3rd POSTGRADUATE

CLL Conference

Bologna
November 14-15
2022

Royal Hotel Carlton

President:
Pier Luigi Zinzani

The best potential combination - BTKi plus venetoclax:

Acalabrutinib + venetoclax

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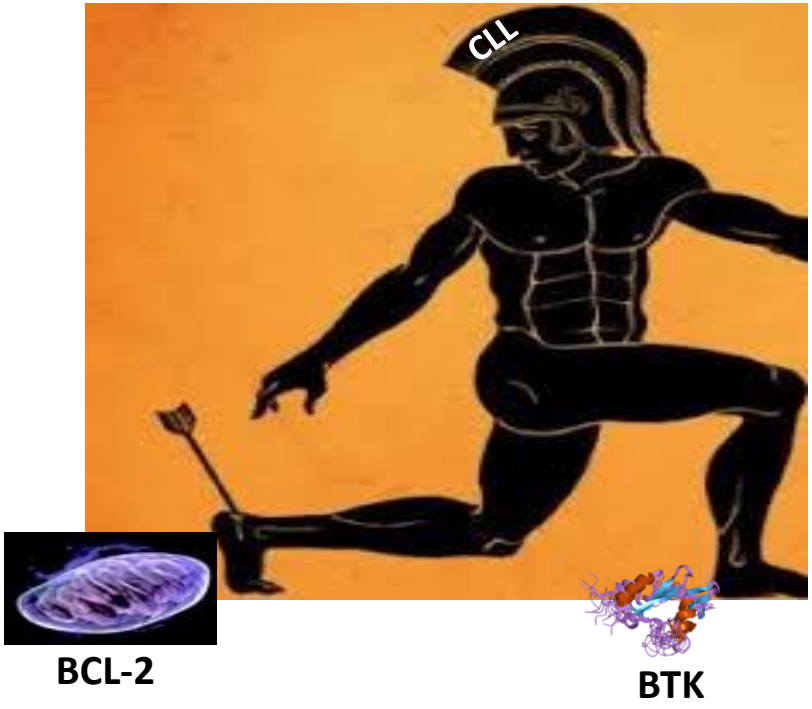
15 November 2022

Disclosures of Matthew S. Davids, MD, MMSc

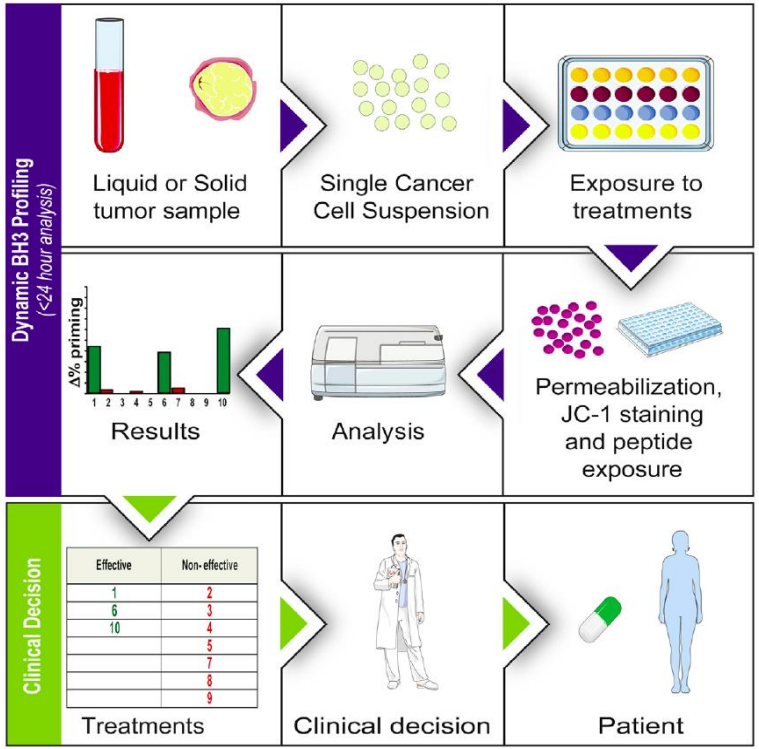
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	✓		✓			✓	
Adaptive Biotechnologies			✓			✓	
Ascentage Pharma	✓		✓				
AstraZeneca	✓		✓			✓	
BeiGene			✓			✓	
Bristol-Myers Squibb			✓			✓	
Eli Lilly			✓			✓	
Genentech	✓		✓			✓	
Janssen			✓			✓	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

What is the preclinical rationale for combining acala and ven?

BCL-2 and BTK are two Achilles heels of CLL



Dynamic BH3 profiling (DBP) is a functional precision medicine technique to identify novel drug combination strategies



Montero et al., *Cell*, 2015

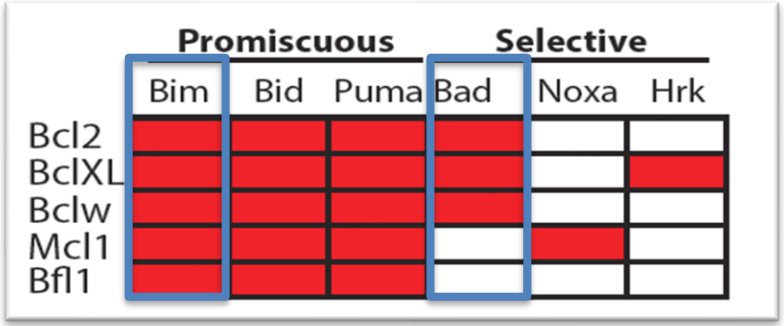
Leukemia (2017), 1–10

www.nature.com/leu

ORIGINAL ARTICLE

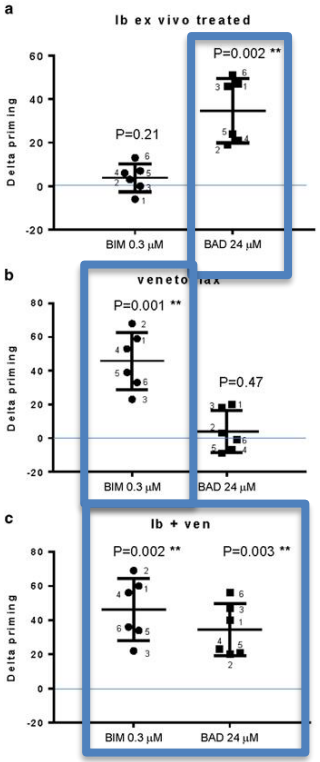
Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia

J Deng, E Isik, SM Fernandes, JR Brown, A Letai[1] and MS Davids[1]



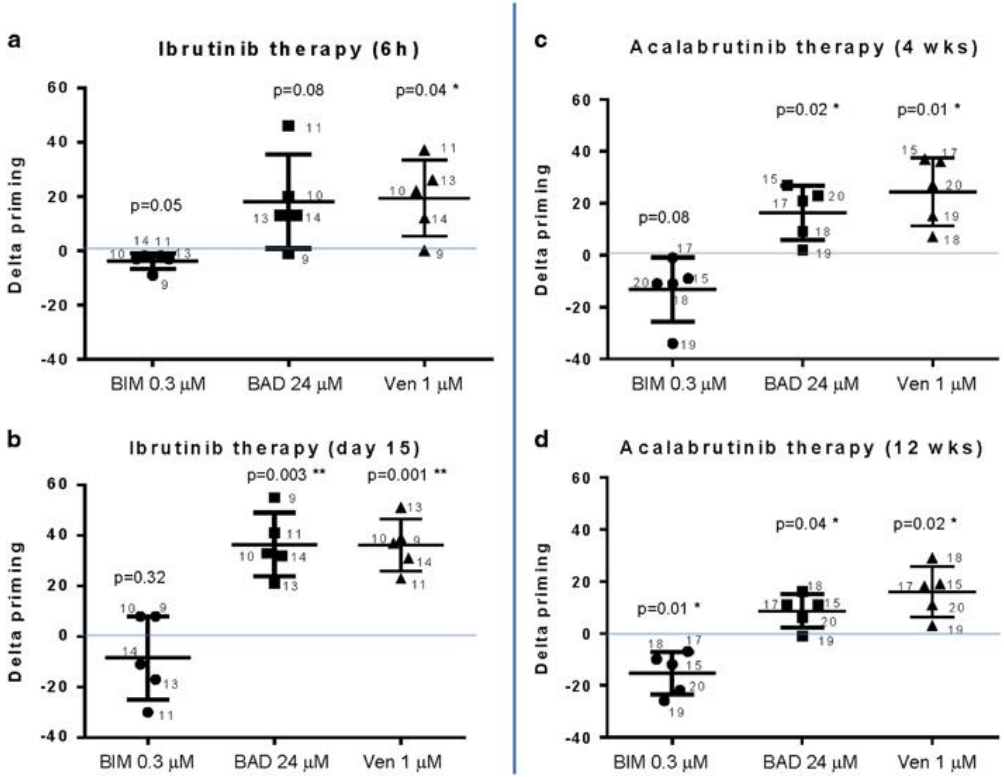
Certo et al, Cancer Cell, 2006

Ibrutinib **Acalabrutinib**



Deng et al., *Leukemia*, 2017

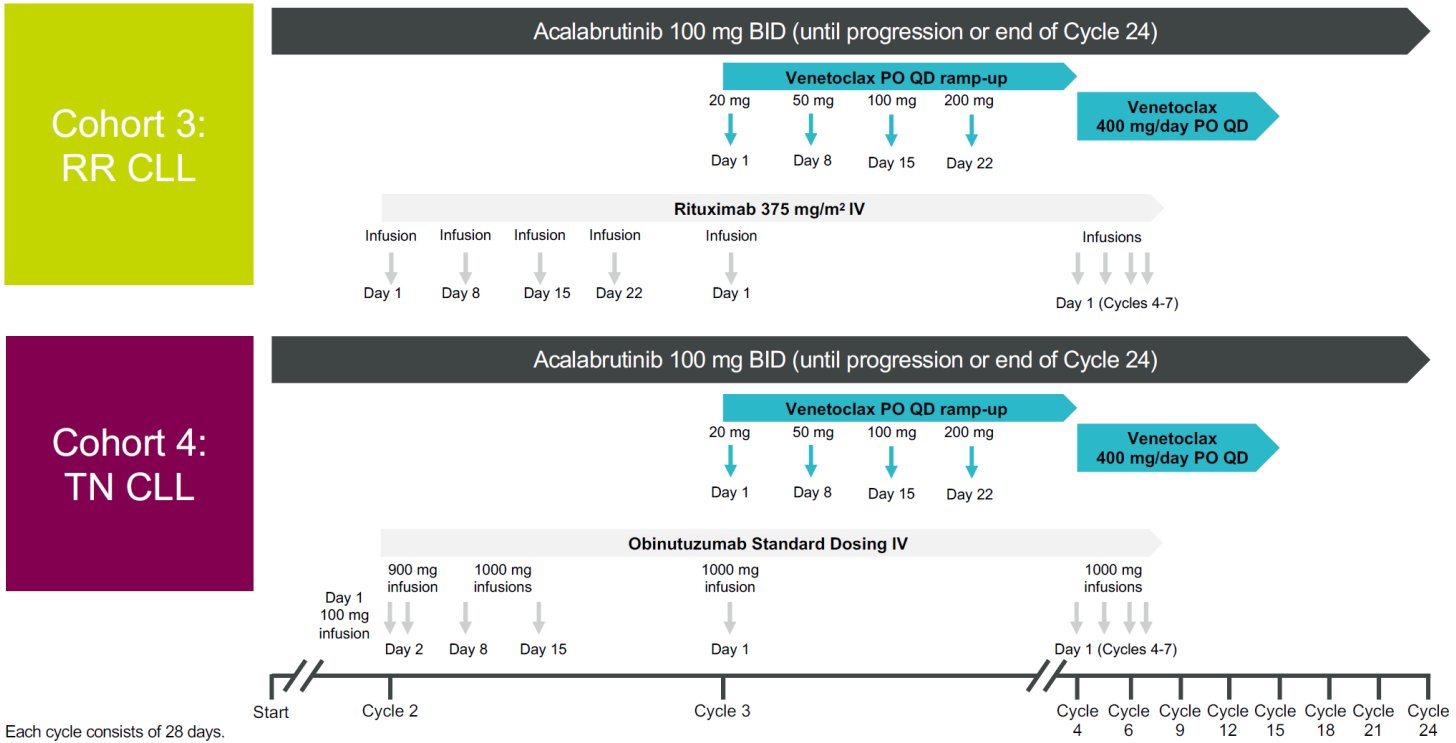
In vivo BTKi increases BCL-2 dependence in primary CLL cells



Deng et al., *Leukemia*, 2017

What clinical data are available for the combination of acala + ven?

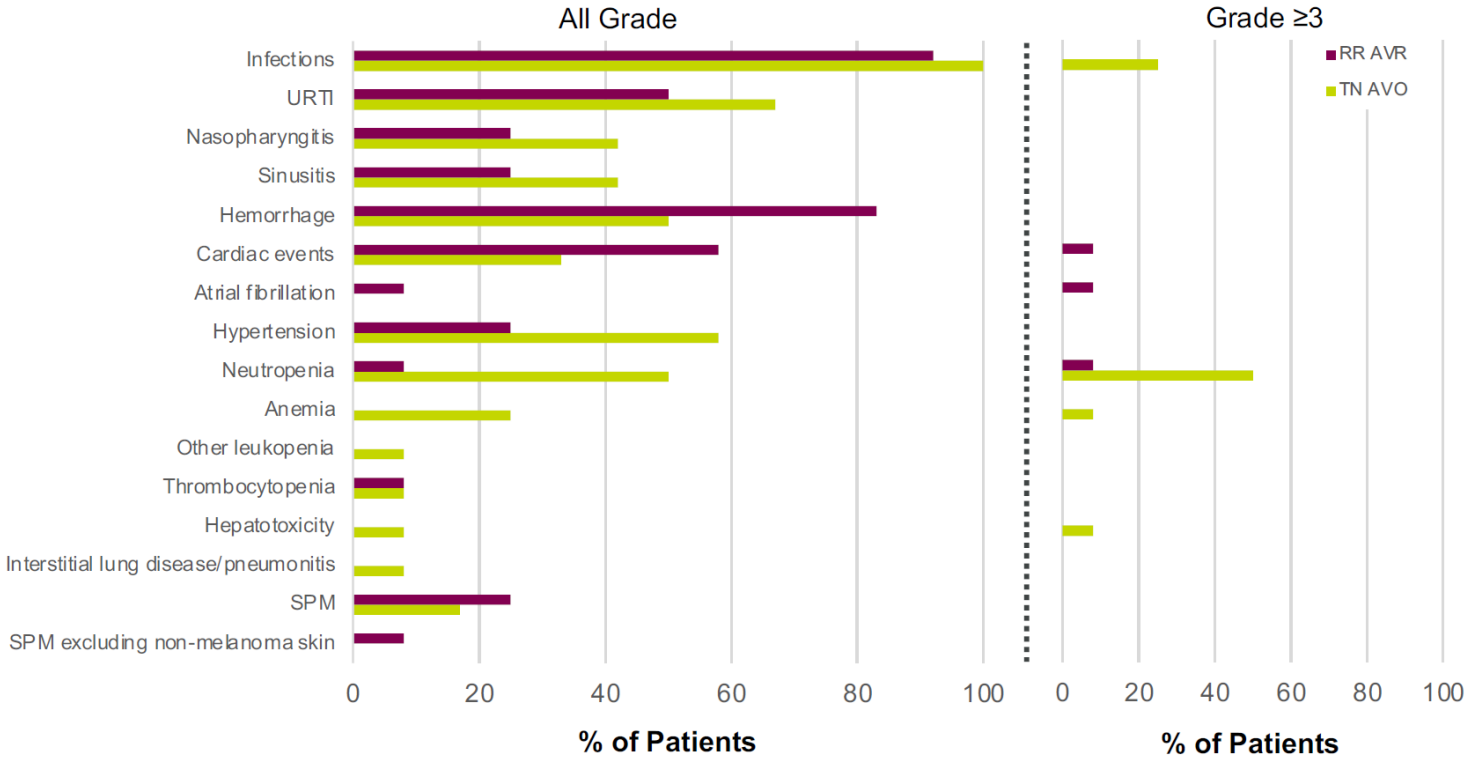
ACE-CL-003: Phase 1b Study (primary endpoint = safety)



Each cycle consists of 28 days.
BID, twice daily; CLL, chronic lymphocytic leukemia; IV, intravenous; PO, orally; QD, once daily; RR, relapsed/refractory; TN, treatment-naïve.

Woyach et al., ASH, 2020

Adverse Events (AEs) of Interest

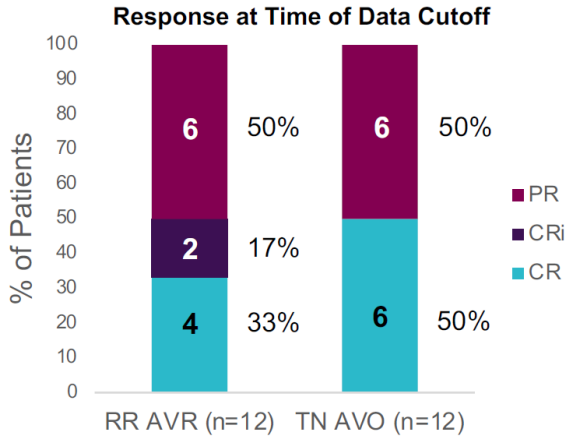


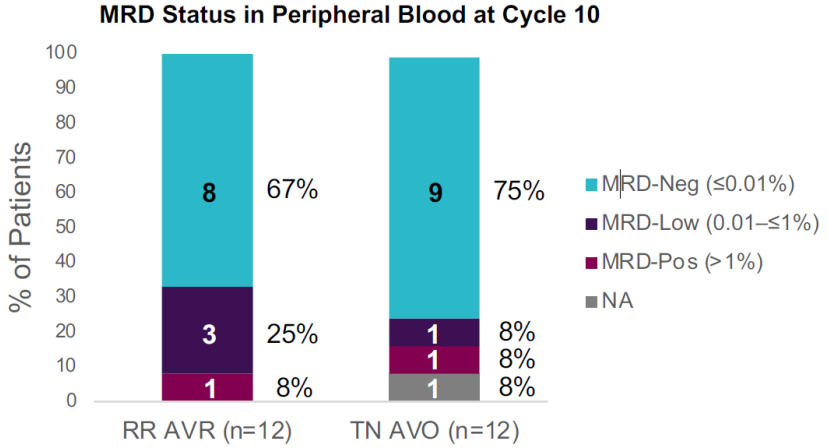
- No tumor lysis syndrome was reported
- Grade ≥3 infections occurred in 3 TN patients and no RR patients

Woyach et al., ASH, 2020

Efficacy, MRD, and PK

- After 16 cycles, ORR was 92% (95% CI: 62–100) in RR and 100% (95% CI: 74–100) in TN patients
- At the time of data cutoff, 50% of patients in each cohort had achieved CR (33% in RR, 50% in TN patients) or CRi (17% in RR patients)
- All patients with CR or CRi achieved uMRD (10^{-4}) in peripheral blood at the time of CR/CRi or earlier





- Median DOR, PFS, and OS were not reached in either group
  - Estimated 18-month PFS and OS rates were 100% (95% CI: not estimable) in both cohorts
- In the triple combination setting, the PK of acalabrutinib, its active metabolite (ACP-5862), and venetoclax were consistent with PK observed as monotherapy[1]

MRD data for one patient was not available at Cycle 10, but this patient achieved MRD undetectable status (≤0.01%) at Cycle 7 and Cycle 16 evaluations.

1. Salem et al. *J Clin Pharmacol*. 2017;57:484-92.

Woyach et al., ASH, 2020

Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: a single-arm, open-label, phase 2 study

Matthew S Davids, Benjamin L Lampson*, Svitlana Tyekucheva, Zixu Wang, Jessica C Lowney, Samantha Pazienza, Josie Montegaard, Victoria Patterson, Matthew Weinstock, Jennifer L Crombie, Samuel Y Ng, Austin I Kim, Caron A Jacobson, Ann S LaCasce, Philippe Armand, Jon E Arnason, David C Fisher, Jennifer R Brown*

Summary

Background Both continuous therapy with acalabrutinib and fixed-duration therapy with venetoclax–obinutuzumab are effective for previously untreated chronic lymphocytic leukaemia. We hypothesised that frontline time-limited, minimal residual disease (MRD)-guided triplet therapy with acalabrutinib, venetoclax, and obinutuzumab would induce deep (ie, more patients with undetectable MRD) and durable remissions.

Lancet Oncol 2021

Published Online
September 14, 2021
https://doi.org/10.1016/S1470-2045(21)00455-1

*Contributed equally

Methods: Key Eligibility Criteria

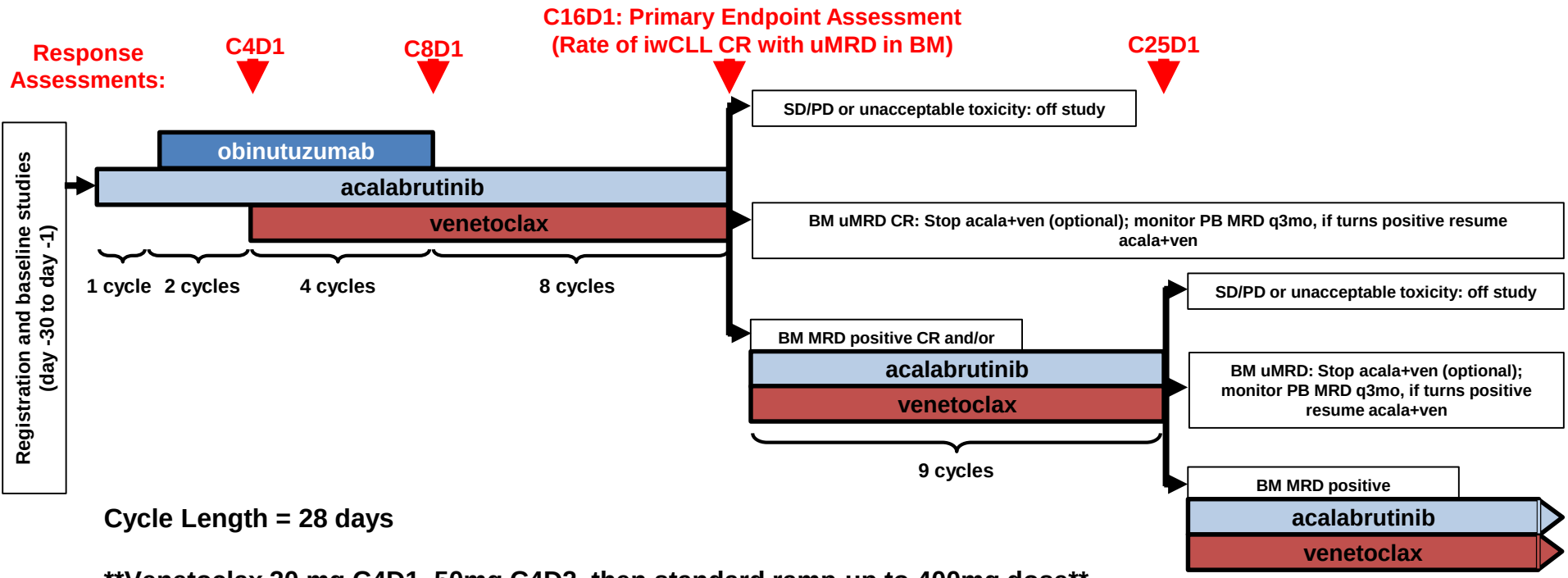
Inclusion

- Confirmed diagnosis of previously untreated CLL/SLL with an indication for treatment per 2018 IW-CLL criteria
- Age ≥ 18 years and ECOG performance status ≤ 2
- ANC ≥ 500 cells/mm^3 and platelets ≥ 30k/mm^3
- Adequate hepatic and renal function (CrCl ≥ 50mL/min)
- Initial cohort of all-comers (n=37)
- A protocol amendment added 35 pts with *TP53* aberrant CLL in a new cohort

Exclusion

- Known bleeding disorder or recent CVA
- Requires warfarin (other anticoagulants allowed) or PPI therapy (H2 antagonists allowed)
- Known or suspected Richter's transformation or known CNS involvement

Methods: Study Schema



Cycle Length = 28 days

****Venetoclax 20 mg C4D1, 50mg C4D2, then standard ramp-up to 400mg dose****

Acalabrutinib and obinutuzumab at standard doses PJP and HSV/VZV PPX mandatory

AVO: Safety

	Grade 1–2	Grade 3	Grade 4
Haematological adverse events			
Neutropenia	15 (41%)	12 (32%)	4 (11%)
Thrombocytopenia	20 (54%)	8 (22%)	2 (5%)
Anaemia	20 (54%)	2 (5%)	0

	Grade 1–2	Grade 3	Grade 4
Non-haematological adverse events			
Fatigue	32 (86%)	1 (3%)	0
Headache	27 (73%)	1 (3%)	0
Bruising	22 (59%)	0	0
Nausea	16 (43%)	0	0
Maculopopular rash	14 (38%)	0	0
Gastro-oesophageal reflux disease	11 (30%)	0	0
Hypocalcaemia	10 (27%)	1 (3%)	0
Diarrhoea	10 (27%)	0	0

Adverse Events of Special Interest:

- Grade 3 or higher infections: 1 (2.3%, grade 3 lung infection)
- Infusion related reactions (*n*=11, 25% (23% grade 1/2, 2% gr3)
- Hypertension (*n*=5, 11%, no gr≥3)
- Atrial fibrillation (*n*=1, gr3)
- Laboratory TLS, grade 3 (*n*=2): both occurred after obinutuzumab initiation and prior to venetoclax

Davids MS, et al. *Lancet Oncol*, 2021

AVO: patient disposition

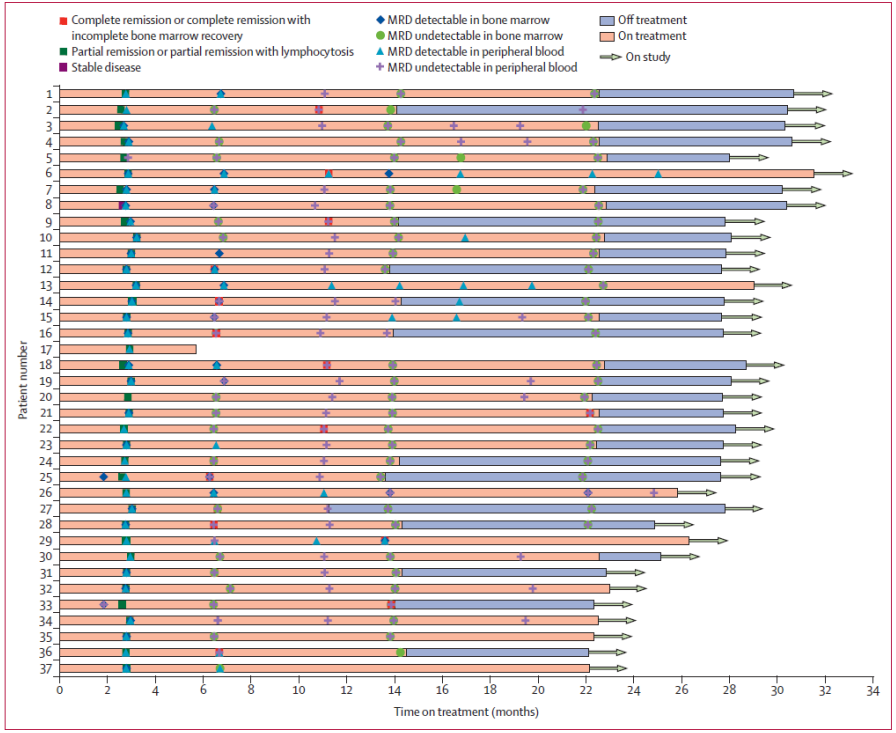


Figure 4: **Swimmer plot of responses of each patient over time**
The timepoint at which each patient first reached the indicated response is shown. MRD=minimal residual disease.

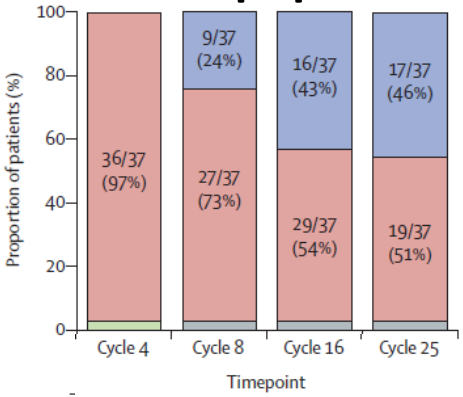
Davids MS, et al. *Lancet Oncol*, 2021

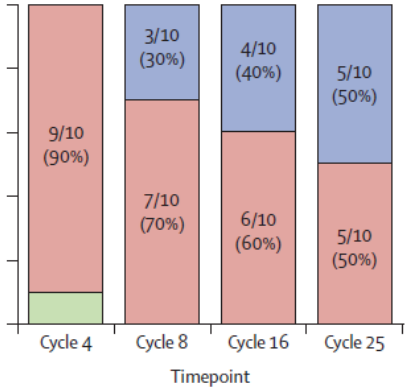
AVO: Efficacy

Overall population

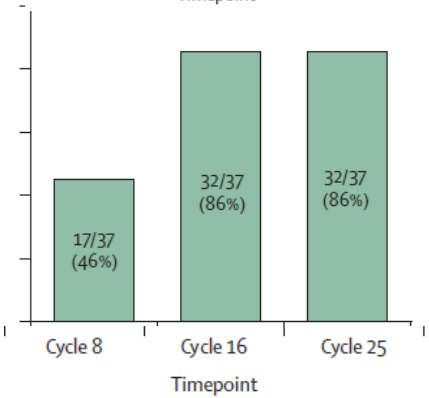
TP53 aberrant population

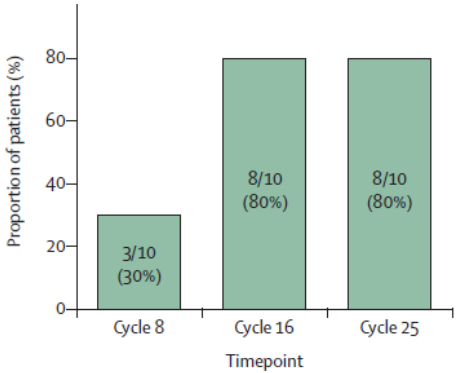
iwCLL Response





BM-MRD





Davids MS, et al. *Lancet Oncol*, 2021

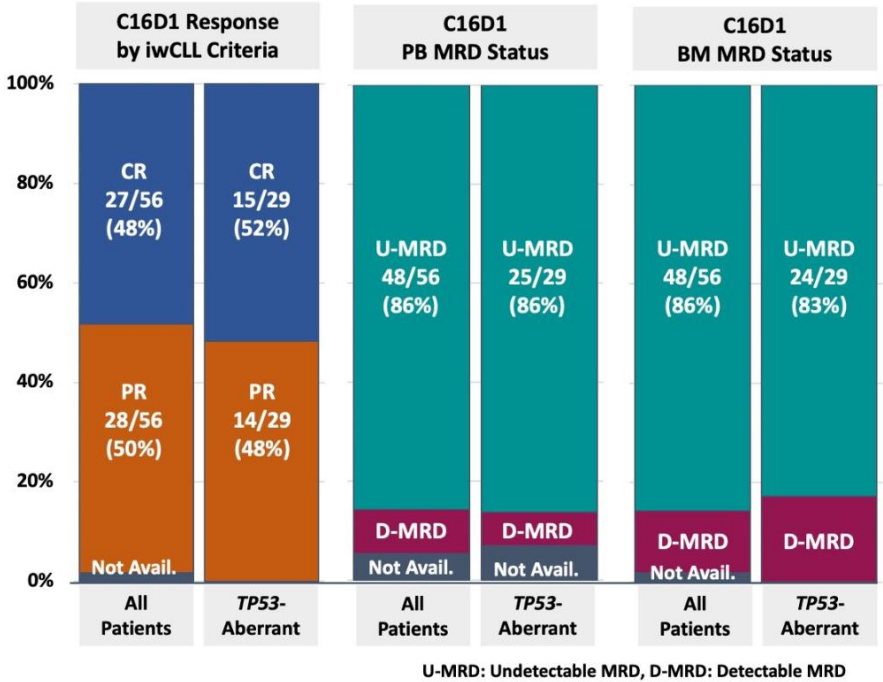
344 Updated Results from a Multicenter, Phase 2 Study of Acalabrutinib, Venetoclax, Obinutuzumab (AVO) in a Population of Previously Untreated Patients with CLL Enriched for High-Risk Disease

Program: Oral and Poster Abstracts
Type: Oral
Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Targeted Triplet Combinations and Richter's Transformation
Hematology Disease Topics & Pathways:
Lymphoid Leukemias, CLL, Combination therapy, Diseases, Therapies, Lymphoid Malignancies, Minimal Residual Disease

Saturday, December 10, 2022: 4:15 PM

Christine E. Ryan, MD[1], *Benjamin L. Lampson, MD, PhD*[1], *Svitlana Tyekucheva, PhD*[2*], *Liam R. Hackett, AB*[1*], *Yue Ren, MS*[2*], *Samantha J. Shupe, BS*[1*], *Stacey M. Fernandes, BS*[1*], *Jennifer L. Crombie, MD*[1*], *Samuel Ng, MD, PhD*[1*], *Austin I. Kim, MD*[1], *Inhye E. Ahn, MD*[3], *Matthew J Weinstock, MD*[4], *Samantha Pazienza, BS*[1*], *Josie S. Montegaard, NP*[1*], *Victoria Patterson, RN*[1*], *Caron A. Jacobson, MD*[1], *Ann S. LaCasce, MD*[1], *Philippe Armand, MD, PhD*[1], *David C. Fisher, MD*[1*], *Jon E. Arnason, MD*[5], *Steve Lo, MD*[6*], *Adam Olszewski, MD*[7*], *Jennifer R. Brown, MD, PhD*[1] *and Matthew S. Davids, MD*[1]

[1]*Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA*



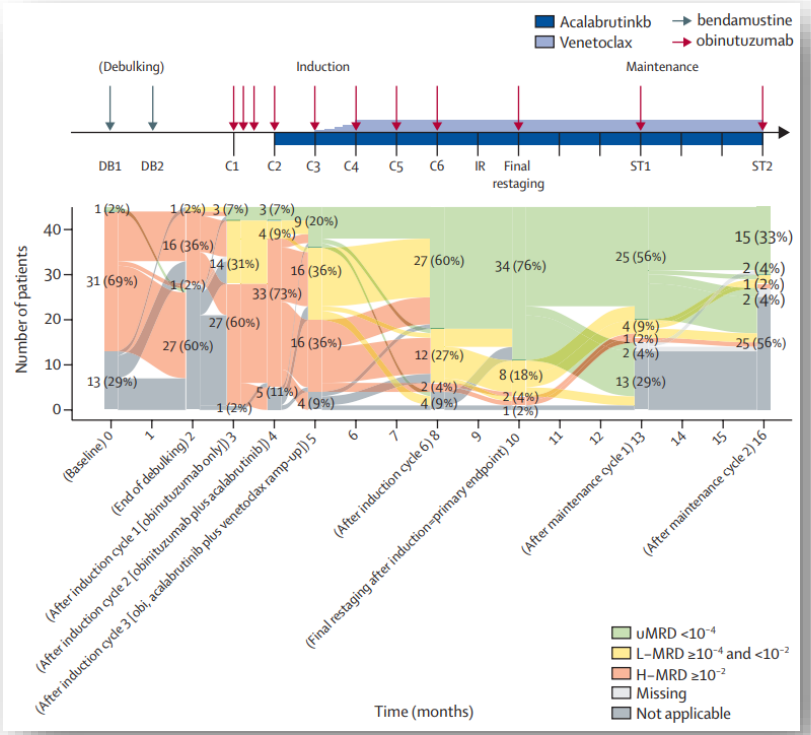
U-MRD: Undetectable MRD, D-MRD: Detectable MRD

Ryan et al., ASH, 2022

Obinutuzumab, acalabrutinib, and venetoclax, after an optional debulking with bendamustine in relapsed or refractory chronic lymphocytic leukaemia (CLL2-BAAG): a multicentre, open-label, phase 2 trial

Paula Cramer, Moritz Fürstenau, Sandra Robrecht, Adam Giza, Can Zhang, Anna-Maria Fink, Kirsten Fischer, Petra Langerbeins, Othman Al-Sawaf, Eugen Tausch, Christof Schneider, Johannes Schetelig, Peter Dreger, Sebastian Böttcher, Karl-Anton Kreuzer, Anke Schilhabel, Matthias Ritgen, Monika Brüggemann, Michael Kneba, Stephan Stilgenbauer, Barbara Eichhorst, Michael Hallek

	Cohort (n=45)
Overall response	45 (100%)
Complete response or complete response with incomplete recovery of bone marrow	8 (18%)
Partial response	37 (82%)*
Stable disease	0
Progressive disease	0
Undetectable minimal residual disease	34 (76%)
Minimal residual disease in peripheral blood	
Undetectable ($<10^{-4}$)	34 (76%)
Intermediate ($\geq 10^{-4}$ and $<10^{-2}$)	8 (18%)
Positive ($\geq 10^{-2}$)	2 (4%)
Missing	1 (2%)
Minimal residual disease in bone marrow	
Undetectable ($<10^{-4}$)	7 (16%)
Intermediate ($\geq 10^{-4}$ and $<10^{-2}$)	3 (7%)
Positive ($\geq 10^{-2}$)	0
Missing	35 (78%)



Cramer et al., *Lancet Haematol*. 2022 Oct;9(10):e745-e755.

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Circulating Tumor DNA–Based MRD Assessment in Patients with CLL Treated with Obinutuzumab, Acalabrutinib, and Venetoclax

Moritz Fürstenau[1], Jonathan Weiss[1], Adam Giza[1], Fabian Franzen[1], Sandra Robrecht[1], Anna-Maria Fink[1], Kirsten Fischer[1], Christof Schneider[2], Eugen Tausch[2], Stephan Stilgenbauer[2], Matthias Ritgen[3], Anke Schilhabel[3], Monika Brüggemann[3], Barbara Eichhorst[1], Michael Hallek[1], and Paula Cramer[1]

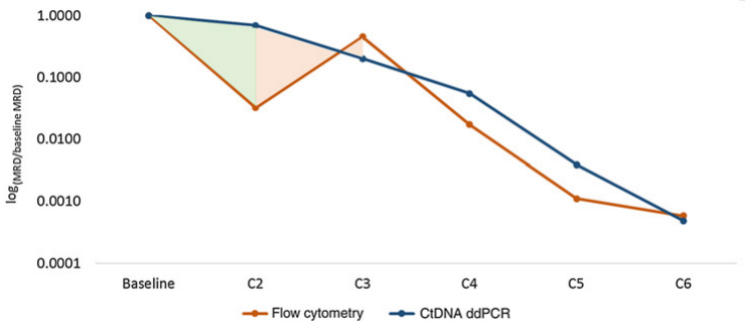
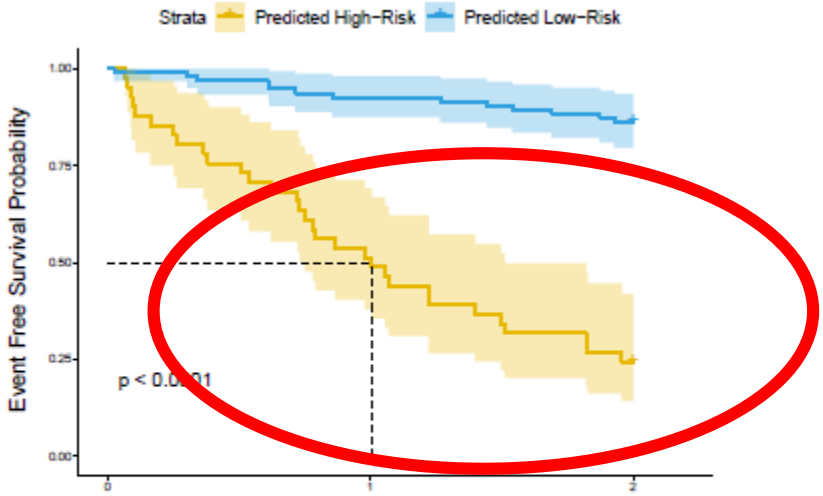


Figure 4.
Median levels of MRD are shown for ctDNA-based assessment (blue curve) and 4-color flow cytometry (red curve) in the course of induction treatment. For better comparability of both methods, median MRD levels are divided by the baseline MRD level of the respective method. The green area between the curves shows the faster decrease of MRD levels by flow cytometry during obinutuzumab monotherapy while the orange area between the curves illustrates the contrary dynamics (flow cytometry: increase; ctDNA: decrease) of ctDNA- and flow cytometry–based MRD during the beginning of acalabrutinib treatment (presumably redistribution from lymph nodes to PB).

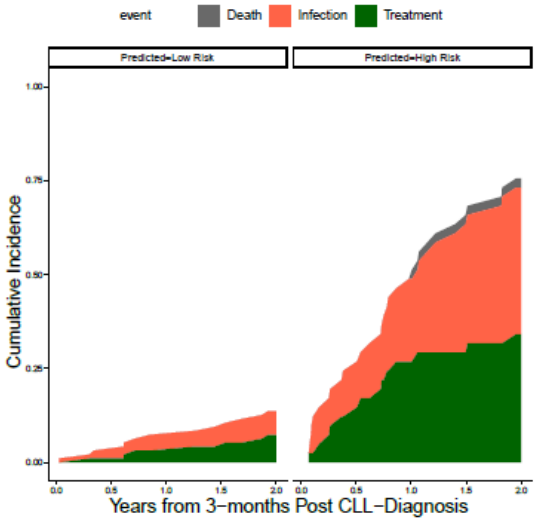
Fuerstenau et al., Clin Cancer Res. 28(19), Oct 1, 2022

What ongoing studies will provide data on the acala + ven doublet?

PreVent-ACaLL – Clinical trial



Changing the natural history of CLL…



Patients selected based on model, >65% risk of infection/and or CLL treatment <2 years

Acalabrutinib

Venetoclax

1:1 Randomization

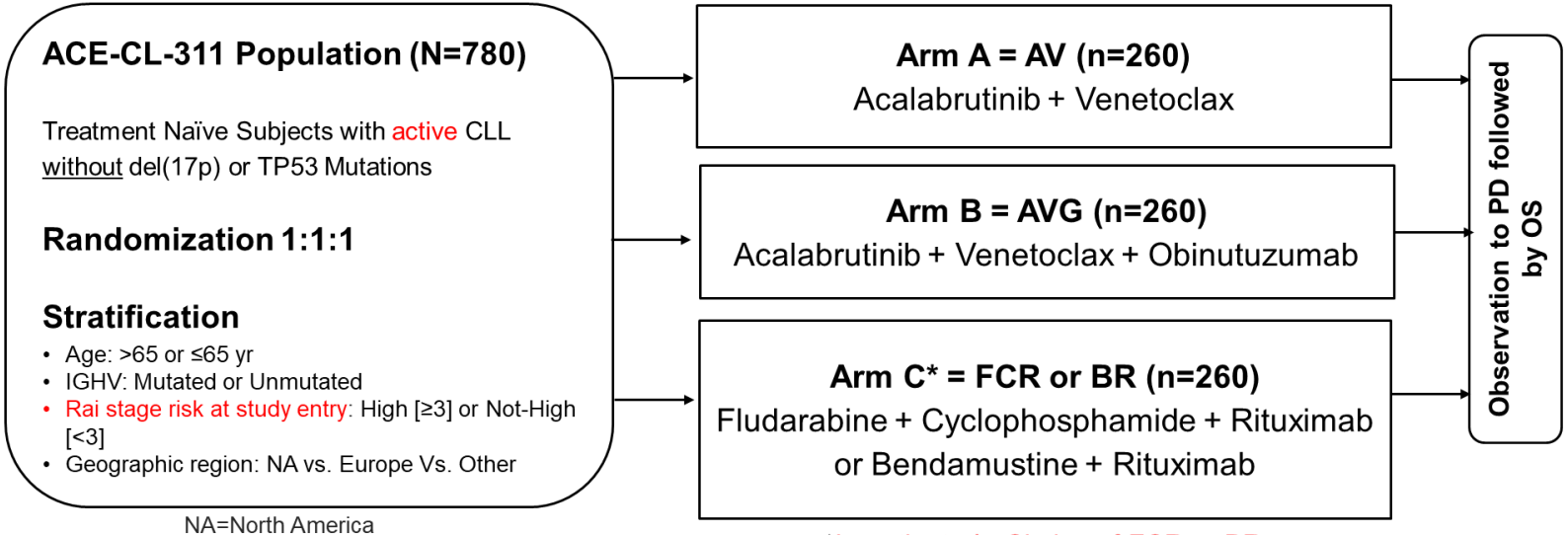
Watch & Wait

- 3 cycles of 28 days
- Venetoclax ramp up from C1D1
- N= 50, 25 / arm, phase 2 part
- Extensive immunephenotyping

(slide adapted from C. Niemann)

Agius et al, *Nat Comm*, 2020

ACE-CL 311 Study Design

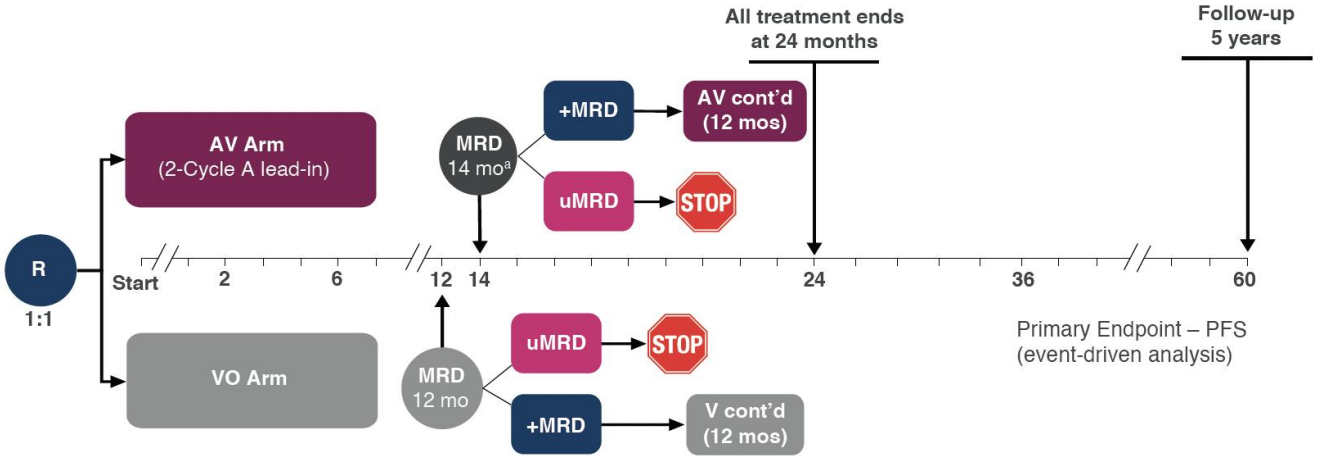


Acalabrutinib given Cycle 1 to 14; Venetoclax given Cycle 3 to 14; Obinutuzumab given Cycle 2 to 7 fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (BR), given cycle 1 to 6.

(slide courtesy of J. Brown)

The global MAJIC phase 3 study seeks to define the optimal MRD-guided venetoclax doublet for frontline CLL treatment

- N=~750 patients to be recruited
- Global study with ~40 sites
- FPI: Sept 2022



Key Eligibility Criteria

- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Anti-thrombotic agents permitted except for warfarin or equivalent vitamin K antagonists

Primary endpoint: INV-assessed PFS

Co-Principal Investigators

Matthew Davids
Anthony Mato
Jeff Sharman
In
Collaboration

Davids et al., ASH, 2021. Abstract 1553

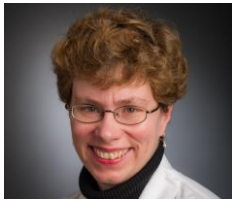
Conclusioni

- **The best BTKi + ven combo is the one with the most robust data supporting the optimal balance of efficacy and safety**
- **Ibrutinib + ven combos are effective but tolerability is a concern in older patients and those with co-morbidities**
- **Zanubrutinb + ven combos are promising but very little data are available**
- **Acalabrutinib + ven (+/- obinutuzumab) is likely to be the best potential combination for patients with CLL**

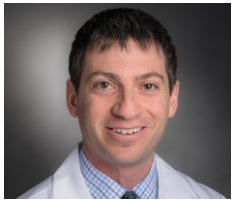
Dana-Farber Cancer Institute

Harvard Medical School

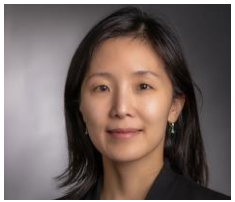
DFCI CLL Center



Jennifer Brown, MD, PhD



Matthew Davids, MD, MMSc



Inhye Ahn, MD

Catherine Wu, MD

We hope to welcome you to Boston next fall!