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Stopping CML treatment: Update of treatment-free remission studies

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Conflict of interest disclosure

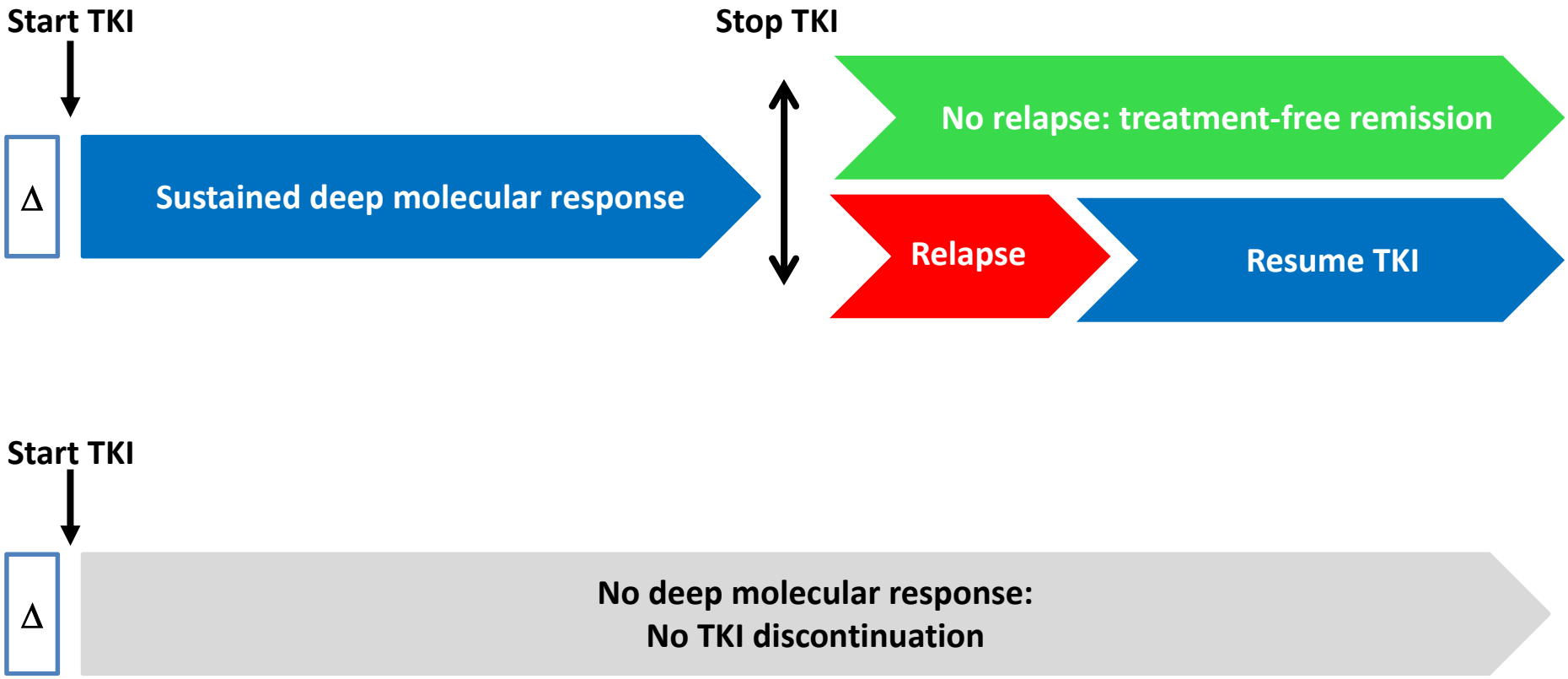
- Honoraria: BMS, Incyte, Novartis and Pfizer
- Membership on scientific advisory boards: BMS, Novartis
- Clinical trial steering committee member: BMS, Novartis

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.

TKI discontinuation: principles

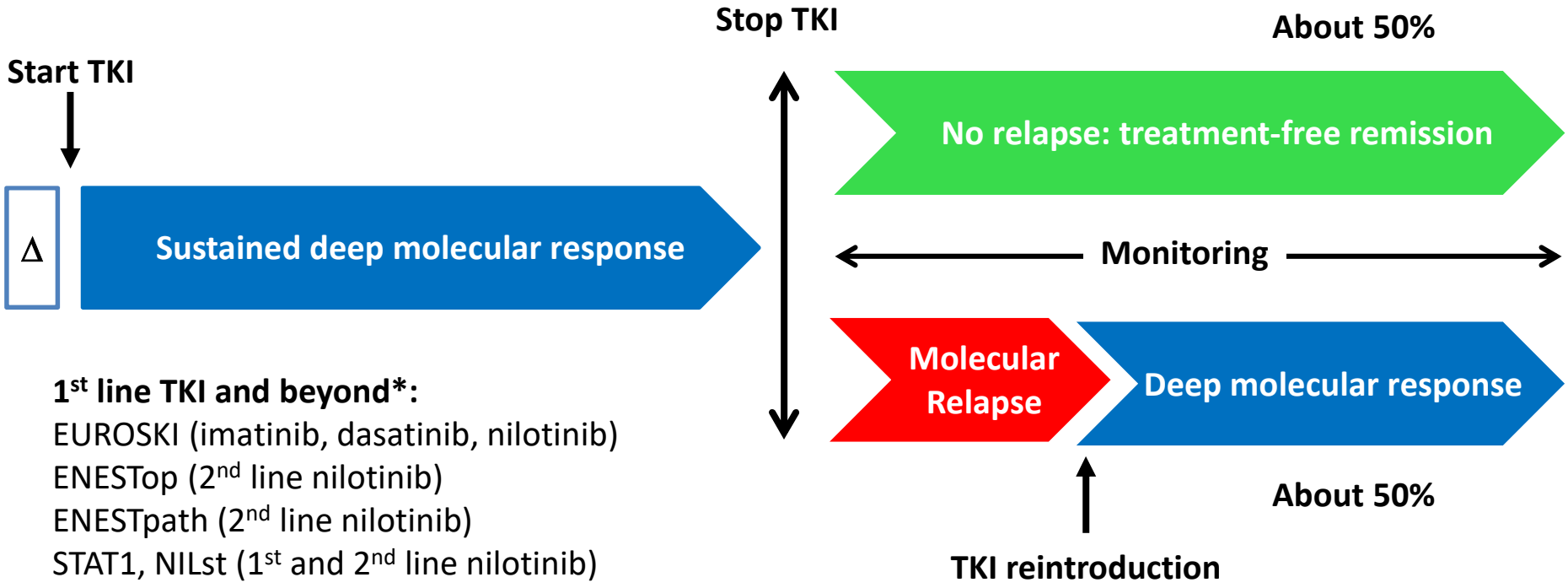


Δ: Chronic phase CML at diagnosis

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)

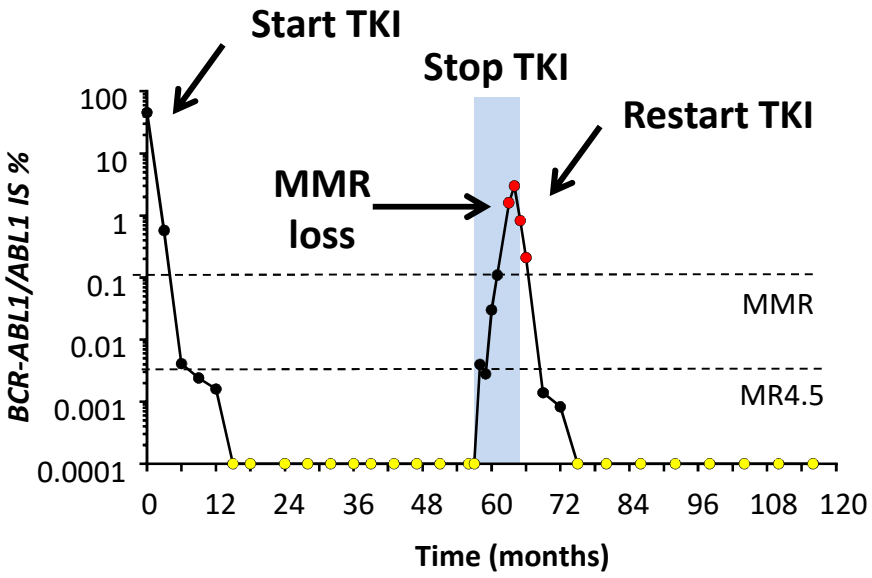
Δ: Chronic phase CML at diagnosis

*non exhaustive list.

Relapses after TKI discontinuation

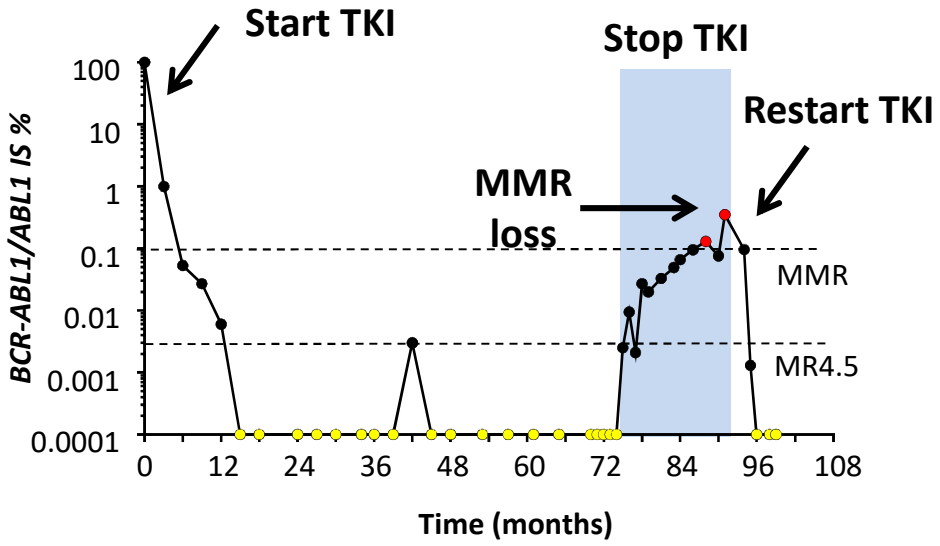
Early relapses: fast kinetics

Example 1:
0,5 to 1 log increase per month in 5 months
MMR loss at 5 months



Later relapses: slower kinetics

Example 2:
1 log increase in 18 months
MMR loss at 18 months



MMR loss

Undetectable *BCR-ABL1* with at least 32000 copies of *ABL1*

Treatment-free phase

D. Rea personal data

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

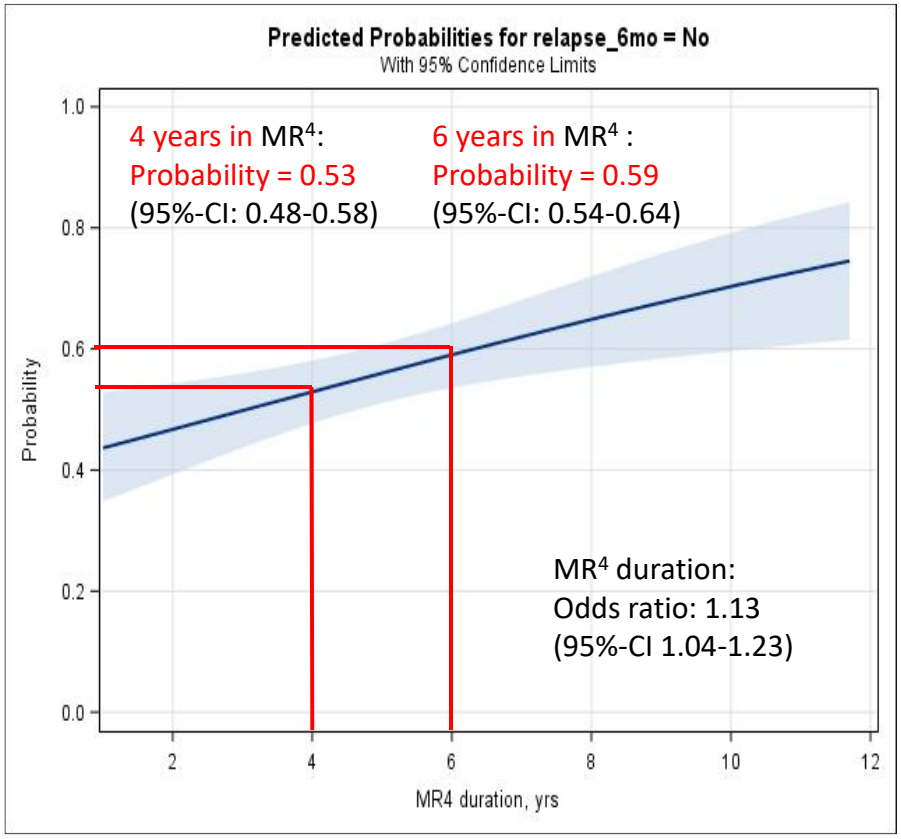
Prognostic factors of TFR in TKI discontinuation studies

Factor category	Factor	Prognostic value
Patient	Age, sex	No (adults only)
Disease	Prognostic scores at diagnosis	Non-high Sokal best (1^{st} 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

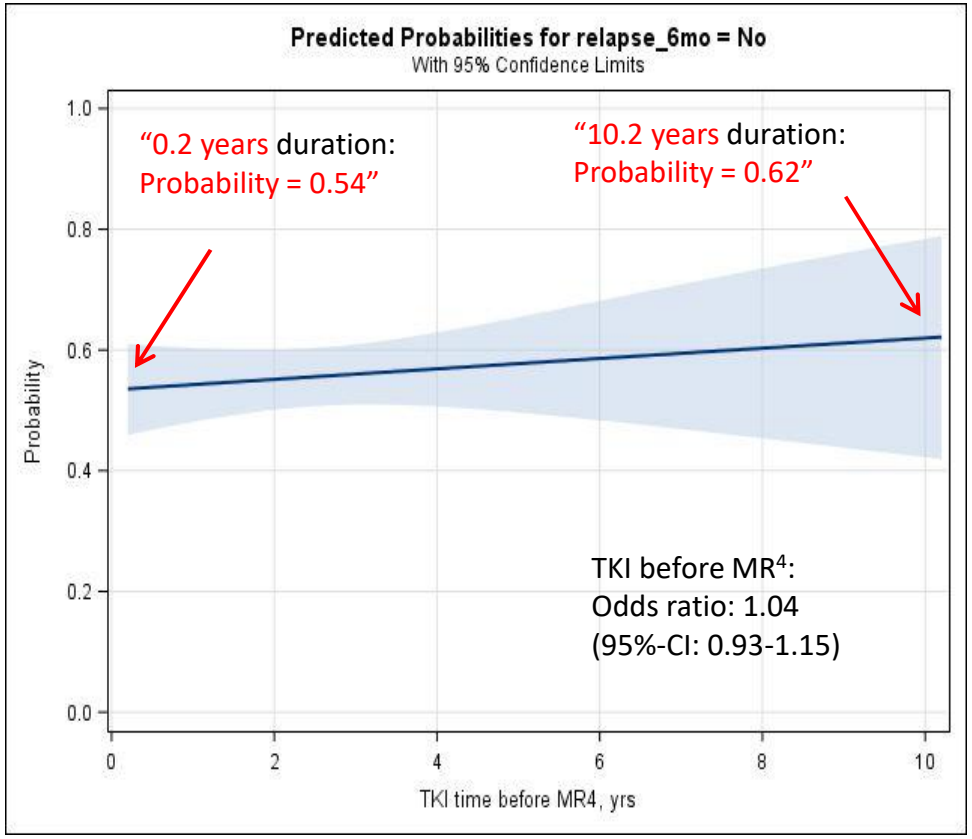
Mahon et al, 2010; Etienne et al, 2017
Imagawa et al, 2015; Mahon et al, 2016
Rea et al, 2017 Hochhaus et al, 2017, Ross et al, 2017

Impact of imatinib treatment and deep molecular response duration on TFR in EUROSKI

Deep molecular response duration (MR4 at least)

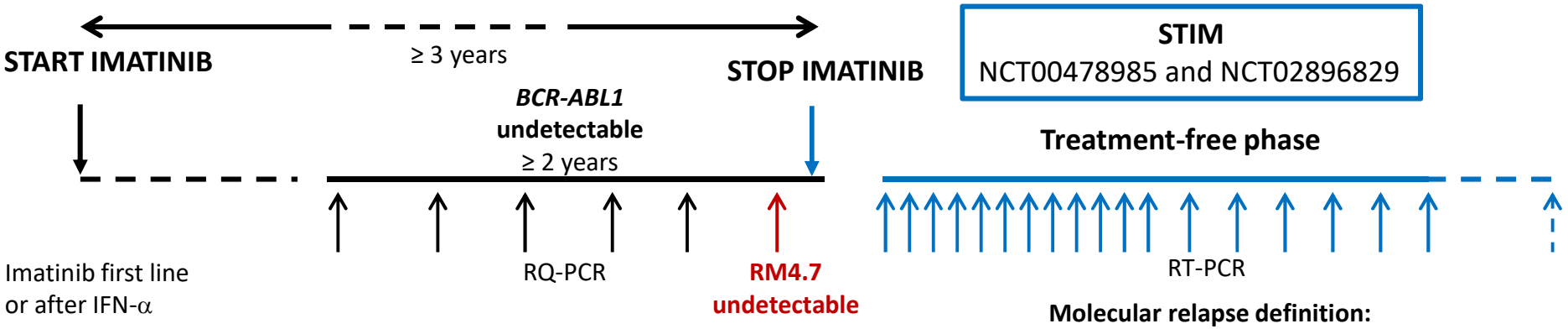


TKI treatment duration before deep molecular response



Saussele et al. Blood (ASH) 2017: abstract 313.

Long-term follow-up: data from STIM

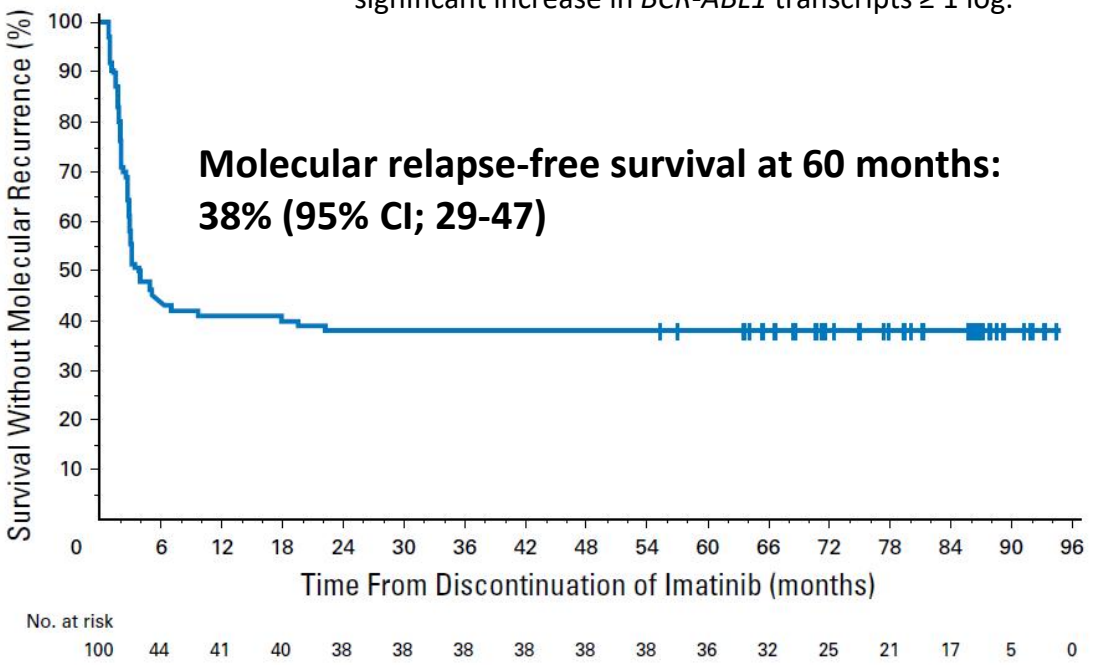


STIM
NCT00478985 and NCT02896829

Treatment-free phase

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)

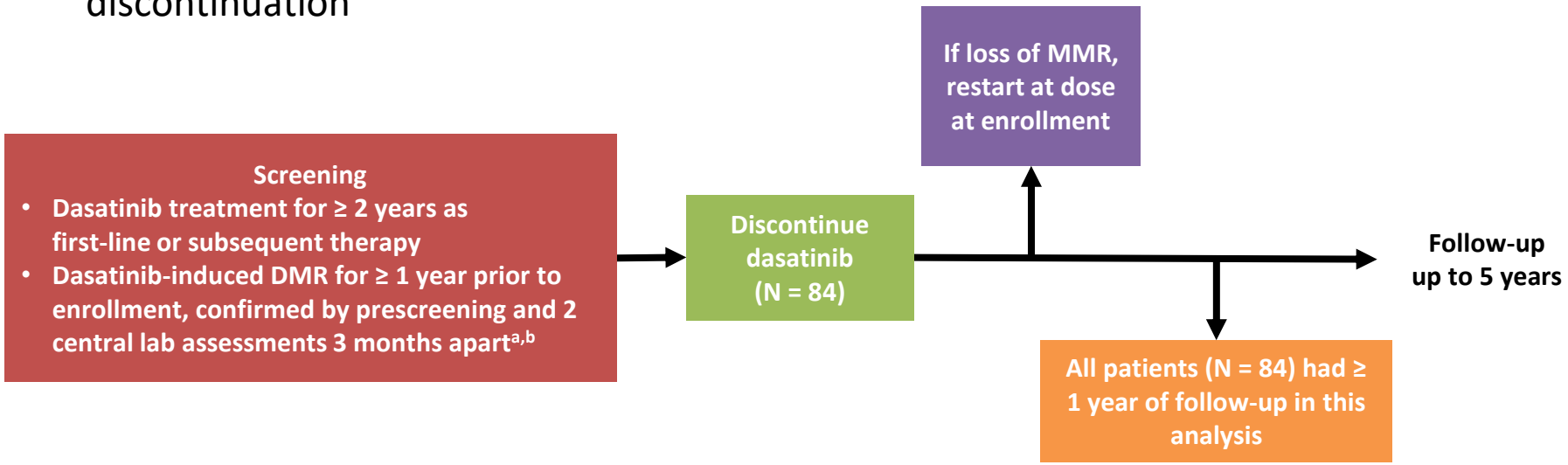


Molecular relapse-free survival at 60 months: 38% (95% CI; 29-47)

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

Trial update: DASFREE
Design

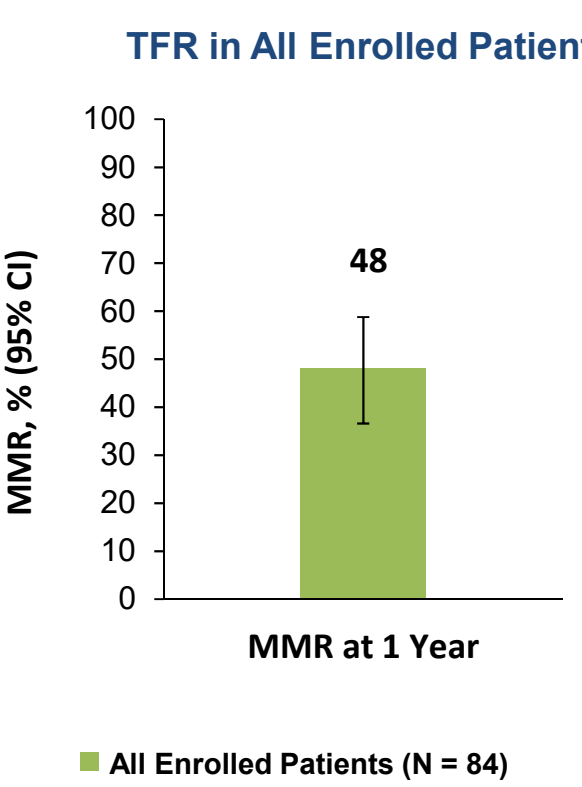
- Phase 2, open-label, single-arm international study
- Eligible patients were required to be in DMR ($MR^{4.5}$ or *BCR-ABL1* ≥ 0.0032% on the IS)
- Primary endpoint: Rate of MMR maintenance 1 year following dasatinib discontinuation

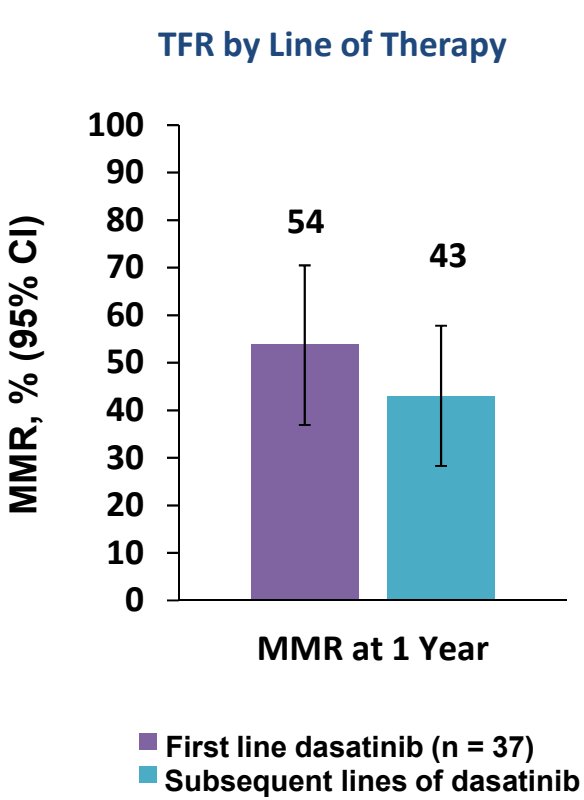


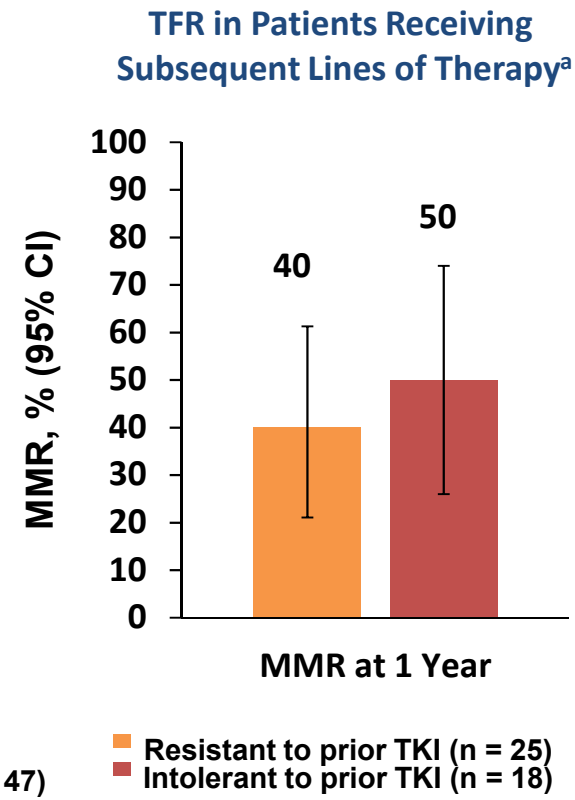
[a]Adults with dasatinib-induced stable DMR for ≥ 9 months, documented by ≥ 3 assessments conducted 2 to 6.5 months apart at a local lab were screened.
[b]For any patient not eligible for enrollment because both assessments at the central lab did not confirm DMR, rescreening was allowed ≥ 9 months after the last central lab screening failure.
DMR = deep molecular response; IS = International Scale; MMR = major molecular response; $MR^{4.5}$ = molecular response with 4.5-log reduction of *BCR-ABL1* transcripts.

Trial update: DASFREE

TFR rates at 1 year

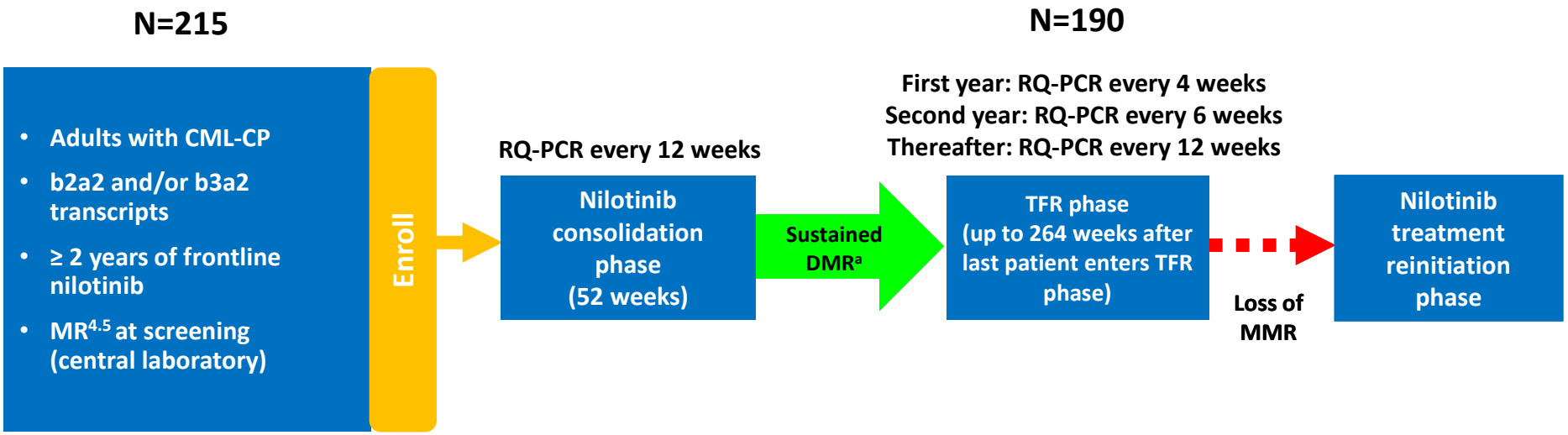






[a]Resistance or intolerance to prior TKI therapy was classified as "other" in 4 patients receiving subsequent lines of dasatinib.
CI = confidence interval; MMR = major molecular response; TKI = tyrosine kinase inhibitor; TFR = treatment-free remission.

Trial update: ENESTfreedom: *Design*



$MR^{4.5}$, *BCR-ABL1*^{IS} ≤ 0.0032%; RQ-PCR, real-time quantitative polymerase chain reaction.

[a] Defined as the following (in the last 4 quarterly PCR assessments): $MR^{4.5}$ in the last assessment, no assessment worse than MR^4, and ≤ 2 assessments between MR^4 and $MR^{4.5}$.

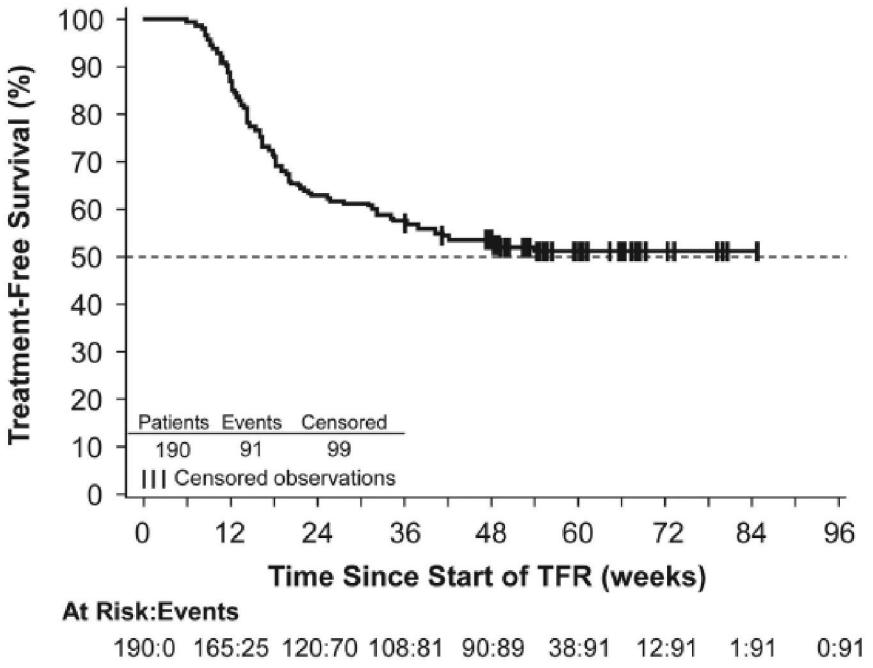
Trial update: ENESTfreedom: *Results by 48 weeks*

Table 1. Baseline characteristics at study entry and nilotinib therapy before TFR phase entry

	TFR population (n = 190)
Baseline characteristics at study entry	
Age, median (range) (years)	55.0 (21–86)
Male, *n* (%)	96 (50.5)
Time from CML diagnosis to study entry, median (range) (months)	32.2 (21.4–80.7)
Time from achievement of $MR^{4.5}$ with nilotinib to study entry, median (range) (months)	18.3 (0.3–70.9)
Nilotinib therapy before TFR phase entry	
Duration of nilotinib therapy, median (range) (months)	43.5 (32.9–88.7)
Actual nilotinib dose intensity during consolidation phase, median (range) (mg per day)	600 (400–600)

Abbreviations: CML, chronic myeloid leukemia; $MR^{4.5}$, molecular response 4.5 (*BCR-ABL1* ⩽0.0032% on the International Scale); TFR, treatment-free remission.

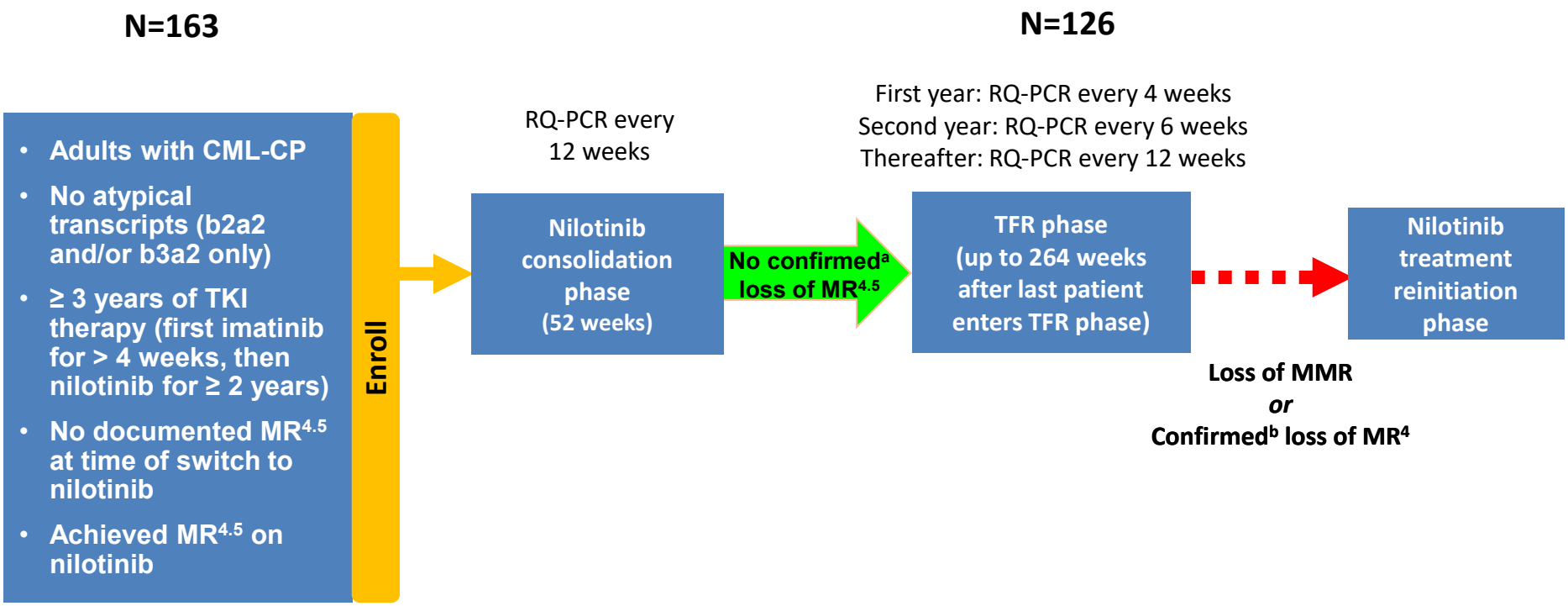
Treatment-free survival



At 48 weeks after stopping nilotinib, 51.6% (95% CI: 44.2-58.9) remained in MMR. 86 patients lost MMR and restarted therapy: 98.8% regained MMR.

Hochhaus A et al. Leukemia 2017; 31: 1525-1531.

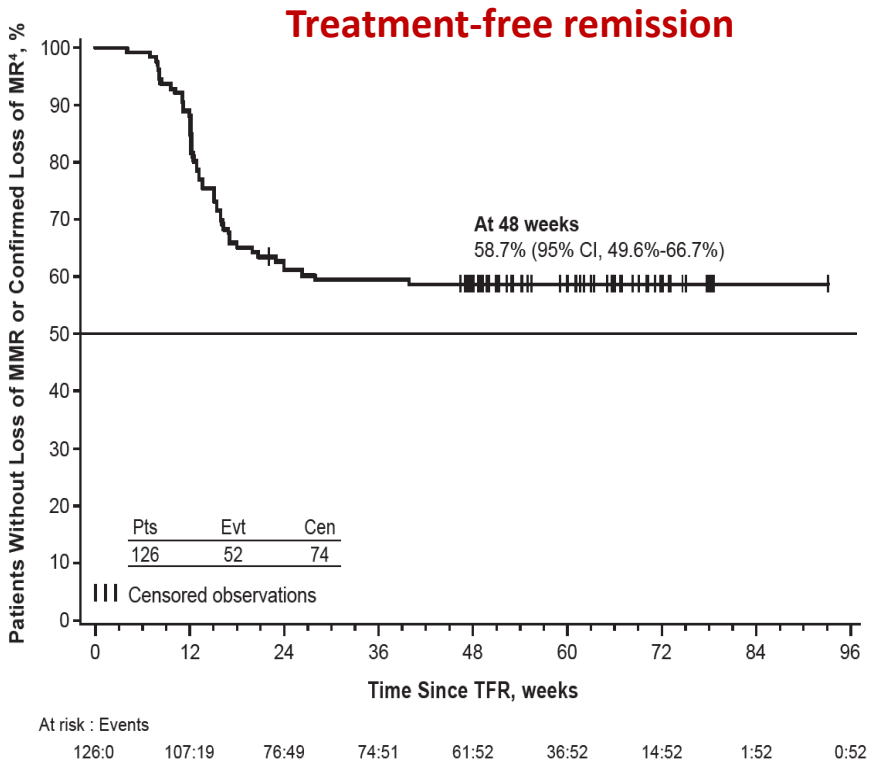
Trial update: ENESTop:
Design



[a] Confirmed loss of MR$^{4.5}$ was defined as *BCR-ABL1*^{IS} > 0.0032%, confirmed in a second assessment within 4 weeks.
[b] Confirmed loss of MR^{4} was defined as *BCR-ABL1*^{IS} > 0.01%, confirmed in a second assessment within 4 weeks.

Trial update: ENESTop:
Results by 48 weeks

Characteristics	N=126 (TFR phase)
Median age	5 years (range: 21-86)
Median duration of TKI treatment	87.7 months (range: 37-159)
Median duration of nilotinib	53 months (range: 37-109)
Treatment history: Intolerance to imatinib Resistance to imatinib Physician preference	 n=51 (40%) n=30 (24%) n=45 (36%)



At 48 weeks after stopping nilotinib, 73 patients (58% (95% CI: 49-67)) remained in MMR. 56 patients lost MMR and restarted therapy: 55 regained MMR or better.

Mahon FX, et al. Ann Intern Med 2018;168: 461-470.

TKI discontinuation in clinical practice: *Emerging recommendations*

	NCCN 2017	ESMO 2017	SPC nilotinib	Fi-LMC 2018
Who?	X	X	X	X
When?	X	X	X	X
How	X	_	X	X
Identifying and treating relapses	X	_	X	X

NCCN Guidelines V2.2017 https://www.nccn.org/
Hochhaus et al, Ann Oncol. 2017 Jul 1;28(suppl_4):iv41-iv51.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000798/WC500034394.pdf
Rea et al. Cancer 2018. Accepted for publication

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, accepted for publication	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

Recommendations for clinical practice: definition and management of relapses

Source	Definition	Treatment
NCCN CML Version 2.2017-January 19, 2017	MMR loss	Restart the same TKI
ESMO 2017 Hochhaus A, et al. Ann Oncol. 2017;28(suppl_4):iv41-iv51.	MMR loss	Restart the same TKI
Nilotinib: EPAR Product Information http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000798/WC500034394.pdf	MMR loss or loss of MR4 confirmed at 4 weeks interval	Restart nilotinib 300mg BID or 400mg QD(1st lne) or 400mg BID (2nd line) within 4 weeks
Fi-LMC 2018 Cancer 2018, accepted for publication	MMR loss	Restart the same TKI

Other important issues for clinical practice

- Spread of knowledge and experience
- Patent information and adhesion
- Access to high quality and affordable molecular biology
- How to improve TKI discontinuation outcome in patients with a history of suboptimal response/resistance?
- Patients with minor *BCR-ABL1* transcripts?
- TKI discontinuation in childhood CML?
- Multiple TKI discontinuation attempts not recommended in clinical practice.

Conclusion

- About 40 to 60% of patients with long-lasting deep molecular response on TKI therapy are likely to remain in prolonged TFR after treatment discontinuation.
- Recommendations for safe TKI discontinuation attempt in clinical practice are emerging.
- TKI discontinuation in clinical practice requires:
  - Widespread access to high quality standardized RT-qPCR
  - Adherence of physicians, molecular biologists and patients to TKI discontinuation programs, which are geared to specific groups of patients and not to the whole CML patient community
- Fundamental and clinical research remains necessary as not all issues have been solved.