



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

Investigator Meeting
22th September 2016
Hamburg

Contact

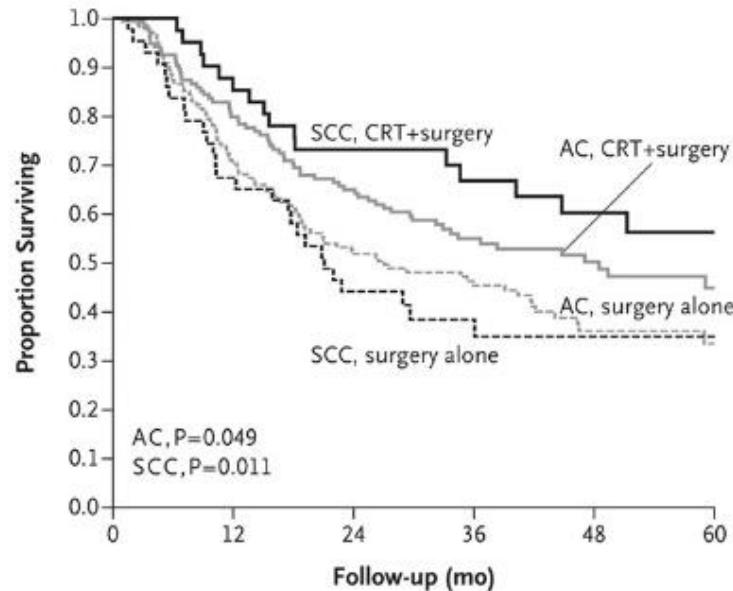
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Rationale and Evidence CROSS

ESOPEC

The NEW ENGLAND JOURNAL of MEDICINE

B Survival According to Tumor Type and Treatment Group



No. at Risk	12	24	36	48	60
AC, CRT+surgery	134	107	87	53	34
AC, surgery alone	141	99	73	50	25
SCC, CRT+surgery	41	35	30	21	15
SCC, surgery alone	43	29	19	11	8
Total	359	270	209	135	82

naCRT: 41,4Gy + Carboplatin/Paclitaxel

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%

Subgroup AC:

5-J ÜL SCC: 44% vs 34%

adjusted HR 0.741; p=0.07

B

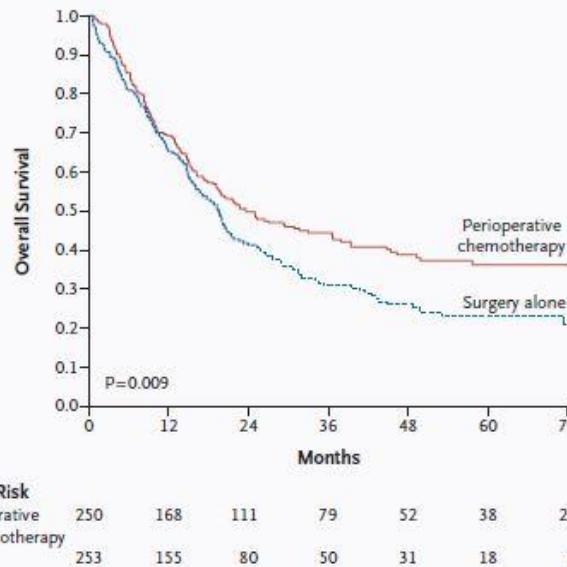


Figure 1. Kaplan–Meier Estimates of Progression-free Survival (Panel A) and Overall Survival (Panel B).

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: Epirubicin/Cisplatin/5-FU

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. Loftus, 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*

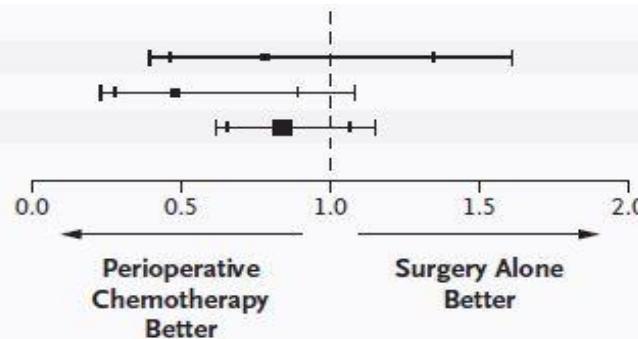
CTX (n=250) vs Surgery alone (n=253)

Esophagus/GEJ 26% / Stomach 74%

Postoperative Morbidity: 46 % vs 45 %

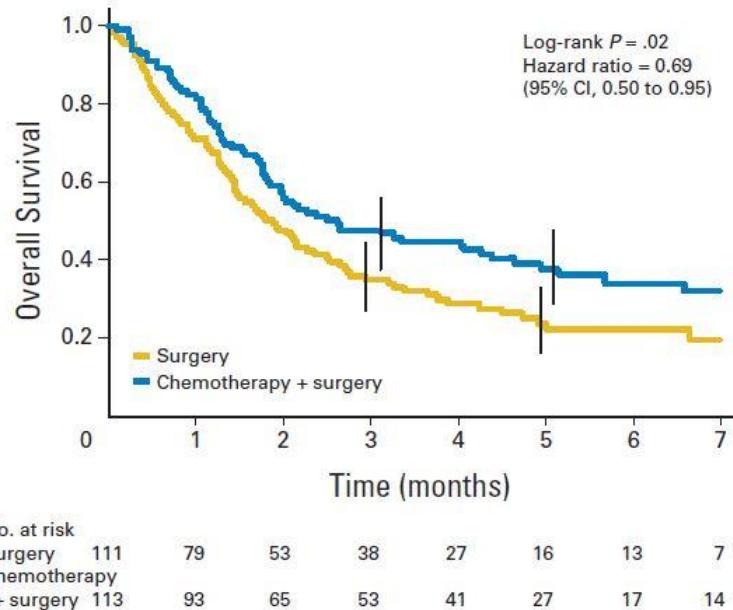
30-day Mortality 5,6 % vs 5,9 %

5-J ÜL: 36% vs. 23%



Rationale and Evidence ACCORD

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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 Ducourtioux, Laurent Bedenne, Jean-Michel Fabre, Bernard Saint-Aubert, Jean Genève, Philippe Lasser, and Philippe Rougier

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

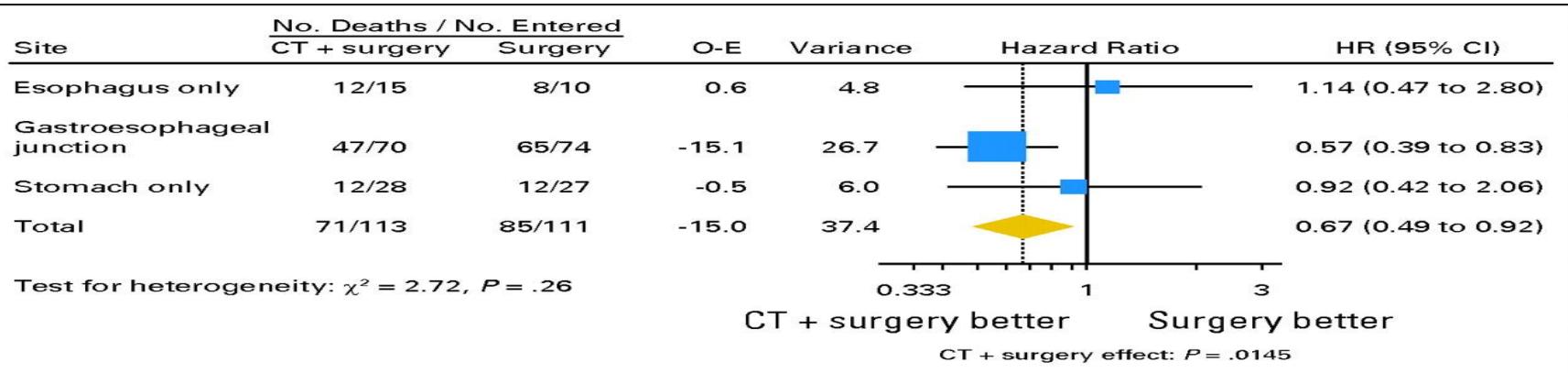
Esophagus/GEJ 75% / Stomach 25%

periCTX: Cisplatin/5-FU

Postoperative Morbidity: 26 % vs 19 %

Postoperative Mortality 4,6 % vs 4,5 %

5-J ÜL: 38% vs. 24%



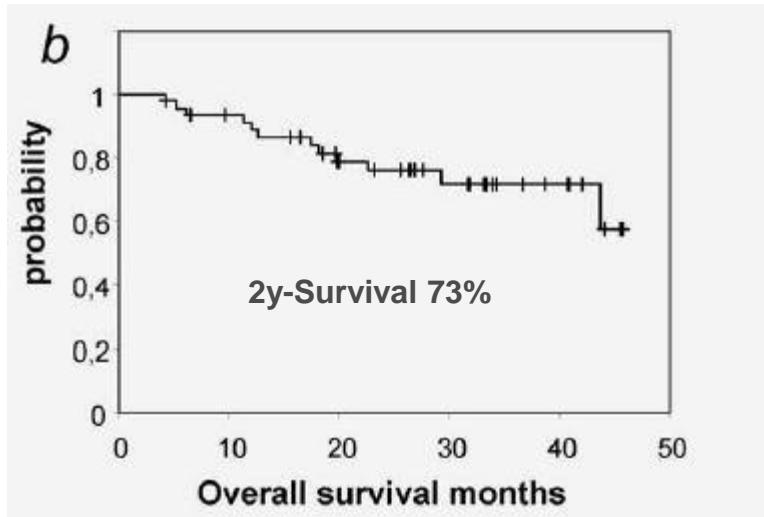


Table 2. Histopathological regression ($n = 46$)

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

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

Nils Homann^{1,2}, Claudia Pauligk³, Kim Luley², Thomas Werner Kraus⁴, Hans-Peter Bruch⁵, Akin Atmaca³, Frank Noack⁶, Hans-Michael Altmannsberger⁷, Elke Jäger³ and Salah-Eddin Al-Batran³

**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

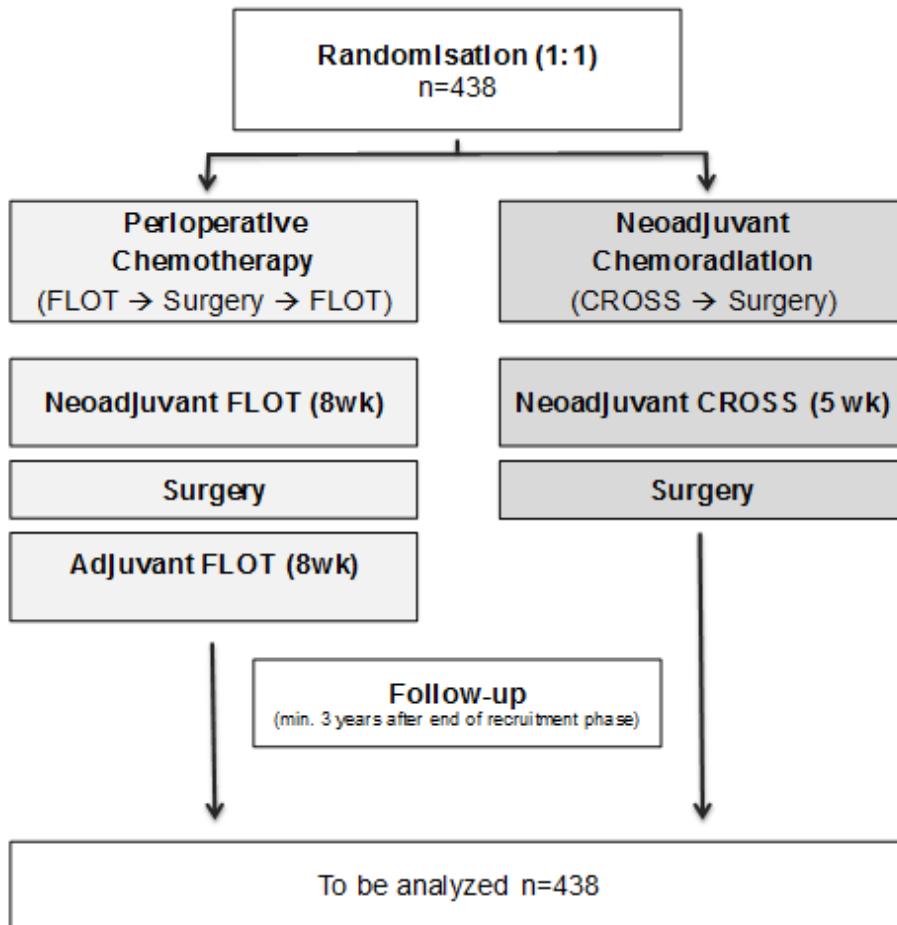
Patient number	Gender	ECOG PS	Location of primary	TNM initial
1	Male	1	Cardia	T3N + M0
2	Female	1	Cardia	T3N + M0
3	Male	1	Cardia	T3N + M1
4	Male	1	Lower oesophagus ¹	T3N + M0
5	Male	1	Cardia	T3N + M0
6	Female	1	Antrum	T3N + M0
7	Male	0	Lower oesophagus ¹	TxNxM1
8	Male	2	Cardia	T3N + M0

- 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

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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

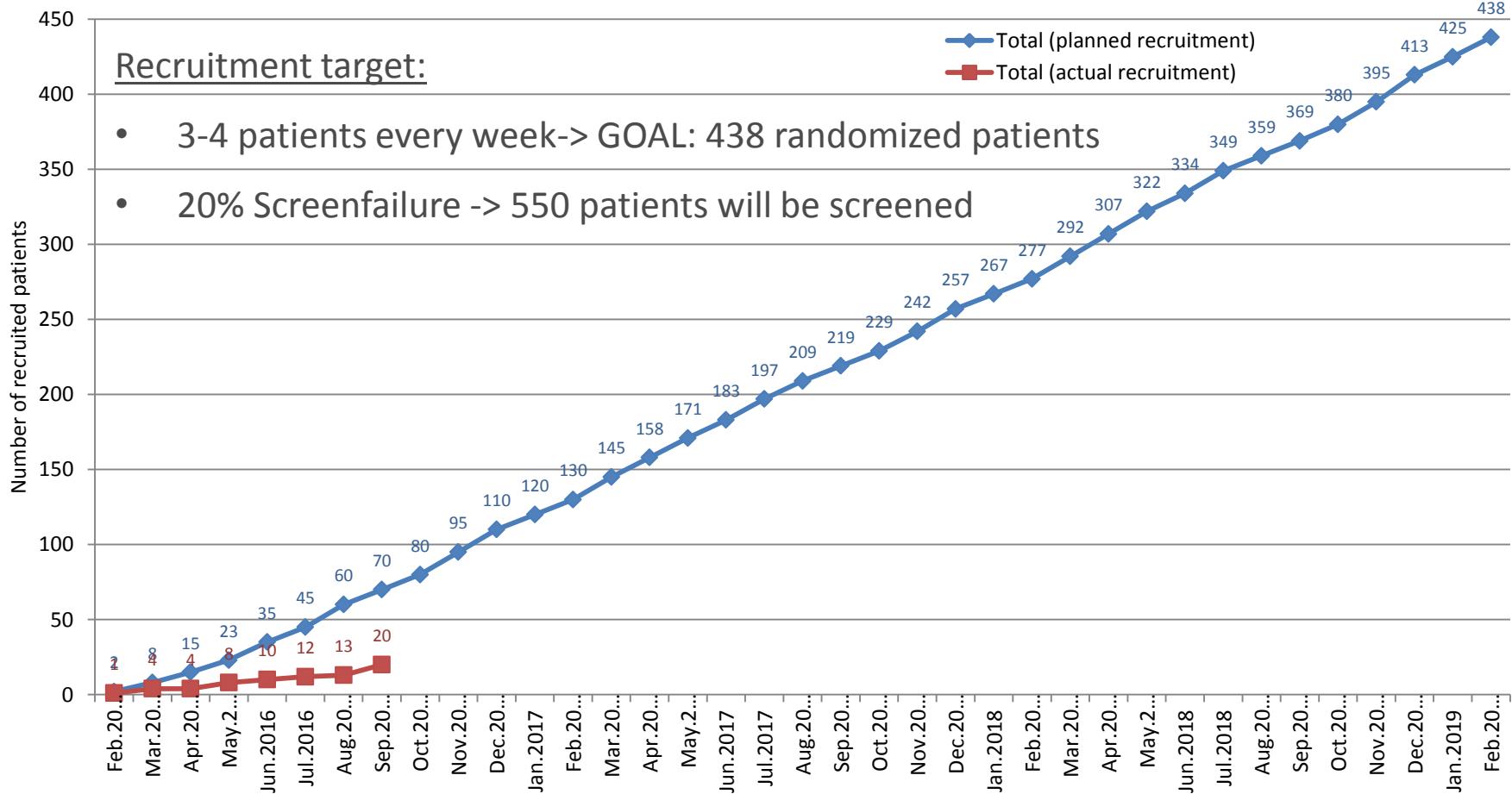
Participating Centers

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

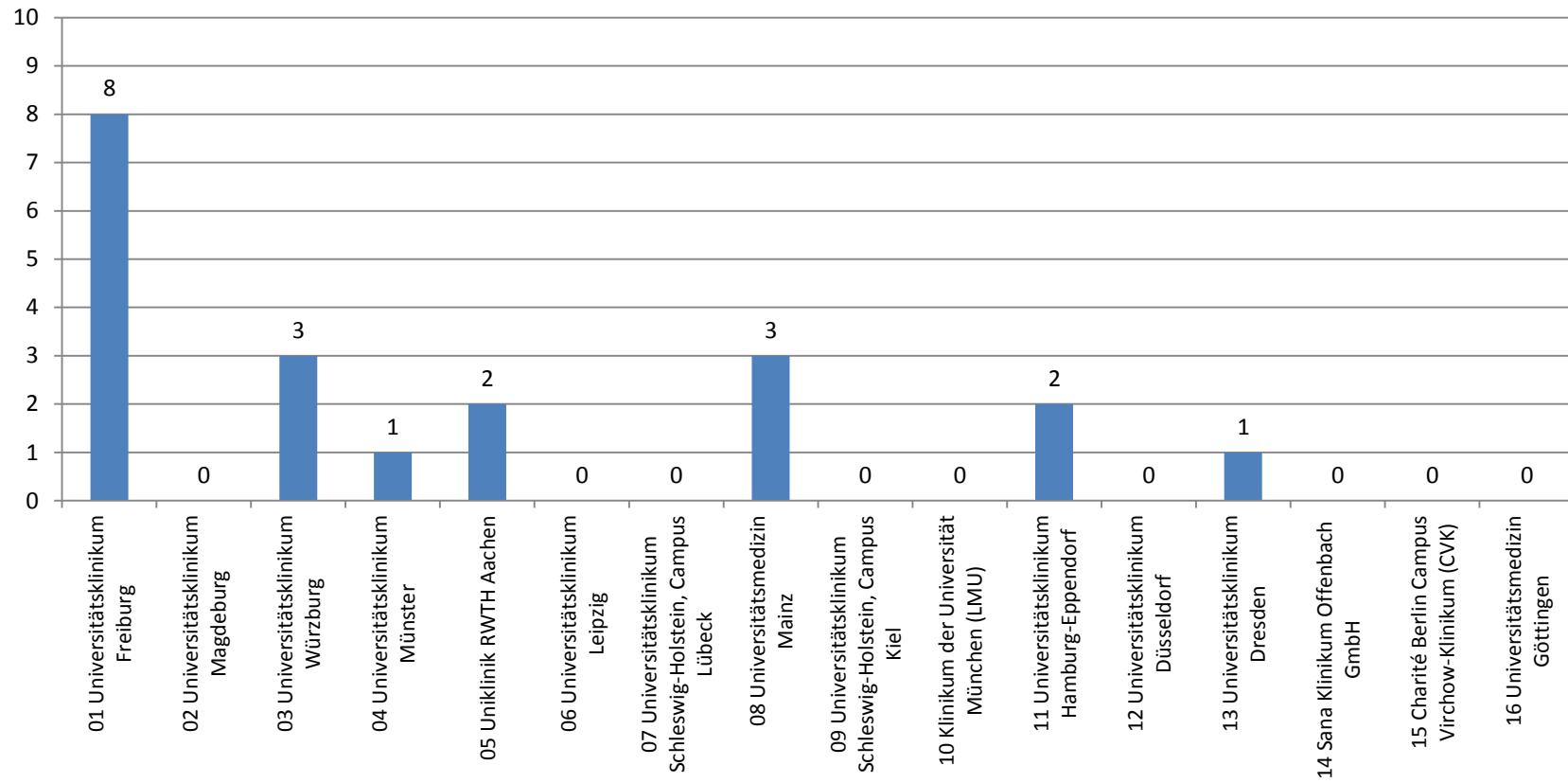
Patient recruitment (21.09.2016)

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Patient recruitment (21.09.2016)

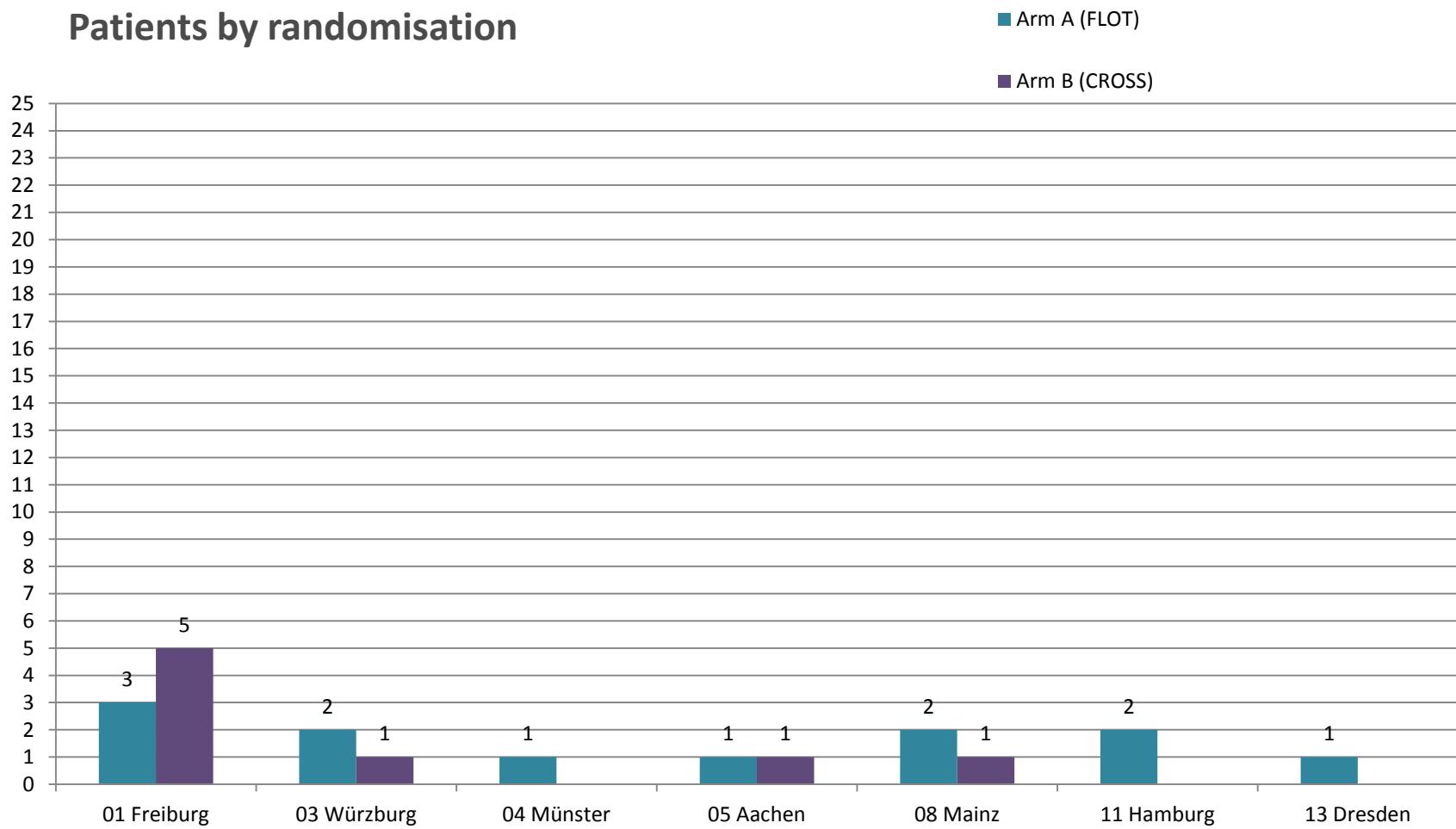
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Patient recruitment (21.09.2016)

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Patients by randomisation



Upcoming sites

Upcoming sites

Klinikum Stuttgart

Universitätsklinikum Frankfurt

Asklepios Klinik Altona

Klinikum Mutterhaus Trier

Johannes Wesling Klinikum Minden
Mühlenkreiskliniken (AöR)

Klinikum Nürnberg

Klinikum St. Elisabeth Straubing

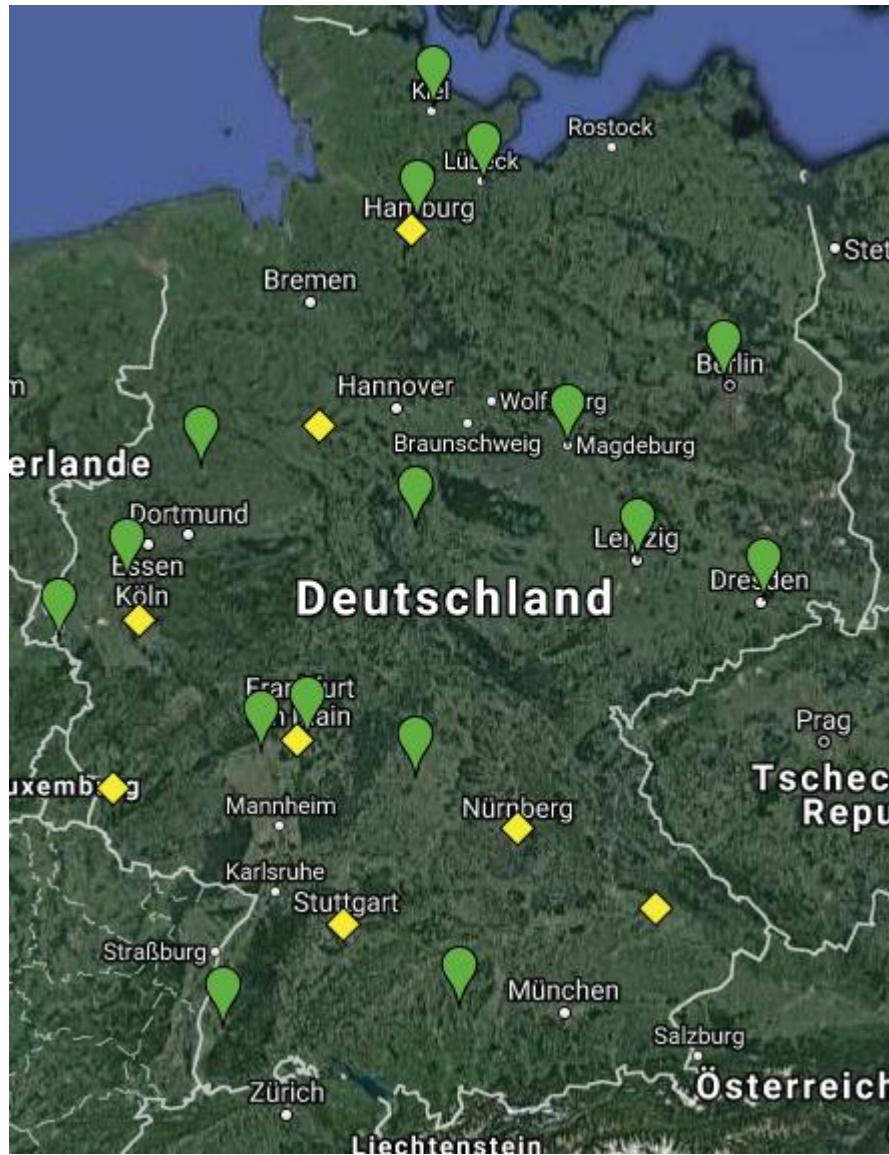
Uniklinik Köln

Klinikum Dortmund

Charité Campus Benjamin Franklin

Participating Centers

ESOPEC



In total 25 sites in Germany

15 recruiting sites

10 upcoming sites (initiation planed for
November / December 2016)

Hoeppner et al. *BMC Cancer* (2016) 16:503
DOI 10.1186/s12885-016-2564-y

BMC Cancer

STUDY PROTOCOL

Open Access



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 Hoeppner^{1*}, Florian Lordick², Thomas Brunner³, Torben Glatz¹, Peter Bronsert⁴, Nadine Röthling⁵, Claudia Schmoor⁵, Dietmar Lorenz⁶, Christian Ell⁷, Ulrich T. Hopt¹ and J. Rüdiger Siewert⁸

Publications

ESOPEC

ASCO 2016

ESOPEC: A prospective randomized controlled multicenter phase III trial comparing perioperative chemotherapy to neoadjuvant chemoradiation in patients with adenocarcinoma of the esophagus (NCT02509286)

Jens Hoepfner¹, Florian Lörick², Thomas B. Brunner¹, Torben Glatz², Claudia Schmoor², Dietmar Lorenz², Christian Ell¹, J. Ruediger Siewert¹, Ulrich Theodor Hopt¹

¹University of Freiburg - Medical Center, Freiburg, Germany; ²University Cancer Center Leipzig, Leipzig, Germany; ³Sana Medical Center Offenbach, Offenbach, Germany



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www.esopec.de

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

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Approval Ethic committee / Competent authority	Nov 2015 / Dec 2015
Initiation first site	19.01.2016
Enrolment of first patient in (FPFV)	09.02.2016
Initiation last site	Dec 2016
Enrolment of 25% of patients (110 patients)	Dec 2016
Enrolment of 50% of patients (219 patients)	Sep 2017
Enrolment of 75% of patients (334 patients)	Jun 2018
Enrolment of last patient (LPI) (438 patients)	Feb 2019
End of trial for last patient (LPLV)	Feb 2022
Final statistical analysis	May 2022

- ✓ 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

- 15 sites are initiated
- Monitoring depends on the number of randomized patients
- Freiburg had the first interim monitoring visit on 27th 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

ESOPEC

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

Circulating Tumor Cells as Biomarker in EAC

Proteomic Determinants of Malignancy in EAC

Prognostic and predictive biomarkers in EAC

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

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

- 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 ...



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

Contact

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