ORYX – Overview

- ORYX GmbH & Co. KG (ORYX) is a privately held company for translational oncology founded in 2007 and located in Baldham/Munich, Germany

- ORYX bridges the gap for new cancer therapies between leading academic research institutions and the pharmaceutical industry

- ORYX is the exclusive licensee of three premier cancer immunotherapy substances of the German Cancer Research Center (DKFZ) and the University of Heidelberg

- ORYX has successfully developed these substances in clinical phase I/IIa trials, has obtained compelling safety and efficacy data in these clinical trials, and is now looking into partnering these substances for the pivotal trials
## ORYX – Pipeline

<table>
<thead>
<tr>
<th>Cancer Immunotherapy Substances</th>
<th>Mode of Action</th>
<th>Current Cancer Indications</th>
<th>Pre-Clinical</th>
<th>Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>POC / Toxicology</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>MicOryx</strong></td>
<td>Synthetic frameshift peptides vaccine</td>
<td>Colorectal</td>
<td></td>
<td>Phase I / IIa completed</td>
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<tr>
<td><strong>VicOryx</strong></td>
<td>Synthetic human cyclin-dependent Kinase inhibitor peptide vaccine</td>
<td>Cervical Head &amp; Neck</td>
<td></td>
<td>Phase I / IIa completed</td>
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<tr>
<td></td>
<td></td>
<td>Concurrent vaccination &amp; chemotherapy</td>
<td></td>
<td>Phase I / IIa completed</td>
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<tr>
<td><strong>ParvOryx</strong></td>
<td>Wild-type rat oncolytic virus</td>
<td>GBM</td>
<td></td>
<td>Phase I / IIa completed</td>
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<td></td>
<td>PDAC</td>
<td></td>
<td>Phase I / IIa ongoing</td>
</tr>
</tbody>
</table>

- **Compassionate Use Programs**: GBM/CRC
MicOryx – Rationale

- Several cancers arise from the lack of DNA mismatch repair (MMR), resulting in the accumulation of single deletions or insertions at coding microsatellites (MSI-H mutations).
- Cancers with MSI-H mutations include:
  - 10-15% of colorectal cancers
  - 20-25% of endometrial cancers
  - 25-30% of upper urinary tract cancers
  - 15-20% of gastric cancers
  - 5-10% of pancreatic cancers
- MSI-H mutations lead to the expression of frameshift peptides (FSPs).
- FSPs are tumor specific antigens which are constantly expressed.
- In patients with MSI-H colorectal cancer a natural humoral and cellular immune response against FSPs is found, which demonstrates that FSPs are recognized by the immune system and can trigger an immune response.
MicOryx 01 – Clinical Phase I/IIa – completed

Trial design

Single center, two part open label, prospective study
• 1st part 6 patients, 2nd part 16 patients (n = 22)
• UICC stage III/IV MSI-H colorectal cancer

Total of 12 s.c. applications with three FSPs one time/week for four consecutive weeks, followed by a four week rest period (one cycle) for a total of three cycles

Results

Primary Objective: Safety
• 22/22 patients (100%)

Secondary Objective: Efficacy
• Specific immune responses against FSPs in 21/22 patients (95.5%)
• Stable Disease in stage III and IV patients

Study Week Subcutaneous injection of FSPs and Montanide ISA 51 VG

| 1 | 2 | 3 | 4 | 9 | 10 | 11 | 12 | 17 | 18 | 19 | 20 | 25 |

Monitoring of toxicity, immune response (including DTH), and tumor response
In many solid cancers the **cyclin-dependent kinase inhibitor p16INK4a** is expressed

- p16\(^{\text{INK4a}}\) positive cancers include:
  - 20-30% of breast cancers
  - 60-70% of small cell lung cancers
  - 90-100% of HR-HPV associated cancers, e.g. cervical cancer, head and neck cancer, anal and vulvar cancer, vaginal and penile cancer

- In cancer cells, p16\(^{\text{INK4a}}\) is a tumor antigen which is **constantly expressed** as an early consequence of cell transformation

- In normal cells, p16\(^{\text{INK4a}}\) is rarely expressed and leads to immediate senescence

- In patients with HR-HPV associated cancers a natural humoral and cellular immune response against p16\(^{\text{INK4a}}\) can be found, which indicates that p16\(^{\text{INK4a}}\) is recognized by the immune system and **can trigger an immune response**
VicOryx 01 – Clinical Phase I/IIa - completed

Trial design

Single center, two part open label, prospective study

- 1st part 10 patients, 2nd part 16 patients (n = 26)
- UICC stage III/IV, advanced HR-HPV- and p16\textsuperscript{INK4a} positive cervix, vulvar, vaginal, penile, anal or head and neck cancer

Total of 12 s.c. applications with a specific p16\textsuperscript{INK4a} peptide one time/week for four consecutive weeks, followed by a four week rest period (one cycle) for a total of three cycles

Results

Primary Objective: Safety

- 26/26 patients (100%)

Secondary Objective: Efficacy

- Specific immune responses against p16\textsuperscript{INK4a} in 18/26 patients (69,2%)
- Stable Disease in stage III and IV patients

Study Week Subcutaneous injection of p16 and Montanide ISA 51 VG

1 2 3 4 9 10 11 12 17 18 19 20 25

Monitoring of toxicity, immune response (including DTH), and tumor response
VicOryx 02 – Clinical Phase I/IIa - completed

**Trial design**

Single center, open label, prospective study

- On concurrent **cisplatin-based chemotherapy combined** with specific p16\(^{INK4a}\) peptide vaccination, 10 patients
- UICC stage III/IV, advanced HR-HPV- and p16\(^{INK4a}\) positive cervix, vulvar, vaginal, penile, anal or head and neck cancer

Total of 12 s.c. applications with a specific p16\(^{INK4a}\) peptide one time/week for four consecutive weeks, followed by a four week rest period (one cycle) for a total of three cycles

- Vaccination is applied one week before the initiation or continuation of cisplatin-based chemotherapy

**Results**

**Primary Objective:**

- Feasibility of vaccination during chemotherapy
- Specific immune response against p16\(^{INK4a}\)

**Secondary Objective:**

- Safety, PFS, OS
- Tumor response according to RECIST

➤ Combined therapy shows excellent safety and tolerability
ParvOryx – Synopsis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Potentials</th>
</tr>
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<tbody>
<tr>
<td>Virus Type</td>
<td>Wild type DNA virus</td>
</tr>
<tr>
<td></td>
<td>• Passes blood brain barrier</td>
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<tr>
<td></td>
<td>• Potential to be armed with tumour specific siRNAs</td>
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<tr>
<td>Safety</td>
<td>Excellent safety profile</td>
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<tr>
<td></td>
<td>• Not pathogenic for humans</td>
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<tr>
<td></td>
<td>• Lyses only tumour cells</td>
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<tr>
<td></td>
<td>• No effect on normal tissue</td>
</tr>
<tr>
<td>Application</td>
<td>it. and/or iv. possible</td>
</tr>
<tr>
<td></td>
<td>• Potential to local and systemic administration</td>
</tr>
<tr>
<td>Immunity</td>
<td>No prior immunity in humans</td>
</tr>
<tr>
<td></td>
<td>• Prolonged therapeutic window</td>
</tr>
<tr>
<td>Booster</td>
<td>Repeated it.- and iv.- application possible</td>
</tr>
<tr>
<td></td>
<td>• Potential for vaccination</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Oncolyis and bystander effect</td>
</tr>
<tr>
<td></td>
<td>• High H-1PV susceptibility in many cancers</td>
</tr>
<tr>
<td></td>
<td>• Change of tumor microenvironment</td>
</tr>
<tr>
<td></td>
<td>• Potential for combined modality treatment</td>
</tr>
</tbody>
</table>
ParvOryx 01 - Clinical Phase I/IIa - completed

Trial design

Single center, open label, prospective, dose escalating study
- 1\textsuperscript{st} group (it) 12 patients, 2\textsuperscript{nd} group (iv) 6 patients (n = 18)
- UICC Stage IV
- progressive primary or recurrent glioblastoma multiforme

It: half of the dose in the tumor, half of the dose in the wall of the resection cavity
Iv: half of the dose in 5 consecutive injections, half of the dose in the wall of the resection cavity

Results

Primary Objective: Safety
- 18/18 patients (100%)

Secondary Objective: Efficacy
- PFS ≥ 6 month: 33% / 10\%\(^\text{1}\)
- OS ≥ 6 month: 80% / 40\%\(^\text{1}\)

Immune response

- Strong cellular immune response against glioma and viral proteins (bystander effect)

\(^{1}\) (www.ncbi.nlm.nih.gov/pubmed/17108063)
ParvOryx 02 – Clinical Phase I/IIa - ongoing

Trial design

Single center, open label, prospective, dose escalating study, 7 Patients

UICC stage IV metastatic inoperable pancreatic cancer

- iv.-administration followed by it.-administration in single liver metastases

Results

Primary Objective: Safety

Secondary Objective:
PFS, OS

Anti-tumor effects
- Specific cellular and humoral immune responses
- Tumor infiltration
- Metastatic necrosis
- Virus activity in the tumor tissue
ParvOryx – Compassionate Use Programs

ParvOryx and Avastin®

Tumor regression in
• 2/2 recurrent GBM patients

ParvOryx and ICI*

Tumor regression in
• 1/1 CRC
• 1/1 recurrent GBM patient

ParvOryx, ICI and Avastin®

Tumor regression in
• 7/7 recurrent GBM patients

* ICI: Immune checkpoint inhibitor
ParvOryx – Controlled adaptive 4-Arm Phase II Study

4-arm run-in-study

- ParvOryx iv and Avastin®
- ParvOryx iv and ICI*
- ParvOryx iv ICI and Avastin®
- Control Arm: CCNU

2-arm main study

- Best Arm
- CCNU

* ICI: Immune checkpoint inhibitor
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ORYX – Partnering Opportunities

Contact
ORYX GmbH & Co. KG
Marktplatz 1
85598 Baldham, Germany
Phone:  +49-8106-21 311-0
Fax:    +49-8106-21 311-66
E-mail: info@oryx-medicine.com
www.oryx-medicine.com