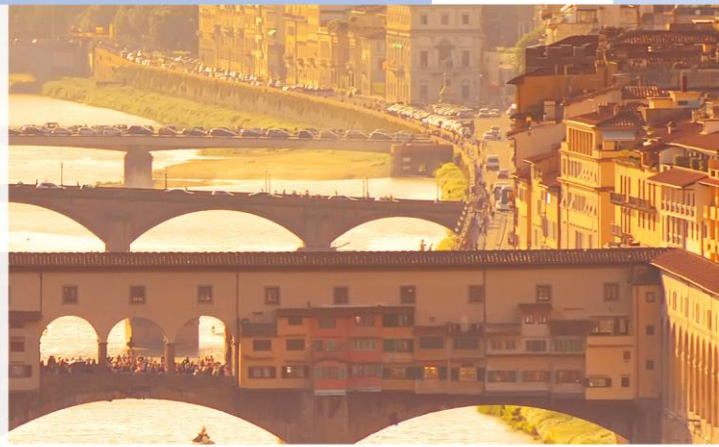
8° WORKSHOP
IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Firenze - Auditorium CTO - A.O.U. Careggi, 22-23 giugno 2023



Unmet needs nel trattamento della CML

Carmen Fava

Disclosures of Carmen Fava

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						x	
Celgene						x	
Pfizer	x						
Incyte	x						

Three drugs commercially available for 1st line treatment:

- Imatinib
- Nilotinib
- Dasatinib

«The choice of therapies for individual patients is determined by considerations of efficacy, tolerability, early and late toxicity and drug costs»

Five drugs commercially available for 2nd line treatment:

- Imatinib
- Nilotinib
- Dasatinib
- Bosutinib
- Ponatinib

ELN 2022

The life expectancy of a newly diagnosed patient with Ph+, BCR-ABL1+ CML in CP is now very close to that of age matched individuals in the general population, at least in western countries.

The goal of CML treatment is normal survival and good quality of life without life-long treatment.

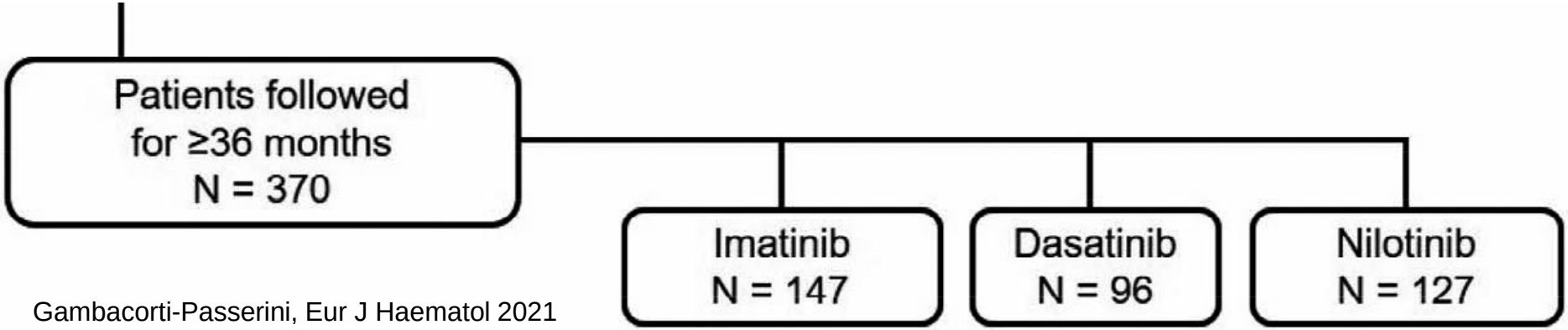
	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

Hochhaus, Leukemia 2020

Treatment patterns and clinical outcomes of tyrosine kinase inhibitors in chronic-phase CML in clinical practice: 3-year European SIMPLICITY data

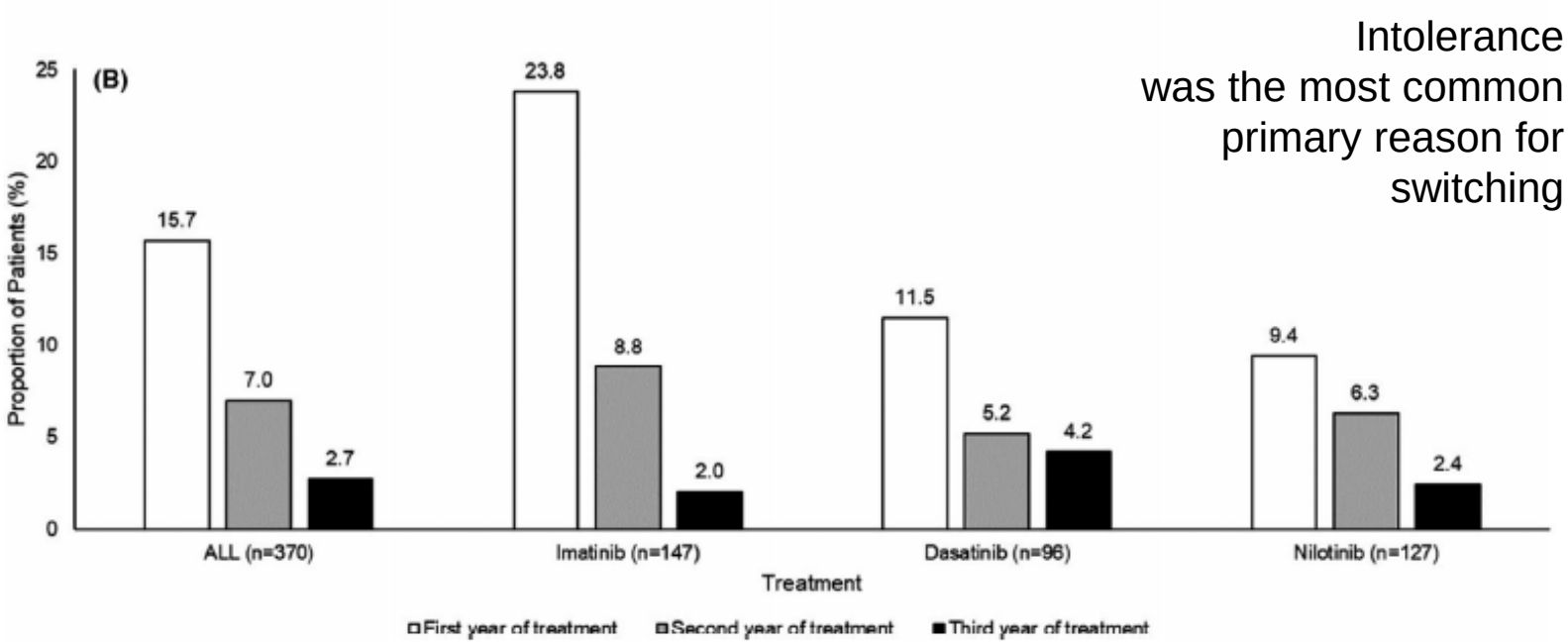
- European cohort (France, Germany, Italy, the Netherlands, Russia, and Spain) included 431 patients. 370 (86%) were followed for ≥3 years.

- The majority of paziente was followed in Academic centers.



Gambacorti-Passerini, Eur J Haematol 2021

Treatment switching by TKI class and year of follow-up



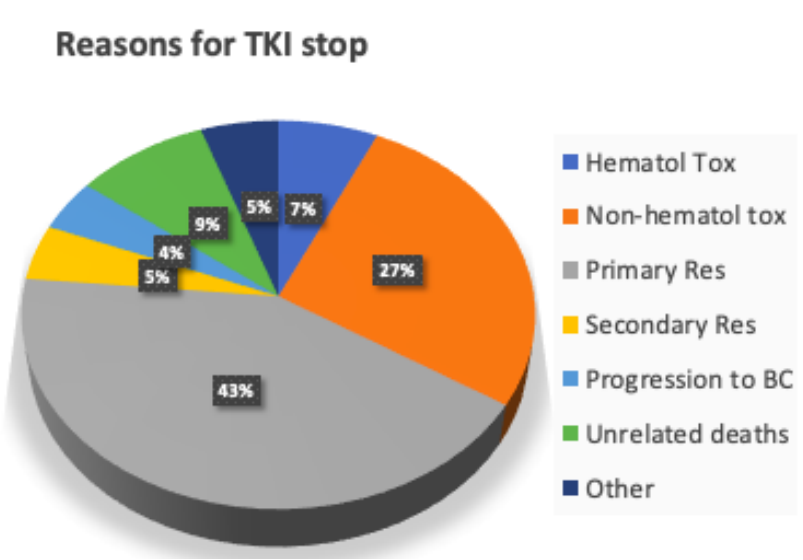
Intolerance was the most common primary reason for switching

Gambacorti-Passerini, Eur J Haematol 2021

Adverse Events

- Imatinib: superficial edema, nausea, diarrhea, muscle cramps, neutropenia.
- Dasatinib: neutropenia, thrombocytopenia. 28% of pleural effusions at 7 years and 5 years in the >2nd line and 1st line setting respectively. Other important AEs were hemorrhage and pulmonary hypertension.
- Nilotinib: rash, pruritus, headache, nausea. Rate of CV AEs was 16.5% after 10 years of 1st line treatment. Other important AEs were hyperglycemia and diabetes.
- Bosutinib: diarrhea, nausea, vomiting, increased transaminases and thrombocytopenia. Pleural effusion, cardiac and vascular events occurred in 13%, 12% and 11%of patients respectively with a 10 year follow-up.
- Ponatinib: rash, dry skin, abdominal pain. After 5 years of PACE trial 25% of arterial occlusive events, 13% of CV events 9% of cerebrovascular events and 11% of peripheral vascular events were reported.

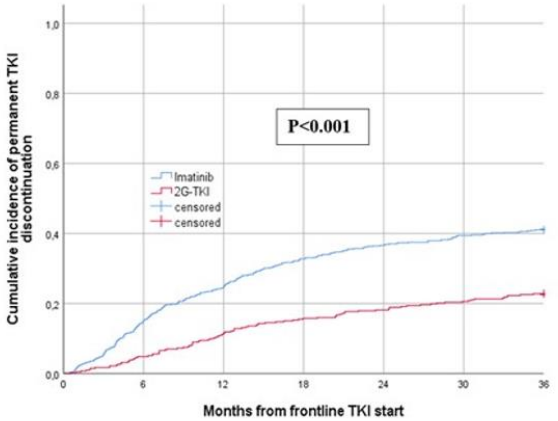
Lipton, Blood Reviews 2022



Independent predictive role on TKI discontinuation at multivariate analysis:

- frontline IMA (HR 3.22; p<0.001),
- WBC ≥ 100 x 10^9/l (HR 2.18; p<0.001),
- spleen enlargement ≥ 5 cm (HR 1.91; p=0.005)
- Sokal high risk (HR 1.78; p=0.007)

- 1168 CP-CML patients diagnosed from 1/2012 to 12/2019 at 21 Hematology Centres in Italy
- 37% treated with imatinib; 67% treated with 2nd gen TKIs



Latagliata, ASH 2022

Simplicity Results

- Complete cytogenetic response (CCyR) was achieved in 87.5% of patients switching TKI within 3 years of initiation vs 91.7% of non-switchers.
- Major molecular response (MMR) was achieved in 82.4% of switchers vs 92.9% of non-switchers.
- Over 3 years, not switching TKI was a strong predictor for achieving CCyR or MMR (both $P < .05$).
- Three-year survival remained high, irrespective of treatment changes (95.3% switchers, 96.4% non-switchers).

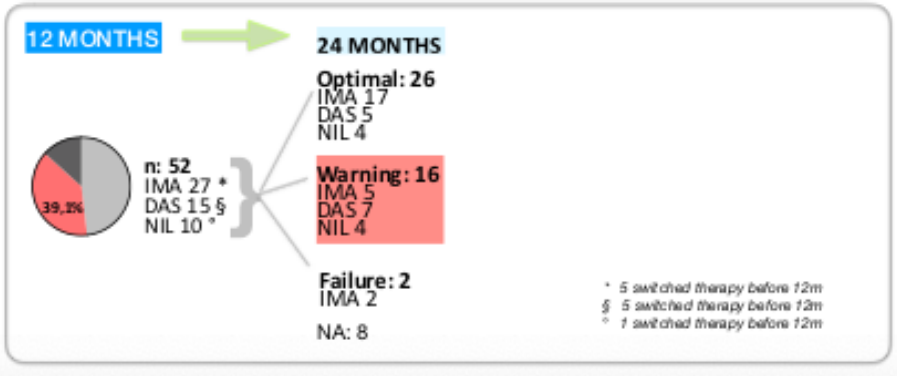
Gambacorti-Passerini, Eur J Haematol 2021

EARLY WARNING RESPONSES IN CML PATIENTS: A REAL-LIFE TURIN EXPERIENCE

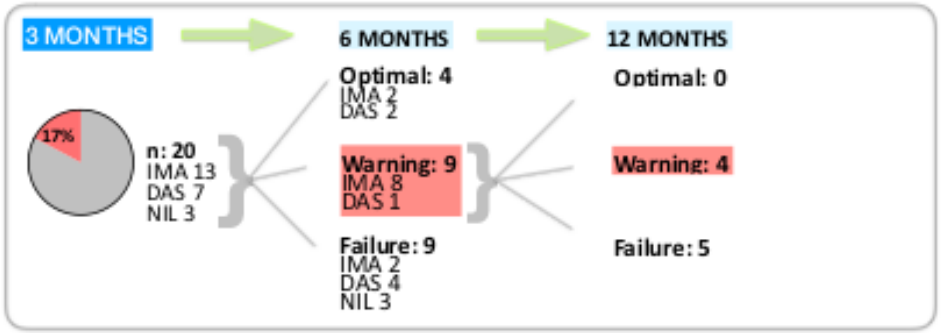
GIAI V. EHA 2022

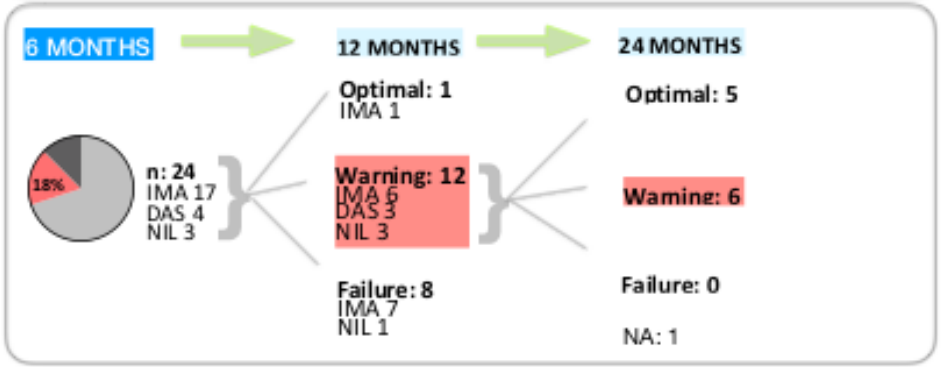
RESULTS: patients

- N: 162
- Male 62% (101/162)
- Median age: 62
- Chronic Phase 97%
- ELTS: high 10,5%, Int 34%, Low 54.3%, Missing 1,2%
- Median follow up: 5,5 years.
- FIRST LINE TKI: IMA 58,6%, DAS 20%, NIL 21,6%



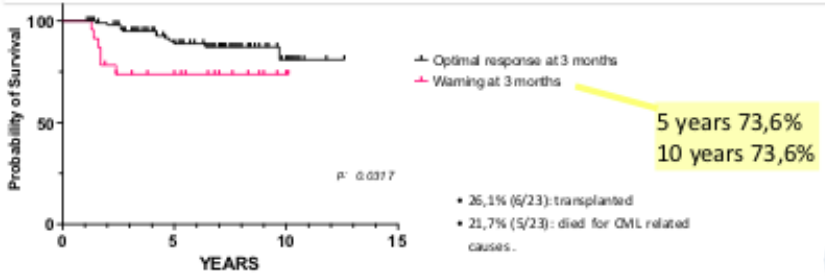
RESULTS: WARNINGS





OS according to WARNINGS

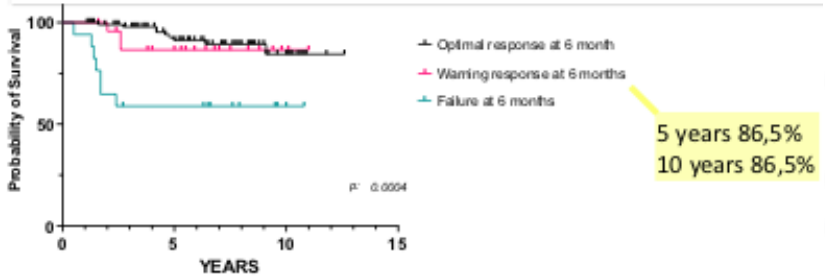
3 MONTHS WARNING



5 years 73,6%
10 years 73,6%

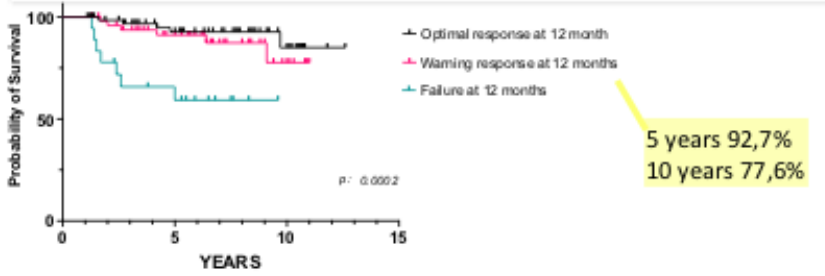
- 26,1% (6/23): transplanted
- 21,7% (5/23): died for CML related causes.

6 MONTHS WARNING



5 years 86,5%
10 years 86,5%

12 MONTHS WARNING



5 years 92,7%
10 years 77,6%

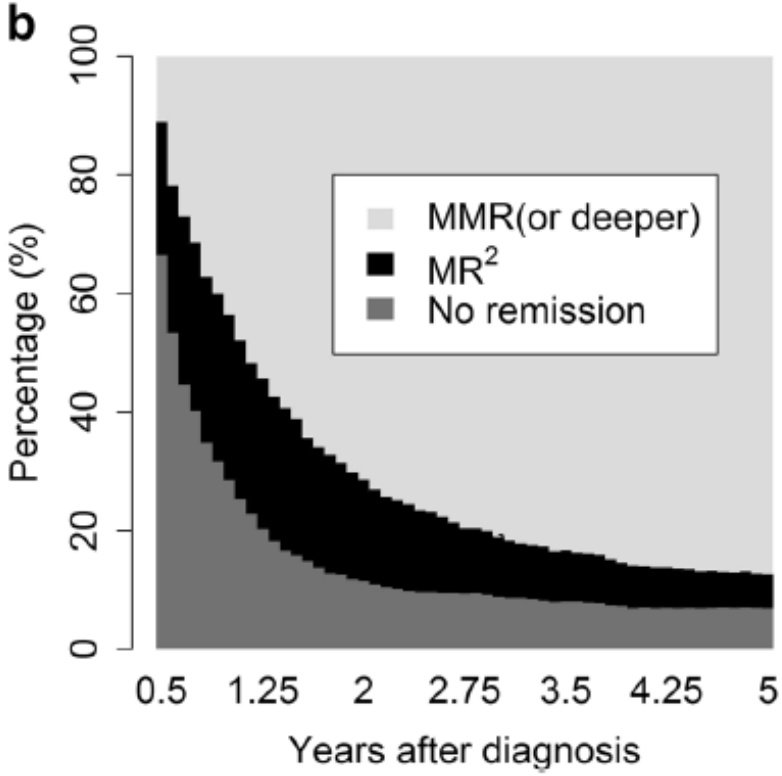
CONCLUSIONS:

- warning patients at 6 and 12 months can reach deeper molecular responses at following timepoints even without switching to a second line treatment.
- OS of warning patients at 6 and 12 months shows no significant differences with optimal response patients OS.
- IMA proved to be a sustainable and effective therapy, together with II gen TKI.
- all 5 patients that died for CML related causes showed a warning response at 3 months, confirming that early responses can anticipate later responses.

GIAI V. EHA 2022

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

Defining therapy goals for major molecular remission in chronic myeloid leukemia: results of the randomized CML Study IV



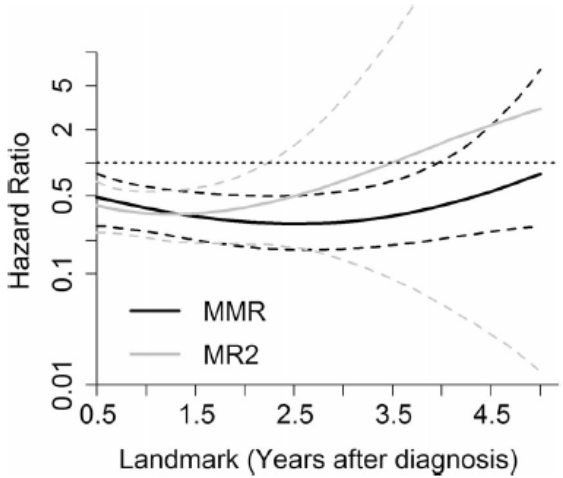
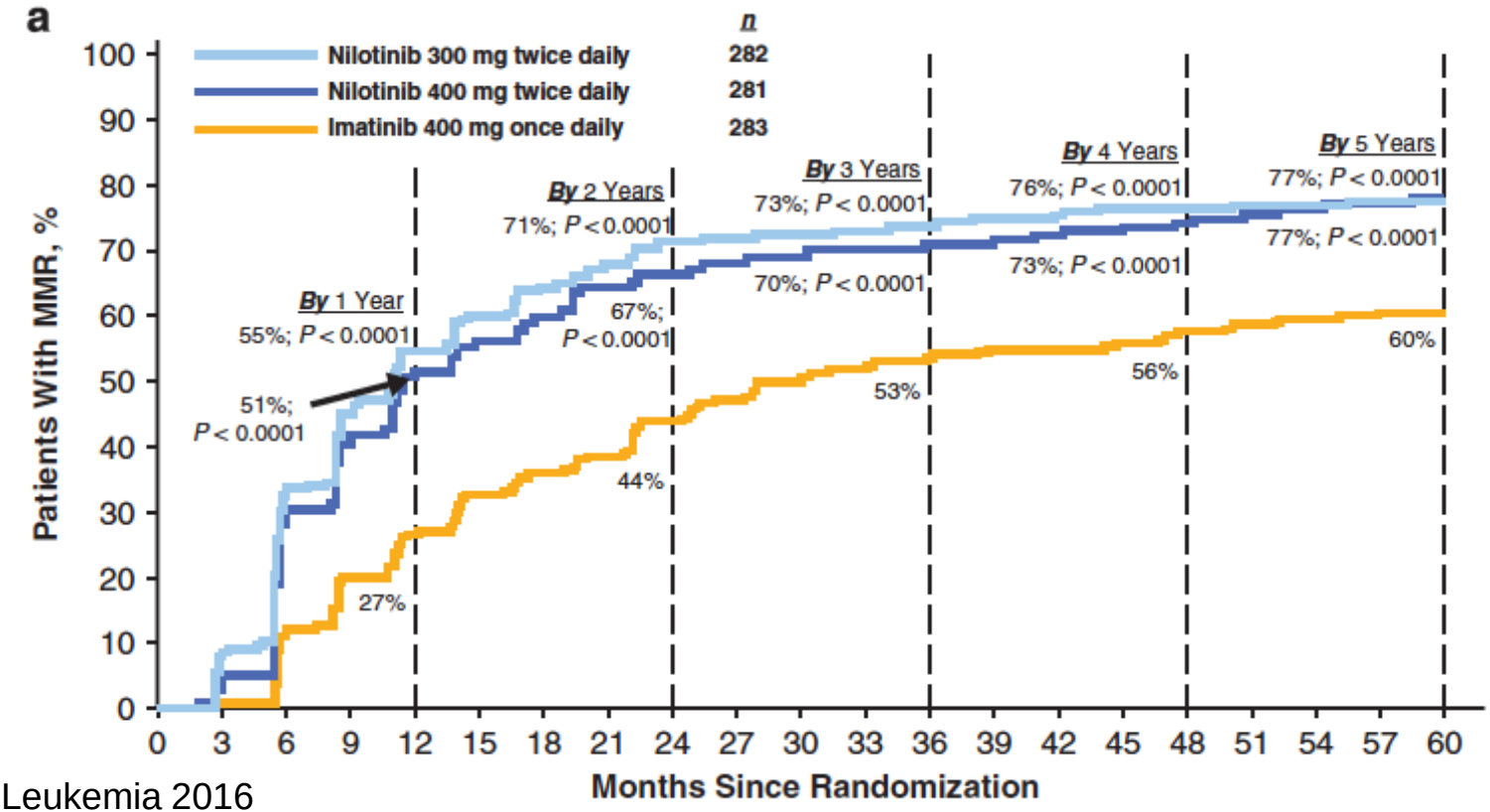


Fig. 3 Median hazard ratio functions for the comparison of patients who had achieved a MMR resp. MR^2 to those who did not have any remission at different landmarks with respect to PFS from 6 months to 5 years together with the 95% confidence intervals. On the *y* axis, the hazard ratio for PFS is plotted on a logarithmic scale. Note that on the *x* axis the landmark time is plotted instead of the event time. A hazard ratio of, e.g., 0.5 at landmark 6 months indicates that patients with MMR have only half the risk of patients with no MMR before or at 6 months

The optimal time to predict PFS in patients with MMR was 2.5 years.

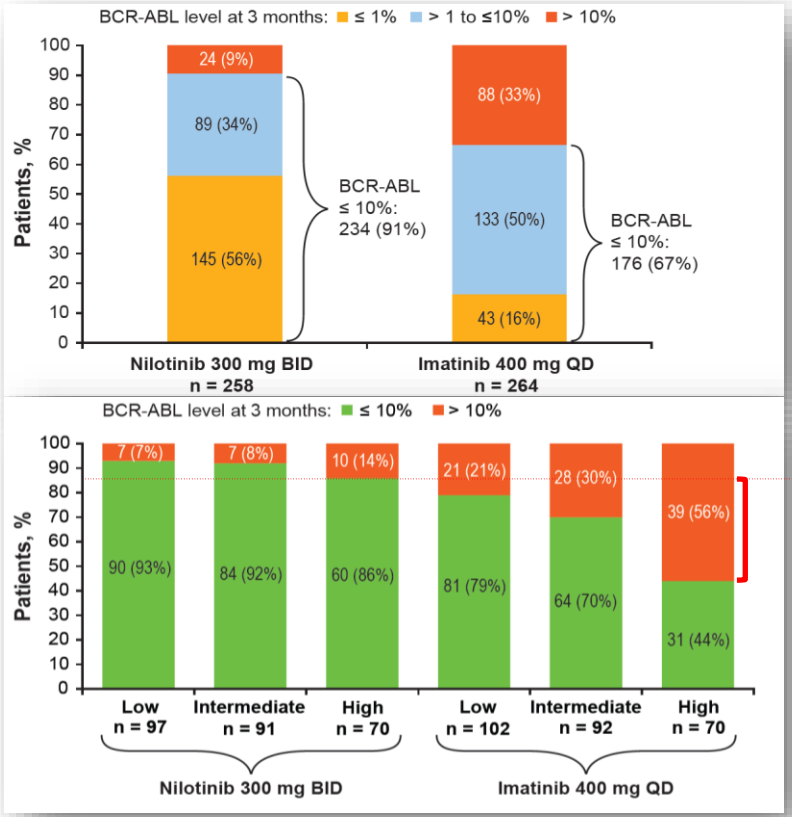
Saussele, Leukemia 2018

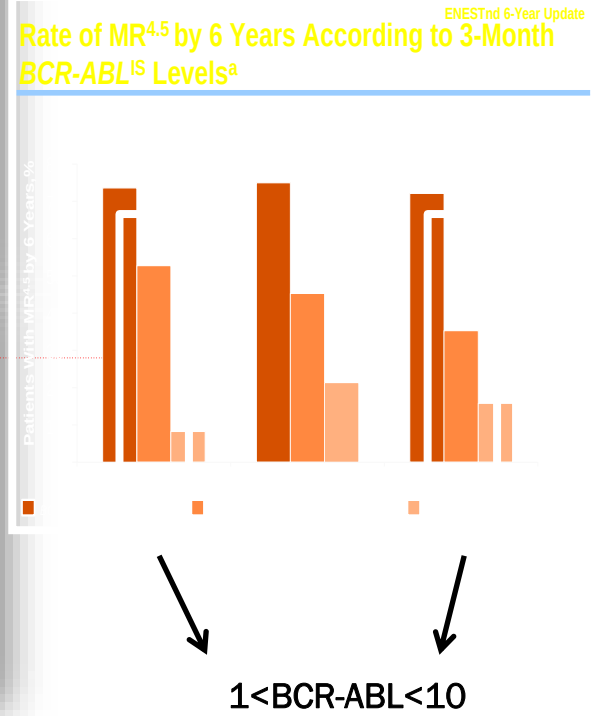
ENESTnd-Five years update



Hochhaus, Leukemia 2016

ENESTnd: EMR according to Sokal score





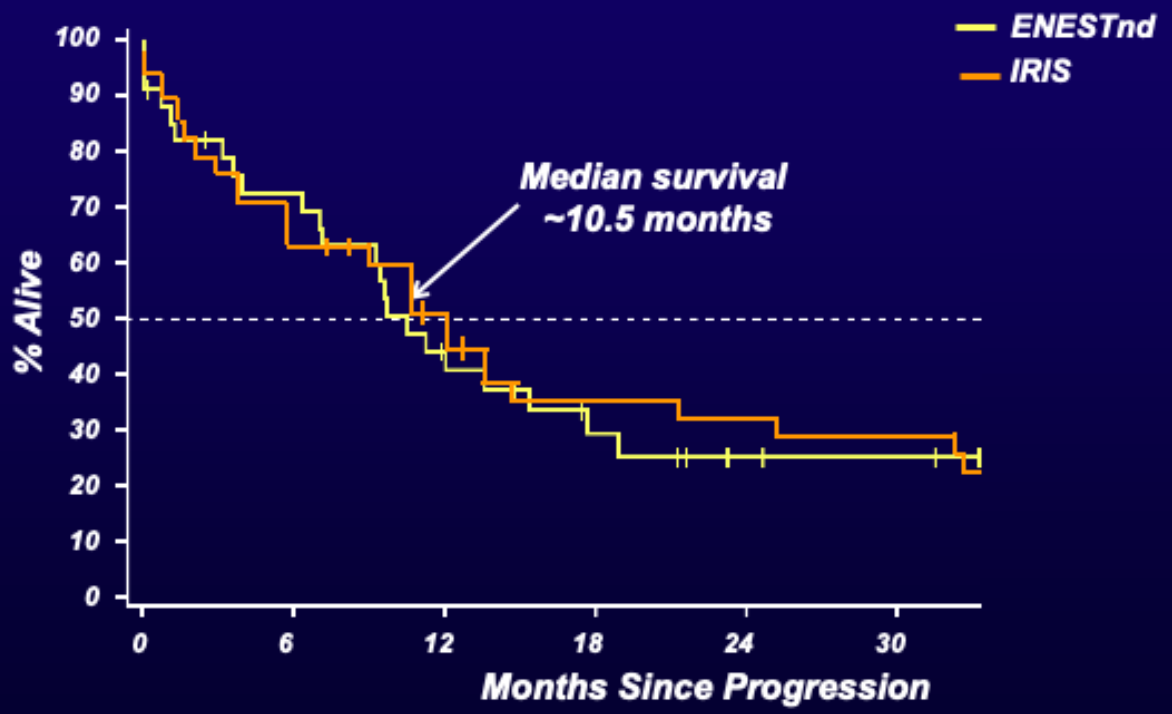
Hughes et al. Blood 2014
Hughes et al. Haematologica 2015

ENESTnd – 5 ys update

	Nilotinib 300 mg twice daily (n = 282)	Nilotinib 400 mg twice daily (n = 281)	Imatinib 400 mg once daily (n = 283)
	2	3	12
Estimated 5-year freedom from progression to AP/BC on core treatment, % (95% CI)[a]	99.3 (98.2–100)	98.7 (97.2–100)	95.2 (92.6–97.9)
HR vs imatinib (95% CI)[b]	0.1599 (0.0358–0.7143)	0.2457 (0.0693–0.8713)	—
P vs imatinib[c]	0.0059	0.0185	—
Progression to AP/BC on study, *n*	10	6	21
Estimated 5-year freedom from progression to AP/BC on study, % (95% CI)[a]	96.3 (94.1–98.6)	97.8 (96.0–99.5)	92.1 (88.8–95.3)
HR vs imatinib (95% CI)[b]	0.4636 (0.2183–0.9845)	0.2753 (0.1111–0.6821)	—
P vs imatinib[c]	0.0403	0.0028	—
EFS			
EFS events on core treatment, *n*	12	7	18
Estimated 5-year EFS on core treatment, % (95% CI)[a]	95.0 (92.1–97.8)	96.9 (94.6–99.2)	92.6 (89.3–95.9)
HR vs imatinib (95% CI)[b]	0.6145 (0.2957–1.2767)	0.3656 (0.1525–0.8769)	—
P vs imatinib[c]	0.1874	0.0188	—
PFS			
PFS events on core treatment, *n*	8	4	13
Estimated 5-year PFS on core treatment, % (95% CI)[a]	96.5 (94.2–98.9)	98.3 (96.6–100)	94.7 (91.9–97.5)
HR vs imatinib (95% CI)[b]	0.5684 (0.2354–1.3729)	0.3011 (0.0981–0.9241)	—
P vs imatinib[c]	0.2032	0.0260	—
PFS events on study, *n*	22	11	24
Estimated 5-year PFS on study, % (95% CI)[a]	92.2 (89.0–95.4)	95.8 (93.4–98.3)	91.0 (87.5–94.4)
HR vs imatinib (95% CI)[b]	0.8883 (0.4980–1.5843)	0.4399 (0.2155–0.8981)	—
P vs imatinib[c]	0.6879	0.0204	—
OS			
Total deaths on study, *n*	18	10	22
Estimated 5-year OS on study, % (95% CI)[a]	93.7 (90.8–96.6)	96.2 (93.9–98.5)	91.7 (88.3–95.0)
HR vs imatinib (95% CI)[b]	0.8026 (0.4305–1.4964)	0.4395 (0.2081–0.9281)	—
P vs imatinib[c]	0.4881	0.0266	—
Deaths due to advanced CML, *n*	6	4	16
Estimated 5-year freedom from death due to advanced CML, % (95% CI)[a]	97.7 (96.0–99.5)	98.5 (97.1–100)	93.8 (90.8–96.7)
HR vs imatinib (95% CI)[b]	0.3673 (0.1437–0.9387)	0.2411 (0.0806–0.7214)	—
P vs imatinib[c]	0.0292	0.0057	—

Hochhaus, Leukemia 2016

Survival after progression to AP/BC (ENESTnd and IRIS)



Data cut-off: 27Jul2011.

Clark RE, et al. Haematologica. 2012;97(s1):237 [abstract 0583]

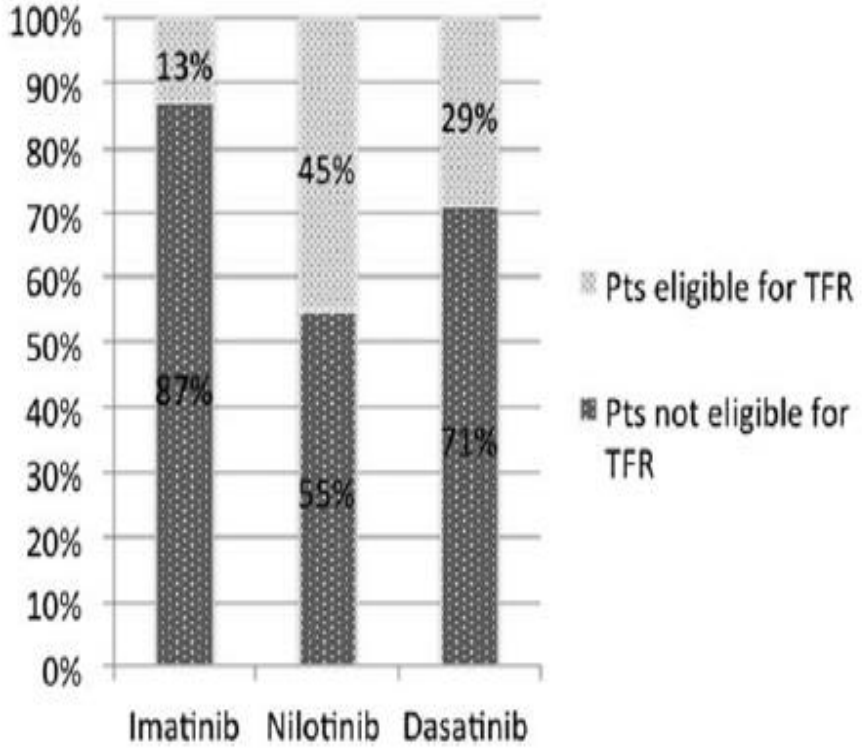
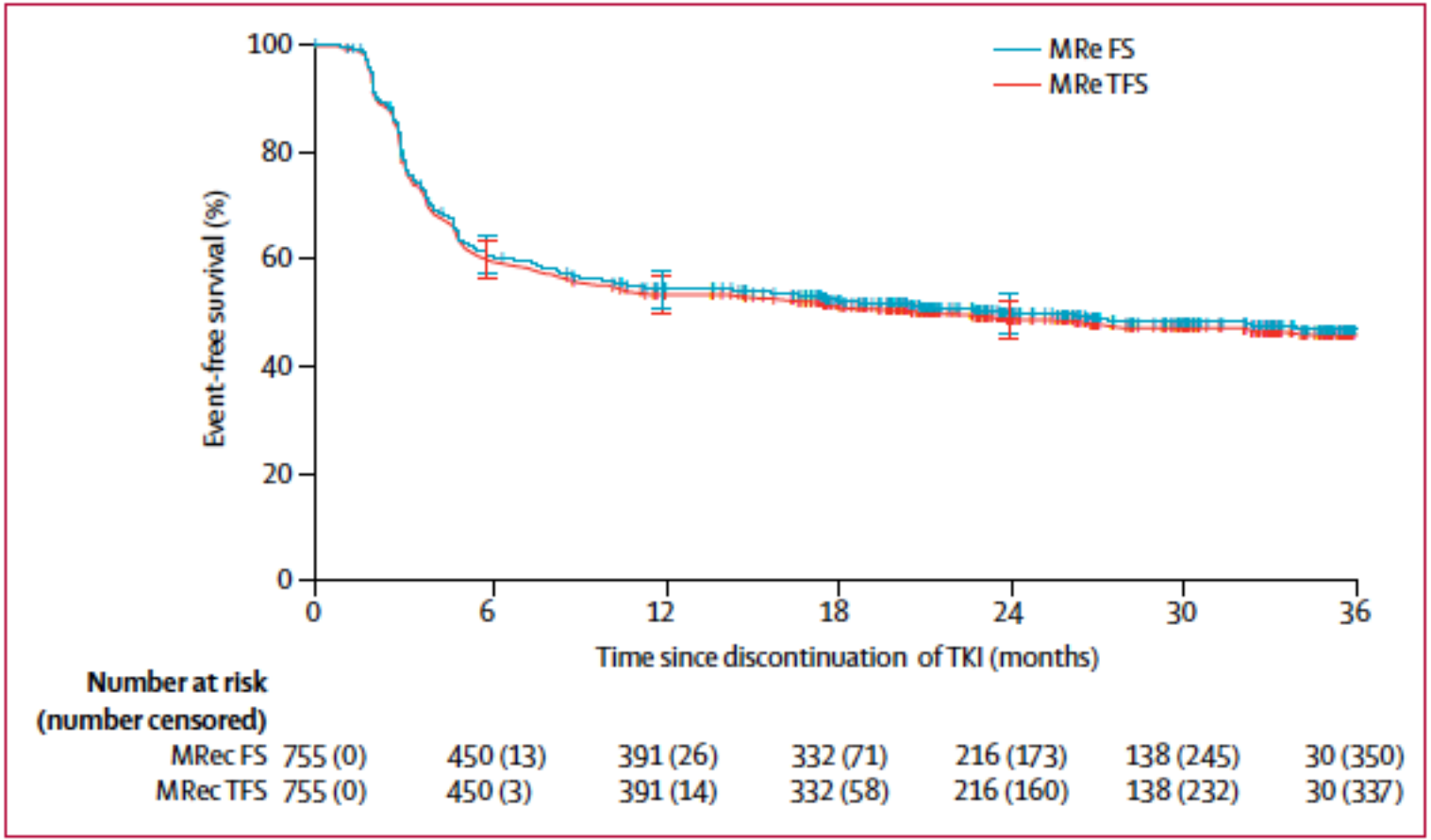


FIGURE 1 Patients eligible for TFR after a median time treatment of 3 years

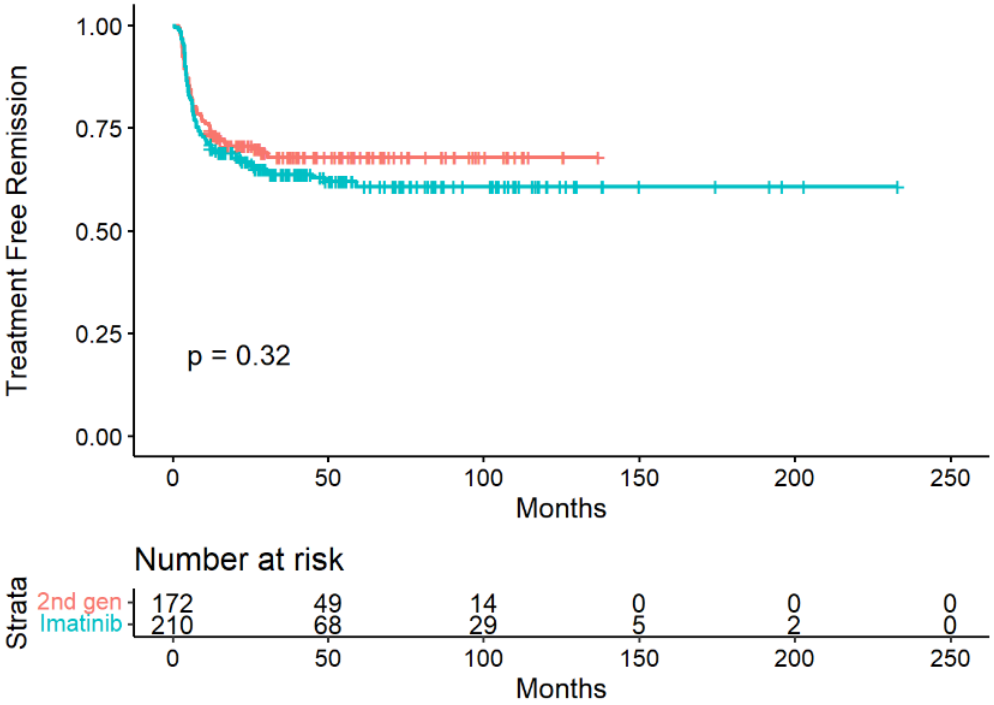
Breccia et al, AJH 2017



Number at risk (number censored)							
MRec FS	755 (0)	450 (13)	391 (26)	332 (71)	216 (173)	138 (245)	30 (350)
MRec TFS	755 (0)	450 (3)	391 (14)	332 (58)	216 (160)	138 (232)	30 (337)

Saussele, The Lancet 2018

TFR-Italian Registry



1st vs 2nd generation TKIs

Fava et al, unpublished

Criteria for TKI discontinuation

	ELN 2020 STOP allowed	ELN 2020 STOP optimal	NCCN 2023
Lines of treatment	1 or 2 if intolerance	1 or 2 if intolerance	Not defined
Time of TKI treatment	> 5 years (> 4 years if 2G TKIs)	> 5 years	≥ 3 years
Duration and depth of DMR	MR4 or better ≥ 2 years	MR4 > 3 years MR4.5 > 2 years	MR4 ≥ 2 years (at least 4 tests 3 months apart)
Type of transcript	Typical b3a2 or b2a2	Typical b3a2 or b2a2	Typical b3a2 or b2a2
Follow-up	Strict follow-up feasible	Strict follow-up feasible	Strict follow-up feasible
Molecular monitoring	Monthly fo 6 months, every 2 mos for 6-12 mos, then every 3 mos	Same	Monthly for 6 months, every 2 mos for 6 mos, then every 3 mos

Type of transcript

	Overall	1° gen TKI	2° gen TKI	P
Transcript (%)				0.48
b2a2	105 (26.0%)	57 (25.4%)	48 (26.7%)	
b3a2	290 (71.8%)	164 (73.2%)	126 (70.0%)	
Rare	9 (2.2%)	3 (1.3%)	6 (3.33%)	

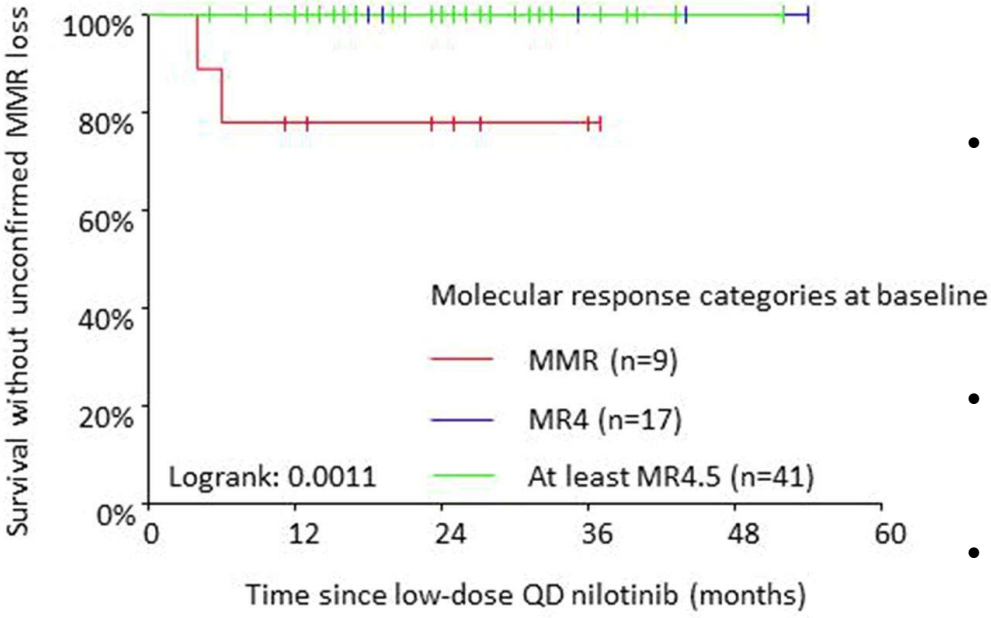
Fava et al. Unpublished

Line of therapy

	Overall
	442
Line of therapy (%)	
1	317 (71.7%)
2	108 (24.4%)
3	12 (2.7%)
4	1 (0.2%)

Nilo-Red: dose optimization of nilotinib

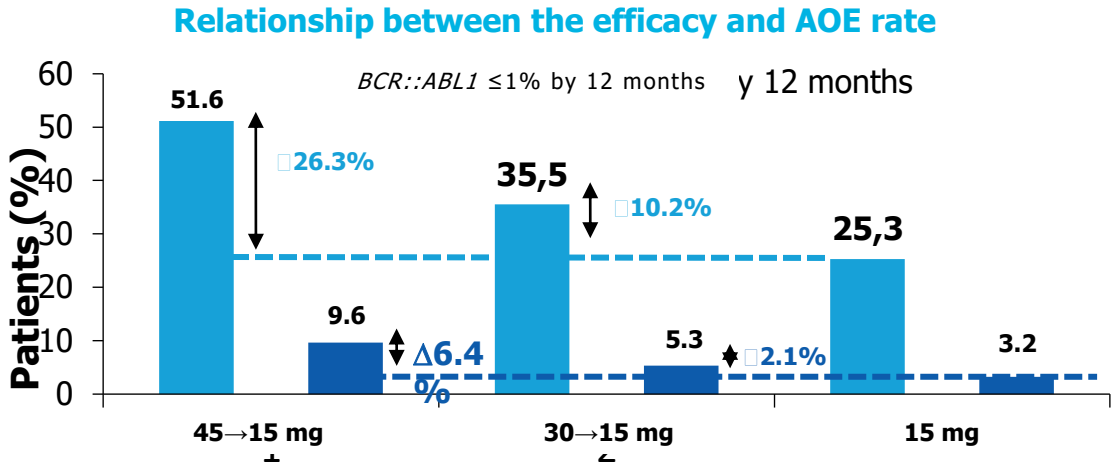
Figure 1: KM analysis of MMR loss by molecular response categories



Rea, Blood 2017

- 67 pts reduced nilotinib 1st line or 2nd line
- Median duration of nilotinib prior switching to a reduced QD dosing was 29 months and median duration of MMR was 25 months (range: 3-212).
- Primary reason for the switch to a reduced QD nilotinib dosing was non-serious adverse events in 37.3% of pts and improvement in pts convenience in 62.7% of pts.
- Nilotinib was reduced down to 450 mg QD, 400mg QD or 300mg QD in 86.6%, 10.4% and 3% of pts.
- Only 2 pts treated with 1st line nilotinib lost MMR, 4 and 6 months after QD dose reduction

OPTIC Trial: Overall Safety and Efficacy by Starting Dose



The percentage of patients with *BCR::ABL1*^{IS} ≤1% decreased with decreasing doses

The incidence of TE-AOEs decreased with decreasing doses

The most favorable benefit-risk profile was achieved with the 45→15 mg response-based dosing regimen

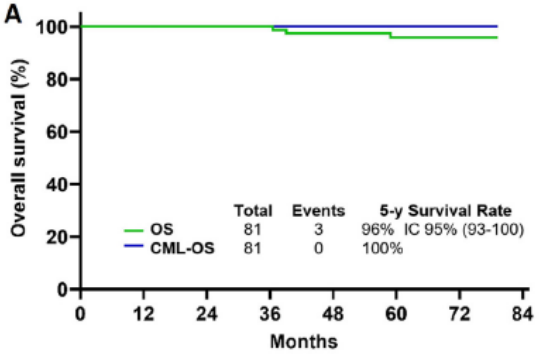
Note: SmPC recommended dose of Ponatinib is 45 mg.

AOE, arterial occlusive event; *BCR::ABL1*, breakpoint cluster region–proto-oncogene tyrosine-protein kinase; IS, International Scale; TE-AOE, treatment-emergent arterial occlusive event; OPTIC, Optimizing Ponatinib Treatment in Chronic Phase Chronic Myeloid Leukaemia.

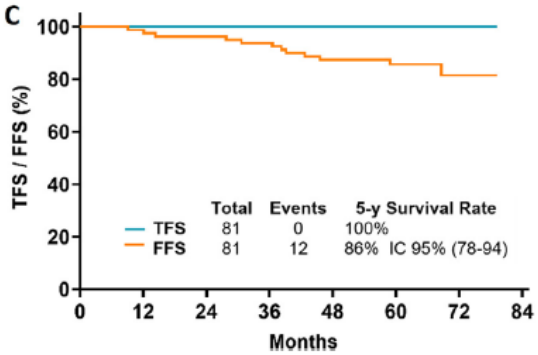
Cortes J, et al. *Blood*. 2021;138(21):2042–2050.

Dasatinib dose optimization in first line

Lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed CML-CP



Number of Responses/Total, (%)					
	3 mo	6 mo	12 mo	24 mo	60 mo
CCyR	41/81 (51)	72/81 (89)	77/80 (96)	76/78 (97)	51/51 (100)
MMR	25/81 (31)	54/81 (67)	65/80 (81)	72/78 (92)	51/51 (100)
MR4	5/81 (6)	28/81 (35)	51/80 (64)	58/78 (74)	46/51 (90)
MR4.5	3/81 (4)	21/81 (26)	43/80 (54)	55/78 (71)	46/51 (90)
CMR	1/81 (1)	13/81 (16)	27/80 (34)	40/78 (51)	42/51 (82)



Safety: Eleven patients (13%) developed pleural effusion with a median time to first event of 28 months. Nine patients (11%) had Grade 1 or 2 pleural effusion; only 2 patients (2%) had Grade 3 to 4 pleural effusion.

Gener-Ricos, Clinical Lymphoma, Myeloma and Leukemia,

P698 BOSUTINIB DOSE OPTIMIZATION IN THE SECOND-LINE TREATMENT OF ELDERLY CML PATIENTS: EXTENDED 3-YEAR FOLLOW-UP AND FINAL RESULTS OF THE BEST STUDY

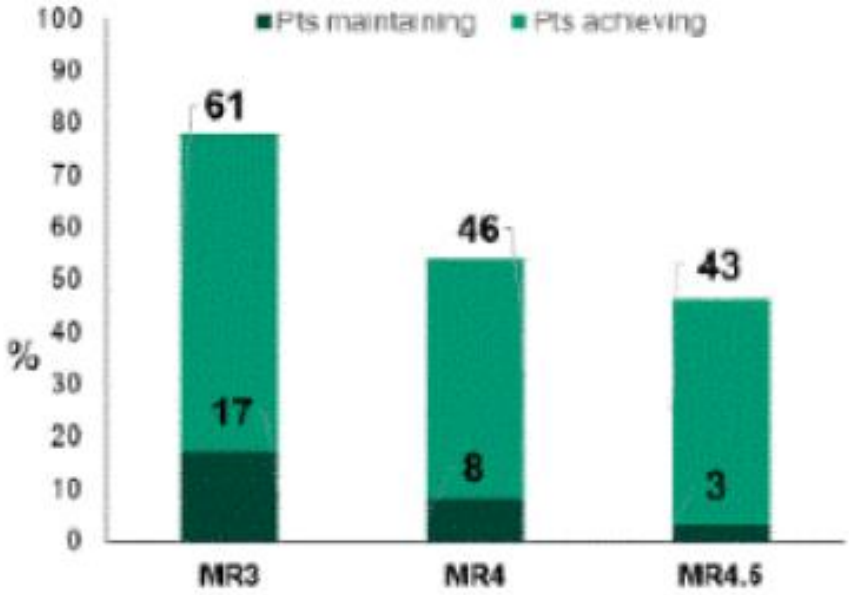


Figure 1. Cumulative probabilities of achieving or maintaining MR3, MR4 and MR4.5 by 36 months

27/62 pts (43%) discontinued the study drug.
Events leading to permanent treatment discontinuation:

- 7 CML unrelated deaths,
- 9 AEs (transaminase increase in 5 pts, skin rash, myalgia, GI toxicity and renal failure in 1 patient each),
- 9 unsatisfactory responses (without progression to advanced phases),
- 1 treatment-free remission attempt, 1 other reason.

Pts with CV AEs: acute coronary syndromes, 6 pts; pericarditis, 2 pts; peripheral arterial thrombosis, 1 pt (all pts had CV risk factors).

Castagnetti, EHA2022

Treatment de-escalation: OpTKIma study

Phase III randomized (1:1) study

Intermittent administration (1 month ON/1 month OFF)
vs
Progressive intermittent administration (1m ON/1 m OFF - 1st year;
1 m ON/2 m OFF - 2nd year; 1 m ON/3 m OFF - 3rd year)

Imatinib, Nilotinib, or Dasatinib without dose modifications

CP Ph+ CML ≥ 60 years in stable MR3.0 or MR4.0 after ≥2 years
Randomization will be stratified by type of TKI (IM, NIL, or DAS)
and by depth of molecular response (MR3.0 or MR4.0).

Primary objective: QoL

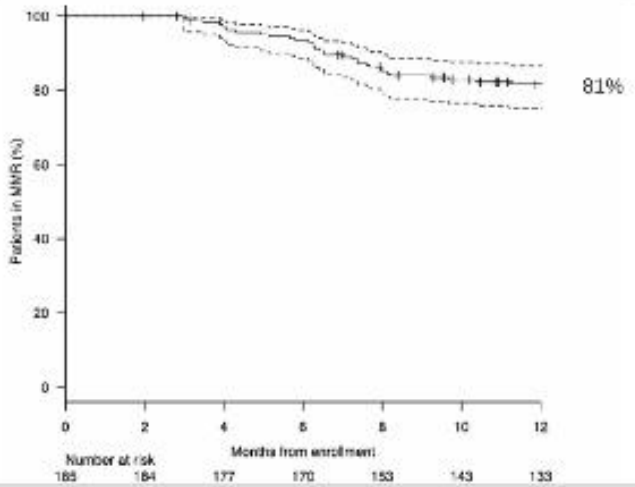
Malagola et al, Cancer Medicine; 2021

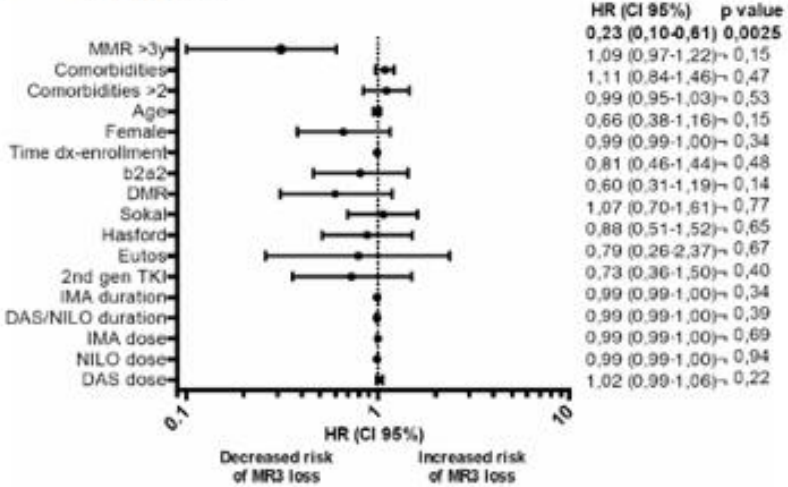
Variable	Total (n = 185)	Fixed (n = 99 – 54%)	Progressive (n = 86 – 46%)	p
M/F	106/79 (57% / 43%)	51/48 (52% - 48%)	55/31 (64% - 36%)	0.10
Median age (range)	71 (60–89)	70 (60–89)	72.5 (60–85)	**0.02**
Molecular response at enrollment				0.48
$MR^{3.0}$	37 (20%)	18 (18%)	19 (22%)	
$MR^{4.0}$	146 (79%)	78 (79%)	67 (78%)	
> $MR^{4.0}$	2 (1%)	2 (2%)	0 (0%)	

TABLE 1 Clinical and biological characteristics of the 185 patients enrolled in OPTkIMA trial

	TOT	IC withdrawn	Second Cancer	Loss of MR3.0
3°Month	14	3	1	10
6°Month	21	1	1	19
9°Month	4	0	1	3
12°Month	8	0	1	7
TOT	47/166 (28%)	4/166 (2%)	4/166 (2%)	39[a]/166 (23%)

TABLE 2 Patients and causes of OPTkIMA discontinuation in the 1st year of intermittent treatment 1 month ON and 1 month OFF





Target Pathway	Inhibitor/s	Stage of Development	Approved/Treated Disease
RAS/RAF/MEK/ERK	• RAF inhibitor: Vemurafenib and Dabrafenib • MEK inhibitors: Trametinib and Cobimetinib (in combination with vemurafenib)	FDA approved FDA approved	BRAF(V600E) melanoma
JAK/STAT	1. JAK1 inhibitor: Rinvoq (upadacitinib) and Cibinqo (abrocitinib) 2. JAK2 inhibitor: Ruxolitinib 3. JAK1/2 inhibitor: Baricitinib	FDA approved FDA approved FDA approved	1. Myelofibrosis and ovarian cancer 2. Refractory moderate to severe atopic dermatitis 3. Rheumatoid arthritis
PI3K/AKT/mTOR	1. PI3K delta inhibitor: Idelalisib 2. PI3K alpha/delta inhibitor: Copanlisib 3. mTOR inhibitor: Sirolimus	FDA approved FDA approved FDA approved	1. Leukaemia and lymphoma 2. Relapsed follicular lymphoma 3. Lymphangioleiomyomatosis
Wnt/β-catenin	CBP/β-catenin antagonist: PRI-724	Phase 2 Clinical Trial (NCT01606579)	Acute myeloid leukaemia and chronic myeloid leukaemia
Tumour suppressor: PP2A	SET: FTY720 (Fingolimod)	FDA Approved	Multiple myeloma and mantle cell lymphoma

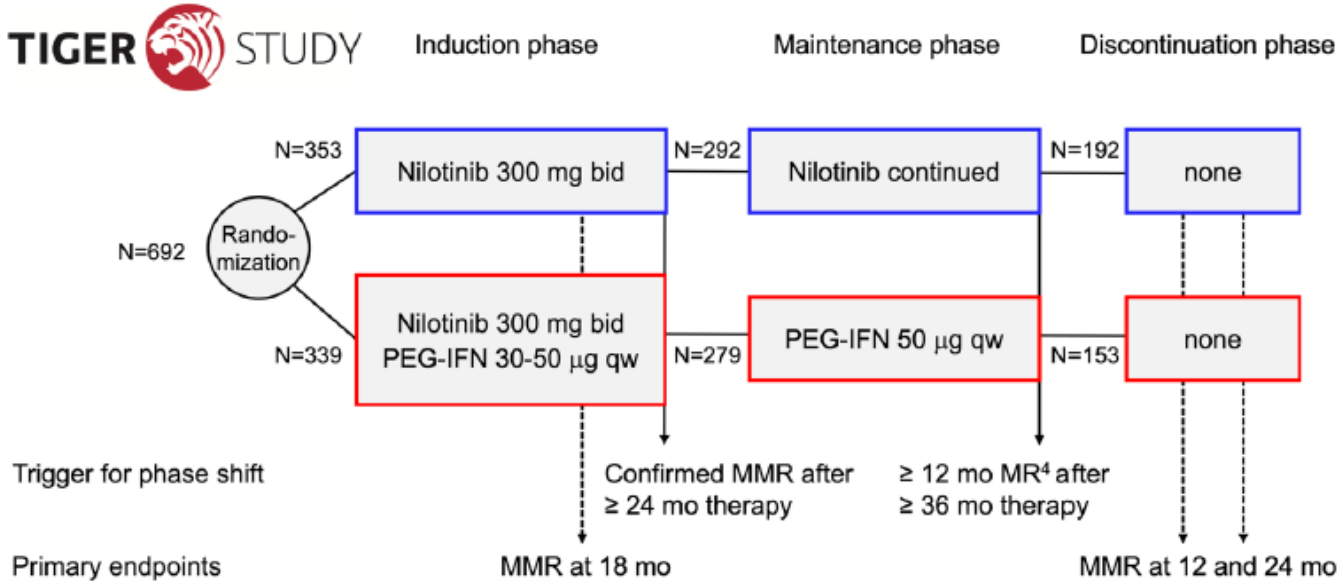
Long-term tolerability and efficacy after initial PegIFN-α addition to dasatinib in CML-CP: Five-year follow-up of the NordCML007 study

Results: After 5 years of follow-up, there were no suspected unexpected serious adverse reactions, no increase in serosal effusions, no disease progressions and no CML-related deaths. Rates of $MR^{3.0}$ (MMR), $MR^{4.0}$ and $MR^{4.5}$ were 84.6%, 64.1% and 51.3% respectively at M60, and 95% of patients reached MMR at some point during the study.

Conclusion: Initial addition of PegIFN-α to DAS shows good long-term efficacy without increased toxicity.

Eur. J. Haematol. 2021

S157 NILOTINIB VS. NILOTINIB + PEG-INTERFERON ALPHA INDUCTION AND NILOTINIB OR PEG-INTERFERON ALPHA MAINTENANCE THERAPY FOR NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA PATIENTS. THE TIGER TRIAL.



EHA2023

Summary/Conclusion: In the context of a well-controlled trial, survival of CML pts has reached probabilities close to normal. The combination of NIL with IFN is associated with a higher rate of molecular responses but also impaired tolerability. IFN maintenance is feasible, but did not result in a significantly improved chance of long-term TFR.

Jak-STAT

Jak-STAT signaling regulates proliferation, survival in leukemia progenitors and stem cells

In a phase 1 clinical trial (NCT01702064, Moffitt Cancer Center and Incyte) the combination of nilotinib and **ruxolitinib** resulted in undetectable BCR::ABL in 40% of CML patients after 6 mos. As a result, this combination was recommended for further investigation in a phase 2 clinical trial to evaluate molecular responses (NCT03654768, NIH) and effectiveness on TFR (NCT03610971, Moffitt).

Sweet, K et al. Leuk Res 2018
Andretta et al. Frontiers in Oncology 2021

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Rational: The phase II clinical trial (NCT02689440) combining TKI (dasatinib) and venetoclax in heavily pretreated blast-phase CML showed encouraging results, with a 75% overall response rate (Maiti et al. Acta Haematol 2020)

Study #2015-1040
Therapy of Early Chronic Phase Chronic Myelogenous Leukemia (CML) with Dasatinib and Venetoclax: A Phase II Study

clinicaltrials.gov NCT No: NCT02689440

Description

This phase II trial studies how well dasatinib and venetoclax work in treating patients with Philadelphia chromosome positive or BCR-ABL1 positive early chronic phase chronic myelogenous leukemia. Dasatinib and venetoclax may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.

Table 1 Differences among possible agents to use in third line

	Kinase activity	Site of action	Recommended dose	Activity on T315I mutation	IC_{50}
Ponatinib	BCR/ABL1 PDGFRa VEGFR2 FGFR1 Src	ATP site	45 mg/day (with reduction to 15 mg after achieving < 1% BCR/ABL transcript)	Yes	0.37 nM
Asciminib	BCR/ABL1	Myristoilic site	40 mg BID	Yes (but recommended dose of 200 mg BID)	0.25 nM
Vodobatinib	BCR/ABL1	ATP site	174 mg QD	No	7 nM
Olverembatinib	Pan-BCR/ABL1	ATP site	40 mg QD	Yes	0.34 nM

Breccia, Adv Ther 2022

Unmet needs under patients perspectives (Cortes, EHA 2023)

- Maintaining/improving QOL
- Reducing/managing potential side effects

Healthcare providers: efficacy of Tx and reaching response milestones

Some patients do not want to stop therapy (Semerad, EHA 2023)

- In Czech Republic only 190/246 eligible patients accept treatment discontinuation
- 45 unwilling to discontinue completed a questionnaire (Anti-HALF)
- Anti-HALF paziente'characteristics: gemale, retired/unemployed, dose reduced, no side effects, minimally stressed during the visits, with fear of disease recurrance or lack of efficacy after retreatment

Conclusions

- Approximately 40% of patients switch treatment within the first 5 years (1st and 2nd lines).
- Sequential use of TKIs is associated with a decreased probability of response. A 2nd line of treatment with a 2nd gen TKI rescues about 45-50% of patients.
- Off-targets effects can lead to long-term safety issues.
- Allo-SCT is considered for patients in advanced phases or patients with poor resposes to front-line 2nd gen TKIs followed by ponatinib, patients with mutant clones poorly responsive to available TKIs, in case of intolerance to multiple TKIs or inadequate recover of normal hematopoiesis.