Updates on Lymphoma Therapy from ASH 2023

Tuesday, February 6, 2024

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Overview

- December 9-12, 2023, in San Diego, California
- Over 30,000 hematologists / oncologists in attendance
- Selected abstracts from the American Society of Hematology Annual Meeting in December, 2023
- Clinically relevant studies that may impact practice in the future

- We will not be covering questions related to your individual health care


HISTORIC HEART OF SAN DIEGO

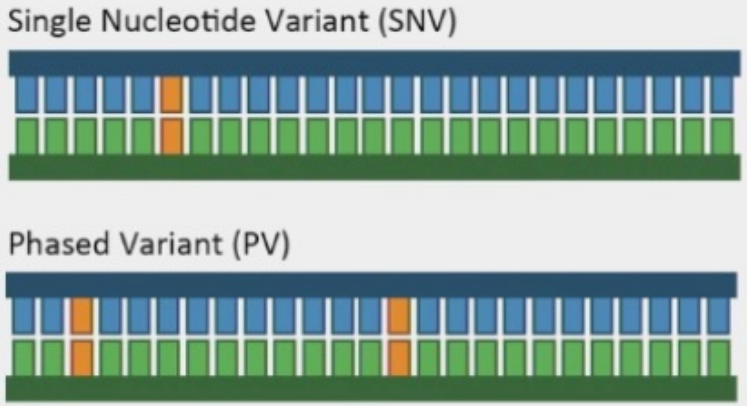
1. Circulating tumour DNA in DLBCL

Prognostic Utility of Minimal Residual Disease (MRD) after Curative Intent Induction Therapy for DLBCL: A Prospective Real-World Ctdna Study – Sworder et al.

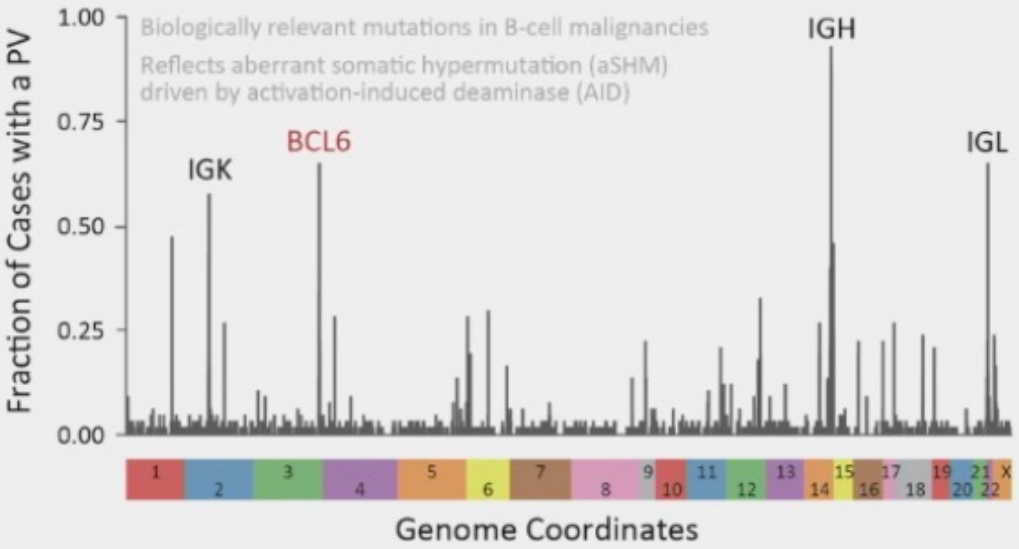
- In patients with aggressive B-cell lymphomas, we use PET/CT scans to assess response to chemotherapy
- Are there additional tools that we could use to help us determine which patients are in remission?
- Patients often ask “Can you look for the cancer on blood tests?”
- Circulating tumour DNA = “Liquid Biopsy”

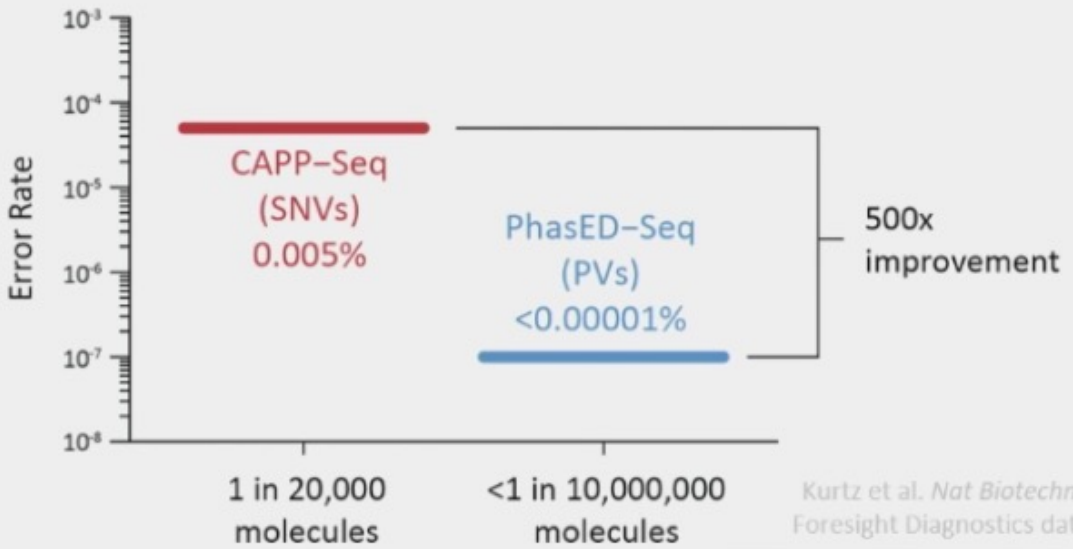
PhasED-Seq improves detection of MRD

Phased Variant Enrichment and Detection Sequencing



- Detection of phased variants greatly reduces background error rate in comparison to SNV detection
- Allows for reliable MRD detection when ctDNA is present at very low levels





Kurtz et al. *Nat Biotechnol.* 2021
Foresight Diagnostics data on file

1. Circulating tumour DNA in DLBCL

- Real world study
- Collected data on patients receiving standard of care first line treatment for DLBCL (R-CHOP or R-EPOCH)
- Used an ultra sensitive ctDNA assay
- ctDNA collected at baseline, interim, and end of treatment
- Compared with:
  - PET/CT imaging
  - Duration of remission
  - Survival data

ctDNA-MRD Testing

- Patients were included in the analysis if:
  - Baseline plasma (median 4mL) was available, *and*
  - Was collected prior to treatment or had sufficient tumor burden for testing
- 364 samples from 99 patients were tested in a blinded manner by PhasED-Seq (Foresight Diagnostics, Inc.)
- Evaluable patients had a viable sample and PET/CT results at the relevant timepoint
  - 83 evaluable patients for interim timepoint
  - 77 evaluable patients for EOT timepoint

Tumor-Specific PVs Identified

- Targeted sequencing of pre-treatment plasma (ctDNA) and paired PBMCs (genomic DNA) using a fixed panel that includes regions of biological relevance for LBCL
- Tumor-specific PV list generated by selecting PVs that are present in ctDNA and are absent or present at low levels in gDNA

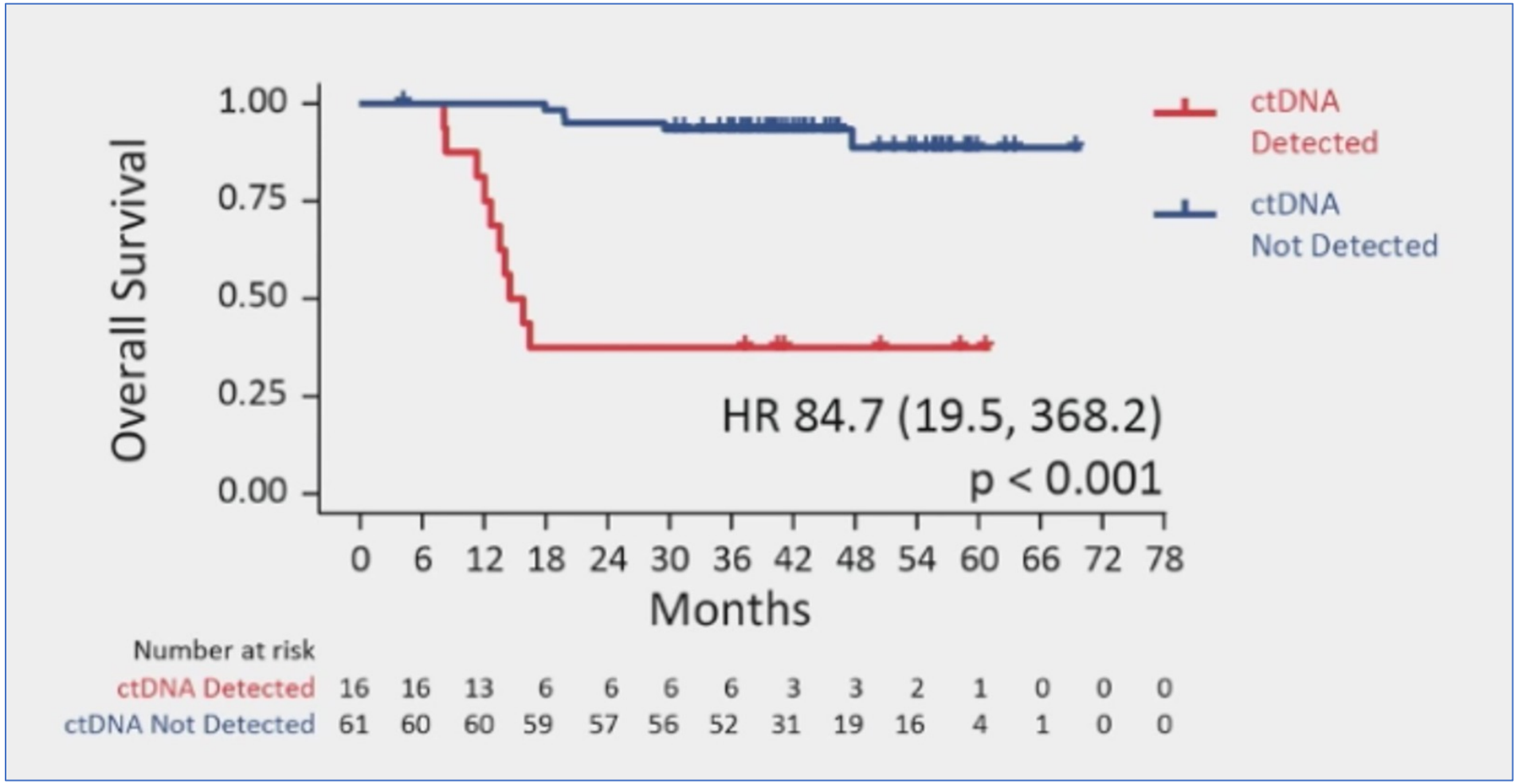
MRD Assessed at Interim and EOT Timepoints

- ctDNA-MRD assessed at interim and EOT timepoints using tumor-specific PV list
- MRD positive if ctDNA levels exceeded an analytical detection threshold (~1:10^6 cfDNA molecules) corresponding to 98% specificity

1. Circulating tumour DNA in DLBCL

- ctDNA was predictive of clinical outcomes
  - Patients with undetectable ctDNA were more likely to remain disease free
  - Patients with undetectable ctDNA had improved survival

  - ctDNA was actually more predictive than PET/CT scans
  - This was true at interim and at end of treatment



Adapted Sworder et al., ASH 2023

1. Circulating tumour DNA in DLBCL

- Sometimes PET scans can lead to “false positives”
  - Inflammation, infection, injury
  - ctDNA was helpful at predicting outcomes in patients who had a positive PET/CT at end of treatment
  - 10 patients in the cohort had positive PET/CT
  - None of the patients with undetectable ctDNA have experienced disease progression so far

1. Circulating tumour DNA in DLBCL

- Testing was feasible, non-invasive
- Provided important prognostic information to patients and providers
- “Real world” study
- Could be used together with PET scans to help risk stratify patients
- At the end of treatment, could potentially eliminate the need for confirmatory biopsy in some patients with positive PET scans

2. Bispecific antibody therapy in DLBCL

Glofitamab Monotherapy in Relapsed or Refractory Large B-Cell Lymphoma: Extended Follow-Up from a Pivotal Phase II Study and Subgroup Analyses in Patients with Prior Chimeric Antigen Receptor T-Cell Therapy and by Baseline Total Metabolic Tumor Volume – Hutchings et al.

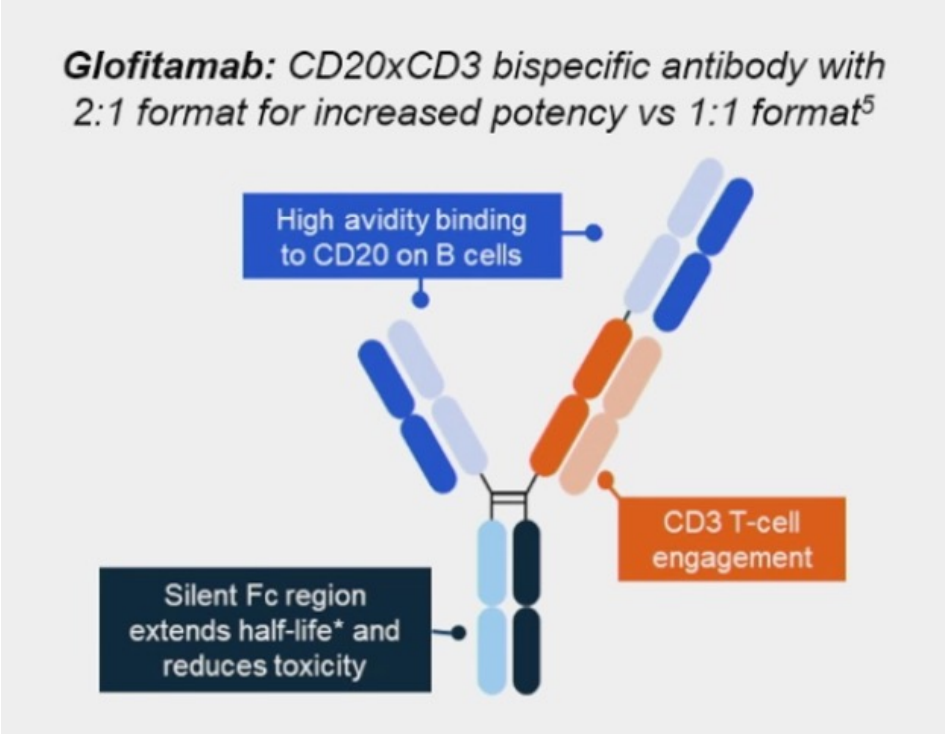
- Patients with DLBCL have potentially curable disease
- Young/fit patients who relapse or have refractory disease after first line therapy may be candidates for high dose chemotherapy and autologous stem cell transplantation
- Patients who relapse or have refractory disease after autologous stem cell transplant (or who are not candidates for auto transplant) may be eligible for CAR-T cell therapy

2. Bispecific antibody therapy in DLBCL

- What about patients who do not live near centres with cellular therapies?
- CAR-T cell manufacturing takes time, logistically challenging
- Although CAR-T cell therapy has greatly changed the treatment landscape, roughly half of patients who achieve a complete response to CAR-T will subsequently relapse
- Outcomes for patients with disease recurrence post CAR-T are poor
- Can we improve upon therapies available to patients post CAR-T?

2. Bispecific antibody therapy in DLBCL

- “Off the shelf” product
- Engages and redirects T-cells to eliminate the cancer cells (B-cells)
- Group presented extended follow-up data
- Specifically presented outcomes in patients who had received prior CAR-T cell therapy



Study design

Pivotal single-arm Phase II study in patients with R/R LBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL, or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - Anti-CD20 antibody
  - Anthracycline

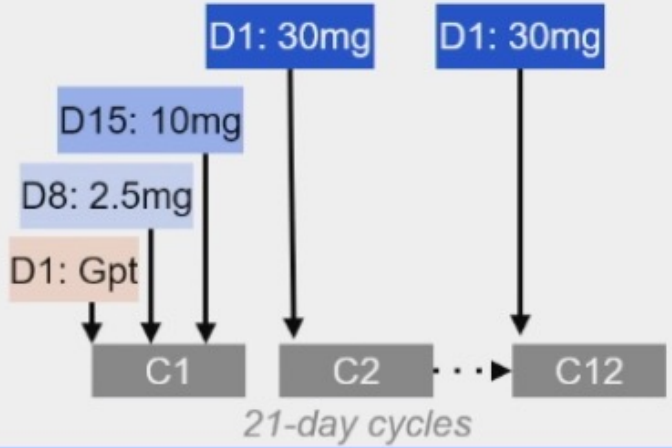
Glofitamab IV administration

Fixed-duration treatment:

- Up to 12 cycles (8.3 months)

CRS mitigation:

- Obinutuzumab IV pre-treatment (1000mg)
- C1 step-up dosing
- Monitoring after first glofitamab dose (2.5mg)



Endpoints

- **Primary:** CR (best response) rate by IRC*
- **Key secondary:** ORR,† DoR,† DoCR,† PFS, and OS

*By PET-CT (Lugano criteria)[1]; †By IRC and investigator. C, cycle; CRS, cytokine release syndrome; D, day; DoR, duration of response; DoCR, duration of complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; Gpt, obinutuzumab pre-treatment; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; IV, intravenous; NOS, not otherwise specified; ORR, overall response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

Baseline characteristics

n (%)*		All patients (N=154)†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I/II	35 (22.7)
	III/IV	116 (75.3)
NHL subtype	DLBCL	110 (71.4)
	trFL	28 (18.2)
	HGBCL	10 (6.5)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	19 (12.3)

n (%)*	All patients (N=154)†
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	61 (39.6)
≥3 prior lines	93 (60.4)
Prior CAR-T	51 (33.1)
Refractory to prior CAR-T§	46 (29.9)
Prior ASCT	29 (18.8)
Refractory to any prior therapy	138 (89.6)
Refractory to last prior therapy	131 (85.1)
Refractory to first line of prior therapy	90 (58.4)
Refractory to any prior anti-CD20	128 (83.1)

The patient population was heavily pre-treated and highly refractory to prior therapy

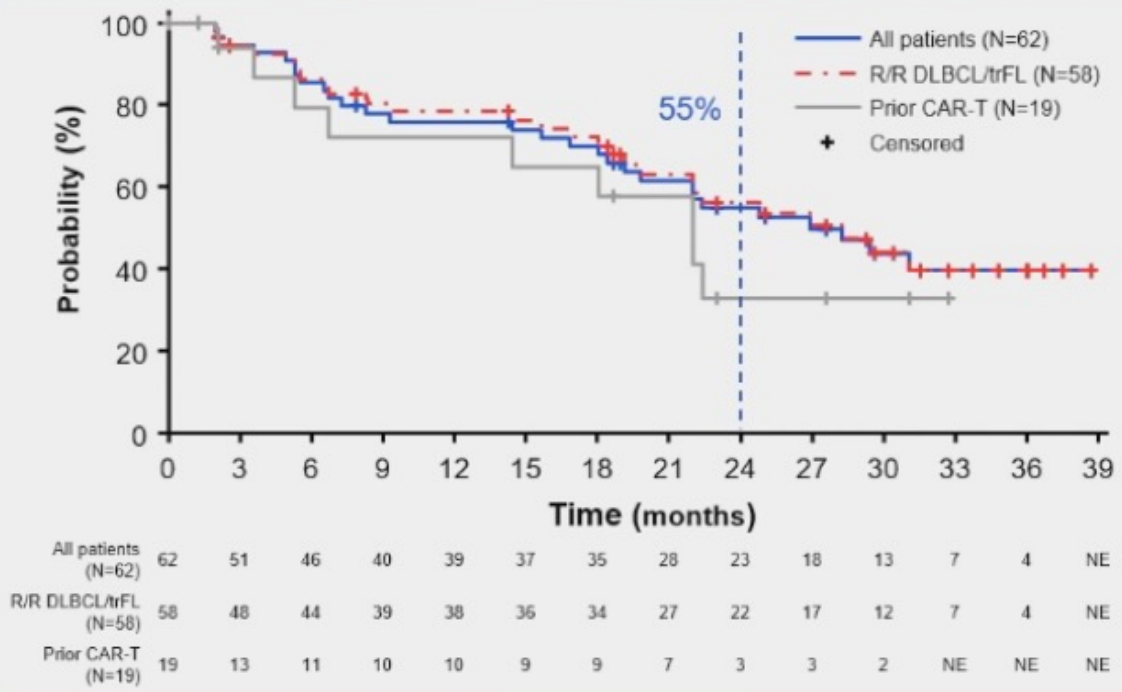
Clinical cut-off date: September 4, 2023. *Unless otherwise specified; †Safety-evaluable population (all treated patients; one patient enrolled in the intent-to-treat population did not receive any study drug and was excluded from the safety-evaluable population); ‡ECOG PS 2, n=1 (0.6%); one patient had an ECOG PS of 1 at enrolment, but deteriorated before the receipt of study treatment;[1] §Patients who had no response or relapsed within 6 months. ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; NHL, non-Hodgkin lymphoma; trFL, transformed follicular lymphoma.

1. Dickinson M, et al. N Engl J Med 2022;387:2220–31.

Response rates and DoCR

	All patients (N=155)*	R/R DLBCL/ trFL (N=132)[1†‡]	Prior CAR-T (N=52)†
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DoCR, months (95% CI)	26.9 (19.8–NR)	28.3 (19.8–NR)	22.0 (6.7–NR)
24-month DoCR, % (95% CI)	55.0 (41.1–68.8)	56.2 (41.9–70.4)	33.1 (7.2–59.0)
Median CR follow-up, months (range)	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)

DoCR by IRC



- Median time on study: 32.1 months (range: 0–43)

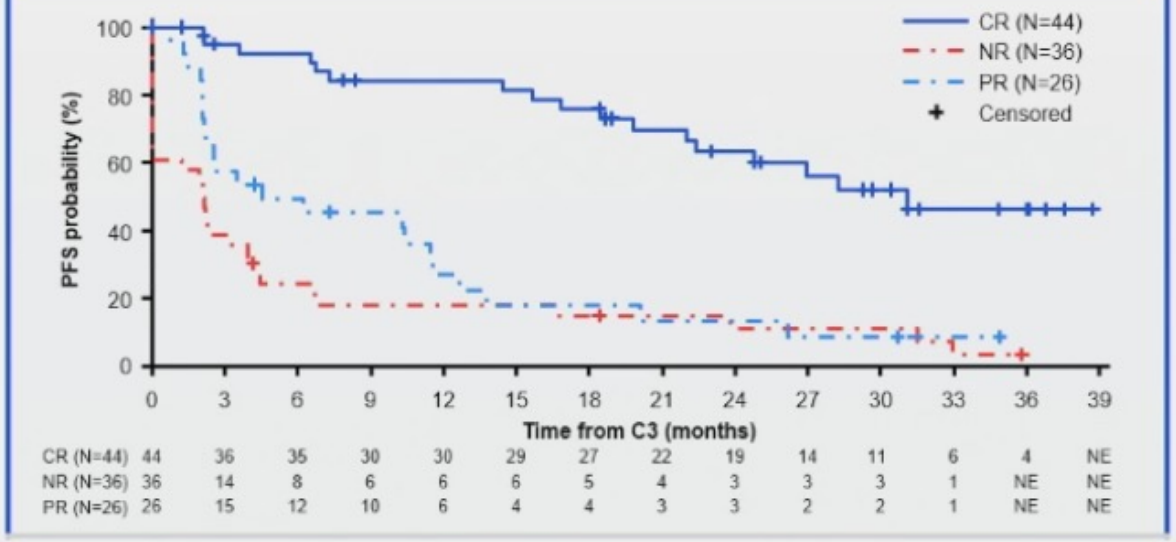
With 32 months median follow-up, glofitamab showed high response rates and durable remissions across subgroups

*Intent-to-treat population (DLBCL, trFL, HGBCL, and PMBCL); †Patients in this subgroup had similar baseline characteristics to the overall population; ‡Primary efficacy population reported in the glofitamab USPI, all patients received at least one dose of glofitamab. CI, confidence interval; NE, not estimable; NR, not reached; USPI, United States prescribing information.

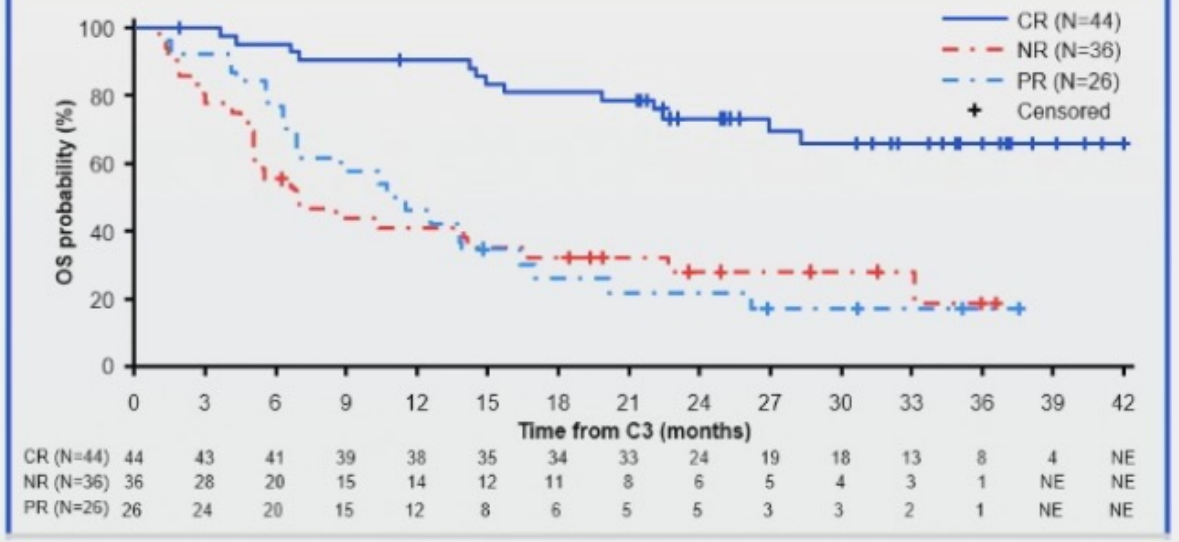
1. COLUMVI USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf.

Landmark analysis by response at Cycle 3

PFS



OS



Landmark PFS from C3 in patients with CR at C3*	N=44
Median PFS, months (95% CI)	31.1 (22.4–NE)
24-month PFS rate, % (95% CI)	63.5 (47.5–79.6)

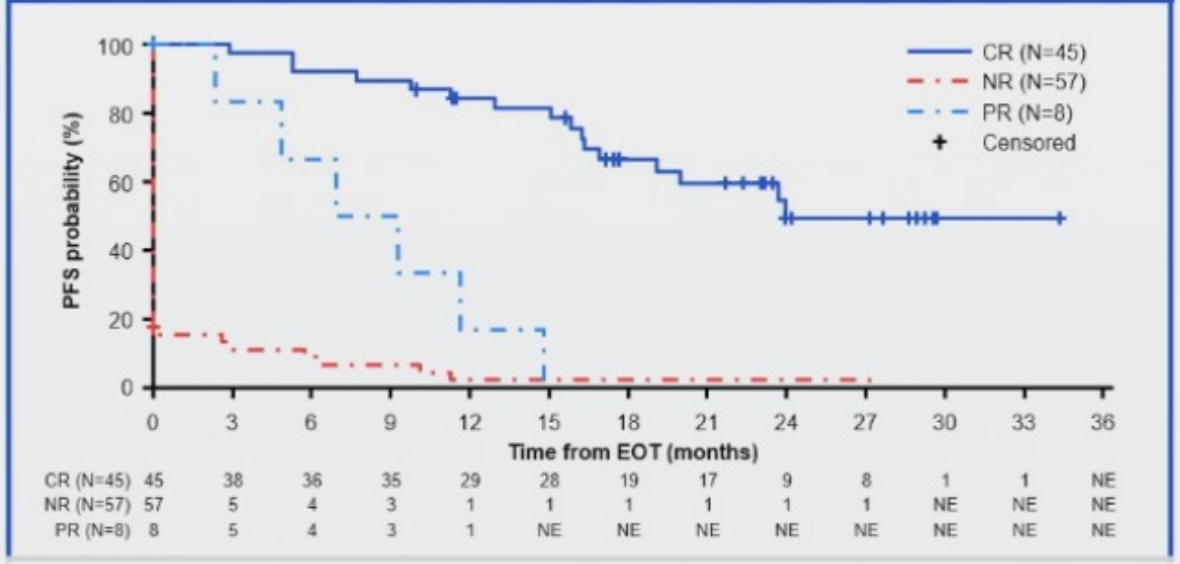
Landmark OS from C3 in patients with CR at C3*	N=44
Median OS, months (95% CI)	NE (NE)
24-month OS rate, % (95% CI)	73.4 (59.9–87.0)

A high proportion of patients with a CR at C3 remained progression-free and alive after 24 months

*KM estimates. NR, no response.

Landmark analysis by response at EOT

PFS



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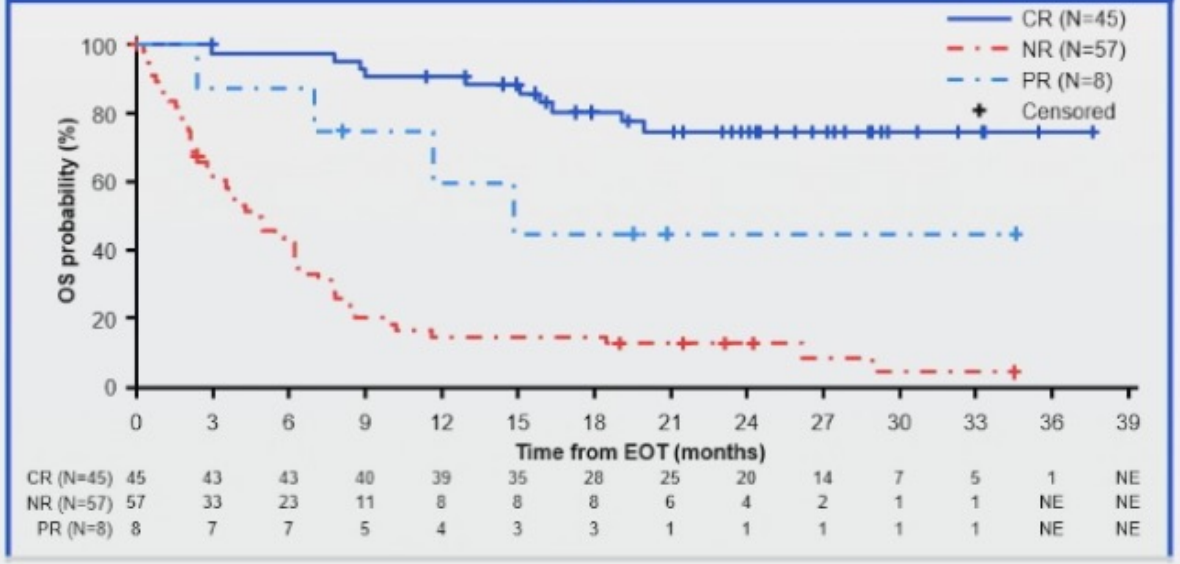


Landmark PFS from EOT in patients with CR at EOT*	N=45
Median PFS, months (95% CI)	24.0 (19.1–NE)
18-month PFS rate, % (95% CI)	66.6 (51.0–82.2)

Landmark OS from EOT in patients with CR at EOT*	N=45
Median OS, months (95% CI)	NE (NE)
18-month OS rate, % (95% CI)	80.7 (68.6–92.8)

Majority of patients with a CR at EOT remained progression-free and alive at 18 months after EOT

*KM estimates.
EOT, end-of-treatment; NR, no response.

Safety summary

- **CRS* remained the most common AE**
  - CRS occurred in 64% of patients
  - CRS events were mostly Grade 1 (48%) or Grade 2 (12%); Grade 3 (3%) and Grade 4 (1%) events were uncommon
- **The incidence of AEs and SAEs was stable compared with earlier analyses[1,2]**
  - No new AEs were reported, including ICANS, CRS, infections, or Grade 5 AEs

N (%)	N=154
AE Glofitamab-related	152 (99) 140 (91)
Grade ≥3 AE Glofitamab-related	100 (65) 69 (45)
SAE Glofitamab-related	75 (49) 46 (30)
Grade 5 (fatal) AE Glofitamab-related	11 (7) 0
AE leading to treatment discontinuation Glofitamab-related	14 (9) 5 (3)
AE leading to dose modification/interruption of glofitamab Glofitamab-related	29 (19) 16 (10)

The safety profile was consistent with previous analyses, with no new AEs reported[1,2]

*By ASTCT grade. AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy criteria; ICANS, immune effector cell-associated neurotoxicity syndrome; SAE, serious adverse event.

1. Dickinson M, et al. N Engl J Med 2022;387:2220–31;
2. Dickinson M, et al. ICML 2023; Oral 095.

Conclusions

- The majority of patients with a CR are in remission at 24 months' follow-up
  - CR rates and DoCR in patients with prior CAR T-cell therapy were consistent with the overall population
- Majority of patients with a CR at EOT were alive and event-free 18 months after EOT
- Higher baseline TMTV may be prognostic for lower PFS and was associated with an increased risk of experiencing Grade ≥2 CRS
- No new AEs were observed since the previous analysis, reflecting the advantage of the fixed duration of glofitamab treatment
- **Fixed-duration glofitamab provides long-lasting remissions for patients with R/R LBCL**

2. Bispecific antibody therapy

- Health Canada conditional approval for Glofitamab and Epcoritamab
- Working group how to safely administer treatments, and how to admit patients smoothly/efficiently when required
- Patient support program for Epcoritamab currently open
- We are working on activating a clinical trial for Glofitamab in R/R MCL at TOH

3. Covalent BTK inhibitors in CLL

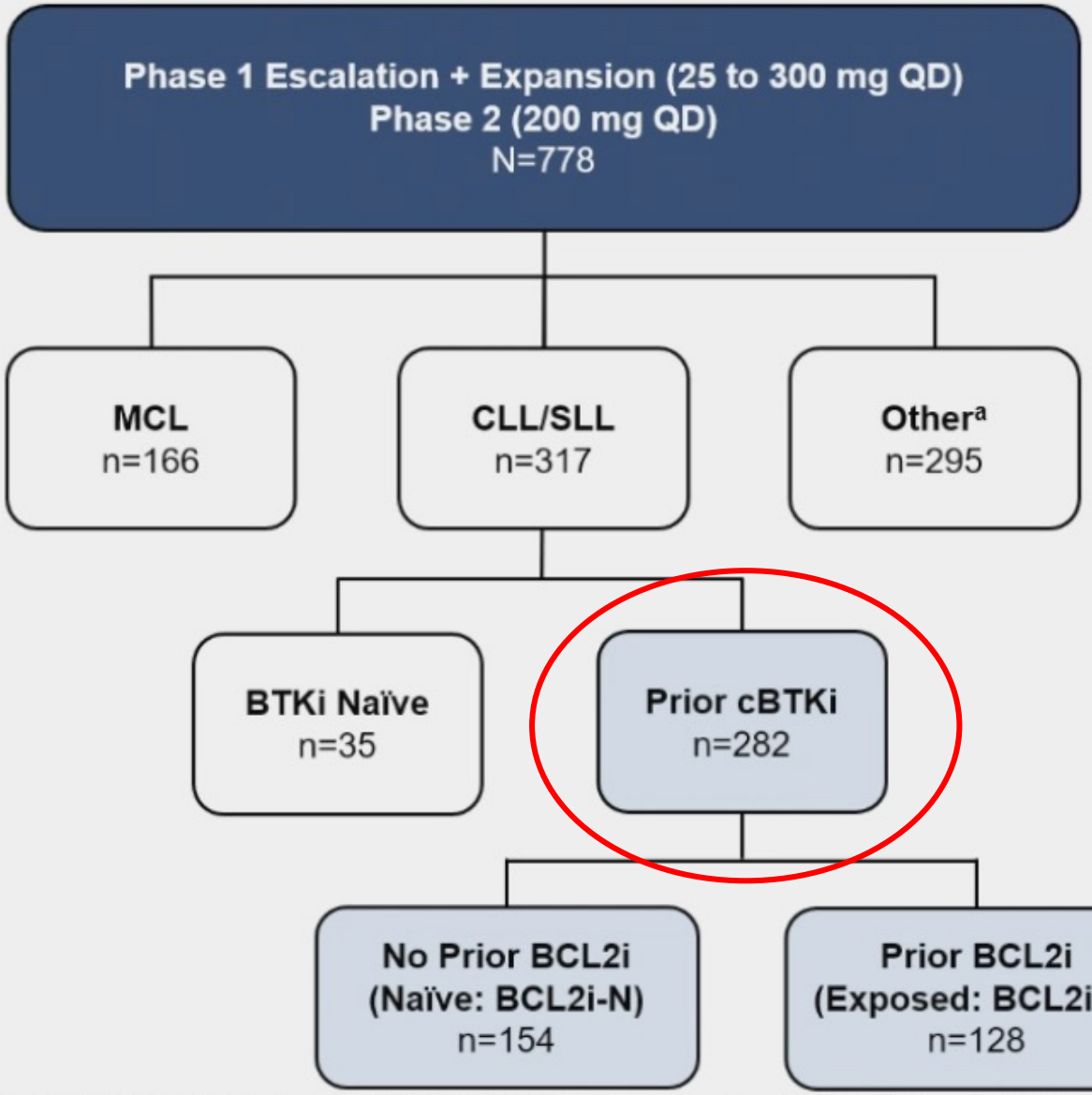
Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-up and Subgroup Analysis With/Without Prior BCL2i from the Phase 1/2 BRUIN Study – Woyach et al.

- In the past 5-10 years, the development of covalent BTK inhibitors (ie. ibrutinib, acalabrutinib, zanubrutinib) and BCL-2 inhibitors (ie. venetoclax) has greatly changed the treatment landscape of patients with CLL
- However, therapy with covalent BTK inhibitors (cBTKi) can fail due to progressive disease or intolerance
- Sometimes this occurs due to acquired mutations

3. Covalent BTK inhibitors in CLL

- Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi
- Pirtobrutinib can be effective in patients with R/R CLL, even if they have previously failed a cBTKi such as ibrutinib
- Effective in patients who have developed a common mutation that results in resistance against ibrutinib
- At ASH 2023, researchers presented an update on the group of CLL patients who had previously been treated with cBTKi

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)

Data cutoff of 05 May 2023 (NCT03740529). [a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

Baseline Characteristics of Patients with CLL/SLL who Received Prior cBTKi

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky Lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy, (range)	4 (1-11)	3 (1-9)	5 (1-11)
Prior therapy, n (%)			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (0)	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR-T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)

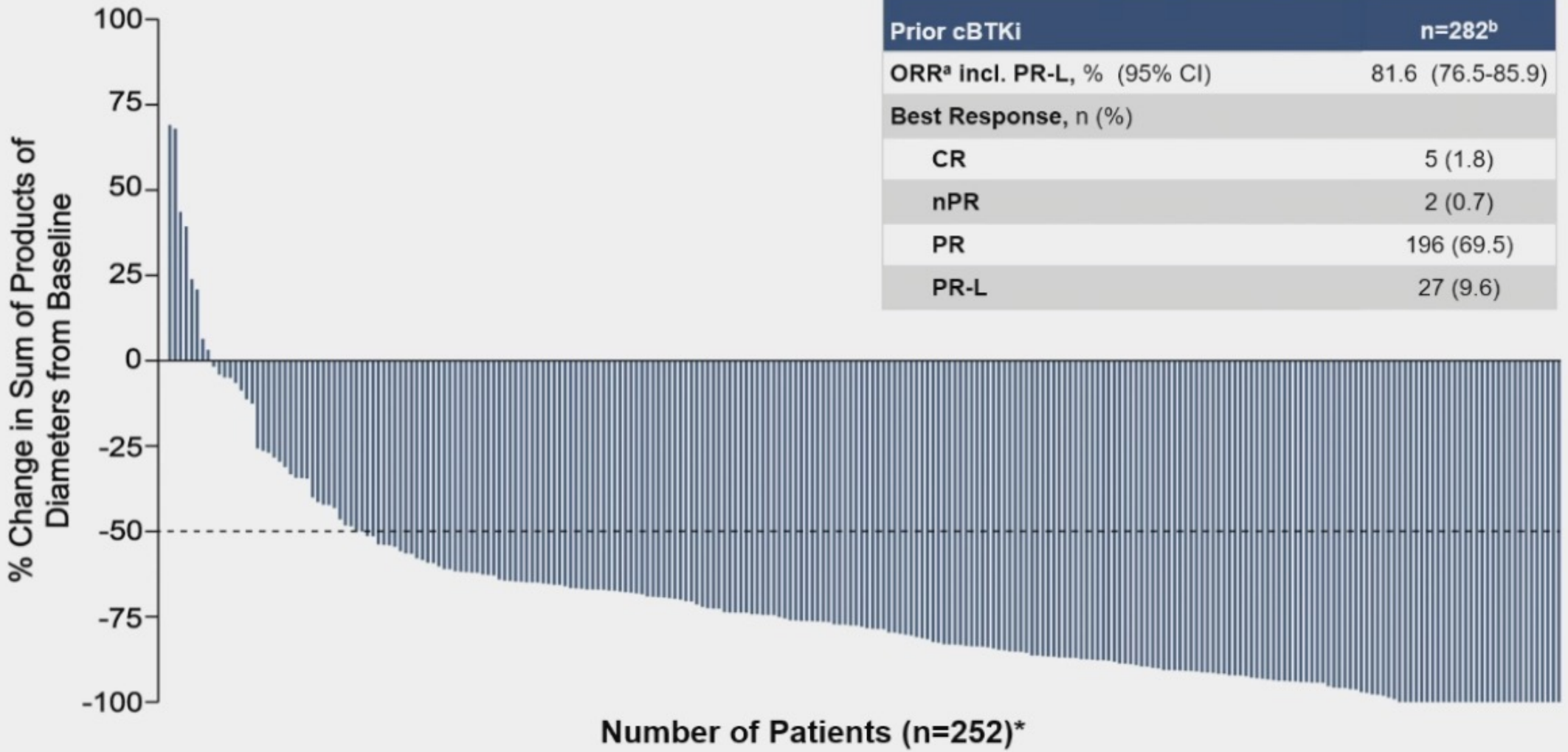
Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High Risk Molecular Features, n/n available (%)			
17p deletion and/or TP53 mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex Karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

[a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control.

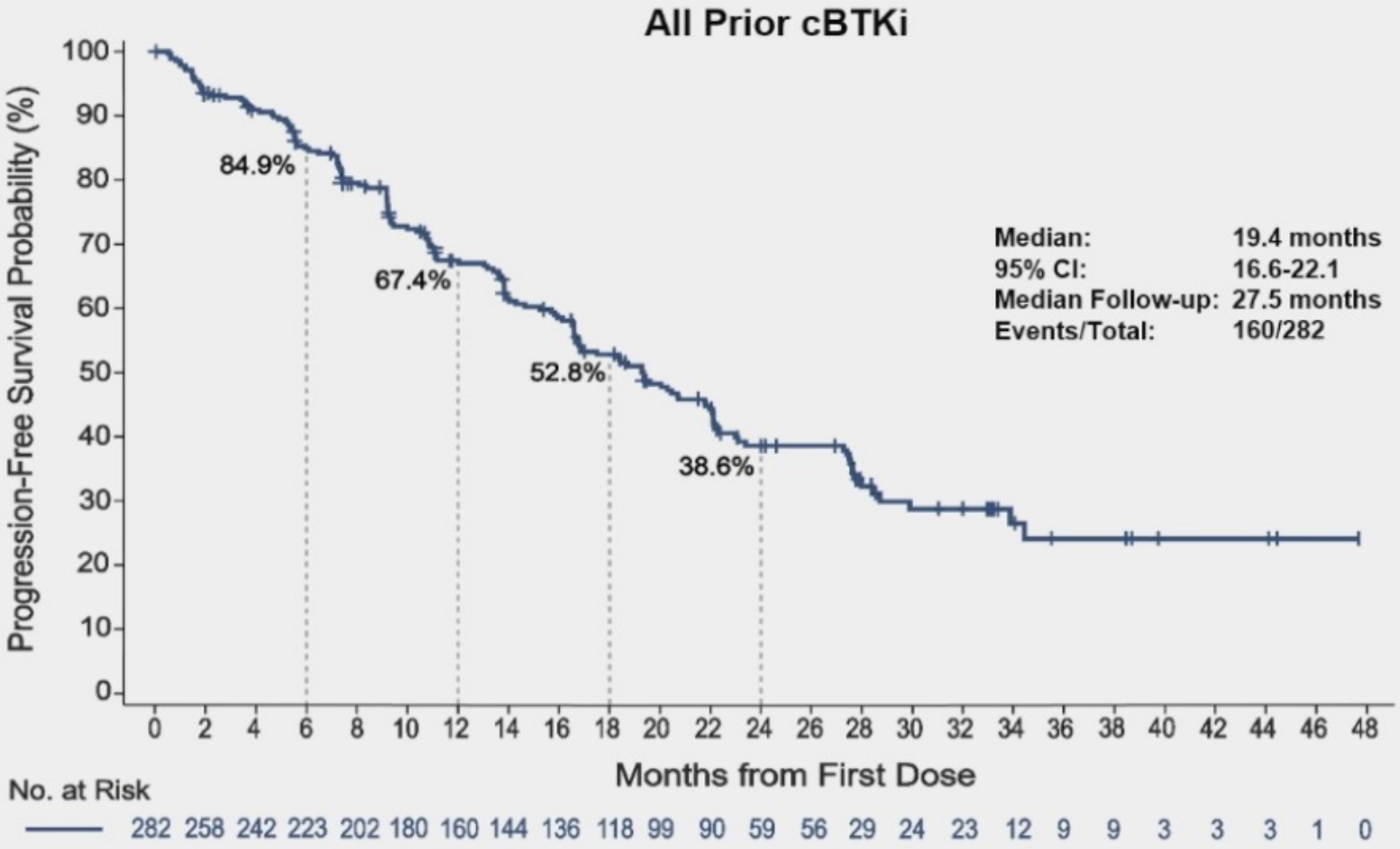
Pirtobrutinib Efficacy in All Patients with CLL/SLL who Received Prior cBTKi

Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)



Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Data for 30/282 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR including PR-L is the number of patients with best response of PR-L or better divided by the total number of patients; 14 patients with a best response of not evaluable (NE) are included in the denominator. [b]Post-cBTKi patients included a subgroup of 19 patients with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had an ORR including PR-L of 89.5% (95% CI: 66.9-98.7). Response status per iwCLL 2018 based on IRC assessment.

Pirtobrutinib Progression-Free Survival in Patients with Prior cBTKi



Pirtobrutinib Safety Profile of Patients who Received Prior cBTKi

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	36.9	1.8	3.5	0.0
Neutropenia[b,c]	34.4	28.4	19.5	15.2
Diarrhea	28.4	0.4	7.8	0.0
Cough	27.3	0.0	1.8	0.0
Contusion	26.2	0.0	17.4	0.0
Covid-19	25.9	4.6	0.7	0.0
Dyspnea	22.3	2.1	0.7	0.4
Nausea	22.0	0.0	3.5	0.0
Abdominal pain	21.3	1.8	2.1	0.4
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	74.1	30.9	12.8	4.3
Bruising[e]	30.1	0.0	19.1	0.0
Rash[f]	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage[g]	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter[h,i]	4.6	1.8	1.4	0.7

Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)
11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib dose reduction
7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib discontinuation
Safety profiles of BCL2i-N and BCL2i-E subgroups were similar and are described via the QR code

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Neutropenia at baseline for prior BTKi (n=282) was 18.4, BCL2i-N (n=154) was 11.0 and BCL2i-E (n=128) was 27.3. [c]Aggregate of neutropenia and neutrophil count decreased. [d]Aggregate of all preferred terms including infection and COVID-19. [e]Aggregate of contusion, ecchymosis, increased tendency to bruise and oral contusion. [f]Aggregate of all preferred terms including rash. [g]Aggregate of all preferred terms including hemorrhage or hematoma. [h]Aggregate of atrial fibrillation and atrial flutter. [i]Of the 13 total afib/aflutter TEAEs in the prior BTKi safety population (n=282), 6 occurred in patients with a prior medical history of atrial fibrillation.

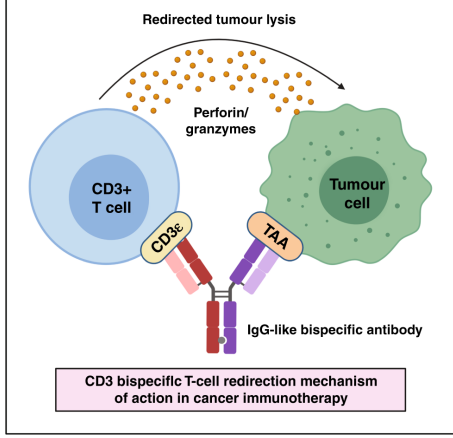
3. Covalent BTK inhibitors in CLL

- With follow-up of 30 months, pirtobrutinib continues to demonstrate clinically meaningful and durable efficacy in patients with previously treated CLL (all receiving prior cBTKi)
- Many patients were heavily pre-treated
- ORR 80% (regardless of prior BCL-2i exposure)
- Median PFS roughly 20 months in the group (slightly longer if no prior BCL-2i exposure)
- Well tolerated, low rates of discontinuation

3. Covalent BTK inhibitors in CLL

- At TOH, we currently have a clinical trial available for nemtabrutinib (another ncBTKi) for various types of lymphomas
- CLL cohort is full and no longer recruiting
- We are trying to activate another trial that will compare nemtabrutinib to cBTKi

4. Bispecific antibody therapy in FL



Mosunetuzumab Monotherapy Continues to Demonstrate Durable Responses in Patients with Relapsed and/or Refractory Follicular Lymphoma after ≥2 Prior Therapies: 3-Year Follow-up from a Pivotal Phase II Study – Schuster et al.

- Treatment options are limited in patients who have relapsed FL after more than 2 lines of therapy

Study design

Pivotal, single-arm, Phase II expansion study in patients with R/R FL and ≥2 prior therapies (NCT02500407)

Key inclusion criteria

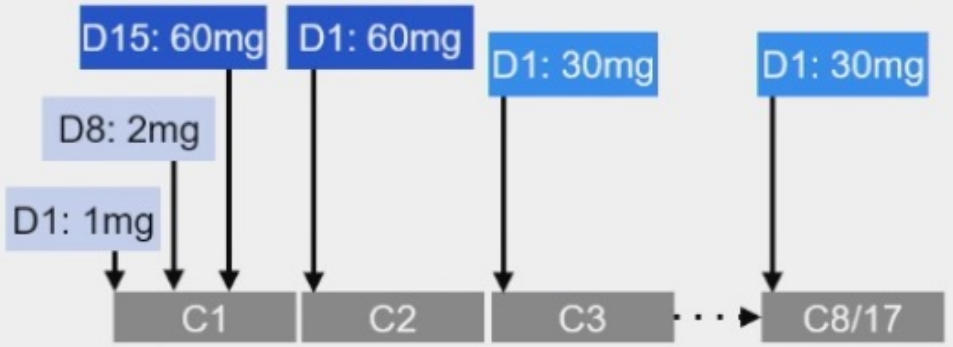
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

- Study met its primary endpoint: 60% CR rate versus 14% historic control ($p<0.0001$)[1,2]
- Updated efficacy and safety analysis with a median follow-up of 37.4 months

Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Retreatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PR, partial response; SD, stable disease.

1. Dreyling M, et al. J Clin Oncol 2017;35:3898–905;
2. Budde LE, et al. Lancet Oncol 2022;23:1055–65.

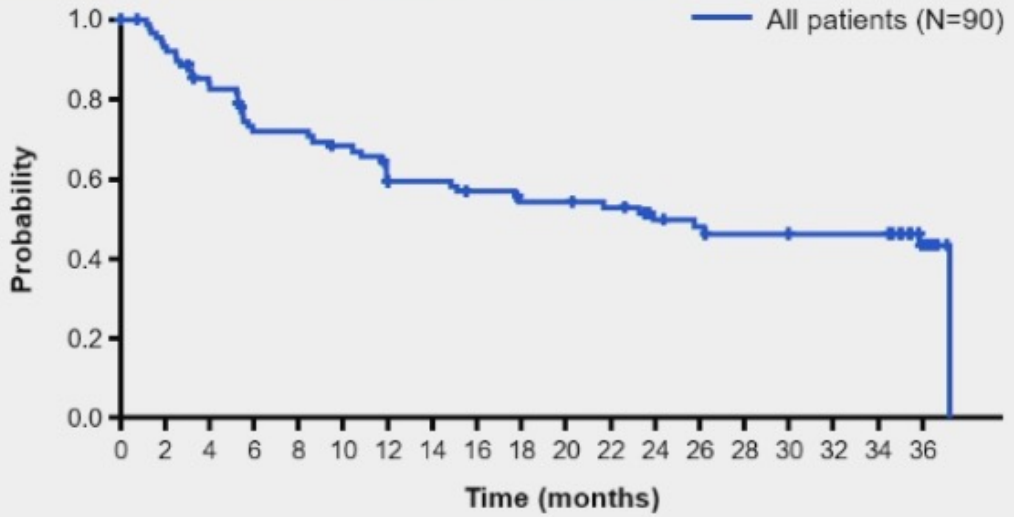
Baseline patient characteristics

n, unless stated	N=90
Median age, years (range)	60 (29–90)
Male	55 (61%)
ECOG PS	
0	53 (59%)
1	37 (41%)
Ann Arbor stage	
I/II	21 (23%)
III/IV	69 (77%)
Median lines of prior therapy, (range)	3 (2–10)
Prior autologous stem cell transplant	28 (31%)*
Refractory to last prior therapy	62 (69%)
Refractory to any prior anti-CD20 therapy	71 (79%)
POD24	47 (52%)
Double refractory to prior anti-CD20 and alkylator therapy	48 (53%)

*Data updated based on subsequent snapshot.

PFS and OS; median follow-up >36 months

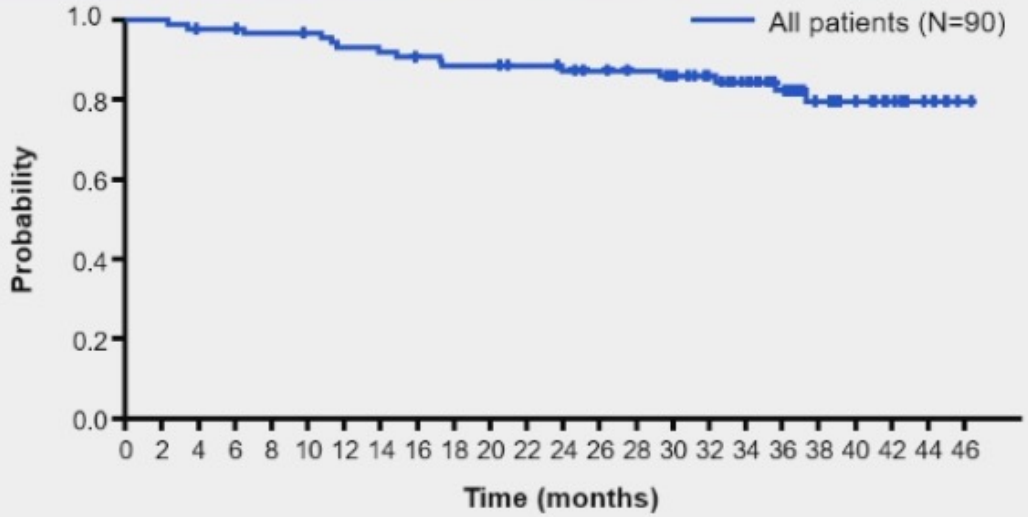
PFS



Patients at risk 90 81 72 60 59 55 47 46 43 40 40 38 30 27 25 25 24 24 13

	N=90
Median PFS, months (95% CI)	**24.0** (12.0–NE)
36-month PFS, months (95% CI)	**43.2%** (31.3–55.2)

OS



Patients at risk 90 89 87 86 85 84 81 80 78 76 76 74 72 70 68 62 56 51 39 26 21 14 8 1

	N=90
Median OS, months (95% CI)	**NR** (NE–NE)
36-month OS, months (95% CI)	**82.4%** (73.8–91.0)

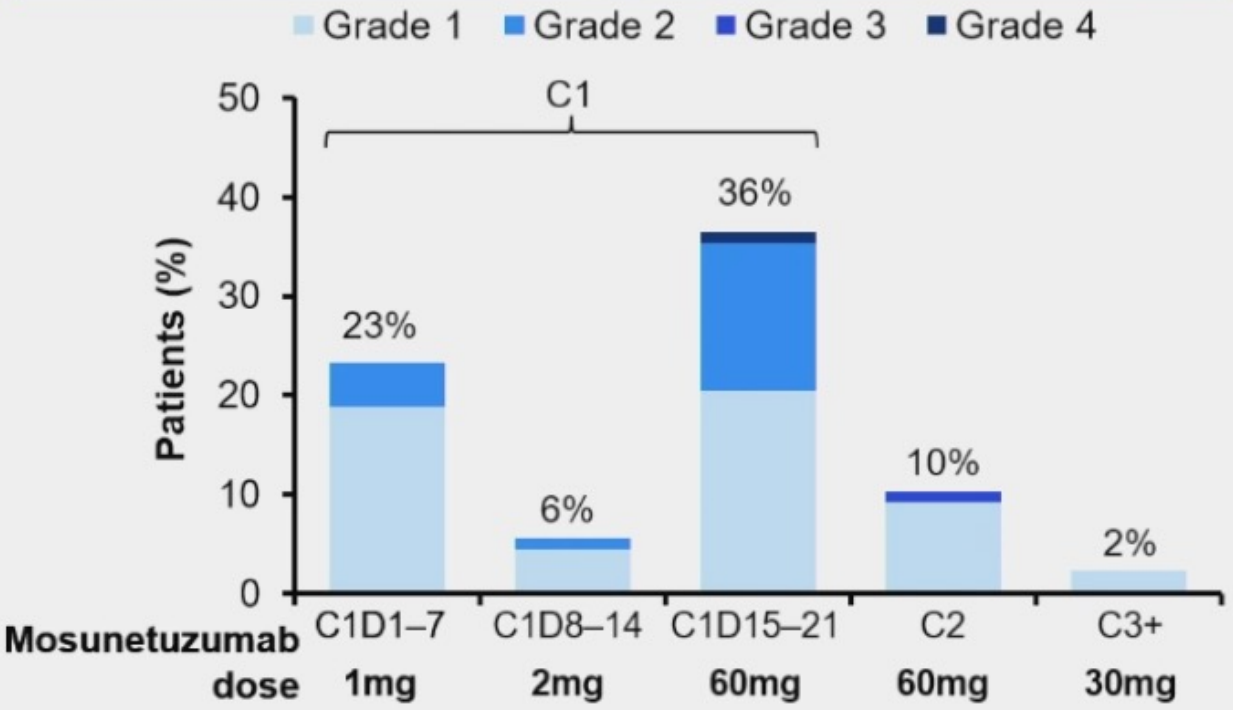
Robust and stable progression-free and overall survival rates at 3 years

OS, overall survival; PFS, progression-free survival.

CRS summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade), n	40 (44%)
Grade 1	23 (26%)
Grade 2	15 (17%)
Grade 3	1 (1%)
Grade 4	1 (1%)
Median time to CRS onset, hours (range)	
C1D1	5 (1–24)
C1D15	27 (0–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n	10 (11%)*
Tocilizumab for CRS management, n	7 (8%)*
Events resolved	100%

CRS by cycle and grade



CRS was predominantly low-grade and occurred during C1
All CRS events resolved; no new events have been reported in this extended follow-up

Data cut-off: August 27, 2021, as no new CRS events occurred subsequently.*Four patients received both corticosteroids and tocilizumab for CRS management. ASTCT, American Society for Transplantation and Cellular Therapy.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

4. Bispecific antibody therapy in FL

- In heavily pre-treated patients with R/R FL, fixed duration treatment with mosunetuzumab was well tolerated and led to long lasting remissions
- In patients who achieved CR: At 30 months, more than 70% were still in remission
- Manageable safety profile
- Outpatient treatment

5. Combination therapy in R/R MCL

LBA-2 Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study – Wang et al.

- Previous studies have shown us that ibrutinib is effective in patients with R/R MCL, and that venetoclax is also effective in this group
- This trial looked at the efficacy of combining the two treatments together
- TOH participated in this trial

5. Combination therapy in R/R MCL

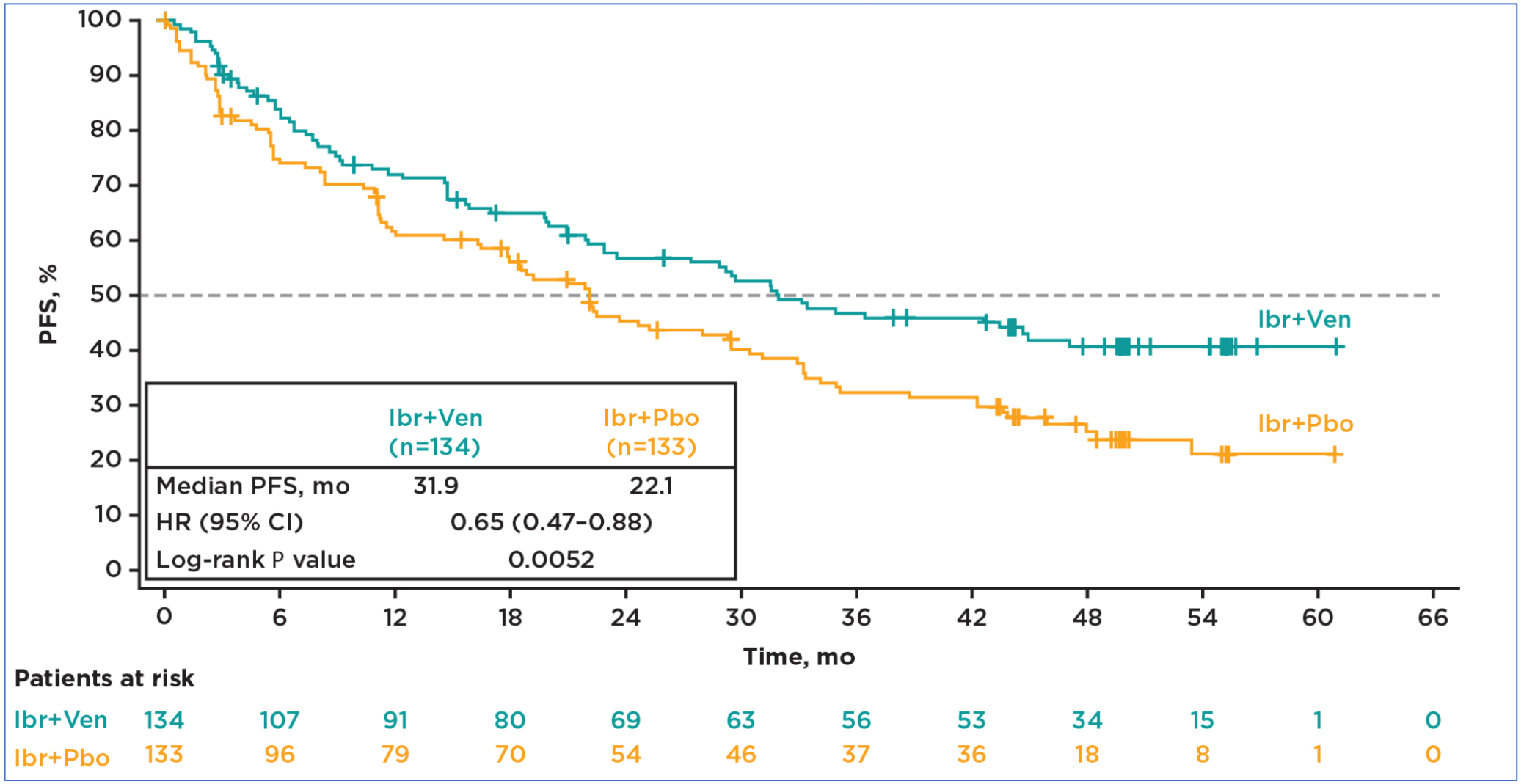
- Phase 3, randomized controlled trial comparing
- Ibrutinib + Venetoclax vs. Ibrutinib + Placebo
- Combination treatment for 2 years, followed by single agent ibrutinib until disease progression or unacceptable toxicity
- Patients with R/R MCL, 1-5 prior lines of therapy

5. Combination therapy in R/R MCL

- 134 patients randomly assigned to receive Ibrutinib + Venetoclax
- 133 patients randomly assigned to receive Ibrutinib + Placebo
- Median age 68
- 17% had >= 3 lines of prior therapy
- Roughly 40% in each group had LN > 5 cm
- Roughly 1/3 had enlarged spleens
- Roughly 1/3 had mutated TP53

5. Combination therapy in R/R MCL

- Median PFS 32 months in Ibrutinib + Venetoclax group vs. 22 months in Ibrutinib + Placebo group
- More effective even in high risk groups (TP53 mutated disease, blastoid variant)


PFS, %
100
90
80
70
60
50
40
30
20
10
0
Ibr+Ven
Ibr+Pbo
Ibr+Ven (n=134)
Ibr+Pbo (n=133)
Median PFS, mo 31.9 22.1
HR (95% CI) 0.65 (0.47–0.88)
Log-rank P value 0.0052
0 6 12 18 24 30 36 42 48 54 60 66
Time, mo
Patients at risk
Ibr+Ven 134 107 91 80 69 63 56 53 34 15 1 0
Ibr+Pbo 133 96 79 70 54 46 37 36 18 8 1 0

5. Combination therapy in R/R MCL

- Most frequent adverse events:
  - Neutropenia (31% vs 11%)
  - Pneumonia (13% vs 11%)
  - Thrombocytopenia (13% vs 8%)
  - Anemia (10% vs 3%)
  - Diarrhea (8% vs 2%)
  - Atrial fibrillation (5% vs 5%)
  - COVID-19 (5% vs 1%)
  - Hypertension (4% vs 9%)

5. Combination therapy in R/R MCL

- Ibr+Ven combination demonstrated improved PFS compared with Ibr+Pbo in pts with R/R MCL
- CR rates and TTNT were also significantly improved with Ibr+Ven
- OS not significantly improved at this interim analysis.
- The safety profile acceptable

Questions?