Creating transformative gene-based medicines for serious diseases

Corporate Overview | April 2021

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CRISPR Therapeutics Highlights

Leading gene editing company focused on translating revolutionary CRISPR/Cas9 technology into transformative therapies

Advancing CRISPR in the clinic with CTX001™ in β-thalassemia and sickle cell disease

Next-generation immuno-oncology platform underlying wholly-owned, potentially best-in-class gene-edited allogeneic cell therapies CTX110™, CTX120™ and CTX130™

Enabling regenerative medicine 2.0 with CRISPR/Cas9-edited allogeneic stem cells

Advancing *in vivo* applications based on in-licensed technologies, platform improvement and strategic partnerships

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The CRISPR/Cas9 Revolution

A **SPECIFIC**, **EFFICIENT** and **VERSATILE** tool for editing genes

Disrupt

Delete

Correct or Insert

"If scientists can dream of a genetic manipulation,
CRISPR can now make it happen"

Science

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Our Pipeline

PROGRAM	RESEARCH	IND-ENABLING	CLINICAL	MARKETED	STATUS	PARTNER	STRUCTURE
Hemoglobinopathies							
CTX001™: β-thalassemia					*Enrolling*	VERTEX	Collaboration
CTX001™: Sickle cell disease (SCD)					*Enrolling*	VERTEX	Collaboration
Immuno-oncology							
CTX110™: Anti-CD19 allogeneic CAR-T					*Enrolling*		Wholly-owned
CTX120™: Anti-BCMA allogeneic CAR-T					*Enrolling*		Wholly-owned
CTX130™: Anti-CD70 allogeneic CAR-T					*Enrolling*		Wholly-owned
Regenerative medicine							
Type I diabetes mellitus					*PhI/II in 2021*	VIACYTE®	Collaboration
***In vivo* approaches**							
Glycogen storage disease Ia (GSD Ia)							Wholly-owned
Duchenne muscular dystrophy (DMD)						VERTEX	License
Myotonic dystrophy type 1 (DM1)						VERTEX	Collaboration
Cystic fibrosis (CF)						VERTEX	License

Additional undisclosed, early stage programs subject to collaboration or license agreements with Vertex and Bayer

Hemoglobinopathies – Devastating Blood Diseases

Sickle Cell Disease (SCD) and β-Thalassemia

Blood disorders caused by mutations in the β-globin gene

Sickled Normal Cell Thalassemic

Significant worldwide burden

ANNUAL BIRTHS

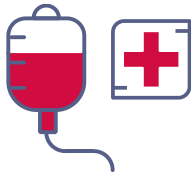
300K
SCD

60K
β-thalassemia

High morbidity and mortality

Anemia Pain Early death

Heavy burden of patient care



Frequent transfusions and hospitalizations

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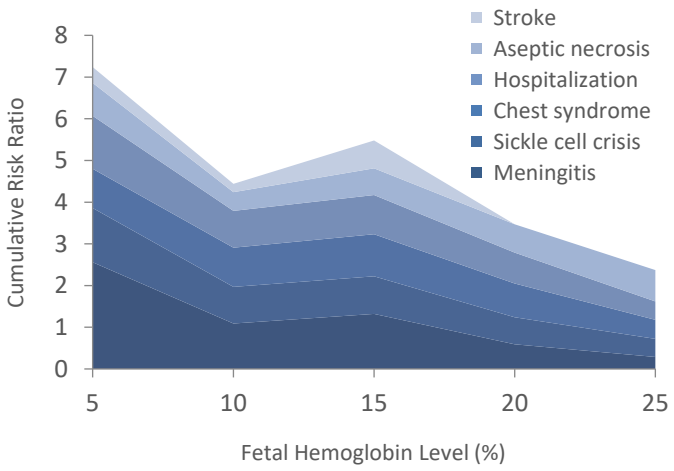
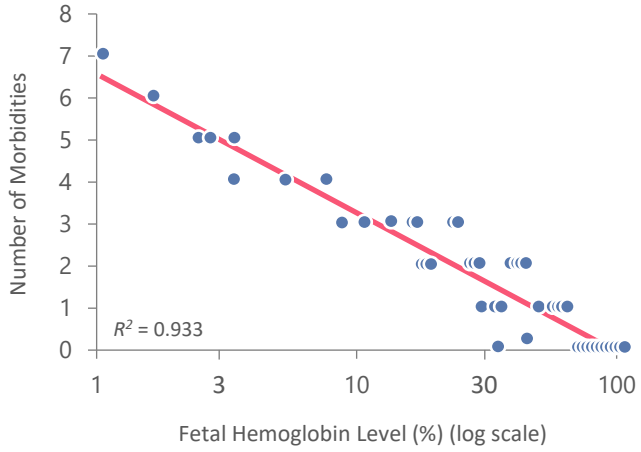
Our Approach – Upregulating Fetal Hemoglobin

Symptoms in SCD and β-Thalassemia Decrease as HbF Level Increases



Powars, *et al*. Blood 1984



Musallam, *et al*. Blood 2012

- **Naturally occurring genetic variants** cause a condition known as **hereditary persistence of fetal hemoglobin** (HPFH), which **leads to reduced or no symptoms** in patients with SCD and β-thalassemia
- **Our gene editing strategy aims to mimic these variants in symptomatic patients,** an approach supported by well-understood genetics

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Pioneering CRISPR Trials

	CLIMB THAL-111	CLIMB SCD-121
Design	**Phase 1/2, international, multi-center, open-label, single arm studies to assess the safety and efficacy of CTX001 in patients with transfusion-dependent β-thalassemia and (TDT) and SCD, respectively**	
Target enrollment	45 patients aged 12 - 35 years with TDT, including β^0 / β^0 genotypes, defined as a history of at least 100 mL/kg/year or 10 units/year of pRBC transfusions in the previous 2 years	45 patients aged 12 - 35 years with severe SCD and a history of ≥2 vaso-occlusive crises/year over the previous two years
Primary endpoint	Proportion of patients achieving sustained transfusion reduction of 50% for at least 6 months starting 3 months after CTX001 infusion	Proportion of patients with HbF ≥ 20%, sustained for at least 3 months starting 6 months after CTX001 infusion

Potential to expand into registrational trials, as well as into additional age cohorts, if supported by safety and efficacy

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TDT: Patient Baseline and Treatment Characteristics

Patients with ≥3-month follow-up (n=7)

Patient baseline		n
Genotype	β^+ / β^+	**2**
	β^0 / β^+ (not IVS-I-110)	**2**
	β^0 / β^+ (IVS-I-110)[1]	**2**
	β^0 / β^0	**1**
Gender Female/Male		**5/2**
		Median (range)
Age at consent Years		**23** (19-26)
Pre-study pRBC transfusions[2] Units/year Transfusion episodes/year		**33.0** (23.5-61.0) **15.0** (12.5-16.5)

Treatment characteristics	**Median** (range)
Drug product cell dose CD34+ cells x 10^6/kg	**11.6** (4.5-16.6)
Neutrophil engraftment[3] Study day[4]	**32** (20-39)
Platelet engraftment[5] Study day[4]	**37** (29-52)
Duration of follow-up Months	**8.9** (3.8-21.5)

Data disclosed December 5, 2020

(1) IVS-I-110 phenotype is severe and similar to β^0 / β^0; (2) Annualized number during the 2 years before consenting to study participation; (3) Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/µL on 3 consecutive days; (4) Study day defined as day after CTX001 infusion; (5) Defined as the first day of 3 consecutive measurements of platelet count ≥20,000/µL on 3 different days after CTX001 infusion, without a platelet transfusion in the past 7 days

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TDT: Summary of Adverse Events

Patients with ≥3-month follow-up (n=7)

AEs were generally consistent with myeloablation and autologous stem cell transplant

	Patients with non-serious AEs, n	Patients with SAEs, n
Relationship[1]		
Related to plerixafor and/or G-CSF	6	0
Related to busulfan only	7	2
Related to CTX001 only	1[2]	1
Related to busulfan and CTX001	3[3]	1
Not related to any study drug	7	4

- 4 of 7 patients experienced at least one post-infusion SAE
- Majority of AEs occurred within first 60 days after CTX001 infusion
- 2 patients experienced a combined total of 5 SAEs related or possibly related to busulfan only: venoocclusive liver disease (in both patients), febrile neutropenia (2 events in 1 patient), and colitis; all resolved
- One patient experienced 4 SAEs related or possibly related to CTX001: headache, haemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome, and idiopathic pneumonia syndrome (latter also related to busulfan). All SAEs occurred in the context of HLH and have resolved

Data disclosed December 5, 2020

(1) Includes related and possibly related AEs; (2) 1 patient experienced a non-serious AE of anaemia possibly related to CTX001 (resolved); (3) 3 patients experienced non-serious AEs related or possibly related to busulfan and CTX001: petechiae, pyrexia, epistaxis, lymphocyte count decreased, neutrophil count decreased, WBC count decreased, and platelet count decreased

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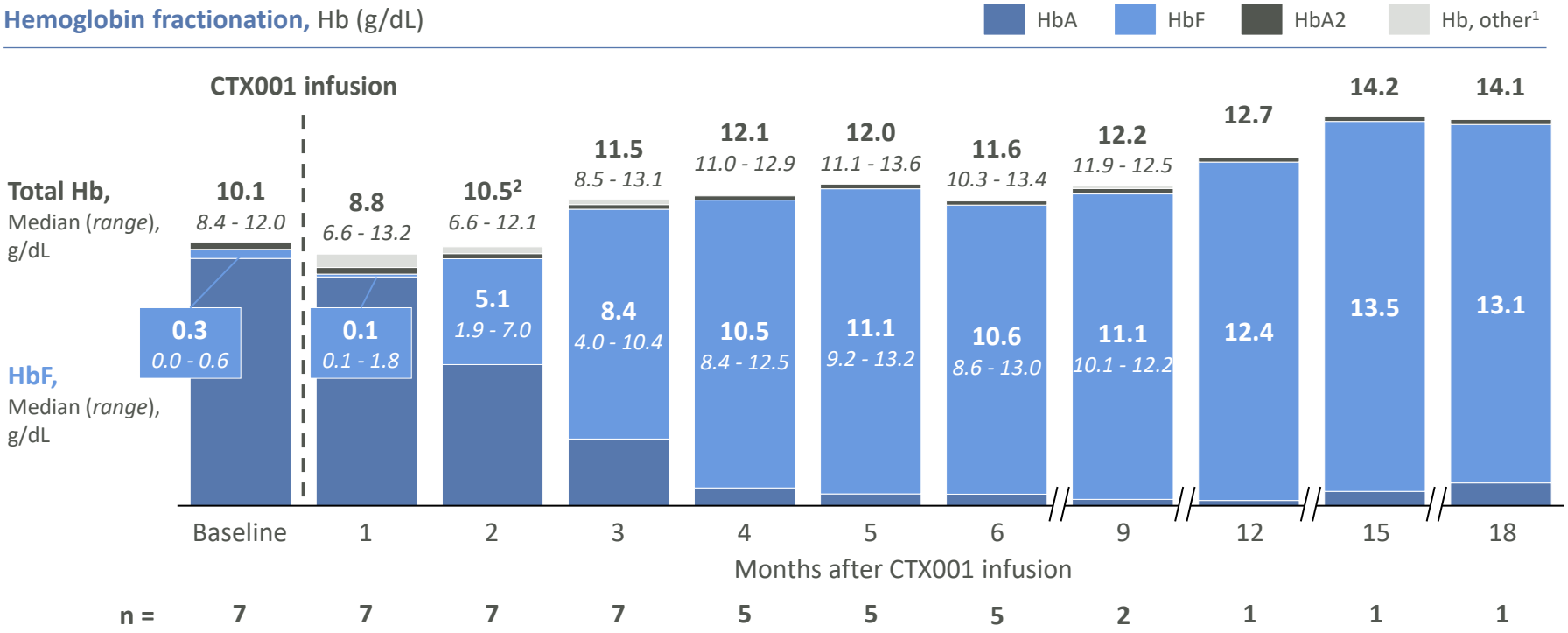
TDT: Clinically Meaningful HbF and Total Hb Are Achieved Early and Maintained

Hemoglobin fractionation, Hb (g/dL)



Data disclosed December 5, 2020

(1) Hb adducts and other variants; (2) With respect to Patient 2, Total Hb from local laboratory and Hb fraction from central laboratory

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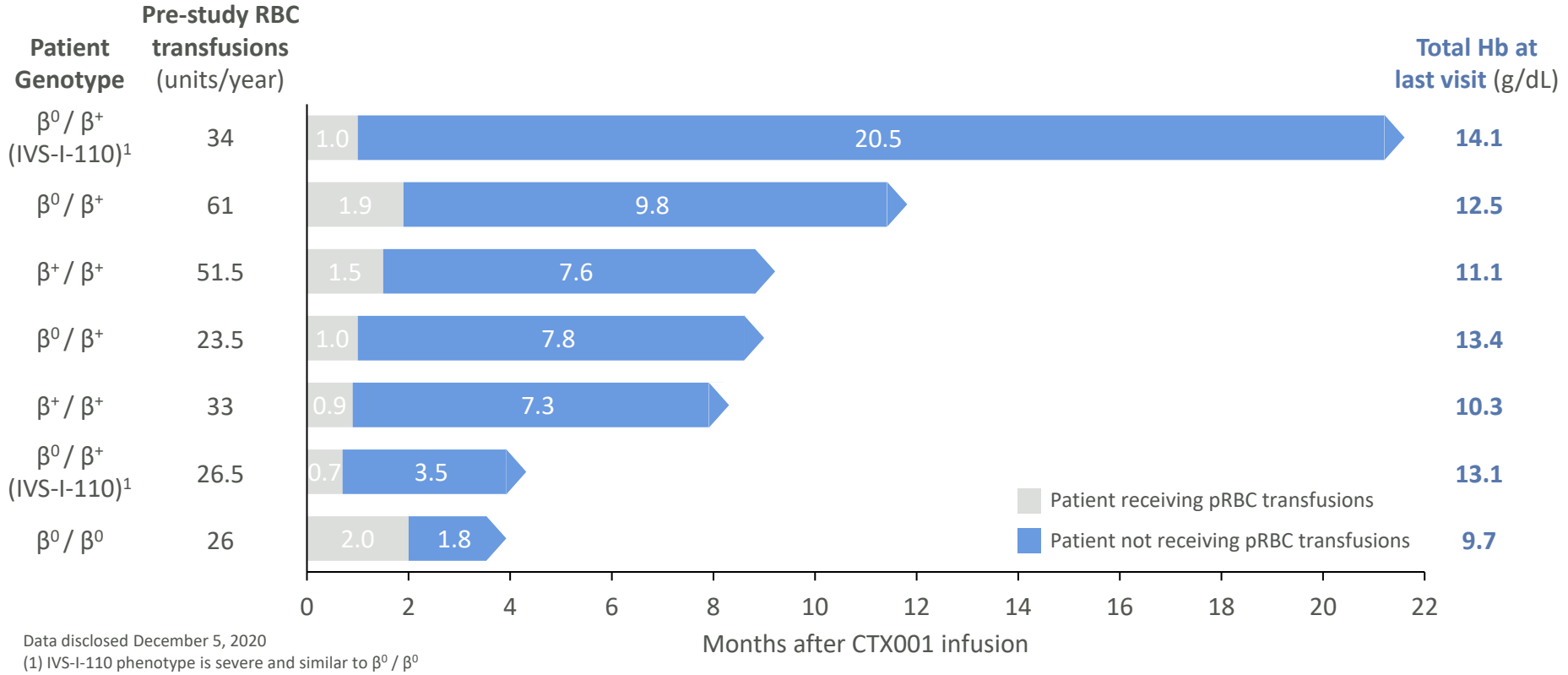
TDT: Duration of Transfusion Independence After CTX001



Data disclosed December 5, 2020

(1) IVS-I-110 phenotype is severe and similar to β^0 / β^0

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SCD: Patient Baseline and Treatment Characteristics

Patients with ≥3-month follow-up (n=3)

Patient baseline		n
Genotype	β^S / β^S	**3**
Gender Female/Male		**2/1**
		Median (range)
Age at consent Years		**22** (22-33)
Pre-study VOCs VOCs/year[1]		**7** (4.0-7.5)

Treatment characteristics	**Median** (range)
Drug product cell dose[2] CD34+ cells x 10^6/kg	**3.8** (3.1-3.9)
Neutrophil engraftment[3] Study day[4]	**22** (17-30)
Platelet engraftment[5] Study day[4]	**30** (30-33)
Duration of follow-up Months	**7.8** (3.8-16.6)

Data disclosed December 5, 2020

(1) Annualized rate during the 2 years before consenting to study participation; (2) Across multiple drug product lots per patient; (3) Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/µL on 3 consecutive days; (4) Study day defined as day after CTX001 infusion; (5) Defined as the first day of 3 consecutive measurements of platelet count ≥50,000/µL on 3 different days after CTX001 infusion, without a platelet transfusion in the past 7 days

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SCD: Summary of Adverse Events

Patients with ≥3-month follow-up (n=3)

AEs were generally consistent with myeloablation and autologous stem cell transplant

	Patients with non-serious AEs, n	Patients with SAEs, n
Relationship[1]		
Related to plerixafor only	3	1
Related to busulfan only	3	1
Related to CTX001 only	0	0
Related to busulfan and CTX001	2[2]	0
Not related to any study drug	3	2

- 1 of 3 patients experienced at least one post-infusion SAE
- Majority of AEs occurred within first 60 days after CTX001 infusion
- 1 patient experienced SAEs related to plerixafor: chest pain, neck pain, headache, and abdominal pain; all resolved
- Post-CTX001, only 1 patient experienced SAEs: sepsis (related to busulfan), cholelithiasis, and abdominal pain (both unrelated to any study drug); all resolved
- There were no SAEs related to CTX001

Data disclosed December 5, 2020
(1) Includes related and possibly related AEs; (2) 2 patients experienced non-serious AEs related or possibly related to busulfan and CTX001: lymphopenia and dermatitis

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SCD: Clinically Meaningful HbF and Total Hb Are Achieved Early and Maintained

Hemoglobin fractionation, Hb (g/dL)

Data disclosed December 5, 2020
(1) Hb adducts and other variants

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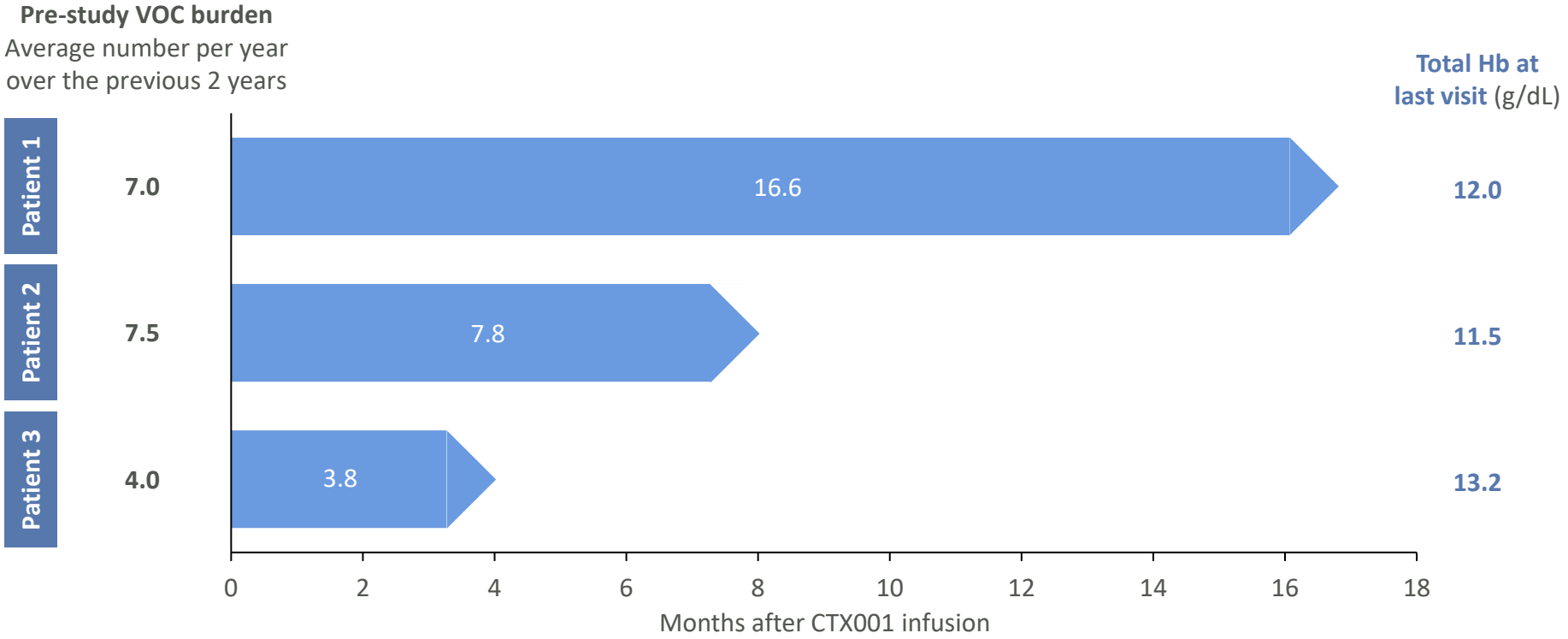
SCD: Duration VOC-Free After CTX001



All patients have detectable haptoglobin and improved LDH, indicating no evidence of hemolysis

Data disclosed December 5, 2020

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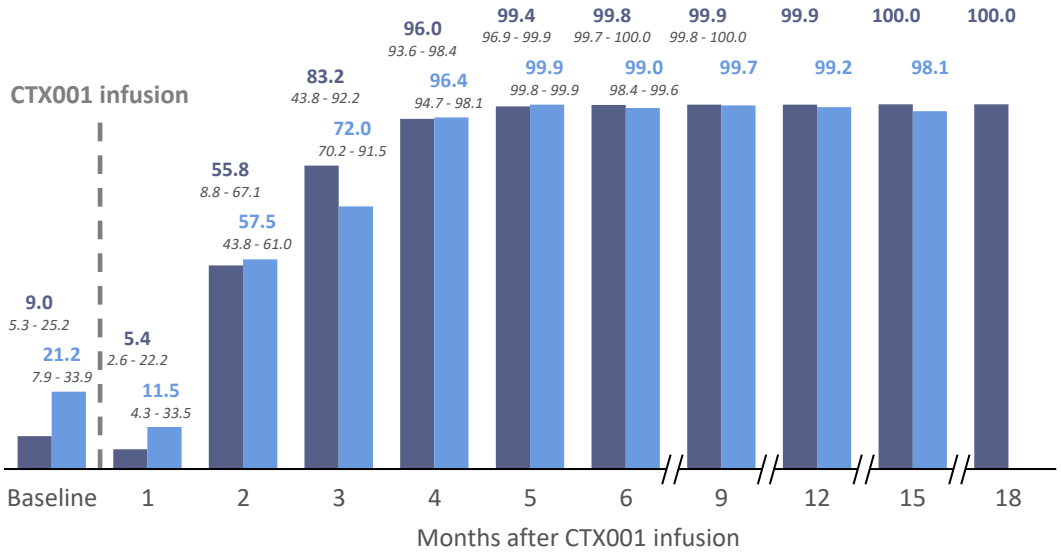
Pancellular HbF Expression and Durable Editing

TDT
SCD

CRISPR THERAPEUTICS

Pancellular expression of HbF maintained

Median % peripheral F-cells (*range*), % circulating RBCs expressing HbF



n (TDT):	7	7	7	7	5	5	5	2	1	1	1
n (SCD):	3	3	3	3	2	2	2	1	1	1	0

Durable BCL11A editing in the bone marrow

Patients with ≥6 months of follow-up[1]

	Total follow-up, months	Allelic editing in CD34⁺ bone marrow cells, %	
		6-month visit	12-month visit
1	21.5	78.1	76.1
2	11.7	41.8	
3	9.1	72.6	
4	8.9	76.6	
5	8.2	88.1	
1	16.6	81.4	80.4
2	7.8	87.3	

Data disclosed December 5, 2020

(1) Bone marrow editing assessments performed starting at 6 months, 12 months, and 24 months of follow-up

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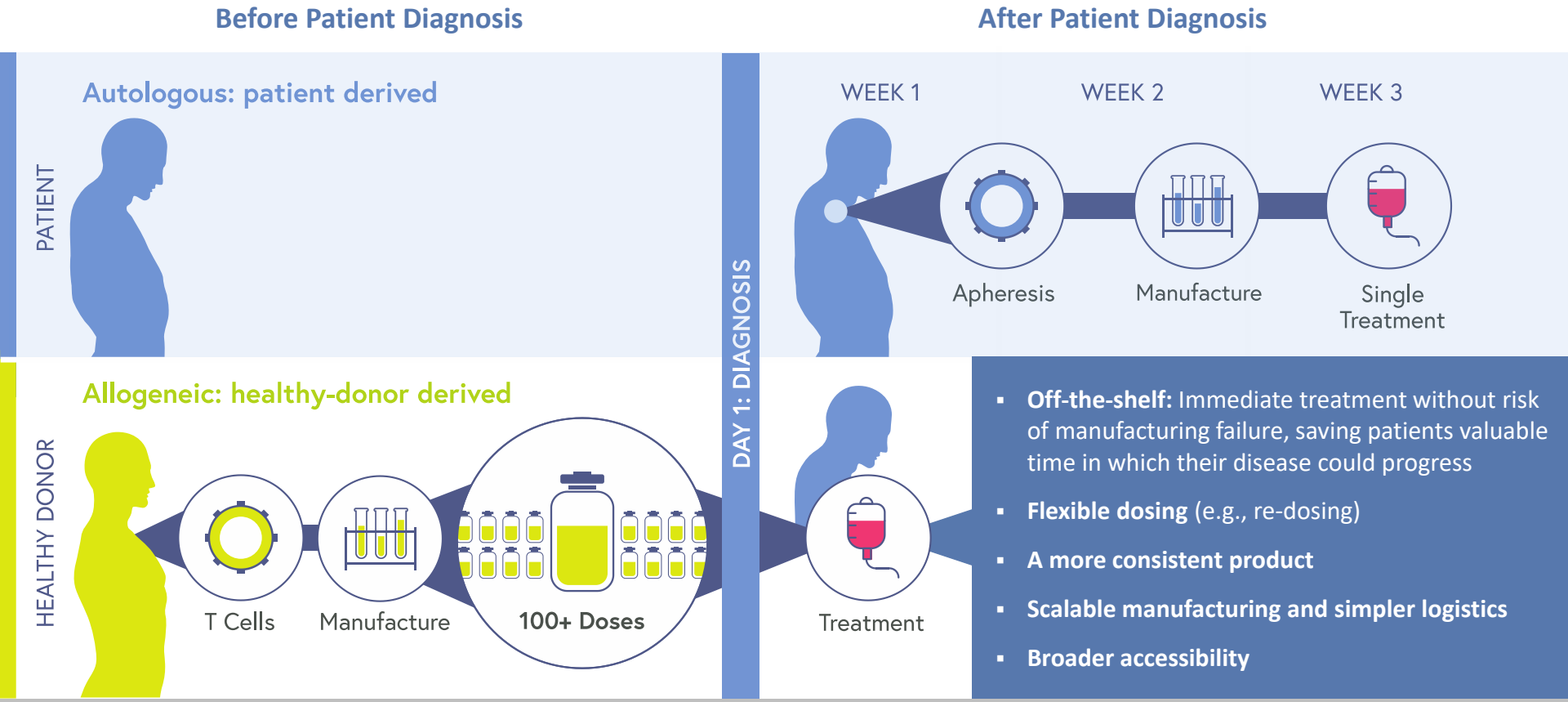
Allogeneic CAR-T Therapy Has Transformative Potential



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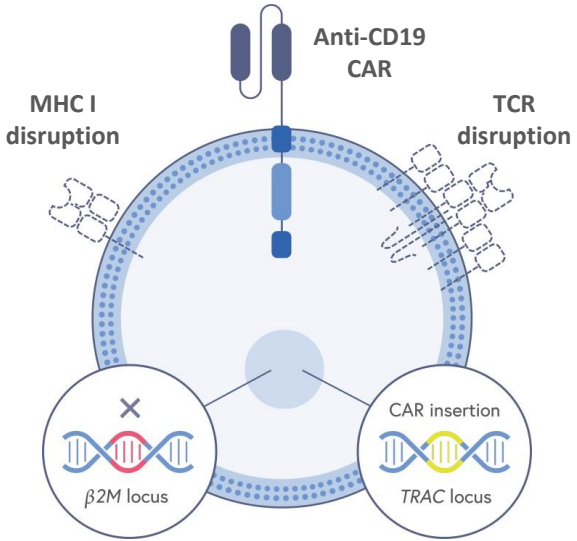
CTX110: Differentiated CRISPR-Edited Allogeneic CAR-T Design

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*

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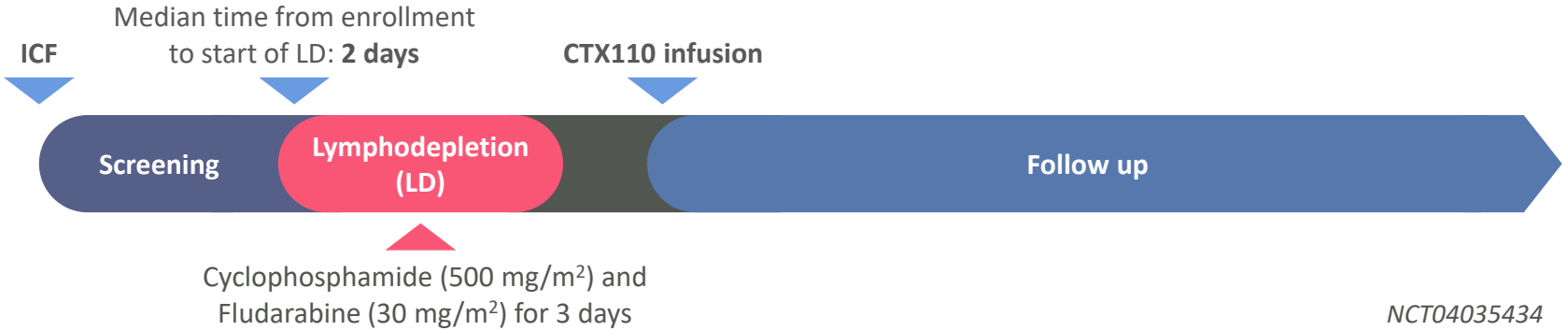
CARBON: Trial Design

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, and on-site availability of CAR-T cell product



NCT04035434

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

- DoR, PFS, and OS

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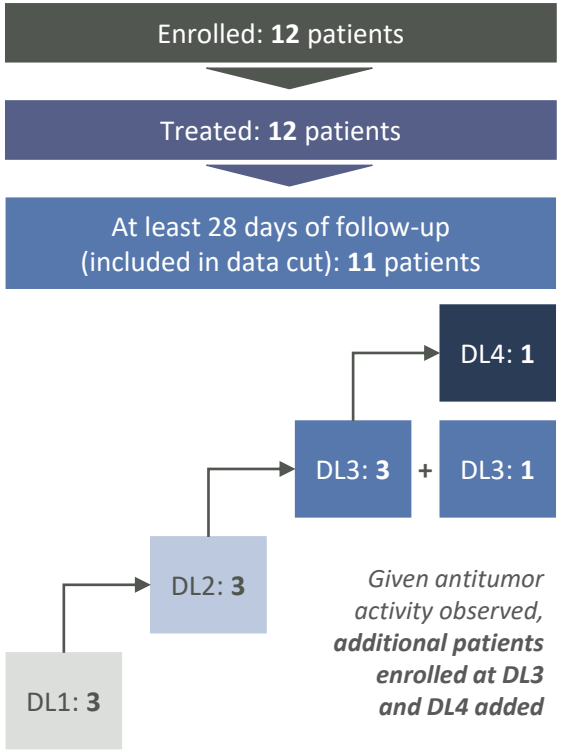
CARBON: Patient Flow and Baseline Characteristics

As of the data cutoff date:



N (%) (unless otherwise noted)

Cell dose (CAR+ T cells)	DL1 30x10⁶ *N=3*	DL2 100x10⁶ *N=3*	DL3 300x10⁶ *N=4*	DL4 600x10⁶ *N=1*
Median age, years (range)	52 (50-61)	64 (58-74)	64.5 (62-74)	72
Male	2 (66.7)	2 (66.7)	1 (25)	1 (100)
Lymphoma subtypes				
Diffuse large B-cell lymphoma (DLBCL)[1]	3 (100)	3 (100)	4 (100)	1 (100)
Follicular lymphoma	0	0	0	0
Current disease stage (per Lugano 2014)[2]				
Stage III	1 (33.3)	1 (33.3)	2 (50)	0
Stage IV	2 (66.7)	2 (66.7)	1 (25)	1 (100)
Prior treatments				
Median number (range)	2.0 (2-8)	3.0 (2-3)	2.0 (2-4)	5
Hematopoietic stem cell transplant	0	0	3 (75)	1 (100)
Refractory to last therapy	3 (100)	3 (100)	0	0

(1) Including high grade lymphoma (e.g., triple hit), transformed follicular lymphoma (tFL), Richter's Transformation; (2) One patient with Stage II disease treated at DL3

Data as of September 28, 2020

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Dose-Dependent Responses Observed with CTX110

Best response per 2014 Lugano criteria[1] by independent central assessment

Cell dose (CAR+ T cells)	DL1 $30x10^6$ *N=3*	DL2 $100x10^6$ *N=3*	DL3 $300x10^6$ *N=4*	DL4 $600x10^6$ *N=1*
Overall response rate (ORR), N (%)	0 (0%)	1 (33%)	2 (50%)	1 (100%)
Complete response (CR) rate, N (%)	0 (0%)	1 (33%)	2 (50%)	1 (100%)

- Early evidence of **dose response, with complete responses achieved in 4 patients**
- **Responses achieved without the use of more toxic lymphodepletion agents,** consistent with engineering of CTX110 for immune evasion
- **CAR-T cells detected at multiple time points in all patients** in DL2-4, with **consistent peak expansion** of CTX110 in the peripheral blood seen around 1-2 weeks post infusion and CTX110 detected out **as late as 180 days** after administration

First efficacy assessment occurs at M1 visit; (1) Cheson, *et al*. *J Clin Oncol*. (2014)

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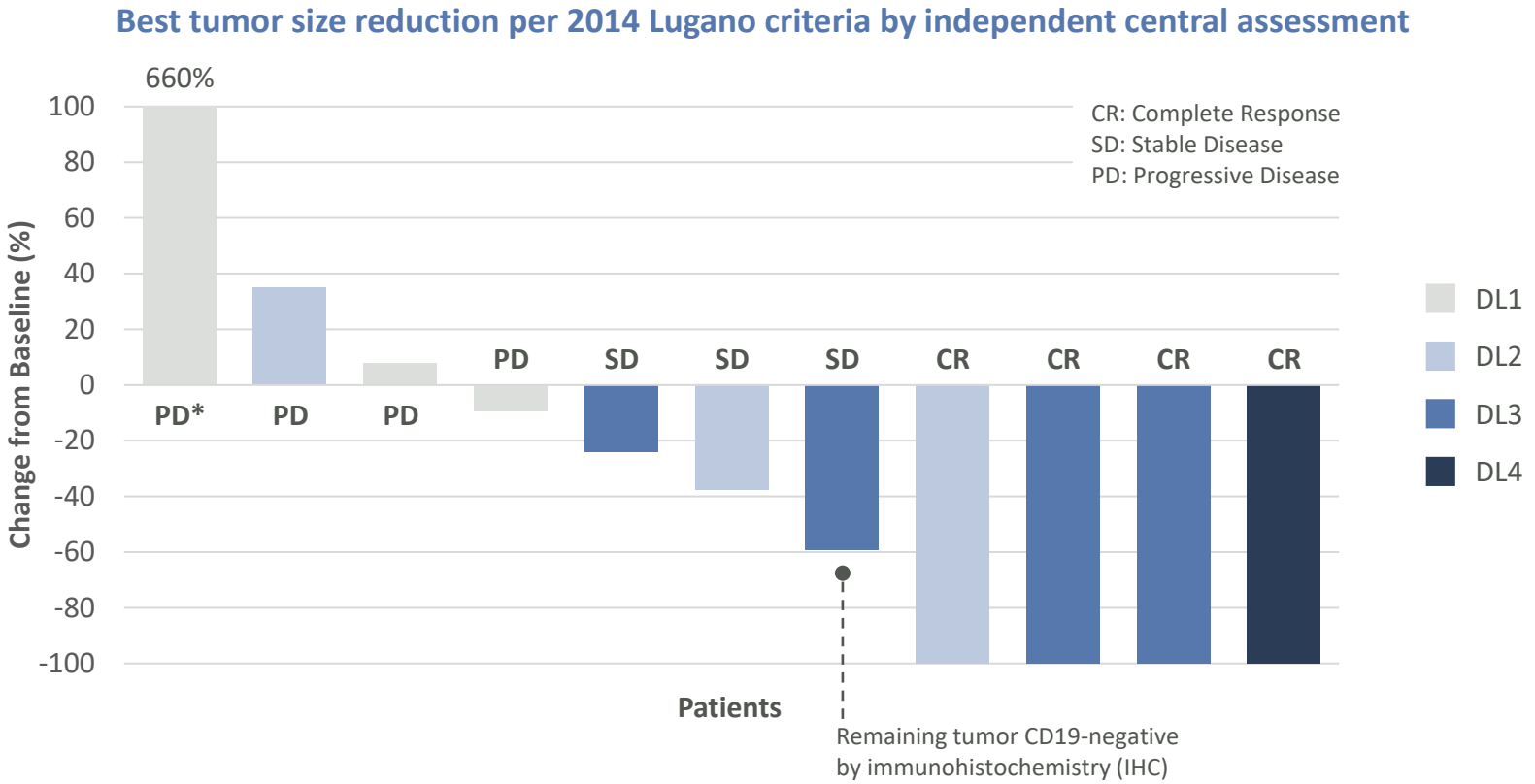
Dose-Dependent Reduction in Tumor Size with CTX110



* Patient subsequently failed autologous CAR-T

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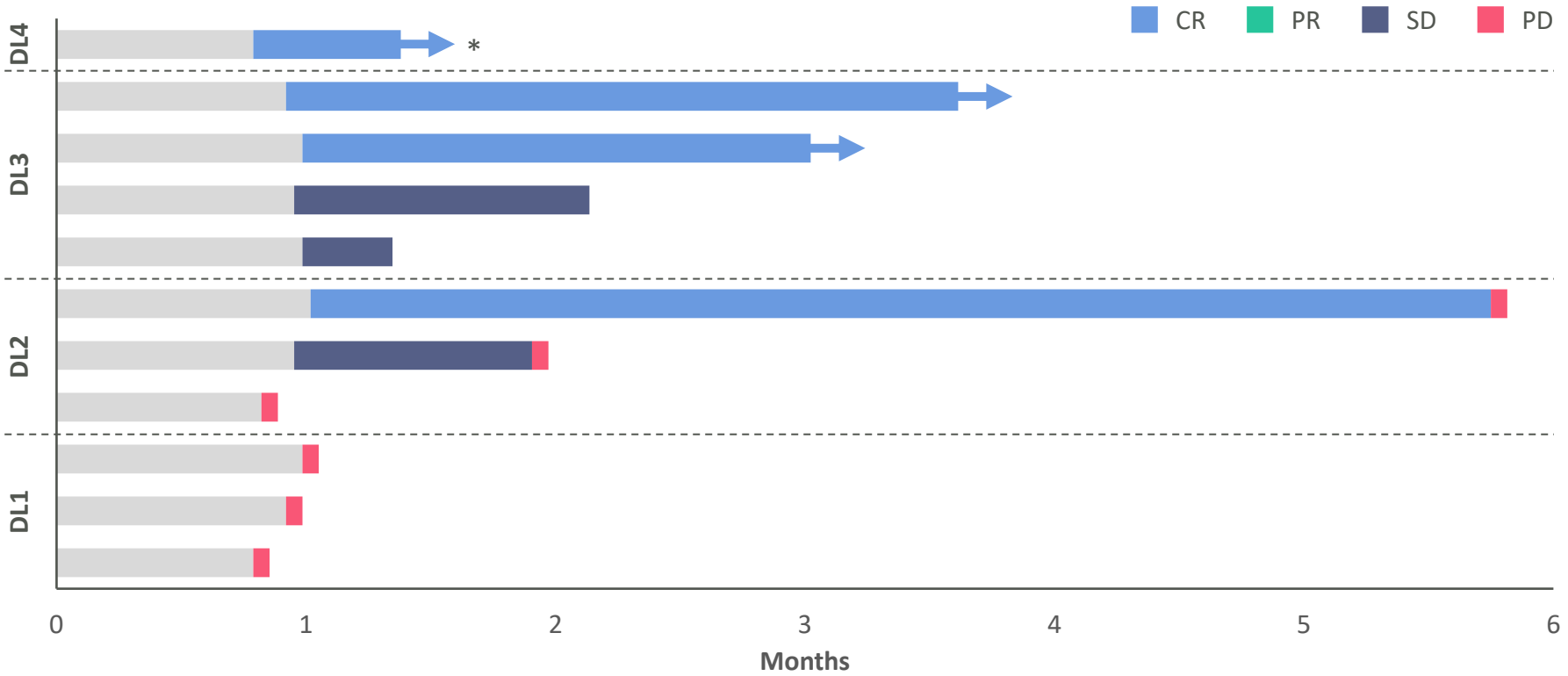
Complete Responses with CTX110 Showed Durability at Month 3 and Beyond



Imaging per protocol occurs at M1, M3, and M6; * Patient died while in CR at Day 52 post CTX110 infusion following data cutoff

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Acceptable Safety Profile with CTX110 at DL3 and Below

Treatment-emergent adverse events (AEs) of special interest in DL1-3, N (%)

N=10	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Graft-versus-Host Disease (GvHD)	0	0	0	0	0
Cytokine Release Syndrome (CRS)[1,2]	1 (10%)	2 (20%)	0	0	0
ICANS[1,3]	0	1 (10%)	0	0	0
Infections	0	0	1 (10%)	0	0

For patients in DL1 through DL3 (N=10):

- **No GvHD** despite all patients with ≤3/12 HLA match to CTX110 donors
- **No CRS or ICANS above Grade 2**
- **No infusion reactions**
- **4 serious adverse events (SAEs) following CTX110 infusion not related to disease progression among 3 treated patients:** ICANS (n=1), CRS (n=1), periorbital cellulitis (n=1), febrile neutropenia (n=1)

Safety for patient treated at DL4 (600x10^6 CAR$^+$ T cells):

- Patient had received five prior lines of therapy, including autologous stem cell transplant
- Experienced Grade 2 CRS at Day 5 that resolved
- Admitted with febrile neutropenia at Day 26 and developed confusion and memory loss starting at Day 28, with further deterioration ultimately requiring intubation for airway protection
- Initially treated for ICANS and later found to have reactivation of HHV-6 and HHV-6 encephalitis
- Despite treatments, patient remained obtunded and died on Day 52 after family requested withdrawal of care

(1) Per ASTCT criteria; other AEs graded per CTCAE; (2) Includes two separate episodes of CRS (1 G1, 1 G2) in single patient; worst grade reported;
(3) Immune effector Cell-Associated Neurotoxicity Syndrome

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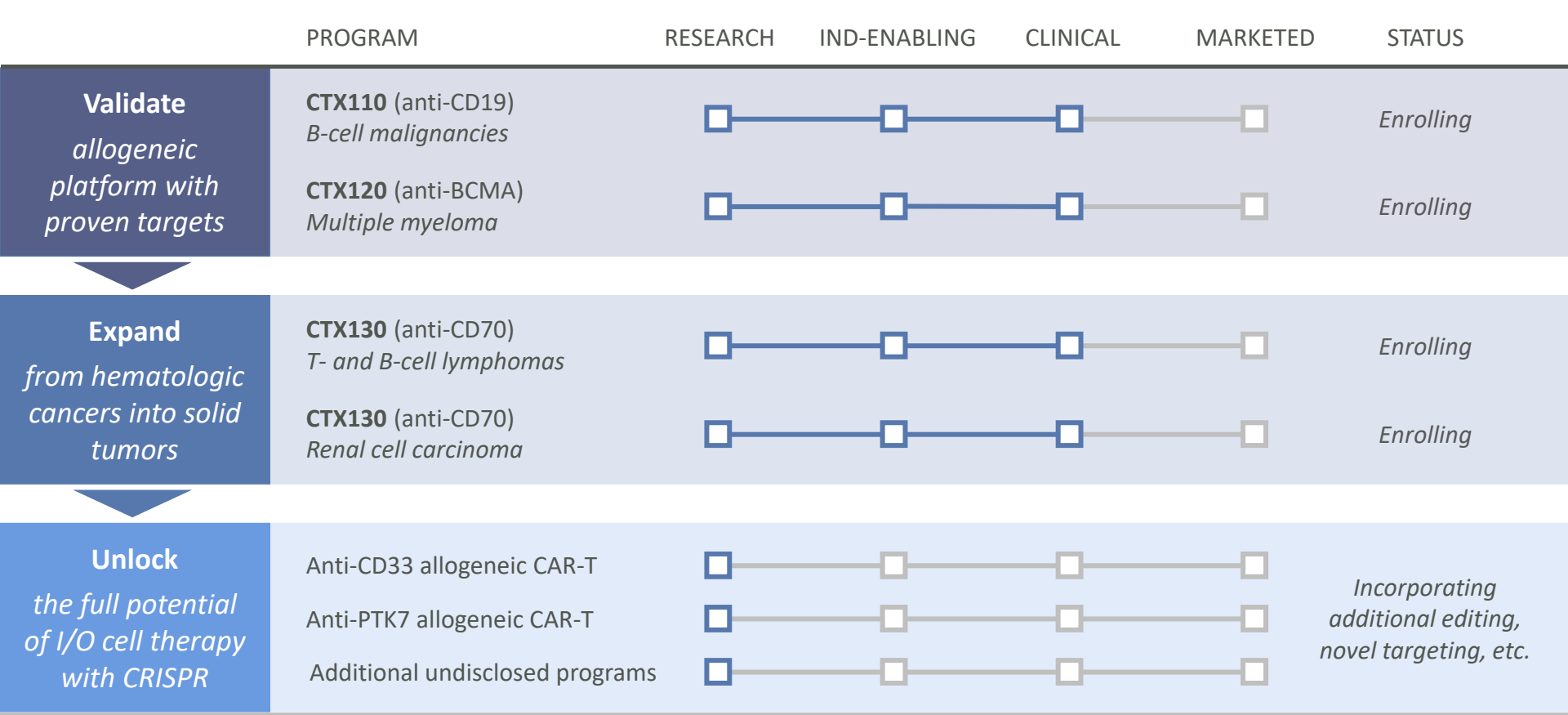
Our I/O Strategy and Allogeneic CAR-T Pipeline



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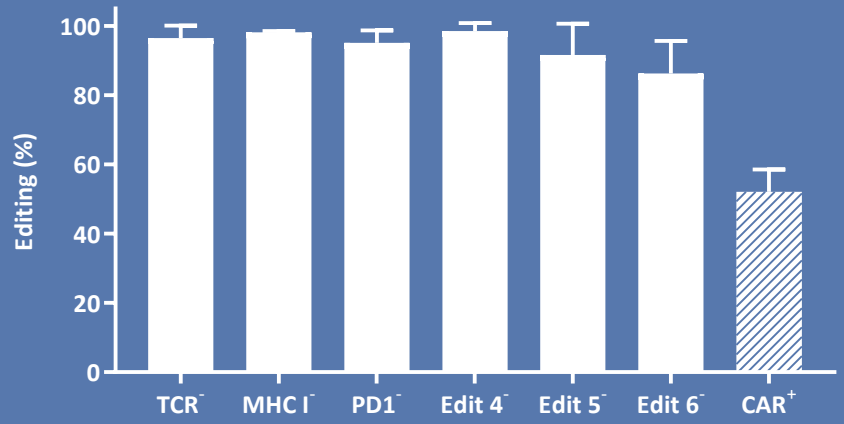
CRISPR Enables the Next Generation of I/O Cell Therapy

CRISPR gene editing facilitates consistent, multiplex editing to:

- Produce allogeneic cell therapies
- Enhance immune cell performance
- Speed the discovery and generation of novel therapeutic candidates

Multiplexed, single-shot 6x knock-out plus CAR insertion performed at high efficiency



6x-edited CAR-T cells show no viability decrease, no cytokine-independent growth and robust target-specific cytotoxicity

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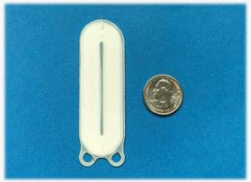
CRISPR Enables Regenerative Medicine 2.0

CRISPR/Cas9 Technology Opens Broader Applications for Regenerative Medicine

CRISPR/ Cas9

Stem Cell Technology

- Allow immune evasion
- Improve cell function
- Direct cell fate



Therapeutic Targets
e.g., diabetes

Exemplified by our collaboration with ViaCyte

- Aim to develop beta-cell replacement product to treat diabetes that does not require immunosuppression
- Applies immune-evasive gene-editing expertise from our allo CAR-T programs to stem cells
- Plan to initiate trials in 2021

ViaCyte®

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Unlocking *In Vivo* Applications of CRISPR/Cas9

AAV Vectors for Neuromuscular Indications

- **Adeno-associated virus (AAV)** to deliver Cas9 and gRNA to muscle, the nervous system and other tissues
- Collaboration with StrideBio to improve tissue specificity and reduce immunogenicity
- Programs include DMD and DM1 in collaboration with Vertex, as well as other early research programs

LNPs for Liver Indications

- **Lipid nanoparticles (LNPs)** containing mRNA encoding Cas9 and gRNA for delivery to the liver
- Lipid technology from MIT and mRNA technology from CureVac
- Programs include GSD Ia and other early research programs

Enabling collaborations

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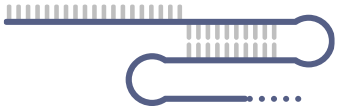
Optimizing the CRISPR/Cas9 Platform

Nuclease Engineering

Enhance CRISPR/Cas9 system through protein engineering

Guide RNA Optimization

Identify optimal guide RNA formats and sequences for therapeutic editing



PLATFORM ENHANCEMENT

Advanced Editing

Improve efficiency of gene correction and multiplexing

Synthetic Biology

Engineer improved cellular therapeutics

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Strong U.S. and Global Foundational IP Position

United States

Charpentier / UC Berkeley / U. Vienna granted patents of broad scope; multiple applications progressing

- **35** Patents of broad scope granted, including the patent involved in the 1st interference
- **25+** Additional patent applications moving forward in parallel with both broad and narrow claims, including 2 patent applications of broad scope allowed
- **2nd** Interference with Broad Institute in priority phase to determine who was first to invent CRISPR/Cas9 gene editing in eukaryotic cells; separate interference declared with Toolgen on same subject matter

Europe and Global

Charpentier / UC Berkeley / U. Vienna granted foundational patents, including use in eukaryotes

- **3** Patents of broad scope granted in the EU
- **31** Patents of broad scope granted in the UK, Germany, Japan, China, Singapore, Hong Kong, Ukraine, Israel, Australia, New Zealand, Mexico, South Africa and elsewhere
- **~80** Jurisdictions worldwide in which applications with both broad and narrow claims are advancing

As of December 2020

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Building a Great Company

EXPERIENCED
Management Team

END-TO-END CAPABILITIES
With >400 Employees

COLLABORATIVE & ENTREPRENEURIAL
Culture