Treatment Options for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma after BTKi and BCL2i therapy

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COH Multidisciplinary Approaches to Cancer Symposium
Oahu, Hawaii
11/7/24

Disclosures

- Consultant for AstraZeneca, Abbvie, BeiGene, Bristol Myers Squibb, and Gilead/Kite.
- On the Speakers Bureau for AstraZeneca, BeiGene, and Bristol Myers Squibb.
- Other Financial/Material Interests in BeiGene (Data Safety & Monitoring Committee).

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Epcoritamab and Bruton's tyrosine kinase (BTK) degraders will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon must contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

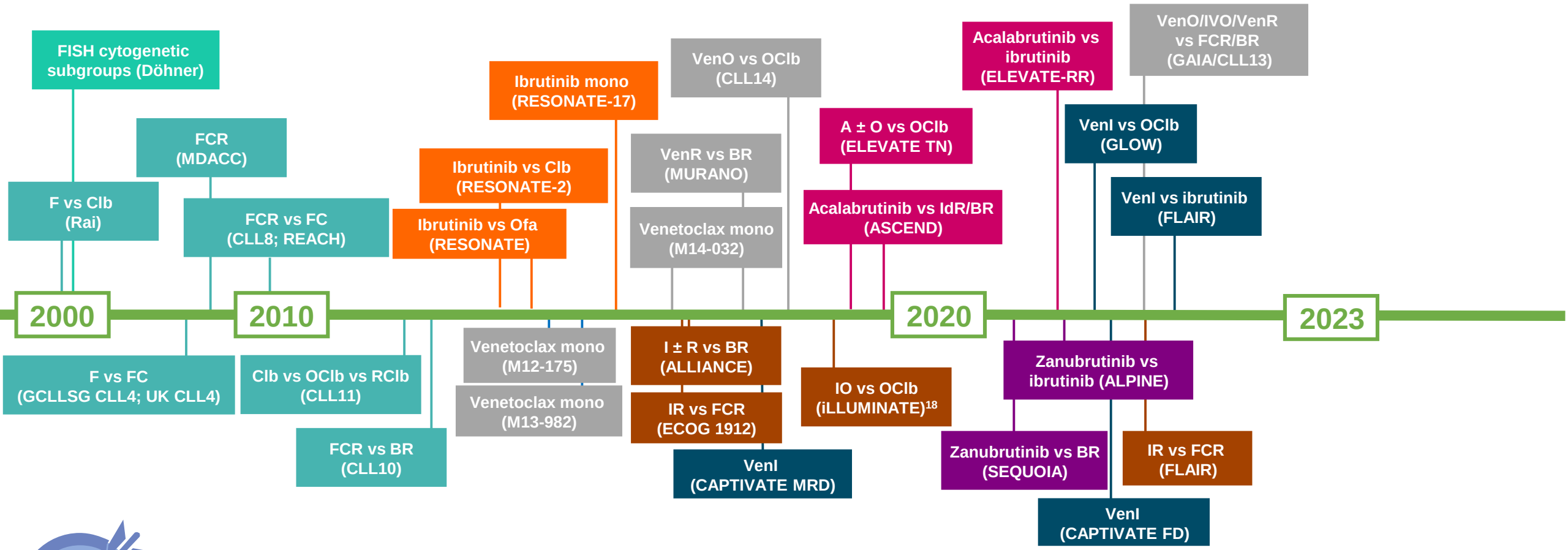
The following CLC & IB components will be addressed in this presentation:

- *Ethnicity and gender differences in treatments/trials.*

Agenda

- Pirtobrutinib
- BTK degraders
- Epcoritamab
- Lisocabtagene maraleucel

Development of CLL therapy



Goals of therapy

Alleviating symptoms → Improving response rates and quality of response → Improving long-term outcomes and tolerability → Improving outcomes in more patients, increasing OS

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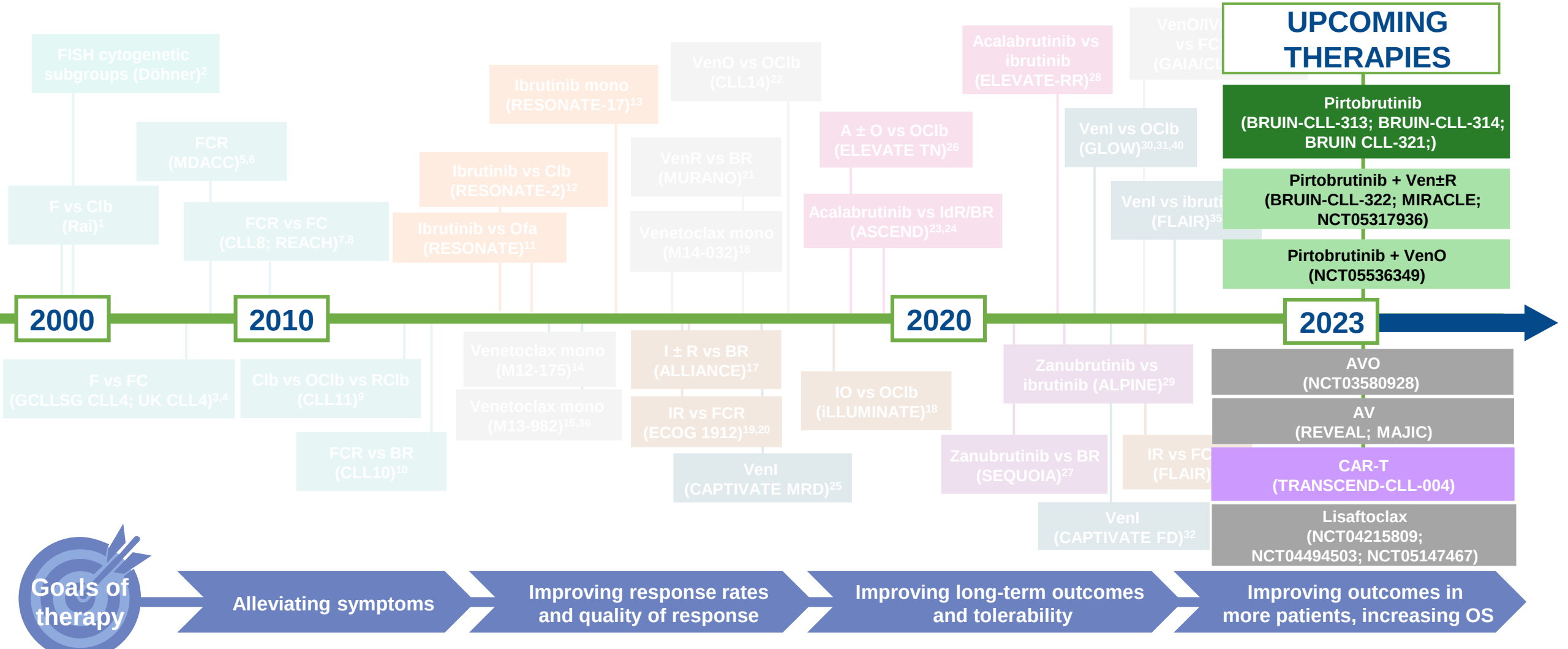
Development of CLL therapy



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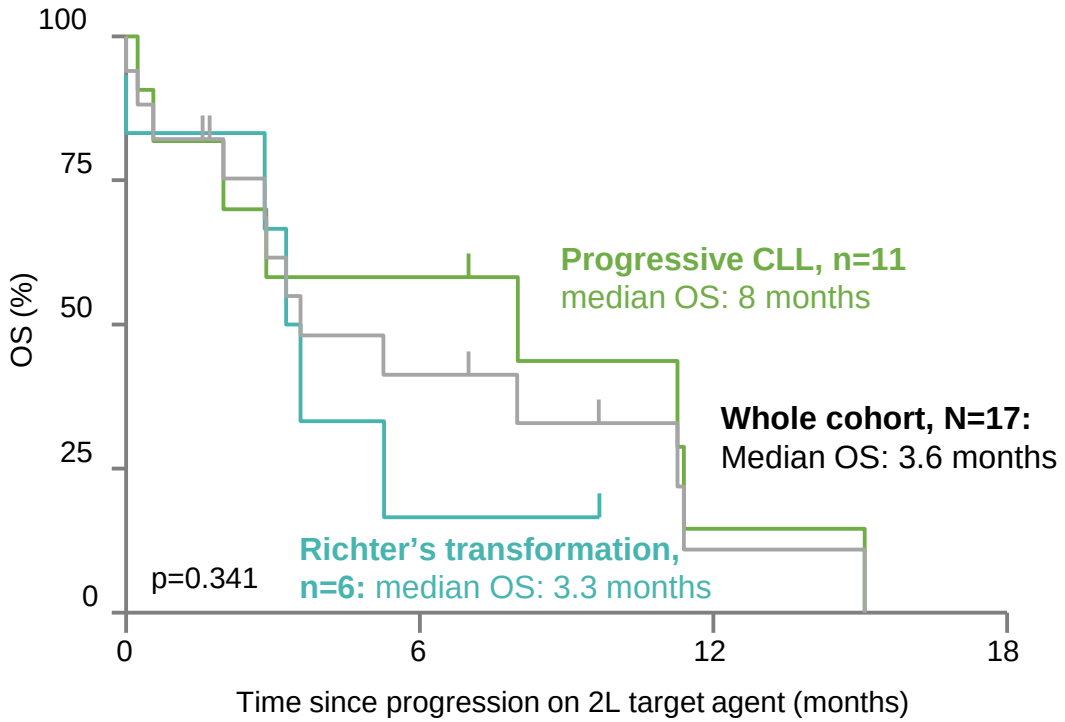
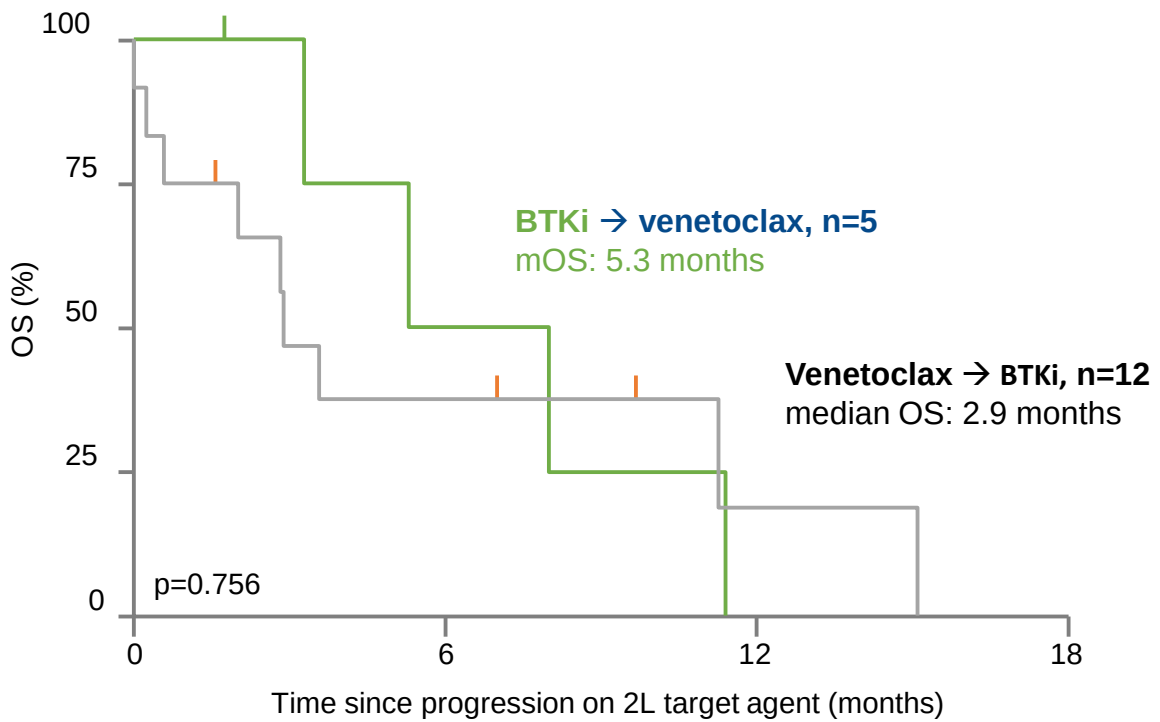
Poor outcomes in patients with double class-resistant CLL: real-world, retrospective study at 2 sites in Australia (N=17)

OS after the development of PD on 2L targeted therapy



OS after the development of PD on 2L targeted therapy, stratified by prior sequencing of targeted agents



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

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

Real-world evidence is collected outside controlled clinical trials and has inherent limitations, including a lesser ability to control for confounding factors Ki, Bruton's tyrosine kinase inhibitor;

BRUIN trial - pirtobrutinib

Table 2. Efficacy of Pirtobrutinib in Patients with CLL or SLL Who Had Previously Received a BTK Inhibitor.*

Variable	Previous BTK Inhibitor (N=247)	Previous BTK Inhibitor + BCL2 Inhibitor (N=100)
Overall response — % (95% CI)		
Including complete response, nodular partial response, or partial response	73.3 (67.3–78.7)	70.0 (60.0–78.8)
Including complete response, nodular partial response, partial response, or partial response with lymphocytosis	82.2 (76.8–86.7)	79.0 (69.7–86.5)
Best response — no. (%)		
Complete response	4 (1.6)	0
Nodular partial response	1 (0.4)	0
Partial response	176 (71.3)	70 (70.0)
Partial response with lymphocytosis	22 (8.9)	9 (9.0)
Stable disease	26 (10.5)	11 (11.0)
Progression-free survival		
Median (95% CI) — mo	19.6 (16.9–22.1)	16.8 (13.2–18.7)
Patients with censored data — no. (%)	126 (51.0)	44 (44.0)
Median follow-up — mo	19.4	18.2

* Response status was assessed by an independent review committee in accordance with the criteria from the 2018 International Workshop on Chronic Lymphocytic Leukemia.

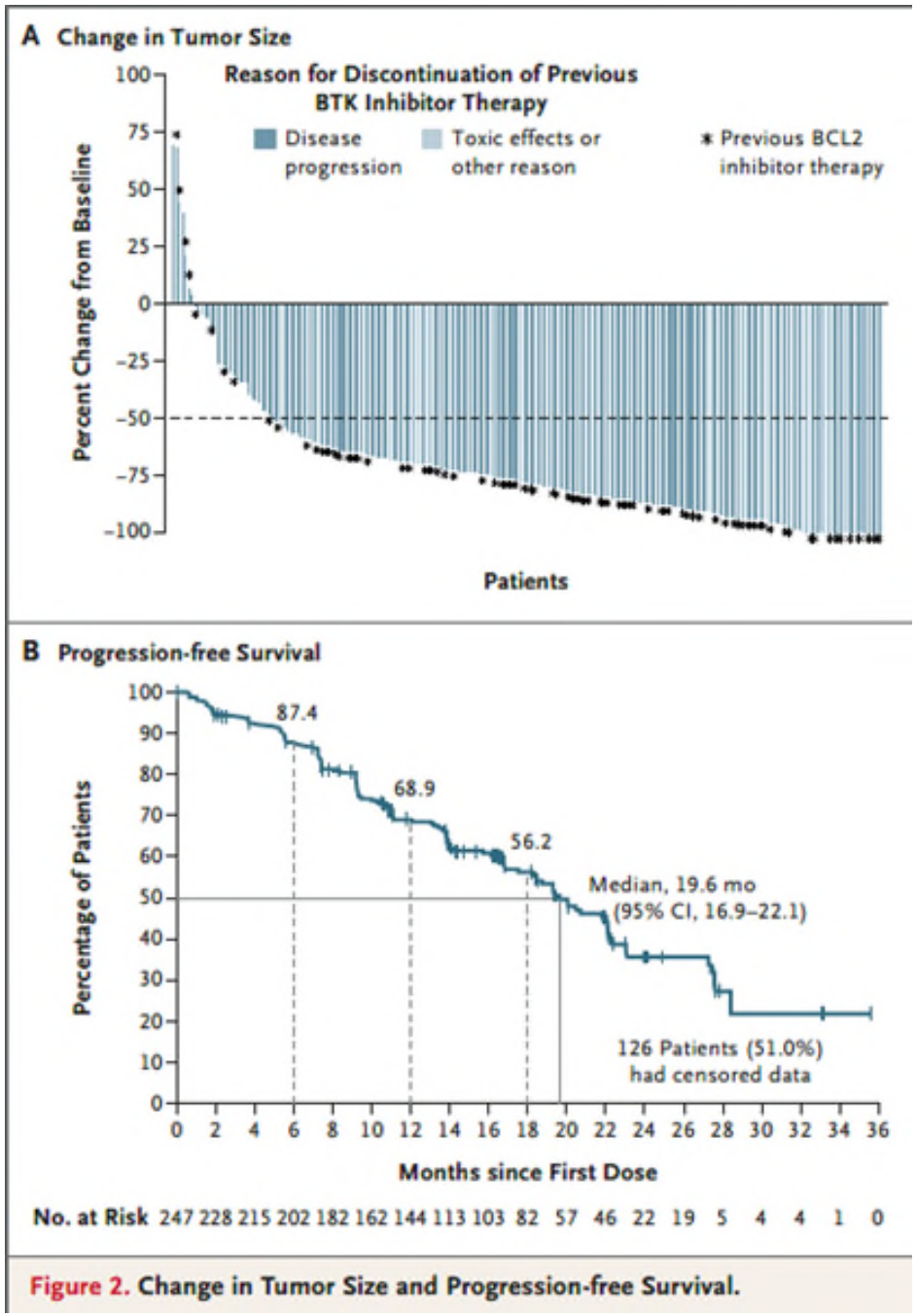
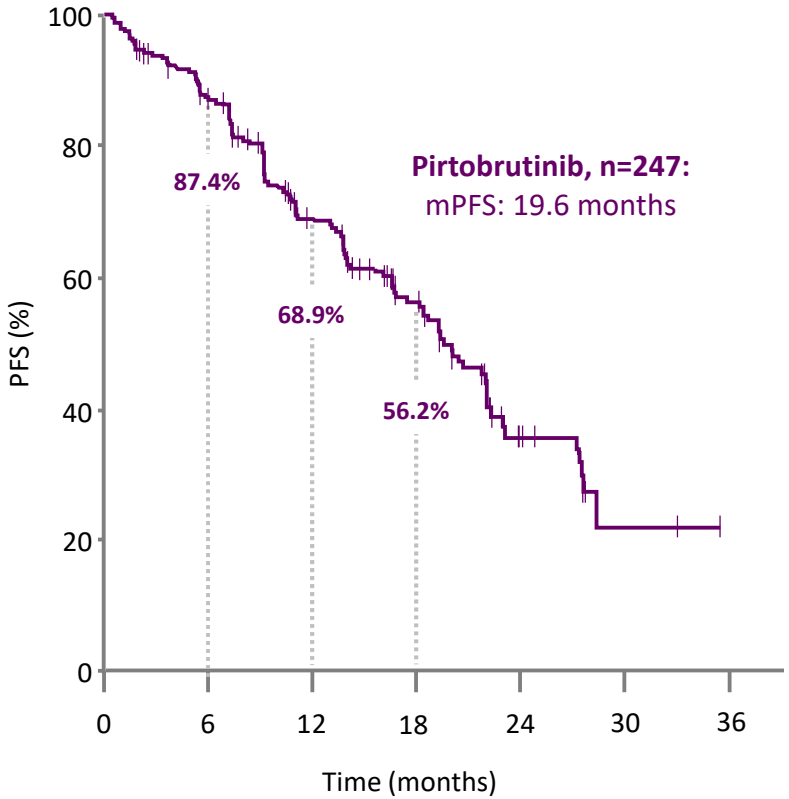


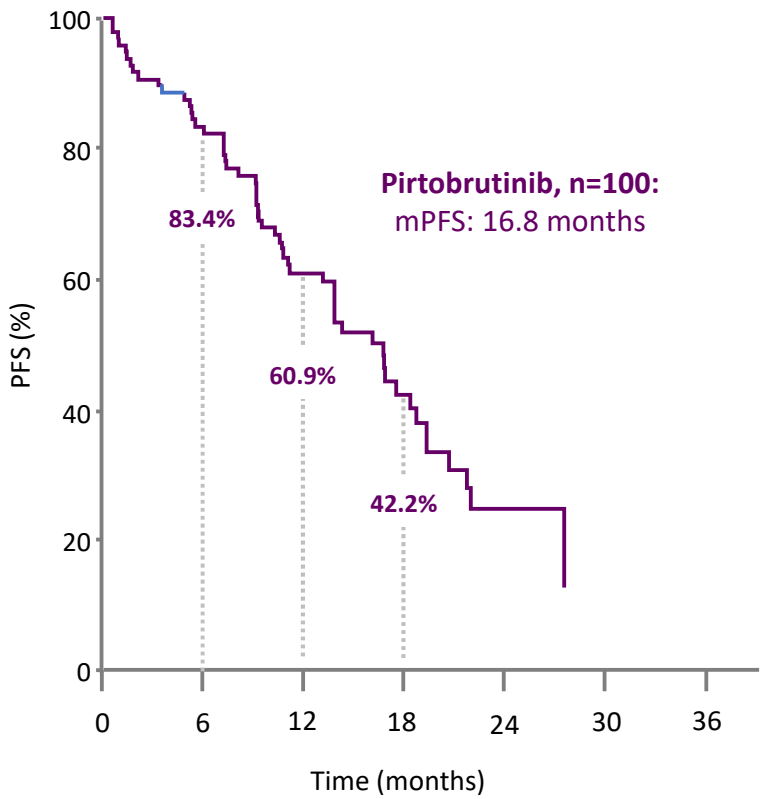
Figure 2. Change in Tumor Size and Progression-free Survival.

Non-covalent BTKi pirtobrutinib in BTKi pre-treated patients: BRUIN Ph 1/2 study (N=247)

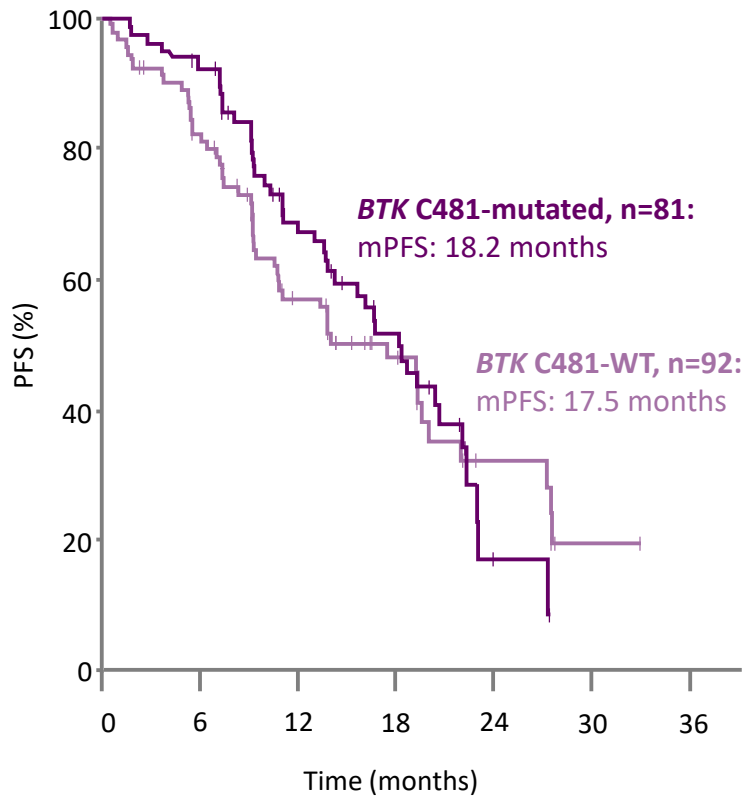
PFS in BTKi pre-treated patients
19.4-month median follow-up
(median prior lines of therapy: 3)



PFS in BTKi and BCL-2i pre-treated patients
16.8-month median follow-up
(median prior lines of therapy: 5)



PFS by *BTK C481* mutation status* in patients with PD on a prior BTKi
18.2-month median follow-up



* *BTK C481* mutation status was centrally determined and based on pre-treatment strategies

Mato AR, *et al.* ASH 2022. Abstract 961 (Oral)

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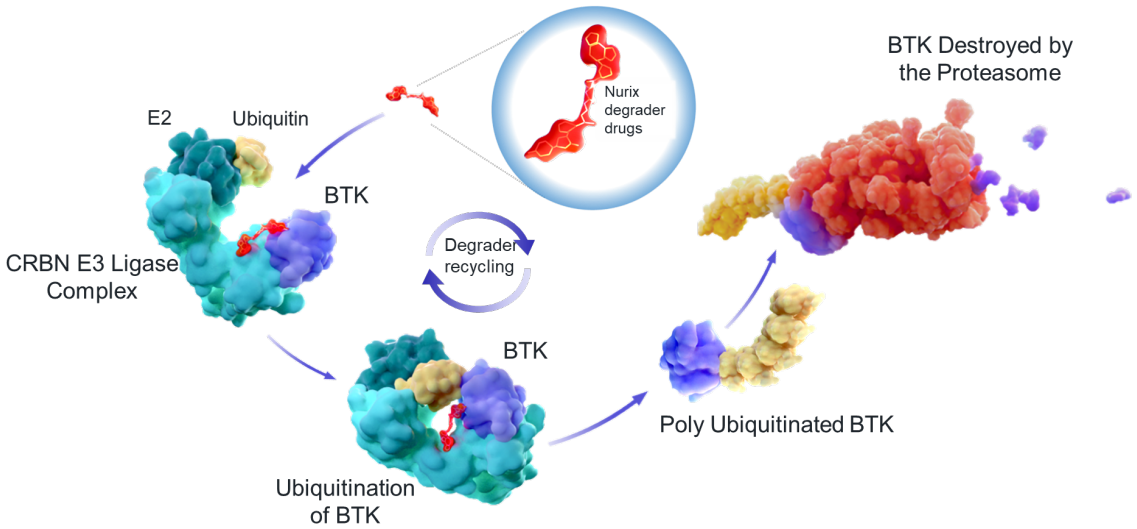
NX-2127: first-in-class targeted protein BTK degrader

Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in hematological malignances



Characteristics	CLL (n=23)	Overall population (N=36)
Median age, years (range)	75 (61–90)	75 (50–92)
Female, n (%)	9 (39.1)	13 (36.1)
Male, n (%)	14 (60.9)	23 (63.9)
Lines of prior therapy, median (range)	5 (2–11)	4 (2–11)
BTKi, n (%)	23 (100)	31 (86.1)
Pirtobrutinib, n (%)	8 (34.8)	11 (30.6)
BTKi and BCL2i, n (%)	16 (69.6)	16 (44.4)
cBTKi, ncBTKi, and BCL2i, n (%)	6 (26.1)	6 (16.7)
***BTK* mutation present**[a], n (%)	10 (48)	11 (35)
C481	5 (24)	5 (16)
L528W	4 (19)	4 (13)
T474	3 (14)	4 (13)
V416L	1 (5)	1 (3)
***BCL2* mutation present**[a], n (%)	4 (19)	4 (13)
***PLCG2* mutation present**[a], n (%)	0 (0)	1 (3.2)

NX-2127 has the potential to address emerging *BTK* mutations

Mato A, et al. ASH annual meeting 2022

NX-2127 safety summary (TEAEs >15% in all patients)

Treatment-emergent AEs occurring in >15% of total population, n (%)	Any grade (N=36)	Grade 3+ (N=36)	SAE (N=36)
Fatigue	19 (52.8)	–	-
Neutropenia[a]	14 (38.9)	13 (36.1)	-
Contusion	10 (27.8)	–	1 (2.8)
Thrombocytopenia[b]	9 (25)	3 (8.3)	-
Anemia	8 (22.2)	4 (11.1)	1 (2.8)
Hypertension	9 (25.0)	1 (2.8)	-
Constipation	7 (19.4)	–	-
Dyspnea	7 (19.4)	1 (2.8)	-
Pruritis	7 (19.4)	–	-
Atrial fibrillation/Atrial flutter[c]	6 (16.7)	3 (8.3)	2 (5.6)
Diarrhea	6 (16.7)	–	-
Petechiae	6 (16.7)	–	-
Rash	6 (16.7)	–	-

1 DLT of cognitive disturbance was observed at 300 mg (CLL); MTD not reached

[a]Aggregate of "neutropenia" and "neutrophil count decreased" [b]Aggregate of "thrombocytopenia" and "platelet count decreased" [c]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of prior AF on ibrutinib (2 cases)

Data cutoff: September 21, 2022

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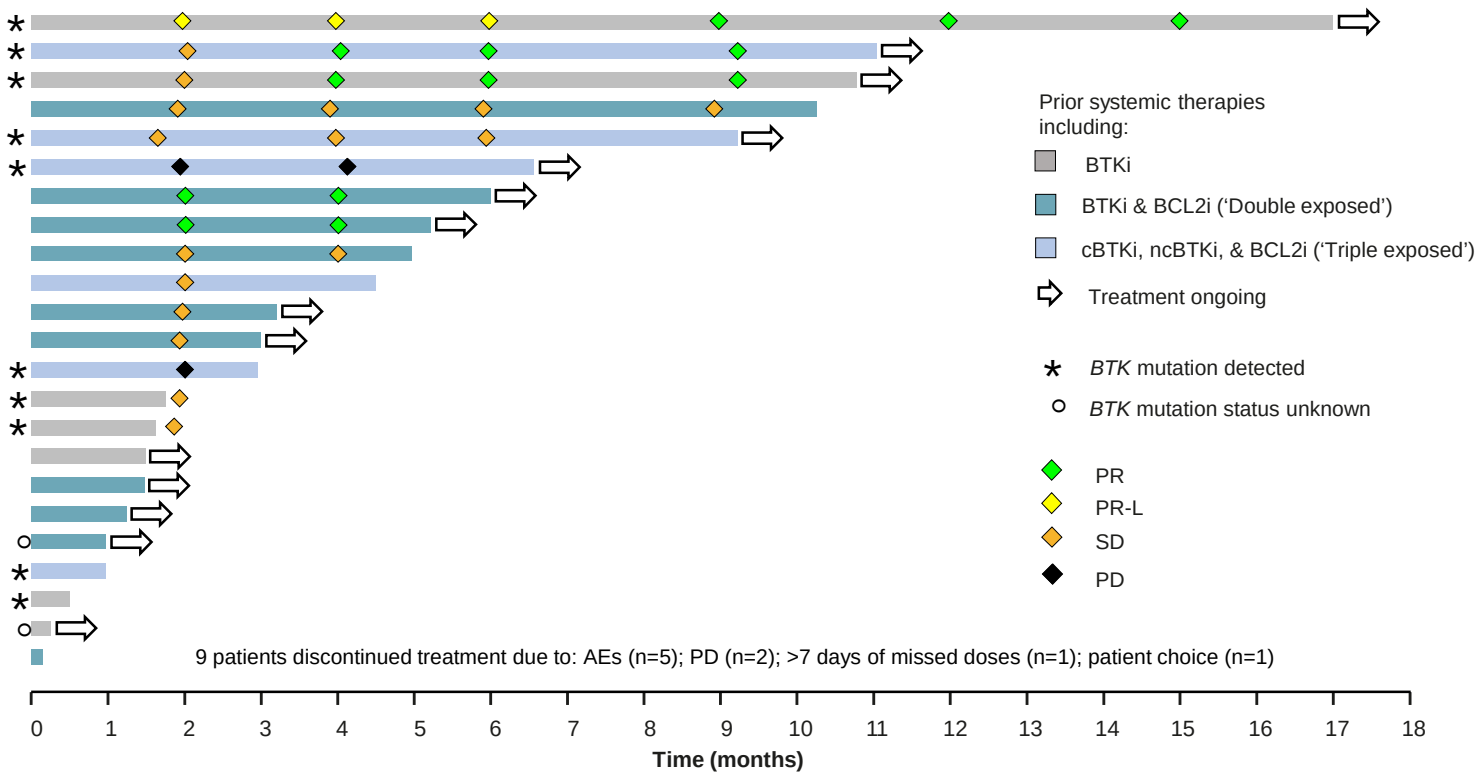
Outcomes and time on therapy with NX-2127 (patients with CLL): Responses seen in double and triple exposed patients



Data cutoff: September 21, 2022

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Subcutaneous Epcoritamab: EPCORE CLL-1 Trial

Open-label, multicenter, phase 1b/2 trial of single-agent epcoritamab in adults with R/R CLL

Key inclusion criteria

- Diagnosis of CLL with evidence of CD20+
- Previously treated with ≥2 prior lines of systemic therapy, including treatment with (or intolerance to) a BTK inhibitor
- Measurable disease with ≥5×10^9/L B lymphocytes *or* measurable lymphadenopathy, *and/or* organomegaly
- ECOG PS 0–2
- Acceptable laboratory parameters

Epcoritamab[a] in 4-wk (28-d) cycles

QW C1–3, Q2W C4–9, Q4W C10+ until progression or unacceptable toxicity

Phase 1b: Dose escalation
- **2 full-dose levels**
  24 mg → 48 mg

Primary objectives:
DLT/Safety and tolerability

Key secondary objective:
Antitumor activity[b]

Phase 2: Expansion
- **2 arms at RP2D (48 mg)**
  - **Cohort 1: R/R CLL**

Primary objective:
Antitumor activity[b]

Data cutoff: October 1, 2021

Prior treatment, n (%)	**BTK inhibitor**	**11 (100)**
	Ibrutinib	9 (82)
	Venetoclax	7 (64)
	CAR-T therapy	2 (18)

Patients were heavily pretreated (median of 6 prior lines of therapy), and the majority had poor-risk features of del(17p) and/or *TP53* mutations

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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.

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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)

Prior therapies and key CLL characteristics reflect a high-risk R/R CLL patient population

Data for CLL characteristics were obtained from local laboratories. [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.

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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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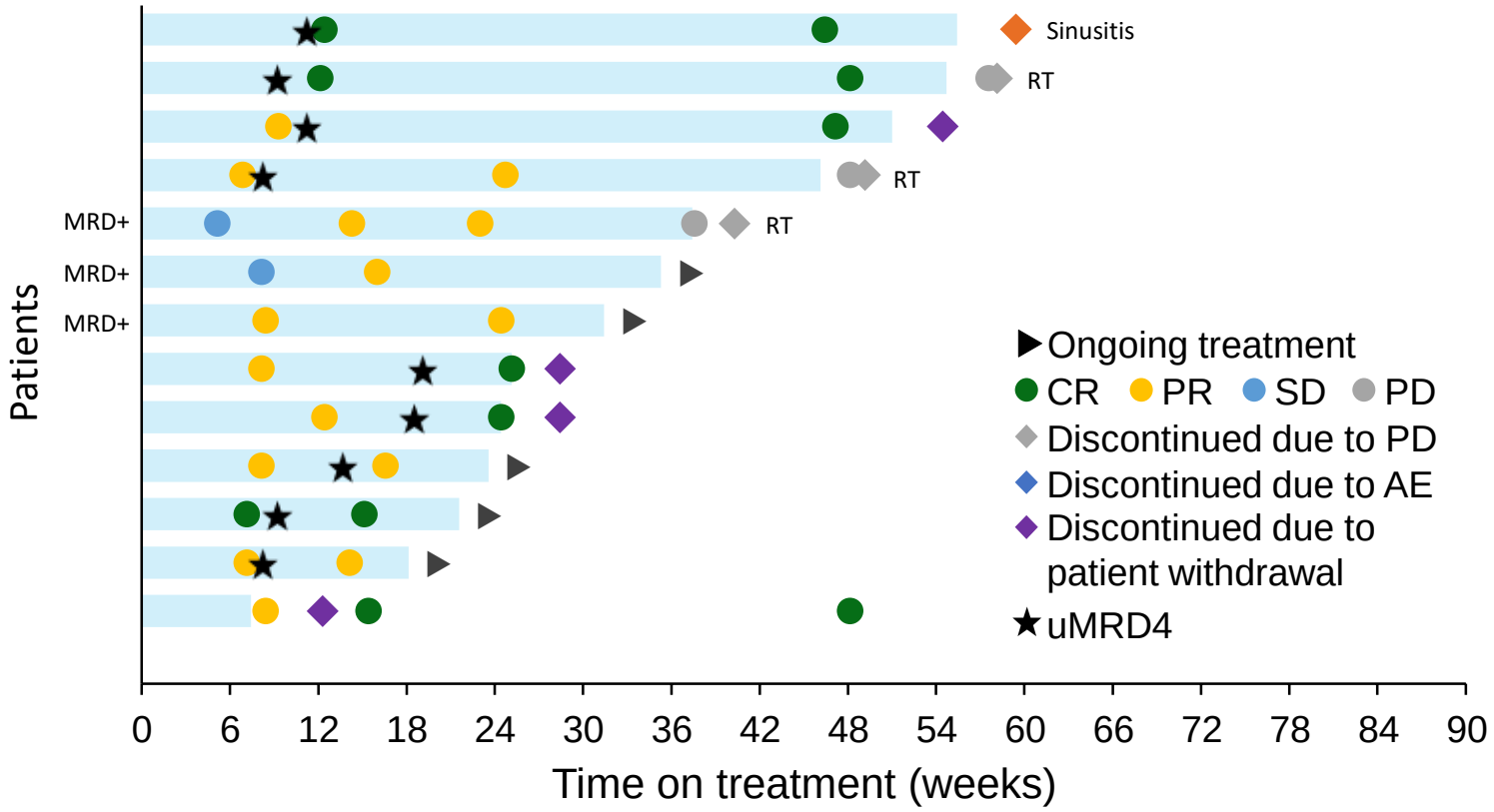
Depth and Duration of Response



	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.

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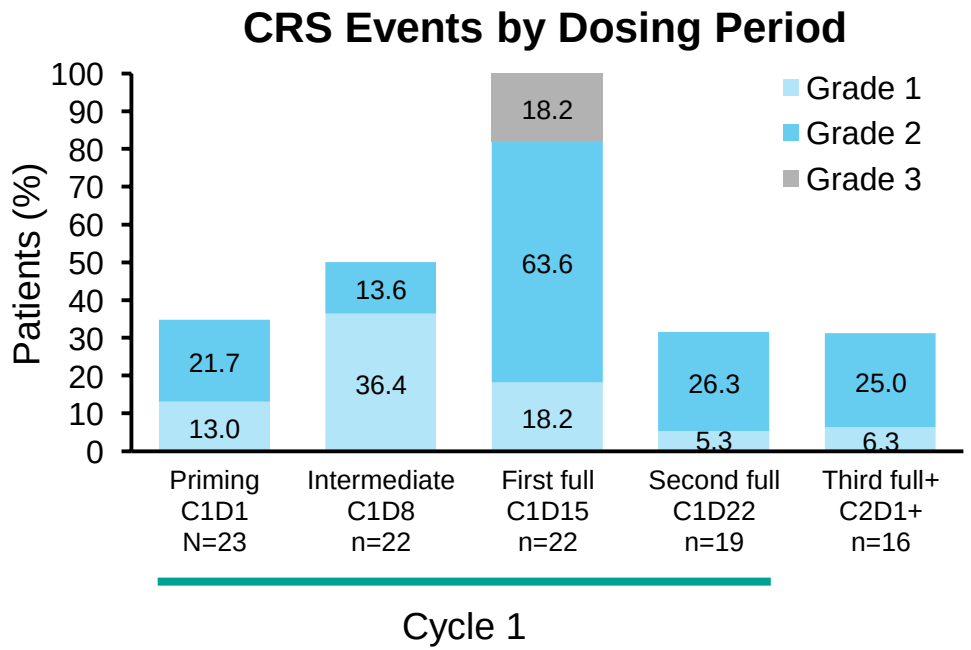
AEs of Special Interest

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.

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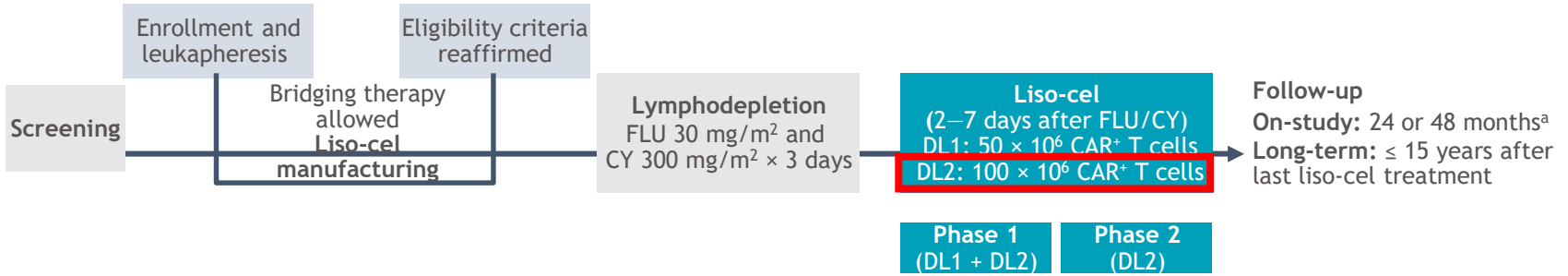
TRANSCEND CLL 004 study design: phase 1/2, open-label, multicenter study



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

Siddiqi T, et al. ASCO 2023 and ICML 2023

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Demographics and baseline characteristics

Characteristic	Full study population (n = 117)	BTKi progression/venetoclax failure subset (n = 70)
Median (range) age, y	65.0 (49—82)	66.0 (49—78)
Median (range) prior lines of systemic therapy	5 (2—12)	5 (2—12)
Bulky lymph nodes,[a] n (%)		
Yes	52 (44)	32 (46)
Unknown	9 (8)	8 (11)
High-risk cytogenetics, n (%)	97 (83)	60 (86)
Prior BTKi, n (%)	117 (100)	70 (100)
BTKi refractory[b]	103 (88)	70 (100)
BTKi relapsed[c]	2 (2)	0
BTKi intolerant only	12 (10)	0
Prior venetoclax, n (%)	94 (80)	70 (100)
Venetoclax refractory[b]	89 (76)	67 (96)
Venetoclax relapsed[c]	0	0
Venetoclax intolerant only	4 (3)	3 (4)
Prior BTKi and venetoclax, n (%)	94 (80)	70 (100)
BTKi progression/venetoclax failure,[d] n (%)	70 (60)	70 (100)
Received bridging therapy, n (%)	89 (76)	55 (79)

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Efficacy outcomes

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

- **All MRD-evaluable responders were uMRD in blood and marrow** and 12 of 20 MRD-evaluable patients with SD were uMRD in blood; majority of patients achieved uMRD by day 30

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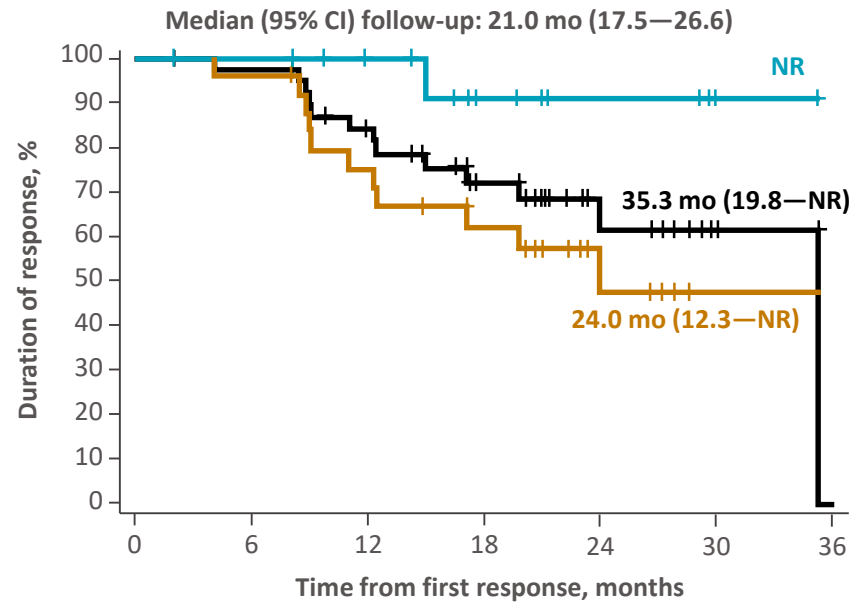
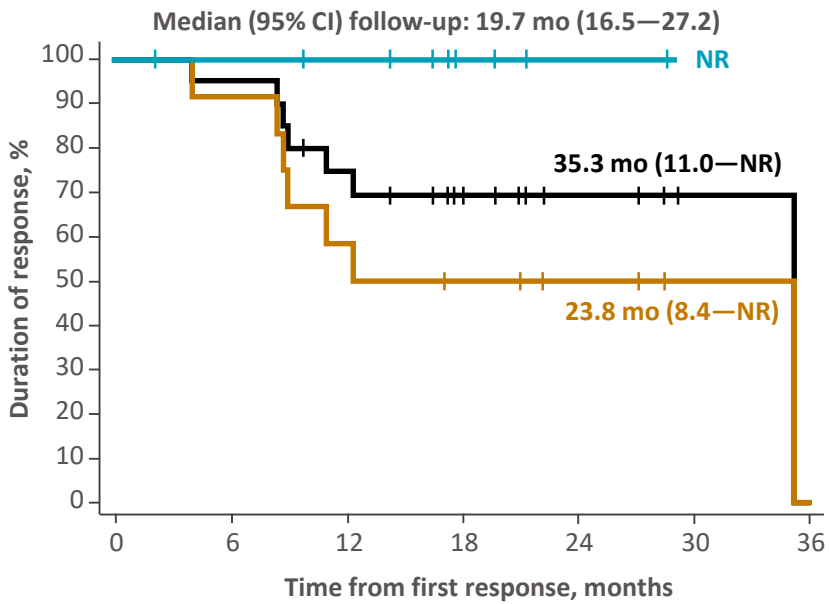
Duration of response by best overall response

(A) Full study population at DL2 (n = 87)



No. at risk							
CR/CRi	16	15	12	7	4	2	0
PR/nPR	25	24	18	13	5	1	0
Responder	41	39	30	20	9	3	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 49)



CR/CRi	9	8	7	3	1	0	0
PR/nPR	12	11	7	5	3	1	0
Responder	21	19	14	8	4	1	0

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Safety: TEAEs, AESIs, and management of CRS and NEs

- The most common grade ≥ 3 TEAEs (≥ 40%) were neutropenia (61%), anemia (52%), and thrombocytopenia (41%)

Patients with CRS and Nes	Full study population (n = 117)
CRS,[a] n (%)	99 (85)
Grade 1/2	43 (37)/46 (39)
Grade 3	10 (9)
Grade 4/5	0
Median (range) time to onset/resolution, days	4.0 (1—18)/6.0 (2—37)
NE,[b] n (%)	53 (45)
Grade 1/2	13 (11)/18 (15)
Grade 3	21 (18)
Grade 4	1 (1)
Grade 5	0
Median (range) time to onset/resolution, days	7.0 (1—21)/7.0 (1—83)

- 81 (69%) patients received tocilizumab and/or corticosteroids for management of CRS and/or NEs

Other AESIs, n (%)	Full study population (n = 117)
Prolonged cytopenia[c]	63 (54)
Grade ≥ 3 infections[d]	20 (17)
Hypogammaglobulinemia[e]	18 (15)
Tumor lysis syndrome	13 (11)
Second primary malignancy[e]	11 (9)
Macrophage activation syndrome	4 (3)

- 5 deaths due to TEAEs were reported
  - 4 considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *Escherichia coli* infection, and invasive aspergillosis)
  - 1 considered related to liso-cel by investigators (macrophage activation syndrome)

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Conclusions

- Explosion of novel therapies for CLL in recent years, including monoclonal and bispecific antibodies, small molecule inhibitors of various kinases and the antiapoptotic pathway (especially Bcl2), BTK degraders, bispecific antibodies, as well as CD19-specific CAR-T cells

- These novel, non-chemotherapeutic agents have done away with the need for standard chemoimmunotherapy in CLL

- Combination studies are underway to improve outcomes further and find a cure

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Thank you for your attention!

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