4th POSTGRADUATE

CLL Conference

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2023

Royal Hotel Carlton

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Pier Luigi Zinzani

Selecting the appropriate BTKi for frontline treatment

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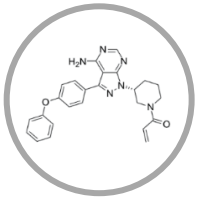
14 November, 2023

Disclosures of Matthew S. Davids, MD, MMSc

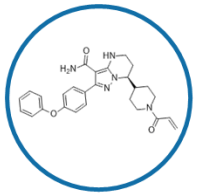
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	✓		✓			✓	
Adaptive Biotechnologies			✓			✓	
Ascentage Pharma	✓		✓				
AstraZeneca	✓		✓			✓	
BeiGene			✓			✓	
Bristol-Myers Squibb			✓			✓	
Eli Lilly			✓			✓	
Genentech	✓		✓			✓	
Genmab			✓				
Janssen			✓			✓	
Merck			✓			✓	
Novartis	✓						
Nuvlaent			✓				
Research to Practice							✓ (Honoraria)
Secura Bio	✓		✓				
Takeda			✓			✓	
TG Therapeutics	✓		✓			✓	

BTK inhibitors: currently available options for 1L CLL



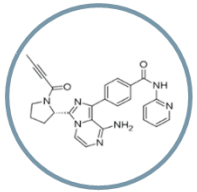
Ibrutinib

- RESONATE-2[a]: superior PFS and OS vs Clb
- iLLUMINATE[b]: superior PFS vs GClb
- ALLIANCE[c]: superior PFS vs BR in older patients
- FLAIR[d]: superior PFS for IR vs FCR
- ECOG 1912[e]: superior PFS and OS for IR vs FCR in younger patients



Acalabrutinib

- ELEVATE-TN[f]: superior PFS and a trend toward better OS with acalabrutinib regimens vs GClb



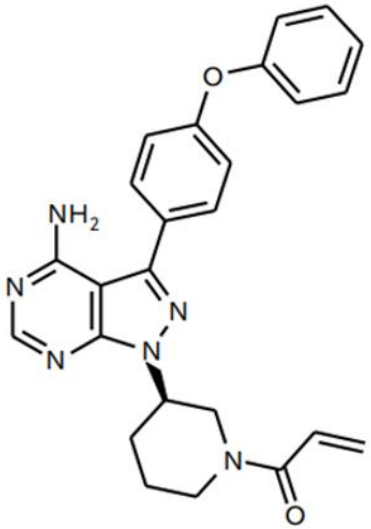
Zanubrutinib

- SEQUOIA[g]: superior PFS vs BR

BR, bendamustine and rituximab; Clb, chlorambucil; IR, ibrutinib and rituximab; PFS, progression-free survival; TN, treatment-naive.

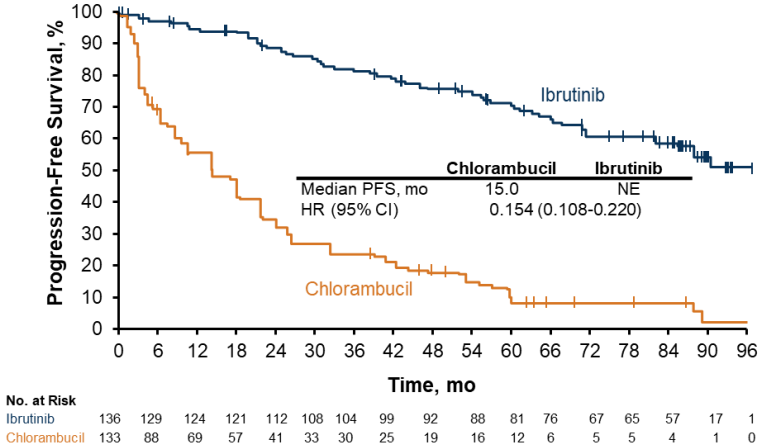
a. Burger JA, et al. Leukemia. 2020;34:787-798; b. Moreno C, et al. Lancet Oncol. 2019;20:43-56; c. Woyach JA, et al. N Engl J Med. 2018;379:2517-2528; d. Hillmen P, et al. Blood. 2021;138:642; e. Shanafelt TD, et al. N Engl J Med. 2019;381:432-443; f. Sharman JP, et al. Lancet. 2020;395:1278-1291; g. Tam CS, et al. Blood. 2021;138:396.

The case for ibrutinib



Older patients: RESONATE-2: 8-Year Follow-Up

- Longest follow-up to date with a single-agent BTK inhibitor from a phase 3 study
- Sustained PFS benefit with ibrutinib versus chlorambucil
- Benefit was similar for mutated and unmutated *IGHV*

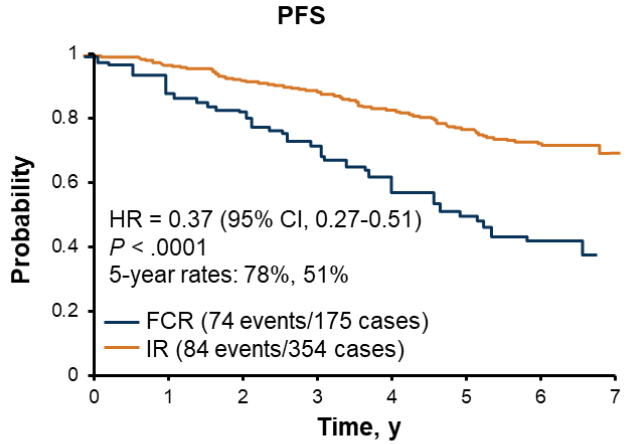


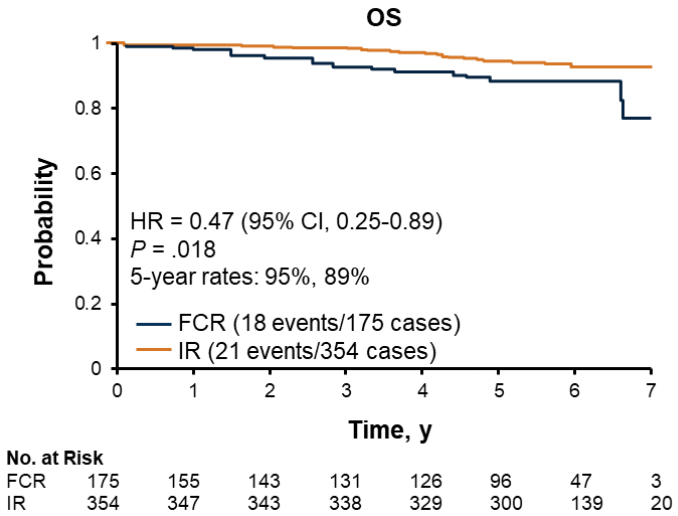
NE, not estimable.

Barr PM, et al. Blood Adv. 2022;6:3440-3450.

Younger patients: ECOG E1912 Update: Median 5.8 Years Follow-Up

- Longer follow-up continues to show PFS and OS benefits with IR vs FCR
- Superior PFS with IR in both mutated and unmutated *IGHV* subgroups





Shanafelt TD, et al. Blood. 2022;140:112-120.

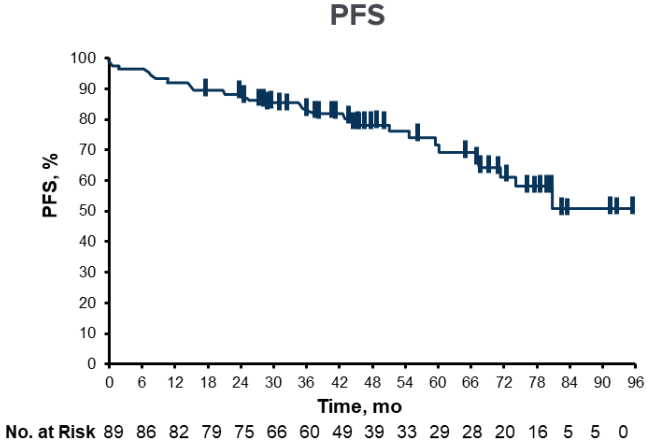
High risk patients: del(17p) and/or *TP53* mutation

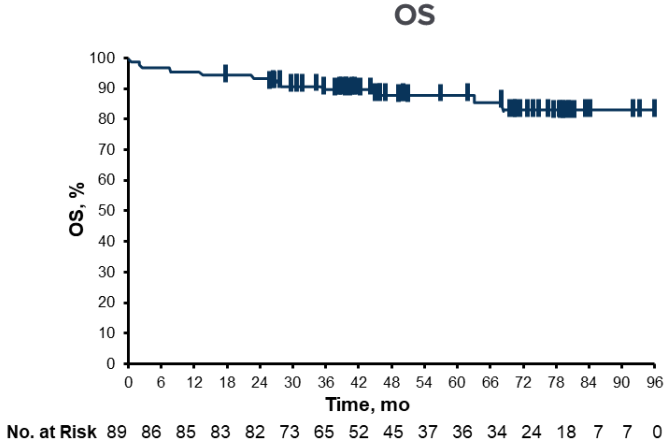
Pooled analysis of 89 patients with del17p and/or *TP53* mutation

Patients received either:
Single-agent ibrutinib in PCYC-1122 or RESONATE-2
-OR-
Ibrutinib + anti-CD20 in iLLUMINATE or E1912

Median follow-up 49.8 months

- Median PFS not reached
- Estimated 4-y PFS 79%
- Estimated 4-y OS 88%





Allan JN, et al. Br J Haematol. 2022;196:947-953.

Ibrutinib's toxicity profile is well-established

Safety Analysis of Four Randomized Controlled Studies of Ibrutinib in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma or Mantle Cell Lymphoma

Susan O'Brien,[1] Peter Hillmen,[2] Steven Coutre,[3] Paul M. Barr,[4] Graeme Fraser,[5] Alessandra Tedeschi,[6] Jan A. Burger,[7] Marie-Sarah Dilhuydy,[8] Georg Hess,[9] Carol Moreno,[10] Paula Cramer,[11] Emily Liu,[12] Stephen Chang,[12] Jessica Vermeulen,[13] Lori Styles,[12] Angela Howes,[14] Danelle F. James,[12] Kalpesh Patel,[15] Thorsten Graef,[12] Rudolph Valentino[12]

Supplemental Figure 2 Prevalence of Most Common (≥ 3%) Grade 3/4 Adverse Events With Ibrutinib Over Time

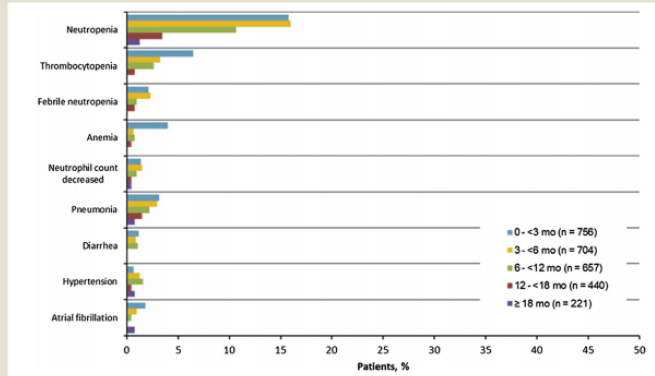


Table 7 Bleeding Events: Cumulative and Exposure-adjusted Incidence Rates

Event	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Any bleeding event[b]	38	0.486	17	0.2628	21.3	0.2232
Grade 3/4 bleeding event	3	0.0252	2	0.0276	0.8	−0.0024
Major hemorrhage	4	0.0348	3	0.0348	1.3	0
Grade 3/4 major hemorrhage	3	0.0252	2	0.0276	0.8	−0.0024

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib.
[a]Negative numbers indicate higher rates with comparator.
[b]Based on the number of patients with any bleeding event by preferred term.

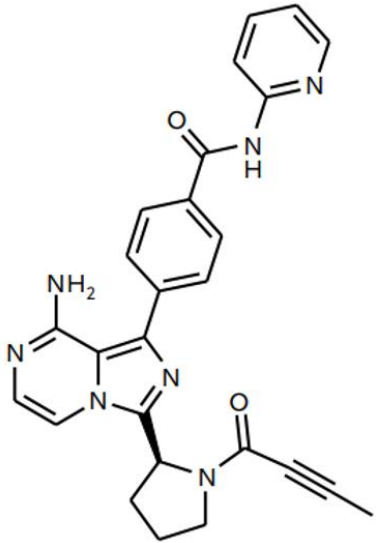
O'Brien et al., *Clin Lymphoma Myeloma Leuk*. 2018 Oct;18(10):648-657.e15

US cooperative group studies suggest Gr 3/4 ibrutinib toxicities may be less in younger patients

Adverse event	IR Arm Alliance n=181	IR Arm E1912 N=352
Median Age Age range	71 yrs 65 – 86	57 yrs 31 - 70
Infection	19%	5%
Atrial fibrillation	6%	3%
Bleeding	4%	1%
Hypertension	34%	7%
Deaths during active treatment +30 days	**7%**	**1%**

Adapted from Shanafelt et al., ASH, 2019

The case for acalabrutinib

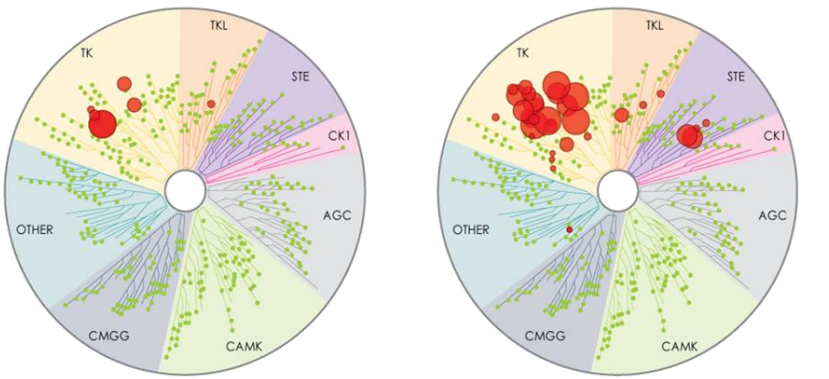


Acalabrutinib

Acalabrutinib

- Highly-selective, potent BTK inhibitor
- Designed to minimize off-target activity, with minimal effects on TEC, EGFR, or ITK signaling

Kinase selectivity profiling at 1 μM

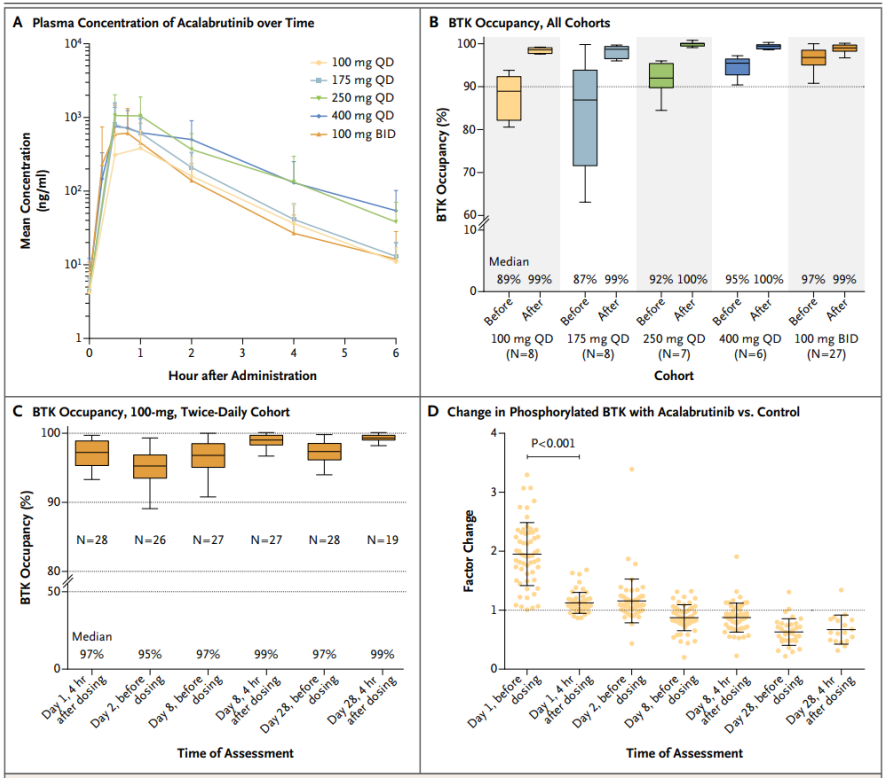


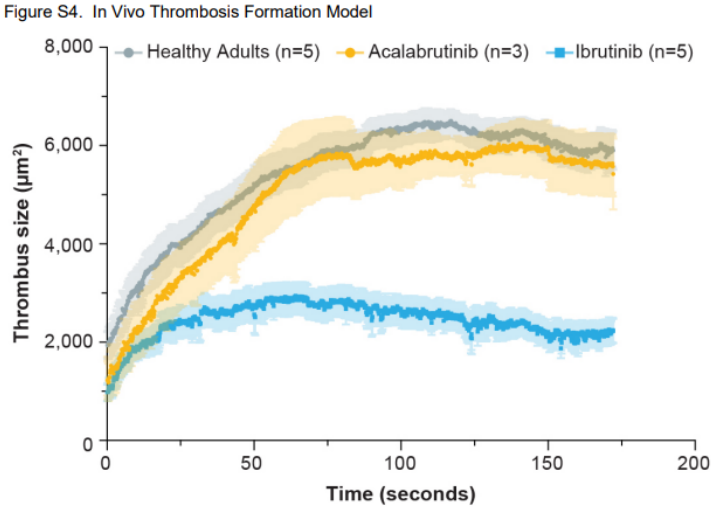
The size of the red circle is proportional to the degree of inhibition.

Kinase Inhibition IC_{50} (nM)		
Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126	10
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

- Barf T, et al. *J Pharmacol Exp Ther.* 2017.

Acalabrutinib: Pharmacokinetics and Pharmacodynamics



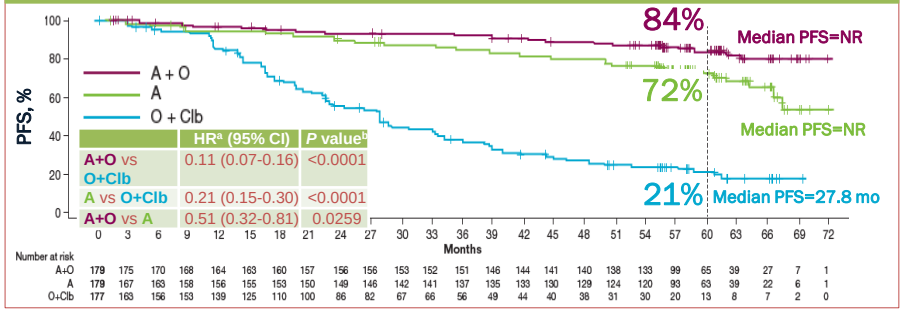


Platelets from patients treated with ibrutinib 420 mg once per day (QD) (n=5) or acalabrutinib 100 mg twice per day (BID) (n=3) were evaluated for their ability to support thrombus formation in laser injured arterioles of VWF^{HA1} mice. Freshly isolated platelets from healthy volunteers (n=5) were used as non-drug treated controls. A minimum of 4 arterioles per mouse was used to assess thrombus formation for each patient/volunteer sample. Median fluorescence intensity as a function of time is provided in the figure (shading denotes standard error of the median).

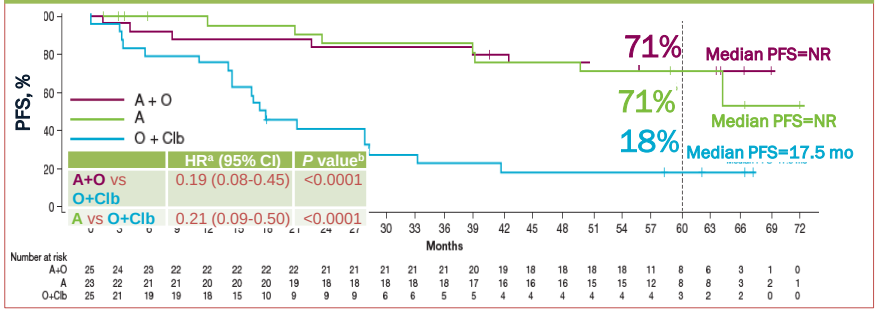
Byrd et al., NEJM, 2016

5-Year Follow-Up of ELEVATE-TN: Acala ± Obin vs Obin + Chl in TN CLL – PFS and OS[1,2]

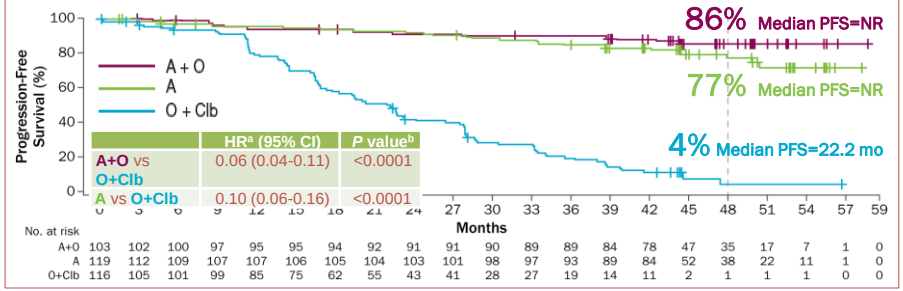
INV-Assessed PFS (Median Follow-Up: 58.2 Months)[1]



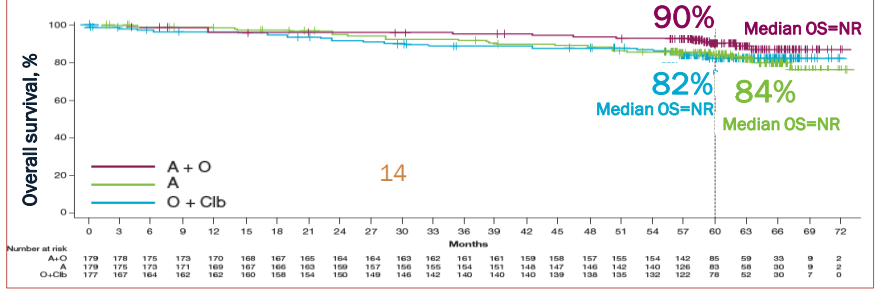
INV-Assessed PFS in del(17p) and/or *TP53*-mut (Median Follow-Up: 58.2 Months)[1]



INV-Assessed PFS in Unmutated *IGHV* (Median Follow-Up: 46.9 Months)[2]



Overall Survival (Median Follow-Up: 58.2 Months)[1]



- At a median follow-up of 58.2 months (range, 0.0-72.0), OS data were immature, and medians were not reached in any treatment arm
- Relative risk for death was lower in the A+O vs O+Clb arm (HR=0.55, 95% CI: 0.30-0.99)
  - Crossover from O+Clb to A occurred after disease progression in 72 patients (41%)
- All analyses are based on descriptive statistics

1. Sharman JP, et al. ASCO 2022. Abstract 7539. **2.** Sharman JP, et al. *Leukemia*. 2022;36(4):1171-1175.

5-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – Safety[1,2]

AEs of Clinical Interest, n (%)	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	43 (24.2)	17 (9.6)	39 (21.8)	18 (10.1)	13 (7.7)	3 (1.8)
Atrial fibrillation	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	6 (3.4)	20 (11.8)	0
Major bleeding[a]	12 (6.7)	8 (4.5)	8 (4.5)	6 (3.4)	2 (1.2)	0
Hypertension	17 (9.6)	8 (4.5)	16 (8.9)	7 (3.9)	6 (3.6)	5 (3.0)
Infections	140 (78.7)	50 (28.1)	135 (75.4)	35 (19.6)	75 (44.4)	14 (8.3)
Secondary primary malignancies	31 (17.4)	14 (7.9)	27 (15.1)	7 (3.9)	7 (4.1)	3 (1.8)
Excluding nonmelanoma skin	17 (9.6)	12 (6.7)	13 (7.3)	5 (2.8)	3 (1.8)	2 (1.2)

[a] Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system.

1. Sharman JP, et al. ASCO 2022. Abstract 7539. **2.** Sharman JP, et al. EHA 2022. Abstract P666.

Acalabrutinib Tablet Formulation

Acalabrutinib tablets are **smaller in size** compared with **acalabrutinib** capsules, and have a film coating to improve swallowing ability[1]

- **PPI Coadministration:** Acalabrutinib tablets can be taken with acid-reducing agents such as PPIs, antacids, or H2-receptor antagonists[1,2]
- **Same Efficacy and Safety Expected:** The new tablet formulation has been proven to be bioequivalent to capsules[1]
- **Same Dosing Schedule:** As with acalabrutinib 100 mg capsules, patients take one 100 mg tablet twice daily[2,3,a]

- Same CYP3A interaction with acalabrutinib tablets and capsules:
  - Strong CYP3A Inhibitors: Avoid co-administration of acalabrutinib with a strong CYP3A inhibitor. If these inhibitors will be used short term, interrupt acalabrutinib. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of acalabrutinib
  - Moderate CYP3A Inhibitors: Reduce the dosage of acalabrutinib to 100 mg once daily when co-administered with a moderate CYP3A inhibitor
  - Strong CYP3A Inducers: Avoid co-administration of acalabrutinib with a strong CYP3A inducer. If co-administration is unavoidable, increase the dosage of acalabrutinib to 200 mg approximately every 12 hours

[a] Approximately every 12 hours.[2]

1. Sharma S, et al. *Blood.* 2021;138(Suppl 1):4365. **2.** Acalabrutinib tablets. Prescribing information. AstraZeneca Pharmaceuticals LP; 2022. **3.** Acalabrutinib capsules. Prescribing information. AstraZeneca Pharmaceuticals LP; 2022.

Acalabrutinib-based Regimens in Frontline or Relapsed/Refractory Higher-Risk CLL: Pooled Analysis of 5 Clinical Trials

Davids MS, et al.

Pooled Analysis of 5 Acalabrutinib Clinical Trials

N=808

- Pts with TN or R/R CLL and higher-risk genomic features
- Treated with A-based regimens

TN CLL (n=320)
A±O (efficacy + safety)

del(17p)/*TP53*m	uIGHV	CK*	CK without del(17p)/*TP53*m
20%	90%	25%	15%

R/R CLL (n=488)
A monotherapy (efficacy) A±O (safety)

del(17p)/*TP53*m	uIGHV	CK*	CK without del(17p)/*TP53*m
45%	87%	33%	14%

Median follow-up

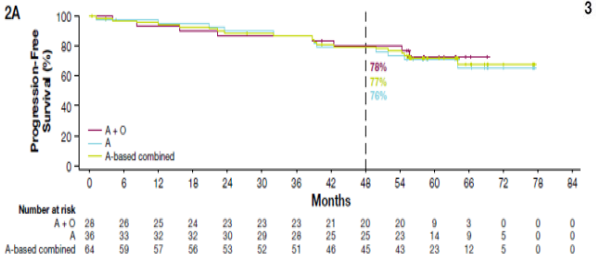
59.1 mo (TN CLL)
44.3 mo (R/R CLL)

High ORR across subgroups

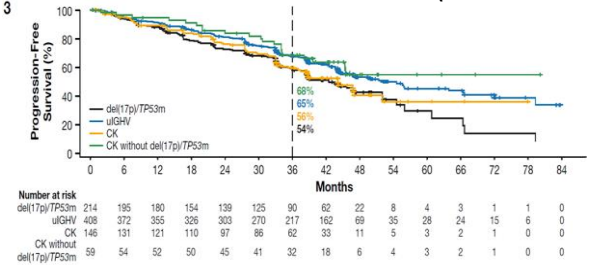
	TN	R/R
del(17p)/*TP53*m	91%	86%
uIGHV	96%	87%
CK	91%	84%

PFS and OS benefits observed across higher-risk subgroups in both cohorts

TN Cohort (TP53 abnl only)



R/R Cohort (A monotherapy) (TP53 abnl only)



AE incidence was similar to the reported overall safety profile of acalabrutinib

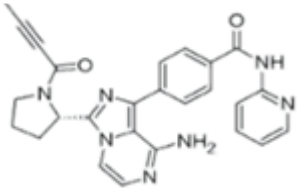
*CK defined as ≥3 chromosomal abnormalities with ≥1 structural abnormality excluding inversion of chromosome 9.
A, acalabrutinib; AE, adverse event; CK, complex karyotype; CLL, chronic lymphocytic leukemia; mo, months; NR, not reached; O, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment naive; *TP53*m, tumor protein p53 mutation; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Conclusions

- PFS and OS rates are high with A-based regimens in pts with higher-risk CLL
- A-based regimens had a consistent tolerability profile
- These data demonstrate the long-term benefit of A-based regimens in pts with CLL and higher-risk genomic features, regardless of line of therapy

Davids et al., *in revision*

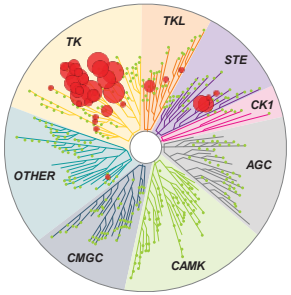
The case for zanubrutinib



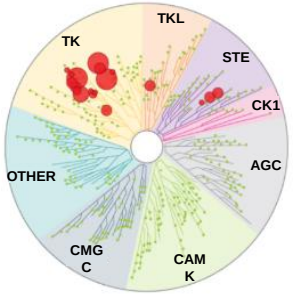
Pharmacokinetics and Selectivity of Zanubrutinib and Ibrutinib

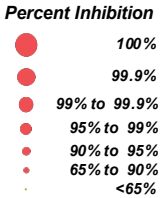
Whole Kinase Panel Selectivity Profiles

Ibrutinib



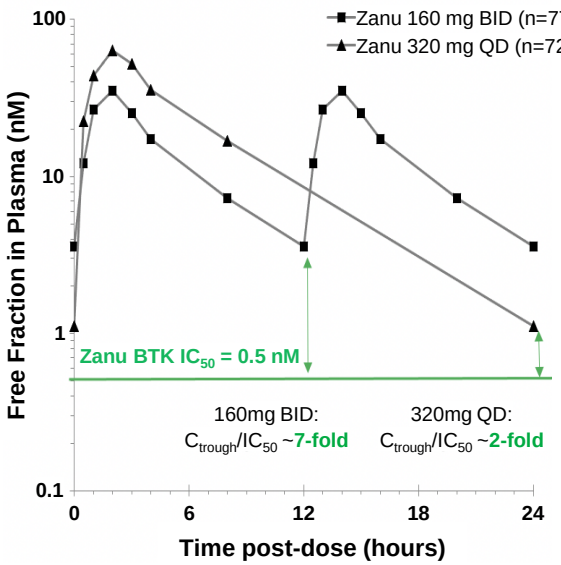
Zanubrutinib



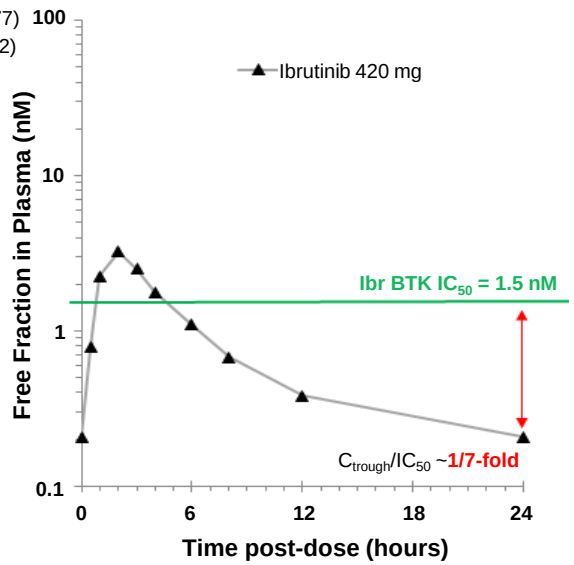


Free Drug Concentration Time Profiles Relative to IC_{50}

Zanubrutinib



Ibrutinib



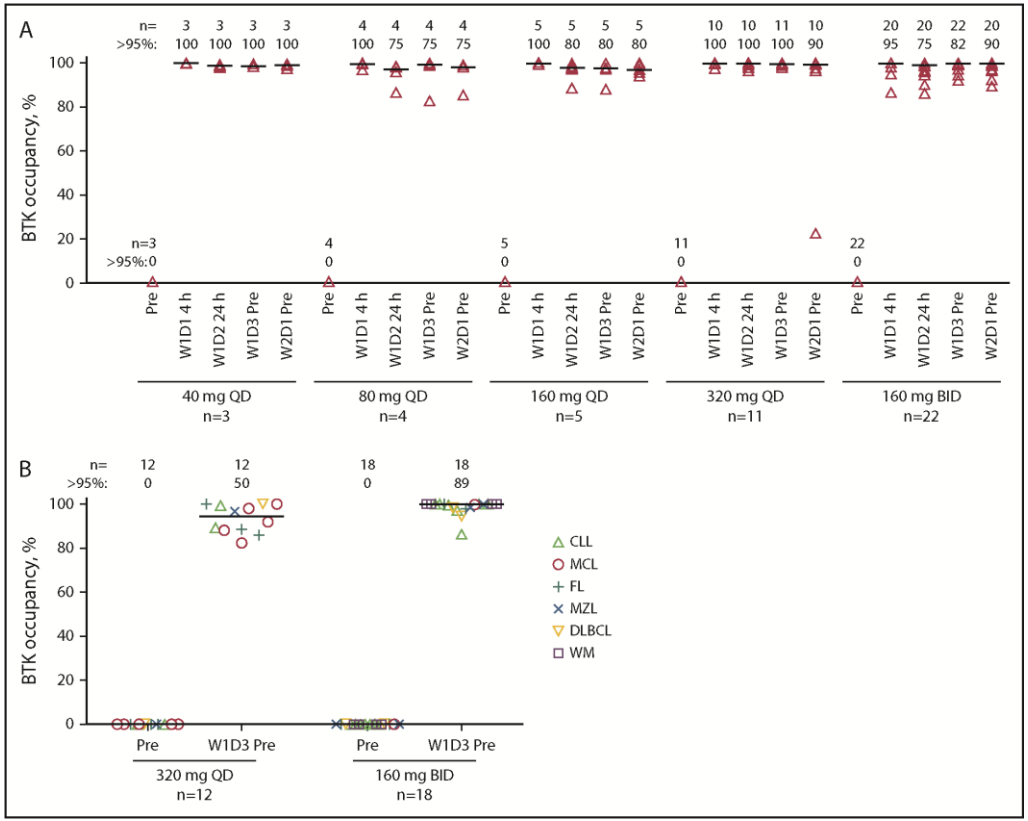
Note: These data are from separate analyses. Limitations of cross-trial comparisons apply.

ALPINE study. Hillmen et al. LB1900 *EHA 2021*.

Zanubrutinib induces sustained BTK occupancy in PBMCs and lymph nodes

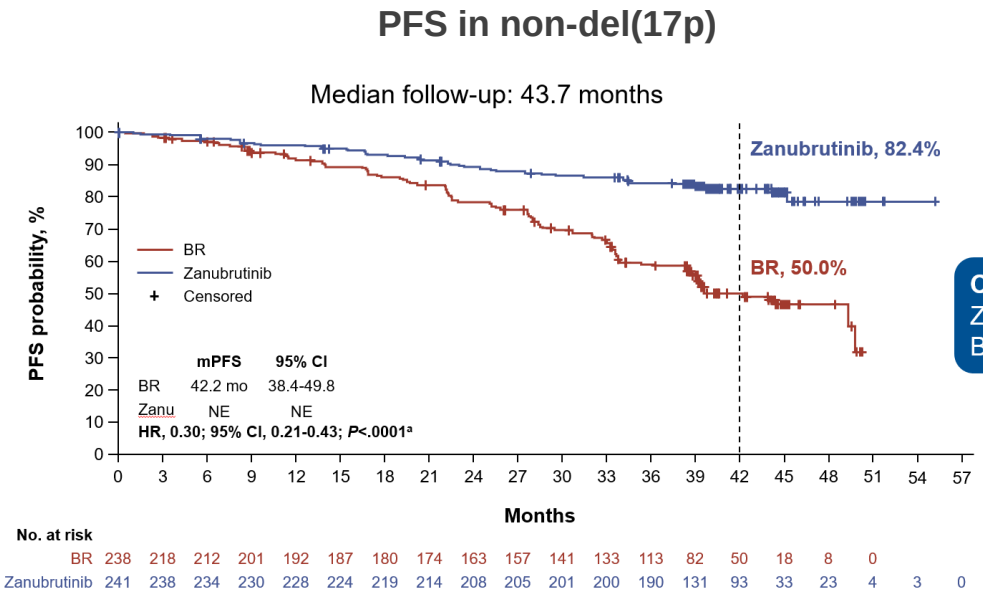
PBMCs

Lymph node tissue



Tam et al., Blood, 2019

Zanubrutinib: *Phase 3 SEQUOIA Study*

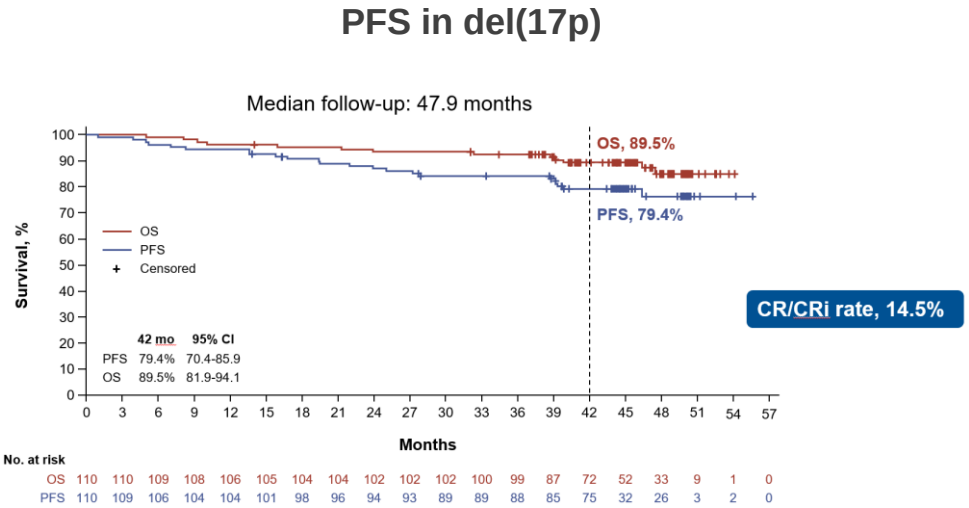


CR/CRi rates:
Zanubrutinib, 17.4%;
BR, 21.8%

Shadman et al., ICML, 2023

Zanubrutinib in CLL With del(17p)/*TP53* Mutation

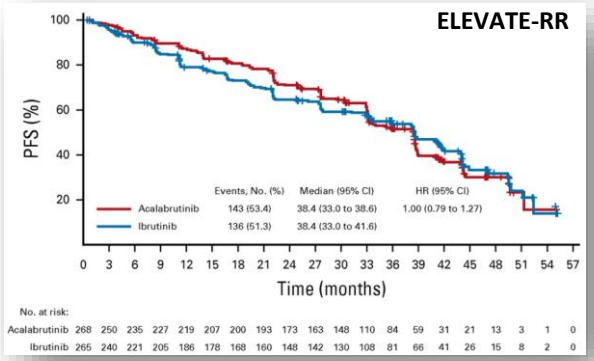
- SEQUOIA del(17p) cohort, N = 110
- Largest prospective dataset in patients with TN del17p CLL



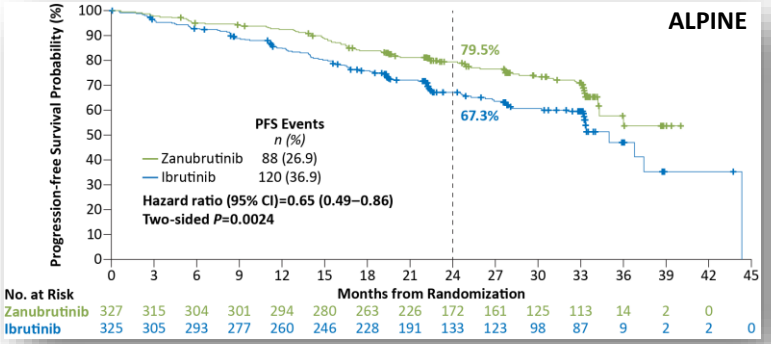
Shadman et al., ICML, 2023

So how do we choose between these 3 options?

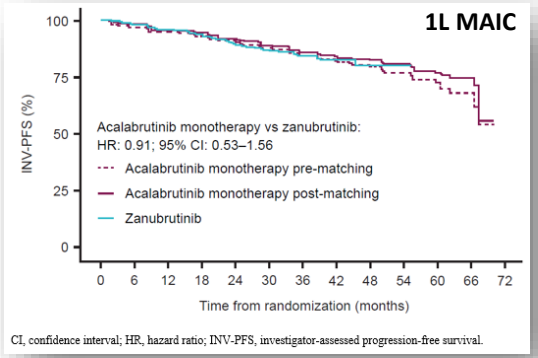
Comparing the covalent BTKi



Byrd JC et al., *J Clin Oncol.* 2021



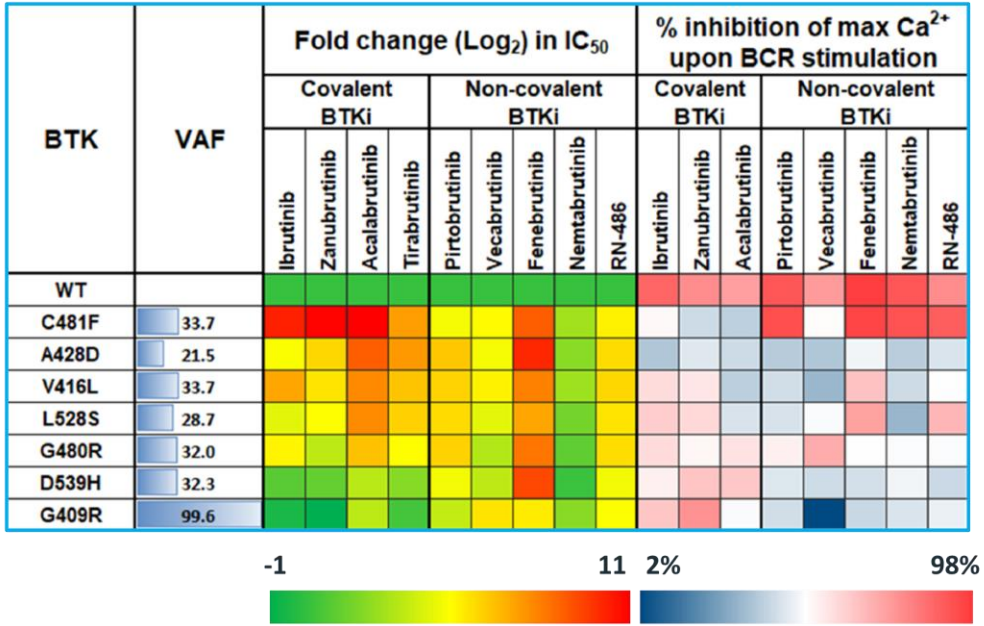
Brown JR, et al. *N Engl J Med*. 2022



(in submission)

--CONFIDENTIAL: DO NOT POST --

Acquired BTK Mutations Associated With Resistance to Non-Covalent BTK Inhibitors: *Response of BTK-Mutant REC-1 Cells to Covalent and Non-Covalent BTK Inhibitors*



Qi J, et al. *Blood Adv.* 2023 (published online1.20.2023).

BTKi Costs

BTK Inhibitor	Dose Strength	Quantity per Bottle	WAC (12-mo supply)	Cost Differential (12-mo supply)
zanubrutinib	80-mg capsules	120 capsules	$167,964	–
acalabrutinib	100-mg capsules	60 capsules	$173,832	−$5,868 (3.5%)
ibrutinib	All tablet strengths	28 tablets[a]	$192,288	−$24,324 (14.5%)

[a]Ibrutinib converted up to 30-day supply, then annualized at 100% dispensed adherence.

Selecting the appropriate BTKi for frontline treatment

77M with del(11q), U-IGHV CLL and poorly-controlled HTN, cytopenias: acala

53M with tri12, U-IGHV CLL, very fit, busy lifestyle and refractory AIHA: ibrut

75F with del(17p), U-IGHV CLL and migraine headaches with bulky lymphadenopathy: zanu

IT'S GOOD TO HAVE OPTIONS

Grazie!