VII Session – Chronic Myeloid Leukemia

Treatment Free Remission

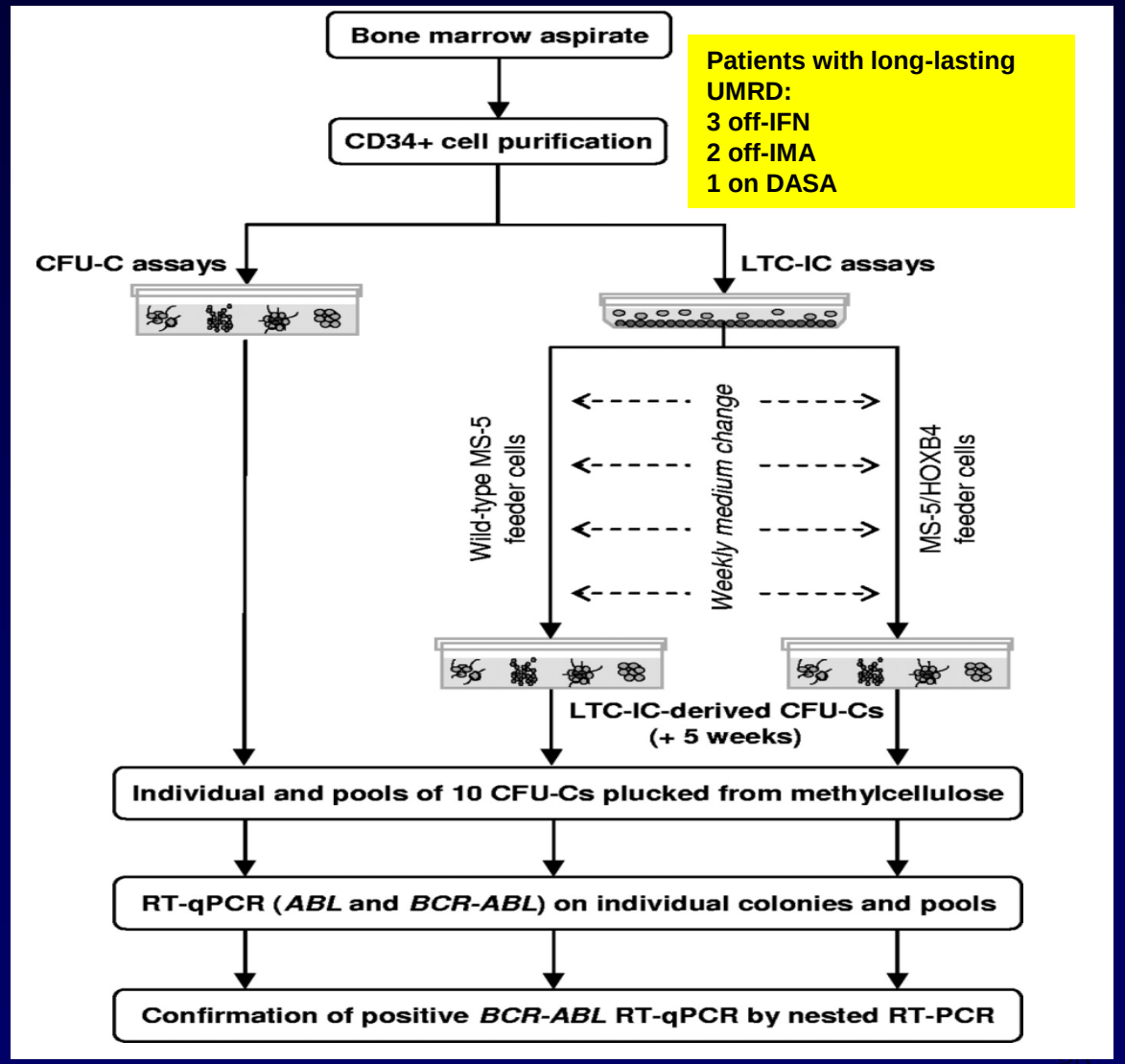
Gianantonio Rosti, Bologna (Italy)

Treatment-free remission: key points

- Treatment-free remission (TFR) refers to the persistence of an optimal molecular response (MMR at least) as assessed by standard RTq-PCR after discontinuation of anti-leukemic therapy in patients with CML.
- TFR is conditioned upon prior on-therapy achievement and maintenance of a deep molecular response.
- TFR corresponds to a state of “operational cure” defined by the absence of overt CML relapse in the long-term despite the presence of a leukemic stem cells reservoir.

Goldman J, Gordon M. Leukemia & Lymphoma. 2006; 47(1): 1-7.

Imatinib-free remission:
Despite LSC persistence



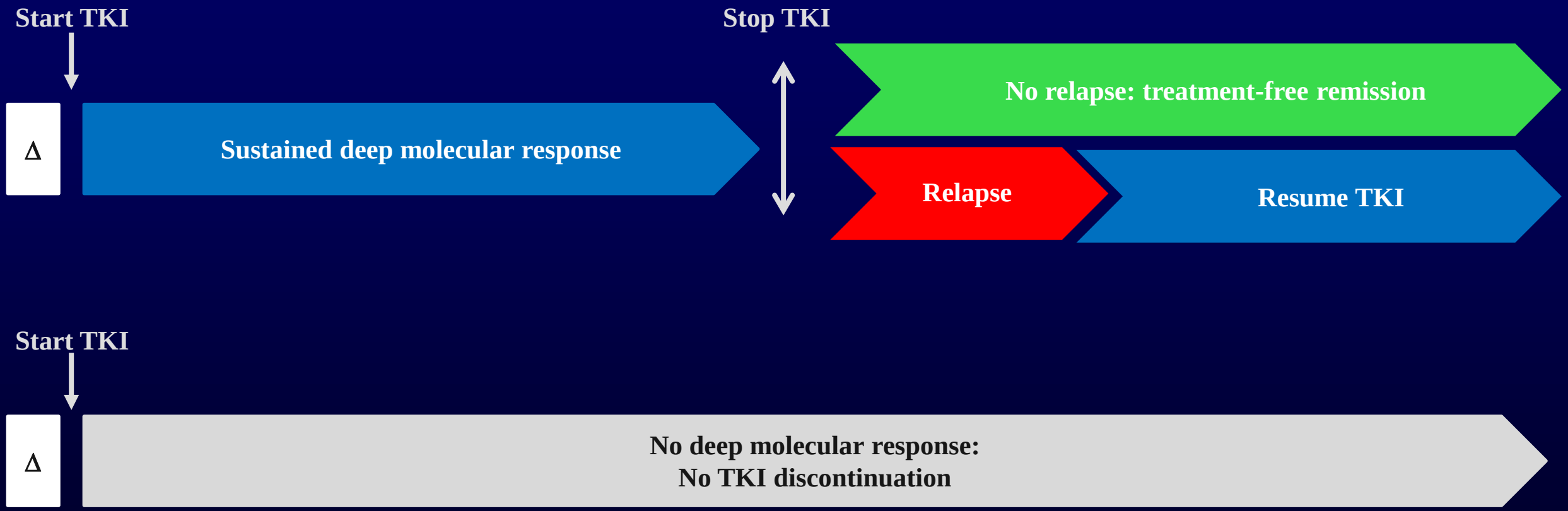
Ross et al. Leukemia 2010; 24: 1719-1724.
Chomel et al. Blood 2011; 118: 3657-3660.

Evolving Goals (Opportunities) of Therapy . Discontinuation of TKIs in CML

Pro's	Con's
• Reducing off-target side effects which cause : - Impaired quality of life - Safety issues - Growth retardation in children - Teratogenicity • Positive effect on adherence? • Feeling "cured" of CML • Cost	• Not recommended in the absence of a deep and stable molecular response • Not recommended in absence of regular high quality molecular monitoring • Leukemic cell persistence despite TKI treatment[1-6]: -Risk of post discontinuation relapse or progression -Risk of resistance or progression upon reinstitution of the same TKI

1. Graham et al. Blood 2002; 99: 319-325
2. Copland et al. Blood 2006; 107: 4532-4539
3. Jorgensen et al. Blood 2007; 109: 4016-4019
4. Konig et al. Blood 2008; 111: 2329-2338
5. Corbin et al. JCI 2011; 121: 396-406
6. Hamilton et al. Blood 2012; 119: 1501-1510

TKI discontinuation: principles

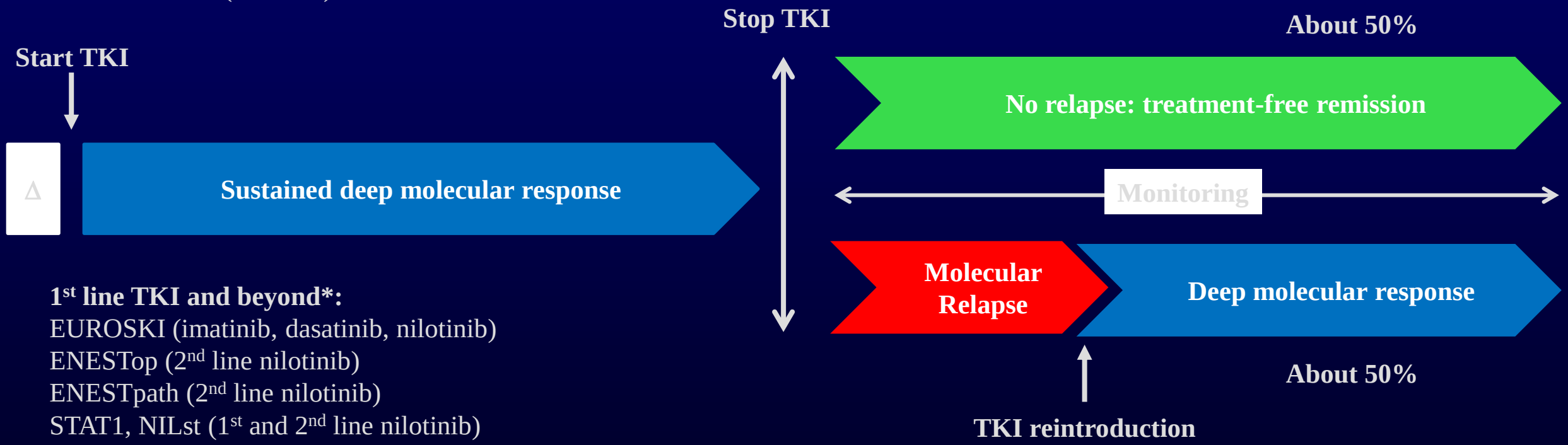


Δ: Chronic phase CML at diagnosis

From: Rea D, Cayuela JM. Int J Hematol. 2017 Jul 8. doi: 10.1007/s12185-017-2295-0.

TKI discontinuation: multiple studies worldwide

1st line TKI*:
STIM, STIM2, TWISTER, JALSG213 (imatinib)
ENESTfreedom (nilotinib)

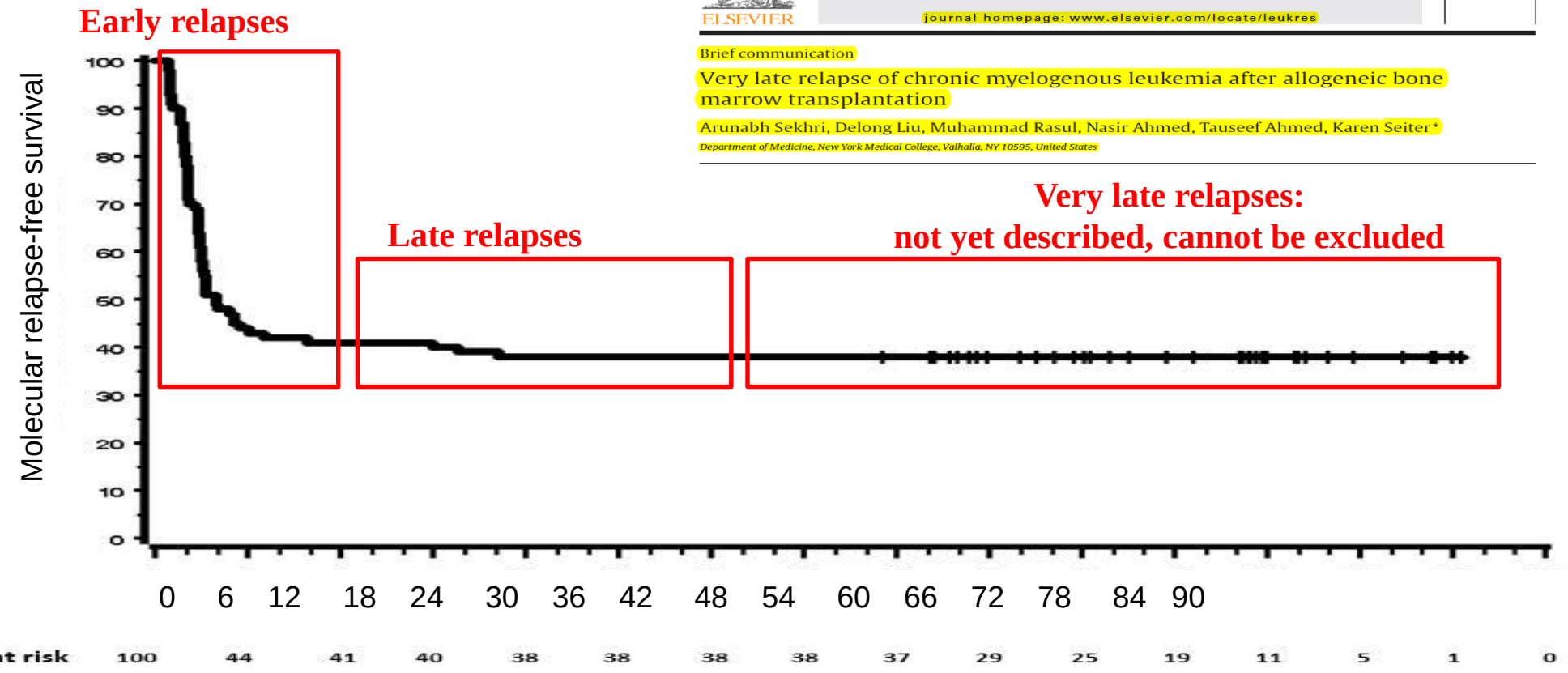


1st line TKI and beyond*:
EUROSKI (imatinib, dasatinib, nilotinib)
ENESTop (2nd line nilotinib)
ENESTpath (2nd line nilotinib)
STAT1, NILst (1st and 2nd line nilotinib)
DADI (≥2nd line dasatinib)
STOP 2G-TKI (nilotinib, dasatinib)
DASFREE, D-STOP (1st and 2nd line dasatinib)

Δ: Chronic phase CML at diagnosis

*non exhaustive list.

Imatinib-free remission:
Long-term follow-up



Contents lists available at ScienceDirect
Leukemia Research
journal homepage: www.elsevier.com/locate/leukres

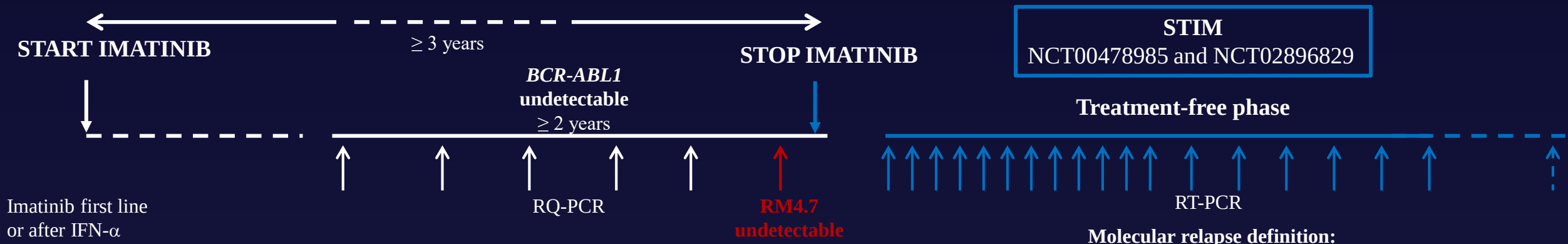
Brief communication

Very late relapse of chronic myelogenous leukemia after allogeneic bone marrow transplantation

Arunabh Sekhri, Delong Liu, Muhammad Rasul, Nasir Ahmed, Tauseef Ahmed, Karen Seiter*
Department of Medicine, New York Medical College, Valhalla, NY 10595, United States

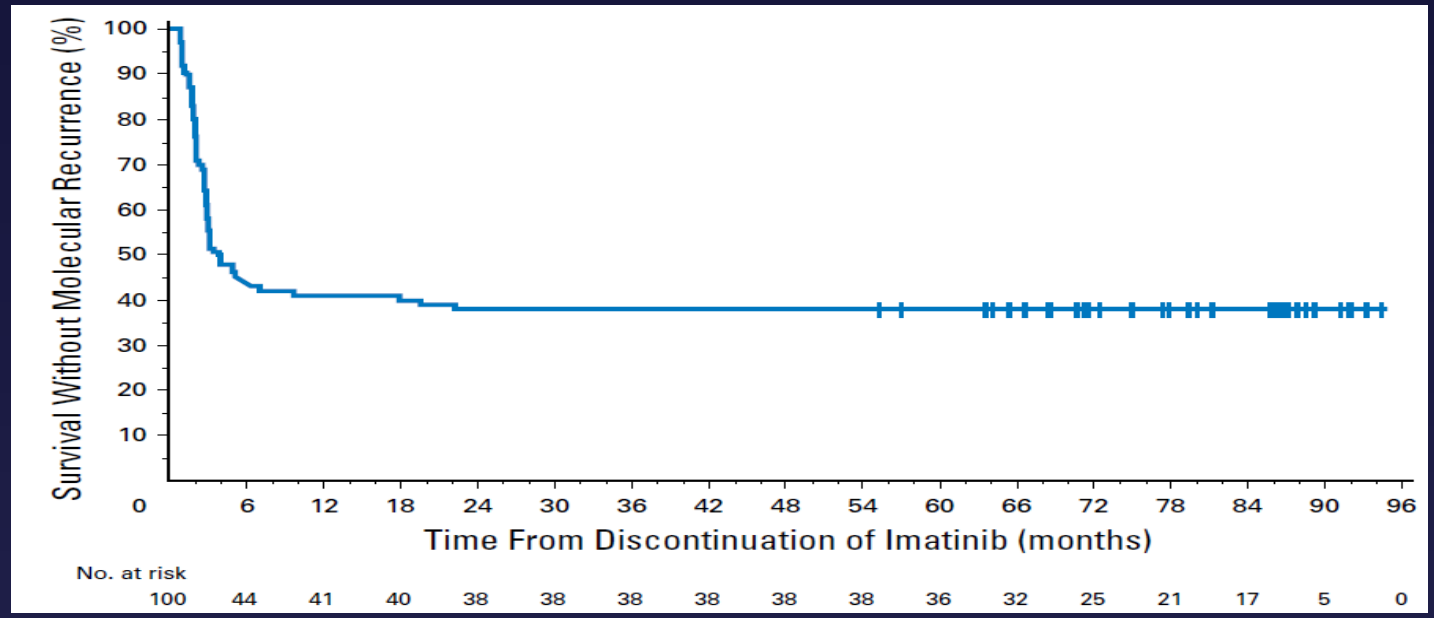
Etienne et al. Blood (ASH) 2015; abstract 345.

Long-term follow-up: data from STIM



Molecular relapse definition:
Detectable *BCR-ABL1* on 2 consecutive tests with a significant increase in *BCR-ABL1* transcripts ≥ 1 log.

Patient characteristics:
100 patients
Median duration of imatinib: 58.8 months (range: 35-112)
Median duration of deep molecular response: 36.4 months (range: 24-107)
Median follow-up: 77 months (range: 9-95)



Mahon et al. Lancet Oncol. 2010 ;11(11):1029-1035.
Etienne et al. J Clin Oncol 2017; 35(3): 298-305.

TFR, 2018 DATA

- 29 Discontinuation studies published enrolling more than 2600 patients

- 20 studies of imatinib discontinuation
- 10 studies of nilotinib discontinuation
- 5 studies of dasatinib discontinuation

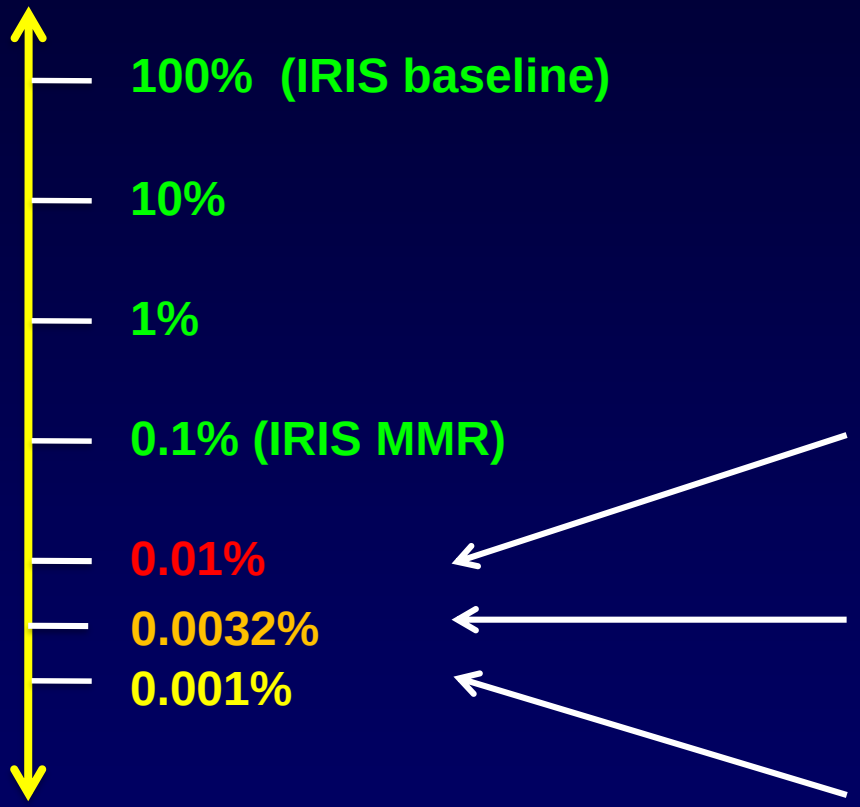
- Follow-up: median of 3 years (13-90 months)
- Median TFR stability around 55%
- Two progressions reported

TKI withdrawal syndrome during the treatment-free phase

- First described after imatinib discontinuation.
- May also occur after 2nd generation TKI discontinuation.
- Onset within 1 to 2 months after TKI discontinuation.
- Consists in new onset or worsening of musculoskeletal pain, arthralgia, usually mild to moderate, in about 30% of patients.
- Usually resolves spontaneously or upon analgesics prescription within a few months or after TKI resumption (in case of molecular relapse).
- Unrelated to molecular response status.
- Exact mechanism unknown.

Richter et al, 2014;
Hochhaus et al, 2017, Ross et al, 2017
Shah et al, 2016

Deep molecular responses



Deep molecular responses: Categories

MR4: ≥4 log reduction; **detectable** disease ≤ 0.01% IS **or undetectable** with ≥ 10000 *ABL1* transcripts

MR4.5: ≥4.5 log reduction; **detectable** disease ≤ 0.0032% IS **or undetectable** with ≥ 32000 *ABL1* transcripts)

MR5: ≥5 log reduction; **detectable** disease ≤ 0.001% IS **or undetectable** with ≥ 100000 *ABL1* transcripts)

log reduction = reduction from IRIS baseline,
not individual pre treatment levels

Cross et al. Leukemia 2015; 29: 999-1003.
Cross et al. Ann Hematol 2015; 94 Suppl 2: S219-S225.

Baccarani et al. Blood 2013; 1242: 872-884.
Cross et al. Leukemia 2012; 26: 2172-2175.

Prognostic factors of TFR in TKI discontinuation studies

Factor category	Factor	Prognostic value
Patient	Age, sex	No (adults only)
Disease	Prognostic scores at diagnosis	Non-high Sokal best (1st line imatinib, nilotinib)?
Treatment history and response to therapy	Type of TKI	No comparative study
	History of suboptimal response or resistance	Decreased TFR probabilities
	TKI treatment duration (total)	Imatinib: yes Dasatinib or nilotinib: not studied yet
	Deep molecular response duration	Imatinib: yes Dasatinib or nilotinib: not studied yet
	Depth of deep molecular response (MR4, MR4.5 or even deeper)	Difficult to assess with current RT-qPCR techniques

Mahon et al, 2010; Etienne et al, 2017
Imagawa et al, 2015; Mahon et al, 2016
Rea et al, 2017 Hochhaus et al, 2017, Ross et al, 2017

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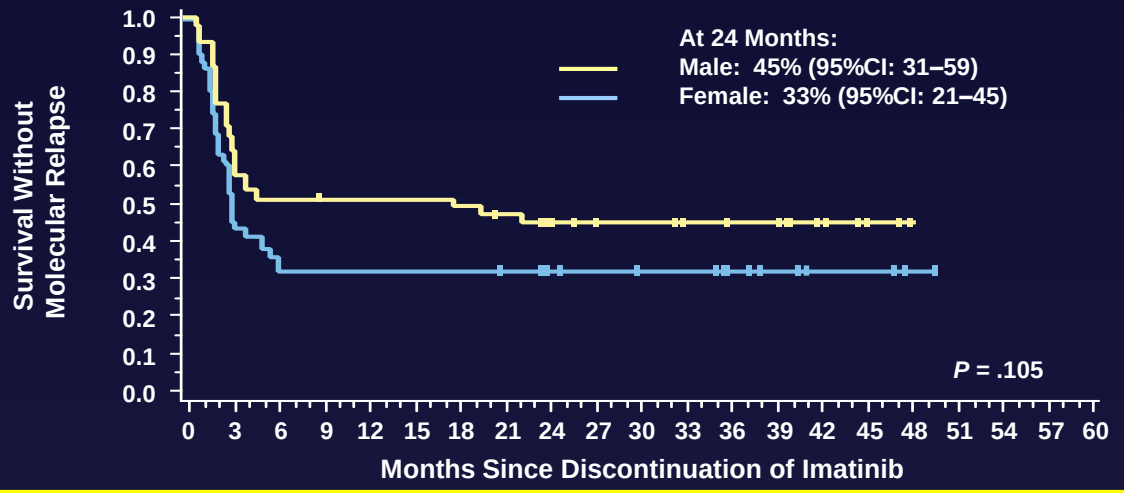
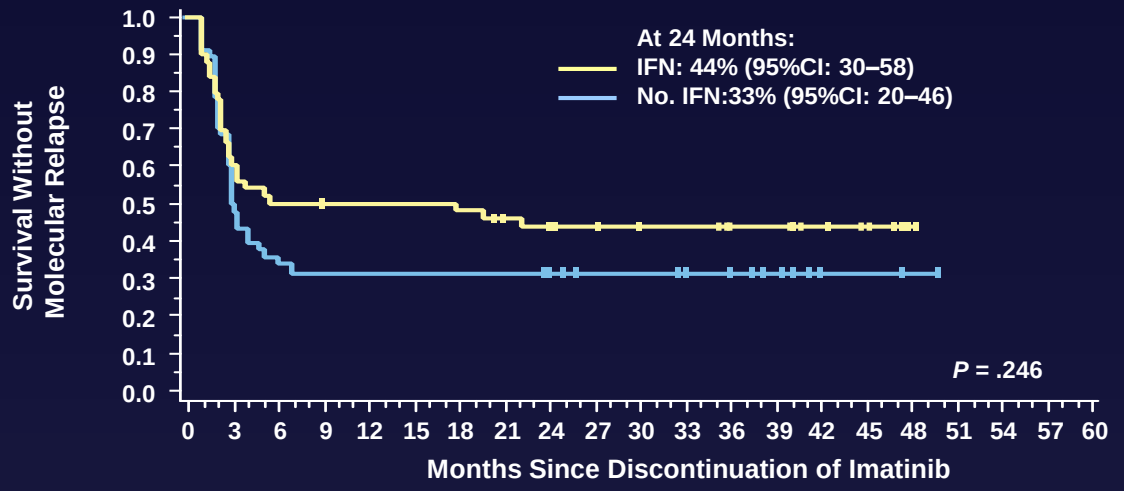
Can We Predict Which Patients Will Relapse? *Relapse-free Survival by Baseline Factor in STIM*

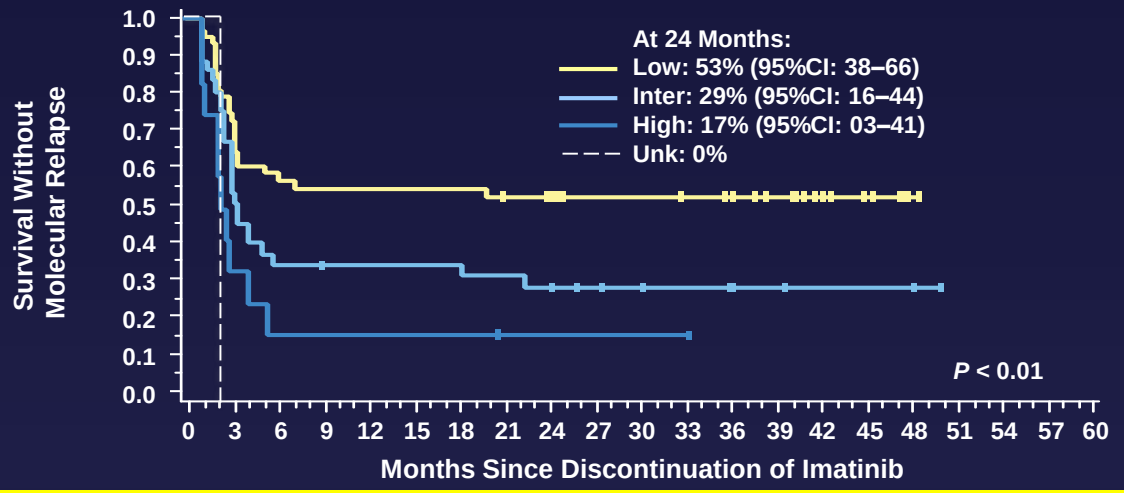
Gender (M/F)



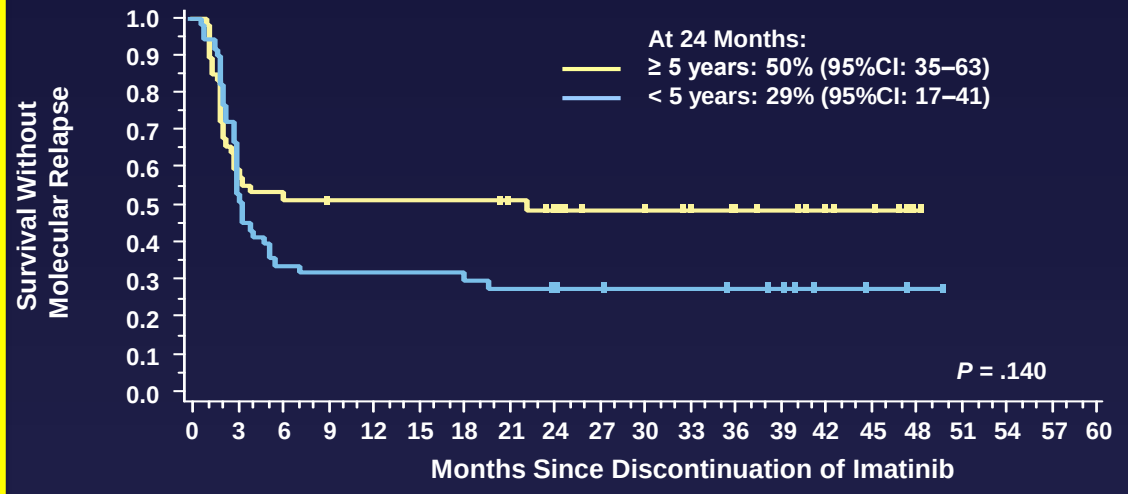
Previous IFN (yes/no)



Sokal risk (Low/Int/High)



Imatinib duration (≥5 y/<5 y)



Mahon FX, et al. *Blood* 2011;118:abstract 603.

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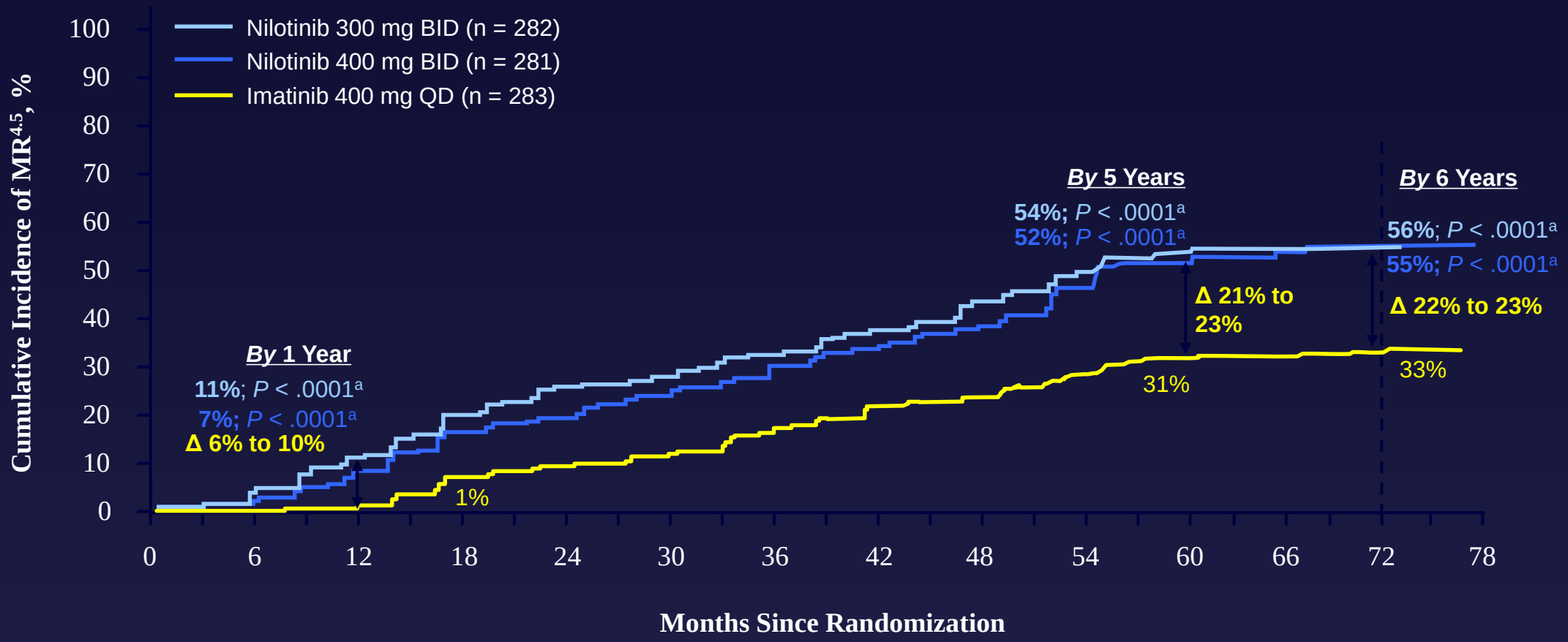
ENESTnd: cumulative incidence of MR4.5 by 6 years



KM-estimated median times to first $MR^{4.5}$ were:

- Nilotinib 300 mg BID: 45.5 months (hazard ratio [HR] vs imatinib, 2.0387 [95% CI, 1.5807-2.6295]; nominal $P < .0001$)
- Nilotinib 400 mg BID: 49.8 months (HR vs imatinib, 1.7770 [95% CI,1.3780-2.2915]; nominal $P < .0001$)
- Imatinib 400 mg QD: 61.1 months

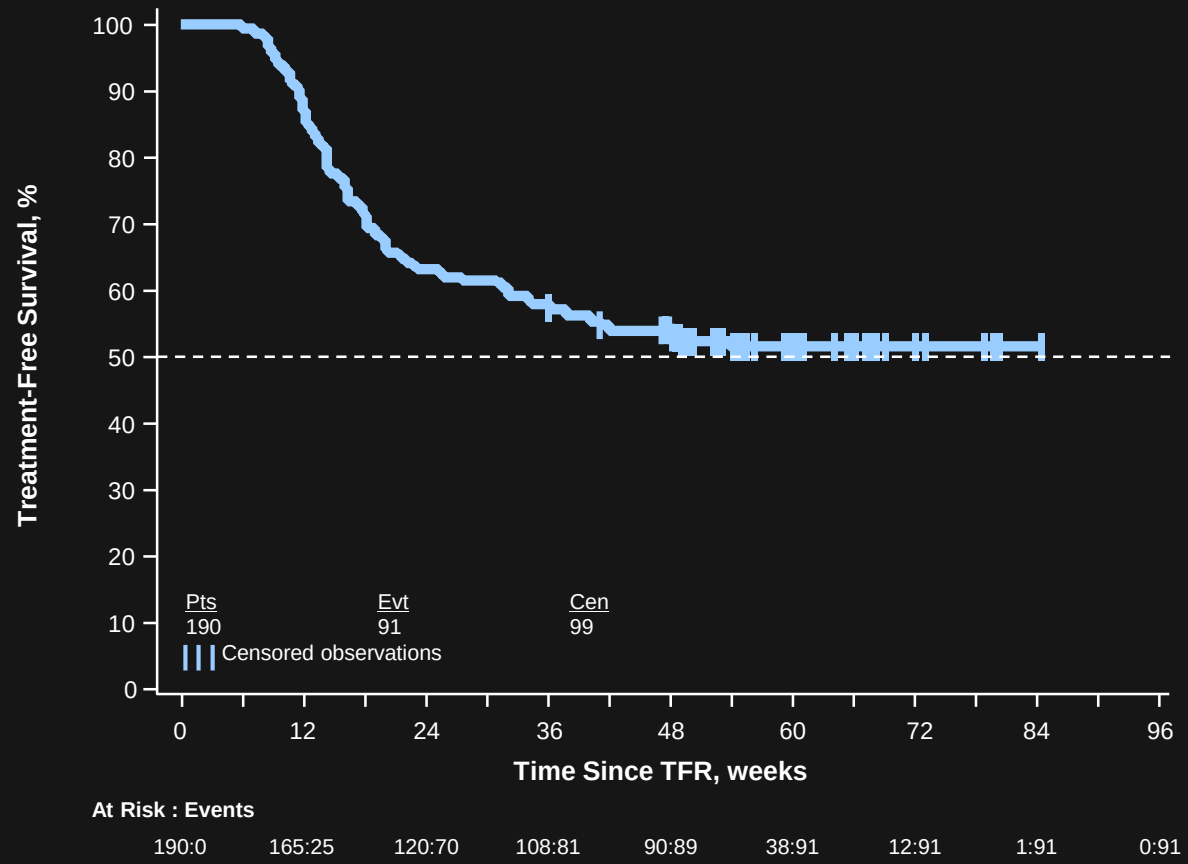
[a] *P* values are nominal.

Larson et al. *Blood*. 2014:[abstract 4541].

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%

Kaplan-Meier Estimated Treatment-Free Survival[a]



[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.

Hypothesis of D/C based on ENESTnd

	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281	Imatinib 400 mg QD N = 283
Patients with $MR^{4.5}$ at any time, n (%)	159 (56.4%)	158 (56.2%)	96 (33.9%)
Estimated durability of responses,%			
$MR^{4.5}$ sustained for ≥1 year	81.5%	84.3%	84.4%
$MR^{4.5}$ sustained for ≥2 years	73.1%	77.8%	76.9%
$MR^{4.5}$ sustained for ≥3 years	66.3%	76.7%	70.6%

Hypothesis: TKI cessation Attempt if ≥2 years of $MR^{4.5}$ → n = 116 (41%) n = 74 (26%)

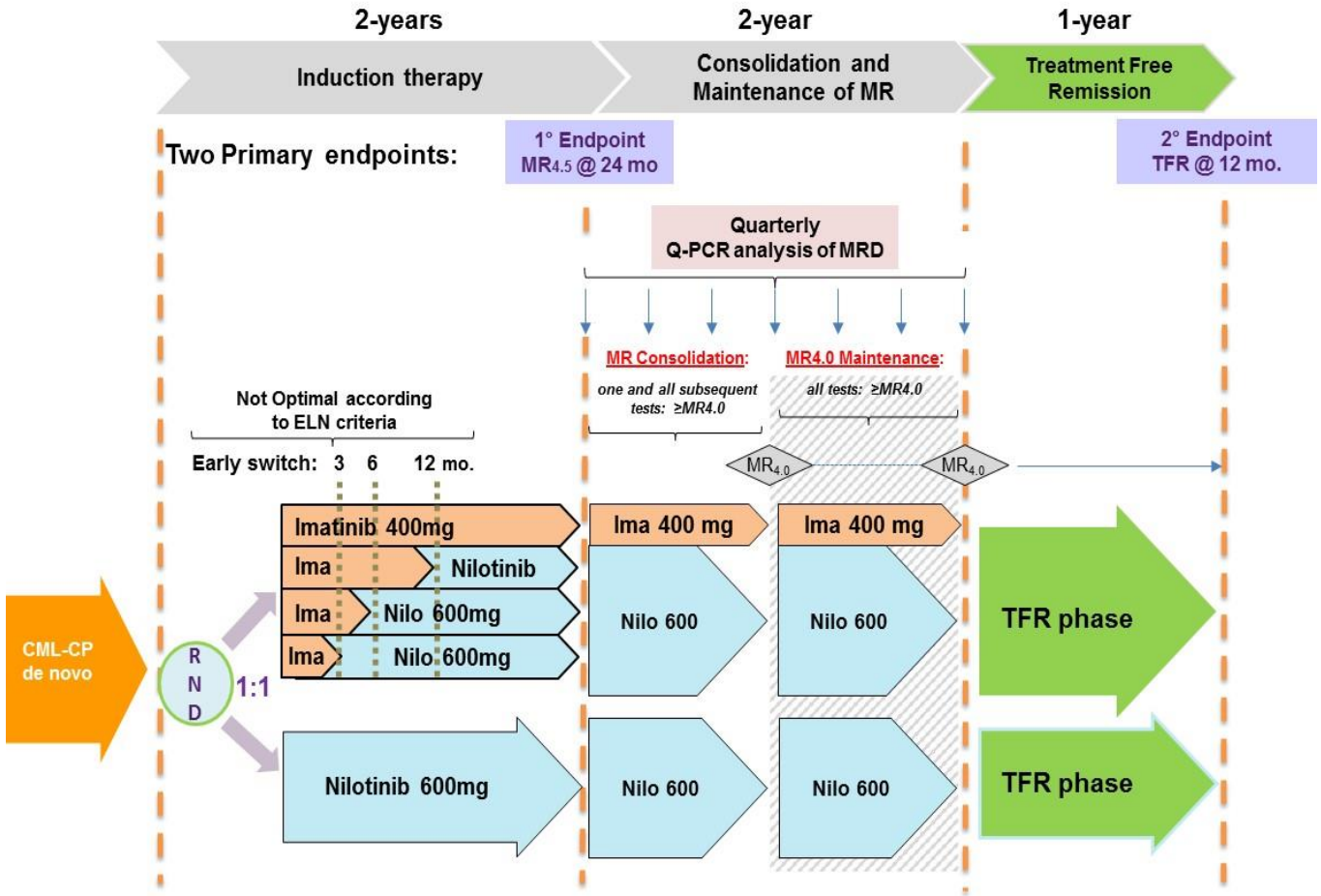
Hypothesis: ~50% TFR success rate (loss of MMR as relapse definition)

n = 58 (20.5%) N = 37 (13.5%)

Hochhaus A, et al. Blood. 2015;126:abstract 2781

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

SUSTRENIM trial



Working Party Chronic Myeloid Leukemia

DR

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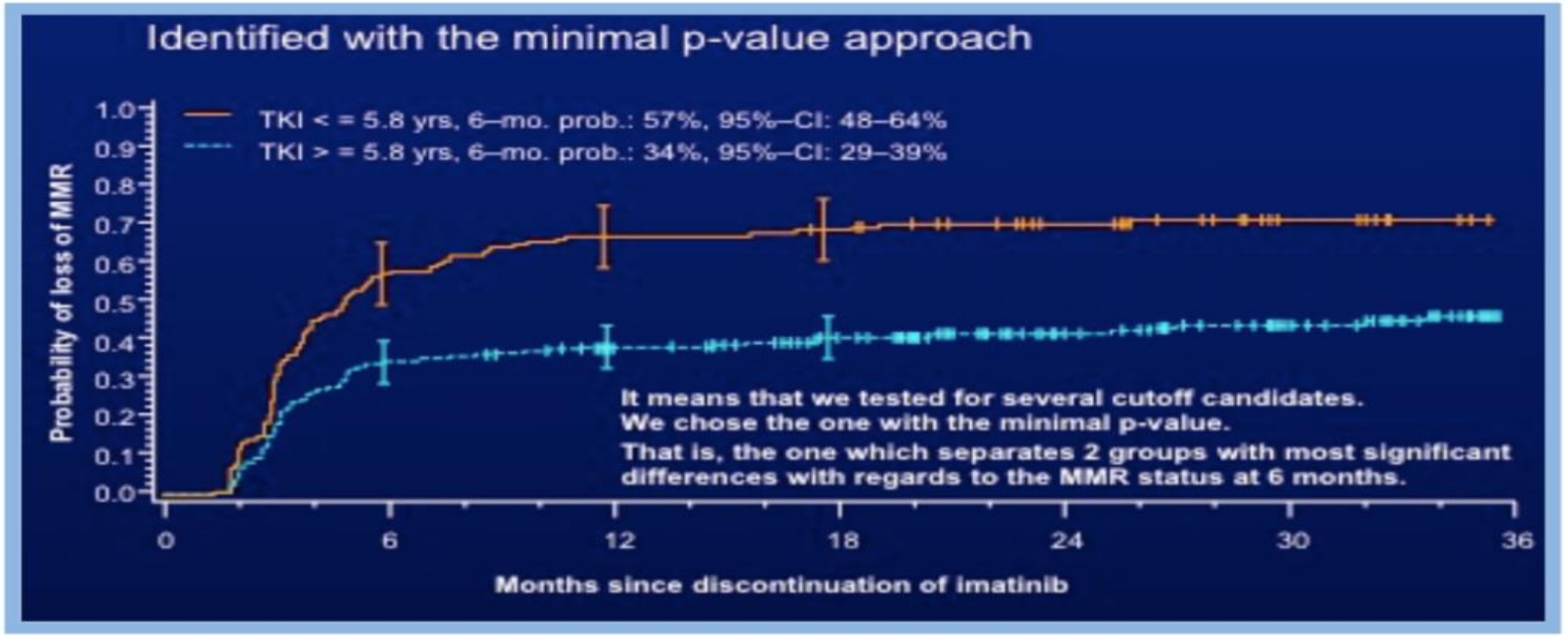
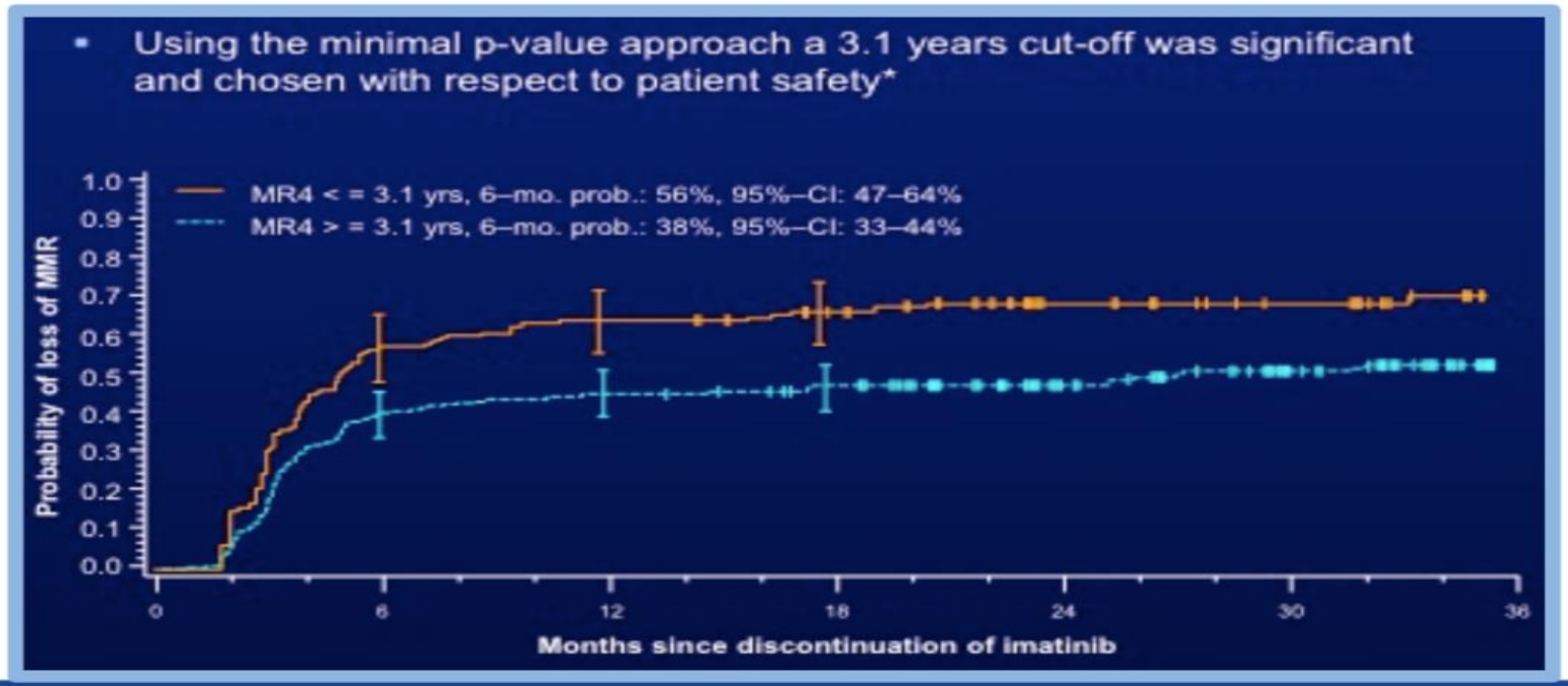
Imagawa et al, 2015; Mahon et al, 2016
Rea et al, 2017 Hochhaus et al, 2017, Ross et al, 2017

Significant association (p<0.001):

- Treatment duration with imatinib
- MR4 duration
- Duration of IFN pre-treatment





TKI < = 5.8 yrs, 6–mo. prob.: 57%
TKI > = 5.8 yrs, 6–mo. prob.: 34%

MR4 < = 3.1 yrs, 6–mo. prob.: 56%
MR4 > = 3.1 yrs, 6–mo. prob.: 38%

Euroski Trial

Prognostic factors of TFR in TKI discontinuation studies

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EURO-SKI: molecular relapse free survival according to MRD

- 357 pts evaluable (follow-up of more than 6 months after discontinuation)

	No. of pts	RFS (at 6 months)
Only MR4 (not in MR4.5)	9%	61%
MR4.5 detectable	35%	51%
MR4.5 undetectbale	56%	62%

- Propensity score* between the detectable and undetectable (119 pts): no differences in RFS (52% e 57%)
- Detectability of BCR-ABL1 transcripts in pts with MR4.5 depends on the number of control gene transcripts (higher the number, higher the sensitivity). No differences in RFS at 6 months
- EHA 2017: no difference among MR4 detectable and undetectable in terms of RFS

*Matching variables were: type (ABL1 or GUSB), number of control gene transcripts, IFN pre-treatment, duration of MR4, and the IM treatment time before observation of MR4

Pfirmann ASH 2016: abstract 789;
EHA 2017 abstract S426

Moving treatment-free remission into mainstream clinical practice in CML

Criteria	GREEN	YELLOW	RED
Institutional criteria met (per Table 1)	Yes	–	No
Sokal score at diagnosis	Non-high	High	–
BCR-ABL transcript at diagnosis	Typical – B2A2 or B3A2 (e12a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to first-line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	>8 years	3–8 years	<3 years
Depth of deep molecular response	$MR^{4.5}$	MR^{4}	Not in MR^{4}
Duration of DMR monitored in a standardised laboratory	>2 years	1–2 years	<1 year

- **ALL GREEN** lights: Strong recommendation to consider TKI withdrawal
- **ANY YELLOW** lights: Only consider TKI withdrawal in high-priority circumstances (eg, significant toxicity or planned pregnancy)
- **ANY RED** lights: TKI withdrawal not recommended

Hughes TP, et al. *Blood*. 2016;128:17-23.

Recommendations for clinical practice: patient selection

Source	Criteria
NCCN CML Version 2.2017-January 19, 2017	CP-CML ≥ 18 years-old Major-type *BCR-ABL1* transcripts TKI treatment for at least 3 years (any type, any line) MR4 for at least 1 year No history of resistance to TKI
ESMO 2017 Hochhaus A, et al. Ann Oncol. 2017;28(suppl_4):iv41-iv51.	CP-CML ≥ 18 years-old Low or intermediate Sokal score TKI treatment for at least 5 years (any type, any line) MR4.5 for at least 2 year No history of resistance or suboptimal response to TKI
Nilotinib: EPAR Product Information http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000798/WC500034394.pdf	CP-CML ≥ 18 years-old Major-type *BCR-ABL1* transcripts First line nilotinib 1ère ligne for at least 3 years 2nd line nilotinib (post imatinib) for at least 3 years MR4.5 for at least 1 year of nilotinib treatment
Fi-LMC 2018 Cancer 2018	CP-CML ≥ 18 years-old Major-type *BCR-ABL1* transcripts TKI treatment for at least 5 years (any type, any line) MR4.5 for at least 2 year No history of resistance or suboptimal response to TKI

Recommendations for clinical practice: monitoring during the treatment-free phase

Source	Specifications
NCCN CML Version 2.2017-January 19, 2017	RT-qPCR monthly during the 1st 6 months, then every 2 months until month 24, then every 3 months.
Nilotinib: EPAR Product Information http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000798/WC500034394.pdf	CBC and RT-qPCR monthly during the 1st year, every 6 weeks the 2nd year then every 12 weeks. In case of MR4 loss without MMR loss: every 2 weeks.
Fi-LMC 2018 Cancer 2018, accepted for publication	CBC and RT-qPCR monthly during the 1st 6 months, then every 2 months until month 12, then every 3 month during the 2nd year, then every 3 to 6 months

TFR: Points to be discussed in 2018

- Will the possibility of achieving TFR influence our first-line therapy approach?
- In what way? Immediately using second-generation TKIs or switching if specific milestones are not achieved?
- Minimum overall TKI duration: 3, 5, 8 years? Different for different TKIs?
- Best level of DRM: MR^4, $MR^{4.5}$?
- “Minimum” duration of DMR: 1, 2, 3, 5 years?
- Only LOW-risk patients?
- TKI alone or associated with inteferon?

VII Session – Chronic Myeloid Leukemia

Treatment Free Remission

Gianantonio Rosti, Bologna (Italy)