Update on Acalabrutinib in Chronic Lymphocytic Leukemia (CLL)

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Disclosure Information

Financial Conflict due to Company Ownership or Patents
Vincerx Pharmaceuticals, Inc
Eilean Therapeutics, Inc
Patents with OSU related to DHODH
Kurome

Other Industry Involvement (no self financial conflict).
Kartos Pharmaecuticals (advisory board)
Newave Pharmaceuticals (research support for clinical trials)
Orange Grove Bio (research support for clinical trials)
Neurix (research support for clinical trials)
Syndax (research support for clinical trials)

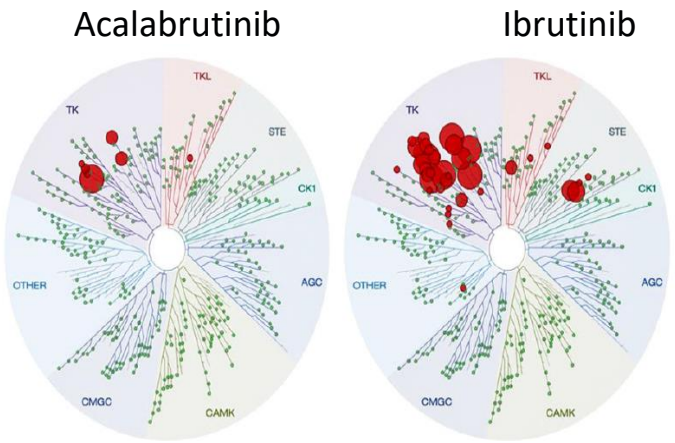
Rationale to Develop a 2nd Generation Covalent BTK inhibitor in CLL

- B-cell receptor signaling and BTK is a validated target in CLL and promotes a high response rate and durable remissions in CLL
- Ibrutinib, while being highly effective in improving outcome of CLL patients has several limitations including
  - Variable absorption with Cmax limited, metabolism, and long half-life for a covalent inhibitor which allows for both reversible and irreversible targets to be influenced
  - Multiple alternative reversible and irreversible targets which promote toxicity
    - Diarrhea and rash (EGFR)
    - Atrial fibrillation, cardiac effects (EGFR, TEC, BMX, SRC kinases)
    - Bleeding (TEC)
    - t
  - Multiple targets may make it more challenging to combine with other agents
  - Long half life and alternative targets prevent dosing ibrutinib BID, an optimal schedule for covalent inhibitors to overcome tumors with rapid BTK re-synthesis
- Hence: An alternative, more selective agent was needed

Acalabrutinib: A More Selective 2nd Generation Covalent BTK Inhibitor

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro and very short half life (1-2 hrs)
- Acalabrutinib Cmax is linear with dosing

Kinase Selectivity Profiling at 1 μM



Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	>1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

CLL 01 Study of Acalabrutinib

- **Untreated Cohort (n=99)**
  - **Median age 64**
  - **Rai stage ¾ 47%**
  - **Del(17)(p13.1) 10%**

  Adverse events often decline with time

  97% overall response (9% CR)

  70 (71%) on therapy at median of 73 months

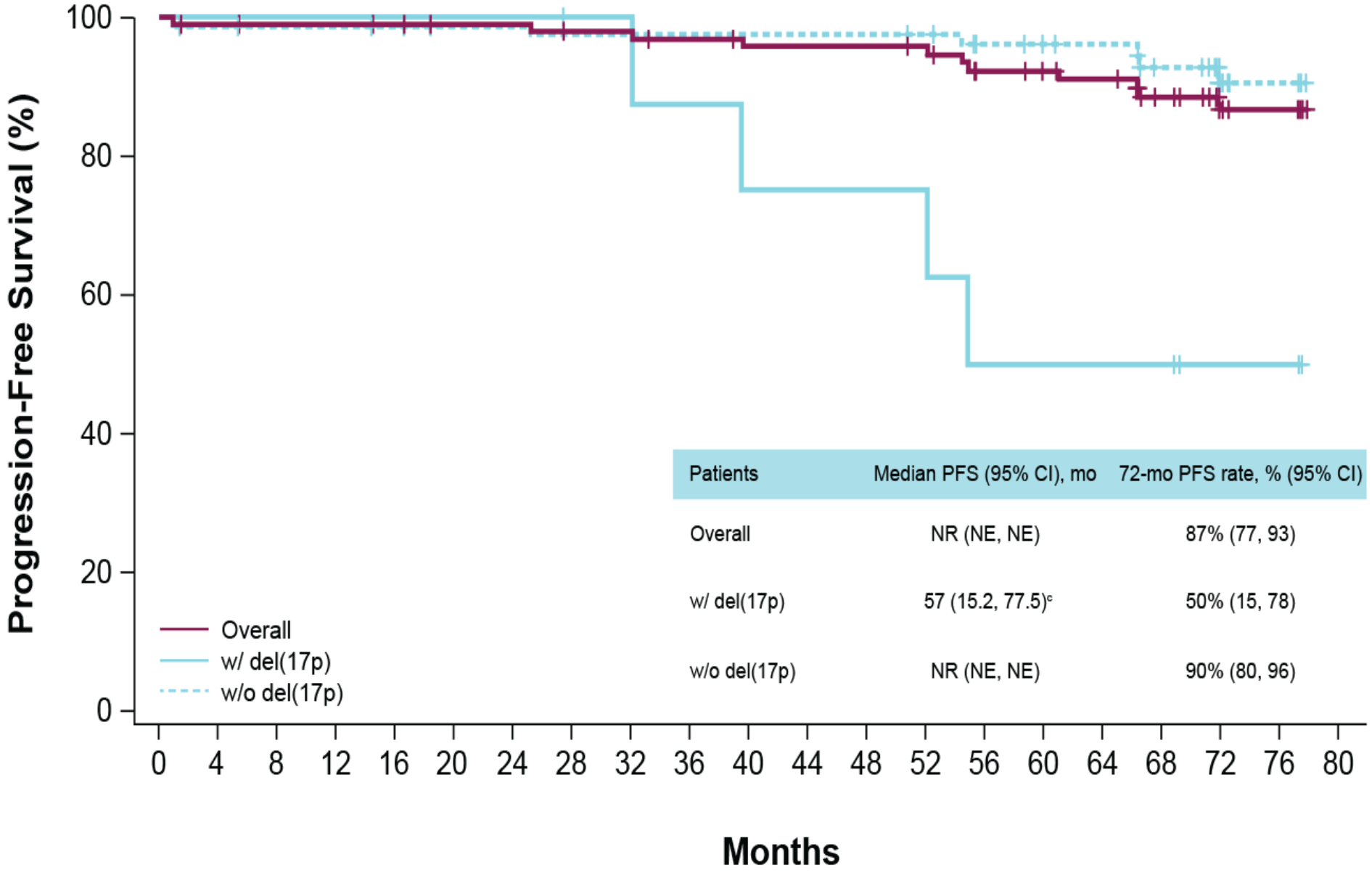
  Off therapy due to adverse events or PD

Byrd JC, et al ASH 2022

Acalabrutinib CLL 01 Adverse Event

	Acalabrutinib (N=99)	
Treatment exposure, median (range), mo	73.7 (0.23–82.4)	
Common TEAEs,[a,b] n (%)	Any Grade	Grade ≥3
Arthralgia	55 (56)	2 (2)
Diarrhea	53 (54)	6 (6)
Contusion	50 (51)	0 (0)
URTI	49 (49)	1 (1)
Headache	48 (48)	5 (5)
Nausea	34 (34)	4 (4)
Cough	32 (32)	0 (0)
Hypertension	28 (28)	12 (12)
Pneumonia	16 (16)	8 (8)
Neutropenia	8 (8)	8 (8)
Syncope	7 (7)	6 (6)
Selected ECIs		
Infections	86 (87)	19 (19)
Bleeding events	73 (74)	7 (7)
Major bleeding events	8 (8)	7 (7)
Hypertension	29 (29)	13 (13)
Secondary primary malignancies, excluding non-melanoma skin	14 (14)	5 (5)
Atrial fibrillation	6 (6)	3 (3)

Outcome on CLL 01 Untreated CLL: Long-Term Follow Up



Patients	Median PFS (95% CI), mo	72-mo PFS rate, % (95% CI)
Overall	NR (NE, NE)	87% (77, 93)
w/ del(17p)	57 (15.2, 77.5)[c]	50% (15, 78)
w/o del(17p)	NR (NE, NE)	90% (80, 96)

Elevate TN Design

TN CLL (N=535)

Key inclusion criteria

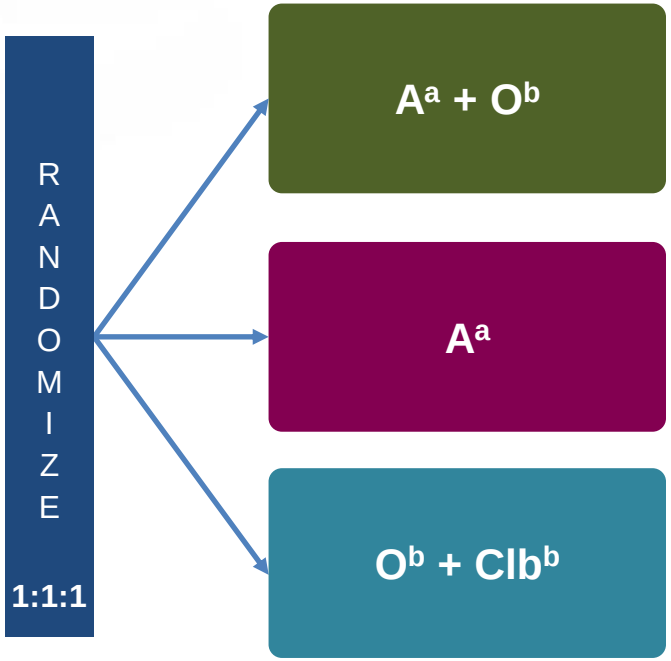
- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Demographics match most cohorts with symptomatic CLL (=538)

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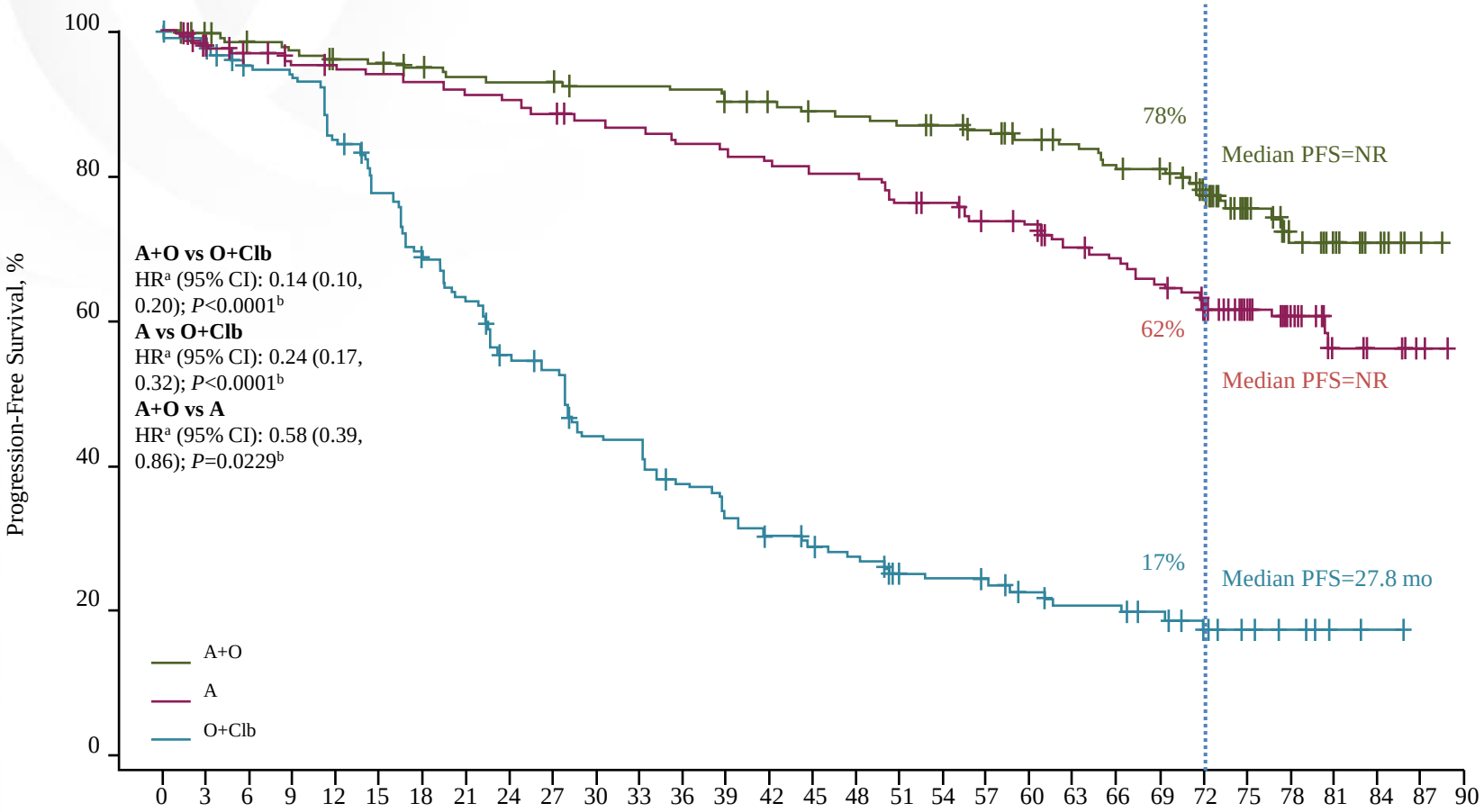
Sharma J, et al: ASH 2023

PFS is Superior for Acalabrutinib Regimens



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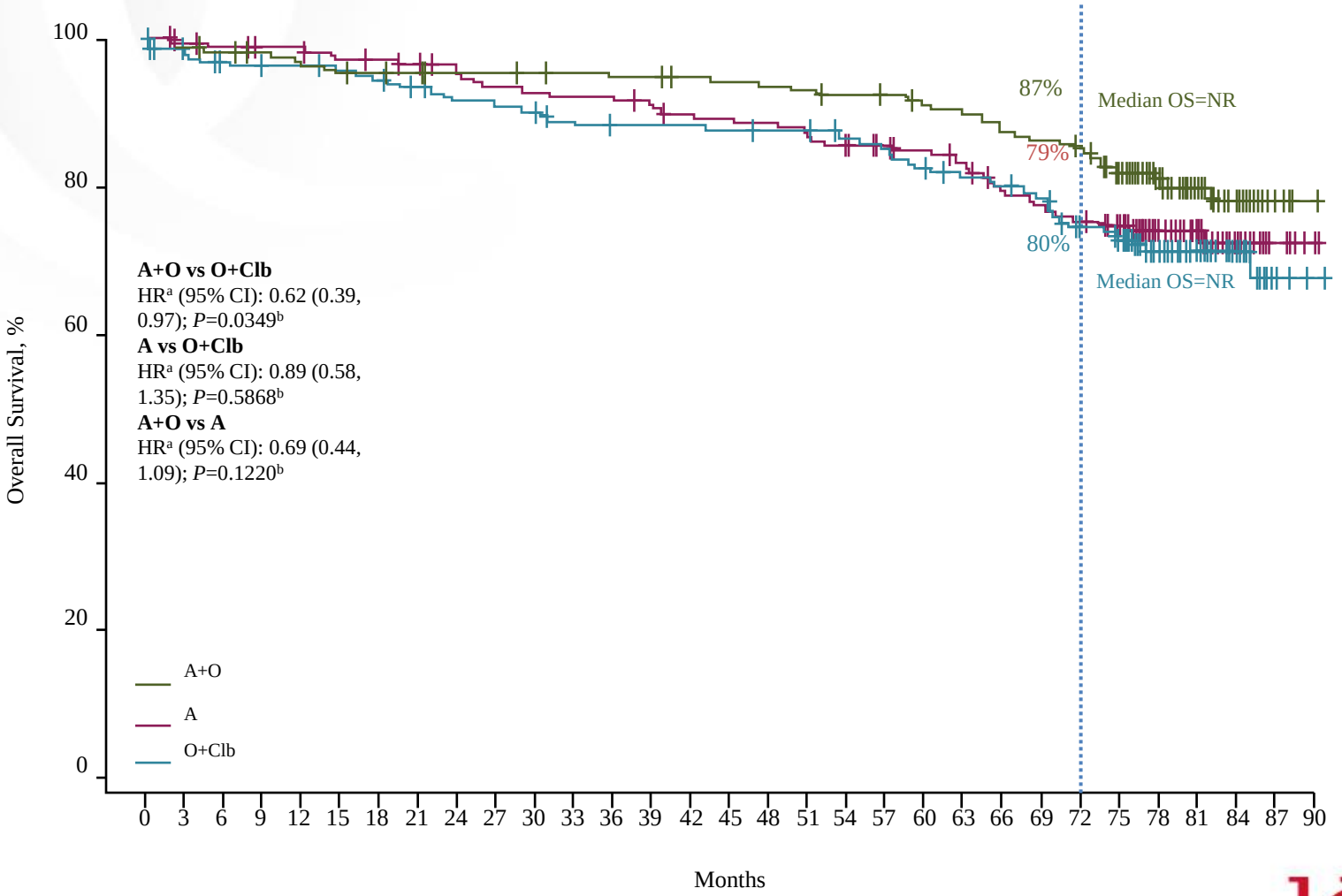
OS is Superior for AO versus CO and trend toward A



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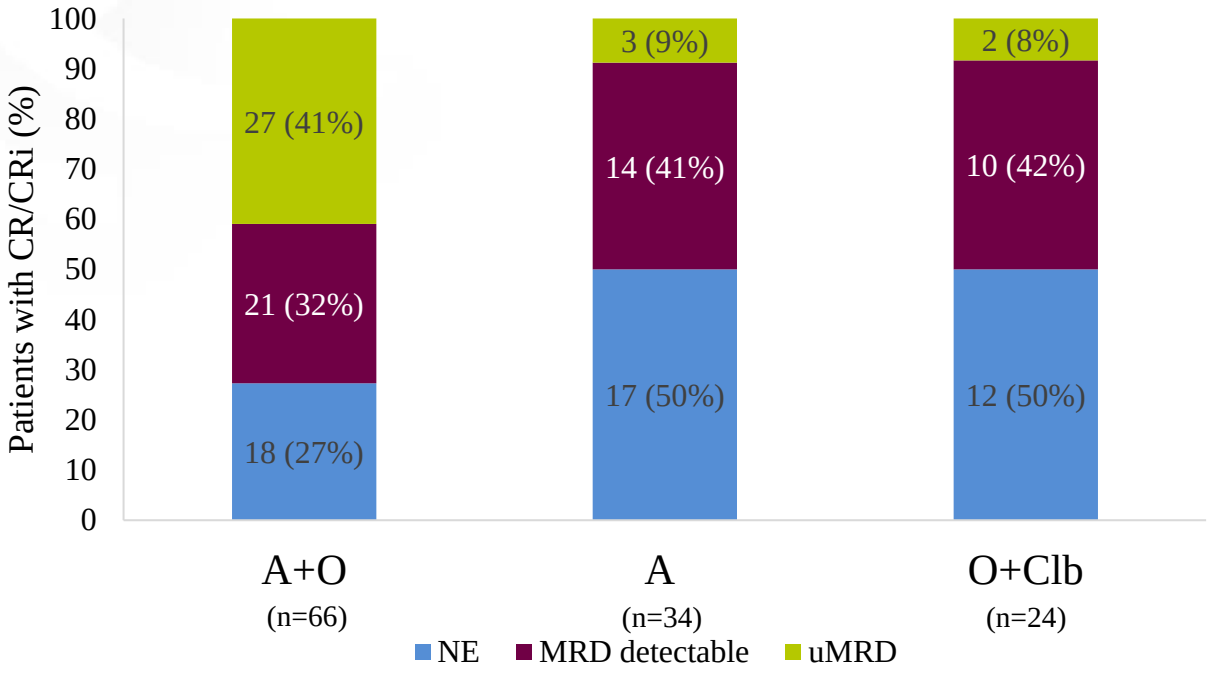
MRD[a] status in patients with CR/CRi



- Among patients with CR/CRi, higher uMRD rates were sustained in a higher proportion of patients receiving A+O vs O+Clb (40.9% vs 8.3%)

Peripheral blood testing to assess MRD occurred for patients with bone marrow–confirmed CR. Peripheral blood MRD status based on last 2 time points (most recent assessments available by the data cutoff) in patients with CR/CRi.
[a]MRD was defined as the proportion of patients with <1 CLL cell in 10^4 leukocytes.

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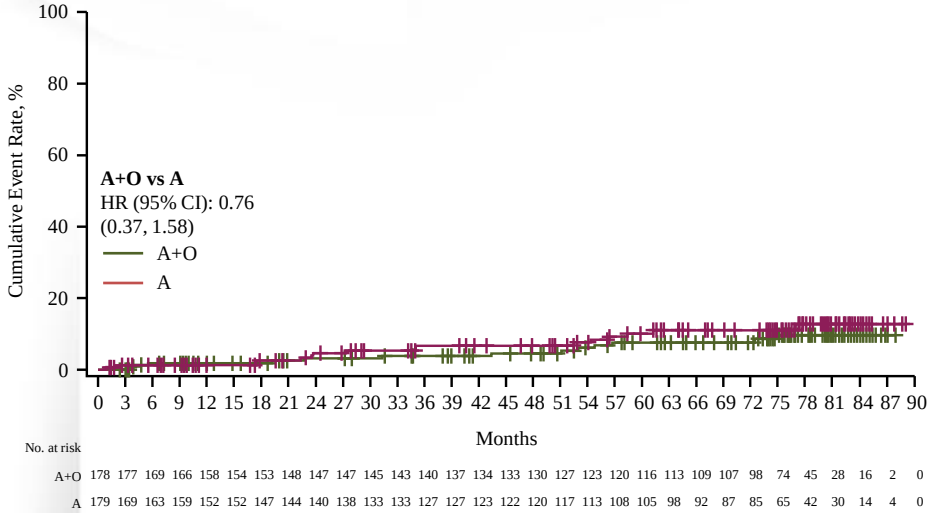
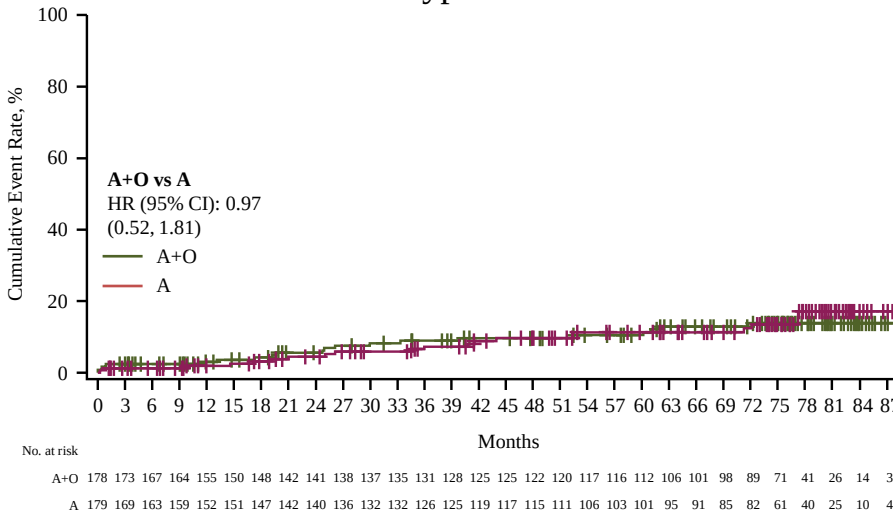
Incidence of cardiac-related AEs remains low

Cumulative incidence of any-grade atrial fibrillation/flutter



Cumulative incidence of any-grade hypertension



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Multivariate analysis of baseline characteristics as predictors of OS in patients treated with acalabrutinib (N=354)

Baseline Characteristic	Ratio	HR (95% CI)[b]	*P*-value[b]
Age	≥70 y/<70 y	2.59 (1.56, 4.32)	**0.0002**
Sex	Male/female	1.06 (0.66, 1.70)	0.8192
ECOG PS	≥2/0−1	2.50 (1.23, 5.08)	**0.012**
del(17p) status	With/without del(17p)	1.72 (0.88, 3.34)	0.1113
IGHV mutational status	mIGHV/uIGHV	0.99 (0.62, 1.58)	0.97

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CLL2-Baag Trial

Demographics include 46 patients with relapsed/refractory CLL including 32% with del(17p) and 34% having received a BTKi or Venetoclax

Induction phase: (6 cycles)

- Obinutuzumab cycles 1-6
- Acalabrutinib 100 mg BID beginning cycle 2-6,
- Venetoclax added cycle 3-6

Maintenance Phase (up to 24 cycles)

- Obinutuzumab Q3m
- Acalabrutinib BID
- Venetoclax 400 mg QD

– Patients followed with high sensitivity flow FACS and digital droplet PCR of plasma at regular intervals
– Therapy stopped if uMRD was not present, by FACS or plasma DNA defined as VDJ rearrangement or CLL specific mutation

Furstenau M, et all: ASH 2023

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CLL2-Baag Trial Outcome

- Median treatment duration was 14.7 mo (range 6-33)
  - 2 pts (4.4%) discontinued treatment during induction due to AEs
  - 25 pts (55.6%) discontinued therapy according to confirmed uMRD CR
  - 9 pts (20.0%) completed the maximum of 8 maintenance cycles due to persisting MRD and/or lack of a complete response
- Estimated 30-mo PFS rate was 88.2% with similar results for del(17)(p13.1)/TP53 mutated, prior BTKi exposure and prior venetoclax exposure
- Plasma DNA was often more sensitive than FACS to identify molecular MRD recurrence

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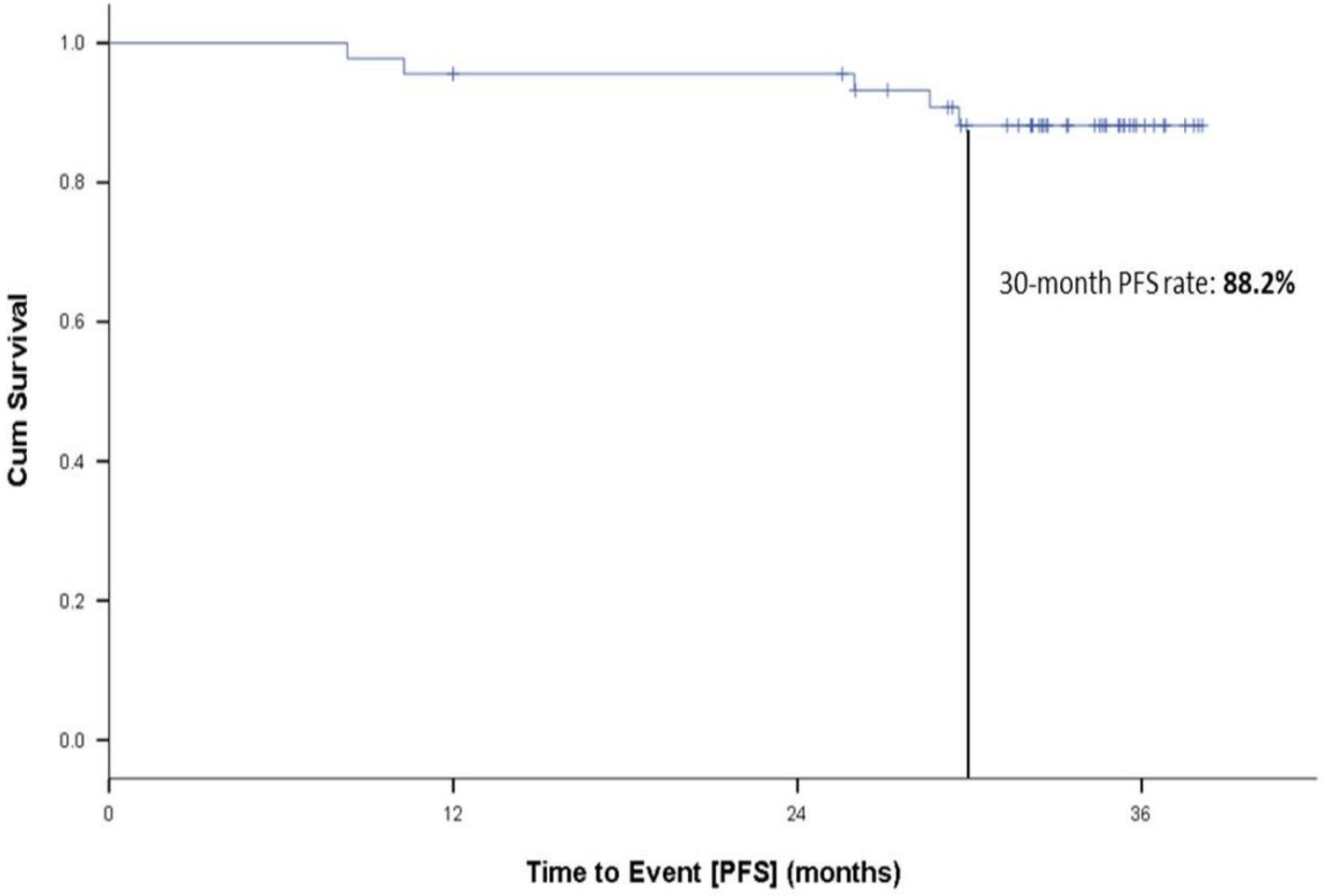
CLL2-Baag Progression Free Survival



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Ibrutinib and Acalabrutinib: Ventricular Arrhythmias

- Ibrutinib
  - Flare Ibrutinib + Rituximab (IR) vs FCR showed sudden cardiac death rate of 500/100,000 years for IR versus vs 100/100,000 yrs of FCR (8 versus 2 pts with sudden cardiac death)(Hillmen P, et al Lancet Oncology 24: 535, 2023)
  - OSU Experience (on and off trials) with ibrutinib 596/100,000 years Guha A, et al. *J Am Coll Cardiol.* 72:697–698, 2018.

Conclusion: Ibrutinib increases Ventricular arrythmias

- Acalabrutinib
  - OSU Experience (Addison D, et al Blood 140(:2142, 2022) shows risk of 394/100,000 years on acalabrutinib and was higher among those intolerant to ibrutinib (685 of 100,000 years)
  - AstraZeneca Phase 3 trial Experience with safety database analysis 109/100,000 years of acalabrutinib vs comparator arm (319/100,000 years. (Sharman J, et all Blood 2023)

Conclusion: Risk of ventricular arrythmias after treatment with acalabrutinib lower, still requires more study

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Acalabrutinib and Resistance

- Subclonal evolution with expansion, loss or acquisition of driver associated with BTKi relapse over 2 year follow up
  - 3 of 8 with C481S mutations which is predicted based upon dependence of covalent binding site

  Black JS et al Blood 140: 401, 2022

- NHLBI Update of Acalabrutinib monotherapy study
  - 10/14 patients with BTK (C481S or T474I), PLCG2, or both (but in different clones)
  - Clonal evolution as defined by Black also common among relapsing patients with acquisition of mutations including *BRAF* (n=4), *CREBBP* (n=4), and *KMT2D* (n=2).

  Sun C, et al: ASH 2023

Conclusions: Acalabrutinib resistance is associated with clonal architect change and classic covalent resistance mutations (C481S, T474I). Acalabrutinib has no activity against these mutations.

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New Directions for Acalabrutinib

- Combination trials with Venetoclax +/- Obinutuzumab to improve deep remission
- Time limited therapy with Obinutuzumab or other therapeutic antibodies
- Exploration of development of resistance and how this differs from other BTKi
- Combination with bispecific antibodies to engage T-cells given acalabrutinib ability to reverse immune suppressive properties of CLL cells

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