Aspectos Prácticos del Uso de iBTK

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Disclosures

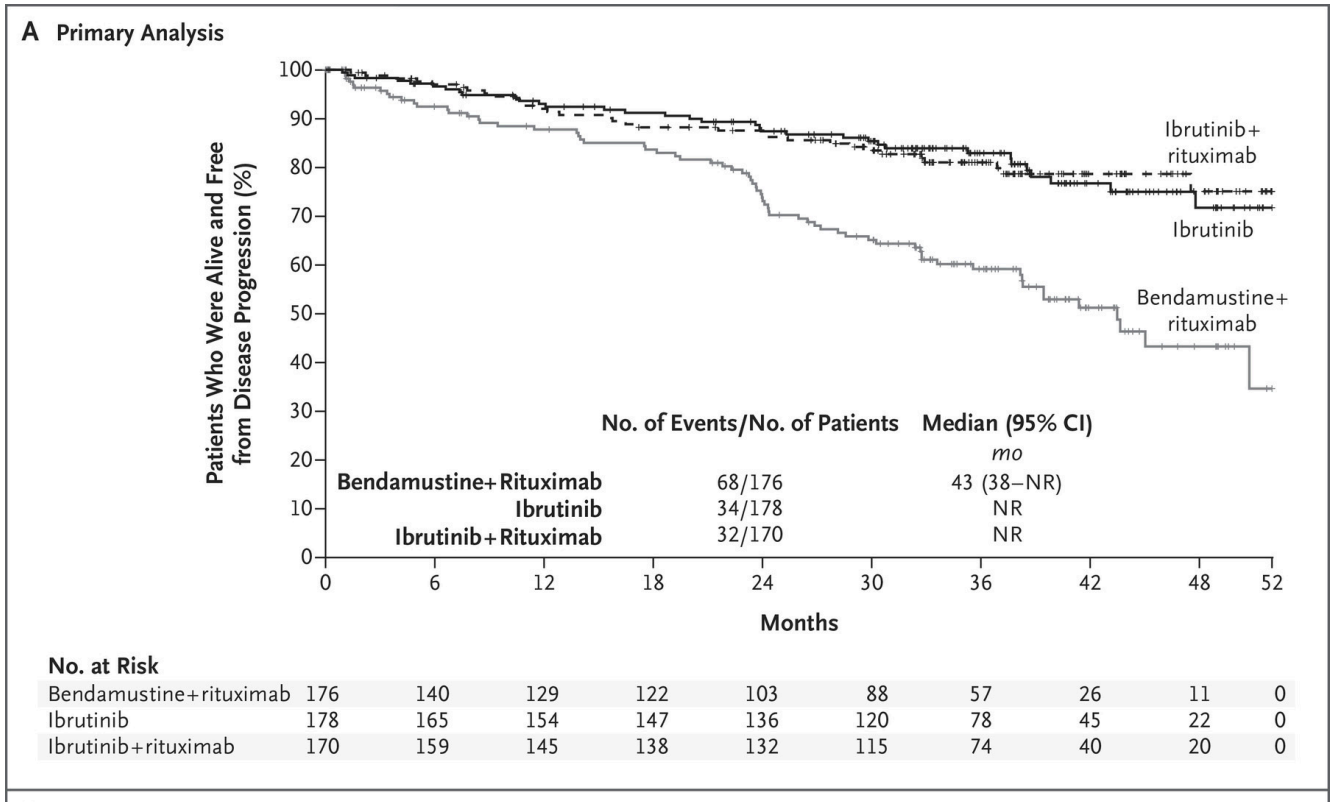
Speaker: Janssen, Roche, Takeda, Abbvie, Astra Zeneca

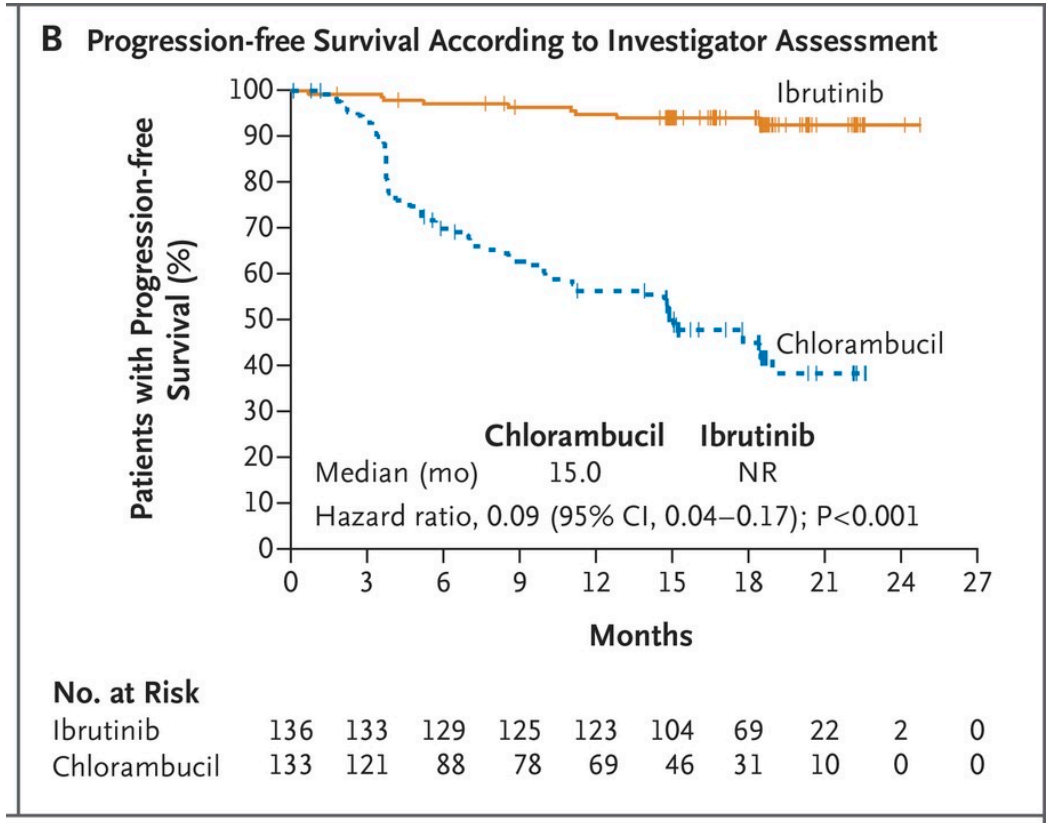
Educacional: Janssen, Takeda, Roche, Abbvie

Advisory Board: Janssen, Abbvie, Astra Zeneca, MSD

Pesquisa: Janssen, Millenium, Merck, Alnylam, Astra Zeneca, MSD, Kartos Therapeutics, Roche

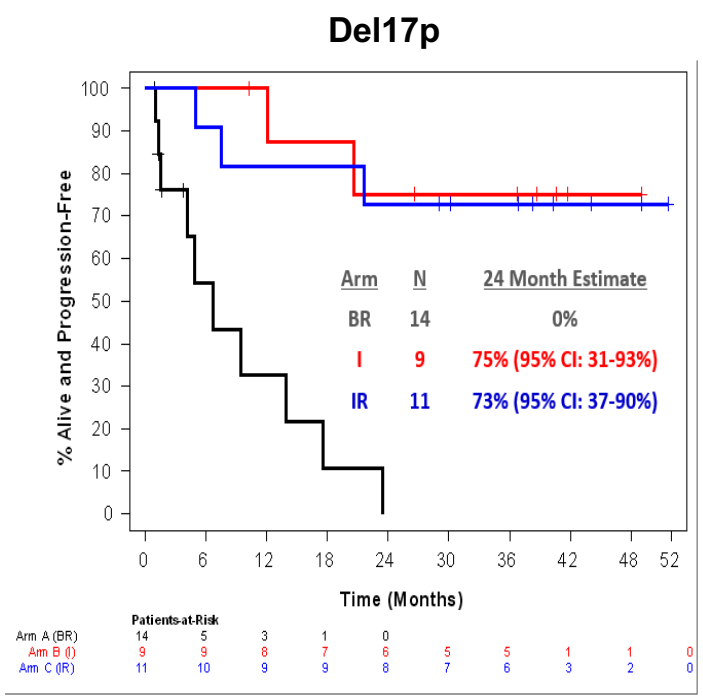
Todos sabemos del impacto de BTKi em LLC

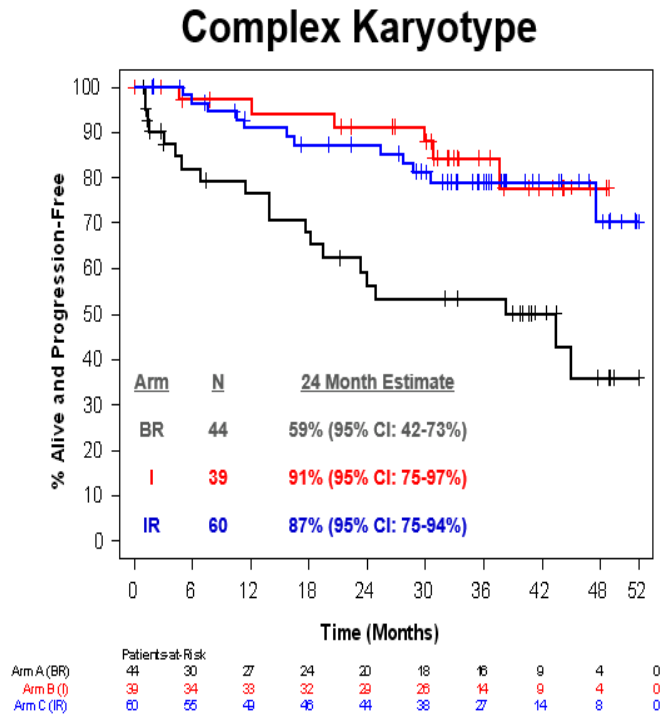


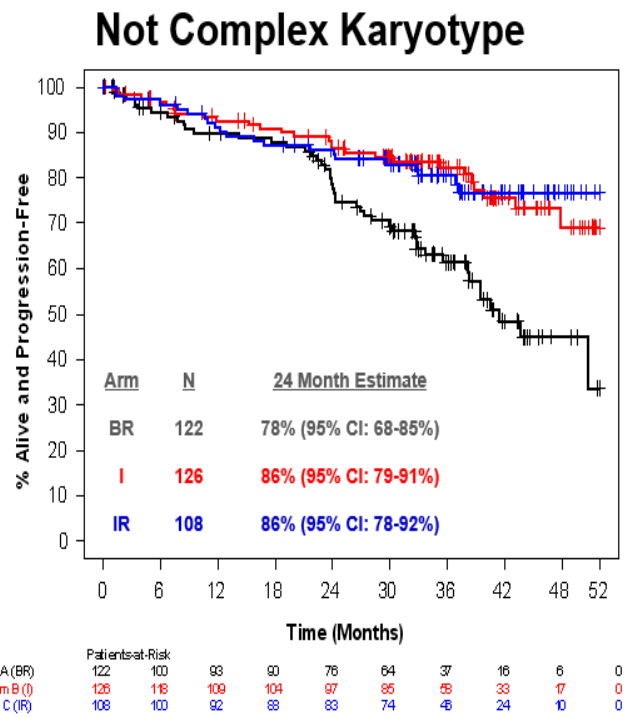


Woyach JA, NEJM 2018; Burger J, NEJM 2015

… especialmente en pacientes de alto riesgo



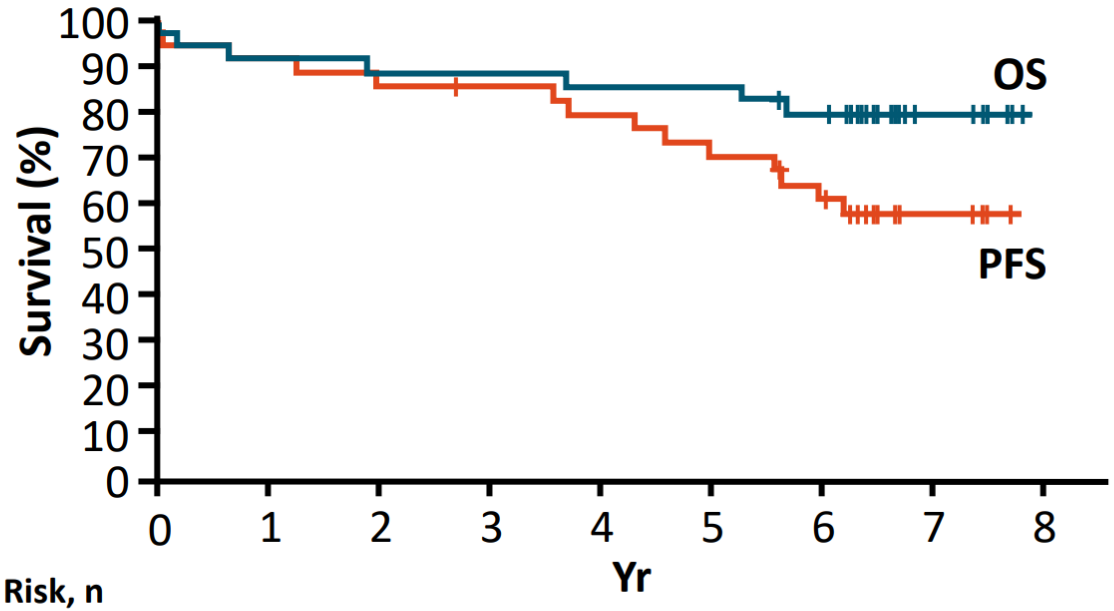




PFS was longer with Ibrutinib-containing regimens than with BR,
Particularly in patients with Del17p, complex and no complex Karyotype

Woyach JA, NEJM 2018

Phase II Trial of First-line Ibrutinib for Patients With CLL and *TP53* Alterations: PFS and OS

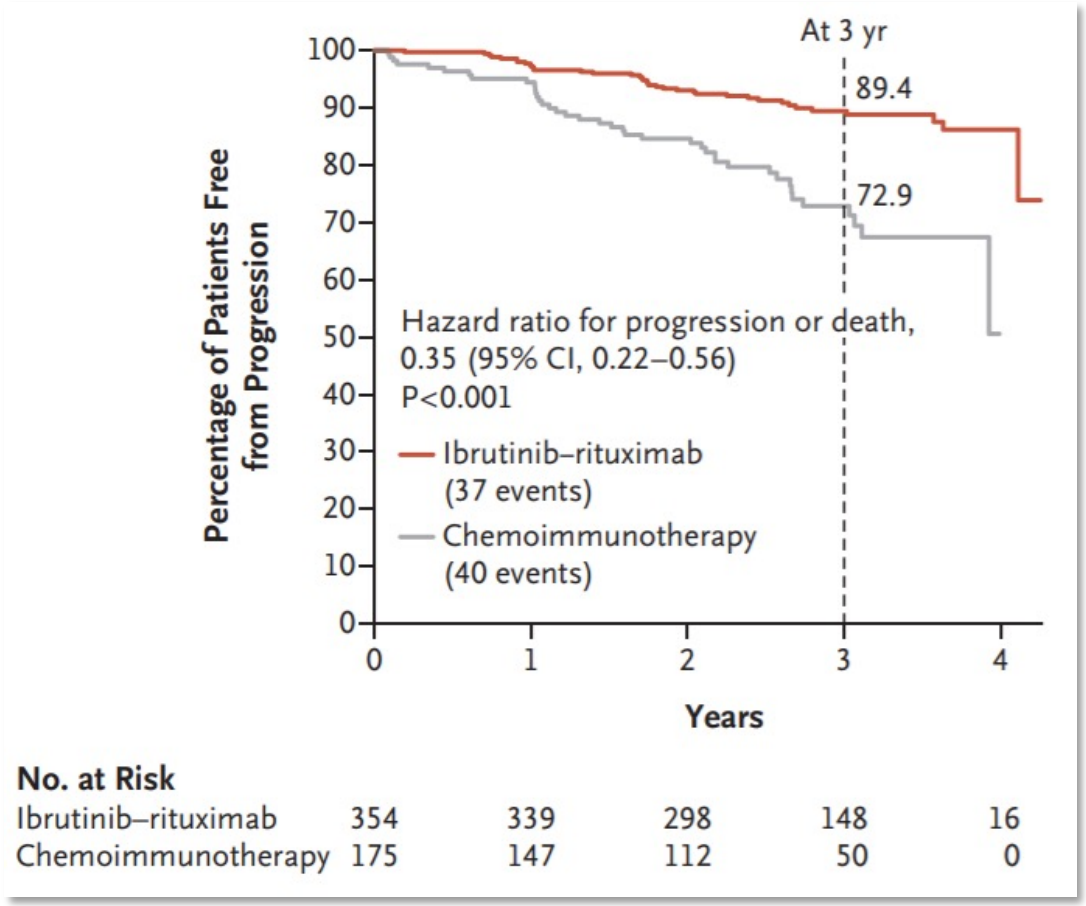


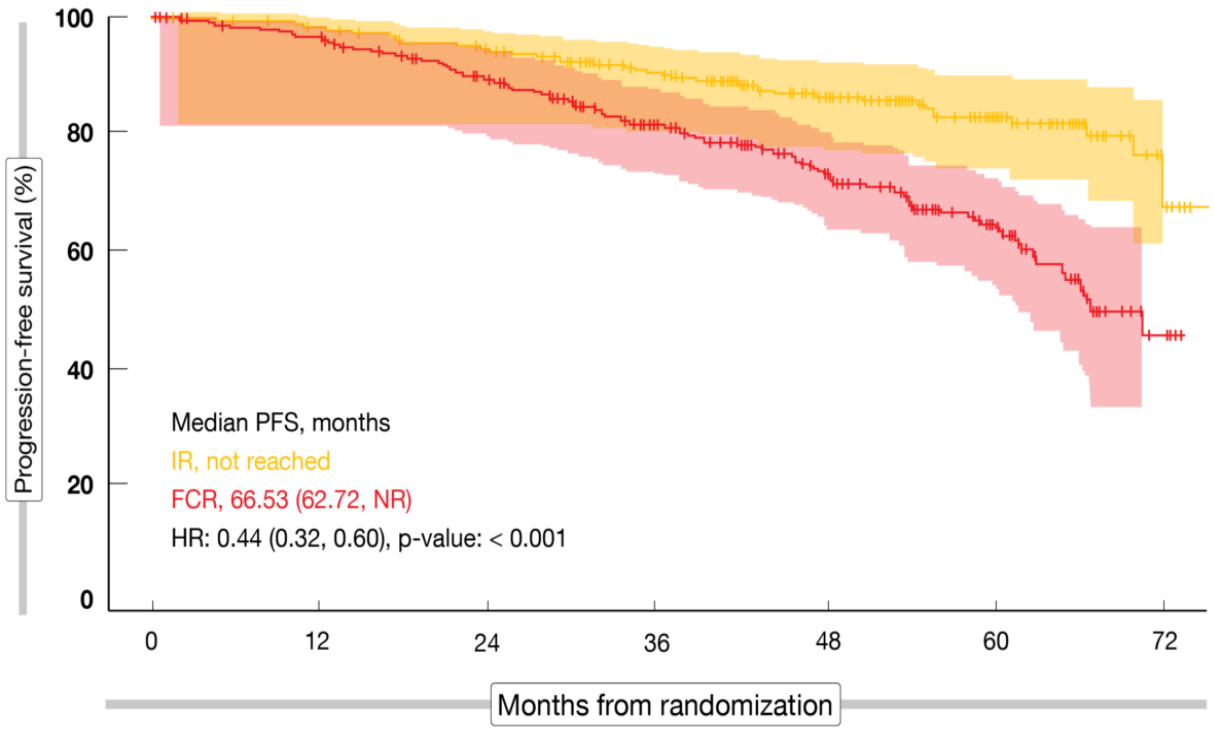
Patients at Risk, n									
OS	34	31	30	30	29	29	26	7	0
PFS	34	31	29	28	26	23	19	6	0

Summary of Survival	2 Yrs	3 Yrs	4 Yrs	5 Yrs	6 Yrs
			% (95% CI)		
OS	88 (78-100)	88 (78-100)	85 (74-98)	85 (74-98)	79 (67-94)
PFS	85 (74-98)	85 (74-98)	79 (67-94)	70 (56-88)	61 (46-80)

Ahn. NEJM. 2020;383:498.

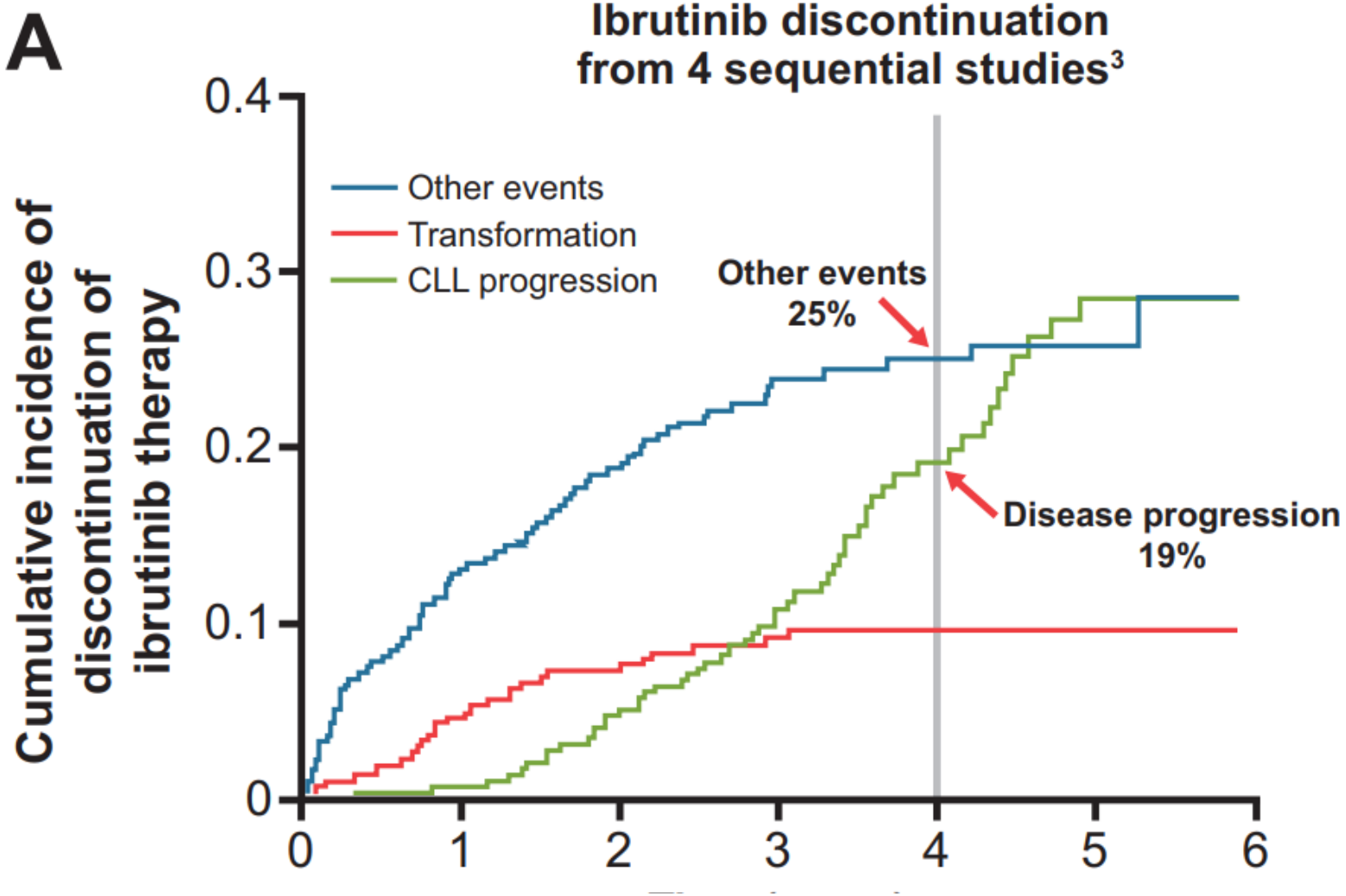
IBTK es superior a FCR em primera línea





Shanafelt , NEJM 2019; Hillmen, ASH 21

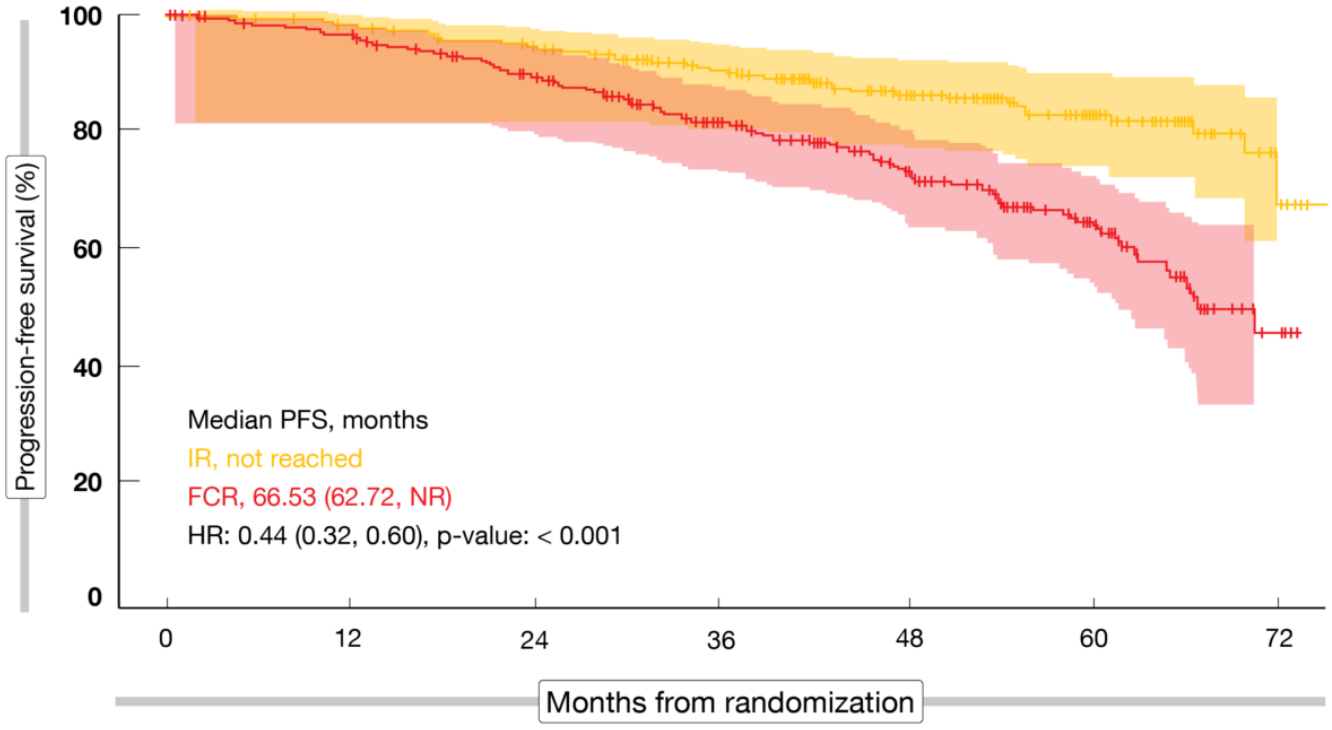
Sin embargo, no es una terapia libre de toxicidad



Mato A, ASH 2021

…Incluso un riesgo cardiovascular

- FLAIR Trial



Cause of death *	FCR (n=29)	IR (n=30)
CLL	4	3
Non-haematological malignancy	4	7
AML/MDS	3	0
ALL	1	0
Richters transformation	3	1
Infections (non-COVID)	6	4
COVID-19	3	3
Haemorrhage	1	2
Cardiac	2	9
Other	2	1
Total	**29**	**30**

Hilmen et al, ASH 2021

Como disminuir el impacto de los iBTK?

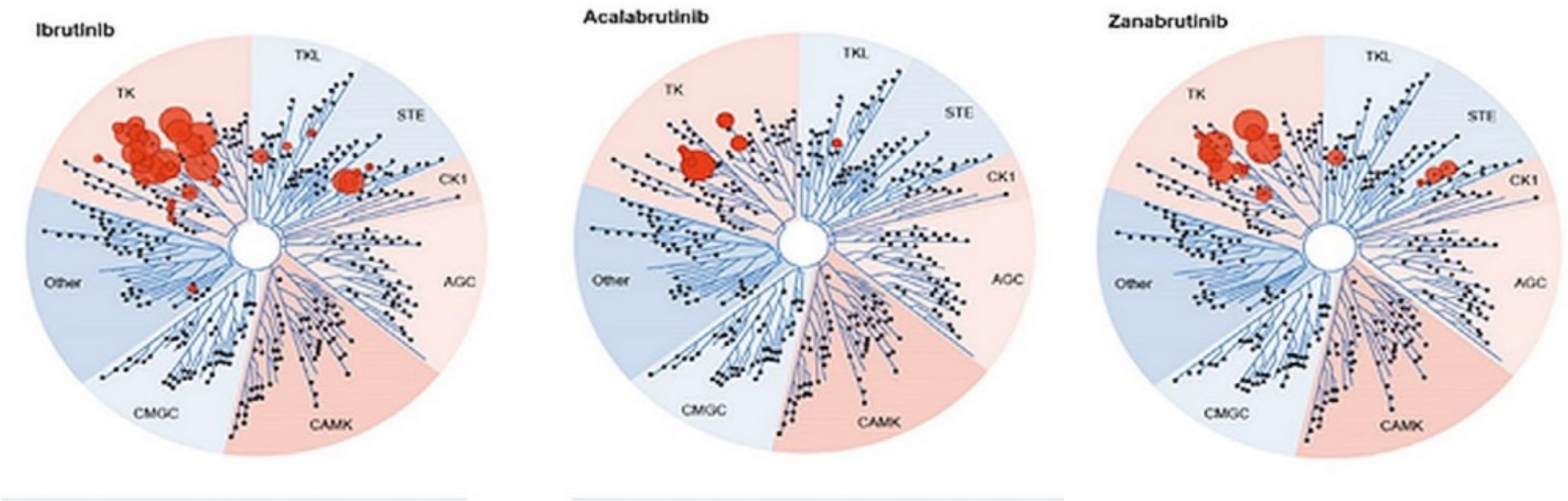
- Inibidores de BTK de 2a generación
  - Como tengo elegido entre Acala e Zanu?

- El impacto de Ibrutinib genérico en nuestra realidad
  - Como evaluar las toxicidades mas importantes?
  - Como manejar las toxicidades?
  - Situaciones especiales

- Como evaluar progression/resistência a los iBTK?

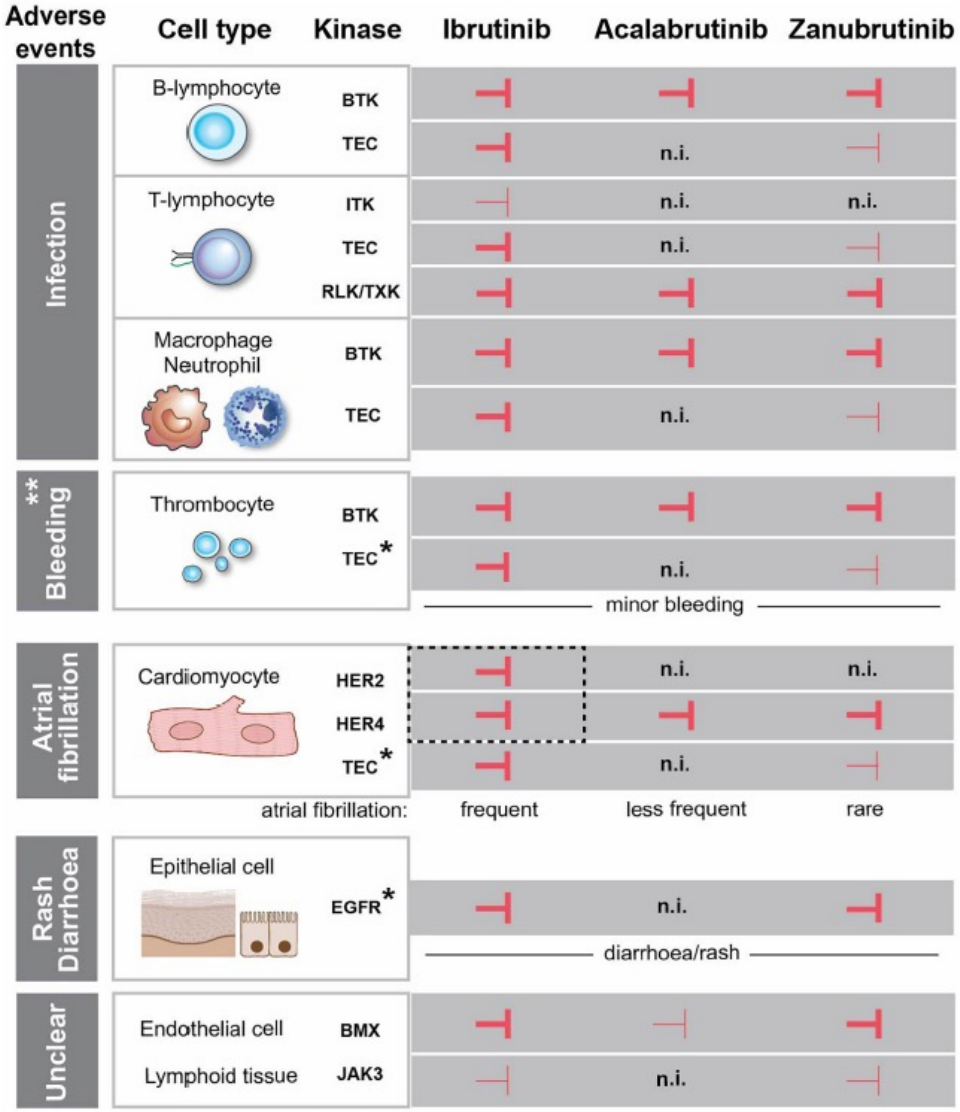
“Everything Good needs replacement”

Satellite, Dave Matthews Band



Banerji V et al, Current Oncol 2020

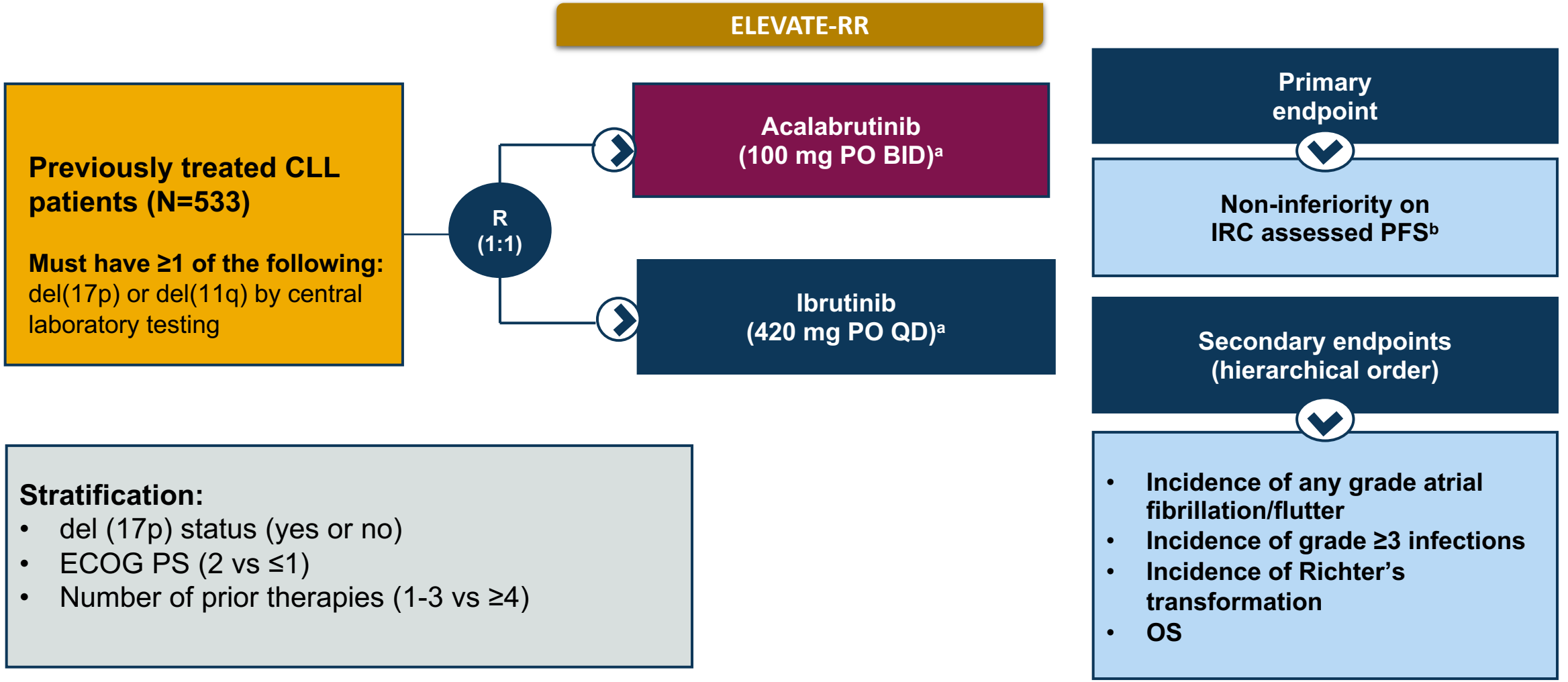
Diferencias entre los iBTK



Muchos dos efectos secundários son relacionados a efectos OFF Target!!

Estupiñan et al, Frontiers in Cel Develop 2021

ELEVATE-RR Study Design

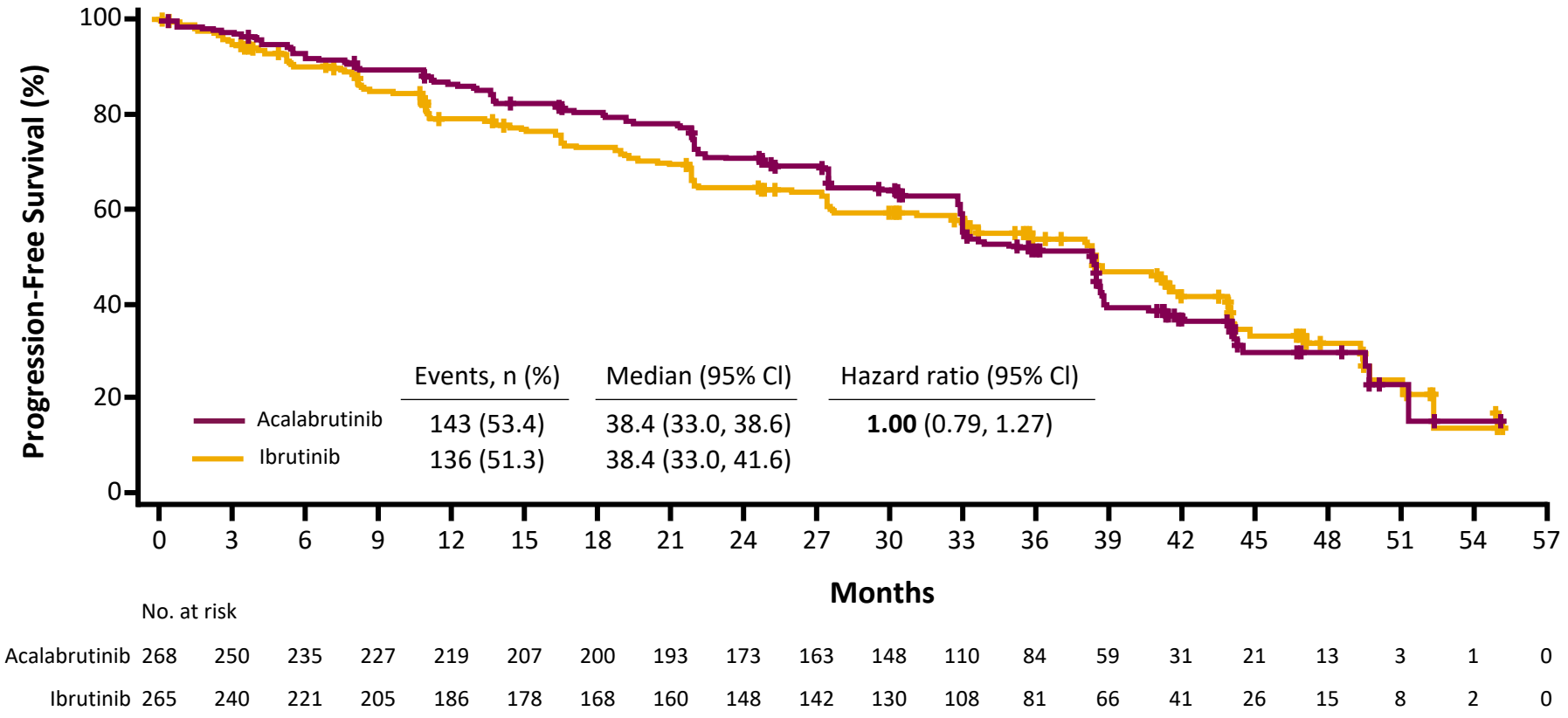


[a]Continued until disease progression or unacceptable toxicity. [b]Conducted after enrollment and accrual of ~250 IRC-assessed PFS events.

1. Byrd JC et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.

Primary Endpoint: Non-inferiority Met on IRC-Assessed PFS

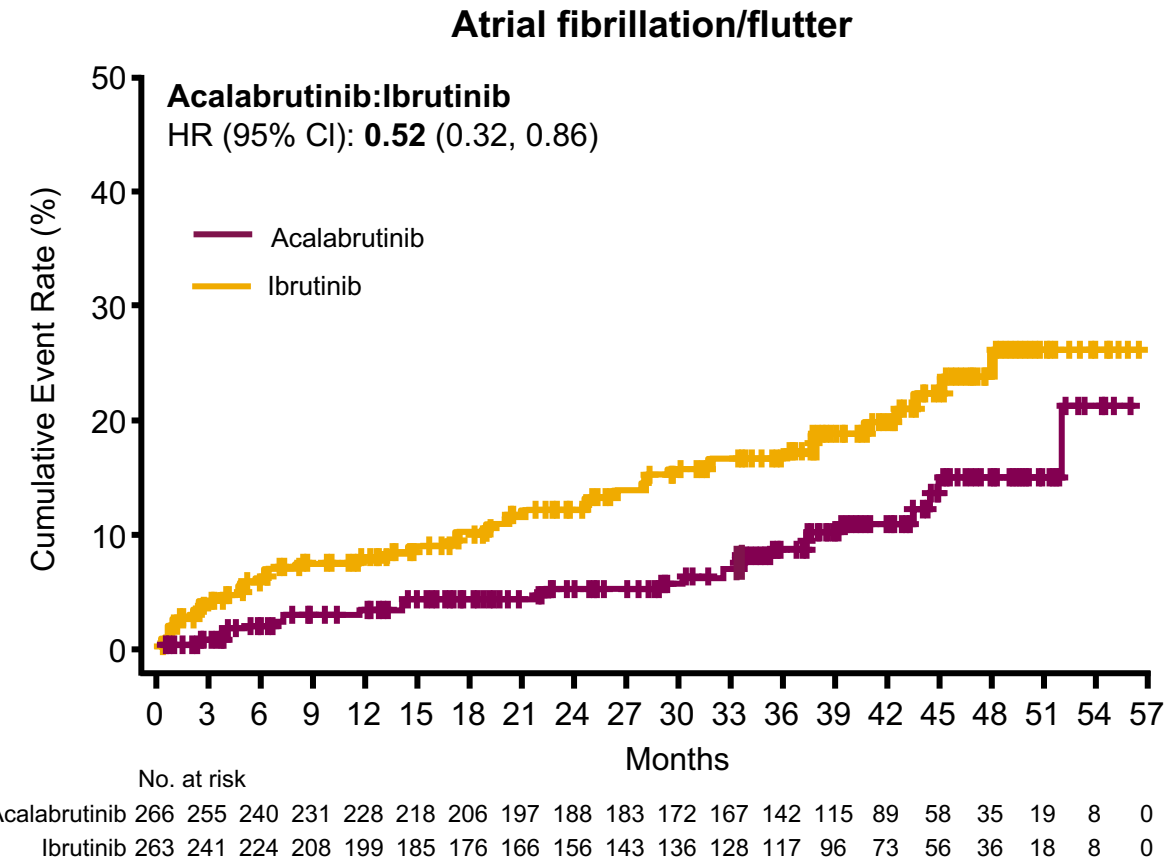
- At a median follow-up of 40.9 months (range 0.0–59.1), acalabrutinib was non-inferior to ibrutinib with a median PFS of 38.4 months in both arms (HR: 1.00; 95% CI 0.79–1.27)

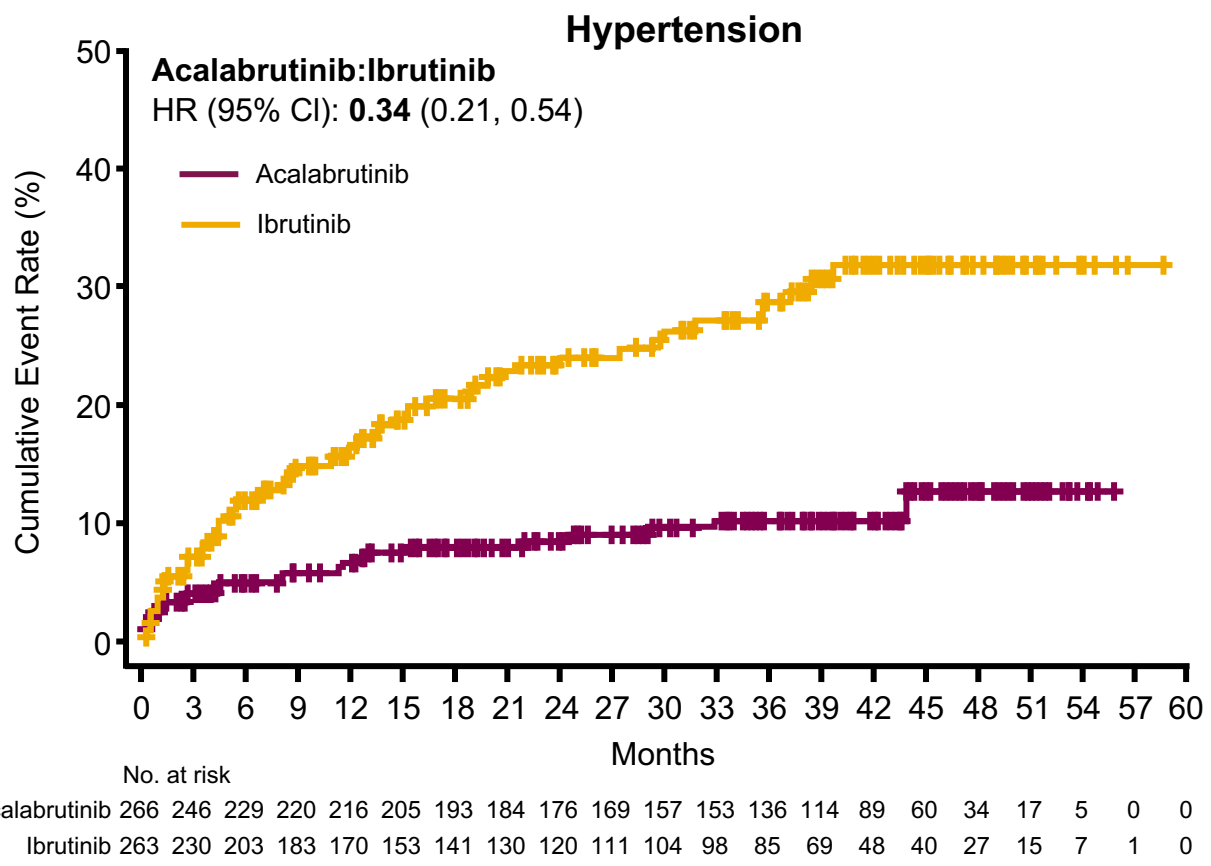


- Byrd JC et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.

Safety: Atrial fibrillation/flutter and Hypertension

- Lower cumulative incidences of any grade atrial fibrillation/flutter and hypertension with acalabrutinib

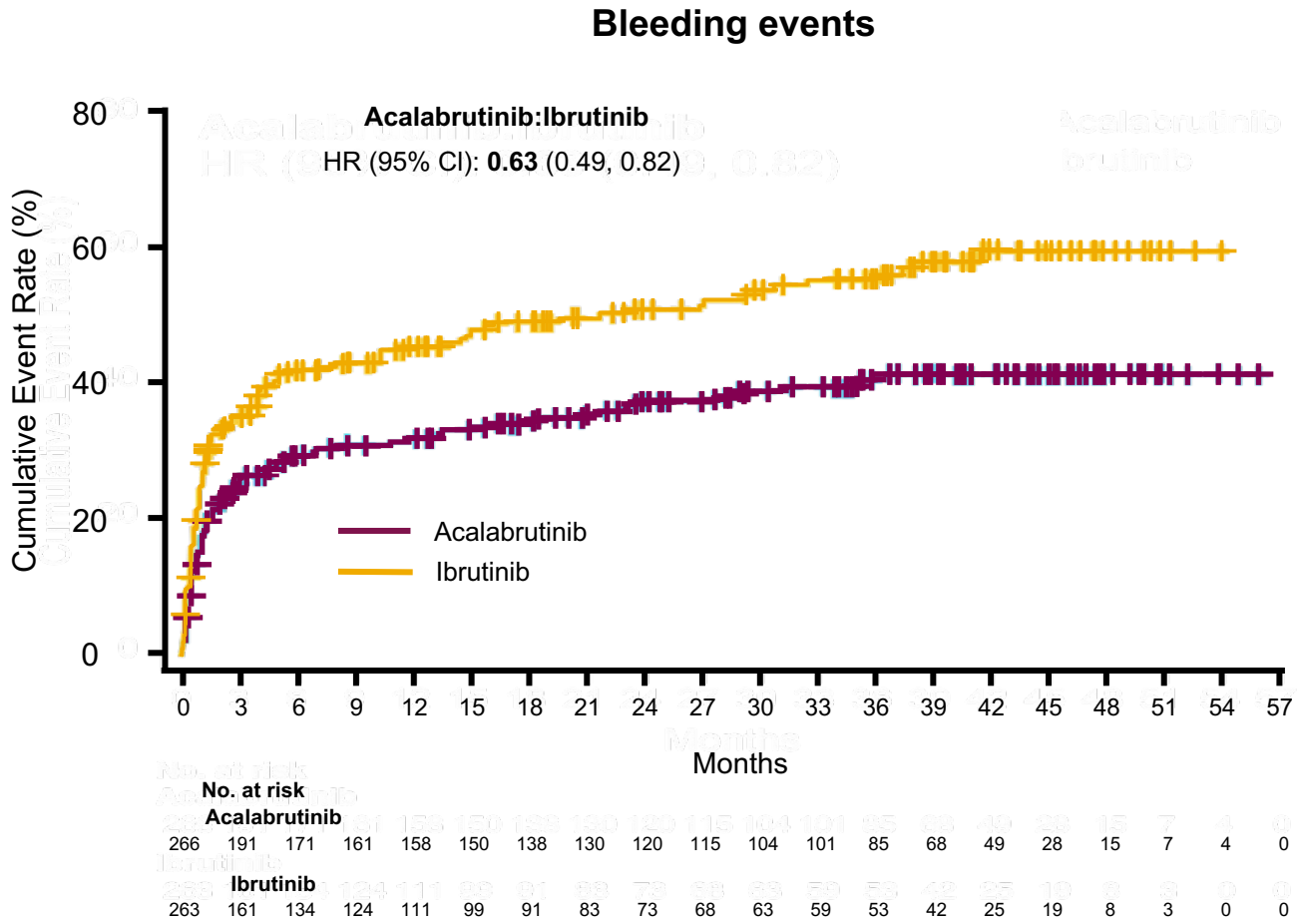




Byrd JC et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.

Safety: Bleeding events

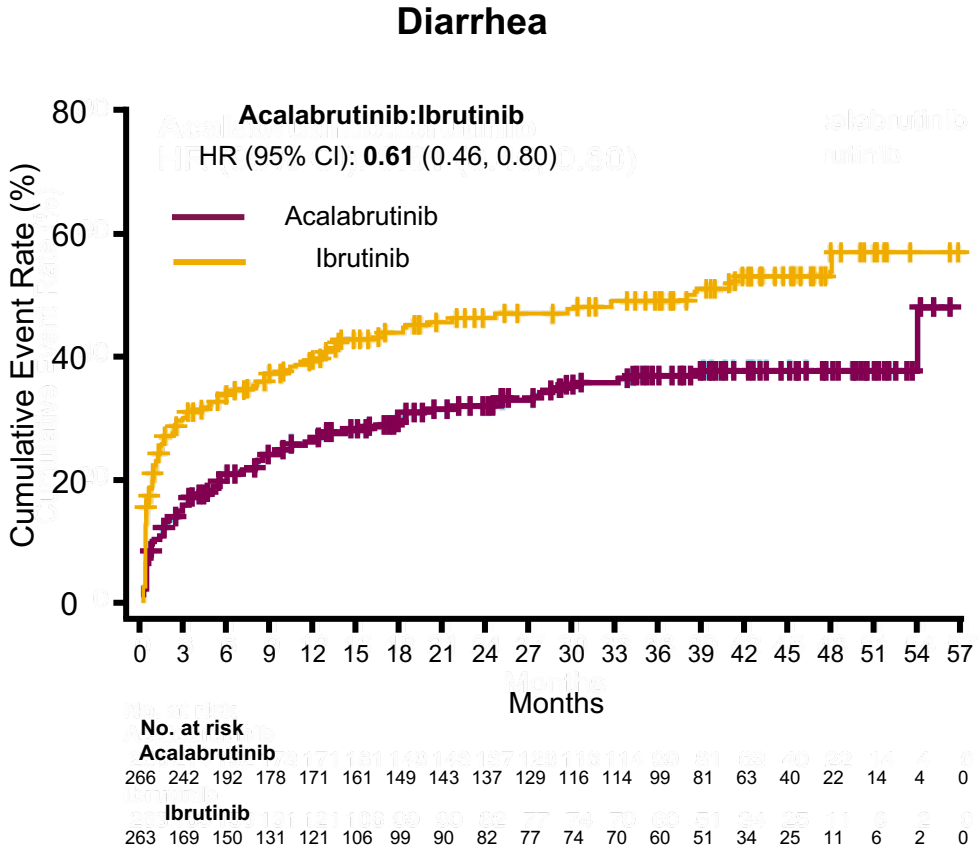
- Lower cumulative incidences of any grade bleeding events with acalabrutinib

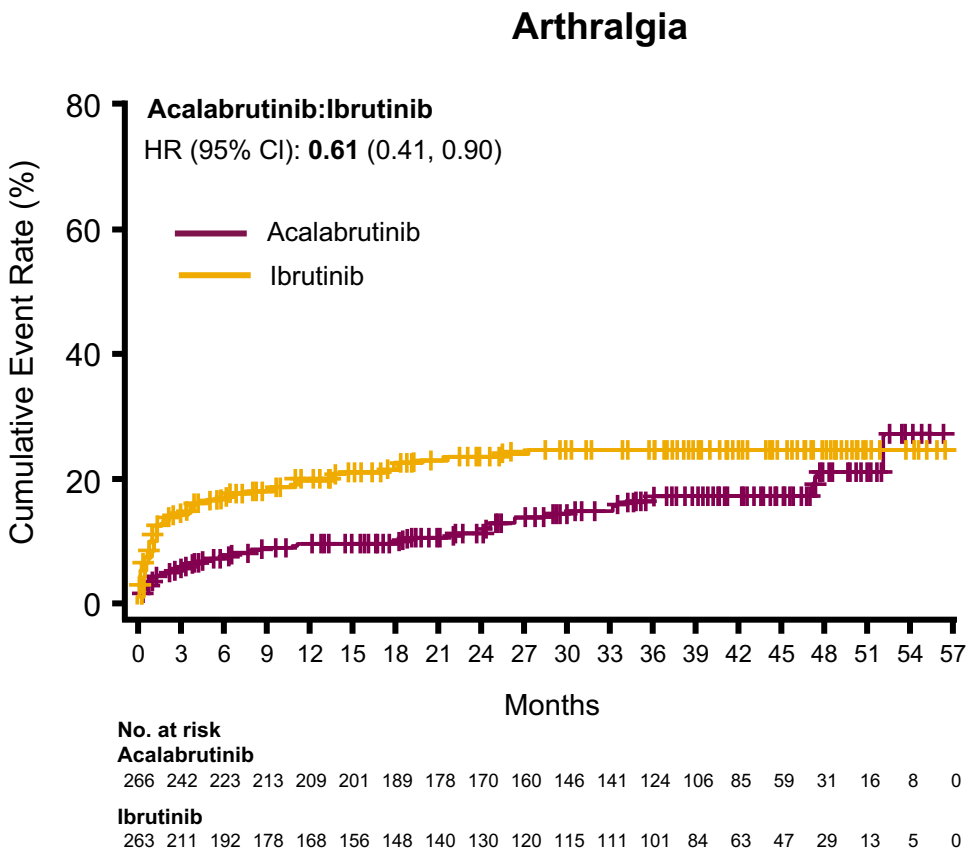


Byrd JC et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.

Safety: Diarrhea and Arthralgia

- Lower cumulative incidences of any grade diarrhea and arthralgia with acalabrutinib





Byrd JC et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

R
1:1

Arm A
Zanubrutinib 160 mg BID

Arm B
Ibrutinib 420 mg QD

Stratification Factors

- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

BID, twice daily; BTK, Bruton tyrosine kinase CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

ALPINE study. Hillmen et al. LB1900 EHA 2021.

EHA2021 VIRTUAL

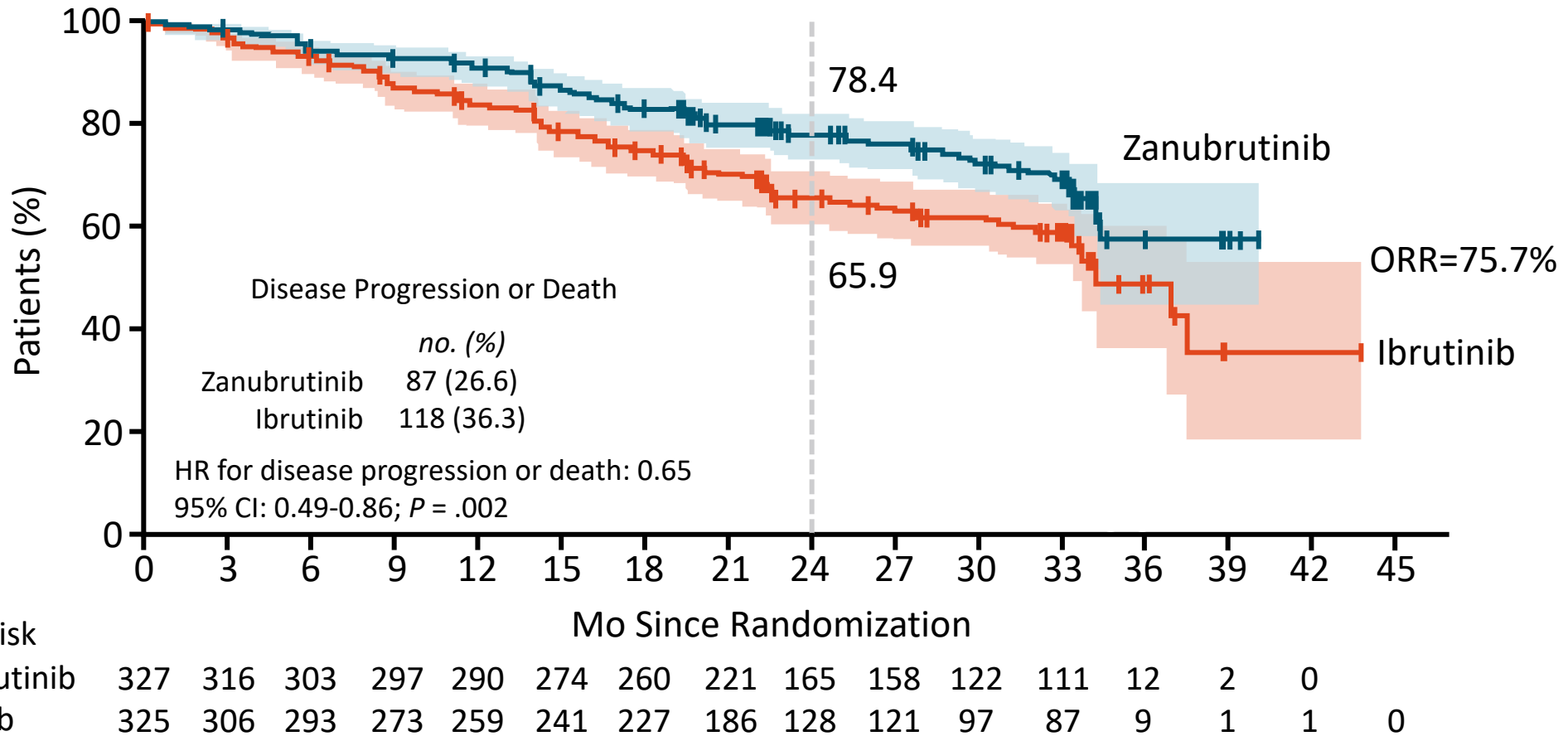
ALPINE: Baseline Characteristics

Characteristic	Zanubrutinib (n = 327)	Ibrutinib (n = 325)
Median age, yr (range)	67 (35-90)	68 (35-89)
▪ ≥65 yr, n (%)	201 (61.5)	200 (61.5)
Male sex, n (%)	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Median prior lines of systemic therapy, n (range)	1 (1-6)	1 (1-12)
▪ >3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%)	75 (22.9)	75 (23.1)
▪ del(17p) with or without *TP53*^{mut}	45 (13.8)	50 (15.4)
▪ *TP53*^{mut} without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	91 (27.8)	88 (27.1)
IGHV mutational status, n (%)		
▪ Mutated	79 (24.2)	70 (21.5)
▪ Unmutated	239 (73.1)	239 (73.5)
Complex karyotype, n (%)*	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

*≥3 abnormalities.

Brown. ASH 2022. Abstr LBA-6. Brown. NEJM. 2022;[Epub].

ALPINE: Investigator-Assessed PFS in ITT Population

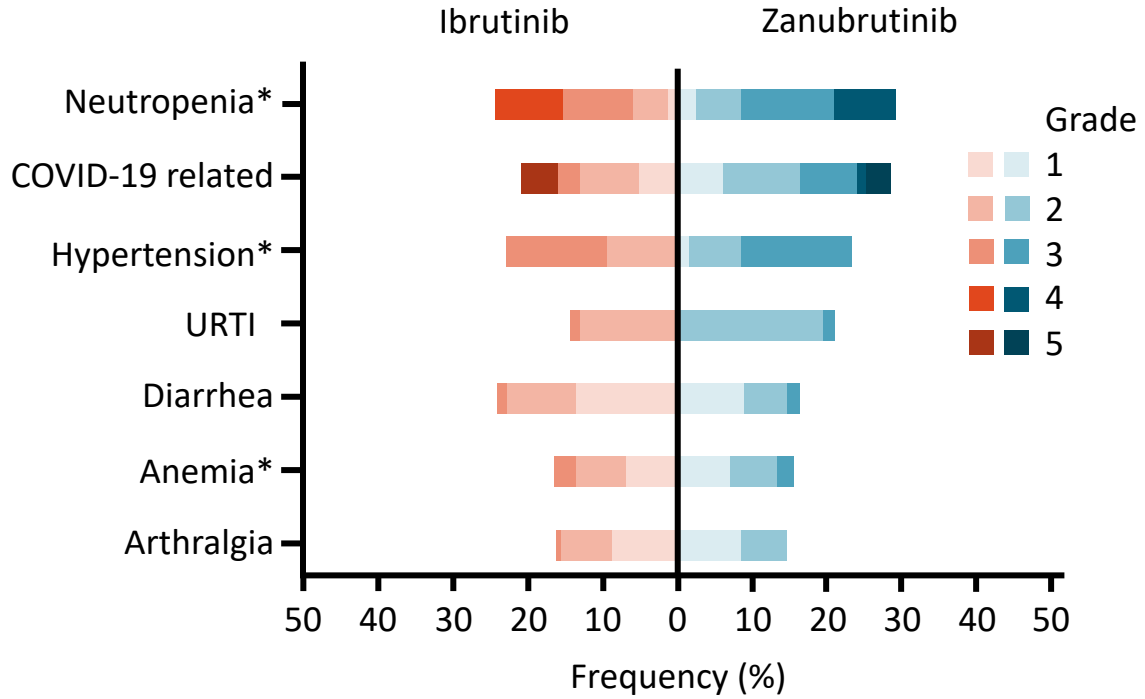


Brown. ASH 2022. Abstr LBA-6. Brown. NEJM. 2022;[Epub].

ALPINE: Overall Safety and Most Common AEs

Event	Zanubrutinib (n = 324)	Ibrutinib (n = 324)
Median treatment duration, mo	28.4	24.3
Any-grade AE, n (%) ▪ Grade ≥3 ▪ Grade 5	318 (98.1) 218 (67.3) 33 (10.2)	321 (99.1) 228 (70.4) 36 (11.1)
SAE, n (%)	136 (42.0)	162 (50.0)
AE leading to the following, n (%) ▪ Dose reduction ▪ Dose interruption ▪ Treatment discontinuation	40 (12.3) 162 (50.0) 50 (15.4)	55 (17.0) 184 (56.8) 72 (22.2)

Most Common AEs (Occurring in ≥15% of Patients)



*Pooled terms.

Brown. ASH 2022. Abstr LBA-6. Reproduced with permission. Brown. NEJM. 2022;[Epub].

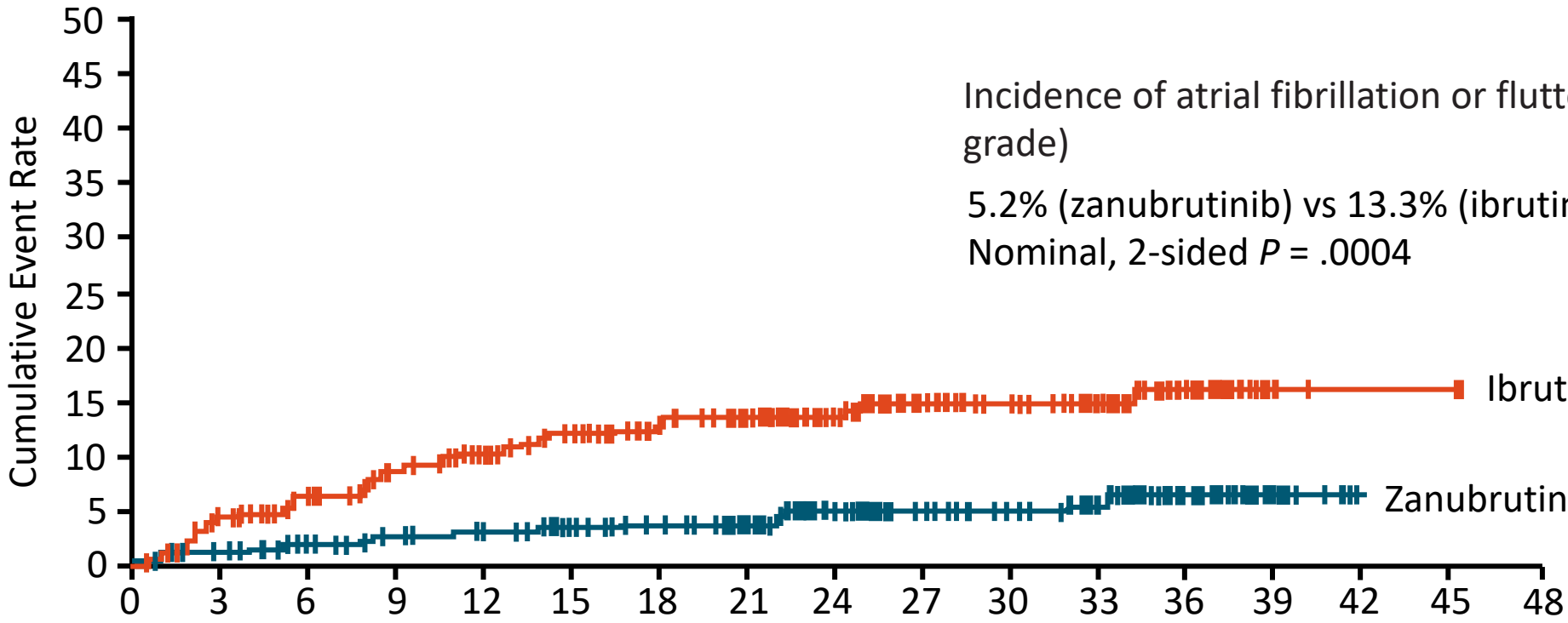
ALPINE: Cardiac Events

Event, n (%)	Zanubrutinib (n = 324)	Ibrutinib (n = 324)
Cardiac AEs	69 (21.3)	96 (29.6)
Serious cardiac AEs*	6 (1.9)	25 (7.7)
Fatal cardiac events	0	6 (1.9)
Cardiac AEs leading to treatment discontinuation	1 (0.3)	14 (4.3)
▪ Ventricular extrasystoles	1 (0.3)	0
▪ Atrial fibrillation	0	5 (1.5)
▪ Cardiac arrest	0	2 (0.6)†
▪ Cardiac failure	0	2 (0.6)
▪ Cardiac failure acute	0	1 (0.3)†
▪ Congestive cardiomyopathy	0	1 (0.3)†
▪ Myocardial infarction	0	1 (0.3)†
▪ Palpitations	0	1 (0.3)
▪ Ventricular fibrillation	0	1 (0.3)

*Atrial fibrillation/flutter, n = 2; MI/ACS, n = 2; CHF, n = 2.

†Cardiac deaths. One death not listed due to MI with ibrutinib discontinuation due to diarrhea 14 days prior to fatal event.

ALPINE: Atrial Fibrillation/Flutter



Incidence of atrial fibrillation or flutter (any grade)

5.2% (zanubrutinib) vs 13.3% (ibrutinib)
Nominal, 2-sided *P* = .0004

No. at risk																	
Zanubrutinib	324	312	302	294	288	277	268	249	199	164	148	120	51	10	0		
Ibrutinib	324	295	278	260	247	230	211	193	153	121	108	89	40	3	2	1	0

Brown. ASH 2022. Abstr LBA-6. Reproduced with permission.

Slide credit: clinicaloptions.com

¿Que nos ensina Elevate-RR e Alpine?

- Acala e Zanu son mas tolerables que Ibrutinib
  - Zanu es superior?
  - En Brasil, Acalabrutinib es hoy el BTK más barato e como consecuencia, mi BTK de elección **en LLC**

- Sin Embargo, tengo muchos pacientes en uso de Ibrutinib que se quedan bien
  - O que hacer con estos pacientes?
  - Generalmente, NADA. Pero hay excepciones…

Intolerancia a los iBTK

- Red Light:
  - Arritmias
  - Hipertención Arterial grave
  - Desmayos, síncope, etc

Cambiar inmediatamente el BTK para 2a generacion
Interrumpir BTKi de 2a Generacion e considerar otra terapia

- Yellow Light:
  - Bleeding
  - Toda otra toxicidad Grado 3

Cambiar el BTK para 2a generacion
Suspender temporariamente el iBTK

- Green Light:
  - Diarrea
  - Artritis e Artralgias

Considerar cambiar el BTK para 2a generacion
Disminiur la dosis de iBTK
Go MacGyver

ACE-CL-001 – Coorte LLC Intolerante a Ibrutinibe

Coorte LLC Intolerante a Ibrutinibe[a]

Critérios de Inclusão

- LLC confirmada e intolerância a Ibrutinibe determinada pelo Investigador[b]
- ≥18 anos
- ECOG PS ≤2

n=33

→

Acalabrutinibe
100mg via oral 2x/d em ciclos de 28 dias até doença progressiva ou toxicidade inaceitável

Desfecho Primário:

- Segurança, incluindo frequência e gravidade de EAs

Critérios de Exclusão:

- Envolvimento de SNC
- Doença cardiovascular significativa[c]

Desfechos Secundários:

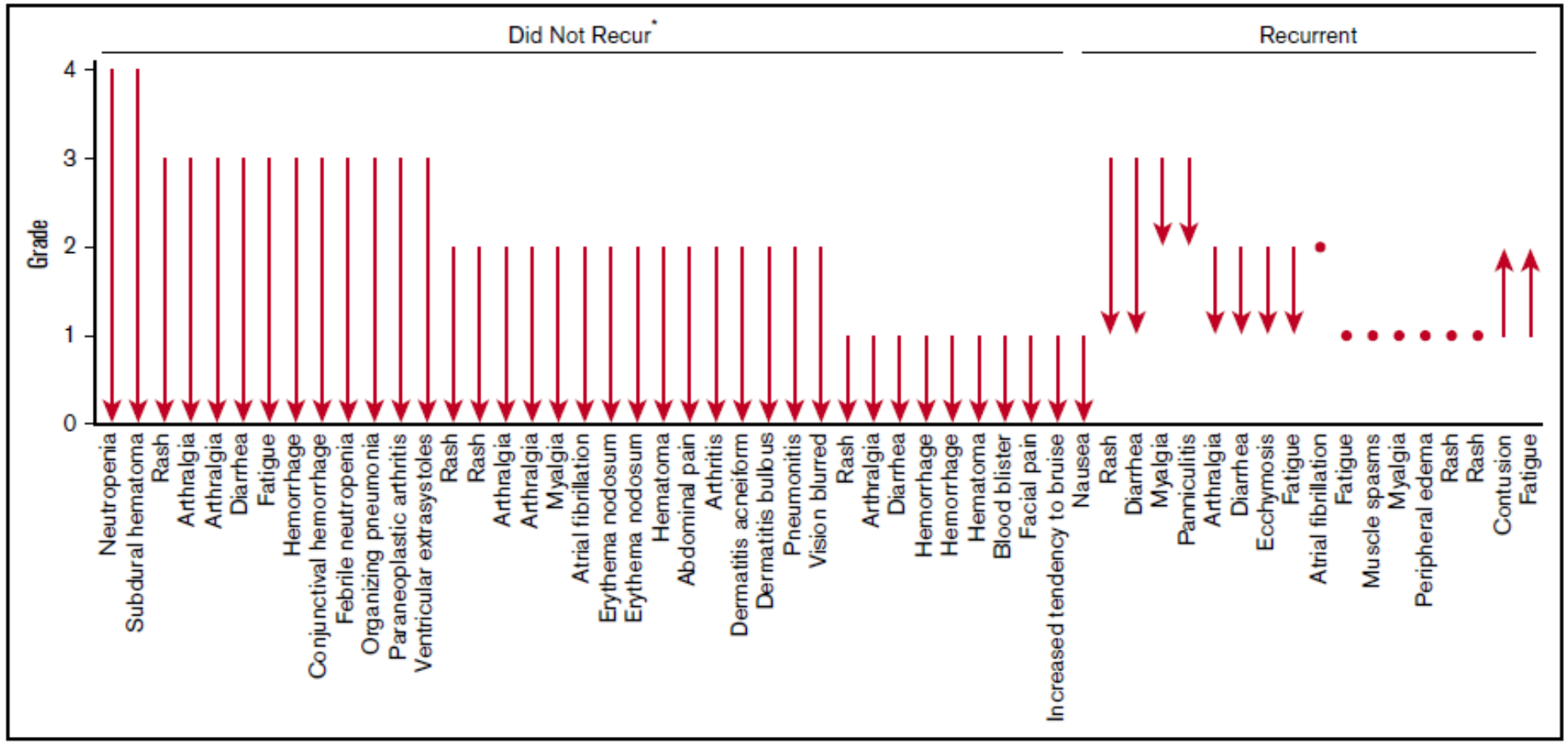
- TRO, DoR, SLP

Seguimento mediano = 19 meses

[a]Inclui 200 mg ao dia (n=3) e 100 mg 2x/d (n=30); [b]Não houve grau de EA predefinido como corte; pacientes não precisavam estar em progressão para iniciar Acalabrutinibe; [c]Inclui arritmia não controlada ou sintomática, insuficiencia cardíaca congestiva, infarto agudo do miocárdio ou qualquer grau de doença cardíaca classe 3 ou 4 pela classificação funcional da NYHA, ou fração de ejeção do ventrículo esquerdo ≤40% até 6 meses do screening.
DoR, duração de resposta; EAs, eventos adversos; ECOG PS = Eastern Cooperative Oncology Group performance status; LLC, leukemia linfocítica crônica; SLP, sobrevida livre de progressão; TRO, taxa de resposta objetiva

Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. *Blood Adv*. 2019;3(9):1553-1562.

Mejora de los EAs con Acalabrutinibe

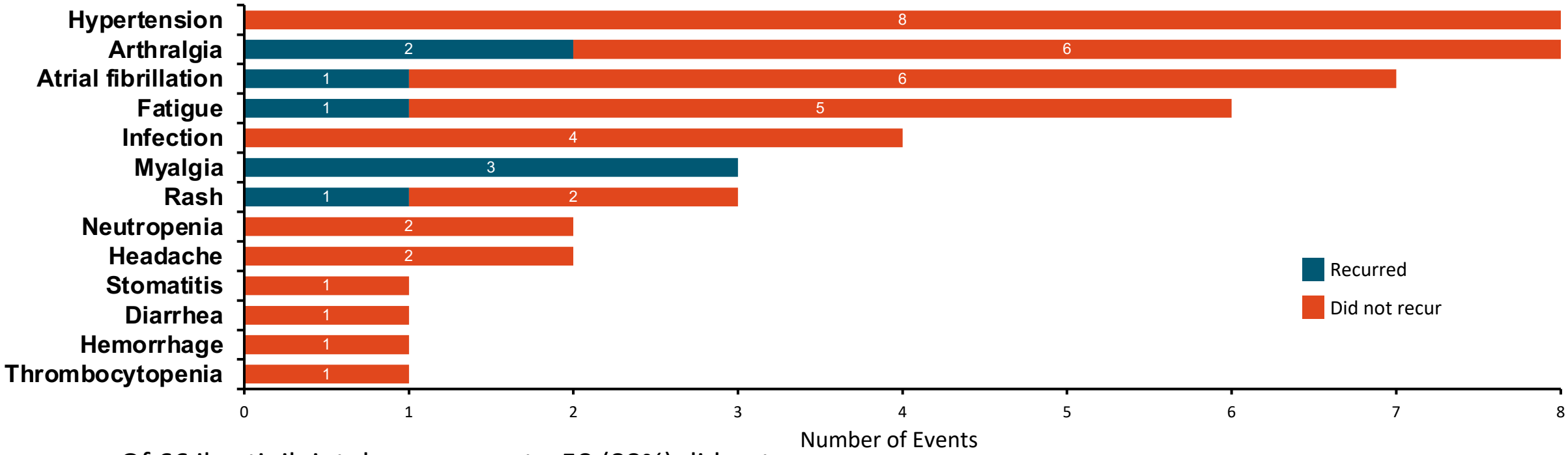


6 eventos de grau desconhecido não recorreram com Acalabrutinibe (rash, diarreia, hemorragia, redução de apetite, dispneia, aumento de peso

Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. Blood Advances 2019;3(9):1553-1562.

Zanubrutinib Efficacy in the Setting of Previous BTK Inhibitor Intolerance

Recurrence and Severity Change From Previous BTK Inhibitor Exposure to Zanubrutinib Exposure (N = 60)

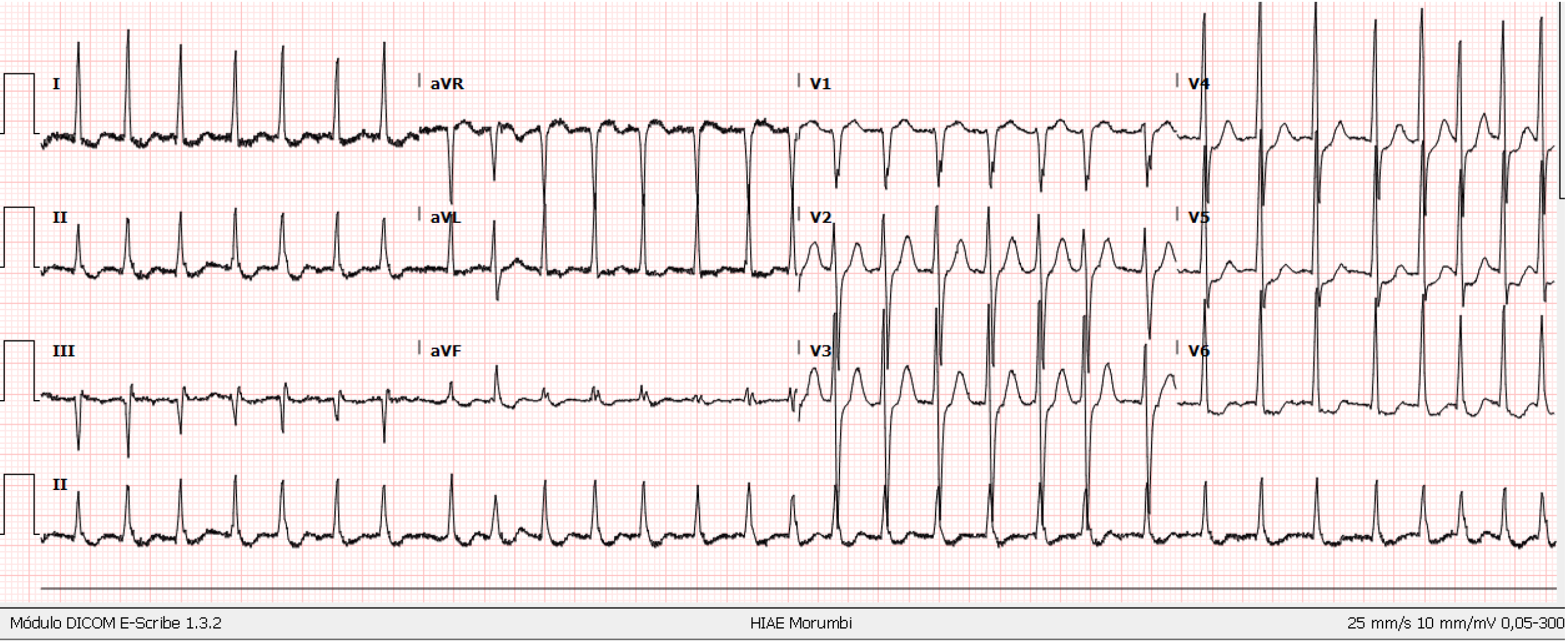


- Of 66 ibrutinib intolerance events, 58 (88%) did not recur
- Of the 4 acalabrutinib-intolerant events, 2 (50%) events of arthralgia did not recur, and 2 (50%) events of myalgia (1 at same and 1 lower grade) recurred

Shadman. ASH 2020. Abstr 2947.

Slide credit: clinicaloptions.com

No todos van ser tan claros como esto...

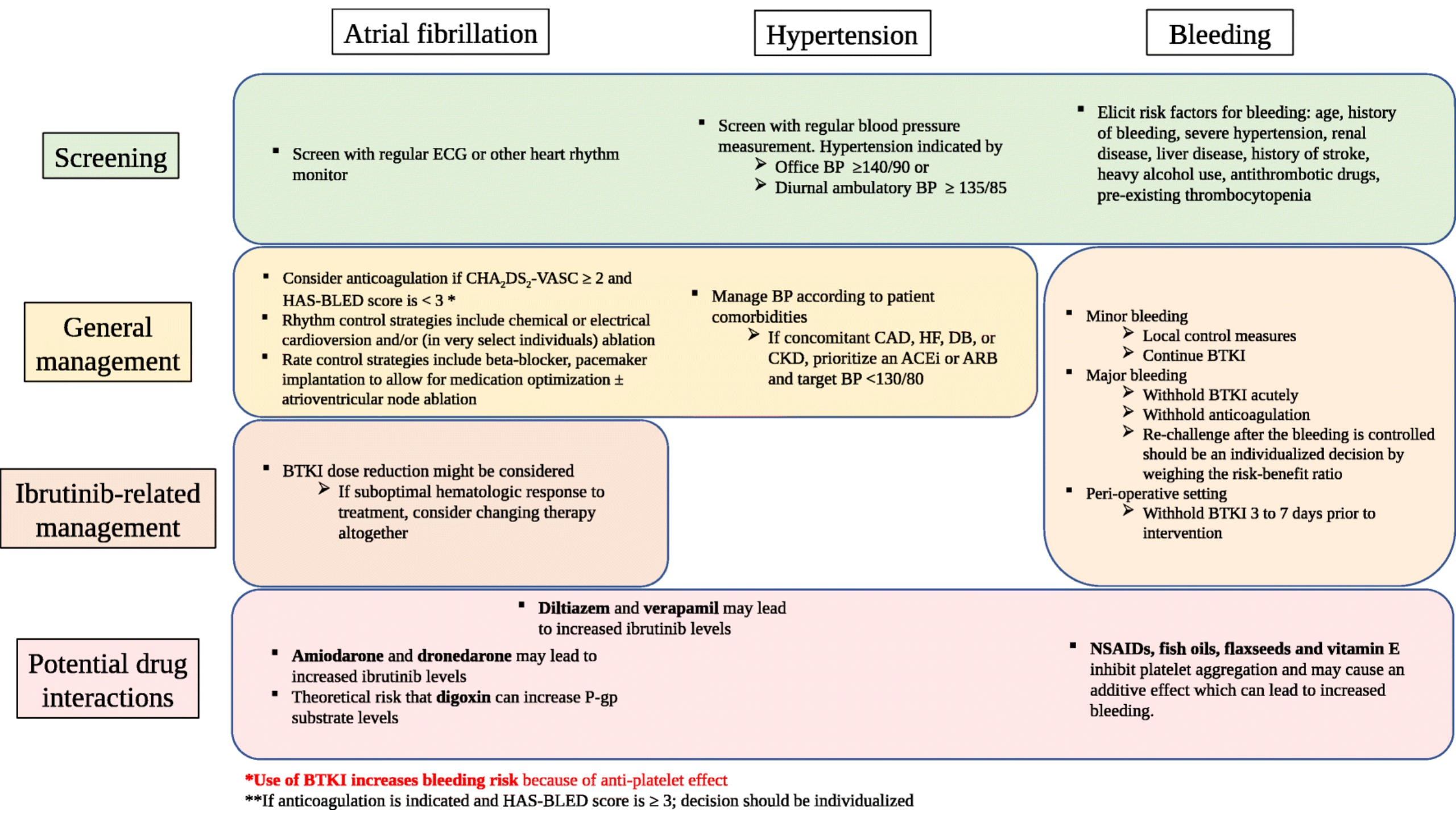


O que hago en mis pacientes se no puedo cambiar?

- MAPA anual e controle pressorico agressivo

- 1x por año: Ecocardiograma y se sintomas, un holter
  - Tenga un cardiólogo junto nestes casos

- Si tiene síntomas de desmayos, palpitaciones u otros problemas cardíacos, considere cambiar el BTKi
  - Esto es mas facil en Brasil por los custos mas baratos de Acala



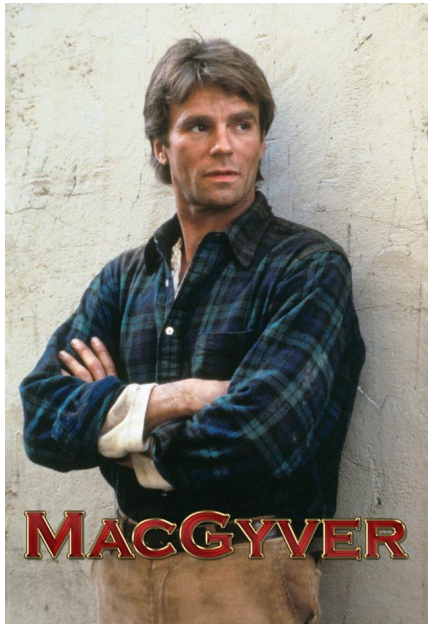
***Use of BTKI increases bleeding risk** because of anti-platelet effect

**If anticoagulation is indicated and HAS-BLED score is ≥ 3; decision should be individualized

Sangramentos en inidores de BTK

- Muchas vezes estan relacionados con otros fármacos juntos:
  - Aspirina/Clopidogrel
  - Suplementos, como Omega-3, oleo de peixe, etc
- Procedimentos eletivos:
  - simples, 2-3 dias off-iBTK
  - mayores, 7 dias
  - Descansos planificados de iBTK no estan relacionados com progression
- Sangramentos Mayores e/o Procedimentos urgentes:
  - Transfusión de plaquetas
  - Considere cambiar el BTK o para otra terapia
- Lo que NUNCA Hago – iBTK + Warfarina
  - Es possible utilizar Zanu com Warfarina hasta un INR de 1.5

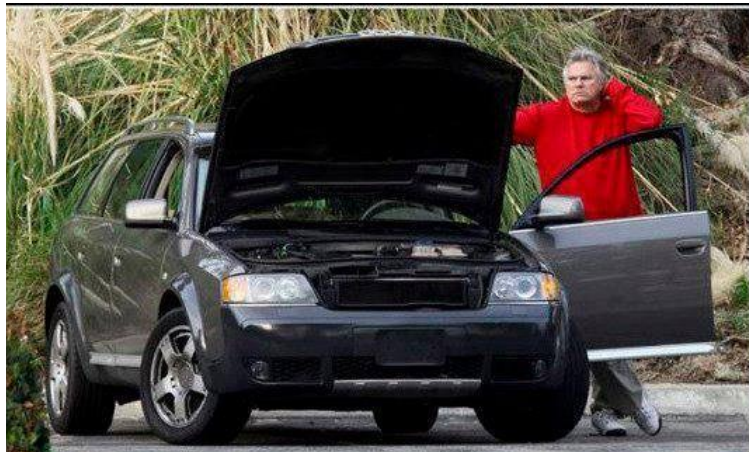
Diarrea e Artralgia/Artritis



- Generalmente, evito cambiar terapia

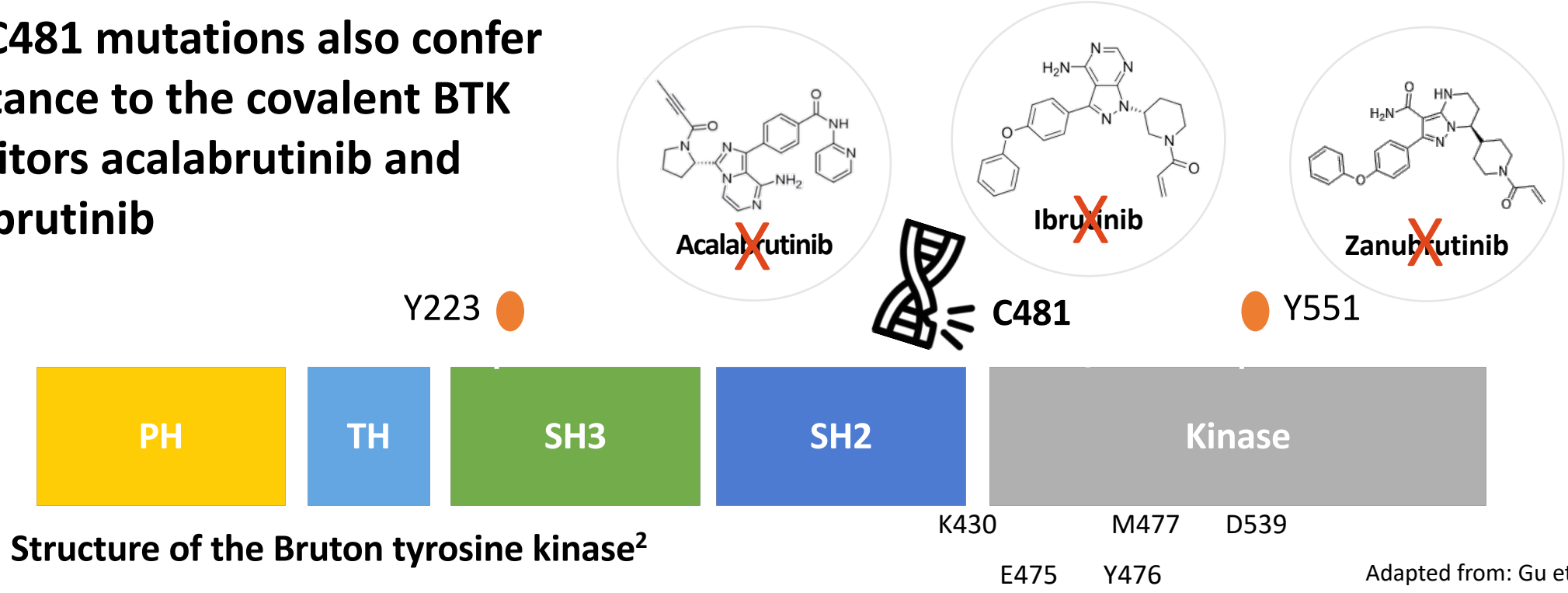
- Diarrea
  - Tomar el remedio a la noche
  - Disminuir la dosis
  - Anti-motility drugs
  - Generalmente, grados bajos, y que mejoran com tiempo

- Artritis/Artralgia
  - Muy raro en mis pacientes
  - AINES, Tonic Water
  - Razon más frecuente de interrupción en estudios del mundo real.



Acquired Resistance to Covalent BTK Inhibitors Is Generally Driven by Mutations in *BTK* at the C481 Site[1]

***BTK* C481 mutations also confer resistance to the covalent BTK inhibitors acalabrutinib and zanubrutinib**



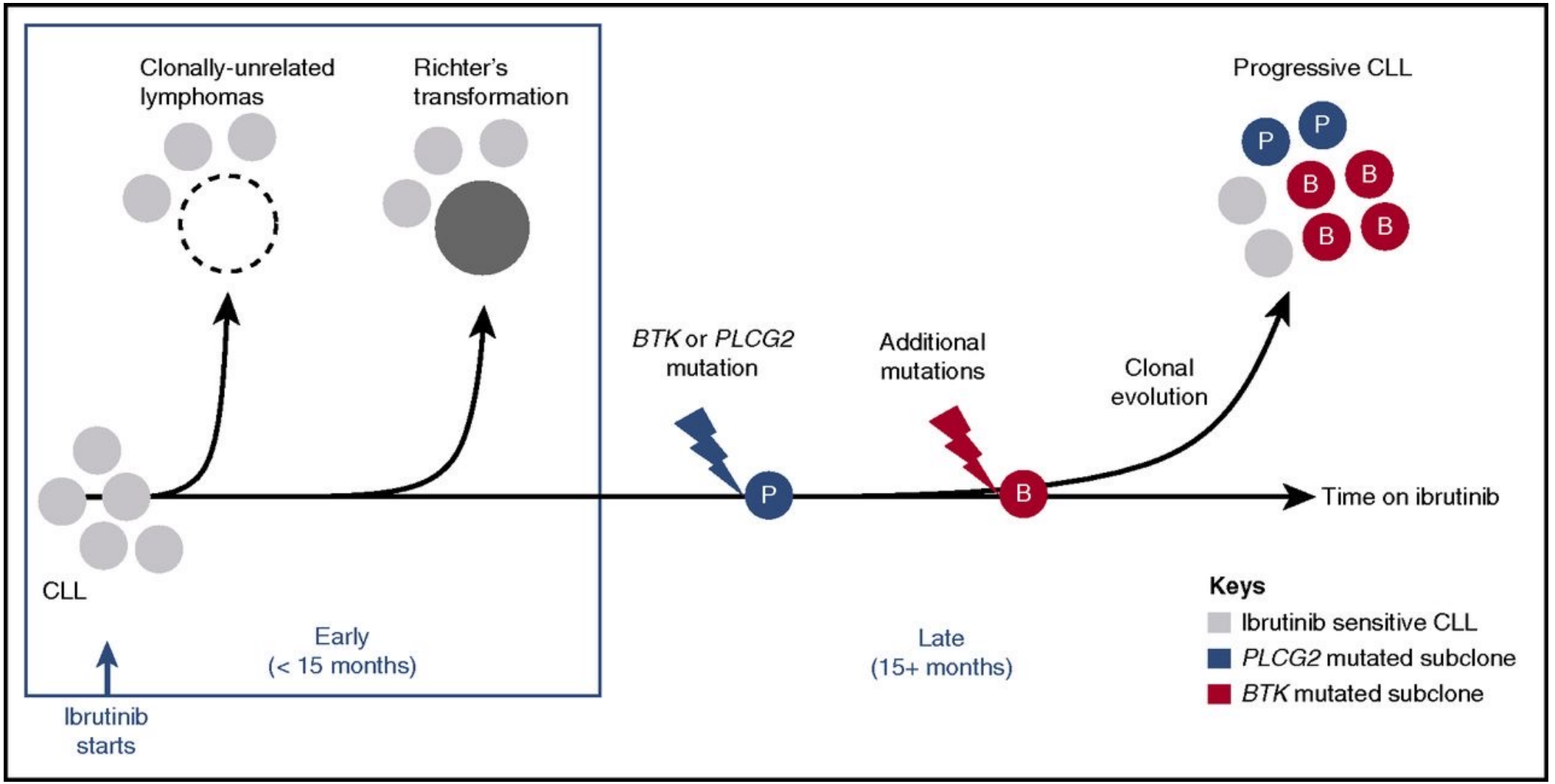
Structure of the Bruton tyrosine kinase[2]

Adapted from: Gu et al. 2021.

In sum, BTK resistance contributes to disease progression and diminishes the efficacy of all covalent BTK inhibitors

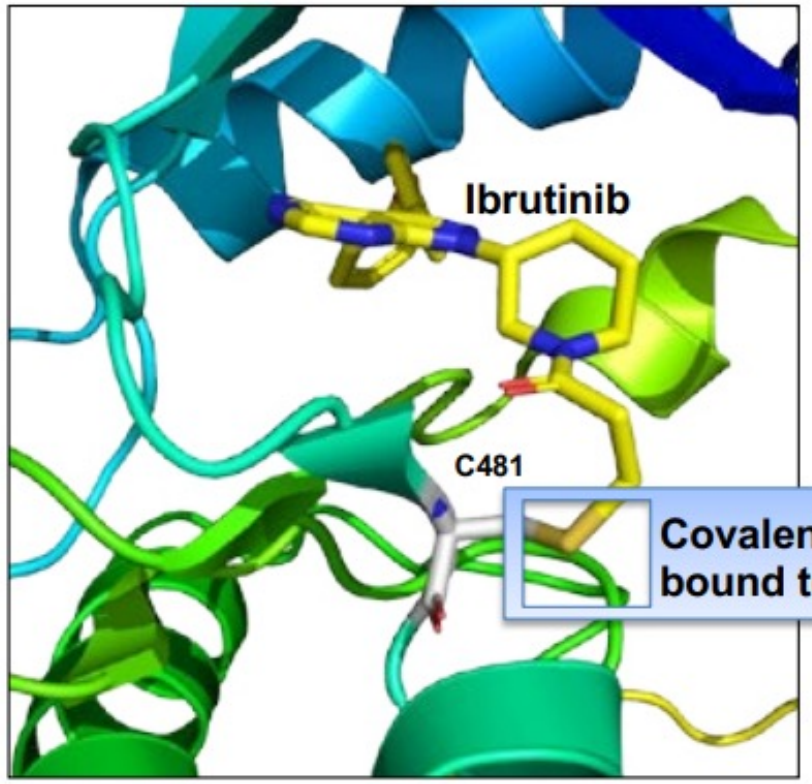
1. Woyach. NEJM 2014;370:2286. 2. Gu. J Hematol Oncol. 2021;14:40

Progressiones rápidas – Suspechar de Richter

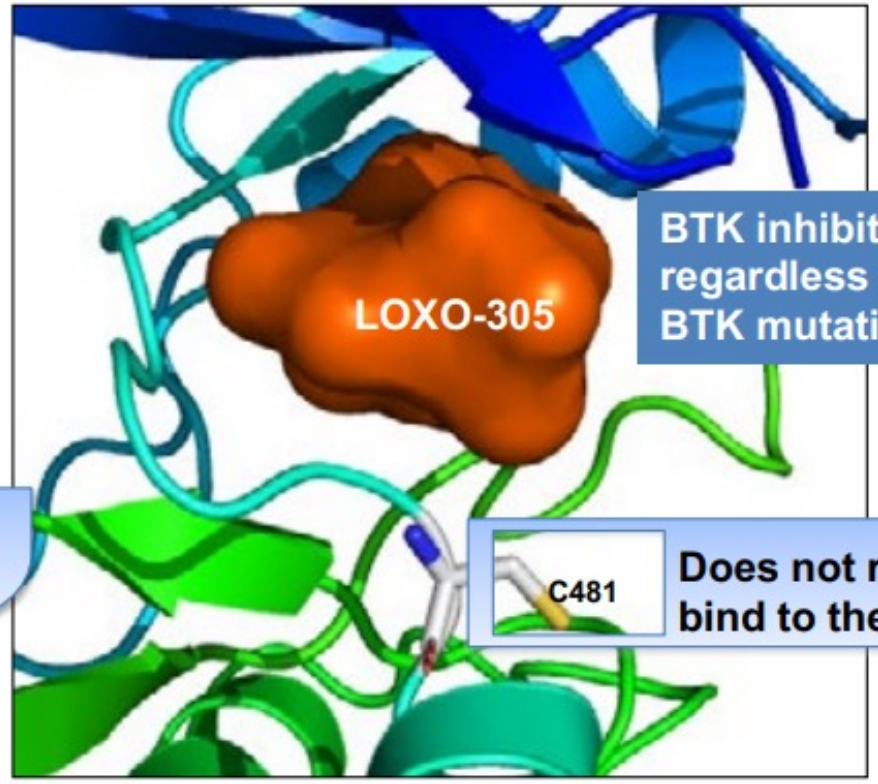


LOXO-305 mechanism of action

Covalent BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) require WT BTK for activity



LOXO-305 is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK



Estamos hacendo BTK mutations en CLL solo

- Los mecanismos de Resistencia en MCL es muy complicado!
- Ahora, no tenemos aprobacion para Pirtobrutinib, Nemtabrutinib o BTK degraders
  - Pero acredito ser importante estos datos
  - Retratamento en futuro?
- Para todos pacientes con progression a BTK continuo, vamos con Venetoclax

BTKi en Linfomas

- El impacto de toxicidad és mucho menor em LCM
  - Menos tiempo de terapia
- Generalmente, empezo con un iBTK de 2a generacion
  - Zanu o Acala
- En Brasil, MW solo tenemos aprobacion de Ib e Zanu

Adverse Events of Available BTK Inhibitors in MCL

Ibrutinib	Acalabrutinib	Zanubrutinib
Cytopenias (grade 3/4)	**Cytopenias (grade ≥3)**	**Cytopenias (grade ≥3)**
▪ Neutropenia: 29% ▪ Thrombocytopenia: 17% ▪ Anemia: 9%	Neutropenia: 15% Thrombocytopenia: 12% Anemia: 10%	Neutropenia: 15% Thrombocytopenia: 5% Anemia: 8%
Infection (grade 3-5)	**Infection (serious or grade ≥3)**	**Infection (grade ≥3)**
▪ 0% to 8% of patients	▪ 19% of patients*	▪ 0% to 10% of patients
Bruising and hemorrhage	**Bruising and hemorrhage**	**Bruising and hemorrhage**
▪ Grade ≥3 bruising/rash/petechiae: 0%/3%/0% ▪ Grade ≥3 hemorrhage: 4%*	▪ Grade ≥3 bruising/rash: -/0.8% ▪ Grade ≥3 hemorrhage: 0.8%	▪ Grade ≥3 rash/bruising: 0%/0% ▪ Major hemorrhage (grade ≥3 hemorrhage or any-grade CNS hemorrhage): 5%
Lymphocytosis	**Lymphocytosis**	**Lymphocytosis**
▪ Lymphocytosis: 33%	▪ Lymphocytosis: 31.5%	▪ Lymphocytosis: 41%

*Across multiple clinical trials enrolling patients with various hematologic malignancies, including MCL.

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI.

Slide credit: clinicaloptions.com

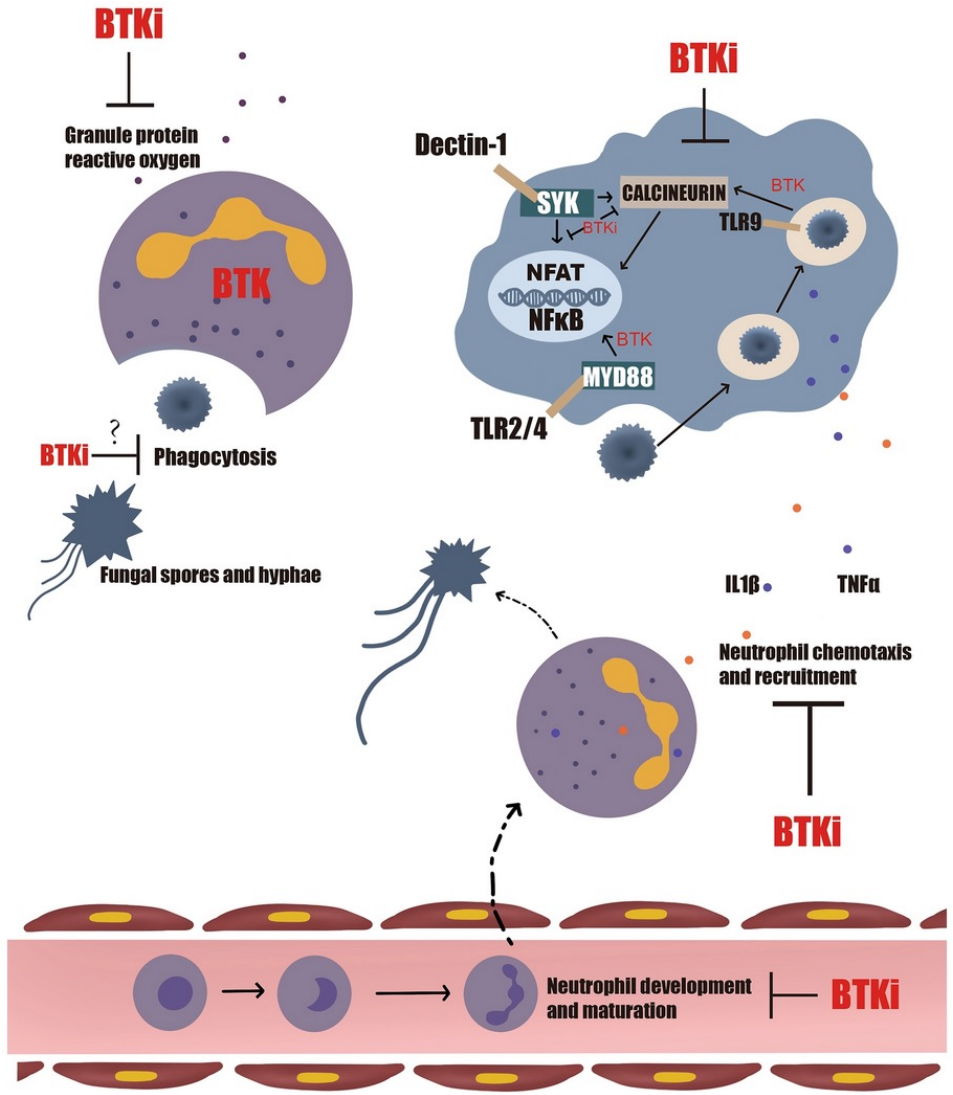
Adverse Events of Available BTK Inhibitors in MCL

Ibrutinib	Acalabrutinib	Zanubrutinib
Gastrointestinal	**Gastrointestinal**	**Gastrointestinal**
▪ Diarrhea: 51% (grade ≥3: 5%) ▪ Nausea: 31% (grade ≥3: 0%)	Diarrhea: 31% (grade ≥3: 3.2%) Nausea: 19% (grade ≥3: 0.8%)	Diarrhea: 23% (grade ≥3: 0.8%) Nausea: NR
Musculoskeletal	**Musculoskeletal**	**Musculoskeletal**
▪ Includes pain, arthralgias, muscle spasms ▪ 11% to 37% of patients (grade ≥3: up to 1%)	▪ Includes myalgia ▪ 21% of patients (grade ≥3: 0.8%)	▪ Includes pain, discomfort, myalgia, back pain, arthralgia, arthritis ▪ 14% of patients (grade ≥3: 3.4%)
Other common AEs	**Other common AEs**	**Other common AEs**
▪ Rash: 25% (grade ≥3: 3%) ▪ Fatigue: 41% (grade ≥3: 5%) ▪ Headache: 13% (grade ≥3: 0%)	▪ Rash: 18% (grade ≥3: 0.8%) ▪ Fatigue: 28% (grade ≥3: 0.8%) ▪ Headache: 39% (grade ≥3: 1.6%)	▪ Rash: 36% (grade ≥3: 0%) ▪ Fatigue: 11% ▪ Headache: 4.2%

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI.

Slide credit: clinicaloptions.com

Infecciones con iBTK



- Mas raros cuando empezamos com iBTK en lineas mais tempranas
- Algunos casos de pacientes com MCL con muchas lineas de terapia
- Evitar uso con steroids

Infecciones con iBTK

- Vacunas:
  - Conjugate pneumococcal vaccine Prevenar13
  - Polysaccharide vaccine Pneumovax23
  - Influenza
  - COVID-19
  - Shingrix?
  - Dengue fever? – Hasta ahora, NO!

- Profilaxias:
  - PJP: Solo en casos de 2a linea o en pacientes mui enfermos
  - Zoster: Si, pero sin datos mui Fuertes
  - Azoles: No, mucha interferencia
  - Imunoglobulina: Mui raro tener que repor, pero considerar en pacientes com mas de 2 infecciones graves en 1 ano

Conclusiones

- BTKi are GREAT drugs!
- Muchos efectos colaterales son mas raros con iBTK de 2a generacion, con una taxa de discontinuación baja!
- Sin embargo, se vamos tener mas pacientes, vamos tener mas efectos secundários
  - Tenemos que aprender a manejarlos
- Los inibidores no covalentes o de 3a generación parecen ser mas seguros e mas tolerables
  - Pero requiere confirmacion en estudios fase 3

Gracias!

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