Advancements in the Management of Relapsed/Refractory B-Cell Malignancies

Integrating Recent Data into Practice to Improve Outcomes

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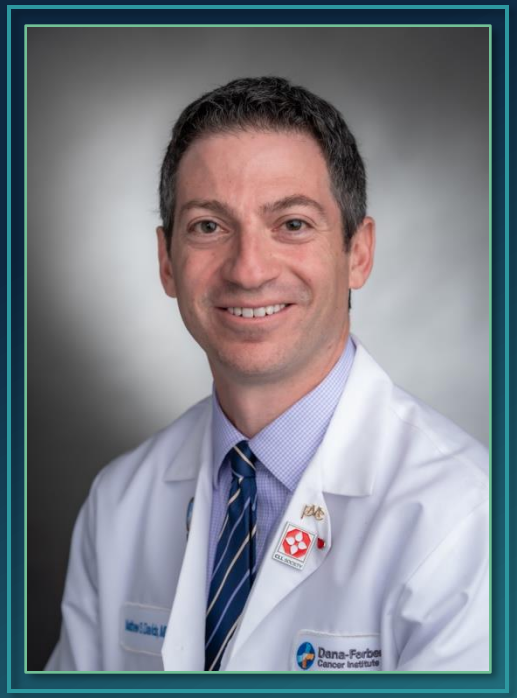

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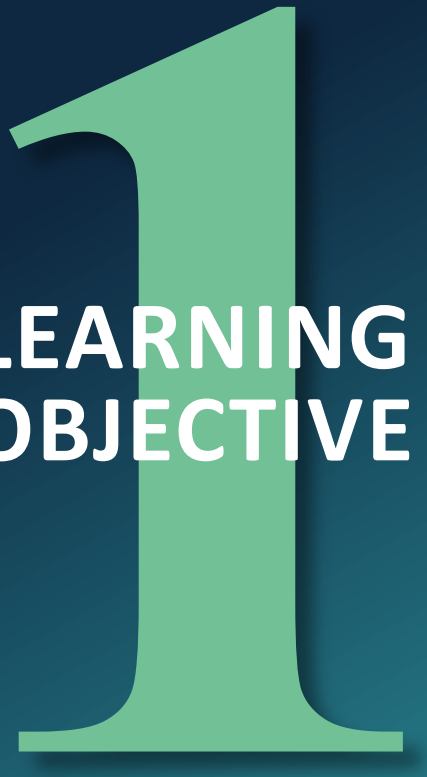


LEARNING OBJECTIVE

Implement novel treatment options for patients with R/R CLL/SLL based on the latest clinical trial data

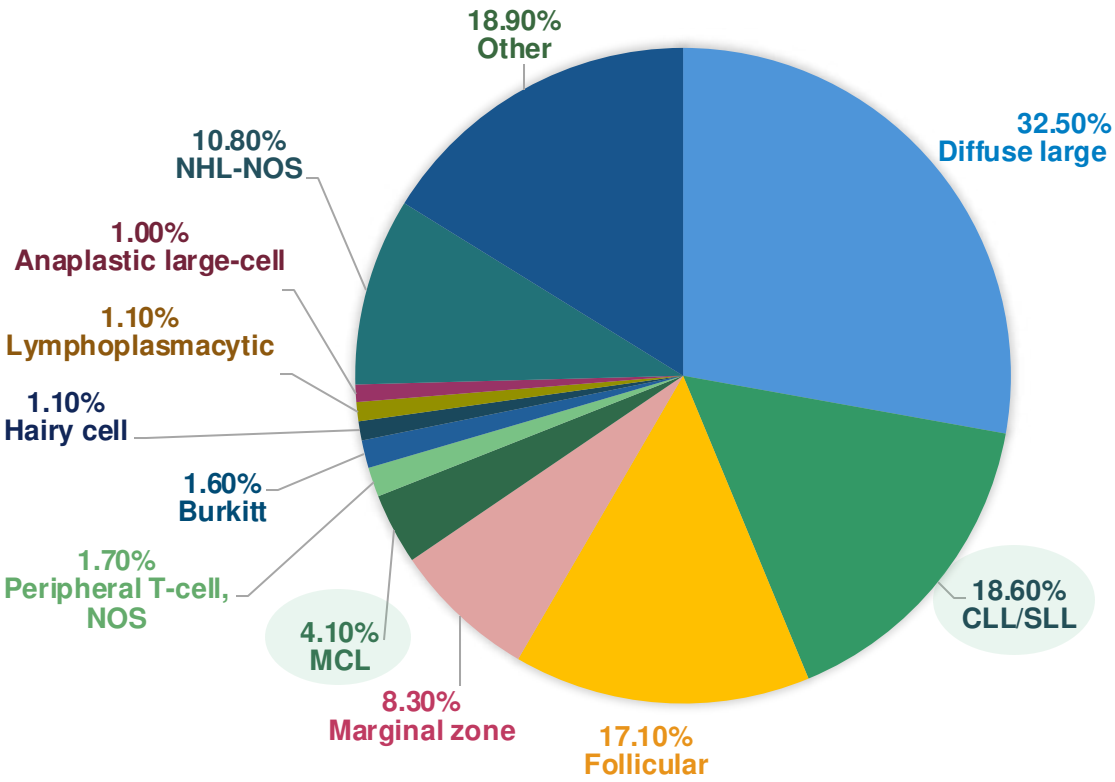
LEARNING OBJECTIVE 2

Utilize an evidence-based approach for personalizing treatment for patients with R/R MCL

LEARNING OBJECTIVE 3

Develop team-based frameworks to oversee and address AEs, prioritizing patient adherence and active engagement

Incidence of Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma



	CLL	MCL
Incidence 2023	20,700	3,383
Average age at diagnosis	70	60-70
Male:Female ratio	2:1	3:1

CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; SLL = small lymphocytic lymphoma.

Al-Hamadari M, et al. *Am J Hematol*. 2015;90:790-795. Seigel RL, et al. *CA Cancer J Clin*. 2023;73(1):17-48. Lynch DT, et al. Mantle cell lymphoma. In: *StatPearls*. 2023. https://www.ncbi.nlm.nih.gov/sites/books/NBK536985/.

NCCN Guideline Preferred Recommendations

	CLL/SLL	MCL
First Line	cBTKi ± obinutuzumab Venetoclax + obinutuzumab	Chemoimmunotherapy HDT/ASCR + anti-CD20 MAb with or without cBTKi maintenance
Subsequent Lines	cBTKi (if not previously given) Venetoclax ± anti-CD20 MAb	cBTKi Lenalidomide + rituximab (LenR)
Relapsed/Refractory (after cBTKi and venetoclax)	ncBTKi CAR T-cell	ncBTKi CAR T-cell

	Covalent BTKi			Non-covalent BTKi	
BTK Inhibitor	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib	Nemtabrutinib
Generation	First	Second	Second	Third	Third
Dosing	420 mg daily	100 mg BID	160 mg BID or 320 mg daily	200 mg daily	65 mg daily (RP2D)

ASCR = autologous stem cell rescue; BID = twice a day; BTKi = Bruton's tyrosine kinase inhibitor; CAR = chimeric antigen receptor; cBTKi = covalent BTKi; HDT = high-dose therapy; MAb = monoclonal antibody; ncBTKi = non-covalent BTKi; RP2D = recommended phase 2 dosing.

National Cancer Center Network (NCCN) Clinical Practice Guidelines in Oncology, B-cell lymphomas, Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

NCCN Clinical Practice Guidelines in Oncology, Chronic lymphocytic leukemia/small lymphocytic lymphoma, Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Chronic Lymphocytic Leukemia (CLL)

Patient Case: 1

A 59-year-old man with hypertension but no other medical conditions is diagnosed with Rai stage 1 CLL. Prognostic markers show normal fluorescence in situ hybridization (FISH), unmutated *IGHV*, *TP53*wt.

Over the next 3 years, he gradually develops cytopenias and a 4- to 5-cm palpable lymphadenopathy. Now, at age 62, he needs frontline therapy for CLL.

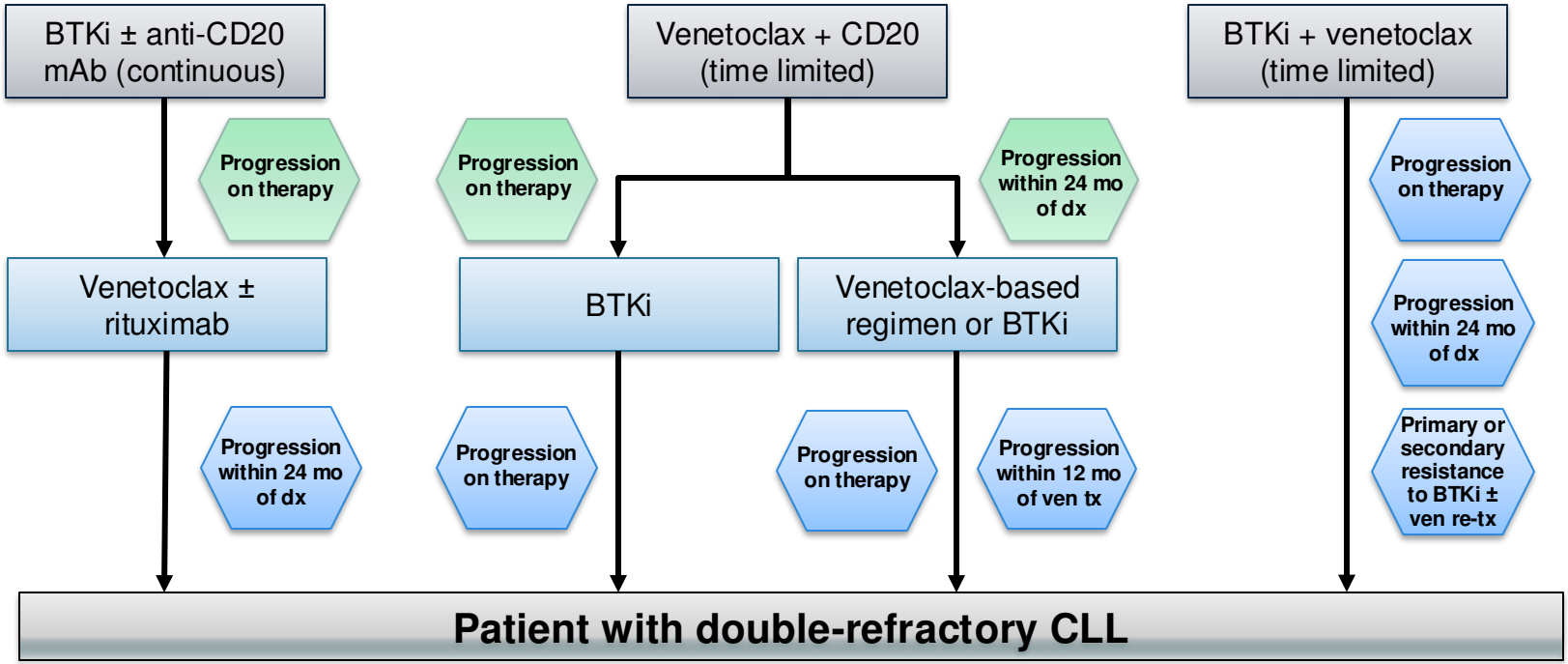
He achieves a partial response (PR) on ibrutinib and stays in remission for about 8 years, but now at age 70 he develops progressive bulky lymphadenopathy, and repeat genetic testing reveals *TP53* mutation.

He starts on venetoclax + anti-CD20 MAb and achieves a PR with undetectable minimal residual disease (MRD) and small residual lymphadenopathy.

After 2 years on venetoclax + anti-CD20 MAb, he develops steadily progressive lymph nodes that are now bulky.

What are his treatment options and what do you recommend?

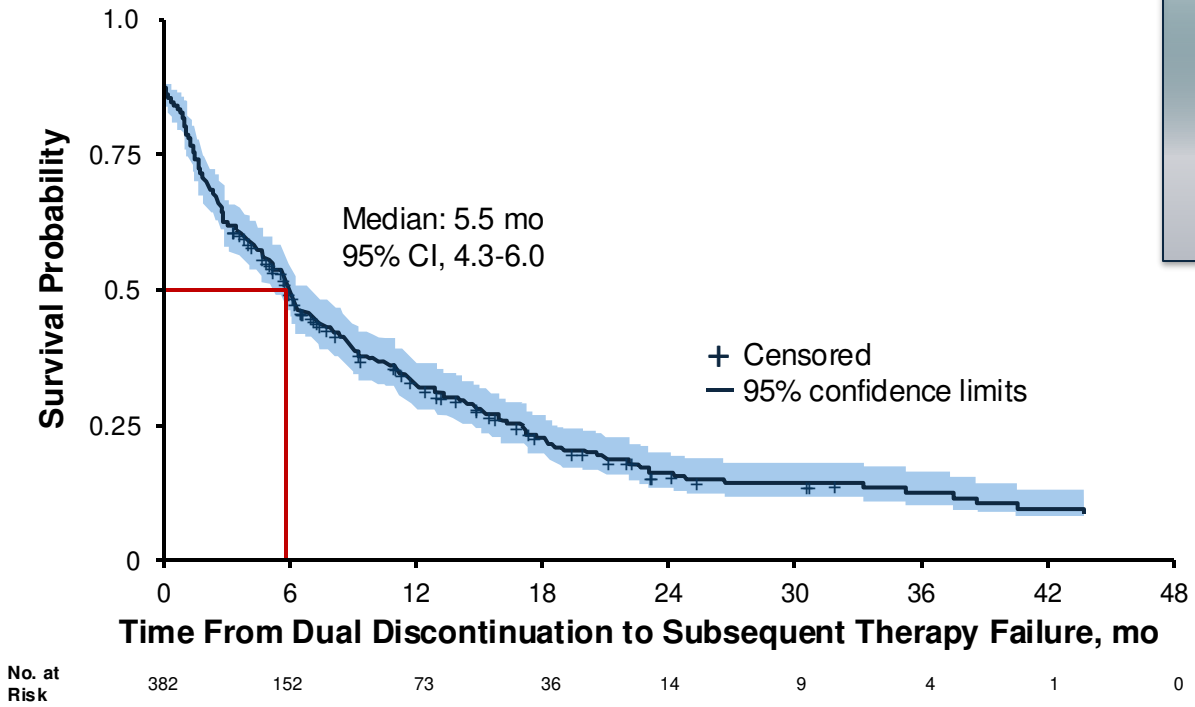
Defining Double-Refractory Disease



dx = diagnosis; re-tx = re-treatment; tx = treatment; ven = venetoclax.

Aronson JH, et al. *Am J Hematol*. 2022;97(suppl 2):S19-S25.

Real-World Data Show That Double-Refractory Disease Represents a Clear Unmet Medical Need in CLL/SLL



Among 382 patients who discontinued covalent BTKi/BCL-2i therapy, median time to discontinuation of the immediate subsequent line of therapy (post–BTKi/BCL-2i therapy) or death was 5.5 months[1]

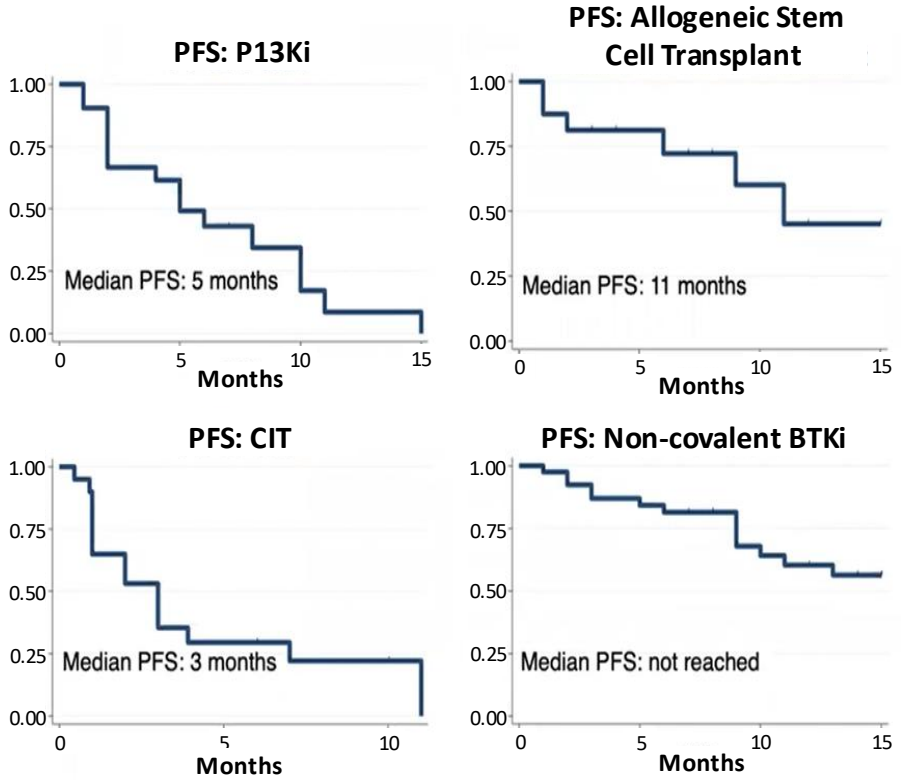
Patients previously treated with <u>both a covalent BTKi and a BCL-2i</u> experience poor outcomes with currently available post-covalent BTKi/BCL-2i therapy

BCL-2i = BCL-2 inhibitor.

1. Mato A, et al. ASH 2021. Abstract 3743.

Real-World Outcomes of Patients with CLL and Prior Exposure to cBTKi and Ven

Subsequent Therapy	CAR-T	AlloSCT	ncBTKi	P13Ki	CIT
Patients Treated	9	17	45	24	23
ORR	85.7% n = 7	76.5% n = 17	75.0% n = 43	40.9% n = 22	31.8% n = 22
Median PFS (months)	4 n = 9	11 n = 16	Not reached n = 40	5 n = 21	3 n = 20
Median Follow-up (months)	3	6.5	9	4	2



AlloSCT = allogeneic stem cell transplantation; CAR-T = chimeric antigen receptor T-cell therapy; CIT = chemoimmunotherapy; ORR = overall response rate; PFS = progression-free survival.

Thompson P, et al. ASH, 2022.

Real-World Efficacy of Subsequent Lines of Therapy

Recent electronic health record (EHR)-derived data of patients initiating CLL therapy on or after 2016 suggest that first-line cBTKi followed by BCL2i + anti-CD20 MAb is associated with the greatest overall survival (OS) benefit

- The use of targeted agents in the first two lines of therapy was uncommon
- Novel treatments (e.g., ncBTKi and CAR T-cell) were not available to these patients (2023 data cutoff)

Rhodes JM, et al. *Blood*. 2024;144:5114.

Where Do We Stand With Treatment for Double-Refractory CLL?

- There are few good options
  - Median time to discontinuation of the immediate subsequent line of treatment (post–BTKi/BCL-2i therapy) or death was 5.5 months
- Novel *BCL-2* mutations have been described in venetoclax-resistant, ibrutinib-resistant CLL with *BTK*/*PLCG2* mutations
- What is being explored?
  - Venetoclax re-treatment
  - Non-covalent BTKi
  - CAR-T therapy
  - Targeted therapies

PLCG2 = phospholipase C gamma 2.
Mato A, et al. ASH, 2021. Abstract 3743. Lucas F, et al. *Blood.* 2020;135:2192-2195.

Is Venetoclax Re-treatment an Option?

- Retrospective study investigating outcomes and safety data for patients with CLL treated with a venetoclax-based regimen (Ven1) in any line of therapy and then re-treated with a second venetoclax-based regimen (Ven2) in a later line of therapy
- Data sources included
  - 15 medical centers (n = 30)
  - CLL Collaborative Study of Real-World Evidence database (n = 5)
  - Patients from the MURANO trial dataset (n = 11)

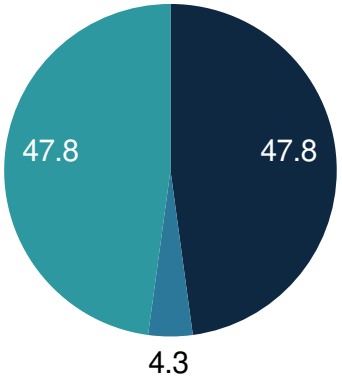
Baseline Characteristics	Results	Patients with Available Data, n
Median age at CLL diagnosis, y (range)	55.5 (24-75)	46
Median age at Ven1 start, y (range)	64 (31-75)	46
Men	73.9%	46
Race	83.3% White 9.5% Black 7.1% other	42
Median prior lines of therapy (range)	2 (0-10)	46
Prior venetoclax	56.5%	46
Ven1 as monotherapy	37%	46
Ven1 as first-line treatment	8.7%	46
Prior BTKi	40%	45
Mutation status		
del(17p)	25%	44
TP53 mutation	15.6%	32
Complex karyotype	20.5%	39
IGHV unmutated	82.1%	39

del = deletion; IGHV = immunoglobulin heavy chain gene; TP53 = tumor protein 53.

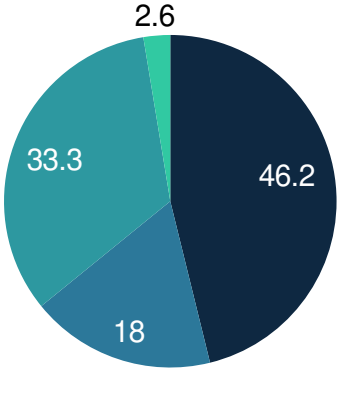
1. Thompson M, et al. *Blood Adv*. 2022;6:4553-4557.

Retrospective Evidence of Venetoclax in Double-Exposed Patients

ORR to Ven1

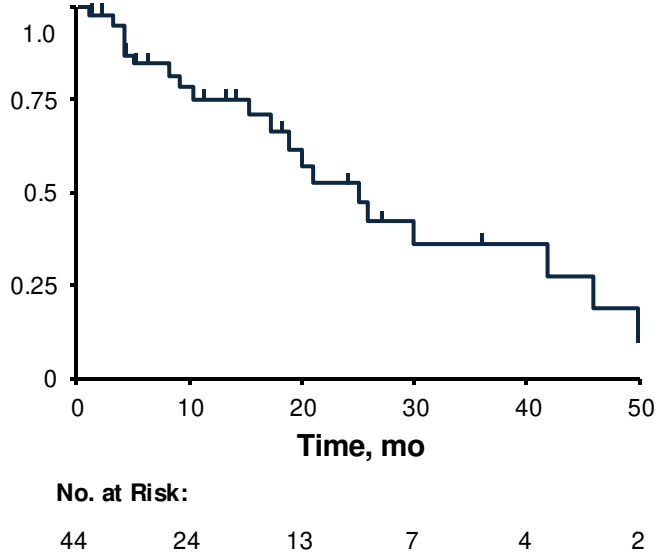


ORR to Ven2



- ORR to Ven2 was 79.5
- ORR of 56.3% in BTKi-exposed patients

PFS for Ven2



Although prospective studies are needed, the high ORR and durability of observed remissions support venetoclax re-treatment, and it appears to be highly active in "double-exposed" CLL

CR = complete response; PD = progressive disease; SD = stable disease; Ven1 = first treatment with a venetoclax-based regimen; Ven2 = re-treatment with a second venetoclax-based regimen.

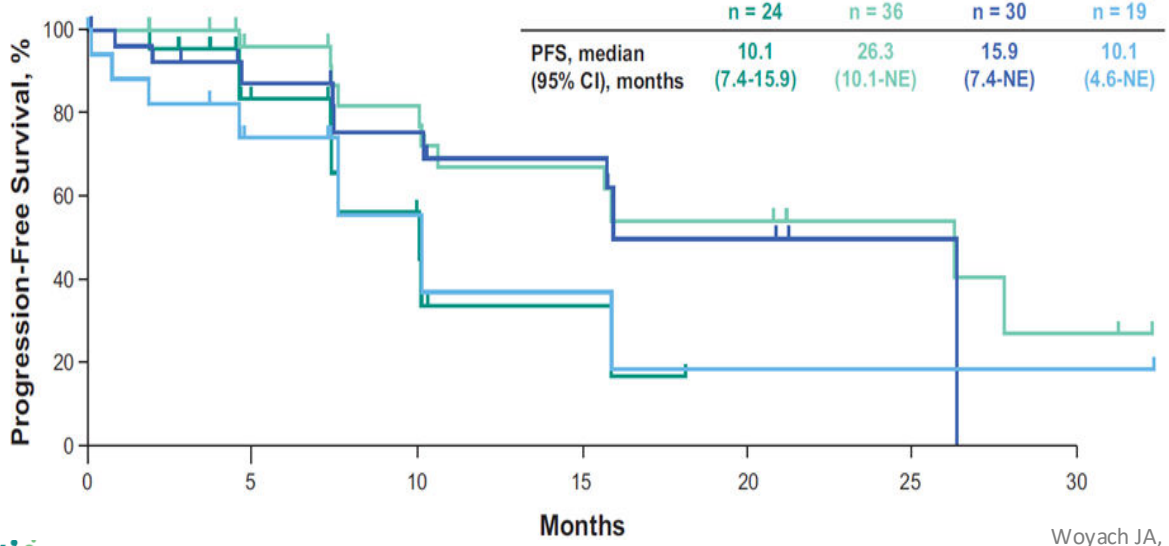
Thompson M, et al. *Blood Adv*. 2022;6:4553-4557.

BELLWAVE-001: Nemtabrutinib

- Phase 1/2, open-label
- Cohort A: ≥2 prior therapies, including a covalent BTKi, with a C481 mutation
- Cohort B: ≥2 prior therapies, intolerant to a BTKi, without a C481 mutation

PFS in Subgroups of Patients with CLL/SLL

	Prior BTK and BCL2 inhibitors n = 24	*BTK*^{C481S} mutated n = 36	No *IGHV* mutation n = 30	del(17p) n = 19
PFS, median (95% CI), months	10.1 (7.4-15.9)	26.3 (10.1-NE)	15.9 (7.4-NE)	10.1 (4.6-NE)



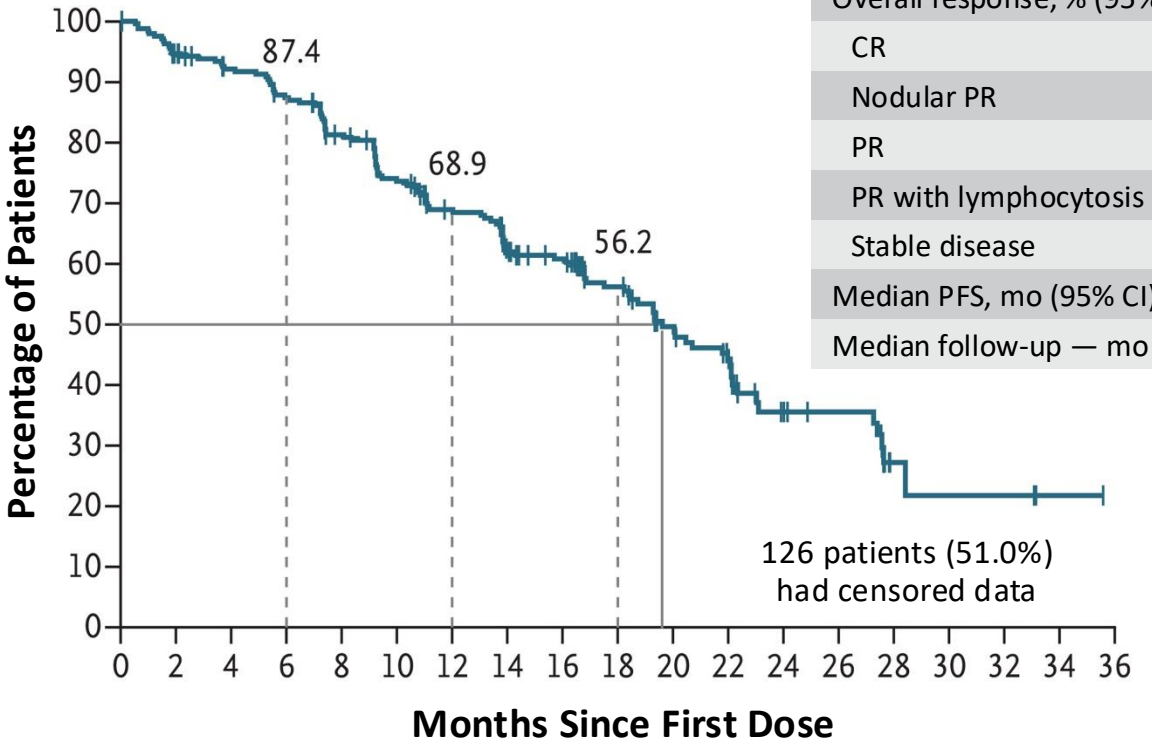
Woyach JA, et al. *Blood*. 2022;140(Suppl 1):7004–7006.
Woyach J, et al. 2023 European Hematology Association Congress. Abstract P628.

BRUIN: Pirtobrutinib After cBTKi in CLL

- Phase 1/2, open-label, pirtobrutinib monotherapy, N = 247
- Median 3 prior therapies (100% cBTKi, 88% anti-CD20, 79% chemotherapy, 41% BCL2i, 18% PI3Ki)
- 29% del(17p), 39% *TP53*-mut, 85% unmutated IGHV
- 38% *BTK-C481* mutation
- Discontinued prior cBTKi due to toxicity (23%) and disease progression (77%)

Mato AR, et al. *N Engl J Med.* 2023;389(1):33-44.

BRUIN: Pirtobrutinib After cBTKi in CLL

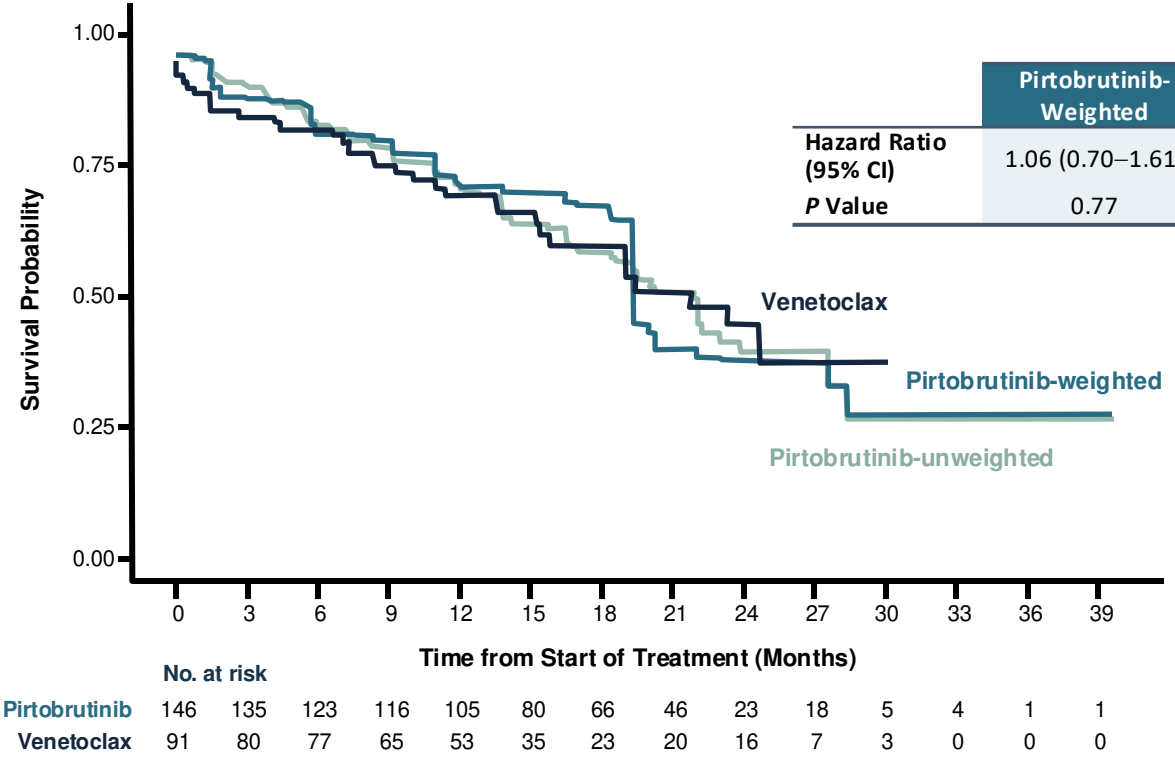


	Previous cBTKi (N = 247)	Previous cBTKi + BCL2i (N = 100)
Overall response, % (95% CI)	82.2 (76.8–86.7)	79.0 (69.7–86.5)
CR	4 (1.6)	0
Nodular PR	1 (0.4)	0
PR	176 (71.3)	70 (70.0)
PR with lymphocytosis	22 (8.9)	9 (9.0)
Stable disease	26 (10.5)	11 (11.0)
Median PFS, mo (95% CI)	19.6 (16.9–22.1)	16.8 (13.2–18.7)
Median follow-up — mo	19.4	18.2

CI = confidence interval.

Mato AR, et al. *N Engl J Med*. 2023;389(1):33-44.

MAIC of Pirtobrutinib vs Venetoclax in BTKi-Pretreated CLL



	Pirtobrutinib-Weighted	Pirtobrutinib-Unweighted
Hazard Ratio (95% CI)	1.06 (0.70–1.61)	1.01 (0.58–1.73)
P Value	0.77	0.98

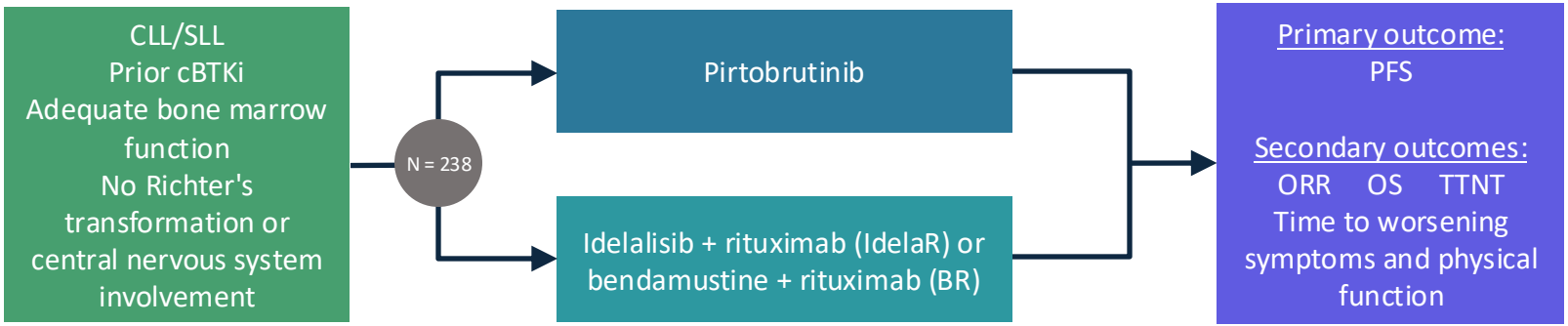
No. at risk														
Pirtobrutinib	146	135	123	116	105	80	66	46	23	18	5	4	1	1
Venetoclax	91	80	77	65	53	35	23	20	16	7	3	0	0	0

An MAIC comparing pirtobrutinib vs venetoclax in cBTKi-pretreated CLL suggests either can be effective

MAIC = matching-adjusted indirect comparison.

Al-Sawaf O, et al. *Haematologica*. 2024;109(6):1866-1873.

BRUIN CLL-321: Pirtobrutinib vs Idelalisib + Rituximab or Bendamustine + Rituximab After Prior cBTKi



Pirtobrutinib vs IC, at 11.6-Month Follow-up (HR, 95% CI)	
PFS	0.55 (0.38-0.78); *P* = .0007
With prior venetoclax	0.54 (0.33-0.86)
With complex karyotype	0.34 (0.21-0.56)
With *TP53*mut/del(17p)	0.52 (0.33-0.84)
Event-free survival	0.35 (0.25-0.50)
TTNT	0.38 (0.25-0.56)
OS	Not mature

Most common TEAE (≥15%) in pirtobrutinib arm
- Anemia 20.7%
- Pneumonia 19.8%
- Neutropenia 16.4%
- Diarrhea 15.5%

Grade ≥ 3 TEAE occurred in 55% vs 72%, pirtobrutinib vs IC
- Discontinuation due to TRAE: 5.2% vs. 18.3%
- Dose reductions due to AE: 7.8% vs. 28.4%
- Any grade atrial fibrillation/flutter: 2.6% vs 0.9%
- Any grade hypertension: 6.0% vs 3.7%
- Grade > 3 hemorrhage: 0.9% each arm

HR = hazard ratio; IC = investigator's choice; OS = overall survival; TEAE = treatment-emergent AE; TRAE = treatment-related AE; TTNT = time to next treatment.

ClinicalTrials.gov Identifier: NCT04666038. Last updated 2024. Sharman JP, et al. *Blood*. 2024;144:886.

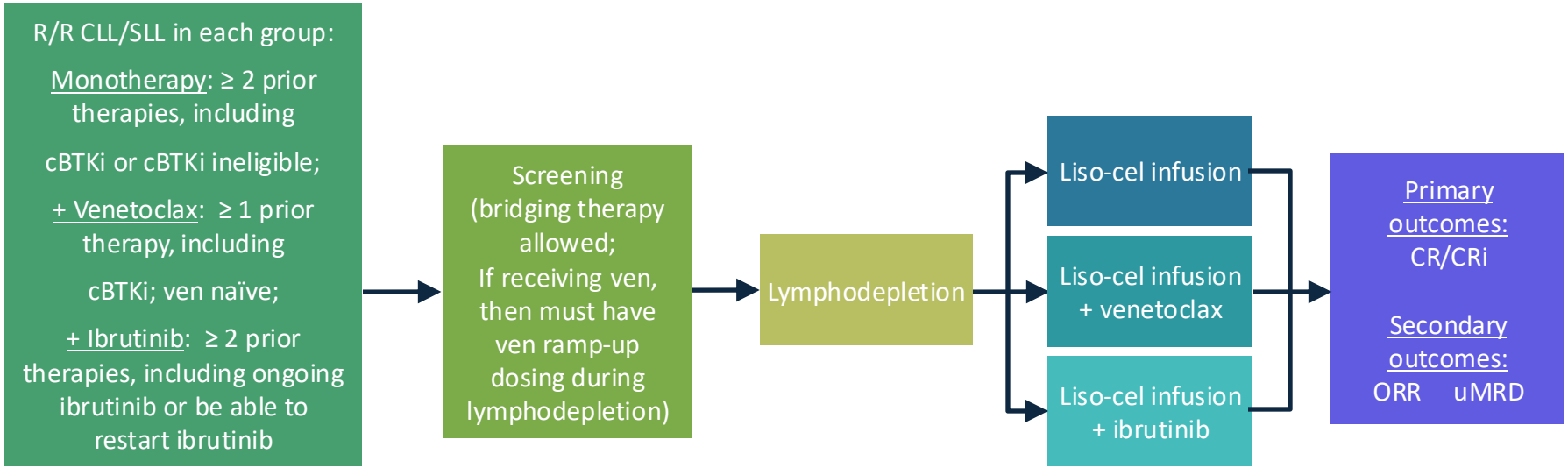
Pirtobrutinib/Venetoclax After cBTKi in CLL

- Phase 1b, open-label, fixed-duration pirtobrutinib plus venetoclax (PV; n = 15) or pirtobrutinib plus venetoclax and rituximab (PVR; n = 10) for 25 cycles
- Median 2 prior therapies (68% cBTKi, 72% anti-CD20, 56% chemotherapy, 12% PI3Ki)
- 39% *BTK-C481* mutation
- Discontinued prior cBTKi due to toxicity (29%) and disease progression (71%)

	PV (n = 15)	PVR (n = 10)
ORR, % (95% CI)	93.3 (68.1-99.8)	100 (69.2-100)
CR	46	30
PR	46	70
SD	7	0
PD	0	0

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

TRANSCEND CLL 004: Liso-cel CAR T-Cell Therapy in R/R CLL



- Primary and key secondary endpoints were tested in a prespecified subset of patients with BTKi progression and venetoclax failure (PEAS) at DL2 by the following hierarchy: CR/Cri rate ($H_0 \leq 5\%$), ORR ($H_0 \leq 40\%$), and uMRD rate in blood ($H_0 \leq 5\%$)

Duration of follow-up was increased to 48 months in protocol amendment 5 (February 16, 2021). Patients still in ongoing response per iwCLL 2018 criteria after the 2-year follow-up were followed for safety, disease status, additional anticancer therapies, and survival for an additional 2 years or until progression.
DL = dose level; uMRD = undetectable minimal residual disease.
Siddiqi T, et al. *Lancet*. 2023;402(10402):641-654.

TRANSCEND CLL 004: Liso-cel Monotherapy

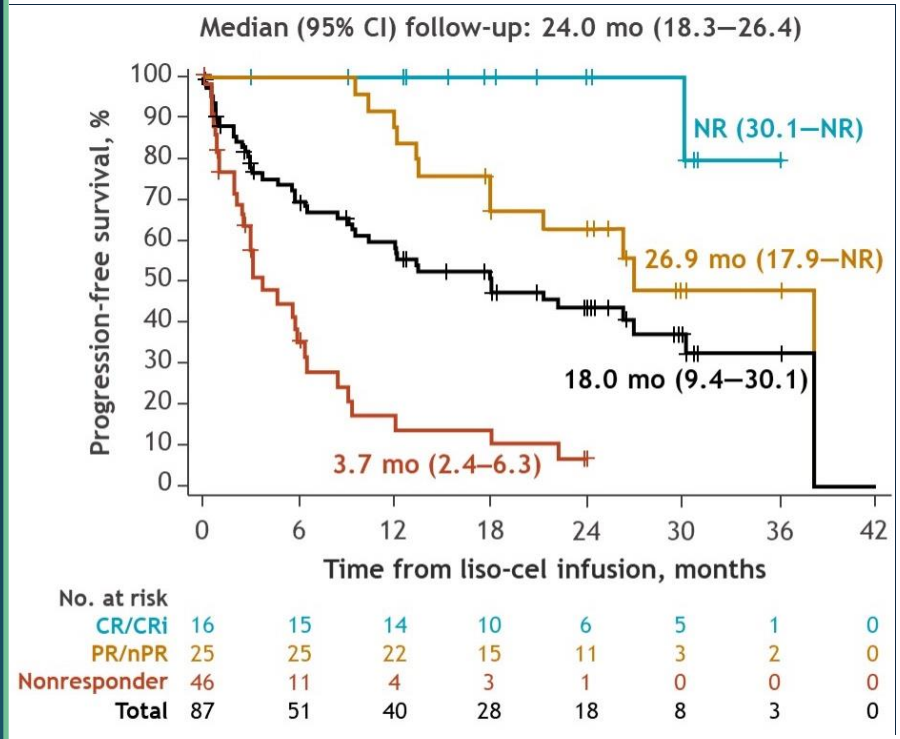
Efficacy	Full Study Population at DL2 (n = 87)	BTKi Progression/ Venetoclax Failure Subset at DL2 (N = 49)
Primary endpoint: IRC-assessed CR/CRi rate (95% CI) per iwCLL 2018, %	18 (11–28)	18 (9–32); *P* = 0.0006*
Key secondary endpoints:		
IRC-assessed ORR (95% CI), %	47 (36–58)	43 (29–58); *P* = 0.3931*
uMRD rate in blood (95% CI), %	64 (53–74)	63 (48–77)†
Exploratory endpoint: uMRD rate in marrow (95% CI), %	59 (48–69)	59 (44–73)
Other secondary endpoints:		
Best overall response, n (%)		
CR/CRi	16 (18)	9 (18)
PR/nPR	25 (29)	12 (24)
SD	34 (39)	21 (43)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Median (range) time to first response, months	1.5 (0.8–17.4)	1.2 (0.8–17.4)
Median (range) time to first CR/CRi, months	4.4 (1.1–17.9)	3.0 (1.1–6.1)

- All MRD-evaluable responders were uMRD in blood and marrow; 12 of 20 MRD-evaluable patients with SD were uMRD in blood

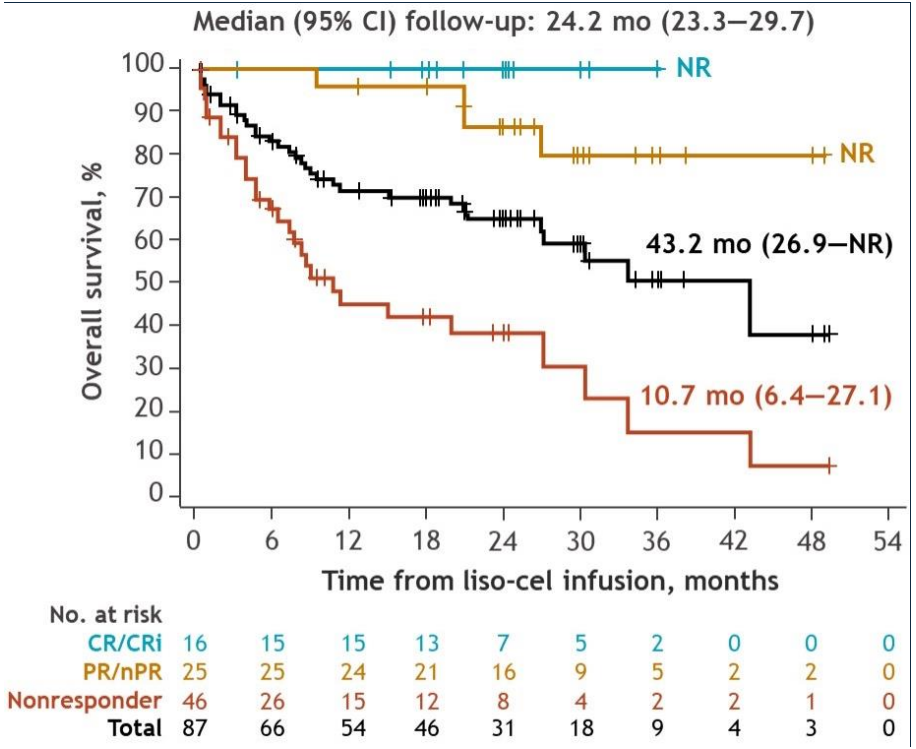
*One-sided *P* value from binomial exact test (H_0 of CR/CRi ≤ 5%; H_0 of ORR ≤ 40%); †*P* value not presented for uMRD rate in blood (H_0 ≤ 5%) because the ORR hypothesis was not rejected at one-sided 2.5% significance level.
MRD = minimal residual disease; nPR = nodular PR; SD = stable disease.
Siddiqi T, et al. *Lancet*. 2023;402(10402):641-654.

TRANSCEND CLL 004: Liso-cel Monotherapy

Progression-Free Survival



Overall Survival



Siddiqi T, et al. *Lancet.* 2023;402(10402):641-654.

TRANSCEND CLL 004: Liso-cel + Ibrutinib

Efficacy	Full Study Population at DL2 (n = 56)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, % (95% CI)	45 (31.1-59.7)
Key secondary endpoints: IRC-assessed ORR (95% CI), % uMRD rate in blood (95% CI), %	 86 (73.7-94.3) 86 (73.7-94.3)
Exploratory endpoint: uMRD rate in marrow, % (95% CI)	84 (71.4-93.0)
Other secondary endpoints: Median (range) time to first response, months Median (range) time to first CR/CRi, months PFS, months OS, months	 1.0 (0.9–6.0) 3.1 (0.9-12.1) 31.4 NR

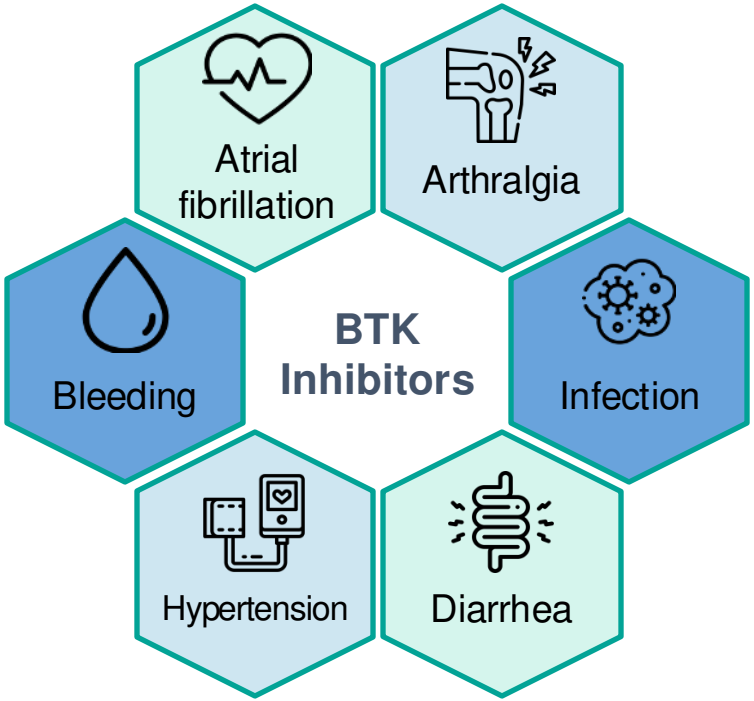
Wierda WG, et al. *Blood*. 2024;144:887.

Patient Case 1 (continued)

- Selecting and sequencing of third-line CLL therapies in patients exposed to BTKi/Ven
- How do prior AEs affect choice?

Overview of BTK Inhibitor Toxicities in CLL

Common Toxicities



Additional Important Toxicities

- Dermatologic changes
- Fatigue
- Ventricular arrhythmia
- Cytopenias

Nixon S, et al. *Curr Oncol*. 2023;30(4):4222-4245.

Serious AEs of BTK Inhibitors

- Hemorrhage
- Atrial fibrillation and flutter; risk factors include:
  - Age ≥ 65, male, history of atrial fibrillation, hypertension, hyperlipidemia, or pre-existing cardiac disease
- Grade ≥ 3 infections, including opportunistic infections
- Grade 3–4 cytopenias
- Secondary primary malignancies

BTKi	Secondary Primary Malignancies
Ibrutinib	10% total, most common was non-melanoma skin cancer 4%
Acalabrutinib	12% total, most common was skin cancer 6%
Zanubrutinib	14% total, most common is non-melanoma skin cancer 8%, solid tumors 4%
Pirtobrutinib	9% total, most common was non-melanoma skin cancer 4%

Lipsky A, Lamanna N. *Am Soc Hematol Educ Program*. 2020;(1):336-345. Mato AR, et al. *N Engl J Med*. 2023;389:33-44. Nixon S, et al. *Curr Oncol*. 2023;30(4):4222-4245.

Lymphocytosis

- Anticipate that your patient may have asymptomatic lymphocytosis after starting therapy with BTK inhibitor
  - Do not mistake this for progressive disease if lymph nodes are decreased
  - Peaks at 1–2 months, followed by slow decline
- Does not require any specific management even when persistent for months
- In a subset of patients, lymphocytosis never resolves; does not affect long-term outcome
  - Due to lymphocyte redistribution

Brown JR. *Blood*. 131(4):379-386.

Bleeding

- Typically presents as bruising and, while it may be concerning to patients, is typically benign

Management Strategies

Grade 1 or 2

- If bleeding, may hold BTK inhibitor
- Resume at same dose
- Monitor

Grade ≥ 3

- Hold BTK inhibitor until bleeding resolves
- Consider transfusing platelets
- Resume at lower dose once bleeding resolves

Procedures

- Hold BTK inhibitor before and after procedure:
  - Minor: 3 days
  - Major: 7 days

Lipsky A, et al. *Hematology Am Soc Hematol Educ Program*. 2020;2020:336-345.

Atrial Fibrillation

Risk Factors

- Older age (≥ 65)
- Male sex
- History of atrial fibrillation
- Hypertension
- Hyperlipidemia
- History of pre-existing cardiac disease

Higher Incidence with Ibrutinib
10% incidence in RESONATE-2 trial

Time to Onset
Median: 2.8 months but can occur any time

Management

Cardiology consultation

CHA2DS2VASc Score 0-1

- Continue BTKi at current dose
- Rate/rhythm control
  - Beta blockers preferred
  - Avoid P-glycoprotein substrates (digoxin, amiodarone) and CYP3A4 inhibitors (verapamil, diltiazem)

CHA2DS2VASc Score ≥ 2

- Hold BTKi until atrial fibrillation control
- Need to treat with anticoagulant
  - DOAC preferred: apixaban 2.5 mg PO BID given CYP3A4 interaction) or LMWH
  - Avoid use of warfarin
- Consider alternative therapy

DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; PO = orally.

Moore DC, Thompson D. *J Adv Pract Oncol*. 2021;12(4):439-447. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program*. 2020;2020:336-345. Stephens DM, Byrd JC. *Blood*. 2019;133(12):1298-1307. Barr PM, et al. *Haematologica*. 2018;103(9):1502-1510.

Management of BTKi AEs: Summary Table

Adverse Event	Management Strategy
Diarrhea	Use antidiarrheal medication (e.g., loperamide) as needed
Headache	Prior to treatment initiation, advise patients that headaches should abate quickly, are easily managed, and are not a long-term consequence of treatment; after treatment initiation, use acetaminophen or caffeine and avoid NSAIDS
Hypertension	Monitor for treatment-emergent HTN, manage with anti-HTN medication, reduce anti-HTN medication dose once BTKis are discontinued
Infection	Consider prophylaxis for patients at an increased risk of opportunistic infection, monitor for signs/symptoms of infection and treat as needed (consider drug-drug interactions with BTKi)
Myalgia/arthralgia	Grade 1 myalgias/arthralgias may not need intervention, use dose reduction or dose interruption as appropriate

O'Brien SM, et al. *Front Oncol*. 2021;11:720704. Nixon S, et al. *Curr Oncol*. 2023;30(4):4222-4245.

Management of BTKi AEs: Summary Table (continued)

Adverse Event	Management Strategy
Nausea	BTKis can be taken at night, but also utilize antinausea therapies to manage
Neutropenia	• 1st–3rd occurrences of grade 3–4: growth factor support is recommended, and dose interruptions can be considered • 4th occurrence: discontinuation of the BTKi should be considered
Rash	Topical steroids and/or oral antihistamines
Thrombocytopenia	• 1st–3rd occurrences of grade 3–4: dose interruptions should be considered • 4th occurrence: discontinuation of the BTKi is recommended (unless thrombocytopenia is related to CLL infiltration in the bone marrow)

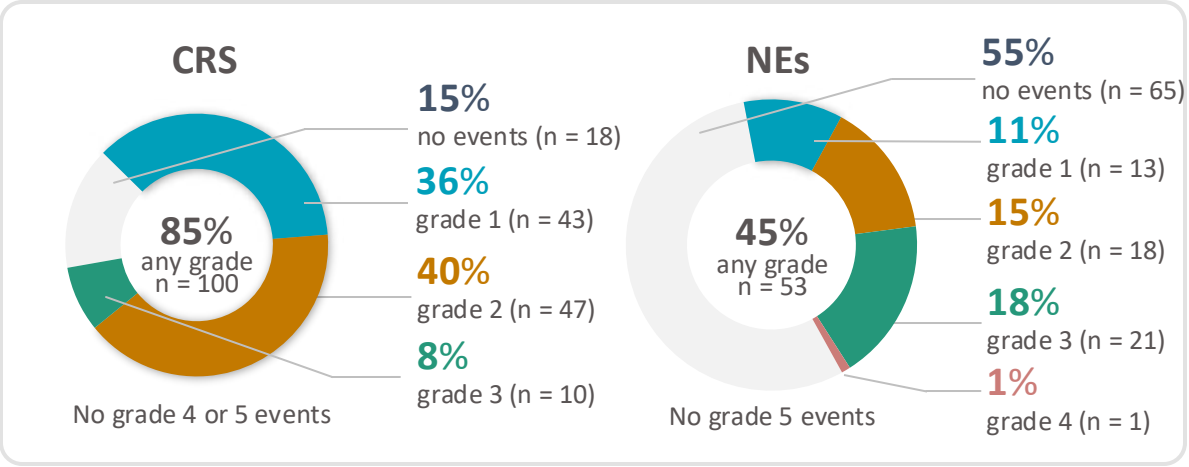
O'Brien SM, et al. *Front Oncol*. 2021;11:720704. Nixon S, et al. *Curr Oncol*. 2023;30(4):4222-4245.

MAIC of Venetoclax vs Pirtobrutinib in BTKi-Pretreated CLL

	Venetoclax (n = 91)	Pirtobrutinib (unweighted) (n = 146)	Unweighted OR (95% CI), *P* Value	Pirtobrutinib (weighted)	Weighted OR (95% CI), *P* Value
Anemia	28.6%	5.5%	0.15 (0.05–0.35), *P* < .001	1.3%	0.04 (0.004–0.16), *P* < .001
Febrile Neutropenia	13.2%	1.4%	0.09 (0.01–0.43), *P* < .001	1.4%	0.10 (0.01–0.47), *P* < .001
Neutropenia	50.5%	19.9%	0.24 (0.13–0.45), *P* < .001	20.3%	0.25 (0.13–0.47), *P* < .001
Thrombocytopenia	28.6%	1.4%	0.04 (0.004–0.15), *P* < .001	1.1%	0.02 (0.00–0.12), *P* < .001
Pneumonia	6.6%	5.5%	0.82 (0.24–2.98), *P* = 0.78	1.2%	0.22 (0.02–1.25), *P* = .06
Treatment Discontinued Due to AEs	6.6%	7.5%	1.15 (0.37–3.95), *P* = 1.00	2.9%	0.44 (0.09–1.92), *P* = .32

MAIC = matching-adjusted indirect comparison.
Al-Sawaf O, et al. Haematologica. 2024;109(6):1866-1873.

TRANSCEND CLL 004: Liso-cel, Monotherapy



	Total (n = 118)	
	CRS	NE
Patients with an event, n (%)	100 (85)	53 (45)
Median (range) time to onset, days	4 (1–18)	7 (1–21)
Median (range) time to resolution, days	6 (2–37)	7 (1–83)
Received tocilizumab and/or corticosteroids for CRS and/or NE	82 (69)	

Other AESIs, n (%)

- Prolonged cytopenias: 64 (54%)
- Grade ≥ 3 infections: 21 (18%)
- Hypogammaglobulinemia: 18 (15%)
- Tumor lysis syndrome: 13 (11%)
- SPM: 11 (9%)
- MAS: 4 (3%)

Deaths due to TEAEs, n = 5 (4%)

- 4 (3%) considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *E coli* infection, and invasive aspergillosis)
- 1 (1%) considered related to liso-cel by investigators (MAS)

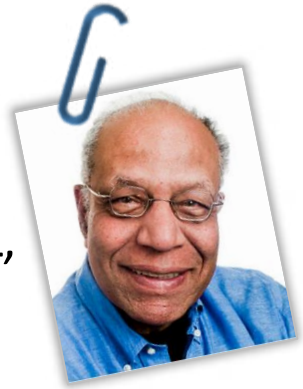
AESI = AE of special interest; CRS = cytokine release syndrome; MAS = macrophage activation syndrome; NE = neurological event; SPM = second primary malignancy.

Siddiqi T, et al. *Lancet*. 2023;402(10402):641-654.

Patient Case 1 (continued)

- Selecting and sequencing of third-line CLL therapies in patients exposed to BTKi/Ven
  - How do prior AEs affect choice?
  - How do expected AEs affect choice?

Patient Case 1 (continued)



- Summary of case
  - A 62-year-old man receives front-line ibrutinib therapy for CLL, achieving a PR for 8 years
  - Now at age 70, his CLL recurs with a *TP53* mutation
  - He starts on venetoclax + anti-CD20 MAb and achieves a PR with undetectable minimal residual disease (MRD) and small residual lymphadenopathy for 2 years
  - His CLL again recurs

- What do you recommend for this patient?

Mantle Cell Lymphoma (MCL)

Patient Case: 2

A 55-year-old female patient diagnosed with stage IVB MCL after presenting with thrombocytopenia and splenomegaly

Medical history includes hypertension, GERD, type 2 diabetes (insulin dependent), and mild peripheral neuropathy

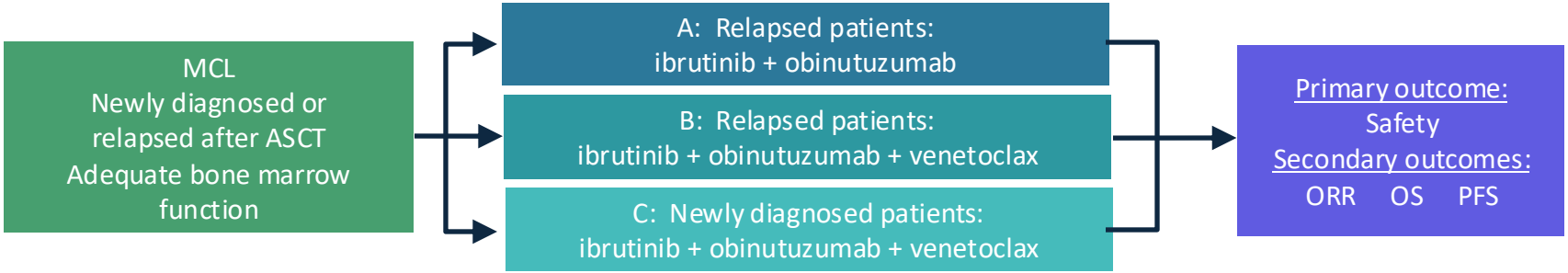
Treatment includes:

- Hyper-CVAD + rituximab, achieving a complete response
- Consolidated with autologous stem cell transplant
- Relapsed 5 years later, started ibrutinib

After 2 years on ibrutinib, she develops steadily progressive lymph nodes that are now bulky

What are her treatment options and what do you recommend?

OASIS: Ibrutinib + Obinutuzumab + Venetoclax for MCL, 5-Year Follow-up



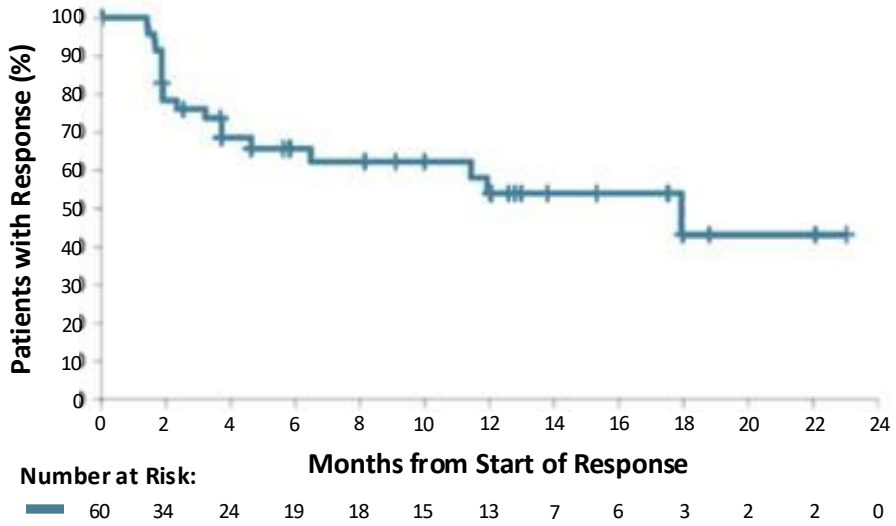
	A: ibr + obi (n = 9)	B: ibr + obi + ven (n = 24)	C: ibr + obi + ven (n = 15)
ORR	89%	71%	93% (87% CR)
6-yr PFS	53%	40%	NR
5-yr PFS	NR	NR	80%

NR = not reached.

Le Gouill S, et al. *Blood*. 2021;137(7):877-887. Tessoulin B, et al. *Blood*. 2024;144(Suppl 1):1657.

BRUIN: Duration of Response of Pirtobrutinib for R/R MCL

- Median follow-up of 8.2 months (range, 1.0 to 27.9 months) for responding patients
- 60% (36 of 60) of responses ongoing 101
- Updated data for cBTKi pre-treated cohort (n = 90):
  - Median response follow-up of 12 months
  - Median DOR by IRC among the 52 responders: 21.6 months
  - Among responding patients, 35% of responses were ongoing at the time of data cutoff, with the longest ongoing response: 26.2 months
  - Efficacy also seen in patients with prior stem cell transplant and CAR-T therapy



DOR = duration of response; IRC = independent review committee.

Adapted from Eyre TA, et al. EHA 2022. Abstract P1101. Wang ML, et al. *J Clin Oncol*. 2023;41(24):3988-3997.

Real-World Efficacy of Pirtobrutinib for R/R MCL

- Retrospective analysis of the efficacy and safety profile of pirtobrutinib in 10 patients with relapsed/refractory MCL, from compassionate use program (CUP)
  - Median 3 lines prior therapy, including cBTKi (9 of 10 patients)
  - Median follow-up, 8.6 months
  - Cross-trial comparison with results of patients with MCL in BRUIN

	CUP (n = 10)	BRUIN	
		cBTKi Pretreated MCL (n = 90)	cBTKi-Naive MCL (n = 14)
Overall response rate, % (95% CI)	70 (34.8 - 93.3)	57.8 (46.9 - 68.1)	85.7 (57.2 - 98.2)
CR	1 (10)	18 (20.0)	5 (35.7)
PR	6 (60)	34 (37.8)	7 (50)
SD	1 (10)	14 (15.6)	—
PD	2 (20)	15 (16.7)	1 (7.1)
Not evaluable	—	9 (10.0)	1 (7.1)
12 months DOR	71.40%	57.10%	
DOR, months, median (95% CI)	NR (2.37 - NR)	21.6 (7.5 - NR)	NR (NR - NR)
12 months PFS	56%	40%	
PFS, months, median (95% CI)	NR (2.56 - NR)	7.4 (5.3 - 12.5)	NR (NR - NR)
OS, months, median (95% CI)	NR (2.73 - NR)	NR (14.8 - NR)	NR (NR - NR)

De SK. *Curr Med Chem*. 2024;31(30):4757-4762. Aydilek E, et al. *Cancer Med*. 2024;13(10):e7289.

Real-World Efficacy of Subsequent Lines of Therapy

- While responses are very common with CAR T-cell therapy, the duration of response is highly variable
- Shorter DOR is associated with shorter PFS and OS

For patients with **MCL**, post cBTKi, ncBTKi, and CAR T-cell therapy are recommended by the NCCN

Outcomes for Patients Relapsing Post CAR T-Cell Therapy in French DESCAR-T Registry (15.3-month follow-up)

	ORR	OS2
Lenalidomide/rituximab	19%	6.7 months
Chemo(immuno)therapy	23%	5.8 months
CD3xCD20 bispecific antibody	43%	Not reached
Radiation	50%	11.3 months
cBTKi/Venetoclax	0%	2.8 months
ncBTKi	not available for study	

Aymard M, et al. *Blood*. 2024;144:239.
NCCN Clinical Practice Guidelines in Oncology, B-cell lymphomas, Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

Patient Case 2 (continued)

- Summary of case
  - A 55-year-old female patient diagnosed with stage IVB MCL receives hyper-CVAD + rituximab, achieving a CR, followed by auto-SCT
  - Relapsed 5 years later, started ibrutinib
  - After 2 years on ibrutinib, she develops steadily progressive lymph nodes that are now bulky

- What do you recommend for this patient?

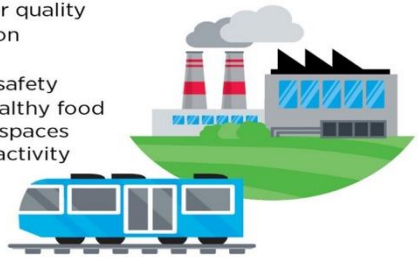
Barriers to Cancer Care

U.S. Cancer Disparities

Complex and interrelated factors contribute to cancer health disparities in the United States. Adverse differences in many, if not all, of these factors are directly influenced by structural and systemic racism. The factors may include, but are not limited to, differences or inequalities in:

ENVIRONMENTAL FACTORS

- Air and water quality
- Transportation
- Housing
- Community safety
- Access to healthy food sources and spaces for physical activity



BEHAVIORAL FACTORS

- Tobacco use
- Diet
- Excess body weight
- Physical inactivity
- Adherence to cancer screening and vaccination recommendations

SOCIAL FACTORS

- Education
- Income
- Employment
- Health literacy

CLINICAL FACTORS

- Access to health care
- Quality of health care

CULTURAL FACTORS

- Cultural beliefs
- Cultural health beliefs

PSYCHOLOGICAL FACTORS

- Stress
- Mental health

BIOLOGICAL AND GENETIC FACTORS

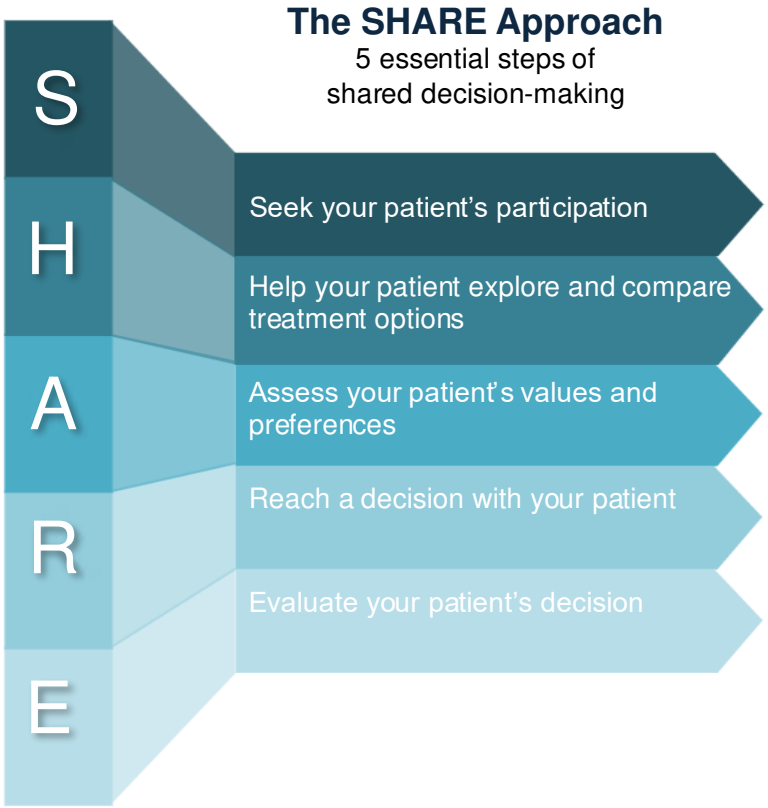
Mitchell E, et al. *J Natl Med Assoc*. 2022.
National Cancer Institute Website. 2024. https://www.cancer.gov/about-cancer/understanding/disparities.

Barriers to Cancer Care

- Insurance or financial resources
- Regular source of medical care
- Access to screening and treatment
- Reliable transportation and/or proximity to care
- Culturally and/or linguistically aligned health providers
- Culturally relevant cancer materials and programs
- Accessible educational and psychosocial support

American Association for Cancer Research (AACR) Website. 2024. https://cancerprogressreport.aacr.org/disparities/.

Building Trust: Shared Decision-Making



Finding the right treatment options will help optimize patient experience, drug adherence, and outcomes

Agency for Healthcare Research and Quality Website. 2024. https://www.ahrq.gov/sdm/share-approach/index.html.

Starting a Patient on a BTK Inhibitor

Multidisciplinary team

- Consistent messaging from across the team is critical to avoid patient confusion

Patient and caregiver counseling

- Reduces confusion and a key to compliance

Patient follow-up and continuity of care

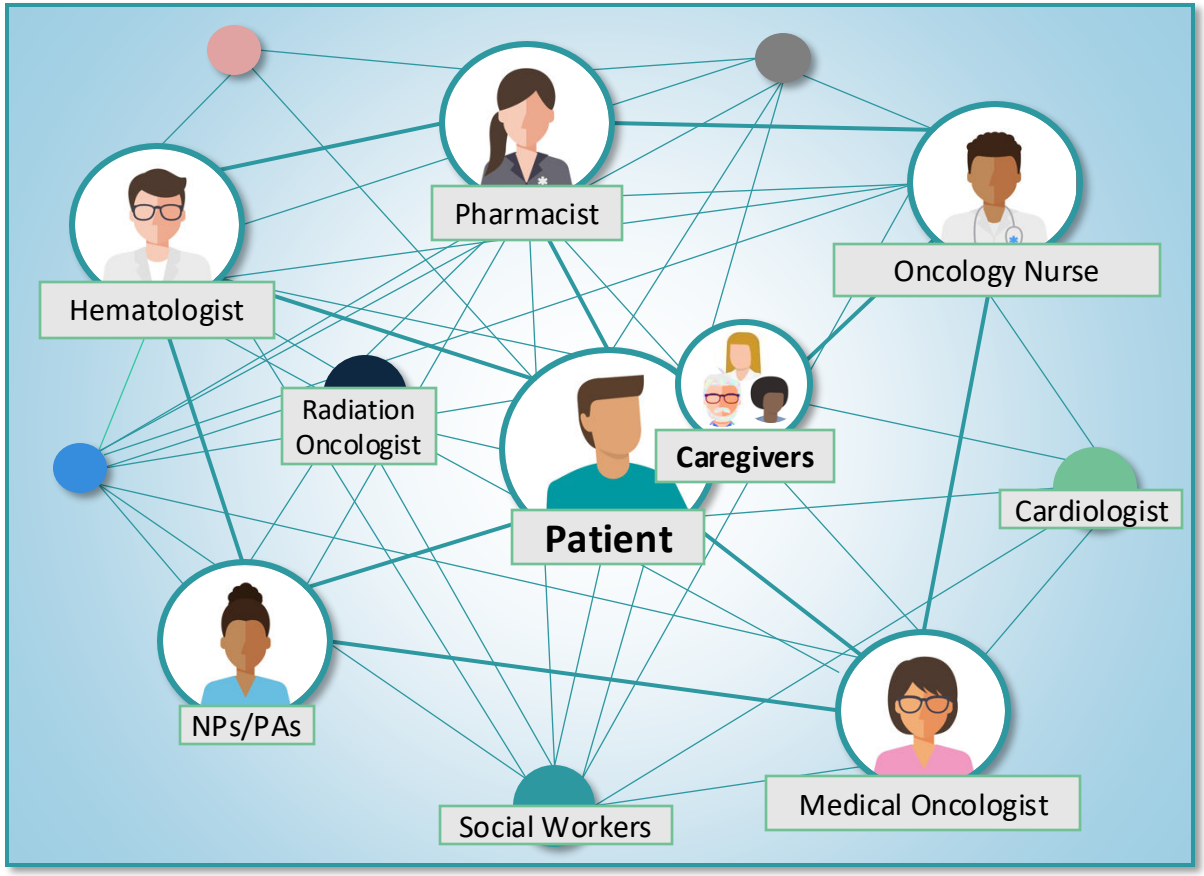
- Important way to catch side effects early and when more easily managed

Continuity of Care

- Continuity of care (CoC): the extent to which healthcare services are received and coordinated, including uninterrupted succession of events consistent with the medical needs of patients
  - Strong relationship between greater CoC and reduced health care resource utilization and improved outcomes in patients with solid tumors
- Current study used data from Optum's de-identified insurance claims database of patients with CLL evaluated using Herfindahl-Hirschman Index (HHI) and CoC Score (CoCS)
- 4,859 patients examined: 77.5% received first-line cBTKi
  - Mean HHI 0.704 ±0.264 and CoCS 0.675 ±0.285
  - With every 0.100 unit increase in CoC score, there were:
    - Lower odds of having an emergency room (ER) visit
    - Lower number of total ER visits
    - Lower odds of inpatient hospitalization
    - Lower number of total hospitalizations
    - Lower hazard of death

Gaballa S, et al. *Blood*. 2024;144:5033.

Team-Based Approach for the Management of B-Cell Lymphomas



Summary

- BTK inhibitors are widely utilized in multiple hematologic malignancies, including CLL and MCL
- Covalent BTKIs are safe and effective
- Non-covalent BTKis can overcome resistance to covalent BTKis
- All BTKis with similar expected side effect, though some differences are seen between BTKis
- Shared decision-making is needed due to multiple options
- Comprehensive and ongoing patient education and diligent monitoring is critical to optimizing patient outcomes

Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- *Incorporate latest clinical trial data* regarding next-generation non-covalent BTK inhibitors into the care of patients with CLL/SLL and MCL, as documented by treatment selection in patient EHR charts.
- *Improve management of potential AEs* from treatment and provide clear patient education on steps that may mitigate AE severity.
- *Provide ideal patient care* by involving the whole care team. Document shared decision-making, patient education, potential barriers to care, and guideline-concordant therapy administration in patient EHR charts.

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

You will be able to download and print your certificate upon completion.

Advancements in the Management of Relapsed/Refractory B-Cell Malignancies

Integrating Recent Data into Practice to Improve Outcomes

This program is supported by an independent educational grant from Lilly.