STATISTICAL ANALYSIS PLAN for

NEOADJUVANT CHEMOTHERAPY, EXCISION AND OBSERVATION FOR EARLY RECTAL CANCER: The NEO Trial.

CCTG Protocol Number: CO.28

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
BSA	Body Surface Area
CAPOX	Chemotherapy with Capecitabine and Oxaliplatin
CCTG	Canadian Cancer Trials Group
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CRM	Clear Circumferential Radial Margin
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DFS	Disease Free Survival
DRR	Distant Relapse Rate
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Cancer Group
EORTC	European Organization for Research and Treatment of Cancer
FOLFOX	Chemotherapy with Oxaliplatin, Leucovorin, and Fluorouracil
FIQL	Fecal Incontinence Quality of Life
INR	International Normalized Ratio
LARS	Low Anterior Resection Syndrome
LKA	Last day the patient is Known Alive
MAX	Maximum
MIN	Minimum
LRR	Locoregional Relapse Rate
MPV	Major Protocol Violation
MRI	Magnetic Resonance Imaging
NA	Not Assessed or Not Applicable
NCI	National Cancer Institute
NR	Not Reported
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
SAS	Statistical Analysis System
STD	Standard Deviation
TAMIS	Transanal Minimally Invasive Surgery
TME	Total Mesorectal Excision
TEMS	Transanal Endoscopic Microsurgery
UNL	Upper Normal Limit

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1. Introduction

This analysis plan describes the final analysis performed by the Canadian Cancer Trials Group (CCTG) for the CO.28 trial. It will be used for the writing of the Canadian Cancer Trials Group study report.

2. Study Description

2.1 Background

Current standard therapy for patients with T1-3 rectal tumours includes radical surgery with Total Mesorectal Excision (TME), and preoperative chemoradiation for patients with T3 tumours or N1 tumours. Although the locoregional relapse rates with modern adjuvant therapy are low (generally 5%), in patients treated with radical resection, ongoing issues with bowel function, incontinence, sexual function and depression persist. These are significantly worse in patients treated with neoadjuvant or adjuvant radiotherapy.

Multiple single arm and randomized phase II studies have explored the use of pelvic chemoradiation followed by Transanal Endoscopic Microsurgery (TEMS) or Transanal Minimally Invasive Surgery (TAMIS) as a means to increase rectal organ preservation for patients with early rectal cancer but neoadjuvant radiation significantly increases wound-healing complications and adversely affects sphincter and sexual function.

Population based studies have documented an increasing use of local excision/ minimally invasive surgery in the treatment of T1N0 or T2N0 rectal tumours but a significant proportion of clinical T1-2N0 tumours are pathologically node positive and the literature demonstrates an increased rate of local relapse with local excision versus surgical resection. Neoadjuvant chemotherapy is a potential approach to reduce local and distant relapse for rectal tumours treated with excision alone since it has been shown to reduce locoregional recurrence in stage II/III rectal cancer but without the toxicities of pelvic radiation. There is, however, virtually no prospective experience of neoadjuvant chemotherapy and excision/surgery for early rectal tumours. This phase II trial was designed to determine the outcomes of the patients with stage 1-2 rectal tumours treated with chemotherapy (FOLFOX or CAPOX) followed by minimally invasive surgery (TEMS or TAMIS). The primary endpoint of the study is the rate of organ preservation.

2.2 Study Design

CO.28 is a single arm, two-stage phase II clinical study of FOLFOX/CAPOX as a neoadjuvant treatment for patients with stage I-II (cT1-3ab/N0) rectal cancer. The study is being conducted by the Canadian Cancer Trials Group.

A total of 50 evaluable patients would be enrolled, in a two-stage minimax design with 22 patients accrued in the first stage. The trial would be stopped at the end of the first stage if the number of patients who avoided radical surgery is 10 or less. Otherwise the trial would proceed to the second stage to accrue 28 additional patients. Allowing for a 15% inevaluable rate, the total sample size would be 58 patients.

This study opened to accrue patients on August 22, 2017. On April 19, 2019, 11 of the 19 patients enrolled in the first stage were found to have avoid radical surgery. It was decided the study would processed to continue accrual of patients to full sample size. The trial was closed to further accrual on May 19, 2020 after 58 patients were accrued.

A final analysis will be performed on a database which will be locked after all patients completed their treatments and all data observed from the patients are cleaned. This plan describes the details of this final analysis.

The CCTG Data and Safety Monitoring Committee (DSMC) has been reviewing safety data annually and as otherwise required. These analyses have been prepared by a CCTG/Queen's Senior Biostatistician.

3. Objectives

3.1 Primary

The primary objective of this study is to determine the organ preservation rate in patients with early (cT1-3a,bN0) rectal cancer treated with neoadjuvant FOLFOX or CAPOX and TEMS or TAMIS.

3.2 Secondary

Secondary objectives are:

- To describe the 3-year Locoregional Relapse Rate (LRR) in patients treated with organ preservation.
- To describe the 3-year Distant Relapse Rate (DRR) in patients treated with organ preservation.
- To describe the 3-year Disease Free Survival (DFS) rate in patients treated with organ preservation.
- To evaluate the rate of post-operative complications following neoadjuvant FOLFOX/CAPOX and tumour excision/surgery.
- To evaluate nature, severity and frequency of acute and long term toxicities in all patients.
- To evaluate Quality of Life (QoL) in all patients.
- To evaluate the cost-effectiveness of the neo-adjuvant chemotherapy approach vs. the current standard approach.

3.3 Tertiary

The tertiary objectives of this study are to evaluate the prognostic value of baseline ctDNA as an independent prognostic value in addition to ypstage and histology.

(Note: The plan to address the last of the secondary objectives, i.e., the cost-effectiveness analysis, and the tertiary objectives will be developed separately later.)

4. Endpoints

4.1 Primary Efficacy

The primary efficacy endpoint is the protocol specified organ preservation rate.

4.2 Secondary Efficacy

The secondary efficacy endpoints are:

- 3 year locoregional relapse rate
- 3 year distant relapse rate
- 3 year disease free survival
- Quality of life

4.3 Safety

The safety endpoints are post-operative complication rate, serious and non-serious adverse events (clinical and laboratory), laboratory parameters, dosing data (including dose interruptions, total delivered dose and dose modifications) and reasons off treatment.

5. Sample Size and Power

The expected organ preservation rate is 50-68% among patients with clinical T1-3N0 rectal tumours treated with chemoradiation and minimally invasive surgery. Based on these historic phase II data, the experimental treatment would be considered of no interest if the protocol specified organ preservation rate is 50% or lower (H0) and as promising if its avoidance rate is 65% or higher (H1).

An optimal two-stage minimax design would be used to test the above hypotheses, which would accrual 22 evaluable patients in the first stage. The trial would be stopped at the end of the first stage if the number of patients who avoided radical surgery is 10 or less. Otherwise the trial would proceed to the second stage to accrue 28 additional evaluable patients. The experimental procedure would be considered as promising if, out of the total patients accrued, 30 or more patients avoided radical surgery. The exact type I error rate and power of this design are respectively 0.1 and 0.8. Allowing for a 15% inevaluable rate, the total sample size would be 58 patients.

6. Data Set Descriptions

Five types of analysis samples will be used:

1. All Accrued Patients:

   All patients accrued in the study.

2. All Chemotherapy Treated Patients:

   All patients who have received at least one dose of FOLFOX or CAPOX.

3. All Chemotherapy & Excision Treated Patients

   All patients who have received at least one dose of FOLFOX or CAPOX and TEMS or TAMIS.

4. All Chemotherapy & Excision/Surgery Treated Patients

   All patients who have received at least one dose of FOLFOX or CAPOX and excision (TEMS or TAMIS) or surgery (TME).

5. All Quality of Life Evaluable Patients

   All patients who have completed at least one quality of life questionnaire.

7. Statistical Analysis

7.1 General Methods

Continuous and ordinal categorical variables are summarized using the mean, median, standard error, minimum and maximum values. All confidence intervals are computed based on normal approximations except those for rates, which will be computed based on the exact method.

Percentages given in the summary tables will be rounded and may therefore not always add up to exactly 100%. Listings, tabulations, and statistical analyses will be carried out using the SAS (Statistical Analysis System, SAS Institute, North Carolina, USA) software.

Baseline evaluations will be those collected on CRF Eligibility Worksheet and Baseline Report and closest to, but no later than, the first day of study medication for treated subjects and closest to, but no later than, the date of enrollment, for subjects who were enrolled but who never received any treatment.

Laboratory results, adverse events, and other symptoms are coded and graded using the NCI CTCAE when available.

When converting a number of days to other units, the following conversion factors will be used:

1 year = 365.25 days

1 month = 30.4375 days

When either day or month of a date is missing, the missing day and/or month will be imputed by the midpoint within the smallest known interval. For example, if the day of the month is missing for any date used in a calculation, the 15th of the month will be used to replace the missing day. If the month and day of the year are missing for any date used in a calculation, the first of July of the year will be used to replace the missing date.

7.2 Study Conduct

All accrued patients are included in the analysis of study conduct.

7.2.1 Patient Disposition and Follow-up

- Number of patients accrued, treated (on study, off study), never treated **(Table 1)**
- Number of alive patients **(Table 2)**
- Median (estimated by Kaplan-Meier method) and range (minimum and maximum) **(Table 2)** of the follow-up time (months) defined as time from the day of accrual to the last day the patient is known alive (LKA) as the latest of dates of enrollment, day 1 of reporting period on CRF Chemotherapy Report, date of attendance on CRF Pre-Excision Report, date of surgery or date definitive decision was made on CRF Surgery Report, and attendance/last contact on CRF Follow-up Report and CRF Short Follow-up Report or censored at the time of death and calculated as

$$[(\text{date of death or LKA} - \text{date of accrual}) + 1)]/30.4375.$$

7.2.2 Accrual Patterns

- Number of patients accrued by center **(Table 3)**
- Accrual of patients by calendar time **(Figure 1)**

7.2.3 Eligibility Violations/Protocol Deviations

Eligibility violations of inclusion or exclusion criteria are centrally reviewed by CCTG; a field (y/n) for eligibility status and reason for ineligibility is entered in the database.

A major protocol violation (MPV) is defined as a deviation from the protocol, initiated by the center or the investigator, serious enough to mean that the patient's data contributes little, if any, information on the efficacy or toxicity of the regimen under study. MPVs are coded by CCTG based on its standard codes.

- Number of patients eligible, not eligible **(Table 4)**
- Reasons for ineligibility **(Table 4)**
- Major protocol violations: % for each type of violations **(Table 4)**

7.3 Study Population

All accrued patients are included in the study population analyses.

7.3.1 Patient Pretreatment Characteristics

- Gender: male, female **(Table 5)**
- Age: median, minimum, maximum values**;** <65, ≥65 **(Table 5)**
- Race: White, Black or African American, Native Hawaiian or other Pacific Islander, Asian, Not reported (or refused), Unknown **(Table 5)**
- Height: median, minimum, maximum values **(Table 5)**
- Weight: median, minimum, maximum values **(Table 5)**
- BSA: median, minimum, maximum values **(Table 5)**
- ECOG Performance Status: 0, 1 **(Table 5)**
- Months from first histological diagnosis of colorectal cancer to enrollment: median, minimum, maximum values **(Table 5)**
- Tumour Invasion based on pelvic MRI: submucosa, muscularis propia, muscularis propia no more than 5 mm into the subserosa/perirectal tissue, muscularis propia more than 5 mm into the subserosa/perirectal tissue, not visible on pelvic MRI **(Table 5)**
- cT-stage: T1, T2, T3a, T3b **(Table 5)**
- Tumour Height from anal verge (cm): median, minimum, maximum values **(Table 5)**

7.3.2 Baseline Pathology Results

- Longest dimension of Invasive Carcinoma: median, minimum, maximum values **(Table 6)**
- Histology: adeno-carcinoma, etc. **(Table 6)**
- Histologic grade: well differentiated, moderately differentiation, not stated in report **(Table 6)**
- Deepest layer of invasion: Mucosa, Lamina Propia, Muscularis mucosa, Submucosa, Muscularis propia, Serosa, Perirectal tissue, Subserosa, Not Stated in Report **(Table 6)**
- Depth of invasion into subserosa: median, min-max **(Table 6)**
- Deep margin: positive for invasive carcinoma, negative, not stated in report, not applicable; median, minimum, maximum values **(Table 6)**
- Mucosal margin: positive for invasive carcinoma, negative, not stated in report, not applicable; median, minimum, maximum values **(Table 6)**
- Pathologic T stage: T0, T1, T2, T3, unknown **(Table 6)**
- Number of nodes examined: median, minimum, maximum values **(Table 6)**
- Number of nodes with tumour: median, minimum, maximum values **(Table 6)**

- Tumour deposits: yes, no **(Table 6)**

7.3.3 Baseline Exams

- Sigmoidoscopy/colonoscopy: normal, abnormal non-malignant, abnormal malignant **((Table 7)**
- Other radiology investigations: normal, abnormal non-malignant, abnormal malignant **(Table 7)**
- Hematology: Hemoglobin, WBC, absolute neutrophil count (ANC), neutrophils, platelets, lymphocytes, basophils, monocytes, eosinophils **(Table 8)**
- Biochemistry: serum creatinine, total bilirubin, ALT, creatinine clearance **(Table 9)**
- Coagulation: PT, INR, PTT **(Table 10)**
- Baseline symptom status **(Table 11)**

7.3.4 Concomitant Medications and Major Medical Problems at Baseline

- Number of patients with concomitant Medication **(Table 12)**
- Number of patients with other past and current major medical problems ongoing at baseline **(Table 13)**

7.3.5 Tobacco Smoking History at Baseline

- Ever smoked any tobacco product: Yes, No, Unknown **(Table 14)**
- Currently smoking: Yes, No **(Table 14)**
- Current average number of cigarettes per day: median, minimum, maximum **(Table 14)**
- Years from quitting smoking to enrollment: median, minimum, maximum **(Table 14)**
- Years from beginning smoking cigarettes to enrollment: median, minimum, maximum **(Table 14)**
- Total number of years of smoking cigarettes: median, minimum, maximum **(Table 14)**
- Average number of cigarettes smoked per day: median, minimum, maximum **(Table 14)**
- Average pack years of cigarettes smoked: median, minimum, maximum **(Table 14)**

7.4 Extent of Neoadjuvant Chemotherapy Exposure

Patients included are those who received at least one dose of FOLFOX or CAPOX as defined in Section 6.

7.4.1 Duration of Chemotherapy

During protocol treatment, the patients are planned to receive either FOLFOX infusion on a 14 day cycle (IV oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 over 2 hours on day 1 and bolus fluorouracil 400 mg/m^2 over 5 - 15 minutes and continuous infusion of fluorouracil 2400 mg/m^2 over 46 to 48 hours on days 1-2) for a total of 6 cycles or CAPOX on a 21 day cycle (IV oxaliplatin 130 mg/m^2 over 2 hours on day 1 and 1000 mg/m^2 capecitabine orally twice daily for 14 days from day 1) for a total of 4 cycles.

Duration of a neoadjuvant chemotherapy treatment (in weeks) during the study is

defined as follows:

- For patients on FOLFOX:
  [last date of the treatment– first date of the treatment+ 14]/7,
- For patients on CAPOX:
  [last date of the treatment– first date of the treatment+ 21]/7

where the first and last date of the treatment are taken from respective treatment administration section of CRF Chemotherapy Report.

The following variables will be summarized using the data set of all chemotherapy treated patients:

- Number of patients by cycle of chemotherapy **(Table 15)**
- Total number of cycles of chemotherapy per patient (**Table 16**)
- Total treatment duration (weeks) per patient (**Table 17**)

7.4.2 Modifications of Neoadjuvant Chemotherapy

The administration of a neoadjuvant chemotherapy drug in a cycle may be modified (given early, delayed, omitted, reduced, interrupted, discontinued, increased, or the infusion rate was increased or decreased) because of toxicity or other reasons. For each drug, the following variables will be summarized using the data set of all chemotherapy treated patients:

- Number of patients with at least one cycle with modifications to administration (**Table 18**)
- Number of patients with modifications to administration by cycle (**Table 18**)
- Reason for these modifications **(Table 18)**

7.4.3 Cumulative dose, dose intensity and relative dose intensity

The cumulative dose (mg/m^2) per patient for capecitabine, oxaliplatin, leucovorin and fluorouracil (bolus and continuous) is defined as the sum over all cycles of the total actual dose received divided by the BSA in a given cycle**.**

The actual dose intensity (mg/m^2/week) per patient for capecitabine, oxaliplatin, leucovorin and fluorouracil (bolus and continuous) is defined as the cumulative dose (mg/m^2) divided by "treatment duration" (in weeks), where "treatment duration" per patient is defined as the duration from first day of drug administration to the last day of drug administration plus 14 days (for patients on FOLFOX) or 21 days (for patients on CAPOX) over all cycles in which the given drug is prescribed.

The median and range of cumulative dose and actual dose intensity will be summarized in respectively **Table 19** and **Table 20**.

The relative dose intensity per patient is defined as the actual dose intensity (mg/m^2/week) divided by the planned weekly dose as assigned in the protocol (42.5 mg/m^2/week for oxaliplatin, 200 mg/m^2/week for leucovorin, 200 mg/m^2/week for bolus fluorouracil, and 1200 mg/m^2/week for continuous fluorouracil for patients on FOLFOX; 43.3 mg/m^2/week for oxaliplatin and 9333.3 mg/m^2/week for capecitabine for patients on CAPOX). The patient relative dose intensities will be grouped according

to the following categories: < 60%, ≥ 60% - <80%, ≥ 80% - < 90%, ≥ 90% (**Table 21**).

7.4.4 Off Neoadjuvant Chemotherapy

The reason for off neoadjuvant chemotherapy will be taken from Off Neoadjuvant Chemotherapy Section of CRF Chemotherapy Report.

The following information will be summarized **(Table 22):**

- Number of patients off neoadjuvant chemotherapy
- Reason off neoadjuvant chemotherapy

7.5 Surgical Treatments

Tumour excision are performed within 2-5 weeks (for patients on FOLFOX) or 3-6 weeks (for patients on CAPOX) after first dose of last cycle of chemotherapy after a pre-excision visit performed within 2 weeks after the first dose of the last cycle (cycle 6) of FOLFOX therapy or within 3 weeks after the first dose of the last cycle (cycle 4) of CAPOX. Information from pre-excision visit and on the surgical treatment will be taken respectively from the CRF Pre-Excision Report and CRF Surgery Report.

7.5.1 Pre-excision Characteristics and MRI results

- Weight: median, minimum, maximum values **(Table 23)**
- BSA: median, minimum, maximum values **(Table 23)**
- ECOG Performance Status: 0, 1 **(Table 23)**
- cT-stage: T0, Tis, T1, T2, T3a, T3b, T3c, T3d, T4a, T4b, Tx **(Table 23)**
- Node positive disease: Yes, No **(Table 23)**
- Clear circumferential radial margin (CRM): Yes, No **(Table 23)**
- Progressive Disease: Yes, No **(Table 23)**

7.5.2 Pre-excision Exam

- Sigmoidoscopy/colonoscopy: normal, abnormal but non-malignant, abnormal and malignant **(Table 24)**
- Other radiology investigations: normal, abnormal but non-malignant, abnormal and malignant **(Table 24)**

7.5.3 Pre-excision Extent of Disease

- Number of patients with disease assessment**,** number of patients with disease progression, site of diseases, number of disease sites, largest measure **(Table 25)**
- Number of patients with new lesions, site of new lesions, number of new lesions **(Table 25)**

7.5.4 Plan of Surgical Treatment

Based on the results of pre-excision assessments, a plan of surgical treatment is developed by the investigator. The following information will be summarized **(Table 26):**

- Number of patients with each choice of surgical treatment

7.5.5 Surgical Treatment

The following information on the surgeries performed will be summarized:

- Number of patients who received tumour excision **(Table 27)**
    - Procedure performed: TEMS, TAMIS, TME, other **(Table 27)**
    - Time in operating room: median, minimum, maximum **(Table 27)**
    - Resection margins: R0, R1, R2 **(Table 27)**
    - Mesorectal excision: Total/complete, incomplete, unknown **(Table 27)**
    - Subsequent surgery recommended: Not applicable, Yes but declined by patient, No because complete tumour resection and ypT0 or ypT1good, No other **(Table 27)**
- Number of patients with definitive decision not to have tumour **(Table 27)**
    - Reasons for definitive decision not to have tumour excision **(Table 27)**

7.5.6 Pathology Results after surgical treatment

- Site of the tumor: rectum, nodes, other **(Table 28)**
- Longest dimension of Invasive Carcinoma: median, minimum, maximum values **(Table 28)**
- Lymphatic invasion: Yes, No **(Table 28)**
- Vascular invasion: Yes, No **(Table 28)**
- Histology: adeno-carcinoma, etc. **(Table 28)**
- Histologic grade: well differentiated, moderately differentiation, not stated in report **(Table 28)**
- Deepest layer of invasion: Mucosa, Lamina Propia, Muscularis mucosa, Submucosa, Muscularis propia, Serosa, Perirectal tissue, Subserosa, Not Stated in Report **(Table 28)**
- Depth of invasion into subserosa: median, min-max **(Table 28)**
- Deep margin: positive for invasive carcinoma, negative, not stated in report, not applicable; median, minimum, maximum values **(Table 28)**
- Mucosal margin: positive for invasive carcinoma, negative, not stated in report, not applicable; median, minimum, maximum values **(Table 28)**
- Pathologic T stage: T0, T1, T2, T3, unknown **(Table 28)**
- Number of nodes examined: median, minimum, maximum values **(Table 28)**
- Number of nodes with tumour: median, minimum, maximum values **(Table 28)**
- Tumour deposits: yes, no **(Table 28)**

7.6 Radiation Treatments

Pelvic radiation is recommended for patients when the excisional specimen demonstrates ypT3+ or N+ disease and requires radical TME surgery. The following information will be summarized for patients who received any pelvic radiation therapy prior to TME surgery:

- Site of Radiotherapy: Rectum, Sigmoid colon, Anus **(Table 29)**
- Duration of Radiotherapy (days): median, minimum, maximum **(Table 29)**
- Total dose of radiation: median, minimum, maximum **(Table 29)**

7.7 Efficacy

7.7.1 Organ Preservation Rate

After completion of neoadjuvant chemotherapy, the protocol requires that patients with lesions that on pre-excision (post-chemotherapy) MRI and/or endoscopy showing evidence of progression or no response to chemotherapy to be treated with immediately

the radical TME surgery. Other patients will be treated with local excision TEMS or TAMIS. Patients with ypstage T0/T1goodN0 tumours based on local pathology ypstaging review after TEMS or TAMIS are treated with surveillance while patients with tumours with ypT2, N+ or ypT1 tumours with poor prognostic features are treated with radical TME surgery within 6-8 weeks after local excision. The numbers of enrolled patients who were treated with respectively neoadjuvant chemotherapy, TME and TEMS or TAMIS immediately after completion of neoadjuvant chemotherapy, and TME or surveillance after TEMS or TAMIS will be summarized **(Table 30)**.

Organ preservation rate, the primary endpoint of this study, is defined as the proportion of patients with tumour downstaging to ypT0/T1good N0 who avoid radical surgery (TME) among all patients treated with FOLFOX or CAPOX and TEMS or TAMIS. The 95% confidence interval for the organ preservation rate will be calculated **(Table 30).**

Organ preservation rate will additionally be calculated among all patients that have received neoadjuvant chemotherapy.

7.7.2 3 Year Loco-Regional Relapse Rate

Locoregional relapse is defined as reappearance of a tumour within the rectum or pelvis. The number of patients with each site (rectum, pelvis, pelvic lymph nodes, and others) of locaregional relapse will be summarized **(Table 31)**.

Locoregional relapse free survival is calculated as time from complete tumour surgical excision date (with pathology results negative for malignant disease within 1 mm of surgical margins) to the first date of definitive evidence (clinical, radiological or pathological) of locoregional relapses. Patients with distant relapse only, died, loss to follow up, or alive at clinical cut-off will be censored at respectively last date of distant relapses, date of death, date of lost to follow-up, and last disease assessment date calculated as the last of dates of attendance/last contact on Follow-up Report.

Kaplan-Meier method **(Figure 2)** will be used to estimate the 3 year loco-regional relapse rate and associated 95% confidence interval first among all patients treated with FOLFOX or CAPOX and TEMS or TAMIS **(Table 31)** and additionally among all patients that have received neoadjuvant chemotherapy.

7.7.3 3 Year Distant Relapse Rate

Distant relapse is defined as appearance of rectal cancer disease at sites remote from the rectum. The number of patients with each site of distant relapse (Lung, Liver, Brain, Distant lymph nodes, Bone, Skin, Ascites, Pleural effusion, Adrenal glands, Other) will be summarized **(Table 31)**.

Distant relapse free survival is calculated as time from complete tumour surgical excision date (with pathology results negative for malignant disease within 1 mm of surgical margins) to the first date of definitive evidence (clinical, radiological or pathological) of distant relapses. Patients died, loss to follow up, or alive at clinical cut-off will be censored at respectively date of death, date of lost to follow-up, and last disease assessment date calculated as the last of dates of attendance/last contact on CRD Follow-up Report.

Kaplan-Meier method **(Figure 3)** will be used to estimate the 3 year distant relapse rate and associated 95% confidence interval first among all patients treated with FOLFOX

or CAPOX and TEMS or TAMIS **(Table 31)** and additionally among all patients that have received neoadjuvant chemotherapy.

7.7.4 3 year Disease Free Survival

Disease-Free Survival (DFS) is defined as the interval from complete tumour surgical excision date (with pathology results negative for malignant disease within 1 mm of surgical margins) to date of first occurrence of the events in the below.

- Locoregional relapse reported in CRF Relapse Report
- Distant disease reported in CRF Relapse Report
- Non-protocol radiotherapy, chemotherapy, or biologic therapy without documentation of the site of failure and reported in CRF Chemotherapy Report, Pre-Excision Report, and Surgery Report
- Death due to any other reason reported in CRF Death Report

Patients who are alive without locoregional or distant relapse or receiving non-protocol radiotherapy, chemotherapy, or biologic therapy without documentation of the site of failure at the analysis data cutoff date will be censored at their last disease assessment date calculated as the last of dates of attendance/last contact on Follow-up Report.

A frequency table will be provided describing DFS events and censorings as follows:

- Number of patients who had a DFS event (Relapse (locoregional, distant), non-protocol therapy, death (due to any other reason) **(Table 31)**
- Number of patients censored with reasons of censoring (alive at the clinical cut-off, lost to follow-up) **(Table 31)**

Kaplan-Meier method **(Figure 4)** will be used to estimate the 3 year DFS rate and associated 95% confidence interval first among all patients treated with FOLFOX or CAPOX and TEMS or TAMIS **(Table 31)** and additionally among all patients that have received neoadjuvant chemotherapy.

7.8 Safety

The safety analyses will based on the Chemotherapy Treated population defined in Section 6 unless otherwise specified. Adverse events and laboratories are graded and categorized using the NCI CTCAE except where CTCAE grades are not available.

7.8.1 Adverse Events

Adverse events (AEs) are recorded in the Adverse Events (AE) sections of CRF Chemotherapy Report, CRF Pre-Excision Report, CRF Surgery Report, CRF Follow Up Report (only AEs thought to be related to protocol treatment), and CRF Short Follow Up Report (ongoing or new grade 3 or higher AEs which are thought to be related to protocol treatment). Severity grade 5 will be combined with grade 4 for the purpose of this report. Adverse events reported during study treatment (in AE sections of CRF Chemotherapy Report, CRF Pre-Excision Report, and CRF Surgery Report) are defined as acute (on treatment) adverse events. Adverse events reported in AE section of CRF Follow Up Report and CRF Short Follow Up Report will be defined as delayed (long term) AEs.

Treatment (capecitabine, oxaliplatin, leucovorin, surgery, and radiotherpy) related adverse events are those events with a relation to protocol therapy of 3=possible,

4=probable or 5=definite.

Severe adverse events are those events reported with a NCI CTCAE Grade of 3 or higher.

The following variables are summarized:

- Acute adverse events: worst CTCAE grade per patient **(Table 32)**
- Severe acute adverse events: worst CTCAE grade per patient **(Table 33)**
- Treatment related acute adverse events: worst CTCAE grade per patient **(Table 34)**
- Delayed severe adverse events: worst CTCAE grade per patient **(Table 35)**

7.8.2 Laboratory Evaluations

Laboratory evaluations, except coagulation and CEA, reported on CRF Chemotherapy Report and CRF Pre-Excision Report will be included in the calculation laboratory adverse events. Coagulation is only reported on CRF Pre-Excision Report and CEA on CRF Pre-Excision Report and of CRF Follow Up Report, which will be summarized individually. Laboratory results will be classified according to the NCI CTCAE when available.

7.8.2.1 Hematology

- Hemoglobin, WBC, absolute neutrophil count (ANC), neutrophils, platelets, lymphocytes, basophils, monocytes, eosinophils: worst CTCAE grade per patient (**Table 36**)

7.8.2.2 Biochemistry

- Serum creatinine, total bilirubin, ALT, creatinine clearance: worst CTCAE grade per patient **(Table 37)**

7.8.2.3 Other laboratory evaluations

- Pre-excision Coagulation: CTCAE grade of PT, INR, PTT **(Table 38)**
- Serum CEA: The mean and standard deviation of baseline CEA levels and the change of CEA levels from baseline at pre-excision and each follow-up visits **(Table 38)**

7.8.3 Post-operative complications

For patients with a tumour excision attempted, the following post-operative complications reported on CRF Surgery Report will be summarized (**Table 39**):

7.8.3.1 Reoperation

- Patients requiring reoperation: Yes, No
- Reoperation procedure performed: debridement, incision and drainage, diverting ostomy, other

7.8.3.2 Blood loss/transfusion

- Estimated amount (cc) of blood loss during surgery: median, minimum, maximum
- Any transfusions or blood products during surgery: Yes, no
- Type of Transfusion: Red cell concentrates, Platelets, Other

7.8.3.3 Intraoperative injury

- Any intraoperative injury: Yes, no

- Site of injury: Bladder, Ureter, Vein, Artery, Large Bowel, Small Bowel, Nerve, Other

7.8.3.4 Hospitalization

- Any time in intensive care: Yes, No
- Days in intensive care: median, minimum, maximum
- Ongoing hospitalization: Yes, no
- Days from admission to hospital for the tumour excision to discharge: median, minimum, maximum
- Discharge destination: Home, Assisted living (non-medical), Skilled nursing home, Hospice, Chronic care hospital, Rehabilitation facility, Died, Transfer to other hospital, Other

7.8.4 Deaths on Study/Adverse Events Leading to Discontinuations due to Toxicity

- All Deaths: number of patients who died and cause of death from CRF Death Report **(Table 40)**
- Deaths before surgery: number of patients who died and cause of death from CRF Death Report **(Table 41)**
- Adverse events leading to discontinuations of neoadjuvant: number of patients with adverse events leading to discontinuations of treatment as identified from CRF Chemothrapy Report **(Table 42)**

7.8.5 Other safety

7.8.5.1 Sigmoidoscopy/colonoscopy

- Sigmoidoscopy/colonoscopy during protocol treatment (reported on CRF Chemotherapy Report, CRF Pre-Excision Report, and CRF Surgery Report): all normal, at least one abnormal but all non-malignant, all abnormal and malignant **(Table 43)**
- Sigmoidoscopy/colonoscopy during follow-up (reported on CRF Follow Up all normal, at least one abnormal but all non-malignant, all abnormal and malignant **(Table 43)**

7.8.5.2 Other radiologic investigations

- Other radiologic investigations during protocol treatment (reported on CRF Chemotherapy Report, CRF Pre-Excision Report, and CRF Surgery Report): all normal, at least one abnormal but all non-malignant, all abnormal and malignant **(Table 43)**
- Other radiologic investigationsy during follow-up (reported on CRF Follow-up REPORT): all normal, at least one abnormal but all non-malignant, all abnormal and malignant **(Table 43)**

7.8.5.3 Transfusions

- Number of patients who received any blood transfusions (red blood cells, platelets, and/or other) during protocol treatment (reported on CRF Chemotherapy Report, CRF Pre-Excision Report, and CRF Surgery Report) **(Table 44)**
- Number of patients who received any blood transfusions (red blood cells, platelets, and/or other) during follow-up (reported on CRF Follow-Up Report) **(Table 44)**

7.8.5.4 Major medical problems

- Number of patients with each type of medical problems during protocol treatment (reported on Chemotherapy Report, CRF Pre-Excision Report, and CRF Surgery Report) **(Table 45)**
- Number of patients with each type of medical problems during follow-up (reported on CRF Follow-Up Report) **(Table 45)**

7.9 Concomitant Medications and Other Anti-Cancer Treatments

Concomitant medication is defined as medication, other than protocol therapy, which is taken by patients any time on treatment or after end of treatment. Patients may also receive any other anti-cancer treatment during or after being taken off protocol treatment.

- Concomitant medications for patients during protocol treatment (reported on Chemotherapy Report, CRF Pre-Excision Report, and CRF Surgery Report) **(Table 46)**
- Concomitant medications for patients 30 days after excision (reported on CRF Follow-Up Report) **(Table 46)**
- Anti-cancer treatments for patients during protocol treatment (reported on Chemotherapy Report, CRF Pre-Excision Report, and CRF Surgery Report) **(Table 47)**
- Anti-cancer treatments for patients after protocol treatment but before relapse (reported on Follow-Up Report) **(Table 47)**
- Anti-cancer treatments for patients after relapse (reported on Short Follow-Up Report) **(Table 47)**

7.10 Quality of Life

The quality of life of patients in this study is assessed by using EORTC QLQ-C30 (version 3.0), QLQ-CR29, Low Anterior Resection Syndrome Score (LARS), and the Fecal Incontinence Quality of Life (FIQL) Instrument at baseline, pre-excision (2 weeks (FOLFOX) or 3 weeks (CAPOX) after last injection in last cycle of chemotherapy), after excision (months 6, 12, 24, and 36). The following are the scoring algorithms for each of these four QoL instruments.

7.10.1 Scoring Algorithms

7.10.1.1 EORTC QLQ-C30

The EORTC core questionnaire, QLQ-C30 (version 3.0), consists of five Functional Scales, Global Health Status, and nine Symptoms Scales. Each scale in the questionnaire will be scored (0 to 100) according to the EORTC recommendations in the EORTC QLQ-C30 Scoring Manual. The scoring method for EORTC QLQ-C30 is summarized below. In this summary Qi refers to the i-th question on the QLQ-C30.

Functional scale's scores:

- Physical functioning: (1 - ((Q1+Q2+Q3+Q4+Q5)/5 -1)/3) * 100
- Role functioning: (1 - ((Q6+Q7)/2-1)/3) * 100
- Emotional functioning: (1 - ((Q21+Q22+Q23+Q24)/4-1)/3) * 100
- Cognitive functioning: (1 - ((Q20+Q25)/2-1)/3) * 100
- Social functioning: (1 - ((Q26+Q27)/2-1)/3) * 100

Global health status score:

- Global QOL: ((Q29+Q30)/2-1)/6 * 100

Symptom scale's scores:

- Fatigue: ((Q10+Q12+Q18)/3-1)/3 * 100
- Nausea and vomiting: ((Q14+Q15)/2-1)/3 * 100
- Pain: ((Q9+Q19)/2-1)/3 * 100
- Dyspnea: ((Q8-1)/3 * 100
- Insomnia: (Q11-1)/3 * 100
- Appetite loss: (Q13-1)/3 * 100
- Constipation: (Q16-1)/3 * 100
- Diarrhea: (Q17-1)/3 * 100
- Financial difficulties: (Q28-1)/3 * 100

7.10.1.2 EORTC QLQ-CR29

QLQ-CR29 is a colon and rectum cancer site-specific supplemental module to the EORTC core questionnaire, which consists of five Functional Scales, 18 Symptoms Scales as well as stoma status. Each scale in the questionnaire will be scored (0 to 100) according to the EORTC recommendations in the EORTC QLQ-CR29 Scoring Manual. The scoring method for EORTC QLQ-CR29 is summarized below. In this summary Qi refers to the i-th question on the QLQ-CR29.

Functional scale's scores:

- Body image: (1 - ((Q45+Q46+Q47)/3 -1)/3) * 100
- Anxiety: (1 - (Q43)-1)/3) * 100
- Weight: (1 - (Q44-1)/3) * 100
- Sexual Interest (men): (1 - (Q56-1)/3) * 100
- Sexual Interest (women): (1 - (Q58-1)/3) * 100

Symptom scale's scores:

- Urinary frequency ((Q31+Q32)/2-1)/3 * 100
- Blood and mucus in stool ((Q38+Q39)/2-1)/3 * 100
- Stool frequency ((Q52+Q53)/2-1)/3 * 100
- Urinary incontinence (Q33-1)/3 * 100
- Dysuria (Q34-1)/3 * 100
- Abdominal pain (Q35-1)/3 * 100
- Buttock pain (Q36-1)/3 * 100
- Bloating (Q37-1)/3 * 100
- Dry mouth (Q40-1)/3 * 100
- Hair loss (Q41-1)/3 * 100
- Taste (Q42-1)/3 * 100
- Flatulence (Q49-1)/3 * 100
- Fecal incontinence (Q50-1)/3 * 100
- Sore skin (Q50-1)/3 * 100
- Embarrassment (Q54-1)/3 * 100
- Stoma care problems (Q55-1)/3 * 100
- Impotence (Q57-1)/3 * 100
- Dyspareunia (Q59-1)/3 * 100
- Stoma status (Q48-1) * 100

7.10.1.3 Low Anterior Resection Syndrome (LARS) Score

Low Anterior Resection Syndrome (LARS) Score is a scoring system for bowel dysfunction after low anterior resection (LAR) for rectal cancer. It consists of 5 questions and the answers to them are assigned a score based on the following algorithm:

Question 1: Do you ever have occasions when you cannot control your flatus (wind)?

- No, never 0
- Yes, less than once per week 4
- Yes, at least once per week 7

Question 2: Do you ever have any accidental leakage of liquid stool?

- No, never 0
- Yes, less than once per week 3
- Yes, at least once per week 3

Question 3: How often do you open your bowels?

- More than 7 times per day (24 hours) 4
- 4-7 times per day (24 hours) 2
- 1-3 times per day (24 hours) 0
- Less than once per day (24 hours) 5

Question 4: Do you ever have to open your bowels again within one hour of the last bowel opening?

- No, never 0
- Yes, less than once per week 9
- Yes, at least once per week 11

Question 5: Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

- No, never 0
- Yes, less than once per week 11
- Yes, at least once per week 16

LARS total score is defined as the sum of scores to these 5 questions.

7.10.1.4 Fecal Incontinence Quality of Life (FIQL) Instrument

The Fecal Incontinence Quality Of Life (FIQL) Instrument is a disease-specific tool designed to evaluate the impact of Fecal Incontinence (FI). It consists of four scales. Each scale in the instrument will be scored (1 to 4), where 1 is very affected and 4 is not affected, based on the scoring method summarized below. In this summary, Qi refers to the i-th question on the FIQL instrument:

FIQL scale's scores:

- Lifestyle: (Q2A+Q2B+Q2C+Q2D+Q2E+Q2G+Q2H+ Q3B+Q3L+Q3M)/10
- Coping/Behavior: (Q2F+Q2I+Q2J+Q2K+Q2M+Q3C+Q3H+ Q3J+Q3N)/9
- Depression/Self Perception: (Q1+Q3D+Q3FJ+Q3G+Q3I+Q3K+Q4)/7 (Question 1 is reverse coded first)

- Embarrassment: (Q2L+Q3A+Q3E)/3)

For all of questionnaires/instruments, missing items in a scale will be handled by the following methods: Values will be imputed for missing items by "assuming that the missing items have values equal to the average of those items which are present" for any scale in which at least half the items are completed. A scale in which less than half of the items are completed will be treated as missing.

7.10.2 Data Sets

The analyses of quality of life data will be restricted to accrued patients who have completed at least one QoL questionnaire.

7.10.3 Compliance

Compliance will be described, by time of evaluation, by the number and percentage of subjects who filled out a questionnaire (per subject, at least one question answered) in that period of evaluation. The denominator used in calculating the percentage for baseline will be all accrued subjects (**Table 48).**

7.10.4 Analyses of QOL

7.10.4.1 Baseline and Change Score Analysis

For each scale of EORTC QOL-C30 and CR29 and FIQL instrument and total score of LARS, descriptive statistics (mean, standard deviation) will be presented at baseline. The same statistics will be generated for change score from baseline at each time of post-baseline evaluation. (**Table 49** and **Table 50**)

7.10.4.2 Proportions of Deterioration and Improving or Stable for EORTC QLQ-C30 and CR29 at Post-Baseline Assessment

The deterioration is defined as a change score from baseline which is –10 points or lower. The proportions of patients who had improving (defined as change score from baseline of 10 points or higher) or stable (defined as change score from baseline of between –10 and 10 points) **(Table 51)**. QoL response rate and associated 95% confidence interval will be calculated for each scale and item.

7.10.4.3 Proportions of LARS Severity Group at Baseline and Post-baseline Assessment

Based on the LARS total score of LARS, a patient can be classified into one of the following 4 groups: 0 to 20 (no LARS), 21 to 29 (minor LARS), and 30 to 42 (major LARS). Proportions of patients in each of these four groups and associated 95% confidence interval will be calculated at baseline and each time of post-baseline assessments **(Table 52).**

8. Appendices

Appendix 1: Tables and Figures

Table 1. Patient Disposition

Data set: All Accrued Patients	
	Number of patients (%) N=**
Accrued	** (**)
Treated	** (**)
On study	** (**)
Off study [1]	** (**)
Never Treated	** (**)

(1) Off all study therapy

Table 2: Follow-up of Patients

Data set: All Accrued Patients	
	Number of patients (%) N=**
Number of patients alive	*** (%)
Fellow-up (months)	
median	**
Minimum-maximum	**-**

Table 3: Accrual by Center

Data set: All Accrued Patients	
	Number of patients (%) N=**
Center #1	** (**)
Center #2	** (**)
Center #3	** (**)
...	** (**)

Figure 1: Accrual by Calendar Time

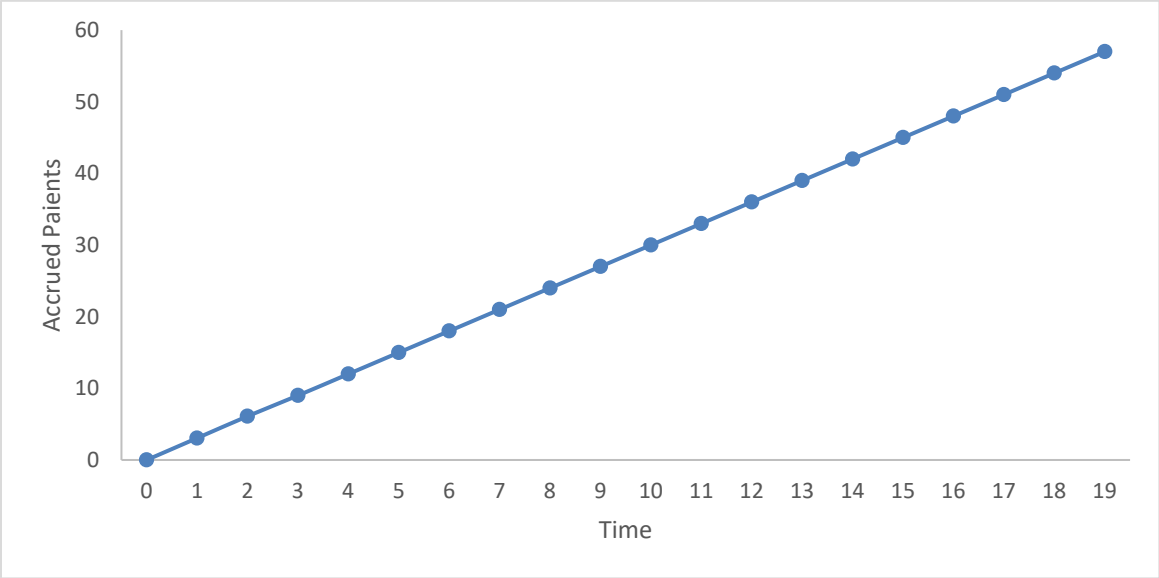

Table 4: Eligibility and Reasons for Ineligibility and Major Protocol Violations

Data set: All Accrued Patients	
	Number of Patients (%) N=**
Eligible	** (**)
Not Eligible	** (**)
Reason for ineligibility	
<Reason 1>	**
<Reason 2>	**
...	**
Major protocol violation	
<violation type 1>	**
<violation type 2>	**
...	

Table 5: Pre-treatment Characteristics at Baseline

Data set: All Accrued Patients

	Number of patients (%) N=**
Gender	
Female	** (**)
Male	** (**)
Age (years)	
N	**
Median	**
Min - Max	** - **
< 65	** (**)
≥ 65	** (**)
Race	
White	** (**)
Black or African American	** (**)
Native Hawaiian or Pacific Islander	** (**)
Asian	** (**)
Not reported (or refused)	** (**)
Unknown	** (**)
Height	
N	**
Median	**
Min-Max	** - **
Weight	
N	**
Median	**
Min-Max	** - **
BSA	
N	**
Median	**
Min-Max	** - **
ECOG Performance Status	
0	** (**)
1	** (**)
Months from First Histological Diagnosis to enrollment	
N	**
Median	**
Min – Max	** - **
Tumour Invasion based on pelvic MRI	
Submucosa	** (**)
Muscularis propia	** (**)
Muscularis propia no more than 5 mm into the subserosa/perirectal tissue	** (**)
Muscularis propia more than 5 mm into the subserosa/perirectal tissue	** (**)
Not visible on pelvic MRI	** (**)
cT-stage (based on pelvic MRI)	
T1	**(**)
T2	**(**)
T3a	**(**)
T3b	**(**)
Tumour Height from anal verge (cm)	
N	**
Median	**
Min – Max	** - **

Table 6: Baseline Pathology Results

Dataset :All Accrued Patients	
	Number of patients (%) N=**
Longest dimension of Invasive Carcinoma	
N	**
Median	**
Min – Max	** - **
Histology	
Adeno-carcinoma	** (**)
Squamous	** (**)
Other	** (**)
Histologic Grade	
Well -Differentiated	** (**)
Moderately Differentiated	** (**)
Not stated in report	** (**)
Deepest Layer of Invasion	
Mucosa	** (**)
Lamina Propia	** (**)
Muscularis mucosa	** (**)
Submucosa	** (**)
Muscularis propia	** (**)
Serosa	** (**)
Perirectal tissue	** (**)
Subserosa	** (**)
Depth of invasion into subserosa	
Median	**
Min-max	**-**
Not Stated in Report	** (**)
Deep Margin	
Positive for invasive carcinoma	**(**)
Median	**
Min-Max	**-**
Negative	**(**)
Not stated in Report	**(**)
Not Applicable	**(**)
Mucosal Margin	
Positive for invasive carcinoma	**(**)
Median	**
Min-Max	**-**
Negative	**(**)
Not stated in Report	**(**)
Not Applicable	**(**)
Pathologic T Stage	
T0	** (**)
T1	** (**)
T2	** (**)
T3	** (**)
Unknown	** (**)
Tumour deposits	
Yes	**(**)
No	**(**)

Table 7: Baseline Sigmoidoscopy/Colonoscopy and Other Radiology Investigations

Data set: All Accrued Patients	
	Number of Patients (%) N=**
Sigmoidoscopy	
Normal	** (**)
Abnormal, Non-malignant	** (**)
Abnormal, malignant	** (**)
Colonoscopy	
Normal	** (**)
Abnormal, Non-malignant	** (**)
Abnormal, malignant	** (**)
Other Radiology 1	
Result 1	** (**)
…	** (**)
…	

Table 8: Baseline Hematology

Data set: All Accrued Patients	
	Number of Patients (%) N=**
Hemoglobin	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
WBC	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
Absolute neutrophil count (ANC)	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
Platelet	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
Lymphocytes	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
Basophils	
Normal	** (**)
>1-1.5xULN	** (**)
>1.5-2.0xULN	** (**)
>2.0-5.0xULN	** (**)
>5.0xULN	** (**)
Not reported [(1)]	** (**)
Monocytes	
Normal	** (**)
>1-1.5xULN	** (**)
>1.5-2.0xULN	** (**)
>2.0-5.0xULN	** (**)
>5.0xULN	** (**)
Not reported [(1)]	** (**)

Eosinophils	
Normal	** (**)
>1-1.5xULN	** (**)
>1.5-2.0xULN	** (**)
>2.0-5.0xULN	** (**)
>5.0xULN	** (**)
Not reported [(1)]	** (**)

Table 9: Baseline Biochemistry

Data set: All Accrued Patients	
	Number of Patients (%)
	Total N=**
Serum Creatinine	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
Total bilirubin	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
ALT	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
Creatinine Clearance	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)

[(1)] Not done or outside the 30-day window prior to enrollment

Table 10: Baseline Coagulation

Data set: All Accrued Patients	
	Number of Patients (%)
	Total N=**
PT	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
INR	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)
PTT	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Not reported [(1)]	** (**)

[(1)] Not done or outside the 30-day window prior to enrollment

Table 11: Baseline Symptoms Status

Data set: All Accrued Patients						
	Number of patients (%) N=**					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with any symptom/ finding at baseline	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with particular symptom/finding, within body system:						
Body System 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Body System 2[(1)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a body system

Table 12: Prior Concomitant Medications (Baseline)

Data set: All Accrued Patients	
	Number of patients (%)
	N=**
Any prior concomitant medication [(1)]	
No	** (**)
Yes	** (**)
Drug Name 1	** (**)
Drug Name 2	** (**)
....	

Table 13: Past or Current Major Medical Problems

Data set: All Accrued Patients	
	Number of patients (%) N=**
Patients Reporting at least one past or current major medical problem at baseline	** (**)
Medical Problem[(1)]	
...	** (**)

(1) patients may report more than one medical problem reported

Table 14: Tobacco Smoking History at Baseline

Data set: All Accrued Patients	
	Number of patients (%) N=**
Ever smoked any tobacco product	
Yes	** (**)
No	** (**)
Unknown	** (**)
Currently smoking	
Yes	** (**)
No	** (**)
Current Average number of cigarettes per day	
N	**
Median	**
Min - Max	** - **
Years from quitting smoking to enrollment	
N	**
Median	**
Min - Max	** - **
Years from beginning smoking cigarettes to enrollment	
N	**
Median	**
Min - Max	** - **
Total number of years of smoking cigarettes	
N	
Median	**
Min - Max	**
Average number of cigarettes smoked per day	
N	
Median	**
Min - Max	**
Average pack years of cigarettes smoked	
N	**
Median	**
Min - Max	** - **

Table 15: Number of Patients by Cycle of Chemotherapy

Data Set: All Chemotherapy Treated Patients		
	Number of Patients (%)	
	FOLFOX N=**	CAPOX N=**
Cycle 1	** (**)	** (**)
2	** (**)	** (**)
3	** (**)	** (**)
...		

Table 16: Number of Cycles of Chemotherapy per Patient

Data Set: All Chemotherapy Treated Patients		
	FOLFOX	CAPOX
Number of Cycles:		
N	**	**
Median	*	*
Min – Max	* - *	* - *

Table 17: Total Duration of Chemotherapy

Data Set: All Chemotherapy Treated Patients		
	FOLFOX	CAPOX
Duration in weeks:		
N	**	**
Median	*	*
Min – Max	* - *	* - *

Table 18: Number of Patients with Modifications of Chemotherapy

Data Set: All Chemotherapy Treated Patients						
	FOLFOX				CAPOX	
	Oxaliplatin	Leucovarin	Bolos Fluorouracil	Continuous Fluorouracil	Oxaliplatin	Capecitabine
Patients with at least one cycle with (type of modification) over all cycles	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Reason for (type of modification)						
Reason 1	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
…	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Dose reduction by cycle						
Cycle 1	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
2	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
...	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)

Table 19: Cumulative Dose

Data Set: All Chemotherapy Treated Patients						
	FOLFOX				CAPOX	
	Oxaliplatin	Leucovarin	Bolos Fluorouracil	Continuous Fluorouracil	Oxaliplatin	Capecitabine
Cumulative dose per patient (<unit>)						
N	***	***	***	***	***	***
Mean (STD)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Median	**	**	**	**	**	**
Min-Max	** - **	** - **	** - **	** - **	** - **	** - **

Table 20: Actual Dose Intensity

Data Set: All Chemotherapy Treated Patients						
	FOLFOX				CAPOX	
	Oxaliplatin	Leucovarin	Bolos Fluorouracil	Continuous Fluorouracil	Oxaliplatin	Capecitabine
Dose intensity						
N	***	***	***	***	***	***
Mean (STD)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Median	**	**	**	**	**	**
Min-Max	** - **	** - **	** - **	** - **	** - **	** - **

Table 21: Relative Dose Intensity

Data Set: All Chemotherapy Treated Patients						
	FOLFOX				CAPOX	
	Oxaliplatin	Leucovarin	Bolos Fluorouracil	Continuous Fluorouracil	Oxaliplatin	Capecitabine
Relative Dose intensity						
≥ 90% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
≥ 80% - < 90% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
≥ 60% - < 80% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
< 60% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)

Table 22: Off Neoadjuvant Chemotherapy Summary

Data set: All Chemotherapy Treated Patients	
	Number of patients (%) N=**
Patients off Chemotherapy	** (**)
Reason off protocol therapy	
Treatment Completed	**
Progressive Disease (objective)	**
Symptomatic Progression	**
Intercurrent Illness – adverse events unrelated to protocol treatment	**
Adverse events related to protocol therapy	**
Patient Refusal (not related to adverse event)	**
Death	**
Other Reason	**
	**

Table 23: Pre-excision Characteristics and MRI results

Data set: All Chemotherapy Treated Patients	
	Number of patients (%) N=**
Weight	
N	**
Median	**
Min-Max	** - **
BSA	
N	**
Median	**
Min-Max	** - **
ECOG Performance Status	
0	** (**)
1	** (**)
cT-stage (based on pelvic MRI)	
T0	**(**)
Tis	**(**)
T1	**(**)
T2	**(**)
T3a	**(**)
T3b	**(**)
T3c	**(**)
T3d	**(**)
T4a	**(**)
T4b	**(**)
Tx	**(**)
Node positive disease	
Yes	** (**)
No	** (**)
Clear circuferential radial margin (CRM)	
Yes	** (**)
No	** (**)
Progressive disease	
Yes	** (**)
No	** (**)

Table 24: Pre-excision Sigmoidoscopy/Colonoscopy and Other Radiology Investigations

Data set: All Chemotherapy Treated Patients	
	Number of Patients (%) N=**
Sigmoidoscopy	
Normal	** (**)
Abnormal, Non-malignant	** (**)
Abnormal, malignant	** (**)
Colonoscopy	
Normal	** (**)
Abnormal, Non-malignant	** (**)
Abnormal, malignant	** (**)
Other Radiology Investigation 1	
Result 1	** (**)
…	** (**)
…	

Table 25: Pre-excision Extent of Disease

Data set: All Chemotherapy Treated Patients	
	Number of patients (%) N=**
Patients with disease assessment	** (**)
Patients with disease progression	** (**)
Number of Disease sites	
1	** (**)
2	** (**)
3	** (**)
4	** (**)
≥5	** (**)
Longest Diameter in mm	
< 2	** (**)
2-5	** (**)
> 5-10	** (**)
> 10	** (**)
Site of Disease[1]	
Abdomen	** (**)
Adrenals	** (**)
Bone	** (**)
Brain	** (**)
Liver	** (**)
Lung	** (**)
Nodes	** (**)
Subcutaneous Tissue	** (**)
....	** (**)
Patients with new lesions	** (**)
Number of new lesions	
1	** (**)
2	** (**)
3	** (**)
4	** (**)
≥5	** (**)
Site of Disease[1]	
Abdomen	** (**)
Adrenals	** (**)
Bone	** (**)
Brain	** (**)
Liver	** (**)
Lung	** (**)
Nodes	** (**)
Pleura	** (**)
Skin	** (**)
Subcutaneous Tissue	** (**)
....	** (**)

Table 26: Plan of surgical Treatment

Data set: All Chemotherapy Treated Patients	
	Number of Patients (%) N=**
TAMIS/TEMS	** (**)
Mesorectal Excision (TME)	** (**)
No Surgery Planned (Patient Refusal)	** (**)
No Surgery Planned (Tumour excision not appropriate)	** (**)
Other	** (**)

Table 27: Surgery Summary

Data set: All Chemotherapy Treated Patients	
	Number of patients (%) N=**
Patients received tumour excision	** (**)
Procedure Performed	
TEMS	** (**)
TAMIS	** (**)
TME	** (**)
Other	** (**)
Time in operating room (minutes)	
Median	**
Min-max	**_**
Resection margins	
R0	** (**)
R1	** (**)
R2	** (**)
Mesorectal excision	
Total/complete	** (**)
Incomplete	** (**)
Unknown	** (**)
Subsequent Surgery Recommended	
Not applicable (TME performed)	** (**)
Yes	** (**)
Yes, but declined by patient	** (**)
No, complete tumour resection and ypT0 or ypT1good	** (**)
Other	** (**)
Patients with definitive decision not to have tumour excision	** (**)
Reason for definitive decision not to have tumour excision	
Intercurrent Illness	** (**)
Progressive Disease	** (**)
Patient Refusal	** (**)
Death	** (**)
Other	** (**)

Table 28: Pathology Results After Surgical Treatment

Dataset: All Chemotherapy and Excision/Surgery Treated Patients

	Number of patients (%) N=**
Site of tumor	
Rectum	** (**)
Nodes	** (**)
Other	** (**)
Longest dimension of Invasive Carcinoma	
N	**
Median	**
Min – Max	** - **
Lymphatic invasion	
Yes	** (**)
No	** (**)
Not stated in the report	** (**)
Vascular invasion	
Yes	** (**)
No	** (**)
Not stated in the report	** (**)
Histology	
Adeno-carcinoma	** (**)
Squamous	** (**)
Other	** (**)
Histologic Grade	
Well -differentiated	** (**)
Moderately differentiated	** (**)
Poorly differentiated	** (**)
Undifferentiated, anaplastic	** (**)
Grade cannot be assessed	** (**)
Not stated in report	** (**)
Deepest Layer of Invasion	
Mucosa	** (**)
Lamina Propia	** (**)
Muscularis mucosa	** (**)
Submucosa	** (**)
Muscularis propia	** (**)
Serosa	** (**)
Perirectal tissue	** (**)
Subserosa	** (**)
Depth of invasion into subserosa	
Median	**
Min-max	**-**
Not Stated in Report	

Deep Margin	
Positive for invasive carcinoma	**(**)
Median	**
Min-Max	**-**
Negative	**(**)
Not stated in Report	**(**)
Not Applicable	**(**)
Mucosal Margin	
Positive for invasive carcinoma	**(**)
Median	**
Min-Max	**-**
Negative	**(**)
Not stated in Report	**(**)
Not Applicable	**(**)
Pathologic T Stage	**(**)
T0	** (**)
T1	** (**)
T2	** (**)
T3	** (**)
Unknown	** (**)
Number of Nodes examined	
N	**
Median	**
Min-Max	** - **
Number of nodes with tumour	
N	**
Median	**
Min-Max	** - **
Tumour deposits	
Yes	**(**)
No	**(**)

Table 29: Radiotherapy Treatment

Data set: All Chemotherapy & Excision Treated Patients	
	Number of patients (%) N=**
Number of Patients with Radiation treatment	** (**)
Site of Radiotherapy	
Rectum	** (**)
Sigmoid colon	** (**)
Anus	** (**)
Duration of Radiotherapy	
Median	**
Min-max	** - **
Total Dose of radiation (cGy)	
Median	**
Min-max	** - **

Table 30: Summary of Organ Preservation

Dataset: All Accrued Patients	
	Number of Patients (%) N=**
Patients received neoadjuvant chemotherapy	
No	**(**)
Yes	**(**)
Disease Progression or no response	
Yes	**(**)
Disease Progression	**(**)
No Response based on Pre-excision MRI	**(**)
cT3ab stage	**(**)
node positive disease	** (**)
not clear circumferential radial margin (CRM)	** (**)
No response based on excision specimen	** (**)
node positive disease	**(**)
ypT2	**(**)
ypT1 tumours with:	
- poorly differentiated histology	**(**)
- lymphovascular invasion	**(**)
- positive margin within <1mm	** (**)
Treated with TME	** (**)
No	
Treated with TEMS/TAMIS	** (**)
Ypstage T0/T1 goodN0	
No	** (**)
Subsequent TME	** (**)
Yes	** (**)
Organ Preservation Rate (%) (95% CI)	
Over All Chemotherapy and Excision Treated Patients	** (**-**)
Over All Chemotherapy Treated Patients	** (**-**)

Table 31: Summary of Disease Outcomes

Data set: All Chemotherapy & Excision Treated Patients	Number of Patients (%) N=**
Patients who had Disease free survival (DFS) event	** (**)
Locoregional Relapse	**(**)
Site of Disease	
Rectum	**(**)
Pelvis	**(**)
Pelvic Lymph nodes	**(**)
Other	**(**)
Distant Disease	**(**)
Site of Disease	
Lung	**(**)
Liver	**(**)
Brain	**(**)
Distant lymph nodes	**(**)
Skin	**(**)
Ascites	**(**)
Pleural effusion	**(**)
Adrenal glands	**(**)
other	**(**)
Non-protocol therapy without documentation of site of failure	** (**)
Radiotherapy	** (**)
Chemotherapy	**(**)
Biologic therapy	
Death (due to any other reason)	**(**)
Patients who were censored	**(**)
Reason Censored	
Alive at the clinical cut-off	**(**)
Lost to follow-up	**(**)
3 year locoregional relapse rate (%) (95% CI)	**(**-**)
3 year distant relapse rate (%) (95% CI)	**(**-**)
3 year Disease free survival rate (%) (95% CI)	**(**-**)

Figure 2: Kaplan-Meier Curve for Locoregional Relapse Free Survival

Figure 3: Kaplan-Meier Curve for Distant Relapse Free Survival

Figure 4: Kaplan-Meier Curve for Disease Free Survival

Note: Same table and figures will be made for all chemotherapy treated patients.

Table 32: Acute Non-Hematologic Adverse Events

Data set: All Chemotherapy Treated Patients							
	Number of patients (%) N=**						
	Worst grade						Any grade
	NR	1	2	3	4	5	
Patients with any AE	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE within category							
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...							
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...							

(1) Patients may have more than one event within a category.

Table 33: Severe Acute Non-Hematologic Adverse Events

Data set: All Chemotherapy Treated Patients				
	Number of patients (%) N=**			
	Worst grade			Any grade 3 or higher AE
	3	4	5	
Patients with any AE	** (**)	** (**)	** (**)	** (**)
Patients with AE within category				
	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)
...				
	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)
...				

(1) Patients may have more than one event within a category.

Table 34: Acute (On-treatment) Adverse Events Related to Oxaliplatin for Patients on FOLFOX

Data set: All Chemotherapy Treated Patients							
	Number of patients (%) N=**						
	Worst grade						Any grade
	NR	1	2	3	4	5	
Patients with any drug related AE	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE within category	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...							
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...							

(1) Patients may have more than one event within a category.

NOTE: Same type of table to be made on adverse events related to leucovorin and 5FU for patients on FOLFOX, to oxaliplatin and capecitabine for patients on CAPOX, to surgery for patients who received surgery, and to radiotherapy for patients who received radiotherapy.

Table 35: Severe Delayed Non-Hematologic Adverse Events

Data set: All Chemotherapy Treated Patients				
	Number of patients (%) N=**			
	Worst grade			Any grade 3 or higher AE
	3	4	5	
Patients with any AE	** (**)	** (**)	** (**)	** (**)
Patients with AE within category	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)
...				
	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)
...				

(1) Patients may have more than one event within a category.

Table 36: Hematology: Worst Grade per Patient

Data set: All Chemotherapy Patients	
	Number of Patients (%) N=**
Hemoglobin	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
WBC	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Absolute neutrophil count (ANC)	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Platelet	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Lymphocytes	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Basophils	
>1-1.5xULN	** (**)
>1.5-2.0xULN	** (**)
>2.0-5.0xULN	** (**)
>5.0xULN	** (**)
Monocytes	
>1-1.5xULN	** (**)
>1.5-2.0xULN	** (**)
>2.0-5.0xULN	** (**)
>5.0xULN	** (**)
Eosinophils	
>1-1.5xULN	** (**)
>1.5-2.0xULN	** (**)
>2.0-5.0xULN	** (**)
>5.0xULN	** (**)

Table 37: Biochemistry: Worst Grade per Patient

Data set: All Chemotherapy Patients	
	Number of Patients (%)
	Total N=**
Serum Creatinine	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Total bilirubin	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
ALT	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Creatinine Clearance	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)

Table 38: Other Laboratory Investigations

Data set: All Chemotherapy Treated Patients	
	Number of Patients (%)
	Total N=**
Pre-excision coagulation	
PT	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
INR	
Grade 0	** (**)
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
PTT	
Grade 1	** (**)
Grade 2	** (**)
Grade 3	** (**)
Grade 4	** (**)
Serum CEA	
At Baseline	
N	**
Mean	**
Standard deviation	**
Change at pre-excision visit from baseline	
N	**
Mean	**
Standard deviation	**
Change at Month 6 follow-up visit from baseline	
N	**
Mean	**
Standard deviation	**
…	

Table 39: Surgery and Post-operative Complications

Data set: All Chemotherapy & Excision/Surgery Treated Patients

	Number of patients (%) N=**
Patients Requiring Reoperation	** (**)
Reoperation procedure performed	
Debridement	**
Incision and drainage	**
Diverting Ostomy	**
Other	**
Blood loss/transfusion	
Estimated amount (cc) of blood loss during surgery	
N	**
Median	**
Min-max	**-**
Any transfusions or blood products during surgery	** (**)
Type of transfusion	
Red cell concentrates	**
Platelets	**
Other	**
Patients with Intraoperative injury	** (**)
Site of Injury	
Bladder	**
Ureter	**
Vein	**
Artery	**
Large bowel	**
Small bowel	**
Nerve injury	**
Other	**
Hospitalization	
Any time in intensive care	
No	** (**)
Yes	** (**)
Days in intensive care	
N	**
Median	**
Min-max	**-**
Ongoing hospitalization	
Yes	** (**)
No	** (**)
Days from admission for tumor excision to discharge	
N	**
Median	**
Min-Max	**-**
Discharge destination	
Home	** (**)
Assisted living (non-medical)	** (**)
Skilled nursing home	** (**)
Hospice	** (**)
Chronic care hospital	** (**)
Rehabilitation facility	** (**)
Died	** (**)
Transfer to other hospital	** (**)
Other	** (**)

Table 40: All Deaths

Data set: All Chemotherapy Treated Patients	
	Number of Patients (%)
	N=**
Number of Patients who died	** (**)
Cause of Death	
Study-specific malignant disease only	**
Adverse event possibly, probably or definitely related to protocol treatment	**
Complication from a non-protocol treatment for this malignancy	**
Other primary malignancy	**
Other condition or circumstance	**

Table 41: Deaths Before Surgery

Data set: All Chemotherapy Treated Patients	
	Number of Patients (%)
	N=**
Number of Patients who died before surgery	** (**)
Cause of Death	
Study-specific malignant disease only	**
Adverse event possibly, probably or definitely related to protocol treatment	**
Complication from a non-protocol treatment for this malignancy	**
Other primary malignancy	**
Other condition or circumstance	**

Table 42: Adverse Event leading to Discontinuation of Neoadjuvant Chemotherapy

Data set: All Chemotherapy Treated Patients	
	Number of patients (%)
	N=**
Number discontinued neoadjuvant chemotherapy from adverse events	** (**)
<Adverse event 1>[(a)]	**
<Adverse event 2>	**
....	

(a): one patient may have more than one adverse event

Table 43: Sigmoidoscopy/Colonoscopy and Other Radiology Investigations

Data set: All Chemotherapy Treated Patients	
	Number of Patients (%)
	N=**
Sigmoidoscopy/colonoscopy during protocol treatment	
All Normal	** (**)
At least one abnormal but all non-malignant	** (**)
All Abnormal and malignant	** (**)
Sigmoidoscopy/colonoscopy during follow-up	
All Normal	** (**)
At least one Abnormal but all non-malignant	** (**)
All Abnormal and malignant	** (**)
Other Radiology investigations during protocol treatment	
All Normal	** (**)
At least one abnormal but all non-malignant	** (**)
All Abnormal and malignant	** (**)
Other Radiology investigations during follow-up	
All Normal	** (**)
At least one abnormal but all non-malignant	** (**)
All Abnormal and malignant	** (**)

Table 44: Transfusion

Data set: All Chemotherapy Treated Patients	
	Number of patients (%)
	N=**
Number (%) of patients transfused during protocol treatment	** (**)
Type of transfusion	
Number of patients received Red Blood Cells	**
Number of patients received Platelets	**
Number of patients received Other Transfusions	**
Number (%) of patients transfused during follow-up	** (**)
Type of transfusion	
Number of patients received Red Blood Cells	**
Number of patients received Platelets	**
Number of patients received Other Transfusions	**

Table 45: Major Medical Problems

Data set: All Chemotherapy Treated Patients	
	Number of patients (%)
	N = ***
Any major medical problem during protocol treatment	
No	** (**)
Yes	** (**)
Type of medical problem during protocol treatment*	
Medical problem A	** (**)
…	** (**)
Any major medical problem during follow-up	
No	** (**)
Yes	** (**)
Type of major medical problem during follow-up*	
Medical Problem A	** (**)
…	** (**)

* one patient may have more than one medical problem

Table 46: Concomitant Medication

Data set: All Chemotherapy Treated Patients	
	Number of patients (%)
	N = ***
Any concomitant medication during protocol treatment	
No	** (**)
Yes	** (**)
Type of concomitant medications during protocol treatment*	
Medication A	** (**)
…	** (**)
Any concomitant medication 30 days after excision	
No	** (**)
Yes	** (**)
Type of concomitant medications 30 days after excision *	
Medication A	** (**)
…	** (**)

* one patient may have more than one medication.

Table 47: Anti-Cancer Treatment

Data set: All Chemotherapy Treated Patients	
	Number of patients (%)
	N = ***
Number of patients with any other anti-cancer treatment during protocol treatment	** (**)
Chemotherapy (1)	** (**)
Drug 1 …	** (**)
Radiotherapy (1)	** (**)
Hormonal therapy (1)	** (**)
Drug 1 …	** (**)
Immunotherapy (1)	** (**)
Drug 1 …	** (**)
Other (1)	** (**)
Drug 1 …	** (**)
Number of patients with any anti-cancer treatment during follow-up but before relapse	** (**)
Chemotherapy (1)	** (**)
Drug 1 …	** (**)
Radiotherapy (1)	** (**)
Hormonal therapy (1)	** (**)
Drug 1 …	** (**)
Immunotherapy (1)	** (**)
Drug 1 …	** (**)
Other (1)	** (**)
Drug 1 …	** (**)
Number of patients with any anti-cancer treatment during after relapse	** (**)
Chemotherapy (1)	** (**)
Drug 1 …	** (**)
Radiotherapy (1)	** (**)
Hormonal therapy (1)	** (**)
Drug 1 …	** (**)
Immunotherapy (1)	** (**)
Drug 1 …	** (**)
Other (1)	** (**)
Drug 1 …	** (**)

(1) Patients could have more than one type of anti-cancer treatment.

Table 48: Compliance Rate with QoL Assessment

Dataset: All Quality of Life Evaluable Patients		
	N = **	
	N	received (%)
Baseline	**	** (**)
Pre-Excision	**	** (**)
Post-Excision		
Month 6	**	** (**)
Month 12	**	** (**)
Month 24	**	** (**)
Month 36	**	** (**)

Table 49: QoL: Summary Baseline Scores

Dataset: All Quality of Life Evaluable Patients	
EORTC QLQ-C30 Functional scales	
Physical N Mean STD	 *** *** ***
...	...
EORTC QLQ-C30 Global QOL N Mean STD	 *** *** ***
EORTC QLQ-C30 Symptom scales	
Fatigue N Mean STD …	 *** *** *** …
EORTC QLQ-CR29 Functional scales	
Body Immage N Mean STD	 *** *** ***
...	...
EORTC QLQ-CR29 Stoma status N Mean STD	 *** *** ***
EORTC QLQ-C29 Symptom scales	
Urinary frequency N Mean STD …	 *** *** *** …
LARS Score Total score N Mean STD	 *** *** ***
FIQL Instrument Scales	
Lifestyle N Mean STD …	 *** *** *** …

Table 50: Summary QOL Change Scores from Baseline for Scale/Domain/Item at Each Time Period*

Dataset: All Quality of Life Evaluable Patients	
Scale/Domain/Item	Change Score
Pre-Excision	
N	**
Mean	**
STD	**
Post-Excision	
Month 6	
N	
Mean	**
STD	**
Month 12	
N	
Mean	**
STD	**
Month 24	
N	
Mean	**
STD	**
Month 36	
N	
Mean	**
STD	**

* Table will be provided for each of EORTC QLQ-C30/CR29 and FIQL instrument scale/domain/item and LARS total score.

Table 51: Proportion of Patients with Deterioration, Improvement or Stable EORTC QLQ-C30 and CR29 domains/items and Global QLQ scales*

All Quality of Life Evaluable Patients	
	N(%)
Deterioration	
Physical function	
Pre-Excision	**(**)
Post-Excision	
Month 6	**(**)
Month 12	**(**)
Month 24	**(**)
Month 36	**(**)
Improvement	
Physical function	
Pre-Excision	**(**)
Post-Excision	
Month 6	**(**)
Month 12	**(**)
Month 24	**(**)
Month 36	**(**)
Stable	
Physical function	
Pre-Excision	**(**)
Post-Excision	
Month 6	**(**)
Month 12	**(**)
Month 24	**(**)
Month 36	**(**)

* Table will be provided for each EORTC QLQ-C30/CR29 scale/domain/item

Table 52: Proportion of Patients in LARS Severity Groups

Dataset: All Quality of Life Evaluable Patients	
	N(%)
No LARS	
Pre-Excision	**(**)
Post-Excision	
Month 6	**(**)
Month 12	**(**)
Month 24	**(**)
Month 36	**(**)
Minor LARS	
Pre-Excision	**(**)
Post-Excision	
Month 6	**(**)
Month 12	**(**)
Month 24	**(**)
Month 36	**(**)
Major LARS	
Pre-Excision	**(**)
Post-Excision	
Month 6	**(**)
Month 12	**(**)
Month 24	**(**)
Month 36	**(**)