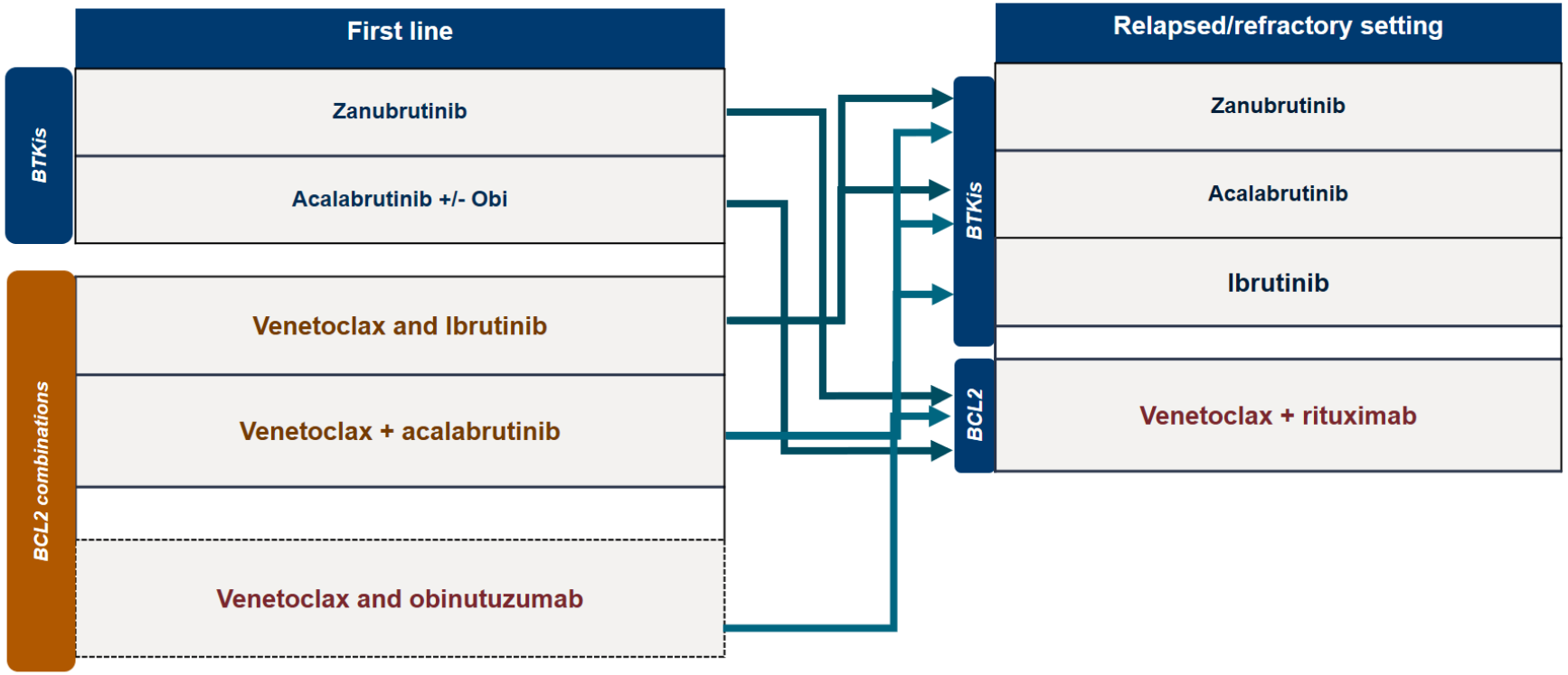
# Biomarkers and Sequencing in CLL

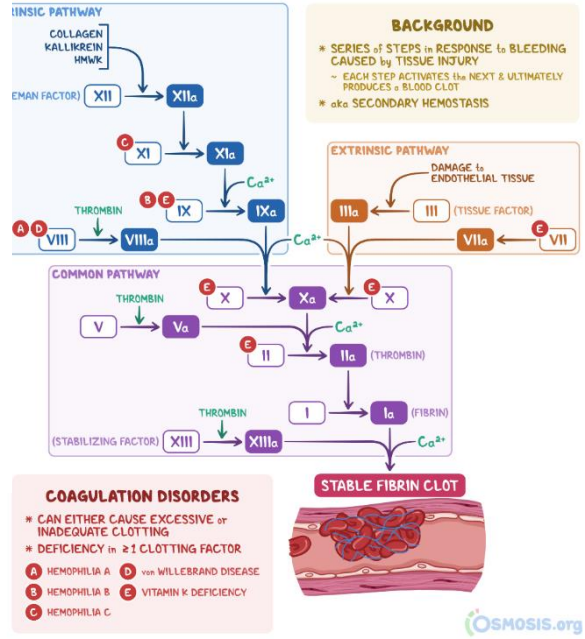
Masa Lasica
Head, CLL and Indolent Lymphoma Service
St Vincent's Hospital, Melbourne

# Disclosures

Advisory Board/Speaker Honoraria: BeOne, Astrazeneca, Janssen, Abbvie, Sobi, Recordati

# The current CLL landscape: PBS-listed options



# CLL characterisation before treatment

- Immunoglobulin heavy chain gene (IGHV) mutational status
- FISH: 17p del
- NGS: TP53 mutation
- Cytogenetics: Complex Karyotype

Ongoing geographic and logistical barriers to access to tests despite reimbursed

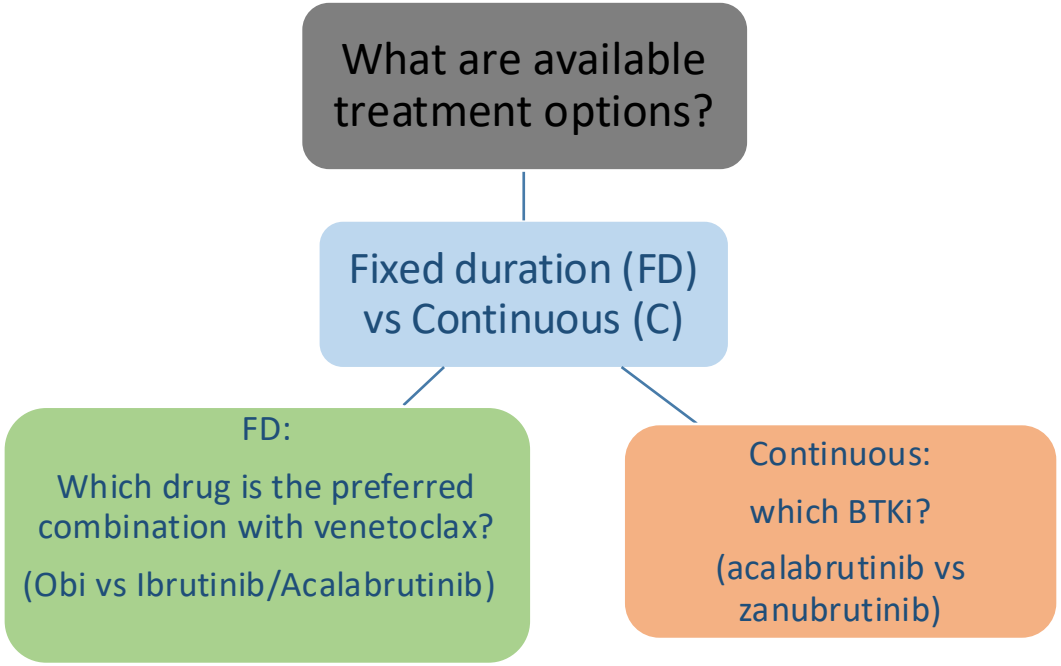
# 1st line therapy dictates what happens down the track
# How to choose

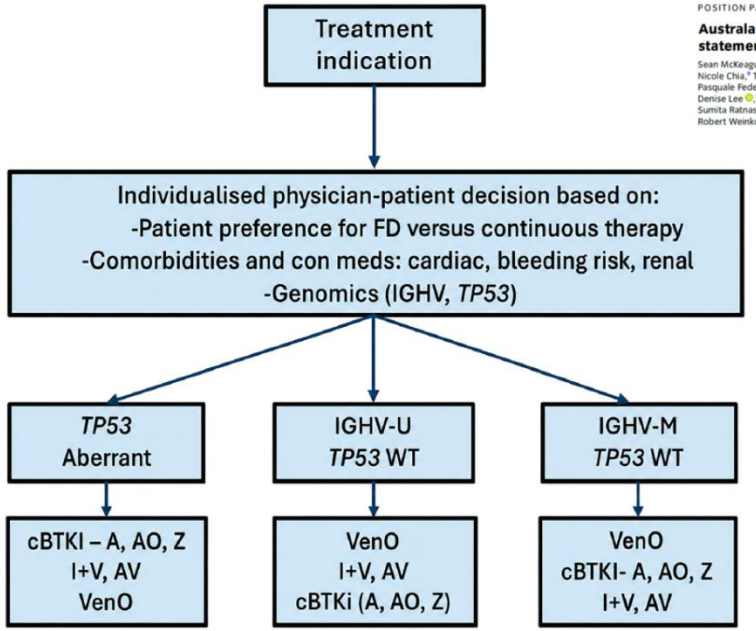
**Genetic information**

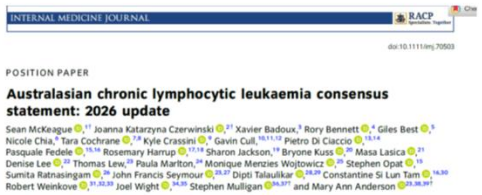
- IGHV mutated vs unmutated
- TP53 WT vs aberrant
- Complex karyotype

**Patient factors**

- Preference
- Co-morbidities
- Life-expectancy
- Social/Geographical factors





INTERNAL MEDICINE JOURNAL

POSITION PAPER

**Australasian chronic lymphocytic leukaemia consensus statement: 2026 update**

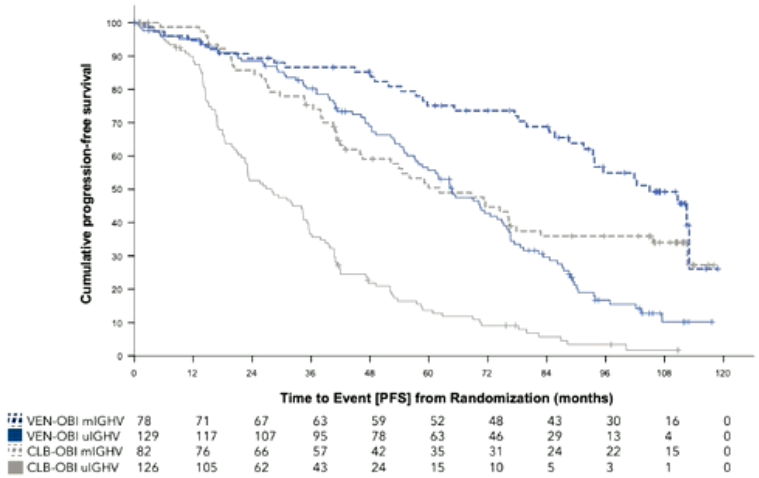
# Good Risk CLL

(IGHV mutated, no high-risk features)

CLL14: 12m Venetoclax-Obi vs Chlor-Obi in 1L CLL in older pts (Median age 72)

GAIA/CLL13: Ven-Obin (+/- I) in younger patient cohort
Median Age 61 (27-84)
TP53 aberrancy excluded
Median FU post EOT: 54m

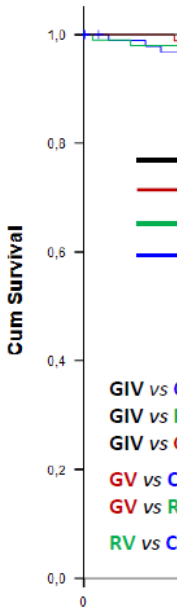
## Progression-Free Survival By IGHV Mutational Status

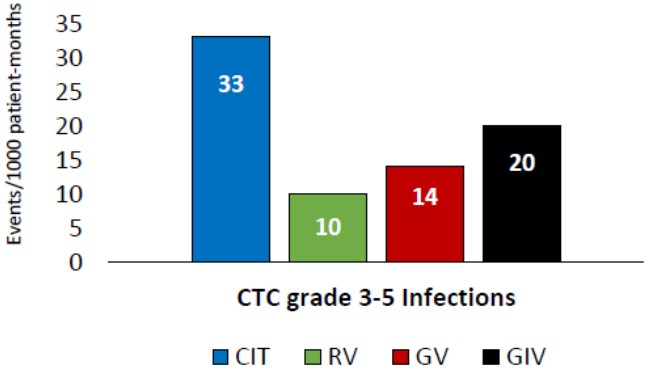


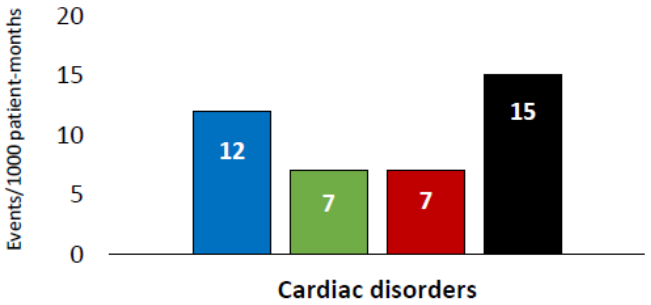

| | |
|---|---|
| MEDIAN OBSERVATION TIME | 110.1 months |
| MEDIAN PFS VEN-OBI & mIGHV | 104.9 months |
| MEDIAN PFS VEN-OBI & uIGHV | 64.7 months |
| HAZARD RATIO | 2.74, 95% CI 1.85-4.06 |
| P VALUE | <0.001 |
| MEDIAN PFS CLB-OBI & mIGHV | 62.2 months |
| MEDIAN PFS CLB-OBI & uIGHV | 28.0 months |
| HAZARD RATIO | 3.13, 95% CI 2.21-4.45 |
| P VALUE | <0.001 |

MEDIAN PFS VEN-OBI mIGHV 8.7 YEARS
MEDIAN PFS VEN-OBI uIGHV 5.4 YEARS

## Incidence rates of certain AEs



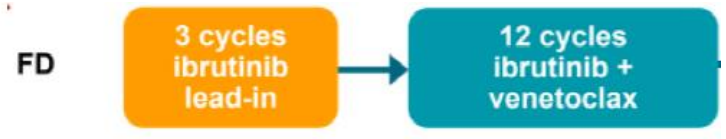

VenO results in long PFS in IGHV mutated CLL
Addition of ibrutinib associated with added toxicity without significant PFS advantage

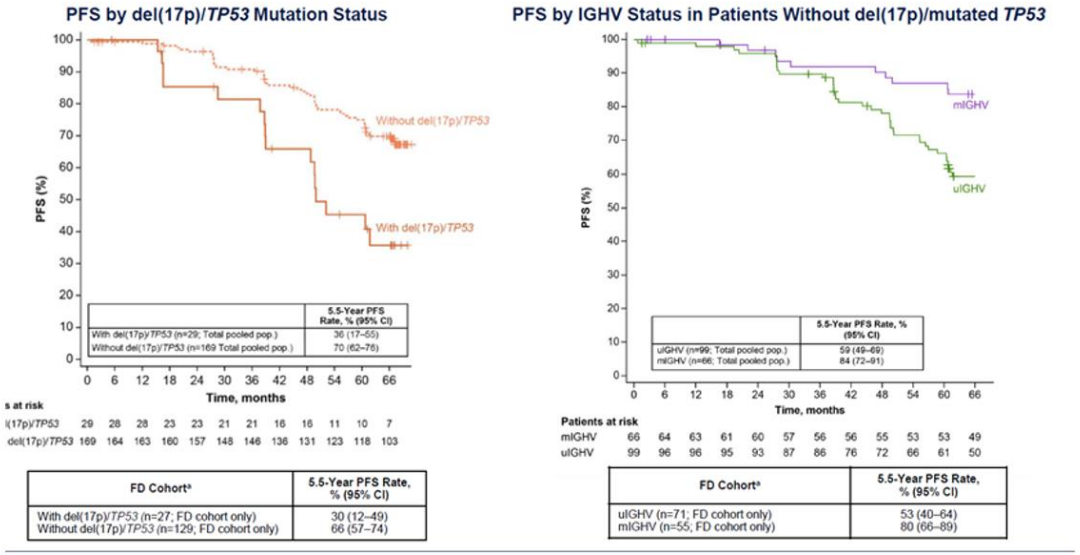
Fischer NEJM 2019 380:2225 ; Al-Sawaf JCO 2021 21.01181; Fürstenau M et al. EHA 2025

## CAPTIVATE: FD Cohort

Median age 60y (33-71)

5.5y PFS in mutated IgHV without del 17p/mutTP53: 84%

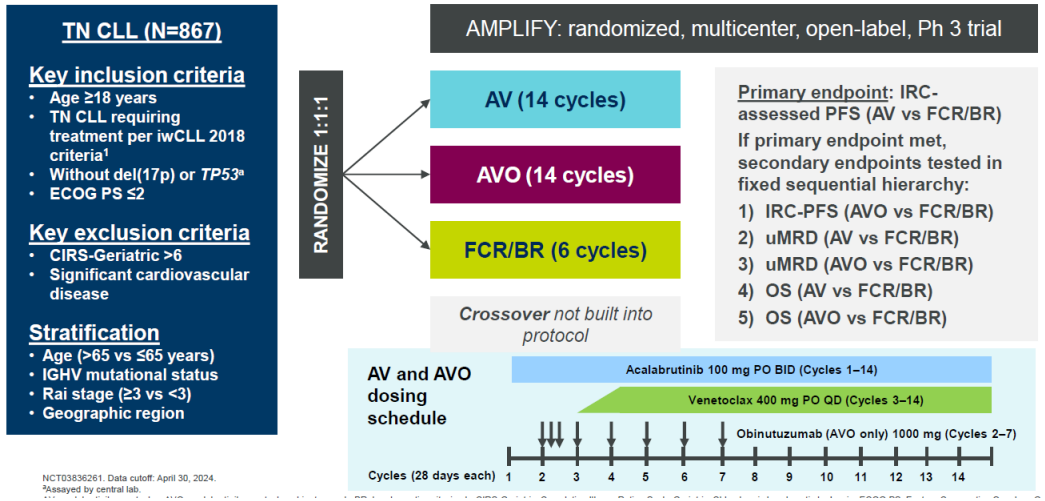






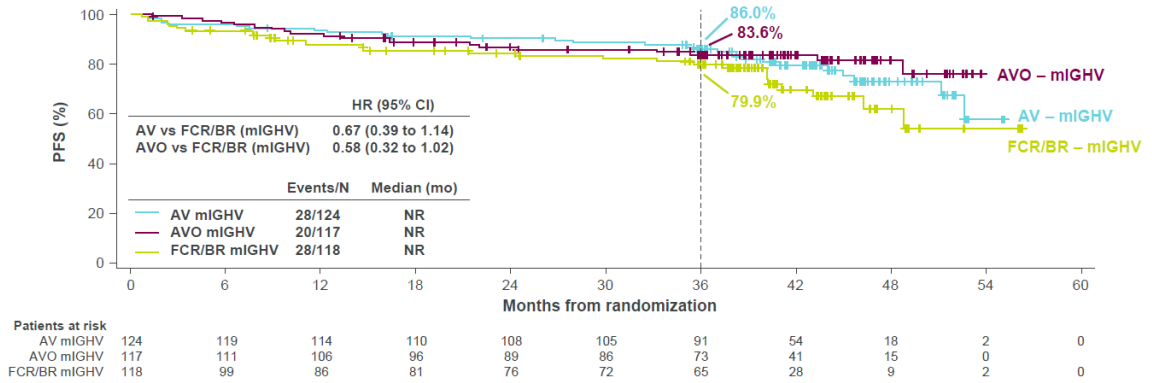
## AMPLIFY Study Design




Interim analysis

Median FU 40.8m

## PFS in the mIGHV Subgroup




mIGHV do very well with FD BTKi/BCL2i

TLS risk reduction and no infusion reactions

Consideration of losing access to PBS obinutuzumab if not accessed in 1L

Ghia P. et al. ICML 2025; Brown J, et al. ASH 2024

# Good risk CLL

INTERNAL MEDICINE JOURNAL

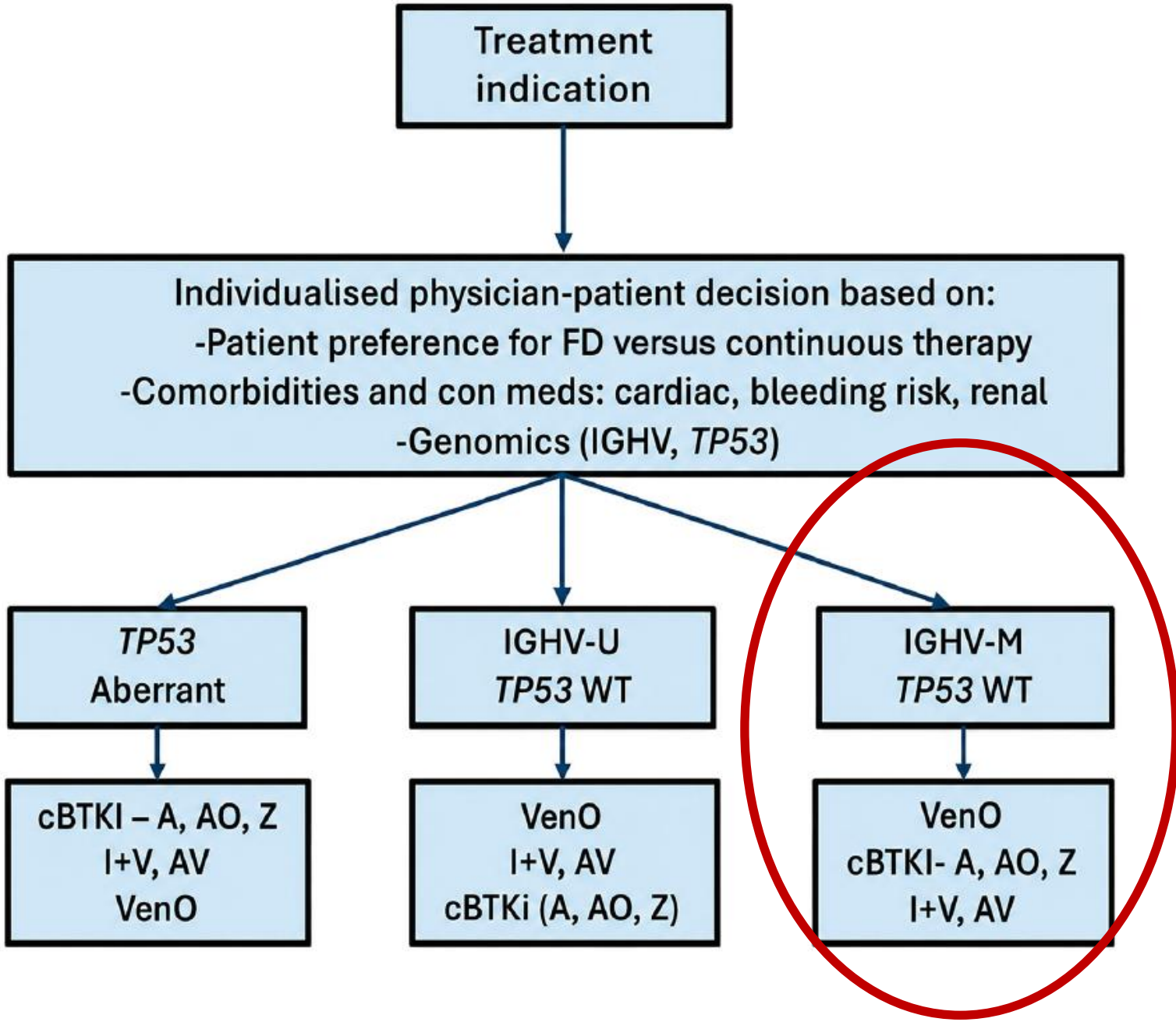
RACP Specialists. Together

doi:10.1111/imj.70503

POSITION PAPER

**Australasian chronic lymphocytic leukaemia consensus statement: 2026 update**

Sean McKeague,[1†] Joanna Katarzyna Czerwinski,[2†] Xavier Badoux,[3] Rory Bennett,[4] Giles Best,[5] Nicole Chia,[6] Tara Cochrane,[7,8] Kyle Crassini,[9] Gavin Cull,[10,11,12] Pietro Di Ciaccio,[13,14] Pasquale Fedele,[15,16] Rosemary Harrup,[17,18] Sharon Jackson,[19] Bryone Kuss,[20] Masa Lasica,[21] Denise Lee,[22] Thomas Lew,[23] Paula Marlton,[24] Monique Menzies Wojtowicz,[25] Stephen Opat,[15] Sumita Ratnasingam,[26] John Francis Seymour,[23,27] Dipti Talaulikar,[28,29] Constantine Si Lun Tam,[16,30] Robert Weinkove,[31,32,33] Joel Wight,[34,35] Stephen Mulligan,[36,37†] and Mary Ann Anderson[23,38,39†]



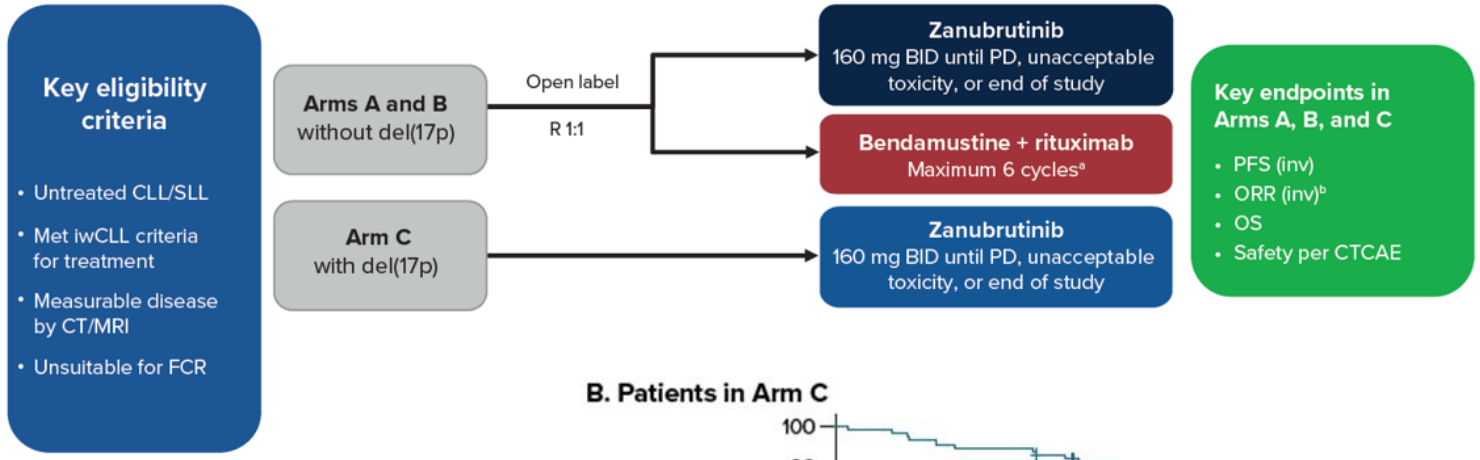
# High risk CLL (TP53 aberrant)?

- If we look at efficacy alone..

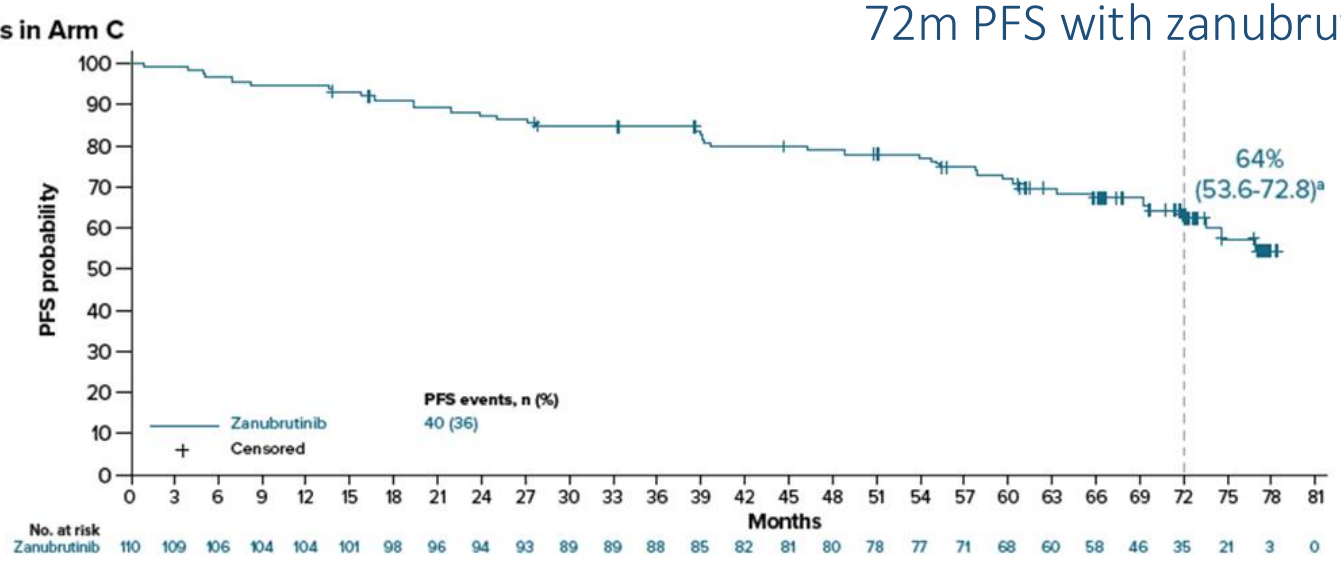
# Sustained efficacy of zanubrutinib vs BR in TN SLL/CLL with continued favorable survival in non-randomized patients with del(17p): 6-year follow-up in the phase 3 SEQUOIA study

Tam S, et al. Poster Presentation at ASH 2025;Poster 2129.

Arm C: Median age 71 (42-87); uIGHV 65%; Complex Karyotype 39%



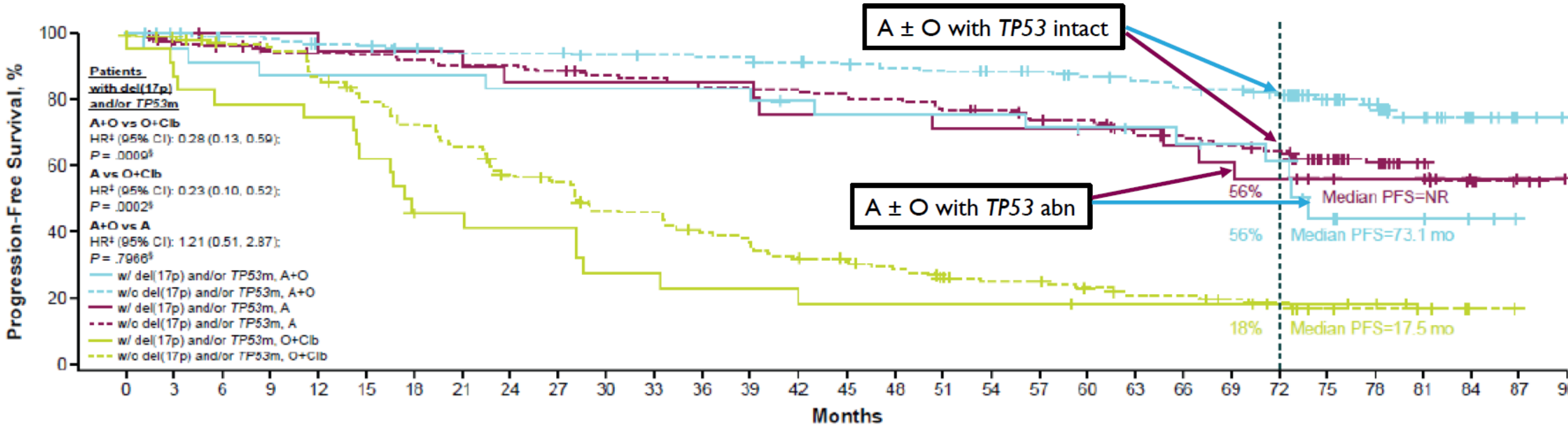

72m PFS with zanubrutinib 64%




Tam et al. Lancet Oncology. 2022. 22;S1460-2045. Tam S, et al. Poster Presentation at ASH 2025;Poster 2129.

# ELEVATE-TN – 6y FU for Acala-Obi in *TP*53 aberrant disease (N=48)

## 6y PFS 56%



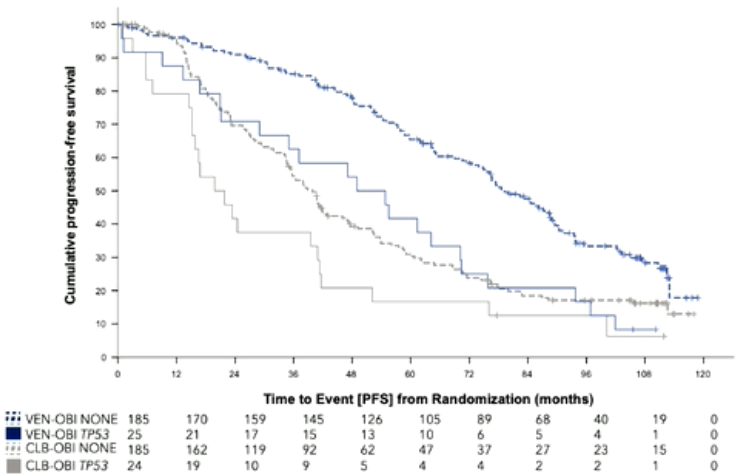

PFS similar in TP53 intact and TP53 aberrant group
No significant benefit from Obinutuzumab

Sharman J et al. Blood. 2025 Sep 11;146(11):1276-1285

# CLL14 (V+O fixed duration)

mPFS by TP53 status 79.2m vs 49m

Progression-Free Survival By *TP53* Del/Mut



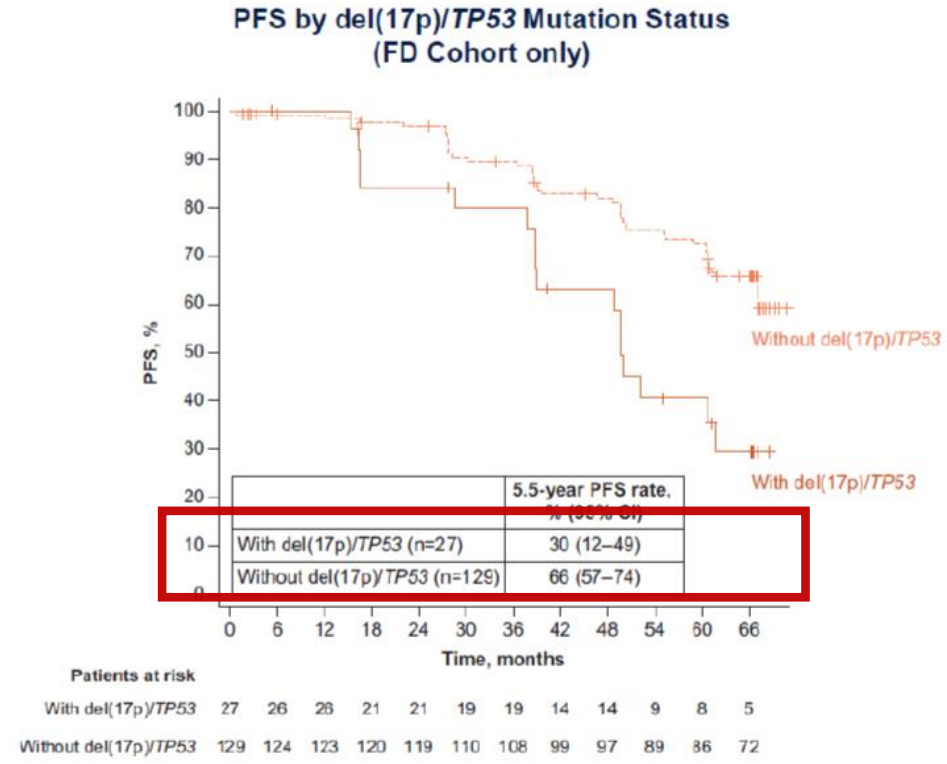

| | |
|---|---|
| MEDIAN OBSERVATION TIME | 110.1 months |
| MEDIAN PFS VEN-OBI & NONE | 79.2 months |
| MEDIAN PFS VEN-OBI & *TP53* | 49.0 months |
| HAZARD RATIO | 2.15, 95% CI 1.36-3.40 |
| P VALUE | =0.001 |
| MEDIAN PFS CLB-OBI & NONE | 39.9 months |
| MEDIAN PFS CLB-OBI & *TP53* | 19.8 months |
| HAZARD RATIO | 1.68, 95% CI 1.07-2.64 |
| P VALUE | =0.024 |

MEDIAN PFS FOR VEN-OBI *TP53*
4.1 YEARS

# CAPTIVATE (I+V fixed duration)

median FU 69m

5.5y PFS rate by TP53 status: 30% vs 66%




Fischer NEJM 2019 380:2225 ; Fisher EHA 2026; Al-Sawaf JCO 2021 21.01181

# CLL17 Study design

**Patients with previously untreated CLL**

1:1:1 randomization
Stratification according to fitness, del17p/*TP53*, IGHV

**Ibrutinib** 420 mg po daily until PD

**Venetoclax** 400 mg po daily (c1 d22 – c12)
**Obinutuzumab** 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)

**Venetoclax** 400 mg po daily (c4 d1 – c15)
**Ibrutinib** 420 mg po daily (c1 d1 – c15)

**976 patients screened, in 174 sites, across 13 countries.**

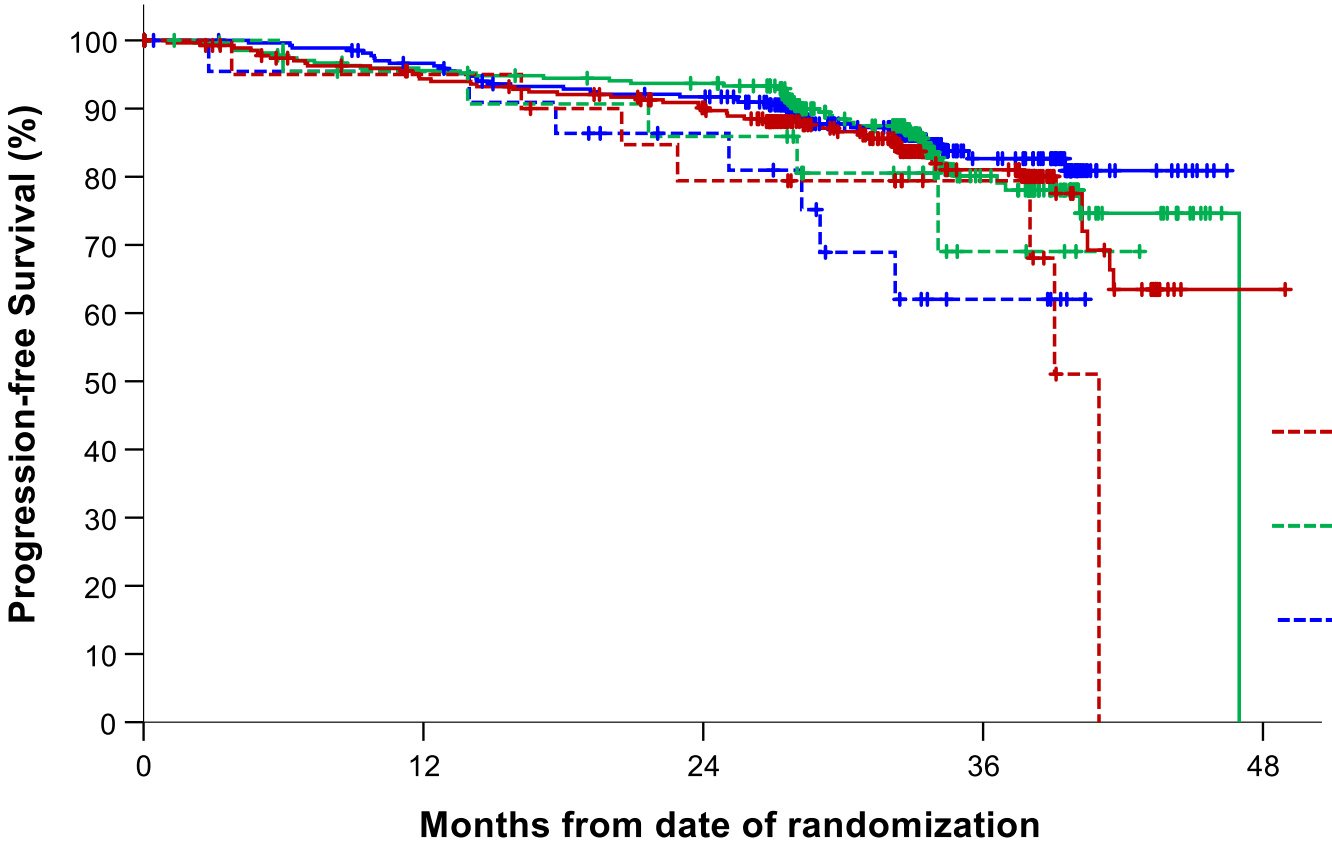
**Patient enrollment from February 2021 to November 2022.**

**Median observation time: 34.2 months (IQR 30.3-39.3)**

*Al Sawaf; ASH; 2025*

# Progression Free Survival

## According to *TP53*/del17p status




**3-year-PFS**

| | | | | |
|---|---|---|---|---|
| ----- | I, *TP53*dys | 79.4% | I, *TP53*-WT | 81.0% |
| ----- | VI, *TP53*dys | 69.0% | VI, *TP53*-WT | 80.1% |
| ----- | VO, *TP53*dys | 62.0% | VO, *TP53*-WT | 82.7% |

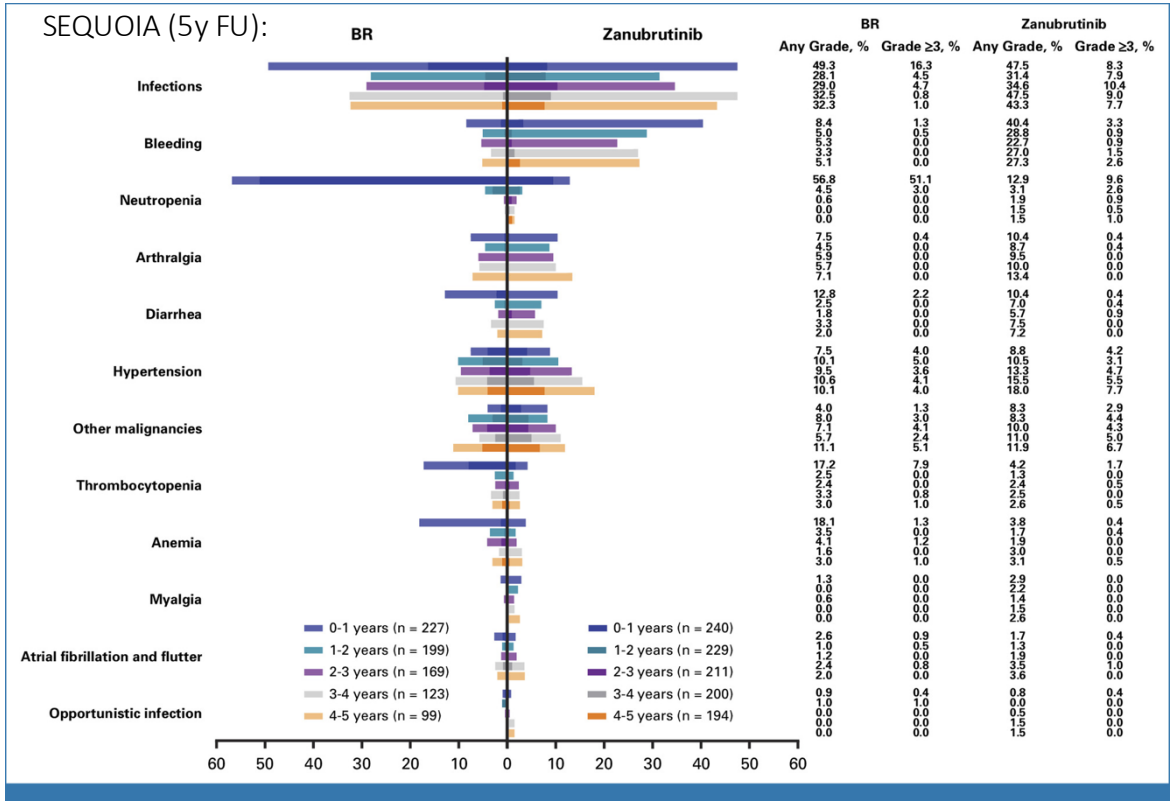
| Patients at risk | | | | | |
|---|---|---|---|---|---|
| VO, del/mut | 23 | 21 | 16 | 5 | 0 |
| VO, WT | 280 | 257 | 240 | 72 | 0 |
| VI, del/mut | 25 | 20 | 18 | 4 | 0 |
| VI, WT | 279 | 257 | 248 | 78 | 0 |
| I, del/mut | 21 | 19 | 15 | 7 | 0 |
| I, WT | 279 | 247 | 227 | 87 | 1 |

***TP53* del/mut:**
VI vs I: HR 0.70, 95% CI 0.22-2.16
VO vs I: HR 1.20, 95% CI 0.40-3.59

*Al Sawaf; ASH; 2025*

# Zanubrutinib toxicity

SEQUOIA (5y FU):



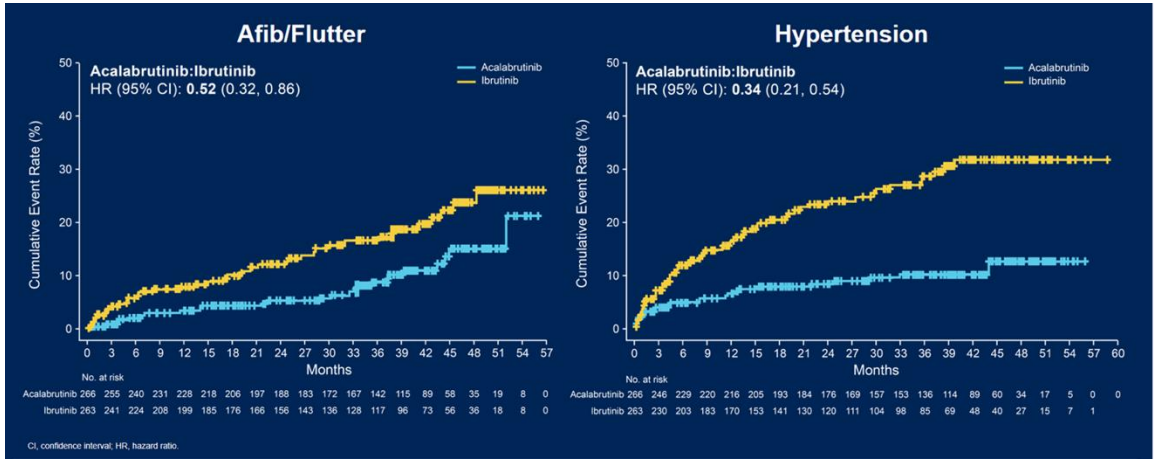

| | BR | | Zanubrutinib | |
|---|---|---|---|---|
| | Any Grade, % | Grade ≥3, % | Any Grade, % | Grade ≥3, % |
| Infections | 49.3 | 16.3 | 47.5 | 8.3 |
| | 28.1 | 4.5 | 31.4 | 7.9 |
| | 29.0 | 4.7 | 34.6 | 10.4 |
| | 32.5 | 0.8 | 47.5 | 9.0 |
| | 32.3 | 1.0 | 43.3 | 7.7 |
| Bleeding | 8.4 | 1.3 | 40.4 | 3.3 |
| | 5.0 | 0.5 | 28.8 | 0.9 |
| | 5.3 | 0.0 | 22.7 | 0.9 |
| | 3.3 | 0.0 | 27.0 | 1.5 |
| | 5.1 | 0.0 | 27.3 | 2.6 |
| Neutropenia | 56.8 | 51.1 | 12.9 | 9.6 |
| | 4.5 | 3.0 | 3.1 | 2.6 |
| | 0.6 | 0.0 | 1.9 | 0.9 |
| | 0.0 | 0.0 | 1.5 | 0.5 |
| | 0.0 | 0.0 | 1.5 | 1.0 |
| Arthralgia | 7.5 | 0.4 | 10.4 | 0.4 |
| | 4.5 | 0.0 | 8.7 | 0.4 |
| | 5.9 | 0.0 | 9.5 | 0.0 |
| | 5.7 | 0.0 | 10.0 | 0.0 |
| | 7.1 | 0.0 | 13.4 | 0.0 |
| Diarrhea | 12.8 | 2.2 | 10.4 | 0.4 |
| | 2.5 | 0.0 | 7.0 | 0.4 |
| | 1.8 | 0.0 | 5.7 | 0.9 |
| | 3.3 | 0.0 | 7.5 | 0.0 |
| | 2.0 | 0.0 | 7.2 | 0.0 |
| Hypertension | 7.5 | 4.0 | 8.8 | 4.2 |
| | 10.1 | 5.0 | 10.5 | 3.1 |
| | 9.5 | 3.6 | 13.3 | 4.7 |
| | 10.6 | 4.1 | 15.5 | 5.5 |
| | 10.1 | 4.0 | 18.0 | 7.7 |
| Other malignancies | 4.0 | 1.3 | 8.3 | 2.9 |
| | 8.0 | 3.0 | 8.3 | 4.4 |
| | 7.1 | 4.1 | 10.0 | 4.3 |
| | 5.7 | 2.4 | 11.0 | 5.0 |
| | 11.1 | 5.1 | 11.9 | 6.7 |
| Thrombocytopenia | 17.2 | 7.9 | 4.2 | 1.7 |
| | 2.5 | 0.0 | 1.3 | 0.0 |
| | 2.4 | 0.0 | 2.4 | 0.5 |
| | 3.3 | 0.8 | 2.5 | 0.0 |
| | 3.0 | 1.0 | 2.6 | 0.5 |
| Anemia | 18.1 | 1.3 | 3.8 | 0.4 |
| | 3.5 | 0.0 | 1.7 | 0.4 |
| | 4.1 | 1.2 | 1.9 | 0.0 |
| | 1.6 | 0.0 | 3.0 | 0.0 |
| | 3.0 | 1.0 | 3.1 | 0.5 |
| Myalgia | 1.3 | 0.0 | 2.9 | 0.0 |
| | 0.0 | 0.0 | 2.2 | 0.0 |
| | 0.6 | 0.0 | 1.4 | 0.0 |
| | 0.0 | 0.0 | 1.5 | 0.0 |
| | 0.0 | 0.0 | 2.6 | 0.0 |
| Atrial fibrillation and flutter | 2.6 | 0.9 | 1.7 | 0.4 |
| | 1.0 | 0.5 | 1.3 | 0.0 |
| | 1.2 | 0.0 | 1.9 | 0.0 |
| | 2.4 | 0.8 | 3.5 | 1.0 |
| | 2.0 | 0.0 | 3.6 | 0.0 |
| Opportunistic infection | 0.9 | 0.4 | 0.8 | 0.4 |
| | 1.0 | 1.0 | 0.0 | 0.0 |
| | 0.0 | 0.0 | 0.5 | 0.0 |
| | 0.0 | 0.0 | 1.5 | 0.0 |
| | 0.0 | 0.0 | 1.5 | 0.0 |

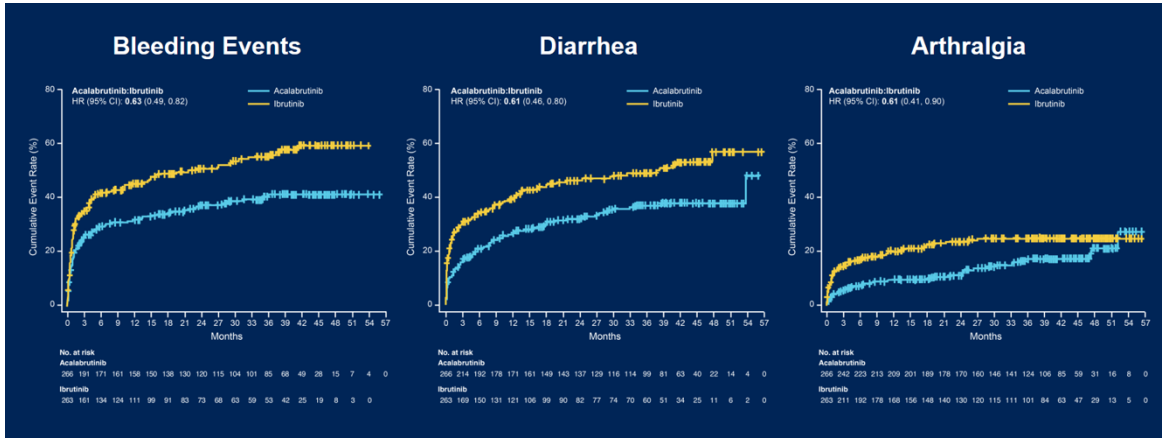
- Median age 70y
- Infection Gr ≥3 unchanged over time
- HTN increased over time
- AF/flutter low rates and slight increase over time
- Diarrhoea and arthralgia persistent

| ALPINE study | zanubrutinib | ibrutinib |
|---|---|---|
| Cardiac events (%) | 25.9% | 35.5% |
| Atrial Fibrillation/flutter (%) | 7.1% | 17.0% |
| Discontinuations due to cardiac events (%) | 0.9% | 4.9% |
| Death due to cardiac AEs (n) | no deaths | 6 deaths |

Shadman M et al. JCO. 2024; Brown JR et al. Blood. 2024; **Byrd JC et al. J Clin Oncol 2021**

# Acalabrutinib toxicity



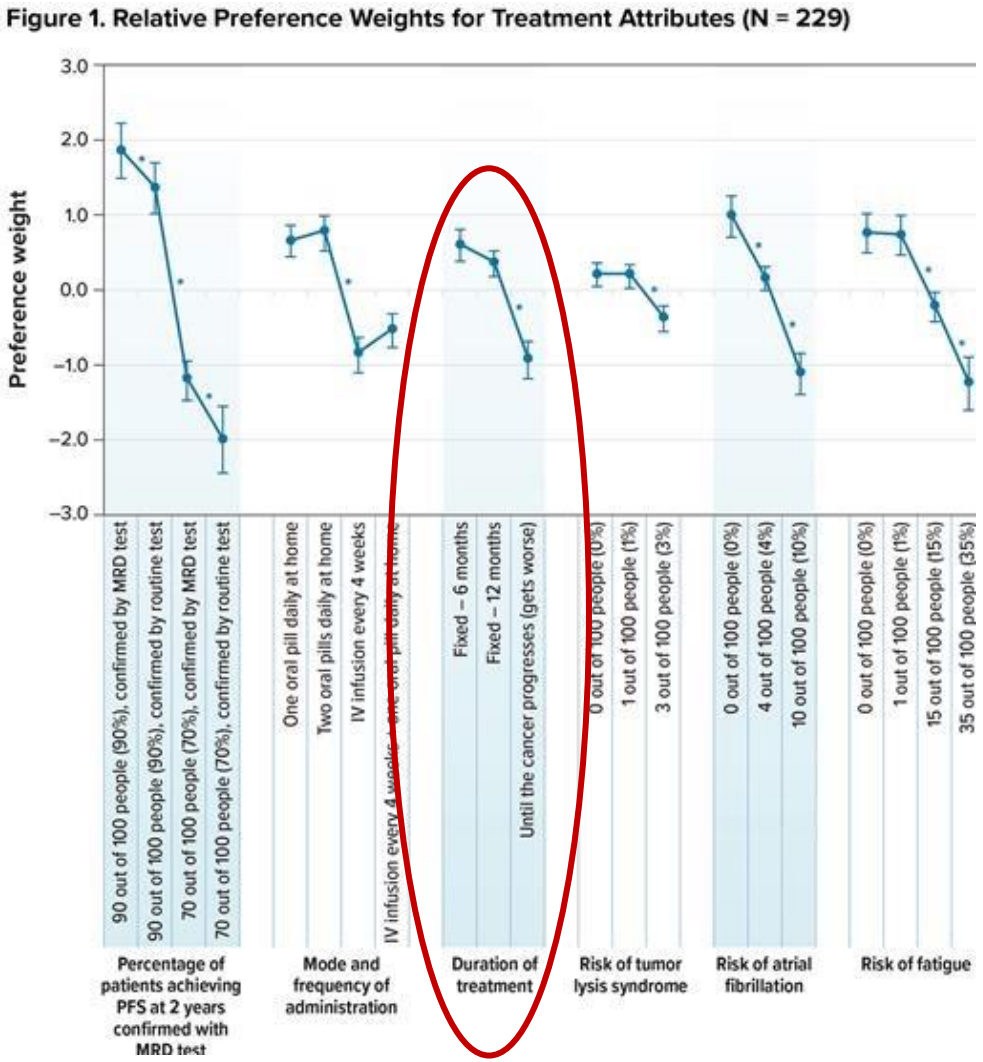




| Toxicity | Ibrutinib (n=263) | Acalabrutinib (n=266) |
|---|---|---|
| Death due to cardiac cause | 2 | 1 |
| Cardiac events | 30% | 24.1% |
| AE-related discontinuation of treatment | 21.3% | 14.7% |

# Patient perspective

With respect to treatment discontinuation:

- each additional grade 2 AE was associated with a 59% increased odds of treatment discontinuation (95% CrI, 1.32 to 1.95),




O'Connell N et al. J Clin Oncol 2023

Ravelo A, et al. ASH 2022

INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

doi:10.1111/imj.70503

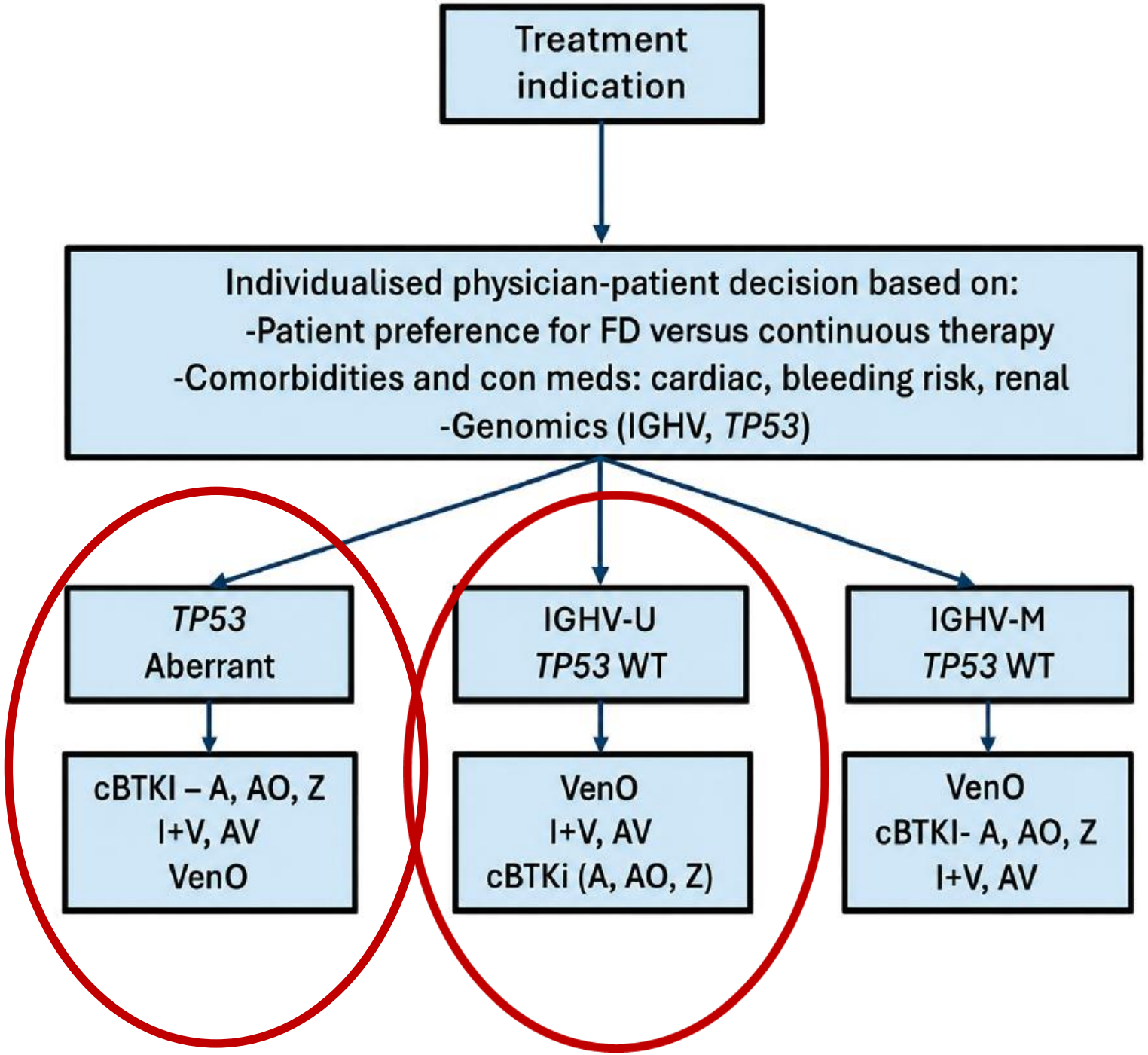
POSITION PAPER

**Australasian chronic lymphocytic leukaemia consensus statement: 2026 update**

Sean McKeague,[1†] Joanna Katarzyna Czerwinski,[2†] Xavier Badoux,[3] Rory Bennett,[4] Giles Best,[5] Nicole Chia,[6] Tara Cochrane,[7,8] Kyle Crassini,[9] Gavin Cull,[10,11,12] Pietro Di Ciaccio,[13,14] Pasquale Fedele,[15,16] Rosemary Harrup,[17,18] Sharon Jackson,[19] Bryone Kuss,[20] Masa Lasica,[21] Denise Lee,[22] Thomas Lew,[23] Paula Marlton,[24] Monique Menzies Wojtowicz,[25] Stephen Opat,[15] Sumita Ratnasingam,[26] John Francis Seymour,[23,27] Dipti Talaulikar,[28,29] Constantine Si Lun Tam,[16,30] Robert Weinkove,[31,32,33] Joel Wight,[34,35] Stephen Mulligan,[36,37†] and Mary Ann Anderson[23,38,39†]

# CLL with TP53 aberrancy

- BTKi associated with superior PFS but requires long-term therapy incl cumulative toxicity
- Fixed duration therapy associated with shorter responses but PFS decent and treatment-holiday
- Resistance mutations rare and encouraging early data on re-treatment
- Patient factors and preferences play a significant role



# What to do in relapsed disease?

# Relapsed disease

INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

doi:10.1111/imj.70503

POSITION PAPER

**Australasian chronic lymphocytic leukaemia consensus statement: 2026 update**

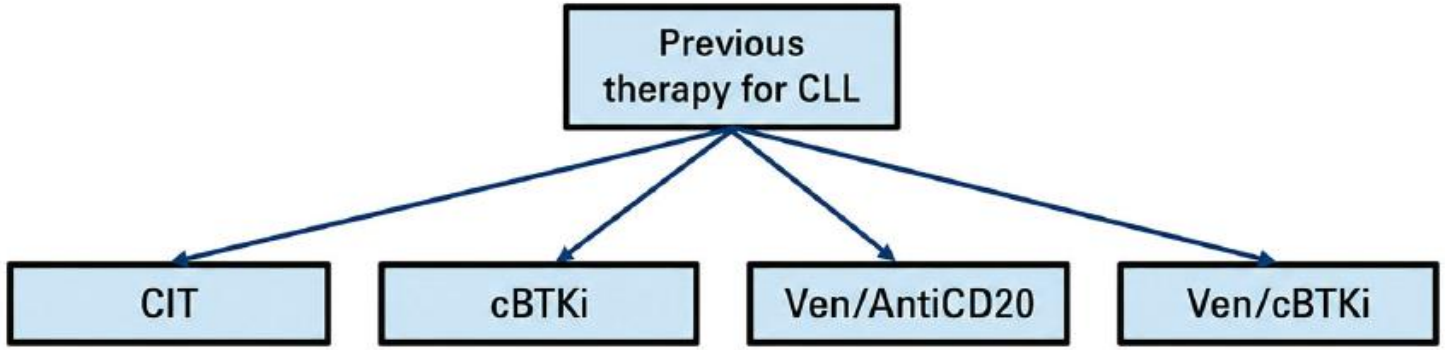
Sean McKeague,[1†] Joanna Katarzyna Czerwinski,[2†] Xavier Badoux,[3] Rory Bennett,[4] Giles Best,[5] Nicole Chia,[6] Tara Cochrane,[7,8] Kyle Crassini,[9] Gavin Cull,[10,11,12] Pietro Di Ciaccio,[13,14] Pasquale Fedele,[15,16] Rosemary Harrup,[17,18] Sharon Jackson,[19] Bryone Kuss,[20] Masa Lasica,[21] Denise Lee,[22] Thomas Lew,[23] Paula Marlton,[24] Monique Menzies Wojtowicz,[25] Stephen Opat,[15] Sumita Ratnasingam,[26] John Francis Seymour,[23,27] Dipti Talaulikar,[28,29] Constantine Si Lun Tam,[16,30] Robert Weinkove,[31,32,33] Joel Wight,[34,35] Stephen Mulligan[36,37†] and Mary Ann Anderson[23,38,39†]

## Questions

1. What were the prior lines of therapy

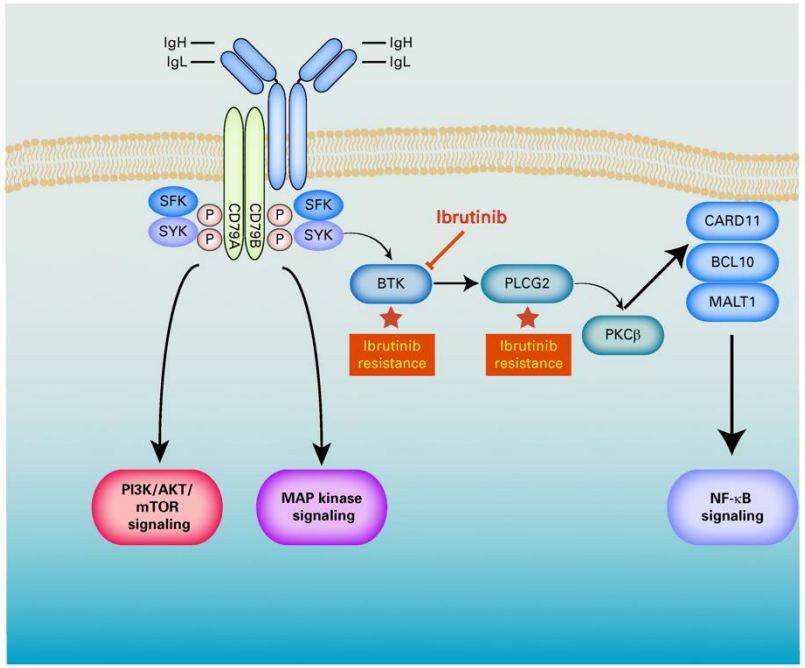
2. Exposed or Refractory
   a) Relapse post limited-duration therapy without on-target mutations
   b) Relapse on continuous therapy often with on-target mutations

3. Tolerance

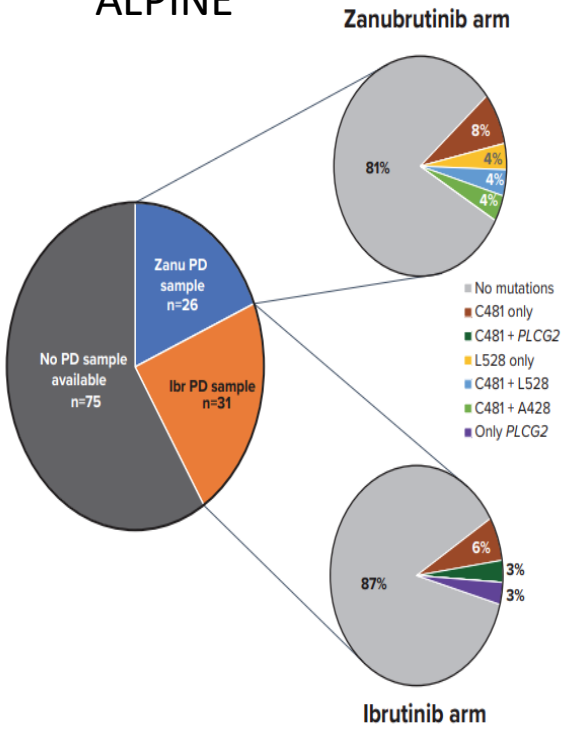


# Relapsed CLL after continuous BTKi therapy

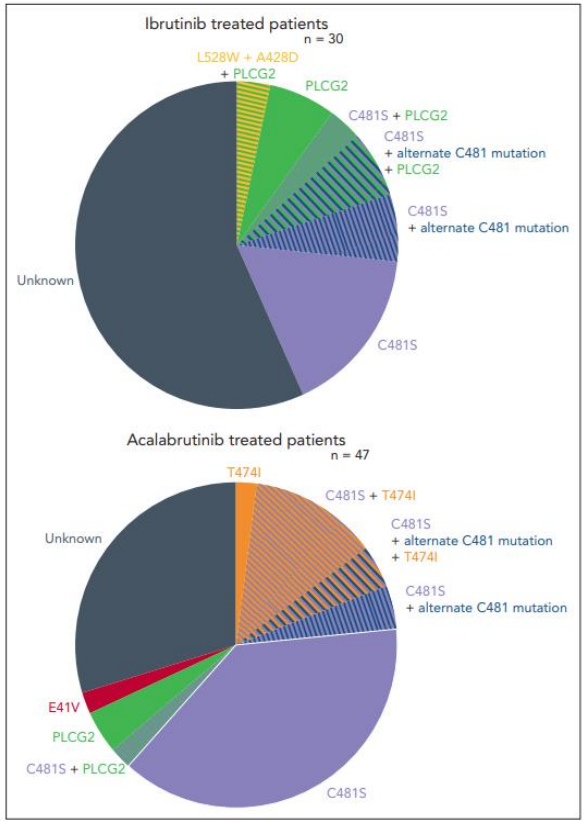
- BTK (esp C481) and PLCG2 mutations key drivers of BTKi-refractory disease
- BTK C481 mutations prevent BTKi from binding to target
- Mutational profile variable btw different cBTKi. Non C481 mutations more prevalent after acala and zanu than ibrutinib




ALPINE




ELEVATE RR




Lenz, JCO, 2017; Woyach,Blood,2024; Roeker, Blood,2024; Brown,ASH,2024

# BTKi resistance profiles relevant to treatment choice

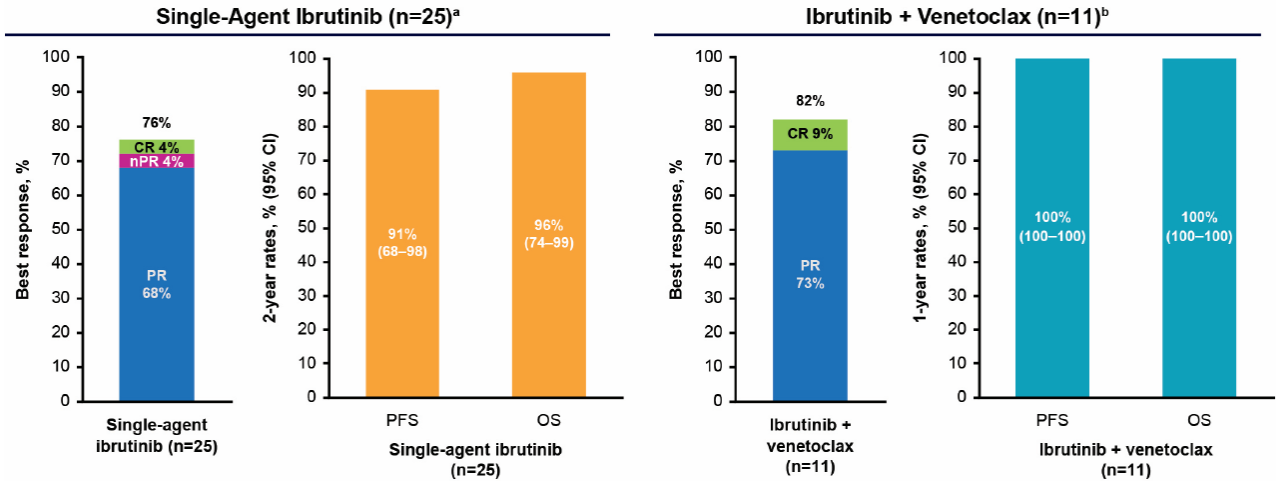
| | | Wild-Type | C481S | T474I | L528W | A428D |
|---|---|---|---|---|---|---|
| Covalent BTKi | Ibrutinib | Normal | Decreased | Normal | Absent | Absent |
| | Acalabrutinib | Normal | Decreased | Decreased | Decreased | Absent |
| | Zanubrutinib | Normal | Decreased | Decreased | Absent | Absent |
| Non-covalent BTKi | Pirtobrutinib | Normal | Normal | Decreased | Absent | Absent |
| Dual covalent + noncovalent BTKi | LP-168 | Normal | Normal | Normal | Absent | Absent |
| BTK Degraders | BGB-16673<br>NX-5948 | Normal | Normal | Normal | Normal | Normal |

Jacobs, Cancers, 2025

# Relapse after limited-duration venetoclax-based therapy

## CAPTIVATE 5.5y FU: no resistance-associated mutations identified at PD

- In the total pooled population (FD and MRD-placebo cohorts) with a median follow-up of more than 5.5 years, 64/202 patients (32%) had PD after FD ibrutinib + venetoclax treatment
- No patients had resistance-associated mutations in *BTK* or *PLCG2* at PD among 53 patients with available samples
- Two patients were found with a subclonal *BCL2 A113G* mutation of unclear significance at PD: variant allele frequencies were only 8% and 9.3%, respectively
  - Patient 1: Achieved partial response with FD ibrutinib + venetoclax retreatment (complete response was not confirmed due to missing bone marrow assessment).
    - *BCL2 A113G* mutation was not detectable at the time of eventual relapse after retreatment[a]
  - Patient 2: Did not receive retreatment in the study



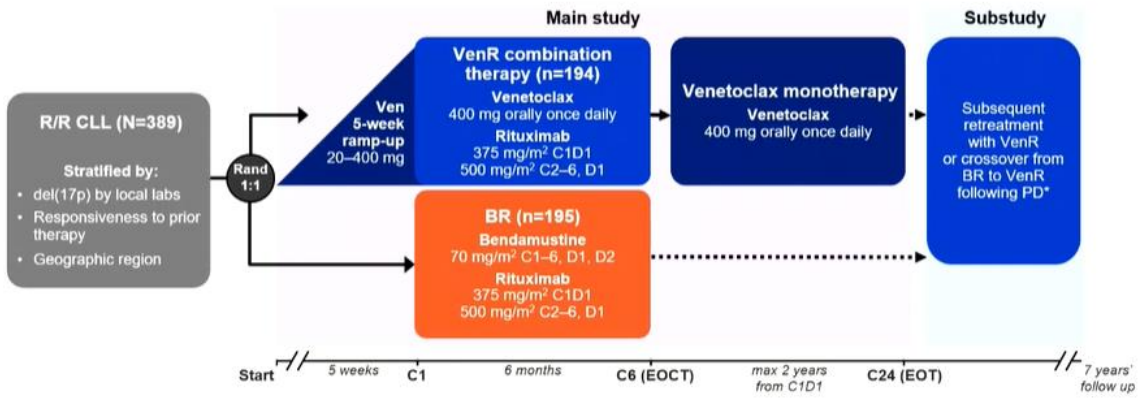

| | Single-agent ibrutinib | FD ibrutinib + venetoclax |
|---|---|---|
| Median duration of follow-up, months (range) | 28.4 (3.7–59.1) | 15.2 (7.4–29.3) |
| Median duration of retreatment, months (range) | 27.0 (1.1–59.1) | 13.8 (6.7–18.3) |

Wierda WG, EHA, 2025; adapted from P. Thompson slide

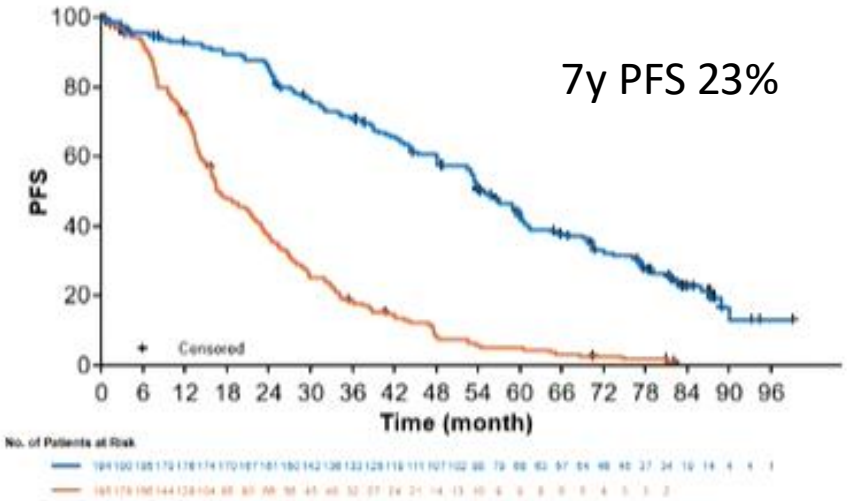
# Venetoclax re-treatment after limited-duration therapy

## MURANO (NCT02005471): study design and prior findings

- Global, Phase III, open-label, randomized study[1]




| | Median PFS (95% CI), months | HR* (95% CI) | 7-year PFS (%) |
|---|---|---|---|
| VenR (n=194) | 54.7 (52.3–59.9) | 0.23 (0.18–0.29) Stratified P-value <0.0001† | 23.0 |
| BR (n=195) | 17.0 (15.5–21.7) | | NE |




7y PFS 23%

VenR-treated patients who achieved **undetectable minimal residual disease** (MRD) (n = 83):


uMRD: median 5.2y until next treatment

Sub-study: VenR re-treatment (n=25)
ORR: 72%, mPFS 23.3m

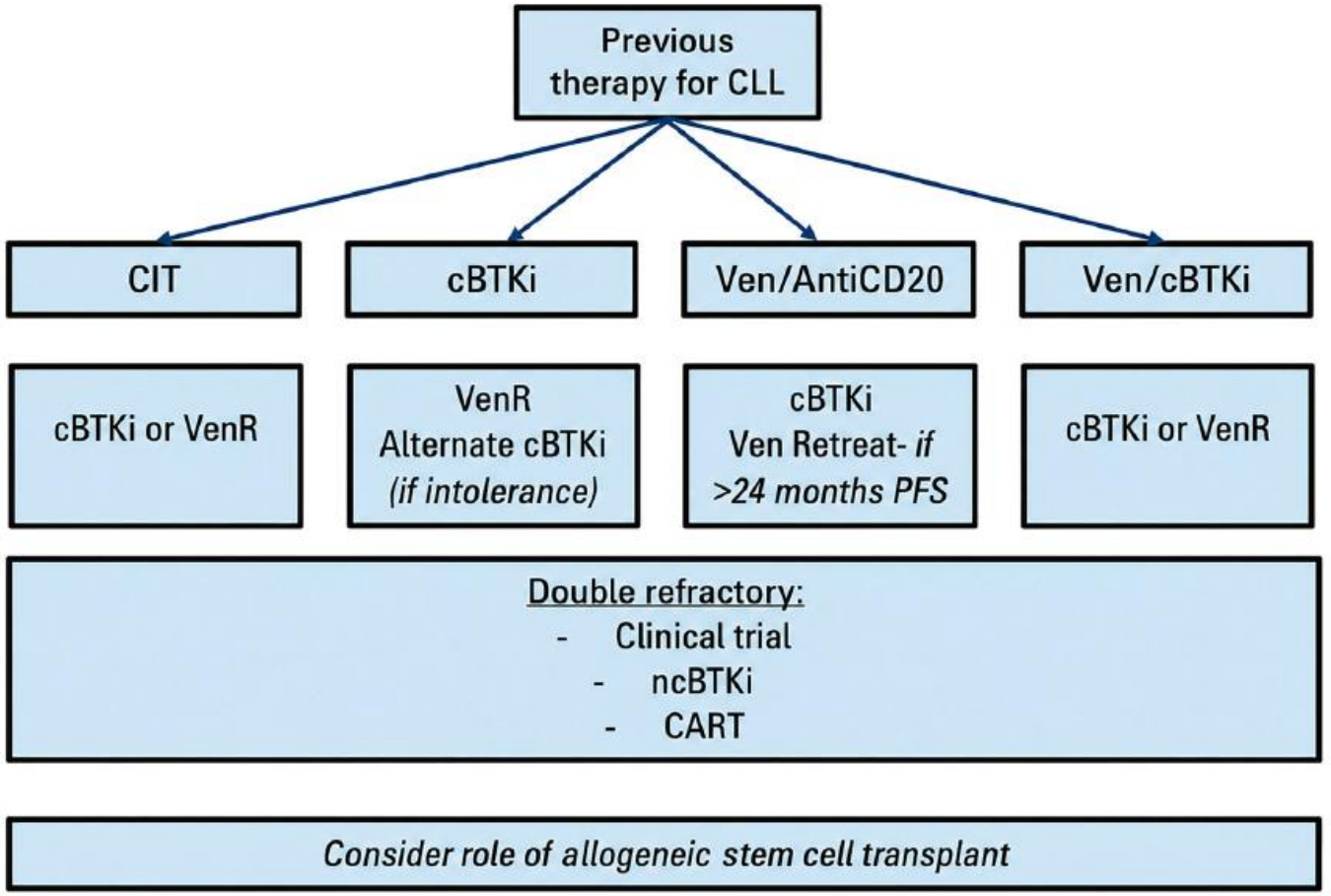
Kater, ASH, 2025

# Questions

1. What were the prior lines of therapy

2. Exposed or Refractory
   a) Relapse post limited-duration therapy without on-target mutations
   b) Relapse on continuous therapy often with on-target mutations

3. Tolerance




INTERNAL MEDICINE JOURNAL
RACP Specialists. Together
doi:10.1111/imj.70503

POSITION PAPER

**Australasian chronic lymphocytic leukaemia consensus statement: 2026 update**

Sean McKeague,[1†] Joanna Katarzyna Czerwinski,[2†] Xavier Badoux,[3] Rory Bennett,[4] Giles Best,[5] Nicole Chia,[6] Tara Cochrane,[7,8] Kyle Crassini,[9] Gavin Cull,[10,11,12] Pietro Di Ciaccio,[13,14] Pasquale Fedele,[15,16] Rosemary Harrup,[17,18] Sharon Jackson,[19] Bryone Kuss,[20] Masa Lasica,[21] Denise Lee,[22] Thomas Lew,[23] Paula Marlton,[24] Monique Menzies Wojtowicz,[25] Stephen Opat,[15] Sumita Ratnasingam,[26] John Francis Seymour,[23,27] Dipti Talaulikar,[28,29] Constantine Si Lun Tam,[16,30] Robert Weinkove,[31,32,33] Joel Wight,[34,35] Stephen Mulligan,[36,37†] and Mary Ann Anderson[23,38,39†]

# Summary

- First line dictates the downstream treatment pathway
- Genomic profile plays a role
- But patient preferences, patient factors (co-morbidities, social circumstances and geography) are key
- No wrong option
- Genomic “re-staging” before each new line if it will change management