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

Investigator Meeting
17th September 2015
CCL Leipzig


**Contact**

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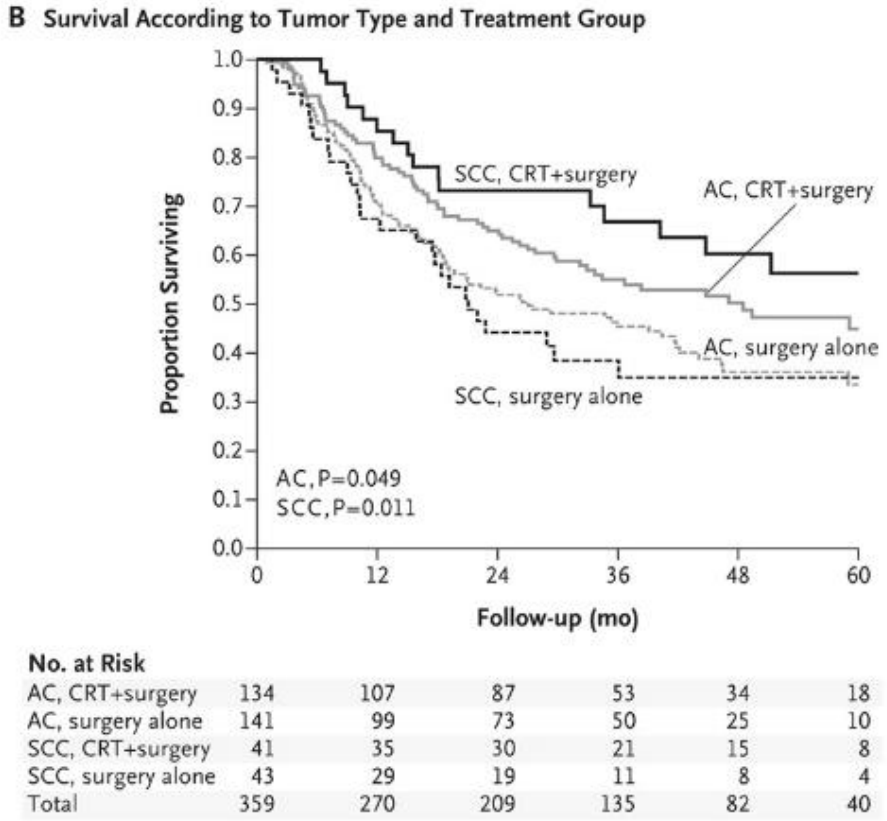
# Rationale and Evidence CROSS




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| AC, CRT+surgery | 134 | 107 | 87 | 53 | 34 | 18 |
| AC, surgery alone | 141 | 99 | 73 | 50 | 25 | 10 |
| SCC, CRT+surgery | 41 | 35 | 30 | 21 | 15 | 8 |
| SCC, surgery alone | 43 | 29 | 19 | 11 | 8 | 4 |
| Total | 359 | 270 | 209 | 135 | 82 | 40 |

**naCRT: 41,4Gy + Carboplatin/Paclitaxel**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.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%

**<u>Subgroup AC:</u>**

**5-J ÜL SCC: 44% vs 34%**

**adjusted HR 0.741; p=0.07**

# Rationale and Evidence MAGIC

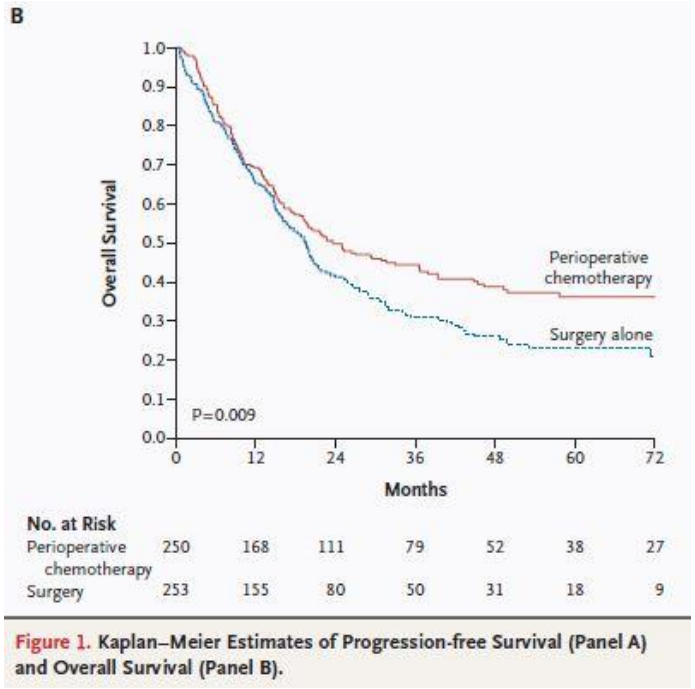



Figure 1. Kaplan–Meier Estimates of Progression-free Survival (Panel A) and Overall Survival (Panel B).

## Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

CTX (n=250) vs Surgery alone (n=253)

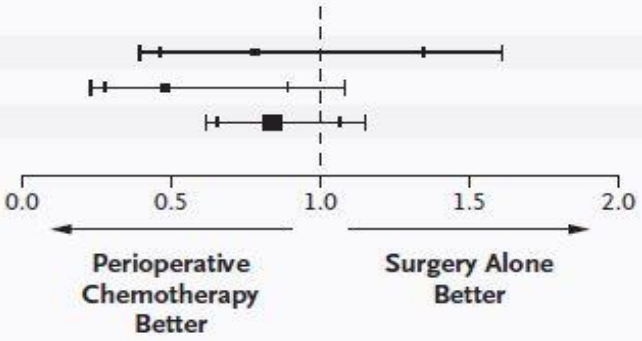
Esophagus/GEJ 26% / Stomach 74%

Postoperative Morbidity: 46 % vs 45 %

30-day Mortality 5,6 % vs 5,9 %

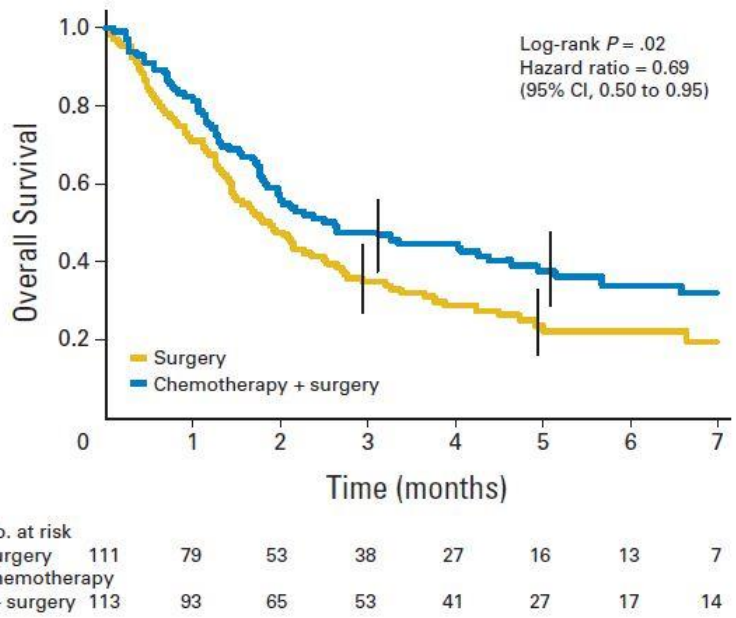
**5-J ÜL: 36% vs. 23%**

| Site of primary tumor | | |
|---|---|---|
| Lower esophagus | 23/37 | 25/36 |
| Esophagogastric junction | 13/28 | 23/30 |
| Stomach | 113/185 | 122/187 |
| Total | 149/250 | 170/253 |




periCTX: Epirubricin/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)

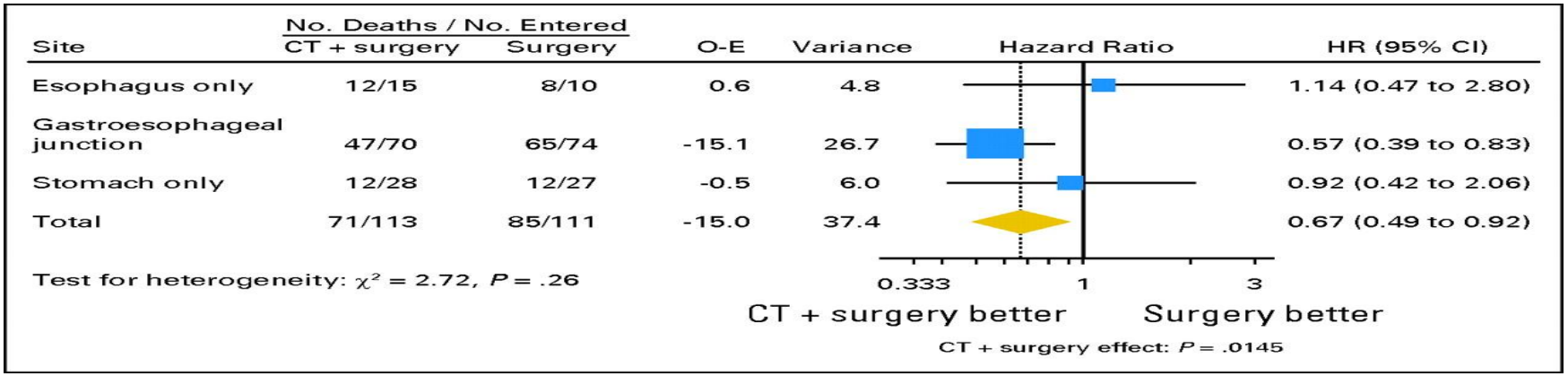
Esophagus/GEJ 75% / Stomach 25%

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

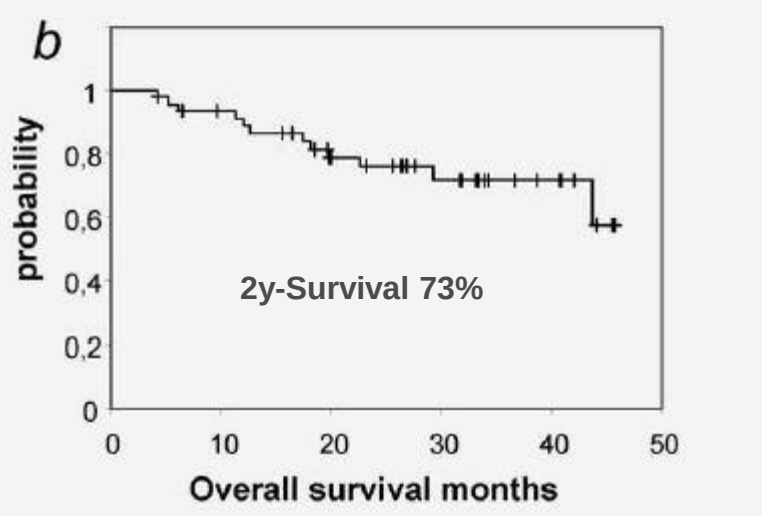



Table 2. Histopathological regression ($n = 46$)

| Pathological regression, grade | No. of patients (%) | 95% CI[1] |
|---|---|---|
| 1a (complete) | 8 (17.4) | 6.6–34.7 |
| 1b (subtotal) | 10 (21.7) | 9.5–40.7 |
| 2 (partial) | 11 (23.9) | 10.0–43.1 |
| 3 (minor/none) | 15 (32.6) | 17.2–52.6 |
| NE[2] | 2 (4.3) | 0.3–18.0 |

uicc global cancer control

IJC International Journal of Cancer

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

Nils Homann[1,2], Claudia Pauligk[3], Kim Luley[2], Thomas Werner Kraus[4], Hans-Peter Bruch[5], Akin Atmaca[3], Frank Noack[6], Hans-Michael Altmannsberger[7], Elke Jäger[3] and Salah-Eddin Al-Batran[3]

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

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

Table 3. Description of patients who achieved a pCR

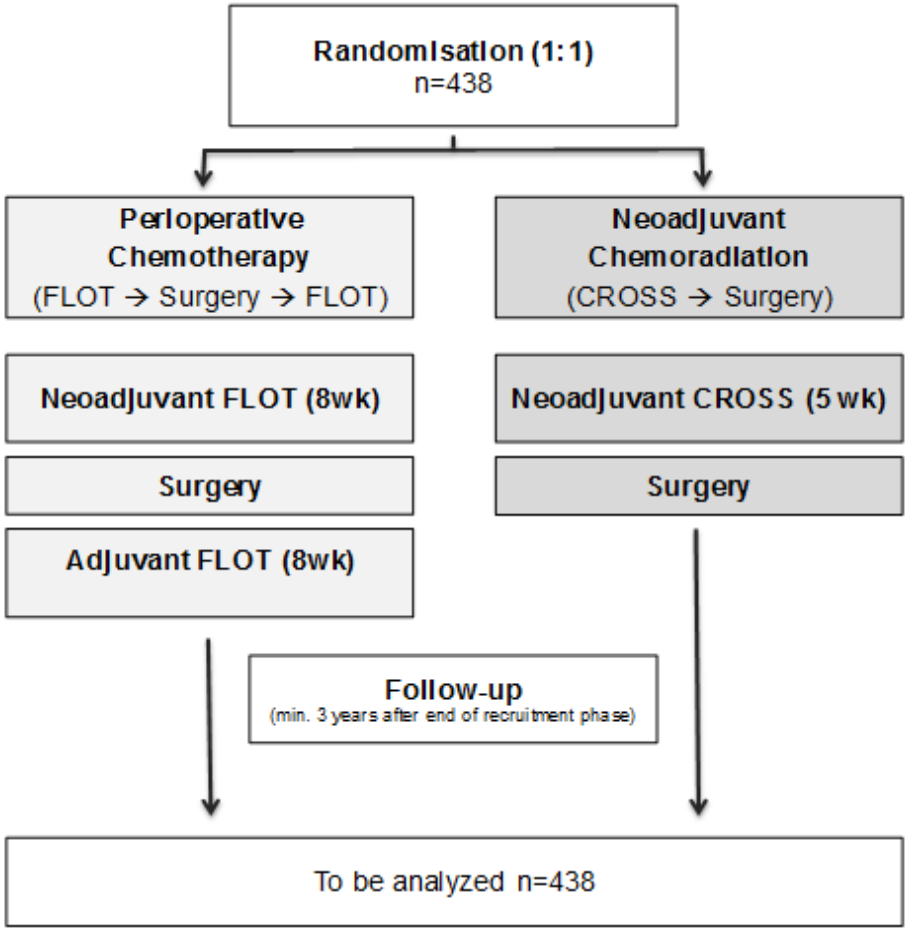
| Patient number | Gender | ECOG PS | Location of primary | TNM initial |
|---|---|---|---|---|
| 1 | Male | 1 | Cardia | T3N + M0 |
| 2 | Female | 1 | Cardia | T3N + M0 |
| 3 | Male | 1 | Cardia | T3N + M1 |
| 4 | Male | 1 | Lower oesophagus[1] | T3N + M0 |
| 5 | Male | 1 | Cardia | T3N + M0 |
| 6 | Female | 1 | Antrum | T3N + M0 |
| 7 | Male | 0 | Lower oesophagus[1] | TxNxM1 |
| 8 | Male | 2 | Cardia | T3N + M0 |

# 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 by 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

# Inclusion criteria (1/2)

- Histologically proven adenocarcinoma of the esophagus according to the UICC TNM7 definition. Both tumors of the esophagus and tumors of which the epicentre is within 5 cm of the esophagogastric junction and also extend into the esophagus are elegible for inclusion into the trial in case of adenocarcinomatous histology.

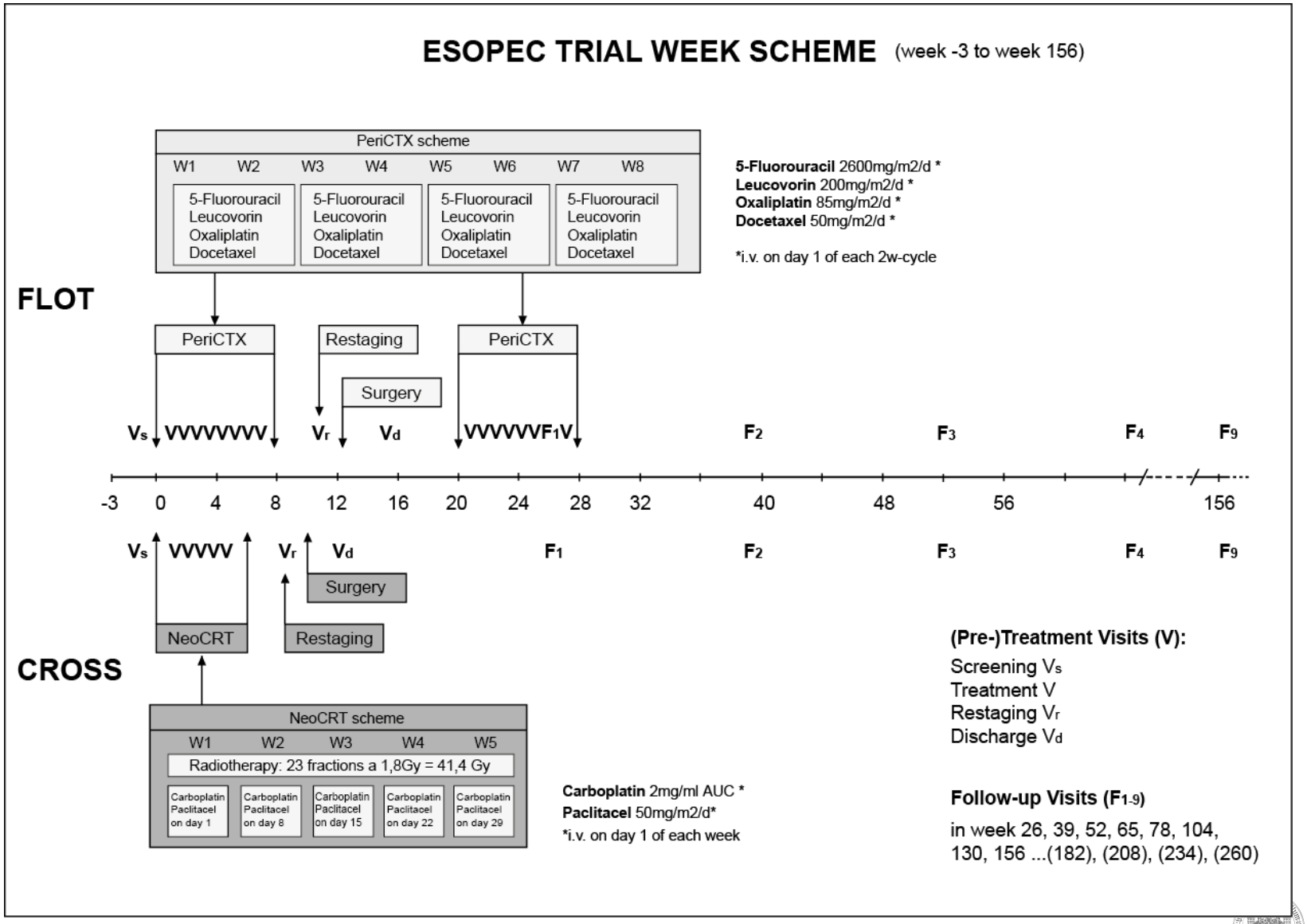
  **Therefore all Type AEG 1 are eligible. Type AEG 2 and Type AEG 3 are eligible in case of tumorous esophageal infiltration.**

- **Pre-treatment stage cT1N+ M0 or cT2-4a N0/N+, M0.**

# Inclusion criteria (2/2)

- Age ≥ 18 years
- No prior abdominal or thoracic radiotherapy
- ECOG Performance status 0-2
- Adequate cardiac function
- Adequate respiratory function
- Adequate bone marrow function
- Adequate renal function
- Adequate liver function
- Written informed consent and ability to understand the nature of the study and the study related procedures and to comply with them

# ESOPEC Study: FLOT vs CROSS



# FLOT-Arm

- The **FLOT arm** consists of 4 cycles of chemotherapy prior to surgery and a further 4 cycles of chemotherapy post-surgery.
- Each cycle of chemotherapy lasts 14 days (2 weeks).
- The drugs used in the FLOT regimen include 5-flourouracil, leucovorine, oxaliplatin and docetaxel.
- They are applied intravenously according to the following scheme: 5-FU 2600 mg/m² (24 hours) day 1 and leucovorin 200 mg/m² (2h), day 1 and oxaliplatin 85 mg/m² (2h) day 1, and docetaxel 50mg/m2 (1h), every two weeks.
- Four neoadjuvant cycles are given over 8 weeks prior to surgery and 4 adjuvant cycles are given over 8 weeks post-surgery.

# CROSS-Arm

- The **CROSS arm** consists of the CROSS protocol, which includes a combination of chemotherapy and radiotherapy prior to surgery.
- The patient will receive 5 weeks of radiation therapy and 5 weekly cycles of chemotherapy.
- Patients will be radiated by external beam radiation, using 3D conformal radiation technique.
- In detail, radiotherapy with concurrent intravenous chemotherapy is given according to the following scheme: Radiotherapy with 41.4Gy given in 23 fractions of 1.8Gy: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31. Chemotherapy: paclitaxel 50mg/m2 (1h) day 1, 8, 15, 22, 29 and carboplatin (2mg/ml/min AUC) (1h) day 1, 8, 15, 22 and 29.

# Surgery (1/4)

- In both arms Surgery is carried out **preferably 4 to 6 weeks** after the end of neoadjuvant treatment.
- **Open or minimally invasive or hybrid resection techniques are allowed** according to local standards.

# Surgery (2/4)

**Resection of EAC**

- **AEG type 1** tumors are treated by transthoracic subtotal esophagectomy.
- **AEG Type 2** tumors are treated either by transthoracic subtotal esophagectomy, transabdominal distal esophageal resection plus gastrectomy or by esophagogastrectomy, depending on both patient characteristics and local centre expertise.
- **AEG Type 3** which are substantially infiltrating the esophagus above the Z-line are surgically treated by transabdominal distal esophageal resection plus gastrectomy.

# Surgery (3/4)

**Extent of Lymphadenectomy**

- In case of abdominothoracic esophagectomy and esophagogastrectomy, a **mediastinal and abdominal 2-field lymphadenectomy** is carried out. In case of transhiatal resection of the distal esophagus plus gastrectomy, **lower mediastinal and abdominal D2-lymphadenectomy** is performed.

# Surgery (4/4)

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**Surgical Reconstruction**

- After transthoracic esophagectomy, the continuity of the digestive tract will be restored by a **gastric tube reconstruction or colonic interposition procedure with an intrathoracic or cervical anastomosis**.
- Reconstruction for transabdominal lower esophageal resection plus gastrectomy will be carried out by **esophagojejunostomy**.

# Endpoints

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**Primary Endpoint**

- Overall survival time of the patient. Calculated as time from start of study treatment to death due to any cause. After randomisation, patients will be followed up for a minimum duration of 36 months or until death.

# Endpoints

**Secondary Endpoints**

*Perioperative endpoints assessed at discharge from hospital after surgery:*

<u>Postoperative pathologic stage:</u>

- Resectional status (R0/R1/R2)
- Histo-pathological regression after neoadjuvant treatment according to Becker et al.
- Postoperative pathology according to the TNM system

# Endpoints

**Secondary Endpoints**

*Perioperative endpoints assessed at discharge from hospital after surgery:*

<u>Surgical site complications:</u>

- Frequency of anastomotic leakage.
- Frequency of intrathoracic fluid collection or abscess requiring invasive treatment
- Frequency of intraabdominal fluid collection or abscess requiring invasive treatment
- Frequency of surgical site infection according to the CDC-Definition

# Endpoints

## Secondary Endpoints

*Perioperative endpoints assessed at discharge from hospital after surgery:*

Non-surgical site complications:

- Postoperative mortality (30-day postoperative mortality)
- Frequency of postoperative pneumonia
- Frequency of postoperative Acute Respiratory Distress Syndrome (ARDS)
- Frequency of postoperative major bronchic sputum with atelectasis
- Frequency of postoperative respiratory failure
- Frequency of postoperative deep venous thrombosis
- Frequency of postoperative lung embolism
- Frequency of postoperative myocardial infarction
- Frequency of postoperative stroke
- Postoperative hospital stay until discharge, in days
- Overall complications (Grade 2 and higher) as stated by MCDC

# Endpoints

**Secondary Endpoints**

*Endpoints assessed 8 months after randomisation:*

- Days of hospitalization for neoadjuvant, surgical and adjuvant treatment, in days.

*Long-term outcome measures assessed at time of randomisation, preoperatively, at day of discharge from hospital and during follow-up:*

- Quality of Life
- Progression-free survival (PFS) time
- Recurrence-free survival (RFS) time

# Follow Up

The **first follow-up** visit is performed **6 months after start of treatment**, even if postoperative chemotherapy is still ongoing at that date.

From then on, follow-up visits are carried out every 3 months (+/- 7days) in the first year of follow up and every 6 months (+/- 7days) from the second year after treatment until the end of follow-up (min. 3 years)

# Randomization


- Randomization will be performed by randomizer.at (online)
- Stratification by centre and by N stage (cN0/cN+)
- Blocks of variable length in a ratio of 1:1
- 438 Patients will be randomized, 550 will be screened

# Case payment

- 1.500 Eur max. / patient

| Milestone | Amount |
|---|---|
| **Randomization** *(successful inclusion of the patient and complete documentation of screening)* | **200 Euro** |
| **Preoperative chemotherapy (5 or 8 weeks)** *(complete documentation)* | **300 Euro*** |
| **FLOT Arm (surgery + postoperative chemotherapy [8 weeks]) or CROSS Arm (OP)** *(complete documentation)* | **500 Euro*** |
| **Follow Up year 1 (every 3 month)** *(complete documentation)* | **250 Euro** |
| **Follow Up completed (at least year 2 and 3)** *(complete documentation)* | **250 Euro** |

*** The amount is based on the total number of cycles. The real amount will be calculated by the achieved number of cycles.**

# Trial timetable

| | |
|---|---|
| Approval Ethic committee / Competent authority | Okt 2015 |
| Initiation first site | Nov 2015 |
| Enrolment of first patient in (FPFV) | Nov 2015 |
| Initiation last site | Jan 2016 |
| Enrolment of 25% of patients | Nov 2016 |
| Enrolment of 50% of patients | Jul 2017 |
| Enrolment of 75% of patients | Feb 2018 |
| Enrolment of last patient (LPI) | Nov 2018 |
| End of trial for last patient (LPLV) | Nov 2021 |
| Final statistical analysis | Feb 2022 |

# Translational projects

***Circulating Tumor Cells as Biomarker in EAC***

- 9ml Screen Cell Tube
- 7,5 ml CellSearch Tube
- No special preparation, can be sent by regular mail (without cooling)
- Collection and shipment material  will be supplied by sponsor

***<u>Central laboratories</u>***

**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

***Proteomic Determinants of Malignancy in EAC***

- All processed tissue slides plus two (tumor and “normal” esophageal mucosa) additional FFPE tissue samples have to be sent to the central pathology
- Slides will be digitalized and immediately sent back
- FFPE samples will be stored in the central biobank (Freiburg)
- Shipment material  will be supplied by sponsor

***<u>Central pathology</u>***

**Dr. Peter Bronsert / Prof. Werner**
Institut für Klinische Pathologie
Universitätsklinikum Freiburg
Breisacher Straße 115a, 79106 Freiburg

# Translational projects

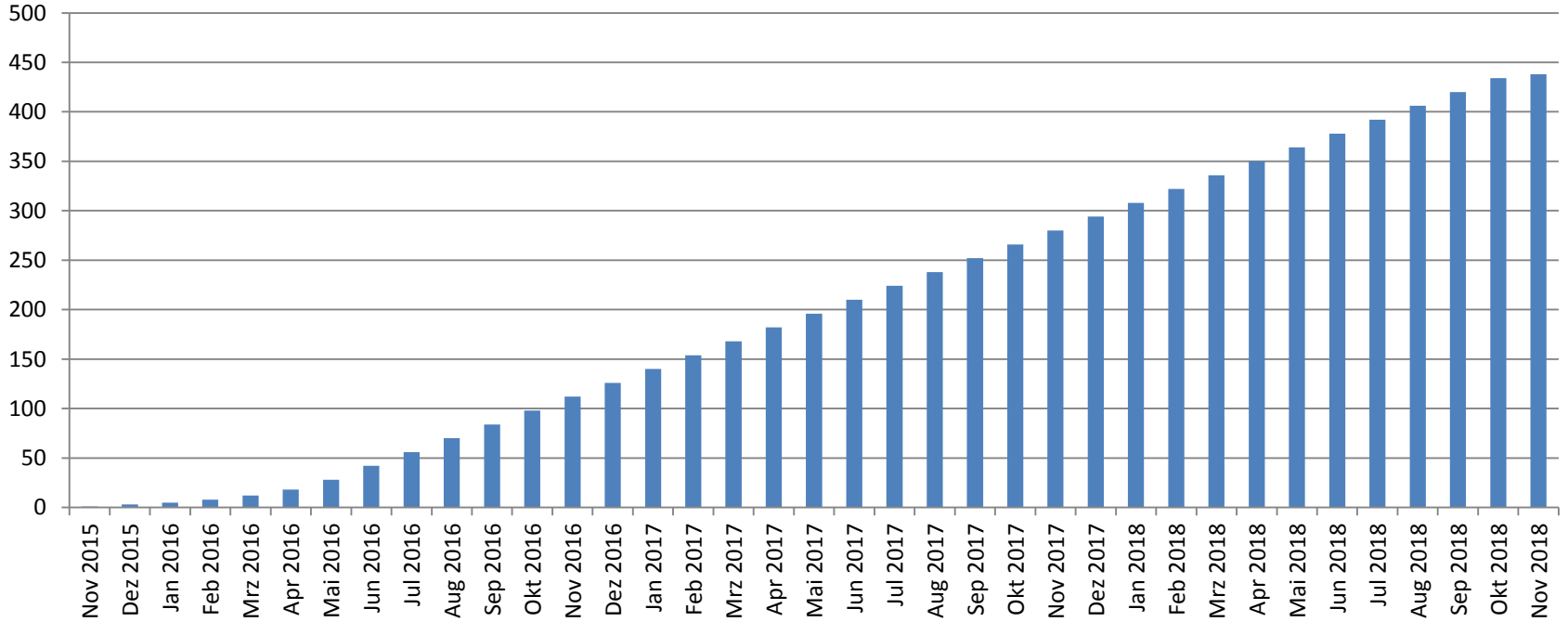
***Prognostic and predictive biomarkers in EAC***

- 10ml EDTA tube
- 10ml Tempus tube
- 10 ml Streck tube
- Collection and shipment material  will be supplied by sponsor

***<u>Central laboratory</u>***

**Prof. Dr. Florian Lordick**
Universitäres Krebszentrum Leipzig (UCCL)
Universitätsklinikum Leipzig AöR
Liebigstraße 20, Haus 4, 04103 Leipzig

# Patient recruitment (Assumption)




Recruitment target:

- 3-4 patients every week-> GOAL: 438 randomized patients
- 20% Screenfailure -> 550 patients will be screened

# Arrangements to support sites

- Homepage
  - Up-to-date recruitment overview
  - Study documents
  - Contact form coordinating investigator and study team
- Flyer / Poster
  - Was ist gewünscht / hilfreich?
- Newsletter
  - Every 3 month update about the study

ESOPEC

UNIVERSITÄTS KLINIKUM FREIBURG

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

## Contact

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