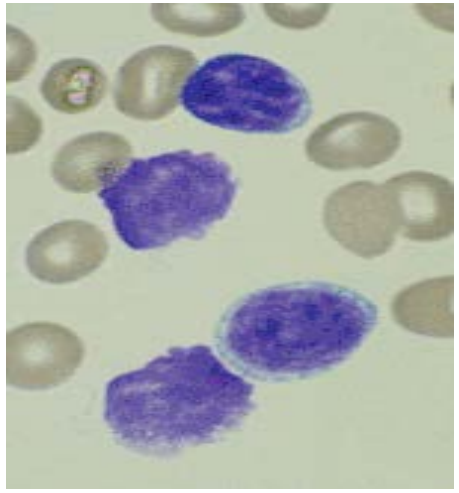
# Chronic Lymphocytic Leukemia: What's In The Treatment Pipeline

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# Disclosures
## *Nicole Lamanna, MD*

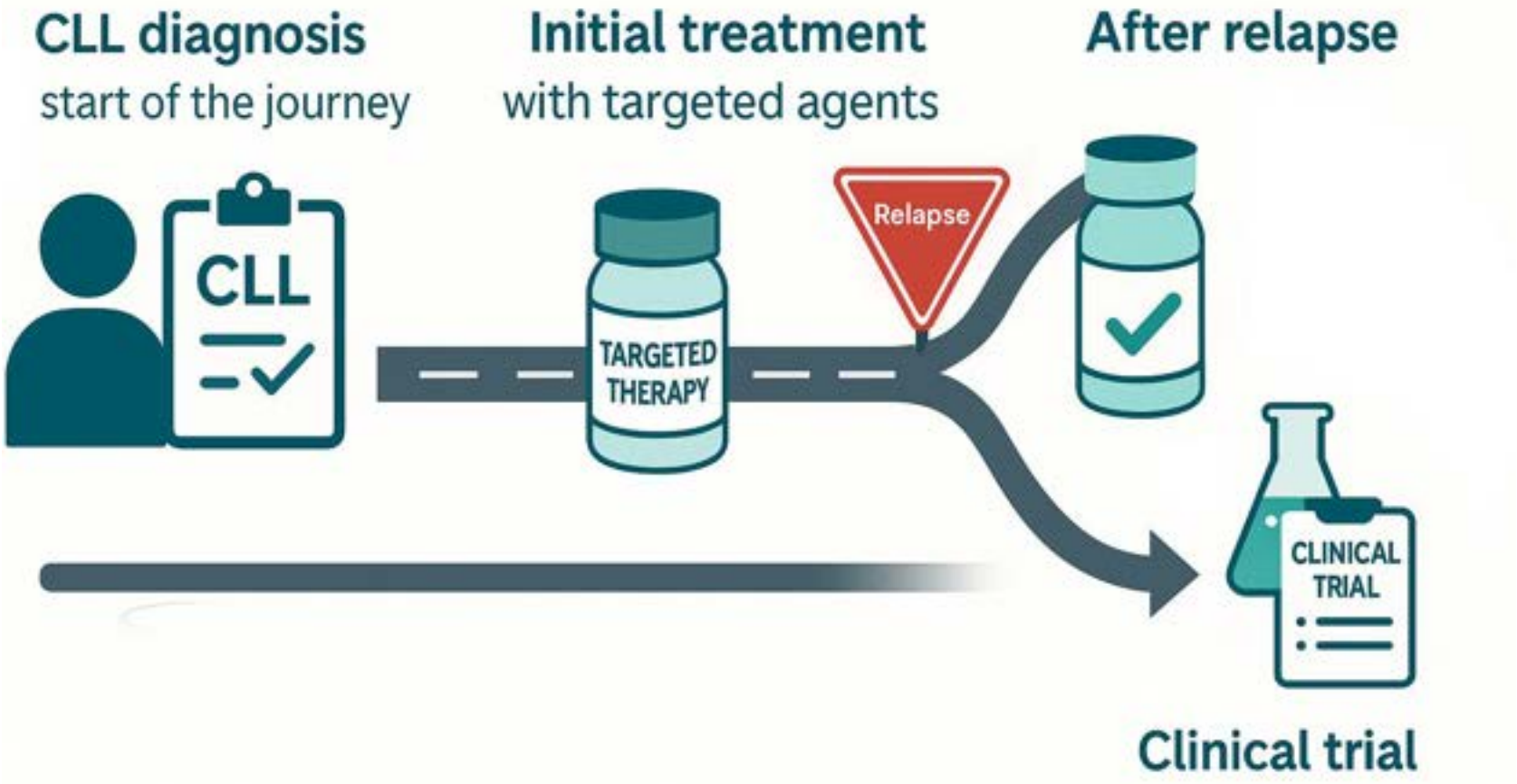
**I have the following financial relationships to disclose:**

**Advisory Board**: AbbVie, Adaptive Biosciences, Allogene Therapeutics, AstraZeneca, BeiGene, Eli Lilly/Loxo, Genentech, Genmab, Janssen, Pharmacyclics;

**Honoraria**: AbbVie, Adaptive Biosciences, Allogene Therapeutics, AstraZeneca, BeiGene, Eli Lilly/Loxo, Genentech, Genmab, Janssen, Pharmacyclics, Aptitude Health, BioAscend, Clinical Care Options, Curio, DAVA Oncology, OncLive, PER, Peerview, Targeted Oncology;

**Institutional Research/Grant Support**: AbbVie, AstraZeneca, BeiGene, Eli Lilly/LOXO, Genentech, Genmab, MingSight, Octapharma, Oncternal, TG Therapeutics

# The CLL Treatment Journey



# Key Principles of novel “Targeted Therapies”

- Cancer treatments that target a particular area, protein, receptor, pathway in CLL cells
- They do not target healthy cells, limiting side effects
- But what do they do?
  - Block or turn off chemical signals that tell the cancer cell to grow and divide
  - Change proteins within the cancer cells so the cells die
  - Trigger your immune system to kill the cancer cells

# Targeted Therapy: FDA Approvals and Current Status in CLL

| Agent | Target | Status in CLL/SLL |
|---|---|---|
| Ibrutinib[1] | BTK (covalent) | Approved |
| Acalabrutinib[2] | | Approved |
| Zanubrutinib[3] | | Approved |
| Pirtobrutinib | BTK (non-covalent) | Approved |
| | | |
| Venetoclax[4] | BCL-2 | Approved |
| Lisocel[7] | CAR-T | Approved |

1. Imbruvica (ibrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf. 2. Calquence (acalabrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. 3.Zanubrutinib prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213217s007lbl.pdf. 4. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf. 5. Zydelig (idelalisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf. 6. Copiktra (duvelisib) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf. 7. Jaypirca (pirtobrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216059s000lbl.pdf.

# What are the best options for Relapsed Disease?


It depends on what initial therapy one received, comorbidities, adverse events of prior therapy and goals of treatment.

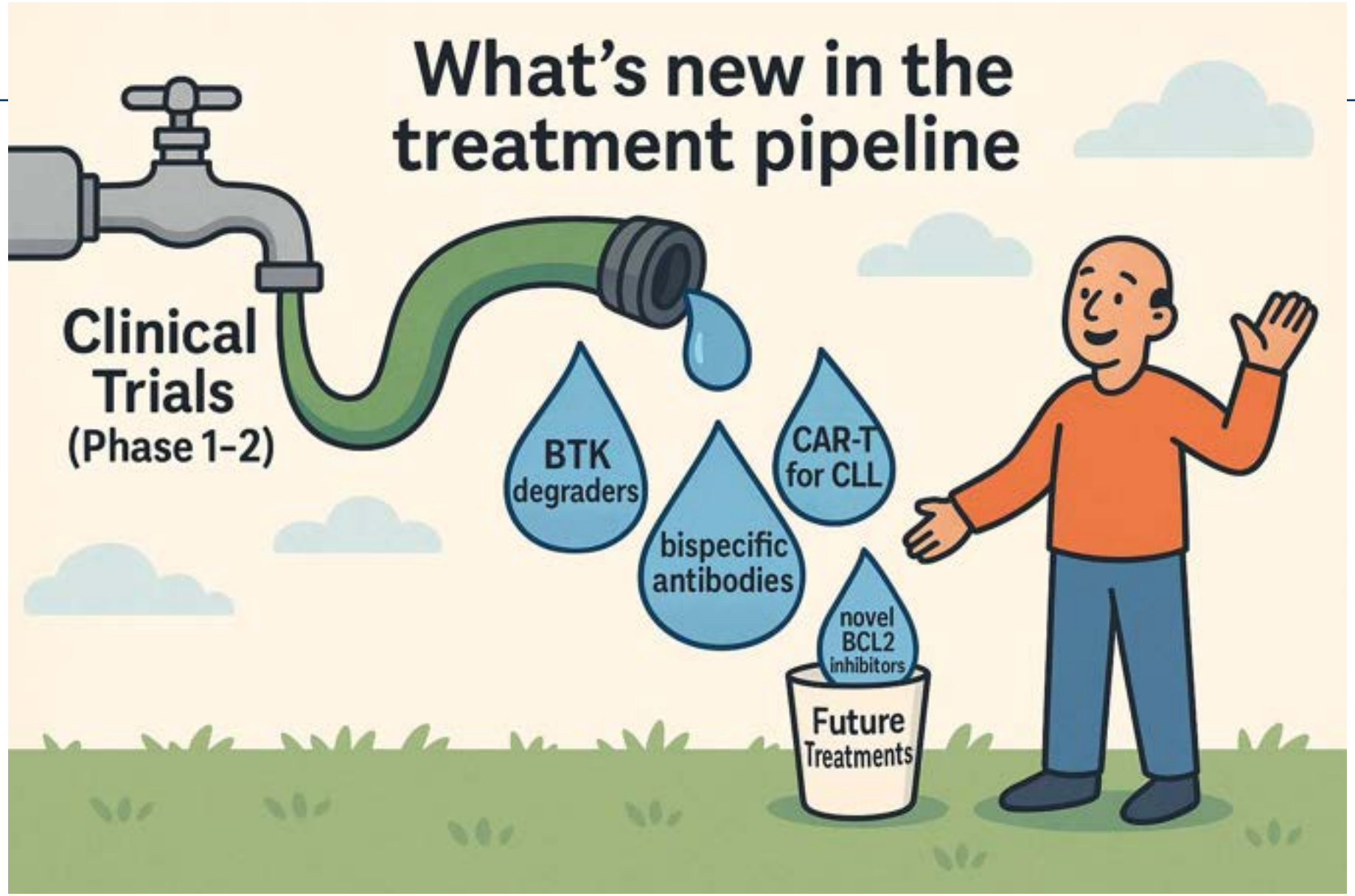
# “Double Exposed” vs “Double Refractory”?

- **Double-exposed:** relapsed CLL after *exposure* to both covalent BTKi and venetoclax
  - Example: progression > 1-2 years after EOT with FD venetoclax regimen
  - Discontinuation of cBTKi for intolerance rather than PD

- **Double-refractory[1]:** relapsed CLL after *progression* on both cBTKi and venetoclax
  - Example: progression < 1 year after EOT with FD venetoclax regimen
  - Progression during treatment with both cBTKi and venetoclax
- The optimal treatment-free remission after completion of fixed-duration therapy has not yet been clarified……stay tuned, clinical trials underway to help clarify this



1. Aronson JH et al. *Am J Hematol*. 2022;97:S19-S25.

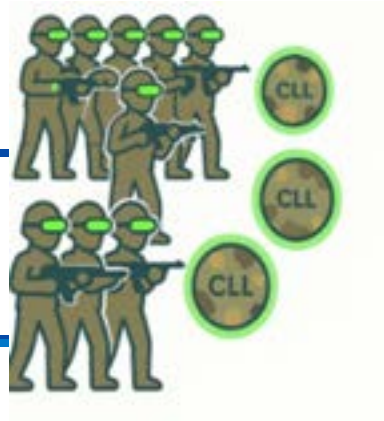

What's new in the treatment pipeline
Clinical Trials (Phase 1-2)
BTK degraders
bispecific antibodies
CAR-T for CLL
novel BCL2 inhibitors
Future Treatments

# Newer agents for dual-exposed patients: Simple Analogies for how they work!

**Non-Covalent BTKi:**


**BTK degraders:**


**CD19 CAR-T cell therapy:**




**BCL2 inhibitors:**


**CD20/CD3 bispecific antibodies:**

# Newer Agents in Pipeline for "Double-Exposed or Double-Refractory" CLL patients

**Non-Covalent BTKi:** BRUIN- Pirtobrutinib[1](FDA approved 12/2023), BELLWAVE-001-nemtabrutinib[2]

**Dual-Activity Covalent/Non-Covalent BTKi:** LP168[3]

**BTK degraders:** NX-2127 (NCT04830137)[5] and BGB-16673 (NCT05006716)[6] and ABBV-101[7]

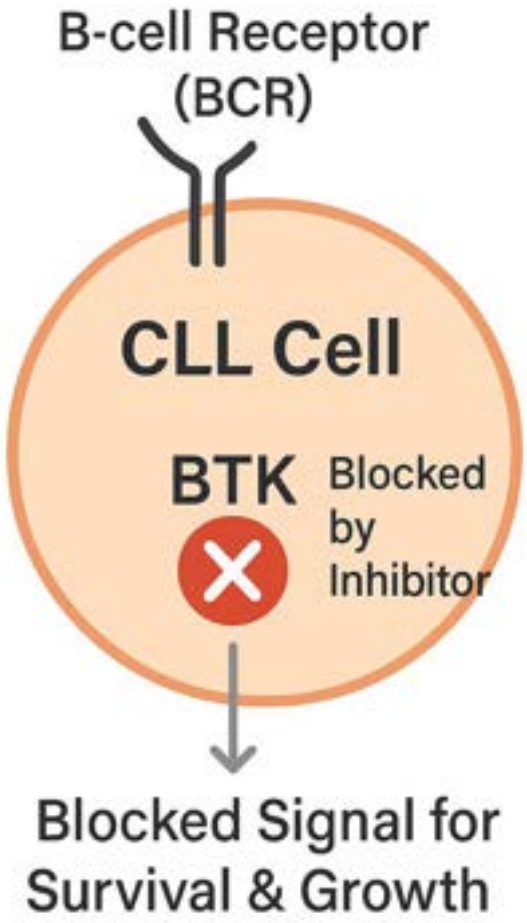
**CD19 CAR-T cell therapy**: TRANSCEND – Lisocel[4] (FDA approved 3/2024)

**BCL2 inhibitors:** Sonrotoclax[8] and lisaftoclax[9]

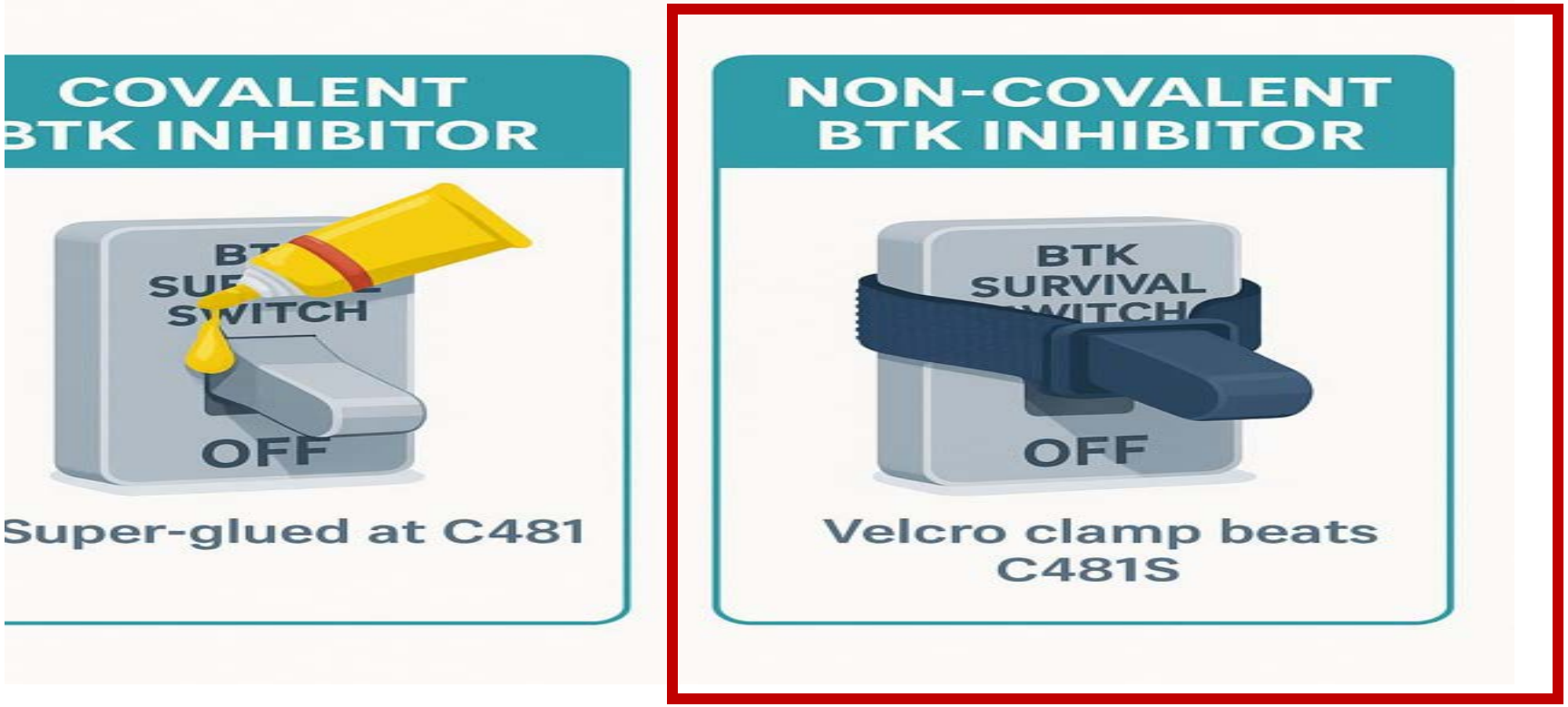
**CD20/CD3 bispecific antibodies:** epcoritamab (NCT04623541) [10,11]; mosunetuzumab (NCT05091424)

1. Mato et al. ASH 2022. Abstract 961. 2. Woyach J et al. EHA 2023. Abstract P628. 3. Woyach J et al. ASH 2023. Abstract 328. 4. Siddiqi T et al. *Lancet.* 2023;402(10402):641-654. 5. Danilov A et al. ASH 2023. Abstract 4463. 6. Seymour JF et al. ASH 2023. Abstract 4401. 7. Linton K et al. EHA 2024. Abstract S155. 8. Pan C et al. AACR 2024. Abstract 605. 8. Opat S et al. EHA 2024. Abstract S156. 9. Davids M et al. ASH 2024. Abstract 4614. 10. Kater AP et al. iwCLL 2023. Abstract 1546171. 11. Danilov A et al. ASH 2024. Abstract 883.

# Inhibiting BTK: A Mainstay of CLL Therapy

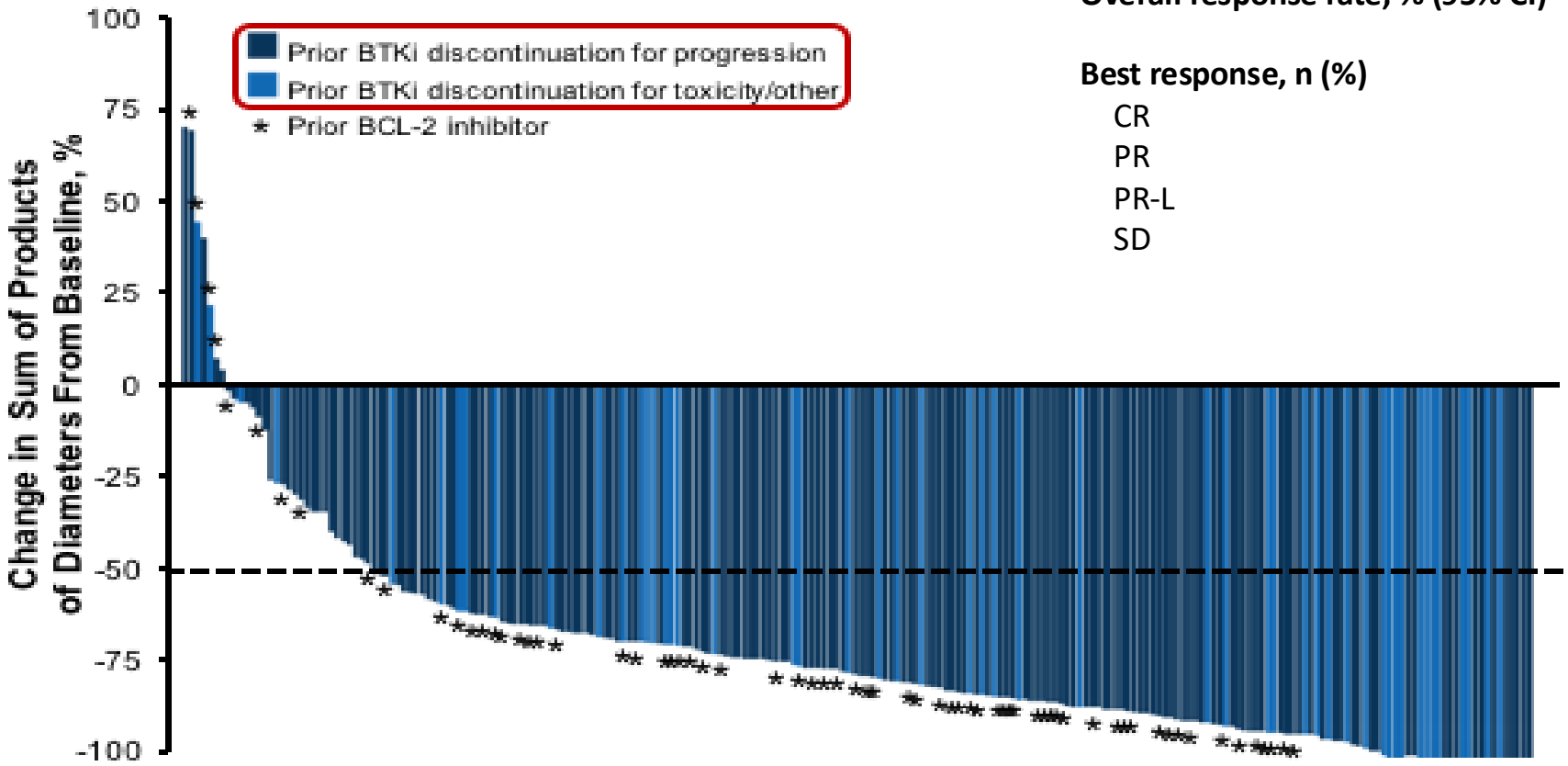


# Multiple Ways to Shut Down BTK




Think of BTK as a light switch that helps turn on signals that allow CLL cells to survive and grow. **Covalent BTK inhibitors** are like using superglue to permanently jam the switch in the "off" position — but if the switch gets damaged or changed, the glue may not stick. That's where **non-covalent BTK inhibitors** come in! These are more like smart Velcro — they can still grip and turn off the switch, even if its shape changes. This gives us another tool to block CLL signals.

# BRUIN Update: Longer Follow-Up Confirms Pirtobrutinib Efficacy in R/R CLL/SLL Patients[1]




| | Prior BTKi (n = 247) | Prior BTKi + BCL2i (n = 100) |
|---|---|---|
| **Overall response rate, % (95% CI)** | **82.2 (76.8-86.7)** | **79.0 (69.7-86.5)** |
| **Best response, n (%)** | | |
| CR | 4 (1.6) | 0 (0.0) |
| PR | 177 (71.7) | 70 (70.0) |
| PR-L | 22 (8.9) | 9 (9.0) |
| SD | 26 (10.5) | 11 (11.0) |

Pirtobrutinib (200 mg QD) demonstrated durable efficacy in patients treated with a prior covalent BTKi, regardless of

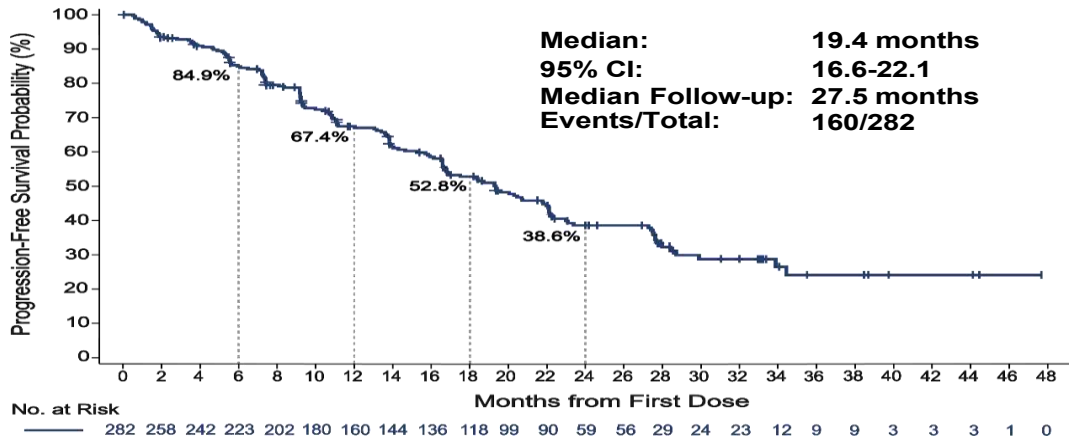
- Prior therapy, reason for prior BTKi discontinuation, or age
- *TP53* mutations, **C481 mutational status**, and/or del(17p)



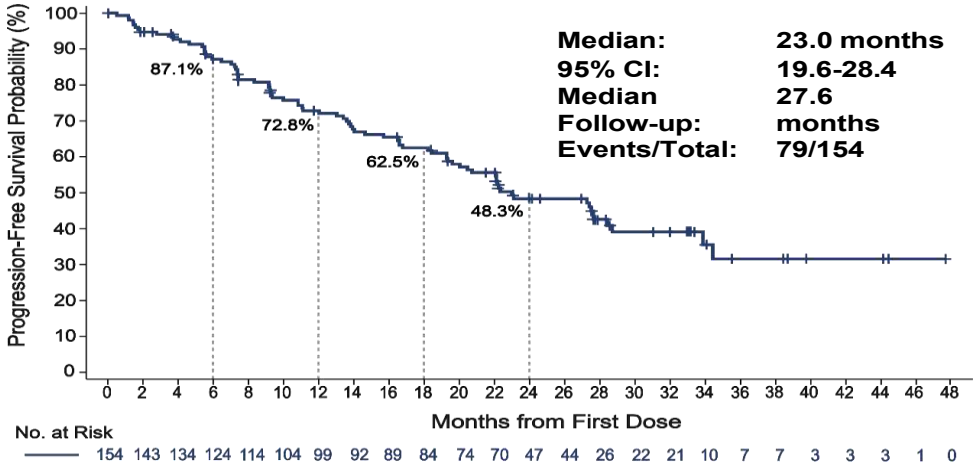
1. Mato A et al. ASH 2022. Abstract 961.

# BRUIN Update: Robust PFS in Covalent BTKi-Pretreated R/R CLL/SLL Patients[1]

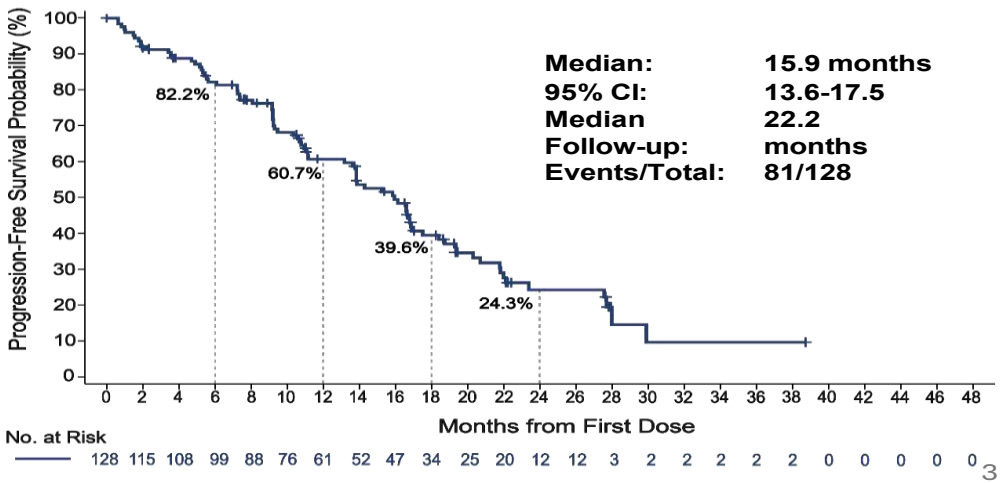
## PFS - All Prior cBTKi




## PFS - BCL2i-N




## PFS - BCL2i-E




Woyach JA, et al. ASH 2023. Abstract 325





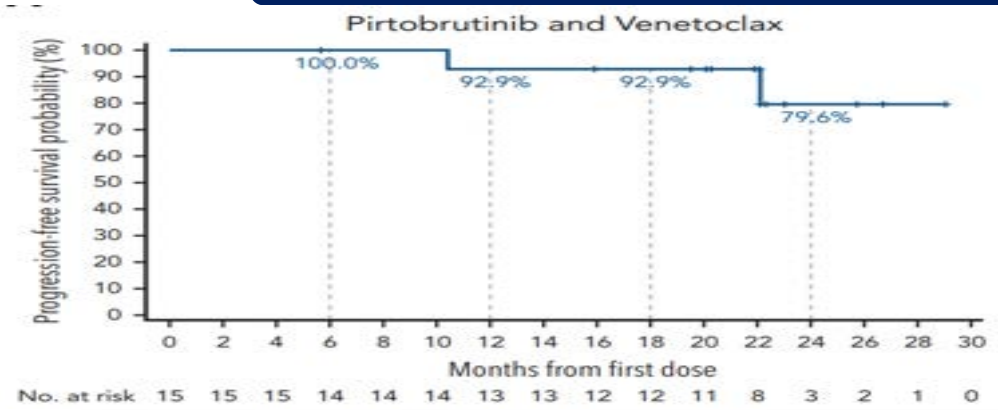
1. Mato A et al. ASH 2022. Abstract 961.

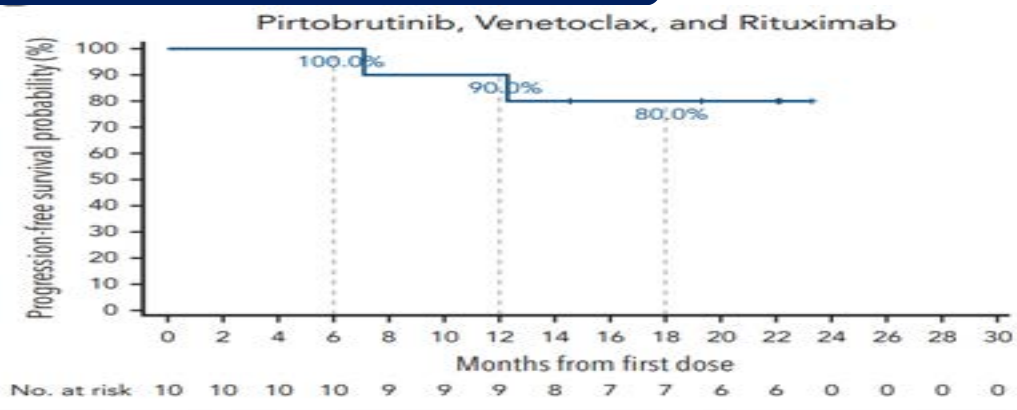
# BRUIN Phase 1b: Fixed-duration Pirtobrutinib + Ven±R

## Best overall response of pirtobrutinib-based combination treatments

| | PV (n = 15) | PVR (n = 10) | Total (N = 25) |
|---|---|---|---|
| | 15 | 10 | 25 |
| ORR, % (95% CI) | 93.3 (68.1-99.8) | 100 (69.2-100) | 96.0 (79.6-99.9) |
| **Best response, n (%)*** | | | |
| CR | 7 (46.7) | 3 (30.0) | 10 (40.0) |
| PR | 7 (46.7) | 7 (70.0) | 14 (56.0) |
| SD | 1 (6.7) | 0 | 1 (4.0) |
| PD | 0 | 0 | 0 |
| Median time to best response, mo (IQR) | 3.9 (1.9- 14.7) | 1.9 (1.8- 10.7) | 2.4 (1.9-14.3) |

## PFS rates



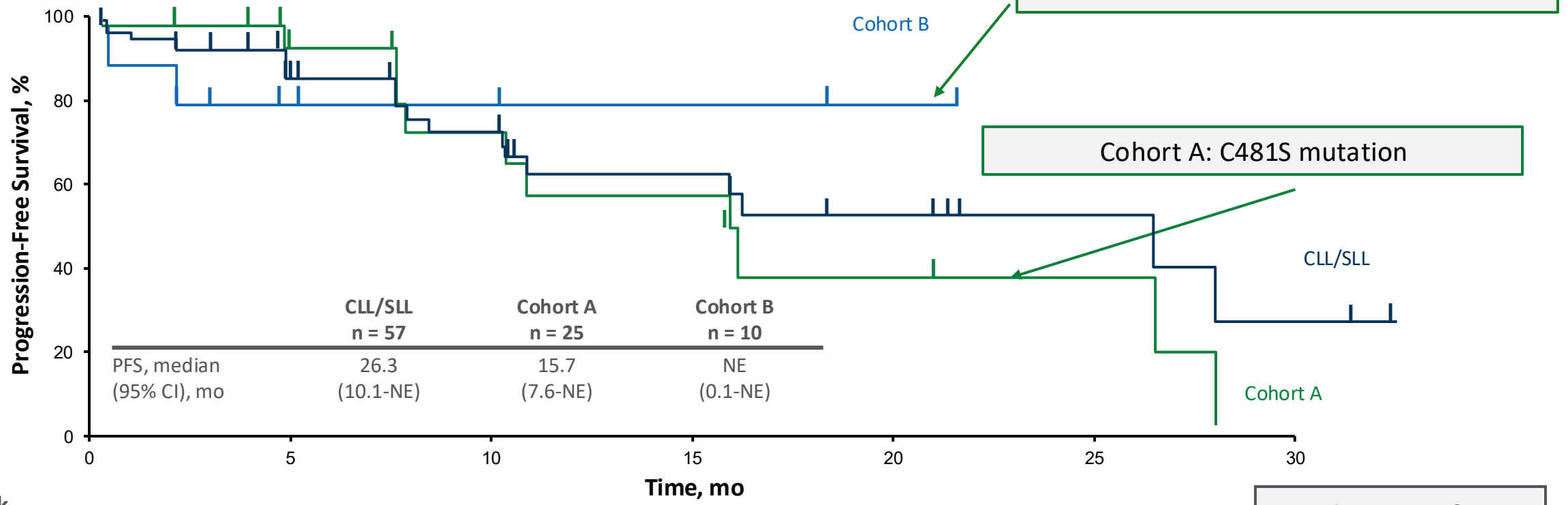






Roeker LE, et al. *Blood*. 2024;144(13):1374-1386.

# BELLWAVE-001/Nemtabrutinib: Response and PFS In Pretreated CLL[1,a]

- Promising and durable antitumor activity in a highly R/R population: ORR: 56%
- ORR of 58% in C481S-mutated disease



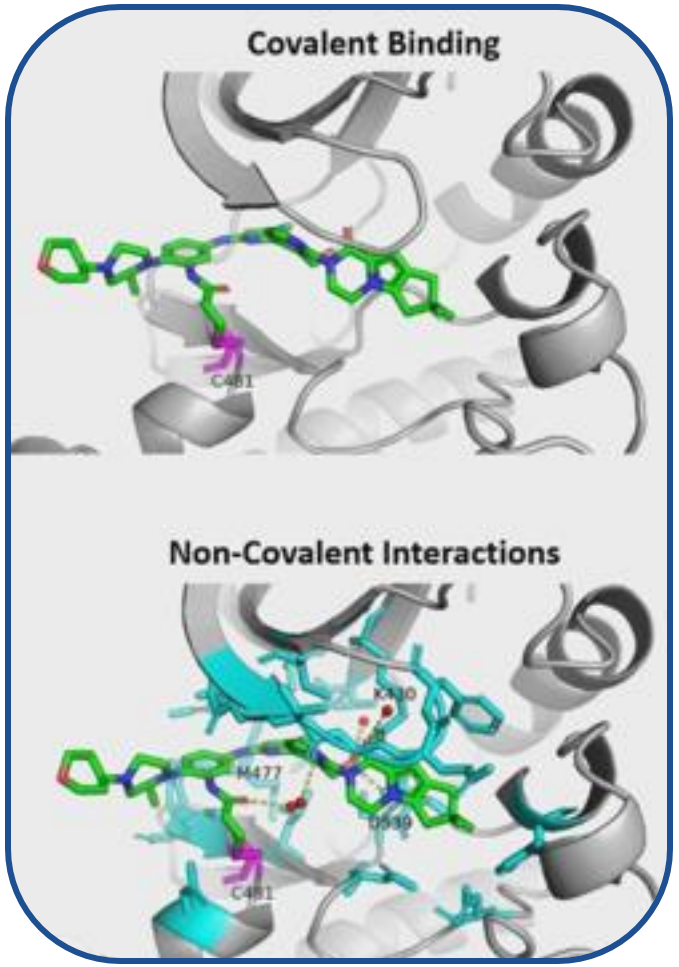

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| CLL/SLL | 57 | 30 | 21 | 15 | 8 | 4 |
| Cohort A | 25 | 15 | 10 | 7 | 3 | 2 |
| Cohort B | 10 | 4 | 2 | 2 | 1 | 0 |

**Median PFS of 15.7 months in cohort A**

[a] Cohort A comprises patients with R/R CLL/SLL who received ≥ 2 prior therapies, including covalent BTKi, and who have C481S mutation. Cohort B comprises patients with R/R CLL/SLL who received ≥ 2 prior therapies, are intolerant to BTKi, and have no C481S mutation.

1. Woyach J et al. EHA 2023. Abstract P628.

# Rocbrutinib: A Dual-Activity c/ncBTKi in R/R CLL[1]




***Rocbrutinib binds covalently in the presence of WT BTK***

***Rocbrutinib binds non-covalently in the presence of C481 mutated BTK***

**LP-168 evaluated in a phase 1 dose-escalation study**

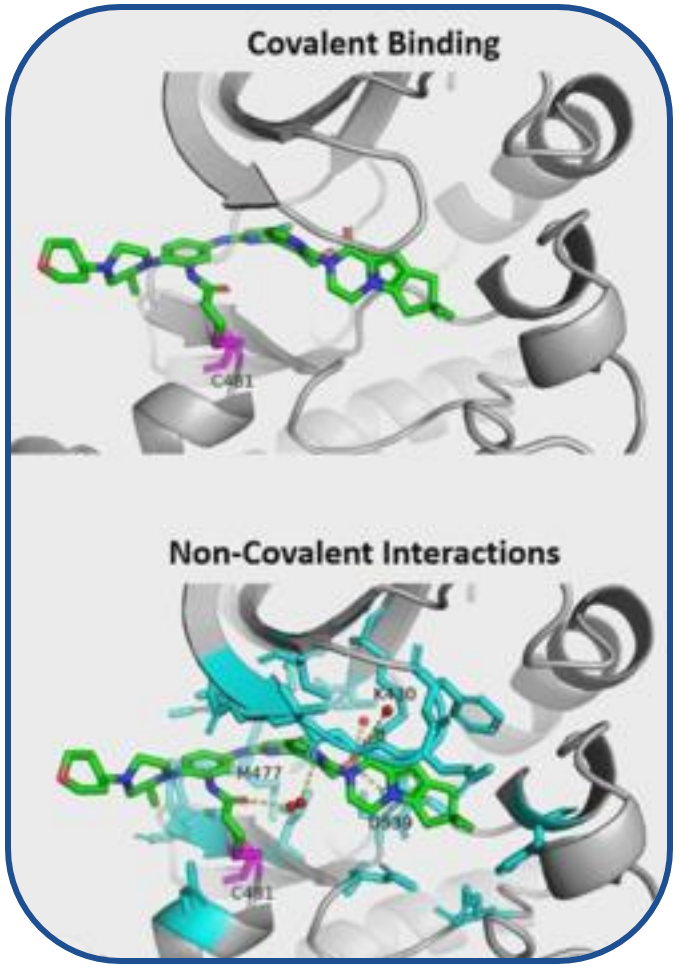
- 35 patients, median of 3 prior therapies
- 94% receiving prior cBTKi
  - 11% a ncBTKi
- Most patients with *BTK* resistance mutations
- 20 patient with del(17p) and/or *TP53m*

**Initial evidence showed an ORR of 55%**

**Doses ≥ 200 mg: ORR was 66.7**

1. Woyach J et al. ASH 2023. Abstract 328.

# Rocbrutinib: A Dual-Activity c/ncBTKi in R/R CLL[1]



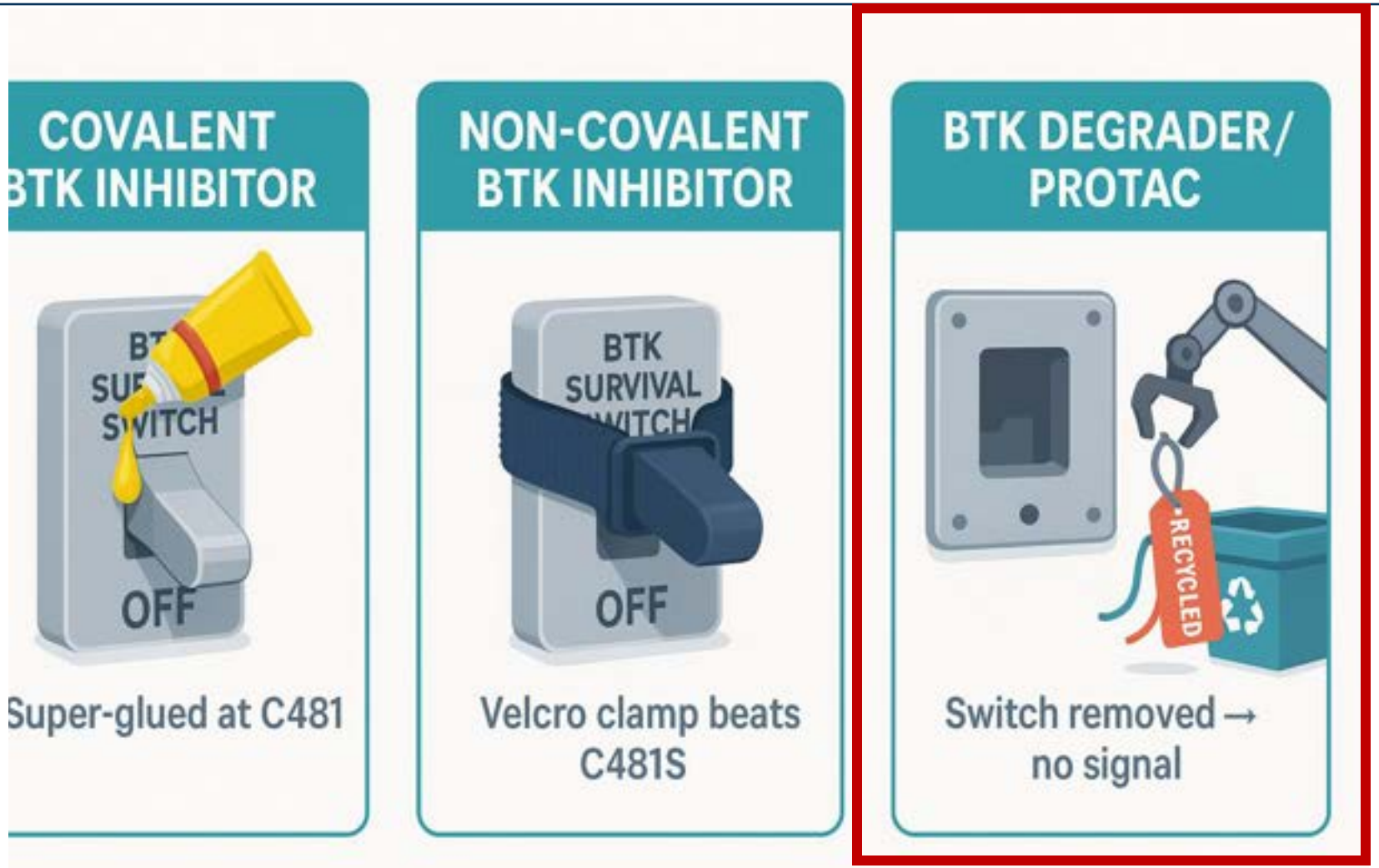

***Rocbrutinib binds <u>covalently in the presence of WT BTK</u>***

***Rocbrutinib binds <u>non-covalently in the presence of C481 mutated BTK</u>***

| Efficacy outcomes in patients with R/R CLL and gatekeeper mutations (N = 47)[2] | |
|---|---|
| 18-month PFS | 68.5% |
| Patient receiving starting doses ≥ 200 mg (n = 22) | 77.3% |

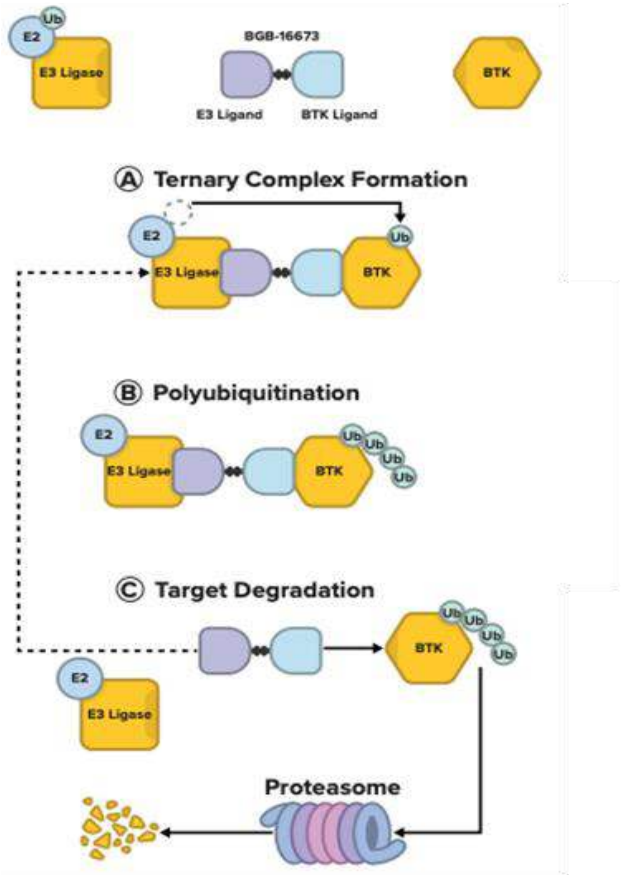
1. Woyach J et al. ASH 2023. Abstract 328. 2. Woyach J et al. ASH 2024. Abstract 4622.

# Multiple Ways to Shut Down BTK – BTK Degraders

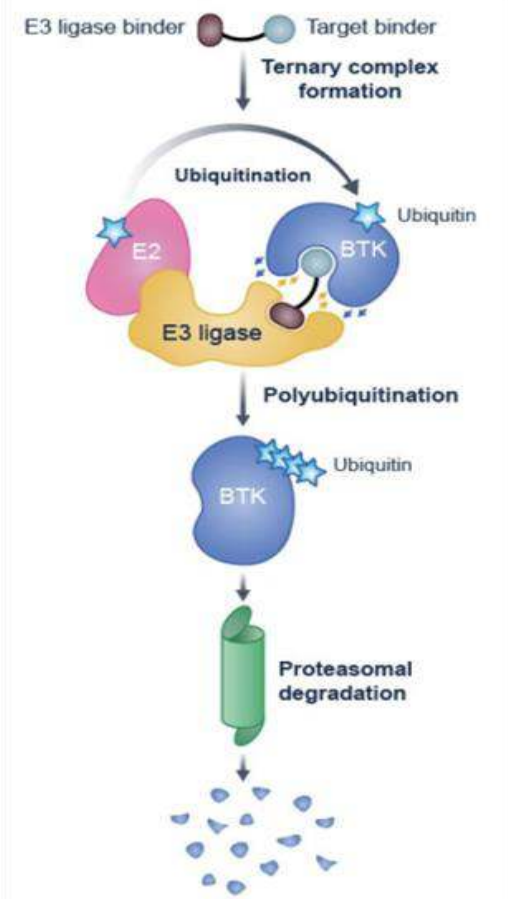


# Can BTK Degraders Overcome Resistance?

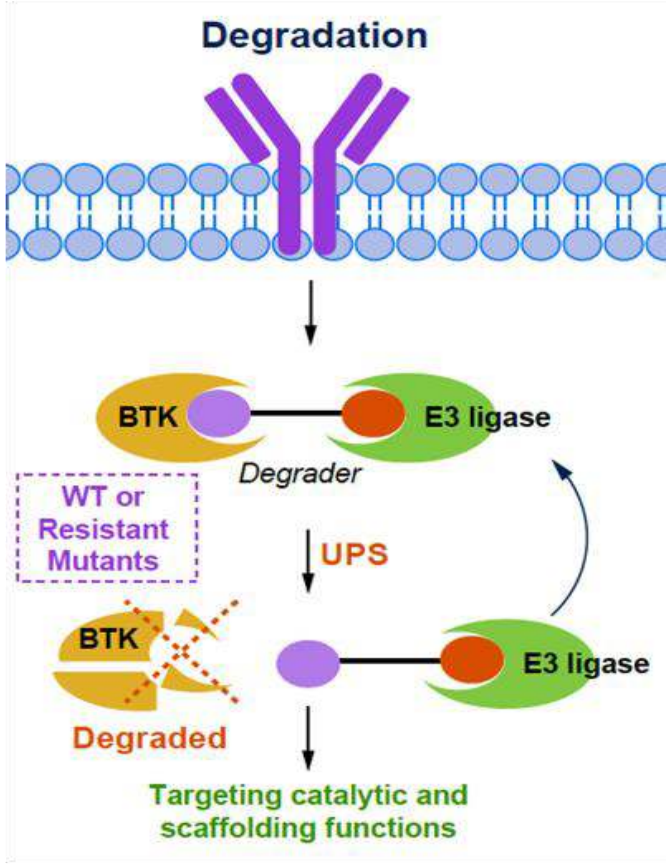
## BGB-16673: A BTK-Targeted CDAC[1]




## NX-5948 Utilizes the Ubiquitin-Proteasome Pathway to Degrade BTK[2]




## ABBV-101 Degrades BTK Targeting in Both the Catalytic and Scaffolding Functions[3]






1. Seymour J et al. ASH 2023. Abstract 4401. 2. Linton K et al. EHA 2024. Abstract S155. 3. Pan C et al. AACR 2024. Abstract 605.

# CaDAnCe-101: Further Evidence Shows the Potential for Deep Responses with BGB-16673 in Heavily Pretreated CLL

N = 49 response-evaluable patients

Median number of prior therapies was 4 (range, 2-10), including

- Prior cBTKis (n = 45), BCL2i (n = 42), and ncBTKi (n = 12)

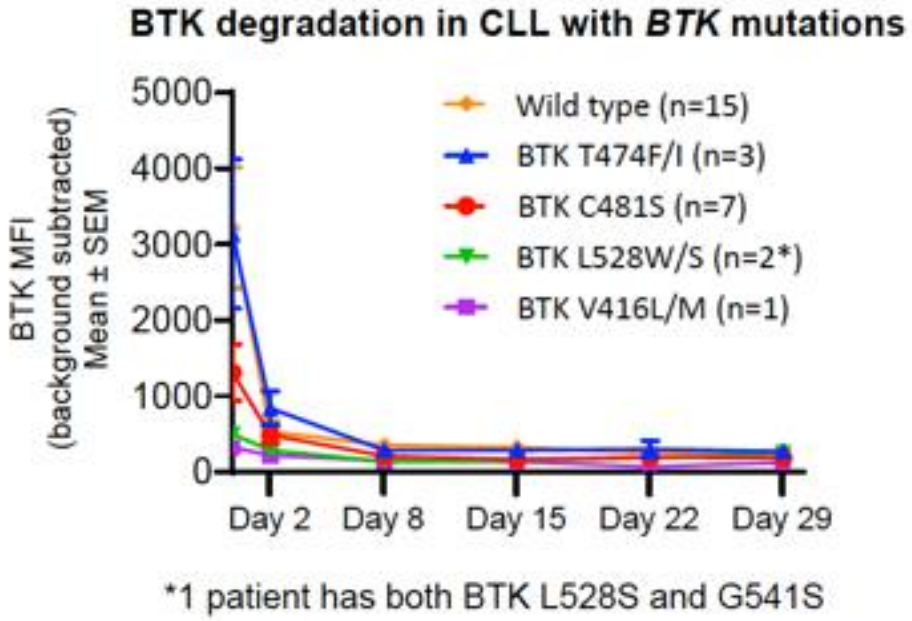
| Response at 200 mg dosing level | N (%) |
|---|---|
| **ORR** | 38 (78) |
| **CR/CRi** | 2 (4) |

- Median time to first response was 2.8 months (range, 2.6-8.3 months)
- 17 patients remained on treatment for ≥ 9 months and all 17 have ongoing responses

Thompson M et al. ASH 2024. Abstract 885.

# In Phase 1 Testing, the BTK Degrader NX-5948 Showed Efficacy Against Poor Prognosis R/R CLL

NX-5948 induced deep and durable clinical responses in a Heavily pretreated CLL population with unfavorable genetic mutations and BTK resistance mutations[1]



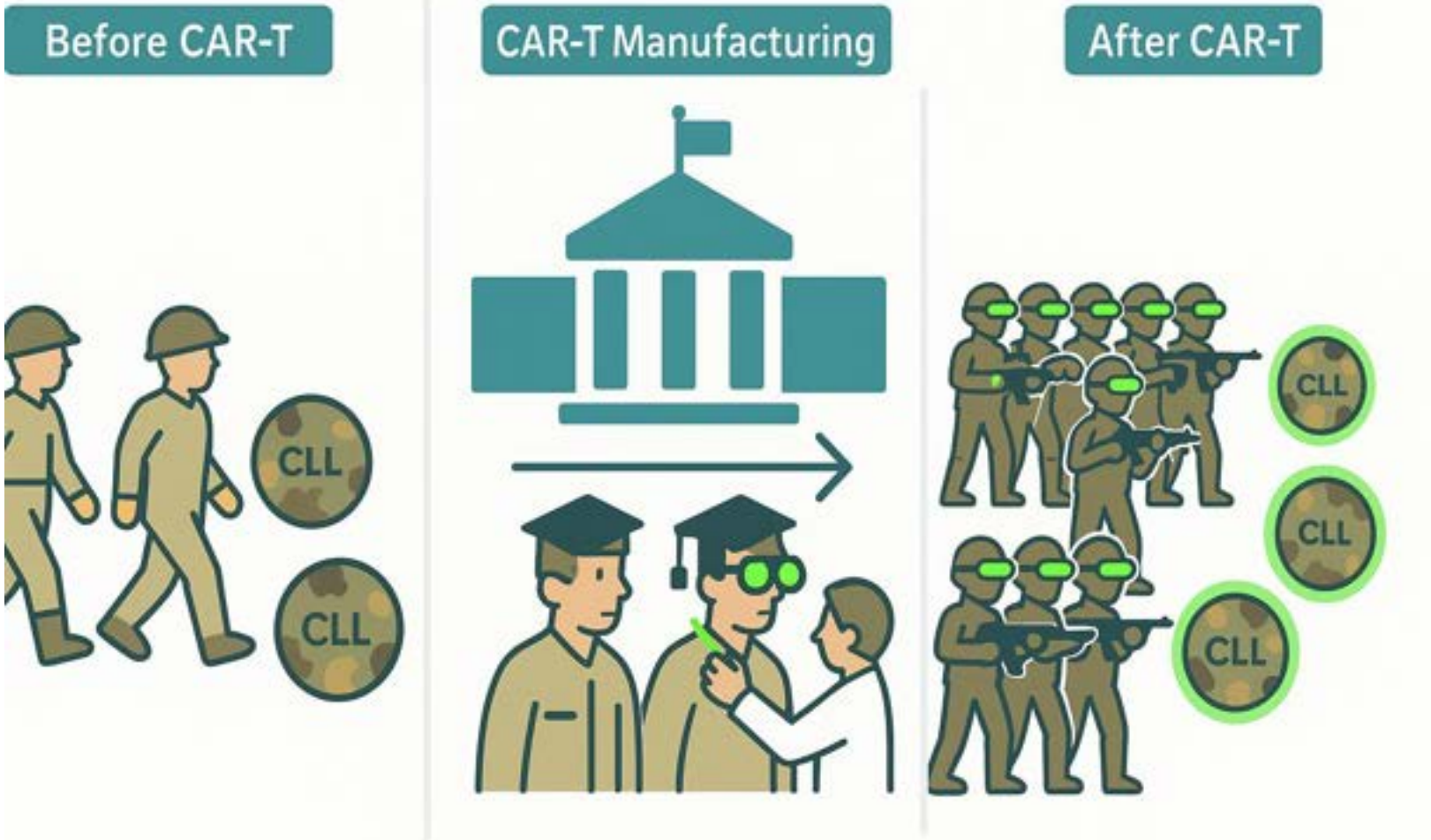

*NX-5948 induces rapid and robust degradation of wild-type and mutant BTK*

| CLL disease-evaluable patients[a] | n=26 |
|---|---|
| **Objective response rate (ORR)[b]**, % (95% CI) | 69.2 (48.2–85.7) |
| **Best response**, n (%) | |
| CR | 0 (0.0) |
| PR / PR-L | 18 (69.2) |
| SD | 6 (23.1) |
| PD | 2 (7.7) |

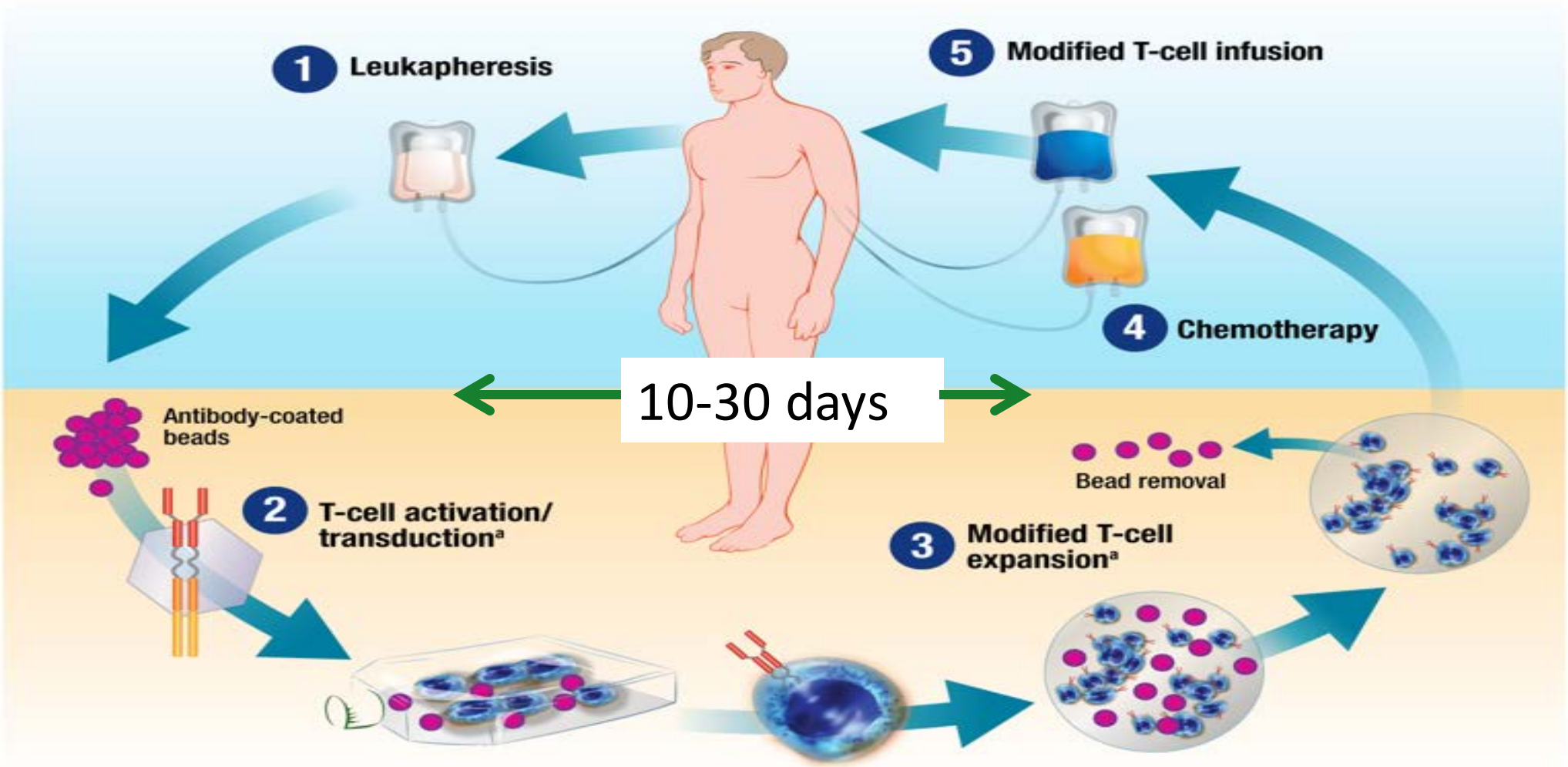
[a]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL, while they may not be represented in waterfall plot; [b]Objective response rate includes CR + CRi + nPR + PR-L + PR

1. Linton K et al. EHA 2024. Abstract S155.

# CAR-T Cells for CLL Therapy: Sending the immune system to military school! Teach them to target and fight CLL!



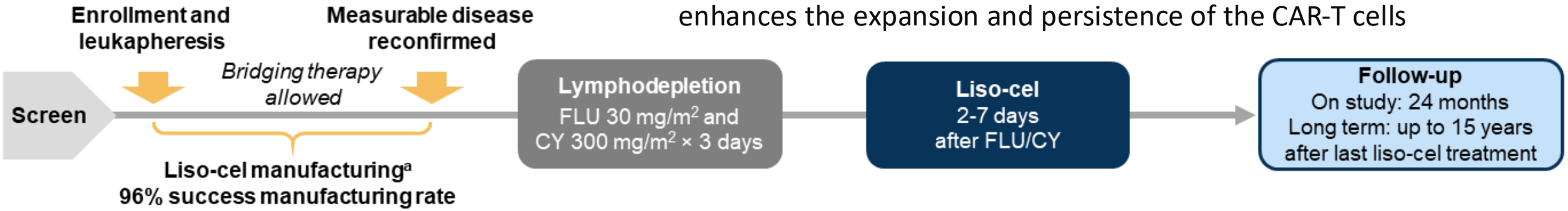
# Patient's Journey with CART




**Timeline varies by product and manufacturer**

# TRANSCEND CLL 004: Exploration of CAR-T in CLL[1]

**Liso-cel**: CD19-directed CAR-T with a 4-1BB costimulatory domain, which enhances the expansion and persistence of the CAR-T cells




## Key Eligibility

- Relapsed/refractory CLL/SLL
- **Failed or ineligible for BTKi[b]**
- **High-risk disease[c]: failed ≥2 prior therapies**
- **Standard-risk disease: failed ≥3 prior therapies**
- ECOG PS of 0-1

## Dose Escalation: mTPI-2 Design[d]

28-day DLT period

*Primary objectives*

- Safety
- Determine recommended dose

*Exploratory objectives*

- Antitumor activity
- Pharmacokinetic profile

| Dose Level | Dose | Evaluable (N = 23) |
|---|---|---|
| 1 | 50 × $10^6$ CAR-T cells | 9 |
| 2 | 100 × $10^6$ CAR-T cells | 14 |

[a] One patient received nonconforming product. [b] Failure defined as SD or PD as best response, or PD after previous response, or discontinuation due to intolerance (unmanageable toxicity). Ineligibility defined as requirement for full-dose anticoagulation or history of arrhythmia. [c] Complex cytogenetic abnormalities, del(17p), *TP53* mutation, or unmutated IGHV. [d] Guo W et al. *Contemp Clin Trials.* 2017;58:23-33.



1. Siddiqi T et al. ASH 2020. Abstract 546.

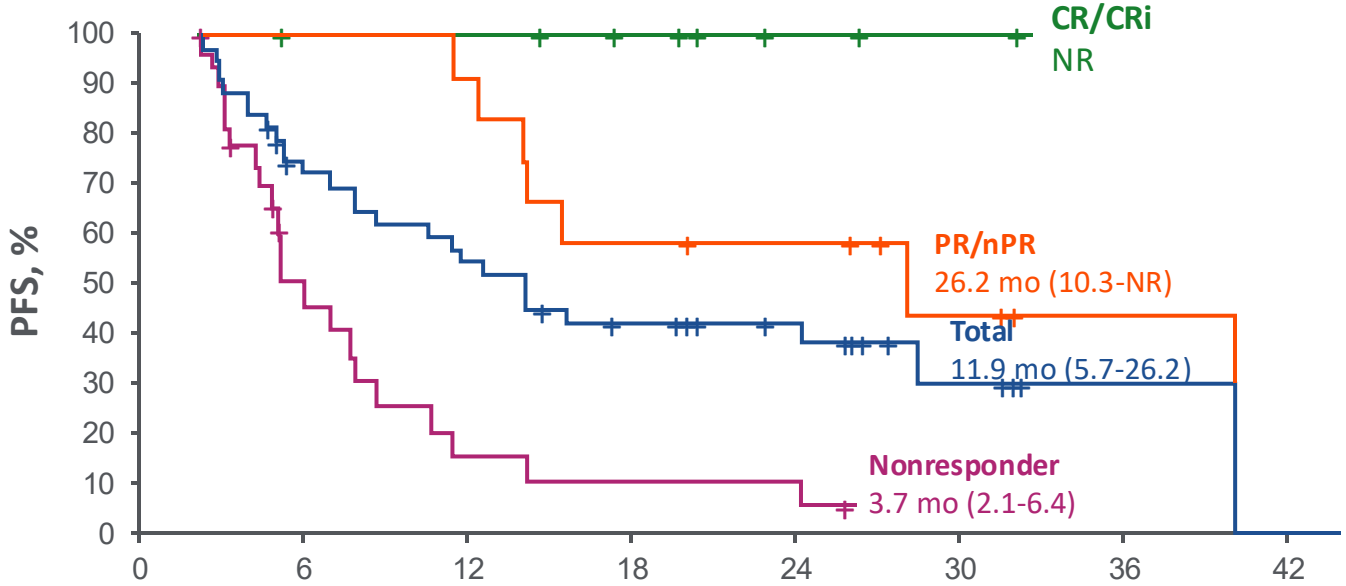
# Liso-Cel Is Effective in Patients With CLL Progressing After Prior BTKi and Venetoclax Therapy

**A single infusion of liso-cel induced complete response or remission (including with incomplete marrow recovery) in patients with R/R CLL/SLL[1]**

- 18.4% CR/CRi in patients with R/R CLL after BTKi progression/venetoclax failure

**Led to US FDA approval in 3/2024 in patients with R/R CLL who have received ≥ 2 prior LOT, including a BTKi and a BCL2i**

**Updated Efficacy Outcomes:**
**BTKi Progression/Venetoclax Failure Subset at DL2 (N = 49)[2]**



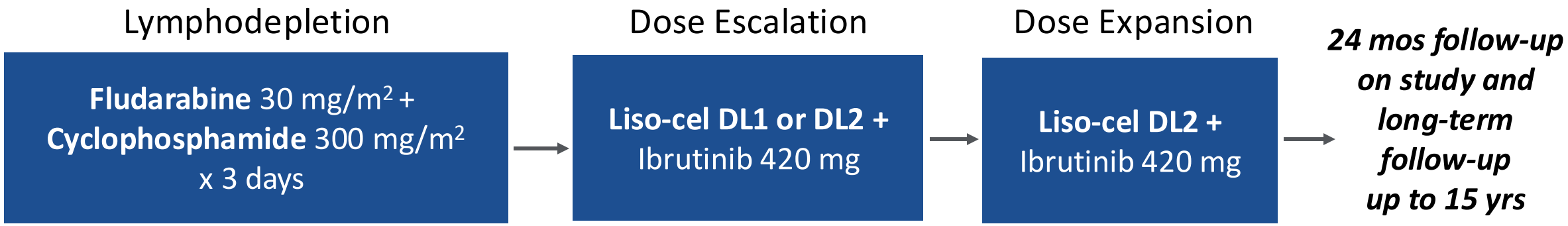

| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CR/CRi | 9 | 8 | 8 | 5 | 2 | 1 | 0 | 0 |
| PR/nPR | 12 | 12 | 9 | 6 | 5 | 1 | 1 | 0 |
| Nonresponder | 28 | 6 | 2 | 2 | 0 | 0 | 0 | 0 |
| Total | 49 | 26 | 19 | 13 | 7 | 2 | 1 | 0 |



1. Siddiqi T et al. *Lancet*. 2023;402(10402):641-654. 2. Siddiqi T et al. ASH 2023. Abstract 330.

# Updates on Combining CAR-T With BTKi in CLL

## TRANSCEND CLL 004 Combination Cohort



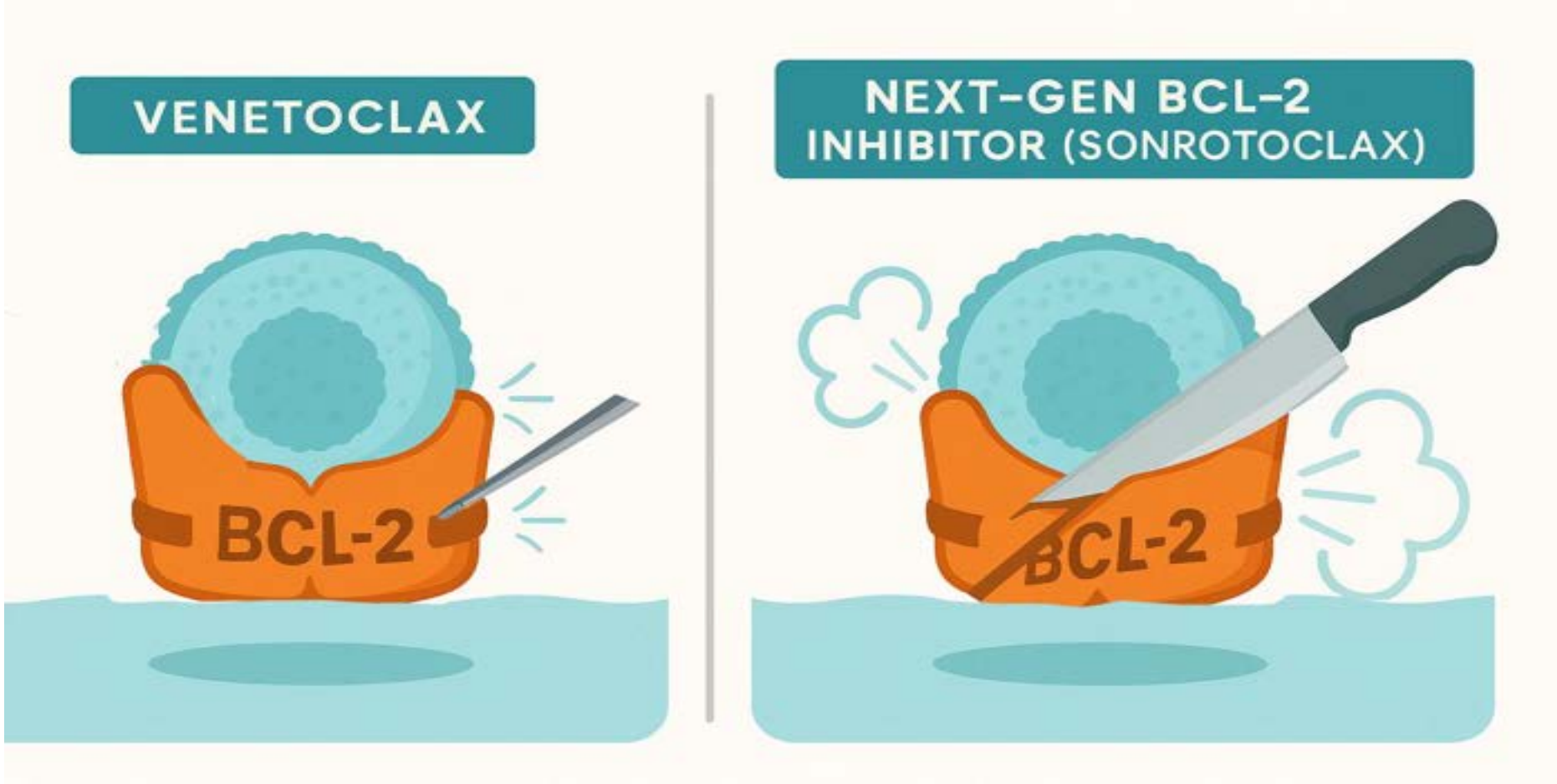

| Combined liso-cel and ibrutinib[1] | Efficacy Outcomes for the DL2 Cohort (n = 51) |
|---|---|
| ORR | 86% |
| PFS | 31.4 mo |
| CR | 45% |
| PB uMRD | 85% |

Combination induced deep remissions in heavily pretreated R/R CLL



Wierda W et al. ASH 2024. Abstract 887.

# Next-Generation BCL2i on the Horizon



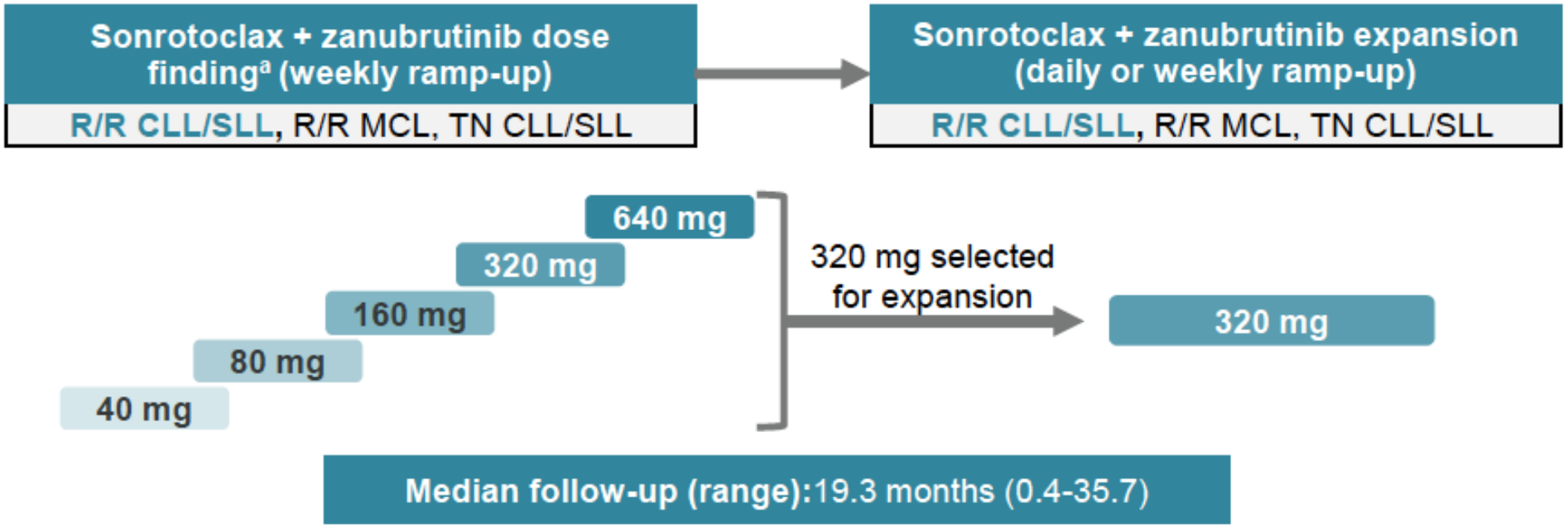

CLL cells use BCL2 as a life vest to survive and stay afloat when they would otherwise die. Venetoclax pin-pricks the life vest. Sonrotoclax (hopefully, slashes it with a huge knife!)

# Next-Generation BCL2i with Sonrotoclax

**Sonrotoclax, a next-generation BCL2i[1]**

- Selective and pharmacologically potent inhibitor of BCL2
- Short half-life, no drug accumulation

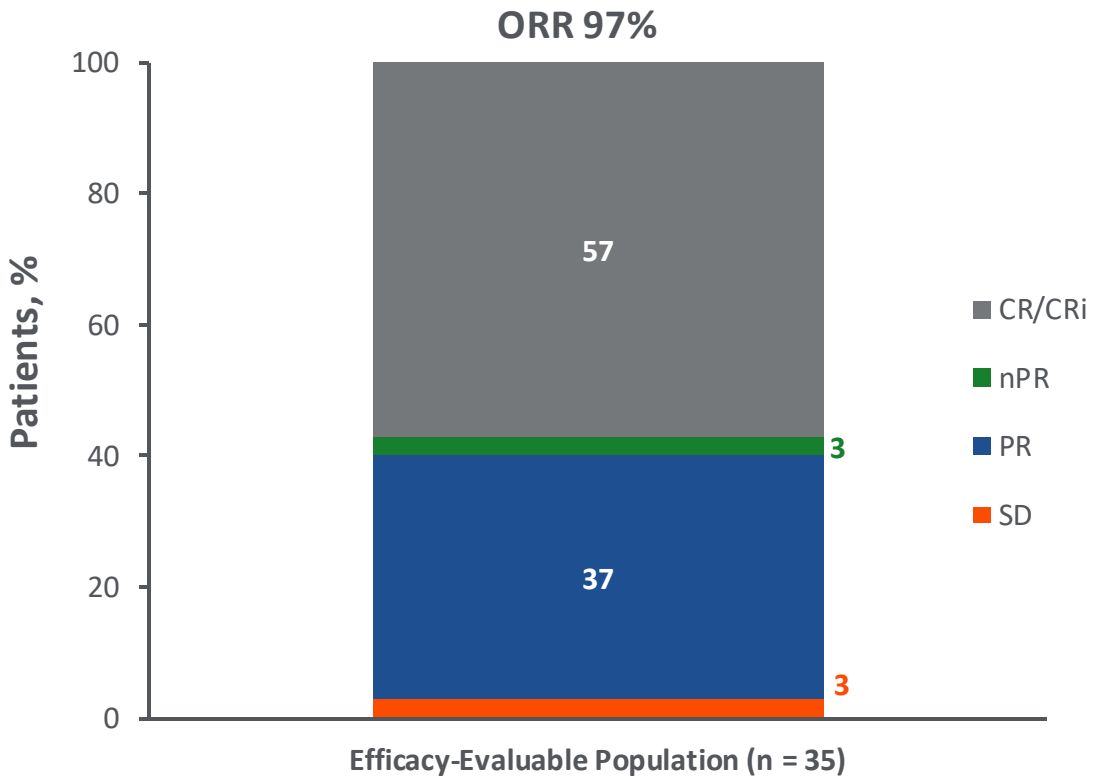
*Study assessed 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), then in combination with sonrotoclax (with weekly or daily ramp-up to target dose)*




1. Opat S et al. EHA 2024. Abstract S156.

# Sonrotoclax + Zanubrutinib Combination Is Highly Active, With No Clinical or Laboratory TLS[1]

*At median study follow-up of 19.3 months, the ORR was 97%, with a 57% CR/Cri rate across all doses*




**Safety**

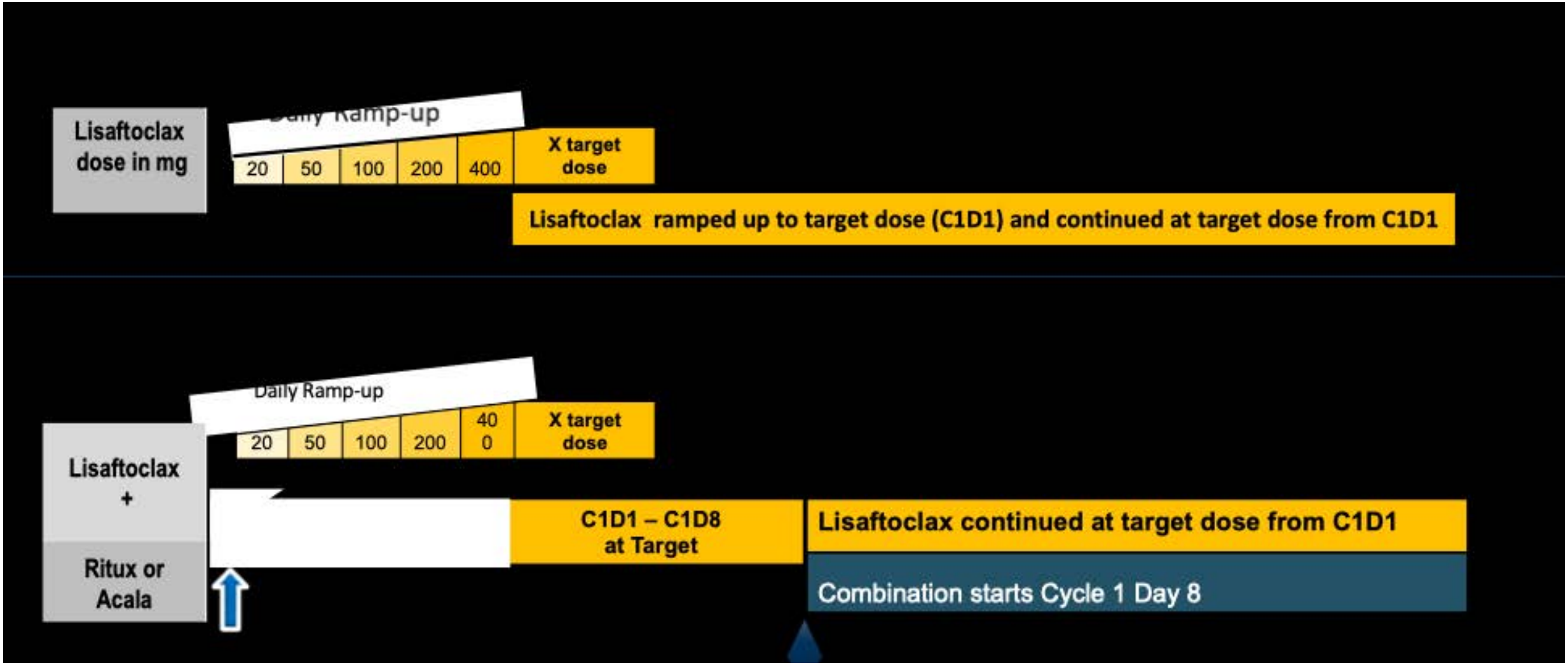
- No TLS, a-fib, febrile neutropenia
- No dose reductions due to diarrhea

**ASH 2024 Update**

- 100% ORR in response evaluable patients (N = 108)
- 90% best uMRD rate in patients in the 320-mg cohort who reached 48 weeks of therapy

1. Opat S et al. EHA 2024. Abstract S156.

# Lisaftoclax: Oral BCL2i With a Short Half-life, Allowing for Daily Ramp-Up Dosing[1]




1. Davids MS et al. ASH 2022;140(suppl 1):2326-2328..

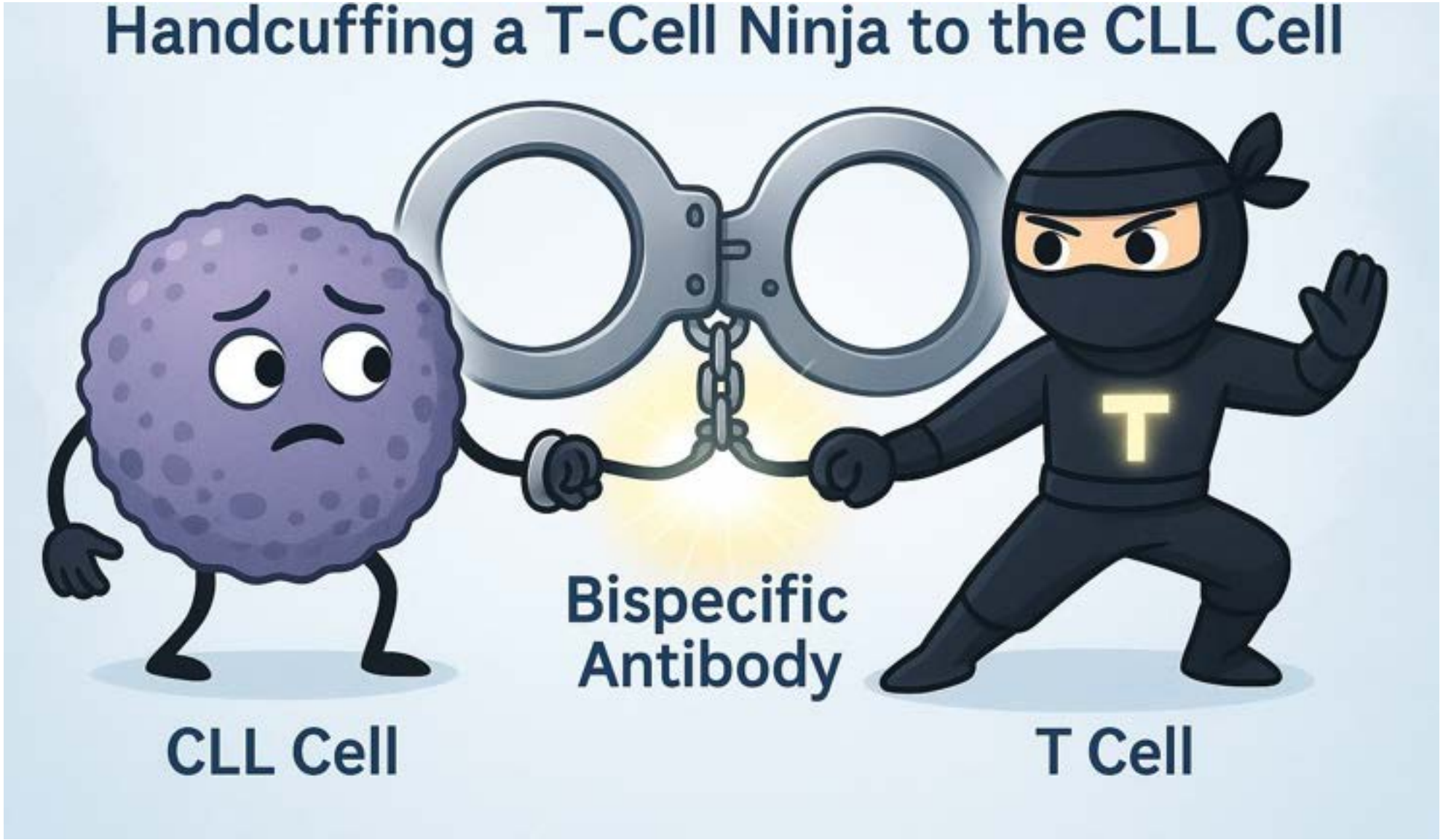
# Can Newer BCL2i Help Optimize Dose Delivery?
## *Updates on Lisaftoclax*

Efficacy in R/R CLL as combination therapy with accelerated ramp-up[1]

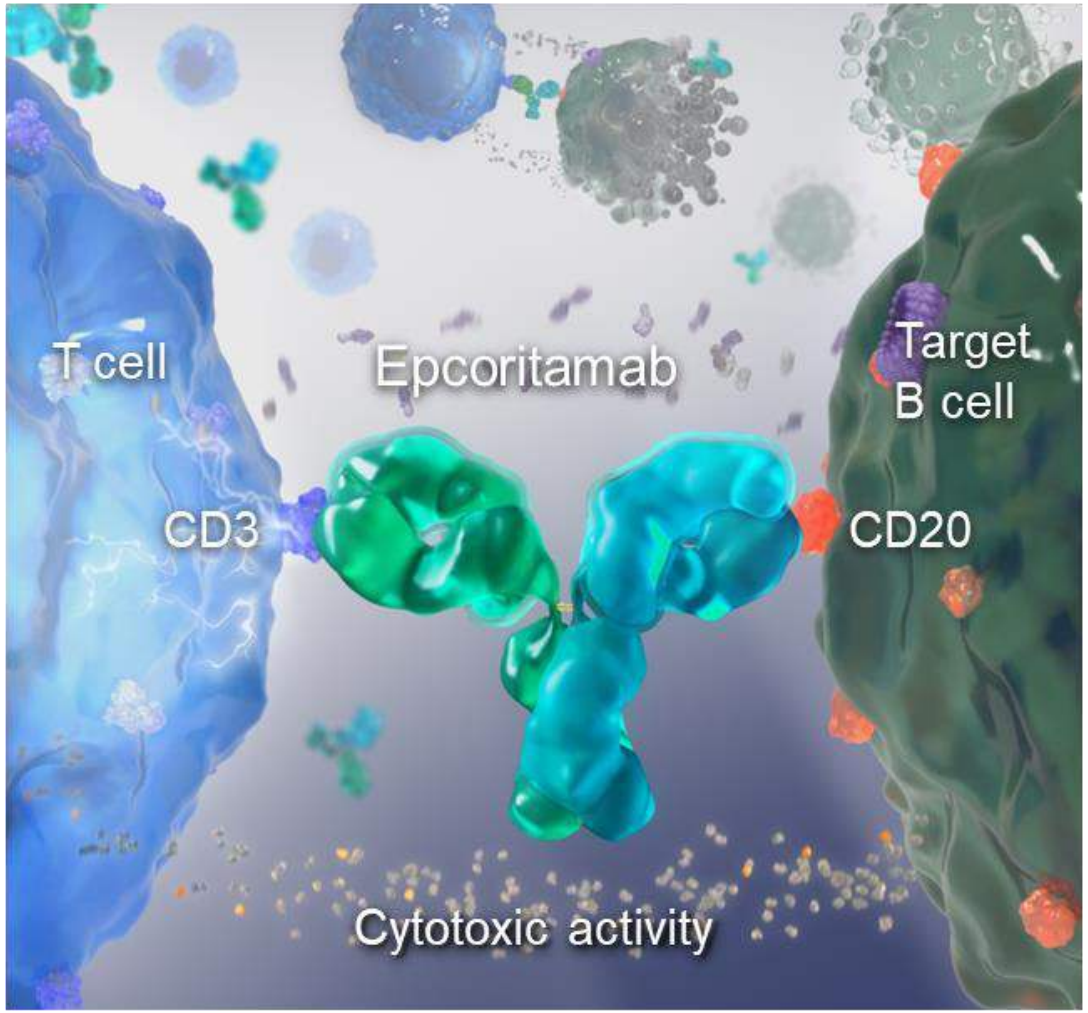
| Lisaftoclax plus acalabrutinib | N = 87 |
|---|---|
| ORR | 96.6% |
| • ven-exposed patients | 85.7% |
| • ven- and BTKi-exposed patients | 66.7% |

1. Davids M et al. ASH 2024. Abstract 4614.

# Bispecific Antibodies for CLL Therapy



# Are Bispecific Antibodies the Next Step for Immunotherapy in CLL?




## CRS Summary From the RS Cohort of the EPCORE CLL-1 Trial

| | Total (N = 10) |
|---|---|
| CRS, n (%)[a] | 9 (90) |
| Grade 1 | 3 (30) |
| Grade 2 | 6 (60) |
| **CRS resolution, n/n (%)** | **9/9 (100)** |
| Median time to onset after first full dose, h (range) | 12.5 (8-394) |
| Median time to resolution, d (range)[b] | 3 (2-9) |
| Treated with tocilizumab, n (%) | 7 (70) |
| **Leading to treatment discontinuation, n (%)** | **0** |

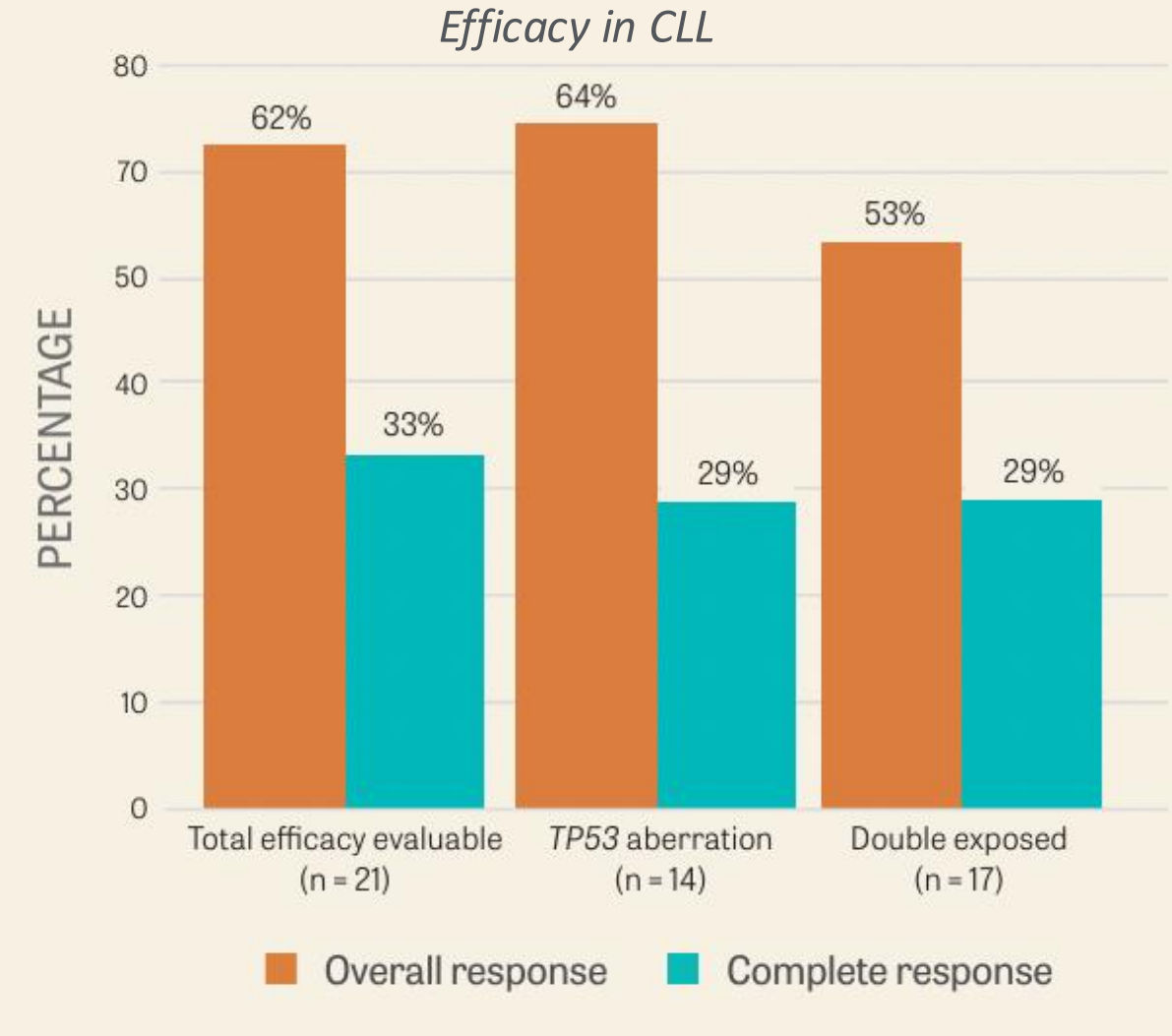
**NCT04623541 – epcoritamab in combination with lenalidomide or RCHOP for RT is ongoing**



Data cutoff: September 16, 2022.

[a] Graded by Lee et al 2019 criteria. [b] Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS.

# EPCORE CLL-1: Unique Bispecific Dosing

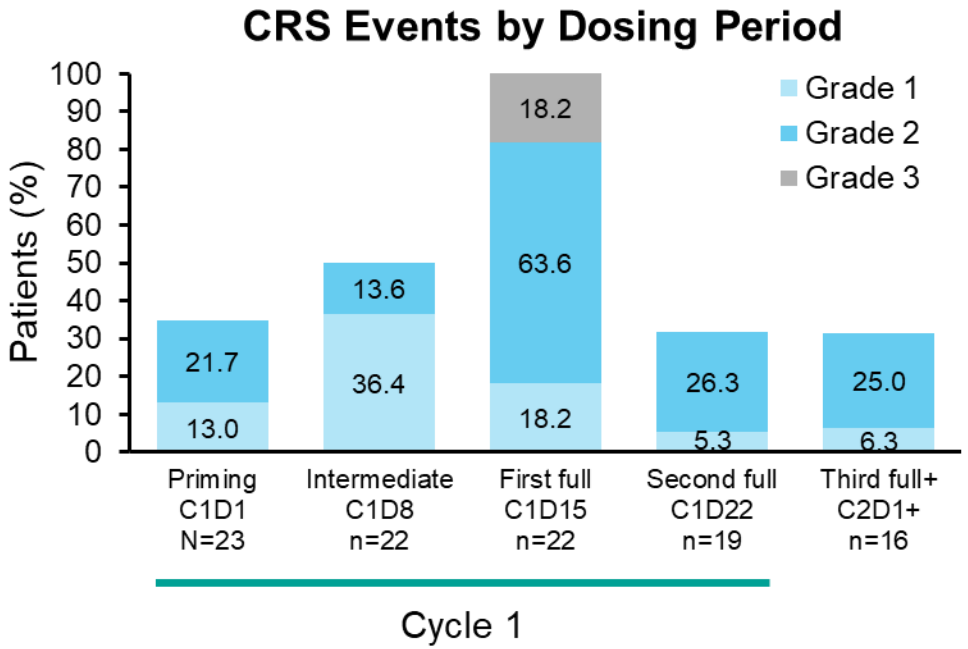



- **Most common TEAEs included CRS, thrombocytopenia, and anemia**
  - In general, CRS is milder with bispecifics than what is typically seen with CAR-T
- **3 cases of RT**
  - 1 of 3 patients found to have a T-prolymphocytic leukemia in the marrow prior to the study

Kater AP et al. iwCLL 2023. Abstract 1546171.

# AEs of Special Interest

| CRS[a] | Total, N=23 |
|---|---|
| Median time to onset after first full dose, h (range) | 7.3 (1–99) |
| Median time to resolution, d (range)[b] | 3 (1–16) |
| Treated with tocilizumab, n (%) | 19 (83) |
| CRS resolution, n/n (%) | 22/22 (100) |




| ICANS & Clinical Tumor Lysis Syndrome | Total, N=23 |
|---|---|
| **ICANS, n (%)[c]** | **3 (13)** |
| Grade 1 | 1 (4) |
| Grade 2 | 2 (9) |
| Median time to resolution, d (range) | 3 (3–4) |
| ICANS resolution, n/n (%) | 3/3 (100) |
| **Tumor lysis syndrome, n (%)** | **1 (4)** |
| Laboratory only | 0 |
| Clinical – grade 2 | 1 (4) |
| Time to resolution, d | 11 |
| Clinical tumor lysis syndrome resolution, n/n (%) | 1/1 (100) |

- CRS occurrence was predictable, with most cases following the first full dose
- No AEs of special interest led to discontinuation, and all resolved

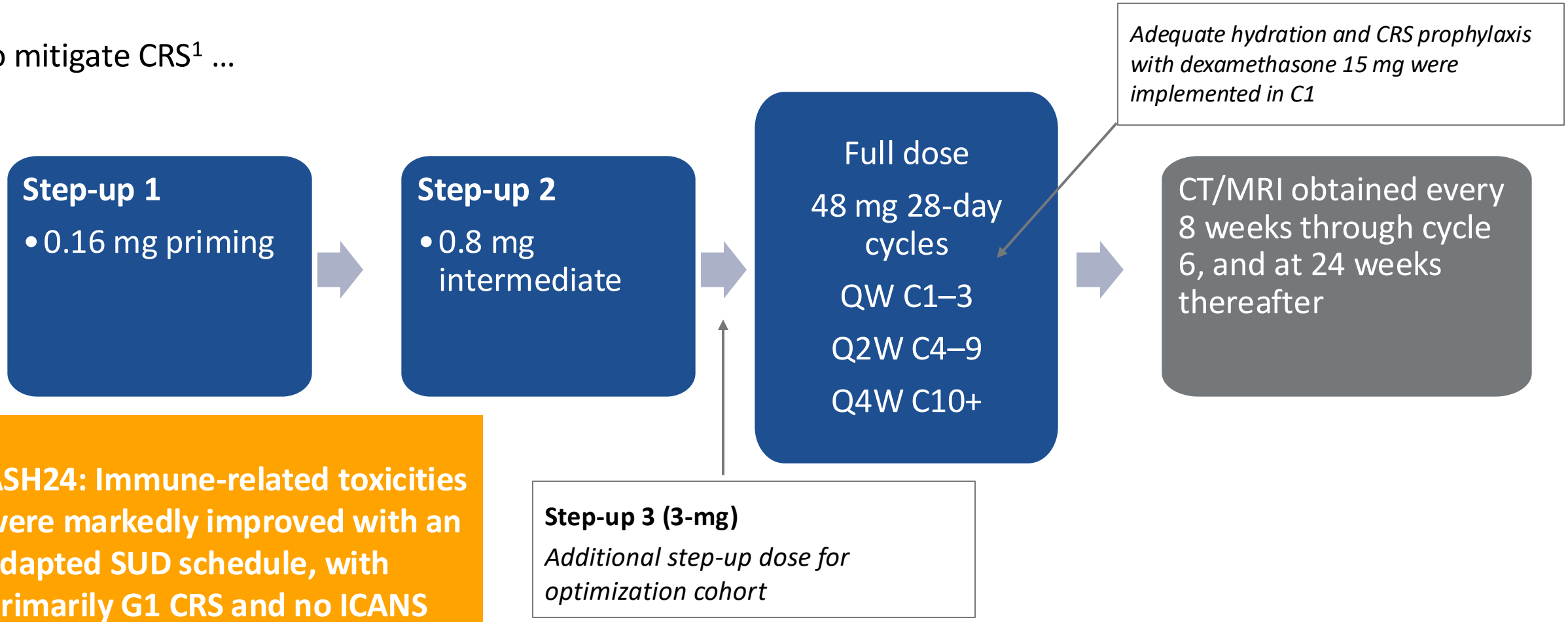
[a] Graded by Lee et al 2019 criteria. [b] Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS. [c] All ICANS events occurred with grade 2 CRS.


Kater AP et al. iwCLL 2023. Abstract 1546171.

# Can Use of Bispecifics Be Optimized?
## *EPCORE CLL-1 Expansion and Optimization Cohorts*

All patients received SC epcoritamab 48 mg at the usual dose

To mitigate CRS[1] …




**ASH24: Immune-related toxicities were markedly improved with an adapted SUD schedule, with primarily G1 CRS and no ICANS**

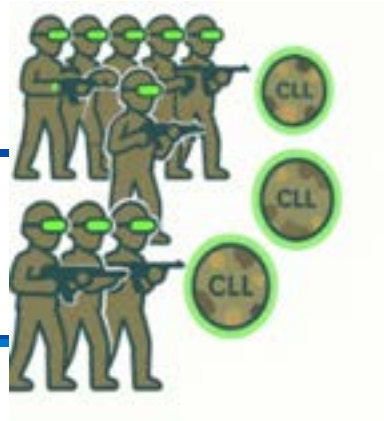
1. Danilov A et al. ASH 2024. Abstract 883.

# Newer agents for dual-exposed patients: Simple Analogies for how they work!

**Non-Covalent BTKi:**


**BTK degraders:**


**CD19 CAR-T cell therapy:**




**BCL2 inhibitors:**


**CD20/CD3 bispecific antibodies:**

# Take-Homes on What's In The Pipeline

- When thinking about what therapies are next - always important to think about what someone has received along their journey
- Good News! Lots of new options of therapy in the pipeline
- Noncovalent BTKis such as pirtobrutinib are useful after progression on covalent BTKis (ibrutinib/acalabrutinib/zanubrutinib) and venetoclax-based therapy. Approved in US/soon to be approved hopefully in Canada. Time-limited studies with pirtobrutinib ongoing.
- BTK degraders are exciting option to overcome potential resistance for patients who have had BTK inhibitors
- CART (lisocel) also an option for multiply relapsed patients with CLL (particularly for patients refractory to many therapies)– studies ongoing to best optimize this therapy
- Bispecific monoclonal antibody therapies showing excellent result in lymphoma and trials in CLL/Richter's syndrome are ongoing

# THANK YOU!

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