Emerging Therapies and the Five-Year Outlook

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Disclosures

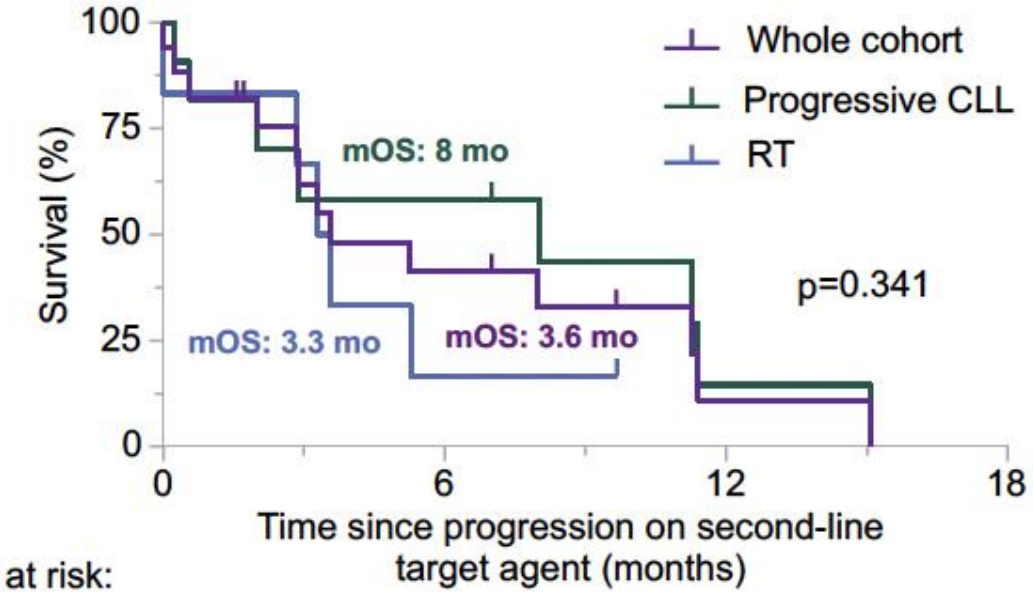
Honoraria/travel support: Astra Zeneca, BeOne, Lilly, Janssen

Advisory board: BeOne, Lilly

Double Refractory CLL

Poor outcomes in patients with double class-resistant CLL

OS after the development of PD on 2L targeted therapy (N=17)

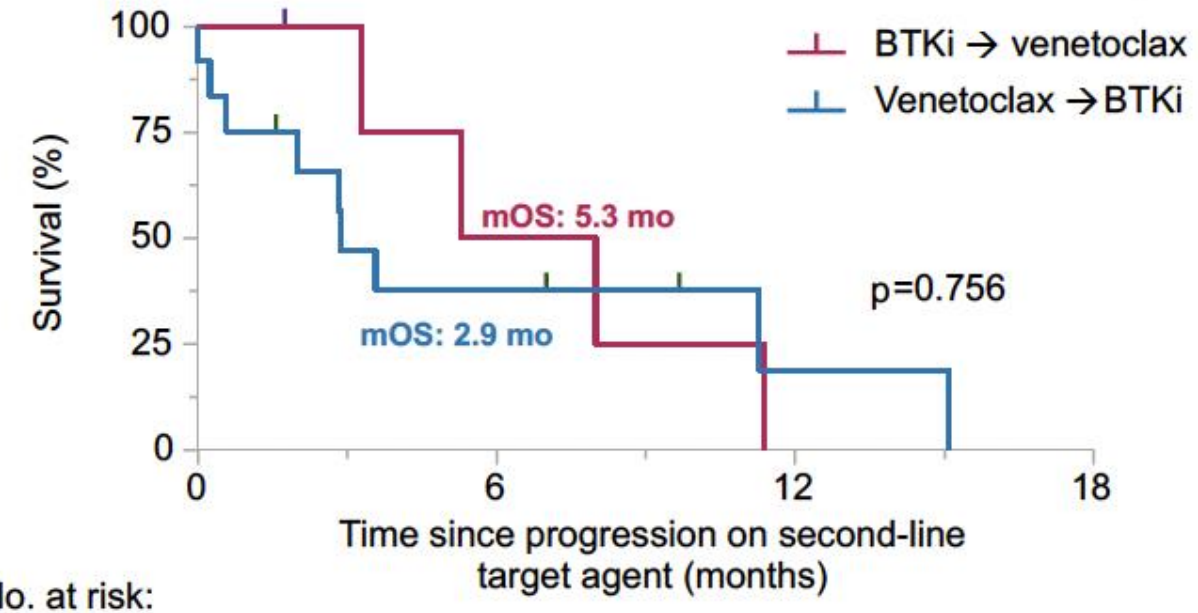


No. at risk:

Whole	17	9	6	4	1
CLL	11	5	5	3	1
RT	6	4	1	1	

No difference in OS between progressive CLL (8 months) and RT (3.3 months)

OS after the development of PD on 2L targeted therapy, stratified by prior sequencing of targeted agents (N=17)



No. at risk:

B→V	5	4	2	1	
V→B	12	5	4	3	1

BTKi, Bruton's tyrosine kinase inhibitor; RT, Richter's transformation.

Lew TE, *et al. Blood Adv* 2021; **5**:4054–4058.

Approaches in Double Refractory CLL

- Small molecule targeted therapies
  - Pirtobrutinib
  - Trials: other ncBTKi, BTK degraders, second generation BCL2i

- Immunotherapies
  - Bispecifics: epcoritamab, mosunetuzumab
  - Cellular therapies: lisocel, allograft

Evaluating the mutational profile when targeting BTK

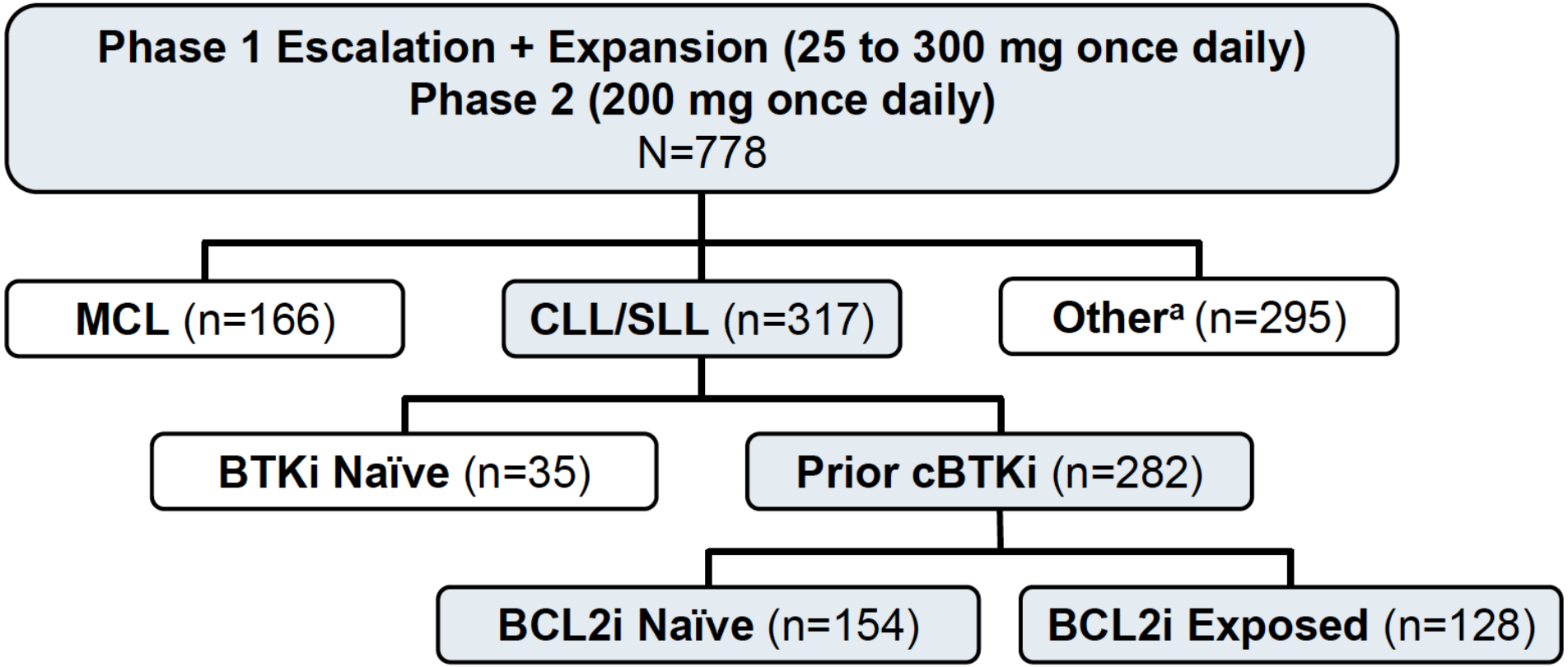
Table 1. Binding affinities and clinical efficacy of available BTKi to known mutations, relative to wild-type BTK [36,37,38,39].

		Wild-Type	C481S	T474I	L528W	A428D
Covalent BTKi	Ibrutinib	Normal	Decreased	Normal	Absent	Absent
	Acalabrutinib	Normal	Decreased	Decreased	Decreased	Absent
	Zanubrutinib	Normal	Decreased	Decreased	Absent	Absent
Non-covalent BTKi	Pirtobrutinib	Normal	Normal	Decreased	Absent	Absent
Dual covalent + noncovalent BTKi	LP-168	Normal	Normal	Normal	Absent	Absent
BTK Degraders	BGB-16673 NX-5948	Normal	Normal	Normal	Normal	Normal

- Jacobs, Cancers, 2025

Non-Covalent BTK Inhibitors

Pirtobrutinib in Post-BTKi CLL/SLL: Final Update From the Phase 1/2 BRUIN Study With > 5-Years Follow-Up



- Wierda et al, ASH, 2025

BRUIN Phase 1/2: cBTKi exposed CLL Cohort

Baseline Characteristics of Patients With CLL/SLL Who Received Prior cBTKi, and by BCL2i Exposure

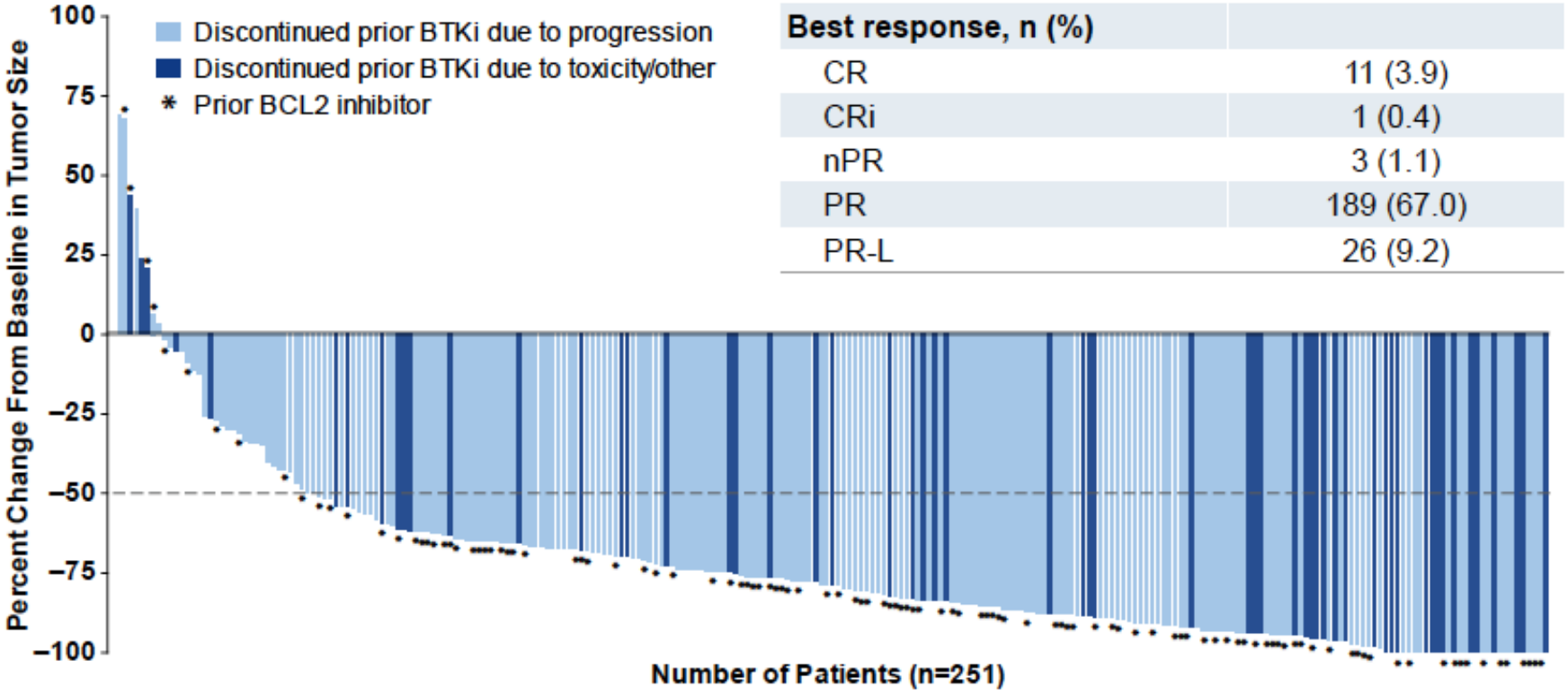
Characteristic	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age (range), years	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy (range)	4 (1-11)	3 (1-9)	5 (1-11)
Prior therapy, n (%)			
BTKi	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2i	128 (45)	0	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR-T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)
Median time from diagnosis to first dose (IQR), years	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation,[a] n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristic[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/N available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481 mutated	96/245 (39)	57/138 (41)	39/107 (36)
PLCg2 mutated	18/245 (7)	10/138 (7)	8/107 (8)
High-risk molecular features, n/N available (%)			
17p deletion and/or *TP53* mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

Excellent Response Rates in Prior cBTKi Treated CLL/SLL

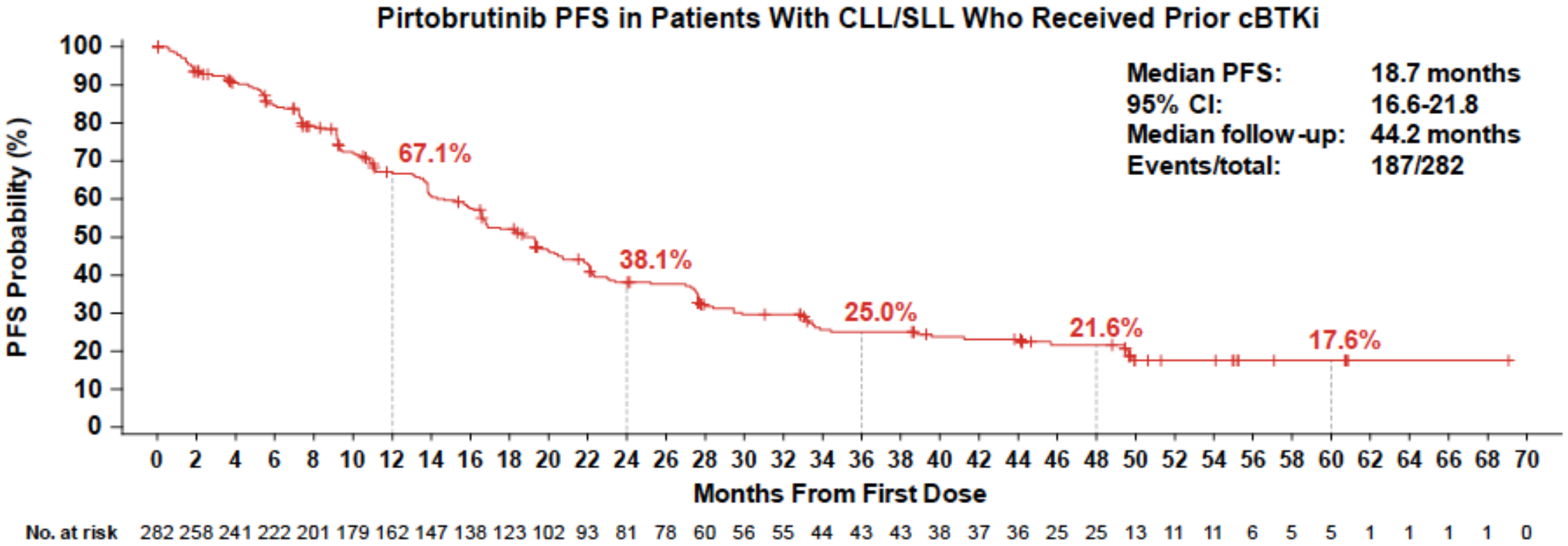
Response in Patients With CLL/SLL Who Received Prior cBTKi

Prior cBTKi	n=282[b]
ORR incl. PR-L,[a] (95% CI),%	81.6 (76.5-85.9)
Best response, n (%)	
CR	11 (3.9)
CRi	1 (0.4)
nPR	3 (1.1)
PR	189 (67.0)
PR-L	26 (9.2)



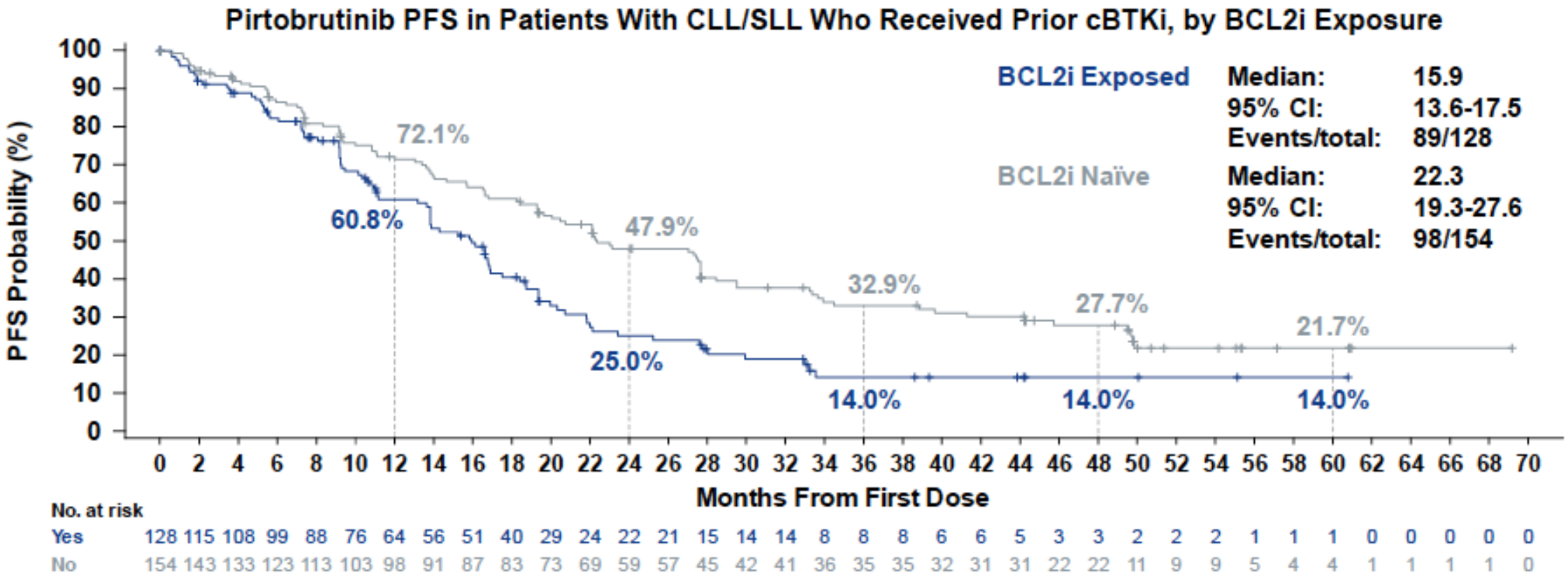
- Wierda et al, ASH, 2025

Pirtobrutinib PFS in CLL/SLL who Received Prior cBTKi



- Wierda et al, ASH, 2025

Pirtobrutinib PFS in Previously cBTKi Exposed Patients – By BCL2i exposure



- Wierda et al, ASH, 2025

Safety Profile

Safety Profile for Patients With CLL/SLL Who Received Prior cBTKi

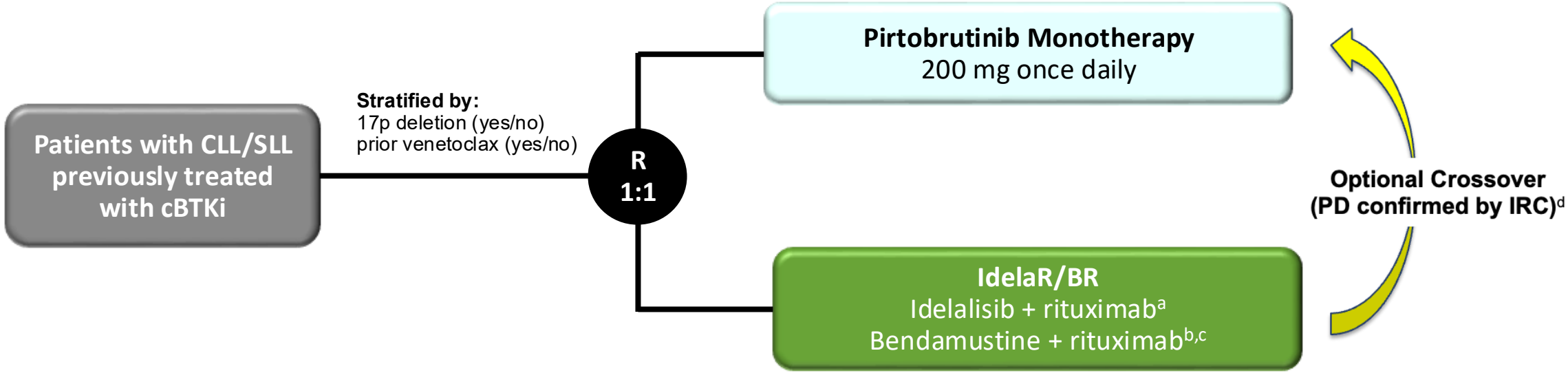
AE, ≥20%	TEAEs in Patients With CLL/SLL (n=282)			
	All-Cause AEs		Treatment-Related AEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	38.7	1.8	3.9	0.0
Neutropenia[a,b]	35.8	29.8	20.6	16.3
Diarrhea	30.5	0.4	8.9	0.0
Cough	29.8	0.0	2.1	0.0
Contusion	27.7	0.0	18.8	0.0
COVID-19	28.4	6.0	0.7	0.0
Dyspnea	23.4	2.5	0.7	0.4
Nausea	23.4	0.0	3.9	0.0
Abdominal pain	21.6	2.1	2.1	0.4
AEs of Interest[c]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	76.2	36.5	14.9	5.7
Bruising[e]	31.2	0.0	20.2	0.0
Rash[f]	25.2	1.1	5.7	0.4
Arthralgia	23.0	1.4	4.6	0.0
Hemorrhage[g]	25.2	3.2	8.2	1.4
Hypertension	16.0	5.3	3.9	0.7
Atrial fibrillation/flutter[h,i]	5.0	2.1	1.4	0.7

Median (IQR) time on treatment was 20.0 (9.6-37.7) months
11 (3.9%) patients had treatment-related AE leading to pirtobrutinib dose reduction
9 (3.2%) patients had treatment-related AE leading to pirtobrutinib discontinuation

- Wierda et al, ASH, 2025

BRUIN CLL-321 Study Design

First randomized Phase 3 clinical trial exclusively in patients with CLL/SLL previously treated with cBTKi



Key Eligibility

- Age ≥18
- ECOG PS 0-2
- Confirmed CLL/SLL requiring treatment per iwCLL 2018
- **Prior cBTKi required**
- **No limit on prior lines of therapy**
- **Prior history of atrial fibrillation allowed**

Key Endpoints

- **Primary Endpoint: PFS assessed by IRC**
- PFS assessed by investigator
- Event-Free Survival
- Time to Next Treatment
- Overall survival
- Safety

Treatment was given in 28-day cycles. PFS assessed based on iwCLL2018. [a]Idelalisib dosed at 150 mg PO BID. Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 4 infusions at 500 mg/m^2 every 2 weeks, next 3 infusions at 500 mg/m^2 every 4 weeks. [b]Bendamustine (70 mg/m^2) administered IV D1, D2 of cycles 1-6. [c]Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 5 infusions day 1 of cycle 2 through cycle 6 at 500 mg/m^2. [d]Eligible patients receiving investigator's choice of IdelaR/BR could crossover to receive pirtobrutinib monotherapy upon confirmation of PD by IRC per protocol and only if they met the eligibility criteria for treatment by iwCLL 2018.

Sharman et al. J Clin Oncol. 2025.

Patient and Disease Characteristics at Baseline

Includes patients with characteristics associated with poor prognosis and heavily pre-treated CLL/SLL

Characteristics	Pirtobrutinib n=119	IdelaR/BR n=119
Median Age, years (range)	66 (42-90)	68 (42-85)
Male, n (%)	83 (70)	83 (70)
Region, n (%)		
North America	24 (20)	39 (33)
Europe	76 (64)	63 (53)
Asia	14 (12)	15 (13)
Australia	5 (4)	2 (2)
Histology, n (%)		
CLL	109 (92)	108 (91)
SLL	10 (8)	11 (9)
ECOG PS, n (%)		
0-1	107 (90)	114 (96)
2	12 (10)	5 (4)
Rai Stage[a], n (%)		
0-II	58 (51)	62 (53)
III-IV	56 (49)	54 (47)
Molecular Characteristics, n/n available (%)		
BTK C481S	37/99 (37)	36/94 (38)
PLCγ2	15/99 (15)	11/94 (12)

Characteristics	Pirtobrutinib n=119	IdelaR/BR n=119
Median Lines of Prior Systemic Therapy, n (range)	3 (1-13)	3 (1-11)
Prior Therapy, n (%)		
cBTKi	119 (100)	119 (100)
Ibrutinib	100 (84)	106 (89)
Acalabrutinib	17 (14)	20 (17)
Zanubrutinib	10 (8)	7 (6)
Other[b]	5 (4)	3 (3)
>1 prior cBTKi	17 (14)	18 (15)
BCL2 inhibitor[c]	60 (50)	62 (52)
Chemotherapy	81 (68)	83 (70)
Anti-CD20 antibody	86 (72)	83 (70)
PI3K Agent	11 (9)	11 (9)
Immunomodulator	2 (2)	3 (3)
Autologous stem cell transplant	1 (1)	0 (0)
Allogeneic stem cell transplant	2 (2)	1 (1)
Reason for Any Prior cBTKi Discontinuation[d], n (%)		
Disease progression	85 (71)	87 (73)
Toxicity	20 (17)	22 (18)
Other	14 (12)	8 (7)

[a]Rai stage at study entry, excludes patients with missing stage. [b]Other includes, orelabrutinib, tirabrutinib, zebutinib and AVL-292-003. [c]2 patients in the IdelaR/BR arm received an investigational BCL2i, all other patients received venetoclax. [d]In the event more than one reason was noted for discontinuation, disease progression was prioritized, then toxicity, then other reasons.

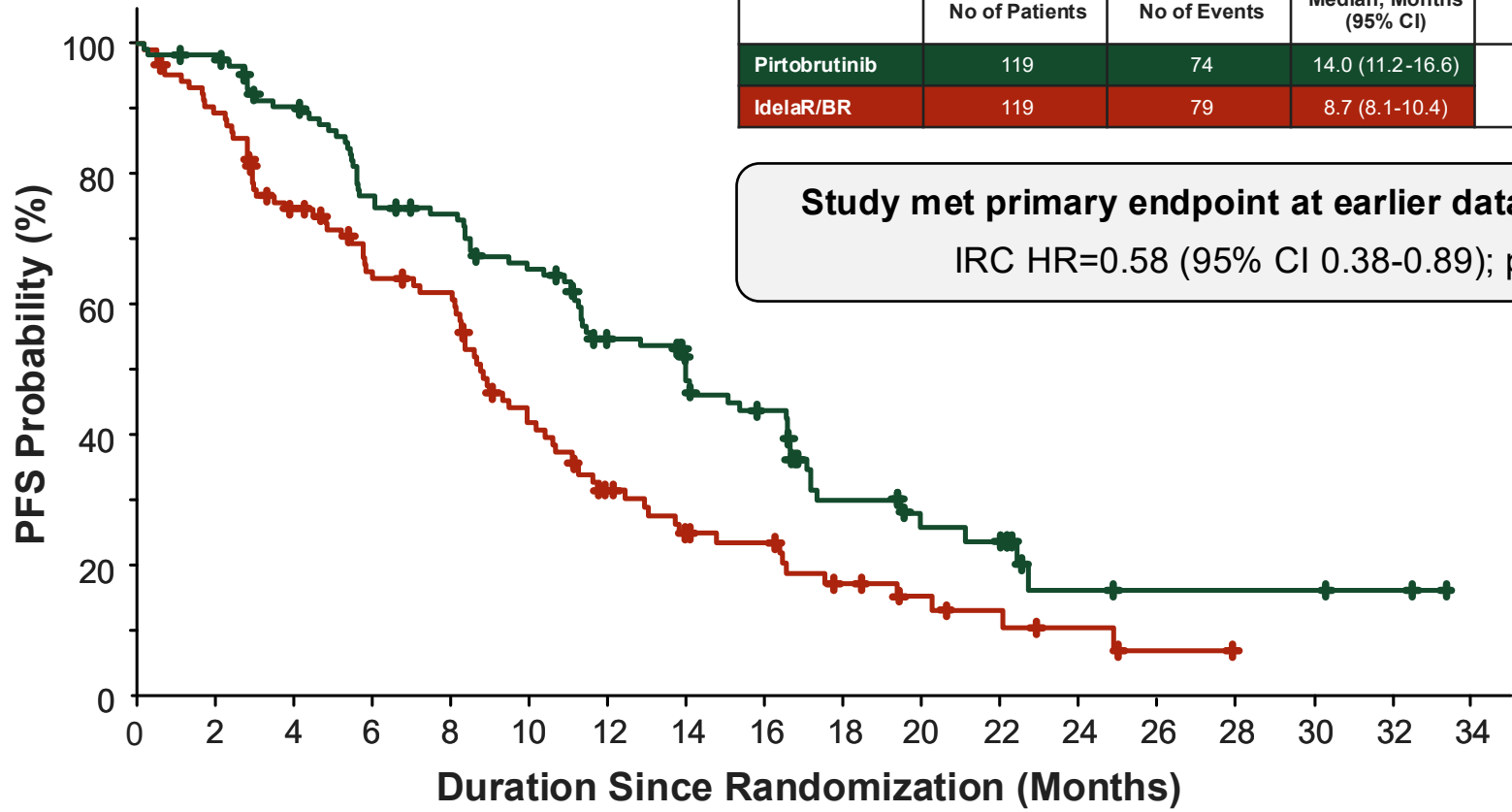
Sharman et al. J Clin Oncol. 2025.

IRC-Assessed Progression-Free Survival

	No of Patients	No of Events	Median, Months (95% CI)	HR (95% CI)	p-Value*
Pirtobrutinib	119	74	14.0 (11.2-16.6)	0.54 (0.39-0.75)	.0002
IdelaR/BR	119	79	8.7 (8.1-10.4)		

Study met primary endpoint at earlier data cut (Aug 2023)

IRC HR=0.58 (95% CI 0.38-0.89); p=0.01



Number at risk																		
Pirtobrutinib	119	113	100	84	79	69	54	44	36	19	12	10	4	3	3	3	2	0
IdelaR/BR	119	92	73	60	57	37	25	18	16	10	7	5	3	1	0	0	0	0

Sharman et al. J Clin Oncol. 2025.

*nominal p-value.

Safety: TEAEs Occurring in ≥15% of Patients

- Dose reductions occurred in 13 (11.2%) patients treated with pirtobrutinib and 40 (36.7%) patients treated with IdelaR/BR
- Treatment discontinuations due to AEs occurred in 20 patients (17.2%) treated with pirtobrutinib and 38 patients (34.9%) treated with IdelaR/BR
  - 6 discontinuations (5.2%) were considered related to pirtobrutinib treatment
  - 23 discontinuations (21.1%) were considered related to IdelaR/BR treatment
- Grade 5 TEAEs occurred in 12 patients (10.3%) treated with pirtobrutinib and 10 patients (9.2%) treated with IdelaR/BR

TEAE	Pirtobrutinib (n=116)		IdelaR/BR (n=109)	
	Any Grade, n (%)	Grade 3/4, n (%)	Any Grade, n (%)	Grade 3/4, n (%)
Anemia	23 (19.8)	13 (11.2)	19 (17.4)	8 (7.3)
Pneumonia	26 (22.4)	18 (15.5)	13 (11.9)	9 (8.3)
Neutropenia	21 (18.1)	17 (14.7)	17 (15.6)	13 (11.9)
Diarrhea	19 (16.4)	0 (0)	34 (31.2)	6 (5.5)
Cough	19 (16.4)	0 (0)	19 (17.4)	0 (0)
COVID-19	15 (12.9)	0 (0)	20 (18.3)	4 (3.7)
Pyrexia	15 (12.9)	1 (0.9)	29 (26.6)	1 (0.9)
Fatigue	13 (11.2)	2 (1.7)	22 (20.2)	1 (0.9)
Nausea	13 (11.2)	1 (0.9)	22 (20.2)	0 (0)
Vomiting	8 (6.9)	1 (0.9)	19 (17.4)	0 (0)
ALT increased	4 (3.4)	1 (0.9)	19 (17.4)	10 (9.2)
Infusion-related reaction	0 (0)	0 (0)	19 (17.4)	3 (2.8)
Weight decreased	4 (3.4)	0 (0)	18 (16.5)	0 (0)

Sharman et al. J Clin Oncol. 2025.

Safety: TEAEs of Clinical Interest

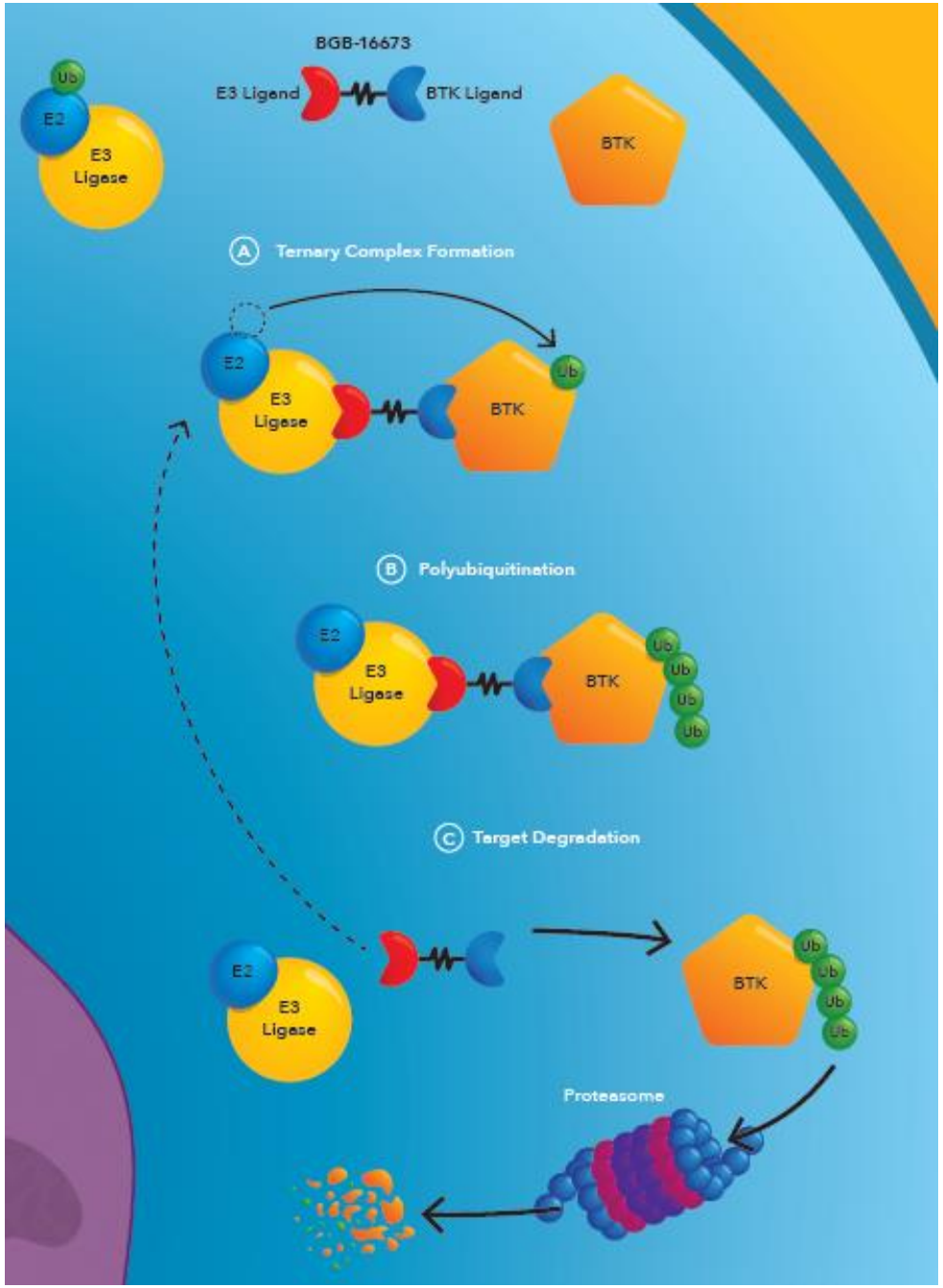
- Bleeding AEs were primarily low-grade with superficial bleeding events
  - 3 patients on pirtobrutinib experienced grade 3 hemorrhage (n=1 each; vaginal hemorrhage, conjunctival hemorrhage, and subdural hematoma)
  - 1 patient treated with IdelaR had grade 5 hemorrhage (hematoma)
- 3 patients (2.6%) experienced atrial fibrillation during pirtobrutinib treatment (2 with previous history of atrial fibrillation associated with cBTKi exposure); 1 patient in the IdelaR/BR group experienced *de novo* atrial fibrillation
- Any-grade hypertension was similar between groups, 8 (6.9%) pirtobrutinib-treated patients and 4 (3.7%) IdelaR/BR treated patients

TEAE	Pirtobrutinib (n=116)		IdelaR/BR (n=109)	
	Any Grade, n (%)	Grade 3/4, n (%)	Any Grade, n (%)	Grade 3/4, n (%)
Anemia[a]	24 (20.7)	13 (11.2)	19 (17.4)	8 (7.3)
Atrial fibrillation and atrial flutter	3 (2.6)	2 (1.7)	1 (0.9)	0 (0)
Bleeding	25 (21.6)	4 (3.4)	11 (10.1)	0 (0)
Bruising[b]	9 (7.8)	1 (0.9)	3 (2.8)	0 (0)
Petechiae and purpura	6 (5.2)	1 (0.9)	1 (0.9)	0 (0)
Hemorrhage[c]	18 (15.5)	3 (2.6)	8 (7.3)	0 (0)
Hypertension	8 (6.9)	3 (2.6)	4 (3.7)	1 (0.9)
Infections[d]	74 (63.8)	25 (21.6)	54 (49.5)	21 (19.3)
Infection without COVID-19	67 (57.8)	26 (22.4)	47 (43.1)	19 (17.4)
Neutropenia[e]	31 (26.7)	24 (20.7)	37 (33.9)	30 (27.5)
Thrombocytopenia[f]	11 (9.5)	9 (7.8)	17 (15.6)	8 (7.3)

[a]Includes anemia and iron deficiency anemia. [b]Includes contusion and ecchymosis. [c]Includes hemorrhage and hematoma. [d]Includes all infection events reported including COVID-19. [e]Includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis. [f]Includes thrombocytopenia and platelet count decreased.

Sharman et al. J Clin Oncol. 2025.

BTK degraders



PROTAC: BGB-16673 BTK degrader

- BGB-16673 is a selective, orally available BTK-targeted protein degrader that engages both wild-type (WT) BTK and its mutant forms carrying resistance-mutations
- BGB-16673 demonstrated binding with BTK and cereblon, the target receptor protein for recruiting the E3 ligase
- BGB-16673 can overcome BTKi resistance mutations including C481S and L528W

CaDAnCe 101 Safety & Efficacy Update: Ph 1 BGB16673 in RR CLL/SLL

- ≥2 prior therapies
- must have previously received a cBTKi

- N = 67 patients with CLL/SLL
- Median age 70 (range, 47-91 years)
- Median study follow-up was 18.0 months

- Seymour et al, ASH, 2025

Ph 1 BGB16673 in RR CLL/SLL - Cohort

- 65.7% (44/67) del(17p) and/or *TP53* mutation
- 77.6% (38/49) unmutated IGHV
- 38.1% (24/63) with *BTK* mutation
- 15.9% (10/63) with *PLCG2* mutation

- Median of 4 prior lines of therapy (range, 2-10)
  - Prior cBTKis (n=63 [94.0%])
  - Prior BCL2is (n=55 [82.1%])
  - Prior ncBTKi (n=14 [20.9%])

- Seymour et al, ASH, 2025

Ph 1 BGB16673 in RR CLL/SLL - Efficacy

- ORR 86.4% (n=57)
  - 4.5% (n=3) complete response (CR)/CRi
- Dose 200 mg ORR was 93.8% (15/16), including 1 CR

- Response rates evaluated by prior lines:

  Prior cBTKi 53/62 [85.5%]

  Prior ncBTKi 10/14 [71.4%]

  Double exposed 39/42 [92.9%]

  Triple exposed 9/12 [75.0%]

- Seymour et al, ASH, 2025

Ph 1 BGB16673 in RR CLL/SLL - Safety

- Common: fatigue (37.3%), contusion/bruising (31.3%), diarrhea (28.4%), and neutropenia (28.4%)

- Grade ≥3 TEAEs in ≥5% of patients were neutropenia (23.9%), pneumonia (10.4%), and thrombocytopenia (6.0%)

- Eight patients (11.9%) had a TEAE leading to dose reduction
- TEAEs led to treatment discontinuation in 12 patients (17.9%)
  - incl subdural hemorrhage, and disseminated aspergillosis
- Four patients (6.0%) had TEAEs that led to death (all due to infections, including 1 fungal infection)

- Seymour et al, ASH, 2025

Ph 1 BGB16673 in RR CLL/SLL - Efficacy

- The 12-month progression-free survival rate was 79.2%
  - 15 patients (22.4%) had PD
    - 2 associated with DLBCL Richter transformation
  - 4 (6.0%) deaths

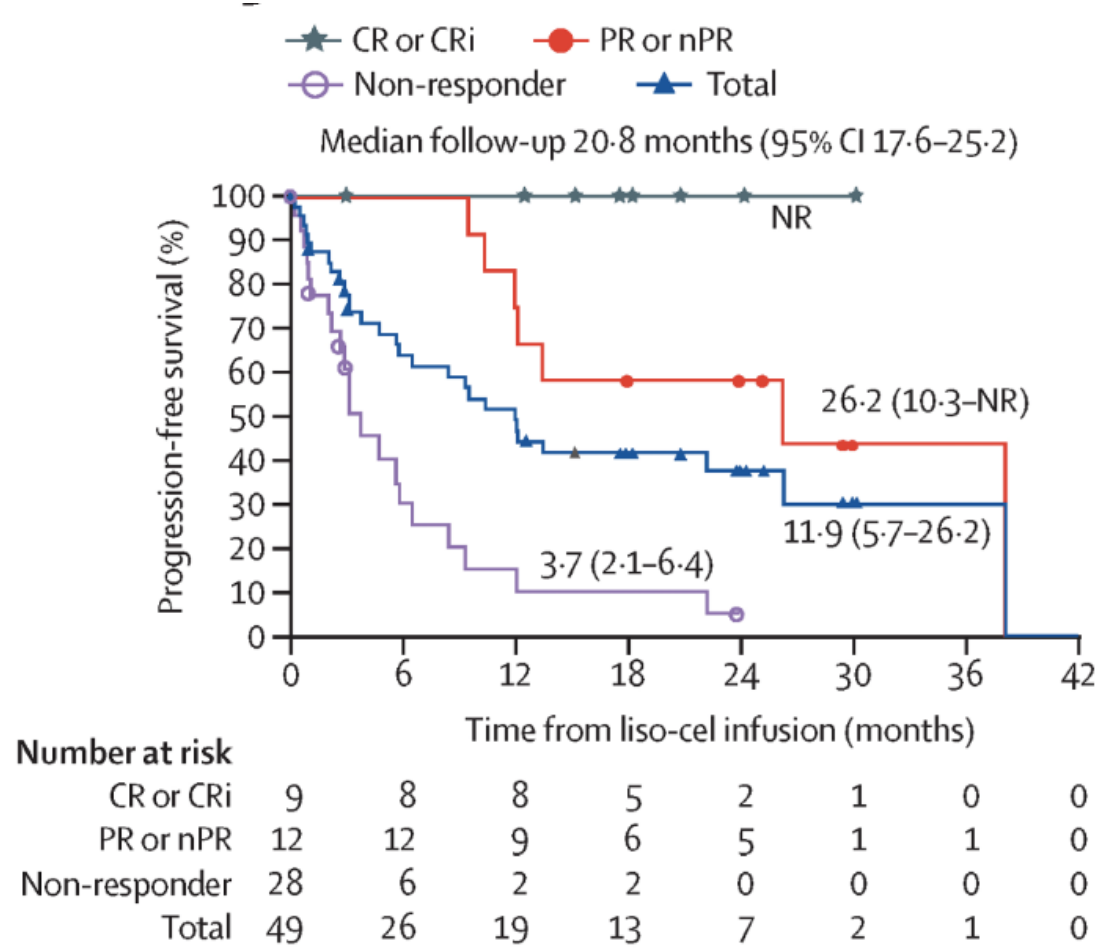
- Seymour et al, ASH, 2025

CAR-T in CLL

CD19 CAR-T: Lisocabtagene maraleucel

- TRANSCEND CLL 004 2 year follow up
- Phase 1/2 US study
- N= 118
  - Median 5 prior lines including cBTKi (PD)
  - High risk group
  - N= 70 prior venetoclax failure

- CRR 20% → MRD negativity
- Median PFS 11.9 months overall



Siddiqi et al, Blood, 2024

TRANSCEND CLL 004

- Estimated 36-mo DOR rate 61%
  - not reached for those in CR
- Median PFS
  - 26.2 mo in pts with blood uMRD
  - 2.8 mo detectable blood MRD
- Median OS, including 19 pts in the LTFU, was 43.2 mo

- AEs:
  - Grade 3 CRS 9% (no grade 4 or 5 events)
  - Grade 3 neurological events 18% and 1% G4 events
- 51 deaths on study → 43 deaths after liso-cel infusion
  - 5 TEAE deaths including 1 death due to MAS-HLH

Siddiqi et al, Blood, 2024

Real-world outcomes of liso-cel in R/R CLL - CIBMTR

- n = 45
- median age 62 y (range, 44–83)
- ECOG PS 0–1 (43/43)
- 57% (21/37) had ≥ 1 comorbidity

- ASCO 2026 Tomasulo et al

Real-world outcomes of liso-cel in R/R CLL - CIBMTR

- Median 6 (range, 1–10) prior therapies
- 71% received liso-cel as fifth-line or later treatment

- 84% were previously exposed to covalent BTKi and BCL2i
- 47% had prior pirtobrutinib
- Bridging therapy was used in 48% (21/44) of pts

- ASCO 2026 Tomasulo et al

Real-world outcomes of liso-cel in R/R CLL - CIBMTR

- Median follow-up of 6.0 mo

- ORR was 84% (70–93)
  - CR rate was 55% (39–70)
  - 81% (13/16) in CR with available data were MRD –

- Median (95% CI) DOR, PFS, and OS were not reached.
- Among responders (n = 36), 6-mo PFS 77% (60–87) and OS 87% (72–95)

- ASCO 2026 Tomasulo et al

Real-world outcomes of liso-cel in R/R CLL - CIBMTR

- CRS rate 80%; grade ≥ 3, 4%
- ICANS 36%; gr ≥ 3, 13%
  - No grade 5 events

- Infections in 40% of pts
- @ D +30: 18% had persistent gr 4 thrombocytopenia and/or neutropenia

- 5 deaths, 2 each were due to relapse/progression or infection, and 1 pt had multiple causes reported
- 6-month NRM was 5% (95% CI, 0.8–14)

- ASCO 2026 Tomasulo et al

TRANSCEND CLL 04: Liso-Cel + Ibrutinib

- Liso-cel with concurrent ibrutinib from enrollment through 90 days after liso-cel infusion or longer per investigator discretion

- N= 56
- Median age 64.5 years (range 44–77)
- Median (range) number of prior therapies was 5 (1–13)
- 98% had high-risk cytogenetics, 55% had progression on cBTKi and venetoclax failure

- Weirda et al, Blood, 2026

TRANSCEND CLL 04: Liso-Cel + Ibrutinib

- Median follow-up 24.8 months
- At DL2
  - CR/CRi rate was 45% (95% CI, 31–60)
  - ORR was 86% (95% CI, 74–94)
  - Median (95% CI) duration of response
    - NR (28.7–NR) for patients with CR/CRi
    - 41.4 months (23.3–NR) for all responders
  - Median progression-free survival was 31.4 months (95% CI, 20.1–NR)

- Weirda et al, Blood, 2026

TRANSCEND CLL 04: Liso-Cel + Ibrutinib

- Most common grade ≥3 TEAE:
  - neutropenia (52%)
  - anemia (41%)
- CRS in 80% (grade 3, 4%; no grade 4/5)
- Neurological events in 41% (grade 3/4, 11%; no grade 5)
- Ibrutinib-related TEAEs were reported in 68% of patients (grade 3/4, 43%; no grade 5)

- Weirda et al, Blood, 2026

Bispecific Antibodies

Epcoritamab

- Ph 1b/2 EPCORE CLL-1
  - Monotherapy and combined with venetoclax

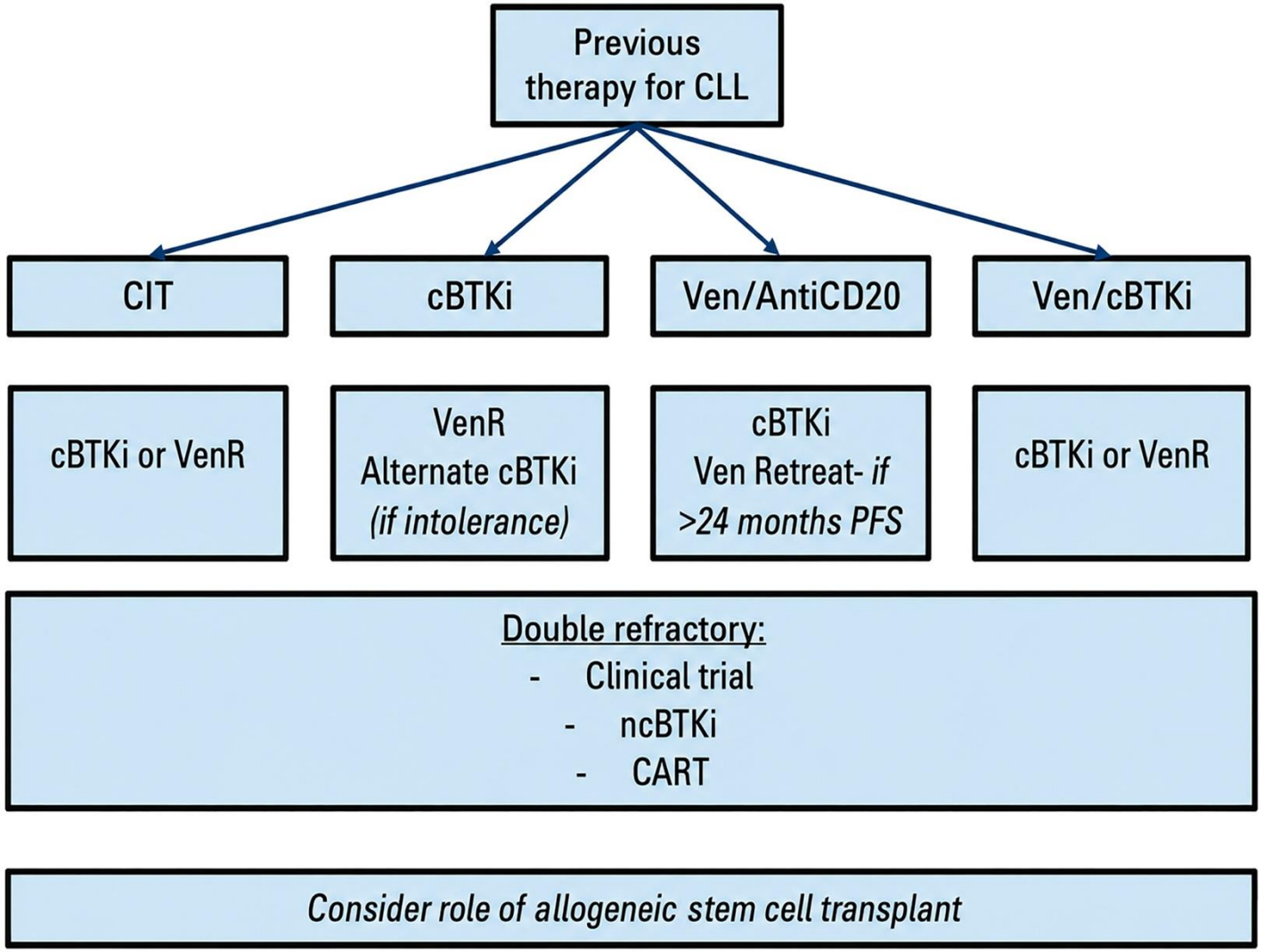
- Monotherapy cohort
  - N = 40
  - Median 4 prior lines
  - All cBTKi exposed and 85% double exposed

- ORR 61% & CRR 39%
- Double exposed: ORR 53% and CRR 37%
- uMRD 75% in responders
- Overall mPFS 12.8 months

- Aes:
  - No CRS > 3
  - No ICANS

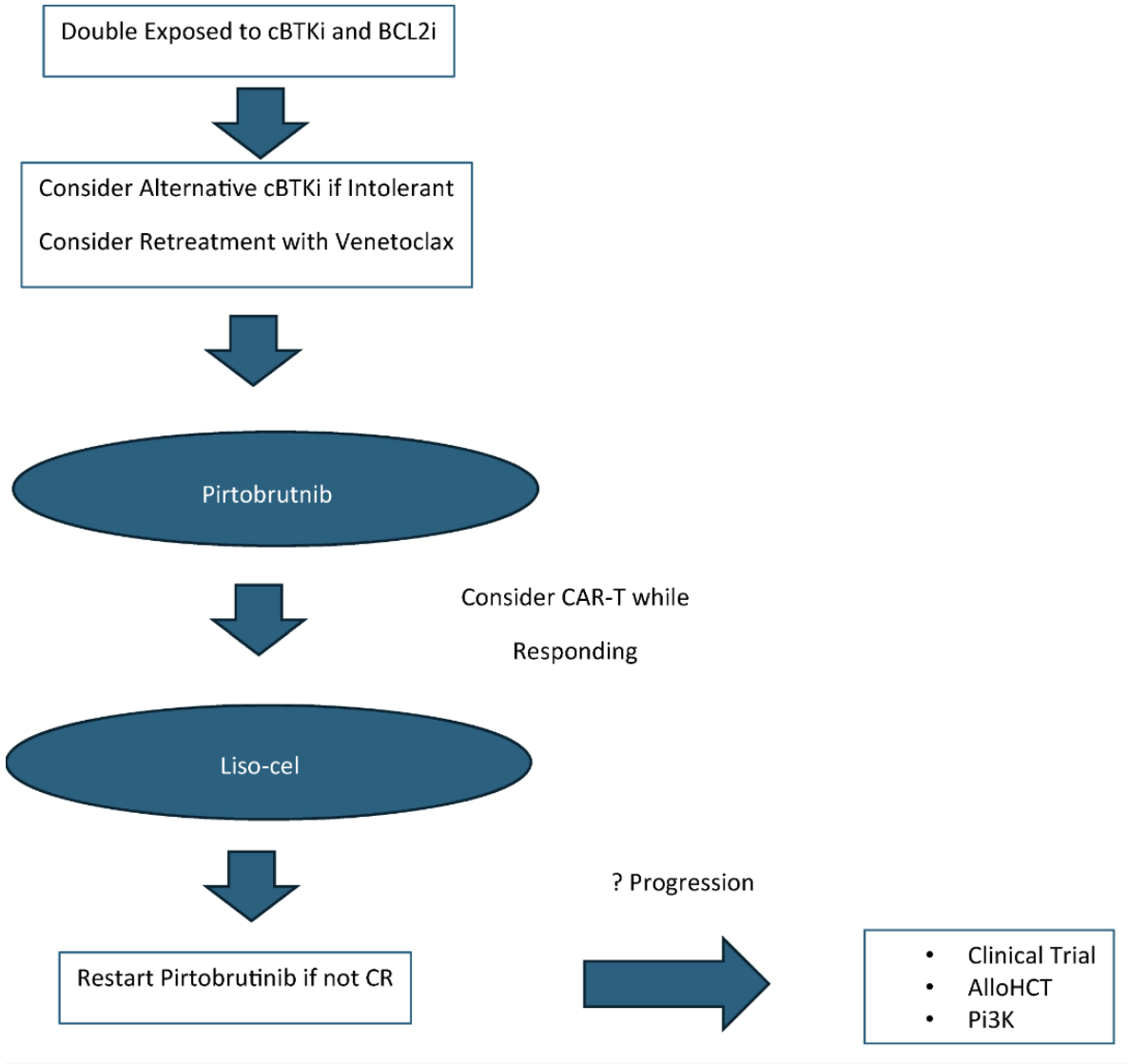
- Danilov, Blood, 2024

Australasian CLL consensus statement: 2026 update



Internal Medicine Journal, Volume: 56, Issue: 8, Pages: 1421-1428, First published: 07 July 2026, DOI: (10.1111/imj.70503)

An approach to double refractory patients … but not in Australia



- Jacobs, Cancers, 2025