Treatment of Patients with CLL Progressing after BTKi and BCL2i

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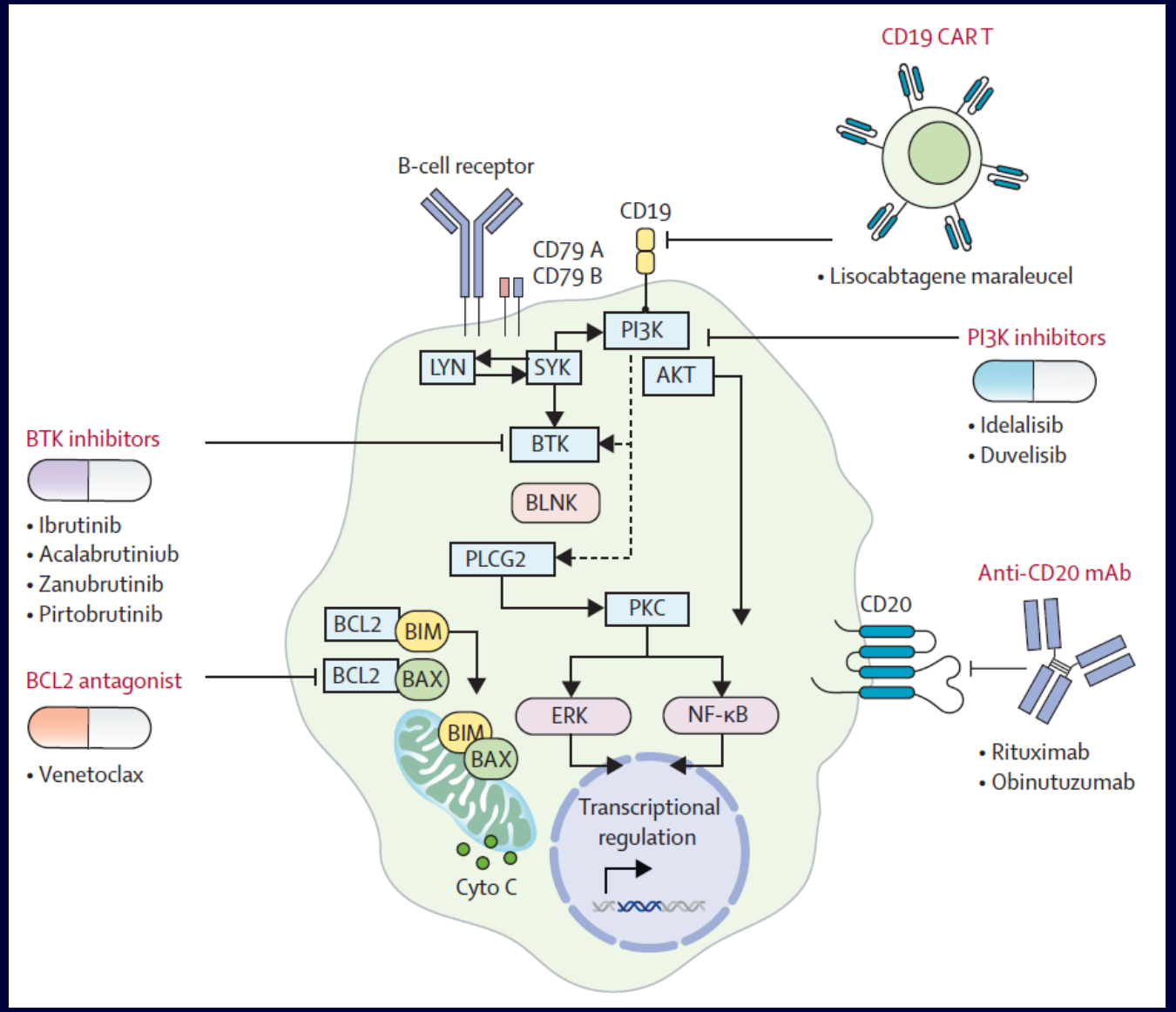
CLL Therapy Armamentarium



Jain, Wierda, O'Brien. Lancet. 2024 Jul 25.

Treatment Evolution in CLL

1960s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1970s

Purine nucleosides
- Fludarabine
- Pentostatin

1980s

Purine nucleosides
- Fludarabine
- Pentostatin

1990s

Purine nucleosides and alkylators

2000s

Chemoimmunotherapy (FCR, BR)
Alemtuzumab
Lenalidomide

2014-

BTK inhibitors (Ibrutinib, Acalabrutinib)
BCL-2 inhibitor (Venetoclax)
Novel CD20 mAb (Obinutuzumab)
PI3K inhibitors (Idelalisib, Duvelisib)

2023

BTK inhibitors (Zanubrutinib, Pirtobrutinib)

2024

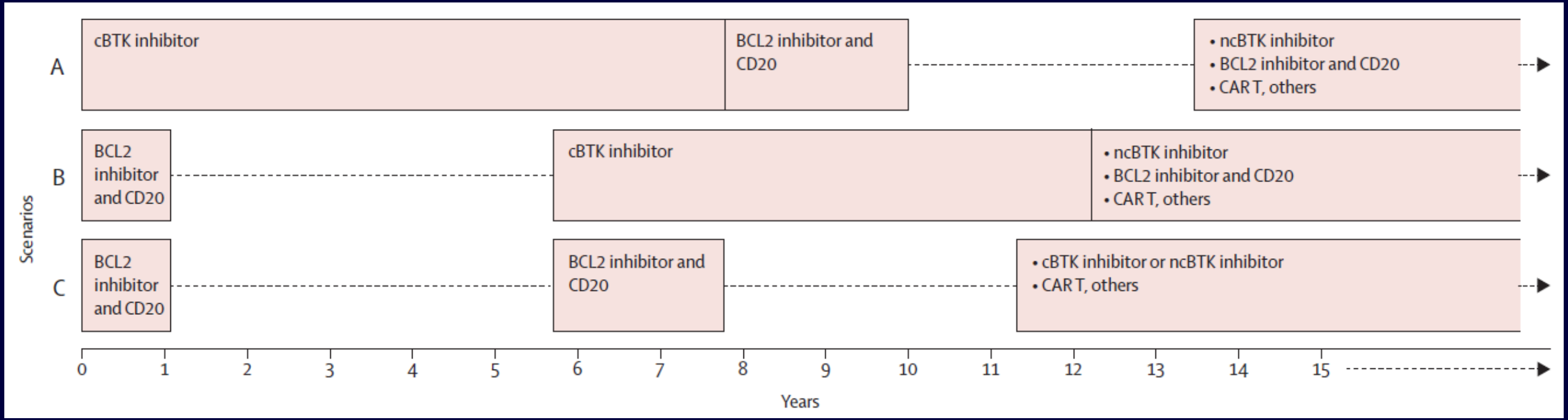
CD19 CAR T (Liso-cel)

2025+

CD20 bispecifics, novel BCL2i, novel BTKi, BTK PROTACs, etc.

RELAPSED CLL

CLL Rx Sequencing Scenarios



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Unmet Medical Need

‘Double-exposed’ or ‘double-refractory’ CLL

- Double-exposed
  - Prior use of BTKi and BCL2i (regardless of the reason for discontinuation)
- Double-refractory
  - PD on BTKi AND
  - PD on BCL2i OR PD within 12-24 mos after planned BCL2i discontinuation

Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-Up and Subgroup Analysis with/without Prior BCL2i from the Phase 1/2 BRUIN Study

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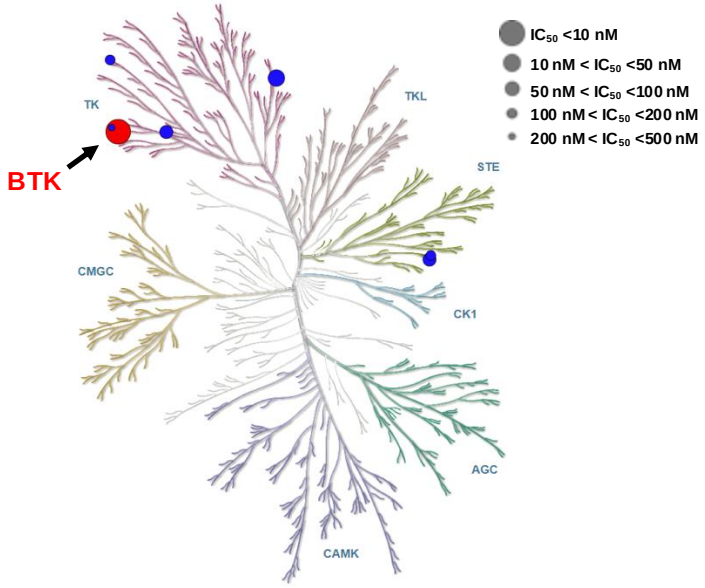
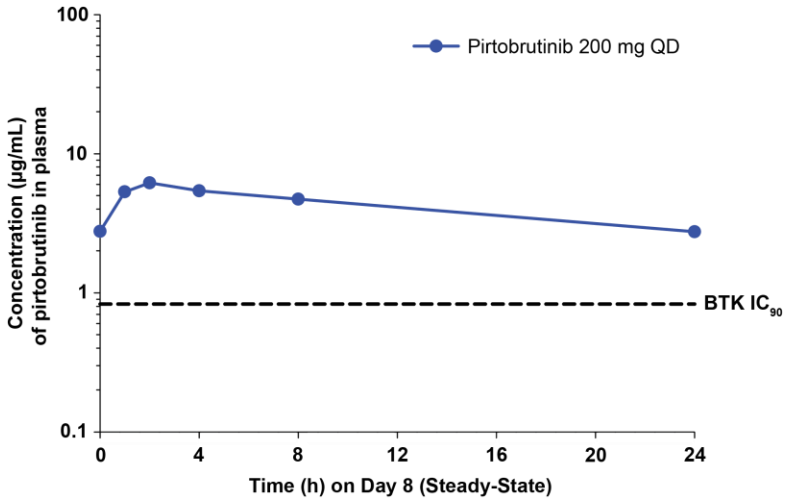
Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

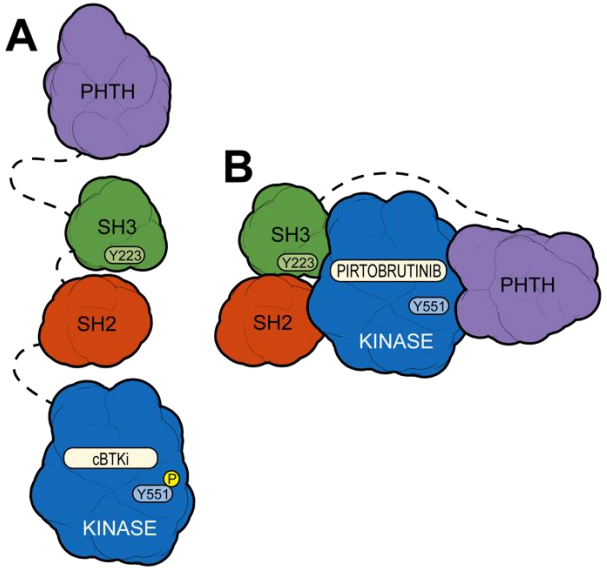
Highly selective for BTK[5,6]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



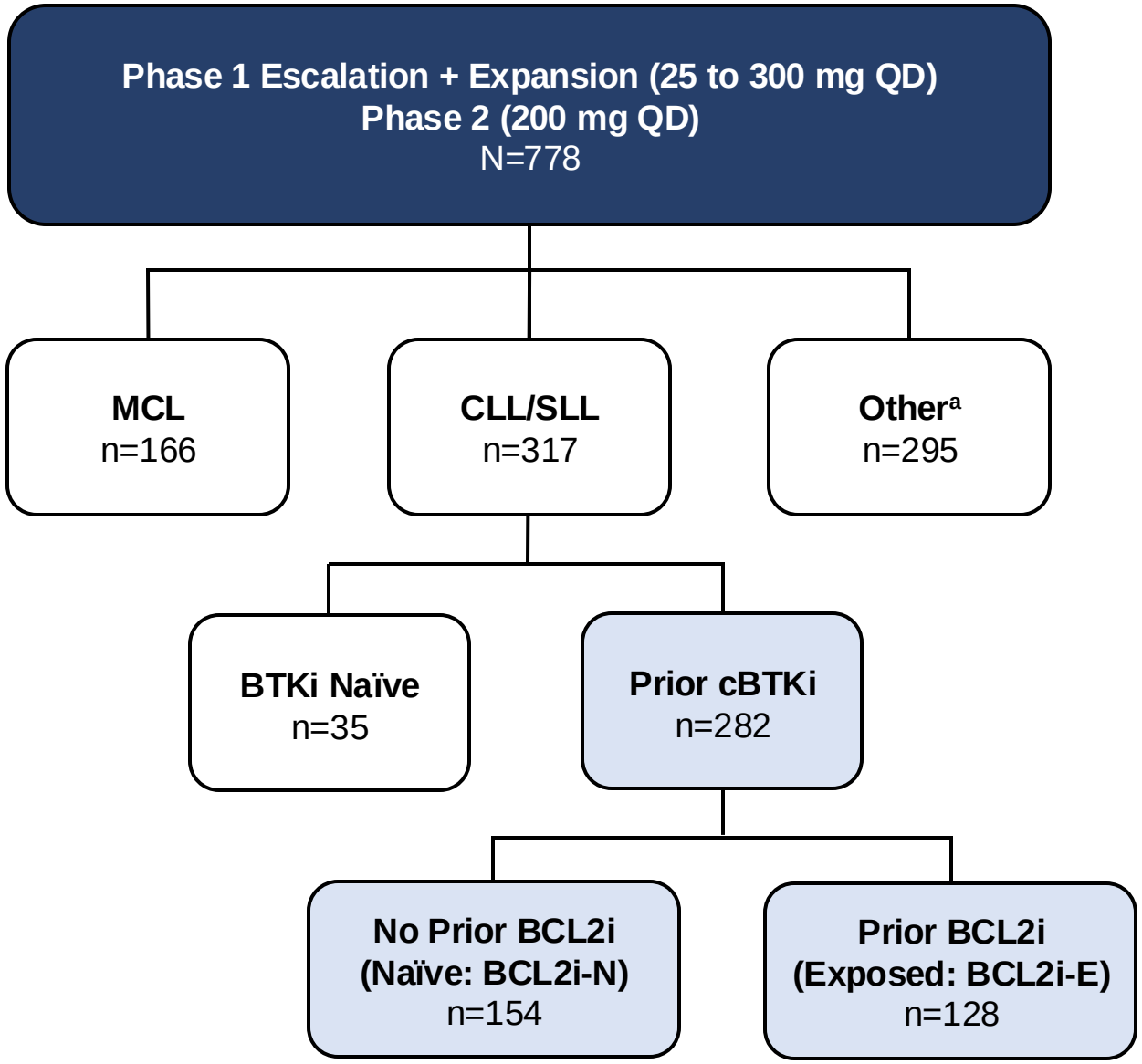
Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[7]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[7]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[7]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[7]

[5]Mato et al, *Lancet* 2021; 397: 892–901. [6]Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018; 18(Suppl.1):S216. [7]Gomez et al. *Blood*.2023; 142(1):62-72.

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)

Data cutoff of 05 May 2023 (NCT03740529); [a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

Baseline Characteristics of Patients with CLL/SLL who Received Prior cBTKi

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
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 (%)			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (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)

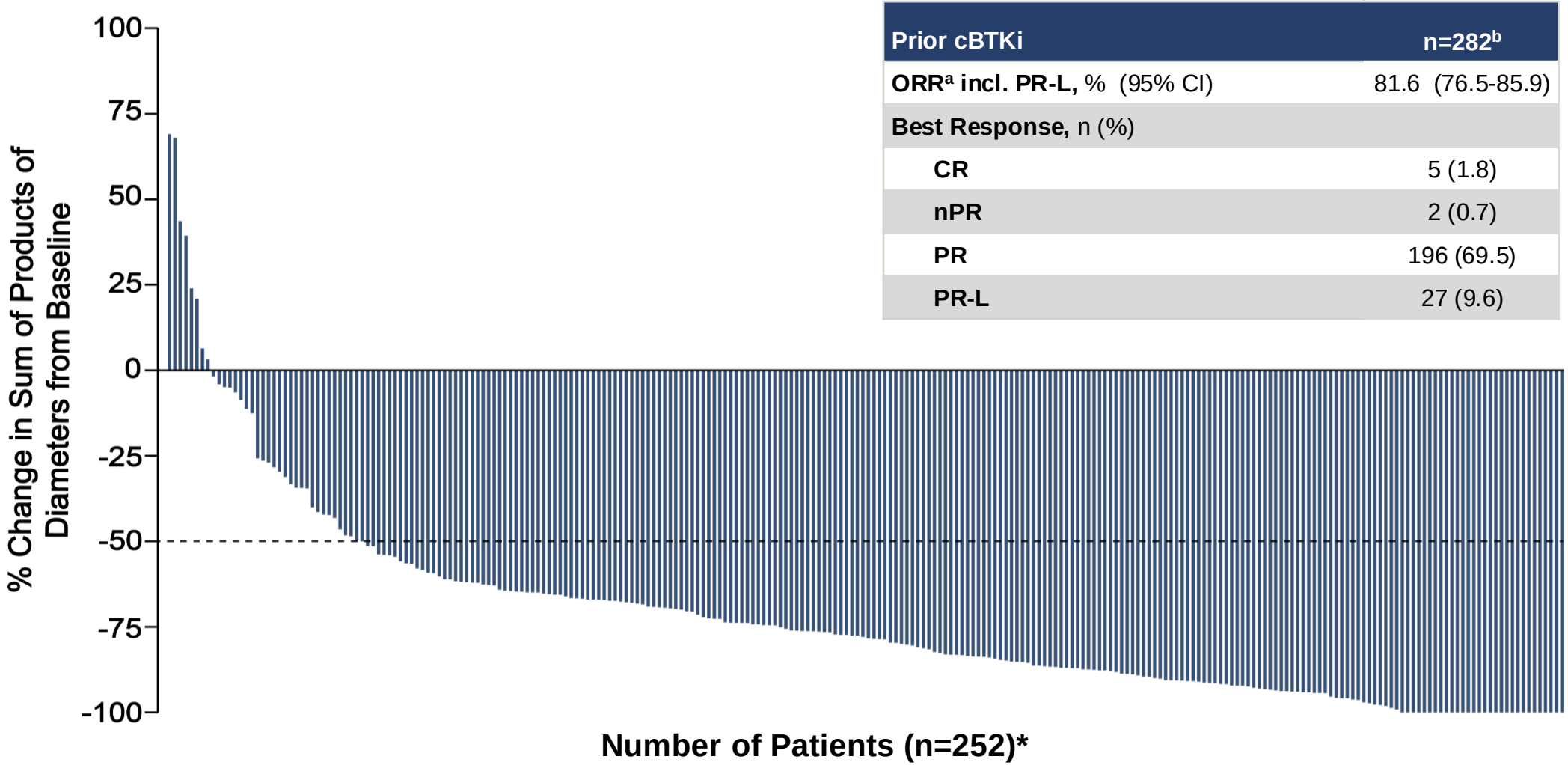
Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristics[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-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	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)

[a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control.

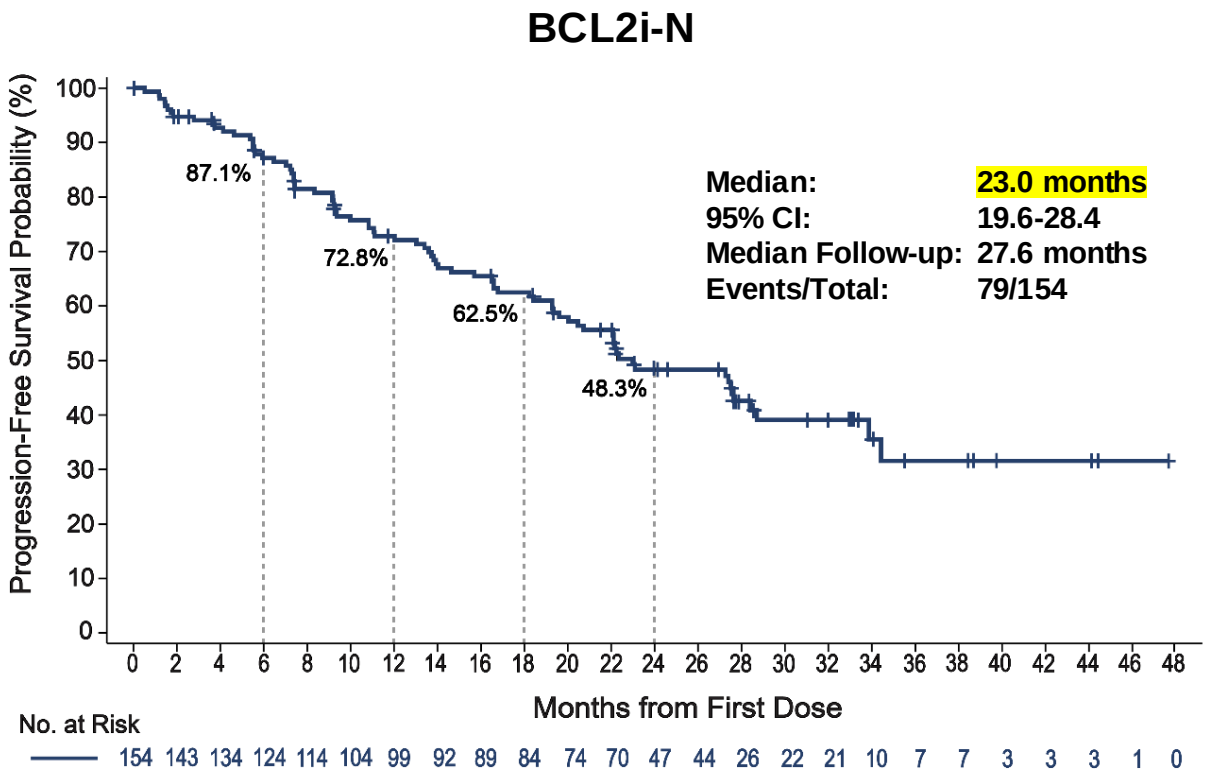
Pirtobrutinib Efficacy in All Patients with CLL/SLL who Received Prior cBTKi

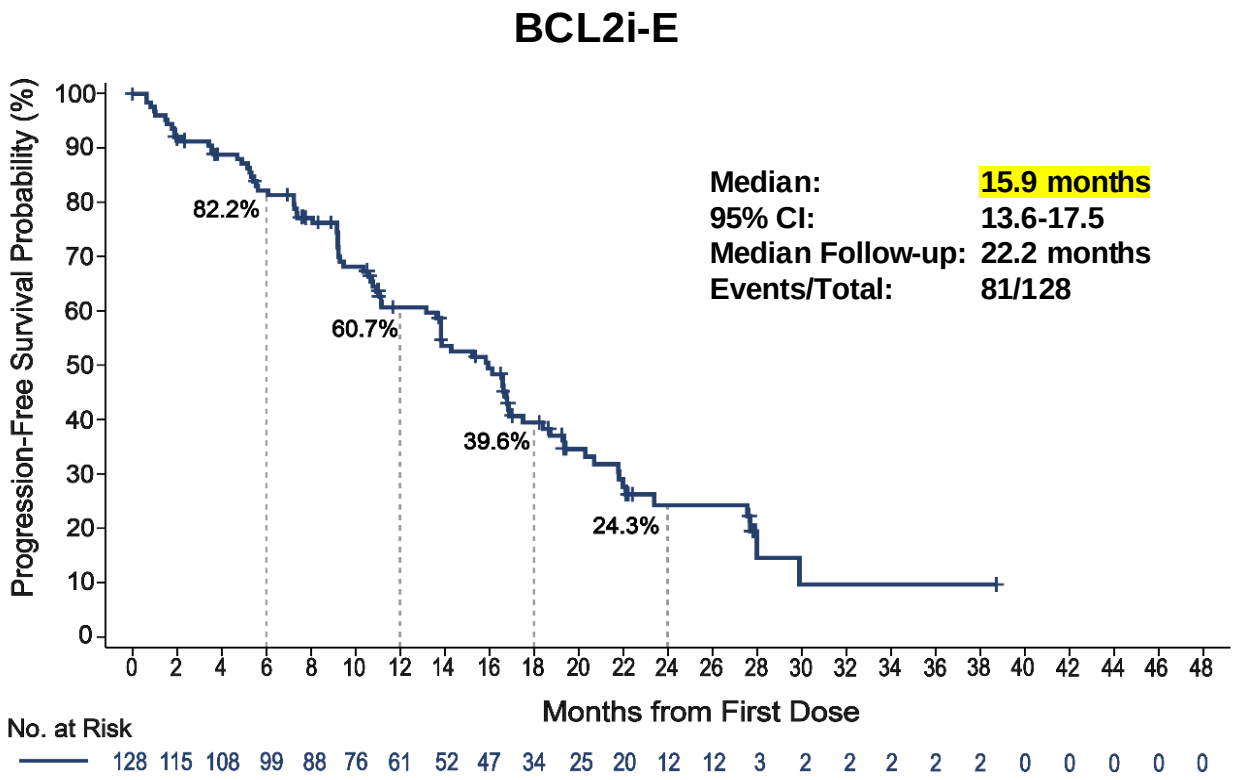
Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)



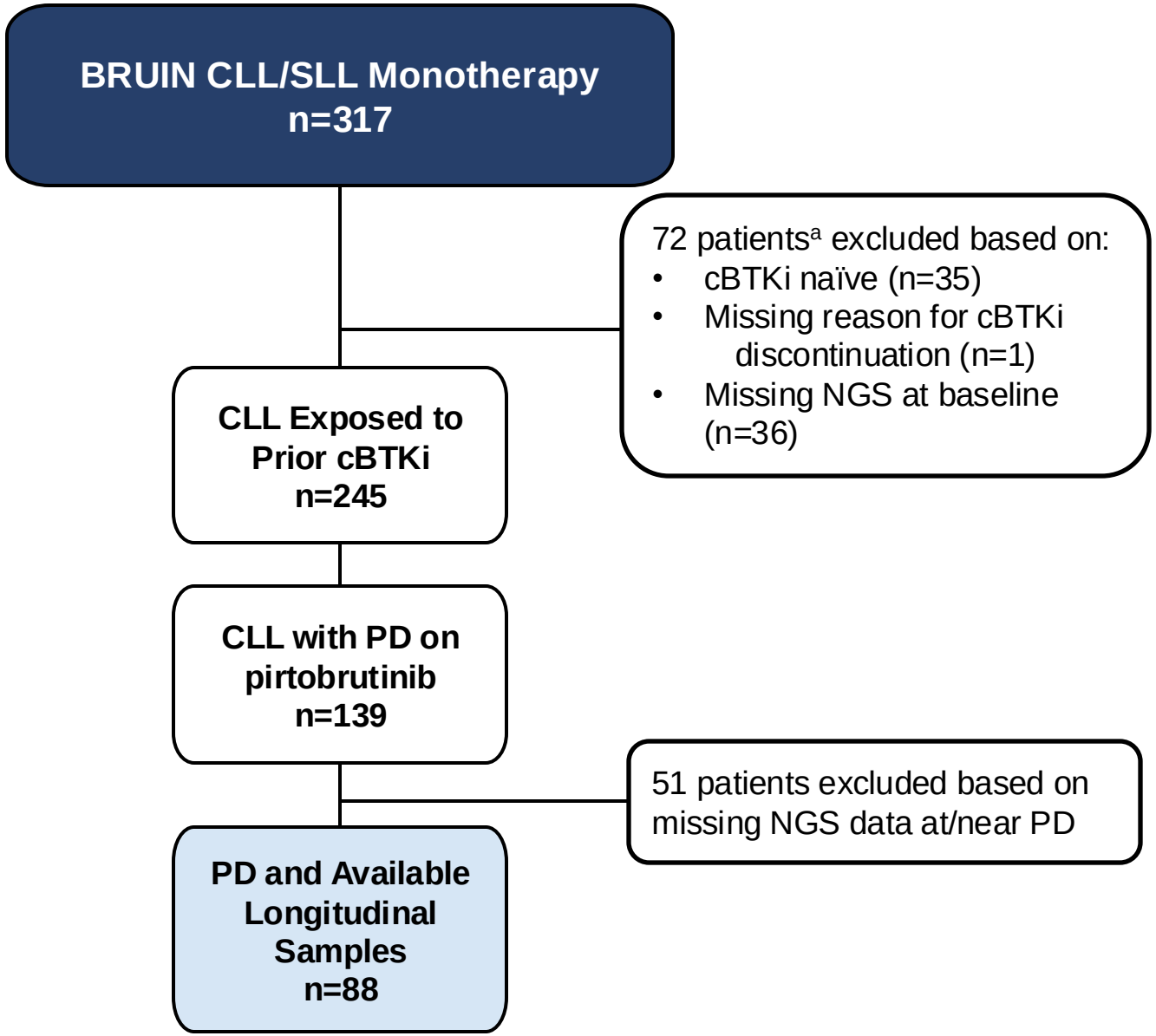
Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Data for 30/282 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR including PR-L is the number of patients with best response of PR-L or better divided by the total number of patients; 14 patients with a best response of not evaluable (NE) are included in the denominator. [b]Post-cBTKi patients included a subgroup of 19 patients with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had an ORR including PR-L of 89.5% (95% CI: 66.9-98.7). Response status per iwCLL 2018 based on IRC assessment.

Pirtobrutinib Progression-Free Survival with Prior cBTKi, with or without Prior BCL2i





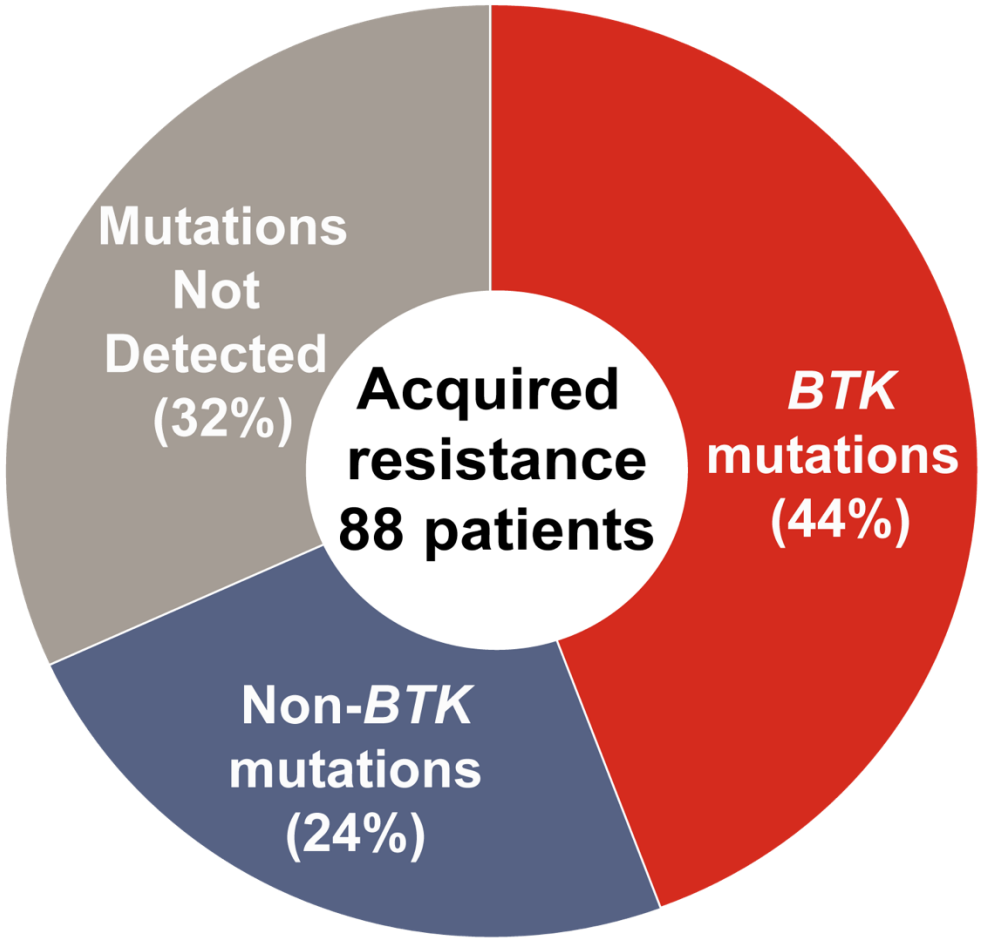
Study Design & Methods

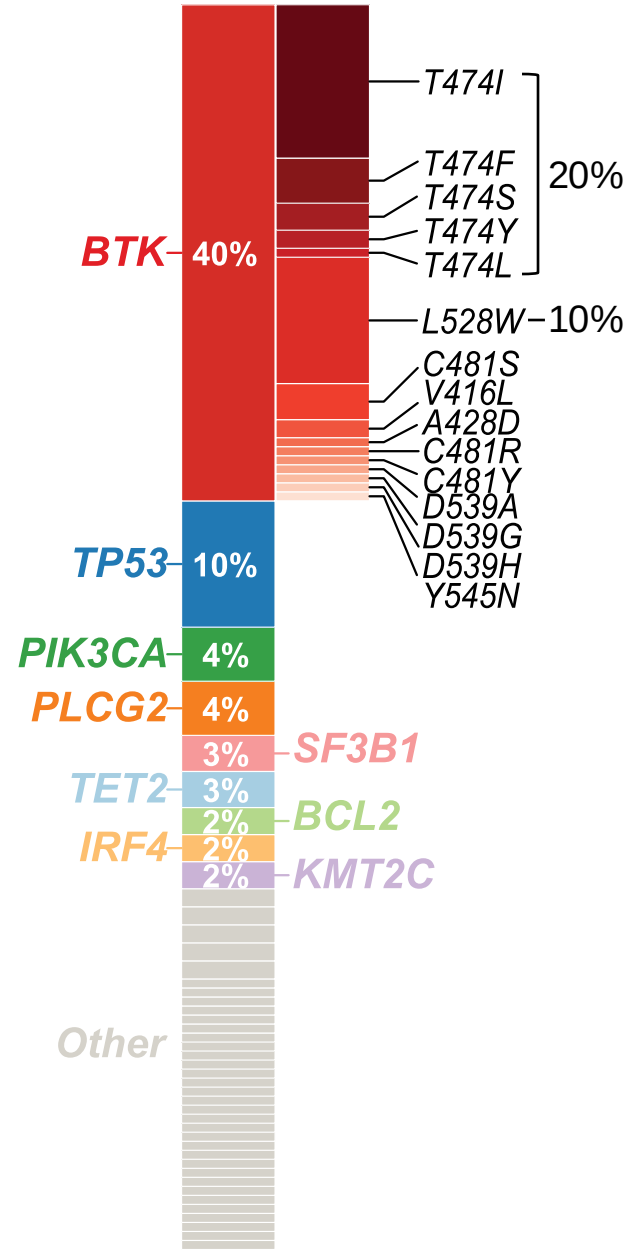


- Next-generation sequencing (NGS) of paired baseline and progression PBMC samples from 88 cBTKi pre-treated CLL patients who progressed on pirtobrutinib
- Targeted NGS (5% VAF limit of detection [LoD]) gene list (all exons, 74 genes):
  - ***BTK***, ***PLCG2***, ***TP53***, *ABL1, APC, ARID1A, ATM, BAP1, BCL2, BCL6, BRAF, BRD4, CARD11, CCND1, CCND3, CD79A, CD79B, CDK4, CDKN2A, CDKN2B, CREBBP, EP300, EPHA7, ERBB3, EZH2, FAS, FGFR1, FLT1, FOXP1, GNA13, GRIN2A, GSK3B, HRAS, IKZF1, IRF4, JAK1, JAK2, KDR, KIT, KLHL6, KMT2C, KMT2D, KRAS, MAP2K1, MED12, MEF2B, MTOR, MYC, MYD88, NFKBIA, NOTCH1, NOTCH2, NRAS, NTRK1, PDGFRA, PIK3CA, PIK3CG, PIK3R1, PIK3R2, PRDM1, PRKDC, PTEN, RAF1, RB1, ROS1, SF3B1, SMARCA4, SOCS1, STAT3, SYK, TET2, TNFAIP3, TNFRSF14, XPO1*
- 79 baseline PBMC samples were re-sequenced using a more sensitive assay (LoD ~ 0.5% VAF) to assess the presence of pre-existing *BTK* mutations

Data cutoff date of 05 May 2023 (NCT03740529). [a]Patients with SLL were excluded from the analysis with these criteria.

Acquired Mutations were Detected at PD in 68% of Patients





- 68% (60/88) acquired mutations at PD
  - 44% (39/88) had at least one acquired *BTK* mutation at PD
    - 64% (25/39) who acquired a *BTK* mutation had a *BTK* mutation at baseline
- 56% (49/88) did not acquire a *BTK* mutation
  - The most frequently acquired non-*BTK* mutation was *TP53*
- 32% (28/88) had no acquired mutations detected at PD

Lisocabtagene Maraleucel Combined with Ibrutinib for Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Results from the Open-label, Phase 1/2 TRANSCEND CLL 004 Study

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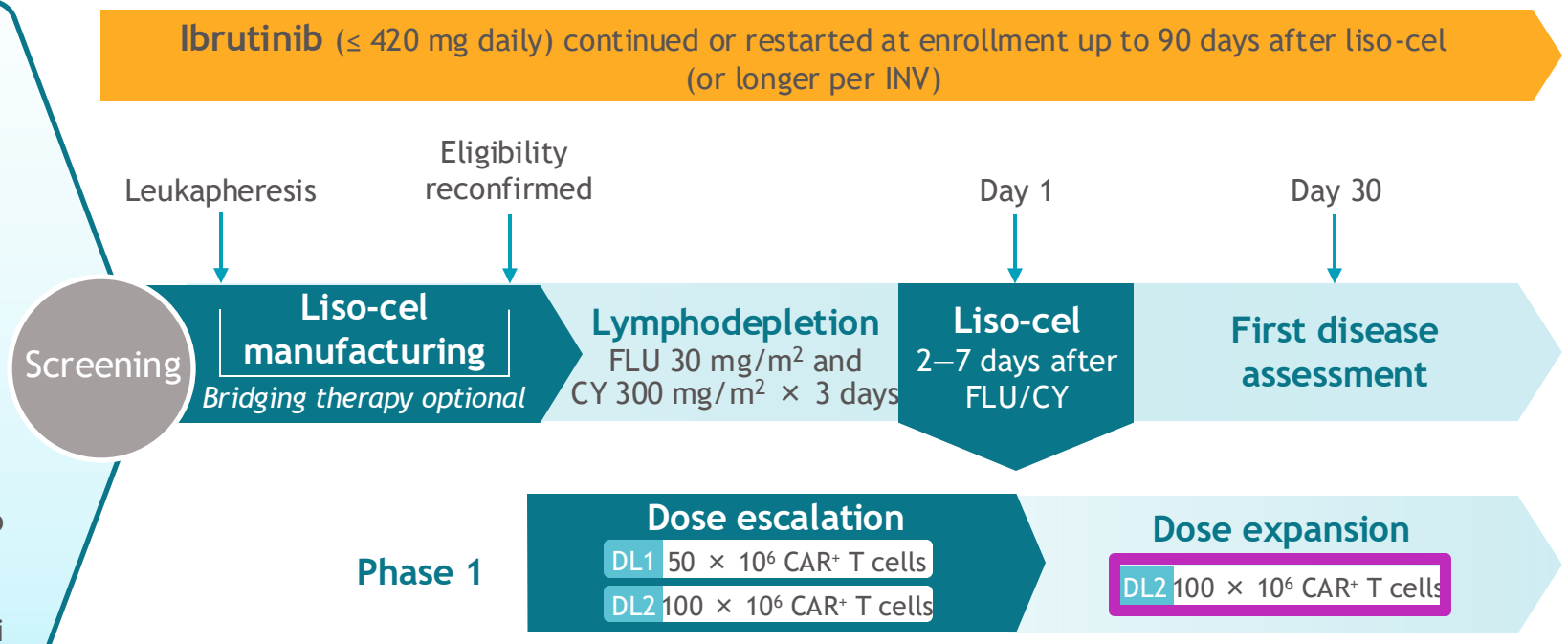
*Affiliation at the time the research was conducted

ASH 2024, Presentation 887

Phase 1/2 TRANSCEND CLL 004 study: liso-cel + ibrutinib combination cohort

Key eligibility criteria for liso-cel plus ibrutinib cohort

- Age ≥ 18 years
- R/R CLL/SLL
- ECOG PS 0—1
- Adequate organ function
- No active CNS involvement
- No Richter transformation
- Met ≥ 1 of the following:
  - Receiving BTKi with progression at study entry
  - High-risk features with < CR after ≥ 6 mo on BTKi
  - *BTK*/*PLCγ2* mutation[a] ± ibrutinib progression
  - Prior BTKi with no contraindications to restart BTKi
- Progression on BTKi and received prior venetoclax (per amendment 5)



Follow-up

On-study: 24 or 48 months

LTFU study (NCT03435796): up to 15 years after liso-cel infusion

Primary endpoint (at DL2)

CR/CRi rate per iwCLL 2018 by INV assessment

Secondary endpoints

Safety (DL1 + DL2); ORR, DOR, DOCR, time to response, time to CR/CRi, PFS, OS, and uMRD4[b] rate in blood at DL2

Exploratory analyses

uMRD4[b] rate in marrow, cellular kinetics (CAR T cell expansion and persistence)

[a]Per local laboratory assessment; [b]MRD was assessed by next-generation sequencing using a clonoSEQ assay. Undetectable MRD was defined as < 1 CLL cell per 10,000 leukocytes at ≥ 1 time point after infusion (uMRD4). CY, cyclophosphamide; DOR, duration of response; DOCR, duration of continued CR after initial CR; FLU, fludarabine; INV, investigator; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; LTFU, long-term follow-up; uMRD4, undetectable minimal residual disease at < 1 in 10^{-4} leukocytes.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

Demographics and baseline characteristics

	DL2 + ibrutinib set (n = 51)	Total liso-cel + ibrutinib combination set (n = 56)
Median (range) age, y	65 (44–77)	65 (44–77)
Median (range) prior lines of systemic therapy	**5 (1–13)**	**5 (1–13)**
≤ 3 prior therapies, n (%)	19 (37)	20 (36)
Prior BTKi, n (%)	51 (100)	56 (100)
Prior venetoclax, n (%)	39 (76)	42 (75)
Prior BTKi and venetoclax, n (%)	39 (76)	42 (75)
BTKi progression/venetoclax failure,[a] n (%)	**28 (55)**	**31 (55)**
High-risk cytogenetics, n (%)	50 (98)	55 (98)
Del(17p)	23 (45)	25 (45)
Mutated *TP53*	23 (45)	24 (43)
Unmutated IGHV	37 (73)	39 (70)
Complex karyotype[b]	25 (49)	29 (52)
Bulky disease (≥ 5 cm) per INV before LDC,[c] n (%)		
Yes	18 (35)	18 (32)
Unknown	4 (8)	5 (9)
Median (range) SPD per INV before LDC,[d] cm^2	29 (1–218)	27 (1–218)
LDH ≥ ULN before LDC, n (%)	22 (43)	24 (43)
Received bridging therapy (in addition to ibrutinib),[e] n (%)	13 (25)	16 (29)

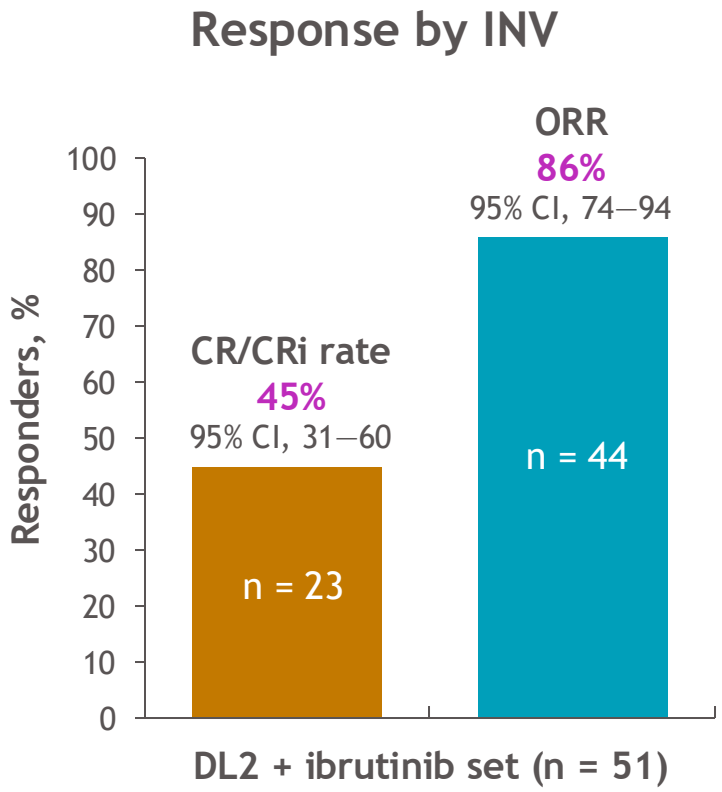
- Median (range) ibrutinib exposure was 34 days (15–188) before and 95 days (6–1517) after liso-cel in the total combination-treated set
- Liso-cel was manufactured for 63/65 (97%) patients in the leukapheresed set
  - Median (range) time from leukapheresis to liso-cel availability was 25 (17–79) days (n = 62)

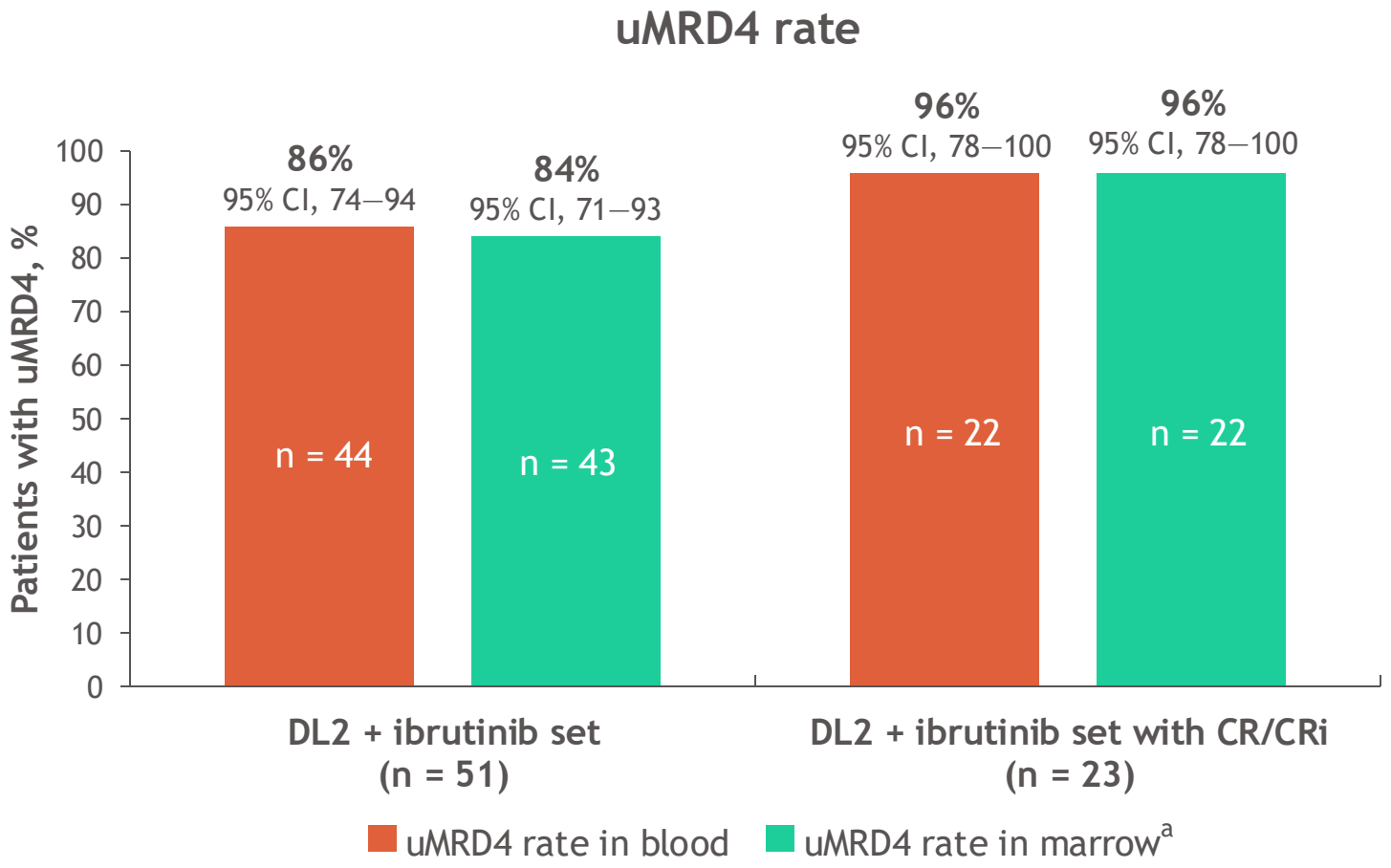
[a]Includes patients who progressed on a BTKi and met 1 of the following criteria: 1) discontinued venetoclax due to disease progression or intolerability and the patient's disease met indications for further treatment per iwCLL 2018 criteria or 2) failed to achieve an objective response within 3 months of initiating therapy; [b]At least 3 chromosomal aberrations; [c]At least 1 lesion with a longest diameter ≥ 5 cm; [d]Forty-seven patients at DL2 and 51 patients in the total combination-treated set had SPD measurements; [e]Included other anticancer therapies in addition to concurrent ibrutinib treatment given for disease control during liso-cel manufacturing. IGHV, immunoglobulin heavy-chain variable region; LDC, lymphodepleting chemotherapy; SPD, sum of the product of perpendicular diameters.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

Efficacy outcomes: response by investigator and uMRD4

- Median (IQR) on-study follow-up (including LTFU): 24.8 months (14.2—34.6)
- Median (range) time to first response: 1 month (0.9—6.0)
- Median (range) time to first CR/CRi: 3 months (0.9—12.1)

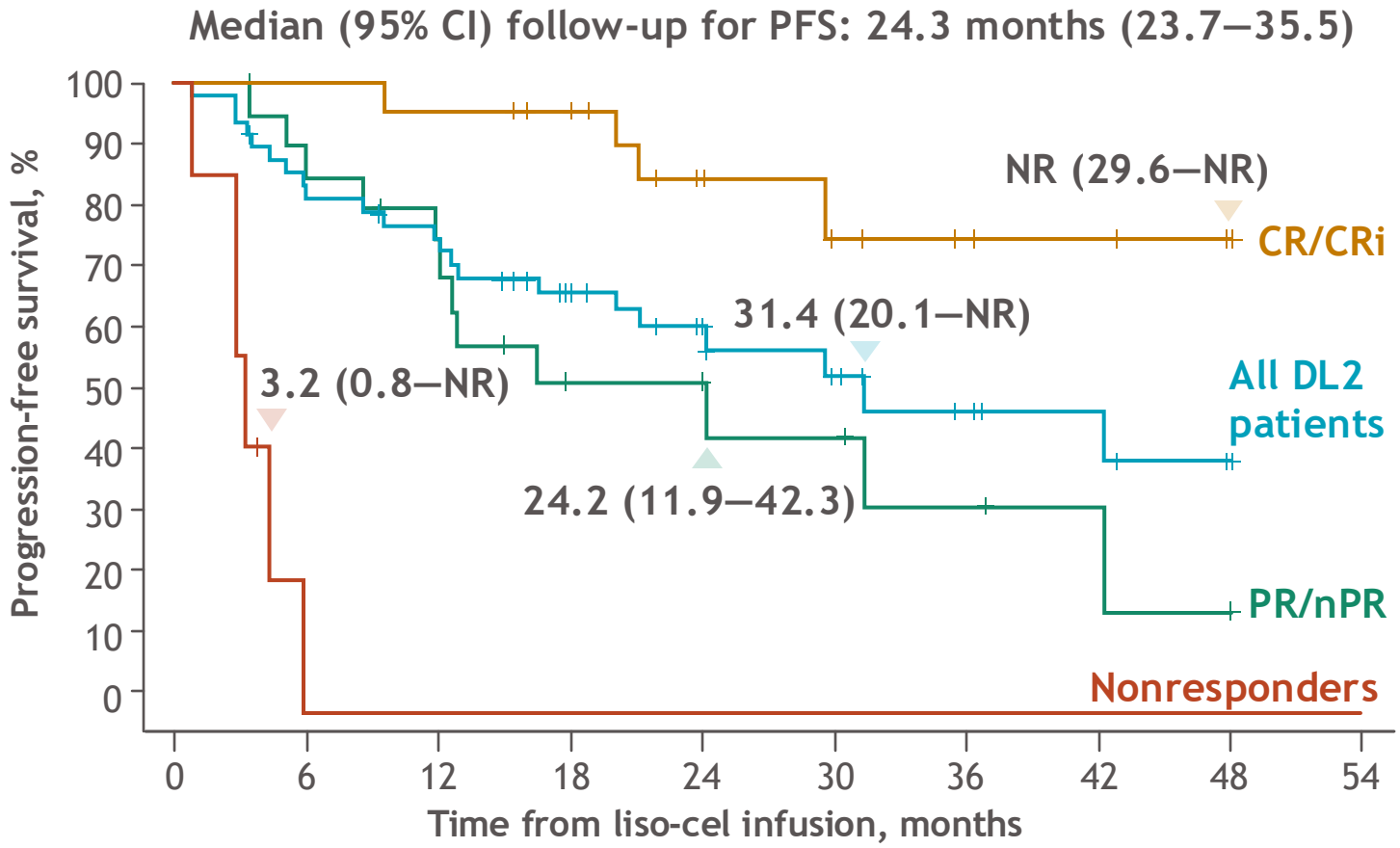




[a]Forty-nine patients (22 with CR/CRi) were evaluable for MRD in marrow.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

Progression-free survival by best overall response at DL2



No. at risk										
CR/CRi	23	23	22	20	12	7	5	4	2	0
PR/nPR	21	17	14	7	6	5	3	2	1	0
Nonresponders	7	0	0	0	0	0	0	0	0	0
All DL2 patients	51	40	36	27	18	12	8	6	3	0

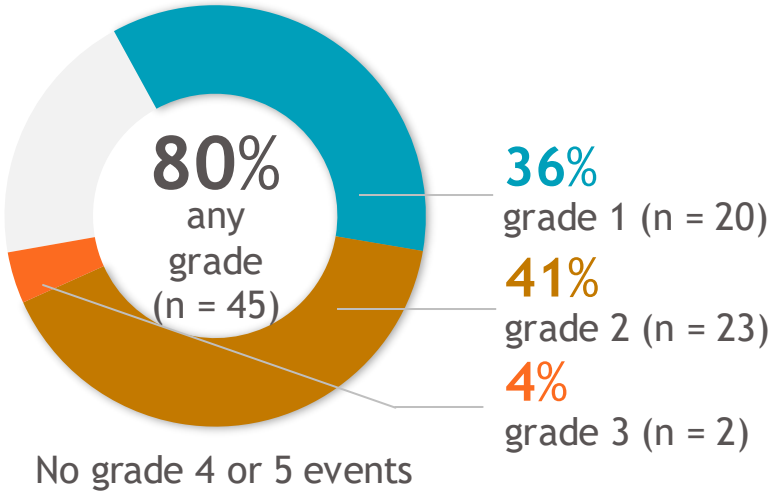
	% progression free (95% CI)	
	12 months	24 months
All DL2 patients (n = 51)	76 (61—85)	62 (46—74)
Patients with CR/CRi (n = 23)	96 (73—99)	85 (60—95)

Data on KM curves are expressed as median (95% CI). No formal landmarking analyses were conducted.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

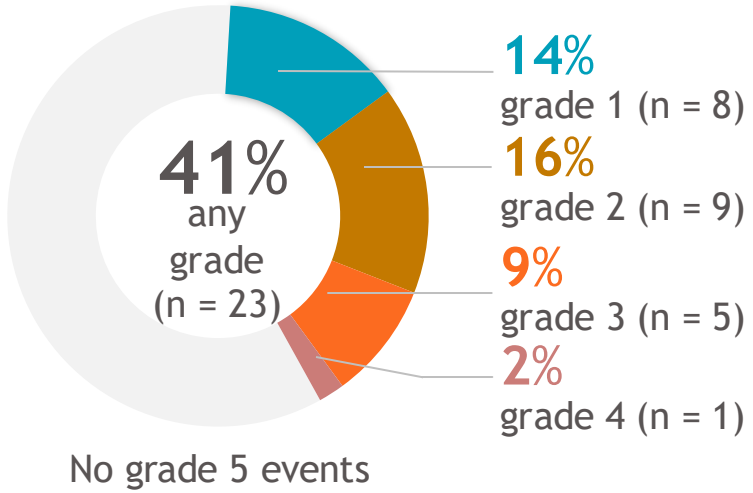
Safety: incidence of CRS and NEs

CRS[a,b]



No grade 4 or 5 events

NEs[a,c]



No grade 5 events

	Total combination-treated set (n = 56)
Median (range) days to CRS onset	7 (1–14)
Median (range) days to CRS resolution	5 (2–18)
Received tocilizumab and/or corticosteroids for CRS and/or NE, n (%)	33 (59)

	Total combination-treated set (n = 56)
Median (range) days to NE onset	8 (1–15)
Median (range) days to NE resolution	8 (1–362)
Received tocilizumab and/or corticosteroids for CRS and/or NE, n (%)	33 (59)

[a]Summed percentages for grouped grades within each graph may not equal the any-grade percentage due to rounding; [b]CRS was graded based on Lee 2014 criteria; [c]NEs were defined as -INV-identified neurological AEs related to liso-cel.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

NEW AGENTS (CLINICAL TRIALS)

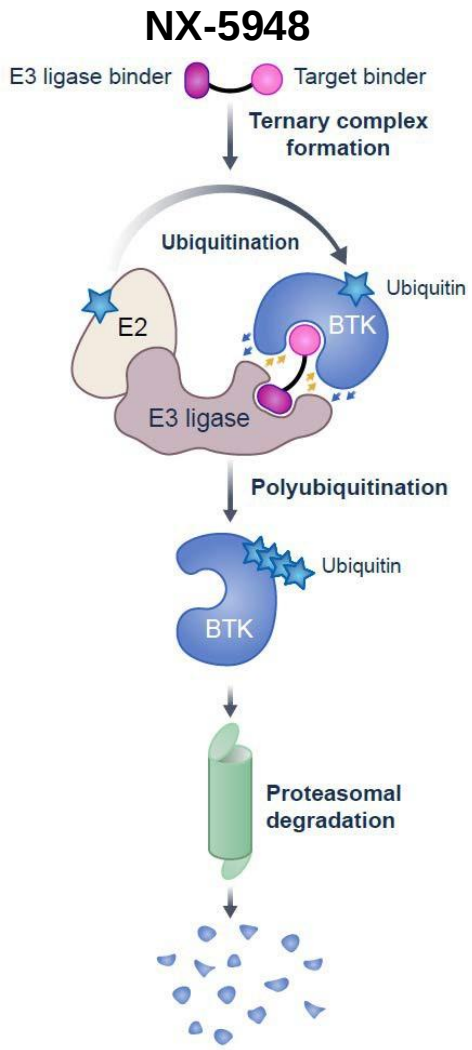
Efficacy and safety of the Bruton’s tyrosine kinase (BTK) degrader NX-5948 in patients with relapsed/refractory chronic lymphocytic leukemia: updated results from an ongoing Phase 1a/b study

Nirav N. Shah, Zulfa Omer, Graham Collins, Francesco Forconi, Alexey Danilov, John C. Byrd, Dima El Sharkawi, Emma Searle, Alvaro Alencar, Shuo Ma, Sarah Injac, Talha Munir

ASH 2024 Annual Meeting, San Diego CA – December 9, 2024

Background

Novel BTK degrader NX-5948 addresses current unmet need in CLL treatment



- The current standard of care in CLL focuses on utilizing the inhibitors of two key signaling pathways – BTK and BCL2
- Unmet need still exists in the CLL treatment landscape:
  - Covalent and non-covalent BTKi resistance mutations[1] are found in more than half of patients who progress on BTKi therapies[2]
  - Some mutations in *BTK* can maintain intact B-cell receptor signaling through a scaffolding function of BTK[3]
  - The number of BCL2i refractory and double (BTKi/BCL2i) refractory patients is growing[4]
- Novel BTK degrader NX-5948 offers an additional treatment modality:
  - Can overcome treatment-emergent BTKi resistance mutations[5] and disrupt BTK scaffolding[3,5]

BCL2, B-cell lymphoma 2; **BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CLL**, chronic lymphocytic leukemia

References
1. Noviski et al. 20th Biennial International Workshop on CLL Meeting, Boston, MA. October 6–9, 2023
2. Molica et al. 66th ASH Annual Meeting, December 7–10, 2024
3. Montoya et al. Science 2024;383
4. Hayama and Riches. Onco Targets 2024;17
5. Linton K, et al. Oral presentation at European Hematology Association Hybrid Congress; 16 June 2024

Baseline Disease Characteristics

Multiple prior lines of therapy and high prevalence of baseline mutations

Characteristics	Patients with CLL/SLL[a] (n=60)
ECOG PS, n (%)	
0	24 (40.0)
1	36 (60.0)
CNS involvement, n (%)	5 (8.3)
Median prior lines of therapy (range)	4.0 (1–12)
Previous treatments[b], n (%)	
BTKi	59 (98.3)
cBTKi	59 (98.3)
ncBTKi[c]	17 (28.3)
BCL2i	50 (83.3)
BTKi and BCL2i	49 (81.7)
CAR-T therapy	3 (5.0)
Bispecific antibody	4 (6.7)
PI3Ki	18 (30.0)
Chemo/chemo-immunotherapies (CIT)	43 (71.7)
Mutation status[d] (n=57), n (%)	
TP53	23 (40.4)
BTK	22 (38.6)
PLCG2	7 (12.3)
BCL2	6 (10.5)

[a]Baseline disease characteristics in CLL cohort were comparable to those in the overall population; [b]Patients could have received multiple prior treatments; [c]All patients who received ncBTKi have also previously received cBTKi; [d]Mutations presented here were centrally sequenced.

BCL2, B-cell lymphoma 2**; BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CAR-T**, chimeric antigen receptor T-cell; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group (ECOG) performance status; **ncBTKi**, non-covalent BTKi; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2; **SLL**, small lymphocytic lymphoma

NX-5948 Safety Profile

TEAEs in ≥10% of overall population or Grade ≥3 TEAEs or SAEs in >1 patient

TEAEs, n (%)	Patients with CLL/SLL (n=60)			Overall population (N=125)		
	Any grade	Grade ≥3	SAEs	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	22 (36.7)	–	–	42 (33.6)	–	–
Fatigue[b]	16 (26.7)	–	–	29 (23.2)	2 (1.6)	–
Petechiae	16 (26.7)	–	–	28 (22.4)	–	–
Thrombocytopenia[c]	10 (16.7)	1 (1.7)	–	26 (20.8)	7 (5.6)	–
Rash[d]	14 (23.3)	1 (1.7)	1 (1.7)	24 (19.2)	2 (1.6)	1 (0.8)
Neutropenia[e]	14 (23.3)	11 (18.3)	–	23 (18.4)	18 (14.4)	–
Anemia	11 (18.3)	4 (6.7)	–	21 (16.8)	10 (8.0)	–
Headache	10 (16.7)	–	–	21 (16.8)	1 (0.8)	1 (0.8)
COVID-19[f]	10 (16.7)	–	–	19 (15.2)	2 (1.6)	2 (1.6)
Diarrhea	12 (20.0)	1 (1.7)	–	18 (14.4)	1 (0.8)	–
Cough	9 (15.0)	–	–	16 (12.8)	1 (0.8)	–
Pneumonia[g]	4 (6.7)	2 (3.3)	2 (3.3)	10 (8.0)	6 (4.8)	6 (4.8)
Lower respiratory tract infection	3 (5.0)	1 (1.7)	1 (1.7)	9 (7.2)	3 (2.4)	2 (1.6)
Fall	1 (1.7)	1 (1.7)	1 (1.7)	8 (6.4)	2 (1.6)	2 (1.6)
Hypertension	2 (3.3)	1 (1.7)	–	7 (5.6)	5 (4.0)	–
Hyponatremia	–	–	–	3 (2.4)	2 (1.6)	–
Pulmonary embolism	1 (1.7)	1 (1.7)	1 (1.7)	2 (1.6)	2 (1.6)	2 (1.6)
Subdural hematoma	1 (1.7)	–	1 (1.7)	2 (1.6)	1 (0.8)	2 (1.6)

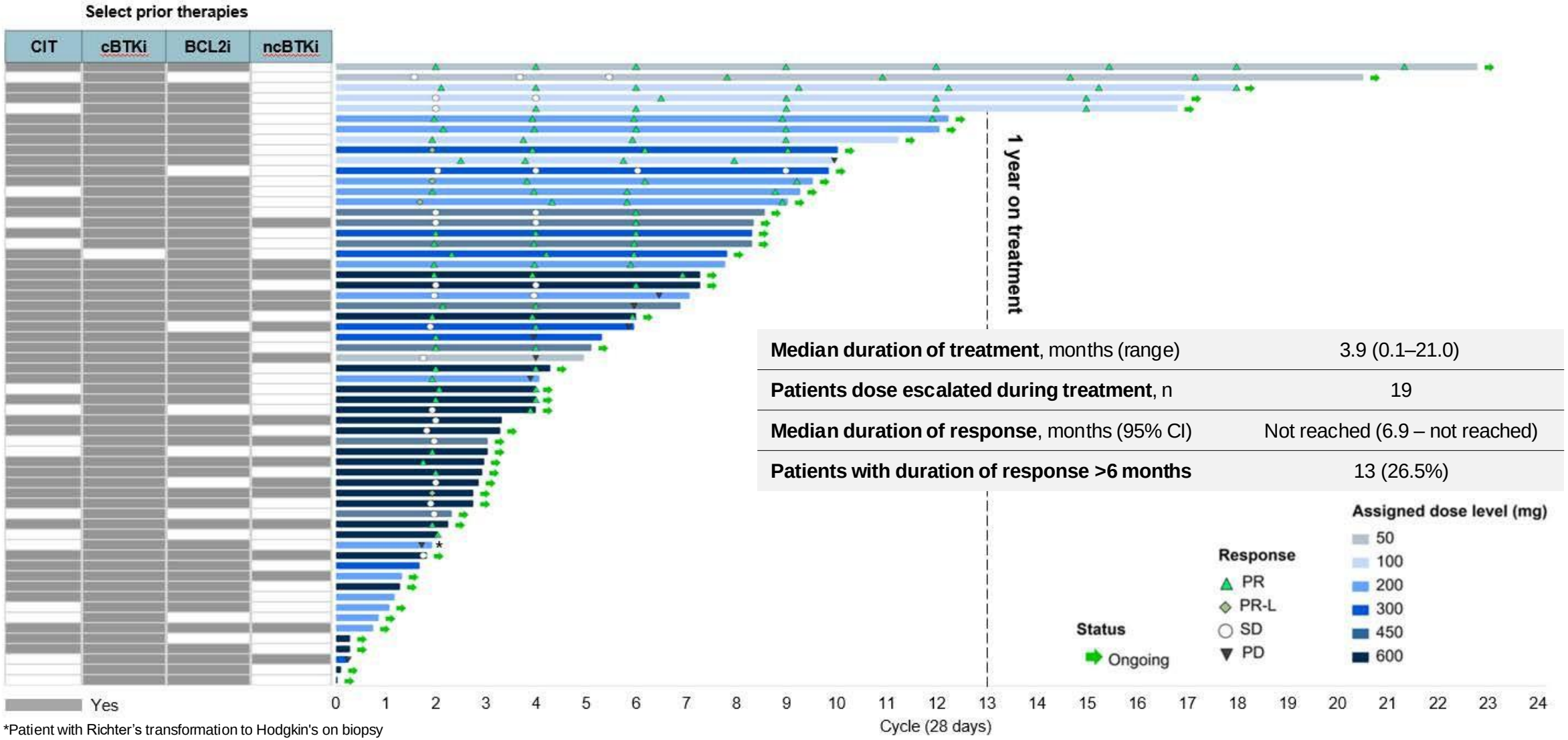
- Tolerable safety profile consistent with prior disclosures
- 1 case of Grade 1 AFib in a CLL patient with pre-existing AFib
- 6 TEAEs resulted in drug discontinuation (1 CLL; 5 NHL)
- 2 Grade 5 AEs (1 pulmonary embolism; 1 case pending) deemed not related to NX-5948

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Fatigue was transient; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [e]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [f]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'; [g]Aggregate of 'pneumonia' and 'pneumonia klebsiella'

AE, adverse event; **AFib**, atrial fibrillation; **CLL**, chronic lymphocytic leukemia; **NHL**, non-Hodgkin's lymphoma; **SAE**, serious adverse event; **SLL**, small lymphocytic lymphoma; **TEAE**, treatment emergent AE

NX-5948 Duration of Treatment

Durable responses regardless of prior therapy



Median duration of treatment, months (range)	3.9 (0.1–21.0)
Patients dose escalated during treatment, n	19
Median duration of response, months (95% CI)	Not reached (6.9 – not reached)
Patients with duration of response >6 months	13 (26.5%)

*Patient with Richter's transformation to Hodgkin's on biopsy

BCL2i, BCL2 inhibitor; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CIT**, chemo/chemo-immunotherapies; **ncBTKi**, non-covalent BTKi; **PD**, progressive disease; **PR**, partial response; **PR-L**, PR with rebound lymphocytosis; **SD**, stable disease; **CI**, confidence interval

Data cutoff: 10 Oct 2024

American Society of Hematology
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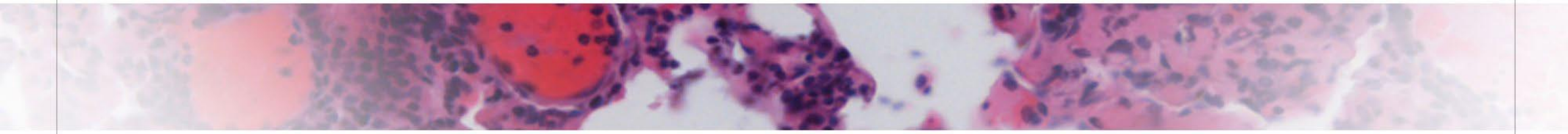

Preliminary Efficacy and Safety of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Results From the Phase 1 CaDAnCe-101 Study

Meghan C. Thompson,[1] Ricardo D. Parrondo,[2] Anna Maria Frustaci,[3] John N. Allan,[4] Paolo Ghia,[5,6] Irina Mocanu,[7] Constantine S. Tam,[8] Judith Trotman,[9] Inhye E. Ahn,[10] Stephan Stilgenbauer,[11] Lydia Scarfò,[5,6] Xiangmei Chen,[12] Kunthel By,[13] Shannon Fabre,[13] Daniel Persky,[13] Amit Agarwal,[13] John F. Seymour[14]

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CaDAnCe-101

Baseline Patient Characteristics

Heavily pretreated, with high-risk CLL features

	Total (N=60)
Age, median (range), years	70 (50-91)
Male, n (%)	39 (65.0)
ECOG PS, n (%)	
0	34 (56.7)
1	25 (41.7)
2	1 (1.7)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	27/56 (48.2)
Unmutated IGHV	38/46 (82.6)
del(17p) and/or *TP53* mutation	40/60 (66.7)
Complex karyotype (≥3 abnormalities)	19/38 (50.0)

	Total (N=60)
Mutation status, n/N (%)	
BTK mutation present	18/54 (33.3)
PLCG2 mutation present	8/54 (14.8)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	43 (71.7)
cBTK inhibitor	56 (93.3)
ncBTK inhibitor	13 (21.7)
BCL2 inhibitor	50 (83.3)
cBTK + BCL2 inhibitors	38 (63.3)
cBTK + ncBTK + BCL2 inhibitors	12 (20.0)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	50/56 (89.3)

Data cutoff: September 2, 2024.

[a] Remaining 6 patients discontinued prior BTK inhibitor due to toxicity (n=3), treatment completion (2), and other (n=1).

cBTK, covalent BTK; ncBTK, noncovalent BTK.

Safety Summary and All-Grade TEAEs in ≥10% of All Patients

- No atrial fibrillation
- No pancreatitis
- Major hemorrhage[b]: 3.3% (n=2; grade 1 subarachnoid hemorrhage [n=1] and grade 3 subdural hemorrhage [n=1])
- Febrile neutropenia: 1.7% (n=1; in the context of COVID-19 pneumonia and norovirus diarrhea)

Patients, n (%)	Total (N=60) All Grade	Grade ≥3
Fatigue	18 (30.0)	1 (1.7)
Contusion (bruising)	17 (28.3)	0
Neutropenia[c]	15 (25.0)	13 (21.7)
Diarrhea	14 (23.3)	1 (1.7)
Anemia	11 (18.3)	0
Lipase increased[a]	10 (16.7)	2 (3.3)
Cough	9 (15.0)	0
Pneumonia	8 (13.3)	5 (8.3)
Pyrexia	8 (13.3)	0
Arthralgia	7 (11.7)	0
COVID-19	7 (11.7)	0
Dyspnea	7 (11.7)	0
Peripheral edema	7 (11.7)	0
Thrombocytopenia[d]	7 (11.7)	2 (3.3)
Amylase increased[a]	6 (10.0)	0
Nausea	6 (10.0)	0
Sinusitis	6 (10.0)	0

Median follow-up: 10.2 months (range, 0.3-26.4+).

[a] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [b] Grade ≥3, serious, or any central nervous system bleeding. [c] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [d] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

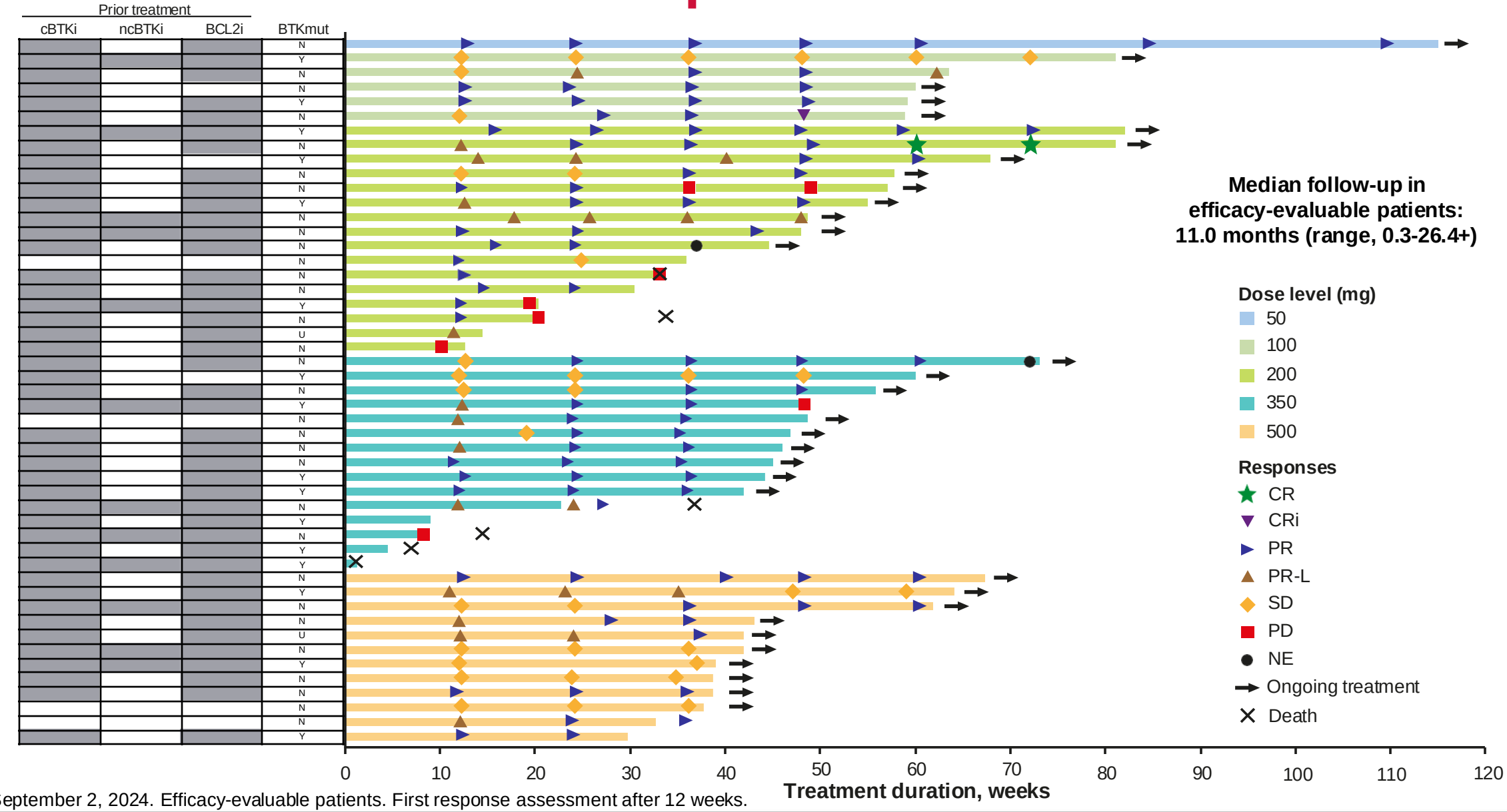
Overall Response Rate

Significant Responses, Particularly at 200 mg Dose Level

	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total[a] (N=49)
Best overall response, n (%)						
CR/CRi	0	1 (20.0)	1 (6.3)	0	0	**2 (4.1)**
PR[b]	1 (100)	3 (60.0)	12 (75.0)	10 (66.7)	7 (58.3)	33 (67.3)
PR-L	0	0	2 (12.5)	0	1 (8.3)	3 (6.1)
SD	0	1 (20.0)	0	1 (6.7)	4 (33.3)	6 (12.2)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (4.1)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (6.1)
ORR, n (%)[c]	1 (100)	4 (80.0)	**15 (93.8)**	10 (66.7)	8 (66.7)	**38 (77.6)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (93.8)	11 (73.3)	12 (100)	44 (89.8)
Time to first response, median (range), months[e]	2.9 (2.9-2.9)	4.2 (2.8-6.2)	2.9 (2.6-8.3)	2.8 (2.6-8.3)	2.8 (2.6-8.3)	2.8 (2.6-8.3)
Time to best response, median (range), months	2.9 (2.9-2.9)	5.6 (2.8-11.1)	3.4 (2.6-13.8)	5.6 (2.6-8.3)	4.2 (2.6-8.6)	3.6 (2.6-13.8)
Duration of exposure, median (range), months	26.4 (26.4-26.4)	13.8 (13.6-18.6)	10.6 (2.9-18.9)	10.3 (0.2-16.8)	9.3 (6.8-15.4)	10.4 (0.2-26.4)

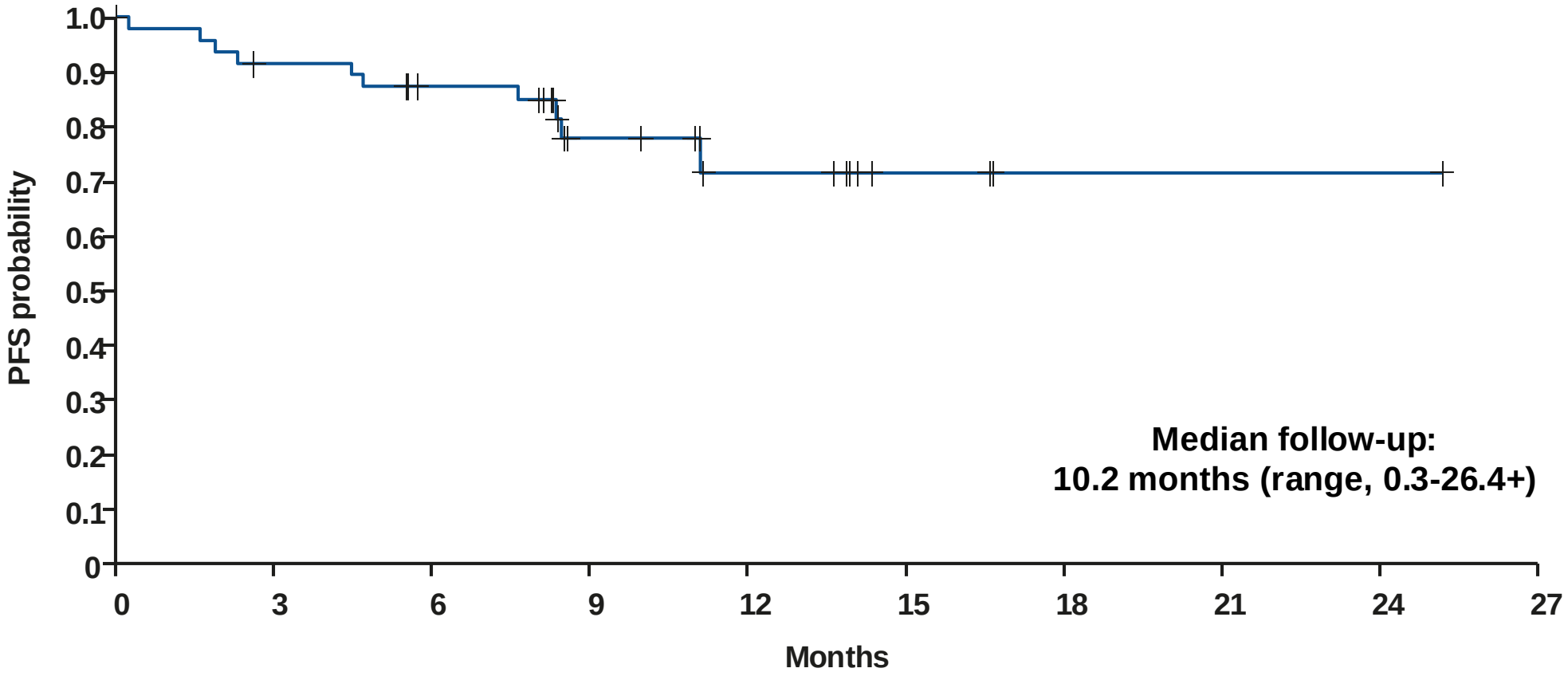
[a] Efficacy-evaluable population. [b] Out of 33 patients with PR, 8 achieved all nodes normalized. [c] Includes best overall response of PR-L or better. [d] Includes best overall response of SD or better. [e] In patients with a best overall response of PR-L or better.
CRi, complete response with incomplete marrow recovery; PR-L, partial response with lymphocytosis.

Treatment Duration and Response



Data cutoff: September 2, 2024. Efficacy-evaluable patients. First response assessment after 12 weeks.

Progression-Free Survival



No. at risk:	60	43	37	20	10	4	1	1	1	0

Data cutoff: September 2, 2024.

Epcoritamab Monotherapy in Patients (Pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from CLL Expansion and Optimization Cohorts of EPCORE CLL-1

Alexey Danilov, MD, PhD,[1] Bita Fakhri, MD, MPH,[2] Farrukh Awan, MD,[3] Hans Herluf Bentzen, MD,[4] Herbert Eradat, MD,[5] Carsten Utoft Niemann, MD, PhD,[6] Fritz Offner, MD, PhD,[7] Christian Bjørn Poulsen, MD,[8] Thor Høyer, MD,[9] Mar Bellido, MD, PhD,[10] Damien Roos-Weil, MD, PhD,[11] Alessandra Ferrajoli, MD,[12] Meghan C. Thompson, MD,[13] Jacob Haaber Christensen, MD, PhD,[14] Ann Janssens, MD, PhD,[15] Tamar Tadmor, MD,[16] Mazyar Shadman, MD, MPH,[17] Pegah Jafarinasabian, MD, PhD,[18] Jimin Zhang, PhD,[19] Marcia Rios, MBA,[19] Alexandra Kuznetsova, PhD,[20] Rebecca Valentin, MD, PhD,[20] Arnon P. Kater, MD, PhD[21]

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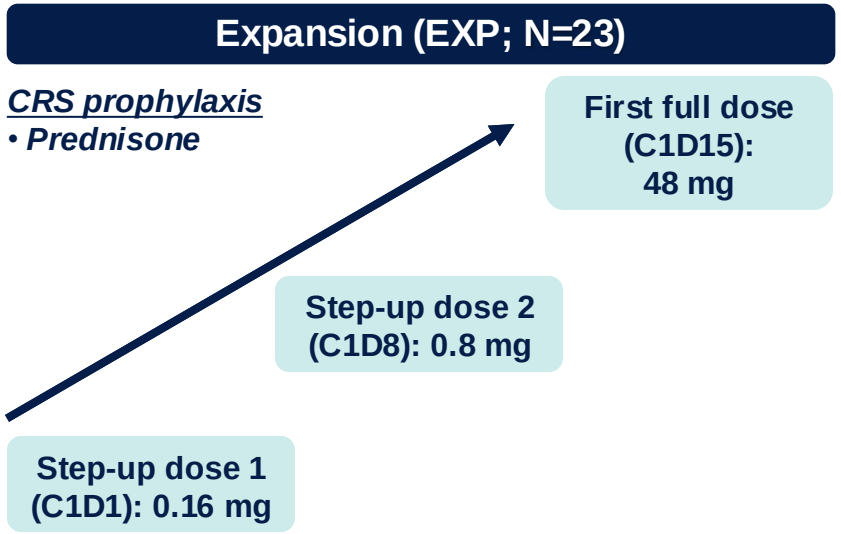
Presented at the American Society of Hematology Annual Meeting; December 7–10, 2024; San Diego, CA

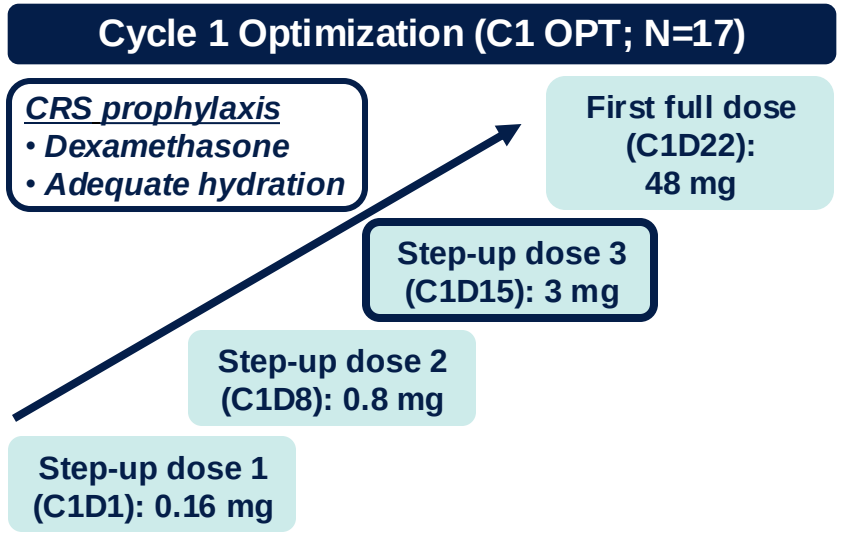
Study Design: EPCORE® CLL-1 Expansion and C1 Optimization

Key inclusion criteria

- $CD20^+$ R/R CLL
- ≥2 prior lines of systemic therapy
- ECOG PS 0–2
- Measurable disease with ≥5×10^9/L B lymphocytes (expansion only)
- No prior allogeneic HSCT



Data cutoff: May 28, 2024
Median follow-up: 22.8 months



Data cutoff: May 28, 2024
Median follow-up: 2.9 months

- **Primary endpoint (EXP):** Overall response rate
- **Primary endpoint (C1 OPT):** Incidence and severity of CRS, ICANS, and clinical TLS
- **Key secondary endpoints (EXP):** CR rate, time to response, MRD (PBMCs using the clonoSEQ® assay), and safety/tolerability

- To ensure patient safety and better characterize CRS, inpatient monitoring was required for at least 24 hours after each epcoritamab dose in C1

ClinicalTrials.gov: NCT04623541; EudraCT: 2023-504828-25.

Comparable High-Risk R/R CLL Populations Between EXP and C1 OPT

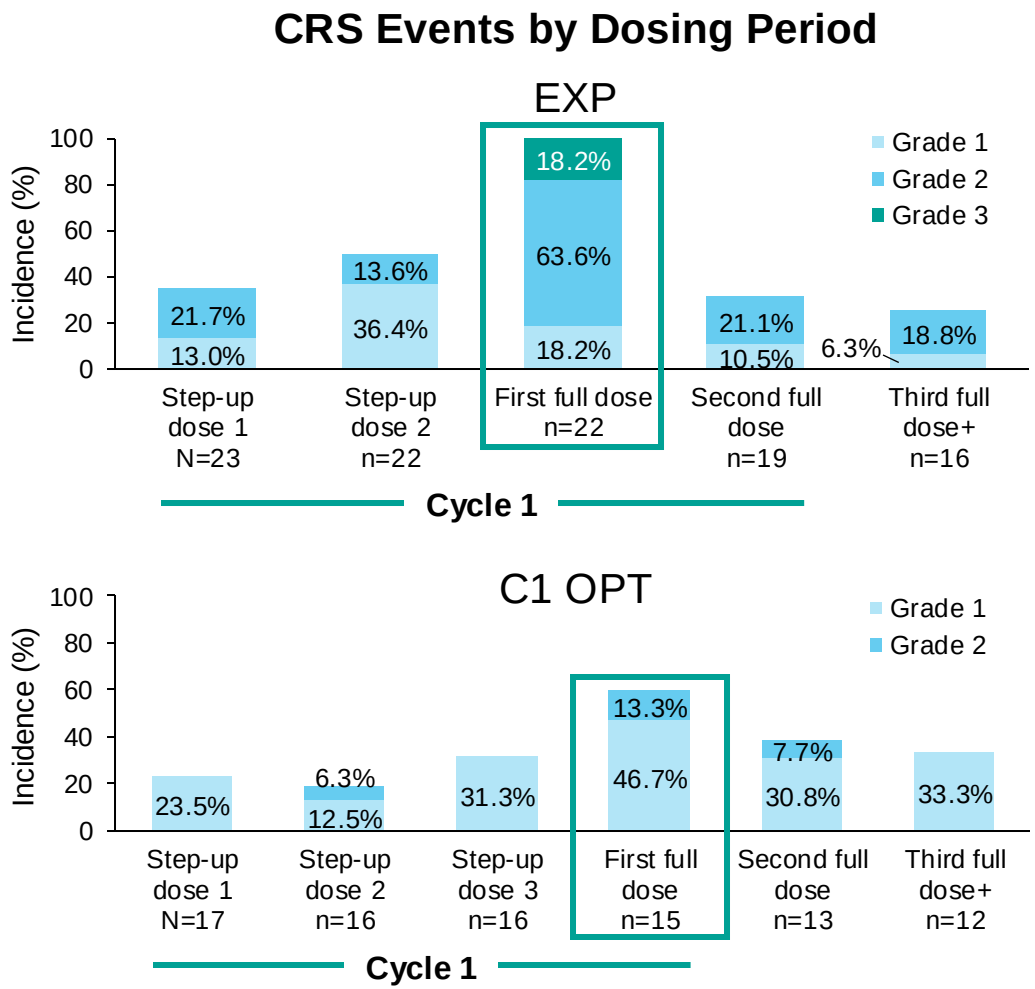
Characteristic	EXP N=23	C1 OPT N=17
Median age, years (range)	72 (55–83)	68 (56–81)
Male sex at birth, n (%)	17 (74)	14 (82)
Race, n (%)[a]		
White	19 (83)	14 (82)
Black or African American	0	1 (6)
Not reported	3 (13)	2 (12)
CLL characteristics (local lab), n (%)		
High risk		
Rai stage III–IV[b]	13 (57)	10 (59)
Binet stage C[c]	2 (9)	6 (35)
Beta-2 microglobulin >3.5 mg/L	19 (83)	10 (59)
IGHV unmutated	16 (70)	12 (71)
Unknown	3 (13)	3 (18)
TP53 aberration	15 (65)	10 (59)
Unknown	2 (9)	2 (12)

Treatment History	EXP N=23	C1 OPT N=17
Median time from initial diagnosis to first dose, **years** (range)	13 (6–19)	11 (6–18)
Median time from last treatment to first dose, **months** (range)	0.7 (0.1–49.4)	1.6 (−0.7–39.6)
Median number of prior lines of therapy (range)	**4 (2–10)**	**4 (2–10)**
≥4 prior lines of therapy, n (%)	14 (61)	9 (53)
Prior therapy, n (%)[d]	23 (100)	17 (100)
Chemoimmunotherapy	23 (100)	12 (71)
Small molecules		
BTK inhibitor[e]	23 (100)	17 (100)
Pirtobrutinib	1 (4)	5 (29)
Refractory to BTK inhibitor	20 (87)	16 (94)
BCL-2 inhibitor	19 (83)	15 (88)
Discontinuation due to progression	10 (43)	10 (59)
Relapsed <12 months from last dose	3 (13)	4 (24)

[a]Race was reported as other for 1 patient in EXP. Ethnicity was reported as Hispanic or Latino for 1 patient in EXP and 1 patient in C1 OPT. Ethnicity was not reported or missing for 17 patients in EXP and 11 patients in C1 OPT. [b]In EXP, Rai staging was performed for 16 patients, and Rai stage was I–II for 3 patients; in C1 OPT, Rai stage was 0 for 1 patient, I–II for 5 patients, and unknown for 1 patient. [c]In EXP, Binet staging was performed for 7 patients, and Binet stage was A for 1 patient and B for 4 patients; in C1 OPT, Binet staging was performed for 14 patients, and Binet stage was A for 2 patients and B for 6 patients. [d]Three patients had received prior CAR T-cell therapy (EXP, n=1; C1 OPT, n=2). [e]All patients received a covalent BTK inhibitor.

C1 OPT Mitigated Adverse Events of Interest Including ICANS and Clinical TLS

	EXP N=23	C1 OPT N=17
CRS, n (%)	**22 (96)**	**14 (82)**
Grade 1	2 (9)	12 (71)
Grade 2	16 (70)	2 (12)
Grade 3	4 (17)	0
Treated with tocilizumab, n (%)	20 (87)	6 (35)
Leading to treatment discontinuation, n (%)	**0**	**0**
CRS resolution, n/n (%)	22/22 (100)	14/14 (100)
Median time to resolution, days (range)	3 (1–16)	3.5 (1–7)
ICANS, n (%)	**3 (13)**	**0**
Grade 1	1 (4)	0
Grade 2	2 (9)	0
Clinical TLS, n (%)	**1 (4)**	**0**
Grade 2	1 (4)	0



Deep Responses Across Subgroups

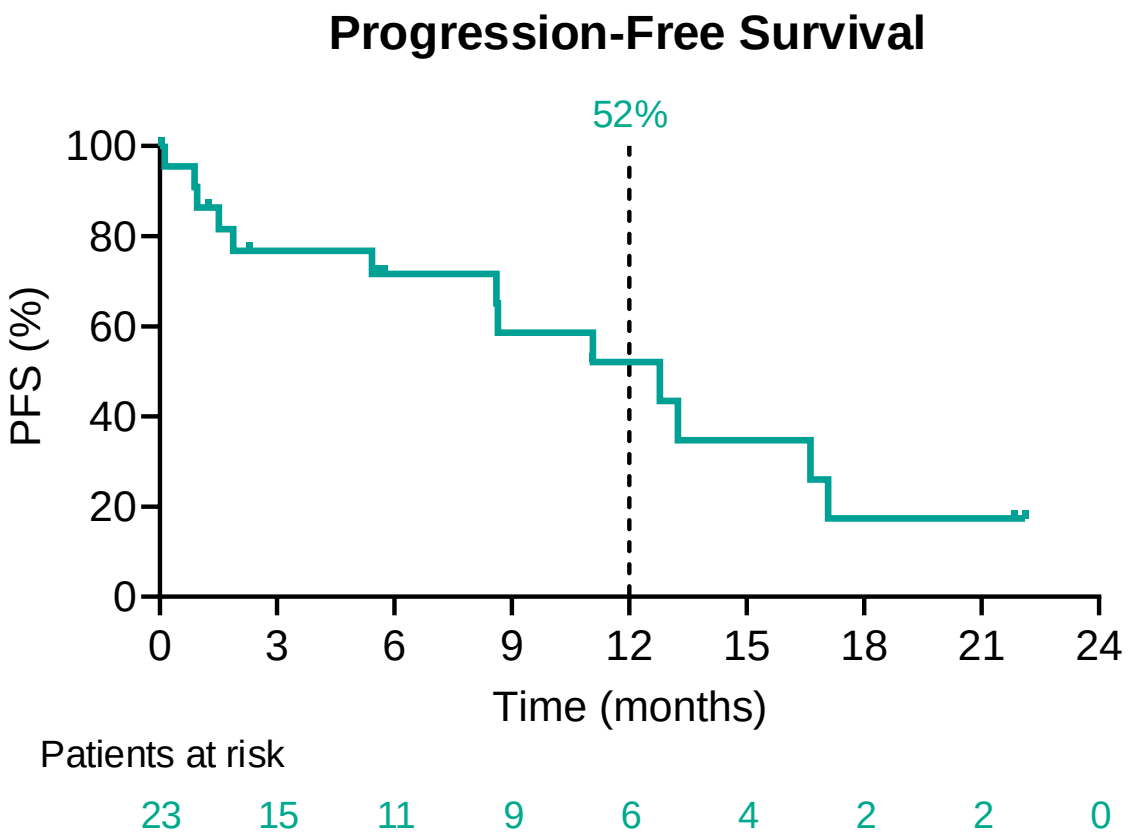
Response, n (%)	EXP mFU: 22.8 months					C1 OPT mFU: 2.9 months
	Full Analysis Set N=23	Response Evaluable n=21	*TP53* Aberration n=15	*IGHV* Unmutated n=16	Double Exposed[a] n=19	Response Evaluable n=10
Overall response[b]	**14 (61)**	**14 (67)**	**10 (67)**	**10 (63)**	**10 (53)**	**6 (60)**
Complete response	9 (39)	9 (43)	5 (33)	7 (44)	7 (37)	1 (10)
Partial response	5 (22)	5 (24)	5 (33)	3 (19)	3 (16)	5 (50)
Stable disease	4 (17)	4 (19)	2 (13)	3 (19)	4 (21)	2 (20)
Progressive disease	1 (4)	1 (5)	1 (7)	0	1 (5)	1 (10)

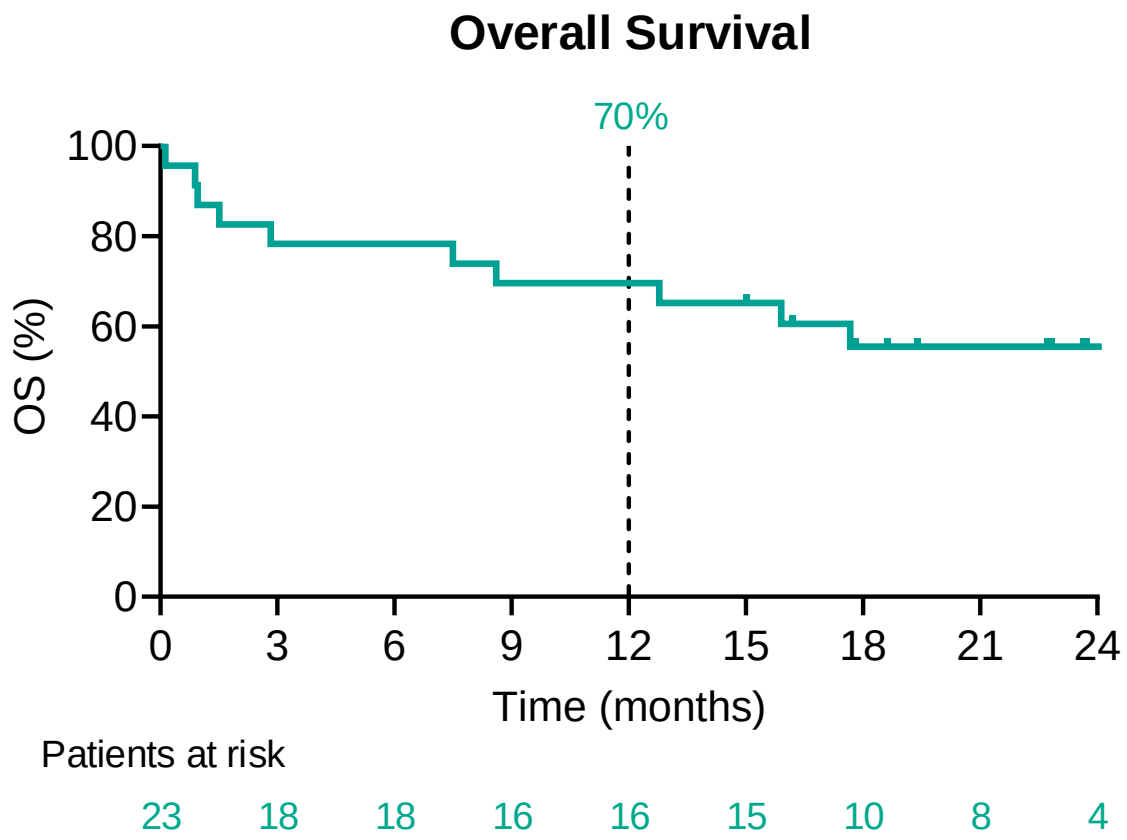
- With limited follow-up, the C1 OPT regimen does not appear to affect epcoritamab efficacy
- uMRD4 in PBMCs was observed in most responders, including all patients with CR who were tested for MRD

EXP MRD Negativity, n/n (%)[c]	uMRD4	uMRD6[d]
Overall response[b]	9/12 (75)	8/12 (67)
Complete response	7/7 (100)	6/7 (86)
Partial response	2/5 (40)	2/5 (40)
Full analysis set	9/23 (39)	8/23 (35)

Four patients (*TP53* aberration, n=2; *IGHV* unmutated, n=3; double exposed, n=4) in EXP and 1 in C1 OPT shown above were not evaluable or had no assessment, including 3 in EXP (*TP53* aberration, n=2; *IGHV* unmutated, n=2; double exposed, n=3) and 1 in C1 OPT who died without postbaseline assessment. [a]Patients previously treated with both a BTK inhibitor and a BCL-2 inhibitor. [b]Response assessment according to iwCLL criteria. [c]Patients evaluated for MRD had at least 1 on-treatment MRD result and were not MRD negative at baseline. MRD was only evaluated in patients with CR or PR. [d]Two of 3 evaluated patients had uMRD6 in bone marrow at or shortly after the first CR assessment. mFU, median follow-up.

Progression-Free and Overall Survival in EXP





- Median PFS was 12.8 months (95% CI, 5.4–17.1); median OS was not reached (95% CI, 8.6 months–NR)

Kaplan–Meier estimates are shown.

Thank you!

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