Como Trato la LMC
Consideraciones Para el Éxito del Tratamiento

Jorge Cortes, MD
Director, Georgia Cancer Center

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

Disclosure Information

- **Grant or research support (to my institution) from *Novartis, Pfizer, Sun Pharma, Ascentage***
- **Paid Consultant for *Novartis, Pfizer, Sun Pharma, Takeda, Incyte, Pint Pharma, Tern Pharma***

Some Things to Discuss

- Initial work-up
- Response assessment and monitoring
- Initial therapy
- Subsequent therapy
- Adverse events
- Treatment discontinuation

2022 CML Classifications

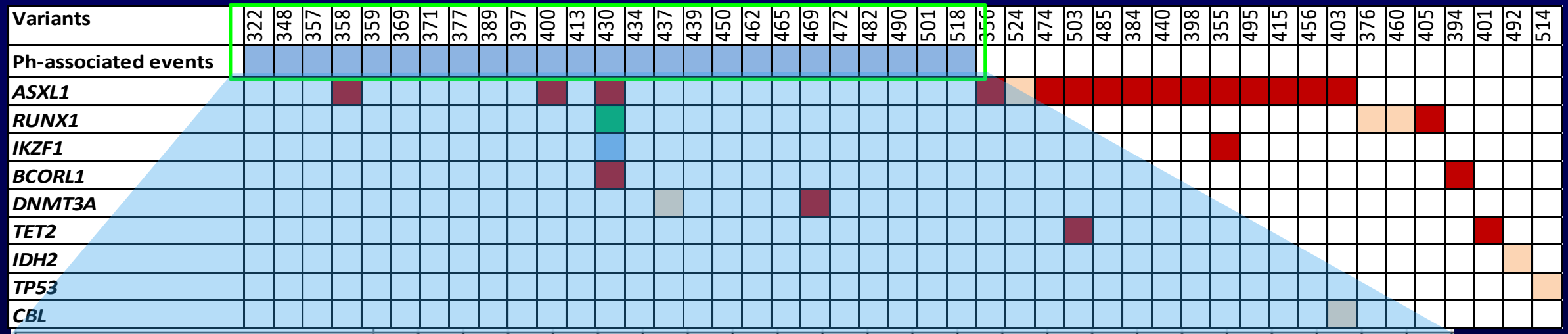
- **WHO**
  - AP is omitted in favor of an emphasis on high risk features associated with CP progression and resistance to TKI.
  - BP criteria: (1) ≥20% myeloid blasts in PB or BM; or (2) extramedullary proliferation of blasts; or (3) increased lymphoblasts in PB or BM. (The optimal cutoff for lymphoblasts and the significance of low-level B-lymphoblasts remain unclear and require additional studies.)
- **ICC**
  - AP criteria: (1) 10-19% blasts in PB or BM; or (2) PB basophils ≥20%; or (3) additional clonal cytogenetic abnormality in Ph+ cells (ACA)[1].
  - BP criteria: (1) ≥20% blasts in PB or BM; or (2) myeloid sarcoma[2]; or (3) morphologically apparent lymphoblasts (>5%)[3] (“warrants consideration of lymphoblastic crisis”).

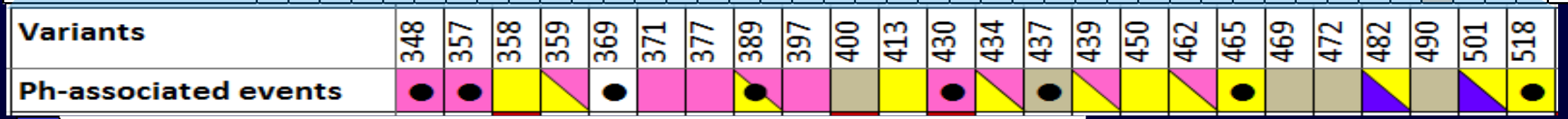
[1]Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or 3q26.2 abnormalities. [2]Extramedullary blast proliferation. [3]Immunophenotypic analysis is required to confirm lymphoid lineage.

Khoury et al. Leukemia 2022; 36: 1703-19; Arber et al. Blood 2022; 140: 120-8

CML Molecular Heterogeneity: Mutational events

- 160 patients from TIDEL-II sequenced with RNA capture panel
- Cancer associated gene mutations 20 pts (12.5%), Ph-associated events 20 pts (12.5%), both 5 pts (3%)





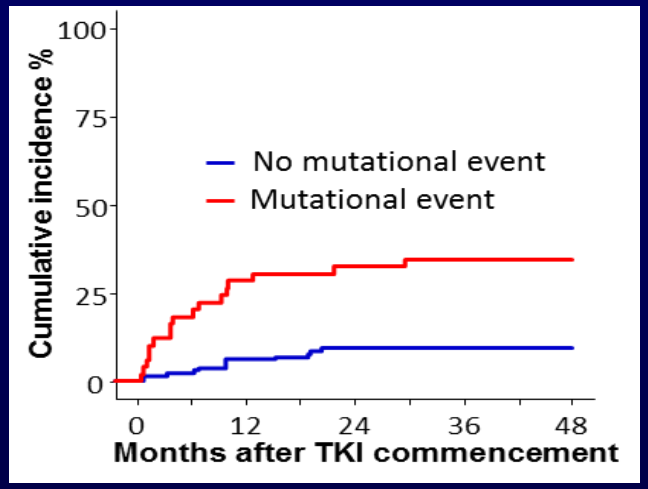
exon duplication
cryptic fusion involving *ABL1*
cryptic fusion involving *BCR*
fusion event involving genes on chromosomes 9 and 22 other than *BCR* or *ABL1*
inversion

fusion
frameshift/nonsense
missense
focal gene deletion

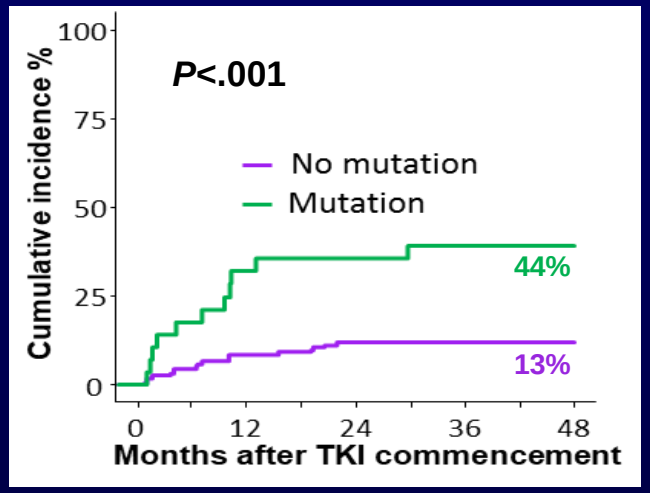
Shanmuganathan et al. Haematologica 2023; 108: 2380-95

CML Molecular Heterogeneity: Outcome by Molecular Abnormalities

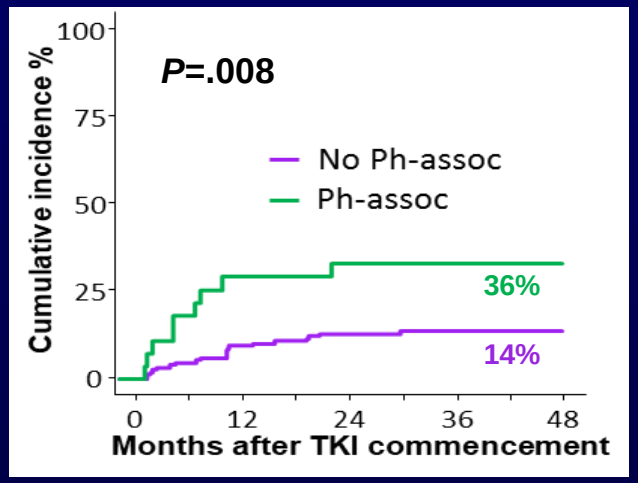
Any mutational event



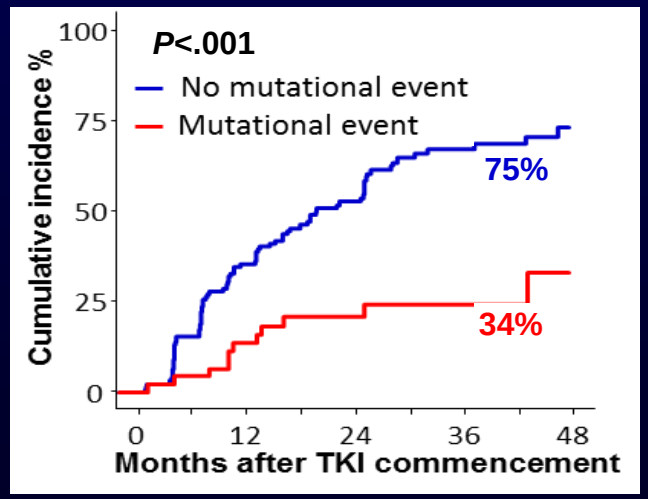
Cancer-associated gene mutations



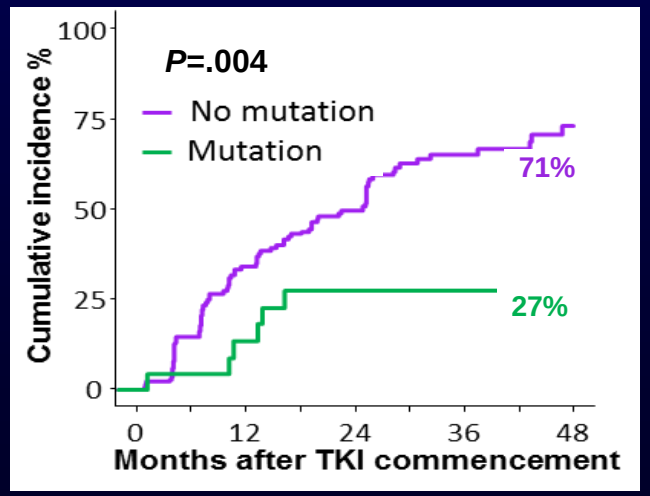
Philadelphia-associated events

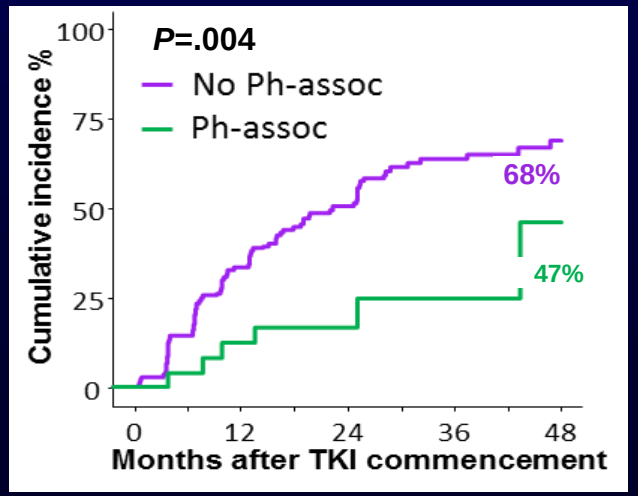


ELN-defined Failure



MR4

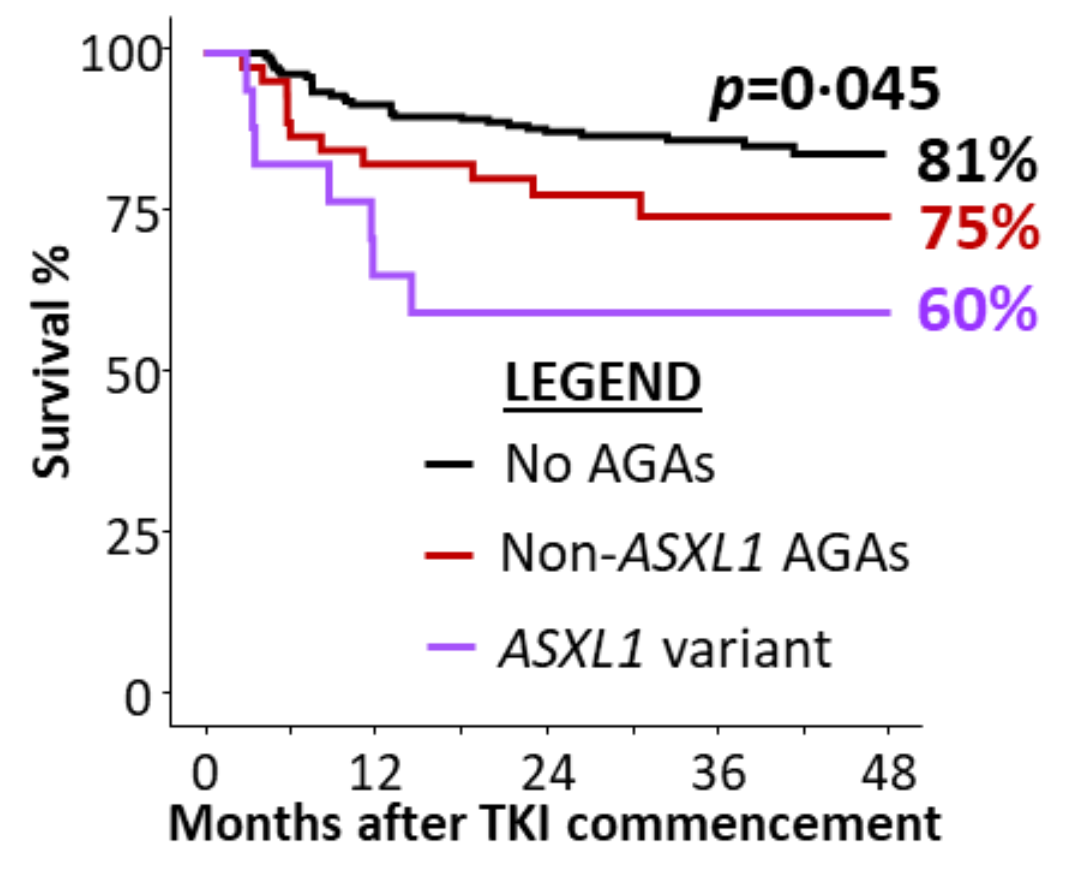




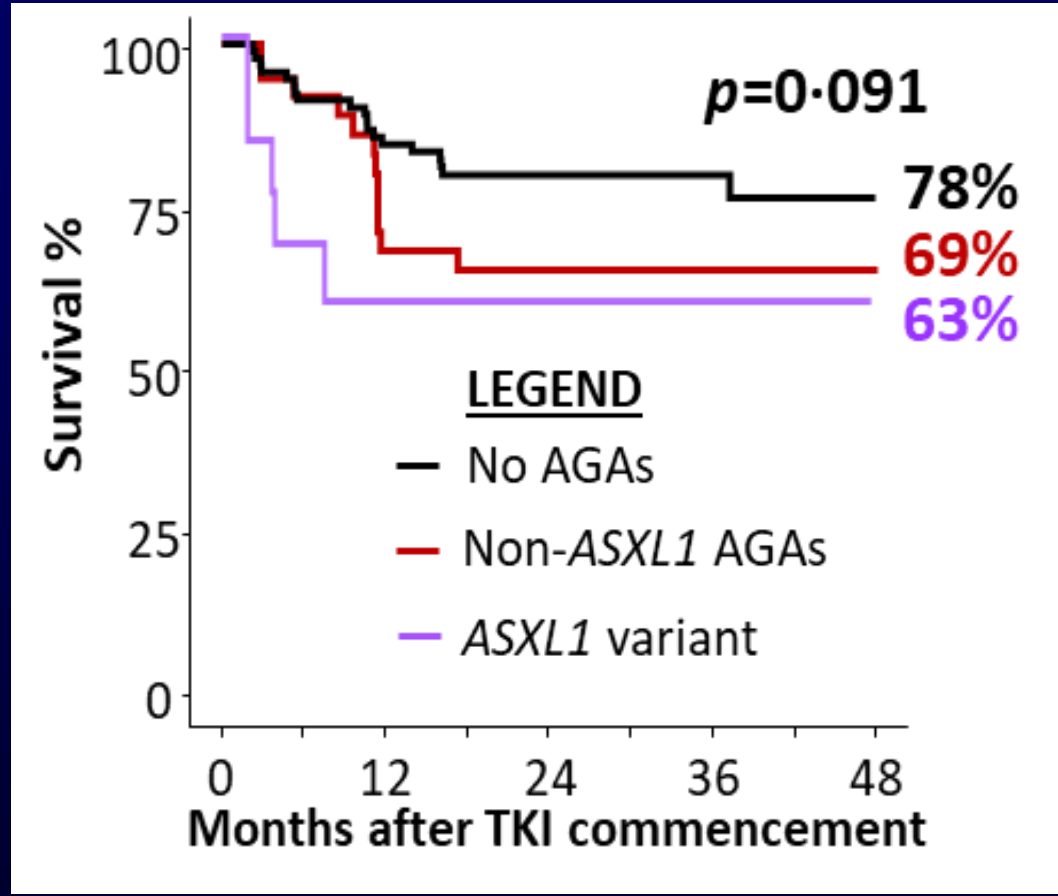
Shanmuganathan et al. Haematologica 2023; 108: 2380-95

Effect of ASXL1 at diagnosis on FFS

Imatinib



2G-TKI

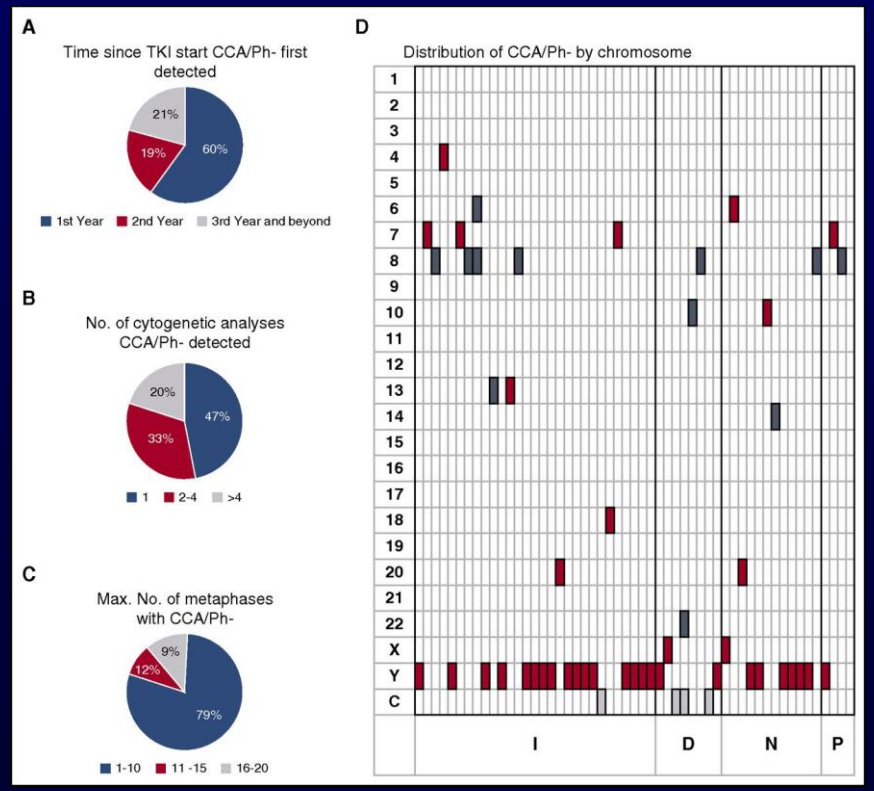


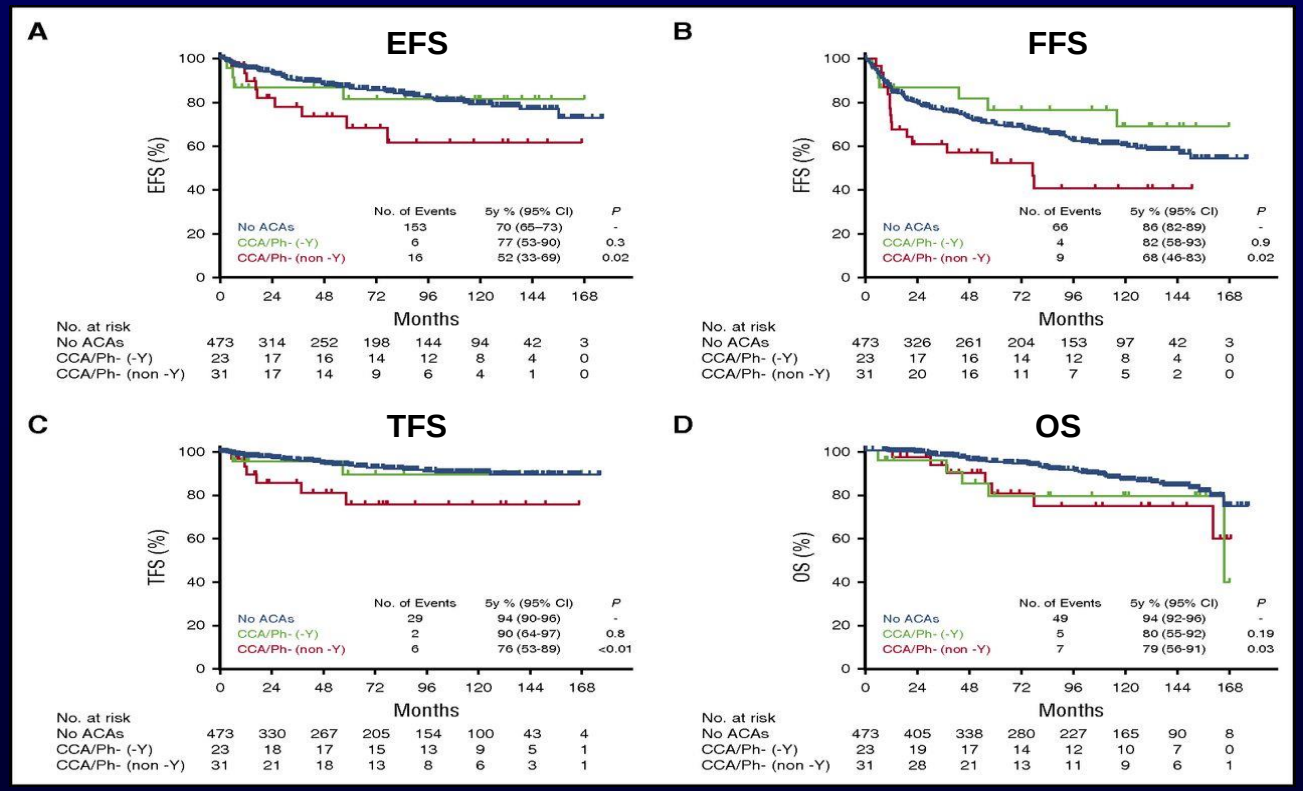
- **Cumulative 48-mo rate KD mutation acquisition on imatinib: ASXL1 variant 22%, non-ASXL1 AGAs 12%, no AGAs 2%**

Shanmuganathan et al. Haematologica 2023; 108: 2380-95

ACA in CML

- 598 pts treated frontline with TKI
- Clonal chromosomal abnormalities in Ph- metaphases occurred in 58 (10%) pts
- Median time to appearance: 6 mo (3-78 mo) (1st occurrence after 12 mo in 39%)
- Transient (≤2 times)in 36 (62%)





Issa et al. Blood 2017; 130: 2084-91

Response Criteria for CML

Cytogenetic response	% Ph*	Molecular response	% BCR-ABL/ ABL (IS)
Minor (mCyR)	36-95		>10
Partial (PCyR)	1-35		1 to <10
			>0.01 to <1
Complete (CCyR)	0	Major (MMR; MR3)	≤0.1
		MR4	≤0.01
		MR4.5	≤0.0032
		Deep molecular response (DMR)	≤0.01 or ≤0.0032

Good
Better
Best
Questionable

* At least 100,000 copies ABL needed

Monitoring Recommendations for CML According to the ELN and NCCN 2020

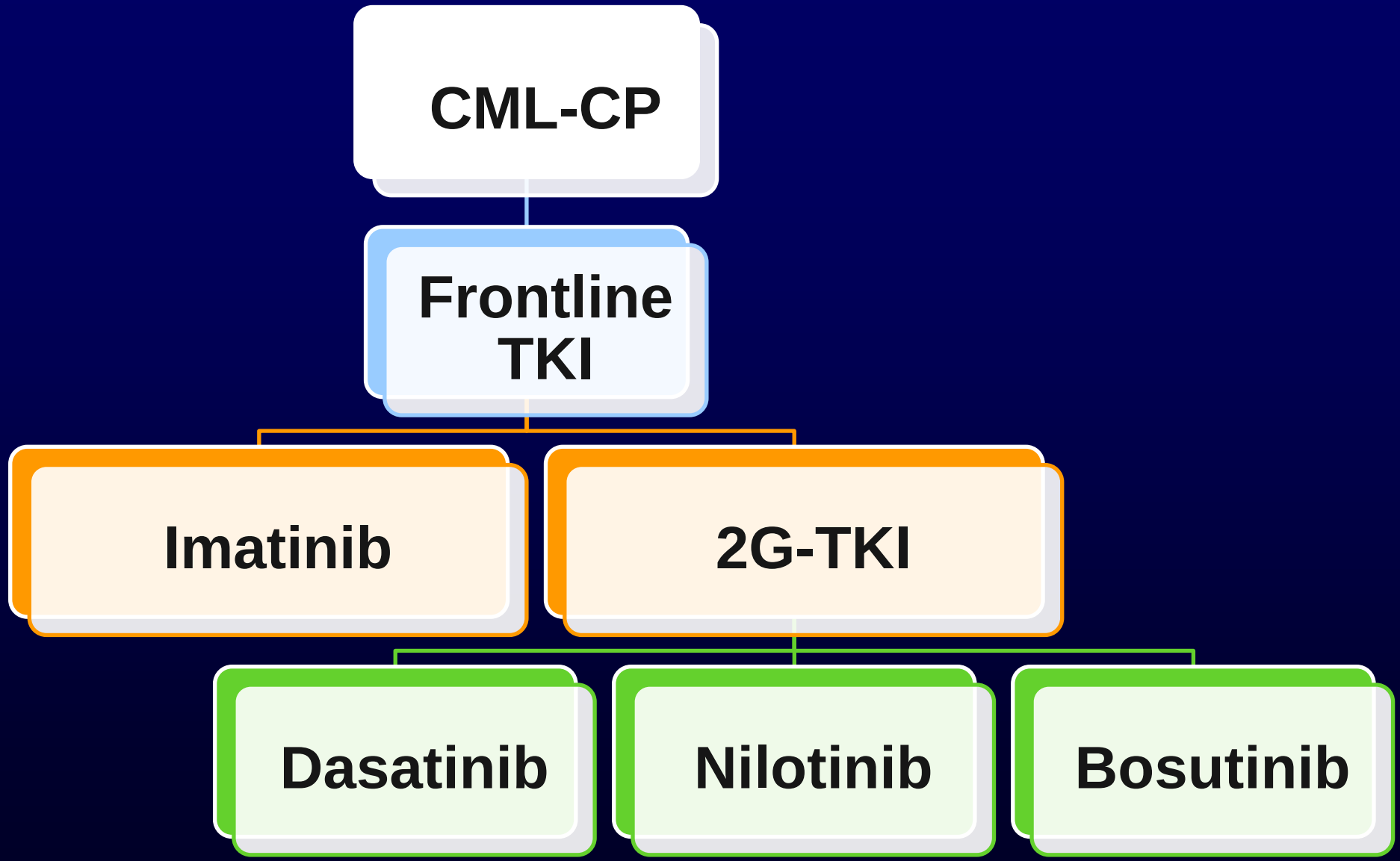
When	ELN	NCCN
At diagnosis	• CG (BM aspiration) • FISH (in case of Ph-) • PCR	• CG (BM aspiration) • FISH (in case of Ph-) • PCR
During treatment	• PCR (IS) every 3 mo • In patients with atypical translocations, rare or atypical BCR-ABL1 transcripts that cannot be measured by qPCR, treatment failure/resistance to exclude ACA, and with progression to AP or BP • FISH may be needed in patients with atypical transcripts	• Every 3 months • Continue every 3 months until 2 years after BCR-ABL1 ≤1% IS • Then every 3-6 months • Repeat in 1-3 months if in MMR and 1-log increase
Failure, progression	• PCR (IS), mutation analysis, cytogenetics • Immunophenotype for BP	• PCR (IS), mutation analysis, cytogenetics
Warning	• Repeat PCR in 1-3 months	

Hochhaus et al. Leukemia 2020; 34: 966-984

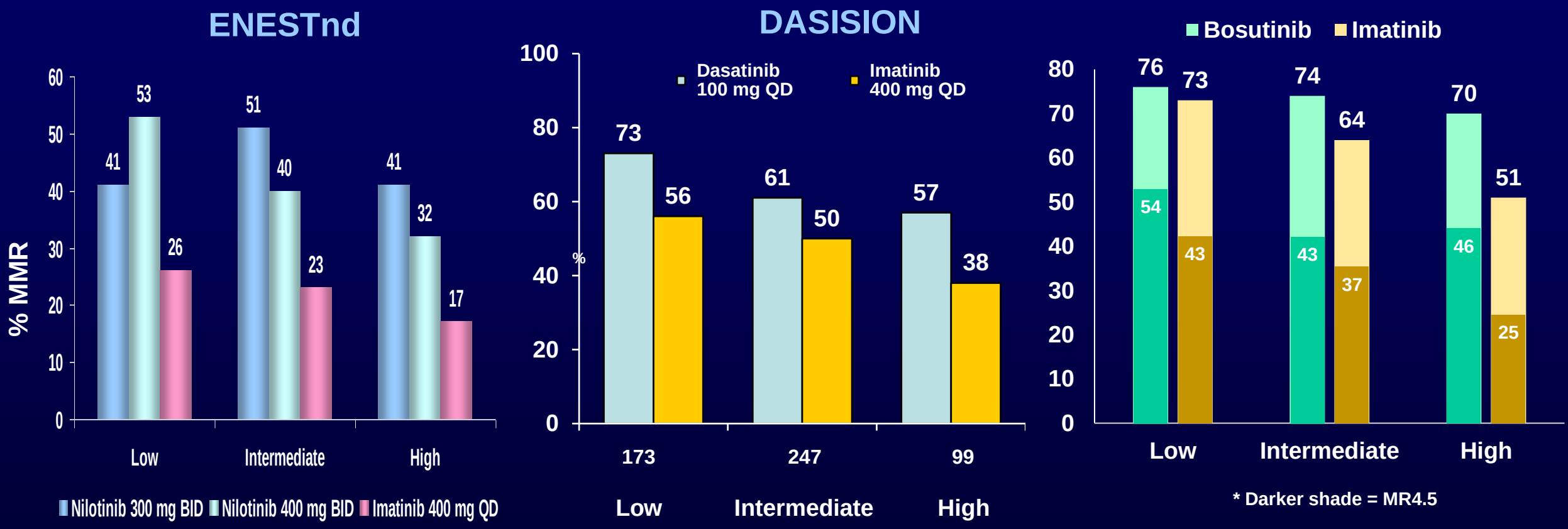
How do I Diagnose and Monitor?

- At diagnosis:
  - Bone marrow aspiration
  - PCR
  - FISH
  - Cytogenetics
- Cytogenetics every ~12 months (bone marrow) x 2 years
  - More often if ACA in Ph(-) metaphases
- PCR every 3 months x~1 year (MMR); then every 6 months
  - Every 3 months if change of dose
  - Almost never more frequently
  - FISH if atypical transcripts
- NGS if resistance to 2 TKIs (not at diagnosis)
- Use 3-phase staging: CP, AP, BP

Selecting Frontline TKI



MMR by Sokal Score



Saglio et al. Blood 2009; 114: abst# LBA-1; Kantarjian et al. ASCO 2011; abstract #6510; Brümmendorf TH, et al. Leukemia 2022; 36: 1825-33.

Outcome across 1st line CML studies

Response at, %	DASISION		ENESTnd		BFORE		TOPS	
	DAS	IMA	NIL[b]	IMA	BOS	IMA	IMA 800	IMA 400
CCyR 12m	77	66	80	65	77	66	70	66
MMR 3m	8	0.4	9	1	4.1	1.7	12	3
MMR 12m	46[a]	28[a]	44	22	47	37	47	40
MMR 5 yr	76	64	77	60	74	66	--	--
MR4.5 5 yr	42	33	54	31	46	36	--	--
AP/BP	2.3	5.0	1	6	2.2	2.6	1.9	3.2
PFS	94	92	96	94	NR	NR	97	94
OS	95.3	95.2	97	96	99	97	99	98

[a] MMR by 12 mo; [b] Nilotinib 300 mg BID

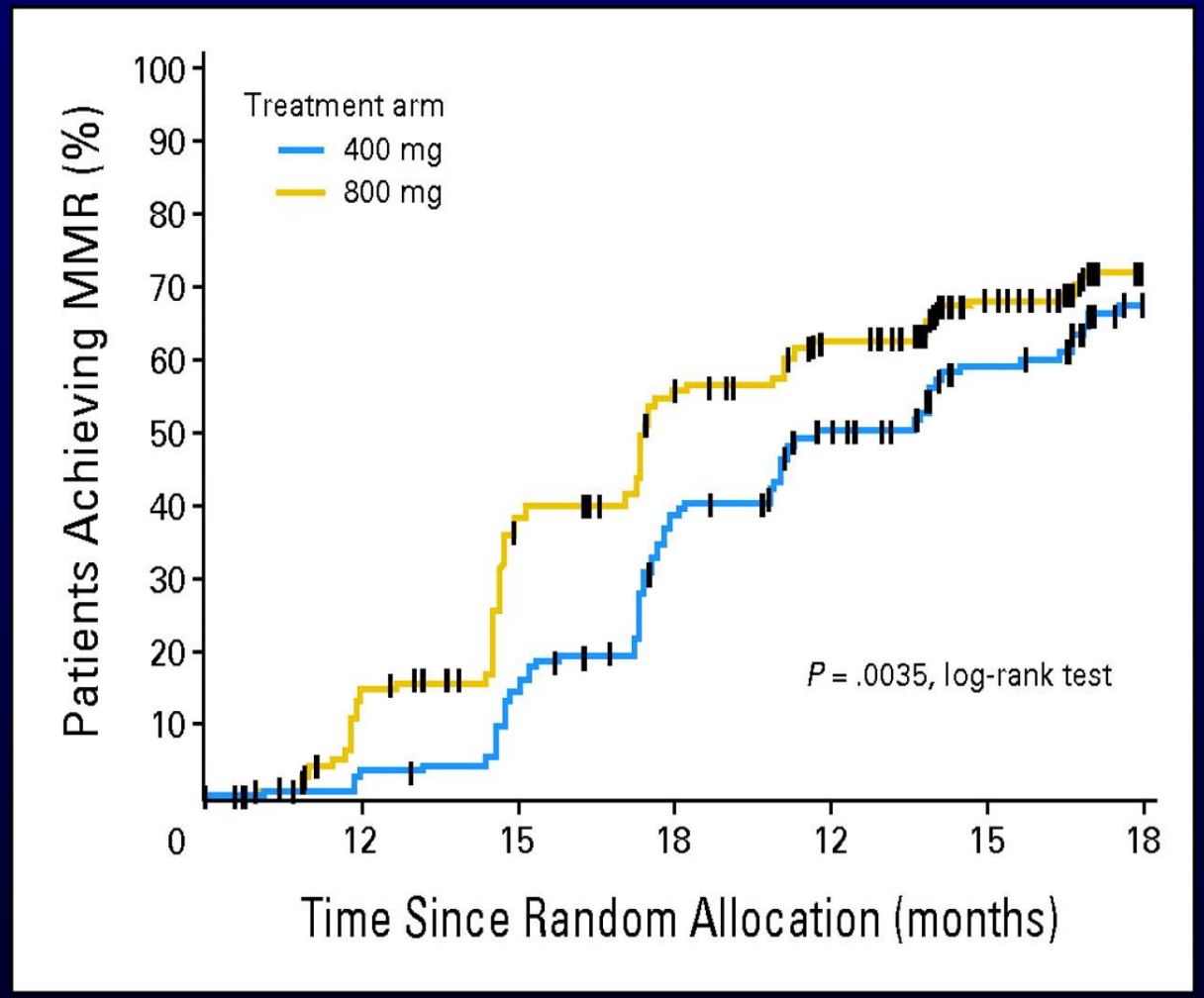
Cortes et al. JCO 2016; 34: 2333-40; Hochhaus et al. Leukemia 2016; 30: 1044-54;
Brümmendorf TH, et al. Leukemia 2022; 36: 1825-33; Cortes et al. JCO 2010; 28: 424-30

HD vs SD Imatinib For CML-CP

- 476 pts randomized 2:1 to imatinib 800 mg (n = 319) or 400 mg (n = 157)

	HD	SD
MMR @ 3 mo	12	3
CCyR @ 6 mo	57	45
PFS @ 18 mo	95	97
PFS @ 18 mo (HR Sokal)	96	88
AP/BP @ 18 mo	1.9	3.2
OS @ 18 mo	99	98

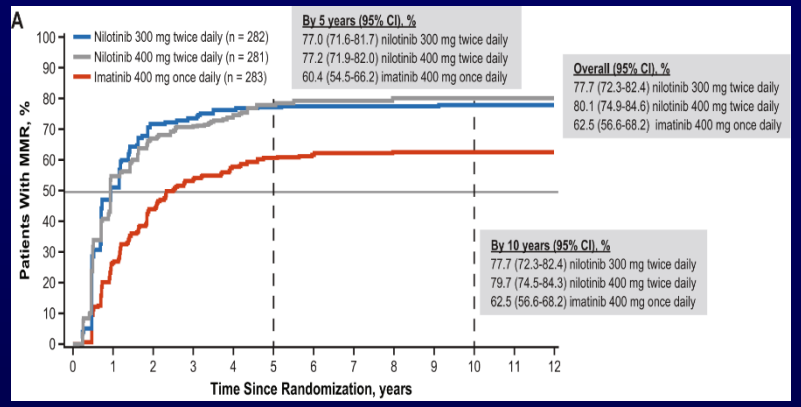
- MMR @ 12 mo: 62% with average dose intensity 600 - 799 mg/d v 38% with 400 - 599 mg/d



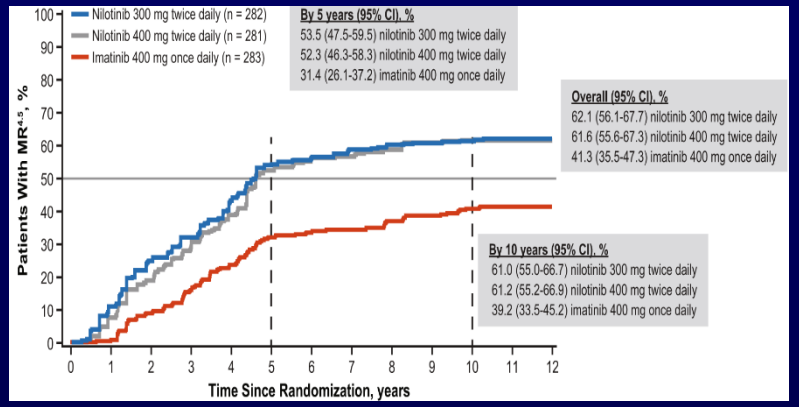
Cortes et al. JCO 2010; 28: 424-30

ENESTnd, 10-Year Results

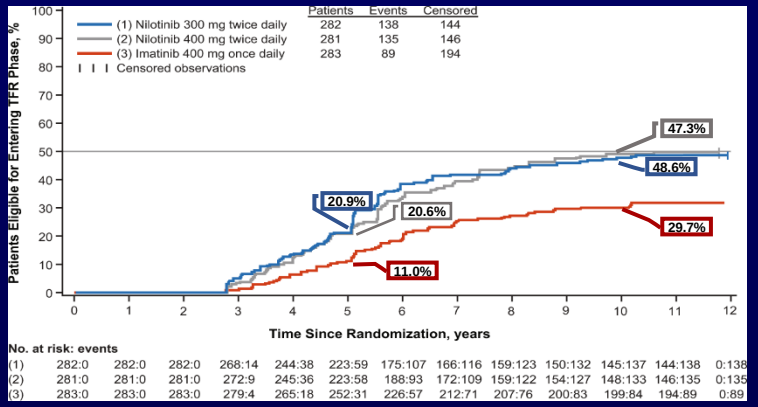
MMR



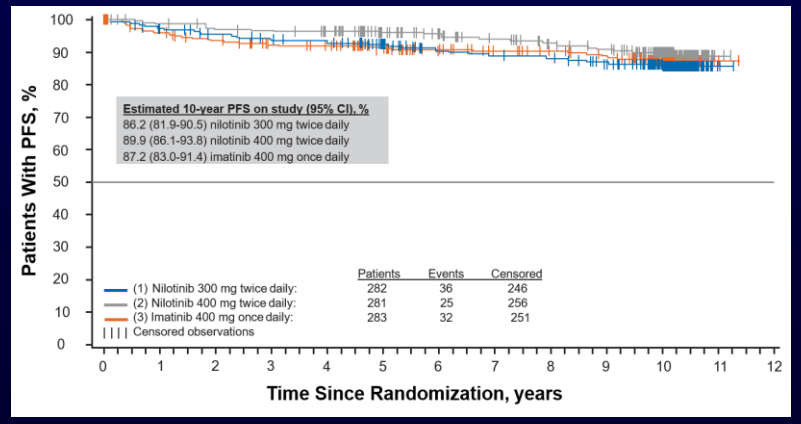
MR4.5



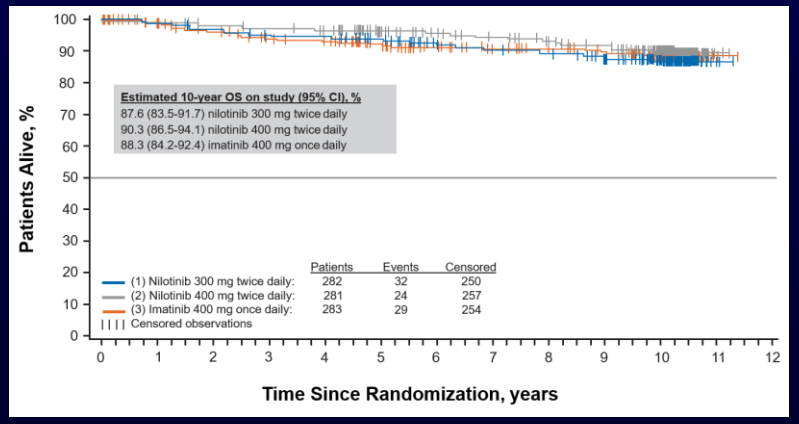
sMR4.5



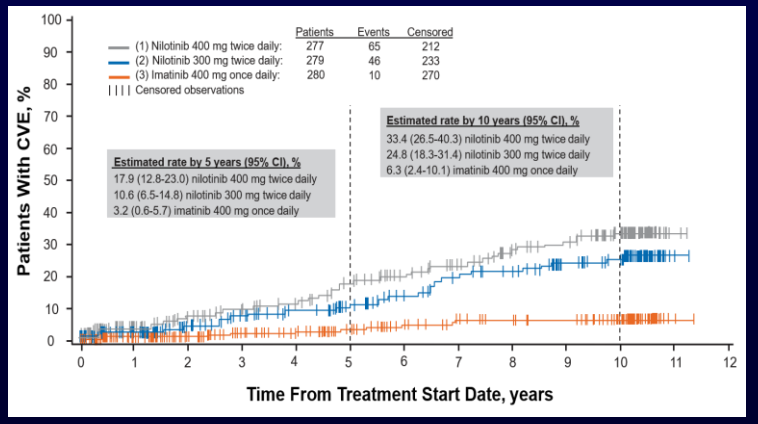
PFS



OS

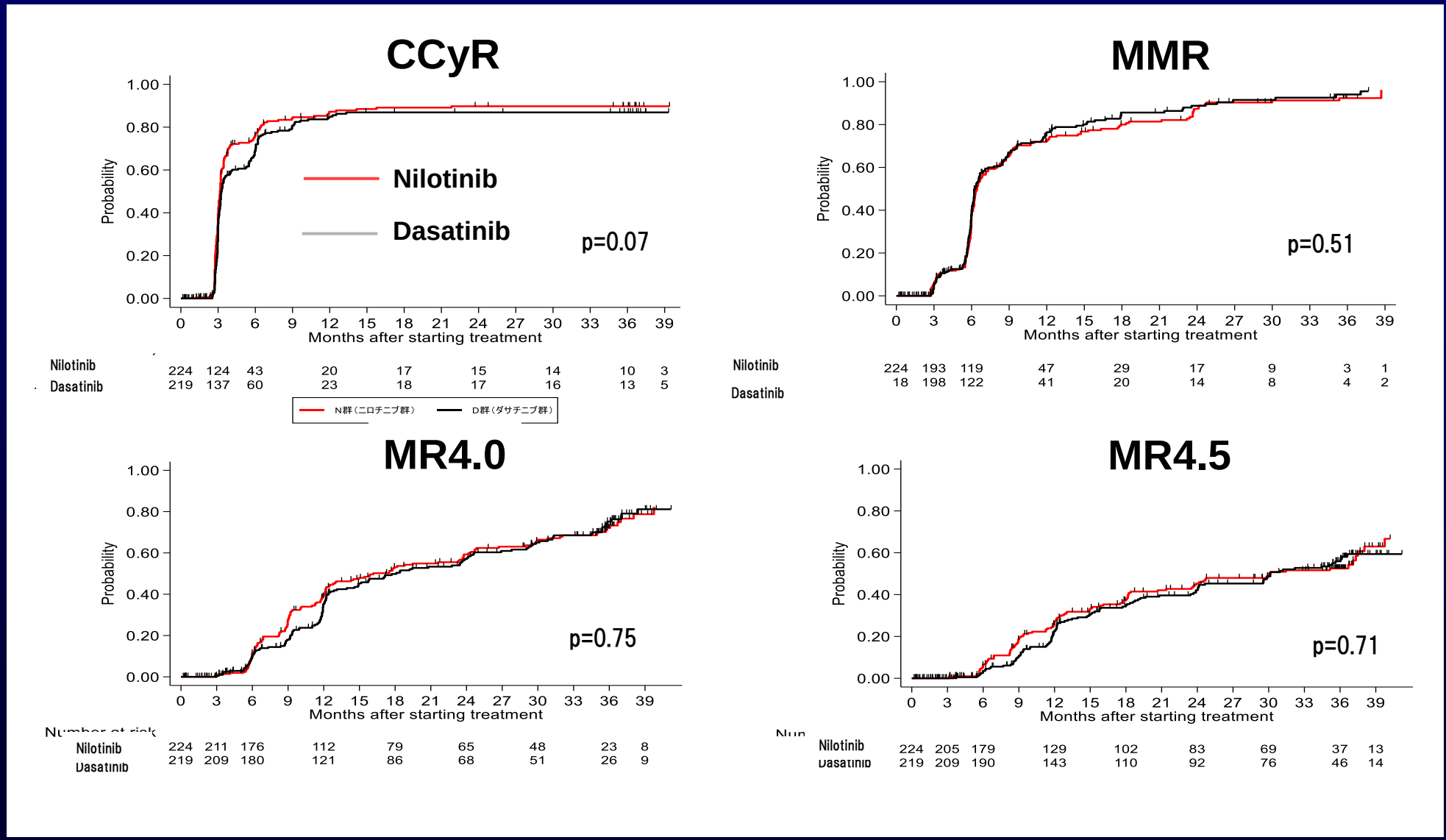


CVE



Kantarjian et al. Leukemia 2021; 35: 440-53

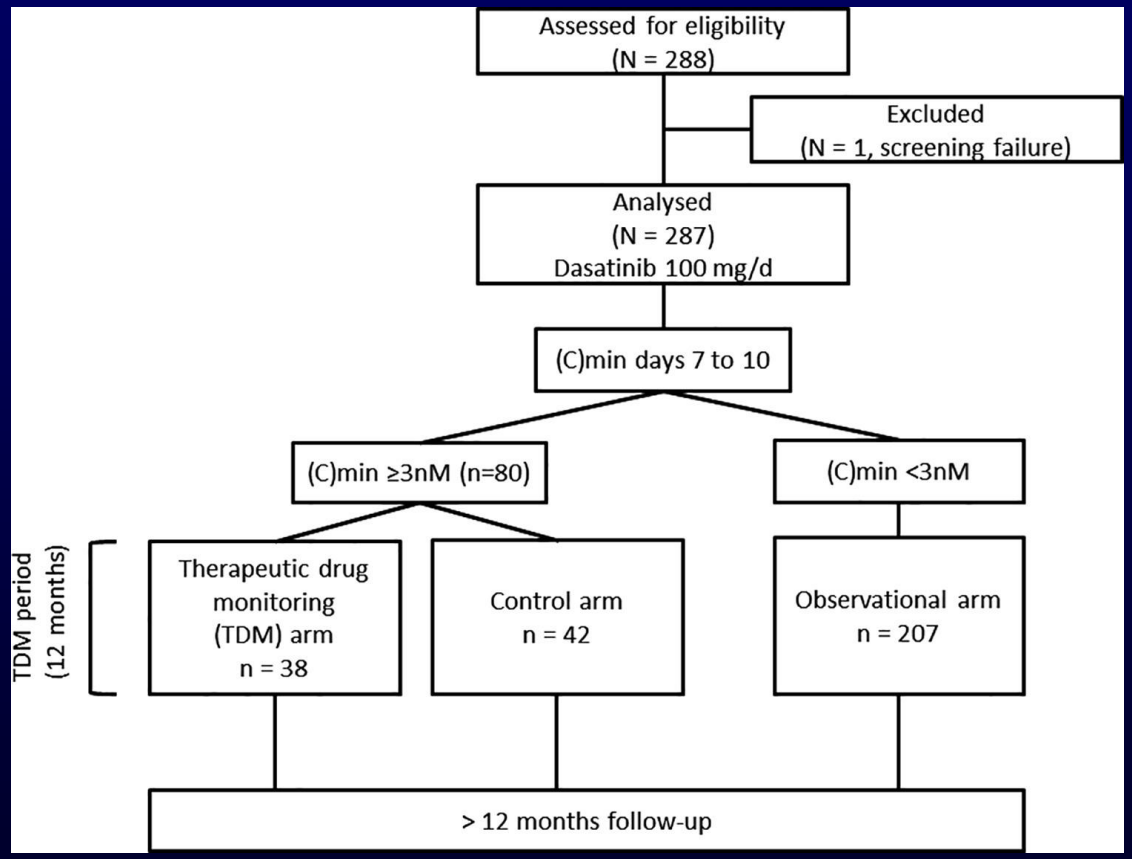
CML212: Randomized Trial of Dasatinib vs Nilotinib for Frontline CML Therapy



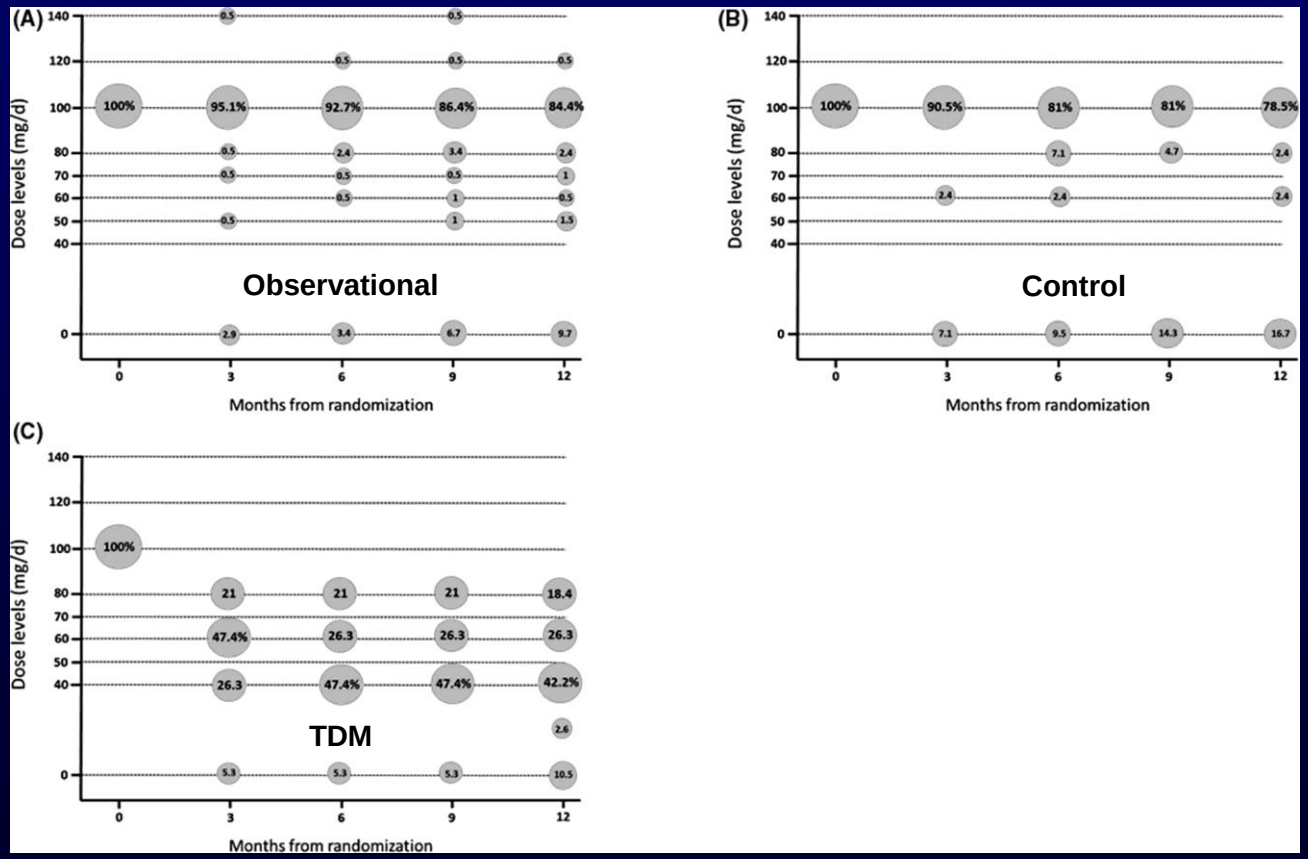
Matsumura I, et al *Blood.* 2020;136(Suppl 1): Abstract 45.

Dasatinib Dose Optimization

Study Design



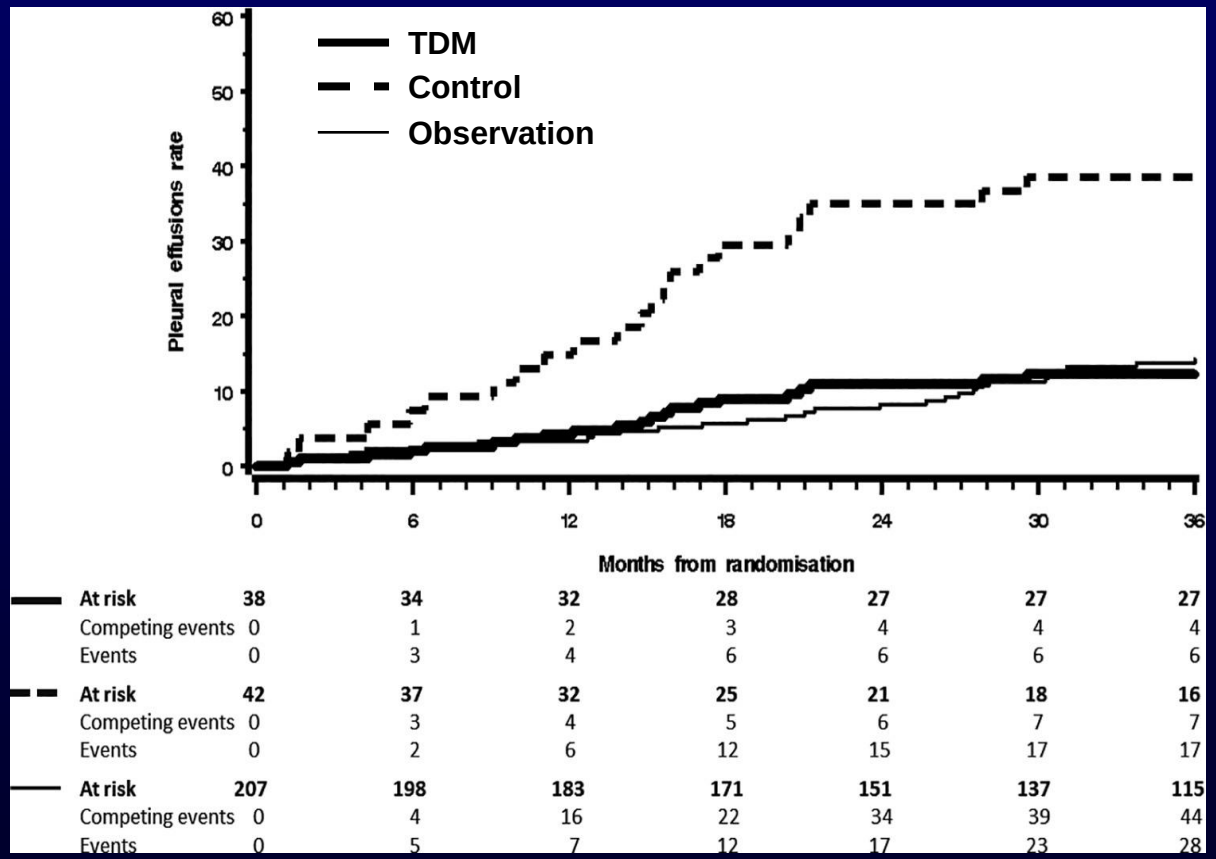
Dose Over Time



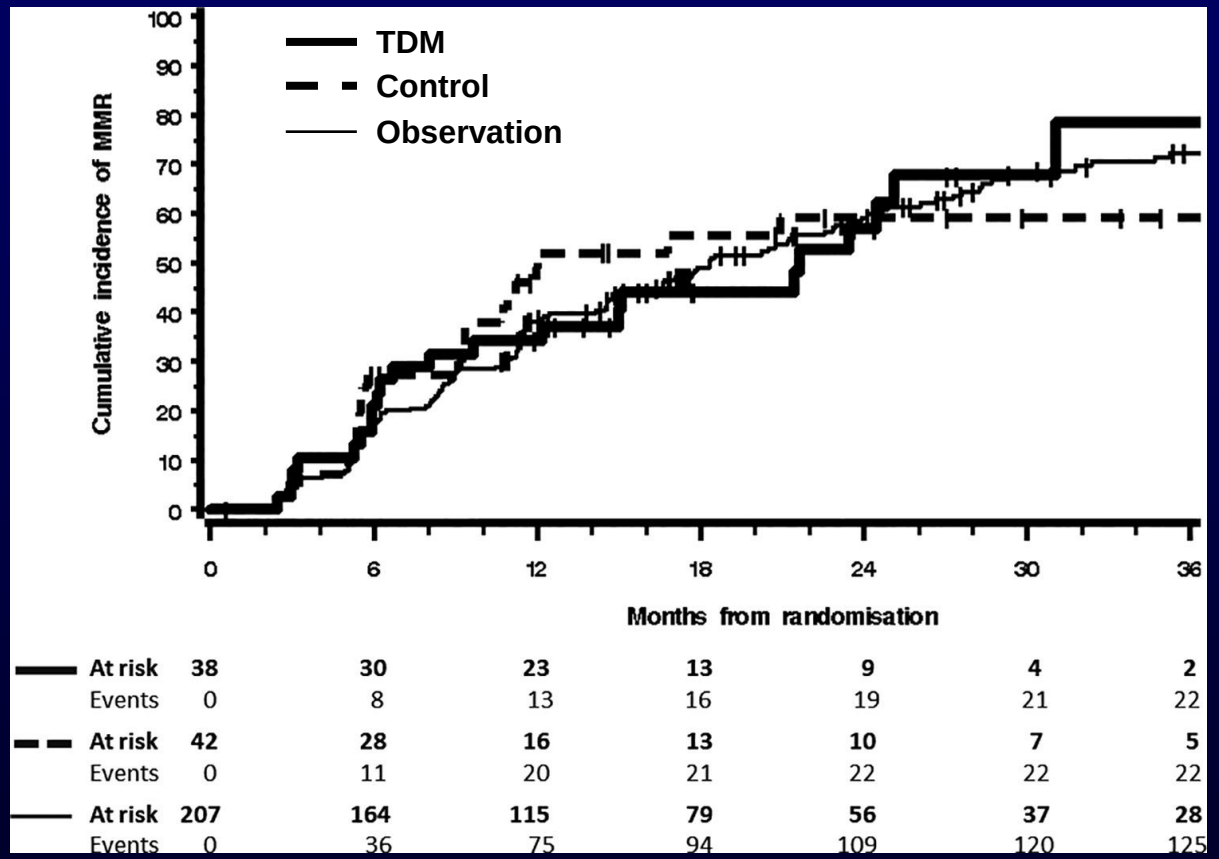
Rousselot et al. Br J Haematol 2021; 194: 393-402

Dasatinib Dose Optimization

Pleural Effusion



MMR



Rousselot et al. Br J Haematol 2021; 194: 393-402

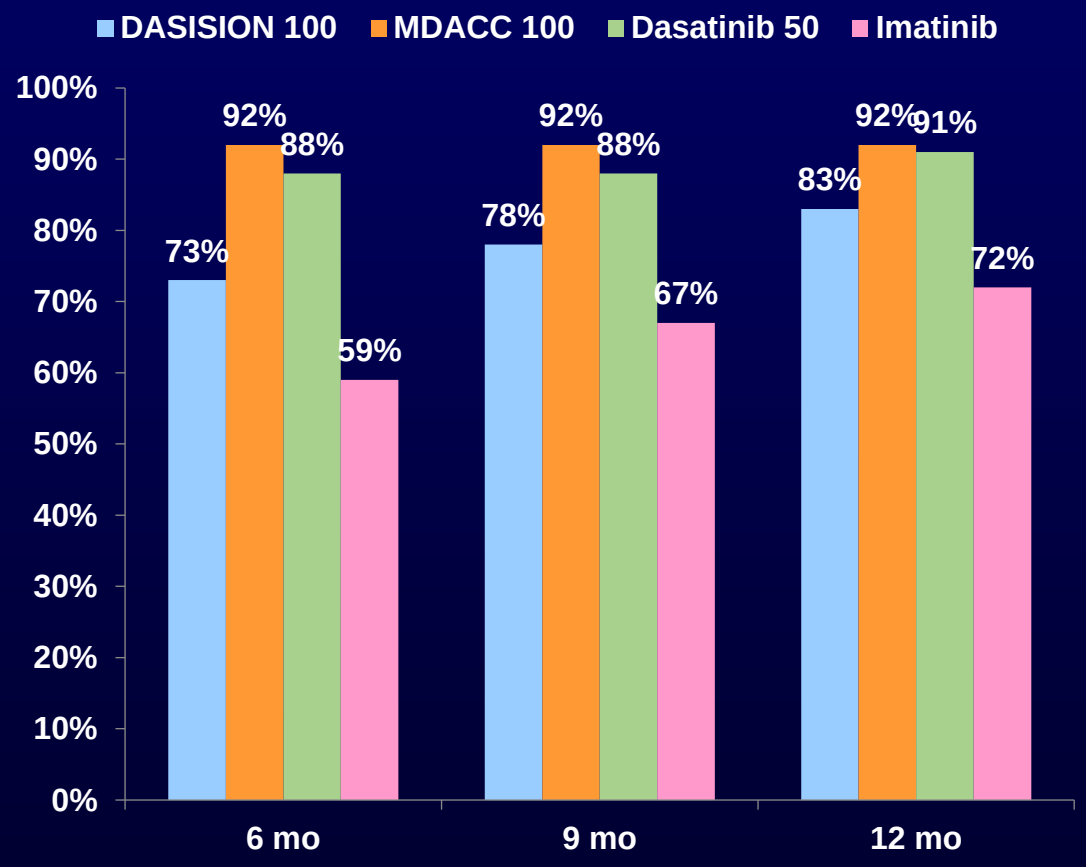
Low Dose Dasatinib in Elderly Patients - DAVLEC

- 52 patients age >70 yrs with untreated CML-CP
  - Median age 77.5 yrs (73.5 – 83)
- Starting dose 20 mg/day
- Increase by 20 mg/day if response not optimal and AEs grade ≤2 at 3, 6 and 9 months
- MMR at 12 months 60%
- Grade 3-4 AEs 23% (neutropenia 6%)

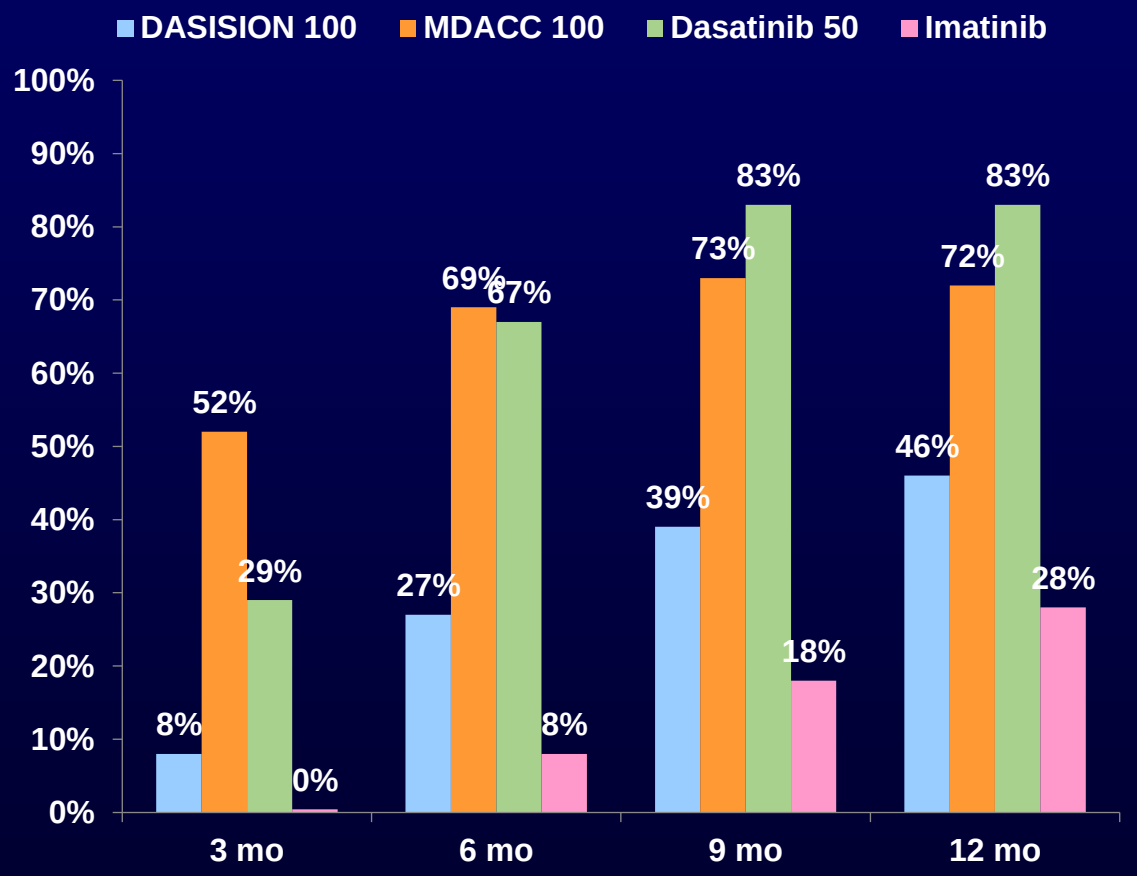
Murai et al. Lancet Hematol 2021; 8: e902-e911

Dasatinib 50 mg Daily as Frontline Therapy in ECP-CML

CCyR



MMR



Naqvi K, et al. Cancer. 2020;126(1):67-75; Jain P, et al. Lancet Hematol 2015; 2: e118-28; Cortes J, et al. JCO 2016; 34: 2333-40

CML Recommendations ELN & NCCN

ELN 2020

	Optimal	Warnings	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	BCR-ABL1 ≤10%	BCR-ABL1 >10%	BCR-ABL1 >10%, if confirmed within 1-3 months
6 months	BCR-ABL1 ≤1%	BCR-ABL1 >1%-10%	BCR-ABL1 >10%
12 months	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1%-1%	BCR-ABL1 >1%
Then, at any time	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1%-1% Loss of ≤0.1% (MMR)[a]	BCR-ABL1 >1%, resistance mutations, high-risk ACA

NCCN

BCR-ABL1 (IS)	3 months	6 months	12 months†
>10%‡	Yellow	Red	
>1–10%	Green		Yellow
>.01%-1%	Green		Light Green
≤0.1%	Green		

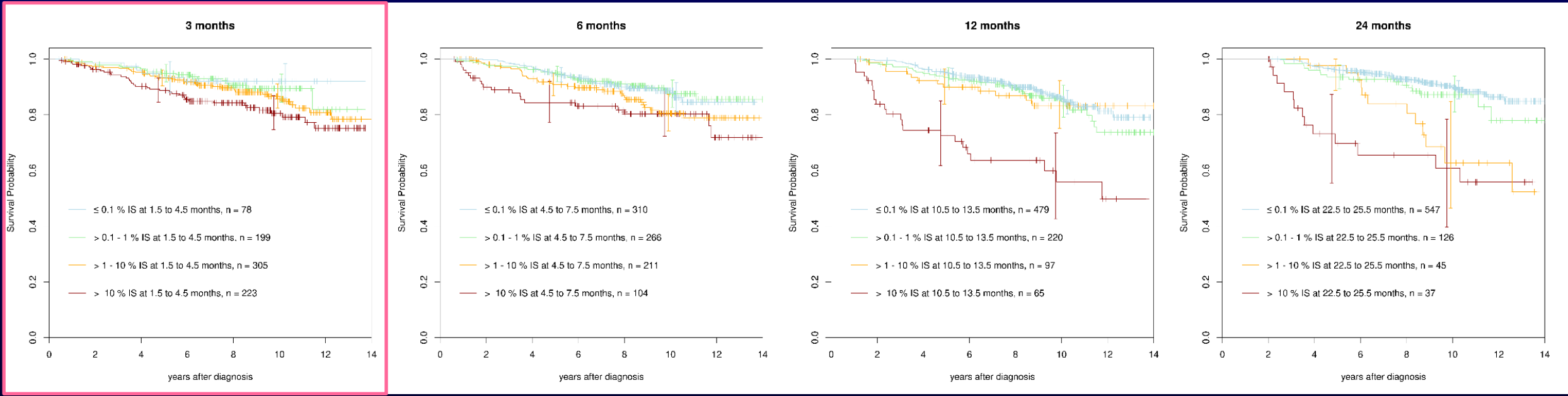
Colour	Concern	Clinical considerations	Second-line treatment
Red	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	• Switch to alternate TKI, and evaluate for allogenic HSCT
Yellow	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 months of CCyR at 12 months	• Switch to alternate TKI, or • Continue same TKI (other than imatinib), or • Imatinib dose escalation (to max 800 mg), and • Consider evaluation for allogenic HSCT
Light Green		• If treatment goal is long-term survival: >0.1%-1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with the patient
Green	TKI-sensitive disease	• Monitor response and side-effects	Continue same TKI¶

Major differences:

- No baseline features in NCCN (warning only in ELN)
- 6-month >1-10% optimal by NCCN, warning by ELN
- 12-month >1-10% “yellow” by NCCN, failure by ELN
- Losses not included in NCCN (“Early treatment milestones”)

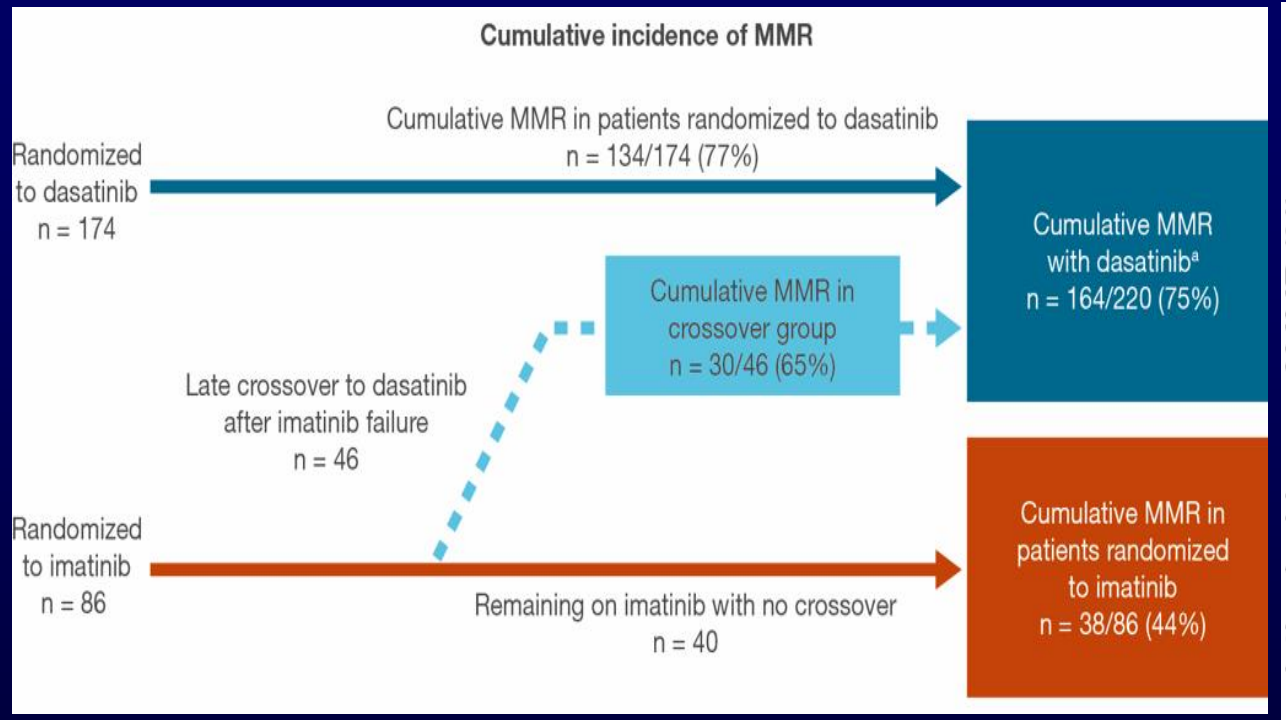
Hochhaus et al. Leukemia 2020; 34: 966-984;
NCCN Version 1.2023 – August 5, 2022 (https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf)

Benefit of TKI Treatment After Failing Milestones

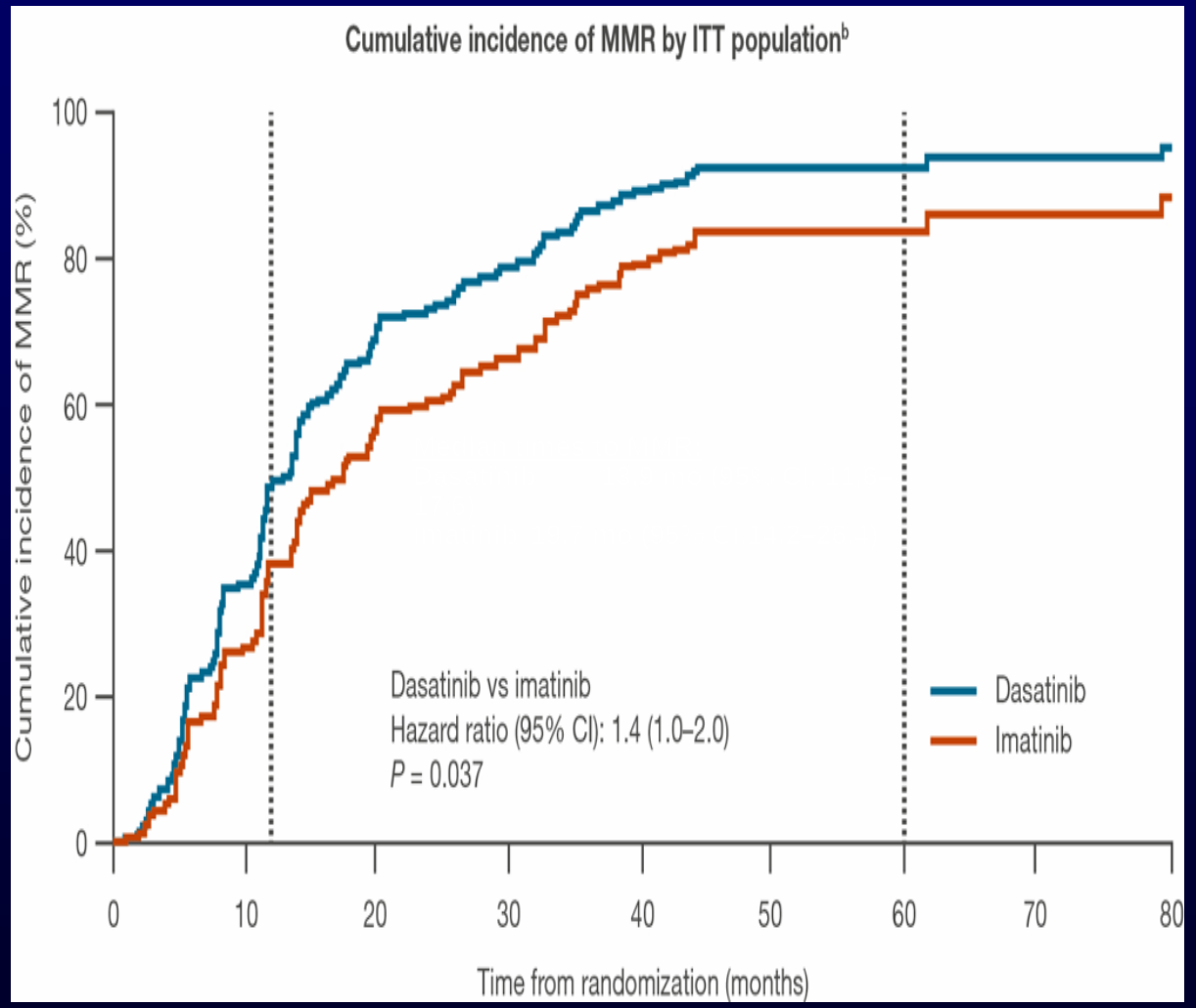


Lauseker et al. Leukemia 2023; 37: 2231–36

DASCERN - Cumulative incidence of Response



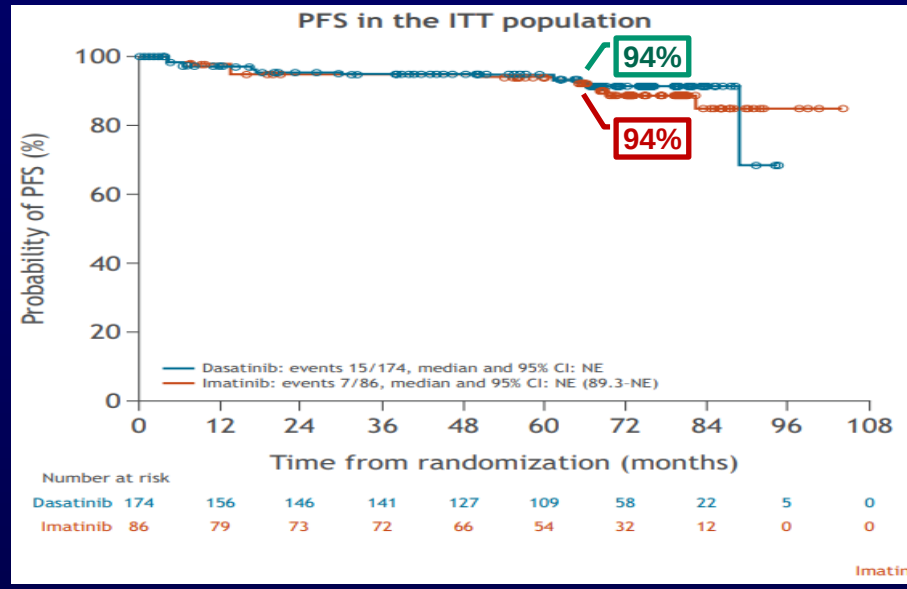
	Dasatinib	Imatinib
MR4	53	31
MR4.5	36	26

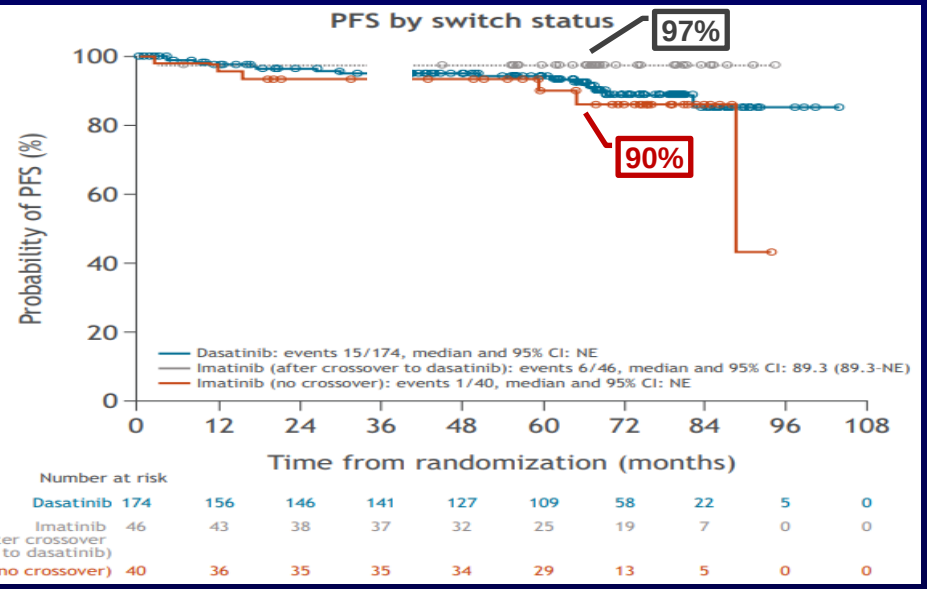


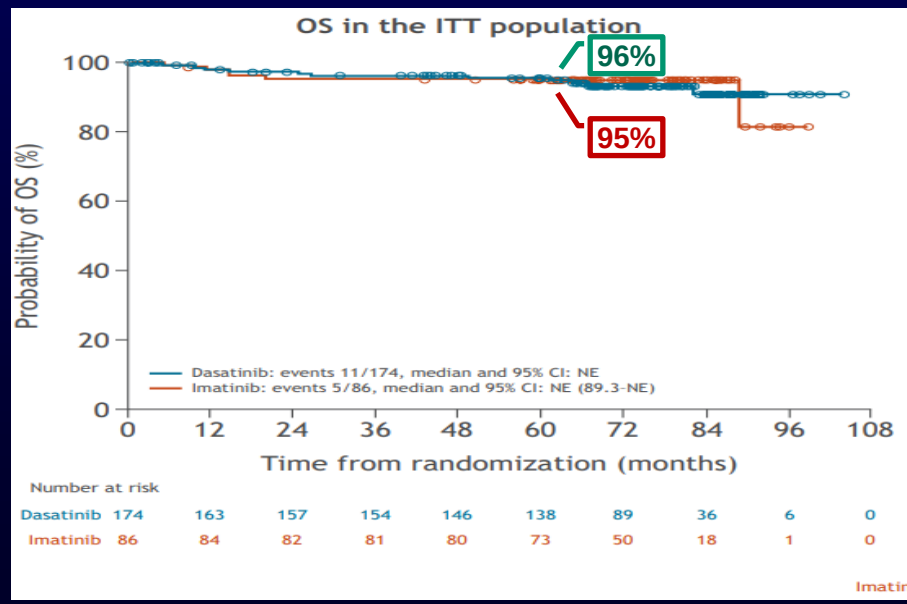
[a]Four patients achieved then lost MMR and subsequently crossed over to dasatinib; [b]The Kaplan–Meier curve accounts for competing risk and censored patients.

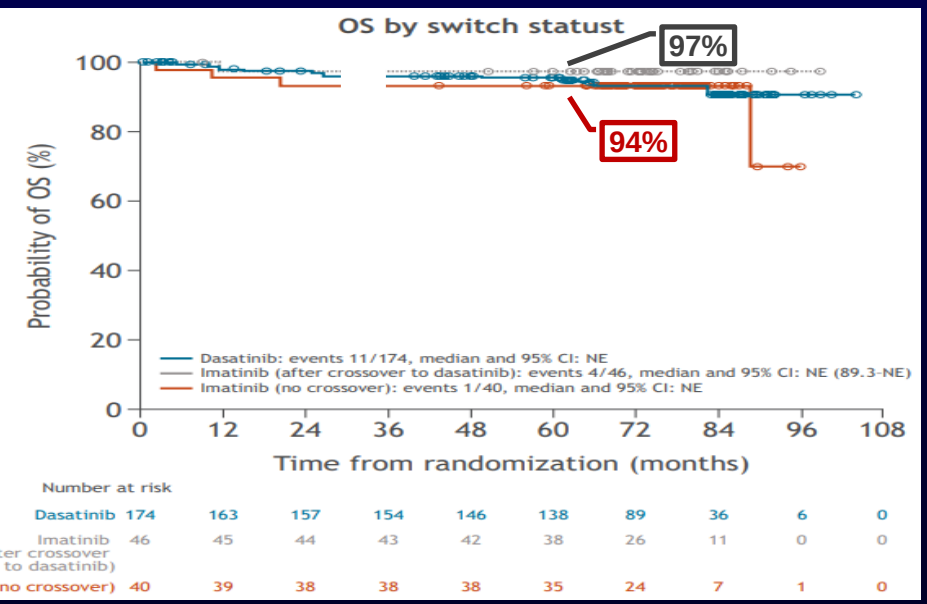
Cortes JE, et al. ASH 2022; abstract #4339

DASCERN - PFS & OS (ITT and By Switch Status)







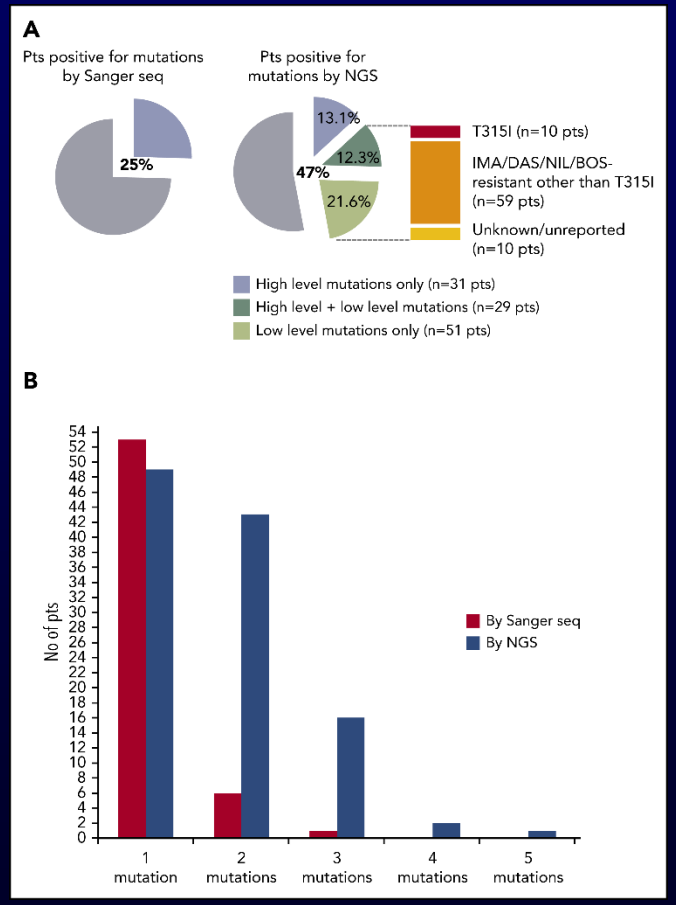


Cortes JE, et al. ASH 2022; abstract #4339

BCR-ABL1 KD mutations After TKI Failure/Warning

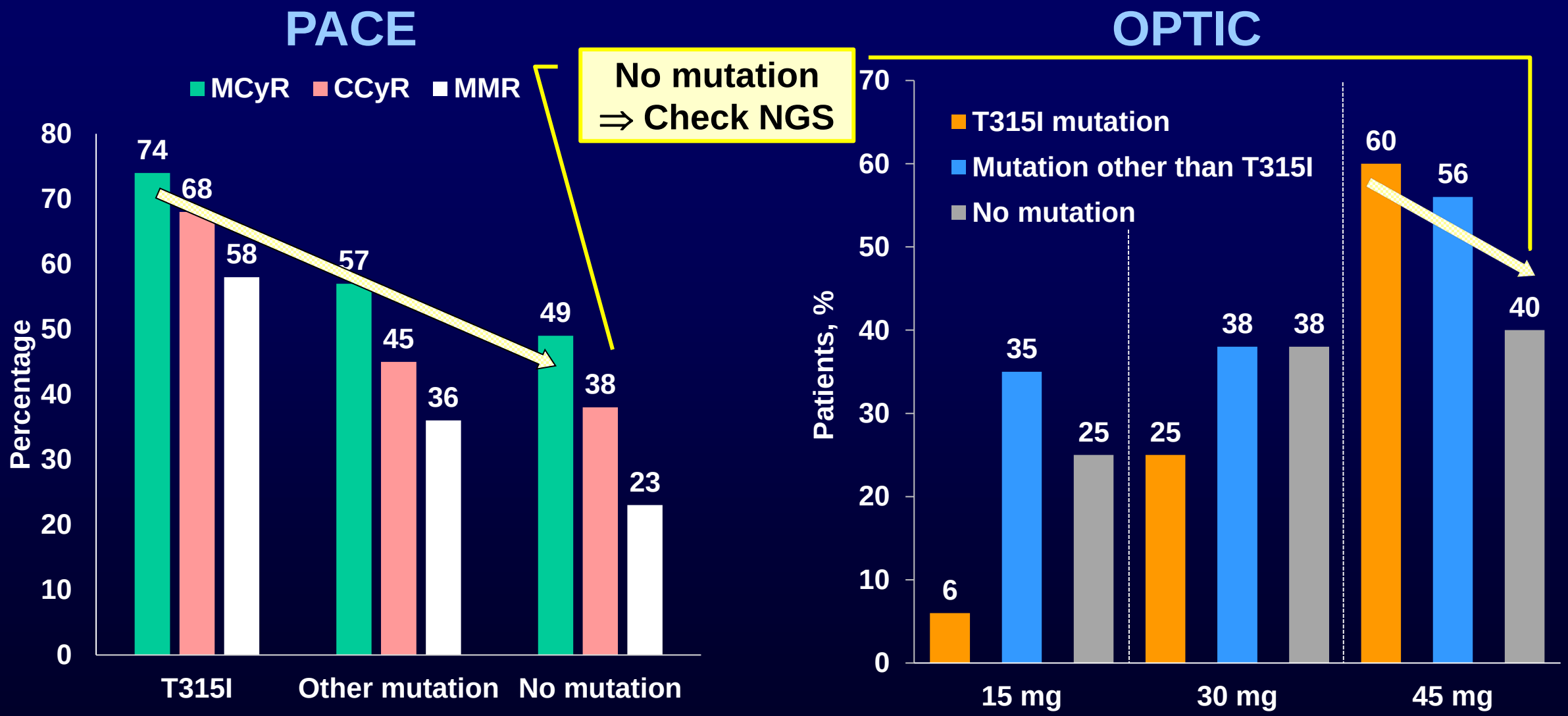
- 236 consecutive CML patients with a non-optimal response to TKI therapy, 124 (53%) failure, 112 (47%) warning

	Mutations by SS	Mutations by NGS
1st-line failure	13/57 (23)	27/57 (47)
1st-line warning	7/68 (10)	23/68 (34)
2nd-line failure	15/39 (38)	20/39 (51)
2nd-line warning	6/37 (18)	17/37 (49)
3rd-line failure	14/21 (67)	17/21 (80)
3rd-line warning	1/7	3/7
4th or 5th-line failure	4/7	4/7
Total	60/236 (25)	111/236 (47)



Soverini et al. Blood 2020; 135: 534-41

Response to Ponatinib by Mutation



Cortes et al. NEJM 2013; 369: 1783-96; Cortes et al. Blood 2021; 138: 2042-50

2nd Generation TKI in CML CP Post-Imatinib Resistance

Response	Percentage		
	Dasatinib†	Nilotinib‡	Bosutinib
FU (mo)	>24	>24	>24
CHR	89	77	85
MCyR	59	56	57
CCyR	44	41	41
24 mo PFS*	80%	64%	79%
24 mo OS*	91%	87%	92%

† 7-yr MMR 43%, PFS 42%, OS 65%; discontinued 78%
‡ 4-yr PFS 57%, OS 78%; discontinued 70%
* All patients (resistant + intolerant)

Shah et al. Haematologica 2010; 95: 232-40; Shah et al. Am J Hematol 2016; 91: 869-74
Kantarjian et al. Blood 2011; 117: 1141-45; Giles et al. Leukemia 2013; 27: 107-112
Cortes et al. Blood 2011; 118; 4567-76; Gambacorti-Passerini et al. Am J Hematol 2014; 89: 732-42

2nd-line Bosutinib in CP CML: ≥10-Year Update Efficacy Summary

- Phase 1/2 bosutinib 500 mg/d
- 284 pts: imatinib resistant 195, intolerant 89
- Median age 53 y (18-91 y), prior IFN 35%, SCT 3%

n (%)	Imatinib-resistant	Imatinib-intolerant	Total
Cytogenetic responses, n	182	80	262
MCyR	59	61	60
CCyR	48	53	50
Molecular responses, n	127	70	197
MMR	46	36	42
MR4	39	33	37
11-y probability of sustaining MMR, % (95%CI)	55 (39-70)	54 (15-93)	56 (41-71)
10-y cumulative incidence progression/death, %	29	14	24
10-y OS, %	71	73	72

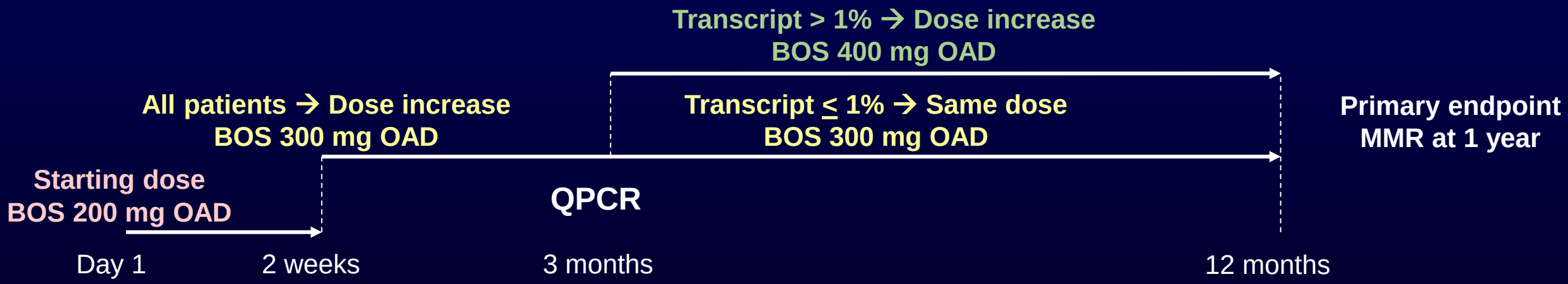
- AEs leading to treatment discontinuation (≥2%): thrombocytopenia 6%, neutropenia 2%, ↑ ALT 2%
- Vascular AEs (overall): Any grade 11%, Grade 3/4 6%

Gambacorti-Passerini et al. Haematologica 2018; 103: 1298-307; updated Brümmendorf et al. Blood 2020;136(Suppl 1): abstract #2152; Gambacorti-Passerini et al. ASCO 2021; abstract #7009

Bosutinib Dosing in Elderly Patients After First-Line TKI Therapy, Study Design

2nd-line bosutinib in resistant or intolerant patients age ≥ 60 years after any first-line TKI
N = 63

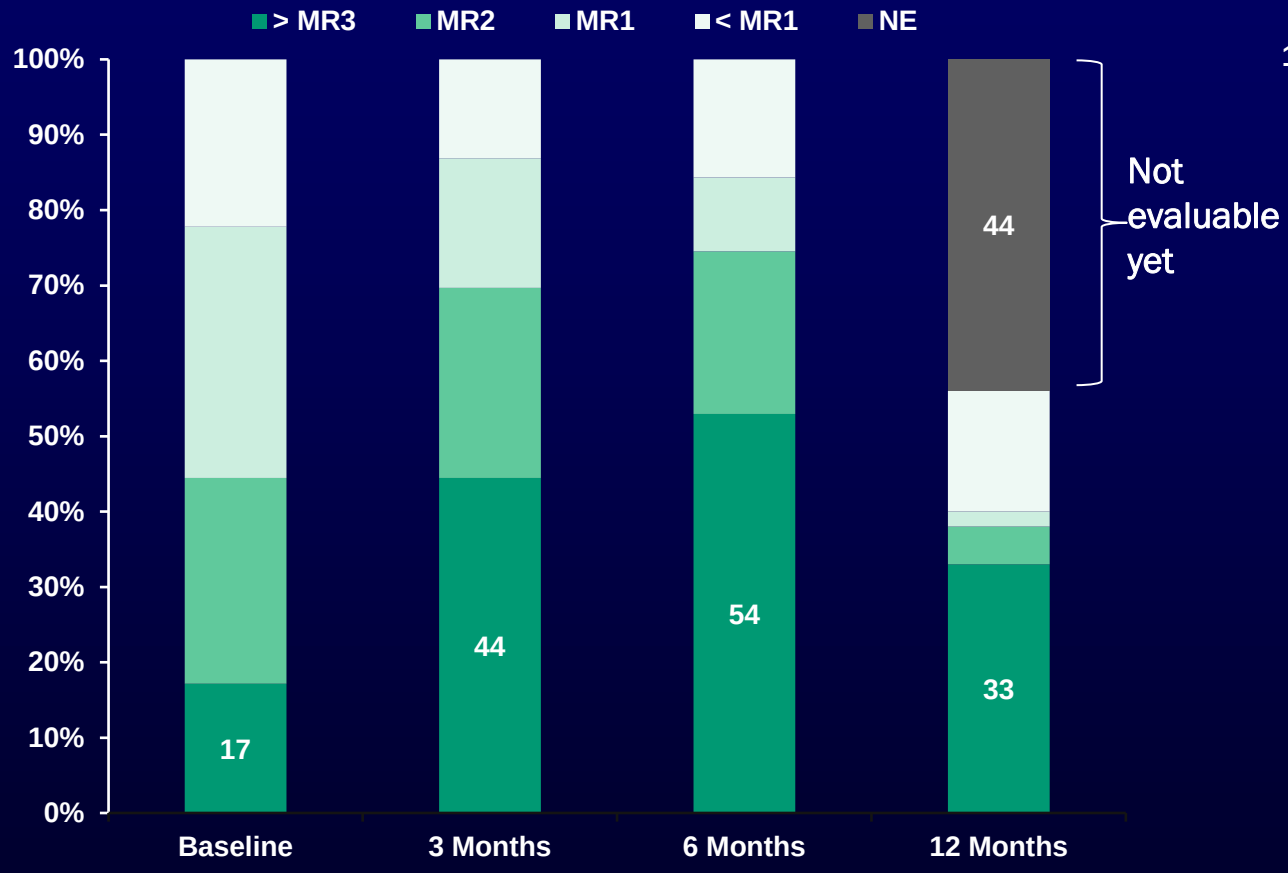
QPCR every 4 weeks until the achievement of stable MMR
In responsive patients, bosutinib dose will be maintained



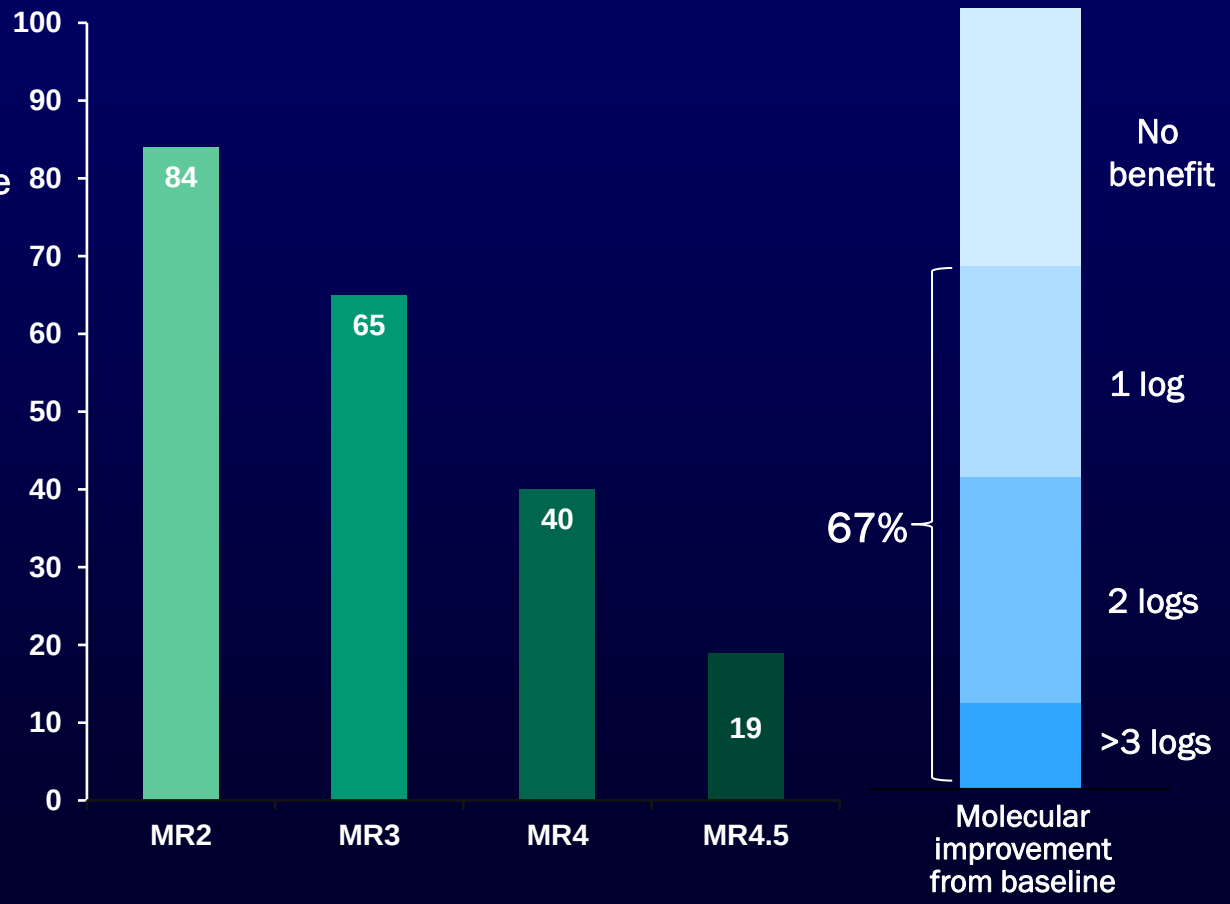
Castagnetti F, et al. ASH 2019. Abstract 496.

Bosutinib Dosing in Elderly Patients After 1st Line TKI Therapy - Response

Molecular Response at Milestones



Cumulative Incidence of Response



- Grade 3-4 diarrhea 8%, LFT 12%; 7 pts discontinued due to AEs

Castagnetti F, et al. ASH 2019. Abstract 496

The Importance of Proper Management

ASCEMBL

- Median Rx duration: asciminib 15 mo, bosutinib 7 mo
- ≥3 TKI: asciminib 48%, bosutinib 60%
- Intolerant prior TKI: asciminib 38%, bosutinib 29%
- MMR (48 wk): asciminib 29%, bosutinib 13%

Variable, n (%)	Asciminib (n=157)	Bosutinib (n=76)
Treated[a]	156 (99.4)	76 (100.0)
Treatment ongoing[b]	62	29
Discontinued treatment	38	71
Before week 24	17	33
Reason for discontinuation		
Lack of efficacy	24	32
Adverse event	5	21
Physician decision	6	8
Patient decision	3	4
Progressive disease	1	4
Lost to follow-up	1	3
Death	1	0
Protocol deviation	1	0

Rea et al. Blood 2021; 138: 2031-41

BYOND

- Median duration of therapy: 24 mo
- Intolerant (all TKIs): 47%
- MMR (1 yr): 71% (2nd 80%, 3rd 75%, 4th 56%)

	Line of Treatment			Total N=156
	2nd n=46	3rd n=61	4th n=49	
Rx duration, median, mo	26	24	12	23.7
Dose intensity, median, mg/d	320.1	309.4	308.0	313.1
Terminated by sponsor, %	7	3	8	6
Treatment discontinuation, %	33	46	51	44
Adverse events	22	26	27	25
Related to study drug	13	20	24	19
Not related to study drug	9	7	2	6
Other	9	15	14	13
Lack of Efficacy	2	3	10	5
Death	0	2	0	1

Hocchaus et al. Leukemia 2020; 34: 2125-37

When Do I Change Therapy?

I do:

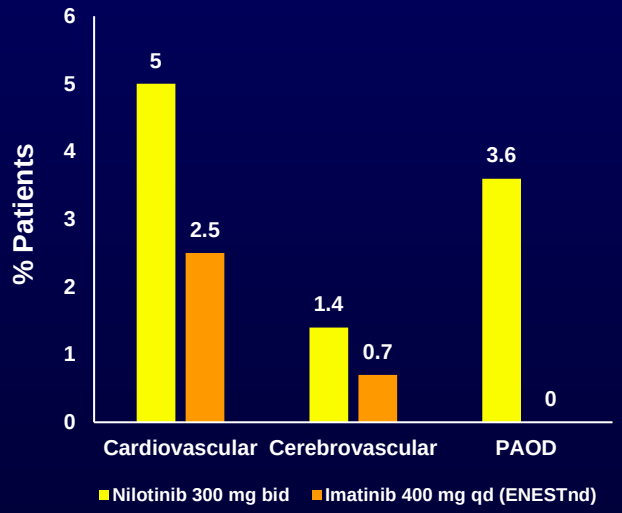
- **ELN failure (mostly)**
- **Loss of CCyR**
- **Intolerance (true)**

I don't:

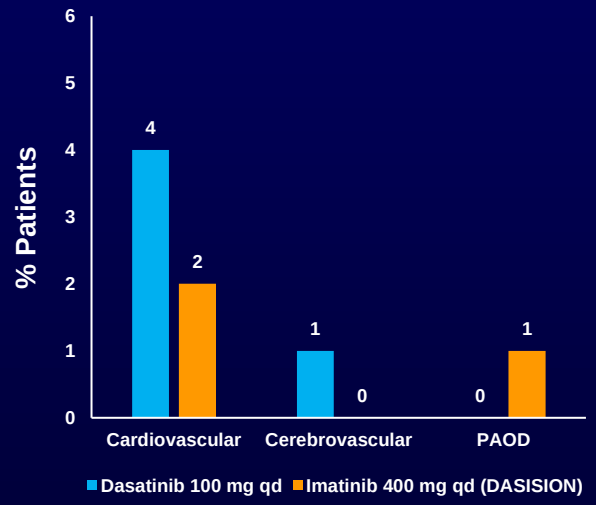
- **3 mo >10%**
- **Increase in PCR (unless loss CCyR)**
- **PCR still detectable or most instances of lack of DMR**
- **1st instance of AE (few exceptions)**

Ischemic Events by TKI From Randomized Trials at 5 years

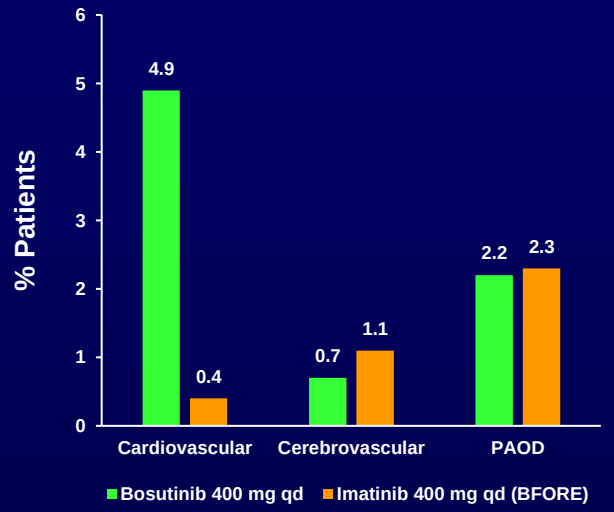
ENESTnd[1]



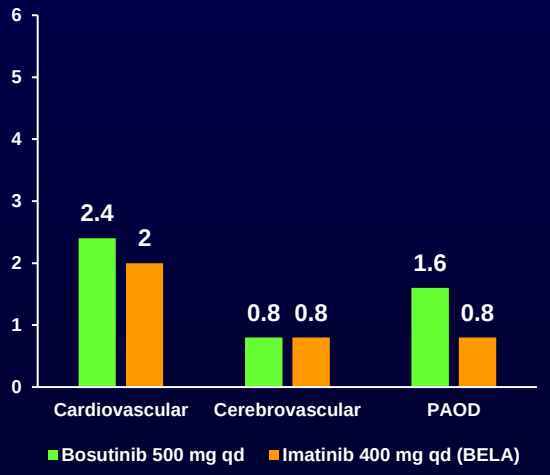
DASISION[2]



BFORE[3]



BELA[4]



[1]Hochhaus et al. Leukemia 2016; 30: 1044-54; [2]Cortes et al. JCO 2016; 34: 2333-40; [3]Brümmendorf et al. ASH 2020; abstract #46; [4]Cortes JE, et al. Am J Hematol. 2016; 91(6):606-616

Ponatinib Adjudication: Retrospective Review of AOEs, VTEs, and Deaths by an Independent Endpoint Adjudication Committee

Independent Adjudication Committee (Blind to dose, dose modification, and investigator causality opinions)

3 x cardiologists

1 x neurologist

1 x vascular specialist

Methodology

Retrospectively review all AOEs, VTEs, associated heart failure outcomes, and deaths in a standardized, rigorous fashion, using American College of Cardiology/American Heart Association (ACC/AHA) definitions

Outcome

Adjudication Committee reviewed all events and classified AOEs vs not AOEs; adjudicated AOEs were considered true MACE events

Case-based Adjudication Analysis

An event is positively adjudicated if the clinical profile contains details consistent with the charter-specified event definition, including, but not limited to:

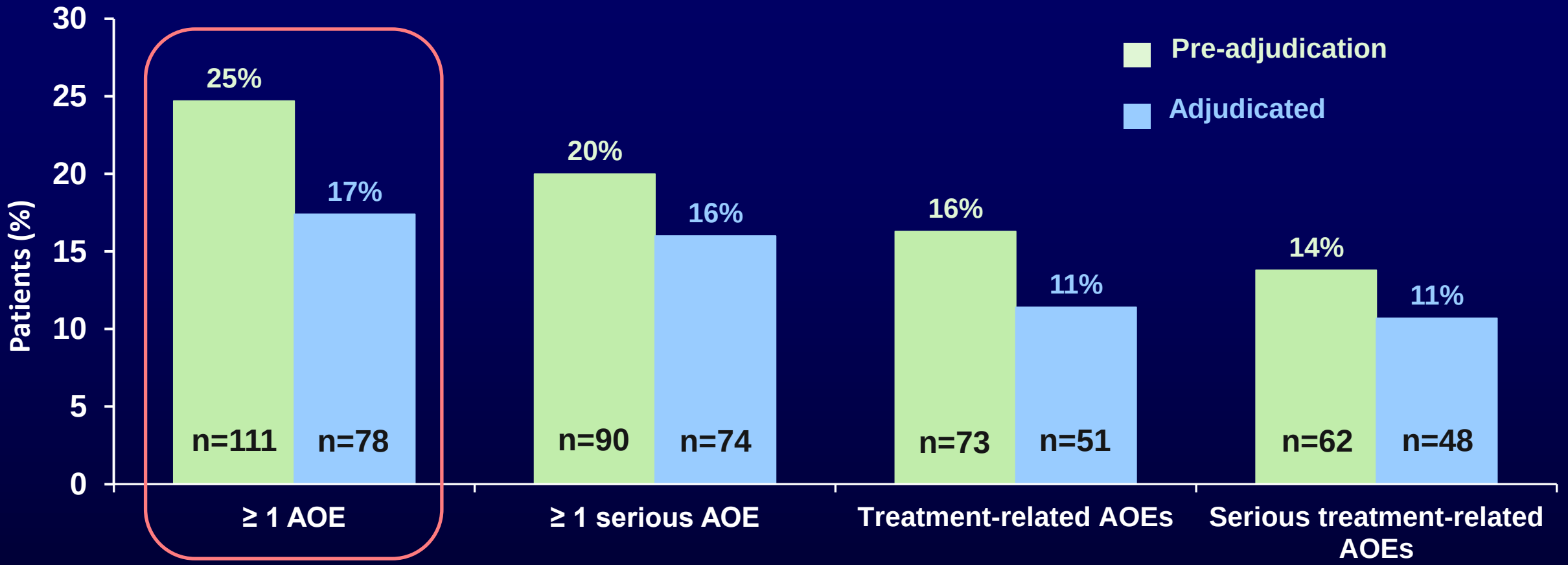
- a change in medication(s)
- medical or surgical intervention
- imaging
- hospitalization
- presence of any changes related to a CV event, or association with a serious or severe event

Similar methodologies have been used to support multiple label updates of other products

AOE, arterial occlusive event; MACE=major adverse cardiac event; VTE, venous thromboembolism

Januzzi et al. J Hematol Oncol 2022; [Epub ahead of print]

PACE 5-Year Adjudication - All patients



- 490 events[a] identified using the Adjudication Committee criteria[b]
- 258/490 (53%) were adjudicated as <u>not</u> AOEs
  - 44% of these events comprised angina pectoris, cardiac chest pain, and non-cardiac chest pain

[a]Fatal and non-fatal

[b]Number of PTs in Broad Plus search strategy was broader than the Nov 2016 USPI (>600 terms)

*Symptomatic, low severity, and commonly non-serious terms that represent symptoms and do not represent a diagnostic condition associated with drug-induced arterial occlusion, i.e. Raynaud's phenomenon, peripheral coldness, chest discomfort, non-cardiac chest pain

Januzzi et al. J Hematol Oncol 2022; [Epub ahead of print]

Monitoring and Management of CV Risk

	Monitoring and management	Comment
A	Risk assessment	At baseline & throughout TKI therapy
	Antiplatelet therapy	No available data in context of TKIs; consider bleeding risk (e.g., dasatinib)
B	Blood pressure	Monitor and manage optimally; ponatinib associated with high blood pressure (also other TKIs?)
C	Cholesterol	More frequently elevated with nilotinib.
	Cigarette/tobacco cessation	
D	Diet & weight management	Rule out (and manage) weight gain from fluid retention
	Diabetes prevention & management	Hyperglycemia more common with nilotinib; lower glucose levels with imatinib
E	Exercise	May help manage fatigue

Adapted from Hsu S, et al. Clin Cardiol. 2013;36:383-393

DLT and Real Life

TKI	DLT	Dose	What matters
Imatinib	None reported	Up to 1000 mg	CHF
Nilotinib	Bilirubin (9), ALT, lipase (1), lipase and amylase (2), hematologic (2), subdural hematoma (1)	>600 mg	AOEs Metabolic syndrome
Dasatinib	None (5 PI eff, all grade 1-2)	Up to 240 mg	Pleural effusion, pulmonary hypertension, AOEs
Bosutinib	Diarrhea, rash	At 200, 300 and 500 mg (1 each); 3/10 at 600 mg	Liver
Ponatinib	Pancreatic enzymes/pancreatitis (4), fatigue (1), ALT (1)	45 mg	AOEs Liver Skin
Asciminib	Lipase (2), myalgia/ arthralgia (1), acute coronary syndrome (1), bronchospasm (1)	At 40, 40, 80, 150 and 200 mg	AOEs

Druker et al. NEJM 2001; 344: 1038-42; Kantarjian et al. NEJM 2006; 354: 2542-51; Talpaz et al. NEJM 2006; 354: 2531-41; Daud et al. Clin Cancer Res 2012; 18: 1092-100; Cortes et al. NEJM 2012; 367: 2075-88; Hughes et al. NEJM 2019; 381: 2315-2326

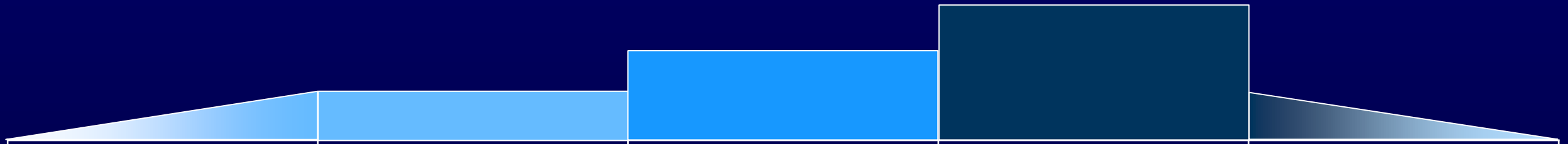
Significance of Dose Adjustments of 2nd Generation TKI in Frontline Therapy

- 98 pts treated with nilotinib 400mg BID (n=50) or dasatinib 50 mg BID or 100 mg QD (n=48) as initial therapy fro CML CP
- Dose reductions in 50 (51%) (nilotinib 42%, dasatinib 60%)

	Percentage	
	Dose reduction	No dose reduction
MCyR	94	88
CCyR	92	88
2-yr FFS	72	83
2-yr OS	100	100

Santos FP, et al. *Br J Haematol.* 2010;150(3):303-312.

Dose Recommendations for TKI



Ramp up	Lower than standard	Standard	Higher than standard	Taper down
• Bosutinib • Multi-intolerant (myelo-suppression)	• 1L Dasatinib • 2+L Intolerant • Very high AOE risk Ponatinib	• Most others • Ponatinib F359, Q252, E255	• Asciminib with E355G, Q252H or F359V	• Prior to TFR • Ponatinib after BCR::ABL1 <1% • All others after response?

Requirements for TKI Discontinuation – ELN & NCCN 2020

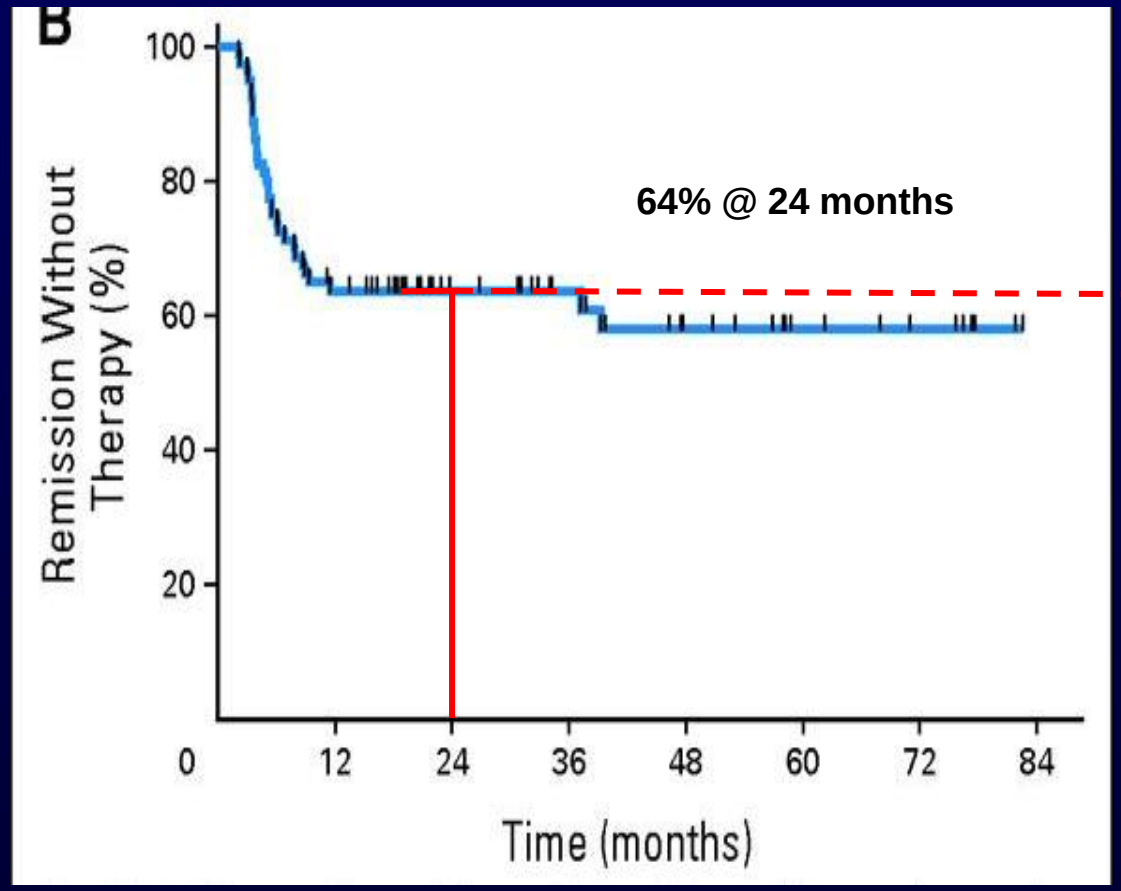
ELN	NCCN
CML 1st CP only (Mand)	CP CML. No history of AP or BP
TKI therapy >5 y (>4 y for 2GTKI) (Min)	On approved TKI ≥3 y
e13a2- or e14a2-BCR–ABL1 transcripts (Min)	Prior evidence of quantifiable BCR-ABL1 transcript.
Duration DMR (MR4 or better) >2 years (Min)	MR4 for ≥2 years (≥4 tests, performed ≥3 mo apart)
Access to high quality quantitative PCR using IS with rapid turn-around for results (Mand)	Access to a reliable qPCR test with sensitivity of at least MR4.5 IS and that provides results within 2 wks.
Patient's agreement to more frequent monitoring after stopping. Monthly for the 1st 6 mo, every 2 mo for mo 6-12, and every 3 mo thereafter. (Mand)	Monthly molecular monitoring for 6 m, then every 2 mo for the 6 m, and every 3 mo thereafter (indefinitely) is recommended.
Motivated patient with structured communication (Man)	Age ≥18 years
1st-line therapy or 2nd-line if intolerance was the only reason for changing TKI (Min)	Prompt resumption of TKI within 4 wks of loss of MMR with monthly monitoring until MMR. If fail to achieve MMR after 3 mo of resumption, mutation testing continue monthly molecular monitoring for another 6 mo.
No prior treatment failure (Min)	

Hochhaus et al. Leukemia 2020; 34: 966-984; NCCN Version 3.2021 – January 13, 2021 (https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf)

Treatment-Free Remission in CML

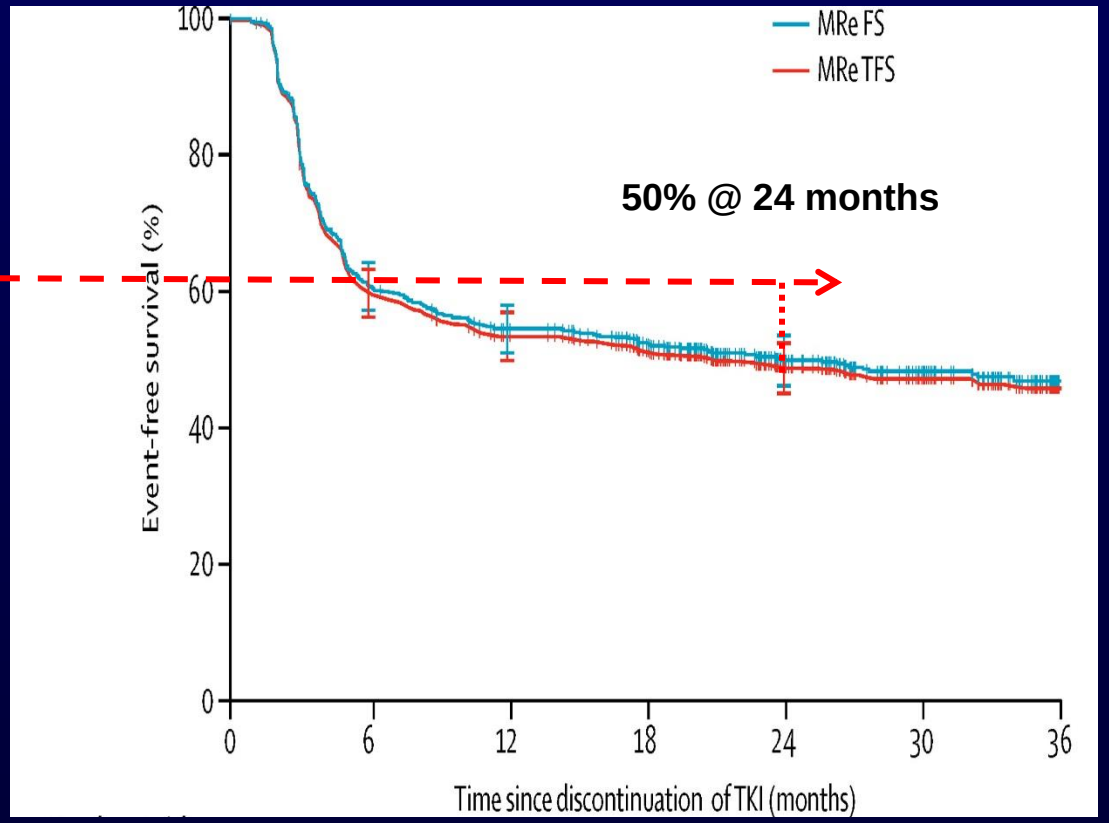
A-STIM

- MR4.5
- ≥2 years



EURO-Ski

- MR4
- ≥1 years

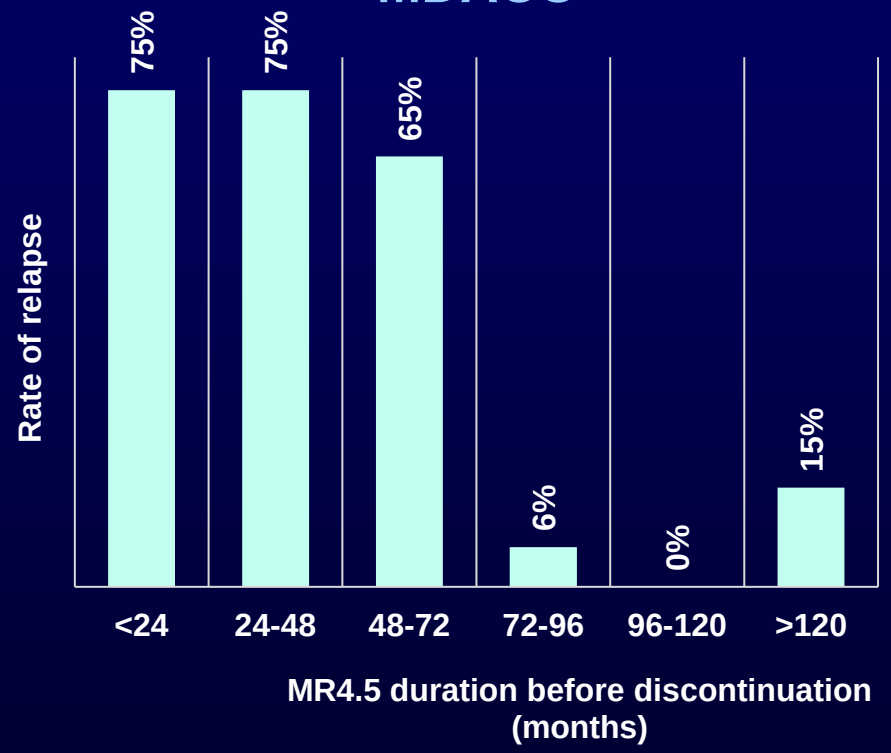


- Occasional relapse in BP (probably <1%) (Alfayez et al. *Br J Hematol* 2019;187:543-545; Rea D, et al. ASH 2019; abstract #30)

Rousselot et al. JCO 2014; 32: 424-30; Saussele et al. Lancet Oncol 2018; 19: 747-757

How to Improve TFR Success? – Wait Longer

MDACC[1]



- MVA: $MR^{4.5}$ duration >72 mo before discontinuation only predictor for durable response (p < 0.001, HR 0.08 [CI 95%, 0.02- 0.27])

EURO-SKI[2]

Years DMR	n/N	% (95% CI) without relapse
1–2	13/28	46% (28–66)
>2 to ≤3	17/31	55% (36–73)
>3 to ≤4	22/37	59% (42–75)
>4 to ≤5	11/17	65% (38–86)
>5 to ≤6	14/20	70% (46–88)
>6 to ≤7	9/15	60% (32–84)
>7	15/23	65% (43–84)

Yearly increase of ~3% in the probability of staying in MMR at 6 months over the observed range of DMR durations.

Chamoun et al. J Hematol Oncol 2019; 12: 1-10; Saussele et al. Lancet Oncology 2018; 19: 747-57

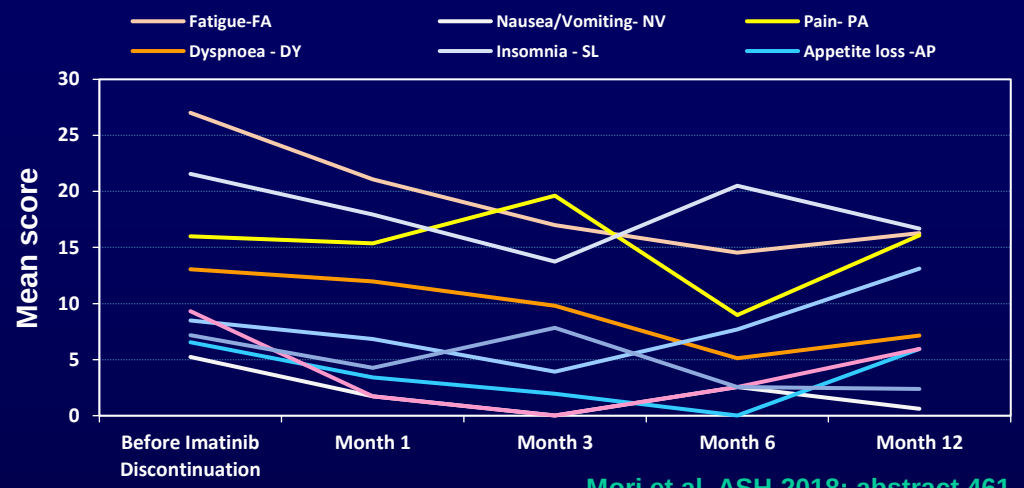
ENESTcmr 48-Month Update

- 207 pts with CML CP treated with imatinib ≥2 years, in CCyR with persistent disease by PCR
- Randomized to continue imatinib vs change to nilotinib.
- MR4.5 @48 mo:
  - Nilotinib: 54%
  - Imatinib: 32% (excluding crossover)
- AOEs:
  - Niloitinib: 13% (2 deaths, 1 from MI, 1 cardiopulmonary failure)
  - Imatinib: 2%
- Switching to nilotinib:
  - 1.68x higher probability of x MR4.5, *but*
  - 6.5x higher probability of AOE (some fatal) → A good trade-off?

Hughes et al. Leukemia 2017; 31: 2529-31

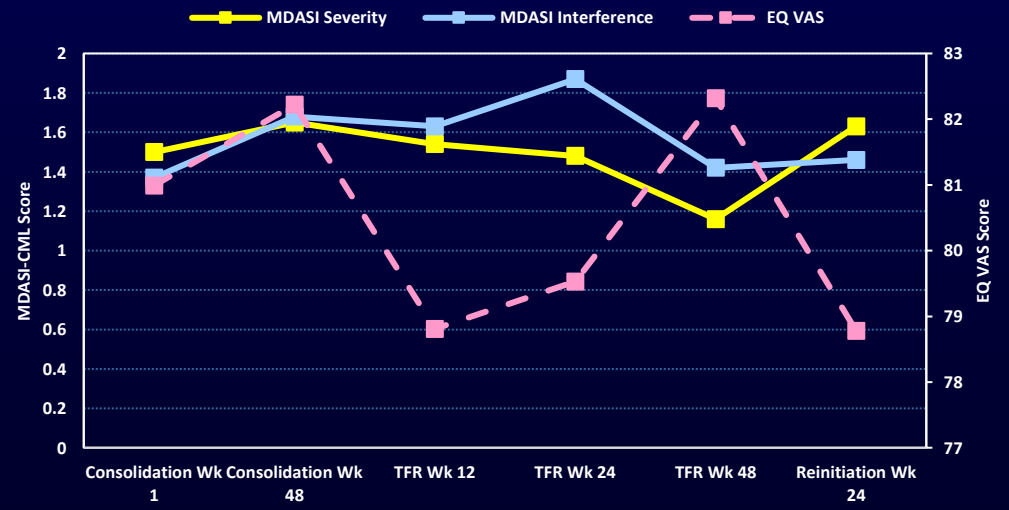
PRO After TKI Discontinuation

ISAV



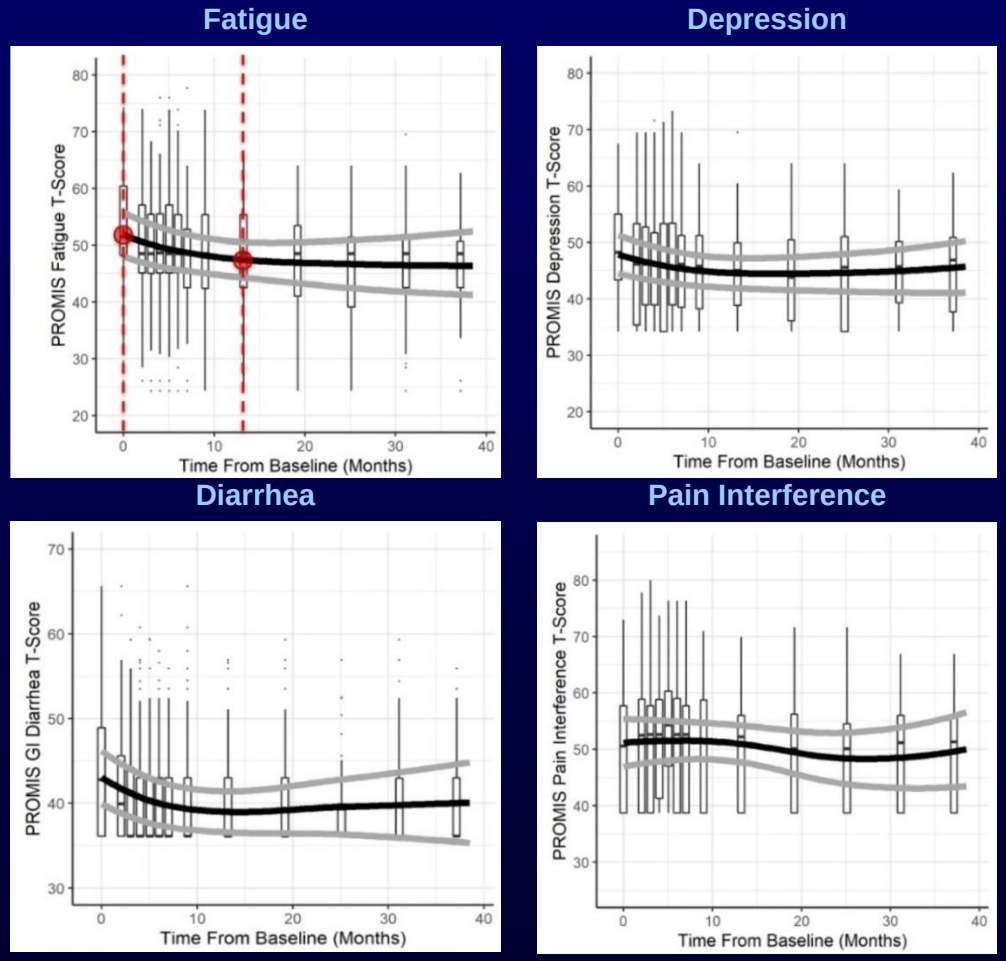
Mori et al. ASH 2018; abstract 461

ENESTstop



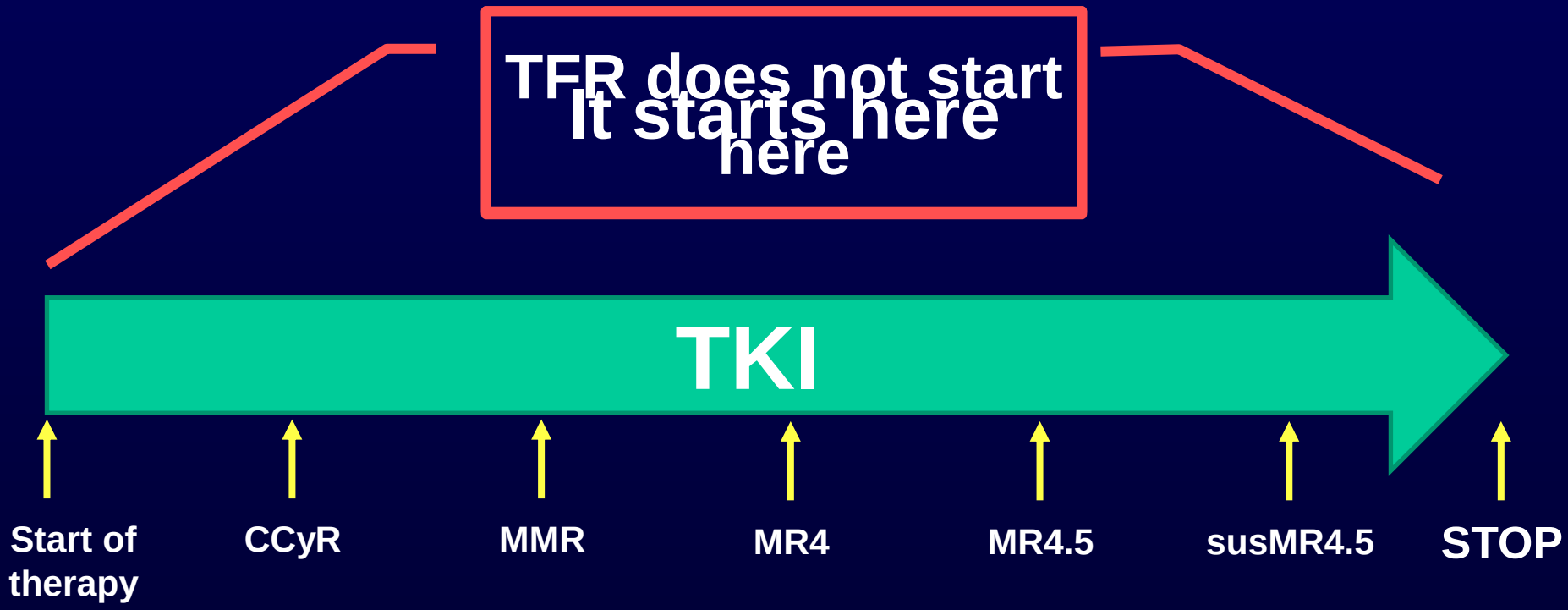
Mahon et al. ASH 2016; abstract #1891

The LAST Trial



Flynn KE, et al. ASH 2019. Abstract 705.

TKI TFR


TFR does not start here
It starts here
TKI
Start of therapy
CCyR
MMR
MR4
MR4.5
susMR4.5
STOP

Adherence to Imatinib

- 87 pts on imatinib for ≥2 years
- Compliance measured by : self reporting, pill count and microelctronic monitoring system (MEMS)

Response	% Response at 6 yrs by Adherence Rate		P value
	>90% N=64	≤90% N=23	
MMR	94	14	<0.0001
CMR	44	0	0.002

- Poor correlation between 3 methods
- MVA for molecular response: adherence (MMR and CMR) and OCT1 (CMR)

Marin et al. JCO 2010; 28: 2381-8

How Do I Approach TFR?

- Start from the start:
  - Educate
  - Aim for best outcome
  - Monitor closely
- 5-year sustained MR4.5 (ideally undetectable ~MR5)
- Monitor: Q1 mo x6, Q2 mo x3, Q3 mo x4, Q6 mo forever (too much?)
- Resume if loss of MMR (or close to it)
- Never if BP
  - 2nd line, AP: maybe

I stop therapy before I start therapy

Management of Pregnancy and CML

- 20 unplanned pregnancies
  - Status at pregnancy: CHR 2, CCyR 3, MMR 6, MR4.5 9
  - Treatment during pregnancy: none 18, hydroxyurea 1, leukapheresis 1
  - Outcome: live birth 11, miscarriage 5, elective termination 3, ongoing 1
  - Response last F/U: MR4.5 10, MMR 7, CCyR 3
- 14 CML diagnosis during pregnancy
  - Treatment: None 5, hydorxyurea 5, IFN 2, leukapheresis 1, TKI 1 (@ 3rd trimester)
  - Pregnancy outcomes: live birth 5, miscarriage 2, elective termination 1
  - Response: MR4.5 = 6, MMR = 7, 1 NR (had received IFN, nor response to dasatinib → BP)
- 9 planned pregnancies (6 CMR pre-conception)
  - 2 ↑ transcripts → observation, 1 lost CHR → hydrea → dasatinib after delivery (MR4)
- No treatment in 25/37 (68%) of eligible patients

Assi et al. ASH 2017, abstract #2881

What I Do

- Bone marrow at diagnosis
- Believe in AP
- Use 2GTKI in nearly all patients (B>N>D)
- Monitor every 3 mo for ~12 mo; then every 6 months
  - Every 3 mo if I change doses
- Aim for MR4.5
  - Accept MMR
- Manage AEs before change
- Monitor and manage co-morbidities (BP, lipids, HgA1c)
- Prefer 6 yrs of MR4.5 before attempt at TFR

What I Do Not

- Change at 3 months
- Change for lack of MR4.5
- Change for AEs without optimal management (few exceptions)
- Avoid a useful drug for fear of side effects
- Stop therapy without sMR4.5 ≥2 years
- Use IFN in pregnancy (or hardly ever anything else)

26th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy

Prague, Czech Republic
September 27-29, 2024
#ESHCML2024

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jorge.cortes@augusta.edu
706-721-0570

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY