ISSUES IN THE MANAGEMENT OF CHRONIC MYELOID LEUKEMIA IN 2022

CHALLENGES IN HEMATOLOGY
MUMBAI HAEMATOLOGY GROUP

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Princess Margaret Cancer Centre UHN

Content

- 1. examine the progress in cml therapy and determine when salvage therapy is indicated
- 2. where does treatment free remission (TFR) fit in
- 3. how to prevent, if possible, the need to switch drugs and at the same time deliver a safe therapy
- 4. what is available for third line therapy – an update
- 5. understanding when to cut bait and run

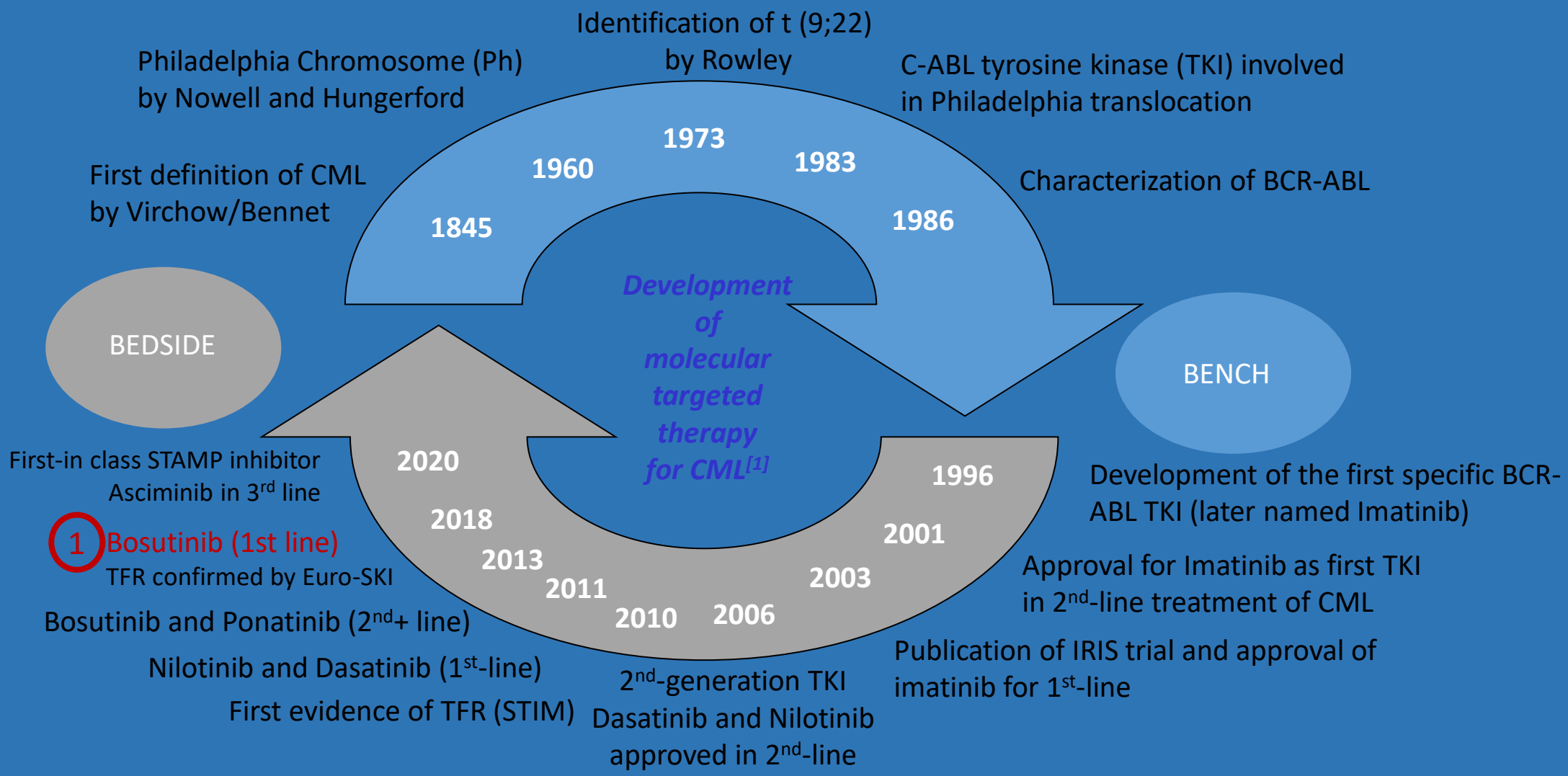
Disclosure

Research Support/P.I.	Pfizer, Takeda, Novartis, Kartos
Employee	
Consultant	BMS, Pfizer, Takeda, Jazz, Paladin, Novartis
Stockholder	
Speakers Bureau	
Scientific Advisory Board	BMS, Takeda, Pfizer, Blueprint, Sanofi, Merck, Sparc
Other	Incyte

Caution

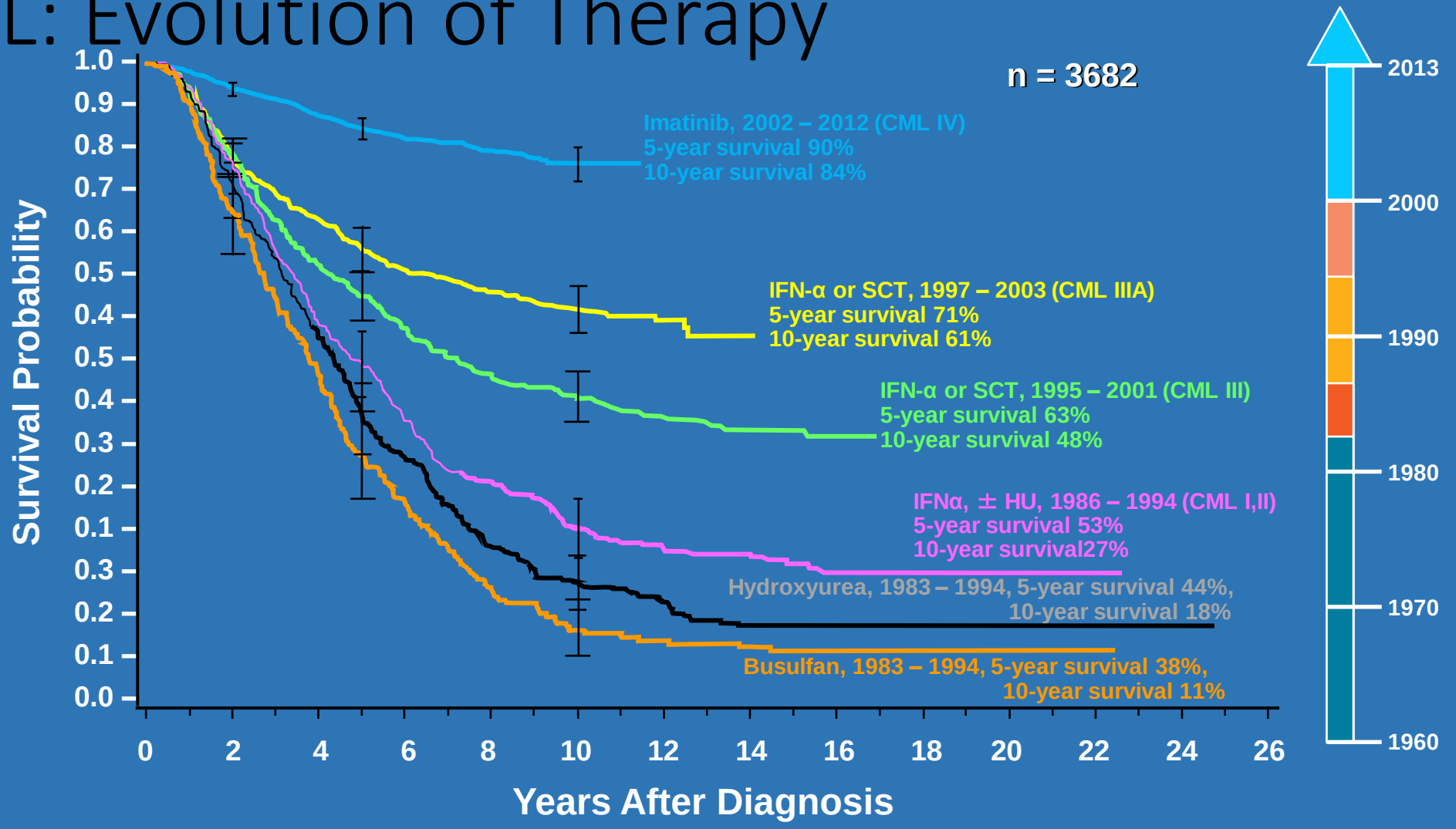
- Not everything to be discussed today reflects what is on the package monograph for the drugs mentioned
- These points should be considered off label at this time
- Discussions of drugs are general and may not apply to what is available in your jurisdiction

Chronic Myeloid Leukemia (CML): A Model Disease in Oncology



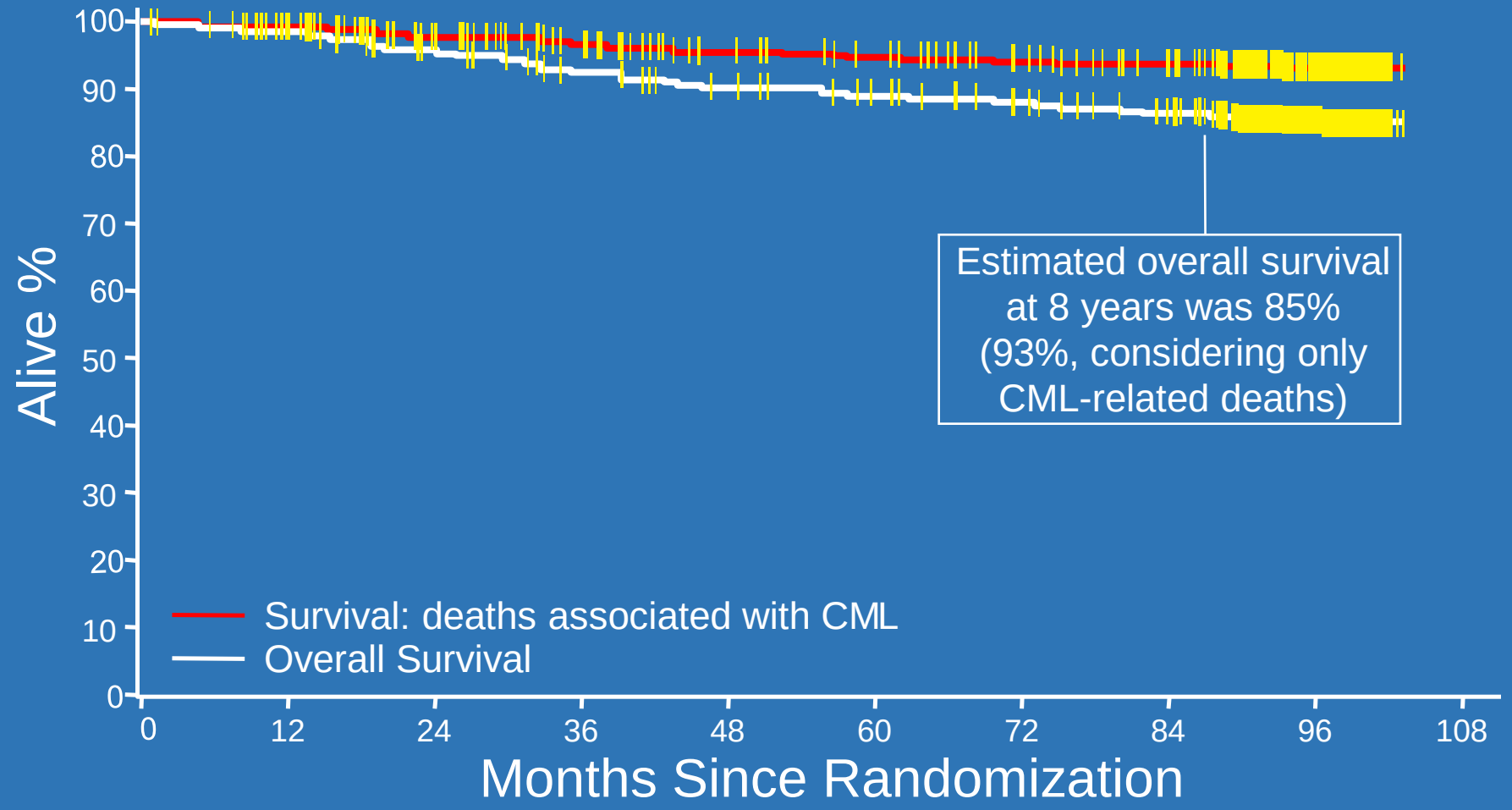
adapted from: Balabanov S. et al. ***Drug Discov Today Technol***. 2014;11:89.

CML: Evolution of Therapy



aCML IV; bCML IIIA; cCML III.
HU, hydroxyurealFN-α, Interferon-alpha; SCT, stem cell transplant.
German CML Study Group, Update 2013.

OS on First-Line Imatinib (IRIS Study)



Deininger M, et al. *ASH Annual Meeting Abstracts.* 2009;114:1126.

Efficacy Data from Studies Using Second Generation Drugs First Line

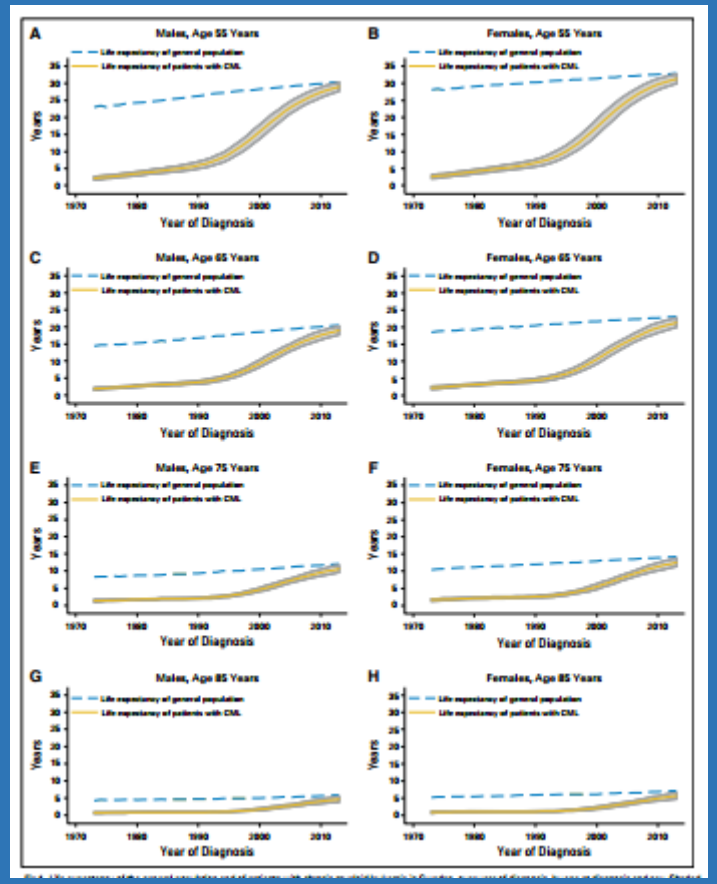
Table 2 Efficacy Data for Studies of BCR-ABL Inhibitors in the First-Line Treatment of CML-CP

Study	Regimen	CCyR by 12 mo	MMR by 12 mo	EFS	OS
IRIS[10,11,15]	Imatinib 400 mg QD	69%[a]	39%[a]	92% at 18 mo	97% at 18 mo
TOPS[5,18]	Imatinib 400 mg QD	66%	40%[b]	95% at 24 mo	97% at 24 mo
	Imatinib 400 mg BID	70%	46%[b]	95% at 24 mo	98% at 24 mo
GIMEMA[17]	Nilotinib 400 mg BID	100%	85%[b]	92% at 30 mo	99% at 30 mo
MDACC[12]	Nilotinib 400 mg BID	97%[b]	81%[b]	90% at 24 mo	100% at 24 mo
MDACC[13]	Dasatinib 50 mg BID or 100 mg QD	98%[b]	71%[b]	88% at 24 mo	100% at 24 mo
ENESTnd[9,18,19]	Nilotinib 300 mg BID	80%	44%[b]	96% at 24 mo	97% at 24 mo
				95% at 36 mo	95% at 36 mo
	Nilotinib 400 mg BID	78%	43%[b]	98% at 24 mo	98% at 24 mo
				97% at 36 mo	97% at 36 mo
	Imatinib 400 mg QD	65%	22%[b]	94% at 24 mo	96% at 24 mo
				93% at 36 mo	94% at 36 mo
DASISION[9,20]	Dasatinib 100 mg QD	83%	46%	94% at 24 mo	95% at 24 mo
	Imatinib 400 mg QD	72%	28%	92% at 24 mo	95% at 24 mo

Jabbour and Lipton, 2013

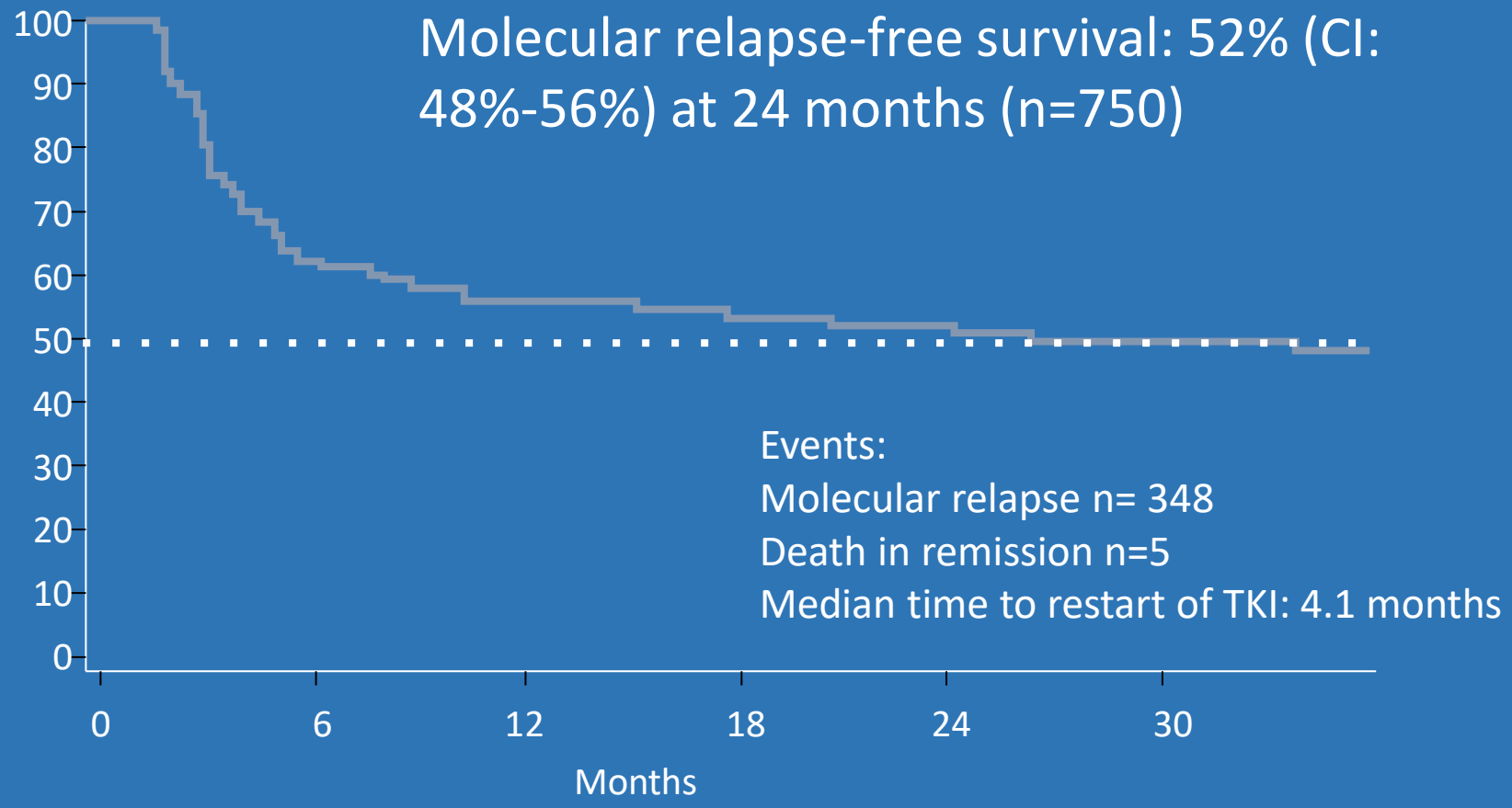
Similar results in the Bosutinib BELA and BFORE and the Ponatinib EPIC Studies

Life Expectancy of Swedish CML Patients Compared to General Population



Bower et al (JCO) 2016

STOPPING TKI IN A VERY LARGE COHORT OF EUROPEAN CML PATIENTS: RESULTS OF THE EURO-SKI TRIAL



Molecular relapse-free survival: 52% (CI: 48%-56%) at 24 months (n=750)

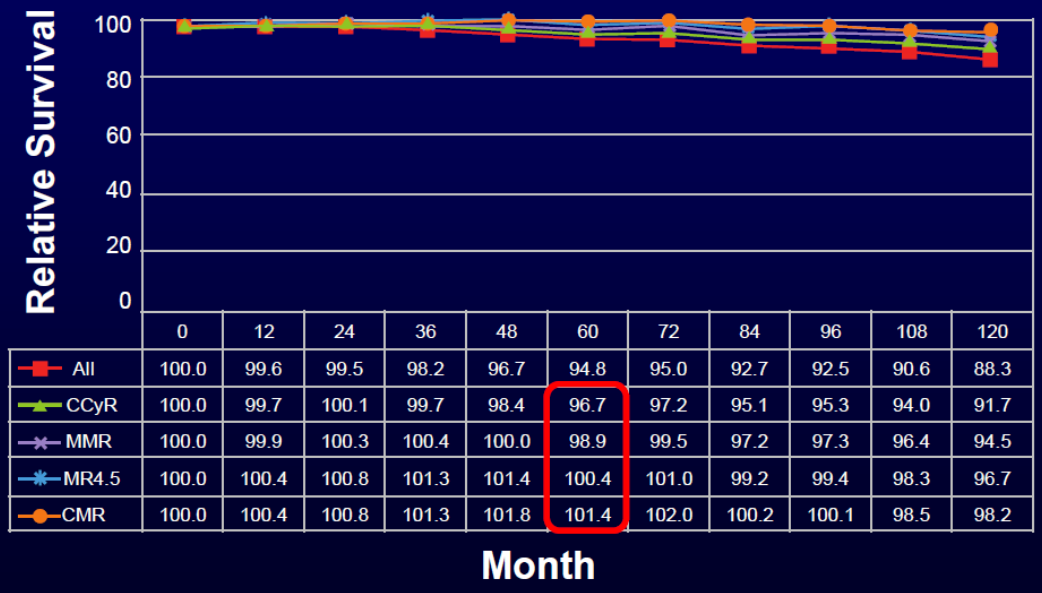
Events:
Molecular relapse n= 348
Death in remission n=5
Median time to restart of TKI: 4.1 months

EURO-SKI presented by Johan Richter at EHA 2016

ELN European LeukemiaNet

Relative Survival with TKI by Response to Therapy

- 483 pts with CML treated with imatinib 400mg (n=71), imatinib 800 mg (n=201), dasatinib (n=111) or nilotinib (n=101)
- 5-yr relative survival 94.8% [92.1 - 97.4]



	0	12	24	36	48	60	72	84	96	108	120
All	100.0	99.6	99.5	98.2	96.7	94.8	95.0	92.7	92.5	90.6	88.3
CCyR	100.0	99.7	100.1	99.7	98.4	96.7	97.2	95.1	95.3	94.0	91.7
MMR	100.0	99.9	100.3	100.4	100.0	98.9	99.5	97.2	97.3	96.4	94.5
MR4.5	100.0	100.4	100.8	101.3	101.4	100.4	101.0	99.2	99.4	98.3	96.7
CMR	100.0	100.4	100.8	101.3	101.8	101.4	102.0	100.2	100.1	98.5	98.2

Sasaki et al. Lancet Hematology 2015

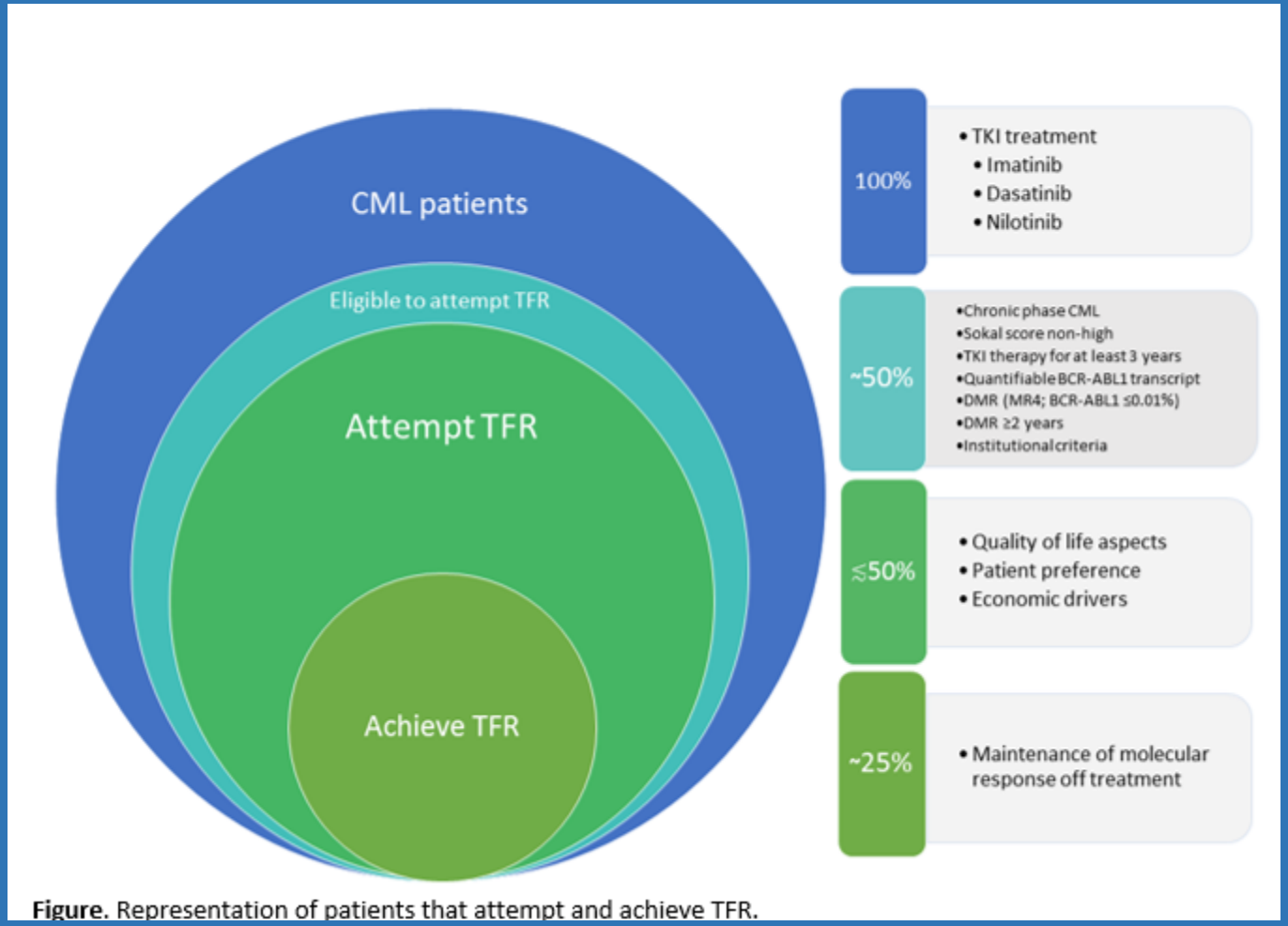


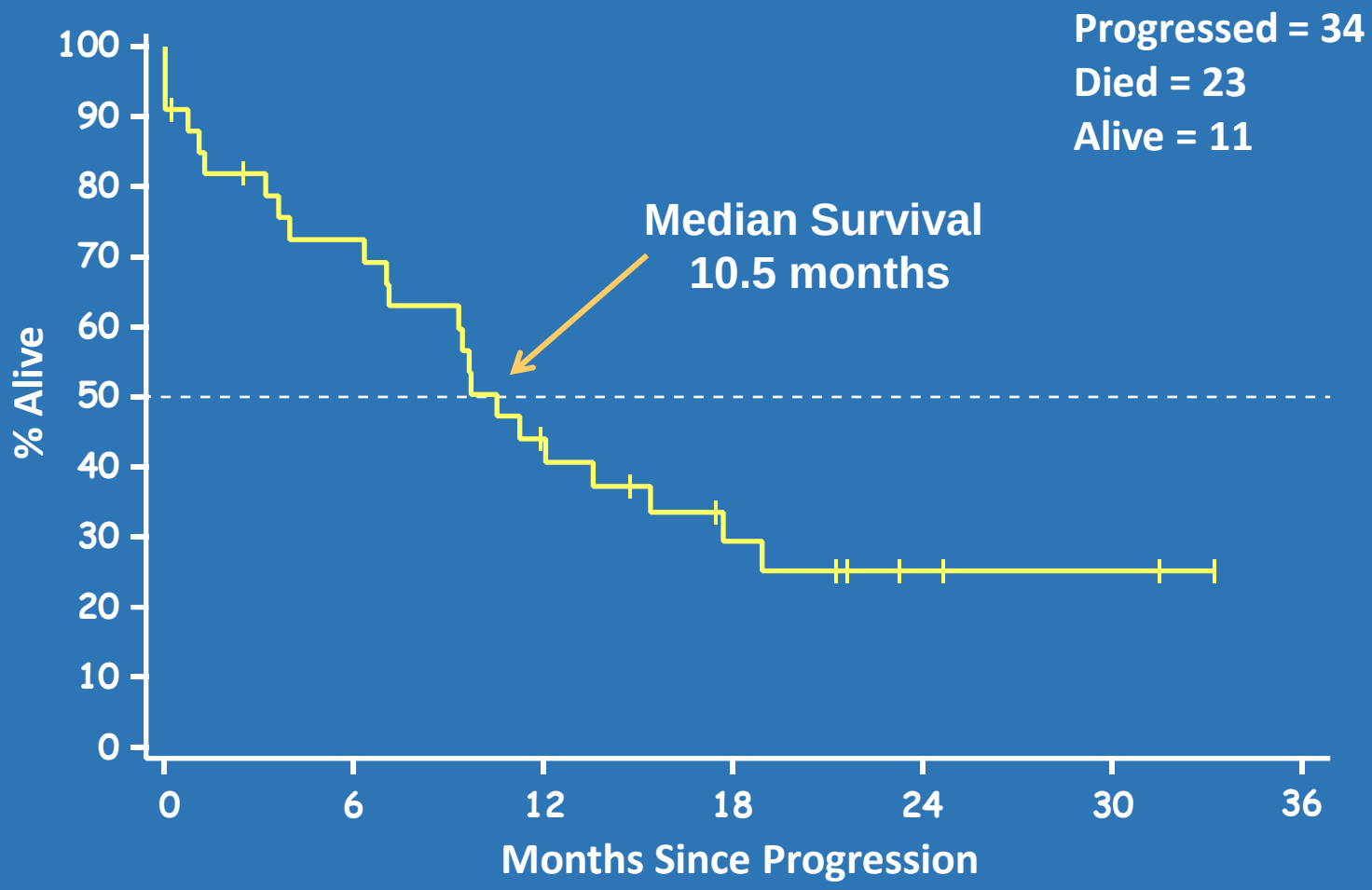
Figure. Representation of patients that attempt and achieve TFR.

Garcia-Horton, Lipton, JNCCN (2020)

Reality

- Although TFR is a noble goal for all new CML patients, in actuality, the majority will not achieve this with currently available management
- Thus we need to prevent patients from disease progression
- We also need to deal with the side effects and adverse events that may occur or be sustained over a long period of time, perhaps indefinitely, so that they will be compliant with therapy

Survival After Progression to AP/BP Imatinib Therapy



Saglio et al, 2011.

Determine the Goal of Therapy

- This is not the same for all patients
- It may depend on age, co-morbidities, patient desires
- Unfortunately, it sometimes depends on guidelines and remuneration of drugs which are not uniform even in one country and depends on public or private payer
- A general agreement between patient and health care provider about long term goals, will often help determine how much in the way of side effects might be tolerated in order to achieve that end

Choosing a Front Line Therapy

- What is approved and reimbursed
- What is safest given the patient's co-morbidities
- Goal of therapy – disease control vs treatment-free remission
- What fits best into the patient's lifestyle
- Patient expresses a preference – Doctor Internet comes into play here
- Familiarity and comfort of the prescriber

Choosing a Salvage Therapy

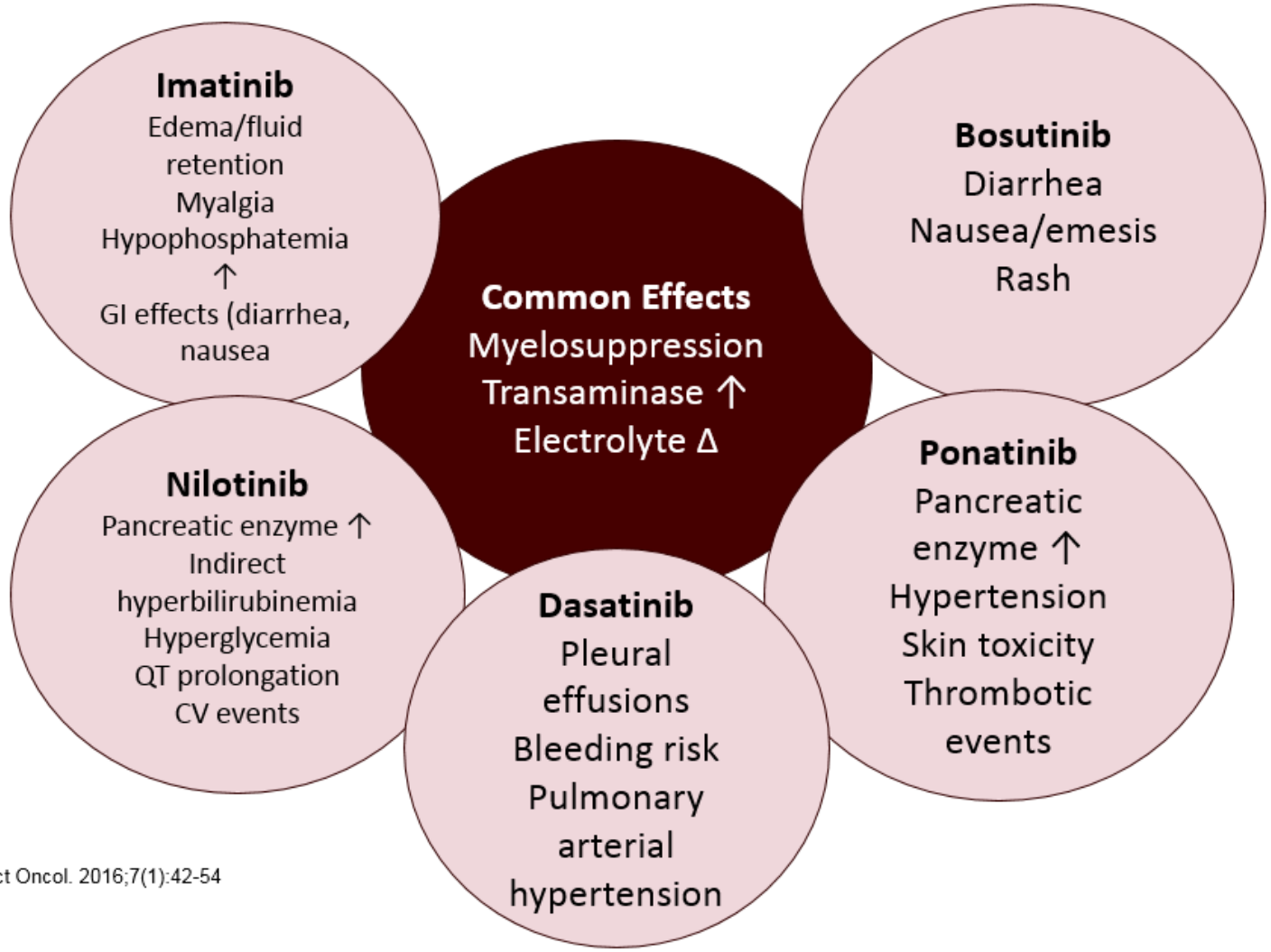
- All the criteria for the front line decision
- Reason for salvage need
  - Intolerance
  - Resistance

Defining Treatment Failure

- Inability to continue therapy because of side effects or toxicity – aka “intolerance”
- Disease resistance
  - Failure to achieve milestones – when does this become resistance?
  - Loss of a previously attained response while on therapy – are loss of DMR (MR4 or MR4.5), MMR (MR3), CCyR (MR2), CHR the same thing?
  - Failed attempt at TFR – are loss of DMR, MMR, CCyR the same thing?

In general, no side effect is unique to any single drug, although some products may be more likely to have that side effect than others

Adverse Event Spectrum of TKIs in CML



Adapred from Bauer S, et al. J Adv Pract Oncol. 2016;7(1):42-54

Most Frequent AEs of Any Grade (and Grade 3/4 Laboratory Abnormalities in CML on 1G and 2G TKIs

	Imatinib	Dasatinib	Nilotinib	Bosutinib
Abdominal pain	X			X
Arthralgia			X	
Constipation			X	
Cough			X	X
Diarrhea	X	x	X	X
Dyspnea		X		
Fatigue	X	X	X	X
Fluid retention	X	X		
Superficial edema	X	X		
Pleural effusion		X		
Headache	X	X	X	X
Hemorrhage	X			
Joint pain	X			
Muscle cramps	X			
Musculoskeletal pain	X	X		
Myalgia	X			

	Imatinib	Dasatinib	Nilotinib	Bosutinib
Nasopharyngitis	X		X	
Nausea	X		X	X
Pain in extremity			X	
Pruritus			X	
Pyrexia			X	X
Rash	X		X	X
URTI	X			
Vomiting	X		X	X
Grade 3/4 lab abnormalities				
Thrombocytopenia		X	X	X
Neutropenia	X	X	X	
Elevated lipase			X	
Hypophosphatemia			X	

Bauer S, et al. J Adv Pract Oncol. 2016;7(1):42-54

We need to pay attention to side effects in the short run. With time, they will continue to be an issue and may worsen.
As well, new long term side effects may develop that can be chronic, serious and/or affect quality of life.

For example - ENESTnd 10-year Update

Table 5 Cardiovascular events (CVEs) before 5 years and after 5 years by Framingham risk category at baseline.

	Framingham general risk of CVE < 10%			Framingham general risk of CVE ≥ 10% to <20%			Framingham general risk of CVE ≥ 20%		
	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg once daily	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg once daily	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg once daily
CVEs occurring before 5 years									
All patients, *n*	178	176	182	41	52	49	40	38	33
All CVEs	4 (2.2)	7 (4.0)	1 (0.5)	5 (12.2)	10 (19.2)	2 (4.1)	6 (15.0)	11 (28.9)	1 (3.0)
Ischemic heart disease	3 (1.7)	5 (2.8)	1 (0.5)	3 (7.3)	6 (11.5)	1 (2.0)	2 (5.0)	5 (13.2)	1 (3.0)
Peripheral arterial occlusive disease	1 (0.6)	0	0	1 (2.4)	1 (1.9)	0	3 (7.5)	5 (13.2)	0
Ischemic cerebrovascular disease	0	1 (0.6)	0	1 (2.4)	4 (7.7)	1 (2.0)	1 (2.5)	1 (2.6)	0
Other CVEs	0	1 (0.6)	0	1 (2.4)	0	0	2 (5.0)	1 (2.6)	0
CVEs occurring after 5 years									
Patients on treatment for > 5 years, *n*	115	125	94	25	33	23	24	21	21
All CVEs	10 (8.7)	19 (15.2)	1 (1.1)	7 (28.0)	16 (48.5)	4 (17.4)	8 (33.3)	7 (33.3)	1 (4.8)
Ischemic heart disease	4 (3.5)	11 (8.8)	1 (1.1)	3 (12.0)	7 (21.2)	2 (8.7)	2 (8.3)	2 (9.5)	1 (4.8)
Peripheral arterial occlusive disease	2 (1.7)	6 (4.8)	0	3 (12.0)	3 (9.1)	0	4 (16.7)	6 (28.6)	0
Ischemic cerebrovascular disease	4 (3.5)	6 (4.8)	0	1 (4.0)	7 (21.2)	1 (4.3)	2 (8.3)	3 (14.3)	0
Other CVEs	0	0	0	0	1 (3.0)	1 (4.3)	0	1 (4.8)	0

Values are *n* (%) unless otherwise noted.

Kantarjian et al (2021) Leukemia

Long Term Side Effects

Long-Term Safety Review of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia - What to Look for When Treatment-Free Remission is not an Option

Jeffrey H Lipton, Tim H Brümmendorf, Carlo Gambacorti-Passerini, Valentin Garcia-Gutiérrez, Michael W Deininger, Jorge E Cortes

Blood Reviews (2022) (Published on Line)

The emergence of increasing frequency of serious long term side effects, has prompted long-term proponents of these medications to suggest a switch to a less risky alternative for long term maintenance, once a deep response has been achieved and TFR deemed unlikely.

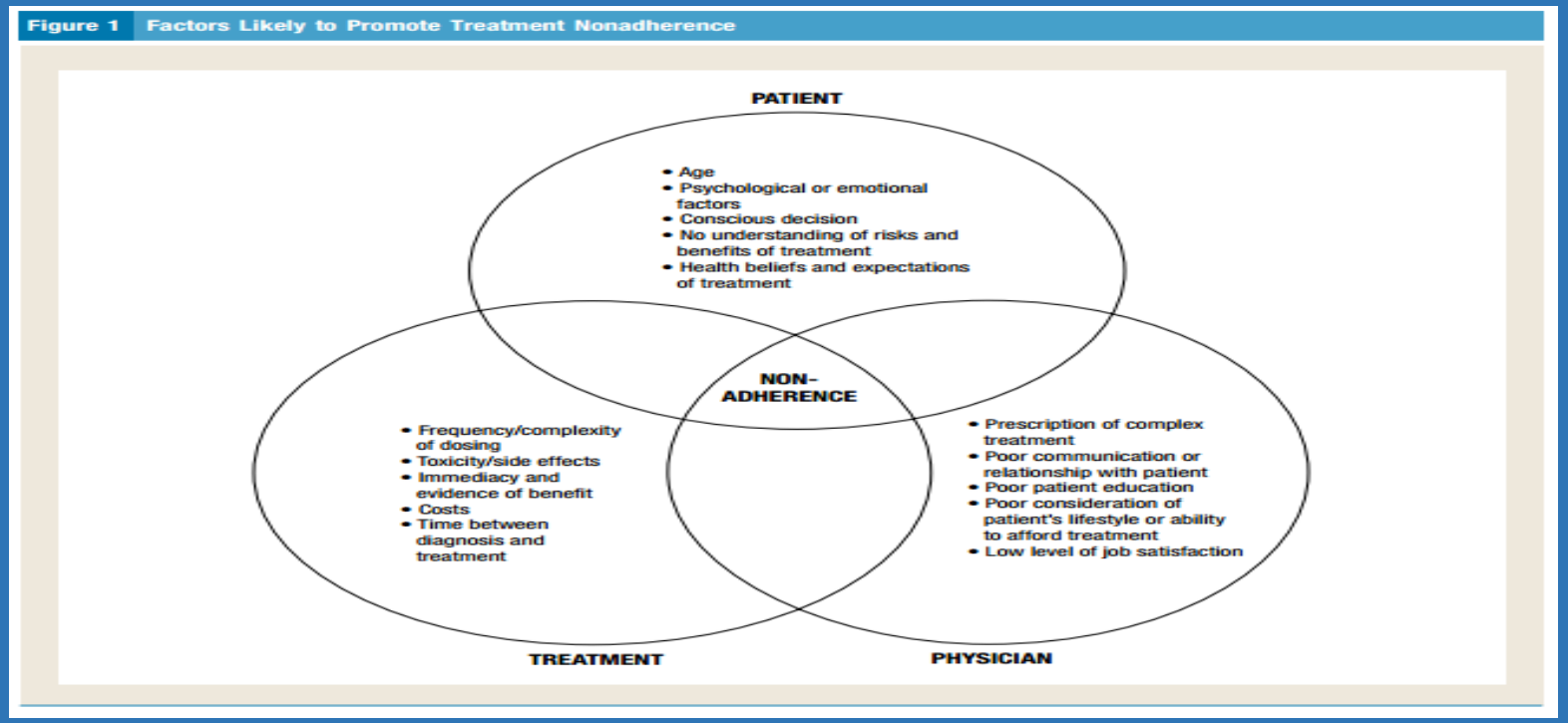
The best way to deal with a side effect is to try to avoid it

- This can be done in several ways
- Getting to know a patient, by getting a detailed clinical history, doing a complete physical exam and performing any laboratory tests needed to define pre-existing conditions or co-morbidities is very important
- Treating co-morbidities to reduce risk is an imperative – whether it is done by the CML treater, the primary physician or health care worker or via a referral is absolutely necessary
- If a number of CML therapies are available, choosing the one with the least potential problems is ideal
- Choosing a drug with which the treating health care worker is most comfortable, may also reduce side effects

General Management Issues

- Review of medications to eliminate if possible drug interactions
  - Eg cyp3a4 meds
- Review of supplements, naturopathic medications, herbal medications to eliminate potential interactions
  - Eg Recreational drugs
- Review of diet to be sure that there are no influences
  - Eg Dairy products in the case of GI problems
- Review of lifestyle to reduce potential influences
  - When a drug is being taken – time of day, relationship to meals, lying down after taking a drug, etc

Compliance…Likely the Most Common Reason for Failure



Jabbour (2012) Clin Lymph Myel Leuk

Factors that May Impact Adherence

- **Lack of personal organization**
  - No specific time set when to take medication
- **TKI-related adverse reactions**
  - Some are avoidable and require prompt intervention
    - Example - In one case, edema was solved by changing calcium channel blocker drug (amlopidine) to a thiazide-based antihypertensive therapy.
- **The quality of information exchanged between healthcare providers and patients**
- **Quality of social support**

Okumura LM, et al. Pharm Pract (Granada). 2015 Apr-Jun;13(2):559.

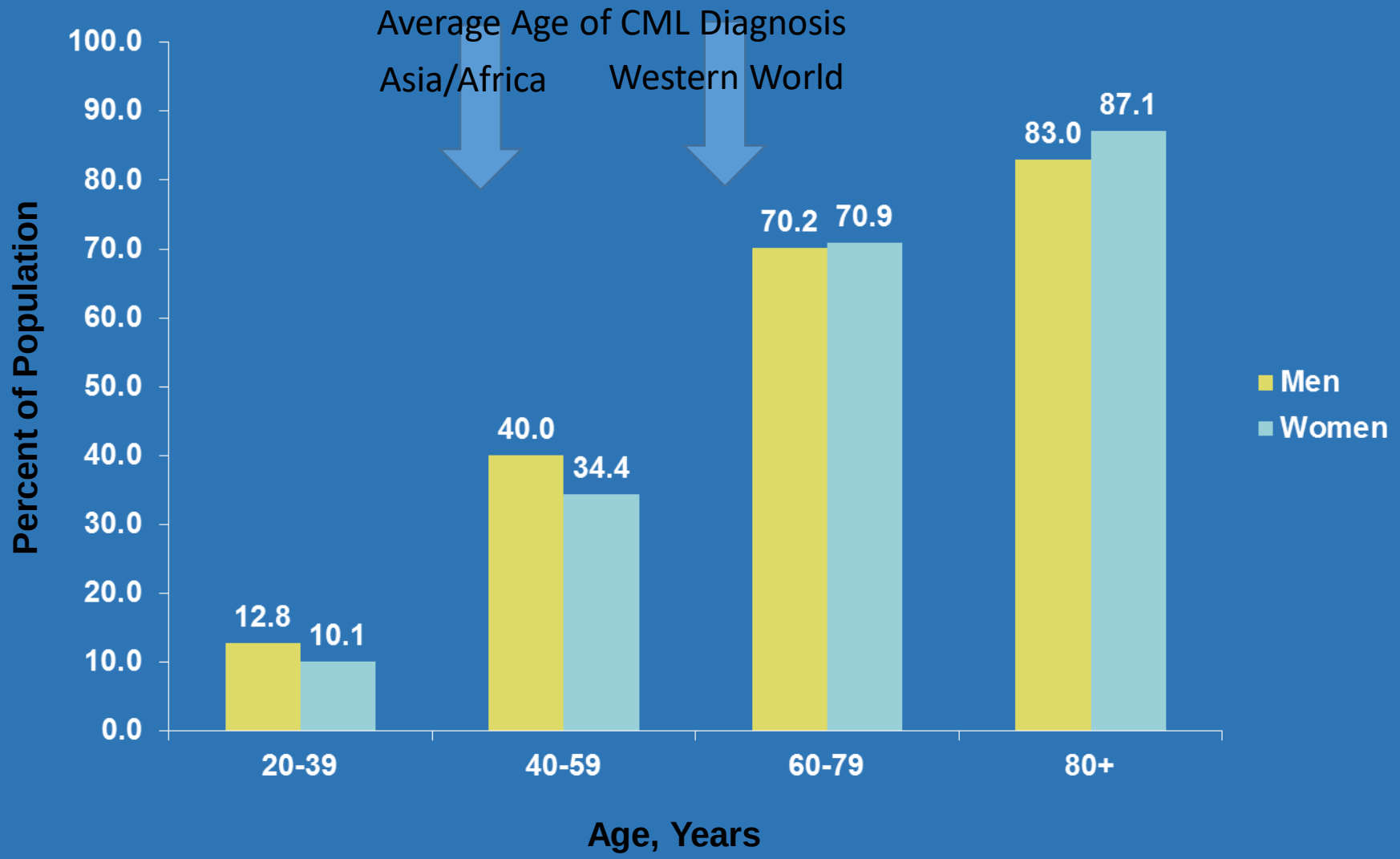
If poor compliance is due to side effects…

- First try to determine if the mode of taking the drug is responsible – timing, with meals, etc
- Secondly determine if there is a manipulation such as another medication that will overcome the side effect – nausea, diarrhea, dyspepsia, etc
- Consider a drug switch, but remember side effects are not unique to any one drug

If compliance is related to the patients lack of motivation or denial or resistance to taking a therapy or a belief that something else will cure them - religion/faith, naturopathy/homeopathy - and not due to side effects, then a change in drug is not likely going to do anything. This is important to determine. You could be batting your head against a brick wall.

Prevalence of Cardiovascular Disease in Adults

National Health and Nutrition Examination Survey 2007-2010



Go A, et al. *Circulation*. 2013;127:e6-e245.

Past Medical History

	IM	NIL	DAS	BOS	PON
Diabetes					
POAD					
CHF					
Prolonged QT					
PHT					
GI Bleeding					
IBS					
Pancreatitis					
Impaired LF					
Thrombembolism					

Problems Potential

- Low
- Somewhat elevated
- Elevated
- Typically contraindicated

- Few absolute contraindications
- Many better or worse picks
- Clinical judgment crucial

Courtesy Deininger

Additional Testing Indicated Prior to Using Various TKIs

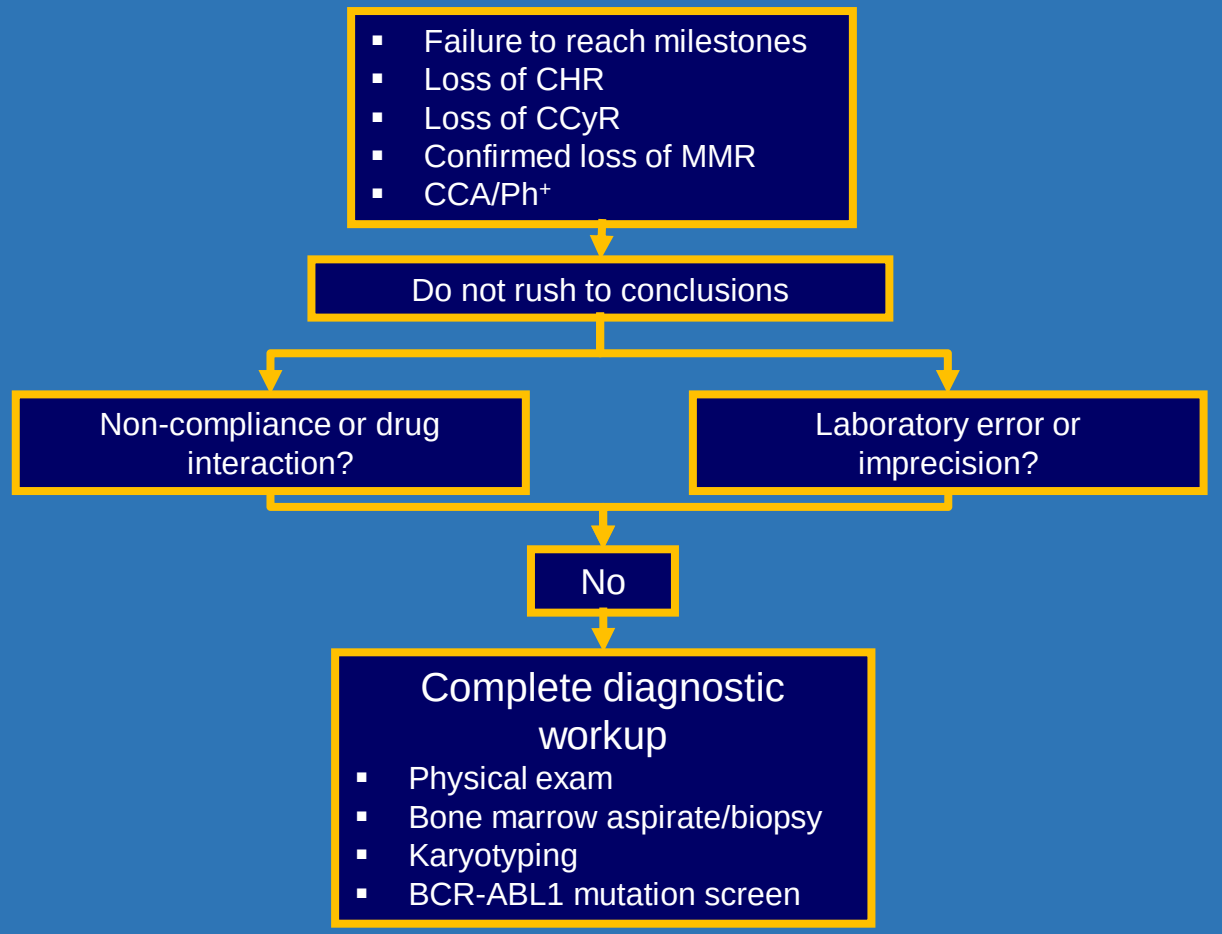
Table 3. Provisional Recommendations for Cardiovascular/Cardiometabolic Follow-Up of Patients Receiving BCR-ABL1 TKIs

Assessment	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Baseline	Follow good clinical practice				
Clinical cardiovascular assessment, including blood pressure		REC	REC	REC	REC
Fasting glucose		REC	ACI	ACI	REC
Fasting lipid panel		REC	ACI	ACI	REC
Echocardiogram		ACI	ACI*	ACI	ACI
ECG		REC†	REC	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC
1-month follow-up					
Clinical cardiovascular assessment		REC	REC	ACI	REC
Blood pressure check		ACI	ACI	ACI	REC
3- to 6-month follow-up					
Clinical cardiovascular assessment		REC	REC	REC	REC
Blood pressure check		REC	ACI	ACI	REC
Fasting glucose		REC	ACI	ACI	ACI
Fasting lipid panel		REC	ACI	ACI	REC
Echocardiogram		ACI	ACI*	ACI	ACI
ECG		ACI†	ACI	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC

NOTE. Practice guidelines regarding prevention of cardiovascular toxicity should be followed, including tobacco cessation counseling. In symptomatic patients or those with high cardiovascular risk, consider referral to cardiologist.
Abbreviations: ACI, as clinically indicated; ECG, electrocardiogram; REC, recommended; TKI, tyrosine kinase inhibitor.
*Low threshold for an echocardiogram in patient considered for treatment or being treated with dasatinib who has cardiopulmonary symptoms.
†ECG prior to starting, after 7 days after starting, and after each dose change (package insert).

Moslehi et al (2015) JCO

Recognizing TKI Failure – Do not Jump to Conclusions



Relative Activity Profile of Various TKIs in Imatinib-Resistant Mutants

Mutation	IC_{50}-fold increase relative to WT (W=1)				
	Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
M244V	0.9	0.9	2.0	1.2	3.2
L248R	14.6	22.9	12.5	30.2	6.2
L248V	3.5	3.5	5.1	2.8	3.4
G250E	6.9	4.3	4.4	4.6	6.0
Q252H	1.4	0.8	3.1	2.6	6.1
Y253F	3.6	1.0	1.6	3.2	3.7
Y253H	8.7	0.6	2.6	36.8	2.6
E255K	6.0	9.5	5.6	6.7	8.7
E255V	17.0	5.5	3.4	10.3	12.9
D276G	2.2	0.6	1.4	2.0	2.1
E279K	3.6	1.0	1.6	2.0	3.0
E292L	0.7	1.1	1.3	1.8	2.0
V299L	1.5	26.1	8.7	1.3	0.6
T315A	1.7	6.0	58.9	2.7	0.4
T315I	17.5	45.4	75.0	39.4	3.0
T315V	12.2	29.3	738.8	57.0	2.1
F317L	2.6	2.4	4.5	2.2	0.7
F317R	2.3	33.5	114.8	2.3	4.9
F317V	0.4	11.5	21.3	0.5	2.3
M343T	1.2	1.1	0.9	0.8	0.9
M351T	1.8	0.7	0.9	0.4	1.2
F359I	6.0	2.9	3.0	16.3	2.9
F359V	2.9	0.9	1.5	5.2	4.4
L384M	1.3	0.5	2.2	2.3	2.2
H396P	2.4	0.4	1.1	2.4	1.4
H396R	3.9	0.8	1.6	3.1	5.9
F486S	8.1	2.3	3.0	1.9	2.1
L248R + F359I	11.7	39.3	13.7	96.2	17.7

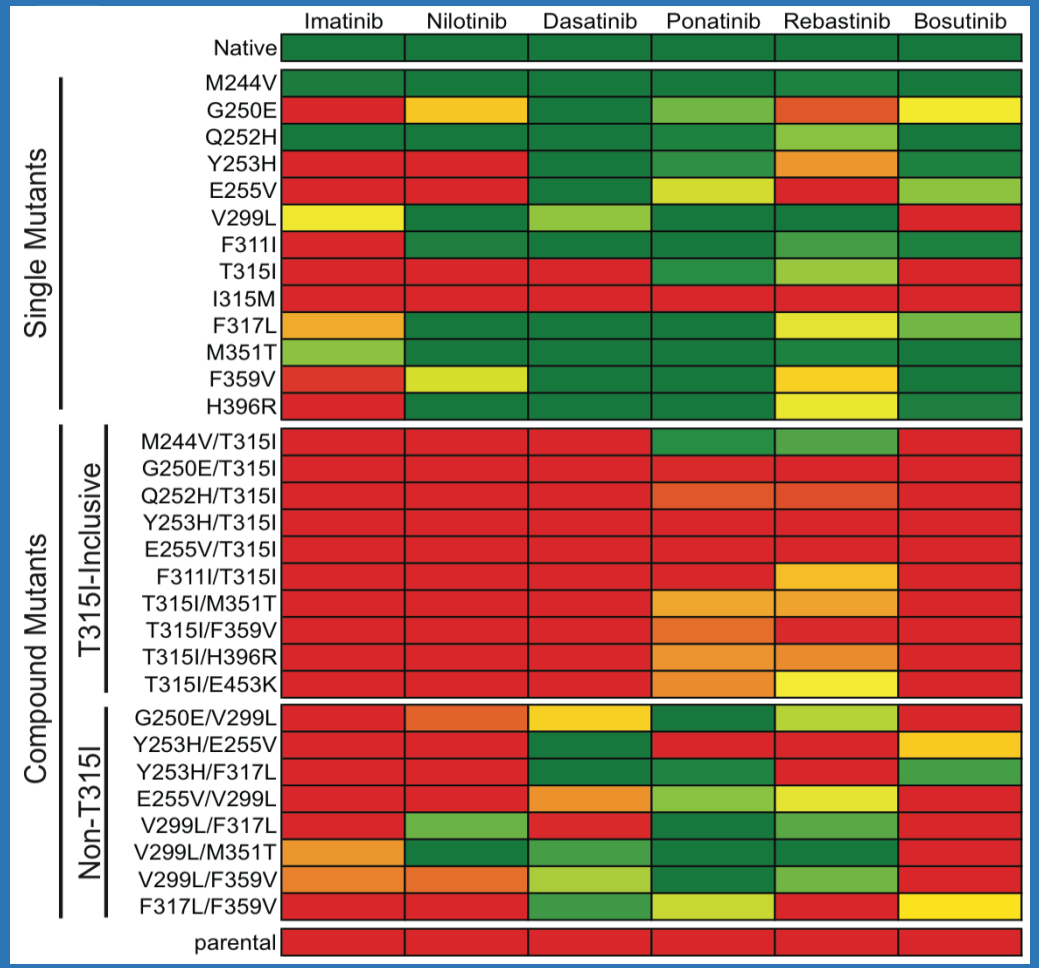
Adapted from Redaelli S et al. *Am J Hematol.* 2012;87:E125-E128.

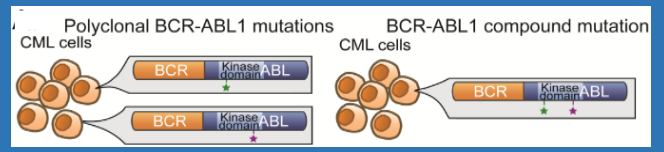
Sensitive	<2-fold difference
Moderately sensitive	2.1- to 4-fold difference
Resistant	4.1- to 10-fold difference
Highly resistant	>10-fold difference

But: In vitro sensitivity is imperfect correlate of in vivo efficacy.

Eiring et al. Genome Biol. 2014;15(9):461

T315I Inclusive Compound Mutations Confer Universal TKI Resistance





Zabriskie et al. Cancer Cell. 2014;26(3):428-42

What will deeper testing bring to the table?

- Uncertain as we really do not have any long term prospective studies on patients from the time of diagnosis to see what will develop and what is a red herring. Most of our data is on patients who have failed therapy and not the majority who have not.
- Possibilities include:
  - Best successful therapy choice
  - A potential early warning system
  - Best chance of predicting successful treatment free remission
  - Most likely right now, cardiovascular risks associated with therapy

Not all Salvage is the Same

- The results of second or third line salvage does depend on what was used previously – salvage after imatinib is very different from salvage after failure of a second generation drug even in the absence of mutations to guide your choice
- Salvage after intolerance is very different from salvage after resistance

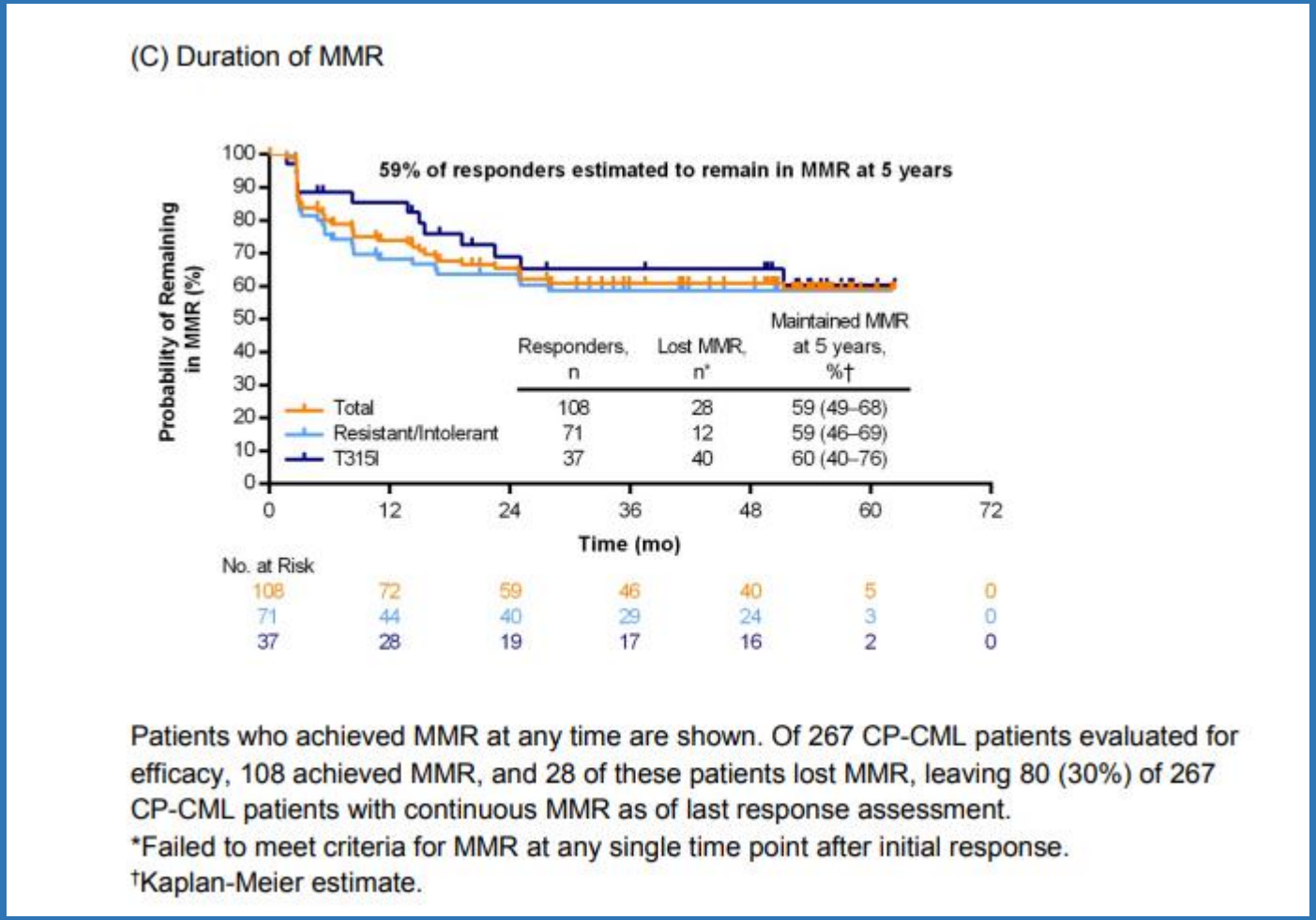
PACE: Ponatinib Phase II Study
Responses at Any Time

	CP-CML			AP-CML	BP-CML	Ph+ ALL
	MCyR	CCyR	MMR	MaHR*	MaHR	MaHR
R/I to das/nil	56%	48%	31%	62%	32%	50%
T315I	72%	70%	58%	61%	29%	36%
Total	60%	54%	38%	61%	31%	41%
Median time to response, months						
	2.8	2.9	5.5	0.7	1.0	0.7

*14 AP-CML pts with baseline MaHR and 1 AP-CML pt with no baseline MaHR assessment counted as non-responders
**Total comprises all eligible pts treated with ponatinib. It excludes 5 pts (3 CP-CML, 2 AP-CML) who were non-cohort assigned (post-imatinib, non-T315I), but treated; all 5 achieved MCyR

Cortes J, et al. *Blood.* 2013;122: Abstract 650.

5 Year PACE Study



Patients who achieved MMR at any time are shown. Of 267 CP-CML patients evaluated for efficacy, 108 achieved MMR, and 28 of these patients lost MMR, leaving 80 (30%) of 267 CP-CML patients with continuous MMR as of last response assessment.

*Failed to meet criteria for MMR at any single time point after initial response.

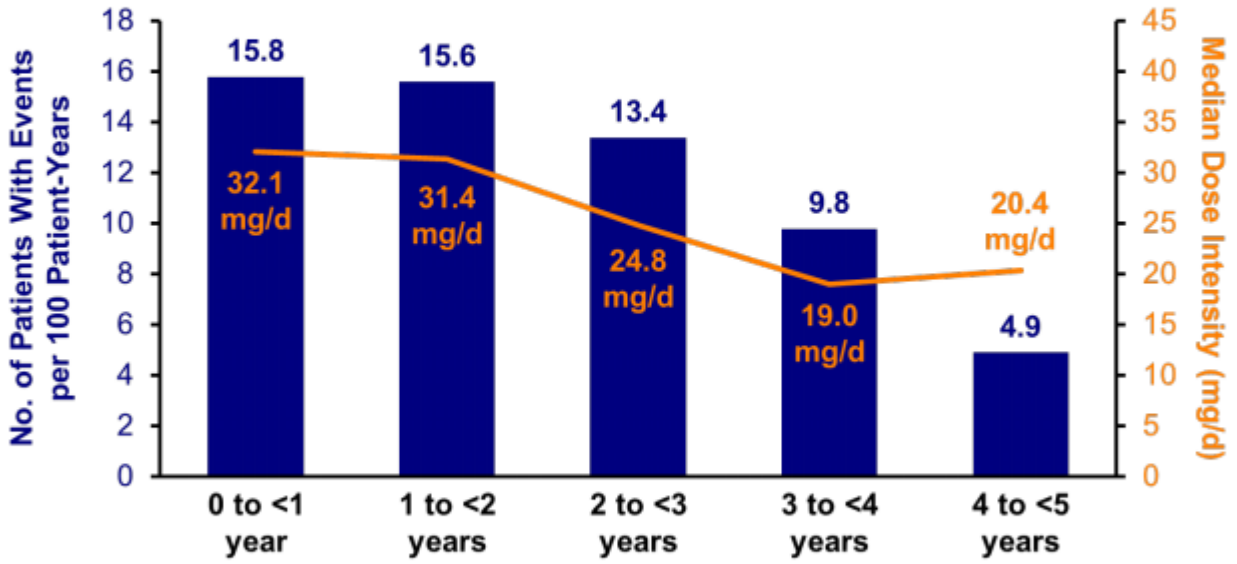
†Kaplan-Meier estimate.

Cortes et al. (2018) Blood

5 Year PACE Study

Figure 4. Exposure-adjusted yearly incidence rates for newly occurring arterial occlusive events and median dose intensity by year. (A) CP-CML patients, and (B) all patients.

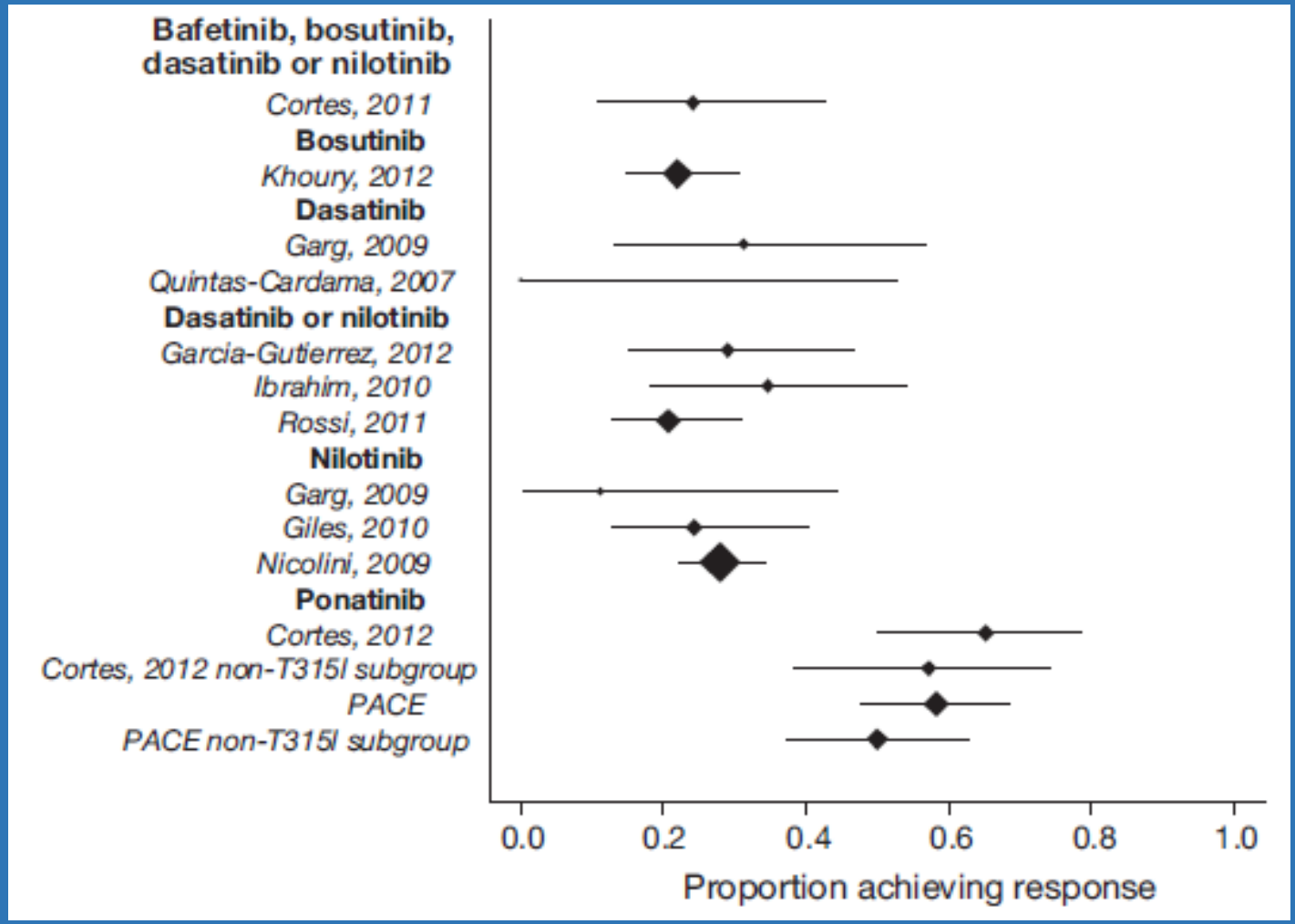
(A) CP-CML patients



For CP-CML patients, in the five intervals shown (0 to <1 year, 1 to <2 years, 2 to <3 years, 3 to <4 years, and 4 to <5 years): 32, 21, 14, 8, and 3 patients had events, respectively, of 270, 152, 121, 91, and 73 patients in each interval, respectively.

Cortes et al. (2018) Blood

Systematic Review of 3rd Line Therapy



Lipton et al, Leuk Res 2015

PACE
Ponatinib Phase II Study
Incidence of Arterial Thrombotic Events Over Time

	N = 449 n (%)			
Data as of:	23 July 2012 (USPI)		03 Sep 2013	
Median follow-up [exposure]	12 months [340 patient-years]		24 months [578 patient-years]	
Category	SAE	AE	SAE	AE
Cardiovascular	21 (5)	29 (6)	28 (6)	41 (9)
Cerebrovascular	8 (2)	13 (3)	18 (4)	25 (6)
Peripheral vascular	7 (2)	17 (4)	16 (4)	28 (6)
Total arterial thrombosis	34 (8)	51 (11)	53 (12)	77 (17)
Venous thromboembolism	10 (2)	15 (3)	13 (3)	23 (5)
Vascular occlusion[a]				
Method 1[b]	41 (9)	62 (14)	62 (14)	91 (20)
Method 2[c]	47 (10)	81 (18)	67 (15)	109 (24)

[a]Combined incidence of cardiovascular, cerebrovascular, peripheral vascular, venous thromboembolism events;
[b]EMA press release, Nov 22, 2013; [c]FDA drug safety communication, Oct 31, 2013; SAE = AE reported as serious by the investigator, per standard criteria

AE, adverse event; EMA, European Medicines Association; SAE, serious AE

Cortes J, et al. *Blood.* 2013;122: Abstract 650.

ADJUDICATED AOEs from PACE – Retrospective Review by an Independent Group of Cardiologists and Neurologists

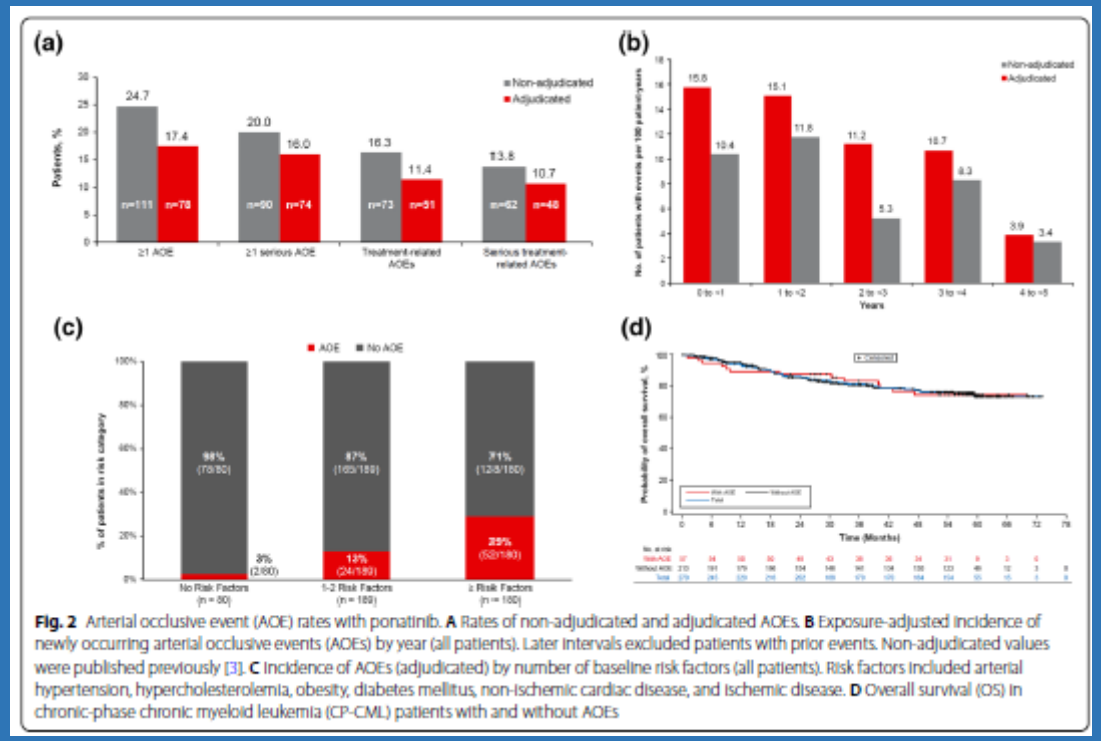


Fig. 2 Arterial occlusive event (AOE) rates with ponatinib. **A** Rates of non-adjudicated and adjudicated AOEs. **B** Exposure-adjusted incidence of newly occurring arterial occlusive events (AOEs) by year (all patients). Later intervals excluded patients with prior events. Non-adjudicated values were published previously [3]. **C** Incidence of AOEs (adjudicated) by number of baseline risk factors (all patients). Risk factors included arterial hypertension, hypercholesterolemia, obesity, diabetes mellitus, non-ischemic cardiac disease, and ischemic disease. **D** Overall survival (OS) in chronic-phase chronic myeloid leukemia (CP-CML) patients with and without AOEs

Januzzi et al (2022) J Hematol Oncol

OPTIC PRIMARY ANALYSIS: A DOSE-OPTIMIZATION STUDY OF 3 STARTING DOSES OF PONATINIB

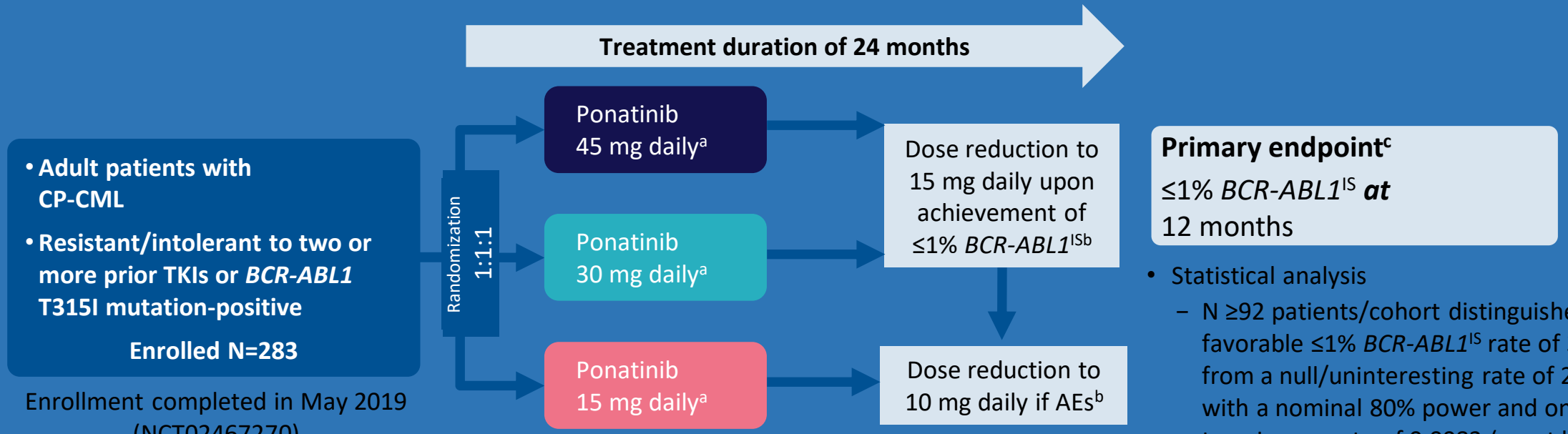
Jorge Cortes,[1] Jane Apperley,[2] Elza Lomaia,[3] Beatriz Moiraghi,[4] Maria Undurraga Sutton,[5] Carolina Pavlovsky,[6] Charles Chuah,[7] Tomasz Sacha,[8] Jeffrey Lipton,[9] James McCloskey,[10] Andreas Hochhaus,[11] Philippe Rousselot,[12] Gianantonio Rosti,[13] Hugues de Lavallade,[14] Michael Mauro,[15] Tracey Hall,[16] Vickie Lu,[16] Shouryadeep Srivastava,[16] Michael Deininger[17]

[1]MD Anderson Cancer Center (currently Georgia Cancer Center at Augusta University), Houston, TX, USA; [2]Russian Academy of Medical Sciences, Moscow, Russia; [3]Almazov National Medical Research Centre, Moscow, Russia; [4]Hospital Jose Maria Ramos Mejia, Buenos Aires, Argentina; [5]Hospital del Salvador, Santiago, Chile; [6]Fundaleu, Buenos Aires, Argentina; [7]Singapore General Hospital, Duke-NUS Medical School, Singapore; [8]Jagiellonian University Hospital in Krakow, Krakow, Poland; [9]University of Toronto, Toronto, Ontario, Canada; [10]The John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ, USA; [11]Universitätsklinikum Jena, Jena, Germany; [12]Hospital Mignot University de Versailles Saint-Quentin-en-Yvelines, Paris, France; [13]IRCCS/SIRHHC "Dino Amadori", Meldola, Italy; [14]King's College Hospital NHS Foundation, London, UK; [15]Memorial Sloan Kettering, New York, NY, USA; [16]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [17]University of Utah, Huntsman Cancer Hospital, Salt Lake City, UT, USA

Cortes et al, EHA 2021

This deck contains data from other ICLUSIG starting dose regimens not included in the current Summary of Product Characteristics (SmPC). Prescribing Information can be found on the last slide.

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



Enrollment completed in May 2019 (NCT02467270)

- Statistical analysis
  - N ≥92 patients/cohort distinguished a favorable ≤1% *BCR-ABL1*^{IS} rate of 35% from a null/uninteresting rate of 20% with a nominal 80% power and one-sided type I error rate of 0.0083 (exact binomial test)

- Median (range) duration of follow-up: 32 months (1–57)
- Minimum follow-up (date last patient was randomized to data cutoff date [5/31/20]): 12.8 months

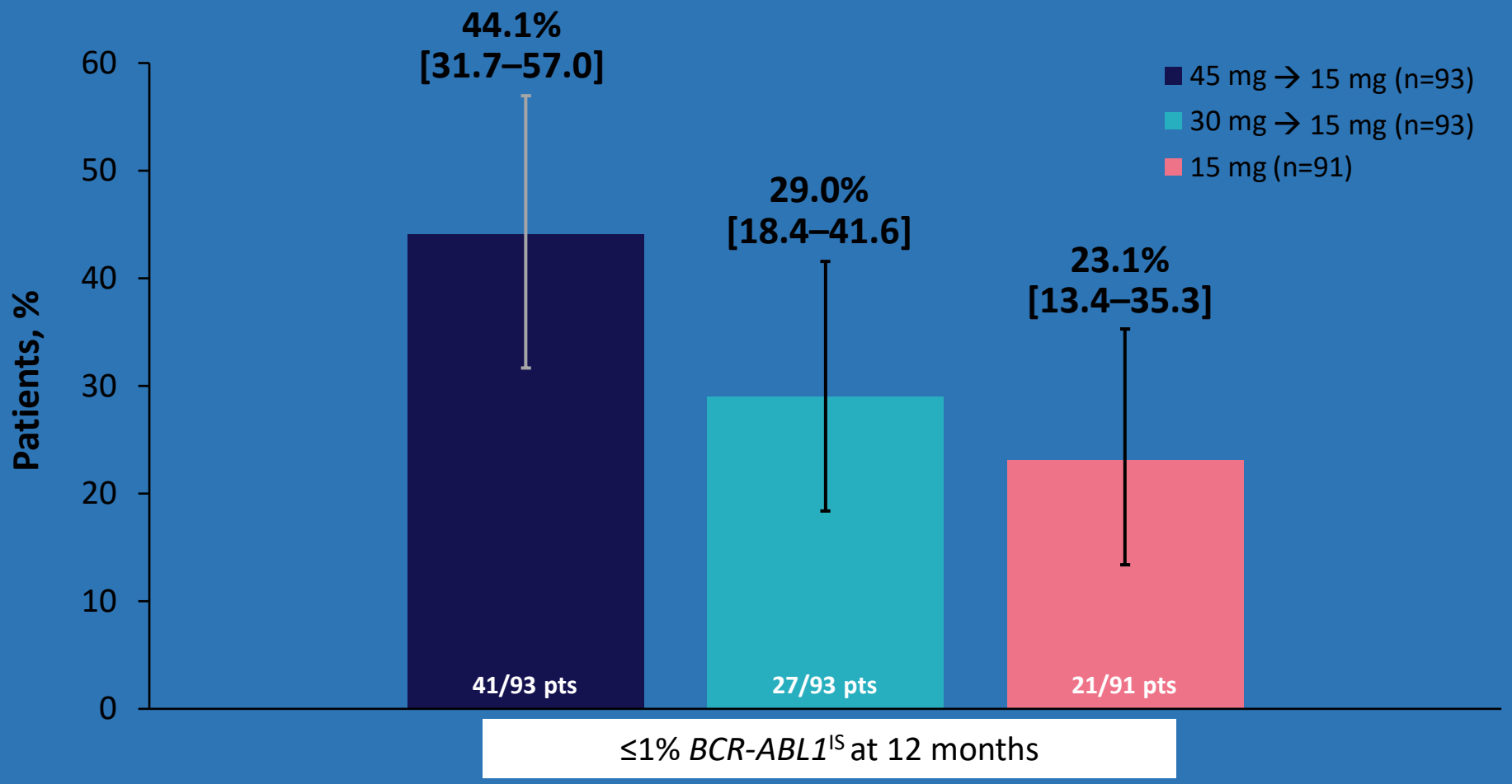
AE, adverse event; CML, chronic myeloid leukemia; CP, chronic phase; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response.
[a]Dose reductions due to AEs were permitted.
[b]Escalation to the starting dose allowed for patients who lost their response following dose reduction; no dose escalation allowed beyond starting dose.
[c]Key secondary endpoints: MMR rate at 12 and 24 months, MCyR rate by 12 months, duration of MMR, and safety across the 3 doses.

Patient Demographics and Baseline Disease

Characteristic	Subcategory	45 mg → 15 mg (N=94)	30 mg → 15 mg (N=94)	15 mg (N=94)
Median age, y (range)		46 (19–81)	51 (21–77)	49 (18–81)
Gender, male, n (%)		50 (53)	38 (40)	53 (56)
ECOG PS score 0 or 1, n (%)		93 (99)	93 (99)	94 (100)
Median time since diagnosis, y (range)		5.5 (1–21)	5.1 (1–29)	5.7 (1–22)
Patients with CV risk factors, n (%)	Arterial hypertension	26 (28)	25 (27)	22 (23)
	Diabetes mellitus	5 (5)	3 (3)	7 (7)
	Hyperlipidemia	19 (20)	14 (15)	16 (17)
Median body mass index — kg/m^2		27	26	26
Prior TKIs, n (%)	1	1 (1)	1 (1)	4 (4)
	2	43 (46)	37 (40)	42 (45)
	≥3	50 (53)	56 (60)	48 (51)
Stopped immediate prior TKI for resistance, n (%)		92 (98)	94 (100)	94 (100)
BCR-ABL1 mutation, n (%)[a]	No mutation	51 (54)	58 (62)	54 (57)
	T315I	25 (27)	21 (22)	21 (22)
	Mutation other than T315I	16 (17)	14 (15)	18 (19)
Best response to last prior TKI, n (%)	CHR or worse	61 (65)	55 (59)	57 (61)
	≤1% BCR-ABL1^{IS} or better	2 (2)	7 (7)	7 (7)

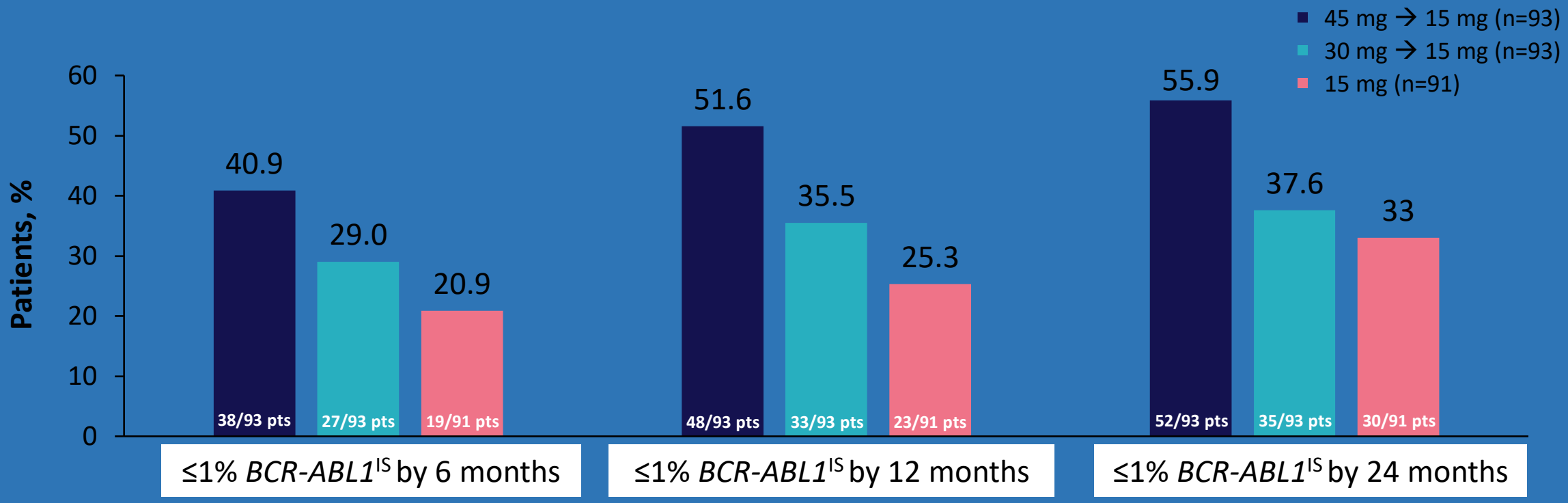
[a]Five patients (2 in 45 mg → 15 mg, 1 in 30 mg → 15 mg, and 2 in 15 mg cohorts) did not have any mutation testing performed at baseline.
CHR, complete hematologic response; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor.

Primary Endpoint: ≤1% *BCR-ABL1*^{IS} at 12 Months



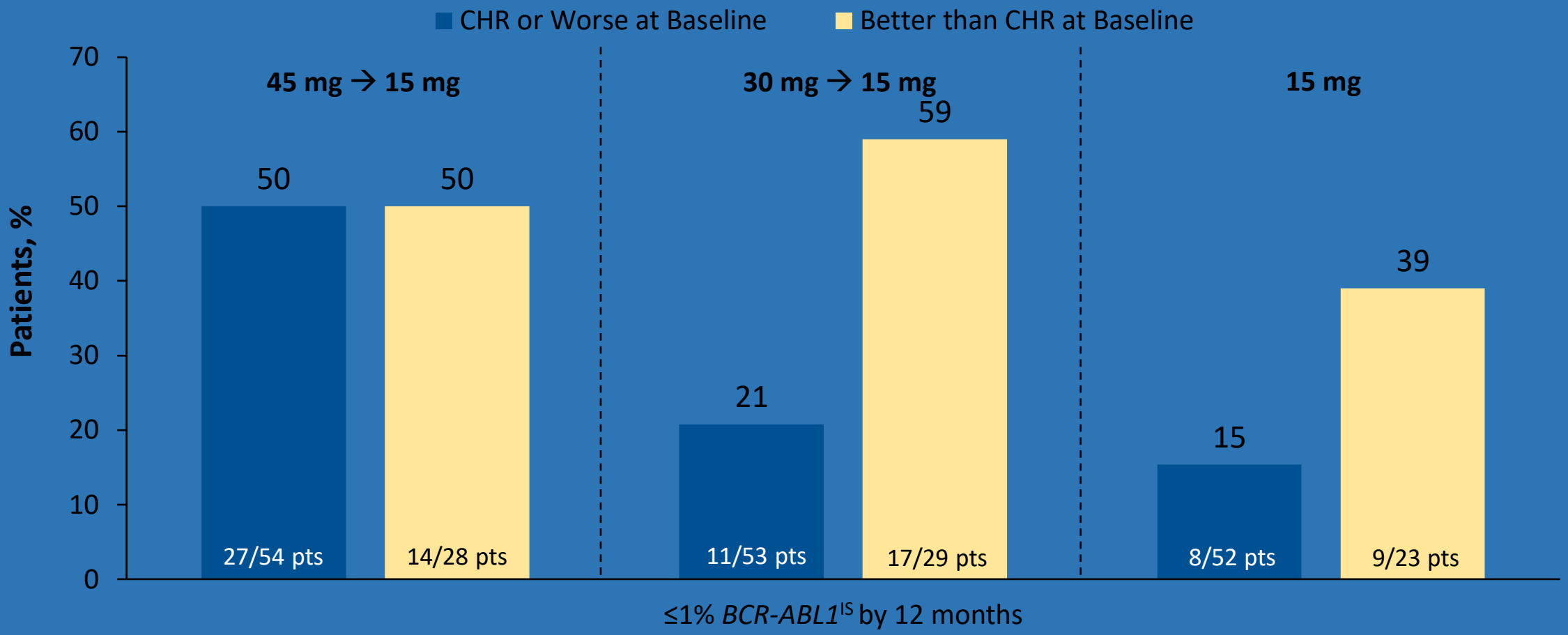
- The response rate was highest with the 45 mg → 15 mg regimen, 44.1% (31.7–57.0)
- The prespecified statistical endpoint was met with the 45 mg → 15 mg regimen (P<0.017)

≤1% *BCR-ABL1*^{IS} by 6, 12, and 24 Months and Median Dose Intensity



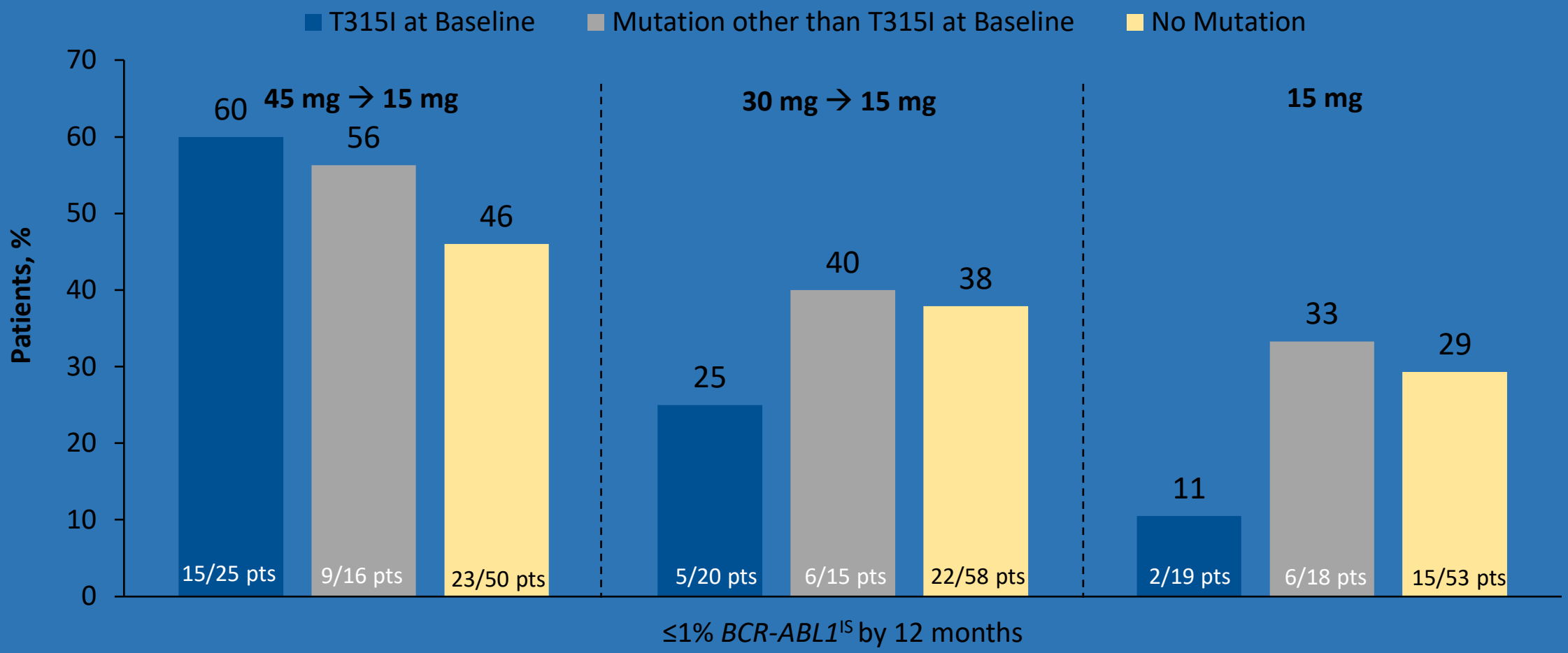
	Median dose intensity, mg/d		
Regimen	6 months	12 months	24 months
45 mg → 15 mg	35	15	15
30 mg → 15 mg	30	28	15
15 mg	15	15	15

≤1% *BCR-ABL1*^{IS} Response Rate by Best Response to Last Prior Therapy



CHR, complete hematologic response

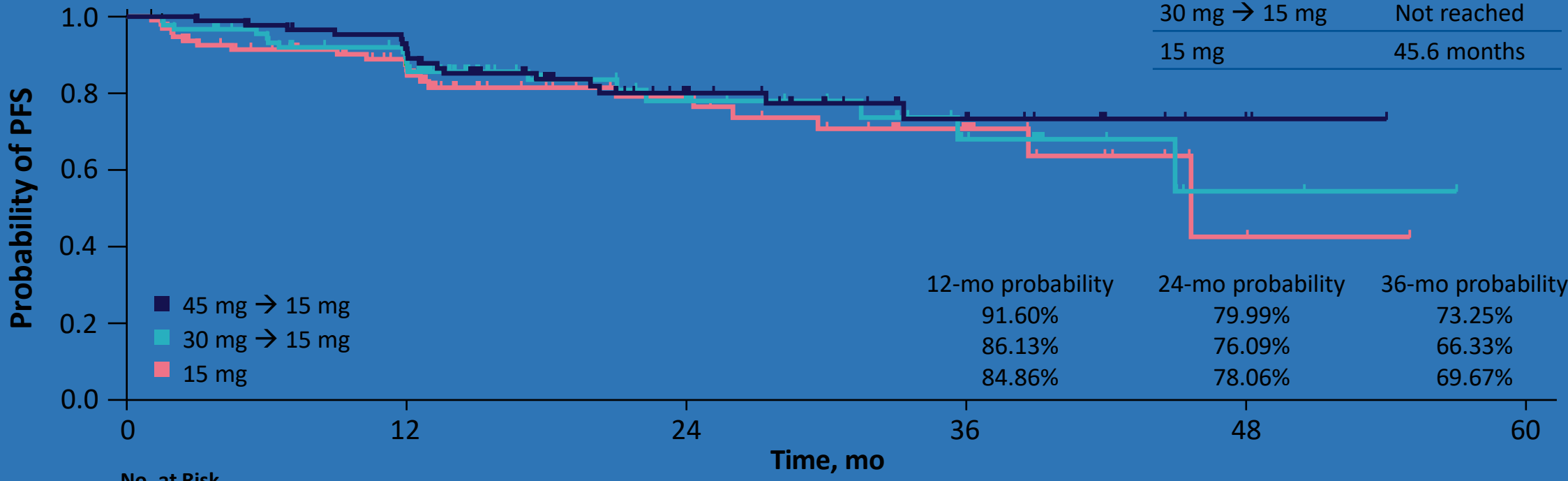
≤1% *BCR-ABL1*^{IS} Response Rate by 12 Months[a] by T315I Baseline Status



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

Progression-Free Survival (PFS[a])

	Median PFS
45 mg → 15 mg	Not reached
30 mg → 15 mg	Not reached
15 mg	45.6 months

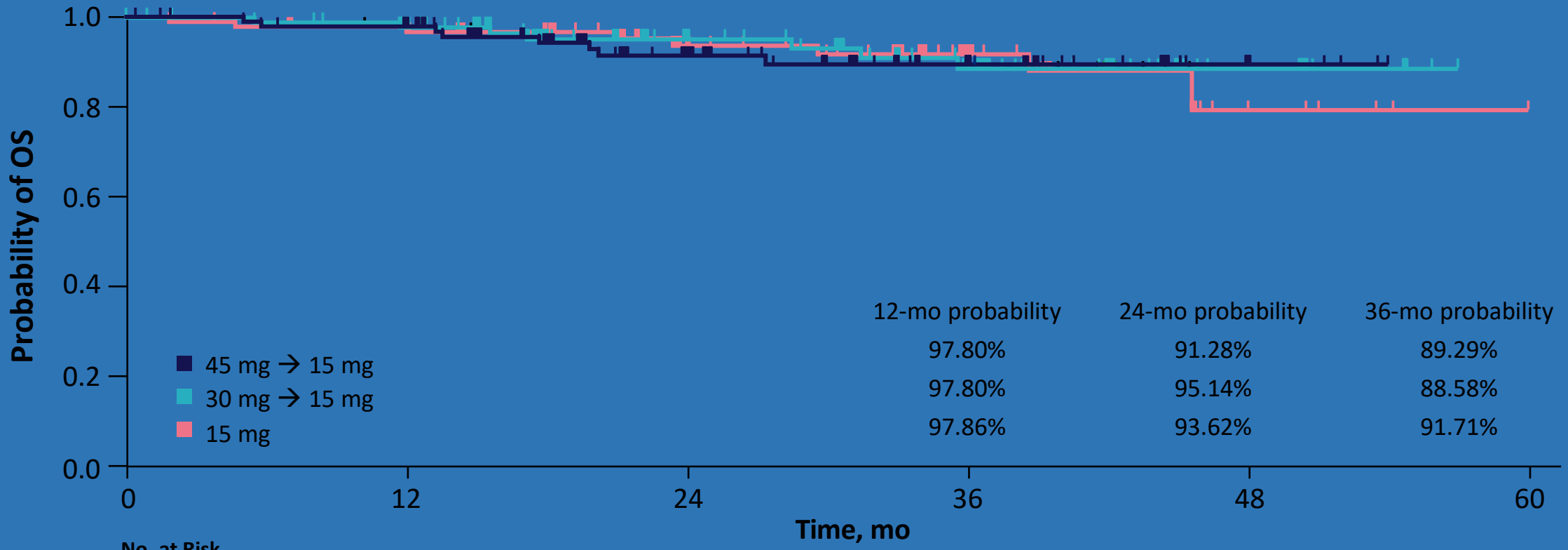


No. at Risk

45 mg → 15 mg	94	83	74	54	35	24	18	6	4	1	0
30 mg → 15 mg	95	83	72	36	25	19	11	6	2	1	0
15 mg	94	79	62	41	30	24	16	7	2	1	0

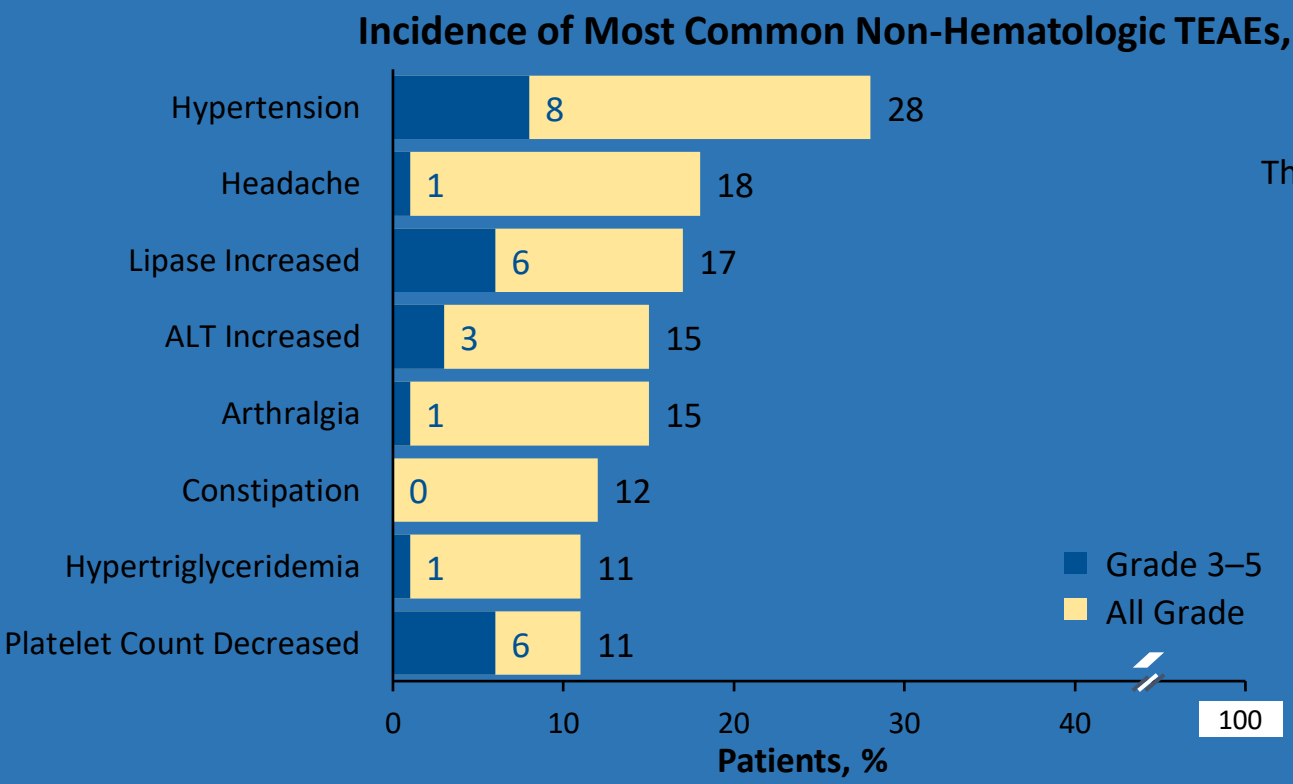
[a]PFS was analyzed according to the criteria in O'Brien et al, 2003 and included: death; development of accelerated-phase or blast-phase chronic myeloid leukemia; loss of CHR (in the absence of cytogenetic response) confirmed by development in complete blood counts at least 4 weeks apart; Loss of major cytogenetic response by bone marrow cytogenetic assessment; increasing white blood cell count in patient without CHR defined by doubling of white blood cell count to >20,000 on 2 occasions at least 4 weeks apart (after the first 4 weeks of therapy).

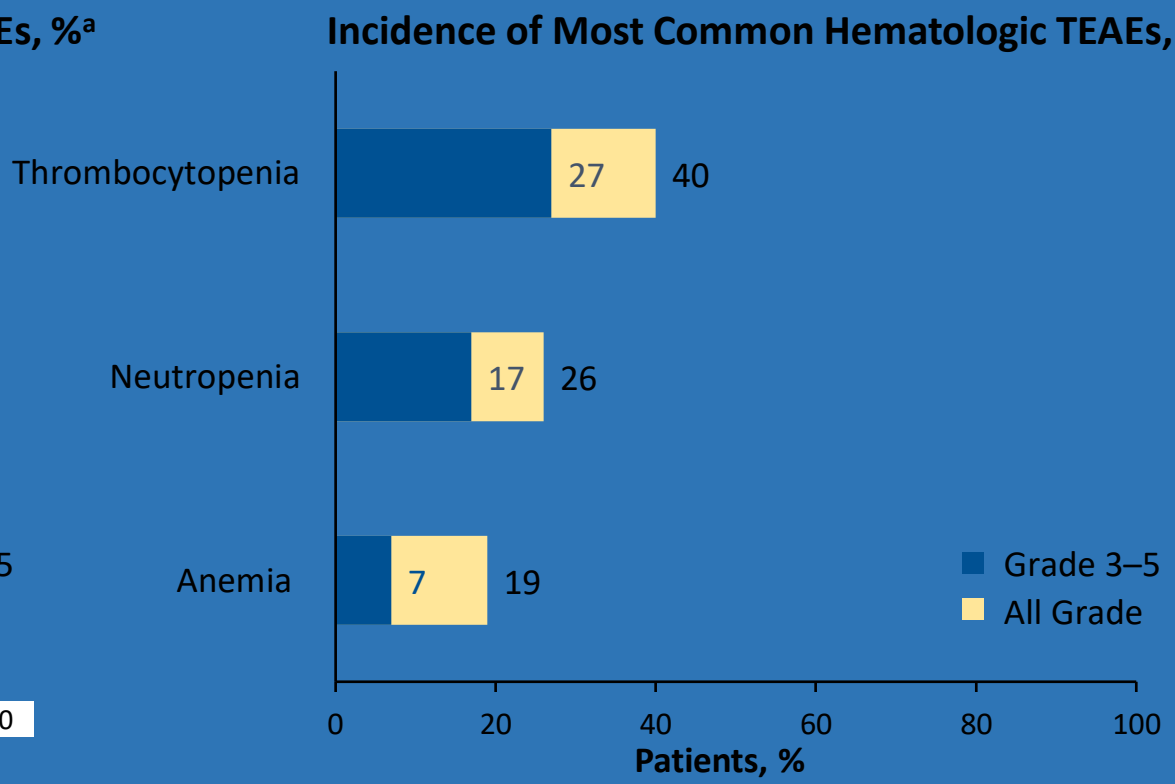
Overall Survival (OS)



No. at Risk										
45 mg → 15 mg	94	89	88	73	53	42	34	15	8	1	0
30 mg → 15 mg	95	91	88	68	54	46	35	17	7	4	0
15 mg	94	91	85	75	55	48	33	17	6	2	1

Most Common Treatment-Emergent Adverse Events





- The most common TEAEs (thrombocytopenia, hypertension, headache, lipase increased) did not appear to be more common in the 45 mg → 15 mg cohort

ALT, alanine aminotransferase; TEAEs, treatment-emergent adverse events.
[a]All Grade events in ≥10% of patients; Grade 3–5 events in ≥5% of patients and Grade 3–5 events of any frequency for All Grade events in ≥10% of patients.

TEAE Summary and Related Dose Modifications/Discontinuations

	45 mg → 15 mg (N=94)	30 mg → 15 mg (N=94)	15 mg (N=94)
TEAEs — n (%)			
Any TEAE	94 (100)	88 (93.6)	89 (94.7)
Grade ≥3 TEAEs	64 (68.1)	58 (61.7)	60 (63.8)
Serious TEAEs	32 (34)	24 (25.5)	31 (33.0)
Grade 5 TEAEs[a]	2 (2.1)	0	2 (2.1)
Dose modifications for TEAEs — n (%)			
Discontinuation	18 (19.1)	15 (16.0)	13 (13.8)
Reduction	43 (45.7)	33 (35.1)	30 (31.9)
Interruption	67 (71.3)	58 (61.7)	55 (58.5)

TEAE, treatment-emergent adverse event.

[a]Grade 5 TEAEs were 2 sudden deaths in the 45 mg → 15 mg cohort and 2 deaths from pneumonia in the 15 mg cohort.

Adjudicated[a] TE-AOE Summary and Related Dose Modifications/Discontinuations

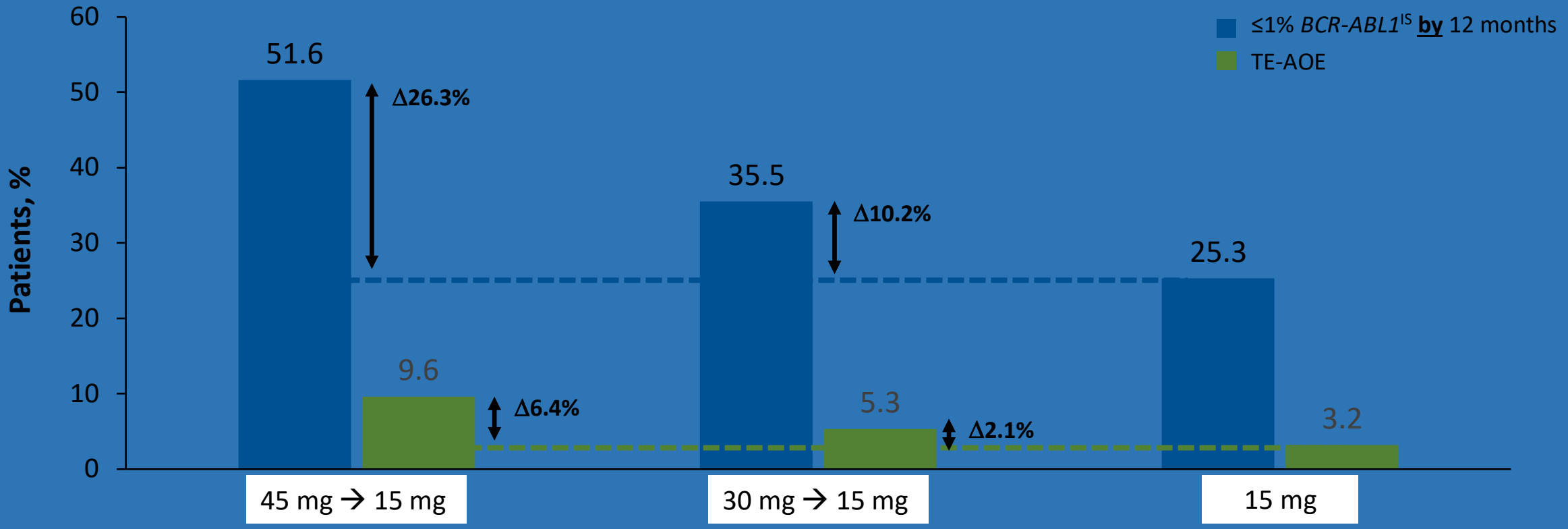
	45 mg → 15 mg (N=94)	30 mg → 15 mg (N=94)	15 mg (N=94)
TE-AOEs — n (%)			
Any AOE	9 (9.6)	5 (5.3)	3 (3.2)
Grade ≥3 TE-AOEs	5 (5.3)	5 (5.3)	3 (3.2)
Dose modifications for AOE — n (%)			
Discontinuation	4 (4.3)	3 (3.2)	1 (1.1)
Reduction	0	1 (1.1)	0
Interruption	2 (2.1)	3 (3.2)	1 (1.1)

- 6% of patients overall experienced a TE-AOE

AOE, arterial occlusive event; TE-AOEs, treatment-emergent arterial occlusive events.

[a]An independent cardiovascular endpoint adjudication committee composed of independent experts reviewed all documentation related to an AOE, including but not limited to clinical features, changes in concomitant medications, urgent revascularization, ECG changes, presence of diagnostic criteria on imaging, or hospitalization. If a serious vascular occlusive adverse drug reaction occurred, treatment was interrupted and not restarted unless the potential benefit outweighed the risk of recurrent arterial or venous occlusions.

Overall Safety and Efficacy by Starting Dose



- 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

Efficacy and Safety Results From ASCEMBL, a Multicenter, Open-Label, Phase 3 Study of Asciminib, a First-in-Class STAMP Inhibitor, vs Bosutinib in Patients With Chronic Myeloid Leukemia in Chronic Phase After ≥2 Prior Tyrosine Kinase Inhibitors: Update After 48 Weeks

Michael J. Mauro, Yosuke Minami, Delphine Réa, Andreas Hochhaus, Elza Lomaia, Sergey Voloshin, Anna Turkina, Dong-Wook Kim, Jane F. Apperley, Jorge E. Cortes, Andre Abdo, Laura Maria Fogliatto, Dennis Dong Hwan Kim, Philipp le Coutre, Susanne Saussele, Mario Annunziata, Timothy P. Hughes, Naeem Chaudhri, Lynette Chee, Valentin García-Gutiérrez, Koji Sasaki, Shruti Kapoor, Alex Allepuz, Sara Quenet, Véronique Bédoucha, Carla Boquimpani

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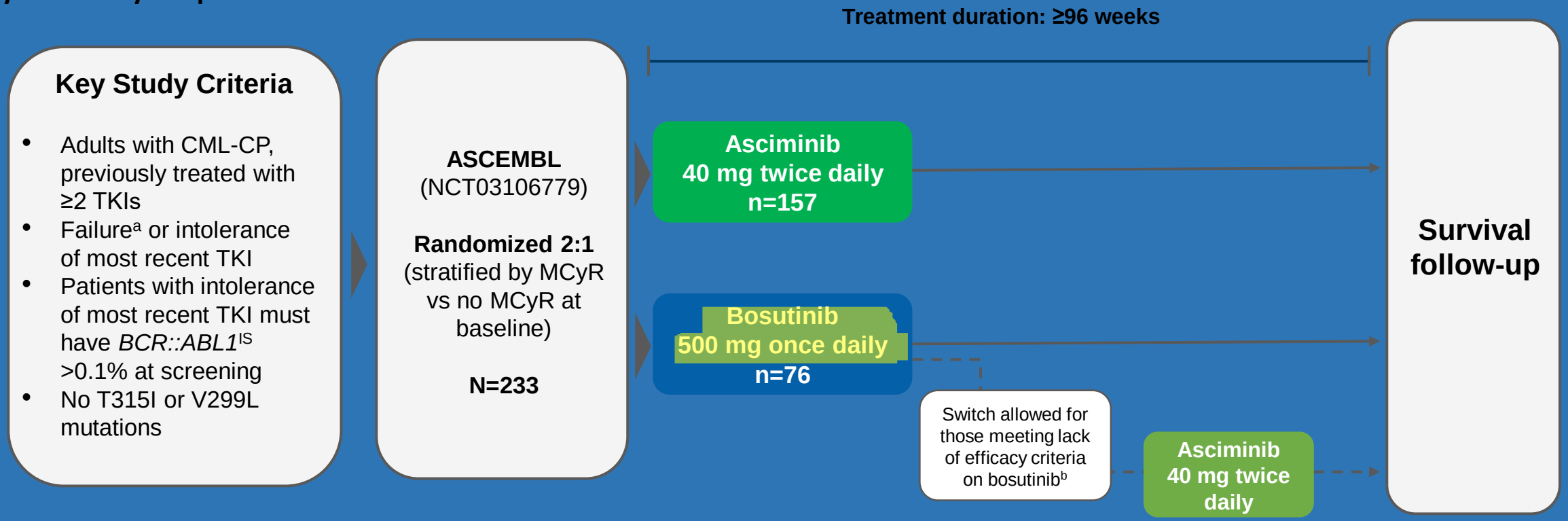
ASCEMBL Study Design

- **Data cutoff for current analysis:** January 6, 2021
- **Follow-up:** 100% of ongoing patients completed week 48 visit and all (except 1) completed week 60 visit
- **Median duration of follow-up:** 19.2 months from randomization to cutoff
- **Primary endpoint:** MMR rate at week 24
- **Key secondary endpoint:** MMR rate at week 96



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Patient Demographics (cont)

Variable	Asciminib 40 mg twice daily (N=157)	Bosutinib 500 mg once daily (N=76)
No. of lines of prior TKI therapy, n (%)[a]		
2	82 (52.2)	30 (39.5)
3	44 (28.0)	29 (38.2)
4	24 (15.3)	10 (13.2)
≥5	7 (4.5)	7 (9.2)
Reason for discontinuation of last TKI, n (%)		
Lack of efficacy[b]	95 (60.5)	54 (71.1)
Lack of tolerability	59 (37.6)	22 (28.9)
Other[c]	3 (1.9)	0
BCR::ABL1^{IS} at baseline, n (%)		
>0.1% to ≤1%[d]	15 (9.6)	4 (5.3)
>1% to ≤10%	45 (28.7)	23 (30.3)
>10%	97 (61.8)	49 (64.5)
Patients with any BCR::ABL1 mutation, n (%)	20 (12.7)	10 (13.2)
Patients with multiple BCR::ABL1 mutations, n (%)	3 (1.9)	0

[a] The number of lines of prior TKI therapy was based on the sequence of treatments.
[b] Lack of efficacy criteria were based on 2013 ELN recommendations for 2L patients.
[c] Includes study medication wrongly assigned, lack of efficacy and tolerability, and optimal response not reached after 5 years of treatment.
[d] All patients with *BCR::ABL1*^{IS} <1% at baseline were intolerant to the last TKI, except 1 in the asciminib arm (who deviated from the protocol).

Patient Disposition

Variable, n (%)	Asciminib 40 mg twice daily (n=157)	Bosutinib 500 mg once daily (n=76)
Patients randomized		
Treated[a]	156 (99.4)	76 (100.0)
Treatment ongoing[b]	**89 (56.7)**	**17 (22.4)**
Discontinued treatment	**67 (42.7)**	**59 (77.6)**
Before week 24	26 (16.6)	25 (32.9)
Week 24 to before week 48	25 (15.9)	29 (38.2)
Week 48 to before week 96	15 (9.6)	3 (3.9)
After week 96	1 (0.6)	2 (2.6)
Reason for discontinuation		
Lack of efficacy	**37 (23.6)**	**27 (35.5)**
Adverse event	**9 (5.7)**	**18 (23.7)**
Physician decision	13 (8.3)	6 (7.9)
Patient decision	4 (2.5)	3 (3.9)
Progressive disease	1 (0.6)	3 (3.9)
Lost to follow-up	1 (0.6)	2 (2.6)
Death	1 (0.6)	0
Protocol deviation	1 (0.6)	0
Switched to receive asciminib	NA	24 (31.6)

- Treatment was ongoing in more than double the proportion of patients receiving asciminib than bosutinib after longer follow-up

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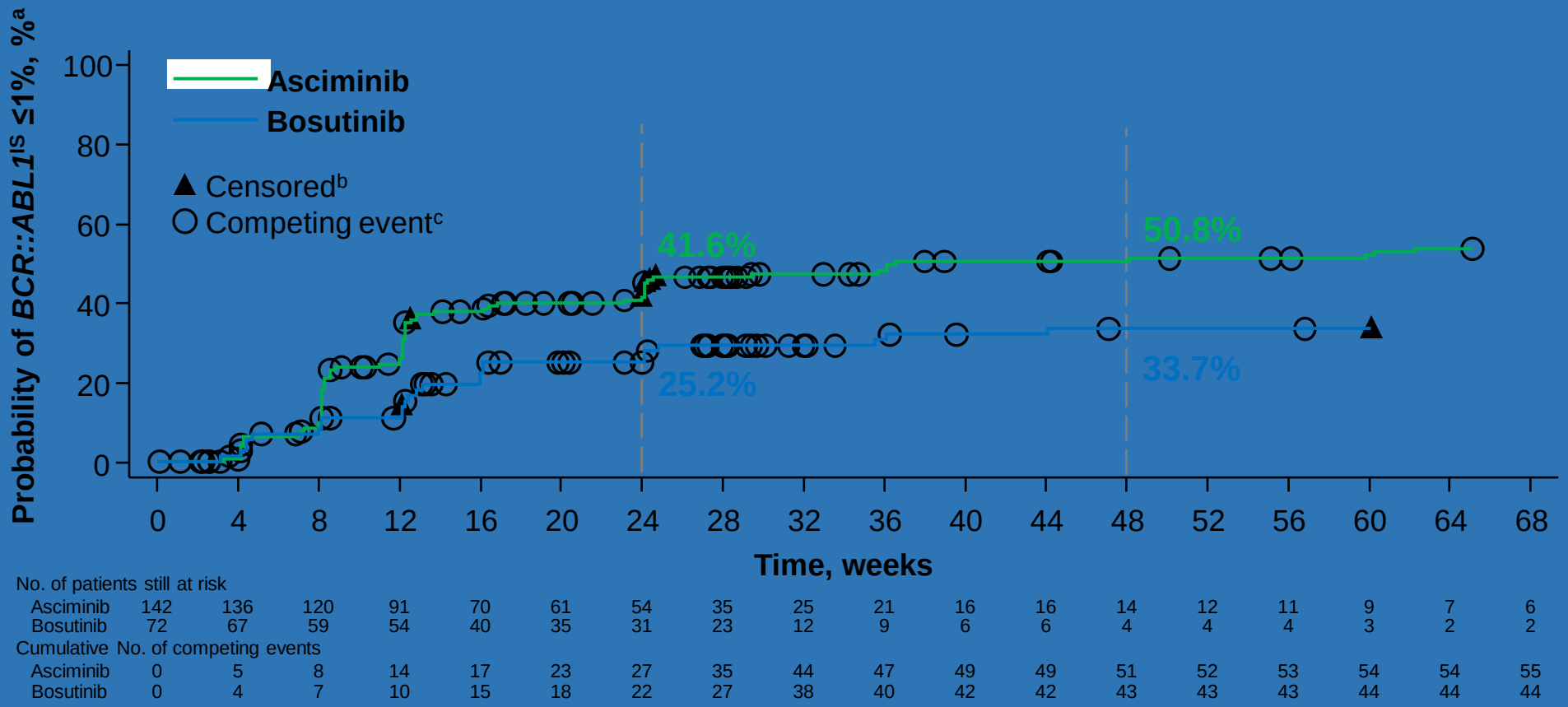
NA, not applicable.

[a] 1 patient in the asciminib arm developed cytopenia after randomization and was not treated per investigator's decision.

[b] Ongoing at the time of data cutoff: January 6, 2021.

Cumulative Incidence of *BCR::ABL1*^{IS} ≤1%



No. of patients still at risk

Asciminib	142	136	120	91	70	61	54	35	25	21	16	16	14	12	11	9	7	6
Bosutinib	72	67	59	54	40	35	31	23	12	9	6	6	4	4	4	3	2	2

Cumulative No. of competing events

Asciminib	0	5	8	14	17	23	27	35	44	47	49	49	51	52	53	54	54	55
Bosutinib	0	4	7	10	15	18	22	27	38	40	42	42	43	43	43	44	44	44

- More patients receiving asciminib than bosutinib continued to achieve *BCR::ABL1*^{IS} ≤1% over time

[a] *BCR::ABL1*^{IS} ≤1% by week 48 was based on 142 of 157 patients (90.4%) receiving asciminib and 72 of 76 (94.7%) receiving bosutinib who did not have this level of response at baseline.

[b] Nonresponders were censored at their last molecular assessment date.

[c] Discontinuation from treatment for any reason, without prior achievement of *BCR::ABL1*^{IS} ≤1%, is considered a competing event.

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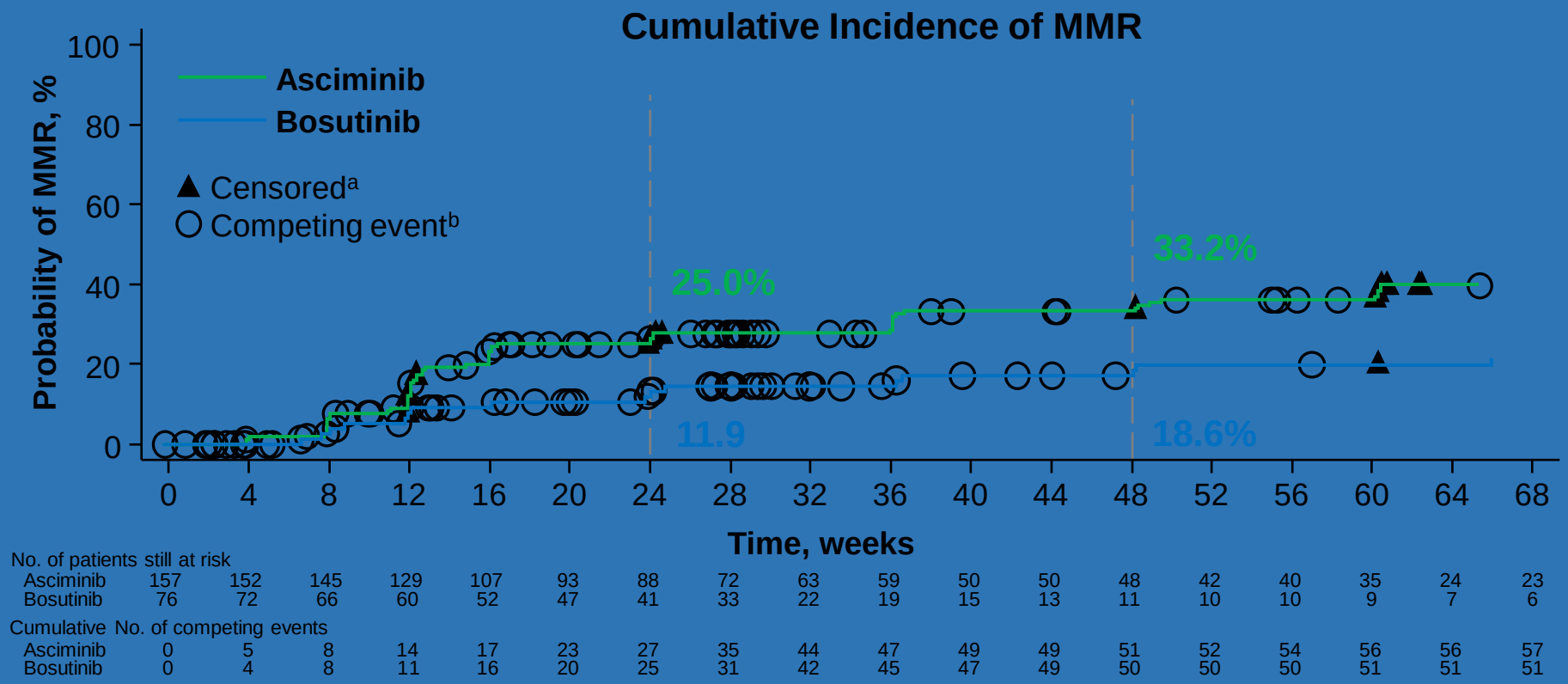
Cumulative Incidence and Duration of MMR



No. of patients still at risk

Asciminib	157	152	145	129	107	93	88	72	63	59	50	50	48	42	40	35	24	23
Bosutinib	76	72	66	60	52	47	41	33	22	19	15	13	11	10	10	9	7	6

Cumulative No. of competing events

Asciminib	0	5	8	14	17	23	27	35	44	47	49	49	51	52	54	56	56	57
Bosutinib	0	4	8	11	16	20	25	31	42	45	47	49	50	50	50	51	51	51

- The MMR rate was consistently higher with asciminib than bosutinib

Duration of MMR

- The probability of maintaining MMR for at least 48 weeks with asciminib was **96.1%** (95% CI, 85.4%-99.0%) vs **90.0%** (95% CI, 47.3%-98.5%) with bosutinib
- 60 of 62 patients receiving asciminib and 17 of 18 receiving bosutinib maintained MMR at the time of their last assessment
  - At data cutoff, the K-M–estimated median duration of MMR was not reached in both treatment arms

K-M, Kaplan-Meier.

[a] Nonresponders were censored at their last molecular assessment date.

[b] Discontinuation from treatment for any reason without prior achievement of MMR is considered a competing event.

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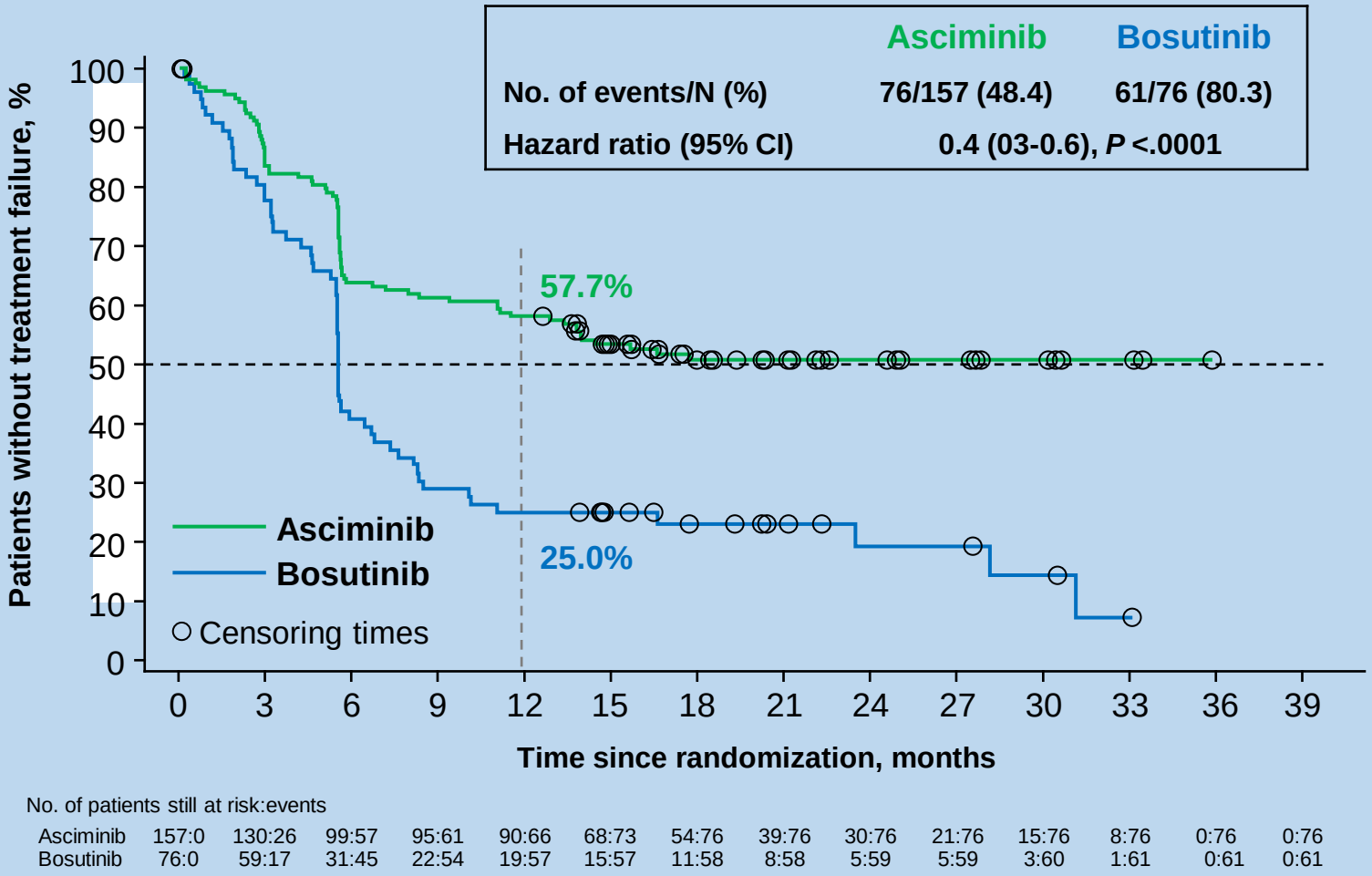
Time to Treatment Failure



- Treatment failure was defined as lack of efficacy (per 2013 ELN recommendations for 2L patients[3]) or discontinuation for any reason
- By data cutoff, fewer patients experienced treatment failure with asciminib (**48.4%**) than bosutinib (**80.3%**)
- The K-M–estimated proportion of patients without treatment failure by **12 months** was **57.7%** (95% CI, 49.5%-65.0%) with asciminib vs **25.0%** (95% CI, 15.9%-35.1%) with bosutinib
- Median time to treatment failure was **not reached with asciminib** and **6 months with bosutinib**

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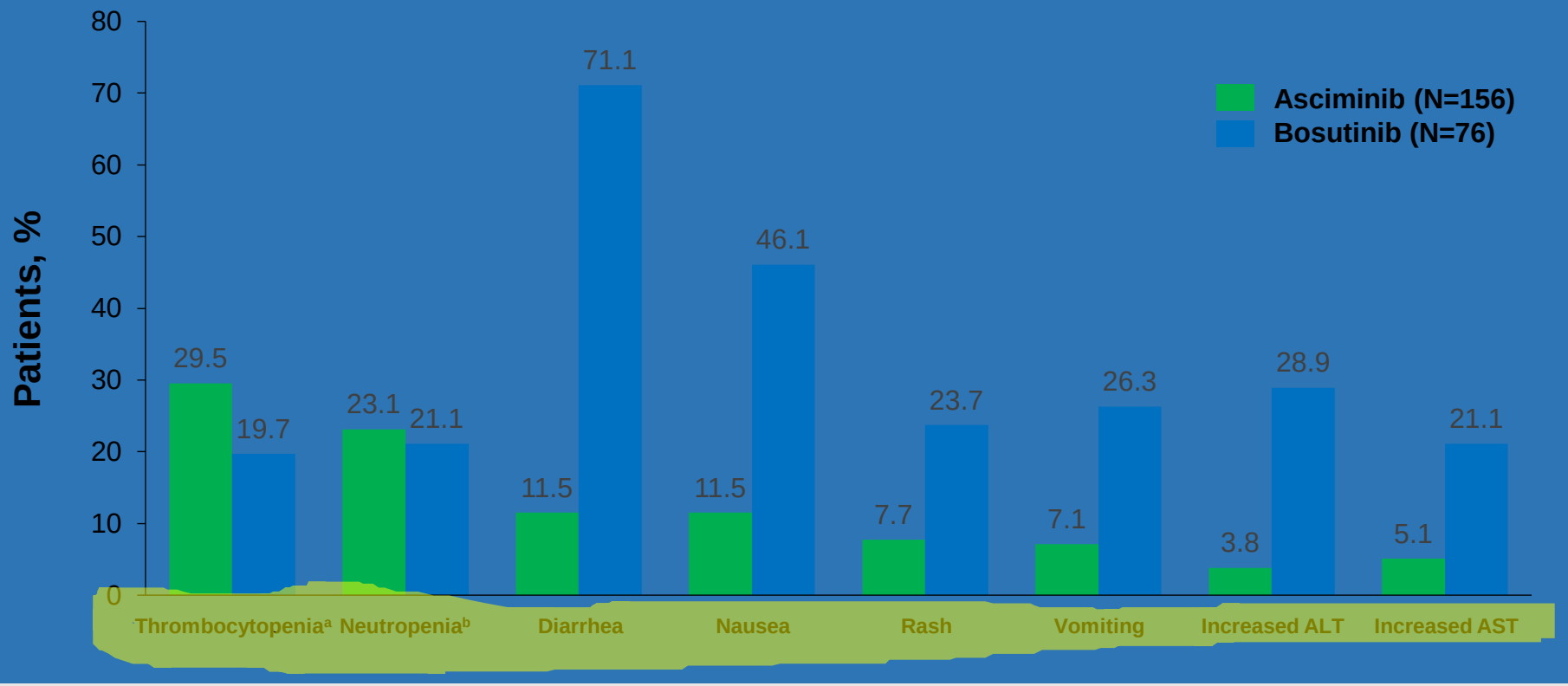
Most Frequent All-Grade AEs (in ≥20% of Patients in Any Arm)



- Despite the longer duration of exposure, the safety and tolerability profile of asciminib continued to be better than that of bosutinib after longer follow-up

[a] Includes thrombocytopenia and platelet count decreased.
[b] Includes neutropenia and neutrophil count decreased.

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Arterial Occlusive Events`

AOE, n (%)	Asciminib 40 mg twice daily (N=156)	Bosutinib 500 mg once daily (N=76)
Patients with AOEs, n (%)	7 (4.5)	1 (1.3)
Patients with events observed by the cutoff for primary analysis		
Myocardial ischemia[a]	2 (1.3)*,†	0
Acute coronary syndrome	0	1 (1.3)
Coronary artery disease[a]	1 (0.6)	0
Ischemic stroke	1 (0.6)*	0
Mesenteric artery embolism/thrombosis[b]	1 (0.6)*,†	0
Additional patients with events observed by cutoff for current analysis		
Cerebral infarction	1 (0.6)*,†	0
Myocardial infarction	1 (0.6)*	0
Exposure-adjusted AOE rate (per 100 patient-years)		
Primary analysis	3.3	2.0
Current analysis	3.4	1.6

Risk of AOEs remained constant and did not increase after additional time receiving asciminib

- Exposure-adjusted AOE rate (per 100 patient-years) in the current analysis (**3.4**) was comparable to that in the primary analysis (**3.3**)

- Of the 7 patients with AOEs receiving asciminib, 7 had prior exposure to nilotinib, *5 to dasatinib, and †3 to ponatinib[b]
- The majority of patients receiving bosutinib discontinued early, thus preventing a meaningful comparison between the arms

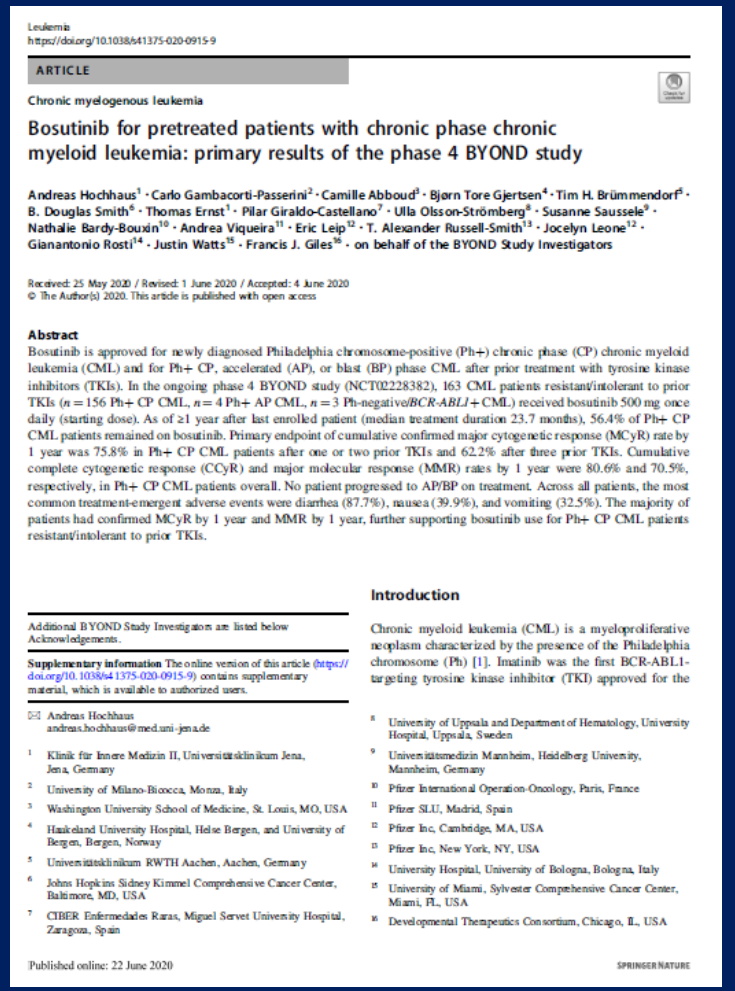
AOE, arterial occlusive event; ECG, electrocardiogram.

[a] Myocardial ischemia (n=2) and coronary artery disease (n=1) in patients receiving asciminib occurred without clinical manifestations and was identified based on ECG performed per protocol after dosing and coronary arteriography performed due to medical history, respectively.

[b] Mesenteric artery embolism/thrombosis occurred 15 days after asciminib discontinuation and following ponatinib treatment for 7 days.

Bosutinib for Pretreated Patients With Chronic Phase Chronic Myeloid Leukemia: Primary Results of the Phase 4 BYOND Study

Andreas Hochhaus[1], Carlo Gambacorti-Passerini[2], Camille Abboud[3], Bjørn Tore Gjertsen[4], Tim H Brümmendorf[5], B Douglas Smith[6], Thomas Ernst[1], Pilar Giraldo-Castellano[7], Ulla Olsson-Strömberg[8], Susanne Saussele[9], Nathalie Bardy-Bouxin[10], Andrea Viqueira[11], Eric Leip[12], T Alexander Russell-Smith[13], Jocelyn Leone[12], Gianantonio Rosti[14], Justin Watts[15], Francis J Giles[16],
on behalf of the BYOND Study Investigators



Leukemia
https://doi.org/10.1038/s41375-020-0915-9

ARTICLE

Chronic myelogenous leukemia

Bosutinib for pretreated patients with chronic phase chronic myeloid leukemia: primary results of the phase 4 BYOND study

Andreas Hochhaus[1] · Carlo Gambacorti-Passerini[2] · Camille Abboud[3] · Bjørn Tore Gjertsen[4] · Tim H. Brümmendorf[5] · B. Douglas Smith[6] · Thomas Ernst[1] · Pilar Giraldo-Castellano[7] · Ulla Olsson-Strömberg[8] · Susanne Saussele[9] · Nathalie Bardy-Bouxin[10] · Andrea Viqueira[11] · Eric Leip[12] · T. Alexander Russell-Smith[13] · Jocelyn Leone[12] · Gianantonio Rosti[14] · Justin Watts[15] · Francis J. Giles[16] · on behalf of the BYOND Study Investigators

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Abstract

Bosutinib is approved for newly diagnosed Philadelphia chromosome-positive (Ph+) chronic phase (CP) chronic myeloid leukemia (CML) and for Ph+ CP, accelerated (AP), or blast (BP) phase CML after prior treatment with tyrosine kinase inhibitors (TKIs). In the ongoing phase 4 BYOND study (NCT02228382), 163 CML patients resistant/intolerant to prior TKIs ($n = 156$ Ph+ CP CML, $n = 4$ Ph+ AP CML, $n = 3$ Ph-negative/*BCR-ABL1*+ CML) received bosutinib 500 mg once daily (starting dose). As of ≥1 year after last enrolled patient (median treatment duration 23.7 months), 56.4% of Ph+ CP CML patients remained on bosutinib. Primary endpoint of cumulative confirmed major cytogenetic response (MCyR) rate by 1 year was 75.8% in Ph+ CP CML patients after one or two prior TKIs and 62.2% after three prior TKIs. Cumulative complete cytogenetic response (CCyR) and major molecular response (MMR) rates by 1 year were 80.6% and 70.5%, respectively, in Ph+ CP CML patients overall. No patient progressed to AP/BP on treatment. Across all patients, the most common treatment-emergent adverse events were diarrhea (87.7%), nausea (39.9%), and vomiting (32.5%). The majority of patients had confirmed MCyR by 1 year and MMR by 1 year, further supporting bosutinib use for Ph+ CP CML patients resistant/intolerant to prior TKIs.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome (Ph) [1]. Imatinib was the first BCR-ABL1-targeting tyrosine kinase inhibitor (TKI) approved for the

Additional BYOND Study Investigators are listed below Acknowledgements.

Supplementary information The online version of this article (https://doi.org/10.1038/s41375-020-0915-9) contains supplementary material, which is available to authorized users.

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SPRINGER NATURE

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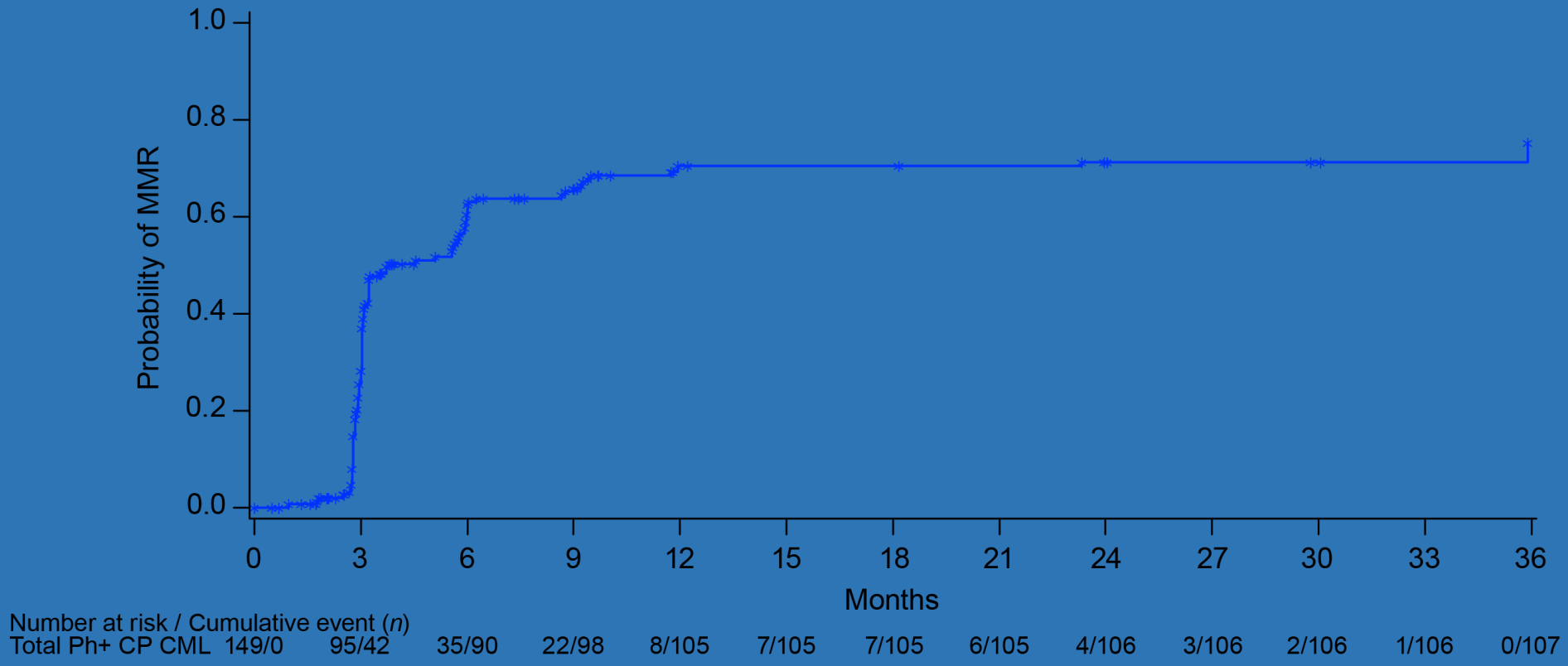
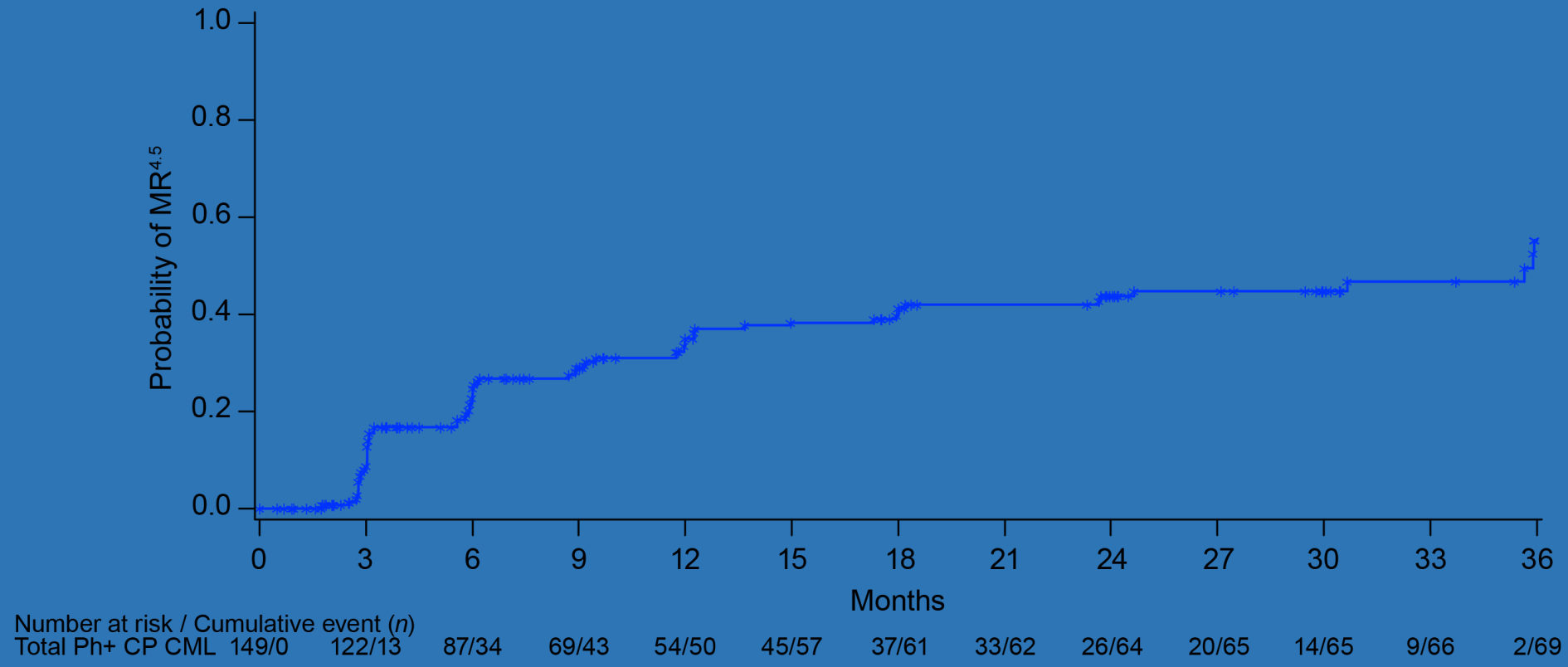
BYOND Study: Figure 2. (A) Cumulative incidence of MMR in patients with Ph+ CP CML



CML=chronic myeloid leukemia; CP=chronic phase; MMR=major molecular response; Ph=Philadelphia chromosome.

Hochhaus et al. *Leukemia.* 2020;34(8); 2125-37.

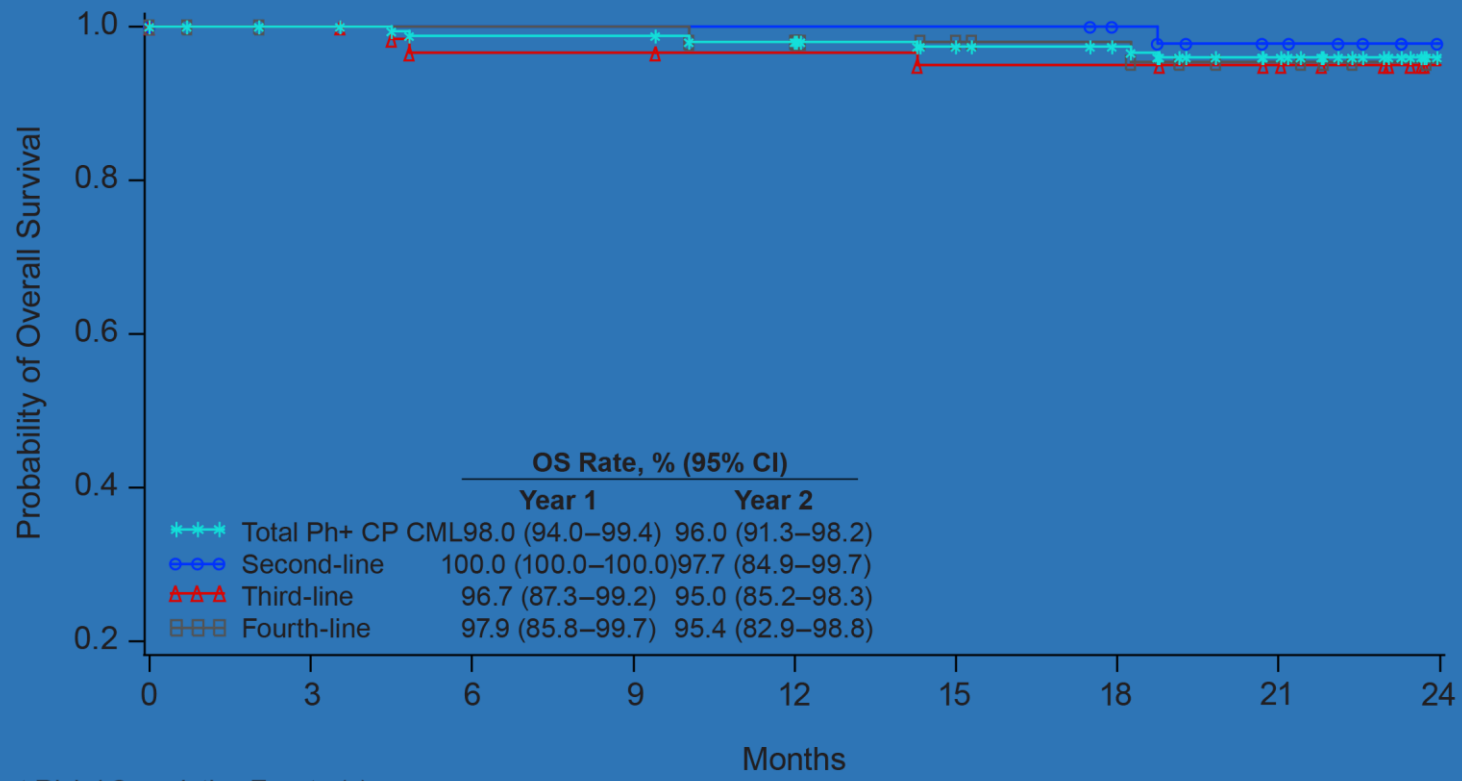
BYOND Study: Figure 2. (C) Cumulative incidence of $MR^{4.5}$ in patients with Ph+ CP CML



CML=chronic myeloid leukemia; CP=chronic phase; MMR=major molecular response; MR= molecular response; Ph+=Philadelphia chromosome- positive.

Hochhaus et al. *Leukemia.* 2020;34(8); 2125-37.

BYOND Study: Supplementary Fig. S2. (A) Overall survival in patients with Ph+ CP CML by line of therapy



Number at Risk / Cumulative Events (*n*)

Total Ph+ CP CML	156/0	154/0	151/2	151/2	149/3	143/4	140/4	132/6	115/6
Second-line	46/0	46/0	46/0	46/0	46/0	46/0	44/0	41/1	35/1
Third-line	61/0	61/0	58/2	58/2	57/2	56/3	56/3	54/3	47/3
Fourth-line	49/0	47/0	47/0	47/0	46/1	41/1	40/1	37/2	33/2

Full analysis set for Ph+ CP CML. Open symbols indicate censored observations.
Four deaths occurred after 24 months.
CI=confidence interval; CP CML=chronic phase chronic myeloid leukemia; OS= overall survival; Ph+=Philadelphia chromosome-positive; TKI=tyrosine kinase inhibitor

BYOND Study: Table 5. TEAEs of special interest (II)

n (%)	Total N=163
Vascular TEAEs	
Any TEAE	19 (11.7)
Cardiovascular	5 (3.1)
Angina pectoris	2 (1.2)
Angina unstable	1 (0.6)
Coronary artery occlusion	1 (0.6)
Myocardial ischemia	1 (0.6)
Cerebrovascular	5 (3.1)
Cerebrovascular accident	2 (1.2)
Transient ischemic attack	2 (1.2)
Carotid artery stenosis	1 (0.6)

n (%)	Total N=163
Peripheral vascular	10 (6.1)
Peripheral arterial occlusive disease	3 (1.8)
Peripheral ischemia	2 (1.2)
Aortic stenosis	1 (0.6)
Arterial rupture	1 (0.6)
Intermittent claudication	1 (0.6)
Peripheral coldness	1 (0.6)
Vascular pain	1 (0.6)

Continued

TEAE=treatment emergent adverse events

And forgotten but not gone….

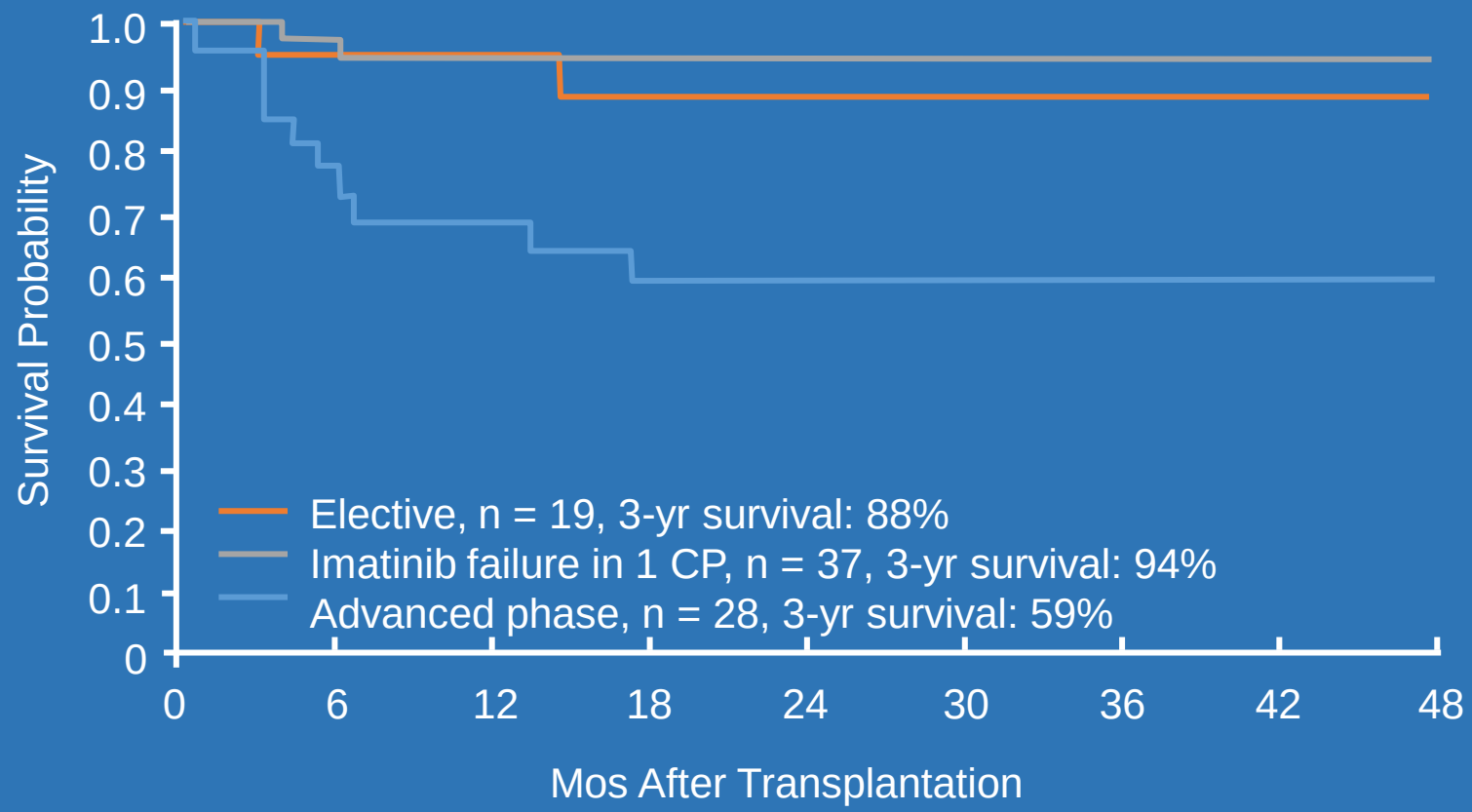
Transplant Indications in CML

Indications for allo-SCT in CML in 2018

Chronic phase
Failure of first-line TKI and predicted poor response to second-line TKI
Failure to respond to first- and second-line TKIs
Presence of *T315I* mutation and/or failure to respond to ponatinib
Presence of repeated grade 4 cytopenias in response to treatment with different TKIs despite appropriate dose reduction and cytokine support
Advanced phase
TKI naïve
TKI naïve with suboptimal response to TKI
TKI resistant
Blast phase
Acquisition of second CP after TKI or chemotherapy salvage

Craddock (2018) ASH Education Session

Allo SCT for CML in the Imatinib Era



Saussele S, et al. *Blood.* 2010;115:1880-1885

Impact of 2G TKI on Allograft Survival

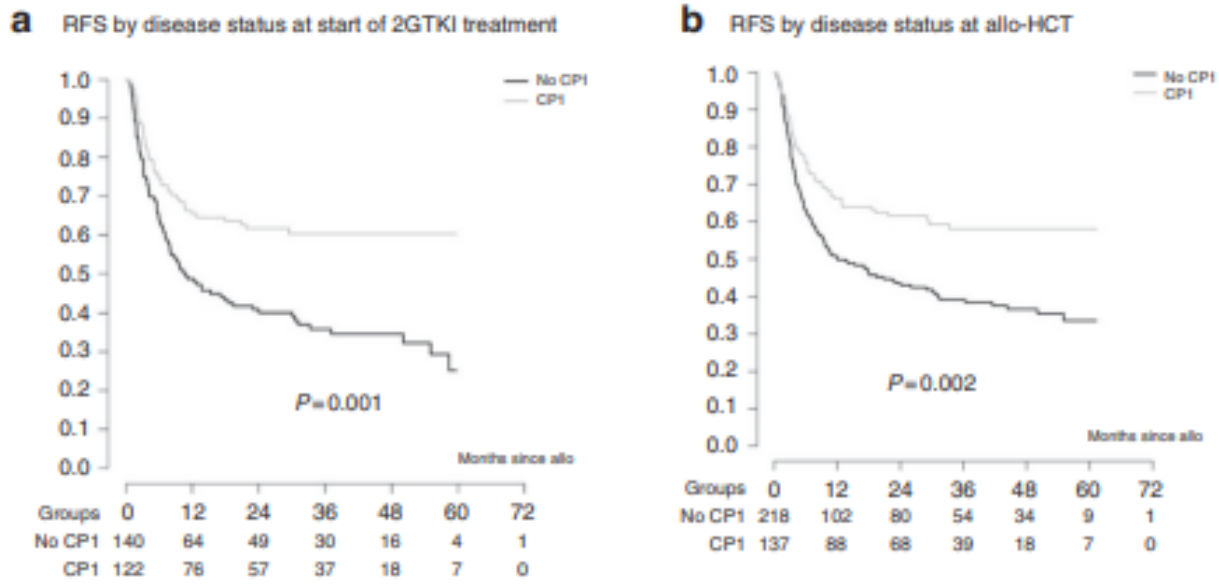


Fig. 4 Impact of disease stage on relapse free-survival (RFS). Advanced disease stage (defined as other than CP1) at start of 2GTKI treatment (**a**) and at time of allo-HCT (**b**) had a negative impact on RFS.

Masouridi-Levrat et al (2022) BMT

PMH CML Transplant Results

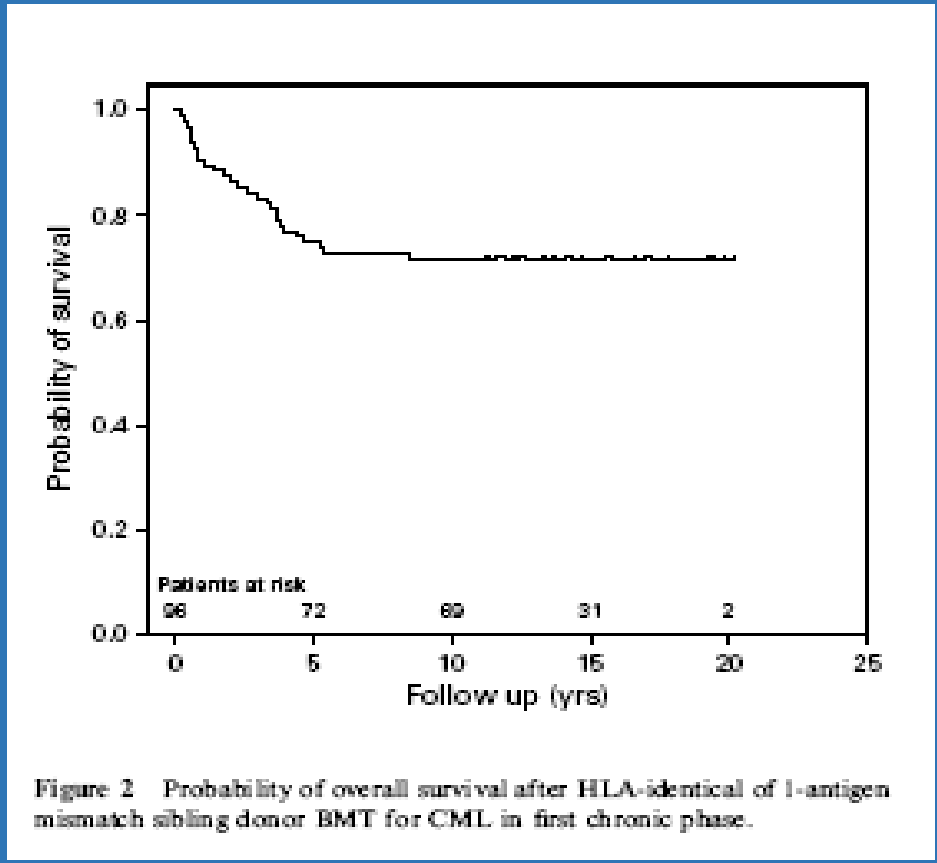


Figure 2 Probability of overall survival after HLA-identical of 1-antigen mismatch sibling donor BMT for CML in first chronic phase.

Zaretsky, BMT (2007)

Summary

- 1. TFR at best will apply to 20-25% of patients
- 2. Most patients will remain on TKI indefinitely and hence appreciation for long term side effects is paramount
- 3. Choice of TKI depends on many features, but the choice narrows with resistance
- 4. Ponatinib and possibly asciminib are good choices for third line therapy or even earlier if first line was a 2G TKI – which is better is uncertain as there is not head to head comparison and the ASCEMBL Study has design issues
- 5. Longer results are available with ponatinib
- 6. OPTIC and adjudication of AOEs have shown that ponatinib has a manageable safety profile as well as effective
- 7. AOEs with asciminib are potentially an issue – only time will tell
- 8. Bosutinib in some cases, can also be effective with a manageable safety profile as an option in salvage therapy
- 9. Preventing side effects by risk identification and management is essential
- 10. Sometimes it is necessary to use a “riskier” drug for disease control
- 11. Stem cell allografting is still appropriate in some cases, but then again, so is palliative therapy with hydroxyurea
- 12. **Current cost of asciminib in the USA is roughly $1.5 million per year at 200mg bid and $300 thousand per year at 40mg bid!!**

Jeffrey H Lipton

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Thank you for spending time with us.

हमारे साथ समय बिताने के लिए धन्यवाद

hamaare Saath Samay biTaaNe ke liye DHaNyavaaD

ہمارے ساتھ وقت گزارنے کے لئے آپ کا شکریہ.

Hamaray sath waqt guzarne ky liye aap ka shukriya!