# Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

# Chronic Lymphocytic Leukemia

**Thursday, January 5, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Jennifer R Brown, MD, PhD**

**Deborah Stephens, DO**

## Moderator

**Neil Love, MD**

RTP Year in Review 2023

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CLL Center Director and Institute Physician
Dana-Farber Cancer Institute
Worthington and Margaret Collette Professor of Medicine in the Field of Hematologic Oncology
Harvard Medical School
Boston, Massachusetts

**Deborah Stephens, DO**
Associate Professor
Director, CLL and Lymphoma Program
Huntsman Cancer Institute at University of Utah
Salt Lake City, Utah

**MODERATOR**
**Neil Love, MD**
Research To Practice
Miami, Florida

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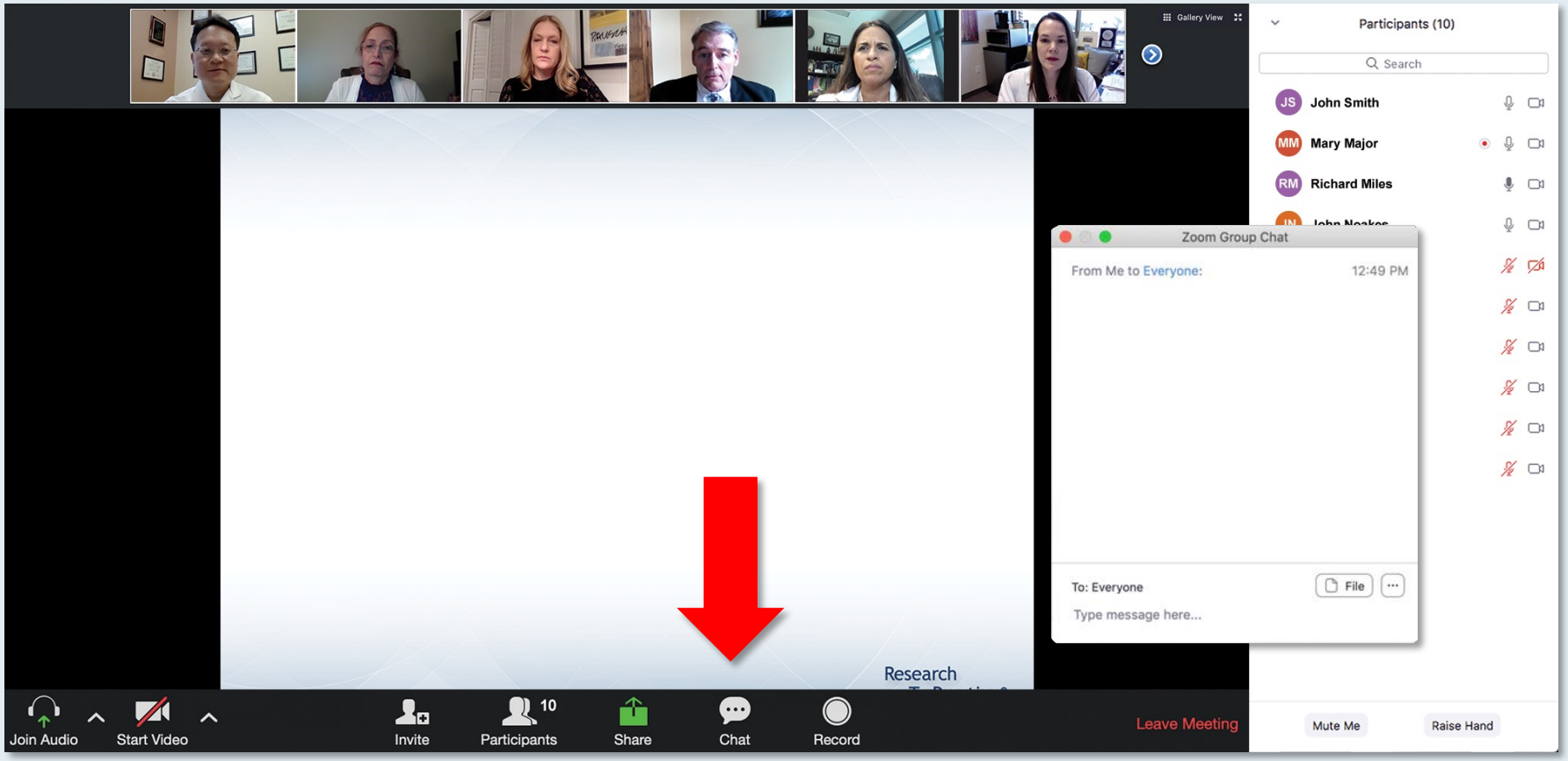


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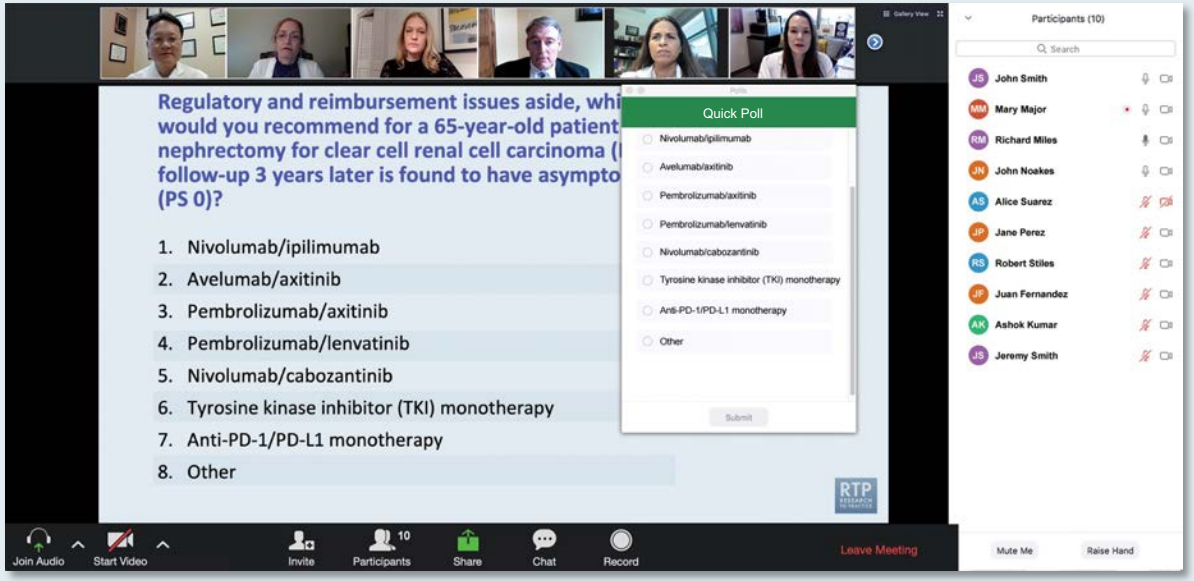


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# ONCOLOGY TODAY

WITH DR NEIL LOVE

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DR PETER HILLMEN
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*Thank you for joining us!*

*CME and MOC credit information will be emailed to each participant within 5 business days.*

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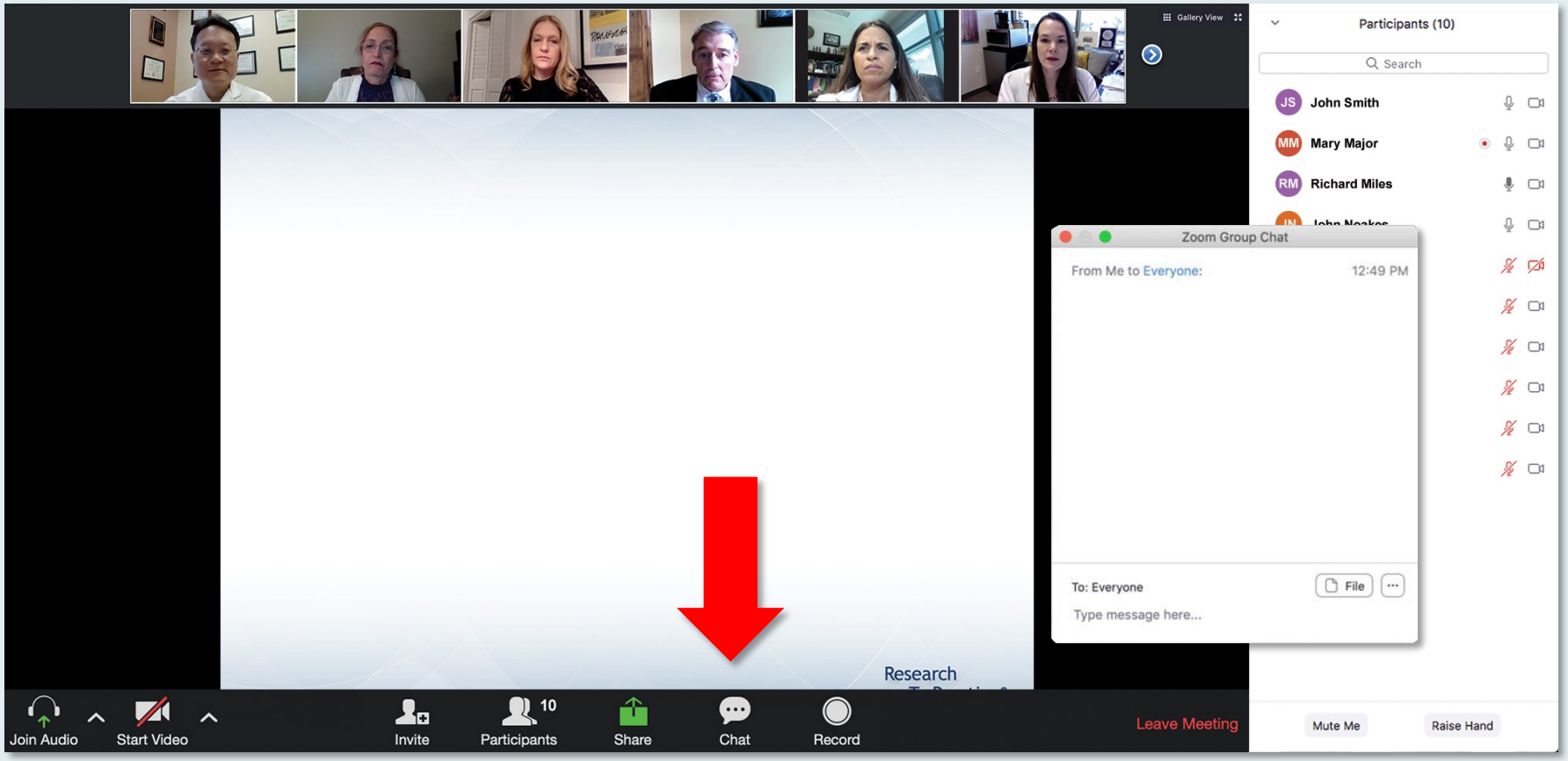


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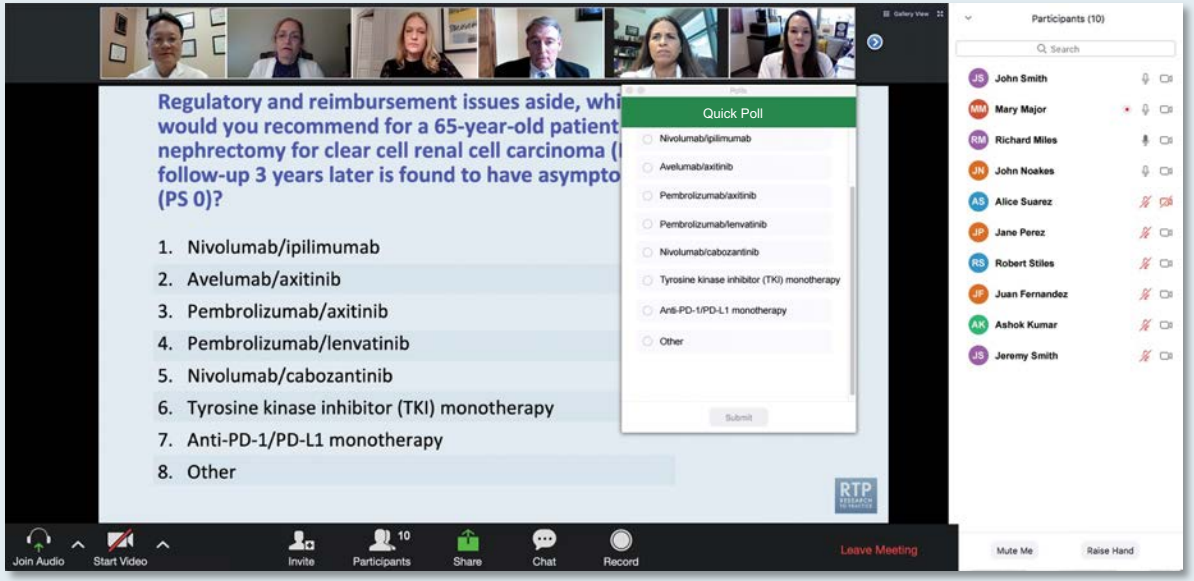


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Dana-Farber Cancer Institute | BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

# Optimizing First-Line Management for Newly Diagnosed CLL

**Jennifer R. Brown, M.D., Ph.D.**
**Director, CLL Center, and Institute Physician**
**Dana-Farber Cancer Institute**
**Worthington and Margaret Collette Professor of Medicine**
**In the Field of Hematologic Oncology**
**Harvard Medical School**

## Treatment of Relapsed/Refractory CLL; Novel and Investigational Strategies

Deborah Stephens, DO

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

U HEALTH UNIVERSITY OF UTAH

# Agenda

**MODULE 1: First-line treatment of CLL**

- Venetoclax
- BTK inhibitors

**MODULE 2: Combining BTK inhibitors with venetoclax; venetoclax consolidation**

**MODULE 3: Noncovalent BTK inhibitors; pirtobrutinib**

**MODULE 4: CAR T-cell therapy; lisocabtagene maraleucel**

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# Conclusions: CLL14

- One year time limited therapy
- Highly active, median PFS > 5 yrs
- Depth of MRD strongly associated with PFS and now also with OS
- Duration of remission depends on prognostic factors
- Potential to re-treat but limited data as yet

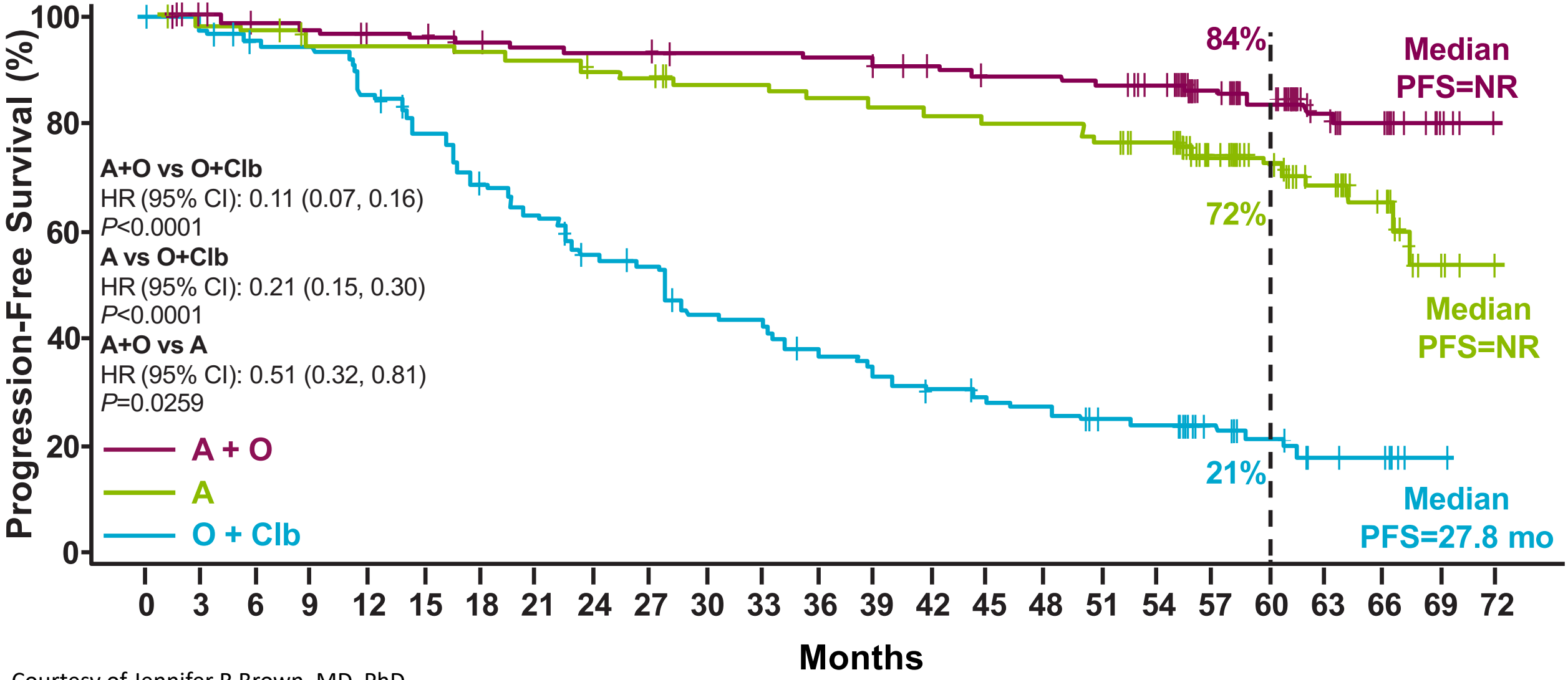
Courtesy of Jennifer R Brown, MD, PhD

# Conclusions: CLL13

- One year time limited therapy in fit patients
- Obinutuzumab containing regimens have the highest uMRD and best PFS (3 yr 88-91%)
- VenR not better than CIT
- FCR in patients < 65 has similar 3 yr PFS to the obinutuzumab containing regimens

Courtesy of Jennifer R Brown, MD, PhD

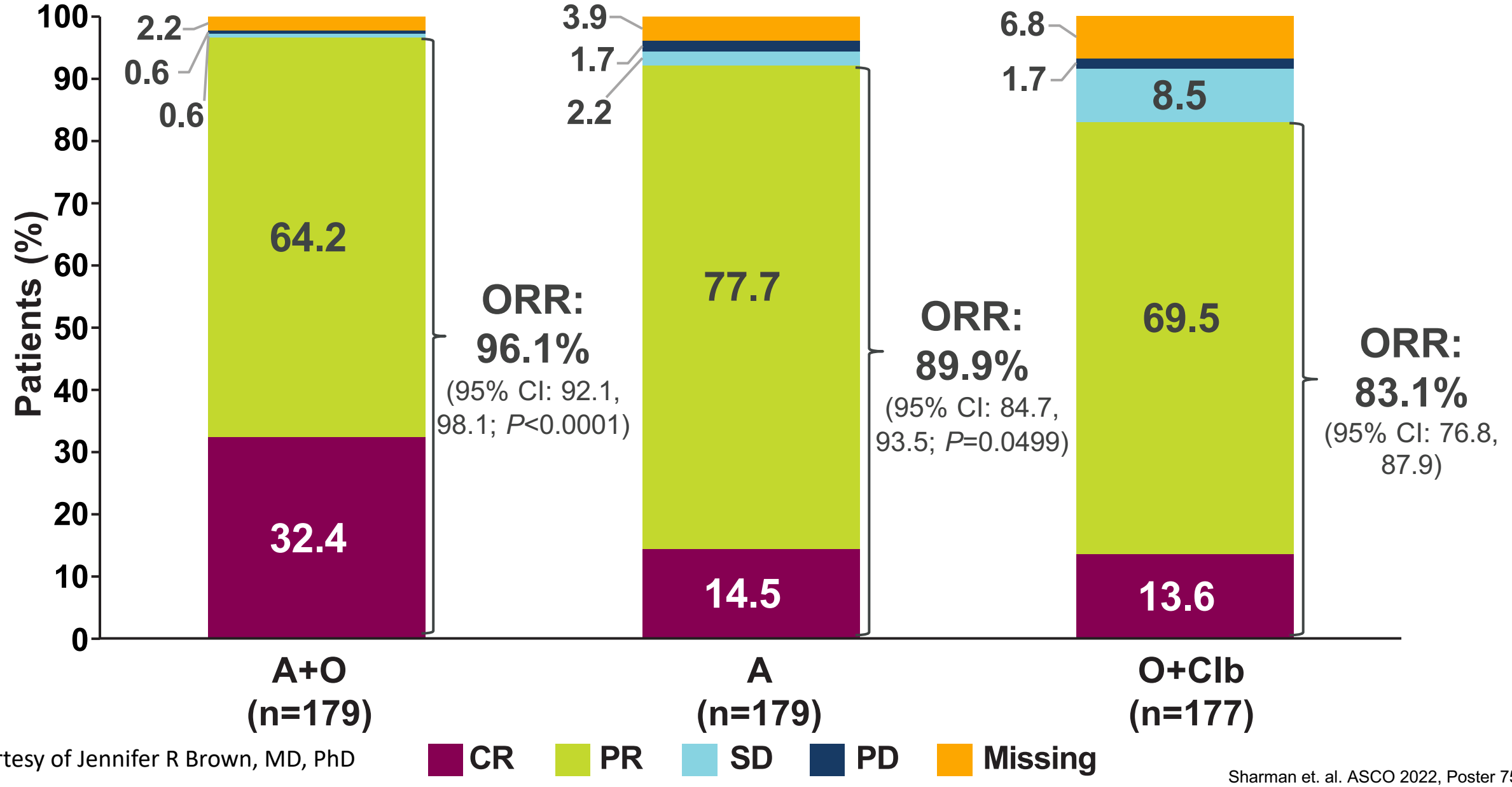
# ELEVATE-TN: 5 Yr Investigator-Assessed PFS




Courtesy of Jennifer R Brown, MD, PhD

Sharman et. al. ASCO 2022, Poster 7539

# ELEVATE-TN: Investigator-Assessed ORR




Courtesy of Jennifer R Brown, MD, PhD

Sharman et. al. ASCO 2022, Poster 7539

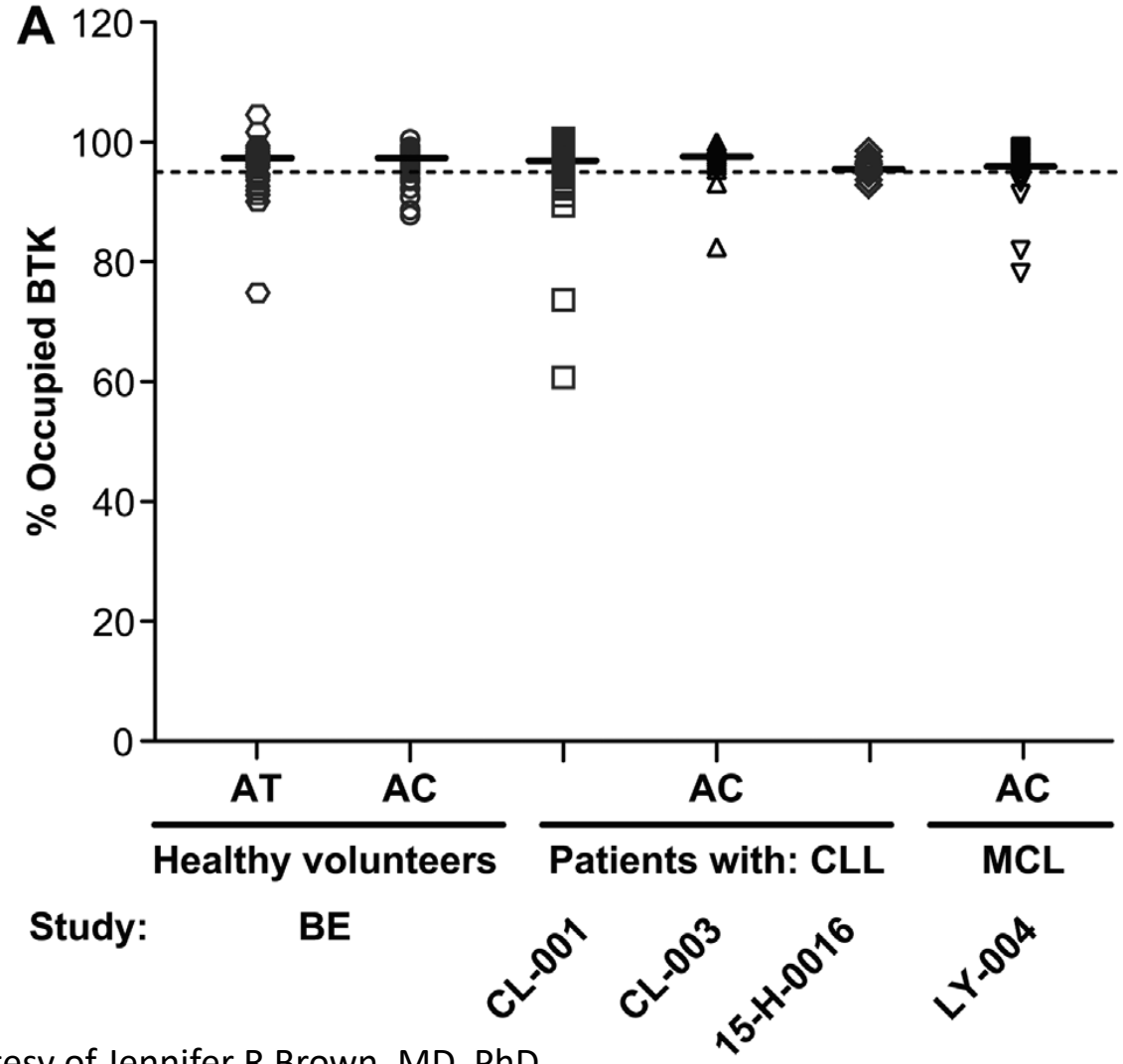
# Conclusions: ELEVATE-TN

- **Addition of obinutuzumab to acalabrutinib improves 5 yr PFS by 12%**
- **Obinutuzumab led to higher CR rate and higher uMRD**
- **Has not been widely adopted – but perhaps should be**

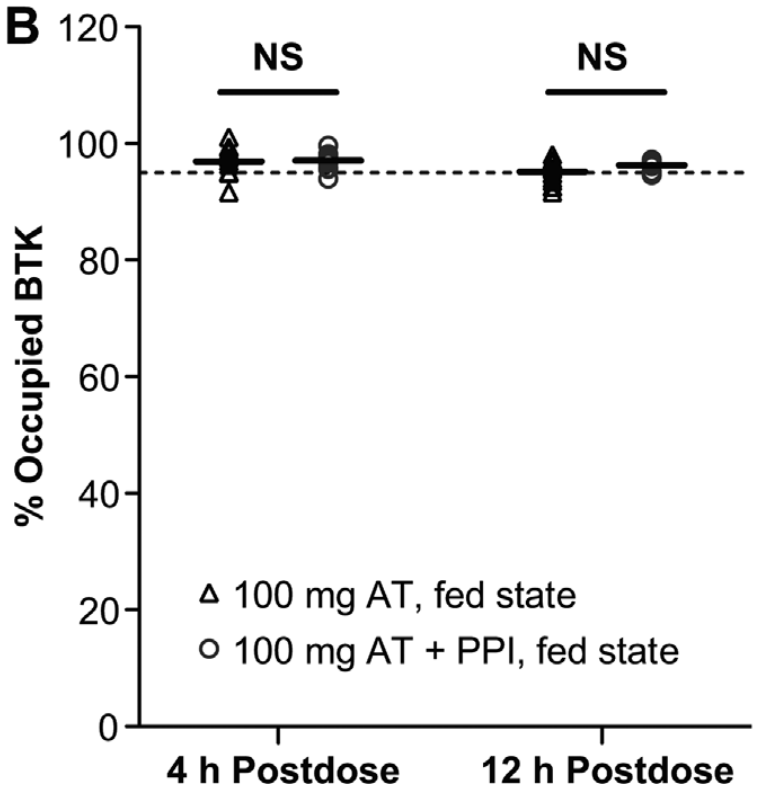
Courtesy of Jennifer R Brown, MD, PhD

# Pharmacodynamics of BTK Receptor Occupancy

**Following Administration of Acalabrutinib: Comparison of AT to AC (Across Several Studies)**




**Following Administration of Acalabrutinib (Fed State) in the Absence or Presence of a PPI (Study 1)**




Courtesy of Jennifer R Brown, MD, PhD

Sharma et. al. *Clin. Pharmacol Drug Dev.* 2022, 11(11) 1294–1307.

# Conclusions: Acala Tablet

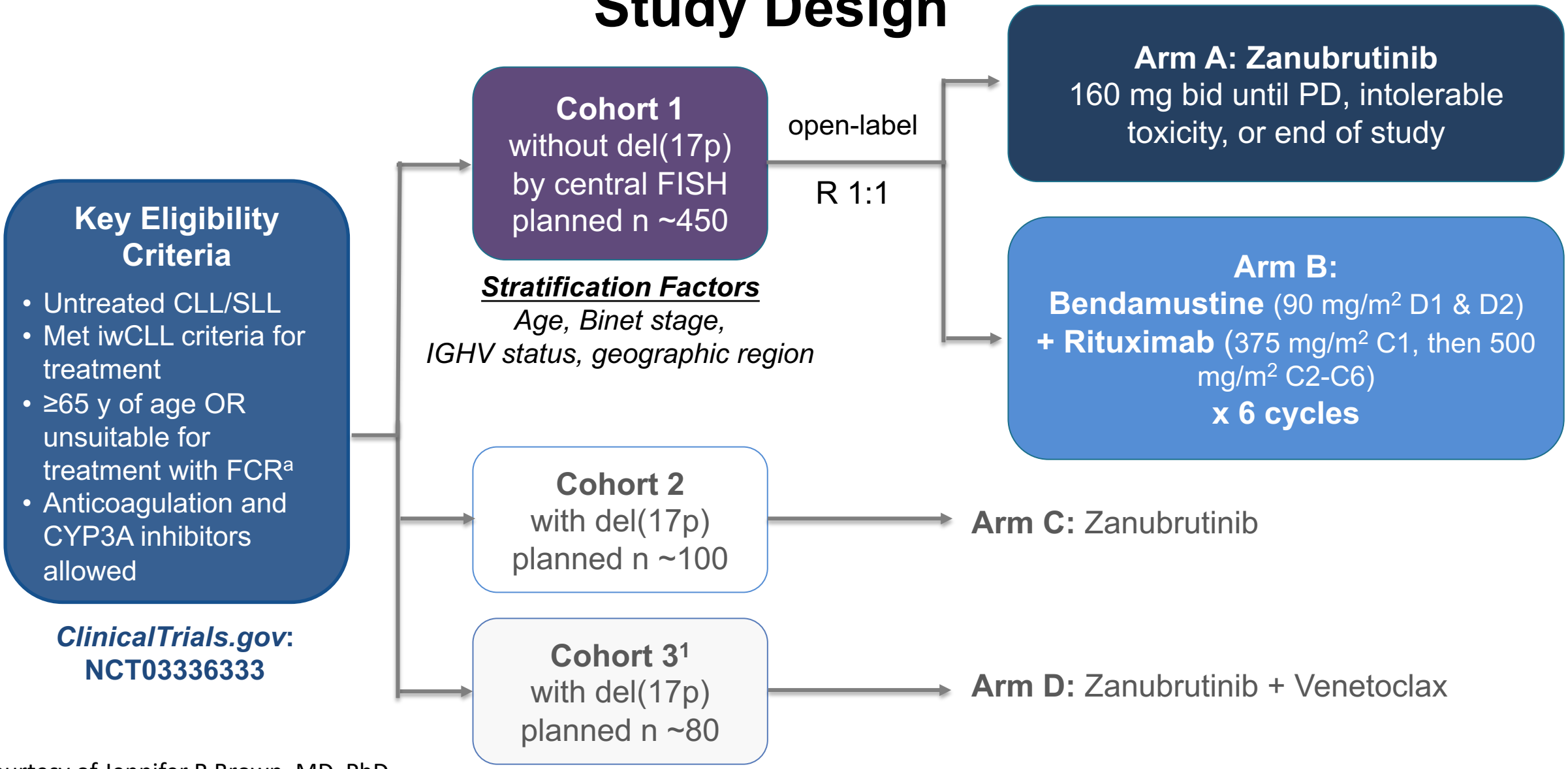
- **Characterization of the acalabrutinib tablet formulation shows similarity to the capsule**

- **Absorption similar regardless of stomach acidity so tablet can be used with PPIs**

Courtesy of Jennifer R Brown, MD, PhD

# SEQUOIA (BGB-3111-304)

## Study Design




Courtesy of Jennifer R Brown, MD, PhD

Tam et al. Lancet Oncology 2022

# Conclusions: SEQUOIA

- Frontline registration trial for zanubrutinib
- 2 yr PFS 86%
- Includes largest dedicated prospective cohort of patients with 17p deletion – 89% 2 yr PFS
- Ongoing cohort of zanu ven

Courtesy of Jennifer R Brown, MD, PhD

# ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

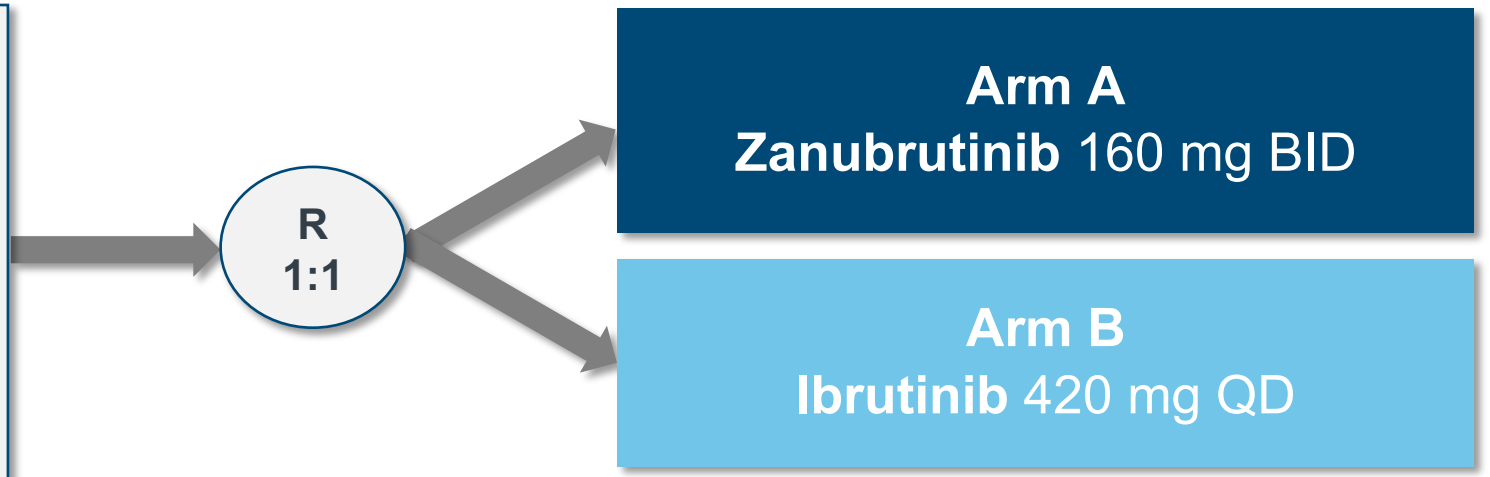
## R/R CLL/SLL with ≥ 1 prior treatment (Planned N=600, Actual N=652)

**Key Inclusion Criteria**

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

**Key Exclusion Criteria**

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists




## Stratification Factors

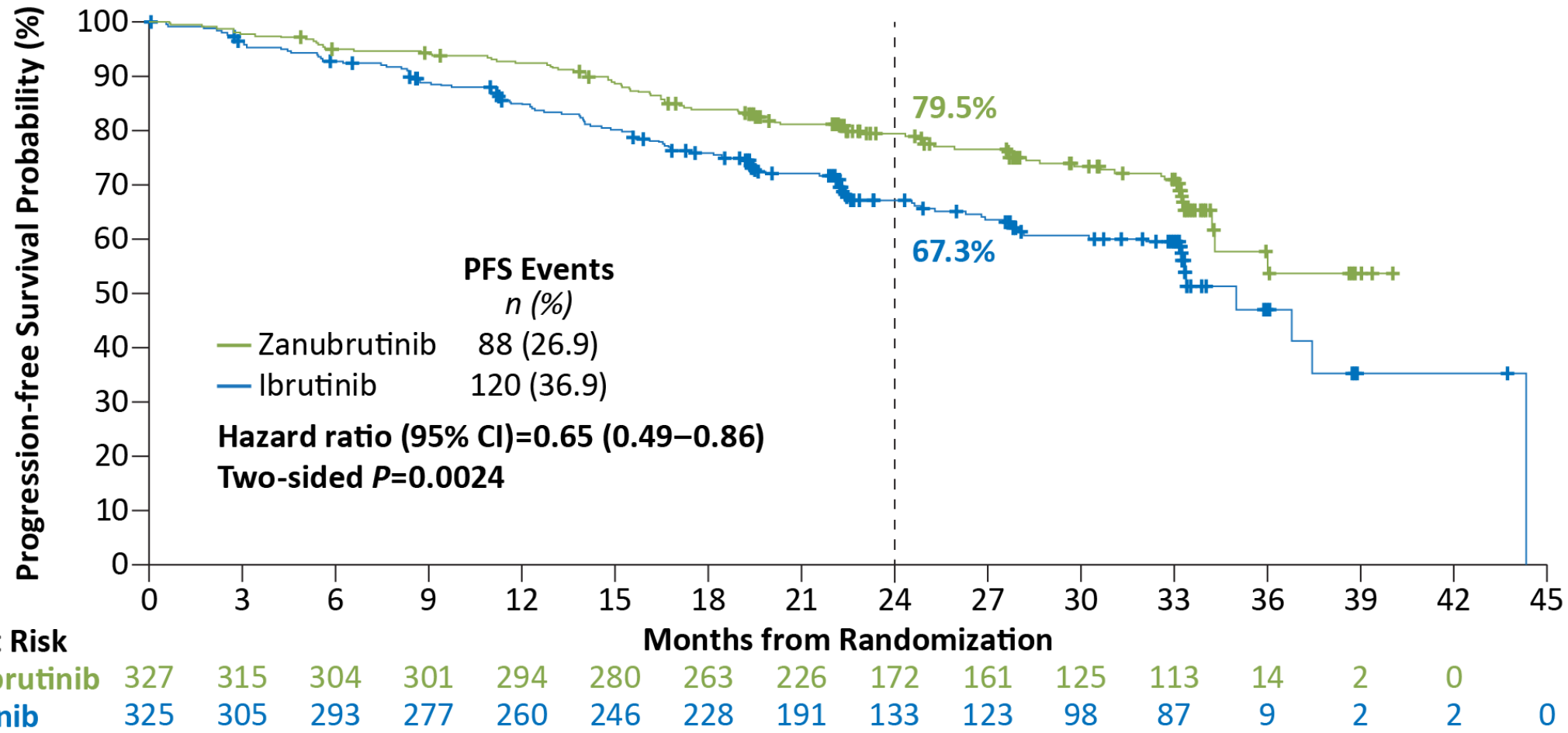
- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

Courtesy of Jennifer R Brown, MD, PhD

ALPINE study. Hillmen et al. LB1900 EHA 2021.

# ALPINE: Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months

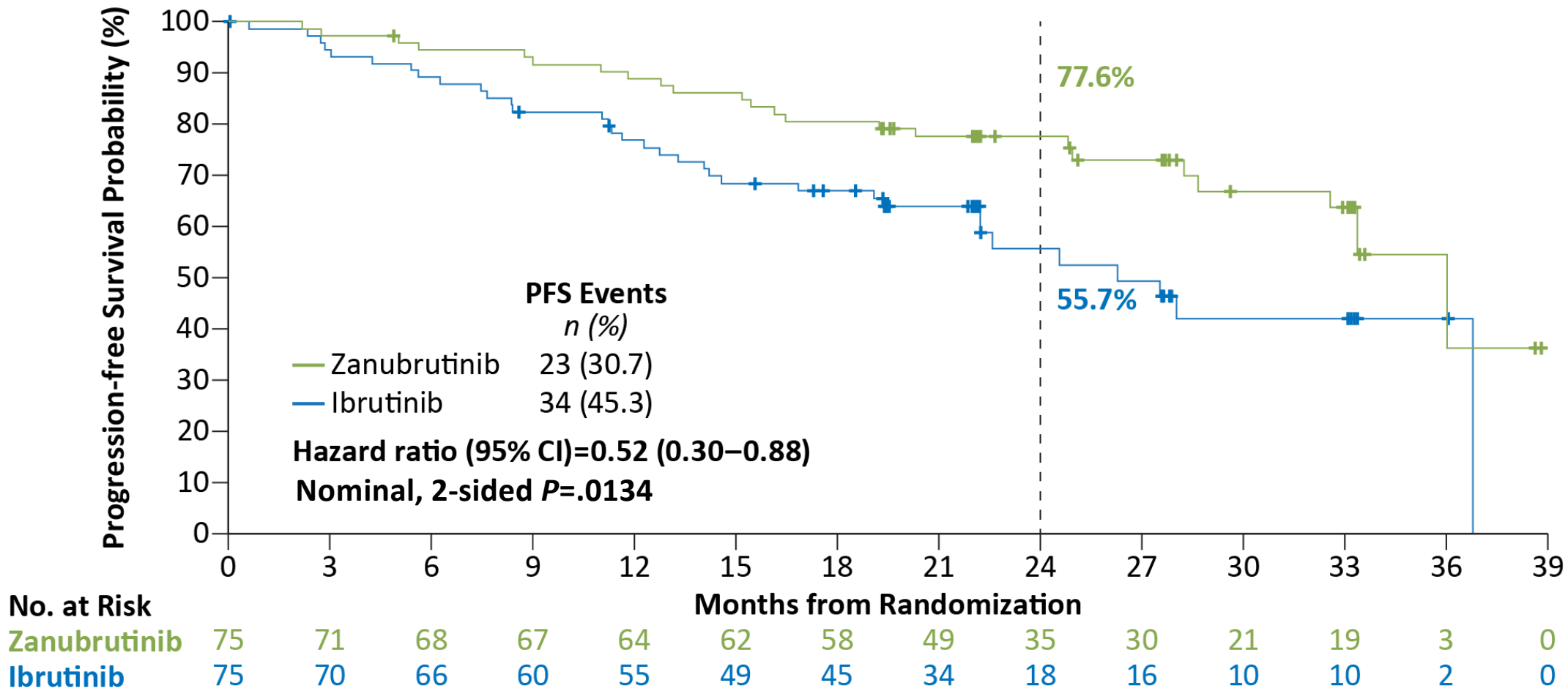



Data cutoff: 8 Aug 2022

Brown JR et al ASH 2022;Abstract LBA-6

Courtesy of Jennifer R Brown, MD, PhD

# ALPINE: Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*$^{mut}$




PFS data assessed by IRC

Data cutoff: 8 Aug 2022

Brown JR et al ASH 2022;Abstract LBA-6

Courtesy of Jennifer R Brown, MD, PhD

# Conclusions: ALPINE

- **First demonstrated efficacy benefit in head-to-head comparison of BTK inhibitors**
- **2 yr PFS improved 12% by zanubrutinib in entire population, 22% in the del17p/TP53 aberrant population**
- **Zanubrutinib also safer: fewer drug holds/ interruptions/ discontinuations**
- **Cardiac safety much better: 1 discontinuation vs 14 with ibrutinib; 0 deaths vs 6 with ibrutinib**

Courtesy of Jennifer R Brown, MD, PhD

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HEALTH
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# GLOW

Median Follow-up = 27.7 months

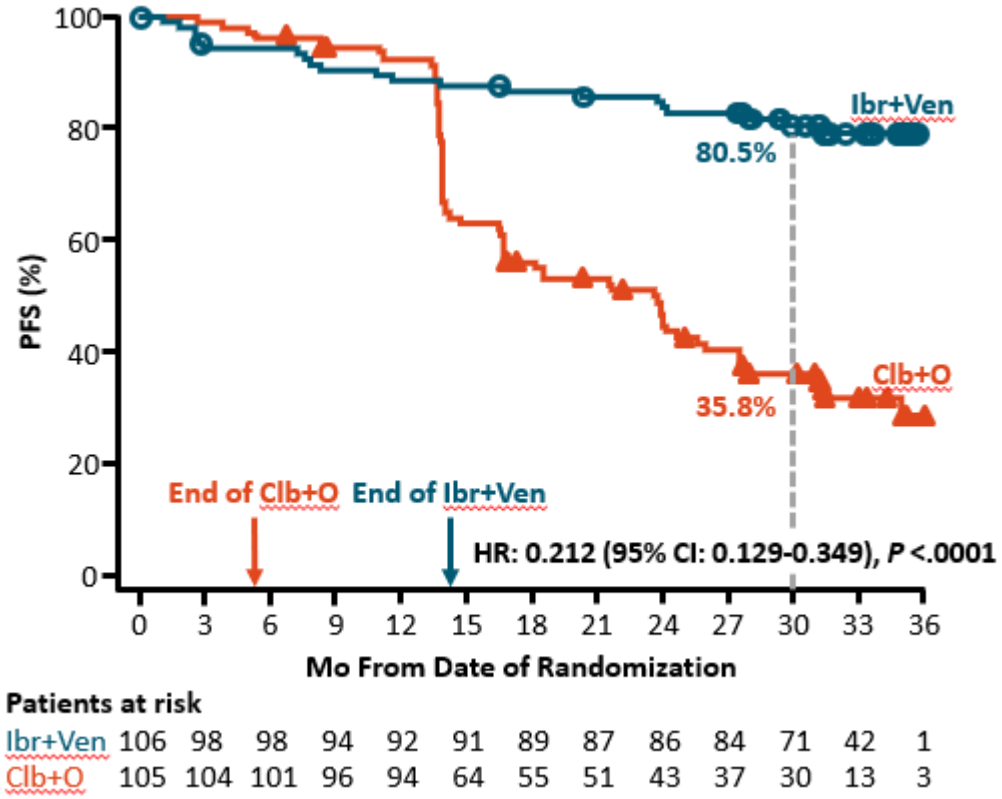
**GLOW**
-TN CLL
->65 years
-No del17p

Ibrutinib x 3 months → Ibrutinib + Venetoclax x 12 months

N=106

Obinutuzumab + Chlorambucil (6m)

N=105

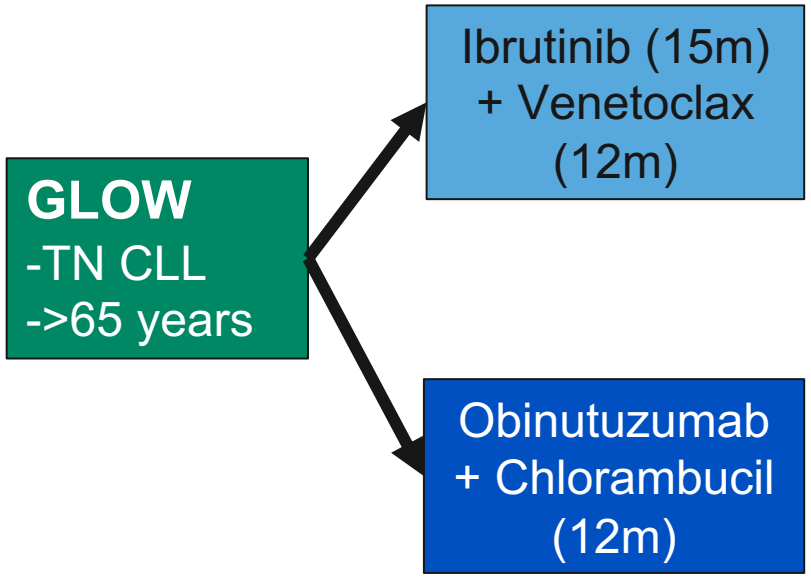



Kater, NEJM Evid 2022

Courtesy of Deborah Stephens, DO

Ibrutinib + Venetoclax ↑ PFS –
Approved for TN CLL patients in Europe

# GLOW- Takeaway




## PROS

- Limits risk of TLS with venetoclax
- Allows for a time-limited frontline BTKi treatment
- Evidence of responses to ibrutinib following relapse

## CONS

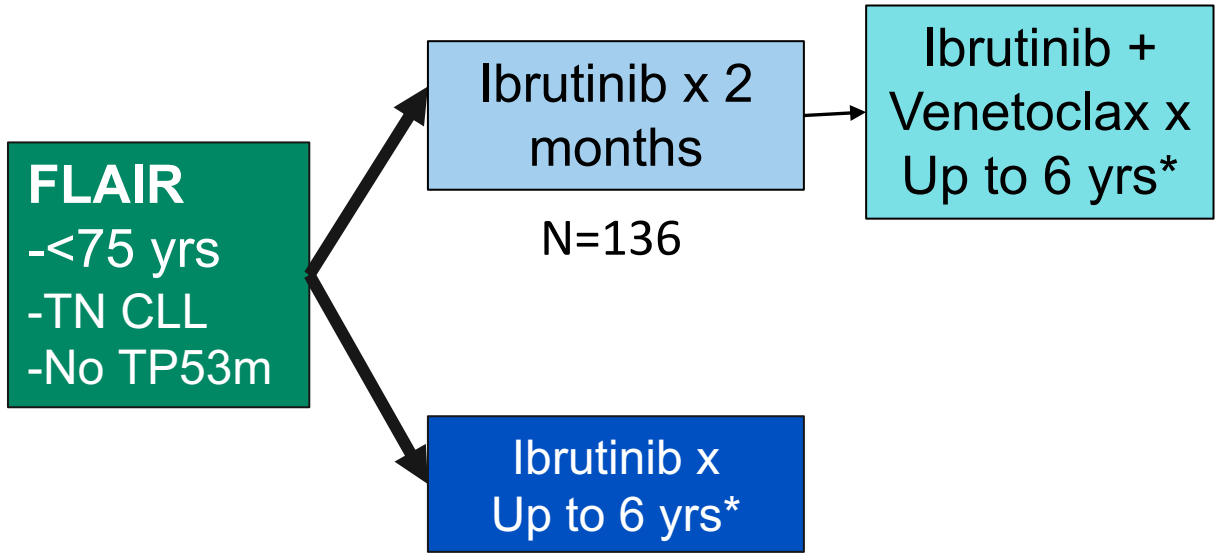
- Toxicity (better with acala?)
- Cost/insurance coverage
- Unclear which population may benefit most
- As of yet, no clear evidence of functional cure

Where to use? Young? High-risk? High Tumor Burden?

Kater, NEJM Evid 2022

Courtesy of Deborah Stephens, DO

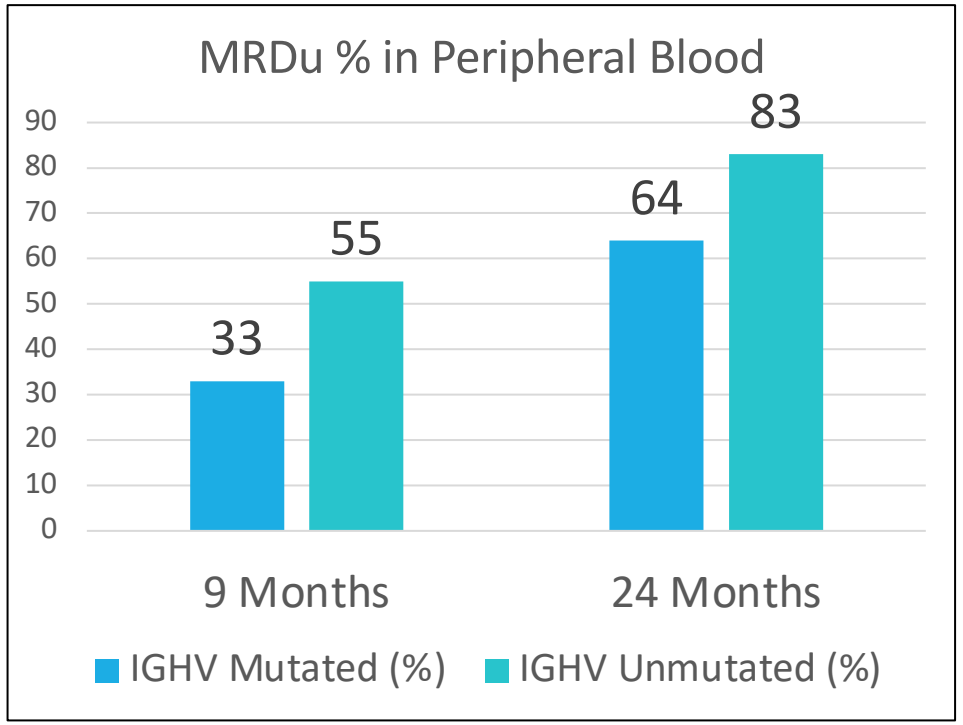
# FLAIR




*Therapy stopped after MRD undetectable (flow < $10^{-4}$) x 3 mos

Primary Endpoint: MRD eradication

Analysis of MRD within 2 yrs of therapy




Munir, ASH 2022

Courtesy of Deborah Stephens, DO

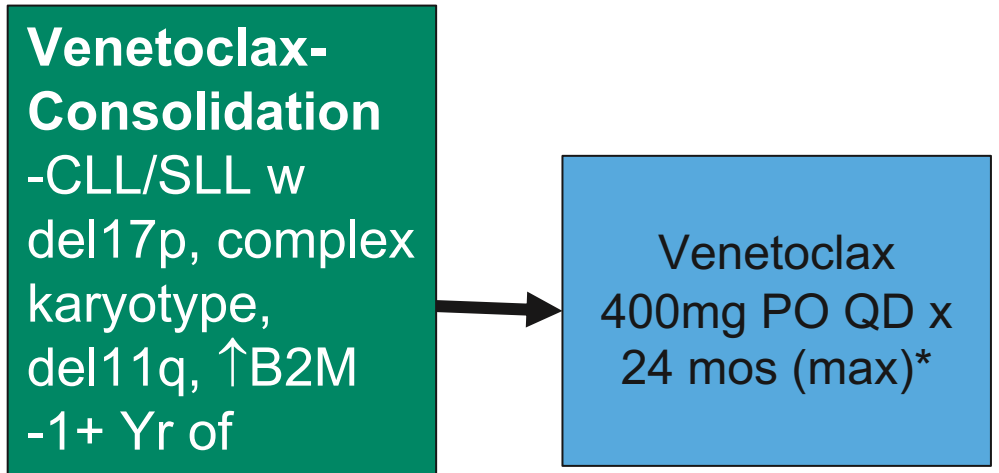
# FLAIR-MRDu - Takeaway

- In frontline CLL treatment with Ibr+Ven:
  - patients with IGHV unmutated status were more likely to achieve MRDu and achieved it at a faster pace than those with IGHV mutated status.
  - 83% of patients with Del(11q) and 55% of patients with del(13q) achieved MRDu within 2 years of treatment
- Unmutated IGHV and del(11q) CLL may be particularly responsive to the Ibr + Ven regimen.
- These subtypes may be more dependent on B-cell signaling.
- Longer follow-up will determine if difference in timing and achievement of MRDu will have on PFS and OS

Munir, ASH 2022

Courtesy of Deborah Stephens, DO

# Venetoclax Consolidation




N = 45

- Median follow-up = 37.5 mos
- Best cumulative rate of MRDu = 73%
- Best rate of CR/Cri = 57%
- Discontinued ibrutinib and venetoclax = 49%
- Patients with progression = 4/45 (9%)
  - 1 – during combination
  - 3 – during ibrutinib maintenance
  - 1 – Richter's transformation

*Venetoclax stopped after CR and BM MRDu (flow < $10^{-4}$) x 6 mos;
Ibrutinib could be discontinued at physician discretion

# Venetoclax Consolidation - Takeaway

Consolidation resulted in high rate of MRDu (73%) and CR/Cri (57%)

Most patients with MRDu at end of venetoclax remain in MRDu

Effective consolidation strategy

Future directions: High risk cohort (del17p and complex karyotype), on treatment with acalabrutinib.

Is consolidation with venetoclax better than sequential therapy with venetoclax?

| | TP53 WT (%) | TP53 MUT (%) |
|---|---|---|
| BM MRDu at C16 | 89 | 83 |

# AVO for Frontline CLL

**AVO:**
-TN
-All comer cohort: N=37
-TP53 or del(17p) mut cohort: N=31

→

Acalabrutinib 100mg PO BID (starting C1)* + Obinutuzumab IV (C2-7) + Venetoclax 400mg PO QD x (starting C4)*

*Venetoclax and acalabrutinib stopped at C16 or C25 if MRDu (flow < $10^{-4}$)

D/c acala + venetoclax = 63% (43/68)

Median time off therapy = 19 mos (range=0-30)

Patients with progression after D/c tx = 4/43 (9%)

- 3 – MRD recurrence only
- 1 – CLL progression

Overall patients with PD or death = 5/68 (7%)

- 1 – CLL progression
- 3 – Transformation events
- 1 – COVID-related death

PFS at 35 months = 93%

Ryan, ASH 2022

Courtesy of Deborah Stephens, DO

# AVO for Frontline CLL - Takeaway

High MRDu rates (>80%) regardless of TP53 mutation status

Durable responses after d/c therapy – supporting time limited therapy option, even for high-risk disease

Future directions: Ongoing AMPLIFY trial = AVO vs AV vs CIT

Will durability of response maintain in high-risk group with longer follow-up?

Ryan, ASH 2022

Courtesy of Deborah Stephens, DO

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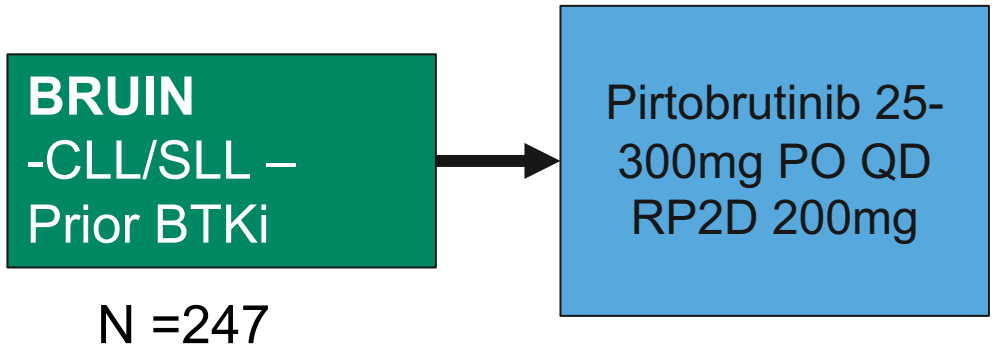
# BRUIN Phase 1/2 - Prior BTKi




Pirtobrutinib = Noncovalent BTKi; binds in C418-independent manner

Most common AEs (mostly Grade 1-2):

- Fatigue, diarrhea, neutropenia, contusion

Grade 3+ AEs: rare

Atrial fibrillation: 3%

| | Prior BTKi (n=247) | Prior BTKi and BCL2i (n=100) |
|---|---|---|
| Best ORR (%) | 82 | 79 |

Median follow-up = 19 mos

# BRUIN Phase 1/2 – Prior BTKi

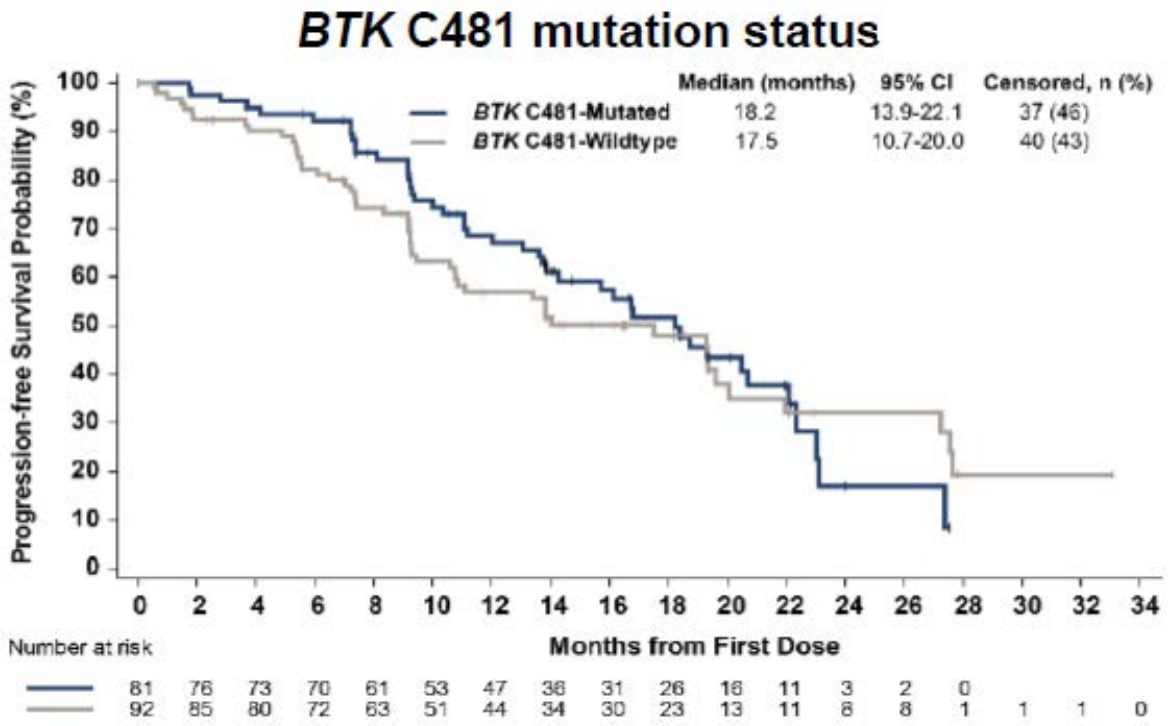
Median follow-up = 19 mos

Median PFS

- All Prior BTKi (median 3 prior Rx; n=247) = 20 mos
- Prior BTKi and BCL2i (median 5 prior Rx; n=100) = 17 mos

No difference in PFS curves for:

- C481 Mut vs WT
- Age < vs > 75 years
- Del(17p) and/or TP53 Mut vs WT




Mato, ASH 2022

Courtesy of Deborah Stephens, DO

# BRUIN- Takeaway

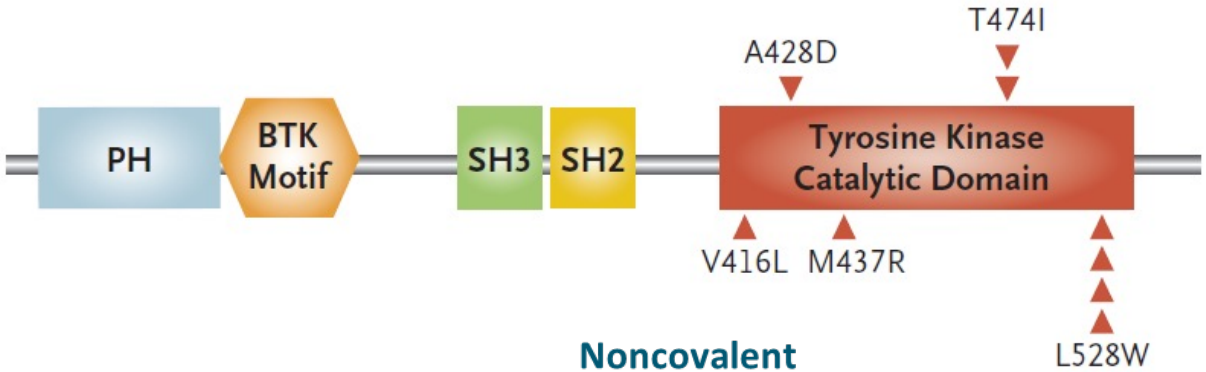
With 1.5 years of follow-up, pirtobrutinib shows efficacy in heavily pretreated and high-risk (C481S and TP53 Mut) CLL.

Toxicity profile continues to be very well-tolerated.

CLL with prior BTKi and BCL2i is still an area of un-met need.

# Resistance to Pirtobrutinib

7 of 9 Patients Analyzed Developed New BTK mutation




**Binding Affinities of BTK Inhibitors**

| | Noncovalent | | | | Covalent | | |
|---|---|---|---|---|---|---|---|
| | **Pirtobrutinib** | **Nemtabrutinib** | **Vecabrutinib** | **Fenebrutinib** | **Ibrutinib** | **Acalabrutinib** | **Zanubrutinib** |
| **Wild-type** | Normal | Normal | Normal | Normal | Normal | Normal | Normal |
| **A428D** | None | Decreased | None | None | None | None | None |
| **M437R** | Decreased | Normal | Decreased | Decreased | Normal | Decreased | Normal |
| **T4741** | Decreased | Decreased | Decreased | Normal | Normal | Decreased | Decreased |
| **L528W** | None | None | Decreased | Normal | None | Decreased | None |
| **C481S** | Normal | Normal | Normal | Normal | Decreased | Decreased | Decreased |

Wang, NEJM 2022

Courtesy of Deborah Stephens, DO

# Pirtobrutinib Resistance- Takeaway

In a small sample of 9 patients, CLL resistance to pirtobrutinib has now been described.

7/9 developed new BTK mutations.

All BTKi tested had different abilities to inhibit the described mutations.

Caution should be used in moving pirtobrutinib to front-line setting unless very durable remissions are seen in this setting.

CLL with prior BTKi and BCL2i is still an area of un-met need.

Mato, ASH 2022

Courtesy of Deborah Stephens, DO

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# TRANSCEND

Lisocabtagene maraleucel = CD19-directed, defined T-cell composition CART product

Phase 1/2 Study = 23 R/R CLL

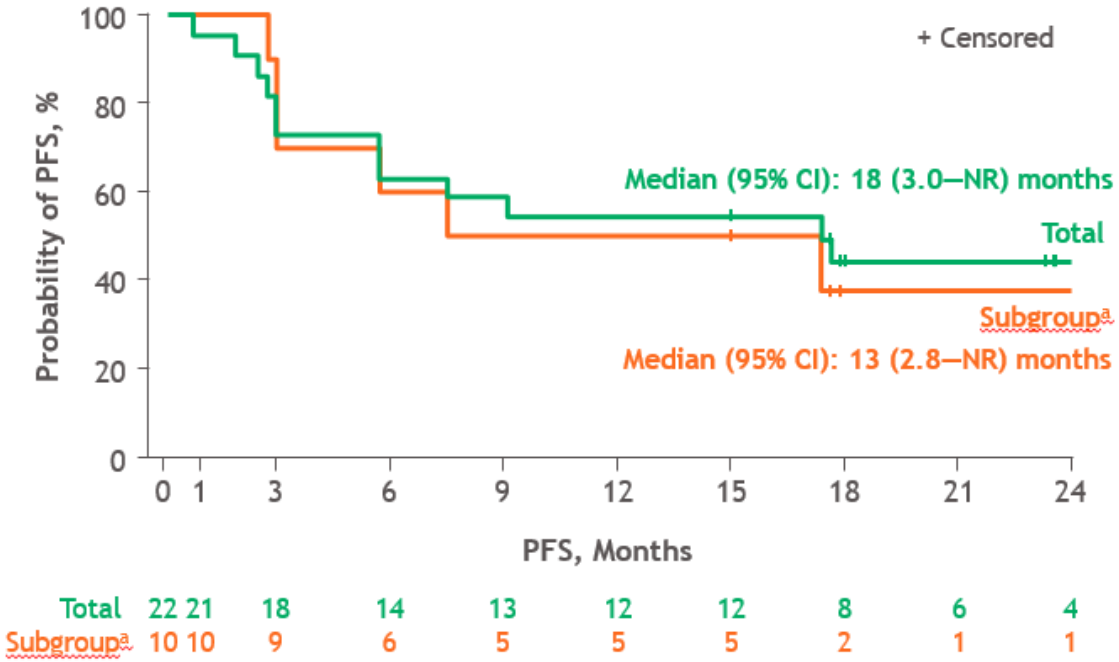
- 11 with prior BTKi and BCL2i

ORR = 82% (CR = 46%, MRDu = 75%)

PFS was similar between double refractory vs not group

Important Toxicities

- Cytokine release syndrome
  - All grade = 74%; Grade 3+ = 9%
- Neurotoxicity
  - All grade = 29%; Grade 3+ = 21%




Median Follow-up 24 months

Siddiqi, Blood 2022

Courtesy of Deborah Stephens, DO

# TRANSCEND- Takeaway

In a high-risk R/R CLL population, Liso-cel led to deep remissions (75% MRDu).

However, especially in patients previously treated with BTKi and BCL2, PFS is similar to what was seen with pirtobrutinib and has more toxicity (and cost) than pirtobrutinib.

Toxicity may limit the population that can receive CART.

Should we use CART as a bridge to more definitive therapy?

CLL with prior BTKi and BCL2i is still an area of un-met need.

Mato, ASH 2022

Courtesy of Deborah Stephens, DO

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# BRUIN Phase 1/2 – Richter's Syndrome

**BRUIN**
-Richter's Syndrome

→ Pirtobrutinib 25-300mg PO QD RP2D 200mg

N =82

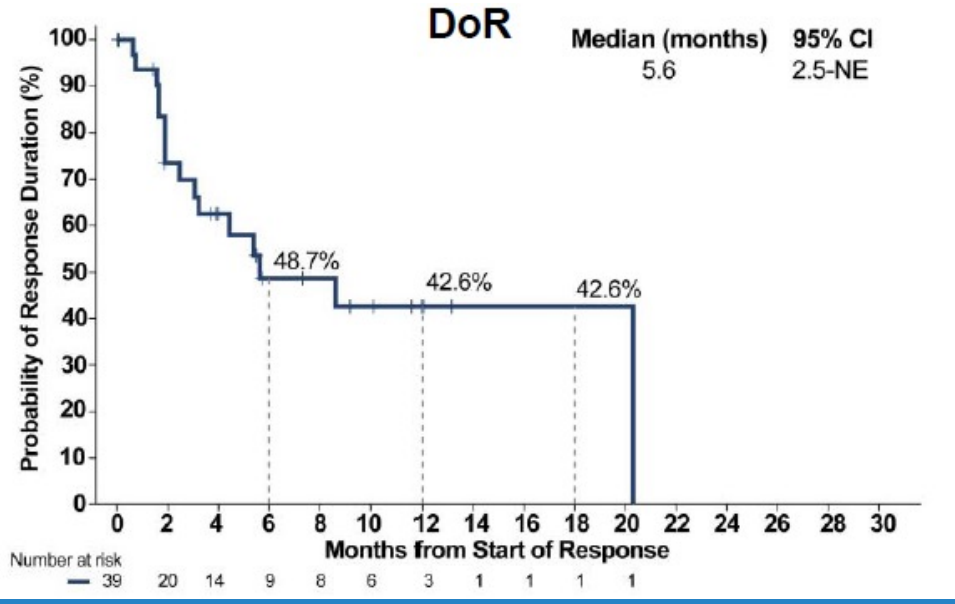
| | ORR | CRR |
|---|---|---|
| Responders, n (%) | 39/75 (52) | 10 (13) |

Median PFS = 3.7 mos

Median OS = 13.1 mos

Heavily Pretreated:

- Median Prior CLL and RT Rx = 4 (0-13)
- Prior BTKi = 34%
- Prior BCL2i = 38%
- Prior CART = 11%




Courtesy of Deborah Stephens, DO

Wierda, ASH 2022

# BRUIN- Richter's Takeaway

Pirtobrutinib led to responses in heavily pretreated patients, including 13% complete responses.

PFS and OS are still short for these patients.

6 patients were able to proceed to curative intent allogeneic stem cell transplant.

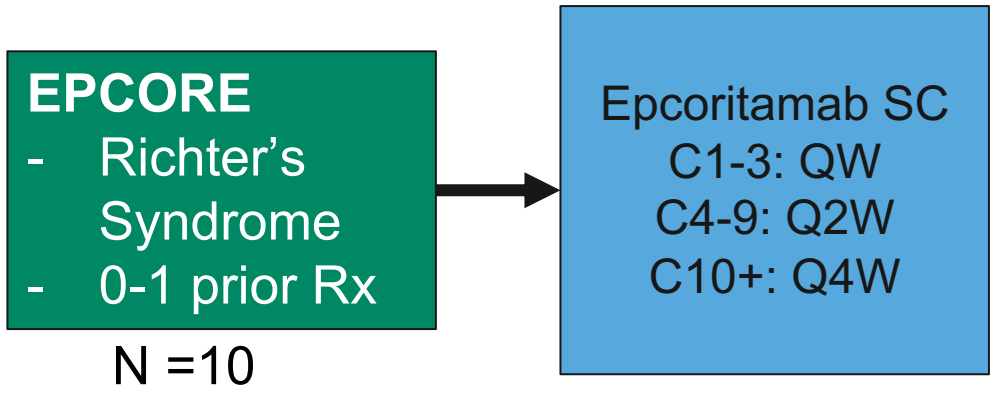
Should we use pirtobrutinib as a bridge to more definitive therapy?

Richter's Syndrome remains an area of un-met need.

Wierda, ASH 2022

Courtesy of Deborah Stephens, DO

# EPCORE– Richter's Syndrome




Bispecific Antibody to CD3/CD20

Median Prior CLL Rx = 3 (0-7)

| | ORR | CRR |
|---|---|---|
| Responders, n (%) | 6/10 (60) | 5/10 (50) |

Cytokine Release Syndrome: n = 90% (all grade 1/2)

- First full dose given C1D15
- Median time from first full dose to CRS = 13 hrs
- Median time to resolution = 3 (2-9) days

Neurotoxicity = 0%

Kater, ASH 2022

Courtesy of Deborah Stephens, DO

# EPCORE- Richter's Takeaway

In a small study of 10 patients with Richter's Syndrome, epcoritamab delivered a 60% ORR and 50% CRR.

Good toxicity profile with low-grade CRS.

Follow-up is short and more information is needed about duration of response.

Should we use epcoritamab as a bridge to more definitive therapy?

Richter's Syndrome remains an area of un-met need.

Kater, ASH 2022

Courtesy of Deborah Stephens, DO

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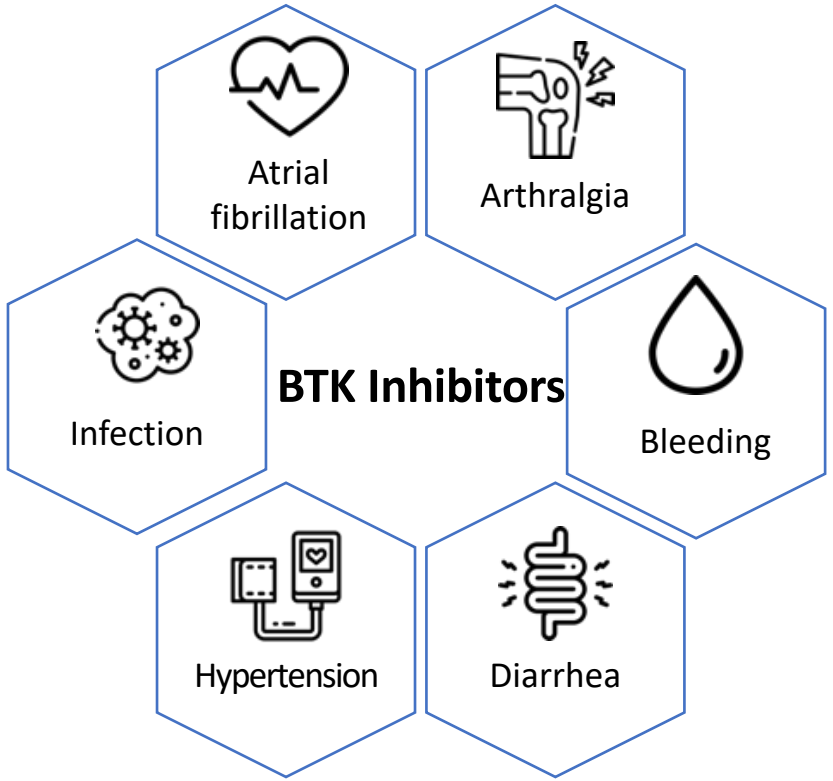
# Summary of AEs with Targeted Agents in CLL

## AEs With BTKi




**Additional important AEs: dermatologic changes, fatigue, cytopenias, and ventricular arrhythmias**

## AEs With Venetoclax

- **TLS**
- **GI events**
- **Infections**
- **Myelosuppression**

Courtesy of Matthew S Davids, MD, MMSc

# General Tips for AE Management in CLL

- In the setting of active infection it is generally best to hold drug at least until seeing signs of clinical improvement (possible exception of mild COVID-19)
- For most toxicities requiring drug hold, it is preferable to either re-challenge with full dose or to start back at dose reduction but then get back to full dose
- I am more hesitant to hold drug soon after starting a novel agent or in a patient who is progressing on a novel agent
- I am less concerned about stopping drug in patients who have been on novel agents for at least a few months and are in a good clinical response
- It is generally safe to give growth factor support concomitantly with novel agents
- Patients who have to permanently discontinue a novel agent due to toxicity do not necessarily need to immediately start on a new therapy

Courtesy of Matthew S Davids, MD, MMSc

# Tips for BTKi toxicity management[1]

- Avoid warfarin when anticoagulation needed
- Hypertension: proactively manage with antihypertensives
- Monitor for and manage cardiac arrhythmia/a-fib; treat appropriately
- Monitor patients for signs of bleeding

- Headaches commonly occur early in therapy with acalabrutinib and typically resolved in 1-2 months (manage with acetaminophen + caffeine)
- Monitor for neutropenia (particularly with zanubrutinib), use GCSF prn
- Monitor for infections and secondary malignancies
- Hold perioperatively depending on how significant the procedure is

Courtesy of Matthew S Davids, MD, MMSc

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

# 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<br>Age range | 71 yrs<br>65 - 86 | 57 yrs<br>31 - 70 |
| Infection | 19% | 5% |
| Atrial fibrillation | 6% | 3% |
| Bleeding | 4% | 1% |
| Hypertension | 34% | 7% |
| **Deaths during active treatment + 30 days** | **7%*** | **1%** |

*including patients with presumed sudden cardiac death

Adapted from Shanafelt et al., ASH, 2018

Courtesy of Matthew S Davids, MD, MMSc

# Reasons for Ibrutinib Discontinuation Outside of Clinical Trials

| Most Common Ibrutinib-related Toxicities as Reasons for Discontinuation | |
|---|---|
| **Relapsed CLL (%)** | **Front-line CLL (%)** |
| Atrial fibrillation (12.3) | Arthralgia (41.6) |
| Infection (10.7) | Atrial fibrillation (25) |
| Pneumonitis (9.9) | Rash (16.7) |
| Bleeding (9) | |
| Diarrhea (6.6) | |

| Median Times to Ibrutinib Discontinuation Stratified by Toxicity | |
|---|---|
| Bleeding | 8 months |
| Diarrhea | 7.5 months |
| Atrial fibrillation | 7 months |
| Infection | 6 months |
| Arthralgia | 5 months |
| Pneumonitis | 4.5 months |
| Rash | 3.5 months |

Mato, et al. *Blood.* 2016;128 (22): 3222

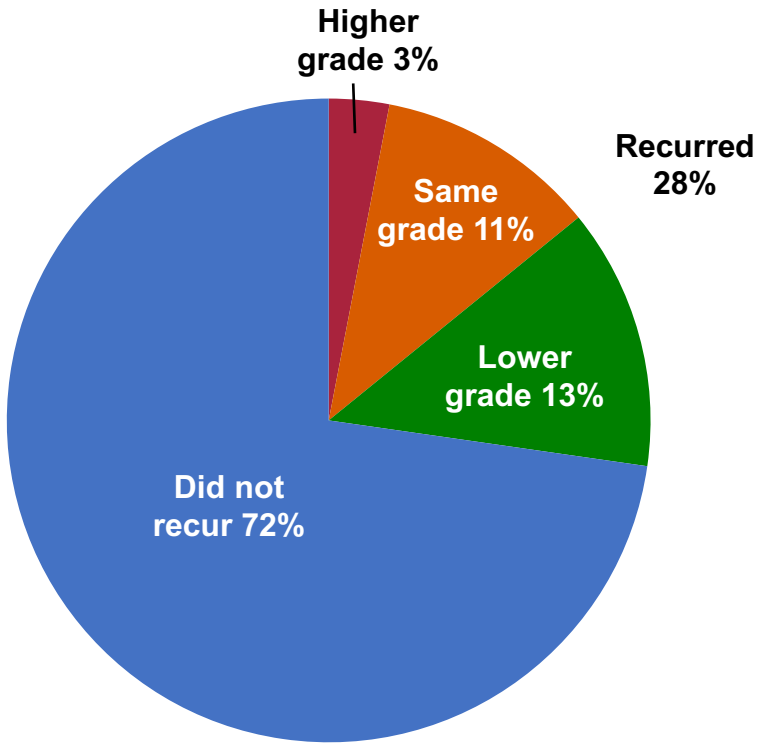
- Ibrutinib discontinuation due to AEs is common in the real-world setting (41% discontinuation at median of 17 mo.)

Mato et al., *Haematologica*, 2018

Courtesy of Matthew S Davids, MD, MMSc

# Acalabrutinib can be well-tolerated in ibrutinib-intolerant patients

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




Recurrence of Ibrutinib-Related Adverse Events (n=61)
During Acalabrutinib Treatment

- ~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

Awan FT, et al. *Blood.* 2019;3(9):1553-1562.

Courtesy of Matthew S Davids, MD, MMSc

# Tips for venetoclax toxicity management

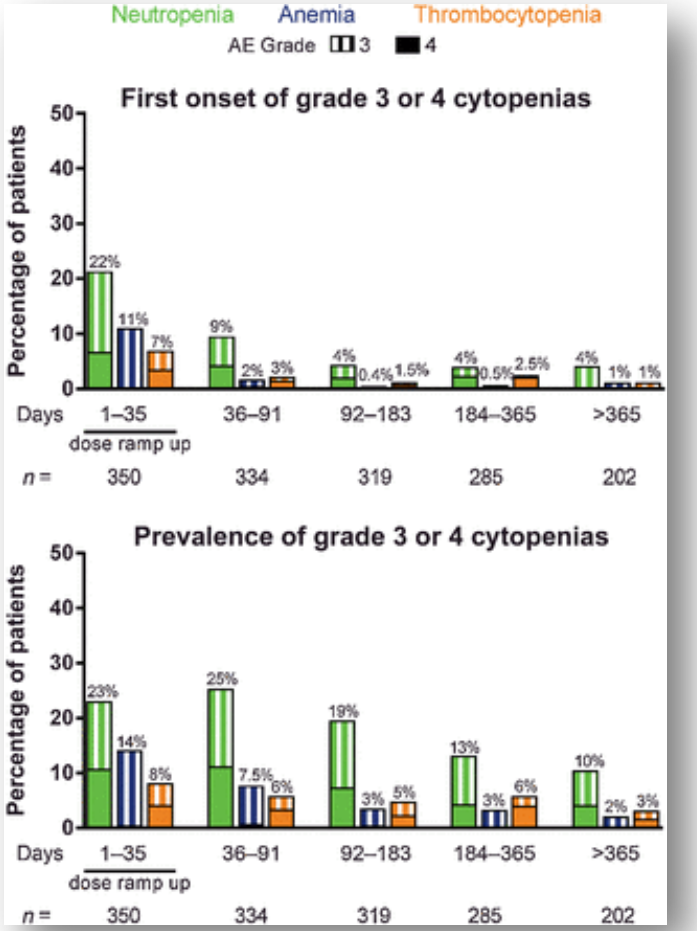
- For neutropenia (e.g. ANC <1,000), it is helpful to give growth factor support (pegfilgrastim when available) and continue venetoclax
  - Individualized frequency based on patient response
- For diarrhea, infectious etiologies should be ruled out and then anti-diarrheals can be used while continuing venetoclax
- For nausea: adjust dose timing and use antiemetics
- Dose interruption and dose reduction can be used for persistent toxicities despite the above measures
- Does **not** need to be held perioperatively

Courtesy of Matthew S Davids, MD, MMSc

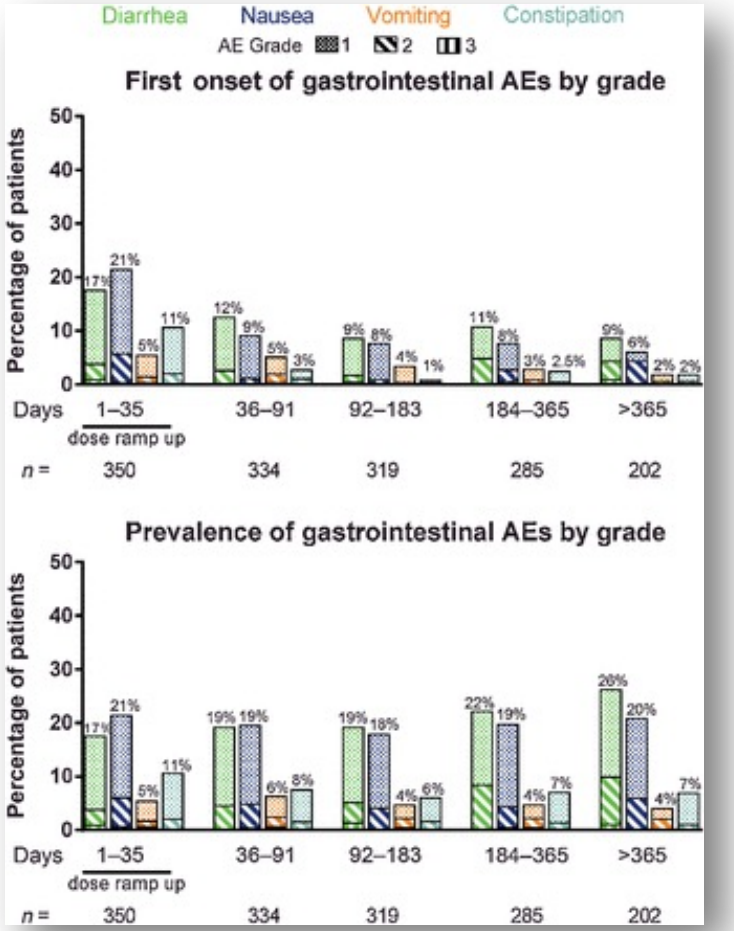
Davids MS. *Blood* 2017;130:1081–1088

# Venetoclax risks tend to decrease over time

## Cytopenias




## GI Toxicities




- **2/166 (1.4%) of patients treated with current dosing algorithm had biochemical laboratory changes in TLS parameters, but none had clinical TLS**

Courtesy of Matthew S Davids, MD, MMSc

Davids MS et al., *Clin Cancer Res*, 2018

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# ASH 2022: Promising investigational agents in CLL

- **BTK Degraders**
  - 965. NX-2127-001, a First-in-Human Trial of **NX-2127**, a Bruton's Tyrosine Kinase-Targeted Protein Degrader, in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia and B-Cell Malignancies
- **Bispecific T cell Engagers**
  - 348. Subcutaneous **Epcoritamab** in Patients with Richter's Syndrome: Early Results from Phase 1b/2 Trial (EPCORE CLL-1)
- **Protein Kinase C β Inhibitor**
  - 963. Initial Results from a Phase 1/2 Dose Escalation and Expansion Study Evaluating **MS-553**, a Novel and Selective PKCβ Inhibitor, in Patients with CLL/SLL
- **ROR1**
  - 1810. First-in-Human Phase I Trial of a ROR1 Targeting Bispecific T Cell Engager (**NVG-111**) in Combination with Ibrutinib or As Monotherapy in Subjects with Relapsed Refractory Chronic Lymphocytic Leukaemia (CLL) and Mantle Cell Lymphoma (MCL)
- **New BCL2i**
  - 962. A Phase 1 Study with the Novel B-Cell Lymphoma 2 (Bcl-2) Inhibitor **Bgb-11417** As Monotherapy or in Combination with Zanubrutinib (ZANU) in Patients (Pts) with CLL/SLL: Preliminary Data
  - 964. **Lisaftoclax** (APG-2575) Safety and Activity As Monotherapy or Combined with Acalabrutinib or Rituximab in Patients (pts) with Treatment-Naïve, Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (R/R CLL/SLL): Initial Data from a Phase 2 Global Study

Courtesy of Lindsey Roeker, MD

# Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

# Multiple Myeloma

**Tuesday, January 10, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Joseph Mikhael, MD, MEd**
**Ajay K Nooka, MD, MPH**

## Moderator

**Neil Love, MD**

RTP Year in Review 2023

*Thank you for joining us!*

*CME and MOC credit information will be emailed to each participant within 5 business days.*

RTP Year in Review 2023