POST-ORLANDO 2025
Novità dal Meeting della Società Americana di Ematologia

# Novità dal Meeting della Società Americana di Ematologia

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**Sessione 3 Leucemia Linfatica Cronica: Terapie di salvataggio**

*Università Vita Salute e IRCCS Ospedale San Raffaele, Milano*

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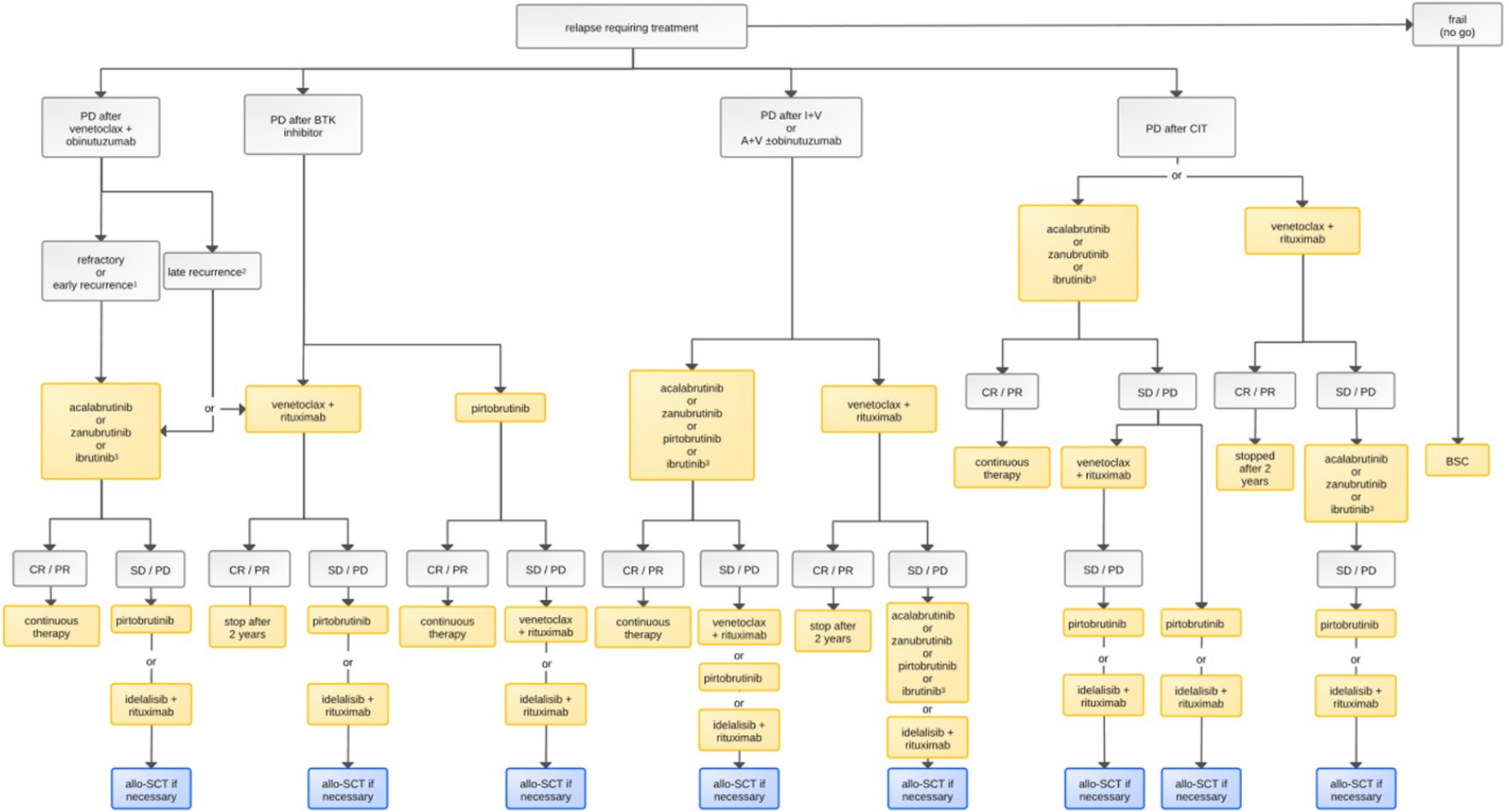
# Current therapeutic landscape in RR CLL




*Onkopedia CLL Guidelines September 2025*

# What about second-line treatment?

# BRUIN-314 Pirtobrutinib vs Ibrutinib: RR cohort

| ITT Population Characteristics[a] | Pirtobrutinib n=331 | Ibrutinib n=331 |
|---|---|---|
| **Median age,** years (range) | 67 (39-90) | 67 (34-86) |
| **Male**, n (%) | 213 (64.4) | 215 (65.0) |
| **Region**, n (%) | | |
| North America | 26 (7.9) | 21 (6.3) |
| Europe | 174 (52.6) | 171 (51.7) |
| South America | 61 (18.4) | 64 (19.3) |
| Asia | 42 (12.7) | 51 (15.4) |
| Other[b] | 28 (8.5) | 24 (7.3) |
| **Histology**, n (%) | | |
| CLL | 306 (92.4) | 294 (88.8) |
| SLL | 25 (7.6) | 37 (11.2) |
| **ECOG PS**, n (%) | | |
| 0-1 | 319 (96.4) | 321 (97.0) |
| 2 | 12 (3.6) | 10 (3.0) |
| **Rai stage[c]**, n (%) | | |
| 0-II | 168 (54.9) | 171 (58.2) |
| III-IV | 135 (44.1) | 119 (40.5) |
| **Median duration of disease,** years (Q1, Q3) | 5.62 (2.20, 8.91) | 5.26 (1.88, 9.73) |
| **Bulky disease[d]**, n (%) | 107 (32.3) | 116 (35.0) |
| **High-risk molecular features**, n/n available (%) | | |
| IGHV unmutated[e] | 199/293 (67.9) | 183/277 (66.1) |
| 17p deletion presence[f] | 50/331 (15.1) | 52/331 (15.7) |
| *TP53* mutation[e] | 92/284 (32.4) | 78/273 (28.6) |
| Complex karyotype[e,g] | 104/259 (40.2) | 78/227 (34.4) |

| R/R Population | Pirtobrutinib n=219 | Ibrutinib n=218 |
|---|---|---|
| **Median lines of prior systemic therapy,** n (range) | 1.0 (1-9) | 1.0 (1-8) |
| **Prior therapy**, n (%) | | |
| BCL2 inhibitor | 22 (10.0) | 17 (7.8) |
| Chemotherapy | 201 (91.8) | 208 (95.4) |
| Anti-CD20 Antibody | 158 (72.1) | 166 (76.1) |
| PI3K inhibitor | 6 (2.7) | 6 (2.8) |
| Immunomodulator | 1 (0.5) | 1 (0.5) |
| Autologous/Allogeneic Stem Cell Transplant | 2 (0.9) | 2 (0.9) |
| **Reason for discontinuation of most recent prior therapy[h]**, n (%) | | |
| Disease progression | 31 (14.2) | 35 (16.1) |
| Toxicity | 23 (10.5) | 25 (11.5) |
| Finished course of therapy | 148 (67.6) | 141 (64.7) |
| Other | 16 (7.3) | 16 (7.3) |

**Baseline characteristics were generally balanced between groups**

*Woyach J et al, Oral Presentation ASH 2025*

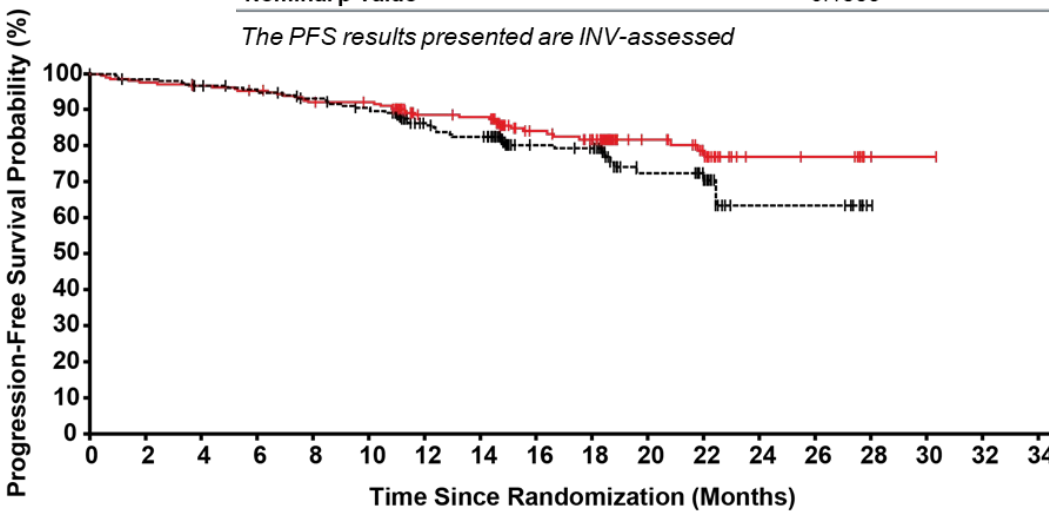
# Efficacy data in RR CLL: ORR and PFS

| | R/R Population | |
|---|---|---|
| | **Pirtobrutinib n=219** | **Ibrutinib n=218** |
| **ORR[a] (PR or better)** | | |
| % | **84.0** | **74.8** |
| 95% CI[b] | 78.48, 88.61 | 68.46, 80.39 |
| Nominal p-value[c] | 0.0175 | |
| **ORR[a] ratio** | | |
| ORR ratio (95% CI) | 1.1233 (1.020, 1.237) | |
| p-value for NI[d] | <0.0001 | |
| **Best Overall Response[e], %** | | |
| CR or CRi | 3.7 | 1.8 |
| PR or nPR | 80.4 | 72.9 |
| PR-L | 3.2 | 4.6 |
| SD | 6.8 | 14.2 |
| PD | 2.3 | 1.8 |
| **ORR including PR-L** | | |
| % | 87.2 | 79.4 |
| 95% CI[b] | 82.05, 91.33 | 73.37, 84.53 |
| Nominal p-value[c] | 0.0286 | |

## R/R population

| | Pirtobrutinib (n=219) | Ibrutinib (n=218) |
|---|---|---|
| **Number of events, n (%)** | 37 (16.9) | 45 (20.6) |
| **18-month PFS rate (95% CI)** | **81.7** (75.1, 86.7) | **79.2** (72.3, 84.6) |
| **Median follow-up, mo** | 18.4 | 15.8 |
| **Hazard ratio (95% CI)** | **0.729 (0.471, 1.128)** | |
| **Nominal p-value[a]** | 0.1563 | |

*The PFS results presented are INV-assessed*




**Number at risk**

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pirtobrutinib | 219 | 212 | 209 | 205 | 197 | 195 | 157 | 155 | 106 | 99 | 56 | 46 | 13 | 12 | 3 | 2 | 0 | 0 |
| Ibrutinib | 218 | 205 | 198 | 192 | 186 | 179 | 138 | 131 | 87 | 84 | 43 | 37 | 12 | 12 | 1 | 0 | 0 | 0 |

***Woyach J et al, Oral Presentation ASH 2025***

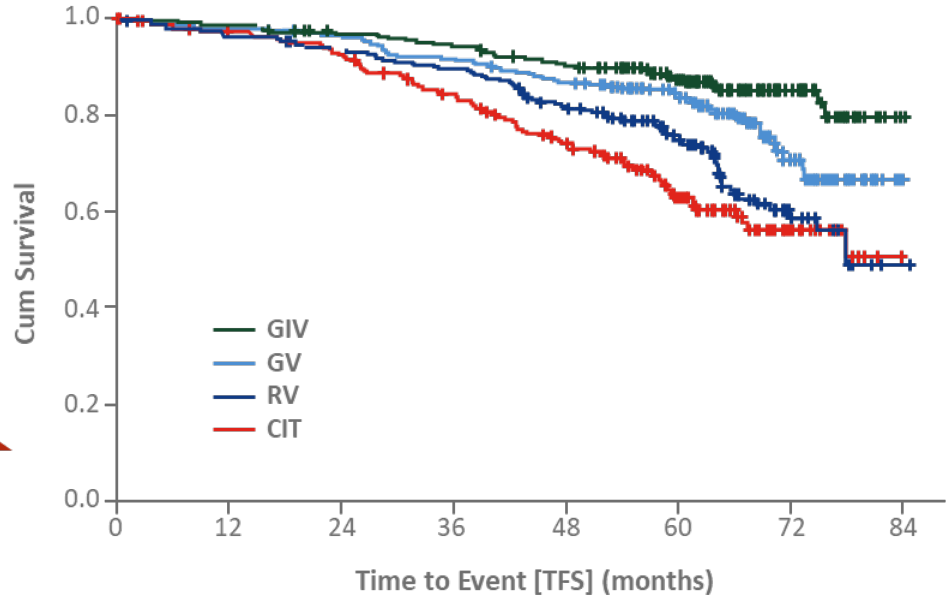
# 2nd Line after Ven-based regimens: CLL13 GAIA results

**Eligibility**

Treatment-naïve, fit patients with CLL, **no *TP53*** aberrations **(centrally screened)**

- **CIT** FCR ≤65y, BR >65y
- **RV** rituximab, venetoclax | FD 12 months
- **GV** obinutuzumab, venetoclax | FD 12 months
- **GIV** obinutuzumab, ibrutinib, venetoclax | 12-36 months

Median observation time 63.8 months




| Patients at Risk | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 |
|---|---|---|---|---|---|---|---|---|
| CIT | 229 | 206 | 196 | 175 | 148 | 88 | 23 | 0 |
| RV | 237 | 227 | 219 | 210 | 188 | 119 | 33 | 1 |
| GV | 229 | 224 | 218 | 206 | 196 | 124 | 36 | 0 |
| GIV | 231 | 228 | 220 | 214 | 202 | 141 | 48 | 1 |

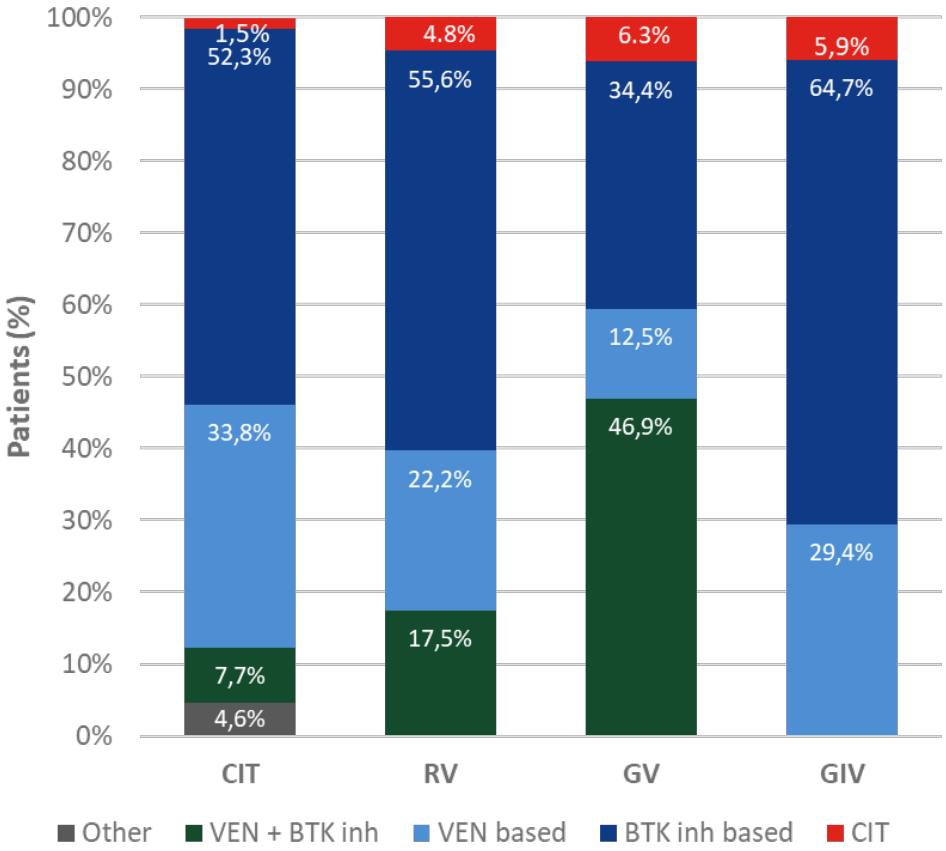
***Niemann C et al, Oral Presentation ASH 2025***

# Baseline characteristics in pts receiving next line treatment

| 1st line Tx: | CIT (n 65) | RV (n 63) | GV (n 32) | GIV (n 17) |
|---|---|---|---|---|
| Age >65 | 30 (46%) | 19 (30%) | 8 (25%) | 5 (29%) |
| CIRS >1 | 42 (65%) | 29 (46%) | 18 (56%) | 14 (82%) |
| ECOG PS >0 | 18 (28%) | 22 (35%) | 10 (31%) | 4 (24%) |
| IGHV unmut | 53 (82%) | 52 (83%) | 27 (84%) | 14 (82%) |
| Complex Karyo ≥3 | 18 (29%) | 15 (24%) | 8 (28%) | 4 (25%) |
| Bulky disease ≥5cm | 24 (37%) | 19 (30%) | 15 (47%) | 5 (29%) |
| Serum $\beta_2$- microglobulin >3.5 mg/L | 54 (83%) | 46 (73%) | 22 (69%) | 9 (60%) |

*Niemann C et al, Oral Presentation ASH 2025*

# Next line treatment based on 1st line treatment




| 1st line Tx: | CIT (n 65) | RV (n 63) | GV (n 32) | GIV (n 17) |
|---|---|---|---|---|
| 2nd line Tx: | | | | |
| CIT | 1 (2%) | 3 (5%) | 2 (6%) | 1 (6%) |
| BTK inh based | 34 (52%) | 35 (56%) | 11 (34%) | 11 (65%) |
| VEN based | 22 (34%) | 14 (22%) | 4 (13%) | 5 (29%) |
| VEN + BTK inh | 5 (8%) | 11 (17%) | 15 (47%) | 0 |
| Other | 3 (5%) | 0 | 0 | 0 |

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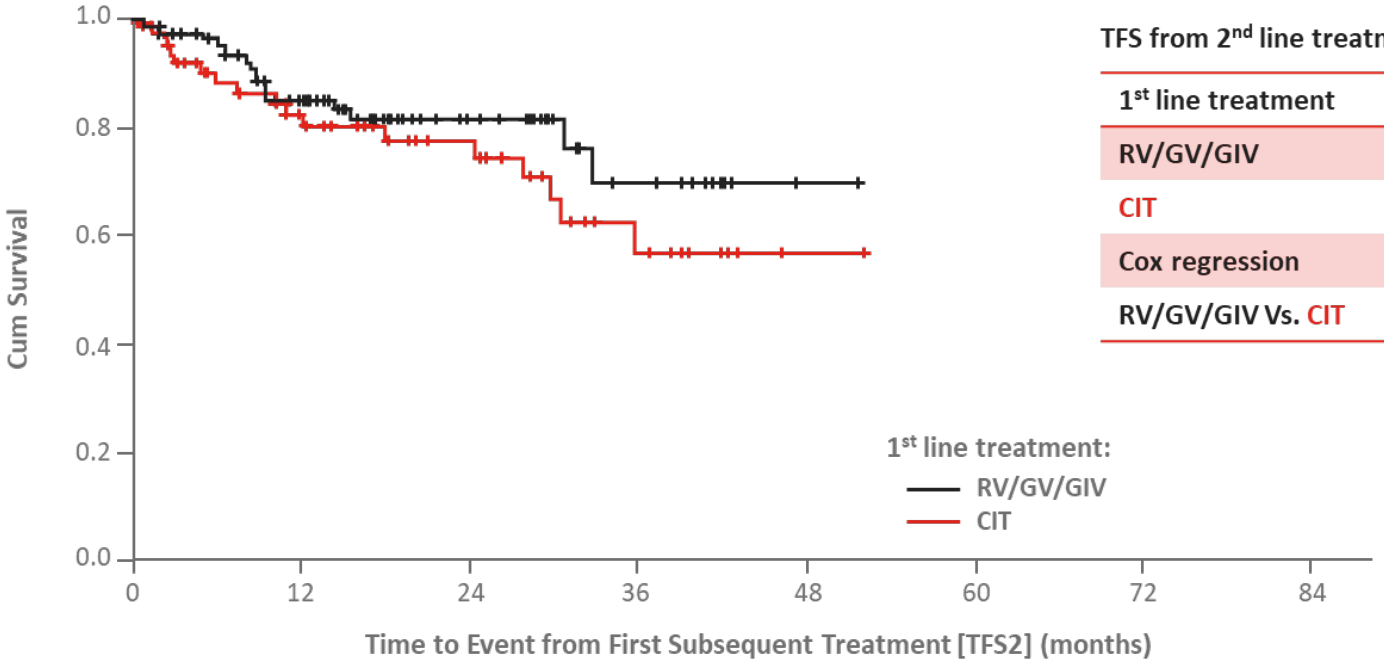
# Treatment free survival from 2nd line treatment (TFS2) based on 1st line treatment




| Patients at Risk | 0 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|
| CIT | 65 | 39 | 25 | 10 | 1 | 0 |
| RV/GV/GIV | 112 | 64 | 26 | 10 | 1 | 0 |

TFS from 2nd line treatment (%)

| 1st line treatment | 1-year rate | 2-year rate |
|---|---|---|
| RV/GV/GIV | 84.9 | 81.5 |
| CIT | 82.3 | 77.6 |
| Cox regression | Hazard ratio (95% CI) | |
| RV/GV/GIV Vs. CIT | 0.691 (0.354-1.347) | |

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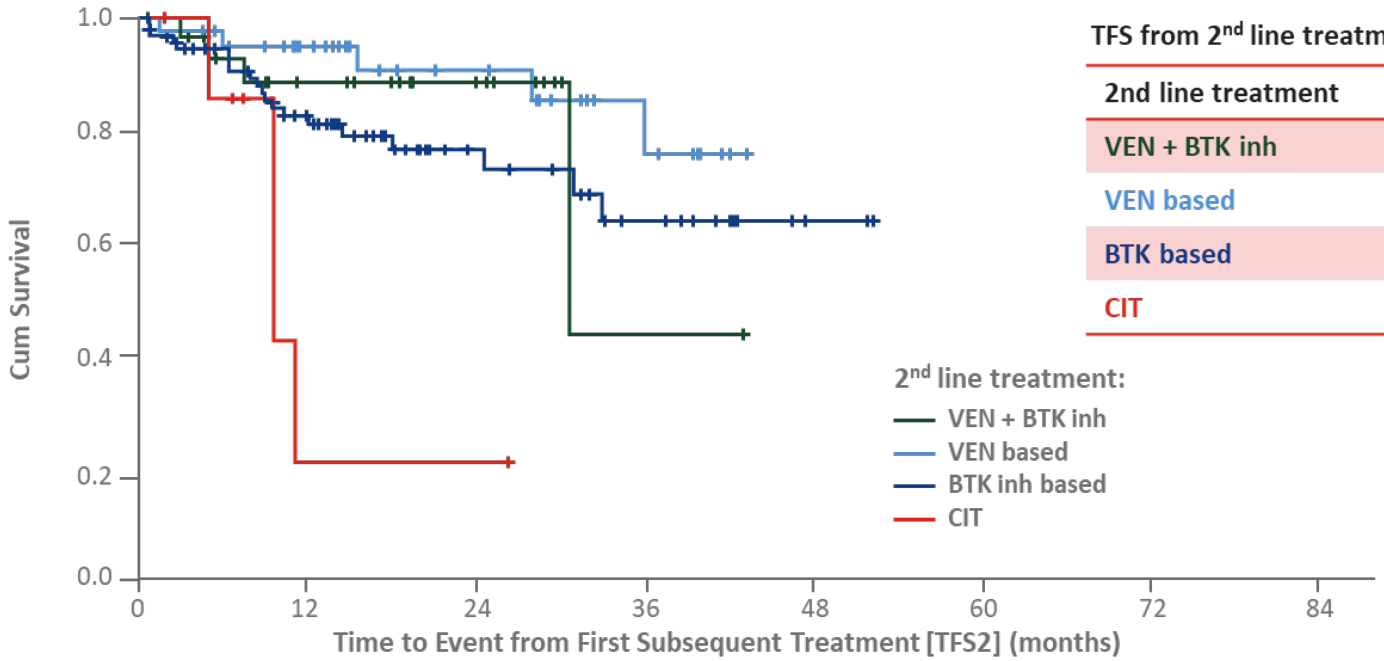
# Treatment free survival from 2nd line treatment (TFS2)




TFS from 2nd line treatment (%)

| 2nd line treatment | 1-year rate | 2-year rate |
|---|---|---|
| VEN + BTK inh | 88.5 | 88.5 |
| VEN based | 94.9 | 90.5 |
| BTK based | **82.4** | 76.6 |
| CIT | 21.4 | 21.4 |

| Patients at Risk | 0 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|
| CIT | 7 | 1 | 1 | 0 | 0 | 0 |
| BTK inh based | 91 | 54 | 22 | 11 | 2 | 0 |
| VEN based | 45 | 30 | 18 | 8 | 0 | 0 |
| VEN + BKT inh | 31 | 17 | 9 | 1 | 0 | 0 |

Patients receiving other treatment are excluded: rituximab for autoimmune disorder (n 2), R-CHOEP for hemophagocytosis (n 1)

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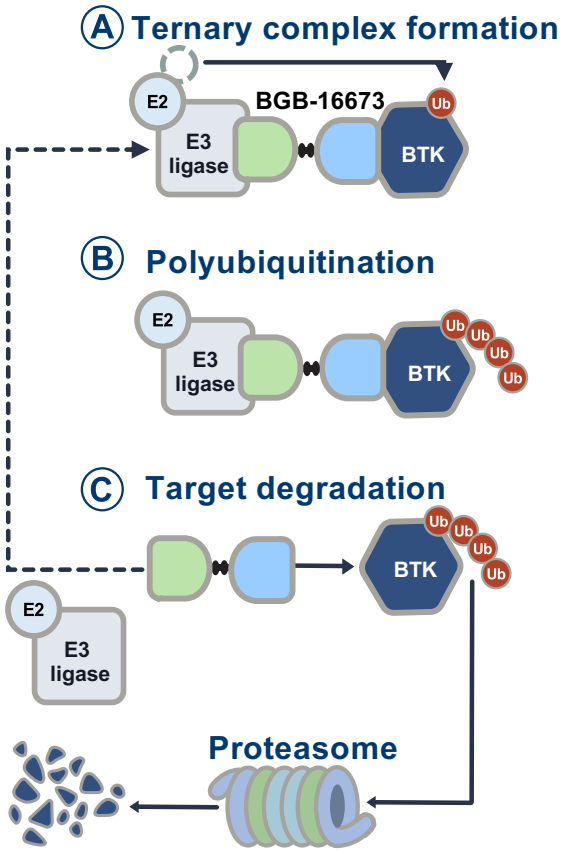
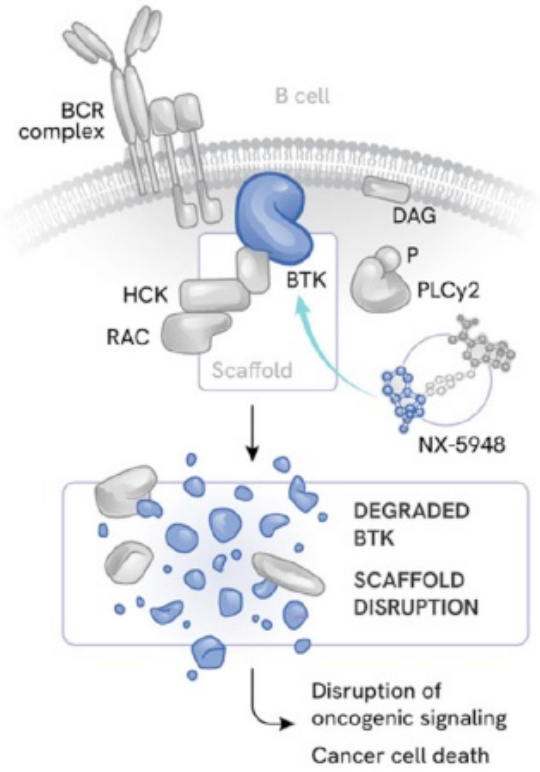
# How to deal with double-exposed/double-refractory disease?

# BTK degraders: BGB-16673 and NX-5948




*Ahn I et al, Oral Presentation ASH 2025; Omer Z et al, Oral Presentation ASH 2025*

# CADAnCE-101 Study: Baseline Pt Features

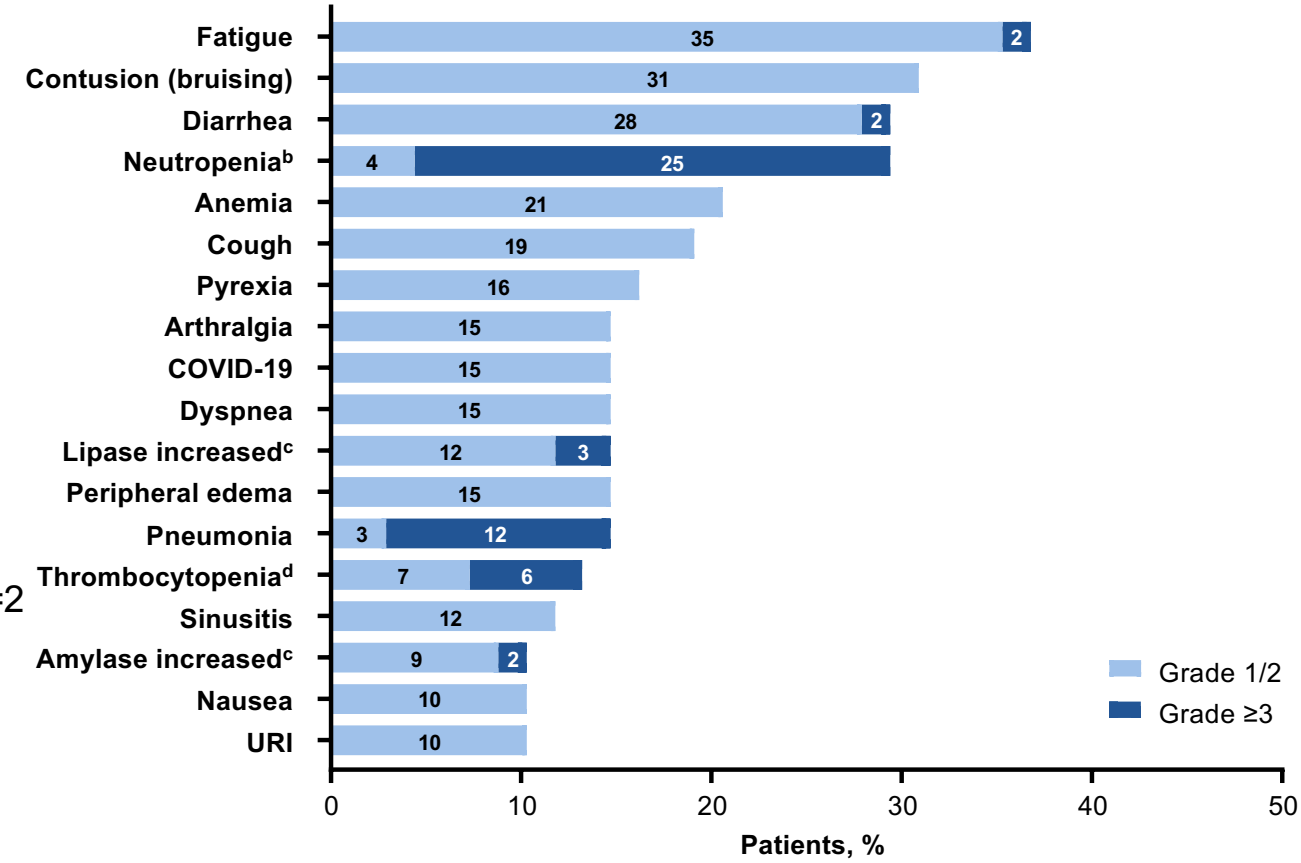
| | Total (N=68) |
|---|---|
| **Age, median (range), years** | 70 (47-91) |
| **Male, n (%)** | 47 (69.1) |
| **ECOG PS, n (%)** | |
| 0 | 38 (55.9) |
| 1 | 29 (42.6) |
| 2 | 1 (1.5) |
| **CLL/SLL risk characteristics at study entry, n/N with known status (%)** | |
| Binet stage C | 29/64 (45.3) |
| Unmutated IGHV | 38/49 (77.6) |
| del(17p) and/or *TP53* mutation | 46/68 (67.6) |
| Complex karyotype (≥3 abnormalities) | 22/44 (50.0) |

| | Total (N=68) |
|---|---|
| **Mutation status, n/N (%)** | |
| *BTK* mutation present | 26/66 (39.4) |
| *PLCG2* mutation present | 10/66 (15.2) |
| *BTK* and *PLCG2* mutation present | 5/66 (7.6) |
| **No. of prior lines of therapy, median (range)** | 4 (2-10) |
| **Prior therapy, n (%)** | |
| Chemotherapy | 49 (72.1) |
| cBTK inhibitor | 64 (94.1) |
| ncBTK inhibitor | 14 (20.6) |
| BCL2 inhibitor | 56 (82.4) |
| cBTK + BCL2 inhibitors | 44 (64.7) |
| cBTK + ncBTK + BCL2 inhibitors | 12 (17.6) |
| **Discontinued prior BTK inhibitor due to PD, n/N (%)[a]** | 57/64 (89.1) |

***Ahn I et al, Oral Presentation ASH 2025***

# CADAnCE-101 Study: Safety Summary

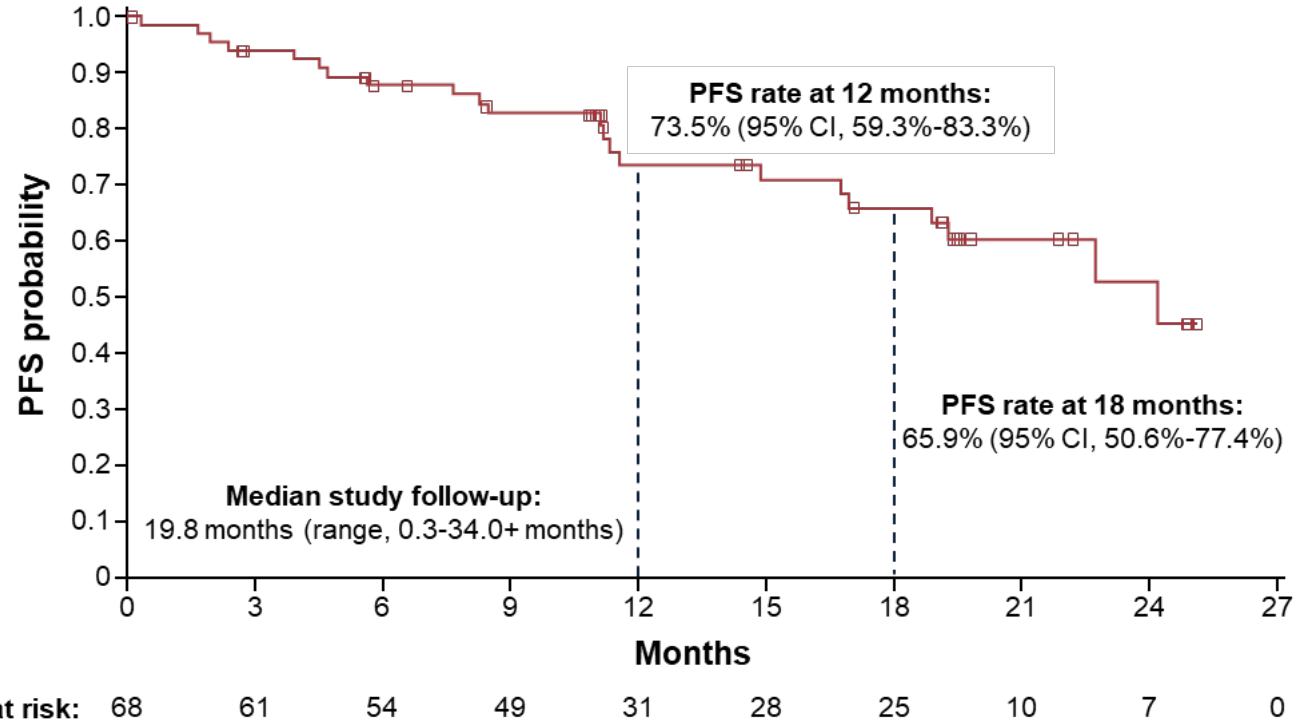
- The most common TEAEs were fatigue (36.8%) and contusion (bruising; 30.9%)
- Grade ≥3 neutropenia: n=17 (25.0%); 16 patients (23.5%) had grade ≥2 neutropenia at baseline
  - Neutropenic fever: n=1
- Atrial fibrillation: n=3 (grade 1, n=1; grade 2, n=2; all transient (2 of them lasting 1 day) in the context of infection and PD, assessed as unrelated to treatment)
- Treatment-related major hemorrhage[a]: n=2 (one grade 3 subdural hemorrhage and one grade 3 post-procedural hematuria)




*Ahn I et al, Oral Presentation ASH 2025*

# CADAnCE-101 Study: Efficacy

| Characteristic, n/N with known status (%) | ORR |
|---|---|
| **Total cohort** | **58/68 (85.3)** |
| **Treated at RPE dose (200 mg)** | **17/18 (94.4)** |
| **Prior cBTKi + BCL2i** | 41/44 (93.2) |
| **Prior cBTKi + BCL2i + ncBTKi** | **9/12 (75.0)** |
| **6 or more prior lines of therapy** | 13/16 (81.3) |
| **del(17p) and/or *TP53* mutation** | 37/46 (80.4) |
| **Complex karyotype (≥3 abnormalities)** | 16/22 (72.7) |
| ***BTK* mutations** | 20/26 (76.9) |
| ***PLCG2* mutations** | 9/10 (90.0) |

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# NX-4948-301 Study: Baseline characteristics

## Multiple prior lines of therapy and a high prevalence of baseline mutations

| Characteristics | Phase 1a/b – all patients (n=126) | Phase 1a (n=48) |
|---|---|---|
| **ECOG PS**, n (%) | | |
| 0 | 45 (35.7) | 19 (39.6) |
| 1 | 81 (64.3) | 29 (60.4) |
| **CNS involvement**, n (%) | 5 (4.0) | 5 (10.4) |
| **Median prior lines of therapy**, n (range) | 3.0 (1–17) | 4.0 (2–12) |
| **Previous treatments,**[a] n (%) | | |
| BTKi | 108 (85.7) | 47 (97.9) |
| cBTKi | 106 (84.1) | 47 (97.9) |
| ncBTKi | 34 (27.0) | 13 (27.1) |
| BCL2i | 78 (61.9) | 40 (83.3) |
| BTKi and BCL2i | 75 (59.5) | 39 (81.3) |
| CAR-T therapy | 9 (7.1) | 3 (6.3) |
| Bispecific antibody | 5 (4.0) | 1 (2.1) |
| PI3Ki | 26 (20.6) | 14 (29.2) |
| Chemo/chemo-immunotherapies | 84 (66.7) | 35 (72.9) |
| **Mutation status,**[b] n (%) | (n=111) | (n=47) |
| *BTK* | 44 (39.6) | 18 (38.3) |
| *TP53* | 44 (39.6) | 21 (44.7) |
| *PLCG2* | 9 (8.1) | 7 (14.9) |
| *BCL2* | 8 (7.2) | 6 (12.8) |

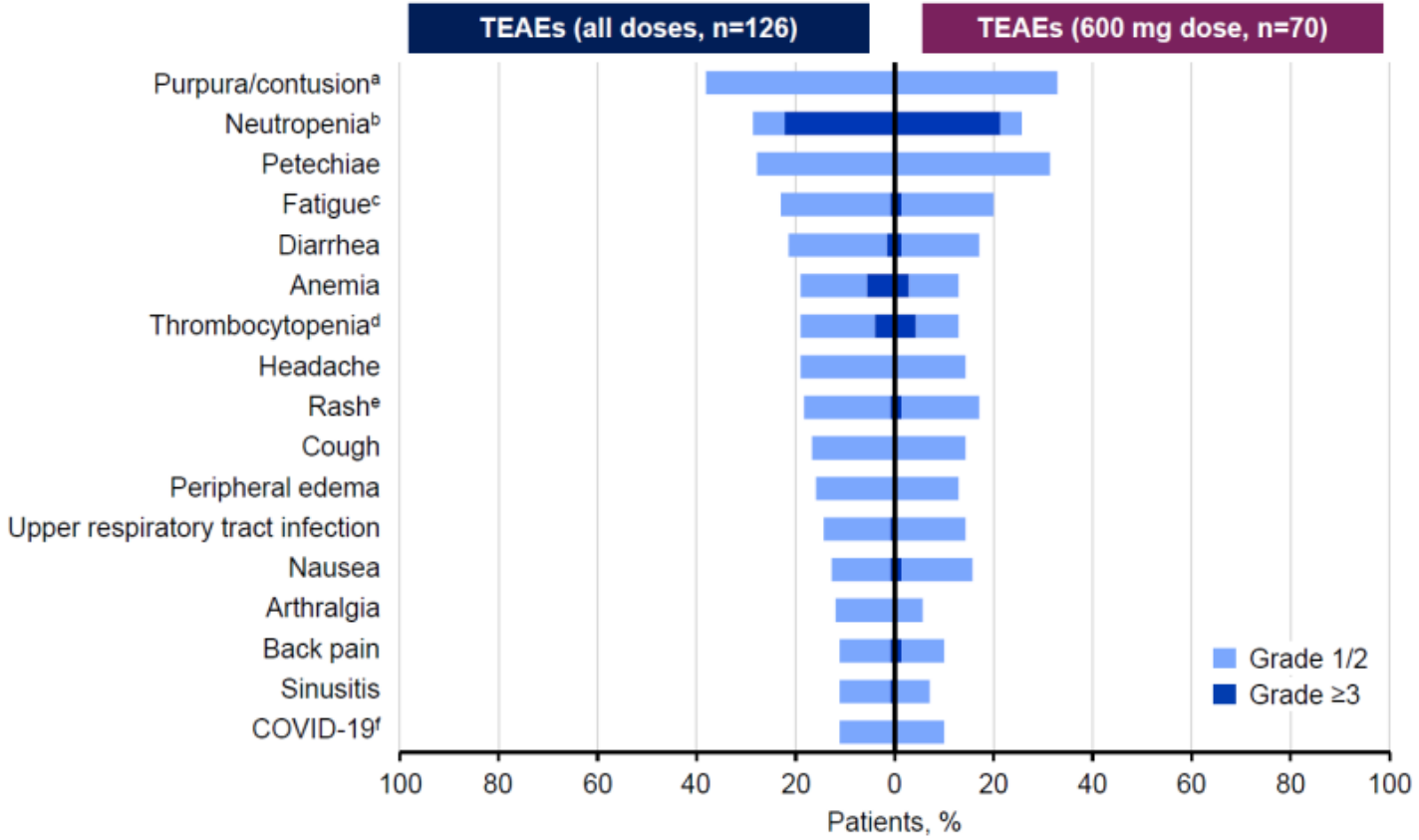
*[a]Patients could have received multiple prior treatments; [b]Mutations presented here were centrally sequenced*
***BCL2**, B-cell lymphoma 2; **BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CAR-T**, chimeric antigen receptor T cell; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ncBTKi**, non-covalent BTKi; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2*

Data cutoff: 19 Sep 2025

***Omer Z et al, Oral Presentation ASH 2025***

# NX-4948-301 Study: Safety Profile

## Comparable AE profile for patients at the RP2D 600mg dose and overall population




- Tolerable safety profile consistent with prior disclosures
- No dose-limiting toxicities
- No systemic fungal infections or Grade 4 infections of any kind reported
- Single event of new onset atrial fibrillation consistent with the rate in the age-matched general population
- 3 Grade 5 AEs (death not otherwise specified; pulmonary embolism; pneumonia; all deemed not related to bexobrutideg)

*[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [c]Fatigue was transient; [d]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [e]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [f]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'*
***AE**, adverse event; **NOS**, not otherwise specified; **RP2D**, recommended Phase 2 dose; **TEAE**, treatment-emergent adverse event*

Data cutoff: 19 Sep 2025

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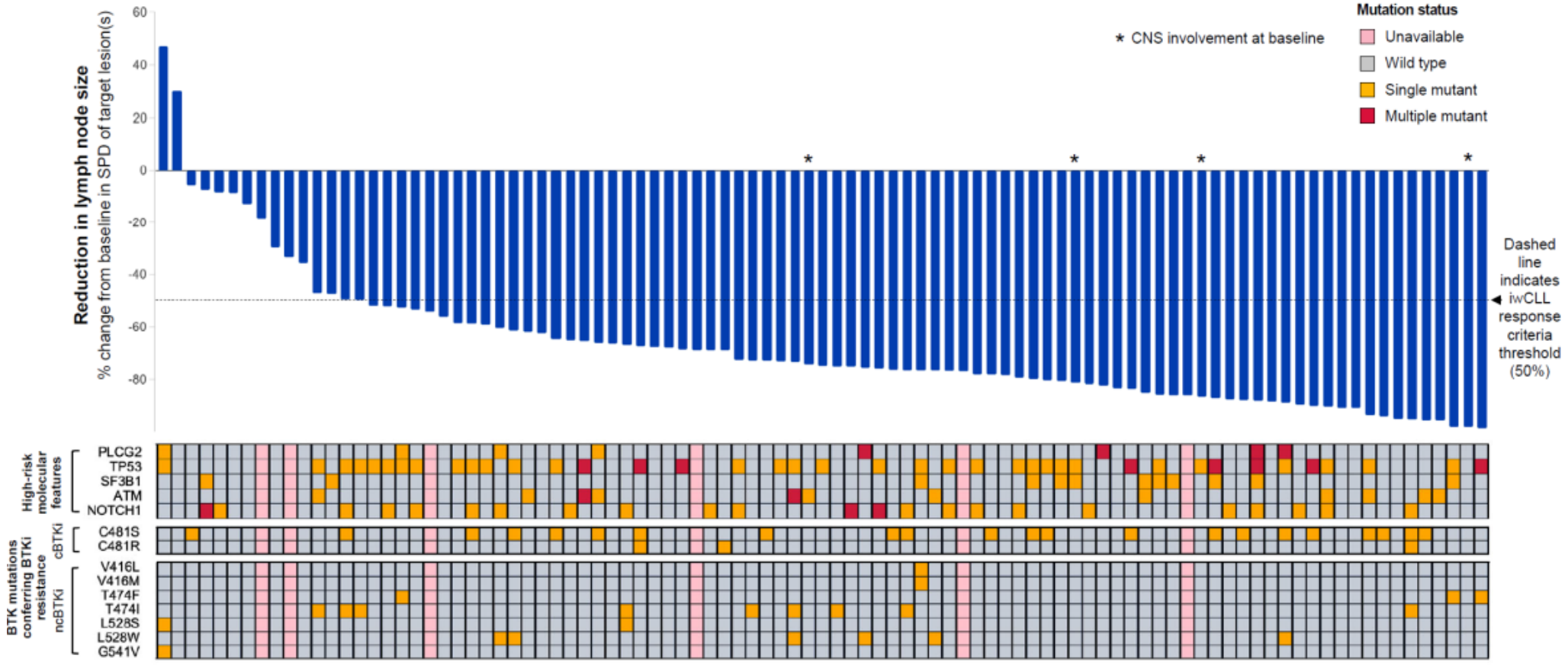
# NX-4948-301 Study: Efficacy Data




[a]*Waterfall plot includes patients with measurable lymph node status (n=93); mutations were reported at VAF >5%;* [b]*Patients could have no mutations, a single mutation, or multiple mutations*

Data cutoff: 19 Sep 2025

***ATM**, ataxia-telangiectasia mutated; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **iwCLL**, International Workshop on CLL; **ncBTKi**, non-covalent BTKi; **NOTCH1**, neurologic locus notch homolog protein 1; **PLCG2**, phospholipase C gamma 2; **SPD**, sum of products diameters*



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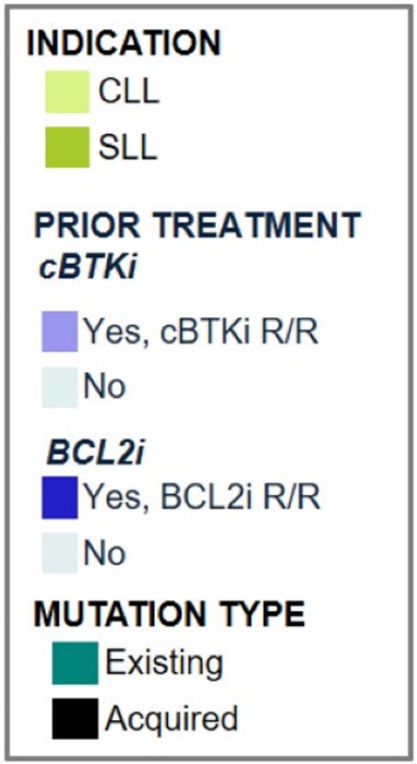
# Acquired mutations in MK-1026-003 Trial

- Acquired *BTK* and *PLCγ2* mutations were rare with low VAF (< 4%)

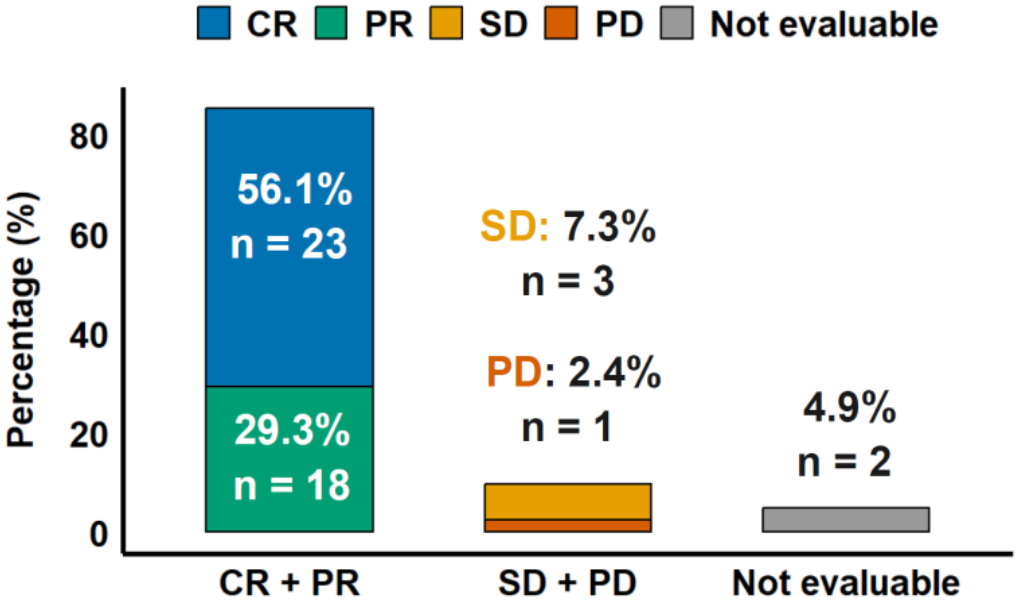

- Both acquired BTK mutations were *BTK T474I* (a coding-region missense mutation in the kinase domain)
- Each were present at low variant allele frequencies (1.16%, C13 and 1.21%, EOT)

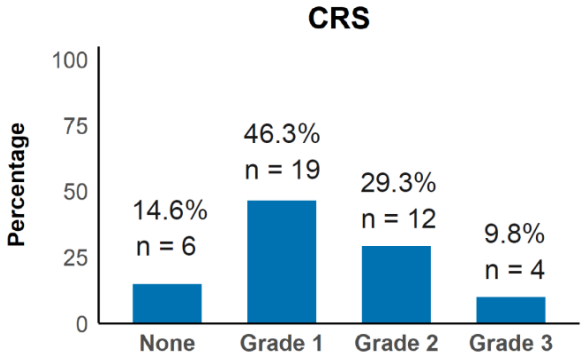
Data cut-off: September 8, 2025. N = 100. VAF, variant allele frequency. Biomarker evaluable population (N = 100). Median treatment duration: 14.65 months (range, 0.16 - 50.83). Median follow up duration: 25.15 months (range, 2.69 - 50.99).

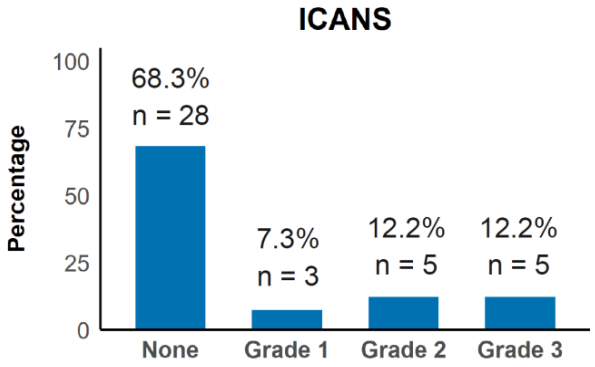
***Kipps T et al, Oral Presentation ASH 2025***

# Real-world outcomes of liso-cel in CLL

41 pts from 17 US sites, 63% *TP53* aberrations, 39% complex karyotype
100% BTKi-exposed, 95% BCL2i-exposed, 90% pirtobrutinib (58.5% last line)
Median FU 3.3 months




Less CR if LN≥5 cm: -1.33 (-3.44 to 0.49)
More CR if continued bridging therapy: 1.69 (0.13-3.69)

2 G2, 1 G5 immune effector cell-associated HLH-like syndrome (IEC-HS)

***Huang JJ et al, Oral Presentation ASH 2025***

# Thank you!

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**Division of Experimental Oncology**

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