Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

Avances en el tratamiento de la leucemia mieloide crónica

Valentín García Gutiérrez

Hospital Universitario Ramón y Cajal

Instituto Ramón y Cajal de Investigación Sanitaria

Universidad de Alcalá

Avances en el tratamiento en Leucemia Mieloide Crónica

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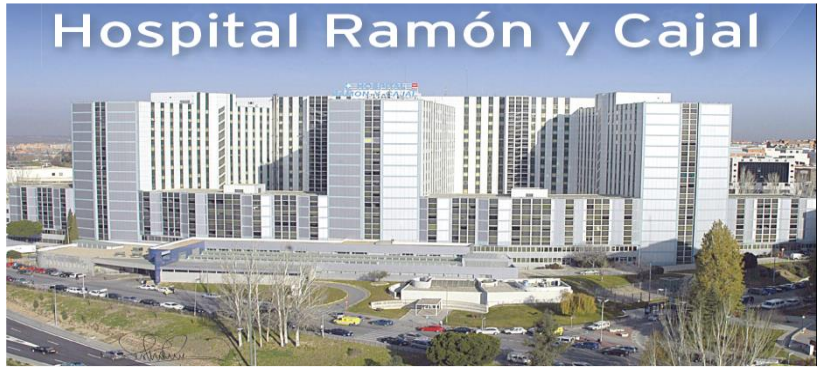


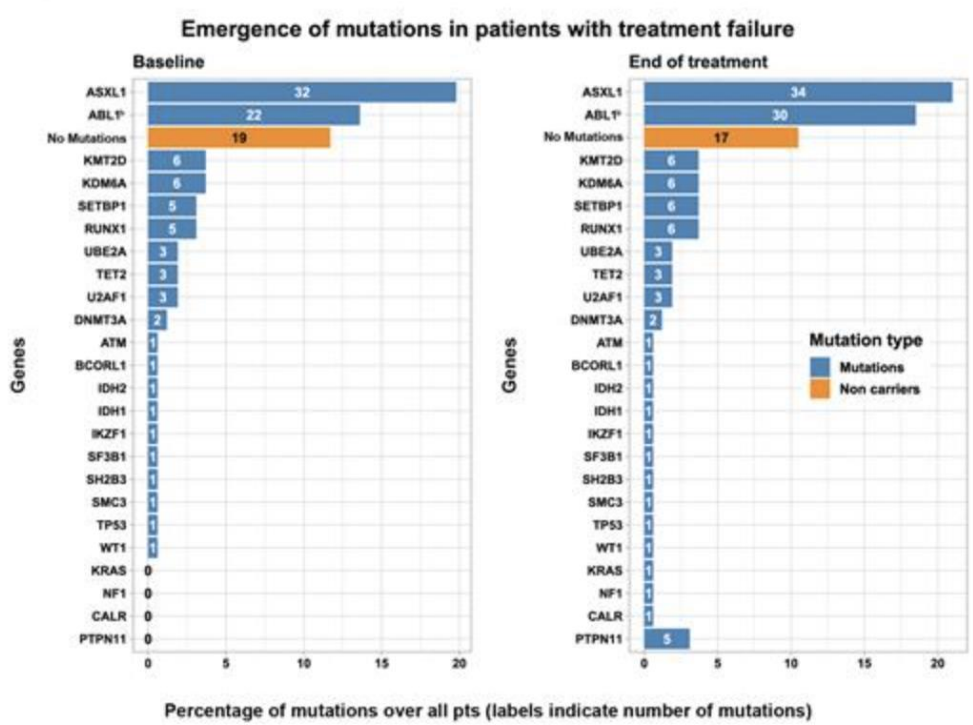
Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal

Durante la presentación hablaremos sobre:

- **Identificación de pacientes alto riesgo**
- Manejo de la primera línea y posibilidad de discontinuación del tratamiento
- Manejo del fracaso terapéutico
- Nuevas opciones terapéuticas

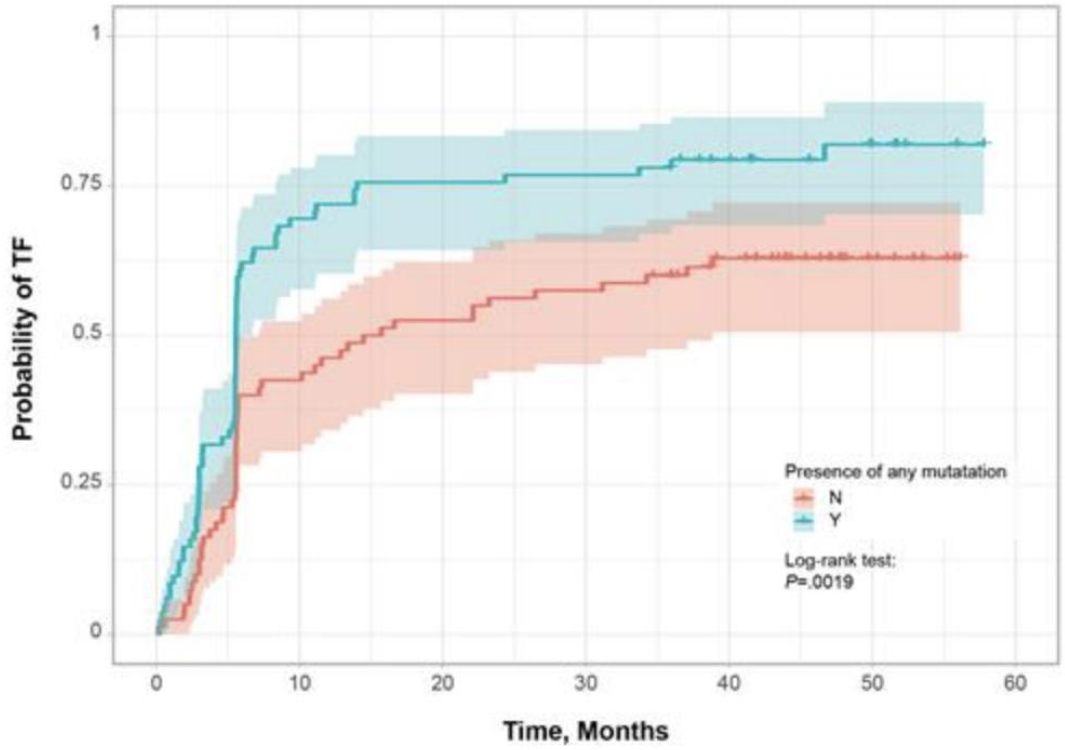
Prognostic implications of cancer-associated mutations in CML

Figure 2. Distribution of mutations at BL and EOT by gene in both treatment arms for pts with TF[a]



BL, baseline; EOT, end of treatment; pt, patient; TF, treatment failure.
[a]The total percentage can exceed 100% due to the presence of multiple mutations in an individual gene in individual pts (e.g., all 5 *PTPN11* mutations in the panel on the right belong to 2 pts). [b]*ABL1* mutations are *BCR::ABL1* mutations.

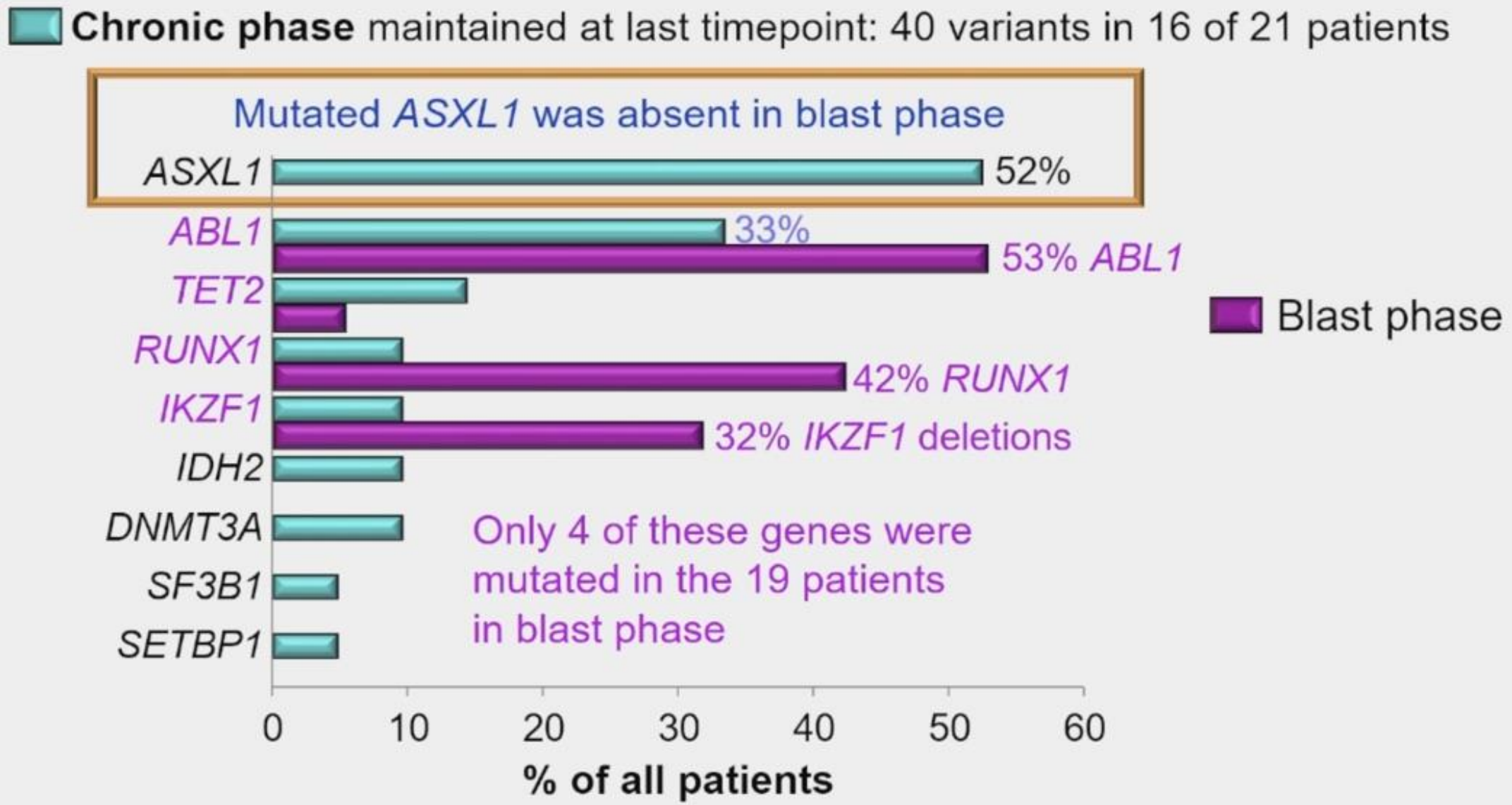
Figure 1. Probability of cumulated TF over time depending on the mutation status of pts at BL



BL, baseline; N, no; TF, treatment failure; Y, yes.

Branford S et al. ASH 2023

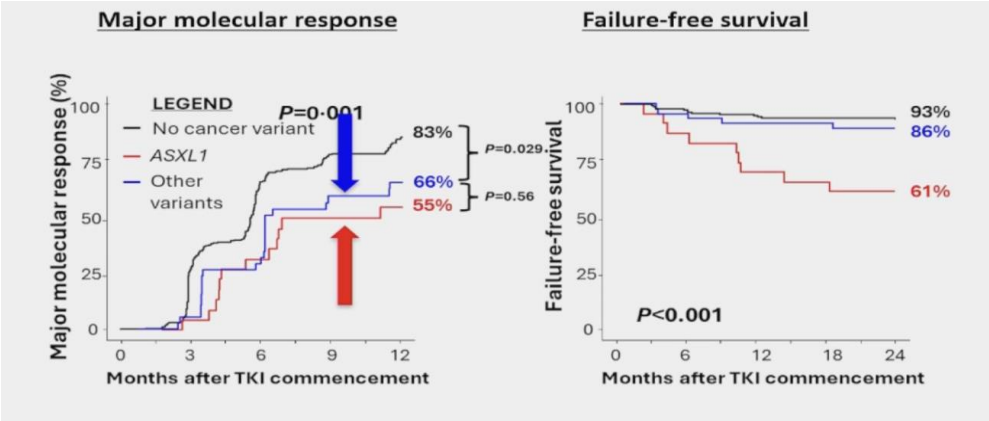
Difference in variant composition at last timepoint tested: chronic vs blast phase



Branford S et al. ASH 2023

Shanmuganathan N. Abstract 991: ***Strong association between cancer gene variants (ASXL1) and emergence of kinase domain mutation-driven resistant in CML patients despite frontline treatment***

Impacto ASXL1 y respuesta al tto



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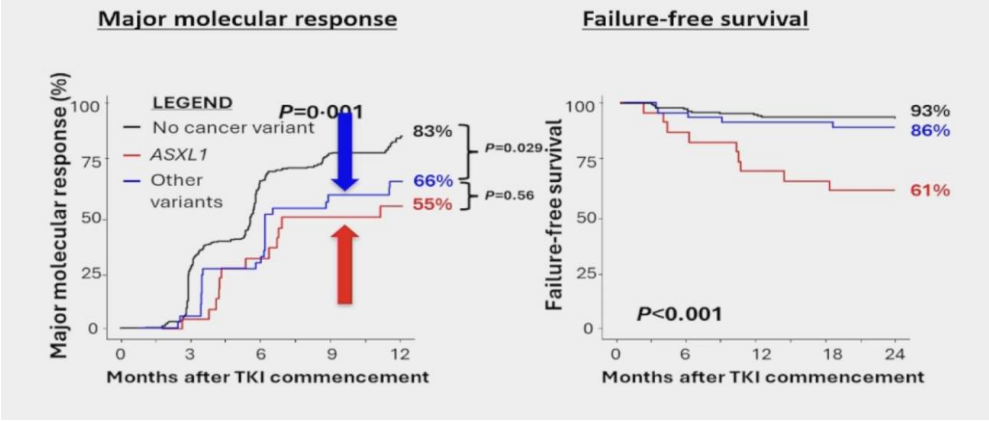
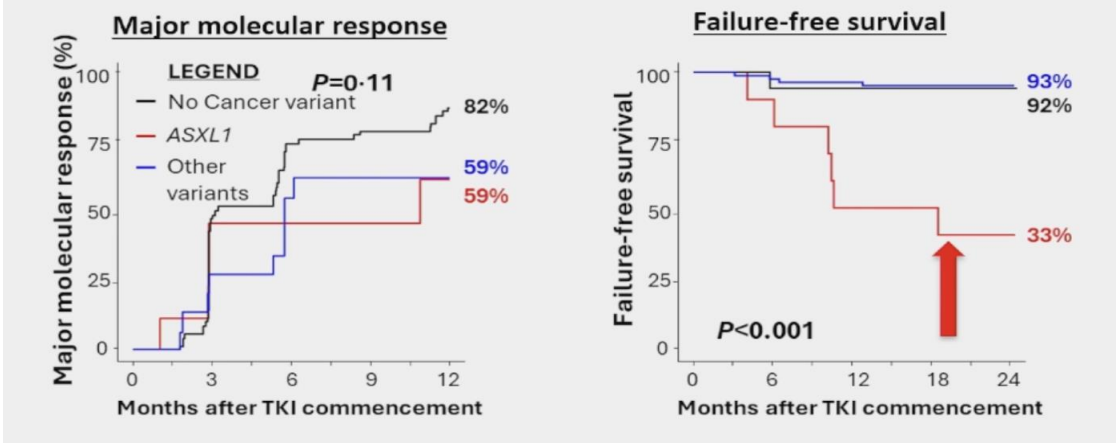


Impacto ASXL1 y respuesta al diagnóstico en pts tratados con ASCIMINIB



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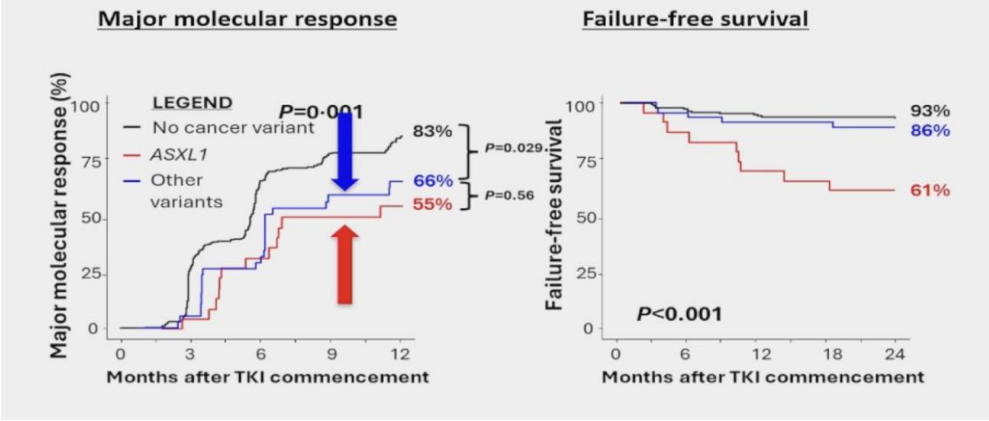
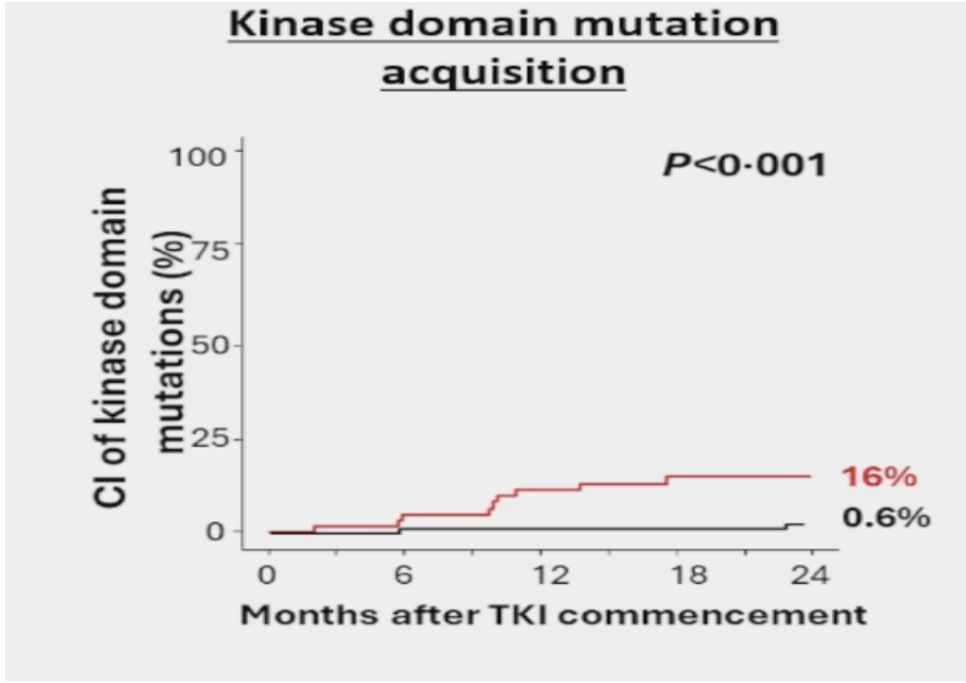


Correlación de *ASXL1* y aparición de mutaciones TKD



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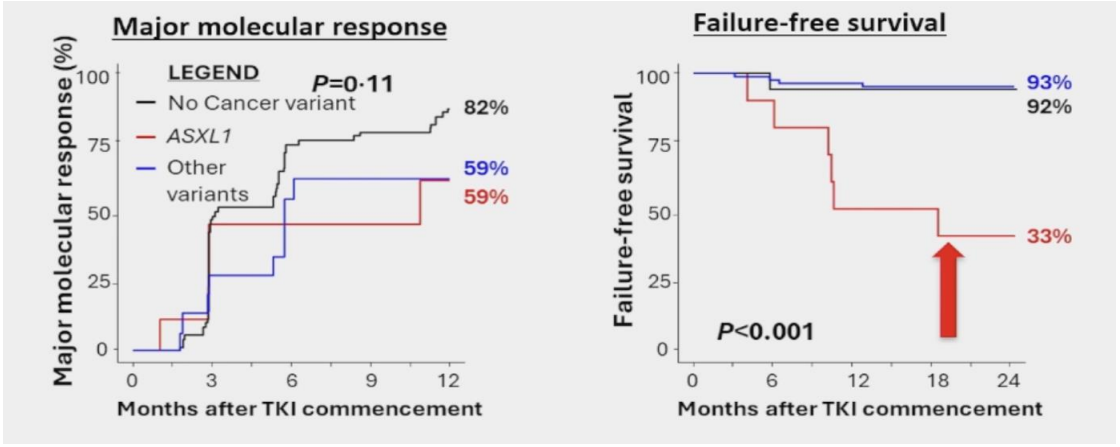

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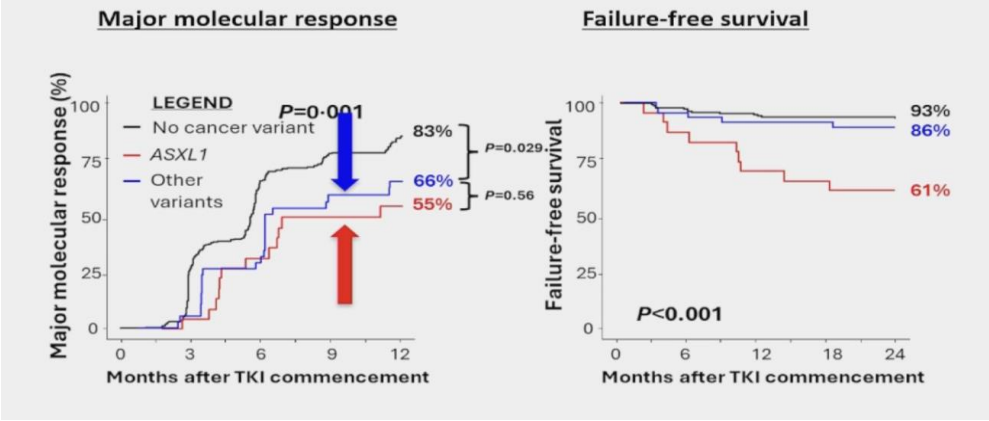

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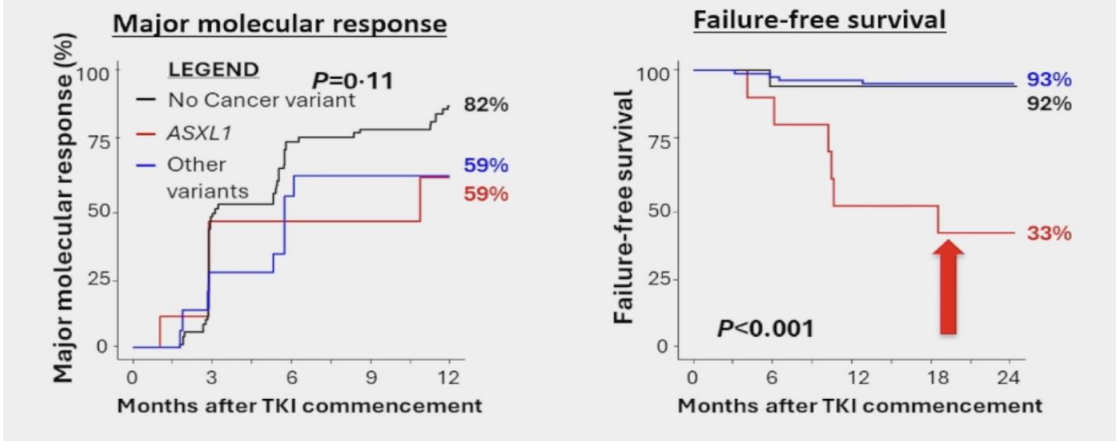

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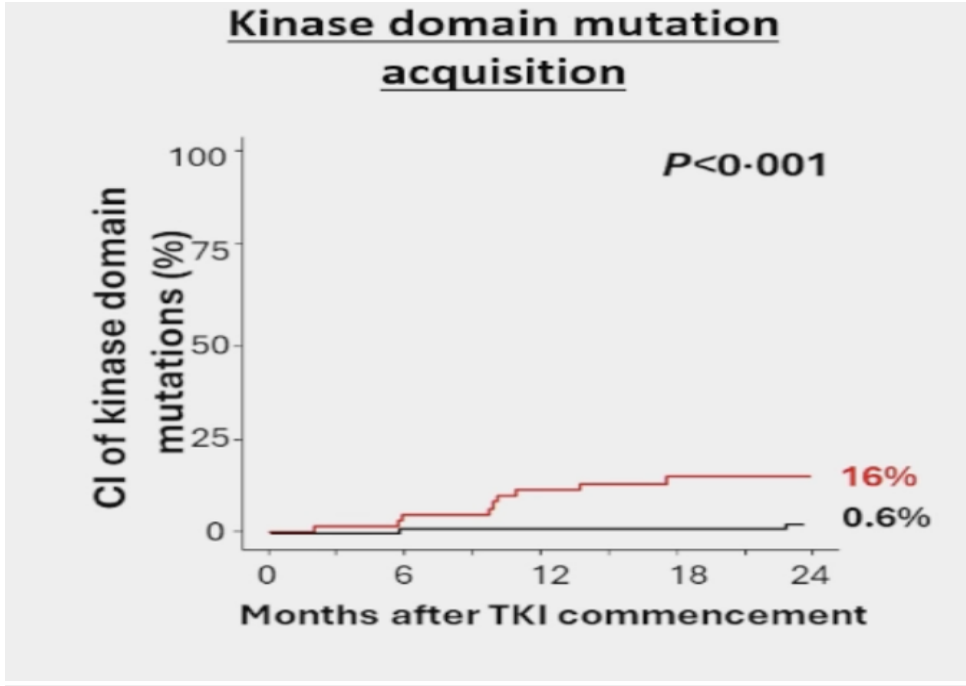

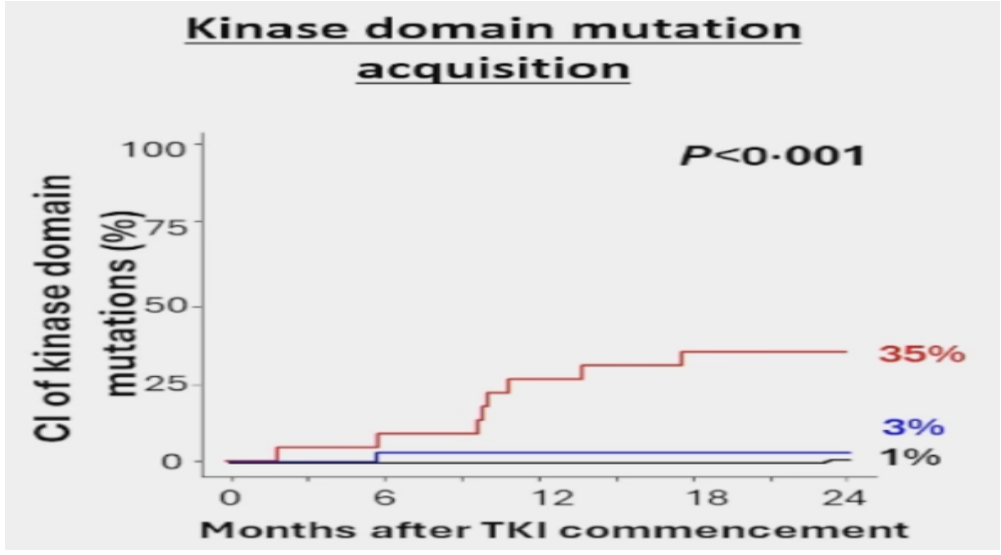

Recomendaciones del GELMC

Diagnóstico	Seguimiento	Fallo a tratamiento	Crisis Blástica
Obligatorio - Cariotipo. - RT-PCR con identificación de tipo de transcrito. *Complementario* - FISH. - RT-PCR cuantitativa.	*Obligatorio* - RT-PCR cuantitativa · Escala Internacional para e13a2 y e14a2 (p210). · IMR para transcritos atípicos. · Importante el número de copias del gen control. *Complementario* - FISH (si no hubiese RT-PCR disponible).	- Mutaciones en el dominio cinasa de *ABL1* · Solo si transcritos ≥0.1% y cumple "fallo" o "aviso" según los criterios de la ELN. · Se recomienda cambio del ITC si la variante es conocida y tiene una VAF ≥15%. · No considera las variantes detectadas si VAF <3% excepto *T315I*. - Cariotipo. - Panel mieloide/linfoide. · si no se identifican mutaciones en TKD.	- Mutaciones en el dominio cinasa de *ABL1*. - Cariotipo. - Panel mieloide/linfoide.

Figura 1. Estudios genéticos y moleculares en Leucemia Mieloide Crónica.
FISH: hibridación *in situ* fluorescente, RT-PCR: *quantitative polymerase chain reaction*, TKD: dominio tirosina cinasa, VAF: fracción de variantes alélicas.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Chronic Myeloid Leukemia
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

Test	Recommendation
Hematologic	• CBC every 1–2 weeks for the first 1–2 months (or until stable normalization of blood counts) and thereafter as indicated based on the persistence of cytopenias
Bone marrow cytogenetics[1]	• At diagnosis • Response milestones not reached • Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1%
qPCR using IS	• At diagnosis • Every 3 months after initiating treatment. After *BCR::ABL1* (IS) ≤1% (MR2.0)[2] has been achieved, every 3 months for 2 years and every 3–6 months thereafter • If there is a 1-log increase in *BCR::ABL1* transcript levels with MMR, qPCR should be repeated in 1–3 months
BCR::ABL1 kinase domain mutation analysis[3]	• CP-CML ‣ Response milestones not reached ◊ Any sign of loss of hematologic response ◊ Any sign of loss of CCyR or its molecular response correlate (MR2.0: *BCR::ABL1* [IS] ≤1%) – defined as an increase in *BCR::ABL1* transcript to >1% ◊ 1-log increase in *BCR::ABL1* transcript levels and loss of MMR • Disease progression to AP-CML or BP-CML[3]

En estos momentos no está incluido, en práctica asistencial, la realización de panel NGS al diagnóstico. En el caso de recaídas,y sobre todo fases avanzadas, debe "considerarse"

Durante la presentación hablaremos sobre:

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- **Manejo de la primera línea y posibilidad de discontinuación del tratamiento**
- Manejo del fracaso terapéutico
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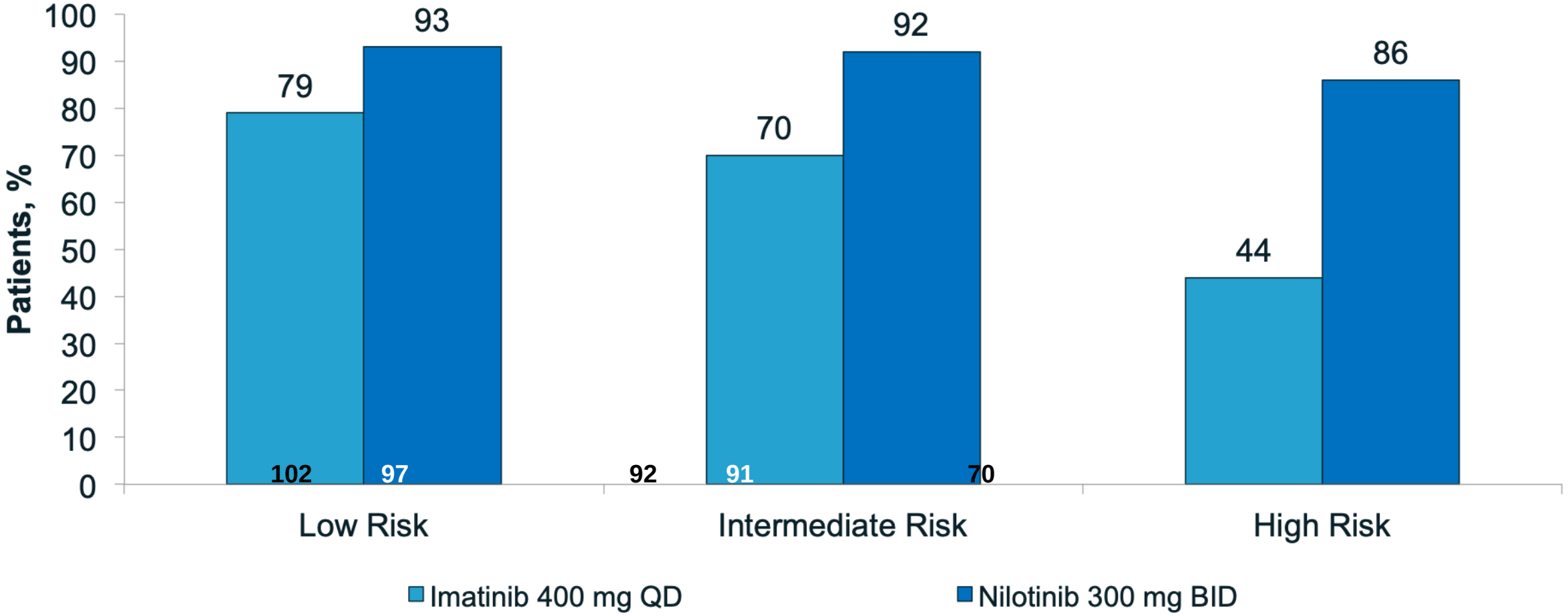
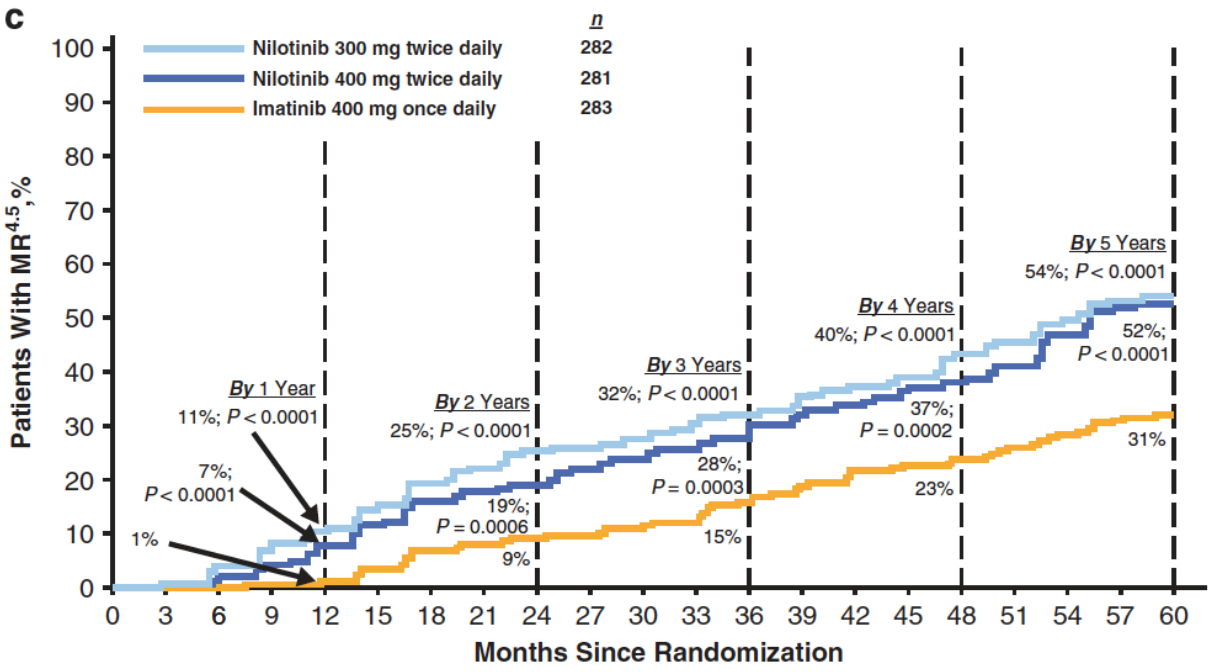
Beneficio de ITC2G sobre imatinib

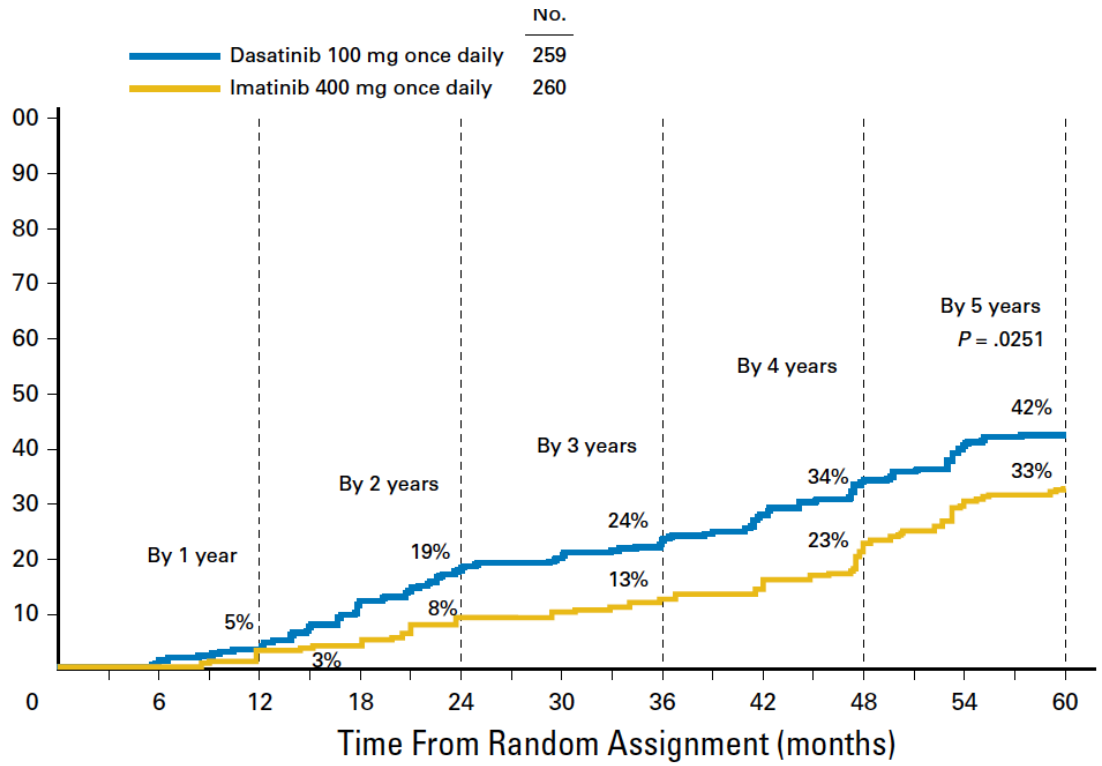
BCR-ABL^{IS} ≤ 10% at 3 Months Regardless of Sokal Risk Score



Hochhaus A. Leukemia (2016) 30, 1044–1054

Probabilidades de RMP en función del tratamiento de primera línea





Cortes J. lin Oncol 34:2333-2340

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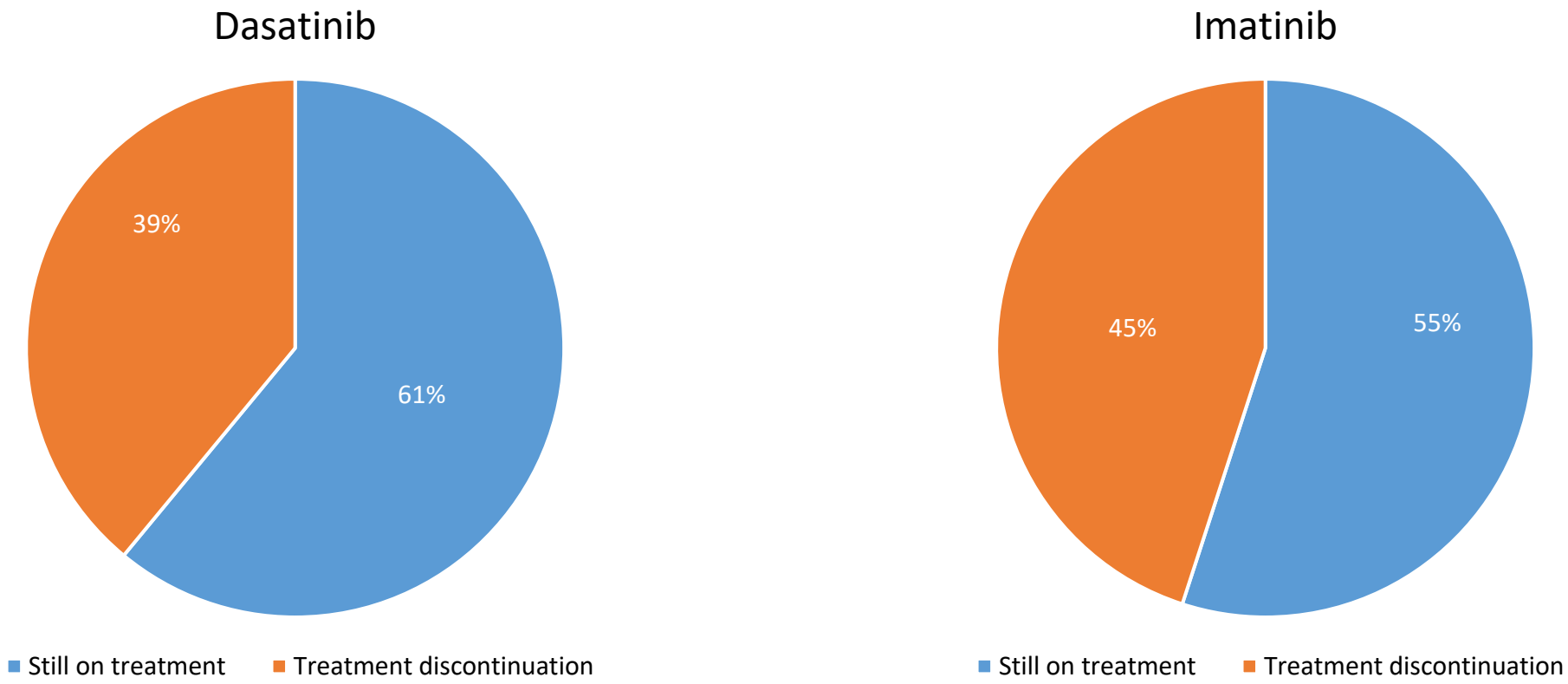
Frequency and Reasons for First-Line Treatment Failure with Imatinib

DASISION trial → **5-year follow-up**



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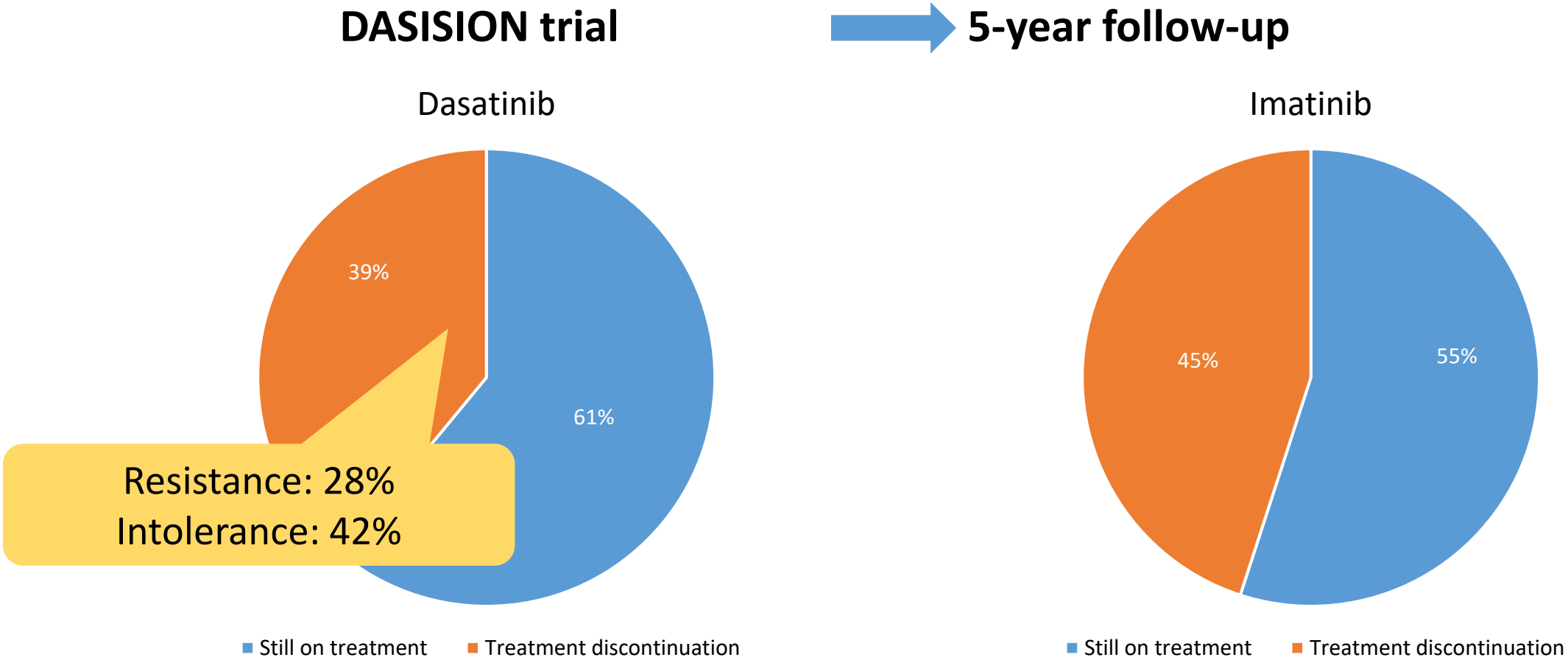

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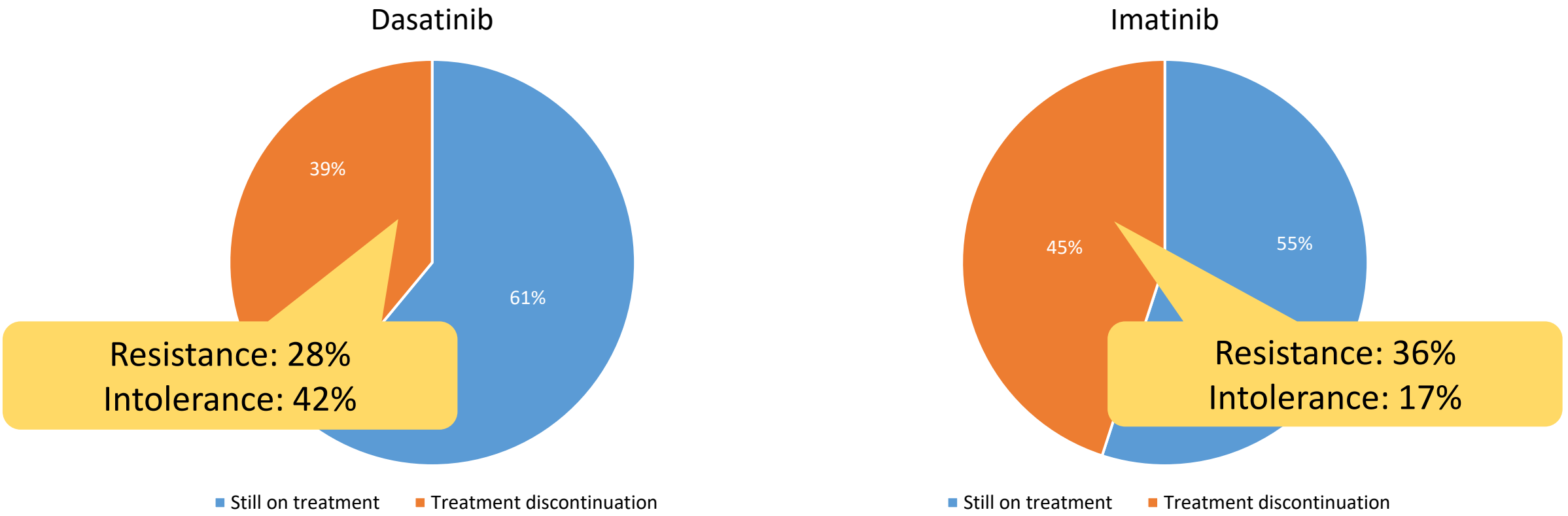
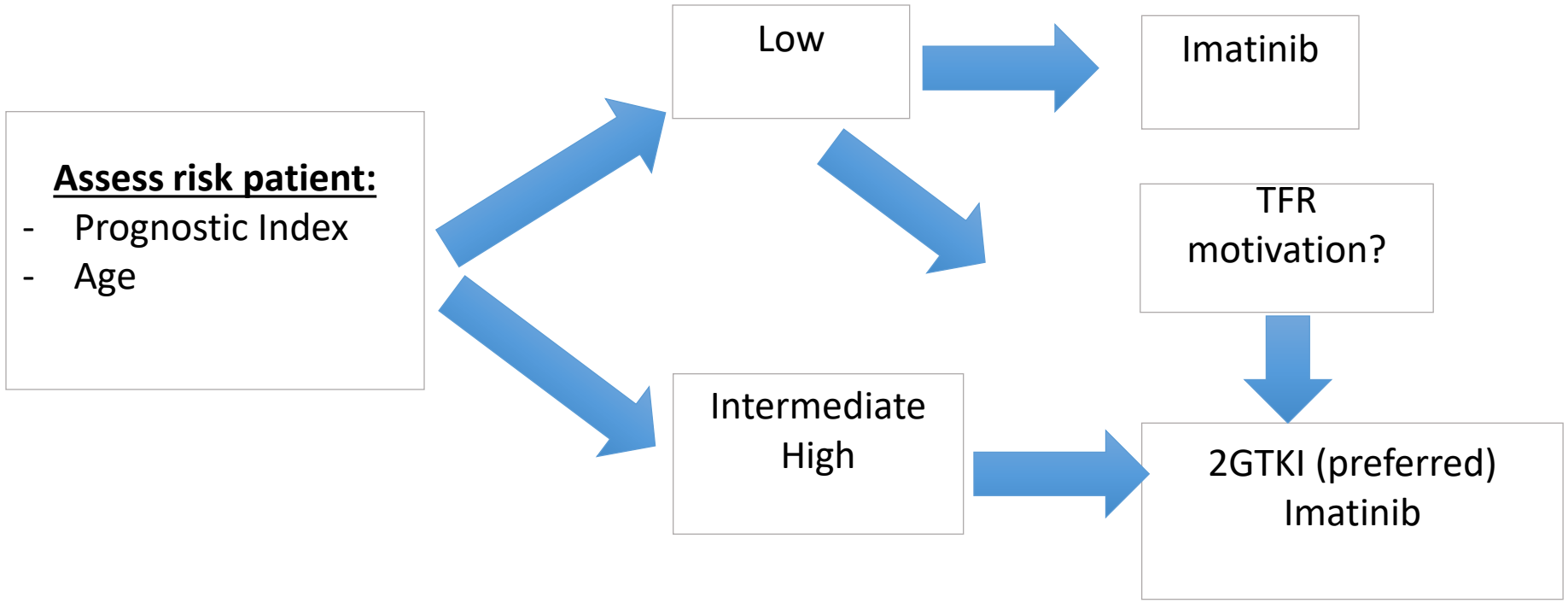


Cortes JE, et al. J Clin Oncol. 2016;34:2333-40.

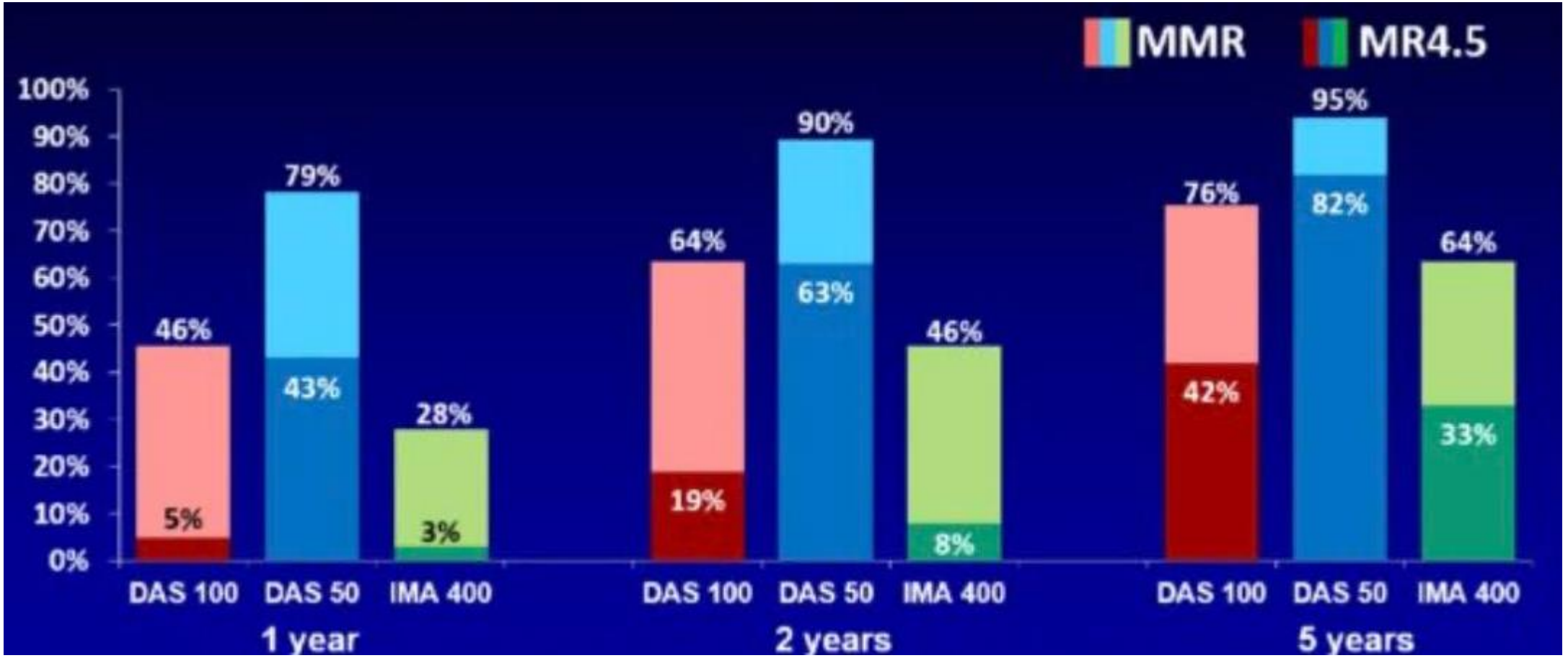
Decisión de tratamiento adapatado al riesgo del paciente



García-Gutiérrez et al. Frontiers in oncology 2019

How can we improve the outcomes of first-line Imatinib treatment?

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



Tolerancia

No. (%) N=81	Any grade	Grade 3-4
Hematologic		
Leukopenia	31 (38)	1 (1)
Neutropenia	23 (28)	6 (7)
Anemia	54 (67)	4 (5)
Thrombocytopenia	27 (33)	5 (6)
Hyperbilirubinemia	5 (6)	0
Increased alanine transaminase	53 (65)	2 (2)
Increased alkaline phosphatase	11 (13)	0
Increased creatinine	15 (18)	0
Fatigue	11 (13)	0
Musculoskeletal	6 (7)	0
Gastrointestinal	2 (2)	0
Skin	2 (2)	0
Cardiovascular/pulmonary	0	1 (1)
Neurologic	3 (2)	1 (1)
Edema	2 (2)	1 (1)
Pleural effusion	10 (12)	2 (2)

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No. (%) / median, [range]	N=83
Age, years	47 [20-84]
Male gender	40 (48)
WBCs, $x10^9$/L	43 [2.7-290]
Hemoglobin, g/dL	12.1 [8.1-17.1]
Platelets, $x10^9$/L	337 [98-1956]
PB basophils, %	3 [0-15]
PB blasts, %	0 [0-4]
BM blasts, %	1 [0-9]
Spleen size, cm	0 [0-11]
Additional CG abnormalities	5 (6)
Sokal risk group	
Low	53 (64)
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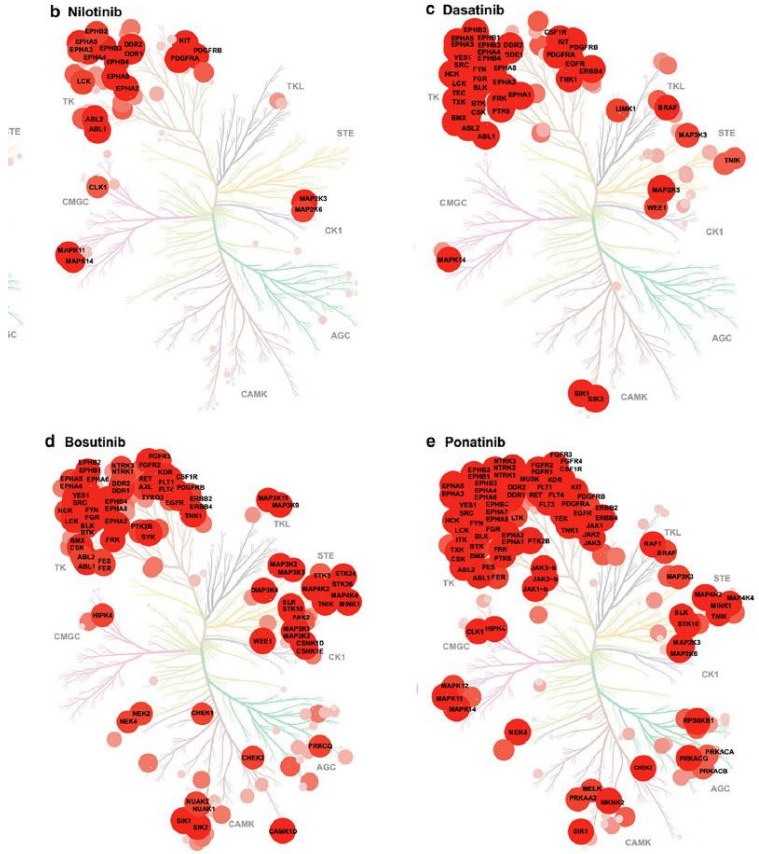
Reasons for Therapeutic Failure to TKIs

Intolerance

Resistance



Drug	BCR-ABL1 Cellular IC_{50} (nM)	Plasma Half-Life (h)	Frontline Treatment at 1 Year: Rate of CCR (%)	Frontline Treatment at 1 Year: Rate of MMR (%)	Frontline Treatment at 1 Year: Rate of $MR^{4.5}$ (%)	Frontline Treatment at 5 Years: Rate of $MR^{4.5}$ (%)	Frontline Treatment at 5 Years: PFS (%)
Imatinib 400 mg	100–500	18	55–66	22–38	1–5	30–35	86–91
High-dose Imatinib			65	45–55	9	58[a]	89
Dasatinib	0.8–1.8	3–5	77	46	5	42	85
Nilotinib	10–25	17	80	44	11	54	96
Bosutinib	42	32–39	77	47	8.1	NA	NA
Ponatinib	0.5	22	100[b]	80[b]	60[b]	NA	NA

Lee H, et al. *Int J Hematol*. 2021;113:632–41

Braun T. Cancer Cell 37, April 13, 2020

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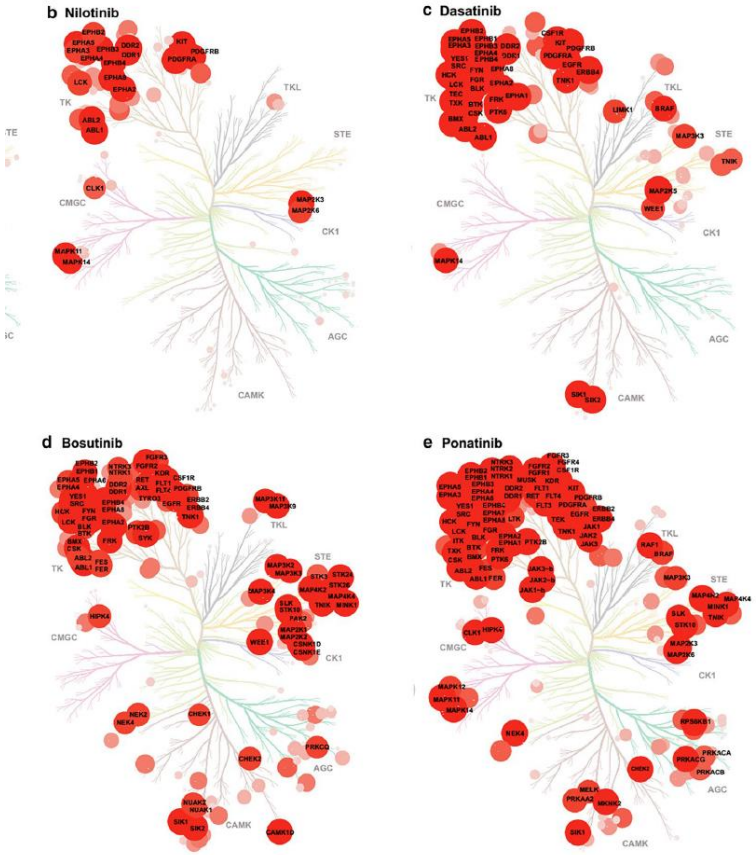

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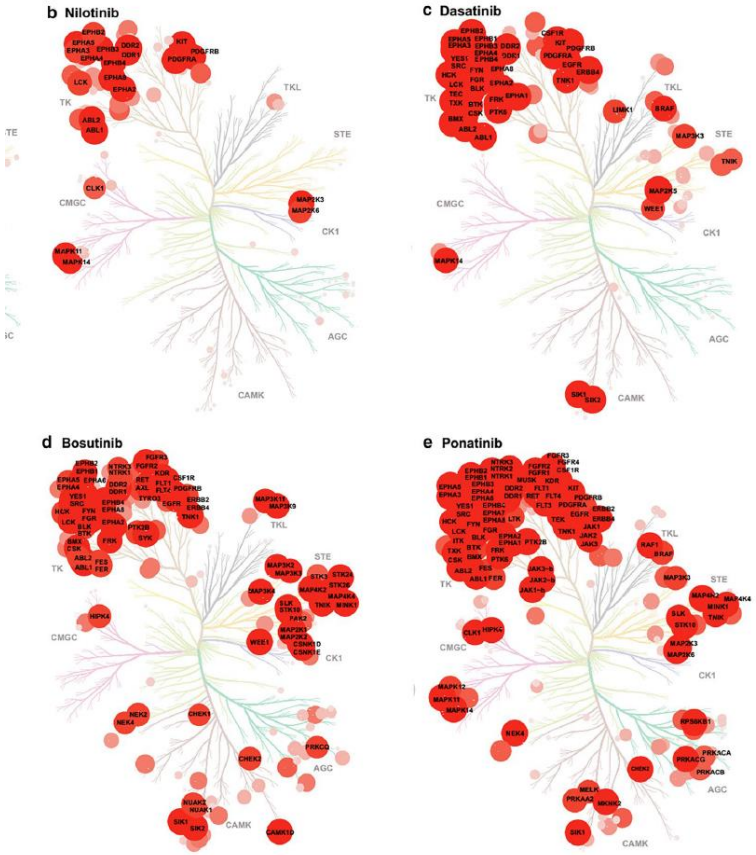

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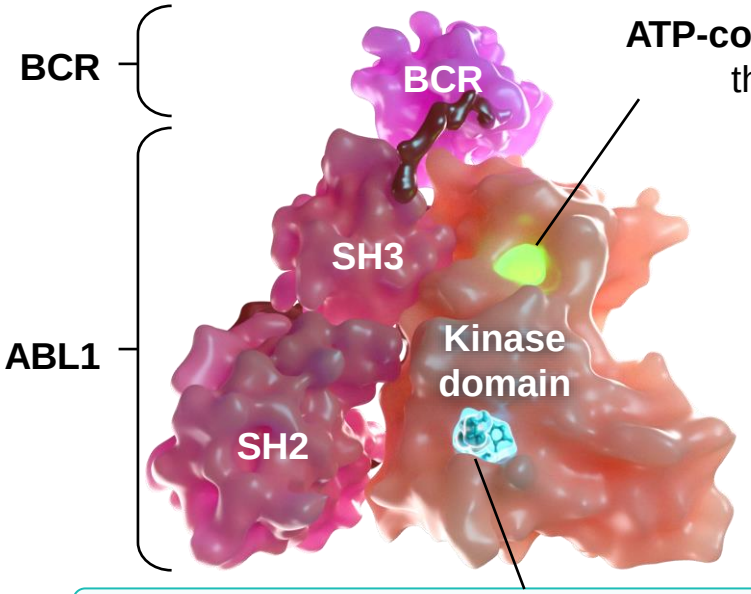
Long-term therapeutic strategies for CML require treatments optimizing safety, tolerability, and efficacy

- Many newly diagnosed patients do not achieve optimal response with standard TKI therapy[1-3]
- Long-term use of 2G TKIs is associated with AEs, such as pleural effusion, GI events, and CV events.[4] Persistent AEs negatively affect patient adherence[5]

Asciminib: intentionally designed to improve efficacy and reduce off-target effects vs current ATP-competitive TKIs[6-8]



ATP-competitive TKIs target the ATP-binding site[8-10]

- *Imatinib*
- *Nilotinib*
- *Dasatinib*
- *Bosutinib*

Frontline TKIs

- *Ponatinib*
- *Olverembatinib*[a]
- *Radotinib*[b]

Asciminib Specifically Targets the ABL Myristoyl Pocket (STAMP)[6]

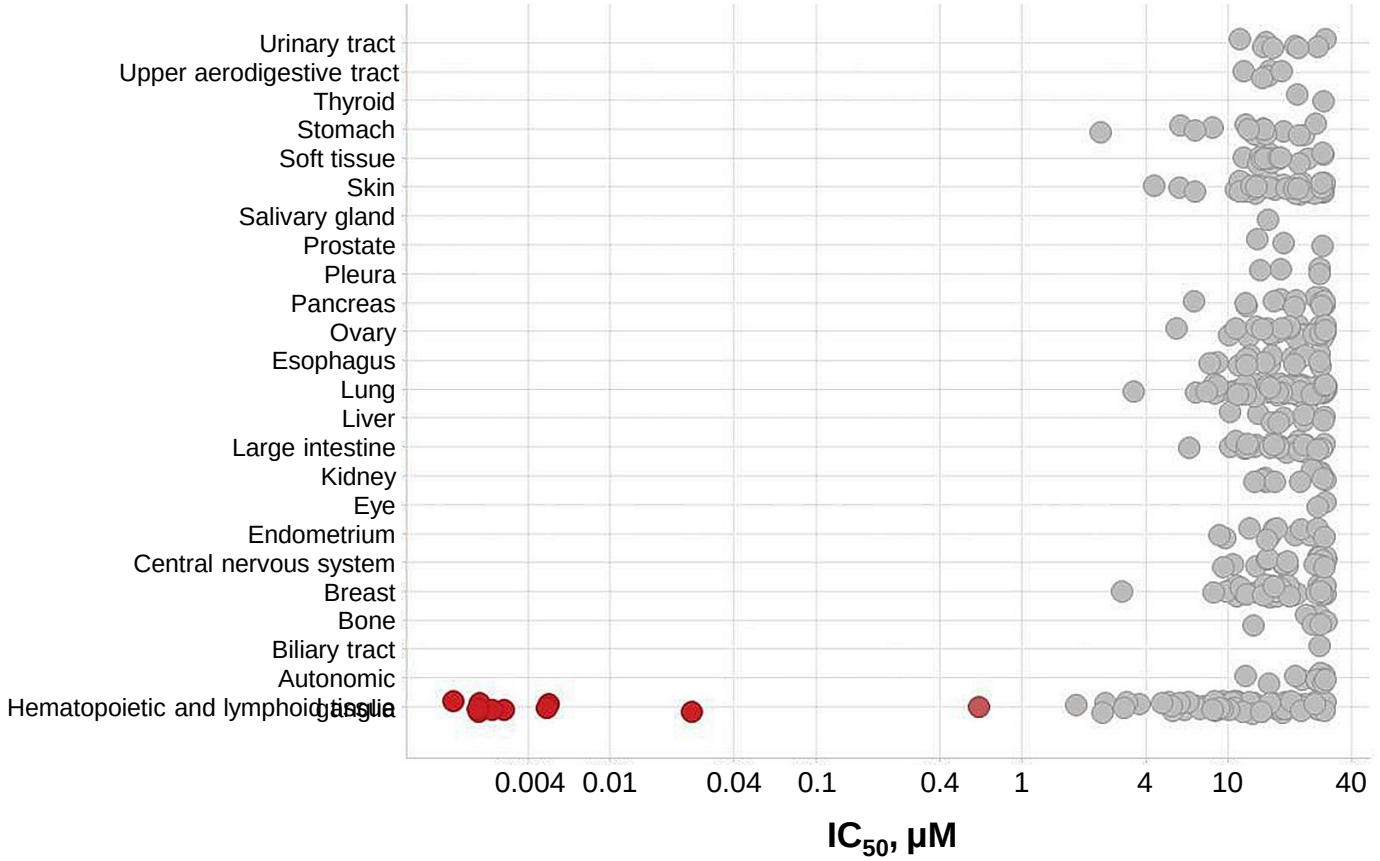
We report primary results from the phase 3 randomized ASC4FIRST trial of **asciminib vs investigator-selected (IS) TKIs** in patients with newly diagnosed CML-CP

AE, adverse event; ATP, adenosine triphosphate; CV, cardiovascular; GI, gastrointestinal; IS-TKI, investigator-selected TKI; SH, Src homology.
[a] Approved in China.
[b] Approved in South Korea.
Figure credit: Mauro MJ, et al. Presented at the 63rd American Society of Hematology Annual Meeting. Abstract 310. Reprinted with permission by the author.

Because of its unique MOA, asciminib binds specifically to ABL1

- Asciminib binds specifically to the myristoyl pocket of ABL1; similar myristoyl binding sites are found in a limited number of kinases (unlike the ATP-binding site, which is conserved among kinases)[1-3]
- No substantial activity was seen on a panel assessing transphosphorylation of 335 wild-type kinases with asciminib concentrations ≤10 μM[1]
- Asciminib selectively inhibited proliferation of cells driven by BCR::ABL1 (represented by red dots on the right)* at low concentrations[1]

Asciminib selectively inhibits proliferation of BCR::ABL1–driven cells[1]



Red dots = BCR::ABL1–expressing CML cell lines and KMS-12-BM cells
Gray dots = cells not expressing BCR::ABL1

1. Manley PW, et al. *Leuk Res.* 2020;98:106458. 2. Wylie AA, et al. *Nature.* 2017;543:733-737. 3. Knight JDR, et al. *PLoSOne.* 2007;2:e982.

ASC4FIRST, a head-to-head study comparing asciminib vs all standard-of-care TKIs in newly diagnosed patients with CML

NCT04971226

Key inclusion criteria

- Newly diagnosed Ph+ CML-CP with ***no*** prior TKIs[a]
- Age ≥18 years

Prerandomization TKI selection

- The TKI a patient will take if randomized to the investigator-selected (IS-TKI) arm
- Selected by the physician in consultation with the patient

Stratification by:

- Prerandomization TKI selection (IMA or 2G TKI)
- ELTS risk category (high, intermediate, low)

R 1:1

N=405

Asciminib (ASC) 80 mg QD

- Imatinib stratum: **ASC^{IMA}**
- 2G TKI stratum: **ASC^{2G}**

All IS-TKIs at label doses

- Imatinib stratum: **IS-TKI^{IMA}**
- 2G TKI stratum: **IS-TKI^{2G}**

End of study: LPFT + 5 years[b]

Data cutoff: Nov. 28, 2023

Primary endpoints:

- MMR at week 48 for asciminib vs all investigator-selected TKIs
- MMR at week 48 for asciminib vs investigator-selected TKI within the imatinib stratum

ASC, asciminib; ELTS, EUTOS long-term survival score; EUTOS, European Treatment and Outcome Study; IMA, imatinib; LPFT, last person first treatment; Ph, Philadelphia chromosome; QD, once daily; R, randomized.

[a] Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted.

[b] Patients will remain on study for 5 years after the last patient first dose, unless they have discontinued early due to treatment failure, disease progression, pregnancy, intolerance, or investigator or patient decision.

More patients are ongoing treatment with asciminib vs all IS-TKIs at cutoff

- The median duration of follow-up was 16.3 months with asciminib and 15.7 months with all IS-TKIs

	Asciminib			IS-TKI		
Randomized patients, %	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All IS-TKI (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Treatment ongoing[a]	**86.1**			**68.6**		
Discontinued from treatment	**13.4**			**29.9**		
Unsatisfactory therapeutic effect	6.0			15.2		
Treatment failure per ELN	5.0			11.8		
Confirmed loss of MMR	0.5			0		
Physician decision	0.5			3.4		
Progressive disease	1.0			2.0		
Adverse event	5.5			10.3		
Protocol deviation	0.5			1.0		
Patient decision	0.5			1.0		
Pregnancy	0			0.5		

ELN, European LeukemiaNet.
[a] Ongoing at the time of the data cutoff date November 28, 2023.

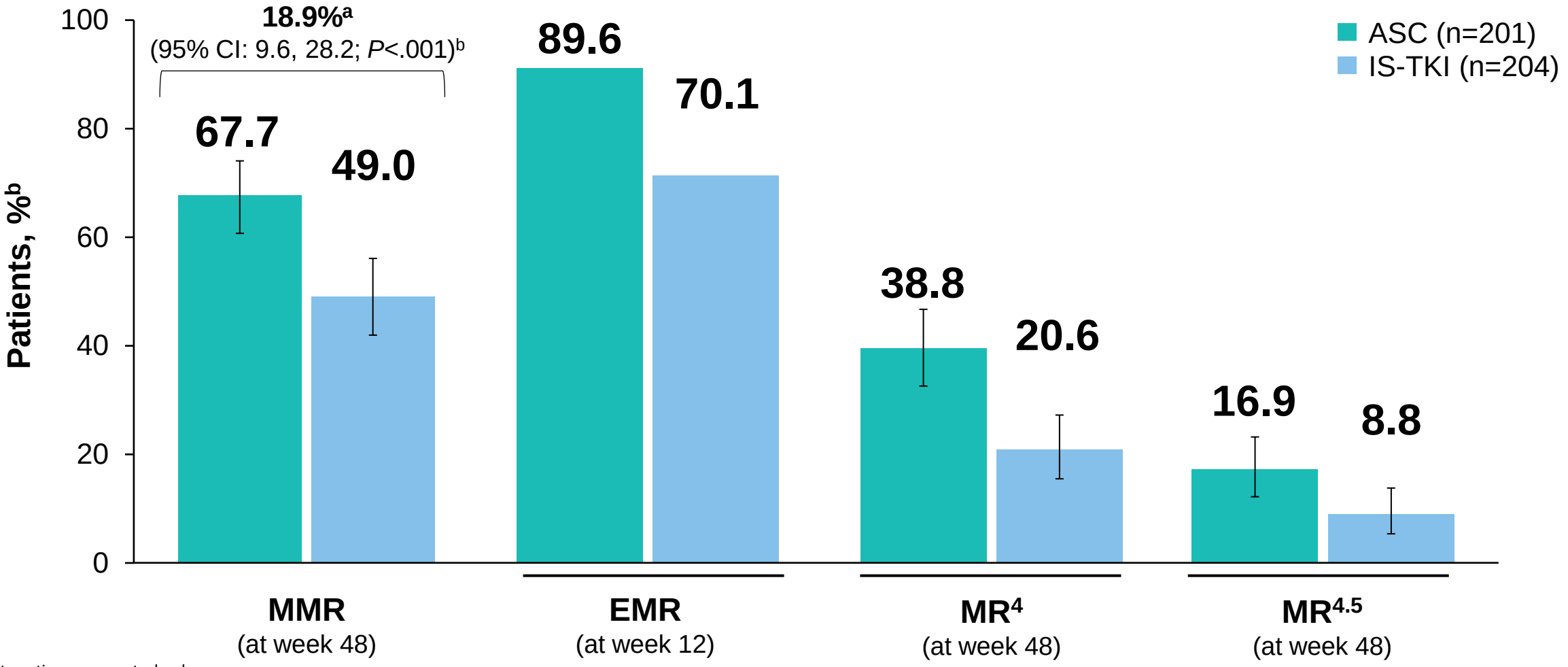
More patients are ongoing treatment with asciminib vs all IS-TKIs at cutoff

- The median duration of follow-up was 16.3 months with asciminib and 15.7 months with all IS-TKIs

	Asciminib			IS-TKI		
Randomized patients, %	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All IS-TKI (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Treatment ongoing[a]	86.1	84.2	**88.0**	68.6	61.8	**75.5**
Discontinued from treatment	13.4	14.9	**12.0**	29.9	36.3	**23.5**
Unsatisfactory therapeutic effect	6.0	5.9	6.0	15.2	20.6	9.8
Treatment failure per ELN	5.0	5.9	**4.0**	11.8	15.7	**7.8**
Confirmed loss of MMR	0.5	0	1.0	0	0	0
Physician decision	0.5	0	1.0	3.4	4.9	2.0
Progressive disease	1.0	2.0	0	2.0	2.9	1.0
Adverse event	5.5	5.9	**5.0**	10.3	10.8	**9.8**
Protocol deviation	0.5	1.0	0	1.0	1.0	1.0
Patient decision	0.5	0	1.0	1.0	1.0	1.0
Pregnancy	0	0	0	0.5	0	1.0

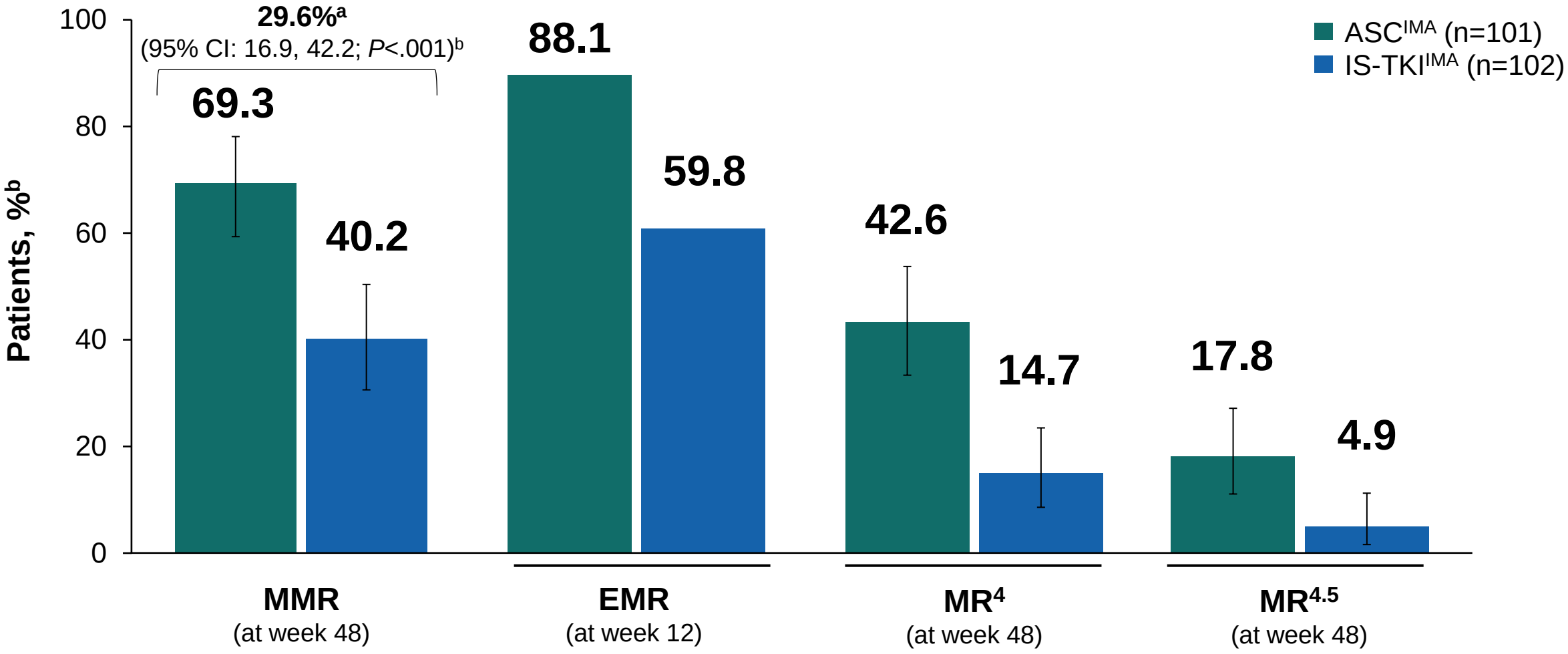
ELN, European LeukemiaNet.
[a] Ongoing at the time of the data cutoff date November 28, 2023.

A higher proportion of patients achieved early and deep molecular responses with asciminib vs all IS-TKIs



IRT, interactive response technology.
Error bars represent 95% CIs.
[a] The common treatment difference and its 95% CI are estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).
[b] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is ≤0.025.

A higher proportion of patients achieved early and deep molecular responses with ASCIMA vs IS-TKIIMA

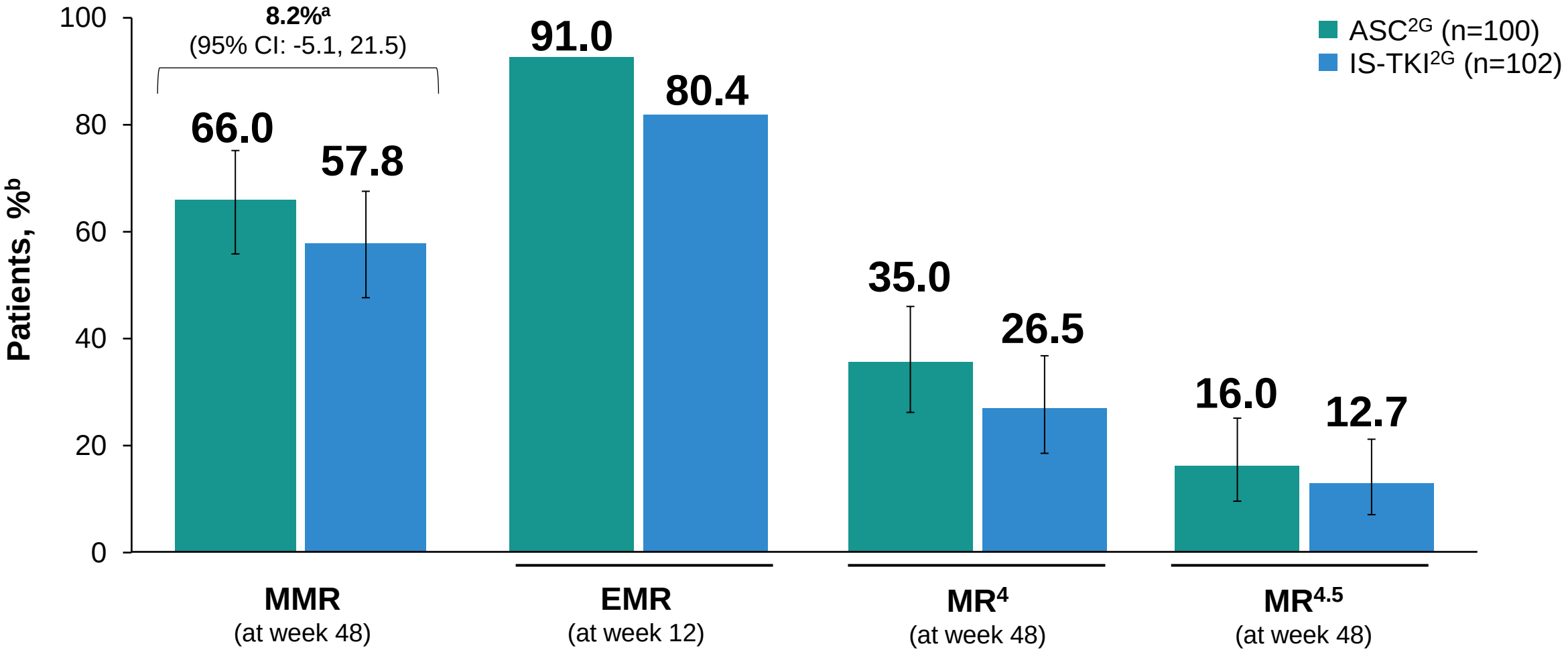


Error bars represent 95% CIs.

[a] The common treatment difference and its 95% CI are estimated using the Mantel-Haenszel method after stratifying for baseline ELTS risk groups (IRT data).

[b] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is ≤0.025.

A higher proportion of patients with ASC2G achieved early and deep molecular responses vs IS-TKI2G

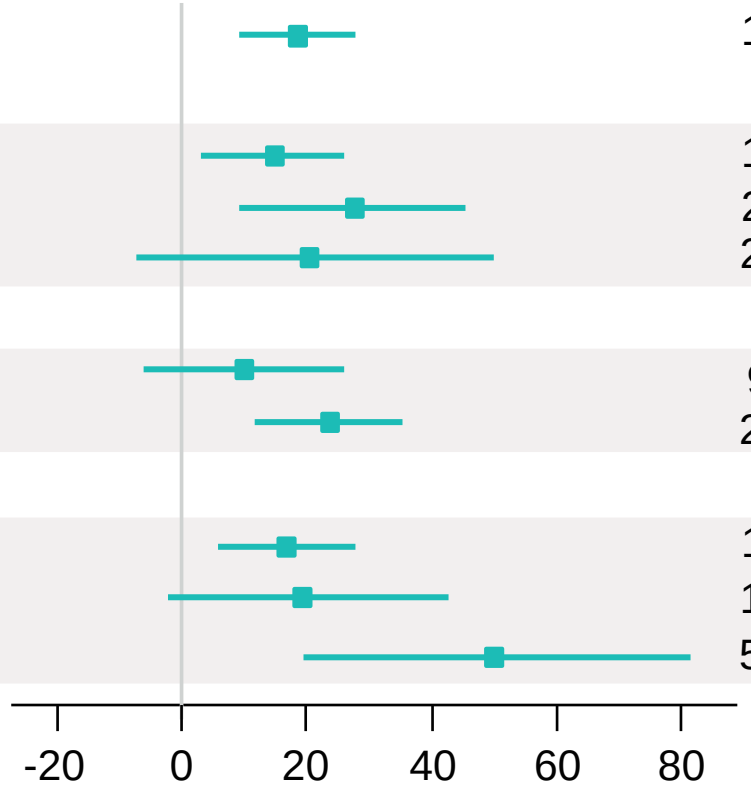


Error bars represent 95% CIs.

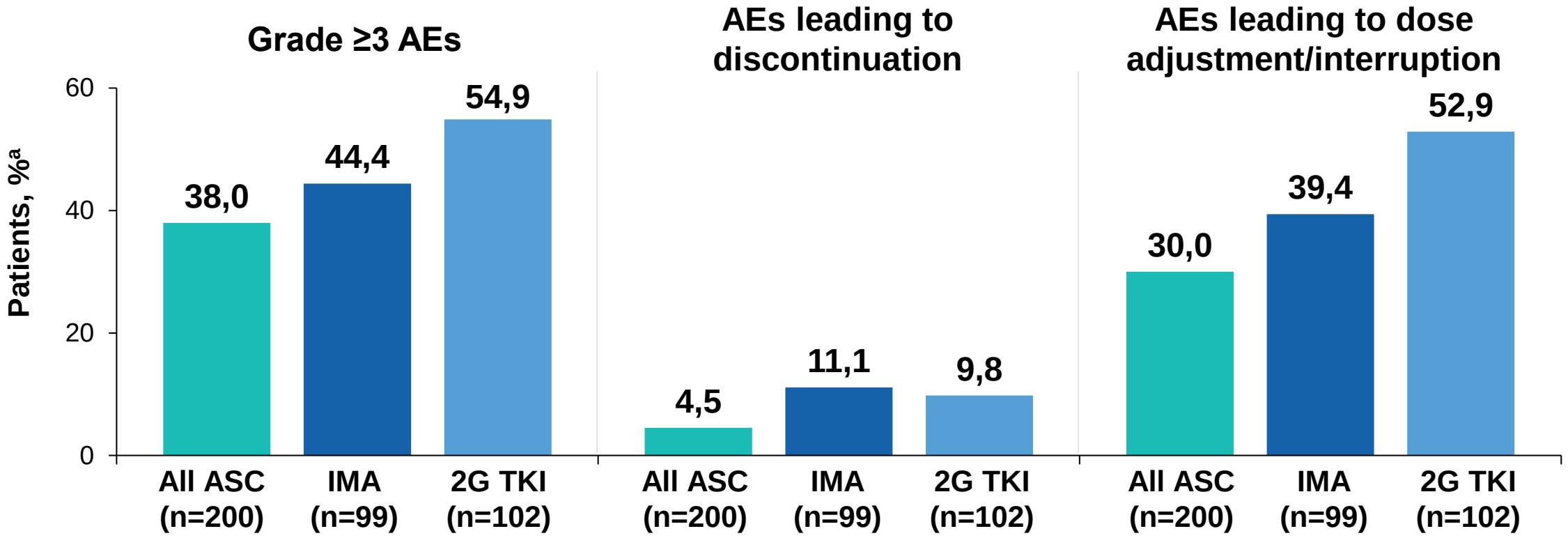
[a] The common treatment difference and its 95% CI are estimated using the Mantel-Haenszel method after stratifying for baseline ELTS risk groups (IRT data).

Asciminib had higher MMR rates across all demographic and prognostic subgroups vs all IS-TKIs

Subgroup	MMR		Treatment difference (95% CI)[a]
	ASC, %	All IS-TKIs, %	
All patients	67.7	49.0	18.6 (9.2 to 28.1)
ELTS			
Low	72.1	57.6	14.5 (2.8 to 26.3)
Intermediate	64.3	36.8	27.4 (9.7 to 45.2)
High	52.2	31.8	20.4 (-7.9 to 48.6)
Sex			
Female	64.3	54.4	9.9 (-5.8 to 25.6)
Male	69.5	45.6	23.9 (12.1 to 35.6)
Age category			
18 to <65 years	64.5	48.4	16.1 (5.2 to 27.0)
65 to <75 years	75.0	55.9	19.1 (-2.8 to 41.0)
≥75 years	90.0	40.0	50.0 (19.0 to 81.0)



Asciminib demonstrated favorable safety and tolerability vs IMA and 2G TKIs

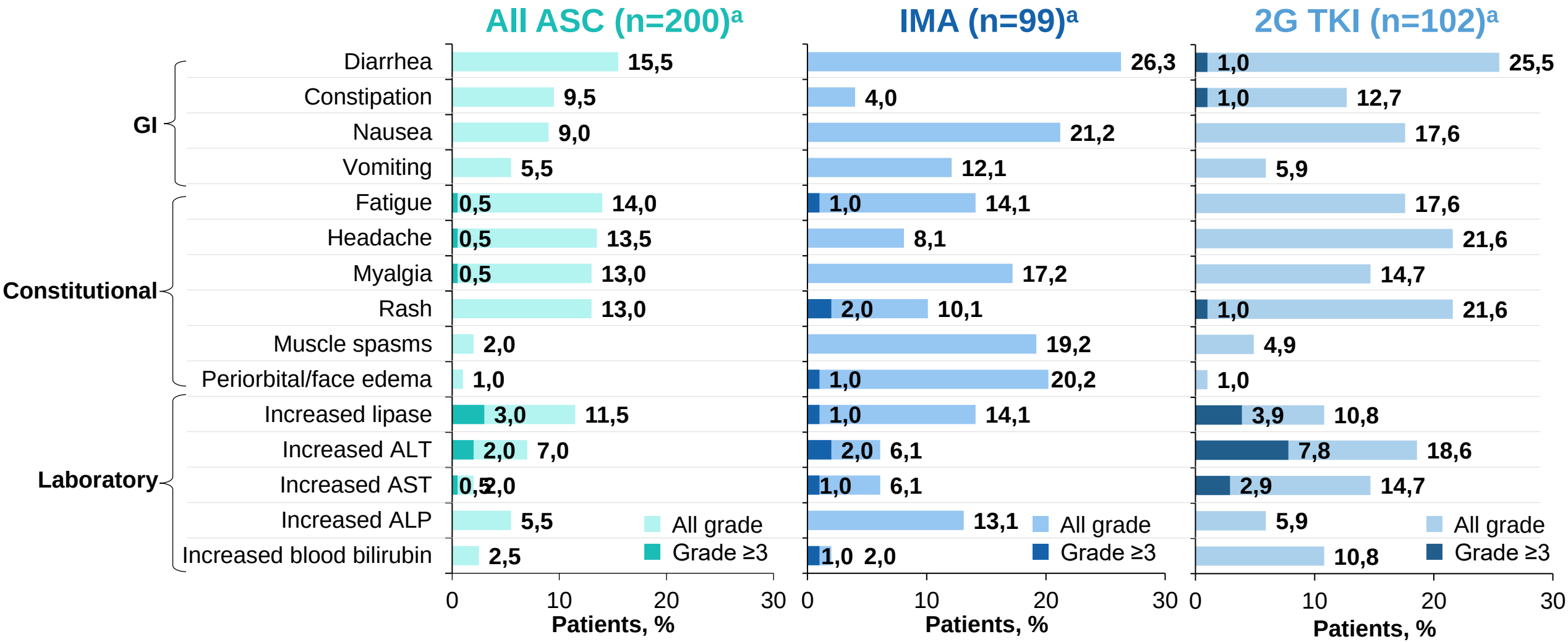


- The median dose intensity was 80.0 mg/day with ASC, 400.0 mg/day with IMA, 595.1 mg/day with NIL, 98.9 mg/day with DAS, and 341.8 mg/day with BOS
- The most common AEs leading to treatment discontinuation were increased lipase with ASC (1.5%), diarrhea and lymphopenia with IMA (2.0% each), and pleural effusion with 2G TKIs (2.0%)

BOS, bosutinib; DAS, dasatinib; NIL, nilotinib.

[a] Safety analyses consisted of patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. A patient with multiple severity grades for an AE is only counted under the maximum grade.

Rates of most non-hematologic toxicities were lower with asciminib



ALP, blood alkaline phosphatase; ALT; alanine aminotransferase; AST; aspartate aminotransferase; GI, gastrointestinal.

[a] Safety analyses consisted of patients who received ≥1 dose of study drug; numbers represent counts of patients. Shown are AEs that occurred during treatment or within 30 days after receiving the last dose of treatment. A patient with multiple severity grades for an AE is only counted under the maximum grade. AEs are ordered by system organ class. COVID-19 and upper respiratory tract infection are not shown.

Arterial-occlusive events were infrequently observed in the study

Patients, n (%)	All ASC (n=200)[a]		IMA (n=99)[a]		2G TKI (n=102)[a]	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
No. of patients with AOEs	2 (1.0)	1 (0.5)	0	0	2 (2.0)	1 (1.0)
Arteriosclerosis coronary artery	1 (0.5)	0	0	0	0	0
Cerebrovascular accident	1 (0.5)	1 (0.5)	0	0	0	0
Myocardial infarction	0	0	0	0	1 (1.0)[b]	1 (1.0)[b]
Myocardial ischemia	0	0	0	0	1 (1.0)[b]	0
Vertebral artery arteriosclerosis	0	0	0	0	1 (1.0)	0

- As incidence of AOEs is known to increase with longer exposure, longer follow-up is needed to better assess the long-term risk of AOEs
- In the phase 3 ASCEMBL trial, AOEs occurred in 5.1% treated with asciminib and 1.3% of patient treated with bosutinib after a median of 2.3 years follow-up, with exposure adjusted rates for asciminib decreasing with longer follow-up[8,11]

AOE, arterial occlusive event.
[a] Safety analyses consisted of patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received.
[b] Myocardial infarction and myocardial ischemia occurred in the same patient with 2G TKIs.

Results: Mutations Associated with Treatment Resistance

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	

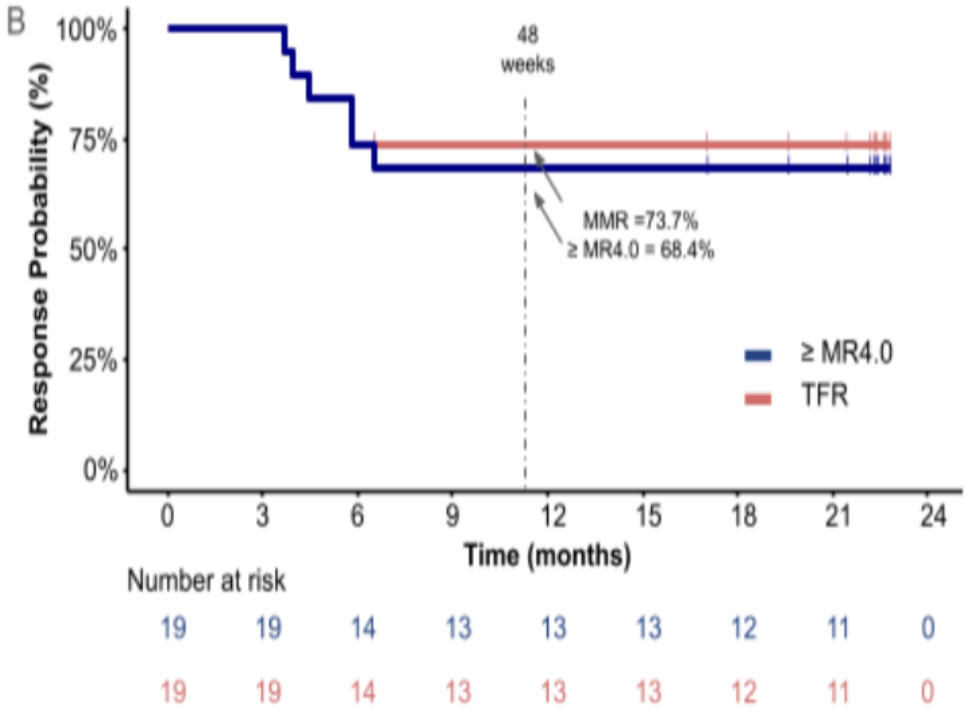
2L+, second line and beyond; AP, accelerated phase; BP, blast phase; CP, chronic phase; HSCT, hematopoietic stem cell transplant; NGS, next-generation sequencing.
[a] A patient with multiple mutations is only counted once. [b] Variant allele frequency was <20%. [c] Patients with new mutations since the week 48 data cutoff (November 28, 2023).

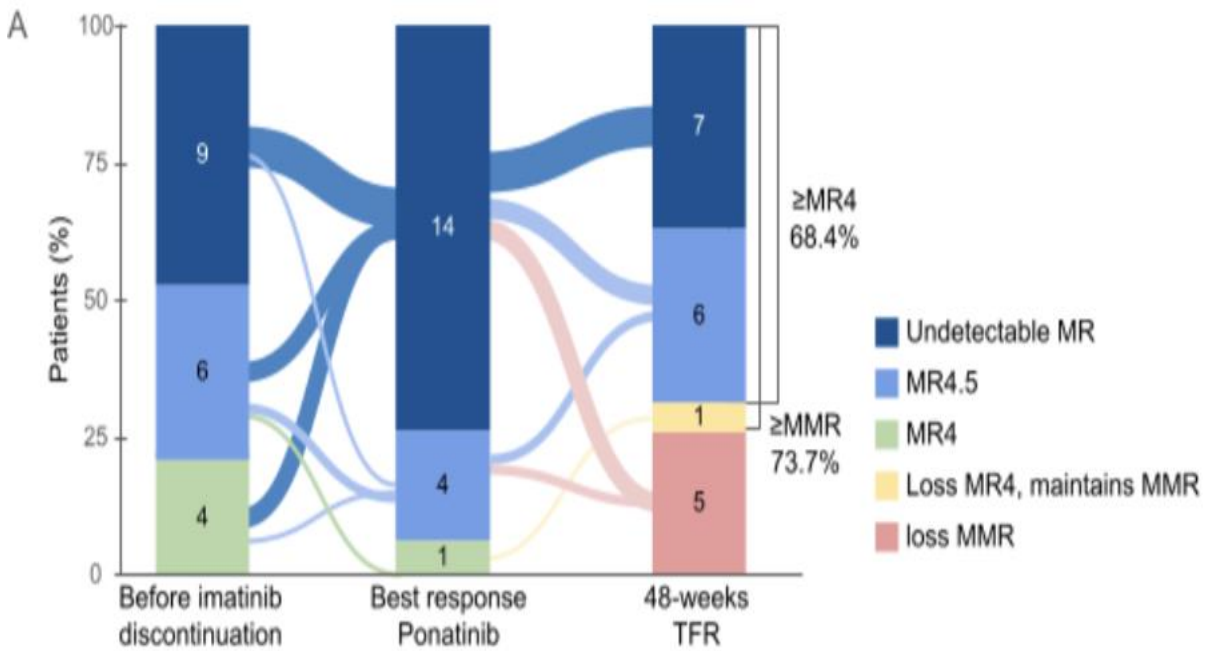
Criterios para la discontinuación de tratamiento

	Hughes 2016	ESMO 2017	NCCN 2020	ELN2020
Evolución de LMC	Solo CP	Solo CP	Solo CP	Solo CP
Riesgo (Sokal)	No alto	No alto		
Respuesta a ITK	Óptima	Óptima	No resistencia	Sin fracaso previo
Tránscrito *BCR-ABL1*	Típic	Medible	Medible	Típico
Duración del tratamiento	**o≥8 años**	**≥5 años**	**≥3 años**	**≥5 años (≥4 años si ITK2G)**
Respuesta molecular	**≥RM4.5**	**≥RM4.5**	**≥RM4.0**	**≥RM4.0**
Duración de respuesta	**≥2 años**	**≥2 años**	**≥2 años**	**≥2 años**
Reinicio de ITK			Pérdida de RMM	Pérdida de RMM
Sensibilidad de RT-qPCR	≤ RM4.5	≤ RM4.5		
Frecuencia de seguimiento	Mensual los primeros 6 meses, posteriormente cada 2-3 meses	Mensual los primeros 6 meses, cada 6 semanas hasta el año, posteriormente trimestral	Mensual el primer año, cada 2 meses hasta el segundo año, posteriormente cada 3 meses	Mensual los primeros 6 meses, cada 2 meses hasta el año, posteriormente cada tres meses
Tiempo de resultado de RT-qPCR	≤4 semanas		≤2 semanas	

Manual para el control y el tratamiento de los pacientes con LMC. GELMC

Ponatinib como “consolidación” previo a discontinuación. PONAZEROstudy (GELMC)





Pérez-Lamas and García-Gutiérrez V. Submited

Durante la presentación hablaremos sobre:

- Manejo de la primera línea y posibilidad de discontinuación del tratamiento
- **Manejo del fracaso terapéutico**
- Nuevas opciones terapéuticas

Opciones terapéuticas tras fracaso a imatinib

	Dasatinib		Nilotinib		Bosutinib	
Variable	Resistentes	Intolerantes	Resistentes	Intolerantes	Resistentes	Intolerantes
Seguimiento	>24m		>24m		24m	
RHC	89%	100%	77%	NR	86%	85%
RCC	44%	66%	41%	51%	41%	41%
SLP 24 meses	80%		64%		79%	
SG 24 meses	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

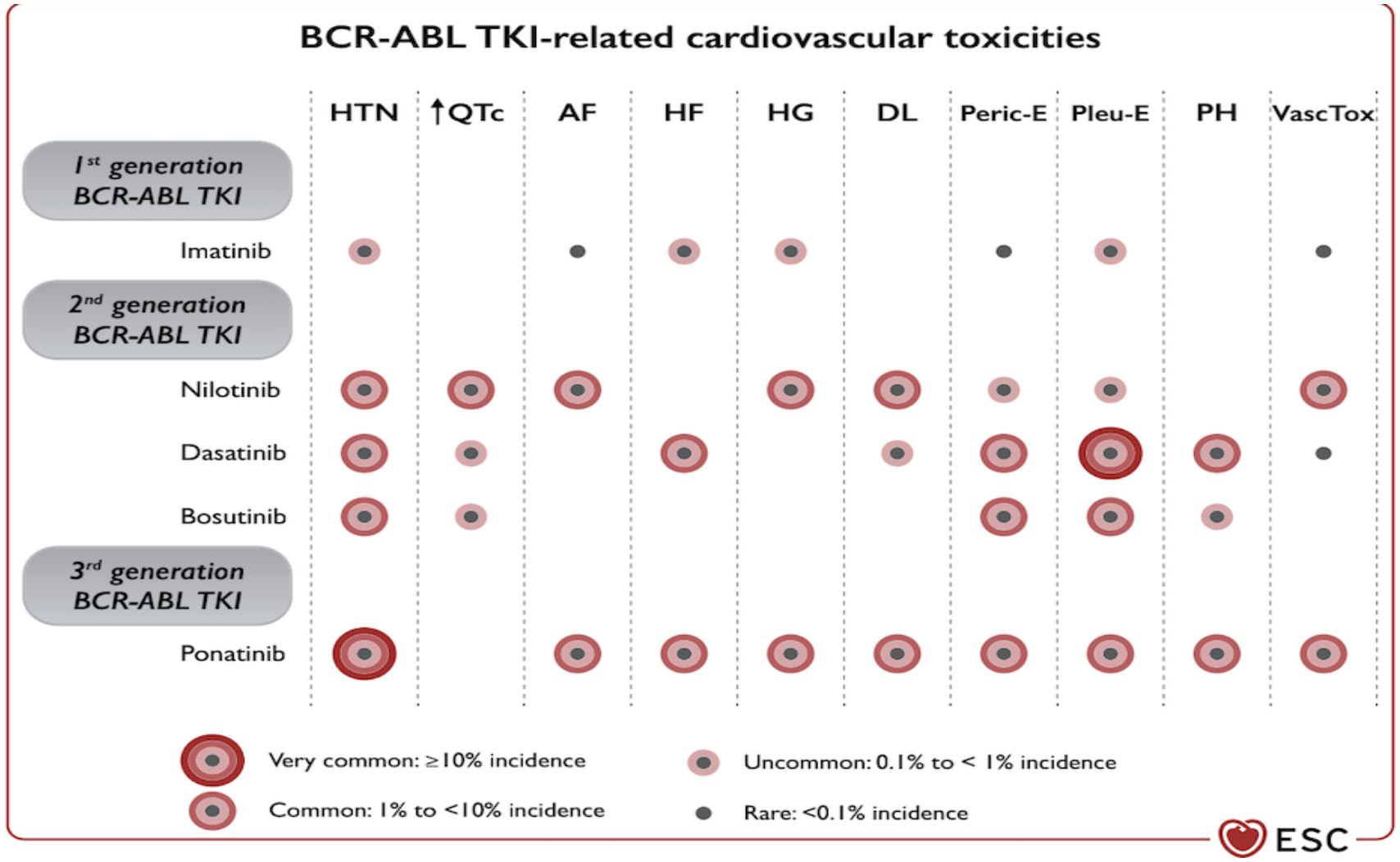
¿Cómo elegimos el tratamiento?

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

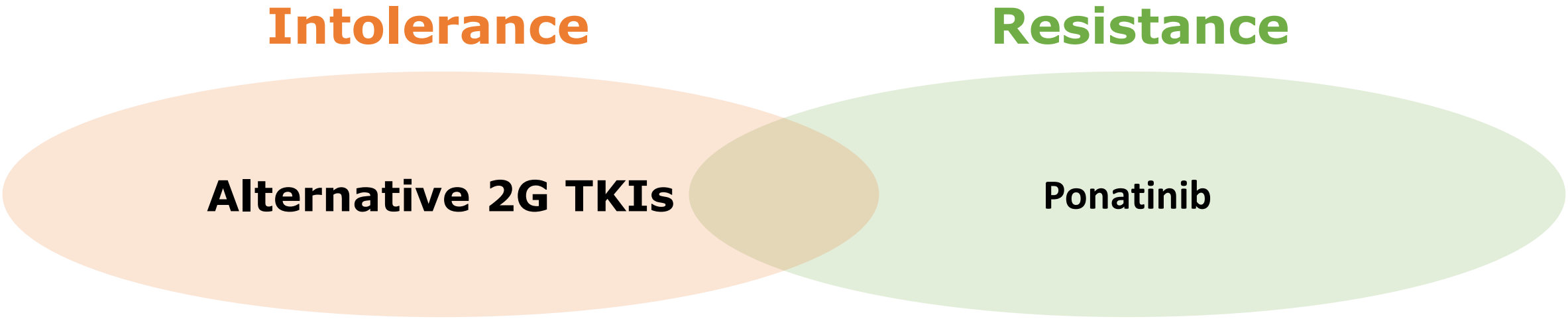
¿Cómo elegimos el tratamiento?



ESC European Society of Cardiology
European Heart Journal (2022) **43**, 4229–4361
https://doi.org/10.1093/eurheartj/ehac244

ESC GUIDELINES

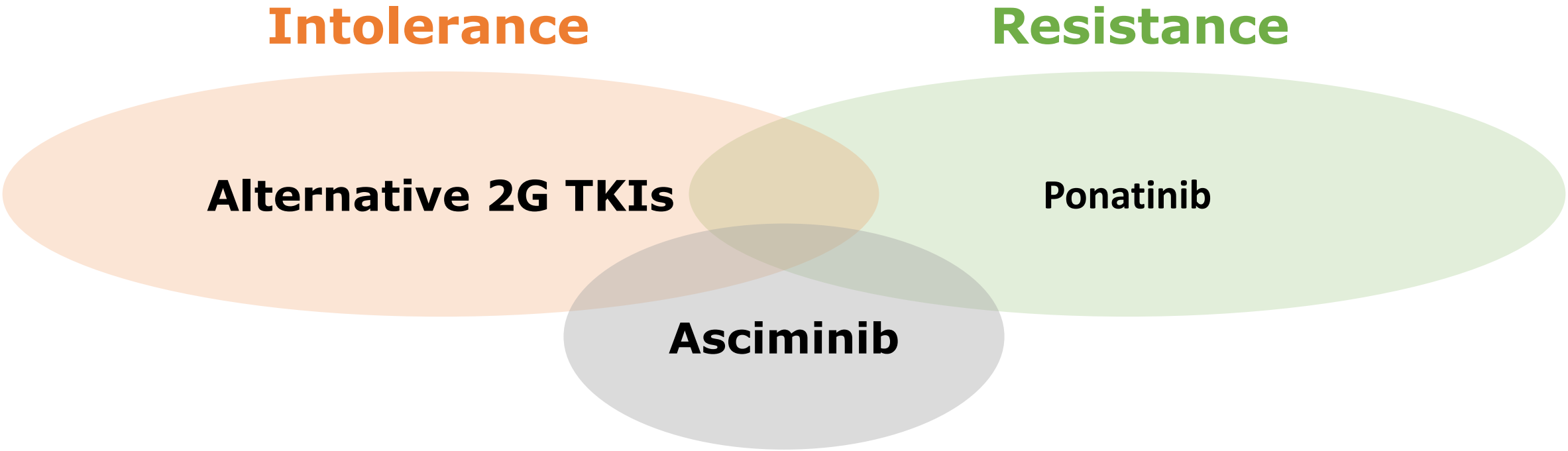
Treatment options after 2G TKI failure



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

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

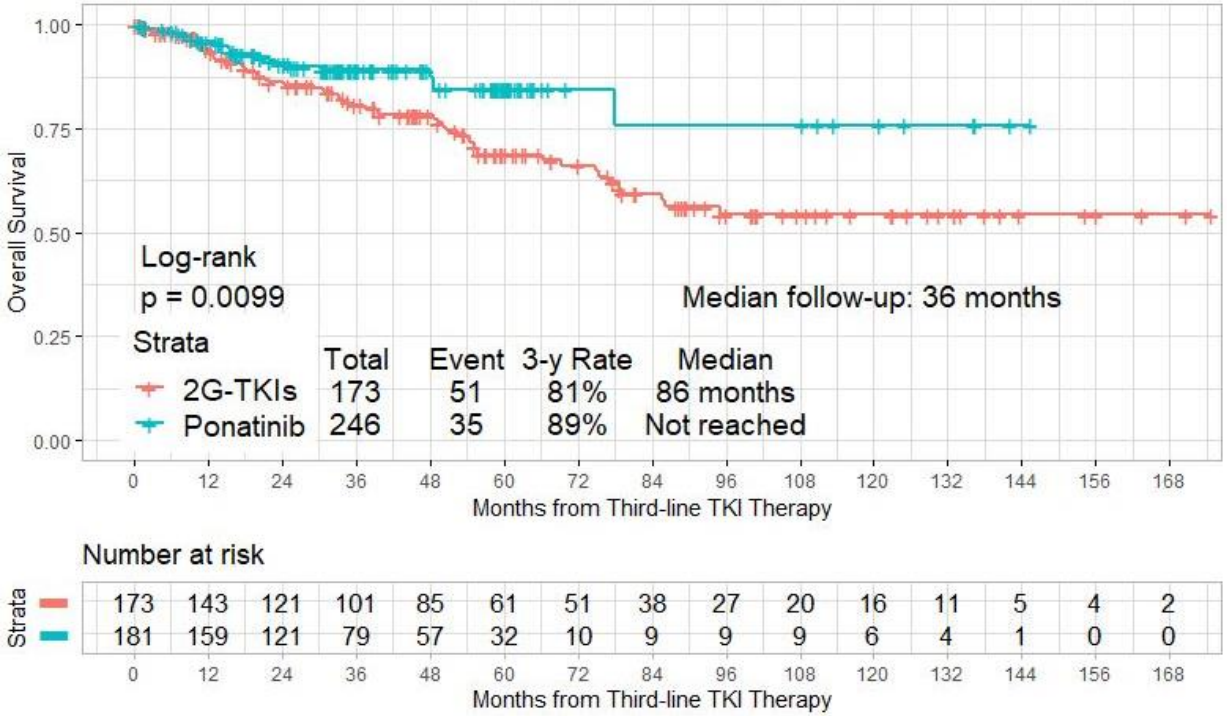
Treatment options after 2G TKI failure



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

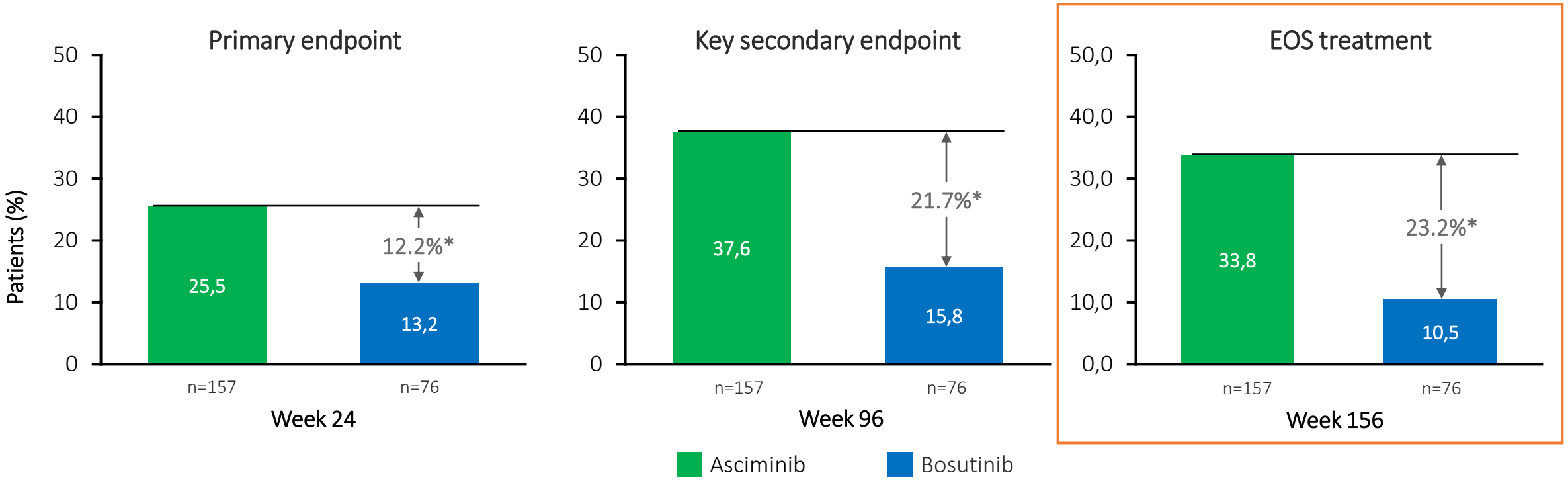
Senapti J, et al. *Blood Cancer J*. 2023;13:58.

Ponatinib vs ITC2G tras fracaso a terapéutico a ITC2G



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

ASCEMBL: MMR rates at weeks 24, 96 and 156



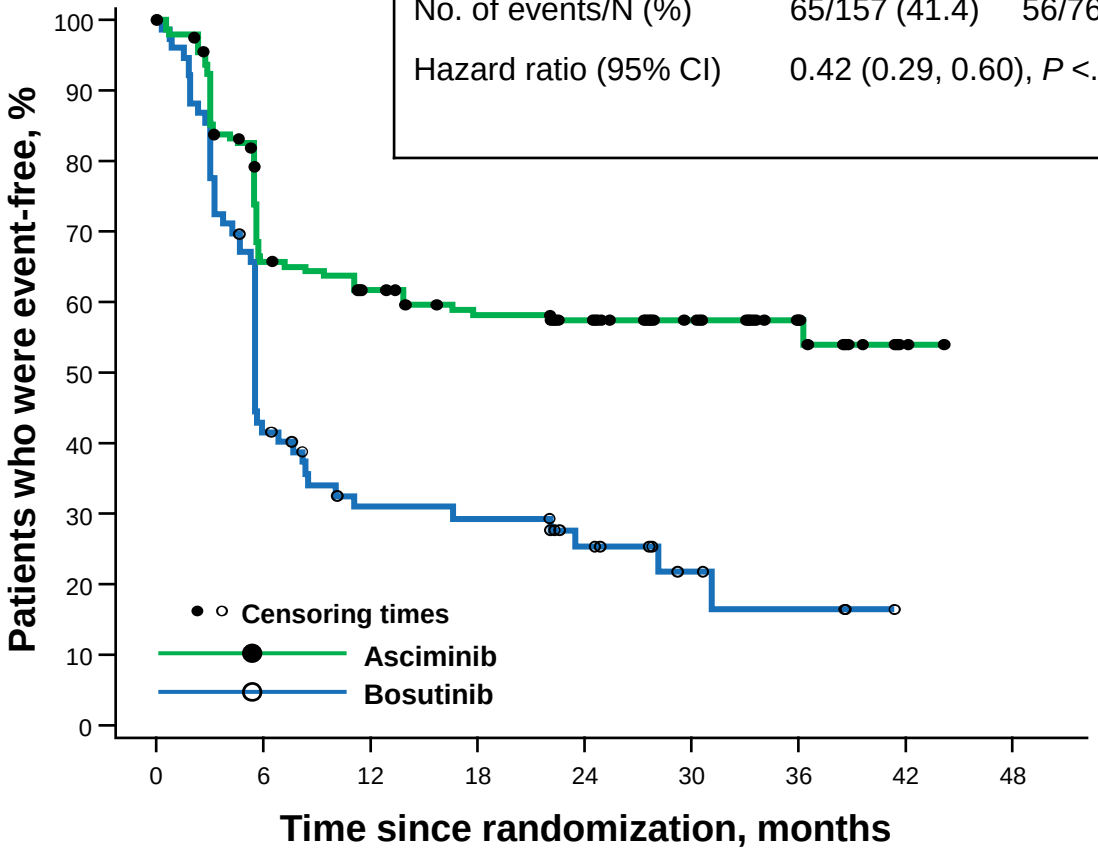
- The MMR rate (BCR::ABL1^{IS} ≤0.1%) at week 156 continued to be higher with asciminib compared with bosutinib, consistent with week 24 and 96 analyses

*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.

Event-Free Survival

	Asciminib	Bosutinib
No. of events/N (%)	65/157 (41.4)	56/76 (73.7)
Hazard ratio (95% CI)	0.42 (0.29, 0.60), *P* <.0001	



Number of subjects still at risk: events

Asciminib	157:0	98:52	89:58	80:63	64:64	38:64	18:64	2:65	0:65
Bosutinib	76:0	31:44	19:51	18:52	11:54	5:55	3:56	0:56	0:56

- The proportion of patients who were event-free* by **2 years** was

  57.4% (95% CI: 49.0%, 64.8%) with **asciminib**
  vs
  25.2% (95% CI: 15.4%, 36.2%) with **bosutinib**

- Median time to event was **not reached** with **asciminib** and was **5.6 months** with **bosutinib**

Lack of efficacy (per 2013 ELN recommendations for 2L patients[5]), disease progression (CML-AP/BP, CML death) or discontinuation due to AEs

How should we manage CML pts failing to 2GTKIs?

- **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 a preferred 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.

Durante la presentación hablaremos sobre:

- Manejo de la primera línea y posibilidad de discontinuación del tratamiento
- Manejo del fracaso terapéutico
- ***Nuevas opciones terapéuticas***

Olverembatinib in Ponatinib pretreated pts

Outcome	No.					
	With T315I variant	No T315I variant	Resistant	Intolerant	Total previously treated	Total study population
Ponatinib						
Ponatinib pretreated						
Efficacy population	13	17	21	6	30	60
Cytogenetic response						
Evaluable patients	13	13	19	4	26	51
Complete cytogenetic response, No. (%)	8 (61.5)	7 (53.8)	10 (52.6)	3 (75.0)	15 (57.7)	31 (60.8)
Molecular response						
Evaluable patients	13	17	21	6	30	59
Major molecular response, No. (%)	6 (46.2)	5 (29.4)	9 (42.9)	1 (16.7)	11 (36.7)	25 (42.4)

Jabbour E. *JAMA Oncol. 2025;11(1):28-35.*

ELVN-001 in Asciminib pretreated pts

ELVN-001 selectively inhibits ABL with low off-target activity against other kinases[1]

Cellular Phosphorylation IC_{50} (nM)

	cKIT	FLT3wt	PDGFRb	VEGFR2	cSRC
ELVN-001	>10,000	>10,000	>10,000	>10,000	>10,000
Ponatinib	30	3.8	89	4.8	630
Nilotinib	200	>10,000	720	2,900	>10,000
Dasatinib	0.6	>1,000	7.1	>1,000	10
Bosutinib	1,000	4,700	7,900	>10,000	16
Imatinib	82	>10,000	230	9,600	>10,000
Asciminib	>10,000	>10,000	>10,000	>10,000	>10,000

Off-target kinase inhibition (IC50) by ELVN-001 vs. approved ABL TKIs in cell-based assays

ELVN-001 maintains activity against T315I and other BCR::ABL1 mutations known to confer resistance to asciminib[1-3]

Fold-Shift from Native BCR::ABL1

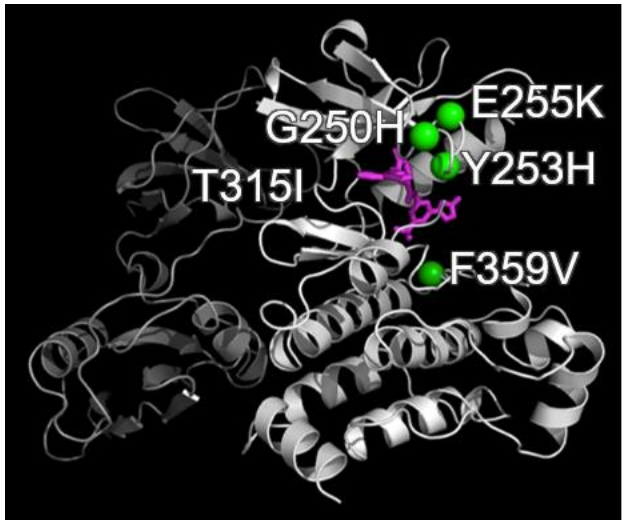
	T315I	M244V	A337T	E355G	F359C	F359V	P465S
Asciminib	96	611	173	>2380	>2380	>2380	>2380
ELVN-001	4	2	1	4	3	2	2
Dasatinib	2935	2	1	3	4	2	2
Bosutinib	113	3	1	4	5	5	4
Ponatinib	3	2	1	3	5	5	2
Imatinib	>20	3	1	8	18	10	4
Nilotinib	>341	2	1	5	33	21	3
Vodobatinib	445	2	1	3	10	7	2
Olverembatinib	5	2	1	3	6	6	2

ASCEMBL = phase 3 study of asciminib vs bosutinib in CML after 2 or more prior TKIs. BCR::ABL1 = breakpoint cluster region-Abelson leukemia virus 1. IC_{50} = half-maximal inhibitory concentration. nM = nanomolar. TKI = tyrosine kinase inhibitor. WT = wildtype. Cell viability measured with Cell titer glo luminescent assay. Values expressed as fold-shift in IC_{50} from $BCR::ABL1^{WT}$.

References: 1. Enliven data on file; 2. Réa D and Hughes TP. Development of asciminib, a novel allosteric inhibitor of BCR-ABL1. Crit Rev Oncol Hematol. 2022;171:103580.; 3. Qiang W et al. Mechanisms of Resistance to the BCR-ABL1 Allosteric inhibitor Asciminib. Leukemia. 2017;31(12):2844-2847.; 4. Réa D et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138:2031-2041.

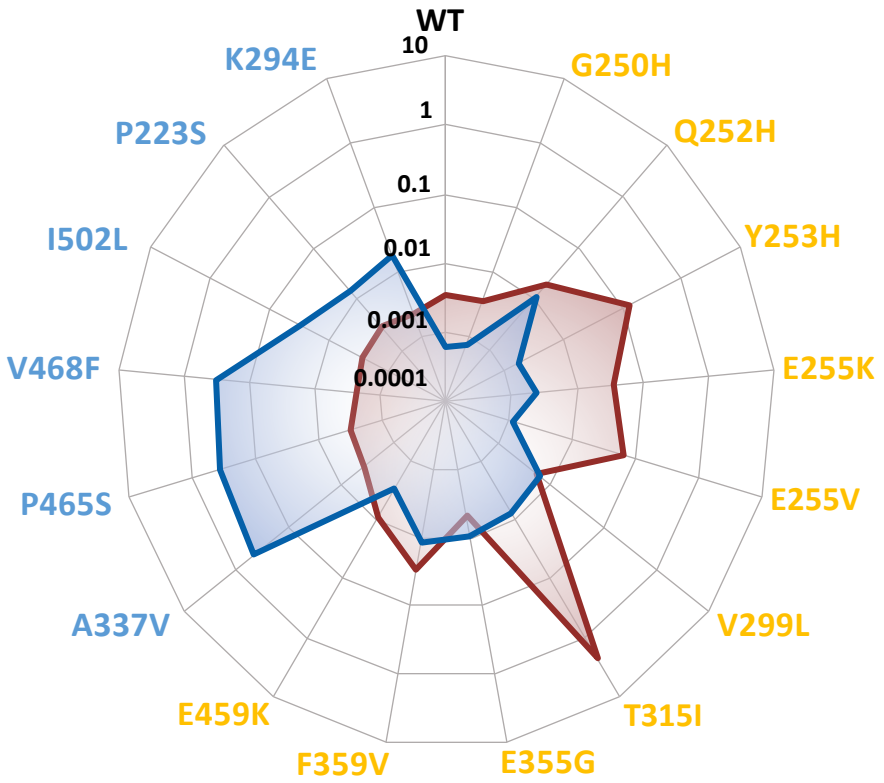
Asciminib and ATP-site TKIs have complementary mutation profiles

ATP binding site mutations



Myristoyl binding site mutations

Inhibition of mutant BCR-ABL1 variants by asciminib or nilotinib



1. Wylie AA, et al. *Nature*. 2017;543(7647):733-737. 2. Ottmann OG, et al. *Blood*. 2015;126 [abstract 138].

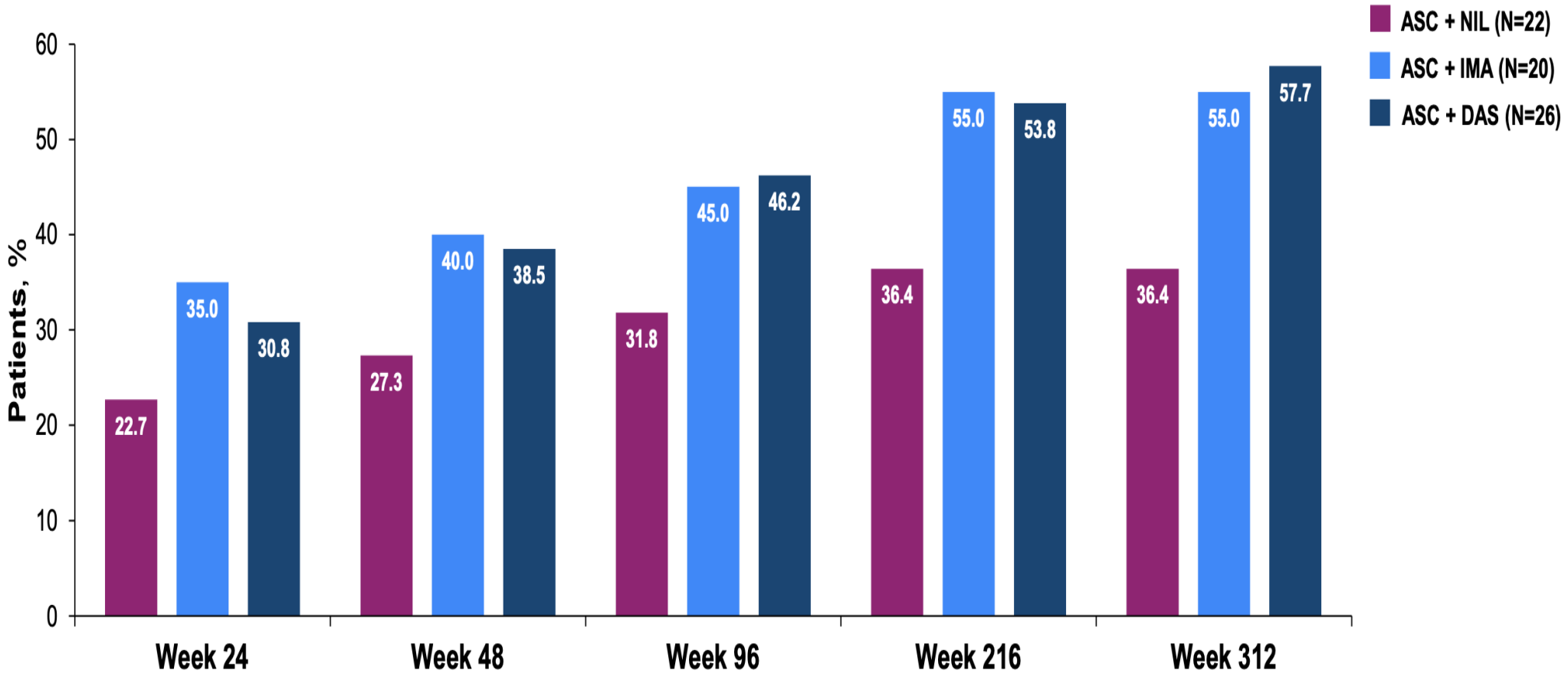
Cortes J. Abstract 868: Asciminib in Combination with Imatinib, nilotinib or dasatinib may be a Potent Treatment Option in pts with CML Chronic Phase: Final results from the Asciminib Phase 1 trial

Characteristic	ASC + NIL (N=26)	ASC + IMA (N=25)	ASC + DAS (N=32)
Median age (range), years	55.5 (23-78)	57.0 (22-79)	52.9 (19-76)
Male, n (%)	16 (61.5)	12 (48.0)	24 (75.0)
CML-CP, n (%)	25 (96.2)	25 (100)	31 (96.9)
No. of prior TKIs, n (%)			
2	10 (38.5)	10 (40.0)	17 (53.1)
3	6 (23.1)	5 (20.0)	9 (28.1)
≥4	10 (38.5)	10 (40.0)	6 (18.8)
Prior treatment with NIL, IMA, or DAS, respectively, n (%)	18 (69.2)	17 (68.0)	18 (56.3)
T315I mutation at screening, n (%)	0 (0.0)	0 (0.0)	2 (6.3)[a]
BCR::ABL1^{IS} at screening, n (%)			
≤0.1%	4 (15.4)	3 (12.0)	4 (12.5)
>0.1% to ≤1%	4 (15.4)	5 (20.0)	7 (21.9)
>1% to ≤10%	5 (19.2)	5 (20.0)	6 (18.8)
>10%	13 (50.0)	10 (40.0)	13 (40.6)
Atypical/p190[b]/unknown transcripts	0 (0.0)	2 (8.0)	2 (6.3)

IS, International Scale.
[a] 1 patient received ASC 40 mg BID + DAS 100 mg QD, and 1 received ASC 160 mg QD + DAS 100 mg QD. [b] Includes *e1a2* and *e1a3* minor transcripts.

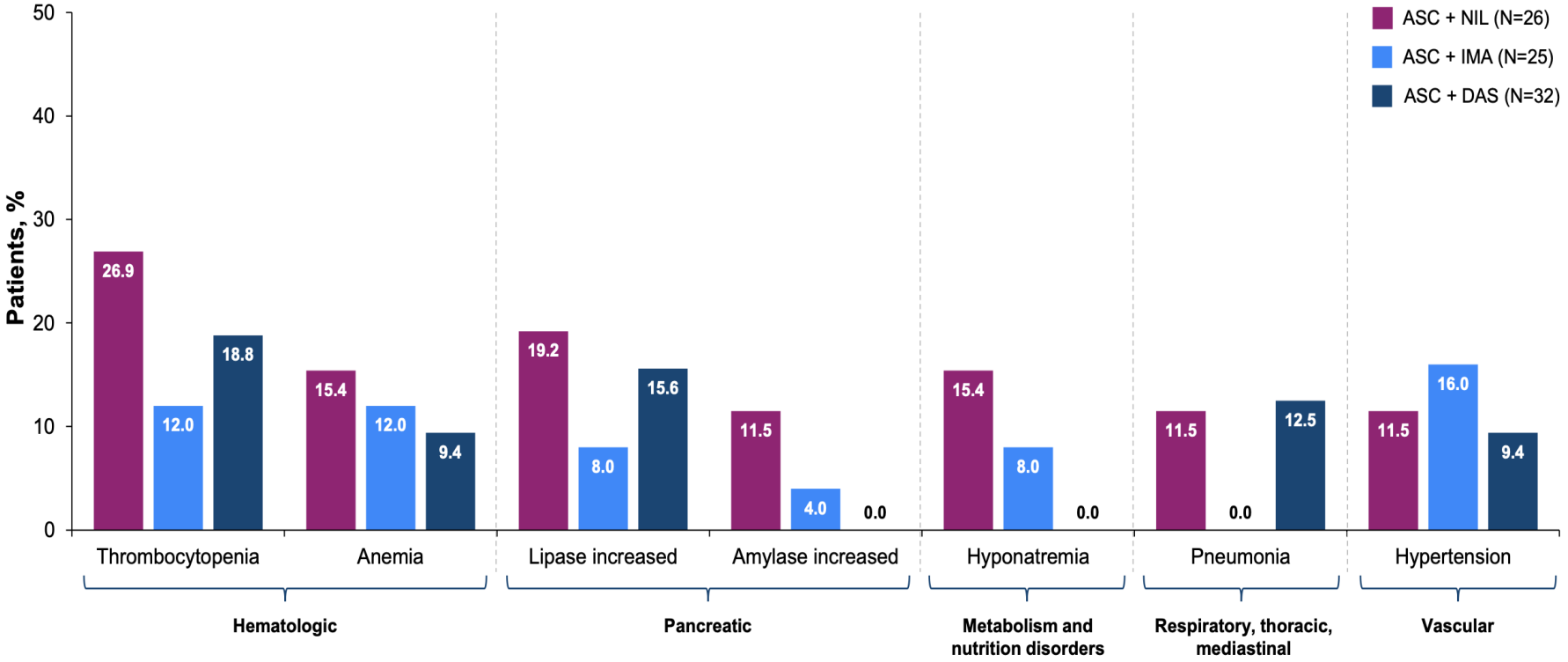
Seguridad

MMR by Time Point in Patients Not in MMR at Screening[a]



Seguridad

Treatment-Emergent Grade ≥3 AEs Occurring in ≥10% of Patients in Any Arm[a]



- Grade 3 AEs were infrequently reported in the **ASC + IMA** arm; thrombocytopenia and lipase increased were the most commonly reported in the **ASC + NIL** (**26.9%** and **19.2%**, respectively) and **ASC + DAS** (**18.8%** and **15.6%**, respectively) arms

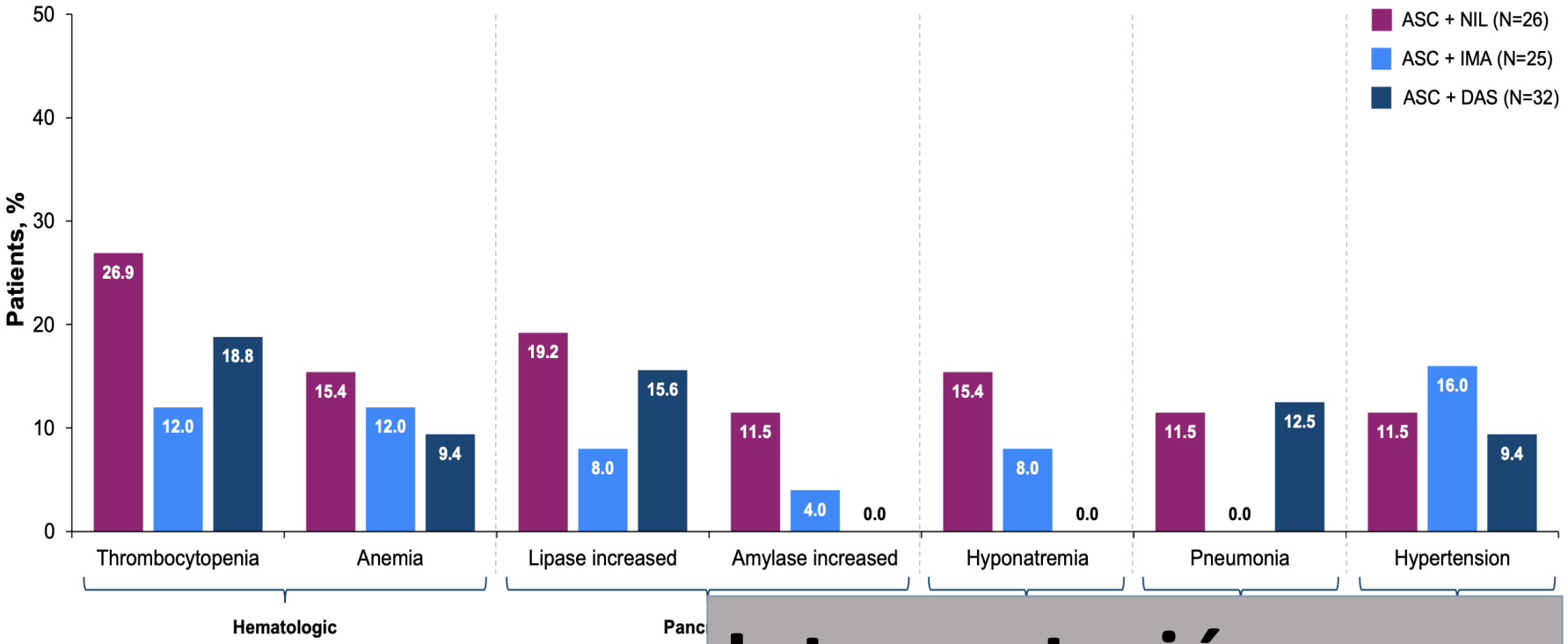
[a] AEs were counted if they occurred after treatment initiation through 30 days after the end of treatment.

Oral presentation at: 65th ASH Annual Meeting & Exposition; December 9-12, 2023; San Diego, California, and virtual.

Cortes J. **Ash 2023.Abstract 868**

Seguridad

Treatment-Emergent Grade ≥3 AEs Occurring in ≥10% of Patients in Any Arm[a]



- Grade 3 AEs were infrequently reported in the ASC + IMA
commonly reported in the ASC + NIL (26.9% and 19.2%,

[a] AEs were counted if they occurred after treatment initiation through 30 days after the end of

Oral presentation at: 65th ASH Annual Meet

Interpretación:

La combinación es segura y eficaz

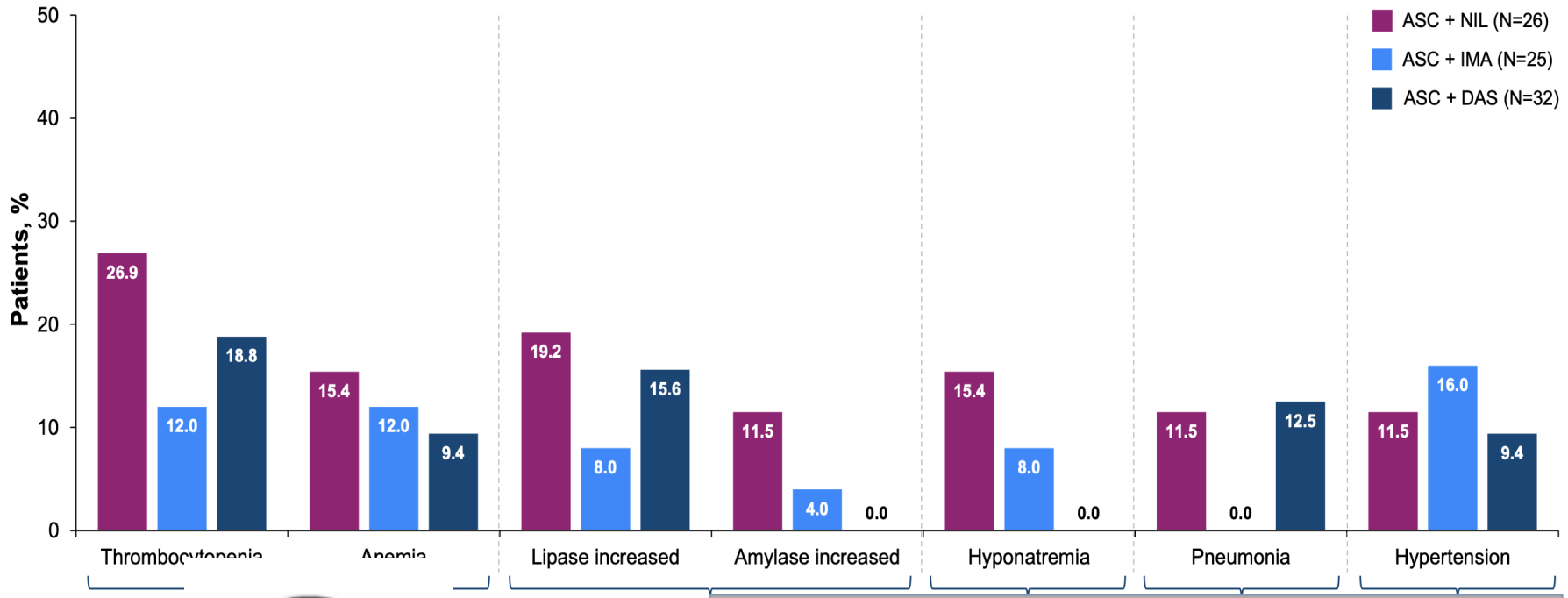
¿Beneficio frente a monoterapia?

¿Qué pacientes se benefician?

Cortes J. Ash 2023.Abstract 868

Seguridad

Treatment-Emergent Grade ≥3 AEs Occurring in ≥10% of Patients in Any Arm[a]



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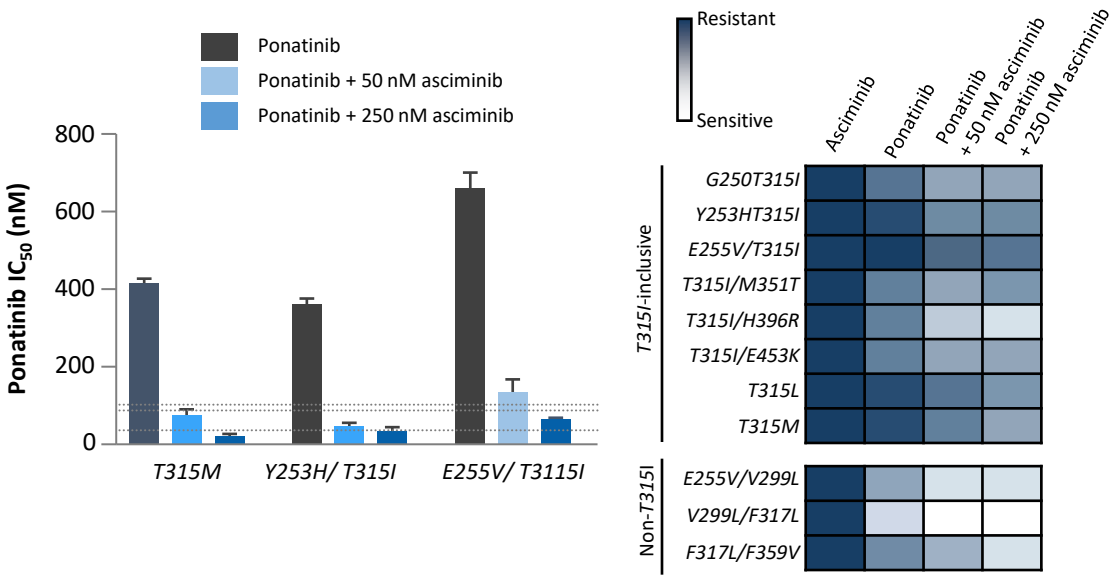
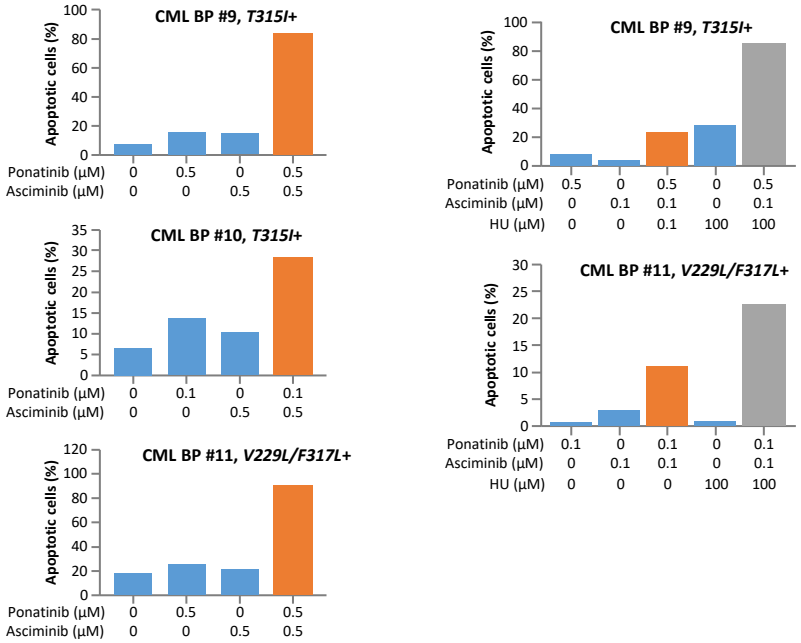
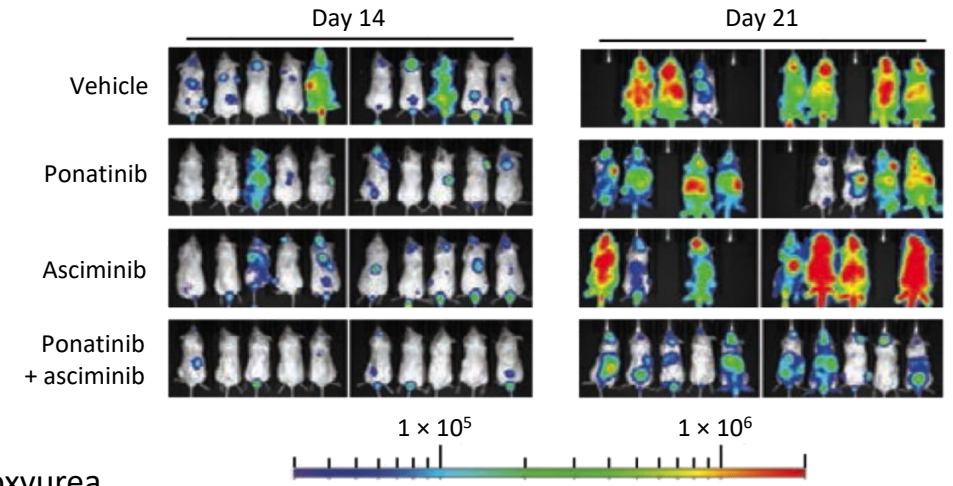
Cortes J. **Ash 2023.Abstract 868**

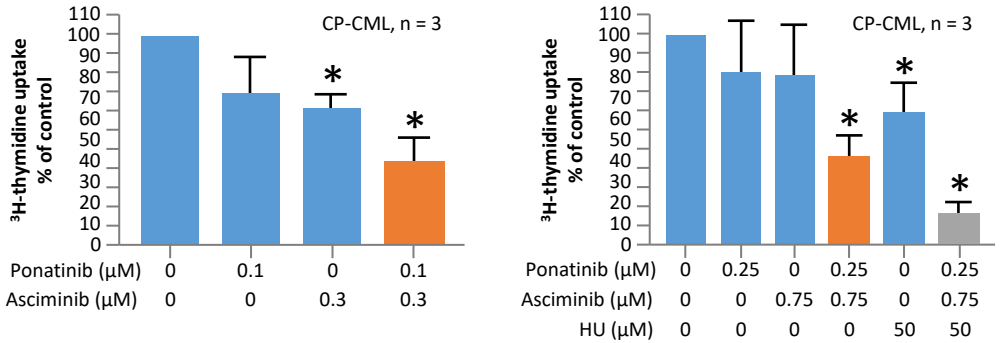
Asciminib–ponatinib combination??







Synergistic effects of asciminib and ponatinib in *BCR::ABL1*^{T315I}+ CML



HU, hydroxyurea.

Eide CA, et al. Cancer Cell. 2019;36:431-3.e5.
Gleixner KV, et al. Am J Cancer Res 2021;11:4470-84.

Conclusiones

- Necesidad de individualización del tratamiento de primera línea. Posicionamiento asciminib?
- La discontinuación de tratamiento es ya un nuevo objetivo en nuestros pacientes con LMC
- Necesidad de identificar el motivo de fracaso terapéutico para la elección de la mejor opción disponible
- Importancia de conocer los efectos secundarios relacionados con cada fármaco para la elección de la mejor opción para cada paciente
- Elección de la mejor dosis para cada inhibidor
- Posicionamiento ponatinib vs asciminib en fracaso a ITC2G
- El futuro pasa por la mejora de la primera línea y posibilidad de combinaciones

Grupo Español de LMC (GELMC)

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