Vispa-cel, an allogeneic anti-CD19 CAR-T cell therapy with a PD-1 knockout, in patients with relapsed/refractory B cell Non-Hodgkin Lymphoma (r/r B-NHL): Updated results from the ANTLER phase 1 trial

Abstract ID: 29592

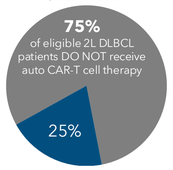
Mehdi Hamadani[1], Houston Holmes[2], James Essell[3], Ayad Hamdan[4], Boyu Hu[5], Elizabeth Brem[6], Rushang D. Patel[7], Sunita Nasta[8], Costas K. Yannakou[9,10], Mohamad Cherry[11], Don A. Stevens[12], Umar Farooq[13], Kenneth Micklethwaite[14,15], Vamsi Kota[16], Abraham S. Kanate[17], Tatyana Feldman[18], Melhem M. Solh[19], David Lavie[20], Benedict Carnley[21,22], Muhammad Husnain[23], Cesar Gentille Sanchez[24], Fevzi Yalniz,[25] Gary L. Simmons[26], Donna Marcy[27], Erin Mullane[27], Jim Peck[27], Ine-Mari Bonman[27], Chris Holland[27], Shally Chung[27], Ashraf Garrett[27], Govind Shah[27], Lindsay McFarland[27], Mara Beth Bryan[27], Karen Lyle[27], Paul Donohoue[27], Elizabeth Garner[27], Pingping Mao[27], Eric W. Stawiski[27], Tom Kochy[27], Justin Skoble[27], Elaine Alambra[27], Enrique Zudaire[27], Tonia Nesheiwat[27], Tina Albertson[27], Maria do Socorro Oliviera Portella[27], Stephen J. Schuster[28], Loretta J. Nastoupil[29], Susan O'Brien[30]

[1]Department of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, [2]Texas Oncology/Baylor Sammons Cancer Center, Dallas, TX, [3]Oncology Hematology Care/Sarah Cannon Research Institute, Cincinnati, OH, [4]Department of Medicine, Division of Hematology and Cellular Therapy, University of California San Diego, La Jolla, CA, [5]Division of Hematology/Hematologic Malignancies, Huntsman Cancer Institute, Salt Lake City, UT, [6]Department of Medicine, Division of Hematology Oncology, Chao Family Comprehensive Cancer Center, University of California Irvine Health, Orange, CA, [7]Blood and Marrow Transplant Center, AdventHealth, Orlando, FL, [8]Division of Hematology Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, [9]Epworth HealthCare, Melbourne, VIC, Australia, [10]Department of Clinical Pathology, The University of Melbourne, Melbourne, VIC, Australia, [11]Carol G. Simon Cancer Center, Atlantic Health System, Morristown, NJ, [12]Norton Cancer Institute, Louisville, KY, [13]University of Iowa Hospitals and Clinics, Iowa City, IA, [14]Haematology Department, Westmead Hospital, Sydney, NSW, Australia, [15]Blood Transplant and Cell Therapies Laboratory, NSW Health Pathology - ICPMR Westmead, Sydney, NSW, Australia, [16]Georgia Cancer Center at Augusta University, Augusta, GA, [17]Transplant & Cellular Therapy, HonorHealth Cancer Transplant Institute, Scottsdale, AZ, [18]John Theurer Cancer Center at Hackensack Meridian Health, HMH School of Medicine, Hackensack, NJ, [19]Blood and Marrow Transplant Program, Northside Hospital Cancer Institute, Atlanta, GA, [20]Hadassah Medical Center, Jerusalem, Israel, [21]Haematology Department, Royal Perth Hospital, Perth, Western Australia, Australia, [22]Cell and Tissue Therapies WA, Perth, Western Australia, Australia, [23]Division of Hematology/Oncology, University of Arizona, Tucson, AZ, [24]UAMS Winthrop P. Rockefeller Cancer Institute, Little Rock, AR, [25]Division of Hematology and Cellular Therapy, University of Kentucky Markey Cancer Center, Lexington, KY, [26]VirginiaOncology Associates, Norfolk, VA, [27]Caribou Biosciences, Inc., Berkeley, CA, [28]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, [29]CommonSpirit Oncology Mercy, Durango, CO, [30]Division of Hematology/Oncology, Department of Medicine, Chao Family Comprehensive Cancer Center, University of California Irvine Medical Center, Orange, CA

BACKGROUND

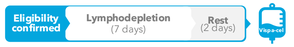
Allogeneic CAR-T cell therapy can fill unmet need in LBCL

Only 25% of 2L DLBCL patients receive autologous CAR-Ts[1], primarily at large academic, authorized treatment centers



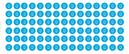
Readily available, single-dose administration with vispa-cel

More patients could be treated by overcoming patient access challenges

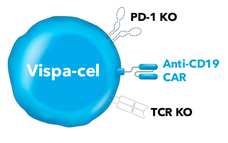


No wait between eligibility confirmation and LD

Sufficient yield for **200-300 doses of vispa-cel** per manufacturing run



Vispacabtagene regedleucel (vispa-cel)



1. ***TRAC* gene knockout (KO)**
   - Eliminates TCR expression, reduces GvHD risk
2. **Anti-CD19 CAR site-specific insertion into *TRAC* locus**
   - 4-1BB costimulatory domain and FMC63 scFv
   - Eliminates random integration, targets tumor antigen
3. **PD-1 KO for enhanced antitumor activity**
   - Reduces CAR-T cell exhaustion
   - Enhanced CAR-T metabolic fitness
   - Potentially contributes to initial tumor debulking

First allogeneic anti-CD19 CAR-T armored with a PD-1 knockout
3 edits made using Cas9 chRDNA genome-editing technology[2]

METHODS

Vispa-cel ANTLER Phase 1 trial (NCT04637763)

Eligibility

- Dose escalation: aggressive r/r B-NHL[a] with ≥2 prior lines of chemoimmunotherapy or primary refractory
- Dose expansion: second-line LBCL[b] refractory or relapsed ≤12 months

Exclusion

- Prior CD19-targeted therapy (except for prior CD19 relapsed cohort)

Vispa-cel dose levels evaluated

- 40, 80, and 120 x10^6 CAR-T cells

ANTLER trial design

Rapidly progressing disease, patients unwilling to go through apheresis or bridging therapy, insurance rejection, or preference for an off-the-shelf therapy are key reasons why investigators enrolled patients in ANTLER trial[c]

[a]B-NHL subtypes include: DLBCL, HGBL, tFL, PMBCL, FL with POD24 (high risk), MCL, MZL
[b]LBCL subtypes include: DLBCL NOS, HGBL, transformed DLBCL from FL or MZL, and PMBCL
[c]Based on survey answers from ANTLER investigators asking why patients were dosed with vispa-cel versus autologous CAR-T cell therapy; 86% of ANTLER sites offer one or more of the approved auto CAR-Ts in 2L LBCL

PATIENT POPULATION

84 patients treated over several parts in ANTLER trial

Dose escalation (N=16)
≥2L B-NHL, CD19 naïve
Doses evaluated: 40M, 80M, 120M
1 DLT observed at 40M in MCL patient

Dose expansion (N=30)
2L LBCL, CD19 naïve
Doses evaluated: 40M, 80M, 120M
RP2D identified as 80M CAR-T cells

Data reported at ASCO 2024 (N=46)
≥4 HLA matched alleles (out of 12 class I/II alleles) associated with improved PFS in retrospective analysis

Prospective enrollment in new patient cohorts to confirm PFS trend

Continued dose expansion (N=11)
2L LBCL, CD19 naïve
<4 HLA matched alleles
80M CAR-T cells

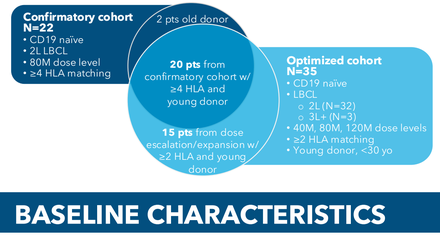
Confirmatory cohort (N=22)
2L LBCL, CD19 naïve
≥4 HLA matched alleles required
80M CAR-T cells

Prior CD19 relapsed cohort (N=5)
≥3L LBCL
≥4 HLA matched alleles required
80M CAR-T cells
(data not reported)

Optimized vispa-cel profile identified

PFS trend confirmed in confirmatory cohort and in patients receiving vispa-cel manufactured from donors <30 yo and ≥2 HLA matched alleles

Confirmatory and optimized cohort criteria and breakdown of patient numbers



BASELINE CHARACTERISTICS

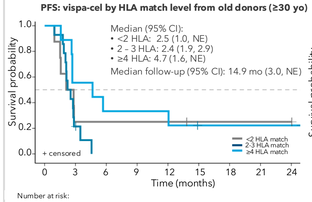
Patient and disease characteristics	All patients[a] N=84	2L LBCL patients N=67	Confirmatory cohort[b] N=22	Optimized profile[c] N=35
Age, years, median (range)	66 (20-86)	66 (20-86)	61 (20-83)	63 (20-86)
Age ≥ 70 years, n (%)	23 (27)	19 (28)	8 (36)	10 (29)
Male, n (%)	64 (76)	51 (76)	16 (73)	25 (71)
ECOG, n (%)				
0	40 (48)	32 (48)	13 (59)	19 (54)
1	44 (52)	35 (52)	9 (41)	16 (46)
NHL subtype, n (%)				
DLBCL, NOS	48 (57)	40 (60)	14 (64)	21 (60)
HGBL	13 (15)	13 (19)	4 (18)	5 (14)
tFL	14 (17)	12 (18)	4 (18)	7 (20)
tMZL	1 (1)	1 (2)	-	1 (3)
PMBCL	2 (2)	1 (2)	-	1 (3)
MCL	3 (4)	-	-	-
FL	2 (2)	-	-	-
MZL	1 (1)	-	-	-
Primary refractory, n (%)	-	33 (49)[d]	11 (50)	17 (49)[d]
Prior lines of therapy, n (%)				
1	67 (80)	67 (100)	22 (100)	32 (91)
2+	17 (20)	-	-	3 (9)
Age-adjusted IPI[e], n (%)				
0-1	-	27 (40)	13 (59)	18 (51)
2	-	24 (36)	5 (23)	10 (29)
≥3	-	16 (24)	4 (18)	7 (20)
Baseline LDH status (%)				
> ULN	46 (55)	50 (75)	11 (50)	18 (51)
> 2x ULN	13 (15)	11 (16)	1 (5)	2 (6)
Bulky disease[f]	17 (20)	13 (19)	2 (9)	4 (11)

[a]Includes 5 patients with exposure to prior CD19-targeting therapy. [b]2L LBCL 4+ HLA matched, dosed with 80M vispa-cel CAR-T cells [c]2L (N=32) and 3L+ (N=3) LBCL patients treated with 40M, 80M, or 120M vispa-cel CAR-T cells optimized for multiple factors, including 2+ HLA matched and young donor. [d]Information is not available for 5 patients. [e]Age-adjusted IPI distribution is presented for LBCL patients only and not applied to other histology subtypes. [f]Bulky disease defined by maximum baseline lesion diameter ≥7.5 cm
Data cutoff 02Sept2025

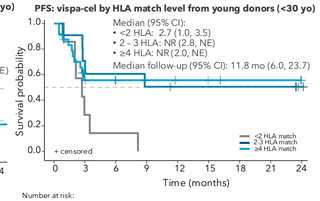
EFFICACY

HLA matching and donor age lead to durable outcomes with vispa-cel in LBCL patients

PFS: vispa-cel by HLA match level from old donors (≥30 yo)



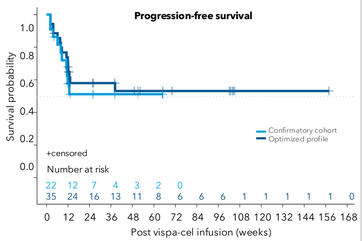
PFS: vispa-cel by HLA match level from young donors (<30 yo)



Patients treated in future trials will receive vispa-cel manufactured from donors <30 yo and HLA best matched to each patient

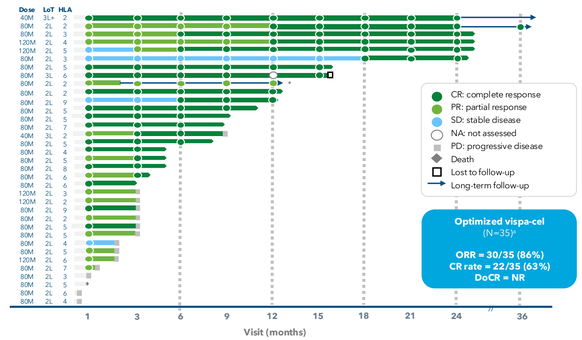
ANTLER trial: Efficacy

	Vispa-cel	
	Confirmatory cohort[a] N=22	Optimized profile[b] N=35
ORR	**82%**	**86%**
CR rate	**64%**	**63%**
Median PFS[c] (95% CI)	**NR** (2.0, NE)	**NR** (2.8, NE)
12-month PFS (95% CI)	**51%** (28, 70)	**53%** (34, 69)
Median DoR[d] (95% CI)	**NR** (1.7, NE)	**NR** (2.1, NE)



[a]2L LBCL 4+ HLA matched, dosed with 80M vispa-cel CAR-T cells. [b]2L (N=32) and 3L+ (N=3) LBCL patients treated with 40M, 80M, or 120M vispa-cel CAR-T cells optimized for multiple factors, including 2+ HLA matched and young donor. [c]Median follow up 6.0 mo for confirmatory; 11.8 mo for optimized. [d]Median follow up 5.1 mo for confirmatory; 7.9 mo for optimized.

Deep and durable responses observed with optimized vispa-cel



*2L (N=32) and 3L+ (N=3) LBCL patients treated with 40M, 80M, or 120M vispa-cel CAR-T cells optimized for multiple factors, including 2+ HLA matched and young donor. *Patient diagnosed with lung adenocarcinoma after D28 scan revealed a non-responsive lung nodule and was taken off study and enrolled on the long-term follow-up study. Patient last known to be in continued response without additional anti-lymphoma therapy at one year post vispa-cel. Long-term follow-up data reflect the last known response; marked timepoints indicate confirmation of no disease progression.
One vispa-cel-related grade 5 IEC-HS occurred on day 25 post-infusion. Certain patients converted from CR or PR to PD at various assessments time points as indicated in the chart above
Efficacy data cutoff date 29Sept2025

SAFETY AND TOLERABILITY

	Vispa-cel					
	All treated N=84		Confirmatory cohort N=22[a]		Optimized profile N=35[b]	
	Any grade	≥ Gr 3	Any grade	≥ Gr 3	Any grade	≥ Gr 3
ICANS, n (%)	12 (14)	3 (4)	1 (5)	0 (0)	1 (3)	0 (0)
CRS, n (%)	46 (55)	1 (1)	13 (59)	1 (5)	19 (54)	1 (3)
Infections, n (%)	43 (51)	21 (25)	9 (41)	4 (18)	20 (57)	6 (17)
Prolonged cytopenias[c]	NA	22/80 (28)	NA	5/19 (26)	NA	7/32 (22
IEC-HS, n (%)[d]	2 (2)	2 (2)	1 (5)	1 (5)	1 (3)	1 (3)
GvHD	0	0	0	0	0	0

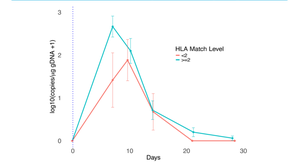
- Notable TEAEs are shown in the table:
  - No GvHD observed
  - For all treated patients (N=84), grade 1 CRS occurred in 46% and grade 2 CRS occurred in 7%
  - Median time to CRS onset was 3 days (0-22) and median duration was 3 days (1-20)
  - Median time to ICANS onset was 8 days (6-34) and median duration was 2 days (1-27)
  - 95% of neutropenia and 86% of thrombocytopenia recover to ≤ grade 2 by Day 60
- No significant safety differences were observed in patients <70 and ≥70 years of age
- Five patients died due to AEs following vispa-cel[e]:
  - 1 related (IEC-HS at day 25)
  - 1 possibly related (bladder perforation at day 172)[f]

[a]2L LBCL 4+ HLA matched, dosed with 80M vispa-cel CAR-T cells. [b]2L (N=32) and 3L+ (N=3) LBCL patients treated with 40M, 80M, or 120M vispa-cel CAR-T cells optimized for multiple factors, including 2+ HLA matched and young donor. [c]Prolonged cytopenias are defined as Grade 3 or 4 neutropenia, thrombocytopenia, or anemia ongoing at day 28 (+/- 5 days) post CAR-T infusion, based on laboratory data, distinct from investigator-reported clinical adverse events. Analysis includes patients with assessments at day 28 (+/-5 days). [d]One vispa-cel-related grade 3 IEC-HS that occurred day 25 post-infusion. [e]3 deaths considered unrelated to vispa-cel per investigator included acute respiratory failure/pneumothorax, ARDS, and HHV6 encephalitis. [f]Death possibly related to vispa-cel per investigator due to complications of a bladder perforation in the context of BK virus hemorrhagic cystitis
Safety data cutoff date 02Sept2025

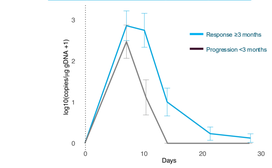
TRANSLATIONAL ANALYSES

Expansion and persistence correlate with HLA match level and DoR

HLA match level (<2 vs ≥2) impact on PK in young donors[a]



PK impact on DoR for optimized profile[b]

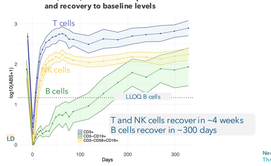


Peak expansion (C_{max}) occurred 7 to 10 days after vispa-cel infusion with persistence observed up to ~30 days

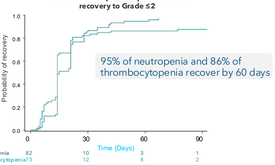
[a]53 of 54 evaluable patients dosed with young donor products. [b]34 of 35 evaluable patients. 2L (N=32) and 3L+ (N=3) LBCL patients treated with 40M, 80M, or 120M vispa-cel CAR-T cells optimized for multiple factors, including 2+ HLA matched and young donor. Mean ± standard error shown; values below LLOQ and D0 set to 0; Visits up to D28 shown; Collection visits with most data not available are not show (D5 n=1, Day 6 n=2, Day 17 n=12). 1 ongoing response with <3 month PFS not shown on right.
Data cutoff date 29Sept2025

Rapid hematologic and immunologic recovery after vispa-cel may contribute to generally well-tolerated safety profile

B cell, T cell, and NK cell depletion and recovery to baseline levels



Absolute neutrophil and platelet count recovery to Grade ≤2



N=84; average of log transformed values shown ± standard error (ribbons). Baseline B cells absolute levels calculated with data points ≥ LLOQ.
Data cutoff for T, B, and NK cell recovery: 09Sept2025; data cutoff for neutrophil and platelet count recovery: 02Sept2025

ANTLER TRIAL CONCLUSIONS AND NEXT STEPS

- Optimized vispa-cel product demonstrates efficacy and durability on par with autologous CAR-T cell therapies in 2L LBCL patients with an **86% ORR, 63% CR, and 53% PFS at 12 months**
- HLA matching and donor age are strong predictors of durable outcomes with vispa-cel in LBCL patients
- **Generally well-tolerated safety profile** of vispa-cel supports outpatient administration
  - Rapid hematologic and immunologic recovery observed after vispa-cel infusion
- **A randomized controlled pivotal trial of vispa-cel versus chemoimmunotherapy in 2L LBCL patients who are ineligible for both autologous CAR-T and transplant is being planned**
  - Optimized vispa-cel product to be implemented in pivotal trial
  - Academic and community sites to participate in pivotal trial

References: 1. Perales, M-A, et al. Poster 549, 2025 Tandem Meetings
2. Lau E et al. *Cytotherapy*. 2023;25(7):750–762 **3.** *Clin Cancer Res*. 2011 July 1; 17(13): 4550-4557. doi:10.1158/1078-0432.CCR-11-0116

Abbreviations: 2L: second line; ≥3L: third line or later; CR: complete response; CRS: cytokine release syndrome; DLBCL: diffuse large B cell lymphoma; DLT: dose-limiting toxicity; DoCR: duration of complete response; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; FL: follicular lymphoma; GvHD: graft versus host disease; HGBL: high-grade B cell lymphoma; HLA: human leukocyte antigen; ICANS: immune effector cell-associated neurotoxicity syndrome; IEC-HS: immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; IPI: International Prognostic Index; LBCL: large B cell lymphoma; LD: lymphodepletion; LDH: lactate dehydrogenase; LLOQ: lower limit of quantification; LoT: line of therapy; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; NA: not applicable; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; NR: not reached; PMBCL: primary mediastinal large B cell lymphoma; tFL: transformed DLBCL from follicular lymphoma; tMZL: transformed marginal zone lymphoma; ULN: upper limit of normal; yo: years old

Disclosures: Mehdi Hamadani, MD
Research support/funding: ADC Therapeutics, Spectrum Pharmaceuticals, Astellas Pharma
Consultancy: Autolus, Forte Biosciences, Byondis, Kite, Daiichi Sankyo, BMS, Caribou
Speaker's bureau: AstraZeneca, ADC Therapeutics, BeiGene, Kite, Sobi
DMC: Myeloid Therapeutics (2023), CRISPR (2024)