**Neoadjuvant Chemoradiation (CROSS) vs. Perioperative Chemotherapy (FLOT) in Esophageal Adenocarcinoma (EAC): ESOPEC − a Randomised Controlled Prospective Multicentre Phase III Trial**

T.B. Brunner,1,2 F. Lordick,3 C. Schmoor,4 H. Schmidberger,5 S. Kirste,6 S. Rieken,7 C. Petersen,8 N.H. Nicolay,9 E. Fokas,10 J. Dunst,11 D. Rades,12 M.J. Eble,13 M. Krause,14 C. Roedel,15 D. Medenwald,16 P. Niehoff,17 A. Wittig-Sauerwein,18 C. Baues,19 A. Grosu,20 and J. Hoeppner21;

*1Medical University of Graz, Dept. of Radiation Oncology, Graz, Austria, 2Department of Radiation Oncology, University Medical Center Freiburg, Freiburg, Germany, 3University of Leipzig, Dept. of Medical Oncology, Leipzig, Germany, 4University Hospitals Freiburg, Clinical Trials Unit, Freiburg, Germany, 5Department of Radiotherapy and Radiation Oncology, University Hospital Mainz, Mainz, Germany, 6German Cancer Consortium (DKTK), Partner Site Freiburg, Heidelberg, Germany, 7Heidelberg University Hospital, Dept. of Radiation Oncology, Heidelberg, Germany, 8Department of Radiotherapy and Radiooncology, University Medical Center HamburgEppendorf, Hamburg, Germany, 9Department of Radiation Oncology, University of Leipzig Medical Center, Leipzig, Germany, 10Department of Radiation Oncology, Cyberknife and Radiotherapy, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, 11Universitätsklinikum Schleswig-Holstein, Campus Kiel, Klinik für Strahlentherapie, Kiel, Ger-€ many, 12Department of Radiation Oncology, University of Lübeck, Lübeck, Germany, 13Department of Radiation Oncology, RWTH Aachen University, Aachen, Germany, 14Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, 15Dept. Radiation Oncology, University Hospitals Frankfurt, Frankfurt, Germany, 16Department of Radiation Oncology, University Hospitals Magdeburg, Magdeburg, Germany, 17Sana Hospital, Offenbach, Germany, 18Department of Radiation Oncology, University Hospital, University of Wuerzburg, Wuerzburg, Germany, 19Department of Radiooncology, Marienhospital Herne, Ruhr University Bochum, Bochum, Germany, Bochum, Germany, 20German Cancer Consortium (DKTK), Partner Site Freiburg, Freiburg, Germany, 21University Hospitals OWL Bielefeld,*

*Dept. of Surgery, Detmold, Germany*

**Purpose/Objective(s)**: When designing the ESOPEC trial, the CROSS (C) regimen provided the highest level of evidence of neoadjuvant therapy for both, squamous cell (ESCC) and EAC. During recruitment into ESOPEC, the FLOT(F)-4 trial identified perioperative 5-fluorouracil, leucovorin (L), oxaliplatin (O) and docetaxel (T) as best evidence of chemotherapy. The ESOPEC trial aimed to compare the two protocols exclusively in EAC and hypothesized F to be superior to C.

**Materials/Methods**: Included were patients with cM0 EAC staged cT1 N+ or cT2-4a, cN0/+. C was the control arm with 41.4 Gy in 23 fractions and 5 weekly simultaneous doses of carboplatin (2 mg/ml/min AUC) and paclitaxel [(50 mg/m2); CP]. GTV and PTV were defined as described by Matzinger et al. (doi: 10.1016/j.radonc.2009.03.018). F was the experimental arm with 5-fluorouracil 2600 mg/m2 (24 hours), d1 L 200 mg/m2, d1 O 85 mg/m2, d1 T 50mg/m2, d1 every two weeks (q2w); 4 neoadjuvant cycles (8 weeks) prior to surgery and 4 adjuvant cycles (8 weeks) postoperatively. Esophagectomy was done 4-6 weeks after neoadjuvant therapies. Primary endpoint was overall survival (OS), secondary endpoints were progression free survival (PFS), ypTNM stage, tumor regression grading, recurrence free survival (RFS) in patients with R0/R1 resection, site of tumor recurrence, postoperative complications, adverse events, and quality of life. Sample size calculation was based on 1-sided significance level of 2.5% and 90% power assuming a hazard ratio (HR) of 0.645 with respect to OS, and required 218 death events (438 patients). Prospectively documented chemoradiotherapy specific variables consisted in administered percentage of planned chemo- and radiotherapy, adherence to target volume definitions, doses to organs at risk, specifically heart and lungs.

**Results:** From 2/16 to 4/20, 438 patients were randomized to C (217) and F (221), intention-to-treat population (ITT). Characteristics were well balanced with mean age of 63 years, 89.3% males, 73.9% cT3, 6.7% cT4, 79.7% cN+. Neoadjuvant treatment was started in 90.3% (196) vs 93.7% (207) in C vs F (per-protocol-population (PP)). In PP, full RT dose was given in 98.0% (192); 75.0% (147), 18.9% (37) and 6.1% (12) had 5, 4 or <4 cycles of CP. In ITT, surgery rates were C 82.9% (180) vs F 86.4% (191). In 371 patients with surgery, local pCR rates were 13.3% (C) vs 18.3% (F), and near CR rates 39.4% (C) vs 25.1% (F). In 368 patients with R0/R1 resection, 3-year RFS after surgery was 36.5% (C) and 52.8% (F), median RFS was 17 (C) vs 43 (F) months (HR 0.68 [0.51 − 0.90]; p = 0.0076). Postoperative morbidity was comparable. In ITT, 3-year-OS was 50.7% (C) and 57.4% (F), and median OS was 37 (C) vs 66 (F) months (HR 0.70 [0.53 − 0.92]; p = 0.012).

**Conclusion**: Both C and F were well tolerated. OS was superior after F vs C, and F should be preferred over C. Posthoc limitations of C were: baseline FDG-PET/CT not mandatory and absence of additive immunotherapy.