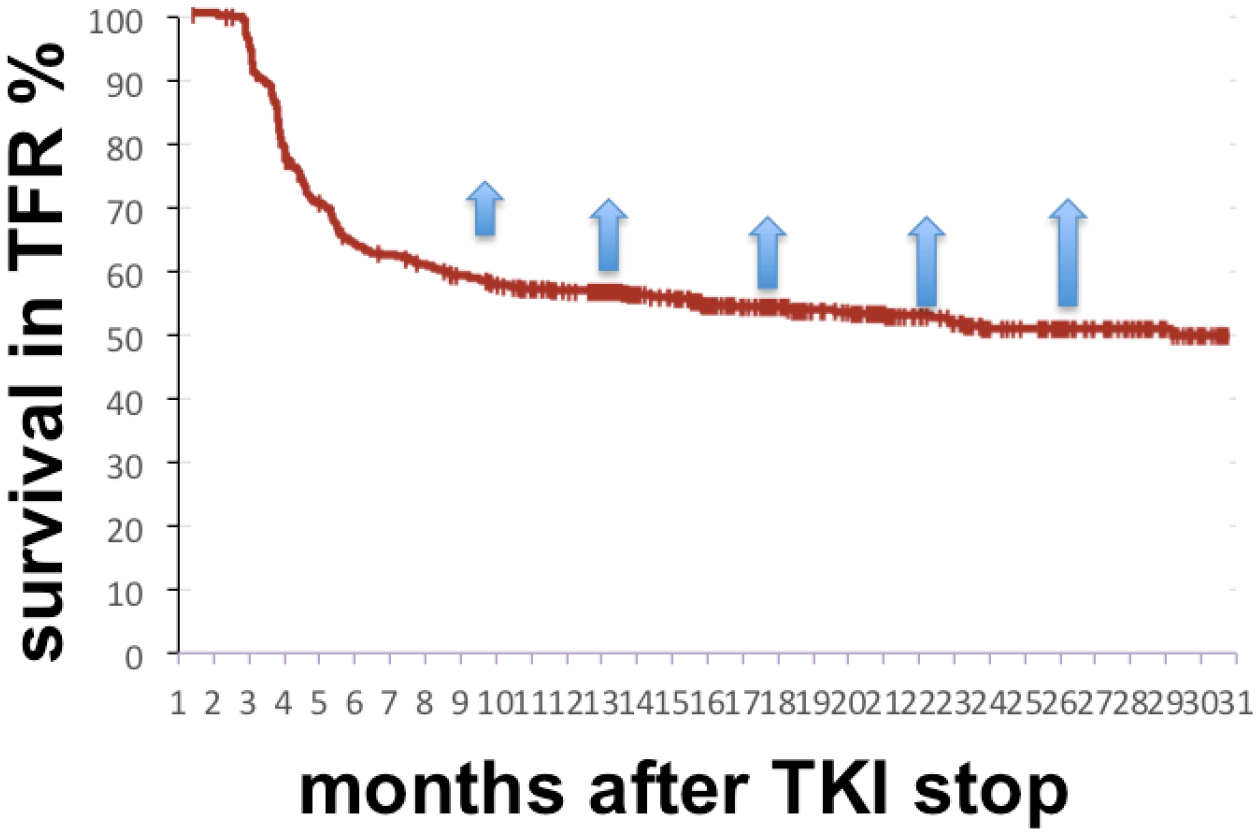
Slides are the property of the author. Permission required for reuse.

Presented by: Prof Andreas Hochhaus

Hochhaus A, et al. Leukemia 2017

Medical Need

EURO-SKI: Survival in TFR (n = 750)



Events:

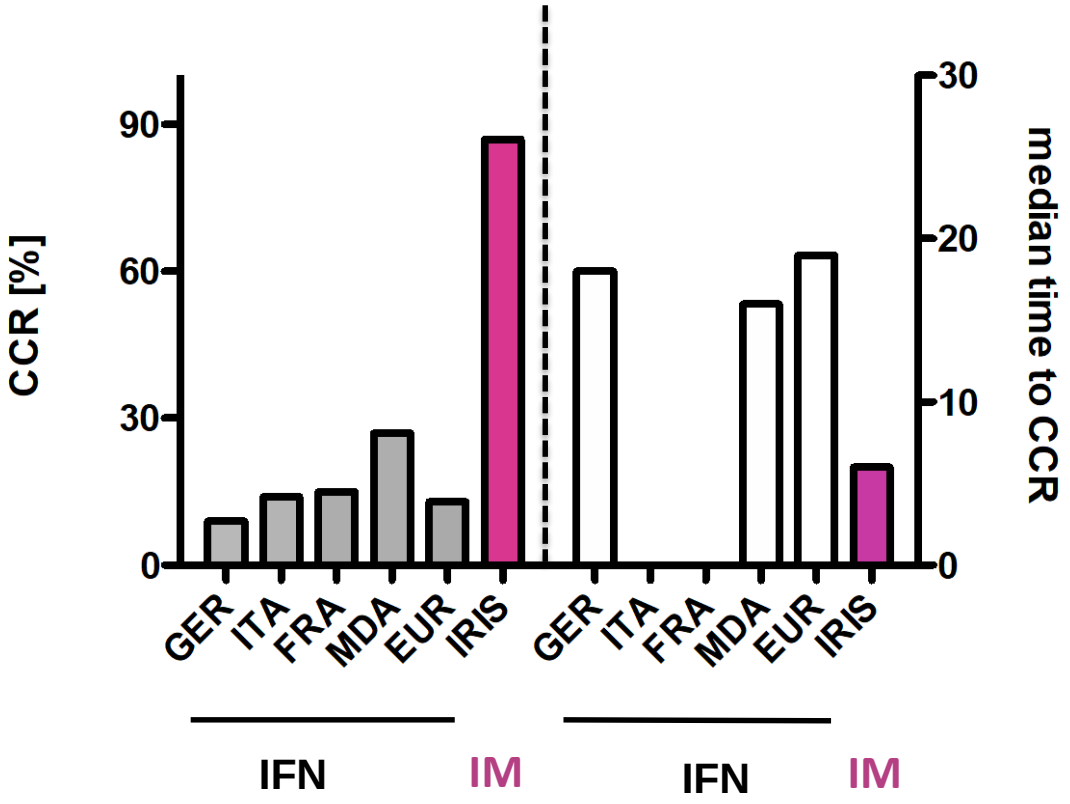
molecular relapse (>0.1% IS, loss of MMR)

Richter et al, Haematologica 2016; [abstract S145]

Interferon – again ?

Rationales ?

Interferon monotherapy is ineffective in CML



Hehlmann et al., Leukemia 2003
Baccarani et al., Blood 2002
Guilhot et al., NEJM 1997
Kantarjian et al., Cancer, 2003
Druker et al., NEJM 2006
Bonifazi et al., Blood 2001

1.

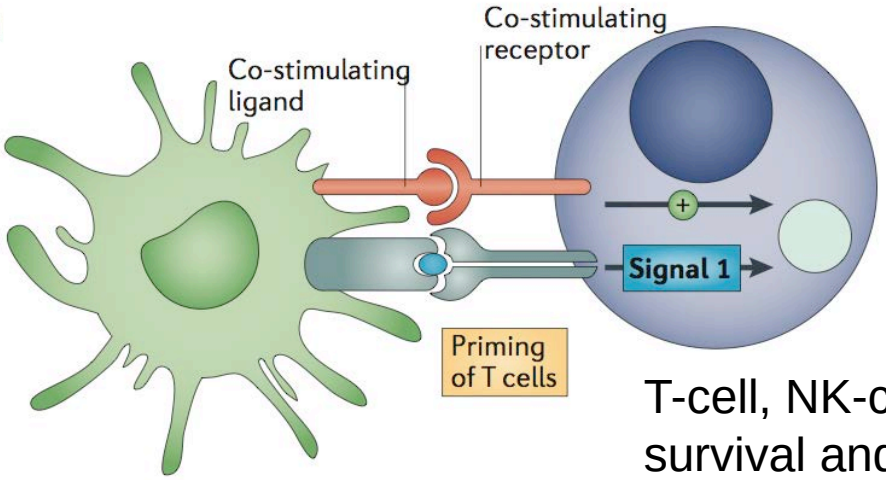
TKI$^{1st,\ 2nd}$ plus/minus IFN: remission depth

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

	12 months MMR	5 years MR$^{4.5}$	
Imatinib	≈ 40%	≈ 30-40%	Cortes et al. ASH 2013 Saglio et al., ASH 2013 Hochhaus A., Leukemia 2016
TKI ^{2nd}	≈ 50%	≈ 40-50%	
Imatinib + IFN	≈ 60%	≈ 40-55%	Baccarani et al. Blood 2002, Palandri et al., Haematologica 2010 Preudhomme et al, NEJM 2010 Simonsson et al., Blood 2011 Hehlmann et al., J Clin Oncol 2011
Nilo or Dasa + IFN	≈ 80%		Nicolini et al., Lancet Haematol 2015 Hjorth-Hansen et al., Leukemia 2016
TKI ^{2nd} after IM MR4.5 failure		≈ + 13% after 2y.	ENESTcmr study Hughes et al., Blood 2014

2.

IFN-α mechanism of action

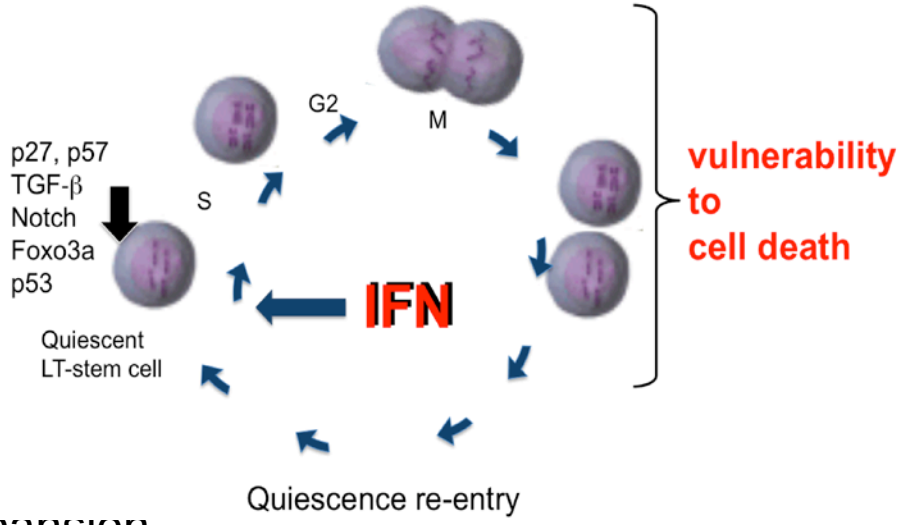


DC: antigen cross-presentation

Luft et al., 1998
Gallucci et al.,1999
Montoya et al., 2002
Gallucci et al., 1999
Le Bon et al., 2001, 2003
Diamond et al., 2011

T-cell, NK-cell survival and expansion

Marrack et al., 1999, Curtsinger et al. 2005
Le Bon et al., 2006



Essers et al., Nature 2009
Pietras et al., JEM 2014

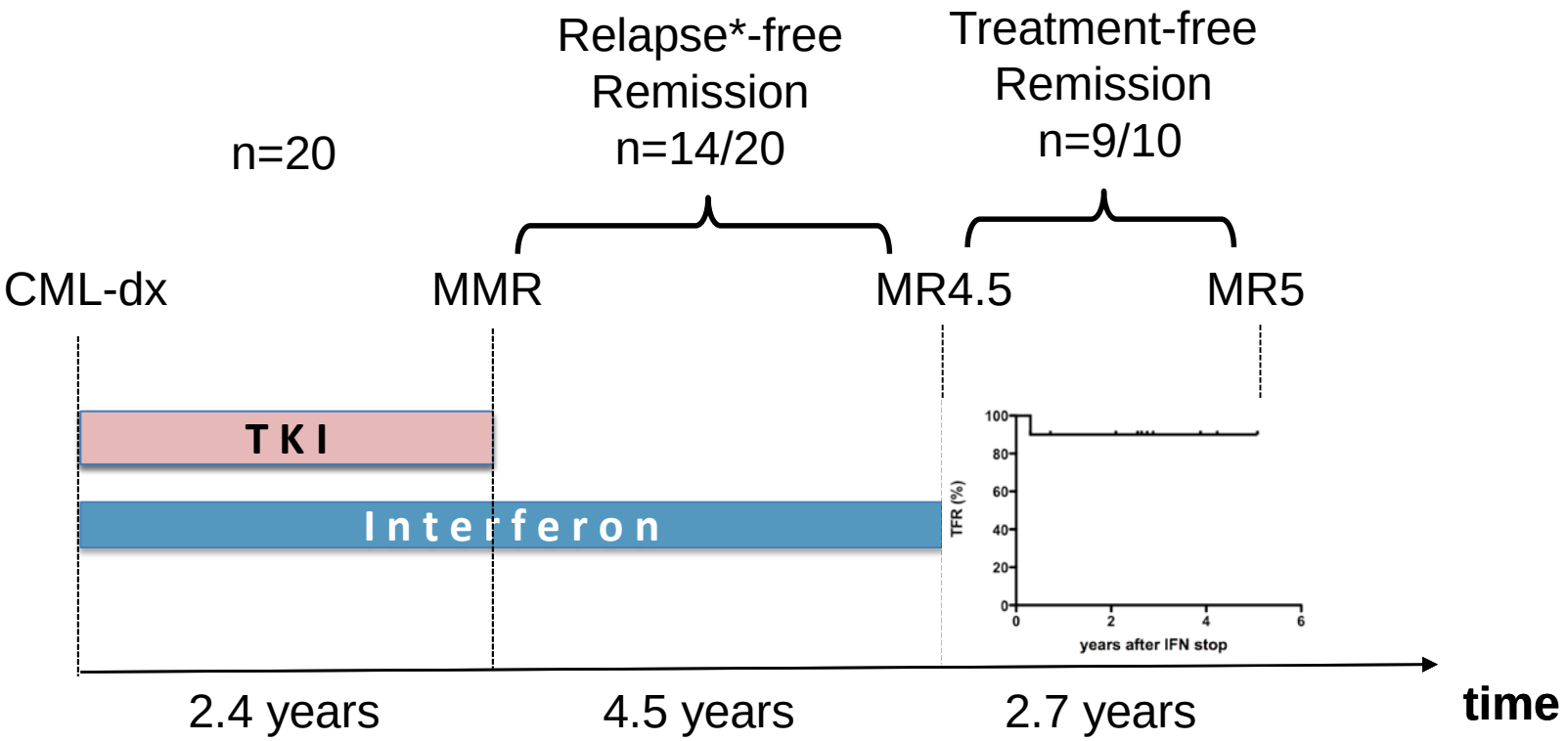
IFN-α/β signaling

Left figure from: Pardoll et al, Nat Rev Cancer 2012

3.

Interferon maintenance after IFN/TKI combination therapy

UKGM
UNIVERSITÄTSKLINIKUM
GIESSEN UND MARBURG

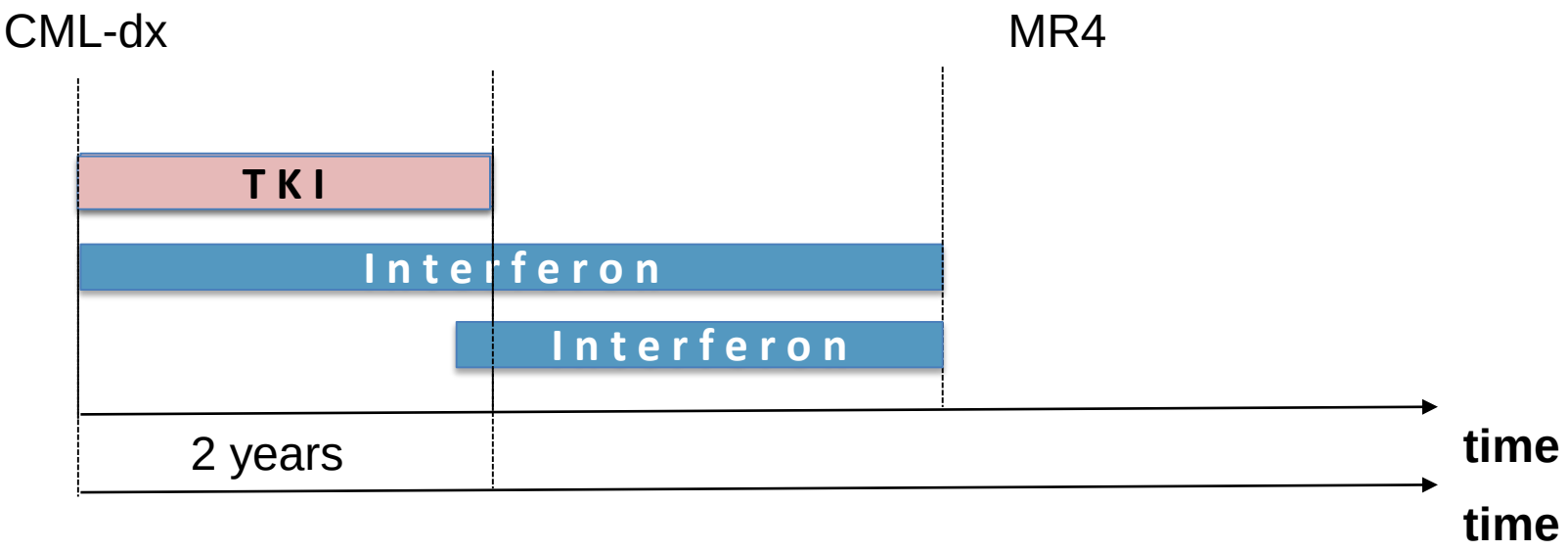


* Relapse defined as PCR-value of > 0.1% at any time later than 3 months after stopping imatinib

Burchert et al., 2010
Burchert et al., 2015

Interferon maintenance after IFN/TKI combination therapy

Interferon maintenance after TKI induced remission (ENDURE)



ENDURE-CML (CML-IX)

EFFICACY AND SAFETY OF PEGYLATED-PROLINE- INTERFERON ALPHA 2B (AOP2014) IN MAINTAINING DEEP MOLECULAR REMISSIONS IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML-IX) WHO DISCONTINUE ABL-KINASE INHIBITOR THERAPY

A randomized, open-label, controlled Phase II, multicenter trial

with Post-Study Follow-up

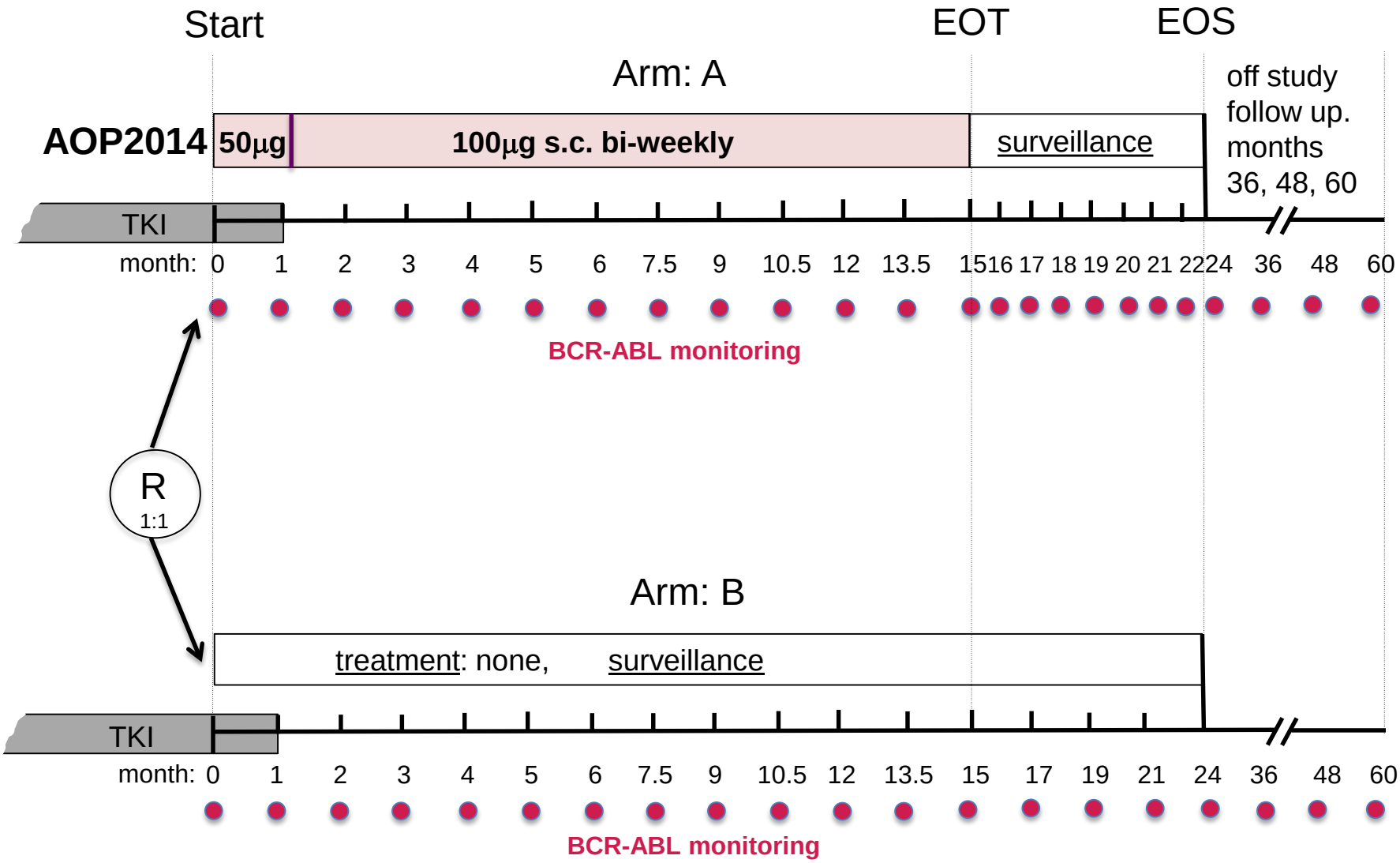
Funding: Deutsches Krebshilfe
Co-Funding: AOP Orphan Pharmaceuticals AG

Coordinating Investigator:
Prof. Dr. Andreas Burchert (Marburg)

EudraCT: 2016-001030-94

8.5 years Imatinib

ENDURE – CML (CML-IX)
Randomized phase II Ropeg-IFN maintenance study



A. Burchert

ENDURE Study
Inclusion and Exclusion Criteria*

Inclusion Criteria:

- At least three years of TKI therapy
- BCR-ABL-positive, chronic phase CML patients with a transcript level according to the international scale (IS) of at least MR^4

  (3 values in the year preceeding study)
- MR4 (or better) must be confirmed before baseline in PCR Laboratories Mannheim or Jena

---

* Only MAIN Inclusion and Exclusion criteria are listed
(please refer to protocol for complete list)

ENDURE Study
Efficacy Variables

Primary endpoint:

- molecular relapse* free survival (RFS) @ month 6 after TKI stop (month 7 after randomisation)

  (*relapse = loss of MMR)

Secondary endpoints:

- molecular relapse*free survival (RFS) @ month 12 & 24
- Treatment outcome correlation with predefined biomarkers

  (> or < 95 $CD86^{+}$pDC before TKI discontinuation, PD-1L, PD1 expression, PR1-CTL and cytokines in peripheral blood measured at date of randomization and at designated time point thereafter).

Concerns against TKI discontinuation unjustified ?

Summary

What will be key developments that will change the treatment landscape in CML over the next 5 Years?

1. **CML first line strategies: goal will be fast achievement of deep MR as a prerequisite for treatment discontinuation and treatment free remission (TFR)**

   - second generation TKI
   - TKI + pegylated IFN induction and maintenance
   - TKI + …. (Ruxolitinib, ABL001, etc.) ???

2. Concepts to treat primary therapy failure and resistance
   - TKI + ABL001

3. Concepts to improve TFR after TKI upfront
   - pegylated IFN maintenance
   - checkpoint inhibitors