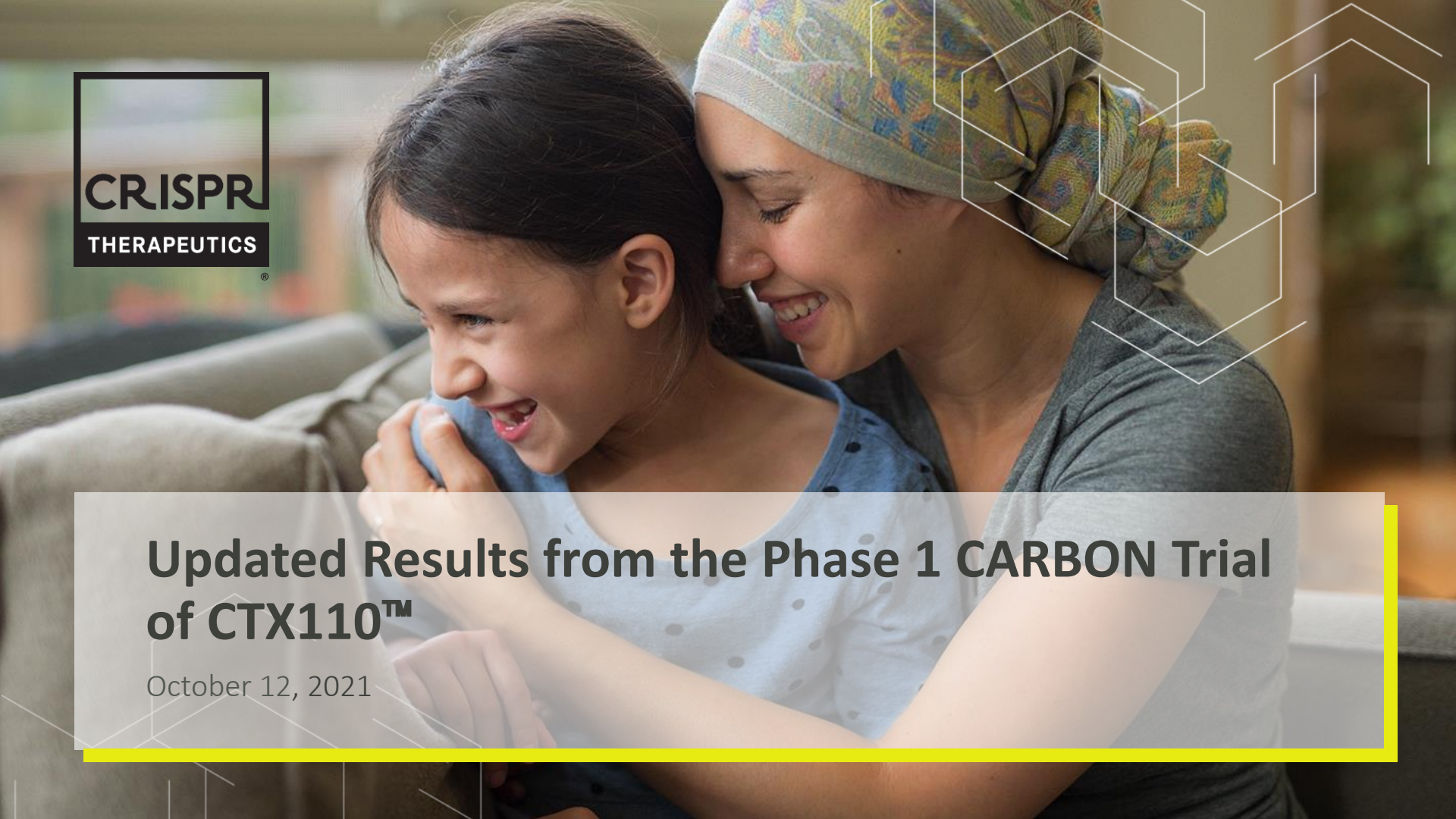


# Updated Results from the Phase 1 CARBON Trial of CTX110™

October 12, 2021

# Forward-looking Statements

*The presentation and other related materials may contain a number of "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including statements regarding CRISPR Therapeutics' expectations about any or all of the following: (i) the safety, efficacy and clinical progress of our various clinical programs, including our CTX110 program; (ii) the status of clinical trials (including, without limitation, the expected timing of data releases, announcement of additional programs and activities at clinical trial sites) and expectations regarding the data that is being presented from our CARBON clinical trial; (iii) the data that will be generated by ongoing and planned clinical trials, and the ability to use that data for the design and initiation of further clinical trials; and (iv) the therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies, including as compared to other therapies. Without limiting the foregoing, the words "believes," "anticipates," "plans," "expects" and similar expressions are intended to identify forward-looking statements. You are cautioned that forward-looking statements are inherently uncertain. Although CRISPR Therapeutics believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those projected or suggested in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: the potential for initial and preliminary data from any clinical trial and initial data from a limited number of patients not to be indicative of final trial results; the potential that clinical trial results may not be favorable; potential impacts due to the coronavirus pandemic, such as the timing and progress of clinical trials; that future competitive or other market factors may adversely affect the commercial potential for CRISPR Therapeutics' product candidates; uncertainties regarding the intellectual property protection for CRISPR Therapeutics' technology and intellectual property belonging to third parties, and the outcome of proceedings (such as an interference, an opposition or a similar proceeding) involving all or any portion of such intellectual property; and those risks and uncertainties described under the heading "Risk Factors" in CRISPR Therapeutics' most recent annual report on Form 10-K, quarterly report on Form 10-Q and in any other subsequent filings made by CRISPR Therapeutics with the U.S. Securities and Exchange Commission, which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date they are made. CRISPR Therapeutics disclaims any obligation or undertaking to update or revise any forward-looking statements contained in this presentation, other than to the extent required by law.*

*Caution should be exercised when interpreting results from separate trials involving separate product candidates. There are differences in the clinical trial design, patient populations, and the product candidates themselves, and the results from the clinical trials of autologous products may have no interpretative value on our existing or future results.*

# Presenters on Today's Call

**Samarth Kulkarni, PhD**
Chief Executive Officer

**Ewelina Morawa, MD**
Vice President, Clinical Development

**Tony Ho, MD**
Executive Vice President, Head of Research & Development

# Building the Leading CRISPR Company

- **By the numbers –** 4 clinical programs; >450 employees; ~$2.5B cash balance

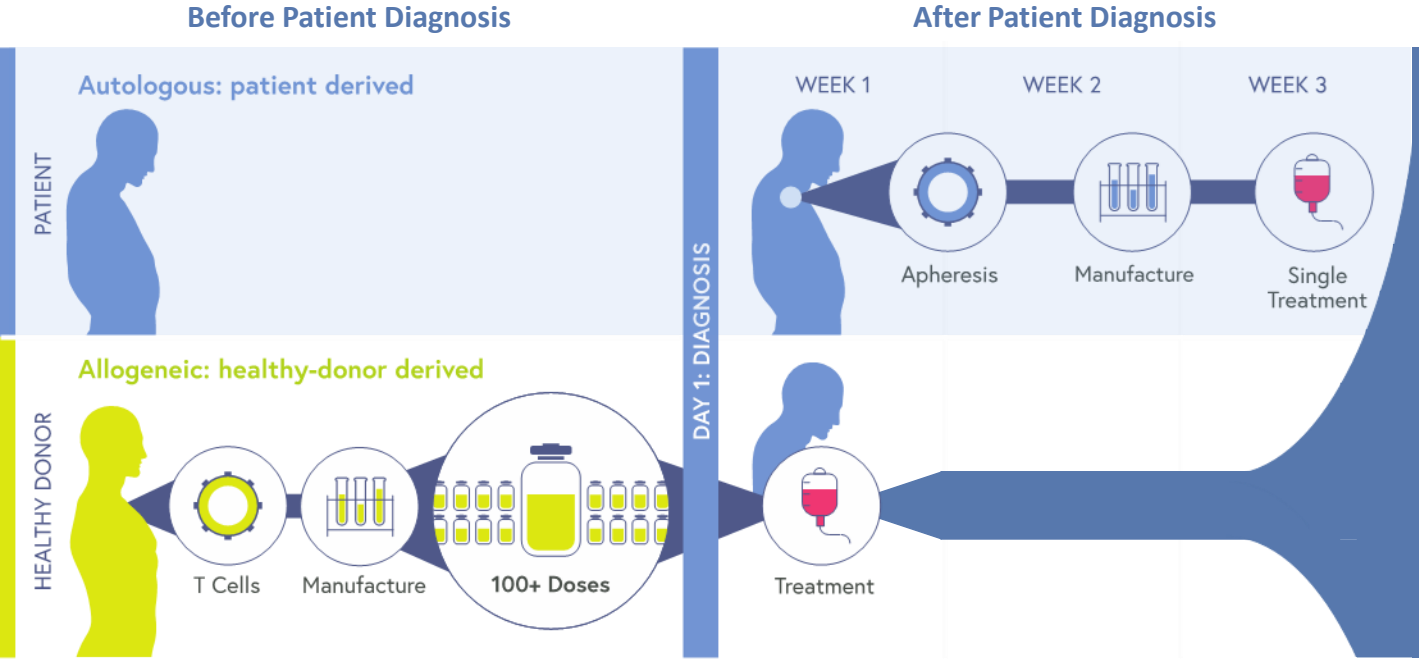
- **Established the first clinical program using CRISPR – now likely to be the first CRISPR product approved**
  - Over 50 sickle cell and beta-thalassemia patients treated with CTX001™ showing a consistent, functionally curative profile
  - Regulatory filings possible in the next 18-24 months with 30,000+ patients suitable for treatment in the U.S. and Europe if approved

- **Advanced three gene-edited allogeneic CAR-T programs into the clinic**
  - Proof of concept achieved with CTX110, paving the way for our CAR-T pipeline
  - Expect to complete construction of state-of-the-art internal manufacturing facility in 2021 and bring facility on-line in 2022

- **Expanded into regenerative medicine and progressed our *in vivo* efforts**
  - On track to initiate clinical trial of our allogeneic stem cell-derived therapy for T1D in 2021 with our partner ViaCyte
  - Expect to move multiple programs utilizing *in vivo* approaches into the clinic in the next 18-24 months

- **Created a sustainable innovation engine with pre-eminent capabilities**

# Allogeneic CAR-T Therapy Has Transformative Potential



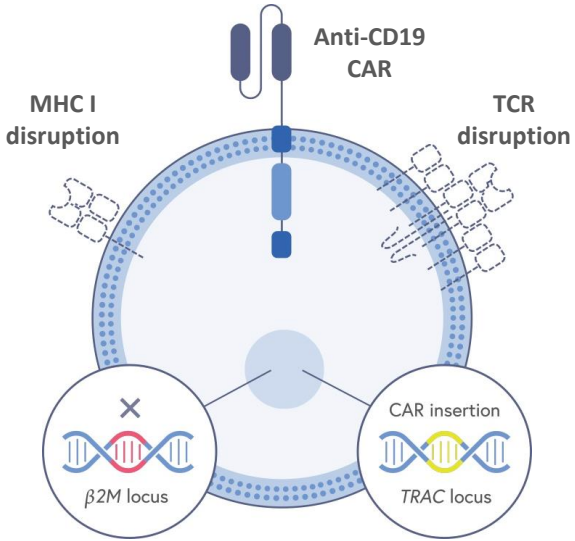

- **Off-the-shelf:** Immediate treatment without risk of manufacturing failure, saving patients valuable time in which their disease could progress
- **Flexible dosing** (e.g., re-infusion)
- **A more consistent product**
- **Scalable manufacturing and simpler logistics**
- **Broader accessibility**

*Specificity, efficiency, and versatility of **CRISPR gene editing** facilitates consistent, multiplex editing to produce allogeneic cell therapies and enhance immune cell performance*

# CTX110: Differentiated CRISPR-edited Allogeneic CAR-T Design

**Multiplex CRISPR gene editing in one step designed to:**

- **Improve persistence in the allo setting** via β2M knock-out to eliminate MHC I expression
- **Avoid need** for more toxic lymphodepletion regimens




- **Prevent GvHD** via TCR disruption
- **Improve consistency and safety by precise insertion** of CAR construct into *TRAC* locus without using lentivirus or retrovirus

*CTX120™ and CTX130™ utilize the **same CRISPR-edited allogeneic T cell design**, but with different CAR targets, as well as additional editing in the case of CTX130*

# CTX110 Has a Profile that Can Compete with Auto CAR-T

- Data from a **24 patient LBCL cohort** shows **intent-to-treat (ITT) efficacy on par with autologous CAR-T:**
  - 58% ORR vs. 34-66% for approved auto CAR-T
  - 38% CR rate vs. 24-47% for approved auto CAR-T
  - 21% 6-month CR rate vs. ~18-36% for approved auto CAR-T

- **Differentiated safety profile** with no Grade 3+ CRS and much lower rates of Grade 3+ ICANS and infection than autologous CAR-T

- **Consolidation dosing has potential to increase response rate and durability** based on established re-dose efficacy and clear dose response relative to tumor burden

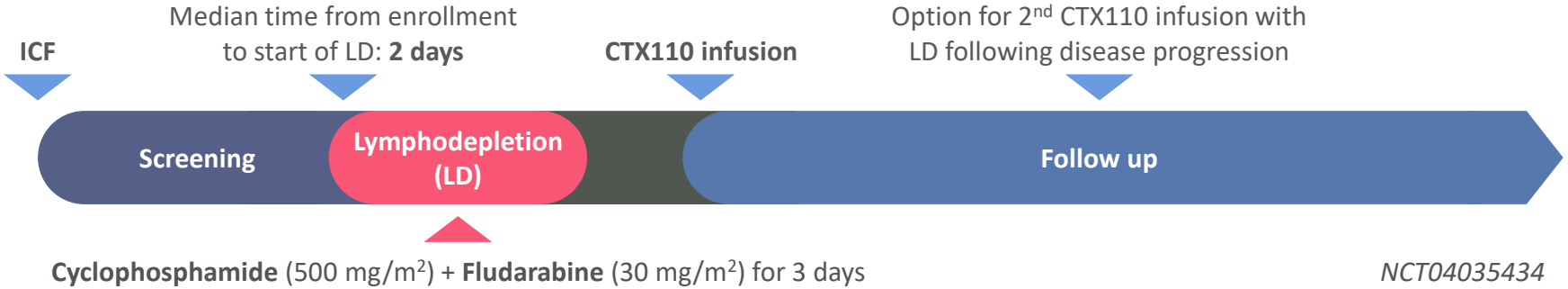
- On track to expand into a **potentially registrational trial in Q1 2022** incorporating consolidation dosing

# CARBON: Trial Design

## CARBON: Single-arm study evaluating the safety and efficacy of CTX110

**Allogeneic CAR-T enables simplified trial design:**

- Short screening timeframe
- No apheresis
- No bridging chemotherapy
- On-site availability of CAR-T cell product




### Key eligibility criteria

- Age ≥18 years
- Relapsed/refractory non-Hodgkin lymphoma, as evidenced by 2+ lines of prior therapy
- ECOG performance status 0 or 1
- Adequate renal, liver, cardiac, and pulmonary organ function
- No prior allogeneic SCT or treatment with CAR-T therapy

### Primary endpoints

- Incidence of adverse events, defined as DLTs
- ORR

### Key secondary endpoints

- CR rate, DoR, and OS

# CARBON: Patient Flow

***As of the data cutoff date:***

**Enrolled: 30** patients

**Treated[1]: 29** patients

**≥28 days of follow-up** (included in data cut): **26** patients

| Dose Level | CAR+ T cells | DL2 and above: 23 patients |
|---|---|---|
| DL4 | 600x10^6 | 8 |
| DL3.5 | 450x10^6 | 6 |
| DL3 | 300x10^6 | 6 |
| DL2 | 100x10^6 | 3 |
| DL1 | 30x10^6 | 3 |

**Modified ITT (mITT) nearly identical to ITT:** just one patient enrolled but not treated

**At DL2 and above:**

- **mITT:** 23 patients infused
- **ITT:** 24 patients enrolled

(1) Includes patients in the process of being treated as of the cutoff date

*Data as of August 26, 2021*

# CARBON Only Enrolled Patients with Aggressive Disease

- **Only patients with LBCL enrolled,** including DLBCL NOS, high-grade lymphoma (e.g., triple hit), and transformed follicular lymphoma
- **High burden of disease** with significant baseline tumor volume
- Both relapsed and refractory patients, including **primary refractory patients that had no prior response to any anti-cancer therapy**
- **History of rapidly progressive disease** – 31% of patients had progressed through 2 or more lines of therapy and received CTX110 within 9 months of their first lymphoma treatment

# CARBON: Baseline Patient Characteristics

N (%) (unless otherwise noted)

| Cell dose (CAR+ T cells) | DL1 30x10^6 N=3 | DL2 100x10^6 N=3 | DL3 300x10^6 N=6 | DL3.5 450x10^6 N=6 | DL4 600x10^6 N=8 |
|---|---|---|---|---|---|
| Median age, years (range) | 52 (50-61) | 64 (58-74) | 69 (62-74) | 67.5 (25-74) | 65.5 (55-75) |
| Female | 1 (33) | 1 (33) | 4 (67) | 2 (33) | 2 (25) |
| **Lymphoma subtypes** | | | | | |
| Large B-cell lymphoma (LBCL)[1] | 3 (100) | 3 (100) | 6 (100) | 6 (100) | 8 (100) |
| **Current disease stage (per Lugano 2014)** | | | | | |
| Stage IV | 2 (67) | 2 (67) | 2 (33) | 5 (83) | 4 (50) |
| **Prior treatments** | | | | | |
| Median number (range) | 2 (2-8) | 3 (2-3) | 2 (2-4) | 2.5 (2-10) | 3 (2-10) |
| Hematopoietic stem cell transplant | 0 | 0 | 3 (50) | 4 (67) | 2 (25) |
| Refractory to last therapy | 3 (100) | 3 (100) | 2 (33) | 1 (17) | 5 (63) |

(1) Including DLBCL NOS, high grade lymphoma (e.g., triple hit), transformed follicular lymphoma (tFL)

*Data as of August 26, 2021*

# Dose-Dependent Responses with CTX110

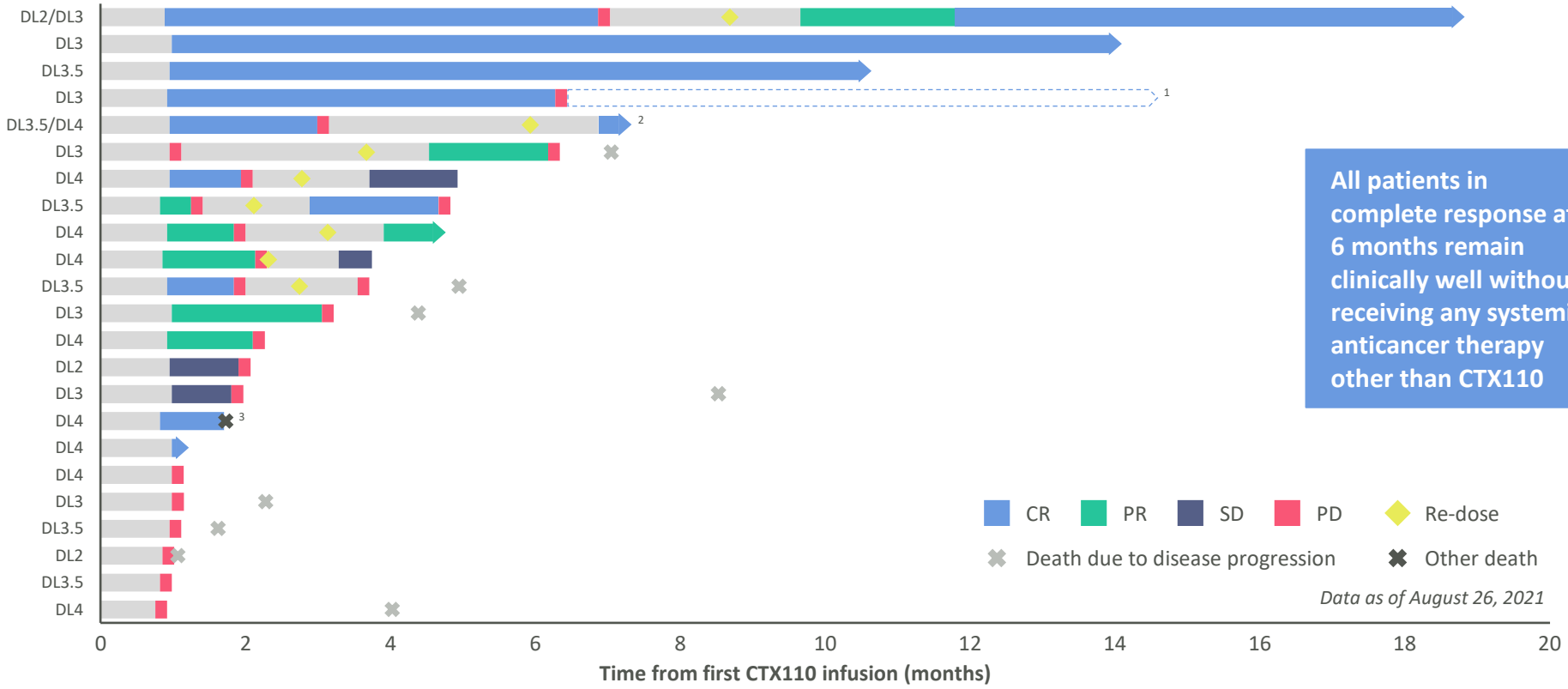
## D28 response following first CTX110 dose per 2014 Lugano criteria[1]

| Cell dose (CAR+ T cells) | DL1 $30x10^6$ *N=3* | DL2 $100x10^6$ *N=3* | DL3 $300x10^6$ *N=6* | DL3.5 $450x10^6$ *N=6* | DL4 $600x10^6$ *N=8* | DL2+ mITT *N=23* | DL2+ ITT *N=24* |
|---|---|---|---|---|---|---|---|
| Overall response rate (ORR), N (%) | 0 (0%) | 1 (33%) | 3 (50%) | 4 (67%) | 6 (75%) | 14 (61%) | 14 (58%) |
| Complete response (CR) rate, N (%) | 0 (0%) | 1 (33%) | 2 (33%) | 3 (50%) | 3 (38%) | 9 (39%) | 9 (38%) |

(1) Cheson, *et al*. *J Clin Oncol*. (2014)

*Data as of August 26, 2021*

# Durable Responses Observed with CTX110




**All patients in complete response at 6 months remain clinically well without receiving any systemic anticancer therapy other than CTX110**

Dose level of re-dose indicated if different from initial dose level; Imaging per protocol occurs at M1, M3, and M6; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease
(1) Patient had a localized tumor recurrence that was excised and is clinically well having received no additional anticancer therapy; (2) Unaudited data as of Oct. 7 after the data cut; (3) As disclosed in Oct. 2020

# CTX110 Was Well Tolerated Across All Dose Levels

**Adverse events of interest** N (%)

| | DL1 (N=3) | | DL2 (N=3) | | DL3 (N=6) | | DL3.5 (N=6) | | DL4 (N=8) | | DL2+ (N=23) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Gr 1-2 | Gr 3+ | Gr 1-2 | Gr 3+ | Gr 1-2 | Gr 3+ | Gr 1-2 | Gr 3+ | Gr 1-2 | Gr 3+ | Gr 1-2 | Gr 3+ |
| CRS[1] | 1 (33) | - | 2 (67) | - | 2 (33) | - | 3 (50) | - | 6 (75) | - | 13 (57) | - |
| ICANS[2] | - | - | 1 (33) | - | - | - | - | - | - | 1 (13) | 1 (4) | 1 (4) |
| GvHD | - | - | - | - | - | - | - | - | - | - | - | - |
| Infusion reactions | - | - | - | - | - | - | - | - | - | - | - | - |
| Infections[3] | - | 1 (33) | - | - | 1 (17) | 1 (17) | 1 (17) | - | 1 (13) | 1 (13) | 3 (13) | 2 (9) |

- **No CRS and only one case of ICANS above Grade 2[4]**
- **No GvHD or infusion reactions**
- **Low rate of infections, with only 2 Grade 3+ events:** HHV-6[4] and pseudomonal sepsis that resolved in 4 days
- **Includes events following re-dosing**

**One treatment-emergent death without disease progression:** ICANS/HHV-6 encephalitis[4]

CRS and ICANS graded per ASTCT criteria; other adverse events graded per CTCAE; (1) Cytokine Release Syndrome; (2) Immune Effector Cell-associated Neurotoxicity Syndrome; (3) All infections (bacterial, fungal, and viral) included; (4) As disclosed in October 2020

*Data as of August 26, 2021*

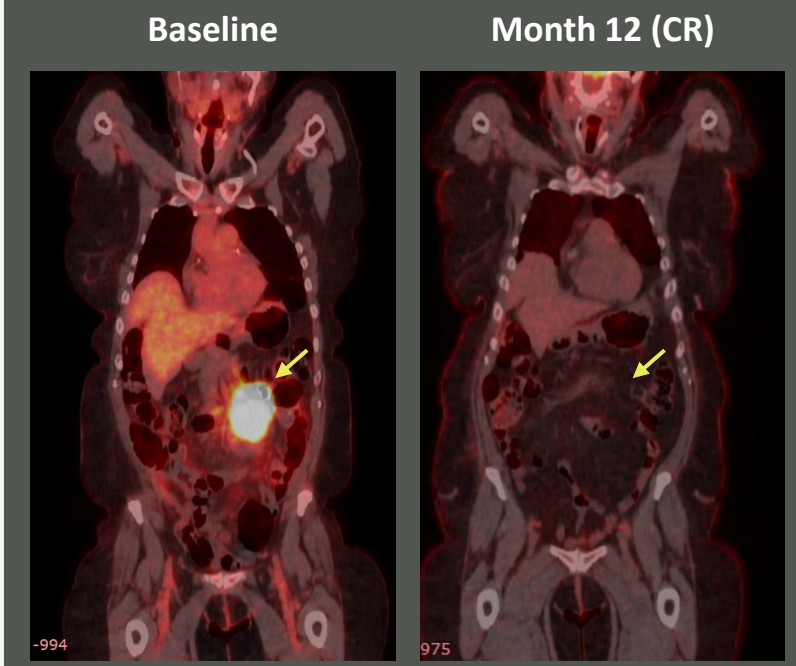
# CTX110 Case Study: On-going Complete Response 12 Months After Single Infusion

## *Patient characteristics*

- 62-year-old female diagnosed with DLBCL
- Relapsed following 2 prior lines of therapy, including autologous SCT
- Treated with CTX110 at DL3 ($300x10^6$ $CAR^+$ T cells)

## *Safety and efficacy data*

- CR at Day 28 after a single dose with no tumor visible
- No CRS, ICANS, or infections
- **CR on-going at 12+ months**



# CTX110 Case Study: 18+ Months of Clinical Benefit After 2 Infusions in a Primary Refractory Patient

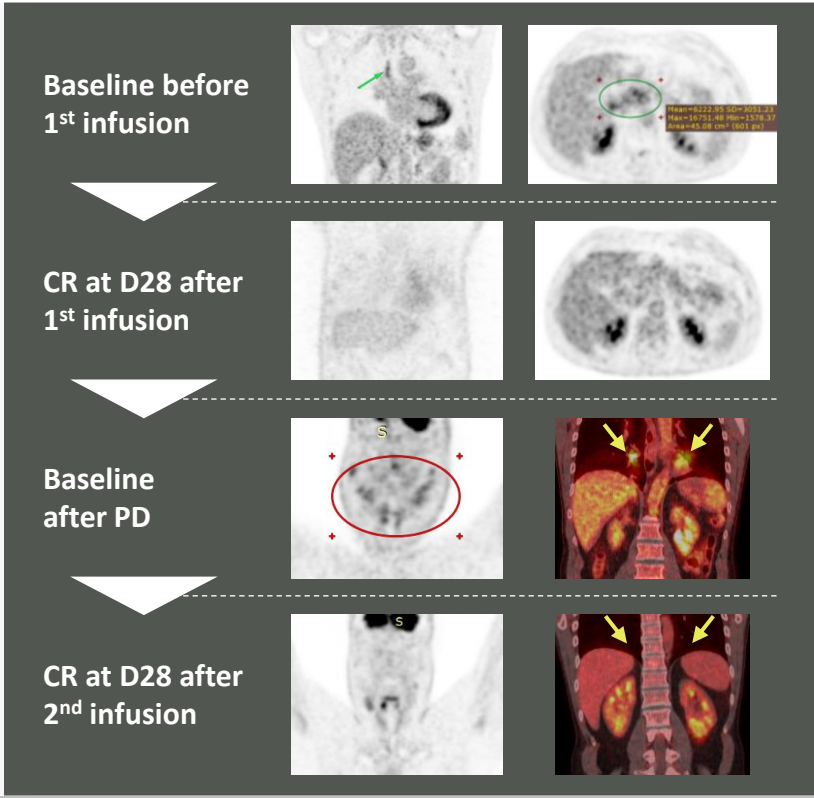
CRISPR THERAPEUTICS

## *Patient characteristics*

- 58-year-old male with Stage IV DLBCL (NOS)
- Refractory to both prior lines of therapy (R-CHOP, R-GDP)

## *Safety and efficacy data*

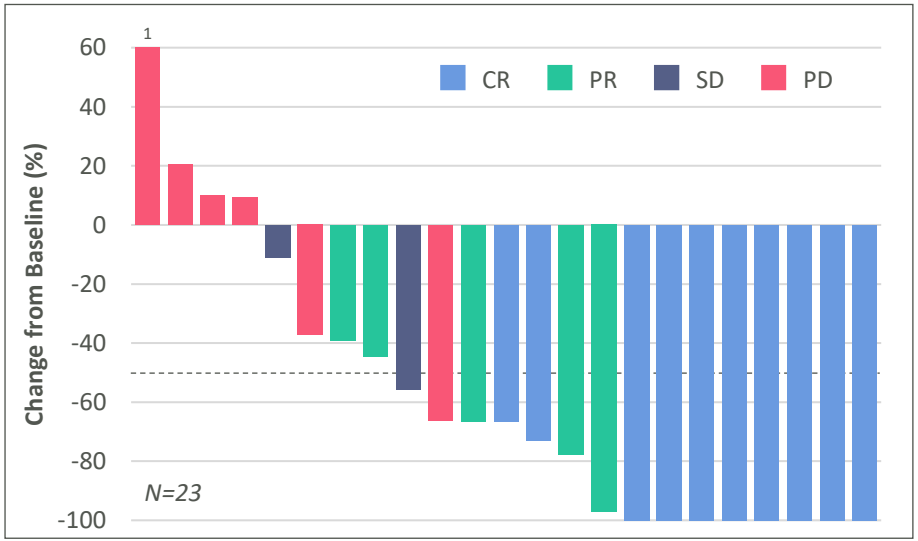
- **1st infusion of CTX110:** DL2 ($100x10^6$ $CAR^+$ T cells)
  - Achieved CR at Day 28, but progressed at ~7 months
- **2nd infusion of CTX110:** DL3 ($300x10^6$ $CAR^+$ T cells)
  - Achieved CR at Month 3 and remains in complete response
- **On-going clinical benefit for >18 months after initial infusion**
- No CRS, ICANS, or other adverse events of special interest to either infusion



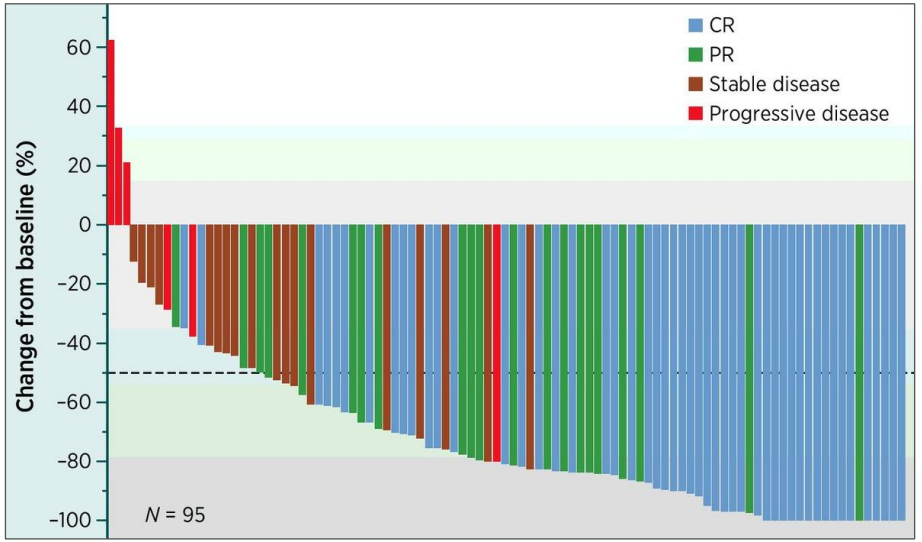
# Deep Reduction in Tumor Size with CTX110

## Maximal reduction in tumor measurements

### CTX110 (DL2+ with re-dosing)




### Axi-cel[2]



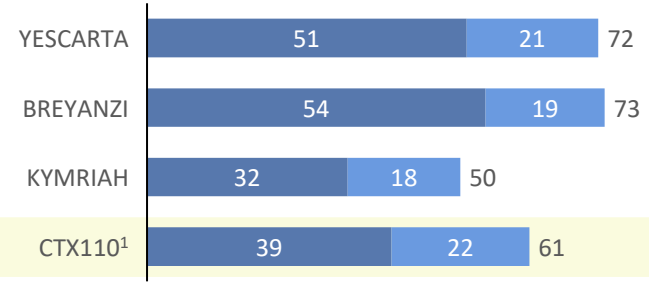

(1) Value extends beyond top of axis (215%); (2) Axicabtagene ciloleucel; Bouchkouj, *et al. Clin Cancer Res.* (2019)

*Data as of August 26, 2021*

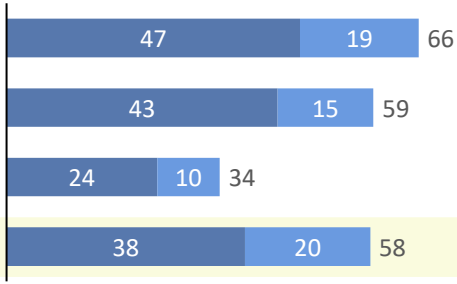
# CTX110 Shows Competitive Efficacy and Differentiated Safety

## EFFICACY

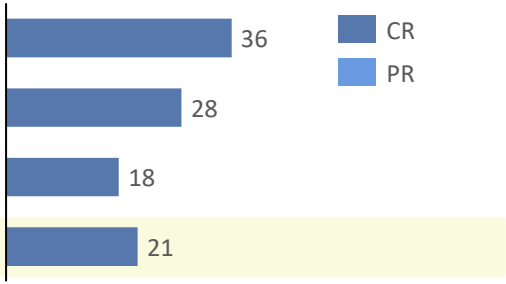
### Response rate – mITT, %




### Response rate – ITT, %

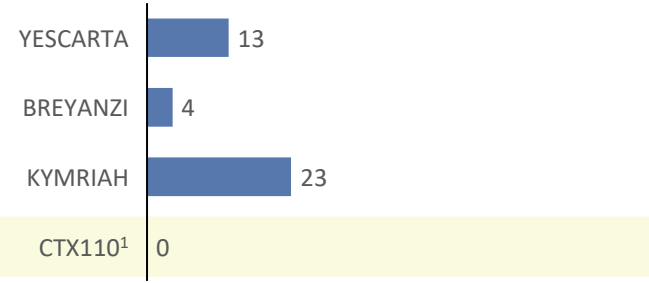



### 6-month CR rate – ITT[2], %

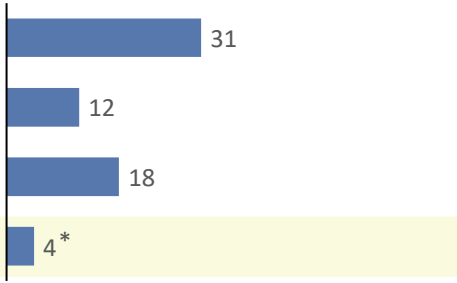



## SAFETY

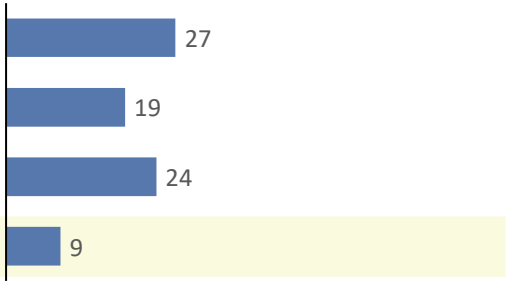
### Grade 3+ CRS[3], %




### Grade 3+ ICANS[4], %



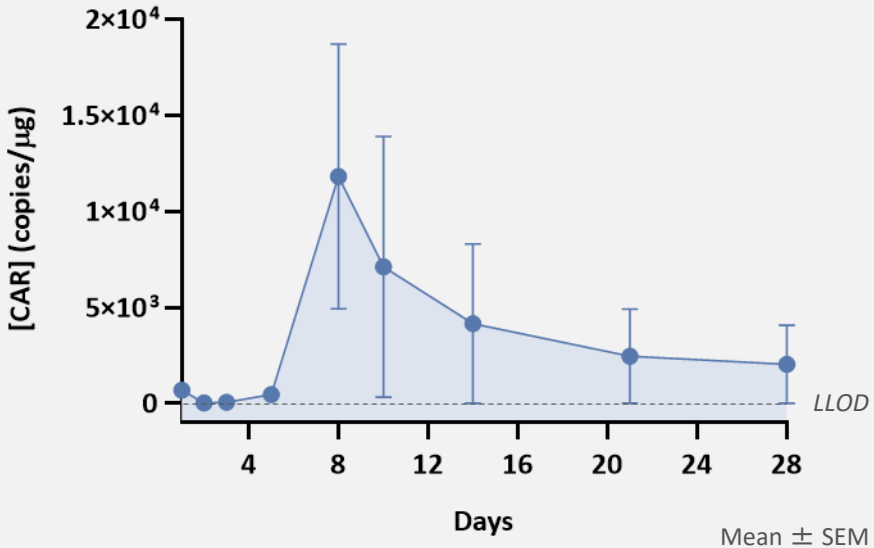

### Grade 3+ Infections, %




(1) Reported for DL2 and above
(2) For CTX110, includes re-dosed patients (5 patients not yet evaluable for 6-month CR rate)
(3) Grading systems: Lee for YESCARTA and BREYANZI, Penn for KYMRIAH, ASTCT for CTX110
(4) Reported as neurologic toxicities for autologous CAR-T programs
* Neurotoxicity observed in patient with concurrent HHV-6 encephalitis
SOURCE: YESCARTA, BREYANZI, and KYMRIAH USPI; Locke, *et al*. *Lancet Oncol.* (2019); KYMRIAH EPAR

# Pharmacokinetic Profile Supports Consolidation Dose at 1 Month

## Peripheral blood CAR levels in patients treated at DL2 and above



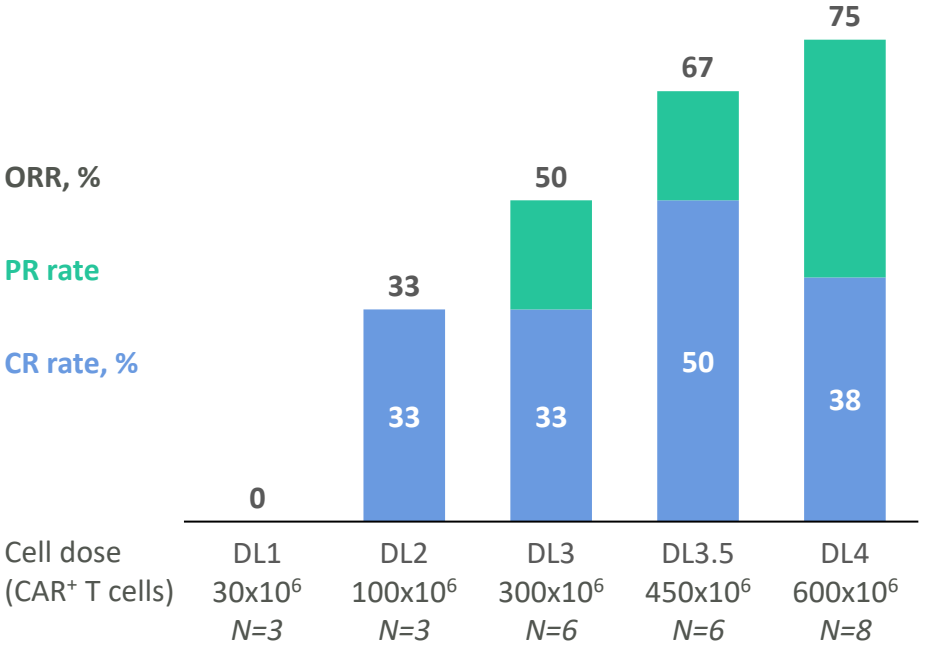

- **Consistent peak expansion** in the peripheral blood around **8 days** post infusion
- **Similar expansion observed in re-dosed patients** with no evidence of accelerated clearance from anti-drug or anti-HLA antibodies
- In many patients, CTX110 levels in the peripheral blood drop **below the lower limit of detection with ddPCR by 3-4 weeks**
- **Supports consolidation dose of CTX110 at around one month**

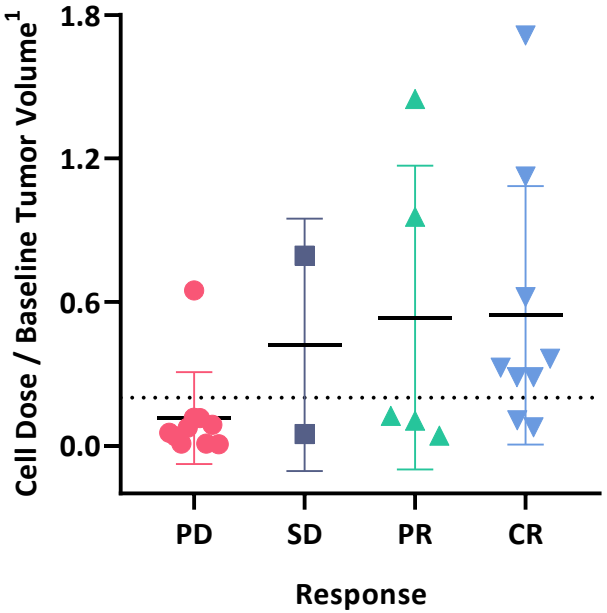
(1) Samples not collected for all patients at every timepoint

*Data as of August 26, 2021*

# Strong Rationale for Consolidation Dose of CTX110

## CTX110 shows a dose response, with better responses achieved with higher "effector:target" ratios




***Consolidation has the potential to create a 2nd round of antitumor activity with favorable "E:T" ratio to increase deep and durable responses***

(1) CAR+ T cells (millions) divided by baseline sum of perpendicular diameters ($mm^2$)

*Data as of August 26, 2021*

# Conclusions

**CTX110 is a potentially best-in-class allogeneic cell therapy in r/r LBCL with a profile that can compete with approved autologous CAR-T therapies**

- **Initial response rates in line** with approved autologous CAR-T therapies
- Ability to achieve **long-lasting complete remissions**
- Positively **differentiated safety profile**
- Potential to **improve profile further with consolidation dosing**

- Expand CARBON into a **potentially registrational trial** in Q1 2022
- Broaden into **outpatient and community settings**
- Further scale manufacturing in our **state-of-the-art facility**
- **Continue to innovate** by advancing additional gene-edited allogeneic CAR-T programs to the clinic, including novel edits for increased potency

# Thank You to Patients and Their Families

**CTX110 sites**

***Thank you to patients and their families, investigators, and site staff***

**United States**

- **Emory University** *Atlanta, GA*
- **Mayo Clinic** *Jacksonville, FL*
- **Oregon Health and Science University** *Portland, OR*
- **Sarah Cannon Research Institute** *Nashville, TN*
- **Texas Transplant Institute** *San Antonio, TX*
- **University of Minnesota** *Minneapolis, MN*
- **University of Chicago** *Chicago, IL*
- **University of Kansas** *Westwood, KS*
- **UT Southwestern Medical Center** *Dallas, TX*
- **Washington University** *St. Louis, MO*

**Europe**

- **Clínica Universidad de Navarra** *Navarra, Spain*
- **University of Hamburg** *Hamburg, Germany*

**Australia**

- **Peter MacCallum Cancer Centre** *Melbourne*
- **Royal Prince Alfred Hospital** *Sydney*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