4th POSTGRADUATE

CLL Conference

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President:
Pier Luigi Zinzani

Acalabrutinib

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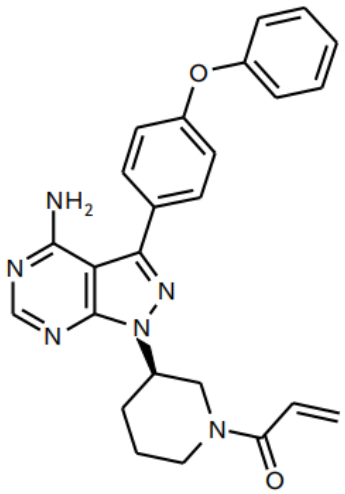
13 November, 2023

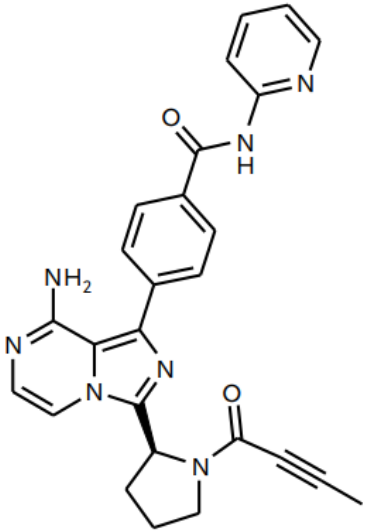
Disclosures of Matthew S. Davids, MD, MMSc

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	✓		✓			✓	

A new generation of covalent BTKi is born



Ibrutinib



Acalabrutinib

Targets and Inhibitory Concentration (nM)

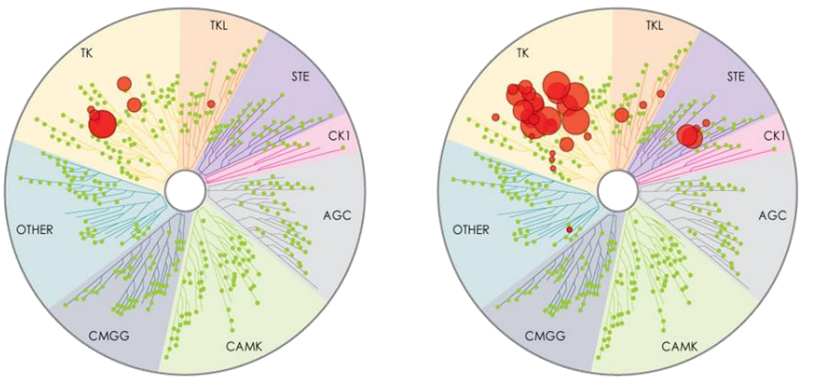
	BTK	ITK	TEC	EGFR
Ibrutinib	1.5	4.9	7	5.3
Acalabrutinib	5.1	>1000	93	>1000

Byrd et al., NEJM, 2016

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

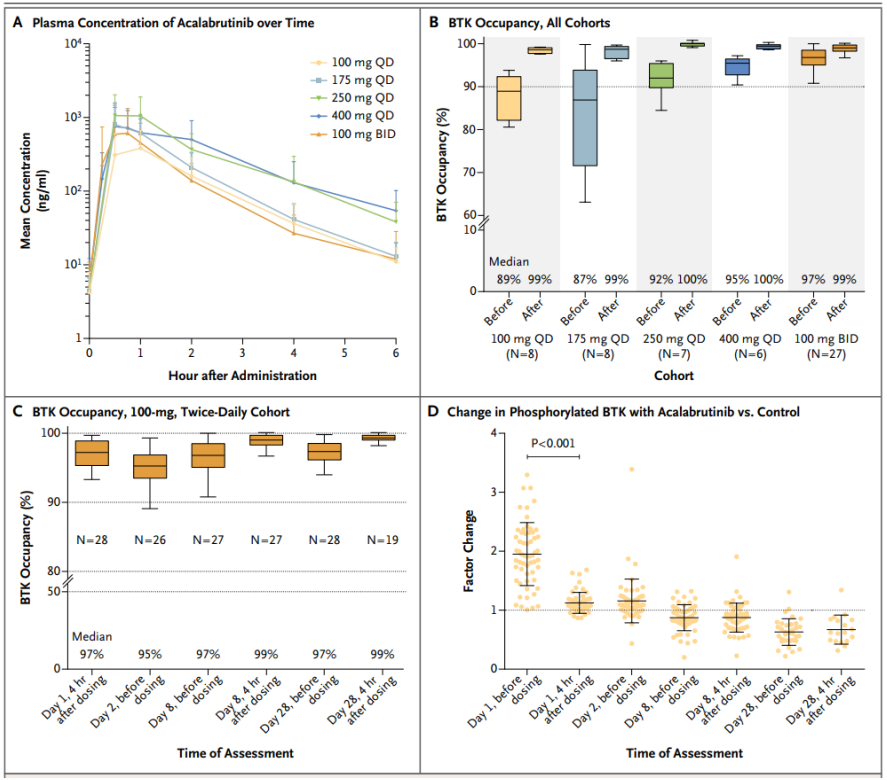


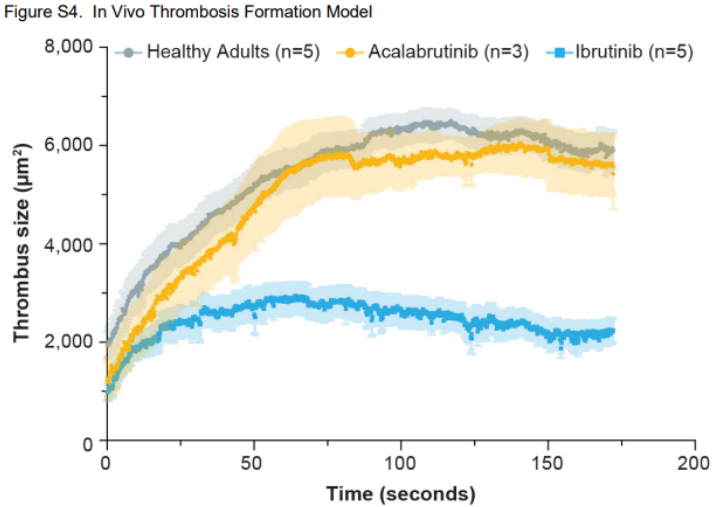
The size of the red circle is proportional to the degree of inhibition.

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

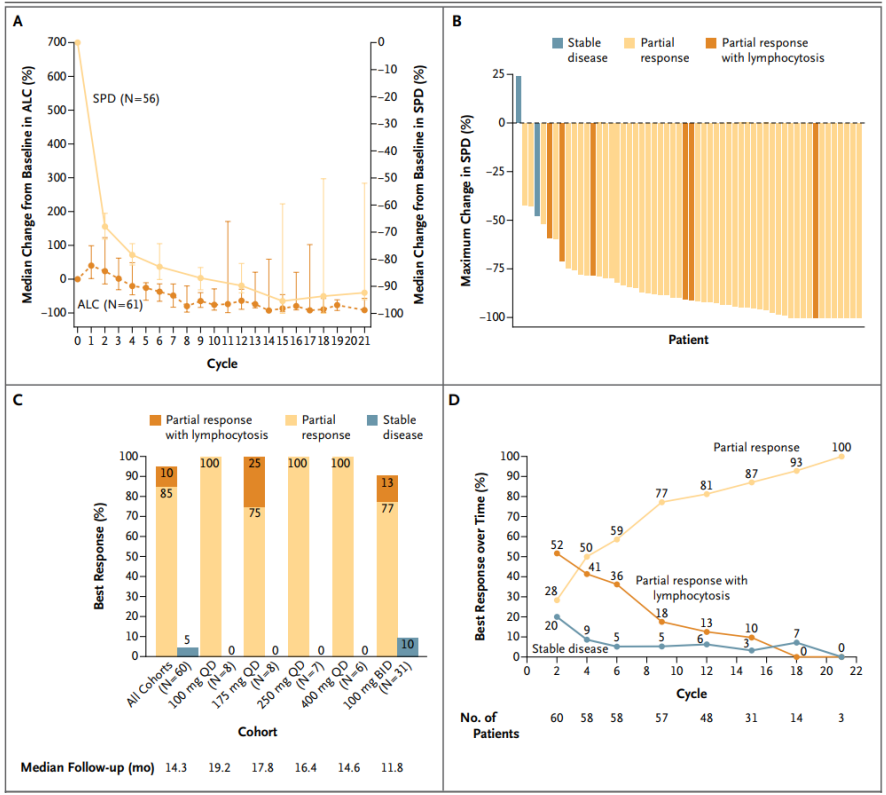




Platelets from patients treated with ibrutinib 420 mg once per day (QD) (n=5) or acalabrutinib 100 mg twice per day (BID) (n=3) were evaluated for their ability to support thrombus formation in laser injured arterioles of VWF^{HA1} mice. Freshly isolated platelets from healthy volunteers (n=5) were used 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

Acalabrutinib: Response

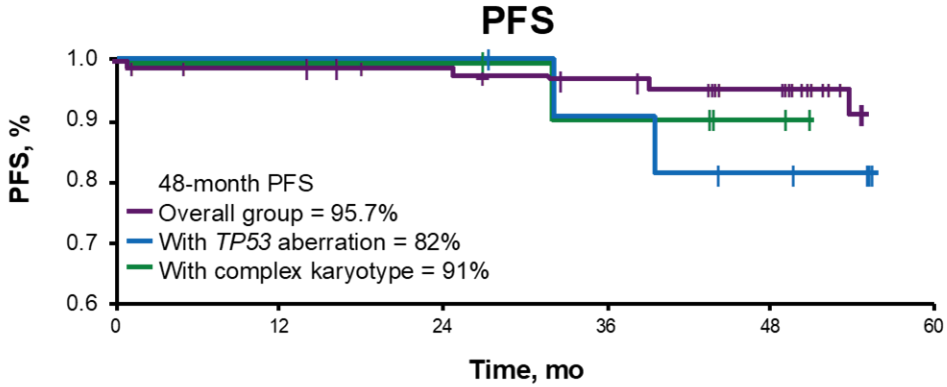


Byrd et al., NEJM, 2016

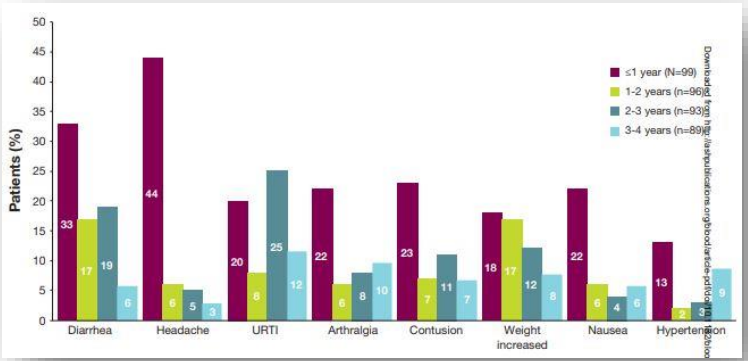
Acalabrutinib in TN CLL: Phase 1/2 Trial

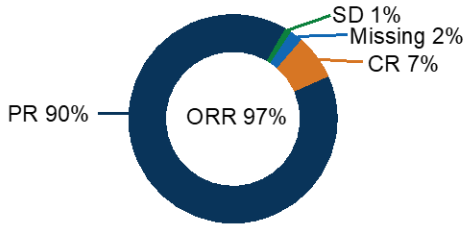
Baseline characteristics (N = 99):

- 46% aged ≥ 65 years
- 18% TP53 aberration
- 18% complex karyotype
- 66% ECOG PS = 1



AE profile by year





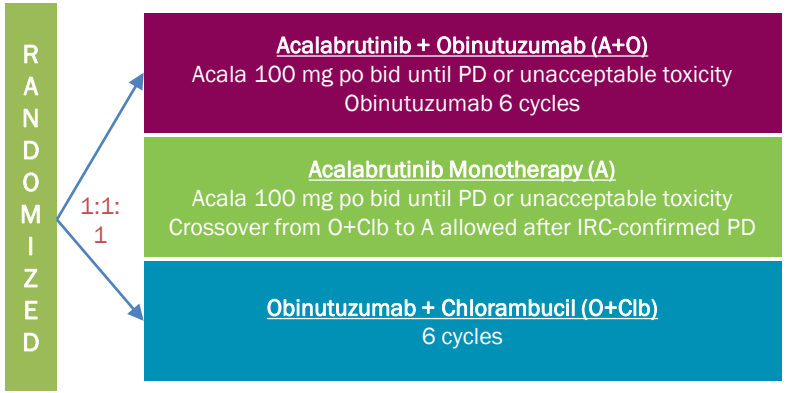
Median DOR not reached

Byrd JC, et al. Blood. 2021;137:3327-3338.

5-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – Study Design and Patient Characteristics[1-3]

Key Eligibility Criteria

- Aged ≥65 years or >18 to <65 years with comorbidities (defined as CrCl 30-69 mL/min and CIRS-G >6)
- Untreated CLL requiring treatment per iwCLL 2008 criteria
- ECOG PS ≤2
- No significant cardiovascular disease



Primary endpoint: IRC-assessed PFS (A+O vs O+Clb)
Secondary endpoints: IRC-assessed PFS (A vs O+Clb), INV-assessed PFS, IRC- and INV-assessed ORR, TTNT, OS, uMRD, safety

Patient Characteristics		A+O (n=179)	A (n=179)	O+Clb (n=177)
Median age (range), years		70 (41-88)	70 (44-87)	71 (46-91)
ECOG PS, n (%)	0-1	169 (94.4)	165 (92.2)	167 (94.4)
	2	10 (5.6)	14 (7.8)	10 (5.6)
Bulky disease ≥5 cm, n (%)		46 (25.7)	68 (38.0)	54 (30.5)
Rai stage, n (%)	III	47 (26.3)	51 (28.5)	40 (22.6)
	IV	38 (21.2)	37 (20.7)	38 (21.5)
Cytogenetics, n (%)	del(17p)	17 (9.5)	16 (8.9)	16 (9.0)
	del(17p) and/or mutated *TP53*	25 (14.0)	23 (12.8)	25 (14.1)
Mutated *TP53*, n (%)		21 (11.7)	19 (10.6)	21 (11.9)
Unmutated *IGHV*, n (%)		103 (57.5)	119 (66.5)	116 (65.5)
Treatment ongoing, n (%)		116 (64.8)	107 (59.8)	0

Data cutoff: October 1, 2021.

1. Sharman JP, et al. EHA 2021. Abstract S148. **2.** Sharman JP, et al. ASCO 2022. Abstract 7539. **3.** Sharman JP, et al. EHA 2022. Abstract P666.

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

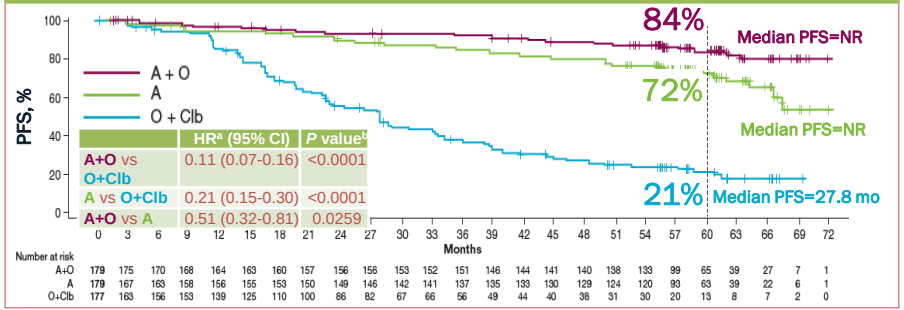
AEs of Clinical Interest, n (%)	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	43 (24.2)	17 (9.6)	39 (21.8)	18 (10.1)	13 (7.7)	3 (1.8)
Atrial fibrillation	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	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.

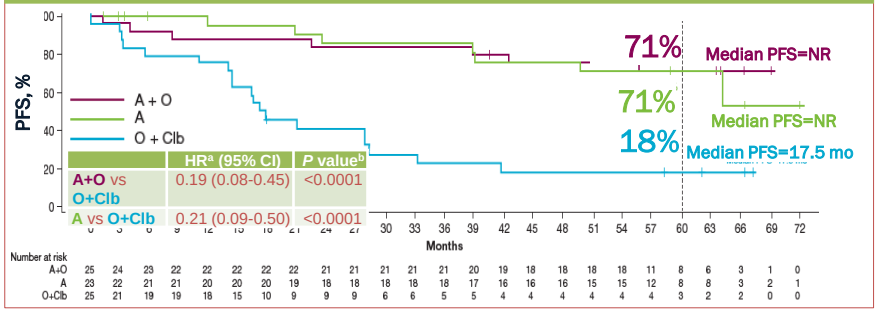
1. Sharman JP, et al. ASCO 2022. Abstract 7539. **2.** Sharman JP, et al. EHA 2022. Abstract P666.

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

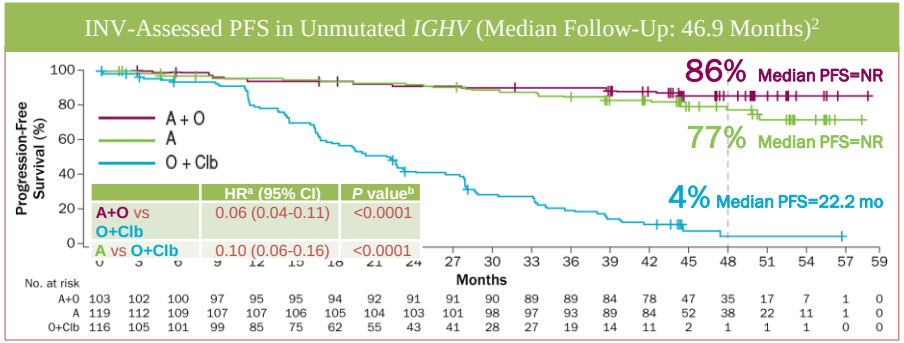
INV-Assessed PFS (Median Follow-Up: 58.2 Months)[1]



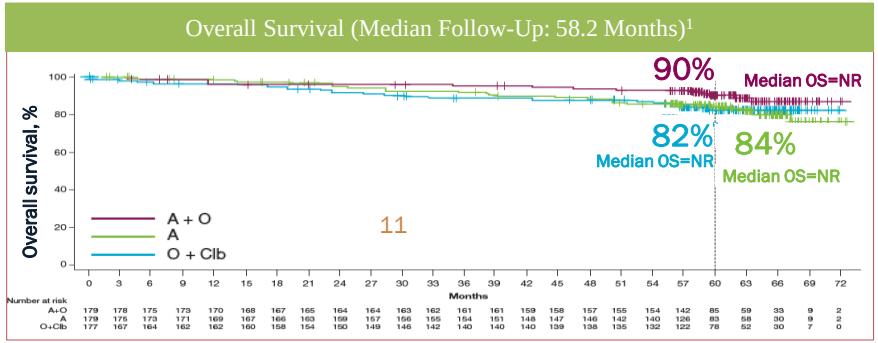
INV-Assessed PFS in del(17p) and/or *TP53*-mut (Median Follow-Up: 58.2 Months)[1]



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

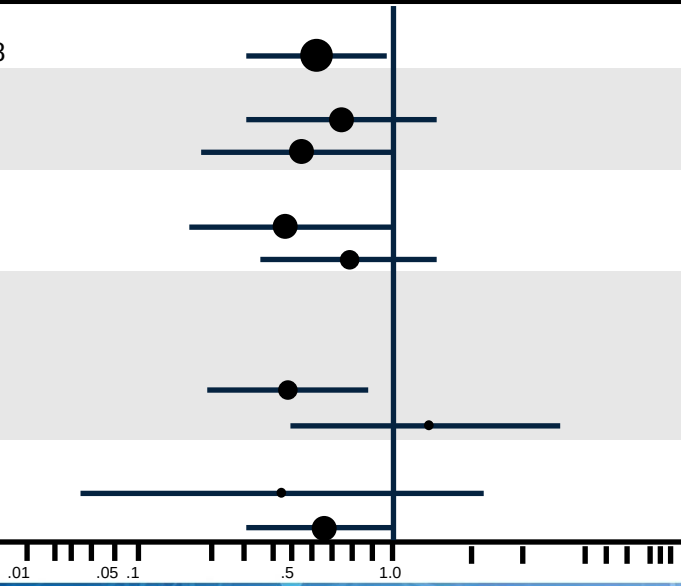
1. Sharman JP, et al. ASCO 2022. Abstract 7539. **2.** Sharman JP, et al. *Leukemia*. 2022;36(4):1171-1175.

Acala/Obin Combo May Provide Benefits in Certain CLL Subgroups[1]

- ELEVATE-TN post hoc analysis of data pooled from 376 patients with TN CLL suggests that for patients with unmutated IGHV, the A + G combination may lead to improved PFS and OS compared with those receiving A monotherapy

Investigator-Assessed PFS: PFS Improved With A + G Versus A in Patients With Unmutated IGHV

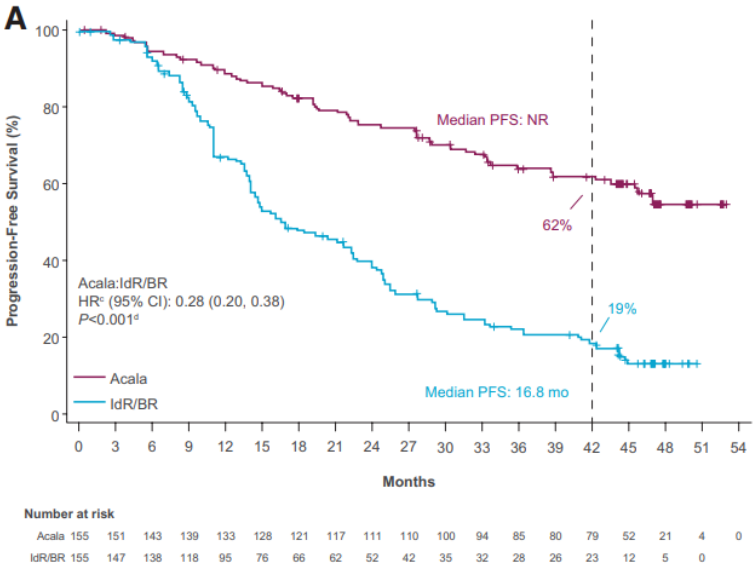
	No. PFS Events/Patients		Hazard Ratio (95% CI)
	A + G	A	
Overall			
Primary analysis	19/112	36/118	0.51 (0.29-0.89)
Age group, y			
<70	10/60	15/59	0.63 (0.28-1.40)
≥70	9/52	21/59	0.45 (0.21-0.99)
Bulky disease (measurable lymph nodes), cm			
<5	8/74	18/66	0.40 (0.17-0.92)
≥5	11/38	18/51	0.67 (0.31-1.41)
CLL-IPI score			
0-1 (normal/low risk)			N/A
2-3 (intermediate risk)	0/8	2/6	NE (NE-NE)
4-6 (high risk)	12/85	29/94	0.41 (0.21-0.81)
7-10 (very high risk)	7/18	5/17	1.32 (0.42-4.16)
B2M at baseline, mg/L			
≤3.5	2/24	4/19	0.39 (0.07-2.16)
>3.5	17/87	32/98	0.55 (0.31-1.00)



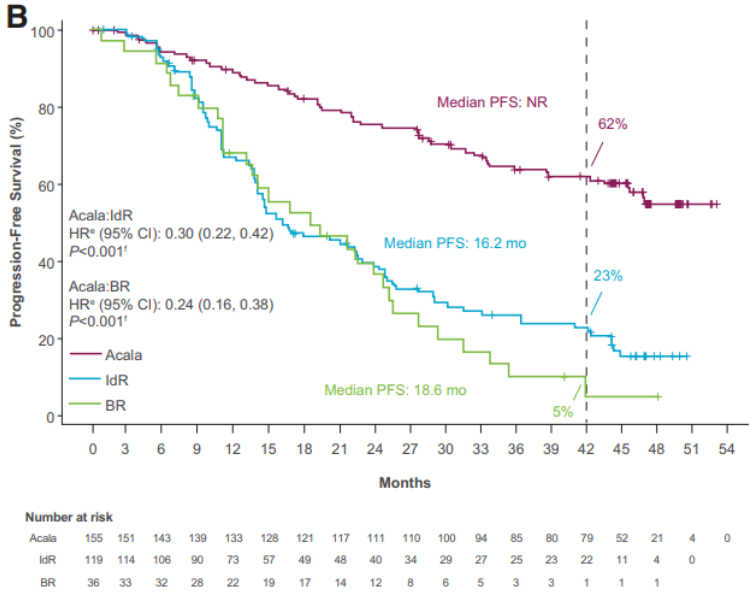
1. Davids M et al. ASH 2022. Abstract 1815.

ASCEND: IRC-assessed PFS was superior for Acala vs Idela-R or B-R in R/R CLL

Final PFS Analysis



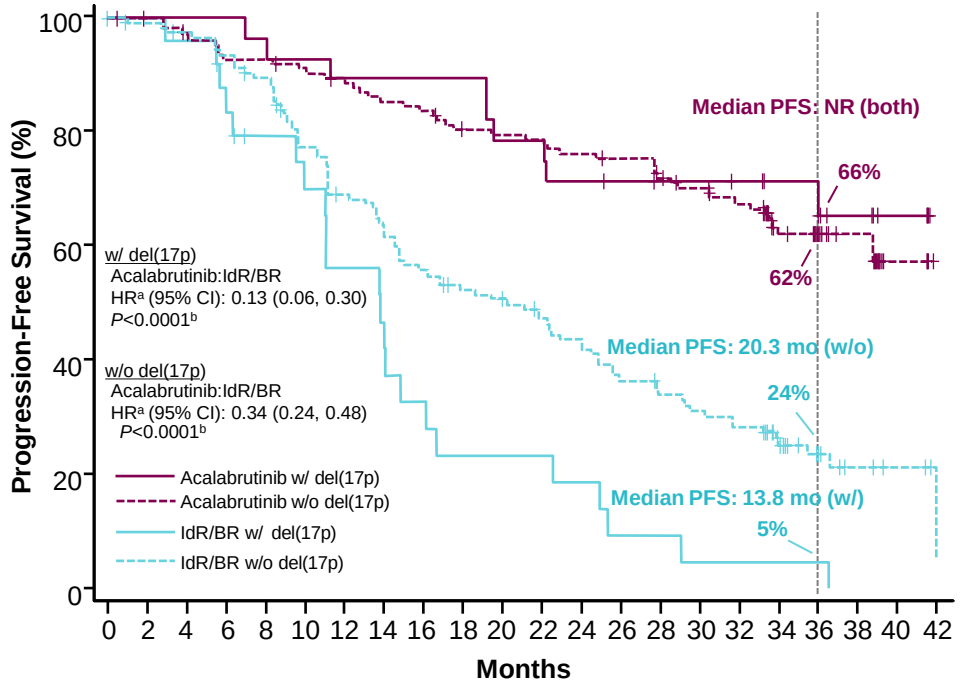
PFS By Treatment Received



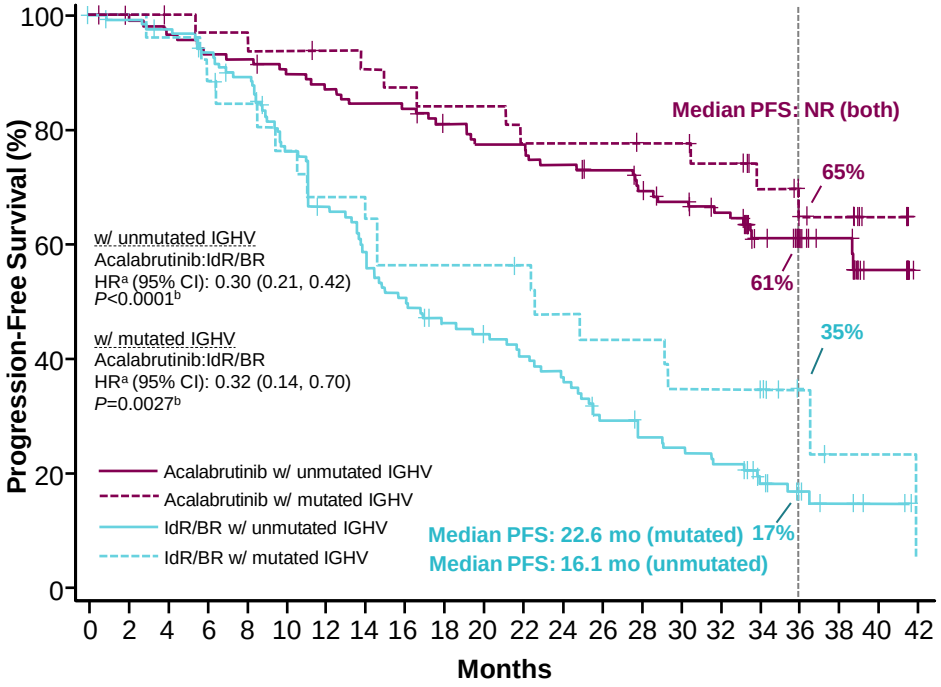
Ghia. Hemasphere. 2022. [epub]

ASCEND: Investigator-Assessed PFS in Patients with High-Risk Features

PFS by del(17p)



PFS by IGHV

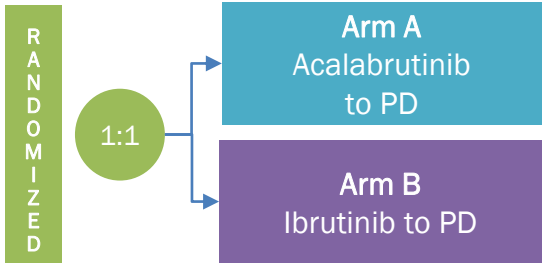


- Acalabrutinib resulted in similar PFS in patients with del(17p)/*TP53* mutations and unmutated IGHV

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Study Design and Patient Characteristics[1,2]

Key Eligibility Criteria

- Previously treated CLL with del(17p) or del(11q)
- ECOG ≤2



N=533

Enrolled from[2]:

- **Europe (75%)**
- **United States (22%)**
- **New Zealand and Australia (3%)**

Primary endpoint:

PFS by IRC

- Noninferiority[a]; tested after 250 events

Stratification by:

- Presence of del(17p)
- ECOG PS (2 vs ≤1)
- Number of prior therapies (1-3 vs ≥4)

Secondary endpoints[b]:

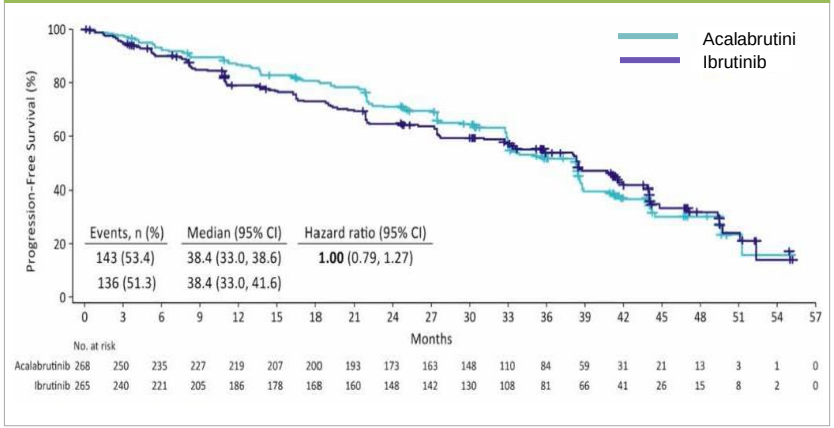
- Incidence of atrial fibrillation
- Incidence of grade ≥3 infections
- Incidence of Richter transformation
- OS

Patient Characteristics[2]	Acalabrutinib (n=268)	Ibrutinib (n=265)
Median age (range), years	66 (41-89)	65 (28-88)
≥75 years, n (%)	44 (16.4)	43 (16.2)
ECOG PS 0-1, n (%)	247 (92.2)	243 (91.7)
Median prior lines of therapy (range), n	2 (1-9)	2 (1-12)
≥4 prior lines, n (%)	33 (12.3)	28 (10.6)
del(17p), n (%)	121 (45.1)	120 (45.3)
TP53-mut, n (%)	100 (37.3)	112 (42.3)
del(11q), n (%)	167 (62.3)	175 (66.0)
Unmutated *IGHV*, n (%)	220 (82.1)	237 (89.4)
Complex karyotype, n (%)	124 (46.3)	125 (47.2)
Bulky disease (≥5 cm), n (%)	128 (47.8)	136 (51.3)

1. Hillmen P, et al. EHA 2021. Abstract S145. **2.** Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients with R/R CLL – Efficacy and Safety Analysis[1]

Primary Endpoint: Noninferiority on IRC-Assessed PFS
(Median Follow-Up: 40.9 Months)



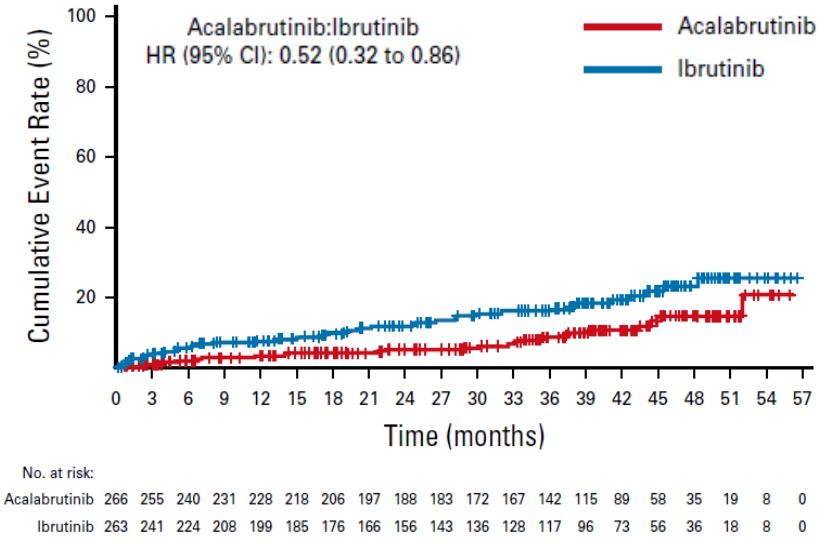
Median follow-up	Treatment ongoing	Most common reasons for discontinuation	Median treatment exposure (range)
40.9 months	46 (Acala) and 41 (Ibr)	PD (31 Acala vs 26 Ibr), AEs (15 Acala vs 22 Ibr)	38.3 mo (0.3-55.9) Acala vs 35.5 mo (0.2-57.7) Ibr

AEs	Any grade		Grade ≥3	
	Acala[a]	Ibr[b]	Acala[a]	Ibr[b]
Events of clinical interest, %				
Cardiac events	24	30	9	10
Atrial fibrillation/flutter	9	16*	5	4
Hypertension[c]	9	23*	4	9*
Bleeding events[d]	38	51*	4	5
Major bleeding events[e]	5[f]	5[g]	4	5
Infections[h]	78	81	31	30
Selected common AEs,[i] %				
Diarrhea	35	46*	1	5*
Headache	35*	20	2*	0
Cough	29*	21	1	<1
Fatigue	20	17	3*	0
Arthralgia	16	23*	0	1
Back pain	8	13*	0	1
Muscle spasms	6	13*	0	1
Dyspepsia	4	12*	0	0

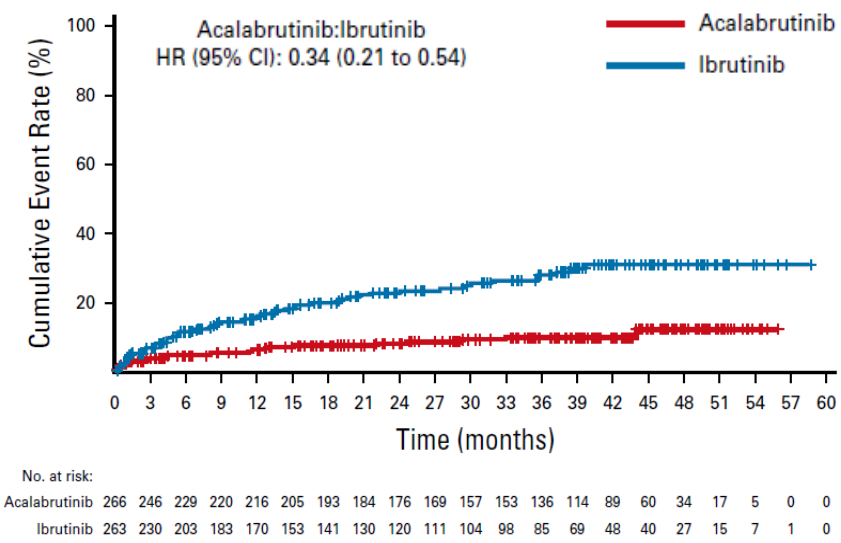
1. Hillmen P, et al. EHA 2021. Abstract S145..

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Additional Safety Analyses

Cumulative Incidence of Atrial Fibrillation/Flutter



Cumulative Incidence of Hypertension

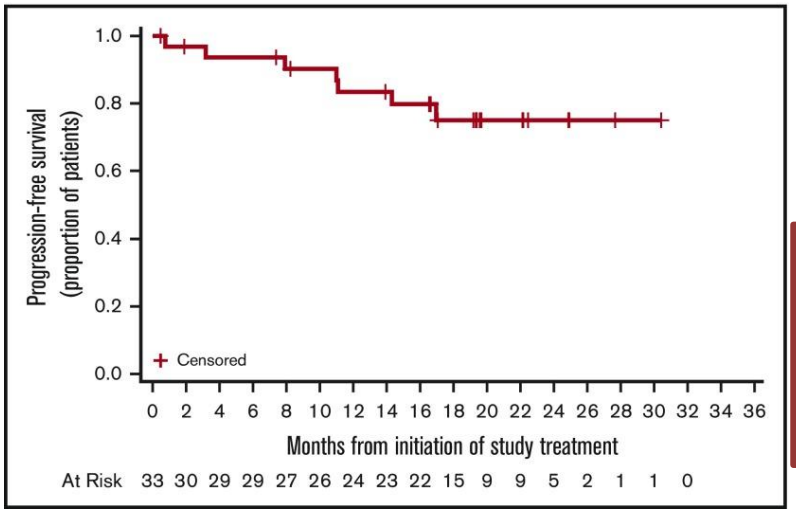


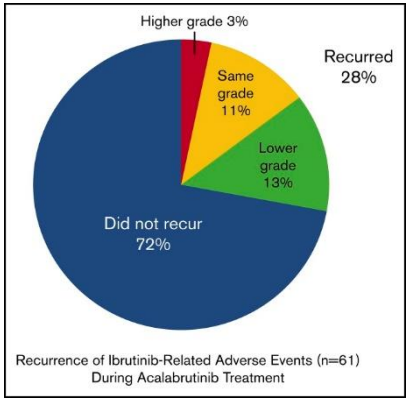
Byrd JC, et al. *J Clin Oncol.* 2021;39:3441-3452.

Acalabrutinib in Ibrutinib-Intolerant Patients

Subset analysis of patients with ibrutinib intolerance enrolled in phase 1/2 ACE-CL-001 (n = 33)

- Median duration of prior ibrutinib, 11.6 months
- ~70% of patients remained on acalabrutinib after a median of 19 months
  - 3 patients had discontinued acalabrutinib due to AEs; 4 patients discontinued due to progressive disease



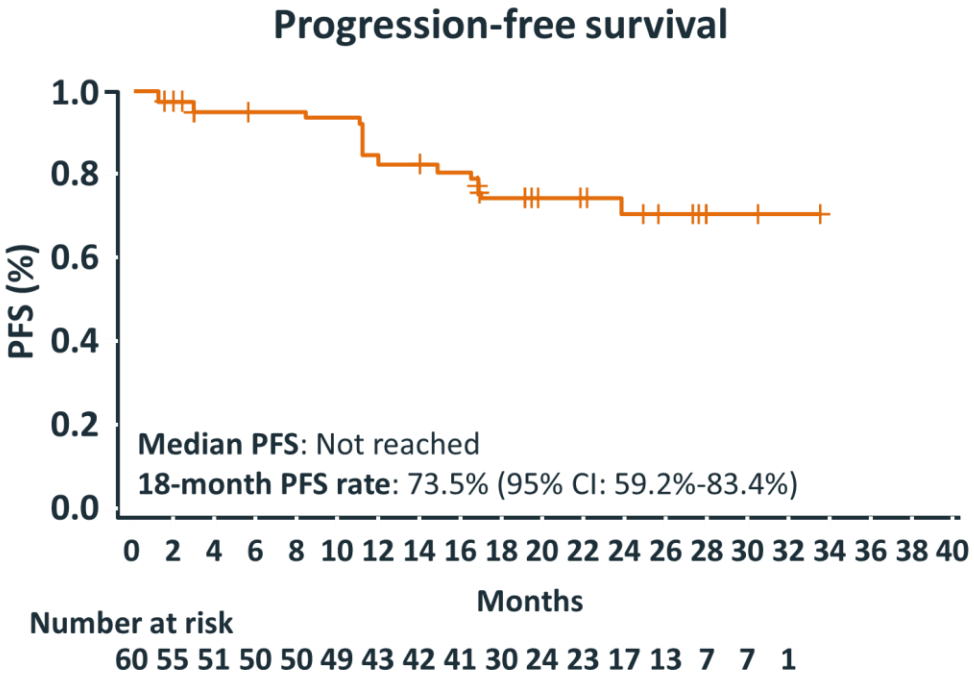


- Median duration of response was not reached
- Median PFS was not reached
- 1-year PFS was 83.4% (95% CI, 64.5%-92.7%)

Awan FT, et al. *Blood.* 2019;3(9):1553-1562. doi: 10.1182/bloodadvances.2018030007.

ACE-CL-208: Acalabrutinib in Patients Who Discontinued Ibrutinib Due to AEs

	N = 60
Follow-up, median (range), months	23 (1-35)
On acalabrutinib, n (%)	37 (62)
Discontinued acalabrutinib, n (%)	23 (38)
Disease progression	9 (15)
Adverse event	7 (12)
Patient withdrawal	3 (5)
Physician decision	2 (3)
Death	1 (2)
Other	1 (2)
Deaths on study, n (%)	8 (13)



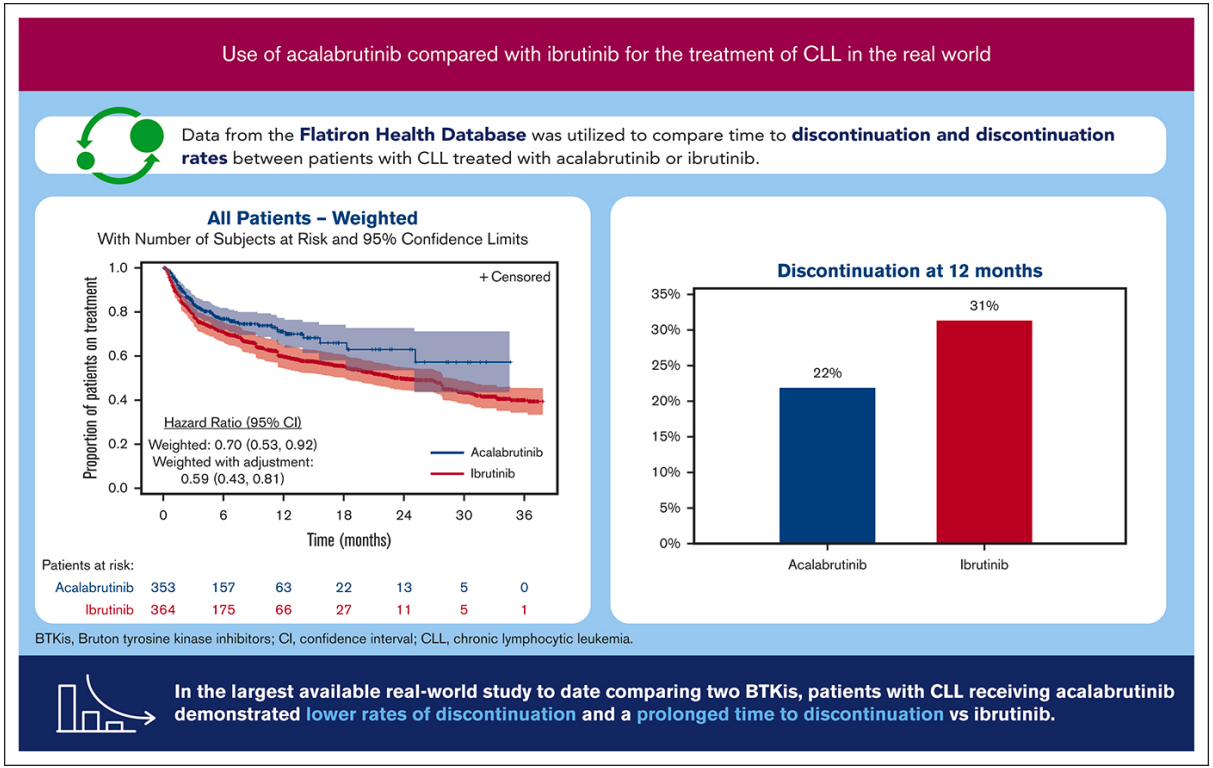
Rogers K, et al. *Haematologica*. 2021:106(9):2364-2373.

ACE-CL-208: Reoccurrence of Adverse Events With Acalabrutinib

			Patients with recurrent AEs on acalabrutinib	
AE	**Patients who discontinued ibrutinib, n**	**Median time to onset on ibrutinib (range), days**	**Total, n**	**Median time to onset on acalabrutinib (range), days**
Atrial fibrillation	16	88 (1-1721)	3	141 (27-311)
Diarrhea	7	26 (2-277)	5	15 (7-713)
Arthralgia	7	27 (1-956)	1	43
Rash	7	1 (1-231)	2	31 (30-32)
Bleeding	7	428 (1-1688)	5	30 (15-441)
Total	**42**	**N/A**	**16**	**N/A**

Rogers K, et al. *Haematologica*. 2021:106(9):2364-2373.

Emerging real-world data confirm improved tolerability of acalabrutinib



Roeker et al, *Blood Adv*, 2023

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]

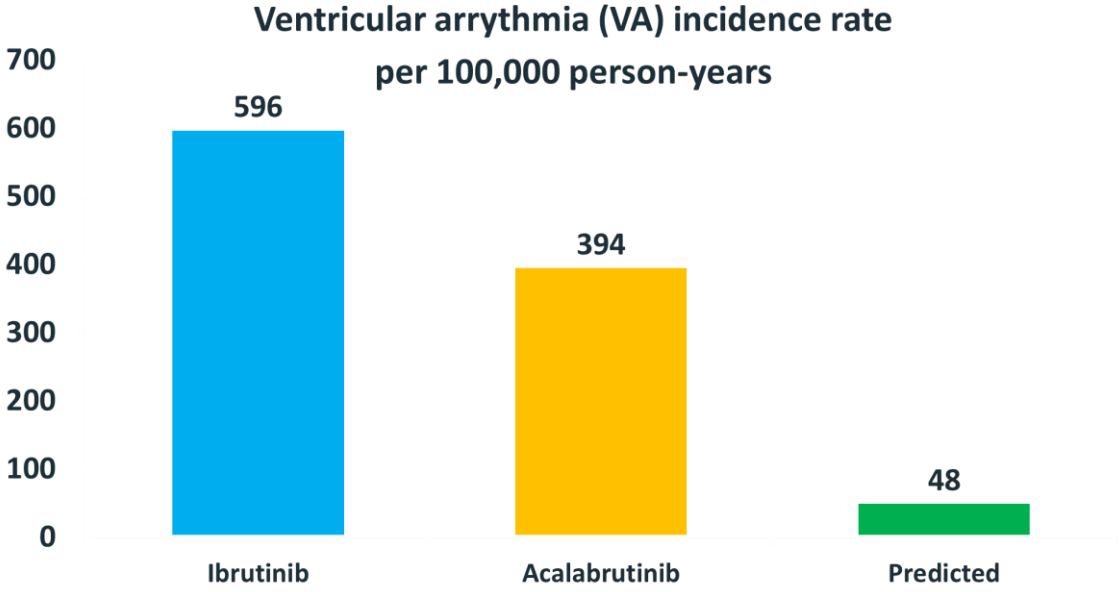
- Same CYP3A interaction with acalabrutinib tablets and capsules:
  - Strong CYP3A Inhibitors: Avoid co-administration of acalabrutinib with a strong CYP3A inhibitor. If these inhibitors will be used short term, interrupt acalabrutinib. After discontinuation of strong CYP3A inhibitor for at least 24 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.

Ventricular Arrhythmias With BTK Inhibitors

Monocentric retrospective study in 394 patients receiving acalabrutinib with historic ibrutinib control



Bhat SA, et al. *Blood*. 2022;140(20):2142-2145.

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

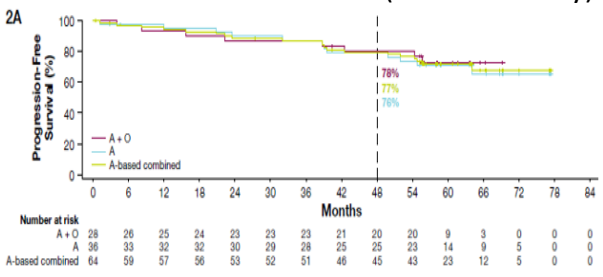
59.1 mo (TN CLL)
44.3 mo (R/R CLL)

High ORR across subgroups

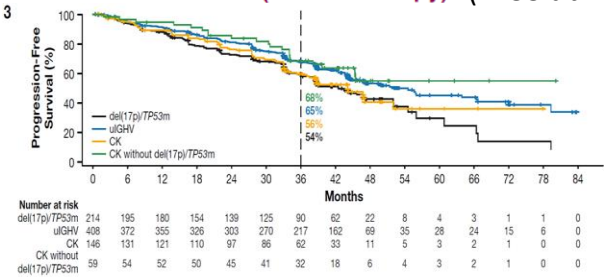
	TN	R/R
del(17p)/*TP53*m	91%	86%
uIGHV	96%	87%
CK	91%	84%

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

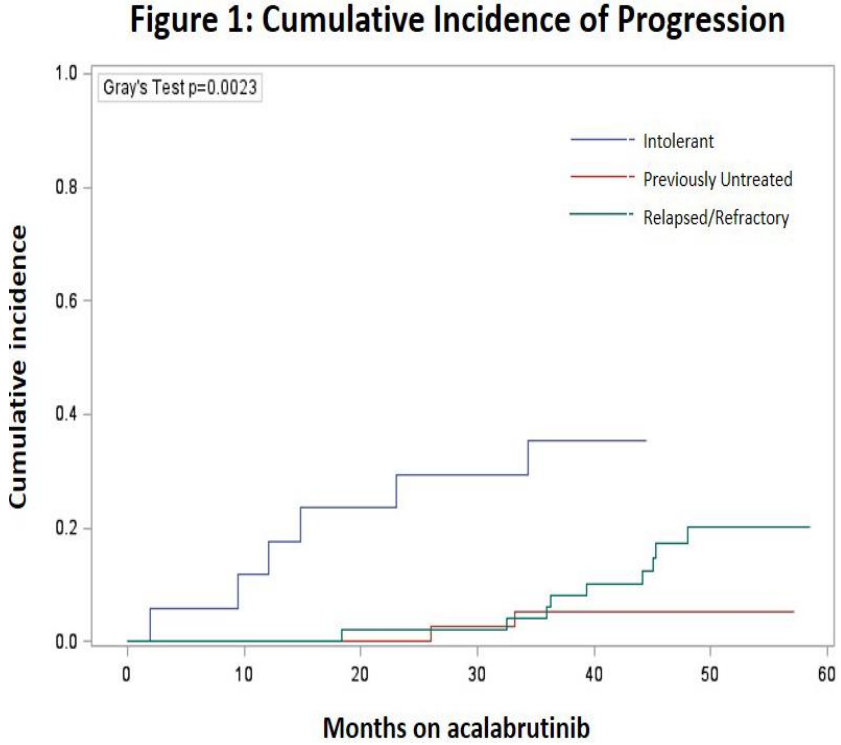
*CK defined as ≥3 chromosomal abnormalities with ≥1 structural abnormality excluding inversion of chromosome 9.
A, acalabrutinib; AE, adverse event; CK, complex karyotype; CLL, chronic lymphocytic leukemia; mo, months; NR, not reached; O, obinutuzumab; ORR, overall response rate; OS, overall survival; 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*

Resistance to Acalabrutinib: *OSU Experience*



- **Of 16 progressors, 11 had *BTK* C481x mut, 2 also *PLCG*2**
- **103 pts were screened, 22 had mut at median 32 mos**
- **Median time to relapse after mut: 12 mos**

Woyach et al, ASH 2019

Could time-limited acala decrease risk of resistance mutations?

ACTIVE, NOT RECRUITING

A Study on Limiting Treatment Time With Acalabrutinib Combined With Obinutuzumab in People With CLL or SLL

ClinicalTrials.gov ID NCT04722172

Sponsor Memorial Sloan Kettering Cancer Center

Information provided by Memorial Sloan Kettering Cancer Center (Responsible Party)

Last Update Posted 2023-08-18

(Clinicaltrials.gov accessed 25 Oct 2023)

Conclusioni

- **Acalabrutinib is a potent covalent BTKi with greater specificity than ibrutinib**
- **Robust phase 3 data support the efficacy and safety of acalabrutinib in TN and R/R CLL**
- **Head-to-head data confirm that acalabrutinib has comparable efficacy and improved safety compared to ibrutinib**
- **Acalabrutinib can be well-tolerated in patients with poor tolerance of ibrutinib**
- **Resistance to acalabrutinib appears to be driven by similar mutations as with ibrutinib**
- **Ongoing combination strategies are incorporating acalabrutinib into time-limited regimens**


Grazie!