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Optimal Dose of TKI's

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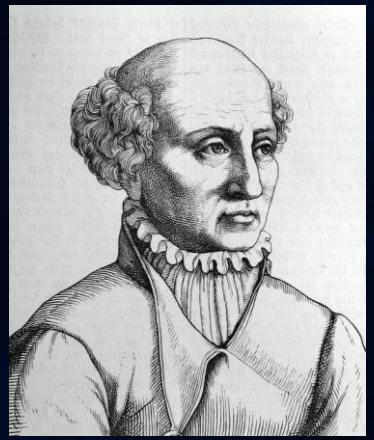
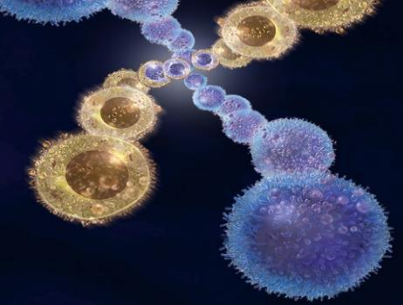
„sola dosis facit venenum“

Paracelsus 1493-1541
Swiss philisopher and botanist



Basic principle of toxicology.

Meaning:
All things are poison and nothing is without poison;
only the dose makes a thing not a poison.



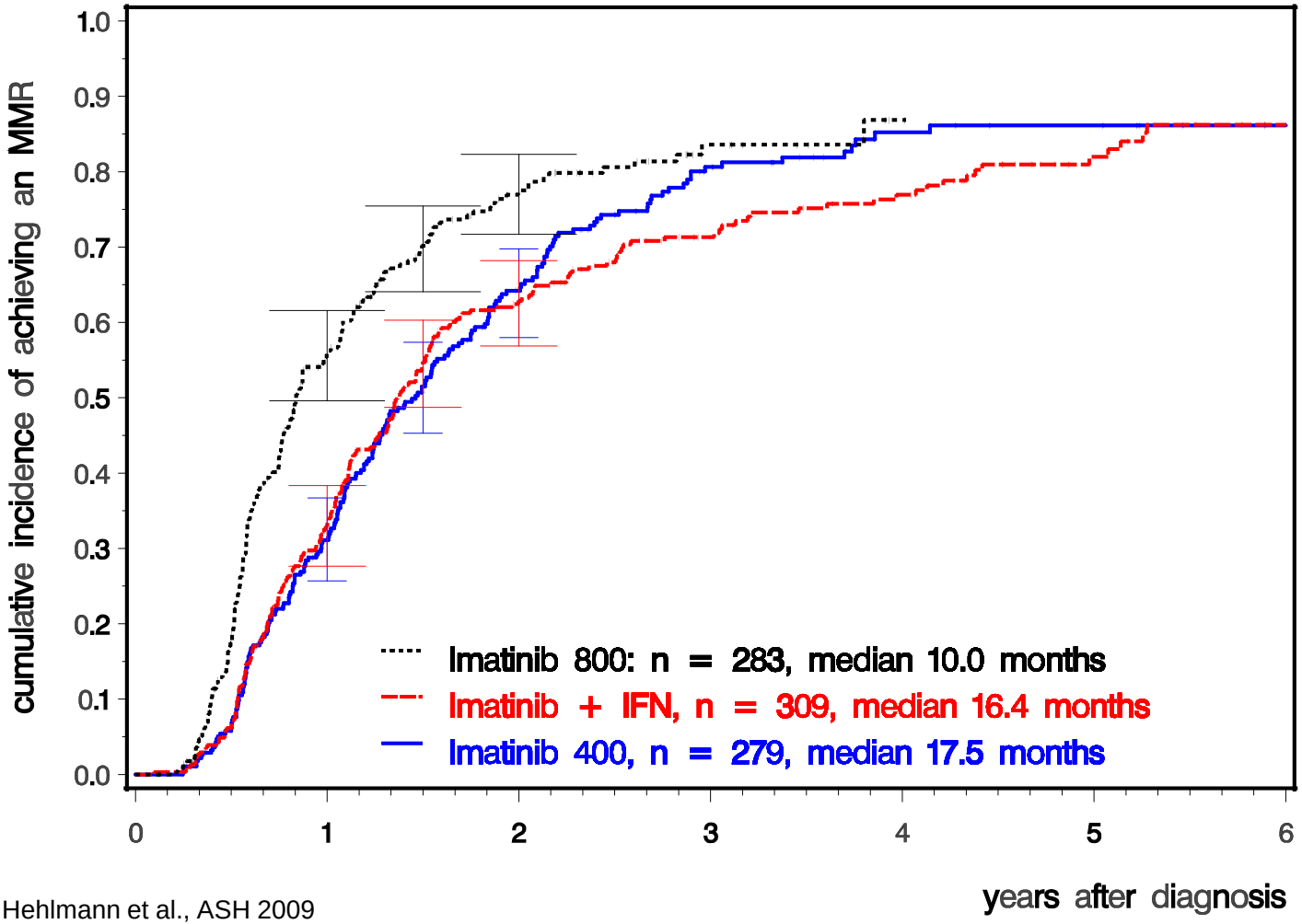
Main messages to doctors treating CML patients

- First, think about the antileukemic effect
- Second, know the toxicity profile of all the drugs you could use
- Third, think about previous comorbidities
- Any adverse event adds up on comorbidity

What is the right dose?

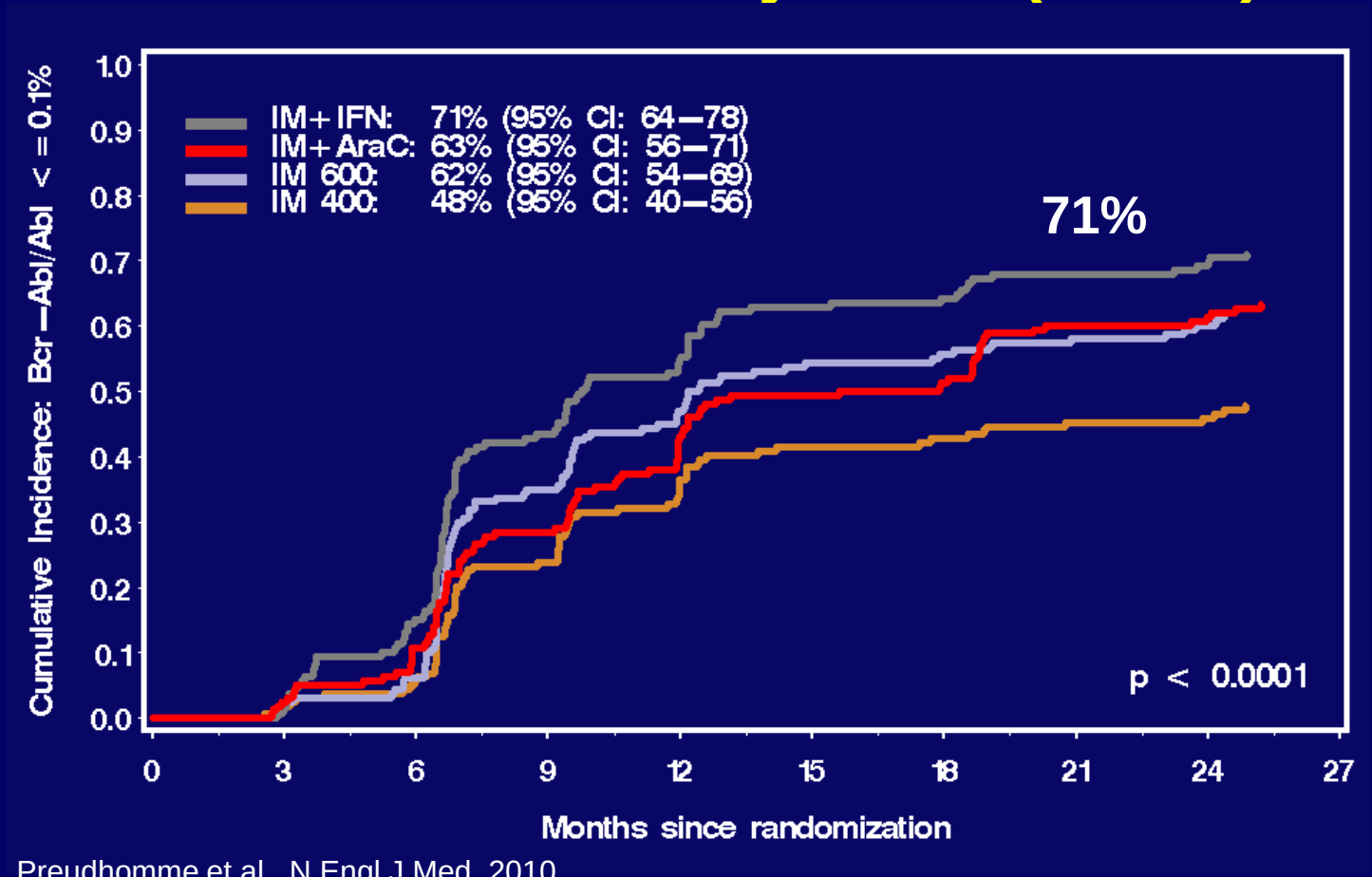
Drug	Salvage			Frontline		
	Initial approval	Current	Should be	Initial attempt	Approved	Should be
Imatinib	400 mg QD	400 mg QD	600-800 mg QD?	400 mg QD	400 mg QD	600-800 mg QD
Dasatinib	70 mg BID	100 mg QD	50-100 mg QD?	100 mg QD	100 mg QD	50-80 mg QD? 5 days/w.?
Nilotinib	400 mg BID	300-400 mg BID	300-400 mg QD?	300-400 mg BID	300 mg BID	300 mg BID
Bosutinib	500 mg QD	500 mg QD	400 mg QD?	500 mg QD	400 mg QD	400 mg QD
Ponatinib	45 mg QD	45→15 mg QD	45→15 mg QD	45 mg QD	--	--

CML IV: Time to MMR



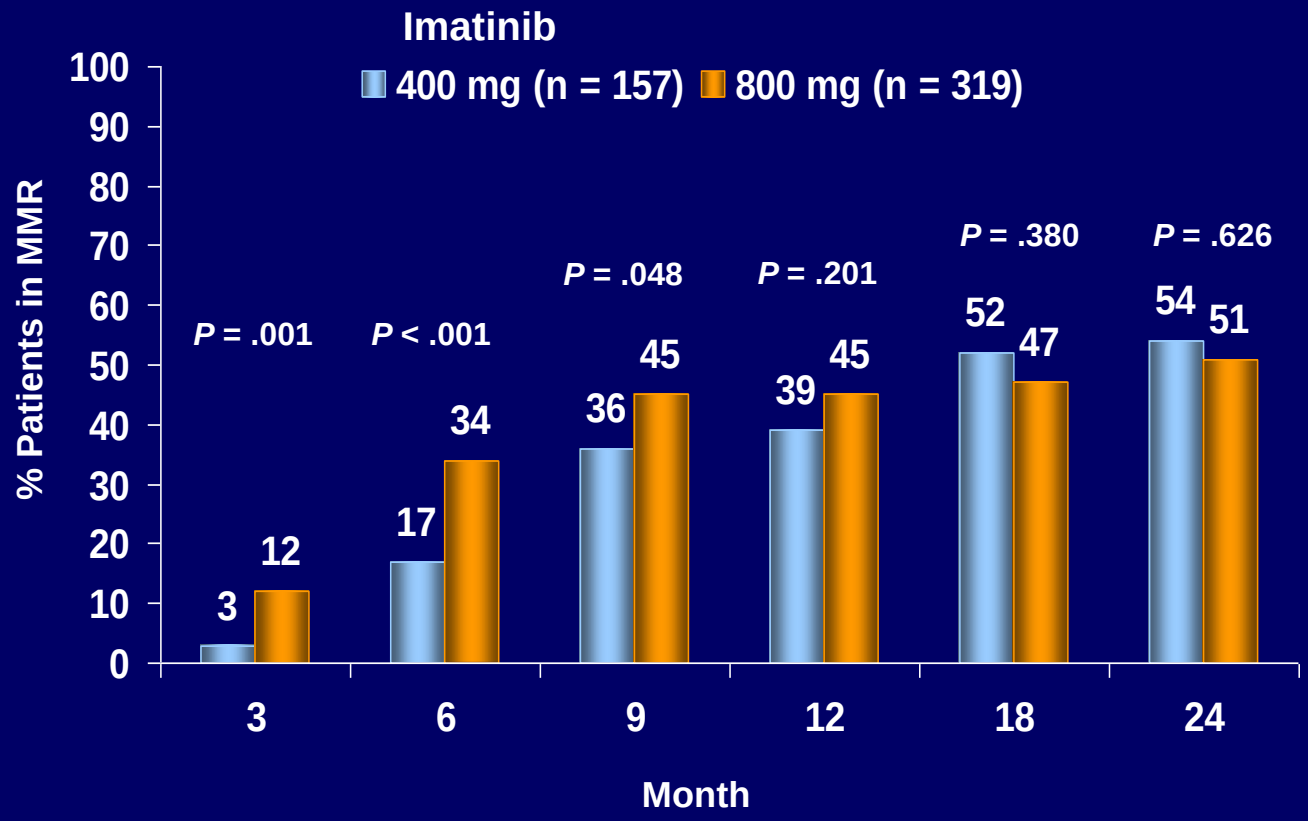
Hehlmann et al., ASH 2009

French SPIRIT-Study: MMR (n=636)



Preudhomme et al., N Engl J Med, 2010

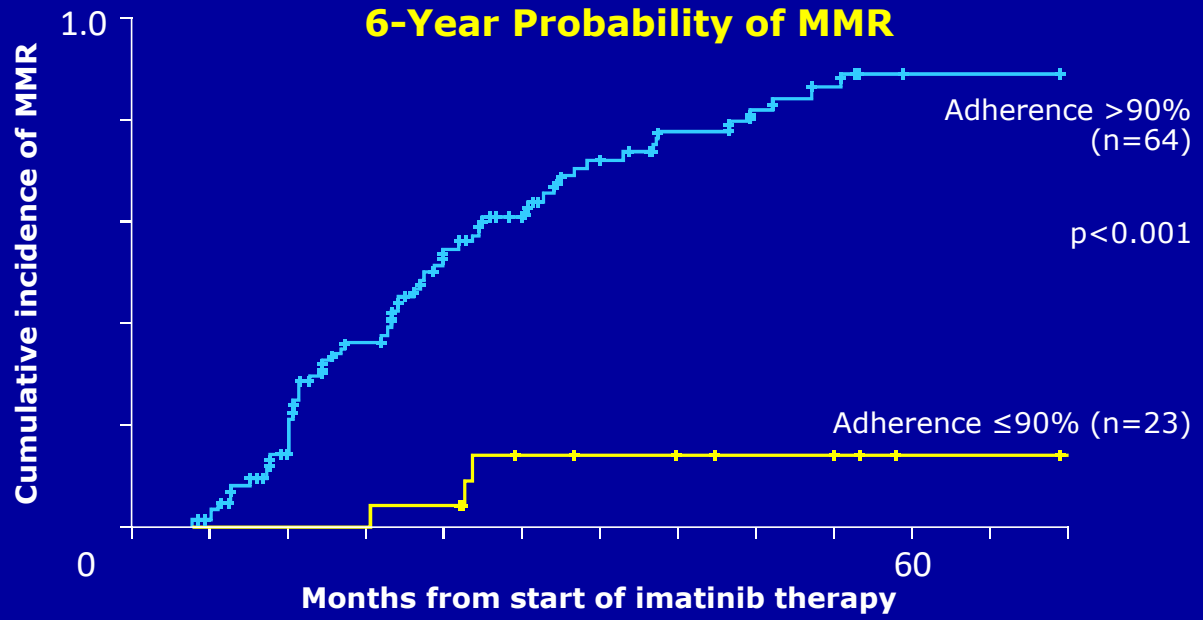
High vs. regular dose imatinib – TOPS trial: MMR over time



Cortes et al., J Clin Oncol 2010

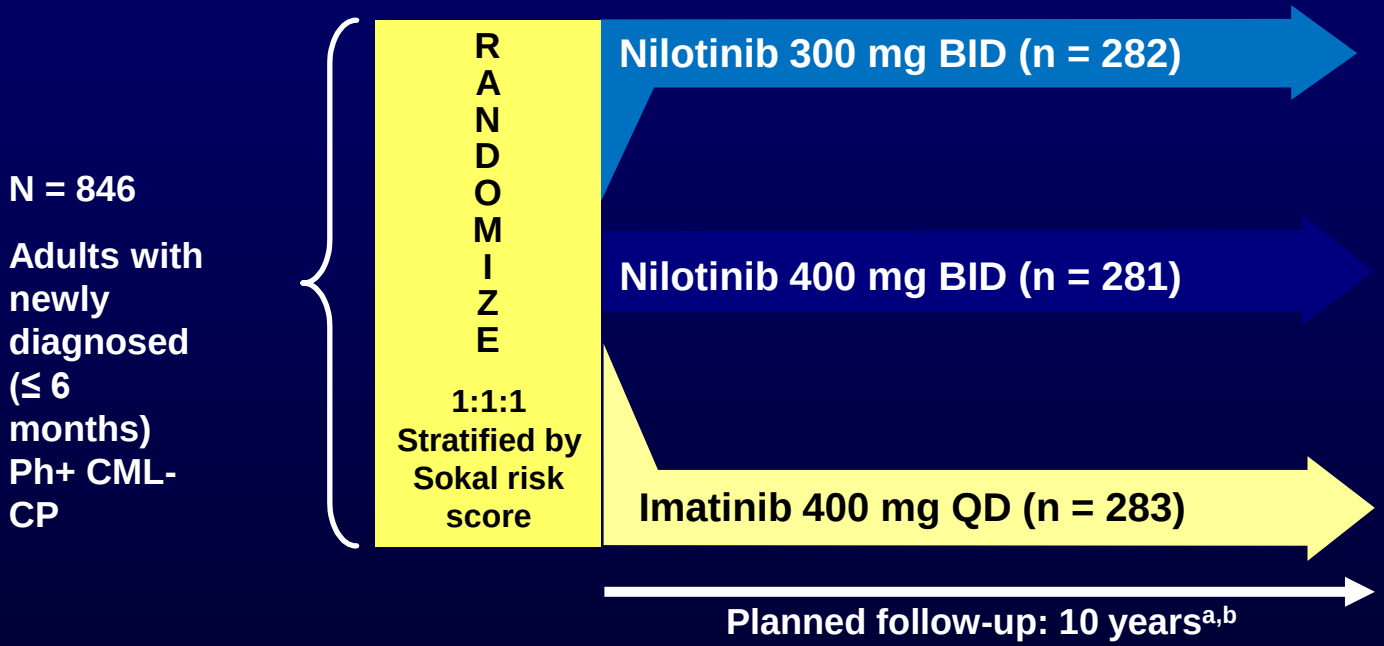
Adherence and Achievement of MMR

- **Poor adherence to therapy significantly reduced molecular response rates for patients (N=87) with CML-CP treated with imatinib**



Marin et al. JCO. 2010;28:2381–2388.

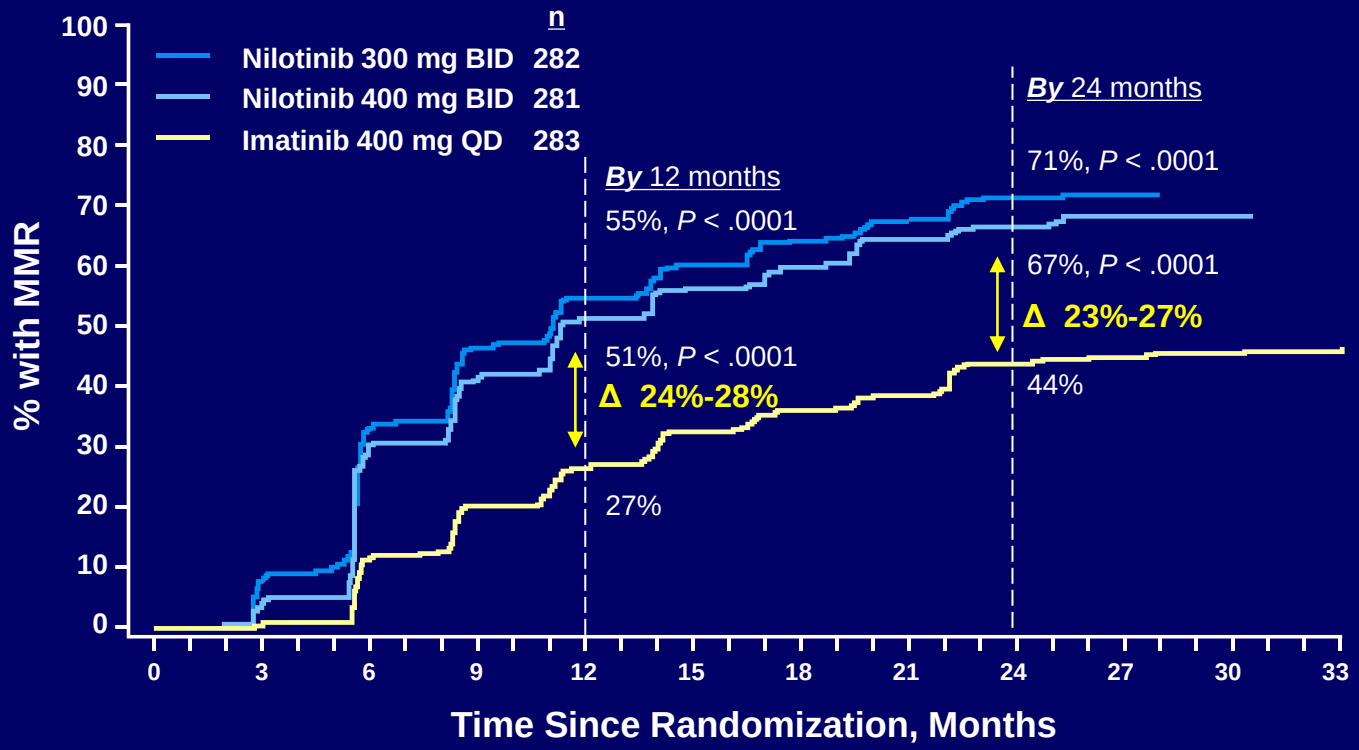
ENESTnd: Nilotinib vs. Imatinib



[a] The ENESTnd study protocol originally called for 5 years of follow-up, which was later extended to 10 years.

[b] Patients randomized to nilotinib 300 mg BID or imatinib who experienced suboptimal response or treatment failure could discontinue core treatment and enter an extension study in which they received nilotinib 400 mg BID. Patients randomized to nilotinib 400 mg BID were initially permitted to enter the extension study and receive imatinib 400 mg QD; however, a protocol amendment after the 36-month data cutoff removed this option. Survival and progression outcomes during extension study follow-up were included in the “on study” analyses for the core study.

ENESTnd: Cumulative incidence of MMR



Larson et al., ASCO 2011

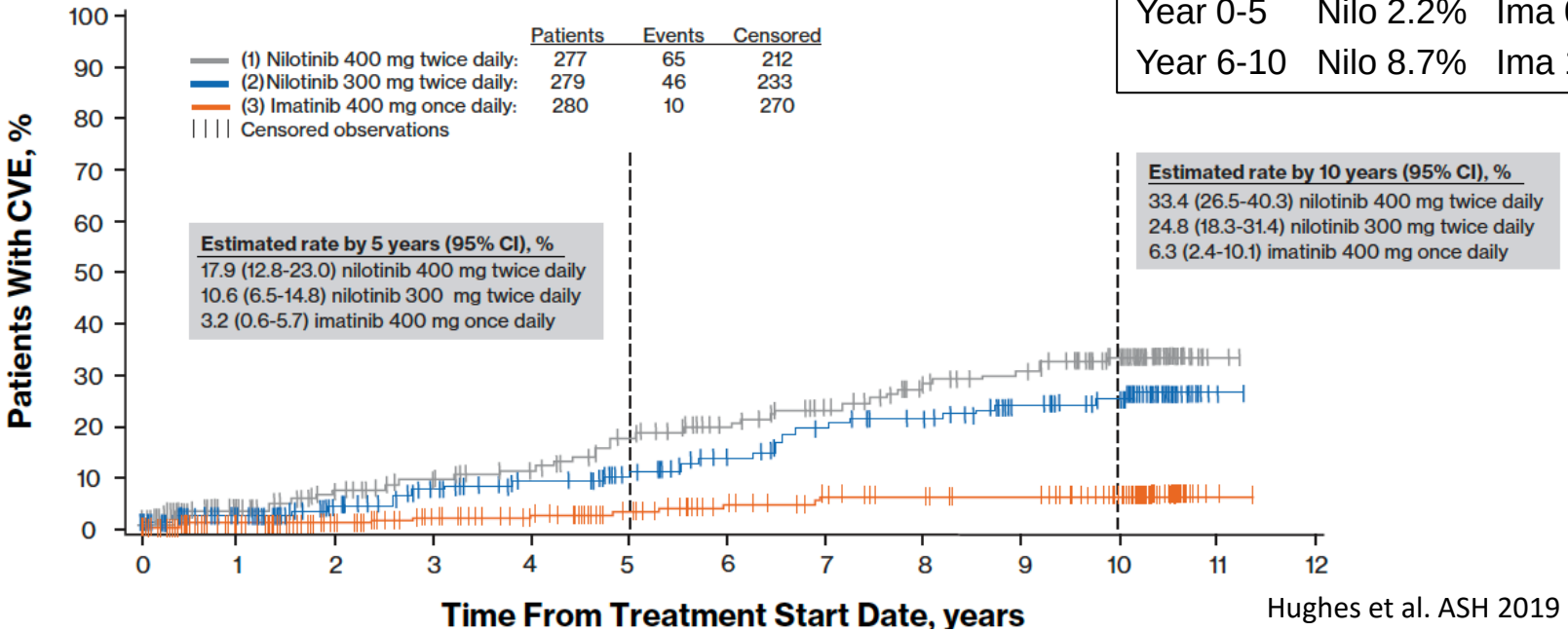
ENESTnd: Nilotinib vs Imatinib First line therapy: Cardiovascular events.

Incidence of cardiovascular events

Framingham low risk:

Year 0-5 Nilo 2.2% Ima 0.5%

Year 6-10 Nilo 8.7% Ima 1.1%



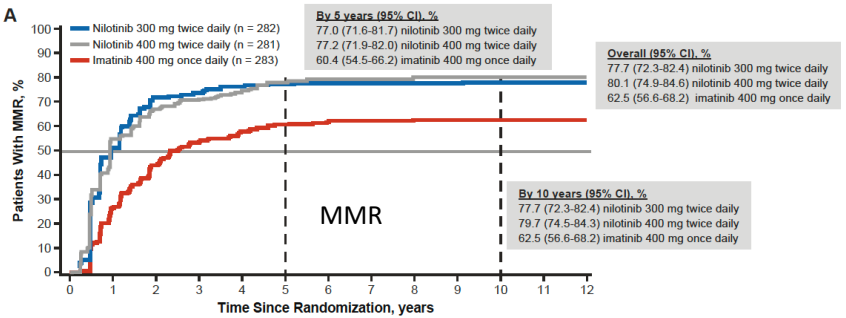
Hughes et al. ASH 2019

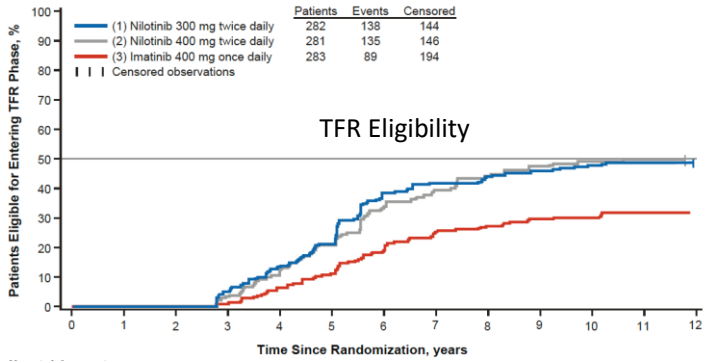
Kantarjian et al. Leukemia. 2021;35:440-53

ENESTnd: Nilotinib vs. Imatinib

Ph+ CML in CP

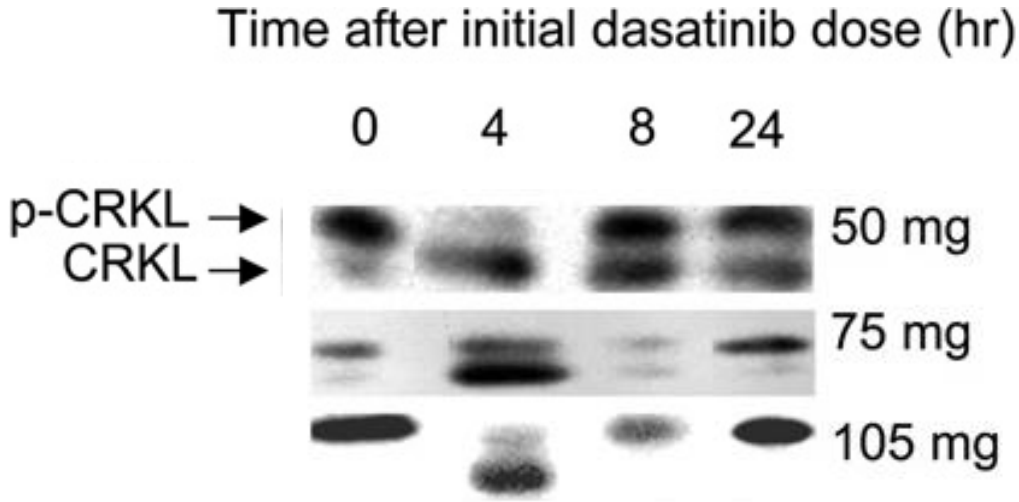
- Nilotinib 2*300 mg/d
- Nilotinib 2*400 mg/d
- Imatinib 400 mg/d





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

Dasatinib: Transient inhibition of BCR-ABL



Shah et al., Cancer Cell 2008

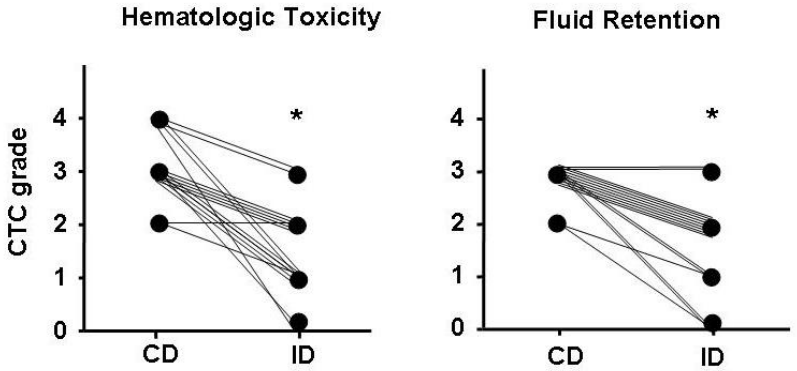
Ann Hematol (2013) 92:1345–1350
DOI 10.1007/s00277-013-1769-2

ORIGINAL ARTICLE

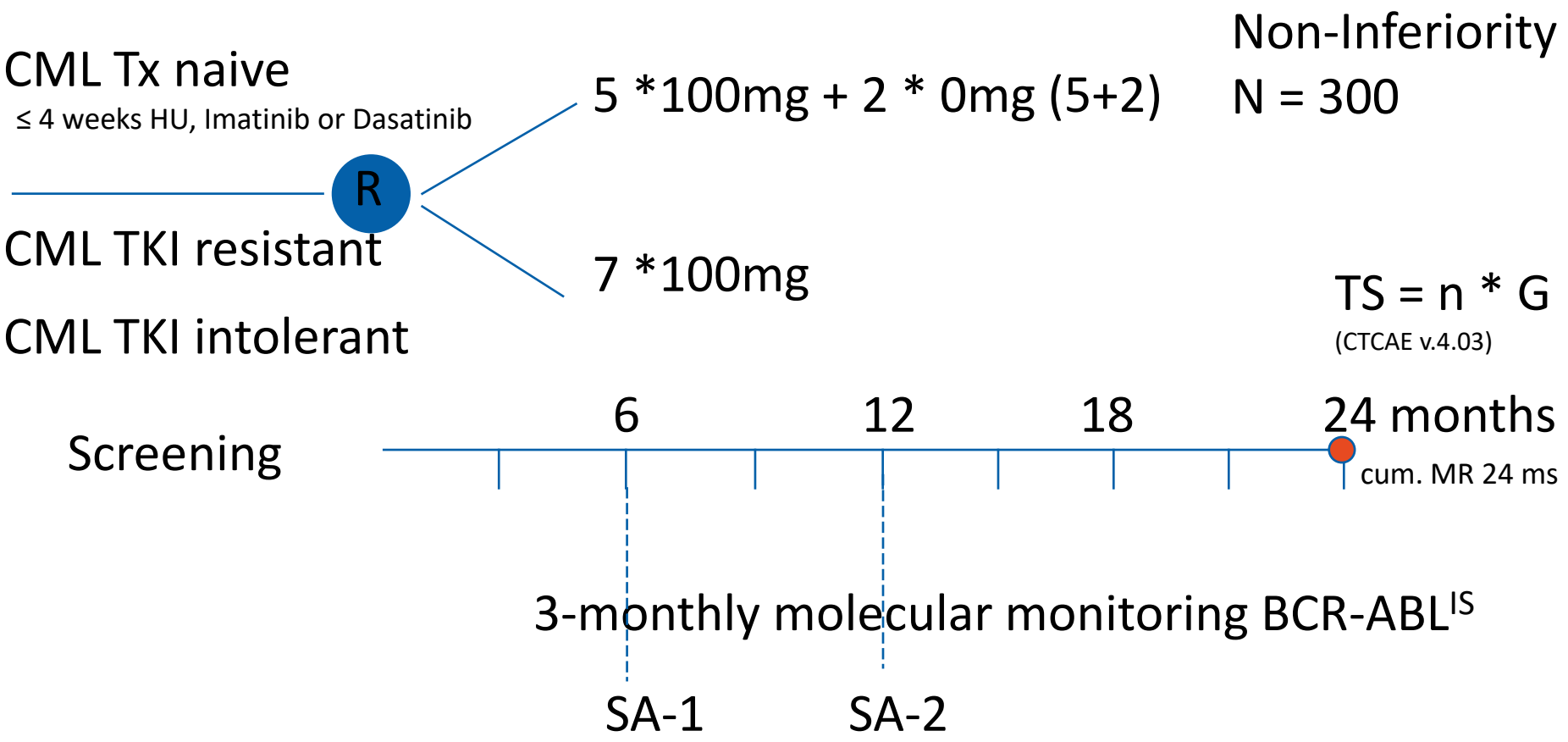
Improved tolerability by a modified intermittent treatment schedule of dasatinib for patients with chronic myeloid leukemia resistant or intolerant to imatinib

Paul La Rosée · Philippe Martiat · Armin Leitner · Thomas Klag · Martin C. Müller · Philipp Erben · Thomas Schenk · Susanne Saussele · Andreas Hochhaus

Toxizitätsreduktion durch Dasatinib *Weekend Holiday*
Das 5 + 2 Schema, n = 33



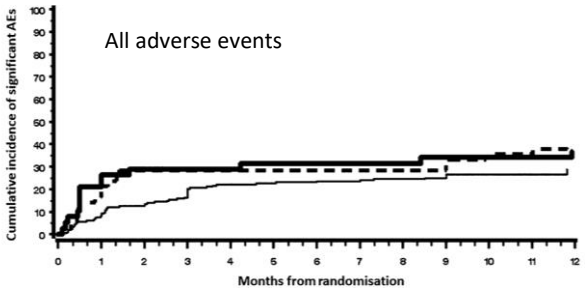
Dasatinib Holiday for Improved Tolerability (DasaHIT)

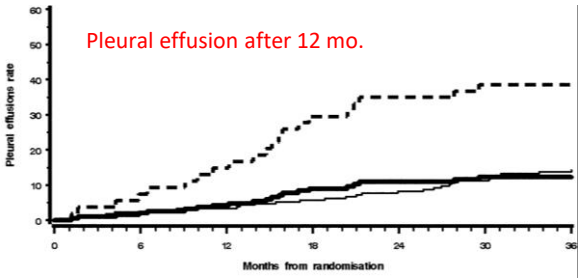


DasaHIT. Interim analysis 2021: Side effects (n= 138)

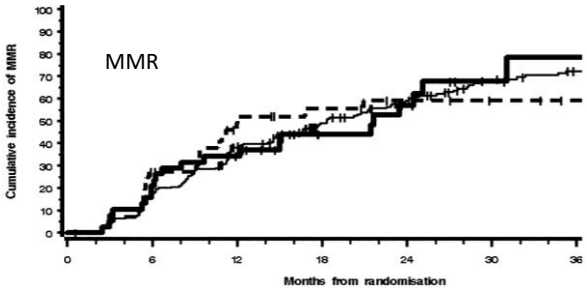
Arm A		Arm B	
1. Thrombocytopenia	n=12, 17%	1. Thrombocytopenia	n=15, 22%
2. Anemia	n=11, 16%	2. Pleural effusions	n=11, 16%
3. Heart failure	n=8, 12%	3. Abdominal pain	n=8, 12%
Pleural effusions	n=5, 7%		

Dasatinib dose optimization by drug monitoring?





TDM-Arm (bold line), Control arm (dotted line), Observation arm (thin line)



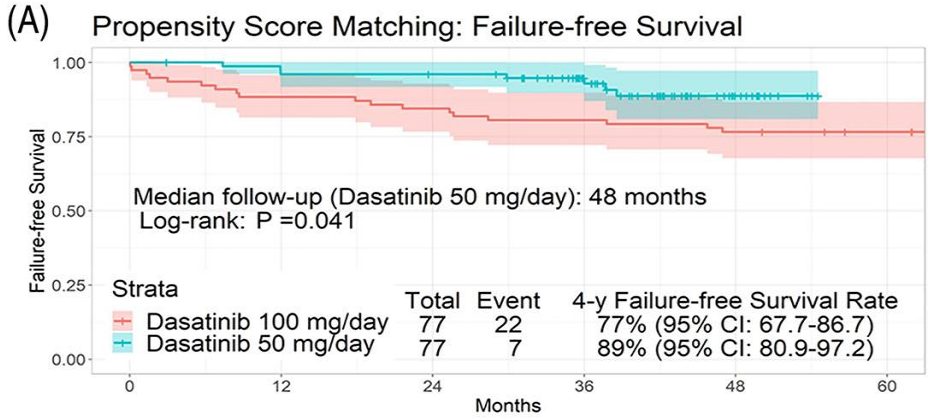
Effect of dose reduction?

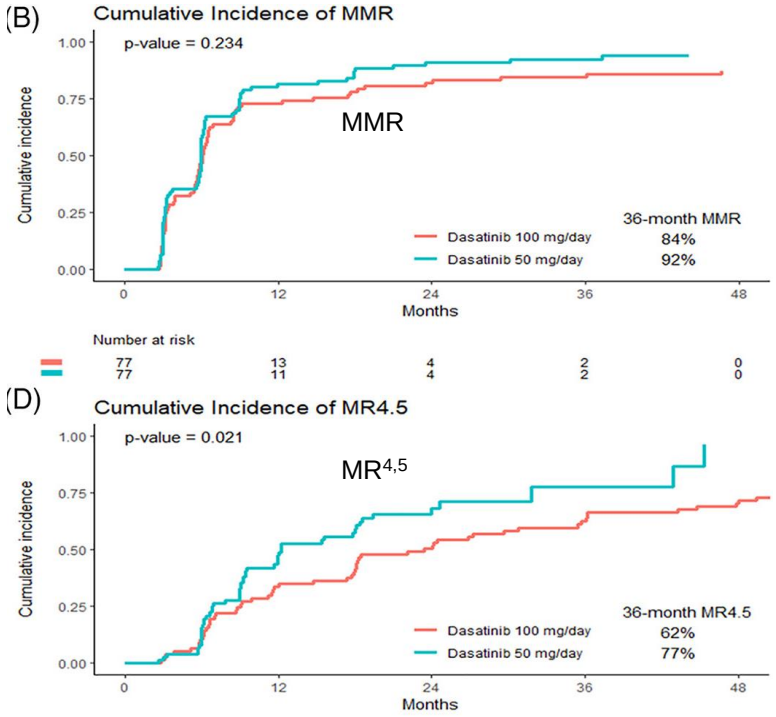
or effect of drug monitoring?

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

Efficacy of low dose dasatinib 50 mg/d

Jabbour et al. Am J Hematol 2022;97:1413-8.



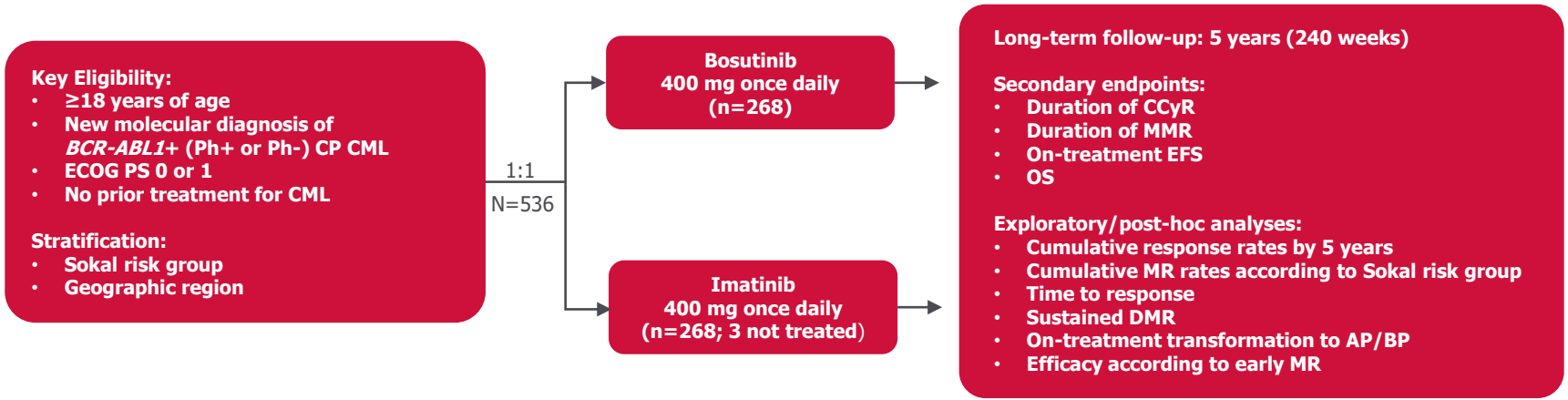


Dasatinib anhydrous (Daruph®)

- **Daruph®: “hybrid medicine”** (similar to an authorised medicine containing the same active substance, but certain differences such as in strength, indication or pharmaceutical form)
- Active substance in Daruph®: **Dasatinib anhydrous** (Sprycel®: Dasatinib monohydrate)
- Intended to allow lower dose of Dasatinib to achieve same effect and concomitant use of PPIs (or H2-Antagonists)
- Market authorisation in 2022 by EMA for newly diagnosed Ph+ CML-CP and CP, AP or BP-CML with resistance or intolerance to prior therapy including imatinib (and Ph+ ALL)

BOSUTINIB: BFORE STUDY DESIGN

- BFORE (NCT02130557) was an open-label, randomized, multicenter, phase 3 trial



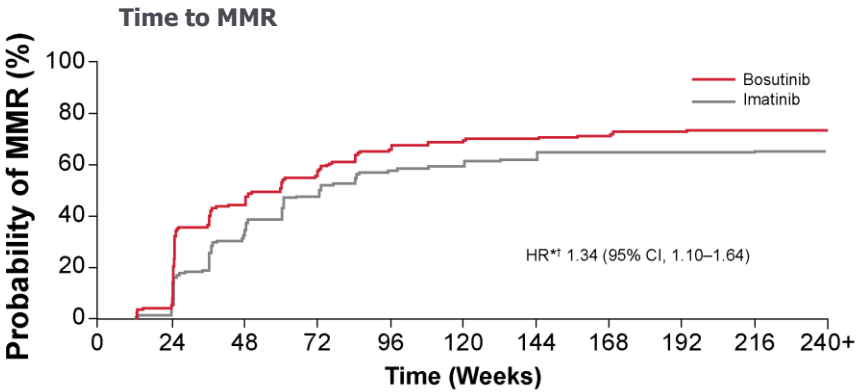
This final analysis was based on a last patient last visit of April 17, 2020 (June 12, 2020 database lock), 5 years after the last enrolled patient.

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; DMR=deep molecular response; ECOG PS=Eastern Cooperative Oncology Group performance status; EFS=event free survival; MMR=major molecular response; MR=molecular response; OS=overall survival

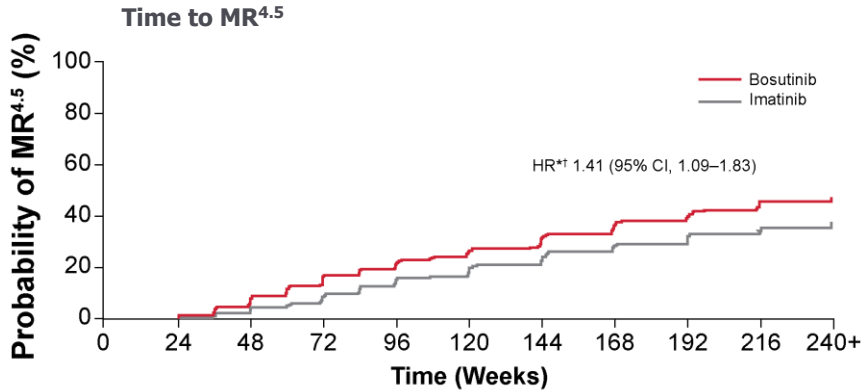
Brümmendorf et al., ASH 2020

MOLECULAR RESPONSE

Cumulative response rates by 60 months, % (95% CI)*	Bosutinib n=268	Imatinib n=268	OR (95% CI)
MMR	73.9 (68.6–79.1)	64.6 (58.8–70.3)	1.57 (1.08–2.28)
MR^4	58.2 (52.3–64.1)	48.1 (42.2–54.1)	1.50 (1.07–2.12)
MR$^{4.5}$	47.4 (41.4–53.4)	36.6 (30.8–42.3)	1.57 (1.11–2.22)



No. at risk											
Bosutinib	246	206	94	58	30	19	12	10	6	4	3
Imatinib	241	204	116	62	29	23	16	10	10	8	5



No. at risk											
Bosutinib	246	218	185	159	138	116	103	89	76	65	50
Imatinib	241	210	188	155	128	118	107	86	79	67	47

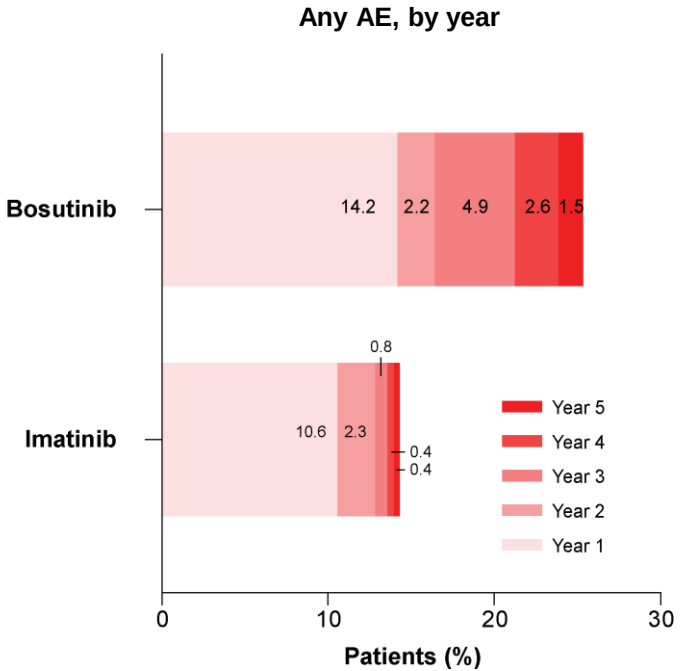
* Adjusted for Sokal risk group and region as determined at the time of randomization.

† From a proportional subdistributional hazards model adjusted for competing risk of treatment discontinuation without a response.

Ratios with 95% CIs excluding 1 are predictive (no adjustment for multiple comparisons). MMR: *BCR-ABL1* IS ≤0.1%. MR^4: *BCR-ABL1* IS ≤0.01%. MR$^{4.5}$: *BCR-ABL1* IS ≤0.0032%.

Brümmendorf et al., ASH 2020

Any Grade AEs Leading to Treatment Discontinuation



n (%)*	Bosutinib n=268	Imatinib n=265
Any AE	68 (25.4)	38 (14.3)
Increased ALT	13 (4.9)	0
Increased AST	7 (2.6)	0
Increased lipase	5 (1.9)	2 (0.8)
Diarrhea	4 (1.5)	3 (1.1)
Thrombocytopenia	3 (1.1)	4 (1.5)
Neutropenia	3 (1.1)	1 (0.4)
Muscle spasms	0	3 (1.1)
Myalgia	0	3 (1.1)

* TEAEs occurring in >1% of patients in the bosutinib or imatinib arm are reported.

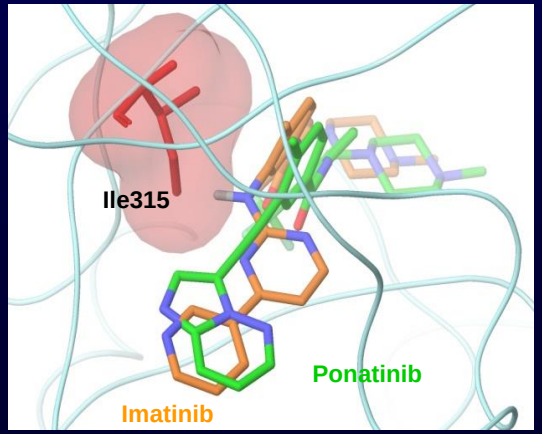
AEs=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase

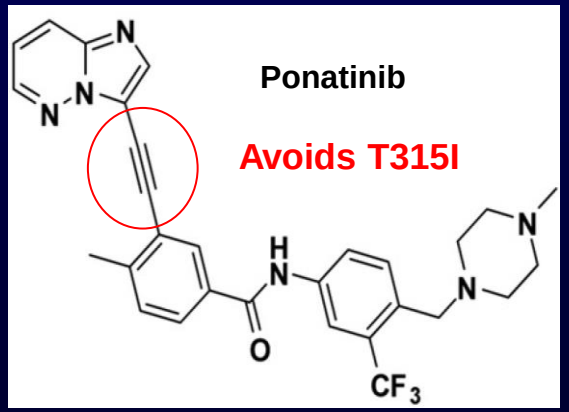
Brümmendorf et al., ASH 2020

Ponatinib
A “Pan”-BCR::ABL1 Inhibitor

- Rationally designed inhibitor of BCR::ABL1
- Active against T315I mutant
- Also targets other therapeutically relevant kinases:
  - Inhibits multiple kinases,
    incl. Vascular Endothelial Growth Factor Receptor, VEGFR

20% vascular events on 45 mg/day





O’Hare T, et al. Cancer Cell. 2009;16:401-412

PACE: Serious Arterial Thrombotic and Venous Thromboembolic Event Rates

	Phase 2 (PACE) N=449	
Datacut Date	**23 Jul 2012**	**03 Sep 2013**
Median Follow-up, Months	**12**	**24**
Arterial Thrombotic Events, n (%)	34 (7.6)	53 (11.8)*
Venous Thromboembolism, n (%)	10 (2.2)	13 (2.9)

Serious arterial thrombotic events are composed of:

- Cardiovascular events (6.2%)
- Cerebrovascular events (4.0%)
- Peripheral vascular events (3.6%)

(Some patients may have more than 1 type of event)

Selected Treatment-Emergent Vascular Occlusive Events by Disease Group

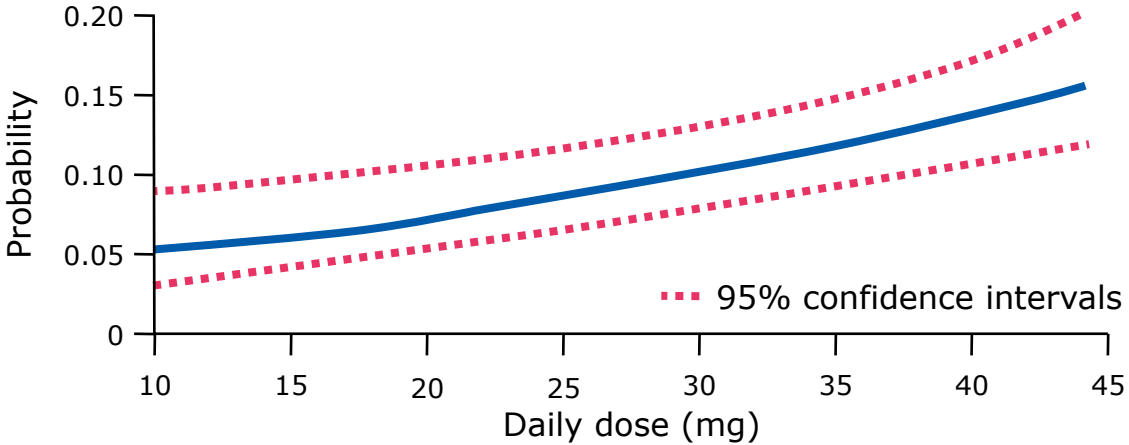
≥5% Incidence in Total Population	CP-CML N=270		AP-CML N=85		BP-CML N=62		Ph+ ALL N=32		Total N=449	
	AE n (%)	SAE n (%)	AE n (%)	SAE n (%)	AE n (%)	SAE n (%)	AE n (%)	SAE n (%)	AE n (%)	SAE n (%)
Vascular occlusive events[b]	67 (25)	49 (18)	19 (22)	13 (15)	10 (16)	7 (11)	5 (16)	3 (9)	101 (23)[c]	72 (16)[d]
Arterial thrombotic	61 (23)	44 (16)	17 (20)	12 (14)	6 (10)	3 (5)	2 (6)	2 (6)	86 (19)	61 (14)
Cardiovascular	27 (10)	20 (7)	12 (14)	7 (8)	3 (5)	2 (3)	1 (3)	0 (0)	43 (10)	29 (7)
Cerebrovascular	27 (10)	18 (7)	5 (6)	4 (5)	0 (0)	0 (0)	1 (3)	1 (3)	33 (7)	23 (5)
Peripheral vascular	23 (9)	14 (5)	3 (4)	2 (2)	3 (5)	1 (2)	2 (6)	2 (6)	31 (7)	19 (4)
Venous thromboembolic	11 (4)	7 (3)	3 (4)	1 (1)	6 (10)	5 (8)	3 (9)	1 (3)	23 (5)	14 (3)

- Median time to onset for venous thrombotic events:
  - Total patients: 161 (3-802) days
  - CP-CML patients: 604 (62-802) days
- Median time to onset for arterial thrombotic events:
  - Total patients: 244 (3-952) days
  - CP-CML patients: 281 (8-952) days

Data as of 6 Jan 2014

PONATINIB: CORRELATION BETWEEN ARTERIAL VASCULAR EVENTS AND DOSAGE

Ponatinib dose and risk of arterial thrombotic events

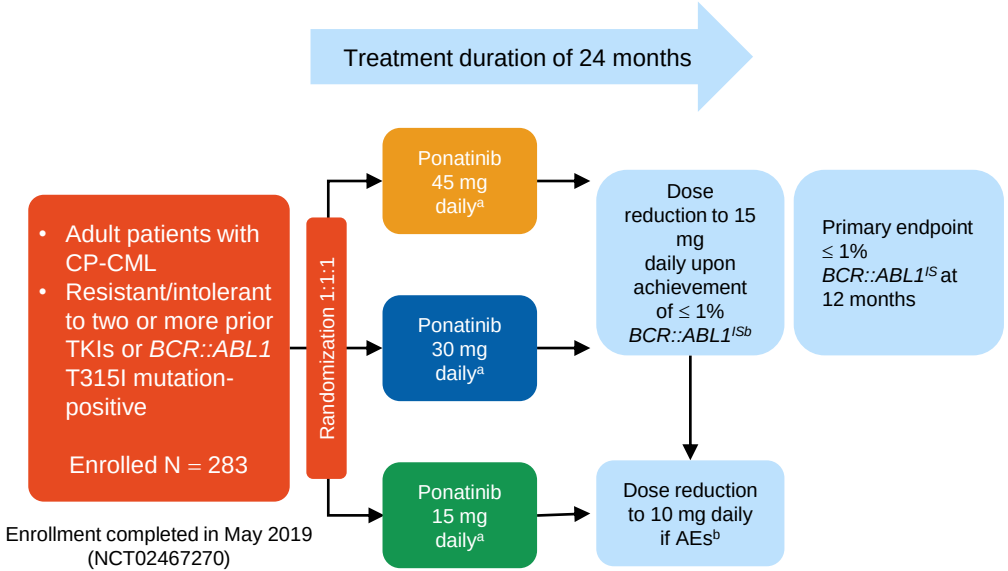


- Strongest independent predictors for an increased risk of arterial thrombotic events: Ponatinib dose, age and history of ischemic episodes.
- A risk reduction of 33 % can be expected with each reduction of 15 mg in the Ponatinib dose.

- The risk of vascular events decreases by 33 % with each dose reduction of 15 mg per day.

Dorer D et al. Leuk Res 2016;48:84–91.

OPTIC (Optimizing Ponatinib Treatment In CP-CML): Ongoing, Multicenter, Randomized Phase 2 Trial

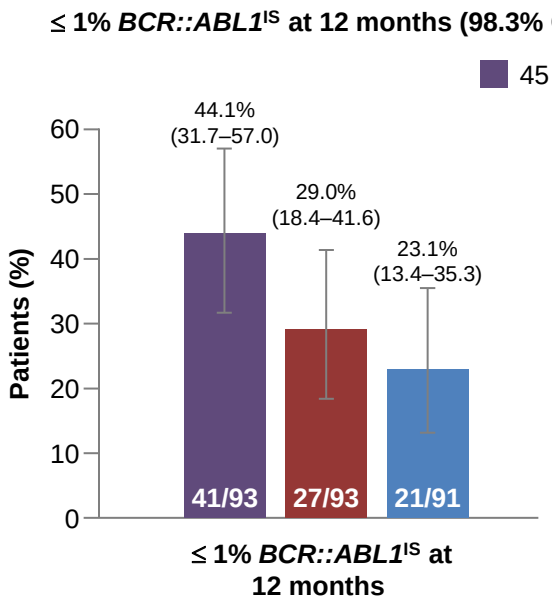


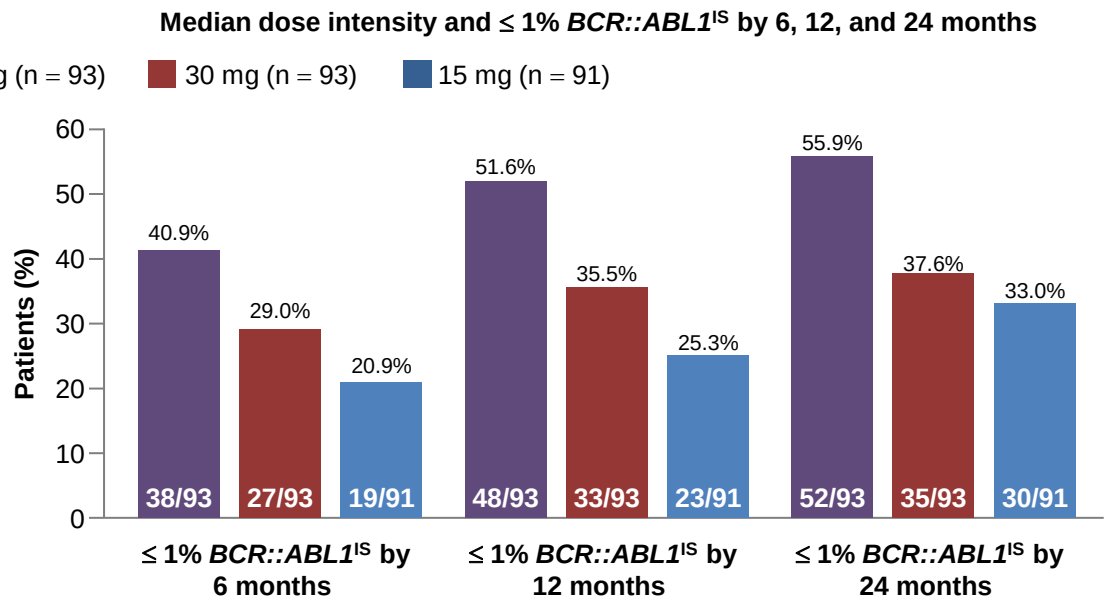
The goal of OPTIC was to optimize ponatinib dose using a novel response-based reduction strategy

[a]Dose reductions due to AEs were permitted;
[b]Escalation to the starting dose allowed for patients who last their response following dose reduction

Cortes J, et al. Blood. 2021;138:2042-50.

OPTIC trial: Ponatinib efficacy by starting dose

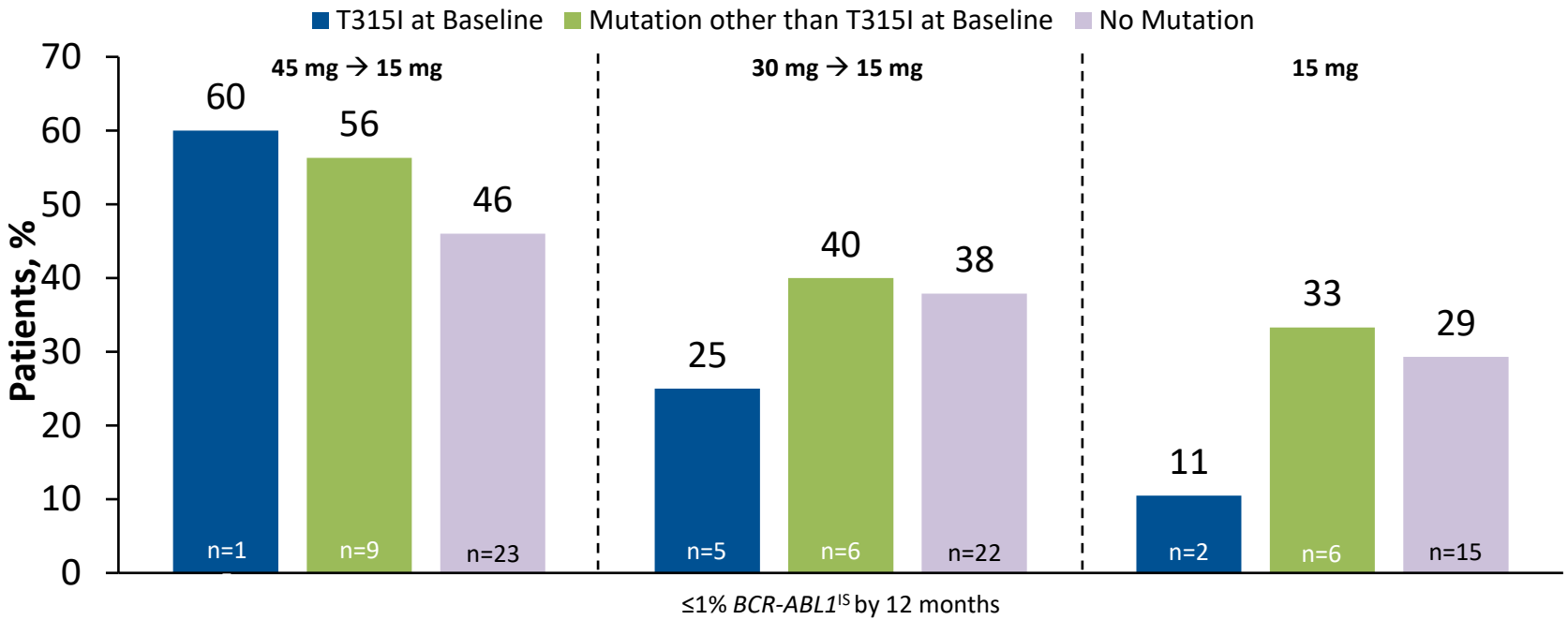




	Median dose intensity, mg/day		
Cohort	6 months	12 months	24 months
45 mg	35.2	15.0	15.0
30 mg	30.0	28.0	15.0
15 mg	15.0	15.0	15.0

Cortes et al. Blood. 2021;138:2042-50.

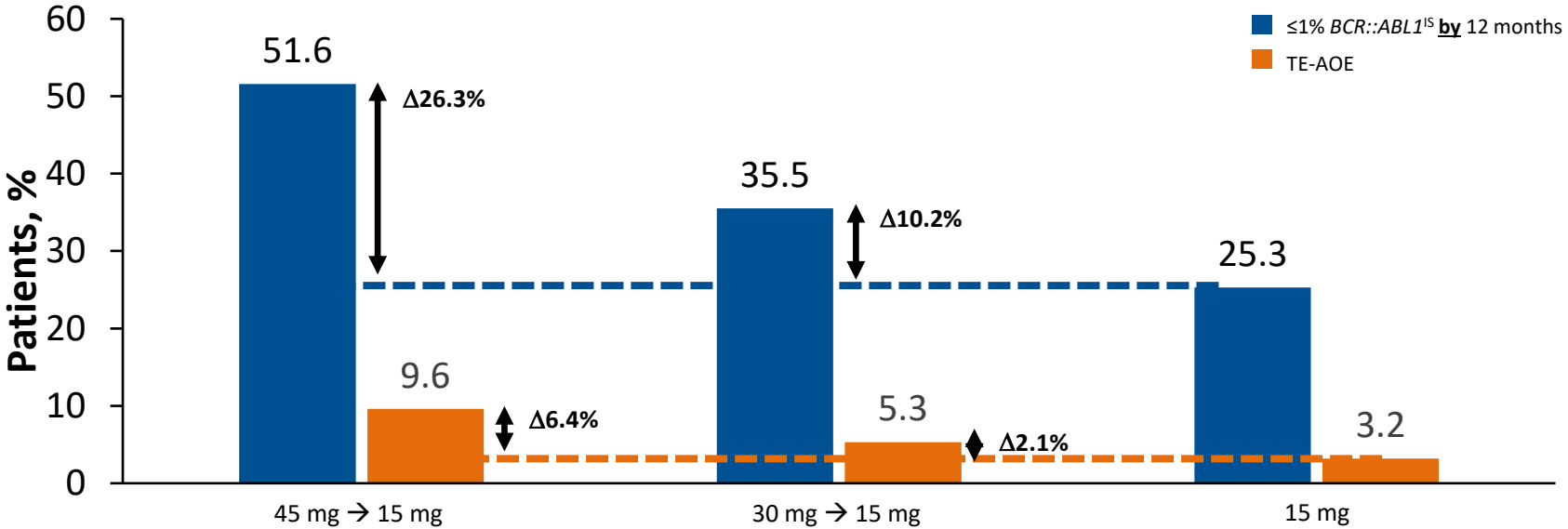
OPTIC: ≤1% BCR::ABL1^{IS} Response Rate to Ponatinib by 12 Months by T315I Baseline Status



[a]Patients on study who had not reached 12 months were excluded from the denominator.

Cortes et al. Blood. 2021;138:2042-50.

OPTIC: Overall Safety and Efficacy by Starting Dose of Ponatinib

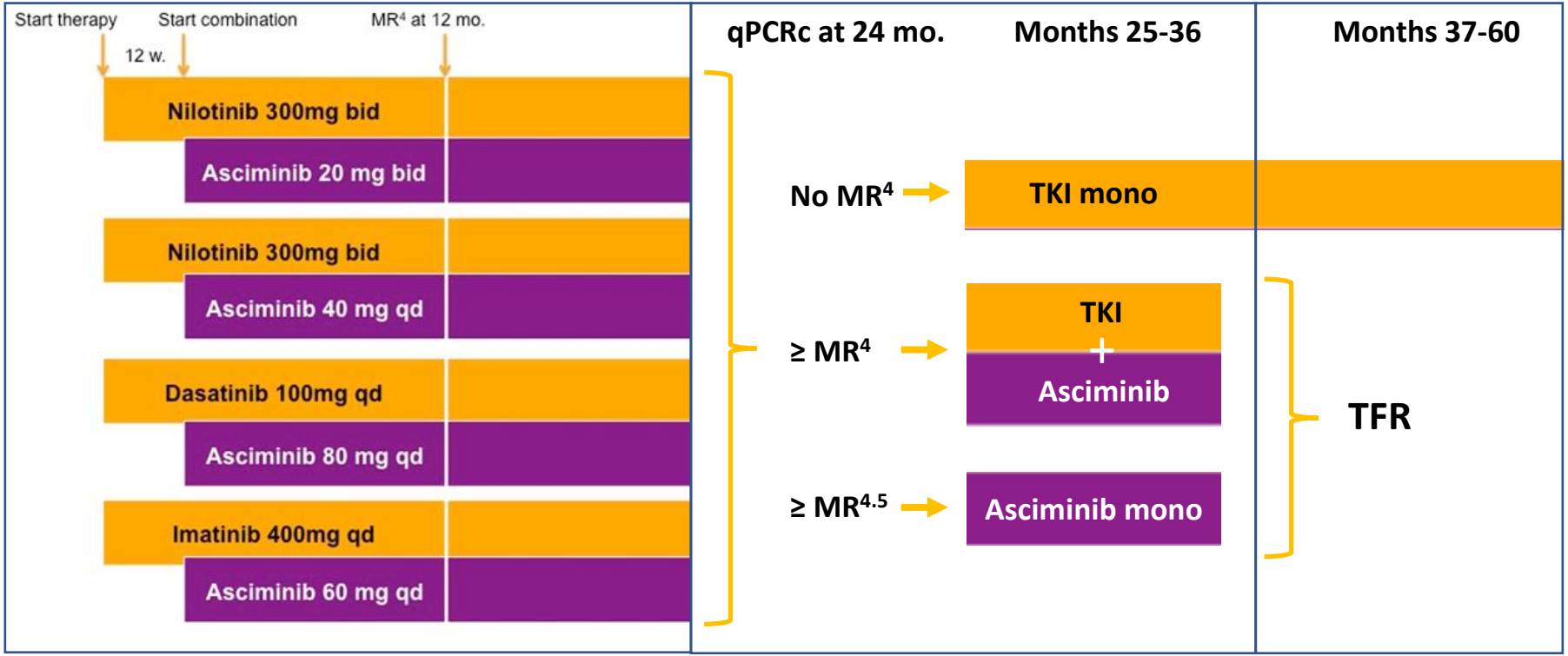


- The percentage of patients with ≤1% *BCR::ABL1*^{IS} decreased with decreasing doses
- The incidence of TE-AOEs decreased with decreasing doses

TE-AOE, treatment-emergent arterial occlusive event

Cortes J, et al. Blood. 2021;138:2042-50.

Fascination: Study design

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