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JANUARY 9, 2025

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THIS PROGRAM IS MADE POSSIBLE THROUGH GENEROUS DONORS AND GRANT SUPPORT FROM

SPEAKERS

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MD
(SPEAKER)

Professor of Medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center (MDACC) in Houston, Texas

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MDCM (retired) MS Ed
(SPEAKER & MODERATOR)

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Director of Scientific Affairs & Research
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ASH 2024 COMES TO YOU

Dr. Brian Koffman
EVP and CMO
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WHY ASH MATTERS FOR CLL PATIENTS

- **ASH is the acronym for the American Society of Hematology Annual Meeting and Exposition**
- **It is the premier hematology conference with over 30,000 attendees from around the world, and it's directed towards hematologists, not patients or advocates or even most doctors**
- **It is where one is most likely to hear the most important news and research results across all areas of hematology including CLL**
- **It is where doctors from across the globe meet to plan new and review ongoing research**
- **Patients, though not the intended audience, can learn about:**
    1. Practice changing research (i.e. - the 1st studies showing ibrutinib was superior to FCR/BR)
    2. New therapies likely to approved soon (i.e. - acalabrutinib + venetoclax)
    3. New treatments coming (i.e. - degraders, bispecifics, CAR T)
    4. New trials that are open or opening that might be a good treatment choice
    5. Problems discovered (i.e. - CLL and COVID-19, cardiac issues with ibrutinib)

ASH is News You can Use to Get Your Best CLL Care

THREE IMMUNOTHERAPY ASH TRIALS

1. **Liso-cel with Ibrutinib (CAR T trial) for R/R (Relapsed/Refractory) CLL**
   - **Bottom Line: Adding ibrutinib significantly improves outcomes**
2. **Epcoritamab Monotherapy in R/R CLL**
   - **Bottom Line: Bispecific antibody may provide even better response rates than CAR T**
3. **Viral Particles Used In Vivo (inside the body) to Produce CAR T cells in Macaw Monkeys**
   - **Bottom Line: First in human trials will be starting soon to simplify the CAR T process by making the CAR T cells in the patients own blood stream and lymph nodes**

Liso-cel with Ibrutinib for Relapsed or Refractory CLL/SLL" Primary Results from the Open-label, Phase 1/2 TRANSCEND CLL 004 Study

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ASH 2024, Abstract 887

Presented at the American Society of Hematology Annual Meeting; December 7–10, 2024; San Diego, CA

INTRODUCTION

- **Liso-cel is an autologous, CD19-directed CAR T that demonstrated rapid and durable efficacy with low rates of severe CRS (cytokine release syndrome) and NEs (neurological events) across multiple R/R B-cell malignancies**
- **In TRANSCEND CLL 004 monotherapy with liso-cel at a target dose of 100 × 10^6 CAR^+ T cells (DL2) resulted in a CR (complete response) rate of 20% and ORR (overall response rate) of 44% in patients with third-line or later R/R CLL/SLL who had progression on a previous BTKi and failed venetoclax[8]**
- **Ibrutinib combined with other CAR T cell therapies showed potential to improve CAR T cell function and proliferation, achieve high ORRs, and reduce CRS severity in patients with R/R CLL/SLL[9,10]**

BTKi, Bruton tyrosine kinase inhibitor; CRi, complete response/remission with incomplete marrow recovery; CRS, cytokine release syndrome; DL, dose level; IRC, independent review committee; liso-cel, lisocabtagene maraleucel; NE, neurological event.

1. Abramson JS, et al. *Lancet* 2020;396:839—852; 2. Abramson JS, et al. *Blood* 2023;141:1675—1684; 3. Morschhauser F, et al. *Nat Med* 2024;30:2199—2207; 4. Sehgal A, et al. *Lancet Oncol* 2022;23:1066—1077; 5. Siddiqi T, et al. *Lancet* 2023;402:641—654; 6. Siddiqi T, et al. *Blood* 2022;139:1794—1806; 7. Wang M, et al. *J Clin Oncol* 2024;42:1146—1157; 8. Siddiqi T, et al. *Blood* 2023;142(suppl 1):330; 9. Gauthier J, et al. *Blood* 2020;135:1650—1660; 10. Gill S, et al. *Blood Adv* 2022;6:5774—5785; 11. Wierda WG, et al. *Blood.* 2020;136(suppl 1):39—40.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

INTRODUCTION

- **These data address the question if adding ibrutinib improves outcomes with liso-cel. Past results suggest ibrutinib:**

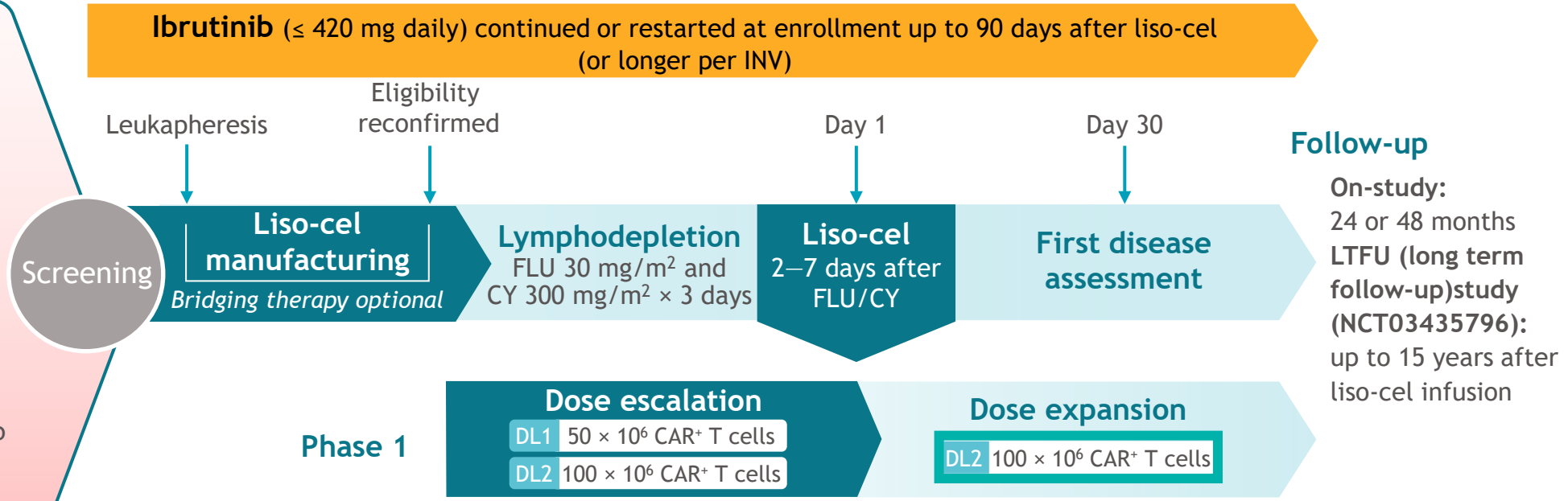
    1. **Can help control CLL while the product is being manufactured.**
    2. **Mitigates the CRS (cytokine release syndrome).**
    3. **Improves T cell function making the CAR-T better “killers”.**

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

PHASE 1/2 TRANSCEND CLL 004 STUDY: LISO-CEL + IBRUTINIB COMBINATION COHORT

Key eligibility criteria for liso-cel plus ibrutinib cohort

- Age ≥ 18 years
- R/R CLL/SLL
- ECOG PS 0–1
- Adequate organ function
- No active CNS involvement
- No Richter transformation
- Met ≥ 1 of the following:
  - Receiving BTKi with progression at study entry
  - High-risk features with < CR after ≥ 6 mo on BTKi
  - *BTK*/*PLCγ2* mutation[a] ± ibrutinib progression
  - Prior BTKi with no contraindications to restart BTKi
- Progression on BTKi and received prior venetoclax (per amendment 5)



Follow-up

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

Primary endpoint (at DL2)

CR/CRi rate per iwCLL 2018 by INV assessment

Secondary endpoints

Safety (DL1 + DL2); ORR, DOR, DOCR, time to response, time to CR/CRi, PFS, OS, and uMRD4[b] rate in blood at DL2

Exploratory analyses

uMRD4[b] rate in marrow, cellular kinetics (CAR T cell expansion and persistence)

[a]Per local laboratory assessment; [b]MRD was assessed by next-generation sequencing using a clonoSEQ assay. Undetectable MRD was defined as < 1 CLL cell per 10,000 leukocytes at ≥ 1 time point after infusion (uMRD4). CY, cyclophosphamide; DOR, duration of response; DOCR, duration of continued CR after initial CR; FLU, fludarabine; INV, investigator; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; LTFU, long-term follow-up; uMRD4, undetectable minimal residual disease at < 1 in 10^{-4} leukocytes.

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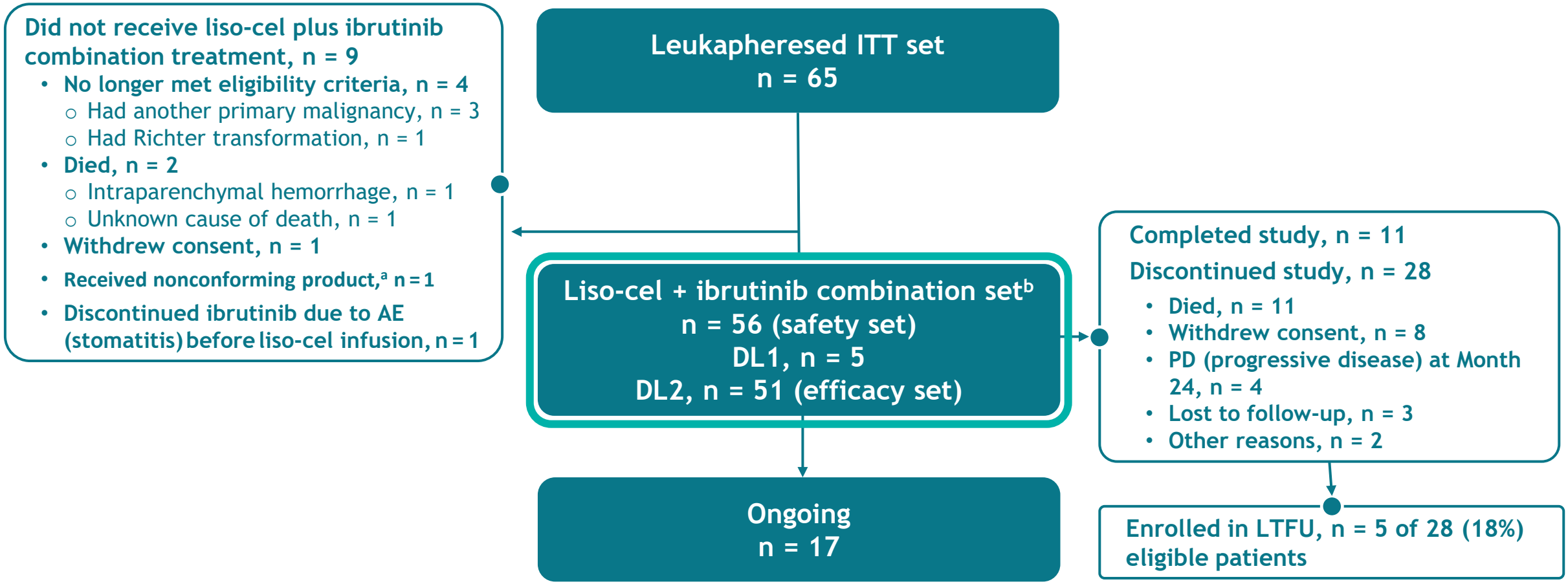
PATIENT DISPOSITION



[a]Defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but could be considered appropriate for infusion; the patient who received nonconforming product was not included in efficacy or safety analyses; [b]All combination–treated patients were efficacy evaluable, defined as all patients who received liso-cel and ≥ 1 dose of ibrutinib who also met the following baseline criteria: 1) had measurable disease present before liso-cel administration based on INV assessment; 2) did not develop Richter transformation or MCL before liso-cel infusion; and 3) for those receiving bridging therapy, patients had baseline disease assessments completed and had measurable disease present on baseline disease assessment after bridging therapy and before liso-cel administration.

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DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	DL2 + ibrutinib set (n = 51)	Total liso-cel + ibrutinib combination set (n = 56)
Median (range) age, y	65 (44—77)	65 (44—77)
Median (range) prior lines of systemic therapy	**5 (1—13)**	**5 (1—13)**
≤ 3 prior therapies, n (%)	19 (37)	20 (36)
Prior BTKi, n (%)	51 (100)	56 (100)
Prior venetoclax, n (%)	39 (76)	42 (75)
Prior BTKi and venetoclax, n (%)	39 (76)	42 (75)
BTKi progression/venetoclax failure,[a] n (%)	**28 (55)**	**31 (55)**
High-risk cytogenetics, n (%)	50 (98)	55 (98)
Del(17p)	23 (45)	25 (45)
Mutated *TP53*	23 (45)	24 (43)
Unmutated IGHV	37 (73)	39 (70)
Complex karyotype[b]	25 (49)	29 (52)
Bulky disease (≥ 5 cm) per INV before LDC,[c] n (%)		
Yes	18 (35)	18 (32)
Unknown	4 (8)	5 (9)
Median (range) SPD per INV before LDC,[d] cm^2	29 (1—218)	27 (1—218)
LDH ≥ ULN before LDC, n (%)	22 (43)	24 (43)
Received bridging therapy (in addition to ibrutinib),[e] n (%)	13 (25)	16 (29)

- Median (range) ibrutinib exposure was 34 days (15—188) before and 95 days (6—1517) after liso-cel in the total combination-treated set
- Liso-cel was manufactured for 63/65 (97%) patients in the leukapheresed set
  - Median (range) time from leukapheresis to liso-cel availability was 25 (17—79) days (n = 62)

[a]Includes patients who progressed on a BTKi and met 1 of the following criteria: 1) discontinued venetoclax due to disease progression or intolerability and the patient's disease met indications for further treatment per iwCLL 2018 criteria or 2) failed to achieve an objective response within 3 months of initiating therapy; [b]At least 3 chromosomal aberrations; [c]At least 1 lesion with a longest diameter ≥ 5 cm; [d]Forty-seven patients at DL2 and 51 patients in the total combination-treated set had SPD measurements; [e]Included other anticancer therapies in addition to concurrent ibrutinib treatment given for disease control during liso-cel manufacturing. IGHV, immunoglobulin heavy-chain variable region; LDC, lymphodepleting chemotherapy; SPD, sum of the product of perpendicular diameters.

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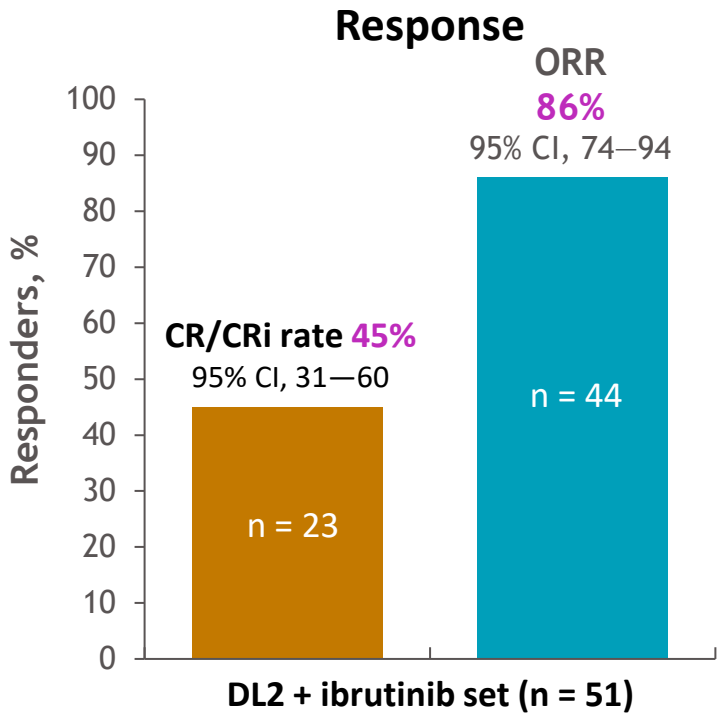
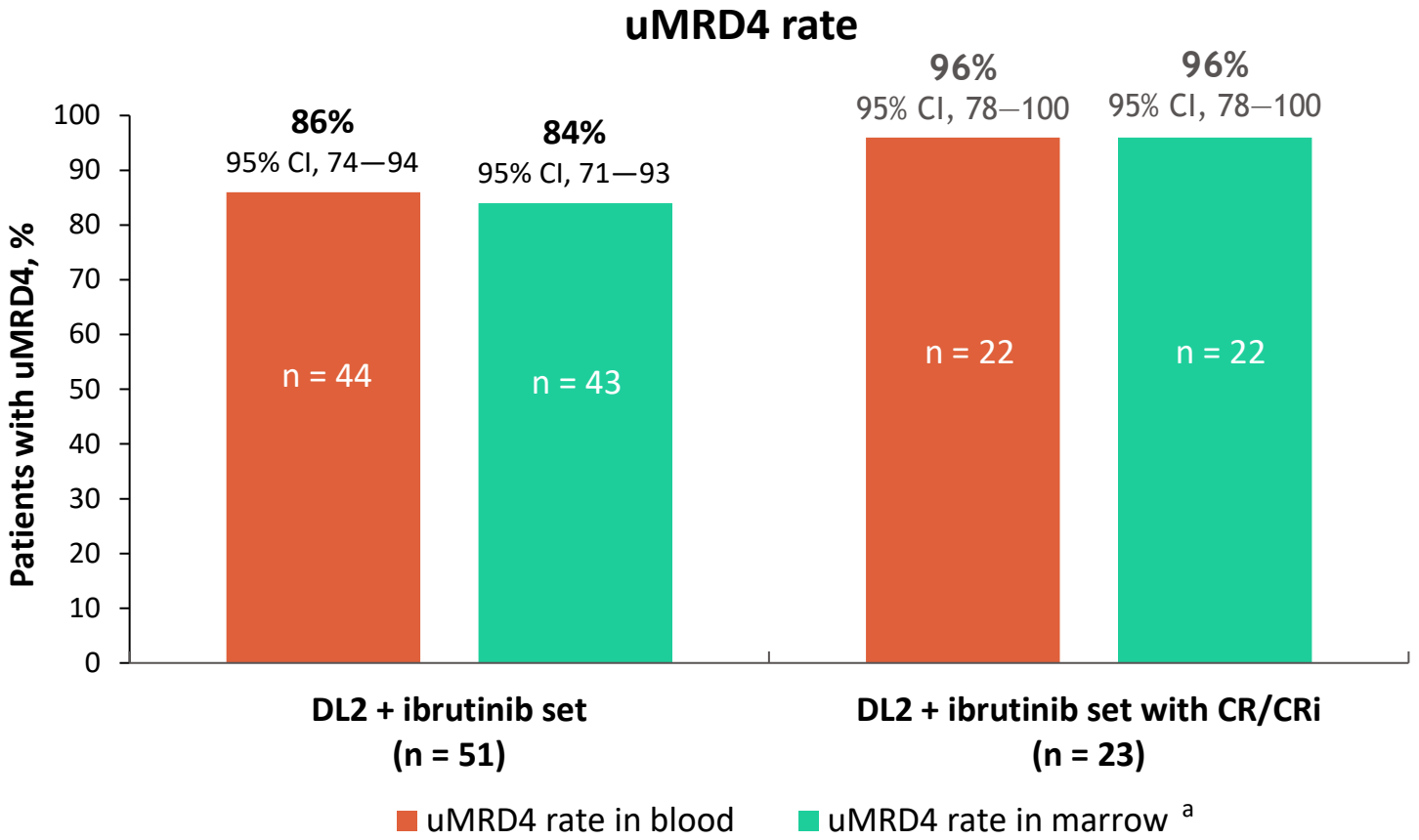
EFFICACY OUTCOMES: RESPONSE BY INVESTIGATOR AND uMRD4

- Median (range) 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)





[a]Forty-nine patients (22 with CR/CRi) were evaluable for MRD in marrow.

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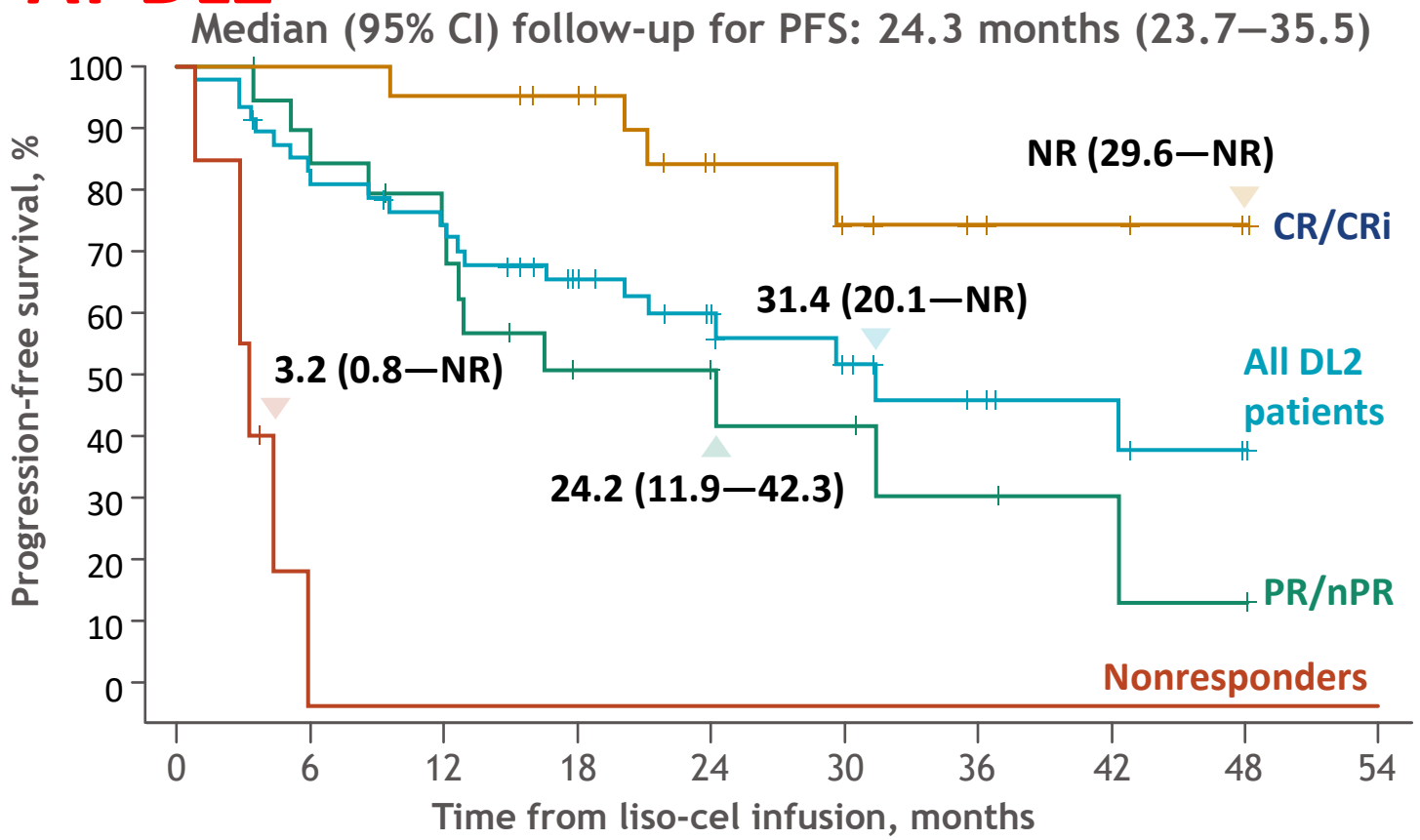
PROGRESSION-FREE SURVIVAL BY BEST OVERALL RESPPONSE AT DL2



No. at risk										
CR/CRi	23	23	22	20	12	7	5	4	2	0
PR/nPR	21	17	14	7	6	5	3	2	1	0
Nonresponders	7	0	0	0	0	0	0	0	0	0
All DL2 patients	51	40	36	27	18	12	8	6	3	0

	% 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)

Data on KM curves are expressed as median (95% CI). No formal landmarking analyses were conducted.

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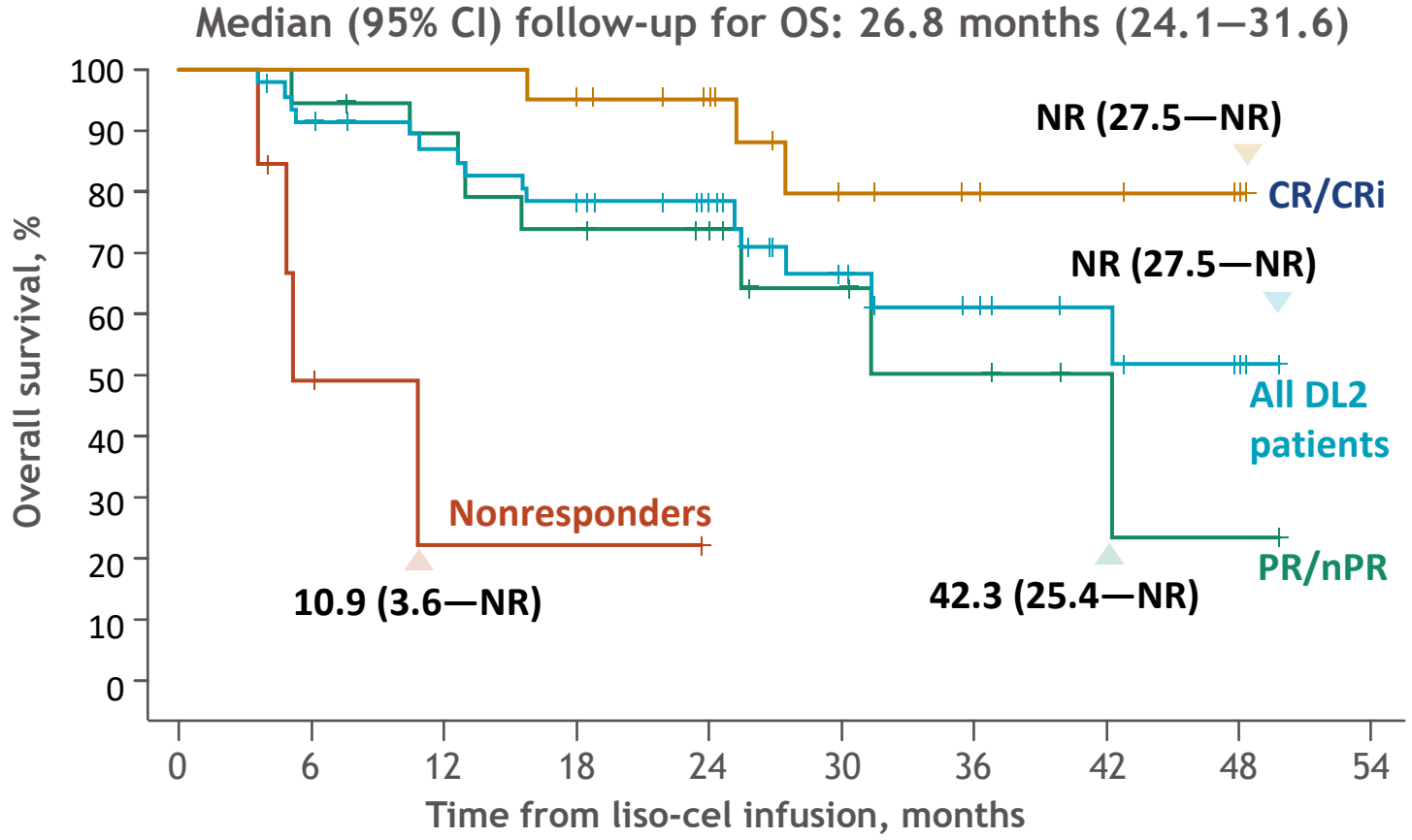
OVERALL SURVIVAL BY BEST OVERALL RESPONSE AT DL2



No. at risk										
CR/CRi	23	23	23	22	17	9	6	5	2	0
PR/nPR	21	20	18	15	12	6	4	2	1	0
Nonresponders	7	3	1	1	0	0	0	0	0	0
All DL2 patients	51	46	42	38	29	15	10	7	3	0

	% survival (95% CI)	
	12 months	24 months
All DL2 patients (n = 51)	88 (75—94)	80 (65—88)
Patients with CR/CRi (n = 23)	100 (NR—NR)	96 (73—99)

Data on KM curves are expressed as median (95% CI). No formal landmarking analyses were conducted.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

SAFETY: MOST COMMON TEAEs[a]

	Total combination-treated set (n = 56)	
	Any grade	Grade ≥ 3
Any liso-cel—related TEAE, n (%)	54 (96)	32 (57)
TEAEs in ≥ 20% of patients		
CRS[b]	45 (80)	2 (4)
Anemia	13 (23)	13 (23)
Neutropenia	13 (23)	12 (21)
Pyrexia	12 (21)	0
Any ibrutinib-related TEAE, n (%)	38 (68)	24 (43)
TEAEs in ≥ 15% of patients		
Neutropenia	11 (20)	11 (20)
Anemia	10 (18)	7 (12.5)

	Total combination-treated set (n = 56)	
	Any grade	Grade ≥ 3
Any TEAE, n (%)	56 (100)	48 (86)
TEAEs in ≥ 25% of patients		
CRS	45 (80)	2 (4)
Neutropenia	30 (54)	29 (52)
Anemia	29 (52)	23 (41)
Fatigue	22 (39)	1 (2)
Headache	22 (39)	0
Diarrhea	21 (37.5)	0
Nausea	18 (32)	0
Hypokalemia	15 (27)	0
Pyrexia	15 (27)	0
Thrombocytopenia	15 (27)	10 (18)

- There were no grade 5 TEAEs
- Ibrutinib-related grade ≥ 3 cardiovascular TEAEs of hypertension (7%) and atrial fibrillation (2%) were observed

All percentages are rounded to whole numbers except those with ".5%".

[a]TEAE was defined as an AE that started within 90 days from initiation of liso-cel administration, or within 30 days after completing ibrutinib, whichever ended the latest; [b]Graded based on Lee 2014 criteria. TEAE, treatment-emergent adverse event.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

SAFETY: OTHER AEs OF SPECIAL INTEREST AND DEATHS

	Total combination-treated set (n = 56)
Prolonged cytopenia,[a] n (%)	25 (45)
Recovered to grade ≤ 2 by Day 90[b]:	
Hemoglobin	3/3 (100)
Neutrophils	14/20 (70)
Platelets	14/14 (100)
Grade ≥ 3 infections,[c] n (%)	8 (14)
Tumor lysis syndrome, n (%)	1 (2)
Second primary malignancy,[d] n (%)	5 (9)
Macrophage activation syndrome, n (%)	1 (2)

Deaths (all > 90 days after infusion), n = 16

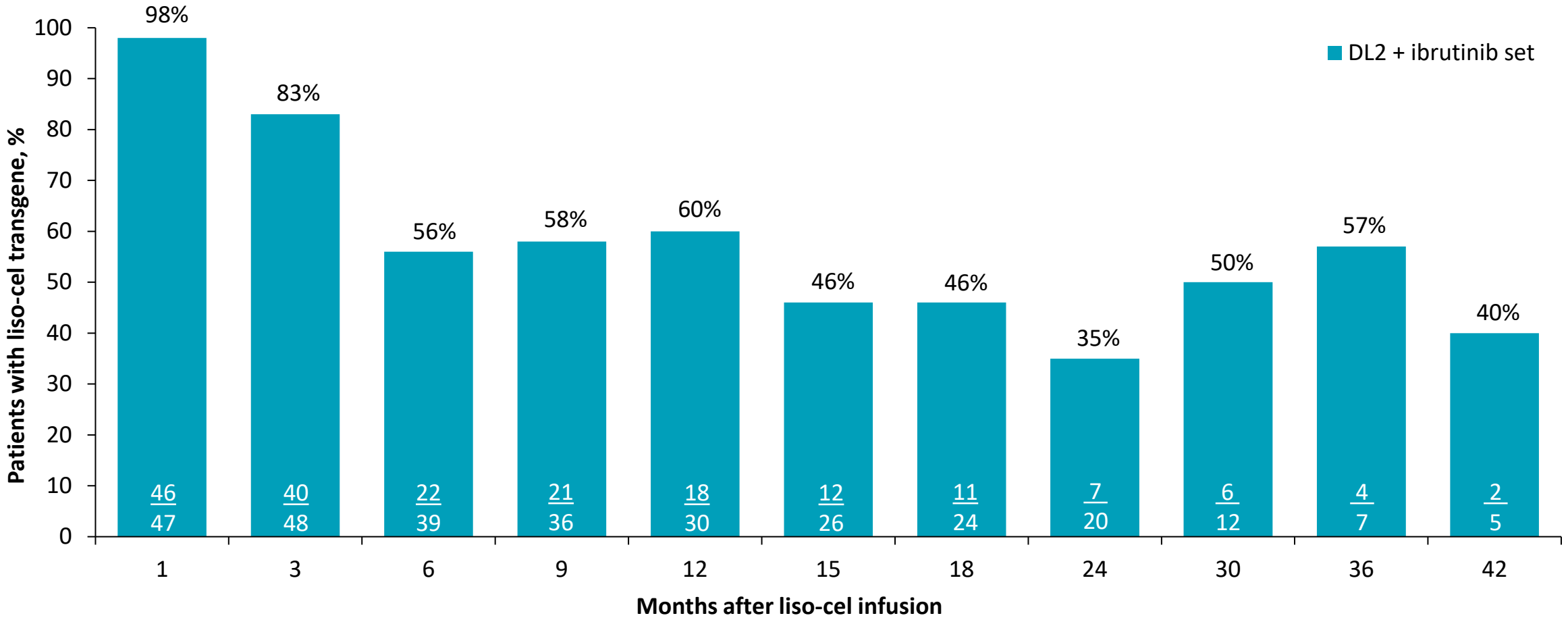
- PD, n = 6
- Unknown,[e] n = 6
- COVID-19, n = 3
- Mixed septic/cardiogenic shock, n = 1

[a]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia at Day 30 after liso-cel infusion; [b]Percentages are calculated out of patients with prolonged cytopenia at Day 30 and with lab results after Day 30; [c]Includes grade ≥ 3 TEAEs from infections and infestations (System Organ Class) by AE high-level group term; [d]AEs from the 90-day treatment-emergent period, posttreatment-emergent period, and LTFU were included; included events of malignant-papillary urothelial carcinoma (n = 1), squamous cell carcinoma of the tonsil (n = 1), squamous cell carcinoma and myelodysplastic syndrome (n = 1), squamous cell carcinoma, skin (n = 1), and basal cell carcinoma (n = 1); [e]Due to withdrawal of consent (n = 3, including 2 patients with disease progression) and cause remains unidentified (n = 3).

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

LISO-CEL PERSISTENCE AT DL2

- Persistence of the liso-cel transgene was detected up to 42 months after liso-cel infusion



Data are number of patients with liso-cel persistence/number of patients with an available sample at the specific time point. Persistence was defined as a transgene count greater than or equal to the lower limit of detection (5 copies/reaction). Concentration values after the initiation of retreatment of liso-cel (including lymphodepletion) or after another anticancer treatment were excluded.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

SUMMARY

- **Combined liso-cel plus ibrutinib demonstrated substantial efficacy with deep, durable remissions in patients with R/R CLL/SLL**
  - **The primary endpoint of CR rate was 45%**
  - **Among secondary endpoints, ORR was 86%, blood uMRD4 rate was 86%, and median DOR was 41.4 months**
- **Safety was manageable with no new safety signals observed, AEs typically of limited duration, and low grade ≥ 3 CRS/NE rates**
  - **Severe cardiovascular events remained infrequent with combination treatment**
  - **There were no early deaths within 3 months of liso-cel infusion**
- **Statistical analyses are currently underway to evaluate liso-cel monotherapy versus combination treatment**
- **These results support combination therapy with liso-cel plus ibrutinib as a promising new therapeutic option and, in conjunction with the efficacy and safety of liso-cel as monotherapy, further demonstrate the effectiveness of liso-cel in patients with R/R CLL/SLL**

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

Epcoritamab Monotherapy in Patients (Pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from CLL Expansion and Optimization Cohorts of EPCORE CLL-1

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ASH 2024, Abstract 883

Presented at the American Society of Hematology Annual Meeting; December 7–10, 2024; San Diego, CA

BACKGROUND

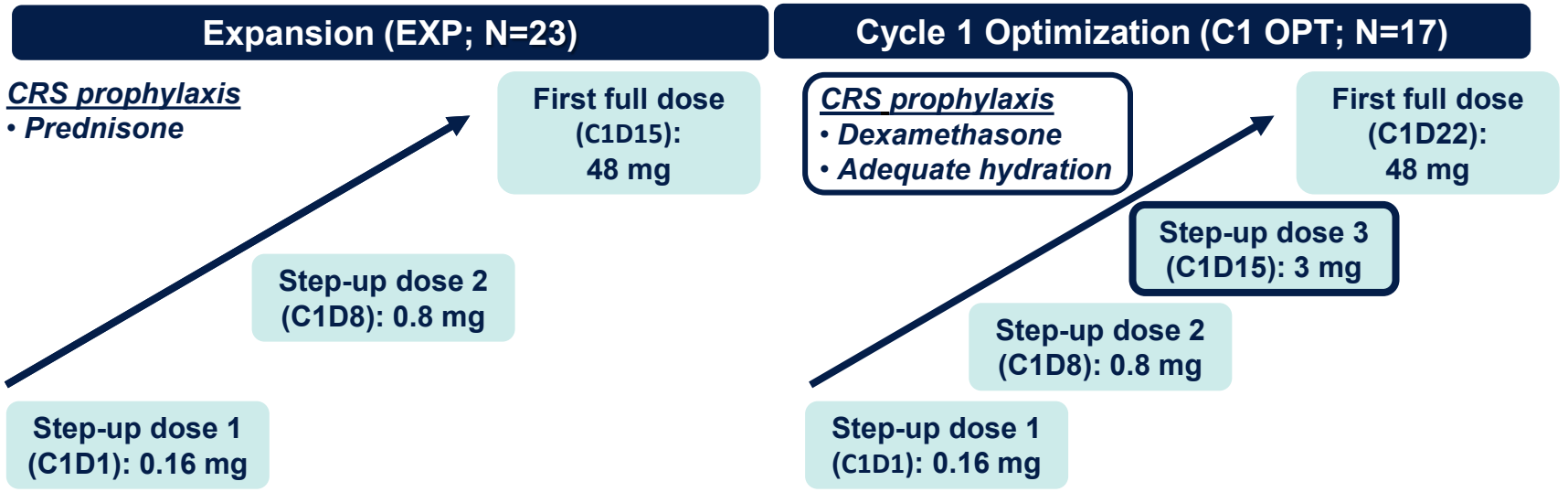
- **Novel treatment options are needed for patients with R/R CLL**
- **Patients with CLL refractory to both a BTK and a BCL-2 inhibitor have a poor prognosis and limited treatment options[1]**
  - **Novel approaches such as CAR T cell therapy offer limited benefits, with complete response rates <20%, indicating a need for novel, effective treatments[2]**
- **Epcoritamab is a subcutaneous CD3xCD20 bispecific antibody**
  - **Approved[a] as monotherapy for the treatment of adults with different types lymphoma**
- **Initial data from EPCORE CLL-1 have shown encouraging efficacy in both R/R CLL and Richter's transformation[5,6]**
  - **Safety was manageable; however, ongoing efforts aim to reduce incidence and severity of CRS and ICANS (Immune effector cell-associated neurotoxicity syndrome)**
- **Results from the CLL expansion cohort and preliminary results from the cycle 1 (C1) optimization part**

[a]Approved in the US and Europe for the treatment of adults with R/R DLBCL, HGBCL (US only), and FL after ≥2 lines of systemic therapy. **1.** Martens AWJ, et al. *Leukemia*. 2023;37:606-16. **2.** Siddiqi T, et al. *Lancet*. 2023;402:641-54. **3.** EPKINLY [prescribing information]. Plainsboro, NJ: Genmab US, Inc.; 2024. **4.** Tepkinly [summary of product characteristics]. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG; 2024. **5.** Kater AP, et al. ASH 2021. Abstract 2627. **6.** Kater AP, et al. ASH 2022. Abstract 348.

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 $\geq 5 \times 10^9$/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

ClinicalTrials.gov: NCT04623541; EudraCT: 2023-504828-25.

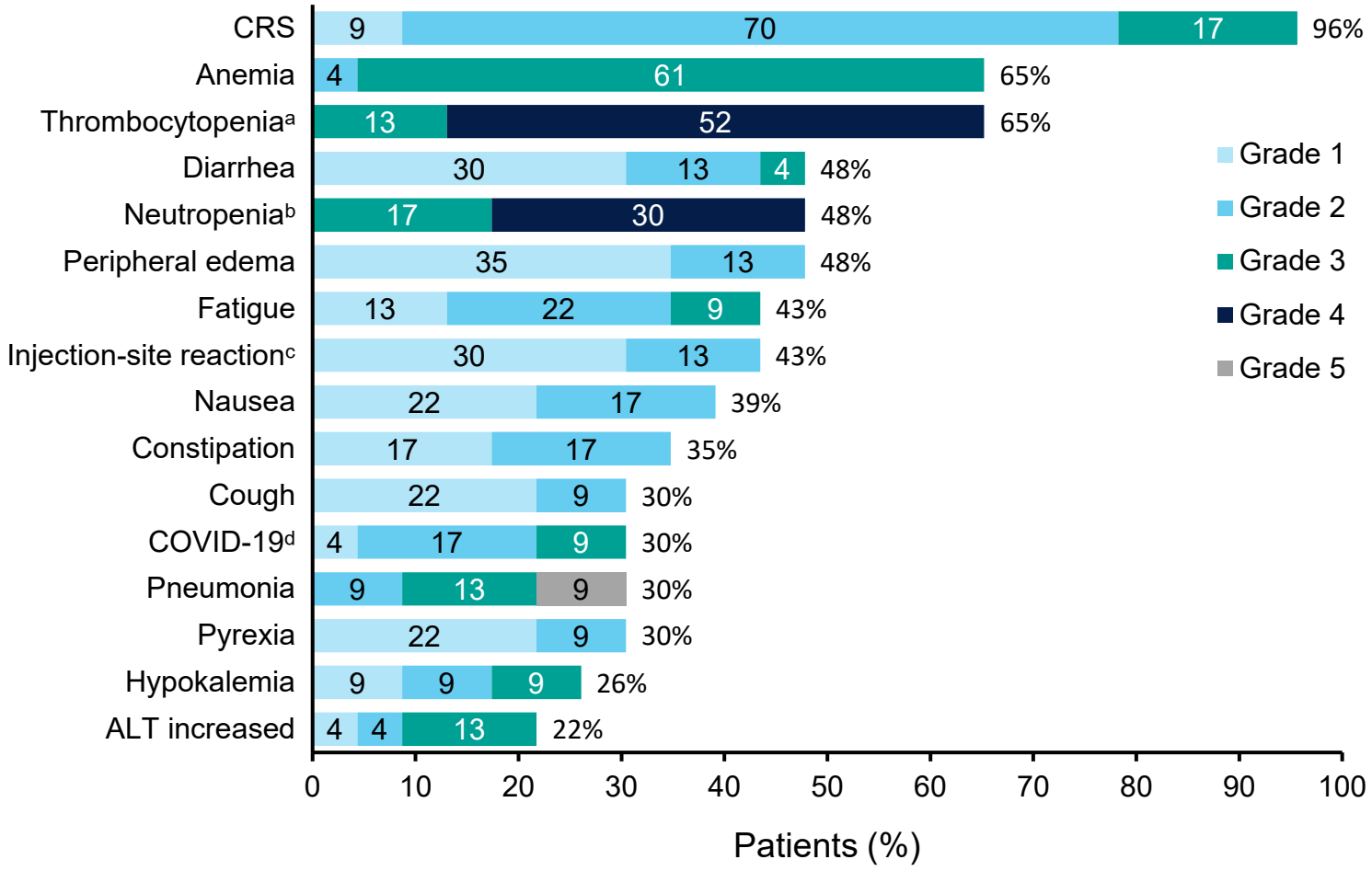
COMPARABLE HIGH-RISK R/R CLL POPULATIONS BETWEEN EXP AND C1 OPT

Characteristic	EXP N=23	C1 OPT N=17
Median age, years (range)	72 (55–83)	68 (56–81)
Male sex at birth, n (%)	17 (74)	14 (82)
Race, n (%)[a]		
White	19 (83)	14 (82)
Black or African American	0	1 (6)
Not reported	3 (13)	2 (12)
CLL characteristics (local lab), n (%)		
High risk		
Rai stage III–IV[b]	13 (57)	10 (59)
Binet stage C[c]	2 (9)	6 (35)
Beta-2 microglobulin >3.5 mg/L	19 (83)	10 (59)
IGHV unmutated	16 (70)	12 (71)
Unknown	3 (13)	3 (18)
TP53 aberration	15 (65)	10 (59)
Unknown	2 (9)	2 (12)

Treatment History	EXP N=23	C1 OPT N=17
Median time from initial diagnosis to first dose, **years** (range)	13 (6–19)	11 (6–18)
Median time from last treatment to first dose, **months** (range)	0.7 (0.1–49.4)	1.6 (−0.7–39.6)
Median number of prior lines of therapy (range)	**4 (2–10)**	**4 (2–10)**
≥4 prior lines of therapy, n (%)	14 (61)	9 (53)
Prior therapy, n (%)[d]	23 (100)	17 (100)
Chemoimmunotherapy	23 (100)	12 (71)
Small molecules		
BTK inhibitor[e]	23 (100)	17 (100)
Pirtobrutinib	1 (4)	5 (29)
Refractory to BTK inhibitor	20 (87)	16 (94)
BCL-2 inhibitor	19 (83)	15 (88)
Discontinuation due to progression	10 (43)	10 (59)
Relapsed <12 months from last dose	3 (13)	4 (24)

[a]Race was reported as other for 1 patient in EXP. Ethnicity was reported as Hispanic or Latino for 1 patient in EXP and 1 patient in C1 OPT. Ethnicity was not reported or missing for 17 patients in EXP and 11 patients in C1 OPT. [b]In EXP, Rai staging was performed for 16 patients, and Rai stage was I–II for 3 patients; in C1 OPT, Rai stage was 0 for 1 patient, I–II for 5 patients, and unknown for 1 patient. [c]In EXP, Binet staging was performed for 7 patients, and Binet stage was A for 1 patient and B for 4 patients; in C1 OPT, Binet staging was performed for 14 patients, and Binet stage was A for 2 patients and B for 6 patients. [d]Three patients had received prior CAR T-cell therapy (EXP, n=1; C1 OPT, n=2). [e]All patients received a covalent BTK inhibitor.

TREATMENT-EMERGENT AEs (>20%) IN EXP

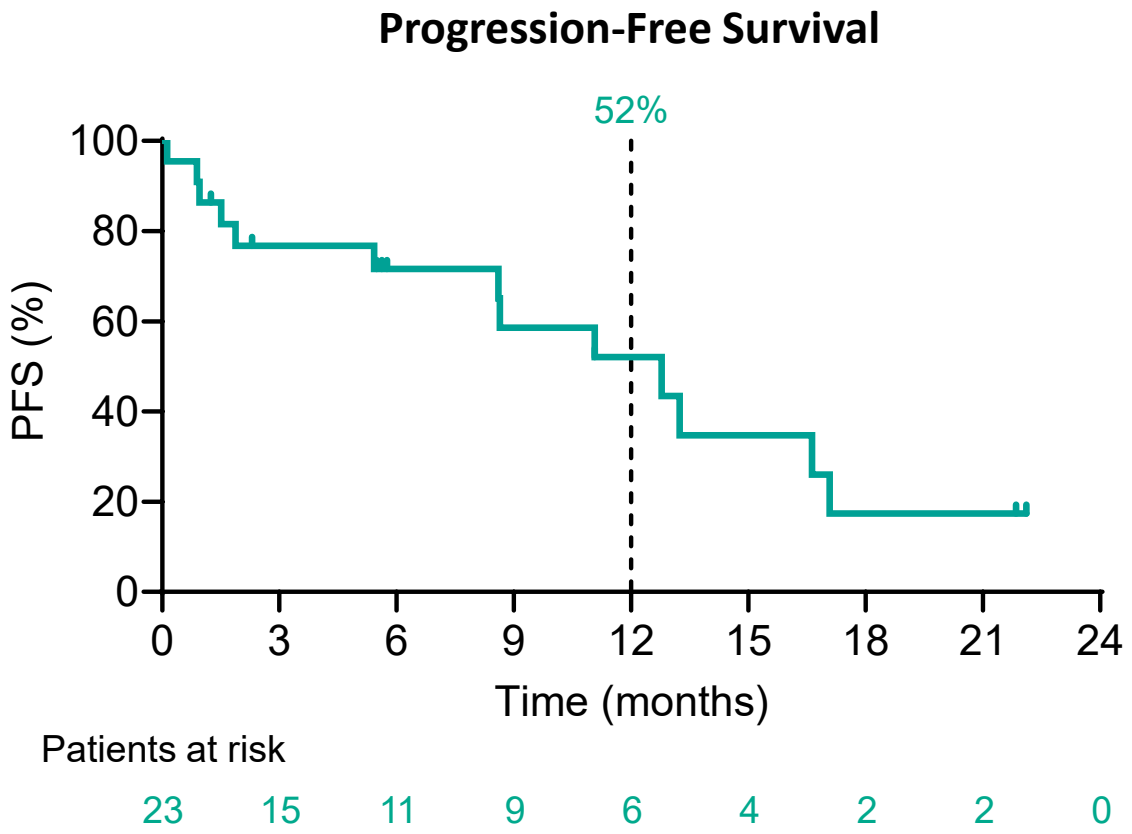


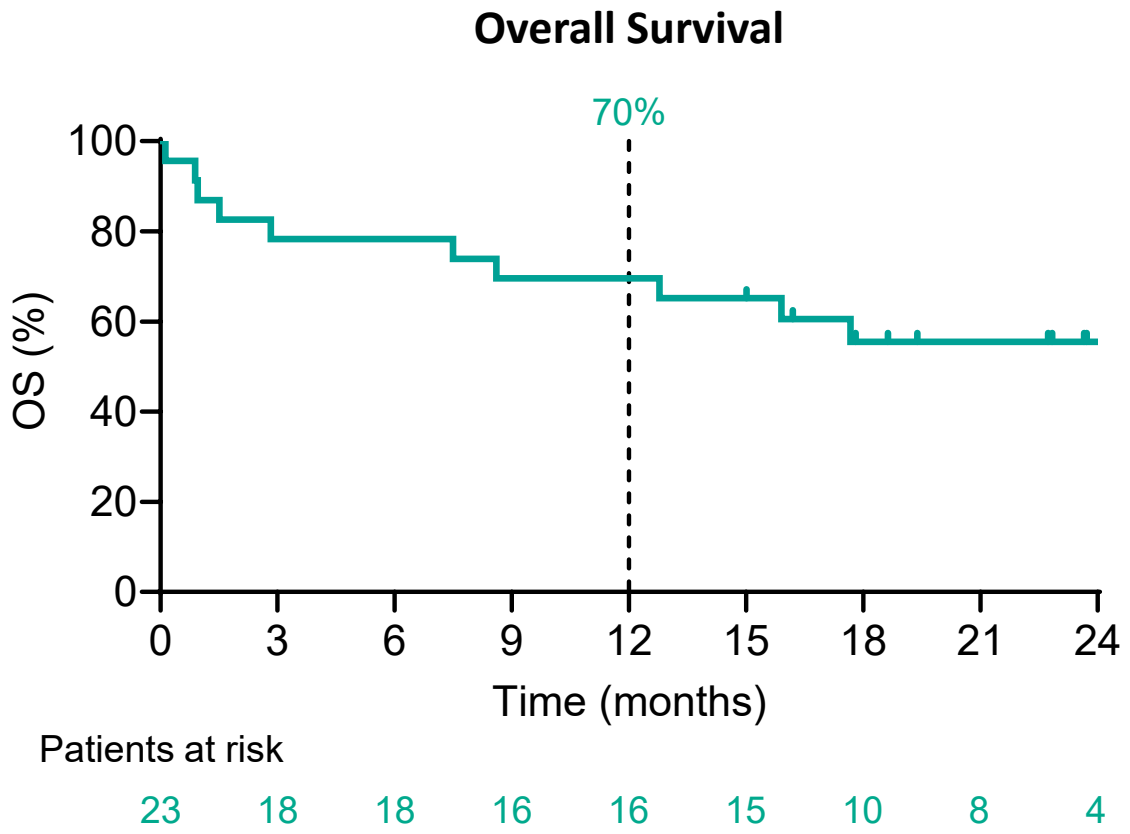
Patients With ≥1 Event, n (%)	EXP N=23
Anemia	15 (65)
At study entry	14 (61)
In first 8 weeks	15 (65)
Thrombocytopenia	15 (65)
At study entry	14 (61)
In first 8 weeks[a]	14 (61)
Neutropenia	11 (48)
At study entry	1 (4)
In fst 8 weeks[b]	11 (48)

- 4 fatal TEAEs[e] occurred in EXP; none occurred in C1 OPT

[a]Combined term includes thrombocytopenia and decreased platelet count. [b]Combined term includes neutropenia, decreased neutrophil count, and febrile neutropenia. Three patients had febrile neutropenia (EXP, n=2 [grades 1 and 3]; C1 OPT, n=1 [grade 3]). [c]Combined term includes injection-site reaction, bruising, erythema, rash, and swelling. [d]Combined term includes COVID-19 and COVID-19 pneumonia. [e]Fatal TEAEs were pneumonia (n=2), sepsis (n=1), and squamous cell carcinoma of the skin (n=1); 1 case of pneumonia was considered related to epcoritamab.

PROGRESSION-FREE AND OVERALL SURVIVAL IN EXP





- Median PFS was 12.8 months (95% CI, 5.4–17.1); median OS was not reached (95% CI, 8.6 months–NR)

Kaplan–Meier estimates are shown.

CONCLUSION

- **Subcutaneous epcoritamab monotherapy led to deep responses in patients with heavily pretreated R/R CLL in the EXP cohort, regardless of high-risk features**
  - 61% ORR and 39% CR rate in full analysis set
  - uMRD4 in 75% of evaluable responders and 100% of evaluable complete responders
- **Simple C1 OPT measures of an additional step-up dose, dexamethasone, and adequate hydration led to decreased risk and severity of adverse events of special interest**
  - CRS was primarily grade 1 and there were no grade 3 CRS events
  - No cases of ICANS or clinical TLS reported
- **These results are highly encouraging given the hard-to-treat patient population**
- **The EPCORE CLL-1 trial (NCT04623541) is currently enrolling and evaluating epcoritamab as monotherapy and in combination for patients with CLL**

Viral Particles Used In Vivo CAR T in NHP or Non-Human Primates (macaw monkeys)

- **Autologous CAR T cell therapy has transformed the treatment of hematologic malignancies, driving durable responses in patients refractory to conventional therapies**
- **However, multiple challenges including complex manufacturing, high cost, and toxic pre- conditioning regimens limits access to these therapies**
- **The VivoVec platform is designed to overcome these challenges and provide an off-the-shelf solution for generation of CAR T cells *in vivo***
- **We previously presented data demonstrating potent and specific generation of functional CAR T cells *in vivo* following intralymphatic delivery in immune competent NHPs (*Macaca nemestrina*)**
- **Following a single IV dose of VivoVec particles, CAR T cells are efficiently generated *in vivo*, expand in response to cognate antigen and eradicate target antigen expressing cells in the absence of lymphodepleting chemotherapy**

Viral Particles Used In Vivo CAR T in Non-Human Primates (macaw monkeys)

Results:

- **VivoVec was well-tolerated in all animals following delivery via both IV and injection into a lymph node with no evidence of toxicity associated within, or shortly after the period of administration**
- **Mild CRS was observed in association with CAR T cell expansions**
- **CD20 CAR T cells were detected in peripheral blood persisted for the duration of the study (28 days). When given IV, up to 42% of total T cells**
- **B-cell started disappearing on day 6- 7**

Viral Particles Used In Vivo CAR T in Non-Human Primates (macaw monkeys)

Conclusions:

- **VivoVecTM enables potent and specific generation of functional CAR T cells *in vivo* following delivery by intralymphatic and IV routes of administration in immune competent NHP models**
- **Peak CAR T expansion observed in NHP following VivoVec administration mirrors peak expansion of *ex vivo* manufactured CAR T cells in human patients**
- **Given the association between *ex vivo* CAR T expansion and efficacy, the results in NHP support potential VivoVec efficacy in human patients**
- **Importantly, the generation and expansion of CAR T cells occurs in the absence of lymphodepleting chemotherapy**
- **VivoVec represents a transformative therapeutic platform in oncology that has the potential to overcome many of the challenges associated with the current *ex vivo* CAR T cell approaches**

CLL SOCIETY

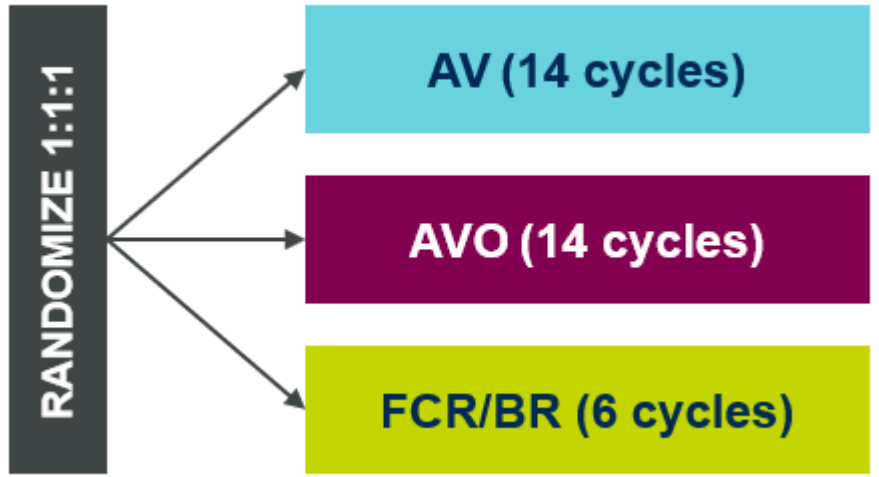
Smart Patients Get Smart Care™

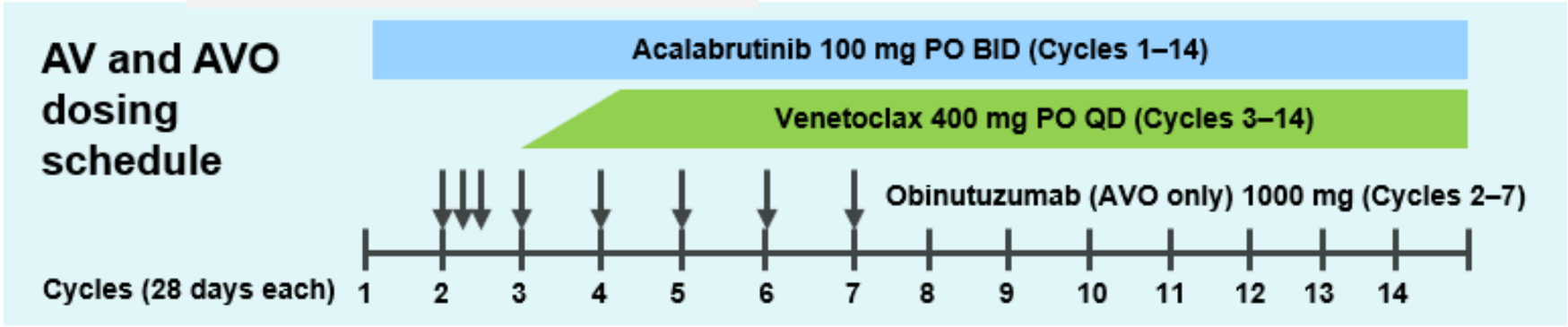
ASH 2024 COMES TO YOU

Nitin Jain, MD
Professor
Department of Leukemia
MD Anderson Cancer Center

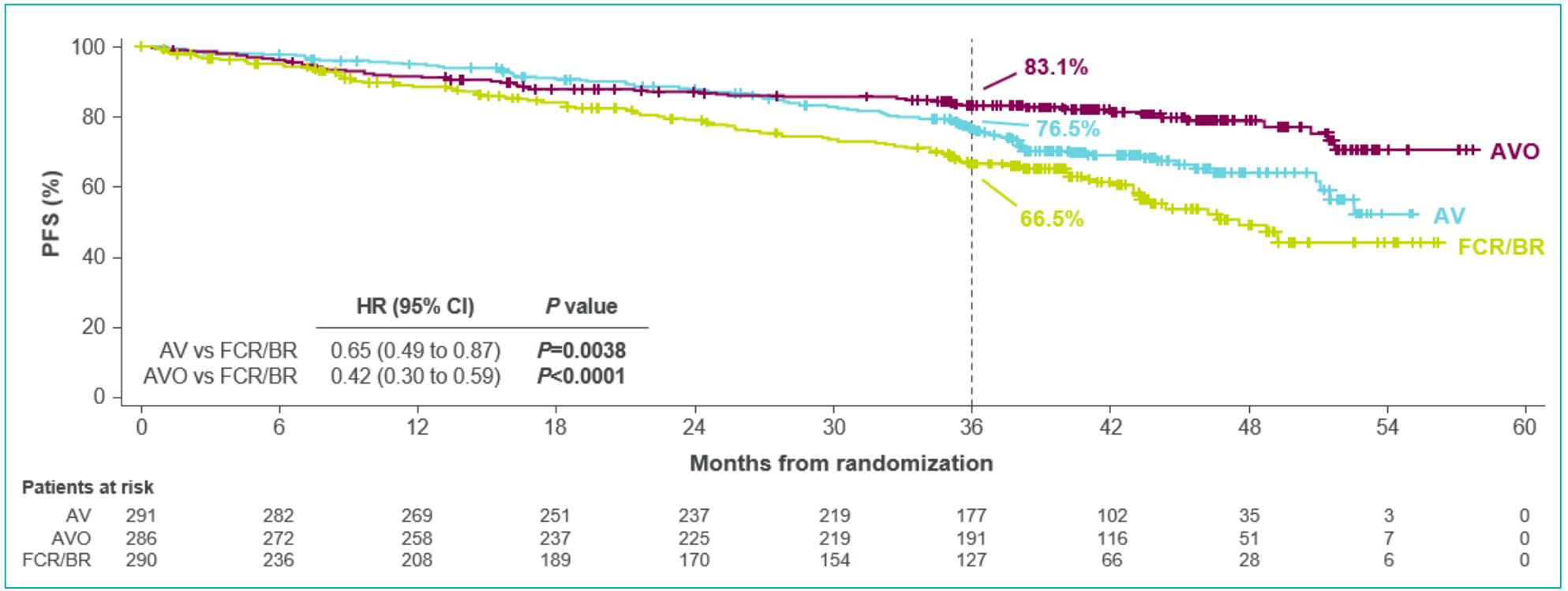
AMPLIFY TRIAL (ASH 2024)

- Age ≥18 years
- Previously untreated CLL requiring treatment per iwCLL 2018 criteria
- Without del(17p) or *TP53* mutation

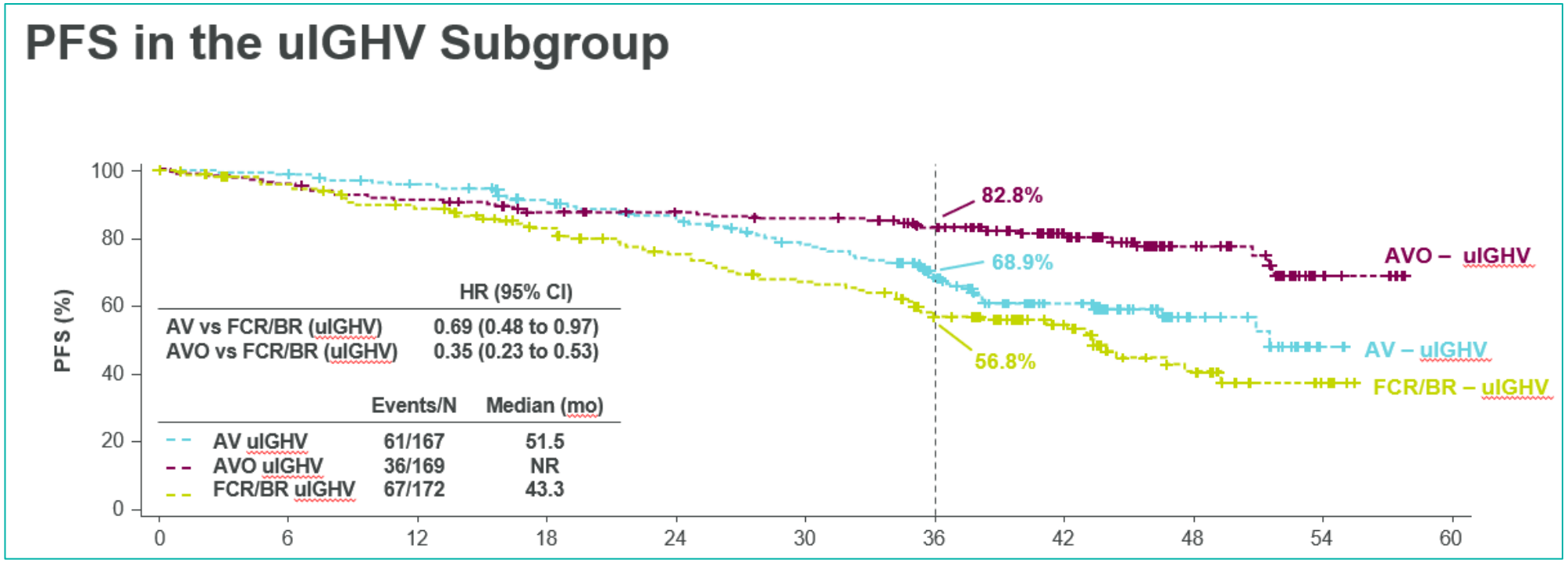




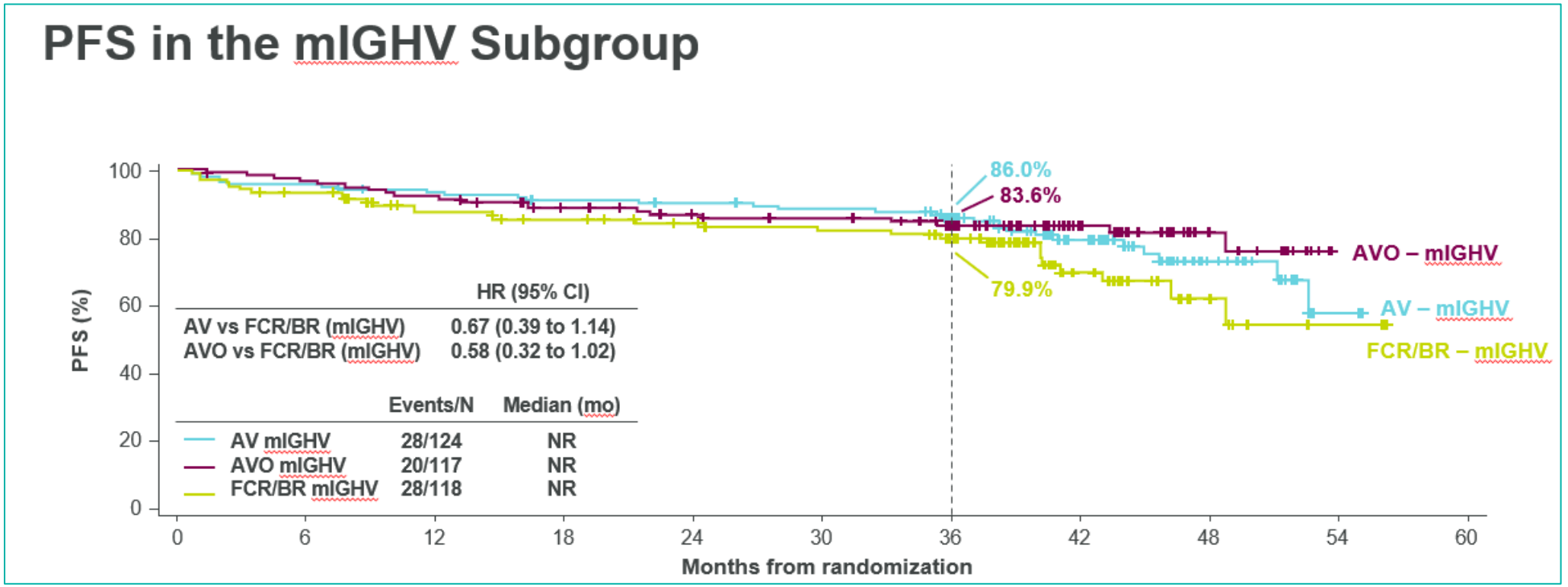
AMPLIFY: PFS (PROGRESSION FREE SURVIVAL)



PFS BY UNMUTATED IGHV



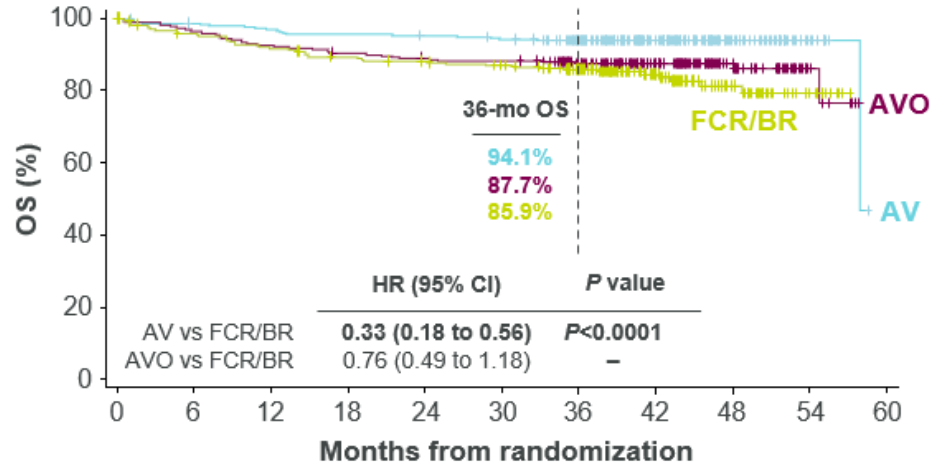
PFS BY MUTATED IGHV



AMPLIFY TRIAL: OS (OVERALL SURVIVAL)

Overall Survival

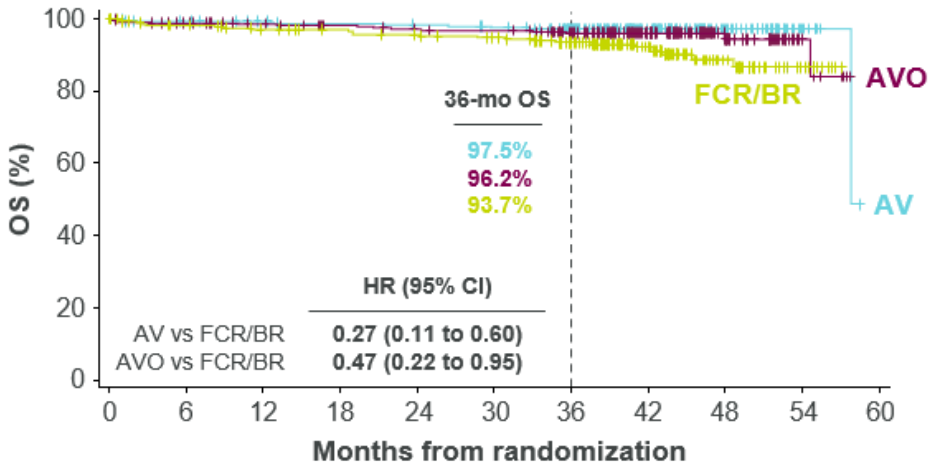
OS Prolonged With AV vs FCR/BR



Patients 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/BR	290	247	236	228	223	217	182	98	45	13	0

OS Prolonged With AV and AVO vs FCR/BR (COVID-19 Deaths Censored)



Patients at risk

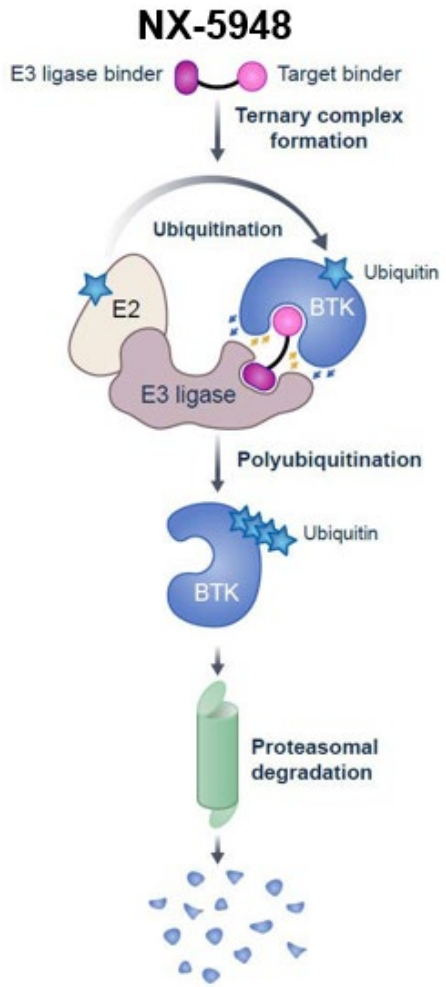
AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

TAKE HOME MESSAGES FROM AMPLIFY TRIAL

- First Phase 3 looking at second generation BTKi (acalabrutinib) with venetoclax as time-limited treatment
- Expected to lead to approval of acalabrutinib + venetoclax (+/- obinutuzumab)

BTK DEGRADER NX-5948 (HOW IT WORKS)



BASELINE DISEASE CHARACTERISTICS

MULTIPLE PRIOR LINES OF THERAPY AND HIGH PREVALENCE OF BASELINE MUTATIONS

Characteristics	Patients with CLL/SLL[a] (n=60)
ECOG PS, n (%)	
0	24 (40.0)
1	36 (60.0)
CNS involvement, n (%)	5 (8.3)
Median prior lines of therapy (range)	4.0 (1–12)
Previous treatments[b], n (%)	
BTKi	59 (98.3)
cBTKi	59 (98.3)
ncBTKi[c]	17 (28.3)
BCL2i	50 (83.3)
BTKi and BCL2i	49 (81.7)
CAR-T therapy	3 (5.0)
Bispecific antibody	4 (6.7)
PI3Ki	18 (30.0)
Chemo/chemo-immunotherapies (CIT)	43 (71.7)
Mutation status[d] (n=57), n (%)	
TP53	23 (40.4)
BTK	22 (38.6)
PLCG2	7 (12.3)
BCL2	6 (10.5)

[a]Baseline disease characteristics in CLL cohort were comparable to those in the overall population; [b]Patients could have received multiple prior treatments; [c]All patients who received ncBTKi have also previously received cBTKi; [d]Mutations presented here were centrally sequenced.

BCL2, B-cell lymphoma 2; **BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CAR-T**, chimeric antigen receptor T-cell; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group (ECOG) performance status; **ncBTKi**, non-covalent BTKi; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2; **SLL**, small lymphocytic lymphoma

Data cutoff: 10 Oct 2024

NX-5948 SAFETY PROFILE

TEAEs IN ≥10% OF OVERALL POPULATION OR GRADE ≥3 TEAEs OR SAEs IN >1 PATIENT

TEAEs, n (%)	Patients with CLL/SLL (n=60)			Overall population (N=125)		
	Any grade	Grade ≥3	SAEs	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	22 (36.7)	–	–	42 (33.6)	–	–
Fatigue[b]	16 (26.7)	–	–	29 (23.2)	2 (1.6)	–
Petechiae	16 (26.7)	–	–	28 (22.4)	–	–
Thrombocytopenia[c]	10 (16.7)	1 (1.7)	–	26 (20.8)	7 (5.6)	–
Rash[d]	14 (23.3)	1 (1.7)	1 (1.7)	24 (19.2)	2 (1.6)	1 (0.8)
Neutropenia[e]	14 (23.3)	11 (18.3)	–	23 (18.4)	18 (14.4)	–
Anemia	11 (18.3)	4 (6.7)	–	21 (16.8)	10 (8.0)	–
Headache	10 (16.7)	–	–	21 (16.8)	1 (0.8)	1 (0.8)
COVID-19[f]	10 (16.7)	–	–	19 (15.2)	2 (1.6)	2 (1.6)
Diarrhea	12 (20.0)	1 (1.7)	–	18 (14.4)	1 (0.8)	–
Cough	9 (15.0)	–	–	16 (12.8)	1 (0.8)	–
Pneumonia[g]	4 (6.7)	2 (3.3)	2 (3.3)	10 (8.0)	6 (4.8)	6 (4.8)
Lower respiratory tract infection	3 (5.0)	1 (1.7)	1 (1.7)	9 (7.2)	3 (2.4)	2 (1.6)
Fall	1 (1.7)	1 (1.7)	1 (1.7)	8 (6.4)	2 (1.6)	2 (1.6)
Hypertension	2 (3.3)	1 (1.7)	–	7 (5.6)	5 (4.0)	–
Hyponatremia	–	–	–	3 (2.4)	2 (1.6)	–
Pulmonary embolism	1 (1.7)	1 (1.7)	1 (1.7)	2 (1.6)	2 (1.6)	2 (1.6)
Subdural hematoma	1 (1.7)	–	1 (1.7)	2 (1.6)	1 (0.8)	2 (1.6)

- Tolerable safety profile consistent with prior disclosures
- 1 case of Grade 1 AFib in a CLL patient with pre-existing AFib
- 6 TEAEs resulted in drug discontinuation (1 CLL; 5 NHL)
- 2 Grade 5 AEs (1 pulmonary embolism; 1 case pending) deemed not related to NX-5948

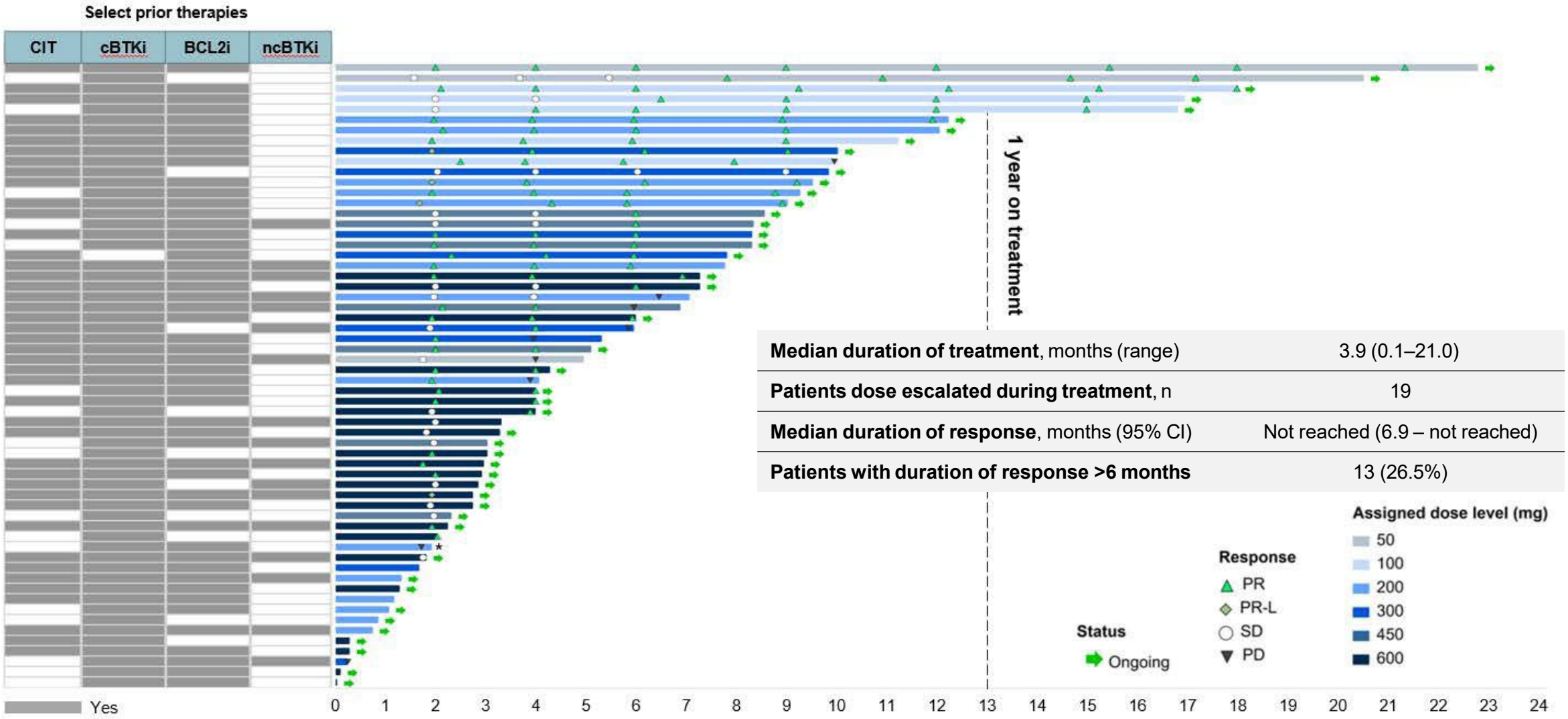
[a]Purpura/contusion includes episodes of contusion or purpura; [b]Fatigue was transient; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [e]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [f]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'; [g]Aggregate of 'pneumonia' and 'pneumonia klebsiella'

AE, adverse event; **AFib**, atrial fibrillation; **CLL**, chronic lymphocytic leukemia; **NHL**, non-Hodgkin's lymphoma; **SAE**, serious adverse event; **SLL**, small lymphocytic lymphoma; **TEAE**, treatment emergent AE

Data cutoff: 10 Oct 2024

NX-5948 DURATION OF TREATMENT

DURABLE RESPONSES REGARDLESS OF PRIOR THERAPY



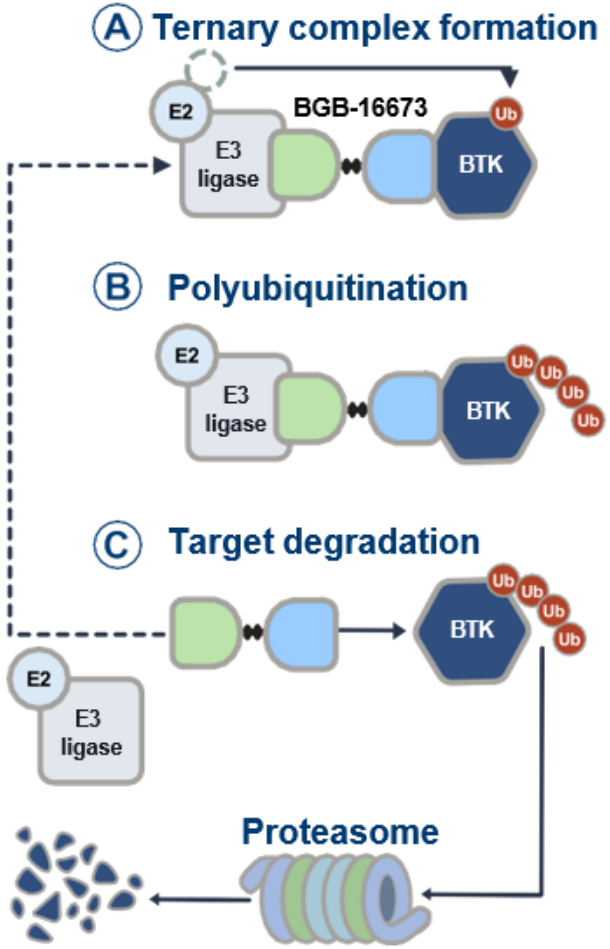
Median duration of treatment, months (range)	3.9 (0.1–21.0)
Patients dose escalated during treatment, n	19
Median duration of response, months (95% CI)	Not reached (6.9 – not reached)
Patients with duration of response >6 months	13 (26.5%)

*Patient with Richter's transformation to Hodgkin's on biopsy

BCL2i, BCL2 inhibitor; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CIT**, chemo/chemo-immunotherapies; **ncBTKi**, non-covalent BTKi; **PD**, progressive disease; **PR**, partial response; **PR-L**, PR with rebound lymphocytosis; **SD**, stable disease; **CI**, confidence interval

Data cutoff: 10 Oct 2024

BTK DEGRADER BGB-16673 (HOW IT WORKS)



BASELINE PATIENT CHARACTERISTCS

HEAVILY PRE-TREATED, WITH HIGH-RISK CLL FEATURES

	Total (N=60)
Age, median (range), years	70 (50-91)
Male, n (%)	39 (65.0)
ECOG PS, n (%)	
0	34 (56.7)
1	25 (41.7)
2	1 (1.7)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	27/56 (48.2)
Unmutated IGHV	38/46 (82.6)
del(17p) and/or *TP53* mutation	40/60 (66.7)
Complex karyotype (≥3 abnormalities)	19/38 (50.0)

	Total (N=60)
Mutation status, n/N (%)	
BTK mutation present	18/54 (33.3)
PLCG2 mutation present	8/54 (14.8)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	43 (71.7)
cBTK inhibitor	56 (93.3)
ncBTK inhibitor	13 (21.7)
BCL2 inhibitor	50 (83.3)
cBTK + BCL2 inhibitors	38 (63.3)
cBTK + ncBTK + BCL2 inhibitors	12 (20.0)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	50/56 (89.3)

Data cutoff: September 2, 2024.

[a] Remaining 6 patients discontinued prior BTK inhibitor due to toxicity (n=3), treatment completion (2), and other (n=1).

cBTK, covalent BTK; ncBTK, noncovalent BTK.

SAFETY SUMMARY AND All-GRADE TEAEs IN ≥10% OF ALL PATIENTS

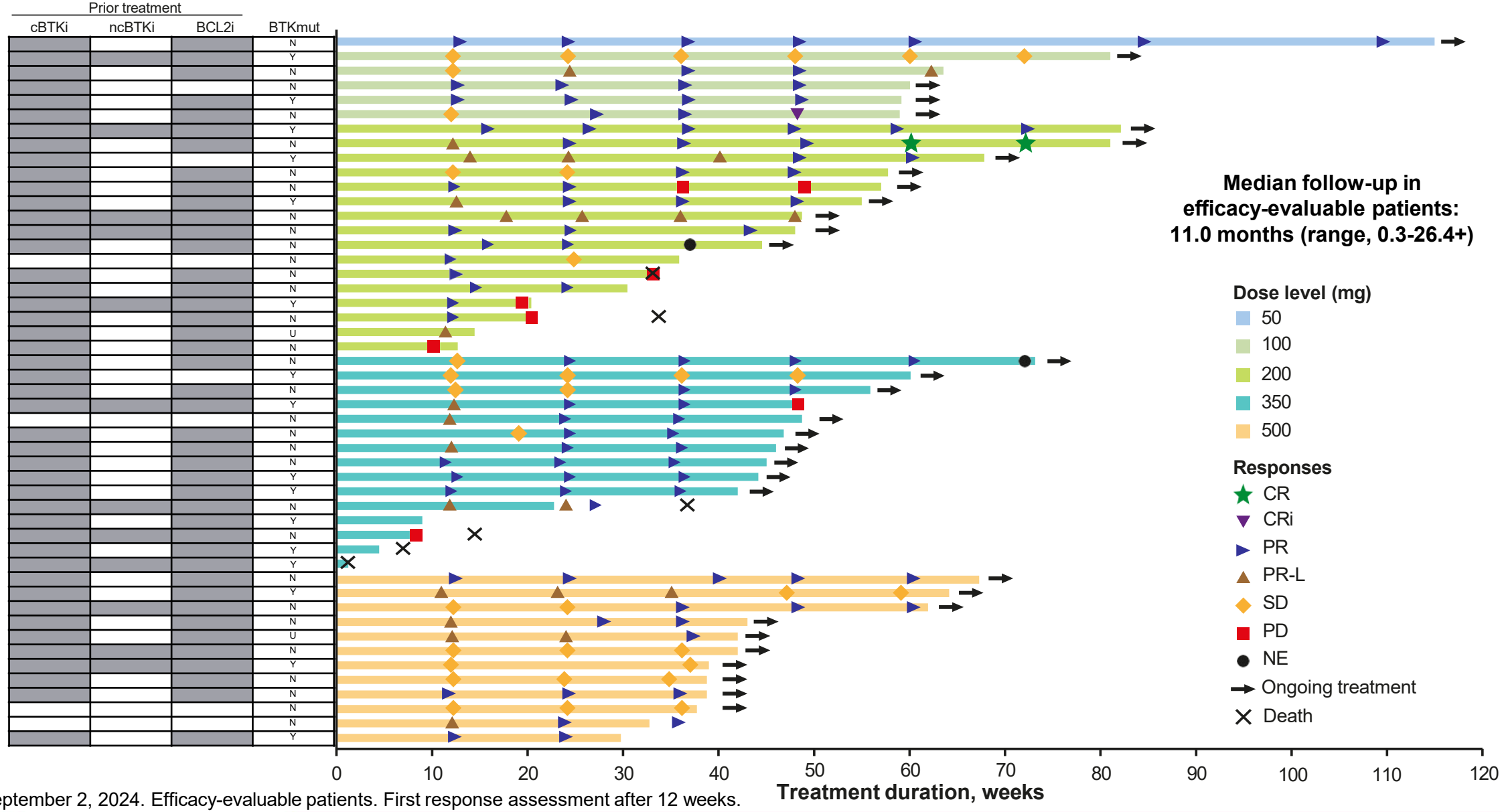
- No atrial fibrillation
- No pancreatitis
- Major hemorrhage[b]: 3.3% (n=2; grade 1 subarachnoid hemorrhage [n=1] and grade 3 subdural hemorrhage [n=1])
- Febrile neutropenia: 1.7% (n=1; in the context of COVID-19 pneumonia and norovirus diarrhea)

Patients, n (%)	Total (N=60) All Grade	Grade ≥3
Fatigue	18 (30.0)	1 (1.7)
Contusion (bruising)	17 (28.3)	0
Neutropenia[c]	15 (25.0)	13 (21.7)
Diarrhea	14 (23.3)	1 (1.7)
Anemia	11 (18.3)	0
Lipase increased[a]	10 (16.7)	2 (3.3)
Cough	9 (15.0)	0
Pneumonia	8 (13.3)	5 (8.3)
Pyrexia	8 (13.3)	0
Arthralgia	7 (11.7)	0
COVID-19	7 (11.7)	0
Dyspnea	7 (11.7)	0
Peripheral edema	7 (11.7)	0
Thrombocytopenia[d]	7 (11.7)	2 (3.3)
Amylase increased[a]	6 (10.0)	0
Nausea	6 (10.0)	0
Sinusitis	6 (10.0)	0

Median follow-up: 10.2 months (range, 0.3-26.4+).

[a] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [b] Grade ≥3, serious, or any central nervous system bleeding. [c] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [d] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

TREATMENT AND DURATION RESPONSE



Data cutoff: September 2, 2024. Efficacy-evaluable patients. First response assessment after 12 weeks.

TAKE HOME MESSAGES FROM BTK DEGRADER TRIALS

- Oral drugs with high clinical activity in patients who have failed prior BTK inhibitors such as ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib
- Follow-up is only <1 year but so far, no major toxicities; BTK associated toxicities appear low

AUDIENCE Q&A

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**If your question was not answered,
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ASK ME ANYTHING – FEATURING JACKIE BROADWAY-DUREN, PhD, DNP, APRN, FNP-BC AND DOREEN ZETTERLUND

FEBRUARY 12th

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