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CHALLENGING CASES

Hematologic Cancers: CLL/SLL

Challenging Cases in…

Hematologic Cancer: CLL/SLL

Program conducted: February – April 2025

Note: Aggregated results and high-level summary based on 5 practices (≤40 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of each presentation.

Participating Practices

- Fort Wayne Medical Oncology and Hematology (n=6) February 5, 2025
- Ironwood Cancer and Research Centers (n=8) February 12, 2025
- Northwestern Medicine (n=7) March 5, 2025
- Live Regional Exchange Atlanta (n=14) March 28, 2025
- Ironwood Cancer and Research Centers (n=5) April 22, 2025

Report finalized: May 15, 2025

High-level Summary

Challenging Cases in… Hematologic Cancers:

CLL/SLL

- In general, first-line treatment choice was zanubrutinib, followed by acalabrutinib with or without obinutuzumab, or venetoclax with obinutuzumab.
  - First-line (1L) treatment preference is influenced by risk, treatment goals, and other patient factors.
  - Some indicated that venetoclax-based therapy was avoided upfront in high-risk patients (TP53 mutation or 17p deletion); reserved for later-lines.
  - Some noted clinical trial efficacy data reinforce confidence in BTK inhibitors (BTKi) upfront.
- If acalabrutinib is used in the 1L setting , then zanubrutinib is the preferred 2L treatment option followed by venetoclax with rituximab or venetoclax with obinutuzumab.
  - Some indicated choice is often guided by patient preference, previous tolerability, and the presence of resistance mutations.
  - Awareness of clinical trial data can influence treatment decisions.
- In general, dose interruption and restarting treatment at a lower dose was viewed as the best strategy to manage intolerance in patients with CLL.
  - Some noted if side effects persisted switching BTK inhibitor was considered an appropriate option only if no BTKi resistance mutation was detected.
  - Some test for BTKi resistance mutations, even in intolerance cases, to better guide next therapy.
  - Some consider switching to a different mechanism of action for patients with confirmed resistance or intolerable toxicities.

High-level Summary

Challenging Cases in… Hematologic Cancers:

CLL/SLL

- In general, most indicated that they would be more likely to switch to a different irreversible (covalent) BTKi for a patient intolerant to a prior BTKi.
  - Some indicated if BTKi resistant mutations are detected then more likely to switch to venetoclax-based regimen.
- In general, venetoclax plus rituximab is the preferred treatment after 2L zanubrutinib therapy.
  - Some considered pirtobrutinib (a non-covalent BTKi) for patients who failed both a covalent BTKi and venetoclax in the 3L setting
- Comorbidities can play a role in determining utilization of a BTKi vs CAR T-cell therapy in the 3L setting.
- CAR T-cell therapy can have additional challenges within the community setting such as lengthy travel distances to treatment centers and or the need for caregiver support which may not be available.
- Some indicated referring patients for CAR T-cell therapy, especially if younger, fit patients with limited options in the 3L setting.

Challenging Cases in… Hematologic Cancers

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

- *What is the optimal first line therapy for patients? Second line therapy?*
- *How do adverse events impact treatment decisions?*
- *How does intolerance impact subsequent treatment decisions?*

Patient History

72-year-old male

Symptoms:

Lymphadenopathy in the neck and axillary region; increased infections

Comorbidities:

Past medical history of hyperlipidemia (taking statin) and
chronic back pain

Diagnosis

CLL involvement with 80 % of the bone marrow

Bone marrow cytogenetics showed trisomy 12 and t(y;8);

With del(17p)/TP53 mutation

Rai Stage 2 disease

What first-line treatment do you recommend?

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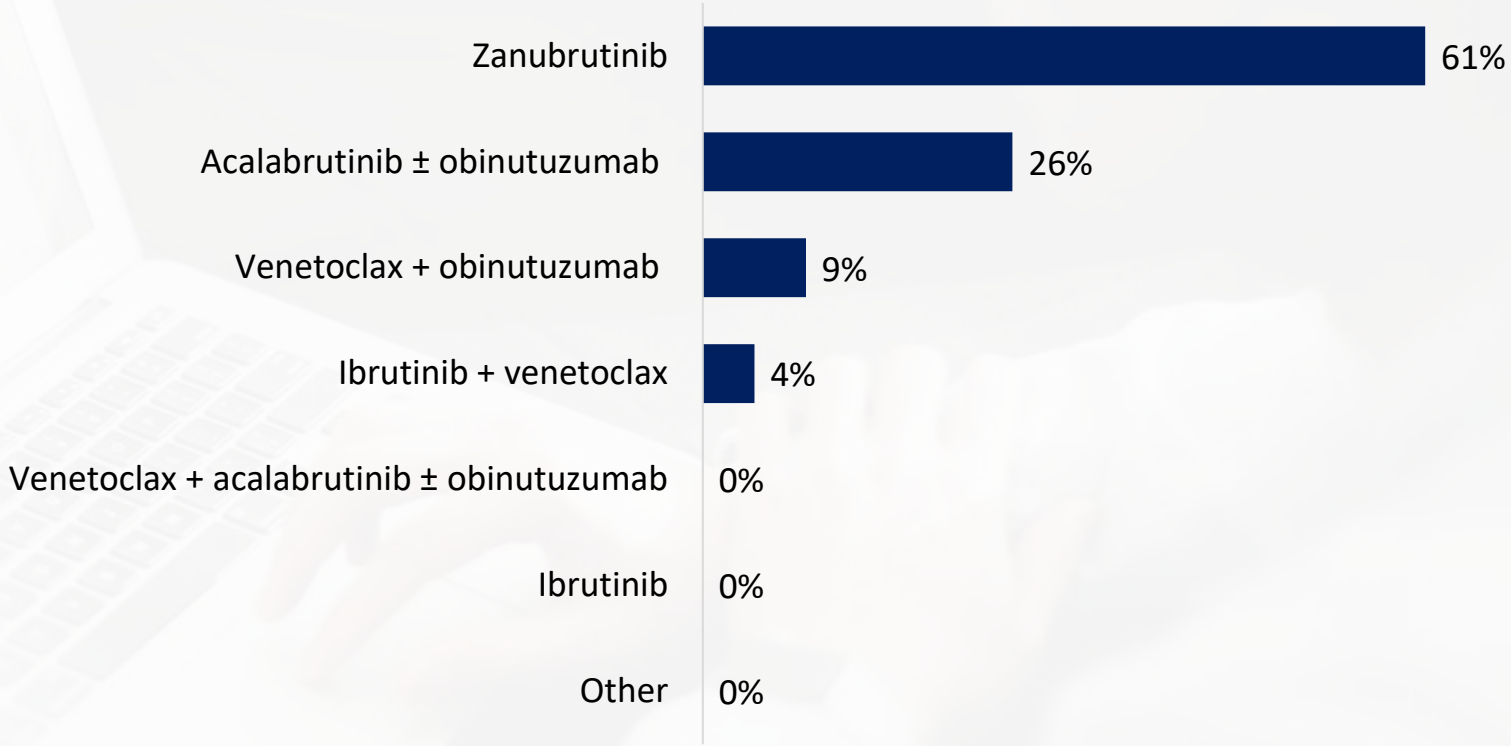
ARS Results from HCP Participants

What first-line treatment do you recommend?



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NCCN Guidelines 1L setting | Version 3.2025 | April 2, 2025

NCCN Guidelines
CLL/SLL without del(17p)/TP53 mutation
Category 1 preferred

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NCCN Guidelines Version 3.2025
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• BCL2i-containing regimens ▸ Venetoclax[f,h] + obinutuzumab (category 1) ▸ Venetoclax[f,h] + acalabrutinib ± obinutuzumab (category 1) • cBTKi-based regimens ▸ Acalabrutinib[f,g] ± obinutuzumab (category 1) ▸ Zanubrutinib[f,g] (category 1)	• BCL2i-containing regimen ▸ Venetoclax[f,h] + ibrutinib[f,g] • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[j,k] • cBTKi-based regimen ▸ Ibrutinib[f,g] + anti-CD20 mAb (category 2B)[l] • Consider when cBTKi and BCL2i are not available or contraindicated or rapid disease debulking needed ▸ Bendamustine[m] + anti-CD20 mAb[l,n] ▸ Obinutuzumab ± chlorambucil[o] ▸ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[l] (category 2B; category 3 for patients <65 y without significant comorbidities)

NCCN Guidelines
CLL/SLL with del(17p)/TP53 mutation
Preferred

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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CLL/SLL With del(17p)/*TP53* Mutation
(alphabetical by category)
CIT is not recommended since del(17p)/*TP53* mutation is associated with low response rates.

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• BCL2i-containing regimens ▸ Venetoclax[f,h] + obinutuzumab ▸ Venetoclax[f,h] + acalabrutinib ± obinutuzumab • cBTKi-based regimens ▸ Acalabrutinib[f,g] ± obinutuzumab ▸ Zanubrutinib[f,g]	• BCL2i-containing regimen ▸ Venetoclax[f,h] + ibrutinib[f,g] • cBTKi-based regimen ▸ Ibrutinib[f,g,i]	• Consider when cBTKi and BCL2i are not available or contraindicated or rapid disease debulking needed ▸ HDMP + anti-CD20 mAb[l] ▸ Obinutuzumab

Regardless of del(17p)/TP53 mutation

Preferred Regimens:

- **Acalabrutinib ± obinutuzumab**
- **Zanubrutinib**
- **Venetoclax + obinutuzumab**
- **Venetoclax + acalabrutinib ± obinutuzumab**

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COMPARISON

1L CLL/SLL

	ELEVATE-TN (Acalabrutinib)			CLL14 (Venetoclax)		SEQUOIA (Zanubrutinib)	
FDA Indication	CALQUENCE is indicated for the treatment of adult patients with CLL/SLL			VENCLEXTA is indicated for the treatment of adult patients with CLL/SLL		BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with CLL/SLL	
Study Design	Randomized, multicenter, open-label study of acalabrutinib ± obinutuzumab in Patients (Pts) With Treatment-Naive CLL/SLL Randomized 1:1:1 (N=535) **with del(17p): 10% vs 9% vs 10%**			A fixed duration regimen of venetoclax + obinutuzumab for 1 year in Patients (Pts) With Treatment-Naive CLL/SLL Randomized 1:1 (N=432) **with del(17p): 9% vs 7%**		Zanubrutinib vs Bendamustine + Rituximab (BR) in Patients (Pts) With Treatment-Naive CLL/SLL Randomized 1:1 (n=479) **without del(17p)**	(n=110) **with del(17p)**
Long term follow-up	~6-year follow-up (median 74.5 months)			~6-year follow-up (median 76.4 months)		~5 year follow up (median 61.2 months)	~4 year follow up (median 43.7 months)
	Acalabrutinib + obinutuzumab	Acalabrutinib monotherapy	Obinutuzumab + Chlorambucil (GClb)	Venetoclax + Obinutuzumab	Obinutuzumab + Chlorambucil (GClb)	Zanubrutinib Vs BR	Zanubrutinib
Primary endpoint: PFS (%)	HR=**0.14**; 95% CI: 0.10-0.20 **78%**	**62%**	17% HR=**0.24**; 95% CI: 0.17-0.32	**53%**	22% HR=**0.40**; 95% CI: 0.31-0.52	**75.8%** 40.1% HR: **0.29** (95% CI 0.21 – 0.40)	**79%**
Reference	BTK Inhibitor for Adult Patients with CLL or SLL| CALQUENCE® (acalabrutinib) 100 mg tablets (calquencehcp.com)			VENCLEXTA® (venetoclax tablets) AML & CLL/SLL Treatment HCP Site (venclextahcp.com)		The BRUKINSA® Difference | BRUKINSA® (zanubrutinib)	

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Considering the number of patients with del(17p) in each study, does that impact your treatment decision in the 1L setting?

Patient History

70-year-old male

Patient has an active and independent lifestyle

History of hypertension, otherwise healthy

Prior treatment

Initial treatment:
Acalabrutinib

Myalgias increased

Experienced headaches

Neutropenia

How do you typically manage intolerance?

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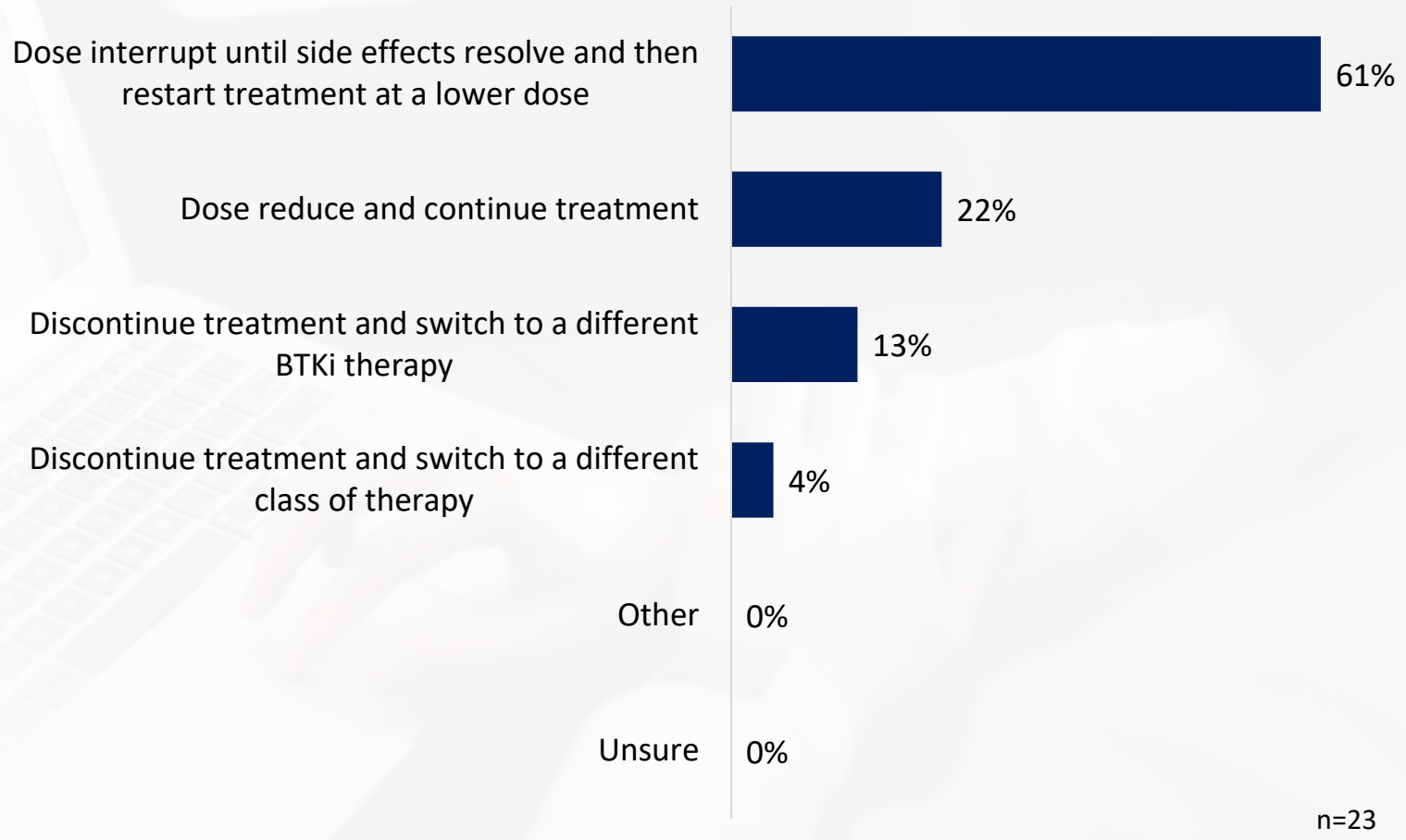
ARS Results from HCP Participants

How do you typically manage intolerance?



Patient History

70-year-old male

Patient has an active and independent lifestyle

History of hypertension, otherwise healthy

Prior treatment

Initial treatment:
Acalabrutinib

Myalgias increased

Experienced headaches

Neutropenia

Stopped treatment due to intolerance

What treatment do you recommend next?

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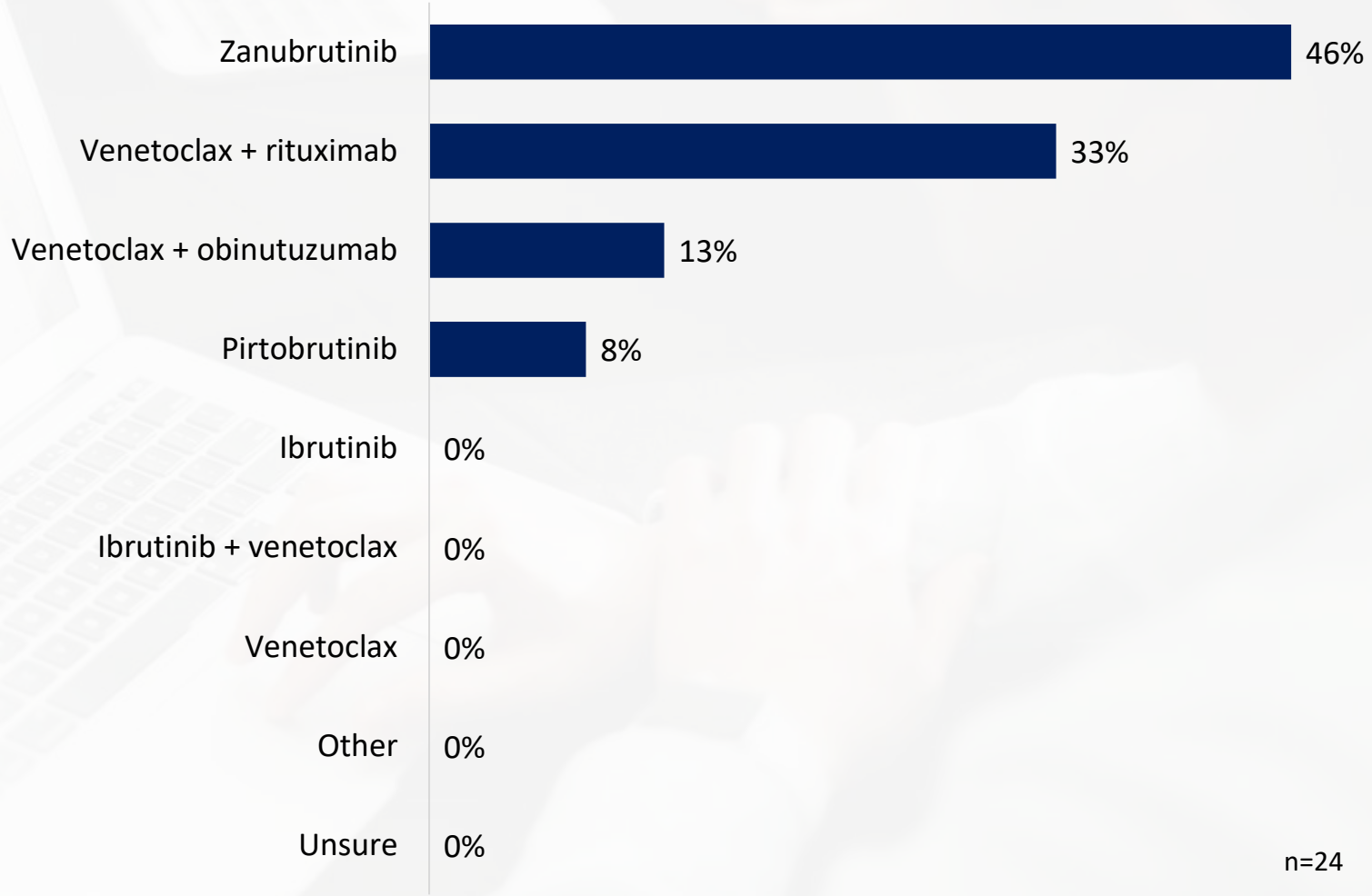
ARS Results from HCP Participants

What is your treatment strategy after first-line acalabrutinib therapy?



NCCN Guidelines 2L+ setting

NCCN Guidelines
CLL/SLL *without*
del(17p)/TP53 mutation

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CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

SECOND-LINE OR SUBSEQUENT THERAPY[e]	
Preferred Regimens	**Other Recommended Regimens**
• BCL2i-containing regimen ▸ Venetoclax[f,h] + obinutuzumab • cBTKi-based regimens ▸ Acalabrutinib[f,g,p] (category 1) ▸ Zanubrutinib[f,g,p] (category 1) • ncBTKi-based regimen:[f] ▸ Pirtobrutinib (resistance or intolerance to prior cBTKi-based regimens)	• BCL2i-containing regimens ▸ Venetoclax[f,h] + rituximab (category 1) ▸ Venetoclax[f,h,*] ▸ Venetoclax[f,h] + ibrutinib[f,g,q] (category 2B) • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)

[*] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.

NCCN Guidelines
CLL/SLL *with*
del(17p)/TP53 mutation

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SECOND-LINE OR SUBSEQUENT THERAPY[e]	
Preferred Regimens	**Other Recommended Regimens**
• BCL2i-containing regimen ▸ Venetoclax[f,h,*] ± obinutuzumab • cBTKi-based regimens ▸ Acalabrutinib[f,g,p] (category 1) ▸ Zanubrutinib[f,g,p] (category 1) • ncBTKi-based regimen: ▸ Pirtobrutinib (resistance or intolerance to prior cBTKi-based regimens)	• BCL2i-containing regimens ▸ Venetoclax[f,h] + rituximab (category 1) ▸ Venetoclax[f,h] + ibrutinib[f,g,q] (category 2B) • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)

[*] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.

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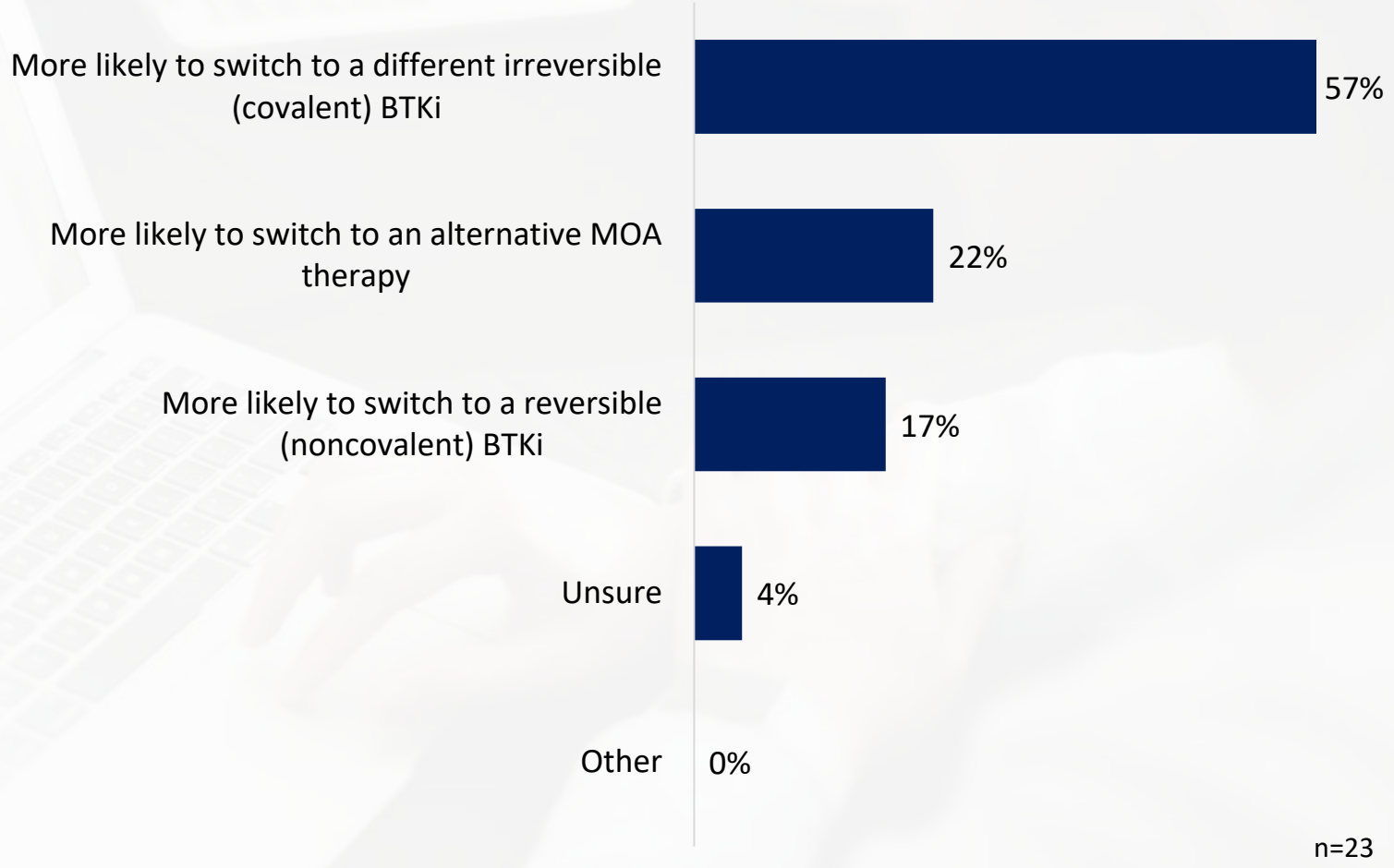
ARS Results from HCP Participants

How will the challenging case impact your prescribing behavior for a patient intolerant to a prior BTKi?



Patient History

70-year-old male

Patient has an active and independent lifestyle

History of hypertension, otherwise healthy

Prior treatment

Initial treatment:
Acalabrutinib

Stopped treatment due to intolerance

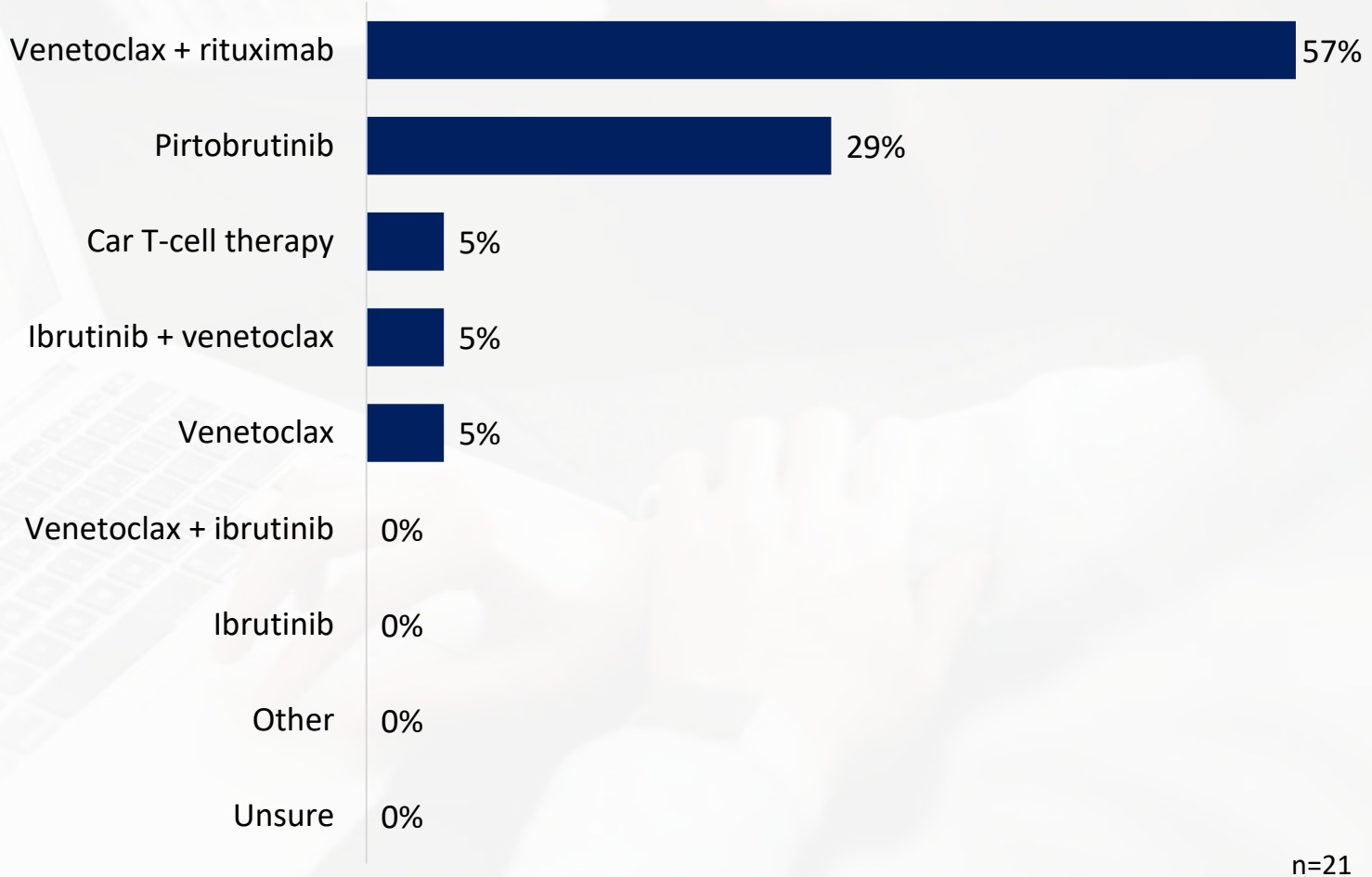
Second line treatment:

Zanubrutinib

What treatment do you recommend next?

ARS Results from HCP Participants

What is your treatment strategy after second-line zanubrutinib therapy?



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NCCN

NCCN Guidelines: Therapy for relapsed or refractory disease after prior BTKi- and Venetoclax-based regimens

NCCN Guidelines
CLL/SLL without del(17p)/TP53 mutation

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THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi-BASED AND BCL2i-CONTAINING REGIMENS[e]	
Preferred Regimens	**Other Recommended Regimens**
• Chimeric antigen receptor (CAR) T-cell therapy ▸ Lisocabtagene maraleucel (CD19-directed)[r] • ncBTKi-based regimen:[f] ▸ Pirtobrutinib (if not previously given)	• PI3Ki-based regimens[f] ▸ Duvelisib ▸ Idelalisib[s] ± rituximab • FCR[k,t] • Lenalidomide[u] ± rituximab • Obinutuzumab • Bendamustine[m] + rituximab[n] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) • HDMP + anti-CD20 mAb[l] (category 2B)

NCCN Guidelines
CLL/SLL with del(17p)/TP53 mutation

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THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi- BASED AND BCL2i-CONTAINING REGIMENS[e]	
Preferred Regimens	**Other Recommended Regimens**
• Chimeric antigen receptor (CAR) T-cell therapy ▸ Lisocabtagene maraleucel (CD19-directed)[r] • ncBTKi-based regimen:[f] ▸ Pirtobrutinib (if not previously given)	• PI3Ki-based regimens[f] (in alphabetical order by category) ▸ Duvelisib ▸ Idelalisib[s] ± rituximab • Alemtuzumab[v] ± rituximab • HDMP + anti-CD20 mAb[l] • Lenalidomide[u] ± rituximab

Discuss treatment options for patients after prior BTKi- and BCL-2 inhibitor

On December 1, 2023, the FDA granted accelerated approval to pirtobrutinib (Jaypirca, Eli Lilly and Company) for adults with CLL/SLL who have received *at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor*.

On March 14, 2024, the FDA granted accelerated approval to lisocabtagene maraleucel (liso-cel; Breyanzi) for the treatment of adult patients with R/R CLL/SLL who have previously received *at least 2 prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor*.

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Key Takeaways

CLL/SLL

- *Awareness of multiple category 1 NCCN Guideline treatments provides options for patients*
  - *Lack of head-to-head trials*
- *New FDA approvals and NCCN Guidelines will play a pivotal role in directing treatment pathways*
- *Mindfulness of clinical trial data can provide support for the best sequence of therapies and improve outcomes for patients*