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Low doses of tyrosine kinase inhibitors in CML

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Conflict of interest disclosure

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

TKI dose finding

1. Phase 1 trial:
   - Dose escalation method:
     - Maximum tolerated dose (MTD), Drug limiting toxicity (DLT), safety and tolerability profile.
     - Pharmacokinetics/dynamics.
2. Phase 2 trial:
   - Evaluation of one or several drug doses considered as best compromise between safety and efficacy in phase 1 studies.
3. Phase 3 trial:
   - Comparison of safety and effectiveness of a new drug against standard of care.
4. Marketing authorization application (new drug or new indication):
   - Recommended (on-label) starting dose.

Dose finding and initial recommended dose: imatinib, nilotinib

	Imatinib	Nilotinib	
Dose range in phase 1	25-1000mg/d	10-1200mg QD; 400 and 600mg BID	
Half life	13-16h	15h	
MTD	-	600mg BID	
	Post IFN and 1st line	>1st line	1st line
Dose evaluated in registration trials (CP-CML)	400mg QD (CP)	400mg BID	400mg BID 300mg BID
Approval	yes	yes	yes
Recommended starting dose (CP-CML)	400mg QD (CP)	400mg BID	300mg BID

Druker BJ et al, New Engl J Med 2001; 344: 1031-1037.
Kantarjian H et al, New Engl J Med 2006; 354: 2542-2551.
Salgio G, et al. New Engl J Med 2010; 362: 2251-2259.

Dose finding and initial recommended dose: bosutinib

	Bosutinib		
Dose range in phase 1	400-600mg QD		
Half life		22-27h	
MTD	Not reached		
	>1st line	1st line	1st line
Dose evaluated in registration trials (CP-CML)	500mg QD	500mg QD	400mg QD
Approval	yes	no	Yes (FDA) Pending (EU)
Recommended starting dose (CP-CML)	500mg QD	NA	400mg QD

Cortes JE et al, Blood 2011; 118: 4567-4576.
Cortes et al, J Clin Oncol 2018; 36: 231-237.

Dose finding and initial recommended dose: ponatinib

	ponatinib		
Dose range in phase 1	2-60mg QD		
Half life	22h*		
MTD	45mg QD		
	>1st line	1st line	>1st line
Dose evaluated in registration trials (CP-CML)	45mg QD	45mg QD	45mg QD, 30mg QD, 15mg QD**
Approval	Yes	Trial prematurely stopped based on safety data	
Recommended starting dose (CP-CML)	45mg QD	-	

*At ≥30mg QD

**ClinicalTrials.gov Identifier: NCT02467270

Cortes JE et al, New Engl J Med 2012; 367: 2075-2088.
Cortes JE et al, New Engl J Med 2013; 369: 1783-1796.
Lipton JH, et al. Lancet Oncol 2016; 17: 612-621.

On-label dose reduction: 1st and 2nd generation TKI

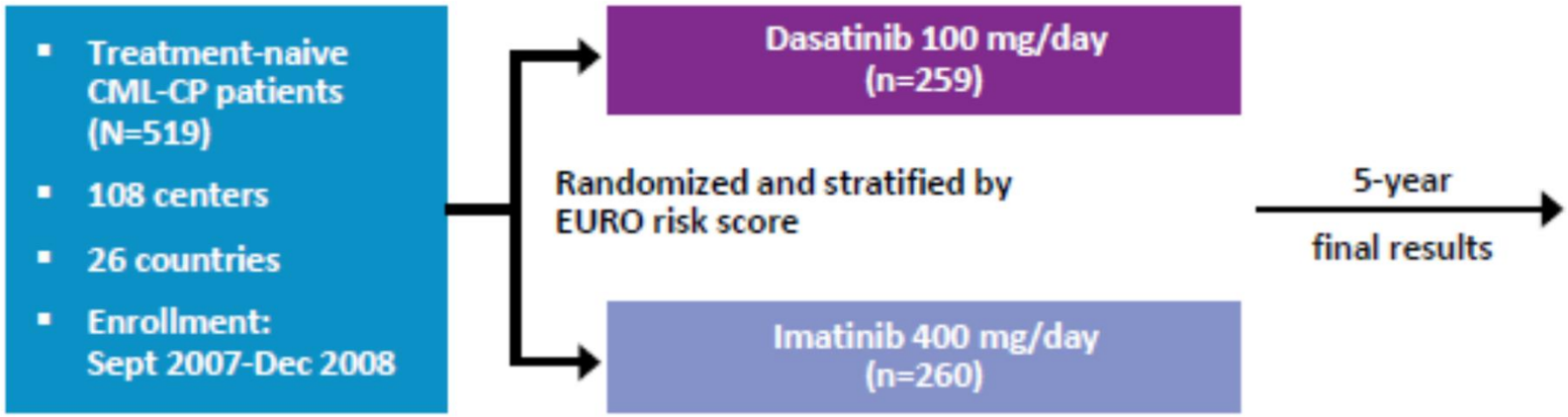
- Start TKI at the initial recommended dose.
- Maintain initial dose if acceptable tolerance.
- Interrupt and resume at a lower dose in case of severe/recurrent toxicity:
  - Consider re-escalation whenever possible.

	CP-CML				
	Imatinib	**Bosutinib >1st line**	**Dasatinib**	**Nilotinib 1st line**	**Nilotinib>1st line**
Initial recommended dose	400mg QD	500mg QD	100mg QD	300mg BID	400mg BID
Lower dose level 1	300mg QD	400mg QD	80mg QD	400mg QD	400mg QD
Lower dose level 2	-	300mg QD	50mg QD	-	-

Refer to SmPCs

TKI dose reduction in the DASISION trial:
5-year data (1)

- Study design:



- Up to 2 dose reduction allowed in case of tolerance issues:
  - Dasatinib: 80mg QD, then 50mg QD
  - Imatinib: 300mg QD, then 200mg QD

Hochhaus A, et al, EHA 22nd congress 2017: abstract E1052.

TKI dose reduction in the DASISION trial:
5-year data (2)

	Dasatinib arm (n=258)	Imatinib arm (n=258)
Patients with dose reductions at any time	95 (37%)	44 (17%)
Number of dose reduction		
1	52 (55%)	33 (75%)
2	32 (3%)	7 (16%)
Median average daily dose	83mg QD (range: 30-122)	328mg QD (range: 125-527)
Median time from treatment initiation to first dose reduction	289 days	160 days

Hochhaus A, et al, EHA 22nd congress 2017: abstract E1052.

TKI dose reduction in the DASISION trial:

5-year data (3)

Table 2. Best Molecular Response Before and After 1st Dose Reduction

	Treated patients, n				
	Response to dasatinib after 1st dose reduction (n=95)				
Response to dasatinib before 1st dose reduction	$MR^{4.5}$ (n=34)	MMR (n=35)	*BCR-ABL1* 0.1-≤10% (n=17)	*BCR-ABL1* >10% (n=5)	Not evaluated (n=4)
$MR^{4.5}$ (n=14)	9	5	0	0	0
MMR (n=26)	15	9	2	0	0
BCR-ABL1 0.1-≤10% (n=27)	5	11	9	1	1
BCR-ABL1 >10% (n=14)	1	4	4	4	1
Not evaluated (n=14)	4	6	2	0	2
	Response to imatinib after 1st dose reduction (n=44)				
Response to imatinib before 1st dose reduction	$MR^{4.5}$ (n=17)	MMR (n=10)	*BCR-ABL1* 0.1-≤10% (n=7)	*BCR-ABL1* >10% (n=7)	Not evaluated (n=3)
$MR^{4.5}$ (n=3)	2	1	0	0	0
MMR (n=5)	3	1	1	0	0
BCR-ABL1 0.1-≤10% (n=14)	5	5	3	1	0
BCR-ABL1 >10% (n=8)	1	2	1	3	1
Not evaluated (n=14)	6	1	2	3	2

IMPROVED RESPONSE | MAINTAINED RESPONSE | LOST RESPONSE

Hochhaus A, et al, EHA 22nd congress 2017: abstract E1052.

On-label dose reduction: ponatinib

- Initial recommended dose 45mg QD of ponatinib.
- Maintain treatment unless progression or unacceptable toxicity.
- Interrupt and restart at a lower dose in case of toxicity:

Dose levels	CP-CML
	Ponatinib
Initial recommended dose	45mg QD
Lower dose level 1	30mg QD
Lower dose level 2	15mg QD

- Consider reducing the dose down to 15mg QD for CP-CML patients who have achieved a major cytogenetic response and closely monitor response.

Iclusig EPAR product information – last updated 19 February 2018

Off-label lower-dose prescribing

General statements

- Doses below the on-label dose range may be necessary in specific subgroups of patients for safety reasons.
- In the absence of tolerance issue, determining patient personal optimal low dose may:
  - Help prevent /reduce adverse side effects.
  - Improve “quality of life”.
  - Reduce medication regimen complexity.
  - Lessen cost of health care.
  - Decrease environmental loadings of excreted drug residues and unintended exposure of bystanders.
  - Reduce waste treatment as a result of non-adherent behavior.
- The use of off-label lower doses should rely on supporting evidence and should not compromise the achievement of therapeutic goals.

Daughton CG and Ruhoy I. Science of the total environment 2013; 443: 324-337.

Can we use off-label lower-TKI doses in CML?

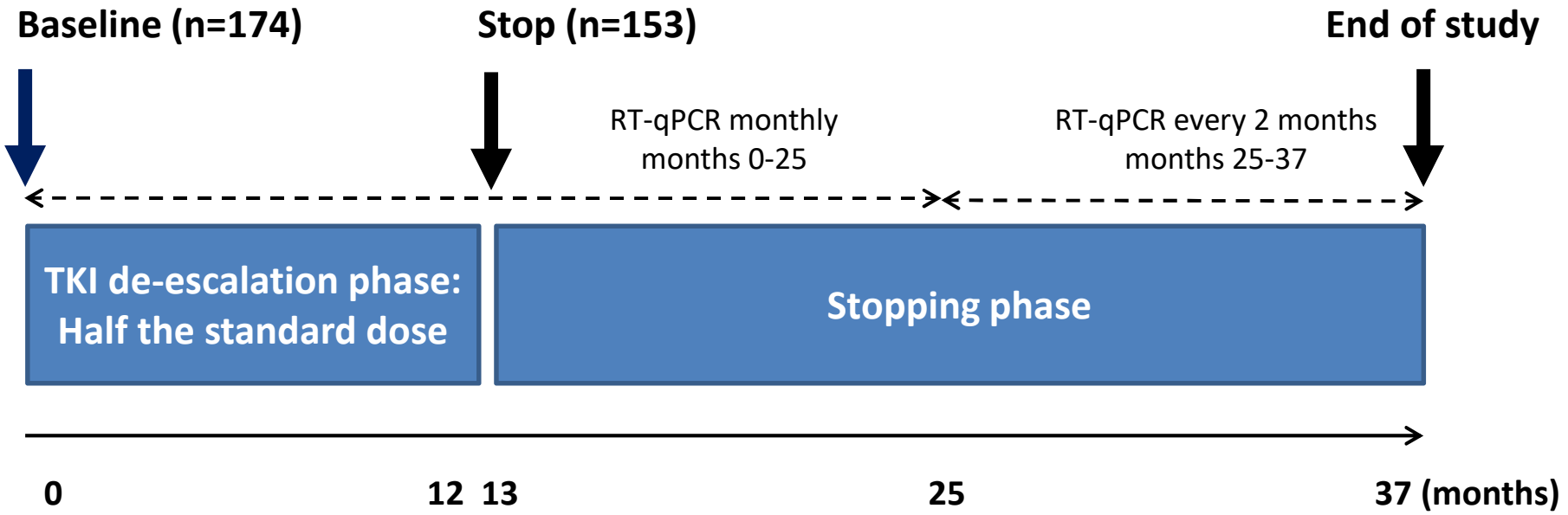
- If so:
  1. Optimal response to therapy should not be compromised.
  2. Situations in which lower doses may be given without individual excess risks need to be identified.
  3. Reducing the dose or reducing dosing frequency?

DESTINY: trial design

Eligibility:
Age ≥18 years
CP-CML, M-bcr
TKI* ≥3 years at standard doses
1st line or switch for intolerance
MR4 ≥1 year (n=125)
MMR ≥1 year (n=49)

Molecular recurrence: MMR loss on 2 consecutive samples 2 weeks apart: resume the standard TKI dose

Primary endpoint:
MMR loss



* imatinib, dasatinib ou nilotinib

Clark RE et al. Lancet Haematology 2017; 4:e310-e316.

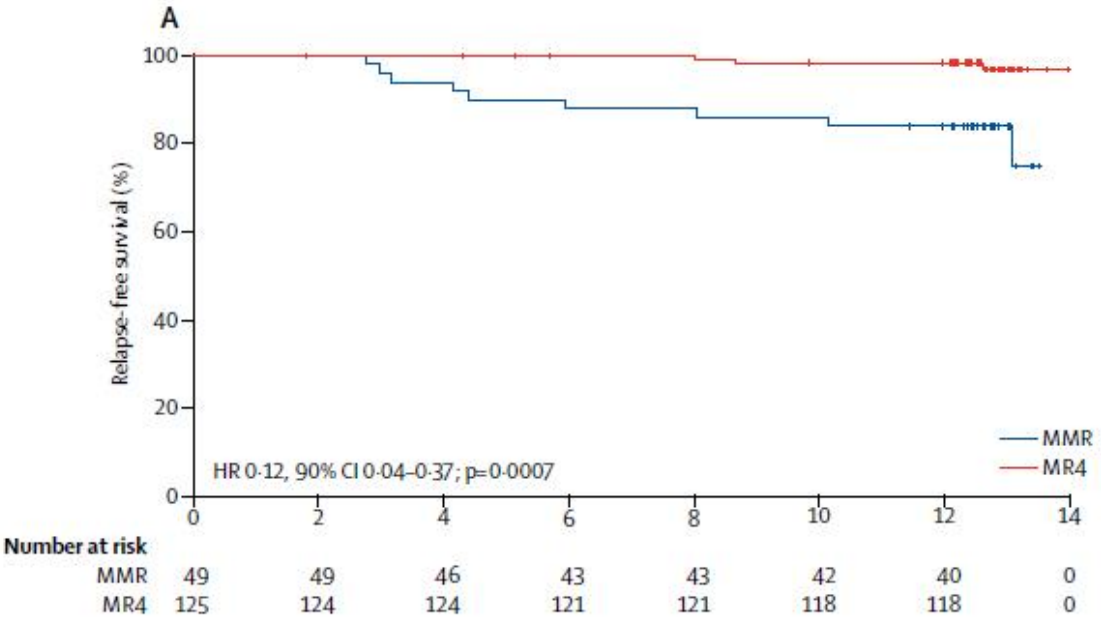
DESTINY: baseline characteristics

	MMR cohort N=49	MR4 cohort N=125	All N=174
Median age (years)	57	61	59
Male sex	25 (51%)	73 (58%)	98 (56%)
Median *BCR-ABL1/ABL1* IS %	0.0047%	0.001	0.001
Median total time on TKI (years)	7.7	6.5	6.9
Medication Imatinib Nilotinib Dasatinib	 43 (88%) 2 (4%) 4 (8%)	 105 (84%) 14 (11%) 6 (5%)	 148 (85%) 16 (9%) 10 (6%)

Clark RE et al. Lancet Haematology 2017; 4: e310-e316.

DESTINY trial: de-escalation phase "Relapse"-free survival

- 12 patients had molecular recurrences during the de-escalation phase (7%).
  - 9 in the MMR cohort (19%), median time to MMR loss 4.4 months.
  - 3 in the MR4 cohort (2%), median time to MMR loss 8.7 months.
- All regained MMR within 4 months of full-dose TKI resumption.
- Adverse events improved during the first 3 months of de-escalation.



Clark RE et al. Lancet Haematology 2017; 4:e310-e316.

NILO-RED observational study

- Primary aim: to ask whether nilotinib-treated CML pts were able to maintain major molecular responses (MMR) after conversion to a more convenient nilotinib QD regimen at reduced doses, regardless of reasons for tapering nilotinib.

Observational 2-center study (Paris Saint-Louis and Bordeaux, France)

Age ≥ 18 years
CML with major-type *BCR-ABL1*
Any line nilotinib
Nilotinib initiated at 300 or 400mg BID
Dose reduction of nilotinib QD for any reason
MMR obtained ≥3 months before dose reduction
QD
No allogeneic HSCT
No history of blast crisis

Primary goal

MMR maintenance by 12 months

Other goals

Evolution of molecular responses overtime
Evolution of adverse events if any
Nilotinib discontinuation and treatment-free remission
Overall and progression-free survival

Rea et al. Blood (ASH) 2017: abstract 318.

NILO-RED: baseline characteristics

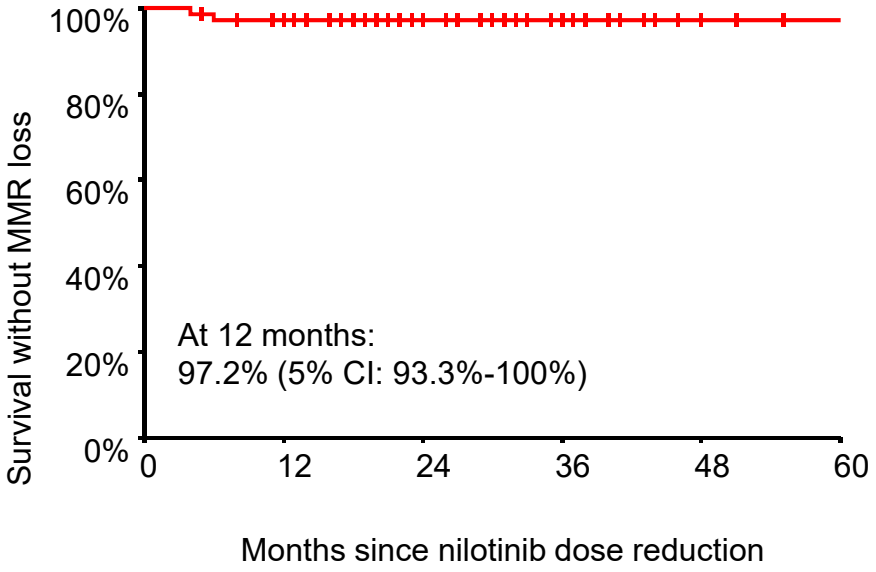
	Whole cohort (n=82)
Median age at diagnosis	47 years (range: 13-81)
Male gender	n=35 (42.5%)
CML phase at diagnosis (ELN)	
CP	n=81 (98.8%)
AP	n=1 (1.2%)
Nilotinib: line of therapy	
1st	n=56 (68.3%)
2nd	n=24 (29.3%)
3rd	n=2 (2.4%)
Median duration of nilotinib prior to dose decrease	29 months (1-112)
MMR duration before nilotinib dose reduction	27 months (3-143)
Primary reason for dose decrease	
Non hematologic side effects (G1-3)	n=27 (32.9%)
Patient convenience	n=55 (67.1%)
New nilotinib dose and schedule	
450mg QD	n=73 (89%)
400mg QD	n=7 (8.5%)
300mg QD	n=2 (2.4%)
Molecular response categories before nilotinib dose reduction	
MR3 only	n=16 (19.5%)
MR4 (detectable)	n=21 (25.6%)
≥MR4.5 (detectable or undetectable)	n=45 (54.9%)

Rea et al. Blood (ASH) 2017: abstract 318.

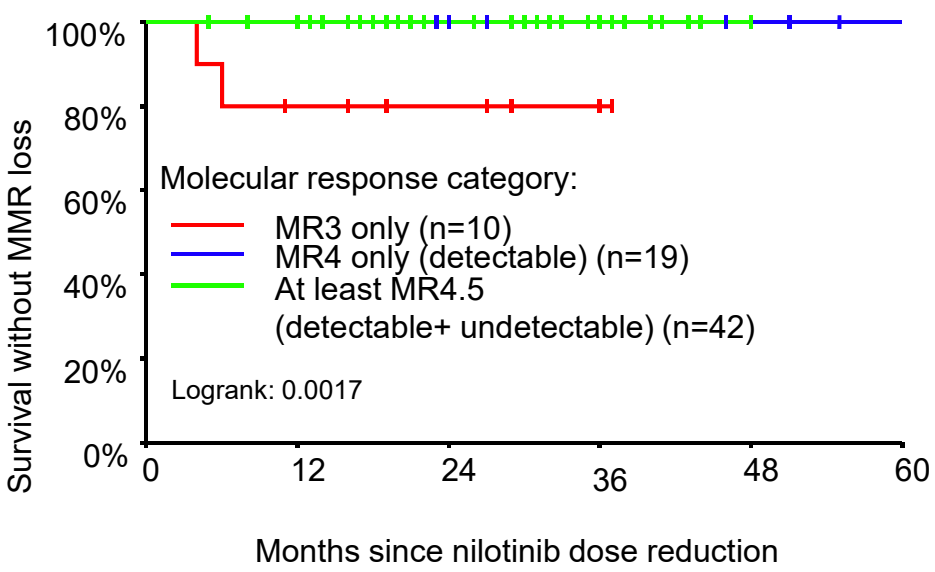
NILO-RED: results

- 2 patients lost MMR 4 and 6 months after nilotinib dose reduction QD and both spontaneously regained MMR without going back to the standard nilotinib dose.

Survival without MMR loss



Survival without MMR loss by molecular response category at baseline



Rea et al. Blood (ASH) 2017: abstract 318.

Summary of available data

- Reducing the dose of TKI (imatinib, dasatinib, nilotinib) in optimal responders (at least in MMR) is safe and improves tolerance.
- Reducing the dose of TKI (imatinib, dasatinib, nilotinib) in optimal responders does not seem to compromise treatment efficacy in the vast majority of patients (no induction of resistance).
- In order to safely transfer available knowledge in clinical practice we need to:
  - Define best candidate patient population.
  - Define adequate timing of dose reduction.
  - Determine monitoring rules after dose reduction and what to do in case of loss of response.

Other areas for investigation

- Reducing the dose or reducing dosing frequency?
- Can we initiate TKI at a lower dose than the standard dose without compromising efficacy, and if so who is it for?
  - 1st line setting?
  - Switches at a lower dose than the on-label dose for intolerance in optimal responders?
  - Switches at a lower dose than the on-label dose for patients with resistance to TKI?
- Dose reduction of TKI after TFR failure and MMR recovery?

La Rosée et al. Annals of Hematology 2013; 92: 1345-1350.
Russo et al. Blood 2013; 121: 5138-5144.
Santana-Hernandez et al. Blood (ASH) 2017; 130 Suppl 1: abstract 5254.

TKIs save lives: now it is time to address overtreatment