Fakultät für Medizin

Klinikum rechts der Isar Technische Universität München

MEMORI

Metabolische und **Mo**lekulare **R**esponseevaluation zur Therapie-**I**ndividualisierung bei Adenokarzinomen des Ösophagus und gastroösophagealen Übergangs

Metabolic and **Mo**lecular **R**esponse Evaluation for Therapy **I**ndividualization in Adenocarcinomas of the Gastroesophageal Junction

Phase II Clinical Trial

Prüfsubstanzen, Investigational Medicinal Products: Paclitaxel, Oxaliplatin, Epirubicinhydrochlorid, Carboplatin, Capecitabin, 5-Fluorouracil, Cisplatin, Folinsäure

Study Code: MEM-0000-SIV-0028-I

EudraCT Number: 2014-000860-16

First Patient First Visit: 05.12.2014 **– Last Patient Last Visit:** 07.08.2020

Termination of Clinical Trial: 07.08.2020 (LPLV)

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Synopsis

1.	**Sponsor:** Technische Universität München (TUM), Fakultät für Medizin Ismaninger Strasse 22, D- 81675 München, Germany **Sponsor Delegated Person (SDP):** Prof. Dr. med. Jens Siveke
2.	**Name of Finished Product:** IMP 1 Paclitaxel*; IMP 2 Oxaliplatin*; IMP 3 Epirubicinhydrochlorid*; IMP 4 Carboplatin*;IMP 5 Capecitabin*; IMP 6 5-Fluorouracil*; IMP 7 Cisplatin*; IMP 8 Folinsäure (Folinic acid)* *all products approved in Germany to be used according to clinical routine in different regimen at the clinical trial sites
3.	**Name of Active Ingredient:** Paclitaxel (ATC Code: L01CD01); Oxaliplatin (ATC Code: L01XA03); Epirubicinhydrochlorid (ATC Code: L01 DB03); Carboplatin (ATC Code: L01XA02); Capecitabin (ATC Code: L01BC06); 5-Fluorouracil (ATC Code: L01BC02) Cisplatin (ATC Code: L01XA01); Folinsäure, (Folinic acid, ATC Code: V03AF03)
4.	**Individual Study Table:** (only required for submissions) n.a.
5.	**Study Title:** **Me**tabolische und **Mo**lekulare **R**esponseevaluation zur Therapie-**I**ndividualisierung bei Adenokarzinomen des Ösophagus und gastroösophagealen Übergangs **Me**tabolic and **Mo**lecular **R**esponse Evaluation for Therapy **I**ndividualization in Adenocarcinomas of the Gastroesophageal Junction
	Study Design: Prospective, open, single arm, therapeutic explorative phase II clinical multi-center trial
	Study (Protocol) Code Number: MEM-0000-SIV-0028-I
	Eudra-CT Number: 2014-000860-16
6.	**Principal Investigators (PI):** # 1: Prof. Dr. Sylvie Lorenzen # 2: Prof. Dr. Martin Angele # 3: Prof. Dr. Jens Siveke # 4: Prof. Dr. Christiane Bruns (not initiated)
7.	**Clinical Trial Sites:** # 1: Klinikum rechts der Isar Technische Universität München Klinik und Poliklinik für Innere Medizin II Ismaninger Straße 22 81675 München, Germany # 2: Klinikum der LMU München Klinik für Allgemeine, Viszeral-, Transplantations-, Gefäß- und Thoraxchirurgie, Marchioninistr. 15 81377 München, Germany # 3: Universitätsklinikum Essen Westdeutsches Tumorzentrum, Innere Klinik, Tumorforschung

	Hufelandstr. 55 45147 Essen, Germany # 4: Universitätsklinikum Köln, Klinik und Poliklinik für Allgemein-, Viszeral- und Tumorchirurgie Kerpener Str. 92 50937 Köln, Germany The clinical trial was planned and conducted as a multi-center clinical trial.
8.	**Publication:** Journal of Clinical Oncology, Volume 37, Issue 15 suppl (May 20, 2019 4018. PET-directed combined modality therapy for gastroesophageal junction cancer: First results of the prospective MEMORI trial. (ASCO abstract)
9.	**Study period:** First patient first visit (FPFV): 05.12.2014; Last patient included: 19.07.2018, Last patient last visit (LPLV): 07.08.2020
	Approvals and Amendments **Approval**: Bundesinstitut für Arzneimittel und Medizinprodukte（BfArM): 14.04.2014; Ethics Committee (EC): 22.04.2014 Clinical Study Protocol (CSP) Version (V) 4.0 26.02.2014 **Amendment 1**: major changes: change of inclusion criteria to include elderly patients Approval AM1: BfArM: 01.07.2014; EC: 12.09.2014, CSP V. 4.1 26.05.2014 **Amendment 2**: There were mainly formatting and minor changes of the CSP V. 4.2 26.07.2014 (for information to BfArM and EC 12.09.2014) **Amendment 3**: major changes: ÖGD and PET can be done on the same day; added routine medication (mFOLFOX); additional deputy coordinating investigator and PI Approval AM3: BfArM: 22.09.2015; EC: 09.09.2015, CSP V. 5.0 30.07.2015 **Amendment 4**: major changes: coordinating investigator moved to Essen Approval AM4: EC: 25.05.2016; CSP Version 5.1 07.04.2016 (non-substantial BfArM) **Amendment 5:** major changes: prolongation of recruitment period; increase of sample size from 75 to 120; additional clinical trial site Köln Approval AM5: BfArM: 17.10.2017; EC: 02.11.2017, CSP V. 6.0 25.09.2017 Recruitment was preliminarily stopped 29.08.2018 due to emerging new routine therapeutic regimen expected to impact ratio PET-responder vs PET-non-responder and improve rate of complete remissions. Follow-up of already included patients was conducted as originally planned.
10.	**Phase of development** Phase II
11.	**Objectives:** **Primary Objective:** Neoadjuvant therapy optimization in metabolic PET-Non-responders (P-NR) for improved R0 resection rates in locally advanced AEG **Secondary Objectives:** Assessment of the following outcome variables in patients with locally advanced AEG • Histological regression defined by Becker Criteria • Overall survival (OS) defined as period from start of study to death (if necessary censored by end of follow-up period)

	• Disease-free survival (DFS), defined as period from start of study to earlier occurring event: death or relapse until end of follow-up; Relapse will be separated into events of "local failure", "distant failure" and "local and distant failure" • Quality of life, analyzed via EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires • Metabolic response rate under neoadjuvant chemotherapy Exploratory: Translational analysis for identification of tumor determinants relevant for prognosis and therapy
12.	**Methodology** According to sequential 18F-FDG PET (PET), only 40–50% of patients (P) respond to neoadjuvant chemotherapy (CTX). In order to assess whether early PET non-responders (P-NR) after induction CTX might benefit from changing to chemoradiation (CRT), a PET-guided treatment stratification for improvement in obtaining negative surgical margins (R0) in resectable gastroesophageal junction (GEJ) adenocarcinoma was evaluated. All procedures and therapies (except for a second gastroesophageal duodenoscopy (GED), and withdrawal of additional blood) followed clinical routine at the clinical trial site, Baseline PET scan followed by 1 cycle of CTX (regimen physicians' choice), e.g. EOX, EOF, CF, XP, or mFOLFOX6). PET was repeated at day 14-21 and responders (P-R), defined as ≥ 35% decrease in SUVmax from baseline, then continued with their CTX regimen for 3 cycles (63 days). P-NR switched to CRT (41.4 Gy/23 fractions with weekly carboplatin/paclitaxel). Patients underwent surgery 4-6 weeks post-CTX/CRT and were followed up (first year: quarterly intervals, second year: biannually) for two years.
13.	**Sample size (planned/analysed):** Planned: 120 patients Included / analysed: 77 / 75 patients, 2 patients excluded from all analyses (screening failures, no medication during study); 67 patients in per protocol (PP) set (75 minus: 5 no surgery, 1 no tumour identified during surgery, 1 misclassification, 1 fourth cycle of CTX not conducted)
14.	**Patient Population (Diagnosis):** Adenocarcinoma of the gastroesophageal junction (GEJ, AEG I-III); ICD-classification C15.5/C16.
	Main criteria for inclusion • Histologically confirmed AEG I-III • Potentially R0-resectable AEG and primary tumor category uT2 -4 • Functional operability: exclusion of surgery-limiting comorbidities • Intense FDG tracer uptake of the tumor during baseline PET/CT-) and thus suitability for monitoring and early response prediction by FDG -PET ([18F] - FDG uptake in the tumor at baseline > 1.35 x liver SUV + 2 x standard deviation of the liver SUV) • Performance status (ECOG) 0 or 1 • Age: ≥ 18 • Creatinine clearance > 60ml/min, measured or calculated • Serum bilirubin ≤ 1.5 times upper limit of normal, serum transaminases (GOT/GPT) ≤ 3 times ULN • Leukocytes ≥ 3.5 g/l, platelet ≥ 100 g/l • Negative pregnancy test (determination of beta- HCG in urine or serum) in women of childbearing potential

	• Signed informed (by MD) consent form **Main criteria for exclusion** • Existing distant metastases (M1b) • Tumor infiltration into the tracheobronchial system • Previous radiotherapy targeted at the thorax • Inability of the patient to adhere to the protocol • Manifested heart failure despite of optimal medication> NYHA I • Existing angina pectoris at rest or stress without clarification via interventional cardiology and / or myocardial infarction within the last 6 months • Existing pregnancy or lactation • Childbearing potential or fertility without using acknowledged safe methods of contraception • Coexisting other malignant diseases with the exception of non-melanoma localized skin tumors or carcinoma in situ of the cervix • Missing signed informed consent form
15.	**Test product, dose and mode of administration** **Study treatment:** Paclitaxel 50 mg/m^2 i.v. Oxaliplatin 130 mg/m^2 i.v. (9: 100 mg/m^2 i.v.) Epirubicinhydrochlorid 50 mg/m^2 i.v. Carboplatin 2 mg/ml i.v. Capecitabine 625 mg/m^2 oral or 1000 mg/m^2 oral 5-Fluorouracil (5-FU) 200 mg/m^2 i.v., 1000 mg/m^2 i.v.; 400 mg/m^2 i.v.; 2400 mg/m^2 i.v. Cisplatin 80 mg/m^2 i.v. Folin acid 200 mg/m^2 i.v. IMP administration followed different peri-operative CTX regimen combining different IMP according to clinical routine at the clinical trial sites. **Batch-No. (Ch.-B):** NAV (routine medication)
16.	**Duration of administration** EOX: Oxaliplatin 130 mg/m^2, Day (D)1; Epirubicin 50 mg/m^2, D1; Capecitabine 625 mg/m^2 twice daily D1-D21 (EOX was repeated for three pre-operative cycles in P-R) EOF: Oxaliplatin 130 mg/m^2, D1; Epirubicin 50 mg/m^2, D1; 5-FU 200 mg/m^2 Infusion 24 h, D1-D21 (EOF was repeated for three pre-operative cycles in P-R) CF: Cisplatin 80 mg/ m^2, D1; 5-FU 1000mg/m^2, infusion 24 h, D1-D4 (CF was repeated for three pre-operative cycles in P-R) XP: Cisplatin 80 mg/m^2, D1; Capecitabin 1000 mg/m^2, twice daily D1-D14 (XP was repeated for three pre-operative cycles in P-R) mFOLFOX6: Oxaliplatin 100 mg/m^2 Inf. D1; Folinic acid 200 mg/m^2, Inf. D1; 5-FU 400 mg/m^2, Inf. bolus D1; 5-FU 2400 mg/m^2, Inf. D1-D2 (infusion 48h) (mFOLFOX6 was repeated for three pre-operative cycles in P-R) (P-NR switched to CRT for five weeks with weekly carboplatin/paclitaxel).
17.	**Background therapy:** standard of care **Comparator:** no

	Blinding: No
18.	**Criteria for evaluation:** **Primary endpoint:** R0 resection rate of patients suffering from metabolically (following PET criteria) chemotherapy-resistant, locally advanced AEG, who receive intensive neoadjuvant radio-chemotherapy (INRCT) R0 resection rate for P-NR [on day of surgery (in between D 28 to D 43 after CRT)] **Secondary endpoints:** 1. Histological regression defined by Becker Criteria (on day of surgery (in between day 28 to day 43 after radio-chemotherapy) 2. Overall survival defined as period from start of study to death (if necessary censored by end of follow-up period) from day 0 to follow up visit 6 (24 months after surgery) 3. Disease-free survival, defined as period from start of study to earlier occurring event: death or relapse until end of follow-up; Relapse will be separated into events of "local failure", "distant failure" and "local and distant failure" (three types of DFS) from day 0 to follow up visit 6 (24 months after surgery) 4. Quality of life, analyzed via EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires from day 0 to follow up visit 6 (24 months after surgery) 5. Metabolic response rate under neoadjuvant chemotherapy from day 0 to one time point of time period day 14 to 24 after chemotherapy) Exploratory: Translational analysis for identification of tumor determinants relevant for prognosis and therapy on day of surgery (in between day 28 to day 43 after radio-chemotherapy
	Efficacy: Efficacy assessments following endpoint analysis
	Safety assessments Safety assessments consisted of monitoring and recording of adverse events (AE) and serious AE (SAE) (grading according to CTCAE V. 4, coding according to MedDRA engl. 17.0), AE/SAE were collected until three months after surgery.
19.	**Statistical methods:** <u>Populations for analysis</u> The safety set consisted of all patients who were treated during the trial (screening failures were excluded) and was used for conducting all safety analyses. The primary analysis was performed in the per protocol population consisting of all patients who were treated according to the study protocol and who underwent elective tumour resection. <u>Statistical analysis</u> *Primary endpoint:* Primarily, the R0 resection rate in PET non-responders that were treated according to the study protocol was compared to a predefined probability of $p_0 = 0.70$ using a one-sided exact binomial test on a significance level of 5%. Absolute and relative frequencies are presented and an exact two-sided 95% confidence interval (Clopper-Pearson interval) is provided. *Secondary endpoints:* Absolute and relative frequencies of histological regression grades (according to Becker criteria) are presented for patients in the PP set stratified for P-R/P-NR. Exact 95% confidence intervals are given for all categories. Survival time distributions and

	distributions of disease-free survival were estimated using the Kaplan-Meier method for P-R and P-NR. Corresponding Kaplan-Meier curves are shown. For metabolic response rate, absolute and relative frequencies are shown and exact 95% confidence intervals are provided. Means, medians, standard deviations and minima and maxima for quantitative PET measures (SUVmean, SUVmax) at baseline and at the time of response evaluation as well as for relative change are presented. Distribution of relative SUVmean changes are visualized by boxplots for patients in the PP set stratified for P-R/P-NR. Results of quality of life questionnaires (EORTC QLQ-C30, QLQ-OG25) are summarized by mean, median, standard deviation, minimum and maximum and are presented stratified for P-R/P-NR and visits. The number of questionnaires available for each visit is given. No replacement of missing values was performed. AE and SAE were summarized by MedDRA Preferred Term and System Organ Class using absolute and relative frequencies. Serious AE and AE which were causally related to study medication were tabulated separately. Data analyses were performed with SAS version 9.4, illustrations were generated with R version 4.1.0.
20.	**<u>Summary - Conclusions:</u>** **Patient demographics and patient disposition** In total 77 patients were initially included, two patients were excluded after initial inclusion due to screening failures. Consequently, 75 patients were treated in the study (FPFV: 05.12.2014, LPI: 19.07.2018, LPLV: 07.08.2020). Of the 75 patients included in the safety analyses, 33 patients completed study participation up until and including FU year 2. Five patients withdrew consent during the course of the study. 49 adult (18-64 years, 65.3%) and 26 elderly (65-84 years, 34.7%) patients were included. The median age was 61 years [range: 34 – 82]. There were 9 female (12.0%) and 66 male patients (88.0%). Distributions of relevant tumour characteristics at baseline (TNM, Grading, AEG subtypes) are given in Table 1 (Appendix). 50 / 75 patients were classified as responders (P-R) according to PET assessment, 25 as non-responders (P-NR). In the PP set consisting of 67 patients (see below), there were 45 P-R and 22 P-NR.
	Compliance: Two patients were excluded due to major violations of the inclusion criteria (screening failures, no study associated treatment). For the remaining 75 patients, there were 4 violations of inclusion or exclusion criteria, which were rated as minor violations. <u>Protocol Violation (PV)</u>: 155 PVs were reported in 34/77 patients: 148/155 PV were rated as minor (i.e. 53 missing – mostly single- or late/early lab and 12 ECG values; 29 visits not as scheduled; 23 missing QLQ; 10 change in IMP administration; 17 changes in timing or missing of EGD; and other). 7 major PV in 7 patients (2 no AEG, 1 no EGD, 1 misclassification; 3 change in dose/missing cycle CTX). <u>Study medication</u>: Overall compliance for procedures and therapies were as expected following clinical routine. Administration of IMP regimen see Table 2 (Appendix). **Safety Assessments (all patients included)** Annual Safety Reports have been provided to BfArM and EC for the following periods: DSUR 1: 14.04.2014 – 13.04.2015 DSUR 2: 14.04.2015 – 13.04.2016

	DSUR 3: 14.04.2016 – 13.04.2017 DSUR 4: 14.04.2017 – 13.04.2018 DSUR 5: 14.04.2018 – 13.04.2019 DSUR 6: 14.04.2019 – 13.04.2020 DSUR 7: 14.04.2020 – 13.04.2021 Adverse Events and Serious Adverse Events were classified according to CTCAE V. 4 and coded according to MedDRA V. 17.0 English.
	Safety Results (AE, SAE, SUSAR) **Adverse Events (AE)** A total of 204 AE were reported in 48 (64%) of 75 patients see Table 3 (Appendix). 124/204 AE were deemed related to treatment administered (AR) (information on 1 AE missing). 82/204 AE were rated Grade 1 (mild), 62/204 Grade 2 (moderate), 43/204 Grade 3 (severe), 12/204 Grade 4 (life-threatening), 0/204 Grade 5 (death) (information on 5 AE missing). **Serious AE (SAE)** A total of 46 SAE (terms) were reported in 16 (21%) of 75 patients see Table 4 (Appendix). **Suspected Serious Adverse Reactions (SAR)** 14 SAE in 8 (11%) of 75 patients were deemed related (SAR) see Table 5 (Appendix). One SAR (pneumonia aspiration) resulted in death. **Suspected Unexpected Serious Adverse Reactions (SUSAR)** No SUSAR were reported in the study. **Non-serious Adverse Events (AE)** A total of 158 non-serious AEs were reported in 47 (63%) of 75 patients see Table 6 (Appendix). 47/158 non-serious AEs were deemed related to treatment administered (AR) (information on 1 AE missing).
	Efficacy Results **Primary Endpoint** R0 resection was achieved in the 19 of 22 P-NR treated according to the study protocol (PP set). R1 resection was observed for 1 of the 22 patients and Rx for 2. Consequently, R0 resection rate for P-NR [on day of surgery (in between D 28 to D 43 after CRT)] was 19 / 22 = 86.4% (two-sided 95% confidence interval 65.1% to 97.1%). The primary null hypothesis (H_0: $P \leq 0.70$) could not be rejected ($p = 0.068$, one-sided test). For P-R (PP set), R0 resection was achieved for 43 / 45 patients (95.6%, 95% ci 84.9% to 99.5%). R1 resection for the other two patients. **Secondary Endpoints** Of the 75 patients in the safety set, 50 were classified as metabolic responders to neoadjuvant chemotherapy (66.7%, 95% ci 54.8 to 77.1%), 25 as non-responders (33.3%, 95% ci 22.9% to 45.2%). In the PP set, the corresponding frequencies were 45 / 67 P-R (67.2%, 95% ci 54.6 to 78.2%) and 22 / 67 P-NR (32.8%, 95% ci 21.8 to 45.4%). Mean relative change of SUVmean values in responders (PP set) was 58% (SD 13%, Min 35%, Max 89%), in non-reponders it was 16% (SD 9%, Min -3%, Max 31%). Descripti.ve statistics for SUVmean and SUVmax values are presented in Table 7, distribution of SUVmean changes are illustrated in Figure 1 (Appendix).

	Histological regression defined by Becker Criteria (on day of surgery (in between day 28 to day 43 after radio-chemotherapy) was grade 1 in 12 of the 22 P-NR (54.6%, 95% ci 32.2 to 75.6%), grade 2 in 6 patients (27.3%, 95% ci 10.7 to 50.2%) and grade 3 for 4 patients (18.2%, 95% ci 5.2 to 40.3%). For P-R, the observed regression grade frequencies were 14 of 45 (31.1%, 95% ci 18.2 to 46.7%) for grade 1, 18 for grade 2 (40.0%, 95% ci 25.7 to 55.7%) and 13 for grade 3 (28.9%, 95% ci 116.4 to 44.3%). Estimated overall survival defined as period from start of study to death after 24 months was 80.3% (95% ci 67.1 to 88.6%) in the total PP set of 67 patients. In the 45 P-R patients, the estimated 24 months overall survival probability was 86.9% (95% ci 71.2 to 94.4%), for P-NR it was 66.2% (95% ci 39.6 to 83.3%). Corresponding Kaplan-Meier curves are shown in Figure 2 (Appendix). In the whole safety population, disease recurrence was documented in 21 / 75 patients. For 19 of these patients, distant recurrence was observed. Local recurrence occurred in 2 of the 75 patients during follow-up. No appearances of local + distant metastases were recorded. Disease-free survival, defined as period from start of study to earlier occurring event: death or relapse, after 24 months was estimated to be 62.8% (95% ci 49.0 to73.8%) in the whole study population (PP set). For the corresponding P-NR patients, it was 59.1% (95% ci 34.5 to 77.1%), for P-R it was 64.5% (95% ci 47.3 to 77.3%). Quality of life as assessed via EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires from day 0 to follow up visit 6 (24 months after surgery) was similar for responders and non-responders. The QLQ-C30 summary score mean values decreased over time (P-NR - baseline: 88.6 [n=16], d14-18/21: 83.8 [n=17], preop: 79.4 [n=13], FU-3 months: 62.9 [n=14], FU-6 months: 68.7 [n=12], FU-9 months: 58.0 [n=10], FU-12 months: 68.6 [n=9], FU-18 months: 72.5 [n=5], FU-24 months: 67.5 [n=7]; P-R - baseline: 80.7 [n=40], d14-18/21: 80.8 [n=33], preop: 78.5 [n=29], FU-3 months: 68.7 [n=30], FU-6 months: 73.4 [n=21], FU-9 months: 76.6 [n=24], FU-12 months: 69.9 [n=26], FU-18 months: 72.3 [n=19], FU-24 months: 68.3 [n=17]). Tables showing mean values for the QLQ-C30 summary scores and the QLQ-C30 and QLQ-OG25 subscales are given in Tables 8 to 11 (Appendix). A visualization of the distribution of the QLQ-C30 summary score over time stratified for P-NR and P-R is shown in Figure 3 (Appendix). Exploratory: Biological material for translational analyses was obtained for 59 patients at baseline and for 54 patients after finishing chemotherapeutic treatment. Methods were established. While imaging and histology based analyses for translational research are in progress, findings show that CTX and CRT lead to genetic changes with shifts in mutation signatures, suggesting treatment induced changes in pathway signalling of tumor cells, also affecting immune architecture of tumour microenvironment.
	Overall Conclusion: While results are promising, significance could not be demonstrated. The response rate was higher than originally assumed due to the emergence of new standard therapy regimen (mFOLFOX6, included as IMP) during the course of the clinical trial (leading to its premature discontinuation). Reported AE/SAE were in accordance with the known safety profile of the established chemo- and radiotherapy regimen administered according to clinical routine.

	In conclusion, while the primary endpoint was not met, the high R0 resection rate in PET-non-responders provides a promising signal towards PET-guided individualized treatment in patients with localized AEG:

APPENDIX

Table 1: Distributions of relevant tumour characteristics at baseline (TNM, Grading, AEG subtypes)

	Overall (N=75)
T	
Tx	2 (2.7%)
Tis	0 (0.0%)
T0	0 (0.0%)
T1	0 (0.0%)
T2	8 (10.7%)
T3	62 (82.7%)
T4	3 (4.0%)
N	
Nx	48 (64.0%)
N0	7 (9.3%)
N1	17 (22.7%)
N2	3 (4.0%)
N3	0 (0.0%)
M	
M0	74 (98.7%)
M1	1 (1.3%)
M1a	0 (0.0%)
M1b	0 (0.0%)
Grading	
N-Miss	4
G1	6 (8.5%)
G2	32 (45.1%)
G3	33 (46.5%)
G4	0 (0.0%)
AEG (Siewert)	
N-Miss	1
AEG I	44 (59.5%)
AEG II	26 (35.1%)
AEG III	4 (5.4%)

Table 2: CTX Regimen Responder, Non-Responder

	Responder (N=50)	Non-Responder (N=25)	Total (N=75)
CTX regimen			
EOX	8 (47.1%)	9 (52.9%)	17 (100.0%)
EOF	1 (100.0%)	0 (0.0%)	1 (100.0%)
CF	0 (0.0%)	1 (100.0%)	1 (100.0%)
mFOLFOX6	36 (76.6%)	11 (23.4%)	47 (100.0%)
Oxaliplatin, Folin acid, 5-FU	1 (33.3%)	2 (66.7%)	3 (100.0%)
XP	4 (66.7%)	2 (33.3%)	6 (100.0%)

Table 3: AE Coding results (MedDRA V. 17.0)

AE - all

		Exposed N=75		
			Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Total AE	**204**	48	(64)
Blood and lymphatic system disorders	**24**	17	(23)
Anaemia	2	2	(3)
Granulocytopenia	1	1	(1)
Leukocytosis	1	1	(1)
Leukopenia	9	8	(11)
Neutropenia	4	3	(4)
Splenic infarction	1	1	(1)
Thrombocytopenia	6	5	(7)
Cardiac disorders	**3**	3	(4)
Acute myocardial infarction	1	1	(1)
Bradycardia	1	1	(1)
Myocardial infarction	1	1	(1)
Eye disorders	**1**	1	(1)
Eye disorder	1	1	(1)
Gastrointestinal disorders	**51**	27	(36)
Abdominal pain	1	1	(1)
Colitis ischaemic	1	1	(1)
Constipation	3	3	(4)
Diarrhoea	10	8	(11)
Dysphagia	12	9	(12)
Gastritis	1	1	(1)
Gastrooesophageal reflux disease	2	2	(3)
Mechanical ileus	2	1	(1)
Melaena	1	1	(1)
Nausea	13	11	(15)
Oesophageal stenosis	1	1	(1)
Stomatitis	1	1	(1)
Vomiting	3	3	(4)
General disorders and administration site conditions	**20**	15	(20)
Asthenia	2	2	(3)
Chest pain	1	1	(1)

	Exposed N=75		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Complication of device insertion	1	1	(1)
Fatigue	5	4	(5)
Impaired healing	1	1	(1)
Mucosal inflammation	4	4	(5)
Pain	1	1	(1)
Pyrexia	4	4	(5)
Thrombosis in device	1	1	(1)
Hepatobiliary disorders	**2**	2	(3)
Gallbladder perforation	1	1	(1)
Hepatic failure	1	1	(1)
Infections and infestations	**10**	10	(13)
Erysipelas	1	1	(1)
Oesophageal candidiasis	1	1	(1)
Pneumonia	5	5	(7)
Post procedural pneumonia	1	1	(1)
Sepsis	2	2	(3)
Injury, poisoning and procedural complications	**9**	8	(11)
Abdominal wound dehiscence	1	1	(1)
Anastomotic complication	6	6	(8)
Anastomotic leak	1	1	(1)
Anastomotic stenosis	1	1	(1)
Investigations	**7**	7	(9)
Blood creatinine increased	1	1	(1)
C-reactive protein increased	1	1	(1)
Electrocardiogram ST segment abnormal	1	1	(1)
Gamma-glutamyltransferase increased	2	2	(3)
Haemoglobin decreased	2	2	(3)
Metabolism and nutrition disorders	**4**	4	(5)
Decreased appetite	2	2	(3)
Dehydration	1	1	(1)
Gout	1	1	(1)
Musculoskeletal and connective tissue disorders	**2**	2	(3)
Critical illness myopathy	1	1	(1)
Musculoskeletal pain	1	1	(1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	1	(1)

	Exposed N=75		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Adenocarcinoma	1	1	(1)
Nervous system disorders	**24**	17	(23)
Critical illness polyneuropathy	1	1	(1)
Dizziness	2	2	(3)
Dysgeusia	3	3	(4)
Headache	2	2	(3)
Motor dysfunction	1	1	(1)
Neuropathy peripheral	1	1	(1)
Polyneuropathy	13	12	(16)
Speech disorder	1	1	(1)
Psychiatric disorders	**3**	2	(3)
Confusional state	1	1	(1)
Restlessness	1	1	(1)
Sleep disorder	1	1	(1)
Renal and urinary disorders	**3**	3	(4)
Dysuria	1	1	(1)
Haematuria	1	1	(1)
Renal infarct	1	1	(1)
Reproductive system and breast disorders	**1**	1	(1)
Testicular swelling	1	1	(1)
Respiratory, thoracic and mediastinal disorders	**23**	14	(19)
Allergic respiratory symptom	1	1	(1)
Cough	2	2	(3)
Diaphragmatic abnormal relaxation	2	2	(3)
Dysphonia	1	1	(1)
Dyspnoea	3	3	(4)
Epistaxis	1	1	(1)
Pleural effusion	4	3	(4)
Pneumonia aspiration	2	2	(3)
Pneumothorax	1	1	(1)
Pulmonary embolism	5	4	(5)
Thoracic haemorrhage	1	1	(1)
Skin and subcutaneous tissue disorders	**7**	4	(5)
Alopecia	5	3	(4)
Erythema	2	1	(1)

		Exposed N=75		
			Subjects affected	
System Organ Class	*Preferred Term*	*Events*	*n*	*(%)*
Surgical and medical procedures		**1**	1	(1)
	Mechanical ventilation	1	1	(1)
Vascular disorders		**8**	6	(8)
	Deep vein thrombosis	1	1	(1)
	Hypertension	1	1	(1)
	Intra-abdominal haematoma	1	1	(1)
	Lymphatic fistula	1	1	(1)
	Thrombophlebitis	3	2	(3)
	Thrombosis	1	1	(1)

Table 4: SAE Coding results (MedDRA V. 17.0)

SAE - all

		Exposed N=75		
			Subjects affected	
System Organ Class	*Preferred Term*	*Events*	*n*	*(%)*
Total SAE		**46**	16	(21)
Blood and lymphatic system disorders		**5**	4	(5)
	Leukopenia	2	2	(3)
	Neutropenia	1	1	(1)
	Thrombocytopenia	2	2	(3)
Cardiac disorders		**1**	1	(1)
	Myocardial infarction	1	1	(1)
Gastrointestinal disorders		**10**	7	(9)
	Abdominal pain	1	1	(1)
	Colitis ischaemic	1	1	(1)
	Diarrhoea	1	1	(1)
	Dysphagia	5	5	(7)
	Mechanical ileus	2	1	(1)
General disorders and administration site conditions		**2**	2	(3)
	Pyrexia	2	2	(3)
Hepatobiliary disorders		**2**	2	(3)

	Exposed N=75		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Gallbladder perforation	1	1	(1)
Hepatic failure	1	1	(1)
Infections and infestations	**5**	5	(7)
Erysipelas	1	1	(1)
Pneumonia	2	2	(3)
Sepsis	2	2	(3)
Investigations	**3**	3	(4)
C-reactive protein increased	1	1	(1)
Gamma-glutamyltransferase increased	1	1	(1)
Haemoglobin decreased	1	1	(1)
Metabolism and nutrition disorders	**1**	1	(1)
Dehydration	1	1	(1)
Musculoskeletal and connective tissue disorders	**1**	1	(1)
Critical illness myopathy	1	1	(1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	1	(1)
Adenocarcinoma	1	1	(1)
Nervous system disorders	**1**	1	(1)
Critical illness polyneuropathy	1	1	(1)
Renal and urinary disorders	**2**	2	(3)
Haematuria	1	1	(1)
Renal infarct	1	1	(1)
Respiratory, thoracic and mediastinal disorders	**11**	6	(8)
Cough	1	1	(1)
Diaphragmatic abnormal relaxation	1	1	(1)
Epistaxis	1	1	(1)
Pleural effusion	2	2	(3)
Pneumonia aspiration	2	2	(3)
Pulmonary embolism	4	3	(4)
Vascular disorders	**1**	1	(1)
Intra-abdominal haematoma	1	1	(1)

Table 5: SAR (MedDRA V. 17.0)

SAE - related to treatment

	Exposed N=75		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Total related SAE (SAR)	**14**	8	(11)
Blood and lymphatic system disorders	**3**	3	(4)
Leukopenia	1	1	(1)
Neutropenia	1	1	(1)
Thrombocytopenia	1	1	(1)
Gastrointestinal disorders	**4**	3	(4)
Abdominal pain	1	1	(1)
Diarrhoea	1	1	(1)
Dysphagia	2	2	(3)
General disorders and administration site conditions	**1**	1	(1)
Pyrexia	1	1	(1)
Hepatobiliary disorders	**1**	1	(1)
Gallbladder perforation	1	1	(1)
Infections and infestations	**2**	2	(3)
Pneumonia	2	2	(3)
Metabolism and nutrition disorders	**1**	1	(1)
Dehydration	1	1	(1)
Respiratory, thoracic and mediastinal disorders	**2**	2	(3)
Cough	1	1	(1)
Pneumonia aspiration	1	1	(1)

Table 6: Total non-SAE AE (MedDRA V. 17.0)

AE - which were not SAE

	Exposed N=75		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Total non-SAE AE	**158**	47	(63)
Blood and lymphatic system disorders	**19**	16	(21)
Anaemia	2	2	(3)
Granulocytopenia	1	1	(1)
Leukocytosis	1	1	(1)

	Exposed N=75		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Leukopenia	7	7	(9)
Neutropenia	3	2	(3)
Splenic infarction	1	1	(1)
Thrombocytopenia	4	4	(5)
Cardiac disorders	**2**	2	(3)
Acute myocardial infarction	1	1	(1)
Bradycardia	1	1	(1)
Eye disorders	**1**	1	(1)
Eye disorder	1	1	(1)
Gastrointestinal disorders	**41**	26	(35)
Constipation	3	3	(4)
Diarrhoea	9	7	(9)
Dysphagia	7	6	(8)
Gastritis	1	1	(1)
Gastrooesophageal reflux disease	2	2	(3)
Melaena	1	1	(1)
Nausea	13	11	(15)
Oesophageal stenosis	1	1	(1)
Stomatitis	1	1	(1)
Vomiting	3	3	(4)
General disorders and administration site conditions	**18**	13	(17)
Asthenia	2	2	(3)
Chest pain	1	1	(1)
Complication of device insertion	1	1	(1)
Fatigue	5	4	(5)
Impaired healing	1	1	(1)
Mucosal inflammation	4	4	(5)
Pain	1	1	(1)
Pyrexia	2	2	(3)
Thrombosis in device	1	1	(1)
Infections and infestations	**5**	5	(7)
Oesophageal candidiasis	1	1	(1)
Pneumonia	3	3	(4)
Post procedural pneumonia	1	1	(1)
Injury, poisoning and procedural complications	**9**	8	(11)

	Exposed N=75		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Abdominal wound dehiscence	1	1	(1)
Anastomotic complication	6	6	(8)
Anastomotic leak	1	1	(1)
Anastomotic stenosis	1	1	(1)
Investigations	**4**	4	(5)
Blood creatinine increased	1	1	(1)
Electrocardiogram ST segment abnormal	1	1	(1)
Gamma-glutamyltransferase increased	1	1	(1)
Haemoglobin decreased	1	1	(1)
Metabolism and nutrition disorders	**3**	3	(4)
Decreased appetite	2	2	(3)
Gout	1	1	(1)
Musculoskeletal and connective tissue disorders	**1**	1	(1)
Musculoskeletal pain	1	1	(1)
Nervous system disorders	**23**	16	(21)
Dizziness	2	2	(3)
Dysgeusia	3	3	(4)
Headache	2	2	(3)
Motor dysfunction	1	1	(1)
Neuropathy peripheral	1	1	(1)
Polyneuropathy	13	12	(16)
Speech disorder	1	1	(1)
Psychiatric disorders	**3**	2	(3)
Confusional state	1	1	(1)
Restlessness	1	1	(1)
Sleep disorder	1	1	(1)
Renal and urinary disorders	**1**	1	(1)
Dysuria	1	1	(1)
Reproductive system and breast disorders	**1**	1	(1)
Testicular swelling	1	1	(1)
Respiratory, thoracic and mediastinal disorders	**12**	10	(13)
Allergic respiratory symptom	1	1	(1)
Cough	1	1	(1)
Diaphragmatic abnormal relaxation	1	1	(1)
Dysphonia	1	1	(1)

	Exposed N=75		
		Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*
Dyspnoea	3	3	(4)
Pleural effusion	2	2	(3)
Pneumothorax	1	1	(1)
Pulmonary embolism	1	1	(1)
Thoracic haemorrhage	1	1	(1)
Skin and subcutaneous tissue disorders	**7**	4	(5)
Alopecia	5	3	(4)
Erythema	2	1	(1)
Surgical and medical procedures	**1**	1	(1)
Mechanical ventilation	1	1	(1)
Vascular disorders	**7**	5	(7)
Deep vein thrombosis	1	1	(1)
Hypertension	1	1	(1)
Lymphatic fistula	1	1	(1)
Thrombophlebitis	3	2	(3)
Thrombosis	1	1	(1)

Table 7: Distribution of SUV values and changes stratified for P-R and P-NR.

	Responder (N=45)	Non-Responder (N=22)
SUVmean at baseline		
N	45	22
Mean	13.6	8.3
SD	9.2	7.6
Range	3.5 - 46.4	3.6 - 38.5
SUVmean 14-18/21 days after start of CTX		
N	45	22
Mean	5.1	7.0
SD	3.4	6.6
Range	1.7 - 22.7	3.1 - 33.7
Change of SUVmean (%)		
N	45	22
Mean	58.5	15.7
SD	13.3	9.3
Range	35.1 - 88.7	-3.3 - 30.6
SUVmax at baseline		

N	45	22
Mean	17.1	10.0
SD	10.8	9.5
Range	4.4 - 53.3	4.5 - 48.6
SUVmax 14-18/21 days after start of CTX		
N	45	21
Mean	6.6	8.8
SD	4.5	8.7
Range	1.6 - 29.0	3.7 - 43.7
Change of SUVmax (%)		
N	45	21
Mean	57.5	14.1
SD	16.4	8.3
Range	23.3 - 93.4	1.4 - 32.8

Table 8: Observed values for the EORTC-QLQC30 questionnaire subscales and summary score over time for metabolic non-responders (PP set).

	Screening (N=18)	Day 14-18/21 after Start CTX (N=18)	Pre-OP (N=13)	FU-3 mon. (N=14)	FU-6 mon. (N=15)	FU-9 mon. (N=12)	FU-12 mon. (N=11)	FU-18 mon. (N=5)	FU-24 mon. (N=7)
Physical functioning									
N	18	18	13	14	14	11	11	5	7
Mean	97.8	93.7	82.1	71.3	72.9	67.3	75.8	85.3	77.1
SD	5.6	10.1	14.5	22.3	20.8	19.7	19.4	5.6	18.8
Range	80.0 - 100.0	66.7 - 100.0	60.0 - 100.0	13.3 - 100.0	26.7 - 100.0	33.3 - 93.3	40.0 - 100.0	80.0 - 93.3	40.0 - 100.0
Role functioning									
N	18	18	13	14	13	11	10	5	7
Mean	84.3	78.7	75.6	44.0	55.1	31.8	56.7	50.0	52.4
SD	24.6	26.1	22.2	28.9	29.2	26.3	29.6	16.7	20.2
Range	33.3 - 100.0	16.7 - 100.0	33.3 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	33.3 - 66.7	16.7 - 66.7
Emotional functioning									
N	18	18	13	14	14	11	10	5	7
Mean	60.2	68.5	59.6	62.5	70.2	57.1	54.2	55.0	57.1
SD	29.1	23.3	25.0	21.4	19.3	18.1	28.7	15.1	27.4
Range	8.3 - 100.0	16.7 - 100.0	0.0 - 91.7	16.7 - 83.3	33.3 - 100.0	25.0 - 83.3	0.0 - 91.7	33.3 - 75.0	25.0 - 100.0
Cognitive functioning									
N	18	18	13	14	14	10	10	5	7
Mean	88.9	88.9	88.5	70.2	81.0	75.0	73.3	76.7	81.0
SD	18.1	19.8	14.2	24.6	21.5	18.0	17.9	9.1	15.0
Range	50.0 - 100.0	33.3 - 100.0	66.7 - 100.0	16.7 - 100.0	33.3 - 100.0	50.0 - 100.0	50.0 - 100.0	66.7 - 83.3	66.7 - 100.0
Social functioning									
N	18	18	13	14	14	10	10	5	7
Mean	75.0	71.3	59.0	54.8	69.0	46.7	61.7	70.0	57.1
SD	26.4	27.3	22.2	30.3	27.6	20.5	34.3	7.5	18.9
Range	16.7 - 100.0	0.0 - 100.0	16.7 - 83.3	0.0 - 100.0	0.0 - 100.0	16.7 - 66.7	0.0 - 100.0	66.7 - 83.3	33.3 - 83.3
Global health status/QoL									
N	18	18	13	14	14	10	10	5	7
Mean	69.4	69.9	61.5	50.6	51.2	50.8	55.8	65.0	71.4
SD	19.2	18.3	21.7	17.4	17.6	20.2	24.5	18.1	12.6
Range	16.7 - 100.0	33.3 - 100.0	16.7 - 83.3	16.7 - 83.3	16.7 - 75.0	16.7 - 83.3	0.0 - 83.3	33.3 - 75.0	50.0 - 83.3
Fatigue									
N	17	17	13	14	13	11	11	5	7
Mean	14.4	18.3	35.0	46.8	47.4	56.6	48.5	44.4	42.9
SD	18.7	15.7	26.4	25.1	27.8	23.5	27.8	13.6	13.5
Range	0.0 - 66.7	0.0 - 44.4	0.0 - 77.8	0.0 - 88.9	0.0 - 100.0	33.3 - 100.0	0.0 - 100.0	33.3 - 66.7	33.3 - 66.7

Nausea and vomiting									
N	18	17	13	14	14	11	11	5	7
Mean	2.8	5.9	12.8	23.8	20.2	21.2	7.6	3.3	11.9
SD	8.6	14.4	23.7	15.6	19.8	23.7	11.5	7.5	12.6
Range	0.0 - 33.3	0.0 - 50.0	0.0 - 83.3	0.0 - 50.0	0.0 - 66.7	0.0 - 66.7	0.0 - 33.3	0.0 - 16.7	0.0 - 33.3
Pain									
N	18	18	13	14	14	11	11	5	7
Mean	11.1	11.1	12.8	31.0	29.8	31.8	30.3	26.7	31.0
SD	19.8	18.1	21.7	25.2	21.9	22.9	24.5	25.3	27.9
Range	0.0 - 66.7	0.0 - 50.0	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7
Dyspnoea									
N	18	18	13	14	14	11	11	5	7
Mean	7.4	5.6	23.1	35.7	40.5	39.4	27.3	26.7	33.3
SD	14.3	12.8	25.0	24.3	35.0	36.0	29.1	27.9	27.2
Range	0.0 - 33.3	0.0 - 33.3	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7
Insomnia									
N	17	17	13	14	14	11	10	5	7
Mean	13.7	13.7	12.8	35.7	26.2	45.5	36.7	20.0	42.9
SD	29.0	20.6	16.9	35.7	19.3	27.0	33.1	29.8	31.7
Range	0.0 - 100.0	0.0 - 66.7	0.0 - 33.3	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0
Appetite loss									
N	17	17	13	14	13	11	11	5	7
Mean	9.8	25.5	23.1	52.4	46.2	45.5	30.3	33.3	19.0
SD	19.6	25.1	28.5	36.3	32.0	34.2	31.5	33.3	26.2
Range	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7
Constipation									
N	18	18	13	14	14	11	10	5	7
Mean	1.9	16.7	7.7	16.7	4.8	21.2	13.3	6.7	14.3
SD	7.9	28.6	14.6	21.7	12.1	30.8	17.2	14.9	26.2
Range	0.0 - 33.3	0.0 - 100.0	0.0 - 33.3	0.0 - 66.7	0.0 - 33.3	0.0 - 100.0	0.0 - 33.3	0.0 - 33.3	0.0 - 66.7
Diarrhoea									
N	18	17	13	14	13	11	10	5	7
Mean	7.4	17.6	5.1	42.9	51.3	42.4	40.0	33.3	52.4
SD	18.3	29.1	12.5	30.5	32.2	26.2	26.3	23.6	17.8
Range	0.0 - 66.7	0.0 - 100.0	0.0 - 33.3	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	33.3 - 66.7
Financial difficulties									
N	17	17	13	14	13	11	10	5	7
Mean	11.8	7.8	25.6	21.4	20.5	15.2	20.0	13.3	19.0
SD	20.2	14.6	30.9	24.8	25.6	17.4	23.3	29.8	26.2
Range	0.0 - 66.7	0.0 - 33.3	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 33.3	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7
SumScore									
N	16	17	13	14	12	10	9	5	7
Mean	88.6	83.8	79.4	62.9	68.7	58.0	68.6	72.5	67.5
SD	9.5	14.2	13.3	16.5	16.5	14.4	17.0	4.1	15.7
Range	72.8 - 100.0	48.9 - 97.8	55.9 - 96.8	33.9 - 85.3	34.7 - 91.0	31.0 - 74.4	38.7 - 94.2	67.7 - 78.6	37.1 - 83.3

Table 9: Observed values for the EORTC-QLQC30 questionnaire subscales and summary score over time for metabolic responders (PP set).

	Screening (N=41)	Day 14-18/21 after Start CTX (N=34)	Pre-OP (N=32)	FU-3 mon. (N=34)	FU-6 mon. (N=26)	FU-9 mon. (N=27)	FU-12 mon. (N=29)	FU-18 mon. (N=22)	FU-24 mon. (N=17)
Physical functioning									
N	41	33	32	31	22	24	29	20	17
Mean	88.6	83.1	81.0	68.6	73.8	79.4	72.9	78.0	72.9
SD	17.8	16.7	20.5	20.9	17.6	19.6	25.4	22.0	22.9
Range	26.7 - 100.0	26.7 - 100.0	26.7 - 100.0	16.7 - 100.0	33.3 - 100.0	26.7 - 100.0	13.3 - 100.0	26.7 - 100.0	40.0 - 100.0
Role functioning									
N	41	33	31	31	22	24	29	20	17
Mean	76.0	73.7	67.7	53.8	62.1	71.5	60.9	63.3	58.8
SD	29.6	22.1	29.8	32.4	28.3	23.3	33.1	34.5	32.9
Range	0.0 - 100.0	16.7 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0

Emotional functioning									
N	41	33	32	31	22	24	29	20	17
Mean	66.7	77.9	72.9	70.5	72.3	75.0	64.4	67.5	67.6
SD	22.8	18.6	20.4	22.7	23.6	23.6	30.1	27.0	30.7
Range	0.0 - 100.0	33.3 - 100.0	25.0 - 100.0	16.7 - 100.0	25.0 - 100.0	16.7 - 100.0	0.0 - 100.0	8.3 - 100.0	0.0 - 100.0
Cognitive functioning									
N	41	33	32	31	22	24	29	20	17
Mean	89.0	91.4	82.3	81.7	81.1	80.6	80.5	78.3	73.5
SD	18.9	18.2	24.3	23.3	17.3	22.9	24.0	29.7	27.7
Range	33.3 - 100.0	16.7 - 100.0	33.3 - 100.0	16.7 - 100.0	33.3 - 100.0	33.3 - 100.0	33.3 - 100.0	0.0 - 100.0	16.7 - 100.0
Social functioning									
N	41	33	32	31	22	24	29	20	17
Mean	75.2	80.8	79.2	64.0	74.2	75.7	66.1	65.0	64.7
SD	27.7	20.0	26.1	34.5	21.7	24.1	33.5	34.2	31.7
Range	0.0 - 100.0	50.0 - 100.0	0.0 - 100.0	0.0 - 100.0	33.3 - 100.0	33.3 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0
Global health status/QoL									
N	39	33	31	31	22	24	26	20	17
Mean	62.8	62.9	65.3	55.1	61.7	69.4	56.7	63.8	63.2
SD	19.6	20.5	24.0	21.8	19.7	15.1	24.9	25.1	19.6
Range	25.0 - 100.0	16.7 - 100.0	16.7 - 100.0	16.7 - 100.0	16.7 - 83.3	33.3 - 100.0	0.0 - 100.0	16.7 - 100.0	16.7 - 83.3
Fatigue									
N	41	33	32	31	22	24	29	20	17
Mean	30.6	31.0	43.4	50.2	38.9	36.1	44.8	40.0	43.1
SD	27.4	22.5	29.9	19.6	21.9	26.9	33.3	30.9	26.0
Range	0.0 - 88.9	0.0 - 77.8	0.0 - 100.0	11.1 - 88.9	0.0 - 77.8	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0
Nausea and vomiting									
N	41	33	32	31	22	24	29	20	17
Mean	17.1	12.6	9.4	23.7	17.4	12.5	17.8	17.5	22.5
SD	24.9	16.7	14.6	28.8	20.9	17.9	24.0	19.8	25.0
Range	0.0 - 100.0	0.0 - 50.0	0.0 - 50.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7
Pain									
N	41	33	32	31	22	24	29	20	17
Mean	21.5	19.7	15.1	24.7	24.2	20.8	28.7	34.2	29.4
SD	26.9	22.2	24.1	25.4	25.6	25.7	33.6	32.2	26.7
Range	0.0 - 83.3	0.0 - 66.7	0.0 - 83.3	0.0 - 66.7	0.0 - 66.7	0.0 - 83.3	0.0 - 100.0	0.0 - 83.3	0.0 - 83.3
Dyspnoea									
N	41	33	31	31	22	24	29	20	17
Mean	13.8	11.1	22.6	26.9	28.8	25.0	32.2	21.7	41.2
SD	19.7	18.0	29.0	23.4	27.8	26.5	33.9	27.1	30.1
Range	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7
Insomnia									
N	41	33	32	31	22	24	29	20	17
Mean	22.8	28.3	27.1	31.2	28.8	26.4	34.5	28.3	43.1
SD	30.2	31.3	29.9	25.7	25.8	26.0	32.7	24.8	28.3
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0
Appetite loss									
N	40	33	31	30	22	24	29	20	17
Mean	23.3	19.2	17.2	34.4	22.7	22.2	37.9	20.0	23.5
SD	30.4	30.1	30.9	30.9	28.0	32.1	41.5	29.4	25.7
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7
Constipation									
N	41	33	32	31	21	24	27	19	17
Mean	10.6	23.2	15.6	11.8	0.0	11.1	3.7	12.3	7.8
SD	20.3	32.8	30.5	23.6	0.0	18.8	10.7	27.7	14.6

Range	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 0.0	0.0 - 66.7	0.0 - 33.3	0.0 - 100.0	0.0 - 33.3
Diarrhoea									
N	41	33	32	31	21	24	28	20	17
Mean	8.9	12.1	9.4	46.2	46.0	31.9	35.7	38.3	39.2
SD	16.7	24.7	21.1	34.1	28.8	25.0	37.3	31.1	33.8
Range	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0
Financial difficulties									
N	40	33	32	31	22	24	29	20	17
Mean	19.2	14.1	18.7	23.7	24.2	33.3	34.5	35.0	43.1
SD	31.9	22.1	28.0	32.4	32.8	32.6	37.2	41.1	38.7
Range	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0
SumScore									
N	40	33	29	30	21	24	26	19	17
Mean	80.7	80.8	78.5	68.7	73.4	76.6	69.9	72.3	68.3
SD	14.5	12.1	15.7	16.1	13.9	17.6	23.0	22.8	21.9
Range	43.2 - 100.0	53.1 - 100.0	37.3 - 99.0	33.3 - 95.6	46.9 - 95.5	29.0 - 98.0	26.1 - 100.0	29.9 - 100.0	21.0 - 98.3

Table 10: Observed values for the EORTC QLQ-OG25 questionnaire subscales over time for metabolic non-responders (PP set).

	Screening (N=18)	Day 14-18/21 after Start CTX (N=18)	Pre-OP (N=14)	FU-3 mon. (N=14)	FU-6 mon. (N=13)	FU-9 mon. (N=12)	FU-12 mon. (N=11)	FU-18 mon. (N=5)	FU-24 mon. (N=7)
OGDYS									
N	18	18	13	13	12	11	11	5	7
Mean	31.5	27.8	16.2	30.8	31.5	38.4	28.3	6.7	17.5
SD	26.7	28.3	17.3	21.4	28.8	30.0	36.3	6.1	32.6
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 77.8	0.0 - 88.9	0.0 - 88.9	0.0 - 88.9	0.0 - 11.1	0.0 - 88.9
OGEAT									
N	17	18	13	13	12	11	11	5	7
Mean	29.9	32.4	35.9	50.0	55.1	62.1	54.5	48.3	45.2
SD	23.8	30.5	22.9	22.8	22.2	22.5	28.2	16.0	19.8
Range	0.0 - 66.7	0.0 - 100.0	0.0 - 83.3	16.7 - 83.3	25.0 - 100.0	33.3 - 91.7	25.0 - 100.0	25.0 - 66.7	25.0 - 83.3
OGRFX									
N	18	18	13	13	12	11	11	5	7
Mean	18.5	21.3	14.1	26.9	25.0	34.8	28.8	20.0	31.0
SD	23.5	23.4	17.8	23.1	29.7	24.1	21.2	21.7	15.0
Range	0.0 - 83.3	0.0 - 83.3	0.0 - 50.0	0.0 - 66.7	0.0 - 83.3	0.0 - 66.7	0.0 - 66.7	0.0 - 50.0	16.7 - 50.0
OGODYN									
N	16	18	13	13	12	11	11	5	7
Mean	22.9	19.4	17.9	23.1	23.6	33.3	24.2	13.3	14.3
SD	20.1	26.4	23.0	25.9	27.9	29.8	31.1	7.5	24.4
Range	0.0 - 66.7	0.0 - 100.0	0.0 - 83.3	0.0 - 83.3	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 16.7	0.0 - 66.7
OGPD									
N	18	18	14	14	12	11	11	5	7
Mean	13.0	10.2	16.7	25.0	27.8	28.8	36.4	36.7	28.6
SD	23.3	14.2	28.5	25.1	32.8	25.9	34.0	38.0	28.4
Range	0.0 - 66.7	0.0 - 33.3	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 83.3	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7
OGANA									
N	17	18	14	14	12	11	11	5	7
Mean	77.5	71.3	70.2	69.0	52.8	53.0	59.1	43.3	40.5
SD	25.6	27.9	26.3	24.3	21.1	26.7	28.2	14.9	35.8
Range	33.3 - 100.0	33.3 - 100.0	33.3 - 100.0	33.3 - 100.0	33.3 - 100.0	33.3 - 100.0	16.7 - 100.0	33.3 - 66.7	0.0 - 100.0
OGEO									
N	17	17	13	13	11	11	11	5	7
Mean	15.7	27.5	23.1	35.9	12.1	30.3	33.3	13.3	19.0

SD	33.6	39.5	28.5	34.6	16.8	31.5	33.3	18.3	17.8
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 33.3	0.0 - 100.0	0.0 - 100.0	0.0 - 33.3	0.0 - 33.3
OGDM									
N	18	18	14	14	12	11	11	5	7
Mean	13.0	24.1	28.6	38.1	27.8	27.3	36.4	20.0	23.8
SD	25.9	27.5	28.8	25.7	34.3	29.1	27.7	18.3	25.2
Range	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 33.3	0.0 - 66.7
OGTA									
N	18	18	13	13	12	11	11	5	7
Mean	0.0	22.2	25.6	33.3	13.9	18.2	21.2	0.0	9.5
SD	0.0	28.0	30.9	23.6	17.2	22.9	30.8	0.0	16.3
Range	0.0 - 0.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 33.3	0.0 - 66.7	0.0 - 100.0	0.0 - 0.0	0.0 - 33.3
OGBI									
N	17	18	14	13	12	11	11	5	7
Mean	7.8	14.8	19.0	23.1	22.2	39.4	27.3	20.0	33.3
SD	14.6	17.0	21.5	28.5	25.9	20.1	20.1	18.3	27.2
Range	0.0 - 33.3	0.0 - 33.3	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 33.3	0.0 - 66.7
OGSV									
N	18	18	14	14	12	11	10	5	7
Mean	14.8	16.7	19.0	19.0	13.9	27.3	20.0	0.0	23.8
SD	28.5	32.8	28.4	21.5	30.0	36.0	42.2	0.0	37.1
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 0.0	0.0 - 100.0
OGCH									
N	17	18	14	14	12	11	11	5	7
Mean	13.7	18.5	4.8	21.4	22.2	30.3	18.2	6.7	23.8
SD	20.6	34.7	12.1	24.8	21.7	23.4	17.4	14.9	25.2
Range	0.0 - 66.7	0.0 - 100.0	0.0 - 33.3	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 33.3	0.0 - 33.3	0.0 - 66.7
OGCO									
N	18	18	14	14	12	10	11	5	7
Mean	18.5	18.5	16.7	28.6	30.6	33.3	30.3	13.3	23.8
SD	26.1	28.5	21.7	22.1	33.2	27.2	23.4	18.3	25.2
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 33.3	0.0 - 66.7
OGSP									
N	18	17	14	14	12	11	10	5	7
Mean	1.9	2.0	7.1	11.9	8.3	6.1	20.0	0.0	4.8
SD	7.9	8.1	14.2	28.1	20.7	13.5	35.8	0.0	12.6
Range	0.0 - 33.3	0.0 - 33.3	0.0 - 33.3	0.0 - 100.0	0.0 - 66.7	0.0 - 33.3	0.0 - 100.0	0.0 - 0.0	0.0 - 33.3
OGWL									
N	18	18	14	14	12	11	11	5	7
Mean	9.3	29.6	38.1	52.4	44.4	69.7	51.5	26.7	33.3
SD	15.4	25.3	31.6	28.4	38.5	31.5	37.6	14.9	19.2
Range	0.0 - 33.3	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 33.3	0.0 - 66.7
OGHL									
N	4	2	8	7	2	4	1	0	3
Mean	8.3	0.0	37.5	28.6	0.0	25.0	33.3	NA	0.0
SD	16.7	0.0	27.8	30.0	0.0	31.9	NA	NA	0.0
Range	0.0 - 33.3	0.0 - 0.0	0.0 - 66.7	0.0 - 66.7	0.0 - 0.0	0.0 - 66.7	33.3 - 33.3	NA	0.0 - 0.0

Table 11: Observed values for the EORTC QLQ-OG25 questionnaire subscales over time for metabolic responders (PP set).

	Screening (N=42)	Day 14-18/21 after Start CTX (N=33)	Pre-OP (N=31)	FU-3 mon. (N=31)	FU-6 mon. (N=25)	FU-9 mon. (N=25)	FU-12 mon. (N=29)	FU-18 mon. (N=20)	FU-24 mon. (N=17)
OGDYS									
N	40	32	31	30	22	23	28	19	17
Mean	33.2	16.7	10.4	24.8	26.8	15.0	18.3	15.2	20.3
SD	29.3	21.1	22.8	26.2	24.9	22.4	21.4	17.8	17.7
Range	0.0 - 100.0	0.0 - 88.9	0.0 - 100.0	0.0 - 100.0	0.0 - 77.8	0.0 - 88.9	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7

OGEAT

N	40	31	31	29	22	23	29	19	17
Mean	42.3	24.3	21.5	43.1	40.8	34.1	46.3	32.0	42.2
SD	34.4	25.4	23.9	29.8	26.5	25.6	34.6	28.2	30.1
Range	0.0 - 100.0	0.0 - 83.3	0.0 - 91.7	8.3 - 100.0	0.0 - 88.9	0.0 - 91.7	0.0 - 100.0	0.0 - 91.7	0.0 - 100.0

OGRFX

N	40	31	31	30	21	23	29	19	17
Mean	15.8	3.2	8.6	15.6	17.5	11.6	18.4	21.9	31.4
SD	26.9	6.7	19.2	21.4	20.1	16.2	20.6	22.9	32.2
Range	0.0 - 100.0	0.0 - 16.7	0.0 - 100.0	0.0 - 66.7	0.0 - 50.0	0.0 - 50.0	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0

OGODYN

N	40	31	31	29	22	23	29	19	17
Mean	35.8	17.7	11.8	14.9	23.5	15.9	21.8	14.0	17.6
SD	30.1	23.5	21.6	22.0	26.1	21.0	23.2	16.9	25.3
Range	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 50.0	0.0 - 66.7

OGPD

N	40	32	31	30	22	23	29	19	17
Mean	23.8	22.4	11.3	30.0	34.8	23.9	32.2	24.6	26.5
SD	30.6	27.0	21.7	26.8	28.6	26.5	31.5	25.7	29.5
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 83.3

OGANA

N	39	31	31	29	21	23	28	19	17
Mean	73.5	53.8	54.8	54.0	44.4	42.0	44.0	44.7	36.3
SD	29.3	31.8	31.1	27.7	29.0	26.0	30.5	29.9	33.5
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0

OGEO

N	40	31	31	28	21	23	29	18	17
Mean	25.0	9.7	4.3	15.5	14.3	11.6	16.1	13.0	19.6
SD	36.8	26.1	18.7	23.1	22.5	21.6	27.6	25.9	31.3
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0

OGDM

N	38	32	30	30	22	23	29	19	17
Mean	17.5	21.9	28.9	31.1	25.8	23.2	26.4	21.1	15.7
SD	28.7	30.1	28.7	26.2	25.1	21.2	33.8	22.8	23.9
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7

OGTA

N	39	32	31	28	21	23	28	19	17
Mean	12.0	12.5	32.3	26.2	15.9	21.7	20.2	12.3	19.6
SD	23.6	22.0	36.0	33.2	25.0	31.2	27.7	19.9	23.7
Range	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7

OGBI

N	38	31	31	28	21	23	27	19	17
Mean	12.3	9.7	21.5	28.6	19.0	14.5	21.0	21.1	31.4
SD	28.4	17.6	30.5	33.6	27.0	24.3	33.5	38.8	36.3
Range	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0

OGSV

N	40	32	31	30	22	23	29	19	17
Mean	11.7	6.2	6.5	12.2	10.6	10.1	16.1	10.5	9.8
SD	24.5	17.8	18.1	23.9	21.5	23.4	24.6	19.4	22.9
Range	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7

OGCH

N	40	32	31	30	22	23	29	19	17
Mean	11.7	5.2	5.4	20.0	25.8	14.5	11.5	15.8	19.6
SD	24.5	12.3	15.1	25.7	32.4	24.3	18.4	20.4	26.5
Range	0.0 - 100.0	0.0 - 33.3	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7	0.0 - 66.7

OGCO									
N	40	32	31	30	22	23	29	19	17
Mean	20.0	18.7	21.5	36.7	37.9	24.6	21.8	26.3	31.4
SD	28.0	20.6	30.5	29.5	29.6	20.6	25.6	30.6	24.9
Range	0.0 - 100.0	0.0 - 66.7	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 66.7	0.0 - 66.7	0.0 - 100.0	0.0 - 66.7
OGSP									
N	40	32	31	30	21	23	28	18	17
Mean	4.2	2.1	8.6	11.1	4.8	7.2	3.6	1.9	5.9
SD	17.2	8.2	17.1	25.3	12.0	22.4	10.5	7.9	17.6
Range	0.0 - 100.0	0.0 - 33.3	0.0 - 66.7	0.0 - 100.0	0.0 - 33.3	0.0 - 100.0	0.0 - 33.3	0.0 - 33.3	0.0 - 66.7
OGWL									
N	39	32	31	29	22	22	29	18	17
Mean	28.2	29.2	18.3	51.7	40.9	24.2	39.1	25.9	23.5
SD	37.9	32.5	28.3	39.4	35.5	31.2	39.9	31.4	32.8
Range	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0	0.0 - 100.0
OGHL									
N	6	9	13	11	5	5	5	5	1
Mean	5.6	14.8	12.8	15.2	20.0	33.3	0.0	13.3	0.0
SD	13.6	24.2	21.7	17.4	29.8	33.3	0.0	29.8	NA
Range	0.0 - 33.3	0.0 - 66.7	0.0 - 66.7	0.0 - 33.3	0.0 - 66.7	0.0 - 66.7	0.0 - 0.0	0.0 - 66.7	0.0 - 0.0

Figure 1 Relative Change of SUVmean

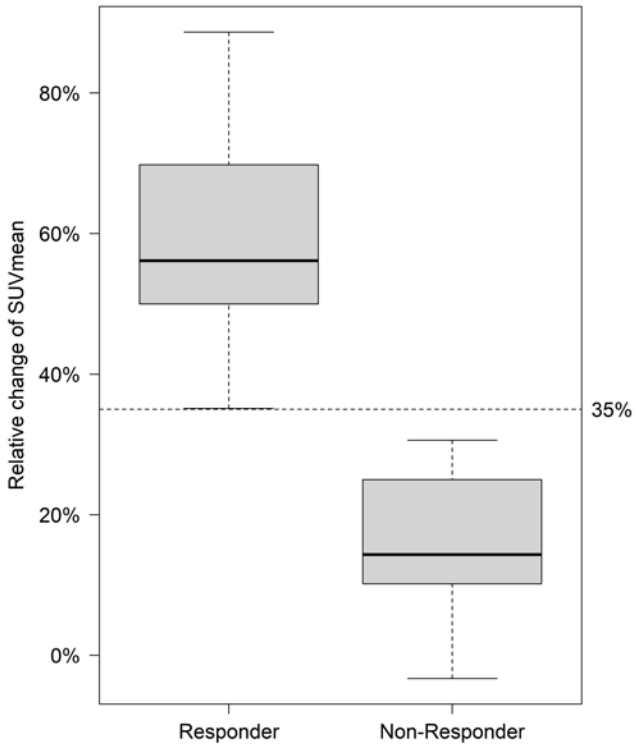

Figure 2 Overall Survival

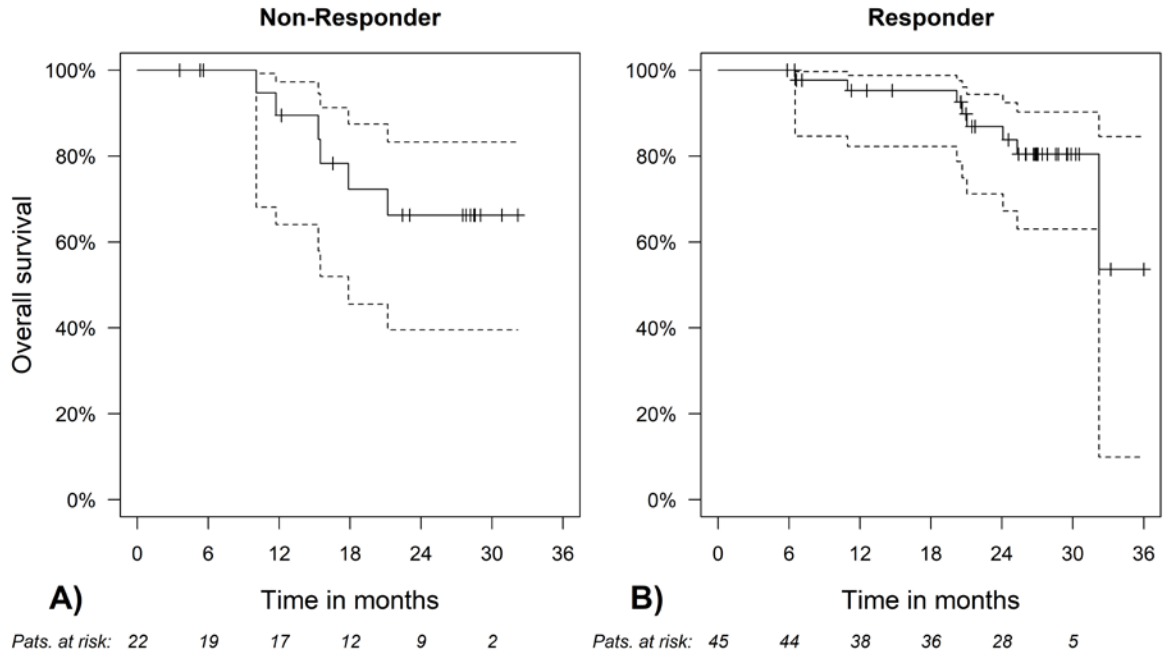

Figure 3 QLQ-C30 Summary Score