ASCO 2023 Review: Lymphoid Malignancies

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The University of Iowa

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Disclosures

None

Outline

- SWOG S1826: N-AVD versus BV-AVD in untreated advanced-stage classic Hodgkin lymphoma

- Alliance A041702: IVO versus IV in older patients with untreated chronic lymphocytic leukemia (CLL)

- TRANSCEND CLL 004: Lisocabtagene maraleucel in patients with relapsed/refractory CLL

- Bispecific antibodies in large-cell lymphomas:
  - EPCORE NHL-1: Epcoritamab in relapsed/refractory large-cell lymphoma
  - Glofitamab in relapsed/refractory large-cell lymphoma

# Classic Hodgkin Lymphoma (cHL): Frontline Therapy

SWOG S1826, a Randomized Study of Nivolumab(N)-AVD Versus Brentuximab Vedotin(Bv)-AVD in Advanced Stage Classic Hodgkin Lymphoma (cHL)

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Late Effects of Treatment in cHL

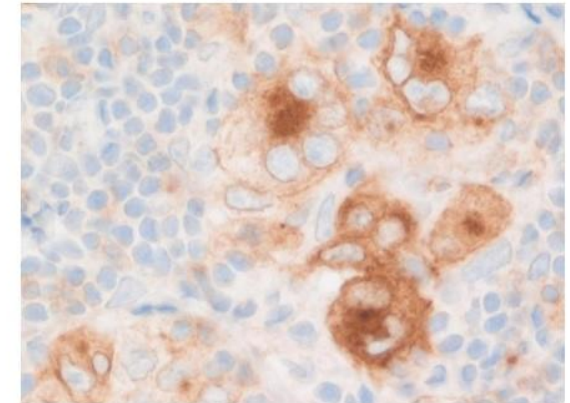- Long-term morbidity and mortality related to treatment remains significant for a largely young patient population[4]
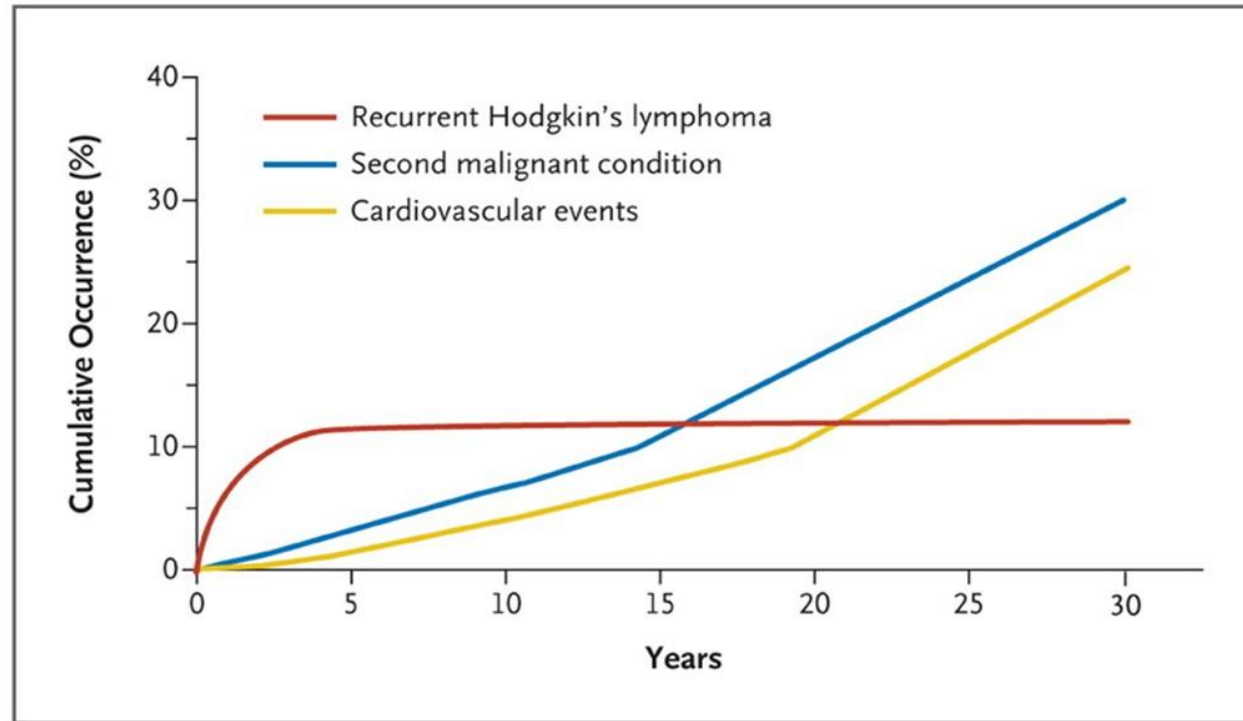
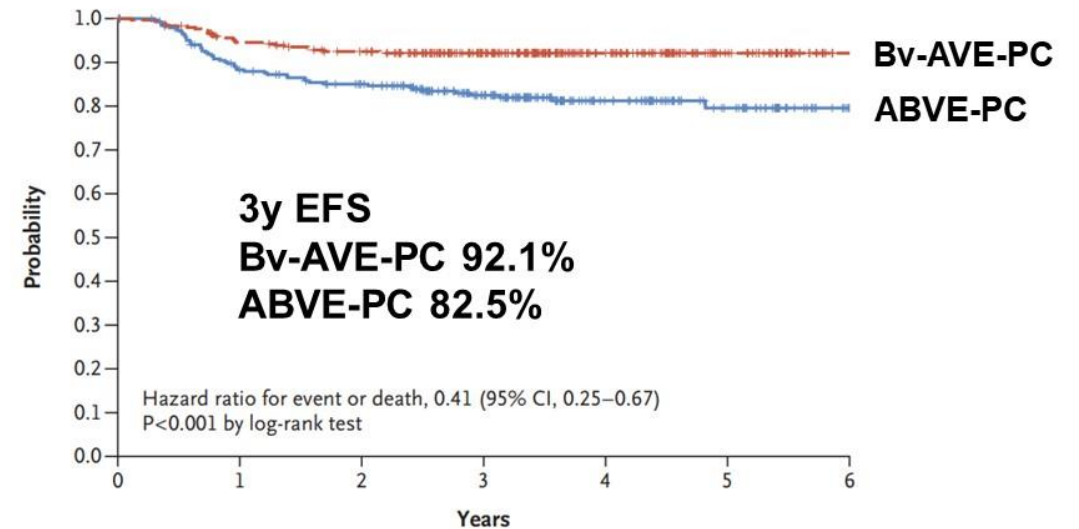4. Armitage JO. N Engl J Med 2010;363:653-662

Advanced Stage cHL (2018-present)

- Brentuximab vedotin (Bv): anti-CD30 antibody drug conjugate

- Bv in frontline treatment of advanced stage cHL improves outcomes in adult (OS) and pediatric (event-free survival) patients[4,5,6]

CD30 on Hodgkin Reed-Sternberg cells

Source: ASH Image Bank/Girish Venkataraman, MD, MBBS; Megan Parilla, MD

Bv-AVD

ABVD

Probability of Overall Survival

6y PFS
Bv-AVD 82.3%
ABVD 74.5%

6y OS
Bv-AVD 93.9%
ABVD 89.4%

No. of Deaths
Bv-AVD 39
ABVD 64

Hazard ratio for death, 0.59
(95% CI, 0.40–0.88)
P=0.009 by log-rank test

Months since Randomization

Bv-AVE-PC

ABVE-PC

Probability

3y EFS
Bv-AVE-PC 92.1%
ABVE-PC 82.5%

Hazard ratio for event or death, 0.41 (95% CI, 0.25–0.67)
P<0.001 by log-rank test

Years
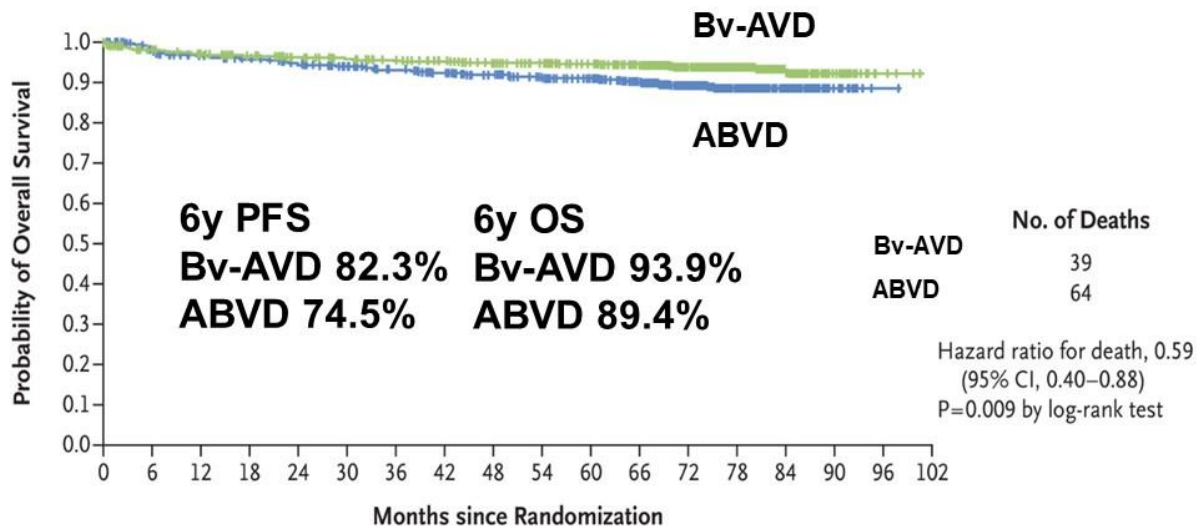
4. Ansell SM et al. NEJM 2022. 5. Castellino SM et al. NEJM 2022. 6. Borchmann P. et al. ISHL, ASH 2022.

S1826 Study Design

Newly diagnosed Stage III-IV Hodgkin lymphoma

RANDOMIZE

1:1

N-AVD x 6 cycles
Nivolumab 240mg days 1,15[a]
Doxorubicin, Vinblastine, Dacarbazine days 1,15[b]
G-CSF optional

470 pts

Bv-AVD x 6 cycles
Bv 1.2mg/kg days 1,15
Doxorubicin, Vinblastine, Dacarbazine days 1,15[b]
G-CSF required

470 pts

EOT RT (residual FDG-avid lesions)

Stratification:
- **Age** (12-17/18-60/>60)
- **IPS** (0-3/4-7)
- **EOT RT intended** (Y/N)

- Primary endpoint: PFS
- Assume 84% 2-year PFS for BV-AVD, 90% 2-year PFS in N-AVD, final analysis @ 179 events

S1826 Baseline Characteristics

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Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)	Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
Age, median (range)	27 (12-83)	26 (12-81)	Stage		
12-17 years	120 (25%)	117 (24%)	III	187 (38%)	167 (34%)
18-60 years	323 (66%)	323 (66%)	IV	301 (62%)	317 (65%)
≥ 61 years	46 (9%)	47 (10%)	Not reported	1 (0.2%)	3 (1%)
Female Sex	218 (45%)	213 (44%)	B symptoms present	286 (58%)	274 (56%)
Race			IPS Score		
White	375 (77%)	364 (75%)	0-3	331 (68%)	330 (68%)
Black	57 (12%)	56 (11%)	4-7	158 (32%)	157 (32%)
Asian	11 (2%)	17 (3%)	Bulky disease > 10cm	155 (32%)	131 (27%)
Other/Unknown	46 (9%)	50 (10%)	HIV+	10 (2%)	5 (1%)
Hispanic	68 (14%)	59 (12%)			

Representative study, inclusive of high-risk pts

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AEs of interest: Infectious

Toxicity	N-AVD n = 483	Bv-AVD n = 473
Febrile Neutropenia	26 (5%)	32 (7%)
Sepsis	9 (2%)	16 (3%)
Infections/Infestations	22 (5%)	36 (8%)

No increased infectious toxicity in N-AVD arm

AEs of Interest: Peripheral Neuropathy

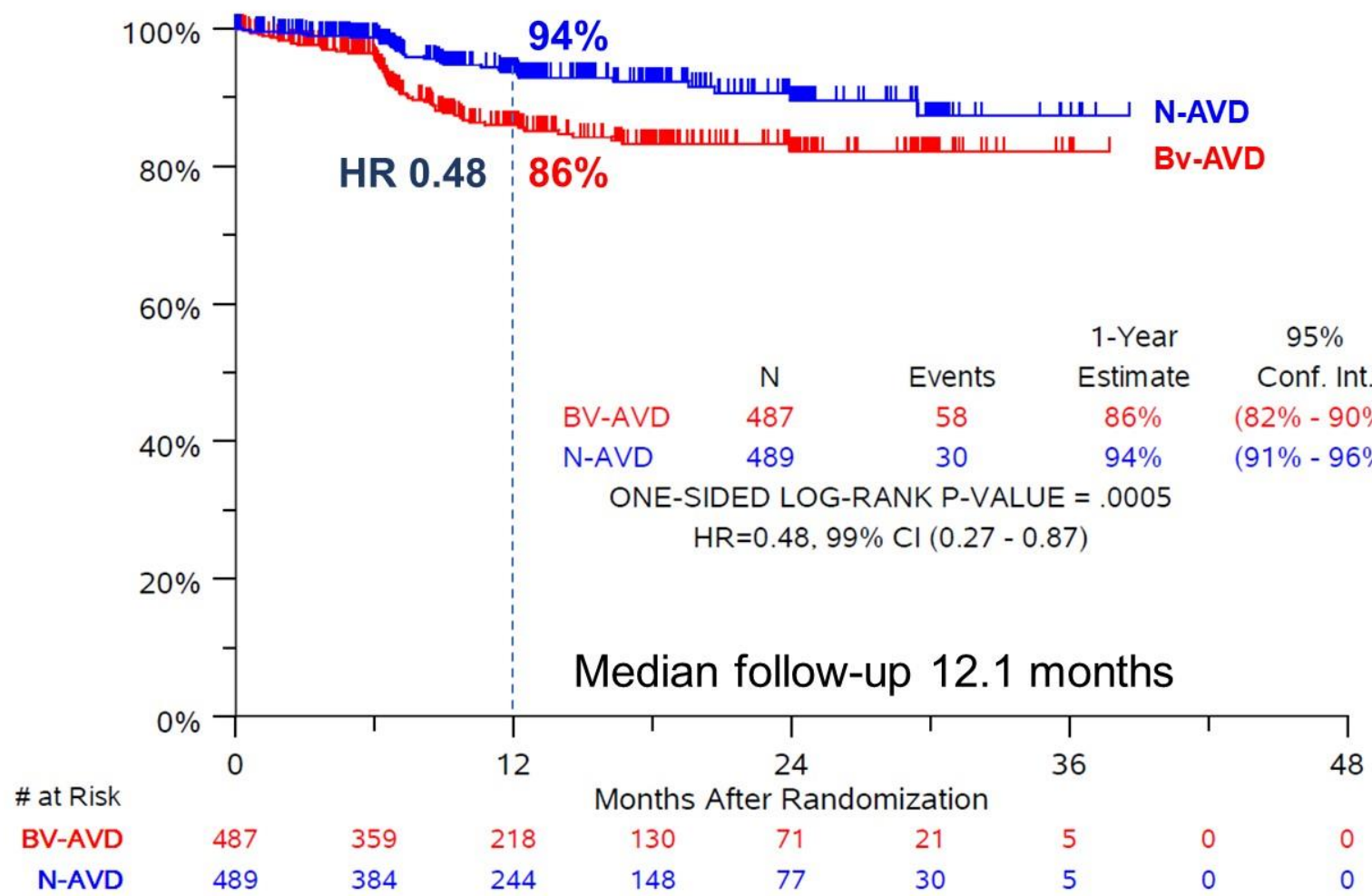| Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Peripheral sensory neuropathy	138 (29%)	6 (1%)	262 (55%)	37 (8%)
Peripheral motor neuropathy	20 (4%)	1 (0%)	35 (7%)	6 (1%)

More neuropathy in Bv-AVD arm

PRESENTED BY: Alex F. Herrera, MD

AEs of Interest: Immune/Other

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Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Grade No (%)	**Grade ≥ 3 No (%)**	**Any Grade No (%)**	**Grade ≥ 3 No (%)**
ALT increased	**156 (32%)**	**22 (5%)**	**194 (41%)**	**22 (5%)**
AST increased	**120 (25%)**	**12 (2%)**	**153 (32%)**	**13 (3%)**
Rash maculo-papular	51 (11%)	4 (1%)	58 (12%)	0 (0)
Hypothyroidism	**33 (7%)**	**1 (0%)**	**3 (1%)**	**0 (0)**
Rash acneiform	18 (4%)	0 (0)	12 (3%)	0 (0)
Pneumonitis	10 (2%)	2 (0%)	15 (3%)	10 (2%)
Gastritis	10 (2%)	3 (1%)	8 (2%)	0 (0)
Hyperthyroidism	**14 (3%)**	**0 (0)**	**0 (0)**	**0 (0)**
Colitis	5 (1%)	1 (0%)	6 (1%)	4 (1%)

Low rates of immune-related adverse events

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N-AVD improves PFS compared to Bv-AVD

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94%

HR 0.48 **86%**

N-AVD
Bv-AVD

1-year PFS
N-AVD 94%
Bv-AVD 86%

	N	Events	1-Year Estimate	95% Conf. Int.
BV-AVD	487	58	86%	(82% - 90%)
N-AVD	489	30	94%	(91% - 96%)

ONE-SIDED LOG-RANK P-VALUE = .0005
HR=0.48, 99% CI (0.27 - 0.87)

Median follow-up 12.1 months

Months After Randomization

# at Risk	0	12	24	36	48				
BV-AVD	487	359	218	130	71	21	5	0	0
N-AVD	489	384	244	148	77	30	5	0	0

PFS benefit consistent across subgroups

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)		P Value
Age					
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)		0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)		0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)		0.013

Subgroup	A+AVD	ABVD	Hazard Ratio (95% CI)	
	no. of events/total no. (%)			
Overall	117/664 (17.6)	146/670 (21.8)		0.77 (0.60–0.98)
Age				
<60 yr	93/580 (16.0)	117/568 (20.6)		0.73 (0.56–0.96)
≥60 yr	24/84 (28.6)	29/102 (28.4)		1.00 (0.58–1.72)

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Overall Survival

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Cause of death	N-AVD	Bv-AVD
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1**	0
Unknown	1	2
Total OS events	**4**	**11**

* 1 death from COVID-19/sepsis
** never received treatment, ineligible on C1D1

Within the graph:

	N	Events	1-Year Estimate	95% Conf. Int.
BV-AVD	487	11	98%	(96% - 99%)
N-AVD	489	4	99%	(98% - 100%)

Median follow-up 12.1 months

at Risk

	0	12		24		36		48
BV-AVD	487	364	238	144	74	22	5	0	0
N-AVD	489	386	256	157	85	32	6	0	0

S1826 Main Findings

- At planned 2nd interim analysis (50% of total PFS events), the SWOG Data and Safety Monitoring Committee recommended to report the primary S1826 results because the primary PFS endpoint crossed the protocol-specified conservative statistical boundary

- N-AVD improved progression-free survival (PFS) compared to Bv-AVD as initial treatment of advanced stage cHL

- N-AVD was well-tolerated
  - Few immune-related adverse events
  - < 1% of patients received radiation therapy (RT)

- Key step towards harmonizing pediatric and adult therapy of cHL

- **N-AVD is poised to be a new standard for treatment of advanced stage cHL**

My Takeaways

- I plan to adopt Nivo-AVD as the new standard of care in patients with advanced-stage cHL, with the caution that this data read-out is still early.

- The toxicities of checkpoint inhibition can still be significant. Longer term follow-up and analysis of patient-reported outcomes (PROs) will be critical to determine impact on survivorship.

- Nivo-AVD may finally represent a true 'standard of care' option for elderly patients with cHL.

Chronic Lymphocytic Leukemia (CLL): Frontline Therapy

Results of A041702: A Phase 3 Study of IVO vs IO for Previously Untreated Older Patients with Chronic Lymphocytic Leukemia and Impact of COVID-19

Jennifer A Woyach, Jun Yin, Jennifer Brown, Shira Dinner, Gerard Lozanski, Richard F Little, Cecelia Miller, Vijay Darmala, Steven Coutre, Wei Ding, Brian Hill, Gabriela Perez, Amy Ruppert, Anna Wall, Diane Feldman, Elie G Dib, Harry Erba, Mark Litzow, Richard Stone, John C Byrd

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Acalabrutinib[f,*] ± obinutuzumab (category 1) • Venetoclax[f,g] + obinutuzumab (category 1) • Zanubrutinib[f,*] (category 1)	• Ibrutinib (category 1)[f,h,*] • Bendamustine[i] + anti-CD20 mAb[d,j,k] • Chlorambucil + obinutuzumab[l] • Obinutuzumab[l] • High-dose methylprednisolone (HDMP) + rituximab or obinutuzumab (category 2B; category 3 for patients <65 y without significant comorbidities) • Ibrutinib[f,*] + obinutuzumab[l] (category 2B) • Ibrutinib[f,*] + rituximab[p] (category 2B) • Ibrutinib[*] + venetoclax[f,g] (category 2B)	(consider for IGHV-mutated CLL in patients age <65 y without significant comorbidities) • FCR (fludarabine, cyclophosphamide, rituximab)[m,n,o]

* Covalent (irreversible) BTK inhibitors.

Study Schema

Previously Untreated CLL patients age ≥ 65

Stratification based upon
- **Rai Stage**
- **+/- del17p**

- Patients in need of therapy (IWCLL 2008 criteria)

R a n d o m i z e

Ibrutinib + Obinutuzumab → Any response → Continue Ibrutinib

Ibrutinib + Obinutuzumab + Venetoclax → uMRD CR → Discontinue Ibrutinib

Ibrutinib + Obinutuzumab + Venetoclax → Any other response → Continue Ibrutinib

End of Cycle 14 response assessment
- **Bone marrow MRD by flow cytometry**
- **CT scans**
- **Bloodwork and exam**

Primary endpoint: Progression-free survival

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3

Patient Characteristics

Characteristic	IO N=232	IVO N=233	Total N=465
Age (years), median (range)	74 (65-89)	74 (65-89)	74 (65-89)
Male, %	70.3%	64.8%	67.5%
ECOG 0-1, %	97%	97%	97%
Del (17p)	13%	13%	13%
IGVH unmutated, %	55%	47%	51%
Rai Stage III/IV, %	55%	55%	55%

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Grade 3, 4, or 5 Adverse Events

Adverse Event	IO N=232	IVO N=233	P-value
All Hematologic -- no. (%)	**112 (48%)**	**142 (61%)**	**.006**
Anemia	18 (8%)	24 (10%)	.339
Neutrophil count decreased	77 (33%)	95 (41%)	.090
Platelet count decreased	20 (9%)	33 (14%)	.060
All Non-hematologic -- no. (%)	**153 (66%)**	**157 (67%)**	**.743**
Pneumonitis	3 (1%)	1 (0.4%)	.313
COVID 19 infection	16 (7%)	31 (13%)	.022
Febrile neutropenia	5 (2%)	6 (3%)	.766
Atrial fibrillation/Atrial flutter*	54 (23%)	58 (25%)	.684
Hypertension	61 (26%)	60 (26%)	.894

*All grades

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8

Primary Endpoint: Progression Free Survival
Eligible Patient Population
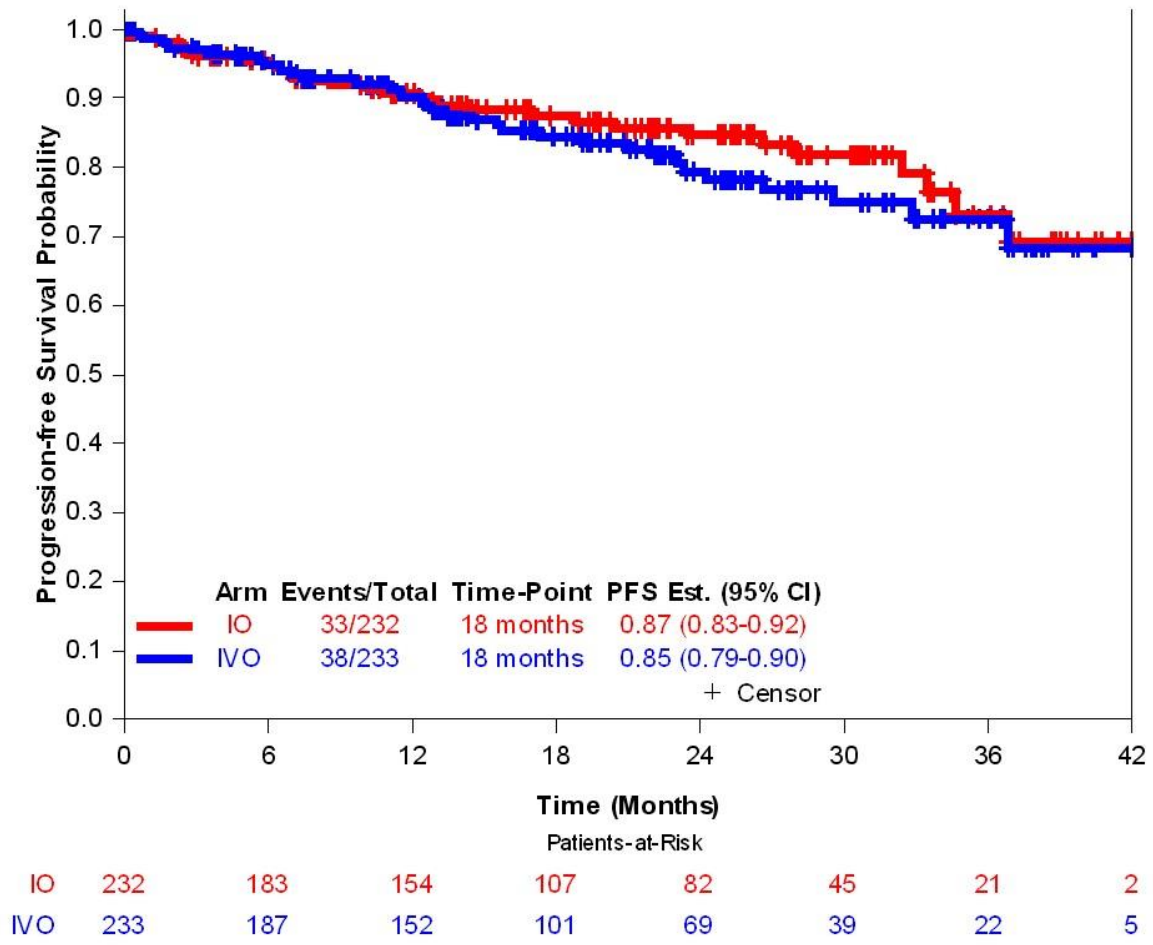
IVO vs IO:
Hazard Ratio 1.12
95% CI: 0.70-1.79

Arm	Events/Total	Time-Point	PFS Est. (95% CI)
IO	33/232	18 months	0.87 (0.83-0.92)
IVO	38/233	18 months	0.85 (0.79-0.90)

+ Censor

Time (Months)

Patients-at-Risk

	0	6	12	18	24	30	36	42
IO	232	183	154	107	82	45	21	2
IVO	233	187	152	101	69	39	22	5

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9

Overall Survival
Intention-to-Treat Patient Population
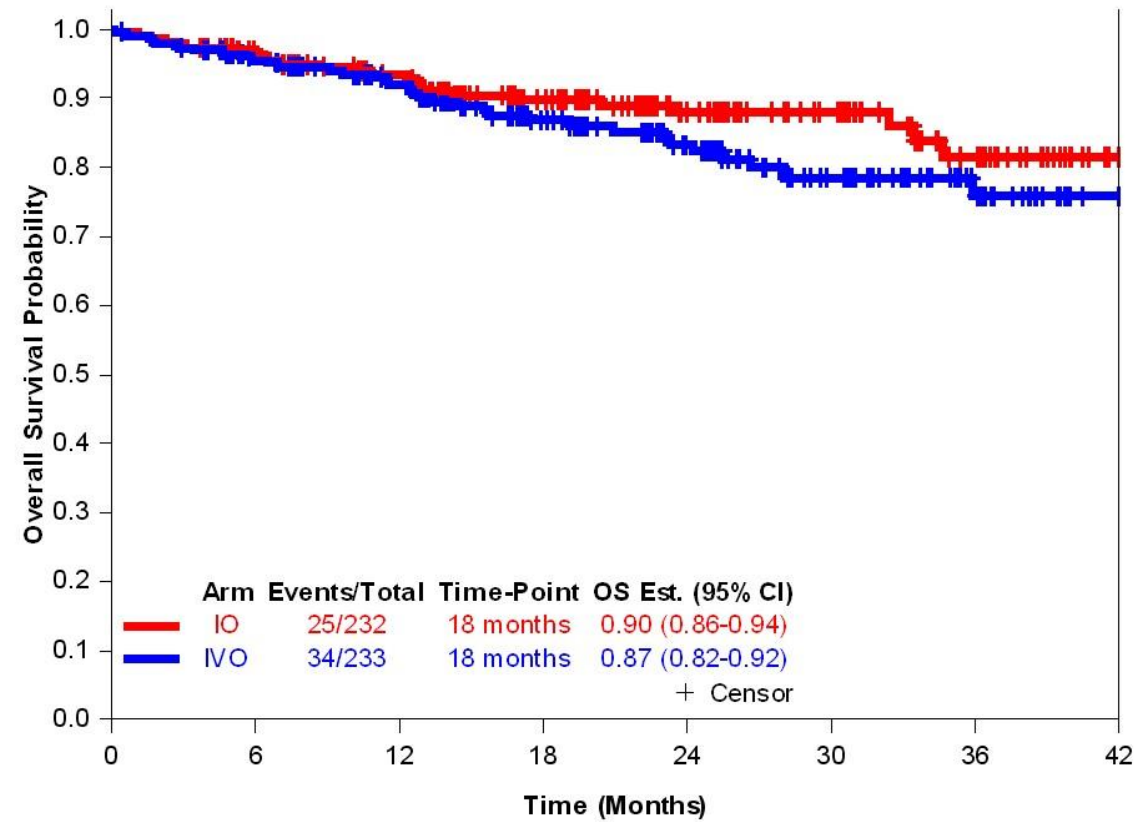
IVO vs IO:
Hazard Ratio 1.34
95% CI: 0.80-2.25
(2-sided P value 0.26)

Arm	Events/Total	Time-Point	OS Est. (95% CI)
IO	25/232	18 months	0.90 (0.86-0.94)
IVO	34/233	18 months	0.87 (0.82-0.92)

+ Censor

Patients-at-Risk

IO	232	201	167	122	88	60	32	3
IVO	233	200	163	116	85	52	28	8

10

Minimal Residual Disease and Response Rate at Re-registration

- Ibrutinib plus obinutuzumab
  - CR: 31.3% (N=102)
  - Undetectable MRD: 33.3% (N=126)

- Ibrutinib plus obinutuzumab plus venetoclax
  - CR: 68.5% (N=111)
  - Undetectable MRD: 86.8% (N=129)

Legend:
- IO (red)
- IVO (blue)

13

PFS of IVO by MRD Status

MRD Status	Events/Total	Time-Point	PFS Est. (95% CI)
Negative	12/112	18 months	0.97 (0.94-1.00)
Positive	1/17	18 months	1.00 (1.00-1.00)

+ Censor

Time (Months)

Patients-at-Risk

Negative	112	112	111	81	58	31	18	3
Positive	17	17	17	9	8	5	1	0

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

14

Conclusions

- In this study, IVO is not superior to IO for the initial treatment of older patients with CLL

- COVID 19 may have significantly altered these results, with data suggesting a death imbalance for patients treated with venetoclax

- At this follow-up, PFS with IVO is not impacted by MRD or response status at end of 14 cycles

- Long-term follow-up of this study will be critical to determine whether some patients benefit from IVO

18

My Takeaways

- Combining our most active agents (BTKi + venetoclax + anti-CD20 mAb) in the frontline treatment of CLL has not yet moved the needle in daily practice.
- Addition of venetoclax to BTKi increases rates of undetectable MRD, but its correlation with clinical outcomes remains unclear.
- Longer follow-up will determine whether the addition of venetoclax to BTKi contributes to clinically valuable benefits (PFS benefit alone may not be "enough").

Chronic Lymphocytic Leukemia (CLL): Relapsed/Refractory Treatment

Lisocabtagene maraleucel in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: primary analysis of TRANSCEND CLL 004

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[1]City of Hope National Medical Center, Duarte, CA, USA; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]Mayo Clinic, Rochester, MN, USA; [4]Duke University Health System, Durham, NC, USA; [5]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [6]Center for Lymphoma, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]The David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL, USA; [8]Medical College of Wisconsin, Milwaukee, WI, USA; [9]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [10]University of California San Francisco, San Francisco, CA, USA; [11]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [12]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [13]John Theurer Cancer Center at Hackensack Meridian Health, HMH School of Medicine, Hackensack, NJ, USA; [14]Northside Hospital Cancer Institute, Atlanta, GA, USA; [15]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]Bristol Myers Squibb, Seattle, WA, USA; [18]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract number 7501

High unmet need in R/R CLL/SLL after BTKi and venetoclax

- Outcomes remain poor for patients with R/R CLL/SLL who have relapsed after prior BTKi and venetoclax failure, with low CR/CRi rates of 0%—5% and short median OS[1—6]

- Real-world evidence indicates progressively worse outcomes as treatment options become exhausted[7]
  - Median time from dual discontinuation of BTKi and venetoclax to subsequent treatment failure or death was 5.6 months

- Liso-cel is an autologous, CD19-directed CAR T cell product administered at equal target doses of CD8$^+$ and CD4$^+$ CAR$^+$ T cells

- Here we report the primary analysis of the liso-cel monotherapy portion of TRANSCEND CLL 004, with a median on-study follow-up of 21.1 months

BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CRi, complete response/remission with incomplete marrow recovery; liso-cel, lisocabtagene maraleucel; SLL, small lymphocytic lymphoma.
1. Patel K, et al. *J Hematol Oncol* 2021;14:69; 2. Sedlarikova L, et al. *Front Oncol* 2020;10:894; 3. Lew TE, et al. *Blood Adv* 2021;5:4054—4058; 4. Jones J, et al. *Blood* 2016;128:637; 5. Mato AR, et al. *Clin Cancer Res* 2020;26:3589—3596; 6. VENCLEXTA® (venetoclax) [package insert]. North Chicago, IL: AbbVie Inc.; June 2022; 7. Mato AR, et al. *Clin Lymphoma Myeloma Leuk* 2023;23:57—67.

TRANSCEND CLL 004 study design: phase 1/2, open-label, multicenter study

ClinicalTrials.gov: NCT03331198

Screening

Enrollment and leukapheresis

Eligibility criteria reaffirmed

Bridging therapy allowed

Liso-cel manufacturing

Lymphodepletion
FLU 30 mg/m^2 and
CY 300 mg/m^2 × 3 days

Liso-cel
(2—7 days after FLU/CY)
DL1: 50 × 10^6 CAR$^+$ T cells
DL2: 100 × 10^6 CAR$^+$ T cells

Phase 1 (DL1 + DL2)	Phase 2 (DL2)

Follow-up
On-study: 24 or 48 months[a]
Long-term: ≤ 15 years after last liso-cel treatment
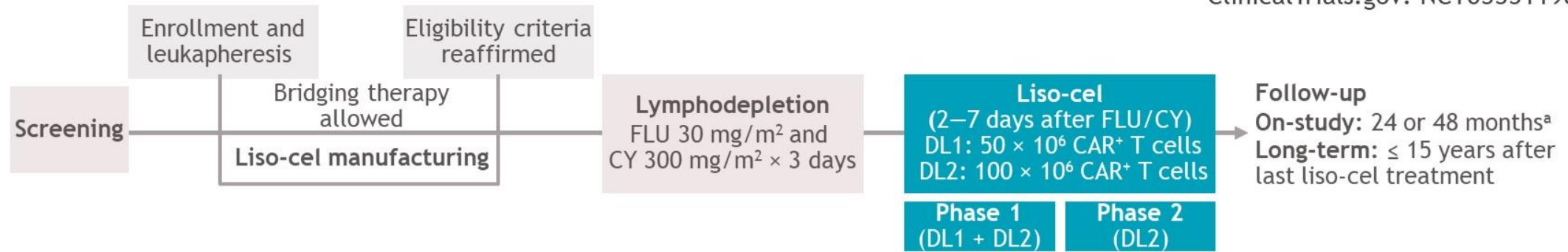
Key patient eligibility criteria
- Age ≥ 18 years
- R/R CLL/SLL with an indication for treatment
- Previously failed or ineligible for BTKi therapy
- Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
- ECOG PS ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy

Primary endpoint (PEAS at DL2)
- CR/CRi rate per iwCLL 2018 by IRC assessment

Key secondary endpoints (PEAS at DL2)
- ORR, uMRD rate in blood

Other secondary endpoints
- DOR, DOCR, PFS, TTR, TTCR per IRC assessment, OS, uMRD CR rate in blood, and safety

- Primary and key secondary endpoints were tested in a prespecified subset of patients with BTKi progression and venetoclax failure (PEAS) at DL2 by the following hierarchy: CR/CRi rate ($H_0 \leq 5\%$), ORR ($H_0 \leq 40\%$), and uMRD rate in blood ($H_0 \leq 5\%$)

[a]Duration of follow-up was increased to 48 months in protocol amendment 5 (February 16, 2021). Patients still in ongoing response per iwCLL 2018 criteria after the 2-year follow-up were followed for safety, disease status, additional anticancer therapies, and survival for an additional 2 years or until progression. CY, cyclophosphamide; DL, dose level; DOCR, duration of complete response/remission; DOR, duration of response; FLU, fludarabine; H_0, null hypothesis; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PEAS, primary efficacy analysis set; TTCR, time to complete response/remission; TTR, time to response; uMRD, undetectable minimal residual disease.

Demographics and baseline characteristics

Characteristic	Full study population (n = 117)	BTKi progression/venetoclax failure subset (n = 70)
Median (range) age, y	65.0 (49—82)	66.0 (49—78)
Median (range) prior lines of systemic therapy	5 (2—12)	5 (2—12)
Bulky lymph nodes,[a] n (%)		
Yes	52 (44)	32 (46)
Unknown	9 (8)	8 (11)
High-risk cytogenetics, n (%)	97 (83)	60 (86)
Prior BTKi, n (%)	117 (100)	70 (100)
BTKi refractory[b]	103 (88)	70 (100)
BTKi relapsed[c]	2 (2)	0
BTKi intolerant only	12 (10)	0
Prior venetoclax, n (%)	94 (80)	70 (100)
Venetoclax refractory[b]	89 (76)	67 (96)
Venetoclax relapsed[c]	0	0
Venetoclax intolerant only	4 (3)	3 (4)
Prior BTKi and venetoclax, n (%)	94 (80)	70 (100)
BTKi progression/venetoclax failure,[d] n (%)	70 (60)	70 (100)
Received bridging therapy, n (%)	89 (76)	55 (79)

[a]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [b]Defined as no response or progression ≤ 6 months from last dose of therapy; [c]Defined as disease progression in a patient who previously had CR/CRi or PR/nPR for ≥ 6 months; [d]Including patients who progressed on a BTKi and met one of the following: (1) discontinued venetoclax due to disease progression or intolerability and patient's disease met indications for further therapy per iwCLL 2018, or (2) failed to achieve an objective response ≤ 3 months of initiating therapy. nPR, nodular partial response/remission.

Efficacy outcomes

Efficacy	Full study population at DL2 (n = 87)	BTKi progression/venetoclax failure subset at DL2 (n = 49)
Primary endpoint: IRC-assessed CR/CRi rate (95% CI) per iwCLL 2018, %	18 (11—28)	18 (9—32); *P* = 0.0006[a]
Key secondary endpoints		
IRC-assessed ORR (95% CI), %	47 (36—58)	43 (29—58); *P* = 0.3931[a]
uMRD rate in blood (95% CI), %	64 (53—74)	63 (48—77)[b]
Exploratory endpoint: uMRD rate in marrow (95% CI), %	59 (48—69)	59 (44—73)
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	16 (18)	9 (18)
PR/nPR	25 (29)	12 (24)
SD	34 (39)	21 (43)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Median (range) time to first response, months	1.5 (0.8—17.4)	1.2 (0.8—17.4)
Median (range) time to first CR/CRi, months	4.4 (1.1—17.9)	3.0 (1.1—6.1)

- **All MRD-evaluable responders were uMRD in blood and marrow**; 12 of 20 MRD-evaluable patients with SD were uMRD in blood

[a]One-sided *P* value from binomial exact test (H$_0$ of CR/CRi ≤ 5%; H$_0$ of ORR ≤ 40%); [b]*P* value not presented for uMRD rate in blood (H$_0$ ≤ 5%) because the ORR hypothesis was not rejected at 1-sided 2.5% significance level. MRD, minimal residual disease; SD, stable disease.

Progression-free survival

(A) Full study population at DL2 (n = 87)

Median (95% CI) follow-up: 24.0 mo (18.3–26.4)

NR (30.1–NR)

26.9 mo (17.9–NR)

18.0 mo (9.4–30.1)

3.7 mo (2.4–6.3)

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 49)

Median (95% CI) follow-up: 20.8 mo (17.6–25.2)

NR

26.2 mo (10.3–NR)

11.9 mo (5.7–26.2)

3.7 mo (2.1–6.4)
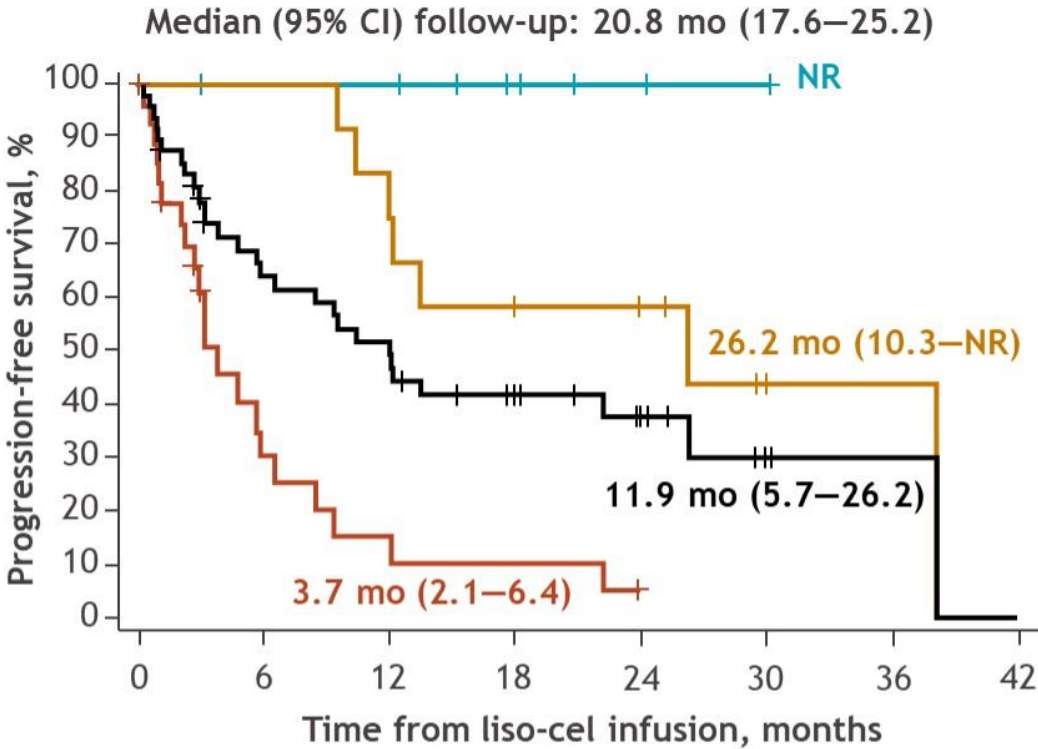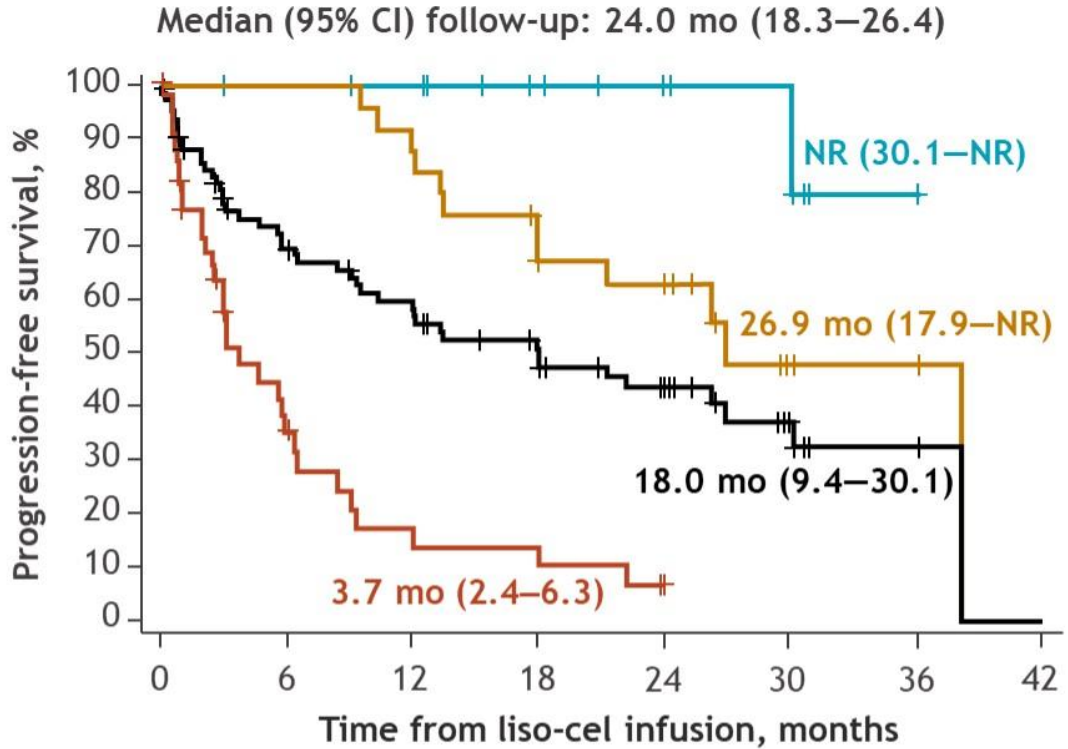
No. at risk								
CR/CRi	16	15	14	10	6	5	1	0
PR/nPR	25	25	22	15	11	3	2	0
Nonresponder	46	11	4	3	1	0	0	0
Total	87	51	40	28	18	8	3	0

9	8	8	5	2	1	0	0
12	12	9	6	5	1	1	0
28	6	2	2	0	0	0	0
49	26	19	13	7	2	1	0

Data on Kaplan-Meier curves are expressed as median (95% CI, if available).

Overall survival

(A) Full study population at DL2 (n = 87)

Median (95% CI) follow-up: 24.2 mo (23.3–29.7)

NR

NR

43.2 mo (26.9–NR)

10.7 mo (6.4–27.1)

Overall survival, %

Time from liso-cel infusion, months
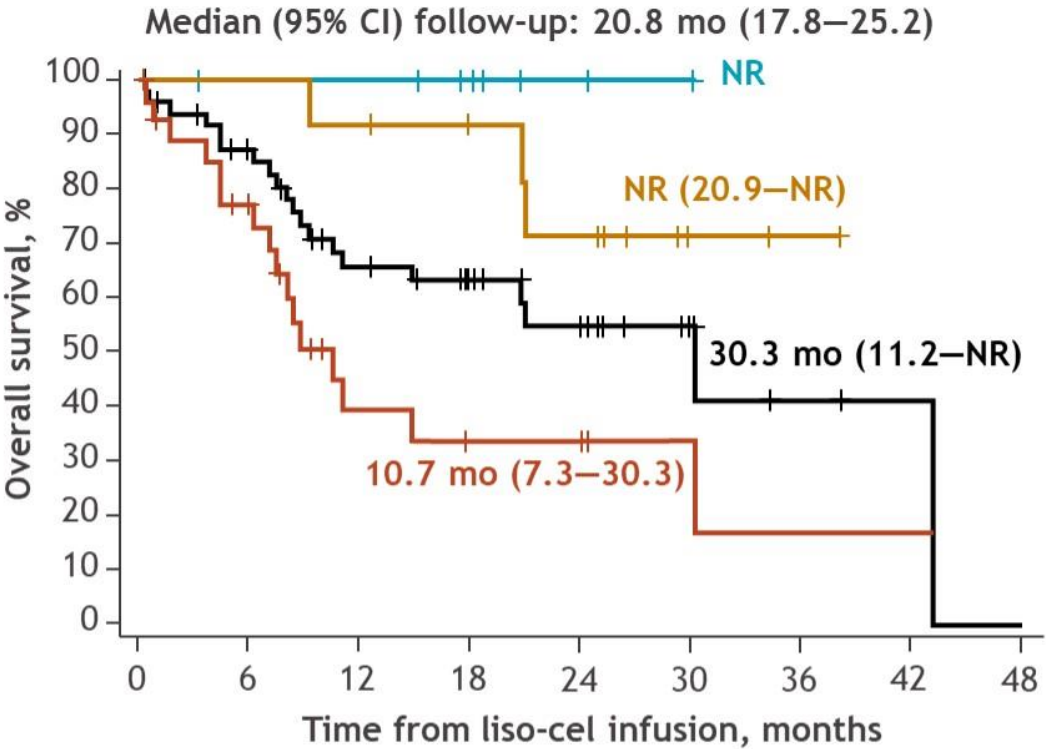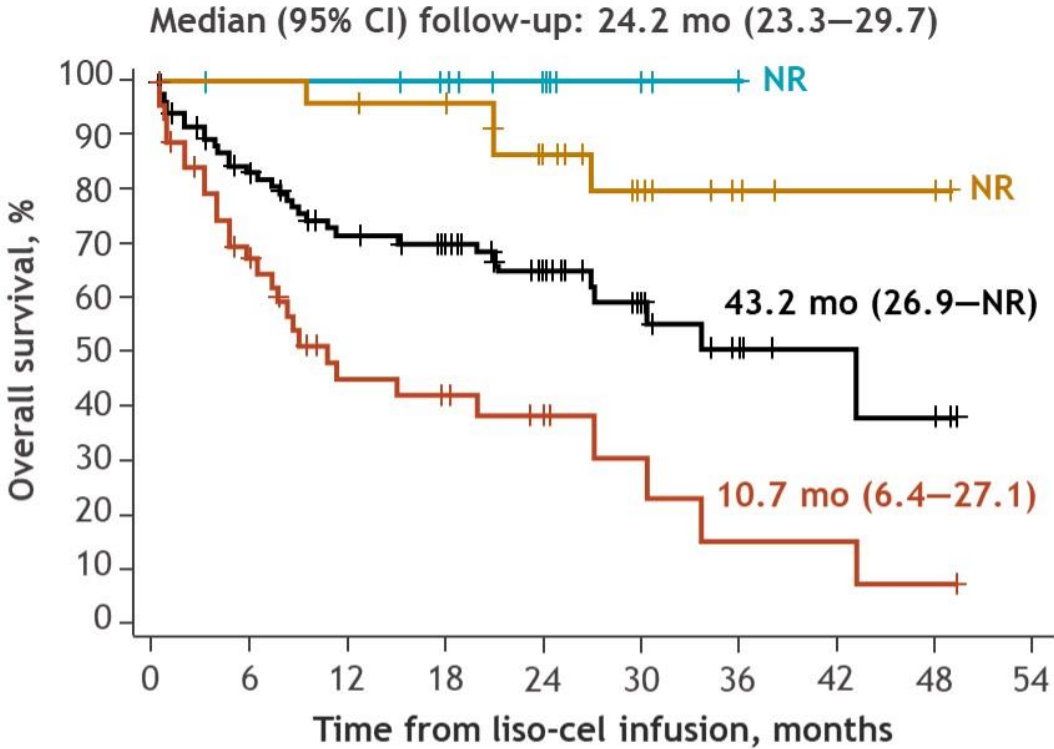
No. at risk

CR/CRi	16	15	15	13	7	5	2	0	0	0
PR/nPR	25	25	24	21	16	9	5	2	2	0
Nonresponder	46	26	15	12	8	4	2	2	1	0
Total	87	66	54	46	31	18	9	4	3	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 49)

Median (95% CI) follow-up: 20.8 mo (17.8–25.2)

NR

NR (20.9–NR)

30.3 mo (11.2–NR)

10.7 mo (7.3–30.3)

Overall survival, %

Time from liso-cel infusion, months

9	8	8	6	2	1	0	0	0
12	12	11	9	7	2	1	0	0
28	18	7	4	4	2	1	1	0
49	38	26	19	13	5	2	1	0

Data on Kaplan-Meier curves are expressed as median (95% CI, if available).

Progression-free survival by uMRD in blood by next-generation sequencing at 10^{-4} sensitivity

(A) Full study population at DL2 (n = 87)[a]
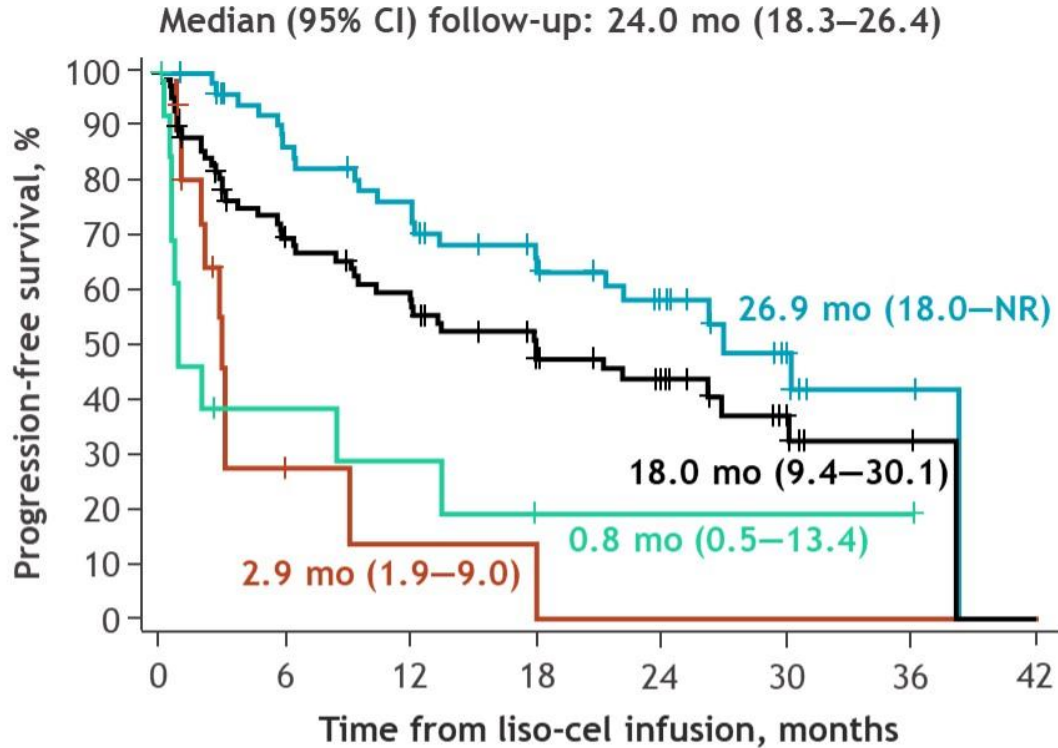
Median (95% CI) follow-up: 24.0 mo (18.3–26.4)

26.9 mo (18.0–NR)

18.0 mo (9.4–30.1)

0.8 mo (0.5–13.4)

2.9 mo (1.9–9.0)

Progression-free survival, %

Time from liso-cel infusion, months
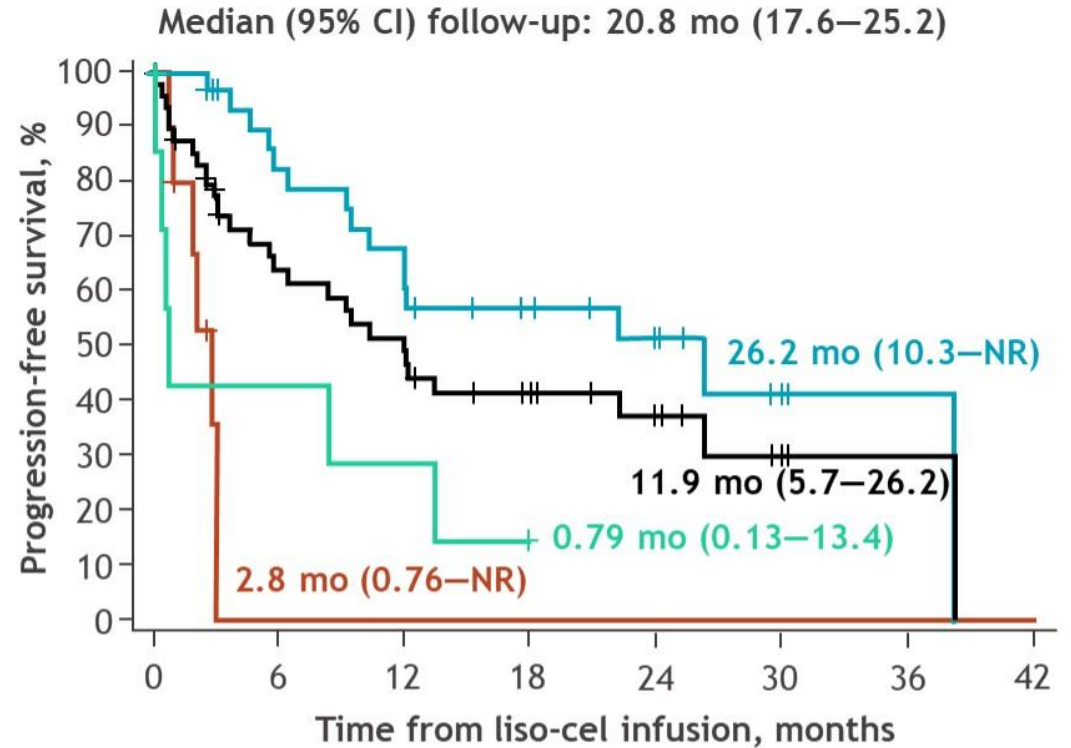
No. at risk

uMRD	56	44	36	27	17	7	2	0
Detectable MRD	16	3	1	0	0	0	0	0
Unknown MRD[b]	15	4	3	1	1	1	1	0
Total	87	51	40	28	18	8	3	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 49)[a]

Median (95% CI) follow-up: 20.8 mo (17.6–25.2)

26.2 mo (10.3–NR)

11.9 mo (5.7–26.2)

0.79 mo (0.13–13.4)

2.8 mo (0.76–NR)

Progression-free survival, %

Time from liso-cel infusion, months

31	23	17	13	7	2	1	0
10	0	0	0	0	0	0	0
8	3	2	0	0	0	0	0
49	26	19	13	7	2	1	0

[a]Data on Kaplan-Meier curves are expressed as median (95% CI, if available); [b]Patients were not evaluable for MRD (eg, calibration failure).

TEAEs, AESIs, and management of CRS and NEs

- The most common grade ≥ 3 TEAEs (≥ 40%) were neutropenia (61%), anemia (52%), and thrombocytopenia (41%)

Patients with CRS and NEs	Full study population (n = 117)
CRS,[a] n (%)	99 (85)
Grade 1/2	43 (37)/46 (39)
Grade 3	10 (9)
Grade 4/5	0
Median (range) time to onset/resolution, days	4.0 (1–18)/6.0 (2–37)
NE,[b] n (%)	53 (45)
Grade 1/2	13 (11)/18 (15)
Grade 3	21 (18)
Grade 4	1 (1)
Grade 5	0
Median (range) time to onset/resolution, days	7.0 (1–21)/7.0 (1–83)

Other AESIs, n (%)	Full study population (n = 117)
Prolonged cytopenia[c]	63 (54)
Grade ≥ 3 infections[d]	20 (17)
Hypogammaglobulinemia[e]	18 (15)
Tumor lysis syndrome	13 (11)
Second primary malignancy[e]	11 (9)
Macrophage activation syndrome	4 (3)

- 81 (69%) patients received tocilizumab and/or corticosteroids for management of CRS and/or NEs

- 5 deaths due to TEAEs were reported
  - 4 considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *Escherichia coli* infection, and invasive aspergillosis)
  - 1 considered related to liso-cel by investigators (macrophage activation syndrome)

[a]CRS was graded based on the Lee 2014 criteria; [b]NEs were defined as investigator-identified neurological AEs related to liso-cel; [c]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, and/or thrombocytopenia at Day 30 after liso-cel infusion; [d]Includes grade ≥ 3 TEAEs from the infections and infestations (system organ class) by AE high-level group term; [e]AEs from the 90-day treatment-emergent period, posttreatment-emergent period, and long-term follow-up were included. AESI, adverse event of special interest; CRS, cytokine release syndrome; NE, neurological event; TEAE, treatment-emergent adverse event.

Summary

- A single administration of liso-cel demonstrated rapid, deep, and durable responses in patients with R/R CLL/SLL

- The study met its primary endpoint, with a CR/CRi rate of 18.4% in patients with R/R CLL/SLL after BTKi progression/venetoclax failure, which compares favorably with historical CR/CRi rates of 0%—5%[1-6]

- Liso-cel achieved high uMRD rates in both blood and marrow

- Efficacy outcomes were similar in the full study population (R/R CLL/SLL after progression on BTKi), demonstrating a clinical benefit of liso-cel in this broader population

- Functional CAR T cells were successfully manufactured, with demonstrated expansion and persistence in most patients
  - Higher liso-cel expansion was observed in responders and patients with uMRD than in nonresponders and patients with detectable MRD

- The safety profile was manageable, with low rates of grade ≥ 3 CRS and NEs

- Overall, these results support liso-cel as a potential new treatment option for R/R CLL/SLL

1. Patel K, et al. *J Hematol Oncol* 2021;14:69; 2. Sedlarikova L, et al. *Front Oncol* 2020;10:894; 3. Lew TE, et al. *Blood Adv* 2021;5:4054—4058; 4. Jones J, et al. *Blood* 2016;128:637; 5. Mato AR, et al. *Clin Cancer Res* 2020;26:3589—3596; 6. VENCLEXTA® (venetoclax) [package insert]. North Chicago, IL: AbbVie Inc.; June 2022; 7. Mato AR, et al. *Clin Lymphoma Myeloma Leuk* 2023;23:57—67.

My Takeaways

- The ability of liso-cel to create durable complete responses in a subset of patients with double-refractory CLL is unprecedented.

- More work needs to be done to clarify the prognostic impact of MRD in CAR-T cell therapy for CLL.

- With this data, I regard liso-cel as a new standard of care option in this patient population, but recognize the challenges in weighing the risk/benefit profile of CAR-T versus other novel agents/trials entering this space (e.g. pirtobrutinib).

Diffuse Large B-cell Lymphoma: Relapsed/Refractory Treatment

Abstract

7525

Effect of follow-up time on the ability of subcutaneous epcoritamab to induce deep and durable complete remissions in patients with relapsed/refractory large B-cell lymphoma: Updated results from the pivotal EPCORE NHL-1 trial

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Background

- Patients with relapsed or refractory large B-cell lymphoma have poor overall outcomes, especially patients with "double-hit" lymphomas, primary refractory disease, or progressive disease following CAR-T cell therapy.

- Epcoritamab is a bispecific T-cell engaging antibody (BiTE) with CD3 x CD20 specificity. It recently gained accelerated FDA approval for treatment of patients with relapsed/refractory large B-cell lymphoma following 2 or more lines of prior therapy.
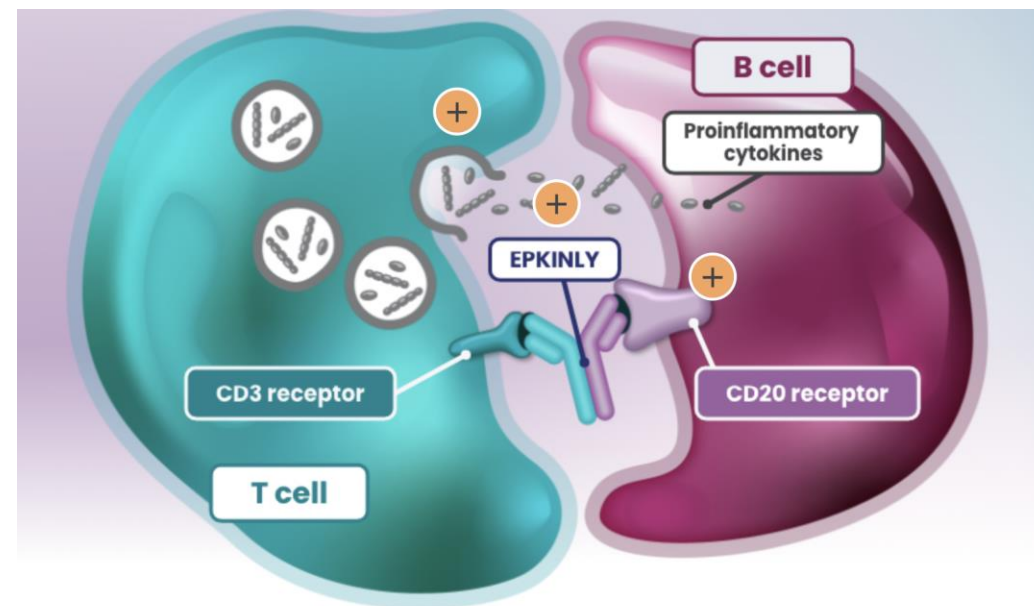
STUDY DESIGN: EPCORE™ NHL-1 LBCL Expansion

Dose escalation

Dose expansion data cutoff: November 18, 2022
Median follow-up: 20.0 mo

B-NHL:
- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key inclusion criteria:
- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T allowed

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
Treatment until PD[b,c] or unacceptable toxicity
LBCL cohort, N=157
DLBCL & HGBCL, n=148; PMBCL, n=4; FL G3B, n=5

SC injections in minutes

QW				Q2W						Q4W
C1	2	3	4	5	6	7	8	9	10	
Wk 0	4	8	12	16	20	24	28	32	36	

- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

[a]Step-up dosing (SUD; priming [SUD 1] 0.16 mg and intermediate [SUD 2] 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [b]Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. [c]≥2 measurable (by CT/MRI) and FDG PET–positive lesions. ClinicalTrials.gov: NCT03625037. EudraCT: 2017-001748-36.

Demographics	DLBCL & HGBCL, n=148	LBCL, N=157
Median age (range), y	65 (22–83)	64 (20–83)
≥75 y, n (%)	29 (20)	29 (18)
ECOG PS, n (%)		
0	71 (48)	74 (47)
1	72 (49)	78 (50)
2	5 (3)	5 (3)

Disease Type, n (%)	DLBCL & HGBCL, n=148	LBCL, N=157
DLBCL[a]	127 (86)	127 (81)
De novo	92/127 (72)	92/127 (72)
Transformed	33/127 (26)	33/127 (26)
HGBCL	21 (14)	21 (13)
PMBCL	0	4 (3)
FL G3B	0	5 (3)

Prior Treatments	DLBCL & HGBCL, n=148	LBCL, N=157
Median time from initial diagnosis to first dose, mo	19	19
Median time from end of last therapy to first dose, mo	2.4	2.4
Median prior lines of therapy (range)	3 (2–11)	3 (2–11)
≥3 Lines of therapy, n (%)	104 (70)	110 (70)
Primary refractory[b] disease, n (%)	88 (59)	95 (61)
Refractory[b] to last systemic therapy, n (%)	122 (82)	130 (83)
Refractory[b] to ≥2 consecutive lines of therapy, n (%)	112 (76)	118 (75)
Prior ASCT, n (%)	27 (18)	31 (20)
Prior CAR T therapy, n (%)	58 (39)	61 (39)
Refractory[b] to CAR T therapy	43/58 (74)	46/61 (75)

[a]De novo versus transformed status of 2 patients with DLBCL was unknown. [b]Refractory disease is defined as disease that either progressed during therapy or progressed within <6 mo of completion of therapy.

Best Overall Response, n (%)	DLBCL & HGBCL, n=148[a]	LBCL, N=157[a]
Overall response	90 (61) [95% CI, 53–69]	99 (63) [95% CI, 55–71]
Complete response	57 (39) [95% CI, 31–47]	62 (39) [95% CI, 32–48]
Partial response	33 (22)	37 (24)
Stable disease	5 (3)	5 (3)
Progressive disease	37 (25)	37 (24)

Based on IRC per Lugano criteria. [a]16 patients were not evaluable.
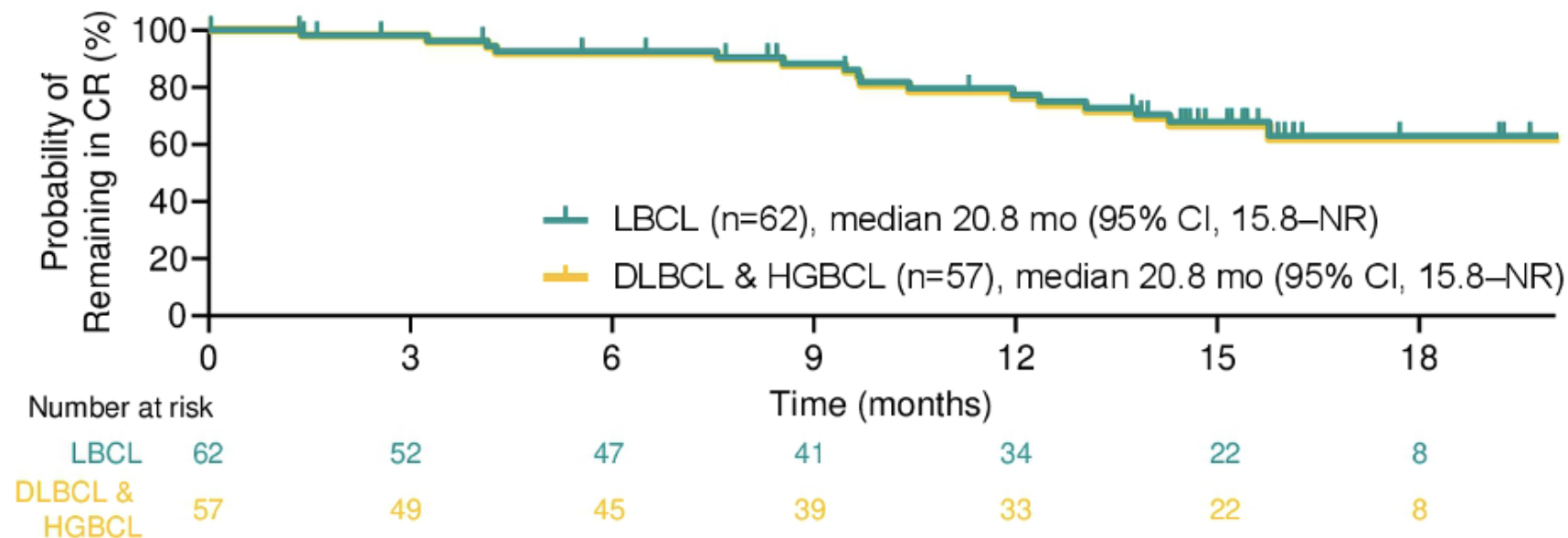
Median OS for overall population: 18.5 months.

Treatment-Emergent Adverse Events in ≥20% of LBCL Patients
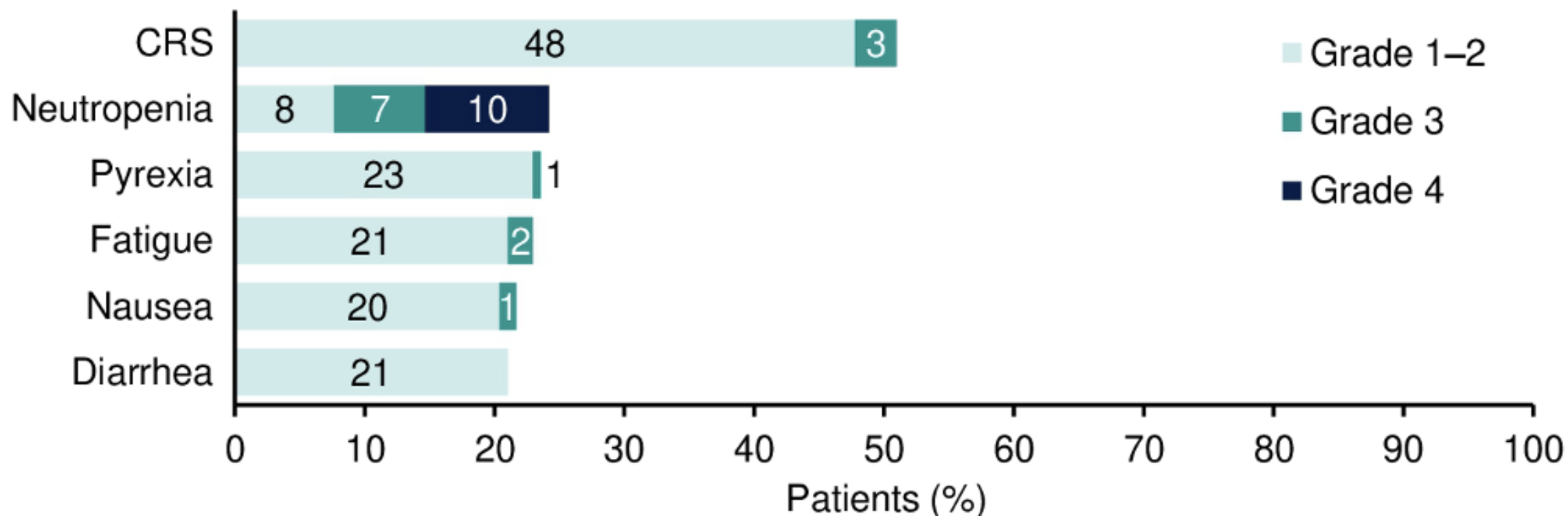
- Safety was consistent with previous findings
- Fatal TEAEs occurred in 15 patients
  - 2 were considered related events (COVID-19 pneumonia and ICANS [in a patient with several confounding factors])

Abstract

P7550

Glofitamab monotherapy in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL): extended follow-up and landmark analyses from a pivotal Phase II study

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Monica Tani,[8] Joaquin Martinez-Lopez,[9] Nancy Bartlett,[10] Antonio Salar,[11]
Joshua Brody,[12] Sirpa Leppä,[13] Estefania Mulvihill,[14] Linda Lundberg,[14]
James Relf,[15] Yuying Xie,[16] Alessia Bottos,[14] Kathryn Humphrey,[15]
Michael Dickinson[17]

Background

- Glofitamab is a T-cell engaging bispecific antibody with a novel 2:1 format, delivered in a fixed course of 12 three-weekly cycles.[1]

- In a Phase II study (NCT03075696), glofitamab induced high CR rates and had manageable toxicity in patients with R/R LBCL.[1,2]

- We present an extended follow-up and landmark analyses to assess the outcomes of patients in CR.

Glofitamab: a CD20xCD3 T-cell engaging bispecific antibody

High avidity binding to CD20 on B cells

Silent Fc region extends half-life and reduces toxicity

CD3 T-cell engagement
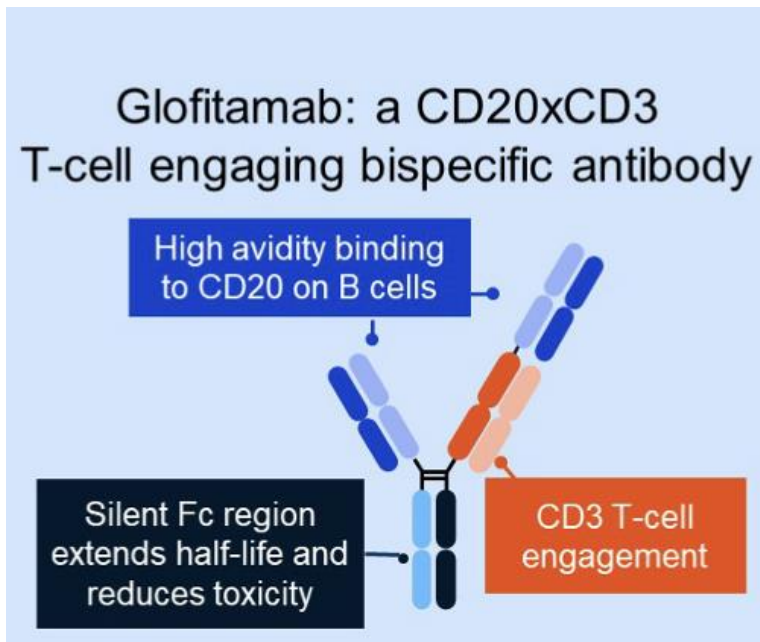
* Gained accelerated FDA approval for treatment of relapsed large B-cell lymphoma following 2 or more lines of therapy in May 2023.

Figure 1. Study overview.

Key inclusion criteria

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

Endpoints

- Primary: CR rate (as BOR) by IRC*
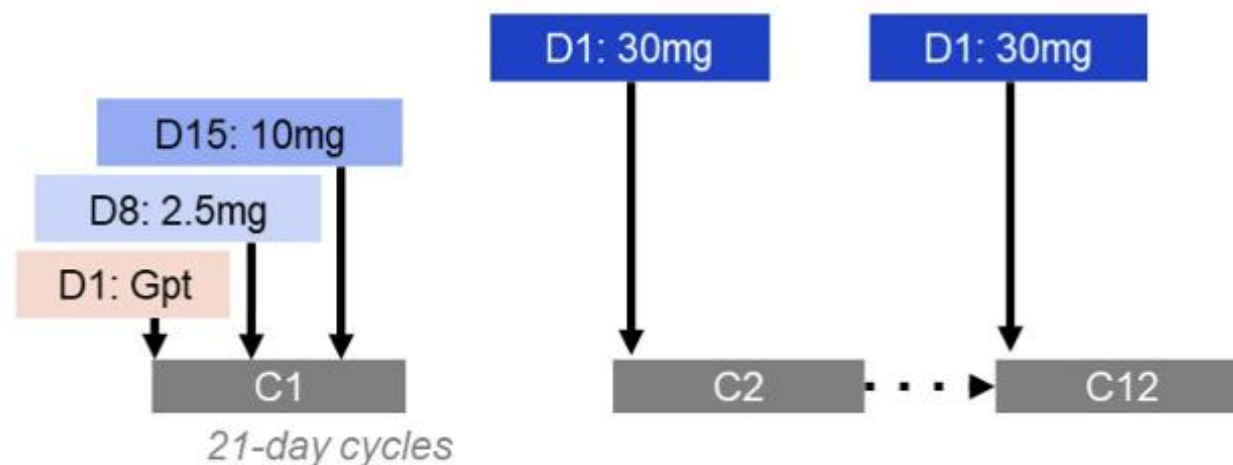- Key secondary: ORR[†], DoR, DoCR[†], PFS, and OS

Glofitamab IV administration

Fixed-duration treatment
- Maximum 12 cycles

CRS[‡] mitigation:
- Obinutuzumab pretreatment (1 x 1000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

| D1: 30mg | D1: 30mg |

D15: 10mg

D8: 2.5mg

D1: Gpt

| C1 | C2 | C12 |

21-day cycles

*By PET-CT (Lugano criteria[3]); [†]By IRC and investigator; [‡]By American Society for Transplantation and Cellular Therapy criteria[4]; BOR, best overall response; CRS, cytokine release syndrome; D, day; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; DoCR, duration of complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt; obinutuzumab pretreatment; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; ORR, overall response rate; PET-CT, positron emission tomography-computed tomography; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma.

## As of Jan 16, 2023, 154 patients had received ≥1 dose of study treatment

- Baseline characteristics were as previously presented.[5]

- The patient population was heavily pretreated and highly refractory
  - The median patient age was 66 years; the median number of prior therapy lines was 3 (range: 2–7), and 61% of patients had received ≥3 prior lines of therapy
  - Overall, 34% of patients had received prior chimeric antigen receptor T-cell therapy, and 85% were refractory to their most recent regimen.

- The median time on study was 21.2 months (range: 0–34).

Table 1. Efficacy summary.

	IRC (N=155)*
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median follow-up, months (range)	18.2 (0–33)
Ongoing CRs, n/N (%)	42/62 (68)
Median DoCR, months (95% CI)	26.9 (18.4–NE)

*Intent-to-treat population; CI, confidence interval; NE, not estimable.

Figure 2. DoCR by IRC.
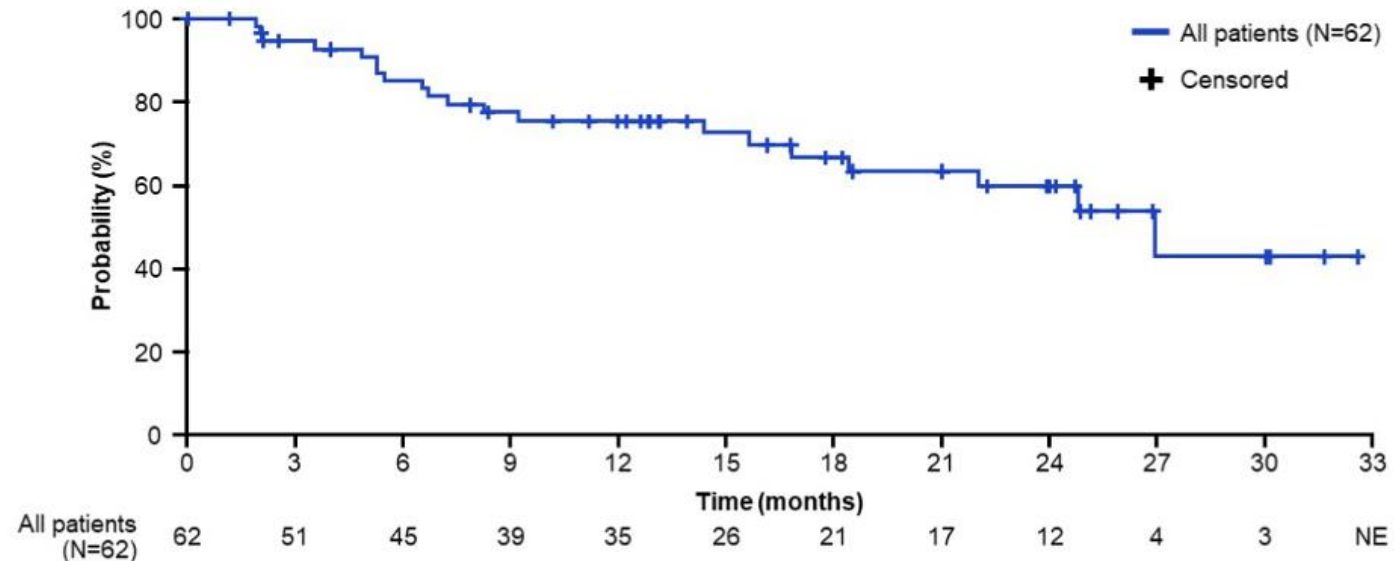
- CRS remained the most common AE, occurring in 64% of patients
  - CRS events were mostly Grade 1 (48%) or Grade 2 (12%); Grade 3 (3%) and Grade 4 (1%) events were uncommon.

Table 2. Safety summary.

N (%)	N=154
AE	152 (99)
Glofitamab related	140 (91)
Grade ≥3 AE	99 (64)
Glofitamab related	68 (44)
SAE	75 (49)
Glofitamab related	46 (30)
Grade 5 (fatal) AE	9 (6)
Glofitamab related	0
AE leading to treatment discontinuation	14 (9)
Glofitamab related	5 (3)
AE leading to dose modification/interruption of glofitamab	29 (19)
Glofitamab related	16 (10)

Conclusions

- With a median CR follow-up of 18.2 months, glofitamab continued to demonstrate durable responses, with most patients in CR at EOT still in remission without new AEs.

- These data support the potential for favorable long-term outcomes with fixed-duration glofitamab for R/R LBCL.

My Takeaways

- Bispecific T-cell engaging (BiTE) antibodies have officially arrived, and represent a landscape-changing treatment option for large B-cell lymphoma. **We don't yet know if they are curative.**

- The ability to deliver this treatment in the community setting gives BiTE therapy a distinct role alongside other treatments (including CAR-T cell therapy) in this space.

- The challenge lies in standardizing resource utilization and patient/staff education in support of BiTE therapies:

  - How often should we electively hospitalize patients for post-dose CRS observation?

  - How do we best monitor patients for CRS as an outpatient? (distance from medical center, educating RN/ED colleagues).

  - Multiple compounds with different administration schedules and durations of therapy.

Thank you!

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