Perioperative Chemotherapy (FLOT) Compared To Neoadjuvant Chemoradiation (CROSS) in Patients With Adenocarcinoma of the Esophagus

Investigator Meeting
22th September 2016
Hamburg

Contact
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Department of General and Visceral Surgery
Hugstetter Str. 55
79106 Freiburg, Germany
Rationale and Evidence CROSS

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer
P. van Hagen, M.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg,

CRT (n=175) vs Surgery alone (n=184)
SCC n=84 / AC n=275

Pulmonary Morbidity: 46 % vs 44 %
Hospital Mortality 4 % vs 4%

Subgroup AC:
5-J ÜL SCC: 44% vs 34%
adjusted HR 0.741; p=0.07

naCRT: 41.4Gy + Carboplatin/Paclitaxel
Rationale and Evidence MAGIC

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer


CTX (n=250) vs Surgery alone (n=253)
Esophagus/GEJ 26% / Stomach 74%
Postoperative Morbidity: 46 % vs 45 %
30-day Mortality 5.6 % vs 5.9 %
5-J ÜL: 36% vs. 23%

periCTX: Epirubicin/Cisplatin/5-FU
Rationale and Evidence ACCORD

Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial

Marc Ychou, Valérie Boige, Jean-Pierre Pignon, Thierry Conroy, Olivier Bouché, Gilles Lebreton, Muriel Ducourtieux, Laurent Bedenne, Jean-Michel Fabre, Bernard Saint-Aubert, Jean Genève, Philippe Lasser, and Philippe Rougier

periCTX (n=113) vs Surgery alone (n=111)

Esophagus/GEJ 75% / Stomach 25%

periCTX: Cisplatin/5-FU

Postoperative Morbidity: 26 % vs 19 %

Postoperative Mortality 4.6 % vs 4.5 %

5-J ÜL: 38% vs. 24%
Rationale and Evidence FLOT

Pathological complete remission in patients with oesophagogastric cancer receiving preoperative 5-fluorouracil, oxaliplatin and docetaxel

Nils Homann1,2, Claudia Pauligk1, Kim Lukey1, Thomas Werner Kraus3, Hans-Peter Bruch5, Akin Atmaca3, Frank Noack6, Hans-Michael Altmannsberger2, Elke Jäger3 and Salah-Eddin Al-Ratran1

Esophagus/GEJ n=23 Stomach n=23
FLOT (4x) – Surgery – FLOT (4x)

Total/subtotal (1a/1b) regression after neoadjuvant FLOT: 39%

Table 2. Histopathological regression (n = 46)

<table>
<thead>
<tr>
<th>Pathological regression, grade</th>
<th>No. of patients (%)</th>
<th>95% CI1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a (complete)</td>
<td>8 (17.4)</td>
<td>6.6–34.7</td>
</tr>
<tr>
<td>1b (subtotal)</td>
<td>10 (21.7)</td>
<td>9.5–40.7</td>
</tr>
<tr>
<td>2 (partial)</td>
<td>11 (23.9)</td>
<td>10.0–43.1</td>
</tr>
<tr>
<td>3 (minor/none)</td>
<td>15 (32.6)</td>
<td>17.2–52.6</td>
</tr>
<tr>
<td>NE2</td>
<td>2 (4.3)</td>
<td>0.3–18.0</td>
</tr>
</tbody>
</table>

Table 3. Description of patients who achieved a pCR

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Gender</th>
<th>ECOG PS</th>
<th>Location of primary</th>
<th>TNM initial</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>1</td>
<td>Cardia</td>
<td>T3N + M0</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>1</td>
<td>Cardia</td>
<td>T3N + M0</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>1</td>
<td>Cardia</td>
<td>T3N + M1</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>1</td>
<td>Lower oesophagus1</td>
<td>T3N + M0</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>1</td>
<td>Cardia</td>
<td>T3N + M0</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>1</td>
<td>Antrum</td>
<td>T3N + M0</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>0</td>
<td>Lower oesophagus1</td>
<td>TNxM1</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>2</td>
<td>Cardia</td>
<td>T3N + M0</td>
</tr>
</tbody>
</table>
Rationale and Evidence

- Benefit for overall survival for neoRCTX and periCTX in RCT
- CROSS, MAGIC, ACCORD: no increase of morbidity and mortality
- PeriCTX RCT only in mixed collectives of EAC and GC
- More benefits of periCTX by EAC/GEJ-tumor (?)
- FLOT is popular in Germany without RCT data
- In US and Netherland CROSS considered and used as best evidence for EAC since 2013. Increasingly also in Germany.

**PeriCTX or neoCRT for EAC?**
Study Design

Adenocarcinoma of the esophagus / GEJ

Prospective RCT / Phase III

Multicenter (18 sites)

438 randomized patients

Primary endpoint: Overall survival

Secondary endpoints:

- PFS / RFS
- postoperative M&M
- Quality of life
## Participating Centers

<table>
<thead>
<tr>
<th>Site No.</th>
<th>City</th>
<th>Initiation date</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Freiburg</td>
<td>19.01.16</td>
</tr>
<tr>
<td>02</td>
<td>Magdeburg</td>
<td>15.04.16</td>
</tr>
<tr>
<td>03</td>
<td>Würzburg</td>
<td>10.05.16</td>
</tr>
<tr>
<td>04</td>
<td>Münster</td>
<td>01.07.16</td>
</tr>
<tr>
<td>05</td>
<td>Aachen</td>
<td>13.07.16</td>
</tr>
<tr>
<td>06</td>
<td>Leipzig</td>
<td>24.05.16</td>
</tr>
<tr>
<td>07</td>
<td>Lübeck</td>
<td><em>Initiation planned</em></td>
</tr>
<tr>
<td>08</td>
<td>Mainz</td>
<td>07.04.16</td>
</tr>
<tr>
<td>09</td>
<td>Kiel</td>
<td>13.05.16</td>
</tr>
<tr>
<td>10</td>
<td>München</td>
<td>06.04.16</td>
</tr>
<tr>
<td>11</td>
<td>Hamburg</td>
<td>24.05.16</td>
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<tr>
<td>12</td>
<td>Düsseldorf</td>
<td>31.08.16</td>
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<tr>
<td>13</td>
<td>Dresden</td>
<td>28.06.16</td>
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<tr>
<td>14</td>
<td>Offenbach</td>
<td>19.05.16</td>
</tr>
<tr>
<td>15</td>
<td>Berlin</td>
<td>15.07.16</td>
</tr>
<tr>
<td>16</td>
<td>Göttingen</td>
<td>10.08.16</td>
</tr>
</tbody>
</table>
Recruitment target:

- 3-4 patients every week -> GOAL: 438 randomized patients
- 20% Screen failure -> 550 patients will be screened
Patient recruitment (21.09.2016)
Patient recruitment (21.09.2016)

Patients by randomisation

- Arm A (FLOT)
- Arm B (CROSS)

01 Freiburg: 3 Arm A, 5 Arm B
03 Würzburg: 1 Arm A, 2 Arm B
04 Münster: 1 Arm A, 1 Arm B
05 Aachen: 1 Arm A, 1 Arm B
08 Mainz: 2 Arm A, 1 Arm B
11 Hamburg: 2 Arm A
13 Dresden: 1 Arm A
# Upcoming sites

<table>
<thead>
<tr>
<th>Upcoming sites</th>
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</thead>
<tbody>
<tr>
<td>Klinikum Stuttgart</td>
</tr>
<tr>
<td>Universitätsklinikum Frankfurt</td>
</tr>
<tr>
<td>Asklepios Klinik Altona</td>
</tr>
<tr>
<td>Klinikum Mutterhaus Trier</td>
</tr>
<tr>
<td>Johannes Wesling Klinikum Minden Mühlenkreiskliniken (AöR)</td>
</tr>
<tr>
<td>Klinikum Nürnberg</td>
</tr>
<tr>
<td>Klinikum St. Elisabeth Straubing</td>
</tr>
<tr>
<td>Uniklinik Köln</td>
</tr>
<tr>
<td>Klinikum Dortmund</td>
</tr>
<tr>
<td>Charité Campus Benjamin Franklin</td>
</tr>
</tbody>
</table>
Participating Centers

In total 25 sites in Germany

15 recruiting sites

10 upcoming sites (initiation planned for November / December 2016)
ESOPEC: prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (NCT02509286)

Jens Hoeppner¹, Florian Lordick², Thomas Brunner³, Torben Glatz¹, Peter Bronsert⁴, Nadine Röthling⁵, Claudia Schmoor⁵, Dietmar Lorenz⁶, Christian Ell⁷, Ulrich T. Hopt¹ and J. Rüdiger Siewert⁸
Hoeppner et al. ESOPEC: A prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy to neoadjuvant chemoradiation in patients with adenocarcinoma of the esophagus (NCT02509286).

J Clin Oncol 34, 2016 (suppl; abstr TPS4131)
## Trial timetable

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Ethic committee / Competent authority</td>
<td>Nov 2015 / Dec 2015</td>
</tr>
<tr>
<td>Initiation first site</td>
<td>19.01.2016</td>
</tr>
<tr>
<td>Enrolment of first patient in (FPFV)</td>
<td>09.02.2016</td>
</tr>
<tr>
<td>Initiation last site</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>Enrolment of 25% of patients (110 patients)</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>Enrolment of 50% of patients (219 patients)</td>
<td>Sep 2017</td>
</tr>
<tr>
<td>Enrolment of 75% of patients (334 patients)</td>
<td>Jun 2018</td>
</tr>
<tr>
<td>Enrolment of last patient (LPI) (438 patients)</td>
<td>Feb 2019</td>
</tr>
<tr>
<td>End of trial for last patient (LPLV)</td>
<td>Feb 2022</td>
</tr>
<tr>
<td>Final statistical analysis</td>
<td>May 2022</td>
</tr>
</tbody>
</table>
Don’t forget Quality of Life Questionnaires

- prior to treatment
- after end of pre-operative treatment
- Discharge
- Follow Up

Recurrence / progression -→ to Freiburg

Premature end of treatment -→ to Freiburg

Each SAE has a corresponding AE
Monitoring Visits

- 15 sites are initiated
- Monitoring depends on the number of randomized patients
- Freiburg had the first interim monitoring visit on 27\textsuperscript{th} July 2016, summary:
  - Corrections must be done GCP conform (in the patient information and in the CRF)
  - 1 patient denied surgery and postoperative treatment
  - 1 patient discontinued pre-operative treatment due to neutropenia
  - CRFs must be signed by the investigator in a timely manner
  - CRF pages must be filled completely (e.g. head of the pages)
Frequently asked Questions

- Treatment (Chemotherapy and radiotherapy)
- Prohibited medication
- Time schedule preoperative treatment / surgery / postoperative treatment
- Diagnostic
- Discontinuation of patients
- Integration of practitioner
Translational projects

Circulating Tumor Cells as Biomarker in EAC
Proteomic Determinants of Malignancy in EAC
Prognostic and predictive biomarkers in EAC
Translational projects background

*Circulating Tumor Cells as Biomarker in EAC*

- To investigate the correlation of the CTC with the final pathologic remission status.
- To investigate the number of patients with CTC in their peripheral blood, to evaluate the change in the number of cells after neoadjuvant chemotherapy/radiochemotherapy and if the cells persist after the treatment course.
- The presence/enumeration of CTC will be correlated with recurrence-free and overall-survival.
- The prediction value of increase or decrease of these CTC should be investigated as a predictive tool in patients with EAC.

*Central laboratories*

**Dr. Matthias Reeh**
Forschungslabor der Allgemeinchirurgie
Universitätsklinikum Hamburg-Eppendorf
Campus Forschung – Gebäude N27
Martinistraße 52, 20246 Hamburg

**Dr. Birte Kulemann**
Klinik für Allgemein- und Viszeralchirurgie
Universitätsklinikum Freiburg
Hugstetter Straße 55, 79106 Freiburg
Translational projects background

Proteomic Determinants of Malignancy in EAC

- Analyse and compare proteomic expression patterns in a validation cohort of primary biopsies, comprising ten responding and ten non-responding patients.

- Up to 10 proteins that distinguish the two cohorts will be immunohistologically translated in a larger testing cohort also comprising responding and non-responding patients.

- The presence of response predicting biomarkers will be analysed in a cohort of resection specimens and correlated as described below.

- Results will be correlated with classical clinic-pathological parameters (TNM classification, overall and disease free survival) and histological tumor regression.

Central pathology

Dr. Peter Bronsert / Prof. Werner
Institut für Klinische Pathologie
Universitätsklinikum Freiburg
Breisacher Straße 115a, 79106 Freiburg
Prognostic and predictive biomarkers in EAC

- Investigate a range of blood derived markers potentially related to the prognosis and/or the prediction of response to neoadjuvant treatment.

- Perform proteomic profiling of amino acids and acylcarnitines by mass-spectroscopy, which were already shown to represent promising biomarkers in EAC.

- Circulating tumor DNA derived from the plasma as well as circulating miRNA will be collected to allow further analysis, holding promise to provide insights into the biology of the tumour and the effects of therapeutic interventions.

Central laboratory

Prof. Dr. Florian Lordick
Universitäres Krebszentrum Leipzig (UCCL)
Universitätsklinikum Leipzig AöR
Liebigstraße 20, Haus 4, 04103 Leipzig
Arrangements to support sites

• What can we do to support your site to recruit patients?
  – Integration of practitioners
  – Cooperation with other study sites for patient treatment close to home

• Recruitment material
  – Flyer, Poster, Letter for practitioners, trial business cards, pocket cards ...

• Other
  – Presentations, trainings ...
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