Hyperthermia European Adjuvant Trial
“HEAT”
Klinische Phase III Studie

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LMU München
Medizinische Klinik III – Campus Großhadern
Pancreatic cancer

*Incidence, mortality rate and total number of new cases per year*

<table>
<thead>
<tr>
<th>cancer</th>
<th>new cases per year in EU estimated for 1997</th>
<th>incidence *</th>
<th>mortality *</th>
</tr>
</thead>
<tbody>
<tr>
<td>cervix</td>
<td>22840</td>
<td>8.2</td>
<td>2.9</td>
</tr>
<tr>
<td>oesophagus</td>
<td>24736</td>
<td>3.7</td>
<td>3.3</td>
</tr>
<tr>
<td>prostate</td>
<td>145060</td>
<td>43.1</td>
<td>14.8</td>
</tr>
<tr>
<td>colon + rectum</td>
<td>221000</td>
<td>30.0</td>
<td>13.7</td>
</tr>
<tr>
<td>pancreas</td>
<td>40600</td>
<td>5.5</td>
<td>5.9</td>
</tr>
<tr>
<td>liver</td>
<td>30900</td>
<td>4.4</td>
<td>4.5</td>
</tr>
<tr>
<td>bladder</td>
<td>75030</td>
<td>10.1</td>
<td>3.5</td>
</tr>
<tr>
<td>ovary</td>
<td>34330</td>
<td>10.6</td>
<td>6.1</td>
</tr>
<tr>
<td>breast</td>
<td>220840</td>
<td>71.3</td>
<td>20.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>815336</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cancer</th>
<th>advanced (%)</th>
<th>new cases per year in EU advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>cervix</td>
<td>25.7</td>
<td>5870</td>
</tr>
<tr>
<td>oesophagus</td>
<td>44.2</td>
<td>10933</td>
</tr>
<tr>
<td>prostate</td>
<td>38.7</td>
<td>56138</td>
</tr>
<tr>
<td>colon + rectum</td>
<td>59.1</td>
<td>130611</td>
</tr>
<tr>
<td>pancreas</td>
<td>59.2</td>
<td>24035</td>
</tr>
<tr>
<td>liver</td>
<td>59.2</td>
<td>18293</td>
</tr>
<tr>
<td>bladder</td>
<td>14.7</td>
<td>11029</td>
</tr>
<tr>
<td>ovary</td>
<td>45.7</td>
<td>15689</td>
</tr>
<tr>
<td>breast</td>
<td>41.2</td>
<td>90986</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>363585</strong></td>
<td></td>
</tr>
</tbody>
</table>

*age standardised (world standard) rates (per 100,000) from EUCAN: http://www.dep.iarc.fr/eucan/eucan.htm*
Pancreatic cancer

20% resectable disease

- 5-year-survival rate 20%
- Median OS 11-20 months

80% unresectable disease

- gemcitabine failure within 6 months
- Median OS w/o treatment 1,9 months

80% recurrent disease

- Retroperitoneum: 35-85%
- Peritoneum: 20-55%
- Liver: 40-70%
- Lungs: 10-30%

Medical need for new treatment approaches
Heating Concepts for Locoregional Cancer at Different Sites

- **Head and neck/breast**: LHT
- **Abdominal/pelvic malignancies**: RHT
  - Pancreatic cancer
  - Sarcoma
- **Liver metastases**: RF ablation
- **Uterine fibroids**: high intensified focussed ultrasound (HIFU)
- **Prostate cancer**: interstitial hyperthermia
- **Glioblastoma**: Nanohyperthermia
- **Soft tissue sarcoma/melanoma**: hyperthermic isolated limb perfusion (HILP)
- **Peritoneal carcinomatosis**: hyperthermic intraperitoneal chemoperfusion (HIPEC)
**2nd-line Treatment in Gemcitabine-Refractory Pancreatic Cancer**

**REGIONAL HYPERTHERMIA** in pancreatic cancer

A phase II trial adding an upper abdominal heating technology (RHT) to gemcitabine and cisplatin as secondline chemotherapy

**Trial Title:**

Gemcitabine plus cisplatin chemotherapy with the addition of regional hyperthermia as secondline treatment in gemcitabine-refractory patients with locally advanced or metastatic pancreatic cancer

**A phase II open clinical trial**

EudraCT-Nummer: 2005-003855-11

**For patients with:**

Failure after:

- Adjuvant gemcitabine-based treatment

- OR

- 1\textsuperscript{st}-line gemcitabine-based treatment

Gemcitabine + Cisplatin + RHT
Additive effect of gemcitabine plus hyperthermia

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Journal</th>
</tr>
</thead>
</table>
Additive effect of cisplatin plus hyperthermia

Hyperthermic potentiation of cis-diamminedichloroplatinum (II) cytotoxicity in Chinese hamster ovary cells resistant to the drug

Wallner KE, DeGregorio MW, Li GC
*Cancer Res.* 1986

The cytotoxic effect of cis-diamminedichloroplatinum (II) on cultured Chinese hamster ovary cells at elevated temperatures: Arrhenius plot analysis

Urano M, Kahn J, Majima H, Gerweck LE
*Int J Cancer* 1995

Enhancement of cisplatin sensitivity and platinum uptake by 40 degrees °C hyperthermia in resistant cells

Ohtsubo T, Saito H, Tanaka N, Matsumoto H, Sugimoto C, Saito T, Hayashi S, Kano E
*Cancer Lett.* 1997

*Cisplatin* sensitization by concurrent mild hyperthermia in parental and mutant cell lines deficient in homologous recombination and non-homologous endjoining repair.

Raaphorst GP, Li LF, Yang DP, LeBlanc JM
*Oncol Rep* 2005
Retrospective data analysis

Gemcitabine + Cisplatin with RHT after firstline gemcitabine-failure

**Firstline Treatment**

G mono (N = 23)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine 1000mg/m²</td>
<td>Cisplatin 25mg/m²</td>
<td>------</td>
<td>Cisplatin 25mg/m²</td>
</tr>
<tr>
<td>------</td>
<td>RHT</td>
<td>------</td>
<td>RHT</td>
</tr>
</tbody>
</table>

Repeat day 15, 29, 43 (bloc I)
A total of two blocs (I + II) are applied
# Toxicity
(according to ctc v4.0)

## Hematological

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
<th>Number of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

## Non-hematological

<table>
<thead>
<tr>
<th></th>
<th>Number of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine elevation (max grade 1/2)</td>
<td>10</td>
</tr>
</tbody>
</table>

## RHT-related toxicity

<table>
<thead>
<tr>
<th></th>
<th>Number of events over all treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort</td>
<td>5</td>
</tr>
<tr>
<td>Pain- Power-related</td>
<td>10</td>
</tr>
<tr>
<td>Pain- Position-related</td>
<td>15</td>
</tr>
</tbody>
</table>
CT-scans during therapy

Patient ID 851
06/2005: First diagnosis
15.06.05: Start Gem mono therapy

CT scan 19.07.05: PD

25.07.05: Start block I Gem+Cis+RHT
20.09.05: NC
11.10.05: Start block II Gem+Cis+RHT

CT scan 12.12.05: PR

07/2005 12/2005
### Disease Control rate: 32%

<table>
<thead>
<tr>
<th>Enrolled / assessable</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>23/16</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

### Time To Progression

<table>
<thead>
<tr>
<th>Number of pts</th>
<th>TTP1 Months</th>
<th>TTP (GP + RHT) Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>5.9 (CI: 2.6; 9.2)</td>
<td>4.3 (CI: 1.2; 7.4)</td>
</tr>
</tbody>
</table>

### Overall Survival

<table>
<thead>
<tr>
<th>Number of pts</th>
<th>Status Alive/Dead</th>
<th>OS</th>
<th>OS (GP + RHT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>1/22</td>
<td>12.9 (CI: 10.6; 18.9)</td>
<td>5.4 (CI: 2.9; 7.9)</td>
</tr>
</tbody>
</table>
Hyperthermia European Adjuvant Trial (HEAT)

Prospective randomized phase III clinical trial
EudraCTNumber: 2008-004802-14

Resectable Pancreatic Cancer

Staging

Surgical Resection
R0/R1 (± N; M0)

Stratification R0/1 and N+/− and T-stage

Randomization

Start: 4-8 weeks postop.

Arm G (n= 183):
gemcitabine 1000 mg/m²
days 1, 8, and 15

total number of courses: 6
total dose of gemcitabine: 18 g/m²

Arm G + Cis + RHT (n= 183):
gemcitabine 1000 mg/m²
days 1 and 15

cisplatin 25mg/m² with regional hyperthermia
days 2, 4 and 16, 18

total number of courses: 6
Total dose of gemcitabine: 12 g/m²

Follow up

Primary endpoint: DFS

DFS: 14 months

DFS: 19 months
Statistical considerations

Hypothesis: Study designed to have 80% power to detect an increase in median disease free survival from 14 to 19 months (HR 0.72).

Sample size:
- 183 patients per treatment arm
- Interim analysis after 99, 198 and 296 events based on a group-sequential design
- Intent to treat analysis (ITT)

<table>
<thead>
<tr>
<th>Primary endpoint:</th>
<th>Disease free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary endpoint:</td>
<td>Overall survival</td>
</tr>
<tr>
<td></td>
<td>Quality of Life</td>
</tr>
<tr>
<td></td>
<td>Toxicity profile</td>
</tr>
<tr>
<td>Recruitment:</td>
<td>122 pts per year</td>
</tr>
<tr>
<td></td>
<td>recruitment period: 3 years</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>2 years</td>
</tr>
</tbody>
</table>

15.04.2011 Application for funding (deutsche Krebshilfe)
Phase III: Regional Hyperthermia (RHT) Technology

ESHO quality assurance guidelines for regional hyperthermia

Regional Hyperthermia
Applicator Adjustment

Abdomen/Pelvis:
- Pancreatic cancer
- Liver metastasis
- Soft tissue sarcoma
Local progression-free (LPFS) survival in patients with macroscopically complete surgical resection (N=149)

HR=0.60 (95% CI 0.37-0.97); p=0.034

Number at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy + RHT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>76</th>
<th>51</th>
<th>26</th>
<th>19</th>
<th>19</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIA + RHT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EIA</td>
<td>73</td>
<td>35</td>
<td>18</td>
<td>11</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
Disease-free survival (DFS) in patients with macroscopically complete surgical resection (N=149)

HR=0.65 (95% CI 0.44-0.96); p=0.031

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>EIA+RHT</td>
<td>76</td>
</tr>
<tr>
<td>EIA</td>
<td>73</td>
</tr>
</tbody>
</table>
Centers - Surgery

(1) University of Munich - Campus Großhadern
(2) University of Munich - Campus Innenstadt
(3) Rotkreuzklinikum, Munich
(4) Klinikum München-Bogenhausen, Munich
(5) Klinikum Ingolstadt
(6) Klinikum Dachau
(7) Klinikum Regensburg
(8) Klinikum Memmingen
(9) University of Berlin – Charité
(10) University of Düsseldorf
(11) University of Tübingen
(12) University of Freiburg
Centers - Hyperthermia

(1) University of Munich - Campus Großhadern
(2) Rotkreuzklinikum, Munich
(3) Klinik Bad Trissl, Oberaudorf
(4) HELIOS Schlossbergklinik, Oberstaufen
(5) University of Erlangen
(6) University of Berlin – Campus Virchow
(7) University of Düsseldorf
(8) University of Mannheim
(9) University of Tübingen
Hyperthermia European Adjuvant Trial (HEAT) – Translational research program

Topics and Participating Centers

- Histopathomorphology
  - Prof. Dr. Th. Kirchner
  - Dept. of Pathology

- Neoangiogenesis
  - PD Dr. Ch. Bruns
  - Dept. Of Surgery

- Stress response
  - PD Dr. E. Noessner
  - HGF, IMI
  - D. K. Lechner
  - KKG Hyperthermia

- Tumor microenvironment
- Gene expression profiling

- Pharmacodynamic studies
  - Prof. Dr. V. Heinemann
  - Med. Clinic III

- HSP27 as predictive factor
  - Dr. E. Gallmaier
  - Med. Clinic II

Prof. Dr. R. D. Issels
Dr. K. Lechner, Dr. E. Kampmann
KKG Hyperthermia
Med. Clinic III

- Paraffin-embedded tissue
- Heparinized blood samples
HEAT
Hyperthermia European Adjuvant Trial®

REGIONAL HYPERTHERMIA in pancreatic cancer

A phase III trial adding an upper abdominal heating technology (RHT) to standard chemotherapy

**Trial Title:**
A randomized two-armed open study on the adjuvant therapy in patients with R0/R1 resected pancreatic carcinoma with Gemcitabine alone vs. Gemcitabine plus Cisplatin with regional hyperthermia

**Trial Design:**
- **For patients with:**
  - Complete (R0) or marginal (R1) resected pancreatic cancer
  - Any ductal adenocarcinoma
  - Age ≥ 18 years
  - ECOG 0 - 2
  - N = 366

**Randomization 1:1**

**Gemcitabine Standard**
Gemcitabine 1000 mg/m²: days 1, 8 and 15, q4w

**Primary Endpoint: Disease-free Survival**

**Gemcitabine + Cisplatin + RHT**
Gemcitabine 1000 mg/m²: days 1 and 15, q4w
Cisplatin 25 mg/m²: days 2, 4 and 16, 18, q4w
Regional Hyperthermia 60 min, 42°C: days 2, 4 and 16, 18, q4w

**Secondary Endpoints:**
- Comparative overall survival (OS) of patients receiving gemcitabine or gemcitabine + cisplatin + regional hyperthermia
- Comparative DFS and OS of the subgroup of patients receiving at least 4 complete courses of gemcitabine or gemcitabine + cisplatin + regional hyperthermia

For more information, please visit www.pancreas-heat.com or call the HEAT Coordinators Trial Office: +49-89-7095 4768
e-mail to: rolf.issels@med.uni-muenchen.de

Supported by the European Society for Hyperthermic Oncology (ESHO)