CML HORIZONS
HYBRID MEETING 2024
Vilnius, Lithuania
24–26 May 2024

New data on first line therapy

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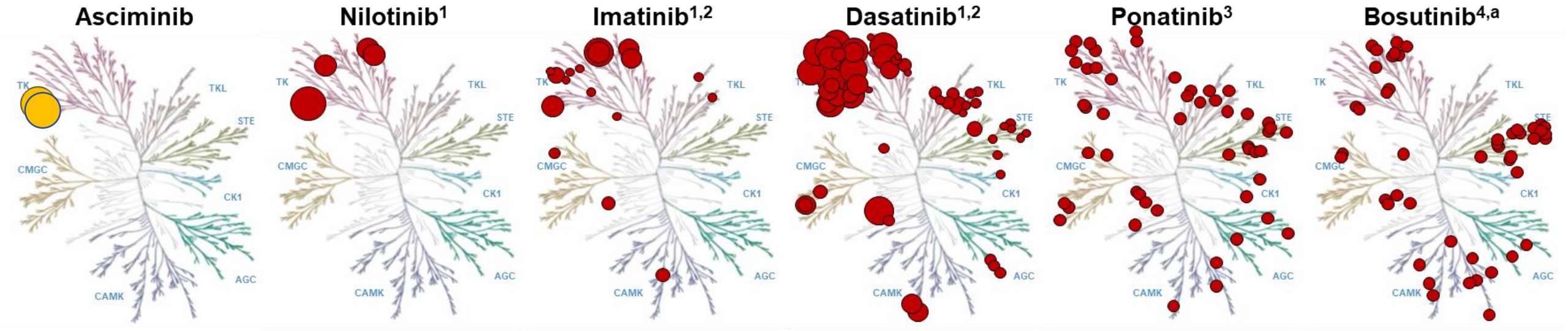
DEUTSCHE CML.ALLIANZ

ELN Recommendations for CML: 2020

	2006	2009	2013	2020
1st line	Imatinib	Imatinib	Imatinib, nilotinib, dasatinib	Imatinib, nilotinib, dasatinib, bosutinib
2nd line	None (high-dose imatinib)	Nilotinib, dasatinib, high-dose imatinib	• Ima → nilo, dasa, bosu • Dasa → nilo, bosu, pona • Nilo → dasa, bosu, pona • T315I: pona	• Ima → nilo, dasa, bosu • Dasa → nilo, bosu, pona • Nilo → dasa, bosu, pona • Bosu → dasa, nilo, pona • T315I: pona
Alt. Options	IFN/allogeneic SCT	None	None	*(Asciminib)*
Salvage	Allogeneic SCT	Allogeneic SCT, nilotinib, dasatinib	Allogeneic SCT	Allogeneic SCT
Milestones	CCyR	CCyR → MR	MMR, major and stable	MMR → DMR
Concerns/ Considerations	• Short follow-up • Emerging mutations	Risk of emerging mutations ↓	TFR, mainly inside the frame of RCTs	Side effects

Courtesy Gianantonio Rosti

Selectivity of kinase inhibitors



Selectivity of kinase inhibitors:

Kinases bound by ATP-competitive TKIs are indicated by **red** circles.
Kinases bound by STAMP inhibitor are indicated by a **yellow** circles.

[a] Bosutinib inhibits additional kinases that are not depicted in the dendrogram.
ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor;
STAMP, Specifically Targeting the ABL Myristoyl Pocket.

1. Steegmann JL, et al. Leuk Lymphoma. 2012;53:2351-2361.
2. Karaman MW, et al. Nat Biotechnol. 2008;26:127-132.
3. Lang JD, et al. Clin Cancer Res. 2018;24:1932-1943.
4. Remsing Rix LL, et al. Leukemia. 2009;23:447-485.

ELN 2020 treatment milestones (First- and second line)

	Optimal	Warning	Failure
Baseline		High risk-ACA High risk ELTS score	
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%
Any time	BCR::ABL1 ≤0.1%	BCR::ABL1 >0.1-1%, Loss of MMR	BCR::ABL1 >1%, Resistance mutations, High-risk ACA

For patients aiming at TFR, optimal response (at any time) is MR^4 (BCR::ABL1 ≤0.01%)

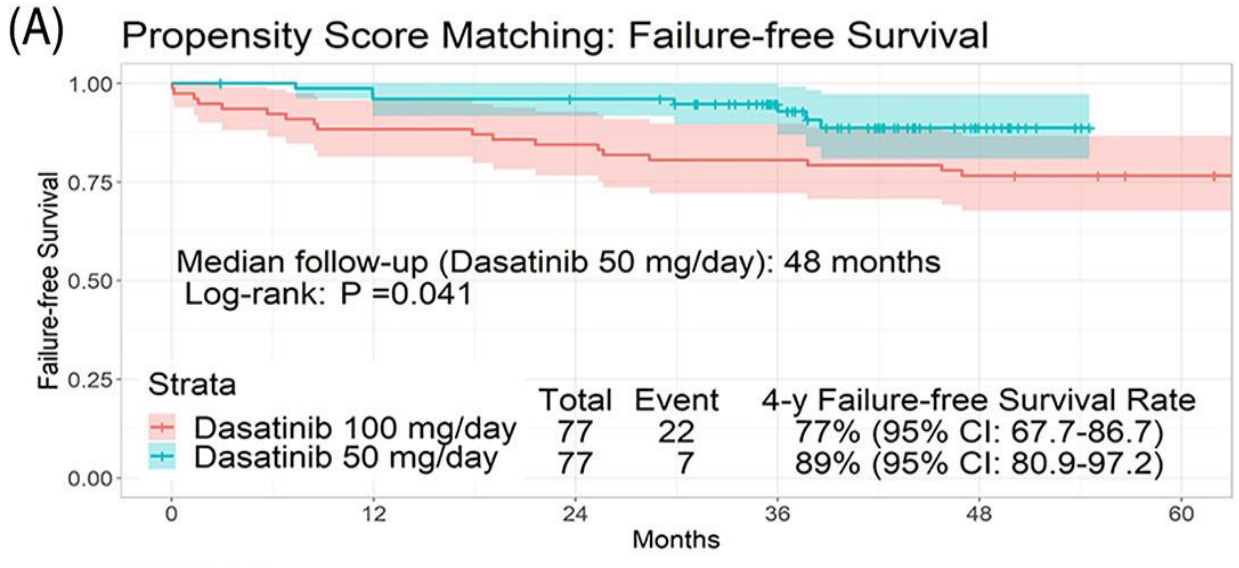
Leukemia 2020; 34:966

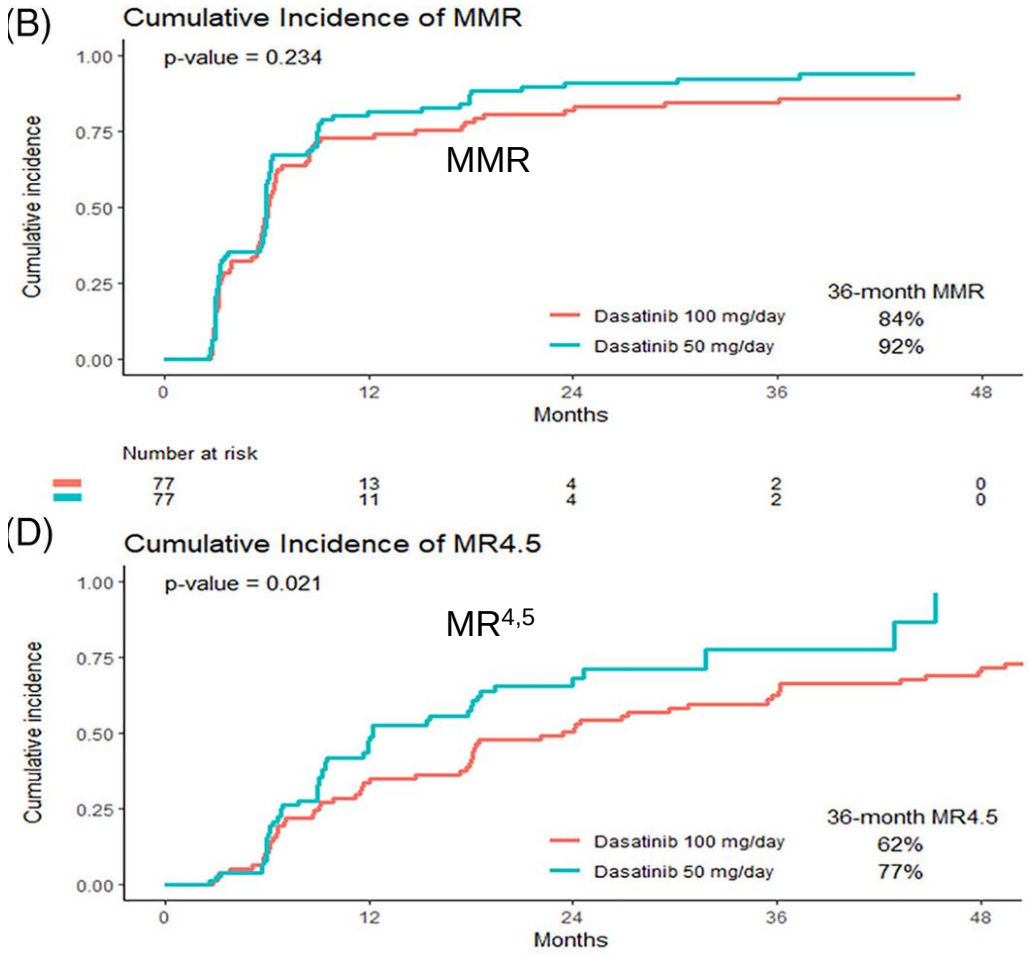
What is the right dose?

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 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	--	--

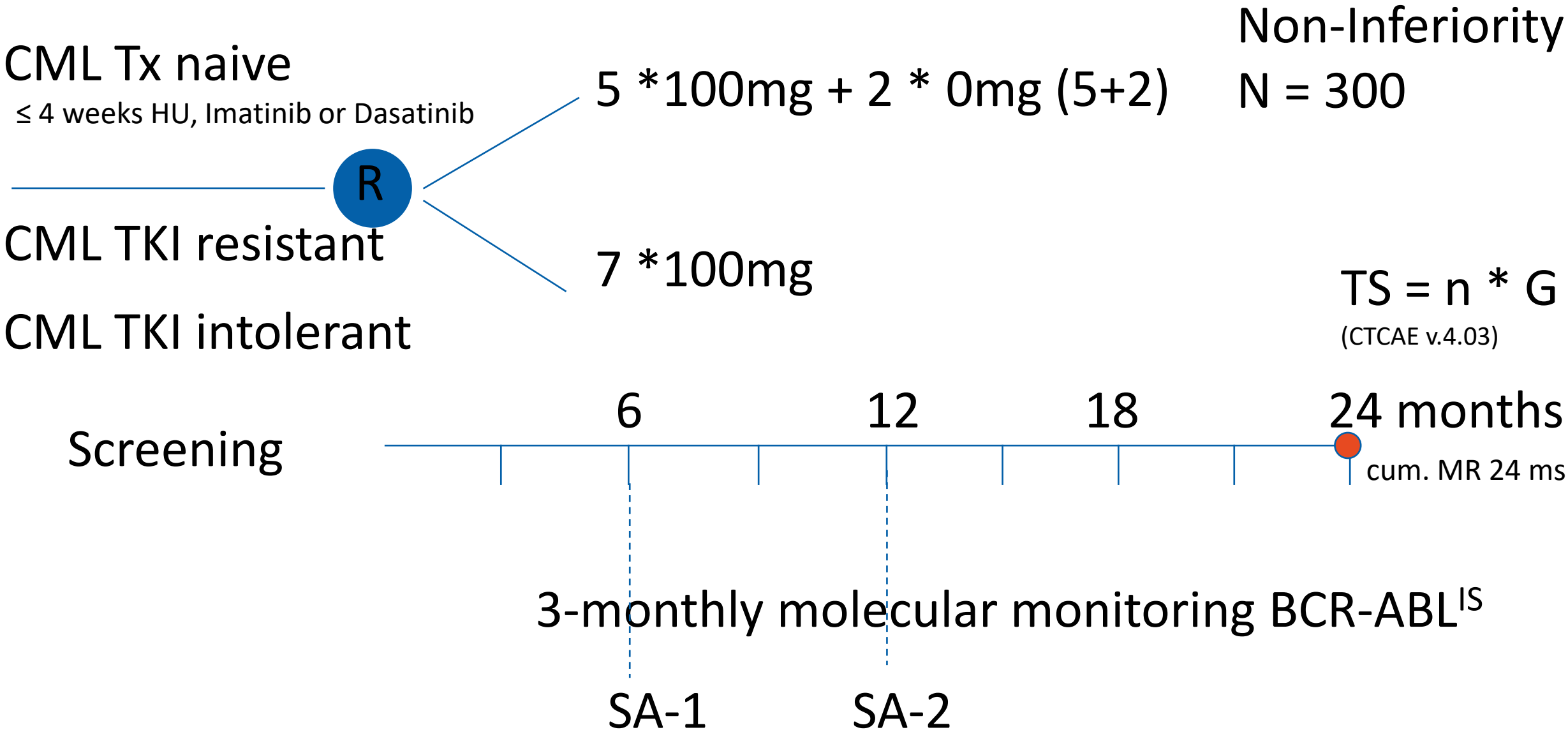
Efficacy of low dose dasatinib 50 mg/d

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





Dasatinib Holiday for Improved Tolerability (DasaHIT)



Study motivation

DasaHIT: Dasatinib-Holiday for Improved Tolerability

Assumptions

- Reduced toxicity with a 5-day regimen instead of 7 days
- Improved drug adherence
- Non-inferiority with regard to efficacy

Patients randomised

Dasatinib	1st line	2nd line	Total
5 days a week	116 (82%)	26 (18%)	142 (49%)
7 days a week	116 (79%)	31 (21%)	147 (51%)
Total	232 (80%)	57 (20%)	289

Two more patients recorded but not randomised:

- Once toxicity already prior to randomisation
- Once withdrawal of consent prior to randomisation

One additional patient was randomised but excluded thereafter since an exclusion criterion had been violated

MMR status at 24 months

Molecular data was available in 254 of 260 evaluable patients

6 of 260 patient died within 24 months, 4 in the 5-day arm. Death was rated as „no MMR“

Dasatinib	No MMR	MMR	Total
5 days a week	29 (22%)	101 (78%)	130
7 days a week	25 (19%)	105 (81%)	130
Total	54 (21%)	206 (79%)	260

MMR status at 24 months, 1st line

Dasatinib	No MMR	MMR	Total
5 days a week	20 (19%)	86 (81%)	106
7 days a week	21 (21%)	79 (79%)	100
Total	41 (20%)	165 (80%)	206

Probability for MMR at 24 months

- **All patients: 80%**, 95% CI: [75%; 86%]
- **5-day arm: 81%**, 95% CI: [74%; 89%]
- **7-day arm: 79%**, 95% CI: [71%; 87%]

MMR status at 24 months, ≥2nd line

Dasatinib	No MMR	MMR	Total
5 days a week	9 (37.5%)	15 (62.5%)	24
7 days a week	4 (13%)	26 (87%)	30
Total	13 (24%)	41 (76%)	54

Probability for MMR at 24 months

- **All patients: 76%**, 95% CI: [65%; 87%]
- **5-day arm: 62.5%**, 95% CI: [43%; 82%]
- **7-day arm: 87%**, 95% CI: [75%; 99%]

Toxicities associated with dasatinib

Supposedly reduced with a 5-day regimen

17 toxicities in focus:

Pleural effusion Lymphedema Pericardial effusion Pulmonary hypertension Pulmonary arterial hypertension Heart failure Pulmonary edema Neutrophil count decreased Febrile neutropenia (only grade III and IV) Anemia Platelets count decreased Myalgia Papulopustular rash, rash acneiform, maculopapular rash Nausea Diarrhea Abdominal pain Vomiting

Adverse events with grade II to IV summarized in a cumulative Toxicity Score (cTS)

Results of the cumulative Toxicity Score

5-day arm: 125 patients evaluable, 70 patients (56%) with AE

- cTS: Minimum=0, Q1=0, Median=2, Q3=4, Maximum=13

7-day arm: 130 patients evaluable, 76 patients (58%) with AE

- cTS: Minimum=0, Q1=0, Median=2, Q3=4, Maximum=13

Assumption of equal distributions of the cTS was not rejected, exact Wilcoxon test: p = 0.83 > alpha2 = 0.048 (two-sided)

Pleural or pericardial effusion

Dasatinib	No MMR	MMR	Total
5 days a week	10 (8%)	115 (92%)	125
7 days a week	21 (16%)	109 (84%)	130
Total	31 (12%)	165 (88%)	255

Chi-square test: p = 0.0468

- Explorative
- Post-hoc

Summary DasaHit

In first line therapy,

dasatinib 5 days per week is

equally effective but less toxic than

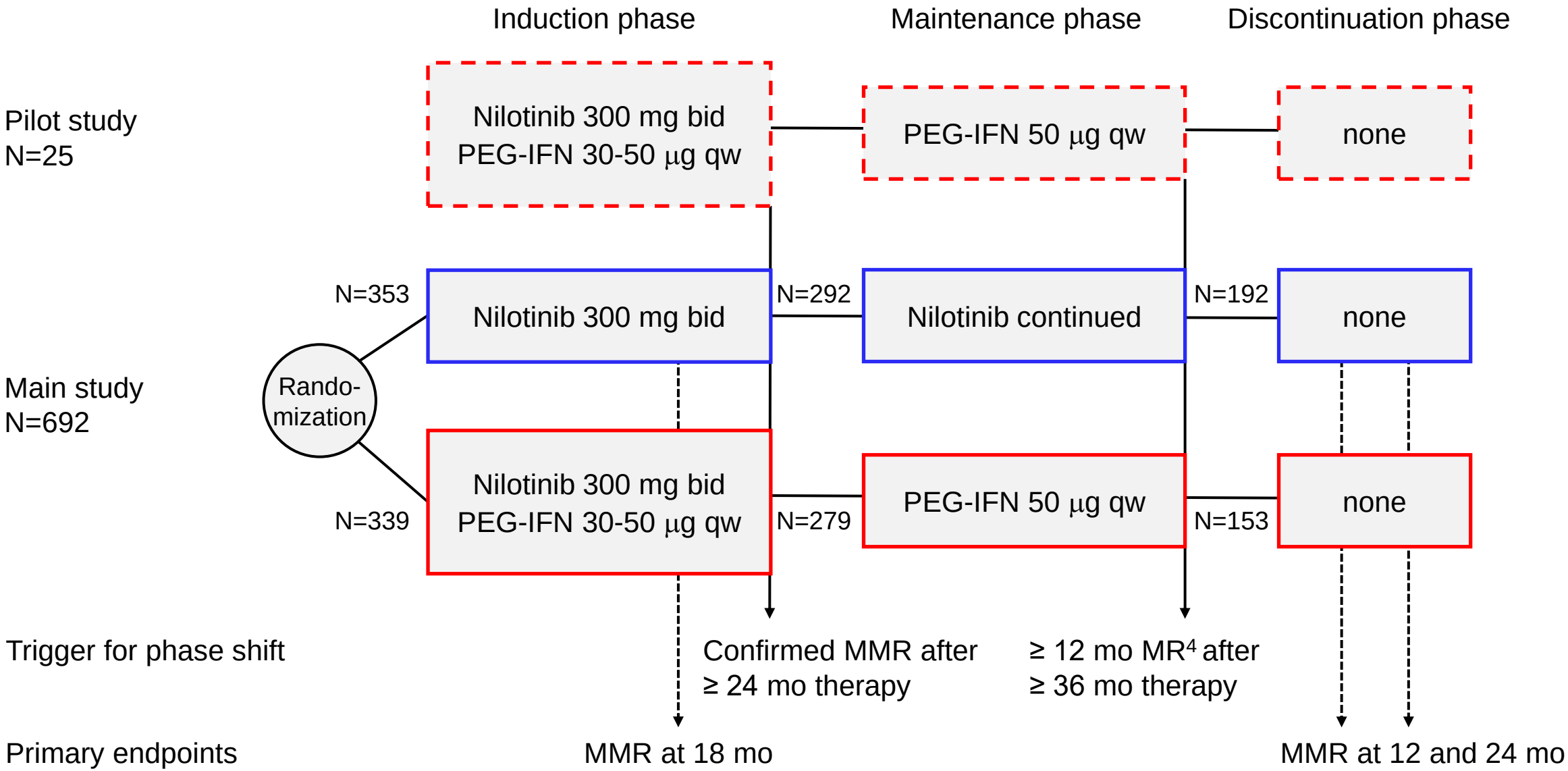
dasatinib 7 days per week.

In later lines of therapy, data is still immature but

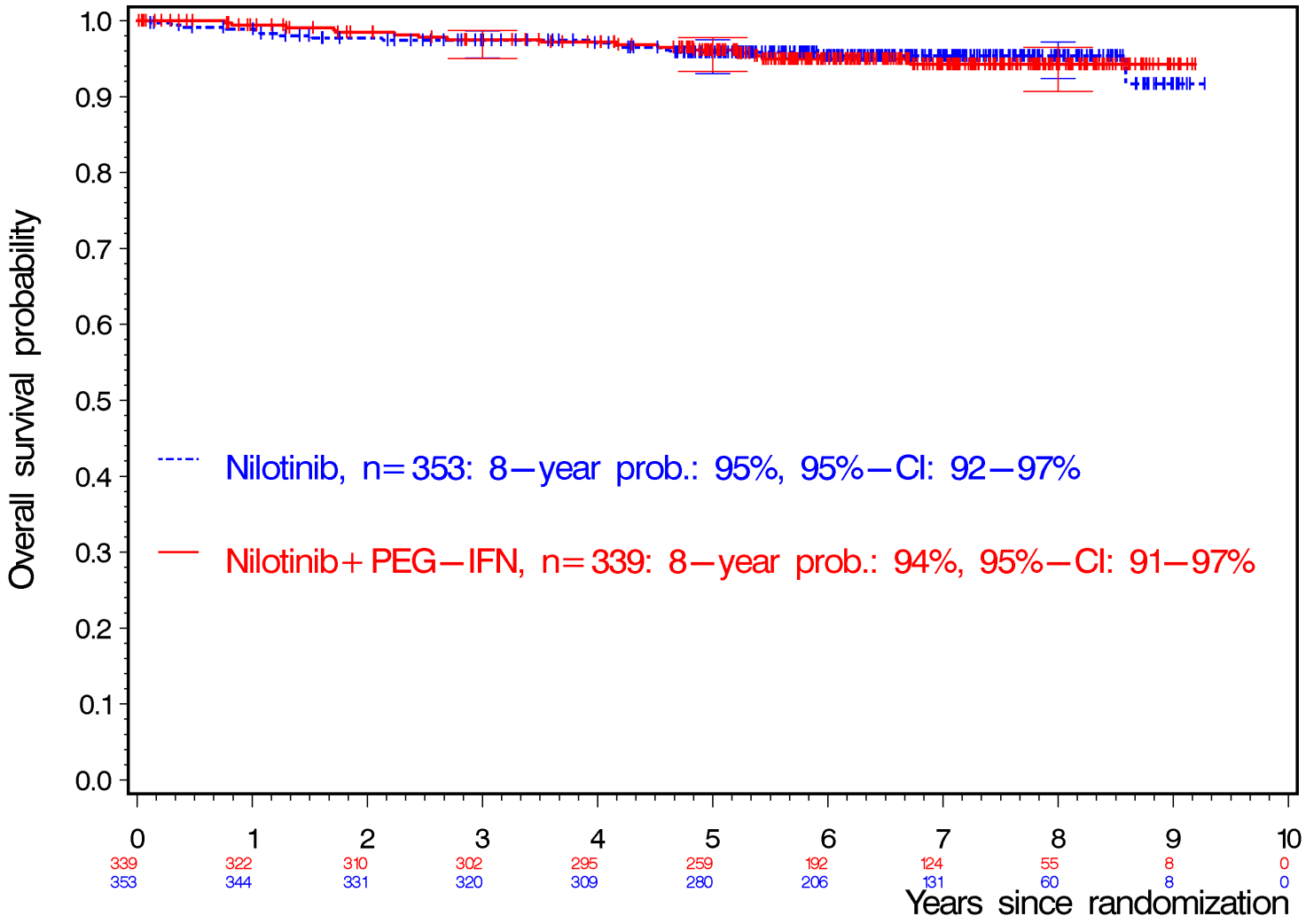
dasatinib 7 days per week might be the preferred option.

TIGER STUDY

N=717 (Median follow up 6.4 years)



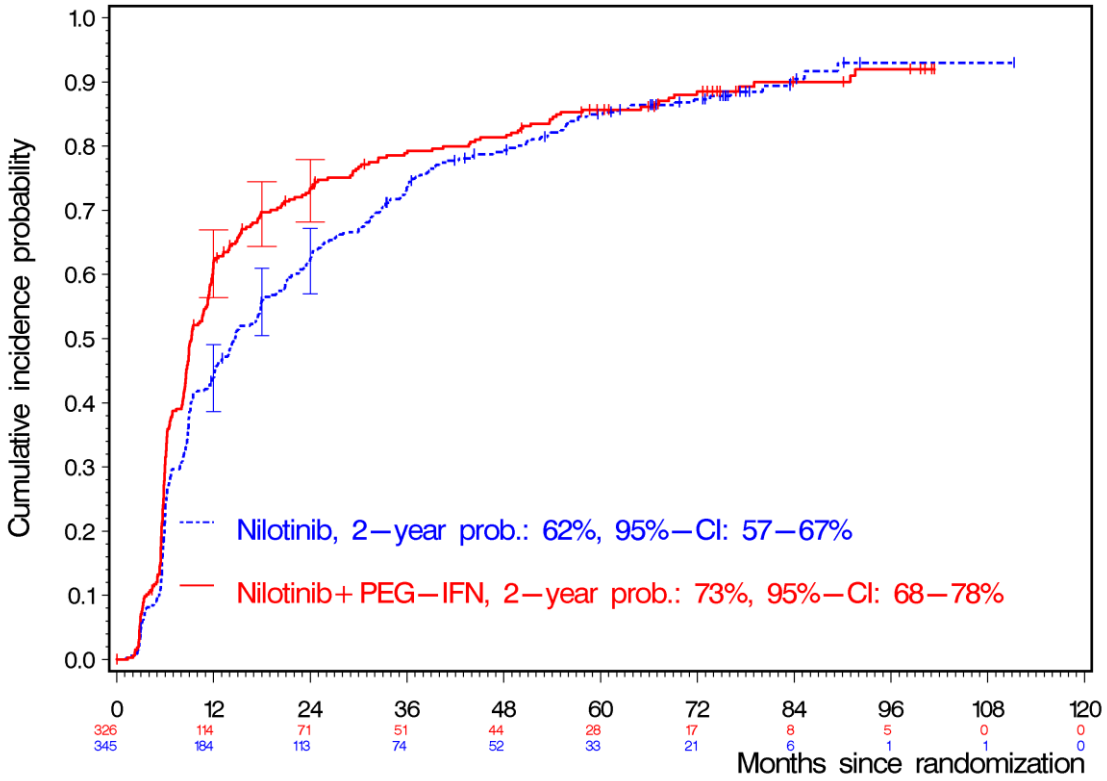
TIGER: 8-year overall survival 95%



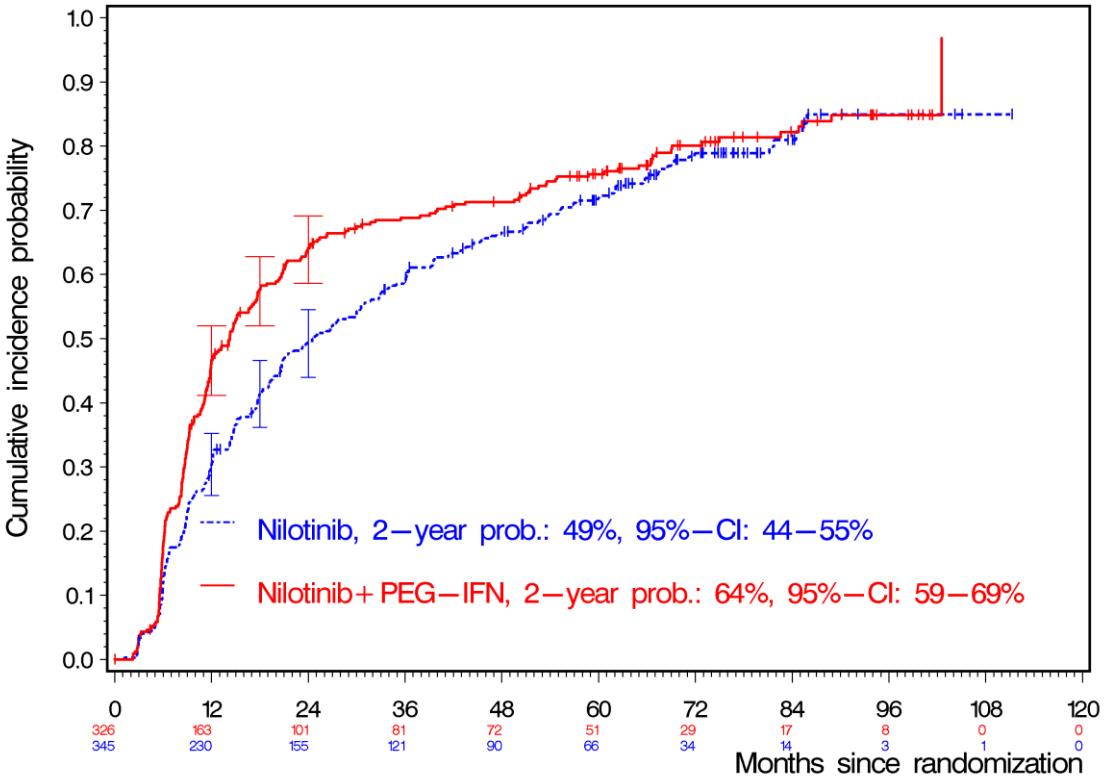
Hochhaus et al. EHA 2023

Cumulative incidence of DMR

MR^4



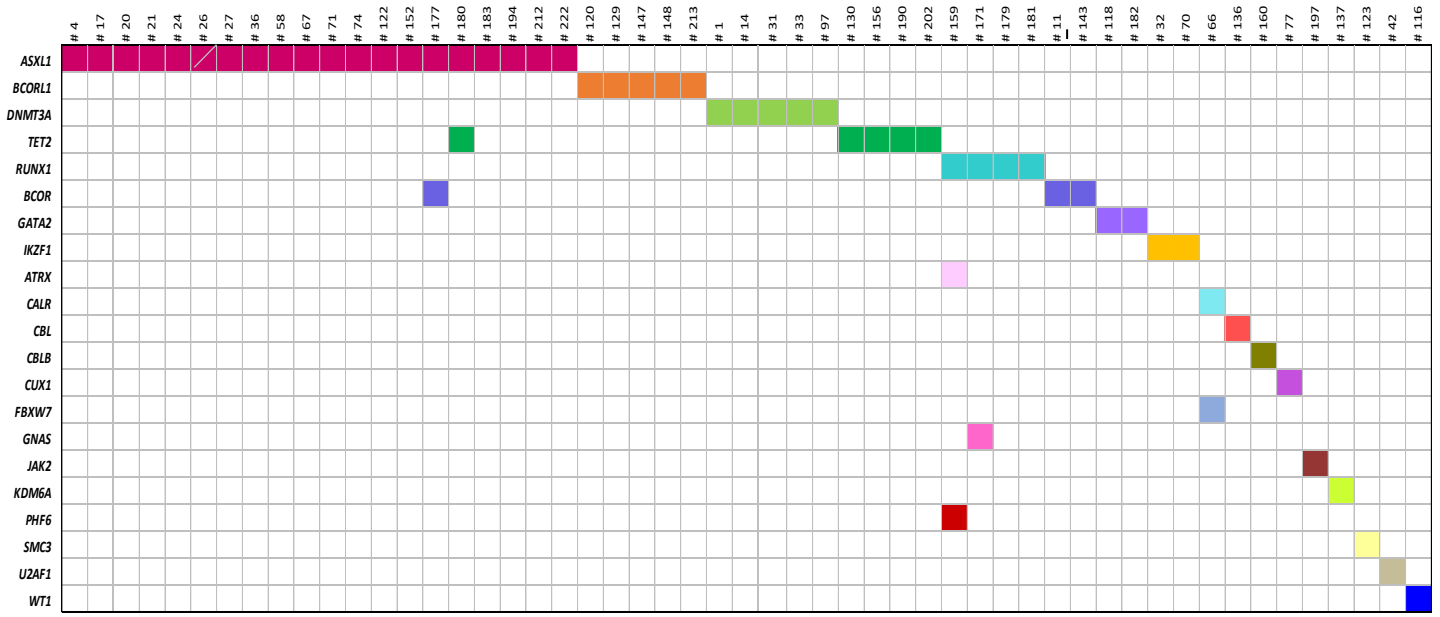
$MR^{4.5}$

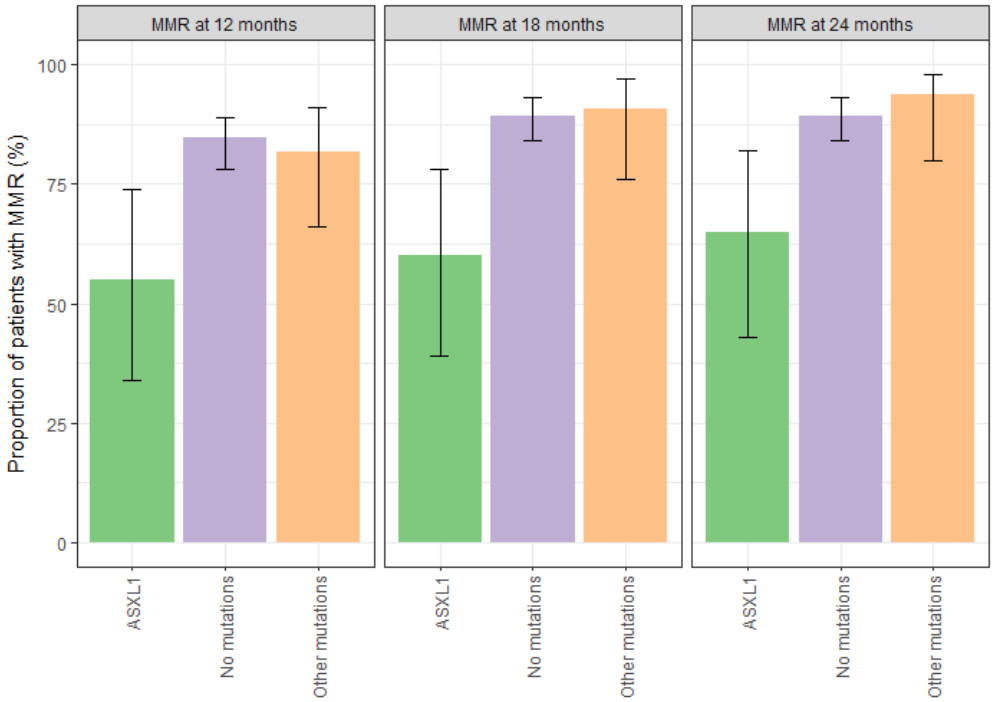


6 EUTOS IS standardized central labs; typical transcripts only

Hochhaus et al., EHA 2023

ASXL1 Mutations Predict Inferior Molecular Response to Nilotinib Treatment in Newly Diagnosed Patients with CP-CML





- Mutations in 24% (53/222) CML patients at diagnosis
- *ASXL1* being most commonly affected (n=20)
- Most patients only have one mutation in addition to *BCR::ABL1*
- Median age of affected patients: 54 years (range 19-78 years)

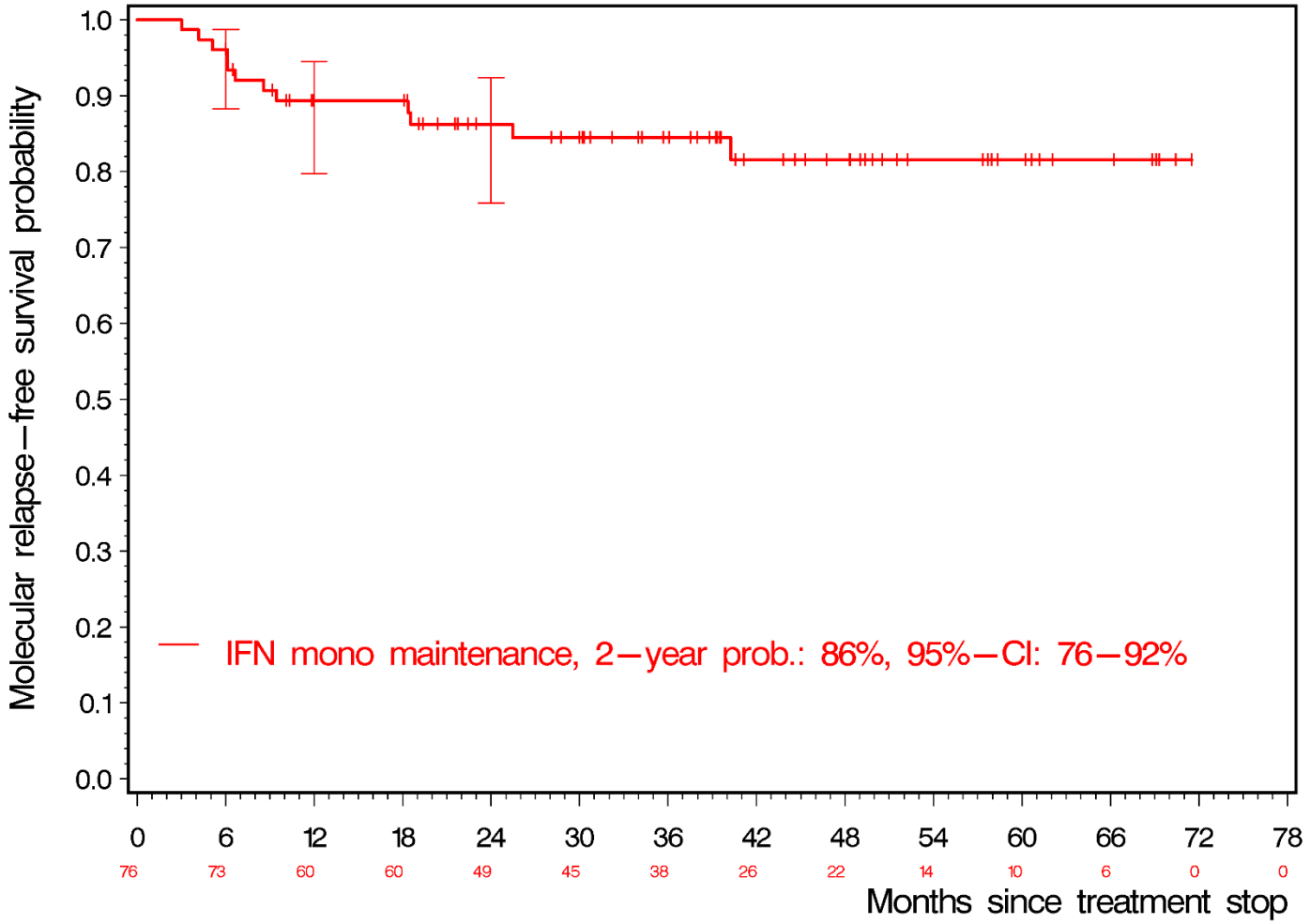
Schönfeld et al., Leukemia. 2022

Molecular relapse free survival after IFN discontinuation

79 patients started TFR phase, median observation time: 39 months

Of these 79 patients

a) 3 had no follow-up
b) 11 lost MMR (1 of 11 with blast crisis)
c) 1 died before loss of MMR
d) 1 restarted TKI before loss of MMR

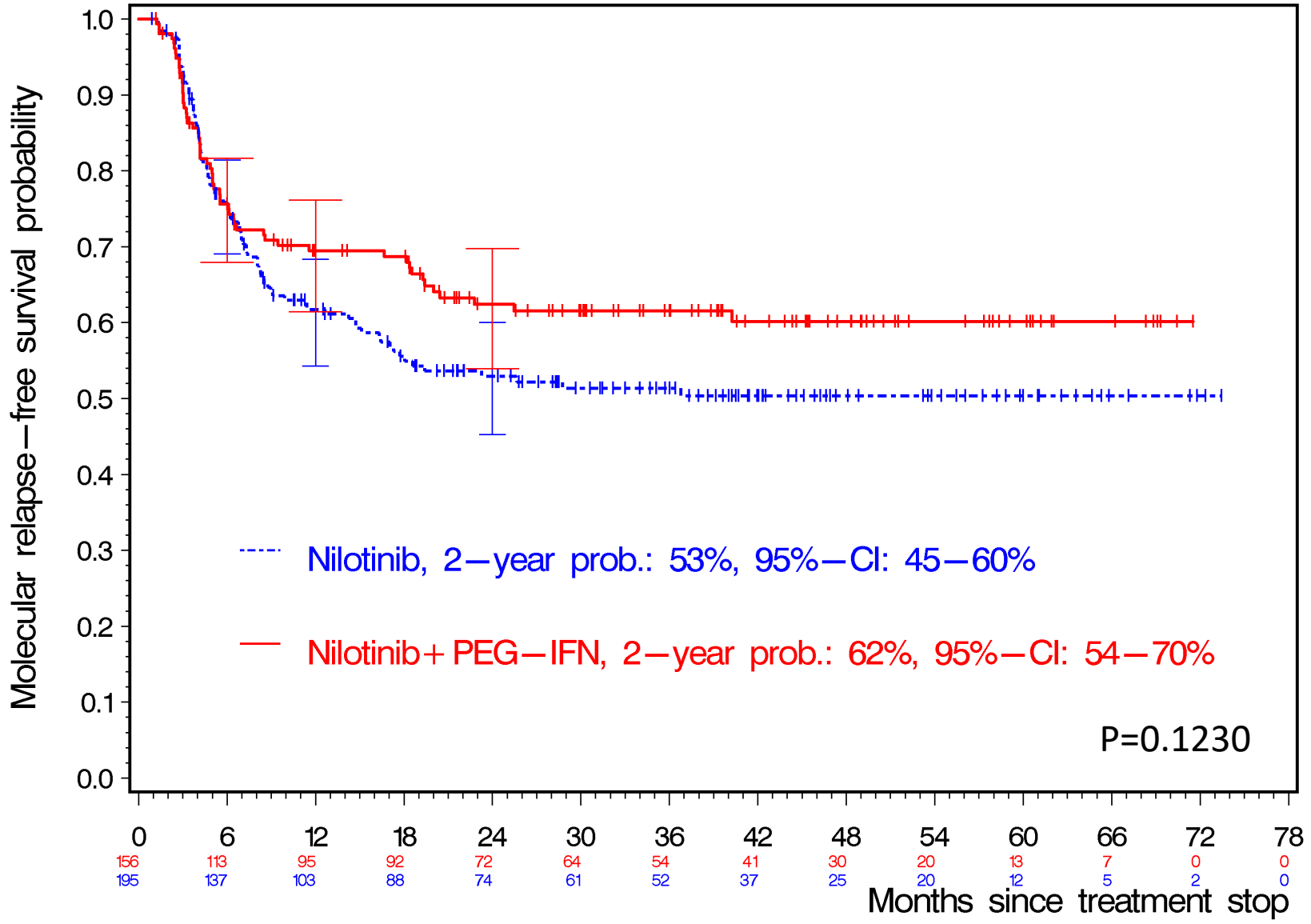


Molecular relapse free survival after treatment discontinuation, ITT

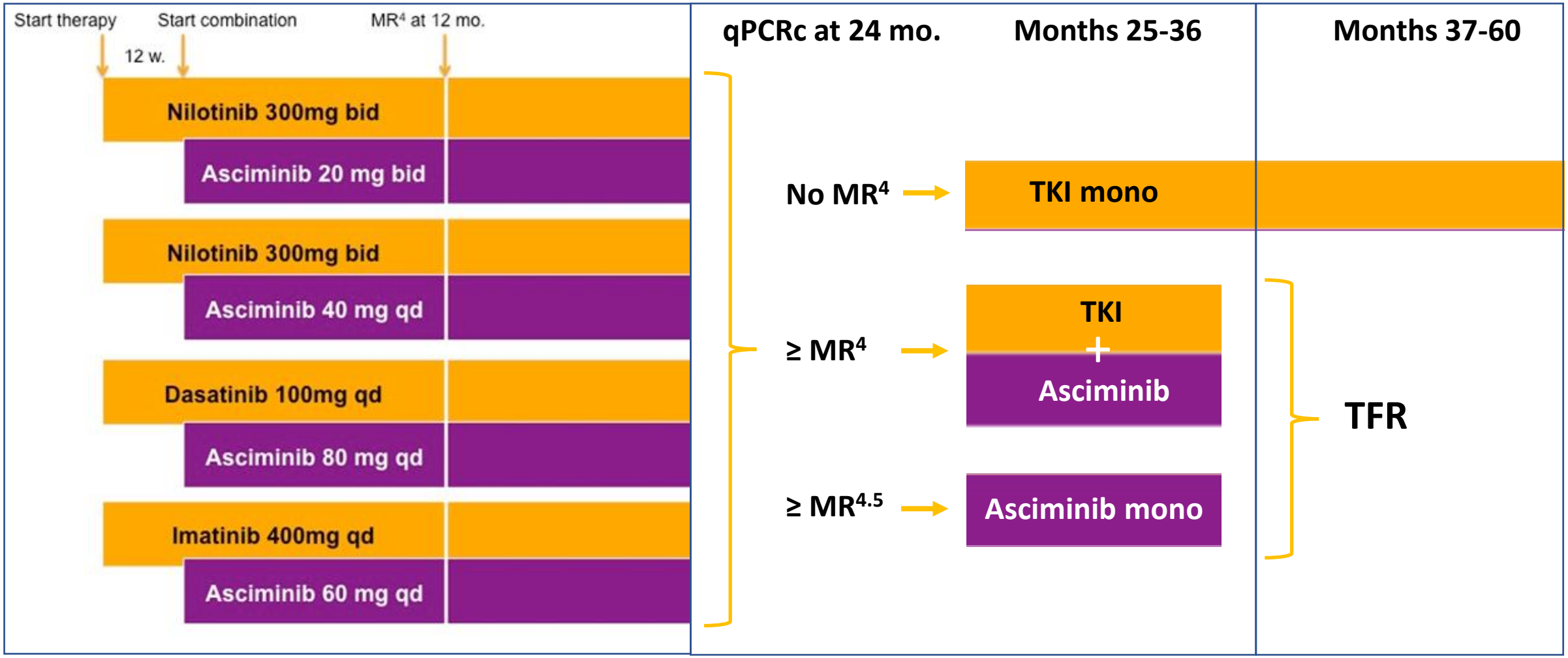
Probability of MMR **at** 12 months after discontinuation:

Nilotinib (n=195):
62% (95%-CI: 54-68%)

Nilotinib + IFN (n=156):
69% (95%-CI: 61-76%)



FASCINATION: Study design



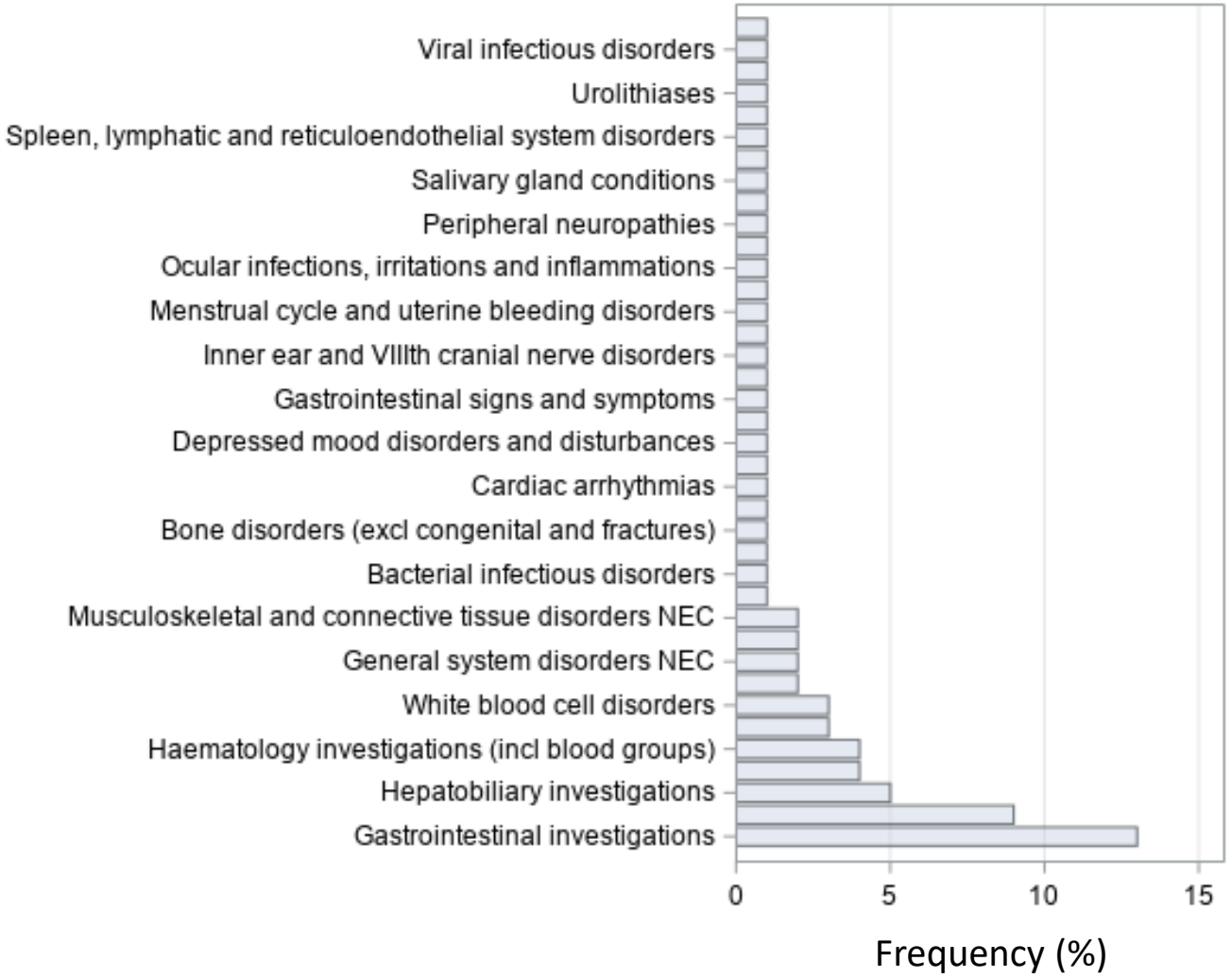
Ernst et al., EHA 2023

Molecular response

	MMR (%)	MR^4 (%)	$MR^{4.5}$ (%)	MR^5 (%)	$MR^{5.5}$ (%)	N (total)
At month 3	26 (21)	5 (4)	2(2)	1 (1)	0	124
At month 6	69 (57)	28 (23)	13 (11)	6 (5)	2 (2)	121
At month 9	73 (63)	33 (29)	19 (17)	6(5)	3 (3)	115
At month 12	77 (68)	43 (38%)	25 (22)	9 (8)	3 (3)	114

Ernst et al., EHA 2023

Adverse events (CTC grades 3 + 4)



Cohort	AE grade 3-4 (%)
Nilotinib + Asciminib (20mg BID)	13 (10)
Nilotinib + Asciminib (40mg QD)	15 (12)
Dasatinib + Asciminib	10 (8)
Imatinib + Asciminib	9 (7)
Total	**47 (38)**

Ernst et al., EHA 2023

ASCEND-CML Treatment Schema

Inclusion:
- CML-CP
- Aged 18+
- Good organ fx
- ECOG 0-2
- e13/14a2 or e1a2

Asciminib 40mg BID

3 months	6 months	12 months	18 months
BCR::ABL1 > 10%	*BCR::ABL1* > 10%	*BCR::ABL1* > 1%	*BCR::ABL1* > 1%

Asciminib + addition of either nilotinib, dasatinib or imatinib (physician discretion)

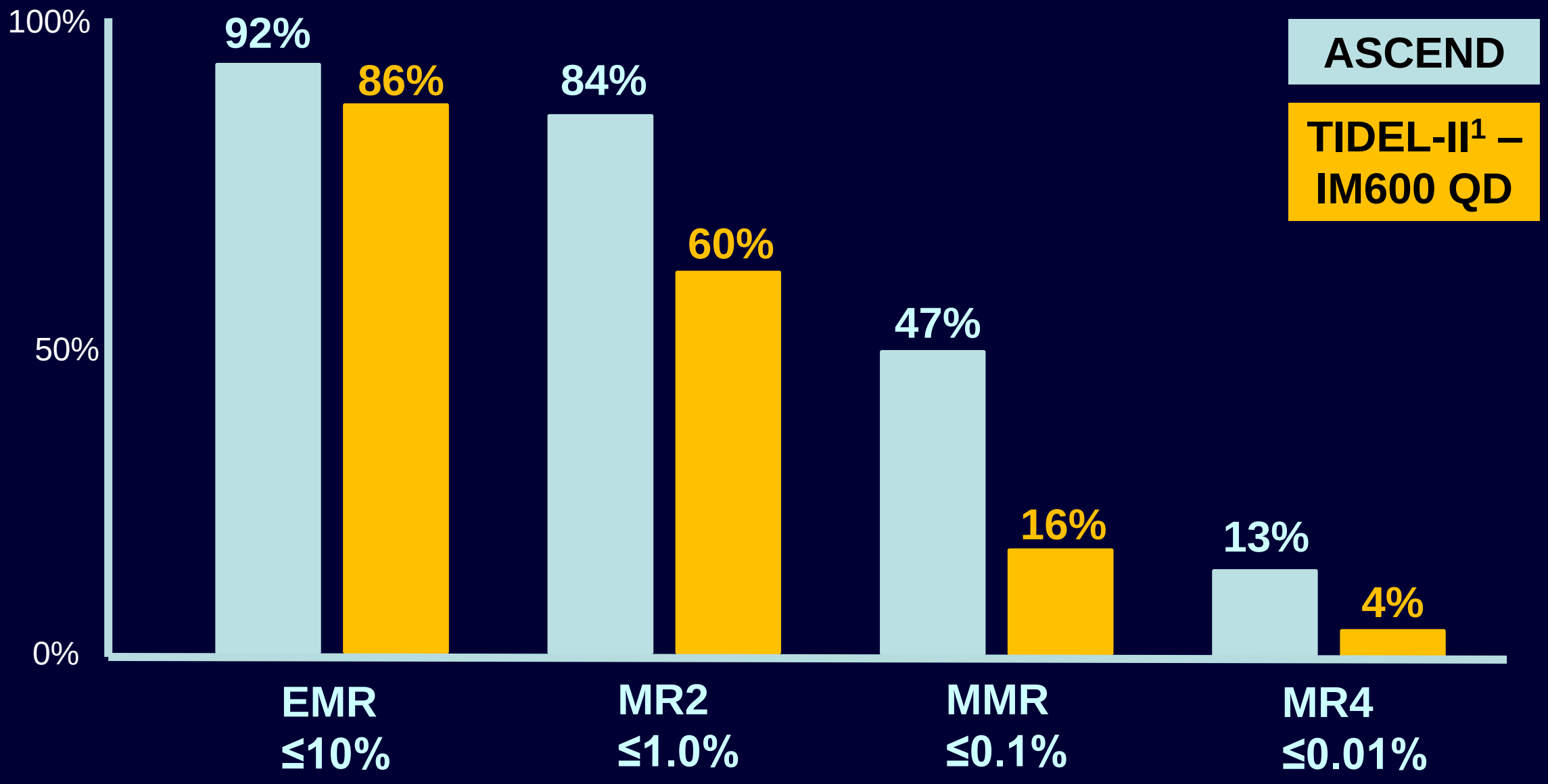
	BCR::ABL1 1.1 - 10%	*BCR::ABL1* 0.11 – 1%	*BCR::ABL1* 0.011 – 1%

Asciminib 80mg BID

BCR::ABL1 ≤10%	*BCR::ABL1* ≤1%	*BCR::ABL1* ≤0.1%	*BCR::ABL1* ≤0.01%

Asciminib 40mg BID (80mg QD)

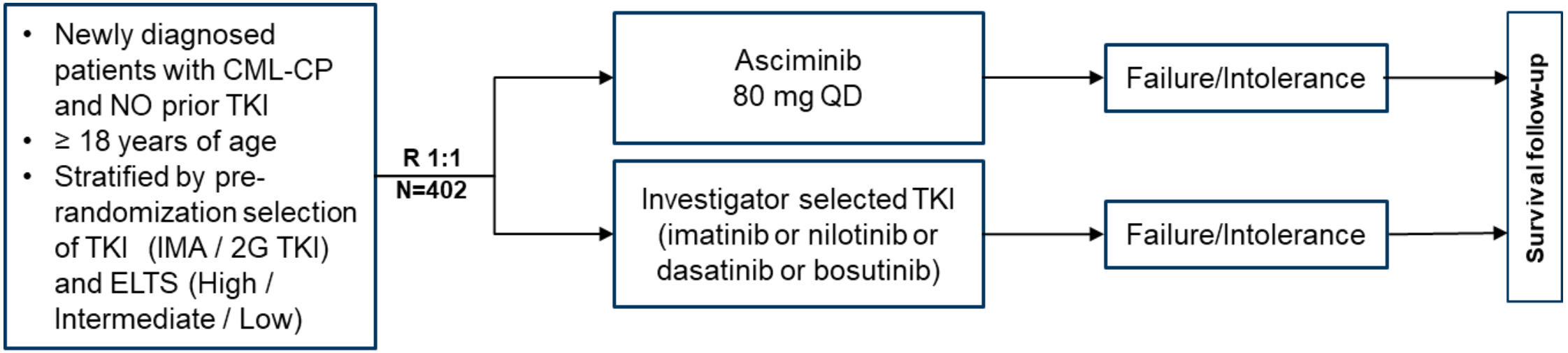
Molecular response at 3 months N=76



1. Yeung et al Blood 2015

Study Design

A phase III, multi-center, open-label, randomized study of oral asciminib versus Investigator selected TKI in newly diagnosed Ph+ CML in Chronic Phase



QD, once daily; CML, chronic myeloid leukemia; CP, chronic phase; 2G: 2nd generation; IMA, Imatinib; R, randomized; ELTS, EUTOS Long-term survival; TKI, tyrosine kinase inhibitor

Data on file. Study Protocol No. CABL001J12301 Clinical Trial Protocol. Novartis Pharmaceuticals Corp.

Novartis Press release, 8.1.2024

Novartis Scemblix® shows superior major molecular response (MMR) rates vs. standard-of-care TKIs in Phase III trial for newly diagnosed patients with chronic myeloid leukemia

- *ASC4FIRST trial **met both primary endpoints** with clinically meaningful and statistically significant results; Scemblix® (asciminib) shows superior MMR rates at week 48 vs. standard-of-care TKIs (imatinib, nilotinib, dasatinib, and bosutinib) in newly diagnosed Ph+ CML-CP patients*[1]

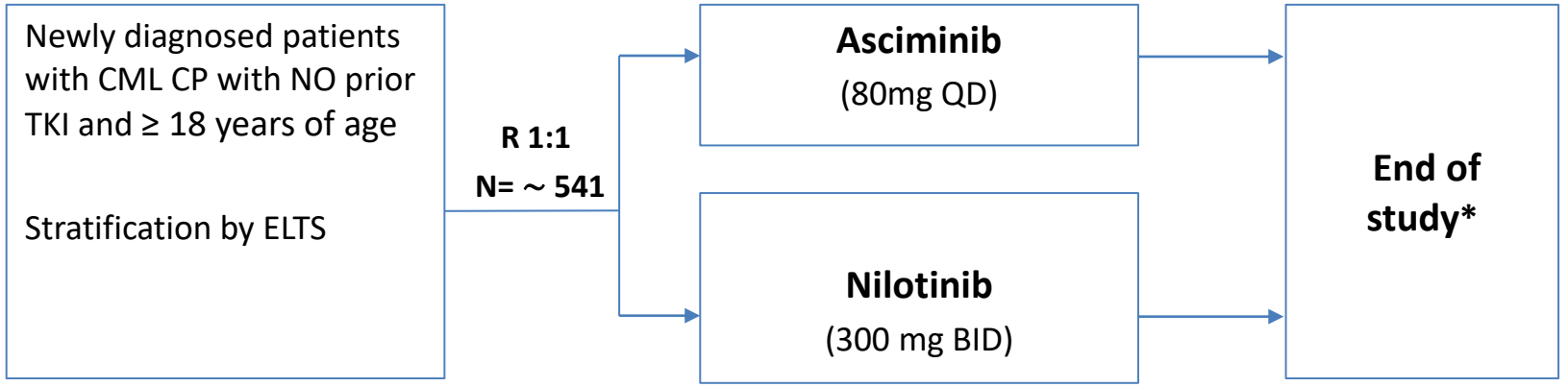
- *Scemblix demonstrated a favorable safety and tolerability profile with fewer adverse events (AEs) and treatment discontinuations vs. standard-of-care TKIs; no new safety signals were observed*[1]

- *With current standard-of-care TKIs, more than 60% of newly diagnosed patients with CML fail to meet molecular response goals at one year; intolerance and AEs remain a primary reason for discontinuing TKI therapy, with discontinuation rates due to AEs of up to 25% by five years*[2-13]

Study Design / Patient Population

ASC4START

A phase IIIb, multi-center, open-label, randomized study of tolerability and efficacy of asciminib versus nilotinib in Ph+ CML in Chronic Phase



*Participants can be treated in the study until approximately 64 discontinuations of study treatment due to AE (TTDAE) are met. End of study is defined as when the necessary number of events has been reached and when end of treatment and the last assessments as per Table 1-1 are completed. Refer to Section 6.1.5 Treatment Duration for additional details.

N= Approximate number of participants required to achieve 64 events (refer to Section 9.9)

Data on file. Study Protocol No. CABL001J12302 Clinical Trial Protocol.

New ideas - ARTIST Study:
Asciminib frontline risk adapted

CML at diagnosis

80 mg Asciminib

ELTS
Cytogenetics
BCR::ABL1/GUSB
NGS

- ELTS high risk
- High risk cytogenetics
- ASXL1 mutations

R

80 mg Asciminib

80 mg Asciminib
+ 50 mg Dasatinib
(or + 15 mg Ponatinib)

(160 mg Asciminib)

CML HORIZONS

HYBRID MEETING 2024

Vilnius, Lithuania

24–26 May 2024