Forward-looking Statements

Statements in this report about future expectations, plans and prospects, as well as any other statements regarding matters that are not historical facts, constitute “forward-looking statements” within the meaning of The Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, statements relating to Legend Biotech’s overall strategies and objectives; Legend Biotech’s ability to achieve milestones under its collaboration with Janssen Biotech; Legend Biotech’s strategy and plans for the development, manufacturing and commercialization of ciltacabtagene autoleucel (cilta-cel), including anticipated regulatory milestones; the preclinical and clinical development strategy for product candidates and the anticipated timing of key regulatory and clinical milestones for such product candidates; the potential benefits afforded by investigational candidates; and the opportunities represented by preclinical data. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors. Legend Biotech’s expectations could be affected by, among other things, uncertainties involved in the development, manufacturing and commercialization of new pharmaceutical products; unexpected or inconsistent preclinical data; unexpected clinical trial results, including as a result of additional analysis of existing clinical data or unexpected new clinical data; unexpected regulatory actions or delays, including requests for additional safety and/or efficacy data or analysis of data, or government regulation generally; unexpected delays as a result of actions undertaken, or failures to act, by our third party partners; uncertainties arising from challenges to Legend Biotech’s patent or other proprietary intellectual property protection, including the uncertainties involved in the US litigation process; competition in general; government, industry, and general public pricing and other political pressures; the duration and severity of the COVID-19 pandemic and governmental and regulatory measures implemented in response to the evolving situation; as well as the other factors discussed in the “Risk Factors” section of the Company’s Annual Report on Form 20-F filed with the Securities and Exchange Commission on April 2, 2021. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described in this report as anticipated, believed, estimated or expected. Legend Biotech specifically disclaims any obligation to update any forward-looking statement, whether as a result of new information, future events or otherwise. In addition, 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 distinct product candidates may have no interpretative value with respect to our existing or future results. Similarly, caution should be exercised when interpreting results relating to a small number of patients or individually presented case studies.
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speakers</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:00 a.m.</td>
<td>Welcome</td>
<td>Jessie Yeung, Head of Corporate Finance</td>
<td>10:00 a.m. – 10:05 a.m.</td>
</tr>
<tr>
<td>10:05 a.m.</td>
<td>Introduction</td>
<td>Dr. Ying Huang, CEO &amp; CFO</td>
<td>10:05 a.m. – 10:15 a.m.</td>
</tr>
<tr>
<td>10:15 a.m.</td>
<td>Global BCMA Program</td>
<td>Dr. Lida Pacaud, VP of Clinical Development, Steve Gavel, VP of Commercial Development</td>
<td>10:15 a.m. – 11:00 a.m.</td>
</tr>
<tr>
<td>11:00 a.m.</td>
<td>Coffee Break</td>
<td></td>
<td>11:00 a.m. – 11:10 a.m.</td>
</tr>
<tr>
<td>11:10 a.m.</td>
<td>Research &amp; Development</td>
<td>Dr. Frank Fan, Chief Scientific Officer</td>
<td>11:10 a.m. – 12:20 p.m.</td>
</tr>
<tr>
<td>12:20 p.m.</td>
<td>Q&amp;A</td>
<td></td>
<td>12:20 p.m. – 12:50 p.m.</td>
</tr>
<tr>
<td>12:50 p.m.</td>
<td>Conclusion</td>
<td></td>
<td>12:50 p.m. – 1:00 p.m.</td>
</tr>
</tbody>
</table>
Introduction

Ying Huang, Ph.D.
Chief Executive Officer & Chief Financial Officer
Legend Biotech is a biotech company that was founded in 2014. The company has made several key milestones in its journey, including:

- **Legend Founded**: Legend Biotech incorporated in 2014.
- **1st MM Patient**: The first Multiple Myeloma patient treated in China with a BCMA CAR-T was treated in 2015.
- **1st US IND**: The first US IND for a BCMA CAR-T was cleared by the US FDA in 2017.
- **Phase II IND**: The Phase II IND for a BCMA CAR-T was cleared by the NMPA in 2018.
- **Breakthrough Designation**: Cilta-cel received Breakthrough Therapy designation from the US FDA in 2019.
- **EU Priority**: Cilta-cel received EMA PRIME Designation in 2020.
- **Breakthrough Designation**: Cilta-cel received Breakthrough Designation from the Center for Drug Evaluation in China in 2021.
- **Belgium Facility**: A state-of-the-art manufacturing facility was announced in Belgium in 2021.
- **BLA Accepted**: Both the US FDA and EMA accepted the BLA filing for cilta-cel and slated it for priority review.
- **Nasdaq IPO**: Legend Biotech went public, raising $487 million, in 2018.
- **PDUFA**: The Prescription Drug User Fee Act target action date is November 29, 2021 for cilta-cel.
Our Presenters

Lida Pacaud, M.D.
Vice-President, Clinical Development

A trained physician, Dr. Lida Pacaud formerly led the CART Global Clinical Program at Novartis and served as the Executive Medical Director of its Cell & Gene Unit.

Steve Gavel
Vice-President, Commercial Development

Steve Gavel has spent 20 years conducting commercial and marketing in the biotechnology industry. At Celgene, Steve headed commercial development activities for the bb2121 program.

Frank Fan, M.D., Ph.D.
Chief Scientific Officer, Co-Founder

Dr. Frank Fan is an applied immunologist who specialized in the field of immunotherapy and pioneered anti-BCMA CAR-T.
Pioneering Cellular Therapy

- In-house antibody generation and CAR-T-specific functional screening technologies
- Diverse allogeneic platforms, including non-gene editing universal CAR-T and NK
- Antibody screening & engineering
- Armoring strategy for solid tumors
- Diverse platform for allogeneic treatments
- Multiple armored CAR-T strategies to overcome challenges in treatment of solid tumors
As of May 2021*:
Disease-free without additional maintenance treatment

What inspires us?

LEGEND-2 Patient #6

- D20: $\lambda$ light chain decreased from 1770 to 0.48 mg/L
- Assessed as MRD- CR

Total dose 0.5 x10^6 CAR+ cells/kg

Day 1
Day 19
Mar 2019
Oct 2020

CAR=chimeric antigen receptor; CR=complete response; MM=multiple myeloma; MRD-neg=minimal residual disease negative.


*Updated follow-up data compared with ASH 2019 presentation.
5-year follow-up
Advancing Treatment Options for Multiple Myeloma

Lida Pacaud, M.D.
Vice President of Clinical Development

Steve Gavel
Vice President of Commercial Development
Current Clinical Development Plan

Ciltacabtagene autoleucel (cilta-cel)

CARTITUDE-1
Phase 1b/2, registrational
(ASCO 2021 update)

CARTITUDE-2
Phase II, Multi-cohort study in various MM settings
(Cohort A at ASCO & EHA 2021)

CARTITUDE-4
Phase III, 1-3 prior lines MM

CARTITUDE-5
Phase III, Newly diagnosed, transplant not intended/eligible

CARTITUDE-2
Phase II, Multi-cohort study in various MM settings
(Cohort A at ASCO & EHA 2021)

CARTITUDE-4
Phase III, 1-3 prior lines MM

CARTITUDE-5
Phase III, Newly diagnosed, transplant not intended/eligible
CARTITUDE-1: Unprecedented responses in relapsed/refractory multiple myeloma (ASCO 2021)

- 18 months median follow up
- 97.9% ORR
  - 94.8% ≥VGPR
  - 80.4% sCR
  - 91.8% MRD $10^{-5}$ negative CR (61 evaluable patients)$^b$
- Response rates were comparable across different subgroups
  - number of prior lines of therapy refractoriness, extramedullary plasmacytomas, and cytogenetic risk)$^a$

Data cut-off: Feb 11, 2021
CR, complete response; MRD, minimal residual disease; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response. ORR assessed by independent review committee. $^a$Subgroups by number of prior lines of therapy (≤4, >4), refractoriness (triple-class, penta-drug), cytogenetic risk (high risk, standard risk), baseline bone marrow plasma cells (≤30%, >30 to <60%, ≥60%), baseline tumor BCMA expression (≥median, <median), and baseline plasmacytomas (including extramedullary and bone-based). $^b$MRD was assessed in evaluable samples (ie, patients with identifiable clone at baseline and sufficient cells for testing at 10-5 threshold in post treatment samples) by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients at Day 28, and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine.

CARTITUDE-1: Long-term clinical benefit measured by PFS (ASCO 2021)

- Median duration of follow-up of 18 months
- Lower CI indicates minimum 22.8mo PFS benefit in all patents
- Median PFS will mature with further follow-up
- No new safety signals with longer follow-up
  - CRS: All grade 94.6% (Grade ≥3, 5.2%)
  - Neurotoxicity: All Grade 20.6%(Grade ≥3, 10.3%)

Data cut-off: Feb 11, 2021; NE, not estimable; PFS, progression-free survival; OS, overall survival; sCR, stringent complete response.
Usmani S, et al. ASCO Annual Meeting (Virtual), June 4-8, 2021. Abstract 8005
Commercial Assumptions & Implications

• Indication assumption* (Patients meeting label requirements)
  - US: 5L+ Prior lines of therapy patient opportunity
    ▪ US: ~12,000
  - EU/JP: 4L+ Prior lines of therapy patient opportunity
    ▪ EU: ~6,000
    ▪ Japan: ~4,000

• Go to market model
  - 50/50 US co-promote with Janssen
  - Legend deployment will largely be hospital based

• Cilta-cel Product Positioning: Three critical dimensions
  - Clinical
  - Operational
  - Access

*Estimate includes patients eligible for lead indication; Lead indication label assumptions:
  - US label assumption of 5L+ is in-line with Abecma label
  - EU label assumption of 4L+ is in-line with Abecma approval in EU
  - JP label assumption of 4L+

Source: Kantar Health and Precision-IQ
## CARTITUDE-2: Phase II Multi-Cohort Study in Various Multiple Myeloma Settings (n ≈ 160)

<table>
<thead>
<tr>
<th>Cohort A</th>
<th>Progressive disease after 1-3 lines of MM therapy and len refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort B</td>
<td>Early relapse: ≤12 months after frontline therapy or ≤12 months after ASCT</td>
</tr>
<tr>
<td>Cohort C</td>
<td>RRMM after PI, IMiD, anti-CD38, and BCMA-targeting therapy*</td>
</tr>
<tr>
<td>Cohort D</td>
<td>&lt;CR after ASCT with or without consolidation in NDMM</td>
</tr>
<tr>
<td>Cohort E</td>
<td>NDMM, transplant not planned, with no prior therapy and high-risk per ISS stage III criteria</td>
</tr>
<tr>
<td>Cohort F</td>
<td>NDMM standard risk per ISS stage I/II NDMM, post-induction with D-VRd and other quad/triplets</td>
</tr>
</tbody>
</table>

### Screening

<table>
<thead>
<tr>
<th>Induction if applicable</th>
<th>Apheresis</th>
<th>Bridging therapy (as needed)</th>
<th>Lymphodepletion Cy/Flu</th>
<th>Cilta-cel infusion (Target: 0.75 × 10⁶ CAR+ T cells/kg)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort D DVRd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### T-cell transduction and expansion to manufacture cilta-cel

<table>
<thead>
<tr>
<th>Cohort D + Len (2 years)</th>
<th>Cohort E + Len Dara (2 years)</th>
</tr>
</thead>
</table>

---


*Excluding prior BCMA-targeting cellular therapy
CARTITUDE-2 Cohort A (n=20): 95% ORR in 1 – 3 prior lines RRMM (ASCO & EHA 2021)

• MM after 1–3 prior lines of therapy, refractory to lenalidomide
• Median prior lines of therapy was 2 (range, 1-3); 1 patient treated in an outpatient setting

• Median follow-up of 5.8 months
• 95% ORR
  • 85% had ≥ VGPR, 75% of ≥ CR
  • No progression of disease at in responding patients
  • All patients (n=4) with MRD-evaluableb samples at the 10-5 threshold were MRD negative at data cut-off

• The safety profile was manageable
  • CRS occurred in 85% (n=17); mostly grades 1/2; median time to CRS onset was 7 days (range, 5–9)
  • Neurotoxicities occurred in 20% (n=4) of patients; no grade ≥3; no incidence of movement and neurocognitive TEAEs

Data cut-off date: Jan 2021; aPatient who did not respond had stable disease. bMRD was assessed in evaluable samples (ie, patients with identifiable clone at baseline and sufficient cells for testing at 10-5 threshold in post treatment samples) by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients. CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; TEAE, treatment-emergent adverse events; VGPR, very good partial response.

CARTITUDE-4: Phase III Study in 1-3 prior line RRMM (NCT04181827)

**PRIMARY OBJECTIVE**
- To compare efficacy (PFS) of cilta-cel infusion to the standard treatments of PVd or DPd

**KEY INCLUSION CRITERIA**
- Age ≥18 with diagnosed MM
- 1–3 prior lines of therapy (PI+IMiD or PI+IMiD+CD38 exposed), and lenalidomide-refractory

**KEY EXCLUSION CRITERIA**
- Prior CAR-T or BCMA-targeting therapy

PVd: Pomalyst, Velcade, dexamethasone
DPd: Darzalex, Pomalyst, dexamethasone
CARTITUDE-4 - Study Schema

- Study start date: June 2020
- ~100 study locations, in 17 countries in North America, Europe and Asia.

PVd: Pomalyst, Velcade, dexamethasone
* Physician’s choice and dependent on prior anti-myeloma therapy.
** Conditioning regimen: cyclophosphamide/ fludarabine
Study start/locations source: clinicaltrials.gov
# Myeloma RRMM Triplet Efficacy Outcomes - Current SoC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>% Len Refractory</th>
<th>Median PFS (Months)</th>
<th>Median PFS for Len Refractory Patients (Months)</th>
<th>Median Lines of Therapy (Publication)</th>
<th>Study Name and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dvd arm (n=251)</td>
<td>17.9% (Dvd)</td>
<td>16.7</td>
<td>9.3</td>
<td>2</td>
<td>CASTOR; Spencer 2018</td>
</tr>
<tr>
<td>Pvd arm (n=281)</td>
<td>71% (Pvd)</td>
<td>11.2</td>
<td>9.5</td>
<td>2</td>
<td>OPTIMISMM; Richardson 2019</td>
</tr>
<tr>
<td>Dpd (n=103)</td>
<td>89%</td>
<td>8.8</td>
<td>NA</td>
<td>4</td>
<td>EQUULEUS; Chari 2017</td>
</tr>
</tbody>
</table>

Dvd: Darzalex, Velcade, dexamethasone  
Pvd: Pomalyst, Velcade, dexamethasone  
Dpd: Darzalex, Pomalyst, dexamethasone
CARTITUDE-4
RRMM: 1-3 PL (PI+IMiD exposed + lenalidomide refractory)

First Phase III Global BCMA CAR-T cell therapy Clinical Trial in 1-3 prior line setting

Cilta-cel indication assumption
- 1-3 prior lines of therapy
  - Does not require prior daratumumab exposure
    - ~80% of patients in 2L setting have not been daratumumab exposed
    - *Eligible patient opportunity, across US/EMEA/Japan, is ~80,000 (2-5L) patients
  - Timing: TBD

Competitive assumption
- 2-4 Prior lines of therapy
  - Requires prior daratumumab exposure
  - Timing: Q4 2022 - 1H 2023

*Data Source: Kantar Health and Precision-IQ
CARTITUDE-5: Phase III Study in newly diagnosed MM, not intended for transplant (NCT04923893)

**PRIMARY OBJECTIVE**
- To compare efficacy of VRd followed by cilia-cel vs VRd followed by Rd therapy

**KEY INCLUSION CRITERIA**
- Newly diagnosed multiple myeloma
- Not considered candidate for high-dose chemotherapy with ASCT due to advanced age or presence of comorbid condition(s) or defer high-dose chemotherapy with ASCT as initial treatment

**KEY EXCLUSION CRITERIA**
- Frailty index of ≥2 according to Myeloma Geriatric Assessment
- Prior CAR-T or BCMA-targeting therapy
- Any prior therapy for multiple myeloma or smoldering myeloma

VRd: Darzalex, Revlimid, dexamethasone
Rd: Revlimid, dexamethasone
ASCT: autologous stem cell transplant
**Study start date:** August 2021  
**~118 study locations**

- Participants who received 1 cycle of VRd therapy prior screening, will only receive 5 cycles of VRd.  
- Conditioning regimen: cyclophosphamide/ fludarabine  
Study start/locations source: clinictrials.gov
## VRd Regimen in Newly Diagnosed Multiple Myeloma - Current SoC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>PFS for VRd</th>
<th>Study Name and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd arm (n=242)</td>
<td>43 months</td>
<td>SWOG S0777; Durie 2017</td>
</tr>
<tr>
<td>VRd arm (n=350)</td>
<td>36 months</td>
<td>IFM/DFCI2009; Attal 2017</td>
</tr>
</tbody>
</table>

VRd: Darzalex, Revlimid, dexamethasone
**CARTITUDE-5**

**Frontline: Transplant not intended (TNI)**

*First* Phase 3 Global BCMA CAR-T cell therapy Clinical Trial in Frontline Setting

**Commercial Assumptions/Implications**

- Cilta-cel indication assumption
  - 64,000 newly diagnosed patients across US/EU/Japan
  - *Transplant not intended eligible patient populations*
    - 50% US: ~17,000
    - 40% EU: ~9,000
    - 25% Japan: ~1,600
  - Indication represents significant downstream cost avoidance opportunities

*Transplant not intended (TNI) = clinically transplant ineligible + clinically transplant eligible but deferred
Data Source: Kantar Health and Precision-IQ
## Clinical Program - Cilta-cel Studies in Multiple Myeloma

### Late Line Studies of Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTITUDE-1¹</td>
<td>Phase II, multi-center registrational study of cilta-cel in RRMM</td>
</tr>
<tr>
<td>CARTITUDE-2³</td>
<td>Fully enrolled and ongoing in US and Japan</td>
</tr>
<tr>
<td>CARTIFAN-1²</td>
<td>Phase II, multi-center registrational, confirmatory study of cilta-cel in RRMM</td>
</tr>
<tr>
<td></td>
<td>Ongoing in China</td>
</tr>
</tbody>
</table>

### Earlier Lines of Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTITUDE-2³</td>
<td>Global, multi-cohort study</td>
</tr>
<tr>
<td>CARTITUDE-4⁴</td>
<td>Phase II open-label study of cilta-cel in various clinical settings to evaluate MRD negativity</td>
</tr>
<tr>
<td>CARTITUDE-5⁵</td>
<td>Enrolling in US/EU/Israel</td>
</tr>
</tbody>
</table>

### Notes

- ASCT, autologous stem cell transplant; DPd, daratumumab, pomalidomide, dexamethasone; EU, European Union; JP, Japan; PVd, pomalidomide, bortezomib, dexamethasone; RRMM, relapsed and/or refractory multiple myeloma; SoC, standard of care; US, United States; VRd, bortezomib, lenalidomide, dexamethasone
- CARTITUDE-1 is global registrational study; CARTITUDE-2 is global registrational study for China only; CARTITUDE-4 is global registrational study for China only; CARTITUDE-5 is global registrational study.
- CARTITUDE-1 is registrational study for China only; CARTITUDE-4 is registrational study for China only; CARTITUDE-5 is global registrational study.
- CARTITUDE-1¹ is global registrational study; CARTITUDE-2³ is global registrational study; CARTITUDE-4⁴ is global registrational study; CARTITUDE-5⁵ is global registrational study.
Conclusion: Global BCMA Program

- Cilta-cel has demonstrated potential best-in-class efficacy in CARTITUDE-1 study in RRMM
- Preliminary data from CARTITUDE-2 shows early promise for cilta-cel in early line MM
- CARTITUDE-4 is enrolling well and positions cilta-cel well in 2+ line MM
- CARTITUDE-5 is the first pivotal global Phase III trial for a BCMA targeting CAR-T in 1st line MM

Potential best-in-class efficacy
Coffee Break

The presentation will resume in 10 minutes
In Fierce Pursuit of Novel Therapies

Frank Fan, M.D., Ph.D.
Chief Scientific Officer
Overview
- Introduction of R&D culture
- Ab discovery expertise
- Diverse technology platforms

Solid Tumors
- Gastric cancer & Pancreatic cancer
- HCC and NSCLC
- SCLC

Allogeneic Platforms
- Unique non-genome editing allogeneic CAR-T platform
- Legend CAR-NK platform
The Strengths of Our R&D Program

CORE TECHNOLOGIES
• Outstanding CAR target identification expertise
• High-throughput antibody screening and engineering capability
• Proprietary multi-specific CAR-T platform
• A series of innovative CAR enhancing strategies
• Unique non-genome editing allogeneic CAR-T platform
• Robust LGkine energized CAR-NK platform
• Legend armored CAR-γδ-T platform
• TCR-T

HIGHLIGHTS FROM OUR PIPELINE
• Highly selective Claudin 18.2 targeting CAR for gastric and pancreatic cancers
• Armored GPC-3 CAR targeting HCC, NSCLC, etc.
• Novel CAR targeting DLL-3 for SCLC
• Allogeneic CAR products for BCMA
• CAR-NK designed to further antitumor efficacy
Legend NGS and Bioinformatics Capabilities

NGS Platform

- In-house 10X Genomics single cell sequencing platform
- In-house HPC and AWS cloud computation
- Sophisticated NGS and bioinformatician teams

Bioinformatics Platform

- TME Analysis
  - TME cell type analysis
  - Guide armor strategy
- Drug Product Characterization
  - Phenotype
  - Gene expression profile
- Clinical Study
  - Cell dynamical change
  - Bio-marker & MOA study

Support pre-clinical R&D, processing development and clinical study
Multiple Antibody Development Platforms

- Llama or mouse
- Target screening
- mAb development, screening
  Sequencing and humanization
- In vitro pharmacology
- In vivo pharmacology
- Safety assessment of CAR-T

- Immunization
- sdAb library
- Lead sdAb sequence
- CAR-T screening and optimization
- In vitro in vivo pharmacology
• Improved CAR expression and stability
• Easier access to novel and hidden epitopes, which specifically facilitates the design of membrane proximal binders
• Robust engineering flexibility for the design of complex multi-specific CAR
Challenges in Treating Solid Tumor by T-cell Therapy

Mackall et al., Nature Biomedical Engineering, 2018
Optimized CAR design by Legend CAR screening platform (Linker, Hinge, TM domain, CAR ICD)

High affinity
- High specificity
- Superior efficacy over benchmarks

Conditional armor activation
Armor does not alter tumor specificity

Reducing COGS

Complementary Suite of Technologies

Selected binder
Optimized CAR design
CAR-driven armor strategy
Overcome TME suppression
Smart manufacture process

Enhanced CAR-T expansion
- Expansion within TME
- Resistance to exhaustion
- Improved persistence

Technologies for Conquering Solid Cancers
Modification of intracellular molecules in CAR-T cells could resist inhibitory signal from cell surface and increase their persistence and activity in tumor microenvironment.

Our intracellular modulator KO CAR-T cells showed a more energetic and younger phenotype.
Capability Summary of the Legend R&D Team

- Skilled professionals established a dedicated biomarker platform
- Extensively experienced team on customized PD for individual program
- Multi-specific VHH-based CAR technology
  Competitive IP portfolio
- Professional IP team
  Highly motivated RA and PM groups
- Broad suite of technologies
  CAR-T, TCR-T, allogeneic CAR-T/NK, γδ- T
- Talented analytic development teams
- Large candidate profile
  Faster-than-fast screening capability
Solid Tumors: LB1908
LB1908: CLDN18.2 CAR-T

For gastric cancer and pancreatic cancer

**TARGET**

- Claudin (CLDN) are a family of tight junction proteins
- CLDN18.2 is commonly expressed on multiple cancers including gastric cancer and pancreatic cancer
- CLDN18.2 is highly conservative cross species, extracellular domain 1 are identical between human and mouse

**MOA/SCIENTIFIC RATIONALE**

- LB1908 targets CLDN 18.2 through a high-affinity VHH antibody identified in-house
- The VHH antibody binds to CLDN 18.2 only, but not to the closely related CLDN 18.1
- Balance of safety and efficacy was fine-tuned in a relevant murine toxicology model

**CLINICAL DEVELOPMENT STRATEGY**

- IIT clinical study in China is ongoing for the treatment of adult patients with advanced gastric cancer
- Promising early sign of safety and efficacy supports expansion to multi-center trials and endorses dose escalation above 3 million/kg
- US IND is being developed with planned submission in 1H2022

---

Claudin18.2 Expression is Gastric Tissue-restricted

Homology between CLDN18.2 and CLDN18.1

85% AA Identity

100% AA Identity

Claudin18.2 protein expression in pit region and the base of gastric glands

https://www.proteinatlas.org/ENSG00000066405-CLDN18/tissue/lung#img

*Clin Cancer Res 2008;14(23) December 1, 2008

Moderate Claudin 18.1 expressed in human lung tissue (Alveolar cells)
### Claudin18.2 Protein is Widely Expressed in GC and PDAC

#### Presence of Claudin18.2 protein in human cancer tissues (66 tissue IHC, EU)

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Any Labeling</th>
<th>≥2+ in ≥60% Cells</th>
<th>Significant Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>51/66 (77%)</td>
<td>37/66 (56%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>15/20 (75%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal</td>
<td>21/45 (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus AC</td>
<td>17/22 (78%)</td>
<td>11/22 (50%)</td>
<td></td>
</tr>
<tr>
<td>Esophagus SCC</td>
<td>0/7</td>
<td>0/7</td>
<td></td>
</tr>
<tr>
<td>PDAC</td>
<td>8/10 (80%)</td>
<td>6/10 (60%)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic islet cell carcinoma</td>
<td>0/5</td>
<td>0/5</td>
<td></td>
</tr>
</tbody>
</table>

#### Claudin 18.2 expression in gastric tumor and LN metastases (262 cases IHC, Japan)

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Any Labeling</th>
<th>≥2+ in ≥60% Cells</th>
<th>Significant Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>228/262 (87.0%)</td>
<td>135/262 (51.5%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>119/134 (88.8%)</td>
<td>77/134 (57.5%)</td>
<td></td>
</tr>
<tr>
<td>Intestinal</td>
<td>47/59 (79.7%)</td>
<td>23/59 (39%)</td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td>6/7 (85.7%)</td>
<td>1/7 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7/10 (70%)</td>
<td>3/10 (30%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>49/52 (94.2%)</td>
<td>31/52 (59.6%)</td>
<td></td>
</tr>
</tbody>
</table>

#### Metastases

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC, LN metastasis</td>
<td>15/29 (51%)</td>
</tr>
<tr>
<td>GC, ovarian metastasis</td>
<td>23/33 (69%)</td>
</tr>
<tr>
<td>Colorectal cancer, ov metastasis</td>
<td>0/28</td>
</tr>
<tr>
<td>Unknown primary, ov metastasis</td>
<td>6/12 (50%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AC, adenocarcinoma; SCC, squamous cell carcinoma; LN, lymph node.

Source: CLIN CANCER RES 2008;14(23) DECEMBER 1, 2008

Source: Japanese Journal of Clinical Oncology, 2019, 1–7

---

**CLDN18.2 expression in matched pairs of primary tumors and corresponding LN metastases.**

X-axis: CLDN18.2+% tumor cells in the primary tumor;

Y-axis: CLDN18.2+% tumor cells corresponding LN metastasis

Japanese Journal of Clinical Oncology, 2019, 1–7
LB1908 Modality and Features

- LB1908 (LCAR-C18S) consists of autologous T cells genetically modified to express a CAR utilizing a lentiviral vector.
- Preclinical studies demonstrate a target-specific profile of efficacy as well as safety.

- Highly specific VHH characterized by human frozen tissue array by IHC, restricted to gastric tissues.
- Highly specific to Claudin18.2; no off-target binding to Claudin18.1.
- Superior CAR-T anti-GC and anti-PDAC potency in vivo over benchmarks.

LB1908 VHH Binding Patterns and Performance

- High specificity is the premise and cornerstone of developing a safe, live drug targeting CLDN18.2
- LB1908 VHH strongly and specifically binds to CLDN18.2, but not to CLDN18.1
LB1908 CAR-T Showed Cytotoxicity Only to Claudin18.2

- Toxicity was not shown to Claudin18.1+cells or a set of human primary cells

CLDN18.1\textsuperscript{high}/CLDN18.2\textsuperscript{neg} Pancreatic cancer cell line PANC1-hu18.1

CLDN18.1\textsuperscript{neg}/CLDN18.2\textsuperscript{high} Pancreatic cancer cell line PANC1-hu18.2

Human Normal Primary Pulmonary Artery Endothelial Cells; HPAEC(ATCC® PCS-100-022™)

Human Normal Primary Lung Fibroblast HLF(ATCC® PCS-201-013™)

Human Normal Primary Pulmonary Artery Smooth Muscle Cells; PASMC(ATCC® PCS-100-023™)

Representative data from the Incucyte® Live-Cell Analysis System;
Red dye labeling target cells by IncuCyte CytoLight Rapid Red Reagent
Green dye labeled by IncuCyte® Caspase-3/7 Green Apoptosis Reagent
PC019 (CD19 targeting CAR-T, assay control)
LB1908: Anti-tumor Efficacy in Gastric Tumor CDX Model

Model:
NCG mouse (NOD-Prkdc<sup>em26Cd52</sup>Il2rg<sup>em26Cd22</sup>/NjuCrl)

Tumor engraftment:
Subcutaneous CDX xenograft (human GC cell line NUGC4, CLDN18.2+)

For LB1908 (C18S): tumor free can achieved in 75% 1M group and all 3M/5M; for benchmark 1: No tumor free at 5M but tumor relapsed.
LB1908: Anti-tumor Efficacy in PDAC CDX Model

Model:
NCG mouse (NOD-Prkdc<sup>em26Cd52</sup>Il2rg<sup>em26Cd22</sup>/NjuCrl)

Tumor engraftment:
Subcutaneous CDX xenograft (human PC cell line AsPC1.CLDN18.2)

Tumor volume monitoring
Animal bodyweight monitoring
In vivo CAR expansion monitoring

For LB1908 (C18S): tumor free can achieved in 100% at 3M; for benchmark 2: all mice died within 10 days.
Human Tissue Cross-reactivity with LB1908 Antibody

**Tissue IHC:** 30 different normal human tissues from 3 individuals.

- **Tissue list**
  - Adrenal
  - Bone Marrow
  - Breast
  - Cerebrum
  - Cerebellum
  - Pituitary
  - Colon
  - Artery
  - Esophagus
  - Fallopian Tube
  - Heart
  - Kidney
  - Liver
  - Lung
  - Lymph Node
  - Ovary
  - Pancreas
  - Placenta
  - Prostate
  - Skin
  - Spinal Cord
  - Spleen
  - Striated muscle
  - Stomach
  - Testis
  - Thymus
  - Thyroid
  - Ureter
  - Uterus
  - Cervix

LB1908 antibody: Strong specific membrane staining in gastric mucosal epithelial cells

Isotype Control: lack of IHC staining

*Cell membrane staining restricted to gastric mucosal epithelial cells.*
LB1908 Investigator Initiated Clinical Trial
A Clinical Study to Evaluate CAR-T Cell-based Medicinal Product in the Treatment of Advanced Gastric Cancer

Key Inclusion and Exclusion Criteria

Inclusion:
Aged 18-75 years; Claudin18.2 positive recurrent or metastatic advanced G/GEJAC; previous total gastrectomy/subtotal gastrectomy, and adequate standard of care recommended by NCCN 2019 V3 or the CSCO 2019; documented disease progression after most recent therapy; ECOG 0-1; Expected survival ≥ 3 months

Exclusion:
Prior CAR-T or Claudin18.2-targeted treatment; treatment for certain other malignancies or recent antitumor therapy; Presence of local recurrence of gastric lesions; Brain metastases with central nervous system symptoms; Gastric perforation, pyloric obstruction et al (all details please refer to Clinicaltrial.gov)

STUDY DESIGN

Screening (28 days) → Apheresis → Bridging therapy → Day -7 to -5: Start 3-day conditioning regimen cy & flu → Day 1: LCAR-C18S infusion → Follow-up and assessment

T-cell transduction and expansion to manufacture LCAR-C18S

Site: Shanghai East Hospital
Principal Investigator: Jin Li, MD, PhD
Actual Study Start Date: September 21, 2020
Estimated Primary Completion Date: November 2022

Abbreviations: Dose-limiting toxicity (DLT); treatment-emergent adverse events (TEAEs); Maximum tolerated dose (MTD) and recommended Phase II dose (RP2D); Overall response rate (ORR); Duration of remission (DOR); Progress Free Survival (PFS); Overall Survival (OS); Disease control rate (DCR); Time to Response (TTR); pharmacokinetics (PK); anti-drug antibody (ADA).
Study Design and Status

- A Phase I, Open-Label Study Evaluating the Safety, Tolerability and Efficacy of LB1908, a CAR-T Cell Therapy targeting Claudin18.2 in Patients With Advanced Gastric Cancer

- Study Objectives: the **safety, tolerability, PK profile, efficacy** of LB1908 in advanced GC

- Study Status: 4 subjects dosed, last subject dosed with 3.0M*/kg CAR+ viable T cells. 3 subjects completed DLT observation and no DLT observed

*M = 1×10^6

**Interim Analysis : 30 days after the last patient of dose escalation receiving LB1908
**Case Report**

- First dosed subject, Female/41, Gastric Adenocarcinoma, HER-2 (-), Claudin18.2 IHC (>75%,+++)
  - Sep 2017: radical gastrectomy
  - From Nov 2019 to Jul 2020: received 5 prior lines systemic treatment for recurrent disease

**RESULTS**

- No DLT or SAE
- Efficacy assessment on Day 180 is continuous **SD**, with **large pelvic tumor** as target lesions achieved ~15% regression, the ascites and pelvic effusion as non-target lesions achieved significant decrease
- CAR-T expansion was detected from Day 2 and not detectable since Day 92
- Continue long term follow-up

*CMR = complete metabolic response*
## CASE REPORT

Single injection at the lowest dose level (0.5 million/kg)

<table>
<thead>
<tr>
<th></th>
<th>Baseline (2021-03-04) (mm)</th>
<th>Day 45 (2021-04-28) (mm)</th>
<th>Day 90 (2021-06-16) (mm)</th>
<th>Day 180 (2021-09-09) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Pelvic Lesion</td>
<td>132.7</td>
<td>119.4</td>
<td>113.08</td>
<td>118.8</td>
</tr>
<tr>
<td>2. Pelvic Lesion</td>
<td>128.1</td>
<td>109.7</td>
<td>107.2</td>
<td>105.0</td>
</tr>
<tr>
<td>SOD</td>
<td>260.8</td>
<td>229.1 (-12.15%)</td>
<td>221.1 (-15.22%)</td>
<td>223.8 (-14.19%)</td>
</tr>
<tr>
<td><strong>Non-Target Lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Ascites</td>
<td>Large amount</td>
<td>Significantly decreased</td>
<td>Exist, same as last visit</td>
<td>Exist, same as last visit</td>
</tr>
<tr>
<td>2. Pelvic effusion</td>
<td>Large amount</td>
<td>Significantly decreased</td>
<td>Exist, same as last visit</td>
<td>Exist, same as last visit</td>
</tr>
<tr>
<td><strong>New Lesions</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Prior CAR-T injection**
- Huge pelvic lesion
- Acute upper tract obstruction
- Acute renal injury needs bilateral pyelostomy
- Large amount of ascites need abdominal drainage

**Post CAR-T injection**
- Reduction of lesion
- Resume urination
- Removal of pyelostomy catheters
- Removal of abdominal drainage
Case Report: PK Profile

- CAR-T cells and CAR copies were detected from Day 2 and thereafter, with $C_{\text{max}}$ on Day 12.
- CAR-T cell returned to low level on Day 45 and kept at low level on Day 58.
Conclusion: LB1908

- Claudin 18.2 is a very promising target for gastric cancer and pancreatic cancer
- Claudin 18.2 is also a very challenging target for developing a safe but efficacious CAR-T product
- LB1908 has demonstrated anti-tumor efficacy using both in vitro and in vivo models
- In a currently ongoing IIT, anti-tumor activities were observed in the first dosed GC patient; dose escalation has now reached 3.0 million cells per kg
- Encouraging safety signals have allowed us to expand the IIT to multi-center trials, with 3 additional sites
- The US IND preparation for LB1908 is currently in progress
Solid Tumors:
LB2101
LB2101: The Armored CAR-T Targeting GPC-3

TARGET
- GPC3 is a promising target with highly specific over-expression in solid tumors
- Significantly upregulated in liver cancer (76%), lung SCC (52%), germ-cell cancers (44-100%) et al.¹

MOA/ SCIENTIFIC RATIONALE
- In house developed humanized scFv with high affinity and specificity to GPC3
- Innovative armor platform: Utilize immunosuppressive signal in TME to augment CAR-T potency
- Optimized CAR design outperforms benchmarks in vivo

CLINICAL DEVELOPMENT STRATEGY
- Plans to pursue an IND in China and follow with phase I studies in other markets
- Plans to earn proof-of-concept data from HCC and expand to additional indications

GPC3=Glypican 3; HCC=hepatocellular carcinoma; SCC=squamous cell cancer; TME=tumor microenvironment
¹Am J Pathol. 2018 Sep;188(9):1973-1981
GPC3: A Well-Validated Target for Multiple Cancer Indications

- GPC3, an oncofetal protein, is absent in normal vital tissues.
- GPC3 has been found to be significantly upregulated in Liver Cancer (76%), Lung SCC (52%), Germ-cell Cancers (44-100%) et al\(^1\).

### Indications

<table>
<thead>
<tr>
<th>Indications</th>
<th>%GPC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Cancer</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>76%</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>100%</td>
</tr>
<tr>
<td>Lung cancer</td>
<td></td>
</tr>
<tr>
<td>SCC (NSCLC)</td>
<td>52%</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td></td>
</tr>
<tr>
<td>Extragonadal YST</td>
<td>100%</td>
</tr>
<tr>
<td>Germ cell tumors NOS</td>
<td>44%</td>
</tr>
<tr>
<td>Nondysgerminomas</td>
<td>100%</td>
</tr>
<tr>
<td>Nonseminomas</td>
<td>52%</td>
</tr>
<tr>
<td>Esophageal Cancer</td>
<td></td>
</tr>
<tr>
<td>Esophageal SCC</td>
<td>27%</td>
</tr>
<tr>
<td>CNS tumors</td>
<td></td>
</tr>
<tr>
<td>Atypical teratoid rhabdoid tumor</td>
<td>77%</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>67%</td>
</tr>
<tr>
<td>Medullary</td>
<td>40%</td>
</tr>
<tr>
<td>Wilms Tumor</td>
<td>38%</td>
</tr>
</tbody>
</table>

\(^1\) Am J Pathol. 2018 Sep;188(9):1973-1981

GPC3 in Hepatoblastoma\(^2\). A (H&E) and B (IHC)
Design of GPC3-CAR (H93) Using scFv as a Binder

- Humanized single chain antibody fragment (scFv)
- Targeting C-terminus of GPC3, unaffected by shedding of N-terminus of GPC3
- High affinity to human GPC3: 73 ± 8.7 pM (SPR)
- No off-target binding in normal human tissues (TMA)
- Superior in vivo anti-tumor efficacy over benchmarks
Legend’s approach focuses on modifying CAR-T cells to improve intrinsic T-cell functionality in the solid tumor microenvironment.

Legend's Innovative Armor Platform

Utilize TME signals to augment CAR-T functions

LB2101 components:

- **CAR**: humanized scFv with optimized CAR design to target and eliminate cancer cells
- Innovative armoring strategy, with the objective of overcoming TME immunosuppression
  - Membrane bound protein with restricted functions in CAR-T cells
  - Conditional activation: Armor is activated by CAR signal and TME signal, thus will not alter CAR-T specificity to GPC3
  - Improved CAR-T infiltration into tumor
  - Enhanced expansion and persistence with improved anti-tumor efficacy
The Armoring Strategy for LB2101 Markedly Improves CAR-T Functions

- **Conditional armor activation**: Improved LB2101 (H93T) expansion in the presence of GPC3 and the TME signal only
- **Potency**: LB2101 showed tumor-free efficacy **at a very low dose**
- **Improved CAR-T expansion** of H93T (LB2101) in vivo compared with un-armored H93
- No observed bodyweight loss or other in vivo toxicity
Conclusion: LB2101

• LB2101 is a novel investigational CAR-T therapy for the treatment of HCC and SCLC by specifically targeting GPC3
• LB2101 shows superior suppression of tumor growth compared to the benchmark-based CAR-T in the HCC model
• Legend’s innovative armoring strategy improves CAR-T persistence and overcomes immunosuppressive TME in a non-clinical model
• The first-in-human study is being planned for HCC and the indication may be expanded to other cancers in the future
• Further development of allogeneic approaches for LB2101 are also in progress
Solid Tumors:
LB2102
**LB2102: Legend Armored CAR-T Targeting DLL-3**

**TARGET**
- DLL-3, a promising target with prevalent and homogeneous expression in SCLC (~80% positive) and other neuroendocrine tumors
- Minimal to no expression in normal tissues
- SCLC --- market size: 15% of all lung cancers, ~270,000 new cases globally per year
- SCLC --- unmet medical needs: median OS with extensive stage SCLC <10 mo, 5-yr OS ~3%

**MOA/SCIENTIFIC RATIONALE**
- Tandem humanized sdAb-derived binders with high DLL3 binding affinity and specificity
- Superior efficacy in SCLC animal models in comparison to selected benchmarks
- An armor overcoming hostile microenvironment to boost the *in vivo* anti-tumor efficacy with increased proliferation and infiltration of CAR-T cells in tumors

**SAFETY & CLINICAL DEVELOPMENT STRATEGY**
- Well-tolerated *in vivo* in s.c and pulmonary orthotopic xenograft models
- Development of US IND is in preparation
Delta-like Ligand 3 (DLL3) is an Emerging Target for SCLC

**DLL3 in SCLC tumors**
- Highly and homogeneously expressed
- Both on plasma membrane and in cytoplasm

**DLL3 in normal tissues**
- Minimal to no expression
- Exclusive in cytoplasm

**DLL3 protein expression by IHC**
- (A) NSCLC
- (B) LCNEC
- (C) Naïve SCLC
- (D) Recurrent/refractory SCLC

**DLL3 expression in SCLC-A/N subtypes**
- ASCL1 dominant: 110 (69%)
- NEUROD1 dominant: 27 (17%)
- Double negative: 22 (14%)

Source: Saunders, Sci Transl Med, 2015

Baine, J Thorac Oncol, 2020
LB2102: DLL3-targeting CAR-T Cell for SCLC

- Similar to the design of cilta-cel, **two VHH binding domains targeting** DLL3 were coupled to deliver activation signal to CAR-T cells.
- An armor is integrated alongside the CAR to overcome the immunosuppressive tumor microenvironment.
- Preclinical pharmacology and toxicology demonstrated superior anti-tumor activity with minimized potential safety concerns.
In Vitro Pharmacology of LB2102

- Legend proprietary biparatopic targeting strategy significantly enhanced CAR-T persistence.
- Persistence of armored CAR-T cells was significantly prolonged during repetitive challenges with target cells.
- The armor resisted the inhibition of cytokine production and T cell exhaustion under tumor microenvironment-mimicking conditions.
In Vivo Pharmacology of LB2102

- The armored CAR-T showed significantly superior tumor inhibition, when compared to conventional CAR-T, along with higher peripheral blood CAR-T proliferation and more prominent CAR-T infiltration in the tumors.
In Vivo Safety Study of LB2102

• A **high dose** of CAR-T cells was well tolerated in SHP-77 s.c. tumor-bearing mice;

• A **high dose** of CAR-T cells was well tolerated as of Day 28 post-infusion in a SHP-77-luc-derived pulmonary orthotopic SCLC model in NCG mice, mimicking tumor burden in the lung.
Conclusion: LB2102

- DLL3 is a promising target expressed in SCLC but barely in normal tissues.
- Leveraging a biparatopic tandem VHH sdAb-design and TME-resistant armor strategy, LB2102 has demonstrated potent cytotoxicity, improved proliferation, persistence and tumor infiltration, and these led to efficient in vivo tumor growth inhibition.
- Well-tolerated in tumor-bearing animal models.
Allogeneic Platforms:
Non-Gene Editing LUCAR Platform
“Mainstream” Allogeneic CAR-T Approach

Gene editing
- ZNF
- TALEN
- CRISPR-Cas9

Knockout strategy
- TCRα KO to avoid GvHD
- B2M KO to evade HvG
- CD52 KO to increase persistence

Advantages
- Availability of diverse gene-editing tools
- Permanent gene KO

Disadvantages
- Off-target concerns
- Chromosomal aberration/translocation
- 2-steps: LV transduction of CAR + gene KO
- IP issues
Legend’s Unique Non-gene-editing Allogeneic Platform

Auto-CART

TCRα/TCRβ heterodimer (functional TCR complex)

Gene-editing Allo-CART

No TCRα/TCRβ heterodimer (no functional TCR complex)

Legend Biotech Allo-CART

No TCRα/TCRβ heterodimer (no functional TCR complex)
"Autologous-like" CMC process for highly homogeneous LUCART cells.
Safety: Disruption of the TCR Complex and Its Function

Phenotype of LUCAR-20S

- TCRαβ negative cells >97% in final product

Mixed Lymphocyte Reaction (MLR)

- Lack of activation by LUCAR-20S signifying GvHD free potential

**Only 2 phenotypes**

- TCRαβneg+CARpos >97% % in DP
- TCRαβpos+CARneg
Allogeneic LUCAR-20S CAR-T Against CD20

TARGET
• CD20 is a cell surface protein on B cells with role in development and differentiation into plasma cells
• Expressed in majority of mature B-cell neoplasms, including plasma cell myelomas, B-lymphoblastic neoplasms, Hodgkin lymphomas, T-cell neoplasms, and AMLs

MOA/SCIENTIFIC RATIONALE
• Novel non-gene-editing allogeneic platform to target CD20
• Co-express Gene X to disrupt T-cell receptor for inhibiting GvHD (basic version: LUCAR-20S)
• Innovative armoring strategies to control HvG and promote persistence (full version: LUCAR-20SD)

CLINICAL DEVELOPMENT STRATEGY
• Limited cell expansion and efficacy were obtained from exploratory IIT of LUCAR-20S, a basic version which only implemented anti-GvHD solution
• Preliminary clinical data indicated promising safety profile in preventing GvHD
• Exploratory IIT trial is planned to obtain proof-of-concept data for full version LUCAR-20SD, in which anti-rejection (HvG) armoring strategies are also implemented

Main Challenges of Allogeneic CAR-T Platform

**Graft-versus-host Disease (GvHD)**

- Necessitates design to prevent GvHD and resist HvG at the same time.

**Host-versus-graft cells (HvG)**

- (https://www.nhl-info.de/)

Necessitates design to prevent GvHD and resist HvG at the same time.
Proof-of-concept Clinical Studies by Exploratory IIT

CAR (CD20 scFv) → Targets Antigen → Efficacy
Gene X → Prevents GvHD → Safety
Study Design of LUCAR-20S

• An open label, single arm, Phase I study to evaluate the safety, tolerability, and pharmacokinetics of LUCAR-20S CAR-T cells in patients with relapsed or refractory CD20+ non-Hodgkin lymphoma

• Study Objectives: the safety, tolerability, PK profile, efficacy of LUCAR-20S in r/r NHL

• Study Status: 5 subjects dosed, last subject dosed with 300M* CAR+ viable T cells. 3 (60%) subjects achieved partial response(PR) and no DLT was observed

\[ M = 1 \times 10^6 \]

**Interim Analysis**: 30 days after the last patient of dose escalation receiving LUCAR-20S

Site A: Hematological Department, People's Hospital of Jiangsu Province

Site B: Oncology Department, The First Affiliated Hospital of USTC west district
Case Report: LUCAR-20S

- Female/50, Follicular Lymphoma, Grade 3A, CD20 (+)
  - Diagnosed on Feb 2018
  - 4 prior lines of therapy, including anti-CD20 monoclonal antibody (Rituximab)

**RESULTS**

- No GvHD, no SAE, no DLT.
- Efficacy assessment on Day 30 is PR, with all target and non-target lesions regressing to normal or absent on CT, and CMR* on PET-CT, but remaining positive on BM biopsy.
- Continued follow-up is needed

---

*CMR = complete metabolic response*
LUCAR-20SD Will Be Studied in Exploratory IIT

- CAR (CD20 scFv) Targets Antigen ➔ Efficacy
- Gene X Prevents GvHD ➔ Safety
- Gene Y Controls HvG with Drug Y ➔ Persistence
Safety: GvHD Assessment in Murine Model

Absence of GvHD response suggesting efficient downregulation of TCR

<table>
<thead>
<tr>
<th>Days after infusion</th>
<th>GvHD Score</th>
<th>Body Weight</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>UnT</td>
<td>LCAR-20S</td>
<td>LUCAR-20SD</td>
</tr>
<tr>
<td>7</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S TCRα KO</td>
<td>UnT</td>
</tr>
<tr>
<td>14</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S</td>
</tr>
<tr>
<td>21</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S</td>
</tr>
<tr>
<td>28</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S</td>
</tr>
<tr>
<td>35</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S TCRα KO</td>
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</tr>
<tr>
<td>42</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S TCRα KO</td>
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<tr>
<td>48</td>
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<td>LCAR-20S TCRα KO</td>
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</tr>
<tr>
<td>60</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S TCRα KO</td>
<td>LCAR-20S</td>
</tr>
</tbody>
</table>

LCAR-20S Conventional CAR (Autologous)
LUCAR-20SD Legend full version allogeneic CAR
Resistance of LUCAR-20SD to HvG

Host cells and graft LUCAR-20SD cells in the MLR co-culture system

Drug Y facilitates resistance of LUCAR-20SD to HvG by host cells
Conclusion: LUCAR Platform

• A proprietary non-gene-editing allogeneic CAR-T platform that avoids multiple gene editing and their inherited risks of off-target effects or genotoxicity

• All-in-One vector design for single step modification
  - High homogeneity in drug product to ensure stability and safety
  - Simple and efficient CMC for high yields and low COGS

• Solutions for both GvHD and HvG
  - Preliminary clinical data supports that the non-gene-editing platform successfully manages GvHD in humans

• The full version LUCAR-20SD, which incorporates an anti-HvG function, will be studied in a clinical trial
Allogeneic Platforms:
CAR-NK with LGkine Armoring
Unique Features of CAR-NK Immunotherapy

- NK cells are rapid and efficient killers of tumor cells
- CAR-NK provides a promising solution to overcome TAA escape through recognition of tumor cells by multiple mechanisms
- CAR-dependent killing
- CAR-independent killing (e.g. NKG2D, NCRs, etc.)
- Antibody-mediated ADCC
- Flexible combination with therapeutic antibody drugs
- Clinical benefits and excellent safety profiles have been documented in multiple trials

Challenges of Allogeneic CAR-NK Therapy

- Short persistence
- Feeder cell-based NK expansion processes
- Low transduction efficiency
- Fragility after cryopreservation

- Long term anti-tumor activity by LGkine armoring
- Feeder cell-free expansion process
- >500 doses/batch
- Robust transduction efficiency
- Cryopreserved product maintains viability and functionality
Key Features of CAR-NK Product

- High purity
- High transduction efficiency
- Robust feeder cell-free expansion process
- Strong in vitro anti-tumor efficacy
- Cryopreserved product maintains viability and functionality
Feeder-Free Cord-Blood NK Platform

- Scalable feeder free expansion, potentially providing >500 doses/donor
- High purity: >90% NK cells, <1% T cell contamination
- Robust CAR transduction

~15,000 fold expansion

>60% CAR+ NK cells

>90% purity

% Cytotoxicity

E/T Ratio

CD56

CD3
Rationally Designed LGkine Can Achieve a Balance between Efficacy and Safety

- Long-term anti-tumor activity and extended animal survival were observed in animals treated with LGkine-armored CAR-NK cells
Highlights of Legend’s CAR-NK Product

**EXPANSION**
- Feeder cell free expansion process
- High transduction efficiency
- >1000 doses per batch manufacture

**PERSISTENCE**
- Long-term anti-tumor efficacy
- Strong IP position

**TUMOR TARGETING**
- Optimized CAR structure for NK cells
- Enhanced CAR independent tumor killing mechanisms

**CRYOPRESERVATION**
- Minimal loss of viability after thaw
- Strong anti-tumor efficacy by frozen product
Global R&D Strategy

Institutional R&D Model that accelerates Cell Therapy Discovery and Development

>300 employees
One of the largest global cell therapy R&D teams

Potential best-in-class proprietary technology platforms

Global innovation development
US, China, Europe

Strong intellectual property position

**CORE TECHNOLOGY**

- CAR-T
- TCR-T
- NK
- γδ - T

**PRODUCT PLATFORM**

- Autologous
- Allogeneic

**DISEASE AREAS**

- Hematologic malignancy
- Solid tumor
- Autoimmune
- Infectious Disease

**CLINICAL PLAN**

Multiple Phase I programs in China

Multiple clinical programs in US
Q&A

Questions can be submitted by chat or by card
THANK YOU