PHASE I STUDY
WITH PHOTOCHEMICAL INTERNALISATION (PCI)—A NOVEL TECHNOLOGY FOR TREATMENT OF PERIHILAR CHOLANGIOCARCINOMA

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**CHOLANGIOCARCINOMA (CCA)**

- Malignant proliferation of cholangiocytes – the epithelial cells lining the biliary tree

- ‘Cholangiocarcinoma’ includes
  - Intrahepatic tumours (10%*)
  - Perihilar tumours (60-70%*)
  - Distal tumours (20-30%*)
  - Differences in incidence, pathobiology and management

- Over 90% of CCA are adenocarcinomas

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

**Perihilar bile duct cancer is the initial target for PCI treatment**
CCA – Current Treatment Options

- Yearly incidence of 1-2 per 100,000 in the western world (higher incidences in Asia)
- Five-year survival rate < 5%
  - 0% when inoperable – average approx. 12 months survival

- Current management
  - Surgery
    - Only potentially curative treatment for CCA.
    - Less than ⅓ are resectable at presentation
  - Endoscopic treatment
    - Palliative endoscopic stenting
    - Photodynamic therapy (PDT)
  - Chemotherapy
    - Most commonly gemcitabine and cisplatin (ABC02 trial)

Key components of PCI

Targeted illumination is done using standard endoscopic procedure

Gemcitabine effect enhanced by PCI

PHOTOCHEMICAL INTERNALISATION (PCI)

- Endosomal release triggered through illumination
Photochemical internalisation (PCI) enhances the effect of gemcitabine \textit{in vitro} and \textit{in vivo}

- PCI enhances the effect of gemcitabine in bile duct cancer cells \textit{in vitro}
- PCI enhances the effect of gemcitabine in animal cancer \textit{in vivo} model
CHOLANGIOCARCINOMA (CCA)- CLINICAL PHASE I TRIAL

A Phase I/II Dose Escalation Study to Assess the Safety, Tolerability and Efficacy of Amphinex®-induced Photochemical Internalisation (PCI) of Gemcitabine followed by Gemcitabine/Cisplatin Chemotherapy in Patients with Advanced Inoperable Cholangiocarcinomas

Phase I

- Determination of tolerable dose and safety profile of Amphinex-induced PCI of gemcitabine followed by cis/gem chemotherapy
  - PCI + up to 8 cycles of cis/gem
  - 3+3 dose escalation design (light and/or Amphinex (fimaporfin) dose)
  - Cohort review committee evaluates each cohort
  - DLT window until d21 of 1st cycle cis/gem
  - Endpoints: DLTs, safety (AEs, labs, physical findings), PK
TRIAL STATUS

Phase I

- Dose escalation completed
  - 11 European study sites (UK, Germany, Norway)
  - 16 patients treated in 4 dose cohorts (4th cohort expanded)

- 11/16 patients completed 8 cycles of chemotherapy

- No mortality on-study

- No Dose Limiting Toxicity (DLT) observed

- Adverse Events seen during the DLT window
  - Photosensitivity reactions (mostly mild)
  - Abdominal pain
  - Cholangitis
TRIAL RESULTS

Response at target tumour level

6 months radiology data: Cohort III & IV – response at single lesion level

<table>
<thead>
<tr>
<th>Measurable lesions</th>
<th>Lesion shrinkage</th>
<th>Stable lesion</th>
<th>Lesion growth</th>
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| 19 (total number of targets selected across the two independent readers) | 17 | 5  
12 (lesion not detectable) | 1  
(<20% reduction & <10% increase) | 1  
(>10% mass increase) |

- Independent radiological evaluation of all patient images (Cohort III and IV)
- Images evaluated separately by two expert radiologists
- **Shrinkage of near 90% of selected target lesions, with more than 60% being undetectable at 6 months**

- **“Change in tumor size by RECIST correlates linearly with overall survival in Phase I oncology studies”**  
  (analysis of 24 phase I studies)  

1 Jain et al 2012 – JCO 30:2684–90
6 months radiology data: Cohort III & IV - (n=7 evaluable perihilar tumours)

<table>
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<tr>
<th>RECIST</th>
<th>PD</th>
<th>SD</th>
<th>PR</th>
<th>CR</th>
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- PD: Progressive disease (>20% growth)
- SD: Stable Disease
- PR: Partial Response (>30% shrinkage)
- CR: Complete Response (no visible tumour)

- Independent evaluation of patient images from Cohort III and IV per RECIST
- Images evaluated separately by two experts in bile duct cancer/cholangiocarcinoma

- Response rate exceeding 50% –
  far above expected results with standard treatment (Cis/Gem chemotherapy*)

Valle J. et al.
and personal communication
CONCLUSIONS

- PCI boosts the effect of gemcitabine locally in the bile duct

- Maintenance of biliary drainage is critical in this patient population
  survival benefit through local tumour control

- Phase-I includes low number of patients,
  nevertheless results indicate high objective tumor response rate

- Early indicators of efficacy using PCI treatment with fimaporfin and gemcitabine
  are encouraging