Rewriting the Treatment Script in CLL

Guidance on Integrating Modern Targeted and Next-Gen Options Into Patient Care

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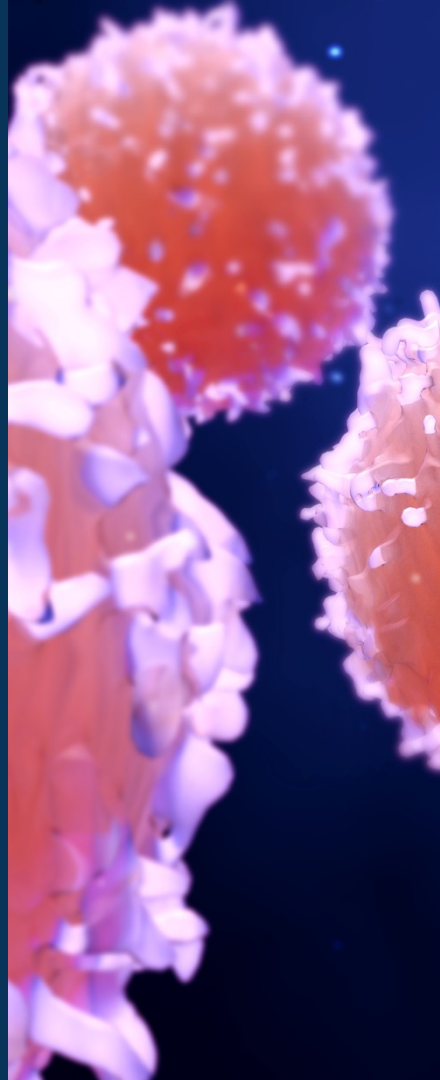

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Targeted Therapy: FDA Approvals and Current Status in CLL

Agent	Target	Status in CLL/SLL
Ibrutinib[1]	BTK	Approved
Acalabrutinib[2]		Approved
Zanubrutinib[3]		Phase 3 SEQUOIA
Pirtobrutinib		Phase 3 BRUIN CLL-321 (NCT04666038) Phase 3 BRUIN CLL-313 (NCT05023980)
Venetoclax[4]	BCL-2	Approved
Idelalisib[5]	PI3K	Approved
Duvelisib[6]		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. Brukinsa (zanubrutinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.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.

Despite These Advances, Real-World Data Suggest More Work Needs to Be Done

- **ASH 2021: real-world (N = 3,037) data showed a significant gap in prognostic testing[1]**
  - Over half did not receive risk factor testing
  - Suboptimal testing was more common in vulnerable populations
- **ASH 2021: updates from the informCLL registry (N = 1,462)[2]**
  - One-third of patients with del(17p)/*TP53* mutation did not receive NCCN-recommended regimens
  - A majority of patients in the registry lacked del(17p)/*TP53* mutation data and therefore may have received suboptimal treatment

1. Chanan-Khan A et al. 63rd American Society of Hematology Annual Meeting (ASH 2021). Abstract 4078. 2. Barrientos J et al. ASH 2021. Abstract 1976.

Tonight's MasterClass Agenda

1. How innovative targeted therapy became the "present" of CLL care and changed disease management
2. The "future" of CLL therapy—from novel combination therapy to sequential strategies
3. Case-based discussions linked to each MasterClass lecture

Thank You to Our Partners

CLL Society is an inclusive, patient-centric, physician-curated nonprofit organization that addresses the unmet needs of the chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) community through patient education, advocacy, support, and research.

CLL Society Is an Excellent Resource For Professionals, CLL Patients, and Caregivers

- Professionals and patients can utilize **CLLSociety.org** to receive up-to-date information on new CLL research findings and treatment options
- CLL Society provides many *free* resources for patients and their caregivers, including:
  - CLL patient and caregiver support groups (taking place virtually)
  - Patient-friendly basic and advanced information on CLL-related topics and hematology, as well as recent updates from blood cancer conferences
  - Patient-centric research
  - Patient and caregiver educational events and webinars
  - A COVID-19 Action Plan, updates on COVID-19, and CLL-specific guidelines
  - The Ask the Expert Support Inbox—patients and caregivers can email their CLL-related questions to a CLL physician, lab scientist, registered nurse, or palliative care physician
  - CLL Society's Expert Access™ Program—patients can apply to receive a free online second opinion from a CLL expert physician
  - Test Before Treat™ resources/handouts
  - Resources to help with the psychosocial, financial, and practical stressors associated with a CLL/SLL diagnosis

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SMART PATIENTS GET SMART CARE™

A New Script for Managing CLL: Choosing Customized Initial Therapy With Targeted Agents

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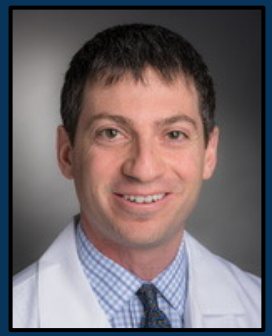

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BTK and BCL-2 Inhibitors Are the Preferred Upfront Treatment Options in TN CLL…[1]

Preferred regimens

Patients aged ≥65 y
OR
Patients aged <65 y with significant comorbidities (CrCl <70 mL/min)

- Acalabrutinib ± obinutuzumab (category 1)
- Ibrutinib (category 1)
- Venetoclax + obinutuzumab (category 1)
- Zanubrutinib

BR remains an "other recommended" regimen for older patients

Patients aged <65 y without significant comorbidities

- Acalabrutinib ± obinutuzumab (category 1)
- Ibrutinib (category 1)
- Venetoclax + obinutuzumab (category 1)
- Zanubrutinib

FCR is an "other recommended" regimen for younger patients

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

… Including in High-Risk Settings[1]

NCCN-Suggested Regimens for First-Line Therapy in CLL With Del(17p)/*TP53* Mutations

Preferred Regimens	Other Recommended Regimens
• Acalabrutinib ± obinutuzumab • Ibrutinib • Venetoclax + obinutuzumab • Zanubrutinib	• Alemtuzumab ± rituximab • HDMP + rituximab • Obinutuzumab

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Major Phase 3 Trials Support the Use of Targeted Agents in TN and R/R CLL[1-9]

Ibrutinib[1-4]

- ✓ **RESONATE-2:** superior PFS and OS vs Clb
- ✓ **iLLUMINATE:** superior PFS vs GClb
- ✓ **ECOG 1912:** superior PFS and OS vs FCR in younger patients
- ✓ **ALLIANCE:** superior PFS vs BR in older patients

Acalabrutinib[5-7]

- ✓ **ELEVATE-TN:** superior PFS for acalabrutinib regimens vs GClb
- ✓ **ASCEND:** improved PFS vs IdelaR or BR
- ✓ **ELEVATE-RR:** noninferior PFS vs ibrutinib and improved safety profile

Zanubrutinib[8]

- ✓ **SEQUOIA**: superior PFS vs BR
- ✓ **ALPINE:** improved safety profile vs ibrutinib

Venetoclax[9,10]

- ✓ **CLL14:** VenG superior to GClb
- ✓ **MURANO:** VenR superior to BR

1. Shanafelt TD et al. *N Engl J Med*. 2019;381:432-443. 2. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528. 3. Moreno C et al. *Lancet Oncol*. 2019;20:43-56.
4. Burger JA et al. *Leukemia*. 2020;34:787-798. 5. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 6. Ghia P et al. *J Clin Oncol*. 2020;38:2849-2861.
7. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452. 8. Tam C et al. ASH 2021. Abstract 396. 9. Al-Sawaf O et al. *Hematol Oncol*. 2021;39(suppl):201-203.
10. Harrup RA et al. ASH 2020. Abstract 3139.

Recent Updates to Major Trials of Continuous BTKi Therapy and Time-Limited Venetoclax

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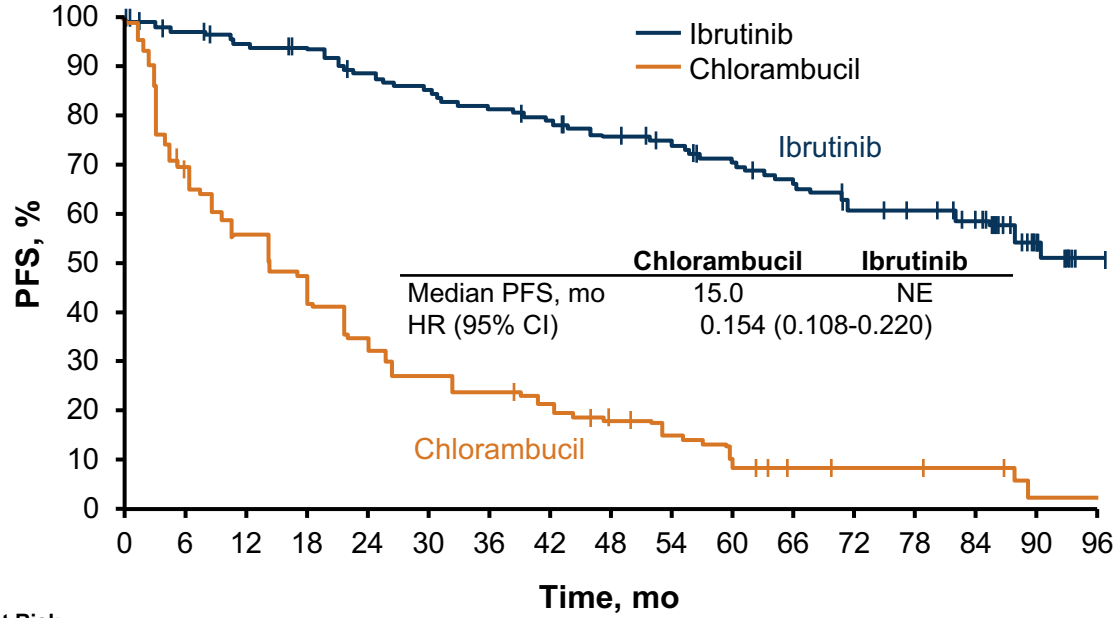
Up to 8-Year Follow-Up From RESONATE-2 Continues to Show Clinical Benefit of Ibrutinib Monotherapy in CLL[1]

- Longest follow-up to date with a single-agent BTK inhibitor from a phase 3 study[1]
- Sustained PFS benefit with ibrutinib vs chlorambucil
- PFS was 59% for ibrutinib vs 9% for chlorambucil at 7 years
- Benefit was similar for mutated and unmutated IGHV



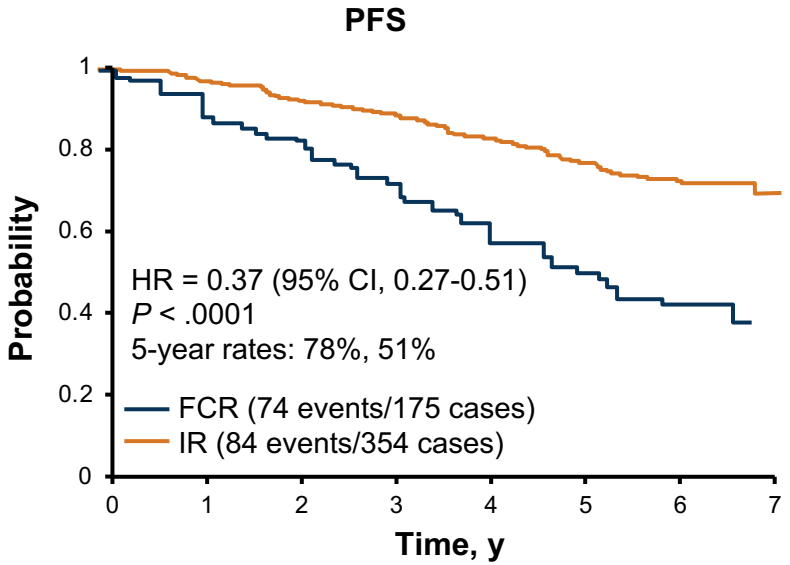
No. at Risk

Ibrutinib	136	129	124	121	112	108	104	99	92	88	81	76	67	65	57	17	1
Chlorambucil	133	88	69	57	41	33	30	25	19	16	12	6	5	5	4	1	0

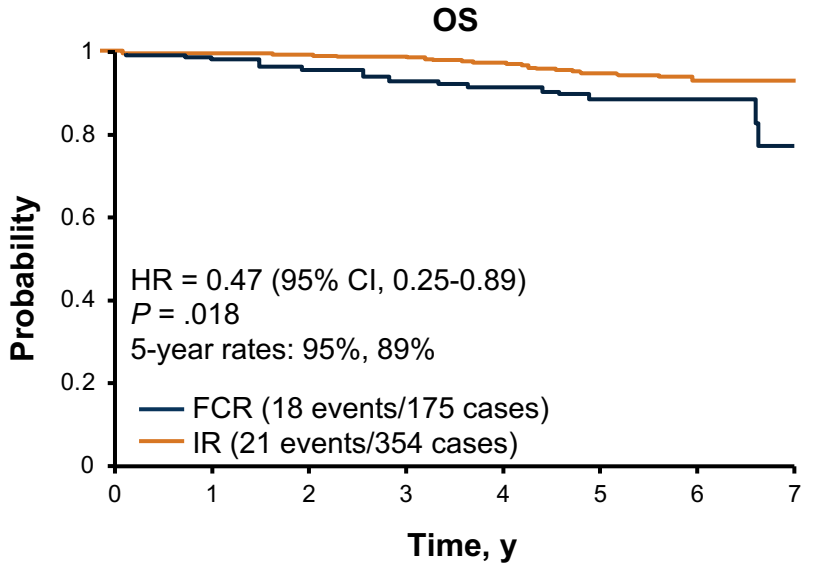
1. Barr PM et al. *Blood Adv.* 2022 Apr 4 [Epub ahead of print].

ECOG E1912 Update Continues to Show PFS and OS Benefits With IR vs FCR in Patients Aged <70 Years With CLL

Median Follow-Up of 5.8 years[1]



No. at Risk								
FCR	175	145	123	98	62	45	21	0
IR	354	339	321	306	248	193	110	7

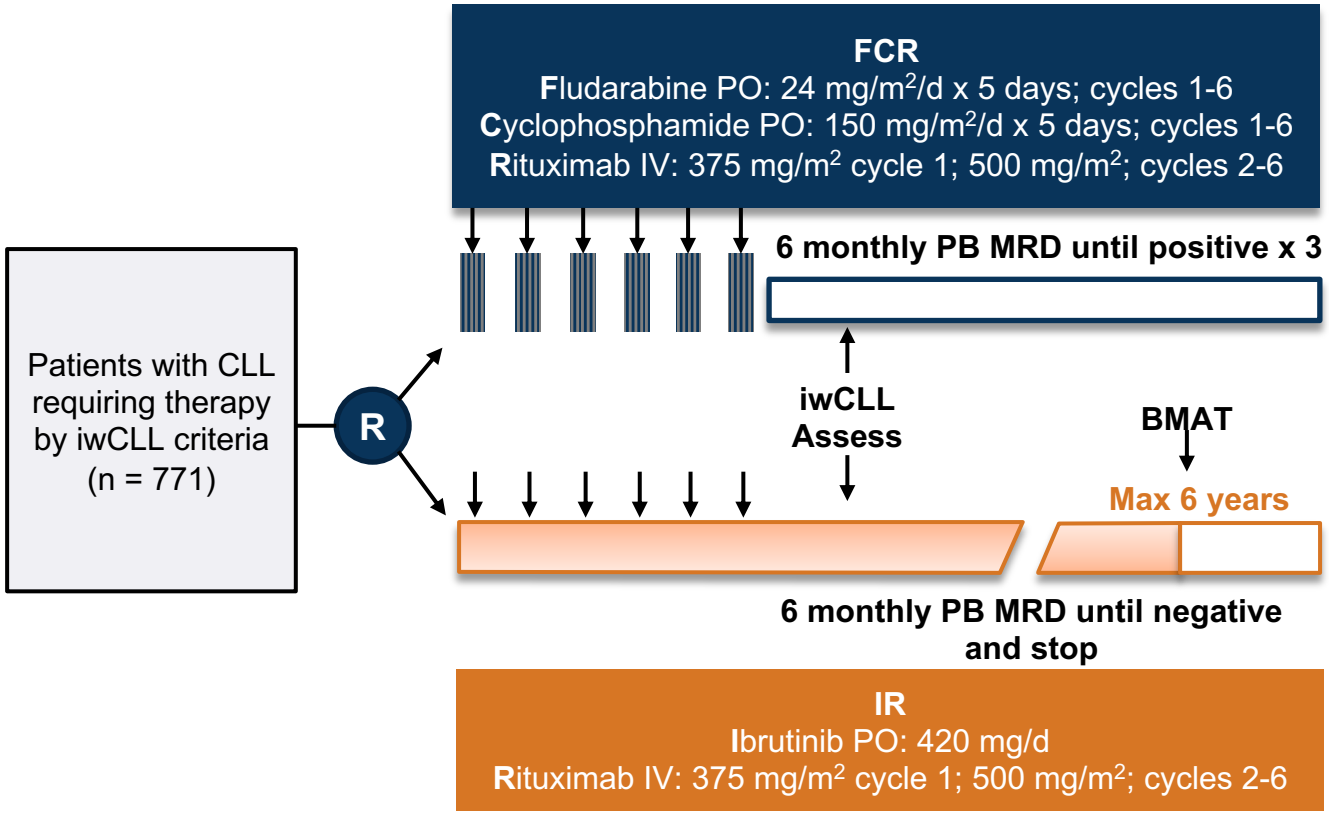


No. at Risk								
FCR	175	155	143	131	126	96	47	3
IR	354	347	343	338	329	300	139	20

Patients on the IR arm also had superior PFS in both *IGHV* unmutated (HR = 0.27, $P < .001$) and *IGHV* mutated subgroups

1. Shanafelt TD, et al. Blood 2022 Apr 15; Online ahead of print.

FLAIR: UK Study Testing IR vs FCR in Patients Aged ≤75 Years With CLL[1]



Primary endpoint

- To assess whether IR is superior to FCR in terms of PFS

Key secondary endpoints

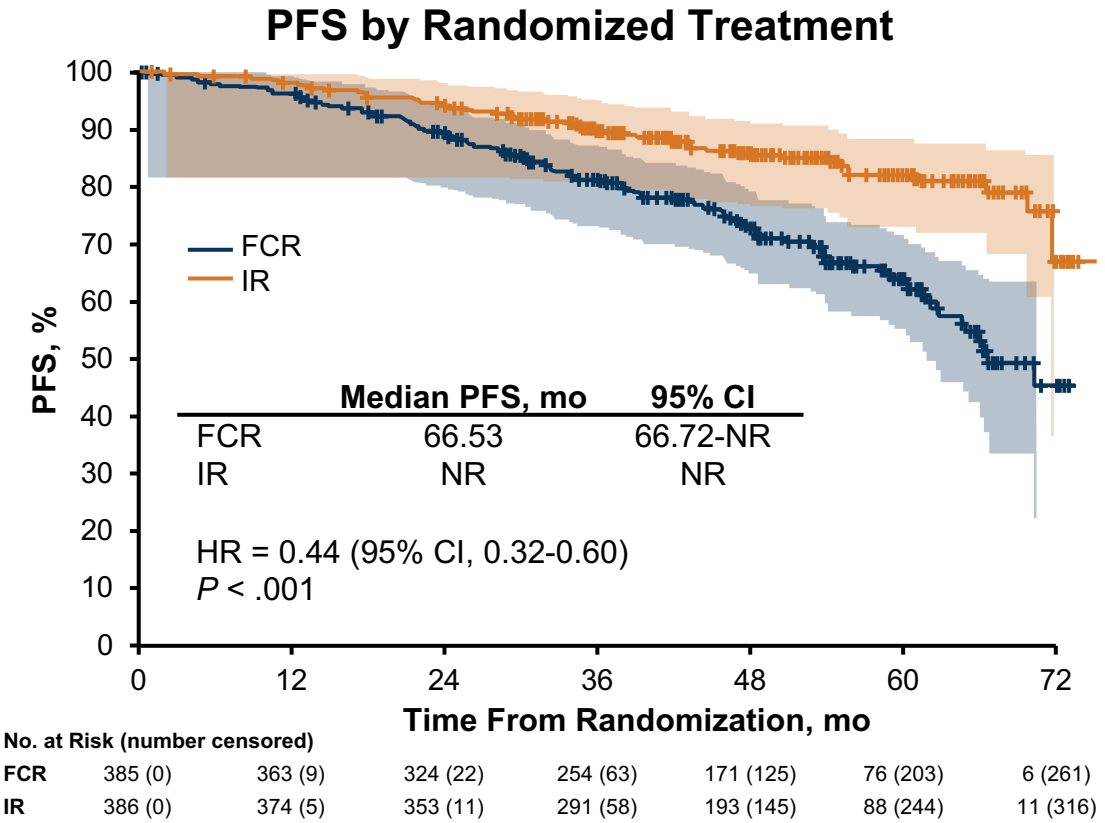
- OS
- Response, including MRD
- Safety and toxicity

1. Hillmen P et al. ASH 2021. Abstract 642.

FLAIR: Substantial PFS Improvement With IR vs FCR

Median follow-up, 52.7 mo[1]

- Median PFS not yet reached with IR vs 66.53 months with FCR (HR = 0.44; *P* < .001)
- PFS significantly better with IR in patients with IGHV-unmutated CLL but not for patients with IGHV-mutated CLL
- No differences in OS



1. Hillmen P et al. ASH 2021. Abstract 642.

ACE-CL-001: 53-Month Follow-Up Shows Benefits of Continuous Acalabrutinib Therapy in TN CLL[1]

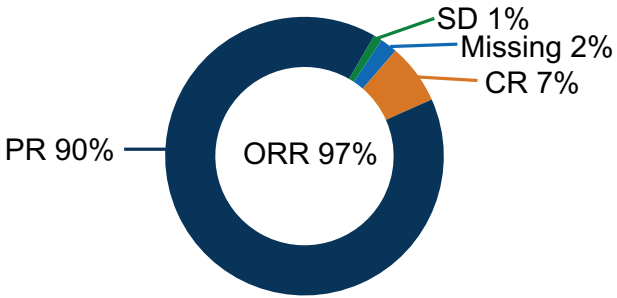
TN CLL/SLL (N = 99)

46% aged ≥65 years

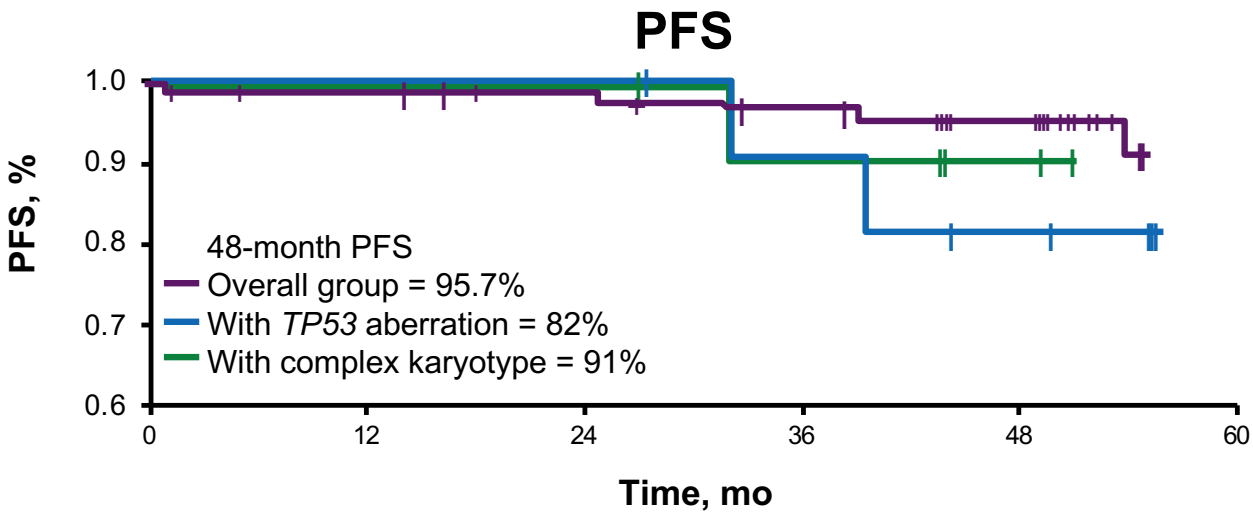
18% *TP53* aberration

18% complex karyotype

66% ECOG PS score = 1

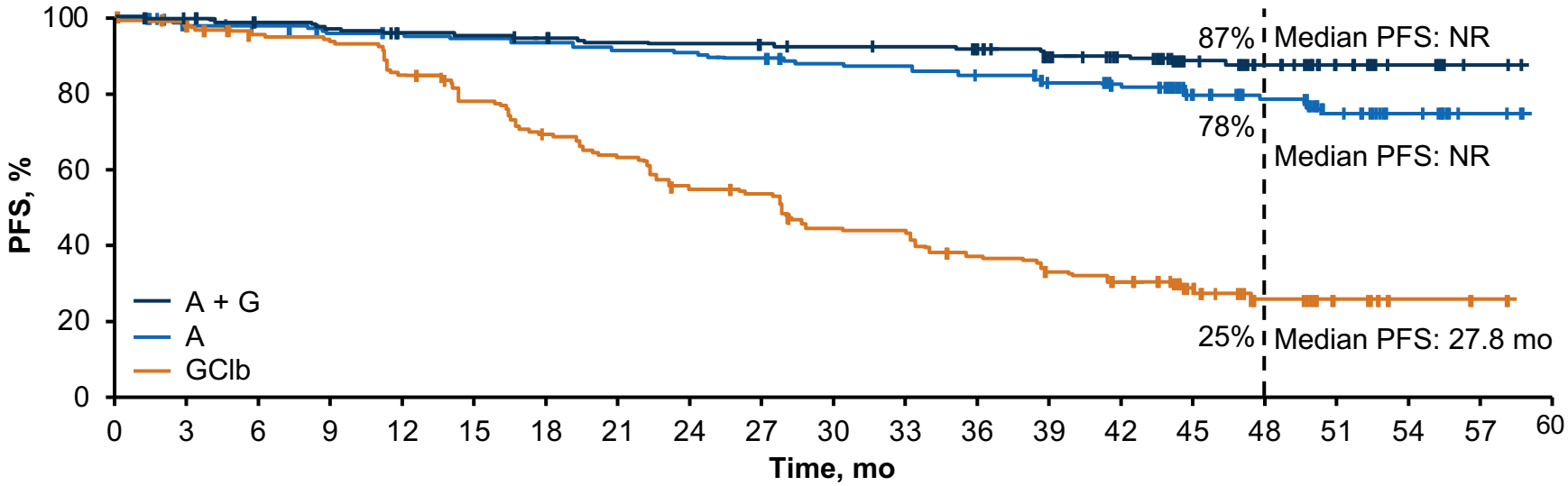


Median DOR not reached



1. Byrd JC et al. *Blood*. 2021;137:3327-3338.

Longer Follow-Up From ELEVATE-TN Confirms PFS Benefit With Acalabrutinib ± Obinutuzumab[1,2]



	HR (95% CI)	*P*
A + G vs GClb	0.10 (0.07-0.17)	<.0001
A vs GClb	0.19 (0.13-0.28)	<.000
A + G vs A	0.56 (0.32-0.95)	.0296

In the unmutated IGHV subgroup (original publication),[2] 24-mo PFS was 91% for A + G vs 33% for GClb

- **ASCO 2022: 5-year update to be presented (Abstract 7539)[3]**

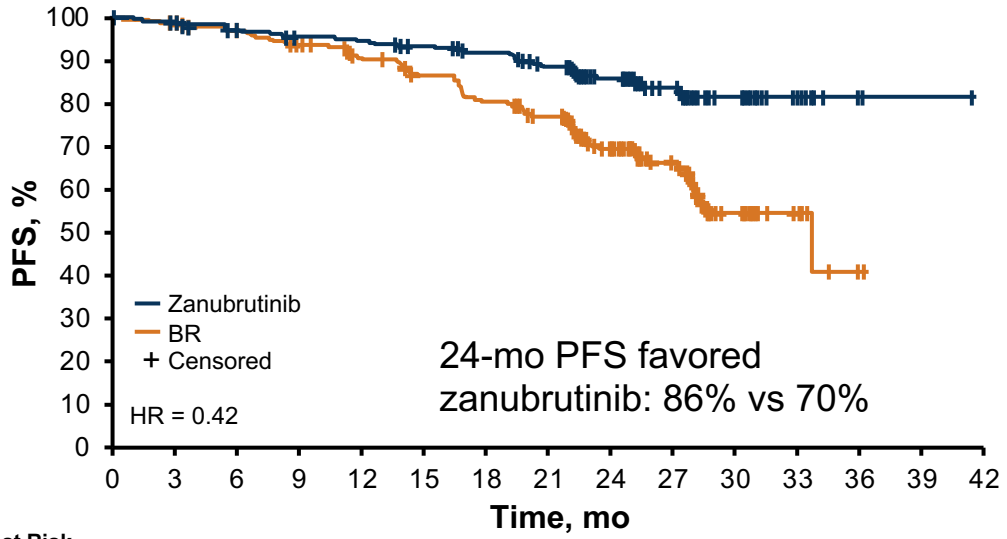
1. Sharman JP et al. ASCO 2021. Abstract 7509. 2. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 3. Sharman JP et al. ASCO 2022. Abstract 7539.

SEQUOIA: Zanubrutinib Prolongs PFS vs BR in TN CLL

Phase 3 Trial of 479 Patients With CLL Without Del(17p);
Subjects Randomized to Zanubrutinib (n = 241) and BR (n = 238)[1]

After median follow-up of 26.2 mo

- PFS significantly prolonged with zanubrutinib vs BR (HR = 0.42; *P* < .0001)
- Benefit with zanubrutinib was observed across subgroups for age, Binet stage, bulky disease, and del(11q)
- **Treatment benefit was also observed for patients with unmutated IGHV (HR = 0.24, 1-sided and 2-sided *P* < .0001),** but not for mutated IGHV



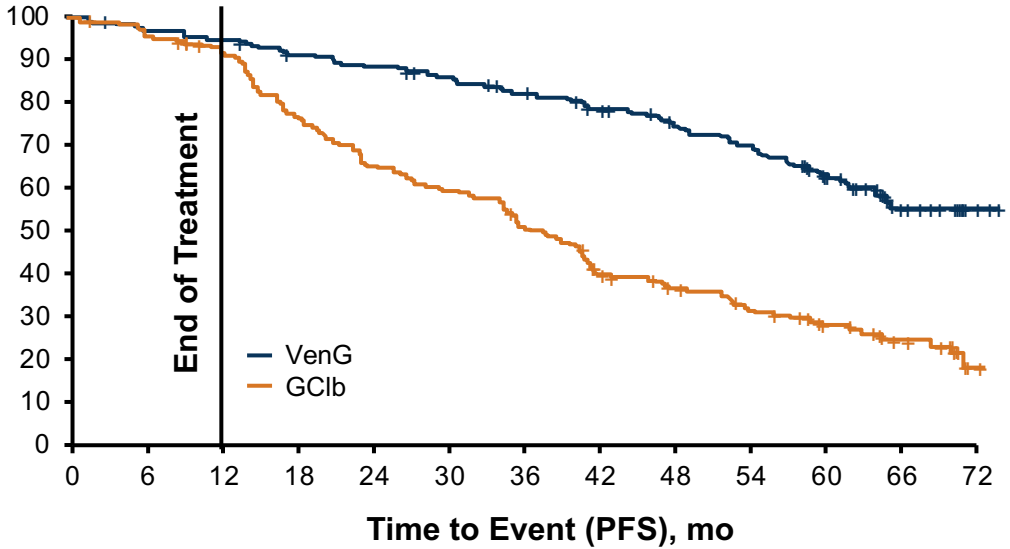
No. at Risk

Zanubrutinib	241	237	230	224	222	214	208	195	123	79	31	17	2	1	0
BR	238	218	210	200	187	176	164	150	89	54	20	8	1	0	–

1. Tam C et al. ASH 2021. Abstract 396.

CLL14: 5-Year Follow-Up Shows Efficacy of Frontline VenG vs GClb[1]

At 5 years after randomization estimated PFS was 62.6% after VenG and 27.0% after GClb[2]



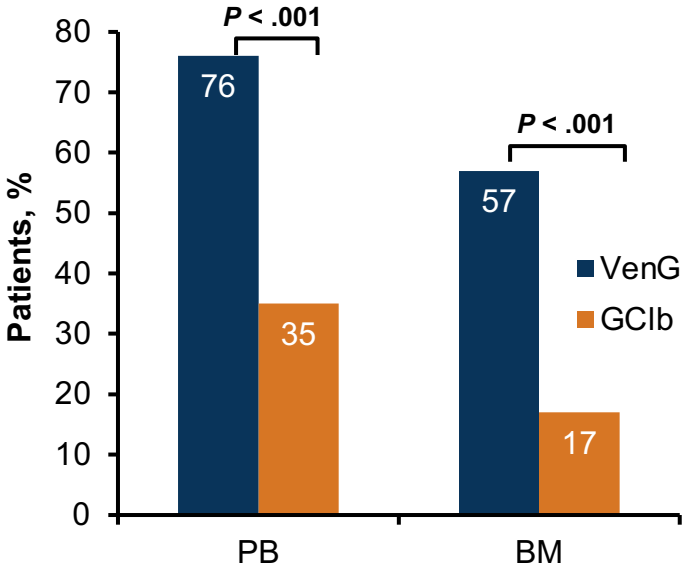
1. Al-Sawaf O et al. European Hematology Association 2022. Congress (EHA 2022). Abstract S148.

CLL14: VenG Achieved High uMRD and Improved PFS[1,2]

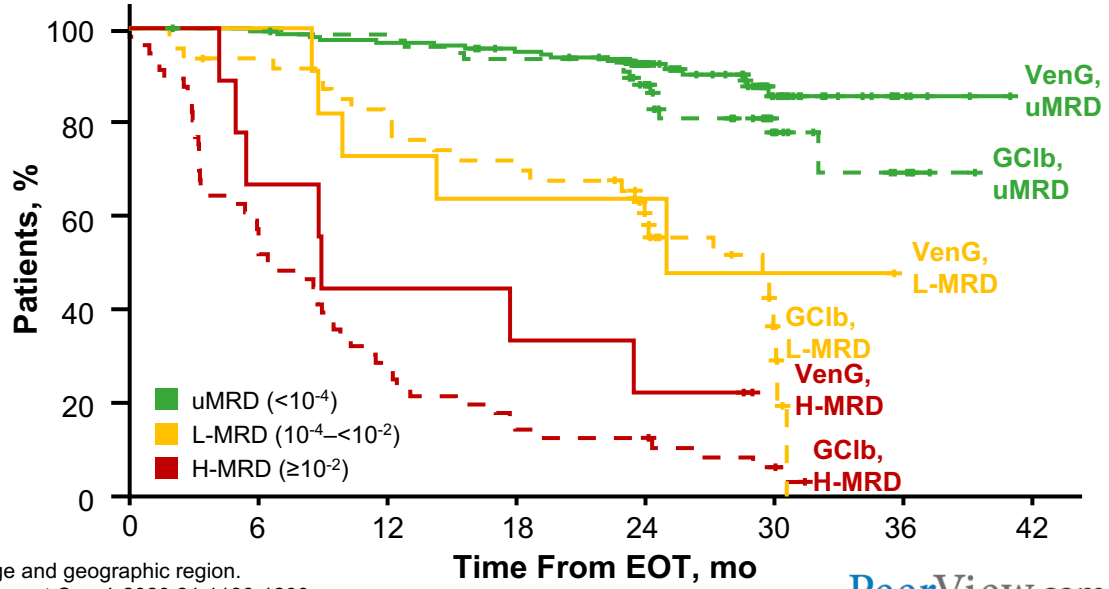
VenG vs GClb as Initial Tx in Patients With CLL and Comorbidities (N = 432)[a]
MRD assessment via clonoSEQ assay

In a landmark analysis from EOT, **uMRD patients had longer PFS vs L-MRD or H-MRD (HR = 0.10)**

uMRD ($<10^{-4}$) by ASO-PCR 3 mo After EOT[1]



PFS by PB MRD Status at EOT (Median Follow-Up: 39.6 mo; 2 y after EOT)[2]



[a] Comparison done by Cochran-Mantel-Haenszel tests stratified by Binet stage and geographic region.

1. Fischer K et al. *N Engl J Med*. 2019;380:2225-2236. 2. Al-Sawaf O et al. *Lancet Oncol*. 2020;21:1188-1200.

Targeted Therapy in Higher-Risk CLL

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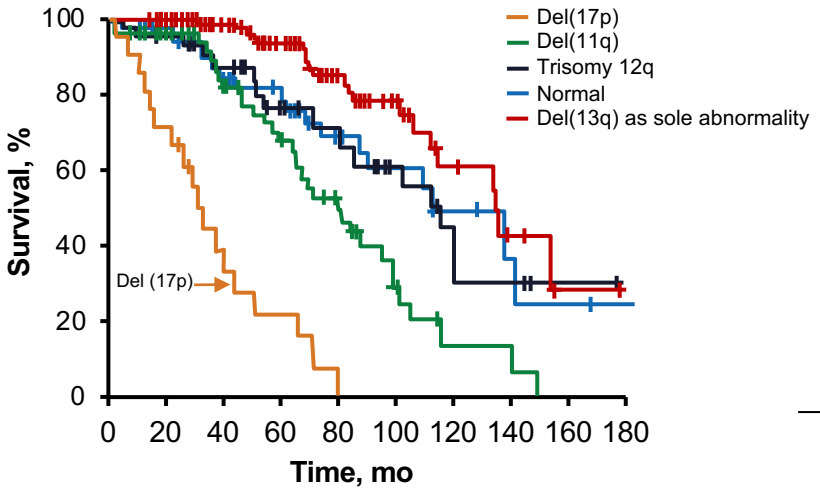
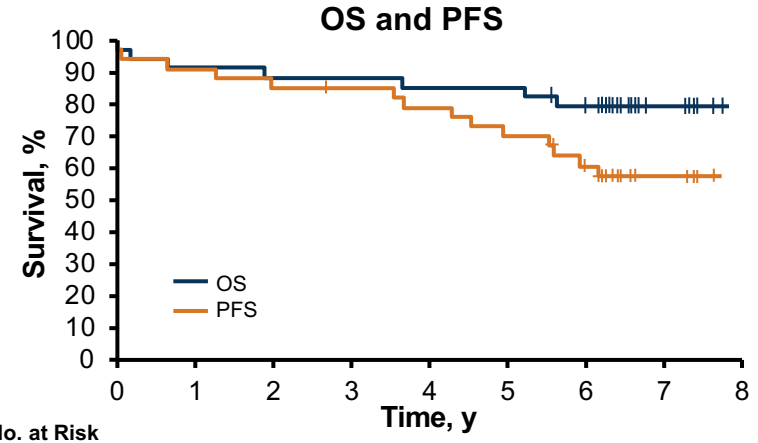
BTKi Therapy: A Major Step Forward Against *TP53* CLL

Döhner et al (2000)[1]



Ahn et al (2020)[2]



No. at Risk									
OS	34	31	30	30	29	29	26	7	0
PFS	34	31	29	28	26	23	19	6	0

Summary of Survival

% (95% CI)	2 y	3 y	4 y	5 y	6 y
OS	88 (78-100)	88 (78-100)	85 (74-98)	85 (74-98)	79 (67-94)
PFS	85 (74-98)	85 (74-98)	79 (67-94)	70 (56-88)	61 (46-80)

N = 34 patients with CLL with *TP53* alterations treated with ibrutinib as first-line therapy

1. Döhner H et al. *N Engl J Med*. 2000;343:1910-1916. 2. Ahn IE et al. *N Engl J Med*. 2020;383:498-500.

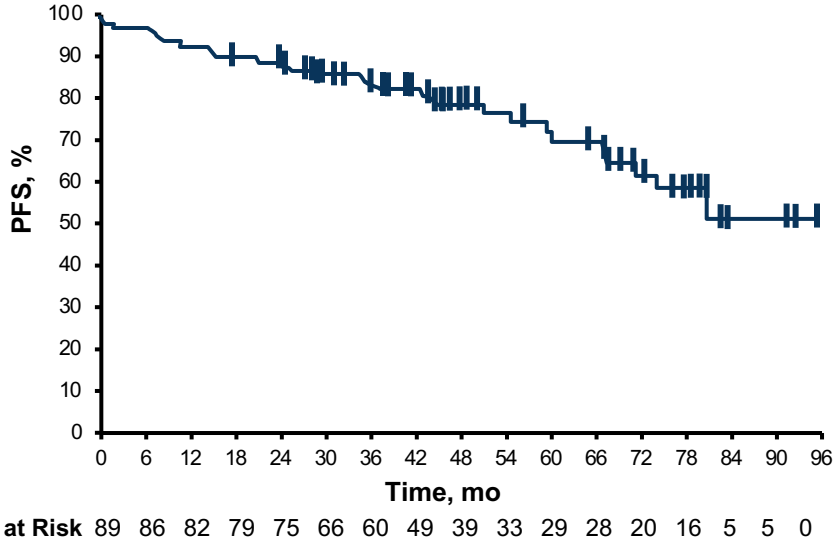
Pooled Analysis Shows the Benefit of Ibrutinib in Del(17p)/*TP53*-Mutated CLL[1]

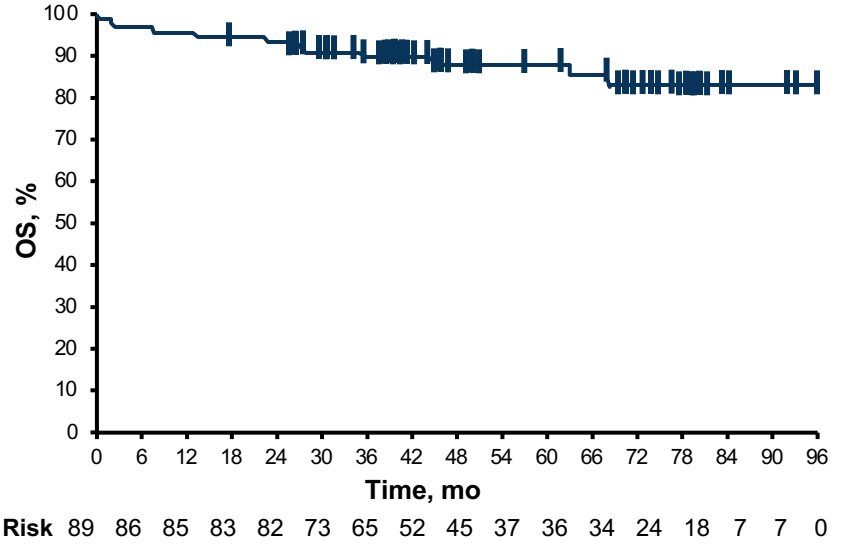
Patients receiving

- Single-agent ibrutinib in PCYC-1122 or RESONATE-2; ibrutinib-CD20 combination therapy: iLLUMINATE or E1912
- All 89 patients had del(17p) and/or *TP53* mutation

Median follow-up of 49.8 months

- Median PFS not reached
- PFS and OS estimates at 4 years were 79% and 88%, respectively





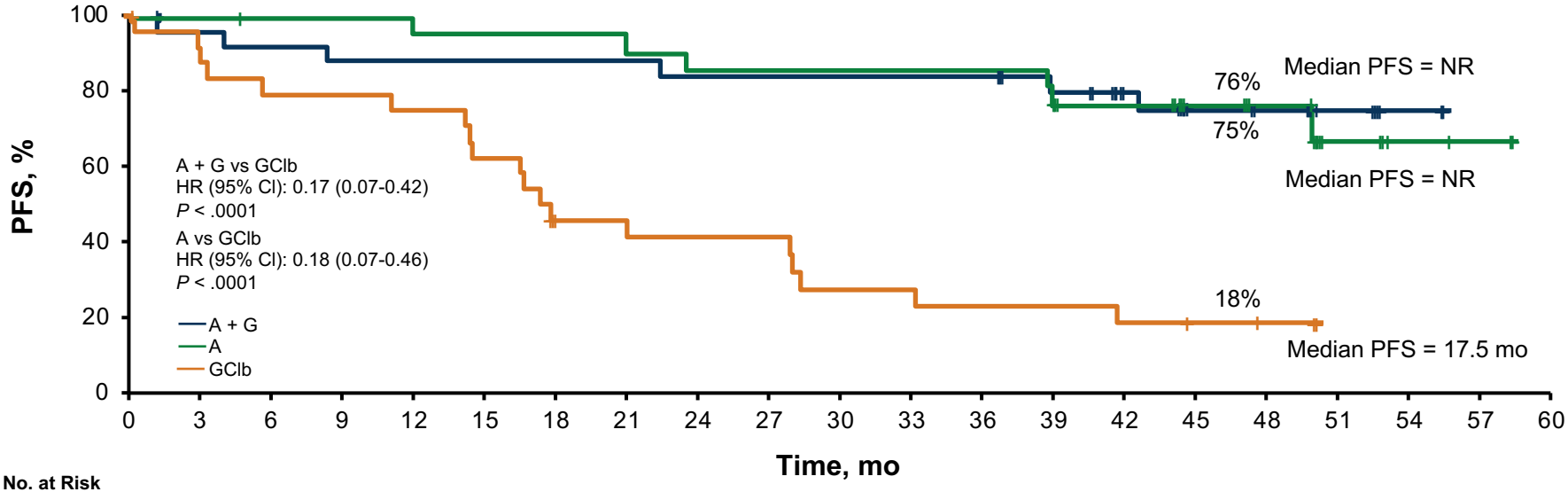
1. Allan JN et al. *Br J Haematol*. 2022;196:947-953.

ELEVATE-TN: Longer Follow-Up Shows Sustained PFS Benefit in Del(17p)/*TP53*-Mutated CLL[1]

- ≥65 years
- 18-65 years and comorbidities

ELEVATE-TN: Acalabrutinib vs Acalabrutinib + G vs GClb[1]

Median follow-up: 4 years



No. at Risk

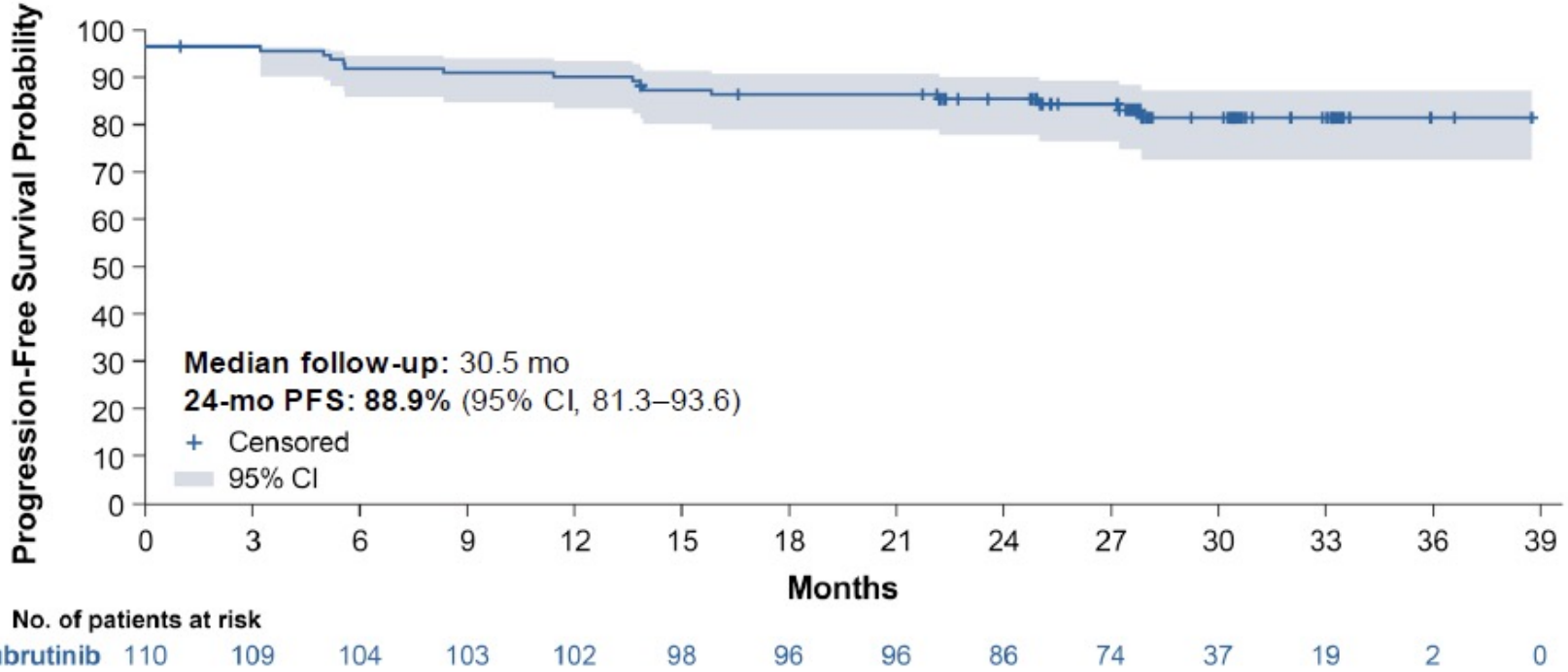
A + G	25	24	23	22	22	22	22	22	21	21	21	21	21	19	16	9	8	3	1	0	0
A	23	22	21	21	20	20	20	19	18	18	18	18	18	15	15	11	9	5	2	1	0
GClb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	3	2	0			0

1. Sharman JP et al. ASCO 2021. Abstract 7509.

EHA 2022: Davids M, et al. Pooled analysis for acalabrutinib regimens in *TP53* CLL

SEQUOIA Cohort 2: Zanubrutinib Monotherapy Is Effective Against High-Risk CLL[1]

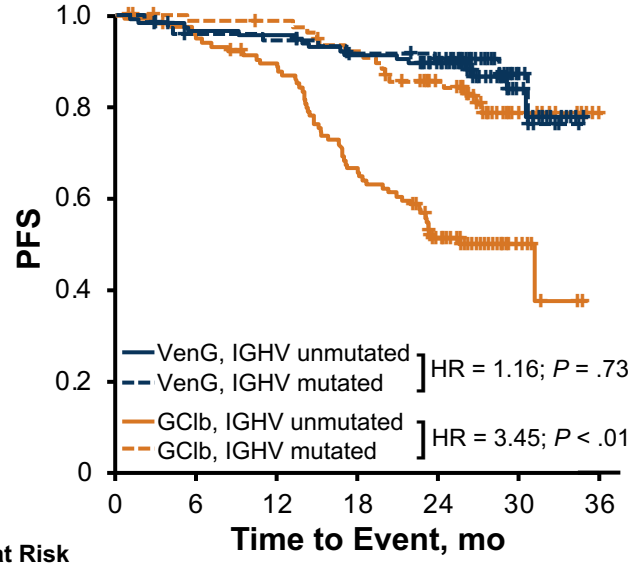
Cohort 2: PFS Per IRC Assessment in Patients With Del(17p)



1. Tam C et al. ASH 2021. Abstract 396.

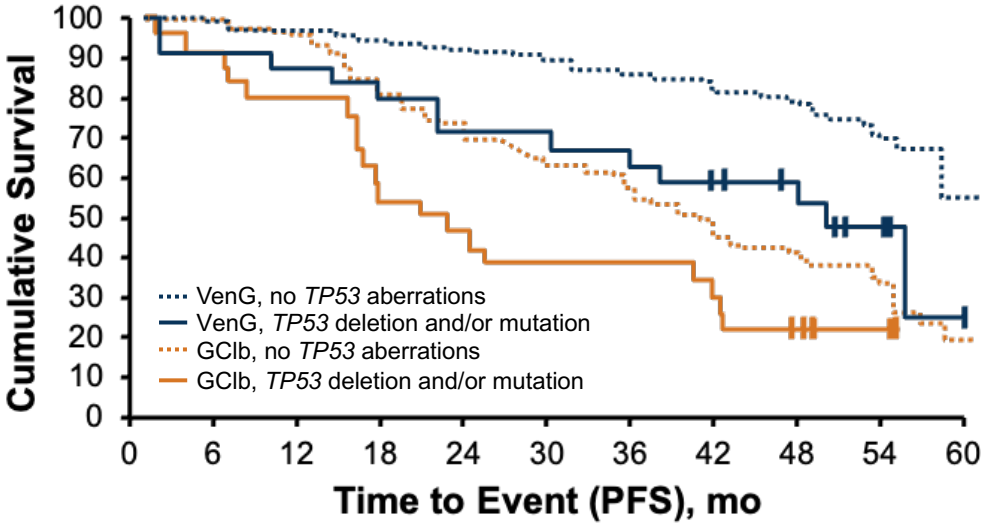
CLL14: Prognostic Implications of Higher-Risk Disease

Influence of IGHV[1]



No. at Risk

5-Year PFS Update by Del(17p)/*TP53*[2]



1. Tausch E et al. *Blood*. 2020;135:2402-2412. 2. Al-Sawaf O et al. EHA 2022. Abstract S148 (online abstract).

Principles of Safety Management With Targeted Agents

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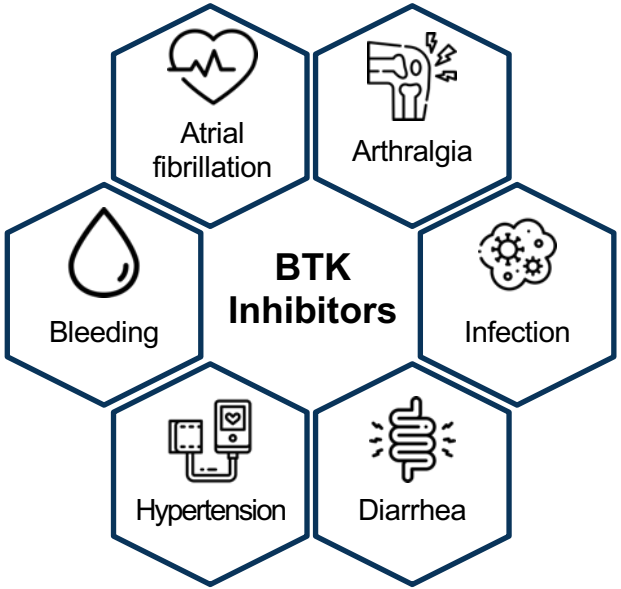
The Safety Experience to Date

What to Expect With BTK Inhibitors and Venetoclax in CLL[1,2]

Common Toxicities With BTKi



Additional important AEs: dermatologic changes, fatigue, cytopenias, and ventricular arrhythmia

AEs to Watch With Venetoclax

- TLS
- GI events
- Infections
- Myelosuppression

1. Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program.* 2020;1:336-345. 2. Seymour JF et al. *N Engl J Med*. 2018;378:1107-1120.

Summary of BTKi Safety Monitoring Approaches[1]

- Don’t give concomitantly with warfarin; for new onset a-fib, consider non-warfarin anticoagulation + monitoring
- Hypertension: manage with antihypertensives
- Monitor for and manage cardiac arrhythmia/a-fib; treat appropriately
- Monitor patients for signs of bleeding

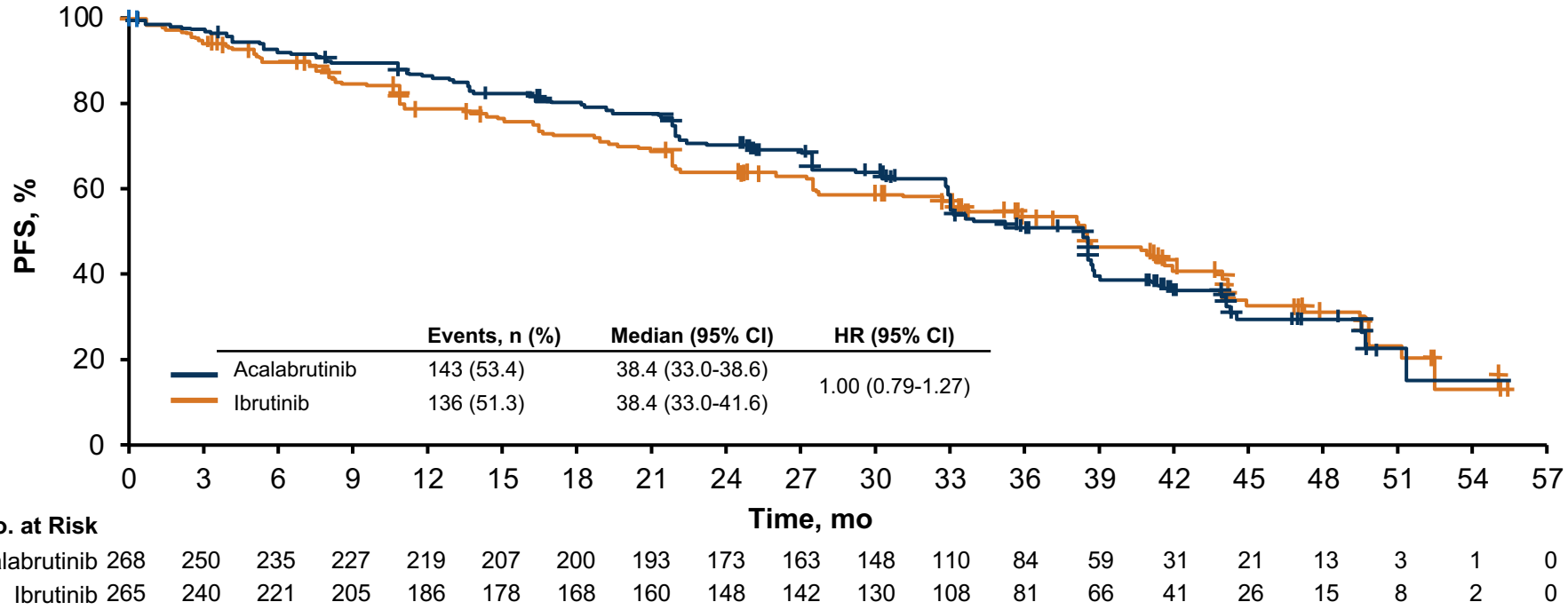
- Headaches commonly occur early in therapy with acalabrutinib and typically resolved in 1-2 months
  - Manage with acetaminophen + caffeine
- Monitor for neutropenia (particularly with zanubrutinib)
- Monitor for infections and secondary malignancies

Tools provided by the CLL Society can help patients understand the spectrum of BTKi toxicity (cllsociety.org/patient-education-toolkit/)

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Head-to-Head Trials: In ELEVATE-RR, the Primary Endpoint of PFS Noninferiority Was Met

PFS With Acalabrutinib Was Noninferior to Ibrutinib in the R/R CLL Setting[1]



1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

ELEVATE-R/R: Lower Incidence of Any Grade A-fib/Flutter, Hypertension, Bleeding With Acalabrutinib vs Ibrutinib[1]

Events, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
A-fib[a]	**25 (9.4)**	13 (4.9)	**42 (16.0)**	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	**25 (9.4)**	11 (4.1)	**61 (23.2)**	24 (9.1)
Bleeding events	**101 (38.0)**	10 (3.8)	**135 (51.3)**	12 (4.6)
Major bleeding events[a]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)

A-fib/flutter leading to treatment discontinuation: 0 in acalabrutinib arm, 7 (16.7) in ibrutinib arm

[a] Includes A-fib/flutter. [b] Includes hypertension, blood pressure increased, and blood pressure systolic increased.

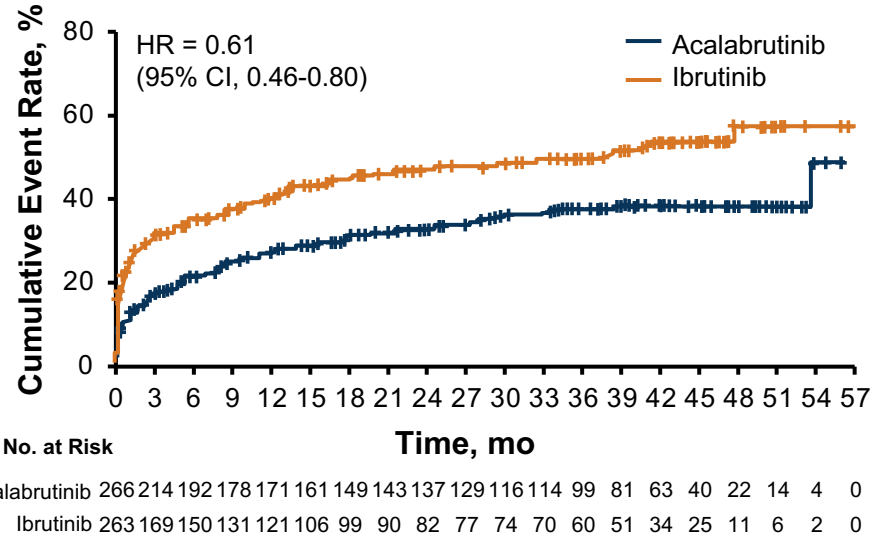
1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

ELEVATE-R/R: Lower Cumulative Incidence of Several Common BTKi Toxicities With Acalabrutinib[1]

Lower cumulative incidences of

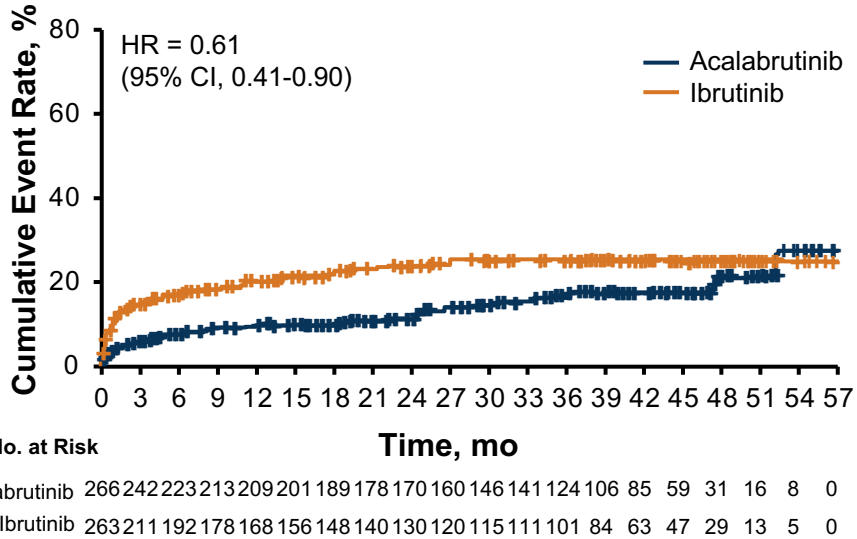
- A-fib/flutter (HR = 0.52)
- Hypertension (HR = 0.34)
- Bleeding (HR = 0.63)
- Diarrhea (HR = 0.61)
- Arthralgia (HR = 0.61)

Diarrhea



No. at Risk																			
Acalabrutinib	266	214	192	178	171	161	149	143	137	129	116	114	99	81	63	40	22	14	4	0
Ibrutinib	263	169	150	131	121	106	99	90	82	77	74	70	60	51	34	25	11	6	2	0

Arthralgia

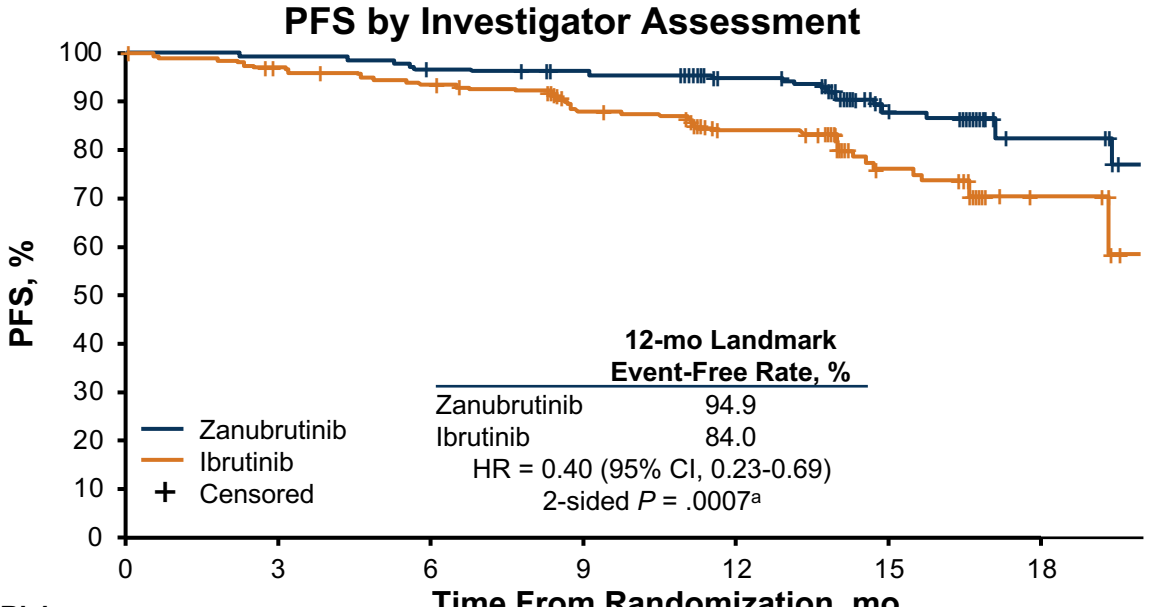


No. at Risk																			
Acalabrutinib	266	242	223	213	209	201	189	178	170	160	146	141	124	106	85	59	31	16	8	0
Ibrutinib	263	211	192	178	168	156	148	140	130	120	115	111	101	84	63	47	29	13	5	0

1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

Head-to-Head Trials: In ALPINE, Improved ORR and PFS With Zanubrutinib vs Ibrutinib in R/R CLL/SLL[1]

- ORR improved with zanubrutinib: 78.3 vs 62.5 for ibrutinib
- Superiority 2-sided *P* = .0006 compared with prespecified alpha of .0099

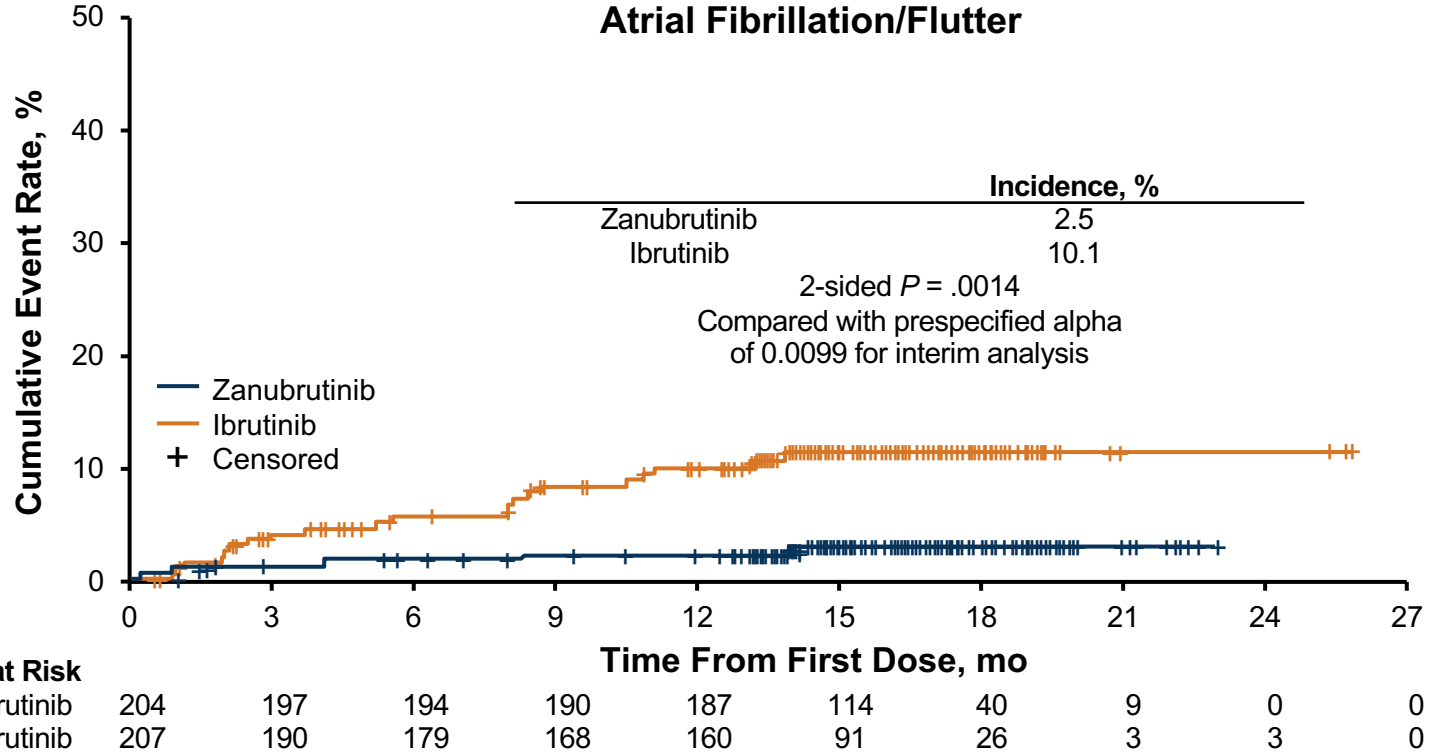


Median PFS follow-up was 14 months for both zanubrutinib and ibrutinib arms

[a] Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events is reached.

1. Hillmen P et al. EHA 2021. Abstract LB1900.

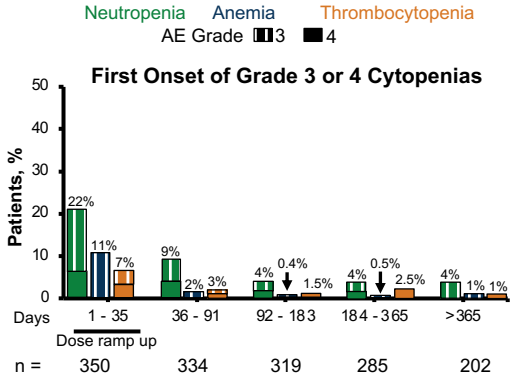
ALPINE: Safety Analysis Showed Lower Rates of A-fib/Flutter With Zanubrutinib[1]

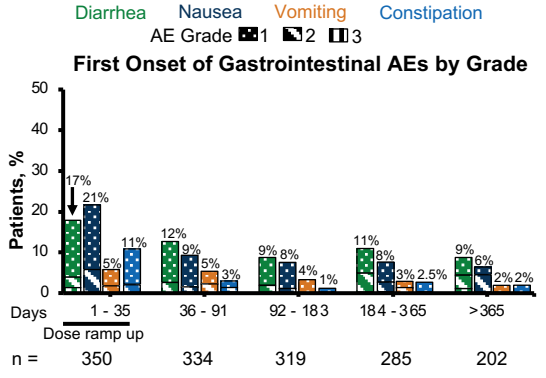


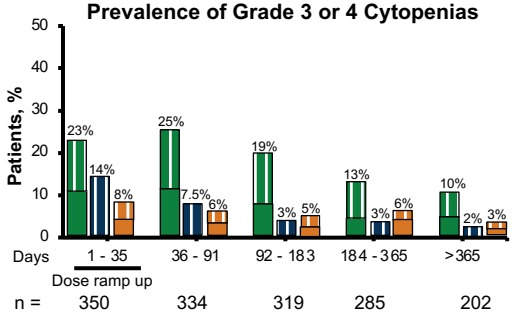
Overall AEs leading to treatment discontinuation: 16 in zanubrutinib group (8%) vs 27 for ibrutinib (13%)

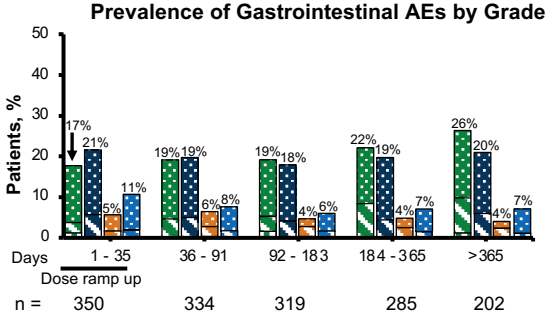
1. Hillmen P et al. EHA 2021. Abstract LB1900.

Safety Analysis Shows Prevalence of Venetoclax Toxicities Decreases Over Time[1]









2/166 (1.4%) of patients treated with current dosing algorithm had biochemical laboratory changes in TLS parameters, but none had clinical TLS

1. Davids MS et al. *Clin Cancer Res.* 2018;24:4371-4379.

Venetoclax: AE Monitoring and Management[1-3]

- **Myelosuppression:** manage with dose interruption/reduction
  - For grade ≥3 neutropenia, consider G-CSF and/or antibiotics
- **Monitor for signs and symptoms of infection** and treat promptly
  - Grade 3/4 infection: withhold until resolution and resume at same or reduced dose
- **GI events**
  - Diarrhea: rule out infectious causes; treat with antidiarrheals and PO hydration
  - Nausea: adjust dose timing and use antiemetics
- **Do not administer live attenuated vaccines prior to, during, or after treatment until B-cell recovery**

1. Stilgenbauer S et al. *Lancet Oncol.* 2016;17:768-778. 2. Seymour JF et al. *N Engl J Med*. 2018;378:1107-1120.
3. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf.

Venetoclax: AE Monitoring and Management[1-3]

Assess TLS risk in all patients preparing for venetoclax therapy; perform a pretreatment CT scan to assess burden of internal lymphadenopathy

Premedicate with antihyperuricemics; ensure adequate hydration

As overall TLS risk increases, employ more intensive measures

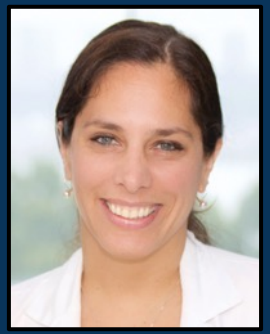
1. IV hydration
2. Frequent monitoring
3. Hospitalization

Tools provided by the CLL Society can help patients understand the safety considerations associated with venetoclax (cllsociety.org/patient-education-toolkit/)

1. Stilgenbauer S et al. *Lancet Oncol.* 2016;17:768-778. 2. Seymour JF et al. *N Engl J Med.* 2018;378:1107-1120.
3. Venclexta (venetoclax) Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208573s009lbl.pdf.

Case Forum: Customizing Treatment With Upfront Options

Nicole Lamanna, MD
Associate Professor of Medicine
Director of the Chronic Lymphocytic Leukemia Program
Hematologic Malignancies Section
Herbert Irving Comprehensive Cancer Center
New York-Presbyterian/Columbia University Medical Center
New York, New York



PeerView
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Susan, an Older Patient With Symptomatic TN CLL

- **74 years old**
- **Symptomatic CLL (iwCLL criteria) after an extensive watch and wait period**
- **Comorbid diabetes and well-controlled HTN**

Initial assessment

- CBC: WBC 245 x 10^9/L; Ly 238 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Abdominal adenopathy, max 4 cm
- Splenomegaly, 19 cm
- ECOG PS 0-1; CrCl 53 mL/min
- Unmutated IGHV

What are the options for this patient, now that she has symptomatic CLL?

- Continuous BTKi therapy?
- Time-limited venG?
- Any role for CIT?

Susan, an Older Patient With Symptomatic TN CLL

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- Abdominal adenopathy, max 4 cm
- Splenomegaly, 19 cm
- ECOG PS 0-1; CrCl 53 mL/min
- Unmutated IGHV

Recommendations

- Multiple options could be considered for Susan
- Both BTKi and venetoclax are effective in this setting
- Discuss pros and cons of continuous vs fixed duration therapy with patients

Supporting Evidence Across Pivotal First-Line Studies Supports Novel Agents Over CIT in Older/Unfit CLL

Study	Population	Design	PFS Benefit for Experimental Arm?
ALLIANCE[1]	Fit, older, del(17p) allowed	3 arms: BR vs IR vs I	**Yes**
iLLUMINATE[2]	Unfit (CIRS >6 or CrCl <70) or *TP53* del/mut	GClb vs G + ibrutinib	**Yes**
ELEVATE-TN[3]	Unfit (CIRS >6 or CrCl <70)	GClb vs acalabrutinib vs G + acalabrutinib	**Yes**
SEQUOIA[4]	Older, no del(17p)	BR vs zanubrutinib	**Yes**
CLL14[5]	Unfit (CIRS >6 or CrCl <70)	GClb vs venG	**Yes**

Continuous therapy / fixed duration

1.. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528. 2. Moreno C et al. *Lancet Oncol*. 2019;20:43-56.
3. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 4. Tam C et al. ASH 2021. Abstract 396. 5. Fischer K et al. *N Engl J Med*. 2019;380:2225-2236.

What if Susan Had Presented With Higher-Risk CLL?

- **74 years old**
- **Symptomatic CLL (iwCLL criteria) after an extensive watch and wait period**
- **Comorbid diabetes and well-controlled HTN**

Initial assessment

- CBC: WBC 245 x 10^9/L; Ly 238 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Abdominal adenopathy, max 4 cm
- Splenomegaly, 19 cm
- ECOG PS 0-1; CrCl 53 mL/min
- Unmutated IGHV
- ***TP53* mutation on NGS**

Do the options change based on the presence of a TP53 mutation?

- Continuous BTKi therapy?
- Time-limited venG?
- Any role for CIT?

What if Susan Had Presented With Higher-Risk CLL?

- **74 years old**
- **Symptomatic CLL (iwCLL criteria) after an extensive watch and wait period**
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- Abdominal adenopathy, max 4 cm
- Splenomegaly, 19 cm
- ECOG PS 0-1; CrCl 53 mL/min
- Unmutated IGHV
- ***TP53* mutation on NGS**

Recommendations

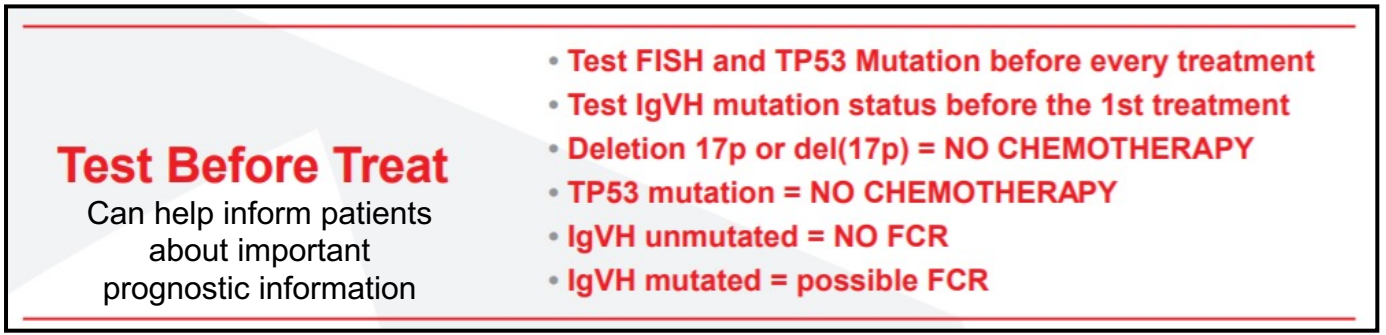
- Although BTKi therapy and time-limited venG are effective in higher-risk CLL, continuous BTKi treatment currently appears to have more robust efficacy in del(17p)/*TP53* CLL
- No role for CIT

Counsel Patients on Prognostic Factors and Implications for Treatment Decisions

Poor prognostic factors are well-documented in CLL

	Adverse Prognostic Factor When
***TP53* (17p)**	**Mutated and/or deleted**
IGHV status	Unmutated
Beta-2 microglobulin	>3.5
Clinical stage	Binet B/C or Rai I-IV
Age	>65 years

CLL Society Toolkit: Test Before Treat™ Campaign



Does Favorable-Risk Disease Make a Difference?

- **74 years old**
- **Symptomatic CLL (iwCLL criteria) after an extensive watch and wait period**
- **Comorbid diabetes and well-controlled HTN**

Initial assessment

- CBC: WBC 245 x 10^9/L; Ly 238 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Abdominal adenopathy, max 4 cm
- Splenomegaly, 19 cm
- ECOG PS 0-1; CrCl 53 mL/min
- **Mutated IGHV**

Recommendations

- Continuous BTKi therapy?
- Time-limited venG?
- Any role for CIT?

Does Favorable-Risk Disease Make a Difference?

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Initial assessment

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- Abdominal adenopathy, max 4 cm
- Splenomegaly, 19 cm
- ECOG PS 0-1; CrCl 53 mL/min
- **Mutated IGHV**

Recommendations

- Time-limited venG is a potent option that could result in a deep remission, particularly in this favorable prognostic setting (supported by CLL14)
- Continuous BTKi therapy is also an option

Explain the Modern Goals of Therapy to Patients With CLL

- Modern therapy is very effective but can achieve different goals
- Be prepared to review goals of care with patients and empower their decision-making

Continuous Therapy	Goal of Therapy
• BTK inhibitors	• Disease control • Prolonged PFS • Independent from response, MRD

Fixed Duration	Goal of Therapy
• Venetoclax + obinutuzumab	• Disease eradication • Prolonged PFS • Undetectable MRD

Does Age Make a Difference?

- **58 years old**
- **Symptomatic CLL (iwCLL criteria) after an extensive watch and wait period**
- **Comorbid diabetes and well-controlled HTN**

Initial assessment

- CBC: WBC 245 x 10^9/L; Ly 238 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Abdominal adenopathy, max 4 cm
- Splenomegaly, 19 cm
- ECOG PS 0-1; CrCl 53 mL/min
- **Mutated IGHV**

Recommendations

- Continuous BTKi therapy? BTKi + CD20?
- Time-limited venG?
- Any role for CIT?

Does Age Make a Difference?

- **58 years old**
- **Symptomatic CLL (iwCLL criteria) after an extensive watch and wait period**
- **Comorbid diabetes and well-controlled HTN**

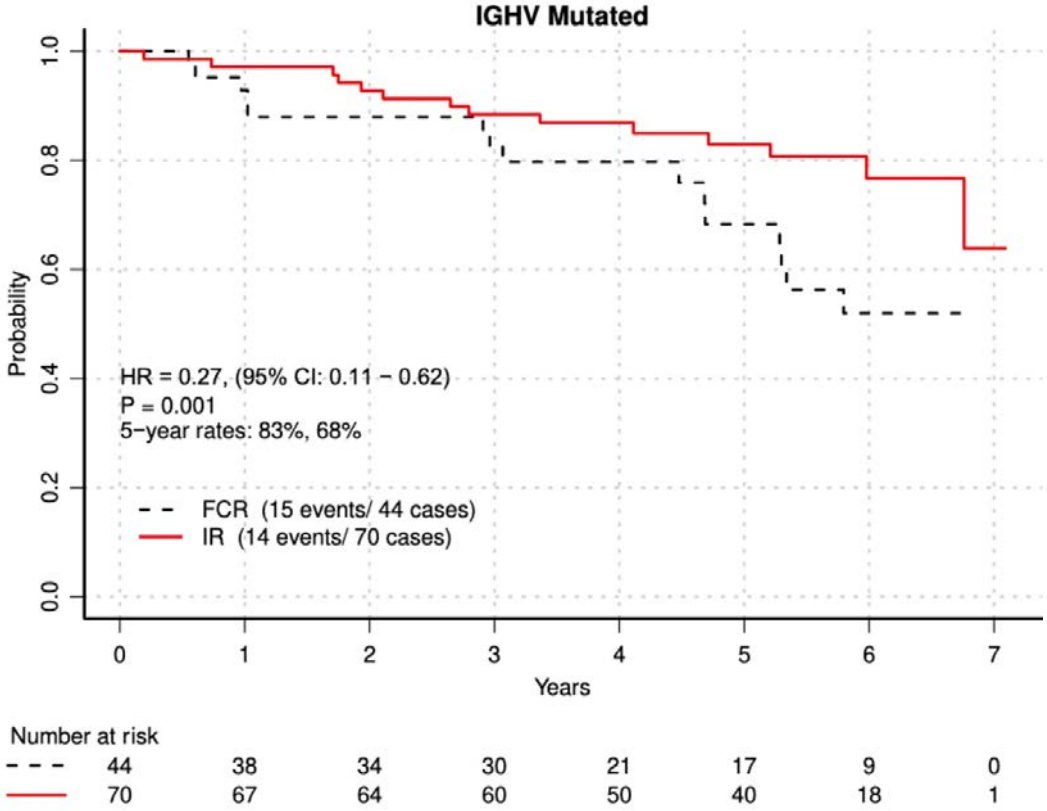
Initial assessment

- CBC: WBC 245 x 10^9/L; Ly 238 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Abdominal adenopathy, max 4 cm
- Splenomegaly, 19 cm
- ECOG PS 0-1; CrCl 53 mL/min
- **Mutated IGHV**

Recommendations

- E1912 supports the use of ibrutinib regimens
- Time-limited venG, extrapolating from CLL14, is another potent option to consider
- Any role for CIT?

E1912: Is This the End for CIT in Favorable-Risk CLL?



1. Barr PM et al. Blood Adv. 2022 Apr 4 [Epub ahead of print].

Patient Voices: How CLL Society Resources Can Help Inform and Educate on Treatment Choices

"I was diagnosed with CLL in June of 2014 … I was prescribed FCR …In hindsight, this was a mistake. The chemotherapy was brutally difficult, and my cancer did not respond well.

I switched oncologists, underwent extensive genetic testing, and discovered my CLL was 17p deleted, had complex karyotype, and was unmutated. If I had known this information beforehand, I would not have undergone FCR therapy.

Luckily, I was quickly enrolled in a clinical trial and on acalabrutinib monotherapy for almost four years [subsequently] I was switched to another monotherapy, ibrutinib. I have responded very well to both …."

Tammi Garrett
Ontario, Canada
CLL Patient since 2014

"The CLL Society is an invaluable resource to help you navigate throughout your journey by helping you stay informed and asking the right questions …

Test Before Treat™ is not just a saying–it can literally save your life!"

Writing the Future Script Now in CLL: Next-Gen Strategies, Novel Combinations, and Cellular Therapy

Catherine C. Coombs, MD
Assistant Professor of Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

PeerView
Live

Novel Combinations with Targeted Agents as "The Future" of CLL

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Live

How Can We Do Better in CLL?
Novel First-Line Combination Strategies

Chemoimmunotherapy Based[1-3]

- iFCG (MDACC)
- I + G followed by iFCG (ICLL-07 FILO)
- iFCR (DFCI)

Chemotherapy-Free Regimens[4-7]

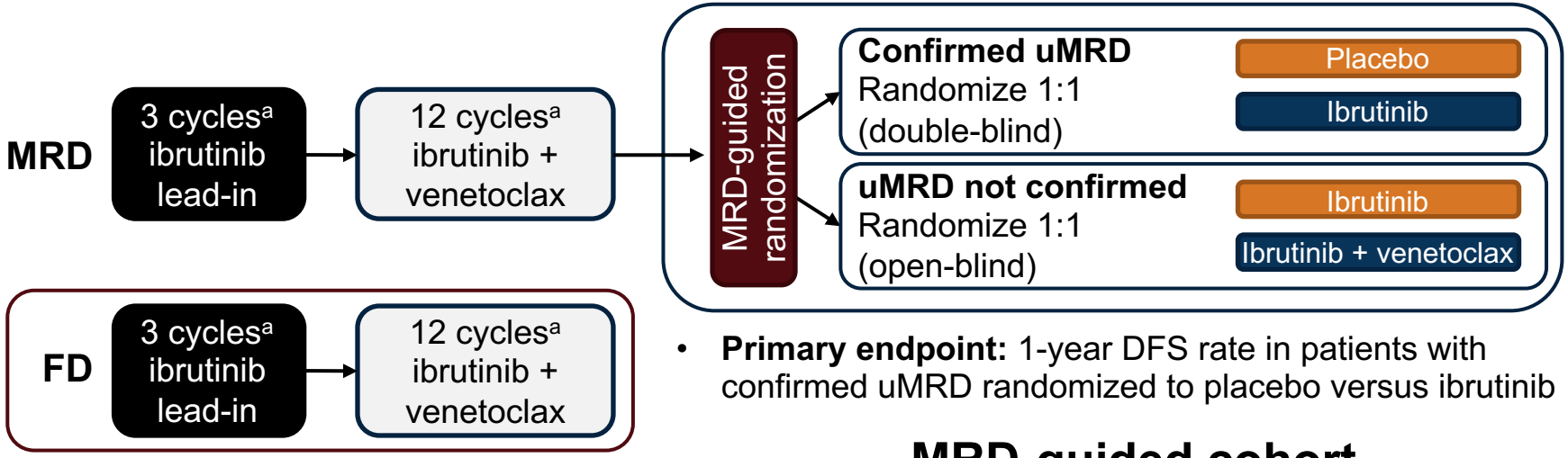
- I + venetoclax (MDACC, CAPTIVATE)
- IVO (OSU)
- Acala + VenG (DFCI)
- Zanu + VenG (BoVEN)
- Zanu + Ven (SEQUOIA)

1. Jain N et al. *Leukemia*. 2021 May 18. 2. Michallet AS et al. *Blood*. 2021;137:1019-1023. 3. Davids M et al. *Lancet Haematol*. 2019;6:e419-e428.
4. Siddiqi T et al. EHA 2020. Abstract S158. 5. Jain N et al. ASH 2020. Abstract 3138. 5. Rogers KA et al. *J Clin Oncol*. 2020;38:3626-3637.
6. Davids M et al. ASH 2020. Abstract 2216. 7. Soumerai JD et al. ASH 2020. Abstract 1307.

Clinical Rationale for BTKi + BCL-2 Combinations

- Preclinical synergy
- Differential “compartment effect”—venetoclax more effectively clears marrow
- Nonoverlapping toxicity profile
- Reduced likelihood of resistance during combination therapy
- Potential for highly-effective time-limited therapy

Phase 2 CAPTIVATE Study Assessed Ibrutinib + Venetoclax in Two Cohorts[1-3]



- **Primary endpoint:** CR/CRi rate in patients without del(17p)

Fixed-duration IV cohort

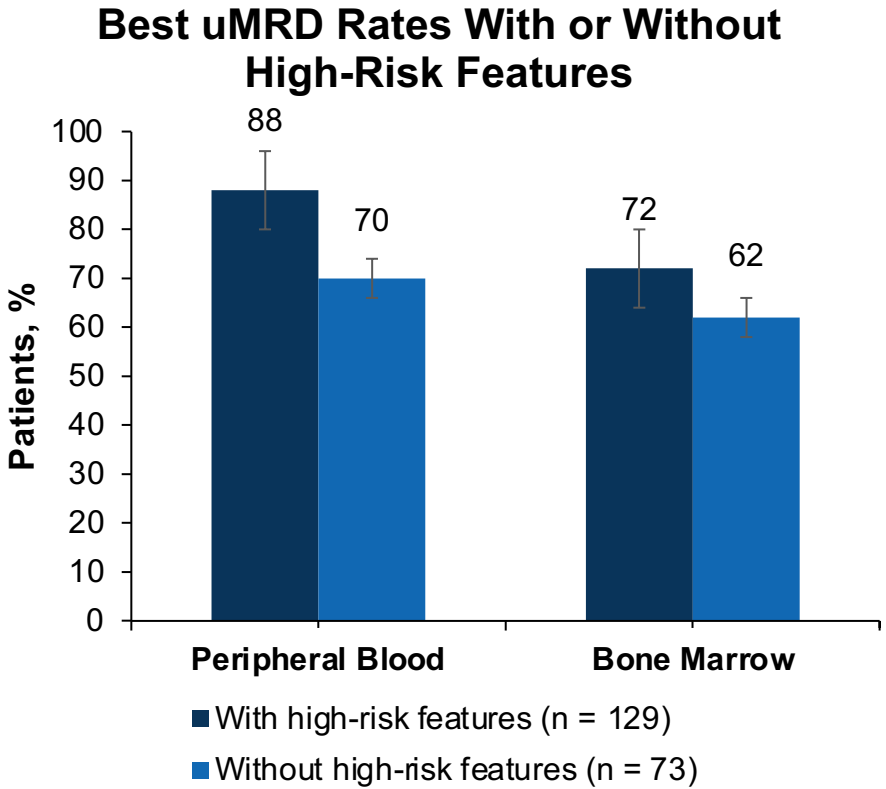
- **Primary endpoint:** 1-year DFS rate in patients with confirmed uMRD randomized to placebo versus ibrutinib

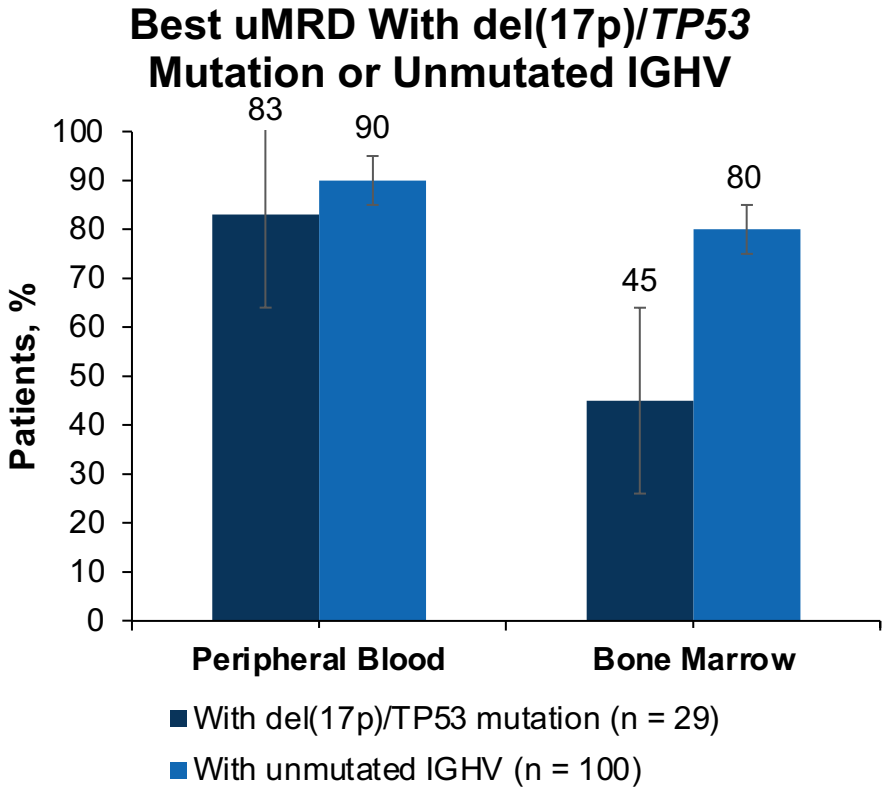
MRD-guided cohort

[a] One cycle = 28 days.

1. Wierda W et al. ASH 2020. Abstract 123. 2. Ghia P et al. ASCO 2021. Abstract 7501. 3. Ghia P et al. ASH 2021. Abstract 68.

CAPTIVATE: FD Therapy Induces High uMRD Rates in Patients With and Without High-Risk Features[1]

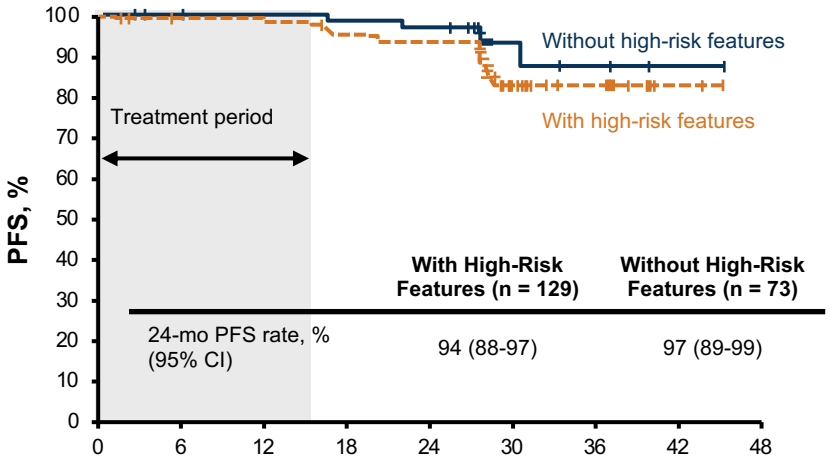




1. Allan JN et al. American Association for Cancer Research Annual Meeting 2022 (AACR 2022). Abstract CT028.

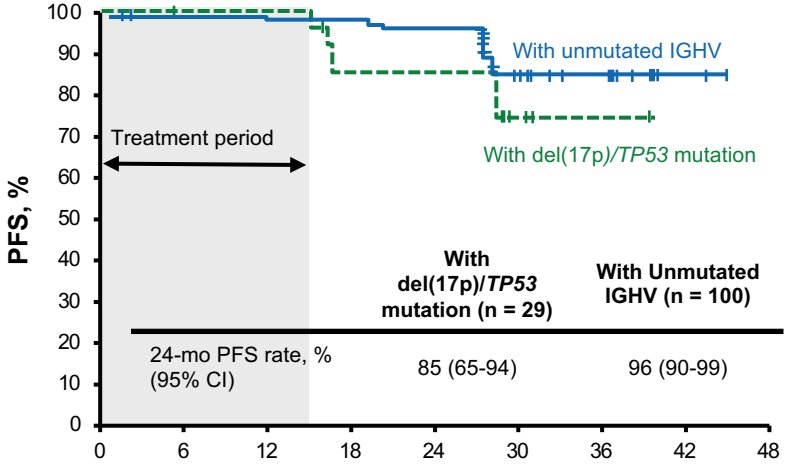
CAPTIVATE: Similarly, High PFS Rates in Patients With and Without High-Risk Features[1]

PFS With or Without High-Risk Features



No. at Risk									
Without high-risk features	73	71	70	68	67	16	12	1	0
With high-risk features	129	125	125	119	117	36	29	3	0

PFS With del(17p)/*TP53* Mutation or Unmutated IGHV



No. at Risk									
With unmutated IGHV	100	97	97	96	94	32	27	3	0
With del(17p)/*TP53* mutation	29	28	28	23	23	4	2	0	–

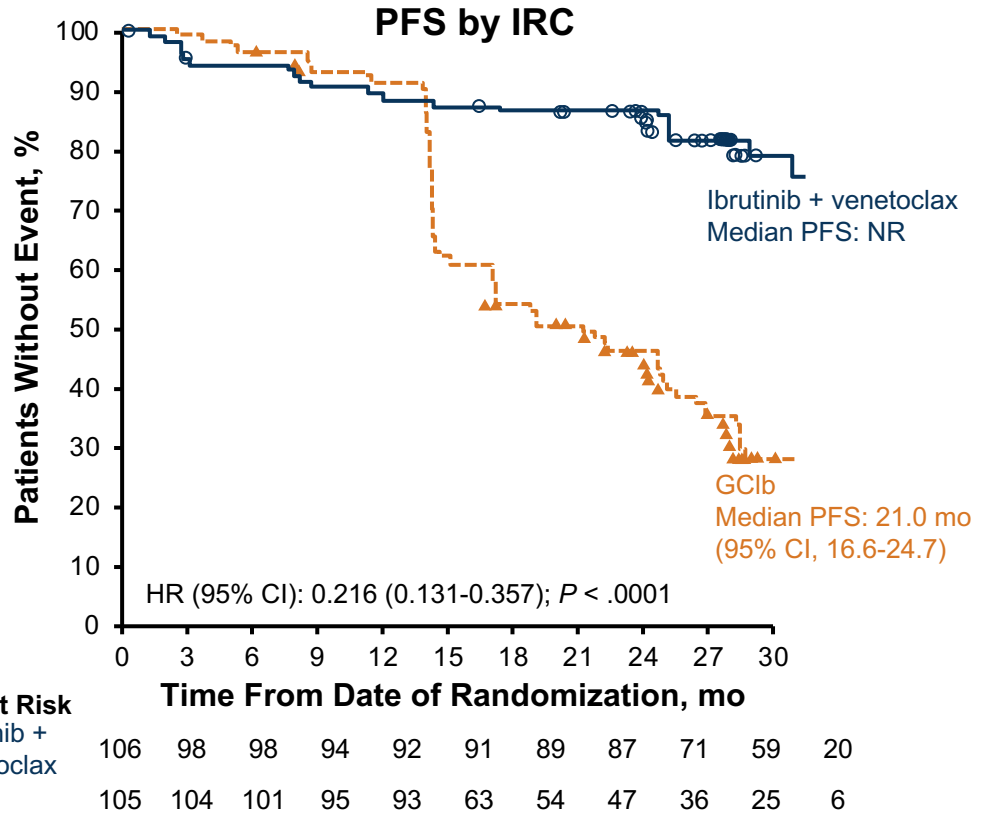
Compared with the relatively consistent PFS rates among patients with and without high-risk features, analysis of PFS by individual high-risk features showed a decrease in PFS among the small subset of patients with del(17p)/*TP53* mutation

1. Allan JN et al. AACR 2022. Abstract CT028.

GLOW: Improved PFS and CR With Fixed-Duration Ibrutinib and Venetoclax vs Chemoimmunotherapy in TN CLL[1]

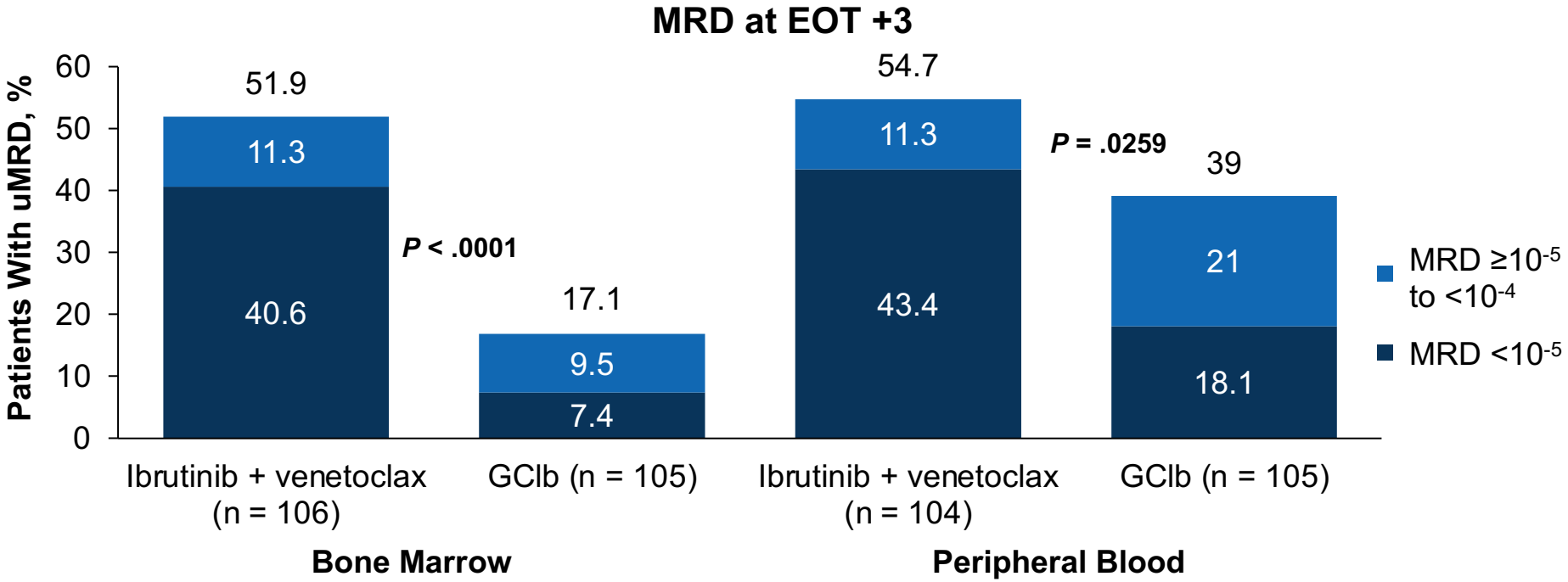
Phase 3 assessment of fixed-duration ibrutinib + venetoclax vs GClb in an elderly or unfit TN CLL population[1]

- **Ibrutinib + venetoclax reduced risk of progression or death by 78% vs GClb**
  - HR = 0.216 (95% CI, 0.131-0.357; *P* < .0001)
- **CR/CRi rates were significantly higher for ibrutinib + venetoclax vs GClb by both IRC and INV assessments**
  - 38.7% vs 11.4% by IRC (*P* < .0001)
  - 45.3% vs 13.3% by INV (*P* < .0001)



1. Kater A et al. EHA 2021. Abstract LB1902.

GLOW: More Patients Achieved uMRD With Ibrutinib + Venetoclax vs Chemoimmunotherapy[1]



- Most patients with uMRD $<10^{-4}$ in the ibrutinib + venetoclax arm had deep responses of uMRD $<10^{-5}$
- PB/BM uMRD concordance with ibrutinib + venetoclax was 90.9% vs 36.8% for GClb

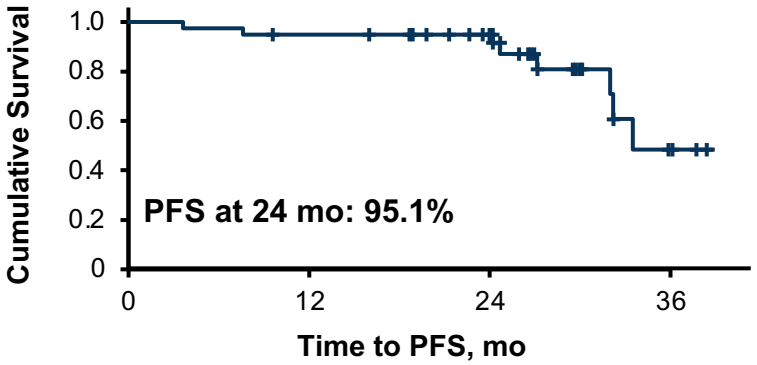
1. Munir T et al. ASH 2021. Abstract 70.

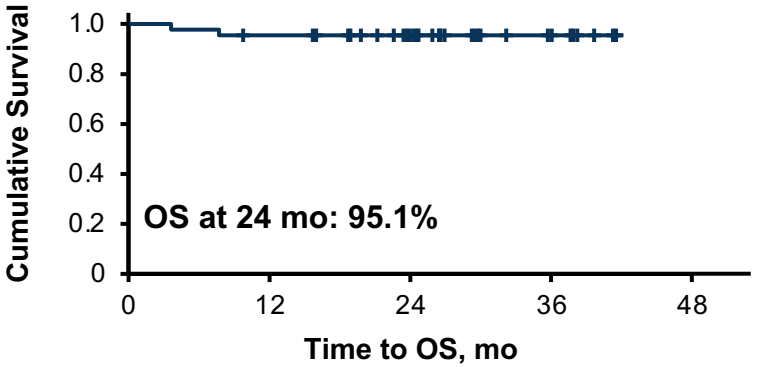
CLL2-GIVe: An Induction/Maintenance Approach Appears Feasible in High-Risk TN CLL[1]

Time-limited therapy with ibrutinib, venetoclax, obinutuzumab followed by maintenance ibrutinib[1]

N = 41 patients, all with del(17p) and/or *TP53*-mutated CLL

	Efficacy Outcome
CR at cycle 15	58.5% (primary endpoint met)
uMRD at final restaging	PB: 78.0% BM: 65.9%

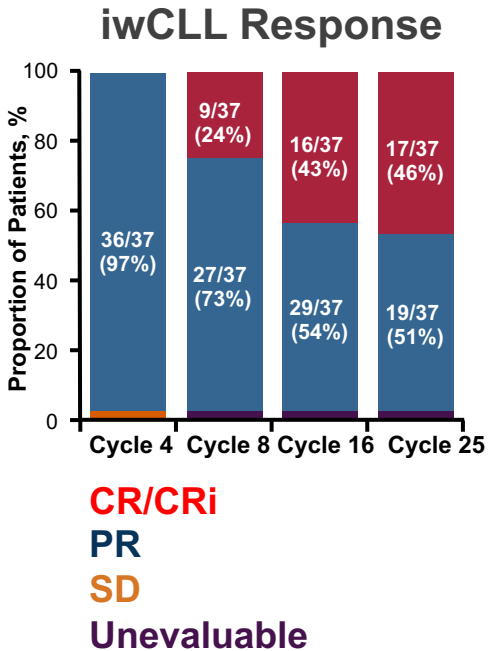




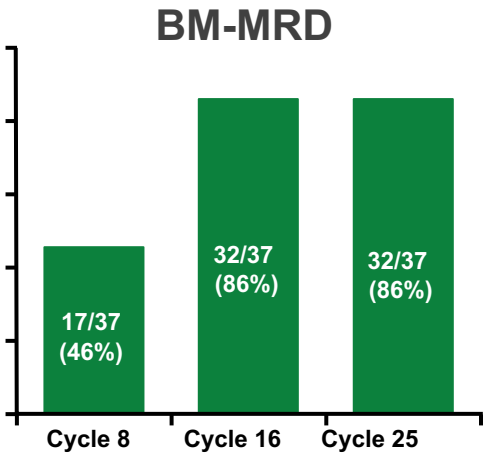
1. Huber H et al. *Blood*. 2022;139:1318-1329.

Novel Triplets: Time-Limited Acalabrutinib, Venetoclax, and Obinutuzumab (AVO) Is Active in TN CLL

Phase 2 Study of Frontline Time-Limited, MRD-Guided Triplet Therapy With Acalabrutinib, Venetoclax, and Obinutuzumab in CLL[1]



Rates of complete remission and undetectable MRD with AVO were similar ***regardless of TP53 and IGHV mutation status***

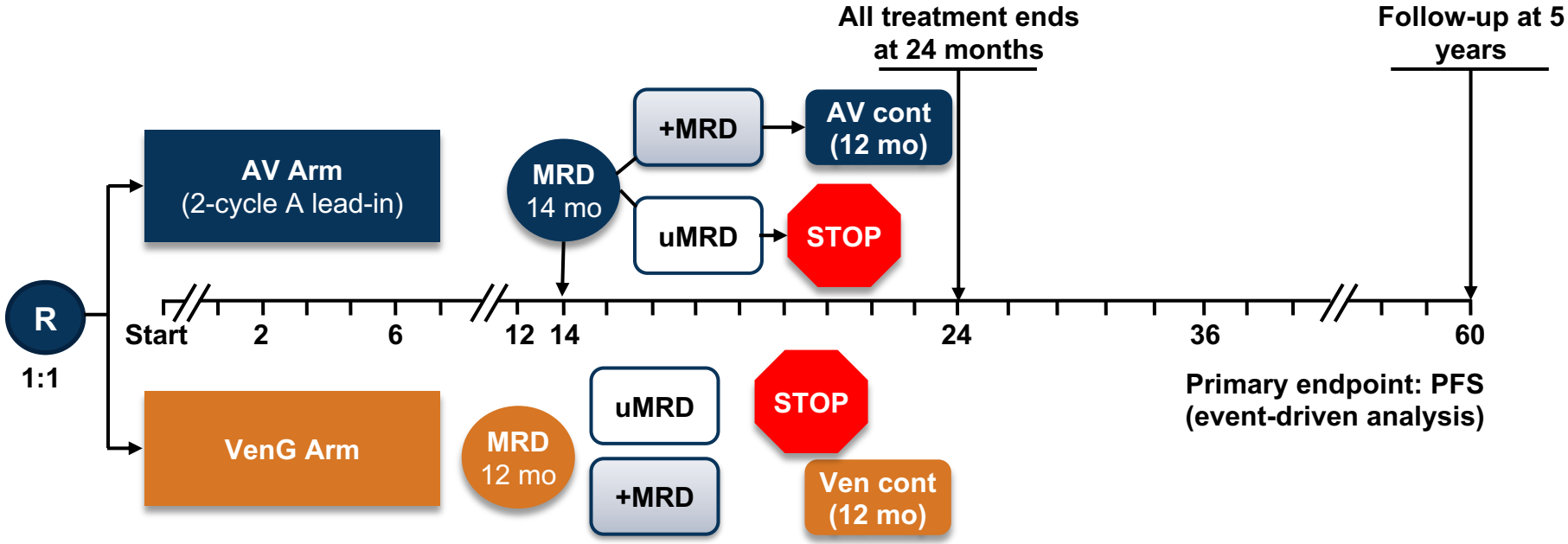


1. Davids MS et al. *Lancet Oncol*. 2021;22:1391-1402.

MAJIC Phase 3 Study Will Test Acalabrutinib-Venetoclax Combination in Patients With CLL/SLL[1]

- ~750 patients to be recruited
- 40 sites around the world

Key Eligibility Criteria
- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Antithrombotic agents permitted except for warfarin or equivalent vitamin K antagonists

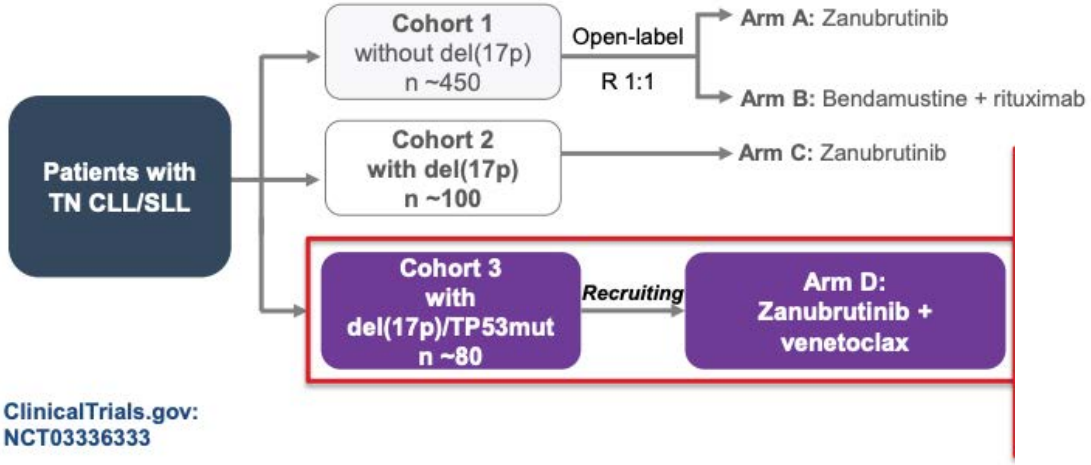


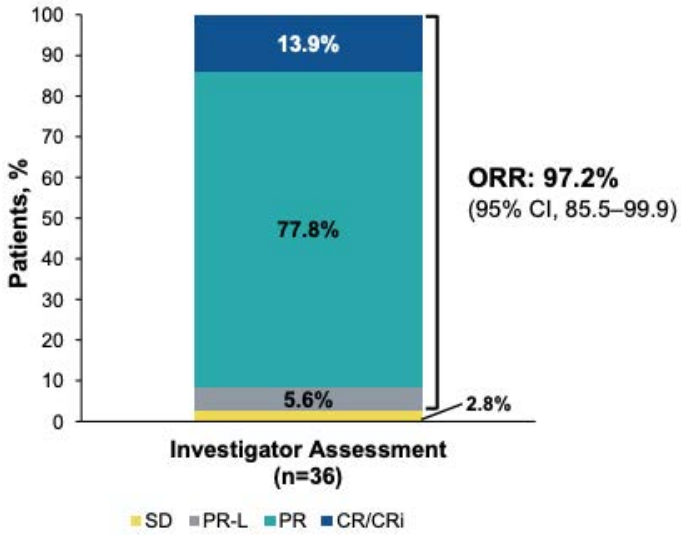
1. Davids MS et al. ASH 2021. Abstract 1553.

Zanubrutinib-Venetoclax Combination Is Active in Del(17p)/*TP53* CLL

SEQUOIA Arm D Tested Zanubrutinib-Venetoclax in High-Risk CLL[1]

Of 36 evaluable patients, 14 were treated with the combination therapy for at least 12 months

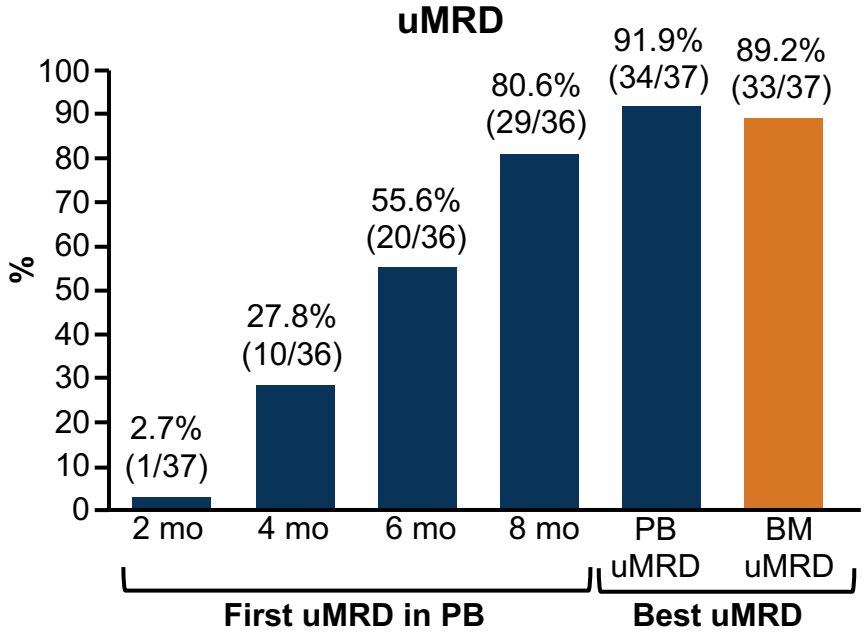




1. Tedeschi A et al. ASH 2021. Abstract 67.

BOVen: Zanubrutinib Plus Venetoclax and Obinutuzumab Is Highly Active, With Robust uMRD Rates in TN CLL

Phase 2 trial of 39 Patients With Previously Untreated CLL, ECOG PS ≤2, ANC ≥1,000/µL, PLT ≥75,000/µL (ANC ≥0/µL, PLT ≥20,000/µL if due to CLL)[1]



89.2% (33/37) have achieved uMRD in PB and BM and stopped therapy after a median of 10 months (8 months of triplet)

1. Soumerai JD et al. ASH 2020. Abstract 1307.

Characterizing Safety With Novel Time-Limited Combinations

Phase 3 GLOW (median follow-up of 28 mo[1])	• Similar rate of grade ≥3 AEs (76% for I + V; 70% for GClb) • SAEs in ≥5% of patients for I + V vs GClb: infections (12.3% vs 8.6%) and a-fib (6.6% vs 0%) • 2 (1.9%) patients in the I + V arm discontinued ibrutinib due to a-fib
CAPTIVATE (median follow-up of 27.9 mo[2])	• Most common grade ≥3 AEs were neutropenia (33%) and hypertension (6%) • AEs led to dose reductions of ibrutinib only in 9 patients (6%), venetoclax only in 18 patients (11%), and both ibrutinib and venetoclax in 6 patients (4%)
CLL14 (median follow-up of 36.9 mo[2])	• Similar rates of grade 3/4 neutropenia in venG and GClb (53%/48%) • SAEs in venG arm: venetoclax-related infections (n = 10; 5%) • 33 patients (16%) discontinued venG due to AE; mostly neutropenia

Take-home: Combinations appear to be highly effective, but safety may be a consideration, especially in older patients

[a] Includes neutrophil count decreased. Grade ≥3 febrile neutropenia: 1.9% for ibrutinib + V vs 2.9% for GClb. [b] Includes multiple preferred terms.

1. Kater A et al. EHA 2021. Abstract LB1902. 2. Tam CS et al. *Blood*. 2022 Feb 23 [Online ahead of print.] 3. Al-Sawaf O et al. *Lancet Oncol*. 2020;21:1188-1200.

Current and Future Sequential Strategies

PeerView
Live

In Current Guidelines, BTK Inhibitors and Venetoclax Regimens Are Preferred Options for R/R CLL

NCCN Recommendations for Second-Line and Subsequent Therapy, No del(17p)/*TP53* Mutations[1]

Patients aged ≥65 y OR Patients aged <65 y with significant comorbidities (CrCl <70 mL/min)	• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Zanubrutinib
Patients aged <65 y without significant comorbidities	• Acalabrutinib (category 1) • Ibrutinib (category 1) • Venetoclax + rituximab (category 1) • Zanubrutinib

Acalabrutinib, ibrutinib, and venetoclax-rituximab are also preferred options in R/R CLL with del(17p)/*TP53* mutations

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Why Planning for Sequential Therapy Is Important
Therapeutic Intolerance, Resistance at Progression

Toxicity/Intolerance[1,2]

- BTKi discontinuation rates are ~40% in some real-world reports
- Largely driven by toxicity
- Incidence of AEs greatest in the first 6 months

Disease Progression[3]

- Progression on covalent BTKi is often accompanied by resistance mutations
- Mutations such as *BTK* C481S confer resistance to all covalent BTKi

Double-Refractory CLL[4]

- Few good options
- Median time to discontinuation of the immediate subsequent LOT (post–BTKi/BCL-2i therapy) or death was 5.5 months

1. Mato AR et al. *Haematologica*. 2018;103:874-879. 2. Aarup K et al. *Eur J Haematol*. 2020;105:646-654.
3. Woyach JA et al. *J Clin Oncol*. 2017;35;1437-1443. 4. Mato A et al. ASH 2021. Abstract 3743.

Sequential Use of Acalabrutinib in Patients With Ibrutinib Intolerance Is an Effective and Safe Option (ACE-CL-208)[1]

ORR (≥PR) was 73%, with an 8% CR/CRi rate

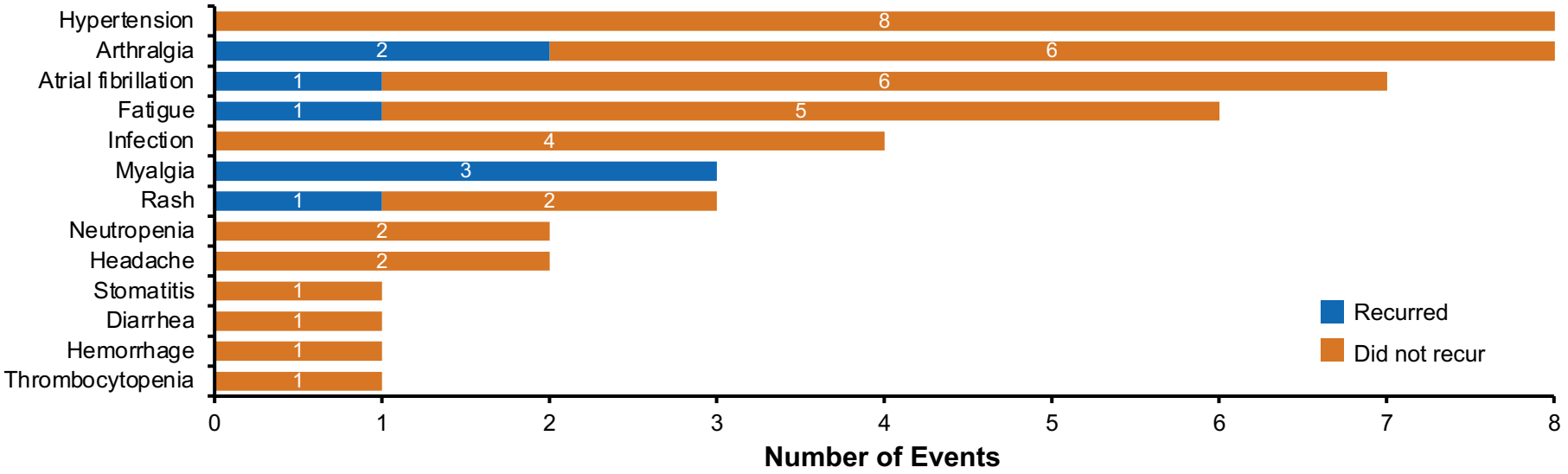
AE	No. of Patients With Ibrutinib Intolerance[a]	Acalabrutinib Experience for Same Patients, n			
		Total	Lower Grade	Same Grade	Higher Grade
AF	16[b]	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding[c,d]	6	5	3	2	0
Arthralgia	7[e]	2	1	1	0

[a] Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of ≥1 (43 events in total) of the following categories of ibrutinib-intolerance events: atrial fibrillation, diarrhea, rash, bleeding, or arthralgia. [b] Includes patients with atrial flutter (n = 2). [c] Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. [d] All but 1 patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. [e] Includes 1 patient with arthritis.

1. Rogers K et al. *Haematologica*. 2021;106:2364-2373.

Similarly, Zanubrutinib Is Effective in the Setting of BTK Inhibitor Intolerance

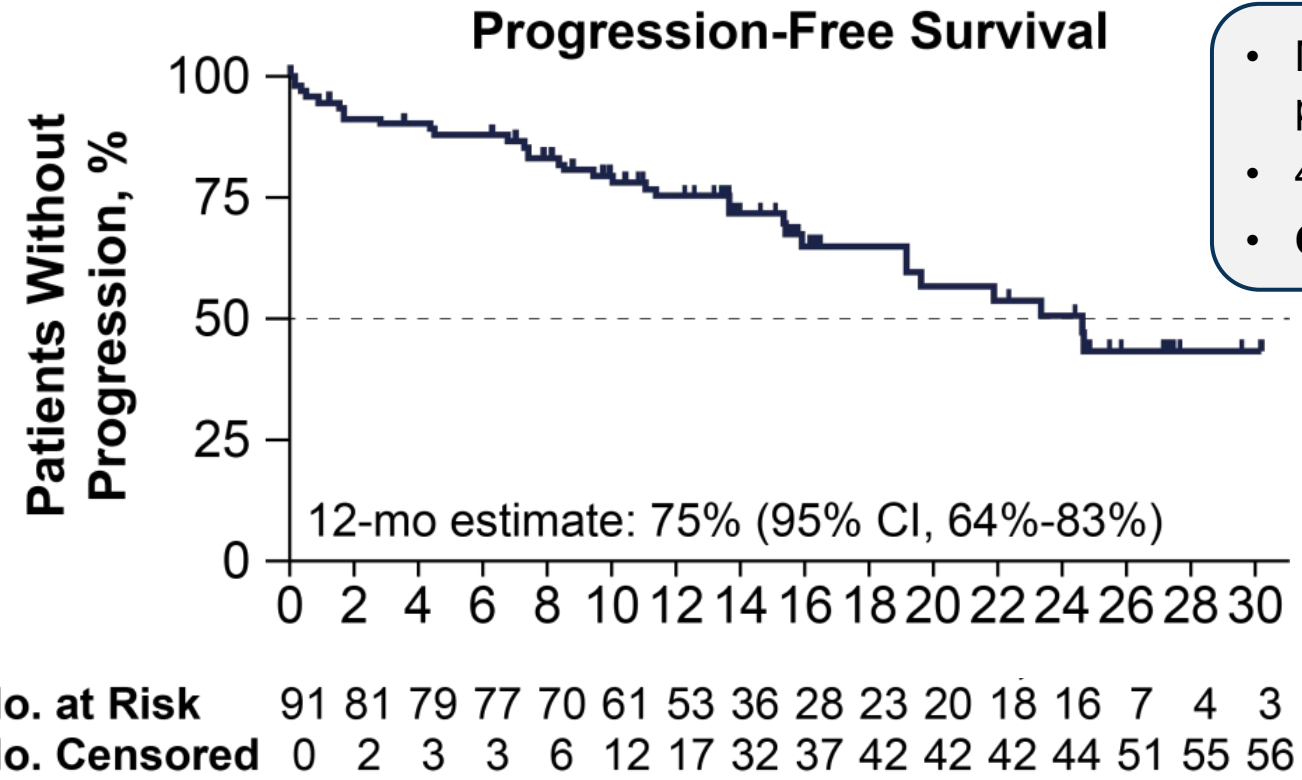
Recurrence and Severity Change From Prior BTK Inhibitor Exposure to Zanubrutinib Exposure (N = 60)[1]



- Of the 66 ibrutinib-intolerant events, 58 intolerant events (88%) did not recur
- Of the 4 acalabrutinib-intolerant events, 2 intolerant events (both arthralgia) did not recur and 2 recurred (myalgia; 1 at lower grade and 1 at the same grade)

1. Shadman M et al. ASH 2020. Abstract 2947.

Venetoclax Is an Active Option in Ibrutinib-Refractory/-Intolerant Patients[1]



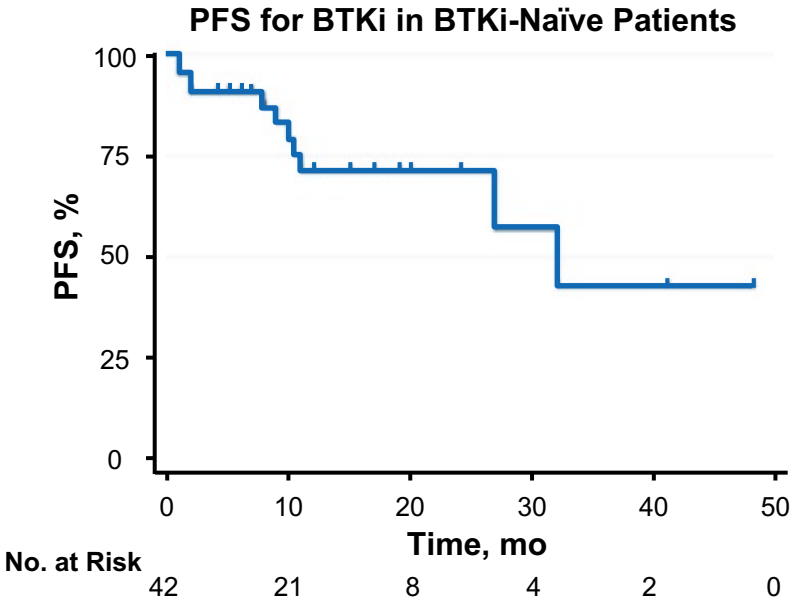
- Median of 4 prior therapies
- 47% del(17p)
- **ORR:** 70%

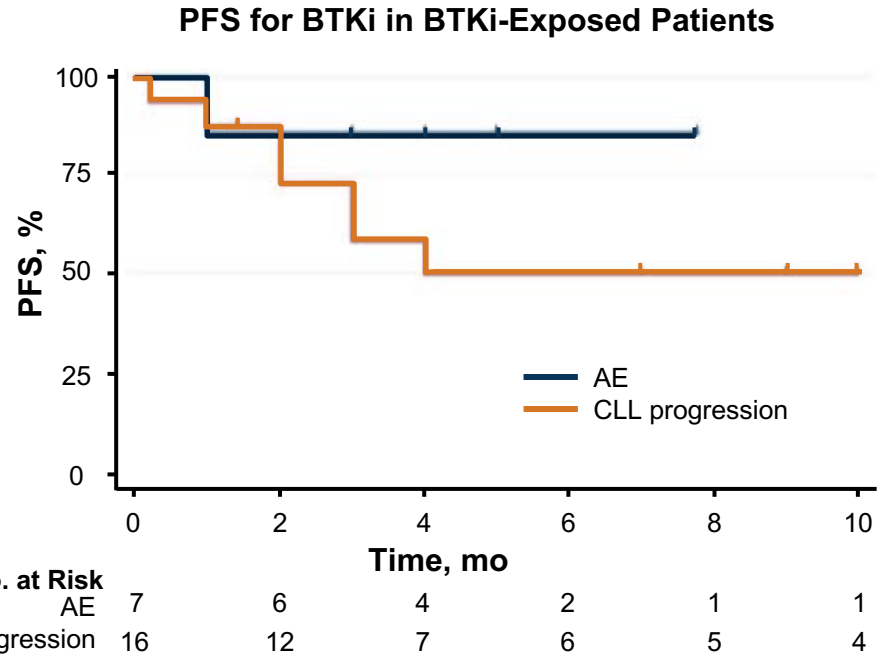
1. Jones JA et al. *Lancet Oncol*. 2018;19:65-75.

Post-Venetoclax Use of BTKi Is Effective in BTKi-Naïve Patients[1]

BTKi-naïve patients: BTKi therapy results in high ORR and durable remissions

BTKi-exposed patients: BTKi therapy is not effective in the setting of BTKi resistance

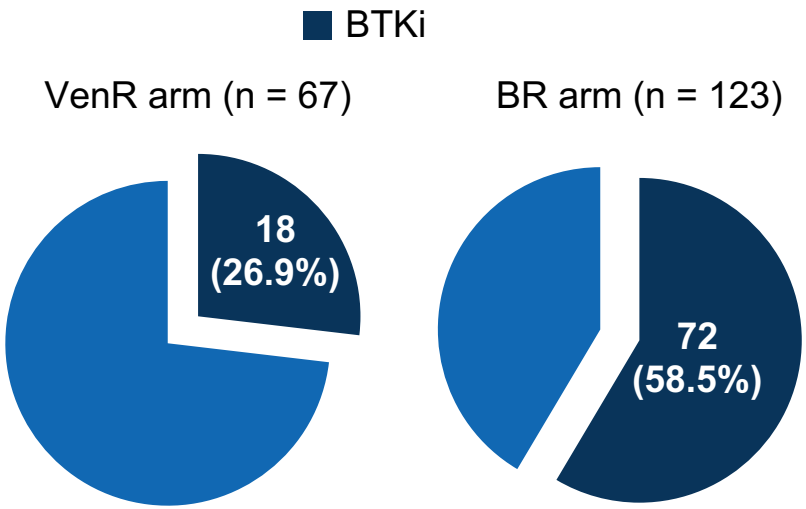




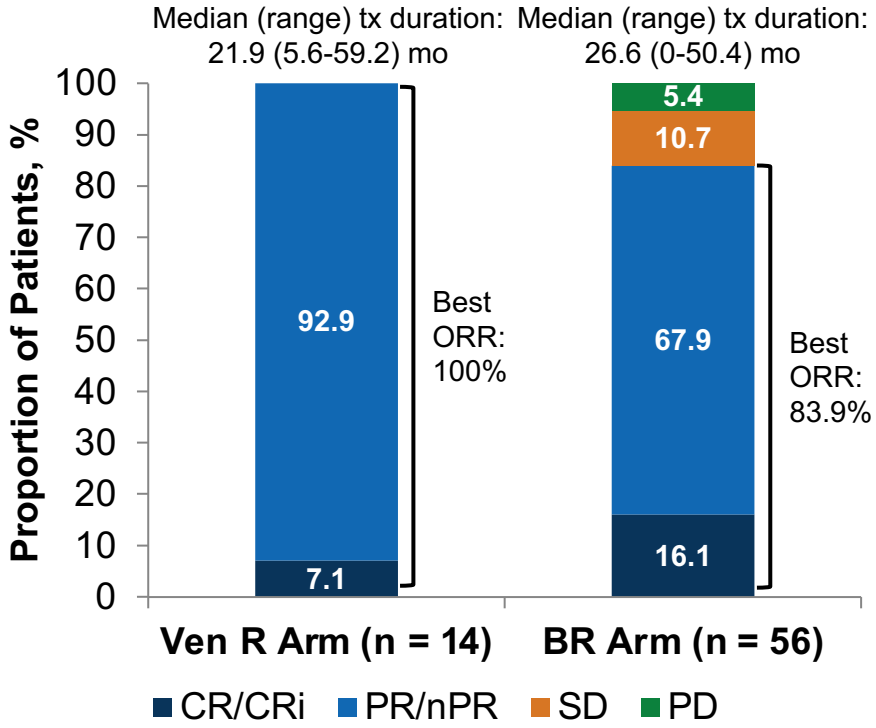
1. Mato A et al. *Clin Cancer Res*. 2020;26:3589-3596.

MURANO: Use of BTKi Therapy After Venetoclax/Rituximab Is Highly Active[1]

Subsequent Therapy (ITT)



Best ORR to Subsequent BTKi-Based Therapy



1. Harrup RA et al. ASH 2020. Abstract 3139.

Is Re-Exposure to VenG an Option After Time-Limited Therapy?

ReVenG: A Phase 2 Study of VenG Retreatment in R/R CLL[1]

Key Eligibility Criteria
- Relapsed CLL
- Completed 12 cycles of first-line venG and achieved a clinical response[1]
- Minimum of 1 year progression-free period after completing first-line ven treatment
- PD by iwCLL criteria

Cohort 1 (n = 60)
>2 years between last dose of fixed-duration Ven in first-line setting and PD

Study Treatment
VenG 6 cycles, then
Ven monotherapy 6 cycles

Cohort 2 (n = up to 15)
1-2 years between last dose of fixed-duration Ven in first-line setting and PD

Study Treatment[2]
VenG 6 cycles, then
Ven monotherapy 18 cycles

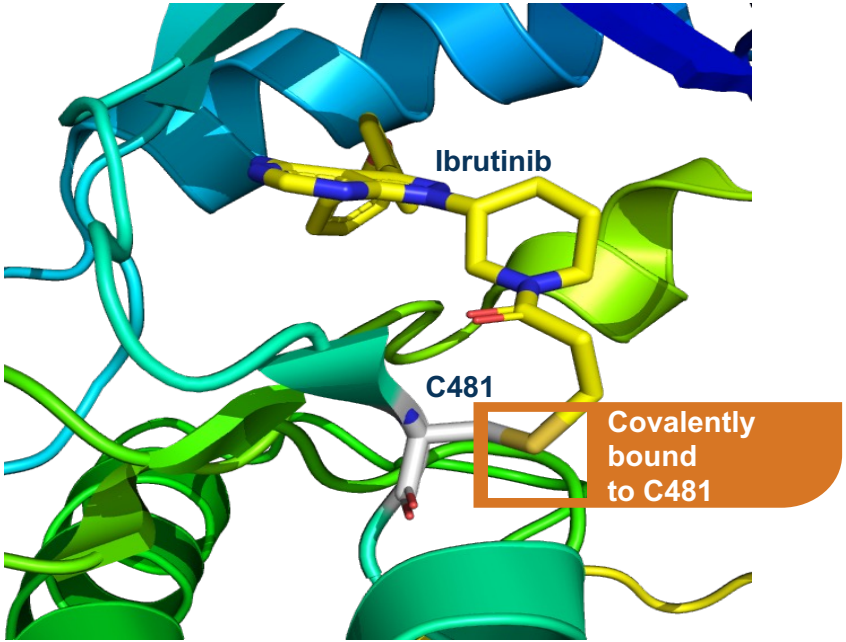
Primary endpoint
- ORR at EoCT (cycle 6 + 3 months)

Key secondary endpoints
- CR/CRi
- ORR at EOT
- DOR
- uMRD 10^{-4}
- PFS
- OS
- TTNT
- Safety

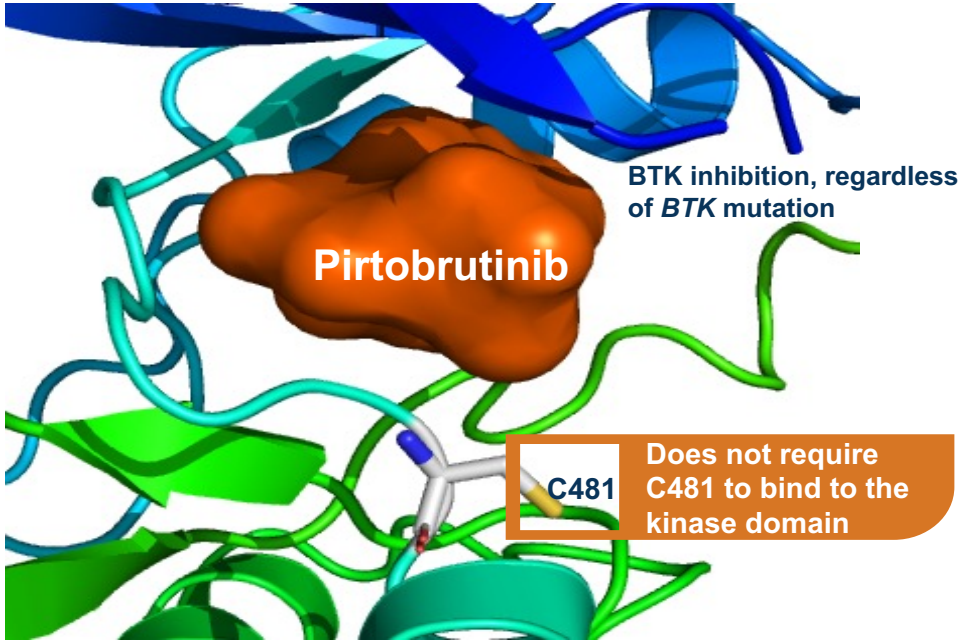
1. Davids M et al. ASH 2021. Abstract 2634.

How Noncovalent BTK Inhibitors Overcome Resistance

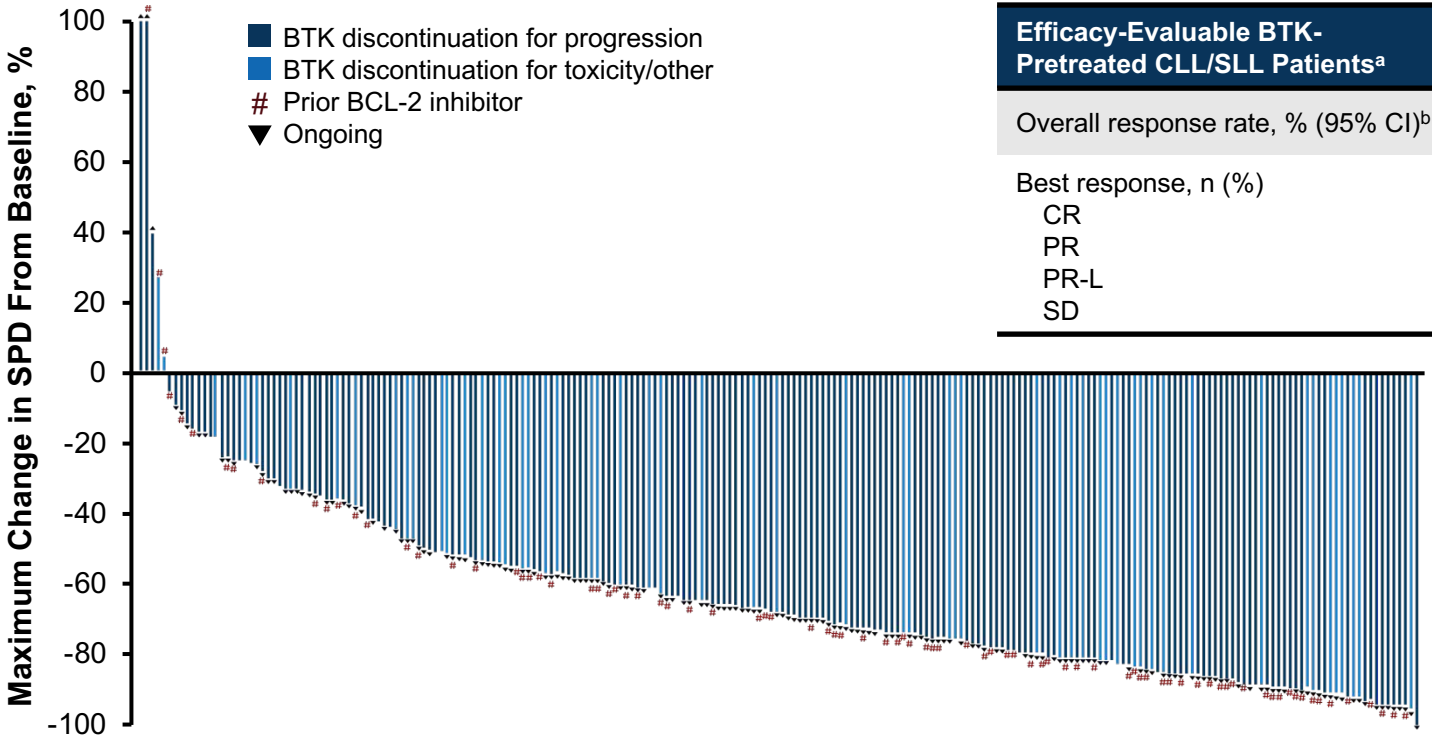
Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, and Zanubrutinib) Require WT *BTK* for Activity



Pirtobrutinib Is a Noncovalent BTK Inhibitor That Is Potent Against Both WT and C481-Mutated *BTK*



Updated Results From BRUIN Continue to Show Pirtobrutinib Is Active in R/R CLL/SLL[1]



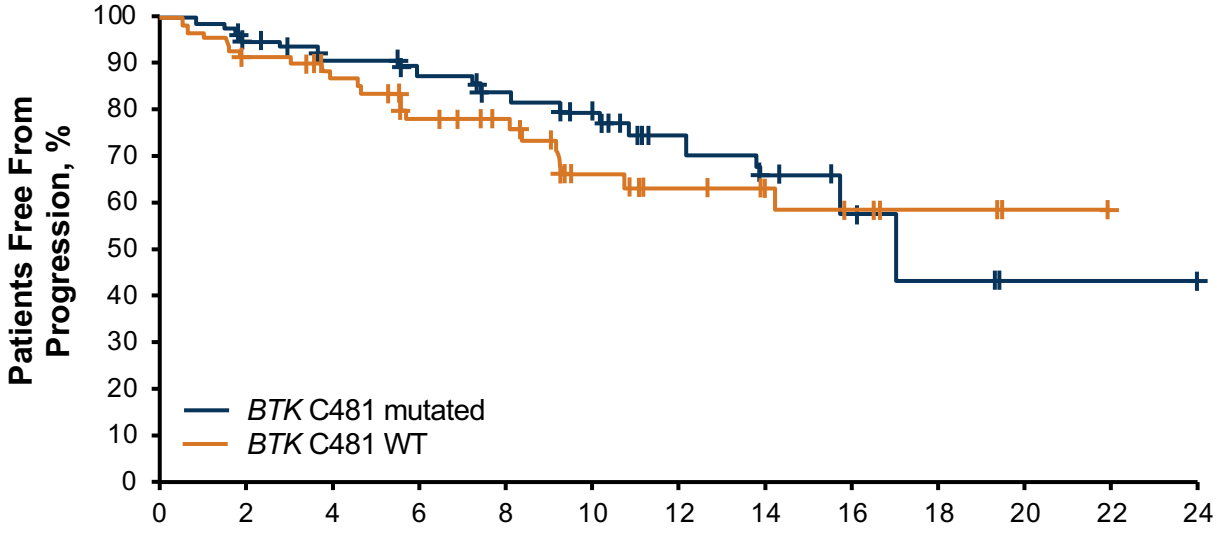
Efficacy-Evaluable BTK-Pretreated CLL/SLL Patients[a]	N = 252
Overall response rate, % (95% CI)[b]	68 (62-74)
Best response, n (%)	
CR	2 (1)
PR	137 (54)
PR-L	32 (13)
SD	62 (25)

[a] Efficacy-evaluable patients are those who had ≥1 postbaseline response assessment or had discontinued treatment prior to first postbaseline response assessment. [b] ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total percentage may be different than the sum of the individual components because of rounding.

1. Mato A et al. ASH 2021. Abstract 391.

BRUIN: *BTK* C481 Mutation Status Is Not Predictive of Pirtobrutinib Benefit[1]

Progression-Free Survival by *BTK* C481 Mutation Status[a] in CLL/SLL Patients With Progression on a Prior BTK Inhibitor



No. at Risk												
BTK C481 mutated	84	68	54	49	40	33	18	10	7	3	1	1	0
BTK C481 WT	74	62	52	40	35	23	19	13	11	5	1	0	–

[a] *BTK* C481 mutation status was centrally determined and based on pretreatment strategies.

1. Mato A et al. ASH 2021. Abstract 391.

Nemtabrutinib Has Also Demonstrated Robust and Durable Clinical Responses in *BTK* C481S-Mutated CLL

n (%) [95% CI]	CLL/SLL 65 mg Every Day (N = 38)
ORR	22 (57.9) [40.8-73.6]
CR	1 (2.6) [0.0-13.8]
PR	12 (31.6) [17.5-48.6]
PR-L	9 (23.7) [11.4-40.2]
SD	15 (39.5) [24.0-5.6]

Open-label, single-arm phase 2 study with multiple cohorts[1]

- N = 51 patients with R/R CLL/SLL
- 32 patients (63%) with *BTK* C481S mutation
- ORR of 58% in 38 evaluable patients

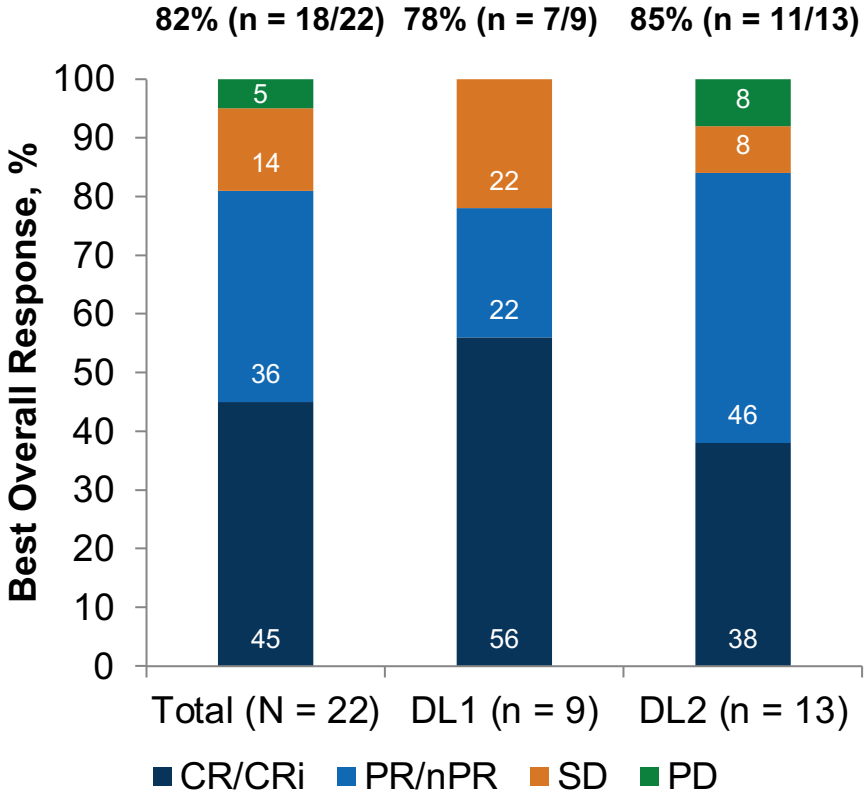
1. Woyach JA et al. ASH 2021. Abstract 392.

Robust Efficacy of Liso-Cel in Pretreated CLL Patients[1]

In the TRANSCEND CLL 004 trial, patients

- Failed or were ineligible for BTKi
- Had high-risk disease: failed ≥2 prior therapies
- Had standard-risk disease: failed ≥3 prior therapies

In this heavily pretreated population: high rates of response (82% ORR)



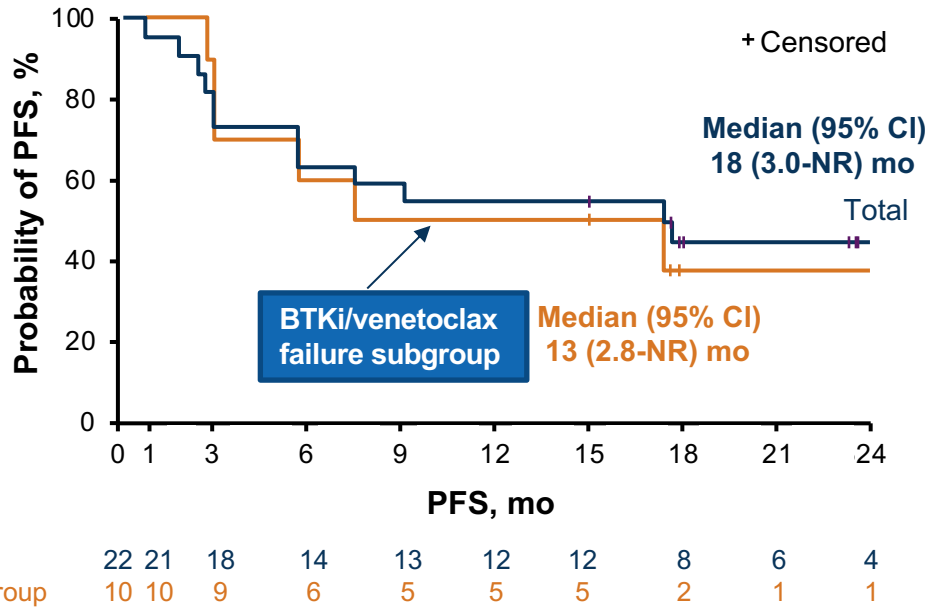
1. Siddiqi T et al. *Blood*. 2022;139:1794-1806.

Robust Efficacy of Liso-Cel in Pretreated CLL Patients[1] (Cont'd)

In the TRANSCEND CLL 004 trial, patients

- Failed or were ineligible for BTKi
- Had high-risk disease: failed ≥2 prior therapies
- Had standard-risk disease: failed ≥3 prior therapies

In this heavily pretreated population: high rates of response (82% ORR)



1. Siddiqi T et al. *Blood*. 2022;139:1794-1806.

Case Forum: Exploring New Combinations & Next-Gen Agents

Anthony R. Mato, MD, MSCE
Associate Attending
Director, Chronic Lymphocytic Leukemia Program
Memorial Sloan Kettering Cancer Center
New York, New York

PeerView
Live

Jonathan Presents With Symptomatic TN CLL and High-Risk Features

- **55 years old**
- **Symptomatic CLL (iwCLL criteria)**
- **No major medical comorbidities (normal renal function)**

Initial assessment

- CBC: WBC 95 x 10^9/L; ALC 23 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Unmutated IGHV
- Complex karyotype
- *TP53* mutation on NGS
- Patient asks about time-limited options

What are the options for Jonathan, given his presentation?

- Continuous BTKi therapy?
- Time-limited venG?
- Role for novel time-limited/doublet combination?

Jonathan Presents With Symptomatic TN CLL and High-Risk Features

- **55 years old**
- **Symptomatic CLL (iwCLL criteria)**
- **No major medical comorbidities (normal renal function)**

Initial assessment

- CBC: WBC 95 x 10^9/L; ALC 23 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Unmutated IGHV
- Complex karyotype
- *TP53* mutation on NGS
- Patient asks about time-limited options

Recommendations

- Continuous BTKi could be considered
- Novel BTKi-venetoclax combinations have shown robust efficacy in this population (CAPTIVATE)

How Would the Presence of Comorbidities Affect the Treatment Choice?

- **55 years old**
- **Symptomatic CLL (iwCLL criteria)**
- **History of comorbid cardiovascular events/a-fib**

Initial assessment

- CBC: WBC 95 x 10^9/L; ALC 23 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Unmutated IGHV
- Complex karyotype
- *TP53* mutation on NGS
- Patient asks about time-limited options

What are the options?

- How to choose between current strategies?

How Would the Presence of Comorbidities Affect the Treatment Choice?

- **55 years old**
- **Symptomatic CLL (iwCLL criteria)**
- **History of comorbid cardiovascular events/a-fib**

Initial assessment

- CBC: WBC 95 x 10^9/L; ALC 23 x 10^9/L; Hb 10.8 g/dL; PLT 72 x 10^9/L
- Unmutated IGHV
- Complex karyotype
- *TP53* mutation on NGS
- Patient asks about time-limited options

Recommendations

- Continuous BTKi with second-generation BTKi could be considered (based on ELEVATE-RR and ALPINE)
- Novel BTKi-venetoclax combinations have shown robust efficacy in this population; ongoing trials are testing FD combinations with more selective BTKi (MAJIC)

Mark, an Older Patient Relapsing After FD Therapy

- **68 years old**
- **Symptomatic CLL (iwCLL criteria)**
- **Unmutated IGHV**
- **Comorbid COPD and HTN**

Treatment history

- Pretreatment CT scan to assess burden of internal lymphadenopathy
- TLS risk assessment performed

VenG

- Achieves a remission after 1 year of treatment
- After 3 years: returns to clinic with progressive lymphadenopathy and night sweats

What are the options for Jonathan, given his presentation?

- Start a covalent BTKi?
- Re-challenge with venetoclax?

Mark, an Older Patient Relapsing After FD Therapy

- **68 years old**
- **Symptomatic CLL (iwCLL criteria)**
- **Unmutated IGHV**
- **Comorbid COPD and HTN**

Treatment history

- Pretreatment CT scan to assess burden of internal lymphadenopathy
- TLS risk assessment performed

VenG

- Achieves a remission after 1 year of treatment
- After 3 years: returns to clinic with progressive lymphadenopathy and night sweats

Recommendations

- Ibrutinib or acalabrutinib are standard, evidence-based options (NCCN, RESONATE, and ASCEND)
- Venetoclax re-challenge in this type of patient is currently being explored

What if Mark Progresses on a Second-Line BTKi?

- **68 years old**
- **Symptomatic CLL (iwCLL criteria)**
- **Unmutated IGHV**
- **Comorbid COPD and HTN**

Treatment history

VenG>>followed by progression 3 years after EOT

Responds to subsequent acalabrutinib, but progresses again after 2 years

What are the options for this "double-refractory" patient?

- Re-challenge with a covalent BTKi?
- Re-challenge with venetoclax?
- Treat with a PI3Ki?
- Treat with noncovalent BTKi?
- CAR-T?

What if Mark Progresses on a Second-Line BTKi?

Mark, a 68-year-old patient with symptomatic unmutated IGHV CLL

- Comorbid COPD and HTN
- Now progressing after venG upfront and subsequent covalent BTKi therapy

What is the case for noncovalent BTKi therapy?

- Re-exposure to a covalent BTKi or venetoclax is unlikely to benefit Mark
- Noncovalent BTKi via clinical trial enrollment is an attractive option, supported by current phase 2 evidence with pirtobrutinib and nemtabrutinib

What is the case for CAR-T?

- Based on TRANSCEND CLL, cellular therapy may also be a potent option
- However, **be prepared for the unique suite of toxicities associated with CAR-T cell therapy**

Treatment-Emergent AEs With Liso-Cel Included CRS and Neurologic Toxicity[1]

No late or delayed AEs of concern have emerged with longer follow-up

Parameter	Monotherapy Cohort (N = 23)	BTKi Progression/Venetoclax Failure Subgroup (n = 11)
Common grade 3/4 TEAEs, n (%)		
Anemia	17 (74)	7 (64)
Thrombocytopenia	16 (70)	6 (55)
Neutropenia/neutrophil count decrease	16 (70)	8 (73)
Leukopenia	10 (43)	2 (18)
CRS		
All-grade CRS, n (%)	17 (74)	7 (64)
Median time to CRS onset, days (range)	3 (1-10)	1 (1-10)
Median duration of CRS, days (range)	12 (2-50)	15 (5-50)
Grade 3 CRS, n (%)	2 (9)	2 (18)
NEs		
All-grade NEs, n (%)	9 (39)	5 (46)
Median time to NE onset, days (range)	4 (2-21)	4 (2-21)
Median duration of NE, days (range)	20.5 (6-50)	38 (6-50)
Grade ≥3 NEs, n (%)	5 (22)	3 (27)

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

Informed Patients & CLL Society Programs Can Enhance Care in an Era of Rapidly Changing Science

"[The CLL Society Expert Access Program] confirmed things I had previously researched and brought to light things I didn't know … It also helped me narrow my focus while further researching treatment options.

I had a follow-up with my local oncologist and had extra confidence to ask the right questions thanks in large part to my conversation with the physician I saw through the Expert Access Program.

This was the best and most informative visit I've had with my oncologist so far."

Suzy Kelly
Nevada
CLL Patient since 2018

Expert Access™

- ✓ Free consultations for patients
- ✓ Expert opinions to share with local treatment teams

Abbreviations

1L: first line
a-fib: atrial fibrillation
A: acalabrutinib
AF: atrial fibrillation
ALC: absolute lymphocyte count
ANC: absolute neutrophil count
ASCO: American Society of Clinical Oncology
ASO: allele-specific oligonucleotide
AV: acalabrutinib and venetoclax
AVO: acalabrutinib, venetoclax, and obinutuzumab
BCL-2: B cell lymphoma 2
BM: bone marrow
BMAT: bone marrow aspiration and trephine biopsy
BR: bendamustine plus rituximab
BTK: Bruton tyrosine kinase
BTKi: Bruton tyrosine kinase inhibitor
CAR-T: chimeric antigen receptor T cell
CD: cluster of differentiation
CIRS: Cumulative Illness Rating Scale
CIT: chemoimmunotherapy
Clb: chlorambucil
CLL: chronic lymphocytic leukemia
COVID-19: coronavirus disease 2019
CR: complete response
CrCl: creatinine clearance
CRi: complete response with incomplete marrow recovery
CRS: cytokine-release syndrome
del: deletion
DFCI: Dana–Farber Cancer Institute
DFS: disease-free survival
DL1: dose level 1
DL2: dose level 2
DOR: duration of response
ECOG: Eastern Cooperative Oncology Group
ECOG PS: Eastern Cooperative Oncology Group performance status
EoCT: end of combination treatment
EOT: end of treatment
FCR: fludarabine, cyclophosphamide, and rituximab
FD: fixed duration
FILO: French Innovative Leukemia Organization
FISH: fluorescence in situ hybridization
G-CSF: granulocyte colony-stimulating factor
G: obinutuzumab
GClb: obinutuzumab and chlorambucil
HDMP: high-dose methylprednisolone
H-MRD: high minimal residual disease
HTN: hypertension
I: ibrutinib
iFCG: ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab
iFCR: ibrutinib, fludarabine, cyclophosphamide, and rituximab
IGHV: immunoglobulin heavy-chain gene
IGVH: immunoglobulin variable heavy chain
INV: investigator
IR: ibrutinib and rituximab
IRC: Independent Review Committee

Abbreviations

iwCLL: International Workshop on Chronic Lymphocytic Leukemia
Liso-cel: lisocabtagene maraleucel
L-MRD: low minimal residual disease
LOT: line of treatment
Ly: lymphocyte
MDACC: MD Anderson Cancer Center
MRD: minimal residual disease
NCCN: National Comprehensive Cancer Network
NE: not evaluable
NE: neurologic event
NGS: next-generation sequencing
nPR: nodular partial response
NR: not reached
O: obinutuzumab
ORR: overall response rate
OSU: The Ohio State University
PB: peripheral blood
PD: progressive disease
PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase
PI3Ki: phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitor
PLT: platelets
PR-L: partial response with lymphocytosis
PR: partial remission
R/R: relapsed/refractory
SAE: serious adverse event
SD: stable disease
SLL: small lymphocytic lymphoma
TEAE: treatment-emergent adverse event
TLS: tumor lysis syndrome
TN: treatment naïve
TP53: tumor protein 53
TTNT: time to next treatment
uMRD: undetectable minimal residual disease
Ven: venetoclax
VenG: venetoclax plus obinutuzumab
VenR: venetoclax plus rituximab
WT: wild type
zanu: zanubrutinib

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