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

Investigator Meeting
14th September 2017
Dresden

Contact

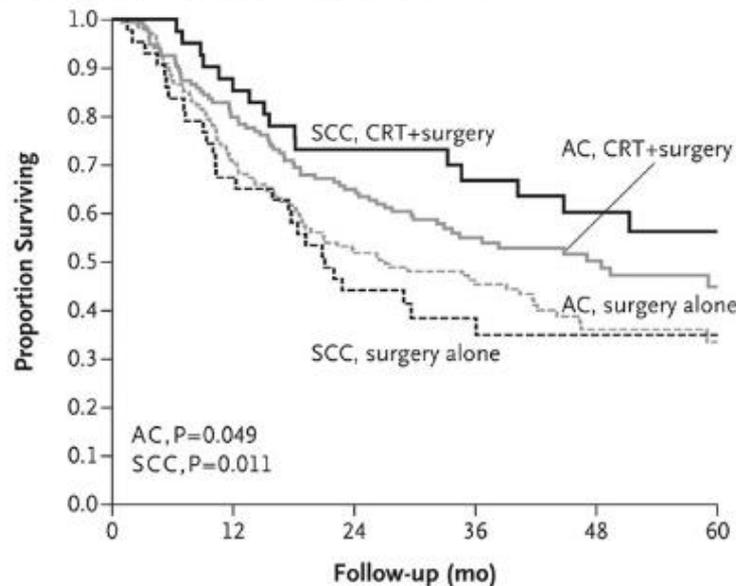
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The NEW ENGLAND JOURNAL of MEDICINE

B Survival According to Tumor Type and Treatment Group



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

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

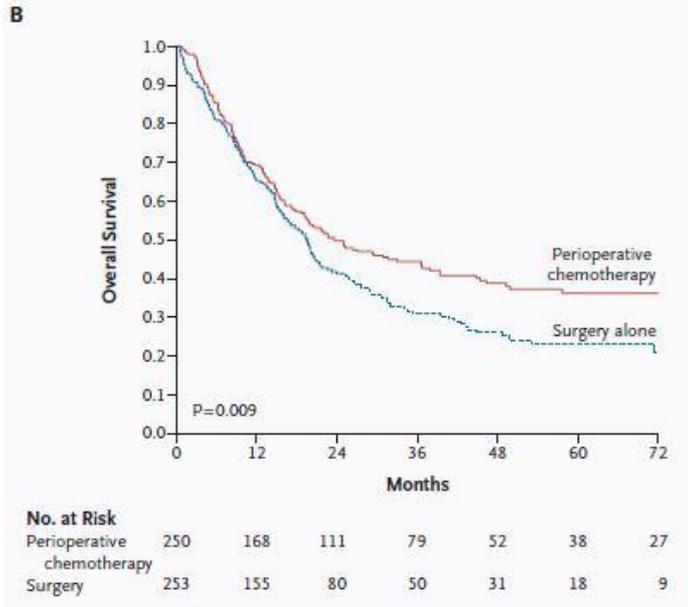


Figure 1. Kaplan–Meier Estimates of Progression-free Survival (Panel A) and Overall Survival (Panel B).

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 Weedon, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

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

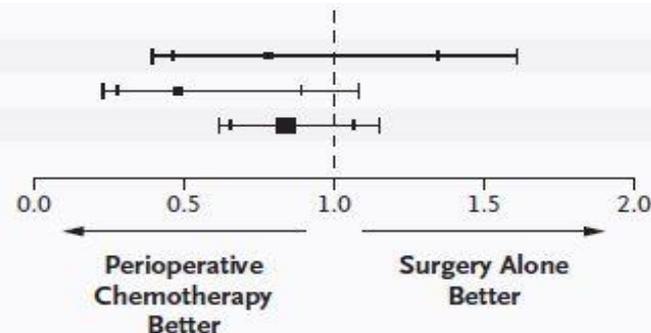
Esophagus/GEJ 26% / Stomach 74%

Postoperative Morbidity: 46 % vs 45 %

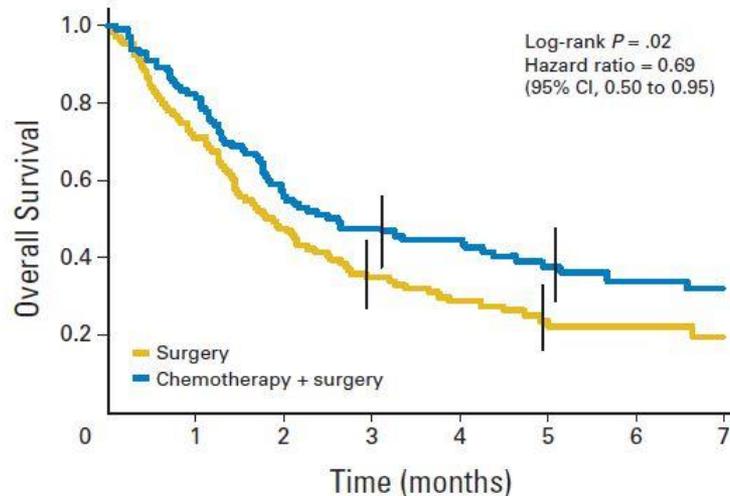
30-day Mortality 5,6 % vs 5,9 %

5-J ÜL: 36% vs. 23%

Site of primary tumor	Perioperative chemotherapy	Surgery alone
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



No. at risk	0	1	2	3	4	5	6	7
Surgery	111	79	53	38	27	16	13	7
Chemotherapy + surgery	113	93	65	53	41	27	17	14

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

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

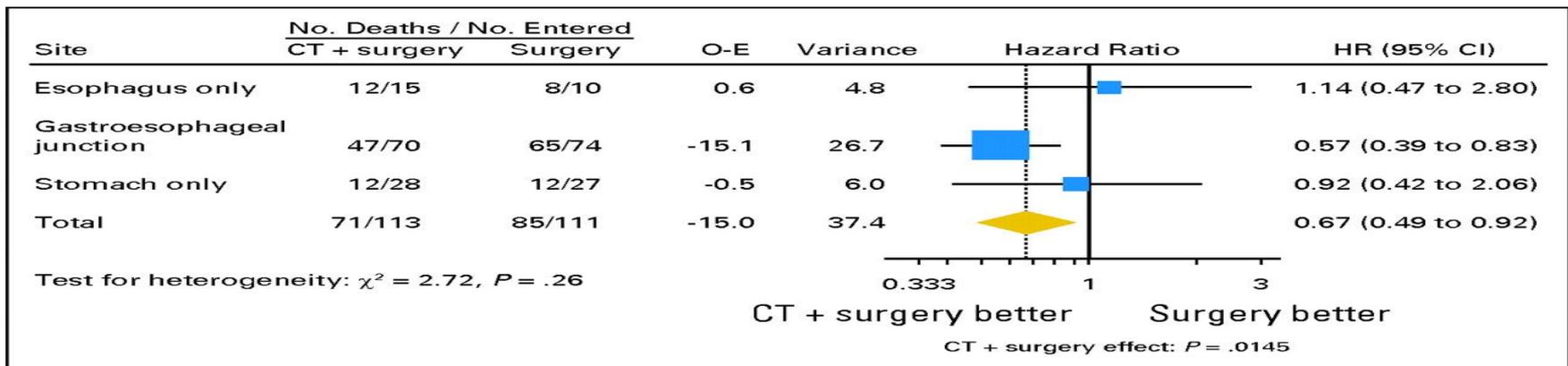
Esophagus/GEJ 75% / Stomach 25%

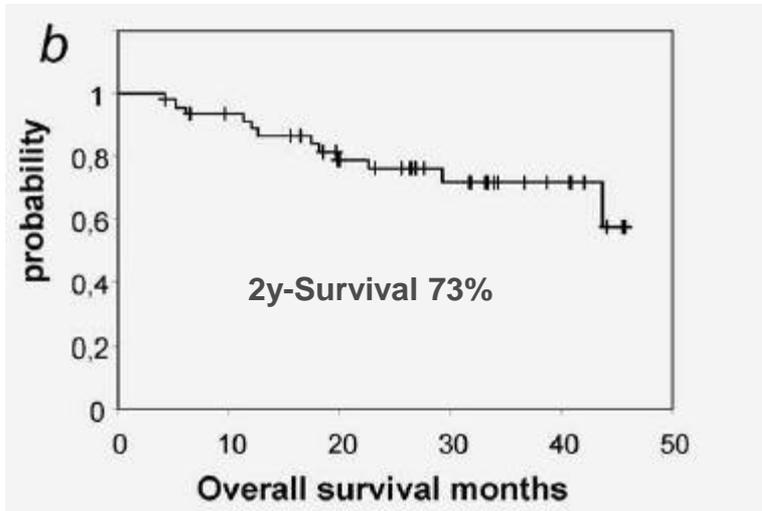
periCTX: Cisplatin/5-FU

Postoperative Morbidity: 26 % vs 19 %

Postoperative Mortality 4,6 % vs 4,5 %

5-J ÜL: 38% vs. 24%





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 2. Histopathological regression (n = 46)

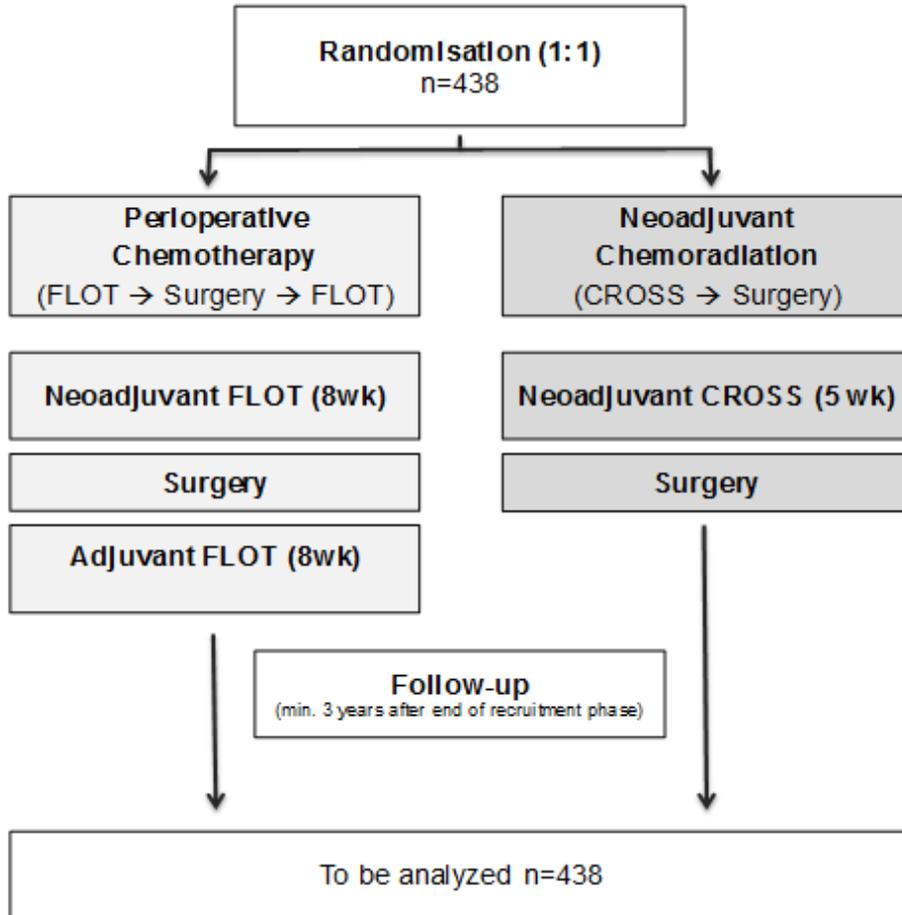
Pathological regression, grade	No. of patients (%)	95% CI ¹
1a (complete)	8 (17.4)	6.6–34.7
1b (subtotal)	10 (21.7)	9.5–40.7
2 (partial)	11 (23.9)	10.0–43.1
3 (minor/none)	15 (32.6)	17.2–52.6
NE ²	2 (4.3)	0.3–18.0

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 ?



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

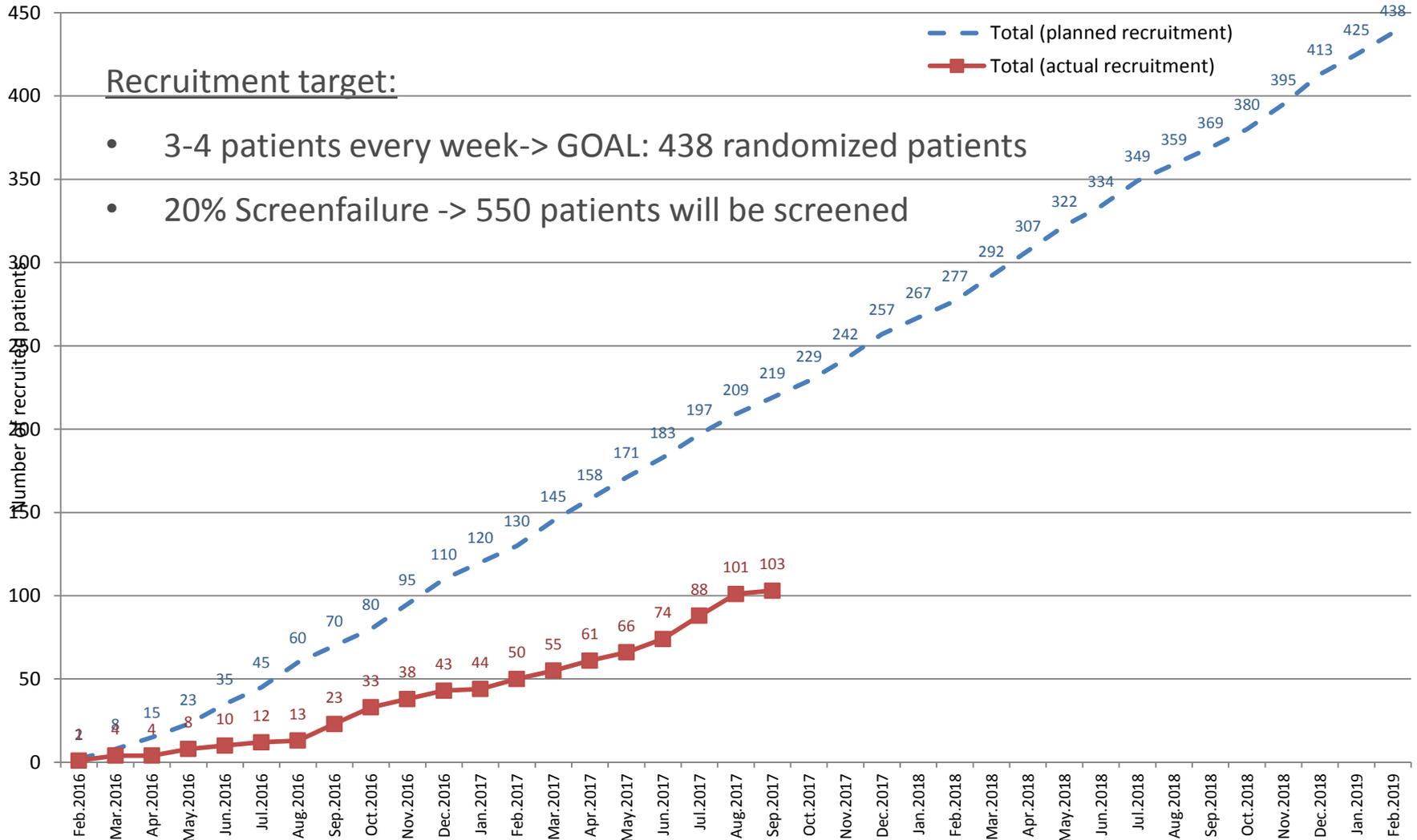
Participating Centers

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	21.02.17
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

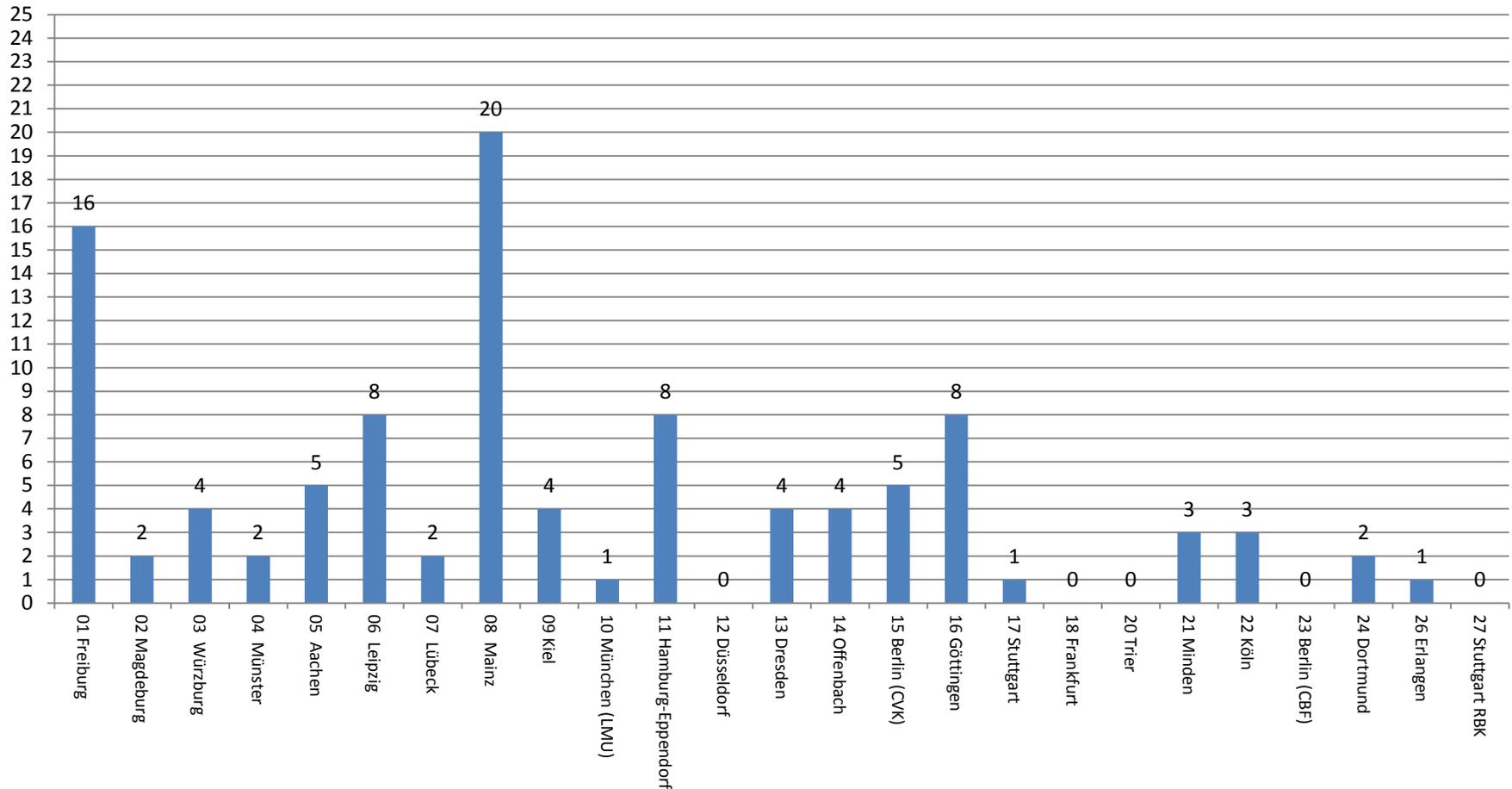
Participating Centers

Site No.	City	Initiation date
17	Stuttgart	16.05.17
18	Frankfurt	16.05.17
20	Trier	22.06.17
21	Minden	28.03.17
22	Köln	06.06.17
23	Berlin CBF	07.06.17
24	Dortmund	07.06.17
25	Homburg	approval process
26	Erlangen	10.07.17
27	Stuttgart RBK	03.08.17
28	Neuruppin	approval process
29	Regensburg	approval process

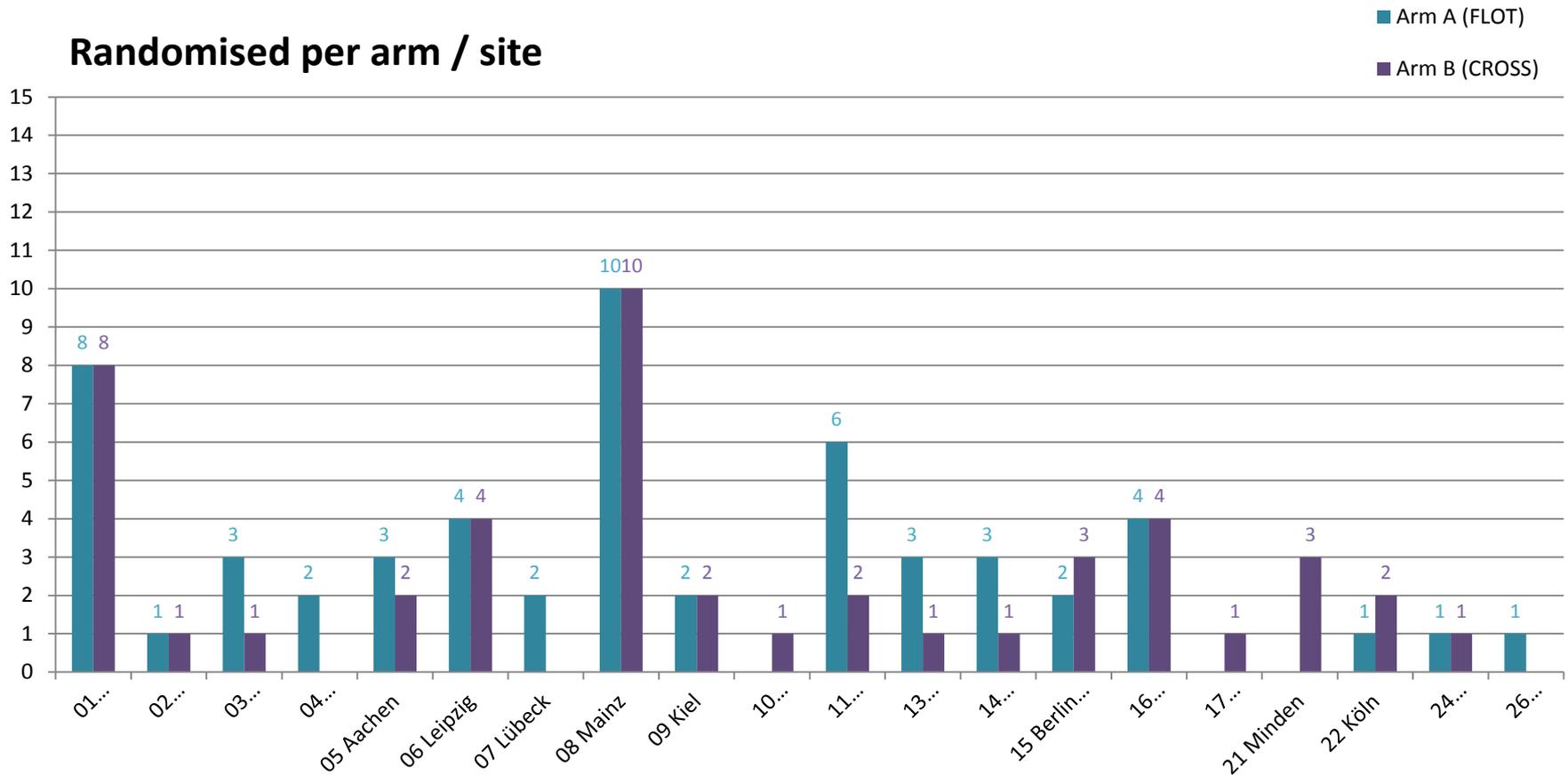
Patient recruitment (07.09.2017)



ESOPEC: Anzahl randomisierter Patienten pro Zentrum (Stand: 07.09.2017)



Randomised per arm / site





In total 28 sites in Germany

25 recruiting sites

3 upcoming sites (initiation planned for
October – December 2017)

	Arm A (FLOT) n = 46	Arm B (CROSS) n = 40
Sex		
Male	35 (76%)	36 (90%)
Female	11 (24%)	4 (10%)
Age (years)		
< 60	17 (37%)	15 (38%)
60 – 69	20 (43%)	16 (40%)
≥ 70	9 (20%)	9 (22%)
Localisation of tumor		
AEG 1	24 (52%)	19 (47%)
AEG 2	14 (30%)	15 (37%)
AEG 3	3 (7%)	1 (3%)
proximal GEJ	1 (2%)	1 (3%)
<i>missing</i>	4 (9%)	4 (10%)

*based on currently available CRF data

	Arm A (FLOT) n = 46	Arm B (CROSS) n = 40
T stage		
T1	0	1 (3%)
T2	6 (13%)	6 (15%)
T3	34 (74%)	27 (67%)
T4	2 (4%)	2 (5%)
<i>missing</i>	4 (9%)	4 (10%)
N stage		
N0	9 (20%)	7 (18%)
Npositive	31 (67%)	24 (60%)
<i>missing</i>	6 (13%)	5 (12%)

*based on currently available CRF data

	Arm A (FLOT) n = 46	Arm B (CROSS) n = 40
Resection type		
Transthoracic esophagectomy	16 (35%)	12 (30%)
transabdominal esophageal resection	2 (4%)	4 (10%)
other	4 (9%)	4 (10%)
<i>missing</i>	24 (52%)	20 (50%)
Lymphadenectomy		
yes	22 (48%)	20 (50%)
<i>missing</i>	24 (52%)	20 (50%)
Reconstruction		
gastric tube	21 (46%)	16 (40%)
Esophagojejunostomy	1 (2%)	2 (5%)
other	0	2 (5%)
<i>missing</i>	24 (52%)	20 (50%)

*based on currently available CRF data

	Arm A (FLOT) n = 46	Arm B (CROSS) n = 40
Classification according MCDC		
0	5 (11%)	4 (10%)
1	6 (13%)	1 (2%)
2	5 (11%)	5 (12%)
3	2 (4%)	3 (8%)
<i>missing</i>	28 (61%)	27 (68%)
Histo-pathological regression		
1a	4 (9%)	1 (2%)
1b	2 (4%)	6 (15%)
2	7 (15%)	5 (12%)
3	6 (13%)	3 (8%)
<i>missing</i>	27 (59%)	25 (63%)
Resection status		
R0	18 (39%)	14 (35%)
R1	1 (2%)	1 (2%)
<i>missing</i>	27 (59%)	13 (63%)

*based on currently available CRF data

	Arm A (FLOT)	Arm B (CROSS)
ypT stage		
0	3 (7%)	1 (2%)
1b	1 (2%)	1 (2%)
2	2 (4%)	6 (15%)
3	13 (28%)	8 (21%)
4	1 (2%)	0
<i>missing</i>	26 (57%)	24 (60%)
ypN stage		
0	7 (15%)	7 (18%)
1	4 (9%)	5 (12%)
2	5 (10%)	1 (2%)
3	4 (9%)	3 (8%)
<i>missing</i>	26 (57%)	24 (60%)
yM stage		
0	18 (39%)	14 (35%)
1	1 (2%)	0
X	1 (2%)	2 (5%)
<i>missing</i>	26 (57%)	24 (60%)

*based on currently available CRF data

45 serious adverse events until 31 August 2017

Body system	Arm A (FLOT)	Arm B (CROSS)
Blood and lymphatic system disorders	2	2
Anemia		1
Leukocytosis		1
Neutropenia	2	
Cardiac disorder	1	1
Atrial fibrillation		1
Myocardial infarction	1	
Congenital, familial and genetic disorders	1	
Pyloric stenosis	1	
General disorders	3	0
General physical health deterioration	2	
Pyrexia	1	0
Injury, poisoning and procedural complications	1	
Anastomotic stenosis	1	
Renal and urinary disorders	1	0
Acute kidney injury	1	

45 serious adverse events until 31 August 2017

Body system	Arm A (FLOT)	Arm B (CROSS)
Gastrointestinal disorders	9	1
Ascites		1
Diarrhoea	1	
Gastrointestinal inflammation	1	
Gastrooesophageal reflux disease	1	
Ileus	1	
Impaired gastric emptying	1	
Nausea	1	
Vomiting	3	
Metabolism and nutrition disorders	1	
Dehydration	1	
Nervous system disorders	2	0
Cerebral ischaemia	1	
Hemiparesis	1	
Vascular disorders	1	2
Aortic perforation		1
Lymphatic fistula	1	1

45 serious adverse events until 31 August 2017

Body system	Arm A (FLOT)	Arm B (CROSS)
Infections and infestations	8	5
Bacterial sepsis	1	
Infection	1	
Infection pleural effusion	2	
Oesophageal candidiasis	1	
Pneumonia	2	4
Sepsis		1
Urinary tract infection	1	
Respiratory, thoracic and mediastinal disorders	3	4
Dyspnoea	1	1
Oesophagobronchial fistula		1
Pleural effusion		1
Pneumonia aspiration	2	
Pneumothorax		1
Surgical and medical procedures	0	1
Oesophageal anastomosis		1

	Arm A (FLOT) n = 56	Arm B (CROSS) n = 47
Premature study termination		
yes	10 (18%)	7 (15%)
no	45 (82%)	39 (85%)
Reason		
Reccurent / progressive disease	3	1
Serious adverse event	1	0
Patient wish / consent withdrawn	3	3
Decision Investigator	2	0
Metastasis / second malignancy	1	3

	Arm A (FLOT) n = 56	Arm B (CROSS) n = 47
Recurrent / progressive disease		
yes	7 (13%)	6 (13%)
no	48 (87%)	40 (87%)
Lokalisation		
local	1	2
regional	2	1
distant	4	3

	Arm A (FLOT) n = 56	Arm B (CROSS) n = 47
Death		
yes	3 (5%)	3 (7%)
no	52 (95%)	43 (93%)
Reason		
Progression	2	1
General condition worsening	1	0
Sepsis	0	1
Perforation of aorta	0	1

- Time window assessments during Screening for CT (28 days)
 - In the discretion of the investigator (preserve the patient), but -> protocol violation
- PET CT during screening
 - not necessary in the ESOPEC protocol, if it is local standard: ok; but -> no study specific assessment
- Patient consent withdrawn after randomisation
 - clearly informed consent process, to avoid consent withdrawn

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