1ST INTERNATIONAL CONFERENCE ON
Ph/Leukemias
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Second and third-line therapy in CML

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Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal

Disclosures Valentín García Gutiérrez

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	X		X		X	X	
BMS	X		X		X	X	
Incyte	X				X	X	
Pfizer	X		X		X	X	
GSK	X		X			X	
MSD			X			X	

During the presentation, we will discuss about:

- How frequent is the need of second/third line treatment?
- How can we identify CML treatment failures?
- How should we manage CML treatment failures?
- Can we improve current results?

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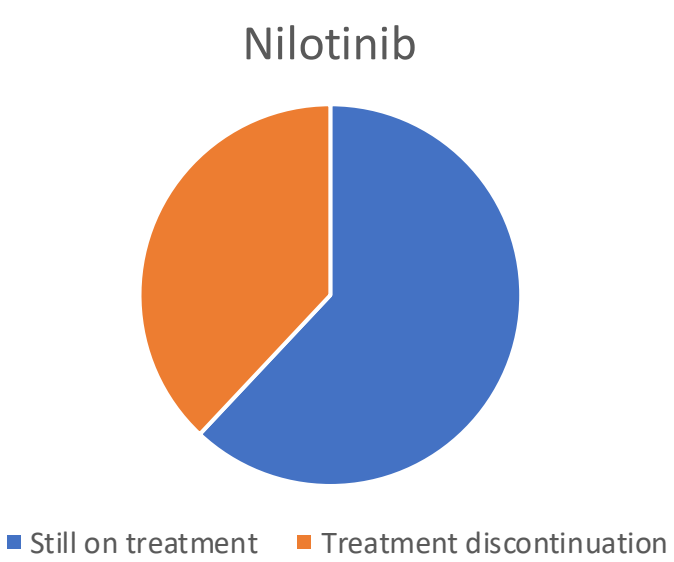
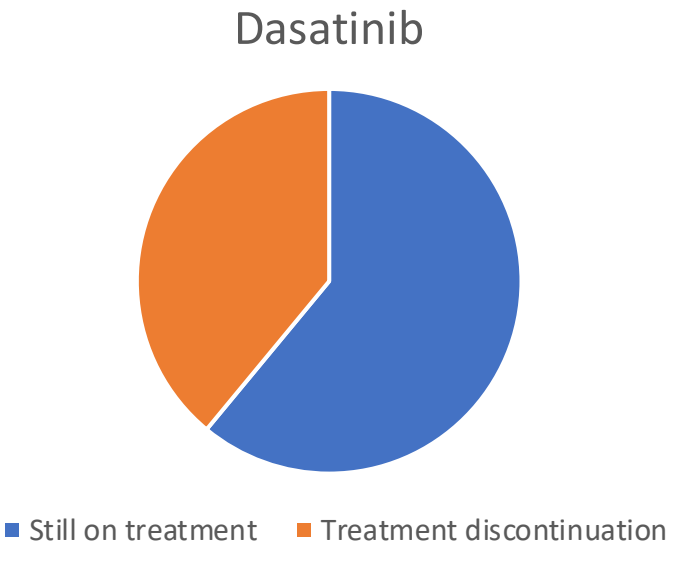
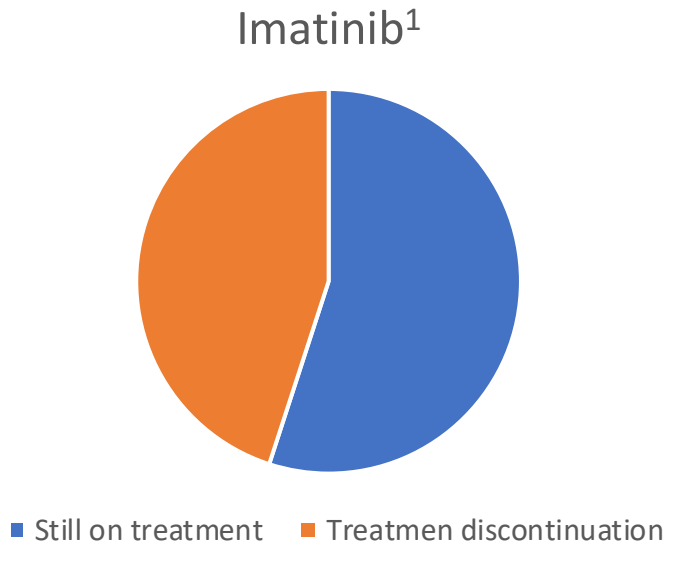
How frequent is treatment failure in CML pts first line?

ENESTnd and DASISION studies → 5 years follow up







This data comes from different studies and should not be compared

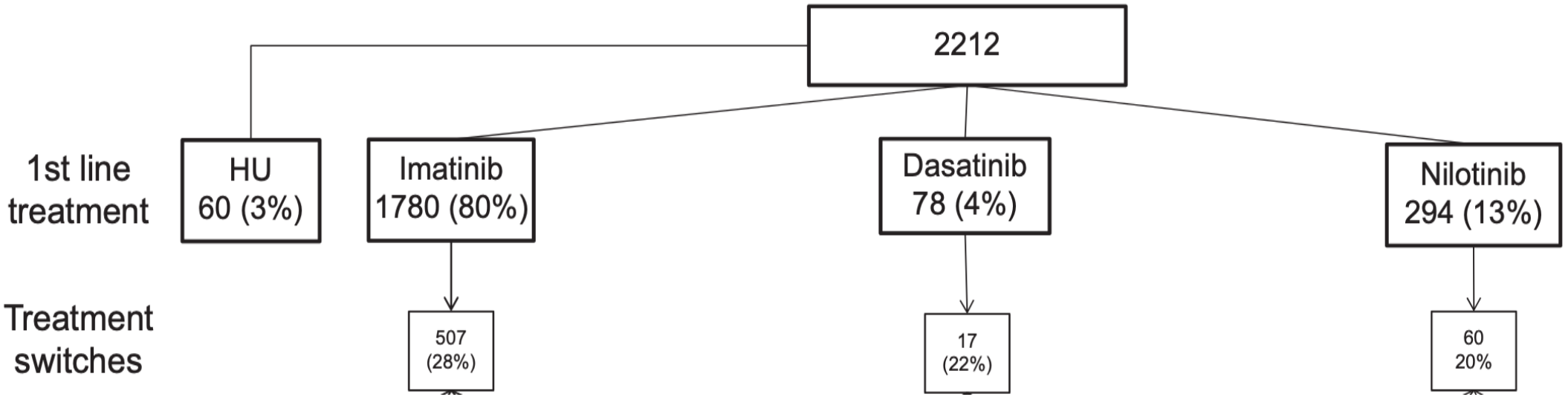
1. Imatinib treatment interruption differs from 37%-49%

Adapted from: Cortes J, J Clin Oncol. 2016 Jul 10;34(20):2333-40

Hochhaus A. Leukemia. 2016 May;30(**5**):1044-54

How frequent is treatment failure in CML pts first line? Real world experience

EUTOS population registry → 19 meses seguimiento



Leukemia (2017) **31,** 593–601

During the presentation, we will discuss about:

- How frequent is the need of 2nd/3th line treatment?
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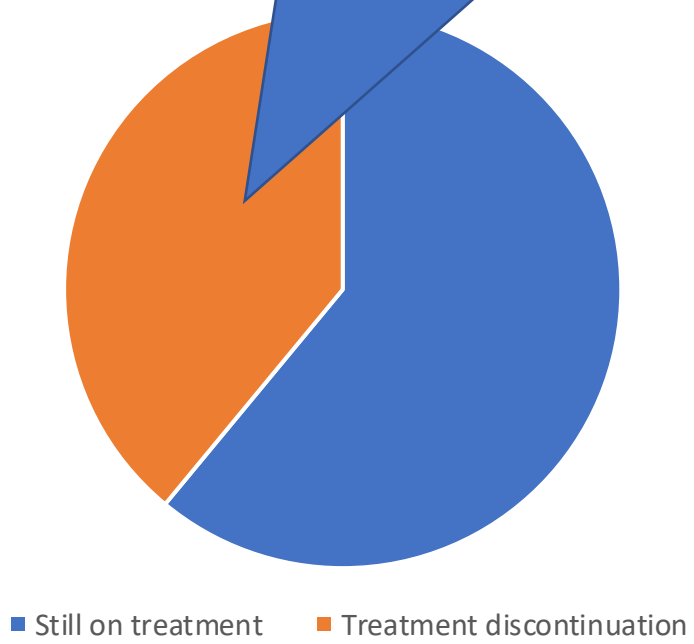
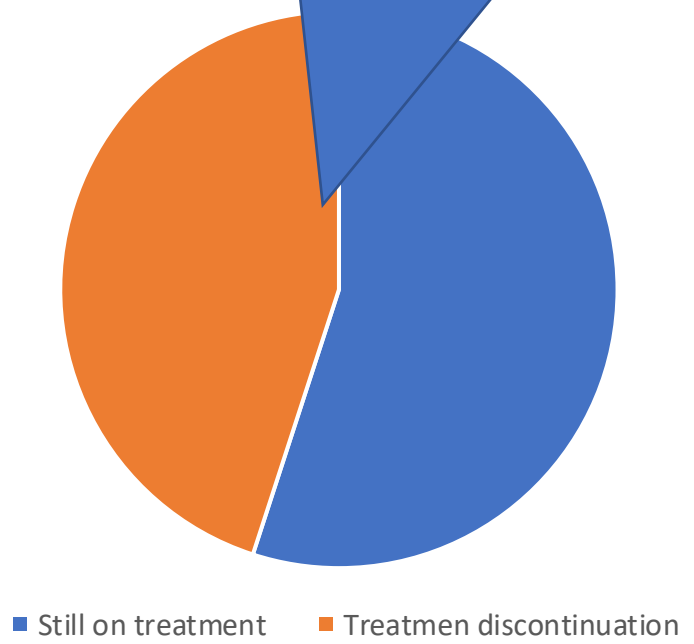
Can we predict treatment failures reasons?

Lack of efficacy: 28%
Intolerance: 42%

ON trial

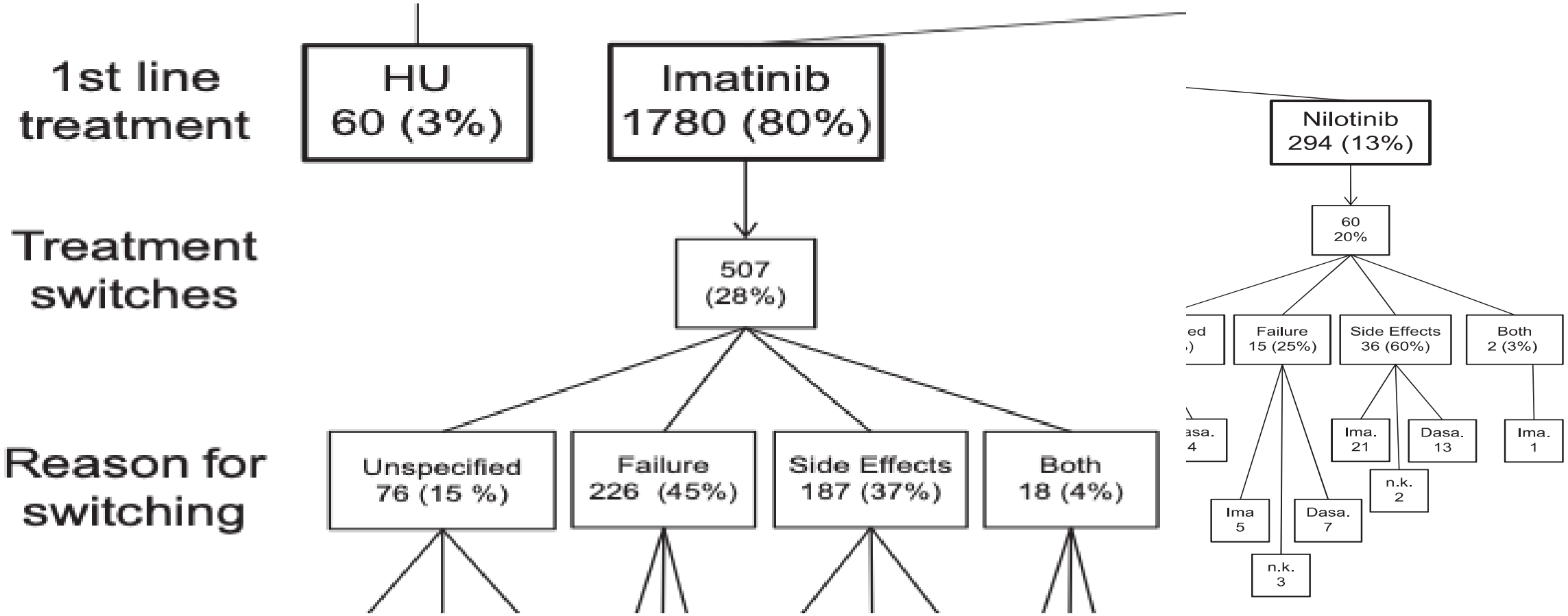


Lack of efficacy: 36%
Intolerance: 17%



Adapted from Cortes J, J Clin Oncol. 2016 Jul 10;34(20):2333-40

Can we predict treatment failures reasons?



Leukemia (2017) **31,** 593–601

How to classify TKIs failures: lack of efficacy

Time	Definition of TKI failure
3 months	*BCR-ABL1* (IS) > 10% if confirmed within 1–3 months
6 months	*BCR-ABL1* (IS) > 10%
12 months	*BCR-ABL1* (IS) > 1%
Any time	*BCR-ABL1* (IS) > 1%, resistance mutations, high-risk ACA

Hochhaus A. Leukemia (2020) 34:2125–2137

How to classify TKIs failures: intolerance

"In case of intolerance and treatment related complications, the decisión to change is in part subjective, depending upon the patient, physician, options for supportive care, and also upon the level of response"

Hochhaus A. Leukemia (2020) 34:2125–2137

How is intolerance defined in CML clinical trials?

Imatinib	Recurrence of nonhematologic toxicity of at least grade 3 despite appropriate dose reductions and optimal symptomatic management
Dasatinib	Occurrence of at least a grade 3 nonhematologic or grade 4 hematologic toxicity lasting >7 days during treatment with imatinib at any dose
Niotinib	Patients with symptoms of intolerance who had never achieved a major cytogenetic response. Any grade 2 nonhematologic toxicity lasting >1 month or recurring >3 despite supportive care and maximum dose reduction. Any grade 3 or higher nonhematologic toxicity. Any grade 4 hematologic toxicity lasting >7 days
Bosutinib	Inability to take the TKI because of drug-related grade 4 hematologic toxicity lasting more than 7 days, drug-related grade 3 or 4 nonhematologic toxicity, persistent grade 2 toxicity not responding to dose reduction and medical management, or loss of previously attained response on lower-dose TKI therapy with an inability to receive a higher dose because of drug-related toxicity at higher doses

Pinila-Ibarz et al. Cancer. 2011 Feb 15;117(4):688-97.

Kantarjian HM et al. Blood. 2014 Feb 27;123(9):1309-18

Can we really distinguish between intolerant and resistant patients?

- **Subgroup Analysis of Patients Potentially Intolerant of Prior TKI Therapy in Asciminib clinical trial**
- Patients enrolled ≤ 1% at baseline

	All Patients (N = 48)
Number of TKIs received, n (%)	
1	1 (2.1)[a]
2	19 (39.6)
> 2	28 (58.3)
Reason for TKI discontinuation, n (%)[b]	
Both resistance to and intolerance of TKIs	24 (50.0)
Only intolerance of TKIs	13 (27.1)
Only resistance to TKIs	11 (22.9)

T Hugues. EHA20, 06/12/20; 294990; S170

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Treatment options in CML pts previously treated with imatinib first line

	Dasatinib		Nilotinib		Bosutinib	
Variable	Resistance	Intolerants	Resistance	Intolerants	Resistance	Intolerants
Follow up	>24m		>24m		24m	
CHR	89%	100%	77%	NR	86%	85%
CCyR	44%	66%	41%	51%	41%	41%
PFE 24 months	80%		64%		79%	
OS 24 months	91%		87%		92%	

Shah et al. *Haematologica. 2010 Feb;95(2):232-40*
Kantarjian et al. Blood. 2011 Jan 27;117(4):1141-5
Cortes et al. Blood. 2011 Oct 27;118(17):4567-76

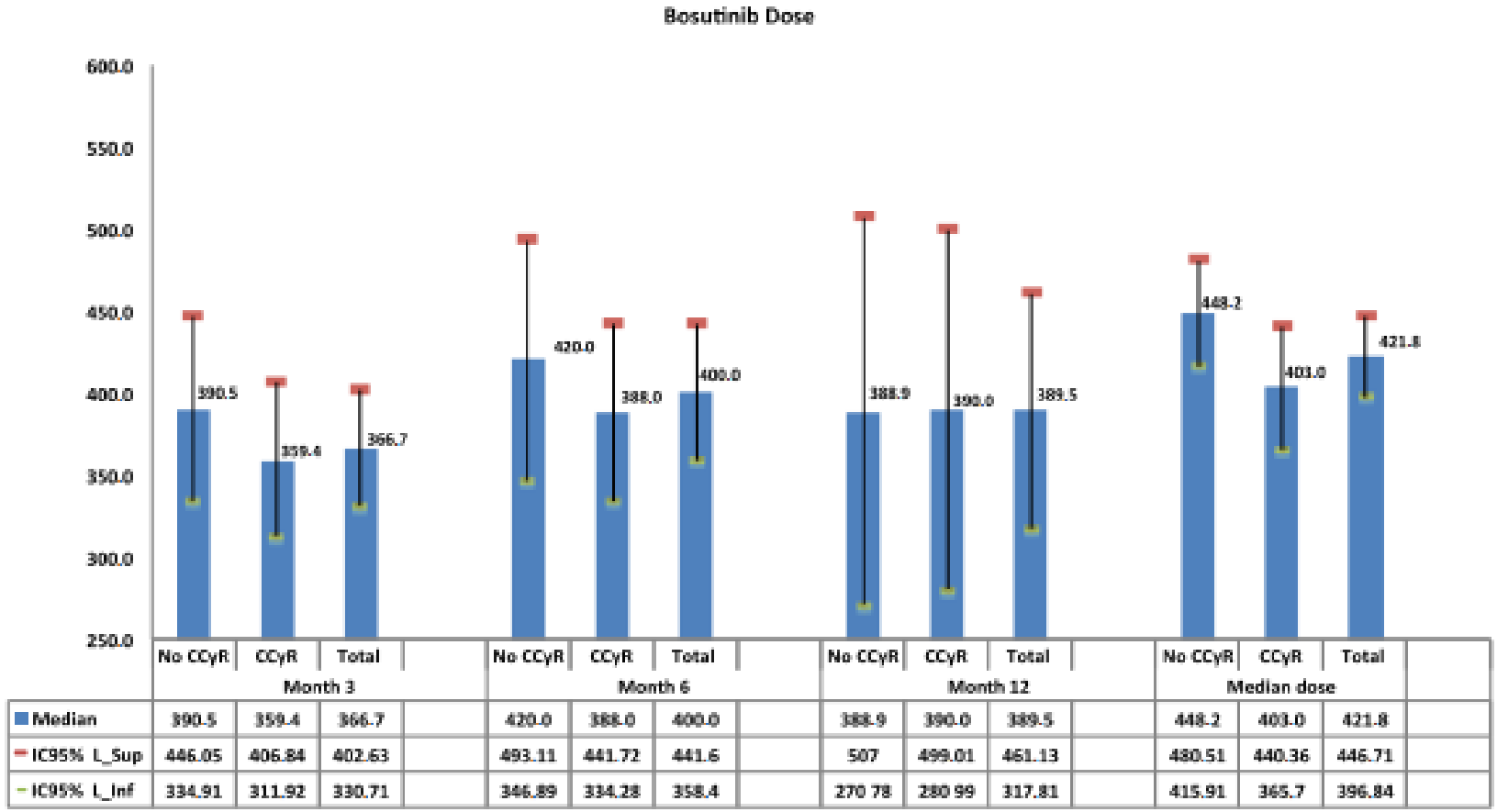
How do we choose the best second line option?

Comorbidity	Preferred	Less preferred
Diabetes	Imatinib, dasatinib, bosutinib	Nilotinib
Pulmonary disease/pulmonary arterial hypertension	Imatinib, bosutinib, nilotinib	Dasatinib
Gastrointestinal issues	Nilotinib, dasatinib	Imatinib, bosutinib
Cardiovascular	Imatinib, bosutinib	Nilotinib, dasatinib
Peripheral arterial	Imatinib, bosutinib (dasatinib?)	Nilotinib
Liver	Imatinib, dasatinib (nilotinib?)	Bosutinib
Renal	Nilotinib, dasatinib	Imatinib, bosutinib

Nilotinib	Dasatinib	Bosutinib	Ponatinib
T315I	T315I/A	T315I	Mutaciones compuestas*
Y253H	F317L/V/I/C	F317L	
E255K/V	V299L	V299L	
F359C/V			

Cortes J. ASH 2020. Educational Program

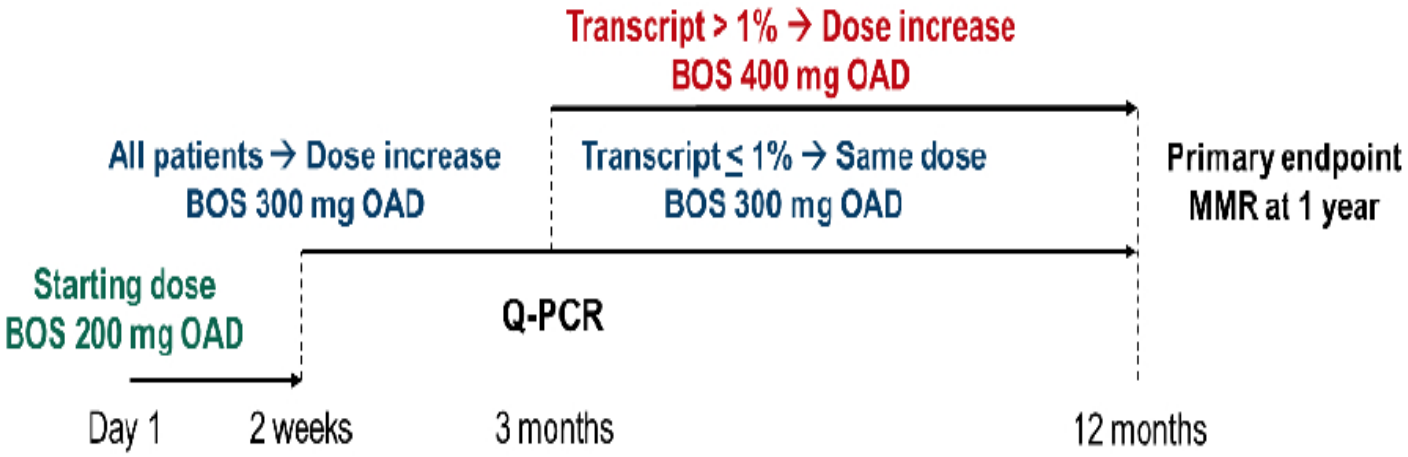
Should bosutinib doses be modified according to reason of treatment failure?



	No CCyR	CCyR	Total	No CCyR	CCyR	Total	No CCyR	CCyR	Total	No CCyR	CCyR	Total
	Month 3			Month 6			Month 12			Median dose		
Median	390.5	359.4	366.7	420.0	388.0	400.0	388.9	390.0	389.5	448.2	403.0	421.8
IC95% L_Sup	446.05	406.84	402.63	493.11	441.72	441.6	507	499.01	461.13	480.51	440.36	446.71
IC95% L_Inf	334.91	311.92	330.71	346.89	334.28	358.4	270 78	280 99	317.81	415.91	365.7	396.84

García-Gutiérrez V. Am J Hematol. 2015 May;90(5):429-33
García-Gutiérrez V, et al. Ann Hematol. 2019;98:321-30.

BEST study (Bosutinib 2L pacientes mayores)



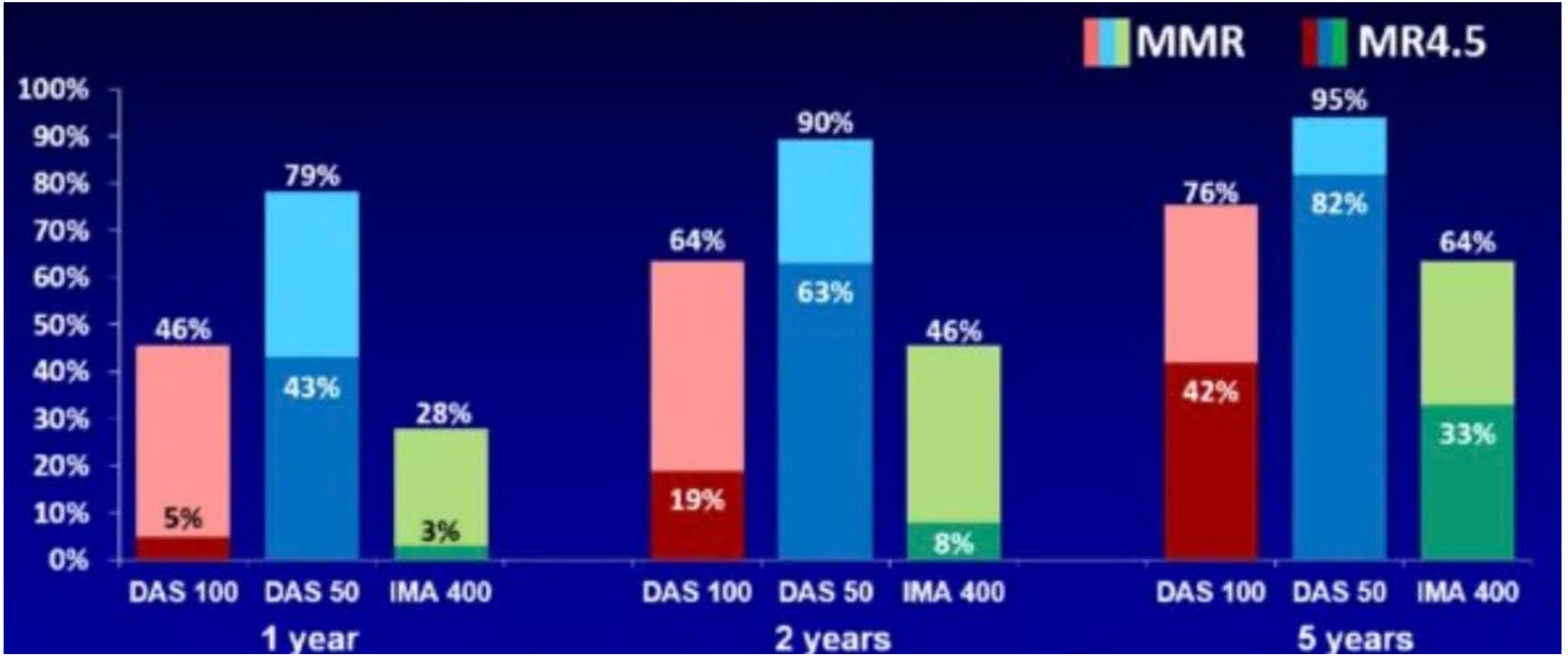
Bosutinib dose escalation (N = 63)

	200 mg	300 mg	400 mg
Maximum dose, n (%)	3 (5%)	48 (76%)	12 (19%)

Median age (range), years	73 (60-90)
Age distribution	
• 60-69 years	29%
• 70-79 years	49%
• ≥ 80 years	22%
Sokal score	
• Low	19%
• Intermediate	49%
• High	32%
First-line treatment	
Imatinib - Nilotinib - Dasatinib	83% - 6% - 11%
Resistant / Inotolerant	37% - 63%
Median follow-up (range), months	13 (9-37)

F Castagnetti. EHA200; 6/12/20; 294658; EP740

Gener G. OC. ASH 2023.Abst 619 **Long-Term Follow Up results of low dose (50mg) Dasatinib as front line treatment in CML patients**



Failure of 2G TKIs is a common situation

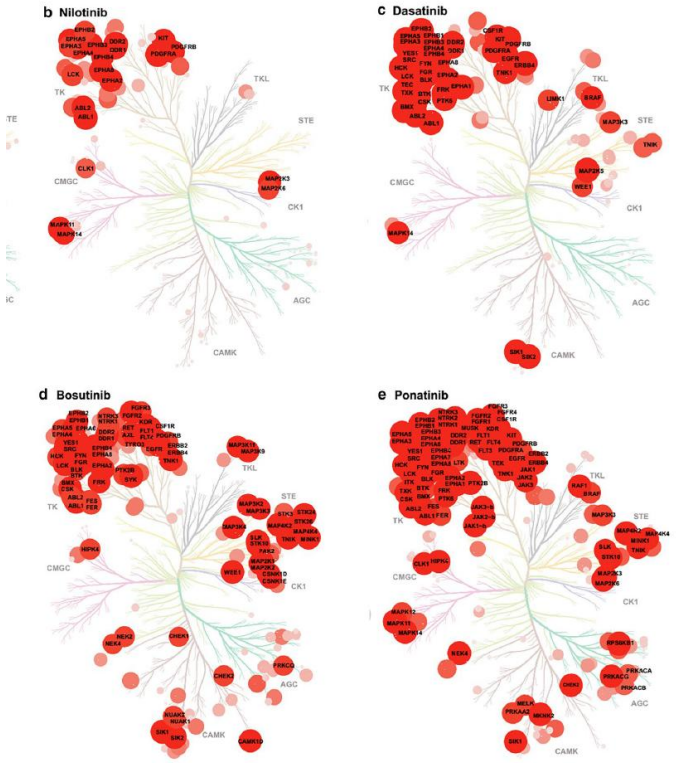
	Nilotinib 400 mg BID (4 years)	Dasatinib 100 mg QD (7 years)	Bosutinib 500 mg QD (5 years)
Total discontinuation	70%	78%	60%
Lack of efficacy	30%	21%	24%
Adverse events	28%	30%	23%

How should we treat these patients?

2G, second-generation; BID, twice a day; TKI, tyrosine kinase inhibitor; QD, once daily.
Masarova L, et al. *Cancer*. 2020;126:1448–59; García-Gutiérrez, personal opinion; Shah NP, et al. *Am J Hematol*. 2016;91(suppl):869–74; Gambacorti-Passerini C, et al. *Haematologica*. 2018;103:1298–1307.

Why do patients fail current TKIs?

Intolerance



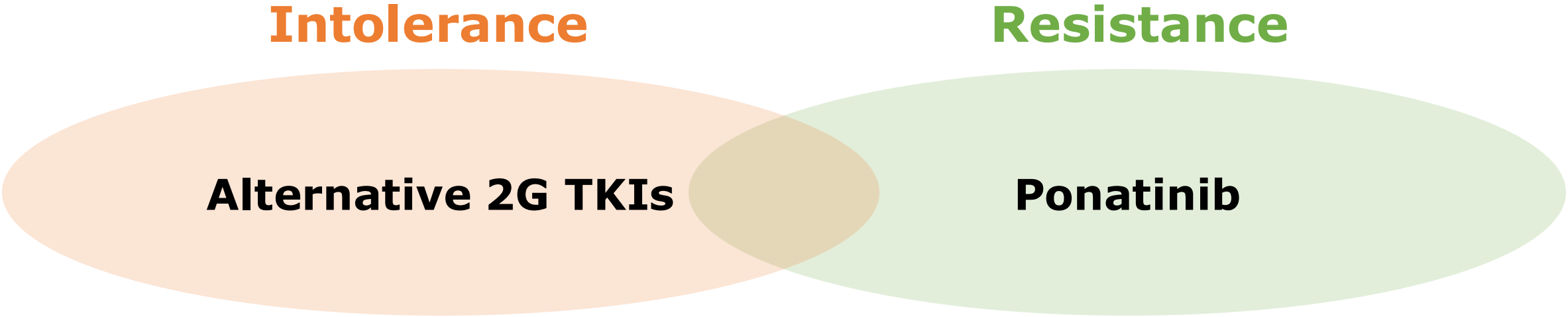
Resistance

- Pharmacokinetic differences in drug absorption, bioavailability and time of target inhibition may play a role in disease response
- Evidence suggests that high potency BCR::ABL1 TKIs with increased half-life may drive improved disease responses
- However, there is no clear relationship between plasma half-life and disease response

ABL1, Abelson tyrosine kinase 1; BCR, breakpoint cluster region; TKI, tyrosine kinase inhibitor.

Lee H, et al. *Int J Hematol*. 2021;113:632–41; Braun T, et al. *Cancer Cell*. 2020;37:530–42.

Treatment options after 2G TKI failure



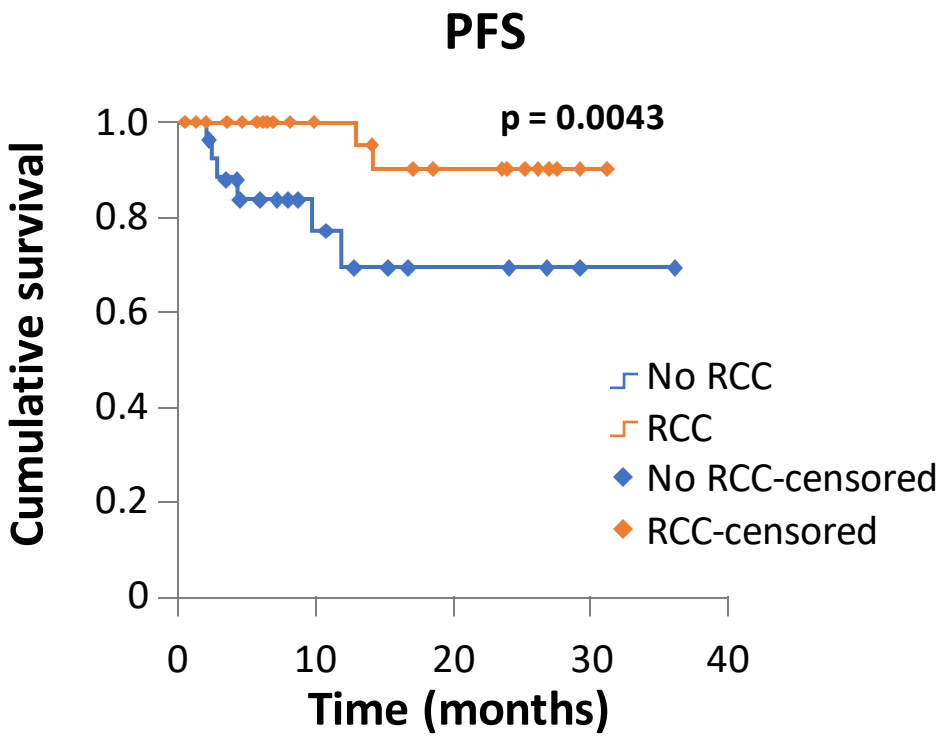
2G, second-generation; TKI, tyrosine kinase inhibitor.

Senapti J, et al. *Blood Cancer J*. 2023;13:58.

Does response to 2nd-generation TKIs differ due to reason for failure?

The GELMC experience in 61 CML patients treated with bosutinib in the 4th line

			CCyR	No CCyR
Best response to bosutinib, n/N (%)	All patients	CCyR[a]	31/33 (94)	7/28 (25)
		MR3[a]	21/33 (64)	4/28 (14)
		MR4.5[a]	9/33 (27)	1/28 (4)
	Patients without a response at baseline	CCyR[b]	NA	7/28 (25)
		MR3[b]	8/19 (42)	4/28 (14)
		MR4.5[b]	6/29 (21)	0



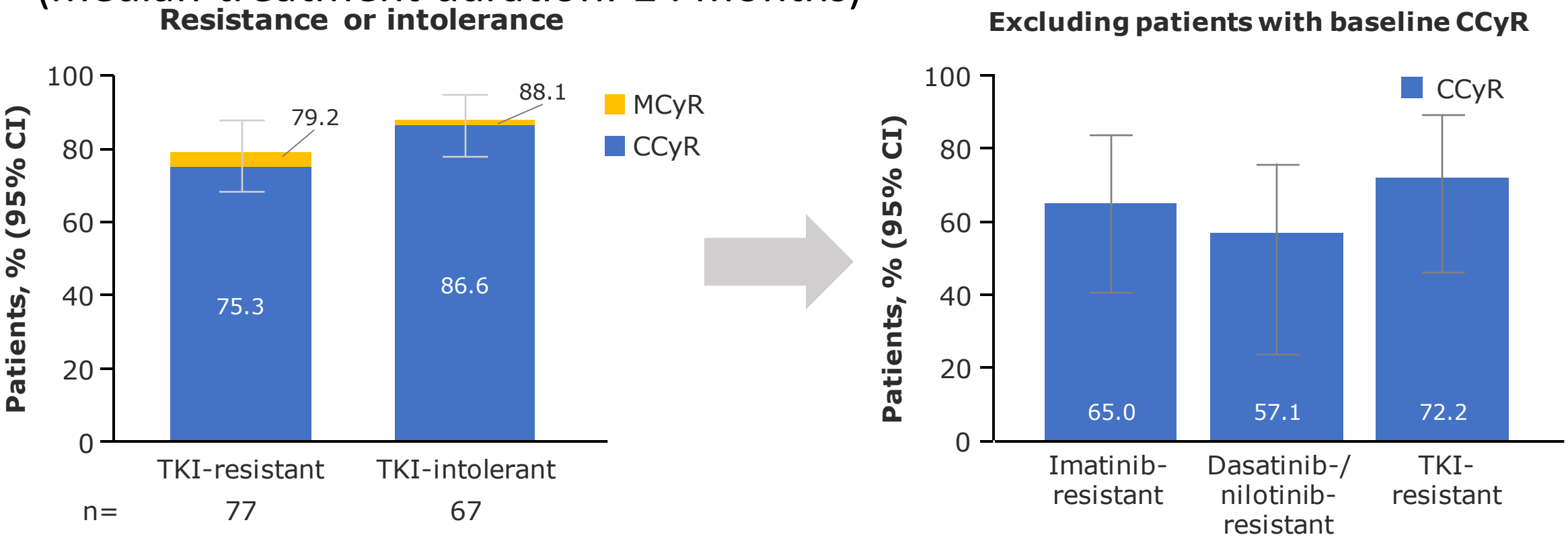
[a] Patients with CHR, CCyR, MR3, or MR4.5 at baseline were evaluable for haematologic, cytogenetic, or molecular response and were considered responders if they maintained their response.
[b] Evaluable patients without a CCyR, MR3, or MR4.5 at baseline.

GELMC, Spanish CML Group; MR4.5, molecular response 4.5 (*BCR-ABL1*^{IS} ≤ 0.0032%); RCC, renal cell carcinoma.

García-Gutiérrez V. Am J Hematol. 2015 May;90(5):429-33
García-Gutíerrez V, et al. Ann Hematol. 2019;98:321-30.

Bosutinib in patients previously treated with 2G TKIs

- BYOND study: 163 pre-treated patients with CML received bosutinib (median treatment duration: 24 months)



2G, second-generation; CI, confidence interval; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; MCyR, major cytogenetic response; TKI, tyrosine kinase inhibitor.

Hochhaus A, et al. *Leukemia*. 2020;34:2125–37; Smith DB, et al. *Blood*. 2019;134(Suppl 1):1650.

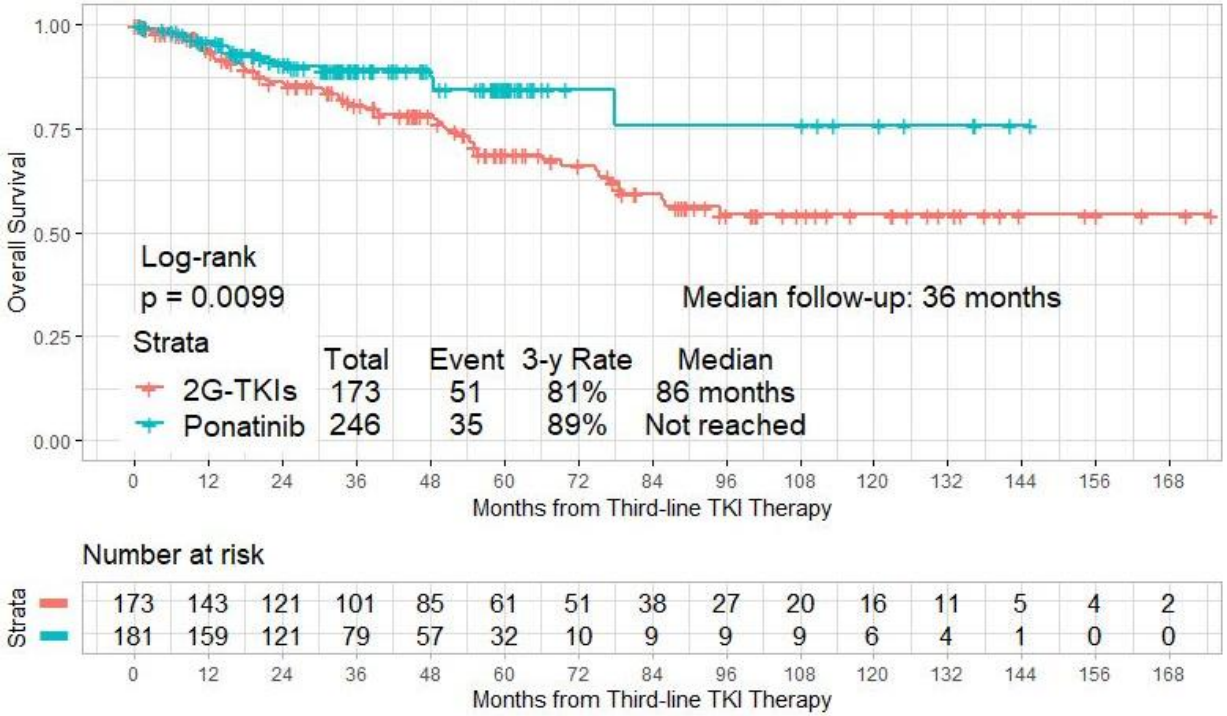
PACE and OPTIC trials: Ponatinib efficacy in patients who received prior 2G TKIs

Response	PACE CP-CML (n=270)	OPTIC 45 mg→15 mg (n=93)*
≤1% BCR::ABL1^{IS} by:		
12 months, %	49	52
24 months, %	52	56
60 months, %	54	NA
PFS at:		
2 years, %	67	80†
OS at:		
2 years, %	88	91†

*Assessed in the intention-treat-population (n=93); †assessed in the full 45-mg population (n=94).
2G, second-generation; CML, chronic myeloid leukaemia; CP, chronic-phase; IS, international scale; NA, not applicable; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

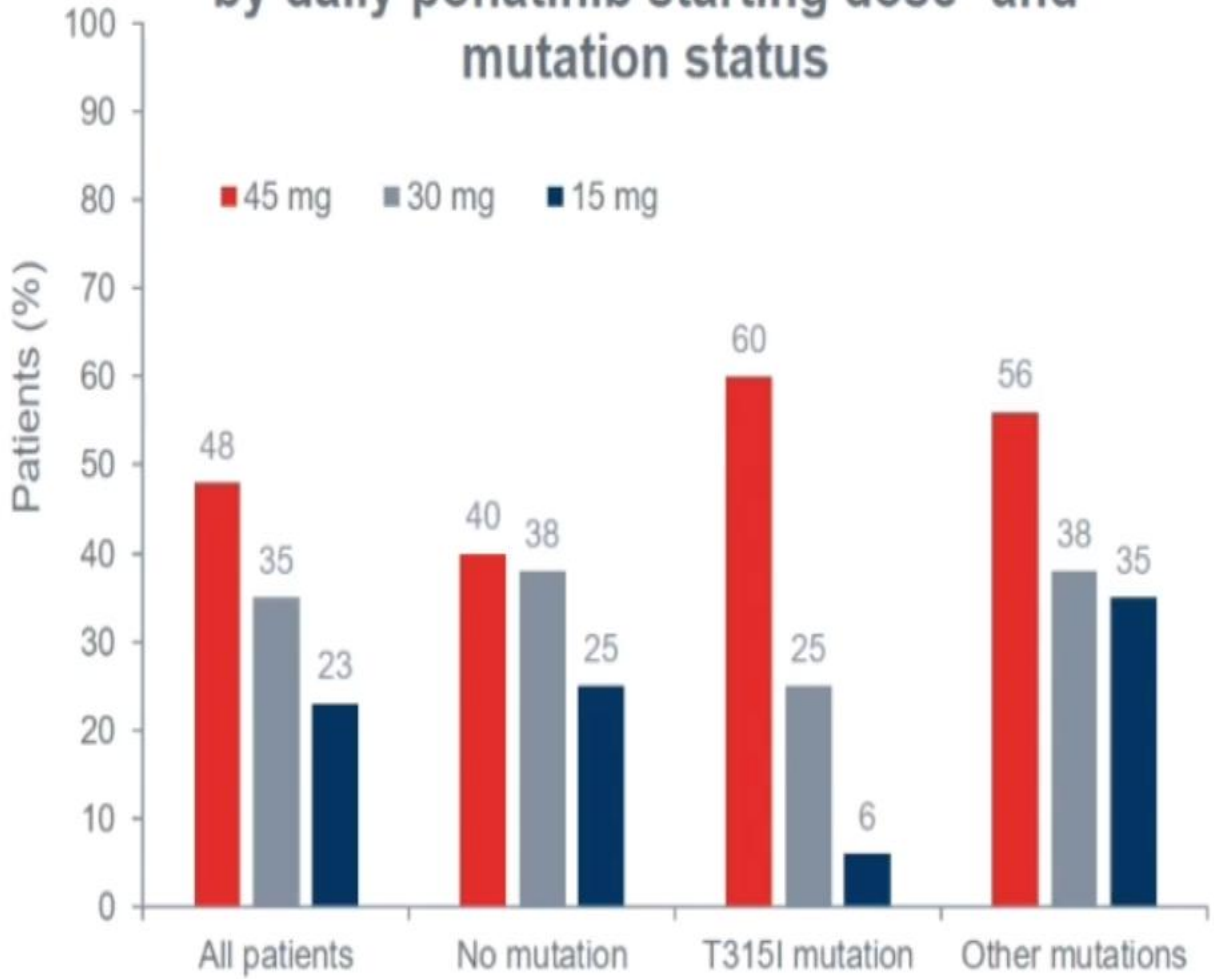
Jabbour E, et al. *Leukemia*. 2024;38:475–81.

Third-line TKI in CML. OS by Third-line TKI Before and After Propensity Score Matching



Jabbour E. Am J Hematol. 2023 Apr;98(4):658-665. doi: 10.1002/ajh.26852/ASH 2022

≤1% *BCR-ABL1*^{IS} rates at 12 months by daily ponatinib starting dose[a] and mutation status



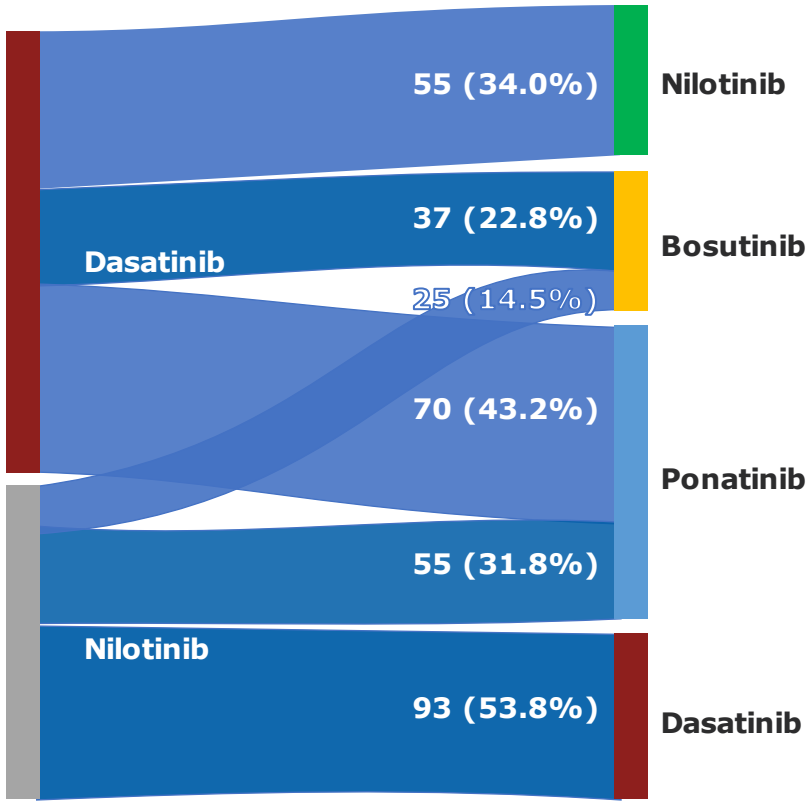
The greatest differences between treatment arms were found in patients with the T315I mutation

Cortes J. ASH 2020. CO 45

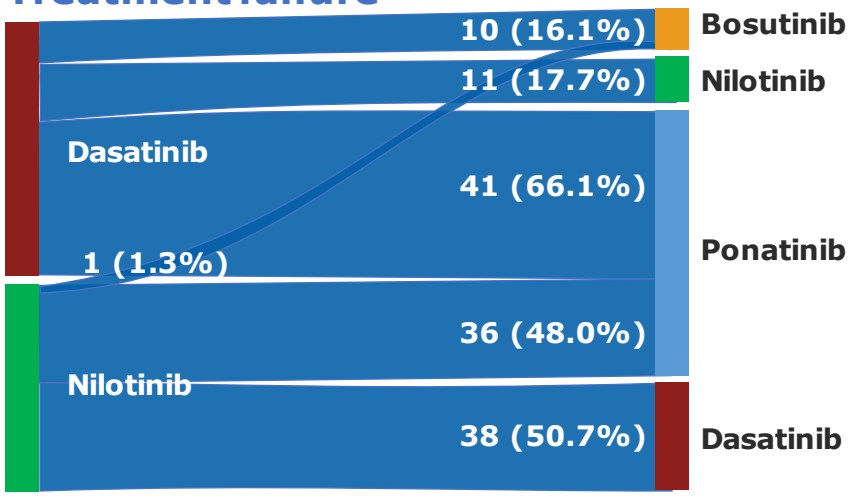
Treatment approach in 1L CML patients who fail on 2G TKIs: The Italian experience

- 2420 patients treated with 1L 2G TKIs
- 13% of patients required a treatment change (16.3% dasatinib/11.3% nilotinib)

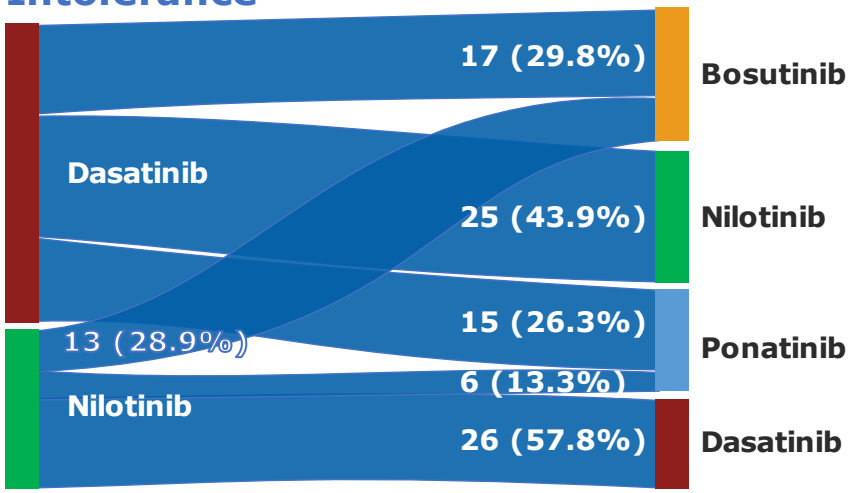
Treatment change for any reasons



Treatment failure



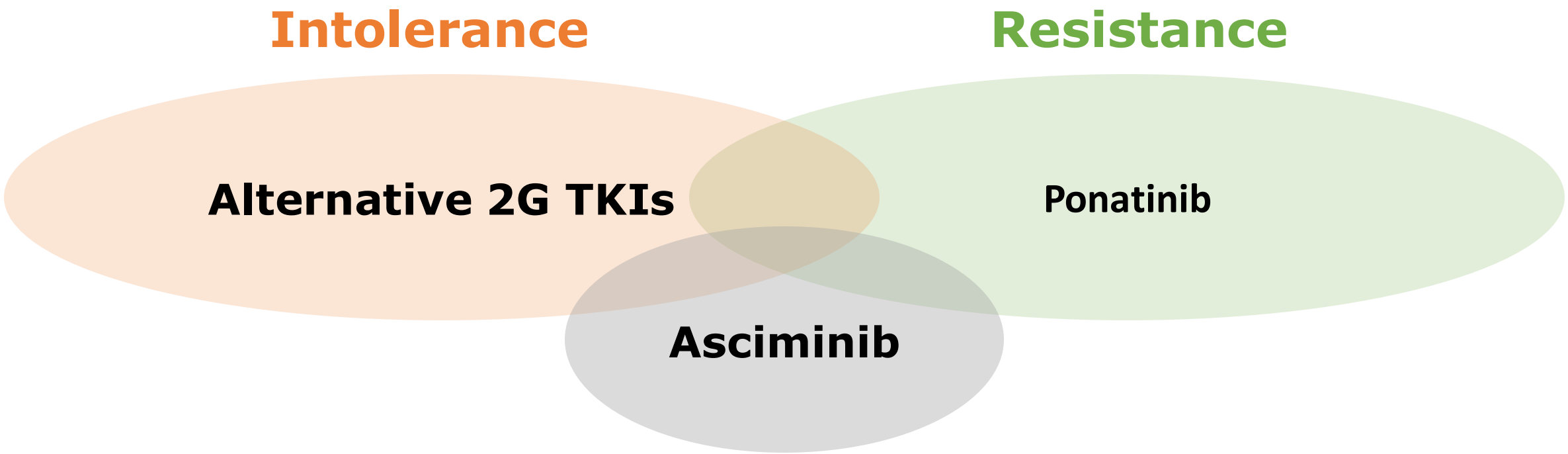
Intolerance



1L, first-line; 2G, second-generation; CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

Breccia M, et al. *Cancer Med*. 2020;9:4160–5.

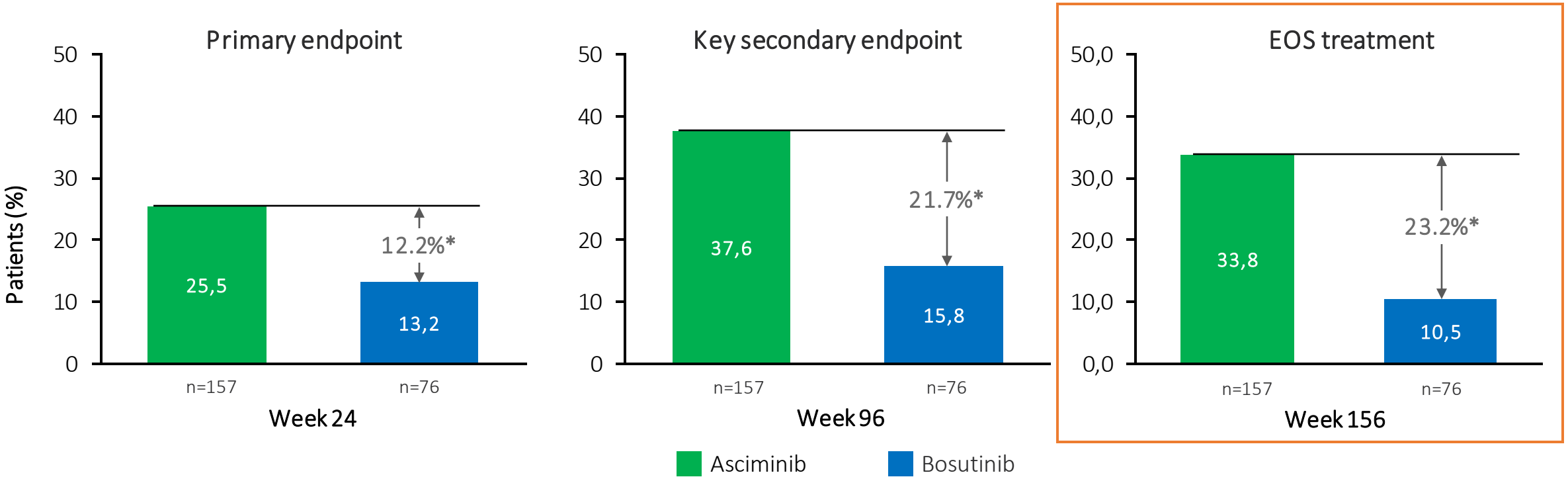
Treatment options after 2G TKI failure



2G, second-generation; TKI, tyrosine kinase inhibitor.

Senapti J, et al. *Blood Cancer J*. 2023;13:58.

ASCEMBL: MMR rates at weeks 24, 96 and 156

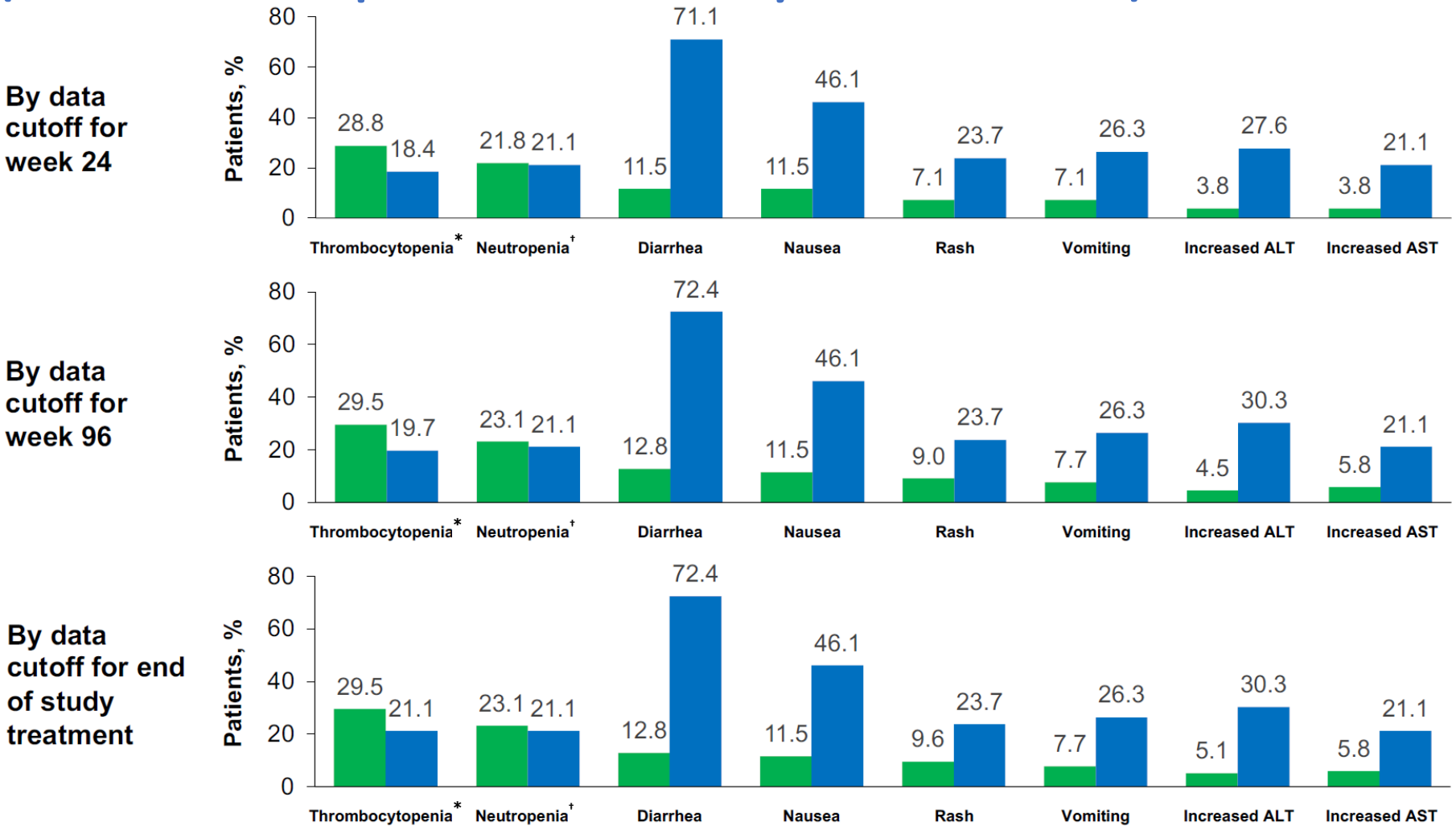


- The MMR rate (BCR::ABL1^{IS} ≤0.1%) at week 156 continued to be higher with asciminib compared with bosutinib, consistent with week 24 and 96 analyses

*The treatment difference after adjustment for the baseline MCyR status was 12.2% (95% CI, 2.19–22.3%; two-sided *P*=0.029) at week 24, 21.7% (95% CI, 10.53–32.95%; two-sided *P*=0.001) at week 96 and 23.2% (95% CI, 13.14–33.18%; two-sided *P*<0.001) at week 156.
CI, confidence interval; EOS, end of study; IS, international scale; MCyR, major cytogenetic response; MMR, major molecular response.

Mauro M, et al. Poster presentation at ASH 2023; Abstract 4536.

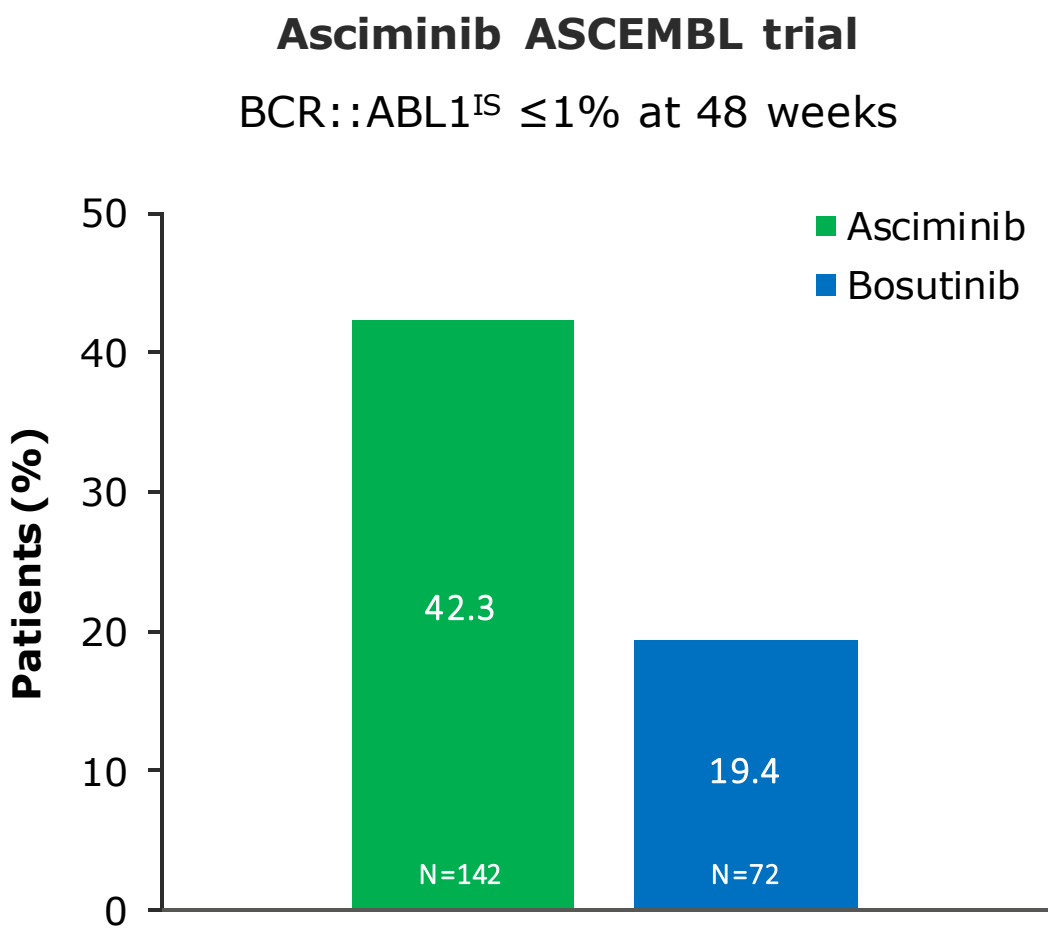
ASCEMBL: Most frequent all-grade AEs (in ≥20% of patients in any treatment)

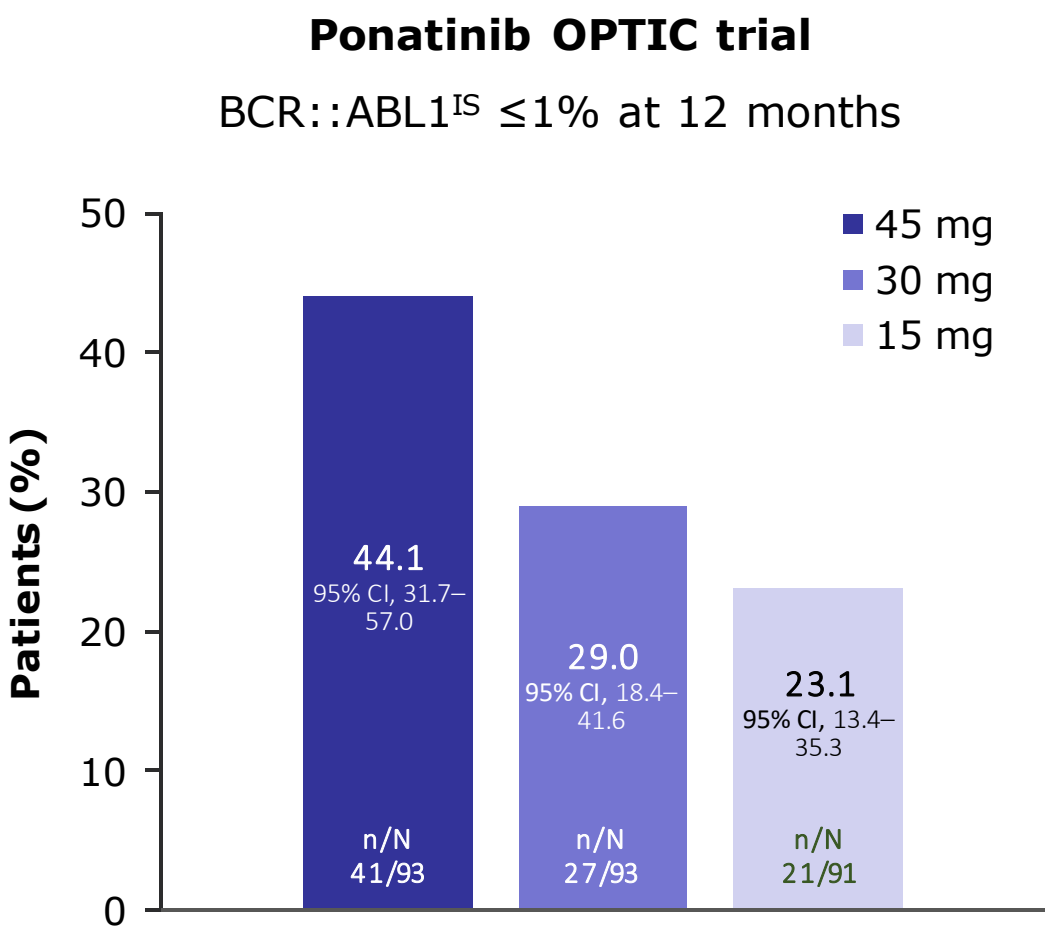


- Regardless of the longer duration of exposure, safety and tolerability of **asciminib** remained consistent with that at the time of the primary and week 96 analysis and continued to be better than with **bosutinib**, with longer follow-up by the end of study treatment cutoff

*Includes thrombocytopenia and platelet count decreased; †Includes neutropenia and neutrophil count decreased.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Mauro M, et al. Poster presentation at ASH 2023; Abstract 4536.

Ponatinib vs asciminib (indirect comparison)





ABL1, Abelson tyrosine kinase 1; BCR, breakpoint cluster region; CI, confidence interval; IS, international scale.

Mauro MJ, et al. Oral presentation at ASH 2021; Abstract 310; Cortes J, et al. *Blood*. 2021;138:2042–50. Figure (right) reprinted with permission from Elsevier © 2021 The American Society of Hematology and Elsevier.

What are current recommendations to manage failure of 2G TKIs

- **INTOLERANCE:** In case of intolerance to ≥2 TKIs, asciminib is considered to be the preferred treatment option:
  - Asciminib has shown superiority against bosutinib
  - Asciminib has not been compared against ponatinib in intolerants patients. However, ponatinib is not considered as an appropriate treatment option for intolerant patients (lack of data in trials, risk of cardiovascular events)

- **RESISTANCE:**
  - Ponatinib has been considered as the preferred treatment options in CML patients with resistance to previous TKIs (one 2G TKI or patients harbouring T315 mutation)
  - Since asciminib has not been compared against ponatinib, there are 'reasonable' doubts regarding what should be considered as the best treatment option in resistant patients

2G, second-generation; CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

Rea D, et al. *Blood*. 2021;138:2031–41; Hochhaus A, et al. *Leukemia*. 2020;34:1495–502; García-Gutiérrez, personal opinion.

During the presentation, we will discuss about:

- How frequent is the need of 2nd/3th line treatment?
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- How should we manage CML treatment failures?
- **Can we improve current results?**

Study design[1-3]

Primary objective: determine efficacy of asciminib in patients with CML-CP treated with 1 prior TKI
Primary endpoint: MMR at 12 months

Key study criteria

Both cohorts[a]

- Age ≥18 years
- CML-CP (no previous AP or BC)
- No T315I mutation

and

2nd treatment cohort

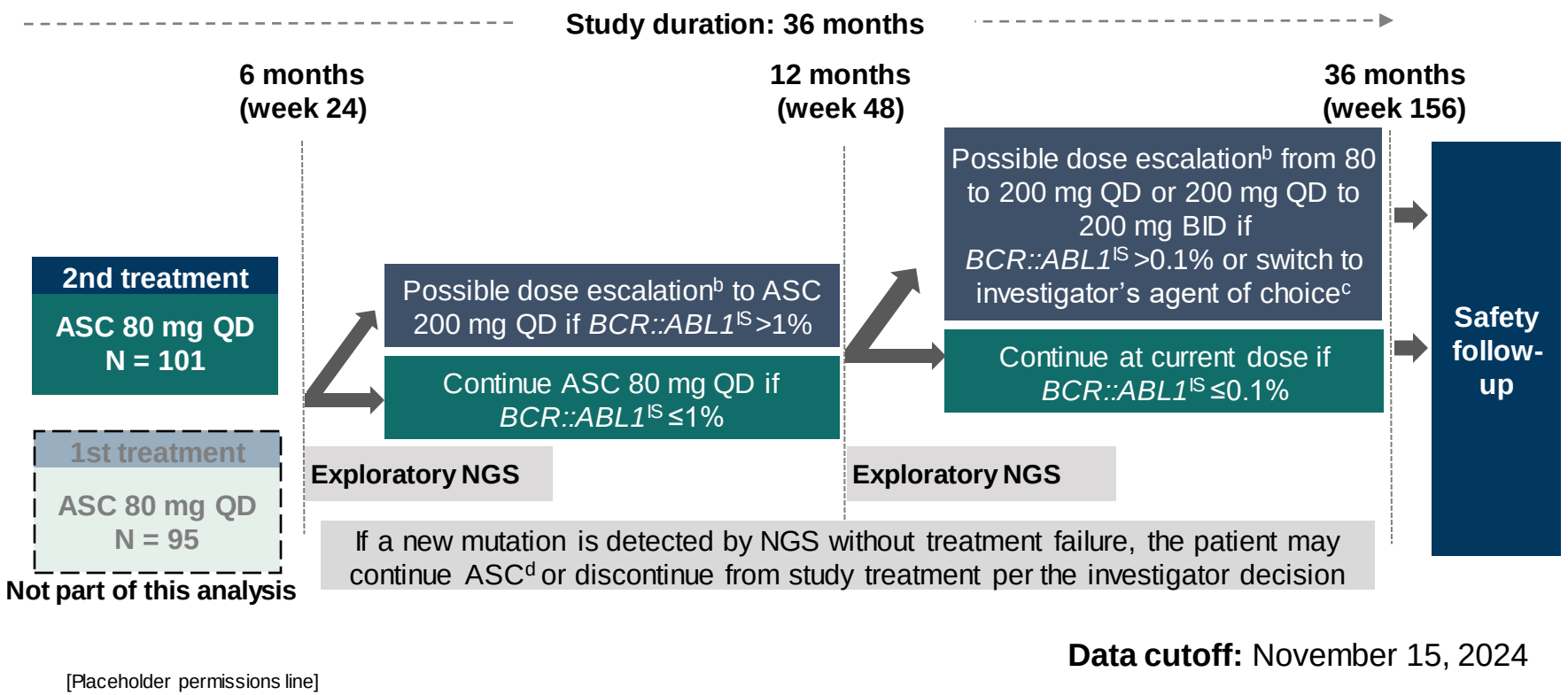
- Warning or failure (per ELN 2020) with 1st TKI at the time of screening

or

- Intolerance of 1st TKI and *BCR::ABL1*^{IS} >0.1% at screening

1st treatment cohort

- Patients with newly diagnosed with CMP-CP (treatment with a prior TKI for ≤4 weeks is allowed)



Data cutoff: November 15, 2024

[Placeholder permissions line]

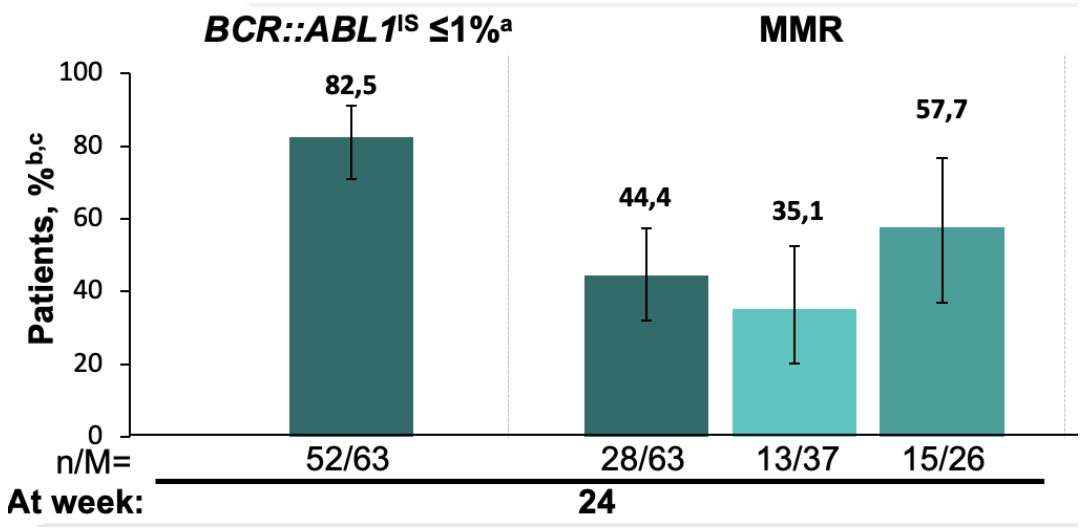
AP, accelerated phase; ASC, asciminib; BC, blast crisis; BID, twice daily; CML-CP, chronic myeloid leukemia in chronic phase; ELN, European LeukemiaNet; IA, interim analysis; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); NGS, next-generation sequencing; QD, once daily; TKI, tyrosine kinase inhibitor.
[a] For newly diagnosed CML-CP (1L cohort), treatment with 1 prior TKI (imatinib, dasatinib, nilotinib, or bosutinib) for ≤4 weeks was allowed. [b] For any grade 3 or 4 toxicity, or persistent grade 2 toxicity unresponsive to optimal management, the dose escalation did not apply, and patients were continued on the current ASC dosage. [c] Patients switching to investigator's agent of choice were taken off study. [d] At the same dose unless meeting dose-escalation criteria.

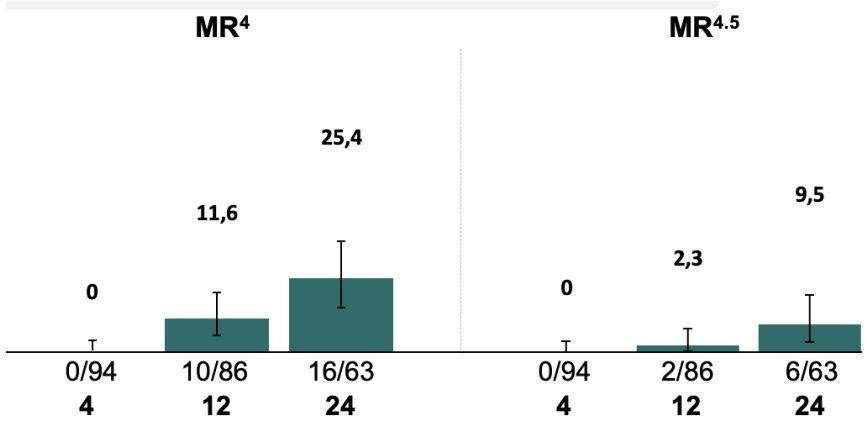
1. Sasaki K, et al. Presented at: 64th ASH Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA, and virtual. Abstract 3020. 2. Data on file. Clinical Trial Protocol CABL001AUS08 v01. Novartis Pharmaceutical Corporation; 2023. 3. Andorsky, D. Oral presentation at: 2025 ASCO Annual Meeting; May 30-June 3, 2025; Chicago, IL. Oral 6516.

Disposition

Patients, n (%)	All patients (N=101)
Treated	101 (100)
Treatment ongoing	92 (91.1)
Discontinued treatment	9 (8.9)
AEs	4 (4.0)[a]
Patient decision	3 (3.0)
Lost to follow-up	1 (1.0)
Physician decision	1 (1.0)

Efficacy





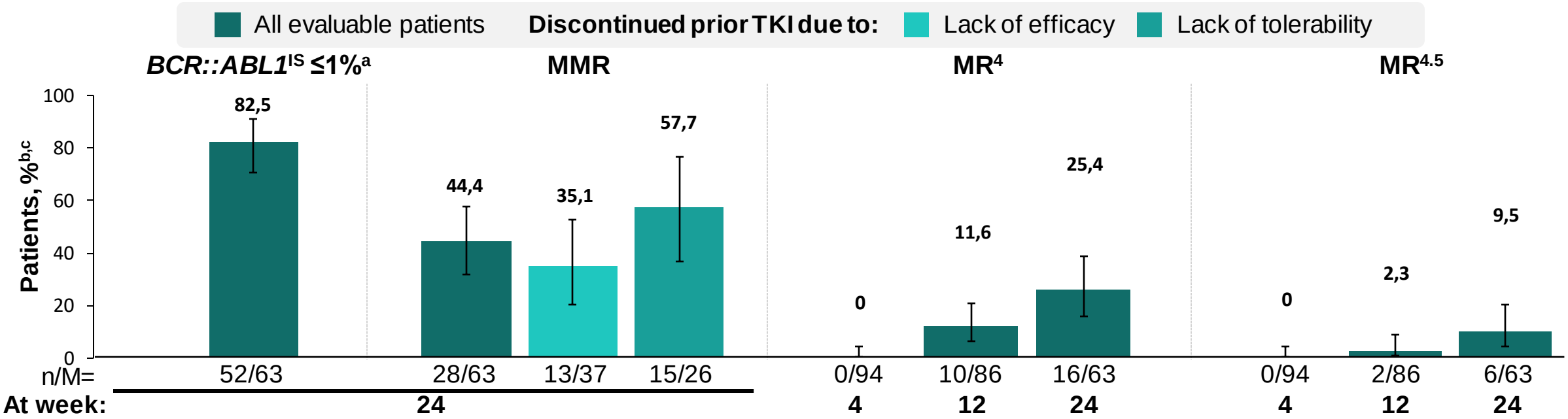
AE, adverse events; IA, interim analysis.

[a] One of these adverse events occurred off treatment, defined as >30 days after the last dose of asciminib. [b] Relative dose intensities included >90% to 110% in 80 (79.2%), >75% to 90% in 4 (4.0%), and ≤75% in 17 (16.8%) patients. [c] Per the study protocol, dose escalation was only considered in patients not achieving response milestones at 24 and 48 weeks.

Andorsky, D. Oral presentation at: 2025 ASCO Annual Meeting; May 30-June 3, 2025; Chicago, IL. Abstract 6516.

Molecular response rates in patients with adequate follow-up

BCR::ABL1^{IS} level at baseline, n (%)	All evaluable patients (n=63)	Discontinued prior TKI due to: Lack of efficacy (n=37)	Lack of tolerability (n=26)
>0.1% to ≤1%	22 (34.9)	15 (40.5)	7 (26.9)
>1% to ≤10%	21 (33.3)	15 (40.5)	6 (23.1)
>10%	20 (31.7)	7 (18.9)	13 (50.0)

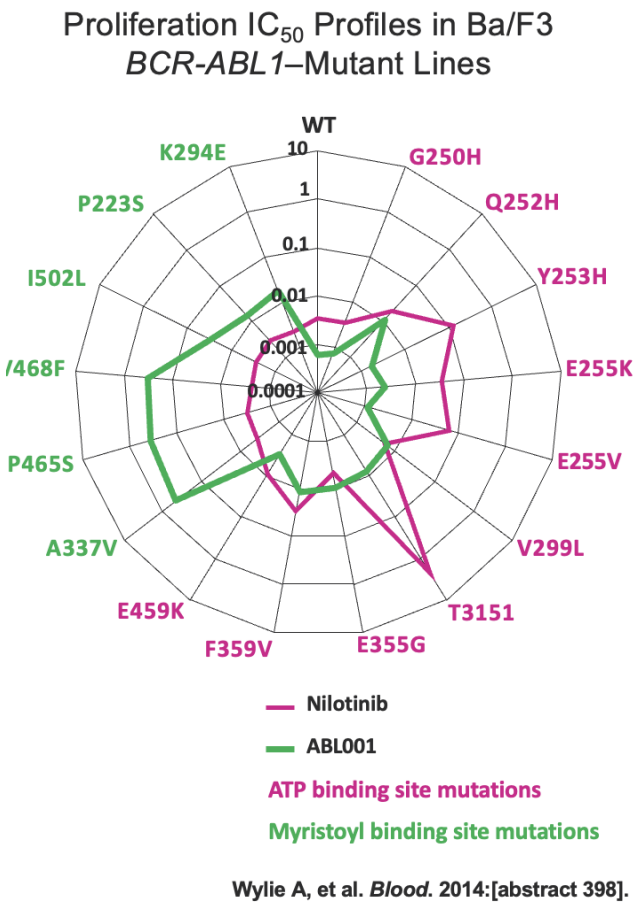


- Most patients had *BCR::ABL1*^{IS} ≤1%, which was the first dose escalation cutoff
- MMR rates at week 24 were higher in patients who discontinued their prior TKI due to lack of tolerability vs efficacy
- The rate of deep molecular responses increased over time

NOVARTIS

IA, interim analysis; MR^4, *BCR::ABL1*^{IS} ≤0.01%; MR$^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%.
[a] Included patients with this response at baseline. [b] Included patients with adequate follow-up (M), defined as those with assessments within the corresponding analysis time interval or who discontinued early. [c] Error bars represent 95% CIs calculated using the Clopper-Pearson 2-sided method.
Andorsky, D. Oral presentation at: 2025 ASCO Annual Meeting; May 30-June 3, 2025; Chicago, IL. Abstract 6516.

The importance of mutation detection in asciminib treated patients

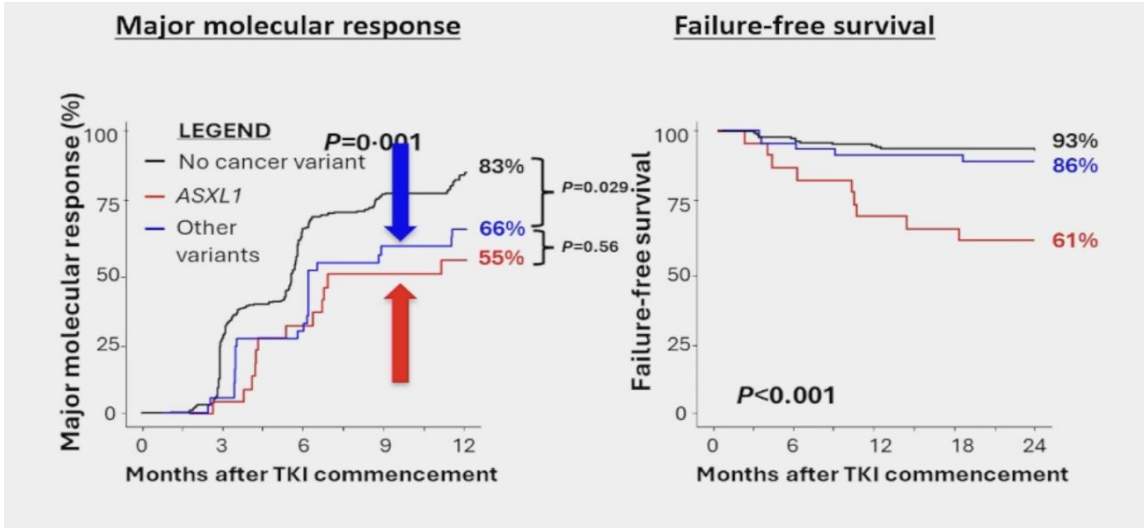


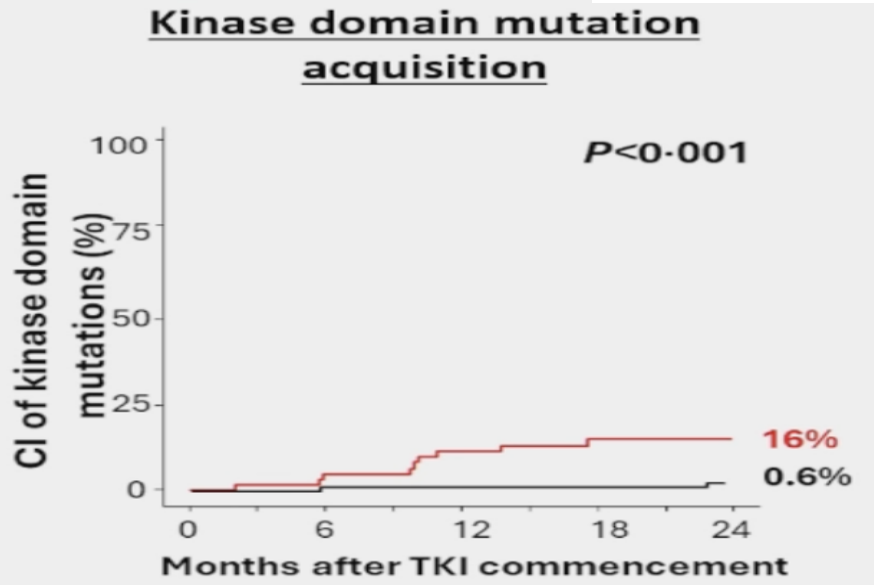
Wylie A, et al. *Blood*. 2014:[abstract 398].

Patients	Post-baseline mutations[a]	Discontinuation reason	Postprotocol therapy (2L+)	Last disease/survival status
Asciminib	**Myristoyl pocket**			
1	A433D	Treatment failure per ELN	Bosutinib, dasatinib	CP/alive
2	A337V, V506M[b]		Dasatinib	CP/alive
3	A337T, A344P,[b] P465Q,[b] I502N[b]		Dasatinib	AP/alive
4	A433D		Dasatinib, olverembatinib	AP/alive
5	A337T, V506M[b]		Ponatinib	Discontinued study
6	L340Q		Not available	Discontinued study
7[c]	A337T	Confirmed loss of MMR	Dasatinib	Discontinued study
8	A337T, L340Q	Unsatisfactory therapeutic effect (other)	Dasatinib	CP/alive
9	A337T,[b] F497L[b]	Progressive disease (BP)	Ponatinib	CP/death post HSCT
10[c]	A337V	Ongoing on study	Not applicable	
Imatinib	**ATP-binding domain**			
1	L248V, E255V,[b] G250E[b]	Treatment failure per ELN	Flumatinib, olverembatinib	BP/death post HSCT
2[c]	F317L[b]		Imatinib	CP/alive
3	L248V, E450G[b]		Nilotinib	CP/alive
4[c]	E459K	Confirmed loss of MMR	Dasatinib	CP/alive
Nilotinib	**ATP-binding domain**			
5[c]	Y253H	Treatment failure per ELN	Dasatinib	CP/alive
6	Y253H		Dasatinib, ponatinib	CP/alive
7	Y253H[b]	Ongoing on study	Not applicable	

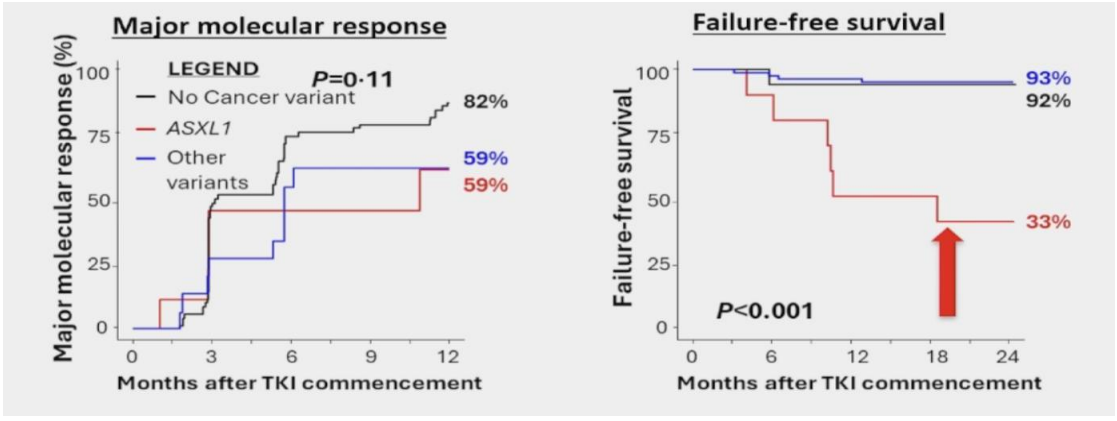
J Cortes. ASH 2024. Abstract 475

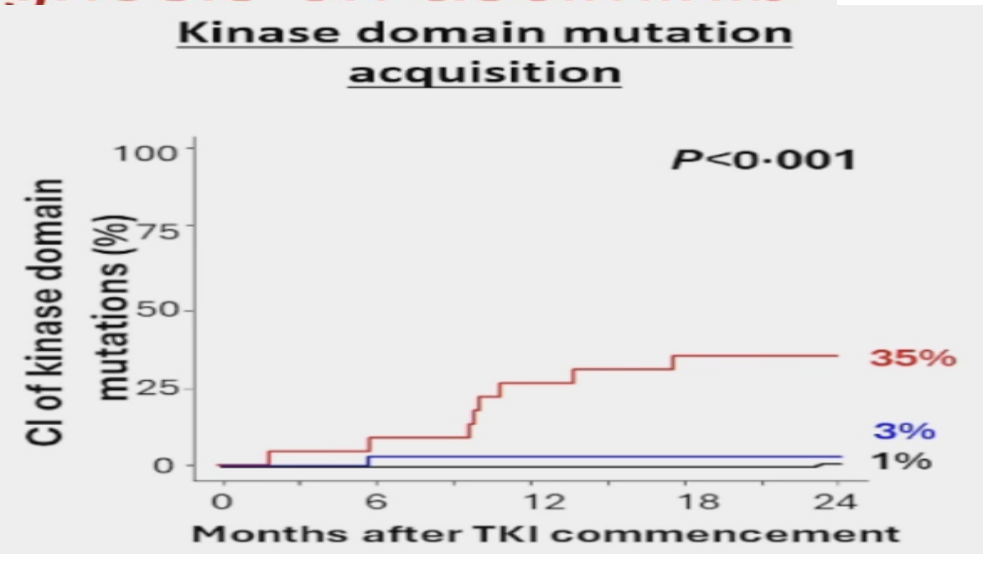
Impact of mutated *ASXL1* at diagnosis for patients treated with potent BCR::ABL1 inhibitors, n=315





Impact of mutated *ASXL1* at diagnosis on asciminib treated patients, n=99





Most Promising Drugs in Development for CML
(size and color by relevance and mechanism)

Olverembatinib (HQP1351) – ATP-site TKI

ELVN-001 – ATP-site TKI (selective, 3rd gen)

TERN-701 – STAMP allosteric inhibitor

Combinations (allosteric + ATP TKIs)

Ruxolitinib – JAK inhibitor (in combos)

Vodobatinib (K0706) – ATP-site TKI

BCR::ABL1 degraders (PROTACs)

Others in development

Conclusions

- Treatment failure in CML is relatively frequent and requires early detection to optimize outcomes.
- Choice of second-line therapy should be individualized: intolerance vs resistance, patient comorbidities, and mutational profile.
- Dose also plays a relevant role, since adaptation may improve tolerability or efficacy depending on the reason for failure.
- Asciminib is the preferred option in patients with intolerance; in resistant patients, ponatinib or asciminib should be considered, balancing prior response, mutational status, and cardiovascular risk.
- New agents and strategies (combinations, degraders) may further improve long-term disease control.

Thank you very much!!

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