ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

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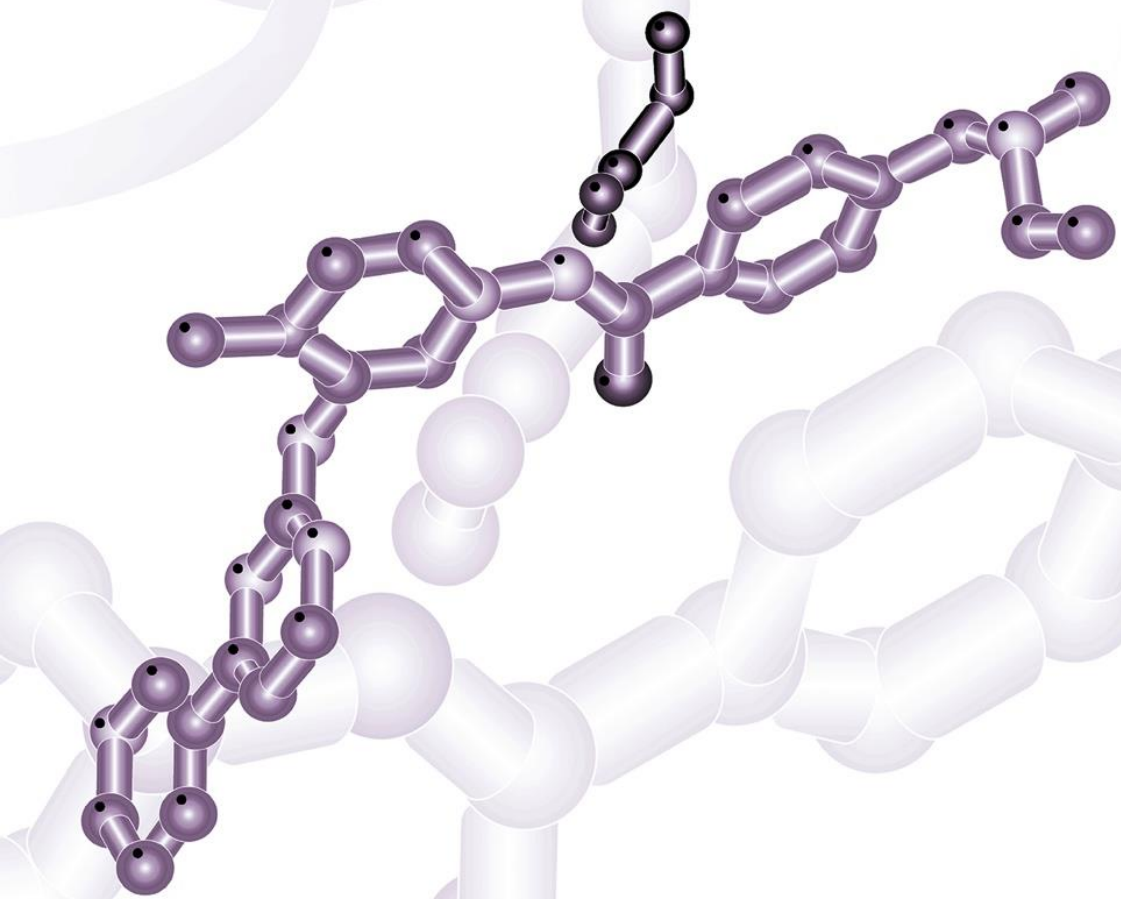

New Drugs in Hematology

President: Pier Luigi Zinzani

Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
May 18-20, 2022

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

Ponatinib

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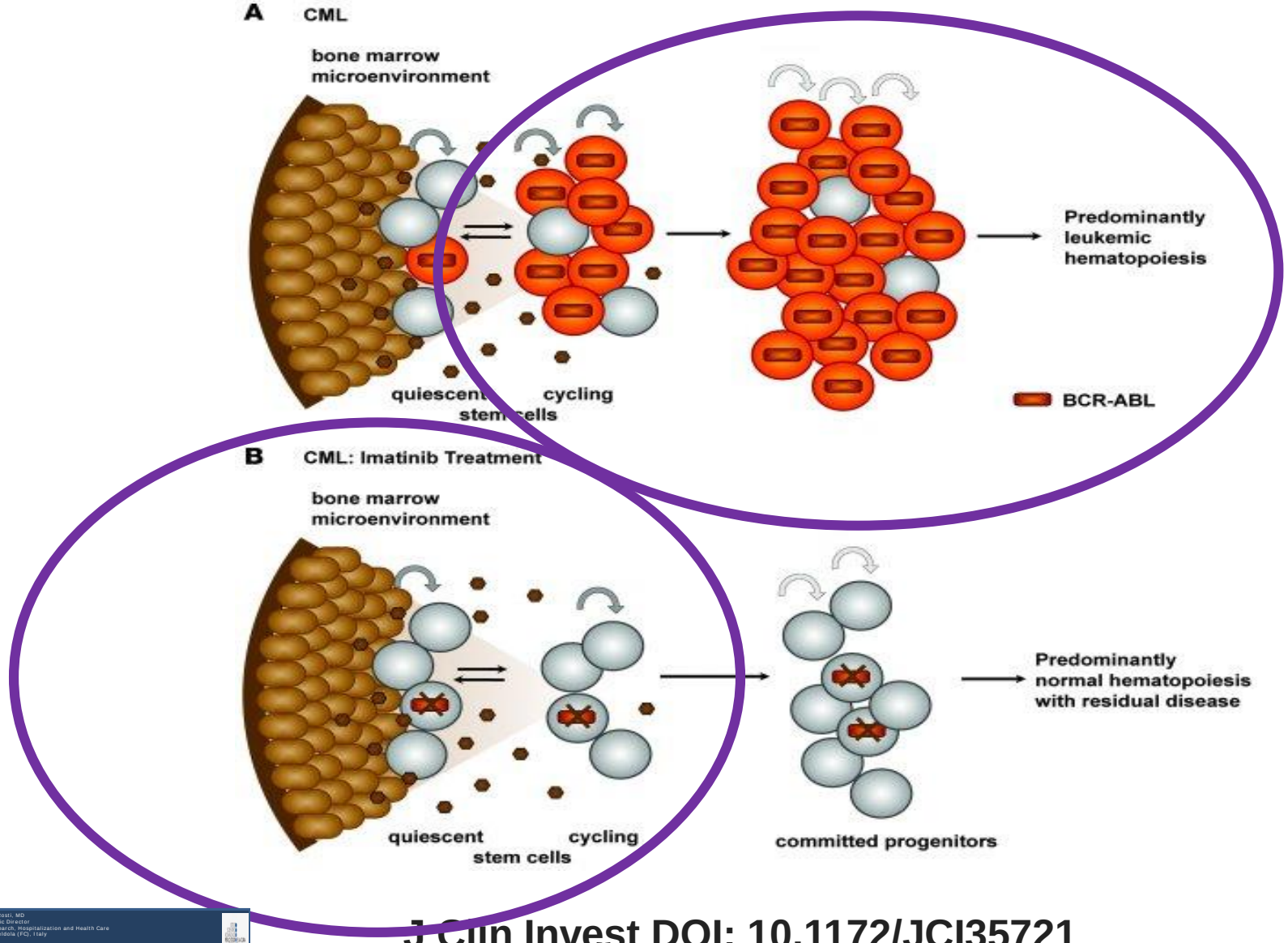
Company	Research Support	Employee	Consultant	Stocks Holder	Speaker Bureau	Advisory Board
Novartis	YES	NO	YES	NO	YES	YES
BMS	YES	NO	NO	NO	YES	NO
Pfizer	YES	NO	YES	NO	YES	NO
Incyte	Yes	NO	YES	NO	Yes	YES

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	
Nilotinib	400 mg BID	400 mg BID	400 mg QD/BID?	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	200 > 300 mg? 300 > 400 mg? 400 mg QD
Ponatinib	45 mg QD	45 mg QD	45, 30, 15 mg QD?	45 mg QD	--	--

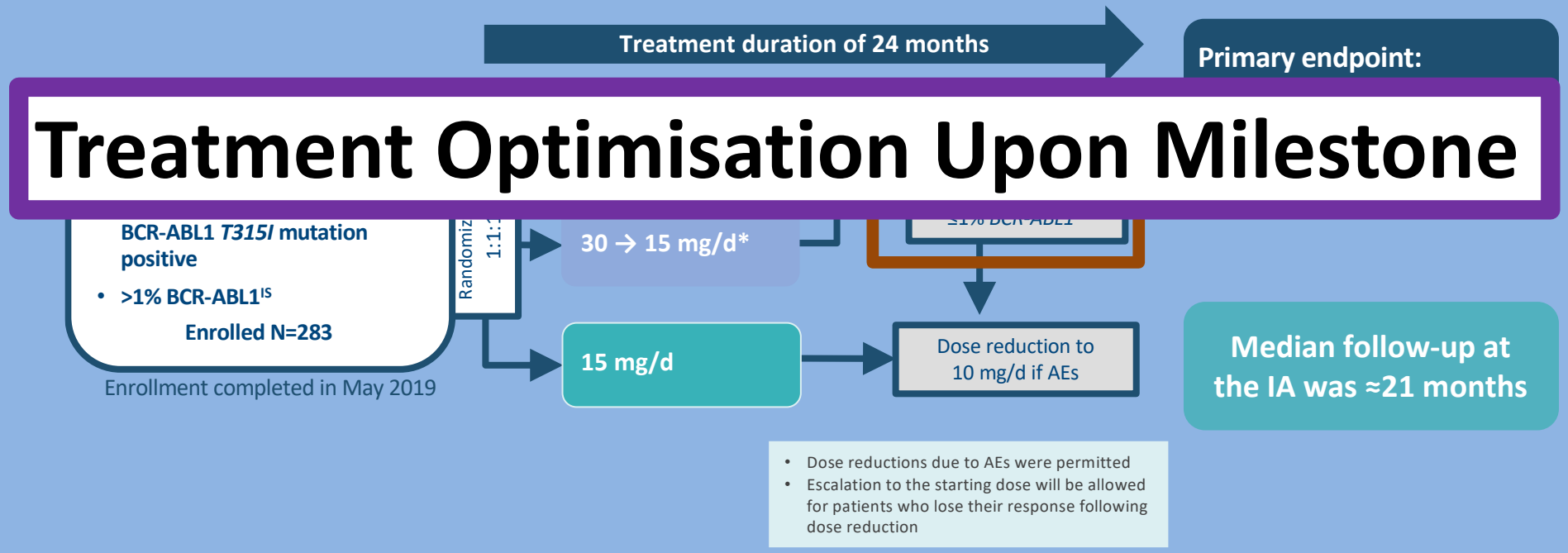
Figure 8: Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity



J Clin Invest DOI: 10.1172/JCI35721

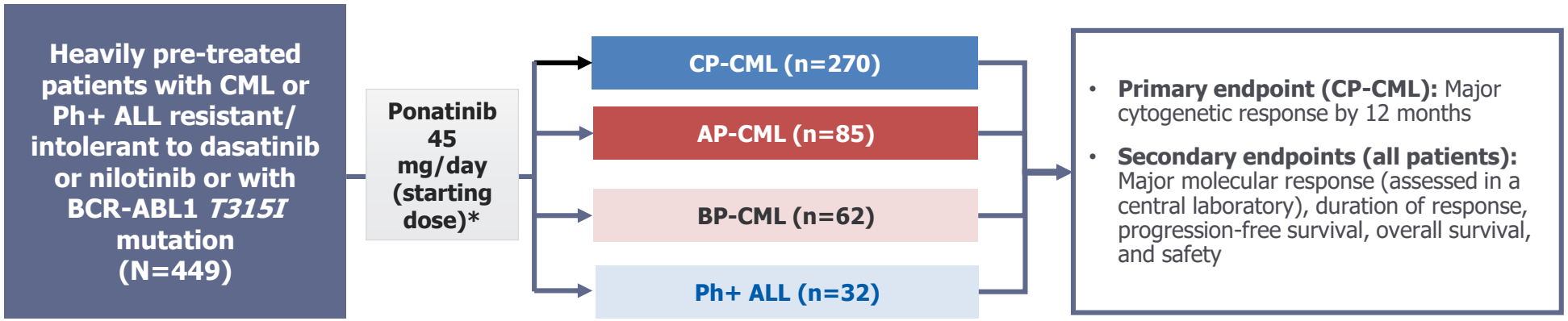
Ponatinib (today)
(Starting dose and dose optimization)

OPTIC (OPTIMIZING PONATINIB TREATMENT IN CP-CML)



Ponatinib (yesterday – all my troubles seem so far away)

PACE: PHASE 2, OPEN-LABEL TRIAL DESIGN (NCT01207440)



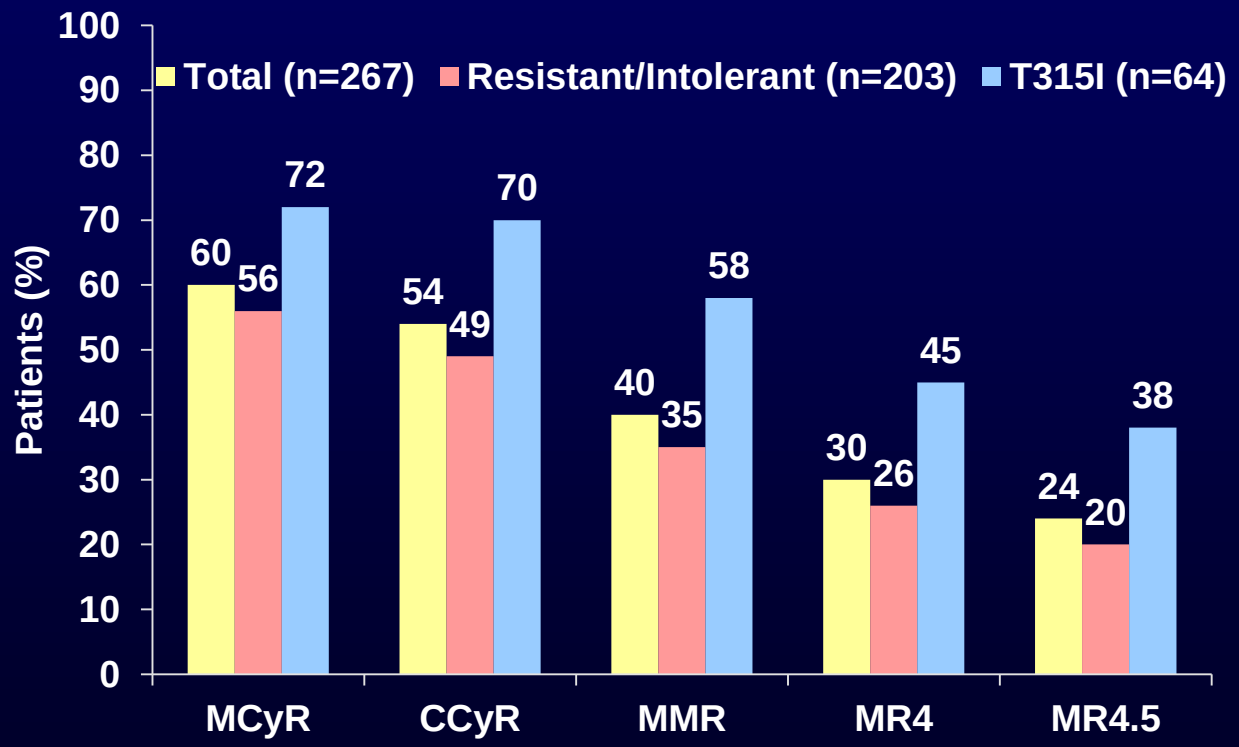
Study start: September 21, 2010; study completion: August 31, 2017

Dose reductions were permitted for toxicity and mandated in October 2013 to manage the risk of arterial occlusive events (AOEs) in response to an observed accumulation of AOEs with longer follow-up in the ponatinib clinical program

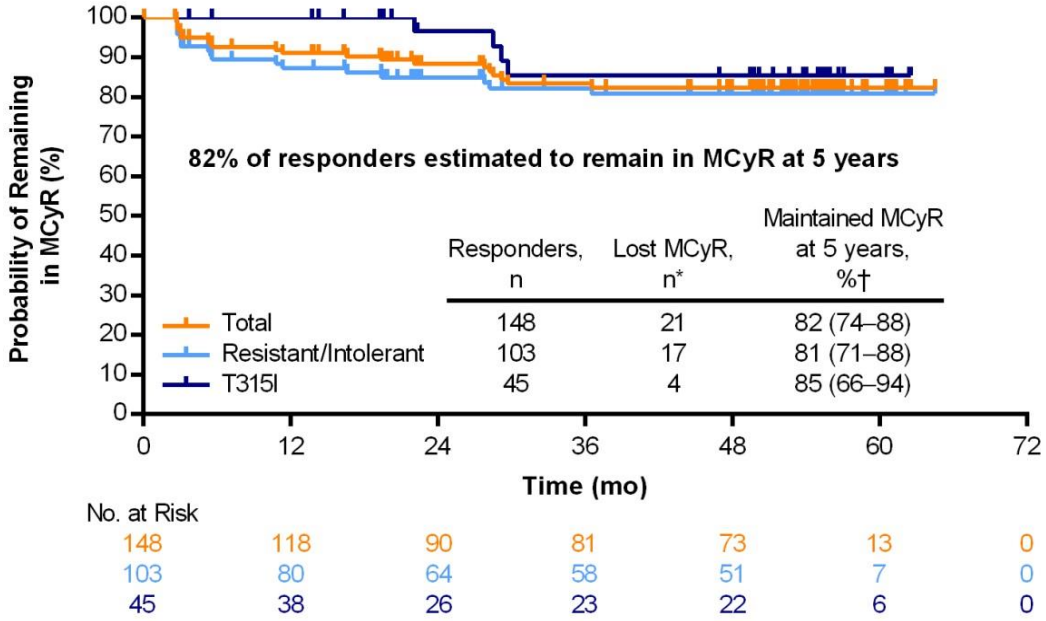
Efficacy of Ponatinib in CP-CML

- Median times to MCyR 2.8 (1.6–58.0) mo, CCyR 2.9 (1.6–58.0) mo, and MMR 5.5 (1.8–55.4) mo

Responses at Any Time



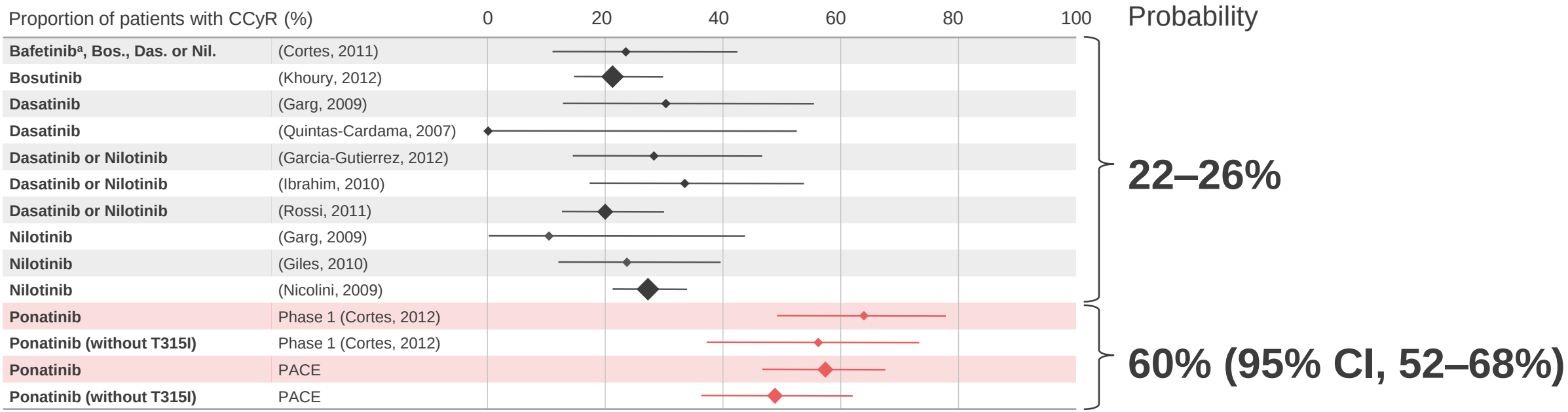
Duration of MCyR



Cortes et al. Blood 2018; 132: 393-404

Sequential use of 2G TKIs: Comparing effectiveness

- Proportion of CP-CML patients who achieve a CCyR (after failure of ≥1 2G TKI and ≥2 prior TKI therapies)



- The probability of achieving CCyR with ponatinib was more than twice that achieved by sequential use of 2G TKIs [1]

The size of the diamonds in the figure represents the number of patients; the length of the lines shows the 95% confidence intervals.
The expected probability of achieving a CCyR was 22–26% vs. 60% under ponatinib.
[a] Bafetinib is not approved for the treatment of patients with CML, treatment only in the context of clinical studies.
2G, second-generation; Bos, bosutinib; CCyR, complete cytogenetic response; CI, confidence interval; CML, chronic myeloid leukaemia; CP, chronic phase; Das, dasatinib; Nil, nilotinib; TKI, tyrosine kinase inhibitor.

Lipton JH et al. *Leuk Res* 2015;39:58–64.

PACE: response rates by mutation status

PACE response rate,[1] n (%)

Mutation status at entry, CP-CML	MCyR*	CCyR*	MMR†
No mutation detected (n=136)	**66 (49)**	**52 (38)**	**43 (32)**
Any mutation (n=131)	82 (63)	71 (54)	62 (47)
T315I mutation only (n=50)	37 (74)	34 (68)	30 (60)
Mutations other than T315I (n=67)	37 (55)	29 (43)	25 (37)
Mutations in addition to T315I (n=14)	8 (57)	8 (57)	7 (50)

- In preclinical and clinical studies, no single mutation that conferred resistance to ponatinib has been identified
- In a post-hoc analysis, patients with T315I mutations were younger, were more recently diagnosed, had received fewer prior TKIs, and a higher dose intensity of ponatinib than otherwise resistant/intolerant patients[2]
- Notable: Ponatinib has substantial activity in patients with no mutations, where mechanism of resistance is assumed to be non–BCR-ABL dependent

*By 12 months. †At anytime

SOURCES: 1. ARIAD Pharmaceuticals, Inc. Data on file as of Aug 2015.
2. Mauro, et al. ASH 2012 (Abstr 3747).

Vascular Occlusive Events in Ponatinib Phase 2 Trial: 60-Month Final Report

	CP-CML (n=270)		Total (n=449)	
	AE	SAE	AE	SAE
Cumulative exposure, patient-years	615.7		826.0	
AOEs, n (%)	84 (31)	69 (26)	111 (25)	90 (20)
Cardiovascular	42 (16)	33 (12)	59 (13)	44 (10)
Cerebrovascular	35 (13)	28 (10)	41 (9)	33 (7)
Peripheral vascular	38 (14)	31 (11)	48 (11)	38 (8)
Exposure-adjusted* incidence of ATEs	14.1	10.9	13.8	10.6
VTEs, n (%)	15 (6)	13 (5)	27 (6)	23 (5)
Exposure-adjusted* incidence of VTEs	2.1	1.8	2.8	2.4

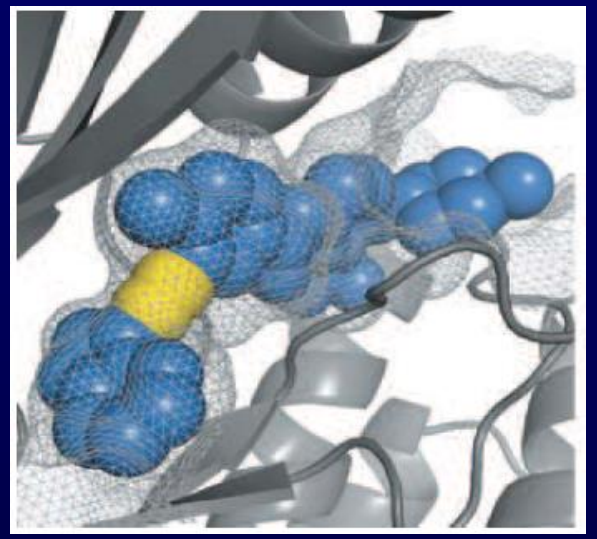
- Median (range) time to ATE onset in CP-CML: 14.1 (0.3-44.0) mo
- Median (range) time to VTE onset in CP-CML: 22.3 (2.0-40.2) mo
- 46 CML-CP and 57 overall had >1 AOE

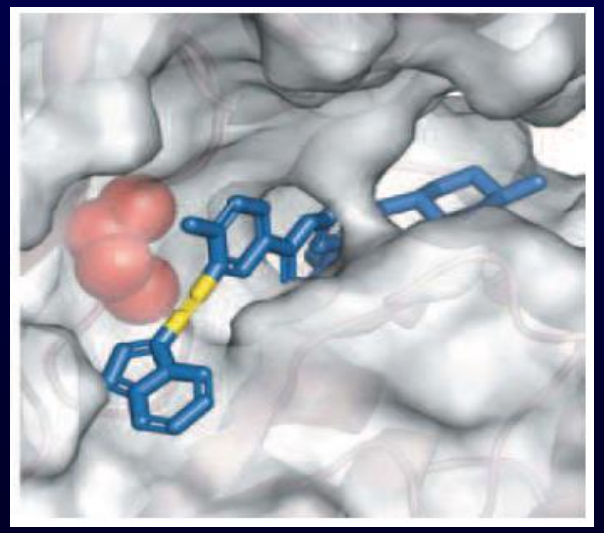
*Number of patients with events per 100 patient-years. Median follow-up time was 42.3 months.

Cortes et al. Blood 2018; 132: 393-404; Cortes JE, et al. EHA 2015; abstract P234

Ponatinib
A Pan-BCR-ABL Inhibitor

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Once-daily oral activity
- Half-life ≈ 22 hours
- Also targets other therapeutically relevant kinases:
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT





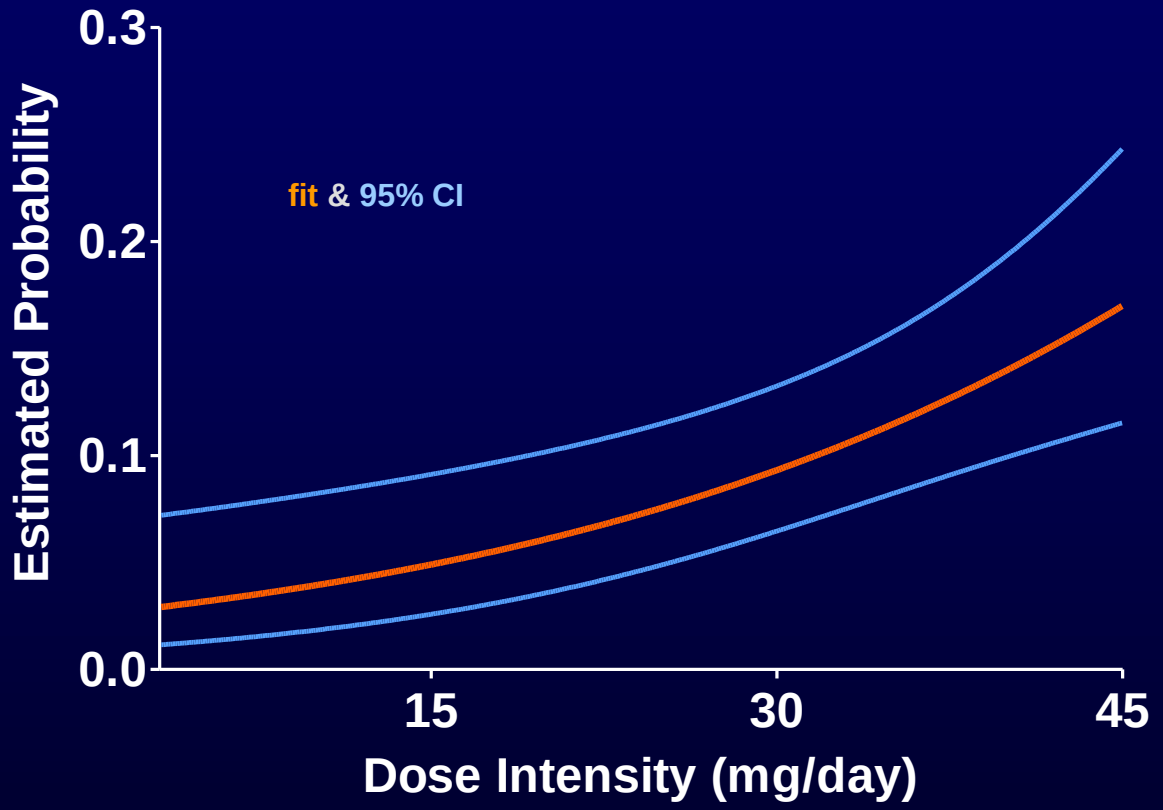
O'Hare T, et al. Cancer Cell. 2009;16:401-412

Ponatinib Phase 2 Study
Demographics & CV Risk Factors

	No Arterial Thrombotic AE N=372	Any Arterial Thrombotic AE N=77
Age ≥65 yrs, n (%)	120 (32)	35 (45)
≥1 Risk factor, n (%)[a]	218 (59)	67 (87)
Hypertension, n (%)	179 (48)	60 (78)
Diabetes, n (%)	34 (9)	23 (30)
Hypercholesterolemia, n (%)	79 (21)	37 (48)
History of any ischemic disease, n (%)	65 (17)	35 (45)
History of myocardial infarction, n (%)	8 (2)	10 (13)
History of CAD, n (%)	18 (5)	15 (19)
History of coronary revasc, n (%)	6 (2)	8 (10)
History of stroke, n (%)	3 (1)	3 (4)
Prior exposure to any TKI[b]		
Mean yrs [range]	4.8 [0.1-12.1]	6.3 [0.4-13.3]
Prior exposure to nilotinib		
n (%)	242 (65)	47 (61)
Mean yrs [range]	1.2 [0.01-5.9]	1.6 [0.02-5.8]

[a]Risk factors = hypertension, hypercholesterolemia, diabetes and obesity; [b]Includes approved (imatinib, dasatinib, nilotinib and bosutinib) and investigational TKIs

Ponatinib Phase 2 Study
Multivariate Analysis of Arterial Thrombotic AEs



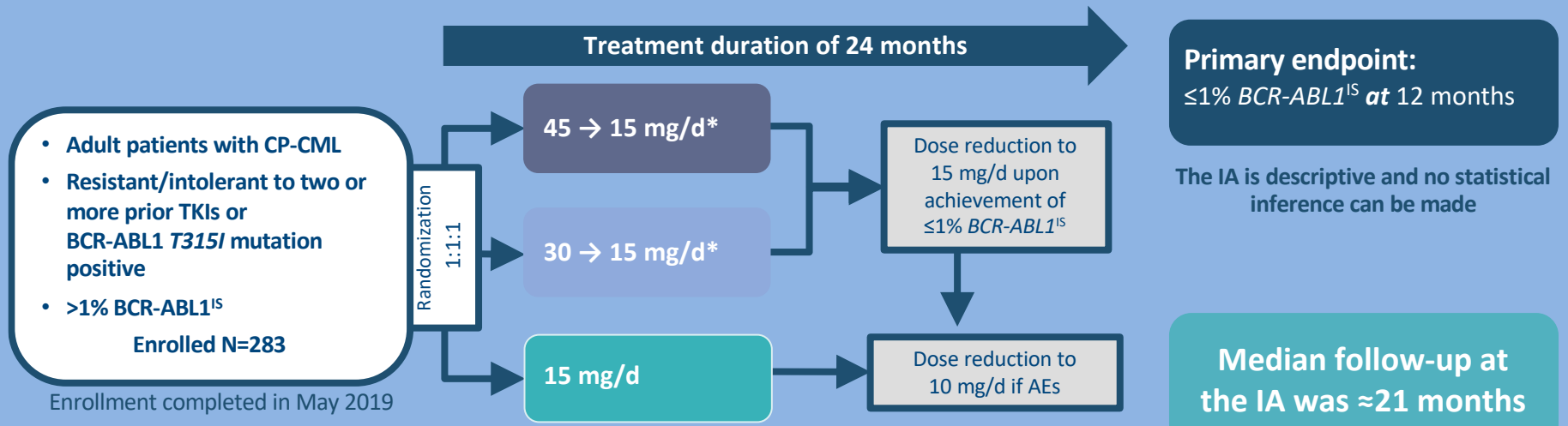
- **Risk factors significantly associated with arterial thrombotic AEs:**
  - **Older age (p<0.0001)**
  - **History of diabetes (p=0.0003)**
  - **Higher dose intensity to time of 1st event (p=0.0009)**
  - **History of ischemia (p=0.0087)**
  - **Longer time since diagnosis (p=0.0228)**
  - **Higher baseline neutrophils (p=0.0276)**
  - **Higher baseline platelets (p=0.0466)**

- **Each 15 mg/day reduction in dose intensity results in a predicted reduction of ~40% in the risk of an arterial thrombotic event**

Ariad, data on file.

Ponatinib (today)
(Starting dose and dose optimization)

OPTIC (OPTIMIZING PONATINIB TREATMENT IN CP-CML)



Enrollment completed in May 2019

Primary endpoint:
≤1% *BCR-ABL1*^{IS} ***at*** 12 months

The IA is descriptive and no statistical inference can be made

Median follow-up at the IA was ≈21 months

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

Ponatinib Dose-Ranging Study in Chronic-Phase Chronic Myeloid Leukemia: A Randomized, Open-Label Phase 2 Clinical Trial

Jorge Cortes, Jane F Apperley, Elza Lomaia, Beatriz Moiraghi, Maria Soledad Undurraga, Carolina Pavlovsky, Charles Chuah, Tomasz Sacha, Jeffrey H Lipton, Charles A. Schiffer, James McCloskey, Andreas Hochhaus, Philippe Rousselot, Gianantonio Rosti, Hugues de Lavallade, Anna Turkina, Christine Rojas, Christopher Arthur, Lori J Maness, Moshe Talpaz, Michael J Mauro, Tracey Hall, Vickie Lu, Shouryadeep Srivastava, Michael W Deininger; *Blood* 2021; blood.2021012082.

[a]Dose reductions due to AEs were permitted;
[b]Escalation to the starting dose allowed for patients who lose their response following dose reduction; no dose escalation allowed beyond starting dose
AE, adverse event; AOE, arterial occlusive event; CCyR, complete cytogenetic response; CP, chronic-phase; CV, cardiovascular; IA, interim analysis; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor; VTE, venous thromboembolism

Cortes JE, et al. J Clin Oncol 2020;15(15S):abstract 7502.

Overall study population
Baseline mutational status and treatment characteristics

Demographic/disease characteristic[1,2]		15 mg/d (n=94)	30 → 15 mg/d (n=94)	45 → 15 mg/d (n=94)
Mutation at baseline*, n (%)	No mutation detected	54 (57.4)	58 (61.7)	51 (54.3)
	Any mutation	38 (40.4)	35 (37.2)	41 (43.6)
	T315I	20 (21.3)	21 (22.3)	25 (26.6)
	Other†	18 (19.1)	14 (14.9)	16 (17.0)
	1 mutation detected	33 (35.1)	29 (30.9)	31 (33.0)
	≥2 mutations detected	5 (5.4)	6 (6.4)	10 (10.6)
Reason prior therapy stopped, n (%)	Resistant	94 (100.0)	94 (100.0)	92 (97.9)
Prior TKIs, n (%)	1	4 (4.3)	1 (1.1)	1 (1.1)
	2	42 (44.7)	37 (39.4)	43 (45.7)
	≥3	48 (51.0)	56 (59.6)	50 (53.2)

>99% were resistant to immediate prior therapy

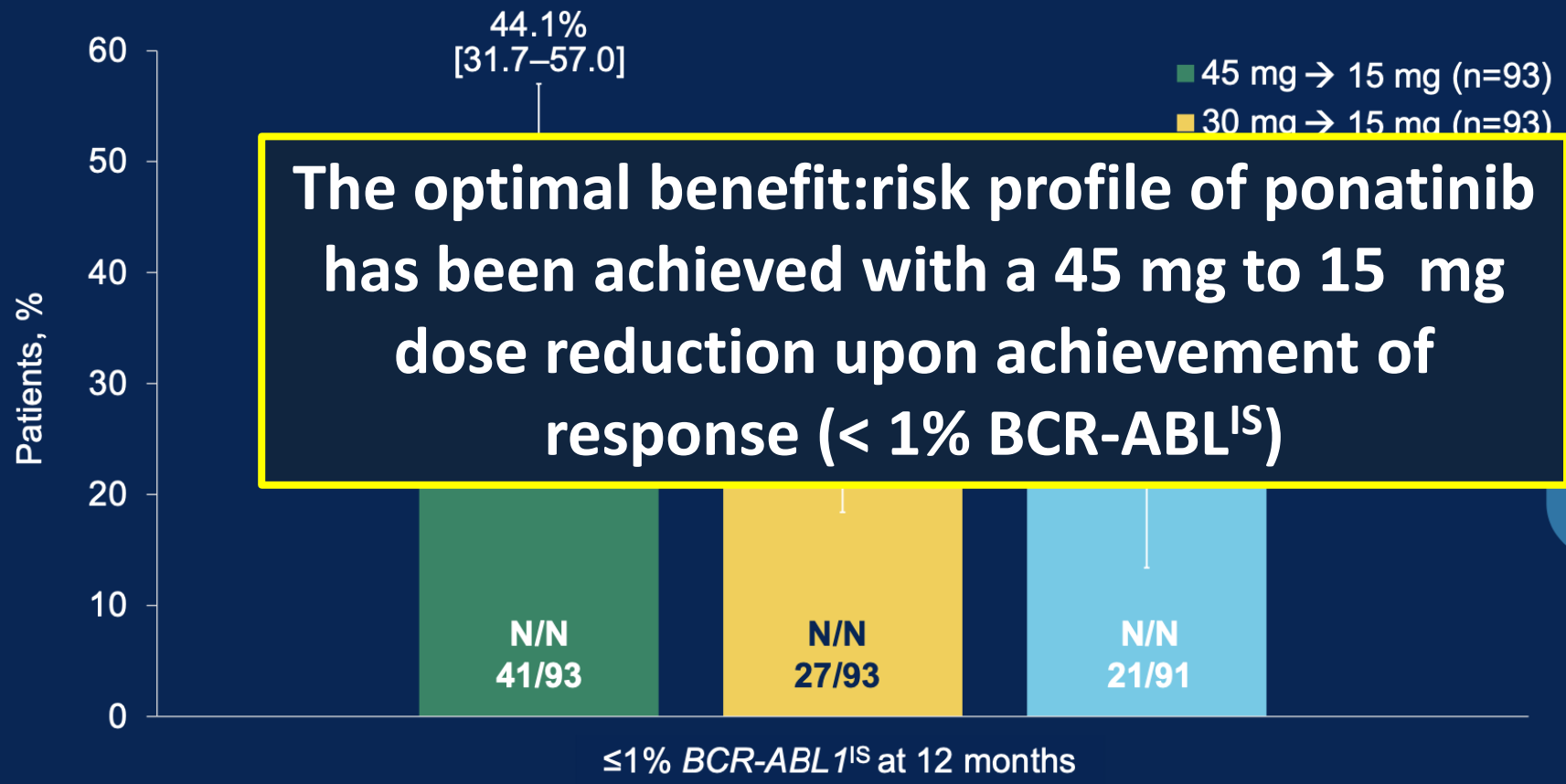
Almost all patients were treated with ≥2 prior TKIs

*Sanger sequencing was used for mutation testing. Five patients (2 in 15 mg/d cohort, 1 in 30→15 mg/d cohort, and 2 in 45→15 mg/d cohort) did not have any mutation testing performed at baseline; †Mutation other than *T315I*

TKI, tyrosine kinase inhibitor

1. Cortes JE, et al. ASCO 2020 [abstract 7502/oral presentation]; 2.Cortes JE, et al. ASH 2020 [abstract 632/oral presentation]

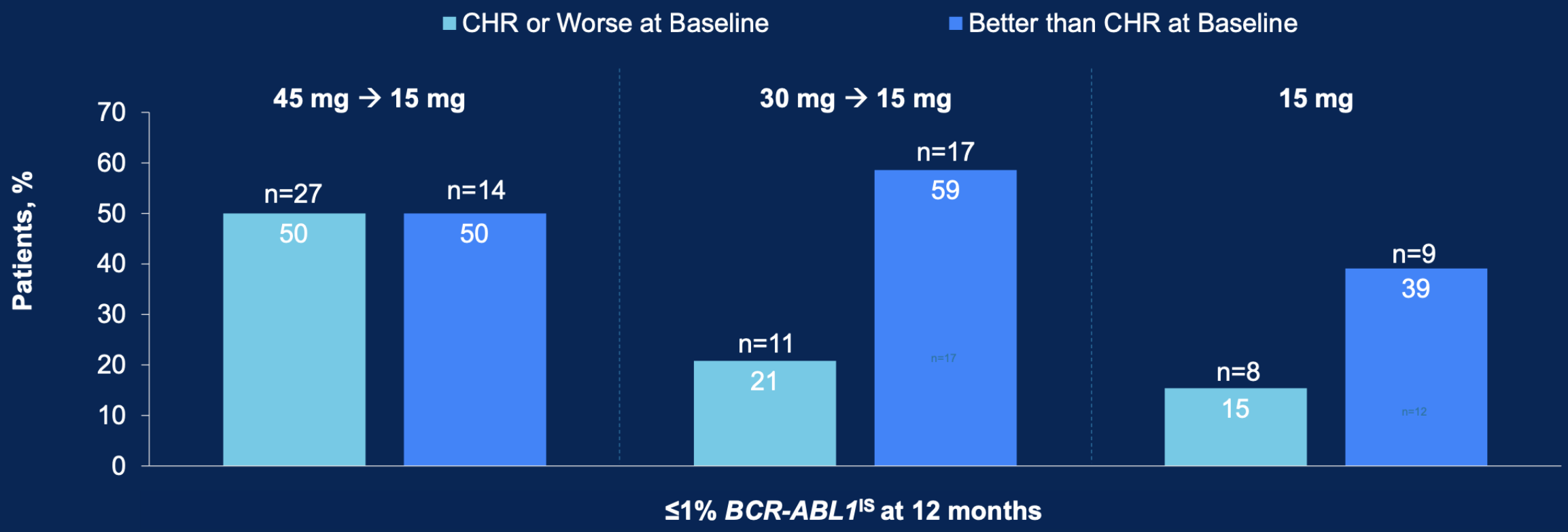
Primary Endpoint: *BCR-ABL1*^{IS} ≤1% at 12 Months



The optimal benefit:risk profile of ponatinib has been achieved with a 45 mg to 15 mg dose reduction upon achievement of response (< 1% BCR-ABL^{IS})

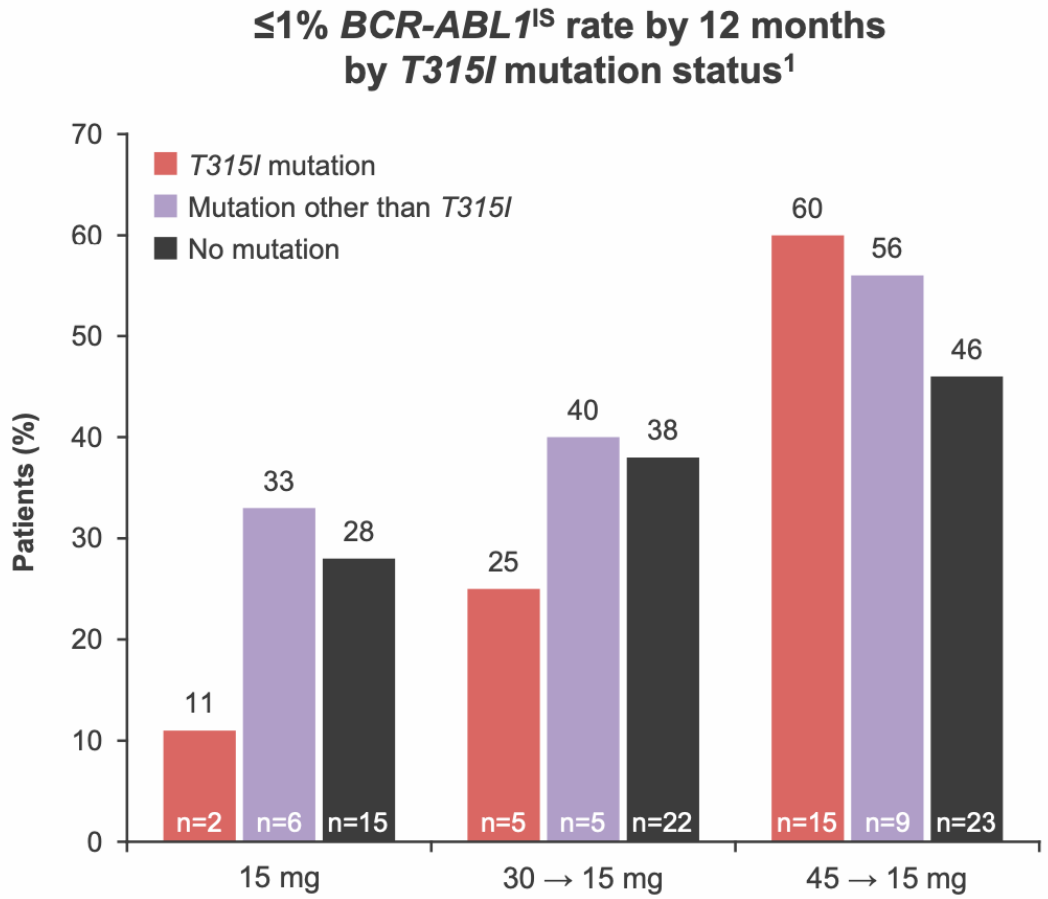
- The response rate was highest with the 45 mg → 15 mg regimen, 44.1% (31.7–57.0)
- The pre-specified statistical endpoint was met with the 45 mg → 15 mg regimen (*P*<0.017)

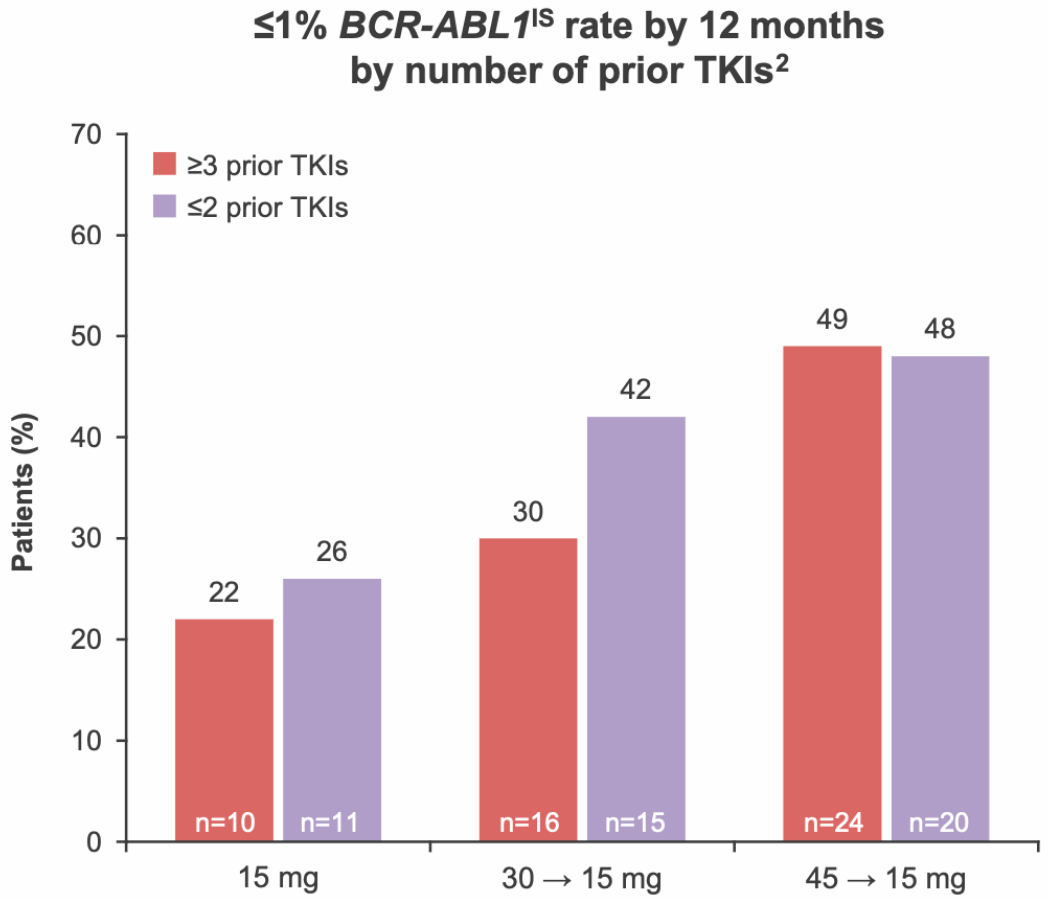
BCR-ABL1^{IS} Response Rate by Best Response to Last Prior Therapy



CHR, complete hematologic response

Outcome by mutation status and line of treatment in OPTIC, a dose-ranging study of 3 starting doses of ponatinib in patients with CP-CML





The recommended starting dose of ponatinib is 45 mg once daily.

CML, chronic myeloid leukaemia; CP, chronic phase; IS, international scale; OPTIC, Optimizing Ponatinib Treatment In CP-CML; TKI, tyrosine kinase inhibitor.

1. Cortes JE, et al. *Blood*. 2021. Epub ahead of print;
2. Cortes JE, et al. Oral Presentation at ASH 2020; Abstract 48.

Characteristic		PACE CP-CML (n=257)	OPTIC 45 → 15 mg/d (n=93)
Age, years	Median	61	46
Gender, n (%)	Male	134 (52)	49 (53)
Time since dx, years	Median	7	6
Mutation at baseline, n (%)	No mutation	136 (53)	52 (56)
	Any mutation	121 (47)	40 (43)†
	T315I	54 (21)	24 (26)
	Other*	67 (26)	16 (17)
CV risk factor, n (%)	Hypertension	99 (39)	29 (31)
	Diabetes	33 (13)	5 (5)
	Hypercholesterolemia	65 (25)	3 (3)
Reason for prior treatment D/C, n (%)	Resistance	247 (96)	91 (98)

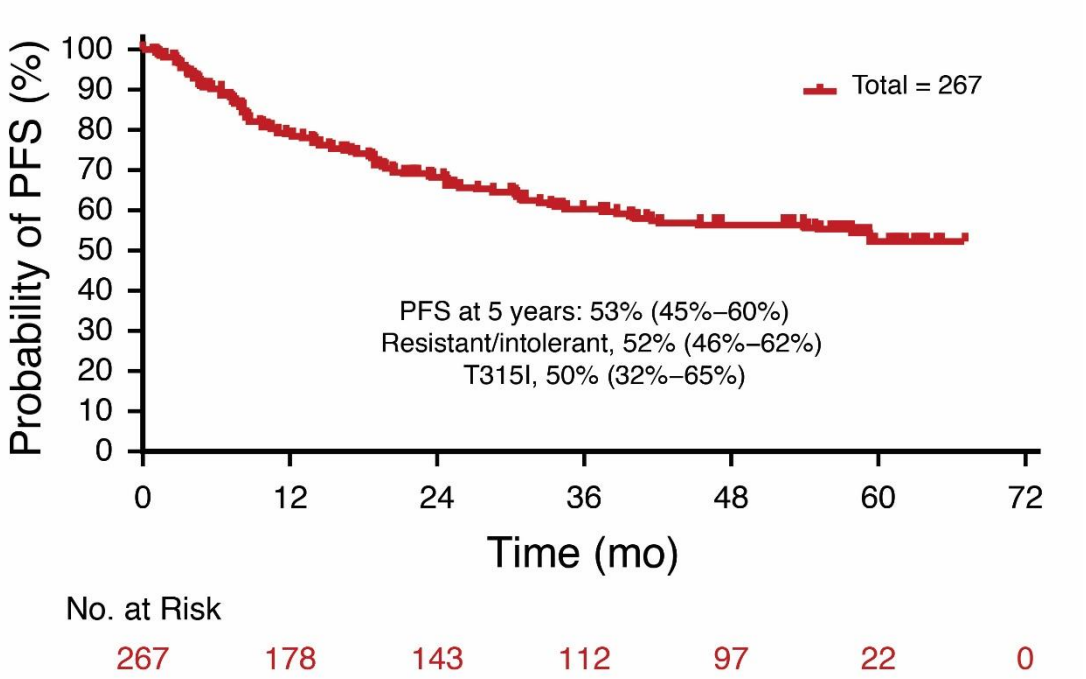
97% (338/350) were resistant to ≥1 prior 2G TKI

Kantarjian H, et al. ASH 2020 [abstract 647/oral presentation]

Results

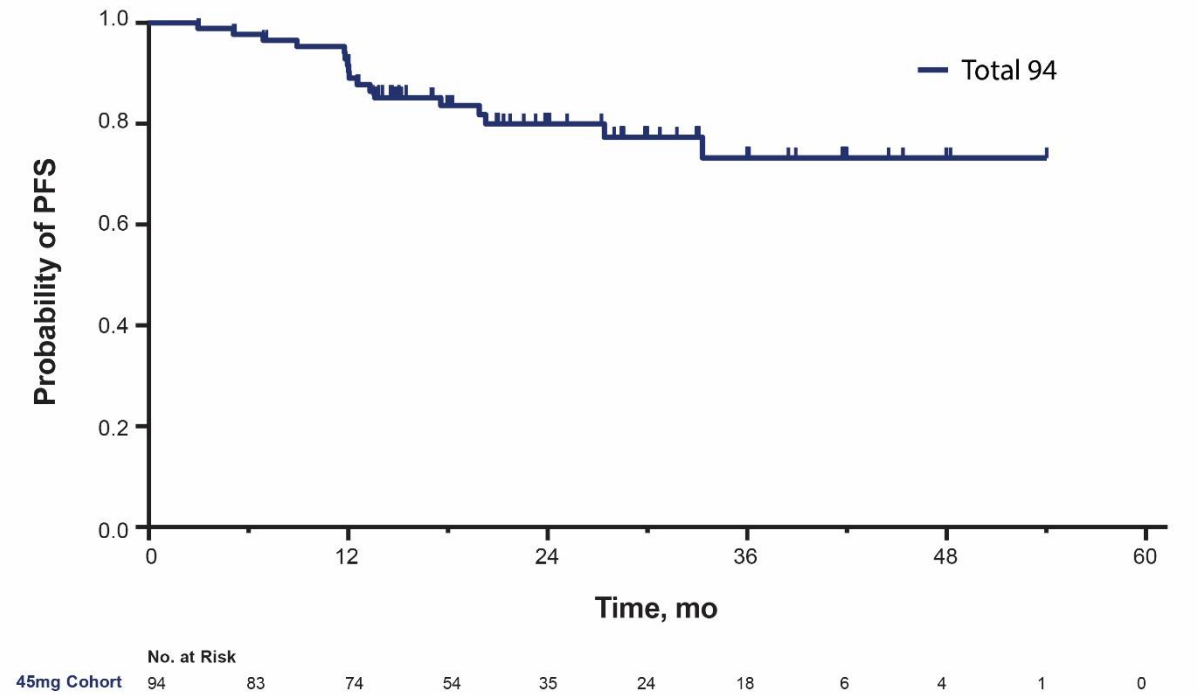
Figure 5: Progression-Free Survival

PACE PFS



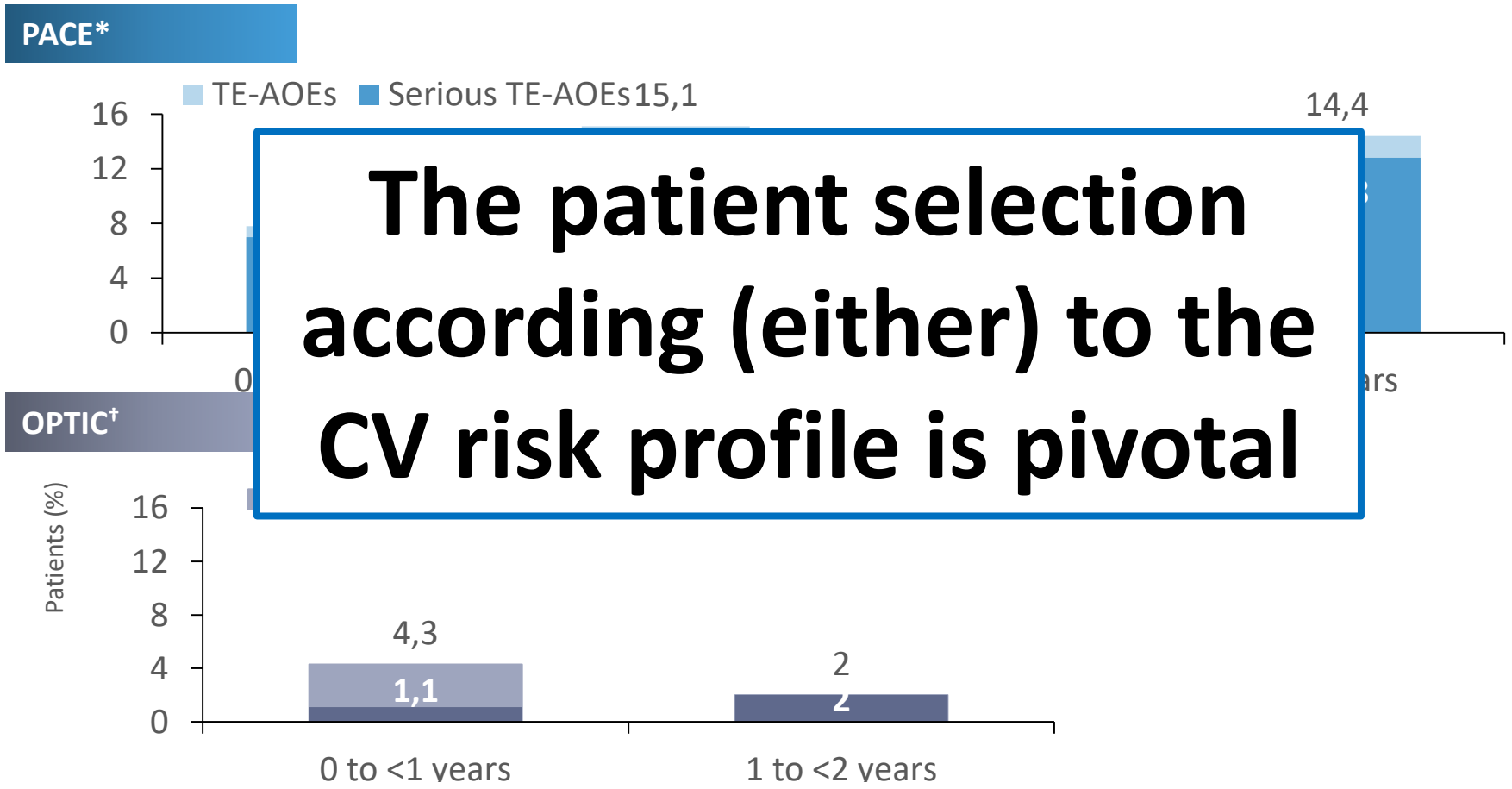
- Median follow-up: 57 months
- 80% of patients stopped prior treatment due to resistance

OPTIC PFS (45 mg > 15 mg cohort)



- Median follow-up: 32 months
- 98% of patients stopped prior treatment due to resistance

Exposure-adjusted cumulative adjudicated TE-AOEs over time



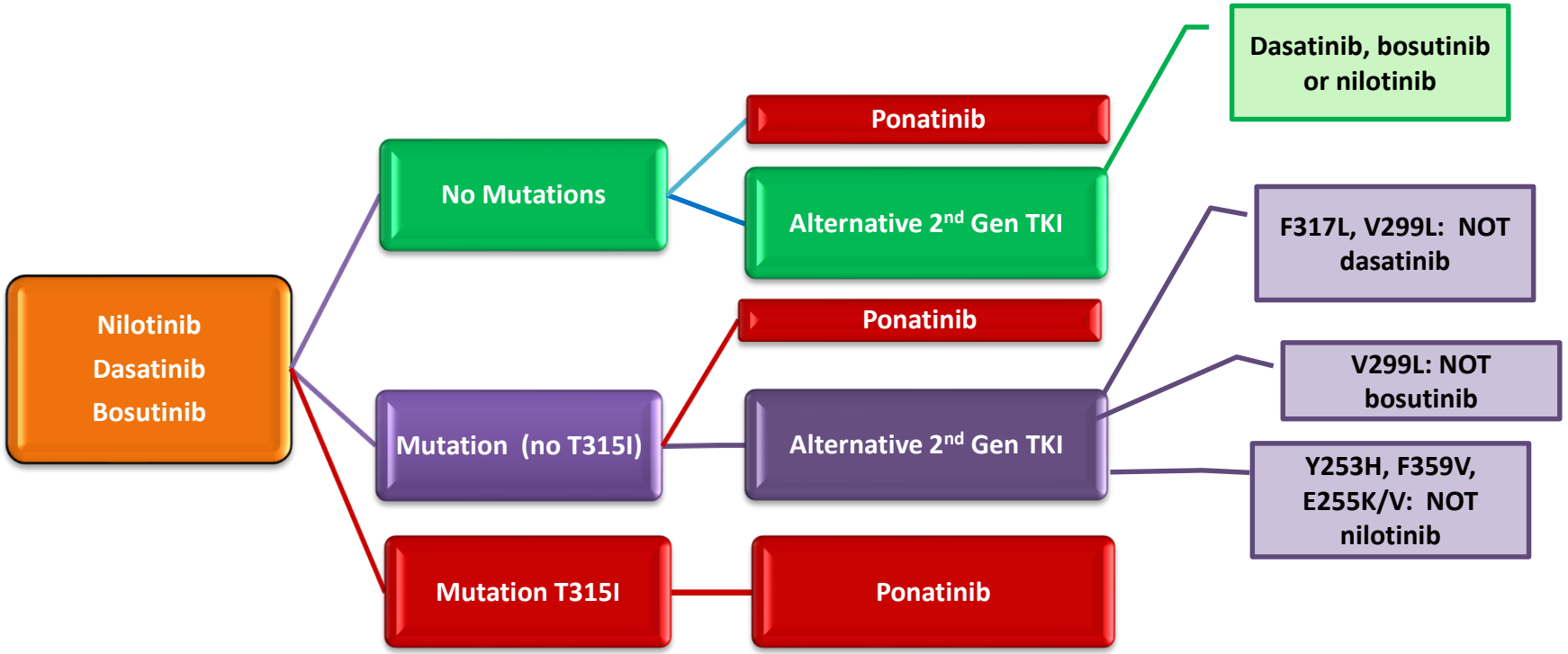
The patient selection according (either) to the CV risk profile is pivotal

*Median follow-up 57 months; †Median follow-up 21 months

2G, second generation; ALL, acute lymphoblastic leukemia; (TE-)AOE, (treatment-emergent-)arterial occlusive event; CML, chronic myeloid leukemia; CP, chronic phase; OPTIC, Optimizing Ponatinib Treatment In CP-CML; PACE, Ponatinib Ph+ ALL and CML Evaluation; Ph+, Philadelphia chromosome-positive; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor

Kantarjian H, et al. ASH 2020 [abstract 647/oral presentation]

Resistance to a 2nd gen TKI in first line (2023)



Thank you for your kind attention!

Gianantonio Rosti, MD
Deputy Scientific Director
IRCCS/SIRHHC Scientific Institute for Research, Hospitalization and Health Care
«Dino Amadori» – Meldola (FC), Italy

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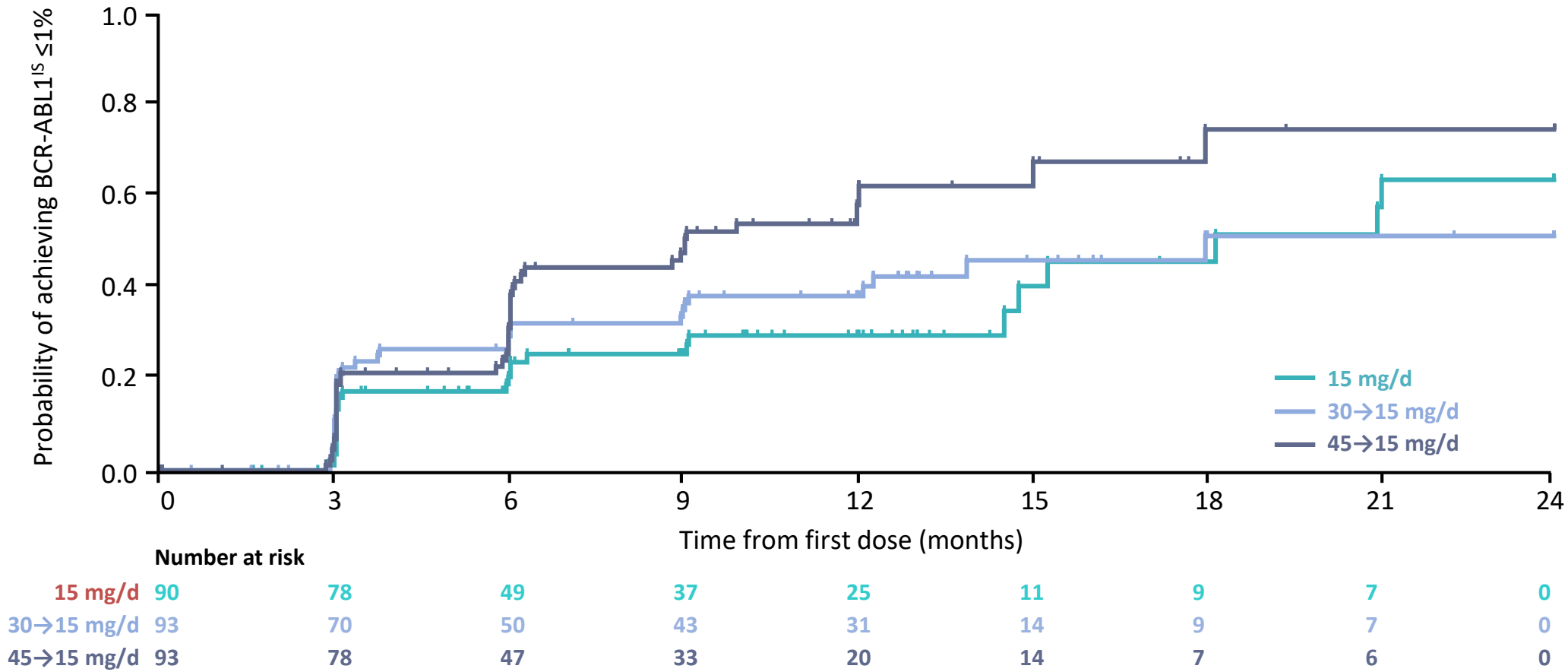
Overall study population

Time to ≤1% BCR-ABL1^{IS} response by ponatinib starting dose



Number at risk									
15 mg/d	90	78	49	37	25	11	9	7	0
30→15 mg/d	93	70	50	43	31	14	9	7	0
45→15 mg/d	93	78	47	33	20	14	7	6	0

- ≤1% BCR-ABL1^{IS} was achieved as early as 2.9 months in all three dosing regimens
- The 45→15 mg/d cohort demonstrated the highest ≤1% BCR-ABL1^{IS} rate, and these rates were maintained until 24 months

Cortes JE, et al. ASCO 2020 [abstract 7502/oral presentation]

Overall study population
Patient demographics and baseline disease characteristics

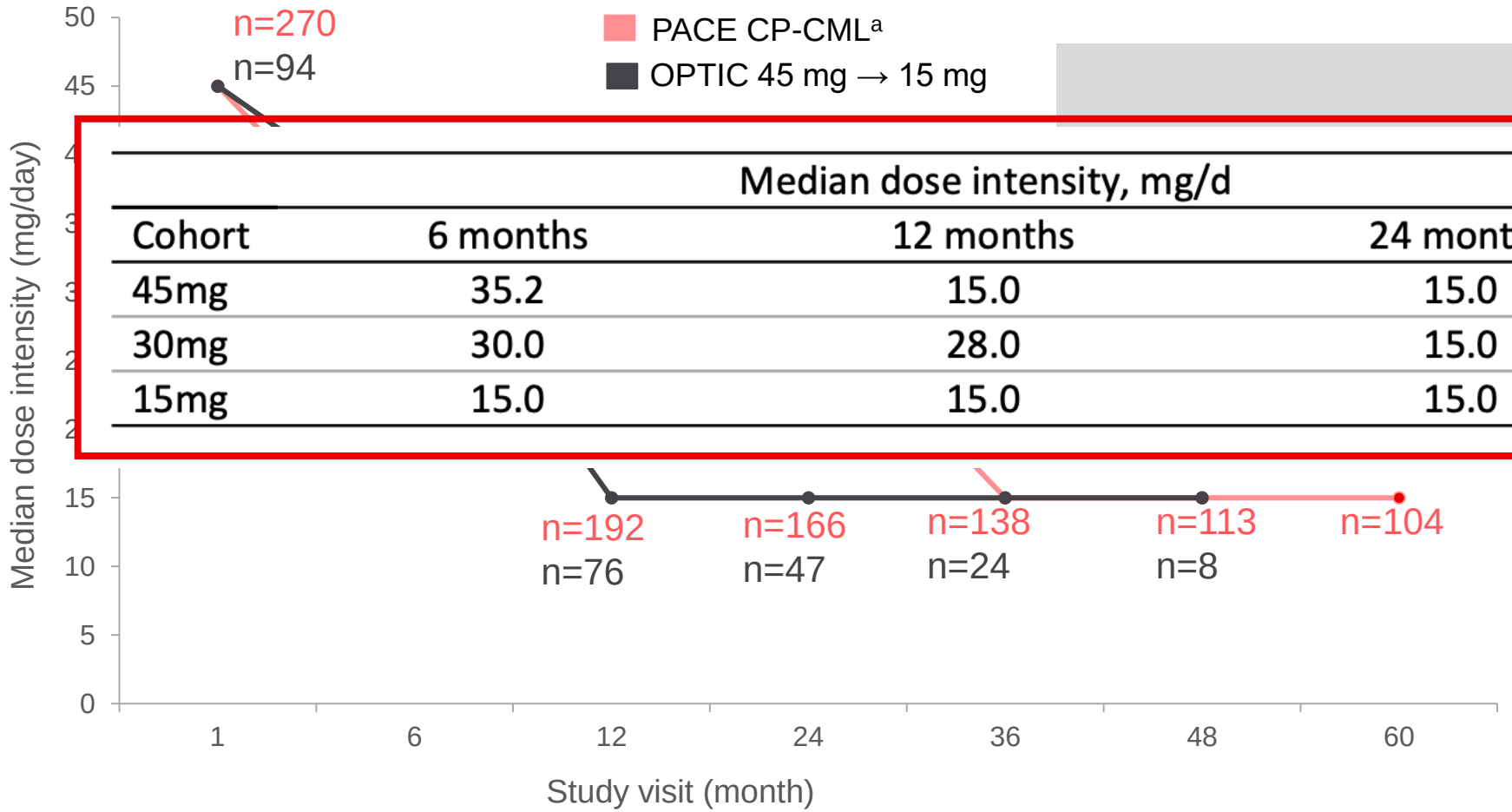
Demographic/disease characteristic[1,2]		15 mg/d (n=94)	30 → 15 mg/d (n=94)	45 → 15 mg/d (n=94)
Age, years	Median (range)	49.0 (18–81)	50.5 (21–77)	46.0 (19–81)
Gender, n (%)	Male	53 (56.4)	38 (40.4)	50 (53.2)
ECOG PS, n (%)	0 or 1	94 (100)	93 (98.9)	93 (98.9)
Time since diagnosis, years	Median (range)	5.7 (1–22)	4.9 (1–29)	5.5 (1–21)
Patients with CV risk factors, n (%)	Arterial hypertension	22 (23.4)	25 (26.6)	26 (27.7)
	Diabetes mellitus	7 (7.4)	3 (3.2)	5 (5.3)
	Hypercholesterolemia	15 (16.0)	14 (14.9)	19 (20.2)
	Median BMI (kg/m^2)	26	26	27

- **OPTIC excluded patients with *uncontrolled* hypertension or diabetes (as well as patients with significant uncontrolled or active CV disease), but did include patients with *controlled* hypertension or diabetes[3]**

BMI, body mass index; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status

1. Cortes JE, et al. ASCO 2020 [abstract 7502/oral presentation]; 2.Cortes JE, et al. ASH 2020 [abstract 632/oral presentation];
3. Data on file, AP24534-14-203 CSR (Apr 23, 2020)

Median Dose Intensity Over Time in PACE and OPTIC



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

PACE CP-CML[a]	OPTIC 45 mg → 15 mg (N=94)
mo	15 (at 12-mo and 24-mo visits)
lo	

[a]PACE: Includes CP patients not T315I+ at study entry and not resistant to dasatinib or nilotinib.
[b]Dose intensity at time of study visit; Dose intensity=total cumulative dose (mg)/duration of exposure (days).

CML, The TKI dose

According to your Sokal, Euro, MDACC, ELTS scores, MDR genotype OCT-1 activity, GEP, Cytogenetics, OCA, ACA, whole genome sequencing, age, sex, race, PK, BCR-ABL IC50, pharmacodynamic and comorbidities and co-treatments your tailored dose of TKI is 12,23 mg four times a day, more or less…..

Characteristic		PACE CP-CML (n=257)	OPTIC 45 → 15 mg/d (n=93)
Number of prior 2G TKIs, n (%)	1	6 (2)	0
	2	92 (36)	43 (46)
	3	146 (57)	42 (45)
	4	13 (5)	8 (9)
Best response to prior TKI, n (%)*	None/PD	61 (24)	12 (13)
	CHR	68 (26)	54 (58)
	MCyR	63 (25)	7 (8)
	CCyR*	36 (14)	7 (8)
	MMR	10 (4)	12 (13)
BCR-ABL1^{IS} at baseline, n(%)	>10%	194 (75)	73 (78)
	>1–10%	49 (19)	16 (17)
	≤1%	12 (5)	2 (2)

Kantarjian H, et al. ASH 2020 [abstract 647/oral presentation]

Ponatinib efficacy post-2G TKI by baseline mutational status

Outcome		PACE CP-CML (n=257)				OPTIC 45 → 15 mg/d (n=93)			
		None (n.136	*T315I* (n=54)	Other* (n=67)	Any (n=121)	None (n=52)	*T315I* (n=24)	Other* (n=16)	Any (n=40)
≤1% BCR-ABL1[IS] by:	1 year, %	36	56	43	49	38	63	53	59
	2 years, %	40	59	46	52	46	63	56	60
	5 years, %	42	61	46	53	N/A	N/A	N/A	N/A
PFS at:	2 years, %	71	70	57	63	81	83	76	80
	5 years, %	58	47	46	45	N/A	N/A	N/A	N/A
OS at:	2 years, %	91	78	80	79	90	100	92	95
	5 years, %	80	62	67	64	N/A	N/A	N/A	N/A

Kantarjian H, et al. ASH 2020 [abstract 647/oral presentation]

Ponatinib efficacy post-2G TKI by baseline mutational status

Outcome		PACE CP-CML (n=257)				OPTIC 45 → 15 mg/d (n=93)			
		None (n.136	*T315I* (n=54)	Other* (n=67)	Any (n=121)	None (n=52)	*T315I* (n=24)	Other* (n=16)	Any (n=40)
≤1% BCR-ABL1^{IS} by:	1 year, %	36	56	43	49	38	63	53	59
	2 years, %	40	59	46	52	46	63	56	60
	5 years, %	42	61	46	53	N/A	N/A	N/A	N/A
PFS at:	2 years, %	71	70	57	63	81	83	76	80
	5 years, %	58	47	46	45	N/A	N/A	N/A	N/A
OS at:	2 years, %	91	78	80	79	90	100	92	95
	5 years, %	80	62	67	64	N/A	N/A	N/A	N/A

Kantarjian H, et al. ASH 2020 [abstract 647/oral presentation]