BTK Inhibitors in CLL and Lymphomas: Overview and Current Indications

IMBRUVICA® (Ibrutinib)億珂® 膠囊
CALQUENCE (Acalabrutinib)克瘤康膠囊
BRUKINSA® (Zanubrutinib)百悅澤®

Clinical pharmacist : Lihua Fang

2024/11/27

Outline

- BTK 治療歷史 (History of Bruton's tyrosine kinase)
- Role in Cancer treatment （ Type of cancer, Driven gene, role of treatment ）
- Drug mechanism
- Indication
  - Clinical measurement
  - Followed up : Lab data
  - Drug studies and comparison (ORR, OS)
  - ADR
- Side effect management
- Education
- Conclusion

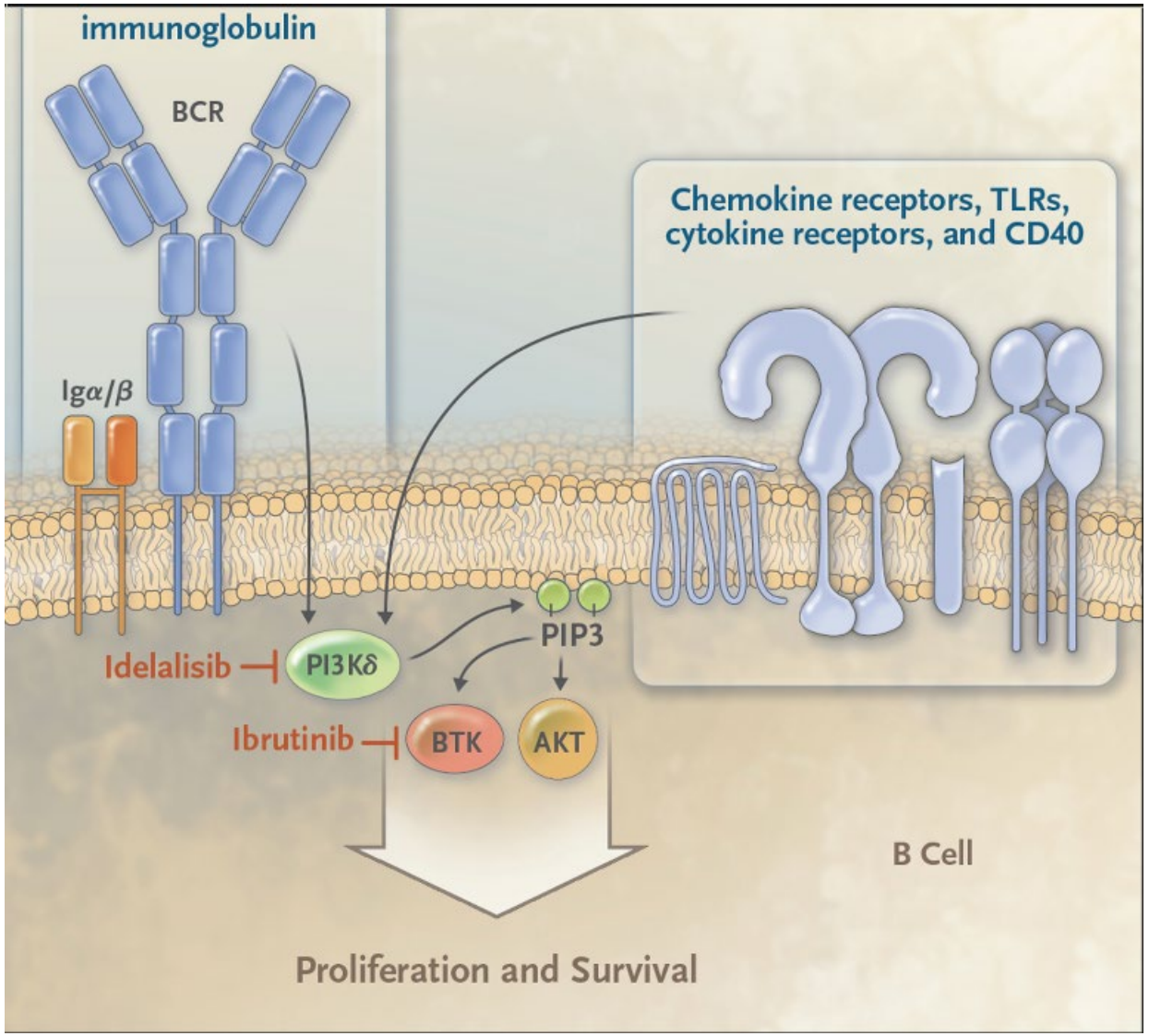
Ogden Bruton: Bruton's Agammaglobulinemia

- Chief of Pediatrics at Walter Reed National Military Medical Center
- Described "*a hitherto unrecognized entity manifested by complete absence of gamma globulin with otherwise normal serum proteins and recurrent pneumococcal sepsis is described in an 8-yr-old male*"
- The causal genetic defect has since been mapped to the gene for Bruton's tyrosine kinase (*BTK*), at band Xq21.3
  - BTK plays a crucial role in B-cell maturation, but when mutated can result in the immunodeficiency disorder XLA
- Patients with XLA have normal pre–B-cell populations in their bone marrow but these cells fail to mature and enter the circulation

Bruton. Pediatrics. 1952;9:722.

Slide credit: clinicaloptions.com

A PI3Kδ Inhibitor for B-Cell Cancers Idelalisib



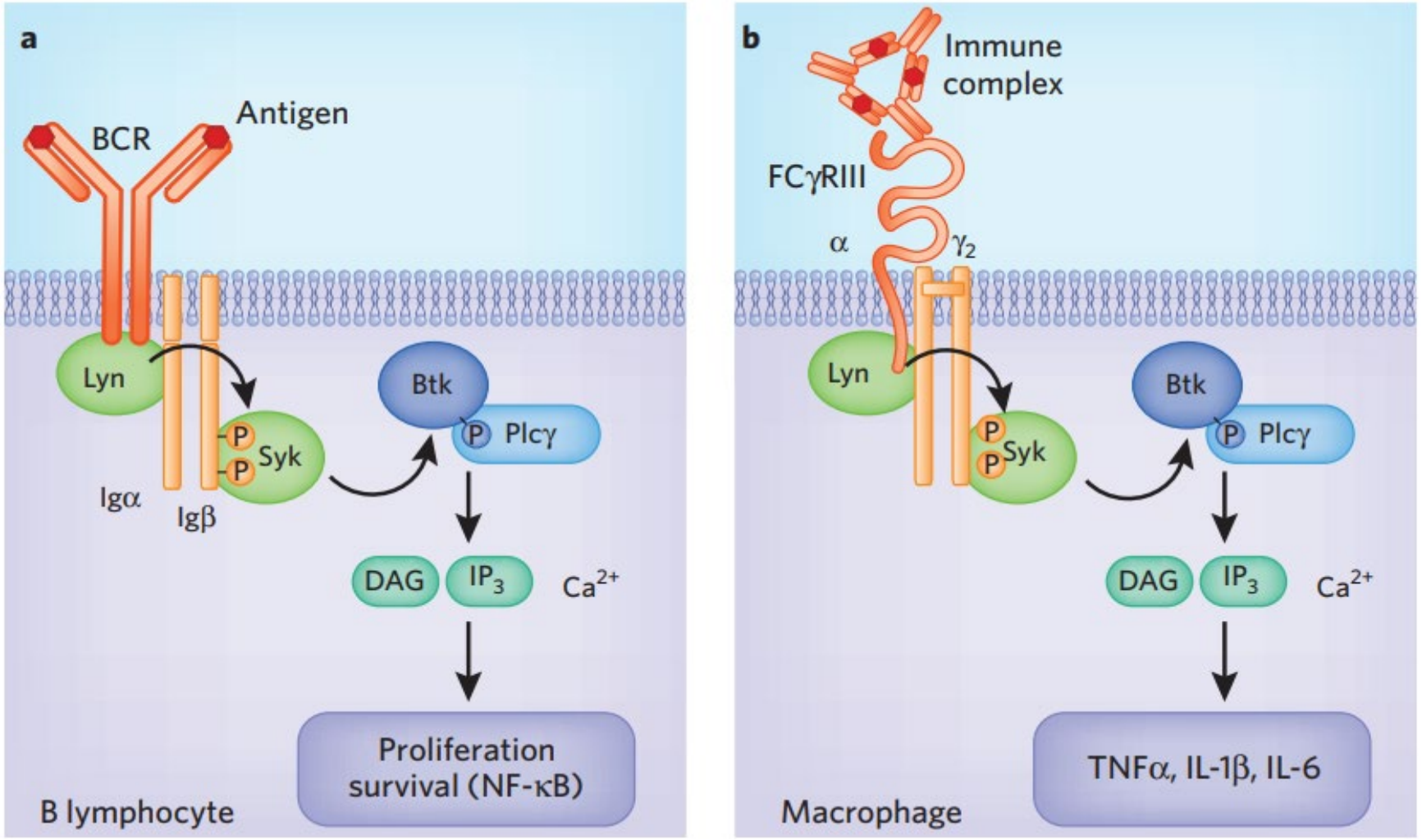
B 細胞受體 (BCR) 訊號傳導會活化磷酸肌醇 3- 激酶 (PI3K)，產生第二信使磷酸肌醇 3,4,5- 三磷酸酯 (PIP3)，進而活化布魯頓酪氨酸激酶 (BTK) 和 AKT，AKT 是一種可結合 PIP3 的促生存激酶，在許多實體腫瘤中扮演關鍵角色。
Idelalisib 是 PI3K δ 異構型的選擇性抑制劑，針對惡性 B 細胞中 BCR 下游的信號轉導，而 ibrutinib 則針對 BTK。PI3K 和 BTK 也會在 B 細胞上許多其他受體的下游被活化，包括 CD40、細胞激素受體、化學因子受體和 toll-like 受體 (TLR)。BCR 由與 Igα 和 Igβ 兩種訊號鏈相關的抗體重鏈和輕鏈組成。

N Engl J Med 2014;370:1061-1062

Bruton's tyrosine kinase (Btk): cytoplasmic protein tyrosine kinases and is expressed in many hematopoietic cell lineages. Dual mechanism of action:

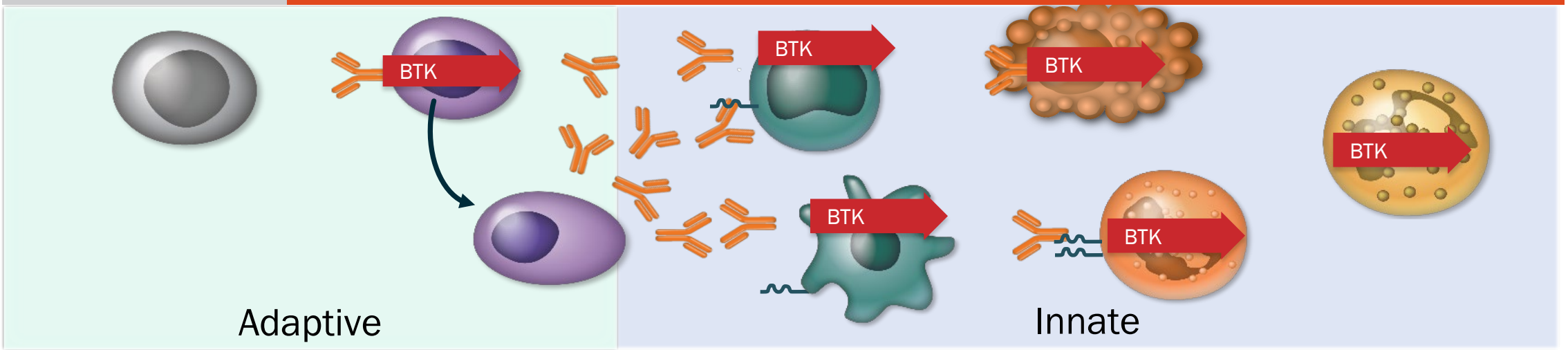
(i) inhibition of BCR-dependent B cell proliferation and autoantibody production

(ii) suppression of myeloid cell–dependent inflammatory cytokine production



BTK Inhibition Targets Both Adaptive and Innate Drivers of Immune-Mediated Disease

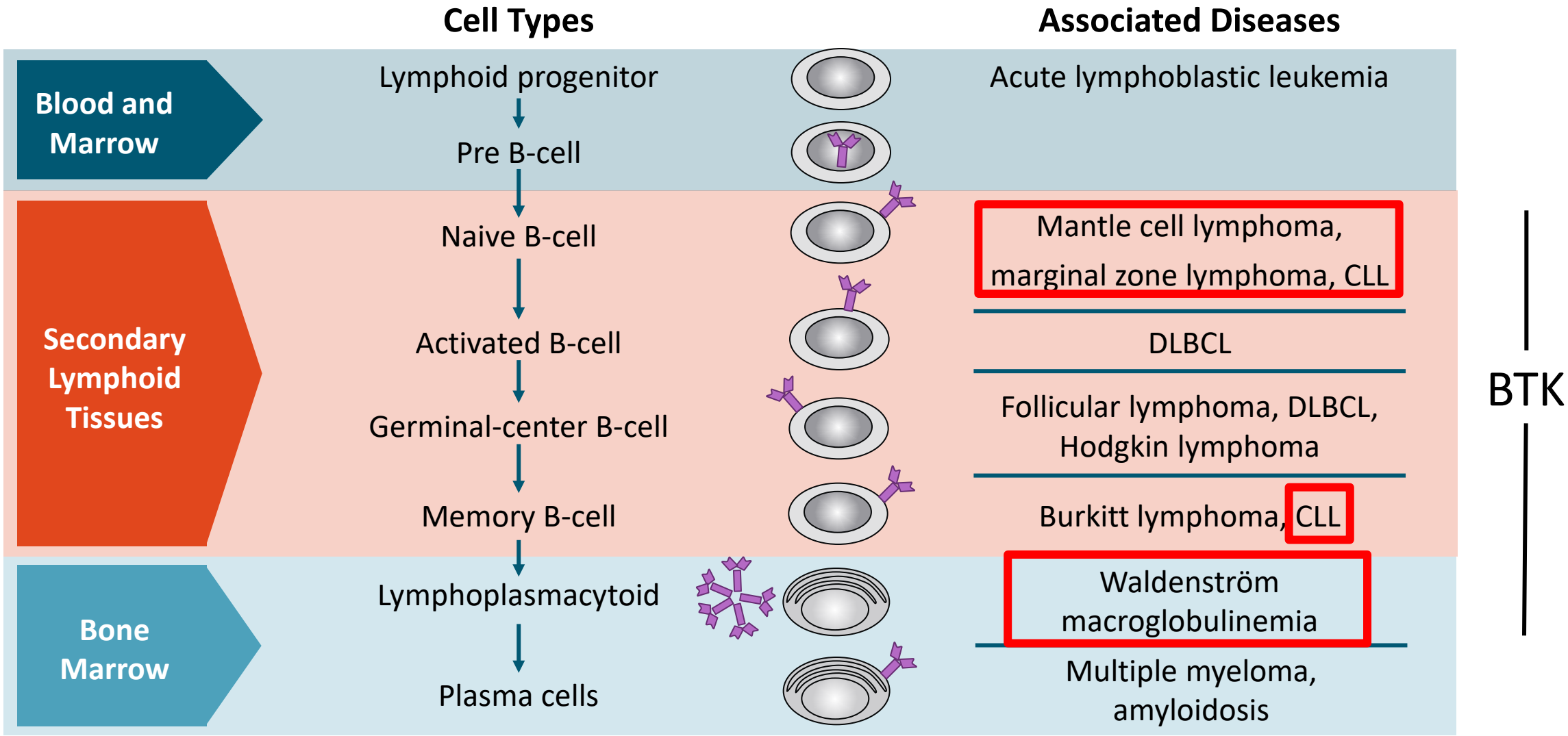
T-Cells	B-Cells, Plasma Cells	Monocytes, Macrophages	Mast Cells, Basophils	Neutrophils
No effect	Blocks B-cell receptor Inhibits plasma cell differentiation and antibody production	Blocks IgG-mediated FcgR activation, phagocytosis, inflammatory mediators	Blocks IgE-mediated FceR activation and degranulation	Inhibits activation, adhesion, recruitment, and oxidative burst
	BTK Inhibition			



Lopez-Herrera. J Leukoc Biol. 2014;95:243. Langrish. J Immunol. 2021;206:1454.

Slide credit: clinicaloptions.com

B-Cell Malignancies: Cell Types and Associated Diseases



Burger. Nat Rev Cancer. 2018;18:148. Marti. In: Isvoranu, editor. Lymphocyte Updates - Cancer, Autoimmunity and Infection. 2017. NCI. Adult ALL treatment (PDQ®). NCI. Adult NHL treatment (PDQ®). NCI. Adult HL treatment (PDQ®). NCI. Plasma cell neoplasms (including multiple myeloma) treatment (PDQ®).

Slide credit: clinicaloptions.com

BTK in B-Cell Malignancies

- The BCR pathway plays a role in the growth, proliferation, and survival of normal and malignant B-cells
- BTK an essential enzyme in the BCR signaling pathway; downstream of BCR
- Inhibition of BTK can lead to the downstream mitigation of cell growth, proliferation, adhesion, migration, and survival of malignant B-cells
- BTK inhibitors approved in multiple lymphoma settings: CLL, MCL and MZL, and Waldenström macroglobulinemia

Indications for Available BTK Inhibitors

Ibrutinib
Adults with **MCL** treated with ≥1 prior tx
Adults with **CLL/SLL** with or without 17p deletion
Adults with **Waldenström macroglobulinemia**
Adults with **MZL** requiring systemic tx and treated with ≥1 prior anti–CD20-based tx
Adults with **chronic GVHD** after failure of ≥1 lines of systemic tx

Acalabrutinib
Adults with **MCL** treated with ≥1 prior tx
Adults with **CLL/SLL**

Zanubrutinib
Adult with CLL or SLL
R/R Follicular lymphoma (in combination with obinutuzumab) ≥2 lines of systemic therapy.
Adult with R/R Mantle cell lymphoma treated with ≧ 1 prior tx
Adult with R/R MZL treated with ≧ 1 Anti-CD20 base Tx
Adult with Waldenström macroglobulinemia

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI.

Mechanisms of Action and Properties of Approved BTK Inhibitors

Ibrutinib[1]	Acalabrutinib[2-4]	Zanubrutinib[5]
▪ First-generation BTK inhibitor	▪ Second-generation BTK inhibitor	▪ Second-generation BTK inhibitor
▪ Potent and irreversible	▪ Highly selective, potent, irreversible	▪ Highly selective, potent, irreversible
Approved: ▪ CLL/SLL ± del(17p) ▪ WM ▪ MCL with ≥ 1 prior therapy ▪ MZL in patients who require systemic tx and had ≥1 CD20-targeted tx ▪ Chronic GVHD	Approved: ▪ MCL with ≥1 prior therapy ▪ CLL/SLL	Approved: ▪ MCL with ≥1 prior therapy ▪ Adult with R/R MZL treated with ≧ 1 Anti-CD20 base Tx ▪ CLL/SLL ▪ WM
▪ Once-daily dosing – 420 mg PO daily for CLL/SLL, WM – 560 mg PO daily for MCL, MZL	▪ Twice-daily dosing – 100 mg PO q12h for MCL, CLL/SLL	▪ Once-daily dosing – 320 mg PO daily for MCL ▪ Twice-daily dosing – 160 mg PO q12h for MCL

1. Ibrutinib PI. 2. Acalabrutinib PI. 3. Byrd. NEJM. 2016;374:323. 4. Barf. J Pharmacol Exp Ther. 2017;363:240. 5. Zanubrutinib PI.

Slide credit: clinicaloptions.com

Current Treatment Landscape in CLL

First-line Treatment Options

No *del(17p)/TP53* mutations

FCR (*IGHV* mutated and <65 yrs/fit)
Ibrutinib
Acalabrutinib ± obinutuzumab
Venetoclax + obinutuzumab

With *del(17p)/TP53* mutations

Ibrutinib
Acalabrutinib ± obinutuzumab
Venetoclax + obinutuzumab

Second-line Treatment Options

With or without *del(17p)/TP53* mutations

Ibrutinib
Acalabrutinib
Venetoclax + rituximab
Idelalisib + rituximab
Duvelisib

The development of treatment for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)

- Chemotherapy and Chemoimmunotherapy
  - Alkylating Agents: chlorambucil and cyclophosphamide
  - Fludarabine-Based Regimens: In the 1990s, fludarabine superior efficacy over chlorambucil. Fludarabine with cyclophosphamide (FC),
  - Chemoimmunotherapy (FCR): The addition of rituximab, fludarabine and cyclophosphamide (FCR) (high response rates and prolonged remissions)
- Monoclonal Antibodies (anti-CD20 monoclonal antibody)
  - Rituximab: as backbone for combination regimens.
  - Newer anti-CD20 antibodies : Ofatumumab and Obinutuzumab

The development of treatment for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)

- BTK Inhibitors (Bruton's tyrosine kinase inhibitor)
  - The introduction of ibrutinib in the 2010s marked a shift to targeted therapies for CLL.
  - Remarkable efficacy in relapsed or refractory CLL and significantly improved PFS and OS, especially in del(17p) and TP53 mutations.
  - However, long-term use was associated with cardiovascular side effects.
  - Second-Generation BTK Inhibitors : Acalabrutinib and Zanubrutinib (similar efficacy to ibrutinib but with reduced toxicity)
- BCL-2 Inhibitors
  - Venetoclax: targets the anti-apoptotic protein BCL-2, which is overexpressed in CLL. (high efficacy in combination with anti-CD20 antibodies in del(17p) or TP53 mutations)
  - Deep remissions and are used as a finite-duration (有限) treatment, allowing for treatment-free periods after therapy completion

The development of treatment for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)

- PI3K Inhibitors
  - Another targeted option with relapsed/refractory CLL. often combined with rituximab, showed efficacy in heavily pretreated patients. However, the risk of immune-mediated side effects has limited their use in favor of BTK and BCL-2 inhibitors

Current Treatment Landscape in Mantle Cell Lymphoma

First-line Treatment Options

Aggressive Chemotherapy

R-DHAP (cisplatin, carboplatin or oxaliplatin)
R-CHOP/R-DHAP
NORDIC (maxi-CHOP/R + HD cytarabine)

Consolidation and Maintenance

HDT + ASCT → R maint for 3 yrs

Less Aggressive Chemotherapy

BR
VR-CAP
R-CHOP
Lenalidomide + R

Maintenance

After R-CHOP: R maint until PD

Second-line Treatment Options

Chemoimmunotherapy

Ibrutinib
Acalabrutinib
Zanubrutinib
Lenalidomide ± R
Venetoclax (off-label)

Slide credit: clinicaloptions.com

Marginal Zone Lymphoma and Waldenström Macroglobulinemia: A Brief Overview

Marginal Zone Lymphoma

- Rare diseases with a heterogeneous clinical presentation
  - Extranodal MZL of the MALT is the most common (~70% of MZLs)
  - Splenic MZL (~20% of MZLs)
  - Given their rarity, it is often difficult to conduct clinical trials specifically designed for patients with MZL
  - Ibrutinib and Zanubrutinib safety, efficacy has been established

Waldenström Macroglobulinemia

- Indolent lymphoplasmacytic infiltrate in bone marrow and IgM paraprotein in serum
  - Ibrutinib has demonstrated efficacy as monotherapy for rituximab-resistant cases, especially with *MYD88* mutations
  - Trend toward improved responses and less toxicity with Zanubrutinib

Slide credit: clinicaloptions.com

Dosing and Administration of BTK Inhibitors in CLL

	Ibrutinib[a]	Acalabrutinib[b]	Zanubrutinib[c,d]
Dosing	420 mg orally once daily	100 mg orally twice daily	160 mg orally twice daily or 320 mg orally once daily
Half-life	4 to 6 hours	1 hour	2 to 4 hours
Median T_{max}	1 to 2 hours	0.9 hours	2 hours
BTK occupancy	90% up to 24 hours after doses of 2.5 mg/kg/d	≥ 95% over 12 hours after 100 mg every 12 hours	100% up to 24 hours at total daily dose of 320 mg
Dose forms and strengths	Capsules: 70 mg, 140 mg Tablets: 140 mg, 280 mg, 420 mg, 560 mg	Capsules: 100 mg	Capsules: 80 mg
Renal impairment	No adjustment	No adjustment	No adjustment
Hepatic impairment			
Child-Pugh Class A (mild)	140 mg daily	No adjustment	No adjustment
Child-Pugh Class B (moderate)	70 mg daily	No adjustment	No adjustment
Child-Pugh Class C (severe)	Avoid use	Avoid use	80 mg twice daily

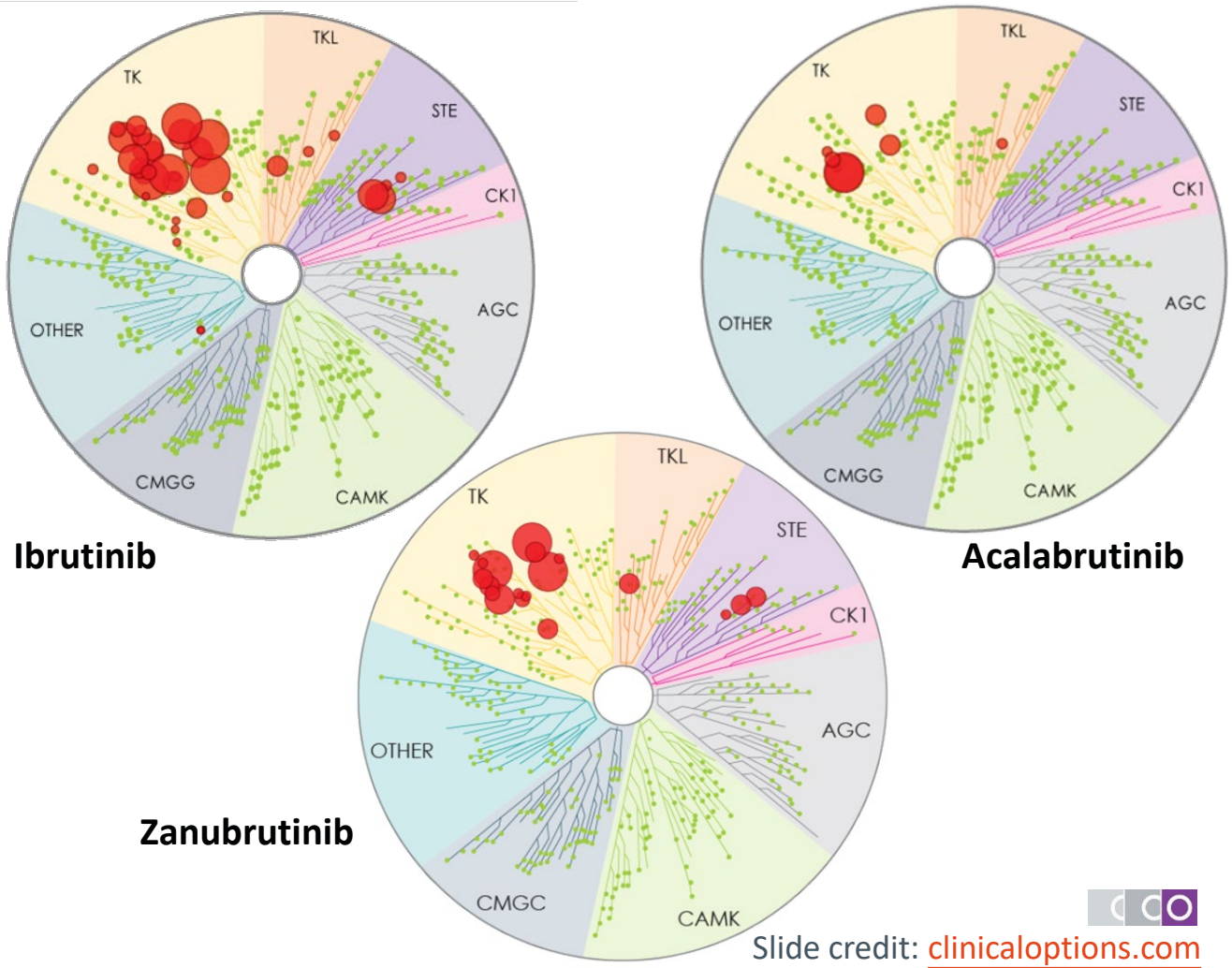
a. Imbruvica® (ibrutinib) [PI]. 2020; b. Calquence® (acalabrutinib) [PI]. 2019; c. Brukinsa™ (zanubrutinib) [PI]. 2019; d. NCCN. CLL/SLL. Version 4.2021.

Kinase Selectivity of BTK Inhibitors

IC_{50}/EC_{50} (nM)
(Inhibitory Concentration 50%)/(Effective Concentration 50%):

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

Kinase Selectivity Profiling at 1 μmol/L (in vitro)
Larger red circles represent stronger inhibition



Kaptein. ASH 2018. Abstr 1871.

Slide credit: clinicaloptions.com

Potential Effects Due to Off-Target Inhibition

BTK kinase

- Platelet effects[a,b]

TEC kinase

- Platelet effects[a,b]

Tyrosine-protein kinase expressed in hepatocellular carcinoma.

ITK kinase

- Antibody-dependent cellular cytotoxicity[a]

Interleukin-2-inducible T-cell kinase

BMX kinase

- Cardiac toxicity[a]

Bone Marrow tyrosine kinase on chromosome X.

EGFR kinase

- Rash[c]
- Cardiac toxicity[d]
- Diarrhea[c]

ERBB4 kinase

- Cardiac toxicity[a,d]

JAK3 kinase

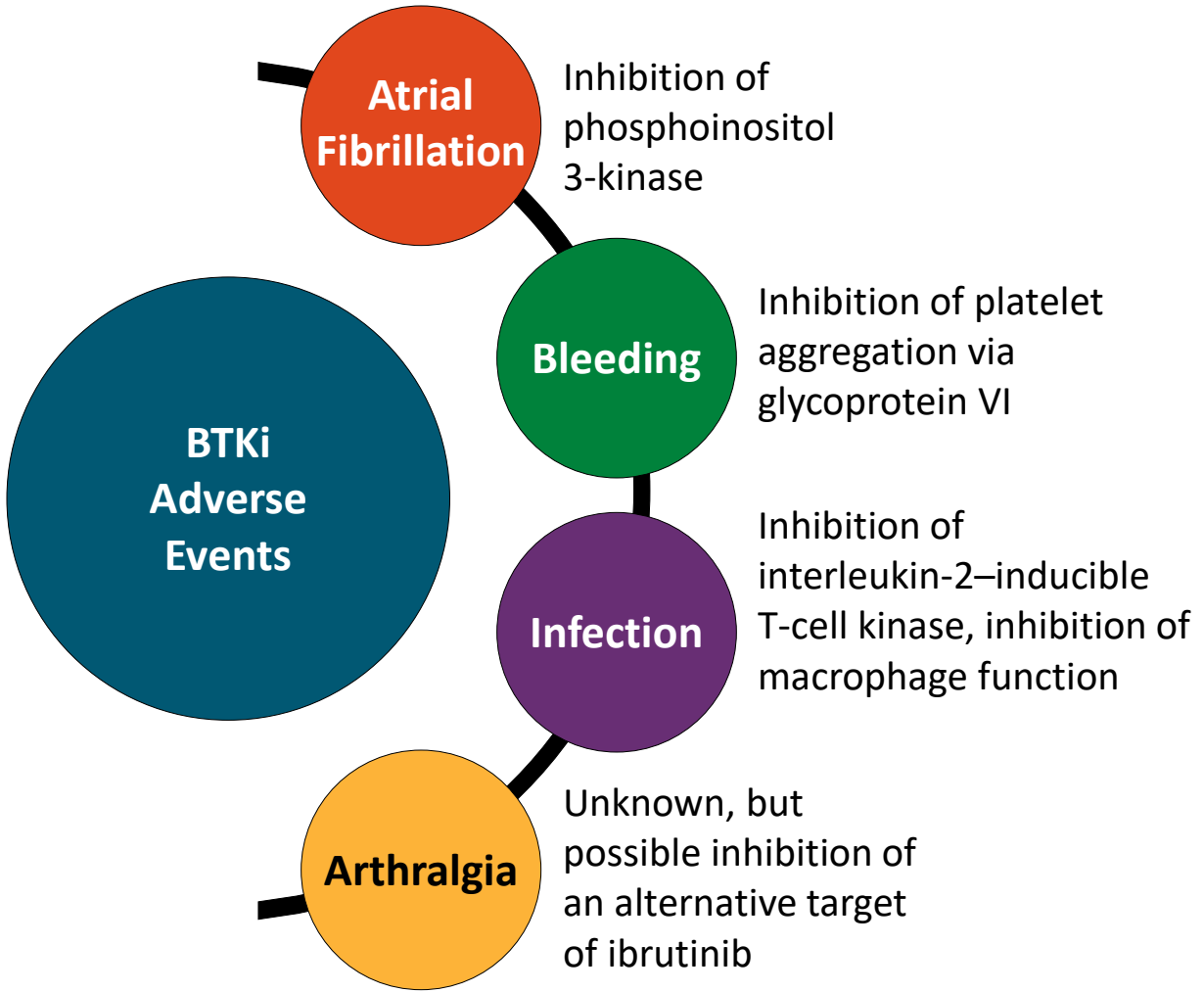
- Immune effects[a]

BLK kinase

- ----

a. Berglöf A, et al. *Scand J Immunol*. 2015;82:208-217; b. Shatzel JJ, et al. *J Thromb Haemost*. 2017;15:835-847; c. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program*. 2020;2020:336-345; d. Estupiñán HY, et al. *Front Cell Dev Biol*. 2021;9:630942.

Potential Mechanisms of Off-Target Inhibition



Stephens. Blood. 2019;133:1298.

Slide credit: clinicaloptions.com

Ibrutinib by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company: Summary of Trials Supporting Approvals

CLL	MCL	MZL	WM
Approved in frontline and relapsed/refractory settings, various studies ▪ ALLIANCE (A041202): First-line BR vs ibrutinib ± rituximab in CLL/SLL[1] ▪ Phase III E1912: Ibrutinib + rituximab vs FCR in patients ≤70 yrs with previously treated CLL/SLL[2] ▪ Phase III RESONATE 2: ibrutinib in older patients with treatment-naive CLL/SLL[3]	Approval based on phase II PCYC-1104 trial of previously treated patients with relapsed or refractory MCL[4]	Approval based on open-label phase II study in previously treated patients.[5] Single-agent ibrutinib induced durable remissions (ORR: 58%) with a favorable benefit–risk profile. ▪ Inhibition of BCR signaling with ibrutinib provides a treatment option without hemotherapy for an MZL population with high unmet need	Evaluated in both the frontline and relapsed/refractory settings[6] ▪ Median follow-up: 59 mo ▪ ORR: 90.5% ▪ Major response rate: 79.4%

1. Shanafelt. NEJM. 2019;381:432. 2. Woyach. NEJM. 2018;379:2517. 3. Burger. NEJM. 2015:373:2425.
4. Wang. NEJM. 2013;369:507. 5. Noy. Blood. 2020;24:5773. 6. Treon. JCO. 2021;39:565.

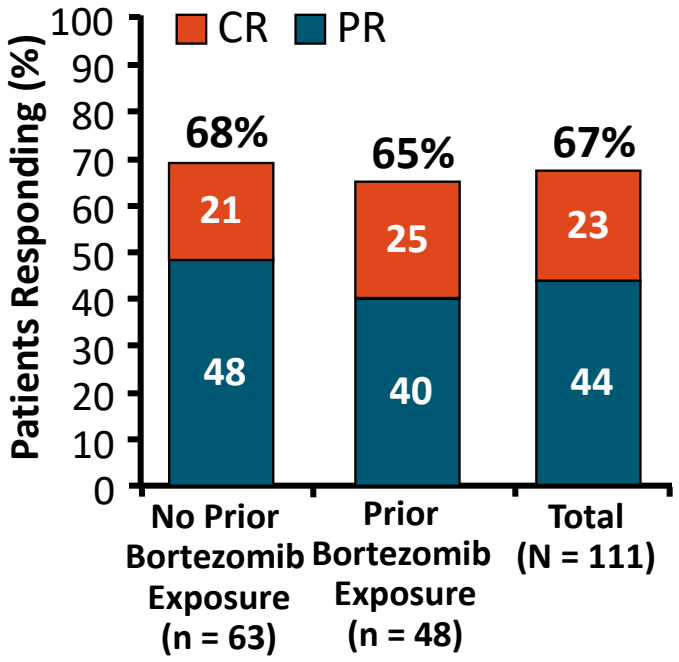
Slide credit: clinicaloptions.com

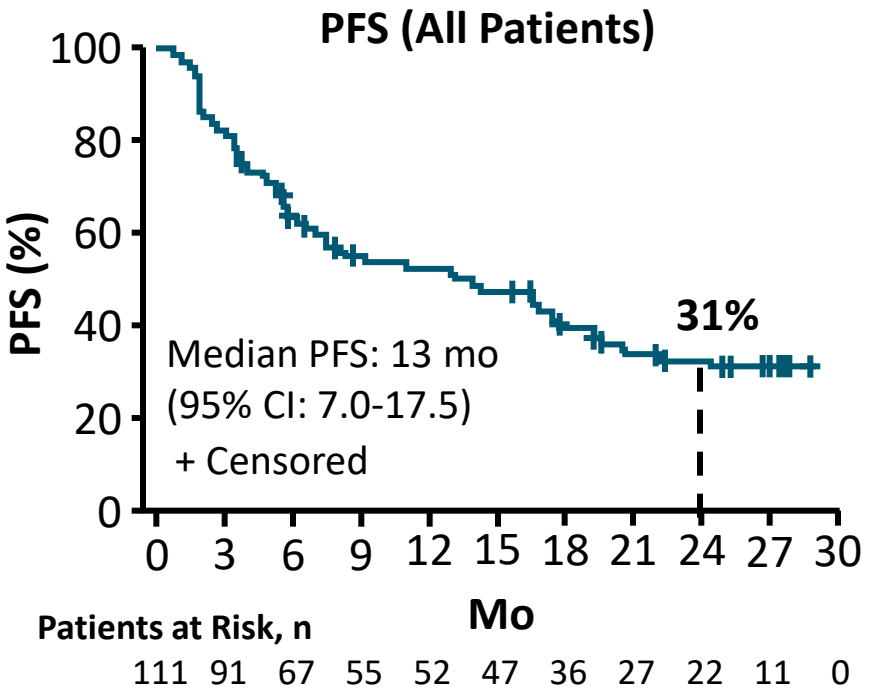
Phase II PCYC-1104: Targeting BTK With Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma

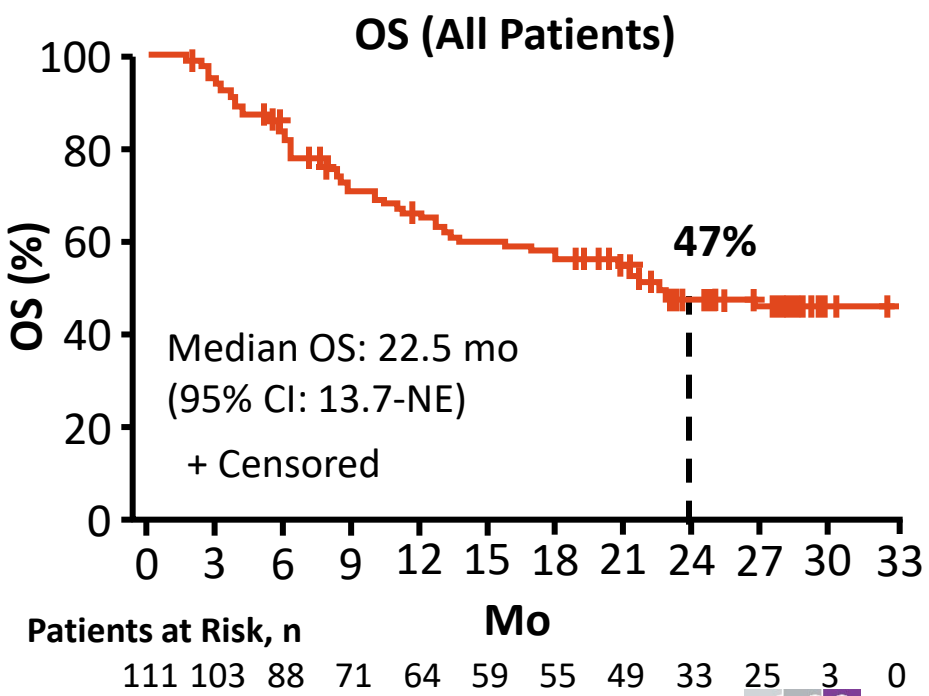
Patients with MCL and measurable disease (LN diameter ≥2 cm); 1-5 previous lines of tx; no <PR to the most recent tx or PD after the most recent tx; adequate organ function (N = 111)

→ **Ibrutinib**
560 mg PO daily →

Continue until PD or unacceptable AE occurred







Wang. NEJM. 2013;369:507. Wang. Blood. 2015;126:739.

Slide credit: clinicaloptions.com

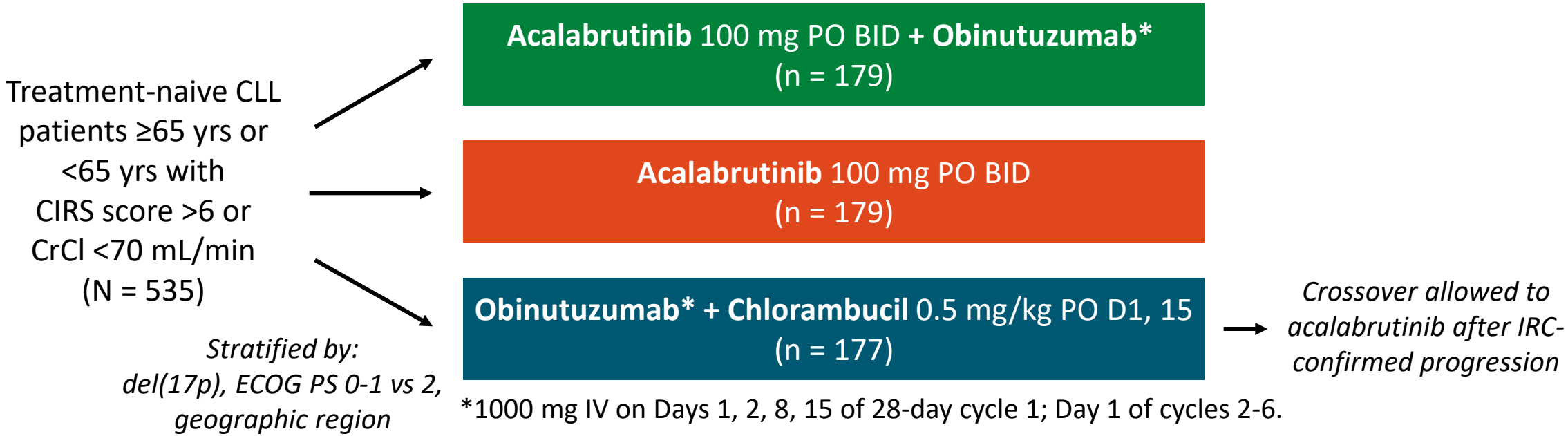
Acalabrutinib (by AstraZeneca): Key Studies

CLL	MCL
Phase III ELEVATE-TN: acalabrutinib ± obinutuzumab in patients with treatment-naive CLL[1] Phase III ASCEND: head-to-head study of 2 small-molecule inhibitors, idelalisib and acalabrutinib, plus BR or rituximab[2] Phase III ELEVATE RR: head-to-head study of acalabrutinib and ibrutinib[3]	Phase II ACE-LY-004 trial: open-label, single arm study of acalabrutinib in relapsed/refractory MCL[4]

1. Sharman. Lancet. 2020;395:1278. 2. Ghia. JCO. 2020;38:2849.
3. Byrd. ASCO 2021. Abstr 7000. 4. Wang. Lancet. 2018;391:659.

Slide credit: clinicaloptions.com

Phase III ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Chlorambucil + Obinutuzumab in Treatment-Naive CLL



*1000 mg IV on Days 1, 2, 8, 15 of 28-day cycle 1; Day 1 of cycles 2-6.

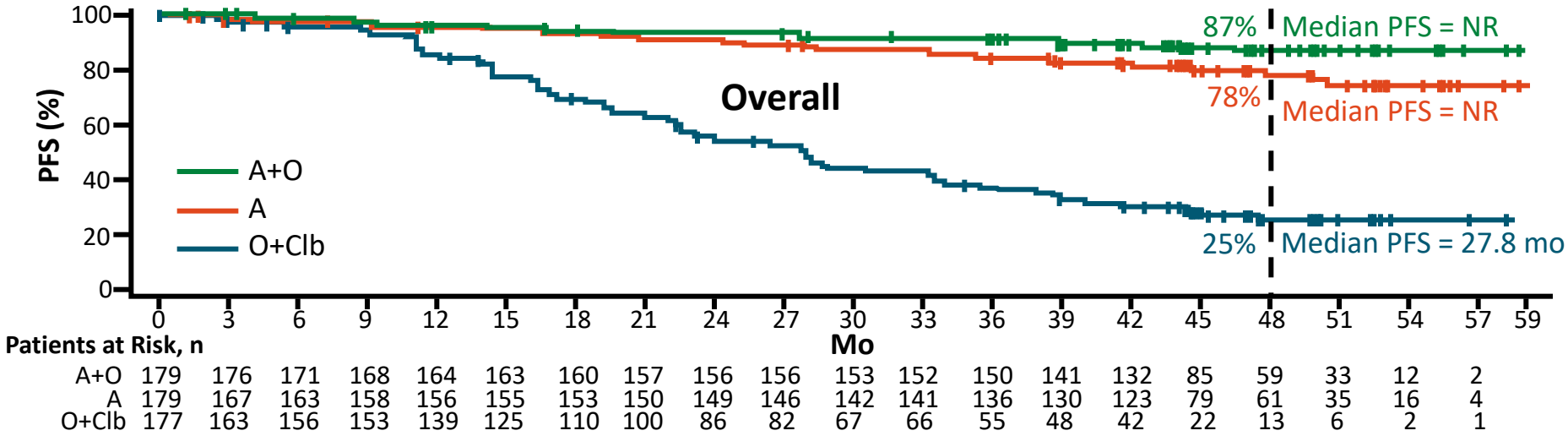
- Primary endpoint: PFS by IRC of acalabrutinib + obinutuzumab vs obinutuzumab + chlorambucil
- Key secondary endpoints: PFS of acalabrutinib vs obinutuzumab + chlorambucil, ORR by IRC and investigators, time to next treatment, OS, safety

Sharman. Lancet. 2020;395:1278.

Slide credit: clinicaloptions.com

ELEVATE-TN: PFS With 4-Yr Follow-up

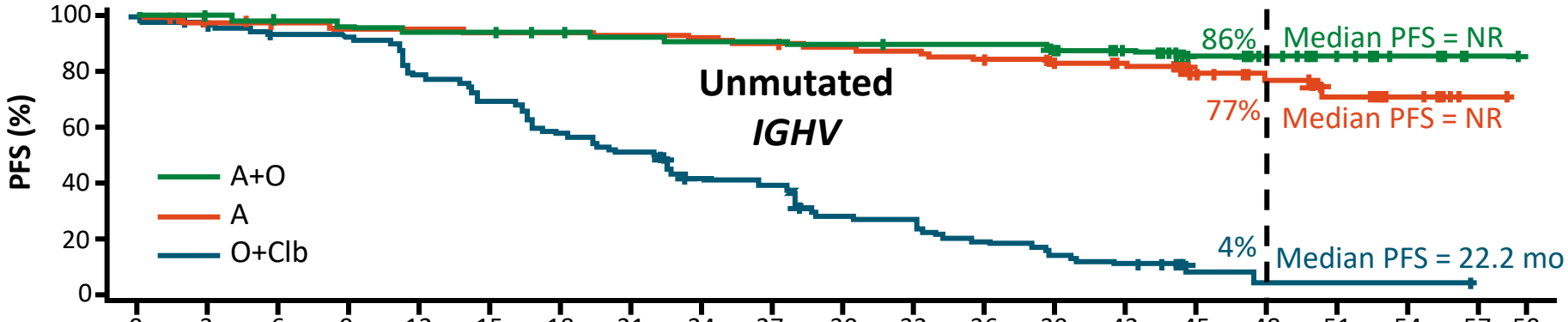
A+O vs O+Clb
HR: 0.10 (95% CI: 0.07-0.17)
P <.0001
A vs O+Clb
HR: 0.19 (95% CI: 0.13-0.28)
P <.0001
A+O vs A
HR: 0.56 (95% CI: 0.32-0.95)
P = .0296



Patients at Risk, n

A+O	179	176	171	168	164	163	160	157	156	156	153	152	150	141	132	85	59	33	12	2
A	179	167	163	158	156	155	153	150	149	146	142	141	136	130	123	79	61	35	16	4
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	55	48	42	22	13	6	2	1

A+O vs O+Clb
HR: 0.06 (95% CI: 0.04-0.11)
P <.0001
A vs O+Clb
HR: 0.10 (95% CI: 0.06-0.16)
P <.0001



Patients at Risk, n

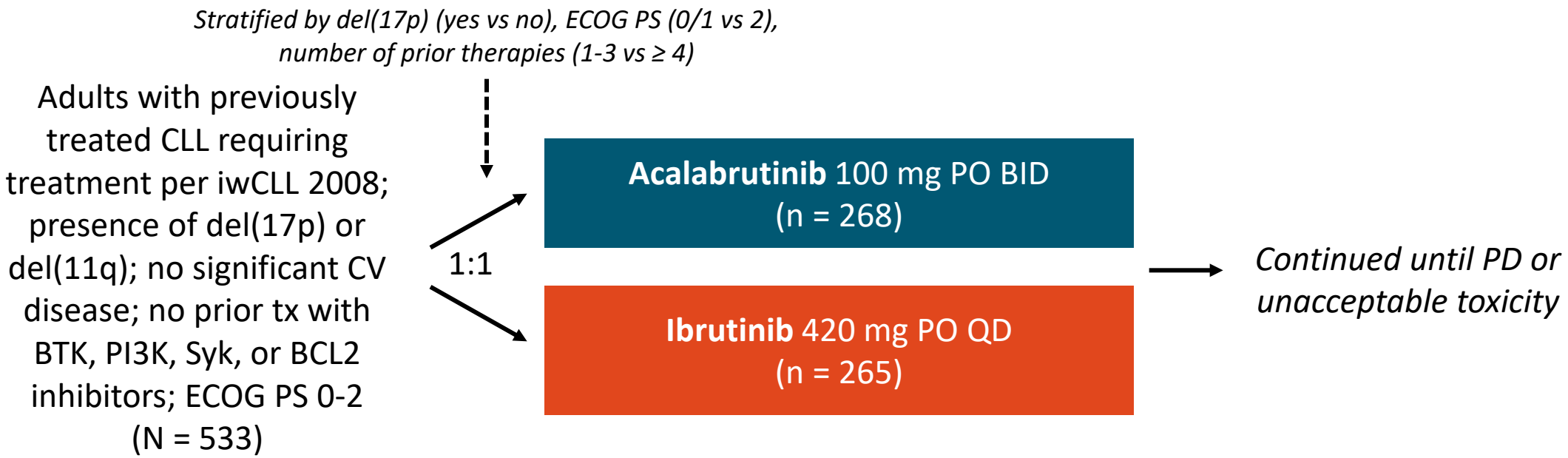
A+O	103	102	100	97	95	95	94	92	91	91	90	89	89	84	78	47	35	17	7	1
A	119	112	109	107	107	106	105	104	103	101	98	97	93	89	84	52	38	22	11	1
O+Clb	116	105	101	99	85	75	62	55	43	41	28	27	19	14	11	2	1	1	1	0

Sharman. ASCO 2021. Abstr 7509.

Slide credit: clinicaloptions.com

Acalabrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial

- Randomized, open-label, phase III noninferiority trial

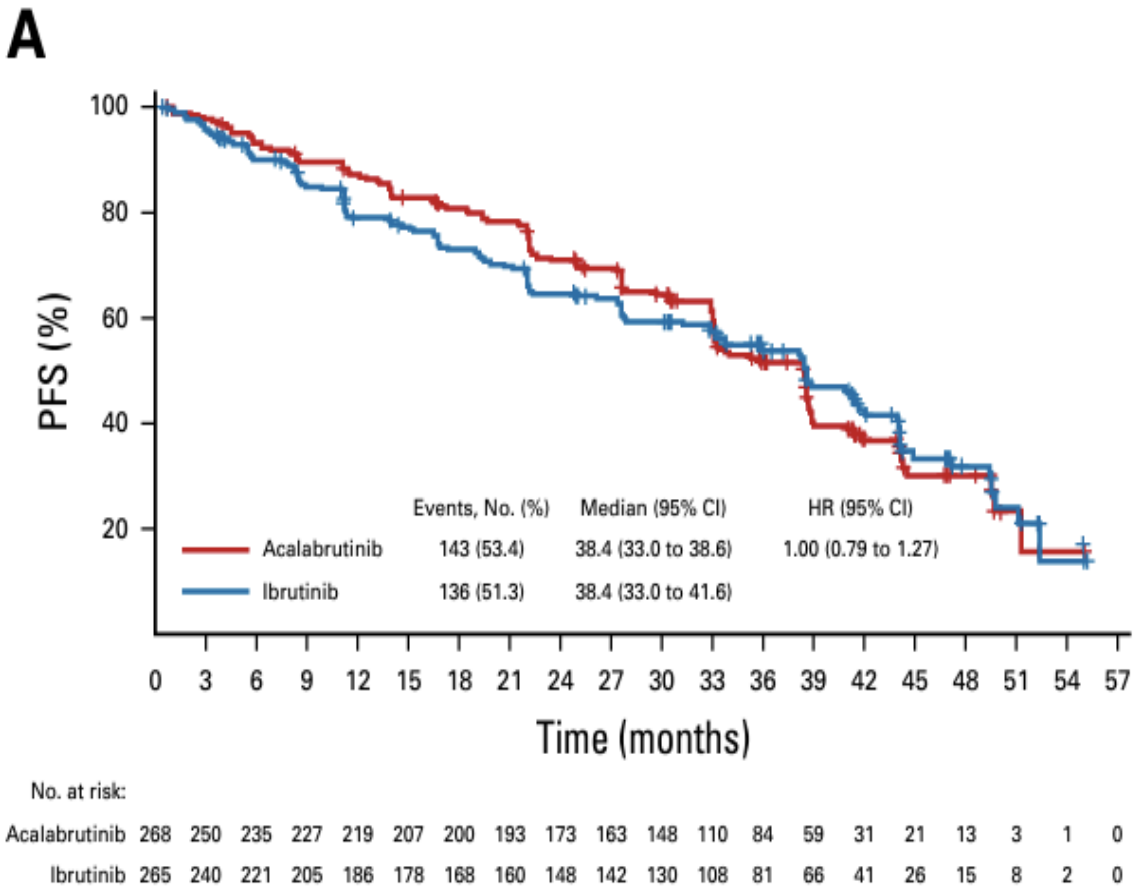


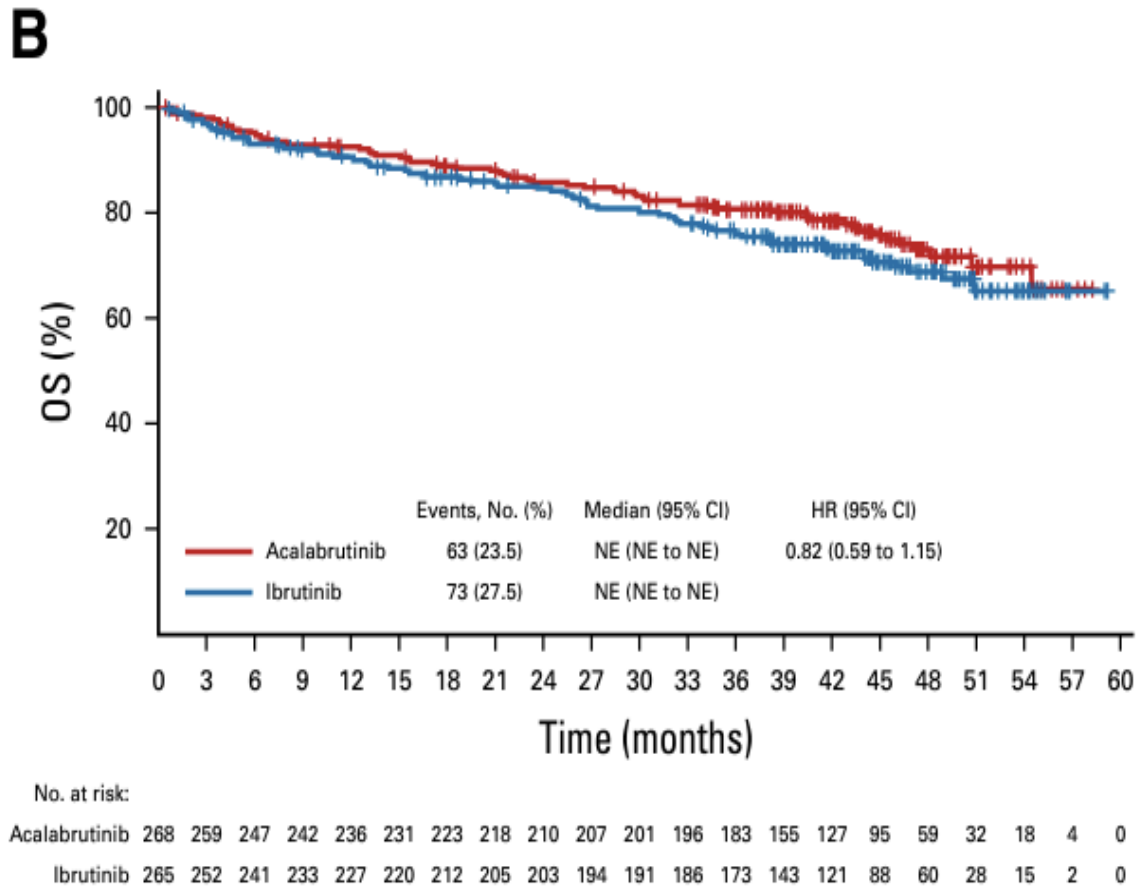
- Primary endpoint: noninferiority of IRC-assessed PFS (upper bound of 2-sided 95% CI for HR <1.429)
- Secondary endpoints: any-grade atrial fibrillation/flutter, grade ≥3 infection, Richter transformation, OS

Byrd. ASCO 2021. Abstr 7500.

Slide credit: clinicaloptions.com

ELEVATE-RR: PFS Noninferiority met on PFS and OS





J Clin Oncol. 2021 Nov 1;39(31):3441-3452.

Detailed Safety Profile of Acalabrutinib vs Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia in the ELEVATE-RR trial

Patients
Previously treated CLL (N = 533)

Randomized 1:1

Acalabrutinib
PO 100 mg BID
n = 266 treated

OR

Ibrutinib
PO 420 mg QD
n = 263 treated

Secondary Safety Analysis

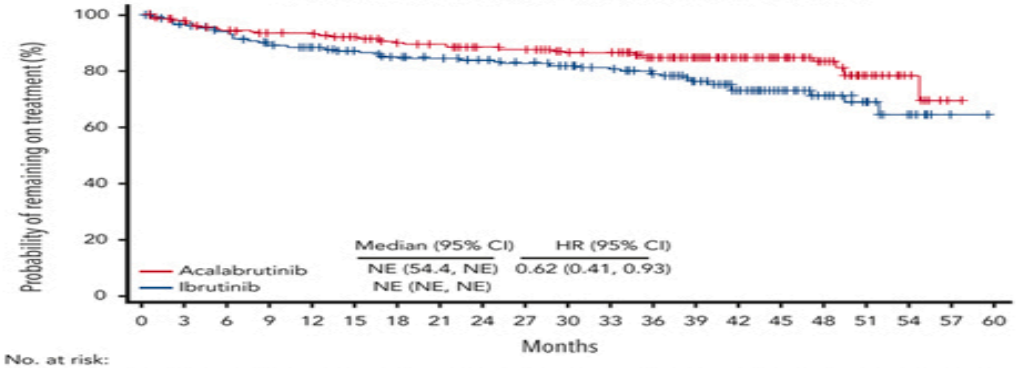
- Exposure-adjusted incidence rates in events per 100 person-months
- Subgroup analyses for ECIs: age, number of prior lines of therapy, prior history of event, AE management
- AE burden score: considers AE duration, recurrence, and grade weighting of the AE in a single score

Median time on study **40.9 months**

Exposure-adjusted Incidence

- Diarrhea, arthralgia, UTI, back pain, muscle spasms, and dyspepsia incidence rates were 1.5- to 4.1-fold higher with ibrutinib
- Headache and cough incidence rates were 1.6- and 1.2-fold higher, respectively, with acalabrutinib
- Afib/flutter, hypertension, and bleeding incidence rates were 1.6- to 2.8-fold higher with ibrutinib

Time to Treatment Discontinuation Due to AEs

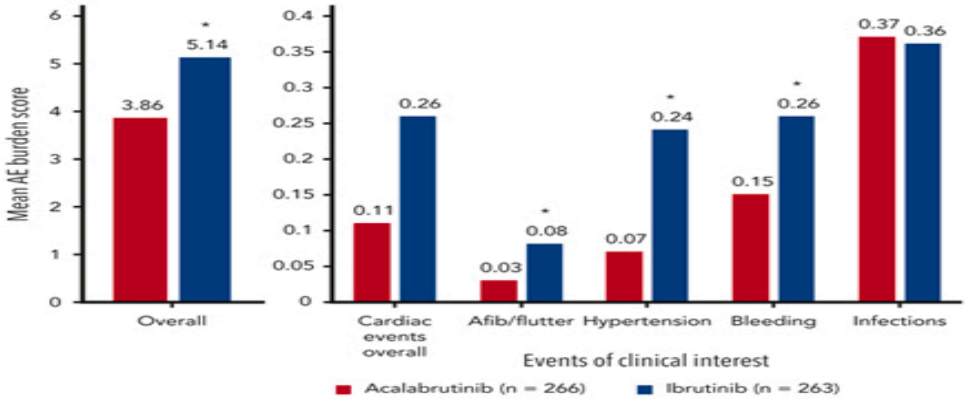


No. at risk:

Acalabrutinib	268	251	240	233	230	222	208	202	194	189	174	172	150	123	94	66	39	21	9	1	0
Ibrutinib	265	245	229	215	201	191	183	175	165	156	149	141	129	104	82	60	41	18	9	1	0

AE, adverse event; Afib/flutter, atrial fibrillation/atrial flutter; BID, twice daily; CI, confidence interval; CLL, chronic lymphocytic leukemia; ECI, event of clinical interest; HR, hazard ratio; NE, not estimable; PO, orally; QD, once daily; UTI, urinary tract infection.

AE Burden Score Overall and for ECIs (Grade 1-4)



*Two-sided *P*-value < .05 without multiplicity adjustment based on Wilcoxon rank-sum test. *P*-value compares difference in overall distribution rather than mean score.

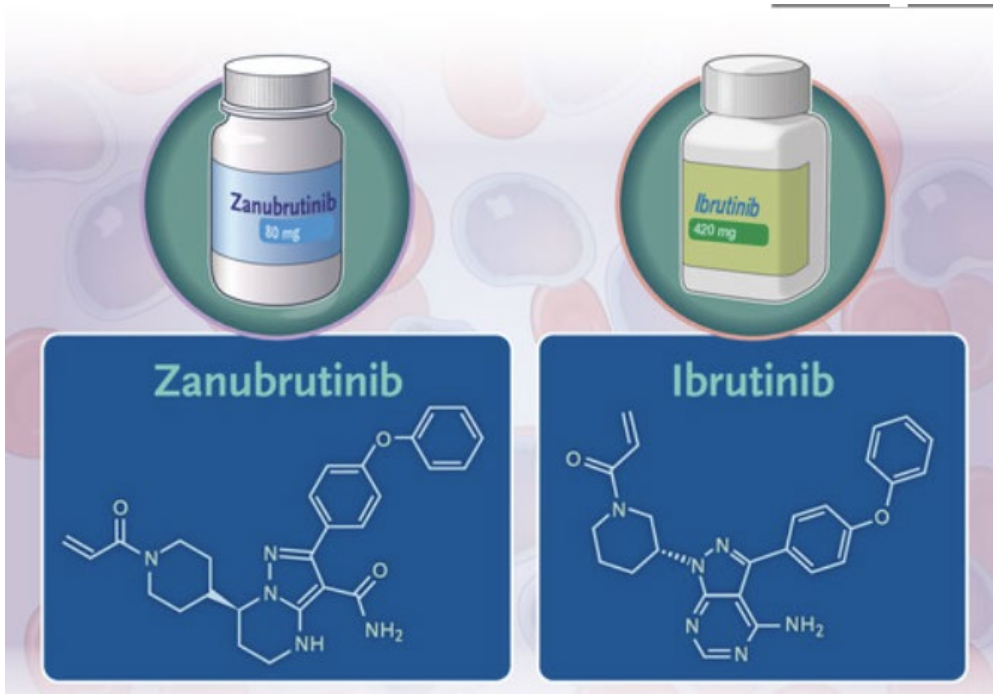
Conclusions:

1) Event-based analyses and AE burden scores demonstrated higher AE burden both overall and specifically for afib/flutter, hypertension, and hemorrhage with ibrutinib vs acalabrutinib

2) AE for which both event-based outcomes and AE burden scores were higher with acalabrutinib was limited to headache

*Seymour et al. DOI: 10.1182/**blood**.2022018818*

***Blood* Visual Abstract**



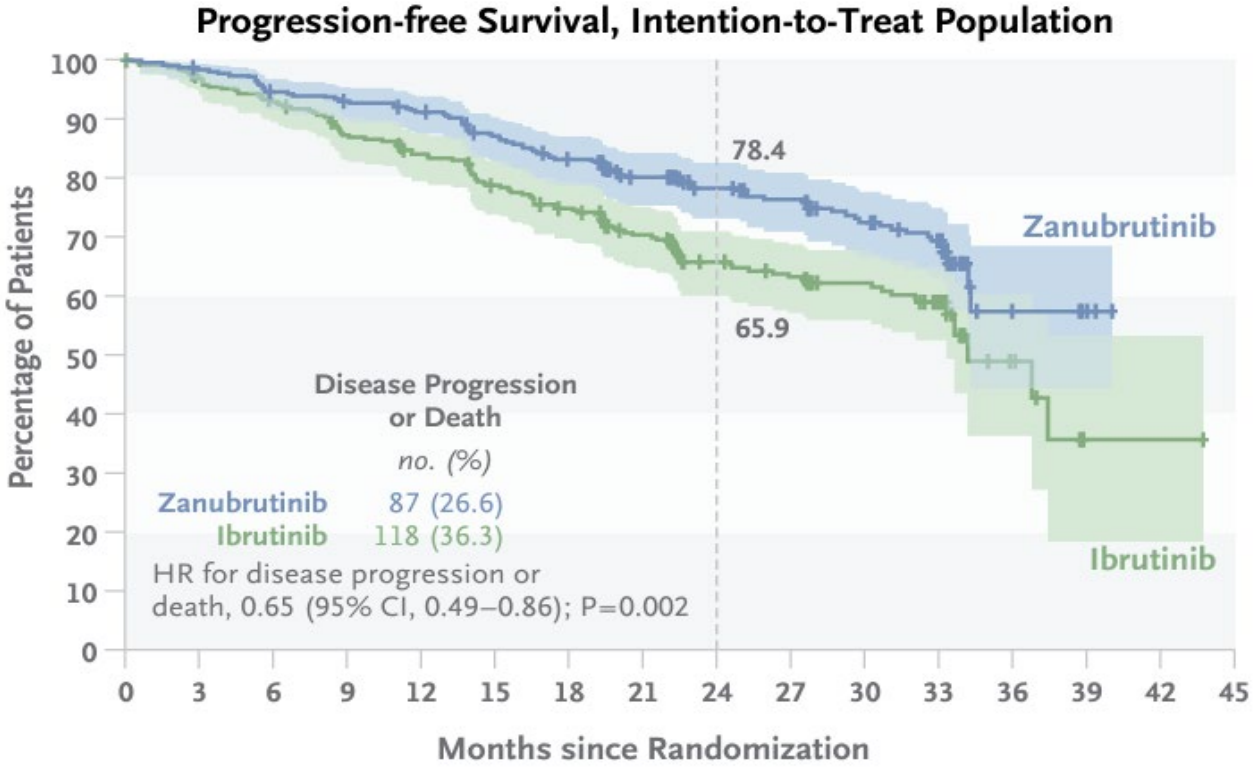
Zanubrutinib indication (百濟神州（BeiGene）
Adult with CLL or SLL
R/R Follicular lymphoma (in combination with obinutuzumab) ≥2 lines of systemic therapy.
Adult with R/R Mantle cell lymphoma treated with ≧ 1 prior tx
Adult with R/R MZL treated with ≧ 1 Anti-CD20 base Tx
Adult with Waldenström macroglobulinemia

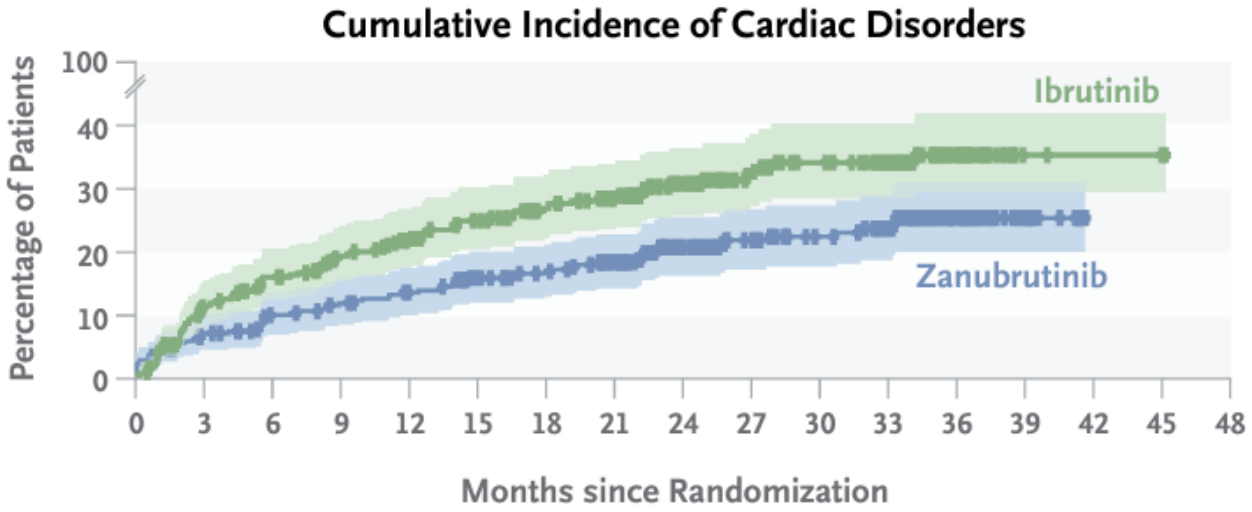
Zanubrutinib or Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)

Design: phase 3, open-label, randomized, controlled trial compared the efficacy and safety of zanubrutinib vs ibrutinib in patients with R/R CLL or SLL.

Pts : 652 adults with R/R at least one previous line of therapy

Drugs : zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily) until the occurrence of disease progression or unacceptable toxic effects.





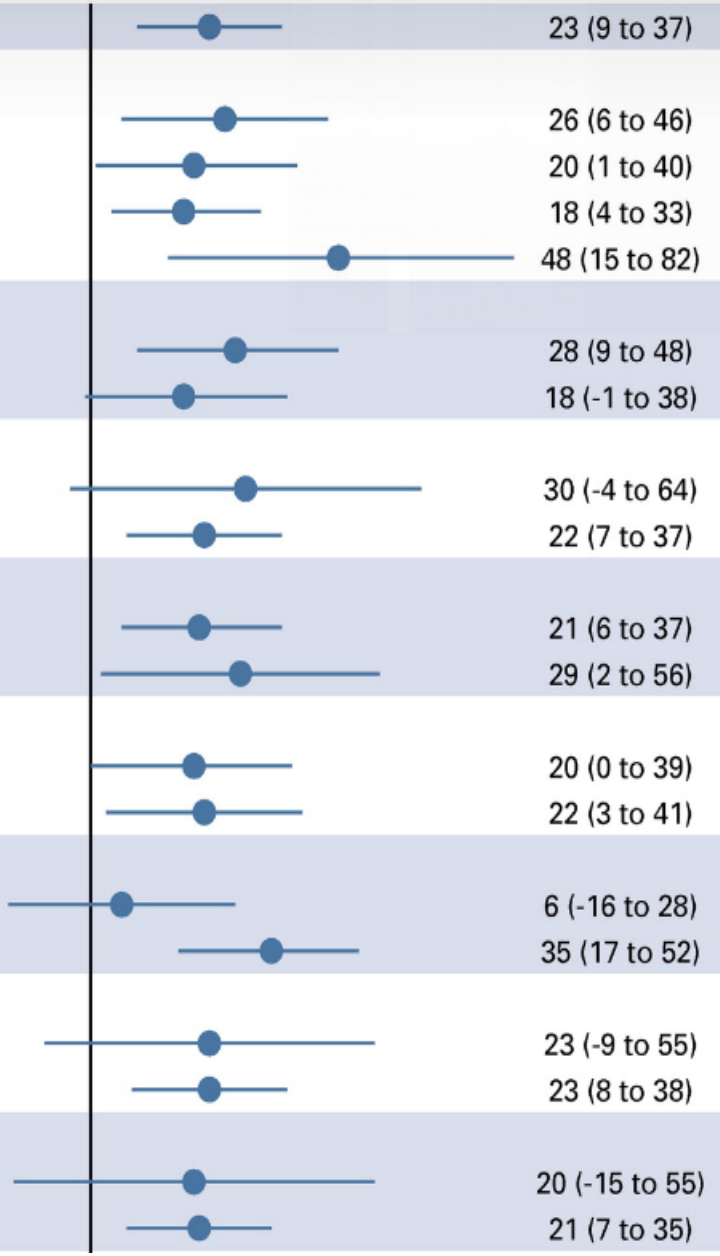
Engl J Med 2023;388:319-332

ROSEWOOD: A Phase II Randomized Study Zanubrutinib Plus Obinutuzumab Vs Obinutuzumab in Patients With R/R Follicular Lymphoma

- Patients with R/R FL who had received ≥2 lines of therapy, including an anti-CD20 antibody and an alkylating agent.
- Pt (ZO, 145; O, 72), 2:1 to receive ZO or obinutuzumab (O).
- Results
  - Median study follow-up : 20.2 months.
  - ORR : 69% (ZO) vs 46% (O; P = .001), 18 months DOR : 69% (ZO) vs 42%
  - CR : 39% (ZO) Vs 19% (O)
  - Median PFS : 28.0 months (ZO) vs 10.4 months (O; hazard ratio, 0.50 ; P < .001).
- ADR : thrombocytopenia, neutropenia, diarrhea, and fatigue; incidences of atrial fibrillation and major hemorrhage were 3% and 1%, respectively.

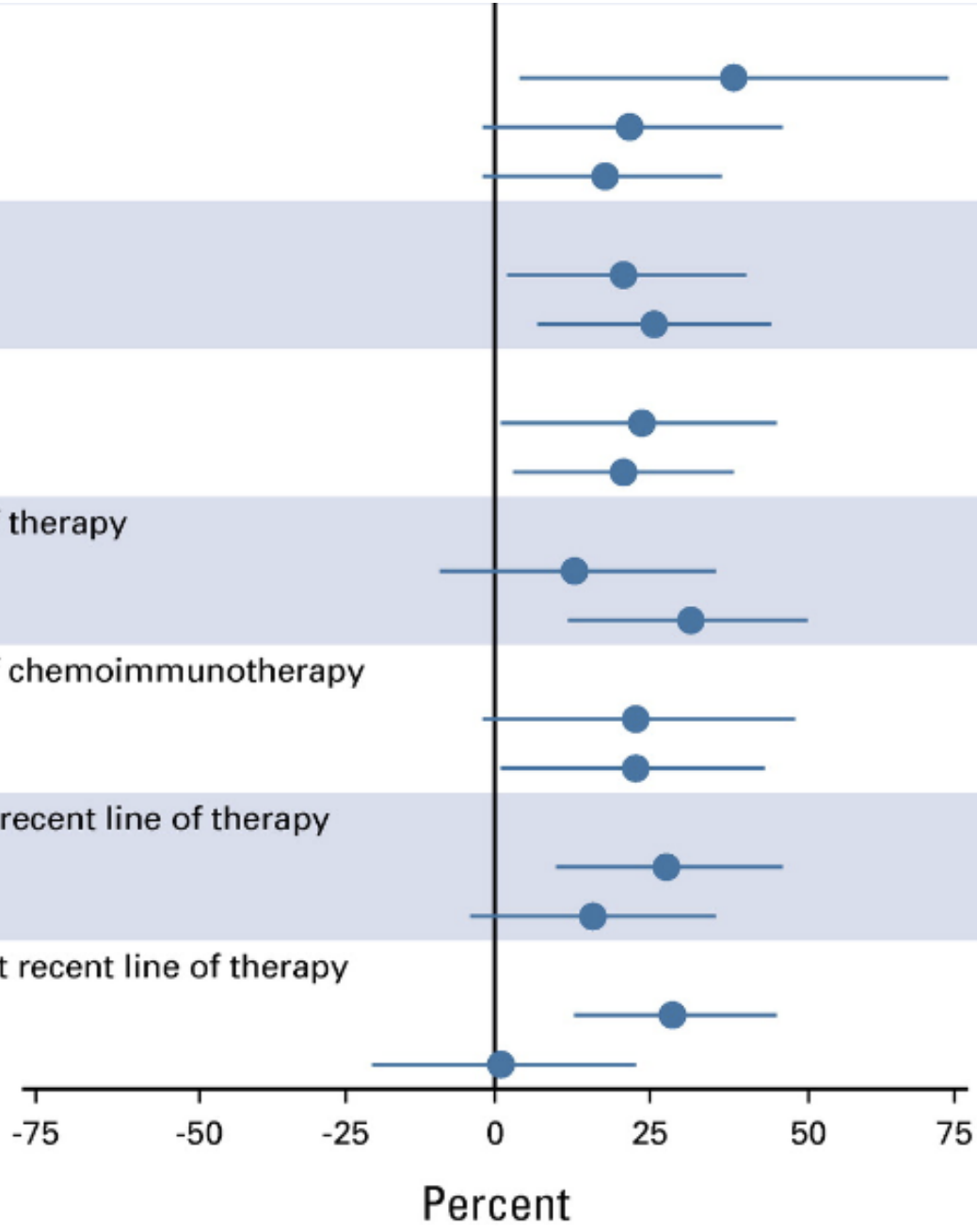
Clin Oncol . 2023 Nov 20;41(33):5107-5117.

Subgroup	Response/Patients (%) O	Response/Patients (%) ZO	Risk Difference, % (95% CI)
All patients in ITT	33/72 (46)	100/145 (69)	23 (9 to 37)
Age, years			
<65	14/32 (44)	58/83 (70)	26 (6 to 46)
≥65	19/40 (48)	42/62 (68)	20 (1 to 40)
<75	30/60 (50)	89/130 (68)	18 (4 to 33)
≥75	3/12 (25)	11/15 (73)	48 (15 to 82)
Sex			
Male	14/33 (42)	53/75 (71)	28 (9 to 48)
Female	19/39 (49)	47/70 (67)	18 (-1 to 38)
Geographic region			
China	5/12 (42)	15/21 (71)	30 (-4 to 64)
Ex-China	28/60 (47)	85/124 (69)	22 (7 to 37)
Previous lines of therapy			
2-3	27/54 (50)	77/108 (71)	21 (6 to 37)
>3	6/18 (33)	23/37 (62)	29 (2 to 56)
Baseline ECOG PS			
0	17/31 (55)	64/86 (74)	20 (0 to 39)
≥1	16/41 (39)	36/59 (61)	22 (3 to 41)
Bulky disease: any target lesion longest diameter ≥5 cm			
Yes	15/31 (48)	31/57 (54)	6 (-16 to 28)
No	18/41 (44)	69/88 (78)	35 (17 to 52)
Bulky disease: any target lesion longest diameter ≥7 cm			
Yes	3/12 (25)	11/23 (48)	23 (-9 to 55)
No	30/60 (50)	89/122 (73)	23 (8 to 38)
Bulky disease: any target lesion longest diameter ≥10 cm			
Yes	0/6 (0)	1/5 (20)	20 (-15 to 55)
No	33/66 (50)	99/140 (71)	21 (7 to 35)



Clin Oncol . 2023 Nov 20;41(33):5107-5117.

FLIPI risk category			
Low (0-1)	3/9 (33)	21/29 (72)	39 (4 to 74)
Intermediate (2)	13/24 (54)	26/34 (76)	22 (-2 to 47)
High (≥3)	17/37 (46)	49/77 (64)	18 (-2 to 37)
Rituximab-refractory status			
Refractory	14/36 (39)	47/78 (60)	21 (2 to 41)
Not refractory	19/36 (53)	53/67 (79)	26 (7 to 45)
Refractory status to the most recent line of therapy			
Refractory	11/29 (38)	29/47 (62)	24 (1 to 46)
Not refractory	21/42 (50)	66/93 (71)	21 (3 to 39)
Progression of disease within 24 months of starting the first line of therapy			
Yes	14/30 (47)	30/50 (60)	13 (-9 to 36)
No	15/35 (43)	55/74 (74)	32 (12 to 51)
Progression of disease within 24 months of starting the first line of chemoimmunotherapy			
Yes	9/22 (41)	25/39 (64)	23 (-2 to 49)
No	14/31 (45)	40/59 (68)	23 (1 to 44)
Progression of disease within 6 months of completion of the most recent line of therapy			
Yes	12/39 (31)	42/71 (59)	28 (10 to 47)
No	19/30 (63)	53/67 (79)	16 (-4 to 36)
Progression of disease within 12 months of completion of the most recent line of therapy			
Yes	17/52 (33)	59/95 (62)	29 (13 to 46)
No	14/17 (82)	36/43 (84)	1 (-20 to 23)



Clin Oncol . 2023 Nov 20;41(33):5107-5117.

Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study (FDA approved in 2019)

Patients with MCL and ≥ 1 prior lines of tx; ECOG PS 0-2; no notable CVD; no prior BTK inhibitors (N = 86)

→ **Zanubrutinib** 160 mg PO BID →

Up to 3 yrs or until PD, unacceptable toxicity, or death

Phase 2

86

Patients with R/R **MCL**

Median follow-up **35.3 months**

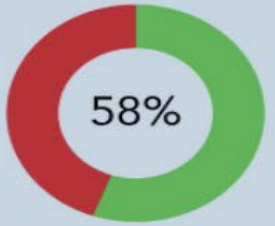
Response

Median DOR

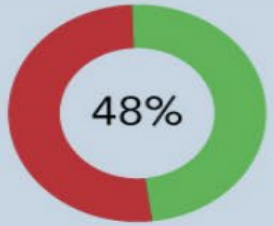
Not reached
(95% CI: 24.9 months to NE)

PFS

2 years

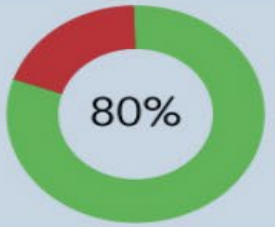


3 years

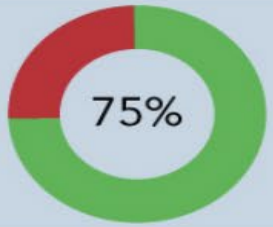


OS

2 years



3 years



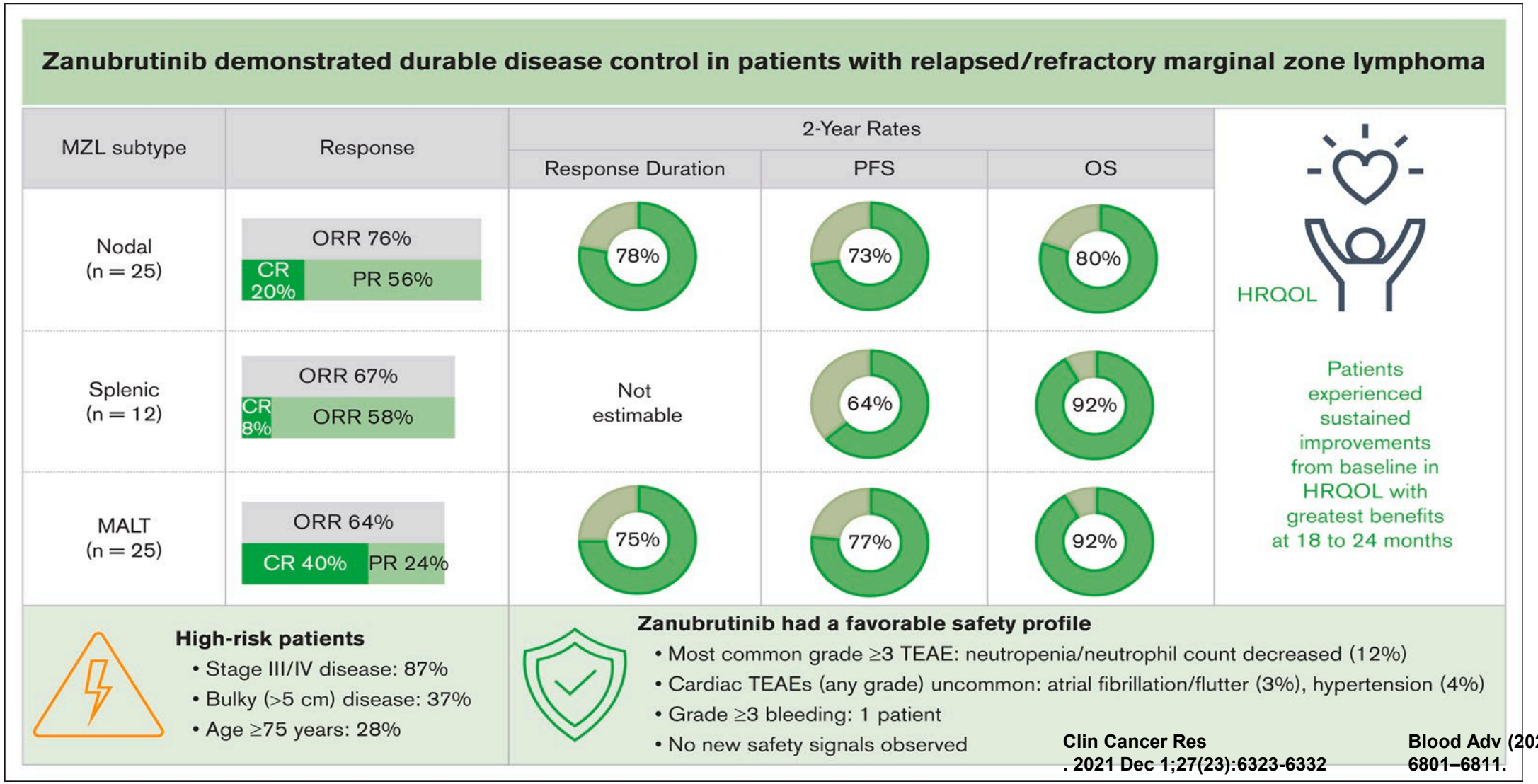
Zanubrutinib was well tolerated

- Few discontinuations (9.3%) due to AEs
- Majority of AEs: low-grade severity
- No atrial fibrillation/flutter
- No second primary malignancies

Blood (2022) 139 (21): 3148–3158.

AEs adverse events; CR complete response; DOR duration of response; MCL mantle cell lymphoma; NE not estimable; ORR overall response rate; OS overall survival; PFS progression-free survival; R/R relapsed/refractory.

Safety and efficacy of zanubrutinib in relapsed/refractory marginal zone lymphoma: final analysis of the MAGNOLIA study



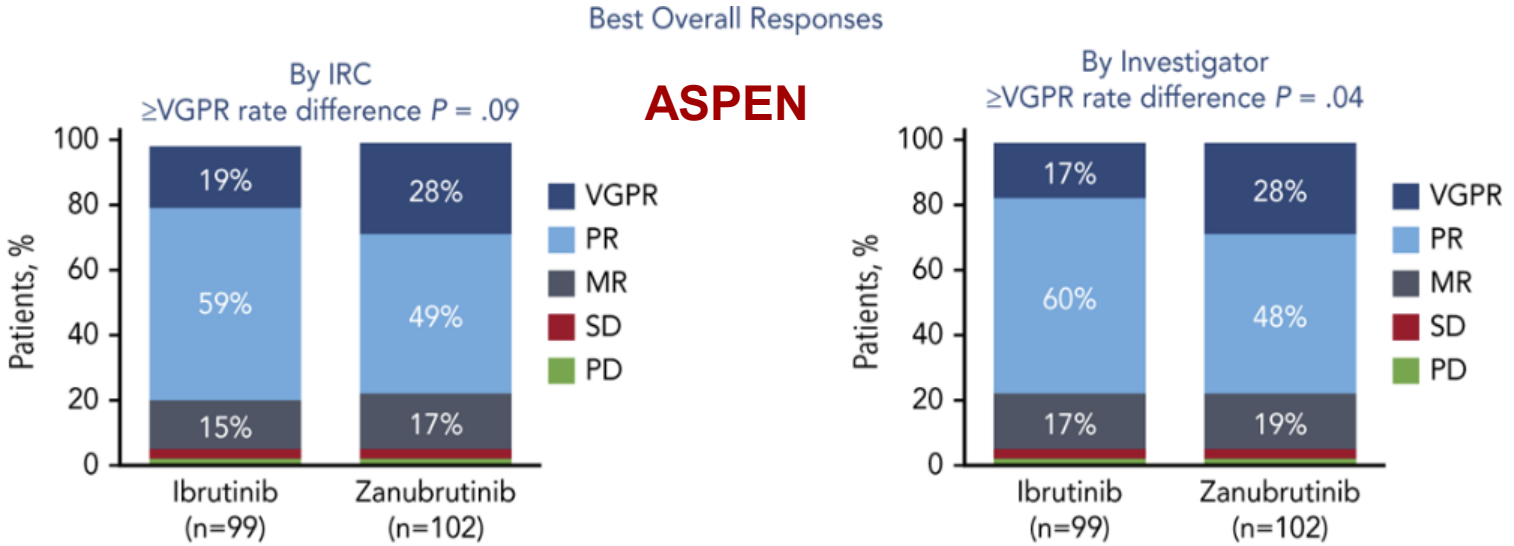
Clin Cancer Res . 2021 Dec 1;27(23):6323-6332

Blood Adv (2023) 7 (22): 6801–6811.

Zanubrutinib in Waldenström Macroglobulinemia

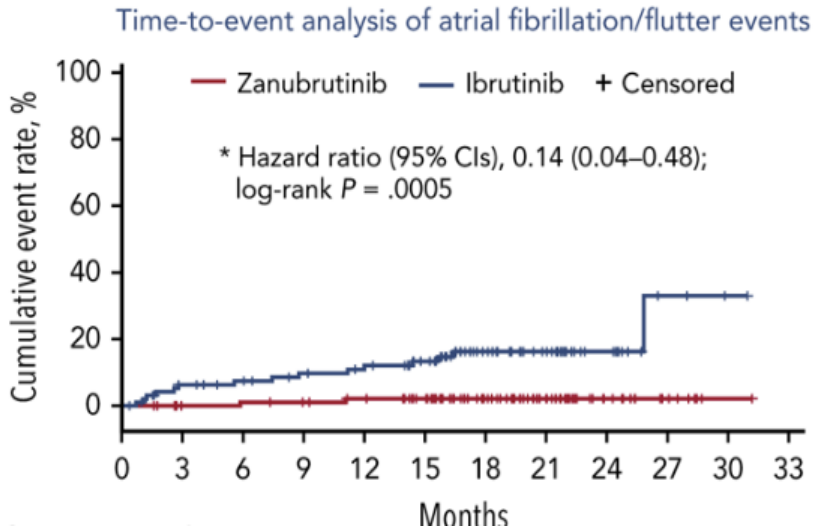
- FDA approved in 2019 for the treatment of relapsed/refractory MCL after at least 1 prior therapy[1]
  - Approval based on the results of an open-label, single-arm phase II trial showing high and durable ORR and CR rates with good tolerability[2]
- Zanubrutinib noninferior to ibrutinib in Waldenström macroglobulinemia in phase III ASPEN study[3]
  - Trend toward improved responses and less toxicity with zanubrutinib

ASPEN



AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)
Hemorrhage	58 (59.2)	49 (48.5)
Major hemorrhage	9 (9.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)
Neutropenia*	13 (13.3)	30 (29.7)
Infection	66 (67.3)	67 (66.3)

*Descriptive 2-sided $P < .05$



1. Ibrutinib PI. 2. Song. Clin Canc Res. 2020;26:4216. 3. Tam. Blood. 2020;136:2038.

Adverse Events Associated With BTK Inhibitors in CLL

Patients With Any Grade AEs, %	BTK Inhibitor (as Monotherapy or in Combination)		
	Ibrutinib (in CLL clinical trials)	Acalabrutinib (in CLL clinical trials)	Zanubrutinib (in MCL clinical trials)†
Atrial fibrillation or flutter	5-7	3.6-5	2
Hemorrhage	19-31	16-20	11
Diarrhea	34-59	18-39	23
Arthralgias	16-41	8-22	14
Musculoskeletal pain*	25-61	15-37	
Hypertension	11-42	3.2-5	12
Rash	21-49	18-25	36
Headache	12-40	9-26	4.2
Infection (grade ≥ 3)	1-12	14-22	0-10

*Includes myalgias.
†Zanubrutinib is not currently FDA-approved for the treatment of CLL, and data from zanubrutinib in CLL clinical trials is not published.

a. Imbruvica (ibrutinib) [PI]. 2020; b. Calquence (acalabrutinib) [PI]. 2019; c. Brukinsa (zanubrutinib) [PI]. 2019.

Adverse Events of Available BTK Inhibitors: Cytopenias, Infection, Bruising and Hemorrhage, Lymphocytosis

Ibrutinib	Acalabrutinib	Zanubrutinib
Cytopenias (Grade 3/4)	**Cytopenias (Grade 3/4)**	**Cytopenias (Grade 3/4)**
▪ Neutropenia 13% to 29% ▪ Thrombocytopenia 5% to 17% ▪ Anemia 0% to 13%	▪ Neutropenia 10% to 23% ▪ Thrombocytopenia 5% to 8% ▪ Anemia 5% to 11%	▪ Neutropenia 26% ▪ Thrombocytopenia 11% ▪ Anemia 8%
Infection (Grade 3-5)	**Infection (Grade 3-5)**	**Infection (Grade 3-5)**
▪ 14% to 29% of patients	▪ 11% to 18% of patients	▪ 27% of patients
Bruising and Hemorrhage	**Bruising and Hemorrhage**	**Bruising and Hemorrhage**
▪ Bleeding consistent with “hemostatic failure” with bruising and subcutaneous bleeding with minor trauma in up to 50% ▪ Grade ≥3 hemorrhage: up to 6%	▪ Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 30% of patients ▪ Grade ≥3 hemorrhage: up to 3%	▪ Any-grade hemorrhage: 35% ▪ Grade ≥3 hemorrhage: 3.4%
Lymphocytosis	**Lymphocytosis**	**Lymphocytosis**
▪ Up to 77% of patients	▪ 26% of patients	▪ 41% of patients

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI.

Slide credit: clinicaloptions.com

Adverse Events of Available BTK Inhibitors: GI, Musculoskeletal, and Other Common AEs

Ibrutinib	Acalabrutinib	Zanubrutinib
Gastrointestinal	**Gastrointestinal**	**Gastrointestinal**
▪ Diarrhea 34% to 63% (up to 5% grade ≥3) ▪ Nausea 21% to 31% (2% grade ≥3)	▪ Diarrhea 18% to 35% (up to 1.3% grade ≥3) ▪ Nausea 22% (0% grade ≥3)	▪ Diarrhea 22% to 23% (0.8% to 3% grade 3) ▪ Nausea 13% to 18% (0% grade ≥3)
Musculoskeletal	**Musculoskeletal**	**Musculoskeletal**
▪ Includes pain, arthralgias, myalgias ▪ 21% to 37% of patients (up to 6% grade ≥3)	▪ Includes pain, arthralgias, myalgias ▪ 16% to 23% of patients (1.1% grade ≥3)	▪ Includes pain, arthralgias, myalgias ▪ 14% to 45% of patients (1.1% to 9% grade ≥3)
Other Common AEs	**Other Common AEs**	**Other Common AEs**
▪ Rash 22% to 27% (up to 3% grade ≥3) ▪ Fatigue 21% to 41% (up to 5% grade ≥3) ▪ Headache 13% to 19% (up to 2% grade ≥3)	▪ Rash 25% (<1% grade 3) ▪ Fatigue 15% to 23% (up to 1.9% grade ≥3) ▪ Headache 22% to 39% (up to 1.1% grade ≥3)	▪ Rash 21% to 36% (0% grade ≥3) ▪ Fatigue 21% to 31% (1% to 2.3% grade ≥3) ▪ Headache 4.2% to 18% (1% grade ≥3)

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI.

Slide credit: clinicaloptions.com

Adverse Events of Available BTK Inhibitors: Hypertension, Atrial Fibrillation, and Cardiac Arrhythmias

Ibrutinib

- Hypertension up to 19%
- Incidence of atrial fibrillation:
  - MCL: 11%
  - CLL: 5% (8% all cardiac dysfunction)
  - WM: 2% (7% all cardiac dysfunction)

Acalabrutinib

- Hypertension up to 5%
- Incidence of atrial fibrillation:
  - MCL: 0% (8% other cardiac dysfunction)
  - CLL: 3%
  - WM: 5%

Zanubrutinib

- Hypertension 12% to 14%
- Atrial fibrillation and atrial flutter have occurred in 2.8% (grade ≥3: 0.8%)

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI.

Slide credit: clinicaloptions.com

BTK Inhibitor AE Management: Bleeding and Infections

- **Hemorrhage/Bleeding**
  - Increased risk of bleeding on concomitant anticoagulant or antiplatelet therapy
  - Manage low-grade bleeding with supportive care
  - Manage significant bleeding by holding BTK inhibitor, consider platelet transfusion
  - Consider risks and benefits of withholding for 3-7 days before and after surgery
  - Requires initial and ongoing patient education
- **Infections**
  - Cases of progressive multifocal leukoencephalopathy, *P jirovecii* pneumonia, herpes simplex virus, hepatitis B reactivation have occurred
  - Immunocompromise or long-term corticosteroid use increases risk; consider prophylaxis
  - Monitor and evaluate patients for fever and infections; treat appropriately
  - No standard guidelines/ recommendations for antimicrobial prophylaxis

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI. Moore. J Adv Pract Oncol. 2021;12:439. Stephens. Blood. 2019;133:1298. Rogers. J Adv Pract Oncol. 2017;8:97. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: chronic lymphocytic leukemia/small lymphocytic lymphoma. v.4.2021. nccn.org. Accessed August 4, 2021.

Slide credit: clinicaloptions.com

BTK Inhibitor AE Management: Lymphocytosis, Headache, Rash, and Second Primary Malignancies

- **Lymphocytosis**
  - Presents in initial few weeks of therapy, typically resolves within 2 mo
- **Headache**
  - Typically low grade, observed early in therapy, and resolves over 1-2 mo
  - Generally well managed with analgesics (eg, acetaminophen, caffeine supplements)
  - More frequent with acalabrutinib
  - Avoid NSAIDs due to increased risk of bleeding
- **Rash**
  - May be asymptomatic petechial, or palpable, eruptive pruritic rash with pustules
  - Eruptive rash management: topical antihistamines, corticosteroids
  - Severe cases may require oral antihistamines or corticosteroids, plus dose interruption or reduction
- **Second primary malignancies**
  - Most common: skin cancer
  - Advise protection from sun exposure, and encourage regular cancer screening

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI. Moore. J Adv Pract Oncol. 2021;12:439. Stephens. Blood. 2019;133:1298. Rogers. J Adv Pract Oncol. 2017;8:97. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: chronic lymphocytic leukemia/small lymphocytic lymphoma. v.4.2021. nccn.org. Accessed August 4, 2021.

Slide credit: clinicaloptions.com

Risk Factors for Developing Atrial Fibrillation

- Hypertension
- Heart failure
- Diabetes mellitus
- Age
- Obesity
- Excess alcohol consumption
- Valvular heart disease, murmur
- COPD
- Hyperthyroidism
- Obstructive sleep apnea
- Chronic kidney disease
- Acute infections

1. Careful history and assessment—numerous risk score calculators
2. Optimize modifiable factors
3. Reassess on regular basis
4. Educate patient and caregivers

Stuhlinger. Wien Klin Wochenschr. 2019;132:97. Wiczer. Blood Adv. 2017;1:1739.
www.framinghamheartstudy.org/fhs-risk-functions/atrial-fibrillation-10-year-risk/

Slide credit: clinicaloptions.com

BTK Inhibitors: Cardiovascular Adverse Event Management

- **Atrial fibrillation/flutter**
  - Regularly monitor for cardiac arrythmias; ECG if symptoms develop (eg, palpitations, lightheadedness, syncope, chest pain) or new-onset dyspnea
  - Cardiology comanagement recommended
  - **Not an absolute indication to discontinue BTK inhibitors**
  - Use anticoagulation with caution
  - Manage cardiac arrythmias as appropriate
  - For persistent atrial fibrillation, consider dose modification
- **Hypertension**
  - Document baseline blood pressure
  - Monitor for new/ uncontrolled hypertension
  - Initiate hypertensives as needed
  - New or worsening hypertension increases risk of major cardiovascular events

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI. Rogers. J Adv Pract Oncol. 2017;8:97. National Comprehensive Cancer Network clinical practice guidelines: CLL/SLL (v4.2021). Dickerson. Blood. 2019;134:1919.

BTK Inhibitors: Musculoskeletal Adverse Event Management

- **Arthralgias/Myalgias**
  - Usually occur early in treatment course
  - Consider acetaminophen or short course of prednisone
  - Anti-inflammatory agents (eg, ibuprofen) should be avoided to minimize bleeding
  - Transition to selective BTK inhibitor can diminish or resolve arthralgias and myalgias
- **Other Musculoskeletal AEs**
  - Musculoskeletal pain
  - Muscle spasms
  - Treat like arthralgias and myalgias

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI. Rogers. J Adv Pract Oncol. 2017;8:97.
National Comprehensive Cancer Network clinical practice guidelines: CLL/SLL (v4.2021).

Slide credit: clinicaloptions.com

Drug-Drug Interactions of BTK Inhibitors

Dose Modification Recommendations

	Ibrutinib[a]	Acalabrutinib[b]	Zanubrutinib[c]
Moderate CYP3A4 inhibitor	280 mg daily	100 mg daily	80 mg twice daily
Voriconazole 200 mg twice daily Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg daily	—	80 mg daily
Posaconazole suspension 200 mg TID or 400 mg twice daily Posaconazole IV 300 mg once daily Posaconazole delayed-release tablets 300 mg once daily	70 mg daily	—	80 mg daily
Other strong CYP3A4 inhibitors	Avoid use; if short-term (≤ 7 days) interrupt treatment		
Strong CYP3A4 inducers	Avoid use	Avoid use; if unable 200 mg twice daily	Avoid use

a. Imbruvica® (ibrutinib) [PI]. 2020; b. Calquence® (acalabrutinib) [PI]. 2019; c. Brukinsa™ (zanubrutinib) [PI]. 2019.

Impact on AEs and Treatment Efficacy

- CYP3A4 inducers (eg, rifampin) and inhibitors (eg, itraconazole)
  - Medications
  - Herbal supplements
  - Foods
- P-gp substrates
- PPIs, H2-receptor antagonists, and antacids

Concurrent Medications With Overlapping Toxicities

May Increase Likelihood of Complications and Impact Ability to Stay on BTK Inhibitor Therapy

Anticoagulants[a-c]	• DOACs • LMWH • Warfarin (contraindicated in patients with blood dyscrasias)
Antiplatelets[a-c]	• Aspirin • P2Y12 receptor blockers • NSAIDs • SSRIs
Atrial fibrillation[a-c]	• Verapamil • Diltiazem • Amiodarone • Digoxin
Infection[a-c]	• Azole antifungals
Arthralgia, myalgia, headache[a-c]	• NSAIDs • Aspirin-containing products
GI toxicity[a-c]	• PPIs • H2RAs • Antacids
OTC products and supplements	• Vitamin E[d] • Fish oil[d] • Flaxseed oil

a. Imbruvica® (ibrutinib) [PI]. 2020; b. Calquence® (acalabrutinib) [PI]. 2019; c. Brukinsa™ (zanubrutinib) [PI]. 2019;
d. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program*. 2020;2020:336-345.

Recommendations to Reduce Drug–Food Interactions With BTK Inhibitors

BTK Inhibitor	How Supplied	Recommended Dosage and Administration
Acalabrutinib	100-mg capsules	▪ 100 mg orally twice daily ▪ Can be taken with or without food ▪ Advise patients to swallow capsules whole with water
Ibrutinib	**Capsules:** 70 mg, 140 mg **Tablets:** 140 mg, 280 mg, 420 mg	▪ Advise patients to swallow capsules whole with water ▪ Do not cut, crush, or chew the tablets ▪ The administration of ibrutinib with a high-fat and high-calorie meal increased ibrutinib C_{max} by 2- to 4-fold and AUC by approximately 2-fold, compared with administration of ibrutinib after overnight fasting
Zanubrutinib	80-mg capsules	▪ 160 mg twice daily or 320 mg once daily ▪ Can be taken with or without food ▪ Advise patients to swallow capsules whole with water

Acalabrutinib PI. Ibrutinib PI. Zanubrutinib PI.

Slide credit: clinicaloptions.com

BTK Inhibitor Drug–Drug Interactions

Dosing Recommendation by Inhibitors/Inducers	Ibrutinib	Acalabrutinib	Zanubrutinib
Strong CYP3A inhibitor	▪ Avoid concomitant use ▪ Dose modification is recommended ▪ If strong inhibitor intended for short-term use (eg, up to 7 days as anti-infectives), hold ibrutinib	▪ Avoid concomitant use ▪ Dose modification is recommended ▪ If strong inhibitor intended for short-term use (eg, up to 7 days as anti-infectives), hold acalabrutinib	▪ 80 mg once daily ▪ Interrupt dose as recommended for adverse reactions
Moderate CYP3A inhibitor	▪ 280 mg once daily	▪ 100 mg once daily	▪ 80 mg twice daily ▪ Modify dose as recommended for adverse reactions
Strong CYP3A inducer	▪ Avoid concomitant use	▪ Avoid concomitant use ▪ If inducers can not be avoided, increase acalabrutinib dose to 200 mg every 12 hr	▪ Avoid concomitant use
Gastric acid–reducing agents	▪ N/A	▪ Avoid coadministration with proton pump inhibitors ▪ Take acalabrutinib 2 hr before an H2 receptor antagonist ▪ Separate dosing by at least 2 hr before and after antacids	▪ N/A

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI.

Slide credit: clinicaloptions.com

Conclusions

- BTK inhibitors have shown potent efficacy for treatment of CLL, MCL, MZL, and WM
  - Ibrutinib (first-generation BTK inhibitor) indicated in CLL, MCL, MZL, and WM
  - Acalabrutinib (second-generation BTK inhibitor) indicated in MCL and CLL
  - Zanubrutinib (third-generation BTK inhibitor) indicated in CLL, MCL, MZL, FL and WM
- BTK inhibitors are generally well tolerated but can be associated with treatment-related AEs such as diarrhea, bleeding, rash, and atrial fibrillation
- Open-ended treatment requires ongoing diligent management of AEs to ensure best outcomes
- Selecting optimal BTK inhibitor therapy for patients with CLL, MCL, MZL, and WM should be based on efficacy, safety profiles as well as patient preferences and comorbidities

Thank you for listening

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