Living Immunotherapies

PRESENTATION AT BAADER INVESTMENT CONFERENCE
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Immunotherapy – the future of cancer treatment

Classical Mainstays
- Surgery
- Radiation
- Chemotherapy

Targeted Treatments
- Hormone therapies
- Small molecule targeted therapies
- Antibody therapies

Cancer Immuno-therapies
- Stem cell transplantation
- Immune response modifiers
- DC vaccines
- Latest developments:
  - Adoptive cell therapies
  - CARs and TCRs

Before 1990 1990-2010 From 2010
Fighting cancer with cutting-edge technologies

**T cell receptors (TCRs)**
Generating large numbers of cancer-specific T cells to recognize and kill cancer cells.

**Dendritic cells (DCs)**
An entirely new generation of DC vaccines being developed.

**T cell-specific antibodies (TABs)**
Developing monoclonal antibodies to recognize T cells.
## Progress of immunotherapy pipeline

<table>
<thead>
<tr>
<th>PROJECT</th>
<th>INDICATION (TARGET)</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC vaccine</td>
<td>Acute myeloid leukemia (WT-1 / PRAME)</td>
<td>CTA submitted</td>
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<tr>
<td>TCR clinical trial 1</td>
<td>AML, MDS*, MM** (PRAME)</td>
<td>CTA submitted</td>
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<tr>
<td>TCR clinical trial 2</td>
<td>Undisclosed</td>
<td>CTA submitted</td>
<td></td>
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<tr>
<td>TCR-IIT ***</td>
<td>Multiple myeloma (MAGE-A1)</td>
<td>CTA submitted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TABs</td>
<td>T cell leukemias + new applications</td>
<td>CTA submitted</td>
<td></td>
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</table>

* Myelodysplastic syndromes
** Multiple myeloma
*** Investigator-initiated trial (IIT) of a publicly funded collaboration between MDC, Charité and Medigene.

Additional IITs utilizing Medigene’s DC vaccine technology are ongoing at LMU Munich (Phase I/II in AML) and Oslo University Hospital (Phase II in prostate cancer)
Personalized cancer treatment with TCRs

1. Leukapheresis & T cell isolation
2. GMP: activation of T cells and transfer of TCR from TCR pipeline
3. GMP: expansion, freezing and quality tests
4. Thawing and re-infusion into patient

TCR T-cell product

Patient

Leukapheresis & T cell isolation

GMP: activation of T cells and transfer of TCR from TCR pipeline
DCs are major players in the immune system and initiating T cell responses

Dendritic Cell (DC)

DC presents antigens via MHC complex

Tumor antigens presented by MHC complex, e.g. HLA-A2

Activation of T cells → immune response

T cell with T cell receptor (TCR)
Interconnected technology platforms

Step 1
Loading with tumor-associated antigens (ivt-RNA)

Step 2
Priming process: priming T cells of healthy donors

Vaccination of patient
→ T cells recognize DC vaccines and tumor cells

Adoptive T-cell therapy
→ T cells target tumor cells
Different types of antigen for TCRs and DC vaccines

**Virus-derived antigens:**
Example: EBV, HPV  
**Indication:** lymphomas, specific cancers

**Minor histocompatibility antigens:**
Example: H-Y, HA-1,-2, -3,…  
**Indication:** stem cell transplantation, donor lymphocyte infusion

**Differentiation antigens:**
Example: gp100, tyrosinase, PSA  
**Indication:** melanoma, prostate cancer

**Overexpressed antigens:**
Example: survivin, hTERT  
**Indication:** most tumors

**Neoantigens (mutations):**
Example for shared antigens: K-ras, bcr-abl  
**Indication:** selected tumors  
Example for individual antigens: patient-defined  
**Indication:** most tumors

**Cancer-testis antigens:**
Example: MAGE-A1, PRAME, NY-ESO-1  
**Indication:** hematological malignancies, diverse solid tumors
Medigene’s TCRs target a broader spectrum of tumor targets compared to CARs

**CARs target surface proteins:**
- App. 30% of human proteome
- Limited to cell surface antigens, only tens of options
- Recognition is MHC*-independent
- Higher risks of side effects

**TCRs target intracellular proteins:**
- App. 70% of human proteome
- Recognize intracellular targets, with many thousands of options (more addressable targets)
- Recognition is MHC-restricted (adds specificity)
- Lower risk for side effects if TCRs are natural, non-mutated structures

*MHC: Major Histocompatibility Complex*
Automation dramatically increases throughput

- Highest level of standardization and reproducibility
- Exemplified by output over 12 month timeframe:
  - 45,000 wells automatically screened
  - 15,000 screened clones
  - 1,500 characterized specific T cell clones

Selection of T cells
Screening of TCR candidates
High-throughput TCR analysis
Rapid and efficient TCR lead candidate identification

Medigene’s profound knowledge of:

- Bioinformatics,
- T cell biology, allo- and auto-priming, characterization, specificity and safety tests, functional tests, immune monitoring

TCR pipeline

**Selection**
- 0 weeks Antigen selection

**Preparation**
- 3 weeks Set up *in vitro* cultures

**Priming**
- 6 weeks Sort and expand T cells

**Expansion**
- 8 weeks Test clones + NGS

**Selection**
- 1 week TCR sequences available
- 6-8 weeks Functional testing

TCR lead candidate selection
Supporting immune monitoring facility

- Assay development
- Assay validation
- Assay training
- Inter-laboratory controls

- Multi-color ELISPOT
- Cytokine assays
- Cytotoxicity assays
- Self-peptide analysis
- Alanine scan
- Expitope® (in silico)
- Nanostring® methods
- Statistical data evaluation

- GCP/GCLP-compliant immune monitoring
- FACS sorting
- Multi-color flow cytometry
- Cytokine secretion assay

- Data evaluation
- Documentation
- Validated IT Environment

Lead:
- R&D
- preclinical
- clinical
- commercial

Therapy:
- Target validation ✓
- Safety analyses ✓
- Potency evaluation ✓
- Quality control ✓
- Clinical monitoring ✓
- Release testing ✓
Value creation in TCR development

TCR discovery collaborations

Unique discovery capabilities, immune monitoring platform

TCR development collaborations

cGMP process potentially of interest to other parties

TCR clinical stage partnerships

MAGE-A1 development in MM with academic partners

Medigenes PRAME TCR study in 2017

Proprietary TCR therapies
TCR discovery collaboration with bluebird bio

- bluebird bio collaboration validates TCR technology

- Deal structure:
  - Upfront payment of US$ 15 million in 2016
  - Fully funded R&D activities
  - Potential preclinical, clinical, regulatory and commercial milestone payments up to US$ 1 billion
  - Royalties on net sales

- T cell receptor (TCR) therapeutic candidates against four targets

- Medigene generates and delivers TCR leads to bluebird bio

- Joint preclinical development of all product candidates

- bluebird bio gains worldwide development and commercial rights and exclusive license for IP covering the TCRs

- Medigene retains all rights for its proprietary TCR development programs
Medigene’s TCR studies in preparation

- Medigene’s first company sponsored trial (2017): MDG1011
  - Additional viral vector production capacities secured at EUFETS
  - Commercial manufacturing partner selected and cell GMP process nearing completion
  - Centers selected for clinical study
  - CTA submitted to Paul-Ehrlich-Institute (July 2017)

- Grant-funded IIT with Charité Hospital and MDC in Berlin (2017):
  - Clinical indication Multiple Myeloma
  - T-cell receptor selected
  - Viral vector produced by EUFETS GmbH
  - GMP process established
  - CTA submitted

- Developments needed to drive Medigene’s clinical TCR studies:
  - Identification of TCRs and preclinical work
  - Process development for GMP-compliant patient-individualized cell products
MDG1011 Phase I/II study: CTA submitted

Target:
- PRAME (Preferentially Expressed Antigen in Melanoma)
- PRAME is a well characterized tumor antigen overexpressed in multiple hematological and solid tumor indications

MDG1011:
- T cells expressing a HLA-A2:01 restricted T cell receptor (TCR) specific for PRAME
- Has demonstrated favorable preclinical safety and efficacy

Clinical trial outline, pending regulatory discussion and approval:
- Planned is a combined Phase I/II safety and feasibility
- Disease indications are acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), multiple myeloma (MM); all in advanced stages
- Phase I part: dose escalation, testing up to 4 dose cohorts in a 3+3 design
- Phase II part: will expand the dose cohort from Phase I and include a prospective control group
- Multi-centric study planned in three sites
- CTA submitted in July 2017 – review ongoing
The CTA is submitted for the first company-sponsored TCR-based clinical study – MDG1011

Selection of lead TCR candidate: PRAME

SIN-RV vector

Manufacturing process development

cGMP-process development at EUFETS

Submission of clinical trial application (CTA)

Approval and start of clinical study

Q4 2017
Interconnected technology platforms

**Step 1**

Loading with tumor-associated antigens (ivt-RNA)

**Step 2**

Priming process: priming T cells of healthy donors

Vaccination of patient

→ T cells recognize DC vaccines and tumor cells

Adoptive T-cell therapy

T cells target tumor cells

TCR pipeline
Personalized cancer treatment with DC vaccines

1. Isolation of DC precursor cells from patient’s blood
2. GMP: generation of DCs and loading with tumor-target antigens
3. GMP: freezing of vaccine cells in multiple aliquots and quality testing
4. Thawing and vaccination

DC vaccine product
Medigene’s “new generation” DCs mature fast and show optimal immunotherapeutic potential

Best biological properties for improved clinical efficacy

- Defined antigen loading with ivt-RNA replaces unknowns of loading with peptides or tumor lysates
- Use of full length antigen requires no need for patient HLA selection
- Positive co-stimulatory profile is optimal with young 3-day mature dendritic cells
- Optimal cytokine polarization supports both innate and adaptive immune responses
- High quantity yields of DCs allow for 20+ vaccinations (>85% mature polarized DCs)

Best product characteristics for commercialization

- 3-day production is cost effective and amenable to automation
- RNA as source of antigens is versatile, inexpensive and has no need for tumor material
- Single-batch production reduces time, costs and is patient friendly (only one apheresis)
- Frozen vaccine formulation gives 2+ years of shelf-life and simplified logistics
DC trial in AML: Phase II part ongoing

**Trial Design:**
- **Phase I/II:** open-label, prospective, non-randomized trial
- **20 AML patients:** 6 phase I + 14 phase II, complete remission after chemotherapy, not eligible for allo-transplantation
- Patients selected with AML expressing the vaccine antigens: 
  - WT-1 with or without PRAME
- **Continuous vaccination for 2 years or until progression/ death**

**Study objectives:**
- **Primary:** feasibility and safety
- **Secondary:** overall survival (OS), progression free survival (PFS), control of minimal residual disease (MRD), time to progression (TTP), induction of immune responses

ClinicalTrials.gov Identifier: NCT02405338
Results from IIT* and Compassionate Use**
DC vaccine treatment in AML patients

- High success rate for GMP generation of DC vaccines
- Efficient logistics for DC vaccine delivery
- Vaccine antigens demonstrate immunogenicity
- T cell responses as potential biomarkers of DC activity
- Excellent safety profile of DC vaccines

Production efficiency & safety profile allow extensive vaccination

(*IIT at Ludwig-Maximilians-University Munich; **CU Patients at Oslo University Hospital)
T-cell-specific antibodies (TABs)

- Full-scope platform for antibody isolation
- Unique animal models to assess mode of action and clinical efficacy
- Proof-of-principle is established
- **Removal of unwanted T cells:**
  - T-cell leukemia therapy
- **TCR-modified T cells:**
  - Tool for *ex vivo* tracking of T cells
  - *In vivo* removal of T cells
- **Status quo:**
  - Ongoing studies establish proof-of-concept in preclinical models
Summary
Outlook for 2017

**MDG1011, Medigene’s first TCR trial**
- Clinical trial authorization
- Study start

**TCR IIT, Berlin**
- Clinical trial authorization
- Study start

**DC trial in AML, Oslo**
- Completion of enrollment
- Final read-out in 2019

**Progress in bluebird collaboration**
Shareholder structure

Key share information

- Listed on Frankfurt Stock Exchange (Prime Standard) Symbol: MDG1; ISIN: DE000A1X3W00; TecDax
- Number of outstanding shares: 22.1 m
- Current market cap of approx. € 280m
- > 28% of shares owned by US investors

Shareholder structure by countries

As of 30.6.2017, rounded
Based on Medigene AG information and estimates

Numbers based on last voting right notifications
**shareholding below 3%
Financial guidance for 2017 confirmed

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<thead>
<tr>
<th></th>
<th>2016</th>
<th>GUIDANCE 2017</th>
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</thead>
<tbody>
<tr>
<td>Total revenue</td>
<td>€ 9.7m</td>
<td>€ 8-10m</td>
</tr>
<tr>
<td>R&amp;D expenses</td>
<td>€ 11.5m</td>
<td>€ 16-18m</td>
</tr>
<tr>
<td>EBITDA loss</td>
<td>€ 12.3m</td>
<td>€ 16-18m</td>
</tr>
<tr>
<td>Cash usage</td>
<td></td>
<td>€ 23-27m</td>
</tr>
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</table>

- Cash & cash equivalents as of June 30, 2017: €59.9 m
- Sufficient financial resources beyond the forecast horizon of two years and to the time points that data from DC trial and TCR trials become available