ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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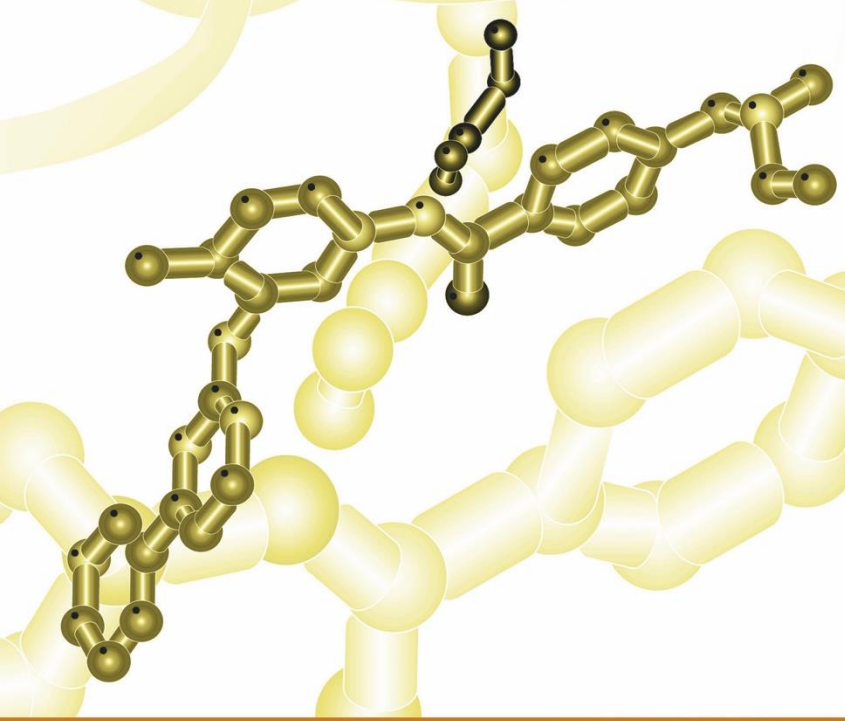


New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

Disclosures of Massimo Breccia

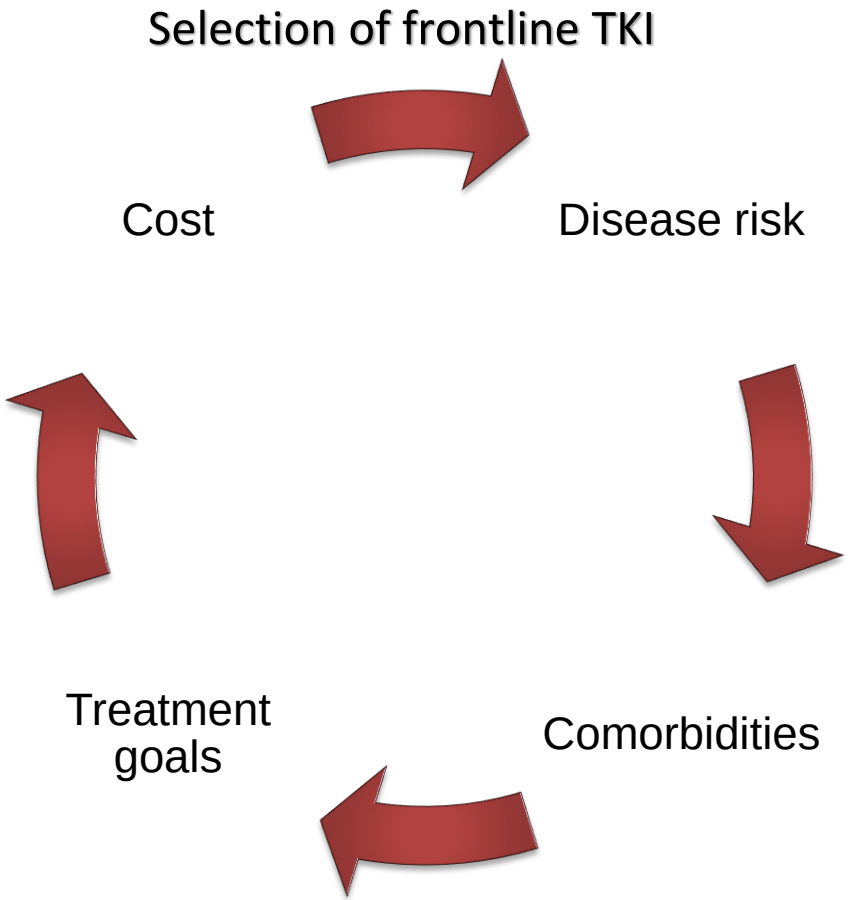
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis			x			x	xx
Incyte			x			x	
Pfizer					x		
Abbvie					x		
BMS					x	x	
AOP					x	x	
Jazz					x		
GSK					x		

STATUS OF THE ART OF TREATMENT

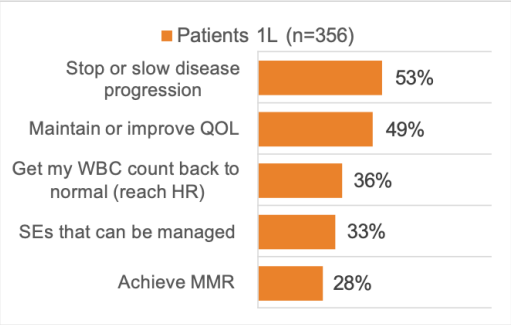
Massimo Breccia
Sapienza University
Rome

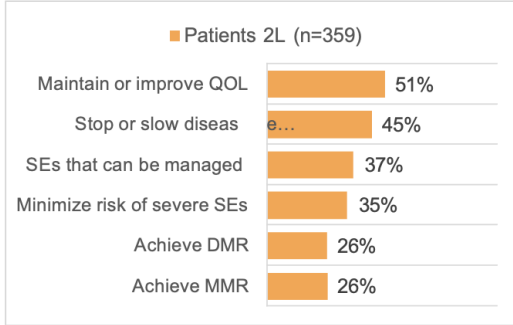
The current status

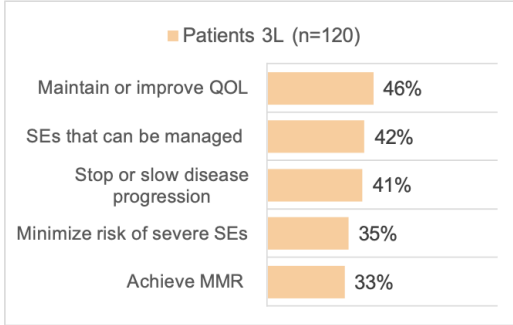
- 6 TKIs approved
- Low rate of transformation in advanced phase of disease
- High rates of response
- Life expectancy near to normal life
- Final endpoint (not for all): TFR

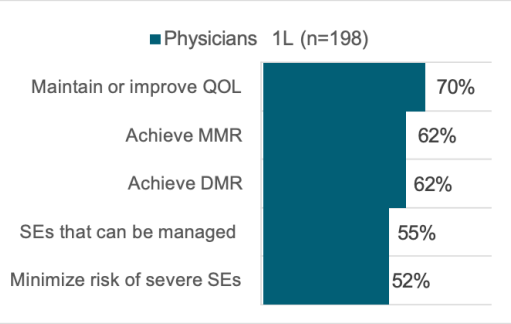

Selection of frontline TKI
Disease risk
Comorbidities
Treatment goals
Cost

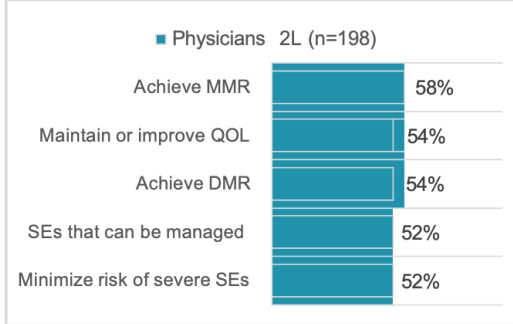
SUN survey: considering different top goals

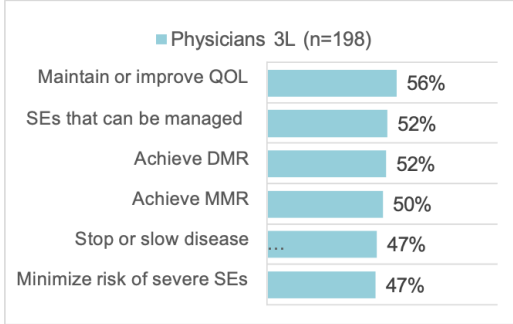










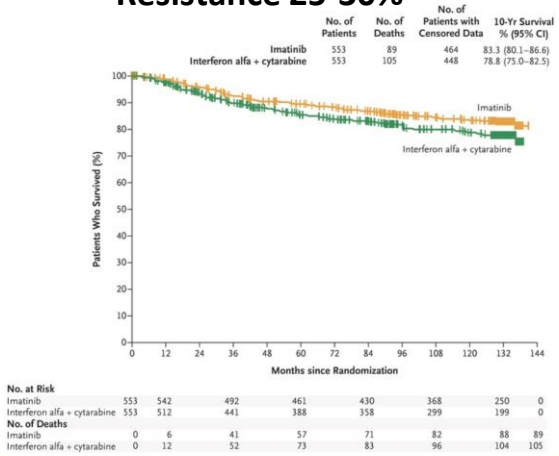


- Patients focused on stopping/slowing disease progression, maintaining/improving QOL, and minimizing/managing SEs as treatment goals, while physicians placed higher emphasis than patients on molecular response goals
- Stopping/slowing disease progression did not rank in the top 5 treatment goals for physicians until 3L, although patients reported this goal across lines of therapy

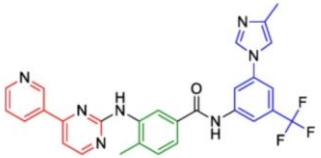
Different TKIs available

Imatinib

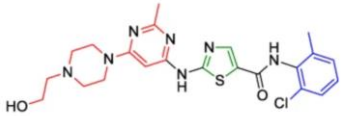
- **OS > 90%**
- **Resistance 25-30%**



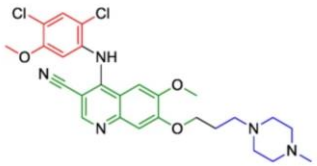
a Nilotinib



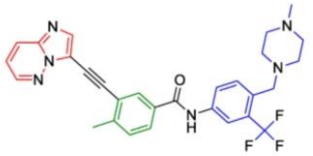
b Dasatinib



c Bosutinib



d Ponatinib



- **OS > 90%**
- **Progression rate decreased**
- **Resistance 20%**
- **Deep molecular response increased**
- **Increased off-target effects rate**

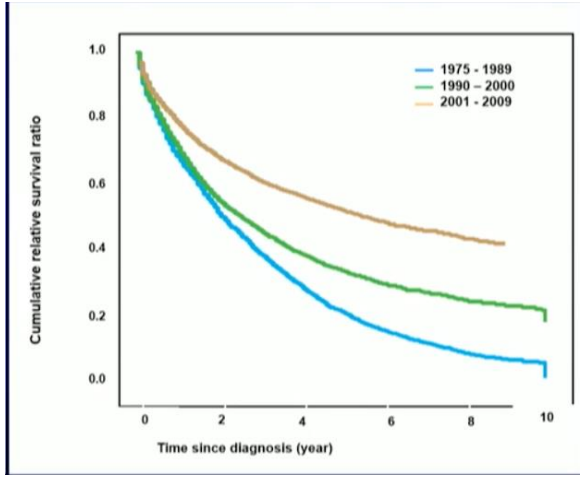
Results of frontline trials

Trial	N =	Treatment	CCyR	MMR	MR$^{4.5}$	TFS	OS
IRIS (18 mo)	553	IM 400	74% (est. at 18 mo)	57% (est. at 12 mo)	NA/NR	96.7% (at 18 mo)	97.2% (est. at 18 mo)
IRIS (60 mo)	553	IM 400	87% (est. at 60 mo)	NA/NR	NA/NR	93% (at 60 mo)	89% (est. at 60 mo)
IRIS (10.9 y)	553	IM 400	83% (at 10.9 y)	NA/NR	NA/NR	92% (at 10.9 y)	83.3% (at 10.9 y)
TOPS (42 mo)	157	IM 400	80.3% (by 42 mo)	51.6% (at 42 mo)	NA/NR	94.4% (est. at 48 mo)	94.0% (est. at 48 mo)
	319	IM 800	81.5% (by 42 mo)	50.2% (at 42 mo)	NA/NR	95.8% (est. at 48 mo)	93.4% (est. at 48 mo)
ENESTnd (10 years)	282	NIL 600	NA/NR	77.0% (by 60 mo)	53.5% (by 60 mo)	96.3% (est. by 60 mo)	93.7% (est. by 60 mo)
	281	NIL 800	NA/NR	77.2% (by 60 mo)	52.3% (by 60 mo)	97.8% (est. by 60 mo)	96.2% (est. by 60 mo)
	283	IM 400	NA/NR	60.4% (by 60 mo)	31.4% (by 60 mo)	92.6% (est. by 60 mo)	91.7% (est. by 60 mo)
DASISION (60 mo)	259	DAS 100	NA/NR	76% (by 60 mo)	33% (by 60 mo)	95.4% (by 60 mo)	91% (est. by 60 mo)
	260	IM 400	NA/NR	64% (by 60 mo)	42% (by 60 mo)	92.7% (by 60 mo)	90% (est. by 60 mo)
BFORE (~15 mo)	246	BOS 400	77.4% (by 12 mo)	73.9% (at 60 mo)	47.4% (at 60 mo)	93.3% (by 60mo)	94.5% (est. by 60 mo)
	241	IM 400	66.4% (by 12 mo)	64.6% (by 60 mo)	36.6% (at 60 mo)	90.7% (by 60 mo)	94.6% (est. by 60 mo)

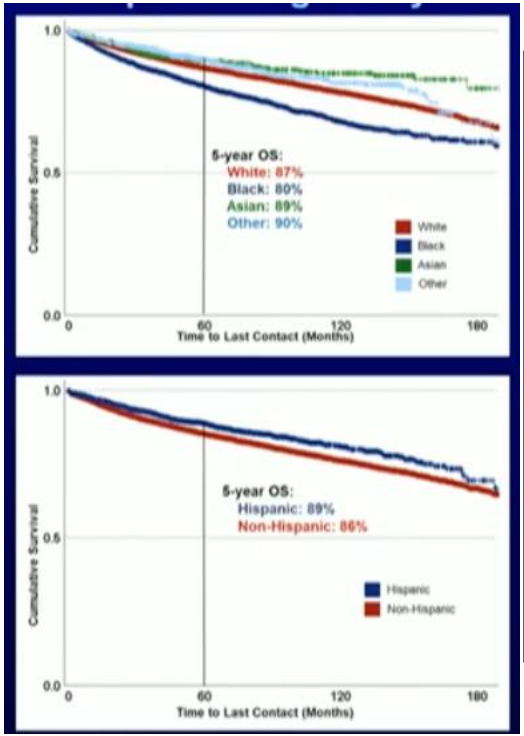
- Higher rate of MMR with 2gen TKIs do not translate into increased OS
- Higher rate of DMR, but TFR eligibility is less than 50%
- OS is > 90% regardless of frontline TKI

Survival in CML

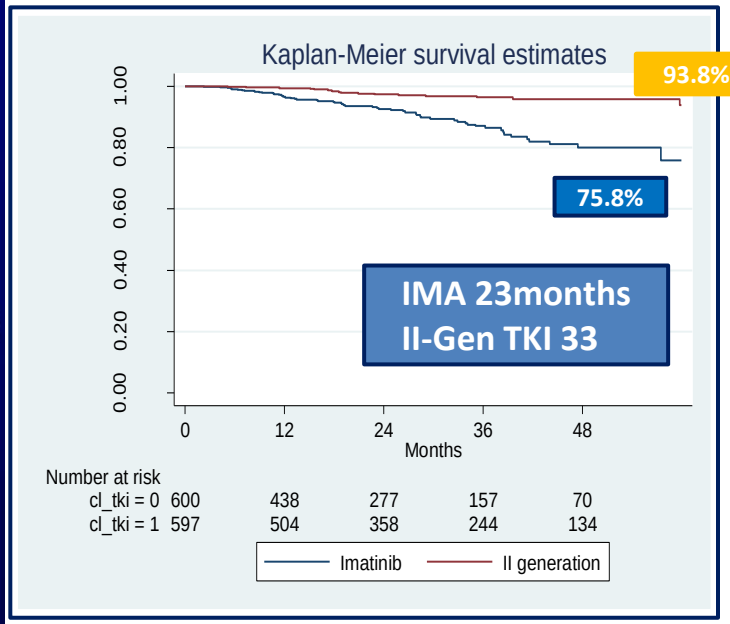
SEER



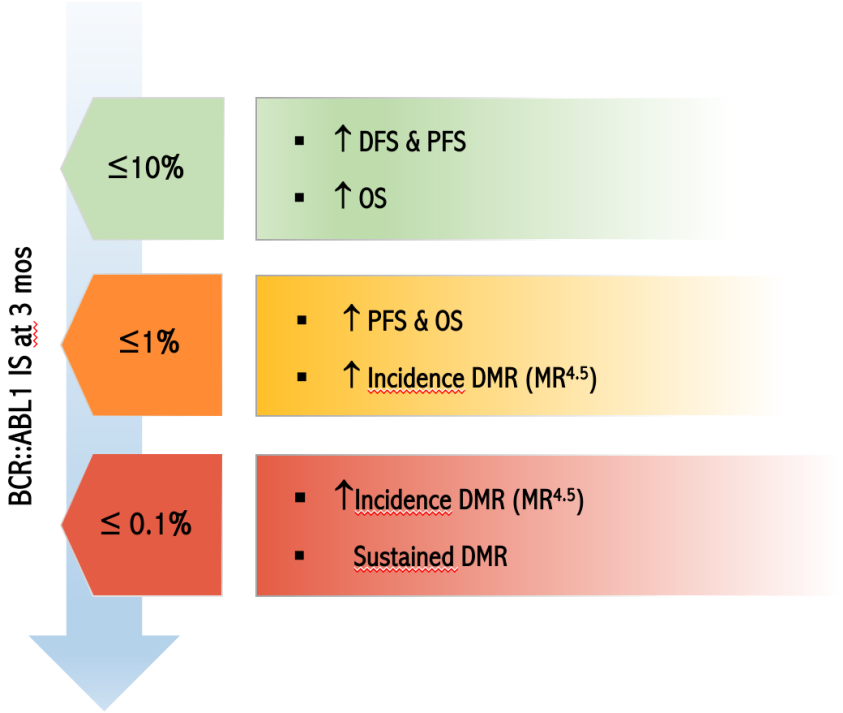
National Cancer Database



Italian registry



Response at 3 mos can identify the candidate to TFR

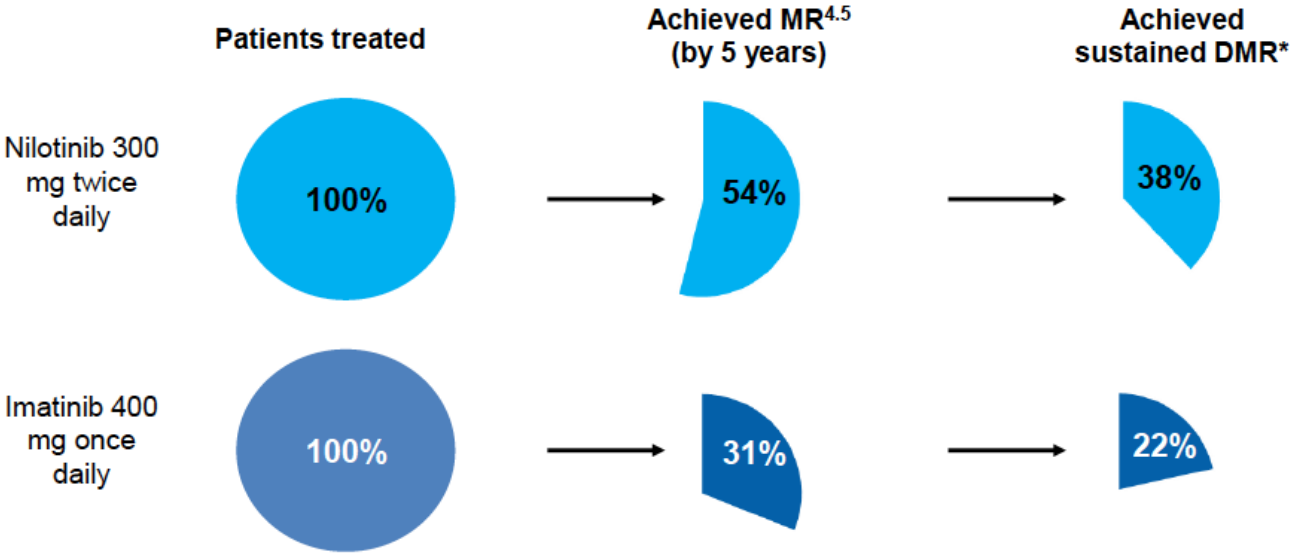


Branford S, Yeung DT, Ross DM, et al. *Blood*. 2013; Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. *Leukemia*. 2013; Hanfstein B, Shlyakhto V, Lauseker M, et al. *Leukemia*. 2014; Hughes TP, Saglio G, Kantarjian HM, et al. *Blood*.

Where do we stand?

- About 30% of pts required a second line
- About 60% achieved a DMR by 10 years
- Of them, only 40% have sustained DMR
- After TFR, more than 50% of pts have to resume the treatment
- Long-term off-target effects (in particular CV)

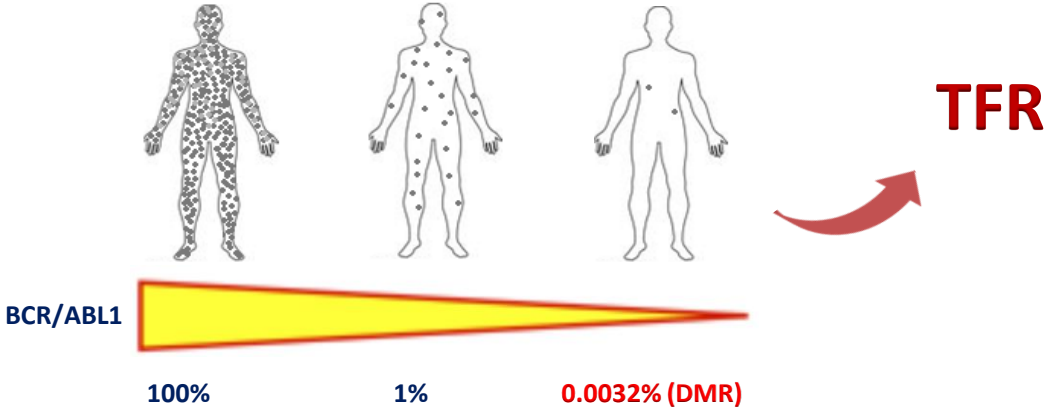
DMR= increased probability of discontinuation (TFR)

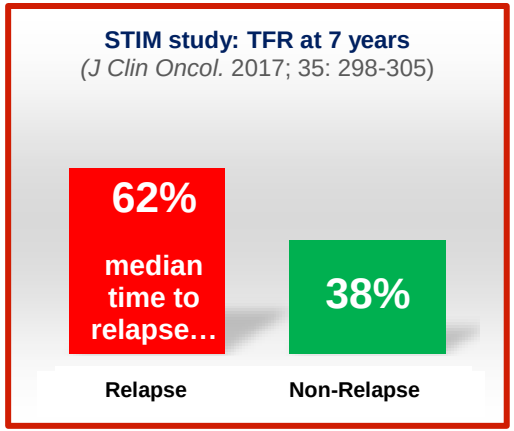


Sustained DMR defined per ENESTfreedom criteria, i.e., achievement of $MR^{4.5}$ at any time after ≥ 2 years of frontline treatment, followed by 1 year of sustained response with no assessment worse than MR^4, ≤ 2 assessments between MR^4 and $MR^{4.5}$, and $MR^{4.5}$ in the last assessment.

Hochahaus et al Blood 2015 abstract 2781

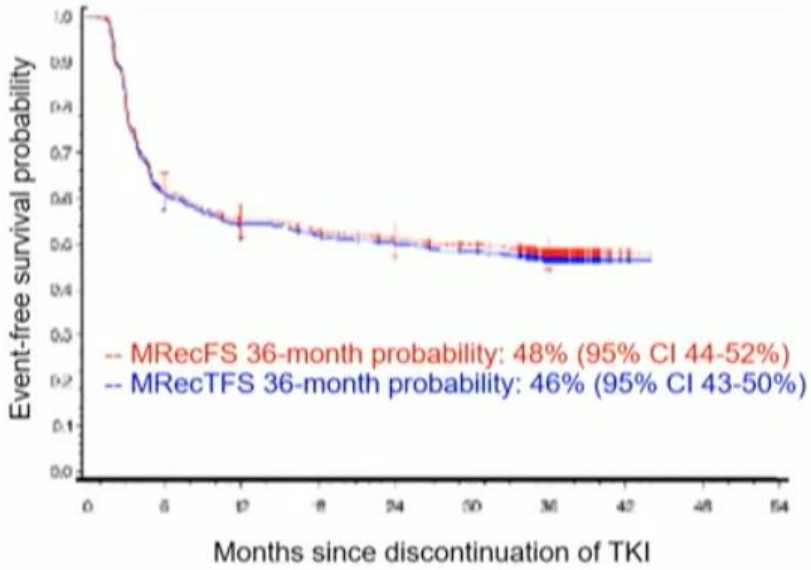
TFR: a new and significant goal of CML management





Discontinuation should be considered for patients in stable DMR after careful discussion in the shared decision-making process

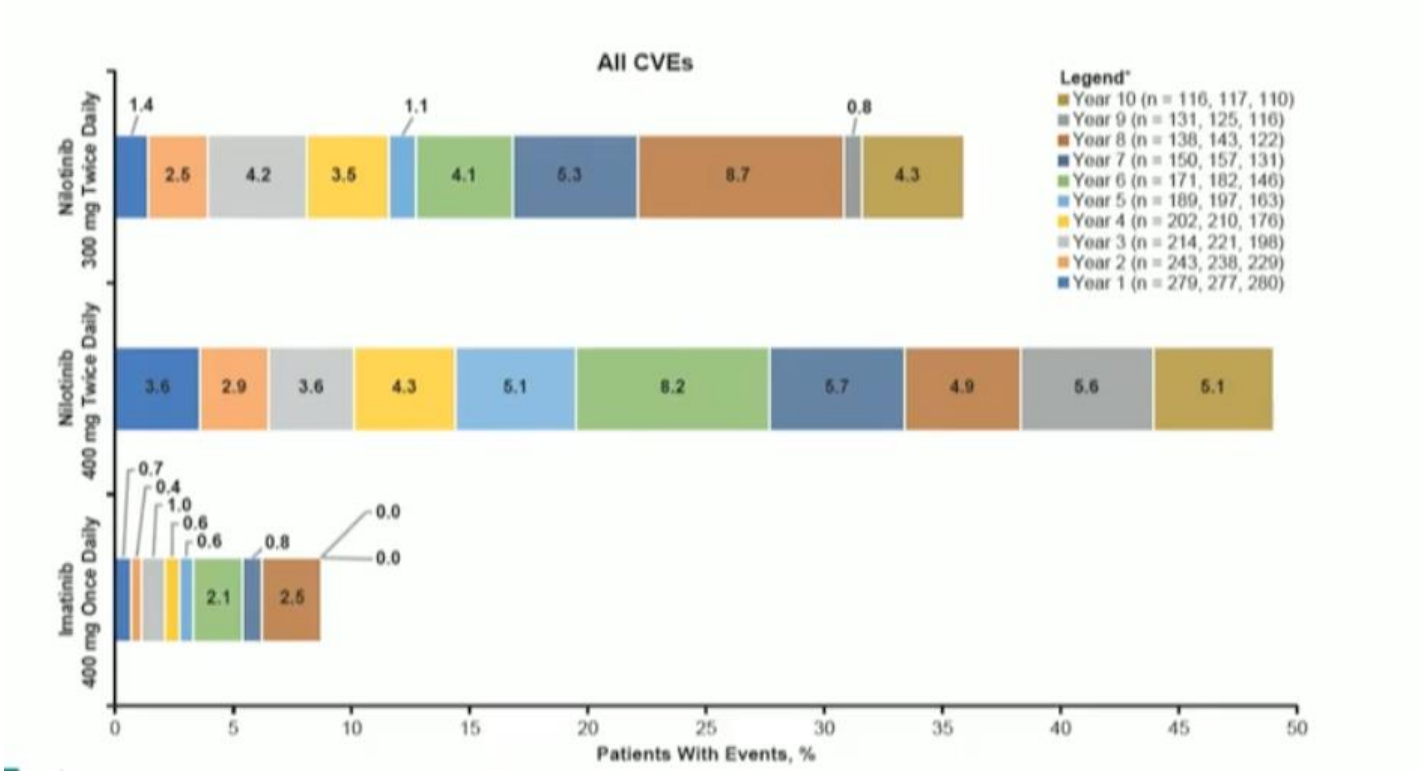
Final analysis of the EURO-SKI trial



- N = 728
- Median duration of TKI treatment 7.5 years
- Median duration of MR^4 before TKI cessation 4.7 years
- At 36 months, 46% (95% CI: 42–49) of analyzable pts in MMR → reject null hypothesis of 35% ($p<0.0001$)
- MRecFS 48% (95% CI: 44–52%)
- MRecF- and treatment-free survival (MRecTFS) 46% (95% CI: 43–50%)
- No blast phase transformation

Mahon et al, ASH 2020

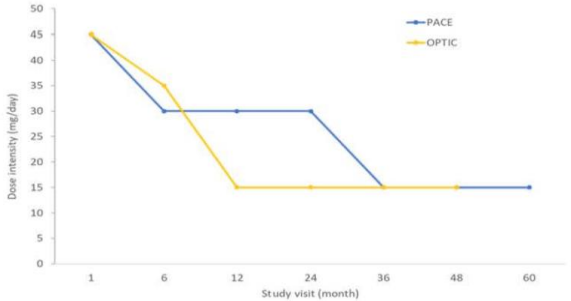
CV events in the long-term: nilotinib experience



Kantarjian et al, Leukemia 2021

OPTIC vs PACE: dose modification dynamics

- 364 pts received 45 mg
- Efficacy outcomes were generally comparable or better in OPTIC when compared with PACE, including ≤1% *BCR-ABL1*^{IS} response by 24 months (PACE, 52%; OPTIC, 56%), 2-year PFS (68%; 80%), and 2-year OS (86%; 91%).
- Median time to ≤1% *BCR-ABL1*^{IS} response, 5.6 months (PACE) and 6 months (OPTIC).
- Median relative dose intensity was 27 mg/d in PACE and 15 mg/d in OPTIC, and dose reduction occurred more rapidly compared with PACE median. Dose reductions due to AEs occurred in 82% of patients in PACE and 46% in OPTIC.
- A 60% reduction in relative risk for AOEs in OPTIC vs PACE was observed



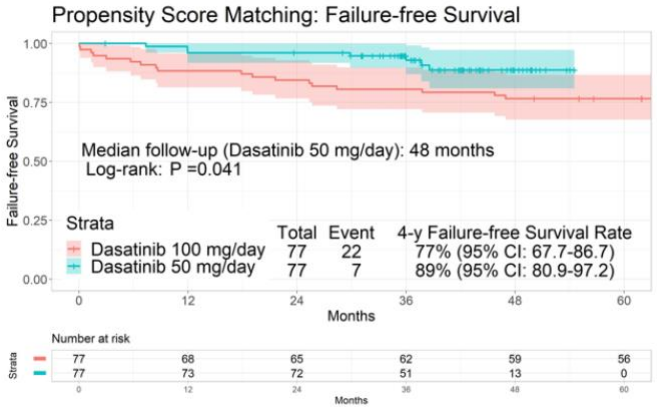
Safety Parameter	PACE CP-CML (N=270)	OPTIC 45 mg → 15 mg (N=94)
Any TEAE, n (%)[a]	270 (100)	94 (100)
Grade 3/4, n (%)	221 (82)	64 (68)
Exposure-adjusted AOEs (per 100 patient-years)		
0–1 y	15.8	7.6
1–2 y	15.1	5.9

Jabbour et al ASH 2021 abst 2550

DASATINIB 50 mg vs 100 mg: propensity score

- 233 pts (low-dose 83 and 100 mg/day 150 pts)
- Propensity score matched 77 patients in each cohort with a median FU of 60 months
- The 12-month major molecular response (MMR) rates were 82% and 75% 50 mg vs 100 mg, respectively (P=0.229).
- The 1-year cumulative incidence of MR4, MR4.5, and CMR rates were 63% and 43%, 53% and 36%, and 46% and 33% for each (P=0.009; P=0.031; P=0.060).
- The incidence of pleural effusion was 6% and 21% for 50 mg vs 100 mg, respectively (P=0.016).
- The 4-year FFS rates were 89% and 77% in the low-dose dasatinib and standard-dose dasatinib, respectively (P=0.041)

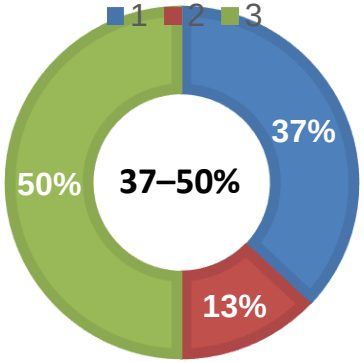
No. (%)	Dasatinib 50 mg/day N= 77		Dasatinib 100 mg/day N= 77		P
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	
Leukopenia	31 (40)	1 (1)	39 (51)	3 (4)	0.315
Neutropenia	23 (30)	6 (8)	30 (39)	7 (9)	0.481
Hemoglobin	54 (70)	4 (5)	50 (65)	2 (3)	0.500
Thrombocytopenia	27 (35)	5 (7)	39 (51)	4 (5)	0.095
Hyperbilirubinemia	5 (7)	0	9 (12)	0	0.215
Alanine transaminase	53 (69)	2 (3)	46 (60)	2 (3)	0.495
Alkaline phosphatase	11 (14)	0	16 (21)	1 (1)	0.388
Creatinine	15 (20)	0	28 (36)	0	0.015
Pleural effusions	4 (5)	2 (3)	16 (21)	8 (10)	0.016



Sasaki et al ASH 2021 abst 631

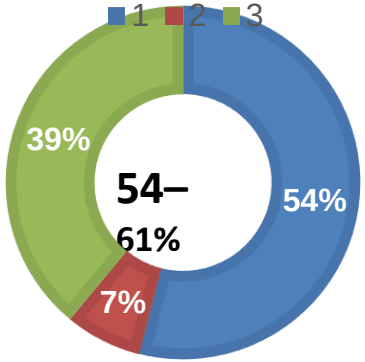
How many patients can be rescued with a 2nd, 3rd line?

Imatinib in the first-line setting: Rate of discontinuation at 5 years



- **5–7%** discontinued due to toxicities
- **15–20%** did not respond

Nilotinib, dasatinib, bosutinib in the second-line setting: Rate of discontinuation at study cut-off

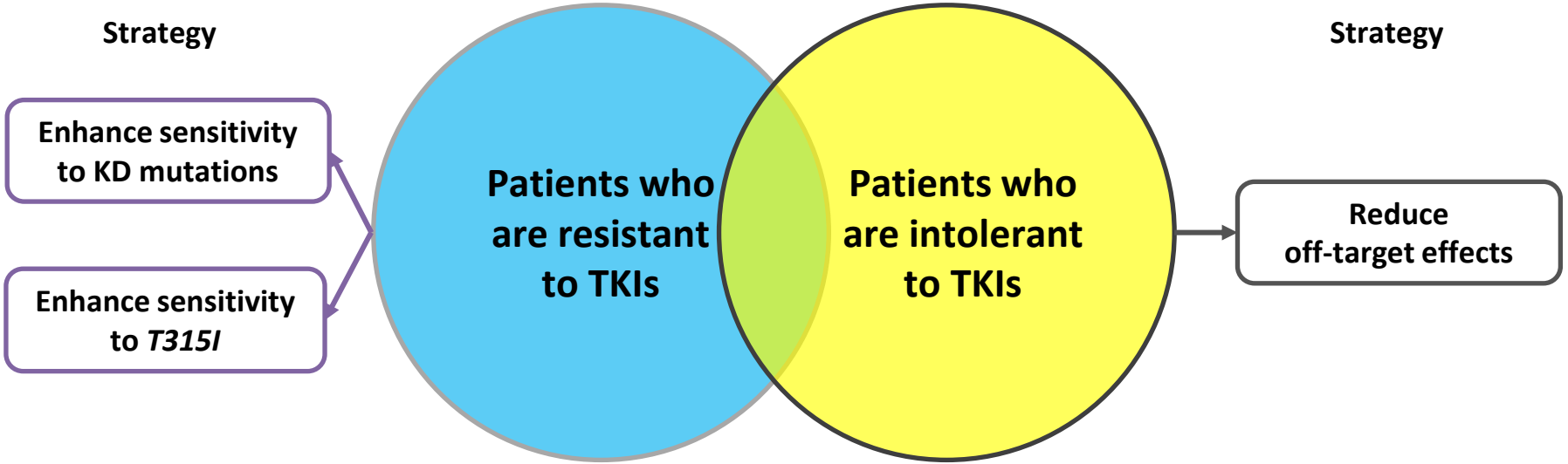


- **50–56%** fail to achieve CCyR
- **60–70%** fail to achieve MMR

Patients with treatment failure/resistance to second-line therapy have limited options

• Cortes J, Lang F. *J Hematol Oncol*. 2021;14:44.
Kantarjian et al, Leukemia 2021

There are two key unmet needs motivating the search for additional TKIs to manage CML

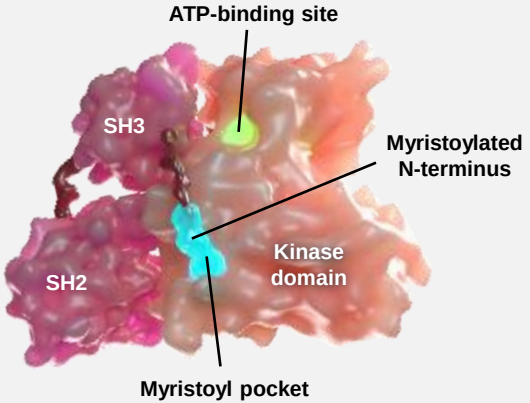


Breccia M. *Adv Ther*. 2022;39:1101–6.

Asciminib is the 1st and only BCR::ABL inhibitor that works by STAMP (Specifically Targeting the ABL Myristoyl Pocket)

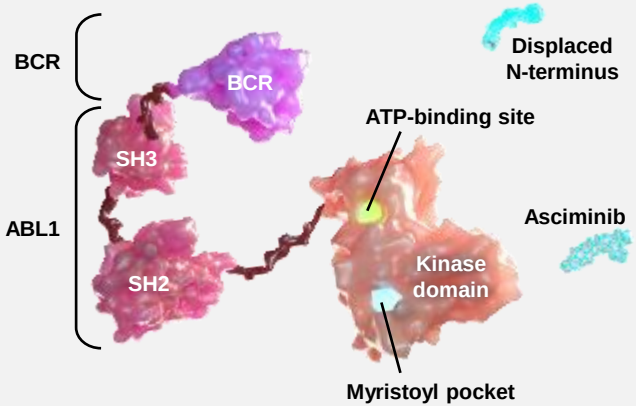
Normal conditions

Inactive ABL1
with N-terminus binding



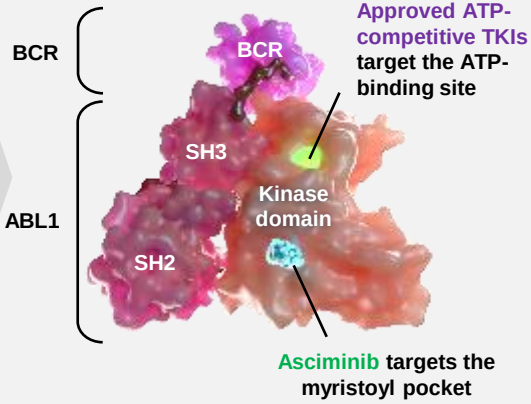
In CML

Constitutively active BCR::ABL1
with loss of N-terminus



In CML with asciminib

Inactive BCR::ABL1
with asciminib binding



ABL1, Abelson tyrosine kinase 1; ATP, adenosine triphosphate; BCR, breakpoint cluster region; CML, chronic myeloid leukemia; MOA, mechanism of action; SH, Src homology; TKI, tyrosine kinase inhibitor.

1. Colicelli J. *Sci Signal.* 2010;3:re6. 2. Hughes TP, et al. *N Engl J Med.* 2019;381:2315-2326. 3. Hantschel O. *Genes Cancer*. 2012;3:436-446. 4. Manley PW, et al. *Leuk Res.* 2020;98:106458.

Olverembatinib vs BAT: registrational phase 2 study in later lines

Table 1. Patient Characteristics and Response N = 144

	Olverembatinib group (n = 96)	BAT group (n = 48)
Demographic and clinical characteristics of the patients at baseline in the ITT population		
Media age (range), yr	48.5 (18-77)	49.0 (24-75)
Sex, n (%)		
Male	70 (72.9)	30 (62.5)
Female	26 (27.1)	18 (37.5)
ECOG PS, n (%)		
0	56 (58.3)	25 (52.1)
1	39 (40.6)	22 (45.8)
2	1 (1.0)	0
Median time from diagnosis to randomization (range), yr	6.12 (0.3-19.2)	6.54 (0.6-17.5)
Treatment status of patients		
Median duration of treatment (range), mo	21.40 (0.6-40.9)	2.99 (0.2-40.4)
Discontinued treatment	56 (58.3)	41 (85.4)
Response rates, n (%)		
Hematologic response		
Evaluable patients	60	23
CHR	51 (85.0)	8 (34.8)
Cytogenetic response		
Evaluable patients	88	37
MCyR	42 (47.7)	11 (29.7)
CCyR	32 (36.4)	6 (16.2)
Molecular response		
Evaluable patients	88	37
MMR	24 (27.3)	3 (8.1)
$MR^{4.0}$	19 (21.6)	1 (2.7)
$MR^{4.5}$	19 (21.6)	1 (2.7)
CMR	18 (20.5)	1 (2.7)
Data cutoff date: April 30, 2023		

- 144 pts (96, olverembatinib; 48, BAT) were enrolled
- 66 (45.8%) pts had >1 *BCR::ABL1* mutation and 39 (27.1%) $BCR::ABL1^{T315I}$
- Any-grade AEs (> 20% incidence) included thrombocytopenia; leukopenia; anemia; neutropenia; elevated CPK, ALT, and AST; and hypertriglyceridemia. Serious AEs (SAEs) (>5%) included thrombocytopenia.
- Estimated EFS at 6, 12, and 24 months was 73%, 58.7%, and 46.9%, respectively. In the BAT group, it was 32.6%, 26.1%, and 16.9%, respectively. Median OS was NR in either group.

Jiang et al ASH 2023; 869

Vodobatinib efficacy according to lines of previous TKIs

- 43 pts
- 15 pts in 2L, 28 in 3L, 15 3L including ponatinib, and 3 pts in 3L including pona and asciminib

- 56% resistant, 15 with mutations
- MMR was achieved in 5 (33.3%), 14 (50.0%) and 8 (53.3%) in 2T, 3T and PON, respectively.
- Of the 20 pts with MMR as best response, 10 (23.6%) achieved molecular response M4

- Dose intensity was similar for all groups
- 2/16 who progressed, developed compound mutations

- AEs: thrombocytopenia 14%
  GI events
  increased amylase/lipase

- 10 pts experienced CV effects (GR3 in 2 pts)

Table 1: Efficacy Outcomes and Drug Exposure

Status	2T (N = 15)		3T (N = 28)		PON (N = 15)		ASC (N = 3)		Overall (N = 43)	
Hematological	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**
CHR	1 (6.7)	7 (46.7)	14 (50.0)	21 (75.0)	9 (60.0)	12 (80.0)	2 (66.7)	3 (100.0)	15 (34.9)	28 (65.1)
Missing[1]	5 (33.3)	0	2 (7.1)	0	1 (6.7)	0	1 (33.3)	0	7 (16.3)	0
Cytogenetic	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**
Major cytogenetic response	4 (26.7)	11 (73.3)	8 (28.6)	17 (60.7)	5 (33.3)	10 (66.7)	0	1 (33.3)	12 (27.9)	28 (65.1)
Complete cytogenetic response	2 (13.3)	10 (66.7)	5 (17.9)	14 (50.0)[2]	4 (26.7)	7 (46.7)[2]	0	1 (33.3)	7 (16.3)	24 (55.8)
Partial cytogenetic response	2 (13.3)	1 (6.7)	3 (10.7)	3 (10.7)	1 (6.7)	3 (20.0)	0	0	5 (11.6)	4 (9.3)
Minor response	1 (6.7)	0	6 (21.4)	1 (3.6)	3 (20.0)	1 (6.7)	2 (66.7)	1 (33.3)	7 (16.3)	1 (2.3)
Minimal response	2 (13.3)	3 (20.0)	5 (17.9)	4 (14.3)	1 (6.7)	1 (6.7)	0	0	7 (16.3)	7 (16.3)
No response	8 (53.3)	1 (6.7)	7 (25.0)	4 (14.3)	4 (26.7)	2 (13.3)	0	1 (33.3)	15 (34.9)	5 (11.6)
Missing	0	0	2 (7.1)	2 (7.1)	2 (13.3)	1 (6.7)	1(33.3)	0	2 (4.7)	2 (4.7)
Molecular	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**	**Baseline**	**Best Response**
Major molecular response (M3)	0	5 (33.3)	1 (3.6)	15 (53.6)	0	8 (53.3)	0	0	1 (2.3)	20 (46.5)
Molecular Response (M4)	0	2 (13.3)	1 (3.6)	9 (32.1)	0	4 (26.7)	0	0	1 (2.3)	11 (25.6)
No response	14 (93.3)	10 (66.7)	24 (85.7)	12 (42.9)	13 (86.7)	7 (46.7)	1 (33.3)	3 (100.0)	38 (88.4)	22 (51.2)
Missing	1 (6.7)	0	3 (10.7)	1 (3.6)	2 (13.3)	0	2 (66.7)	0	4 (9.3)	1 (2.3)
Average dose received per day across all cycles (median, range in mg)	**174.00 (58.7 – 204.0)**		**127.7 (48.0 – 215.1)**		**123.7 (66 -0 – 215.1)**		**123.7 (66.0 – 167.7)**		**166.6 (48.0 – 215.1)**	

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Conclusions

- A patient centred approach in 1st line. 2gen TKIs increased the rate of deep MR.
- Life expectancy increased.
- TFR is not for all patients and about 50% of them relapsed after discontinuation. Strategies to improve the eligibility are needed.
- Unmet needs in later lines remained. New options are now approved or ongoing and will change the therapeutic scenario.