BeiGene-sponsored Satellite Symposium at
EHA 2024 Hybrid Congress
15 June 2024, 18:00-18:45 CEST
Madrid, Spain

All you need to know when managing CLL or indolent lymphoma patients under BTKi treatment

BeiGene

Introduction

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Disclosures

- **Honoraria, research funding, advisory boards, speakers' bureau, and other:** AbbVie, Amgen, AstraZeneca, BeiGene, BMS, Gilead, GSK, Hoffmann-La Roche, Janssen, Lilly, Novartis, Sunesis

Disclaimers (1)

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Disclaimers (2)

- Zanubrutinib ▼*. Refer to Brukinsa SmPC (MAH: BeiGene Ireland Ltd)
  - as **monotherapy** is indicated in the European Union (EU) for the treatment of adult patients with:
    - Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemoimmunotherapy
    - Chronic lymphocytic leukaemia (CLL)
    - Marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy
  - in **combination** with obinutuzumab is indicated in the EU for the treatment of adult patients with:
    - Refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies (FL is not reimbursed in Spain)

Indications may differ outside of the EU. Prescribing information may vary depending on local approval in each country. For the country where you practice medicine, consult the zanubrutinib prescribing and reimbursement information and the local materials, such as the PI and/or the SmPC for guidance on prescribing.

* ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
CLL, chronic lymphocytic leukemia; EU, European Union; FL, follicular lymphoma; MAH, marketing authorization holder; MZL, marginal zone lymphoma; PI, prescribing information; SmPC, summary of product characteristics; WM, Waldenström's macroglobulinaemia.

Disclaimers (3)

- Acalabrutinib ▼*. Refer to Calquence SmPC (MAH: AstraZeneca AB).
- Ibrutinib. Refer to Imbruvica SmPC (MAH: Janssen-Cilag International NV).
- Venetoclax. Refer to Venclyxto SmPC (MAH: AbbVie Deutschland GmbH Co. KG)

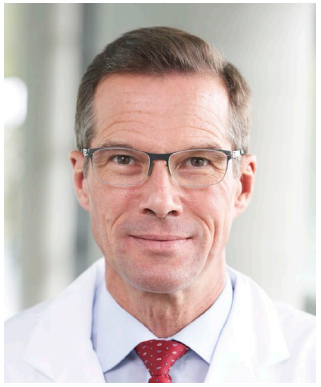
* ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
MAH, marketing authorization holder; SmPC, summary of product characteristics.

Learning Objectives

After this session, participants should have increased confidence in using BTKis, while appreciating differences among first- and next-generation BTKis

BTKi, Bruton's tyrosine kinase inhibitor.

Chair and Speakers



Prof. Stephan Stilgenbauer
Comprehensive Cancer Center,
Ulm, Germany

Dr. Alessandra Tedeschi
ASST Grande Ospedale
Metropolitano Niguarda, Milan, Italy

Prof. Joe-Elie Salem
Sorbonne University,
Paris, France

Prof. Giorgio Minotti
University Campus Bio-Medico,
Rome, Italy

All you need to know when managing CLL or indolent lymphoma patients under BTKi treatment

Timing	Topic	Speaker
3 mins	Welcome and introduction to the Roundtable discussion	Stephan Stilgenbauer, Ulm, Germany (moderator)
	Roundtable discussion – topics distributed as follows:	
10 mins	BTKi introduction, mutations under BTKi treatment, BTKi switching	Alessandra Tedeschi, Milan, Italy
10 mins	Safety profile of BTKis, managing cardiovascular events (AF, hypertension)	Joe-Elie Salem, Paris, France
10 mins	Pharmacokinetics / pharmacodynamics of BTKis	Giorgio Minotti, Rome, Italy
10 mins	Audience Q&A	All faculty
2 mins	Closure & farewell	Stephan Stilgenbauer

AF, atrial fibrillation; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; Q&A, questions and answers.

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Allows you to:

- Ask your **questions** to the faculty.
- Provide your **feedback** and help BeiGene to better meet your educational needs in the future.

Audience test poll question

- Will Italy win the UEFA European Football Championship again this year? *(choose one answer only)*

1. Yes ☐
2. No ☐

BTKi introduction, mutations under BTKi treatment, BTKi switching

Alessandra Tedeschi, MD, PhD

ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Disclosures

- **Honoraria:** Janssen SpA, AbbVie, BeiGene, AstraZeneca
- **Advisory boards:** Janssen SpA, AbbVie, BeiGene, AstraZeneca, Lilly
- **Speakers' bureau:** Janssen SpA, AbbVie, BeiGene, AstraZeneca

Audience poll question

- After 6 months of treatment with ibrutinib your 62-year-old TN del(17p) patient shows a recurrent episode of grade 3 stomatitis and cutaneous lesions.

You decide to: *(choose one answer only)*

1. Discontinue treatment with BTKi and start venetoclax-based treatment
2. Reduce ibrutinib dosage and if new recurrence, start venetoclax-based treatment
3. Reduce ibrutinib dosage and, if new recurrence, switch to zanubrutinib
4. Discontinue ibrutinib and switch to a next-generation BTKi such as zanubrutinib

BTKi, Bruton's tyrosine kinase inhibitor; del(17p), deletion of the short arm of chromosome 17; TN, treatment naïve.

BTKis for CLL in clinical practice

We have several approved BTKis (1st gen – Ibru[1]; next gen – Zanu[2], Acala[3]) for treating TN and R/R CLL

The efficacy, safety and mutational profiles of these drugs are well characterized

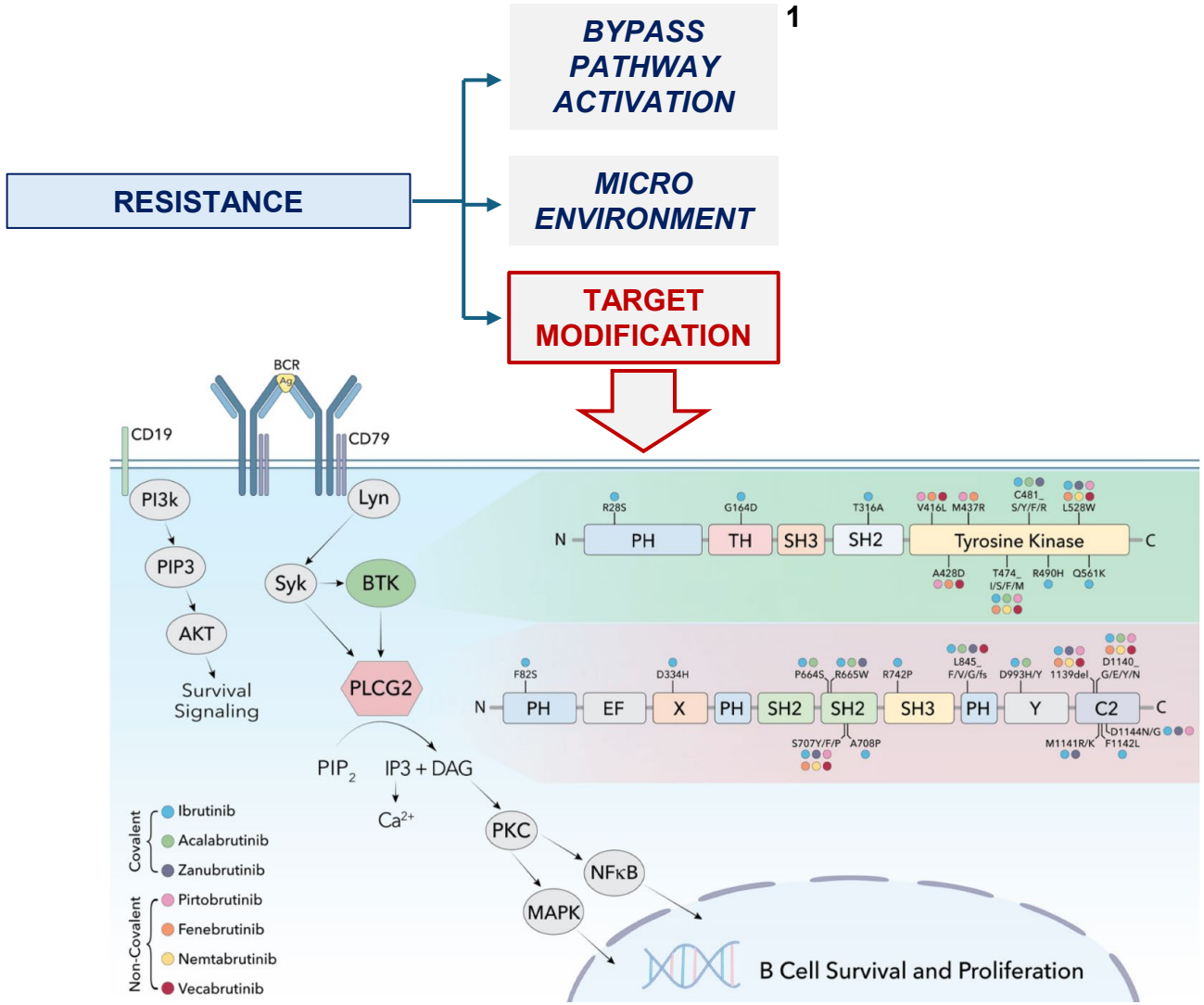
The choice and sequencing of these BTKis depends on patient and disease factors

We have options!

Acala, acalabrutinib; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; gen, generation; Ibru, ibrutinib; R/R, relapsed/refractory; TN, treatment naïve; Zanu, zanubrutinib.

1) Imbruvica SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica; 2) Brukinsa SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/brukinsa; 3) Calquence SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/calquence.

Acquired resistance to cBTKi in CLL



REAL WORLD EVIDENCE[2]
One-third of patients with CLL relapsing on ibrutinib do not carry *BTK*/*PLCG2* mutations, even with a 0.1% sensitivity

AKT, Ak strain transforming; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; C2, complement C2 gene; Ca^{2+}, calcium ions; cBTK, covalent BTK; CD19, cluster of differentiation 19; CLL, chronic lymphocytic leukemia; DAG, diacylglycerol; EF, elongation factor; IP3, inositol 1,4,5-trisphosphate; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; PH, Philadelphia chromosome; PI3Ki, phosphoinositide 3-kinases; PIP3, phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P3); PKC, protein kinase C; PLCG2, phospholipase C gamma 2; SH2 or 3, src homology 2 or 3; Syk, spleen tyrosine kinase; TH, tyrosine hydroxylase gene.

1) Extracted from Montoya S and Thompson MC, Cancers 2023, 15(14):3648; 2) Bonfiglio S et al, Blood Adv. 2023;7(12):2794–2806.

Acquired mutations in patients with R/R CLL who progressed in the ALPINE study

Acquired BTK and PLCG2 mutations by patient

Patient ID	Treatment Arm	Acquired BTK Mutation at PD: Coding DNA Description (VAF, %)	Acquired BTK Mutation at PD: Protein Description	Acquired PLCG2 Mutation at PD: Coding DNA Description (VAF, %)	Acquired PLCG2 Mutation at PD: Protein Description	Duration of Treatment, Months
1	Ibrutinib	1442G>C (1.29)	C481S	Not detected	Not detected	30.8
2	Ibrutinib	1442G>C (7.95)	C481S	Not detected	Not detected	34.5
3	Ibrutinib	1442G>C (0.88) 127G>C (0.51)	C481S D43H	2535A>C (0.60)	L845F	11.8
4	Ibrutinib	Not detected	Not detected	3422T>A (5.69)	M1141K	18.8
5	Zanubrutinib	1442G>C (8.80)	C481S	Not detected	Not detected	34.2
6	Zanubrutinib	1283C>A (31.10) 1442G>C (4.72) 1441T>A (2.48)	A428D C481S C481S	Not detected	Not detected	28.0
7	Zanubrutinib	1442G>C (16.22) 1583T>G (8.22) 1441T>A (4.28) 1442G>A (1.83) 1442G>T (1.70) 1441T>C (1.01)	C481S L528W C481S C481Y C481F C481R	Not detected	Not detected	29.7
8	Zanubrutinib	1583T>G (1.76)	L528W	Not detected	Not detected	33.8
9	Zanubrutinib	1442G>C (74.39) 1441T>C (2.30) 1441T>A (0.45)	C481S C481R C481S	Not detected	Not detected	18.4

- No **BTK mutations** were identified **at baseline**
- 5/24 patients who progressed on zanubrutinib acquired BTK mutations
- Among the 24 patients who progressed on zanubrutinib, T474I and L528W mutations were reported in 0% and 8.3% (n=2) of patients, respectively
- These data suggest that ***BTK* and/or *PLCG2* mutations** are **not the main factors driving PD** in this population

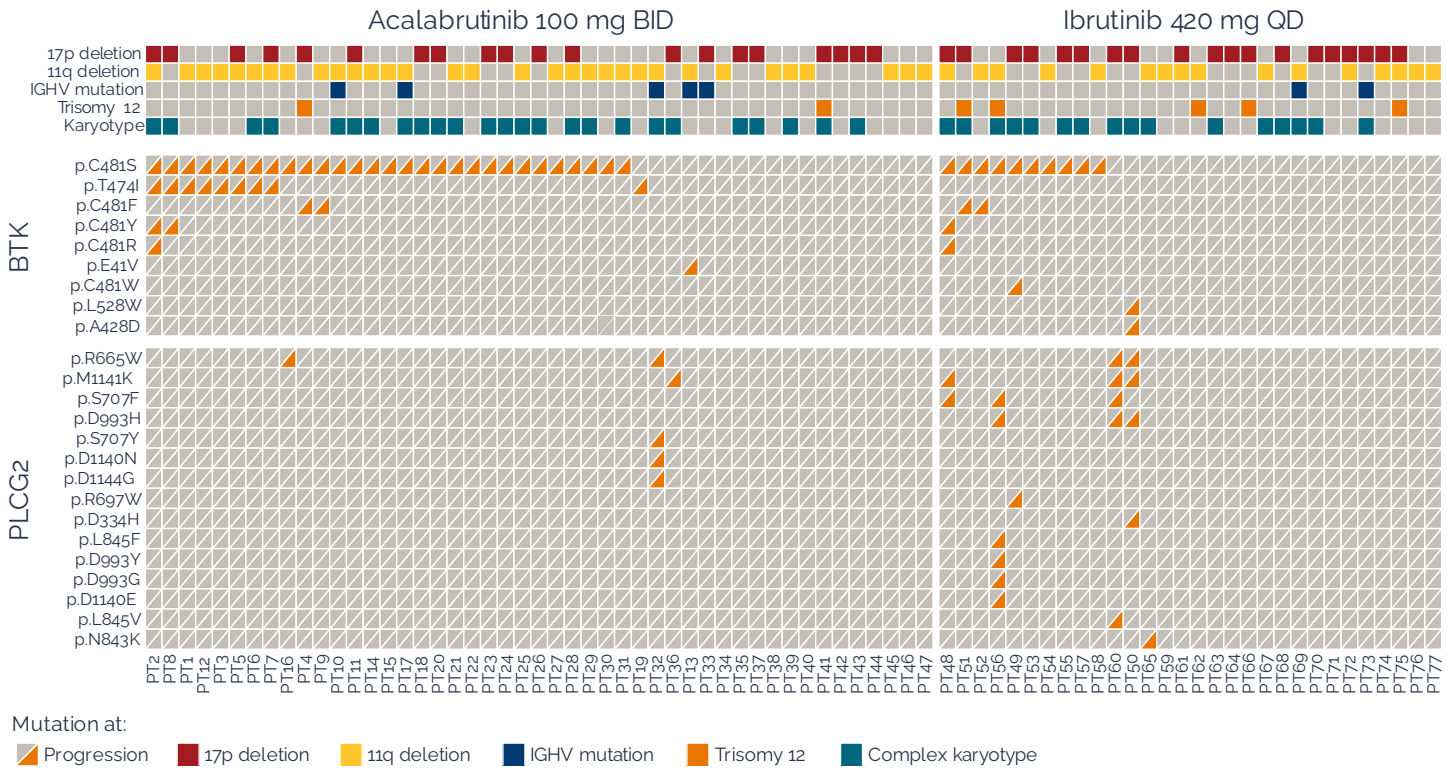
BTK(i), Bruton tyrosine kinase (inhibitor); CLL, chronic lymphocytic leukemia; m, months; PD, progressive disease; PLCG2, phospholipase C gamma 2. R/R, relapsed/refractory.

Extracted from Brown JR, Li J, Eichhorst BF, Lamanna N, O'Brien SM, Tam CS et al. Acquired Mutations in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia Who Progressed in the ALPINE Study. Presented at the 65th ASH Annual Meeting and Exposition; December 9–12, 2023, San Diego, CA, USA. Abstract 1890 (Accessed 12 June 2024).
Available at: Brown_BGB-3111-305_Biomarkers_ESH-CLL_Presentation_2024.pdf.

Resistance to pirtobrutinib

BTK mutations at T474 and L528 lead to resistance to pirtobrutinib[1]

Patient ID	Treatment Arm	Acquired BTK Mutation at PD: Coding DNA Description (VAF, %)	Acquired BTK Mutation at PD: Protein Description	Acquired PLCG2 Mutation at PD: Coding DNA Description (VAF, %)	Acquired PLCG2 Mutation at PD: Protein Description	Duration of Treatment, Months
1	Ibrutinib	1442G>C (1.29)	C481S	Not detected	Not detected	30.8
2	Ibrutinib	1442G>C (7.95)	C481S	Not detected	Not detected	34.5
3	Ibrutinib	1442G>C (0.88) 127G>C (0.51)	C481S D43H	2535A>C (0.60)	L845F	11.8
4	Ibrutinib	Not detected	Not detected	3422T>A (5.69)	M1141K	18.8
5	Zanubrutinib	1442G>C (8.80)	C481S	Not detected	Not detected	34.2
6	Zanubrutinib	1283C>A (31.10) 1442G>C (4.72) 1441T>A (2.48)	A428D C481S C481S	Not detected	Not detected	28.0
7	Zanubrutinib	1442G>C (16.22) 1583T>G (8.22) 1441T>A (4.28) 1442G>A (1.83) 1442G>T (1.70) 1441T>C (1.01)	C481S L528W C481S C481Y C481F C481R	Not detected	Not detected	29.7
8	Zanubrutinib	1583T>G (1.76)	L528W	Not detected	Not detected	33.8
9	Zanubrutinib	1442G>C (74.39) 1441T>C (2.30) 1441T>A (0.45)	C481S C481R C481S	Not detected	Not detected	18.4



Among the 24 patients who progressed on zanubrutinib in the ALPINE trial, **T474I** and **L528W** mutations were reported in **0%** and **8.3% (n=2)** of patients, respectively.[2]

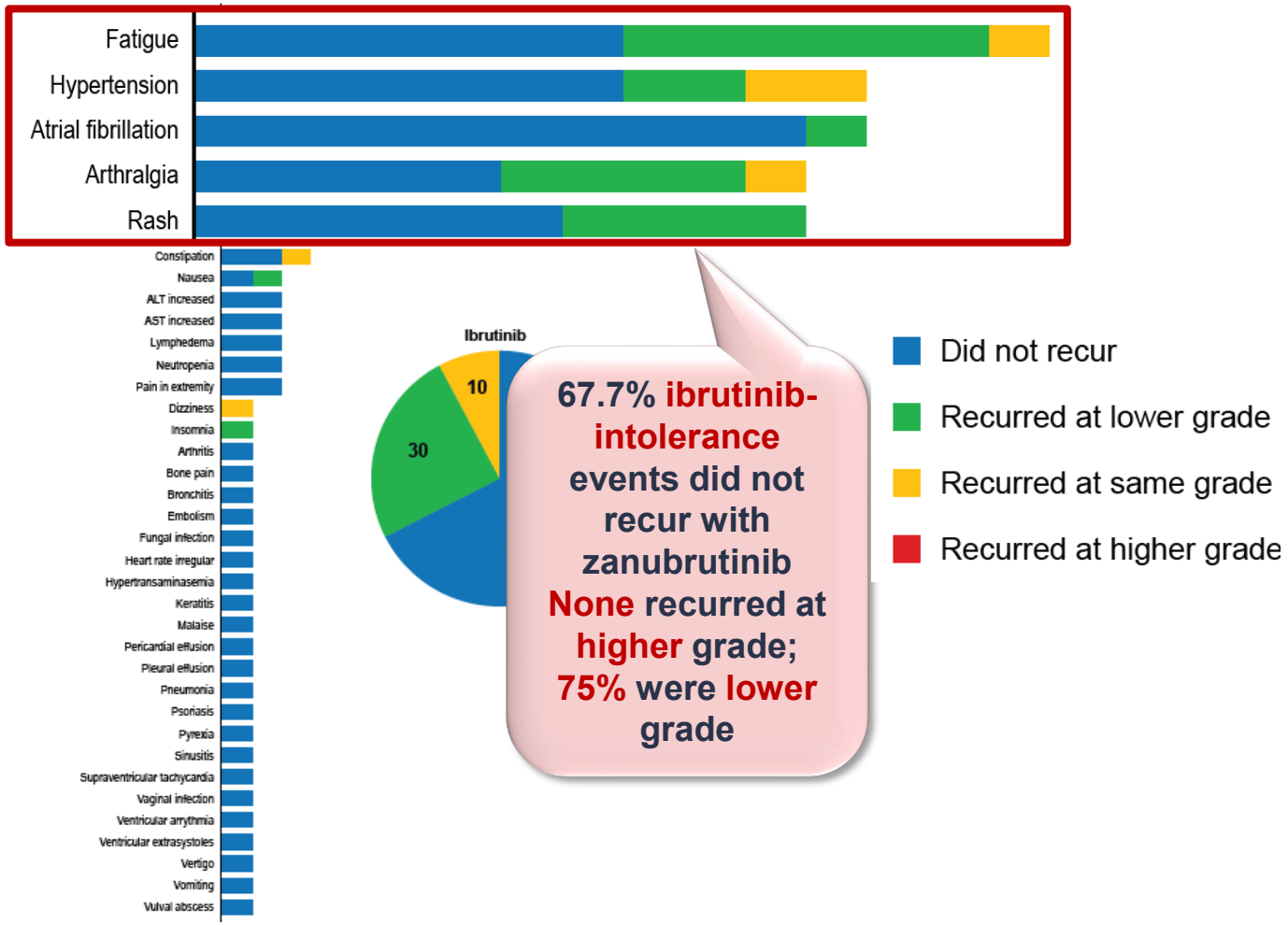
Among the 47 patients who progressed on acalabrutinib in the ELEVATE-RR trial, **T474I** and **L528W** mutations were reported in **19.1% (n=9)** and **0%** of patients, respectively.[3]

BID, twice daily; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; Ibr, ibrutinib; PD, progressive disease; PLCG2, phospholipase C gamma 2; QD, once daily; R/R, relapsed/refractory.

Extracted from 1) Naeem A et al. Blood Adv. 2023;7(9):1929-1943; 2) Brown JR, Li J, Eichhorst BF, Lamanna N, O'Brien SM, Tam CS et al. Acquired Mutations in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia Who Progressed in the ALPINE Study. Presented at the 65th ASH Annual Meeting and Exposition; December 9–12, 2023, San Diego, CA, USA. Abstract 1890 (Accessed 12 June 2024). Available at: Brown_BGB-3111-305_Biomarkers_ESH-CLL_Presentation_2024.pdf; 3) Woyach JA al. Blood. 2024; https://doi.org/10.1182/blood.2023023659.

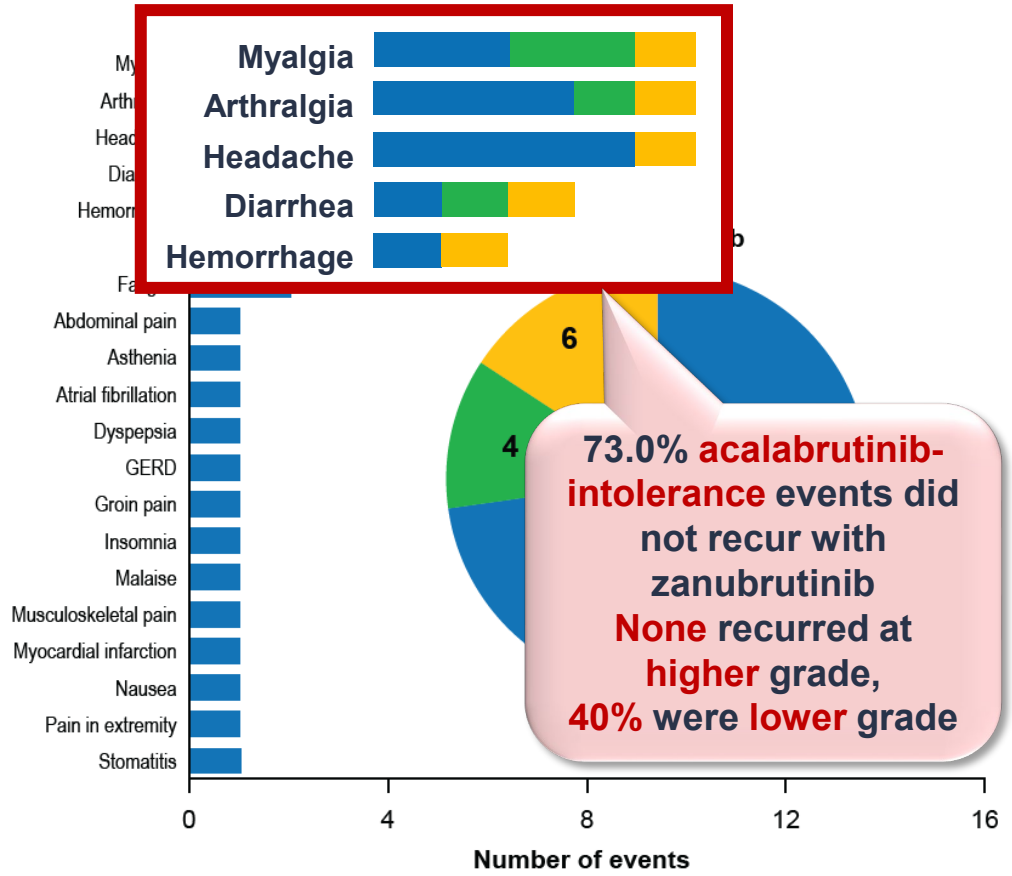
Zanu in Ibru- and/or Acala-intolerant patients with B-cell malignancies
Phase 2 study BGB-3111-215, previously treatment CLL/SLL, WM, MCL, or MZL

Ibrutinib-intolerance events



67.7% ibrutinib-intolerance events did not recur with zanubrutinib
None recurred at higher grade; 75% were lower grade

Acalabrutinib-intolerance events



73.0% acalabrutinib-intolerance events did not recur with zanubrutinib
None recurred at higher grade, 40% were lower grade

Acala, acalabrutinib; CLL, chronic lymphocytic leukemia; Ibru, ibrutinib; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic leukemia; WM, Waldenström's macroglobulinemia; Zanu, zanubrutinib.

Extracted from Shadman M, Levy MY, Burke JM, Cultrera JL, Misleh J, Sharman JP et al. Updated Safety and Efficacy Results of Zanubrutinib in Patients With B-Cell Malignancies Who Are Intolerant of Ibrutinib and/or Acalabrutinib. Presented at EHA 2023 Hybrid Congress; June 8-15, 2023; Frankfurt, Germany. Abstract P633 (Accessed 12 June 2024). Available at: Shadman_BGB-3111-215_EHA_Poster_2023.pdf.

Safety profile of BTKis and managing cardiovascular events

Joe-Elie Salem, MD, PhD

Sorbonne University, APHP,

Pitié-Salpêtrière Hospital, Paris, France

Disclosures

- **Honoraria**: BeiGene, BMS, Novartis, Ipsen, Eisai, Servier
- **Research funding**: BMS, Novartis
- **Advisory boards**: BeiGene, CRC Oncology, BMS, Repare

Which cardiovascular toxicities can be associated with BTK inhibitors?

- Atrial fibrillation (AF)
- Hypertension (HT)
- Heart failure
- Cardiac conduction disorders
- Ventricular arrhythmias (VA)*
- Sudden death*

For acalabrutinib and ibrutinib[2]

Moslehi et al (2024)[1]

- Pooled analysis 10 Zanu studies
- Overall and exposure-adjusted incidence rates of AF, HT, and symptomatic VA were lower with Zanu vs Ibru

Acala, acalabrutinib; AE, adverse event; AF, atrial fibrillation; CLL, chronic lymphocytic leukemia; CV, cardiovascular; HT, hypertension; Ibru, ibrutinib; MCL, mantle cell lymphoma; VA, ventricular arrhythmias; WM, Waldenström's macroglobulinemia; Zanu, zanubrutinib.

Extracted from 1) Moslehi JJ et al. Blood Adv. 2024;8(10):2478-2490; 2) Quartermaine C et al, JACC CardioOncol. 2023;5(5):570–590.

Cardiovascular toxicities associated with ibrutinib

IC_{025} >0 = signal detection

	Ibrutinib	Entire Database (Since Inception)	IC/IC_{025}	Entire Database (Since 2013)	ROR ($_{95}$CI)
Total number of ICSRs available	13,572	16,343,451		8,318,890	
Number of ICSRs and statistics by CV-ADR subgroups					
Cardiac supraventricular arrhythmias	**959 (7.07)**	**68,597 (0.42)**	**4.06/3.97**	**28,242 (0.34)**	**23.1 (21.6-24.7)**
CNS hemorrhagic events	**505 (3.72)**	**179,621 (1.10)**	**1.76/1.63**	**85,402 (1.03)**	**3.7 (3.4-4.1)**
Heart failure	**363 (2.67)**	**142,502 (0.87)**	**1.61/1.46**	**65,680 (0.79)**	**3.5 (3.1-3.8)**
Cardiac ventricular arrhythmias	**70 (0.52)**	**33,504 (0.20)**	**1.32/0.96**	**9,220 (0.11)**	**4.7 (3.7-5.9)**
Cardiac conduction disorders	**50 (0.37)**	**26,008 (0.16)**	**1.19/0.76**	**8,834 (0.11)**	**3.5 (2.7-4.6)**
CNS ischemic events	**254 (1.87)**	**161,618 (0.99)**	**0.92/0.73**	**70,529 (0.85)**	**2.2 (2.0-2.5)**
Hypertension and related end-organ damages	**295 (2.17)**	**239,232 (1.46)**	**0.57/0.40**	**109,148 (1.31)**	**1.7 (1.5-1.9)**
Cardiac valve disorders	30 (0.22)	25,500 (0.16)	0.49/−0.07	NA	NA
Myocardial infarction	149 (1.10)	163,908 (1.00)	0.13/−0.11	NA	NA
Cardiac death or shock	131 (0.97)	144,825 (0.89)	0.12/−0.13	NA	NA
Venous thrombo-embolic events	108 (0.80)	134,718 (0.82)	−0.05/−0.34	NA	NA
Vascular neoplasms	2 (0.01)	2,687 (0.02)	−0.13/−2.72	NA	NA
Pulmonary hypertension and cardiac involvements	19 (0.14)	30,718 (0.19)	−0.42/−1.14	NA	NA
Hyperglycemia, diabetes	112 (0.83)	233,007 (1.43)	−0.79/−1.07	NA	NA
Torsade de pointes/QT prolongation	9 (0.07)	20,938 (0.13)	−0.91/−2.01	NA	NA
Myocarditis	2 (0.01)	5,515 (0.03)	−1.02/−3.61	NA	NA
Dyslipidemia	14 (0.10)	64,555 (0.39)	−1.90/−2.75	NA	NA

- Real world study of Ibru-associated CV ADRs
- ~20 million case safety reports
- Ibru was disproportionately associated with many CV ADRs

ADR, adverse drug reaction; CV, cardiovascular; Ibru, ibrutinib; IC_{025}, lower limit of the 95% credibility interval for the information component.
Extracted from Salem J-E et al, J Am Coll Cardiol. 2019;74(13):1667-1678.

Cardiovascular toxicities of BTKi in CLL

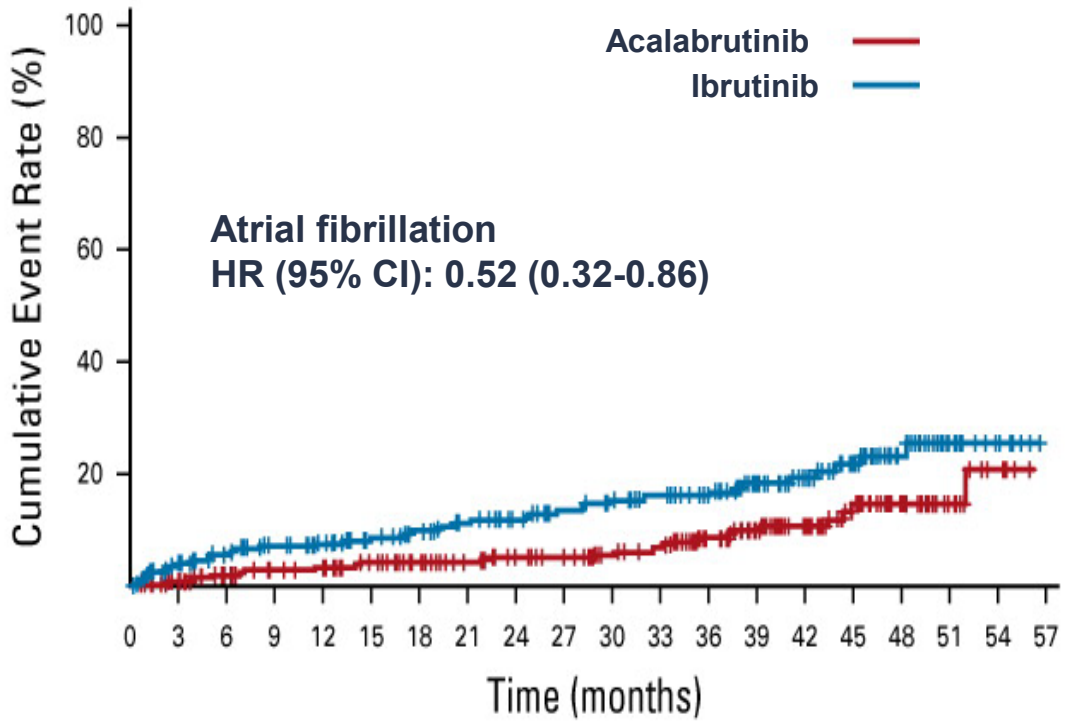
Table 1. Target and Indications for Approved BTK Inhibitors

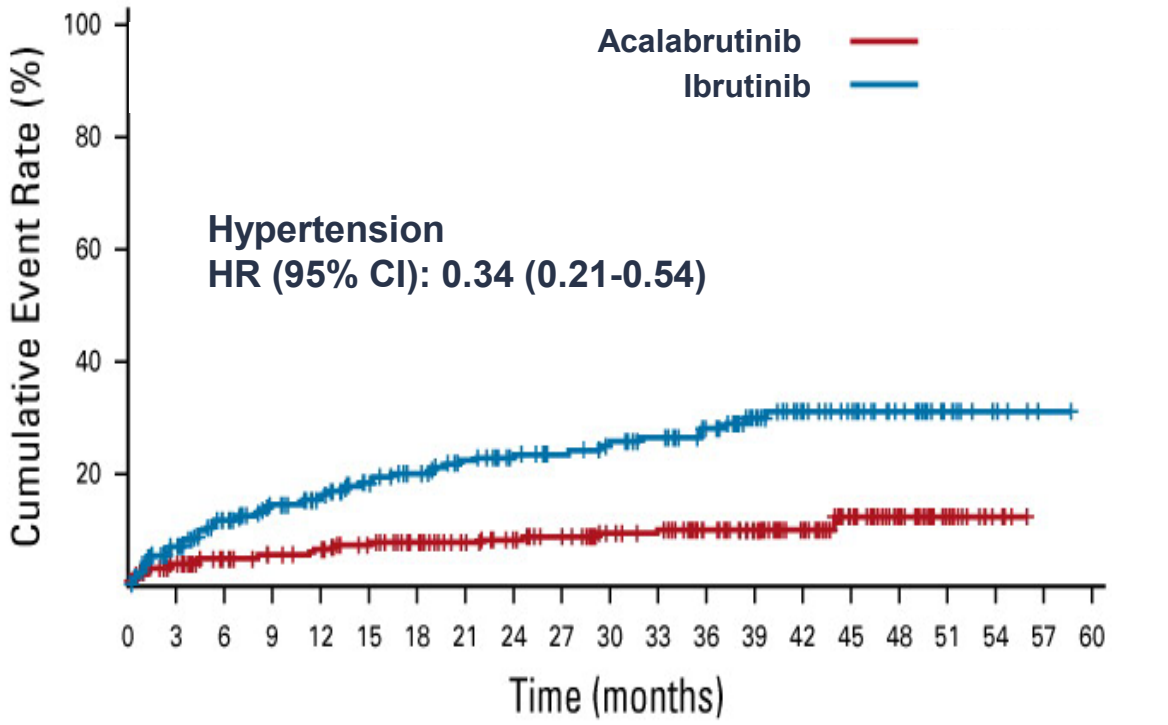
Drug	Mechanism of Action	Current Indications (or Phase of Clinical Testing)	Cardiotoxic Effects Reported
Ibrutinib	Irreversible inhibitor of BTK at C481 via covalent bond	• CLL - Newly diagnosed - Relapsing/remitting • Mantle cell lymphoma • Marginal zone lymphoma • Waldenström's macroglobulinemia • Chronic graft vs host disease after failure of 1 or more lines of systemic therapy	• Atrial fibrillation • Hypertension • Heart failure • Ventricular arrhythmia/sudden death
Acalabrutinib	Irreversible inhibitor of BTK at C481 via covalent bond	• CLL - Newly diagnosed - Relapsing/remitting • Mantle cell lymphoma	• Atrial fibrillation • Hypertension • Heart failure • Ventricular arrhythmia/sudden death
Zanubrutinib	Irreversible inhibitor of BTK at C481 via covalent bond	• CLL - Newly diagnosed - Relapsing/remitting • Waldenström's macroglobulinemia • Mantle cell lymphoma - For patients who have received at least 1 prior therapy • Marginal zone lymphoma - For patients who have received at least 1 anti-CD20-based regimen	• Atrial fibrillation • Hypertension
Pirtobrutinib	Reversible inhibitor of BTK via noncovalent bond formation	• CLL (phase III) ongoing • Mantle cell lymphoma (phase III)	• Atrial fibrillation

- Ibru: associated with AF, VA, HF and other CV tox
- Zanu and Acala: less CV tox but still present
- Increased incidence of AF and new/worse HT common with all 3 drugs
- A cardio-oncologic approach is recommended for optimal BTKi use

Acala, acalabrutinib; AF, atrial fibrillation; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CV, cardiovascular; HT, hypertension; Ibru, ibrutinib; VA, ventricular arrhythmias; Zanu, zanubrutinib.
Quartermaine C et al, JACC CardioOncol. 2023;5(5):570–590.

ELEVATE-RR: Acalabrutinib vs ibrutinib in previously treated CLL – results of the first randomized Phase 3 trial

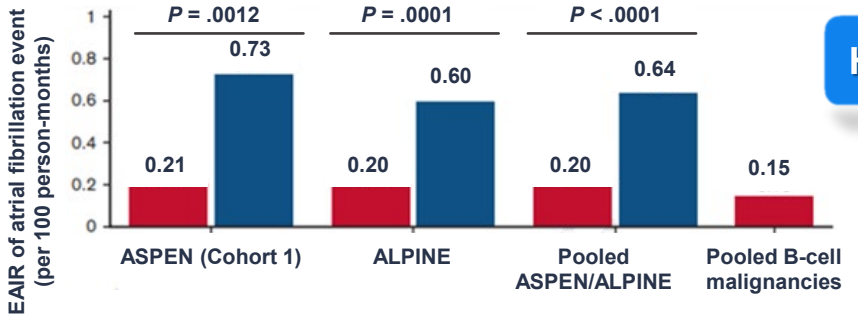




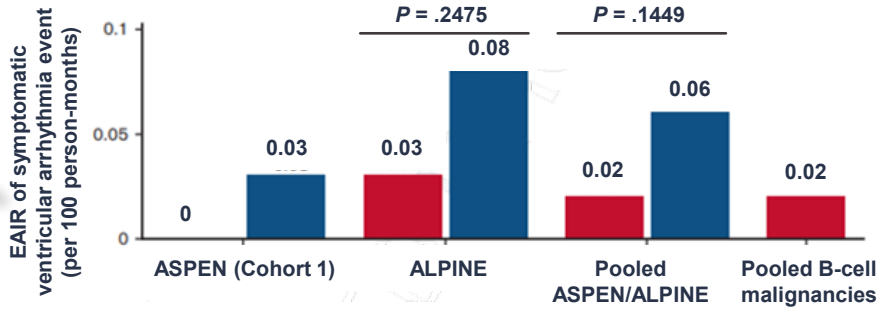
CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio.
Extracted from Byrd JC et al, J Clin Oncol. 2021;39(31):3441-3452.

Cardiovascular events reported in patients with B-cell malignancies treated with zanubrutinib

Atrial Fibrillation

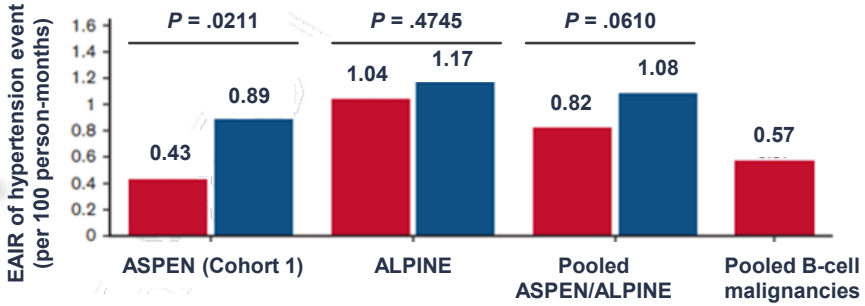


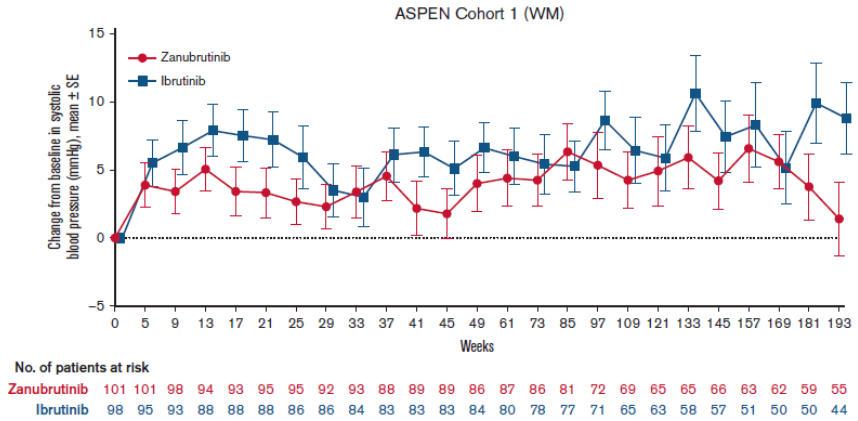
Ventricular Arrhythmia

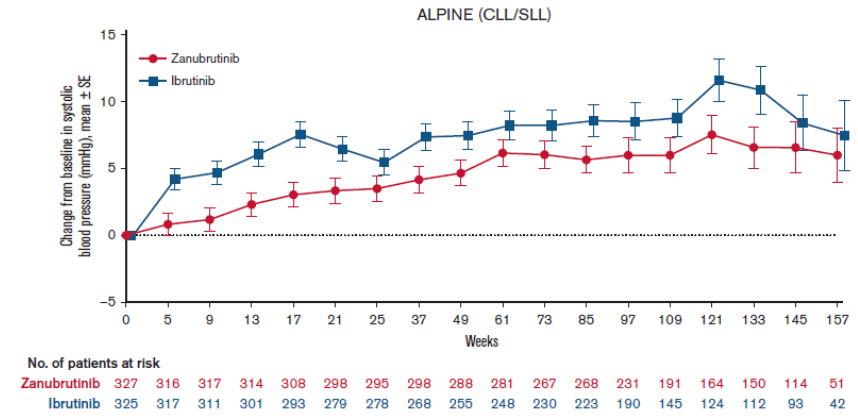


Zanubrutinib Ibrutinib

Hypertension

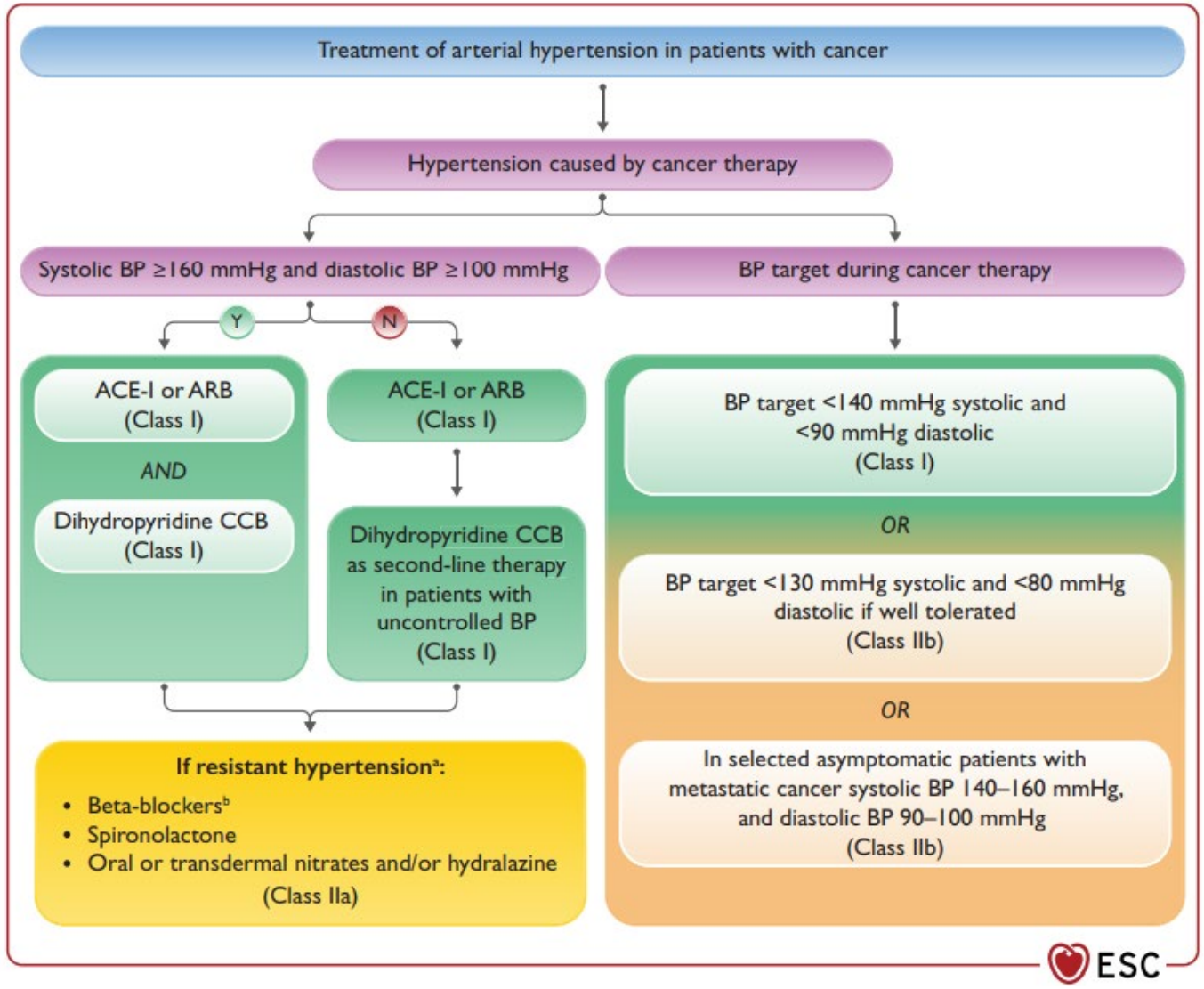






CLL, chronic lymphocytic leukemia; EIAR: exposure-adjusted incidence rates; SLL, small lymphocytic leukemia; WM, Waldenström's macroglobulinemia.
Extracted from Moslehi JJ et al. Blood Adv. 2024;8(10):2478-2490.

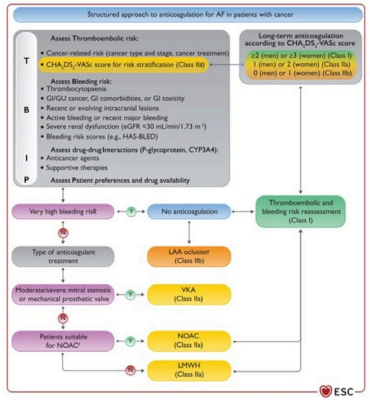
Management of hypertension



Main aspects:

- Target BP and treatment of HT are supported by varying evidence levels
- General recommendation (Class I evidence): **target BP <140/<90 mmHg**
- Patient characteristics also influence
- If outside target: use ACE-I or ARB
- If first BP ≥160/≥100 mmHg: combine with CCB

Atrial fibrillation management included in same guidelines



ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BP, blood pressure; CCB, calcium channel blocker; HT, hypertension.

2022 ESC Cardio-Oncology Guidelines.

Pharmacokinetics and pharmacodynamics of BTKis

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Disclosures

- **Honoraria**: Servier
- **Research funding**: Incyte, Astellas
- **Advisory boards**: Incyte, BeiGene
- **Speakers' bureau**: Janssen, Incyte, BeiGene

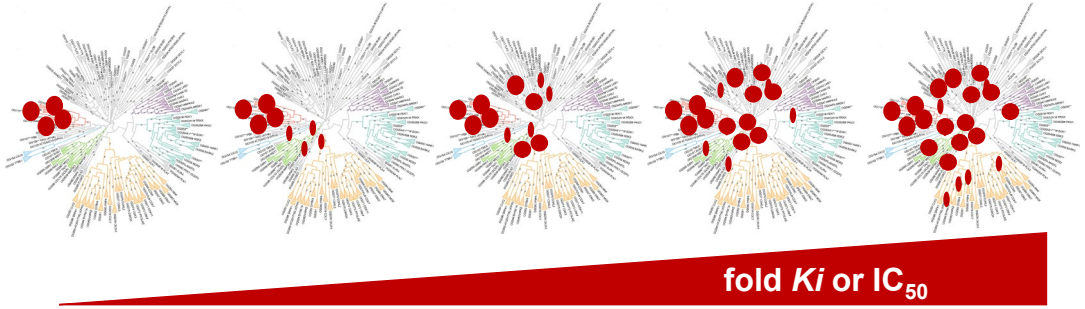
Audience poll question

- How would you define the off-target effects of covalent BTKi? *(choose one answer only)*

1. Analogue-related
2. Class-related
3. Predictable from kinome experiments
4. The lower the IC_{50} for BTK, the higher the likelihood of off-target effects

BTK(i), Bruton tyrosine kinase (inhibitor); IC_{50}, half-maximal inhibitory concentration.

Kinome assays for covalent BTKi



Reported selectivity (from high to low)	IC_{50} (μM)	*Ki** (μM)	BTKi in the assay (μM)	Selectivity conditions vs IC_{50}	Selectivity conditions vs *Ki*
acalabrutinib	0.005	0.181	1		
ACP-5862†	0.005	0.188	1		
zanubrutinib	0.0005	0.126	1		
ibrutinib	0.0015	0.054	1		
zanubrutinib	0.00071	0.126	0.071		
acalabrutinib	0.0240	0.181	2.400		
ibrutinib	0.00032	0.054	0.032		
ACP-5862†	0.0630	0.188	6.300		

- Ibru, Zanu, Acala are covalent BTKi
- First **bind** (k_i) and then **inactivate** (k_{inact}) BTK
- Should be evaluated at [C] ≤ k_i or IC_{50} (surrogate of k_{inact})[1,2]

- BTK is homologous with other kinases[3]
- So BTKi unavoidably target more >1 kinase
- In kinome assays, the number of «innocent» kinases increases as [BTKi] > k_i or IC_{50}

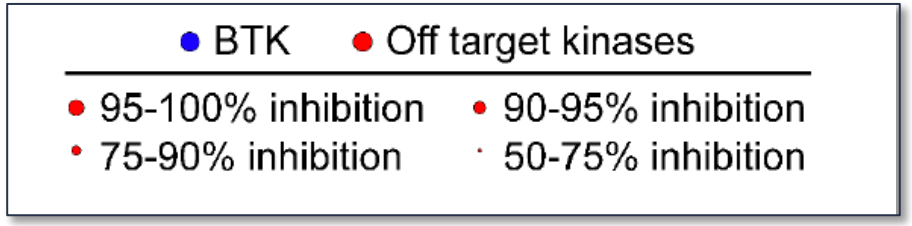
- In published kinome assays, BTKi used at 1 μm (>>> k_i) [4] or at 100xIC_{50} [5]

- Selectivity conditions, [BTKi] ≤ k_i only achieved for Ibru and Zanu in 100xIC_{50} assay: **Zanu more** selective than Ibru[5]
- We need kinome assays that achieve selectivity conditions for all 3 BTKi + Acala metabolite (M27/ACP-5862)[6]

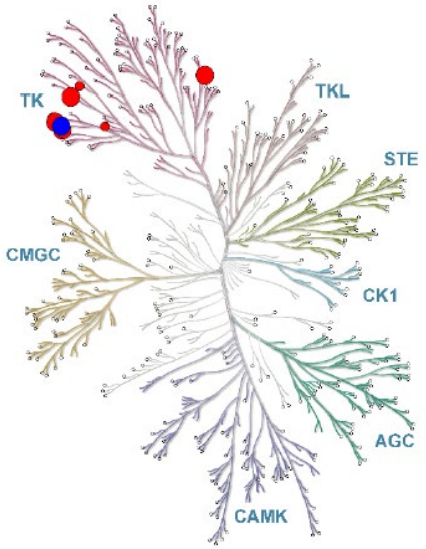
1) Lonsale R and Ward RA. Chemical Society Reviews. Structure-based design of targeted covalent inhibitors. 2018. Issue 11.
2) Strelow JM, SLAS Discov. 2017;22(1):3-20; 3) Speaker's own; 4) Podoll T et al, J Pharmacol Exp Ther. 2023;384(1):173-186;
5) Shadman M et al, Lancet Haematol. 2023; 10(1):e35-e45;**6)** Minotti G, Blood Adv. 2024 (in press); table modified.

Acala, acalabrutinib; BTK(i), Bruton tyrosine kinase (inhibitor); Ibru, ibrutinib; IC_{50}, half-maximal inhibitory concentration; kinact/KI , a rate constant describing the efficiency of covalent bond formation resulting from the potency (KI) of the first reversible binding event and the maximum potential rate (kinact) of inactivation; Zanu, zanubrutinib.

Kinase selectivity of zanubrutinib, ibrutinib, acalabrutinib, and acalabrutinib metabolite M27

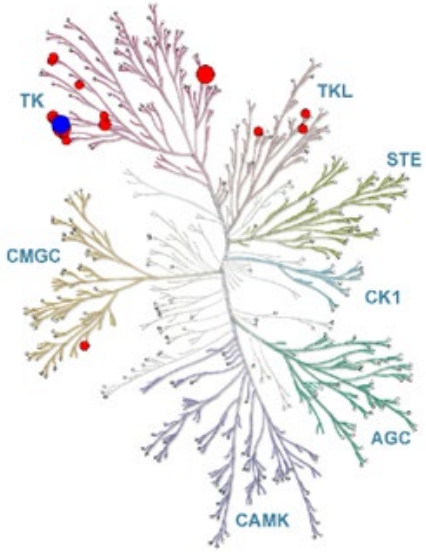


Zanubrutinib



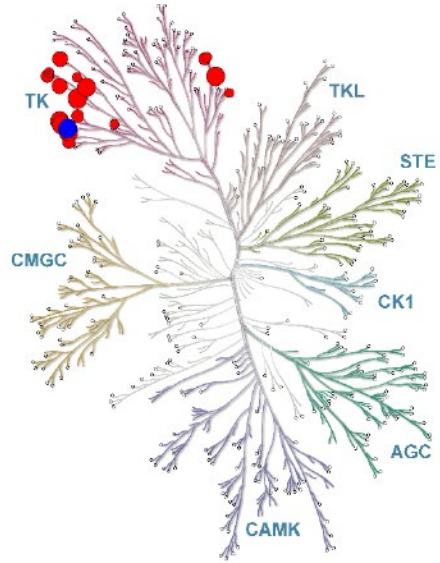
7/370 >50% inhibition

Acalabrutinib



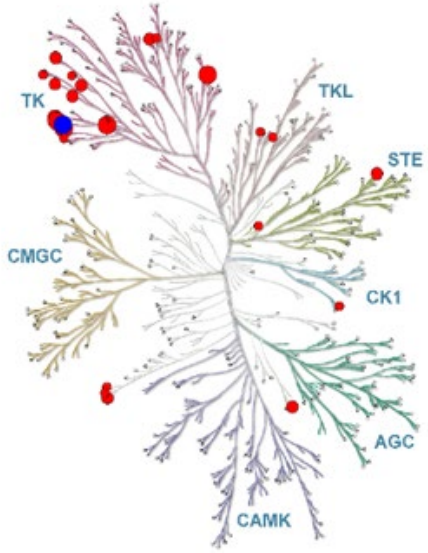
15/370 >50% inhibition

Ibrutinib



17/370 >50% inhibition

M27



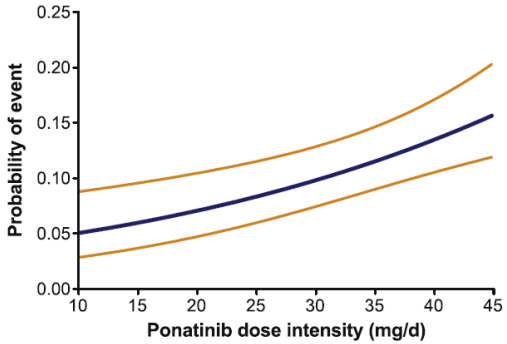
23/370 >50% inhibition

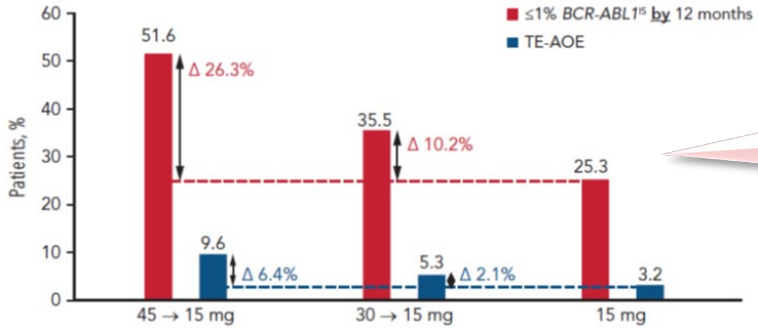
Assayed by Reaction Biology Corp. at **100X of IC50** (against BTK) concentration with IC50 (BTK)s of 0.71±0.09, 0.32±0.09, 24±9.2, and 63±28 nM (n=3), for zanubrutinib, ibrutinib, acalabrutinib, and M27, respectively.

BTK, Bruton tyrosine kinase; IC_{50}, half-maximal inhibitory concentration.

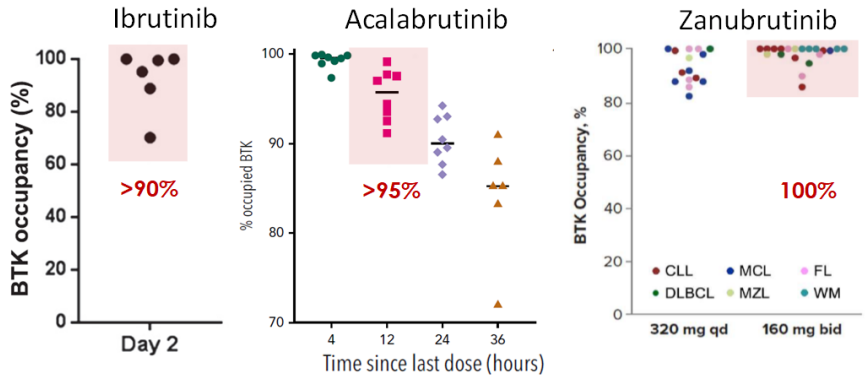
Extracted from Shadman M, Flinn IW, Kingsley EC, Freeman BB, Levy MY, Farber CM et al. Zanubrutinib in Acalabrutinib-Intolerant Patients With B-Cell Malignancies. Presented at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023, San Diego, CA. Abstract 3279. (Accessed 12 June 2024). Available at: Shadman_BGB-3111-215_ASH_Poster.

BTKi dose and BTK occupancy





- With other TKIs, like ponatinib, risk of CV ADR correlates with dose intensity[1]
- But reducing dose can jeopardize drug response (in this case, in CML)[2]



- With BTKi, need to weigh impact of dose reduction on CV ADRs with risk of reduced BTK occupancy in LN
- LN biopsy studies suggest BTK occupancy: Zanu > Acala > Ibru[3]

BTKi	Vd (L)
Ibrutinib	683
Acalabrutinib	723
Zanubrutinib	881

- Zanu's greater distribution volume might account for this[4-6]
- This might make Zanu a better candidate for dose reductions

Acala, acalabrutinib; ADR, adverse drug reaction; BTK(i), Bruton tyrosine kinase (inhibitor); CML, chronic myelogenous leukemia; CV, cardiovascular; Ibru, ibrutinib; LN, lymph node; TKI, tyrosine kinase inhibitor; Vd, volume of distribution; Zanu, zanubrutinib.

1) Dorer DJ et al, Leuk Res. 2016;48:84-91; 2) Cortes J et al, Blood. 2021;138(21):2042–2050; 3) Tam CS et al, Expert Rev Clin Pharmacol. 2021;14(11):1329-1344 (figure adapted from reference);
4) Alsuhebany et al, Blood Lymph Cancer: Targets Ther. 2023;13:67–76; 5) Bose P et al, Expert Opin Drug Metab Toxicol. 2016;12(11):1381-1392; 6) Xu Y et al, J Clin Pharmacol. 2022;62(6):812-822.

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Audience Q&A

Take-home messages

- **BTKi have revolutionized CLL therapy**[1]
- **The first- and next-generation BTKis provide treatment options for patients**[1]
- **BTKi mutations** under BTKi treatment: BTK and/or PLCG2 mutations may not be the main factors driving PD[2]
- **BTKi switching**: most ibrutinib- and acalabrutinib-intolerance events did not recur with zanubrutinib[3]
- **Cardiovascular toxicity**: ibrutinib is associated with many CV ADRs, zanubrutinib and acalabrutinib less so, with some differences in ADR profiles; hypertension is manageable; a cardio-oncologic approach supports optimal BTKi use[4-8]
- **BTKi dose and BTK occupancy**: weigh impact of dose reduction on CV ADRs with risk of reduced BTK occupancy in LN; zanubrutinib's high LN occupancy and distribution volume may make it the best candidate for dose reduction[9-14]

BTK(i), Bruton tyrosine kinase (inhibitor); CLL, chronic lymphocytic leukemia; PD, progressive disease; PLCG2, phospholipase C gamma 2.

1) Frustaci AM et al, Cancers (Basel). 2023;15(5):1504; 2) Brown JR et al. Poster 1890 at ASH 2023; San Diego, CA, USA, December 9–12, 2023; 3) Shadman M et al. Poster presented at EHA 2023; Abstract P633; 4) Moslehi JJ et al. Blood Adv. 2024;8(10):2478-2490; 5) Quartermaine C et al, JACC CardioOncol. 2023;5(5):570–590; 6) Salem J-E et al, J Am Coll Cardiol. 2019;74(13):1667-1678; 7) Byrd JC et al, J Clin Oncol. 2021;39(31):3441-3452; 8) 2022 ESC Cardio-Oncology Guidelines; 9) Dorer DJ et al, Leuk Res. 2016;48:84-91; 10) Cortes J et al, Blood. 2021;138(21):2042–2050; 11) Tam CS et al, Expert Rev Clin Pharmacol. 2021;14(11):1329-1344; 12) Alsuhebany et al, Blood Lymph Cancer: Targets Ther. 2023;13:67–76; 13) Bose P et al, Expert Opin Drug Metab Toxicol. 2016;12(11):1381-1392; 14) Xu Y et al, J Clin Pharmacol. 2022;62(6):812-822.

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