CLL:Therapeutics Advances 2024

Javier Pinilla-Ibarz, MD, PhD.

Senior Member

Head of Lymphoma section and

Director of Immunotherapy

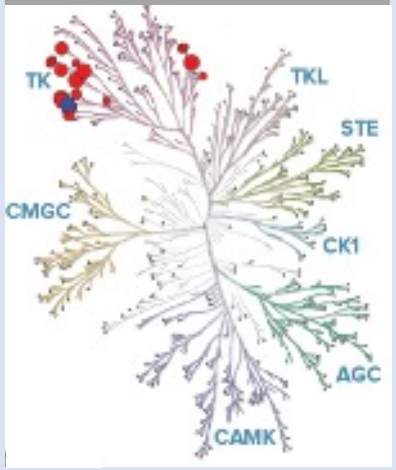
Malignant Hematology Department

MOFFITT CANCER CENTER

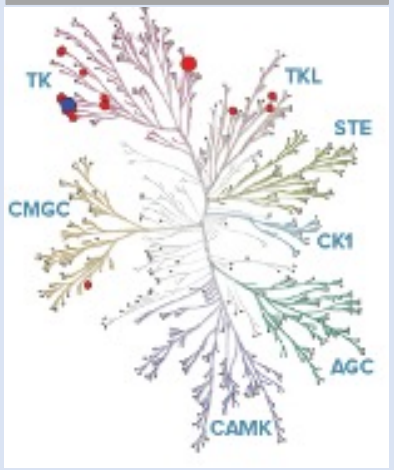
Several Covalent BTKi to Consider With Differences in BTKi Specificity, MOA, and Potential for Off-Target Effects

Covalent

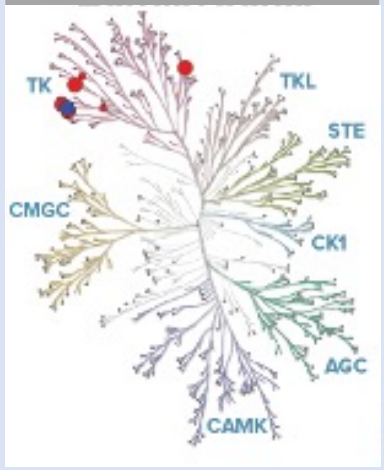
Ibrutinib[1]

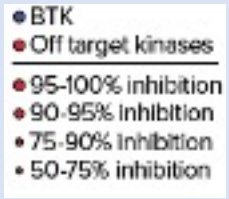


Acalabrutinib[1]



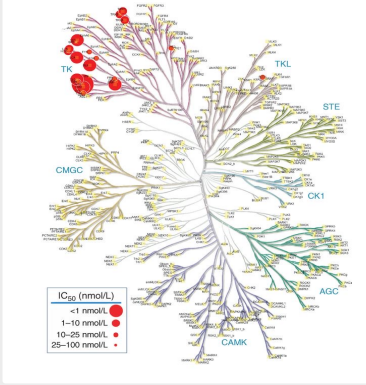
Zanubrutinib[1]



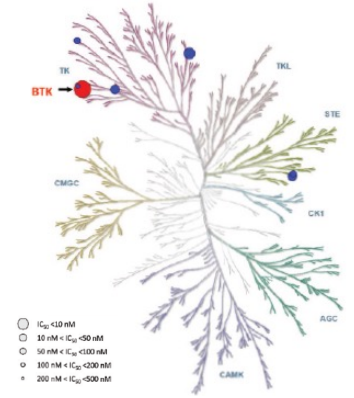


Noncovalent

Nemtabrutinib[2]

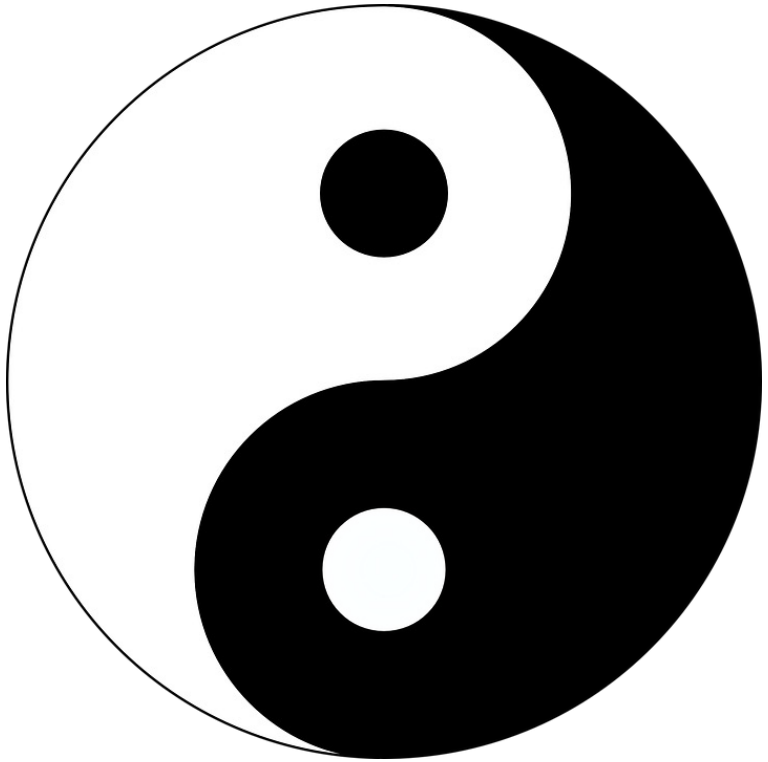


Pirtobrutinib[3]



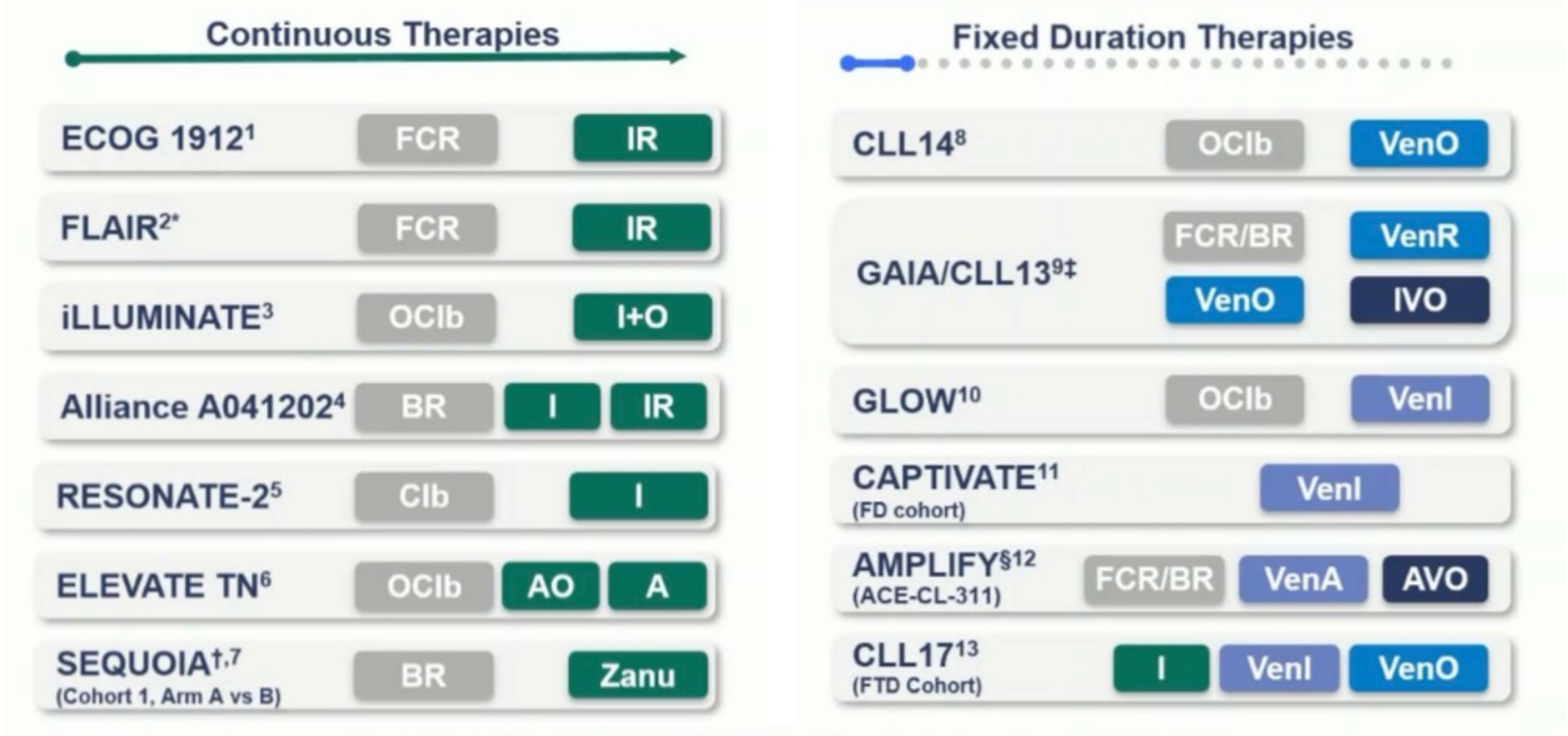
1. Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45. 2. Reiff SD, et al. *Cancer Discov*. 2018;8(10):1300-1315.
3. Brandhuber B, et al. SOHO 2018. Abstract CLL-200.

The dilemma continue between long term therapy vs fixed duration



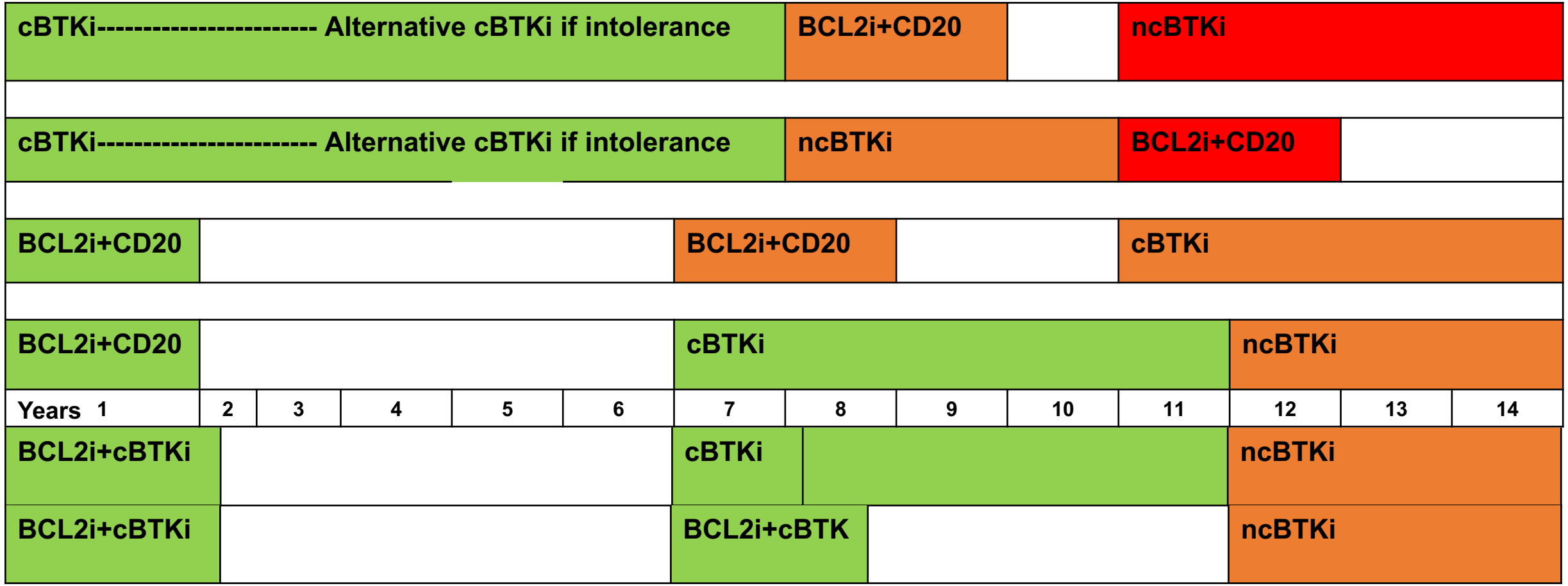
Author’slide

Continuous therapy vs Fixed Duration



1. Shanafelt TD et al, *N Engl J Med*. 2019;**381**(5):432-443. 2. Hillmen P, et al. *Lancet Oncol*. 2023;**24**(5):535-552.
3. Moreno C, et al, *Lancet Oncol*. 2019;**20**:43-56. 4. Woyach JA, et al, *Blood* 2021;**138**:639.
5. Barr PM, et al. *Blood Adv*. 2022;**6**(11):3400-3450. 6. Sharman JP, et al, *Leukemia* 2022; **36**(4):1171-1175.
7. Tam CS, et al, *Lancet Oncol*. 2022;**23**(8):1031-1043. 8. Al Sawaf O, et al. *Nat Commun*. 2023;**14**:2147.
9. Eichhorst B, et al. *N Engl J Med*. 2023;**388**(19):1739-54. 10. Kater AP, et al, *NEJM Evid*. 2022;**1**(7).
11. Tam CS, et al. Blood 2022;139(22):3278-3289.
12. Clinicaltrials.gov. NCT03836261. Accessed May 2024. 13. Clinicaltrials.gov. NCT04608318. Accessed May 2024.

• Sequencing targeted CLL therapies



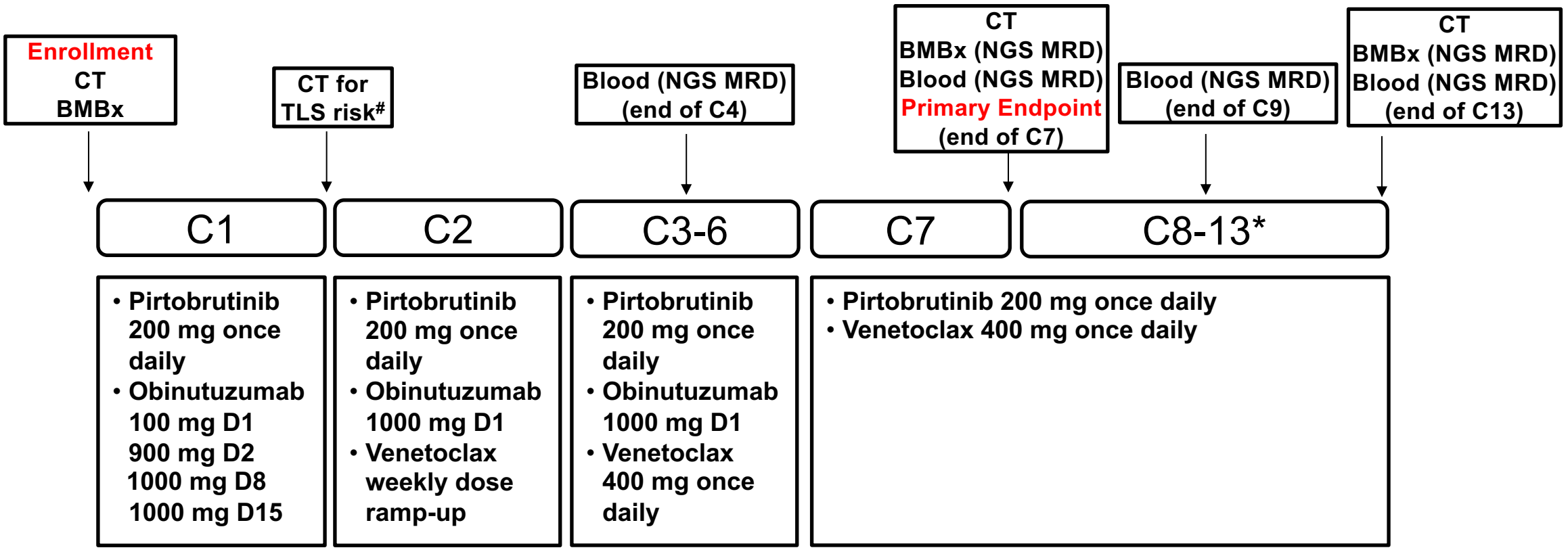
cBTKi = covalent BTKi
ncBTKi = non-covalent

Author opinion

<u>Double Exposed *vs.* Double Refractory</u>:

- Exposed ≠ Refractory
- Refractory=progression on treatment

Combined Pirtobrutinib, Venetoclax, and Obinutuzumab in First-line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL): A Phase 2 Trial



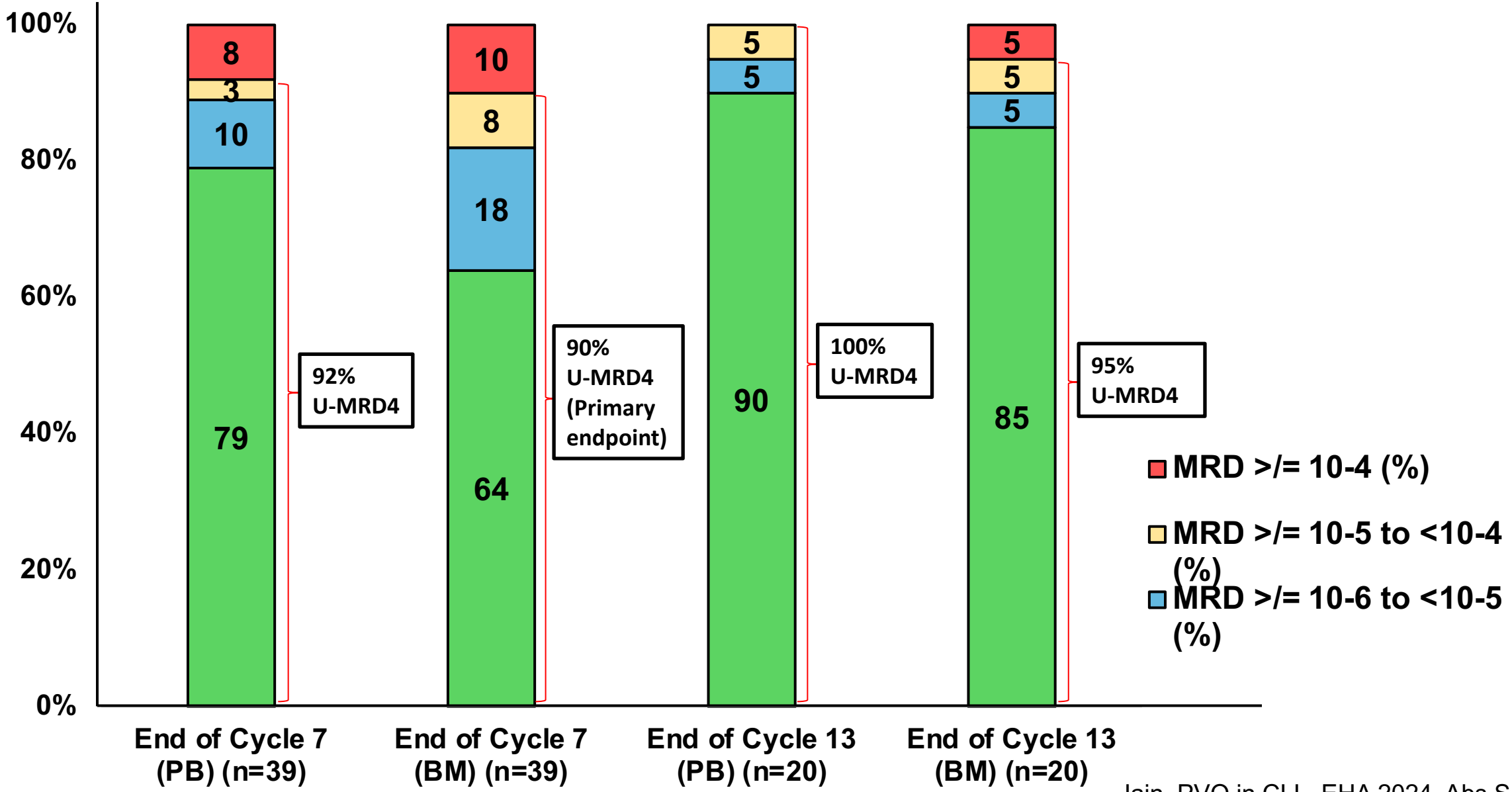
#only if baseline CT had nodes ≥5 cms

- *For pts who are MRD+ at ≥10^{-5} in either PB or BM at end of C13 can continue pirtobrutinib + venetoclax for an additional 12 cycles
- All pts will be monitored by PB NGS MRD q3 mos for first 12 mos off therapy, and then q6 mos
- NGS MRD assessed by clonoSEQ assay (Adaptive Biotechnologies) with 10^{-6} sensitivity
- Each cycle is 28 days

Jain, PVO in CLL, EHA 2024, Abs S164

Pirtobrutinib, Venetoclax, Obinutuzumab Trial

MRD at Serial Time-Points in Blood and Bone Marrow



Jain, PVO in CLL, EHA 2024, Abs S164

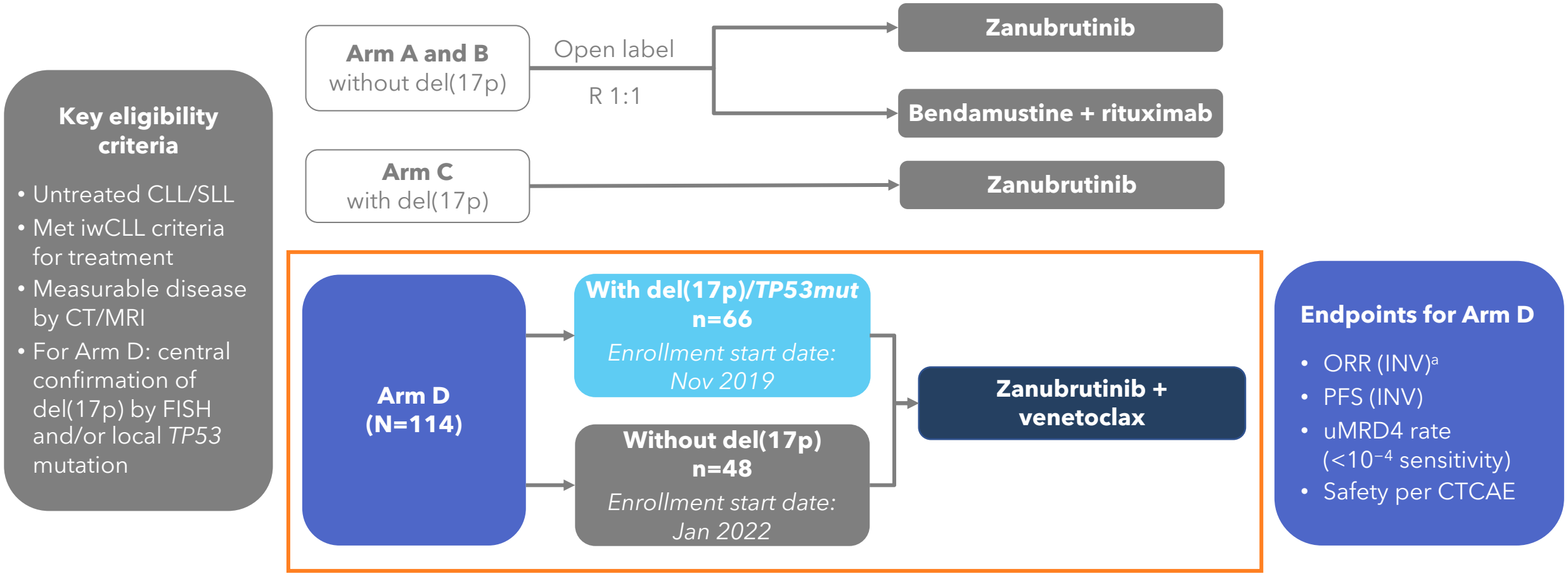
Pirtobrutinib, Venetoclax, Obinutuzumab Trial
Adverse Events

- Grade 3-4 neutropenia and thrombocytopenia occurred in 24 (60%) and 7 (18%) pts, respectively. 22 (55%) pts required G-CSF
- 3 pts had neutropenic fever (diverticulitis, n=1; pneumonia, n=1; cellulitis, n=1)
- Pirtobrutinib was dose-reduced in 12 (30%) pts (100mg, n=7; 50mg, n=3; discontinued early, n=2)
- Venetoclax was dose-reduced in 12 (30%) pts (300mg, n=2; 200mg, n=4; 100ng, n=4; discontinued early, n=2)
- Most common reason for dose reduction for both pirtobrutinib and venetoclax was neutropenia
- 1 pt developed atrial fibrillation (grade 2)

Jain, PVO in CLL, EHA 2024, Abs S164

SEQUOIA Study Design – Arm D Cohort With del(17p) and/or TP53mut

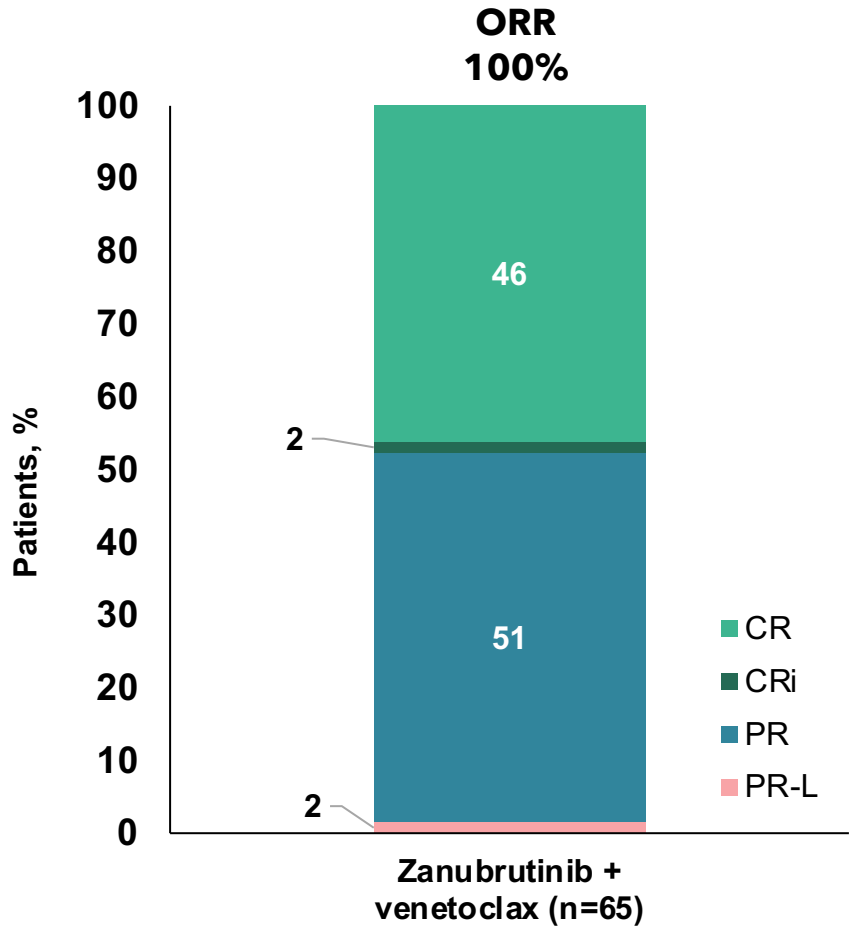
SEQUOIA – Arm D



Ma et al EHA 24

In 65 Response-evaluable Patients[a] with del(17p) and/or TP53 Mutation, ORR[b,c] was 100% and the CR+CRi rate was 48%

SEQUOIA – Arm D



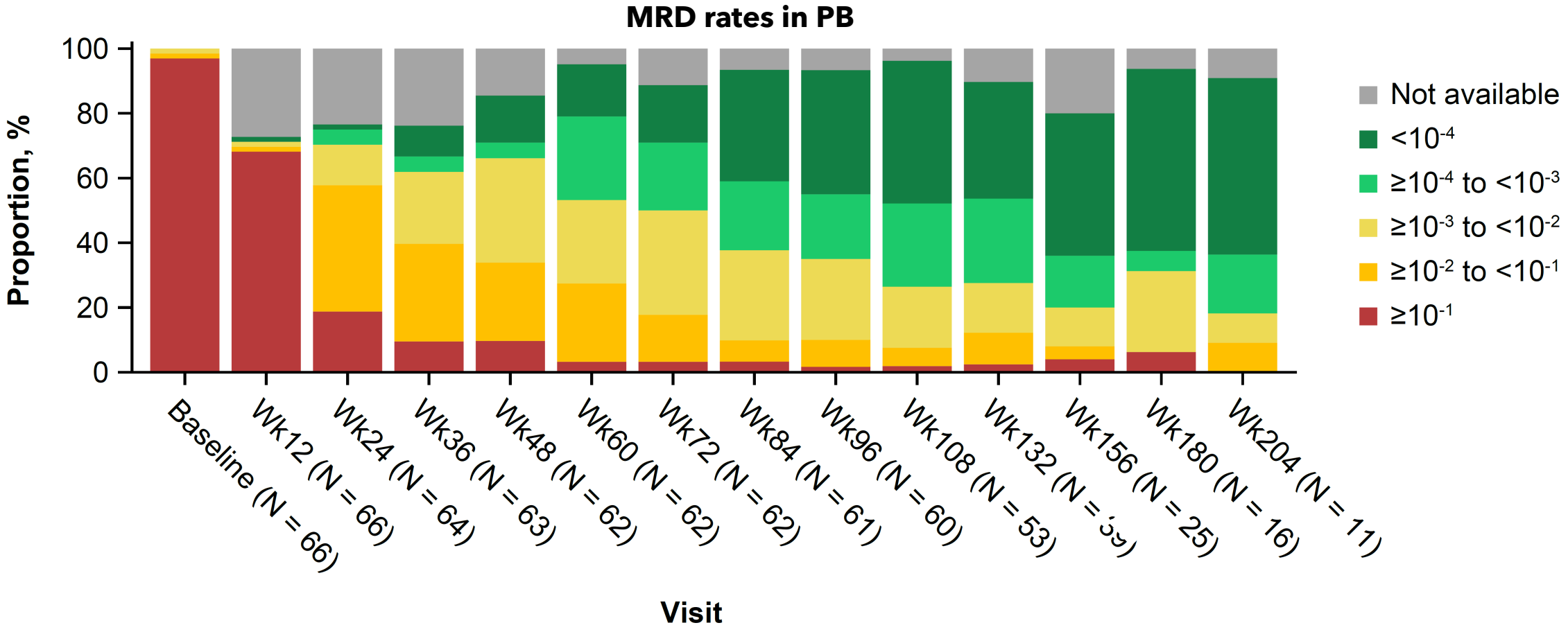
Median study follow-up: 31.6 (0.4-50.5) months

Ma et al EHA 24

Rates of uMRD in PB Increased with Longer Treatment Duration

SEQUOIA – Arm D

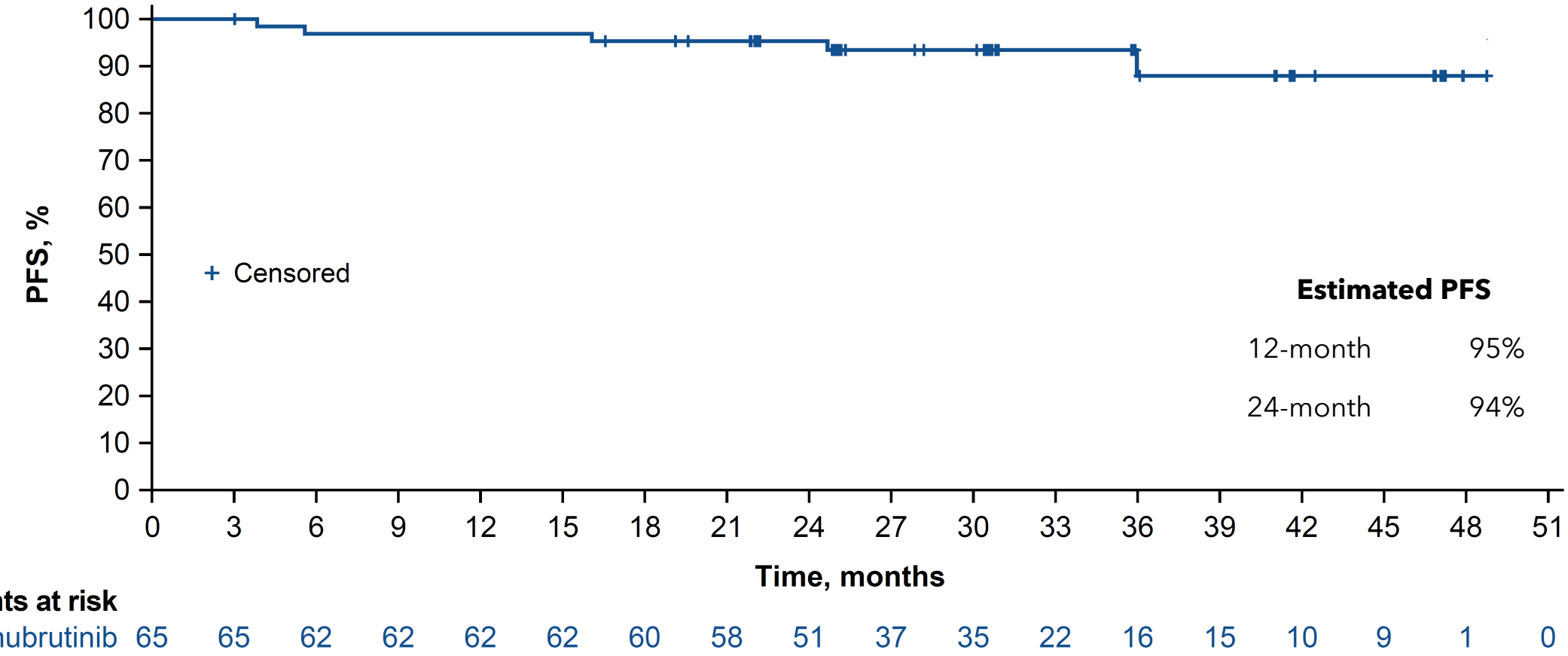
- Best uMRD rate: 59% (39/66) in ≥1 PB sample; 37% (13/35) in ≥1 BM sample[a]



Ma et al EHA 24

With Median Study Follow-up of 31.6 Months, Median PFS was Not Reached

SEQUOIA – Arm D



No. of patients at risk

Zanubrutinib	65	65	62	62	62	62	60	58	51	37	35	22	16	15	10	9	1	0

Ma et al EHA 24

Author Conclusions

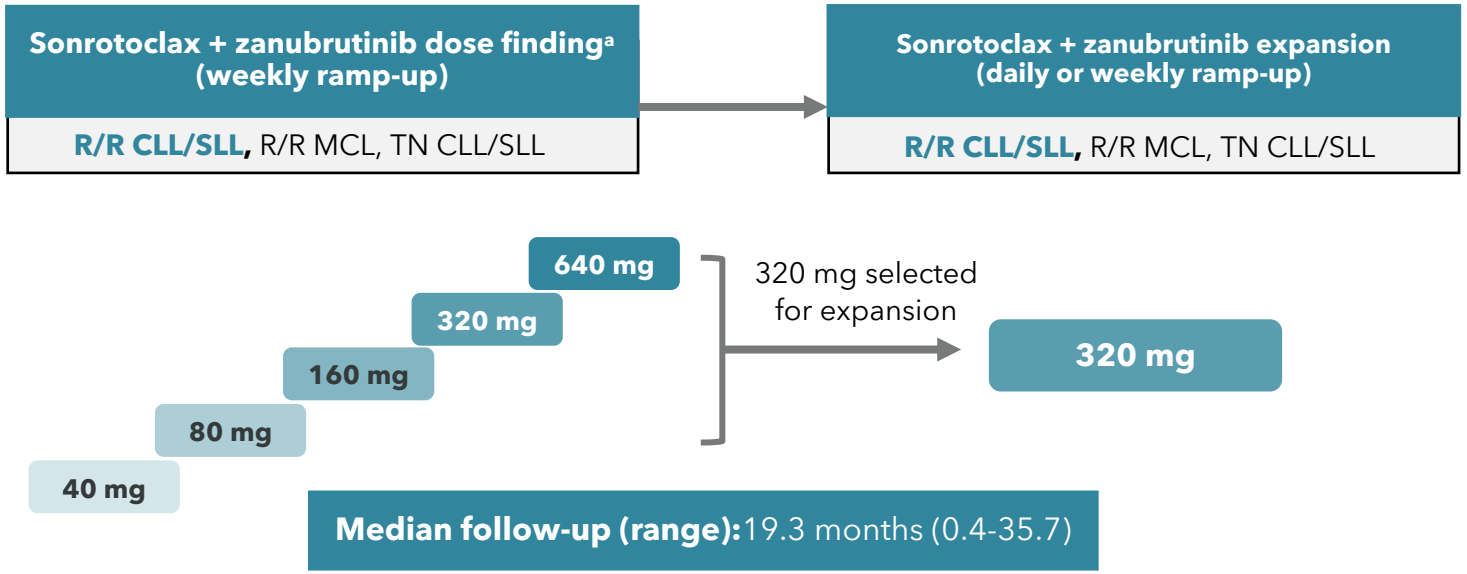
SEQUOIA – Arm D

- Preliminary results for treatment with zanubrutinib + venetoclax in patients with high-risk TN CLL/SLL with del(17p) and/or TP53 mutation showed favorable safety and tolerability
  - Rates of atrial fibrillation/flutter and hypertension were low (2% and 9%, respectively)
- Promising efficacy was seen in this high-risk population with deep and durable responses
  - An ORR of 100% and a high rate of uMRD were achieved
  - With a median follow-up of 31.6 months, high 12- and 24-month PFS estimates were seen (95% and 94%, respectively)
- The study is ongoing and results in patients who meet MRD-guided early stopping rules will be reported as data mature
- The ongoing phase 3 CELESTIAL-TNCLL trial (BGB-11417-301) is evaluating zanubrutinib in combination with sonrotoclax, a next-generation and potent BCL2 inhibitor, as fixed duration therapy in patients with TN CLL

Ma et al EHA 24

Results from the phase 1 study of the novel BCL2 inhibitor sonrotoclax (sonro) in combination with zanubrutinib (zanu) for relapsed/refractory (R/R) CLL/SLL show deep and durable responses

- BGB-11417-101 is a global phase 1/1b study evaluating sonrotoclax as monotherapy, or in combination ± zanubrutinib, and ± obinutuzumab in patients with B-cell malignancies
- The primary endpoints were safety per CTCAE v5.0, MTD, and RP2D
- Treatment consisted of 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), then in combination with sonrotoclax (with weekly or daily ramp-up to target dose) until disease progression



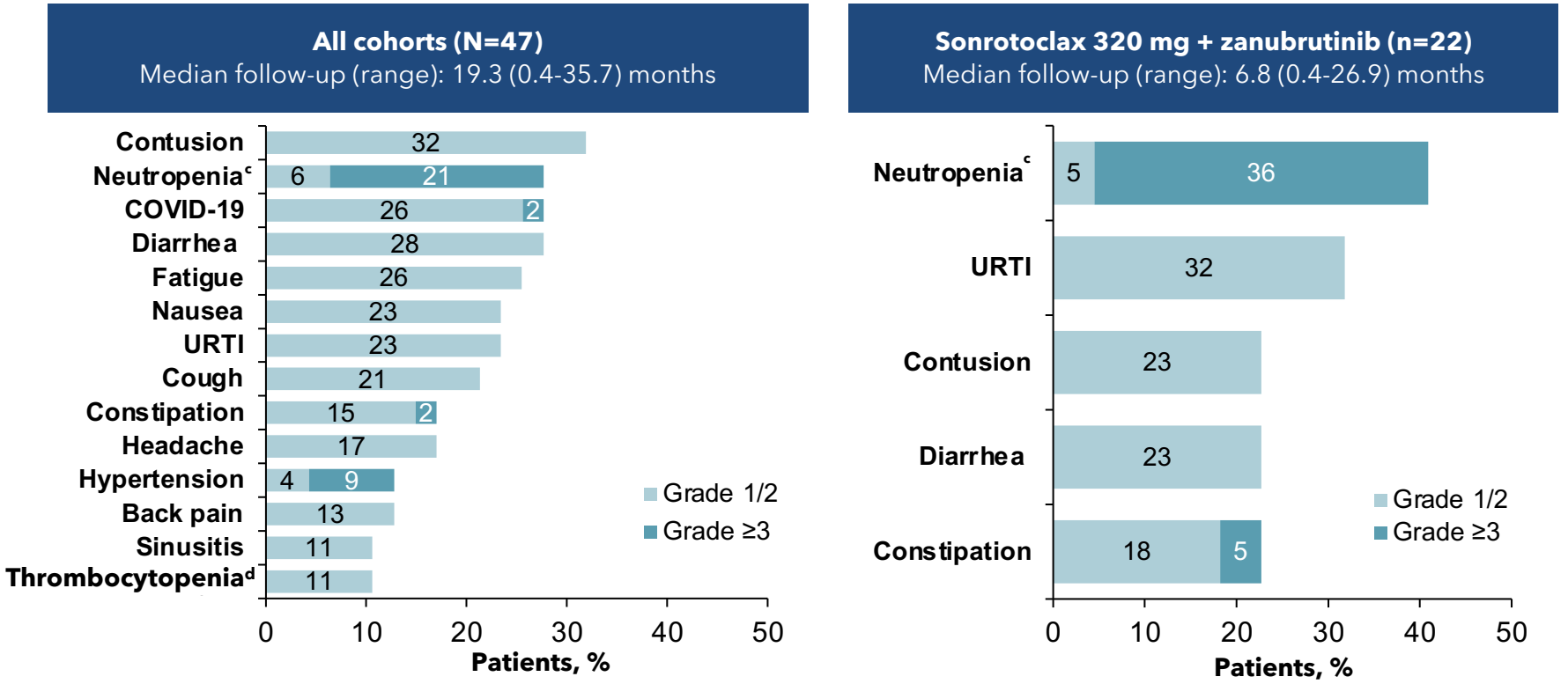
Opat et al EHA 2024

TEAEs Observed With Sonrotoclax + Zanubrutinib Were Mostly Low Grade and Transient

BGB-11417-101 – R/R CLL/SLL

- No TLS
- No atrial fibrillation
- No febrile neutropenia
- No dose reductions due to diarrhea

TEAEs in ≥5 patients of all patients and those treated at sonrotoclax RP2D of 320 mg[a,b]

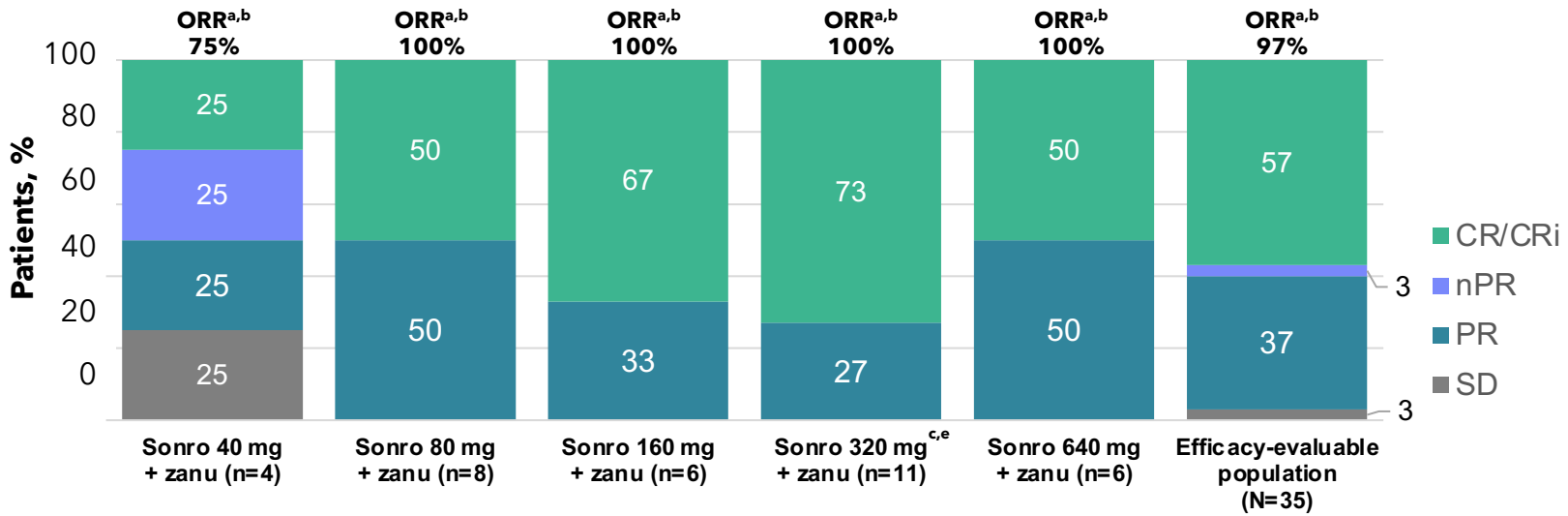


Opat et al EHA 2024

Sonrotoclax + Zanubrutinib Achieves Deep Responses Across All Dose Levels

BGB-11417-101 – R/R CLL/SLL

- With a median study follow-up of 19.3 months, the ORR was 97%, with a 57% CR/CRi rate across all doses
  - In the 320 mg cohort, the ORR was 100%, with a 73% CR/CRi rate
- The median time to CR or CRi was 9.8 months (range, 5.3-22.8 months)
- Of 6 evaluable patients with prior BTK inhibitor therapy, 4 achieved PR and 1 achieved CR

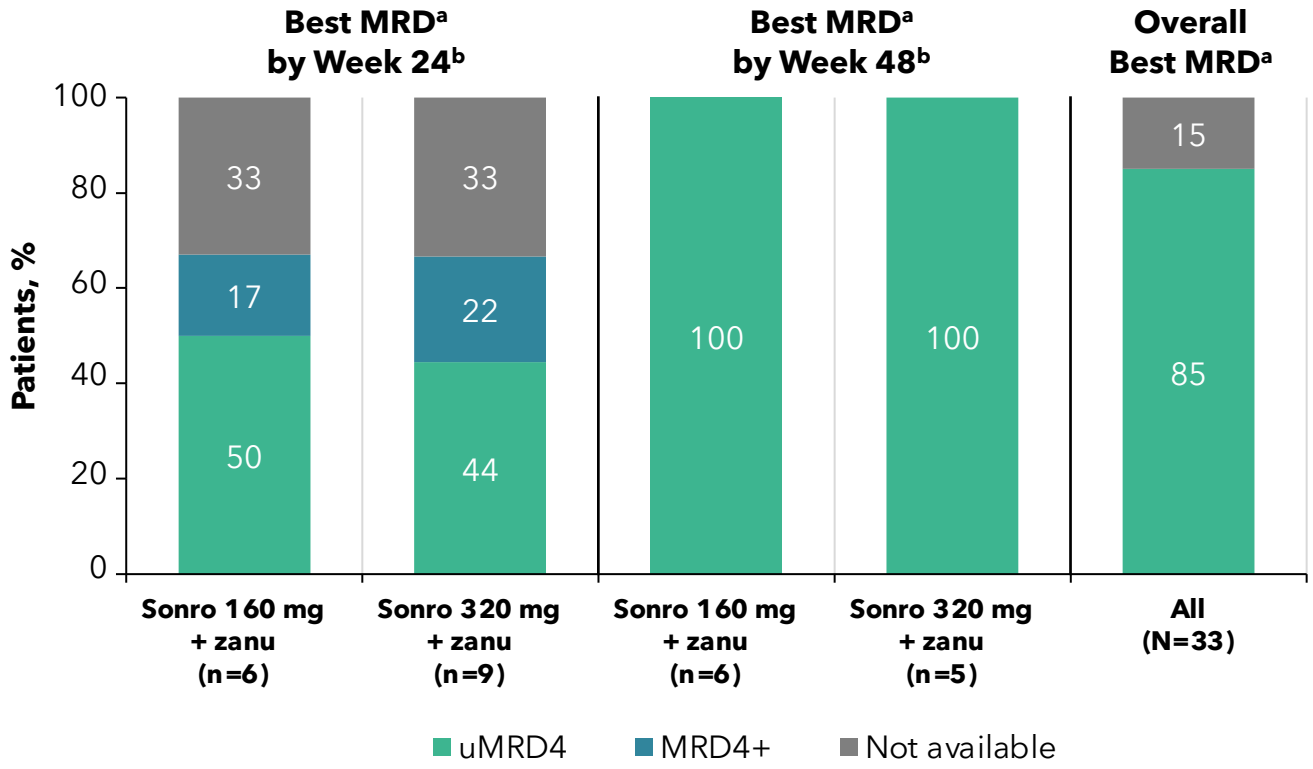


Follow-up time[d], median (range), months	Sonro 40 mg + zanu (n=4)	Sonro 80 mg + zanu (n=8)	Sonro 160 mg + zanu (n=6)	Sonro 320 mg[c,e] + zanu (n=11)	Sonro 640 mg + zanu (n=6)	Efficacy-evaluable population (N=35)
	34.0 (10.2-35.7)	27.7 (10.0-34.5)	29.2 (28.3-30.8)	6.8 (0.4-26.9)	18.1 (10.9-22.6)	19.3 (0.4-35.7)

Opat et al EHA 2024

Sonrotoclax + Zanubrutinib Achieved High Rates of uMRD in Peripheral Blood

- Of 33 MRD-evaluable patients, 28 (85%) had uMRD at time of data cutoff
- Data shows evidence of responses deepening over time
- All patients in the 160 mg, 320 mg and 640 mg cohorts who reached week 48 achieved uMRD

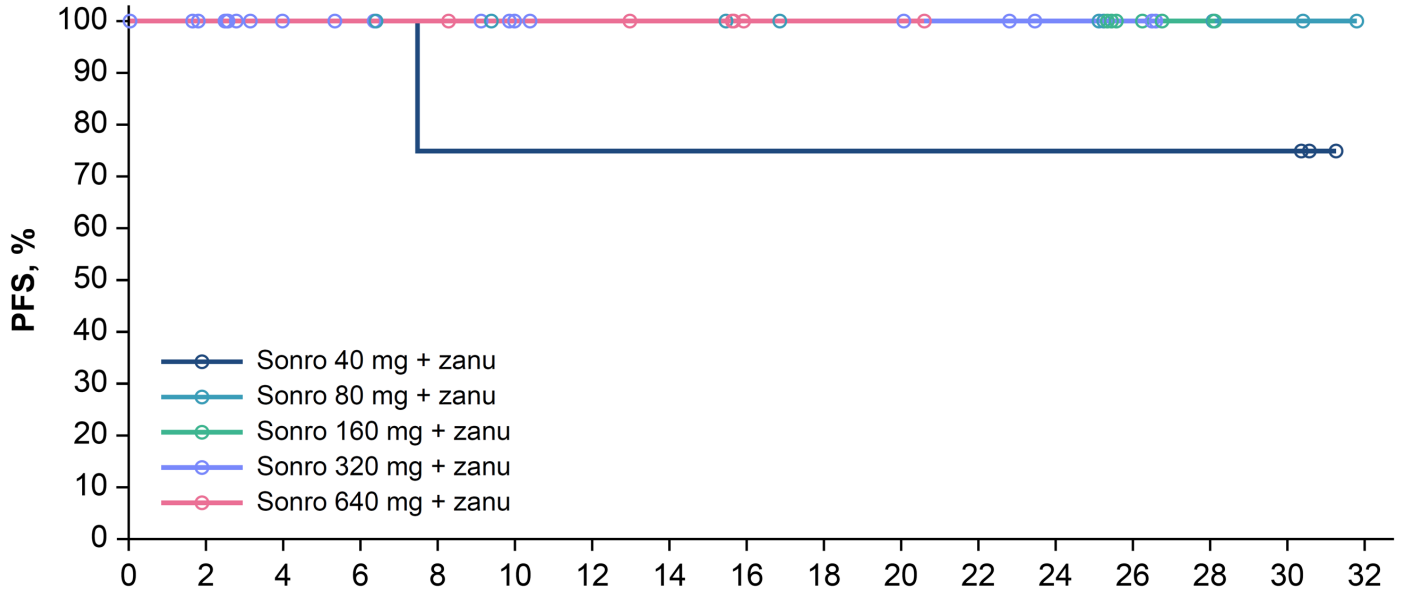


Opat et al EHA 2024

Progression-Free Survival

BGB-11417-101 – R/R CLL/SLL

- With a median study follow-up of 19.3 months, only 1 PFS event occurred in the 40 mg cohort

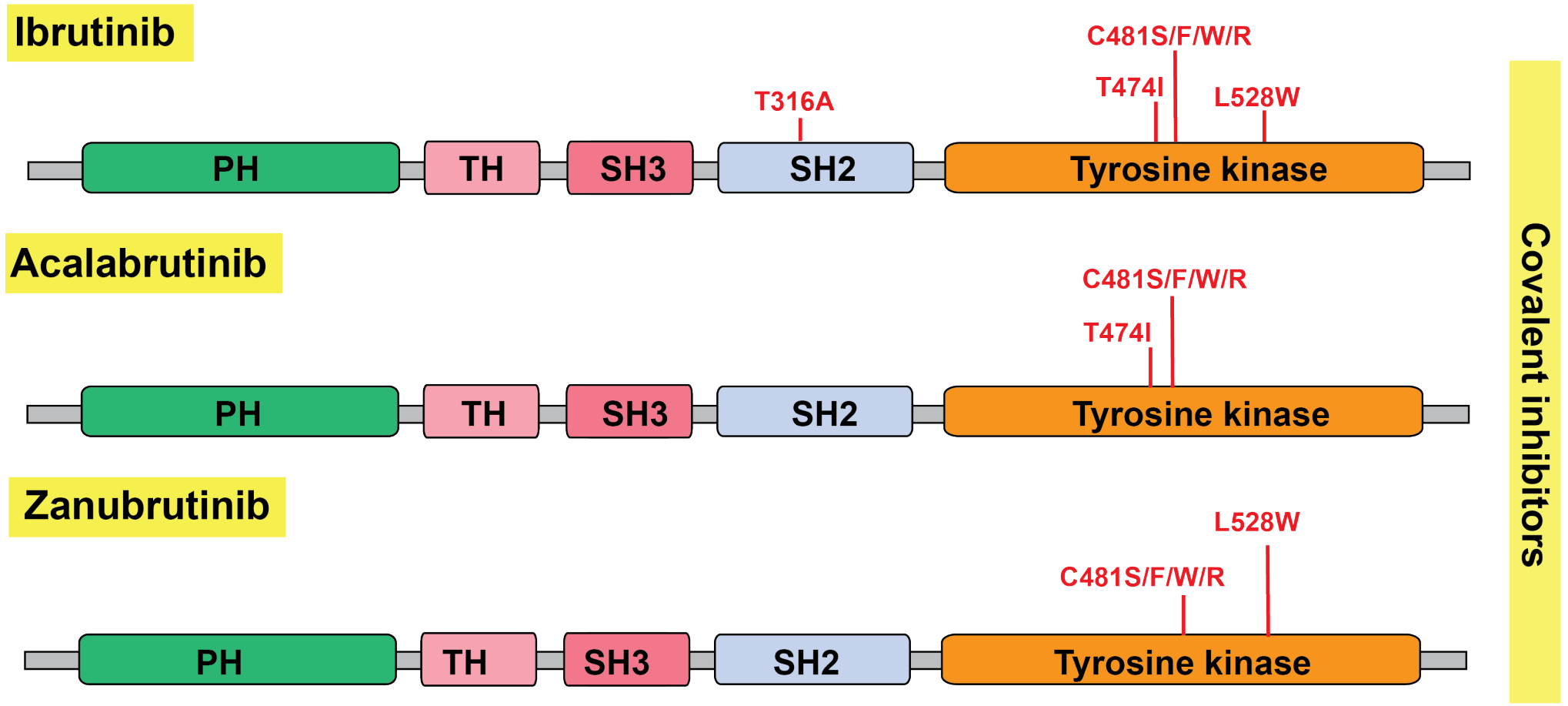


No. of patients at risk

Sonro 40 mg + zanu	4	4	4	4	4	4	4	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	1	0
Sonro 80 mg + zanu	9	9	9	9	9	9	9	8	8	8	7	7	7	7	7	7	6	5	5	5	5	5	5	5	5	5	3	3	3	2	2	1	0
Sonro 160 mg + zanu	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	3	1	1	0	0	0	0
Sonro 320 mg + zanu	22	19	17	13	11	11	10	9	9	9	6	5	5	5	5	5	5	5	5	5	5	4	4	3	2	2	2	0	0	0	0	0	0
Sonro 640 mg + zanu	6	6	6	6	6	6	6	6	6	5	5	5	5	4	4	4	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0

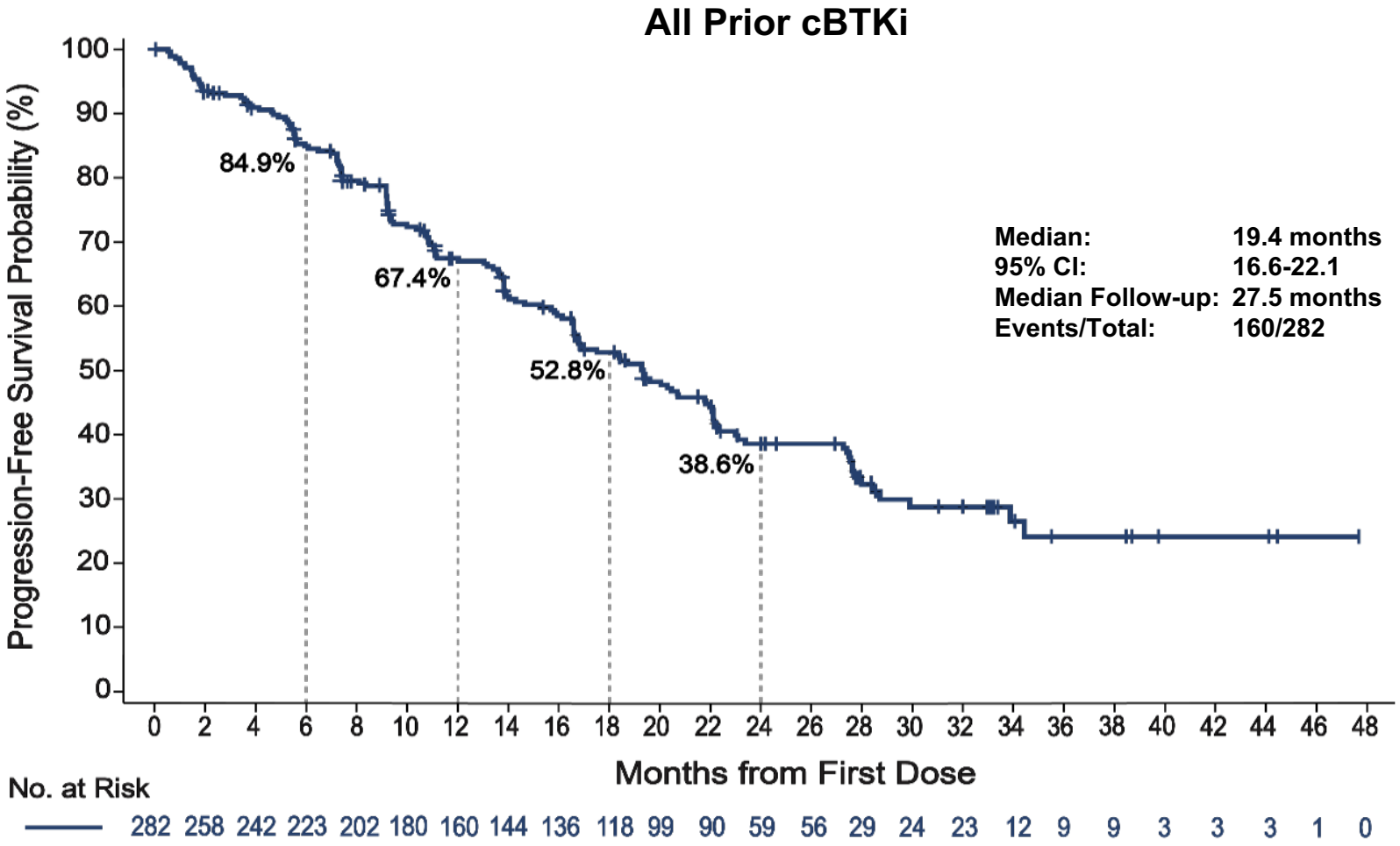
Opat et al EHA 2024

Diverse BTK mutations cause resistance to covalent BTK inhibitors



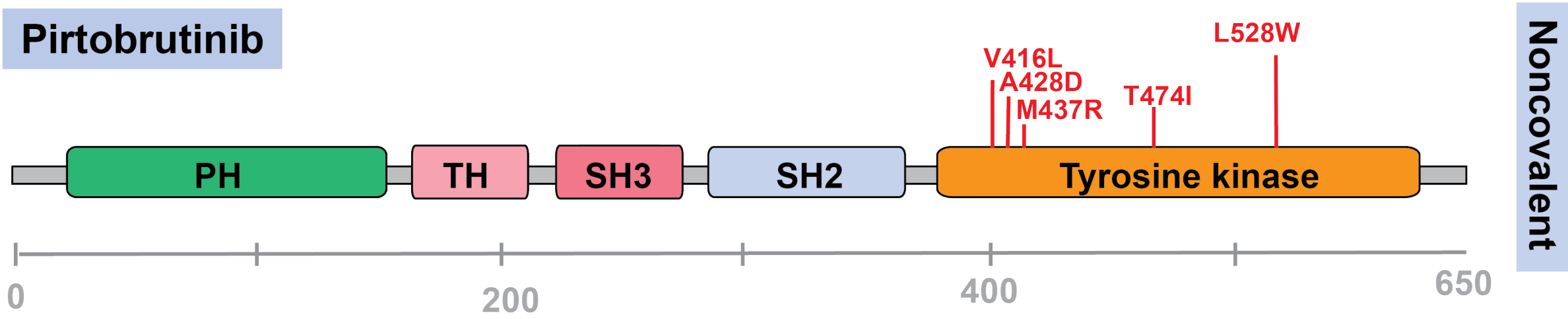
Montoya et al ASH 2022

Pirtobrutinib Progression-Free Survival in Patients with Prior cBTKi



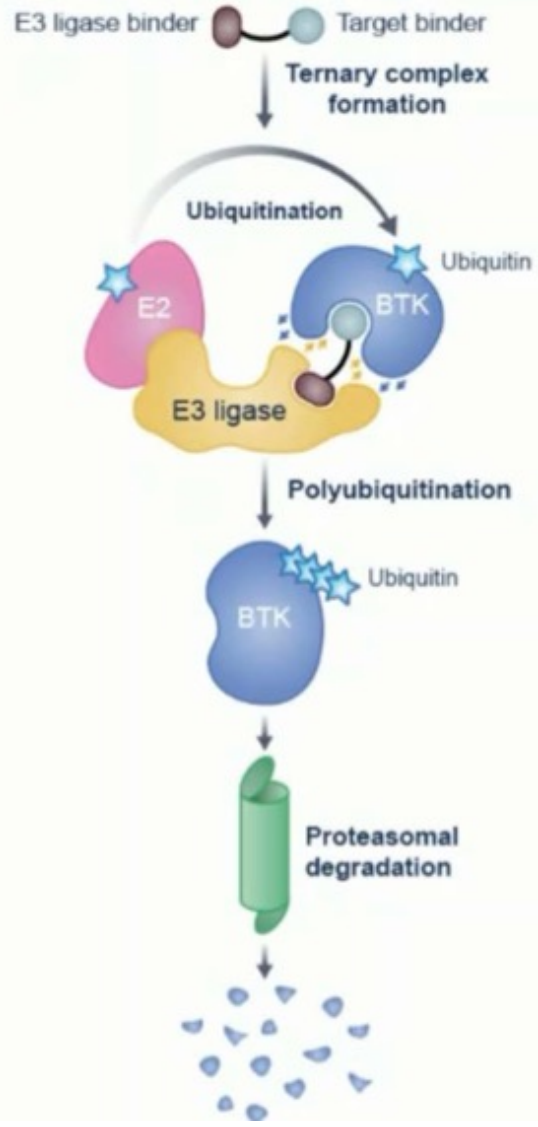
Woyach et al.; ASH 2023

Diverse BTK mutations cause resistance to non- covalent BTKi



Montoya et al ASH 2022

Phase I a / b Study of NX-5948, a Selective Bruton's Tyrosine Kinase (BTK) Degrader, in Patients with Relapsed/Refractory CLL and Other B-cell Malignancies



BTK degraders can overcome treatment-emergent resistance mutations

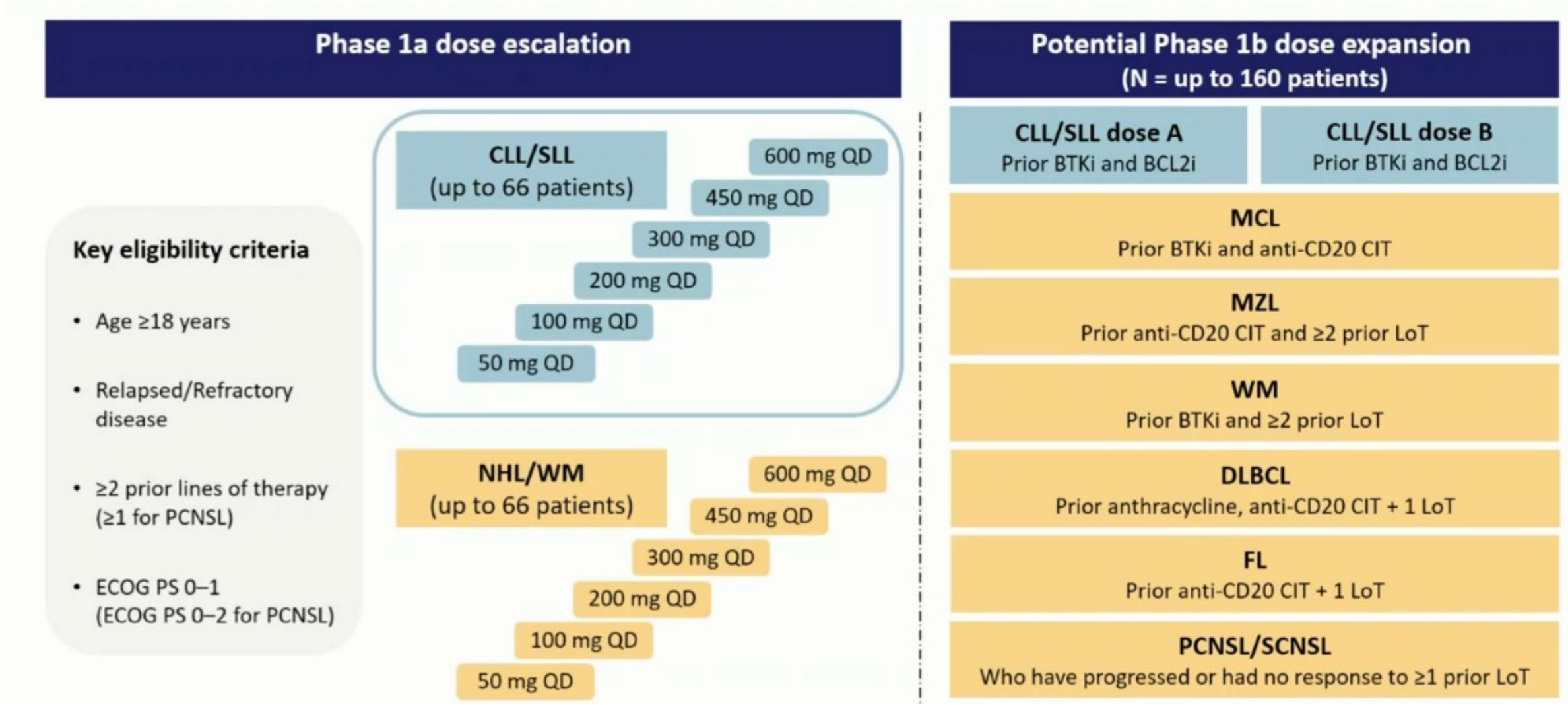
BTK degraders address BTK scaffolding function

BTK degraders show emerging activity in various B-cell malignancies

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

Linton et al EHA24

NX-5948-301: Trial Design



Linton et al EHA24

NX-5948-301: Safety/AE

TEAEs, n (%)	Patients with CLL (n=31)			Overall population (N=79)		
	Any grade	Grade ≥3	SAEs	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	13 (41.9)	–	–	28 (35.4)	–	–
Thrombocytopenia[b]	7 (22.6)	1 (3.2)	–	21 (26.6)	7 (8.9)	–
Neutropenia[c]	7 (22.6)	6 (19.4)	–	16 (20.3)	12 (15.2)	–
Fatigue	7 (22.6)	–	–	14 (17.7)	2 (2.5)	–
Anemia	6 (19.4)	1 (3.2)	–	13 (16.5)	3 (3.8)	–
Petechiae	7 (22.6)	–	–	13 (16.5)	–	–
Rash[d]	8 (25.8)	–	1 (3.2)	13 (16.5)	1 (1.3)	1 (1.3)
Headache	6 (19.4)	–	–	12 (15.2)	–	–
Cough	4 (12.9)	–	–	11 (13.9)	1 (1.3)	–
Diarrhea	5 (16.1)	1 (3.2)	–	9 (11.4)	1 (1.3)	–
COVID-19[e]	2 (6.5)	–	–	8 (10.1)	2 (2.5)	2 (2.5)
Hypertension	1 (3.2)	1 (3.2)	–	6 (7.6)	4 (5.1)	–
Pneumonia[f]	2 (6.5)	1 (3.2)	1 (3.2)	5 (6.3)	4 (5.1)	4 (5.1)

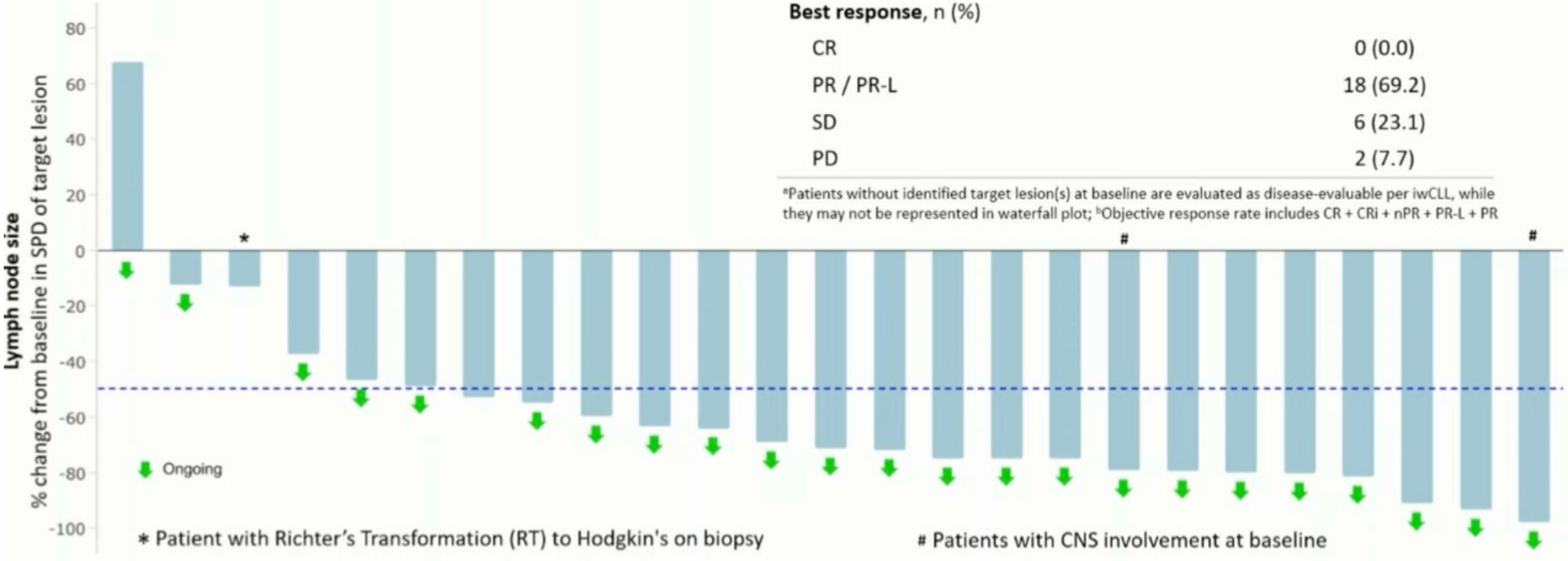
- 1 DLT (non-protocol mandated drug hold; NHL)
- 2 TEAEs resulting in drug discontinuation (both NHL)
- 1 related SAE (TLS based on labs, no clinical sequelae)
- Grade 5 AE (pulmonary embolism, not deemed NX-5948 related)
- No additional safety signal with higher doses

Linton et al EHA24

NX-5948-301 Efficacy: Clinical Response

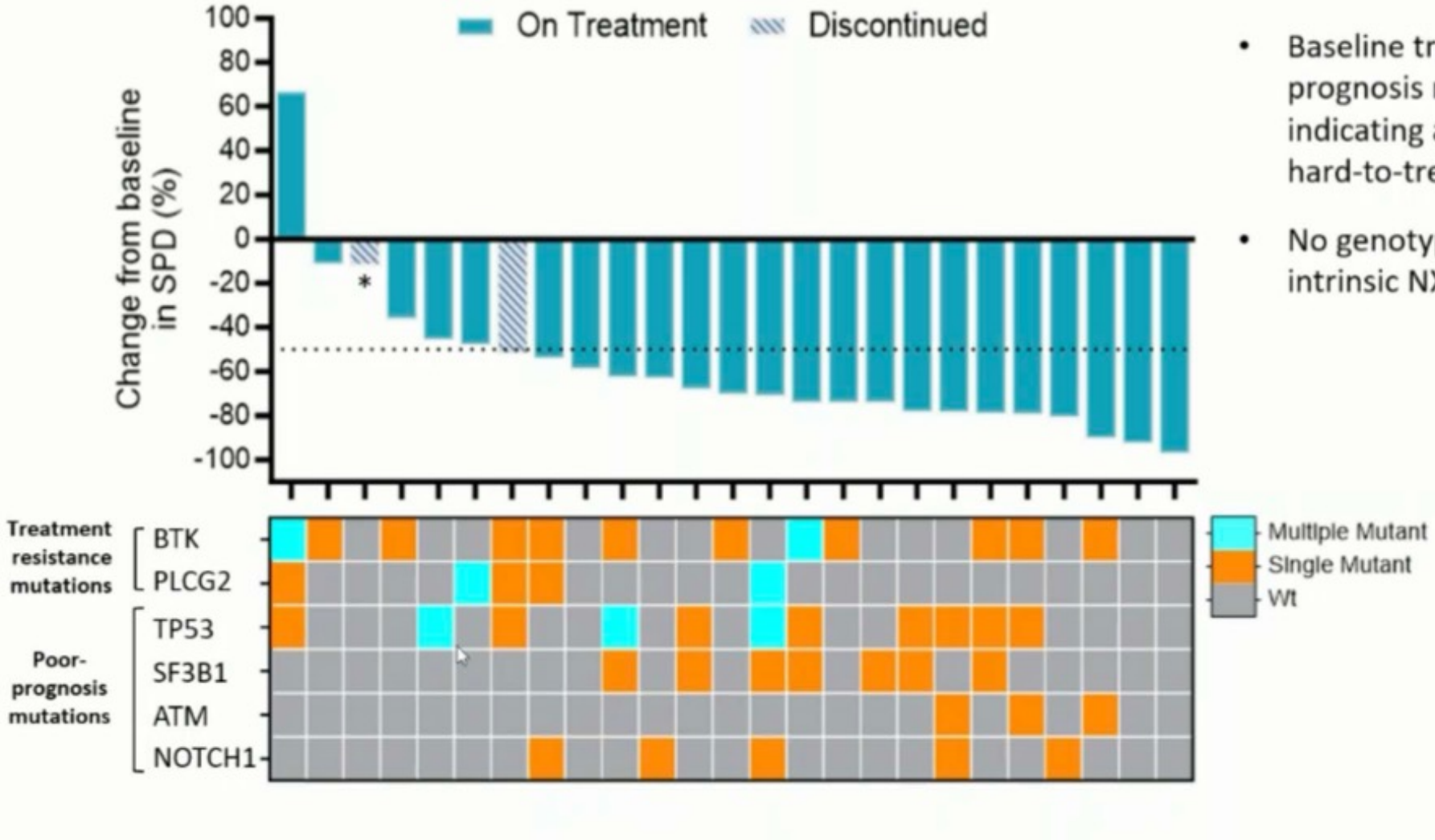
CLL disease-evaluable patients[a]	n=26
Objective response rate (ORR)[b], % (95% CI)	69.2 (48.2–85.7)
Best response, n (%)	
CR	0 (0.0)
PR / PR-L	18 (69.2)
SD	6 (23.1)
PD	2 (7.7)

[a]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL, while they may not be represented in waterfall plot; [b]Objective response rate includes CR + CRi + nPR + PR-L + PR



Linton et al EHA24

NX-5948-301 Clinical Activity in pts with baseline mutations



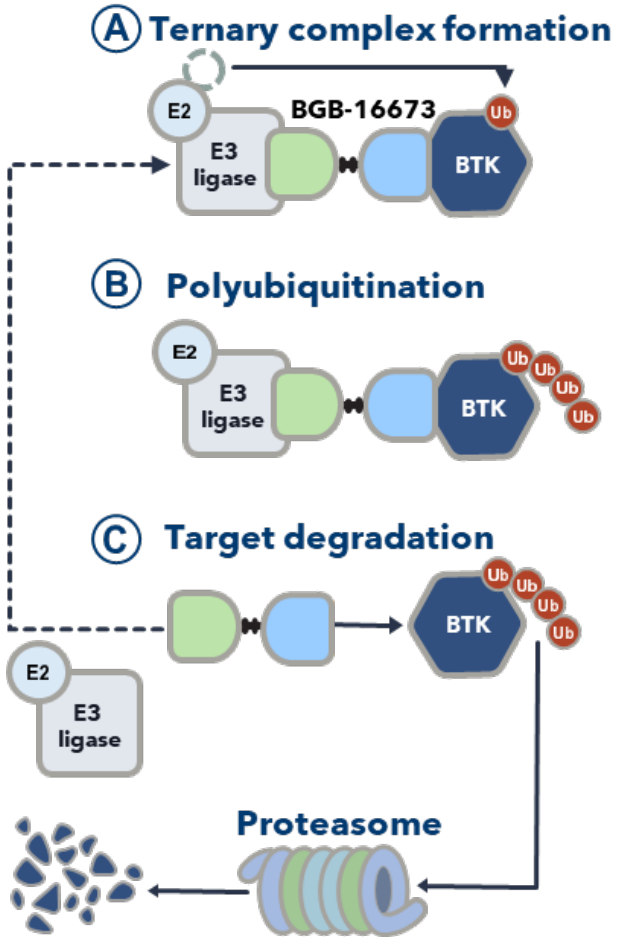
- Baseline treatment-resistance and poor prognosis mutations were common, indicating a genetically diverse and hard-to-treat CLL patient population
- No genotypic profile was linked to intrinsic NX-5948 resistance

Linton et al EHA24

Preliminary efficacy and safety of the Bruton tyrosine kinase (BTK) degrader BGB-16673 in patients with relapsed or refractory (R/R) CLL/SLL: Results from the phase 1 BGB-16673-101 study

BGB-16673-101 – CADANCE-101 (R/R CLL/SLL)

- Many patients with CLL/SLL experience disease progression after BTK inhibitors[1-3]
- BGB-16673, a CDAC, is a bivalent molecule comprising a BTK-binding moiety + linker + E3 ligase binder that induces BTK degradation via polyubiquitination[4]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to covalent and noncovalent BTK inhibitors,[a] leading to tumor suppression[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue in the first-in-human study[6]
- Here, the updated safety and efficacy results are presented from patients with R/R CLL/SLL in the ongoing CaDAnCe-101 study

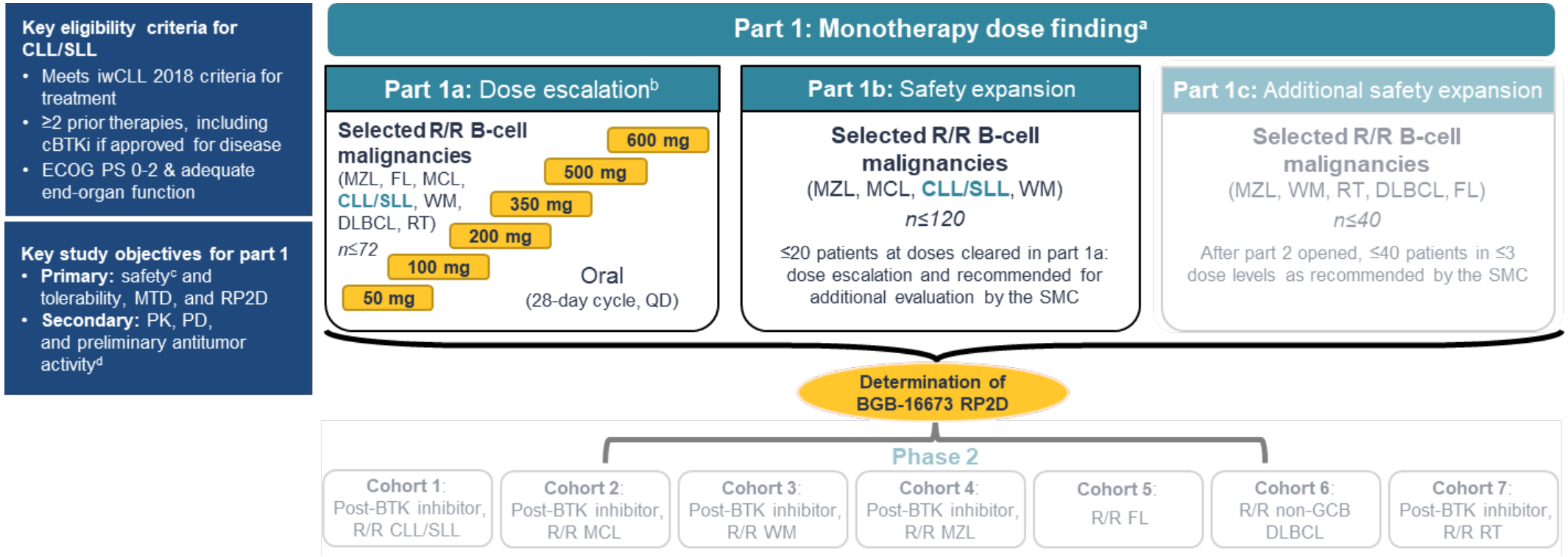


Parrondo et al EHA2024

Study Design

BGB-16673-101 – CADANCE-101 (R/R CLL/SLL)

- CaDAnCe-101 (BGB-16673-101, NCT05006716) is a phase 1/2, open-label, dose-escalation and dose-expansion study evaluating BGB-16673 in adults with R/R B-cell malignancies



Parrondo et al EHA2024

Most Frequent Adverse Events

BGB-16673-101 – CADANCE-101 (R/R CLL/SLL)

Patients, n (%)	Total (N=49)[a]	
	All Grade	Grade ≥3
Fatigue	16 (33)	1 (2)
Contusion	14 (29)	0
Anemia	11 (22)	1 (2)
Diarrhea	11 (22)	0
Neutropenia/neutrophil count decreased	11 (22)	10 (20)
Pneumonia	8 (16)	6 (12)
COVID-19	7 (14)	0
Cough	7 (14)	0
Dyspnea	7 (14)	0
Amylase increased[b]	6 (12)	0
Lipase increased[b]	6 (12)	1 (2)
Pyrexia	6 (12)	0
Thrombocytopenia/platelet count decreased	6 (12)	0
Arthralgia	5 (10)	0
Decreased appetite	5 (10)	0
Nausea	5 (10)	0

No cases of atrial fibrillation or grade ≥3 hypertension were reported

Parrondo et al EHA2024

Overall Response Rate

BGB-16673-101 – CADANCE-101 (R/R CLL/SLL)

- The ORR was 72% (31/43) in response-evaluable patients with CLL/SLL
- The ORR for the 200-mg group was 88%, with 2 patients achieving CR

	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=14)	500 mg (n=7)	Total (N=43)
Best overall response, n (%)[a]						
CR	0	0	2 (13)	0	0	**2 (5)**
PR	1 (100)	4 (80)	10 (63)	6 (43)	1 (14)	**22 (51)**
PR-L	0	0	2 (13)	2 (14)	3 (43)	**7 (16)**
SD	0	1 (20)	1 (6)	2 (14)	3 (43)	**7 (16)**
PD	0	0	1 (6)	1 (7)	0	**2 (5)**
Discontinued prior to first assessment	0 (0.0)	0	0	3 (21)	0	**3 (7)**
ORR, n (%)[b]	**1 (100)**	**4 (80)**	**14 (88)[c]**	**8 (57)**	**4 (57)**	**31 (72)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (94)	10 (71)	7 (100)	**38 (88)**
Follow-up time, median, months	19.8	7.2	6.3	3.9	3.3	**4.6[e]**
Time to first response, median (range), months[f]	2.9 (2.9-2.9)	4.2 (2.8-6.2)	2.8 (2.6-4.1)	2.8 (2.6-5.6)	2.8 (2.6-2.8)	**2.8 (2.6-6.2)**

Parrondo et al EHA2024

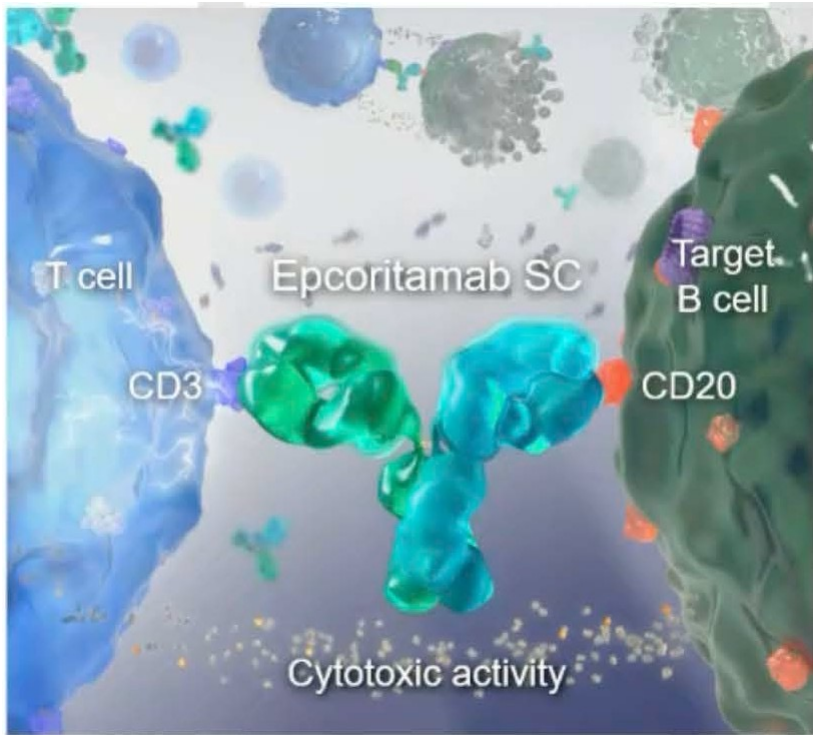
Epcoritamab, a Subcutaneous Bispecific Antibody

- Epcoritamab binds to CD3 on T cells and CD20 on B cells to induce T-cell-mediated killing of co20+B cells[1,2]

  Approved in the US, Europe, the UK, and Japan for adults with R/R DLBCL and different subtypes of LBCL after 2 lines of systemic therapy[3-6]

- Previously showed promising single-agent antitumor activity in difficult-to-treat, high-risk patients with R/R CLL: ORR 62%, CR rate 33%[7]

- Initial data from 10 patients with RT treated with single-agent epcoritamab showed promising antitumor activity (ORR 60%) with a manageable safety profile[8]



First disclosure of data from the fully enrolled RT monotherapy expansion cohort

Kater et al EHA2024

Study Design: EPCORE® CLL-1 RT Expansion Cohort

Key RT inclusion criteria

- ≤2 prior lines of therapy for RT
- Ineligible for or declined chemotherapy
- Prior clinical history of CLL or SLL
- Biopsy-proven transformation to CD20+ DLBCL
- ECOG PS 0–2
- Measurable disease by PET and/or CT/MRI

Median follow-up: 12.9 mo (range, 0.5+ to 28.6)

RT expansion, N=42 (fully enrolled)

2 step-up doses[a]

Epcoritamab 48 mg 28-d cycles

QW C1–3
Q2W C4–9
Q4W C10+

→ Efficacy assessment by PET-CT obtained Q6W until C6, and then Q24W thereafter

→ Treatment until disease progression

- To ensure patient safety and better characterize CRS, inpatient monitoring was required for 24 h after the first full dose of epcoritamab (C1D15)
- **Primary endpoint:** ORR by IRC
- **Key secondary endpoints:** CR rate, time to response, and safety/tolerability

Kater et al EHA2024

Best Overall Response and by Line of Therapy

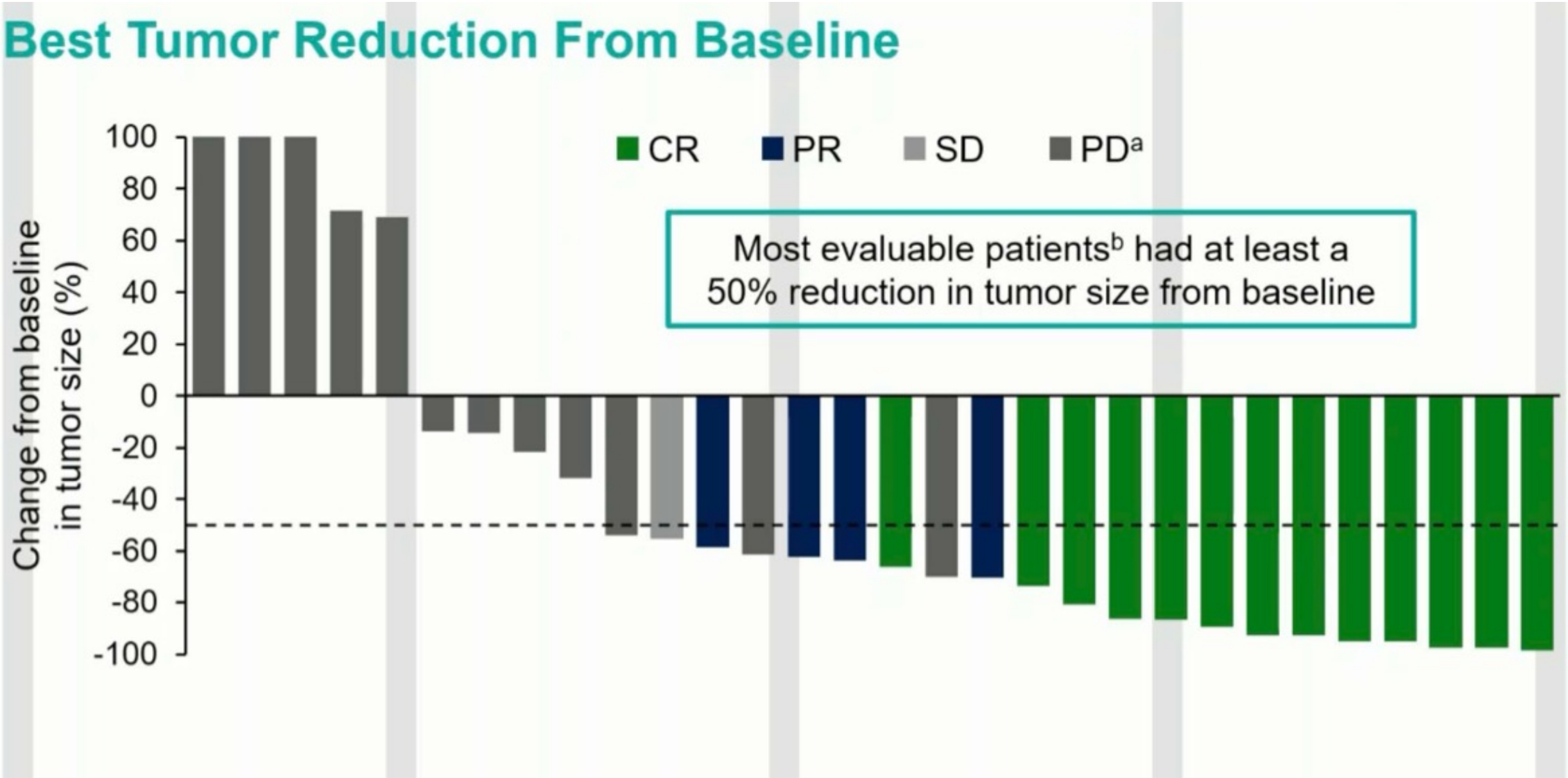
Response, n (%)[a]	Total Efficacy Evaluable n=38[b]	1L RT n=20	2L+ RT n=18
Overall response	**20 (53)**	**12 (60)**	**8 (44)**
Complete response	16 (42)	10 (50)	6 (33)
Partial response	4 (11)	2 (10)	2 (11)
Stable disease	1 (3)	0	1 (6)
Progressive disease	14 (37)	6 (30)	8 (44)

Median follow-up: 12.9 mo (range, 0.5+ to 28.6). [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and/or patients who died within 60 d of first dose. Response assessment according to Lugano 2014 criteria. [b]Three patients died without postbaseline assessment (2 in the 1L RT population and 1 in the 2L+ RT population).

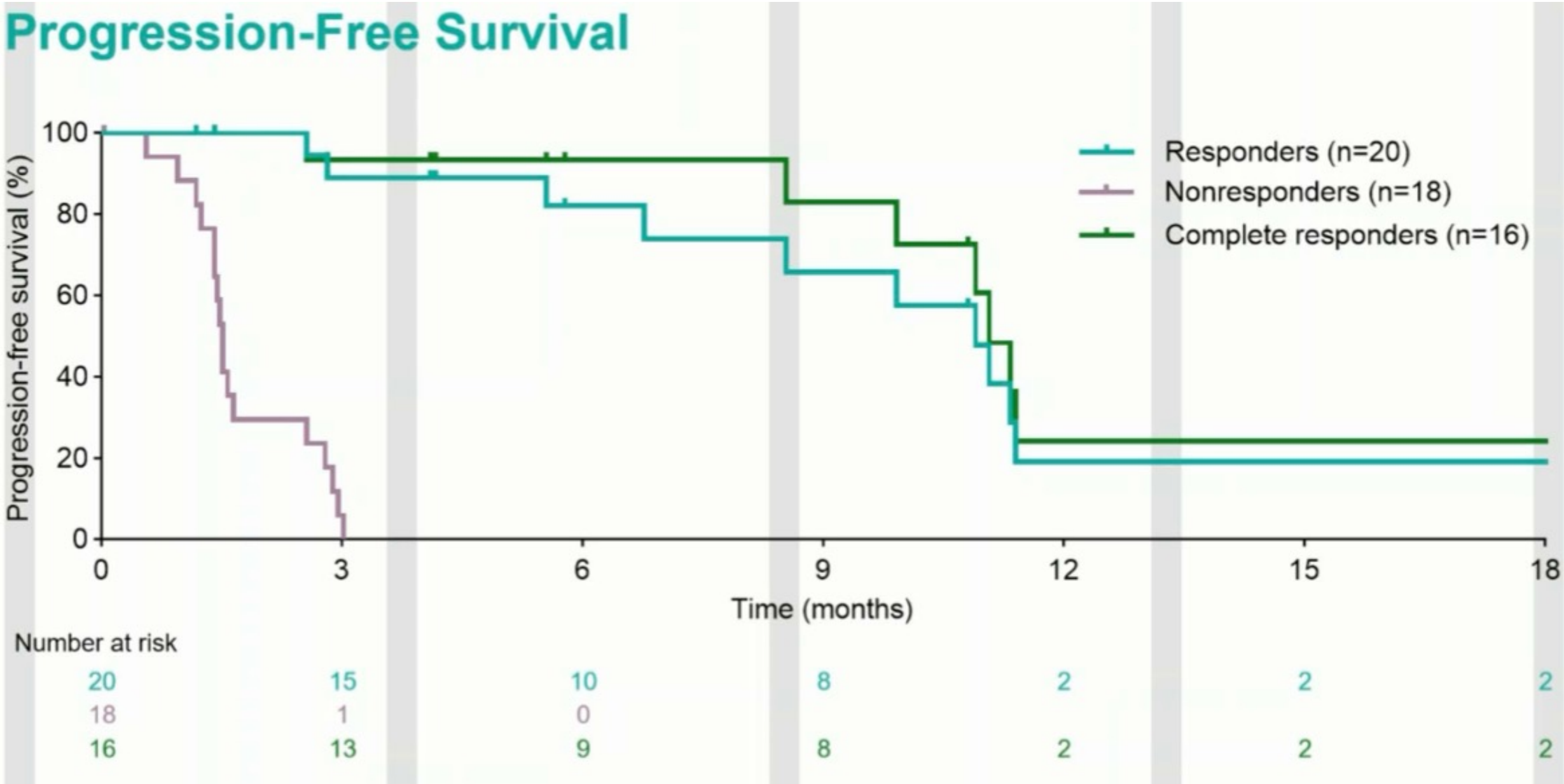
High response rates observed, particularly in 1L RT patients

Kater et al EHA2024

Best Tumor Reduction From Baseline



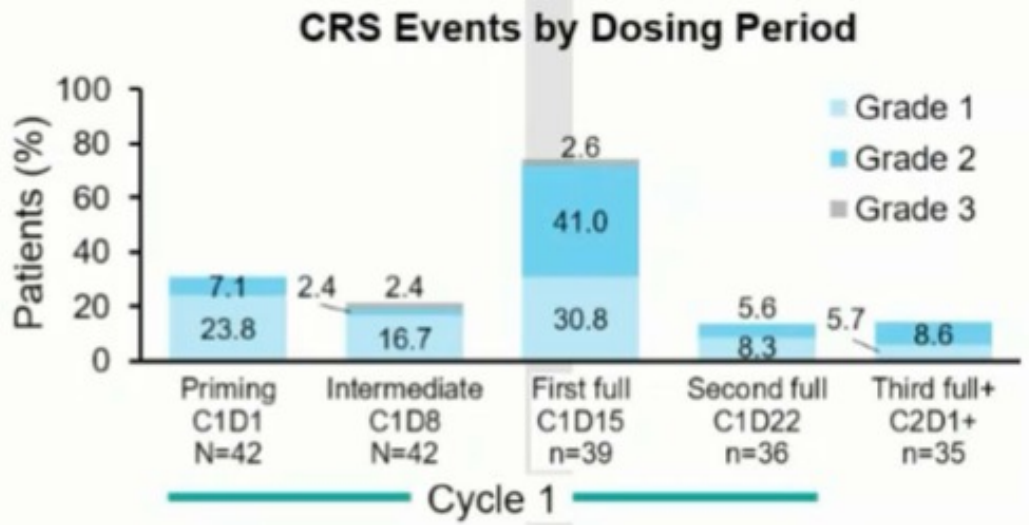
Kater et al EHA2024



Kater et al EHA2024

AEs of Special Interest

CRS[a]	Total, N=42
CRS, n (%)	**35 (83)**
Grade 1	14 (33)
Grade 2	19 (45)
Grade 3	2 (5)
Median time to onset after first full dose, h (range)	14 (3–480)
Median time to resolution, d (range)[b]	3.5 (1–16)
Treated with tocilizumab, n (%)	20 (48)
CRS resolution, n/n (%)	34/35 (97)[c]



ICANS[a] & CTLS[d]	Total, N=42
ICANS, n (%)[e]	**5 (12)**
Grade 1	2 (5)
Grade 2	3 (7)
ICANS resolution, n/n (%)	4/5 (80)[c]
Median time to resolution, d (range)[b]	2 (1–11)
Tumor lysis syndrome, n (%)	**4 (10)**
Laboratory only	1 (2)
Clinical – grade 2	2 (5)
Clinical – grade 3	1 (2)
CTLS resolution, n/n (%)	2/3 (67)
Median time to CTLS resolution, d (range)[b]	3 (3–3)

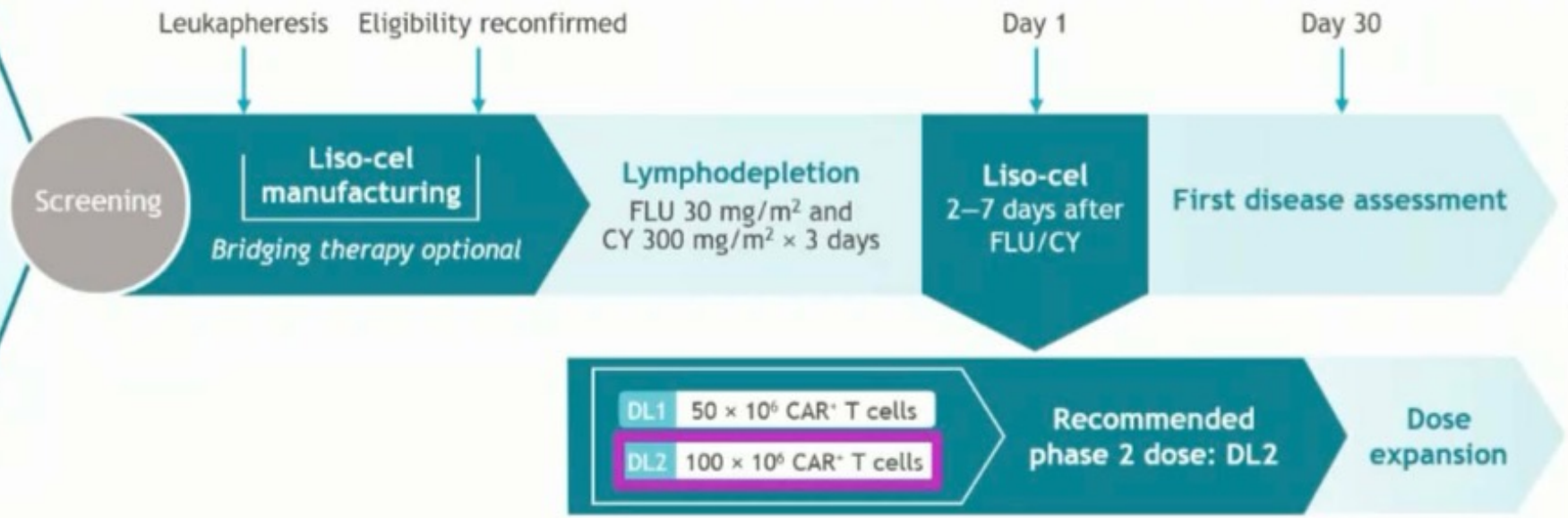
- CRS occurrence was predictable, with cases primarily occurring following the first full dose
- No AEs of special interest led to discontinuation

Kater et al EHA2024

TRANSCEND CLL 004: 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

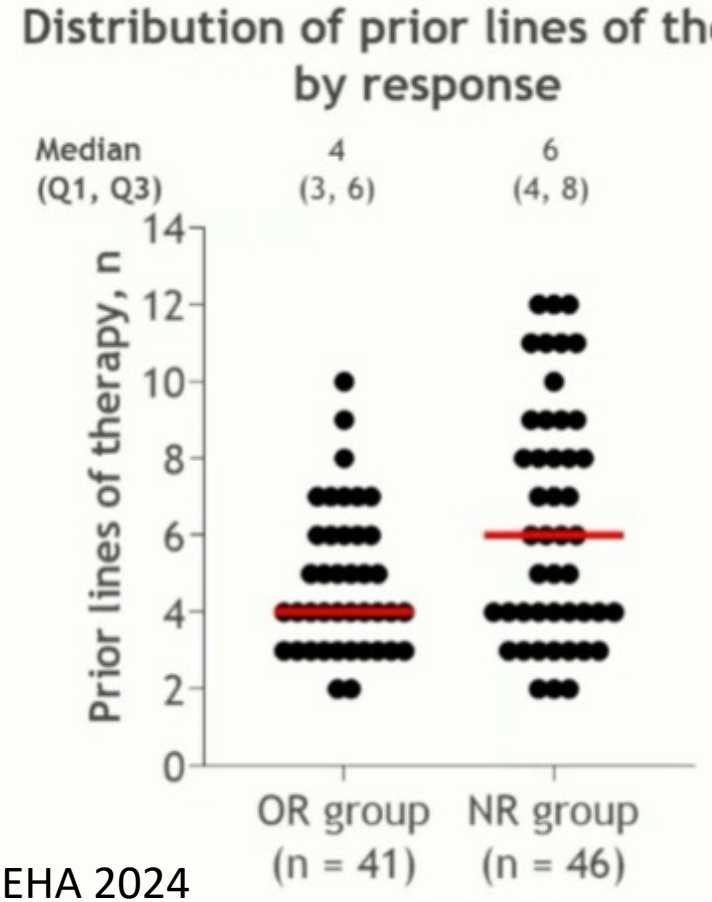


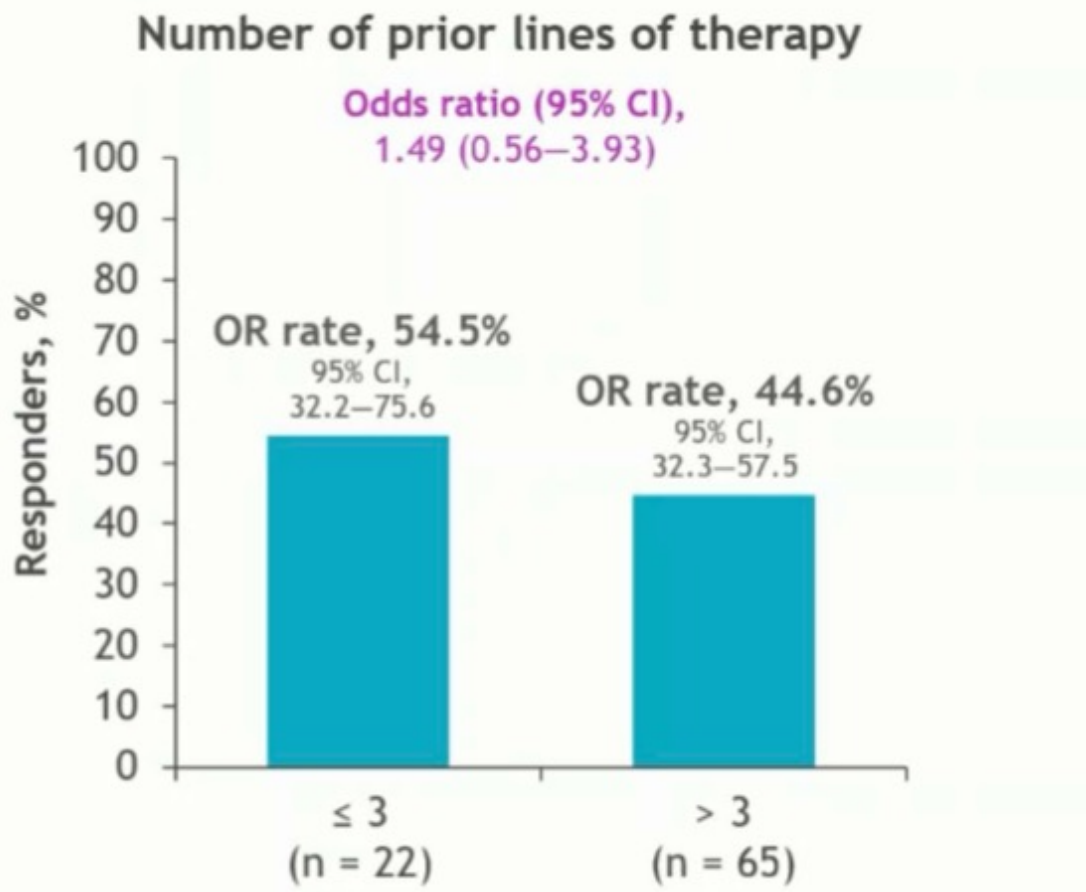
Primary analysis data cut: September 29, 2022		Full efficacy-evaluable set[b] at DL2 (n = 87)
Primary endpoint	CR/CRi rate	18% (95% CI, 11–28%)
Secondary endpoints	OR rate[c]	47% (95% CI, 36–58%)
	Median DOR	35.3 months (95% CI, 19.8–not reached)
	Median PFS	18.0 months (95% CI, 9.4–30.1)
	Median OS	43.2 months (95% CI, 26.9–not reached)

Weirda et al EHA 2024

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

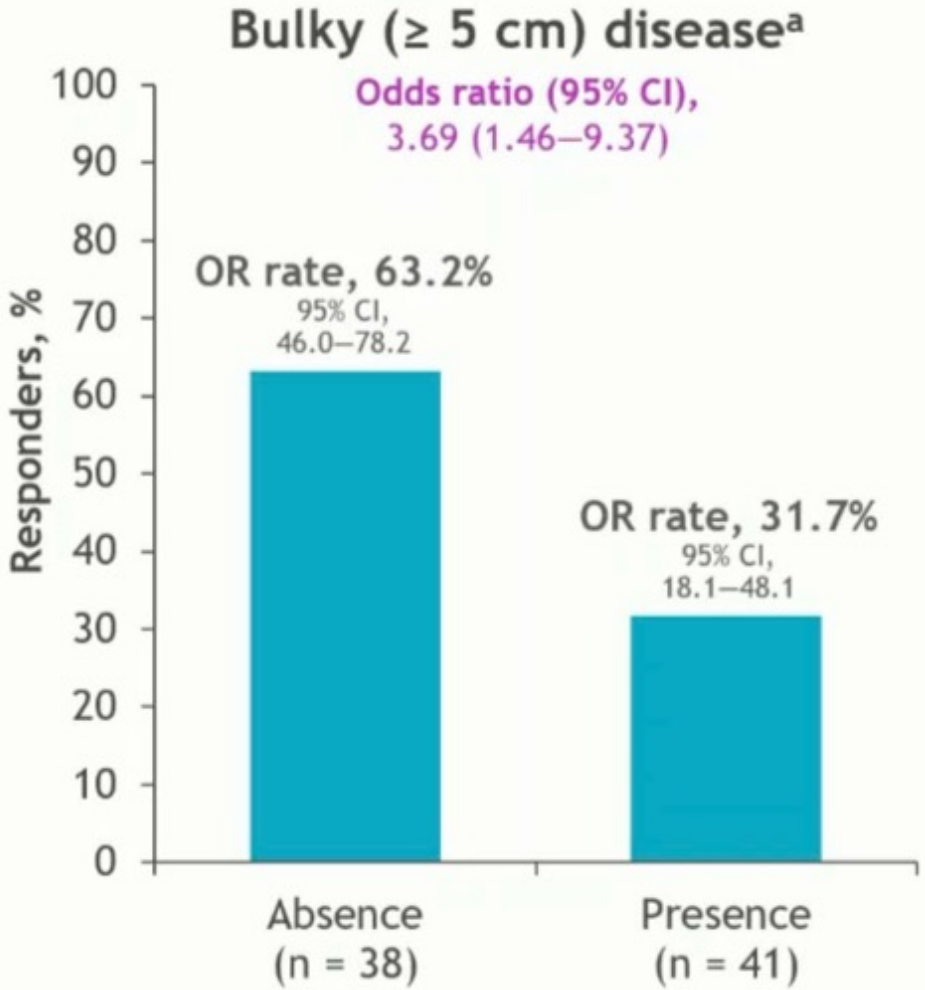


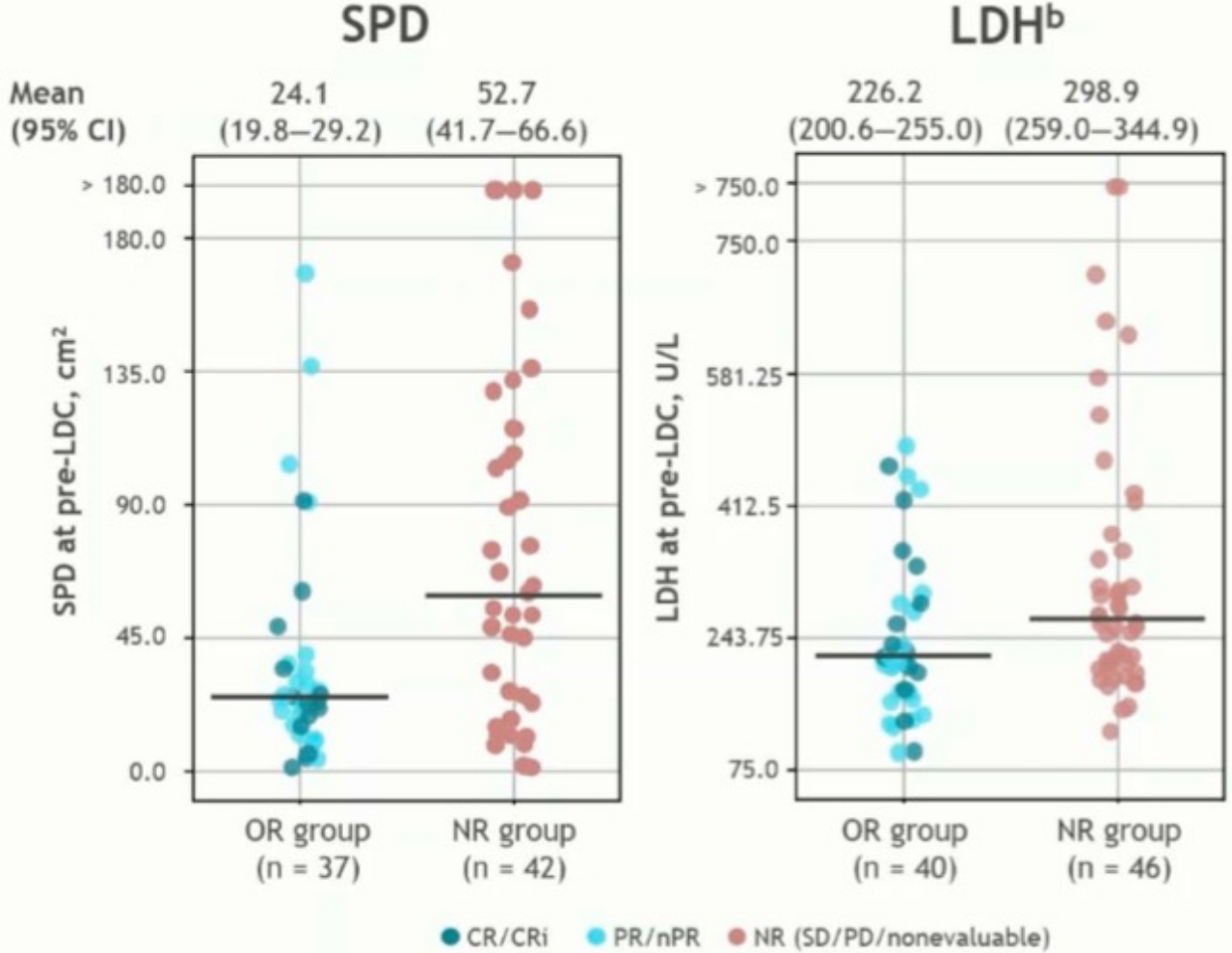


Weirda et al EHA 2024

TRANSCEND CLL 004: Tumor burden correlation with overall response

- Lower tumor burden was correlated with overall response





Weirda et al EHA 2024