PCI BIOTECH
Unlocking the potential of innovative medicines
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PCI BIOTECH

Unlocking the potential of innovative medicines

The challenge
- Several classes of drugs need access to the inside of target cells in order to be effective
- Many drug substances cannot freely enter cells, but are by nature encapsulated in so-called endosomes
- Once inside the cell, the active compound may hence be trapped in endosomes, unable to exert its therapeutic effect

The solution
- PCI Biotech’s patented investigational drug fimaporfin is able to “unlock” intracellular endosomes
- Hence, fimaporfin may unlock the true potential of novel therapies, as well as established chemotherapies
PCI TECHNOLOGY

► The solution to a key challenge for several modalities

**fimaCHEM**

- Enabling approved drugs to fulfill unmet local treatment need
  - Clinical programme
  - Localised cancer treatment in areas of high unmet need
  - First-in-man study published in Lancet Oncology*

**fimaVACC**

- Enhancing cellular immune responses important for therapeutic effect
  - Clinical programme
  - Aim is to out-license the vaccination platform on non-/semi-exclusive basis
  - Opportunity to develop own vaccines

**fimaNAC**

- Providing a delivery solution for nucleic acid therapeutics
  - Pre-clinical programme
  - Aim is to out-license the technology on non-/semi-exclusive basis

* Lancet Oncology (2016) 17(9): p1217–1229
PCI BIOTECH AT A GLANCE

- Unlocking the potential of innovative medicines

- A listed (PCIB:NO) cancer-focused biotech company

- Photochemical internalisation ("PCI") technology, originating from the Norwegian Radium Hospital

<table>
<thead>
<tr>
<th>Programme</th>
<th>Indications / Therapeutics</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>fimaCHEM</td>
<td>Bile duct cancer / gemcitabine</td>
<td></td>
<td></td>
<td></td>
<td>- Promising Phase I results for treatment in the orphan indication bile duct cancer - Plan to initiate pivotal study 1H 2018</td>
</tr>
<tr>
<td>fimaVACC</td>
<td>Therapeutic cancer vaccines</td>
<td></td>
<td></td>
<td></td>
<td>- Ongoing Phase I study in healthy volunteers - Promising initial immune results - One active R&amp;D collaboration</td>
</tr>
<tr>
<td>fimaNAc</td>
<td>Nucleic acid therapeutics</td>
<td></td>
<td></td>
<td></td>
<td>- Four active R&amp;D collaborations</td>
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</tbody>
</table>

An oncology focused company with three well differentiated assets
PCI TECHNOLOGY

▶ fimaCHEM – mode of action

Cancer cell

Chemotherapeutics

E.g.

- Cytotoxic antibiotics
- Anti-metabolites
- Anti-microtubule agents

DNA intercalation; free radical formation; etc.
DNA /RNA synthesis inhibition; DNA damage
Cell cycle arrest

Endocytosis
Lysosomal Breakdown

Release into cytosol

 PCI technology

lysosome

Nucleus

endosome

chemotherapeutic
Often referred to as cholangiocarcinoma

The cancer cells originate from the cells inside the bile duct (called cholangiocytes)

Cholangiocarcinoma includes:
- Intrahepatic tumours (10%*)
- Perihilar tumours (60-70%*)
- Distal tumours (20-30%*)
- Different incidence, pathobiology and management

Perihilar bile duct cancer is the initial target for PCI treatment

* Bile duct cancer, Am Cancer Soc, 10/30/2013
**Bile Duct Cancer**

**Excellent fit between medical need and fimaCHEM**

- Orphan indication, yearly incidence rate of 1-2 per 100,000 in the western world – higher in Asia
- Five-year survival rate of less than 5% and almost 0% when inoperable
- Average survival inoperable: ≈12 months
- Current management
  - Surgery
    - Only potentially curative treatment
    - Less than ⅓ are resectable at presentation
  - Stenting
    - Endoscopic stenting for palliative biliary drainage
  - Chemotherapy
    - No approved chemotherapy
    - Recommended: gemcitabine and cisplatin

**fimaCHEM:**

**Enhancing the active and recommended chemotherapy**
- Combination therapy with gemcitabine and cisplatin is recommended
- Gemcitabine is significantly enhanced by fimaCHEM
- Enhancing systemic therapy locally

**Easy illumination through standard endoscopic methods**
- Patients are treated with endoscopic methods (ERCP) for diagnosis and stenting
- Optic fibre and illumination easily included in the ERCP procedure

**Boosting chemotherapy effect where it is most needed**
- Tumours tend to block the bile duct
- Liver function is often affected
- Biliary drainage is key for patient treatment and survival
**Bile Duct Cancer**

- A sizeable orphan market potential

- Immediate target market is as first line treatment
  - Incidence: close to 15,000 across Europe and the US
  - Immediate target: inoperable patients with locoregional disease
    - Approximately 3,000 assumed eligible for fimaCHEM
  - Possible upside in distal and more advanced metastatic disease
  - Higher incidences in Asia

- Attractive price potential
  - No approved pharmaceutical treatment options
  - Diseases with <10,000 in US support annual pricing >$100,000

- Potential significant majority share of the market
  - Anticipated benefits
    - No competing marketable treatment alternatives
    - Greater efficacy due to local chemotherapy boost
    - Easy light access through established standard procedures

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*Bile duct cancer Incidence*: Europe: 6-8,000 USA: 5-6,000

45% of patients 55% of patients

Local disease Metastatic disease

Operable disease
- Surgery and chemotherapy

Inoperable disease
- Stenting and chemotherapy

*Source; Khan et al, Lancet 2005; 366:1303
Gatta et al, Eur J Cancer 2011; 47:2493
Bragazzi et al, Transl Gastrointest Cancer 2012; 1:21

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1 LifeSciCapital, OD Market Sector Analysis 2016
INOPERABLE EXTRAHEPATIC BILE DUCT CANCER

- An underserved patient population

- No approved medical treatment
- Combination therapy with gemcitabine and cisplatin recommended

**Presentation:**
- Pain, jaundice, abnormal liver function tests, abnormality on imaging

**Workup:**
- Biliary drainage (stenting)

**Treatment:**
- Gemcitabine/cisplatin combination therapy
- Fluoropyrimidine-based treatment / Clinical trial
- Best supportive care
INOPERABLE EXTRAHEPATIC BILE DUCT CANCER

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*Phase I treatment*
Early promising signs of durable response in Phase I dose escalation

6 months radiology data from all dose cohorts – local read

<table>
<thead>
<tr>
<th>Cohort (I-IV)</th>
<th>PD</th>
<th>SD</th>
<th>PR</th>
<th>CR</th>
<th>NA**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort IV</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cohort III</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cohort II</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cohort I</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Response Evaluation Criteria In Solid Tumours (rules defining when cancer patients improve, stay the same or worsen during treatments)*  
**Not measurable / Not radiologically evaluable

- Subjects are in the study for 6 months after *fimaCHEM* treatment and thereafter followed for survival only
- Commissioned central independent radiological expert evaluation of Cohort III & IV, as this is an expected requirement from regulatory authorities

- PD: Progressive disease (>20% growth)  
- SD: Stable Disease  
- PR: Partial Response (>30% shrinkage)  
- CR: Complete Response (no visible tumour)
Bile Duct Cancer – Clinical Phase I/II Study

- Encouraging early signs of efficacy in Phase I dose escalation

- Interim average overall survival (OS) of all 16 patients in Phase I was 16.5 months per November 2017, with 25% of the patients still being alive. Median OS ended at 14.4 months.

Best Overall Response (all radiologically evaluable patients; N=11)
Bile Duct Cancer — Phase I Extension Study

► Repeating the **fimaCHEM** treatment with the aim to further enhance efficacy

**fima CHEM**

A three step treatment procedure

1. Intravenous injection of fimaporfin
2. Intravenous administration of gemcitabine
3. Endoscopic laser light application

- 4 days
- 3 ± 1 hrs

► Exploring safety of repeating the **fimaCHEM** treatment in an extension to Phase I

► The study will include six patients evaluable for safety and is done in parallel with all other preparations for the next pivotal phase

► May allow for repeated treatment in the pivotal study

**fimaCHEM 1**

- ▼ fimaporfin
- ▼ gemcitabine + light

**fimaCHEM 2**

- ▼ gemcitabine + cisplatin

4 days | 7-21 days | C 1 (21 days) | C 2 | C 3 | C 4 | 4 days | C 5 (up to 8 cycles (C) in total)
**INOPERABLE EXTREHEPATIC BILE DUCT CANCER**

- Status and strategy going forward

  - **Phase I completed with good tolerability and promising early signs of efficacy**
    - Tumour shrinkage in almost all radiologically evaluable patients
    - Interim average overall survival (OS) of 16.5 months with 25% of patients still alive; median OS ended at 14.4 months

  - **Exploring safety of repeated treatment as a Phase I extension**
    - First patient included in August 2017

  - **Regulatory interactions with authorities (EMA & FDA) to determine fastest way to market**
    - A single randomised pivotal study, planned initiated 1H 2018
    - Potential for accelerated/conditional approval based on interim results

  - **Orphan designation**
    - Granted in EU and US

  - **Engaging US key opinion leaders (KOL’s)**
    - Involving US KOL’s in the study design for Phase II
PCI TECHNOLOGY

► fimaVACC – mode of action

Dendritic cell

Vaccine

MHC I

MHC II

Nucleus

proteasomes

endosome

PCI

vaccine antigen

Endocytosis

MHC Class I

Generate more disease specific cytotoxic T-cells

Attack cancer and virus-infected cells more efficiently

MHC Class II

Antibodies and helper T-cells
**fimaVacc Strongly Enhances Vaccination Effects**

- Impressive effects with clinically relevant HPV therapeutic vaccine in mice

### Cytotoxic (CD8) T-cells

- Most important immune cells to fight tumours
- Difficult to induce with vaccination
- **fimaVacc** strongly enhances the ability of vaccines to induce CD8 T-cells:
  - >20 and >40 times enhancement seen in spleen and blood cells, respectively
  - Generation of immunological memory

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**Amount of activated antigen-specific CD8 T-cells in blood**

**Amount of activated antigen-specific CD8 T-cells in spleen**

**Vaccination without fimaVacc**

- 1.0%

**Vaccination with fimaVacc**

- 44.3%

- 0.9%

- 18.9%
HBV SURFACE ANTIGEN

► *fimaVACC* enhances both CD8, CD4, and antibody responses

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**Immune response with *fimaVACC***

<table>
<thead>
<tr>
<th>Type of immune response</th>
<th>Fold increase compared to HBV alone</th>
<th>Fold increase compared to HBV + poly(IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8</td>
<td>110x</td>
<td>9x</td>
</tr>
<tr>
<td>CD4</td>
<td>75x</td>
<td>5x</td>
</tr>
<tr>
<td>Antibody</td>
<td>33x</td>
<td>9x</td>
</tr>
</tbody>
</table>

*Elicit strong effects in all important aspects of immune response*

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*PCI = *fimaVACC*
**THERAPEUTIC VACCINATION IN TUMOUR MODEL**

- fima\textit{Vacc} induces cytotoxic T-cells that infiltrate tumours

Therapeutic fima\textit{Vacc} vaccination with OVA in animal tumour model (B16-OVA melanoma/OT-1)

**Tumour volume at different time points after inoculation**

(mean values; n=5/group)

- Without vaccination
- Vaccination with tumour cell antigen
- PCI* vaccination with tumour cell antigen

**Tumour infiltration of CD8\(^+\) T-cells**

*PCI = fima\textit{Vacc}*
Two tumours inoculated simultaneously

Intra-tumoural immunisation (↓) generates an immune response capable of destroying untreated tumours.

Two tumours in TC-1 model. Median tumour volume of at least 4/6 animals in each group.
PROGRESSING CLINICAL TRANSLATION

Phase I study in healthy volunteers

Overall objective:
- Determine safety, tolerability and immune response of fimaVacc in healthy subjects

Design:
- Open-label, antigen-adjuvant controlled study (up to total 170 subjects)

Study consists of three parts:
1. Tolerability; 2. Dose finding; 3. Optimisation

Status:
- More than 80 subjects treated
- Part 1 completed
- Part 2 ongoing
  - Initial results indicate enhanced overall T-cell responses at tolerable dose levels, with early responses and high response rates
  - Dose finding continue to further explore efficacy
- Part 3 completion expected 2H 2018
THERAPEUTIC VACCINATION WITH fimaVACC

- Opportunity to play a key role in second generation immunotherapy

- Unique mode of action
  - induction of antigen specific cytotoxic T-cells by MHC class I antigen presentation in dendritic cells

- Broad applicability
  - peptide and protein antigens
  - particulate antigen formulations
  - prophylactic & therapeutic vaccination

- Initial results indicate enhanced T-cell induction at well tolerated dose levels

- Excellent stability
  - stable at room temperature
  - stable in solution
  - can be autoclaved

Patented disposable “band-aid-like” device for user-friendly illumination of the vaccination site
PCI TECHNOLOGY

► fimaNAC – mode of action

Target cell

Nucleic Acid Therapeutics

Endocytosis

Release into cytosol

Lysosomal Breakdown

siRNA
miRNA
mRNA
DNA
CRISPR

Knockdown of gene expression
Therapeutic protein production
Repair of genetic defects

nucleic acid therapeutic
**ENHANCING mRNA DELIVERY**

- Strongly increased GFP synthesis with increasing light doses

**fimaNAC** with polyethylenimine (PEI) vehicle

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>Control: PEI w/o fimaNAC</th>
<th>PEI w/ fimaNAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 s</td>
<td>1.4%</td>
<td>45.6%</td>
</tr>
<tr>
<td>30 s</td>
<td>1.2%</td>
<td>92.4%</td>
</tr>
<tr>
<td>60 s</td>
<td>8.9%</td>
<td>90.2%</td>
</tr>
</tbody>
</table>

**Cell survival**

- Control
- fimaNAC

7% positive vs 75% positive
VERSATILITY OF fimaNAC

- Delivery of many types of nucleic acid with many different vehicles *in vitro*

- **Main bottleneck in the field is delivery**
- **fimaNAC** can deliver many types of nucleic acids
- Enhancement by **fimaNAC** is best under conditions favourable for vehicle safety
  - Low ratio of vehicle to nucleic acid
  - Low concentration of vehicle/nucleic acid complex
- Especially advantageous *in vivo*
  - Difficult to achieve a high concentration of vehicle/nucleic acid complex in target cells
  - Toxicity may limit the amount of vehicle used

<table>
<thead>
<tr>
<th>Type of nucleic acid</th>
<th>Delivery vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmids</td>
<td>PEI, cationic peptides, cationic lipids, polylysine ++</td>
</tr>
<tr>
<td></td>
<td>Targeting to EGF-R, transferrin-R</td>
</tr>
<tr>
<td>siRNA</td>
<td>PEI, cationic peptides, dendrimers, lipofectamine, DOTAP, nanogels, chitosan ++</td>
</tr>
<tr>
<td>PNA (peptide nucleic acids)</td>
<td>None, cationic amino acids attached</td>
</tr>
<tr>
<td>mRNA</td>
<td>PEI, Protamine</td>
</tr>
<tr>
<td>Adenoviral vectors</td>
<td>None, cationic polymers</td>
</tr>
<tr>
<td>AAV vector</td>
<td>None</td>
</tr>
</tbody>
</table>

*Opportunistic approach – pursuing collaboration and partnering opportunities with major players at minimal internal resources*
RESEARCH COLLABORATIONS

Five active collaborations within nucleic acid therapeutics and vaccination

**fimaNAC**

**RXi Pharmaceuticals**
- Initiated Q2 2015. Listed on Nasdaq, developing innovative therapeutic siRNA
- Expanded to immuno-oncology following RXi’s MirImmune acquisition

**Top-10 large pharma**
- Initiated Q3 2015. A global leader in nucleic acid therapeutics
- Expanded in 2017 to include in vivo studies

**BioNTech**
- Initiated Q3 2016. German biotech company developing individualised cancer immunotherapies
- Clinical programmes in melanoma, head & neck, breast, ovarian and pancreatic cancer

**eTheRNA**
- Initiated Q4 2016. A global leader in mRNA-based immunotherapies
- Evaluate synergistic effects between companies’ technologies

**fimaVACC**

**Ultimovacs**
- Initiated Q1 2016. Norwegian immunotherapy company
- Therapeutic cancer vaccine against human telomerase

Research collaborations aim to evaluate synergies between the fima platform and partner technologies, with the potential for further partnerships
GOOD PROGRESS IN ALL AREAS

2017

✓ **fimaCHEM**  Granted orphan designation in the US

✓ **fimaCHEM**  Initiated extension of Phase I for repeated treatment

✓ **fimaCHEM**  Regulatory clarity on pivotal study requirements

✓ **fimaVACC**  Tolerability of the vaccination technology established

✓ **fimaVACC**  Promising initial immune response results

✓ **fimaNAC**  Preclinical research collaborations entering new stages
KEY MILESTONES ANTICIPATED

► 2018

1H 2018  ➢ fimaCHEM  Safety read-out of Phase I extension in bile duct cancer

1H 2018  ➢ fimaCHEM  Initiation of pivotal Phase II in bile duct cancer

2H 2018  ➢ fimaVACC  Completion of Phase I in healthy volunteers
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► Summary and outlook

► **fimaCHEM** – Preparing for pivotal Phase II in bile duct cancer
  – Encouraging tumour response and survival data with single treatment
  – Clinical Phase I study extension for safety of repeated treatments
  – Regulatory clarity on accelerated development path
  – Single pivotal Phase II with interim read planned initiated 1H 2018

► **fimaVACC** – Clinical validation of the vaccination platform
  – Initial vaccination results indicate enhanced cellular immune responses at tolerable dose levels
  – The results also suggest that vaccination trigger early responses and high response rates
  – Continue study to further explore efficacy

► **fimaNAC** – Progressing research collaborations
  – Four active collaborations with key players in the field
  – Opportunistic approach with limited need for resources
PCI BIOTECH HOLDING ASA

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