ASH Updates in Chronic Lymphocytic Leukemia

Javier Pinilla-Ibarz, MD, PhD.

Senior Member

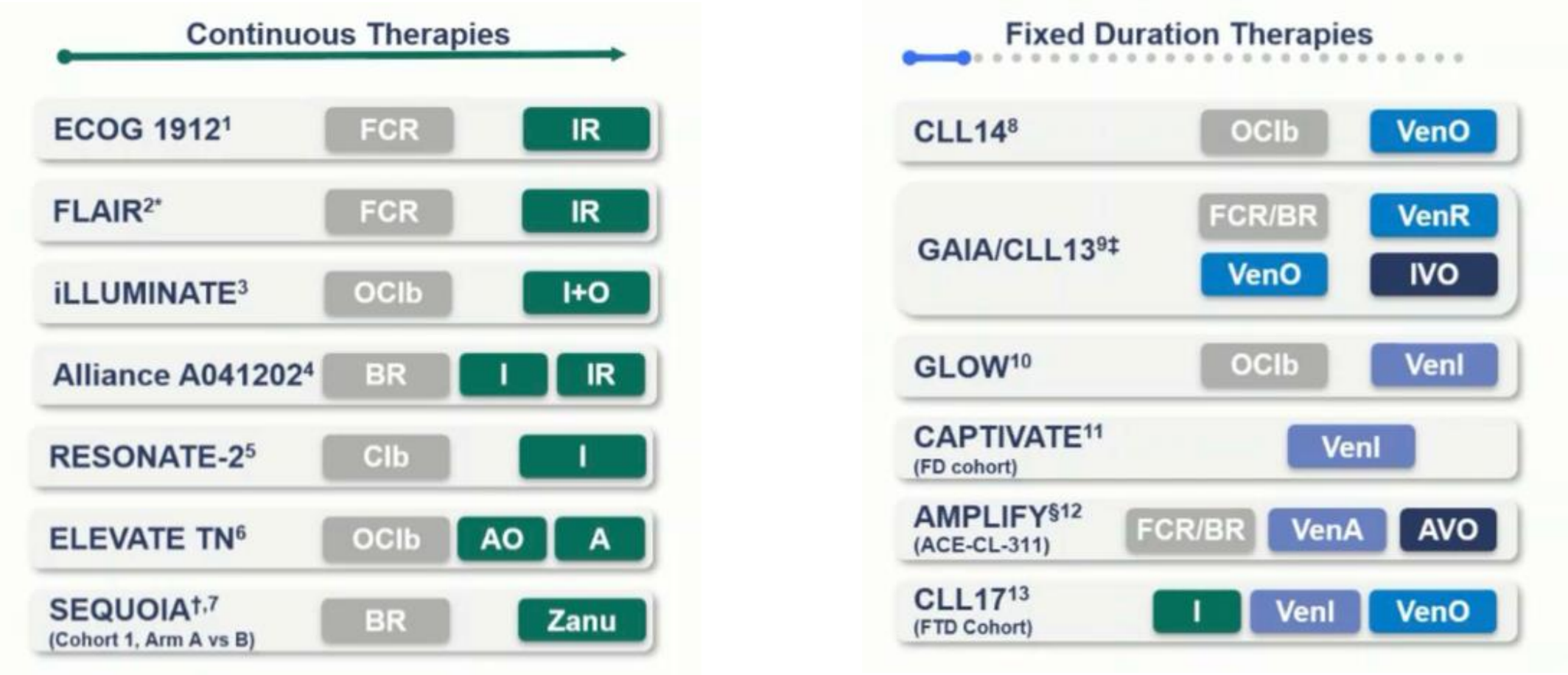
Head of Lymphoma section and

Director of Immunotherapy

Malignant Hematology Department

MOFFITT CANCER CENTER

Continuous Therapy vs Fixed Duration



Shanafelt TD, et al. *New Engl J Med.* 2019; 381:435-443. Hillman P, et al. *Lancet Oncol,* 2023,24:535-552. Moreno C, et al. *Lancet Oncol.* 2019,20:43-56. Woyach JA, et al. *Blood,* 2021;138:639. Barr PM, et al. *Blood Adv.* 2022;6:3400-3450. Sharman JP, et al. *Leukemia.* 2022;36:1171-1175. Tam CS, et al. *Lancet Oncol.* 2022;23:1031-1043. AlSawaf O, et al. *Nat Commun.* 2023;14:2147. Eichhorst B, et al. *N Eng J Med.* 2023;338:1739-1754. Kater AP, et al. *NEJM Evid.* 2022;1:711. Tam CS, et al. *Blood*. 2022;139:3278-3289. National Institute of Health (NIH). Accessed Sept 25, 2024. https://clinicaltrials.gov/study/NCT04608318; NCT03836261

Pivotal Clinical Trials of BTKi Monotherapy

Trail	Agent	Follow-up	ORR	PFS	OS	Common AEs
RESONATE-2[1] (N=269)	**Ibrutinib** vs chlorambucil	8 y	92% vs 37% mDOR NR vs 48.8 mo	mPFS 8.9y vs 15 mo HR 0.154 (0.108-0.220)	mOS NR vs 89 mo HR 0.453 (0.276-0.743)	Diarrhea Fatigue Cough Nausea
ELEVATE TN[2,3] (N=535)	**Acalabrutinib** ± obinutuzumab vs chlorambucil + Obinutuzumab	74.5 mo	93.9% vs 85.5% vs 78.5%	mPFS NR vs NR vs 27.8 mo HR 0.14, 0.23	mOS NR vs NR vs NR HR 0.62	Neutropenia Thrombocytopenia Diarrhea
SEQUOIA[4] (N=479)	**Zanubrutinib** vs BR	43.7 mo	94.6% vs 85.3% mDOR NR vs 30.6 mo	mPFS NR vs 42m HR 0.42 (0.28-0.63)	mOS NR vs NR HR 1.07 (0.51-2.22)	Neutropenia Bleeding Infection

HR, hazard ratio; mDOR, median duration of response; mOS, median overall survival; NR, not reached; ORR, overall response rate

1. Barr PM et al. *Blood Adv*. 2022;6:3440-3450. 2. Sharman JP et al. *Blood*. 2023;142(suppl 1):636. 3. NCT02475681. 4. Tam CS et al *Lancet Oncol*. 2022;23:1031-1043.

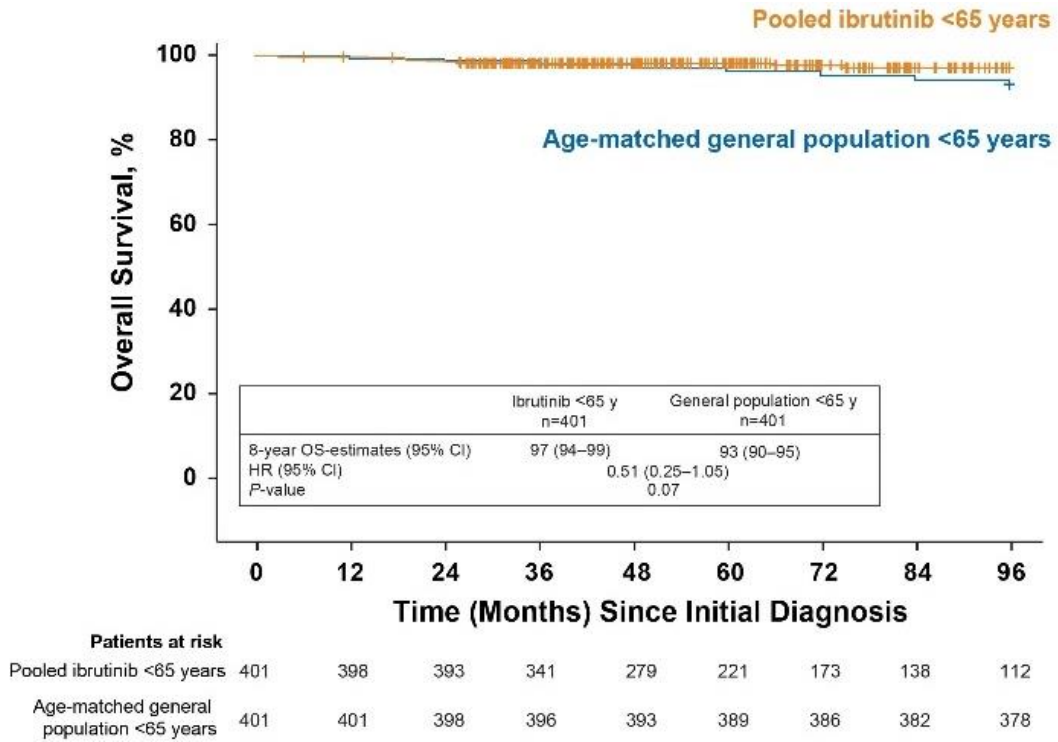
BTKi Monotherapy Clinical Trials and Del(17p)/*TP53* Mutations

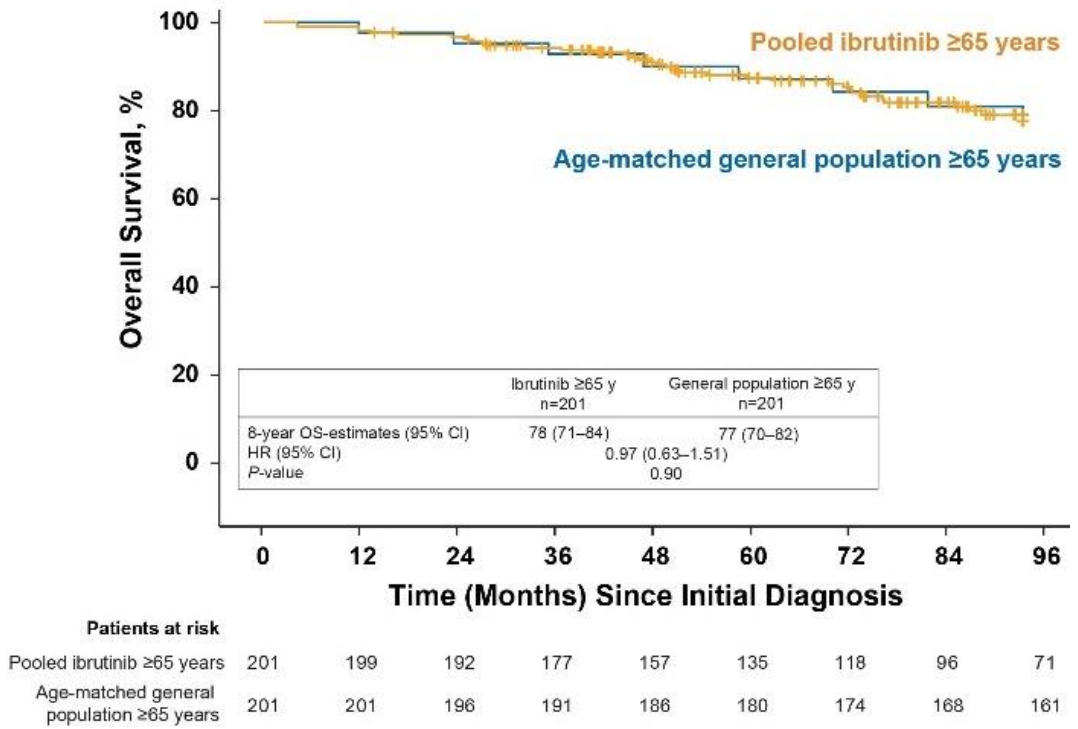
Trail	Agent	N	Follow-up	ORR	PFS	OS
4 pooled RCTs[1]	**Ibrutinib**	89	49.8 mo	93% (CR 39%)	mPFS NR 4-y: 79%	4-y: 88%
PCI-32765[2,3]	**Ibrutinib**	84	113-117 mo	95.8%	mPFS: 81 mo	10-y: 69.7%
ELEVATE TN[4]	**Acalabrutinib or acalabrutinib + obinutuzumab**	23, 25	74.5 mo	Not reported (CR 32%)	mPFS 73m, NR 74-mo: 56%, 56%	Not reported
SEQUOIA[5] (Arm 2)	**Zanubrutinib**	111	47.9 mo	90.0% mDOR: NR	mPFS NR 48-mo: 79.4%	24-mo: 93.6%

CR, complete response

1. Allan JN et al. *Br J Haematol*. 2022;196:947-953. 2. Itsara A et al. *Blood*. 2023;142:201-202. 3. https://clinicaltrials.gov/study/NCT01500733?tab=results. 4. Sharman JP et al. *Blood*. 2023;142 (suppl 1):636. 5. Tam CS et al *Lancet Oncol*. 2022;23:1031-1043..

Patients with CLL Treated with Continuous BTKi Are Living Longer, therefore QoL Becomes Paramount when Selecting Treatment

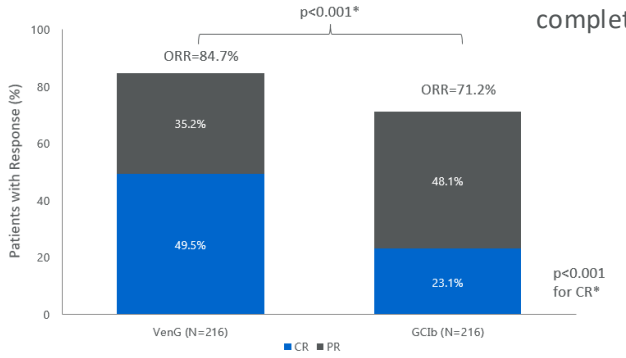




Ghia P, et al. *Hemasphere*. 2024;8(5):e74.

CLL14: Venetoclax + Obinutuzumab in TN CLL

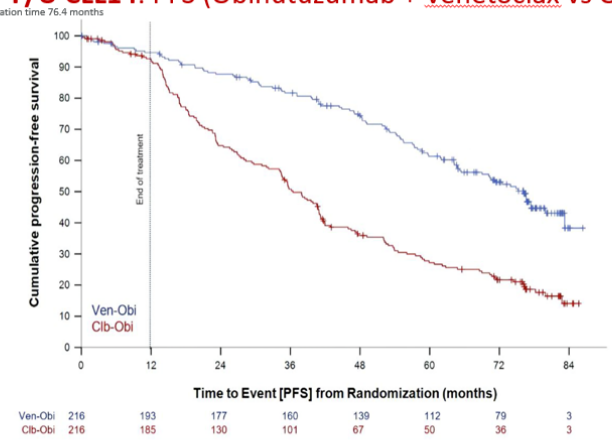
OVERALL AND COMPLETE RESPONSE RATES AT EOT+3



*EOT+3, 3 months after treatment completion.

p<0.001 for CR*

6 Year F/U CLL14: PFS (Obinutuzumab + Venetoclax vs Obinutuzumab + Chlorambucil)



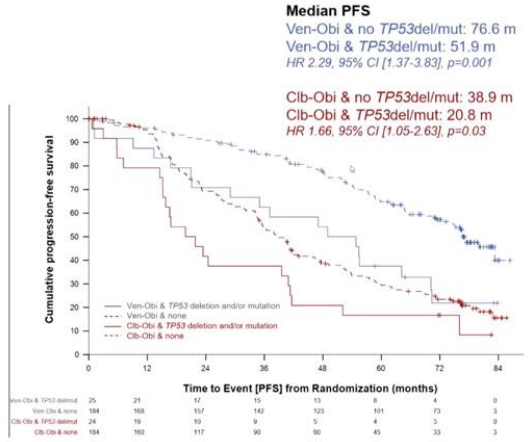
Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

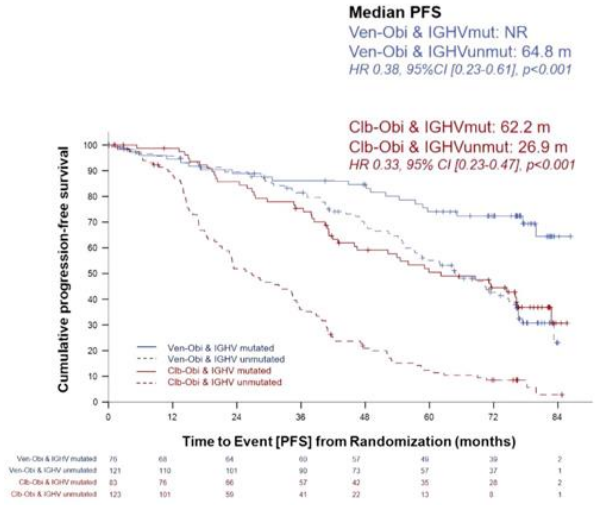
HR 0.40, 95% CI [0.31-0.52]
P<0.0001

Key Takeaway: Obinutuzumab + Venetoclax improved PFS over Obinutuzumab + Chlorambucil
[53% of patients are still in remission 5 years after completing fixed-duration therapy]

PFS by TP53

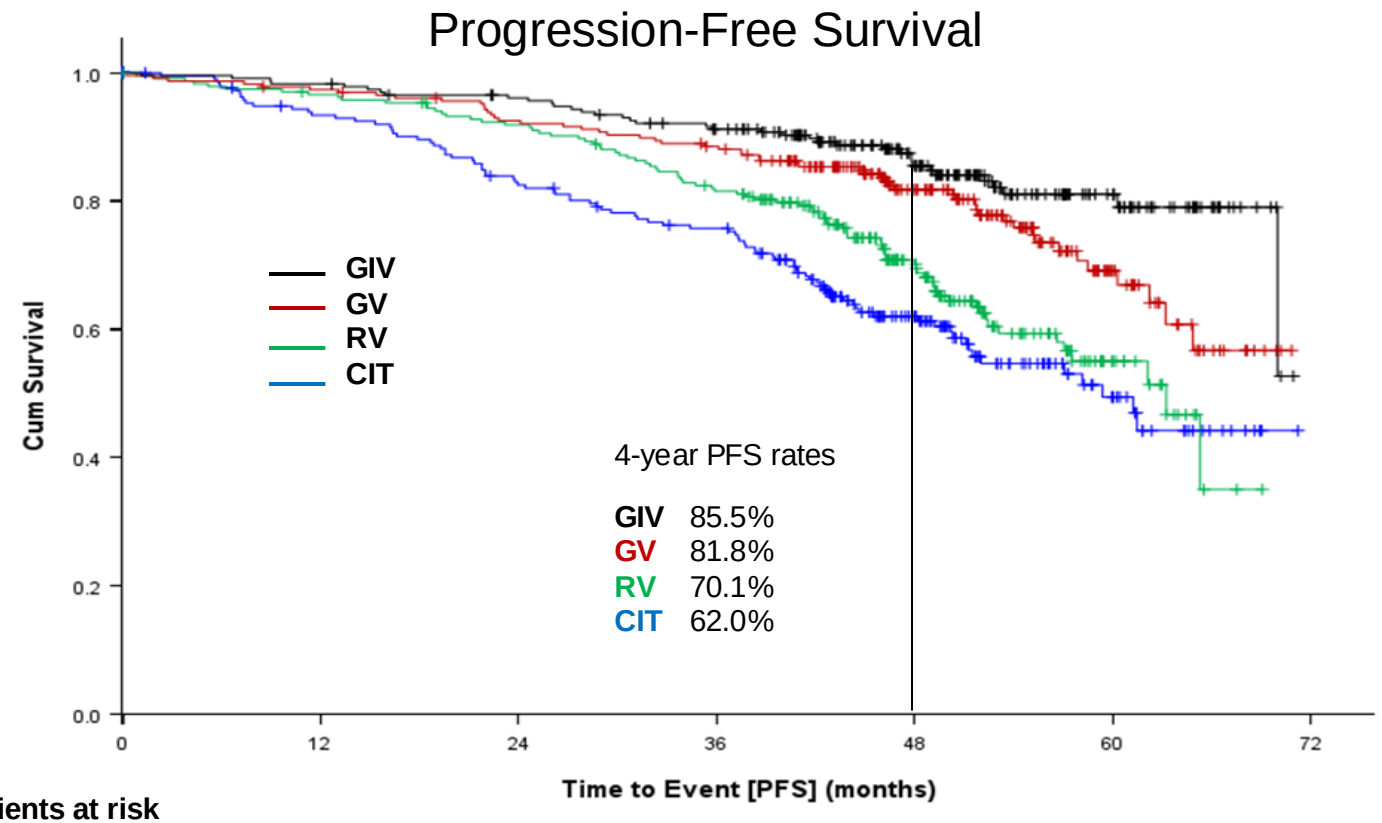


PFS by IGHV



Fischer K, et al. *N Engl J Med.* 2019;380:2225-2236. al-Sawaf O, et al. Presented at: EHA 2023; June 8, 2023; Madrid, Spain. S145.

CLL 13 trial Efficacy: PFS



Patients at risk						
CIT	229	197	173	156	84	24
RV	237	227	214	188	106	21
GV	229	222	209	198	121	32
GIV	231	227	218	201	130	44

PFS comparisons

GIV *vs* **CIT**: HR 0.30, 97.5%CI: 0.19-0.47, ***p<0.001***
GIV *vs* **RV**: HR 0.38, 97.5%CI: 0.24-0.59, ***p<0.001***
GIV *vs* **GV**: HR 0.63, 97.5%CI: 0.39-1.02, *p*=0.03

GV *vs* **CIT**: HR 0.47, 97.5%CI: 0.32-0.69, ***p<0.001***
GV *vs* **RV**: HR 0.57, 97.5%CI: 0.38-0.84, ***p=0.001***

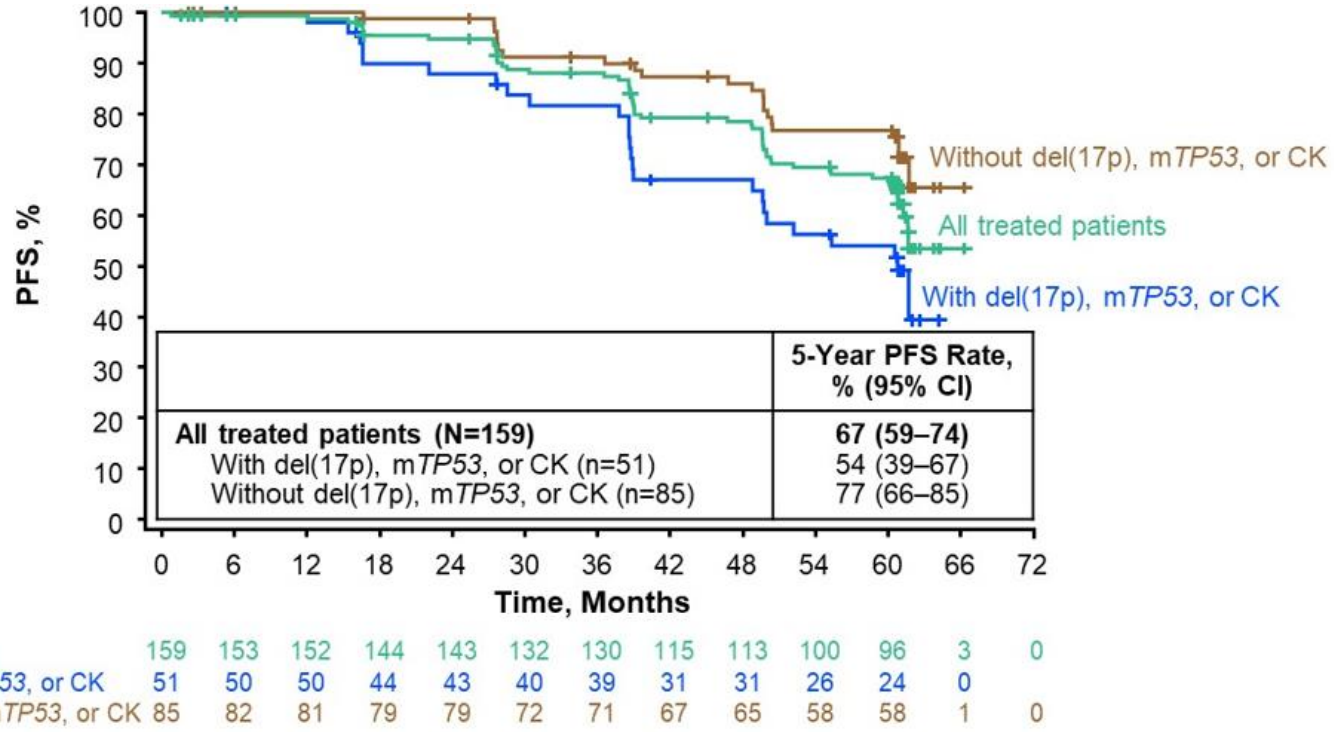
RV *vs* **CIT**: HR 0.78, 97.5%CI: 0.55-1.10, *p*=0.1

Fürstenau M, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 635.

CAPTIVATE: PFS in the FD Cohort

PFS in All Treated Patients and by del(17p), m*TP53,* or CK

Median time on study: 61.2 months (range, 0.8-66.3)

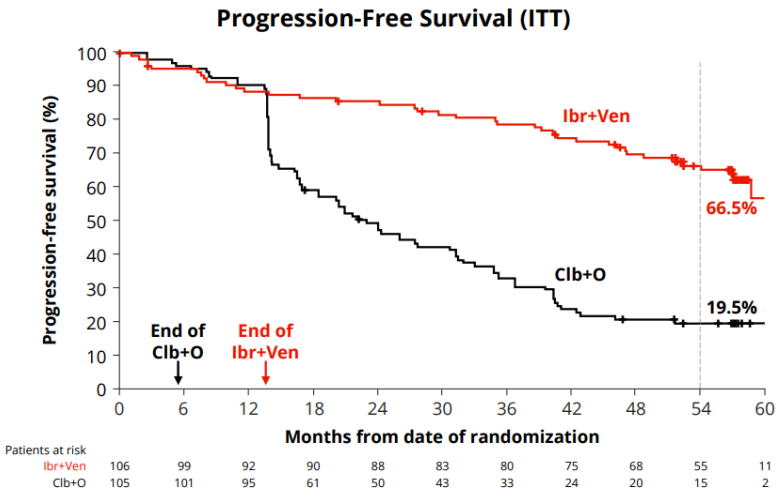


High-risk feature	n	5-year PFS rate, % (95% CI)
With del(17p)/m*TP53*	27	41 (21-59)
Without del(17p)/m*TP53*	129	73 (64-80)
With CK[a]	31	57 (37-72)
Without CK[a]	102	72 (61-80)
With del(11q)[b]	11	64 (30-85)
Without del(11q)[b]	74	79 (67-87)

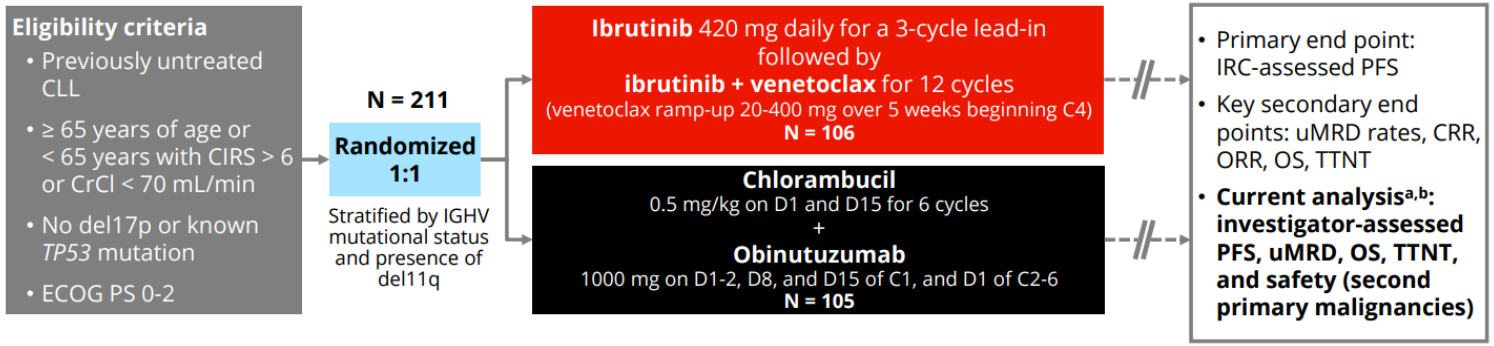
- Overall median PFS was not reached with up to 5.5 years of follow-up

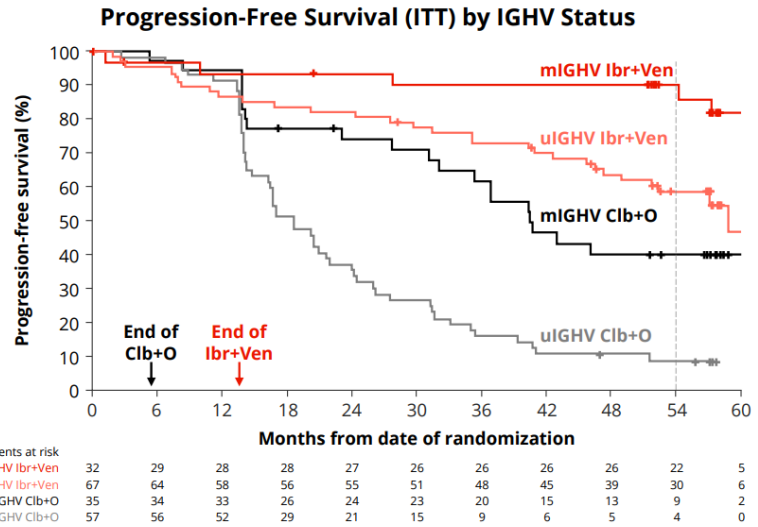
[a]Defined as ≥3 chromosomal abnormalities by conventional CpG-stimulated cytogenetic; [b]Excluding patients with del(17p)/mTP53 or CK.
CK = complex karyotype.
Wierda WG, et al. *JCO*. 42:7009-7009.

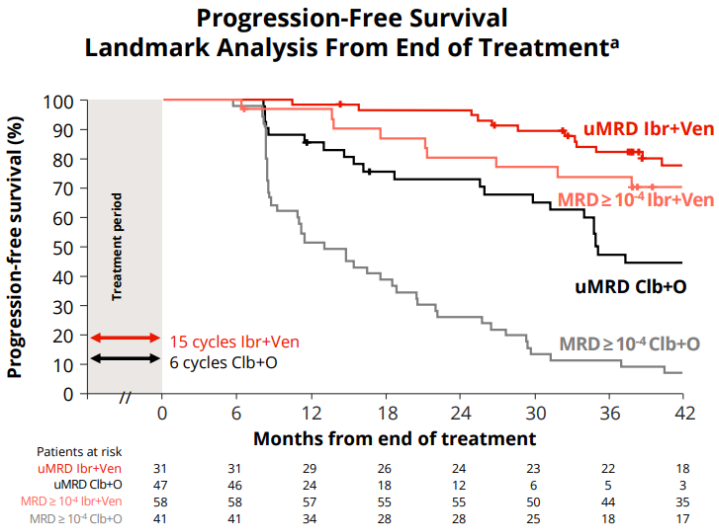
Phase III GLOW Ibrutinib+Venetoclax: Median PFS Was Not Reached with up to 57mo of Follow-Up



- Estimated PFS rates at 42 months post tx
  - mIGHV CLL: 91% for uMRD at EOT+3, 92% for patients with MRD ≥ 10 -4 at EOT+3
  - uIGHV CLL: 78% for patients with uMRD at EOT+3, 50% for patients with MRD ≥ 10-4 at EOT+3







Moreno C, et al. Presented at: ASH 2023; December 10, 2023; San Diego, CA. 634.

AMPLIFY Study Design

TN CLL (N=867)

Key inclusion criteria
- [illegible]
- TN CLL requiring treatment per iwCLL 2018 criteria[1]
- Without del(17p) or *TP53*[a]
- [illegible]

Key exclusion criteria
- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification
- [illegible]
- IGHV mutational status
- [illegible]
- Geographic region

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

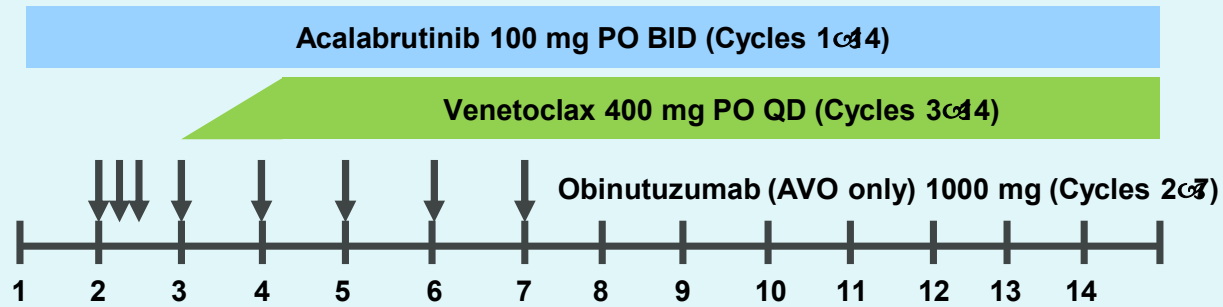
***Crossover** not built into protocol*

Primary endpoint: IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:

1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV vs FCR/BR)
3) uMRD (AVO vs FCR/BR)
4) OS (AV vs FCR/BR)
5) OS (AVO vs FCR/BR)

AV and AVO dosing schedule



Brown et al ASH 2024

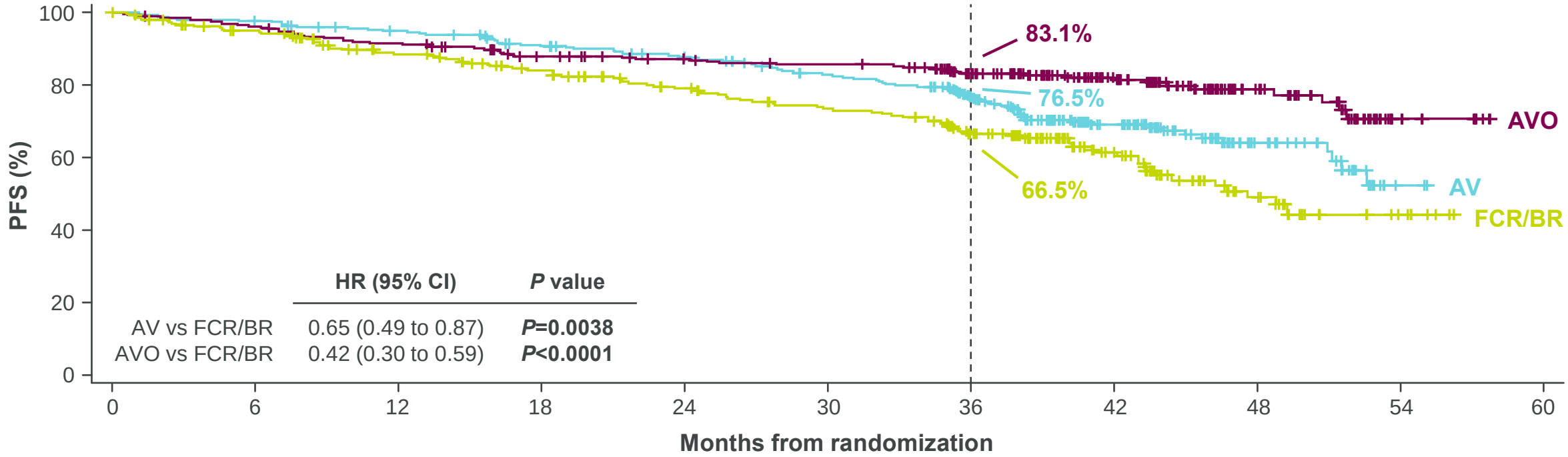
NCT03836261. Data cutoff: April 30, 2024.

[a]Assayed by central lab.

AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CIRS-Geriatric, Cumulative Illness Rating Scale-Geriatric; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine-cyclophosphamide-rituximab; IGHV, immunoglobulin heavy-chain variable region gene; iwCLL, International Working Group on CLL; OS, overall survival; PFS, progression-free survival; TN, treatment-naive; uMRD, undetectable measurable residual disease.

1. Hallek M, et al. *Blood*. 2018;131:2745-60.

IRC-assessed PFS



Patients at risk

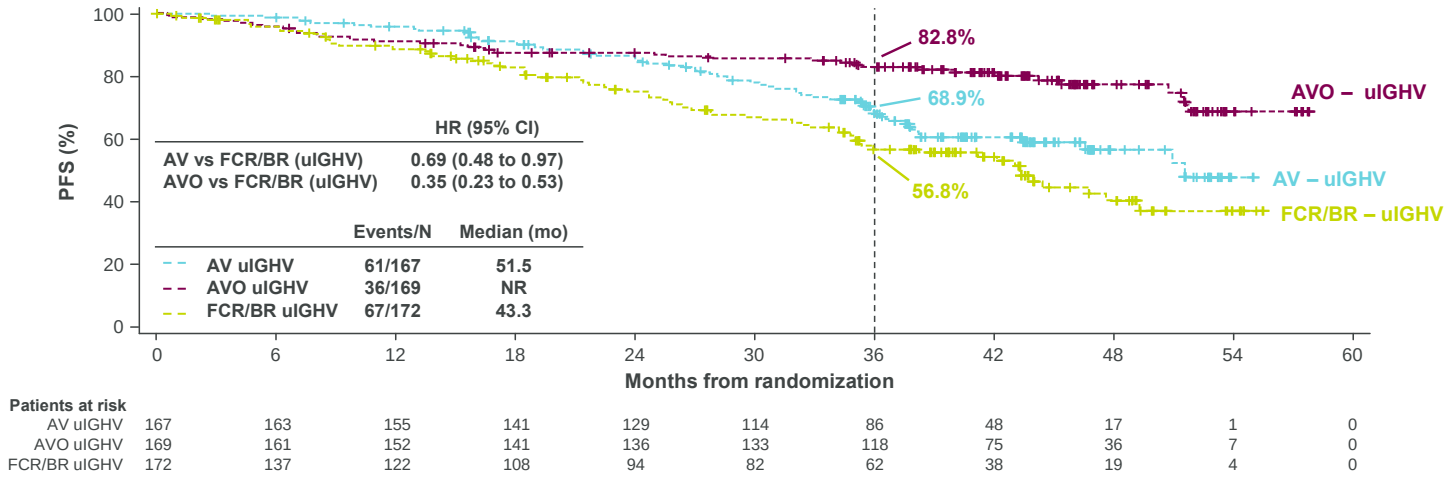
AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR/BR	290	236	208	189	170	154	127	66	28	6	0

Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

ITT population. Median follow-up from randomization: 40.8 months (range, 0–59 months).
Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

Brown et al ASH 2024

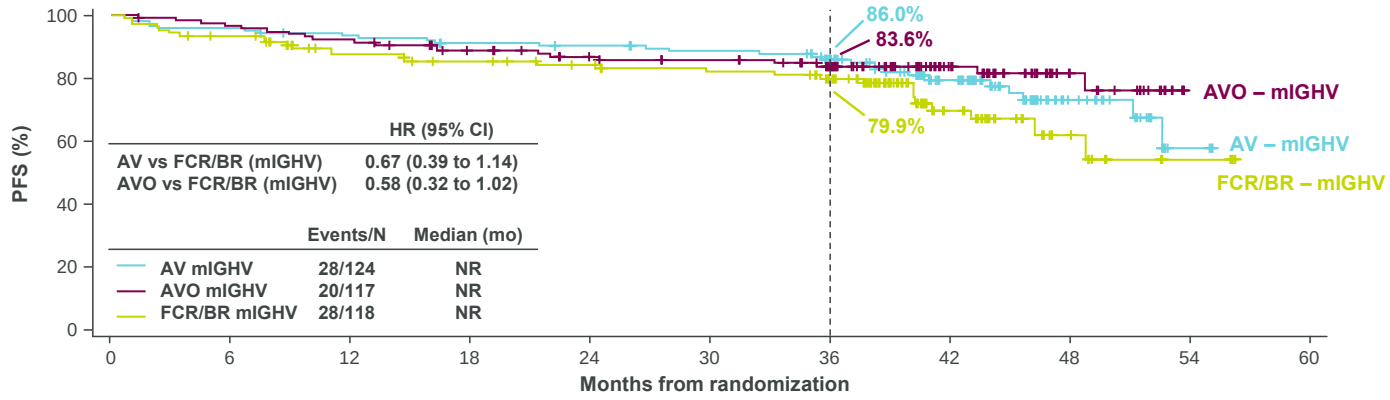
PFS in the uIGHV Subgroup



Patients at risk

AV uIGHV	167	163	155	141	129	114	86	48	17	1	0
AVO uIGHV	169	161	152	141	136	133	118	75	36	7	0
FCR/BR uIGHV	172	137	122	108	94	82	62	38	19	4	0

PFS in the mIGHV Subgroup

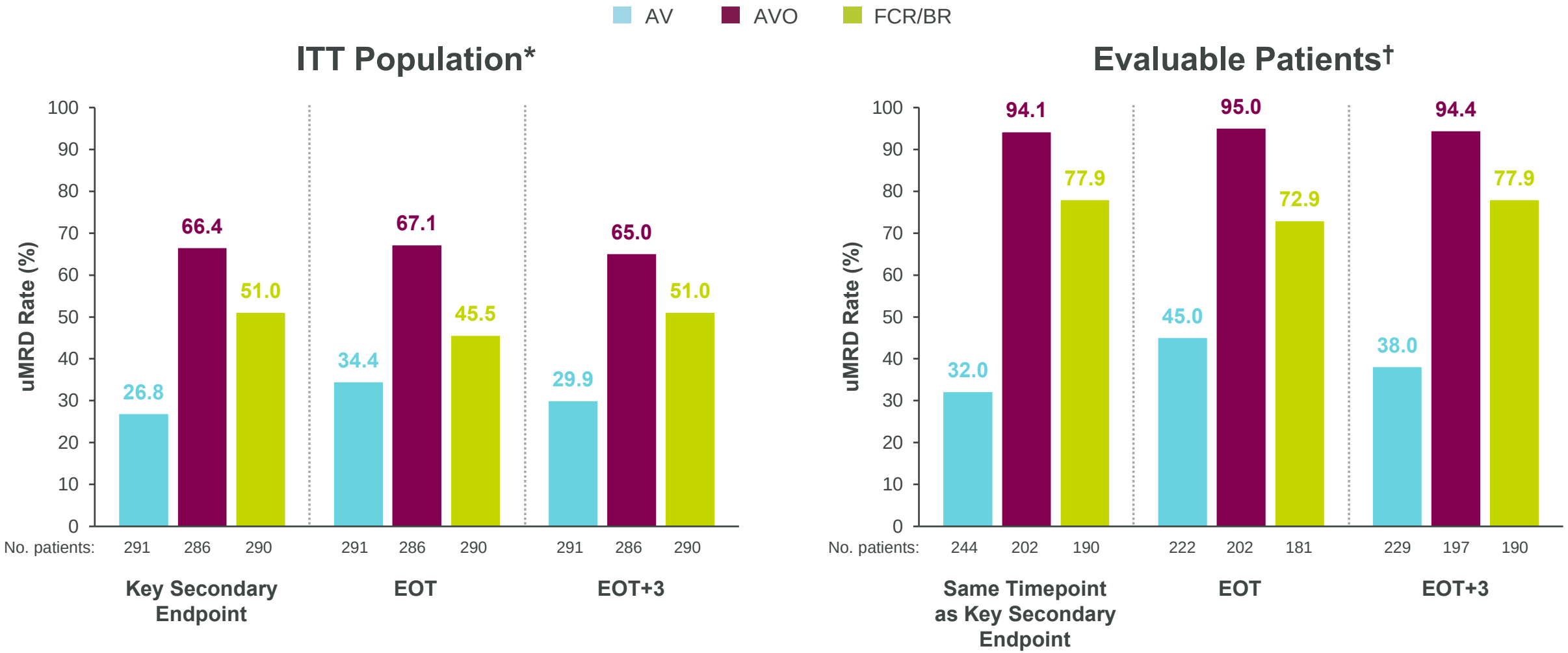


Patients at risk

AV mIGHV	124	119	114	110	108	105	91	54	18	2	0
AVO mIGHV	117	111	106	96	89	86	73	41	15	0	
FCR/BR mIGHV	118	99	86	81	76	72	65	28	9	2	0

Brown et al ASH 2024

uMRD Rates (Flow Cytometry [<10^{-4}] in PB)

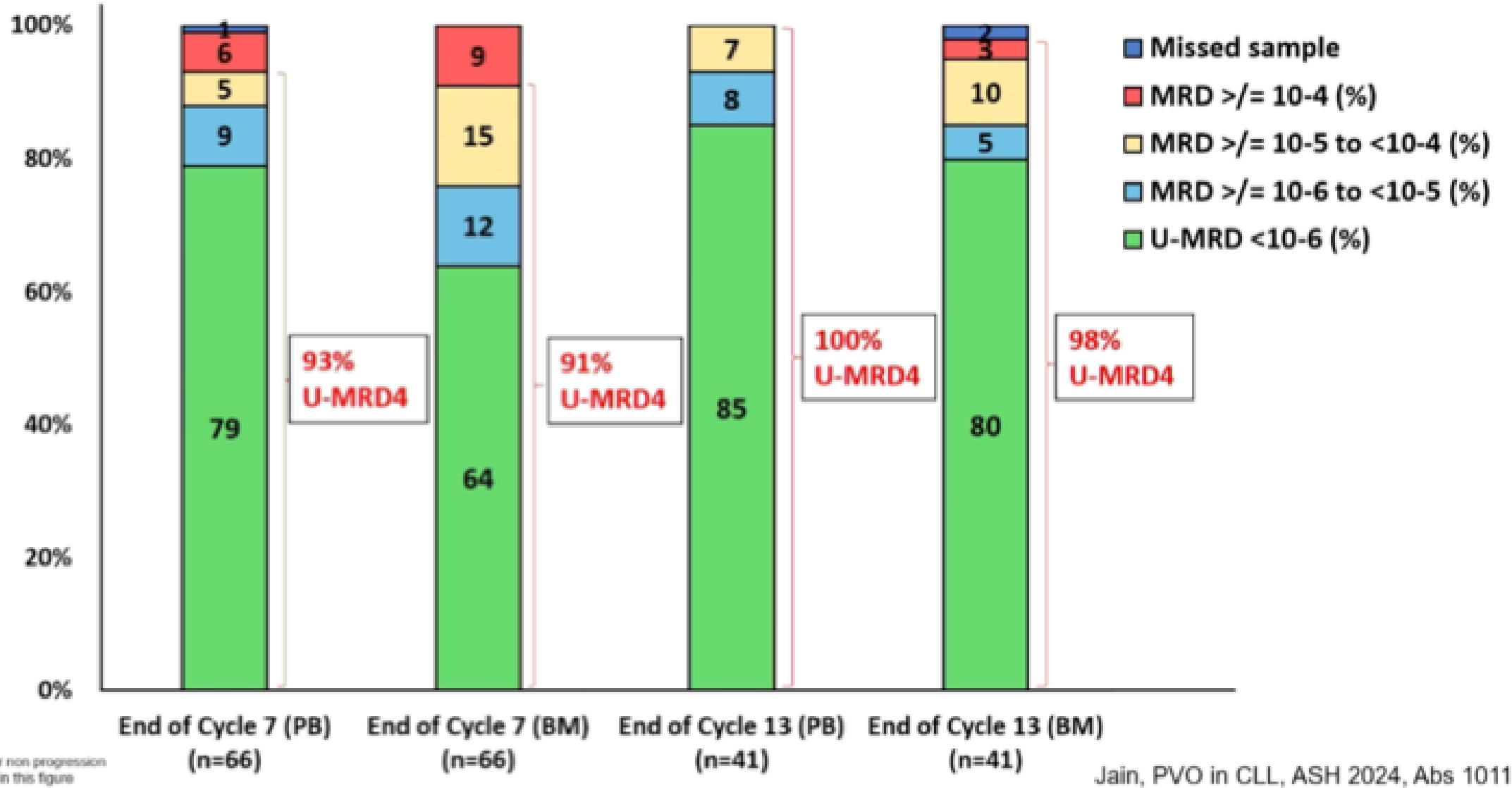


Key secondary endpoint timing: cycle 9, day 1 (AV arm), cycle 10, day 1 (AVO arm), and cycle 6, day 1 plus 12 weeks (FCR/BR)

Brown et al ASH 2024

Pirtobrutinib, Venetoclax, Obinutuzumab Trial

MRD at Serial Time-Points in Blood and Bone Marrow

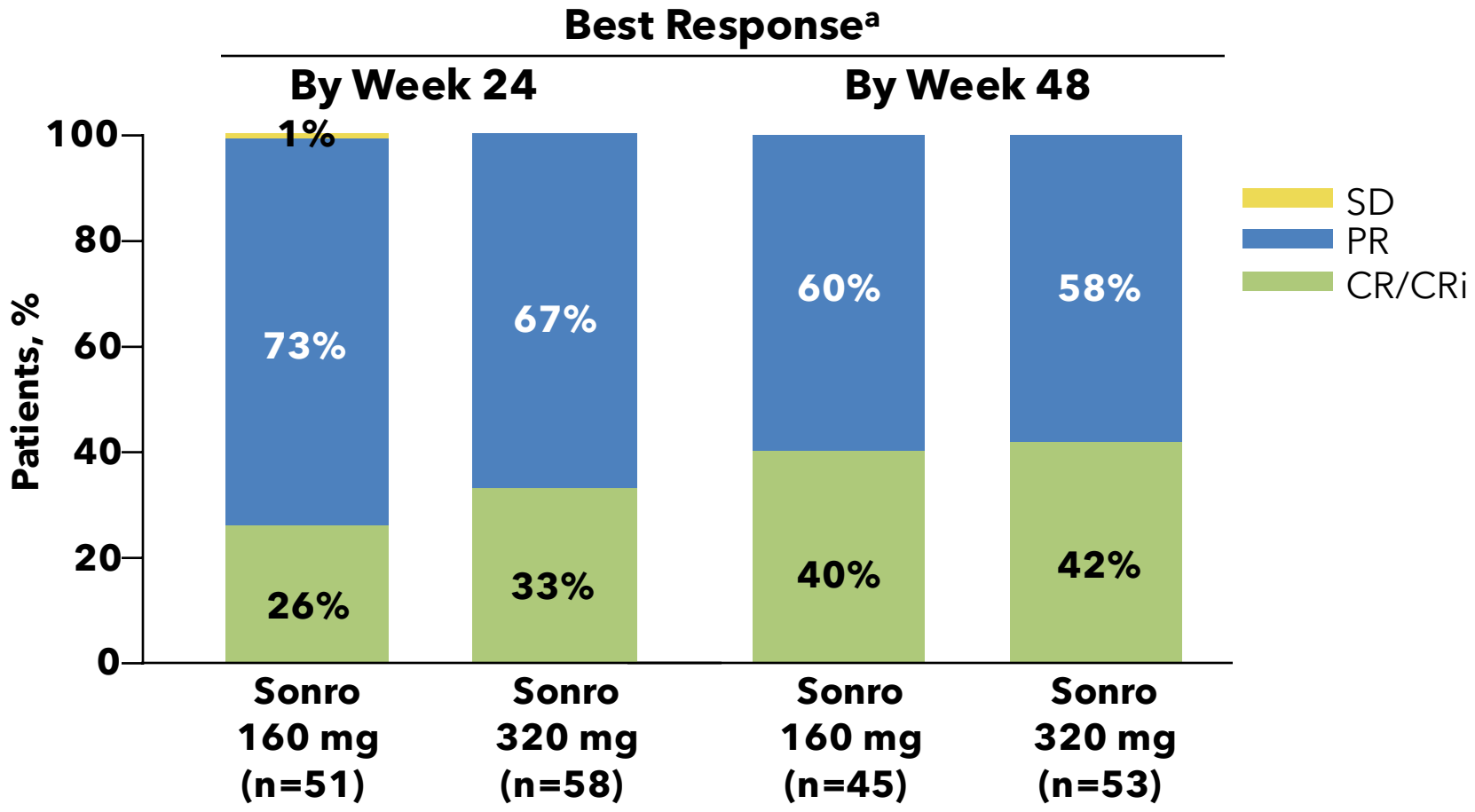


3 pts off study for non progression are not included in this figure

Jain, PVO in CLL, ASH 2024, Abs 1011

Sonrotoclax + Zanubrutinib efficacy in TN CLL

BGB-11417-101: TN CLL

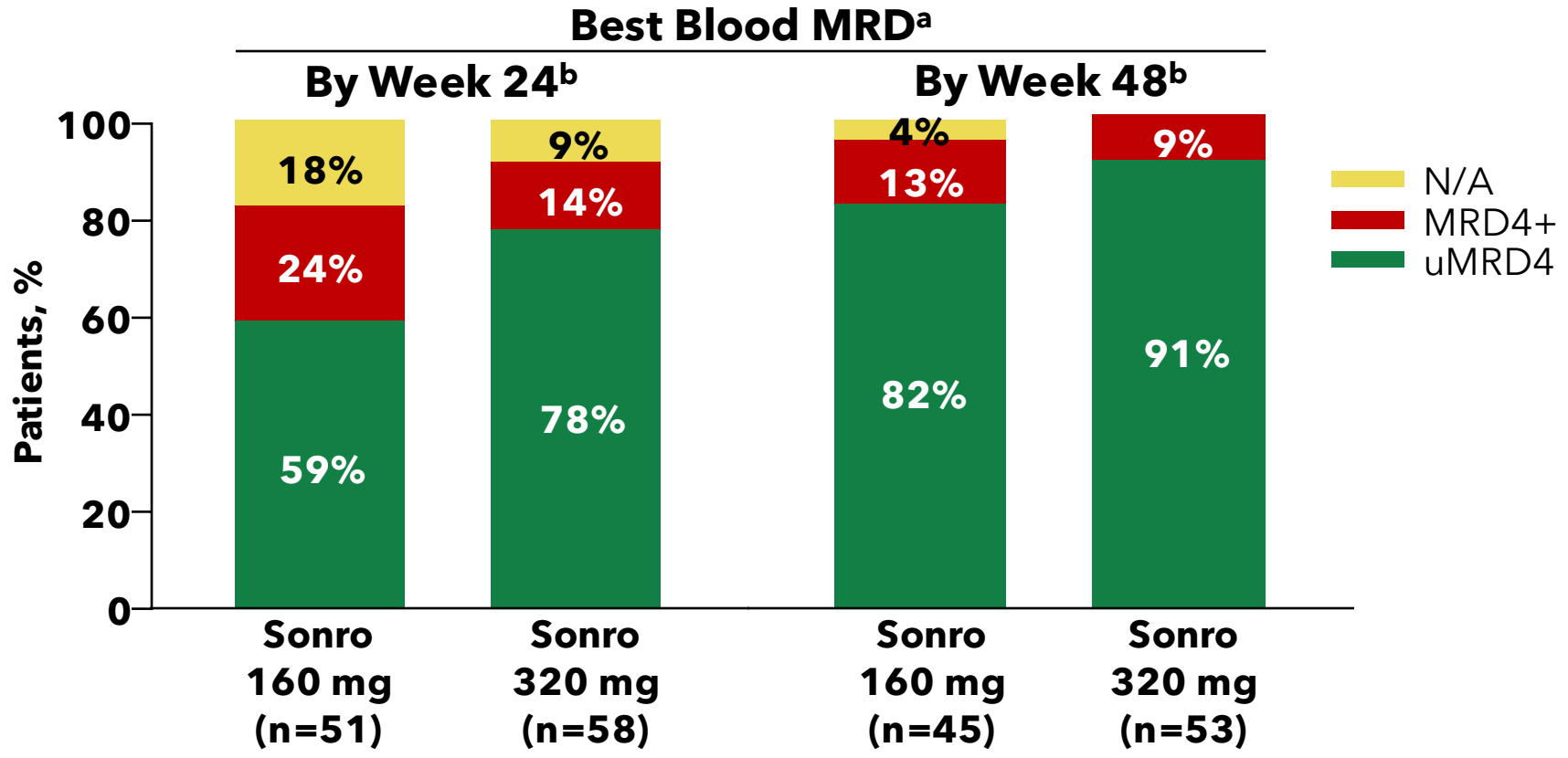


Soumerai JD, et al. ASH 2024;1012.

Sonrotoclax + Zanubrutinib MRD in TN CLL

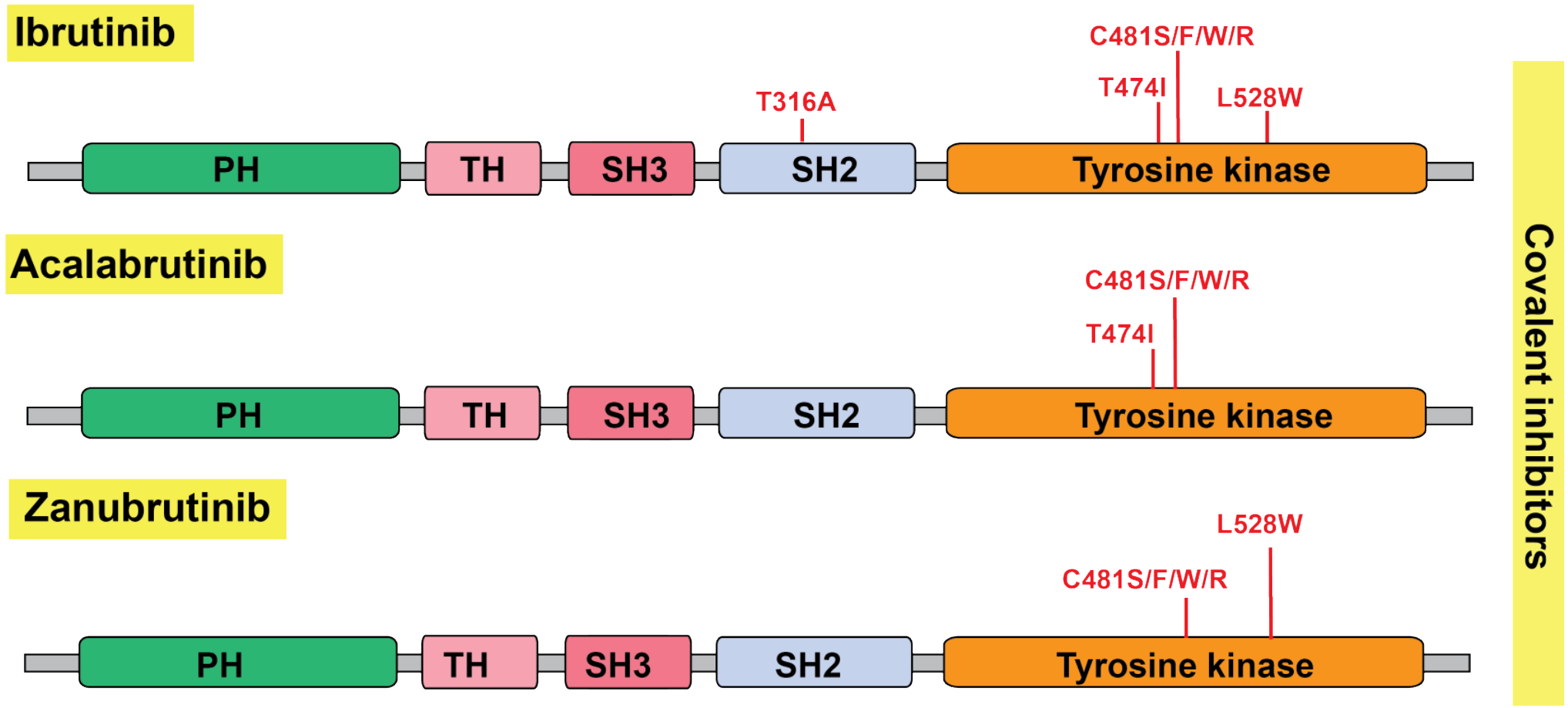
BGB-11417-101: TN CLL

- As of the data cutoff date, no patients had switched from uMRD to MRD4+



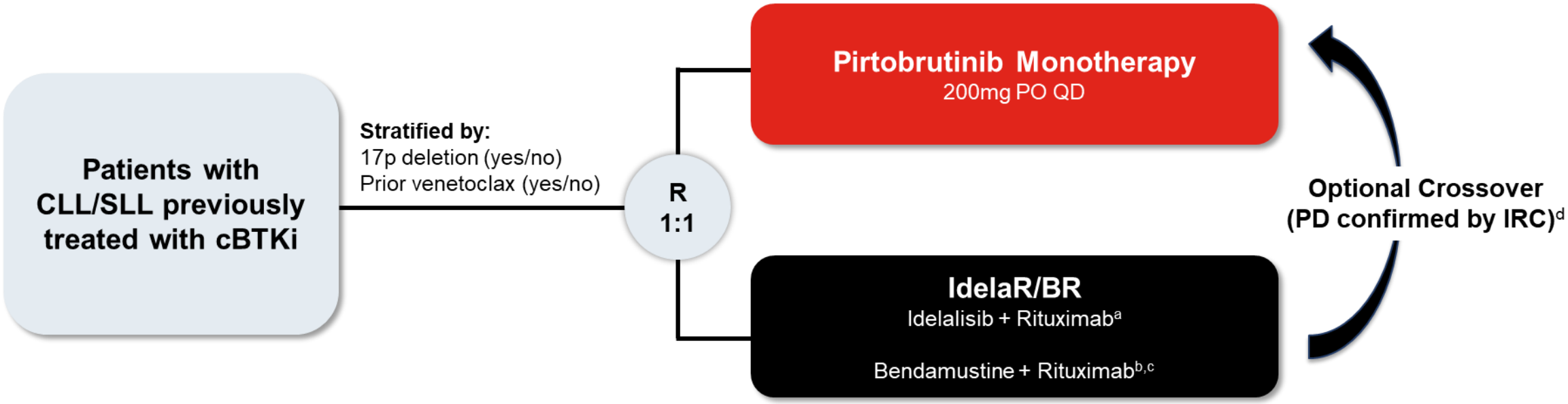
Soumerai JD, et al. ASH 2024;1012.

Diverse BTK mutations cause resistance to covalent BTK inhibitors



Montoya et al ASH 2022

BRUIN CLL-321 Study Design



Key Eligibility

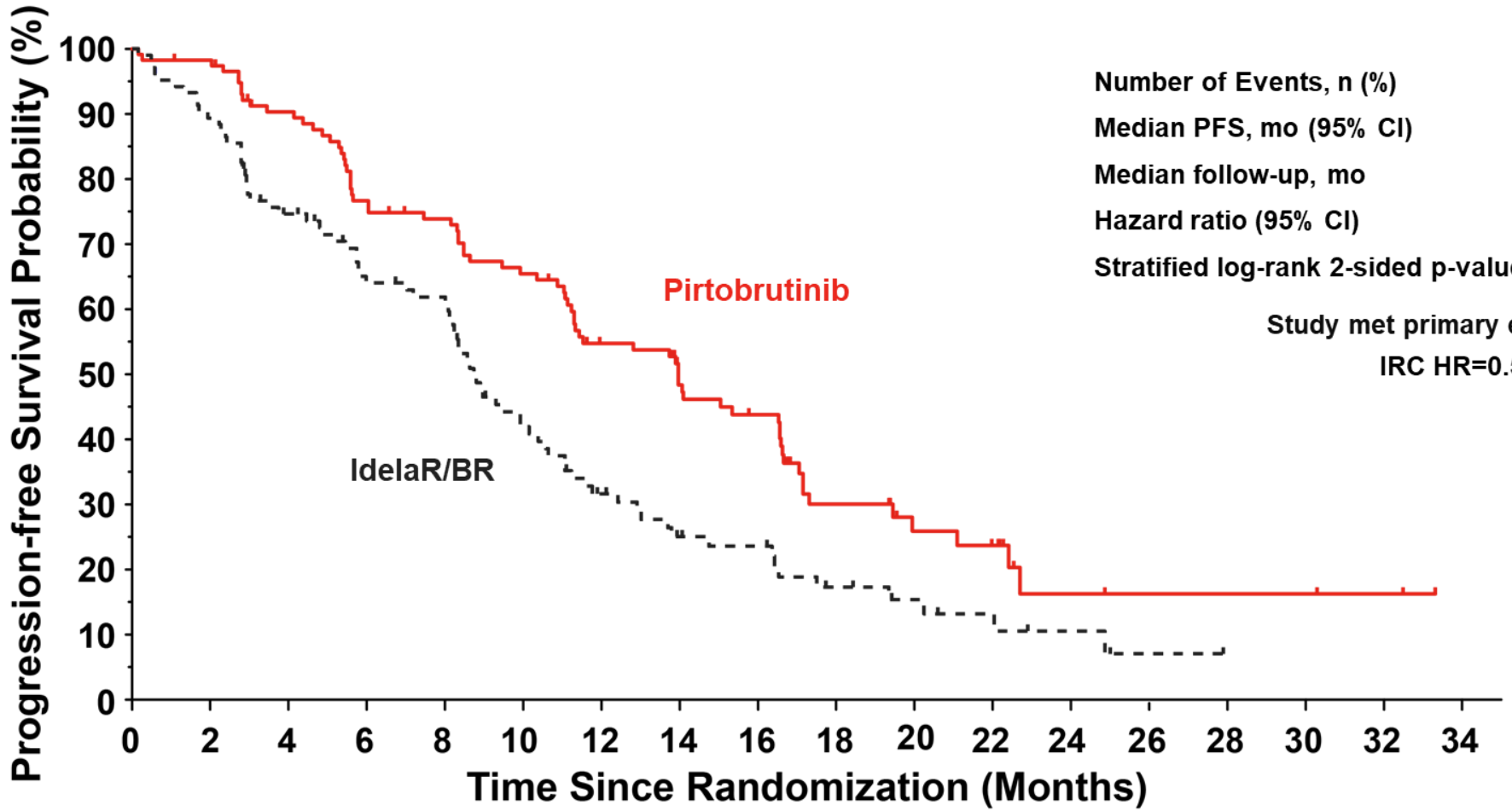
- Age ≥18
- ECOG PS 0-2
- Confirmed CLL/SLL requiring treatment per iwCLL 2018
- **Prior cBTKi required**
- **No limit on prior lines of therapy**
- **Prior history of atrial fibrillation allowed**

Key Endpoints

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

Sharman et al ASH 2024

IRC-Assessed Progression-free Survival



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39-0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR=0.58 (95% CI 0.38-0.89); p=0.01

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

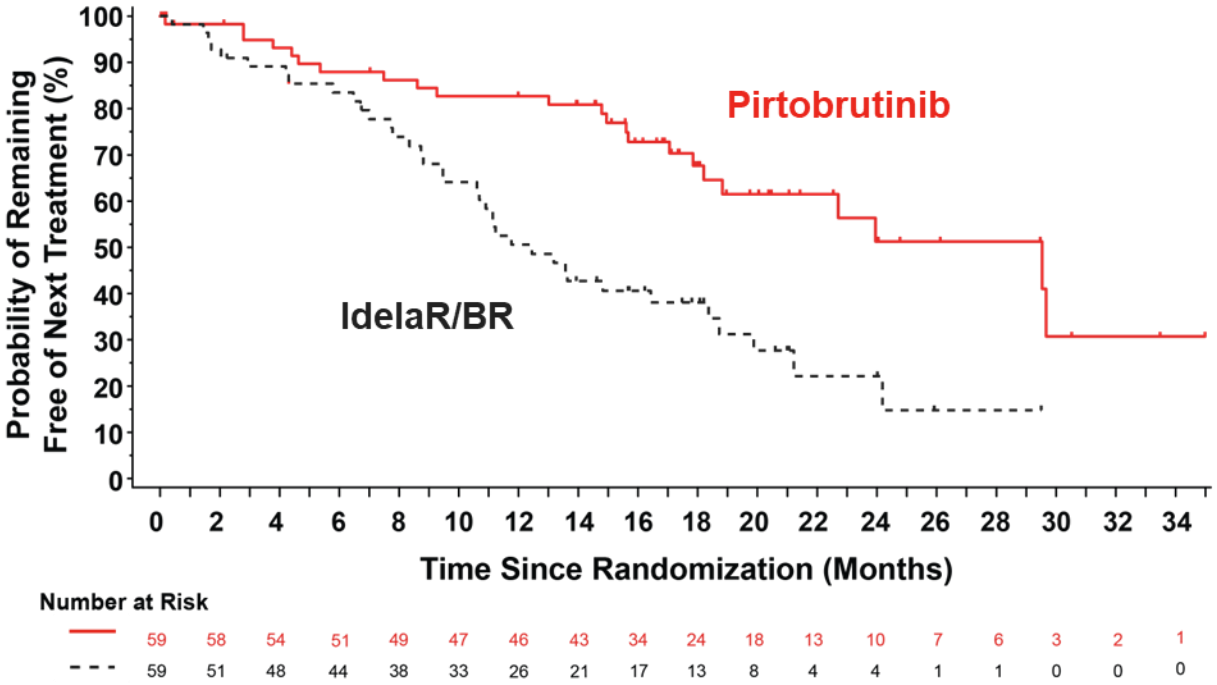
Number at Risk

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

Sharman et al ASH 2024

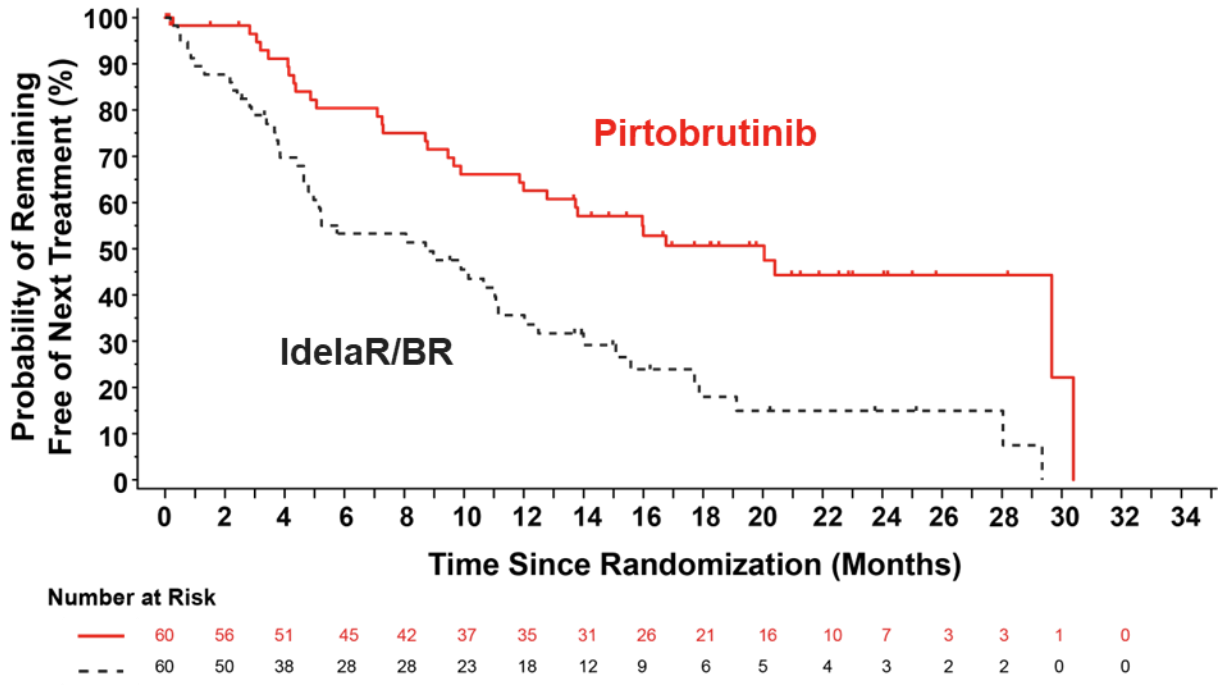
Time to Next Treatment or Death in Venetoclax Naïve and Treated Patients

Venetoclax Naïve



	Pirtobrutinib n=59	IdelaR/BR n=59
Median TTNT, mo (95% CI)	29.5	12.5
Hazard ratio (95% CI)	0.36 (0.21-0.61)	
Stratified log-rank 2-sided p-value	0.0001*	

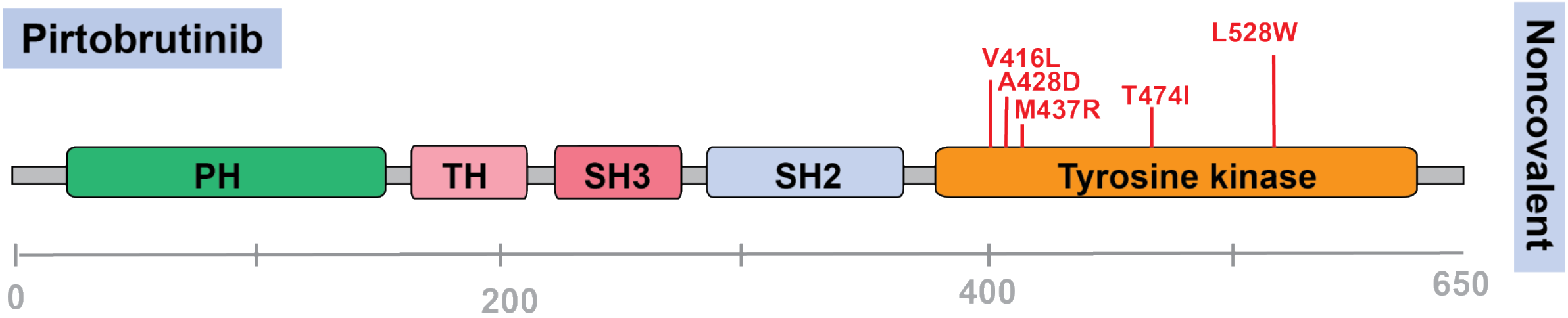
Venetoclax Treated



	Pirtobrutinib n=60	IdelaR/BR n=60
Median TTNT, mo (95% CI)	20.0	8.7
Hazard ratio (95% CI)	0.37 (0.23-0.60)	
Stratified log-rank 2-sided p-value	<0.0001*	

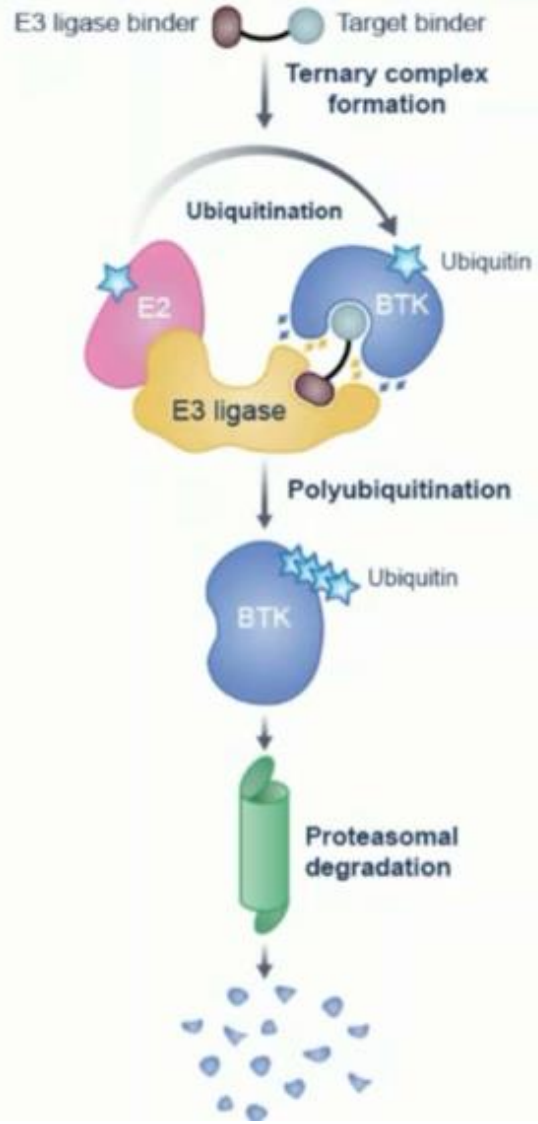
Sharman et al ASH 2024

Diverse BTK mutations cause resistance to non-covalent BTKi



Montoya et al ASH 2022

Efficacy and safety of, Bruton's Tyrosine Kinase (BTK) Degrader NX-5948 in Patients with Relapsed/Refractory CLL: Phase Ia/b trial



BTK degraders can overcome treatment-emergent resistance mutations

BTK degraders address BTK scaffolding function

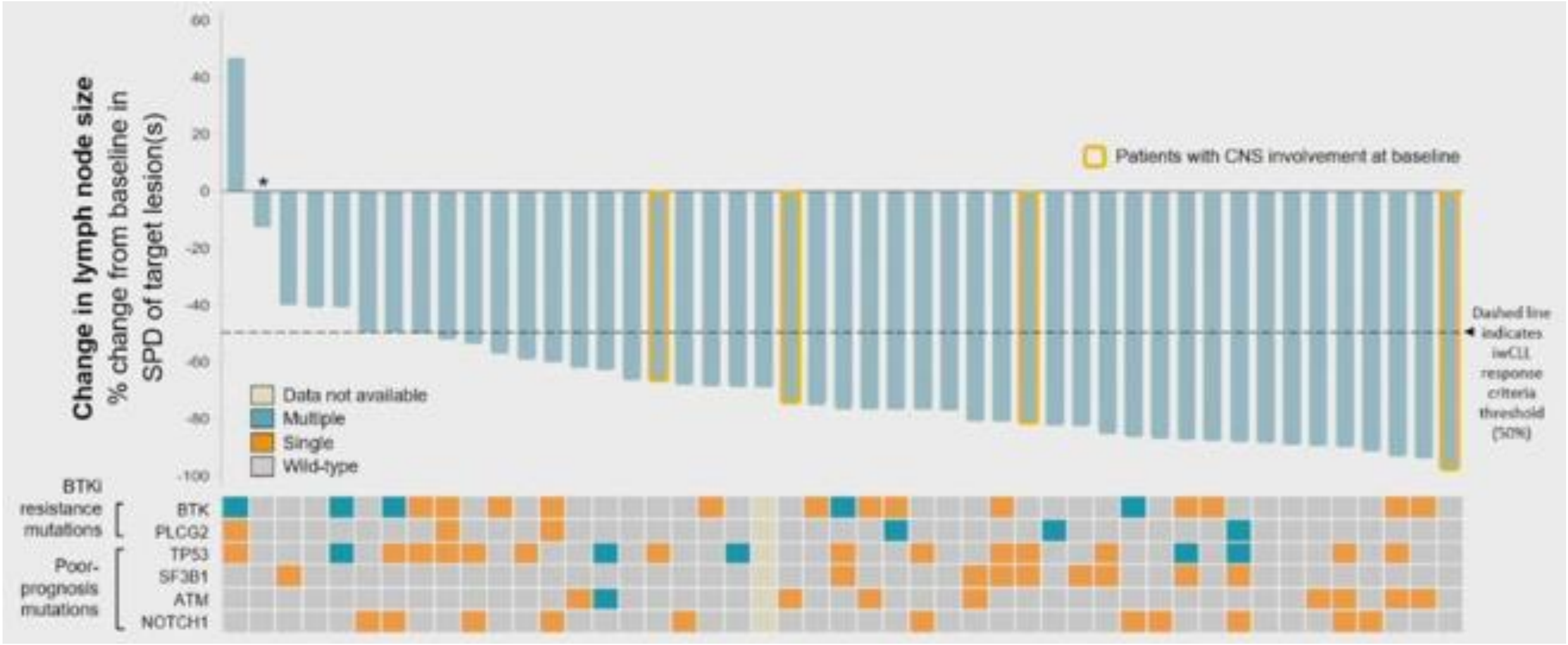
BTK degraders show emerging activity in various B-cell malignancies

BTK degraders have the potential to replace BTK inhibitors in the clinic

Shah et al ASH 2024

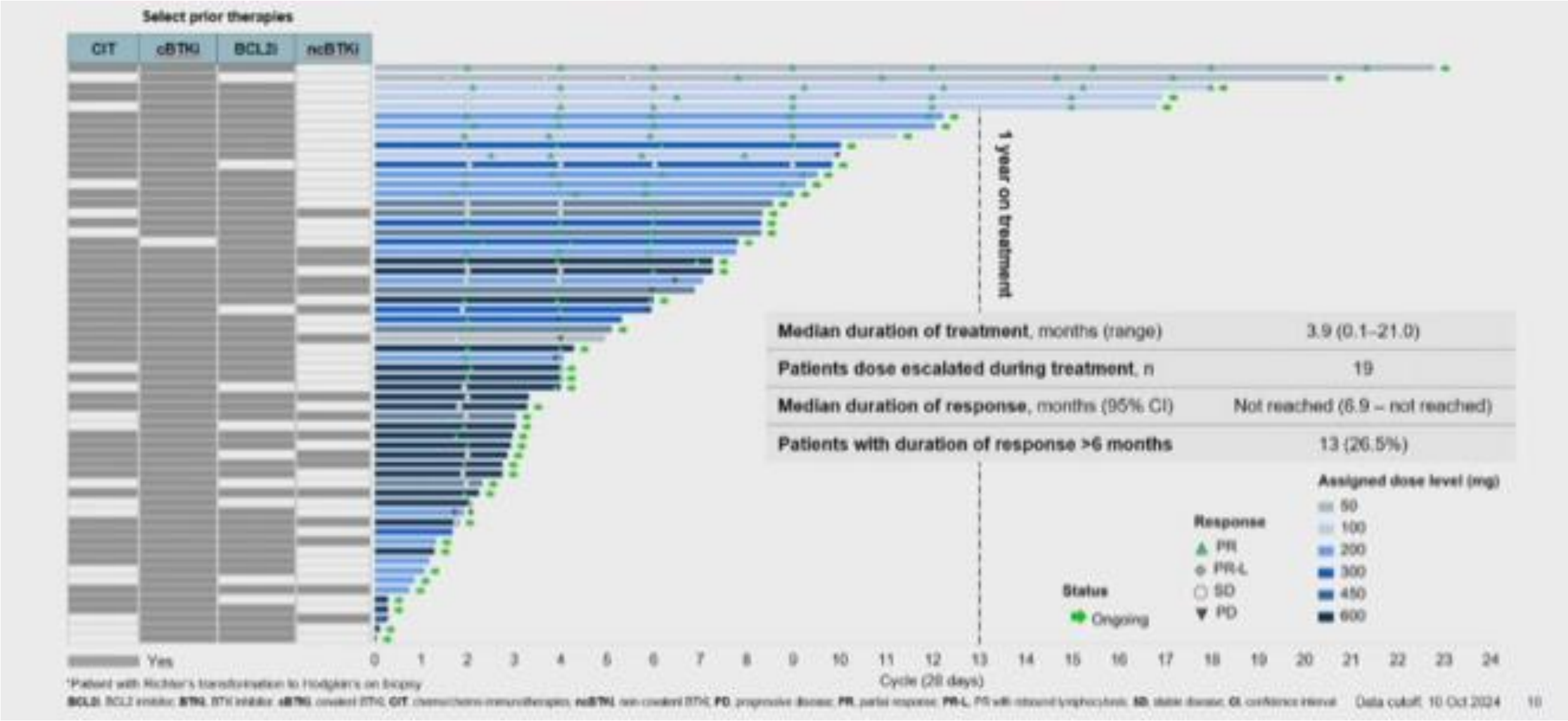
Lymph Node Assessment and High-Risk Molecular Features

Clinical activity in patients with CLL including those with baseline mutations and CNS involvement



Shah et al ASH 2024

NX-5948 Duration of Treatment

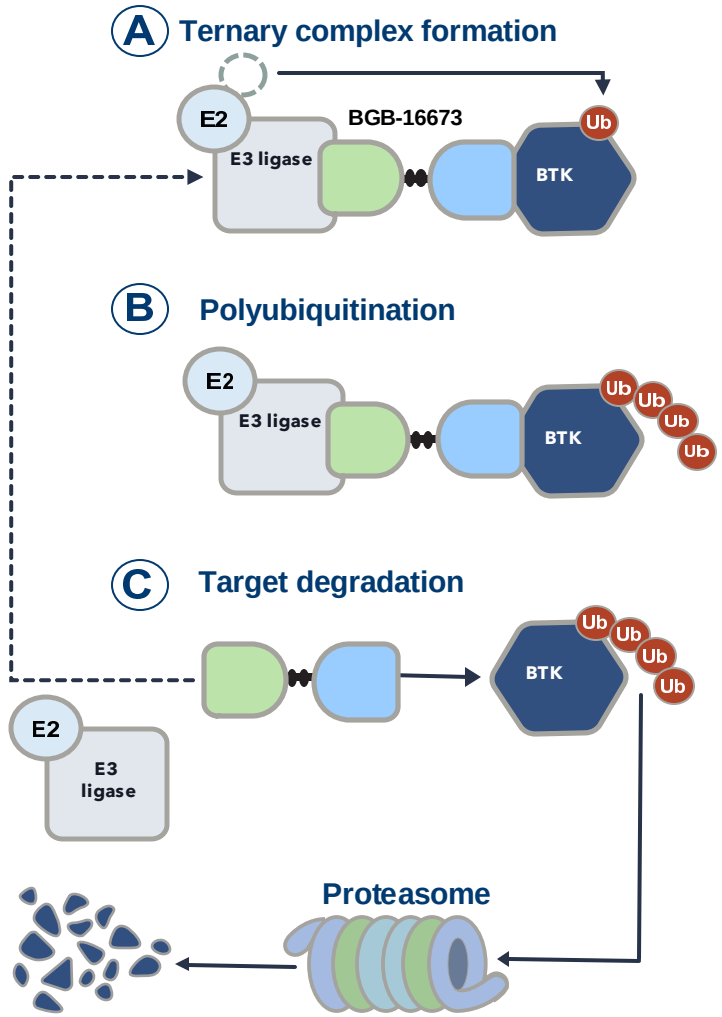


Shah et al ASH 2024

BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

CaDAnCe-101: R/R CLL/SLL

- Many patients with CLL/SLL experience disease progression with BTK inhibitors, which can be caused by resistance mutations in BTK[1-3]
- BGB-16673 is a bivalent CNS-penetrating small molecule that induces BTK degradation by binding specifically to BTK and the E3 ligase[4]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to cBTK (C481S, C481F, C481Y, L528W, T474I) and ncBTK inhibitors (V416L, M437R, T474I, L528W), leading to tumor suppression[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[6]
- We present updated safety and efficacy results in patients with R/R CLL/SLL and preliminary efficacy results in patients with R/R RT from phase 1 of CaDAnCe-101



Thompson et al ASH 2024

High Overall Response Rates in All Biologic Subsets

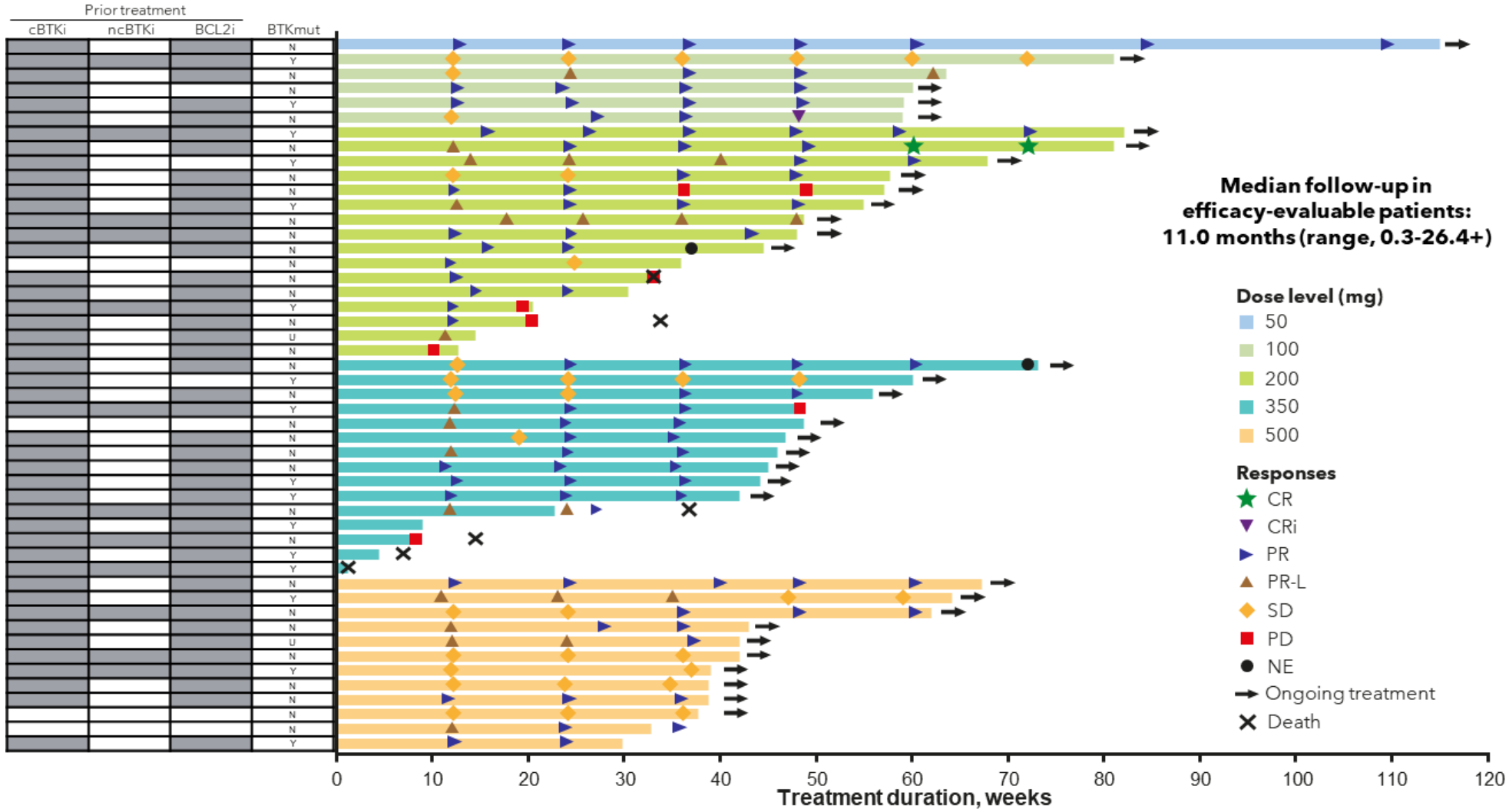
CaDAnCe-101: R/R CLL/SLL

Characteristic, n/N with known status (%)	Total (N=49)[a]
Double exposure (previously received cBTKi + BCL2i)	26/30 (86.7)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	7/12 (58.3)
del(17p) and/or *TP53* mutation	23/31 (74.2)
Complex karyotype	11/15 (73.3)
***BTK* mutations**	10/16 (62.5)
***PLCG2* mutations**	4/6 (66.7)

Thompson et al ASH 2024

Treatment Duration and Response

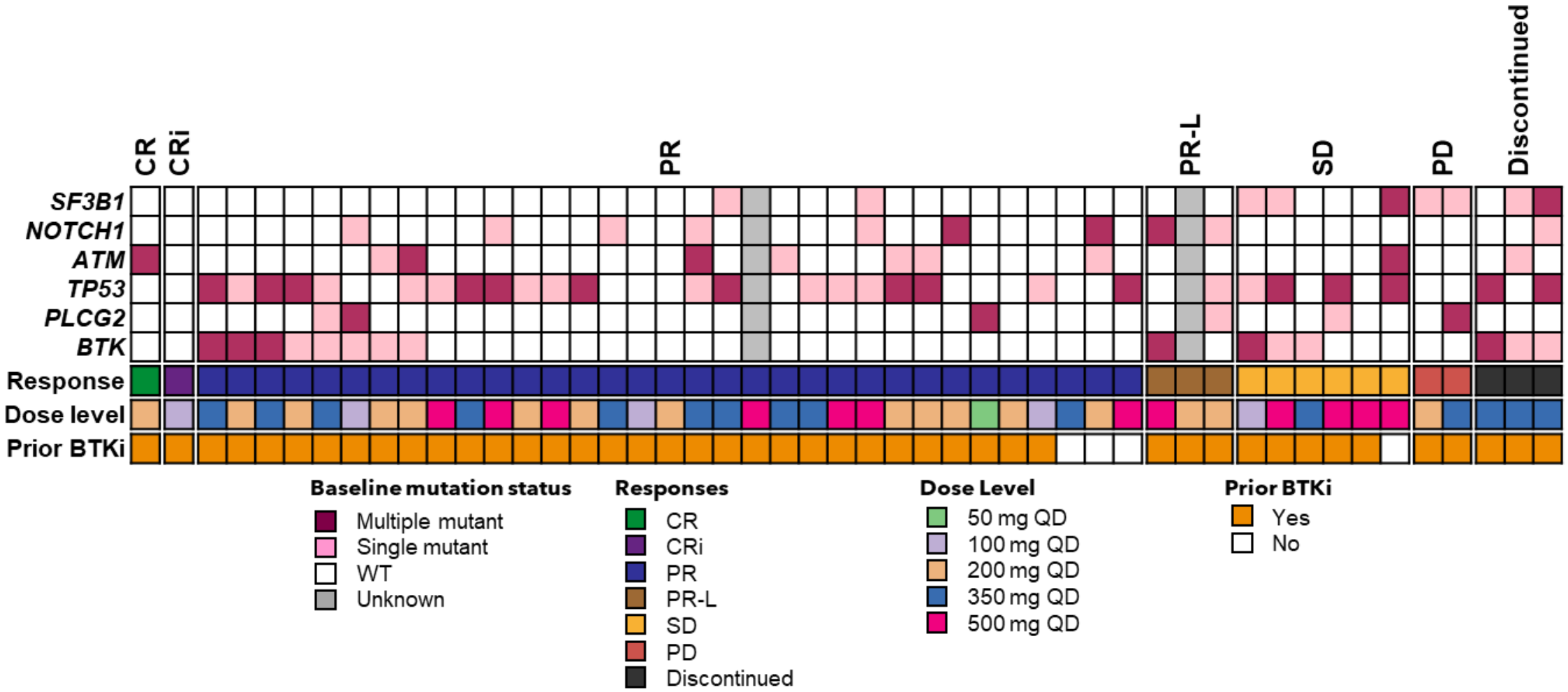
CaDAnCe-101: R/R CLL/SLL



Thompson et al ASH 2024

Responses Occurred Regardless of Specific Mutations
Best Overall Response vs. Baseline Mutation

CaDAnCe-101: R/R CLL/SLL

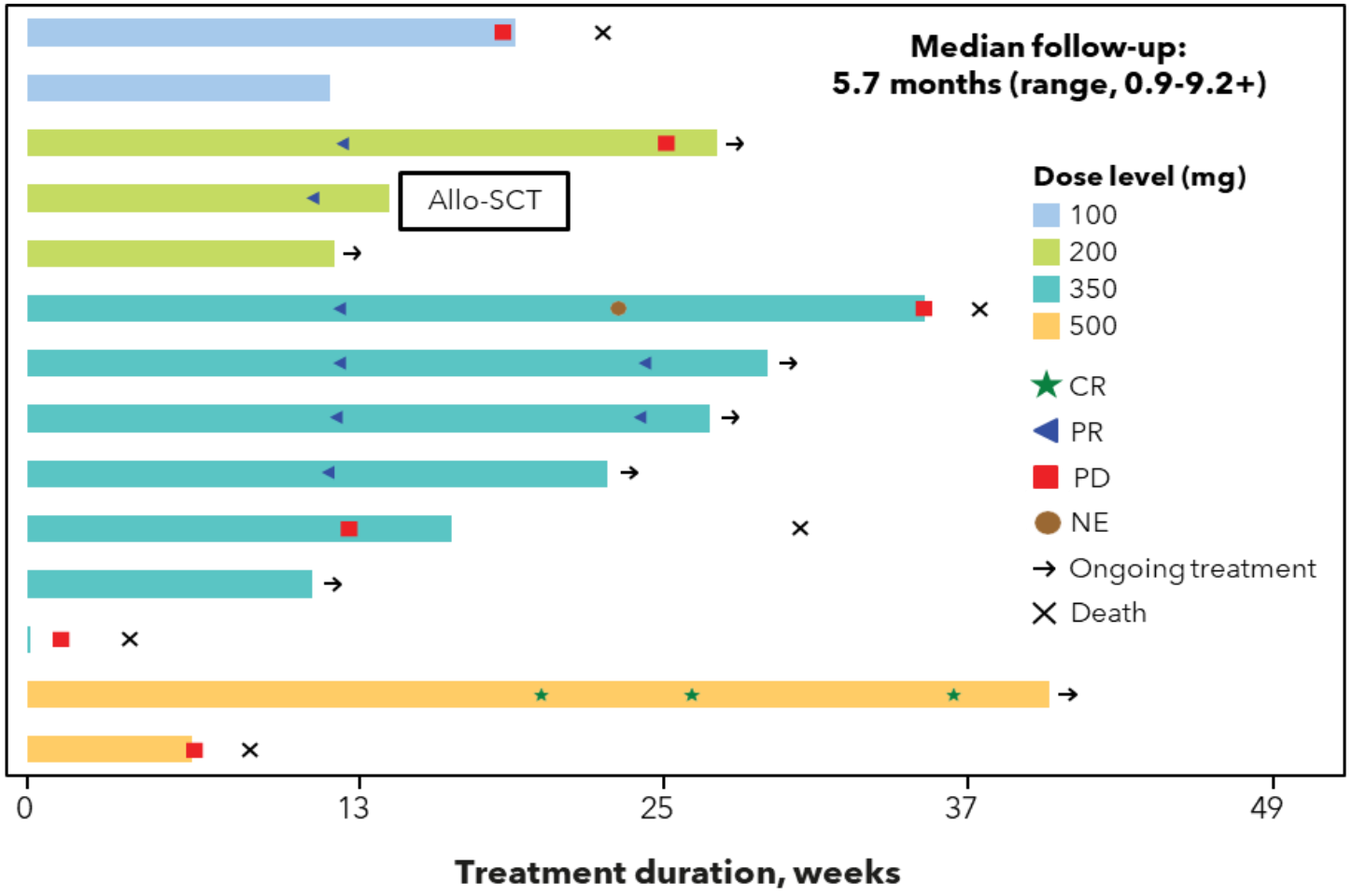


Thompson et al ASH 2024

Promising Activity Also Seen in Patients With Richter Transformation

CaDAnCe-101: R/R CLL/SLL

- Safety-evaluable patients, n=14; efficacy-evaluable patients, n=12
- Median age (range): 64 years (47-80 years)
- Median prior number of therapies for RT (range): 2 (1-9)
- All patients previously received a cBTKi; 12/14 had anthracyclines
- ORR: 58.3% (7/12), CR: 8.3% (1/12)
- 5 of 7 (71.4%) patients with response on treatment for >6 months

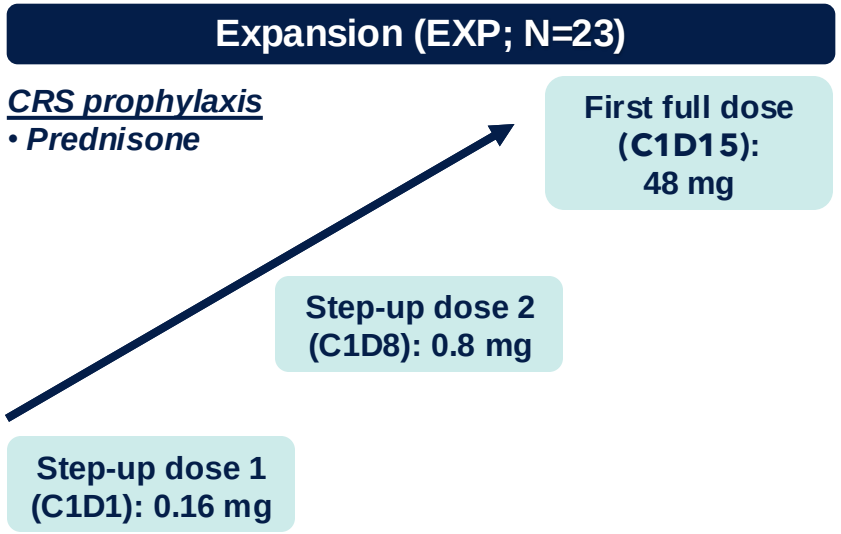


Thompson et al ASH 2024

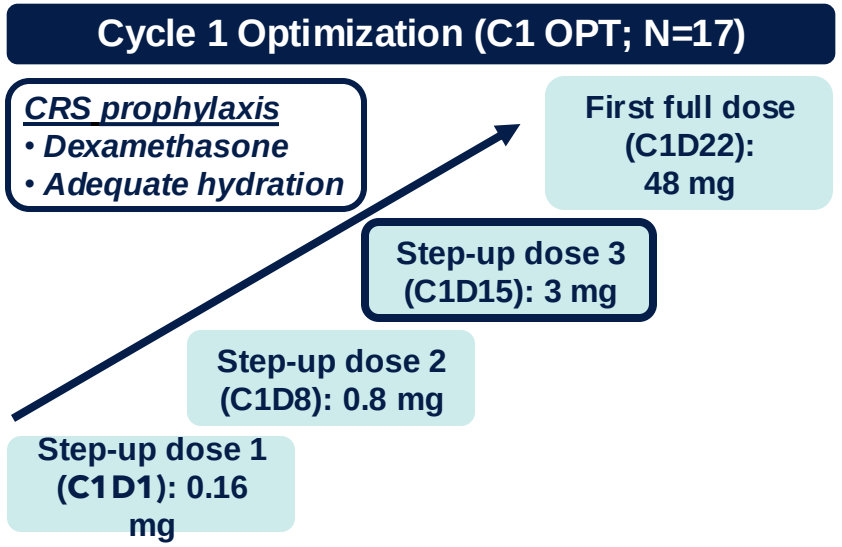
Study Design: EPCORE® CLL-1 Expansion and C1 Optimization

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

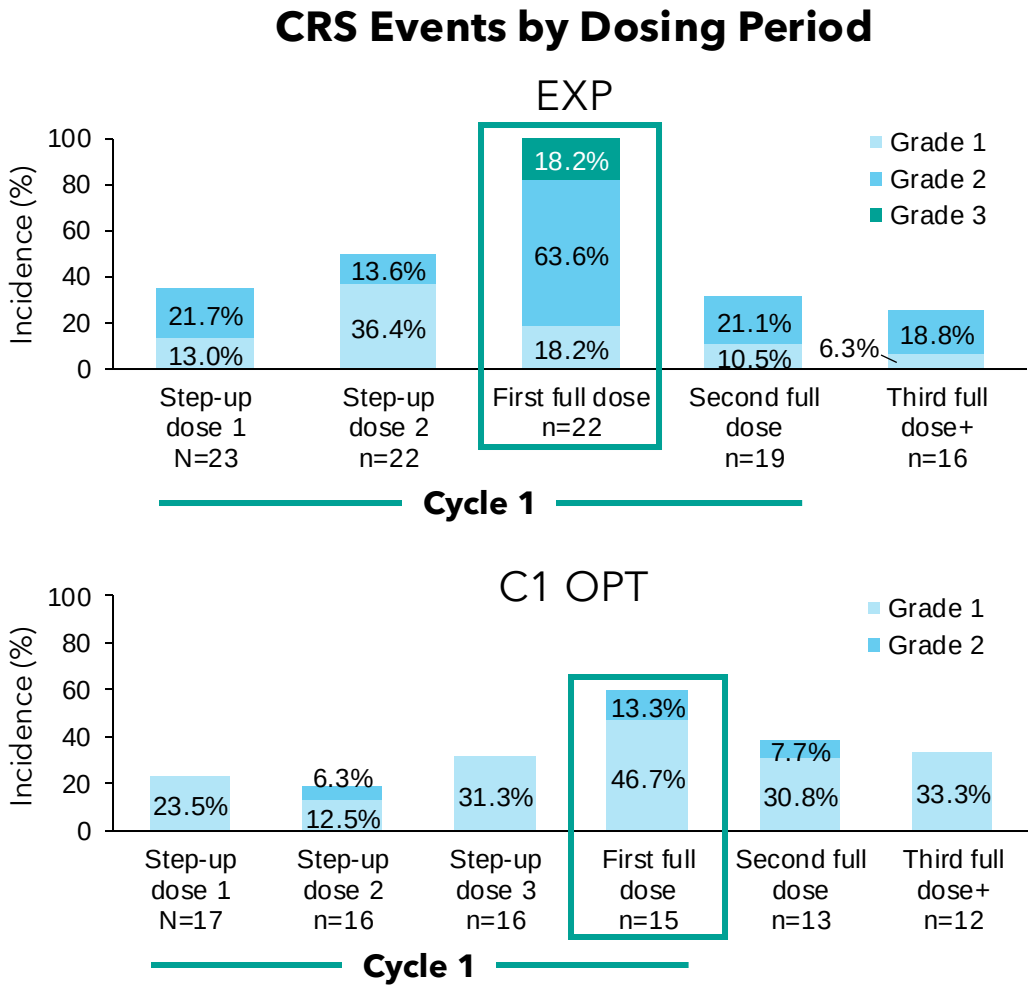
- **Primary endpoint (EXP):** Overall response rate
- **Primary endpoint (C1 OPT):** Incidence and severity of CRS, ICANS, and clinical TLS
- **Key secondary endpoints (EXP):** CR rate, time to response, MRD (PBMCs using the clonoSEQ® assay), and safety/tolerability

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

Danilov et al ASH 2024

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



Danilov et al ASH 2024

Deep Responses Across Subgroups

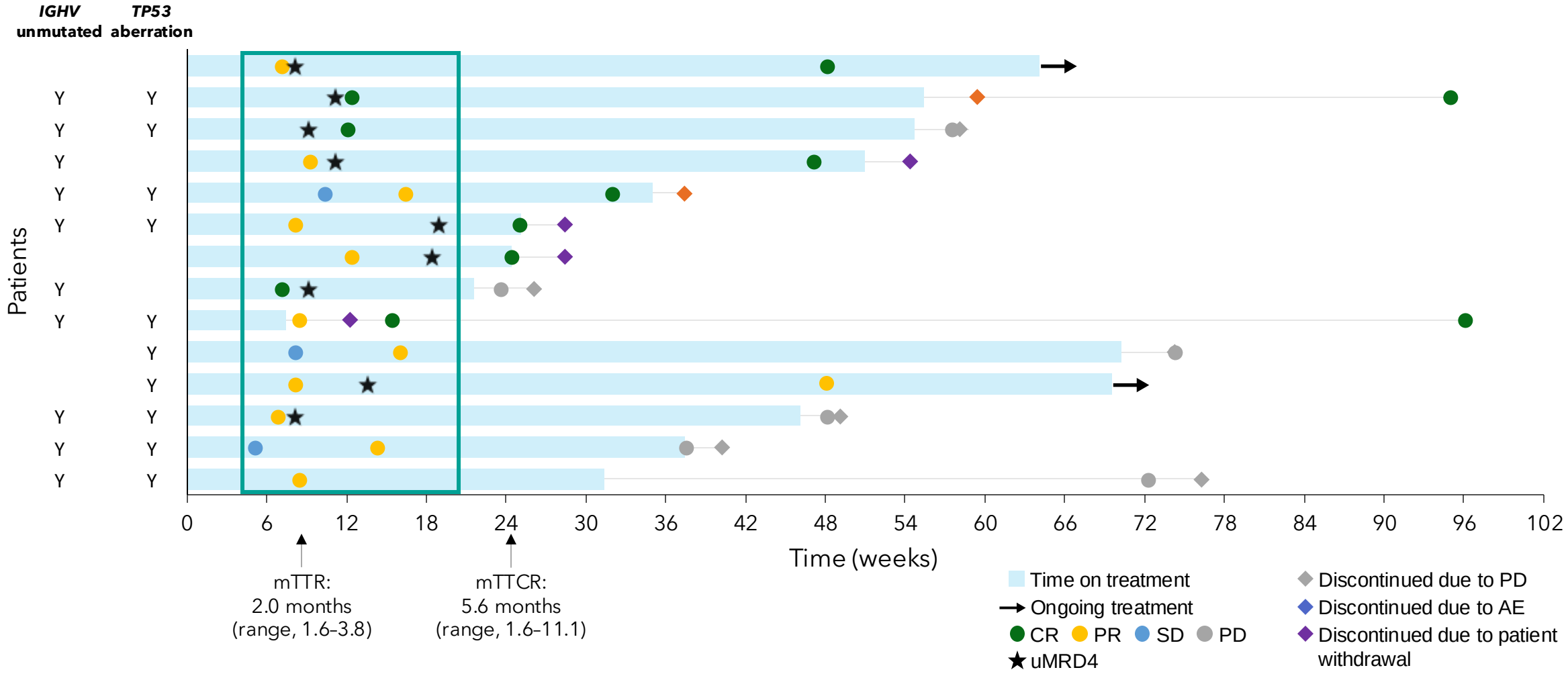
Response, n (%)	EXP mFU: 22.8 months					C1 OPT mFU: 2.9 months
	Full Analysis Set N=23	Response Evaluable n=21	*TP53* Aberration n=15	*IGHV* Unmutated n=16	Double Exposed[a] n=19	Response Evaluable n=10
Overall response[b]	**14 (61)**	**14 (67)**	**10 (67)**	**10 (63)**	**10 (53)**	**6 (60)**
Complete 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)

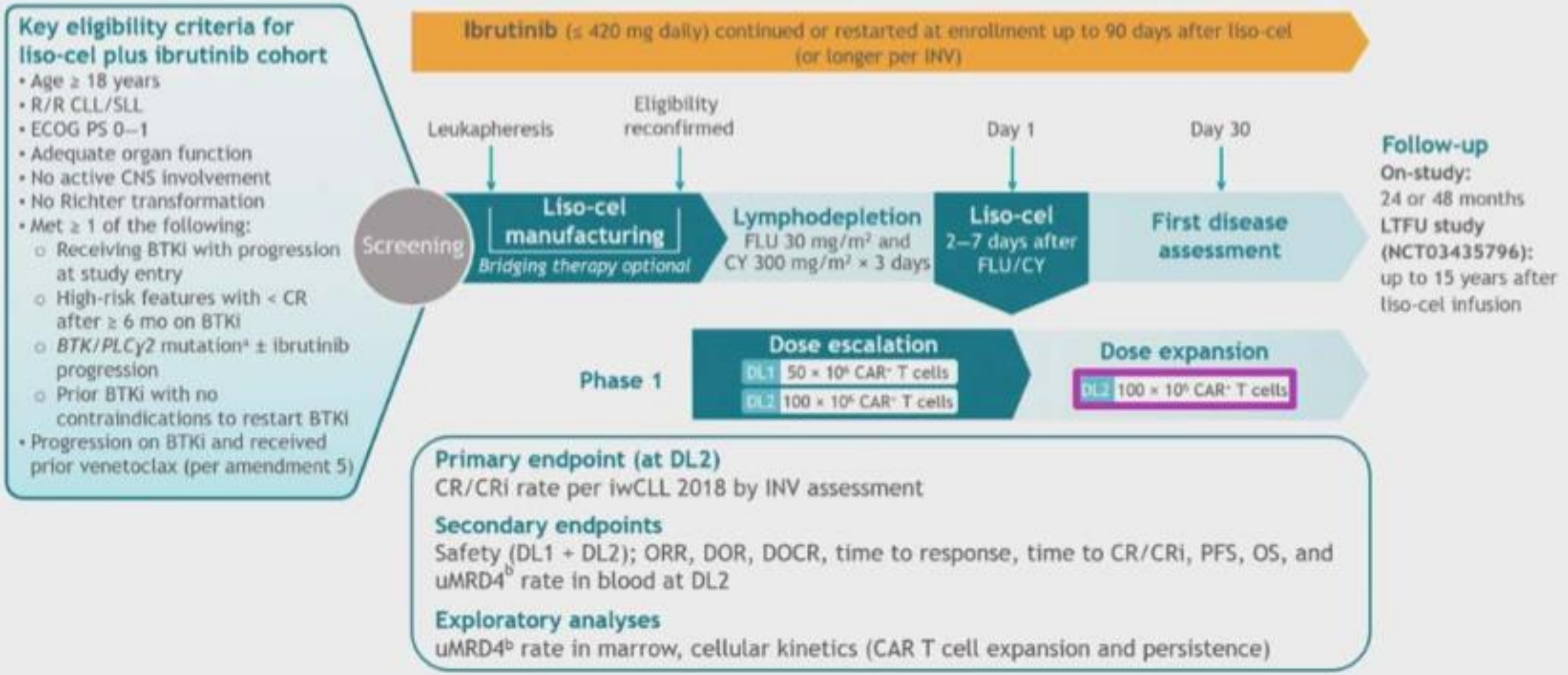
Danilov et al ASH 2024

Depth and Duration of Response in EXP



Danilov et al ASH 2024

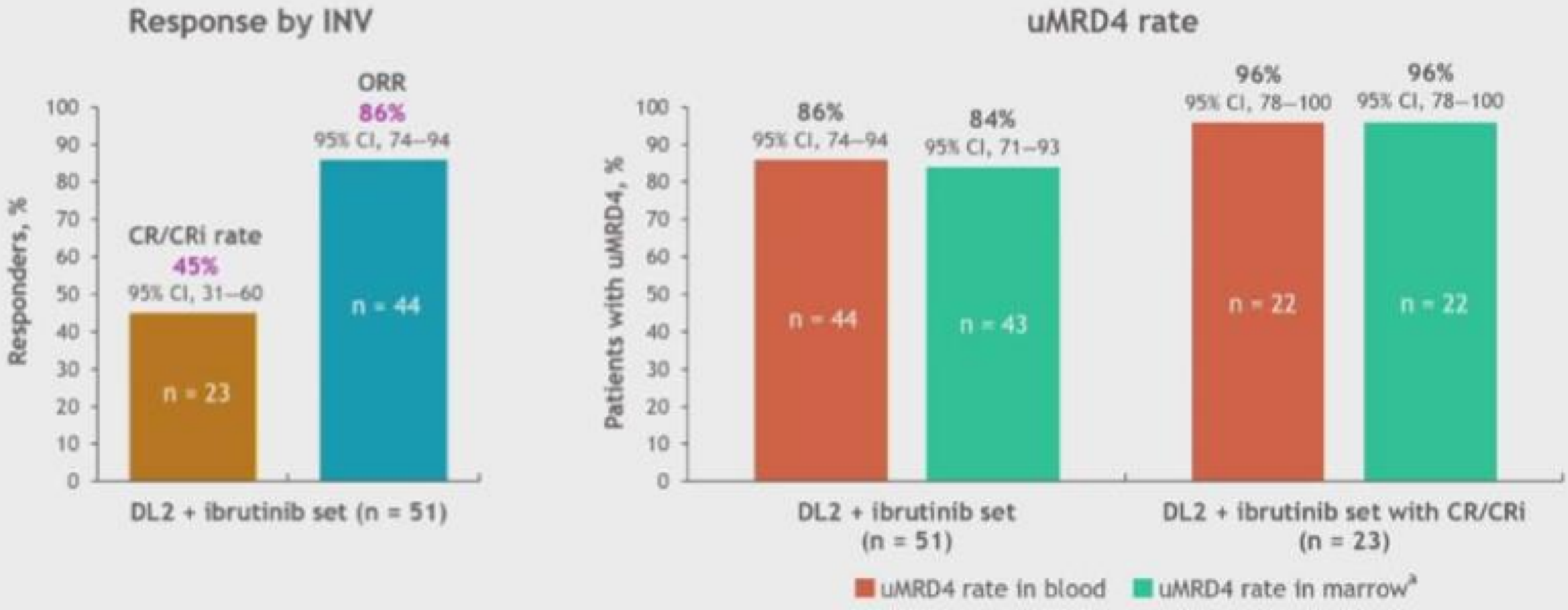
Phase 1/2 TRANSCEND CLL 004 study: liso-cel + ibrutinib combination cohort



Wierda et al ASH 2024

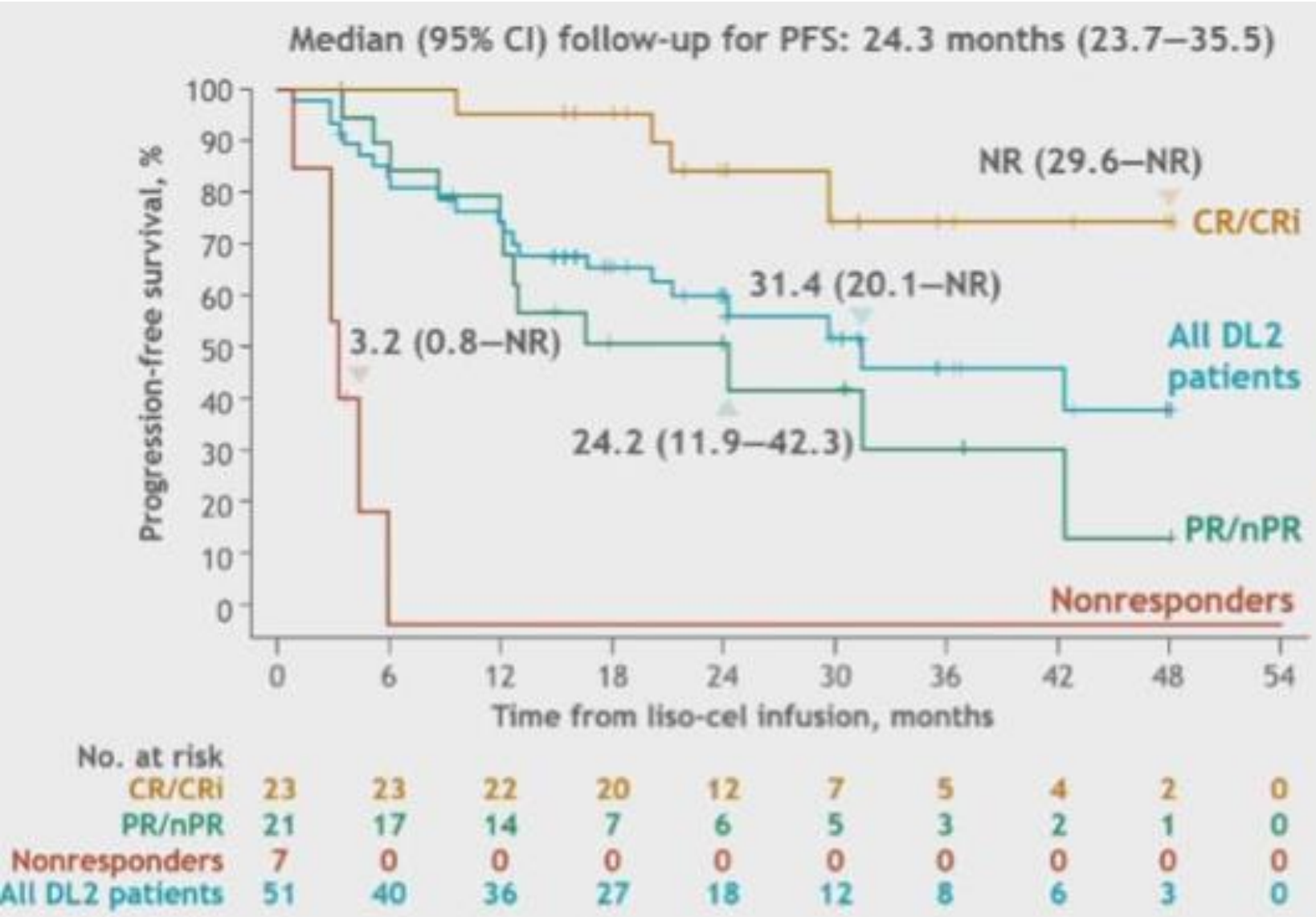
Efficacy outcomes: response by investigator and uMRD4

- 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)



Wierda et al ASH 2024

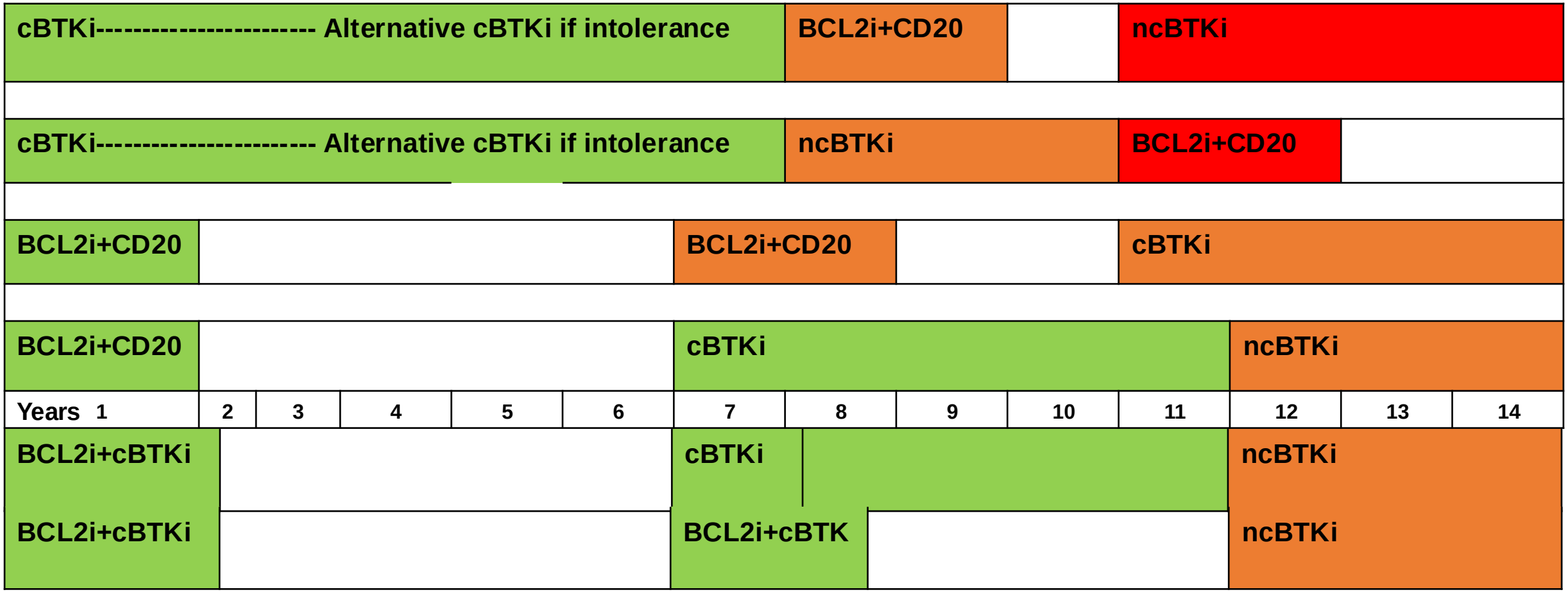
Progression-free survival by best overall response at DL2



	% 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)

Wierda et al ASH 2024

Sequencing Targeted CLL Therapies



cBTKi = covalent BTKi
ncBTKi = non-covalent

<u>Double exposed *vs* double refractory</u>

- Exposed ≠ refractory
- Refractory= progression on treatment

Faculty's opinion.