# Sequencing of CD19-Directed Therapies for the Treatment of DLBCL

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# CD19 as a Therapeutic Molecular Target

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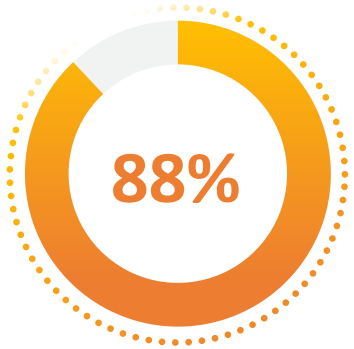
# CD19 as a Therapeutic Molecular Target

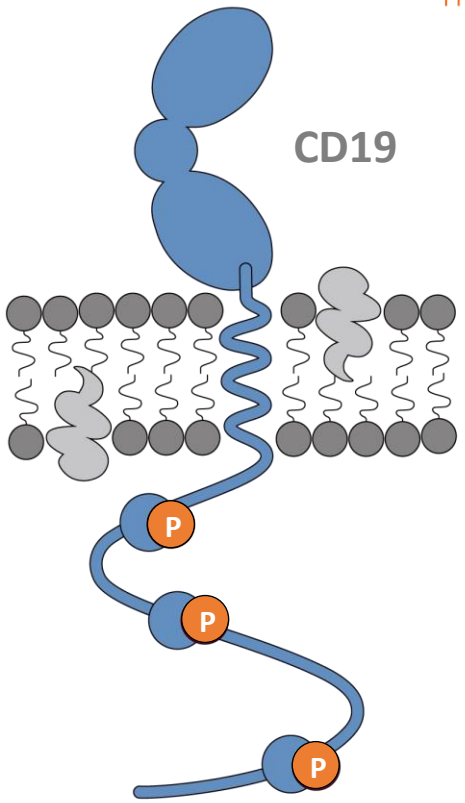
- Human CD19 is a 95 kDa type I transmembrane glycoprotein belonging to the Ig super family[1]
- In normal human cells, CD19 expression continues through pre–B and mature B-cell differentiation until it is downregulated during terminal differentiation into plasma cells[1]
  - The majority of B-cell malignancies express CD19 at normal to high levels[1]


ALL




B-cell lymphomas


B-cell leukemia




**Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) is the first CD19-directed antibody–drug conjugate that is approved for patients with diffuse large B-cell lymphoma after ≥2 systemic therapies[2]**

ALL, acute lymphocytic leukemia; Ig, immunoglobulin; kDa, kilodalton; P, phosphate.

1. Wang K, et al. *Exp Hematol Oncol*. 2012;1:36.
2. ZYNLONTA® (loncastuximab tesirine-lpyl) for injection. Prescribing Information. ADC Therapeutics; 2022. Accessed March 26, 2024. https://www.adctherapeutics.com/wp-content/uploads/2023/10/ZYNLONTA-PI_October-2022_LOCKED.pdf

# Lonca Is a CD19-Directed Antibody–Drug Conjugate

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# Indication and Usage

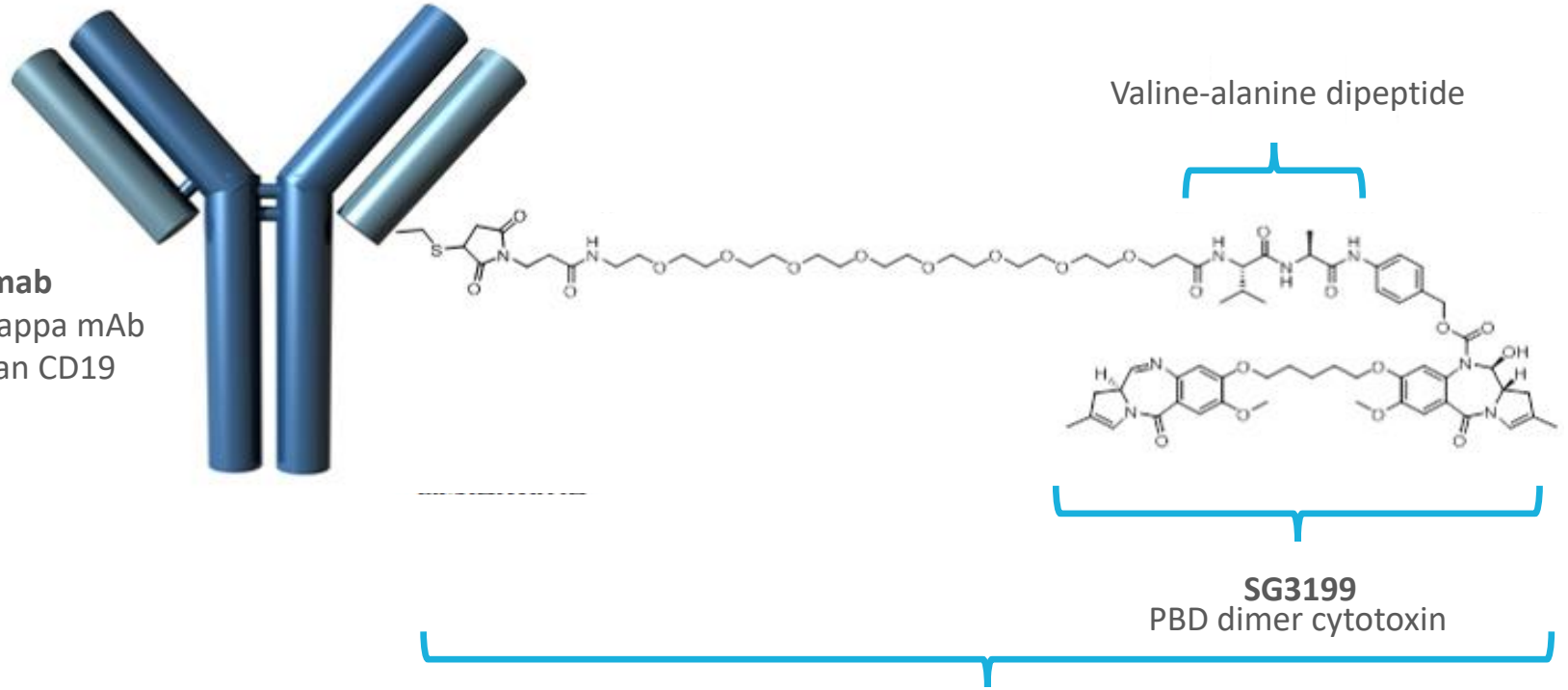
ZYNLONTA® (loncastuximab tesirine-lpyl) is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

This indication is approved under accelerated approval based on the overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DLBCL, diffuse large B-cell lymphoma.

ZYNLONTA® (loncastuximab tesirine-lpyl) for injection. Prescribing Information. ADC Therapeutics; 2022. Accessed March 26, 2024. https://www.adctherapeutics.com/wp-content/uploads/2023/10/ZYNLONTA-PI_October-2022_LOCKED.pdf

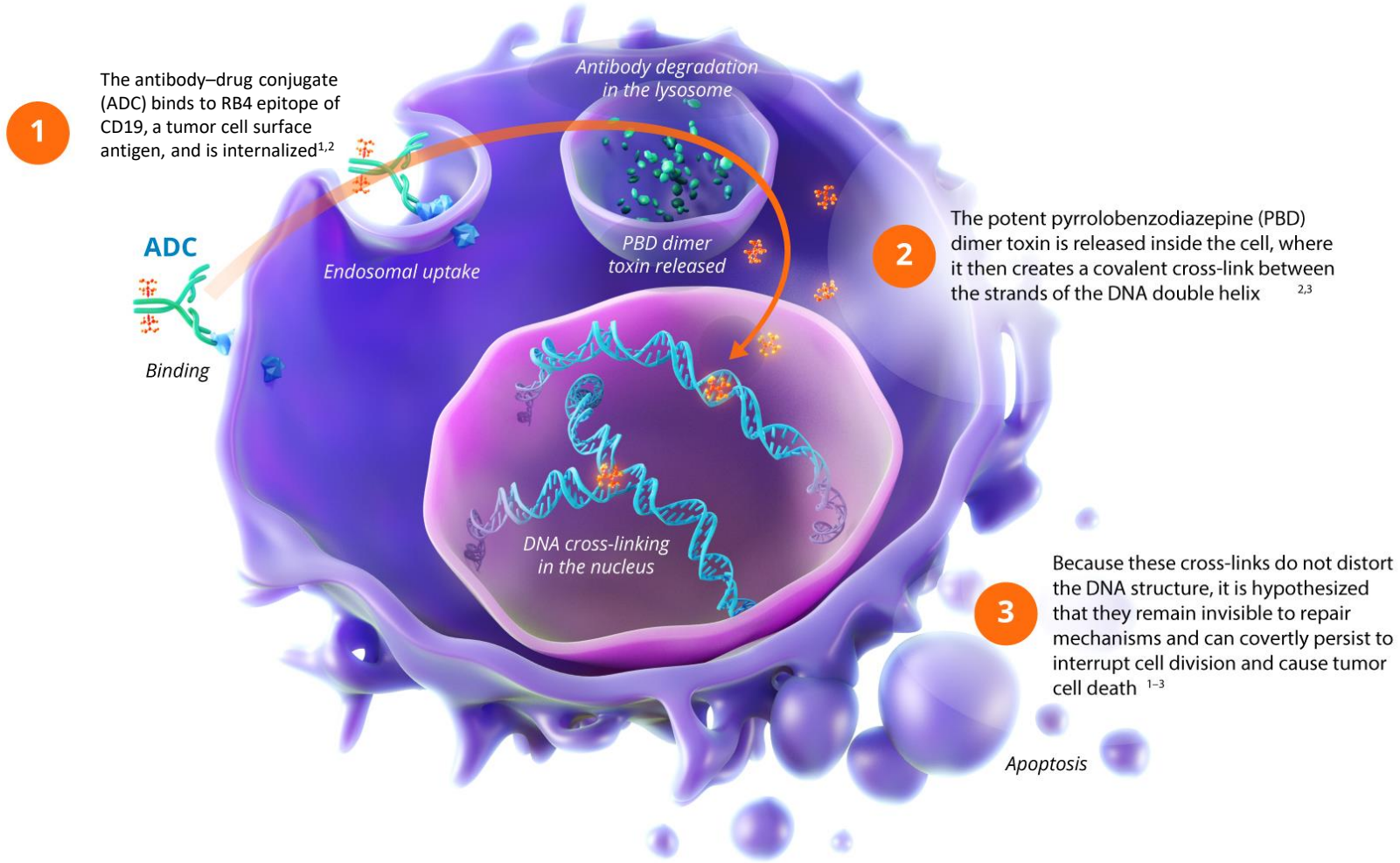
# Molecular Structure of Lonca[1,2]




IgG, immunoglobulin; mAb, monoclonal antibody; PBD, pyrrolobenzodiazepine.

Zynlonta (loncastuximab tesirine-lpyl) prescribing information. Murray Hill, NJ; ADC Therapeutics; October 2022.
Adapted from Zammarchi F, et al. *Blood*. 2018;131(10):1094-1105.

# Mechanism of Action[1-3]




ADC, antibody-drug conjugate; DNA, deoxyribonucleic acid; PBD, pyrrolobenzodiazepine.

1. Kaplon H, et al. *mAbs*. 2020;12:e1703532. 2. Zammarchi F, et al. *Blood*. 2018;131:1094–1105. 3. Hartley JA, et al. *Sci Rep*. 2018;8:10479.

# CD19 Loss and Masking

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## CLINICAL STUDY: CD19 EXPRESSION AFTER CAR-T

# $CD19^{-/lo}$ Escape is a Pathway of Resistance After CD19-Directed CAR-T Therapy for LBCL (Spiegel, et al. *Nat Med* 2021)

### Resistance to CAR-T therapy is associated with $CD19^{-}$ and $CD19^{lo}$ LBCL

- Among 44 patients treated with axi-cel, 23 (52%) experienced progression; 16 of these 23 patients had postprogression biopsies available
- Before treatment with axi-cel, the median CD19 H-score was 285 (IQR: 240-285), and 39 (89%) patients were CD19+[a]
- At disease progression after treatment with axi-cel, only 6 of 16 samples (37.5%) were CD19+
- Among patients with paired pre- and post-therapy H-scores, 9 of 15 (60%) patients converted from CD19+ pretherapy to CD19− at relapse

### Pretreatment quantitative flow cytometry was more sensitive than conventional IHC in identifying lower antigen levels associated with future disease progression

- Patients with LBCL expressing a CD19 site density of ≤3000 molecules per cell had a significantly increased risk of progression after treatment with axi-cel[b]
- H-score did not correlate well with antigen site density as determined by flow cytometry

**Study Conclusions**

- These data demonstrate that progression after axi-cel therapy for LBCL is associated with emergent $CD19^{-/lo}$ disease in a high percentage of patients, but the pretreatment, semiquantitative IHC measurement of CD19 expression is not sensitive enough to identify patients at risk of relapse

axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; H-score, histoscore; IHC, immunohistochemistry; IQR, interquartile range; LBCL, large B-cell lymphoma.

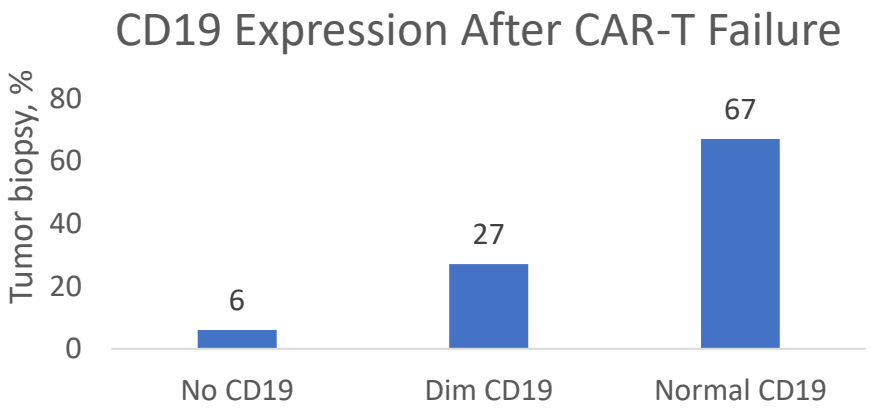
Spiegel JY, et al. *Nat Med*. 2021;27(8):1419-1431.

## CLINICAL STUDY: CD19 EXPRESSION AFTER CAR-T

# Loss of CD19 Expression After CAR-T Therapy Failure Is Infrequent (Alarcon, et al. *Leukemia* 2023)

**Objective:** Report characteristics and outcomes, including CD19 expression levels, of patients with LBCL whose disease relapsed or progressed after CD19-directed CAR-T therapy

**Methods:** This retrospective analysis of patients with R/R LBCL treated with CD19-directed CAR-T cell therapy described patient characteristics and outcomes of the first therapy following CAR-T treatment failure; CD19 expression was assessed by flow cytometry in 52 available post–CAR-T tumor biopsies




Patients with CAR-T resistance had similar CD19 expression at disease progression compared with those with relapsed disease

**Study Conclusions:**

- Loss of CD19 was infrequent (6%), and CD19 expression at CAR-T treatment failure showed no correlation with CAR-T refractoriness versus later relapse
- Persistence of CD19 may render tumors susceptible to further CD19-directed therapies

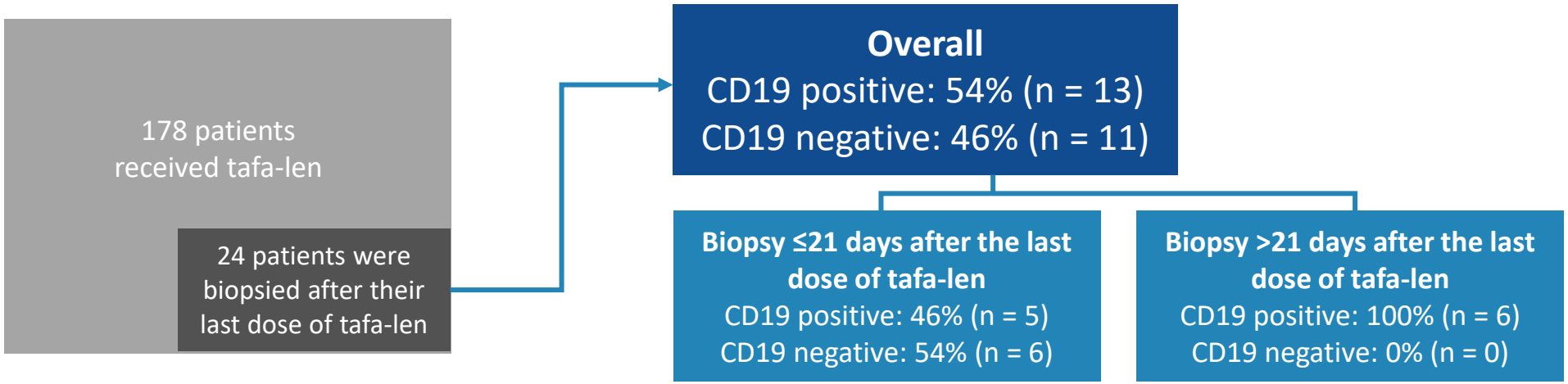
CAR-T, chimeric antigen receptor T-cell; dim, diminished; IHC, immunohistochemistry; LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

Alarcon Tomas A, et al. *Leukemia*. 2023 Jan;37(1):154-163.

## RWE STUDY: CD19 EXPRESSION AFTER TAFA-LEN

# CD19 Expression After Sequential CD19-Directed Therapy in R/R LBLC (Qualls, et al. ASH 2023)

**Objective:** Evaluate CD19 expression after treatment with CD19-directed tafa-len in R/R LBCL
**Methods:** This multicenter retrospective study assessed outcomes with subsequent CD19-directed therapy in patients with R/R LBCL who were treated with prior tafa-len from 8/2020 to 8/2022; CD19 expression was assessed by IHC or flow cytometry per local institution protocols




**Study Conclusions**

- After tafa-len, CD19 negativity was noted in most biopsies within 3 weeks of tafa infusion, but all biopsies were positive more than 3 weeks after tafa
- CD19 expression or trafficking dynamics may explain this finding, rather than true antigen loss

IHC, immunohistochemistry; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; tafa-len, tafasitamab plus lenalidomide.

Qualls DA, et al. Poster 3136. Poster presented at: American Society of Hematology Annual Meeting (ASH 2023); December 9-12, 2023; San Diego, CA.

# CD19 Expression Levels Do Not Predict Response to Lonca

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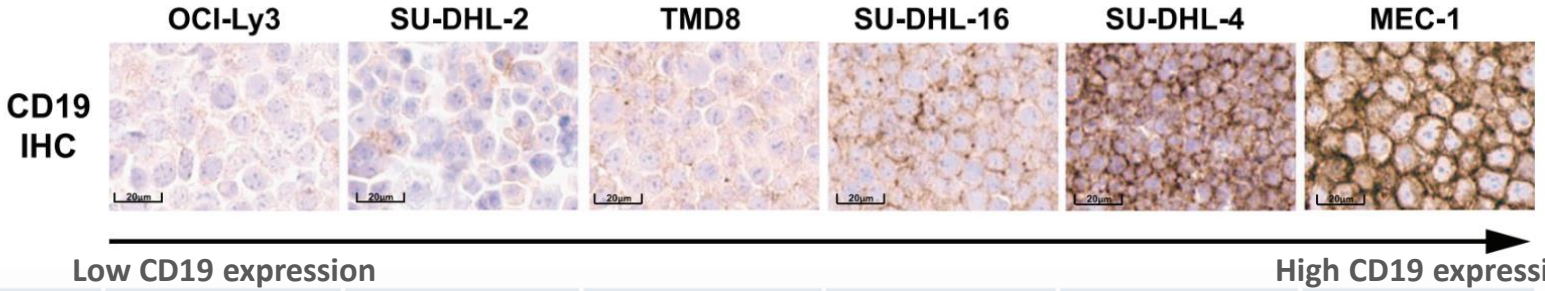
## PRECLINICAL STUDY: CD19 EXPRESSION WITH LONCA

# Lonca Cytotoxicity Observed Across B-NHL Cell Lines With Different Levels of CD19 Expression (Caimi, et al. *eJHaem* 2023)

**Objective:** Evaluate the relationship between CD19 expression and response to Lonca
**Methods:** This preclinical study quantified CD19 expression and Lonca in vitro cytotoxicity in a panel of lymphoma cell lines




| | | | | | | |
|---|---|---|---|---|---|---|
| CD19 H-score (IHC) | 2 | 30 | 55 | 142 | 150 | 265 |
| Percent of CD19-positive cells (IHC) | 2% | 30% | 40% | 80% | 65% | 90% |
| CD19 copy number (±SEM) (Flow cytometry) | 24,420 (±24) | 63,921 (±240) | 61,357 (±555) | 116,553 (±681) | 340,761 (±2301) | 288,531 (±2227) |
| Lonca *in vitro* cytotoxicity IC50 pM (±SEM) | 216 (±15.7) | 12.5 (±1.1) | 47.3 (±10.7) | 3.3 (±1.1) | 9.6 (±3.2) | 17.2 (±1.3) |

**Study Conclusions**
- Lonca showed potent cytotoxicity (IC50 within the pM range) across a panel of 6 B-cell NHL cell lines, including cell lines with very low CD19 expression, as determined by IHC and flow cytometry

Images are at 20x magnification.
B-NHL, B-cell non-Hodgkin lymphoma; H-score, histoscore; IC50, half maximal inhibitory concentration; IHC, immunohistochemistry; Lonca, loncastuximab tesirine-lpyl; SEM, standard error of the mean.
Caimi PF, et al. *eJHaem*. 2023; 5(1):76-83.

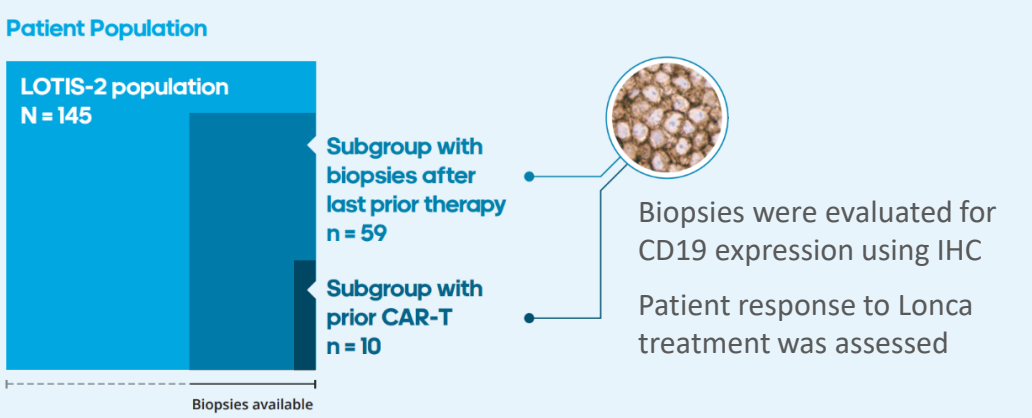
## CLINICAL STUDY AND MODELING: CD19 EXPRESSION WITH LONCA

# CD19 Expression Level Alone Is Not a Predictor of Response to Lonca (Caimi, et al. *eJHaem* 2023; 1 of 2)

**Objective:** To evaluate whether the level of CD19 expression could predict response to treatment with Lonca in patients with DLBCL

**Methods:** CD19 expression was evaluated by IHC in a subset of patients enrolled in the LOTIS-2 study who had available tissue samples collected after their last anticancer therapy and prior to treatment with Lonca (n = 59); quantitative systems pharmacology (QSP) modeling was used to predict response to Lonca

## Evaluation of CD19 Expression by IHC and Patient Response to Lonca




## QSP Modeling to Predict Response to Lonca

A virtual population was developed with the following information:

- LOTIS-2 patient data
  - Patient and disease characteristics
  - CD19 expression level before treatment with Lonca
- Laboratory studies of Lonca
  - Lonca-induced rate of tumor cell death
  - Rate of Lonca internalization
- Scientific literature on Lonca PK

The virtual patient population was used in modeling simulations to evaluate how patient and disease characteristics would affect response to treatment with Lonca

CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; IHC, immunohistochemistry; PK, pharmacokinetics; QSP, quantitative systems pharmacology.

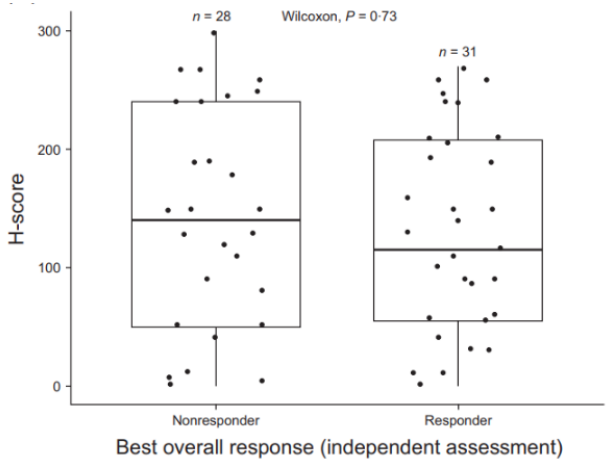
Caimi PF, et al. *eJHaem*. 2023; 5(1):76-83.

## CLINICAL STUDY AND MODELING: CD19 EXPRESSION WITH LONCA

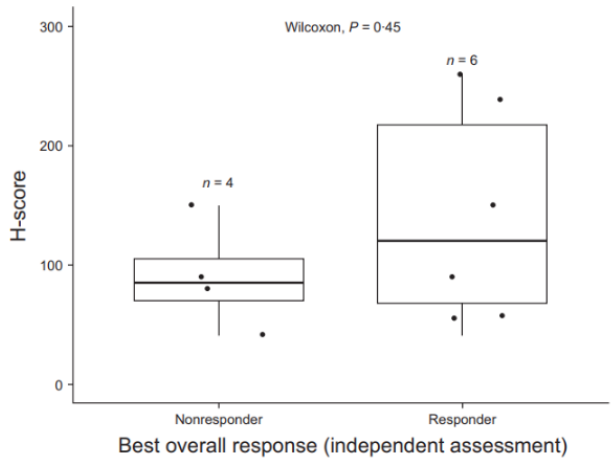
# CD19 Expression Level Alone Is Not a Predictor of Response to Lonca (Caimi, et al. *eJHaem* 2023; 2 of 2)

### Baseline Tumor CD19 H-score by Response (Independent Assessment)[1a]

Subgroup With Biopsies After Last Prior Therapy (n = 59)




Subgroup With Prior CAR-T[b] (n = 10)




| Response Rate by Subgroup Group[1] | ORR |
|---|---|
| Subgroup with biopsies after last prior therapy (n = 59) | 52.5% |
| Subgroup with prior CAR-T (n = 10) | 60% |
| Patients with low CD19 (H-score ≤10; n = 9) | 44% |

### QSP Modeling

- Virtual patient simulations predicted possible disease response to Lonca with CD19 tumor cell surface densities as low as 1,000 molecule/cell, which is below the threshold of 3,000 molecules/cell previously identified as a cutoff for CD19 positivity[2]

**Study Conclusions:**

- Response to Lonca was observed across all ranges of CD19 expression, even very low or undetectable CD19 tumor expression as measured by IHC
- IHC might not be a sensitive enough assay to evaluate CD19 expression
- QSP modeling supported clinical data from LOTIS-2 and showed that Lonca response may occur with CD19 expression below the limit of IHC detection
- Results suggest that Lonca could be given to patients whose disease relapsed or was refractory to other CD19-directed treatments, like CAR-T

[a]No statistically significant differences are apparent among the response categories; data should be interpreted with caution. [b]Ten patients received CAR-T as their last therapy prior to biopsy.
CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; IHC, immunohistochemistry; R/R, relapsed/refractory.
1. Caimi PF, et al. *eJHaem*. 2023; 5(1):76-83. 2. Spiegel JY, et al. *Nat Med*. 2021;27(8):1419-1431.

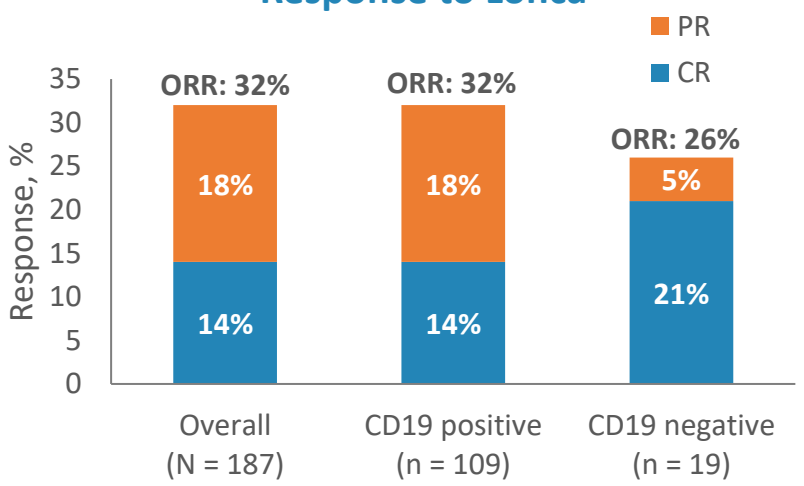
## RWE STUDY: CD19 EXPRESSION WITH LONCA

# Real-World Analysis of Impact of CD19 Expression on Outcomes With Lonca in High-Risk, Heavily Pretreated R/R DLBCL in the US (Zelikson, et al. *Haematologica* 2024; Ayers, et al. ASH 2023)

**Objective:** Assess impact of CD19 expression levels on real-world outcomes of Lonca for the treatment of patients with R/R DLBCL
**Methods:** A multicenter, retrospective chart review in adults diagnosed with R/R DLBCL who received Lonca as commercial therapy through December 1, 2022

| Demographics and Characteristics[1] | N = 187 |
|---|---|
| **Age** | |
| <65 years, n (%) | 72 (39) |
| 65-75 years, n (%) | 66 (33) |
| >75 years, n (%) | 39 (21) |
| **Male, n (%)** | 119 (64) |
| **Advanced stage disease, n (%)** | 161 (86) |
| **Disease histology** | |
| HGBCL, n (%) | 36 (22) |
| De novo DLBCL, n (%) | 85 (53) |
| Transformed DLBCL, n (%) | 28 (18) |
| **Prior CAR-T, n (%)** | 112 (60) |
| **CD19 status overall, n** | 128 |
| Positive, n (%) | 109 (85) |
| Negative, n (%) | 19 (15) |
| **CD19 status post–CAR-T, n** | 90 |
| Positive, n (%) | 70 (78) |
| Negative, n (%) | 20 (22) |

## Response to Lonca[1]




## Median PFS With Lonca by CD19 Status[2]

| | mPFS (months) |
|---|---|
| Overall | 2.1 |
| CD19 positive | 2.3 |
| CD19 negative | 2.0 |

**Study Conclusions**

- Prior CD19 status did not impact outcomes in patients treated with Lonca
- This study is limited by retrospective design and incomplete clinicopathologic data (eg, CD19 staining)

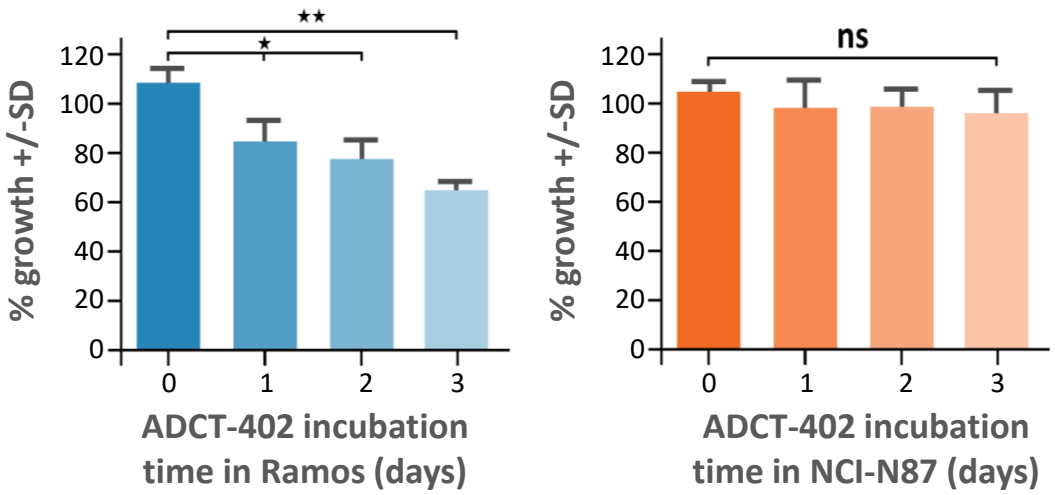
CAR-T, chimeric antigen receptor T-cell; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; PFS, progression-free survival; HGBCL, high-grade B-cell lymphoma; Lonca, loncastuximab tesirine-lpyl; mPFS, median progression-free survival; PR, partial response; ORR, overall response rate; R/R, relapsed/refractory.

1. Zelikson V, et al. *Haematologica*. 2024; doi.org/10.3324/haematol.2024.285977. 2. Ayers E, et al. Oral Presented at: American Society of Hematology Annual Meeting (ASH 2023); December 9-12, 2023; San Diego, CA.

## PRECLINICAL STUDY: CD19 EXPRESSION WITH LONCA

# Bystander Effect Potentially Decreases Likelihood of CD19-Negative Relapse With Lonca (Zammarchi, et al. *Blood* 2018)

- The intratumor release of Lonca may cause the bystander killing of neighboring tumor cells
- Bystander killing of CD19-negative cells by Lonca was observed in preclinical studies, supporting the antitumor activity of Lonca in lymphomas with heterogenous CD19 expression[1]
  - An ADCT-402–conditioned medium elicited a bystander effect after 1-3 days of pretreatment
  - A decrease occurred in the survival percentage in the conditioned medium-treated Karpas-299 cells vs cells in the nonconditioned medium (100% to 86%, 80%, and 65% after 1, 2, and 3 days of pretreatment, respectively; see left panel)[a]
  - The conditioned medium from ADCT-402–treated, CD19-negative NCI-N87 cells did not elicit a bystander effect on CD19-negative Karpas-299 cells, regardless of the preincubation time (see right panel)




**Study Conclusions:**

- The existence of bystander toxicity on target-negative tumor cells decreases the likelihood of CD19-negative tumor cells escaping CD19-directed therapy and transforming to dominant clones

[a]Ramos cells (Burkitt lymphoma cell line) were treated with ADCT-402 for 1, 2, or 3 days before media was transferred onto CD192 Karpas-299 cells and incubating for 96 hours. *P ≤ 0.05; **P ≤ 0.01.
Lonca, loncastuximab tesirine; ns, not significant; SD, standard deviation.
Zammarchi F, et al. *Blood*. 2018;131(10):1094-1105.

# Response to Subsequent CAR-T in Patients Who Previously Received CD19-Directed Therapy

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# Response to ***Subsequent*** CAR-T in Patients Who Previously Received Lonca or Other CD19-Directed Therapies


- LOTIS-1 & LOTIS-2 retrospective analysis
- LOTIS-2 subgroup analysis
- RWE studies

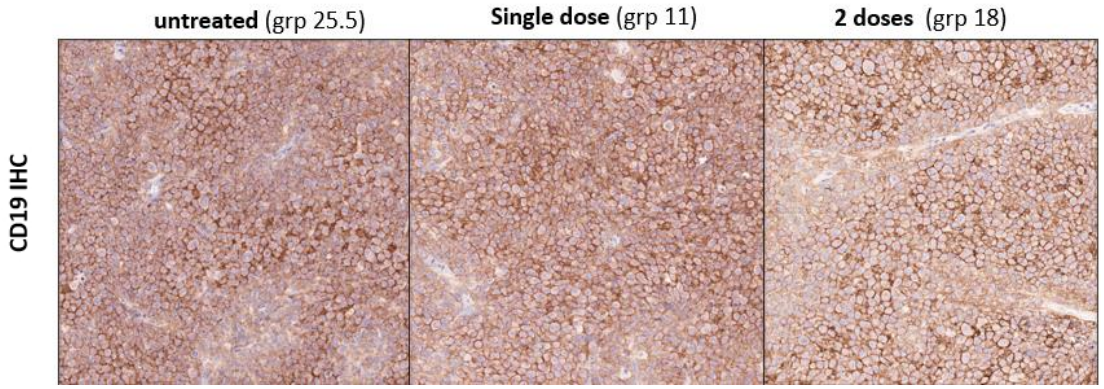

- LOTIS-2 subgroup analysis
- RWE studies

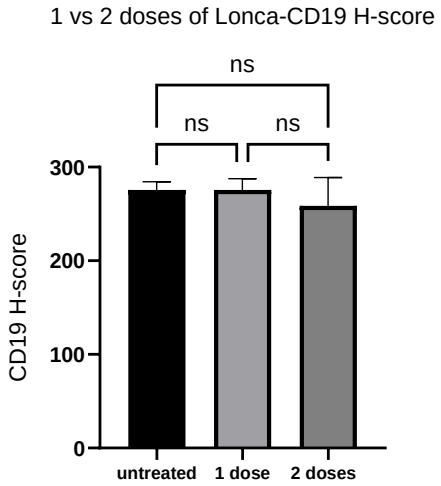
## PRECLINICAL EVIDENCE: LONCA WITH *SUBSEQUENT* CAR-T

1. Lonca is administered at very low dosage (approx. 80x lower than Tafasitamab); therefore, CD19 target occupancy will be low.

2. The Lonca bound fraction is fully fast-internalised (less than 24h) and will not block further anti-CD19 binding-based therapies.

3. CD19 expression remains positive after ADCT-402 treatment in a preclinical xenograft model



## CLINICAL STUDY: LONCA WITH *SUBSEQUENT* CAR-T

# Response to Subsequent CAR-T in Patients Who Previously Received Lonca: Retrospective Analysis From LOTIS-1 & -2 (Thapa, et al. *Blood Adv* 2020; 1 of 2)

**Objective:** To evaluate outcomes of subsequent CD19-directed CAR T-cell therapy in R/R DLBCL previously treated with the CD19-directed therapy Lonca

**Methods:** A retrospective analysis of outcomes in 14 DLBCL patients with disease relapsing or progressing after Lonca and undergoing subsequent CD19-directed CAR–T-cell therapy identified from 2 multicenter, open-label studies of Lonca[a]

| Baseline Characteristics (N = 14)[b] | |
|---|---|
| **Lymphoma subtype** | |
| DLBCL[c] | 10 |
| Transformed DLBCL | 4 |
| **IPI at diagnosis, n (%)** | |
| Low (0, 1) | 3 (21) |
| Low-intermediate (2) | 3 (21) |
| High-intermediate (3) | 5 (36) |
| Unknown | 3 (21) |
| **Advanced stage (III/IV) at diagnosis, n (%)** | 4 (29) |
| ***c-MYC* rearrangement, n (%)** | |
| Yes | 3 (21) |
| No | 8 (57) |
| Unknown | 3 (21) |
| **Median interval between diagnosis and start of Lonca (range), mo** | 21.5 (6.8-258) |
| **Best response to Lonca, n (%)** | |
| Complete response | 1 (7) |
| Partial response | 5 (36) |

[a]LOTIS-1, phase 1: NCT02669017; LOTIS-2, phase 2: NCT03589469.
[b]Thirteen patients were enrolled in LOTIS-2, and 1 patient was enrolled in LOTIS-1.
[c]One patient had mediastinal large B-cell lymphoma.

CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; R/R, relapsed/refractory.
Thapa B, et al. *Blood Adv*. 2020;4(16):3850-3852.

## CLINICAL STUDY: LONCA WITH *SUBSEQUENT* CAR-T

# Response to Subsequent CAR-T in Patients Who Previously Received Lonca: Retrospective Analysis From LOTIS-1 & -2 (Thapa, et al. *Blood Adv* 2020; 2 of 2)

### CD19 Expression After Lonca

- 10/14 patients were screened for CD19, and all had positive CD19 expression by IHC prior to CAR-T
  - 4 patients were not assessed for CD19 expression
  - However, all 4 patients with unknown CD19 expression status after treatment with Lonca achieved CR with subsequent anti-CD19 CAR-T therapy

| CAR–T-Cell Therapy Characteristics | n = 14 |
|---|---|
| **Median time between Lonca and CAR-T, median (range), day**[a] | 120 (22-660) |
| **Type of CAR-T, n (%)** | |
| Axicabtagene ciloleucel | 5 (36) |
| Tisagenlecleucel | 2 (14) |
| Investigational CD19[b] | 4 (29) |
| JCAR017 | 3 (21) |
| **Best response to subsequent CAR-T, n (%)** | |
| Complete response | 6 (43) |
| Partial response | 1 (7) |
| Refractory disease | 7 (50) |

**Study Conclusions:**

- Prior treatment with Lonca in R/R DLBCL does not preclude responses to subsequent CD19-directed CAR–T-cell therapies
- Favorable outcomes of subsequent CAR–T-cell therapy (ORR 50%) were seen in patients with R/R DLBCL after previous treatment with CD19-directed Lonca
- This study is limited by the small sample size and retrospective design

[a]Additional therapy between Lonca and CAR-T included radiation alone (n = 3); radiation with ifosphamide/vinblastine/etoposide (n = 1); radiation with rituximab/methotrexate (n = 1); and lenalidomide, anti-CD47 antibody, and ibrutinib (n = 1).
[b]One patient each received a CD19/CD22-directed CAR and a CD19/CD20-directed CAR. Neither patient responded to CAR treatment.

CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; IHC, immunohistochemistry; Lonca, loncastuximab tesirine; ORR, overall response rate; R/R, relapsed/refractory.

Thapa B, et al. *Blood Adv*. 2020;4(16):3850-3852.

## CLINICAL STUDY: LONCA WITH *SUBSEQUENT* CAR-T

# Response to Subsequent CAR-T in Patients Who Previously Received Lonca[1,2]: Subgroup Analysis of LOTIS-2 (Caimi, et al. *Haematologica* 2023)

**Objective:** Evaluate outcomes of subsequent CD19-directed CAR-T therapy in R/R DLBCL previously treated with the CD19-directed therapy Lonca
**Methods:** A subgroup analysis of outcomes in patients in the LOTIS-2 trial who relapsed or were refractory to Lonca and received subsequent CD19-directed CAR-T therapy

## 16 (11.0%) patients received subsequent CD19-directed CAR-T therapy[a]

Limited baseline characteristics are available for 14 patients

| Characteristics | n = 14 |
|---|---|
| Median age, years (range) | 58.5 (23-71) |
| Male, n | 10 |
| Median # of therapies prior to Lonca, n (range) | 3 (2-5) |
| Median # of Lonca cycles, n (range) | 2 (1-7) |

[a]Type of subsequent CD19-directed CAR–T-cell therapy received is not available.
[b]Only AEs that occurred or worsened after CAR-T were included. Only selected AEs, such as cytokine release syndrome, encephalopathy, edema or effusion, rash, and hepatic toxicity were required per protocol; however, all collected AEs were reported.

Investigator-assessed ORR to CAR-T after Lonca was 56.3% (9/16 patients; 95% CI: 29.9, 80.2)

| Best response to subsequent CAR-T, n (%) | n = 16 |
|---|---|
| Complete response | 8 (50.0) |
| Partial response | 1 (6.3) |
| Stable disease | 1 (6.3) |
| Progressive disease | 5 (31.3) |

- 9/16 patients died after CAR-T due to disease progression
- 2/16 patients experienced AEs of grade ≥3 after CAR-T[b]

**Study Conclusions**
- Lonca has potential as therapy for patients with rapidly progressive disease without preventing response to subsequent CAR–T-cell therapy[3]
- This analysis is limited by the small sample size

AE, adverse event; CAR, chimeric antigen receptor; DLBCL; diffuse large B-cell lymphoma; Lonca, loncastuximab tesirine; ORR, overall response rate; R/R, relapsed/refractory

1. Caimi PF, et al. *Haematologica*. 2023;109(4):1184-1193. 2. ADC Therapeutics, Data on File. 3. Caimi PF, et al. *Lancet Oncol*. 2021;22(6):790-800.

## RWE STUDY: LONCA WITH *SUBSEQUENT* CAR-T

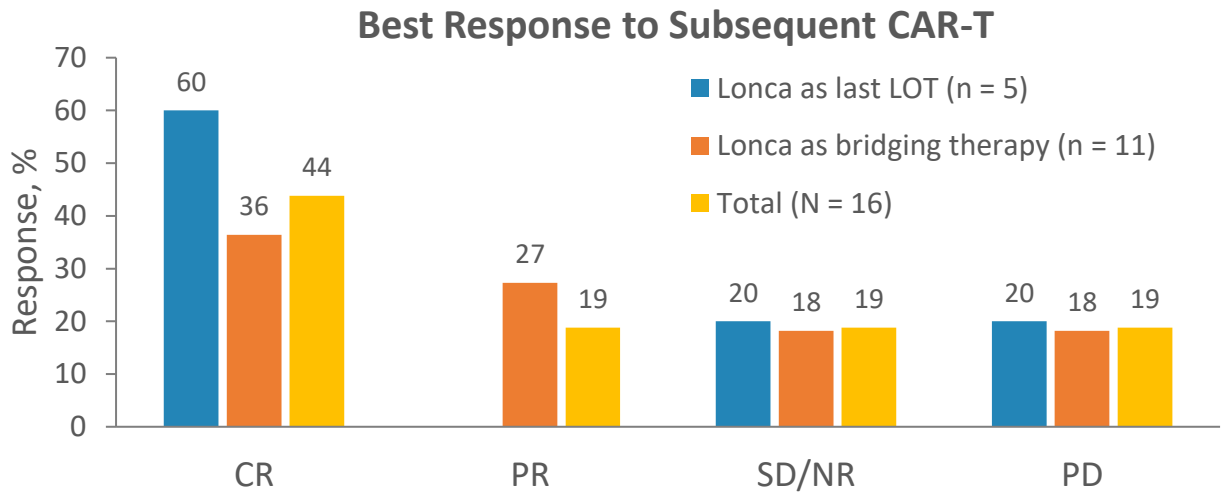
# Real-World Treatment Patterns and Outcomes With Lonca in Patients Who Received Subsequent CAR-T (Hamadani, et al. Tandem 2024/*eJHaem* 2024; 1 of 2)

**Objective:** Examine real-world treatment patterns and outcomes among patients who received subsequent CAR-T therapy after Lonca

**Methods:** This observational, real-world study assessed outcomes for patients who received Lonca between 2018 and 2022 as either a bridging therapy or as the last LOT before their first CD19-directed CAR-T infusion (axi-cel) as identified in the CIMBTR registry

| Patient and Disease Characteristics[1] | N = 16 |
|---|---|
| **Age, median (range), years** | 63.2 (42.5-79.9) |
| **Male, n (%)** | 12 (75.0) |
| **Sub-disease classification, n (%)** | |
| DLBCL | 15 (93.8) |
| Transformed follicular | 1 (6.3) |
| **Stage III/IV at diagnosis, n (%)** | 11 (68.8) |
| **Therapy prior to CAR-T** | |
| No. of prior LOTs, median (range) | 4.0 (2.0-7.0) |
| Prior HCT, n (%) | 4 (25.0) |
| **Refractory to first LOT, n (%)** | 6 (37.5) |
| **Refractory disease status at CAR-T, n (%)** | 10 (62.5) |
| **Lonca therapy, n (%)** | |
| Lonca as last LOT | 5 (31.3) |
| Lonca as bridging therapy | 11 (68.8) |
| No. of cycles, median (range) | 1.0 (1.0-5.0) |
| **Best response to Lonca, n (%)** | |
| Complete response | 2 (12.5) |
| Partial response | 4 (25.0) |
| Stable disease/no response | 1 (6.3) |
| Progressive disease | 5 (31.3) |
| Not assessed | 4 (25.0) |

| Time Intervals and Frequency of Outcomes[2] | Last LOT n = 5 | Bridging Therapy n = 11 | Total N = 16 |
|---|---|---|---|
| Median (range) duration of Lonca line of therapy, days | 57.0 (22.0-107.0) | 43.0 (22.0-95.0) | 43.0 (22.0-107.0) |
| Median (range) time from end of Lonca therapy to CAR-T, days | 211.0 (1.0-257.0) | 13.0 (1.0-100.0) | 16.5 (1.0-257.0) |




Axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor modified T-cell; CIBMTR, Center for the International Blood & Marrow Transplant Research; CR, complete response; DLBCL, diffuse large B-cell lymphoma; HCT, hematopoietic cell transplant; Lonca, loncastuximab tesirine-lpyl; LOT, line of therapy; PD, progressive disease; PR, partial response; R/R, relapsed or refractory; SD/NR, stable disease/no response. 1. Hamadani M, et al. *eJHaem*. 2024;5(5):1110-1113. 2. Hamadani M, et al. Poster presented at: TANDEM 2024. Feb. 21-24, 2024; San Antonio, TX. Poster 492.

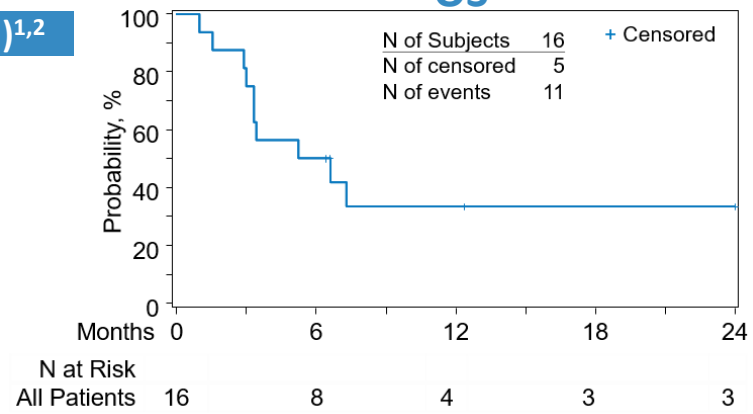
## RWE STUDY: LONCA WITH *SUBSEQUENT* CAR-T

# Real-World Treatment Patterns and Outcomes With Lonca in Patients Who Received Subsequent CAR-T (Hamadani, et al. Tandem 2024/*eJHaem* 2024; 2 of 2)

### OS Post–CAR-T, % (95% CI)[1,2]

| | |
|---|---|
| **Last LOT (n = 5)** | |
| 12 m | 60 (18.7-94) |
| 24 m | 60 (18.7-94) |
| **Bridging Therapy (n = 11)** | |
| 12 m | 15.2 (0.1-47.9) |
| 24 m | NE |
| **Total (n = 16)** | |
| 12 m | 33.3 (11.8-59.4) |
| 24 m | 33.3 (11.8-59.4) |

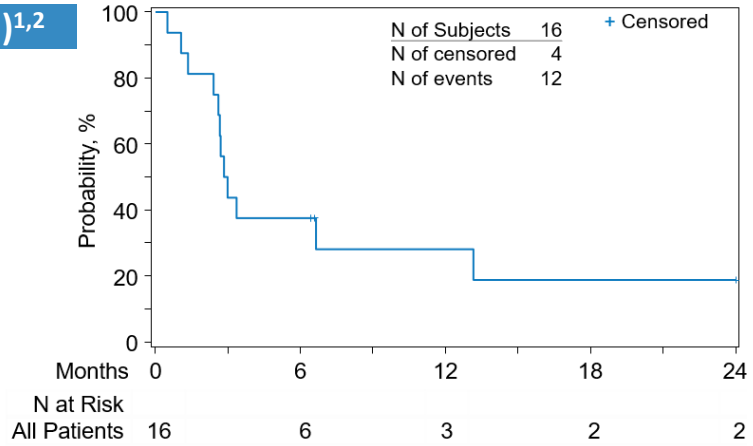
### OS




### PFS Post–CAR-T, % (95% CI)[1,2]

| | |
|---|---|
| **Last LOT (n = 5)** | |
| 12 m | 60 (18.7-94) |
| 24 m | 40 (6-81.3) |
| **Bridging Therapy (n = 11)** | |
| 12 m | NE |
| 24 m | NE |
| **Total (n = 16)** | |
| 12 m | 28.1 (8.4-53.9) |
| 24 m | 18.8 (2.8-44.3) |

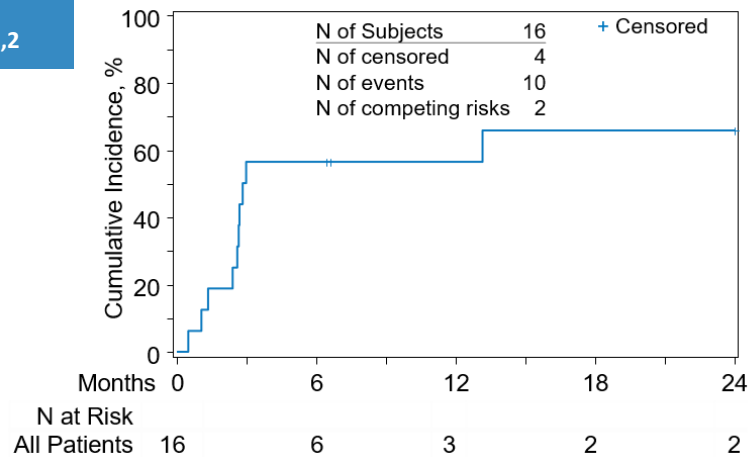
### PFS




### Relapse/Progression Post–CAR-T, % (95% CI)[1,2]

| | |
|---|---|
| **Last LOT (n = 5)** | |
| 12 m | 40 (3.4-85.8) |
| 24 m | 60 (12.8-97.3) |
| **Bridging Therapy (n = 11)** | |
| 12 m | 63.6 (32-89.8) |
| 24 m | 63.6 (32-89.8) |
| **Total (n = 16)** | |
| 12 m | 56.3 (31-79.9) |
| 24 m | 65.6 (36.5-89.4) |

### Relapse/Progression




### Study Conclusions

- In this small real-world study, treatment of patients with Lonca prior to CAR-T infusion did not preclude responses to subsequent CD19-directed CAR-T
- The fast CD19 internalisation post-Lonca treatment, coupled to the low receptor occupancy expected at this Lonca's dosing regime, would not affect overall CD19 expression and further targeted-CD19 therapies

CAR-T, chimeric antigen receptor modified T-cell; DLBCL, diffuse large B-cell lymphoma; Lonca, loncastuximab tesirine-lpyl; LOT, line of therapy; OS, overall survival; PFS, progression-free survival. 1. Hamadani M, et al. *eJHaem*. 2024;5(5):1110-1113. 2. Hamadani M, et al. Poster presented at: TANDEM 2024. Feb. 21-24, 2024; San Antonio, TX. Poster 492.

## RWE STUDY: TAFA-LEN WITH *SUBSEQUENT* LONCA OR CAR-T

# Outcomes of Sequential CD19-Directed Therapy in R/R LBLC (Qualls, et al. ASH 2023)

**Objective:** Evaluate outcomes of CD19-directed CAR-T or Lonca after failure of a prior treatment with tafa-len in R/R LBCL
**Methods:** This multicenter retrospective study assessed outcomes with Lonca or CAR-T in patients with R/R LBCL who were treated with prior tafa-len from 8/2020 to 8/2022

| Characteristics[1] | Prior CAR-T (n = 52) | No Prior CAR-T (n = 126) |
|---|---|---|
| **Median age (range), years** | 66 (38-79) | 78 (26-94) |
| **Female, n (%)** | 27 (52) | 60 (48) |
| **DLBCL subtype** | | |
| DLBCL NOS | 28 (54) | 71 (56) |
| Transformed indolent lymphoma | 15 (29) | 44 (35) |
| HGBCL (nontransformed) | 7 (13) | 8 (6) |
| Other[a] | 2 (4) | 3 (2) |
| ***MYC* + *BCL2* rearrangement, n (%)** | 10 (21) | 12 (12) |
| **Stage III-IV at index** | 47 (94) | 102 (86) |
| **Risk (IPI)** | | |
| 0-2 | 9 (20) | 34 (30) |
| 3-5 | 36 (80) | 78 (70) |
| **Median (range) prior LOT for DLBLC[b]** | 4 (0-11) | 2 (0-7) |
| **Primary refractory** | 27 (52) | 60 (48) |
| **Refractory to last therapy** | 37 (71) | 81 (64) |
| **Prior SCT** | 14 (27) | 8 (6) |

| Treatment After Tafa-len[1] | Number Treated |
|---|---|
| **Anti-CD19 CAR-T** | 14 |
| **Lonca** | 20 |
| **Pola-based** | 31 |
| **Chemotherapy-based** | 17 |

| Outcomes[1] | mEFS,[c] mo (95% CI) | mOS, mo (95% CI) |
|---|---|---|
| **Lonca** | 2.8 (0.9-4.7) | 3.5 (1.2-5.7) |
| CAR-T | 3.7 (0.9-6.5) | 8.1 (0.6-15.7) |

**CD19-directed therapies have similar outcomes to other therapies after tafa-len failure, with no difference in EFS between CAR-T, Lonca, pola-based therapy, or chemo-based therapy (p = 0.76)**

### Study Conclusions

- Limited EFS and OS were seen after treatment with prior tafa-len, regardless of the subsequent therapy that was chosen
- Clear evidence of cross resistance to CD19-directed therapies was not observed in this study

[a]Other diagnoses: TCHRBCL (2), PMBCL (2), PTLD with DLBCL morphology (1). [b]Eleven patients with transformed indolent lymphoma had received prior therapy for indolent disease but not for aggressive LBCL. [c]EFS defined as survival without initiation of a new treatment after CAR-T or Lonca. dCAR-T, chimeric antigen receptor T cell; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; Lonca, loncastuximab tesirine; LBCL, large B-cel lymphoma; LOT, lines of therapy; mos, months; mEFS, median event-free survival; mOS, median overall survival; NOS, not otherwise specified; OS, overall survival; ORR, overall response rate; PMBCL, primary mediastinal large B cell lymphoma; Pola, polatuzumab vedotin; PTLD, post-transplant lymphoproliferative disease; R/R, relapsed or refractory; SCT, stem cell transplant; tafa-len, tafasitamab-lenalidomide; TCHRBCL, T-cell/histocyte-rich-B-cell lymphoma.

1. Qualls DA, et al. Poster presented at: American Society of Hematology Annual Meeting (ASH 2023); December 9-12, 2023; San Diego, CA. Poster 3136. 2. Kaplon H, et al. *mAbs*. 2020;12:e1703532. 3. Zhang Z, et al. J *Immunother Cancer*. 2020;8:e001150. 4. Lownik J, et al., *Clin Cancer Research.* 2024;30:2895-2904.

# Response to CD19-Directed Therapy in Patients Who Received Prior CAR-T

ADC™ THERAPEUTICS
Innovating Science. Inspiring Hope.

# Response to Lonca or Other CD19-Directed Therapies in Patients Who Received ***Prior*** CAR-T


- LOTIS-1 & LOTIS-2 retrospective analysis
- LOTIS-2 subgroup analysis
- RWE studies


- LOTIS-2 subgroup analysis
- RWE studies
- Consolidation with Lonca IIT

## CLINICAL STUDY: LONCA WITH *PRIOR* CAR-T

# Response to Lonca in Patients Who Received Prior CAR-T Therapy (LOTIS-2) (Caimi, et al. *CLML* 2022; Caimi, et al. *Haematologica* 2023; 1 of 2)

**Objective:** Investigate whether Lonca is effective in patients with R/R DLBCL who were treated with prior CAR-T therapy[1]

**Methods:** This post hoc analysis evaluated outcomes of patients with DLBCL whose disease relapsed or was refractory to prior CAR-T therapy and who were subsequently treated with Lonca in the LOTIS-2 trial[1]

**As of the final analysis, 14 (9.7%) patients from LOTIS-2 had received prior CAR-T therapy[2,a]; patient and therapy characteristics are available for 13 patients[1]**

| Patient & Disease Baseline Characteristics (n = 13)[1,b] | |
|---|---|
| **Sex, male, n (%)** | 9 (69) |
| **Race, n (%)** | |
| White | 12 (92) |
| Pacific Islander | 1 (8) |
| **Lymphoma subtype, n (%)** | |
| DLBCL, NOS | 5 (38) |
| Transformed follicular | 4 (31) |
| Richter transformation | 1 (8) |
| HGBCL—DH/TH | 3 (23) |
| **DH/TH, n (%)** | 5 (39) |
| **Stage III-IV at diagnosis, n (%)** | 11 (85) |
| **Primary refractory, n (%)** | 10 (77) |

| CAR-T Therapy Characteristics (n = 13)[1,b] | |
|---|---|
| **Time between diagnosis and CAR-T infusion, median (range), mo** | 10 (2-79) |
| **No. of LOT prior to CAR-T, median (range)** | 3 (1-6) |
| **Time from CAR-T to Lonca, median (range)** | 7 mo (45-400 d)[c] |
| **Type of CAR-T, n (%)** | |
| Axi-cel | 7 (54) |
| Liso-cel | 2 (15) |
| Investigational CD19 | 2 (15) |
| Investigational CD19/CD20 | 1 (8) |
| Investigational CD19/CD22 | 1 (8) |
| **Best response to CAR-T, n (%)** | |
| Complete response | 7 (54) |
| Partial response | 2 (15) |
| No response | 4 (31) |

[a]Data cutoff: September 15, 2022. [b]Data cutoff: April 6, 2020. [c]Lonca was the first treatment after CAR-T in 10 patients; 3 patients received other treatments prior to Lonca, including chemoimmunotherapy (n = 1, R-GemOx) and allogeneic SCT (n = 1), and 1 patient received chemoimmunotherapy (R-GemOx), followed by a clinical trial with venetoclax and a bromodomain inhibitor.

## No prior CAR-T patients who were screened failed due to a lack of CD19 expression[1]

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DH, double hit; DLBCL, diffuse large B-cell lymphoma; HGBCL, high grade B-cell lymphoma; liso-cel, lisocabtagene maraleucel; Lonca, loncastuximab tesirine; LOT, line of therapy; NOS, not otherwise specified; R-GemOx, rituximab + gemcitabine + oxaliplatin; R/R, relapsed/refractory; SCT, stem cell transplant; TH, triple hit.

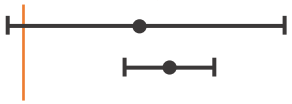
1. Caimi PF, et al. *CLML*. 2022;22(5):e335-e339. 2. Caimi PF, et al. *Haematologica*. 2023;109(4):1184-1193.

## CLINICAL STUDY: LONCA WITH *PRIOR* CAR-T

# Response to Lonca in Patients Who Received Prior CAR-T Therapy (LOTIS-2) (Caimi, et al. *CLML* 2022; Caimi, et al. *Haematologica* 2023; 2 of 2)

### 14 (9.7%) patients from LOTIS-2 had received prior CAR–T-cell therapy[1,2,a]

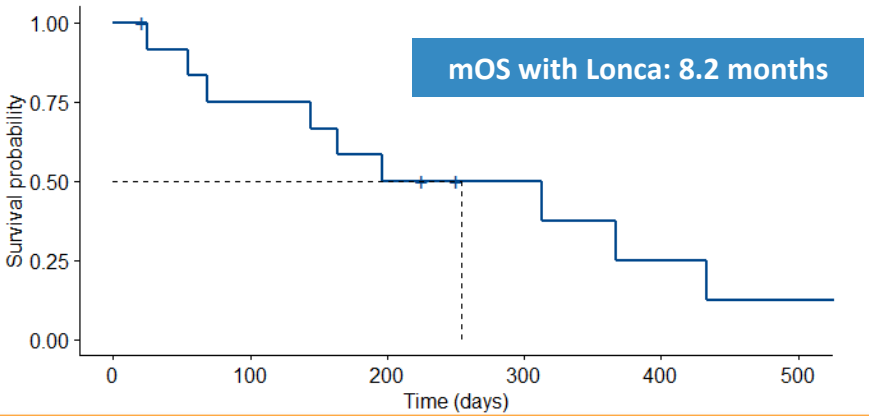
**Response to Lonca in patients with prior CAR-T therapy**



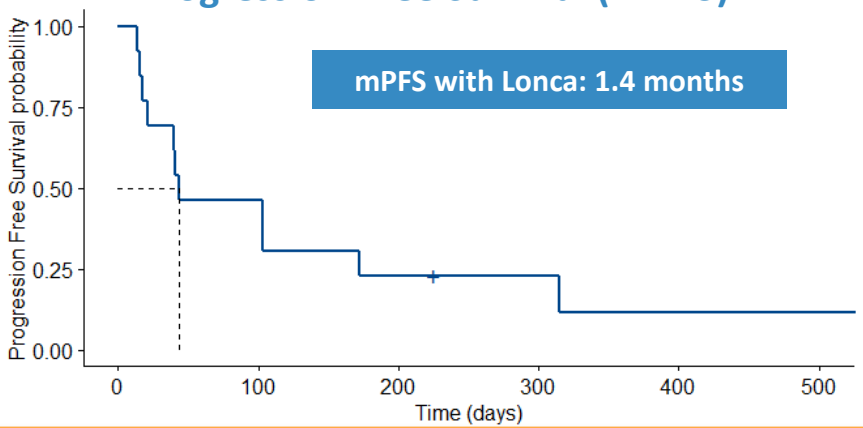
| | | |
|---|---|---|
| Yes | 6/14 | 42.9 (17.7, 71.1) |
| No | 64/131 | 48.9 (40.0, 57.7) |

ORR to Lonca: **42.9%** (6/14 patients)[1]
CRR to Lonca: **21.4%** (3/14 patients)[1]

### Overall Survival (n = 13)[3,b]




### Progression-Free Survival (n = 13)[3,b]




Median (range) cycles of Lonca: 2 (1-9)[3,b]

Median follow-up: 8 months[3,b]

Median DoR: 8 months[3,b]

**Study Conclusions**

- Lonca can achieve responses in patients progressing after prior CD19-directed CAR-T therapy, with an ORR similar to that of the overall population LOTIS-2 (48.3%)[1,3]
- Sequencing CD19-directed therapies is possible in cases without CD19 loss[3]
- This study is limited by the small sample size[3]

[a]Data cutoff: September 15, 2022. [b]Data cutoff: April 6, 2020.
CAR, chimeric antigen receptor; CRR, complete response rate; DoR, duration of response; Lonca, loncastuximab tesirine; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
1. Caimi PF, et al. *Haematologica*. 2023;109(4)1184. 2. ADC Therapeutics, Data on File. 3. Caimi PF, et al. *CLML*. 2022;22(5):e335-e339.

## RWE STUDY: LONCA WITH *PRIOR* CAR-T

# Real-World Clinical Effectiveness of Lonca for the Treatment of Patients With Prior CAR-T in the US (Epperla, et al. *Blood Cancer J* 2024; 1 of 2)

**Objective:** Examine the real-world use and outcomes of Lonca in the treatment of R/R DLBCL in patients with prior CAR-T therapy received at 2L or 3L

**Methods:** This US-based retrospective chart review included adult patients diagnosed with R/R DLBCL who initiated Lonca monotherapy as their next treatment following 2L or 3L CAR-T therapy between April 2021 and the date at least 6 months prior to data entry

| Demographics and Clinical Characteristics | CAR-T in 2L (n = 95) | CAR-T in 3L (n = 23) |
|---|---|---|
| **Median age, years** | 66 | 57 |
| **Male, n (%)** | 58 (61) | 10 (43) |
| **DLBCL subtype, n (%)** | | |
| DLBCL NOS/DLBCL arising from low-grade lymphoma | 44 (46)/32 (34) | 21 (91)/1 (4) |
| HGBCL | 19 (20) | 1 (4) |
| **DHL/THL** | 31 (33) | 3 (13) |
| **Bulky disease at index[a]** | 24 (25) | 2 (9) |
| **Stage III-IV at index** | 73 (77) | 20 (87) |
| **High–intermediate risk/high-risk at index[b]** | 62 (65) | 5 (22) |
| **CAR-T therapy received** | | |
| Axi-cel | 62 (65) | 18 (78) |
| Liso-cel | 33 (35) | 0 (0) |
| Tisa-cel | 0 (0) | 5 (22) |
| **Response to CAR-T therapy** | | |
| CR/PR[d] | 23 (24)/44 (46) | 12 (52)/5 (22) |
| SD | 11 (12) | 4 (17) |
| PD | 16 (17) | 2 (9) |
| Unknown | 1 (1) | 0 (0) |
| **Received bridging therapy to CAR-T therapy** | 12 (13) | 13 (57) |

| Treatment Patterns of Lonca Monotherapy | CAR-T in 2L (n = 95) | CAR-T in 3L (n = 23) |
|---|---|---|
| **Treatment patterns of Lonca monotherapy** | | |
| Median (IQR) time from CAR-T infusion to Lonca monotherapy initiation, days[e] | 203.0 (92.0-280.0) | 297.0 (215.5-358.0) |
| Median (IQR) follow-up duration, months[f] | 8.5 (6.7-13.6) | 12.9 (11.7-13.9) |
| Median (IQR) number of cycles of Lonca monotherapy | 6.0 (3.0-8.0) | 6.0 (6.0-9.0) |
| **Occurrence of treatment interruptions or discontinuations due to adverse events** | | |
| Treatment interruptions, n (%) | 7 (7.4) | 0 (0) |
| Treatment discontinuations, n (%) | 8 (8.4) | 0 (0) |

[a]Tumor ≥7.5 cm in longest dimension. [b]Based on International Prognostic Index risk classification at index (initiation of Lonca monotherapy) of high-intermediate risk (3 points)/high-risk (4-5 points). [c]Refractory to CAR-T therapy is defined as patients who had no response (ie, stable disease or progressive disease) to treatment. [d]Best response to 2L CAR-T therapy was unknown for 3 patients. Complete response and partial response are reported for the best response to CAR-T therapy. [e]The base size for time from CAR-T infusion to Lonca monotherapy initiation was n = 84 (n = 75, 2L CAR-T patients; n = 9, 3L CAR-T patients). [f]Follow-up time is the time from index to last clinical evaluation date or date of death.

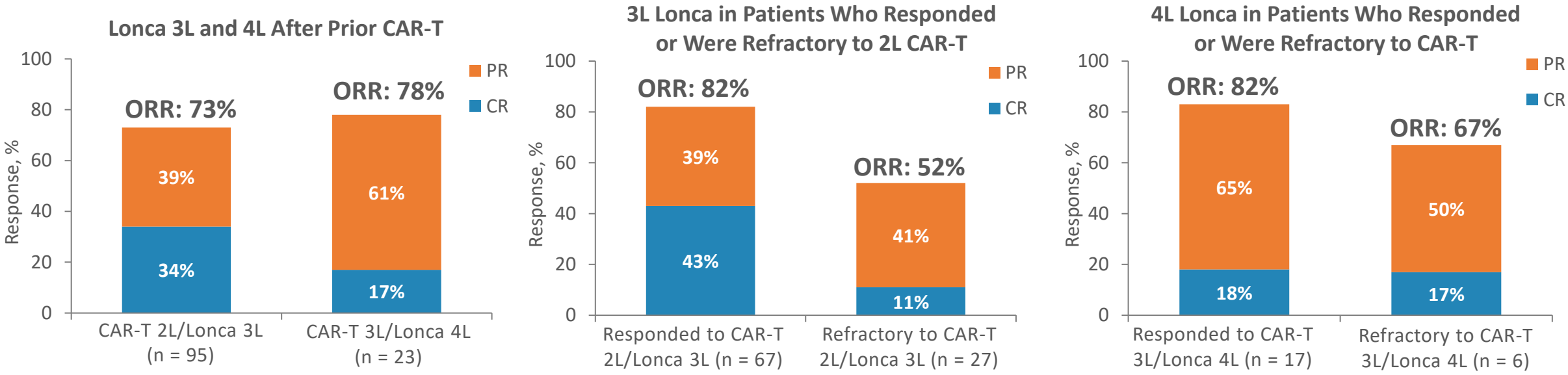
1L, first line therapy; 2L, second line therapy; 3L, third line therapy; 4L, fourth line therapy; Axi-cel, axicabtagene ciloleucel; BR, bendamustine and rituximab; CAR-T, chimeric antigen receptor modified T-cell; CNS, central nervous system; CR, complete response; DHL, double hit lymphoma; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; IQR, interquartile range; liso-cel, lisocabtagene maraleucel; Lonca, loncastuximab tesirine-lpyl; NOS, not otherwise specified; ORR, overall response rate; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-ICE, rituximab with ifosfamide, carboplatin, and etoposide; R/R, relapsed/refractory; SCT, stem cell transplant; SD, stable disease; THL, triple hit lymphoma; tisa-cel, tisagenlecleucel.

Epperla N, et al. *Blood Cancer Journal*. 2024 November 28. doi.org/10.1038/s41408-024-01195-4. Epub ahead of print.

## RWE STUDY: LONCA WITH *PRIOR* CAR-T

# Real-World Clinical Effectiveness of Lonca for the Treatment of Patients With Prior CAR-T in the US (Epperla, et al. *Blood Cancer J* 2024; 2 of 2)

## Best Response to Lonca Monotherapy After Prior CAR-T




**Study Conclusions**

- The findings suggest that prior CAR-T exposure does not prohibit a response to Lonca monotherapy, suggesting that Lonca may be an effective treatment option for patients whose disease is resistant to or progressed after 2L or 3L CAR-T
- This study is limited by retrospective design as well as potential selection and sampling biases

2L, second line therapy; 3L, third line therapy; 4L, fourth line therapy; CAR-T, chimeric antigen receptor modified T-cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; Lonca, loncastuximab tesirine-lpyl; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory.

Epperla N, et al. *Blood Cancer Jour*nal. 2024 November 28. doi.org/10.1038/s41408-024-01195-4. Epub ahead of print.

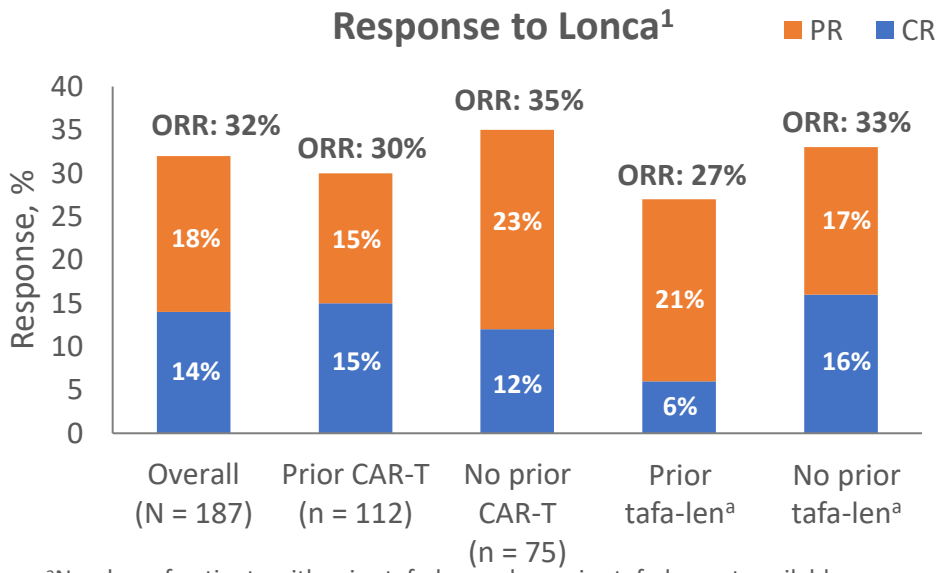
## RWE STUDY: LONCA WITH *PRIOR* CAR-T

# Real-World Analysis of Lonca in High-Risk, Heavily Pretreated R/R DLBCL in the US (Zelikson, et al. *Haematologica* 2024; Ayers, et al. ASH 2023)

**Objective:** Assess real-world outcomes of Lonca for the treatment of patients with R/R DLBCL, including those with prior therapy with CAR-T or tafa-len

**Methods:** A multicenter, retrospective chart review in adults diagnosed with R/R DLBCL who received Lonca as commercial therapy from April 2021 to December of 2022

| Demographics and Characteristics[1] | N = 187 |
|---|---|
| **Age** | |
| <65 years, n (%) | 72 (39) |
| 65-75 years, n (%) | 66 (33) |
| >75 years, n (%) | 39 (21) |
| **Male, n (%)** | 119 (64) |
| **Advanced stage disease, n (%)** | 161 (86) |
| **Disease histology** | |
| HGBCL, n (%) | 36 (22) |
| De novo DLBCL, n (%) | 85 (53) |
| Transformed DLBCL, n (%) | 28 (18) |
| **Prior CAR-T, n (%)** | 112 (60) |
| CAR-T as 2L, n (%) | 11 (10) |
| Median time from CAR-T, months | 7.7 |
| **CD19 status post–CAR-T, n** | 90 |
| Positive, n (%) | 70 (78) |
| Negative, n (%) | 20 (22) |




[a]Number of patients with prior tafa-len and no prior tafa-len not available.

### Median PFS With Lonca by Prior Therapy[2]

| | mPFS, mo |
|---|---|
| Overall | 2.1 |
| Prior CAR-T | 2.0 |
| No prior CAR-T | 2.1 |
| Prior tafa-len | 2.2 |
| No prior tafa-len | 2.1 |

### Study Conclusions[2]

- Prior CAR-T exposure, CD19 status, and line of therapy did not impact outcomes in patients treated with Lonca
- This study is limited by retrospective design and incomplete clinicopathologic data (eg, CD19 staining)

2L, second line; CAR-T, chimeric antigen receptor T-cell; CR, complete response; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; Lonca, loncastuximab tesirine-lpyl; mPFS, median progression-free survival; ORR, overall response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; tafa-len, tafasitamab-lenalidomide.

1. Zelikson V, et al. *Haematologica*. 2024; doi.org/10.3324/haematol.2024.285977.
2. Ayers E, et al. Oral presented at: American Society of Hematology Annual Meeting (ASH 2023). December 9-12, 2023; San Diego, CA. Oral 312.

## RWE STUDY: LONCA WITH *PRIOR* CAR-T

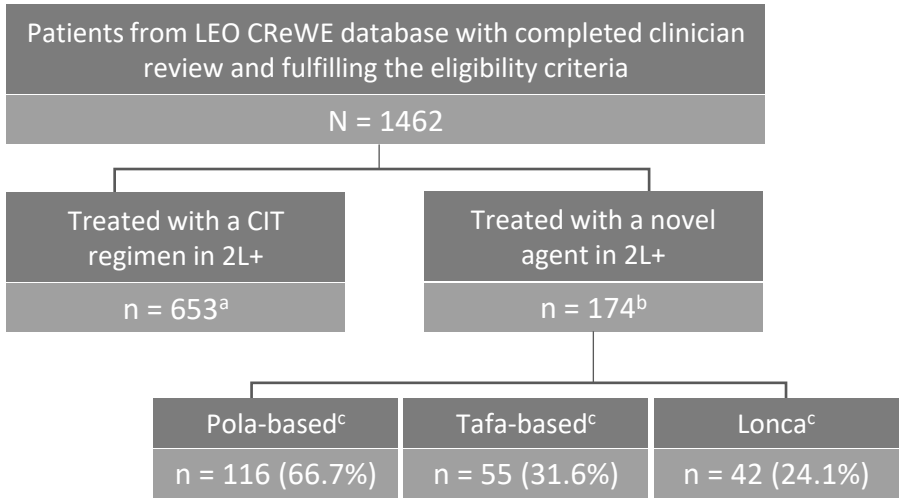
# Effectiveness of CIT and Novel Therapies in 2L+ for Patients With R/R Aggressive LBCL Who Received Prior CAR-T (Nastoupil, et al. ASH 2023; 1 of 2)

**Objective:** Evaluate the effectiveness of CIT and novel therapies, including CD19-directed therapies, in patients with R/R LBCL after ≥1 previous systemic therapy

**Methods:** This multisite, retrospective, observational study analyzed patients treated for R/R LBCL after ≥1 LOT from 01/01/2015 to 02/15/2023 who were treated with CIT or a novel therapy; CIT included salvage/palliative chemotherapy, lenalidomide, rituximab, or obinutuzumab, used alone or in combination, and novel therapy included Pola- or Tafa-based regimens or Lonca

| Characteristic | | | CIT (N = 653) | Pola (N = 116) | Tafa (N = 55) | Lonca (N = 42) |
|---|---|---|---|---|---|---|
| Age at index date, years, median (range) | | | 63 (20-92) | 66 (29-91) | 74 (44-88) | 68 (21-87) |
| Male, n (%) | | | 415 (63.6) | 78 (67.2) | 33 (60.0) | 29 (69.0) |
| White, n (%) | | | 549 (84.1) | 90 (77.6) | 48 (87.3) | 39 (92.9) |
| Clinical Characteristics, n (%) | ECOG performance status ≤1 | | 449 (68.8) | 77 (66.4) | 25 (45.5) | 28 (66.6) |
| | DLBCL (de novo/transformed) | | 522 (79.9) | 95 (81.9) | 47 (85.5) | 35 (83.3) |
| | DH/TH HGBCL | | 84 (12.9) | 17 (14.7) | 6 (14.3) | 8 (14.3) |
| | IPI risk classification ≥3 | | 220 (33.7) | 48 (41.4) | 30 (54.5) | 26 (61.9) |
| Treatment history, n (%) | No. of prior LOTs | 1 | 428 (65.5) | 20 (17.2) | 24 (43.6) | 3 (7.1) |
| | | 2 | 134 (20.5) | 35 (30.2) | 12 (21.8) | 12 (28.6) |
| | Primary refractory status | | 454 (69.5) | 85 (73.3) | 32 (58.2) | 30 (71.4) |
| | Prior ASCT | | 59 (9.0) | 13 (11.2) | 4 (7.3) | 7 (16.7) |
| | **Prior CAR-T** | | **43 (5.1)** | **50 (43.1)** | **18 (32.7)** | **20 (47.6)** |

### Patient Disposition




[a]159 patients were excluded from the CIT cohort. [b]39 patients were excluded from the novel therapy cohort. [c]Not mutually exclusive.

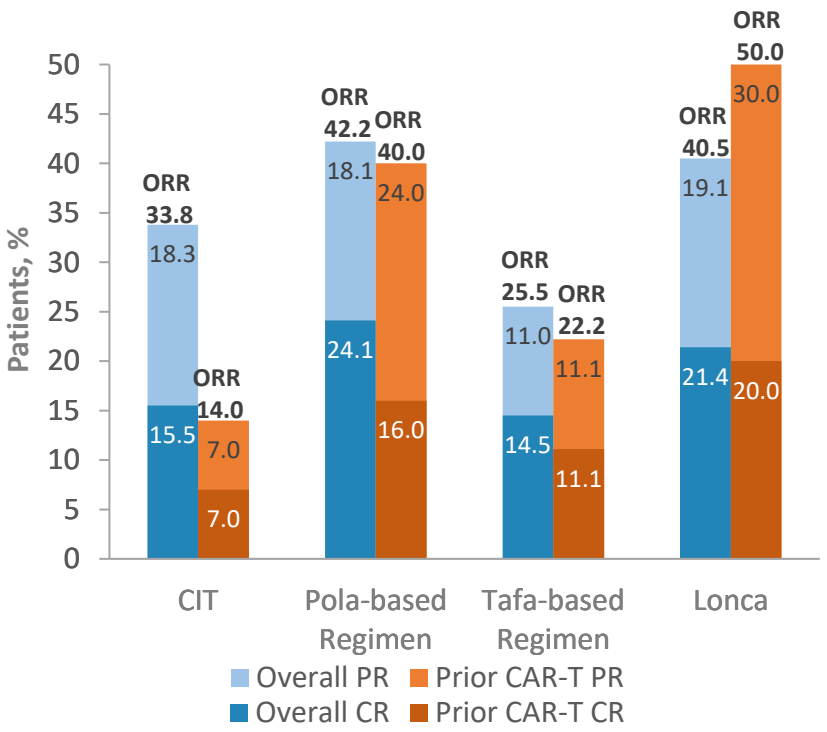
2L, second line; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T cell; CIT, chemo-immunotherapy; CR, complete response; DH/TH, double-hit/triple-hit; DLBCL, diffuse LBCL; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; HGBCL, high-grade B cell lymphoma; IPI, International Prognostics Index; LBCL, large B-cell lymphoma; LEO CReWE, Lymphoma Epidemiology of Outcomes Consortium of Real-World Evidence; Lonca, loncastuximab tesirine-lpyl; LOT, lines of therapy; PMBCL, primary mediastinal LBCL; Pola, polatuzumab; R/R, relapsed or refractory; Tafa, tafasitamab.

Nastoupil L J, et al. Oral presented at: American Society of Hematology Annual Meeting (ASH 2023). December 9-12, 2023; San Diego, CA. Oral 309.

## RWE STUDY: LONCA WITH *PRIOR* CAR-T

# Effectiveness of CIT and Novel Therapies in 2L+ for Patients With R/R Aggressive LBCL Who Received Prior CAR-T (Nastoupil, et al. ASH 2023; 2 of 2)

### CR/ORR in Overall and Prior CAR-T Populations




### Median Time from Treatment to Progression/Death (Months)

| Regimen, median (95% CI) | PFS | | OS | | DOR | |
|---|---|---|---|---|---|---|
| | Overall | Prior CAR-T | Overall | Prior CAR-T | Overall | Prior CAR-T |
| CIT | 1.9 (1.7, 2.1) | 1.6 (1.1, 2.0) | 9.1 (8.1, 10.5) | 3.4 (2.8, 5.8) | 2.6 (2.1, 3.4) | 2.5 (1.4, NR) |
| Pola | 2.5 (2.0, 3.2) | 2.7 (2.1, 4.5) | 7.8 (6.4, 11.8) | 6.1 (4.4, 11.5) | 4.0 (2.8, 11.5) | 3.5 (1.9, NR) |
| Tafa | 2.7 (2.1, 4.2) | 2.0 (1.2, 4.3) | 8.0 (5.3, 12.7) | 4.9 (1.6, NR) | 5.7 (3.1, NR) | 4.4 (0.2, NR) |
| Lonca | 3.0 (2.1, 5.1) | 3.0 (2.0, 9.3) | 4.7 (3.7, 10.8) | 4.7 (3.7, NR) | 3.8 (2.2, 14.7) | 4.0 (1.7, NR) |

**Study Conclusions**

- In this cohort of patients with R/R LBCL, with the majority having primary refractory disease, all treatments analyzed in this study were associated with modest ORR/CR and poor OS
- Outcomes were generally worse in the subgroup of patients who previously received CAR-T therapy except for the Lonca cohort, which demonstrated a slightly higher ORR among patients who received prior CAR-T

2L, second line; CAR-T, chimeric antigen receptor T cell; CIT, chemoimmunotherapy; CR, complete response; DOR, duration of response; HR, hazard ratio; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; Lonca, loncastuximab tesirine-lpyl; LOT, lines of therapy; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Pola, polatuzumab; PR, partial response; R/R, relapsed or refractory; Tafa, tafasitamab.

Nastoupil L J, et al. Oral presented at: American Society of Hematology Annual Meeting (ASH 2023); December 9-12, 2023; San Diego, CA. Oral 309.

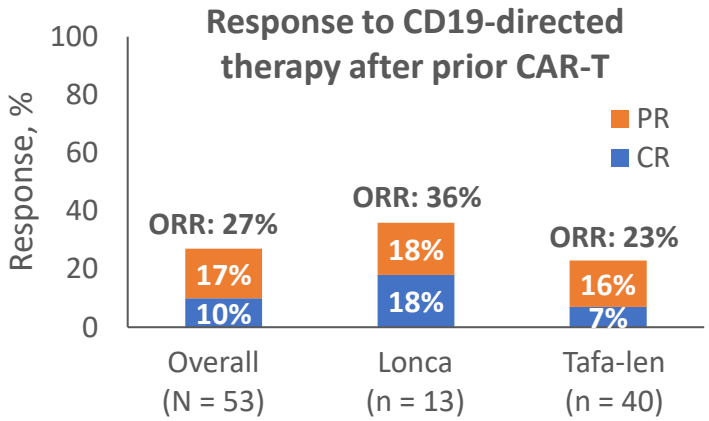
# RWE STUDY: LONCA OR TAFA-LEN WITH *PRIOR* CAR-T

## Efficacy of CD19-Directed Therapy in R/R LBLC Relapsing After Prior CD19-Directed CAR-T (Iqbal, et al. 2024)

**Objective:** Evaluate the efficacy of CD19-directed therapies in patients with R/R LBCL who relapse after CD19-directed CAR-T therapy

**Methods:** This multicenter retrospective study assessed outcomes of patients with R/R LBCL who received either Lonca or tafa-len at any timepoint for R/R disease after prior CD19-directed CAR-T therapy

| Characteristics | N = 53 |
|---|---|
| **Median (range) age at CAR-T infusion, years** | 64 (37-79) |
| **Male, n (%)** | 31 (58) |
| **IPI score 3-5[a], n (%)** | 31 (72) |
| **Median (range) number of systemic therapies pre–CAR-T** | 3 (1-6) |
| **Prior CAR-T therapy, n (%)** | |
| Axi-cel | 32 (60) |
| Tisa-cel | 17 (32) |
| Liso-cel | 1 (2) |
| Other[b] | 3 (6) |
| **Refractory to CAR-T, n (%)** | 19 (36) |
| **Best response to CAR-T, n (%)** | |
| CR/PR | 33 (62) |
| SD/PD | 20 (38) |
| **Median (range) time from CAR-T to tafa-len or Lonca, months** | 7.3 (1.2-38.2) |
| **Median (range) number of LOT between CAR-T and tafa-len/Lonca** | 1 (0-5) |
| **CD19 positivity by IHC[c]** | 22 (61) |




| | mPFS, weeks (95% CI) |
|---|---|
| Overall | 8 (5.1-12.6) |
| Lonca | 6.0 (3.7-NA) |
| Tafa-len | 8.6 (5.1-14.1) |

**Study Conclusions**

- In this real-world study, the use of currently approved CD19-directed therapies Lonca or tafa-len to treat R/R LBCL after prior CD19-directed CAR-T therapy showed limited clinical activity and duration of responses
- Limitations include the retrospective design, relatively small sample size, lack of consistent tissue biopsy specimens, and the assessment of CD19 status prior to treatment with Lonca or tafa-len

[a]The number of evaluable patients was 43. [b]Other therapies were axi-cel + atezolizumab and allo CD19 CAR-T therapies CTX-110 and PBCAR0191.
[c]The number of evaluable patients was 36. Allo, allogeneic; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T cell; CR, complete response; DOR, duration of response; IHC, immunohistochemistry; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; Lonca, loncastuximab tesirine-lpyl; LOT, lines of therapy; mPFS, median progression-free survival; NA, not available; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed or refractory; SD, stable disease; tafa-len, tafasitamab-lenalidomide; tisa-cel, tisagenlecleucel.
Iqbal M, et al. *Bone Marrow Transplant*. 2024;59(2):211-216.

## RWE STUDY: TAFA-LEN WITH *PRIOR* CAR-T

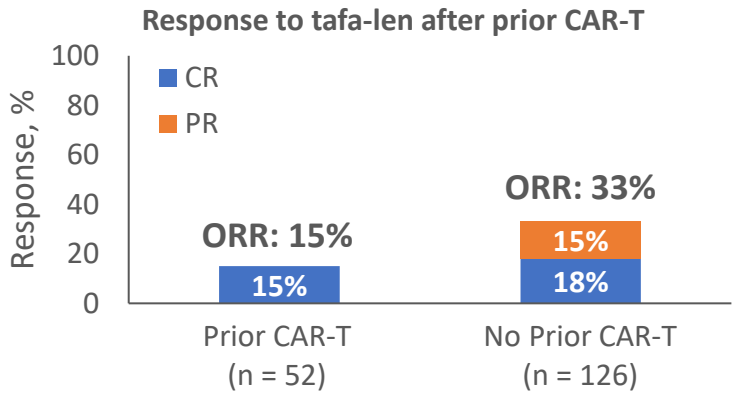
# Outcomes of Sequential CD19-Directed Therapy in R/R LBLC (Qualls, et al. ASH 2023)

**Objective:** Evaluate outcomes with tafa-len after failure of a prior CD19-directed CAR-T therapy in R/R LBCL

**Methods:** This multicenter retrospective study assessed outcomes with tafa-len in patients with R/R LBCL who were treated with prior CAR-T therapy from 8/2020 to 8/2022

| Characteristics | Prior CAR-T (n = 52) | No Prior CAR-T (n = 126) |
|---|---|---|
| **Median age (range), years** | 66 (38-79) | 78 (26-94) |
| **Female, n (%)** | 27 (52) | 60 (48) |
| **DLBCL subtype** | | |
| DLBCL NOS | 28 (54) | 71 (56) |
| Transformed indolent lymphoma | 15 (29) | 44 (35) |
| HGBCL (nontransformed) | 7 (13) | 8 (6) |
| Other[a] | 2 (4) | 3 (2) |
| ***MYC* + *BCL2* rearrangement, n (%)** | 10 (21) | 12 (12) |
| **Stage III-IV at index** | 47 (94) | 102 (86) |
| **Risk (IPI)** | | |
| 0-2 | 9 (20) | 34 (30) |
| 3-5 | 36 (80) | 78 (70) |
| **Median (range) prior LOT for DLBLC[b]** | 4 (0-11) | 2 (0-7) |
| **Primary refractory** | 27 (52) | 60 (48) |
| **Refractory to last therapy** | 37 (71) | 81 (64) |
| **Prior SCT** | 14 (27) | 8 (6) |

[a]Other diagnoses: TCHRBCL (2), PMBCL (2), and PTLD with DLBCL morphology (1). [b]Eleven patients with transformed indolent lymphoma had received prior therapy for indolent disease but not for aggressive LBCL.




| | mPFS, mo (95% CI) | |
|---|---|---|
| Prior CAR-T | 1.6 (1.1-2.5) | HR: 1.46 (1.0-2.5)[c] |
| No Prior CAR-T | 2.1 (1.8-3.2) | |

[c]In a multivariate analysis accounting for other high-risk features, the HR was 1.04 (p = 0.89).

ORR with tafa-len in patients with PD >6 months after CAR-T (n = 19): **31.6%** (all responses were CR)
ORR with tafa-len in patients with refractory disease to CAR-T (n = 33): **6.1%**

**Study Conclusions**

- Responses and PFS were lower in patients receiving tafa-len after prior CAR-T than without prior CAR-T; however, this may be related to other risk factors and not related to CAR-T therapy itself
- Durability of response to prior CAR-T was associated with response to tafa-len

CAR-T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; HR, hazard ratio; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; LOT, lines of therapy; mPFS, median progression-free survival; NOS, not otherwise specified; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PMBCL, primary mediastinal large B cell lymphoma; PR, partial response; PTLD, post-transplant lymphoproliferative disease; R/R, relapsed or refractory; SCT, stem cell transplant; tafa-len, tafasitamab-lenalidomide; TCHRBCL, T-cell/histocyte-rich-B-cell lymphoma.

Qualls DA, et al. Poster presented at: American Society of Hematology Annual Meeting (ASH 2023). December 9-12, 2023; San Diego, CA. Poster 3136.

# IIT: Consolidation with Lonca- Interim Futility Analysis

## Consolidation with loncastuximab tesirine for Large B-cell Lymphoma Patients in Partial Response after CAR-T (Stati et al ASH 2025)

**Objective:** The objective was to assess outcomes of loncastuximab in large B-cell lymphoma patients who achieved a PR to CAR-T, with a planned first interim futility analysis after 10 patients completed treatment to determine whether at least 4 converted to CR and no more than 3 experienced unacceptable toxicity.

**Methods:** This single arm phase 2 study (NCT05464719) was conducted in adult patients with r/r LBCL achieving PR after CAR-T between October 2022 and January 2025 (data cut off 06/2025)

**Primary Objective**: Conversion to CR

**Secondary objectives**: safety and tolerability, DOR, PFS, OS

**Exploratory objectives**: PD, and biomarkers of response

### Select Inclusion Criteria

- DLBCL, HGBCL, PMBCL, tFL
- Treated with SOC CAR-T cell therapy (including upcoming 2nd line)
- D30 PET-CT evidence of PMR CD19 expression (IHC and/or flow cytometry) not required

### Select Exclusion Criteria

- Treatment with experimental CAR-T
- Previous CNS involvement
- ANC < 1000/uL, PLT< 50,000/uL

| Characteristics (N=10) | Number (%), Median (range) |
|---|---|
| Median age (range), years | 74 (45-84) |
| Male, n (%) | 8 (80) |
| Caucasians | 9 (90) |
| ECOG PS > 0 | 8 (80) |
| DLBCL/HGBCL | 10 (100) |
| Prior lines of systemic therapy | 1 (1-3) |
| Axi-cel | 6 (60) |
| Maximum standardized uptake volume >10 | 4 (40) |
| Deauville Score 5 | 3 (30) |
| Lesion diameter (cm) | 3.2 (1.1-7.6) |
| Absolute neutrophil count (K/uL) | 1.9 (1-3.8) |
| Absolute lymphocyte count (K/uL) | 0.8 (0.2-2.8) |

| Characteristics (N=10) | Number (%), Median (range) |
|---|---|
| Hemoglobin (g/dL) | 11.4 (9.5-13.6) |
| Platelet Count (K/uL) | 118 (51-240) |
| Lactate dehydrogenase (U/L) | 224 (170-342) |
| Ferritin (ng/mL) | 647 (108-1591) |
| C-reactive protein (mg/L) | 1 (0.2-55) |
| Biopsy performed | 7 (70) |
| Viable Lymphoma in Biopsy | 3/7 (43) |
| CD19+ viable Lymphoma | 0/3 (0) |

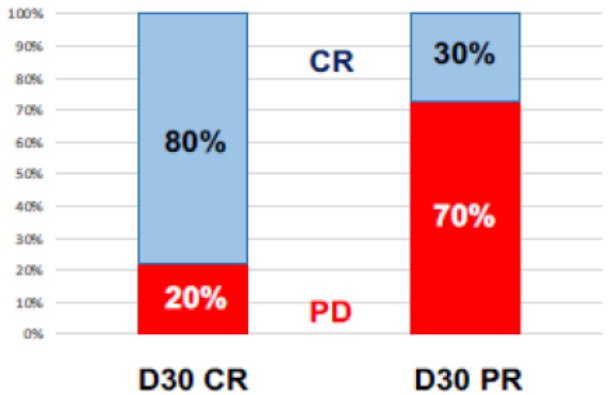



**Figure 1**: High rates of PD after PR at day 30 post CAR19 infusion.

Lonca was given IV, on day 1 of a 21- day cycle, at a dose of 150µg/kg for cycles 1-2, and 75µg/kg subsequently for a total of 6 cycles, median number of lonca cycles was 6 (range, 3-6)



Strati, et al. Poster presented at: American Society of Hematology Annual Meeting (ASH 2025). December 6-9, 2025; Orlando, FL. Poster 5485.

# IIT: Consolidation with Lonca- Interim Futility Analysis

## Consolidation with loncastuximab tesirine for Large B-cell Lymphoma Patients in Partial Response after CAR-T (Stati et al ASH 2025)

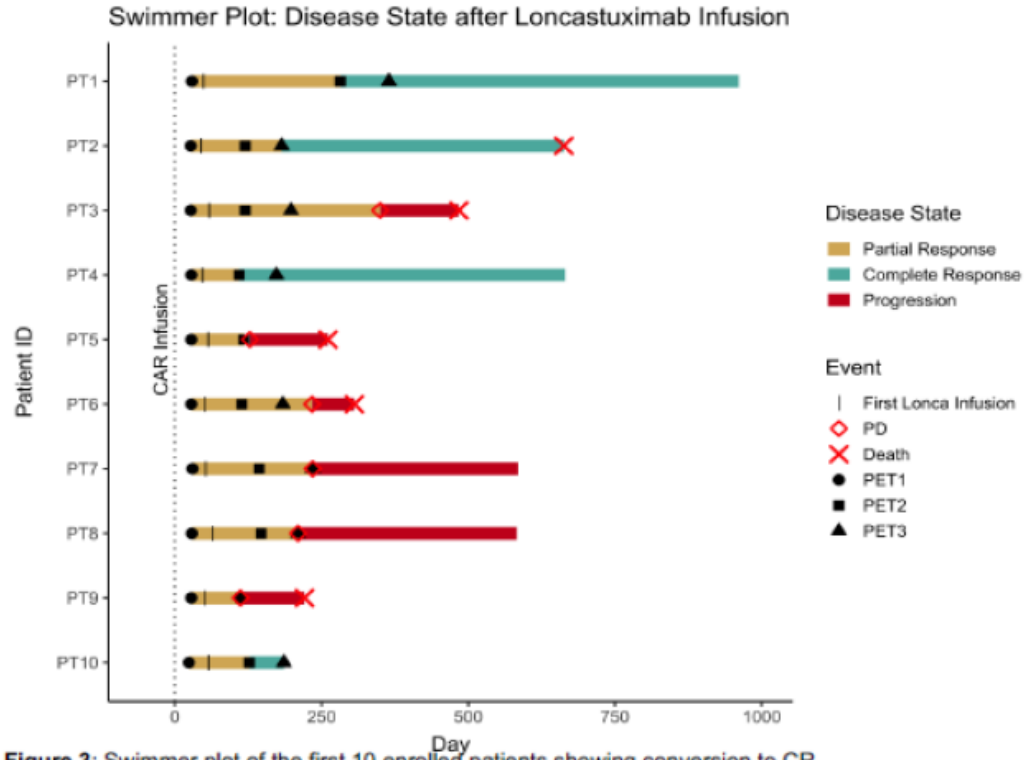



**Figure 3**: Swimmer plot of the first 10 enrolled patients showing conversion to CR

| CMR conversion to CR at 3 and 6 months Patients (N=10) | Number (%), Median (range) |
|---|---|
| PET-3 conversion rate to CMR | 3 (30) |
| PET-6 conversion rate to CMR | 4 (40) |

### Adverse events associated with Lonca consolidation

| Patients (N=10) | Grade 1-2 | Grade 3-4 |
|---|---|---|
| Thrombocytopenia | 3 (30) | 6 (60) |
| Neutropenia | 2 (20) | 6 (60) |
| Anemia | 0 (0) | 2 (20) |
| Infection | 7 (70) | 1 (10) |
| AST elevation | 5 (50) | 1 (10) |
| ALT elevation | 4 (40) | 1 (10) |
| GGT elevation | 2 (20) | 1 (10) |
| Pericardial effusion | 0 (0) | 1 (10) |
| Fatigue | 5 (50) | 0 (0) |
| Skin rash | 4 (40) | 0 (0) |
| Ascites | 3 (30) | 0 (0) |
| Peripheral edema | 3 (30) | 0 (0) |
| Anorexia | 2 (20) | 0 (0) |
| Myalgia | 2 (20) | 0 (0) |
| Pleural effusion | 2 (20) | 0 (0) |
| Photosensitivity | 2 (20) | 0 (0) |

- After a median follow-up of 19 months, 4 patients that converted, remained in CR, 5 patients died (4 due to progressive disease, and 1 due to infection while in CR after 16 months.

**Study Conclusions**

- Results indicate that lonca is a feasible consolidation strategy for LBCL patients who achieve PR after CAR-T
- The study will continue to enroll another 10 patients to achieve the second interim futility analysis.

Strati, et al. Poster presented at: American Society of Hematology Annual Meeting (ASH 2025). December 6-9 2025; Orlando, FL. Poster 5485.

# Summary

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# Summary

- CD19 is a therapeutic target for the treatment of B-cell malignancies, including DLBCL
  - Lonca is an antibody–drug conjugate comprising a CD19-directed monoclonal antibody conjugated to a potent pyrrolobenzodiazepine dimer cytotoxin indicated for the treatment of R/R DLBCL after ≥2 prior therapies
- CD19-negativity may be a pathway of resistance following treatment with CD19-directed therapies, including CAR-T therapy; however, the data on the frequency of CD19 loss is limited
- Response to Lonca was observed across all ranges of CD19 expression in DLBCL, even with very low or undetectable CD19 tumor expression as measured by IHC
- A limited but growing amount of clinical and real-world data exist, demonstrating that the sequencing of CD19 directed therapies in R/R DLBCL is possible
  - Treatment with CD19-directed therapies, including Lonca, may not preclude response to subsequent CD19-directed CAR-T therapy
  - Likewise, prior CD19-directed CAR-T therapy does not appear to prohibit response to subsequent CD19-directed therapies, including Lonca
  - Caution in the interpretation of results of small patient subsets is warranted



CAR-T, chimeric antigen receptor T cell; DLBCL, diffuse large B-cell lymphoma; IHC, immunohistochemistry; Lonca, loncastuximab tesirine; R/R, relapsed/refractory.