From trial data to individual patients in CLL

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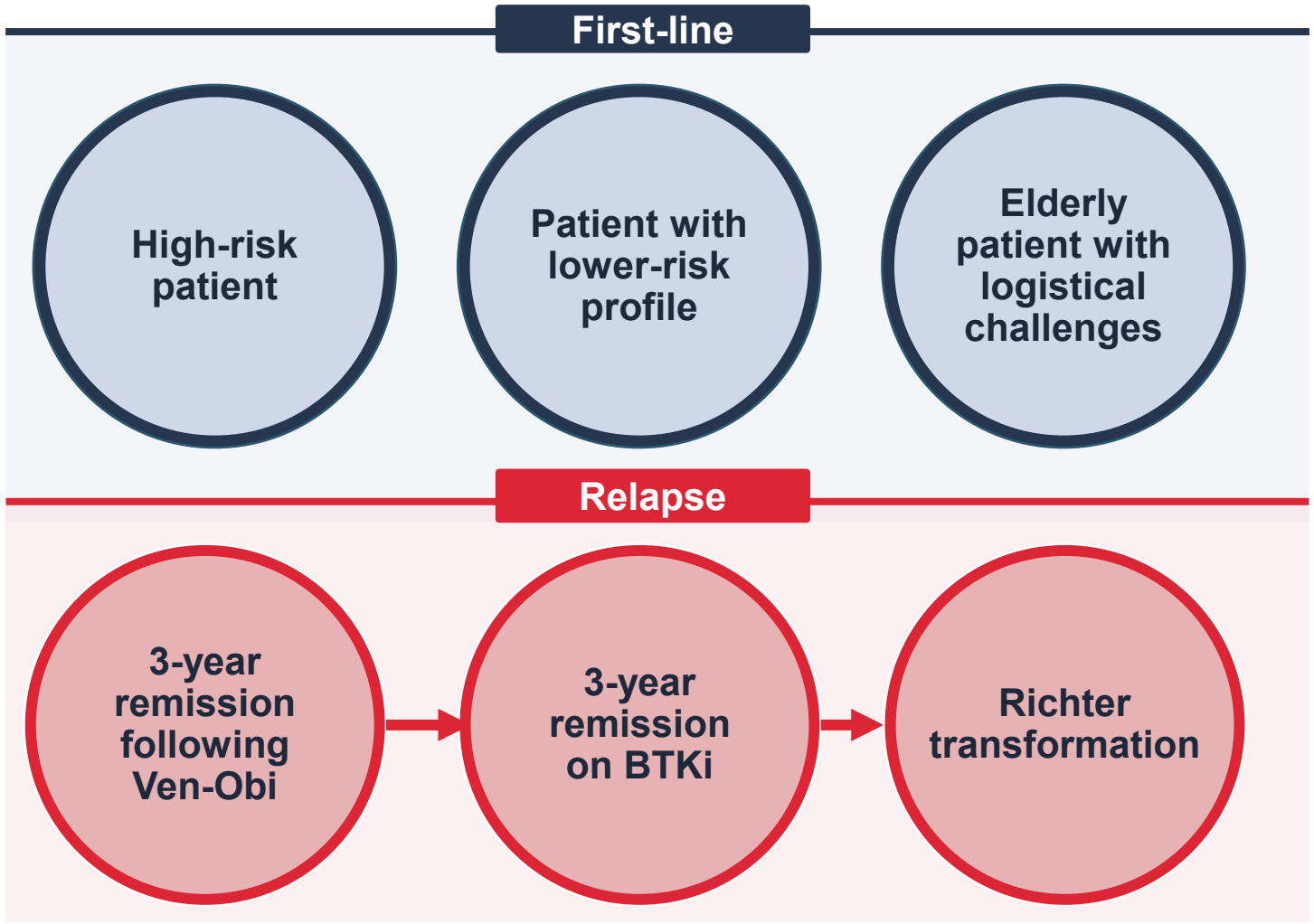
Disclosures

- Advisory board: AbbVie, AstraZeneca, BeiGene, Johnson & Johnson, Lilly
- Speaker bureau: AbbVie, BeiGene, Johnson & Johnson, Lilly

Variations on a CLL case: Exploring different clinical scenarios



How would you manage the patient and why?

How would you make your treatment decision?

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; Ven-Obi, venetoclax-obinutuzumab.

Patient scenario 1

Previously untreated CLL

Age	70 years
History with CLL	Recent CLL diagnosis following a routine examination; experienced increasing fatigue in recent weeks
Patient characteristics	• ECOG PS: 0 • No comorbidities and no comedications
Laboratory findings	• WBC count: 128 × 10^9/L → 70% lymphocytes • Hemoglobin: 9.3 g/dL / 5.8 mmol/L • Platelet count: 75 × 10^9/L
Genetic testing	• Unmutated IGHV • del(17p) • *TP53* mutated

First-line

How would you manage the patient and why?

What further information would be helpful to inform clinical decision-making?

This is a hypothetical patient case scenario intended for educational purposes only.

CLL, chronic lymphocytic leukemia; del, deletion; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IGHV, immunoglobulin heavy chain variable; WBC, white blood cell.

Ask the audience

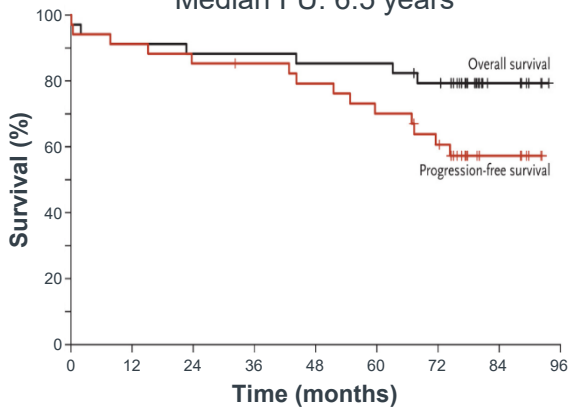
How would you treat this patient?

- Chemoimmunotherapy
- Venetoclax-obinutuzumab
- Continuous zanubrutinib, acalabrutinib, or ibrutinib
- Acalabrutinib-obinutuzumab
- Ibrutinib-venetoclax
- Other
- Clinical trial with novel agent

Studies of continuous BTKi therapies have shown consistent PFS outcomes in patients with and without del(17p) and/or *TP53* mutations

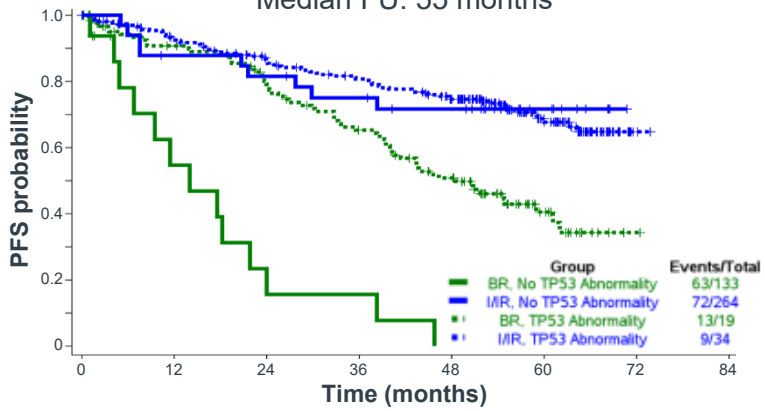
Phase II trial: Ibrutinib monotherapy in patients with *TP53* aberrations[1]

Median FU: 6.5 years



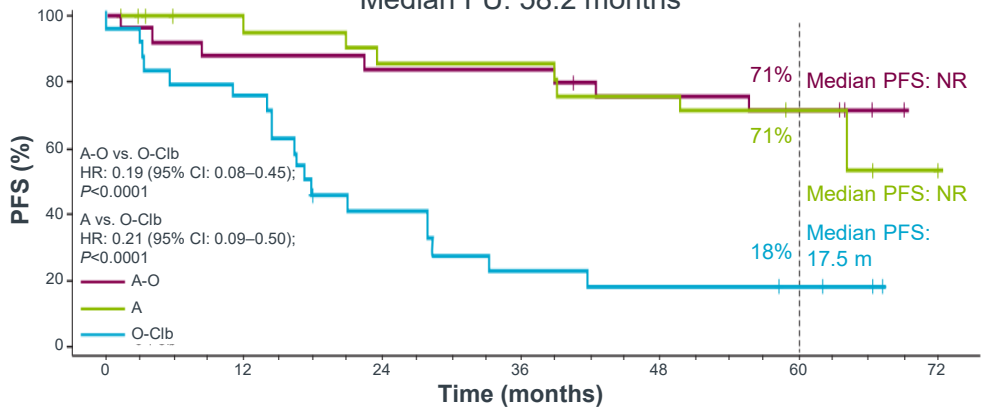
ALLIANCE: Ibrutinib vs. IR vs. BR[2]

Median FU: 55 months



ELEVATE-TN: Acalabrutinib vs. A-O vs. O-Clb in patients with del(17p) and/or mutated *TP53*[3]

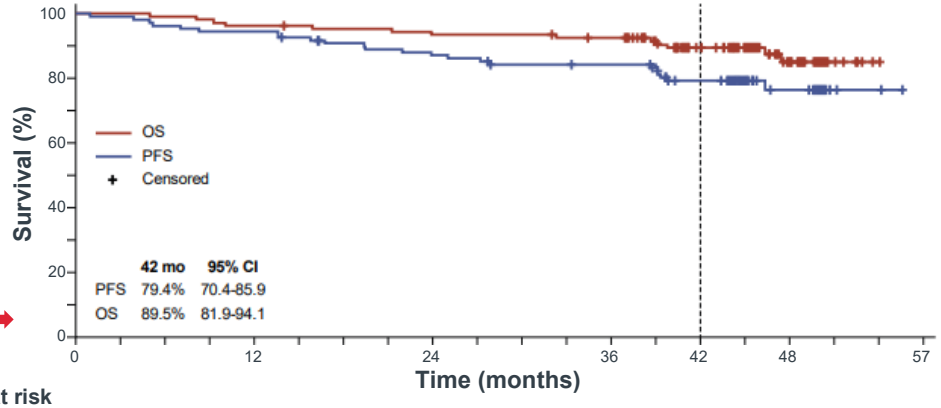
Median FU: 58.2 months



SEQUOIA Arm C: Zanubrutinib monotherapy in patients with del(17p)[4]

Median FU: 47.9 months

110 patients →



No. at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
OS	110	110	109	108	106	105	104	104	102	102	102	100	99	87	72	52	33	9	1	0
PFS	110	109	106	104	104	101	98	96	93	93	89	89	88	85	75	32	26	3	2	0

PFS with BTKi monotherapy is consistent between patients with and without del(17p) and/or *TP53* mutations

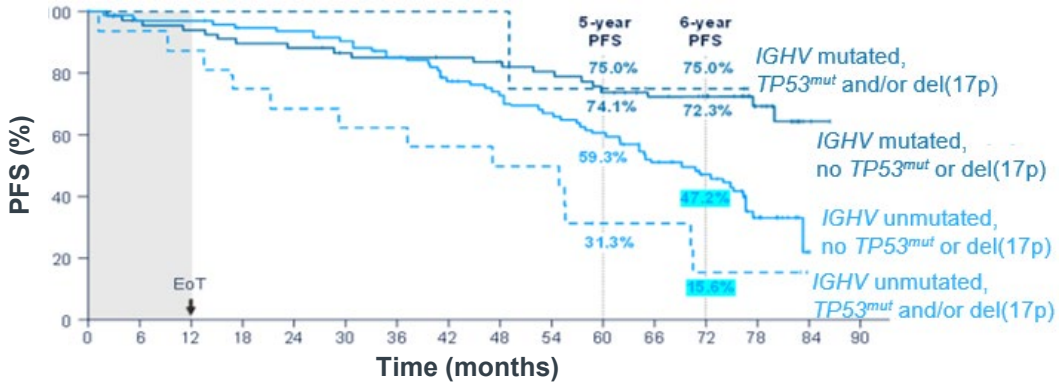
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

A, acalabrutinib; BR, bendamustine-rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; Clb, chlorambucil; del, deletion; FU, follow-up; HR, hazard ratio; I, ibrutinib; IR, ibrutinib-rituximab; NR, not reached; O, obinutuzumab; OS, overall survival; PFS, progression-free survival. 1. Ahn IE *et al*. *N Engl J Med* 2020; 383 (5): 498–500. 2. Woyach JA *et al*. *Blood* 2024; 143 (16): 1616–1627. 3. Sharman JP *et al*. Oral presentation at ASCO 2022; Chicago, IL, USA, June 3–7, 2022. 4. Munir T *et al*. Oral presentation at EHA 2023; Frankfurt, Germany, June 8–11, 2023.

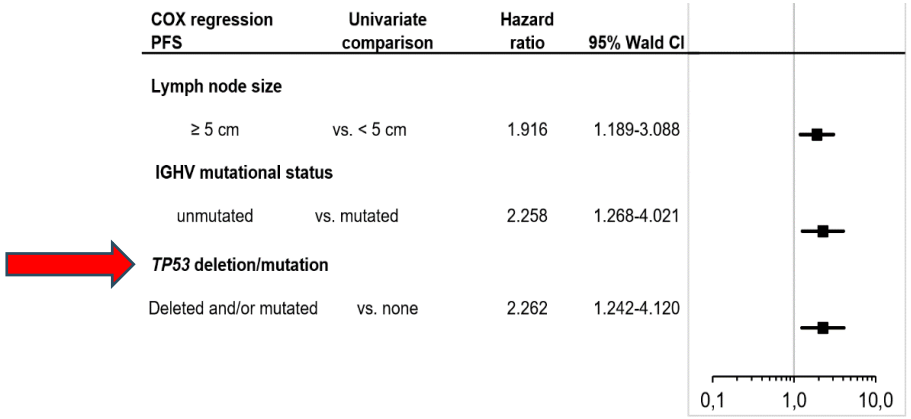
del(17p)/mutated *TP53* was a negative prognostic marker with ibrutinib-venetoclax in the CAPTIVATE study

Venetoclax-obinutuzumab

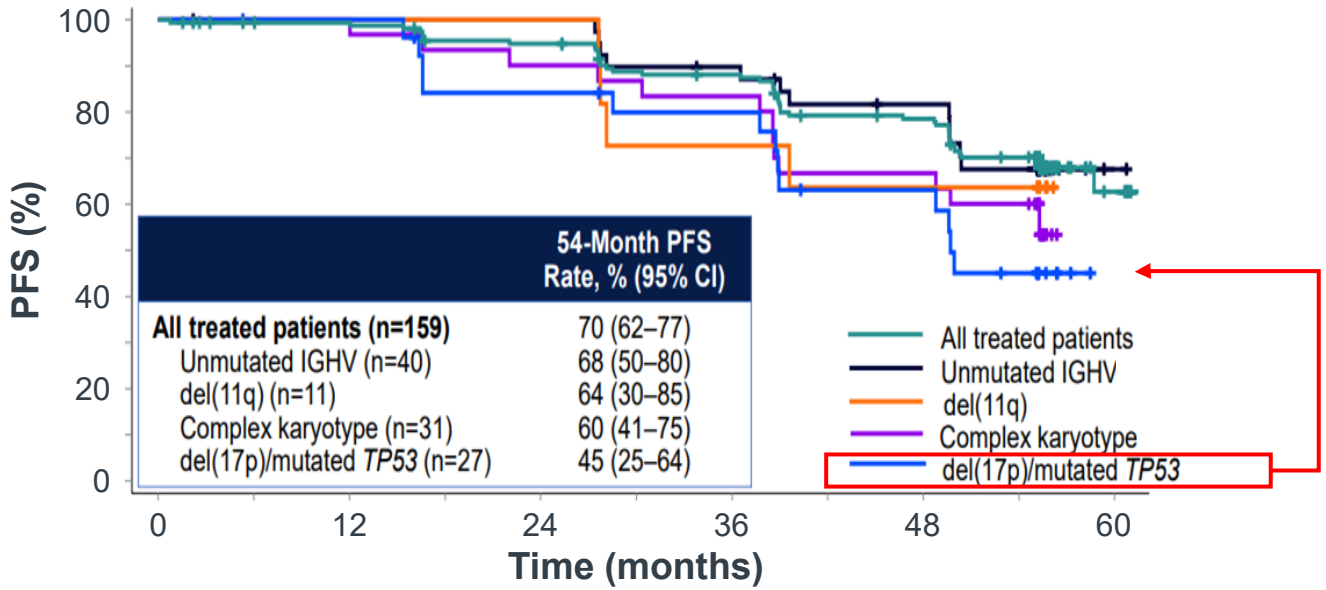
PFS according to IGHV and del(17p)/*TP53*[1]



Negative prognostic factors for PFS[1]



Captivate Phase II: Ibrutinib-venetoclax[2]



CI, confidence interval; del, deletion; EoT, end of treatment; IGHV, immunoglobulin heavy chain variable; mut, mutated; PFS, progression-free survival.

1. Al Sawaf O *et al*. Oral presentation at EHA 2023; Frankfurt, Germany, June 8–11, 2023. 2. Ghia P *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023.

Slide courtesy of Alessandra Tedeschi.

Patient scenario 2

Previously untreated CLL

Age	70 years
History with CLL	Recent CLL diagnosis following a routine examination; experienced increasing fatigue in recent weeks
Patient characteristics	• ECOG PS: 0 • No comorbidities and no comedications
Laboratory findings	• WBC count: 128 × 10^9/L → 70% lymphocytes • Hemoglobin: 9.3 g/dL / 5.8 mmol/L • Platelet count: 75 × 10^9/L
Genetic testing	• Unmutated IGHV • FISH results normal • *TP53* wild-type
Lymph nodes	Abdominal LN: 8 cm

How would you manage the patient and why?

What is the impact of IGHV status and the 8 cm abdominal lymph node on your decision?

This is a hypothetical patient case scenario intended for educational purposes only.

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence *in situ* hybridization; IGHV, immunoglobulin heavy chain variable; LN, lymph node; WBC, white blood cell.

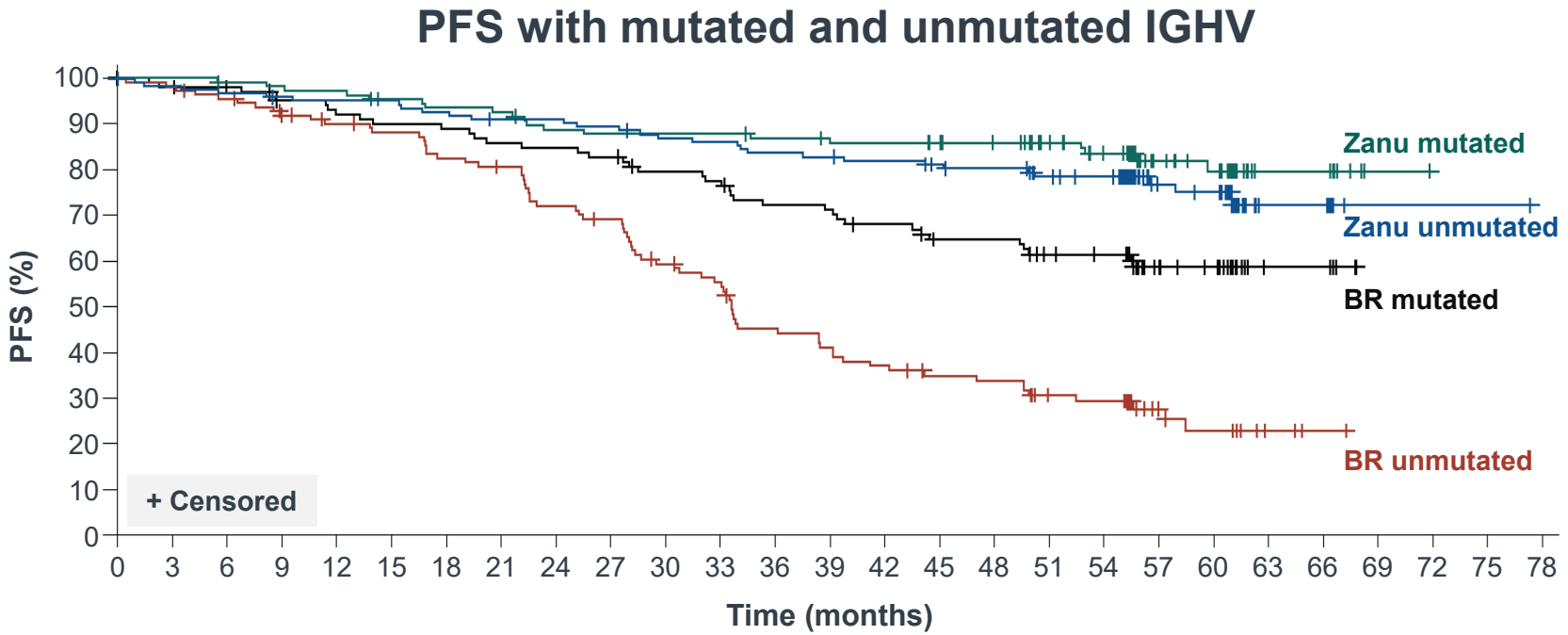
Ask the audience

How would you treat this patient?

- Chemoimmunotherapy
- Venetoclax-obinutuzumab
- Continuous zanubrutinib, acalabrutinib, or ibrutinib
- Acalabrutinib-obinutuzumab
- Ibrutinib-venetoclax
- Other
- Clinical trial with novel agent

PFS outcomes are independent of IGHV status with zanubrutinib

SEQUOIA long-term follow-up



Zanu mIGHV	109	109	107	106	105	101	99	98	93	92	92	92	90	88	88	86	83	77	69	41	36	11	11	1	0		
Zanu uIGHV	125	122	120	118	117	117	114	111	111	109	105	104	101	100	98	93	91	84	81	45	43	8	8	1	1	1	0
BR mIGHV	109	100	98	93	90	88	87	84	83	81	76	74	68	67	63	58	58	52	50	25	22	5	5	0			
BR uIGHV	123	112	108	102	96	93	87	84	75	71	60	55	44	40	36	32	31	24	23	12	9	3	1	0			

Zanubrutinib mIGHV vs uIGHV
HR: 1.35
(95% CI: 0.76–2.40);
P=0.5194

Overall PFS

60-week (95% CI)
- Zanu: 75.8% (69.0–81.3)
- BR: 40.1% (32.7–47.3)

COVID-19 adjusted (95% CI)
- Zanu: 78.7% (69.0–81.3)
- BR: 40.6% (32.7–47.3)

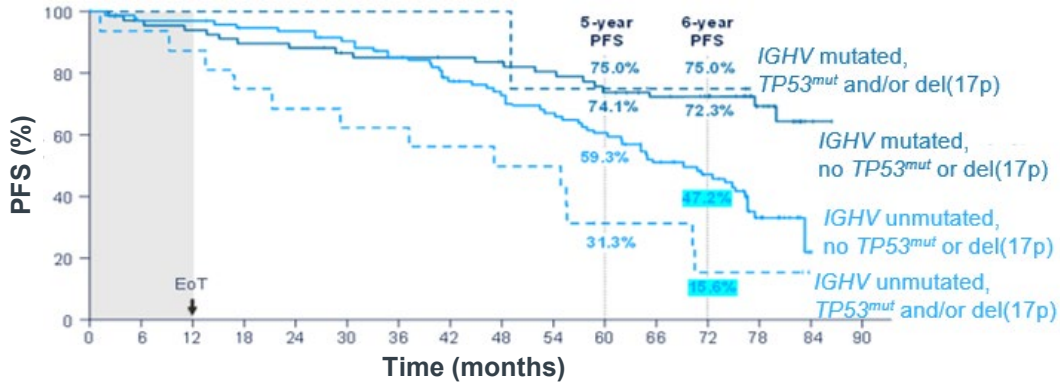
BR, bendamustine-rituximab; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable; PFS, progression-free survival; Zanu, zanubrutinib.

Shadman M *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024.

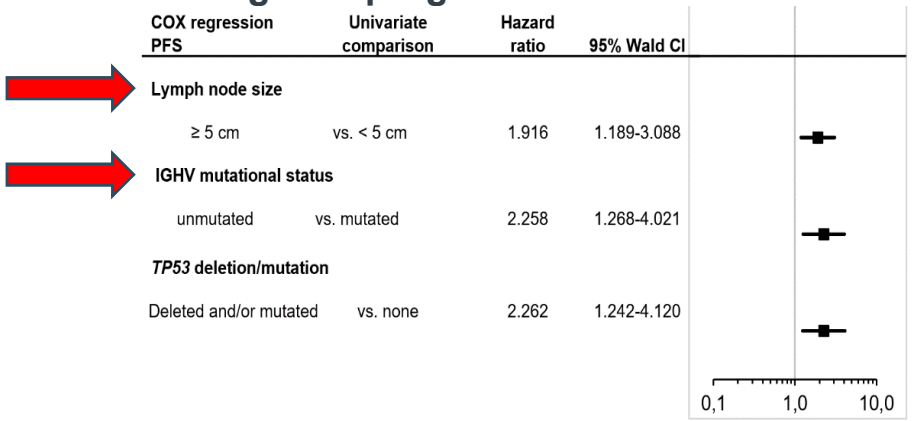
Unmutated IGHV and bulky disease with venetoclax-based fixed-duration therapy*

Venetoclax-obinutuzumab

PFS according to IGHV and del(17p)/*TP53*[1]

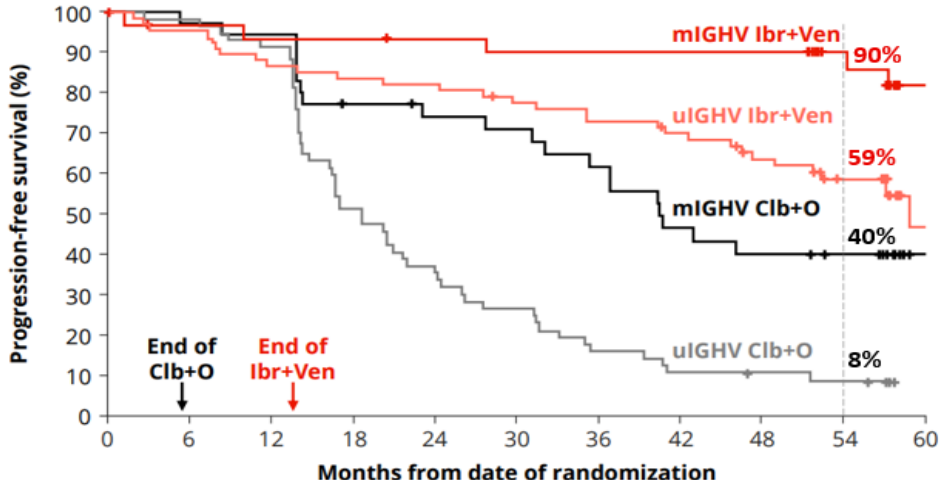


Negative prognostic factors for PFS[1]



Venetoclax-ibrutinib

GLOW:* IV vs. Clb-O[2]



Estimated 60-month PFS rates with IV[3]

- uIGHV: 52.2%
- mIGHV: 82.5%

No difference in TTNT for patients with mIGHV vs. uIGHV
HR (95% CI): 1.20 (0.31–4.60); *P*=0.7878

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

*Patients with del(17p) or known *TP53* mutations at screening were excluded from GLOW. CI, confidence interval; Clb, chlorambucil; del, deletion; Ibr, ibrutinib; IV, ibrutinib-venetoclax; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable; mut, mutated; O, obinutuzumab; PFS, progression-free survival; TTNT, time to next treatment; Ven, venetoclax. 1. Al Sawaf O *et al*. Oral presentation at EHA 2023; Frankfurt, Germany, June 8–11, 2023. 2. Moreno C *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023. 3. Niemann CU *et al*. Poster 1871 presented at ASH 2024; San Diego, CA, USA, December 7–10, 2024.
Slide courtesy of Alessandra Tedeschi.

Patient scenario 3

Previously untreated CLL

Age	83 years
History with CLL	Recent CLL diagnosis
Patient characteristics	• Diabetes, insulin-dependent • Chronic obstructive pulmonary disease
Logistics	• Lives alone • No caregiver • Far from hospital
Genetic testing	• Unmutated IGHV • FISH: trisomy 12 • *TP53* wild-type

How would you manage this patient and why?

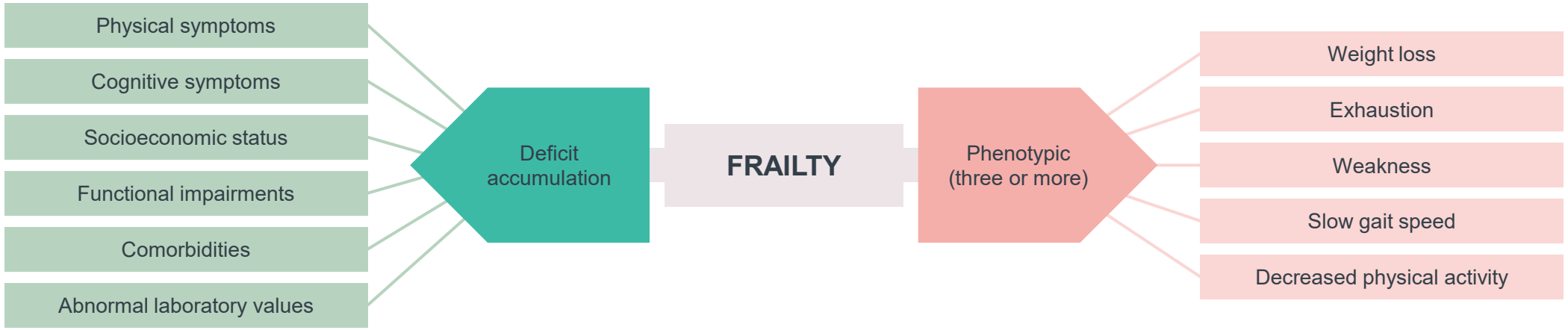
What impact do the comorbidities and logistics have on your decision?

This is a hypothetical patient case scenario intended for educational purposes only.

CLL, chronic lymphocytic leukemia; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable.

Frailty is not a comorbidity (1)

Condition characterized by a decline in physiological reserves and an increased vulnerability to stressors, resulting in a higher risk of adverse outcomes



Source: González-Gascón-y-Marín *et al*. 2023.[1]

- The prevalence of frailty in community-dwelling older adults aged 70 years tends to be **~15–30%**[1]
- In six trials of the German CLL Study Group which evaluated first-line targeted therapy, only 4.6% of the 717 patients were over 80 years of age[1]

CCL, chronic lymphocytic leukemia.

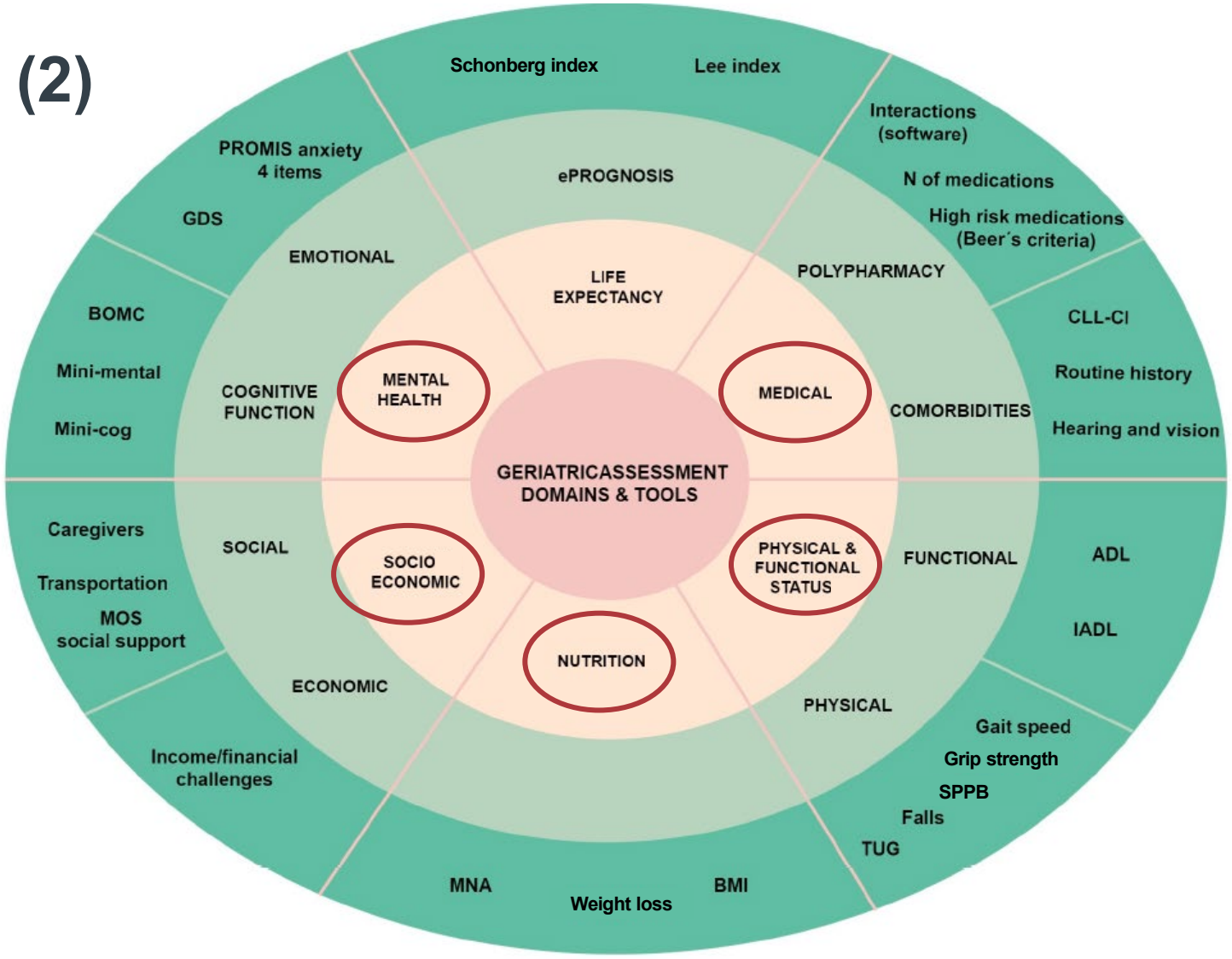
1. González-Gascón-y-Marín I *et al*. *Cancers (Basel)* 2023; 15 (17): 4391.

Frailty is not a comorbidity (2)

- Comprehensive approach for HCPs to develop **personalized care plans tailored to the unique requirements of older patients**[1]
- 2023 ASCO guidelines on managing vulnerabilities in older patients receiving systemic cancer therapy have termed this approach “GA-guided management (GAM)”[2]

Evaluated by the **Practical Geriatric Assessment** tool[2]

Essential domains that GA should encompass according to the 2023 ASCO guidelines[2]



Source: González-Gascón-y-Marín *et al*. 2023.[1]

ADL, activities of daily living; ASCO, American Society of Clinical Oncology; BMI, body mass index; BOMC, Blessed Orientation-Memory-Concentration Test; CLL-CI, chronic lymphocytic leukemia-comorbidity index; GA, geriatric assessment; GDS, Geriatric Depression Scale; HCP, healthcare professional; IADL, instrumental activities of daily living; MNA, Mini Nutritional Assessment; MOS, Medical Outcomes Study; PROMIS, Patient-Reported Outcomes Measurement Information System; SSPB, short physical performance battery; TUG, Timed Up and Go Test.

1. González-Gascón-y-Marín I *et al*. *Cancers (Basel)* 2023; 15 (17): 4391. 2. Dale W *et al*. *J Clin Oncol* 2023; 41 (26): 4293–4312.

Patient scenario 4A

Relapse after venetoclax-obinutuzumab

Age	74 years
History with CLL	First-line Ven-Obi (best response: CR)
Patient characteristics	• ECOG PS: 1 • No comorbidities and no comedications
Laboratory findings	• WBC count: 54 × 10^9/L → 85% lymphocytes • Hemoglobin: 8.7 g/dL / 5.4 mmol/L • Platelet count: 78 × 10^9/L
Genetic testing	• Unmutated IGHV • FISH result: del(11q) • *TP53* wild-type

The patient was treated with first-line venetoclax-obinutuzumab and remained in disease remission for 3 years off-treatment

How would you manage the patient and why?

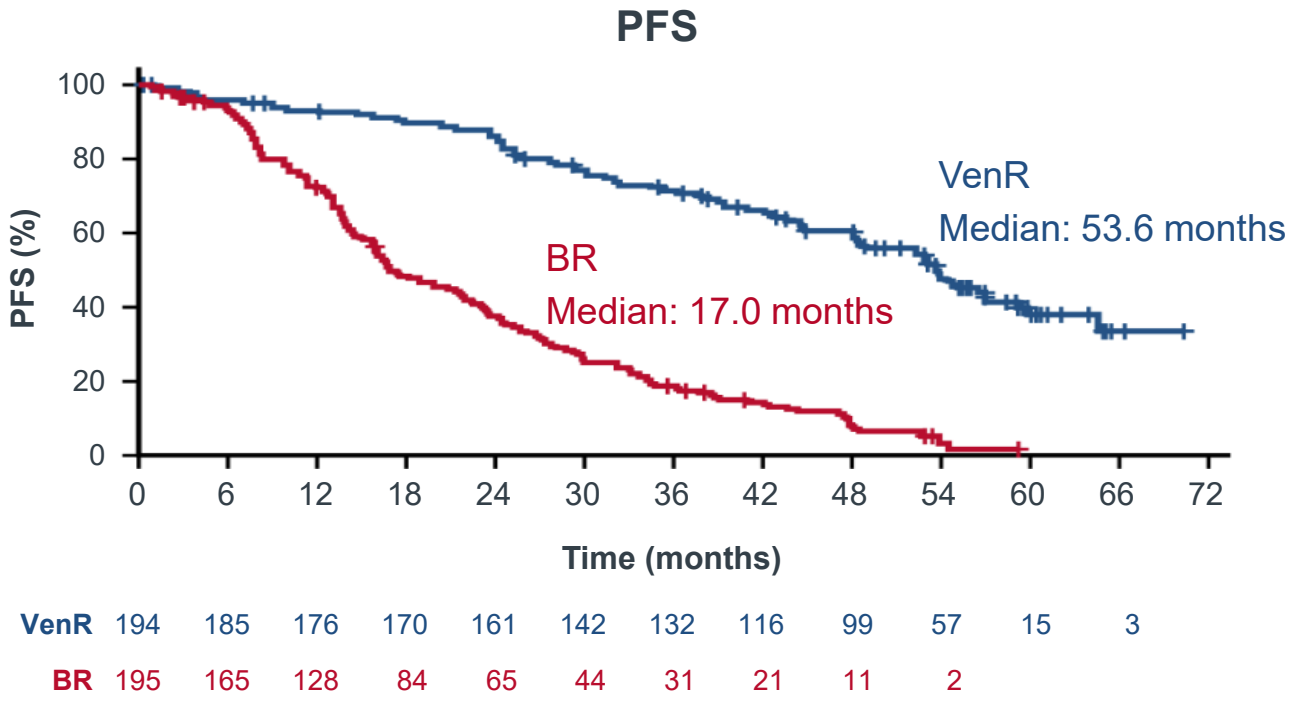
If you favor a BTKi at this stage, which agent would you select for the patient?

This is a hypothetical patient case scenario intended for educational purposes only.

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; del, deletion; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence *in situ* hybridization; IGHV, immunoglobulin heavy chain variable; Ven-Obi, venetoclax-obinutuzumab; WBC, white blood cell.

Venetoclax-rituximab is approved for R/R CLL

The MURANO study



Patients with prior exposure to venetoclax were ineligible for enrolment

Median TTNT

- **VenR**: 57.8 months
- **BR**: 23.9 months

Venetoclax-rituximab is approved by the EMA for R/R CLL based on the MURANO study data

BR, bendamustine-rituximab; CLL, chronic lymphocytic leukemia; EMA, European Medicines Agency; PFS, progression-free survival; R/R, relapsed/refractory; TTNT, time to next treatment; VenR, venetoclax-rituximab.

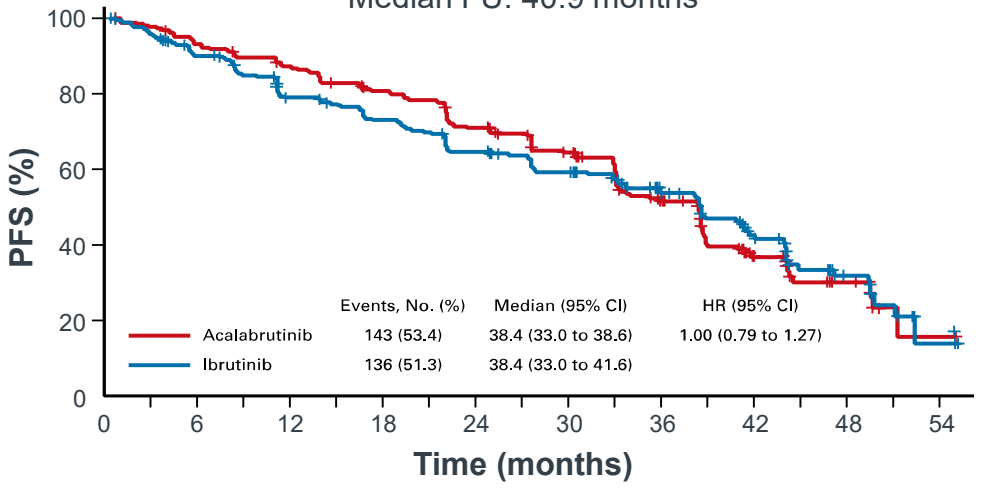
Seymour JF *et al*. *Blood* 2022; 140 (8): 839–850.

Head-to-head trials have compared the BTK inhibitors acalabrutinib and zanubrutinib with ibrutinib in the relapsed setting

ELEVATE-RR in patients with del(17p) and/or del(11q)[1]

Acalabrutinib vs. ibrutinib

Median FU: 40.9 months

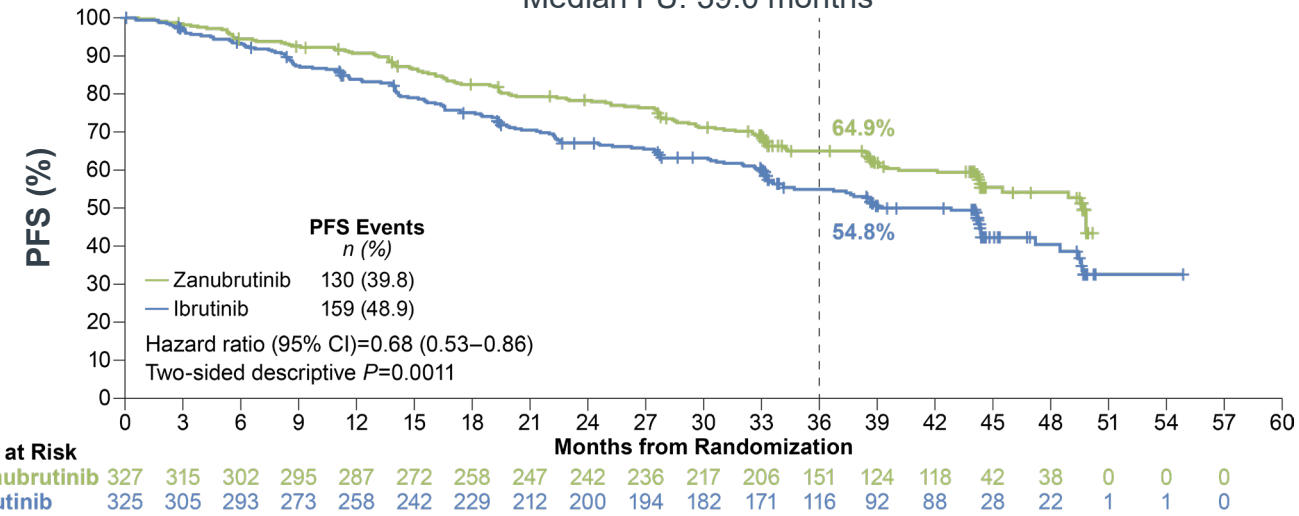


Median PFS with acalabrutinib with del(11q) or del(17p): 38.4 months

ALPINE study[2]

Zanubrutinib vs. ibrutinib

Median FU: 39.0 months



- **Sustained PFS benefit with zanubrutinib over ibrutinib, which was consistent across multiple sensitivity analyses**
  - Accounting only for PD and death events that occurred during active treatment, *P*=0.0206
  - Censoring for new CLL/SLL therapies, *P*=0.0014
  - Censoring for death due to COVID-19, *P*=0.0013
- No OS difference recorded

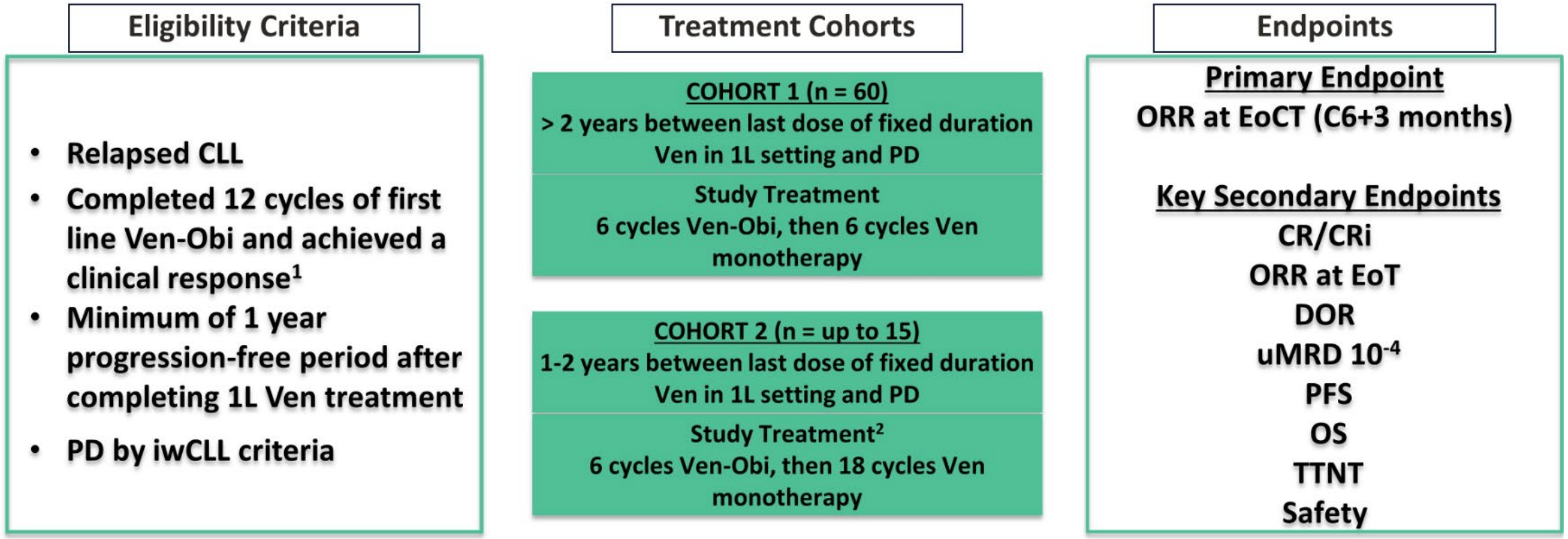
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

BTK, Bruton's tyrosine kinase; CI, confidence interval; CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; del, deletion; FU, follow-up; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; SLL, small lymphocytic leukemia.

1. Byrd JC *et al*. *J Clin Oncol* 2021; 39 (31): 3441–3452. 2. Brown JR *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023.

Venetoclax-obinutuzumab retreatment?

The ReVenG study

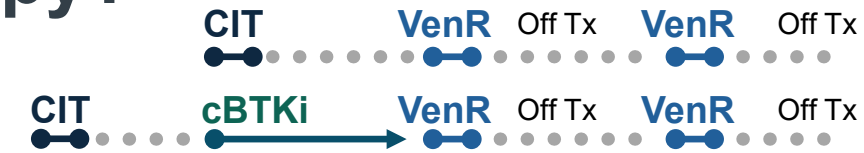


ReVenG is the first prospective clinical trial to evaluate the efficacy and safety of retreatment with Ven-Obi at the time of PD in patients who had initially responded to first-line Ven-Obi for ≥12 months after completing therapy

[1]Patients who stopped 1L VenG therapy earlier than 12 months but completed at least 9 months of therapy and had a documented clinical response may be eligible based on the investigator's discretion
[2]Patients with detectable MRD at EoT may continue venetoclax until PD based on patient choice and investigator discretion
1L, first-line; CLL, chronic lymphocytic leukemia; CR(i), complete remission (with incomplete marrow recovery); DOR, duration of response; EoCT, end of combination therapy (Ven-Obi); EoT, end of therapy; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; TTNT, time to next treatment; uMRD, undetectable minimal residual disease; Ven, venetoclax; Ven-Obi, venetoclax-obinutuzumab.
Davids MS *et al*. *Blood* 2021; 138 (Supplement 1): 2634.

Venetoclax-rituximab as second-line therapy?

The MURANO study



MURANO venetoclax retreatment substudy

- Median prior LOT before first VenR: 1[1]
- BCRi-exposed: 2.6%[1]

Out of **34** patients with PD who entered the retreatment substudy, **25** were retreated with VenR[2]

Phase III
R/R CLL
(N=389)[1]

1:1 randomization

Initial treatment[1]

- n=194: Venetoclax* + Rituximab ×6 cycles
- n=195: Bendamustine* ×6 cycles + Rituximab ×6 cycles

Time off treatment:[2]
Median 2.3 years (range: 1.2–3.1)

mPFS of MURANO full cohort for VenR:
54.7 months
(~4.5 years; 95% CI: 52.3–59.9)

Retreatment†,2:
Up to 2 years on treatment (n=25)

Best ORR: 72%

- Most patients were classified as high risk: 32% had del(17p) and/or *TP53* mutation, 88% IGHV unmutated, 32% GC‡ ≥5
- mPFS: 23.3 months (95% CI: 15.6–24.3)

Median follow-up: 33.4 months

*To PD, unacceptable toxicity, or 2 years[1]; †Median treatment duration: 11.4 (range: 0.7–37.6) months. Responses in patients treated with next line of therapy for insufficient time to have response assessed, or patients who had no response assessments reported were considered unevaluable[2]; ‡≥3 copy number alterations.[2]

BCRi, B-cell receptor pathway inhibitor; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CI, confidence interval; CIT, chemoimmunotherapy; del, deletion; GC, genomic complexity; IGHV, immunoglobulin heavy chain variable; LOT, lines of therapy; mPFS, median progression-free survival; ORR, overall response rate; PD, progressive disease; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; Tx, treatment; VenR, venetoclax-rituximab.

1. Seymour JF *et* al. *N Engl J Med* 2018; 378 (12): 1107–1120. 2. Kater AP *et al*. Oral presentation at EHA 2023; Frankfurt, Germany, 8–11 June 2023.

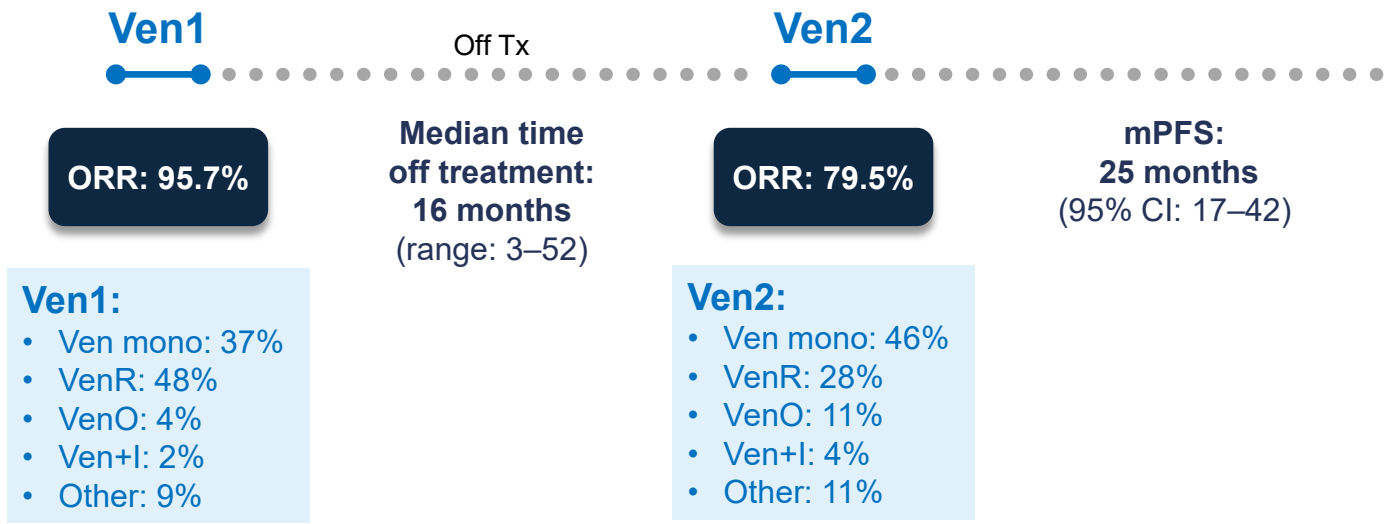
Slide courtesy of Alessandra Tedeschi.

Venetoclax-based retreatment?

A multicenter, international, retrospective study

Multicenter, retrospective study (N=46)

- Median prior LOT: 2 (range: 0–10)
- Prior BTKi: 40%



BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; I, ibrutinib; LOT, lines of therapy; O, obinutuzumab; mPFS, median progression-free survival; ORR, overall response rate; R, rituximab; Tx, treatment; Ven1, initial venetoclax regimen; Ven2, second venetoclax-based regimen.

Thompson MC *et al. Blood Adv* 2022; 6 (15): 4553–4557.

Patient scenario 4B

Relapse on continuous BTKi

Age	77 years
History with CLL	3 years' remission following Ven-Obi (best response: CR); 3 years' remission on BTKi (best response: PR)
Patient characteristics	• ECOG PS: 1 • No comorbidities and no comedications
Laboratory findings	• WBC count: 127 × 10^9/L → 70% lymphocytes • Hemoglobin: 10.1 g/dL / 6.3 mmol/L • Platelet count: 77 × 10^9/L
Genetic testing	• Unmutated IGHV • FISH result: del(11q) • *TP53* wild-type • ***BTK* L528W**

The patient was treated with second-line cBTKi monotherapy and remained in disease remission for 3 years

How would you manage the patient and why?

What is the impact of *BTK* L528W?

This is a hypothetical patient case scenario intended for educational purposes only.

(c)BTKi, (covalent) Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; del, deletion; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence *in situ* hybridization; IGHV, immunoglobulin heavy chain variable; PR, partial response; Ven-Obi, venetoclax-obinutuzumab; WBC, white blood cell.

Ask the audience

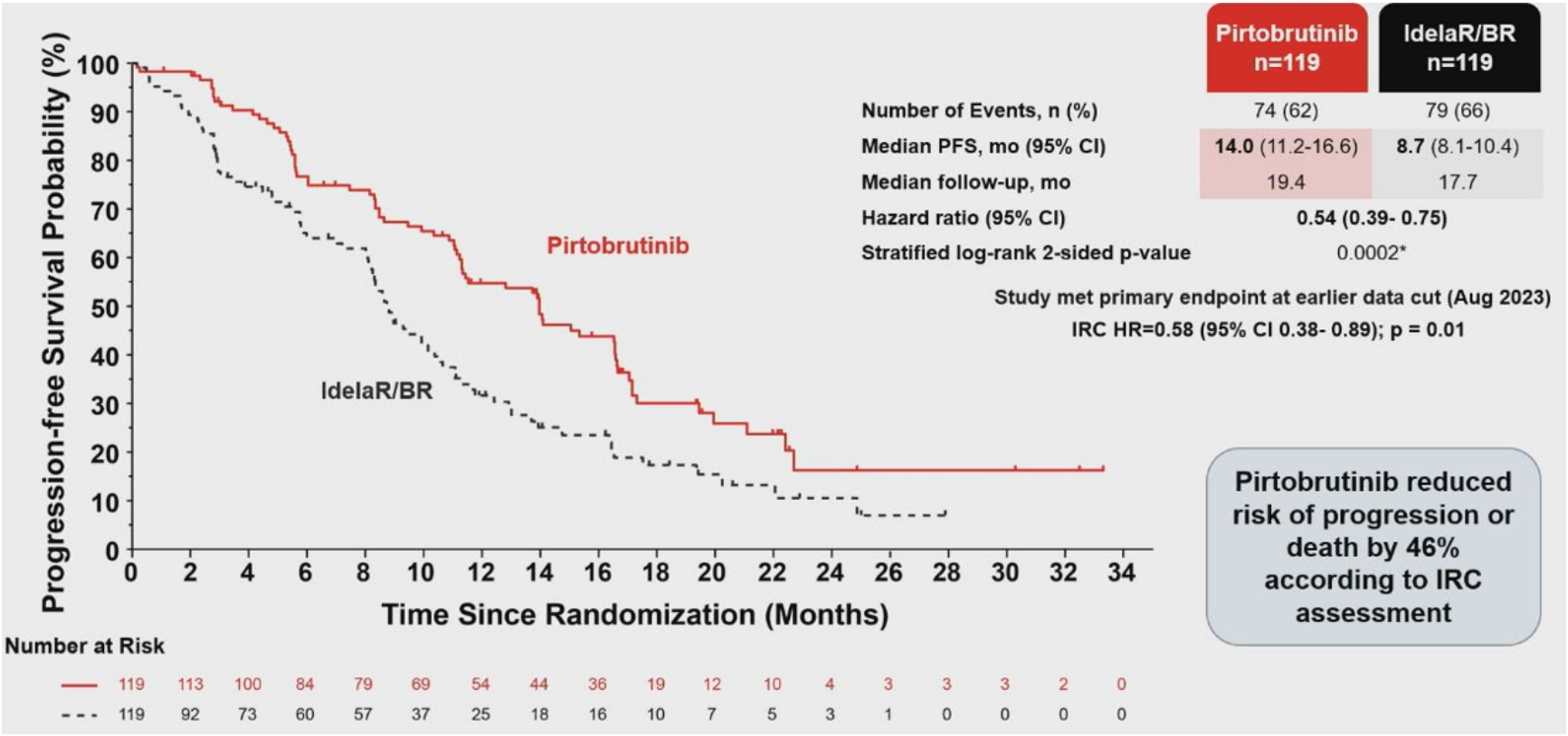
How would you treat this patient?

- Chemoimmunotherapy
- Fixed-duration venetoclax-rituximab
- Continuous zanubrutinib, acalabrutinib, or ibrutinib
- Acalabrutinib-obinutuzumab
- Ibrutinib-venetoclax
- Idelalisib + rituximab
- Pirtobrutinib
- Other
- Clinical trial with novel agent

Non-covalent BTK inhibitors

BRUIN study

High-risk: >50% del(17p) and/or *TP53* mutation and complex karyotype
Heavily pretreated population: 33% received ≥4 prior lines of therapy, ~50% received prior BCL2i



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39- 0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR=0.58 (95% CI 0.38- 0.89); p = 0.01

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

Subgroups

Consistent PFS benefit with pirtobrutinib vs. IdelaR/BR

Safety outcomes

Discontinuations

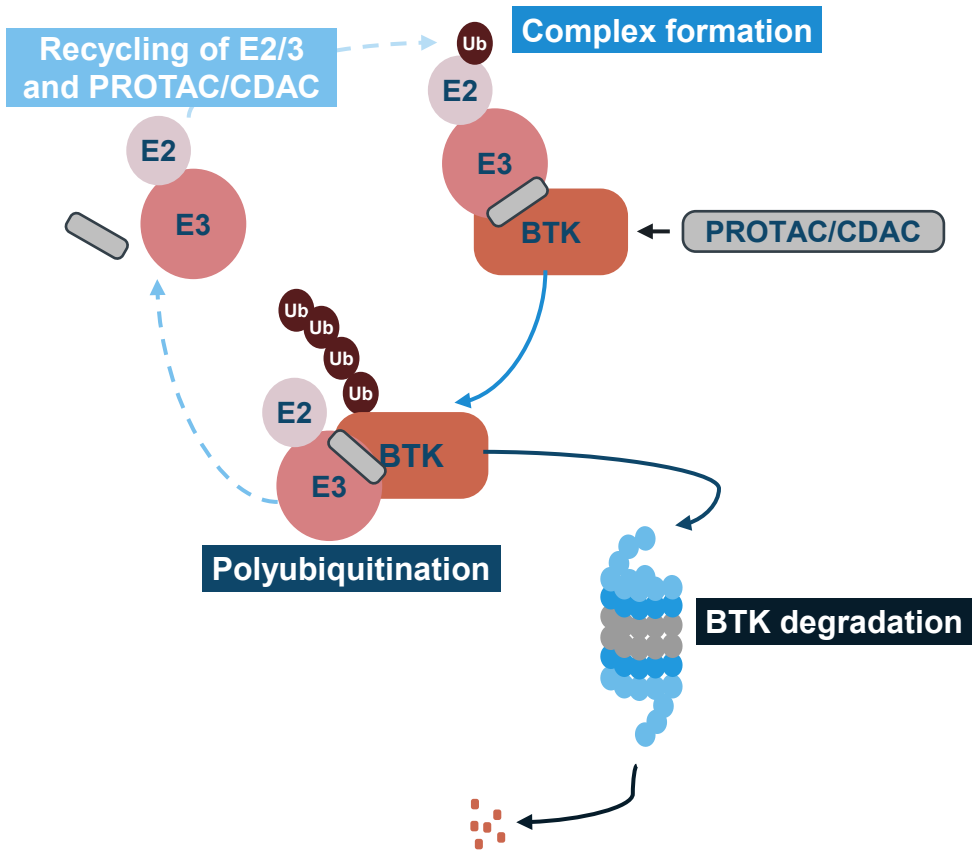
- Pirtobrutinib: 6/116 (5.2%)
- IdelaR/BR: 23/109 (21.1%)

BCL2i, B-cell lymphoma 2 inhibitor; BR, bendamustine-rituximab; BTK, Bruton's tyrosine kinase; CI, confidence interval; HR, hazard ratio; IdelaR, idelalisib-rituximab; IRC, independent review committee; PFS, progression-free survival

Sharman JP *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024.

BTK degraders are a potential future therapeutic option in the R/R setting

Targeting BTK for proteasomal degradation



Phase I
CaDAnCe-101 study of BTK degrader BGB-16673[1]

60 patients with R/R CLL/SLL enrolled
Median 4 prior lines of therapy

Safety
- Well tolerated
- No AF

ORR (n=49)
- Overall: 77.6%
- Prior cBTKi + BCL2i: 86.7%
- Prior cBTKi + BCL2i + ncBTKi: 58.3%

Phase Ia/b of BTK degrader NX-5948[2]

60 patients with R/R CLL/SLL enrolled
Median 4 prior lines of therapy

Safety
- Well tolerated
- One case of Grade 1 AF in a patient with pre-existing AF

ORR (n=49)
- Overall: 75.5%

AF, atrial fibrillation; BCL2i, B-cell lymphoma 2 inhibitor; (c/nc)BTK(i), (covalent/noncovalent) Bruton's tyrosine kinase (inhibitor); CDAC, chimeric degradation activation compound; CLL, chronic lymphocytic leukemia; ORR, overall response rate; PROTAC, proteolysis-targeting chimera; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; Ub, ubiquitin.

1. Thompson MC *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024. 2. Shah NN *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024.

Patient scenario 4C

Richter transformation

Age	78 years
History with CLL	4 years' remission following Ven-Obi; 3 years' remission on BTKi; 1 year of remission on pirtobrutinib
Patient characteristics	• ECOG PS: 1 • No comorbidities and no comedications
Laboratory findings	• WBC count: 7 × 10^9/L → 35% lymphocytes • Hemoglobin: 10.2 g/dL / 6.3 mmol/L • Platelet count: 120 × 10^9/L • PET scan: left axillary 18F-FDG uptake with an SUV of 12 • Biopsy findings: DLBCL transformation

The patient was treated with pirtobrutinib, and remained in disease remission for 1 year before experiencing sudden weight loss and enlarged lymph nodes

PET scan reveals left axillary 18F-FDG uptake with an SUV of 12

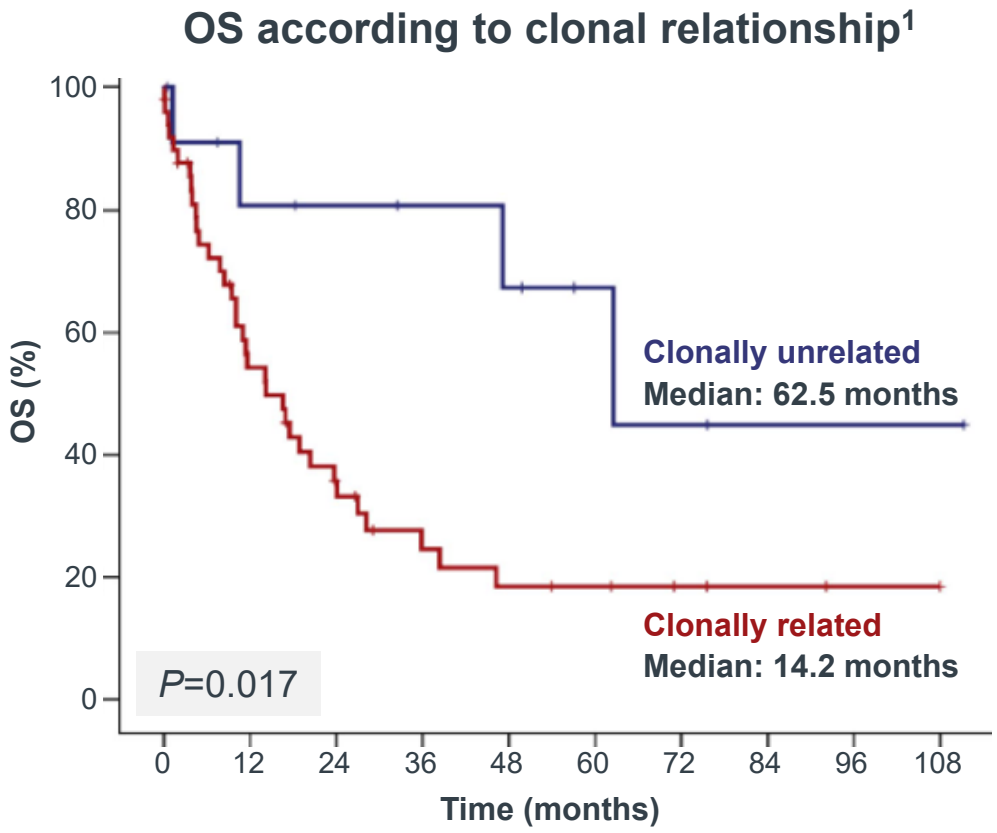
Biopsy confirms DLBCL transformation

What other information could help you make a treatment decision for this patient?

This is a hypothetical patient case scenario intended for educational purposes only.

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDG, fluorodeoxyglucose; FISH, fluorescence *in situ* hybridization; IGHV, immunoglobulin heavy chain variable; PET, positron emission tomography; SUV, standardized uptake value; Ven-Obi, venetoclax-obinutuzumab; WBC, white blood cell.

The clonal relationship of DLBCL-RT to the underlying CLL is a relevant prognostic factor in Richter transformation



~80% of DLBCL-RT are CLL clonally related[2]

Clonality should also guide treatment decisions

CLL, chronic lymphocytic leukemia; DLBCL-RT, Richter transformation diffuse large B-cell lymphoma; OS, overall survival.

1. Rossi D *et al*. *Blood* 2011; 117 (12): 3391–3401. 2. Ryan CE and Davids MS. Practical Management of Richter Transformation in 2023 and Beyond. In: *Am Soc Clin Oncol Educ Book* 2023; 43: e390804.

Patient scenario 4D

Richter transformation

Age	78 years
History with CLL	4 years' remission following Ven-Obi; 3 years' remission on BTKi; 1 year of remission on pirtobrutinib
Patient characteristics	• ECOG PS: 1 • No comorbidities and no comedications
Laboratory findings	• WBC count: 7 × 10^9/L → 35% lymphocytes • Hemoglobin: 10.2 g/dL / 6.3 mmol/L • Platelet count: 120 × 10^9/L • PET scan: left axillary 18F-FDG uptake with an SUV of 12 • Biopsy findings: DLBCL transformation

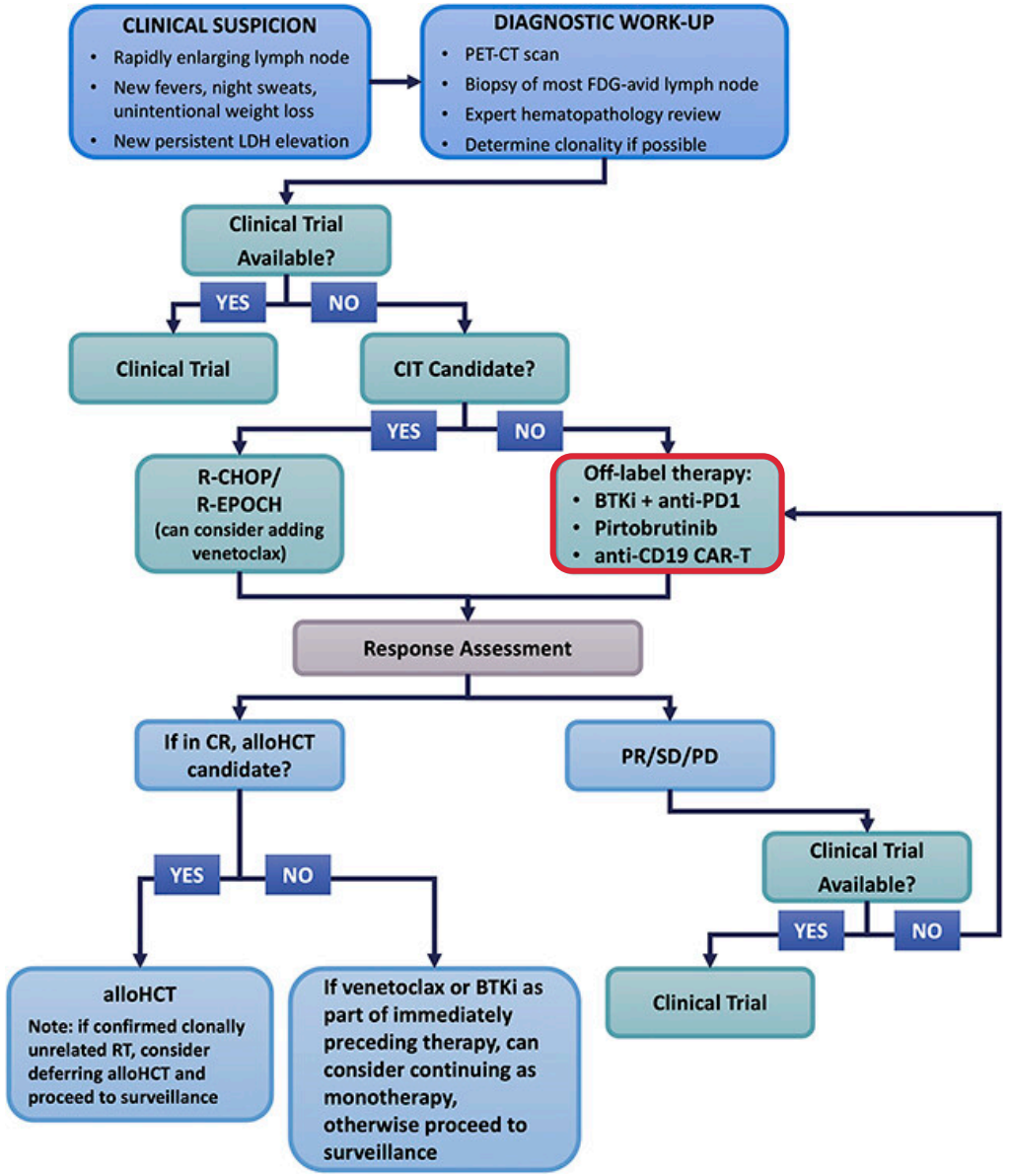
How would you manage this patient if the RT was clonally related to CLL?

How would you manage this patient if the RT was clonally unrelated to CLL?

This is a hypothetical patient case scenario intended for educational purposes only.

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDG, fluorodeoxyglucose; FISH, fluorescence *in situ* hybridization; IGHV, immunoglobulin heavy chain variable; PET, positron emission tomography; RT, Richter transformation; SUV, standardized uptake value; Ven-Obi, venetoclax-obinutuzumab; WBC, white blood cell.

Chemoimmunotherapy is the most commonly used initial therapy for RT

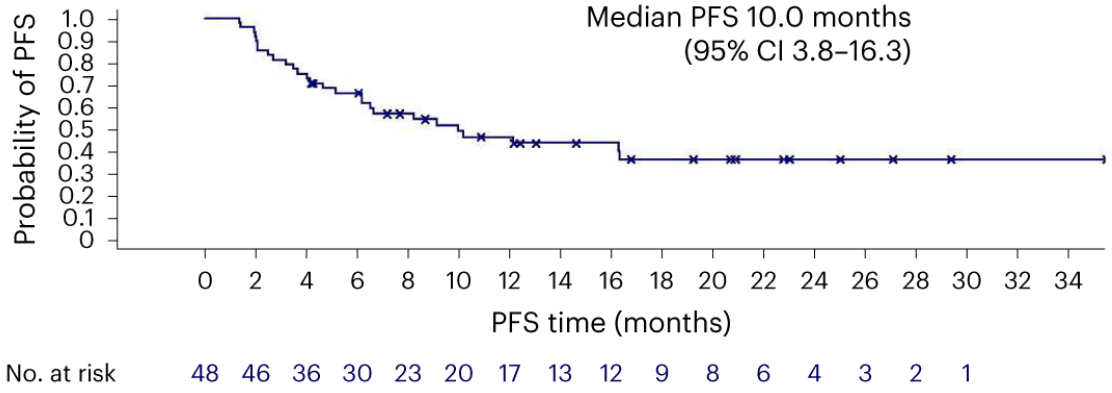


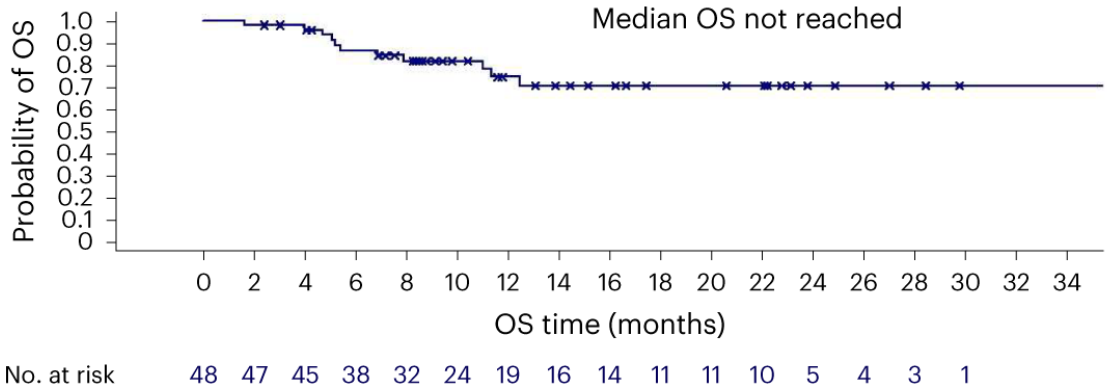
alloHCT, allogeneic hematopoietic cell transplantation; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; CIT, chemoimmunotherapy; CR, complete response; FDG, fluorodeoxyglucose; LDH, lactate dehydrogenase; PD, progressive disease; PET-CT, positron emission tomography-computed tomography; PR, partial response; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; RT, Richter transformation; SD, stable disease.

Ryan CE and Davids MS. Practical Management of Richter Transformation in 2023 and Beyond. In: *Am Soc Clin Oncol Educ Book* 2023: 43: e390804.

Potential future therapeutic options for RT (1)

Tislelizumab plus zanubrutinib





Trial summary

- 48 patients with RT
- Median prior lines for CLL / RT: 3 (range: 1–6)
- Clonal relationship
  - Related: 26 (54.2%)
  - Unknown: 22 (45.8%)

- ORR: 58.3% (95% CI: 43.2–72.4)
- CRR: 18.8%
- PR: 39.6%
- 12-month OS: 74.7% (95% CI: 58.4–91.0)

CI, confidence interval; CLL, chronic lymphocytic leukemia; CRR, complete response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RT, Richter transformation.

Al-Sawaf O *et al*. *Nat Med* 2024; 30 (1): 240–248.

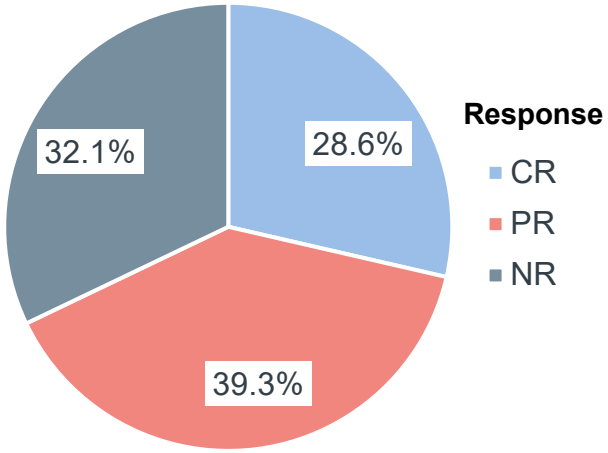
Venetoclax, atezolizumab and obinutuzumab combination in DLBCL-RT

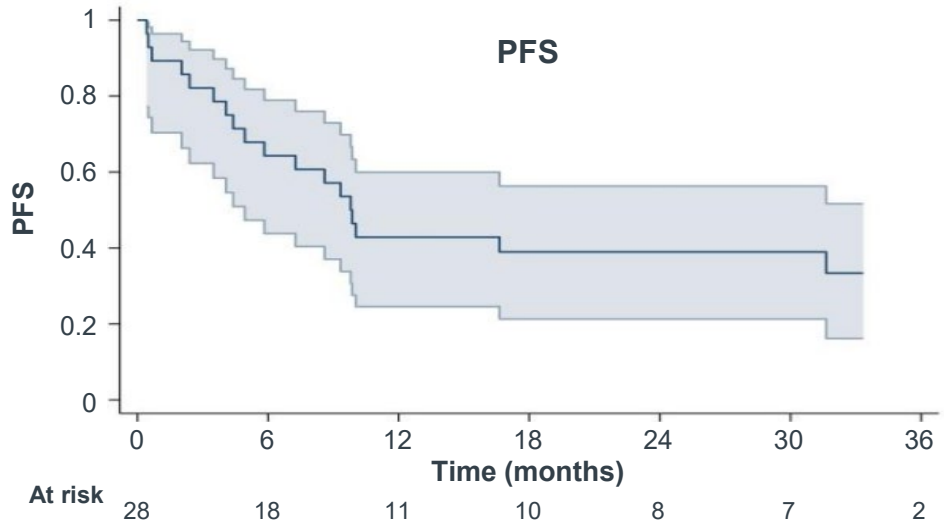
The Phase II MOLTO trial

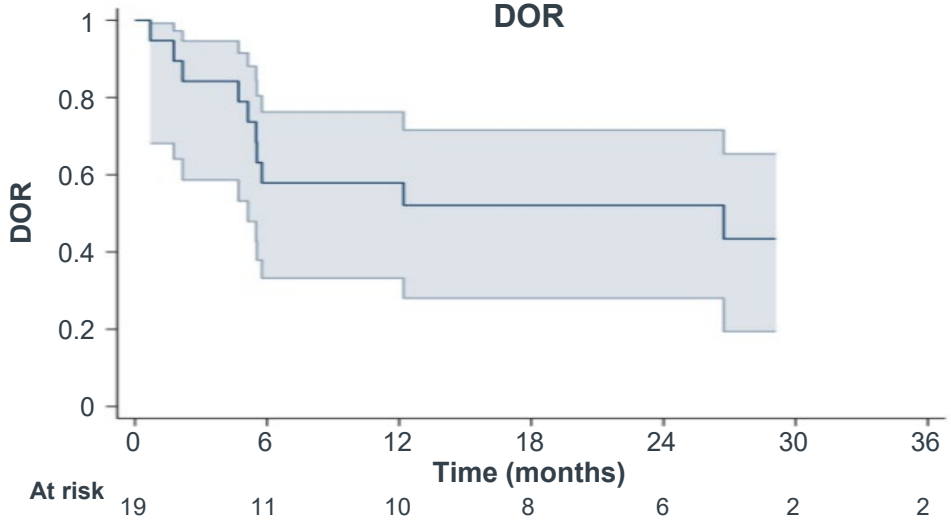
N=28

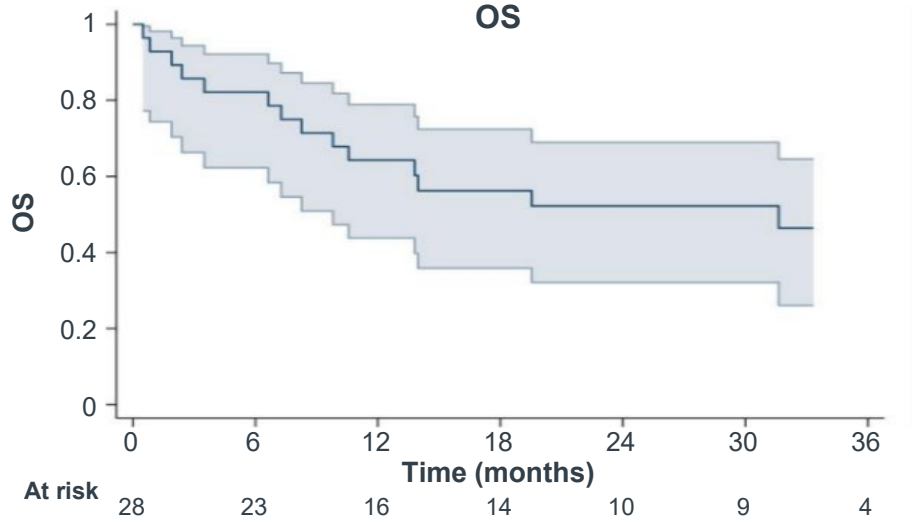
Median no. of previous CLL Tx: 1
Previously untreated RT: 100%
Clonally related: *20/24 (83%)*
Clonally unrelated: *4/24 (17%)*

ORR ITT: 68.3%







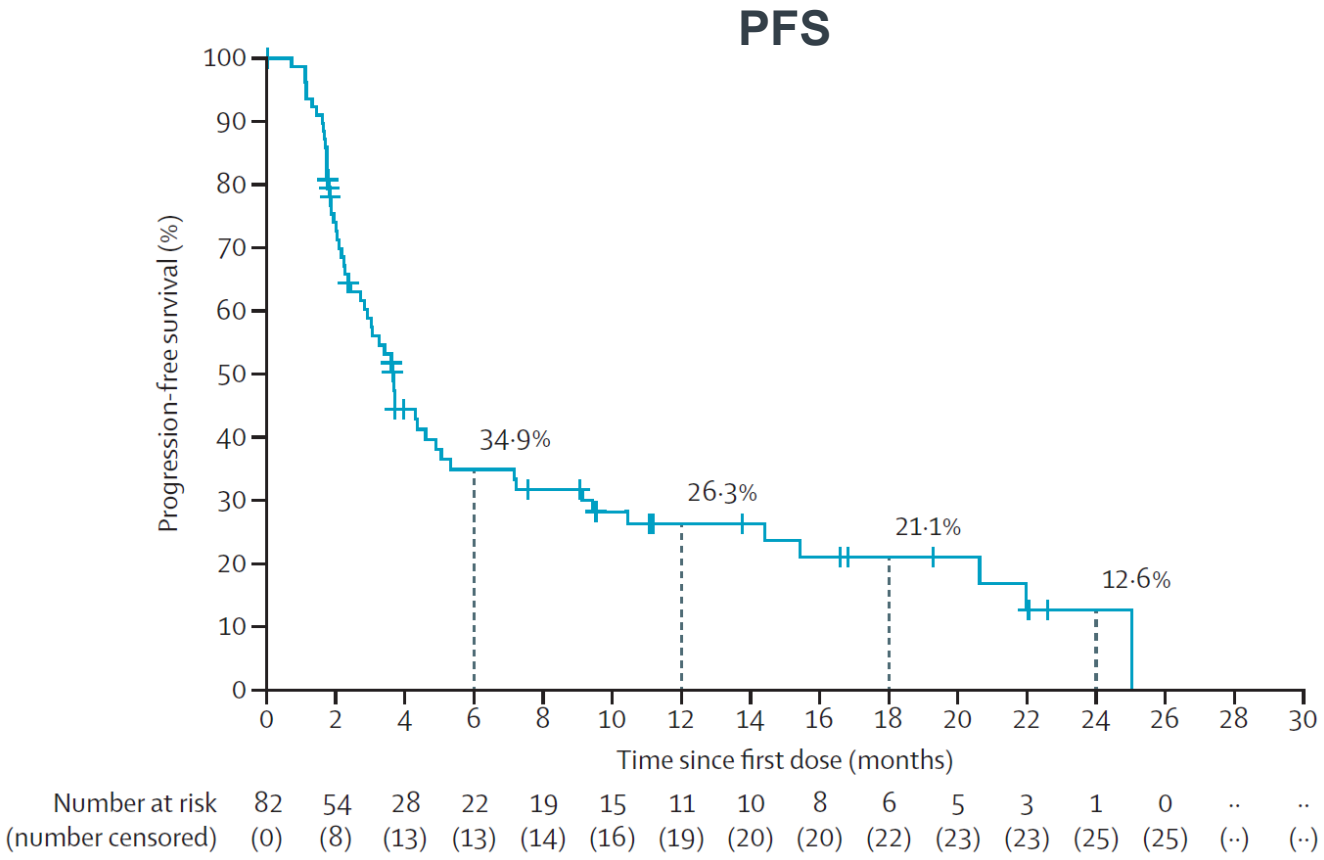


CLL, chronic lymphocytic leukemia; CR, compete response; DLBCL-RT, Richter transformation diffuse large B-cell lymphoma; DOR, duration of response; ITT, intention-to-treat; NR, no response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; RT, Richter transformation; Tx, treatment.

Tedeschi A *et al*. *Lancet Oncol* 2024; 25 (10): 1298–1309.

Potential future therapeutic options for RT (2)

Pirtobrutinib



Trial summary

- 82 patients with RT
- Median prior lines for CLL/RT: 4 (range: 0–13)
- Clonal relationship not reported

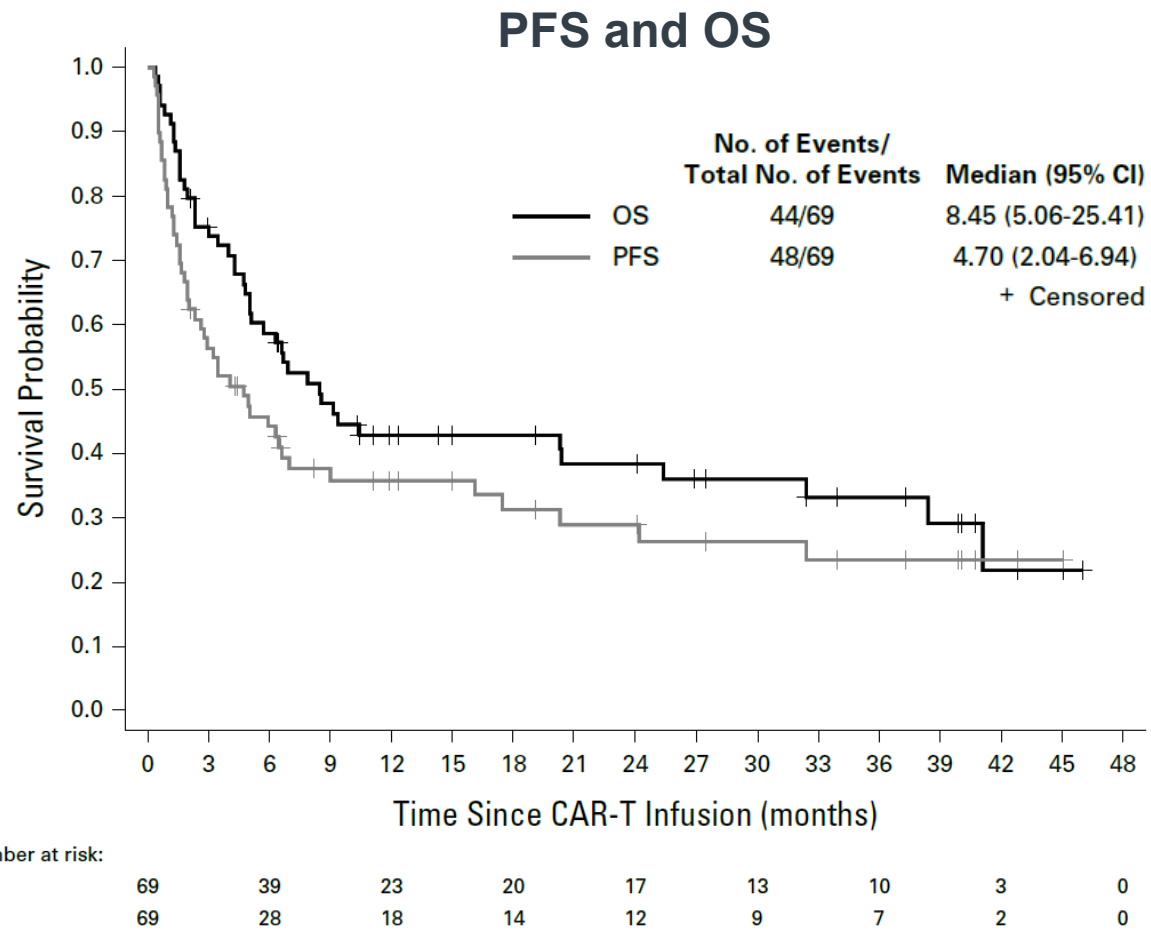
- ORR: 50.0% (95% CI: 38.7–61.3)
- ORR with previous BTKi therapy (n=61): 45.9% (95% CI: 33.1–59.2)
- Median OS: 12.5 months (95% CI: 6.9–20.5)

BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RT, Richter transformation.

Wierda WG *et al*. *Lancet Haematol* 2024; 11 (9): e682–e692.

Potential future therapeutic options for RT (3)

Anti-CD19 targeted CAR-T



Trial summary

- 69 patients with RT
- Median prior lines for CLL/RT: 4 (range: 1–15)
- Clonal relationship
  - Related: 23/69
  - Unknown: 46/69
- CAR-T therapy received
  - Axicabtagene ciloleucel: 44/69 (64)
  - Tisagenlecleucel: 17/69 (25%)
  - Lisocabtagene maraleucel: 7/69 (10%)
  - Brexucabtagene autoleucel: 1/69 (1%)

24 months following CAR-T infusion

- ORR: 63.8%
- CRR: 46%
- PFS: 29%

12 months following CAR-T infusion

- Estimated non-relapse mortality rate: 13%

CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; CI, confidence interval; CLL, chronic lymphocytic leukemia; CRR, complete response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RT, Richter transformation.

Kittai AS *et al*. *J Clin Oncol* 2024; 42 (17): 2071–2079.

Bispecific antibodies are being investigated for RT

Epcoritamab

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 5, 2024

Epcoritamab Monotherapy in Patients (Pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from CLL Expansion and Optimization Cohorts of Epcore CLL-1

Alexey Danilov, Bita Fakhri, Farrukh T. Awan, Hans Herluf Bentzen, Herbert A. Eradat, Carsten Utoft Niemann, Fritz Offner, Christian Bjørn Poulsen, Thor Hoeyer, Mar Bellido, Damien Roos Weil, Alessandra Ferrajoli, Meghan C. Thompson, Jacob Haaber Christensen, Ann Janssens, Tamar Tadmor, Mazyar Shadman, Pegah Jafarinasabian, Jimin Zhang, Marcia Rios, Alexandra Kuznetsova, Rebecca Valentin, Arnon P. Kater

Trial summary

- 40 patients with RT
  - 23 in expansion cohort; 17 in optimization cohort
- Median prior lines for CLL/RT: 4 (range: 2–10)
- Clonal relationship not reported

Expansion cohort

- ORR: 61%
- CR: 39%
- mPFS: 12.8 months
- 15-month OS: 65% alive

CLL, chronic lymphocytic leukemia; CR, complete response; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; RT, Richter transformation.

Danilov A *et al*. *Blood* 2024; 144 (Supplement 1): 883.

Thank you for your attention