4th POSTGRADUATE

CLL Conference

Bologna
November 13-14
2023

Royal Hotel Carlton

President:
Pier Luigi Zinzani

Doublet, triplet: is this the potential future of BTKi plus BCL2i?

Acalabrutinib + venetoclax

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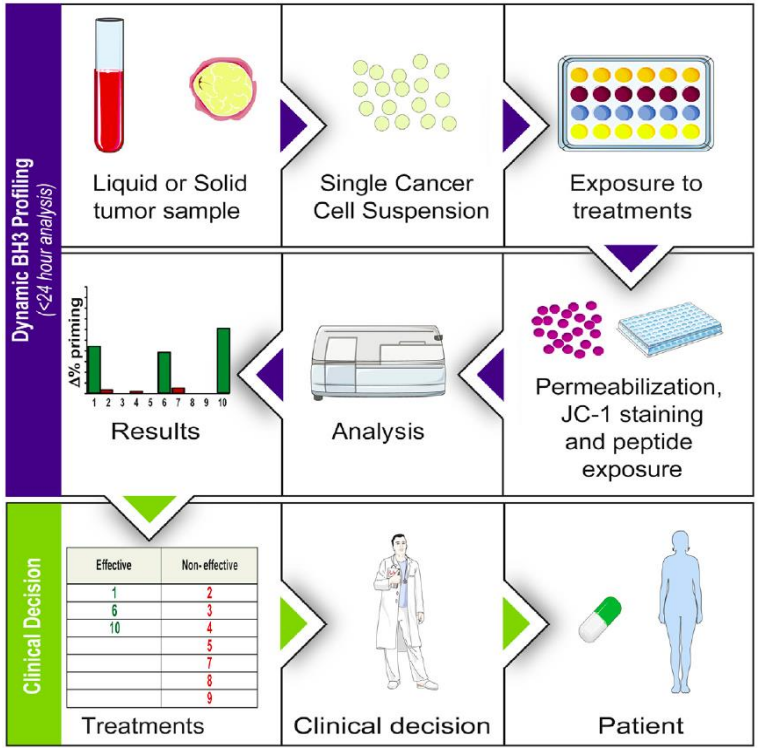
Associate Professor of Medicine | Harvard Medical School
14 November 2023

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	✓		✓			✓	

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

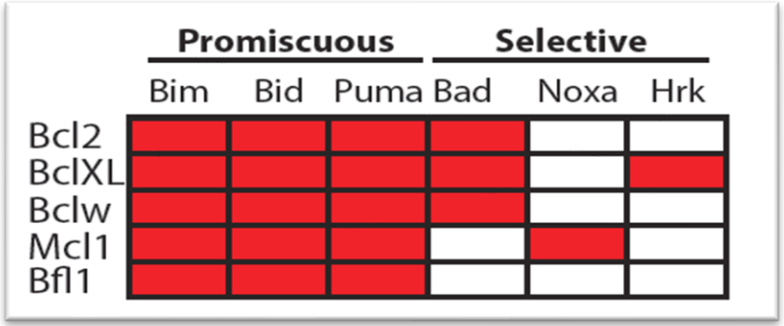
Leukemia (2017), 1–10

www.nature.com/leu

ORIGINAL ARTICLE

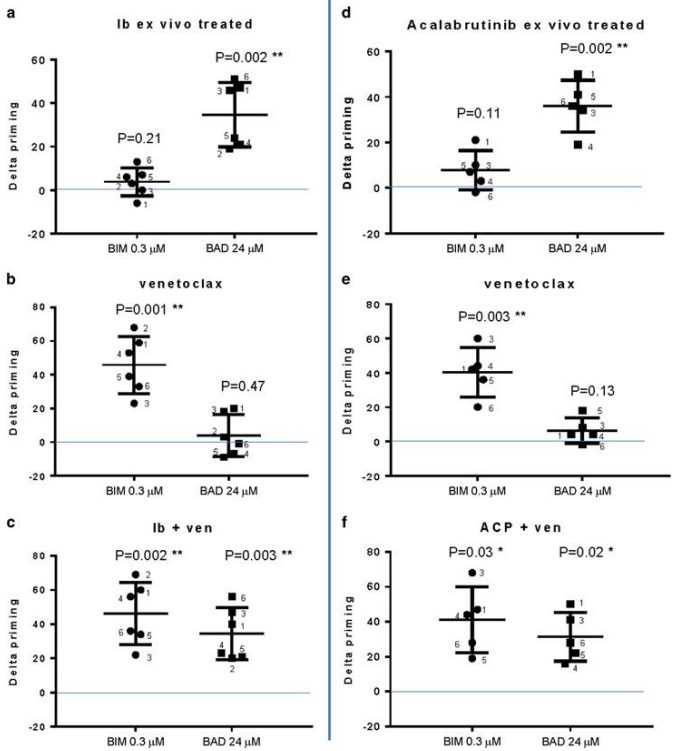
Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia

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



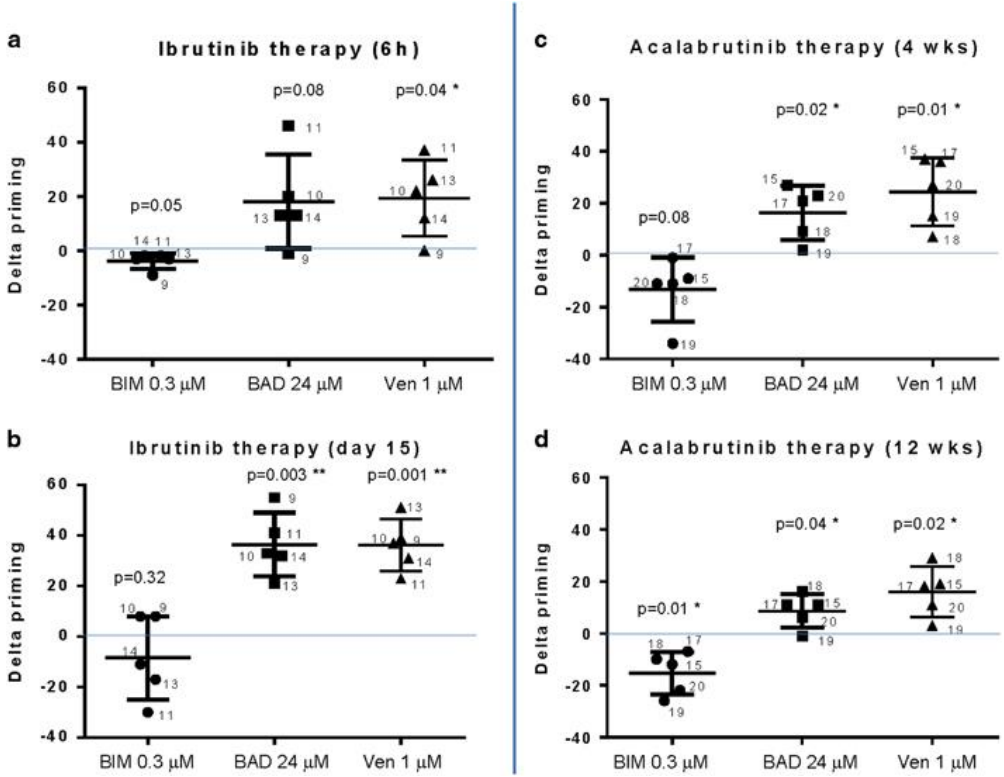
Certo et al, Cancer Cell, 2006

Ibrutinib Acalabrutinib



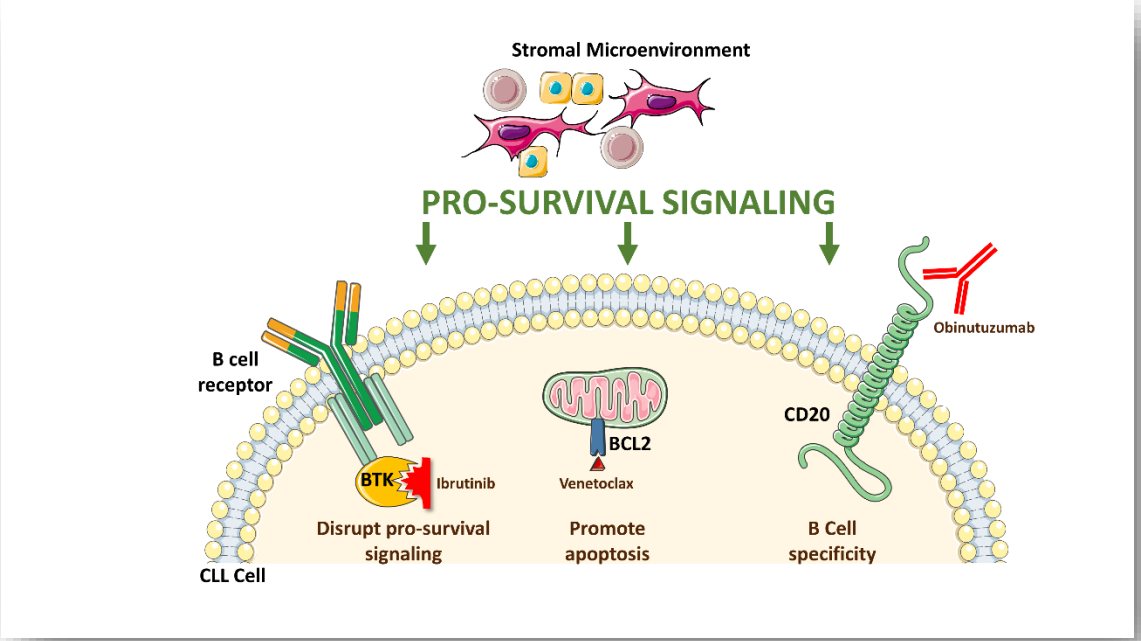
Deng et al., *Leukemia*, 2017

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



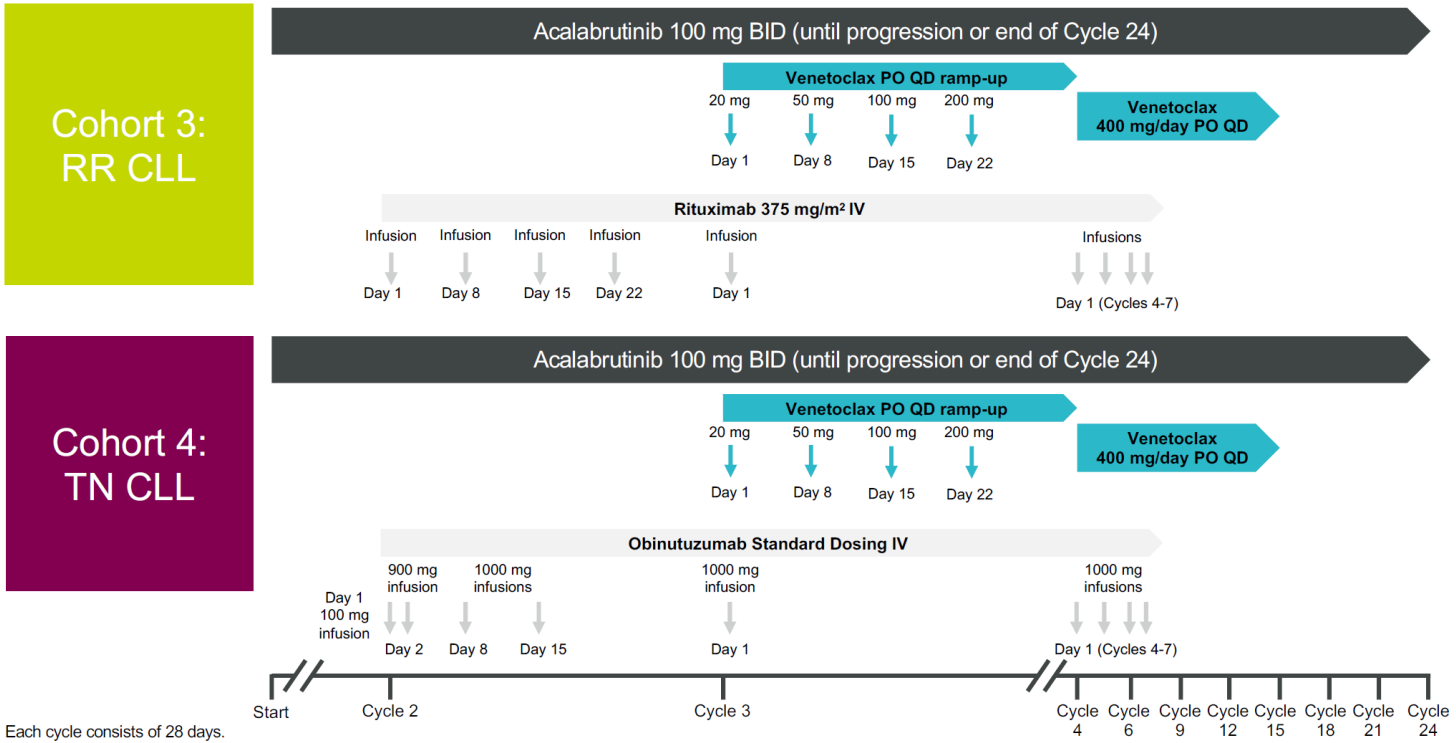
Deng et al., *Leukemia*, 2017

Dual-targeting of BCL-2 and BTK (+/- CD20) may result in even greater efficacy



Lampson and Davids, *Blood*, 2018

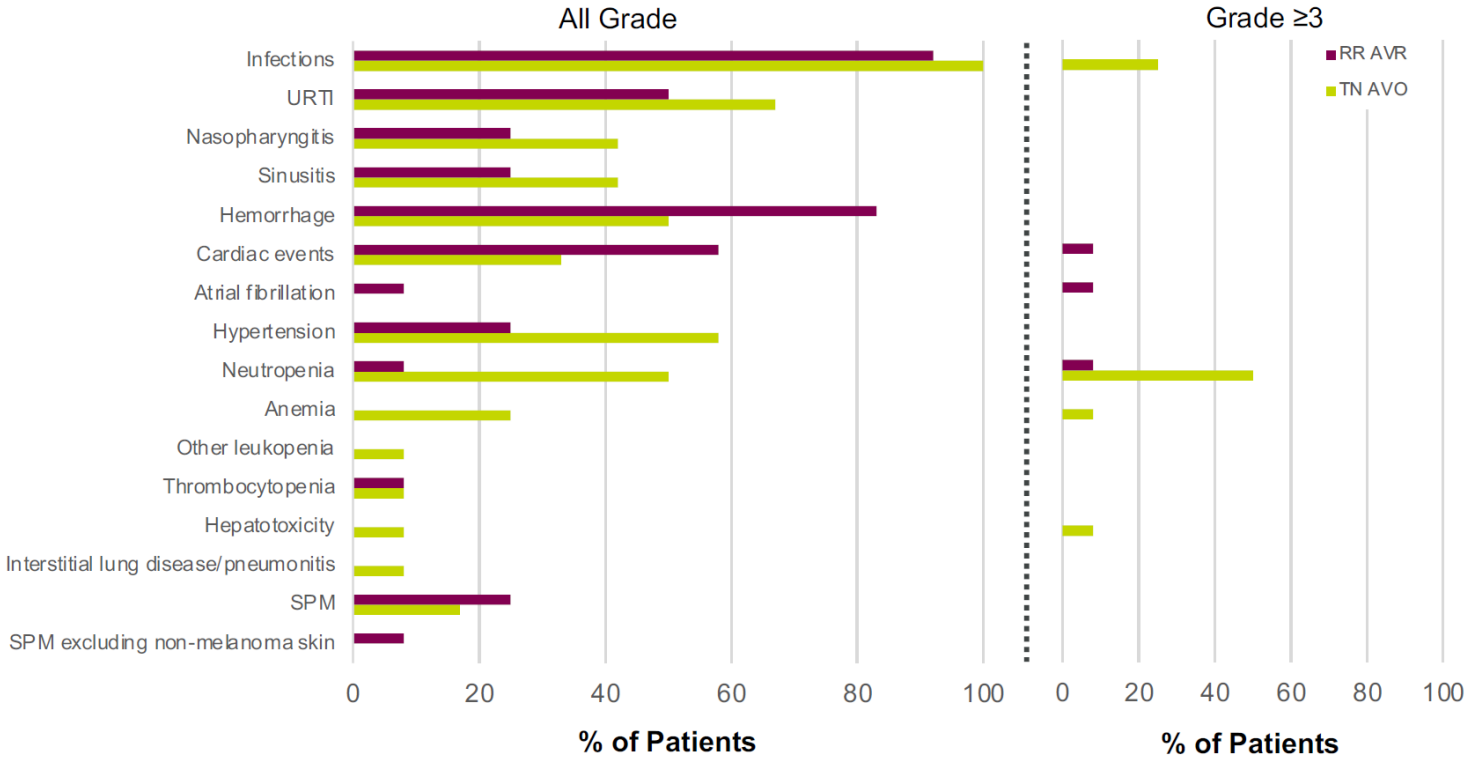
ACE-CL-003: Phase 1b Study (primary endpoint = safety)



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

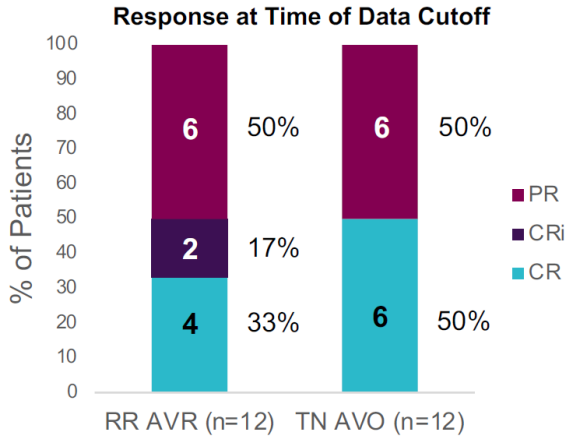


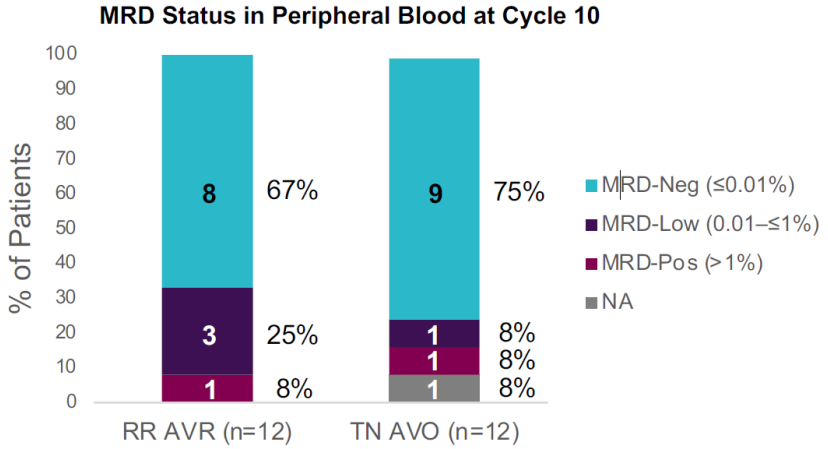
- No tumor lysis syndrome was reported
- Grade ≥3 infections occurred in 3 TN patients and no RR patients

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

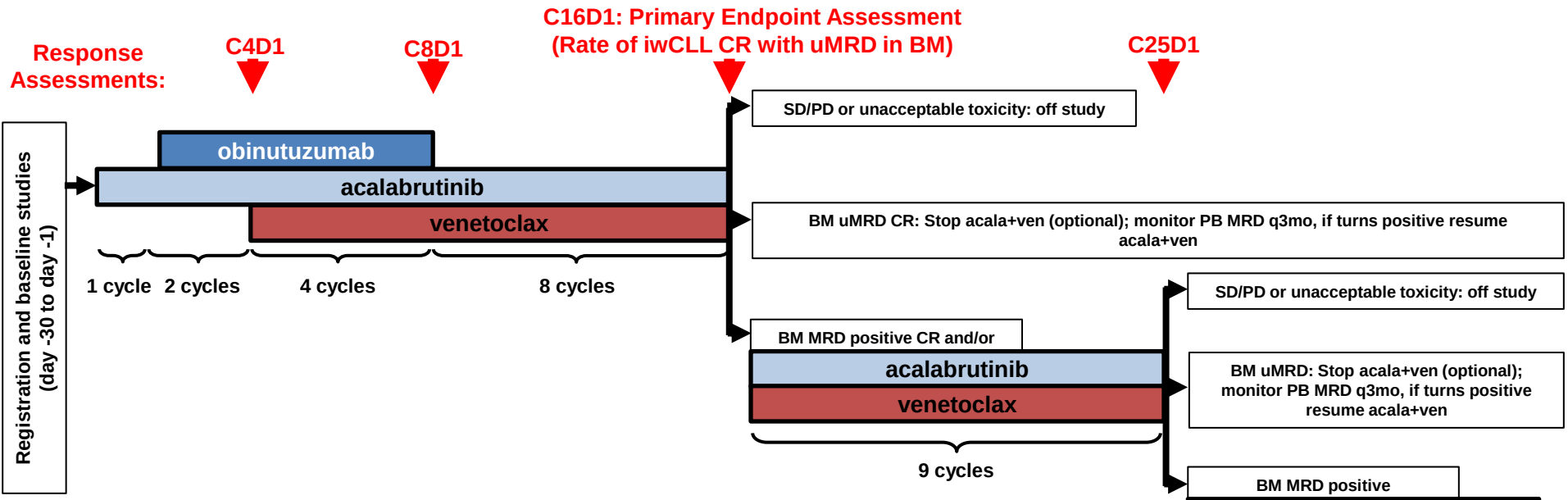
Inclusion

- 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****

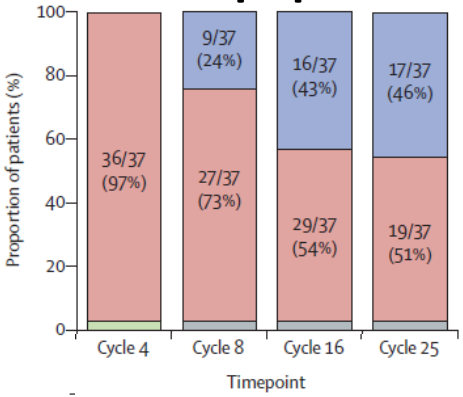
Acalabrutinib and obinutuzumab at standard doses PJP and HSV/VZV PPX mandatory

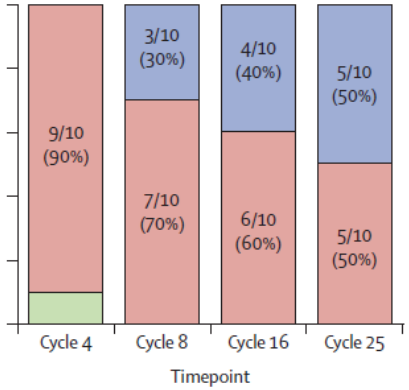
AVO: Efficacy

Overall population

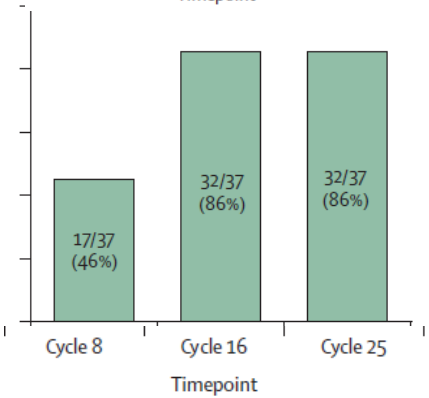
TP53 aberrant population

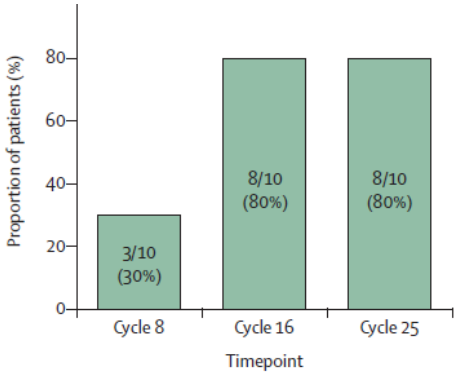
iwCLL Response





BM-MRD





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

AVO: patient disposition

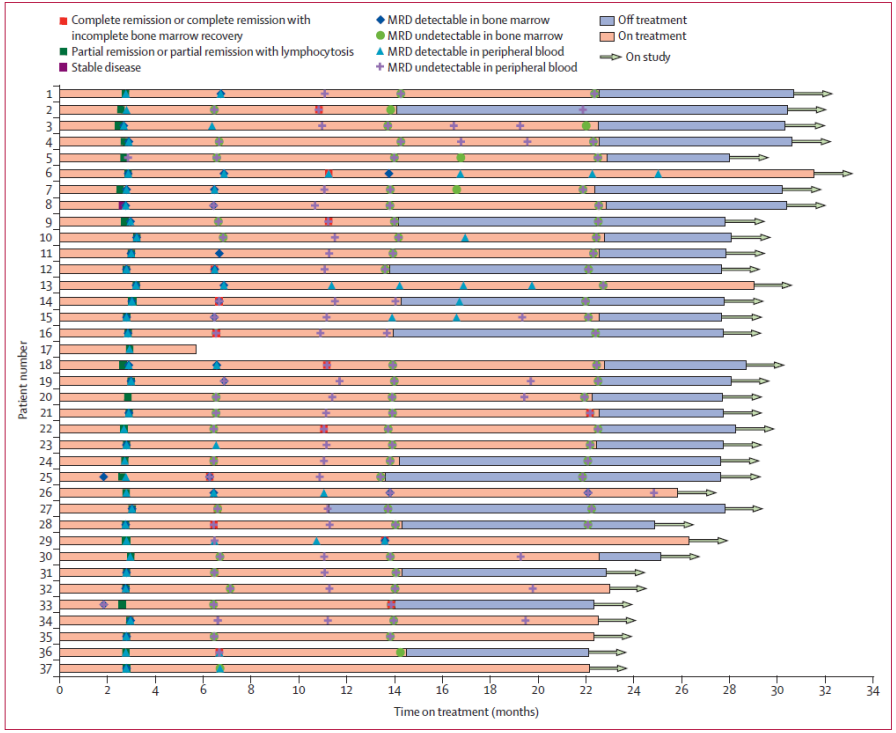


Figure 4: **Swimmer plot of responses of each patient over time**
The timepoint at which each patient first reached the indicated response is shown. MRD=minimal residual disease.

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

We hypothesized that combining acalabrutinib with venetoclax and obinutuzumab (**AVO**) would be an effective and well-tolerated novel-agent-only, time-limited frontline regimen for **high-risk CLL**.

- Dana-Farber Cancer Institute, MA
- Beth Israel Deaconess Medical Center, MA

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- Beth Israel Deaconess Medical Center, MA
- Lifespan / Rhode Island Hospital, RI
- Stamford Hospital, CT

Ryan et al., ASH, 2022

Baseline Patient Characteristics

Total number of patients: 68
- **Initial all-comer cohort:** 37
- **Expansion high-risk cohort:** 31

Characteristic (n=68) [median (range) or n (%)]	
Age, years	63 (36-80)
Male	45 (66.2%)
Rai Stage 3-4	32 (47.1%)
Bulky lymphadenopathy	23 (34.3%)
White blood cell count, $x10^9$ per L	99 (2-602)
Hemoglobin, g/dL	11.3 (7.4-16.4)
Platelets, $x10^9$ per L	146 (38-339)

Characteristic (n=68)	**n**	**%**
***TP53* Status**		
del(17p) and/or *TP53* mutation	41	60.3%
del(17p) and *TP53* mutation	28	41.2%
TP53 mutation only	10	14.7%
del(17p) only	3	4.4%
IGHV Status		
Unmutated	50	73.5%
Mutated	15	22.1%
Unknown	3	4.4%
Other Cytogenetics		
del(11q)	17/65	26.2%
Trisomy 12	11/66	16.7%
Complex karyotype (≥3 cytogenetic abnormalities)	16/61	26.2%
***NOTCH1* Mutation**	10/52	19.2%

Data Cutoff: 07/26/2022

Ryan et al., ASH, 2022

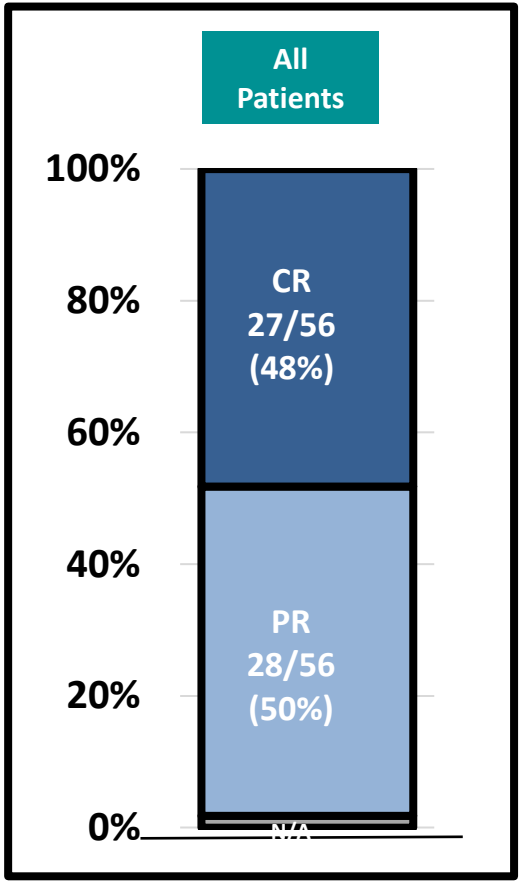
Efficacy: AVO Achieves High Clinical Response Rates by iwCLL Criteria at Cycle 16

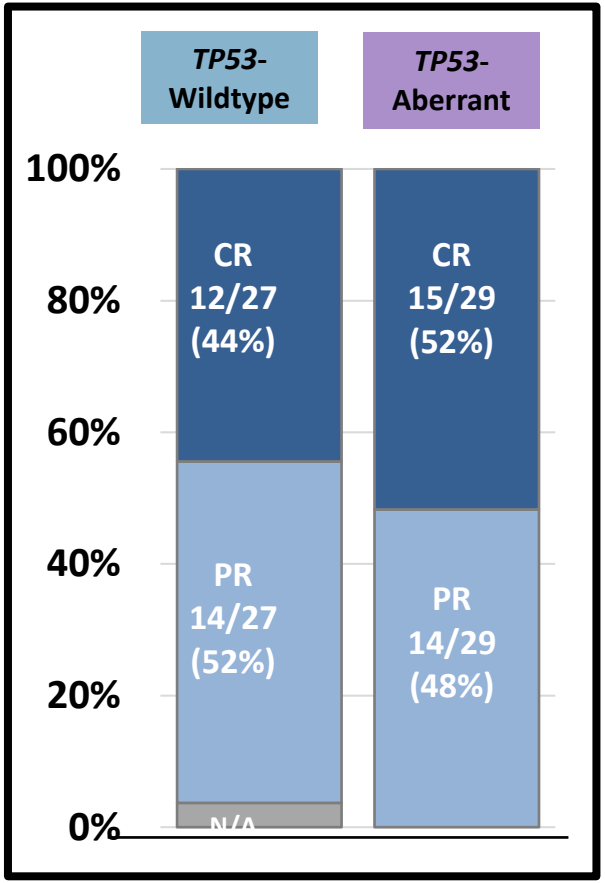
Primary Endpoint:
BM-uMRD CR Rate at Cycle 16

All Patients: 43%
(24/56*)

***TP53*-aberrant: 45%**
(13/29)

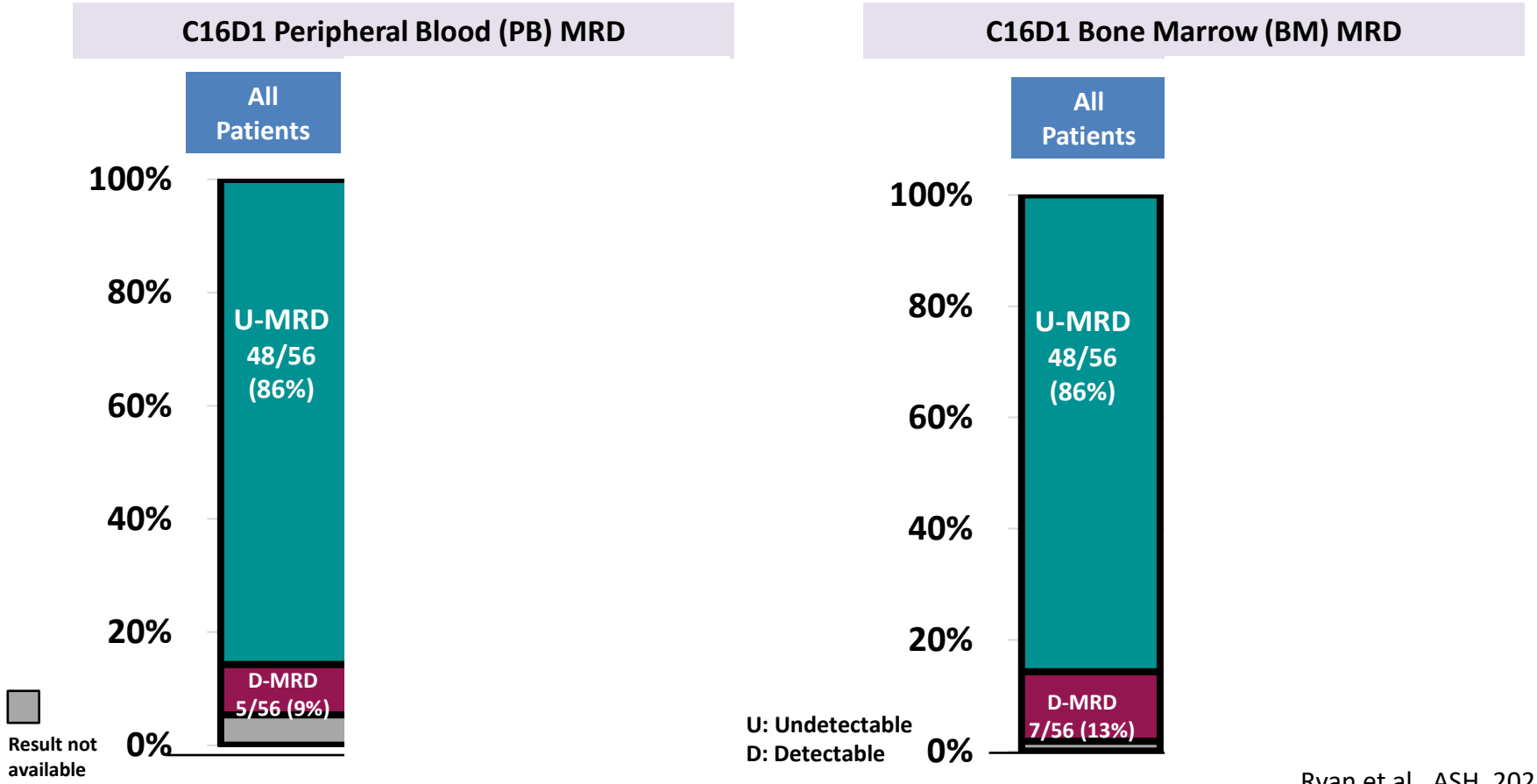
***n=12 patients currently on treatment who have not reached C16 are not yet included in efficacy analysis**





Ryan et al., ASH, 2022

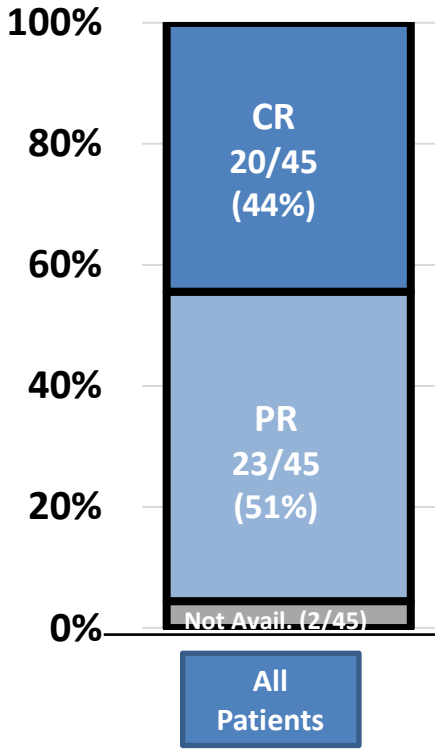
Efficacy: AVO Achieves High Rates of Undetectable MRD by Multicolor Flow Cytometry (10^{-4}) at Cycle 16



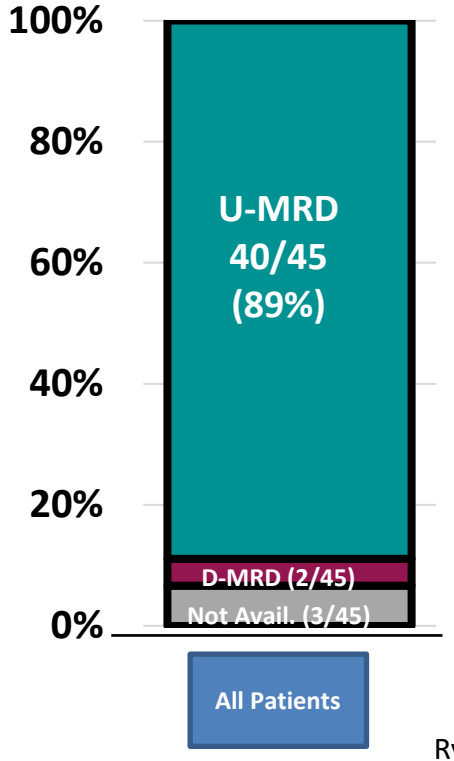
Ryan et al.. ASH. 2022

Efficacy: AVO Achieves High Clinical Response Rates & Undetectable MRD Levels by Flow (10^{-4}) at Cycle 25 (Exploratory Analysis)

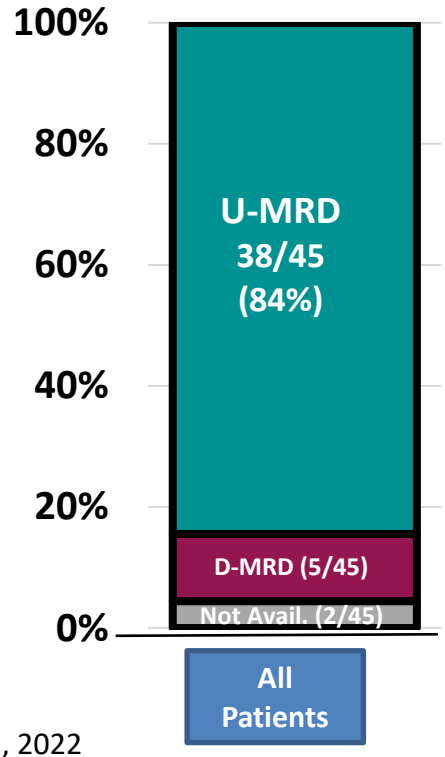
C25D1 Response by iwCLL Criteria



C25D1 Peripheral Blood MRD

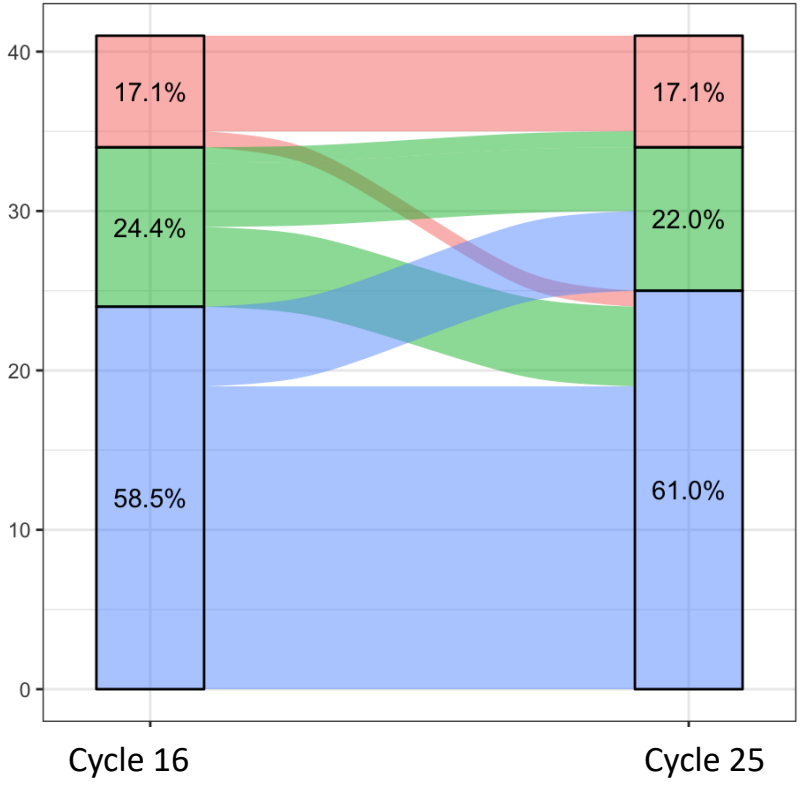


C25D1 Bone Marrow MRD



Ryan et al., ASH, 2022

AVO: NGS (ClonoSeq) Demonstrates Durably High Rates of Undetectable PB MRD



n=41 patients with paired samples available

MRD >= 10^-4

MRD < 10^-4 & >=10^-5 or Indeterminate 10^-5

MRD < 10^-5 & >=10^-6 or Indeterminate 10^-6

- **Rate of uMRD < 10^{-5} at C16: 59%**
- **Rate of uMRD < 10^{-5} at C25: 61%**

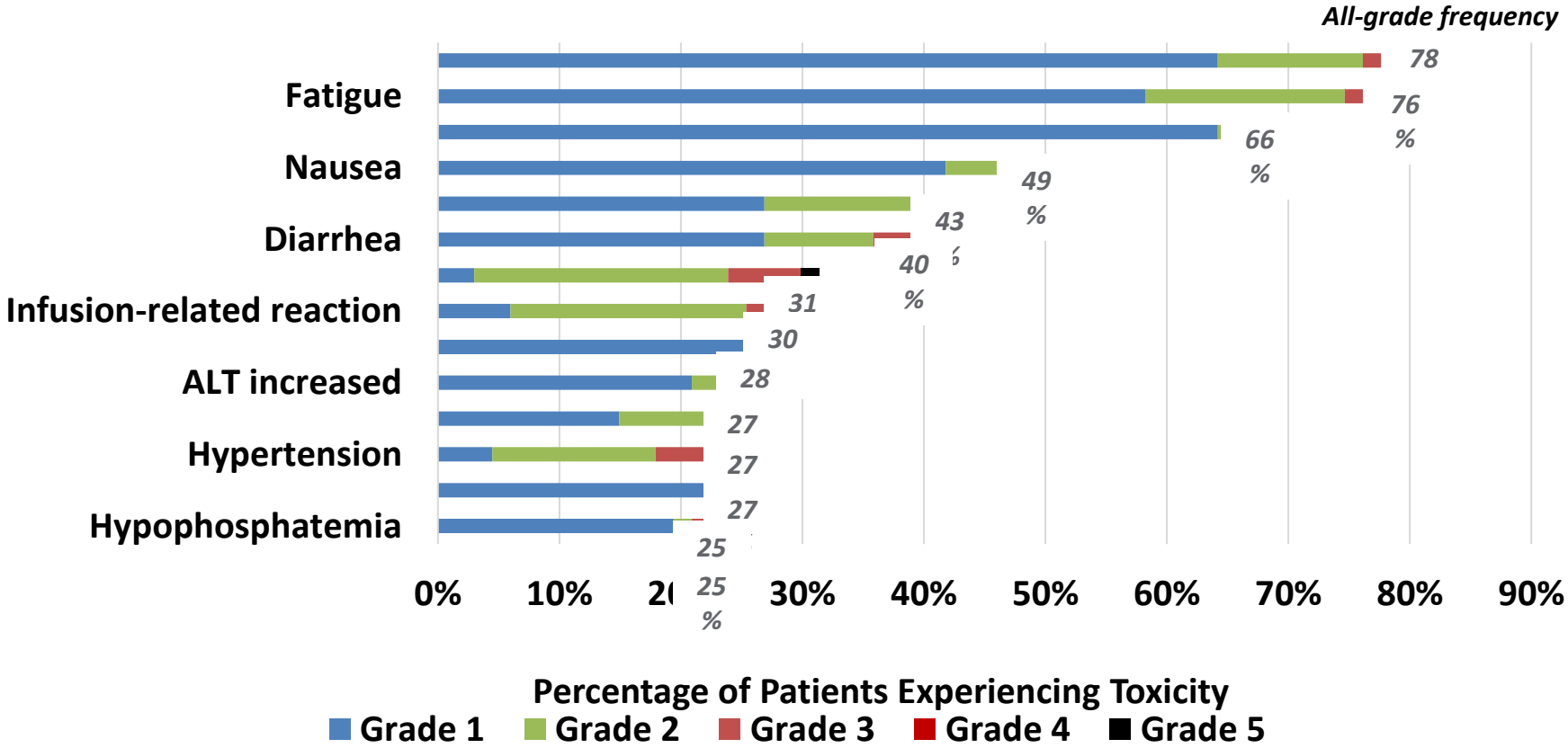
- No apparent difference in NGS-based peripheral blood uMRD rates in patients with or without *TP53*-aberrant disease

Ryan et al., ASH, 2022

AVO: Safety Analysis

Median Follow-Up: 35 months (range: 2-45)

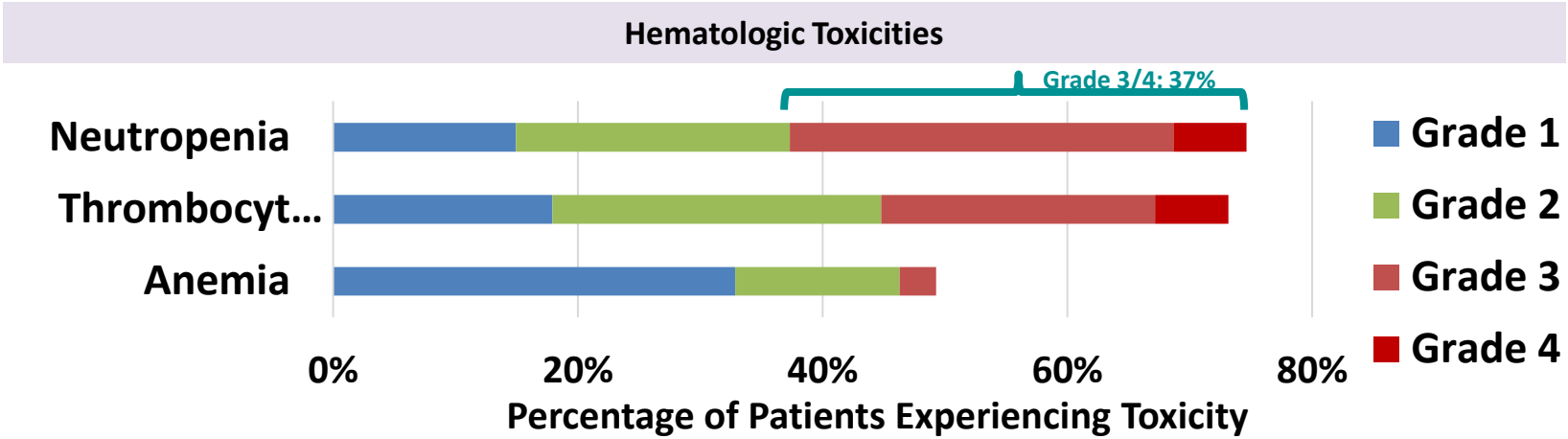
Non-Hematologic Toxicities Occurring in ≥ 25% of Patients



Ryan et al., ASH, 2022

AVO: Safety Analysis

Median Follow-Up: 35 months (range: 2-45)



Adverse Events of Special Interest

- Grade 3 non-COVID infections: 5.8% [pneumonia (n=3), colitis (n=1)]
- COVID-19 Infections: 9.0% (Gr 2 (n=4), Gr 3 (n=1), Gr 5 (n=1)
- AFib: 3.0% (n=1 Gr 2, n=1 Gr 3); no ventricular arrhythmias
- No febrile neutropenia or opportunistic infections
- No major bleeding events

Dose Reductions

14 patients (21%) with any dose reduction

- Acalabrutinib only: n=3
- Venetoclax only: n=6
- Both drugs: n=5

Ryan et al., ASH, 2022

AVO: Elective Treatment Discontinuation and Follow-Up

- 43 patients who achieved BM-uMRD electively discontinued therapy:
  - 21 patients also in CR after 15 cycles
  - 22 patients in CR or PR after 24 cycles
- Median time off therapy: 18.8 months (range 0-30.4)
- 4 patients who electively discontinued therapy after 15 cycles have had disease recurrence:
  - 3 patients with MRD-recurrence only
  - 1 patient with CLL disease progression

Ryan et al., ASH, 2022

AVO: Progression & Overall Survival

4 progression events:

- 1 patient with CLL disease progression (del(17p) & *TP53* mutation)
- 3 patients had transformation events
  - 1 with Hodgkin transformation 13 months after completing study treatment (*NOTCH1* mutation)
  - 1 with Hodgkin transformation 12 months into study treatment (del(17p) & *TP53* mutation)
  - 1 with DLBCL after 15 months on study (del(17p), *TP53* mutation, & complex karyotype)

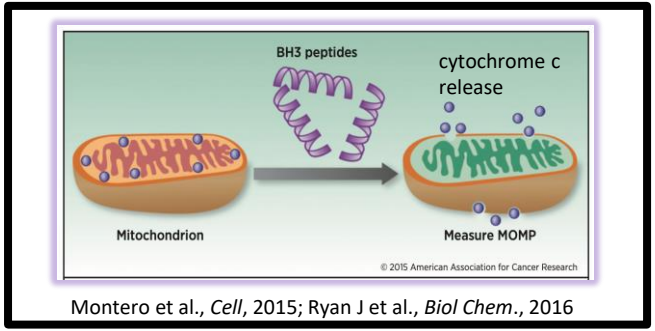
1 death: Due to COVID-19 pneumonia

At a median follow-up of 35 months:

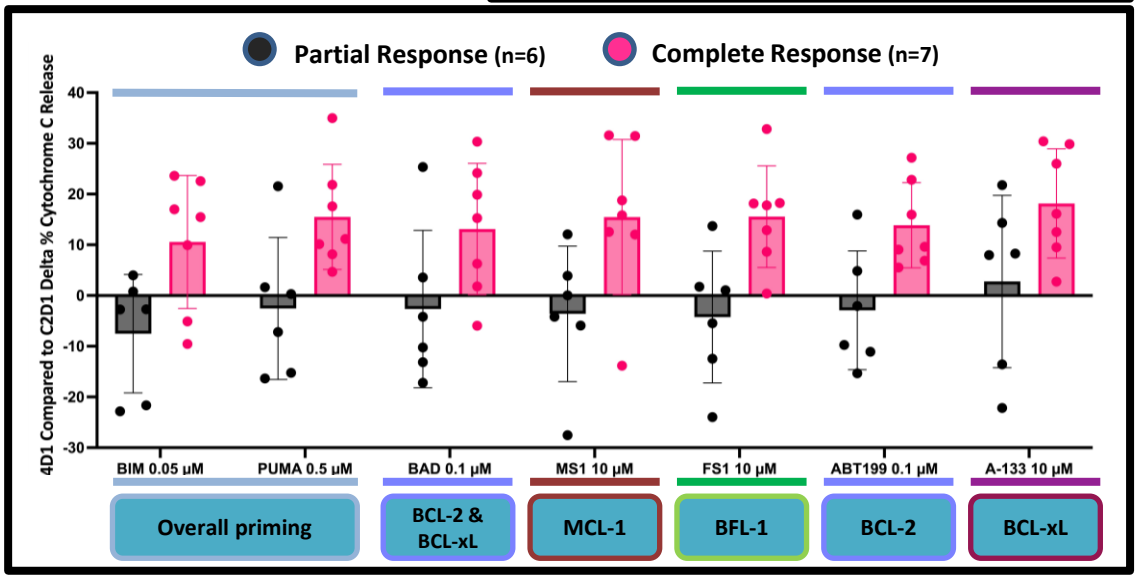
- **92.6% of all patients (63/68) are progression-free and alive**
- **98.5% of all patients (67/68) are alive**

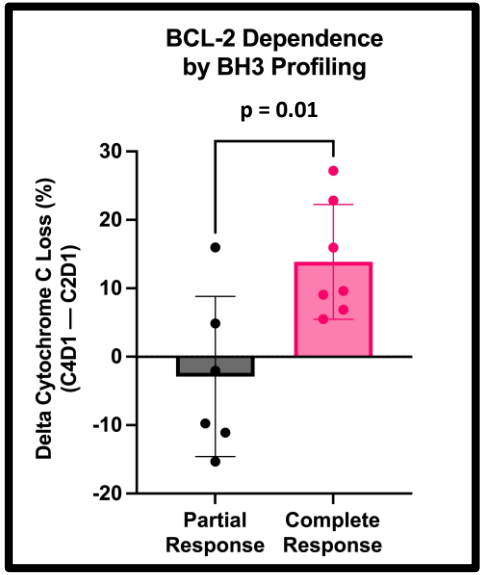
Ryan et al., ASH, 2022

AVO: BH3 profiling demonstrates potential predictive insights into clinical outcomes



Montero et al., *Cell*, 2015; Ryan J et al., *Biol Chem*., 2016





Ryan et al., ASH, 2022

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]

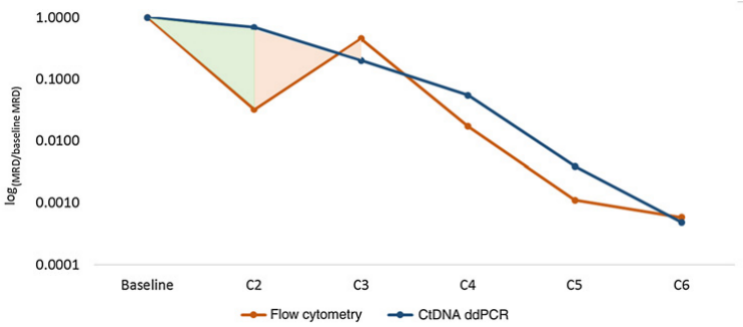


Figure 4.
Median levels of MRD are shown for ctDNA-based assessment (blue curve) and 4-color flow cytometry (red curve) in the course of induction treatment. For better comparability of both methods, median MRD levels are divided by the baseline MRD level of the respective method. The green area between 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).

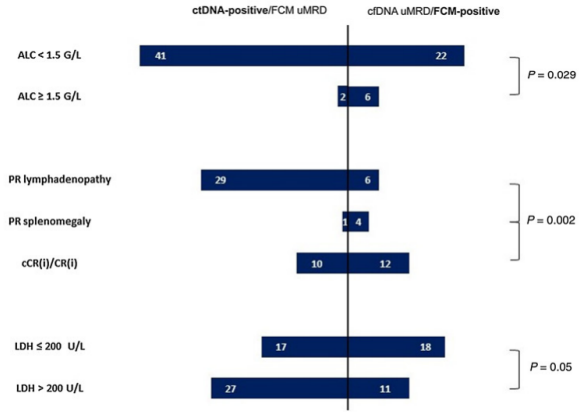


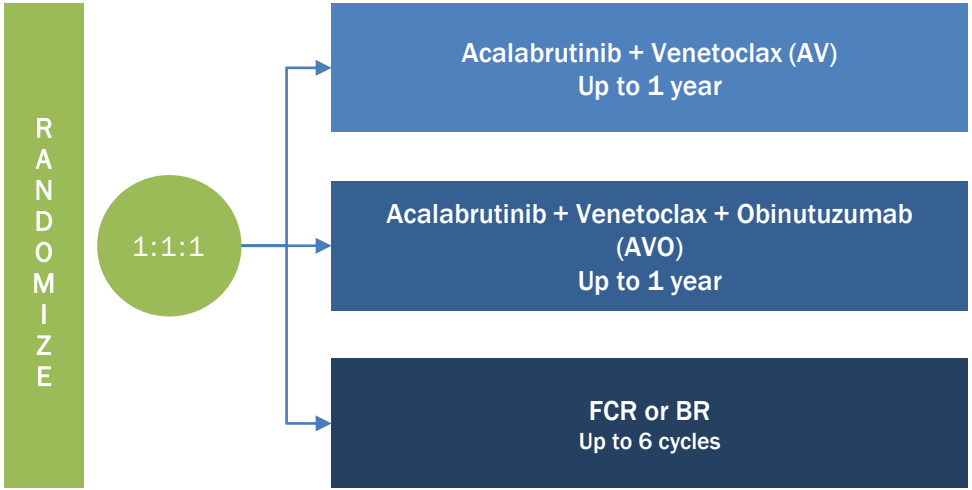
Figure 5.
The tornado chart shows the distribution of discordant results according to variables that potentially influence the detectability of ctDNA. On the left side of the vertical black line, all samples that were assessed as positive by ctDNA and uMRD by flow cytometry are shown. On the right side, all samples that were assessed as uMRD by ctDNA and positive by flow cytometry are shown. χ^2 tests were used to assess the difference in the distribution of discordant results within every group [lymphocyte count, type of response, lactate dehydrogenase (LDH) level] and respective *P* values were calculated. ALC, absolute lymphocyte count; cCR(i)/CR(i), clinical CR/CR and clinical CR/CR with incomplete recovery of the bone marrow; FCM, flow cytometry; PR lymphadenopathy, partial response with enlarged lymph nodes; PR splenomegaly, partial response with enlarged spleen but no enlarged lymph nodes.

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

AMPLIFY (ACE-CL-311): Phase 3 Study of Acalabrutinib + Venetoclax ± Obinutuzumab vs FCR/BR in TN CLL Without Del(17p) or *TP53* Mutations

Key Eligibility Criteria

- Previously untreated CLL
- Without del(17p) or *TP53* mutations
- ECOG PS ≤2



Primary endpoint

- PFS (IRC assessed) of AV vs FCR/BR

Key secondary endpoints

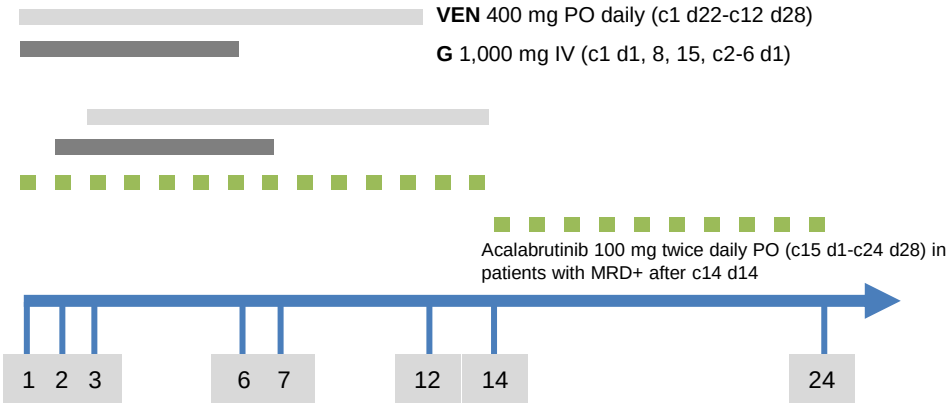
- PFS (IRC assessed) of AVO vs FCR/BR
- PFS (INV assessed) of AV vs FCR/BR

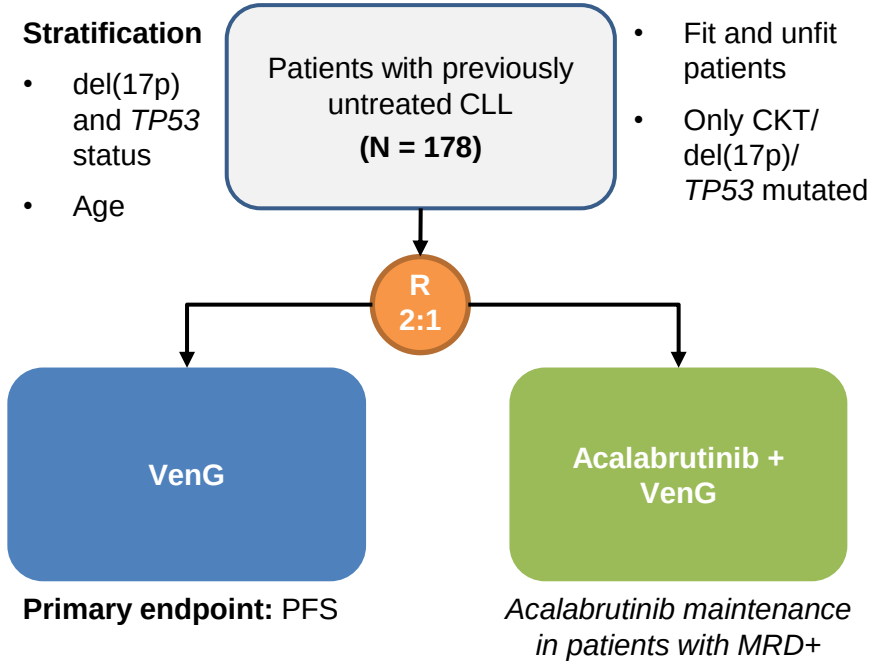
ClinicalTrials.gov identifier: NCT03836261. Accessed October 4, 2022. https://clinicaltrials.gov/ct2/show/NCT03836261

Phase 3 CLL16 Trial: VenG vs AVO in High-Risk CLL[1]

Study is designed to test the efficacy of a BTKi triplet versus an FD venetoclax platform in patients with high-risk features

Treatment Schedule





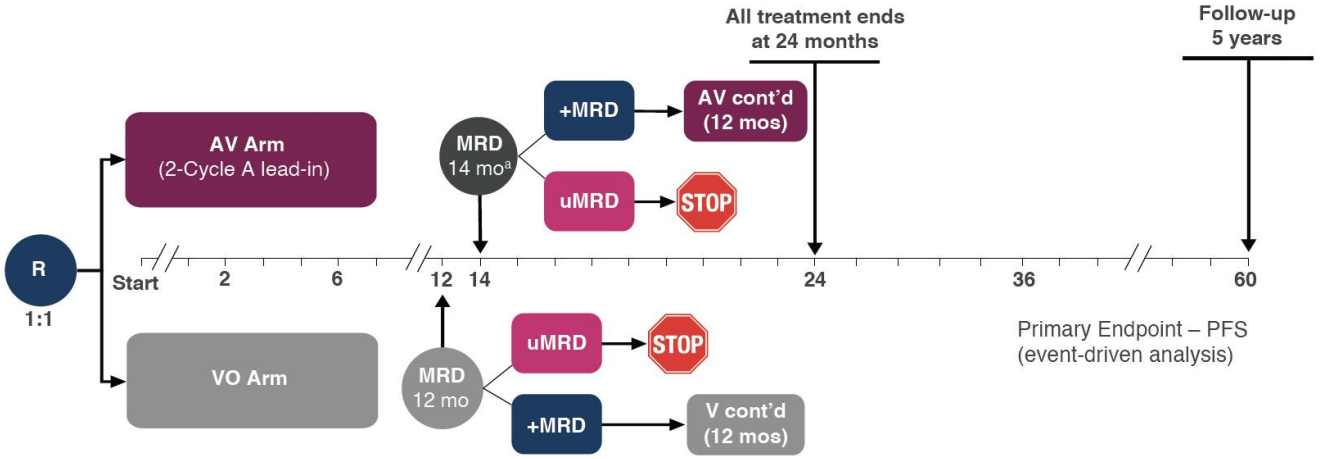
1. https://www.clinicaltrials.gov/ct2/show/NCT05197192.

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

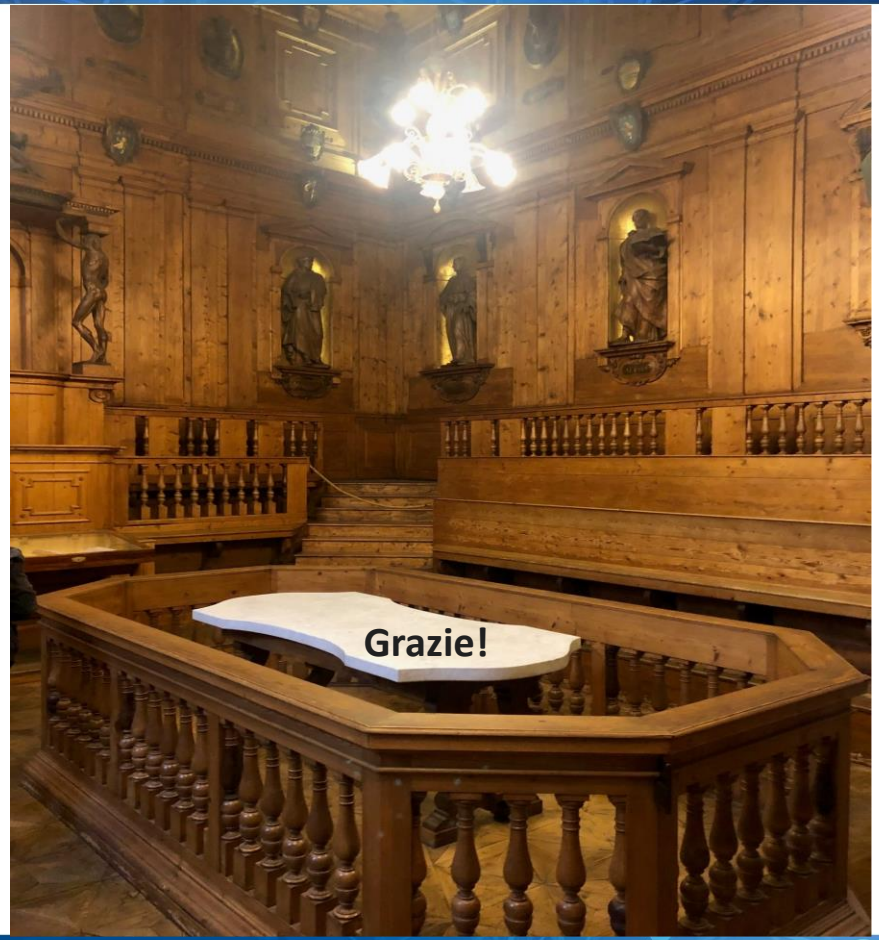
Primary endpoint: INV-assessed PFS



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**


Grazie!