Chronic Lymphocytic Leukemia: Evaluating and Therapeutic Approaches for the Management of the Relapsed/Refractory Patient

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Disclosures

Initial Considerations When Approaching Relapsed CLL

Relapse can take different forms

- Increase in WBC after time-limited therapy is complete
- Detection of lymph nodes by CT scan

Don’t treat

- Detection of lymph nodes by exam
- Increase in WBC during continuous treatment

Don’t treat (yet)

- Return of autoimmune conditions
- Symptomatic increase of nodes or spleen
- Return of fatigue or other constitutional symptoms

Start treatment

NCCN Guidelines

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation

SECOND-LINE THERAPY OR THIRD-LINE THERAPY		
Preferred regimens	**Other recommended regimen**	**Useful in certain circumstances**
• BTKi ‣ Acalabrutinib[f,p,*] (category 1) ‣ Zanubrutinib[f,p,*] (category 1) • BCL-2 inhibitor ‣ Venetoclax[f,g] + rituximab[e] (category 1)	• Ibrutinib (category 1)[f,h,*] • Venetoclax[f,g]	• Retreatment with venetoclax[f,g] + obinutuzumab (for relapse after a period of remission if previously used as first line therapy) • Non-covalent (reversible) BTK inhibitor ‣ Pirtobrutinib (resistance or intolerance to prior covalent BTKi therapy)[q]

[*] Covalent (irreversible) BTK inhibitors.

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with del(17p)/*TP53* mutation
(alphabetical by category)

SECOND-LINE OR THIRD-LINE THERAPY[e]		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Acalabrutinib[f,p,*] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Venetoclax[f,g] • Zanubrutinib[f,p,*] (category 1)	• Ibrutinib[f,h,*] (category 1) • Alemtuzumab[t] ± rituximab • Duvelisib[f] • HDMP + rituximab • Idelalisib[f,u] ± rituximab • Lenalidomide[s] ± rituximab	• Non-covalent (reversible) BTK inhibitor ‣ Pirtobrutinib (resistance or intolerance to prior covalent BTKi therapy)[q]

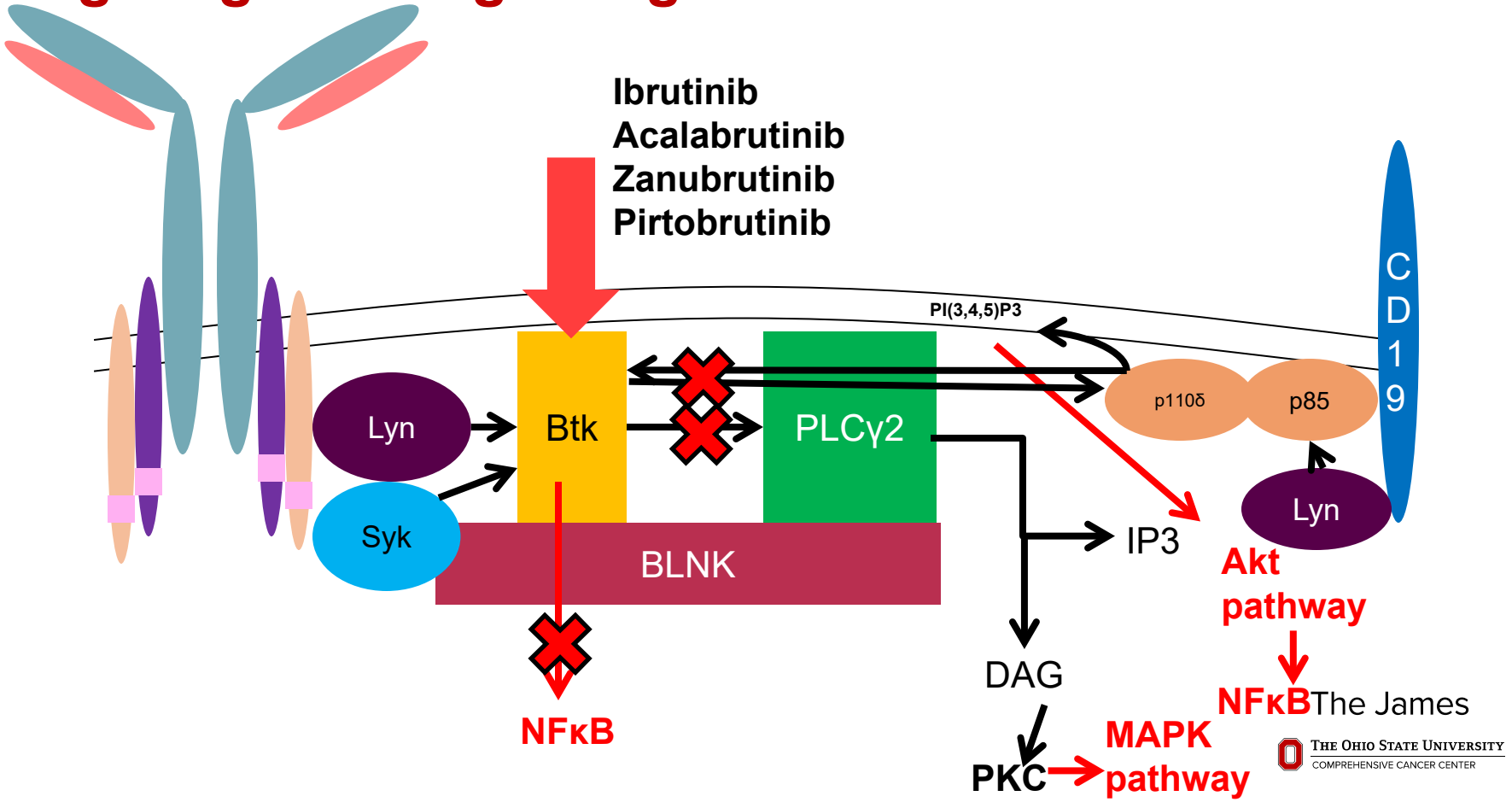
What Was the Initial Treatment?

- Fixed duration therapy?
  - Chemoimmunotherapy
  - Venetoclax + obinutuzumab
- BTK inhibitor given continuously?

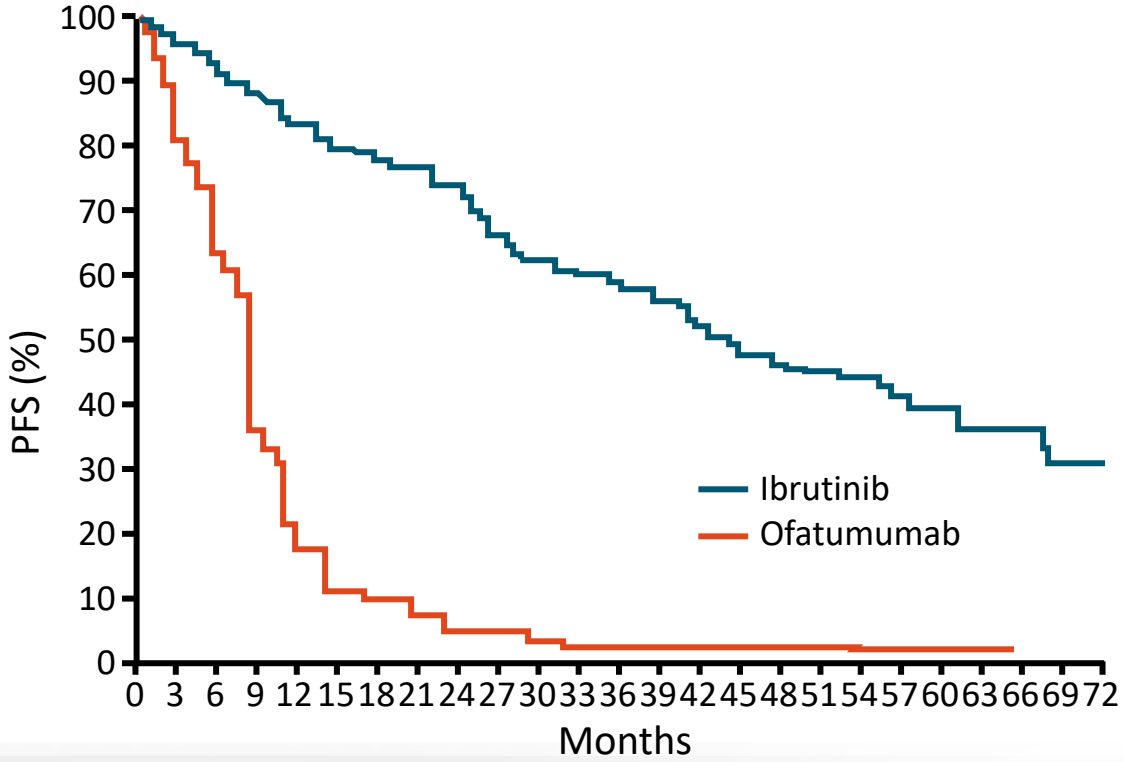
If Initial Treatment Was Chemoimmunotherapy . . .

What do the data show?

Targeting BCR Signaling in CLL



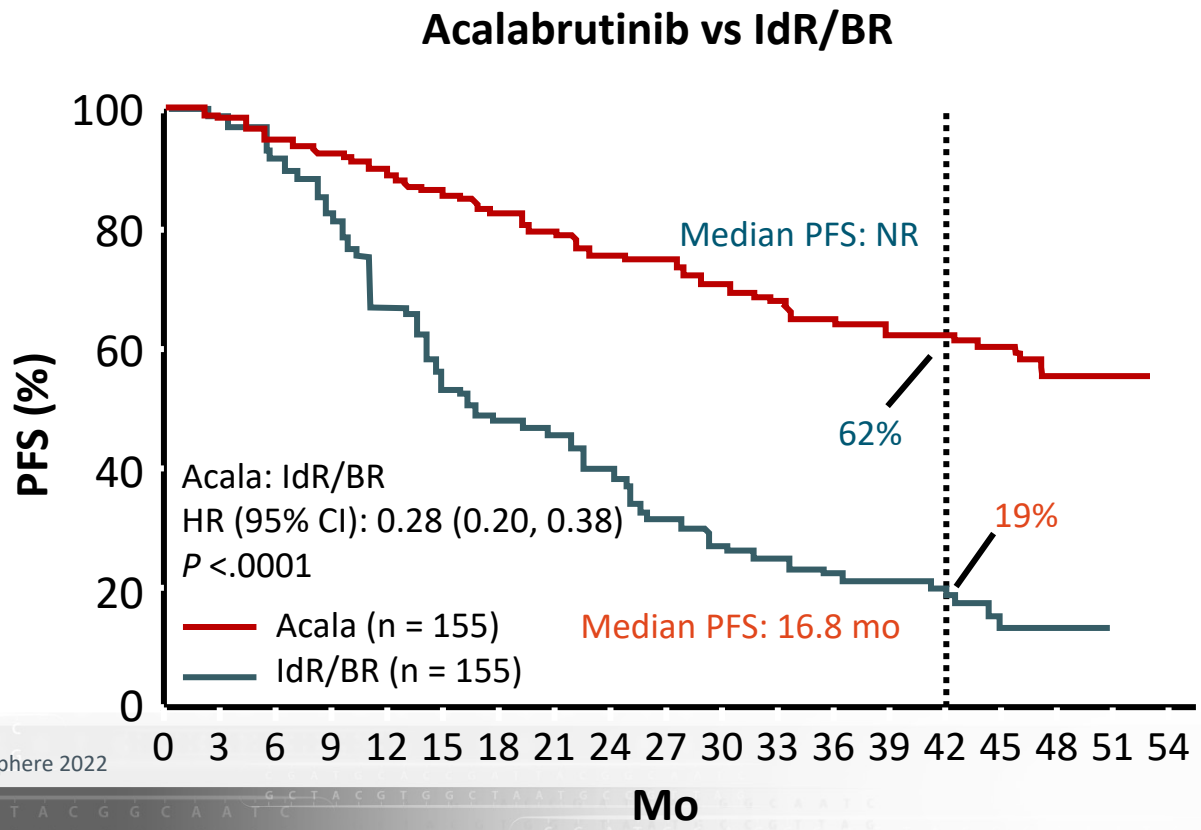
BTK Inhibitors Demonstrate Long Remission Durations: RESONATE



- Randomized, open-label phase III trial of ibrutinib vs ofatumumab for patients with CLL/SLL, ≥1 prior therapy, and measurable nodal disease (N = 391)
- Median PFS 44.1 mo vs 8.1 mo

Munir. Am J Hematol. 2019;94:1353.

BTK Inhibitors Demonstrate Long Remission Durations: ASCEND



- Randomized, open-label phase III trial of **acalabrutinib** vs idelalisib + rituximab or bendamustine + rituximab for patients with R/R CLL, ≥1 prior systemic therapy, and no prior BCL-2 or B-cell receptor inhibitor therapy (N = 310)

Ghia et al, Hemasphere 2022

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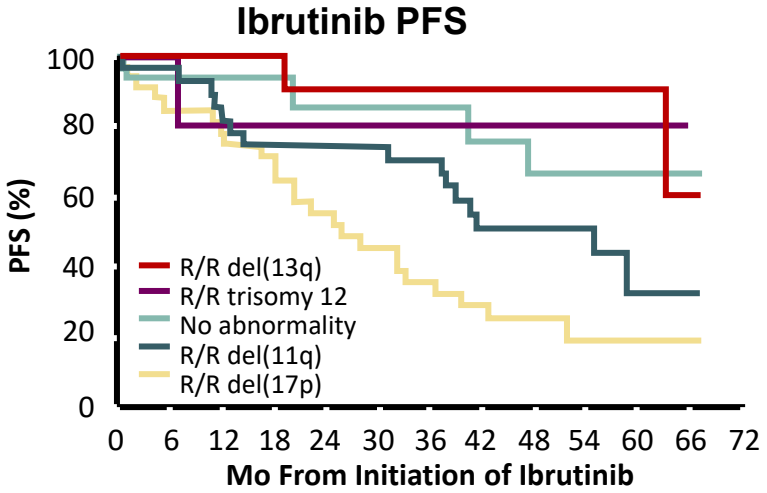
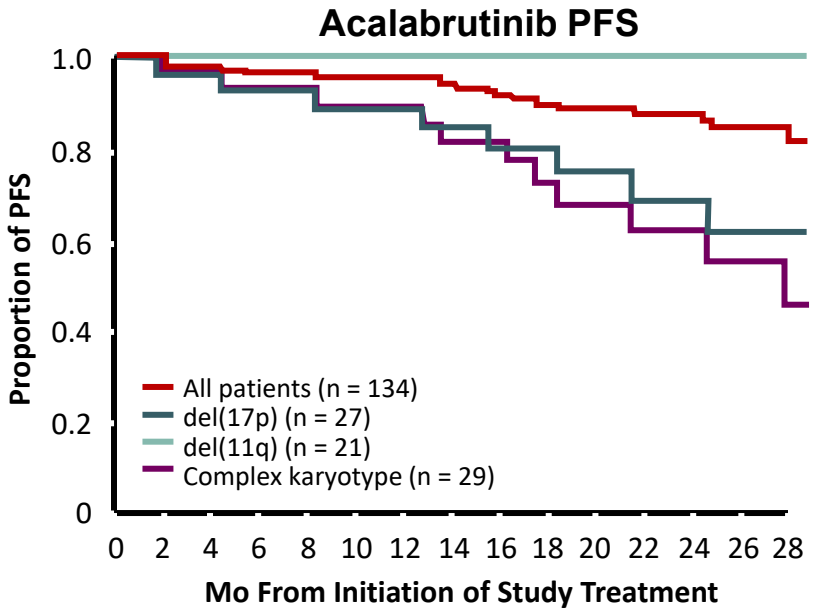
Cytogenetics Are Still Important



Profile	Median PFS, Mo	5-Yr PFS, %
del(17p) (n = 34)	26	19
del(11q) (n = 28)	55	33
Trisomy 12 (n = 5)	NR	80
del(13q) (n = 13)	NR	91
No abnormality (n = 16)	NR	66



O'Brien. Blood. 2018;131:1910. Byrd. NEJM. 2016;374:323.

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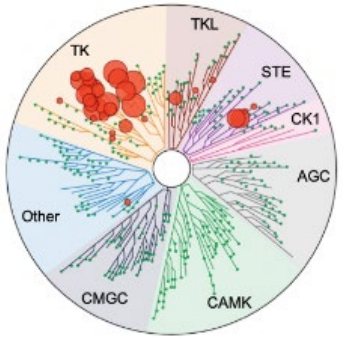
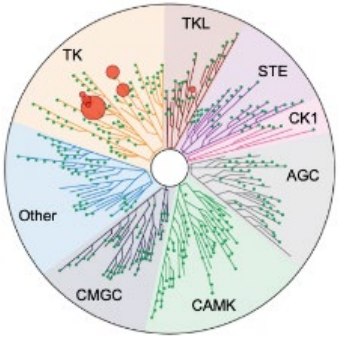
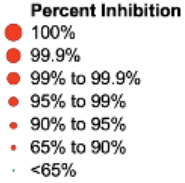
Which BTK Inhibitor Is Best?

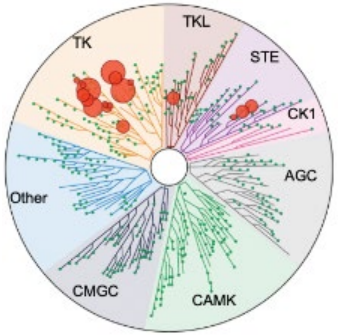


Ibrutinib



Acalabrutinib



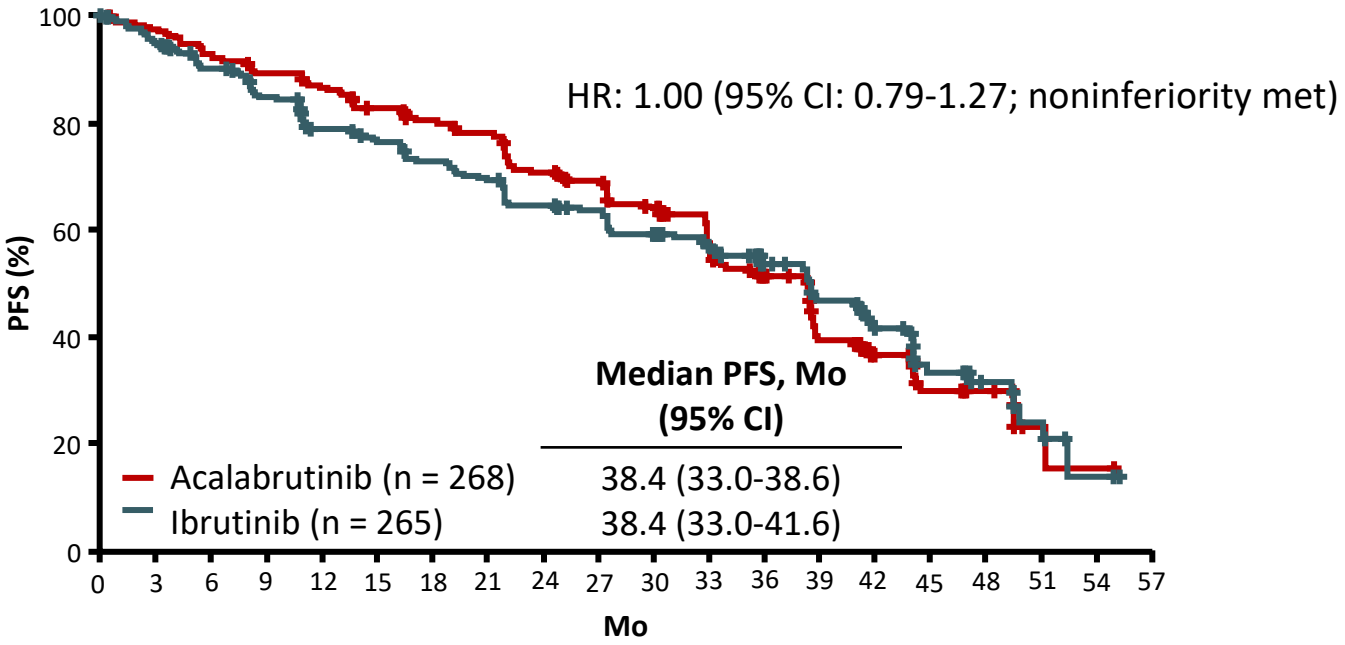


Zanubrutinib

Kaptein. ASH 2018. Abstr 1871.

Acalabrutinib vs Ibrutinib: ELEVATE-RR

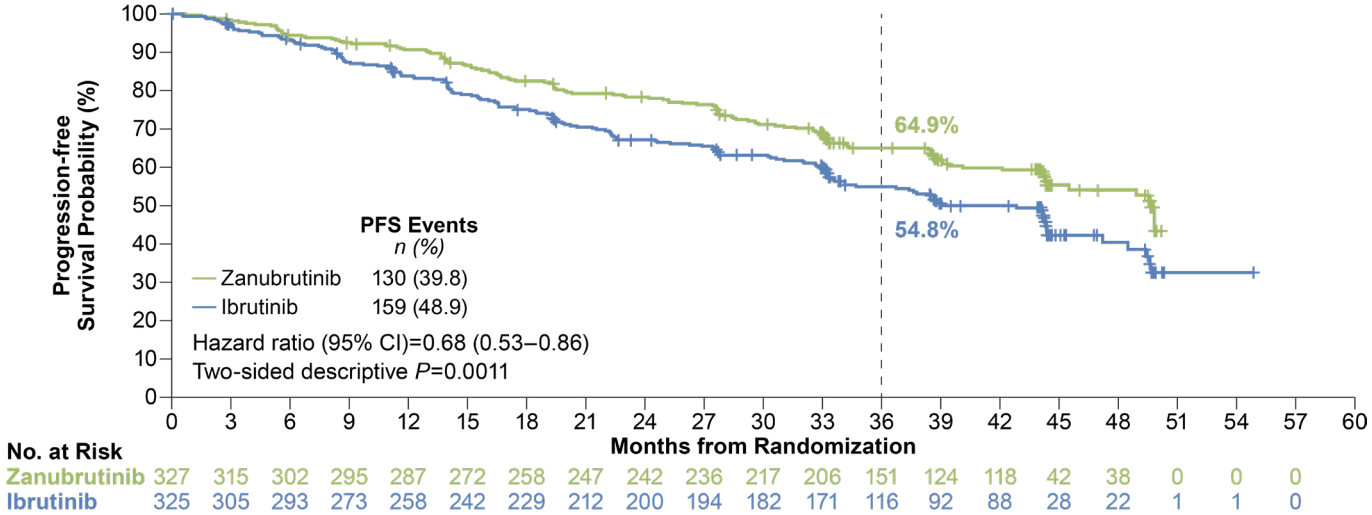
- Randomized phase III noninferiority trial of acalabrutinib vs ibrutinib for patients with previously treated CLL; presence of del(17p) or del(11q); no significant CV disease; no prior BTK, PI3K, Syk, or BCL-2 inhibitors (N = 533)



Byrd. ASCO 2021. Abstr 7500. Byrd. JCO. 2021;39:3441.

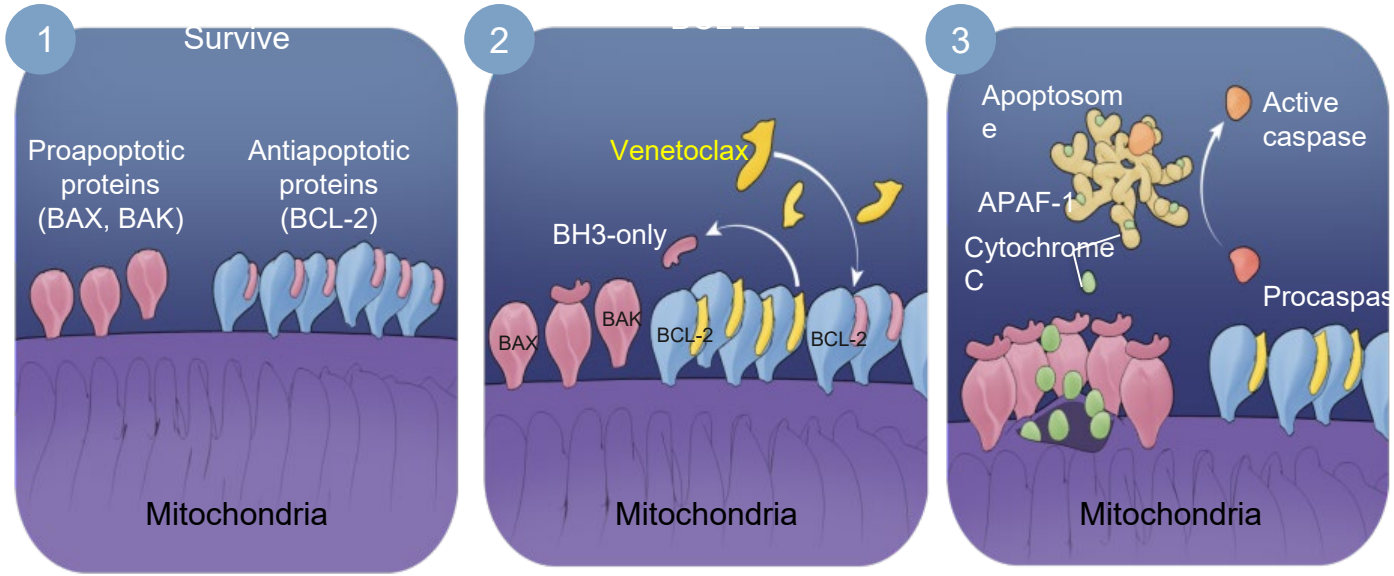
Zanubrutinib vs Ibrutinib: ALPINE

- Randomized phase III trial of zanubrutinib vs ibrutinib for patients with CLL relapsed or refractory to ≥1 previous line of treatment; no prior BTKi



Brown. ASH 2023

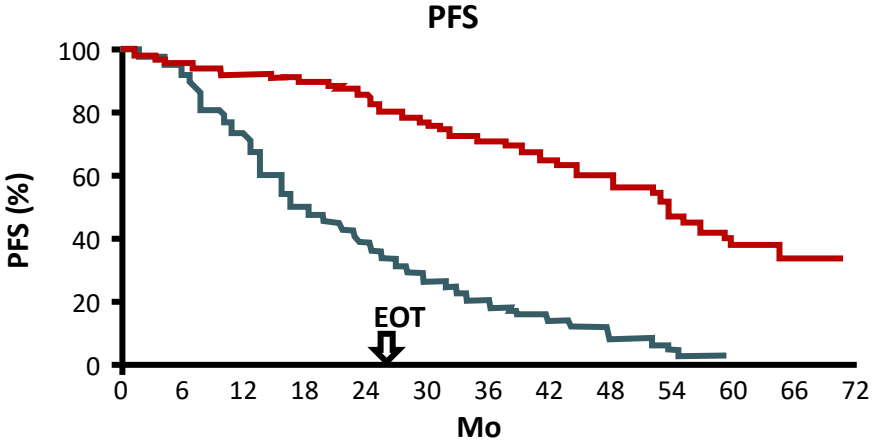
BCL-2 Inhibition With Venetoclax

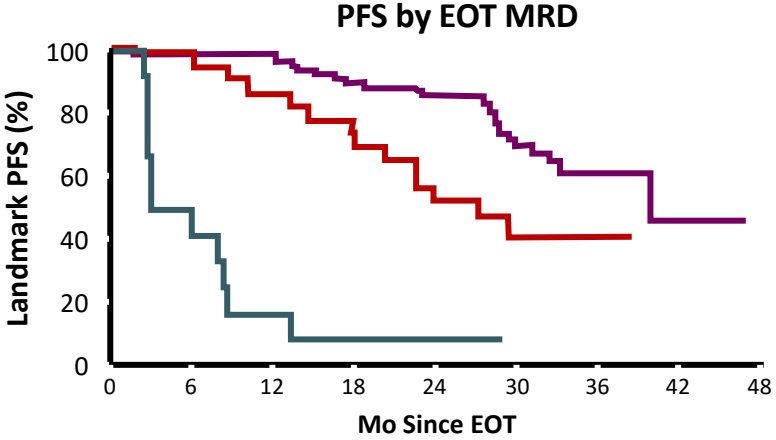


Kumar, ASCO 2015, Abstr 8576

Venetoclax + Rituximab Induces Long Remission Durations: MURANO

- Randomized, open-label phase III trial of venetoclax + rituximab vs bendamustine + rituximab for patients with R/R CLL; 1-3 prior tx lines (with ≥1 CT-containing regimen) (N = 389)





	Median PFS, Mo (95% CI)
VenR (n = 194)	53.6 (48.4-57.0)
BR (n = 195)	17.0 (15.5-21.7)

	PFS Since EOT, %	
Category	24-Mo	36-Mo
uMRD ($<10^{-4}$), n = 83	85.4	61.3
Low-MRD+ ($\geq10^{-4}$-10^{-2}), n = 23	52.2	40.7
High-MRD+ ($\geq10^{-2}$) n = 12	8.3	

Seymour. Blood. 2022;140:839.

What Do These Data Tell Us?

- In the postchemotherapy setting, both BTK and BCL-2 inhibitors are very effective
- Chemotherapy and PI3K inhibitors are not recommended for relapsed CLL
- Second generation BTKi are preferred over ibrutinib for most patients

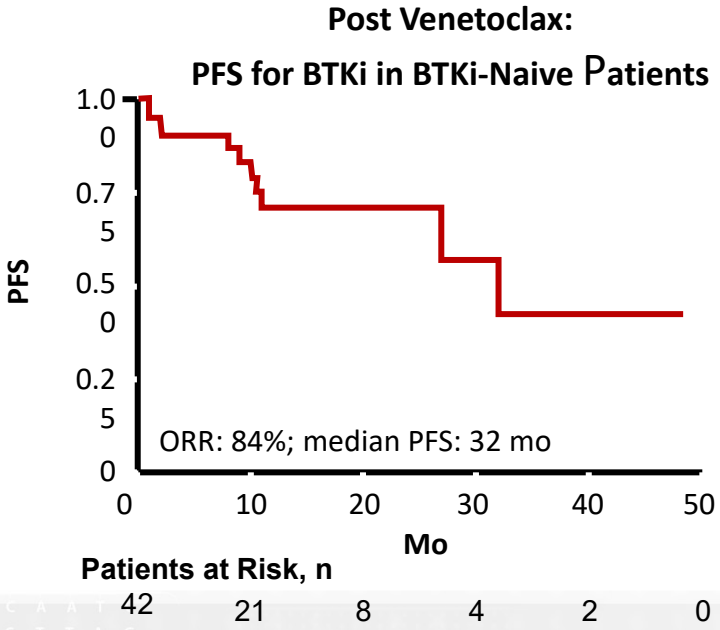
How Would This Be Different if Venetoclax + Obinutuzumab Were the Prior Therapy?

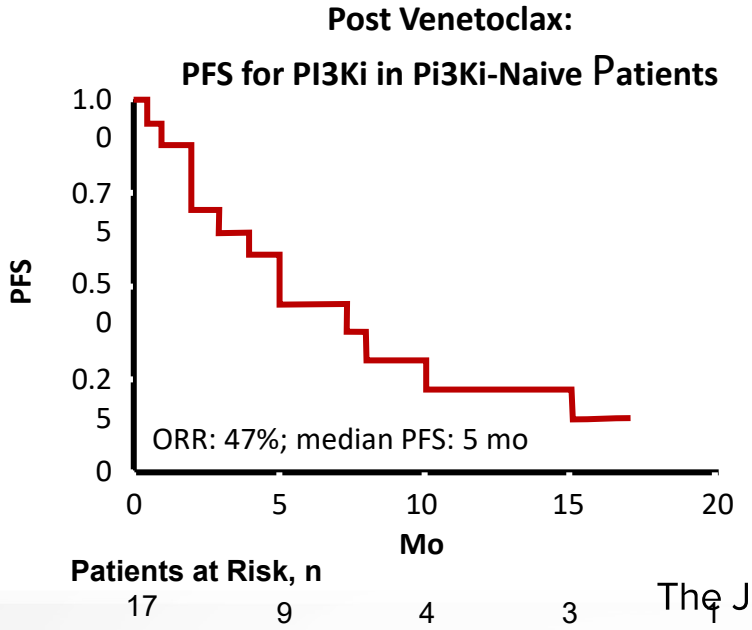
- Many options for targeted therapies
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
  - Idelalisib + rituximab
  - Duvelisib
- Could also consider repeating initial therapy depending on remission duration

What do the data show?

Post-Venetoclax Strategies

- Multicenter, retrospective cohort study of outcomes in patients with CLL who discontinued venetoclax-based therapy (N = 326)

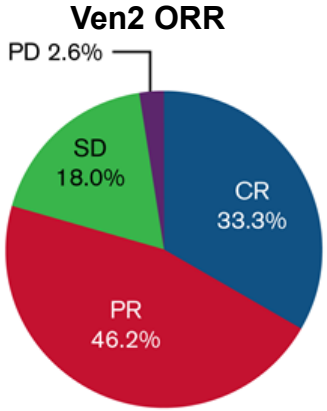


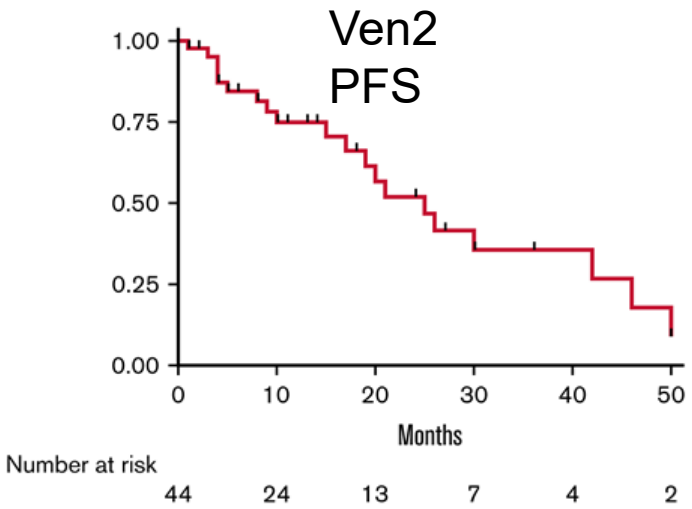


Mato. Clin Cancer Res. 2020;26:3589.

Venetoclax Retreatment Appears Promising

- MURANO retreatment data
  - 18 evaluable patients received subsequent venetoclax post-relapse
    - ORR 72.2%, 5.6% CR/Cri
- Retrospective multicenter data
  - 46 patients, 91% R/R
    - ORR 79.5%, med PFS 25 mo





Seymour. Blood. 2022; Thompson. Blood. 2022

What If Prior Treatment Were Ibrutinib + Venetoclax

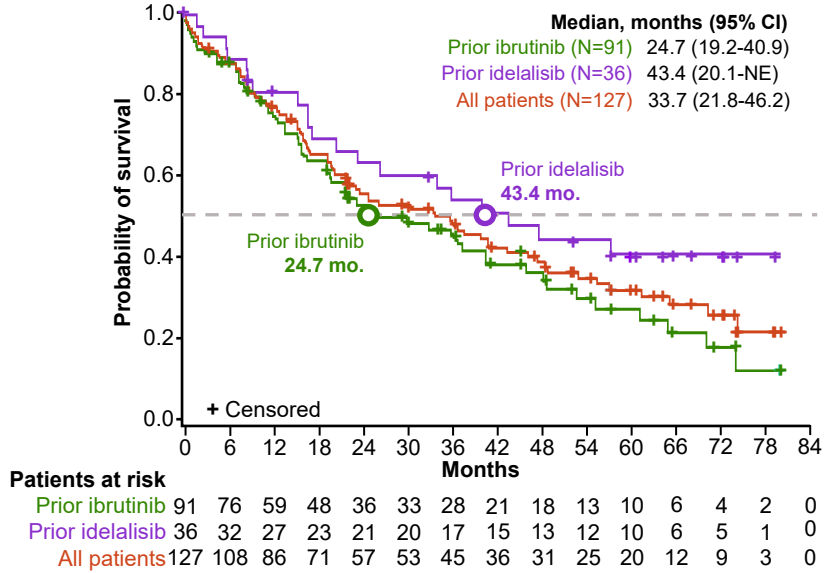
- No prospective data exists (yet)
- Retrospective and anecdotal data suggest retreatment with either component, or potentially both, is effective

If Prior Treatment Was Covalent BTK Inhibitor . . .

- If progression occurs after ibrutinib discontinued for toxicity, treatment with acalabrutinib is effective
- If progression occurs after acalabrutinib discontinued for toxicity, zanubrutinib or other treatments (venetoclax) are likely effective
- If progression occurs during treatment with ibrutinib or acalabrutinib, venetoclax has been shown to be effective
- Resistance to ibrutinib, acalabrutinib, and zanubrutinib is driven primarily by mutations in *BTK* (C481S)
- In the presence of this mutation, covalent inhibitors bind noncovalently, and binding kinetics and short half-life make these agents less effective
- However, the mutation does not appear to alter CLL dependence on the BCR pathway
- Zanubrutinib also can induce L528W mutation in BTK

Venetoclax is Effective in the Post-BTKi Setting

Multicenter study of venetoclax monotherapy in patients previously treated with ibrutinib or idelalisib



Woyach et al. iwCLL 2023

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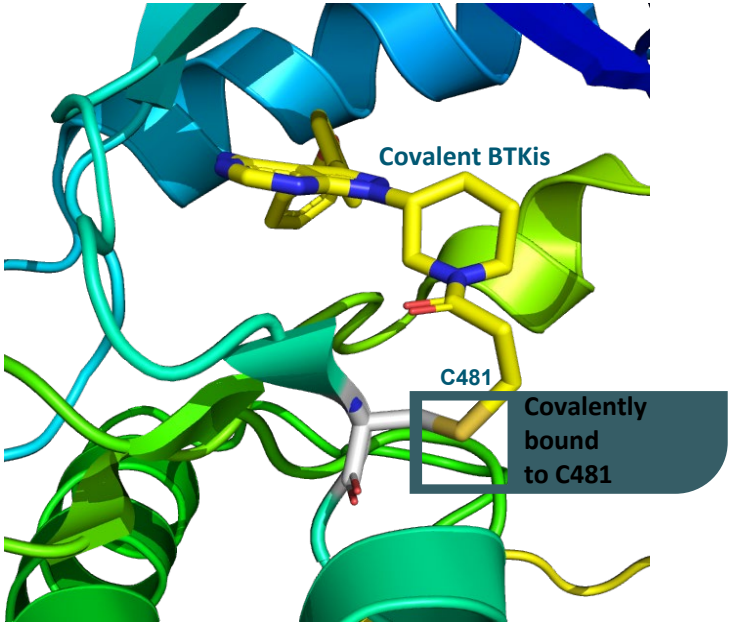
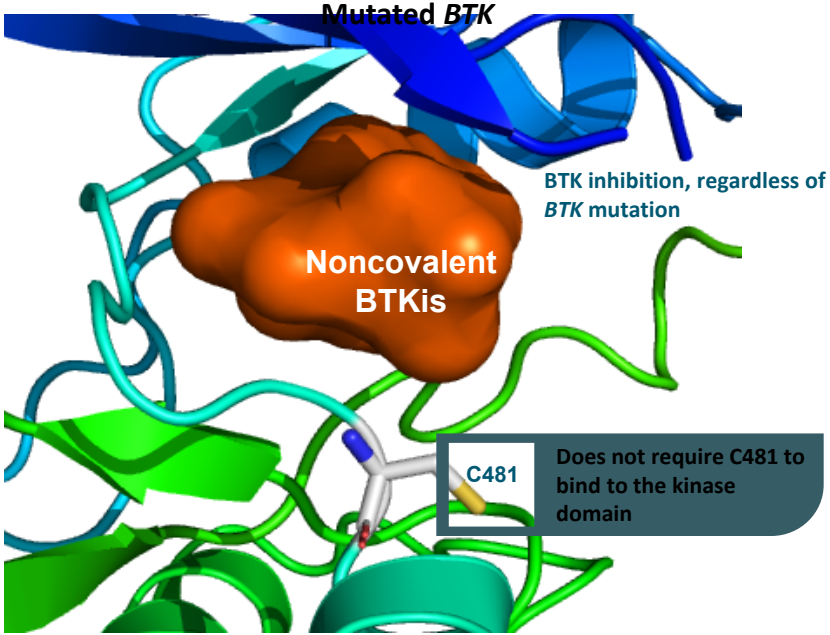
Noncovalent BTK Inhibition

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, Zanubrutinib) Require WT *BTK* for Activity



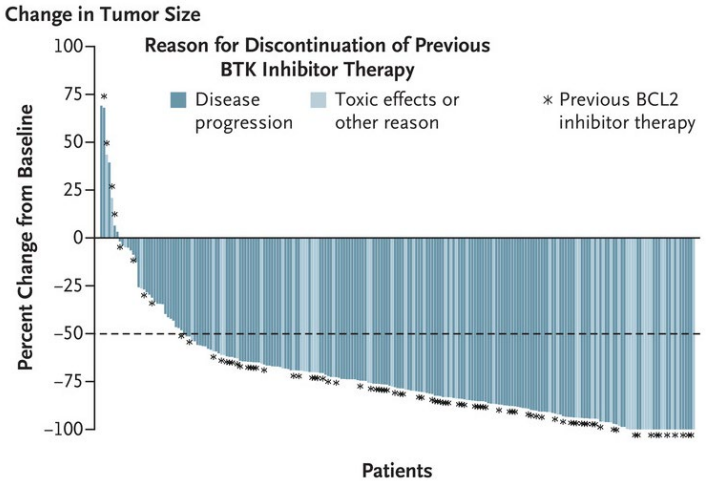
Noncovalent BTK Inhibitors (Pirtobrutinib, Nemtabrutinib) Are Active Against Both WT and C481-Mutated *BTK*

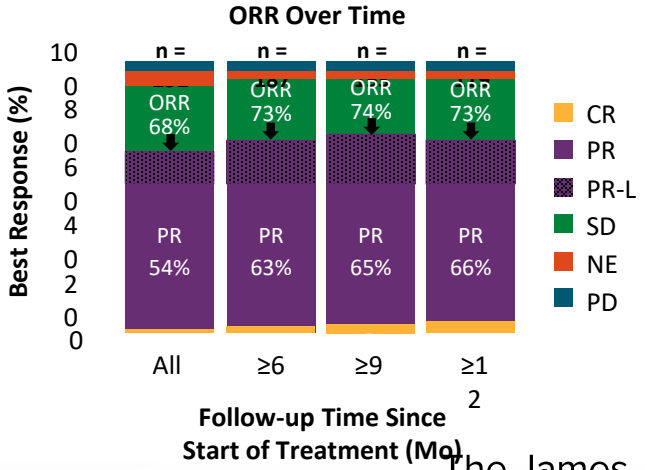


Slide credit: clinicaloptions.com

BRUIN: Pirtobrutinib for Previously Treated CLL/SLL

- Phase I/II study (with dose escalation and expansion in phase I) of pirtobrutinib for patients with CLL/SLL* or B-cell non-Hodgkin lymphoma and ≥2 prior therapies including BTK inhibitor
  - Pirtobrutinib: next-generation, highly selective, **noncovalent** BTK inhibitor that promotes apoptosis and inhibits BCR signaling in xenograft models with wild-type *BTK* and those harboring *BTK* C481S mutation

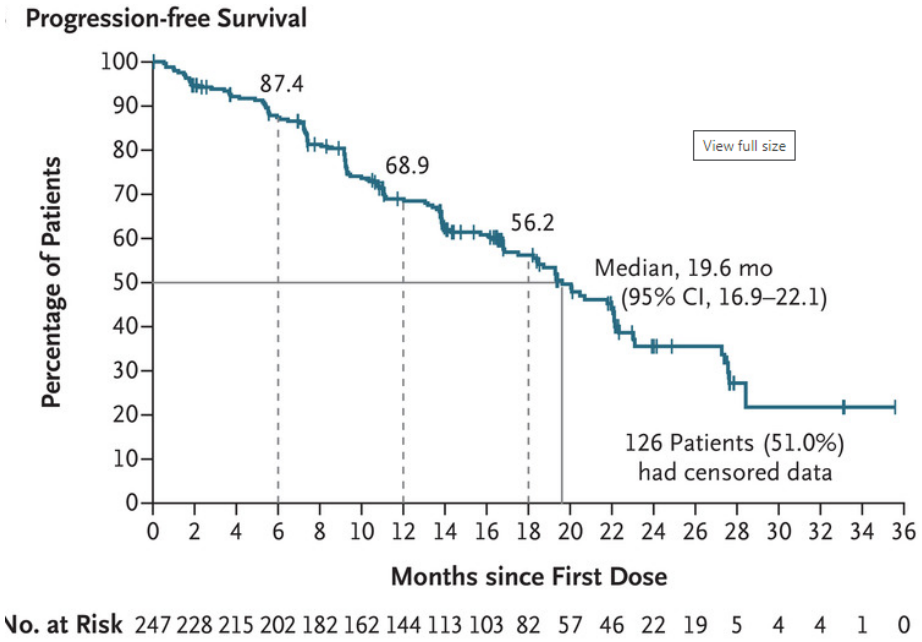


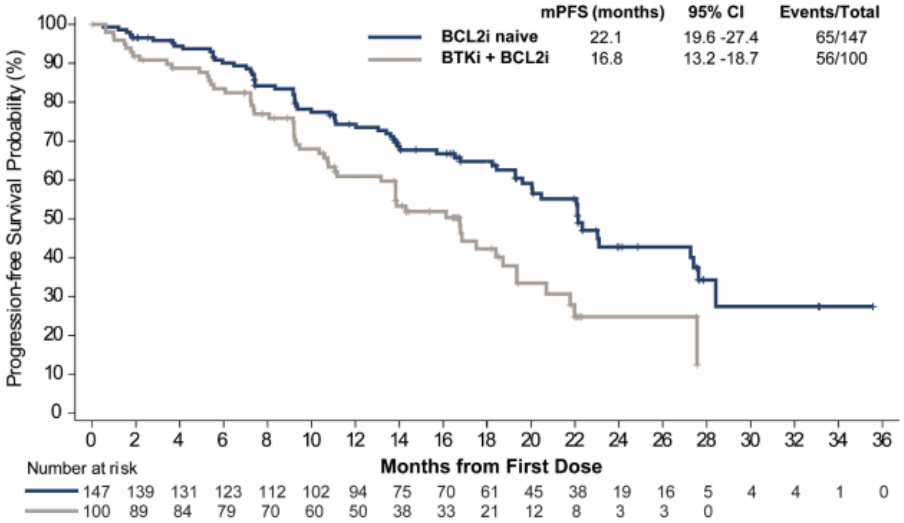


*Safety population: n = 296; efficacy population: n = 252 (all previously treated with BTK inhibitor).

Mato. N Engl J Med. 2023; 289:33-44.

BRUIN CLL/SLL: PFS





Mato, NEJM 2023

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Other Emerging Strategies

- Novel targeted therapies
  - Irreversible/reversible BTKi (nemtabrutinib, LP168)
  - BTK degraders (multiple)
  - Downstream BCR-targeting agents (PI3k)
  - Novel BCL2 or other anti-apoptotic targeting agents (sonrotoclax, LP118)
- Cellular therapies/antibody strategies
  - CAR-T (liso-cel)
  - NK cells
  - Bispecific antibodies (epcoritamab, others)

Conclusions

- Therapy for relapsed CLL is rapidly changing, and patients with relapsed disease have a number of therapeutic options
- Therapy of relapsed CLL depends heavily on what was chosen for frontline treatment
  - Optimal sequencing of therapy is unknown
- There is not a role for chemoimmunotherapy in the relapsed setting (limited role in treating CLL/SLL)
- There is still progress to be made!