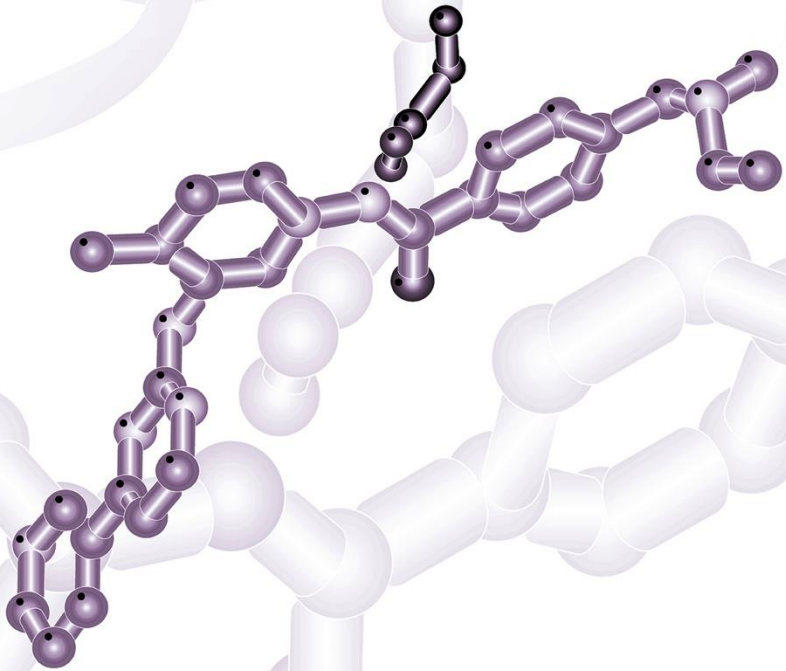
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA
DIAGNOSTICA E SPERIMENTALE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna



New Drugs in Hematology

President: Pier Luigi Zinzani

Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
May 18-20, 2022

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA DIAGNOSTICA E SPERIMENTALE

POLICLINICO DI SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

New Drugs in Hematology

Nilotinib, the correct dose

Massimiliano Bonifacio (Verona)

President: Pier Luigi Zinzani
Co-President: Michele Cavo

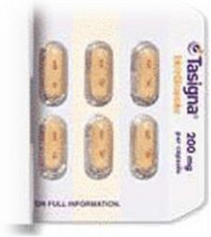
Bologna,
Royal Hotel Carlton
May 18-20, 2022

Disclosures of MASSIMILIANO BONIFACIO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						X	
Pfizer						X	
Incyte						X	
Bristol Myers Squibb						X	

europass

Curriculum Vitae
Europass



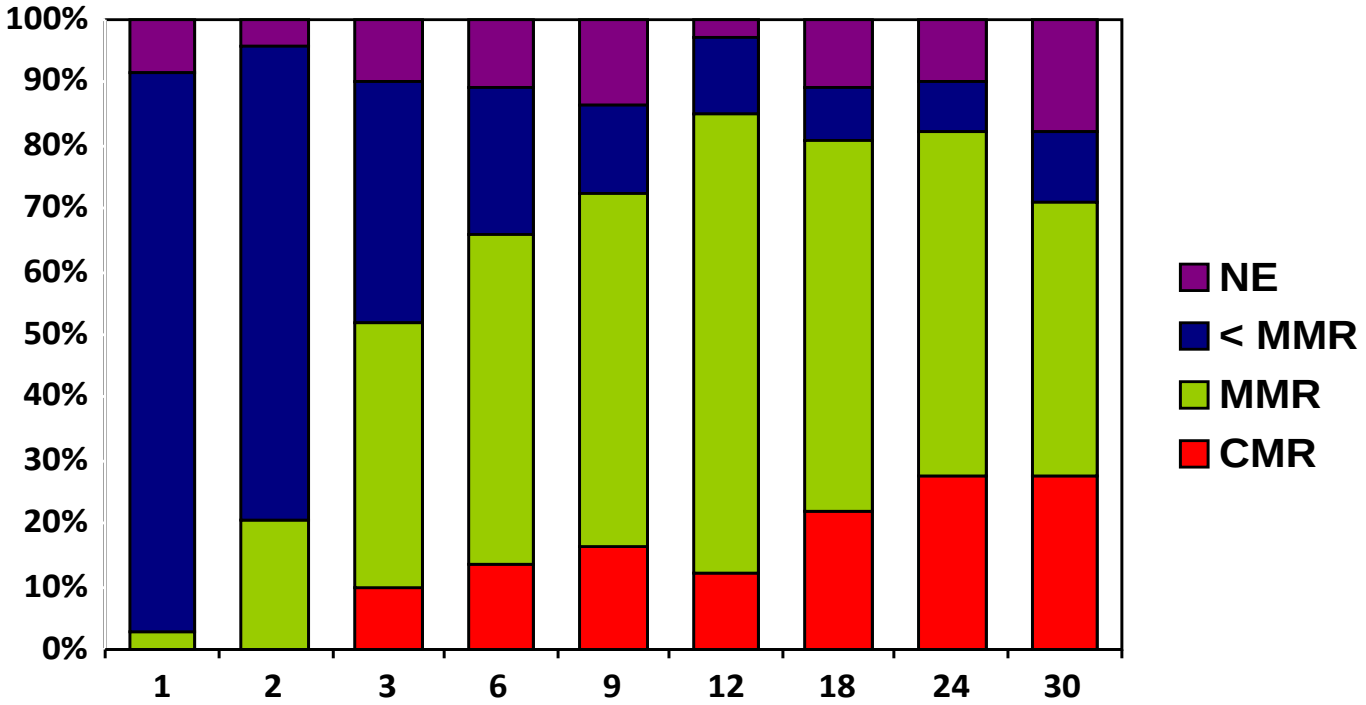
Nilotinib

- Approved in 2007 for patients resistant or intolerant to imatinib and in 2010 for frontline treatment of CML
- A comprehensive program of >10 clinical trials (“Evaluating Nilotinib Efficacy and Safety in clinical Trials”, ENEST studies)
- More than 1300 publications, several systematic reviews
- Patent expiration in 2023 (US) and 2028 (EU)

Agenda

- The issue of dose at treatment start
- The optimal dose and treatment duration for patients aiming at TFR
- The concept of dose optimization for patients in optimal response

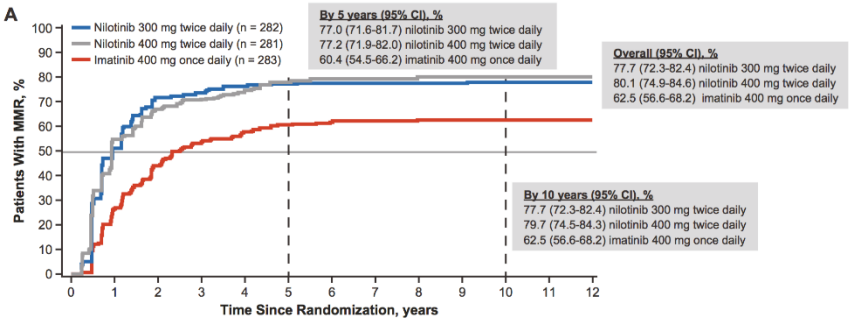
GIMEMA CML0307: the first study of frontline nilotinib (400 mg bid)



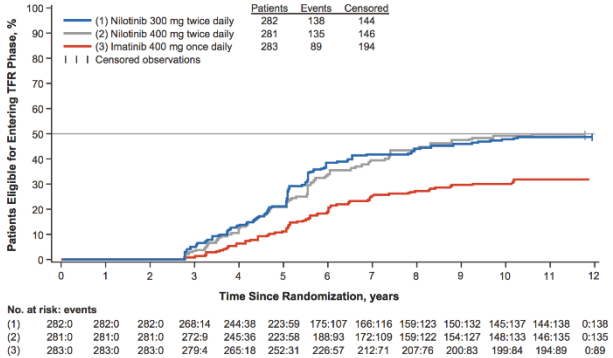
Rosti et al. *Blood* 2009;114:4933-4938.

ENESTnd: Nilotinib versus Imatinib in newly diagnosed CML

Cumulative incidence of MMR



Cumulative incidence of TFR eligibility*

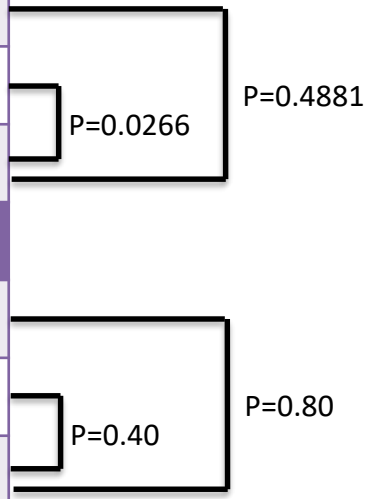


*Patients were considered eligible for TFR if they achieved $MR^{4.5}$ or better and maintained sustained DMR for ≥1 year (no RQ-PCR assessment worse than MR4 and the last assessment showed $MR^{4.5}$ or better).

Kantarjian et al. *Leukemia* 2021;35:440-453.

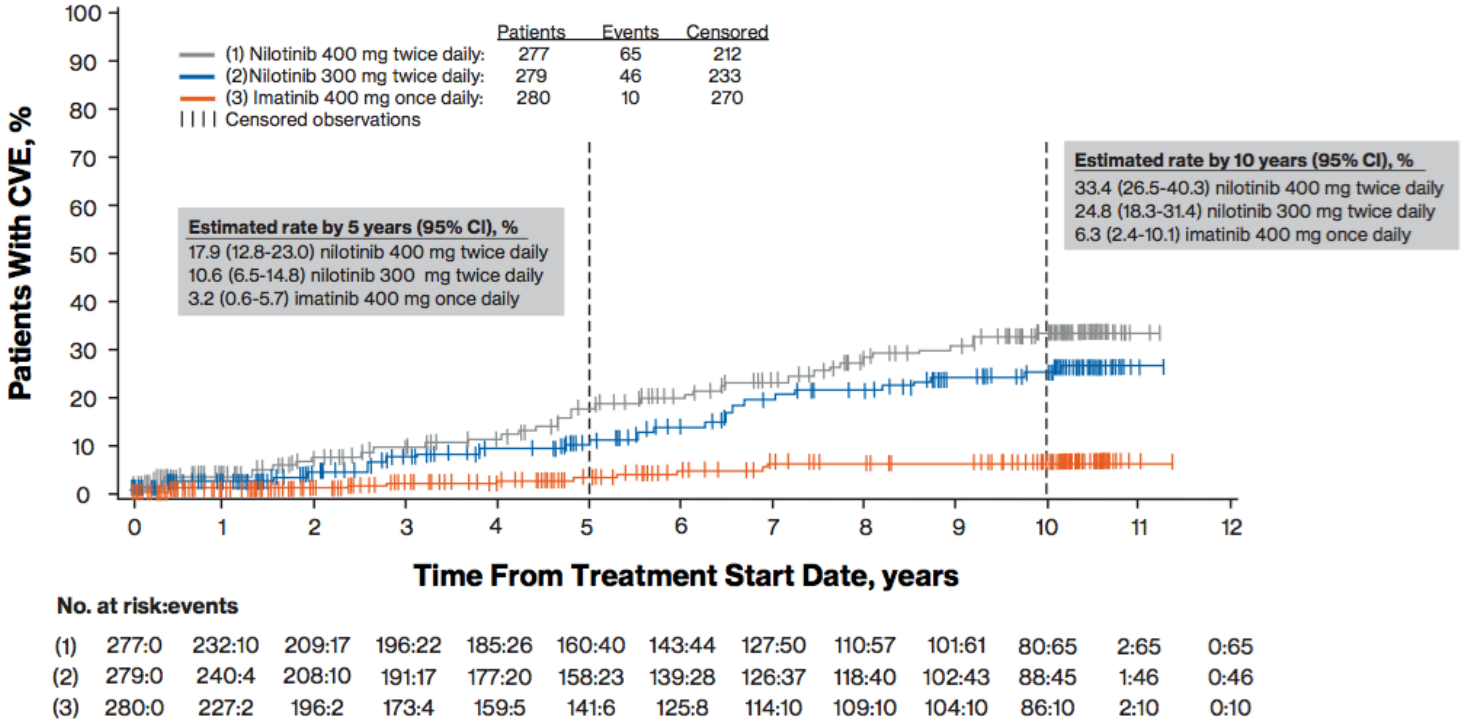
Long-term survival is similar between treatment arms of ENESTnd study

Estimated 5-year OS	% (95% CI)
Nilotinib 300 mg twice daily	93.7 (09.8-96.6)
Nilotinib 400 mg twice daily	96.2 (93.9-98.5)
Imatinib 400 mg once daily	91.7 (88.3-95.0)
Estimated 10-year OS	**% (95% CI)**
Nilotinib 300 mg twice daily	87.6 (83.5-91.7)
Nilotinib 400 mg twice daily	90.3 (86.5-94.1)
Imatinib 400 mg once daily	88.3 (84.2-92.4)



Hochhaus et al. *Leukemia* 2016;30:1044-1054. Kantarjian et al. *Leukemia* 2021;35:440-453.

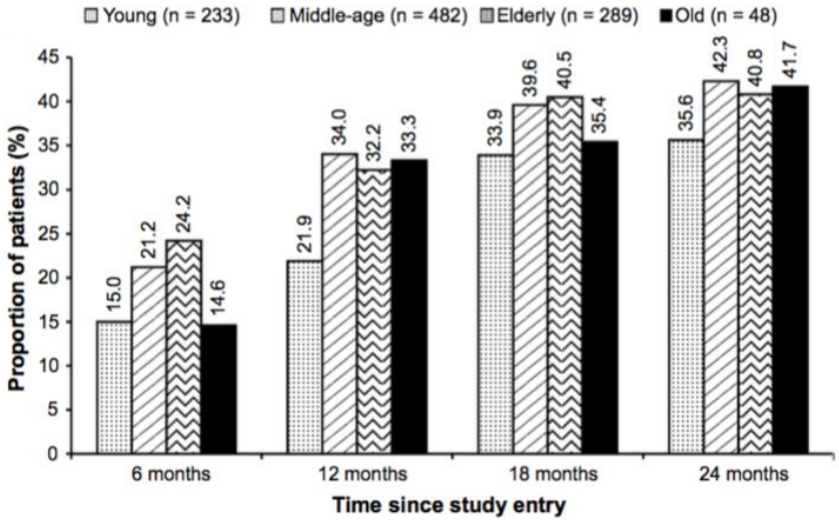
Nilotinib-associated CVE are dose- and time-dependent



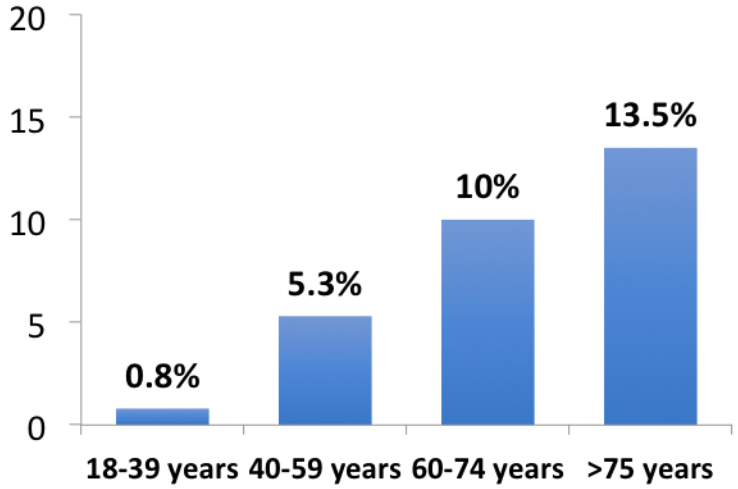
Hughes et al. ASH 2019 Abstr.#2924.

Outcomes of front-line nilotinib 300 mg bid (ENEST1st) across age groups

Rates of MR[4]



CV events



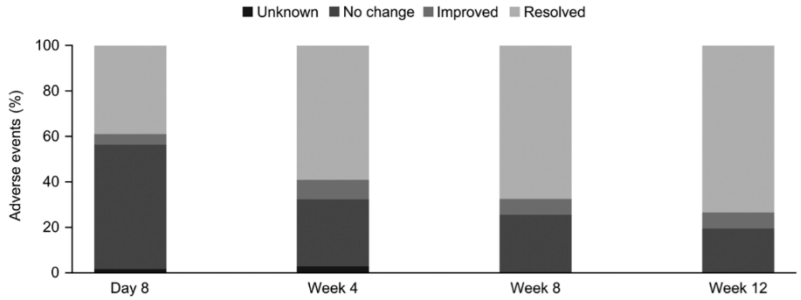
Giles et al. *J Cancer Res Clin Oncol*. 2017;143:1585-1596.

NIL 300 mg twice daily as starting dose in pre-treated patients

- **ENRICH** (Exploring Nilotinib to Reduce Imatinib-related Chronic adverse events)
- **ENESTswift**

Switching patients with chronic low-grade imatinib (or dasatinib) **intolerance** to nilotinib 300 mg twice daily leads to:

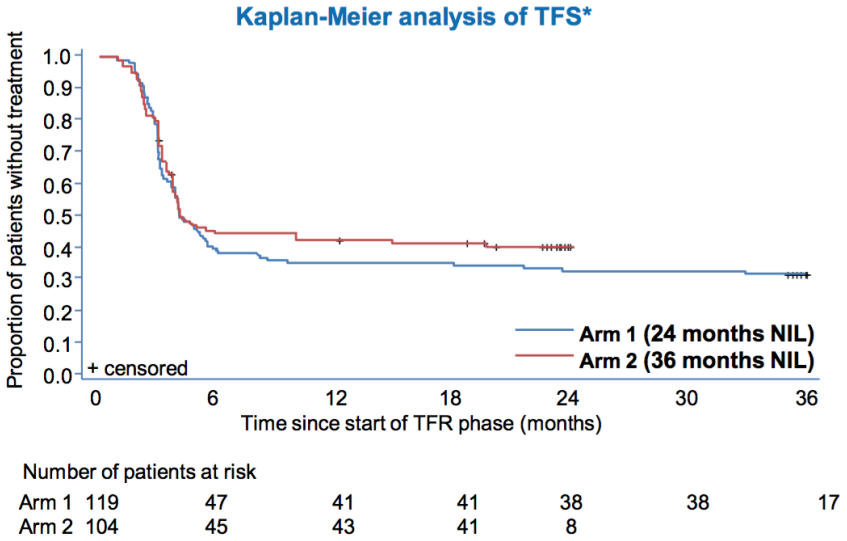
- resolution / mitigation of adverse events
- improved tolerability and better QoL
- deepening of molecular responses



Cortes et al. *Clin Lymph Myel Leuk* 2016;16:286-296. Hiwase et al. *Leuk Res* 2018;67:109-115.

ENESTpath: nilotinib 300 mg bid for patients without DMR after ≥2 years of imatinib

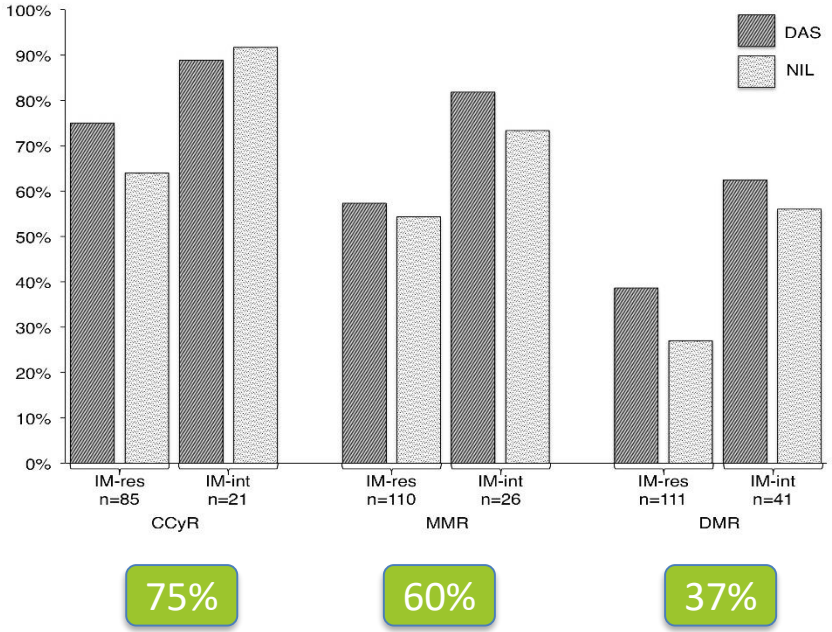
38.5% of patients obtained stable MR[4] after 24 months NIL 300 mg bid and could be randomized



	Arm 1 (24 months NIL) N=119	Arm 2 (36 months NIL) N=104
Median time to TFS, months (95% CI)	4.1 (3.7–5.5)	4.2 (3.7–19.7)
Kaplan-Meier estimates, % (95% CI)		
12 months	34.5 (26.1–43.0)	42.5 (32.9–51.9)
24 months	31.9 (23.8–40.4)	40.5 (30.9–49.8)
36 months	31.1 (23.0–39.5)	-

Rea et al. ASH 2021; abs#635

Real-world data of 2G TKI after imatinib failure

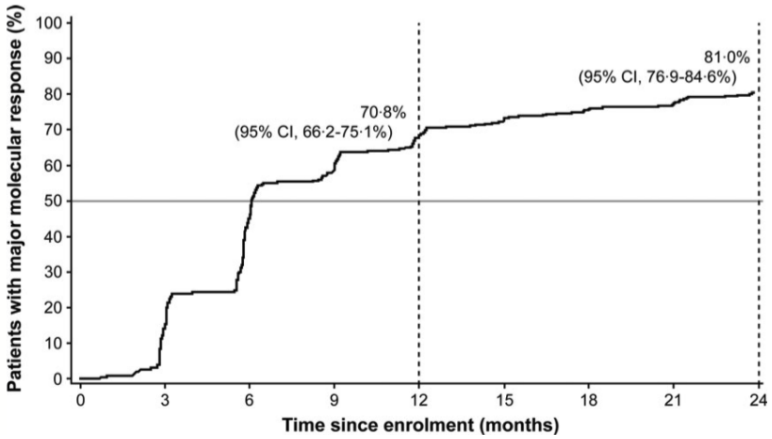


	NILOTINIB starting dose		
	800 mg	600 mg	400 mg
Patients	33	26	9
IM resistant/intolerant	21/12	13/13	3/6
CCyR rate	81%	64%	60%
MMR rate	65%	47%	71%
MR^4 rate	40%	33%	28%

Tiribelli, Bonifacio et al. *Oncotarget* 2018;9:14219-14227.

Dose optimisation upon molecular response: the ENESTxtend study

Protocol allowed nilotinib dose escalation (from 300 to 400 mg twice daily) in case of suboptimal response or treatment failure as well as dose re-escalation for patients with nilotinib dose reductions due to adverse events



Rates of MMR by 24 months according to dose optimization	
Patients with dose reduction due to AE and then re-escalated	79.6%
Patients with dose reduction due to AE and not re-escalated	63.6%
Patients with dose escalation due to lack of efficacy (suboptimal response or treatment failure)	63.6%

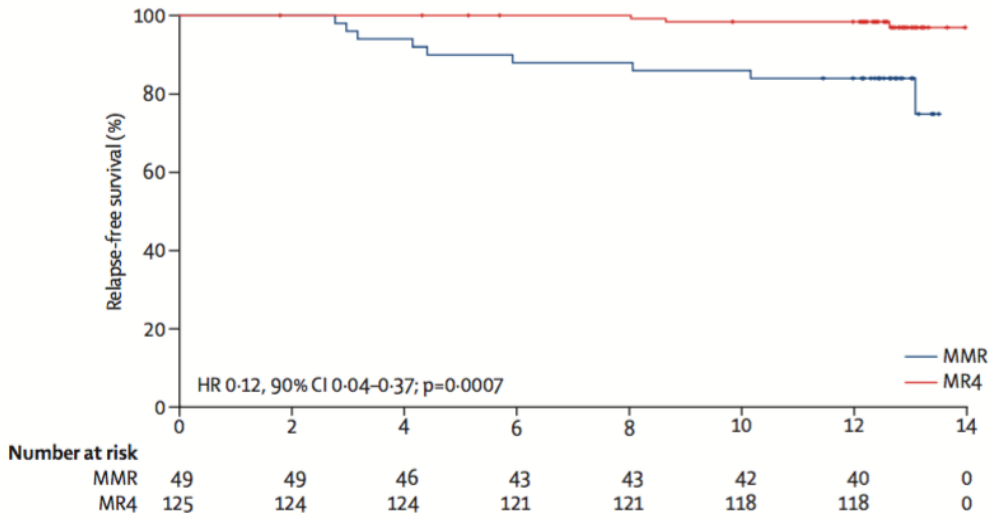
Hughes et al. *Br J Haem* 2017;179:219-228.

De-escalation of treatment is feasible and safe in the majority of patients with stable molecular response

De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel (DESTINY)

- Imatinib 400 → 200 mg daily
- Nilotinib 400 → 200 mg twice a day
- Dasatinib 100 → 50 mg daily

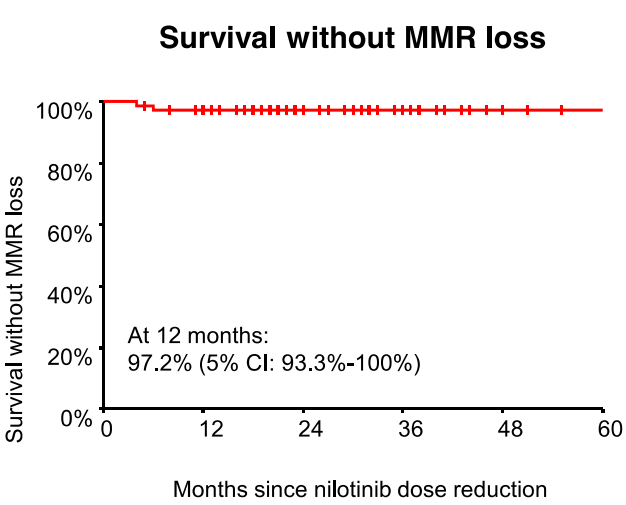
in patients treated for > 3 years and at least in MMR

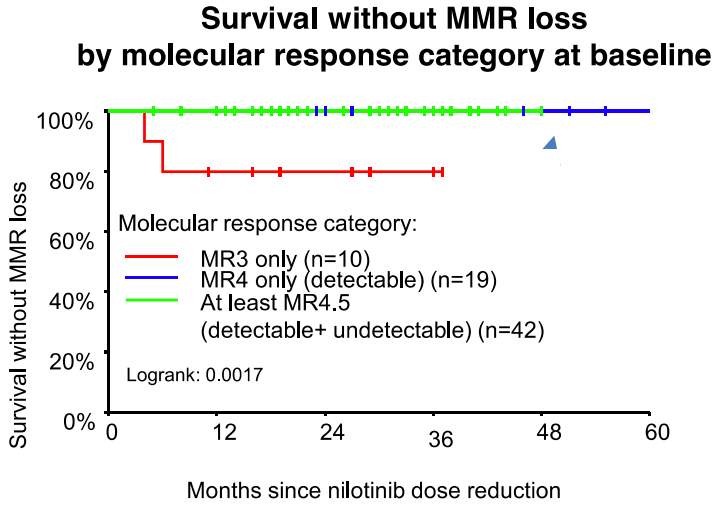


Clark et al. *Lancet Haematol* 2017;4:e310-e316.

NILO-RED: reducing nilotinib to once daily dosing

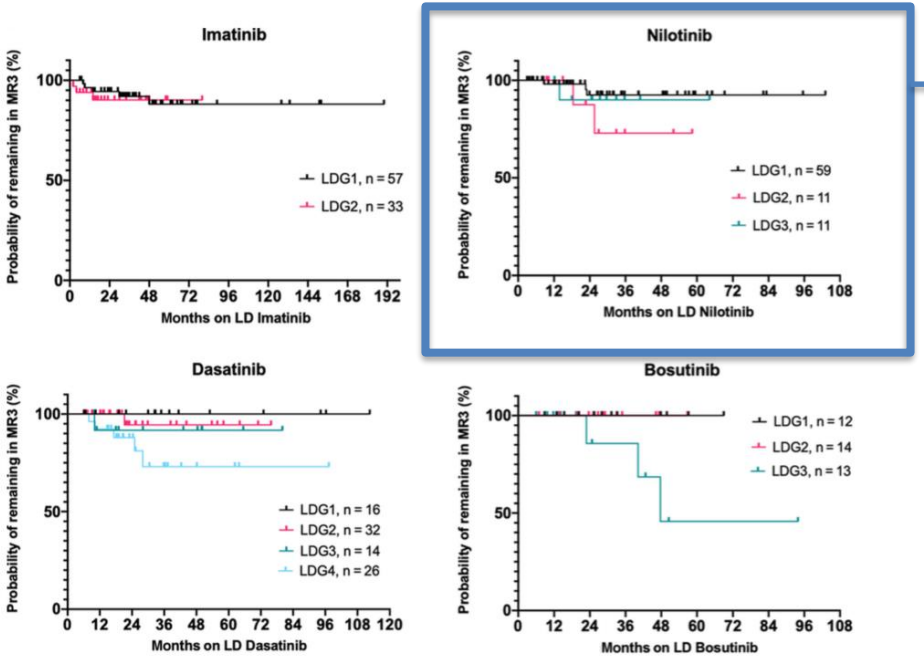
- First dose reduction: 450 mg (86.6%), 400 mg (10.4%) and 300 mg (3%) once daily, with further dose reduction to 300 mg in ≈40% of patients



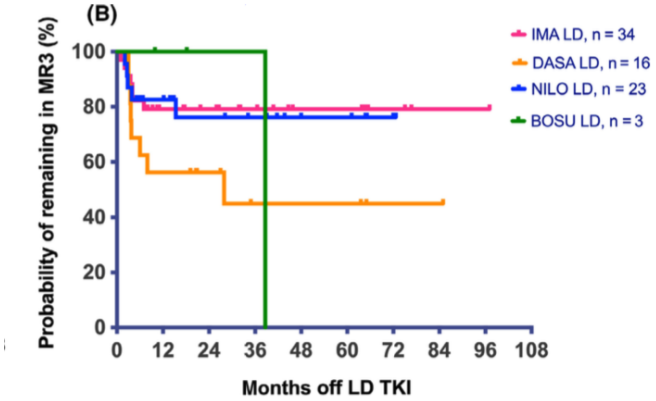


Rea et al. ASH 2017; abs#318.

TKI dose reduction and MMR maintenance in the real-life



- Group 1: 400 mg/d
- Group 2: 300 mg/d
- Group 3: ≤200 mg/d

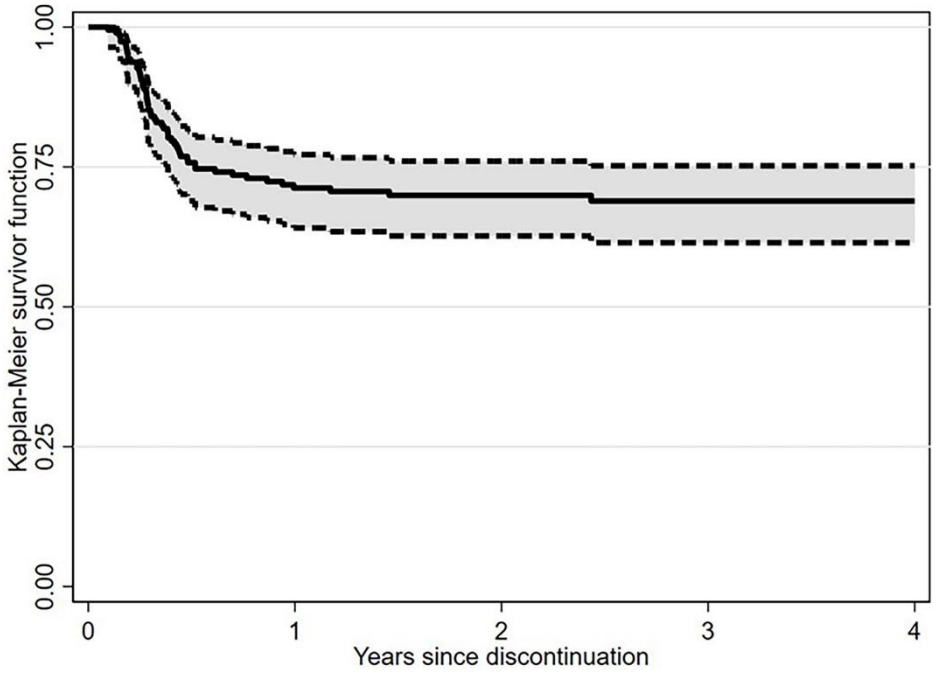


TFR was attempted by 30.9% of patients (whole cohort) and 28.4% of patients in the nilotinib group.

Claudiani et al. *Br J Haematol* 2021;

Dose optimization may not compromise TFR

	Patients (N = 194)
Medication at onset of TKI discontinuation, n (%)	
Imatinib	83 (42.8)
Nilotinib	69 (35.6)
Dasatinib	36 (18.6)
Bosutinib	2 (1.0)
Ponatinib	4 (2.0)
Dosage of imatinib before treatment cessation, n (%)	
300 mg/d	52 (62.6)
200 mg/d	31 (37.4)
Dosage of nilotinib before treatment cessation, n (%)	
200 mg/d	6 (8.7)
300 mg/d	21 (30.5)
400 mg/d	19 (27.5)
450 mg/d	12 (17.4)
600 mg/d	11 (15.9)
Dosage of dasatinib before treatment cessation, n (%)	
20 mg/d	4 (11.1)
50 mg/d	20 (55.6)
80 mg/d	12 (33.3)
Dosage of bosutinib before treatment cessation, n (%)	
400 mg/d	2 (100)
Dosage of ponatinib before treatment cessation, n (%)	
15 mg/d	3 (75.0)
15 mg every other day	1 (25.0)



Iurlo et al. *Front Oncol* 2022;12:839915.

DANTE trial

DeescAlation and discontinuation Nilotinib ThErapy

Screening
Week -4 - 0

Treatment for at least 3 calendar years with nilotinib at approved daily dose of 300 mg BID mg. Treatment at a dose ≥400 mg per day is allowed for intolerance or for clinical practice.

Sustained DMR defined as ≥ MR 4.0 (BCR-ABL level ≤0.01% IS) in all of the last 4 BCR-ABL RQ-PCR assessments performed with a minimum interval of 3 months and a maximum of 6 months

Consolidation Phase Week 0-48
Nilotinib 300 mg QD

- **Sustained DMR** → **TFR Week 48-144**
- **No sustained DMR but ≥ MMR** → **Remain in half-dose treatment until week 144**
- **Loss of MMR** → **Return to standard treatment**

Nilotinib: the correct dose – a proposal from Italian Campus CML