Transforming Patients’ Lives with Cellular Immunotherapy

Presentation to
Jefferies Healthcare Conference

June 2015
## Technology

- **T cell immunotherapy**
  - Clinically proven
  - Platform for addressing a range of diseases

## Therapeutic Areas

- **Oncology**
  - CMD-003 for EBV lymphoma in Phase II

- **Immune reconstitution**
  - Cytovir CMV market launch 2015 / 2016
  - Cytovir ADV in Phase I / II

## Integrated International Model

- Development, manufacturing, marketing
  - 46 specialists in London, Berlin and Houston

- Research and clinical operations
  - Europe, USA and Asia

## Investors

- Long-term investors committed to building a leader
  - $100 million invested to date from Imperial Innovations, Invesco, Woodford, CPRIT, Wellcome Trust
Immuno-oncology strategies

**T Cell Receptor Or Chimeric Receptor**

**Target Antigen (Ag)**

**Killing Response**
+ Mobilization of Immune System

### Patient Specific Treatment

<table>
<thead>
<tr>
<th>T cells</th>
<th>Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Naturally Occurring</td>
<td>• Tumour Vaccines</td>
</tr>
<tr>
<td>• CAR Modified T cells</td>
<td>• Dendritic Cells</td>
</tr>
</tbody>
</table>

- Juno
- Kite
- Adaptimmune
- **Cell Medica**

### Drug Model - Off the Shelf

<table>
<thead>
<tr>
<th>T cells</th>
<th>Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PD1/CTLA4 Blockade</td>
<td>• Oncolytic Virus</td>
</tr>
<tr>
<td>• Bi-specific CD3+Abs</td>
<td>• Immunogenicity</td>
</tr>
</tbody>
</table>

- BMS
- Merck
- Roche
- Amgen

- Argos
- Prima Biomed

- Amgen
- GSK
- Biovest
- Bavarian Nordic
Oncology

Goal = Regulatory Approval for CMD-003
## High % of cancer associated with infections

| Incidence                                                                 | 18% of cancers associated with pathogenic infections  
|---------------------------------------------------------------------------|--------------------------------------------------------------------------
| Examples                                                                  | World Health Organization  
| Examples                                                                  |                               
| Epstein Barr Virus                                                        | Epstein Barr Virus, Hepatitis B/C Virus, Human Papilloma Virus, ....and a growing list of others! |
| Epstein Barr Virus                                                        | 95% of all humans infected with EBV on latent basis  
| EBV – Associated Cancers                                                 | 15 - 20% of LYMPHOMAS (up to 100% of certain subtypes)  
| EBV – Associated Cancers                                                 | 95% of NASOPHARYNGEAL CARCINOMA  
| EBV – Associated Cancers                                                 | 10% of GASTRIC CARCINOMAS  

Expression of EBV antigens in Hodgkin lymphoma

EBV malignancies have been well-studied

In most EBV+ lymphomas and NPC, viral antigen expression includes

- LMP1
- LMP2
- EBNA1
- BARF-1

LMP1-expressed by –

- Reed–Sternberg cells (brown staining, middle/top)
- Hodgkin lymphoma cells (brown staining, bottom)
**Product**

*CMD-003 = EBV Cytotoxic T Lymphocytes (EBV-CTLs)*
For cancers expressing Epstein Barr Virus (EBV) antigens

**First Indication**

*Relapsed NK/T cell lymphoma*
- 100% associated with EBV infection
- unmet clinical need
- no effective treatment for advanced disease
- overall survival < 1 year for relapsed patients

**Orphan Drug Designation**

*FDA orphan designation in March 2015*
- All EBV-associated Non-Hodgkin Lymphomas

**IP Position**

*Exclusive license* from Baylor College of Medicine on clinical data and proprietary T cell expansion system
CMD-003 - Developed with Baylor College of Medicine

Baylor College of Medicine

ALCI Study and others
(>300 patients treated)
- EBV lymphomas
- Nasopharyngeal carcinoma

Convert Academic IND to Commercial IND

Simplified process
Re-engineered to permit closed system
Significant reduction on COGs

CITADEL STUDY
Cell Medica

GRALE STUDY
(Baylor College of Medicine)
CMD-003 = Proprietary Manufacturing System

Patient

Autologous PBMCs*
~5,000 Target T Cells (Anergic?)

Five doses

“Vein to Vein” Time = 40 days (including QC/Release testing)

1

Expand Target Cells by 100 – 1000x

EBV Antigens

Interim Stage Activated T cells but insufficient dose

Dendritic Cells

Cytokines

2

Expand Target Cells by 100 – 1000x

T-cellerator™
Antigen-Specific Dose Expansion

up to ~20,000,000/dose**

Activated EBV T Cells

* PBMCs = peripheral blood mononuclear cells
** Under investigation

* PBMCs = peripheral blood mononuclear cells
** Under investigation
GRALE – Early evidence of activity in lymphoma patients

Investigator-led study at **Baylor College of Medicine**
Patients with EBV+ lymphoma

<table>
<thead>
<tr>
<th>Patients with active disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 5</td>
</tr>
<tr>
<td>1 Complete response</td>
</tr>
<tr>
<td>2 Partial response</td>
</tr>
<tr>
<td>1 Stable disease</td>
</tr>
<tr>
<td>1 No response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients in remission with high risk of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 6</td>
</tr>
<tr>
<td>5 remain in remission</td>
</tr>
<tr>
<td>1 pending response assessment</td>
</tr>
</tbody>
</table>

Example of significant PR in NK/T cell lymphoma patient with history of disease/relapse
Opportunity for Fast Track Designation and Accelerated/Conditional Approval

CITADEL Phase II Trial

Patients with extranodal NK / T cell lymphoma who have failed asparaginase-based salvage regimens

Primary endpoint:
Overall response rate (Simon two-stage, 30%)

N=35 (25 evaluable; 16 stage 1; 9 stage 2)

- Target 1st patient treated February 2015
- Parallel phase I/II GRALE study currently ongoing at Baylor College of Medicine (10 patients treated)

<table>
<thead>
<tr>
<th>USA</th>
<th>Europe</th>
<th>Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor</td>
<td>Hamburg</td>
<td>Samsung</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>Berlin</td>
<td>Korean National</td>
</tr>
<tr>
<td>Dana Farber</td>
<td>Mainz</td>
<td>ASAN</td>
</tr>
<tr>
<td>City of Hope</td>
<td>Würzburg</td>
<td>Yonsei</td>
</tr>
<tr>
<td>Ohio State Univ.</td>
<td>Paris</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limoges</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lyon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clermont Ferrand</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UCL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manchester</td>
<td></td>
</tr>
</tbody>
</table>
Immune Reconstitution

Goal = Commercial launch of Cytovir CMV
Patients undergoing allogeneic hematopoietic stem cell (bone marrow) transplant are immunocompromised for 3-12 months post transplant.
Patients undergoing allogeneic hematopoietic stem cell (bone marrow) transplant are immunocompromised for 3-12 months post transplant.

- **Patient After Chemotherapy**
  - No Immune System
  - High Risk of Infections for 3-9 months

- **Bone Marrow Transplant**
  - Delayed Immune Reconstitution
  - 3-12 months

- **Donor Closely Matched HLA**
  - Healthy Immune System
Adoptive T Cell Therapy based on “second transplant” of virus-specific T cells to treat infections arising before patient’s immune system recovers.

Patient After Chemotherapy

Bone Marrow Transplant

“Second Transplant” Virus-specific T cells

Donor Closely Matched HLA

Virus-specific Immunity

Immunity to Target Virus
<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment of cytomegalovirus (CMV) infections in patients following allogeneic hematopoietic stem cell (bone marrow) transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Need</td>
<td>Effective treatment without toxicities of currently available antiviral drugs</td>
</tr>
<tr>
<td>Product and Mechanism</td>
<td>Cytovir CMV is comprised of CMV-specific T cells selected from the bone marrow donor and transferred to the patient to reconstitute immediate immunity to virus</td>
</tr>
<tr>
<td>IP Position</td>
<td>Exclusive world-wide license on “Streptamer” process</td>
</tr>
</tbody>
</table>
ASPECT Trial showed virus-specific immune reconstitution

Primary endpoint not achieved, Secondary endpoints showed strong evidence of immune reconstitution

Fold increase
(p=.01)

93x

Significantly greater fold increase in CMV-specific T cells for patients receiving Cytovir CMV

Source: ASBMT/CIBMTR Conference, 1 Mar 2014
<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment of adenovirus (ADV) infections in paediatric patients following hematopoietic stem cell (bone marrow) transplant</th>
</tr>
</thead>
</table>
| Medical Need | - Clear unmet clinical need  
- High rate of mortality in patients with high risk donors  
- No effective treatment is currently available for this indication |
| EU Orphan Designation | European orphan drug status granted in 2014 |
| IP Position | Proprietary rapid expansion culture system (patents filed) |
Treatment for adenovirus infections in pediatric patients post bone marrow transplant

Important unmet clinical need – no approved antiviral drug for these patients

High rate of mortality in patients with high risk donors

**ASPIRE Phase I/II Trial**

- Primary endpoint = Safety (Risk of GVHD)
- N = 15 patients  (6 patients treated to date)
- Completion 2016
- Great Ormond Street, Manchester, Newcastle
Cytovir ADV to reduce adenovirus viremia and disease in pediatric patients

Decline in bloodstream viral load correlates with immunity to infection...

CD4 T cell count (10^9/ L)
Cytovir ADV: Early evidence of activity
Strategy

Build a Market Leader
### Building market leading commercialisation capability

**Cancer**
- Manufacturing, Distribution, Reimbursement

**Commercial Sales**

**Market for EBV Cancers (EU, US, Asia) = ~£1.0 billion**

|-------------|-------------|-------------|---------|

**Immune Reconstitution**
- Manufacturing, Distribution, Reimbursement

**Commercial Sales**

**Market for Immune Reconstitution in EU Only = ~£100 million**
Significant label expansion within EBV+ lymphomas

|------|------|------|------|------|------|------|

Phase II CITADEL Trial
NK/T cell lymphoma

Phase I/II CIVIC Trial
Exploratory Hodgkin / DLBCL

Confirmatory Study
Refractory Hodgkin / DLBCL

BLA/MA 1\textsuperscript{st} indication

BLA/MA 2\textsuperscript{nd} indication
Cell Medica GmbH (Berlin)
- Licensed commercial GMP manufacturing of T cell products
- Current capacity ~2,000 products per annum
- First closed system cell therapy manufacturing

Contract Manufacturing (Houston)
- GMP Manufacturing for Phase II cancer trial
- US Commercial manufacturing strategy in planning

Centre for Cell, Gene & Tissue Therapy (London)
Royal Free Hospital
- Phase I/II Manufacturing
- Early Access (Named Patient) Sales
Industrialized production of Cytovir™ CMV

Closed system manufacturing allows significant scale-up and cost efficiencies.

Cell Medica’s manufacturing license is **first ever** based on a closed system manufacturing system.

Open system manufacturing  
Closed system manufacturing
Recently completed $75 million private Series B financing

Oncology Objectives

- Advance CMD-003 to BLA in 2018
- Build pipeline products in T cell immunotherapy
- Strategic Partnerships

Immune Reconstitution Objectives

- Revenues for Cytovir CMV
- Revenues (Early Access) for Cytovir ADV

By 2018
Establish Cell Medica as a leader in T cell immunotherapy