BTKi/Venetoclax-Refractory CLL

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Disclosure Information

Susan O'Brien, MD

I have the following financial relationships to disclose:

Sponsor/Company	Affiliation(s)
AbbVie	Consultant
Acerta	Research Support
Alexion	Consultant
Alliance	Research Support
Amgen	Consultant
Aptose Biosciences Inc.	Consultant
Astellas	Consultant
AstraZeneca	Consultant
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Bristol Myers Squibb	Consultant
Caribou Biosciences, Inc.	Research Support
Celgene	Consultant
DynaMed	Consultant
Eli Lilly and Company	Consultant
Gilead	Consultant/Research Support
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Janssen Oncology	Consultant
Johnson and Johnson	Consultant
Juno Therapeutics	Consultant
Kite	Research Support
Loxo Oncology, Inc.	Research Support
MEI Pharma, Inc.	Consultant
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NOVA Research Company	Consultant
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Regeneron	Research Support
TG Therapeutics	Consultant/Research Support
Vaniam Group LLC	Consultant
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Vida Ventures	Consultant

Updated January 2022

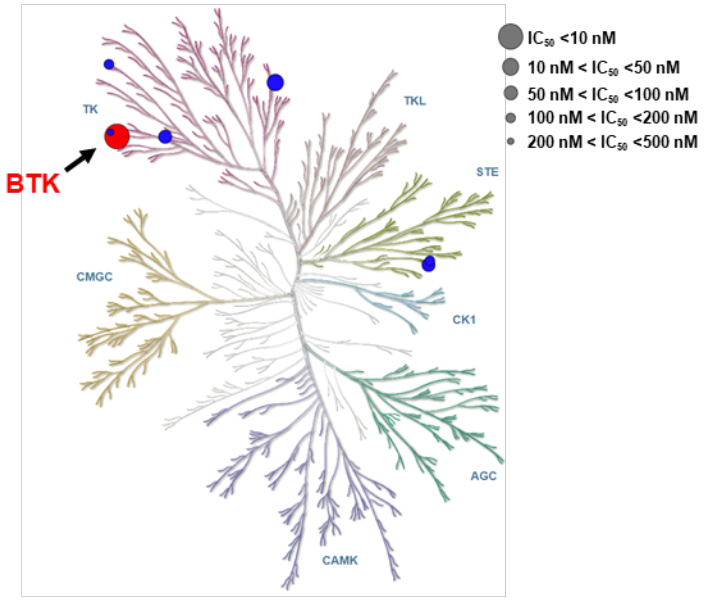
BTKi/Venetoclax-Refractory CLL vs double exposed CLL

Refractory disease: PD on BTKi, not intolerant, PD on Ven-based therapy

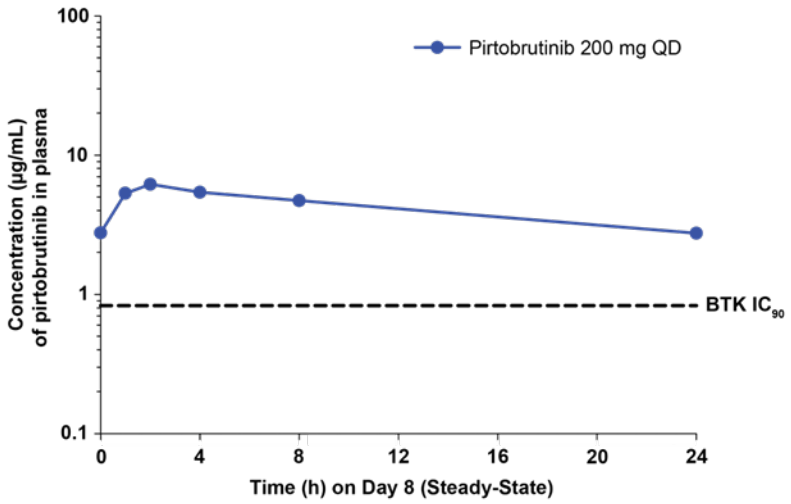
Double exposed: usually PD on BTKi (not intolerant), finite therapy with Ven and relapsed

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

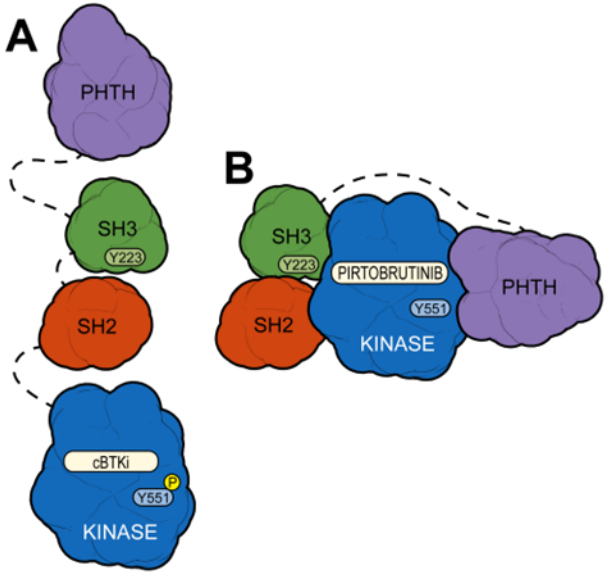
Highly selective for BTK[5,6]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



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

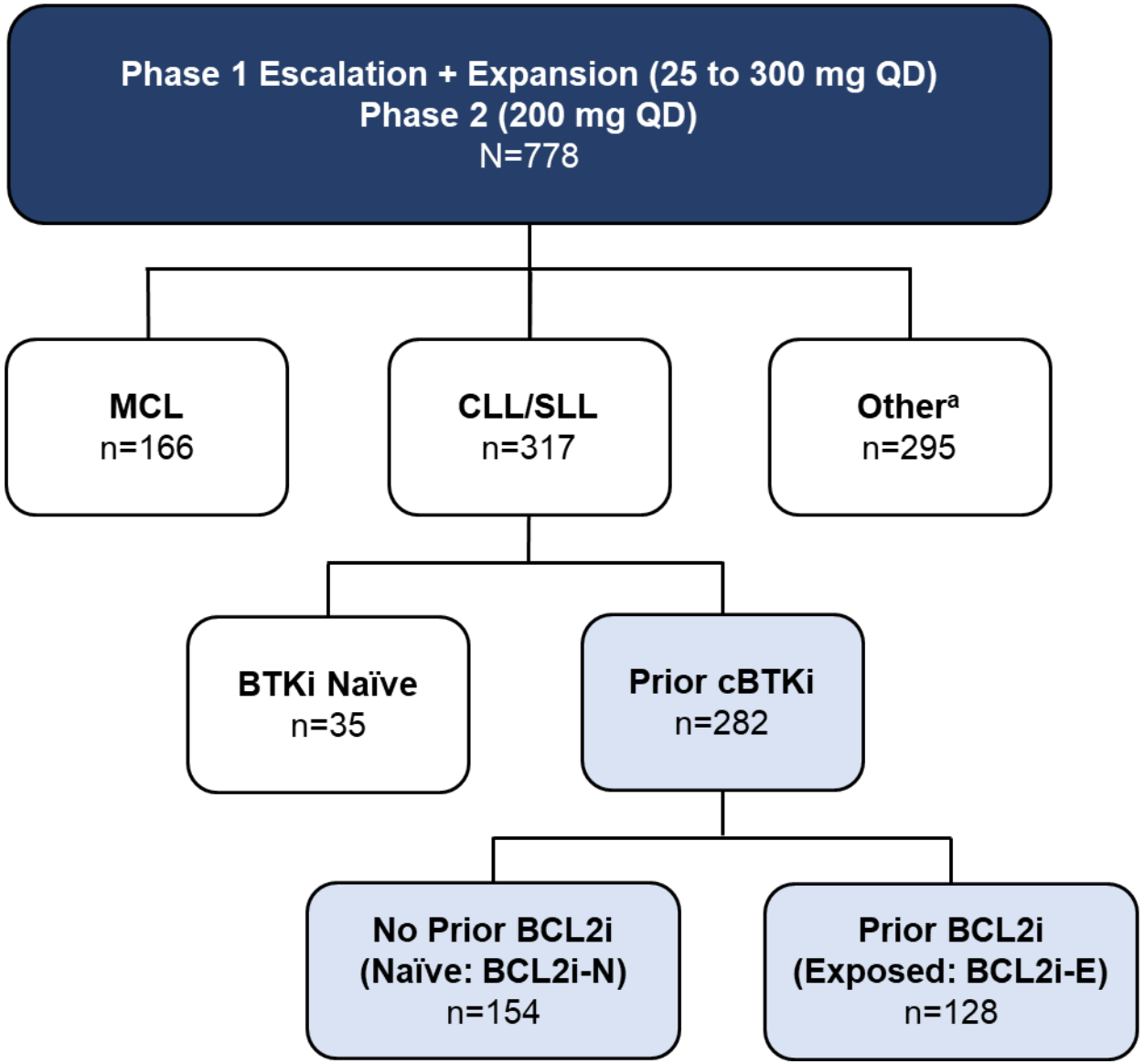


- Inhibits both WT and C481-mutant BTK with equal low nM potency[7]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[7]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access 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.

Woyach et al.; ASH 2023

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.

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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.

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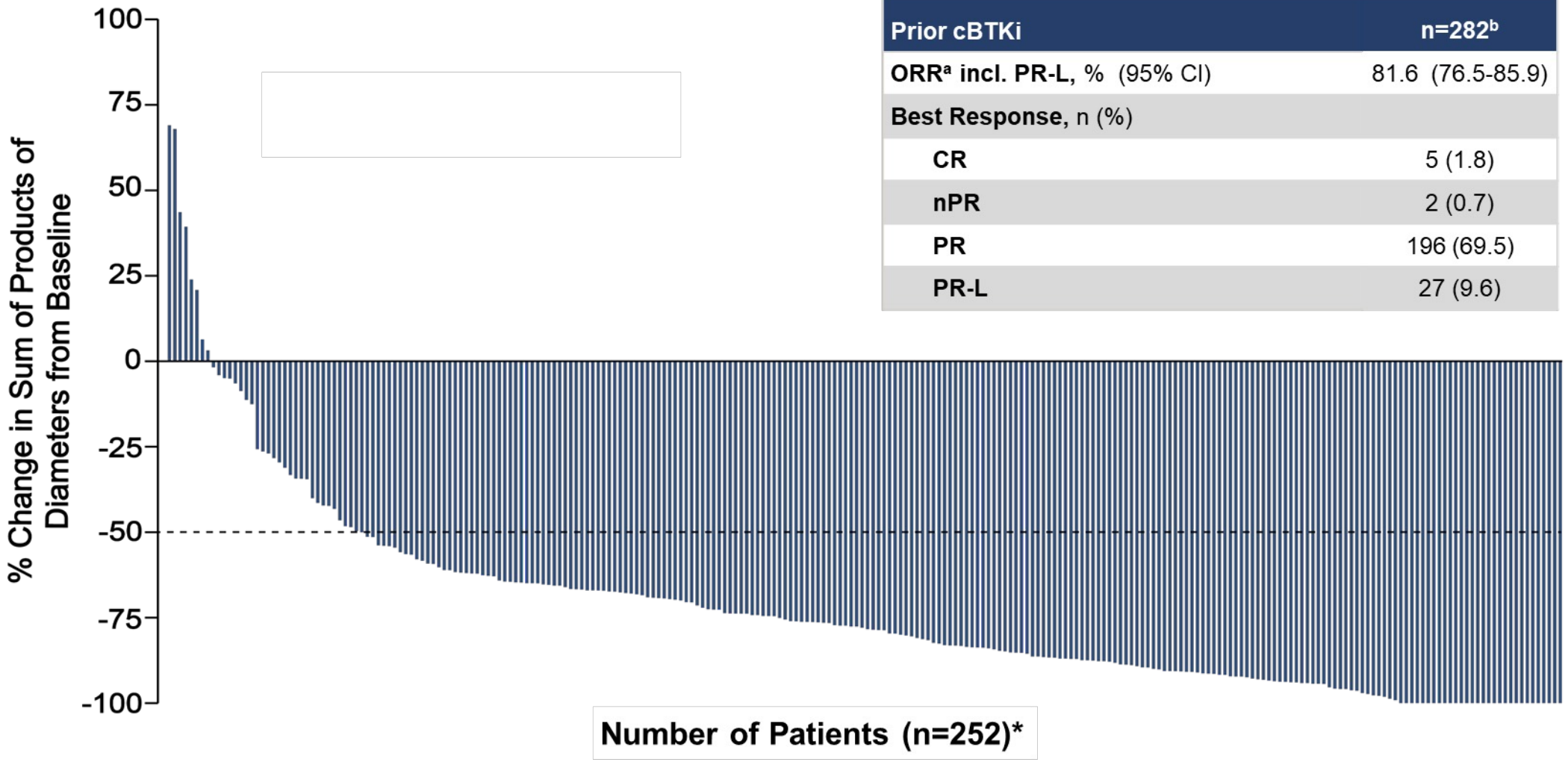
Pirtobrutinib Efficacy in All Patients with CLL/SLL who Received Prior cBTKi



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.

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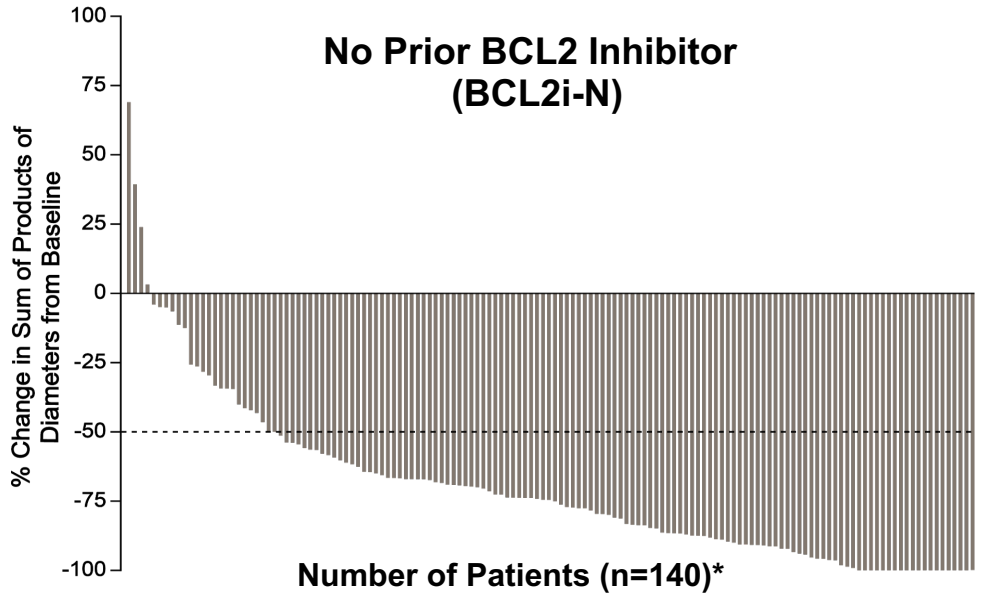
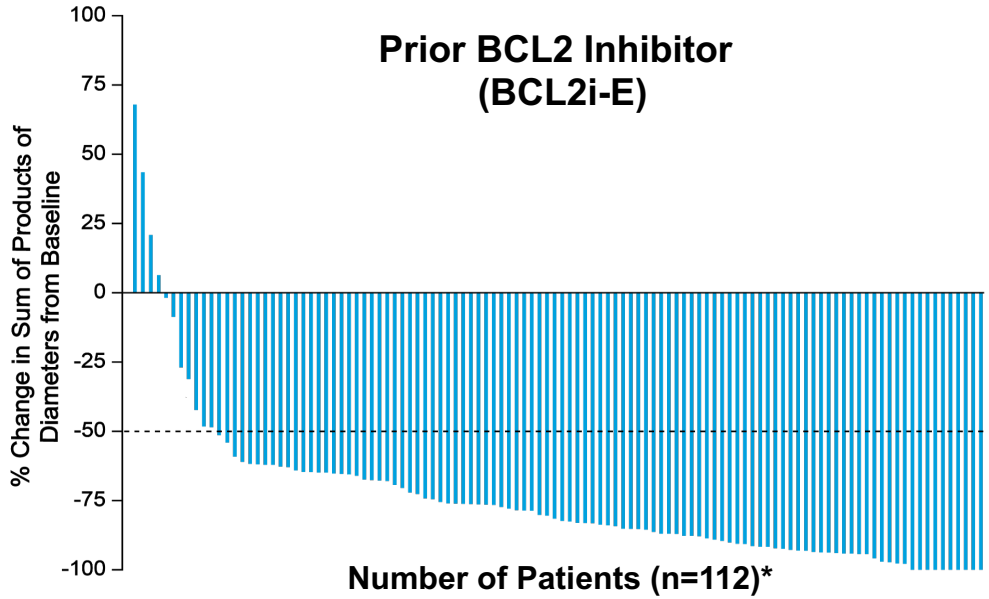
Pirtobrutinib Efficacy in Patients who Received Prior cBTKi, with or without Prior BCL2i





BCL2i-N	(n=154)[b]
ORR[a] incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
Best Response, n (%)	
CR	5 (3.2)
nPR	2 (1.3)
PR	108 (70.1)
PR-L	13 (8.4)

BCL2i-E	(n=128)[c]
ORR[a] incl. PR-L, % (95% CI)	79.7 (71.7-86.3)
Best Response, n (%)	
CR	0 (0)
nPR	0 (0)
PR	88 (68.8)
PR-L	14 (10.9)

Data of patients with baseline and at least one evaluable post baseline tumor measurement.*Data for 14/154 BCL2i-N patients and 16/128 BCL2i-E patients are not shown in the waterfall plots 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 includes patients with a best response of PR-L or better divided by the total number of patients; [b]6 BCL2i-N patients (3.9%) and [c]8 BCL2i-E patients (6.3%) with a best response of not evaluable (NE) are included in the denominators. Response status per iwCLL 2018 criteria based on IRC assessment..

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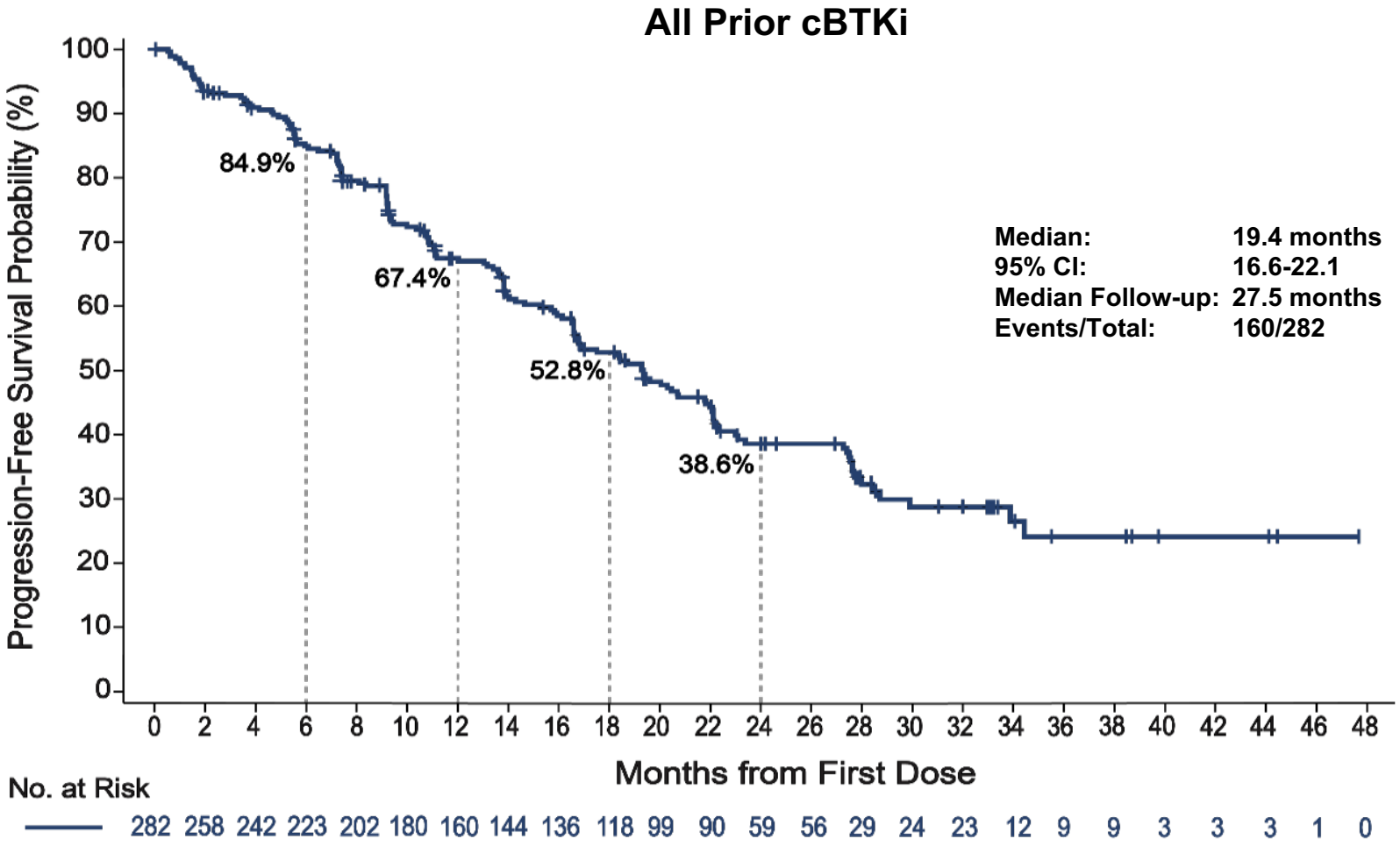
Pirtobrutinib Progression-Free Survival in Patients with Prior cBTKi



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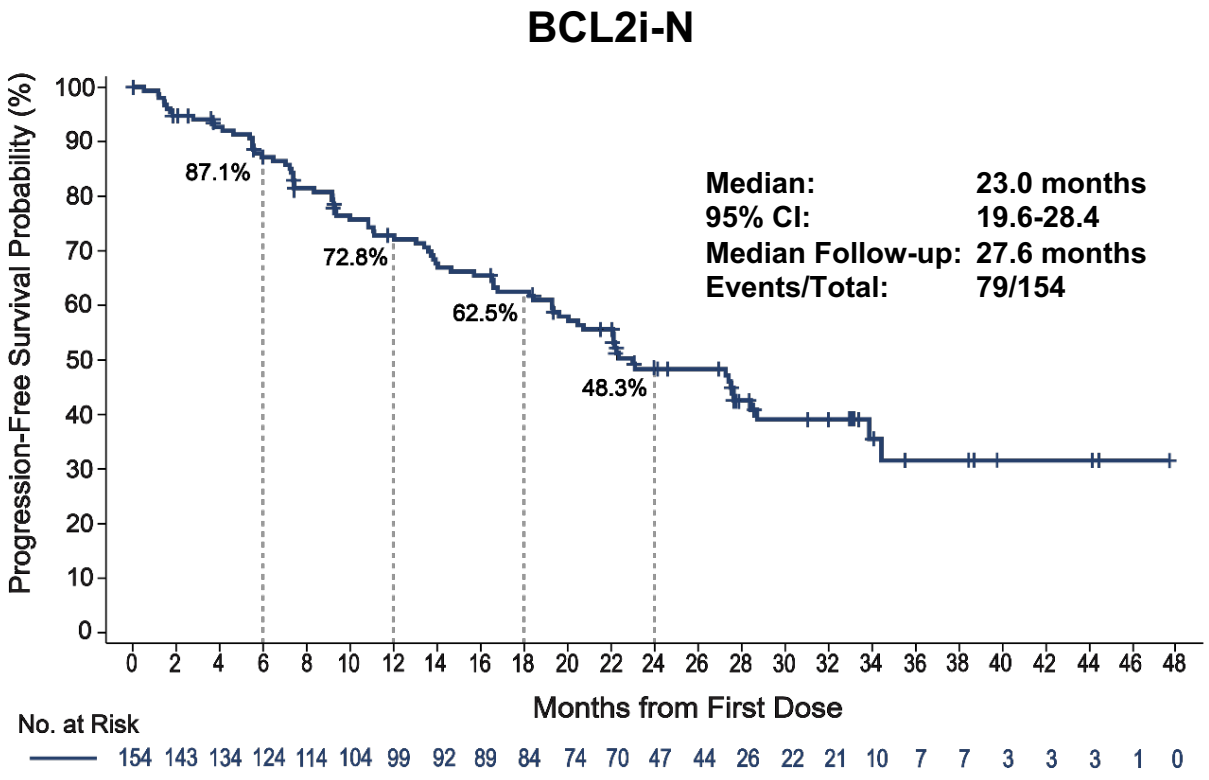
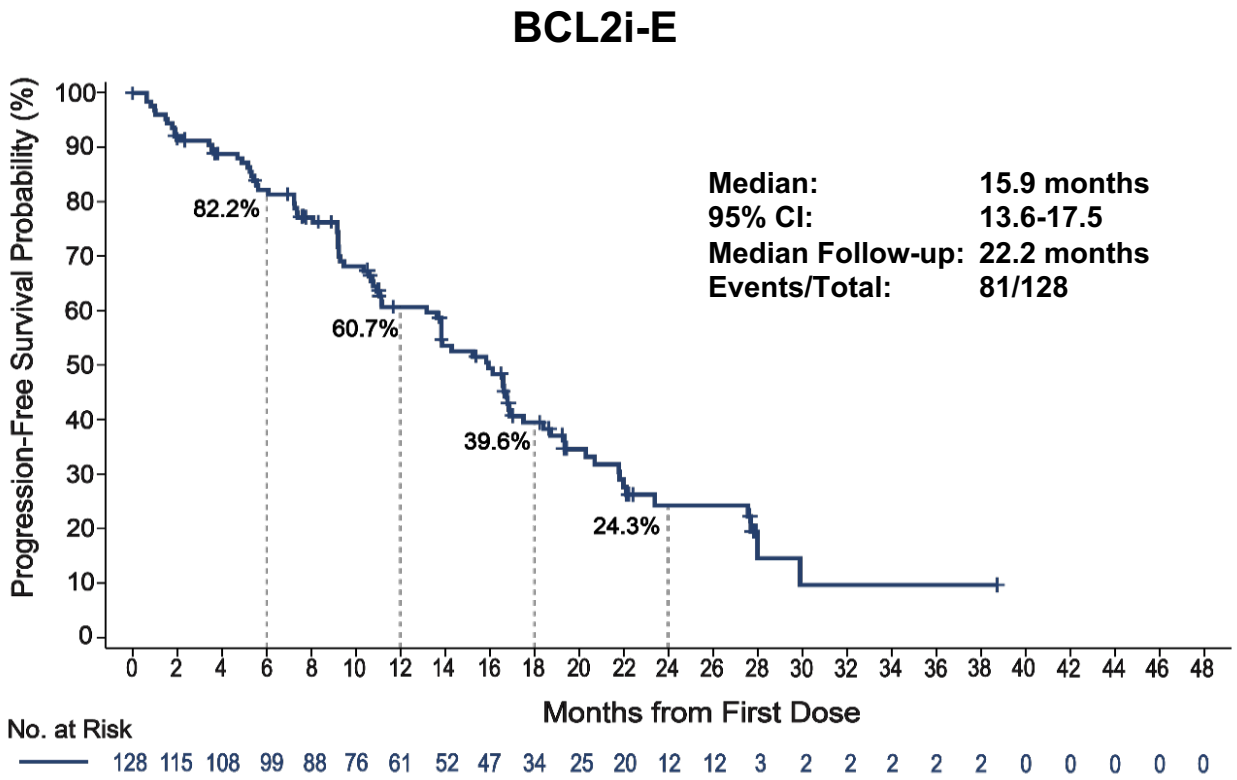
Pirtobrutinib Progression-Free Survival with Prior cBTKi, with or without Prior BCL2i





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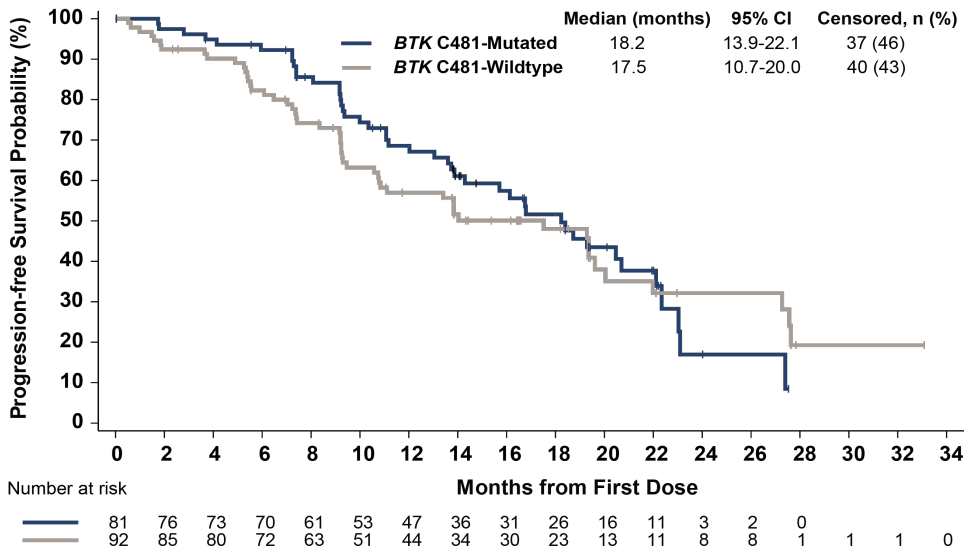
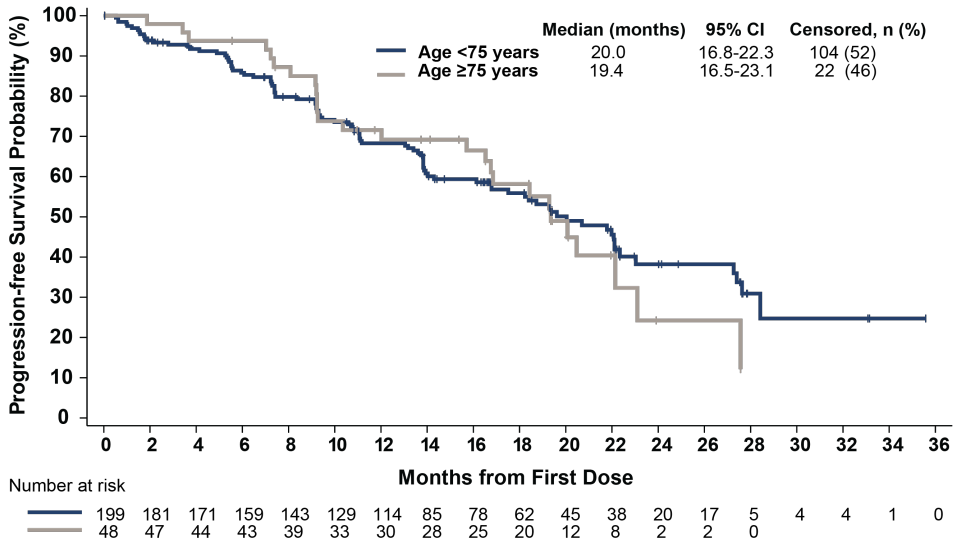
Progression-Free Survival in CLL/SLL Subgroups

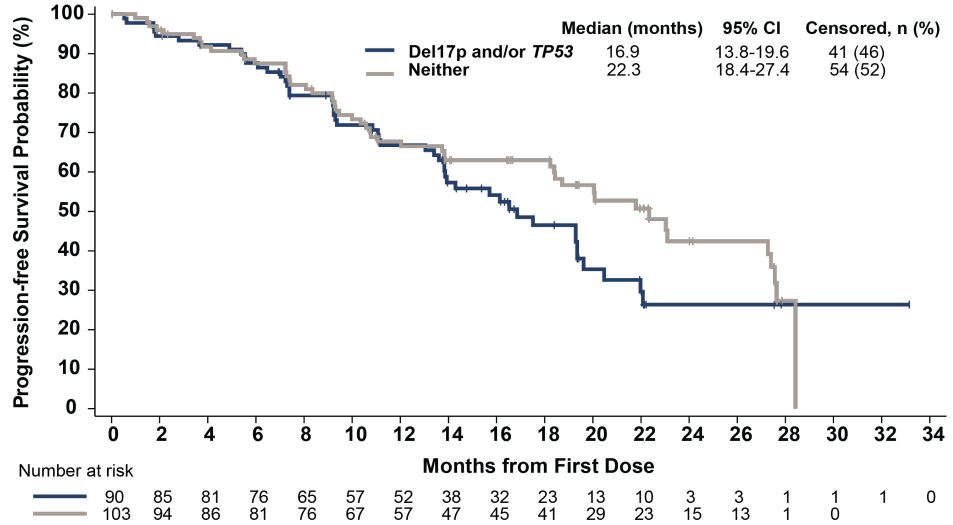
BTK C481 mutation status[a,b]



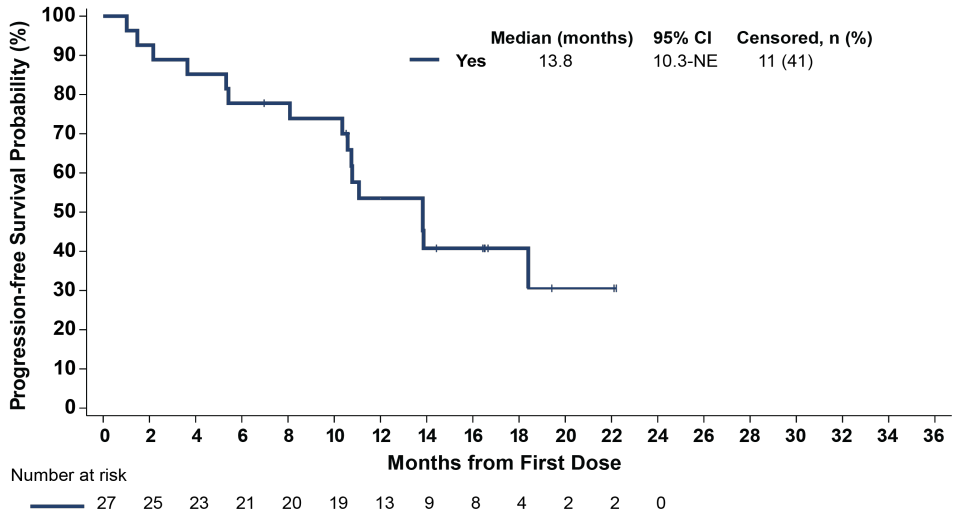
Age



del(17p) and/or *TP53* mutation[a]

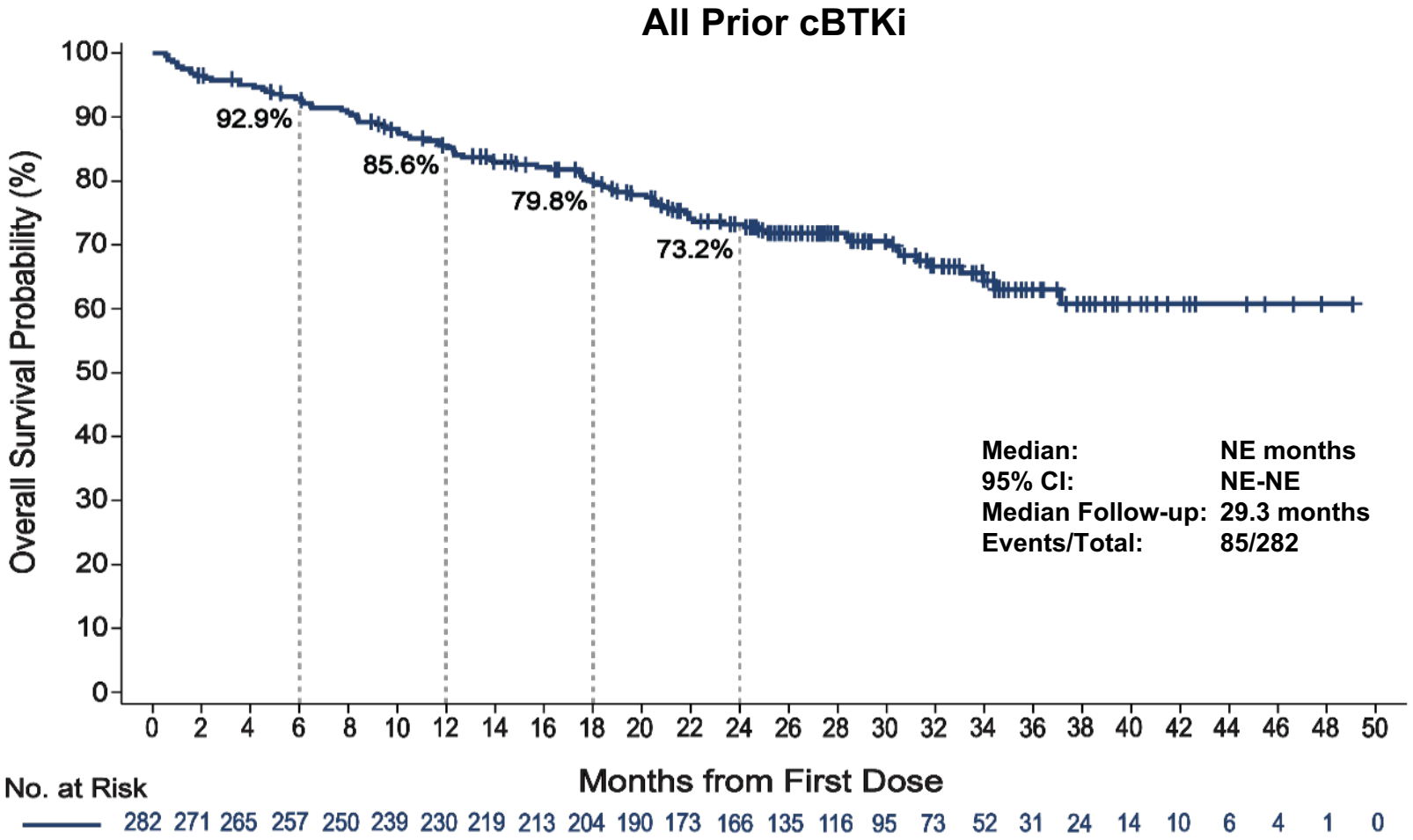


Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment. [a]*BTK* C481 mutation status, del(17p), and *TP53* mutation status were centrally determined and based on pre-treatment samples. [b]Patients with available mutation data who progressed on any prior BTKi.

Pirtobrutinib Overall Survival in Patients with Prior cBTKi



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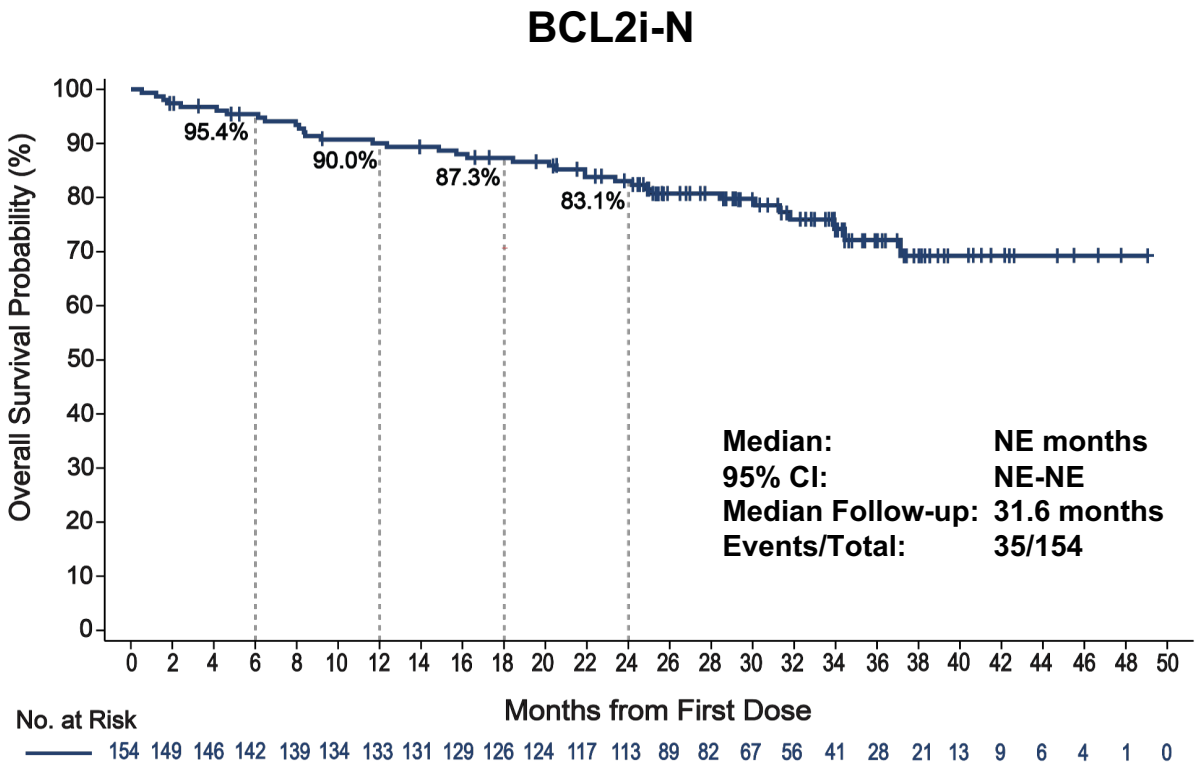
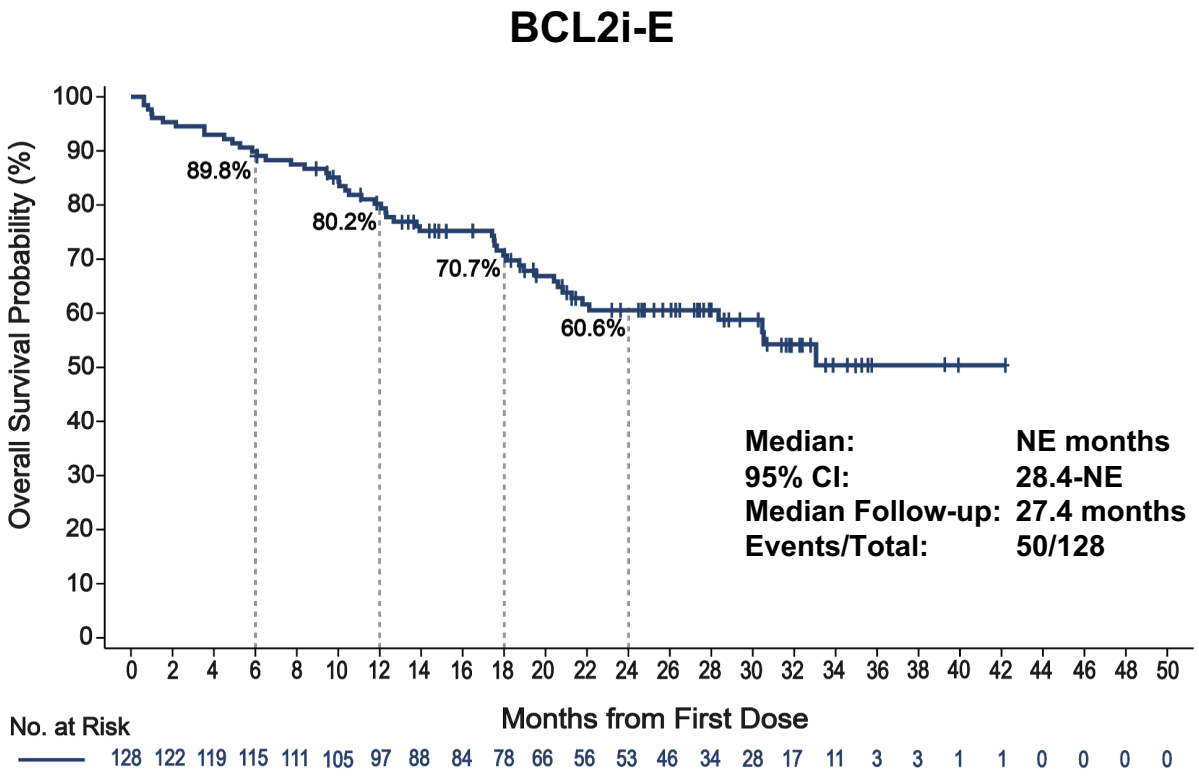
Pirtobrutinib Overall Survival with Prior cBTKi, with or without Prior BCL2i





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Pirtobrutinib Safety Profile of Patients who Received Prior cBTKi

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	36.9	1.8	3.5	0.0
Neutropenia[b,c]	34.4	28.4	19.5	15.2
Diarrhea	28.4	0.4	7.8	0.0
Cough	27.3	0.0	1.8	0.0
Contusion	26.2	0.0	17.4	0.0
Covid-19	25.9	4.6	0.7	0.0
Dyspnea	22.3	2.1	0.7	0.4
Nausea	22.0	0.0	3.5	0.0
Abdominal pain	21.3	1.8	2.1	0.4
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	74.1	30.9	12.8	4.3
Bruising[e]	30.1	0.0	19.1	0.0
Rash[f]	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage[g]	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter[h,i]	4.6	1.8	1.4	0.7

Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)
11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib dose reduction
7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib discontinuation
Safety profiles of BCL2i-N and BCL2i-E subgroups were similar and are described via the QR code

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Neutropenia at baseline for prior BTKi (n=282) was 18.4, BCL2i-N (n=154) was 11.0 and BCL2i-E (n=128) was 27.3. [c]Aggregate of neutropenia and neutrophil count decreased. [d]Aggregate of all preferred terms including infection and COVID-19. [e]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion. [f]Aggregate of all preferred terms including rash. [g]Aggregate of all preferred terms including hemorrhage or hematoma. [h]Aggregate of atrial fibrillation and atrial flutter. [i]Of the 13 total afib/aflutter TEAEs in the prior BTKi safety population (n=282), 6 occurred in patients with a prior medical history of atrial fibrillation.

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Conclusions

- With median follow-up of 30 months, pirtobrutinib continues to demonstrate clinically meaningful and durable efficacy in heavily pretreated patients with CLL/SLL who received prior covalent BTK inhibitor
  - ORR including PR-L was ~80% regardless of prior BCL2 inhibitor exposure
  - Median PFS was 19.4 months overall, with 23.0 months for BCL2i-N patients and 15.9 months for BCL2i-E patients
- Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BCL2i-N and BCL2i-E patients
- These results suggest that continuation of BTK pathway inhibition may be an important sequencing approach to consider in the treatment of CLL/SLL
- **On December 1, 2023, the FDA granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor**

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

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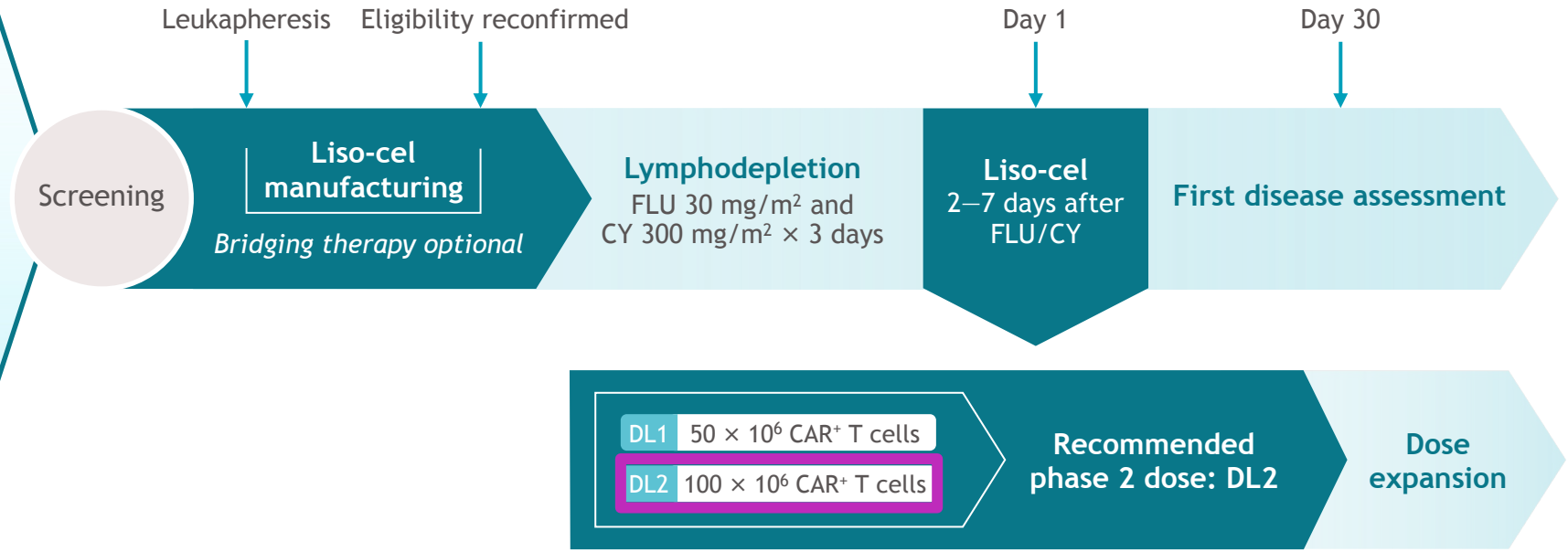
TRANSCEND CLL 004: Liso-cel phase 1/2, open-label, multicenter study

Key eligibility criteria

- Age ≥ 18 years
- R/R CLL/SLL
- Previously failed or ineligible for BTKi
- Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
- ECOG PS ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy



Follow-up

On-study: 24 or 48 months
Long-term (NCT03435796): up to 15 years after liso-cel infusion

Primary endpoint (PEAS at DL2)
CR/CRi rate per iwCLL 2018 by IRC assessment

Key secondary endpoints (PEAS at DL2)
ORR, uMRD rate in blood

Post hoc analyses
Median time to next treatment

ClinicalTrials.gov: NCT03331198.
CY, cyclophosphamide; DL, dose level; FLU, fludarabine; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PEAS, primary efficacy analysis set (prespecified subset of patients with BTKi progression and venetoclax failure); uMRD, undetectable minimal residual disease.

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Demographics and baseline characteristics

	Full study population (n = 118)	BTKi progression/venetoclax failure subset (n = 71)
Median (range) age, y	65.0 (49–82)	66.0 (49–78)
Median (range) prior lines of systemic therapy	5 (2–14)	5 (2–14)
Bulky lymph nodes,[a] n (%)		
Yes	53 (45)	33 (46)
Unknown	9 (8)	8 (11)
High-risk cytogenetics,[b] n (%)	98 (83)	61 (86)
Prior BTKi, n (%)	118 (100)	71 (100)
BTKi refractory[c]	104 (88)	71 (100)
BTKi relapsed[d]	2 (2)	0
BTKi intolerant only	12 (10)	0
Prior venetoclax, n (%)	95 (81)	71 (100)
Venetoclax refractory	90 (76)	68 (96)
Venetoclax relapsed[d]	0	0
Venetoclax intolerant only	4 (3)	3 (4)
Prior BTKi and venetoclax, n (%)	95 (81)	71 (100)
BTKi progression/venetoclax failure,[e] n (%)	71 (60)	71 (100)
Received bridging therapy, n (%)	90 (76)	56 (79)

[a]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [b]Includes del(17p), *TP53* mutation, unmutated immunoglobulin heavy-chain variable region, and complex cytogenetics; [c]Defined as no response or progression ≤ 6 months from last dose of therapy; [d]Defined as disease progression in a patient who previously had CR/CRi or PR/nPR for ≥ 6 months; [e]Including patients who progressed on a BTKi and met one of the following: (1) discontinued venetoclax due to disease progression or intolerability and patient's disease met indications for further therapy per iwCLL 2018, or (2) failed to achieve an objective response ≤ 3 months of initiating therapy.
nPR, nodular partial response/remission.

Siddiqi T, et al. ASH 2023 [Presentation #330]

Efficacy outcomes: DL2 only

	Full study population at DL2 (n = 88)	BTKi progression/venetoclax failure subset at DL2 (n = 50)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	17 (19) [12–29]	10 (20) [10–34]
Key secondary endpoints		
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37–59]	22 (44) [30–59]
uMRD rate in blood, n (%) [95% CI]	58 (66) [55–76]	32 (64) [49–77]
Exploratory endpoint: uMRD rate in marrow, n (%) [95% CI]	53 (60) [49–71]	30 (60) [45–74]
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	17 (19)	10 (20)
PR/nPR	25 (28)	12 (24)
SD	34 (39)	21 (42)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Time to first response, months, median (range)	1.3 (0.8–17.4)	1.1 (0.8–17.4)
Time to first CR/CRi, months, median (range)	5.5 (0.8–18.0)	2.1 (0.8–18.0)

- **uMRD was achieved in MRD-evaluable patients in the full population at DL2 by:**
  - **15/15 (100%) patients with CR/CRi in blood and 15[a]/16 (94%) in marrow**
  - 24/24 (100%) patients with PR/nPR in blood and 23/23 (100%) in marrow
  - 19/32 (59%) patients with SD in blood and 15/32 (47%) in marrow

[a]One patient had an indeterminate status for MRD, which was considered positive as per FDA guidelines. SD, stable disease.

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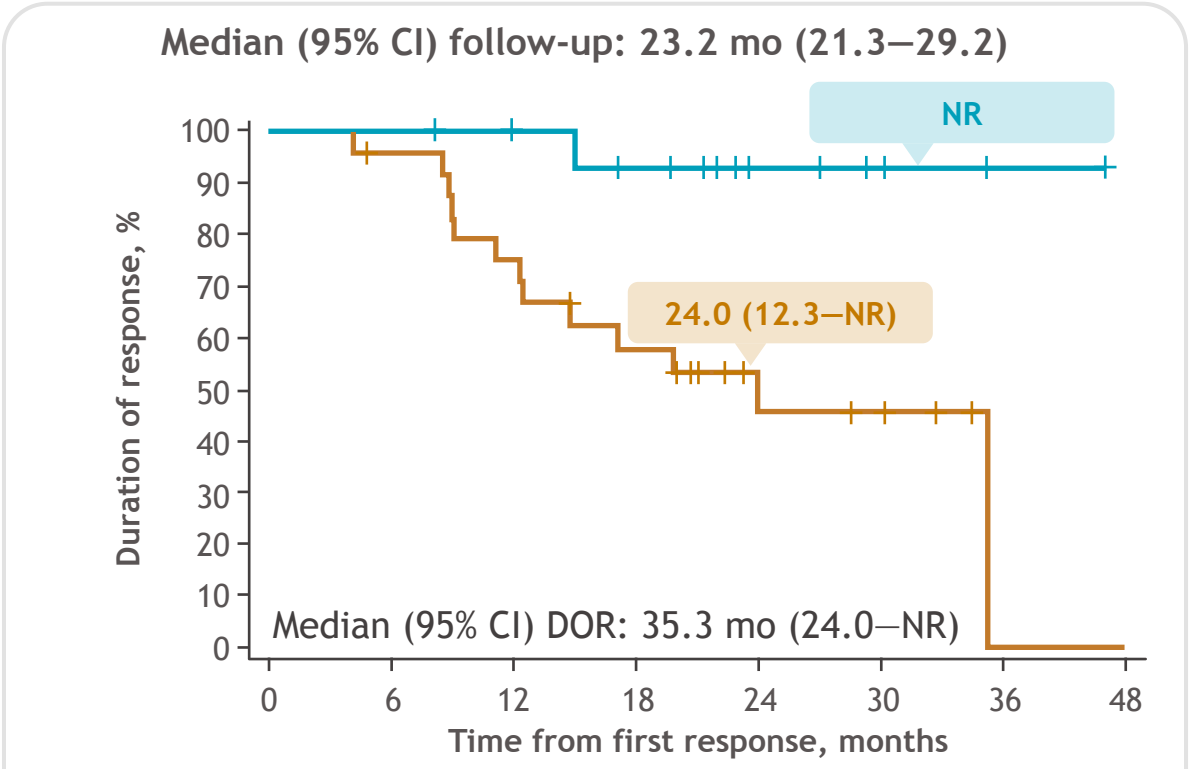
TRANSCEND CLL 004 uMRD
Poster 3263
Papp et al.
6:00–8:00 PM PST, Sunday, December 10, 2023

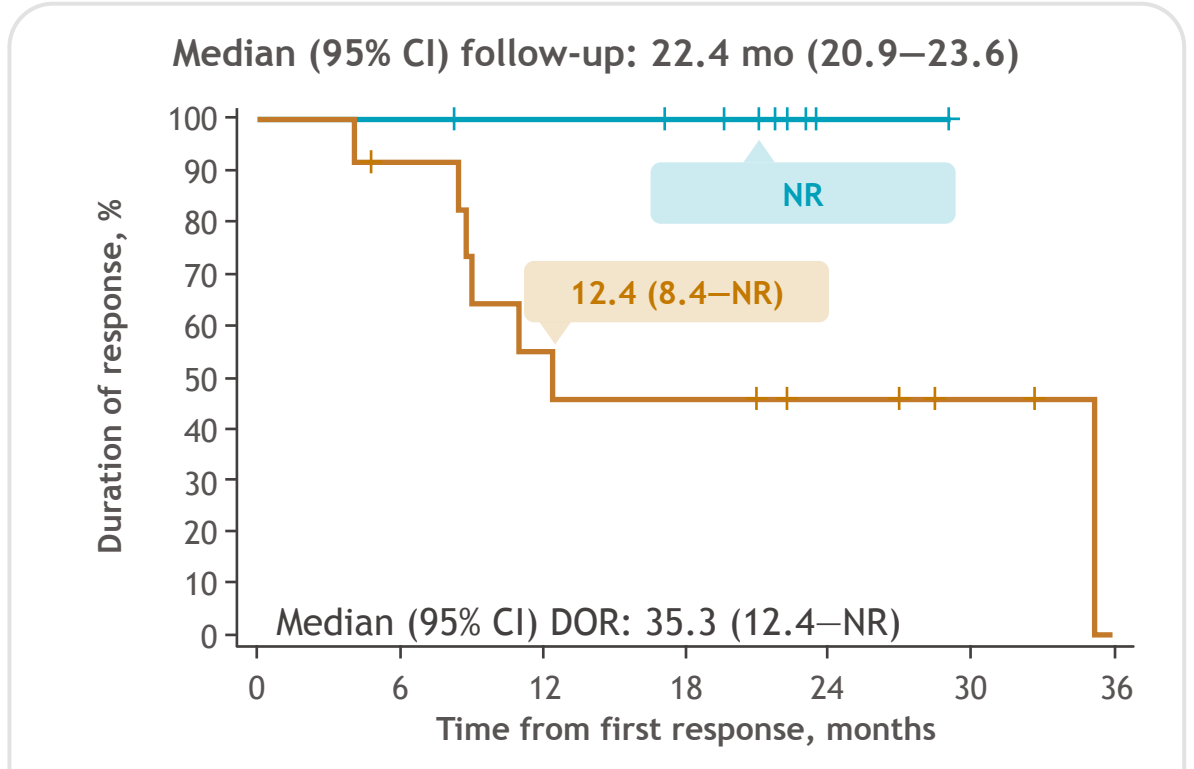
Duration of response by best overall response

(A) Full study population at DL2 (n = 88)



No. at risk								
CR/CRi	17	17	14	12	5	3	1	0
PR/nPR	25	23	18	13	6	5	0	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)

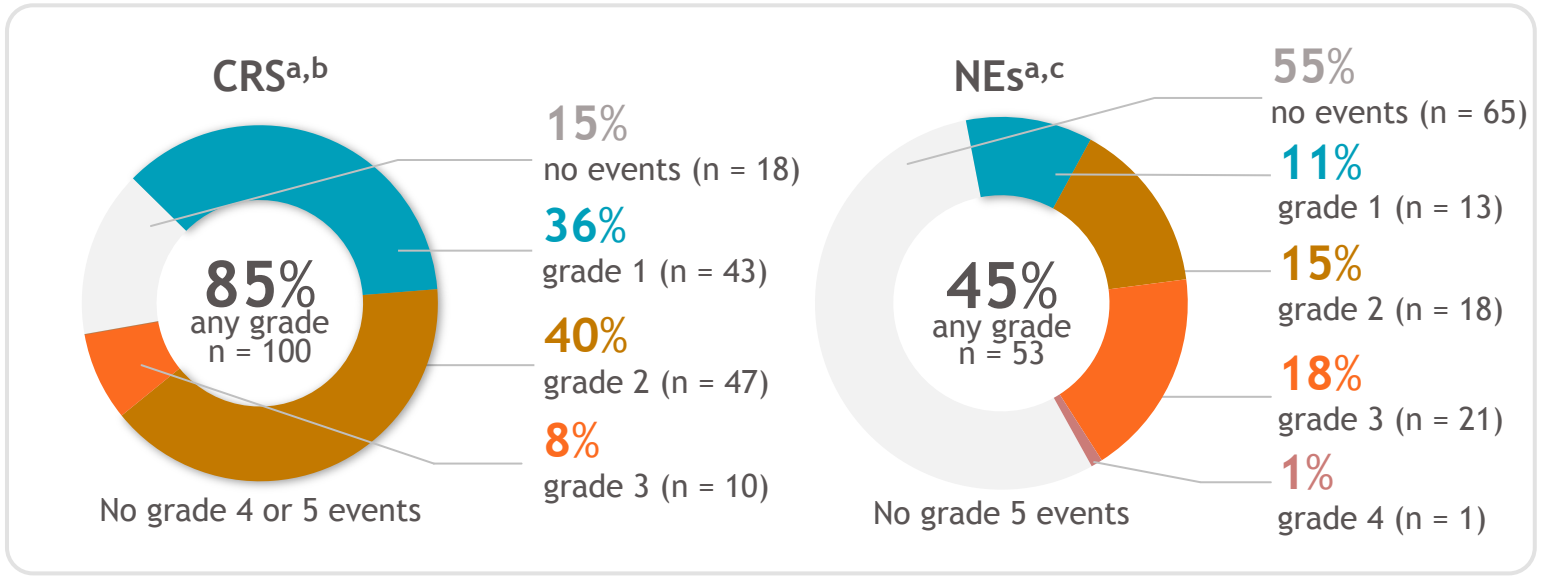


No. at risk							
CR/CRi	10	10	9	8	1	0	0
PR/nPR	12	10	6	5	3	2	0

Data on KM curves are expressed as median (95% CI, if available). DOR, duration of response; NR, not reached.

Siddiqi T, et al. ASH 2023 [Presentation #330]

Safety: full study population (n = 118)



	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[d]: 64 (54%)
- Grade ≥ 3 infections[e]: 21 (18%)
- Hypogammaglobulinemia[f]: 18 (15%)
- Tumor lysis syndrome: 13 (11%)
- SPM[f]: 11 (9%)
- MAS: 4 (3%)

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

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

[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 the Lee 2014 criteria; [c]NEs were defined as investigator-identified neurological AEs related to liso-cel; [d]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia at Day 30 after liso-cel infusion; [e]Includes grade ≥ 3 TEAEs from infections and infestations (System Organ Class) by AE high-level group term; [f]AEs from the 90-day treatment-emergent period, posttreatment-emergent period, and long-term follow-up were included.

AESI, adverse event of special interest; MAS, macrophage activation syndrome; NE, neurological event; SPM, second primary malignancy.

Siddiqi T, et al. ASH 2023 [Presentation #330]

Summary

- A single administration of liso-cel demonstrated sustained, rapid, deep, and durable responses in patients with R/R CLL/SLL, at a median follow-up of 23.5 months
- The study met its primary endpoint; the current data cut demonstrated a CR/CRi rate of 20% in patients with R/R CLL/SLL after BTKi progression/venetoclax failure, which compares favorably with historical CR/CRi rates of 0%—5%[1]
- Efficacy outcomes were similar in the full study population (R/R CLL/SLL after prior BTKi), demonstrating a clinical benefit of liso-cel in this broader population
- Median time to next therapy was considerably longer than that observed in a real-world study of patients with CLL/SLL after prior treatment with a BTKi and B-cell lymphoma 2 inhibitors (6.6 months [95% CI, 3.6—10.1])[2]
- Safety data were consistent with previous reports, demonstrating that the safety profile was manageable, with low rates of grade ≥ 3 CRS and NEs, and no new safety signals
- **Overall, these results support liso-cel as a potential new treatment option for R/R CLL/SLL**

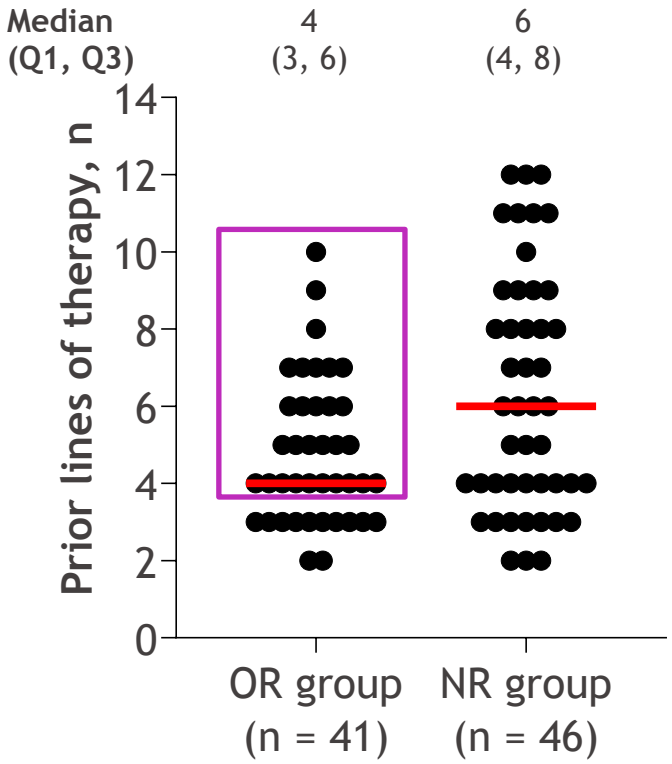
1. Siddiqi T, et al. *Lancet* 2023;402:641—654; 2. Awan FT, et al. ASH 2022; Poster 3123.

Siddiqi T, et al. ASH 2023 [Presentation #330]

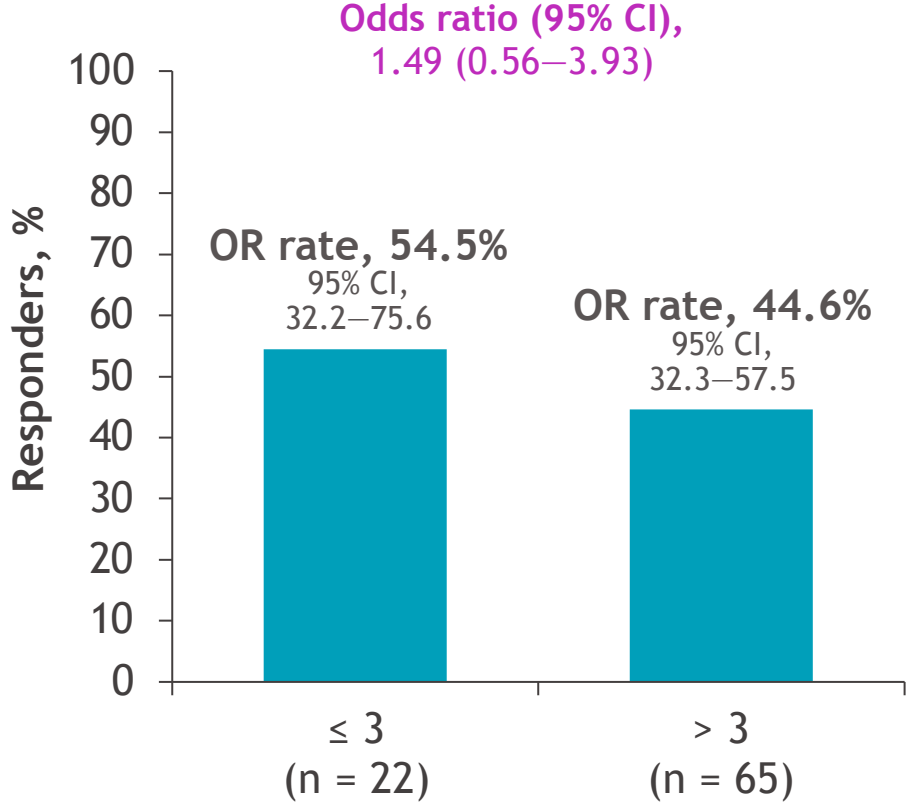
TRANSCEND CLL 004: Number of prior lines of systemic therapy and overall response

- Patients in TRANSCEND CLL 004 had heavily pretreated disease with a median of 5 prior lines of therapy, and responses were observed in patients with multiple prior treatments
- OR rate was numerically higher in patients who received ≤ 3 versus > 3 prior lines of therapy

Distribution of prior lines of therapy by response



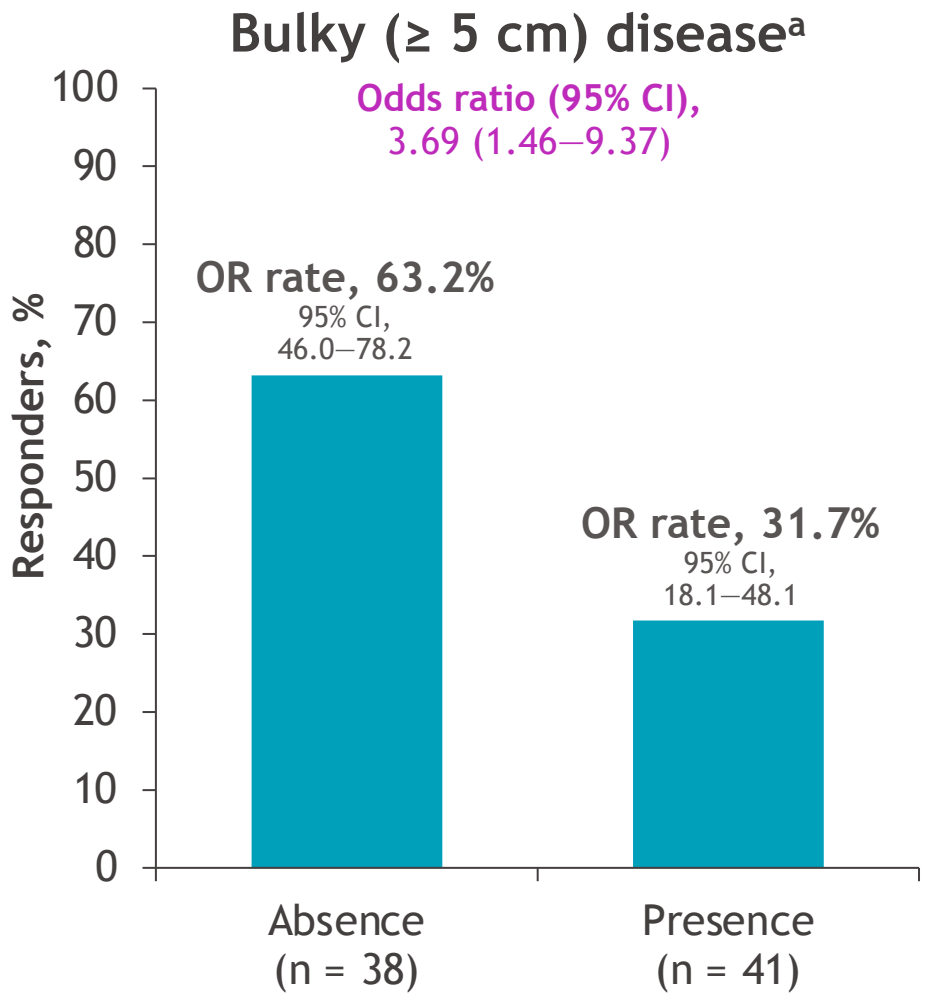
Number of prior lines of therapy

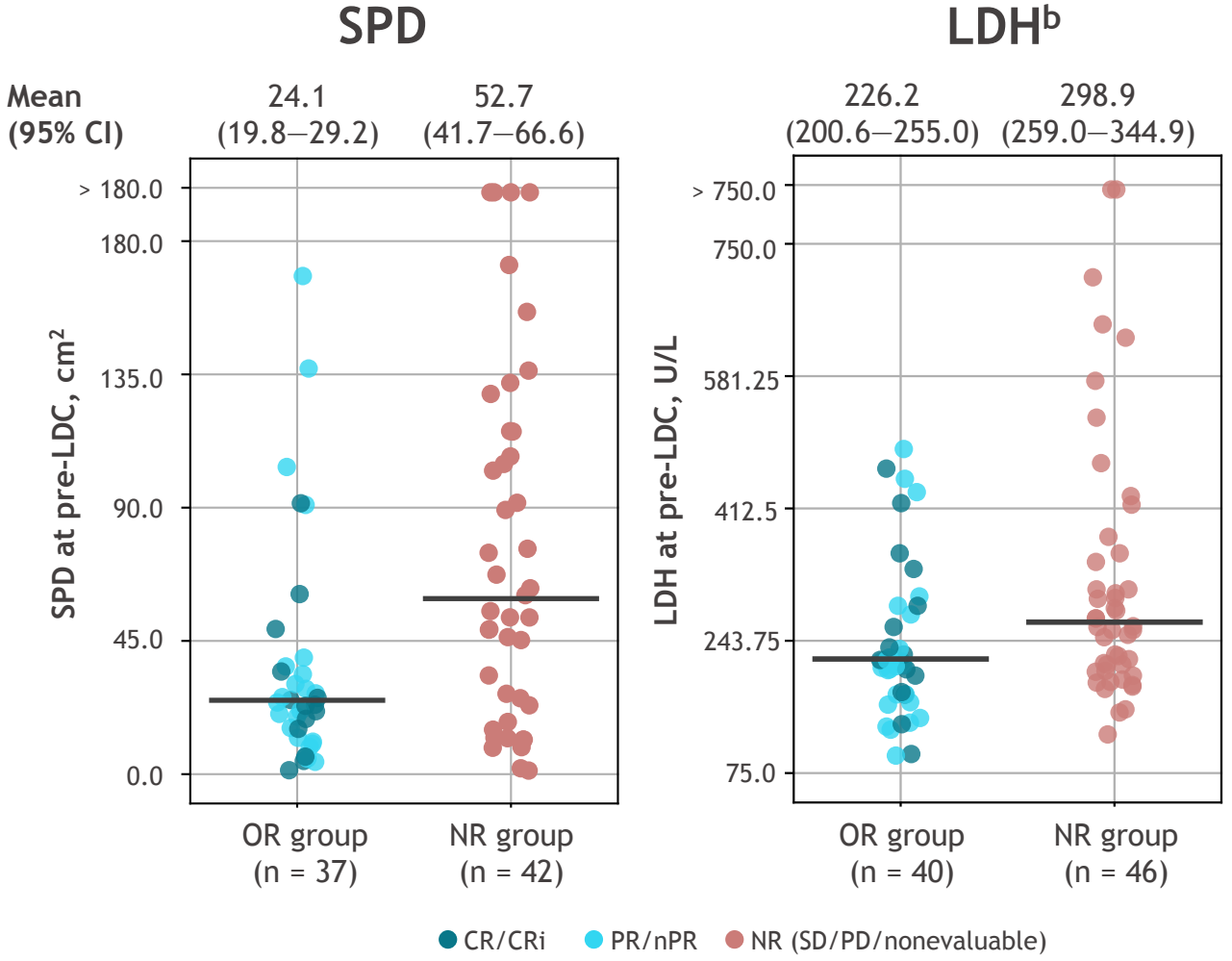


Red lines indicate the median number of prior lines of therapy for each group.

TRANSCEND CLL 004: Tumor burden correlation with overall response

- Lower tumor burden was correlated with overall response





All characteristics were collected at the prelymphodepletion study visit unless otherwise specified. [a]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [b]LDH was also associated with OR when treated as a discrete variable ≤ ULN.

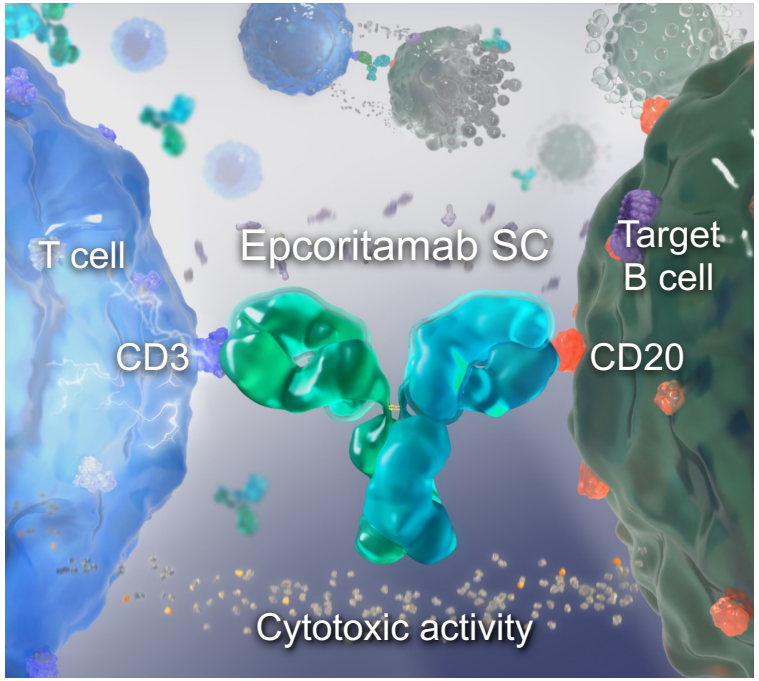
TRANSCEND CLL 004: Summary

- Post hoc exploratory univariable analyses from TRANSCEND CLL 004 indicate that responses to liso-cel are consistent in patients with R/R CLL/SLL regardless of high-risk disease features, including unmutated IGHV, del(17p), *TP53* mutation, and complex karyotype
- Lower baseline tumor burden and fewer lines of prior systemic therapy may be associated with achieving response
  - Additional analyses are required to understand other factors associated with long-term outcomes, including on-treatment variables
- Higher baseline levels of inflammation markers (including CRP and ferritin) and renal insufficiency, in addition to high tumor burden, may be associated with an increased risk of NEs
- **Collectively, these data suggest that patients may have better responses with liso-cel when treated in earlier lines of therapy and when tumor burden is lower, warranting further investigation of the role of debulking bridging therapy**

Novel Treatment Options Are Needed for Patients With R/R CLL

Epcoritamab is a novel CD3xCD20 bispecific antibody

- Approved by the US FDA for the treatment of adults with R/R DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, and HGBCL after ≥2 lines of systemic therapy[4]; also approved by the EMA[a,5] and the Japan PMDA[b,6]
- Previous reports from EPCORE CLL-1 showed encouraging efficacy
- and manageable safety in R/R CLL (dose escalation) and Richter's transformation (dose expansion)[7,8]



[a]Approved in Europe for the treatment of adults with R/R DLBCL after ≥2 lines of systemic therapy. [b]Approved in Japan for the treatment of adults with the following R/R LBCL: DLBCL, HGBCL, PMBCL, and FL G3B after ≥2 lines of systemic therapy.

1. Hallek M, et al. *Lancet*. 2018;391:1524-37. **2.** Dreger P, et al. *Blood*. 2018;132:892-902. **3.** Martens AWJ, et al. *Leukemia*. 2023;37:606-16. **4.** EPKINLY [prescribing information]. Plainsboro, NJ: Genmab US, Inc.; 2023. **5.** Tepkinly [summary of product characteristics]. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG; 2023. **6.** EPKINLY [prescribing information]. Tokyo, Japan: Genmab K.K.; 2023. **7.** Kater AP, et al. ASH 2021. Abstract 2627. **8.** Kater AP, et al. ASH 2022. Abstract 348.

Study Design: EPCORE CLL-1 Expansion Cohort

Key inclusion criteria

- CD20^{+} R/R CLL
- ≥2 prior lines of systemic therapy, including treatment with or intolerance to a BTK inhibitor
- ECOG PS 0–2
- Requiring treatment per iwCLL criteria
- Measurable disease with ≥5×10^{9}/L B lymphocytes or measurable lymphadenopathy or organomegaly
- No minimum life expectancy required

Median follow-up: 12.1 mo (range, 0.1+ to 19.2)

R/R CLL expansion, N=23 (fully enrolled)

Step-up dosing[a]

Epcoritamab SC[b]
RP2D 48 mg

QW C1–3
Q2W C4–9
Q4W C10+

→ Efficacy assessment[c] by CT/MRI obtained Q8W through C6, and Q24W thereafter

→ Treatment until disease progression

- **Primary endpoint:** Overall response rate (ORR)
- **Key secondary endpoints:** Complete response (CR) rate, time to response, safety/tolerability, and measurable residual disease (MRD) in PBMCs using the clonoSEQ next-generation sequencing (NGS) assay

Data cutoff: July 5, 2023. Epcoritamab was administered in 28-d cycles. [a]Patients received epcoritamab SC with step-up dosing (ie, 0.16 mg priming and 0.8 mg intermediate doses before first full dose) and corticosteroid prophylaxis as previously described to mitigate CRS. [b]To ensure patient safety and better characterize CRS, inpatient monitoring was required for the first 4 doses of epcoritamab. [c]Based on iwCLL guidelines. PBMCs, peripheral blood mononuclear cells.

Kater AP, et al. iwCLL 2023 (abstr 1546171).

Patient Characteristics and Treatment History

Characteristic	Total N=23
Median age, y (range)	72 (55–83)
Male, n (%)	17 (74)
CLL characteristic, n (%)	
IGHV unmutated[a]	16 (70)
TP53 aberrations[b]	15 (65)
Lab abnormalities at baseline, n (%)	
Thrombocytopenia	21 (91)
Anemia	20 (87)
Neutropenia	3 (13)
Beta-2 microglobulin >3.5 mg/L	18 (78)

Treatment History	Total N=23
Median time from initial diagnosis to first dose, y (range)	13 (5.5–19.5)
Median number of prior lines of therapy (range)	**4 (2–10)**
≥4 prior lines of therapy, n (%)	15 (65)
Prior therapy, n (%)	23 (100)
Chemoimmunotherapy	23 (100)
Small molecules	23 (100)
BTK inhibitor	23 (100)
Discontinuation due to progression	17 (74)
BCL-2 inhibitor	19 (83)
Discontinuation due to progression	11 (58)
Relapsed <12 months from last dose	4 (21)
CAR T-cell therapy	1 (4)
Median time from last treatment to first dose, mo (range)	1.0 (0.1–49.4)

. [a]*IGHV* status mutated for 4 patients and unknown for 3 patients. [b]*TP53*/del17p status unmutated/negative for 6 patients and unknown for 2 patients.

High Overall and Complete Response Rates

Response, n (%)[a]	Total Efficacy Evaluable n=21	*TP53* Aberration n=14	Double-Exposed[b] n=17	*IGHV* Unmutated n=15
Overall response[c]	**13 (62)**	**9 (64)**	**9 (53)**	**9 (60)**
Complete response	7 (33)	4 (29)	5 (29)	6 (40)
Partial response	6 (29)	5 (36)	4 (24)	3 (20)
Stable disease	4 (19)	2 (14)	4 (24)	3 (20)
Progressive disease	1 (5)	1 (7)	1 (6)	1 (7)

Encouraging overall and complete response rates observed, including in difficult-to-treat, high-risk R/R CLL patients

Three patients were not evaluable or had no assessment, including 2 patients who died without postbaseline assessment. [a]Based on response-evaluable population, defined as patients who received ≥1 full dose of epcoritamab, had ≥1 postbaseline response evaluation, or died within 60 d of first dose. [b]Patients previously treated with both a BTK inhibitor and a BCL-2 inhibitor. [c]Response assessment according to iwCLL criteria.

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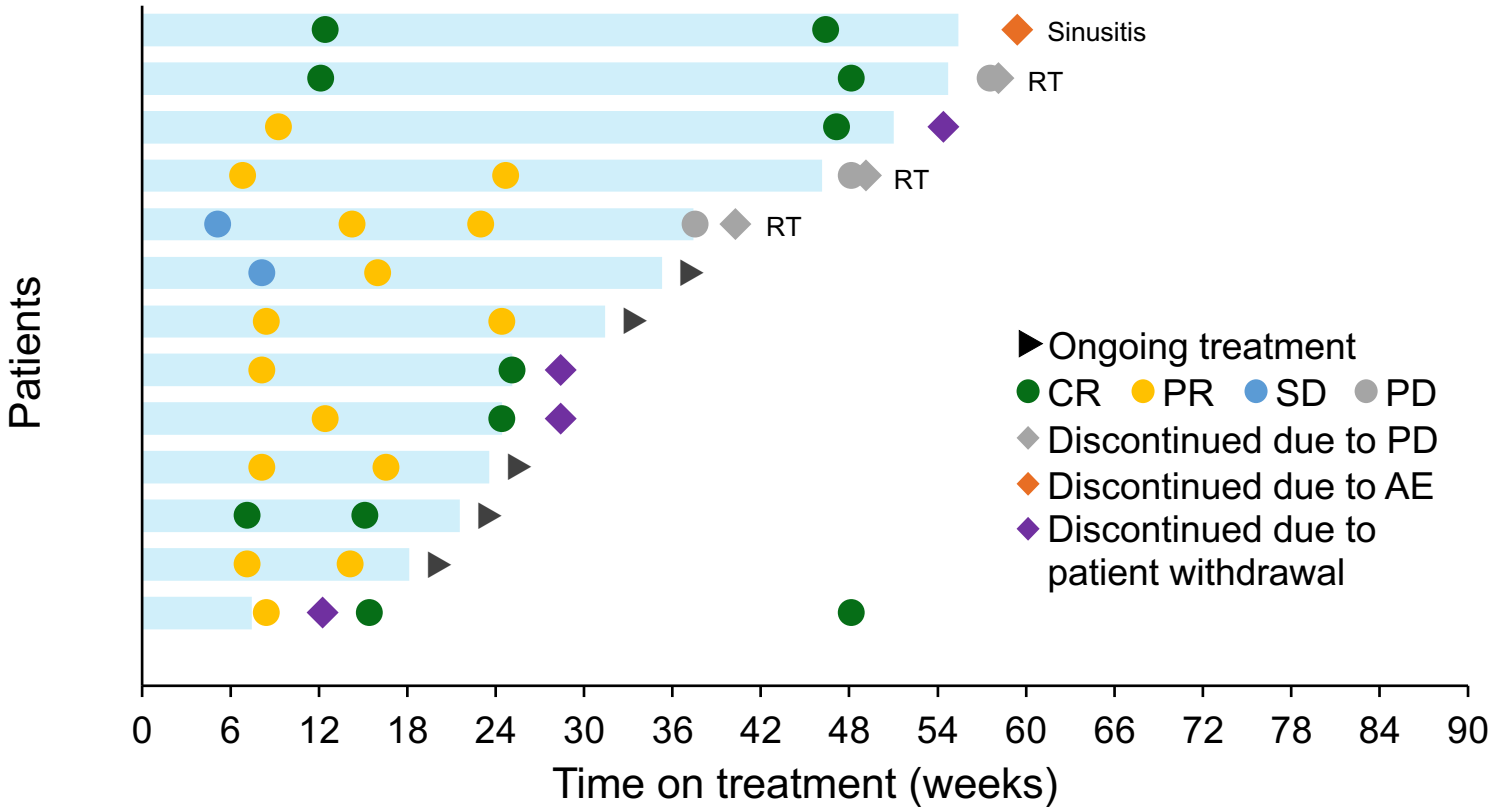
Timing and Duration of Response



	Responders n=13
Median time to response, mo (range)	1.9 (1.6–3.7)
Median time to CR, mo (range)	3.6 (1.6–10.8)
Estimated DOR at 9 mo,[a] %	83

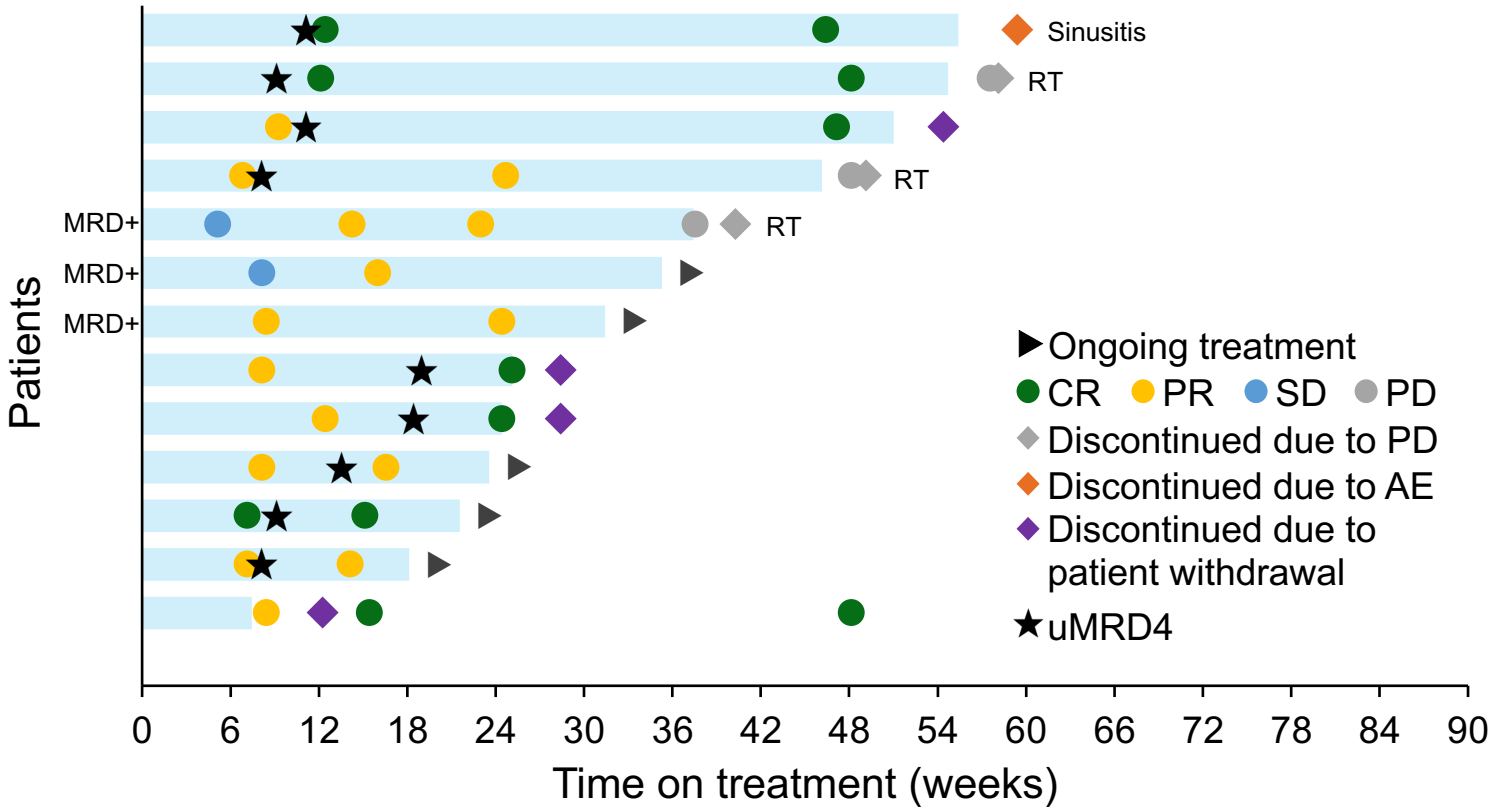
	Efficacy Evaluable n=21
Estimated PFS at 9 mo,[a] %	67
Estimated OS at 9 mo,[a] %	81

[a]Kaplan–Meier estimates.

Responses occurred early and appear durable

Median follow-up, mo (range): 12.1 (0.1+ to 19.2). Median number of treatment cycles initiated (range): 5 (1–14). Median duration of treatment, mo (range): 5.0 (0.03–12.7).
RT, Richter's transformation.

Depth and Duration of Response



	Assessed for MRD n=12
Patients with uMRD4,[a,b] n/n (%)	9/12 (75)
CR with uMRD4	6/6
PR with uMRD4	3/6
MRD-positive patients,[a] n/n (%)	3/12 (25)
> uMRD4 to uMRD2	1/3
MRD > uMRD2	2/3

MRD was evaluated in PBMCs using the clonoSEQ next-generation sequencing assay. [a]Among responders who were tested for MRD. [b]Eight of 12 patients had uMRD6.

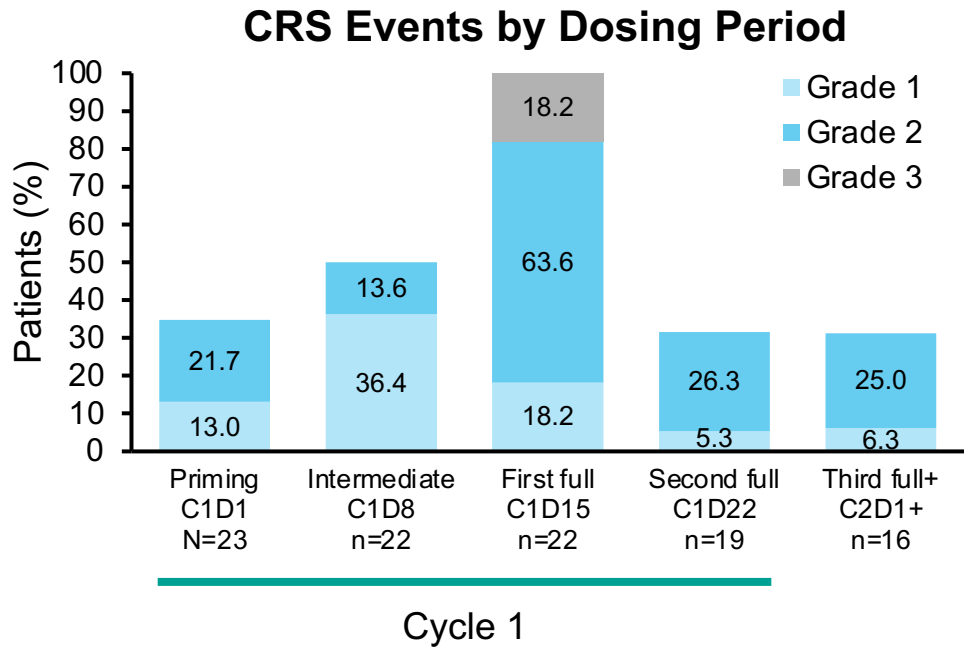
uMRD4 was achieved by most responders, including all patients with CR who were tested for MRD

Median follow-up, mo (range): 12.1 (0.1+ to 19.2). Median number of treatment cycles initiated (range): 5 (1–14). Median duration of treatment, mo (range): 5.0 (0.03–12.7). RT, Richter's transformation; uMRD, undetectable MRD.

Kater AP, et al. iwCLL 2023 (abstr 1546171).

AEs of Special Interest

CRS[a]	Total, N=23
Median time to onset after first full dose, h (range)	7.3 (1–99)
Median time to resolution, d (range)[b]	3 (1–16)
Treated with tocilizumab, n (%)	19 (83)
CRS resolution, n/n (%)	22/22 (100)



ICANS & Clinical Tumor Lysis Syndrome	Total, N=23
ICANS, n (%)[c]	**3 (13)**
Grade 1	1 (4)
Grade 2	2 (9)
Median time to resolution, d (range)	3 (3–4)
ICANS resolution, n/n (%)	3/3 (100)
Tumor lysis syndrome, n (%)	**1 (4)**
Laboratory only	0
Clinical – grade 2	1 (4)
Time to resolution, d	11
Clinical tumor lysis syndrome resolution, n/n (%)	1/1 (100)

- CRS occurrence was predictable, with most cases following the first full dose
- No AEs of special interest led to discontinuation, and all resolved

[a]Graded by Lee et al 2019 criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS. [c]All ICANS events occurred with grade 2 CRS.

Conclusions

- In difficult-to-treat, high-risk patients with R/R CLL, single-agent epcoritamab showed promising antitumor activity
  - Responses (ORR 62%; CR rate 33%) were early and appear durable
  - **Of those evaluated for MRD, uMRD4 was achieved in all complete responders and 50% of partial responders**
- Safety was manageable and consistent with previous reports and other T-cell–engaging strategies;
  there were no new safety signals
- The findings support the continued exploration of epcoritamab in CLL
- EPCORE CLL-1 is currently exploring epcoritamab in combination with venetoclax in R/R CLL/SLL and lenalidomide or R-CHOP in Richter's transformation (NCT04623541)

Kater AP, et al. iwCLL 2023 (abstr 1546171).

Conclusions

- Pirtobrutinib is a non-covalent BTKi that results in high response rates (82%) and durable remissions in highly refractory CLL patients
  - **Dec 2023: Accelerated approval for double exposed (BTKi/Ven) CLL**
- Liso-cell is a CD19 targeted CART (approved in DLBCL) resulting in 20% CR rate and durable remission in double refractory (BTKi/Ven) CLL patients
  - **March 2024: Accelerated approval for double exposed (BTKi/Ven) CLL**
- Epcoritamab is a CD20 bispecific (approved in DLBCL) producing high response rates with uMRD in highly refractory CLL patients
  - CRS rates are higher in CLL patients but mainly grade 1-2 (Gr 3, 8%)
  - Another intermediate dose in the step-up has been added and appears to reduce the rate of CRS, also no Grade 3 seen