The first allogeneic, ‘off-the-shelf’ NK cell product in oncology

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Glycostem Therapeutics

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Glycostem: Who we are

• IPD-Therapeutics B.V. founded in 2007 and is also represented by her trade name Glycostem related to an initial German finding dealing with the use of Glycosaminoglycans in stem cell multiplication (1st patent family).

• Until 2013 Glycostem collaborated as “spin-in company” with Radboud UMC on pre-clinical R&D (patent families 2-5), followed by a Phase I clinical study (EudraCT number 2010-018988-41).

• In 2014 Glycostem moved to new research facilities at the Pivot park in Oss, Netherlands.

**Glycostem is a clinical stage company that develops allogeneic cell products for cancer immunotherapy (NK-cells; Dendritic cells and others).**
Product Strategy

✔ Treatment of haematological indications and solid tumors with our 1st generation products oNKord® (Natural Killer ‘NK’ cells) and/or sDCord® (dendritic cells)

✔ Develop 2nd generation product concepts with dedicated functionality

➢ NK cells and therapeutic antibodies

➢ Genetically modified, so-called “CAR-NK” cells for better targeting and persistence

✔ Strategic partnerships with Pharma/Biotech to develop combinatorial therapies

✔ NK cells and checkpoint inhibition

✔ NK cells and tumor sensitization by targeted chemotherapy (TKI, demethylating agents, alkylating agents and others)
oNKord® is Glycostem’s lead product for use in immuno-oncology

- **Universal donor principle:** As NK cells do not cause GvHD, allogeneic use allows mismatch and enables “off-the-shelf” concept.

- **Unlimited sourcing:** High availability of donor material, as NK cells are derived from umbilical cord blood CD34+ cells.

- **Unrestricted use:** NK cells can attack various type of tumors and enable a multitude of cancer treatment applications as stand-alone or combinatorial therapy.
Clinical evidence that allogeneic use of NK cells in oncology is safe and effective

1st line of evidence from allogeneic hematopoietic stem cell (HSC) transplantation

- Willemze et al. Leukemia 2009

2nd line of evidence from NK cell infusion trials

- Dolstra et al. (elderly AML) ASH 2015
- Shah et al. (refractory MM) ASH 2015
NK cells work based on a balance of inhibitory and activating signals.

- **Inhibitory signals** decrease the likelihood of killing.
- **Activating signals** increase the likelihood of killing.

**Mismatch** indicates a difference between the inhibitory and activating signals, leading to killing.

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NK cells generate from hematopoietic stem and progenitor cells.
Glycostem’s technology protection

- Proprietary own cell culture medium (ADCF & serum free)
- Patented, flexible cell expansion (>50,000 fold) and differentiation platform
- Proprietary composition of expansion and differentiation growth factors
- Highly pure products (99% ± 1%) and patented product composition
- High cytolytic activity vs. various cancer cells
- Fully GMP embedded and patented closed cell culture
- Allogeneic NK cell products, clinical use and combination with immunosuppressive therapy
- Allogeneic dendritic cell products and their clinical use

Source: Spanholtz et al., PlosOne 2010
Tissue distribution of oNKord® cells following adoptive transfer in NSG mice

- **A**: Distribution of 
  \(^{111}\text{In-NK cells} \) at +1h and +24h.

- **B**: Tissue distribution by flow cytometry:
  - Blood: 5.7%
  - Spleen: 10.4%
  - Femur: 0.6%
  - Lung: 2.7%
  - Liver: 2.4%
  - Kidney: 0.0%

- **C**: Graph showing human cell (
  \(h\text{CD45}/(h\text{CD45}+m\text{CD45})\)) distribution over time after NK cell injection (week).

- **D**: Flow cytometry plots for UCB-NK cells with and without IL-15.

Cany et al., PlosOne 2013
oNKord® mediate *in vivo*

a strong and local anti-leukemic response

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*Cany et al., PlosOne 2013*
oNKord®: regulatory status

- Highly pure and activated cell products according SOPs under GMP and ATMP regulations including standardized CoA in a closed bioreactor system

- Approved IMPD (Investigational Medicinal Product Dossier) and clinical protocol approved by Dutch national authority (CCMO (Centrale Commissie Mensgebonden Onderzoek))

- Orphan drug designation for GCT-NK cell product in AML received by EMA & FDA
Clinical trial objectives

- Feasibility, safety and toxicity
- *In vivo* survival, expansion and pharmacokinetics and dynamics
- Effect on disease status (MRD)
# oNKord® release CoA

## In-process controles intermediate TC-NK-cel product

<table>
<thead>
<tr>
<th>CD34 verrijkt product (dag 0):</th>
<th>TC-NK-cel product op dag 28:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omstoten (selecte datum)</td>
<td>Zuiverheid CD56+CD3- cellen</td>
</tr>
<tr>
<td>Aantal CD34+ cellen (=0,75x10^6)</td>
<td>MTA %</td>
</tr>
<tr>
<td>Viabiliteit CD34+ cellen (&gt;60%)</td>
<td>MTA %</td>
</tr>
</tbody>
</table>

### TC-NK-cell product op dag 28

- Microbiologische steriliteitcontrole (negatief):

### TC-NK-cell product

| TC-NK-cell product: TC-NK86062 |
|---------------------------------|-------------------------------|
| Zuiverheid CD56+CD3- cellen (>70%) | 93 %                         |
| Viabiliteit CD56+CD3- cellen (>70%) | 93 %                         |
| Expressie NKG2A (>30%) | 96 %                         |
| Expressie NKG2D (>30%) | 64 %                         |
| Expressie Nkp30 (>30%) | 96 %                         |
| Expressie Nkp44 (>30%) | 98 %                         |
| Expressie Nkp45 (>30%) | 93 %                         |

- Dosis CD56+CD3- NK cellen : 80 x 10^6/kg
- Absolute aantal CD56+CD3- NK cellen : 7,178 x 10^6
- Aantal CD3+ T cellen (<1x10^6/kg) : 0,00 x 10^6/kg
- Absolute aantal CD3+ T cellen : 0,00 x 10^6
- Aantal CD19+ B cellen (<1x10^6/kg) : 0,00 x 10^6/kg
- Absolute aantal CD19+ B cellen : 0,00 x 10^6

- Microbiologische steriliteitcontrole (negatief):

### Infusie datum: 25-6-2015

### Conclusie:

Goele opbrengst en activatie (>30% NKG2D en Nkp receptoren) van TC-NK cell product. Zuiverheid CD56+CD3- cellen is 93%.

### Vrijgafte product:

Dr. Harry Dolstra
Deskundige ATVP

Dr. Frank Prieiers
Stamcelab directeur/VP

Dr. Janine van der Linden
Qualified Person

Date/Signature: 25-6-2015

**Formuliercode: FCT8679. Versienummer: 2**

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Update clinical trial: Leukocyte counts and availability of endogenous IL-15

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oNKord® chimerism analysis
Chimerism flow cytometry follow up of infused oNKord® cell product

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Day 0</th>
<th>Day 0+4h</th>
<th>Day 2</th>
<th>Day 6</th>
<th>BM day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 5</td>
<td>0%</td>
<td>0%</td>
<td>9.0%</td>
<td>1.5%</td>
<td>19.6%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Pt 7</td>
<td>0%</td>
<td>0%</td>
<td>1.4%</td>
<td>2.8%</td>
<td>4.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Pt 8</td>
<td>0%</td>
<td>0.1%</td>
<td>2.0%</td>
<td>3.3%</td>
<td>19.9%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

CD56

CD3

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Flow cytometry follow up of infused oNKord® cell product – upregulation of CD16

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Flow cytometry follow up of infused oNKord® cell product – upregulation of KIR; decrease in NKp44
oNKord® treatment resulted in strong reduction of MRD

UPN7 (30*10⁶ NK cells/kg)
LAP: CD45⁺CD34⁺CD117⁺CD133⁺

Day -14 6.7%

Day +90 <0.01%
oNKord® treatment resulted in strong reduction of MRD

UPN8 (17*10^6 NK cells/kg)
LAP: CD45^+CD34^-CD7^-CD133^+

Day -14
6.3%

Day +90
0.02%
Improved survival after oNKord® treatment

<table>
<thead>
<tr>
<th>NK cell dose (x10⁶)</th>
<th>Patient</th>
<th>Risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>2190</td>
<td>10</td>
<td>Poor</td>
</tr>
<tr>
<td>1693</td>
<td>7</td>
<td>Poor</td>
</tr>
<tr>
<td>1191</td>
<td>8</td>
<td>Very poor</td>
</tr>
<tr>
<td>770</td>
<td>6</td>
<td>Poor</td>
</tr>
<tr>
<td>650</td>
<td>4</td>
<td>Intermediate</td>
</tr>
<tr>
<td>530</td>
<td>5</td>
<td>Poor</td>
</tr>
<tr>
<td>510</td>
<td>9</td>
<td>Very poor</td>
</tr>
<tr>
<td>324</td>
<td>2</td>
<td>Intermediate</td>
</tr>
<tr>
<td>220</td>
<td>1</td>
<td>Good/Interm</td>
</tr>
<tr>
<td>189</td>
<td>3</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

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Summary Phase I trial in AML patients

✔ 10 AML patients treated with oNKord® after Flu/Cy conditioning (EudraCT number 2010-018988-41)

✔ Reliable NK cell production under GMP, showing no T cell impurity

✔ No DLT and Graft versus Host Disease (GVHD) observed in the trial

✔ Chimerism and NK cell expansion detected in PB and BM up to day 14

✔ oNKord® cells home to the bone marrow and target leukemia cells

✔ 26 months median survival of patients treated >1 year ago

✔ 80% survival of patients after 1 year
Take home message

✓ Glycostem has a unique and versatile cell expansion and differentiation platform

✓ Glycostem’s production system has very attractive cost structure

✓ oNKord® has shown to be safe and effective in AML patients

✓ Solid IP position, Freedom to Operate secured

✓ Well documented procedures and protocols for fast transfer to professional partners

✓ Excellent European scientific network available

✓ Production platform has high licensing potential

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Collaborating partners

University Medical Centre Nijmegen, Nicole Blijlevens, Michel Schaap, Harry Dolstra
VUMC - Cancer Centre Amsterdam, Henk Verheul, Hans van der Vliet, Tanja de Gruijl
Erasmus Medical Centre Rotterdam, Jan Cornelissen

All NATURIMMUN partners

Medical University Hannover, Ulrike Köhl, Erhard Hofer
University Medical Centre Würzburg, Hermann Einsele
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