Clinical Trials Focused on Treatment-Free Remission (TFR)

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Arguments in Favor of Making TFR a Key Goal of Therapy

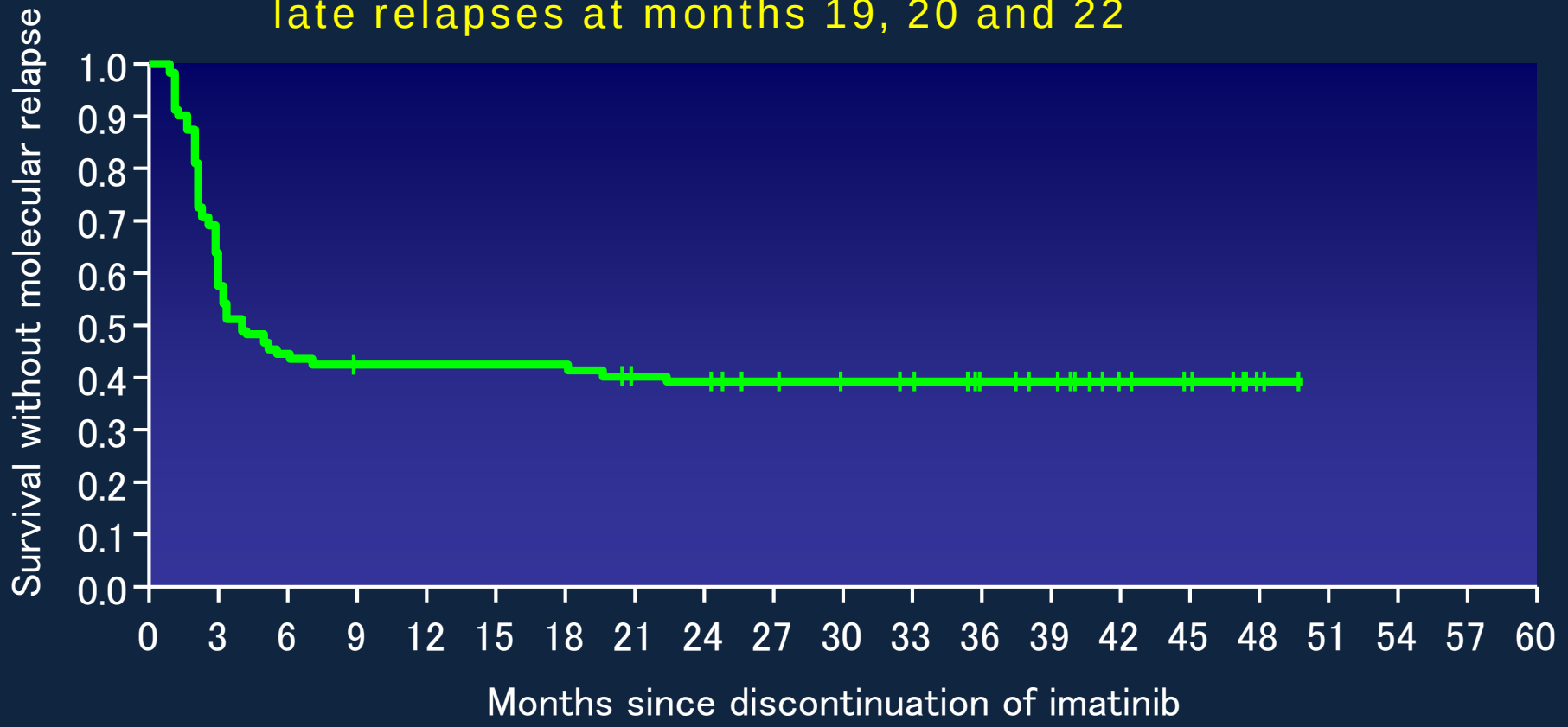
- Potential for long-term toxicity of TKI therapy
- Quality of life impact of TKI therapy
- Safe pregnancies
- Cost of life-time TKI therapy
- Emerging evidence that cure may be possible

Arguments Against Making TFR a Key Goal

- Unknown long-term risk of progression and drug resistance – may be leaving the safe haven!
- Sends wrong or mixed message to patients and community oncologists
- Not realistic goal for vast majority of patients

STIM: CMR after discontinuation of imatinib

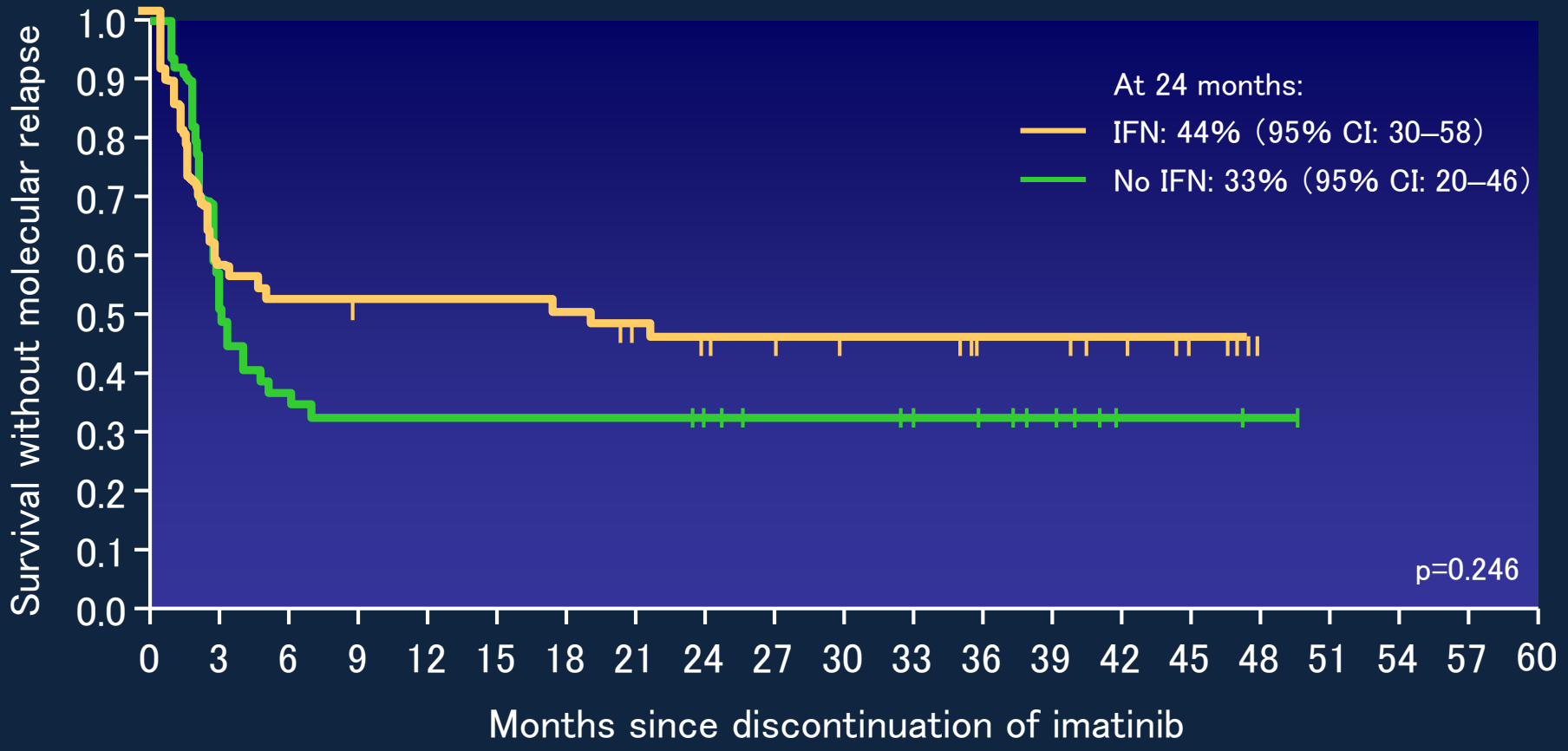
Molecular relapse occurred in 61 pts, with 58 relapses occurring during the first 7 months and 3 late relapses at months 19, 20 and 22



#603-ASH2011 – STIM study

STIM: CMR after discontinuation of imatinib

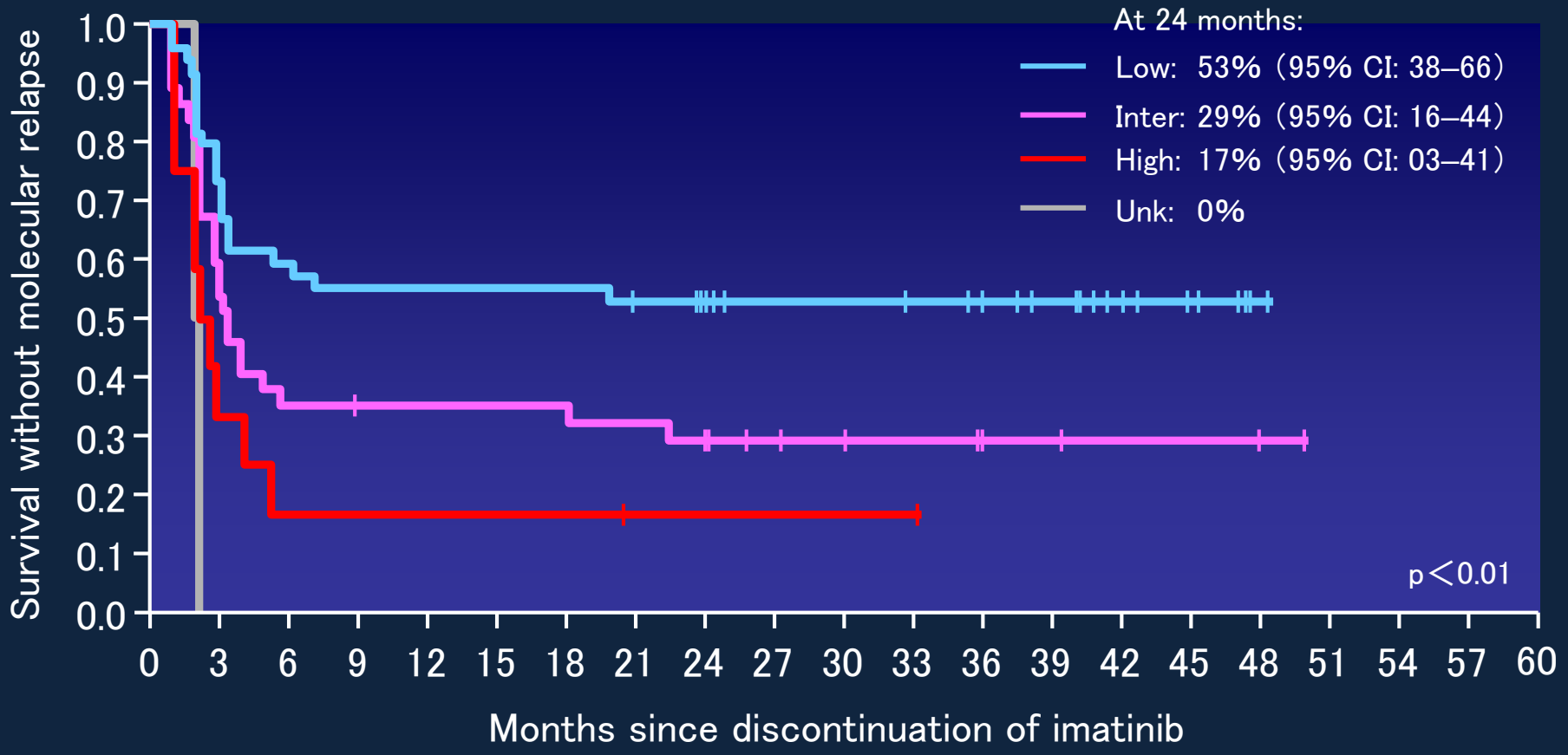
By previous treatment



#603-ASH2011 – STIM study

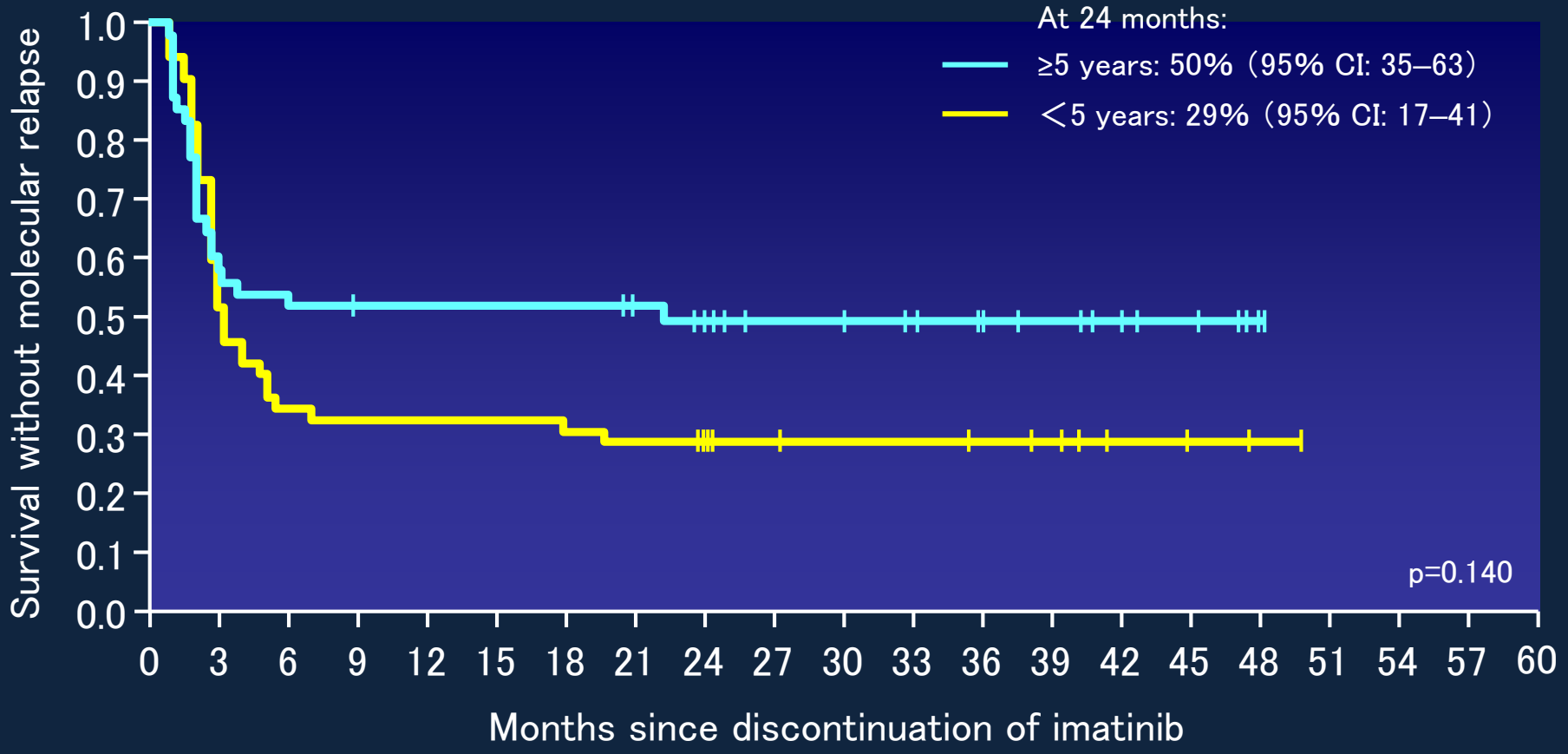
STIM: CMR after discontinuation of imatinib

By Sokal score



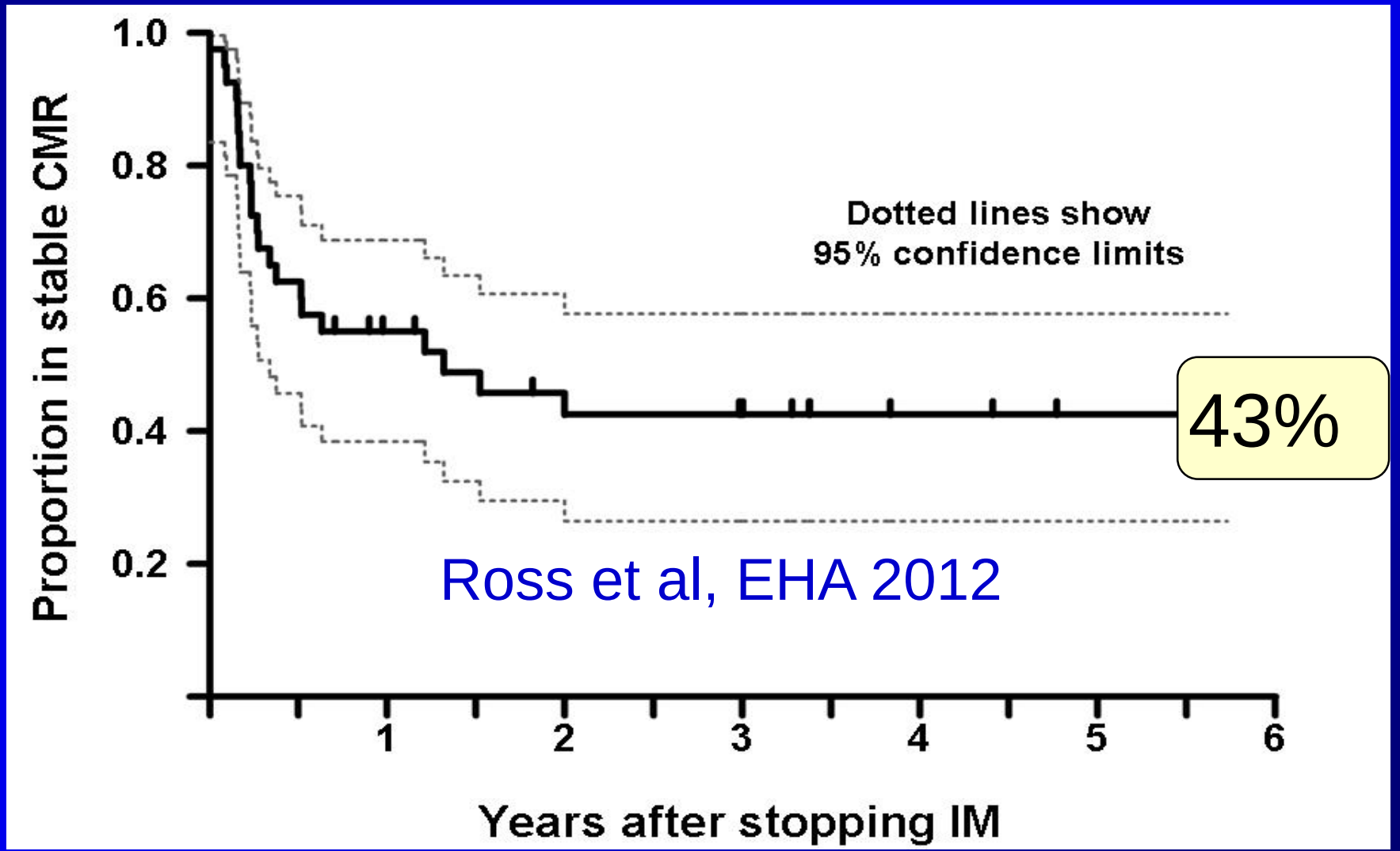
#603-ASH2011 – STIM study

STIM: CMR after discontinuation of imatinib

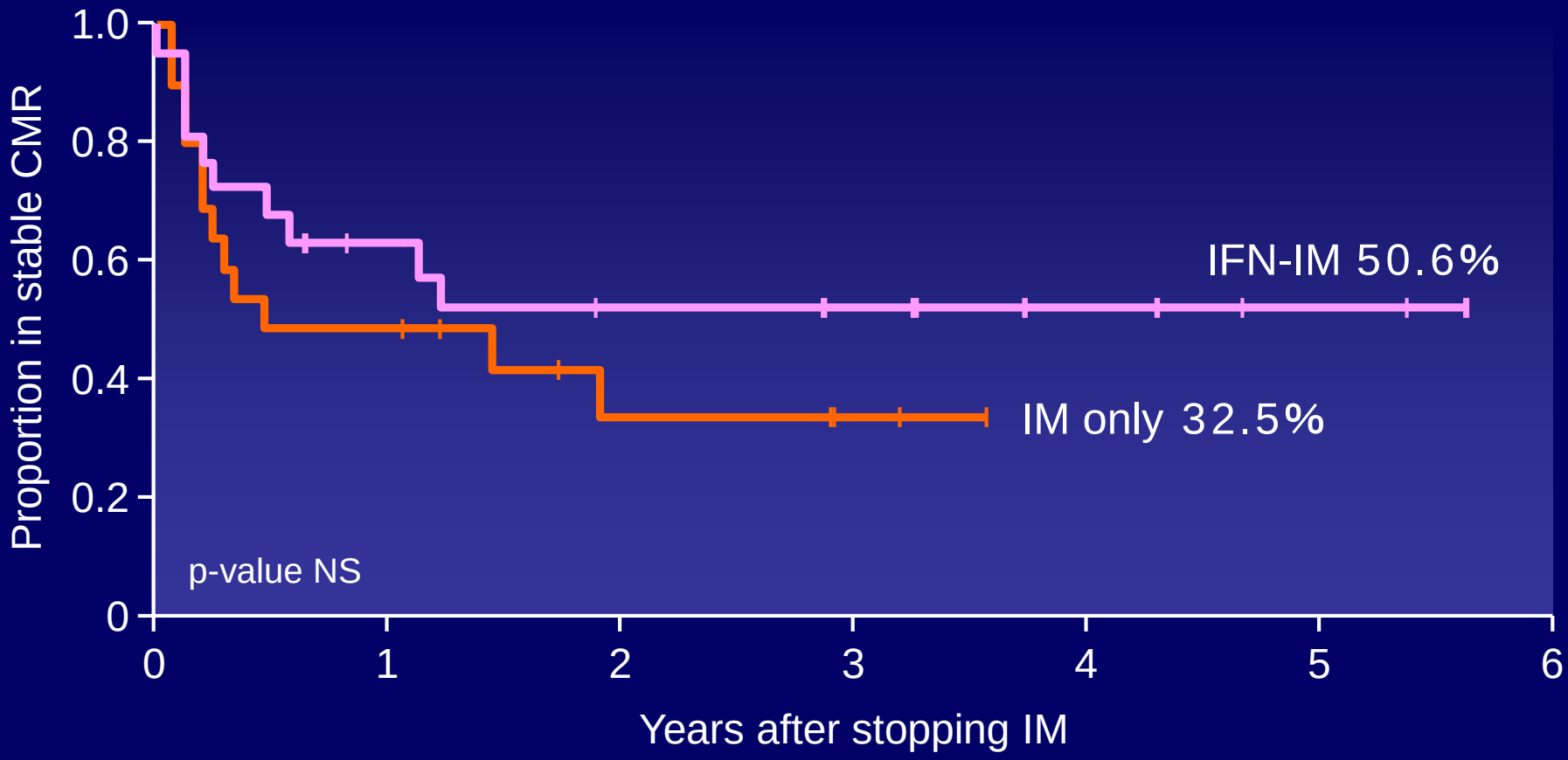


#603-ASH2011 – STIM study

Australian CML8 study (Twister)



Probability of drug-free CMR ±prior IFN: TWISTER



- Recurrence rate was not significantly different between the cohorts of pts with （IFN-IM） and without （IM only） prior IFN treatment.

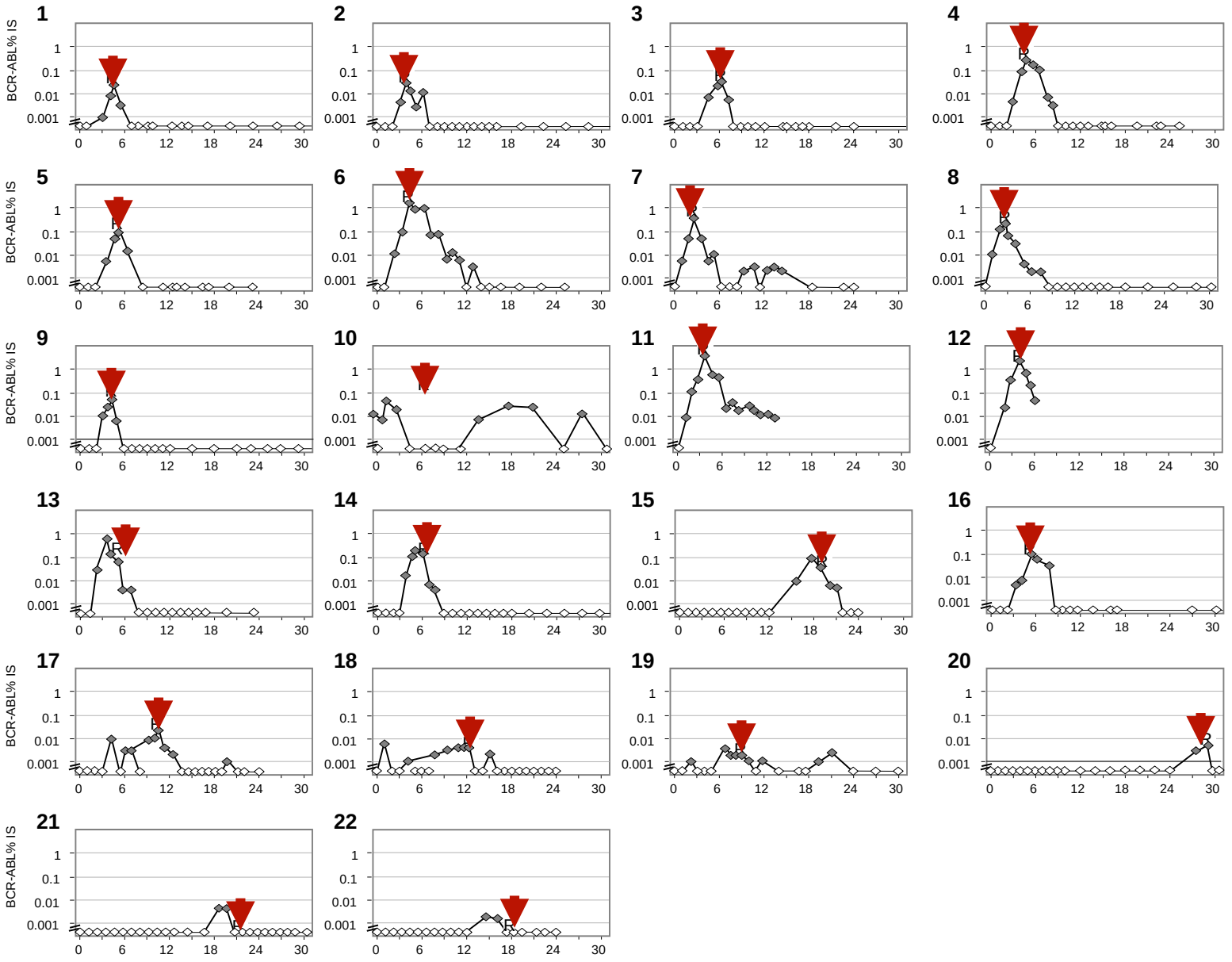
#0189-EHA2012

Univariate analysis: TWISTER

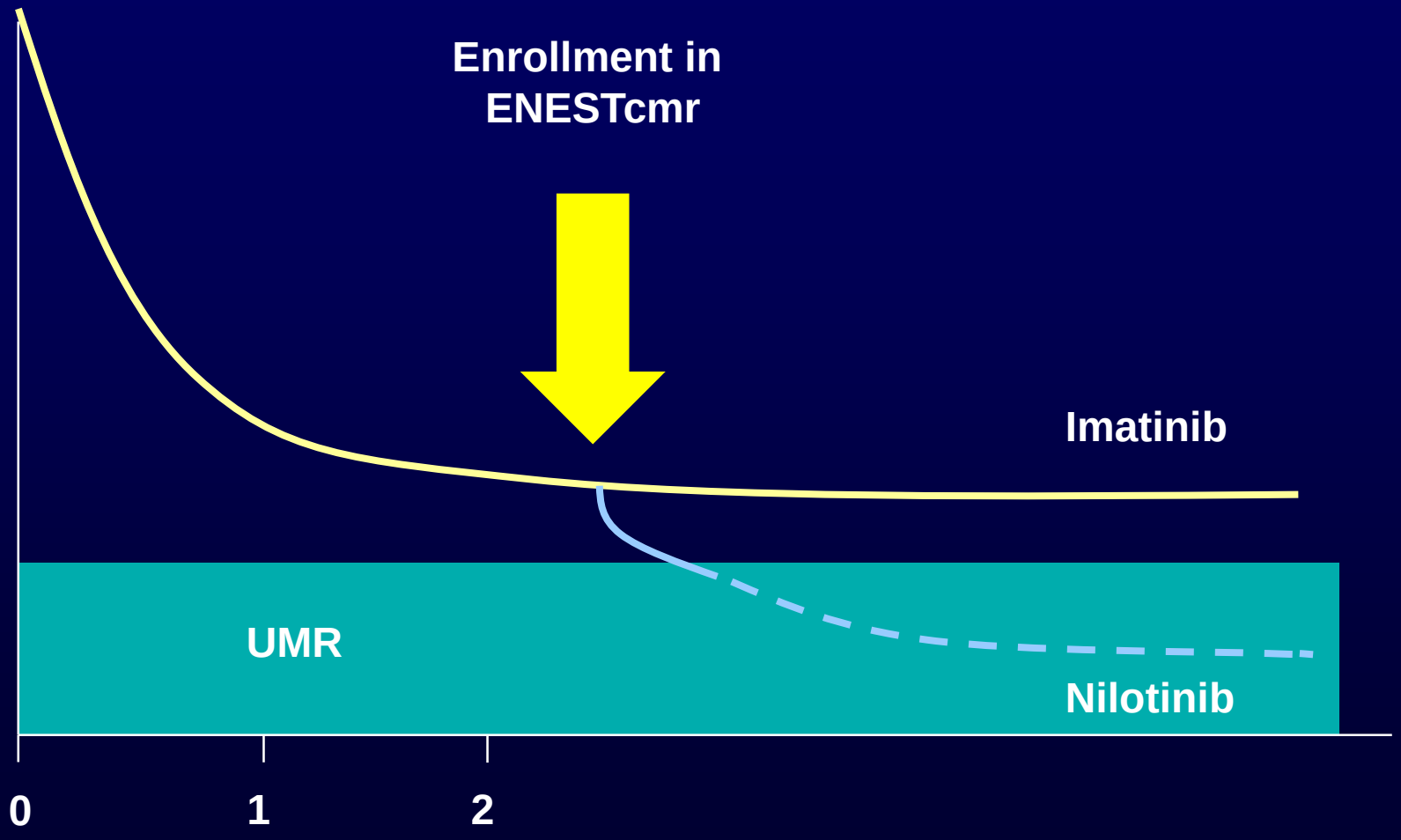
	No.	Relapse-free survival		p-value
Age	40	≤60 yr	>60 yr	NS
		53.3%	33.3%	
Sex	40	M	F	NS
		52.6%	34.6%	
Sokal score	35	Low-Int	High	0.002
		49.3%	14.3%	
Imatinib duration	40	≤70 mo	>70 mo	NS
		43.6%	45.0%	
IFN duration in IFN-IM cohort	21	≤12 mo	>12 mo	0.042
		20.0%	60.0%	
Baseline DNA PCR	25	Neg	Pos	NS
		66.7%	47.4%	

- In univariate analysis high risk Sokal score at diagnosis was the strongest predictor of molecular recurrence.
- Pts with >1 year of IFN treatment had a higher rate of stable CMR. Duration of IFN treatment is likely to be related to the depth of response to IFN.

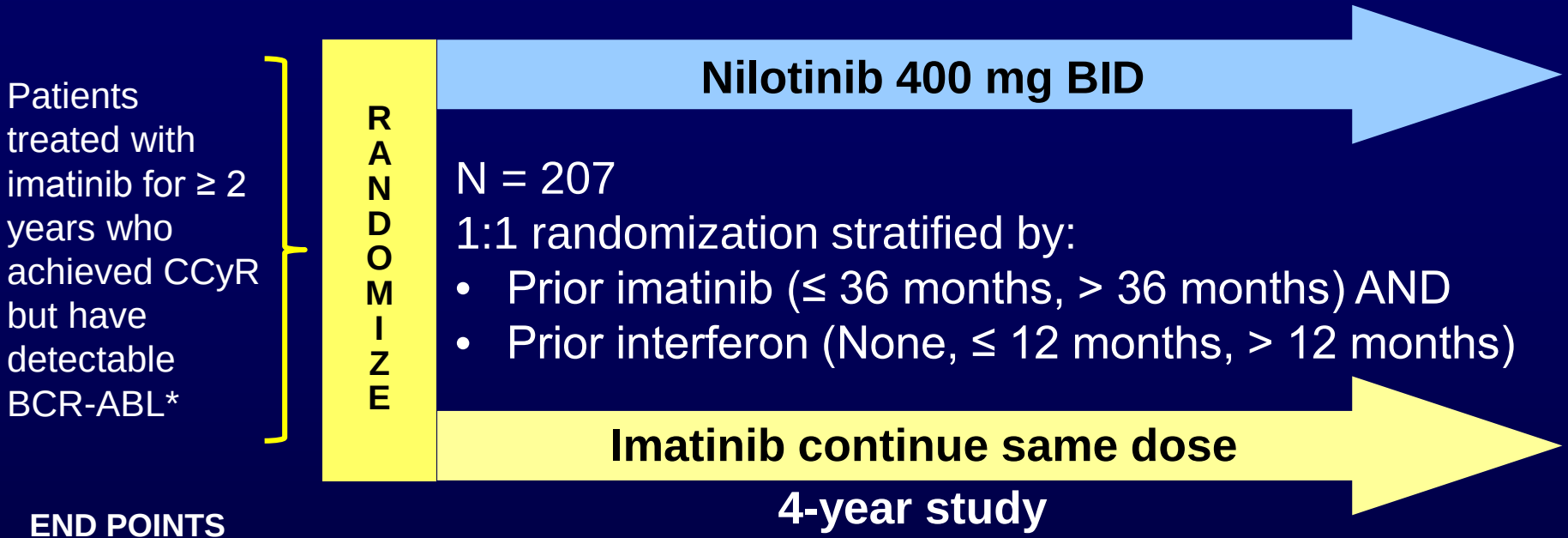
TWISTER: pattern of PCR rise and fall



ENESTcmr Concept



ENESTcmr: Study Design and Endpoints



END POINTS

Primary

- Confirmed undetectable BCR-ABL by 12 months

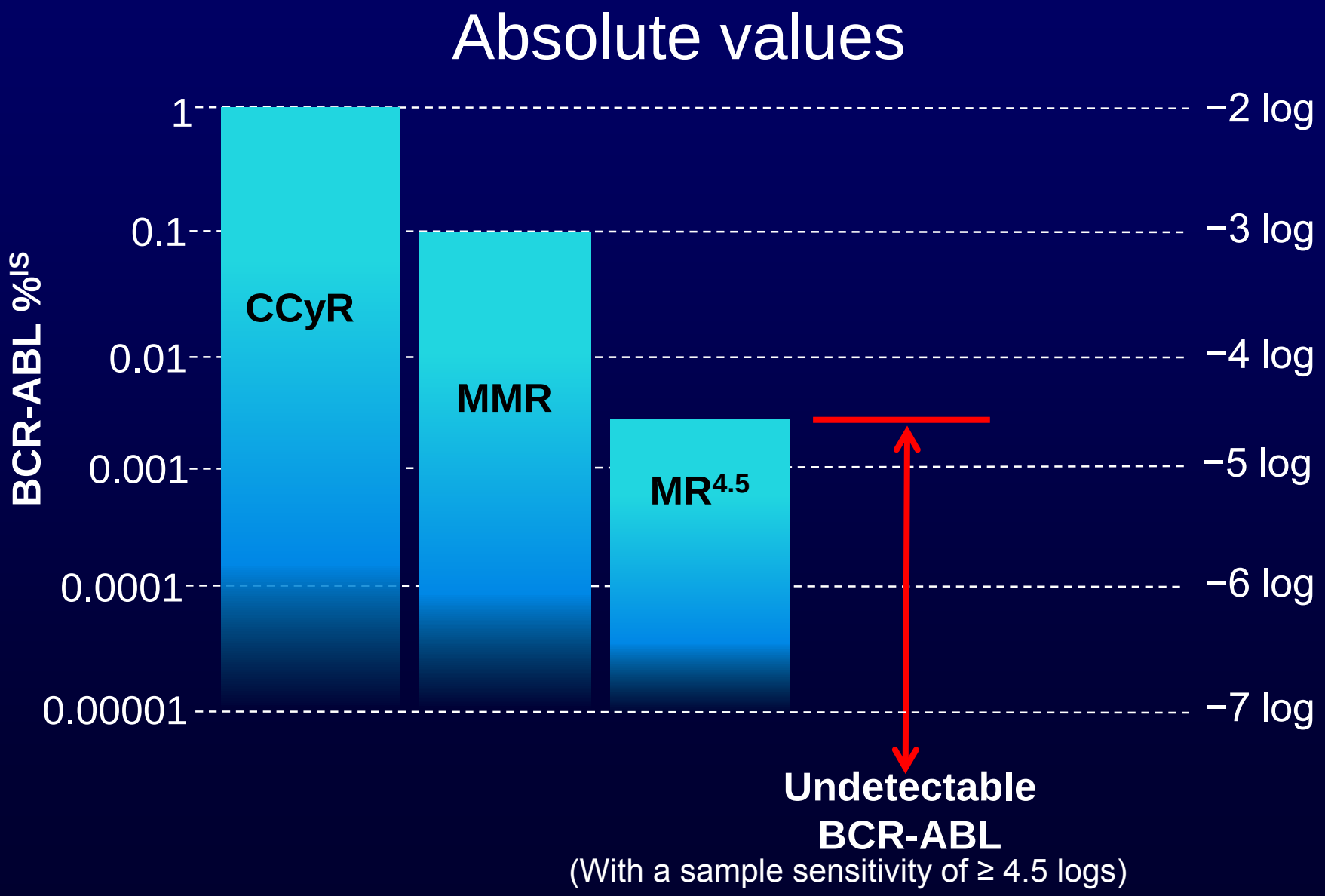
Secondary

- Molecular response ($MR^{4.5}$, undetectable BCR-ABL) in patients without the response in question at baseline
  - RQ-PCR for primary and secondary endpoints was performed every 3 months and assessed at a central laboratory in Adelaide, Australia
- Event-free survival
- Safety profile

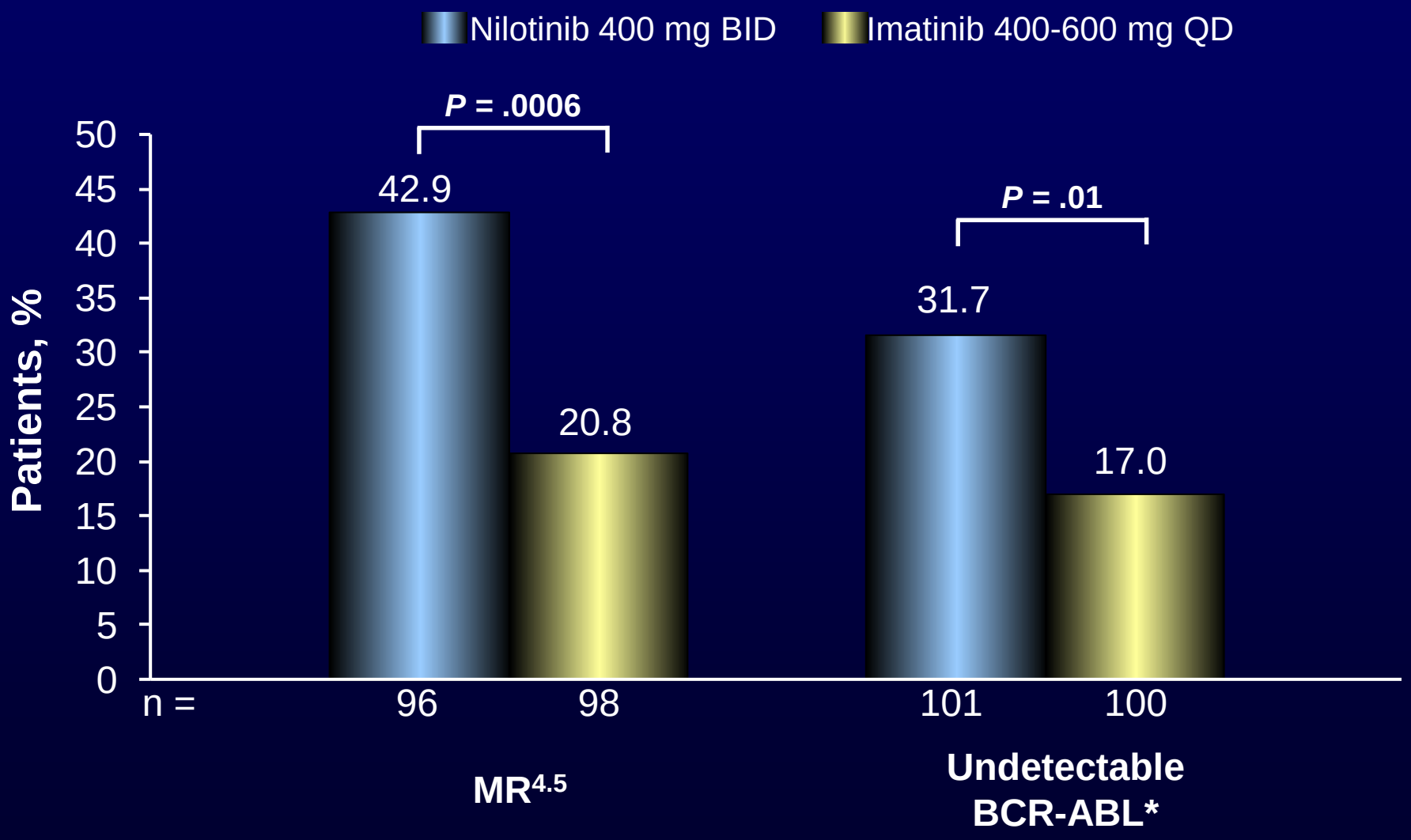
* By RQ-PCR with sensitivity of ≥ 4.5 logs.

RQ-PCR, real-time quantitative polymerase chain reaction..

Definition of Molecular Endpoints



ENESTcmr: Molecular Response Rates by 24 Months



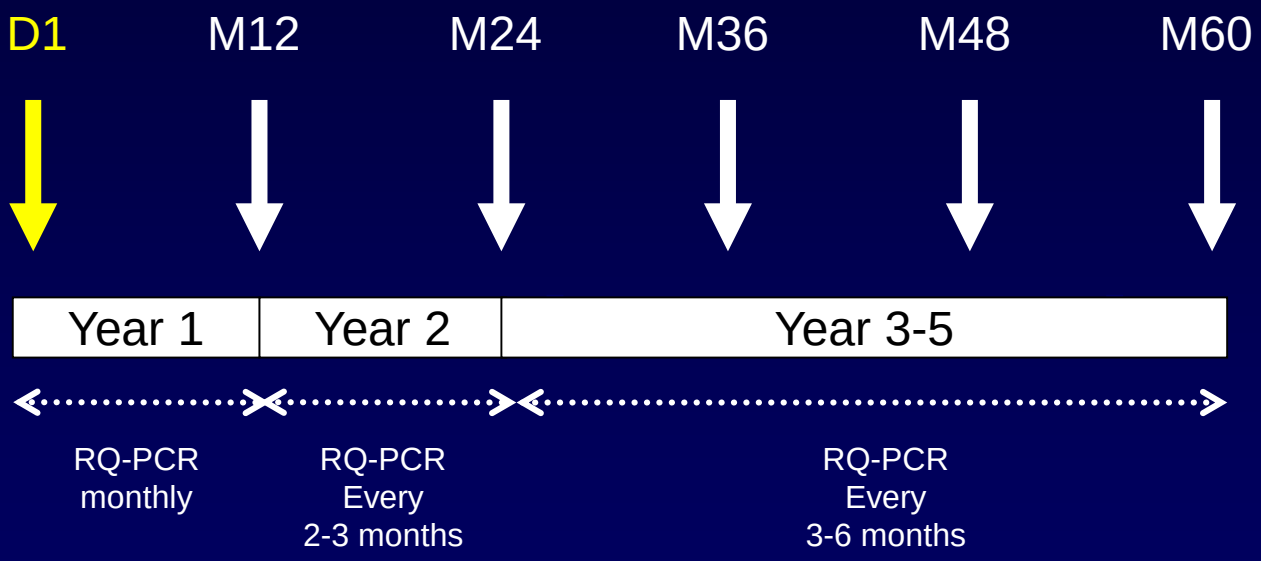
* With ≥ 4.5-log assay sensitivity.

24-month follow-up

STOP 2G-TKI Study design

CP-CML
TKI therapy ≥ 3 years
2G-TKI frontline or
after imatinib intolerance
or resistance

Undetectable
*BCR-ABL** ⟶ STOP 2G-TKI
≥ 24 months



- Primary endpoint: survival without loss of MMR
- Molecular relapse: loss of MMR
- Loss of MMR triggered treatment resumption

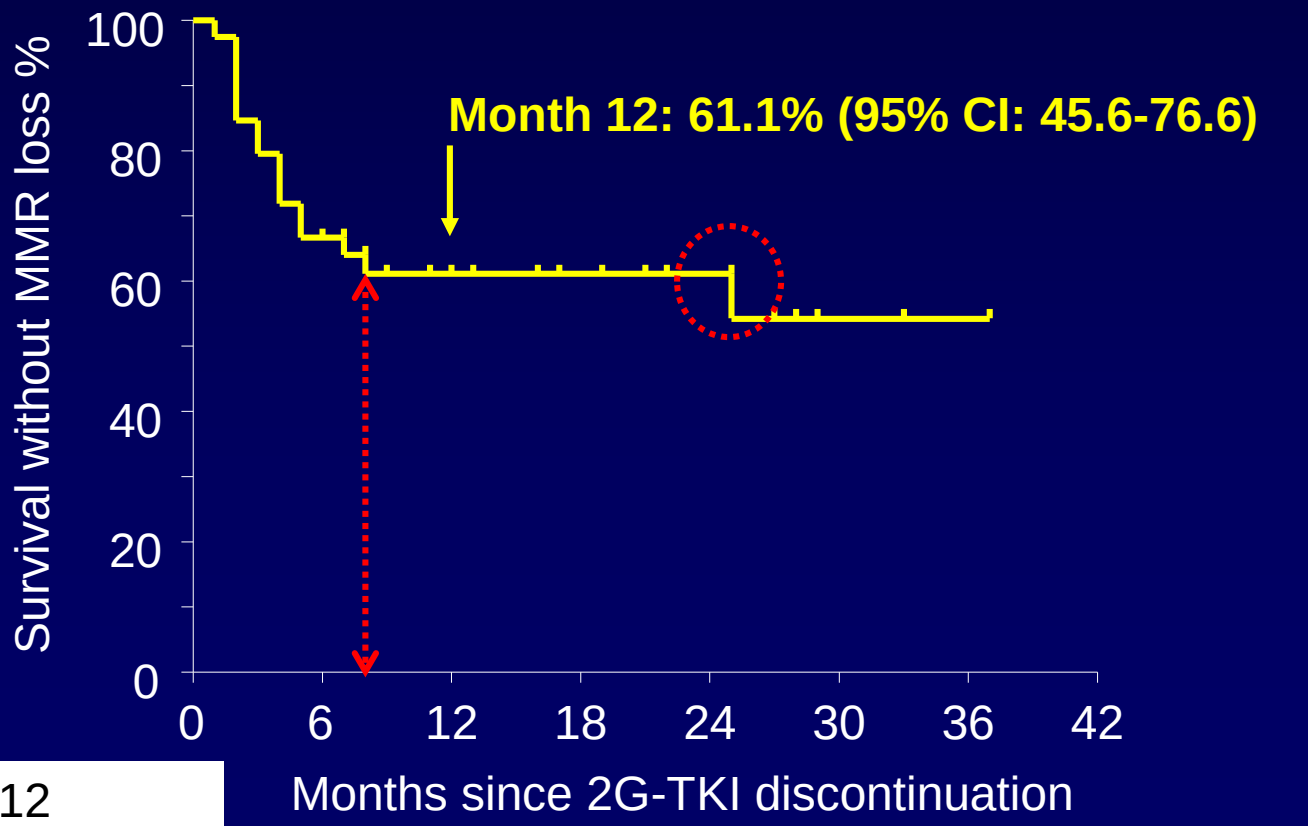
**Molecular monitoring performed in local laboratories filling international standardization requirements.*
**20 000 copies of ABL at least.*

Rea et al ASH 2012

DR

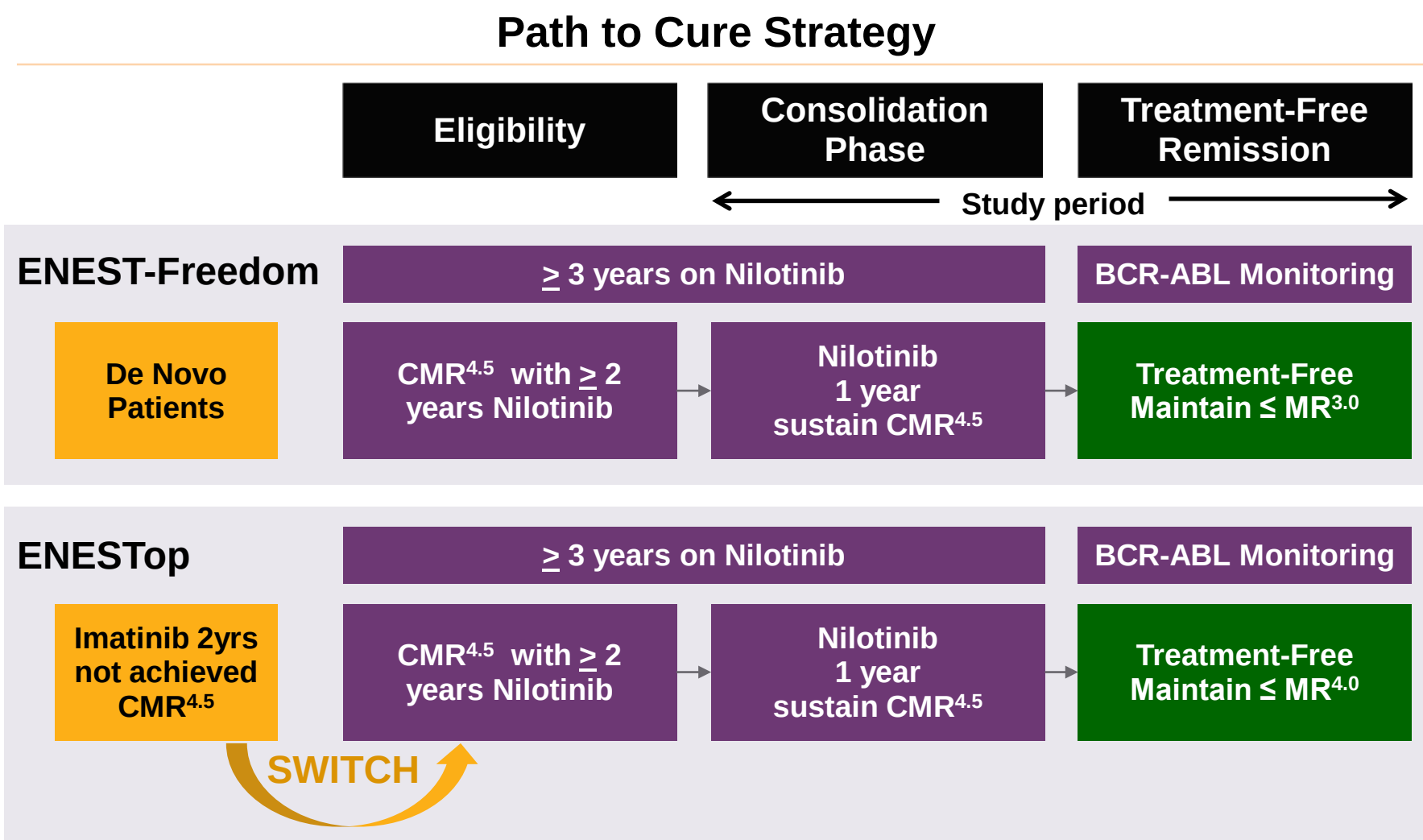
STOP 2G-TKI: Survival without MMR loss

- Following 2G-TKI cessation, median follow-up was 17 months (7-38)
  - 16/39 patients lost MMR
  - Median time to MMR loss was 3 months (1-25)

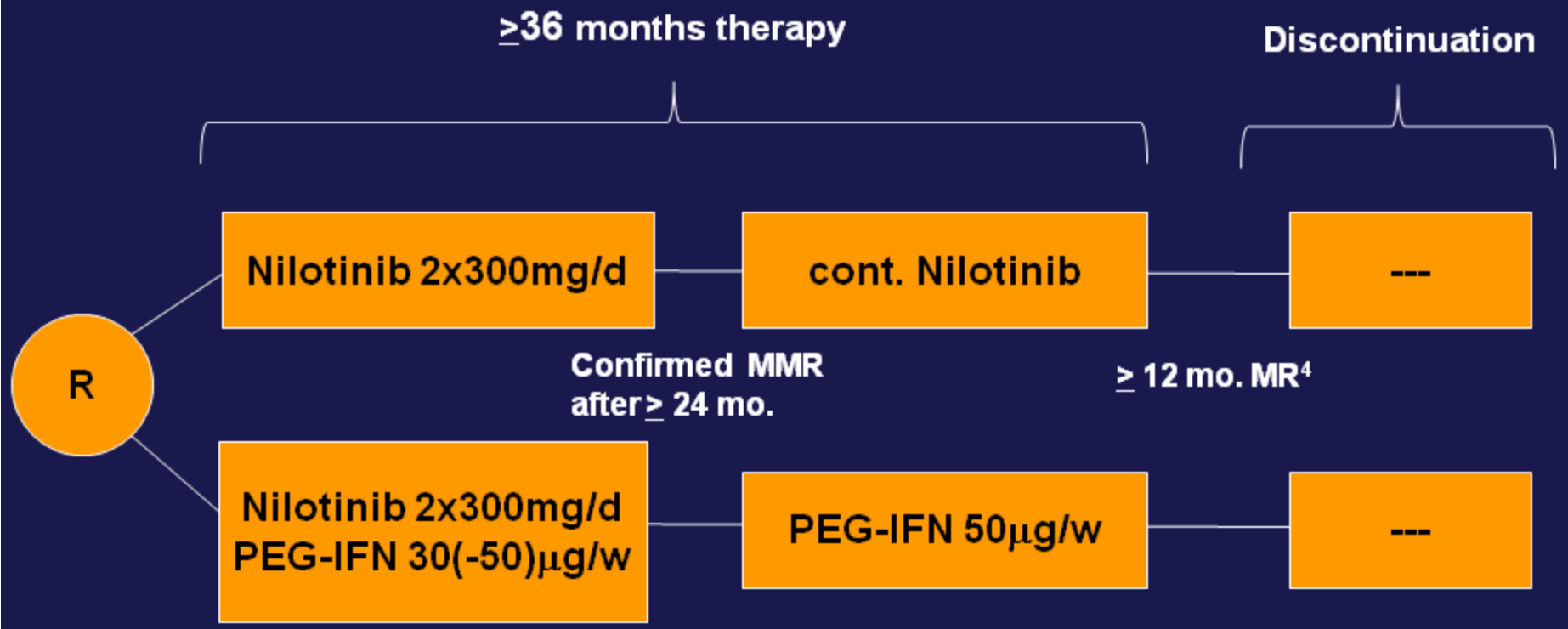


Rea et al ASH 2012

Treatment free remission: 2 international trials expected to start recruitment in Q1 2013



CML V (TIGER) Study



Nilotinib Intolerance → Imatinib
Nilotinib Resistance → Transplantation/Dasatinib
Suboptimal Response → Nilotinib 400 mg BID

Induction **Maintenance** **Cure?**

EURO-Stop Kinase Inhibitor

Main objective

- Evaluation of molecular relapse-free survival after stopping TKI (survival without molecular relapse)
- Definition of relapse defined as BCR-ABL > 0.1% (loss of MMR) on the IS at one time point

Courtesy of ELN

EURO-SKI
Main inclusion criteria

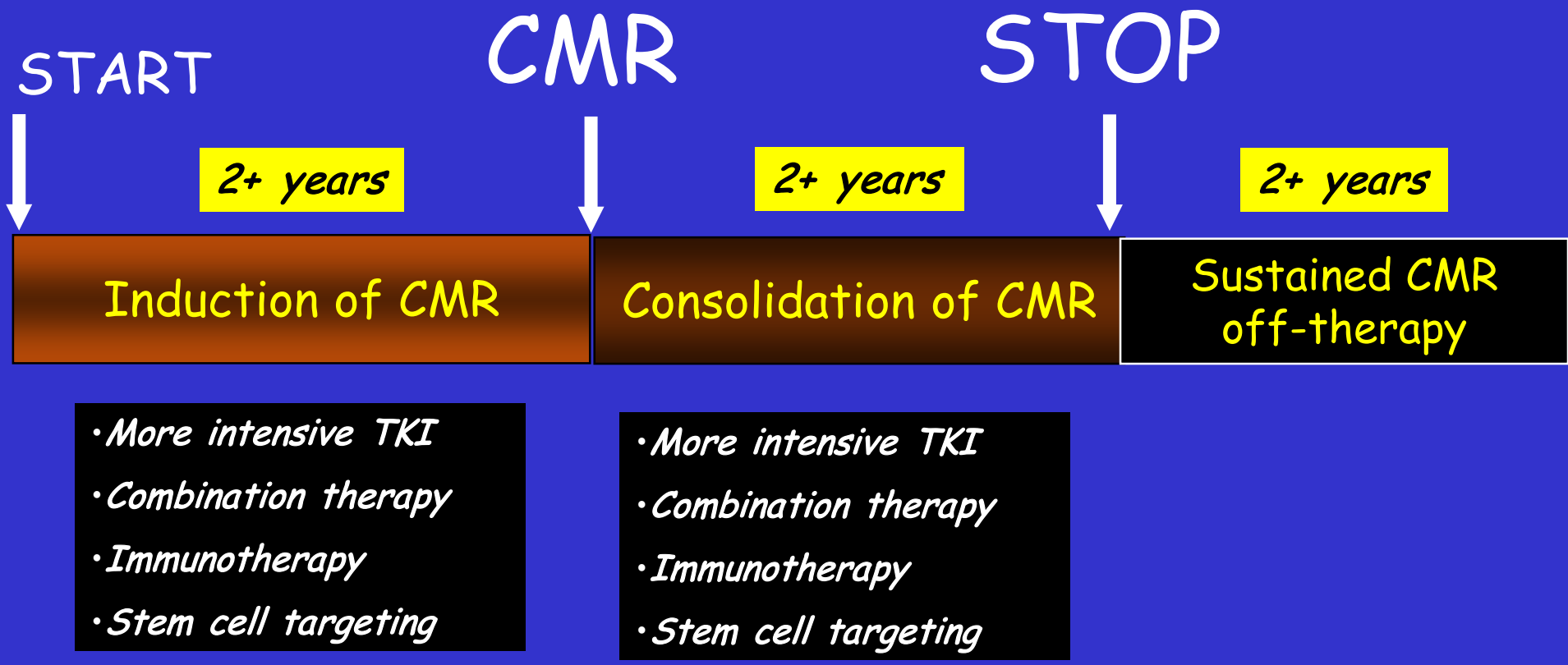
- CML in CP under treatment with **TKI in first line** or in **second line because of toxicity** to first line TKI or with **TKI in combination**
- Duration of TKI treatment before enrolment **at least 3 years**
- At least molecular remission **MR^4** for **at least one year**; at least three PCR-results with MR^4 within the last year (± 2 months) before study entry and no PCR-results >0.01% during the same period

Courtesy of ELN

Estimates of TFR rates

TKI approach	CMR rate	Successful cessation rate	Overall achievement of TFR
Imatinib	40%	30%	12%
Imatinib-NIL/DAS Conservative	(60%)	(20%)	(12%)
Imatinib-NIL/DAS BEST CASE	(70%)	(60%)	(42%)

Future focus of CML studies: *sustained CMR off-TKI*



New model of management for CML – curative intent