



Multidisciplinary Approaches to Cancer Symposium

How We Treat Chronic Lymphocytic Leukemia (CLL) Today and What to Expect in 2030

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Disclosures

- Consultant for AbbVie, AstraZeneca, BeOne Medicines, GenMab, Incyte, Janssen, Lilly Oncology, Merck, Nurix, Prelude, and Regeneron
- Grant/Research Support from Abbvie, Astrazeneca, Bayer Oncology, BeOne Medicines, Bristol Meyers Scribb, Cyclacel, GenMab, Lilly Oncology, MEI, Pharma, TG Therapeutics and Nurix

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 Bexobrutideg, BGB-16673, Epcoritamab 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:

- *Commonalities and differences among the CLL patient population*
- *Disparities of care in CLL*



What are our Life Hopes and Worries for 2030?

HOPES

First Woman President



Redesigns the new Ballroom with actual taste



Strait of Hormuz is Open



Everyone drives this:



WORRIES

SkyNet Reigns Supreme



First Woman President



CLL in 2030: AI Perspective

BIG PICTURE: CLL becomes a managed, precision disease

Most patients will receive targeted and immune-based therapies

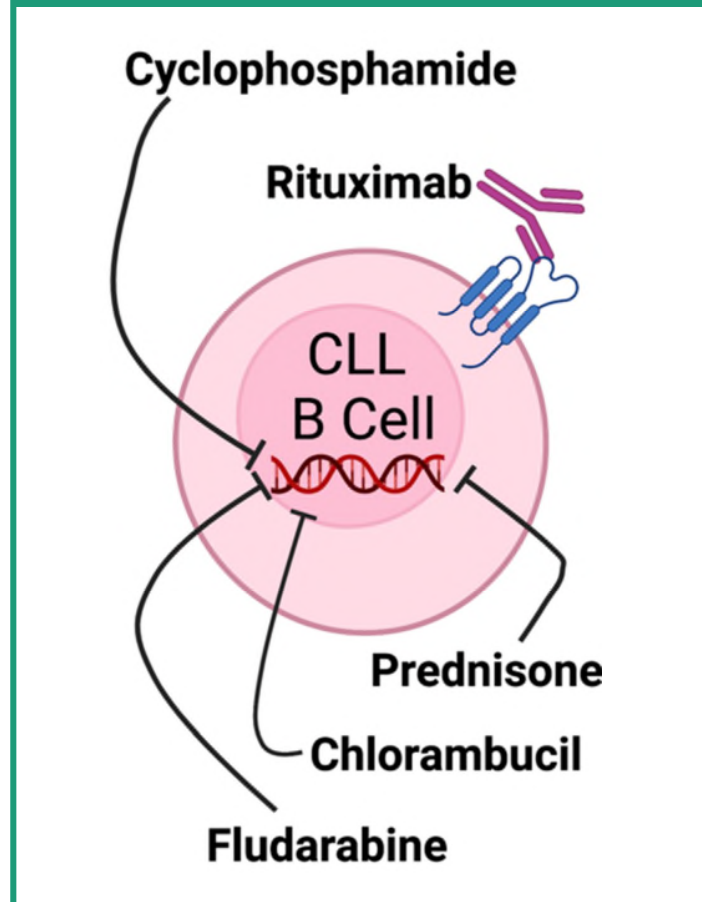
Treatment will be personalized, often based on genetics

“Functional cure” becomes a reality

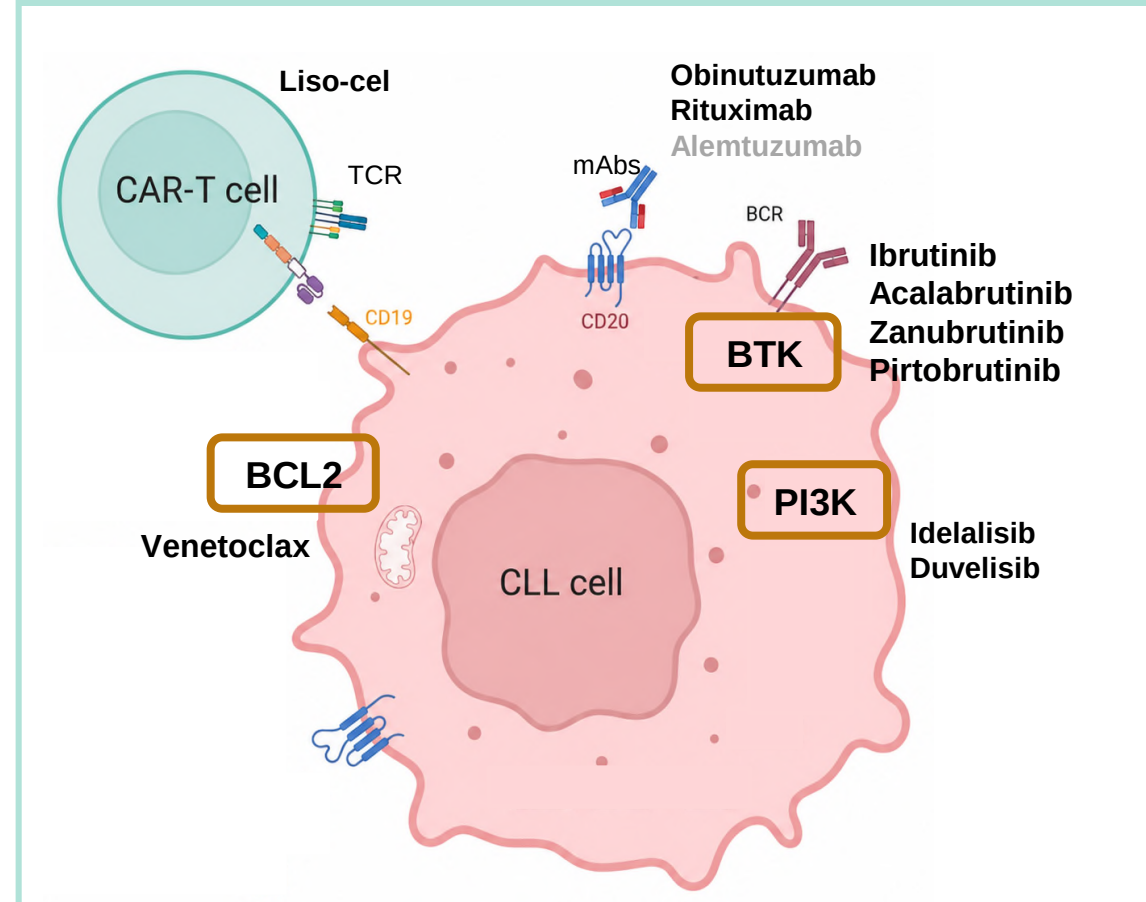


CLL – current treatment landscape

Historical CLL Therapies¹



Current CLL Therapies²



NCCN Guidelines for TN CLL ca. 2026

Preferred Regimens

BCL2i-containing regimens

- Venetoclax/acalabrutinib + obinutuzumab (MRD-guided)
- Venetoclax/Zanubrutinib (MRD-guided)
- Venetoclax + obinutuzumab (fixed duration)

cBTKi-based regimens

- Acalabrutinib (continuous) ± obinutuzumab
- Zanubrutinib (continuous)

Other Recommended Regimens

BCL2i-containing regimens

- Venetoclax + ibrutinib (fixed duration)

Useful in Certain Circumstances

Regimens

- cBTKi-based: Ibrutinib (continuous)
- High-dose methylprednisolone + anti-CD20 mAb
- Consider only when cBTKi and BCL2i are not available or not feasible: Obinutuzumab



Evidence in TN CLL

Trial	N	Arms	F/U	Overall Response	AEs of Clinical Interest
CLL14¹	432	Venetoclax + Obinutuzumab (Ven+O) Obinutuzumab + Chlorambucil (O+Clb)	9Y F/U	Arm: mPFS (mo) Ven+O: 76.6 mo O+Clb: 37.9 mo	Serious AEs (Ven+O) Neutropenia, thrombocytopenia, anemia, febrile neutropenia, TLS
AMPLIFY²	867	Acalabrutinib + Venetoclax (A+V) Acalabrutinib + Venetoclax + Obinutuzumab (AVO) Fludarabine-cyclophosphamide- rituximab (FCR)/ Bendamustine + rituximab (BR)	40.8 mo	Arm: 36-mo PFS (%), mPFS (mo) A+V: 76.5%; NR AVO: 83.1%; NR FCR/BR: 66.5%; 47.6 mo	Serious AEs (A+V, AVO) Cardiac events, neutropenia, infections
SEQUOIA (Arm D)³	114	Zanubrutinib + Venetoclax	38.5 mo	36-mo PFS (%) 87%	Serious AEs Infections, hemorrhage, neutropenia

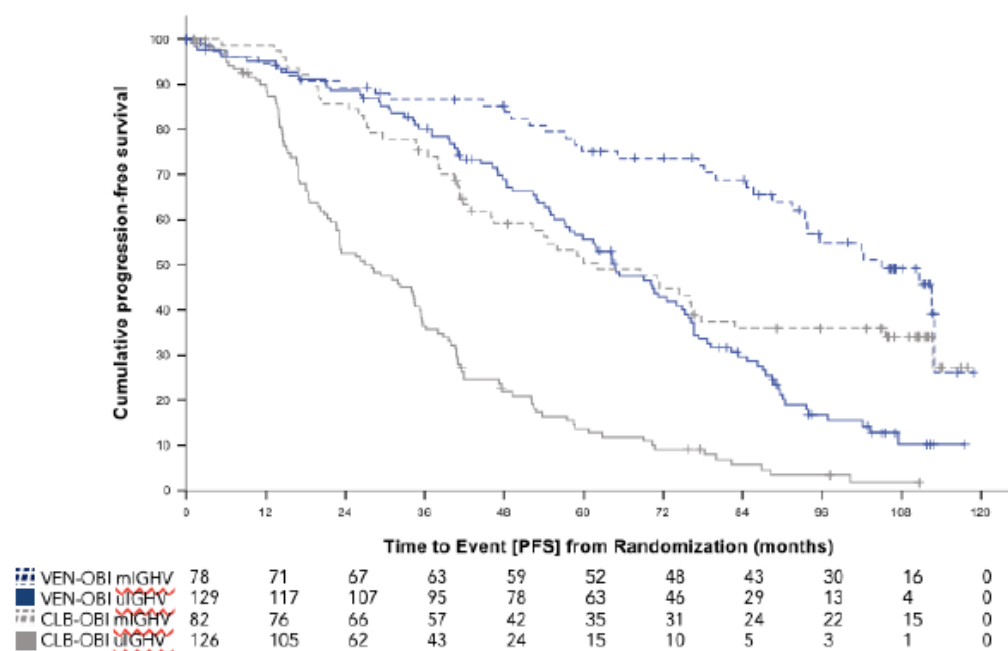
1. Fischer K et al. EHA 2026. 2. Brown JR, et al. *NEJM*. 2025; 392(8). 3. Shadman M, et al. ASH 2025; P7094.



CLL14 – exceptional outcomes with 1-yr finite therapy

105 KAPLAN-MEIER ESTIMATES

Progression-Free Survival By IGHV Mutational Status

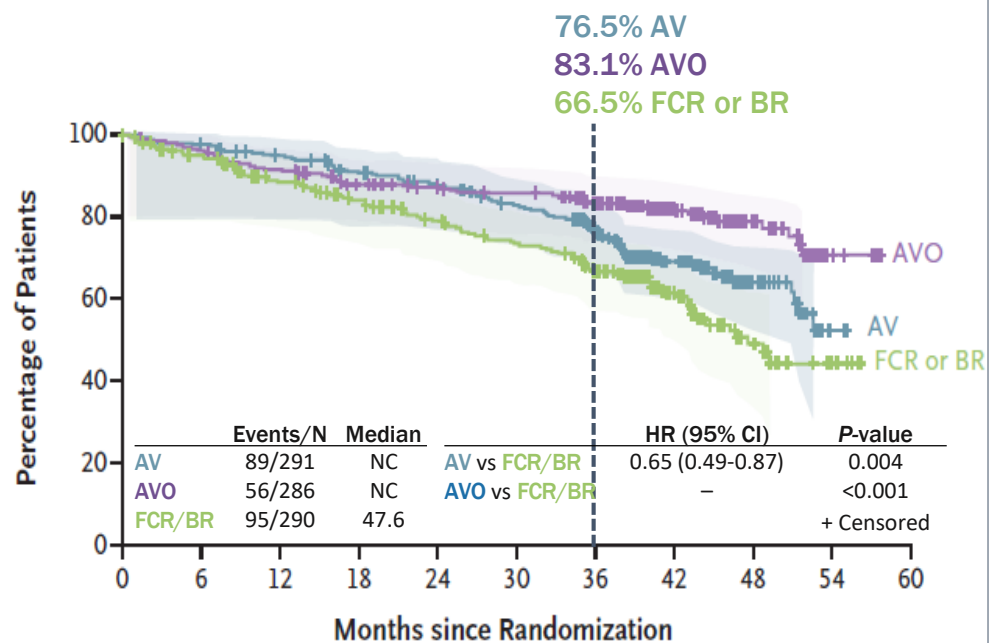


MEDIAN OBSERVATION TIME	110.1 months
MEDIAN PFS VEN-OBI & mIGHV	104.9 months
MEDIAN PFS VEN-OBI & uIGHV	64.7 months
HAZARD RATIO	2.74, 95% CI 1.85-4.06
P VALUE	<0.001
MEDIAN PFS CLB-OBI & mIGHV	62.2 months
MEDIAN PFS CLB-OBI & uIGHV	28.0 months
HAZARD RATIO	3.13, 95% CI 2.21-4.45
P VALUE	<0.001
MEDIAN PFS VEN-OBI mIGHV 8.7 YEARS MEDIAN PFS VEN-OBI uIGHV 5.4 YEARS	



AMPLIFY: Acalabrutinib+Venetoclax +/- aCD20 Ab

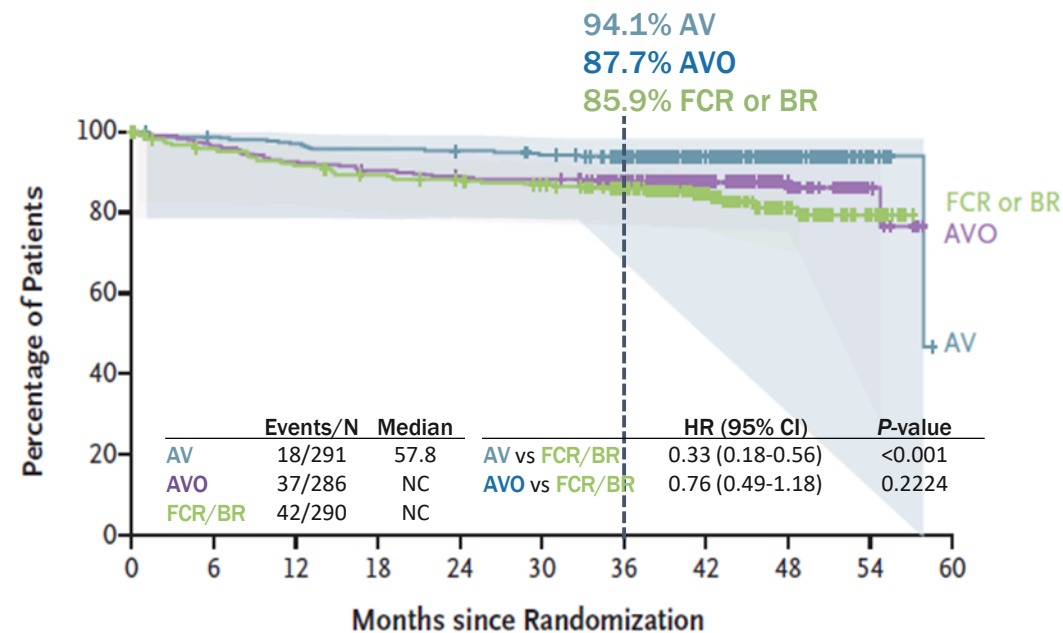
PFS (IRC Assessed)



No. at Risk

AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR or BR	290	236	208	189	170	154	127	66	28	6	0

OS



No. at Risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR or BR	290	247	236	228	223	217	182	98	45	13	0

OS data are still immature (11%, 3 arms)



CLL in 2030: AI Perspective

Smarter targeted drugs (oral, less toxic and highly effective)

- BTK degraders overcome resistance

- Fixed-duration combination regimens over lifelong therapy

- Therapy is adjusted based on MRD

Powerful time-limited combination therapies

- Future treatment combines BTKi, BCL2- and monoclonal antibodies

- “Hit hard, then stop”

GOAL: deep remission with minimal side effects



Trials in TN-CLL that will change the future

CELESTIAL-TN CLL Trial Design

Randomized, open-label, phase 3 study comparing sonrotoclax + zanubrutinib vs venetoclax + obinutuzumab in patients with TN CLL.

Phase 3

Study Identifier:
BGB-11417-301; NCT06073821

Primary Endpoint: PFS (IRC; iwCLL 2018)

Key Secondary Endpoints: CRR^a (IRC and investigator), rates of uMRD4 (BM and PB)^b, OS, PFS (investigator), ORR (IRC, investigator), DoR (IRC, investigator), PROs, safety and tolerability

Key eligibility criteria

- Age ≥18 years
- Confirmed CLL diagnosis, no previous treatment
- Measurable disease by CT/MRI
- ECOG PS of 0-2
- Adequate BM and organ function
- No history of, or currently suspected, Richter's transformation

Stratification factors

- Age (<65 vs ≥65 years)
- IGHV status
- del(17p)/TP53 mutation status

Treatment

Screening

R 1:1

**Zanubrutinib lead-in (3 cycles) followed by
Sonrotoclax + zanubrutinib (12 cycles)**
(n~320)

**Venetoclax (12 cycles) +
obinutuzumab (6 cycles)**
(n~320)

Efficacy will be assessed in accordance with 2018 iwCLL guidelines¹ with modification of treatment-related lymphocytosis for patients with CLL.²

^aDefined as CR or CR with incomplete recovery. ^bAt <10-4 sensitivity at the first post-treatment follow-up based on next-generation sequencing by clonoSEQ[®] and flow cytometry.

1. Hallek M, et al. Blood. 2018;131:2745-2760; 2. Cheson BD, et al. J Clin Oncol. 2012;30:2820-2822.

BM=bone marrow, CLL=chronic lymphocytic leukemia, CR=complete response, CRR=complete response rate, DoR=duration of response, ECOG=Eastern Cooperative Oncology Group, INV=investigator, IRC=independent review committee, ORR=overall response rate, OS=overall survival, PB=peripheral blood, PFS=progression-free survival, PS=performance status, R=randomized, uMRD=undetectable minimal residual disease.

Patten P, et al. Poster Presentation at ASH 2024;3257.1.

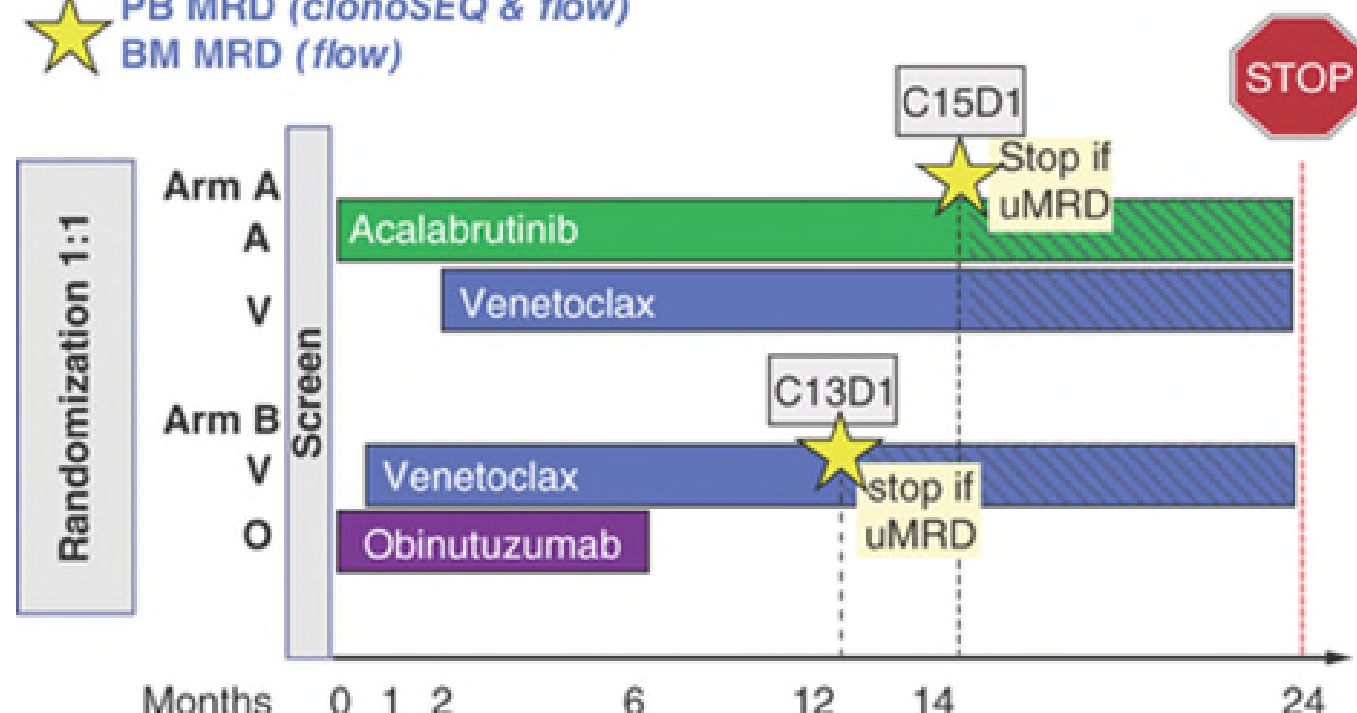


Trials in TN-CLL that will change the future: MAJIC

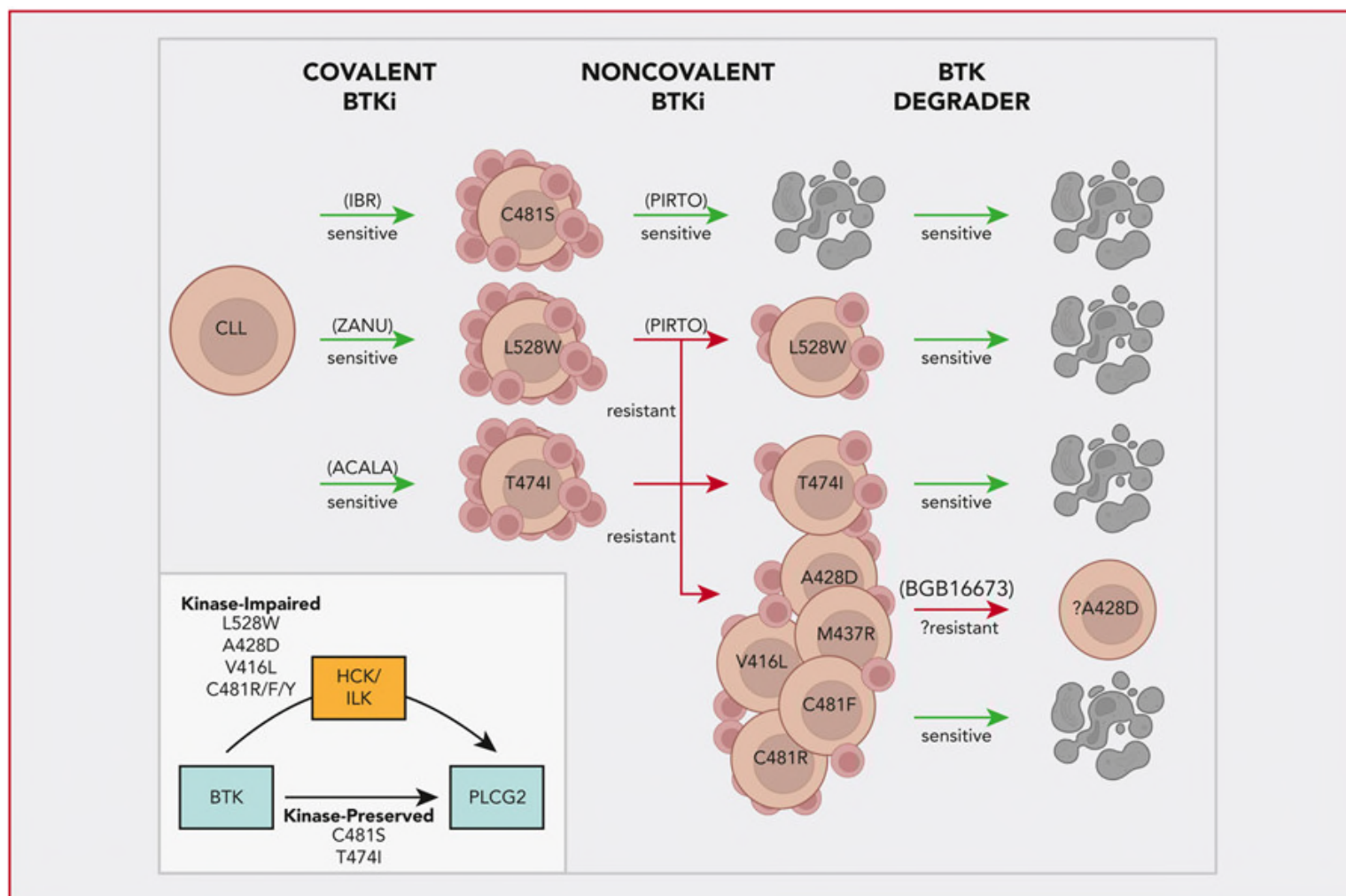
MAJIC schema

- Arm A** Acalabrutinib (A) 100 mg po BID,
Venetoclax (V) 400 mg po daily (C3D1–C14), including 5 week ramp up
STOP if uMRD and at least PR. If MRD+ continue AV to 24 months
- Arm B** Venetoclax (V) 400 mg po daily (C1D22–C12), including 5 week ramp up
Obinutuzumab (O) 1000 mg iv. (C1D1-2/8/15, C2-6 D1)
STOP if uMRD and at least PR. If MRD+ continue V to 24 months

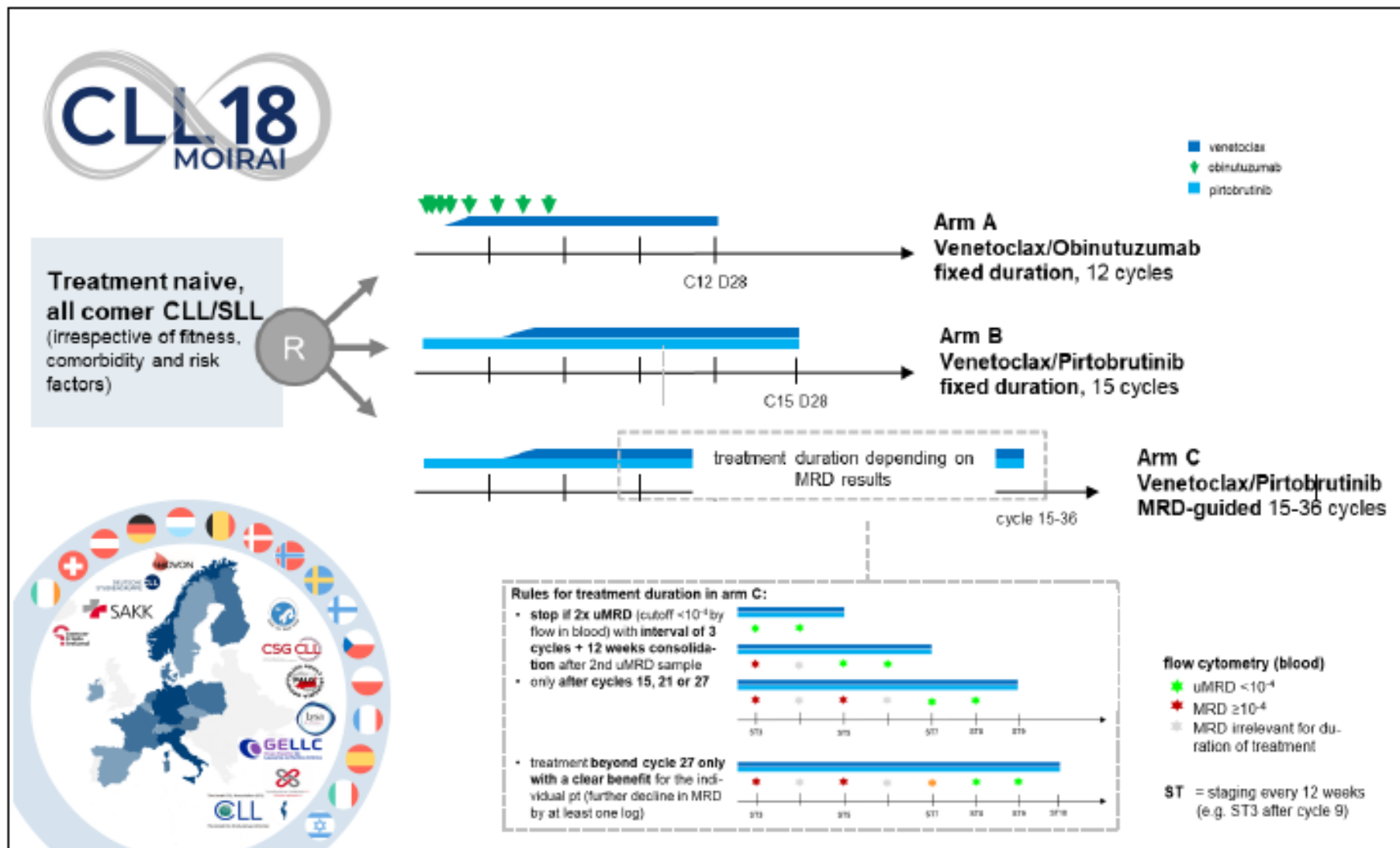
★ PB MRD (*clonoSEQ* & *flow*)
BM MRD (*flow*)



Resistance to BTK inhibitors



Trials in TN-CLL that will change the future: CLL18



Trials in TN-CLL that will change the future

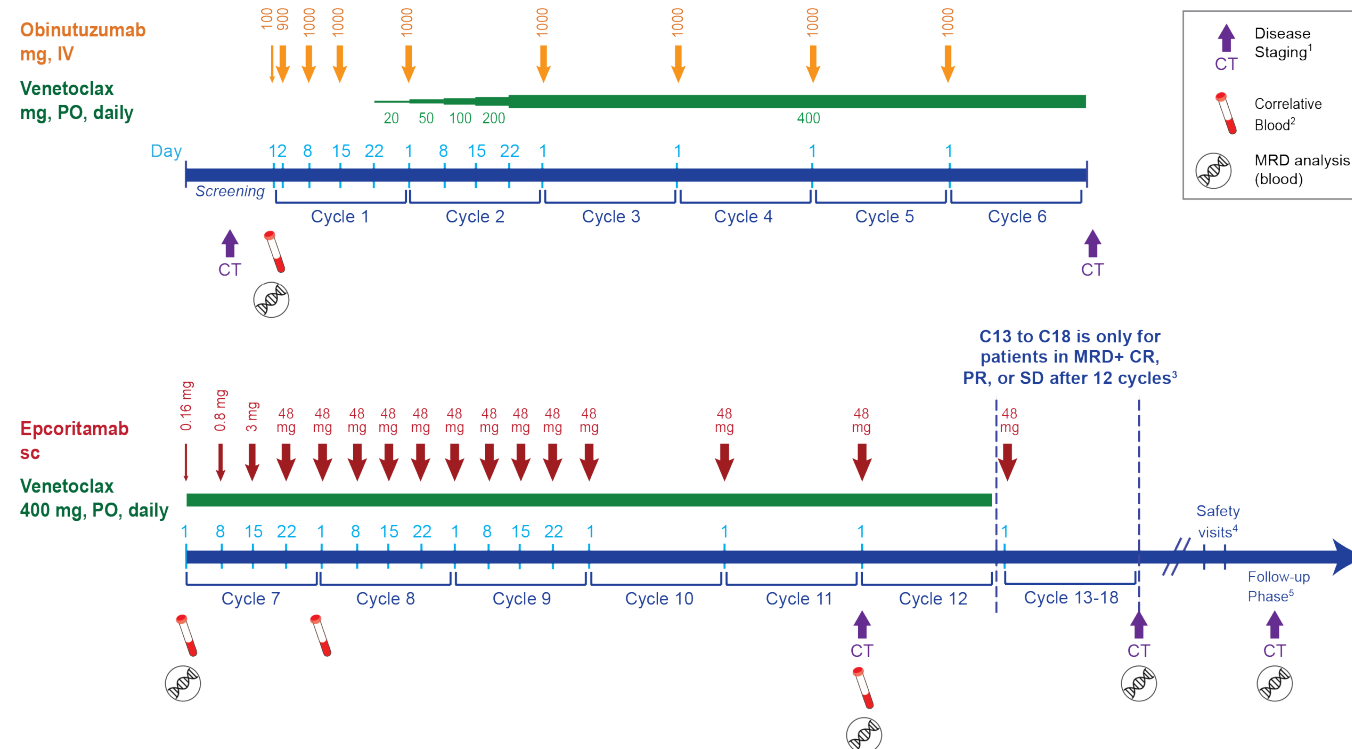
SOUNDTRACK-C1

A Phase III, Randomized, Open-label, Multicentre, Study of Surovatamig as Consolidation Therapy versus Observation after First-line Induction Therapy in Participants with CLL/SLL with Unmutated IGHV

Eligibility:

- Documented diagnosis of CLL/SLL with genomic features defined by unmutated IGHV.
- Treatment received and response at the end of 1L (first-line) finite therapy.

A Phase 2 Study of Venetoclax + Obinutuzumab Followed by Epcoritamab in Previously Untreated CLL/SLL (LonGEVity)



CLL in 2030: AI Perspective

Immunotherapy Revolution

- Safer CAR T, used in earlier lines of therapy
- Off-the shelf immunotherapy, both CAR T and Bi-specifics
- Bi-specific replace CAR T in low risk disease
- Cure is a reality



NCCN Guidelines for R/R CLL

Second-Line or Subsequent Therapy

Preferred Regimens

BCL2i-containing regimens*

Venetoclax + Obinutuzumab

cBTKi-based regimens

Acalabrutinib or Zanubrutinib (continuous) (category 1)

ncBTKi-based regimens

Pirtobrutinib (category 1) (resistance/intolerance to prior cBTKi-based regimen)

- * Ven ± anti-CD20 mAb (obi preferred) or ven + cBTKi after a period of remission.
- * Single agent ven (continuous) can also be considered after a period of remission.

Other Recommended Regimens

BCL2i-containing regimens*

Venetoclax + rituximab (category 1); Venetoclax;

Venetoclax + ibrutinib (category 2B)

cBTKi-based regimens

Ibrutinib (category 1)

R/R after Prior cBTKi-Based & BCL2i-Containing

Preferred Regimens

CAR T-cell Therapy: Lisocabtagene maraleucel

ncBTKi-based regimen: Pirtobrutinib (if not previously given)

Other Recommended Regimens

PI3Ki-based regimens: Duvelisib; Idelalisib ± rituximab

FCR,

Lenalidomide ± rituximab,

Obinutuzumab,

Alemtuzumab ± rituximab (w/ del(17p)/TP53 mutation),

Bendamustine + rituximab (category 2B for ≥65 or <65 w/ significant comorbidities),

HDMP + anti-CD20 MoAb (category 2A w/ del(17p); category 2B w/out del(17p))



Trials that will change the future of R/R CLL: ReVenGe

Study Design & Baseline Characteristics (25 Patients)

Cohort 1 > 2 years response to Ven-Obi



N=60

6 Cycles of Ven-Obi + 6 Cycles Ven monotherapy

Cohort 2 > 1-2 years response to Ven-Obi



N≤15

6 Cycles Ven-Obi + 18 Cycles Ven monotherapy

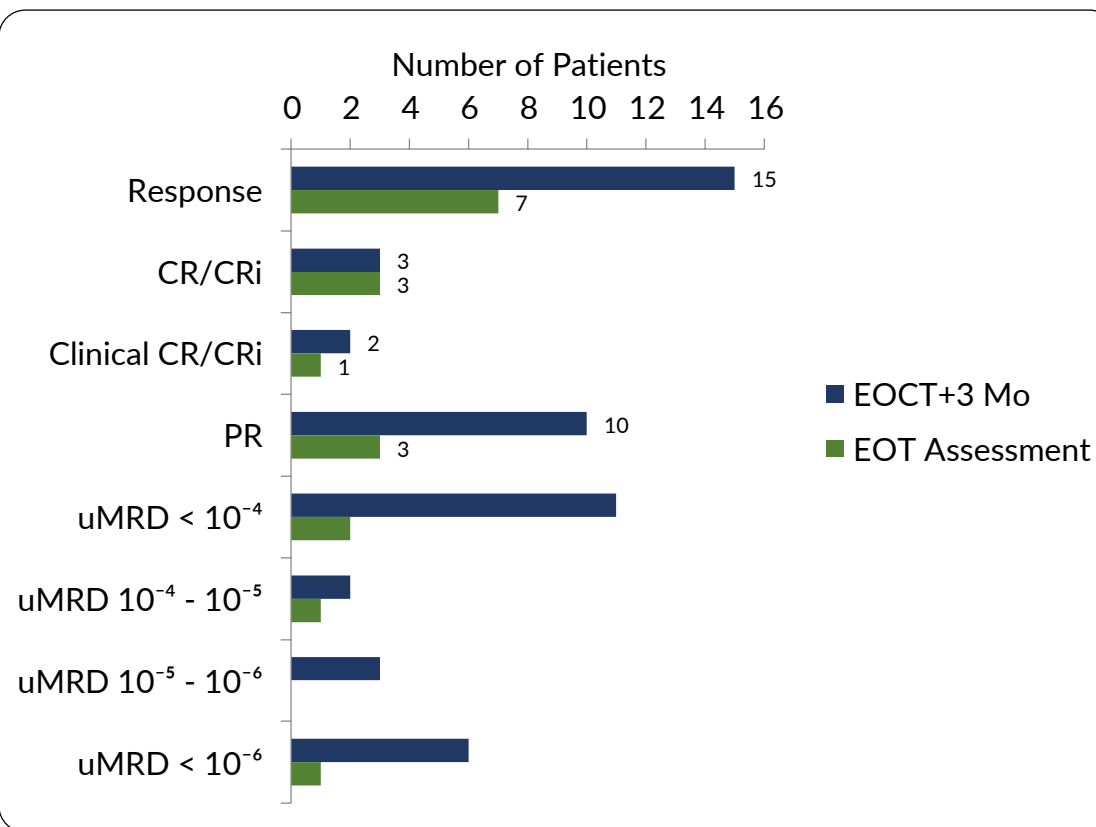
1 endpoint: ORR by 2018 will criteria after end of combination therapy (EOCT) + 3 Mo.

2+ endpoints: ORR after end of treatment (EOT) + 3 Mo, safety, PFS, OS, and uMRD rates

Genetic characteristics (21 with available data); N (%)

17p deletion status – deleted	3 (14)
TP53 mutational status – mutated	8 (38)
Either del(17p) or TP53 mutated	8 (38)
IGHV mutational status – mutated	3 (14)
Acquired mutation in BCL-2	0 (0)

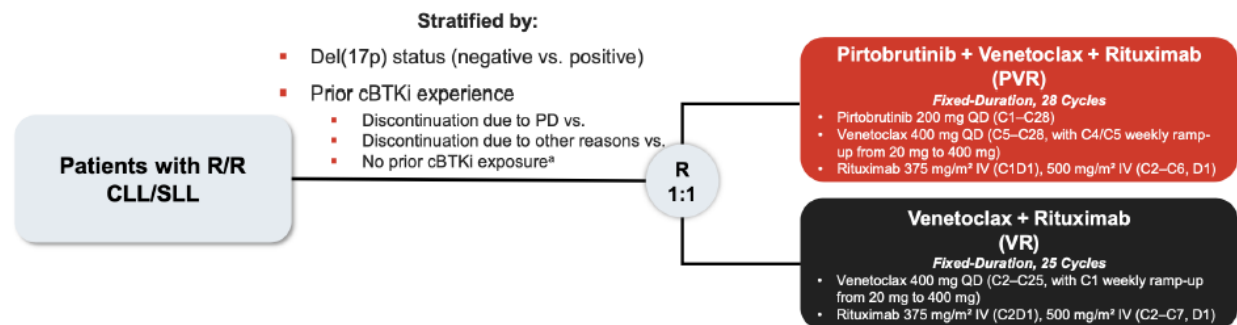
Response (EOCT+3 Mo: N=13; EOT: N=7)



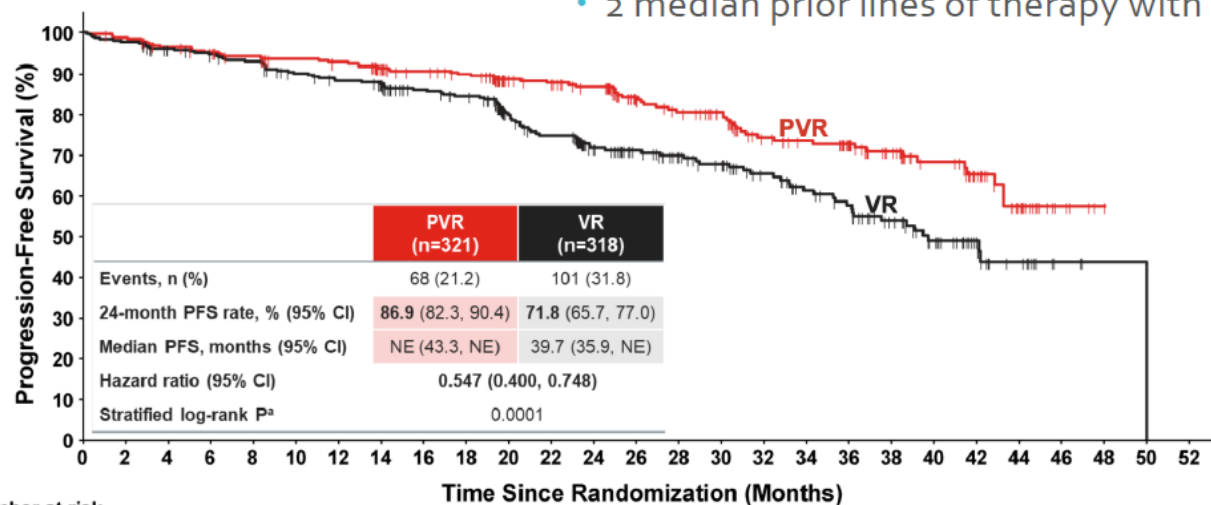
CLL chronic lymphocytic leukemia, Obi obinutuzumab, ORR objective response rate, MRD minimal residual disease, CR complete response, PR partial response



Trials that will change the future of R/R CLL: BRUIN-322



- 2 median prior lines of therapy with 80% pts with prior cBTKi



Number at risk

PVR	321	308	297	291	284	278	275	258	243	237	196	191	182	147	131	123	99	93	86	66	48	32	19	5	1	0	0
VR	318	293	282	276	269	256	249	245	221	215	175	161	127	114	104	94	80	70	63	49	36	21	11	3	1	1	0

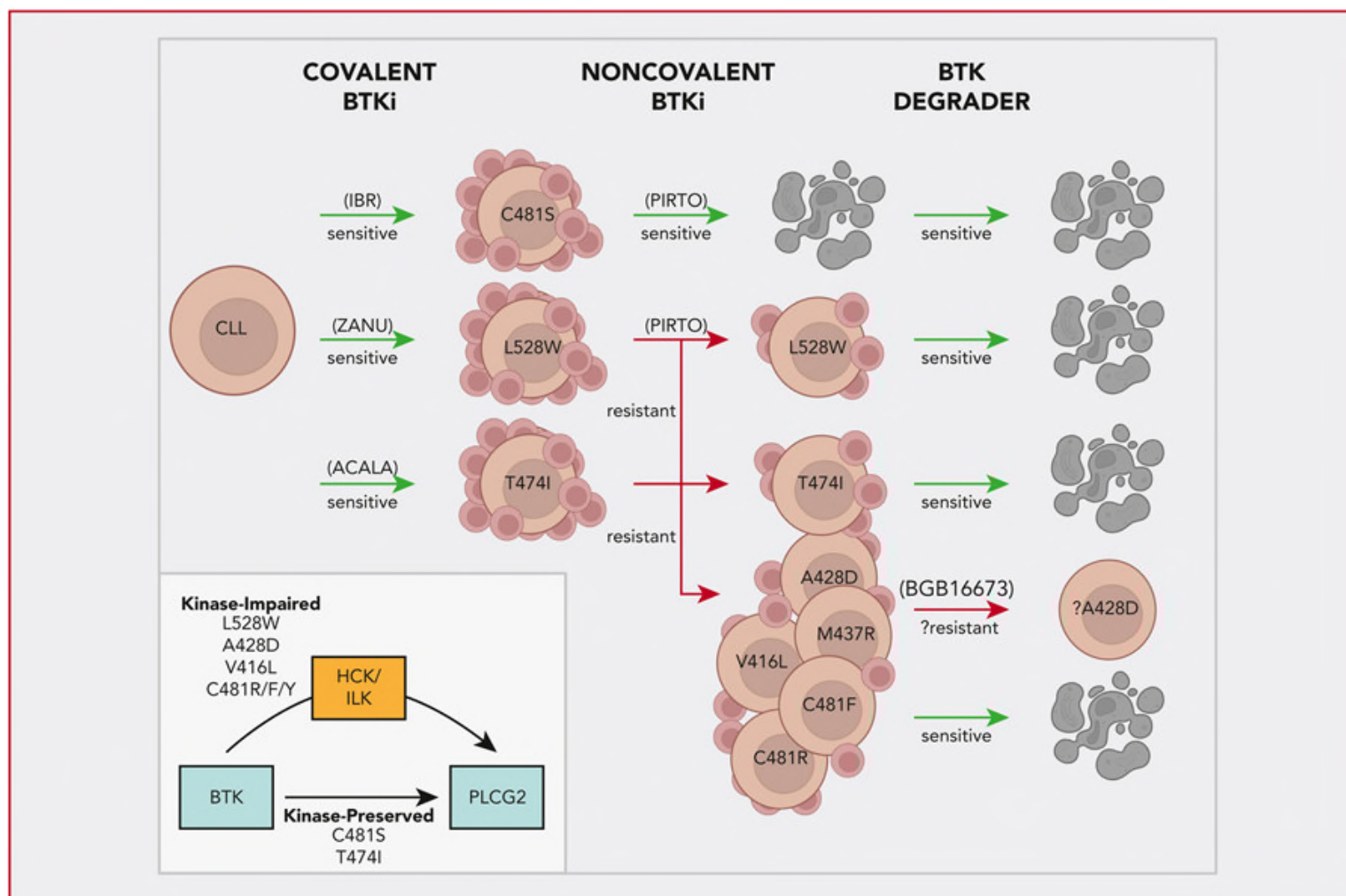
16 events of Richter Transformation occurred in the VR arm vs 8 events in the PVR arm

Patients with evaluable samples at EOT^a

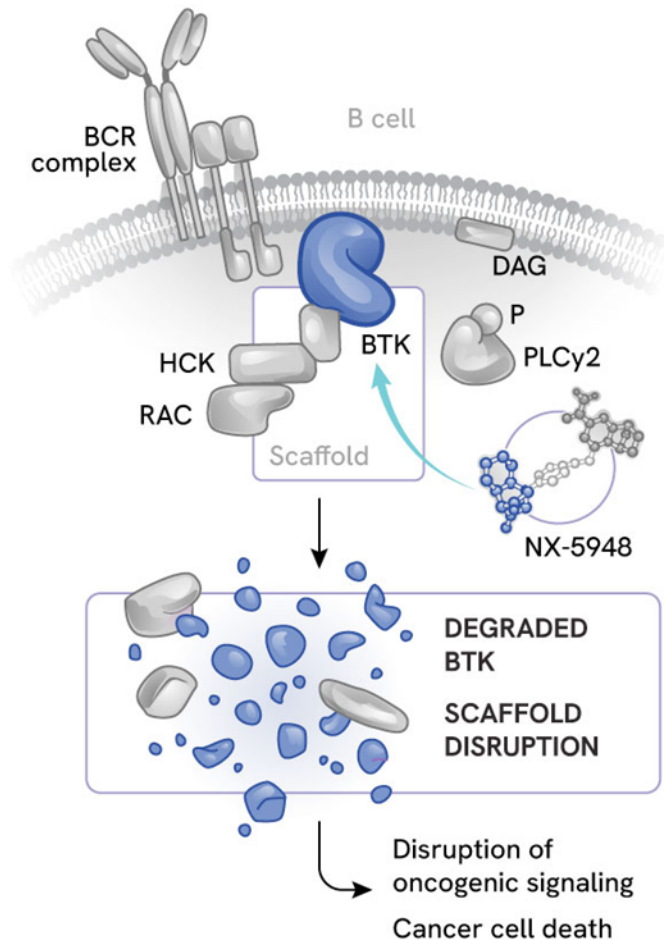
uMRD Threshold, n (%) ^b	PVR N=117	VR N=117	P-value ^c
uMRD4	101 (86.3)	71 (60.7)	<0.0001
uMRD5	87 (74.4)	59 (50.4)	0.0002
uMRD6	61 (52.1)	41 (35.0)	0.0103



Resistance to BTK inhibitors



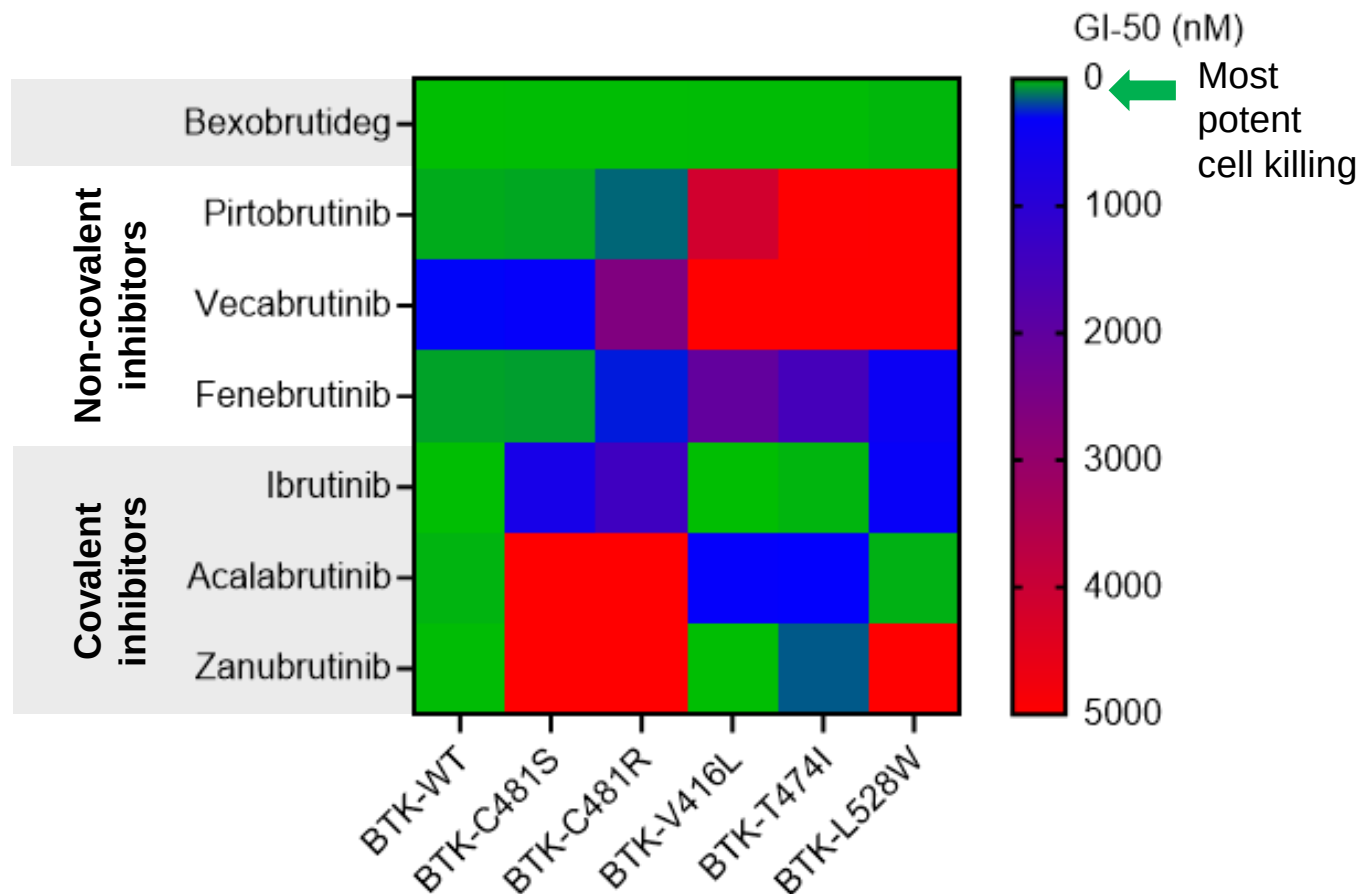
Trials that will change the future of R/R CLL:BTK degraders



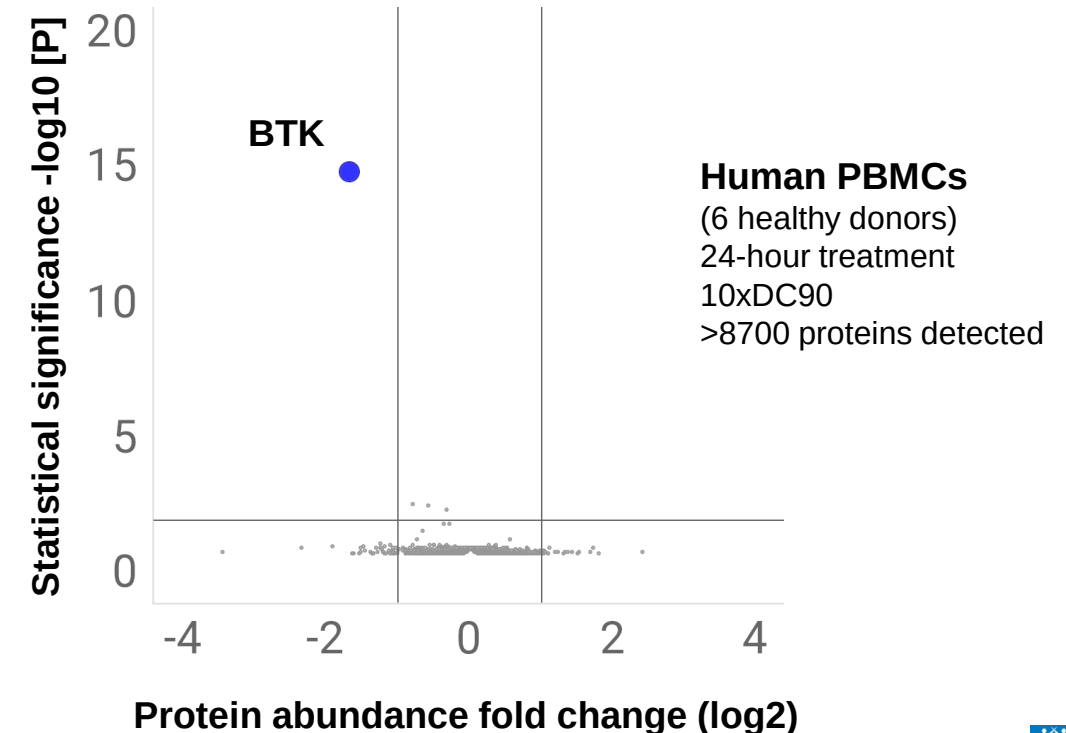
- ✓ Active against not only wildtype BTK but also treatment emergent BTK-inhibitor resistance mutations^{1,2}
- ✓ Addresses both BTK scaffolding and kinase functions, unlike current BTK inhibitors³
- ✓ Acts catalytically, driving degradation at low free-drug plasma concentrations
- ✓ Crosses the blood–brain barrier and demonstrates clinical activity in the CNS⁴
- ✓ Demonstrates robust clinical activity in difficult-to-treat B-cell malignancies^{5–7}

Trials that will change the future of R/R CLL:BTK degrader Bexobrutideg

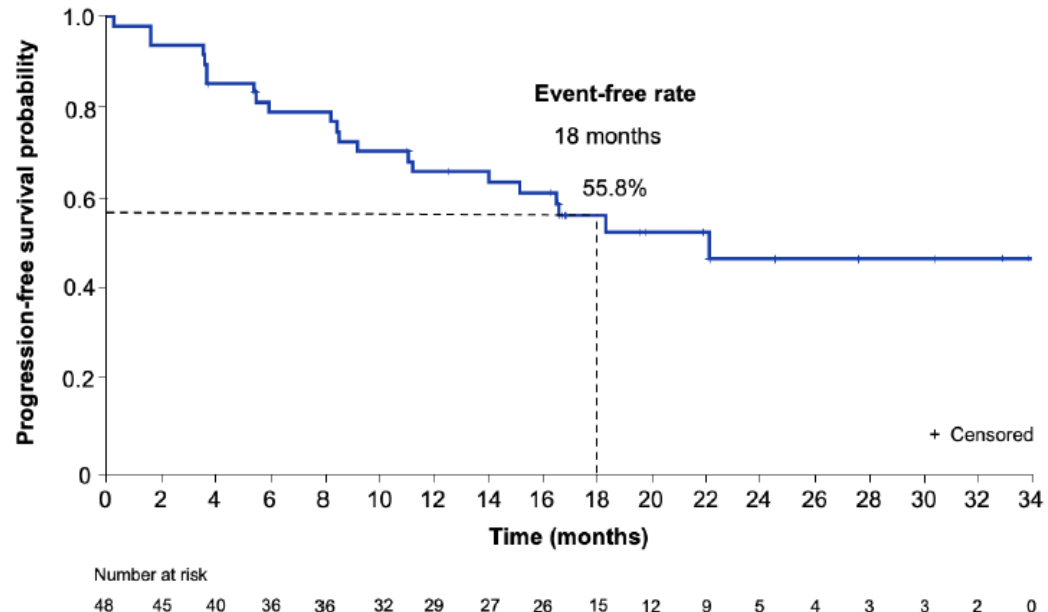
Bexobrutideg shows superior cell killing across mutations compared with BTK inhibitors*



Global proteomics using bexobrutideg show selective degradation of BTK at clinically relevant exposures



Trials that will change the future of R/R CLL: BTK degrader Bexobrutideg

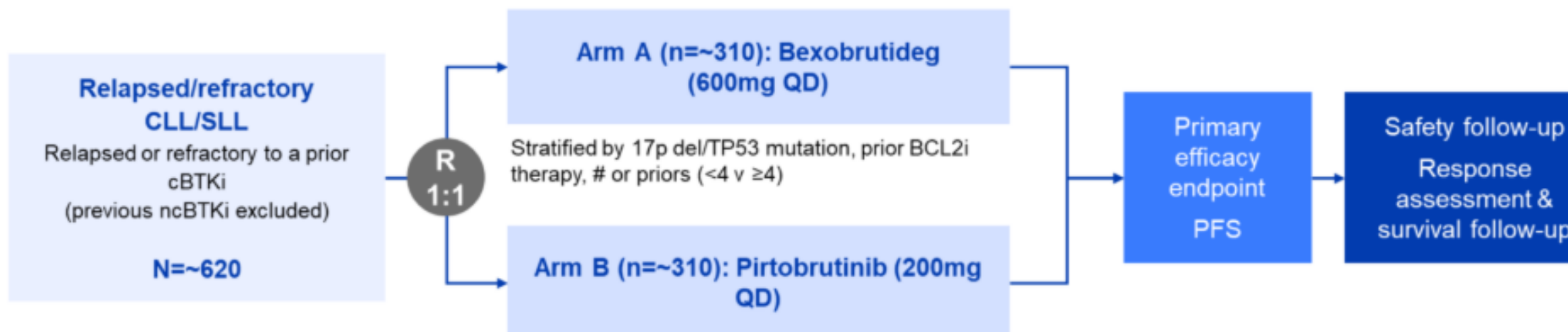


Relapsed/refractory CLL/SLL	
PFS summary	
n=48	
Median PFS ^a , months (95% CI)	22.1 (14.0–NR)
ORR summary	
n=47 ^b	
ORR, % (95% CI) ^c	83.0 (69.2–92.4)
CR	2 (4.3)
nPR	1 (2.1)
PR	36 (76.6)
SD	6 (12.8)
PD	2 (4.3)
Median follow-up, ^d months (range)	22.4 (16.9–35.7)



Trials that will change the future of R/R CLL: CLL-306

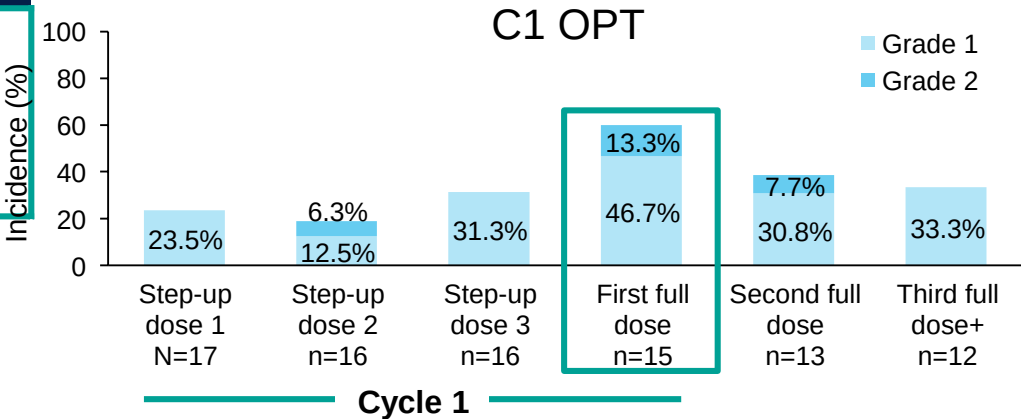
Primary endpoint: PFS per iwCLL as assessed by IRC (superiority)



Trials that will change the future of R/R CLL: Bi-specific Antibodies (Epcoritamab)

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 Exposure ^a n=19	Response Evaluable n=10
Overall response ^b	14 (61)	14 (67)	10 (67)	10 (63)	10 (53)	6 (60)
CR	9 (39)	9 (43)	5 (33)	7 (44)	7 (37)	1 (10)
PR	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)

CRS Events by Dosing Period



CAR T cells in CLL: TRANSCEND 004

Study Design



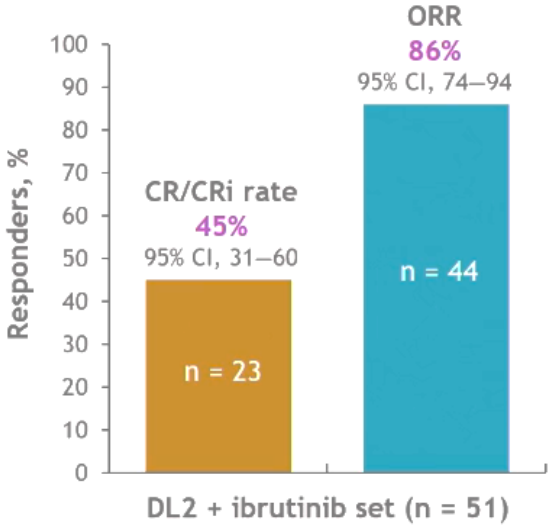
- Key patient eligibility criteria**
- Age ≥ 18 years
 - R/R CLL/SLL with an indication for treatment
 - Previously failed or ineligible for BTKi therapy
 - Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
 - ECOG PS ≤ 1
 - Adequate bone marrow, organ, and cardiac function
 -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

Efficacy: 23.8 mo F/U¹

	Full study population at DL2 (n = 88)	BTKi progression/venetoclax failure subset at DL2 (n = 50)	Prior BTKi exposure and venetoclax-naïve subset at DL2 (n = 18)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	18 (20) [13–30]	10 (20) [10–34]	4 (22) [6–48]
Key secondary endpoints			
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37–59]	22 (44) [30–59]	11 (61) [36–83]
uMRD4 rate in blood, n (%) [95% CI]	58 (66) [55–76]	32 (64) [49–77]	12 (67) [41–87]

Ibrutinib Cohort²

Ibrutinib (≤420mg daily) continued or restarted at enrollment up to 90 days after liso-cel (or longer per INV)



Median (IQR) on study follow-up	24.8 mo (14.2-34.6)
Median (range) TTFR	1 mo (0.9-6.0)
Median (range) TTCR/CRi	3 mo (0.9-12.1)

CLL chronic lymphocytic leukemia, SLL small lymphocytic lymphoma, ORR objective response rate, MRD minimal residual disease, TTFR time to first response, TTCR time to complete response, DL dose level, FLU fludarabine, CY cytarabine

1. Siddiqi T, et al. Blood 2024; 144(suppl_1). 2. Wierda W, et al. ASH, 2024. Oral 887.



CLL in 2030: AI Perspective

AI will guide treatment selection

GOAL: each patient gets a tailored treatment sequence, no “one size fits all”



NCCN Guidelines for TN CLL ca. 2030

Preferred Regimens

Standard risk (mlGHV, no del17p)

- AV / ZS / PV, MRD-adjusted

High-risk (ulGHV, del17p)

- AV/VO/ZS->Suro/EpcO

Other Recommended Regimens

- VO

Useful in Certain Circumstances

Regimens

- Continuous BTKi

Key point: time-limited doublets +consolidation in high-risk patients, MRD adjusted

NCCN Guidelines for R/R CLL ca. 2030

Second-Line or Subsequent Therapy

Preferred Regimens
PVR(O)
Bexo-Ven/Taca-Sonro

3L+ R/R of 2L+ high-risk

Preferred Regimens
Lisocabtagene maraleucel + Pirtobrutinnib
BsAb-based regimen: Ven-Epco/Suro

Time-limited doublets/triplets employing BTK degraders and non-covalent BTKi
CAR-T and BsAb in 2nd/3rd line

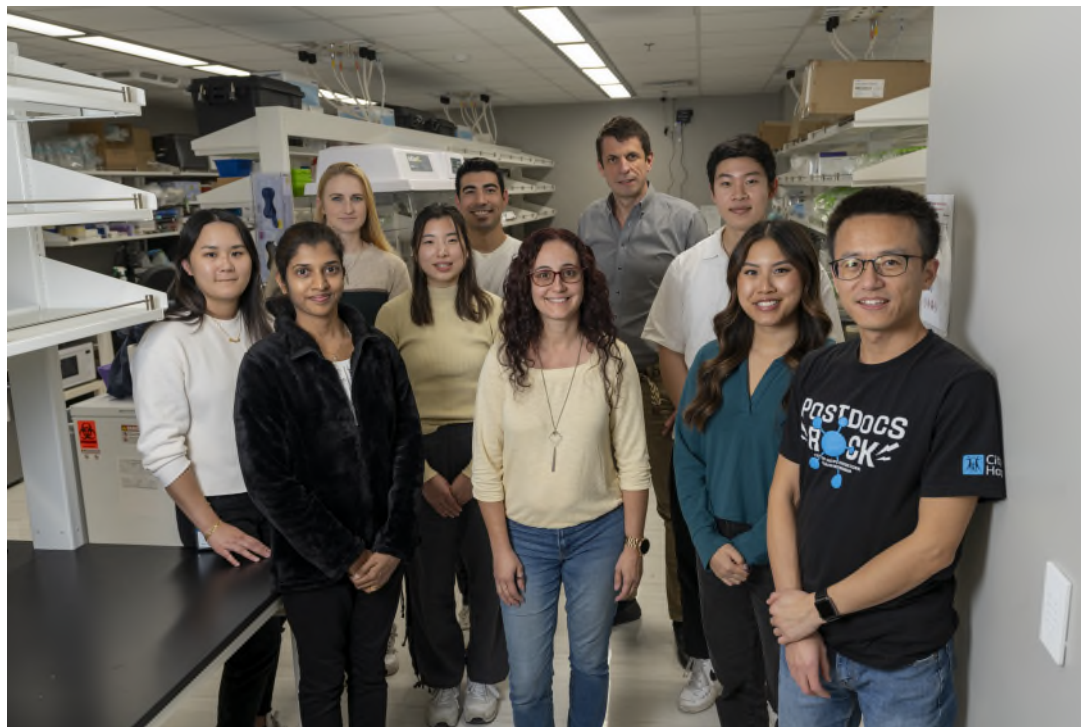


Thank you!

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