
# *LA TERAPIA DELLA LLC IN PRIMA LINEA*

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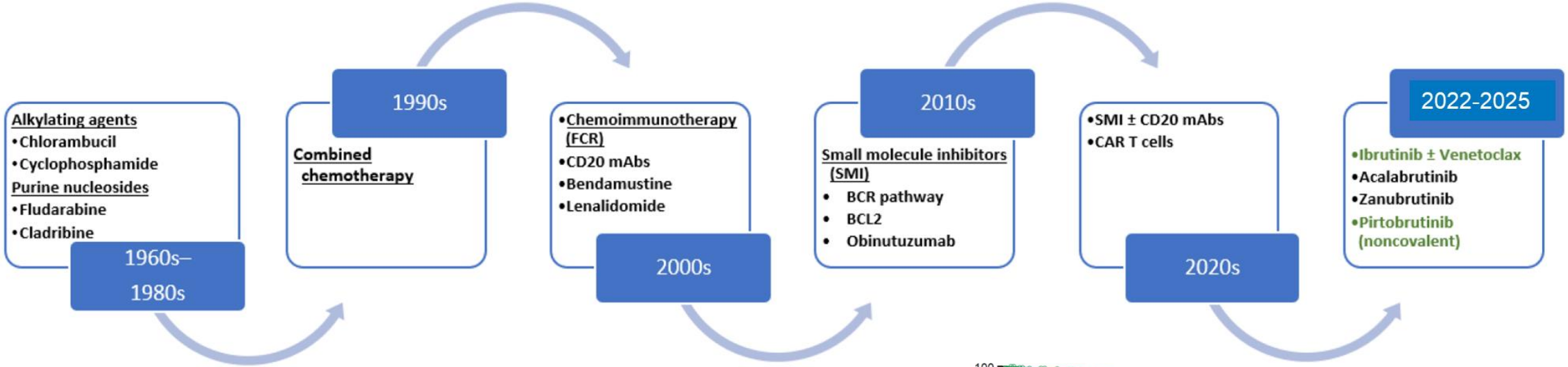
ASST GOM Niguarda

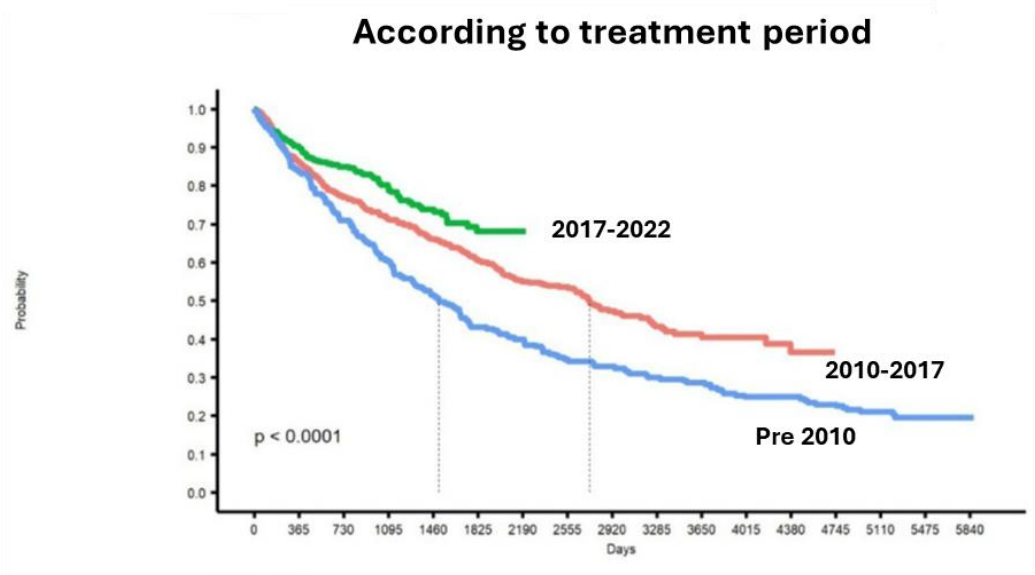
03/10/2025

# Disclosures

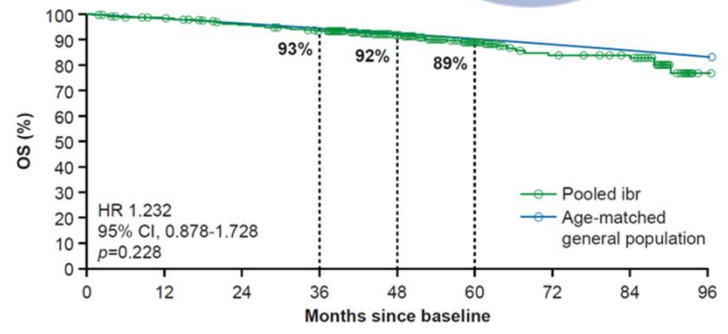
| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Conferences sponsorship |
|---|---|---|---|---|---|---|---|
| Janssen | | | X | | | X | X |
| Beigene | | | X | | | X | X |
| Abbvie | | | | | | X | X |
| AstraZeneca | | | | | | X | X |

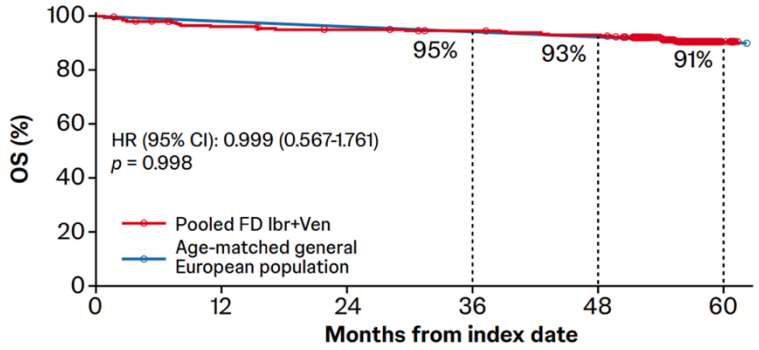
# The successful history of CLL



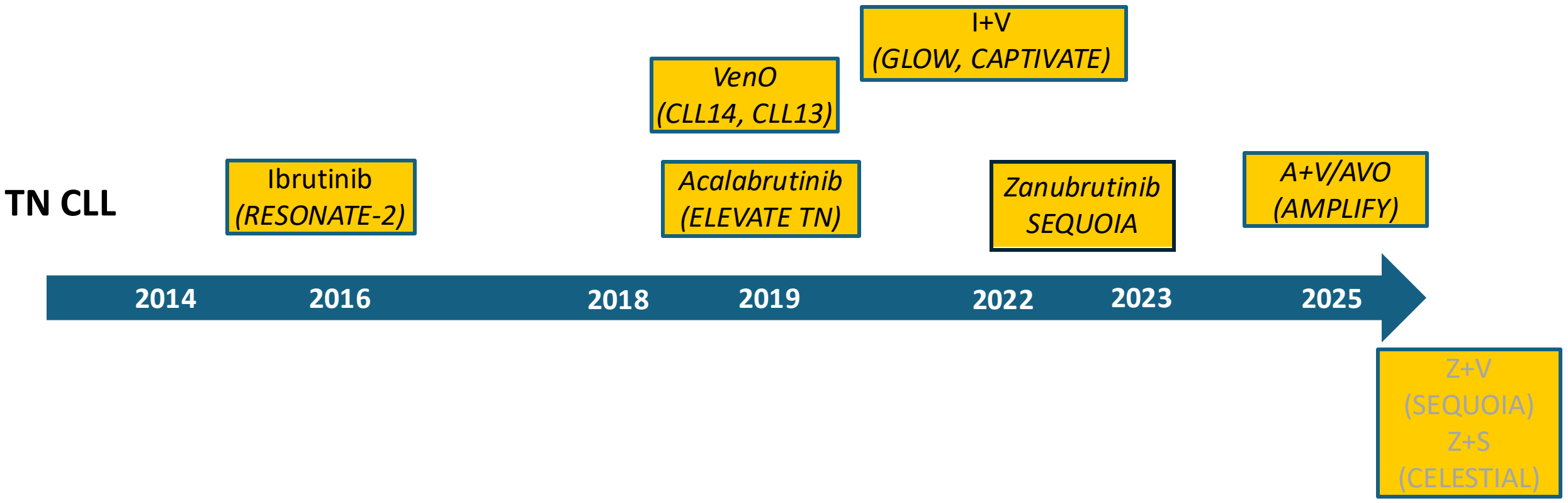




*Tadmor, Hemasphere 2023*



# Chemo-free world: key protocols with targeted agents



# Current treatment scenario in first line

## Continous cBTKi

| | |
|---|---|
| *RESONATE 2*<br>*ALLIANCE*<br>*ECOG1912* | **Ibrutinib** |
| *ELEVATE TN* | **Acalabrutinib** |
| *SEQUOIA*<br>*SEQUOIA ARM C* | **Zanubrutinib** |

## Fixed-duration

| | |
|---|---|
| **Venetoclax + Obinutuzumab** | *CLL13*<br>*CLL14* |
| **Venetoclax + Ibrutinib** | *CAPTIVATE*<br>*GLOW* |

17p-

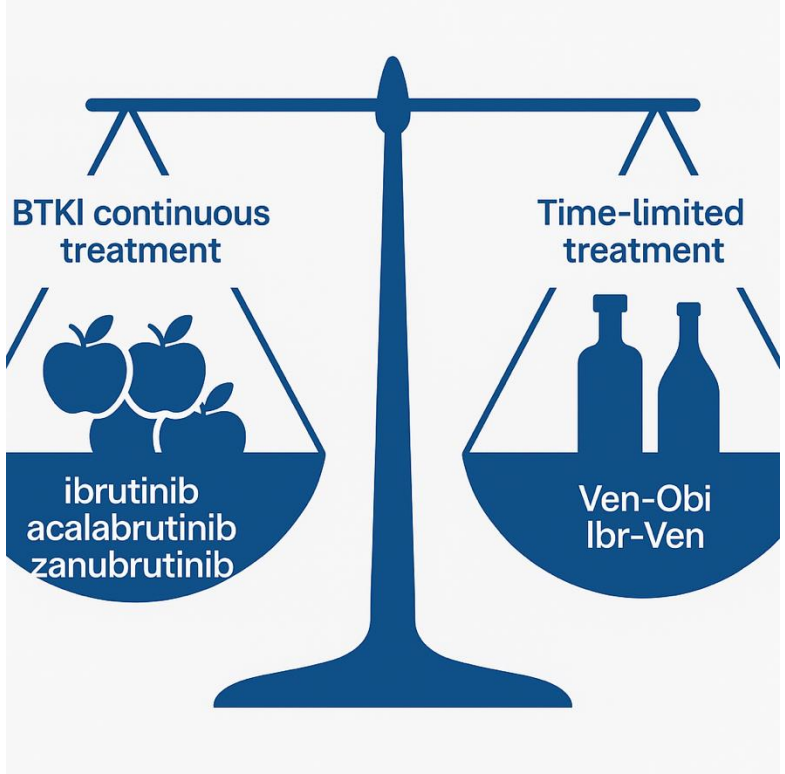
Elderly

# Current treatment scenario in first line (efficacy)

**Minimum common follow up for targeted agents in 1° line trials**

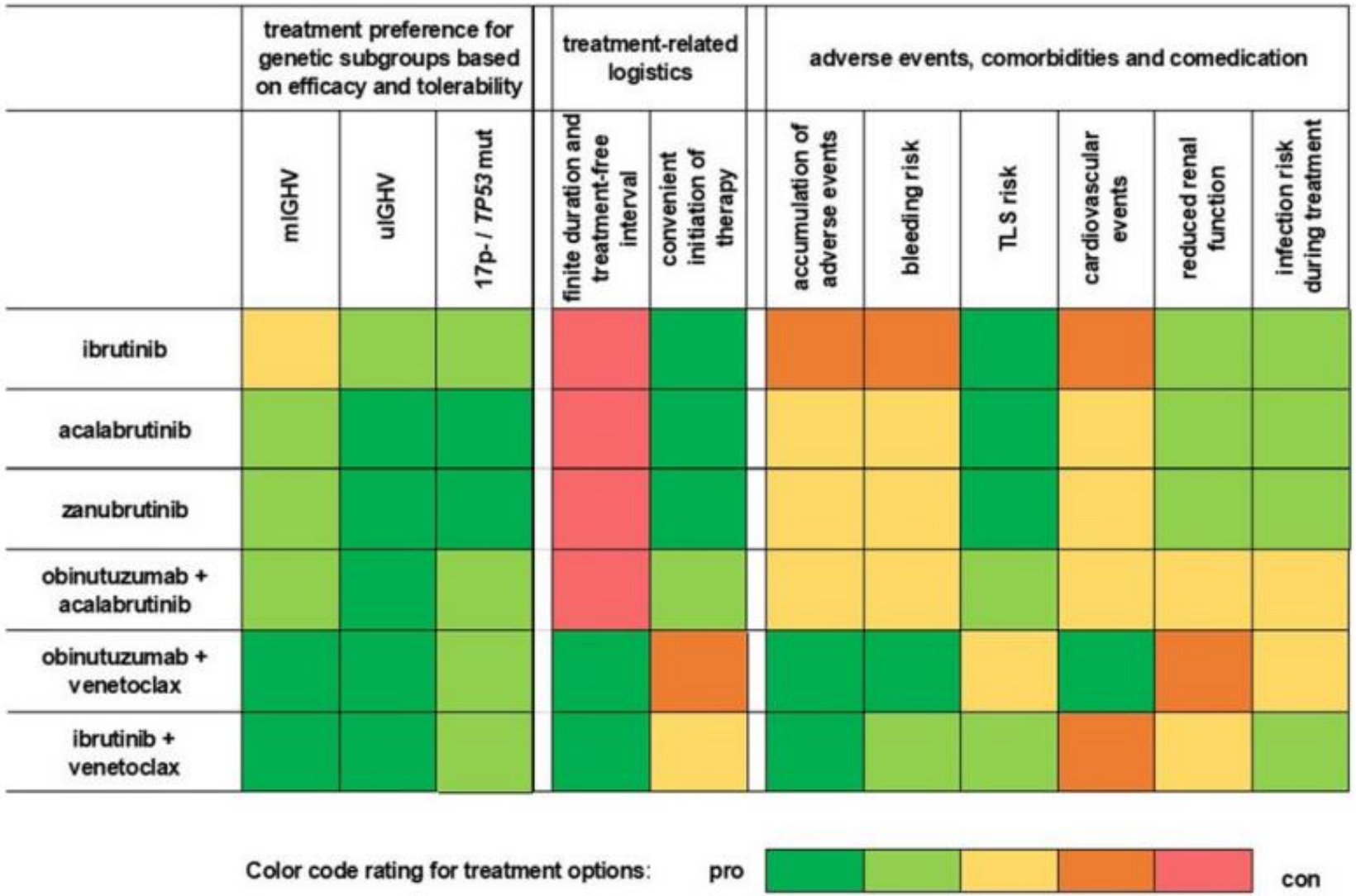
| | Population | Study drug(s) | Progression-free at ~4 y |
|---|---|---|---|
| **RESONATE 2** | Elderly/unfit | ibrutinib | **70% (5 y)** |
| **ALLIANCE** | Elderly/fit | Ibrutinib | **76%** |
| **ECOG1912** | Young/fit | IR | **78% (5 y)** |
| **FLAIR** | Young/fit | IR | **86%** |
| **ELEVATE TN** | Elderly/unfit | acalabrutinib | **78%** |
| **SEQUOIA (arm A)** | Elderly/fit | zanubrutinib | **82%** |
| **SEQUOIA (arm C, 17p)** | Any | zanubrutinib | **79%** |
| **CLL14** | Elderly/unfit | VO | **74%** |
| **CLL13** | Young/fit | VO | **82%** |
| **GLOW** | Elderly/unfit | I+V | **75%** |
| **CAPTIVATE (FD cohort)** | Young/fit | I+V | **79%** |

# Available CLL first-line therapy options in 2025 and drivers of choice



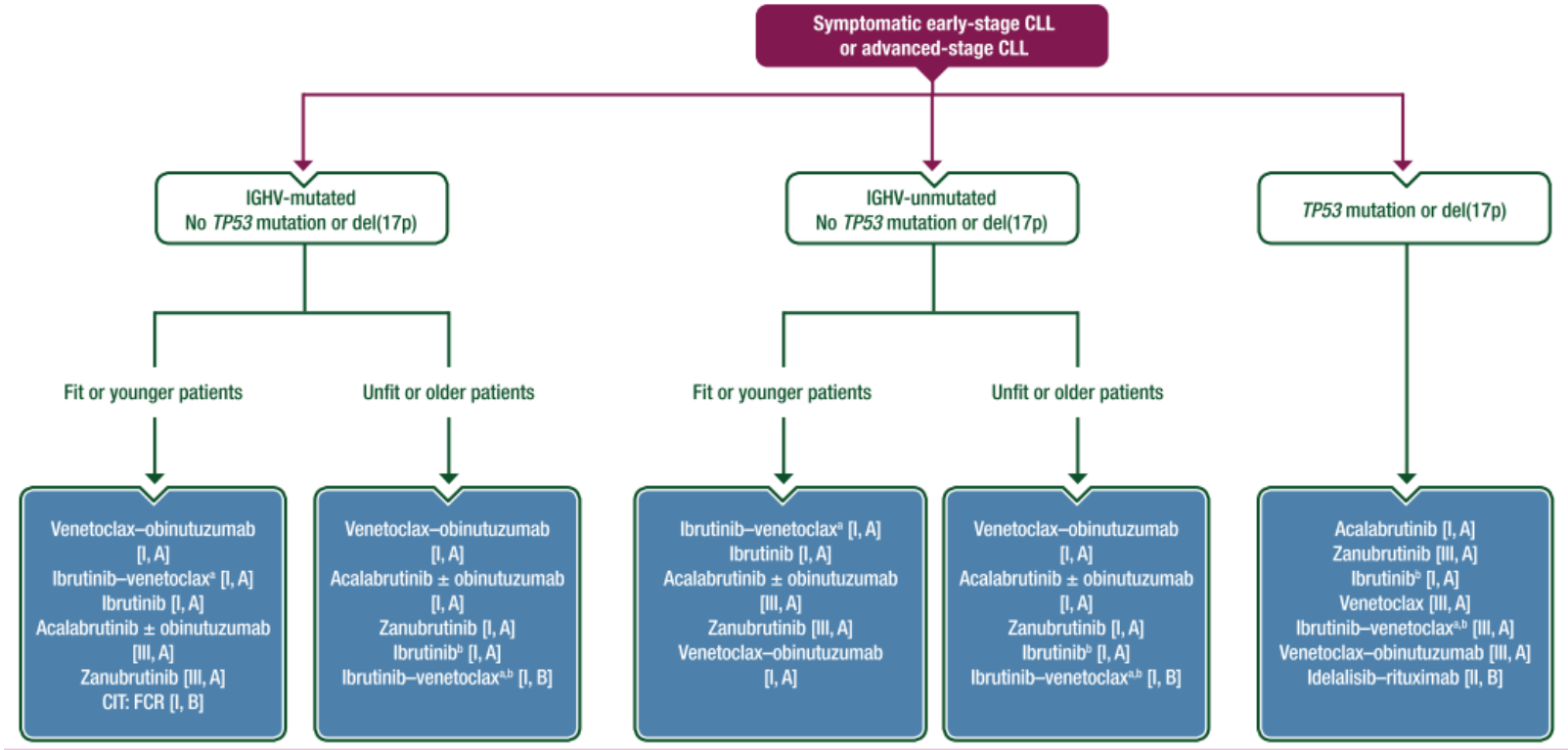

| | |
|---|---|
| **Disease biology** | ▪ TP53 aberrations<br>▪ IgHV status<br>▪ (CK) |
| **Patient' characteristics** | ▪ Age/fitness<br>▪ Cardiocomorbidity<br>▪ Renal comorbidity<br>▪ History of major bleeding<br>▪ Concomitant medications<br>▪ Cognitive status<br>▪ Caregiver/social support |
| **Disease clinical characteristics** | ▪ Disease burden (TLS risk)<br>▪ Cytopenia<br>▪ Need of rapid disease control |

# Optimal first line treatment – Balance of tolerability and efficacy




*Tausch… Stingelbauer ASH Education Program 2024*

# ESMO guidelines: first line treatment




**How the scenario is moving**

FD increasingly preferred in young/fit, NO *TP53*

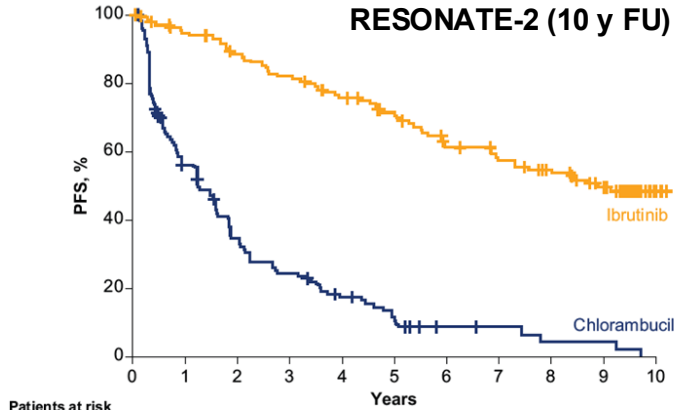
→ will the advent of A+V (or Z+Ven or Sonro) make *all* patients eligible for FD?

Eichhorst et al. Annals of Oncology 2024

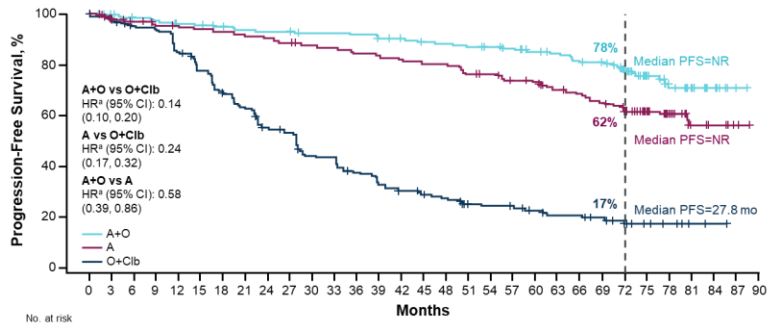
# Continous BTKi in TN CLL: current data

- BTKi are superior to CIT for PFS and OS in both young/fit and elderly/unfit patients

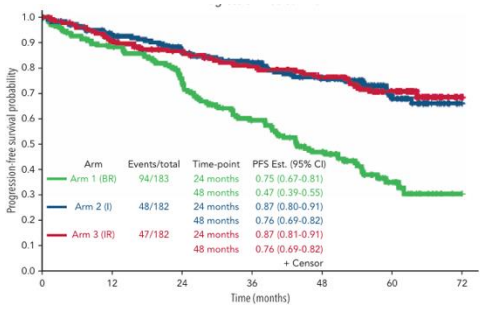
**RESONATE-2 (10 y FU)**



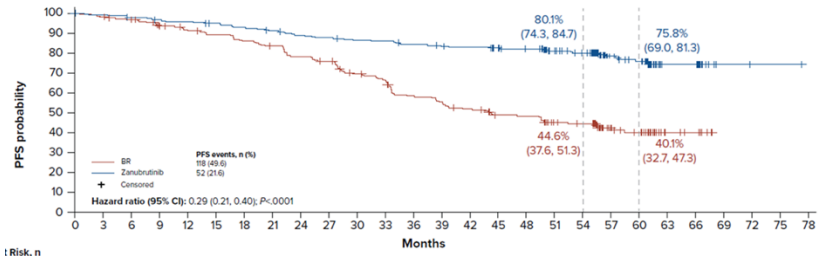

**ELEVATE TN (6y FU)**



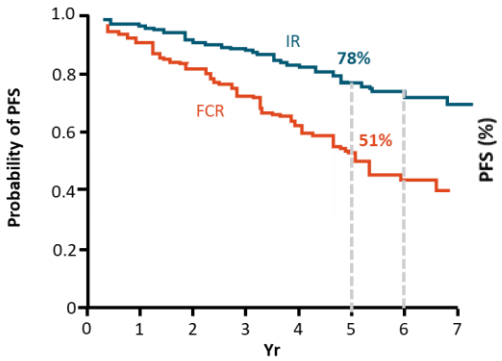

**ALLIANCE (6 y FU)**



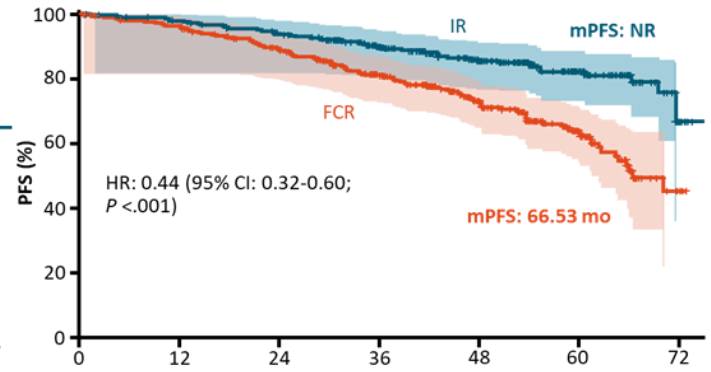

**SEQUOIA (5y FU)**




**ECOG1912 (6 y FU)**




**FLAIR (5.5 y FU)**

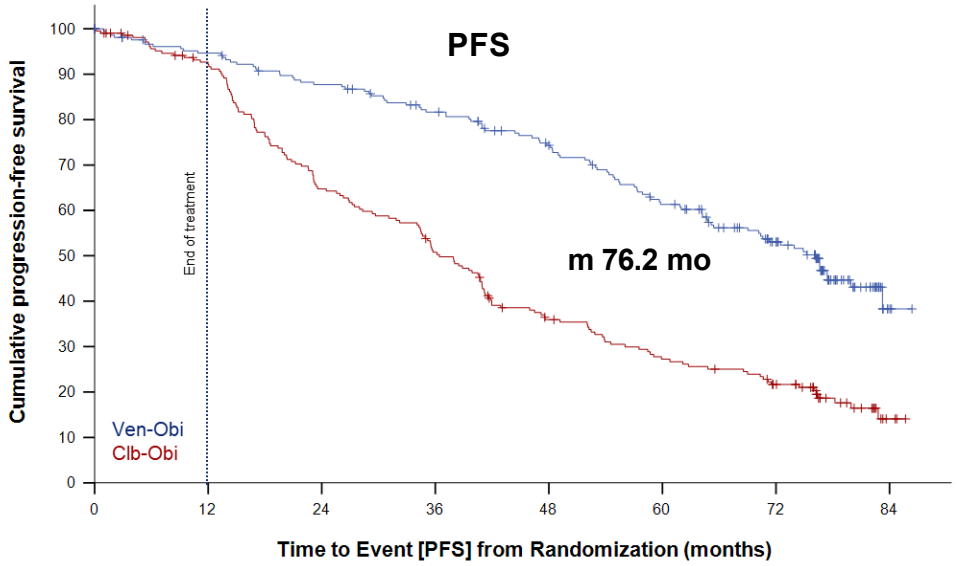



*Burger EHA, 2024; Wojach, Blood 2024; Munir EHA 2023; Sharman ASH 2023; Ghia EHA 2024*

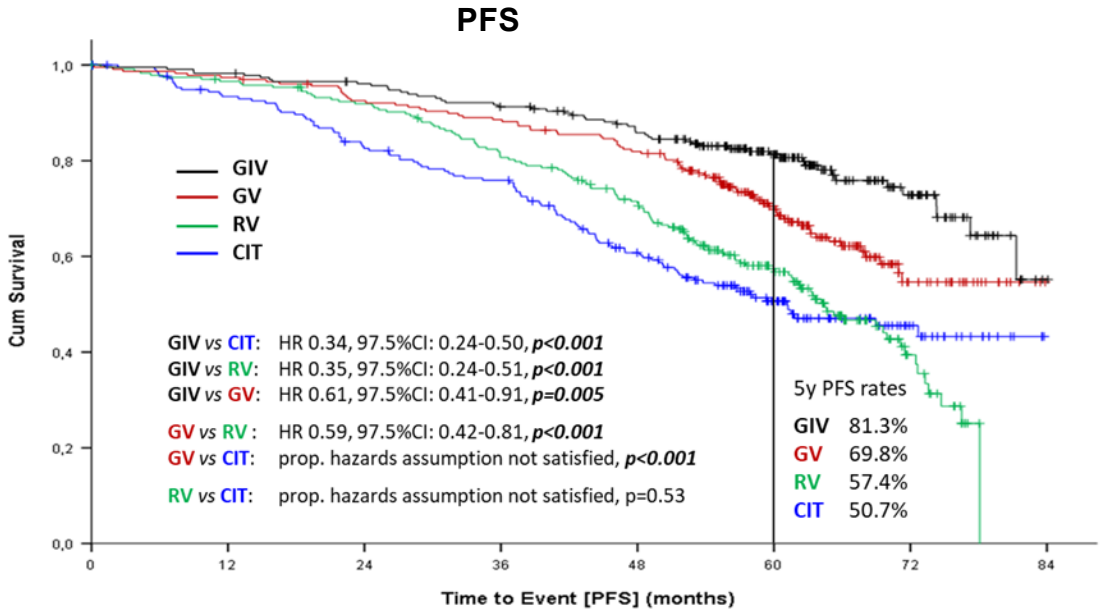
# Fixed-duration VO in TN CLL: current data

- Time-limited VO is superior to CIT and leads to prolonged PFS in both young/fit and elderlyunfit

**CLL14 (6 y FU)**

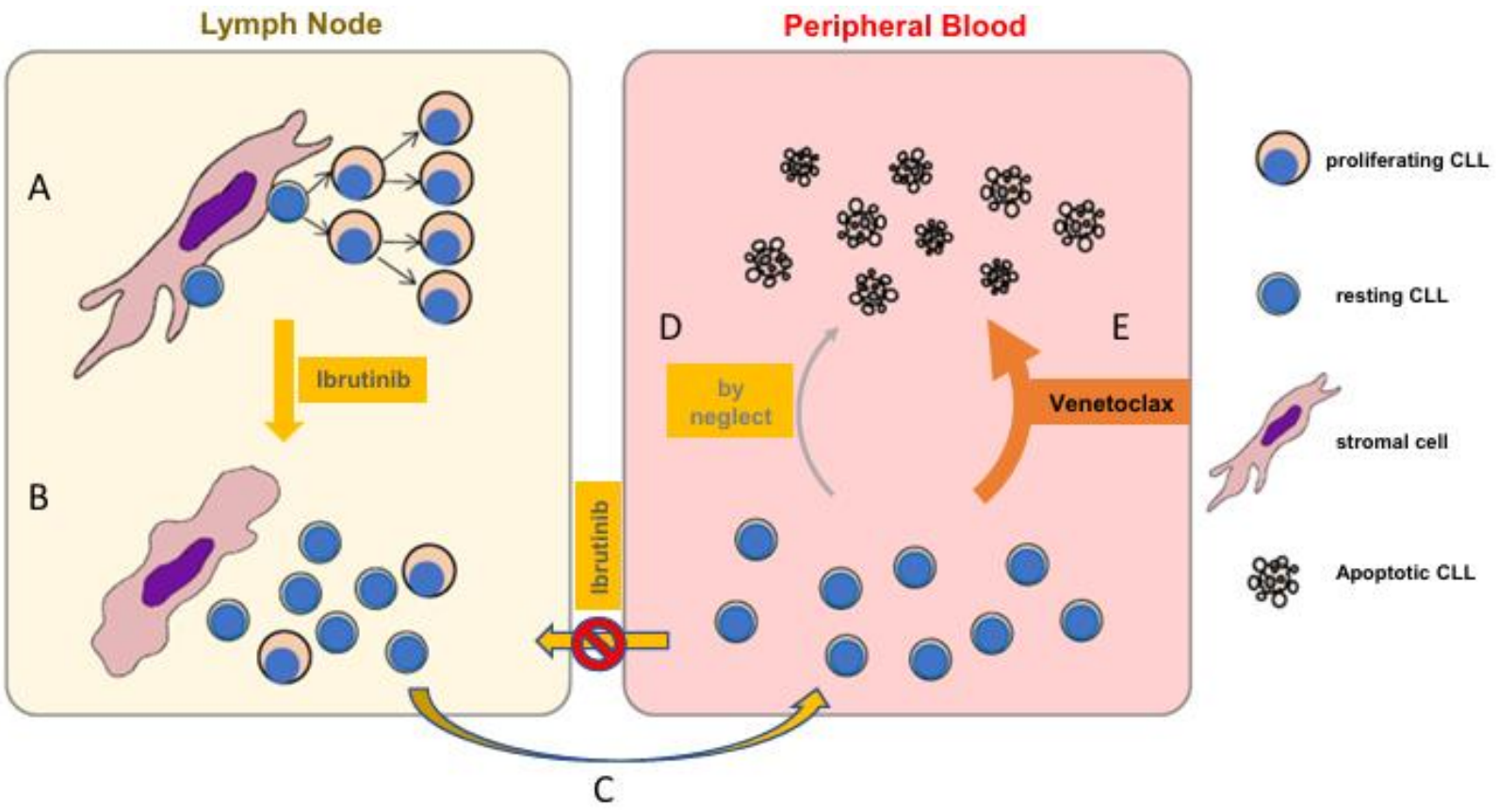



**CLL13 (5 y FU)**




Al Sawaf EHA 2023; Furstenau IwCLL 2025

# The additional value of combining ibrutinib + venetoclax

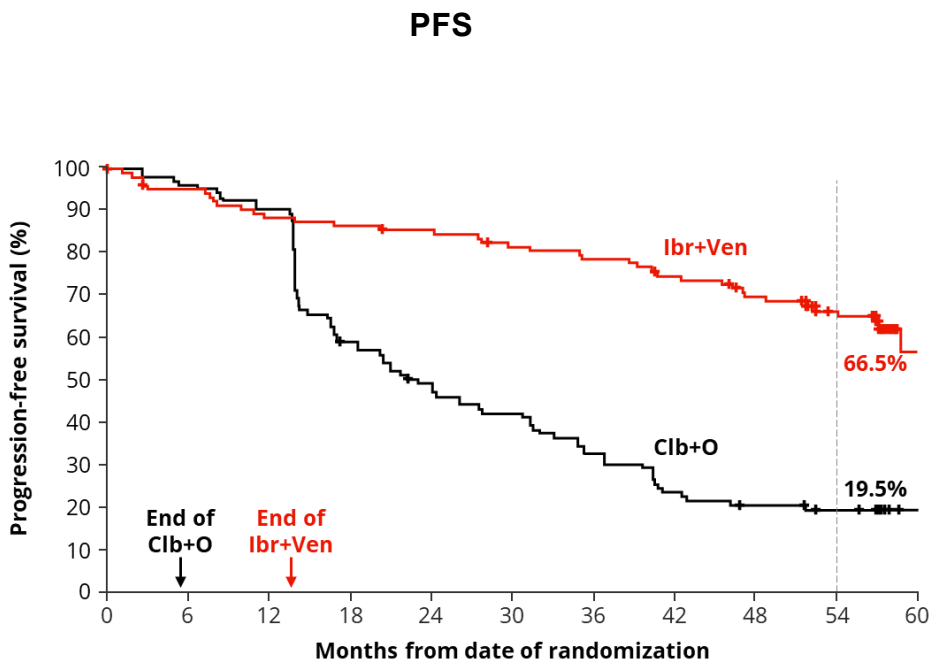



*Lu et al. Blood Cancer Journal (2021*

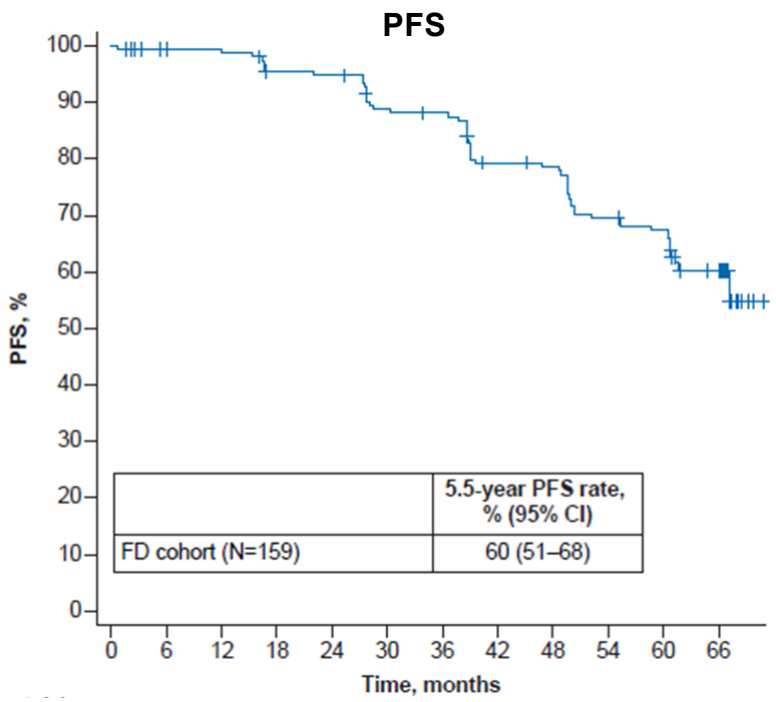
# Fixed-duration I+V in TN CLL: current data

- Time-limited I+V is superior to CIT and leads to prolonged PFS in both young/fit and elderlyunfit

**GLOW (5 y FU)**



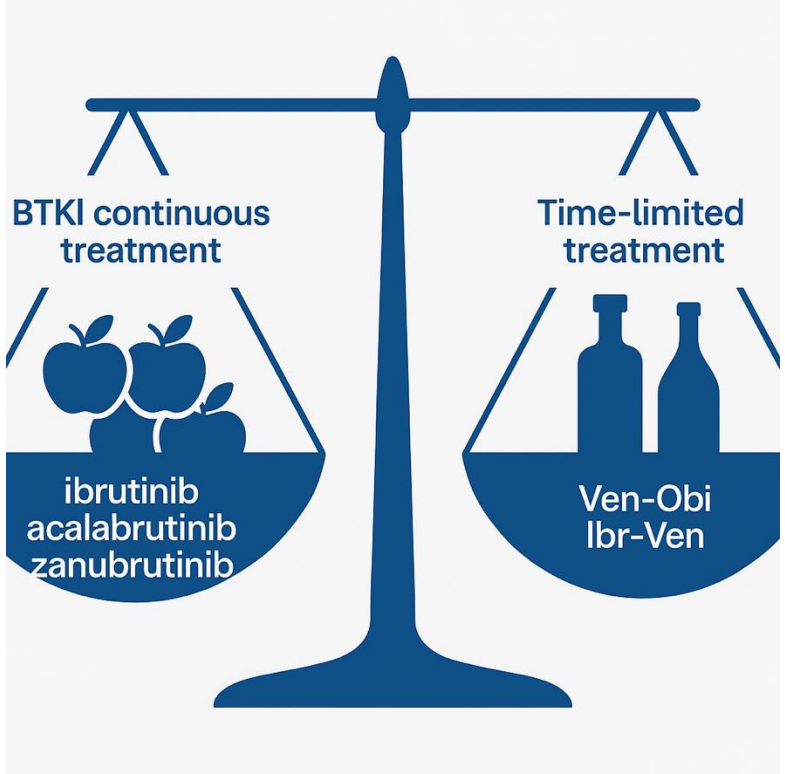

**CAPTIVATE (5.5 y FU)**




**60% FD cohort only**

*Munir, ASH 2023; Ghia, EHA 2025*

# Available CLL first-line therapy options in 2025 and drivers of choice




| | |
|---|---|
| **Disease biology** | ▪ **TP53 aberrations**<br>▪ **IgHV status**<br>▪ **(CK)** |
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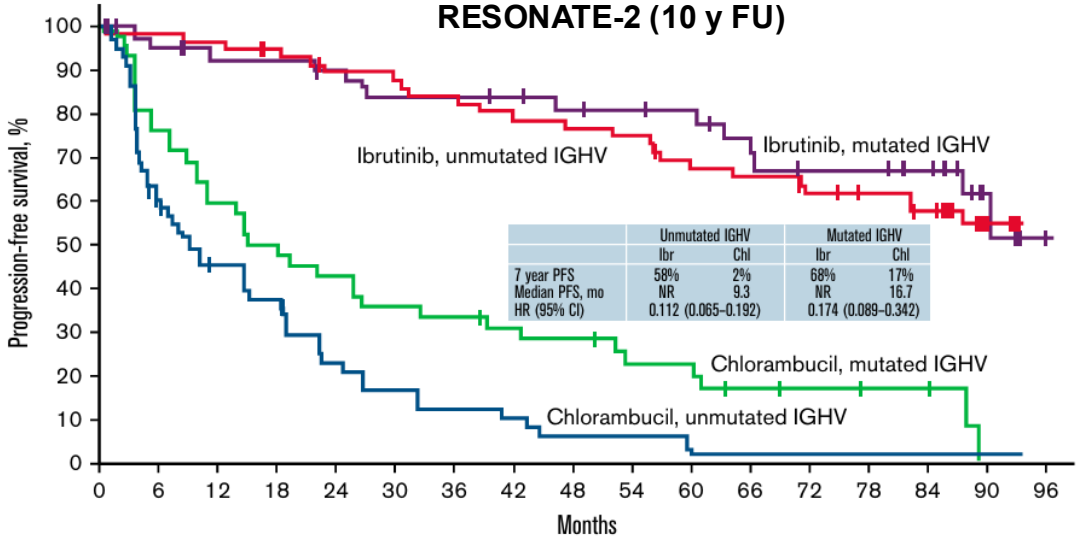
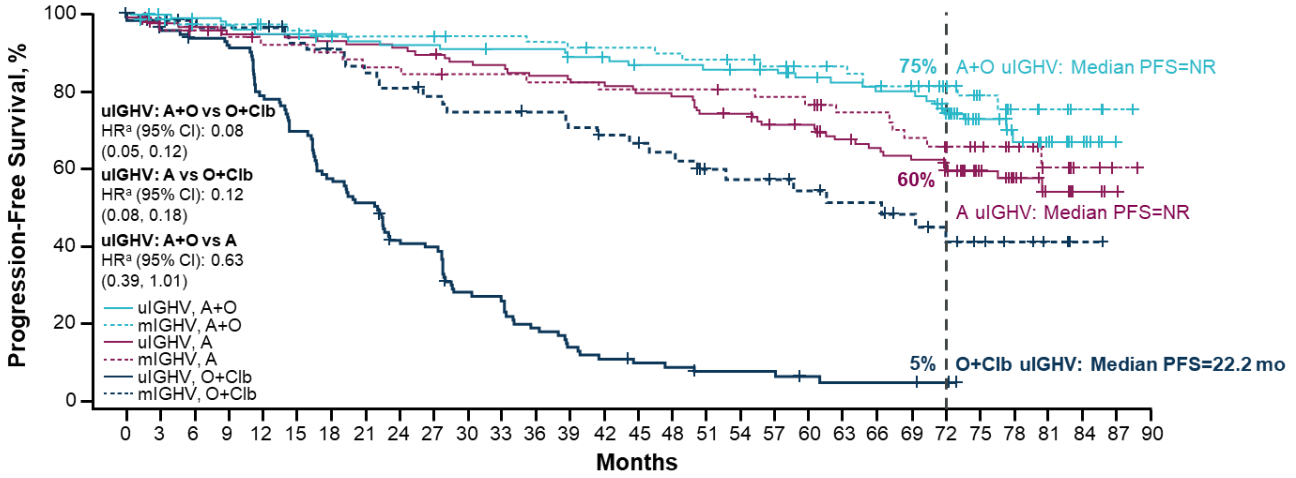
| **Disease clinical characteristics** | ▪ Disease burden (TLS risk)<br>▪ Cytopenia<br>▪ Need of rapid disease control |

# Continous BTKi in TN CLL: IgHV mutational status

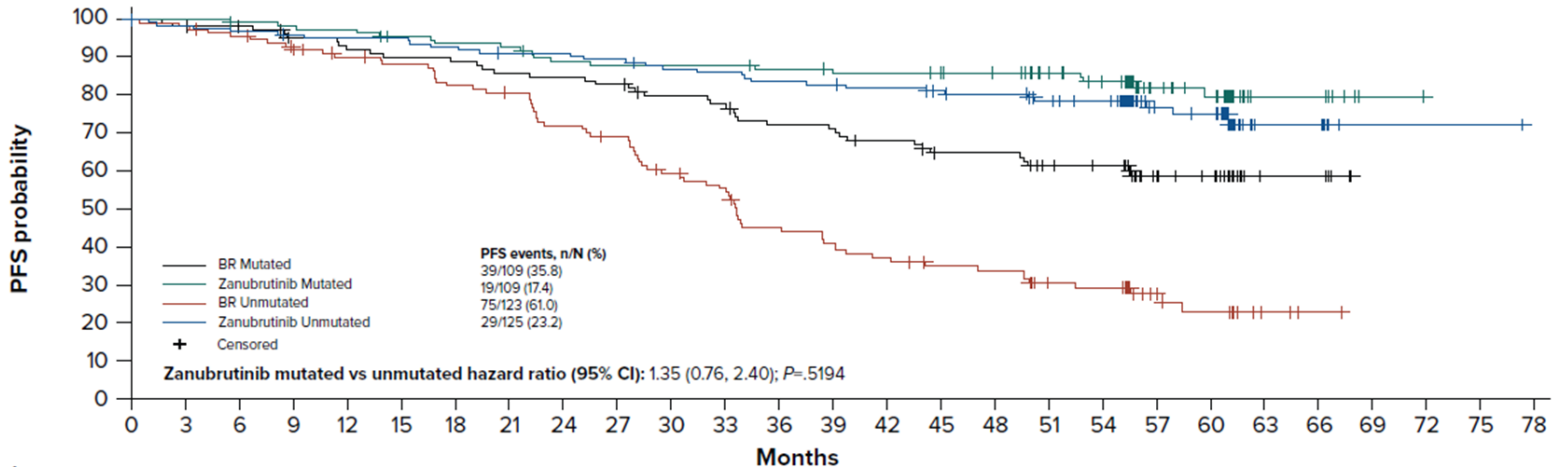
**RESONATE-2 (10 y FU)**




**ELEVATE TN (6y FU)**



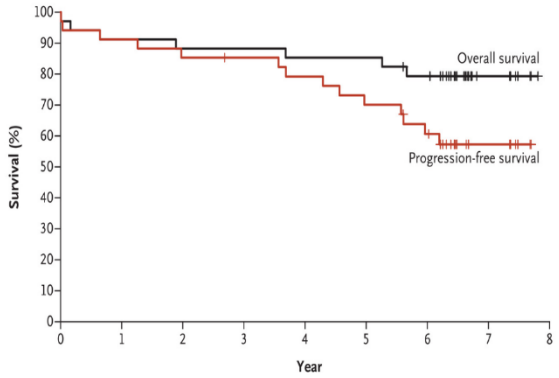

**SEQUOIA (5y FU)**



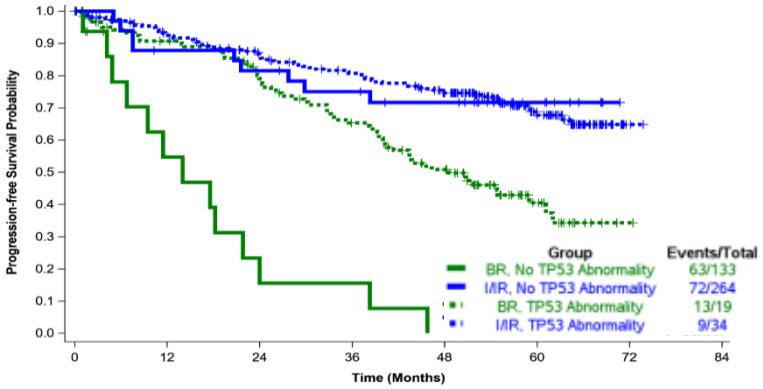

Barr Blood Adv 2022; Burger EHA, 2024; Sharman ASH 2023; Shadman ASH 2024

# Continous BTKi in TN CLL:TP53 aberrations and CK

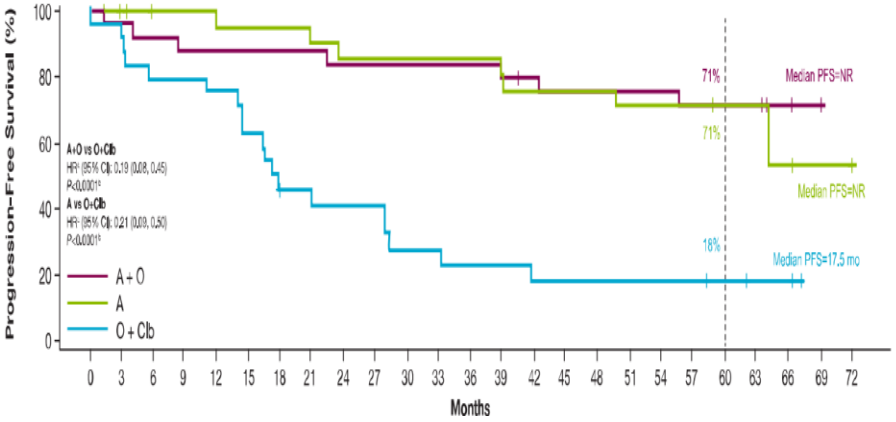
**Phase II trial:**
**Ibrutinib monotherapy[1]**
**Median FU: 6.5 years**



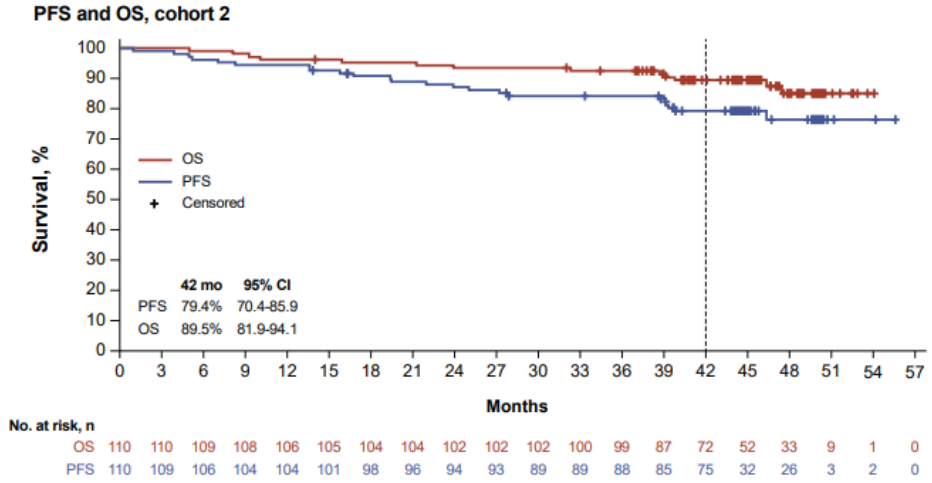

**ALLIANCE:**
**Ibrutinib vs. IR vs. BR[2]**
**Median FU: 55 months**



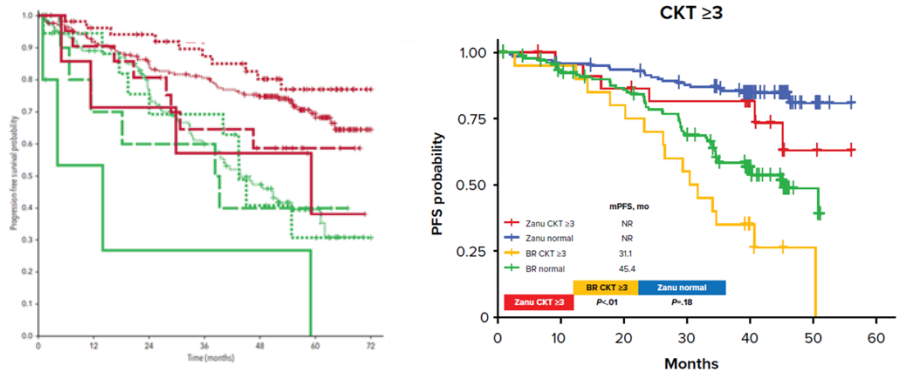

**ELEVATE TN:**
**Acalabrutinib vs. AO vs. O + Clb[3]**
**Median FU: 58.2 months**




**SEQUOIA ARM C**
**Median FU: 47.9 months**
**110 pts**



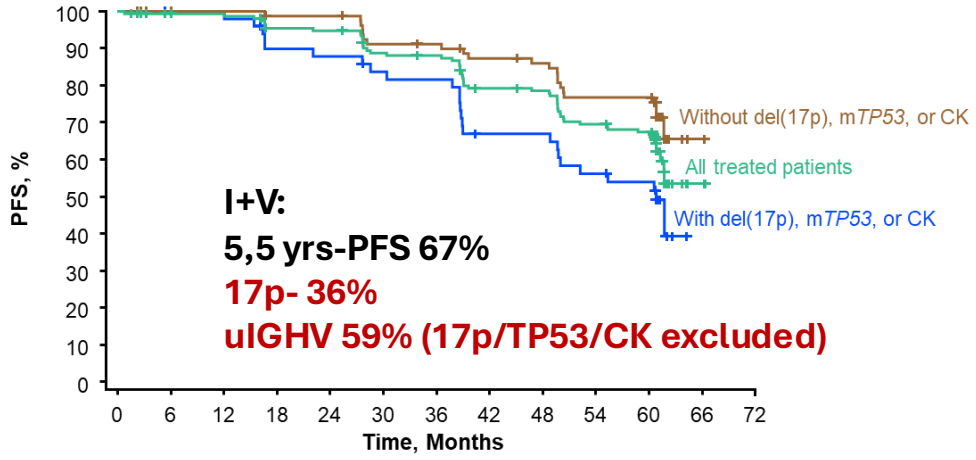

**ALLIANCE (6y FU)**
***Complex Karyotype***




Ahn IE *et al*. *N Engl J Med* 2020; 383 (5): 498–500; Woyach J *et al*. Blood 2023; Sharman JP *et al*. Oral presentation at ASCO 2022; Munir *et al*. Oral presentation at *EHA 2023*

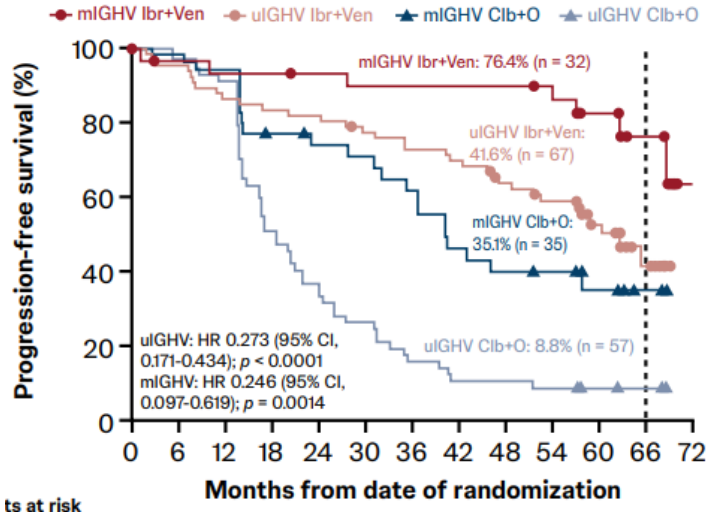
# Has FD same efficacy than continous cBTKi in high risk CLL?

## CAPTIVATE (5.5 y FU)



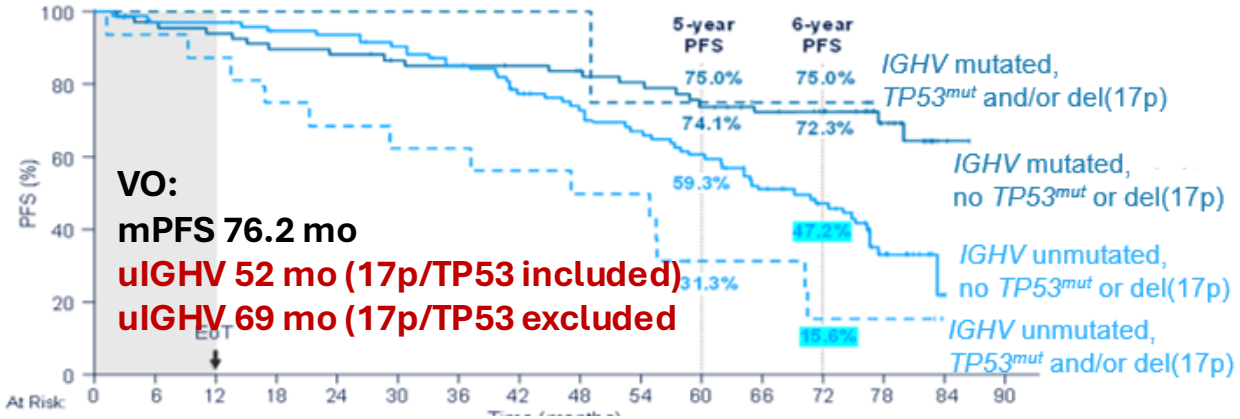

**I+V:**
**5,5 yrs-PFS 67%**
**17p- 36%**
**uIGHV 59% (17p/TP53/CK excluded)**

## GLOW (5.5 y FU)



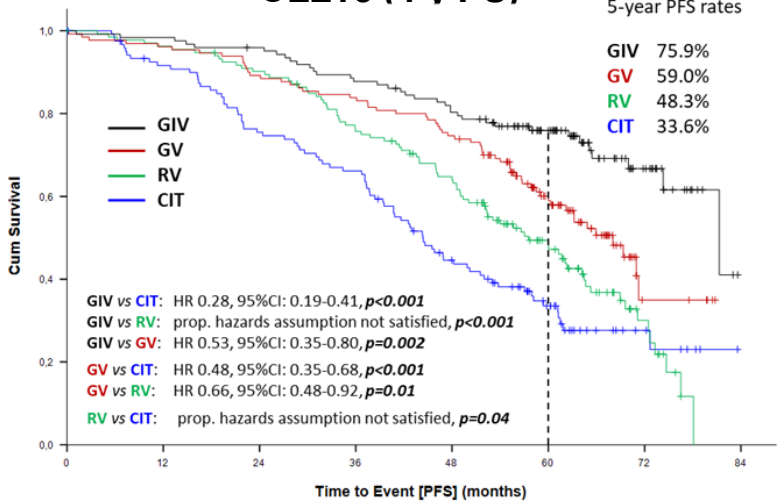

**I+V:**
**66 mo-PFS 51.7%**
**(uIGHV 41.6%)**

## CLL14 (6 y FU)




**VO:**
**mPFS 76.2 mo**
**uIGHV 52 mo (17p/TP53 included)**
**uIGHV 69 mo (17p/TP53 excluded**

## CLL13 (4 y FU)

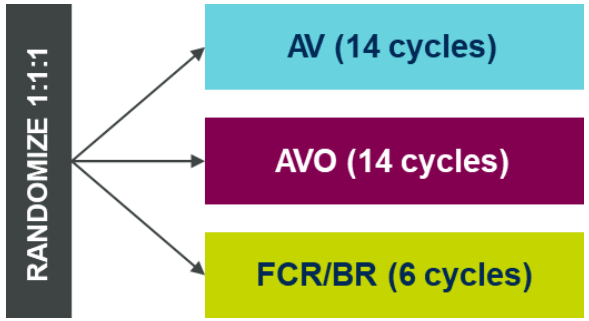



**VO:**
**5y-PFS 69.8%**
**(uIGH 59%)**

Wierda EHA 2024, Ghia EHA 2025; Niemann ASH 2024, Al Sawaf EHA 2023; Furstenau IwCLL 2025

# Fixed-duration in TN CLL: A+V (mFU 40.8 mo)

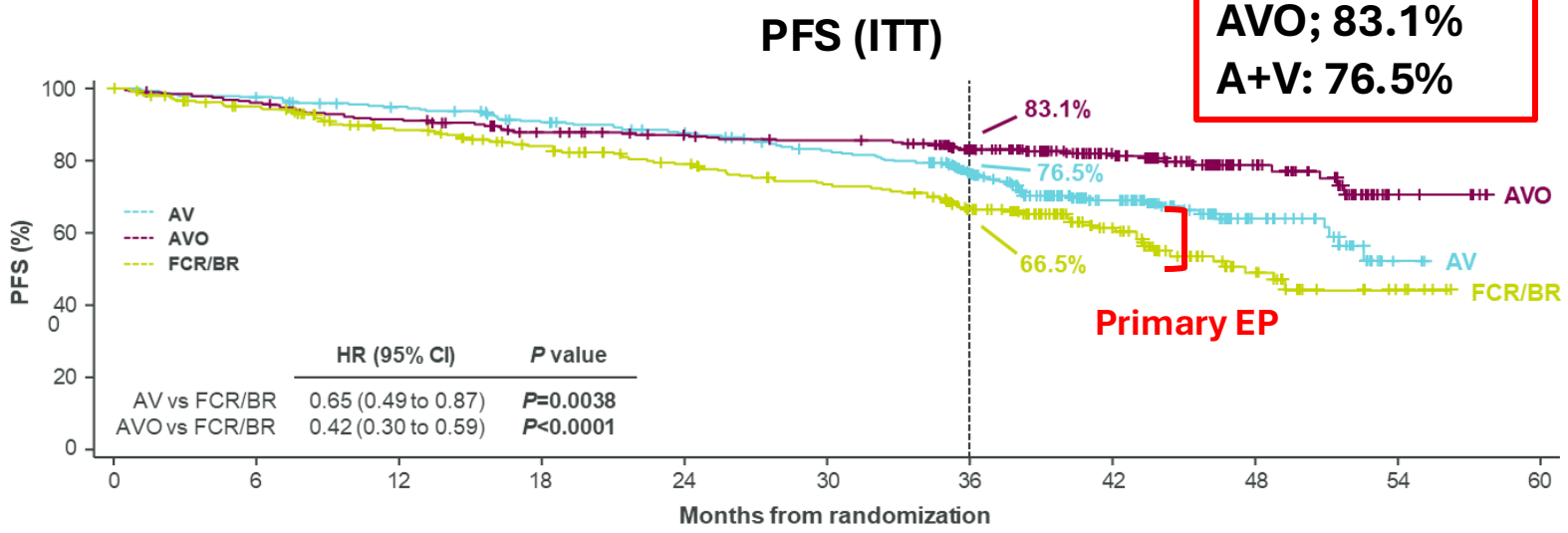
**Key inclusion:**
- NO 17p/*TP53*
- CIRS <6




**Primary EP**: PFS AV *vs* CIT

**Secondary EP**:
PFS AVO *vs* CIT
uMRD AV and AVO *vs* CIT
OS AV and AVO *vs* CIT

**3y PFS**
**AVO; 83.1%**
**A+V: 76.5%**




**3y PFS uIGHV:**
**AVO: 83%**
**A+V: 69%**

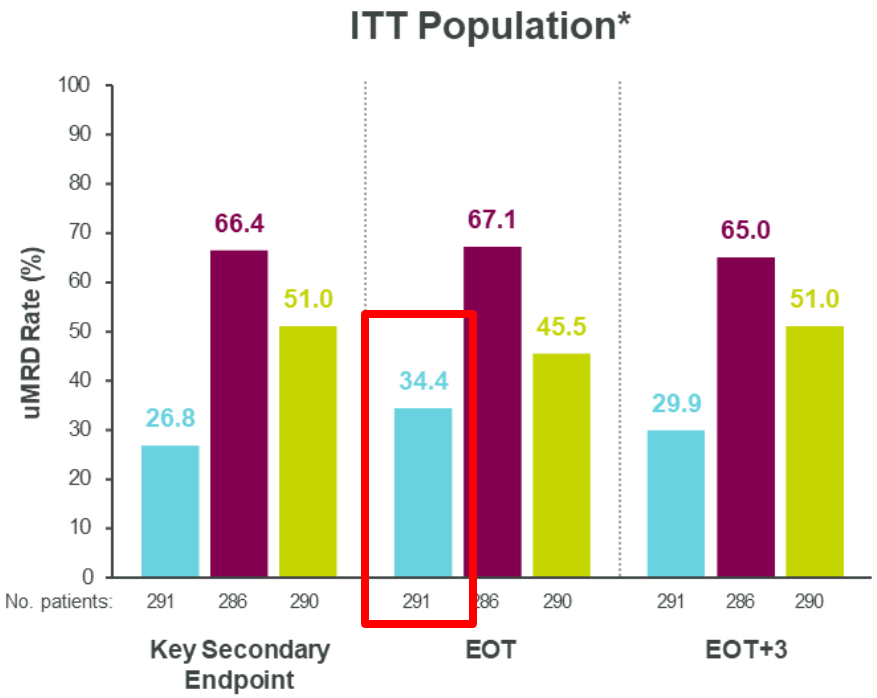
**3y PFS mIGHV:**
**AVO: 83%**
**A+V: 86%**

**Censoring COVID deaths: 3y PFS AVO 91.5%; A+V 78.8%**

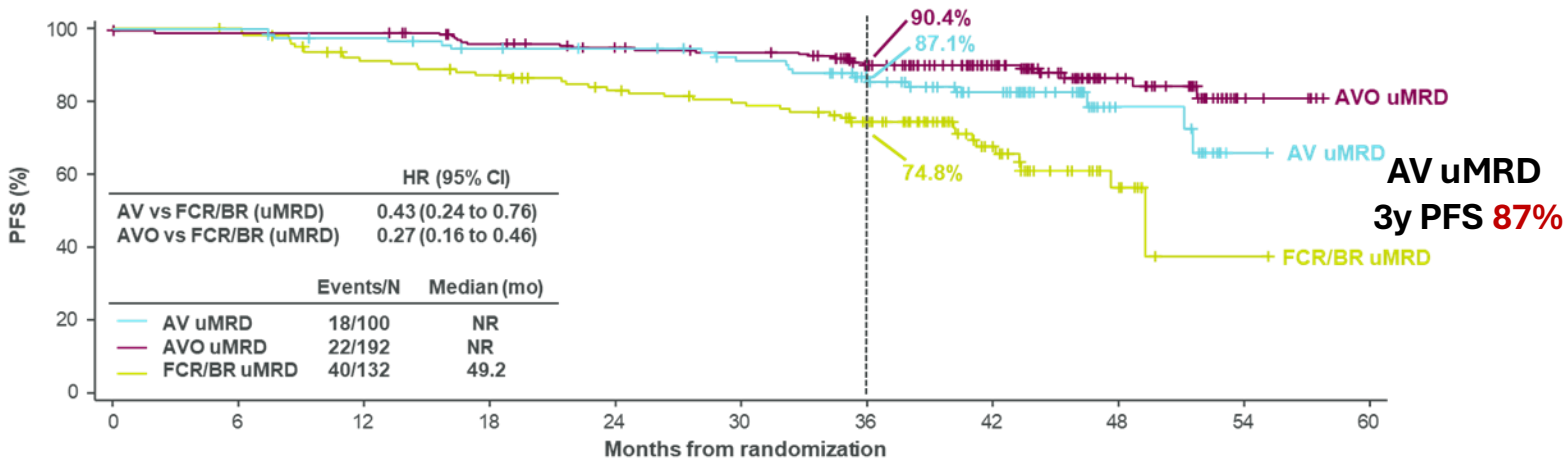
Brown ASH 2024

# Fixed-duration in TN CLL: A+V (mFU 40.8 mo)

**Key inclusion:**
- NO 17p/*TP53*
- CIRS <6

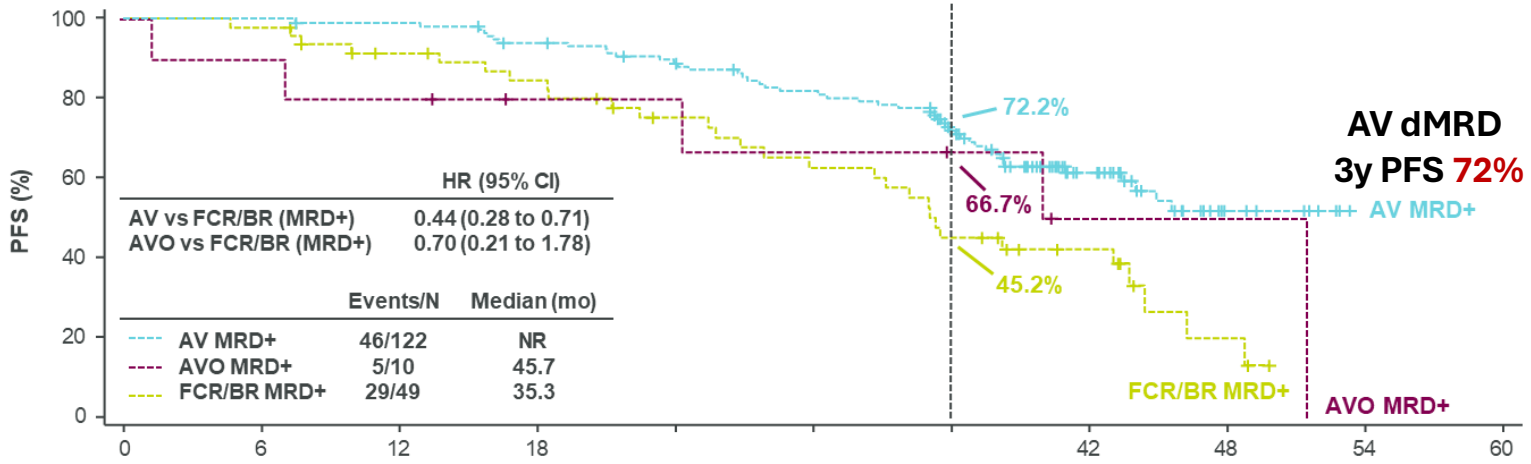



## PFS in uMRD (<$10^{-4}$)




**AV uMRD**
**3y PFS 87%**

## PFS in dMRD (>$10^{-4}$)




**AV dMRD**
**3y PFS 72%**

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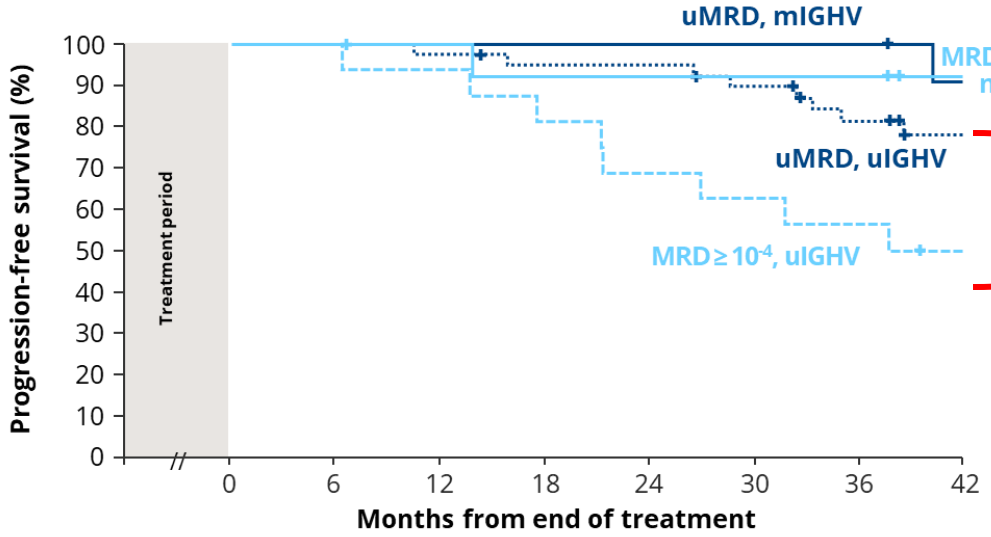
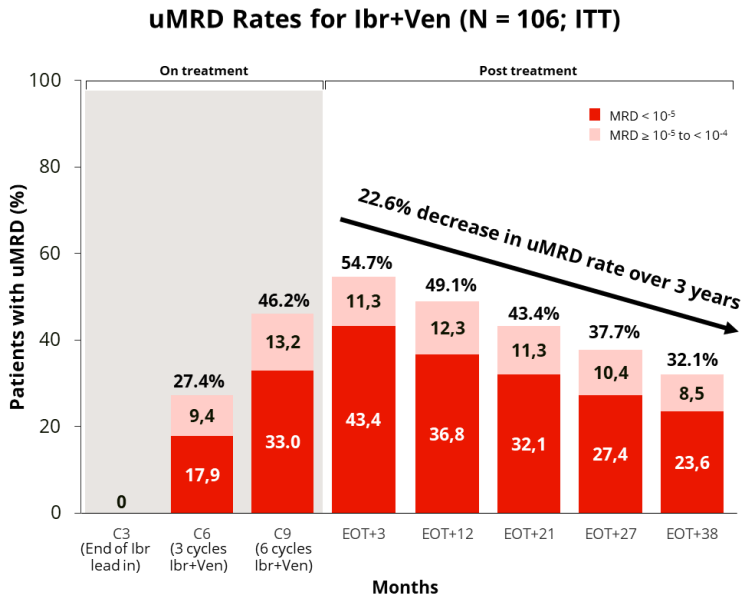
# MRD kinetic with I+V according to IGHV status

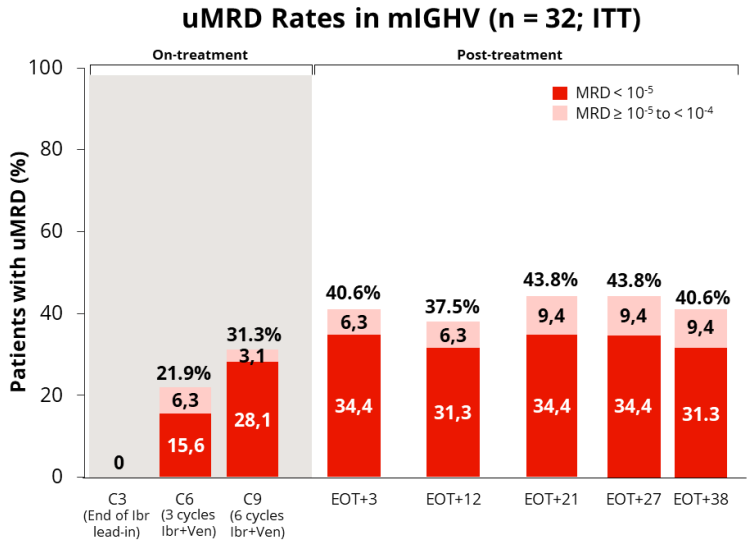


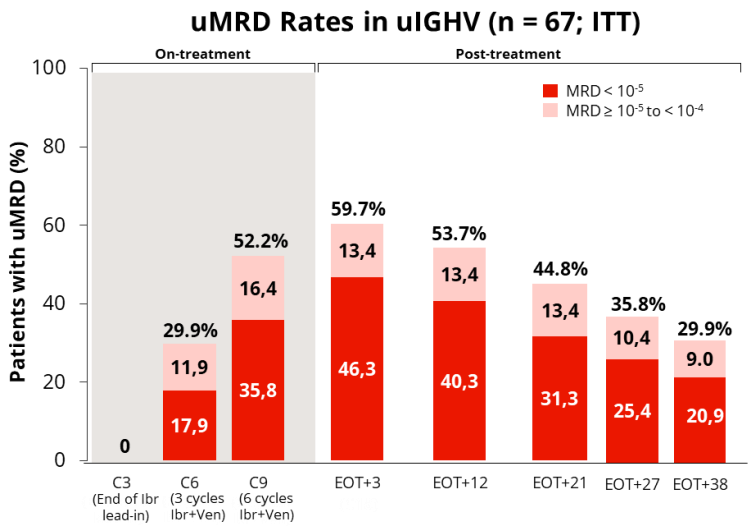

IGHV mutated

4 yrs PFS in Unmutated IGHV:

- 78% for uMRD +3 mo EOT
- 50% for dMRD + 3 mo EOT

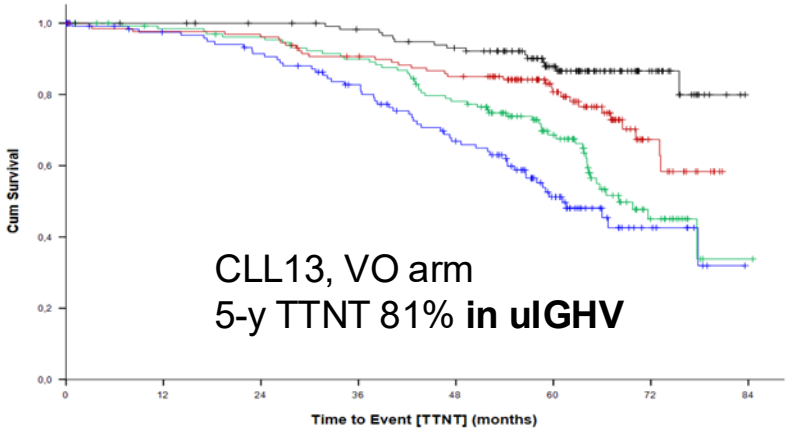


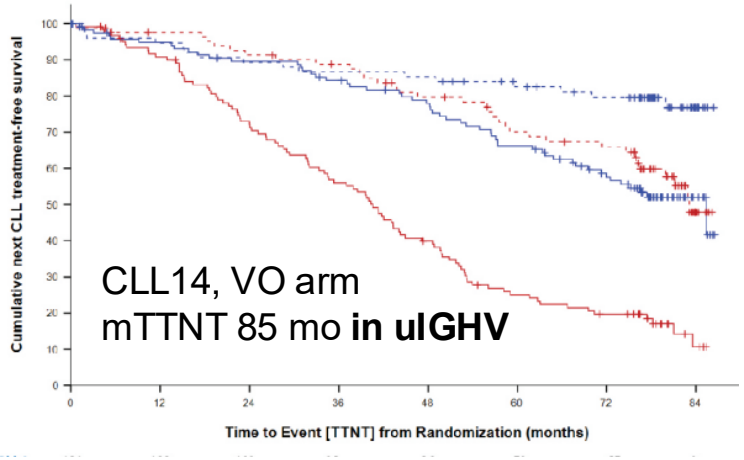



# Should we look at TTNT more than PFS in FD?

## Venetoclax Obinutuzumab: TTNT

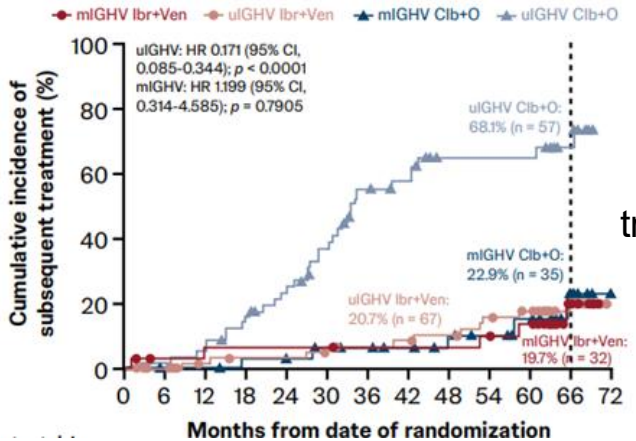



CLL13, VO arm
5-y TTNT 81% **in uIGHV**

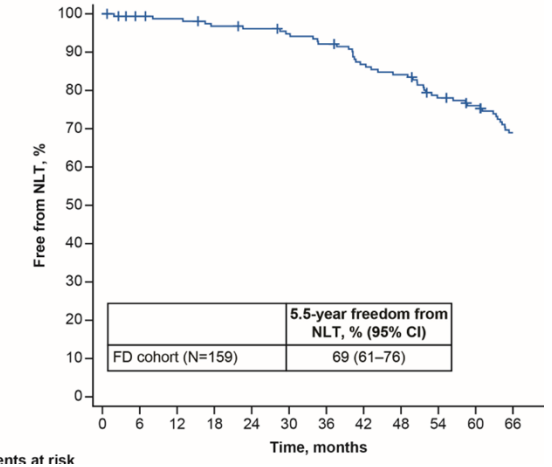



CLL14, VO arm
mTTNT 85 mo **in uIGHV**

## Venetoclax Ibrutinib: TTNT



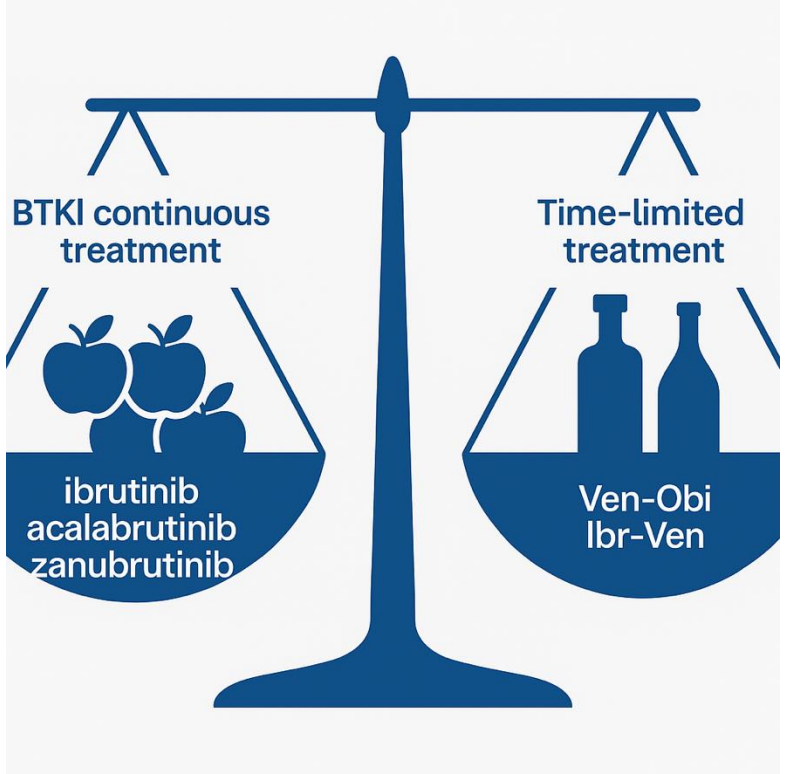

GLOW
66 mo 21% re-treated **in uIGHV**




CAPTIVATE
5.5 yrs TTNT 69%
(FD cohort only)

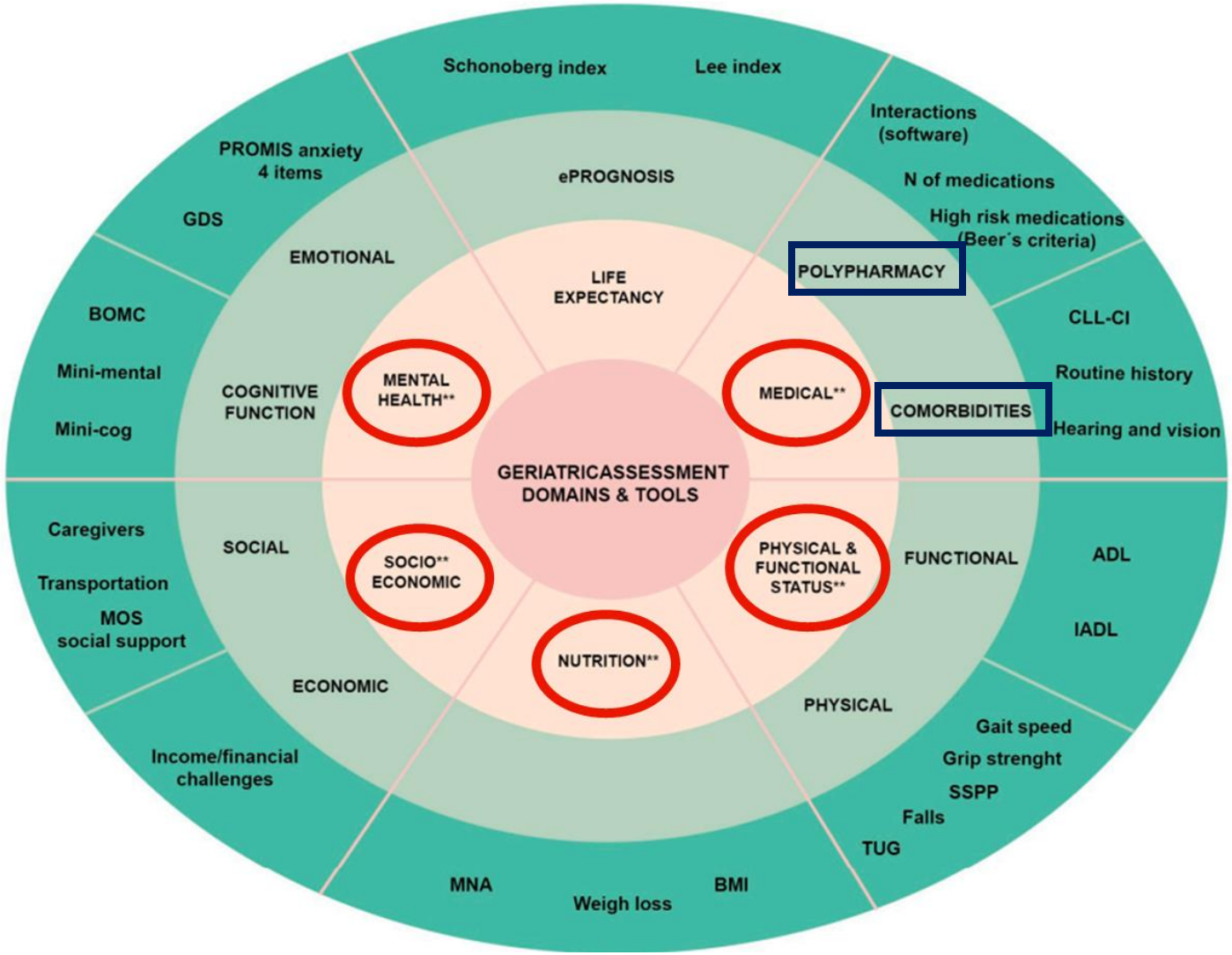
Al Sawaf EHA 2023; Wierda et et al, ,ASCO 2024; Moreno EHA 2023

# Available CLL first-line therapy options in 2025 and drivers of choice




| | |
|---|---|
| **Disease biology** | ▪ TP53 aberrations<br>▪ IgHV status<br>▪ (CK) |
| **Patient' characteristics** | ▪ **Age/fitness**<br>▪ **Cardiocomorbidity**<br>▪ **Renal comorbidity**<br>▪ **History of major bleeding**<br>▪ **Concomitant medications**<br>▪ **Cognitive status**<br>▪ **Caregiver/social support** |
| **Disease clinical characteristics** | ▪ **Disease burden (TLS risk)**<br>▪ **Cytopenia**<br>▪ **Need of rapid disease control** |

# How to assess fitness in CLL patients on




**Any of the geriatric syndromes may impact on:**

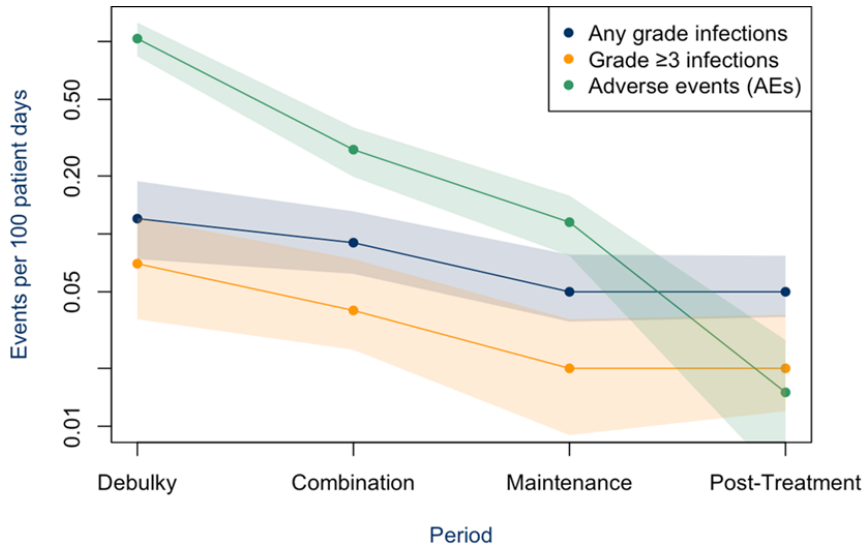
- Adherence
- Tratments accessibility
- Hospitalizations
- Adverse events
- Treatment intensity

**GA may instead:**

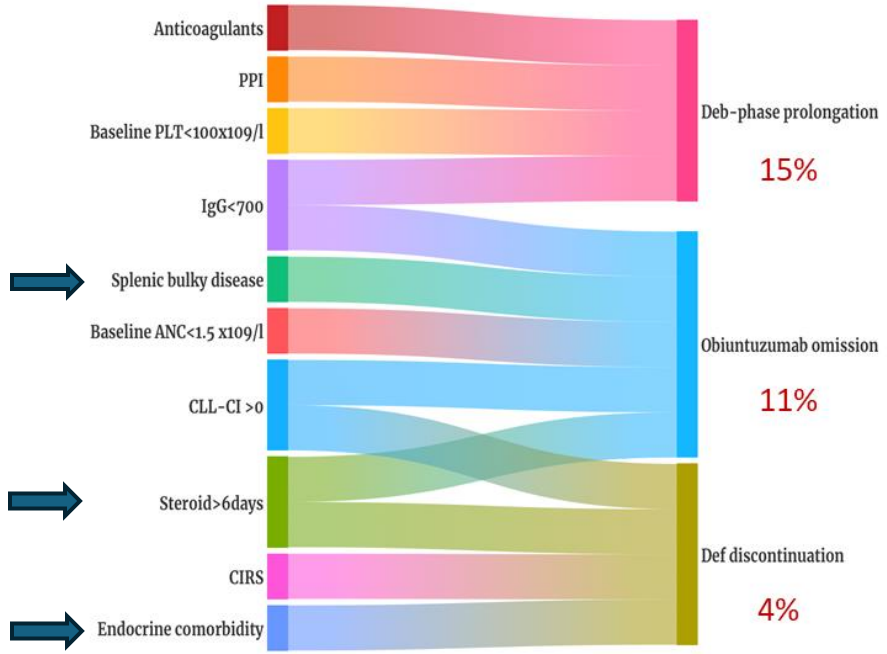
- Address/exclude specific treatments
- Guide early interventions
- Tailor treatment intensity

# Multicentric italian experience on VO in clinical practice

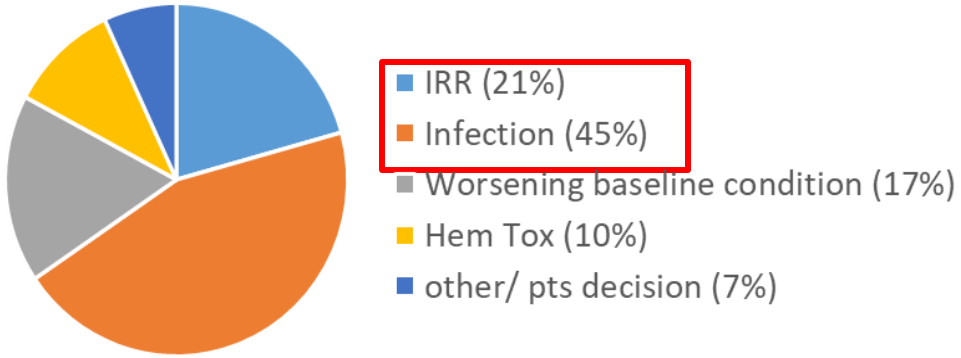
## Infections and G≥3 Aes at different tx phases




## Treatment modifications on debulky phase




## Reasons for Tox-DTD




## Multivariate analysis

| Baseline factor | OR( 95%CI) | p |
|---|---|---|
| **Tox-DTD** | | |
| **Need of caregiver** | 3.1 (1.2 - 8.5) | 0.03 |
| **Endocrine Comorb** | 3.3 (1.3 -7.9) | 0.007 |
| **Steroid>6days** | 3.4 (1.5 - 7.5) | 0.005 |

Galitzia, SIE 2024

# Impact of age/fitness on RCT with targeted agents (~ 4yrs FU)

| | ECOG1912 | RESONATE-2 | ALLIANCE |
|---|---|---|---|
| Median age | 58 | 70 | 71 |
| Tox-related discontinuation at ~4 yrs | 22% | 21% | 18% |

| | SEQUOIA | ELEVATE TN |
|---|---|---|
| Median age | 70 | 70 |
| Tox-related discontinuation at ~4 yrs | 14% | 12% |

| | CLL13 | CLL14 |
|---|---|---|
| Median age | 62 | 72 |
| Tox-related discontinuation at ~4 yrs | 6% | 16% |

| | CAPTIVATE | GLOW |
|---|---|---|
| Median age | 60 | 71 |
| Tox-related discontinuation at ~4 yrs | 5% | 14% |

| | | | |
|---|---|---|---|
| Tachy-brady syndrome, cardiac failure, pneumonia | Ibrutinib lead-in (1) | Tachy-brady syndrome very likely related, cardiac failure and pneumonia probably related | • 80 years old, male, CIRS score 12, ECOG PS 1, Denmark.<br>• History of atrial fibrillation, ischemic heart disease, non-ST segment elevation myocardial infarction (2016), myocardial infarction due to pneumonia (2017, 2018), epilepsy, chronic obstructive pulmonary disease, prostate cancer, transient ischemic attack.<br>• Cerebral bleeding on D15, tachy-brady syndrome and serious infection on D51, pneumonia on D70. |
| Sudden death | Ibrutinib lead-in (3) | Not related | • 63 years old, male, CIRS score 10, ECOG PS 1, Poland.<br>• History of hypertension, hypercholesterolemia.<br>• Cardiac arrest on D85 after 3 cycles of ibrutinib but before first dose of venetoclax.<br>• Date of death: D89. |
| Sudden death | Ibrutinib-venetoclax combination (8) | Not related | • 73 years old, male, CIRS score 11, ECOG PS 2, Russia.<br>• History of hypertension, diabetes mellitus, glaucoma cataract, L-eye |
| Sudden death | Ibrutinib-venetoclax combination (8) | Not related | • 79 years old, male, CIRS score 4, ECOG PS 2, Russia.<br>• History of atrial fibrillation, duodenal ulcer<br>• Fatigue a few days before sudden death at home. No autopsy available.<br>• Date of death: D239. |

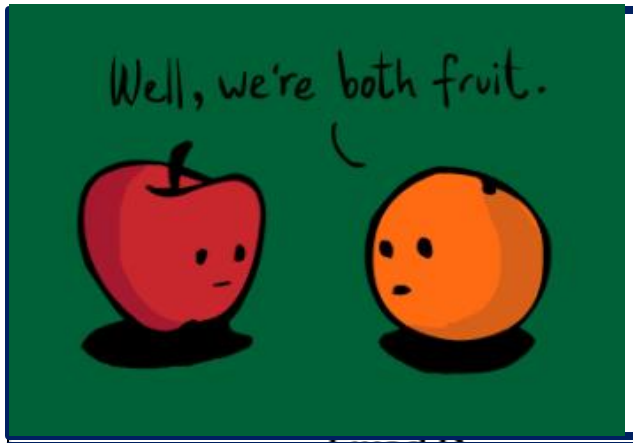
*Barr Blood Adv 2022; Wojach Blood 2023; Shanafelt Blood 2023;Shadman ICML 2023 ; Allan ASH 2022; Kater EHA 2021*

# Are we moving to a fixed-duration for every patient?

**Most clinicians would choose FD therapy if *<u>all</u>* these conditions were met:**

1) It should be **safe** *at least as much* as continuous therapy
2) It should be **effective** *at least as much* as continuous therapy
3) It should be **easy to manage** (both from patients and clinicans pow)

# CAPTIVATE vs AMPLIFY




**Ph 2 *vs* Ph 3**

**159 *vs* 291 pts**

**No COVID *vs* COVID period**

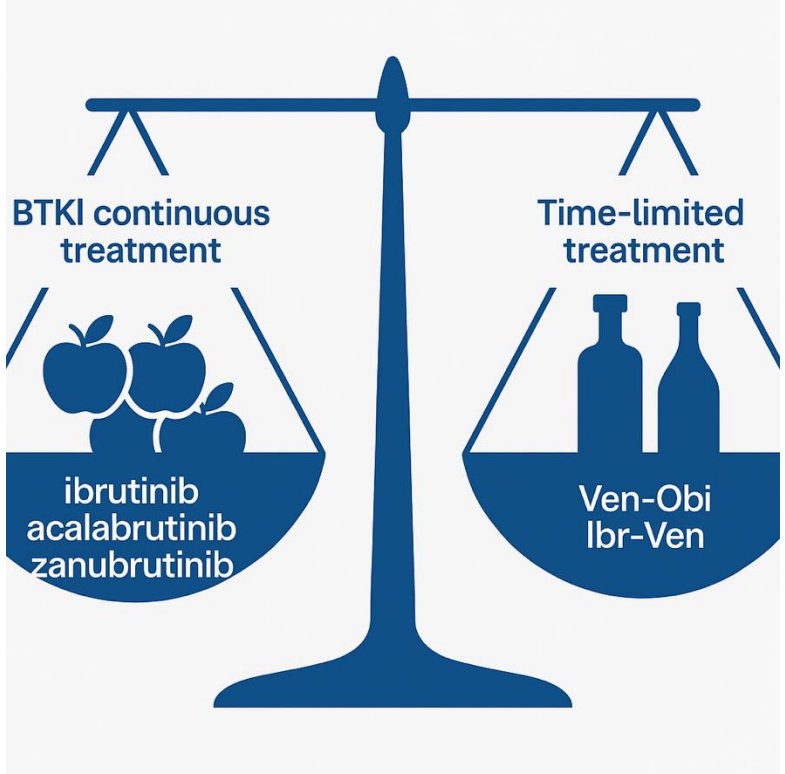
***<u>At the same time…</u>***

***CAN'T safety data from GLOW (elderly, basically unselected), with younger and fit population from AMPLIFY***

**We *could* do something like this only when having <u>from AMPLIFY updates on</u>:**

- **Safety from the <u>elderly</u> group**
  - **Data on <u>TTNT</u>**
- **Data on <u>dose intensity</u>**

# Available CLL first-line therapy options in 2025 and drivers of choice

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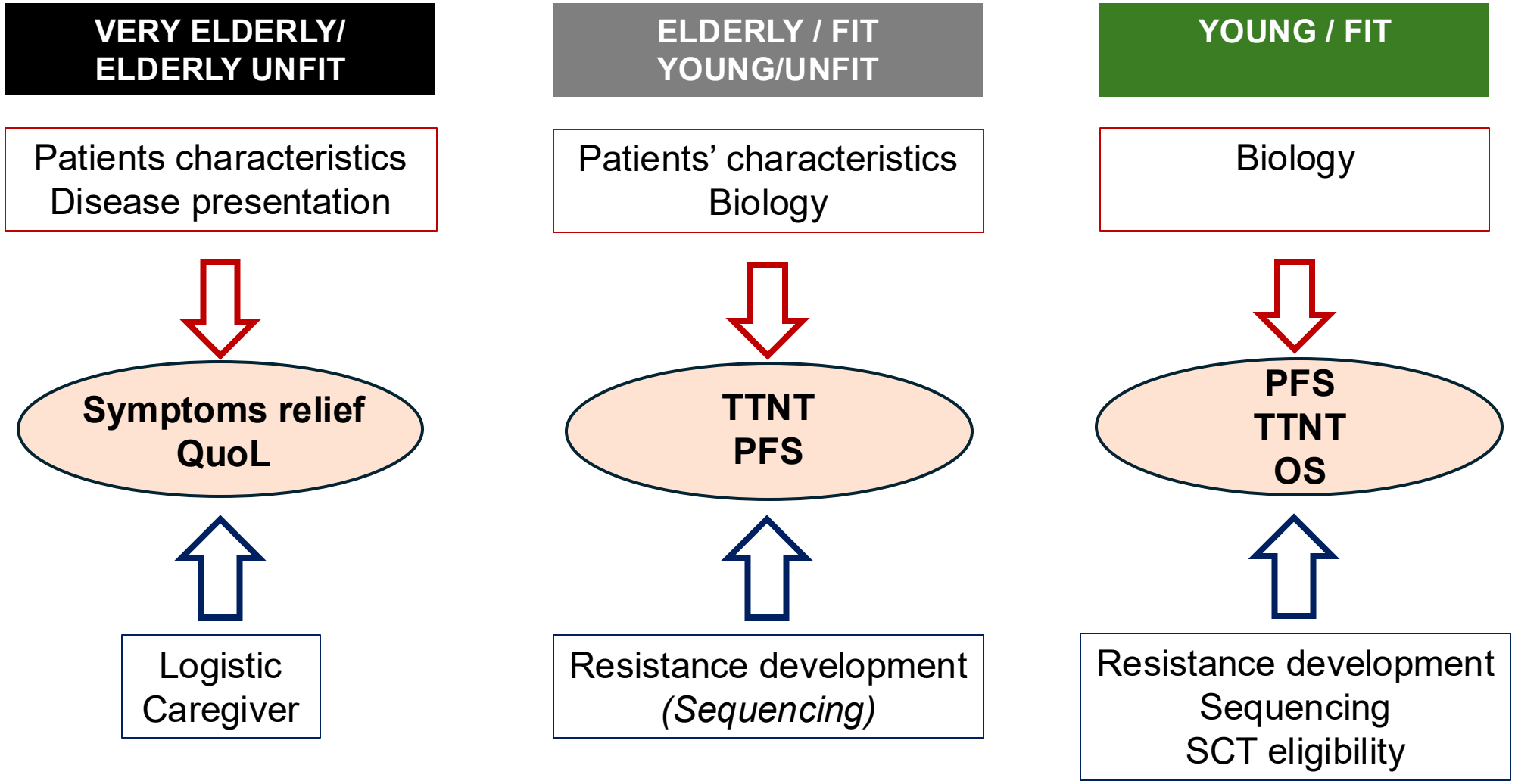
# Independently of fitness, age matters in treatment decisions (*what is treatment goal?*)




*Speaker's personal view*

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