A RANDOMIZED PHASE II STUDY OF REOLYSIN IN COMBINATION WITH FOLFOX6/BEVACIZUMAB OR FOLFOX6/BEVACIZUMAB ALONE IN PATIENTS WITH METASTATIC COLORECTAL CANCER

NCIC CTG Protocol Number: IND.210

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Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN for

A RANDOMIZED PHASE II STUDY OF REOLYSIN IN COMBINATION WITH FOLFOX6/BEVACIZUMAB OR FOLFOX6/BEVACIZUMAB ALONE IN PATIENTS WITH METASTATIC COLORECTAL CANCER

NCIC CTG Protocol Number: IND.210

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Serum Glutamic Oxaloacetic Transaminase
BSA	Body Surface Area
C. I.	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CTG	Clinical Trials Group
DR	Duration of Response
ECOG	Eastern Cooperative Cancer Group
EORTC	European Organization for Research and Treatment of Cancer
IN	Inevaluable
LDH	Serum Lactate Dehydrogenase
LKA	Last day the patient is Known Alive
LNL	Lower Normal Limit
MPV	Major Protocol Violation
NA	Not Assessed or Not Applicable
NC	Not Computed
NCI	National Cancer Institute
OS	Overall Survival
PD	Progression Disease
PFS	Progression Free Survival
PR	Partial Response
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SAS	Statistical Analysis System
SD	Stable Disease
STD	Standard Deviation
UNL	Upper Normal Limit
WBC	White Blood Cells

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1. Introduction

This analysis plan is to describe the final analyses performed by NCIC Clinical Trials Group (NCIC CTG) for I210 trial. It will be used for the writing of NCIC Clinical Trials Group study report.

2. Study Description

2.1 *Study Design*

I210 is an open-label, randomized, non-blinded, phase II clinical study of Reolysin day 1-5 (cycles 1, 2, 4, 6, 8 and alternate cycles thereafter) plus q2 weekly FOLFOX6/bevacizumab versus q2 weekly FOLFOX6/bevacizumab as first line palliative treatment for patients with advanced or metastatic colorectal cancer. Prior to the randomized component 6-9 additional patients will be accrued to ensure safety and tolerability of the combination. The study is being conducted by the NCIC Clinical Trials Group, with support of Oncolytics Biotech Inc. Patients are stratified by KRAS mutation status (if known) and prior adjuvant chemotherapy prior to randomization.

A total of 100 patients would be enrolled (50 on each arm). The final analyses will be conducted respectively after at least 50 progression or deaths have been recorded. This analysis plan describes the analyses performed at the completion of the study.

This study was open to accrue patients on June 11, 2012. The safety run-in component of the study was completed in early 2013 with a total of six patients enrolled. The required minimum number of events for the analysis (50) was observed in February 2015 among a total of 109 patients randomized. March 11, 2015 was decided as the date of data cut-off date and the final analysis will be performed after all data observed up to and including March 11, 2015 are cleaned.

The NCIC CTG DSMC has been reviewing safety data every six months (usually at the time of the bi-annual NCIC CTG Spring and Fall meetings) and as otherwise required. These analyses have been prepared by a NCIC CTG/Queen's Senior Biostatistician.

2.2 Treatment Allocation

The study is planned to randomize 100 subjects with using a 1:1 allocation to Reolysin in combination with FOLFOX6/bevacizumab (ARM A) or FOLFOX6/ bevacizumab alone (ARM B). The randomization is dynamically balanced by KRAS mutation status (if known) and prior adjuvant chemotherapy using the minimization method. A centralized system is used to randomize all patients in this study.

3. Objectives

3.1 Primary

The primary objective of this study is to compare the progression free survival (PFS) of patients with metastatic colorectal cancer treated with Reolysin in combination with FOLFOX6/bevacizumab or FOLFOX6/ bevacizumab alone.

3.2 Secondary

Secondary objectives are to:

- Compare change in CEA level between two treatment arms.
- Compare objective response rates (RR) between the two treatment arms.
- Compare overall survival (OS) between the two treatment arms.
- Compare quality of life between the two treatment arms.
- Evaluate the safety profile of Reolysin in combination with FOLFOX6/ bevacizumab in comparison with FOLFOX6/bevacizumab alone.
- To explore potential molecular factors which may be prognostic, or predictive of response, by assessment of archival tumour tissue and serial blood samples

[Note: The last objective (study of molecular markers) will be addressed separately from this analysis plan].

4. Endpoints

4.1 Primary Efficacy

The primary efficacy endpoint is progression free survival.

4.2 Secondary Efficacy

The secondary efficacy endpoints (covered in this analysis plan) are:

- Change in CEA levels
- Objective Response Rate
- Overall Survival
- Quality of Life (using EORTC QLQ-C30)

4.3 Safety

The safety endpoints are 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 median progression free survival for FOLFOX6/bevacizumab is 8.5 months. With a total sample size of 100 accrued in around 13 months and followed for 6 months to observe 50 PFS events before the final analysis, we will have 80% power to detect a difference between two treatment groups in PFS from 8.5 to 15.5 months (i.e. hazard ratio of 0.55) with a one-sided alpha 0.1.

6. Data Set Descriptions

Three types of analysis samples will be used:

<u>All Randomized Patients</u>:
All patients who have been randomized in the study with the treatment arm will be as randomized. The patients in the safety run-in phase are excluded.

<u>All Accrued Patients</u>:
All patients who have been accrued in the study with the treatment arm will be as

randomized for those who have been randomized. The patients in the safety run-in phase are included in the ARM A.

Response-Evaluable Patients:
All patients with at least one target lesion who have at least one disease assessment after baseline will be considered evaluable for response. In addition, patients who develop progressive disease prior to the scheduled first post-baseline assessment will also be considered evaluable for response.

All Treated Patients:
All patients who received at least one dose of study treatment including patients enrolled in safety run-in phase.

7. Statistical Analysis

7.1 General Methods

All comparisons between treatment arms will be carried out using a one-sided test at an alpha level of 10% unless otherwise specified.

When appropriate, discrete variables are summarized with the number and proportion of subjects falling into each category, and compared using Fisher's exact test. Continuous and ordinal categorical variables are summarized using the mean, median, standard error, minimum and maximum values and when appropriate, compared using the Wilcoxon test. All confidence intervals are computed based on normal approximations except those for rates, which will be computed based on the exact method.

Time to event variables are summarized using Kaplan-Meier plots. Primary comparisons of the treatment groups are made using the stratified log-rank test. Primary estimates of the treatment differences are obtained with the hazard ratios and 95% confidence intervals from stratified Cox regression models using treatment arm as the single factor.

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.

Unless otherwise specified, date of randomization and stratification factors will be taken from the Centralized Randomization File.

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 randomization, for subjects who were randomized but who never received treatment.

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

7.2 Study Conduct

All randomized patients are included in the analyses of study conduct. Information will be tabulated by randomized treatment (unless otherwise indicated) and pooled treatments.

7.2.1 Patient Disposition and Follow-up

- Number of patients randomized, 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 randomization (as recorded in centralized randomization file) to the last day the patient is known alive (LKA) as the last recorded date known alive or censored at the time of death and calculated as

  [(date of death or LKA – date of randomization) + 1)]/30.4375.

7.2.2 Accrual Patterns

- Number of patients randomized by center **(Table 3)**
- Number of patients by stratification factor at randomization **(Table 4)**
- Accrual of patients by calendar time pooled across two treatment arms **(Figure 1)**

7.2.3 Eligibility Violations/Protocol Deviations

Eligibility violations of inclusion or exclusion criteria are centrally reviewed by NCIC CTG; 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 centre 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 NCIC CTG based on its standard codes.

- Number of patients eligible, not eligible **(Table 5)**
- Reasons for ineligibility **(Table 5)**
- Major protocol violations: % for each type of violations **(Table 5)**.

Deviations from randomization will be summarized as follows:

- Treatment as randomized versus as treated **(Table 6)**

7.3 Study Population

All randomized patients are included in the study population analyses. Information will be tabulated by randomized treatment (unless otherwise indicated) and pooled treatments.

7.3.1 Patient Pretreatment Characteristics

- Gender: male, female **(Table 7)**
- Age: median, minimum, maximum values**;** <65, ≥65 **(Table 7)**
- ECOG Performance Status: 0, 1, 2 **(Table 7)**
- Months from first histological diagnosis of colorectal cancer to randomization: median, minimum, maximum values **(Table 7)**

- Months from first relapse to randomization: median, minimum, maximum values
- Type of malignancy: colon only, rectum only, colon and rectum **(Table 7)**
- Histology: adeno-carcinoma, etc. **(Table 7)**
- Grade at diagnosis: low, moderate, high, unknown . **(Table 7)**
- K-ras mutation status: wild-type, mutated, unknown **(Table 7)**
- EGFR protein: positive, negative, unknown . **(Table 7)**
- EGFR copy number: normal, increased-amplified, unknown **(Table 7)**
- EGFR mutation: yes, no, unknown **(Table 7)**
- BRAF mutation status: wild-type, mutated, unknown **(Table 7)**
- PIK3CA mutation status: wild-type, mutated, unknown **(Table 7)**

7.3.2 Prior Surgery

- Number of patients with prior surgery for colorectal cancer **(Table 8)**
- Procedure/site of prior surgery **(Table 8)**

7.3.3 Prior radiotherapy

- Number of patients with prior radiotherapy **(Table 9)**
- Prior radiotherapy by site **(Table 9)**
- Total dose of radiotherapy (cGy): median, minimum, maximum values **(Table 9)**
- Best response: CR/PR, SD, PD **(Table 9)**

7.3.4 Prior Systemic Therapy

- Number of subjects with prior systemic therapy and setting/intent of prior systemic therapy (adjuvant, neo-adjuvant, advanced/recurrent/metastatic) **(Table 10)**
- Prior fluoropyrimidine-based therapy regimens: yes, no **(Table 10)**
- Number of patients with prior systemic drug/agent **(Table 10)**

7.3.5 Extent of Disease

- Number of patients with target lesions**,** number of target lesions, largest measure, site of target lesions, evaluation procedure **(Table 11)**
- Number of patients with non-target lesions, number of non-target lesions, site of non-target lesions, evaluation procedure **(Table 12)**

In both tables, site of disease will be taken from the target (non-target lesions at baseline section in CRF BASELINE REPORT.

7.3.6 Baseline Exams

- Baseline hematology: WBC, absolute neutrophil count (ANC), platelets, lymphocytes **(Table 13)**
- Baseline biochemistry: total bilirubin, alkaline phosphatase, ALT, AST, lactate dehydrogenase (LDH), serum creatinine, total protein **(Table 14)**
- Baseline symptom status **(Table 15)**
- Concomitant medications **(Table 16)**
- Other past and current major medical problems ongoing at baseline **(Table 17)**

7.4 Extent of Exposure

Patients included are those who received at least one dose of protocol therapy as defined in Section 6.

7.4.1 Duration of Study Therapy

During protocol treatment, the patients on both treatment arms are planned to receive FOLFOX6/bevacizumab infusion on day 1 of a 14 day cycle (IV bevacizumab 5mg/kg over 1 hour, oxaliplatin 85mg/m^2 and leucovorin 400 mg/m2 concurrently over 2 hours, bolus fluorouracil 400 mg/m^2 after leucovorin, and continuous infusion of fluorouracil 2400 mg/m2 over 46 hours). Patients on ARM A will receive Reolysin $3x10^{10}$ $TCID_{50}$ over 1 hour on days 1-5 of cycle 2, 4, 6, 8 and alternate cycles thereafter.

Duration of a treatment (in weeks) during the study is defined as follows:

[last date of the treatment– first date of the treatment+ 1]/7,

where the first and last date of the treatment is taken from respective treatment administration section of CRF TREATMENT REPORT.

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

- Number of patients by cycle of therapy **(Table 18)**
- Total number of cycles of treatment per patient **(Table 19)**
- Total treatment duration (weeks) per patient (**Table 20**)

7.4.2 Modifications of Protocol Therapy

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

- Number of patients with at least one cycle delayed, reduced, omitted, reduced, interrupted, increased **(Table 21)**
- Number of patients delayed, delayed, reduced, omitted, reduced, interrupted, increased by cycle and dose **(Table 21)**
- Reason for these dose modifications **(Table 21)**

7.4.3 Cumulative dose, dose intensity and relative dose intensity

The cumulative dose ($TCID_{50}$) per patient for Reolysin is the total dose ($TCID_{50}$) that the patient received. The cumulative dose (mg/kg) per patient for bevacizumab is defined as the sum over all cycles of total actual doses that patient received divided by the weight in a given cycle. The cumulative dose (mg/m^2) per patient for 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 of Reolysin ($TCID_{50}$/week) per patient is defined as:

$$\text{Reolysin Dose Intensity} = \frac{\text{Cumulative dose of Reolysin } (TCID_{50}) - \text{first cycle dose ofReolysin } (TCID_{50})}{[\text{last Reolysin dosing date} - \text{second Reolysin dosing date} + 34]/7}.$$

The actual dose intensity (mg/kg/week or mg/m^2/week) per patient for bevacizumab, oxaliplatin, leucovorin and fluorouracil (bolus and continuous) is defined as the cumulative dose (mg/kg or 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 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 22** and **Table 23**.

The relative dose intensity per patient is defined as the actual dose intensity ($TCID_{50}$/week, mg/kg/week, mg/m^2/week) divided by the planned weekly dose as assigned in the protocol, which is 0.75 $TCID_{50}$/week for Reolysin (after first cycle), 2.5/mg/kg/week for bevacizumab, 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. The patient relative dose intensities will be grouped according to the following categories: < 60%, ≥ 60% - <80%, ≥ 80% - < 90%, ≥ 90% (**Table 24**).

7.4.4 Off Study Therapy

The reason for off of each study therapy will be taken from End of Treatment Section of CRF END OF TREATMENT REPORT.

The following information will be summarized for each of protocol treatment **(Table 25):**

- Number of patients off study treatment
- Reason off protocol therapy

7.5 Efficacy

7.5.1 Progression Free Survival

Progression Free Survival (PFS) will be calculated for all patients from the day of randomization until the first observation of objective disease relapse or progression (as recorded in CRF RELAPSE/PROGRESSION REPORT) or death due to any cause (CRF DEATH REPORT) as the (difference+1).

A patient who goes on to receive anti-cancer therapy prior to documentation of disease relapse/progression or death will be censored on the earliest date cancer treatment began.

If a patient has not relapsed/progressed, died, or receive anti-cancer therapy, PFS will be censored on the date of last disease assessment defined as the earliest test date of target lesion or non-target lesions (if patient has no target lesions).

The comparison of PFS between the two treatment arms is the primary objective of this study. The primary analysis will be the log-rank test **(Table 26)** stratified by the factors coded as:

Stratification Factor (at randomization)

KRAS status	1 = Wild Type 3=Unknown	2 = Mutated
Adjuvant fluoropyrimidine-based therapy	0 =Yes	1 = No

The hazard ratio of Reolysin combined with FOLFOX6/Bevacizumab (ARM A) over FOLFOX6/Bevacizumab alone (ARM B) and two-sided 95% CI will be calculated **(Table 26)** based on the Cox regression model stratified by KRAS status and whether djuvant fluoropyrimidine-based therapy was received, and with treatment arm coded as ARM A=1 and ARM B=0. A Kaplan-Meier curve for proportions of patients alive and free of progression in each treatment arm will be displayed. The 95% confidence intervals for the median PFS will be computed using the method of Brookmeyer and Crowley [2]. One-year PFS rates, based on Kaplan-Meier estimates, will be calculated by treatment arm.

The primary analysis of PFS will include all randomized patients, with patients in the safety run-in phase excluded. A sensitive analysis will be performed to include all patients with patients in the safety run-in phase included in ARM A for analysis.

In order to assess the influence of the potential prognostic factors shown and coded below on the comparison of PFS between treatment arms in an explorative multivariate analysis, a stratified Cox regression model will be used with all variables (treatment arm and prognostic factors) included to estimate hazard ratios and 95% confidence intervals**.**

Prognostic factors (at baseline)

Gender	0 = Female	1 = Male
Age	0 = ≥ 65	1 = <65
LDH	0 = >UNL	1 = ≤ UNL
Alkaline phosphatase	0 = >UNL	1 = ≤ UNL
Hemoglobin	0 = >LLN	1 = ≤ LLN

No interactions will be considered in the model. Univariate comparisons of PFS between levels of prognostic factors listed above will be performed using the stratified log-rank test **(Table 26).**

A frequency table will also be provided describing PFS events and censorings as follows **(Table 27):**

- Number of patients who had a PFS event (objective relapse/progression, death without documented relapse/progression)
- Number of patients censored with reasons of censoring (other cancer treatment, alive at the clinical cut-off without progression, lost to follow-up)

Since patients are still assessed after receiving other cancer treatments, a sensitivity analysis will be performed by not censoring patients who received other anti-cancer therapy.

7.5.2 Progression Free Survival by Subsets

For each level of the following baseline variables, a Kaplan-Meier plot of PFS by treatment arm will be produced as well as medians with 95% C.I. and the hazard ratio (unstratified) with 95% CI of ARM A over ARM B**(Table 28):**

- Performance status at baseline: ECOG 0-1, 2
- Age: <65, ≥65
- Gender: female, male

7.5.3 CEA Levels

CEA is measured at baseline, every 4 weeks (end of every second cycle) during protocol treatment, four weeks after completion of protocol therapy, and every three months thereafter until relapse/PD for patients with CR, PR, or SD ongoing. The mean and standard deviation of CEA levels at baseline and the change of CEA levels from baseline at each assessment time during protocol treatment and 4 weeks after completion of protocol treatment will be presented. The change of CEA levels from baseline at each time during and 4 weeks after protocol treatment between treatment groups will be assessed using a Wilcoxon rank sum test **(Table 29).**

7.5.4 Overall survival

For all randomized patients, survival is calculated from the day of randomization (as recorded in Centralized Randomization File) to death (CRF DEATH REPORT). For alive patients, survival is censored at the last day the patient is known alive (LKA) as the last recorded date known alive. Survival time (in months) is defined as

[(date of death or LKA – date of randomization) + 1)]/30.4375.

Analyses for survival will be similar to that for PFS as previously described. A Kaplan-Meier curve for survival in each treatment arm will be displayed. In the primary analysis, median survival for the two treatments will be compared using the stratified log-rank test **(Table 30).** A stratified Cox regression model will estimate the ARM A over ARM B PFS hazard ratio and 95% CI **(Table 30).** In addition, a stratified Cox regression model adjusted for covariates will be applied to verify the impact of the prognostic factors on the treatment effect **(Table 30).** Univariate comparisons of survival between levels of prognostic variables listed will be performed using the stratified log-rank test **(Table 30).**

Coding for treatment arm, stratification variables and prognostic factors is identical to that presented in Section 7.5.1.

7.5.5 Overall Survival by Subsets

Subset analyses performed for PFS will also be performed for survival **(Table 31).**

7.5.6 Treatment Response

All patients will have their best response on study classified every 8 weeks during protocol treatment, using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria 1.1. The best response to protocol treatment is determined by investigators for patients who permanently discontinued protocol treatment and collected in "best objective response (overall) to protocol therapy" section of CRF END OF TREATMENT REPPORT. For patients who are still on treatment and followed for response at final clinical cut-off, their best response is defined as the "best verified" response they have achieved up to the time of clinical cut-off determined by NCIC CTG Senior Investigator based on data on "Response Assessment" section of CRF TREATMENT REPORT.

Best response to protocol treatment will be summarized for all randomized patients **(Table 32).**

The primary analysis of response will be the comparison of the objective response rate (CR+PR) between treatment arms among all the randomized patients using the Cochran-Mantel-Haenszel (CMH) statistic adjusted for stratification factor for all randomized patients **(Table 33)**.

Objective response rate will also be compared between treatment arms using the CMH statistic adjusted for stratification factors for all response evaluable patients.

In addition, a stratified logistic regression model adjusted for covariates will be applied to verify the impact of the prognostic factors on the treatment effect **(Table 33).** Univariate comparisons of response between levels of prognostic variables will be performed using stratified logistic regression **(Table 33)**. For all stratified logistic regression models, estimates of the odds ratio(s) and 95% confidence interval(s) will be given.

Stratified logistic regression odds ratios will be estimated using PROC PHREG in SAS. A dummy time variable will be created, where all responders will be classified as events with an arbitrary time = t_0, and non-responders as censored with time t_1, where $t_1 > t_0$. The DISCRETE option will be used for tied observations.

Coding for treatment, stratification variable and prognostic factors is identical to that presented in Section 7.5.1.

7.5.7 Treatment Response by Subsets

For all randomized patients, the objective response rate will be presented for each treatment arm in the subgroups defined by the categorical variables listed below **(Table 34).** The same table will be presented for all response evaluable patients. No formal comparisons are planned:

- gender (male, female)
- age (<65 years, ≥65 years)
- performance status at baseline (ECOG 0-1, ECOG 2)

7.5.8 Duration of Response

For patients whose best responses are classified as CR or PR at any reporting period during the study, the duration of response is calculated as the time from CR or PR is documented (whichever is the first) until first observation of objective disease relapse or progression or death due to any cause. If a patient has not relapsed/progressed or died, duration of response will be censored on the date of last disease assessment defined as the earliest test date of target lesion or non-target lesions (if patient has no target lesions, whichever is latest.

All randomized patients with CR or PR are included in this analysis. The median duration of response and associated 95% confidence intervals will be computed and compared by the stratified log-rank test adjusting for stratification factors at randomization **(Table 35).**

7.6 Safety

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

7.6.1 Adverse Events

Adverse events (AEs) will be recorded on the Adverse Events (AE) sections of CRF TREATMENT REPORT, 4-WEEK POST TREATMENT REPORT, and 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 on study treatment ("AE" sections in CRF TREATMENT REPORT and 4-WEEK POST TREATMENT REPORT) are defined as acute (on treatment) adverse events. Adverse events reported on "AE" section of CRF FOLLOW UP REPORT will be defined as delayed (late) AEs.

Drug (Reolysin, bevacizumab, or FOLFFOX6) 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 CTC Grade of 3 or higher.

Comparisons between treatment arms on acute and delayed adverse events (severe vs. other) will be carried out using a two sided Fisher's exact test at an alpha level of 5% for adverse events with incidence of at least 10% at grade 3 or higher in one of treatment arms.

The following variables are summarized. Tabulations of overall adverse events will be presented by treatment group.

- Acute adverse events: worst CTC grade per patient by arm **(Table 36)**
- Any acute adverse events, severe acute adverse events: worst CTC grade per patient by arm **(Table 37)**
- Drug related acute adverse events: worst CTC grade per patient **(Table 38)**
- Delayed adverse events: worst CTC grade per patient by arm **(Table 39)**

7.6.2 Laboratory Evaluations

Laboratory evaluations obtained reported on CRF TREATMENT REPORT and 4-WEEK POST TREATMENT REPORT) and on CRF FOLLOW UP REPORT will be included in the calculation for respective acute and late laboratory adverse events. Laboratory results will be classified according to the NCI CTCAE. Tabulations of laboratory adverse events will be presented by treatment group.

7.6.2.1 Hematology

- Hemoglobin, platelets, WBC, Neutrophils, lymphocytes: worst CTC grade per patient **(Table 40)**

7.6.2.2 Biochemistry

- Serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, LDH, total protein: worst CTC grade per patient **(Table 41)**

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

- All Deaths: number of patients who died and cause of death, by treatment group, from CRF DEATH REPORT **(Table 42)**
- Deaths within 4 weeks of last treatment: number of patients who died and cause of death from CRF DEATH REPORT, by treatment group **(Table 43)**
- Adverse events leading to discontinuations of Reolysin, bevcizumab, FOLFFOX6: number of patients with adverse events leading to discontinuations of treatment as identified from CRF END OF TREATMENT REPORT, by treatment group **(Table 44)**

5.6.3 Other Safety

5.6.3.1 Hospitalizations

Number of patients and cycles for which patients were hospitalized will be summarized by treatment group **(Table 45).**

5.6.3.2 Transfusions

Patients who received transfusions during protocol therapy will be summarized as follows:

- Number of patients who received any blood transfusions (red blood cells, platelets, and/or other) **(Table 46)**

7.7 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 after being taken off protocol treatment.

- Concomitant medications for patients during protocol treatment by treatment group **(Table 47)**
- Anti-cancer treatments for patients during protocol treatment or 4 weeks after completion of protocol treatment, by treatment group **(Table 48)**

- Anti-cancer treatments for patients during follow-up, by treatment group **(Table 48)**

7.8 Quality of Life

The quality of life of patients in this study is assessed by using EORTC QLQ-C30 (version 3.0) at baseline, during chemotherapy (Day 1 cycle 5), off treatment (off study or week 4 after completion of protocol treatment). The following are the scoring algorithms for EORTC QLQ-C30 and Skindex-16.

7.8.1 Scoring Algorithms for EORTC QLQ-C30 and Skindex-16

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

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.

7.8.2 Data Sets

The analyses of quality of life data will be restricted to randomized patients who have a measurement at baseline and at least one measurement after baseline.

7.8.3 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 randomized subjects. The number of subjects who are treated on day 1 cycle 5) or who were off treatment and had assessment at time of off protocol treatment or 4 weeks after completion of protocol treatment will be used for other two time points **(Table 49).**

7.8.4 Analyses of QOL

7.8.5.1 Baseline and Change Score Analysis

Descriptive statistics for EORTC QOL-C30 scores (mean, standard deviation) will be presented for each scale at baseline. The same statistics will be generated at each time of post-baseline evaluation. The change scores from baseline at each time of post-baseline evaluation between treatment groups will be assessed using a Wilcoxon rank sum test for each EORTC QOL-C30 (**Table 50** and **Table 51**).

7.8.5.3 Proportions of Deterioration and Improving or Stable for EORTC QLQ-C30 at Post-baseline Assessment

The deterioration is defined as a change score from baseline which is –10 points or lower. Fisher's exact test will be used to compare the proportions of patients with deterioration in each of QLQ domains, items, and scales at two post-baseline assessment time points between two treatment arms **(Table 52).**

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) QOL domain, items, and scales at two post baseline assessment time points will also be compared between two treatment arms using Fisher's exact test **(Table 52).**

8. Data Conventions

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.

9. Appendices

Appendix 1: Tables and Figures

Table 1: Patient Disposition

Data set: All Randomized Patients			
	Number of patients (%)		
	ARM A	ARM B	Total
Randomized	N=***	N=***	N=***
Treated	*** (**)	*** (**)	*** (**)
On study	*** (**)	*** (**)	*** (**)
Off study (1)	*** (**)	*** (**)	*** (**)
Never Treated	*** (**)	*** (**)	*** (**)

(1) Off all study therapy

Table 2: Follow-up of Patients

Data set: All Randomized Patients			
	Number of patients (%)		
	ARM A	ARM B	Total
Number of patients alive	*** (%)	*** (%)	*** (%)
Fellow-up (months)			
median	**	**	**
Minimum-maxiumu	**-**	**-**	**-**

Table 3: Accrual by Center

Data set: All Randomized Patients			
	Number of patients (%)		
	ARM A N=***	ARM B N=***	Total N=***
Center #1	*** (**)	*** (**)	*** (**)
Center #2	*** (**)	*** (**)	*** (**)
Center #3	*** (**)	*** (**)	*** (**)
...	*** (**)	*** (**)	*** (**)

Table 4: Accrual by Stratification Factor at Randomization

Data set: All Randomized Patients			
	Number of patients (%)		
	ARM A N=***	ARM B N=***	Total N=***
KRAS Status			
Wild type	** (**)	** (**)	** (**)
Mutated	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
Adjuvant fluoropyrimidine-based therapy			
Yes	** (**)	** (**)	** (**)
No	** (**)	** (**)	** (**)

Source: Centralized Randomization File

Figure 1: Accrual by Calendar Time

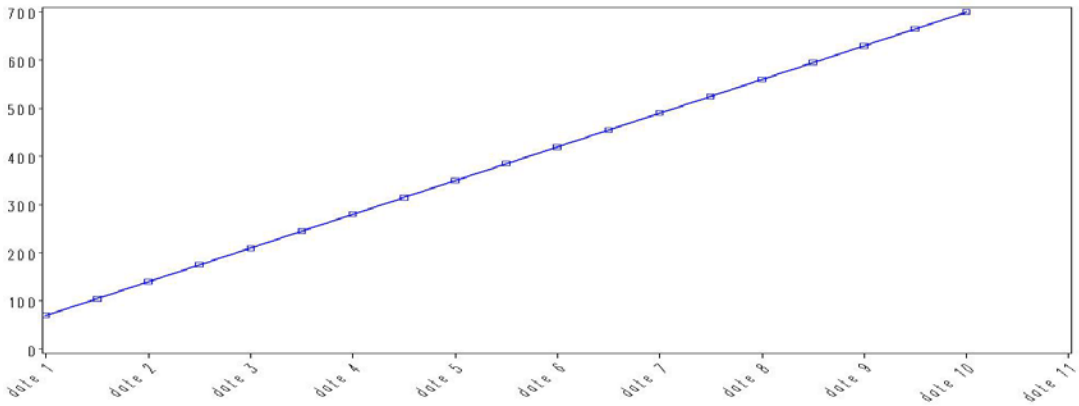

Table 5: Eligibility and Reasons for Ineligibility and Major Protocol Violations

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

Table 6: Treatment as Randomized Versus as Treated

Data set: All Randomized Patients			
	Number of Patients (%) Randomized Arm		
	ARM A N=***	ARM B N=***	Total N=***
Treatment received			
Reolysin+FOLFOX6/bevacizumab	*** (**)	*** (**)	*** (**)
FOLFOX6/bevacizumab	*** (**)	*** (**)	*** (**)
Reolysin only	*** (**)	*** (**)	*** (**)
FOLFOX6 only	*** (**)	*** (**)	*** (**)
bevacizumab only	*** (**)	*** (**)	*** (**)
Not treated	*** (**)	*** (**)	*** (**)

Table 7: Pretreatment Characteristics at Baseline

Data set: All Randomized Patients

	Number of patients (%)		
	ARM A	ARM B	Total
Gender			
Female	** (**)	** (**)	** (**)
Male	** (**)	** (**)	** (**)
Age (years)			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
< 65	** (**)	** (**)	** (**)
≥ 65	** (**)	** (**)	** (**)
ECOG Performance Status			
0	** (**)	** (**)	** (**)
1	** (**)	** (**)	** (**)
2	** (**)	** (**)	** (**)
Type of Malignancy			
Colon only	**(**)	** (**)	** (**)
Rectum only	** (**)	** (**)	** (**)
Colon and rectum	** (**)	** (**)	** (**)
Months from First Histological Diagnosis to Randomization			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Months from First Relapse to Randomization			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Histology			
Adeno-carcinoma	**(**)	**(**)	** (**)
Squamous	** (**)	** (**)	** (**)
Other	** (**)	** (**)	** (**)
Grade at diagnosis			
Low	** (**)	** (**)	** (**)
Moderate	** (**)	** (**)	** (**)
High	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
K-ras mutation status			
Wild-type	** (**)	** (**)	** (**)
Mutated	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
EGFR Protein			
Positive	** (**)	** (**)	** (**)
Negative	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
EGFR Copy Number			
Normal	** (**)	** (**)	** (**)
Increased-Amplified	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)

EGFR Mutation			
Yes	** (**)	** (**)	** (**)
No	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
BRAF mutation status			
Wild	** (**)	** (**)	** (**)
Mutated	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
PIK3CA mutation status			
Wild	** (**)	** (**)	** (**)
Mutated	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)

Table 8: Prior Surgery

Data set: All Randomized Patients

	Number of Patients (%)		
	ARM A N=***	ARM B N=***	Total N=***
Prior surgery			
No	*** (**)	*** (**)	*** (**)
Yes	*** (**)	*** (**)	*** (**)
Procedure / Site			
Procedure / Site 1	*** (**)	*** (**)	*** (**)
Procedure / Site 2	*** (**)	*** (**)	*** (**)
....	*** (**)	*** (**)	*** (**)

Table 9: Prior Radiotherapy

Data set: All Randomized Patients

	Number of patients (%)		
	ARM A N=***	ARM B N=***	Total N=***
Any Prior Radiotherapy			
No	*** (**)	*** (**)	*** (**)
Yes	*** (**)	*** (**)	*** (**)
Site of Any Prior Radiotherapy[(1)]			
Site #1	*** (**)	*** (**)	*** (**)
Site #2	*** (**)	*** (**)	*** (**)
Site #3	*** (**)	***(**)	***(**)
...			
Total Dose of radiotherapy (cGy)	*** (**)	***(**)	***(**)
Best Response			
CR/PR	*** (**)	*** (**)	*** (**)
SD	*** (**)	*** (**)	*** (**)
PD	*** (**)	***(**)	***(**)

[(1)] Patient may have more than one site of radiotherapy

Table 10: Prior Systemic Therapy

Data set: All Randomized Patients

	Number of patients (%)		
	ARM A N=***	ARM B N=***	Total N=***
With at least one prior systemic therapy	*** (**)	*** (**)	*** (**)
Therapy setting/intent [(1)]			
Adjuvant	*** (**)	*** (**)	*** (**)
Neo-adjuvant	*** (**)	*** (**)	*** (**)
Advanced/recurrent/metastatic	*** (**)	*** (**)	*** (**)
Other	*** (**)	*** (**)	*** (**)
Prior adjuvant fluoropyrimidine-based therapy regimens			
Yes	*** (**)	*** (**)	*** (**)
No	*** (**)	*** (**)	*** (**)
Prior systemic drug /agent[(2)]			
Drug 1	*** (**)	*** (**)	*** (**)
Drug 2	*** (**)	*** (**)	*** (**)
…	…	…	…

[(1)] Patients may have more than one setting/intent [(2)] Patient may have more than one drug or regimen

Table 11: Extent of Disease (Target Lesions)

Data set: All Randomized Patients

	Number of Patients with Target Lesions (%)		
	ARM A N=***	ARM B N=***	Total N=***
Presence of Target Lesions			
Patients with at least one target lesion	*** (**)	*** (**)	*** (**)
Number of Target Lesions			
1	*** (**)	*** (**)	*** (**)
2	*** (**)	*** (**)	*** (**)
3	*** (**)	*** (**)	*** (**)
4	*** (**)	*** (**)	*** (**)
…			
Largest Target Lesion in cm			
< 2	*** (**)	*** (**)	*** (**)
2-5	*** (**)	*** (**)	*** (**)
> 5-10	*** (**)	*** (**)	*** (**)
> 10	*** (**)	*** (**)	*** (**)
Site of Target Lesion[(1)]			
Abdomen	*** (**)	*** (**)	*** (**)
Adrenals	*** (**)	*** (**)	*** (**)
Bone	*** (**)	*** (**)	*** (**)
Brain	*** (**)	*** (**)	*** (**)
Liver	*** (**)	*** (**)	*** (**)
Lung	*** (**)	*** (**)	*** (**)
Nodes	*** (**)	*** (**)	*** (**)
Pleura	*** (**)	*** (**)	*** (**)
Skin	*** (**)	*** (**)	*** (**)
Subcutaneous Tissue	*** (**)	*** (**)	*** (**)
....	*** (**)	*** (**)	*** (**)
Procedures for Evaluating Target Lesions			
Imaging [(2)]	*** (**)	*** (**)	*** (**)
Clinical Exam	*** (**)	*** (**)	*** (**)
Imaging [(2)] and Physical Exam	*** (**)	*** (**)	*** (**)

[(1)] Patients may have target lesions at more than one site

[(2)] Bone scan, CT scan, MRI, PET-CT, or X-Ray

Table 12: Extent of Disease (All Non-Target Lesions)

Data set: All Randomized Patients

	Number of Patients (%)		
	ARM A N=***	ARM B N=***	Total N=***
Presence of Non-Target Lesions			
Patients with at least one non-target lesion	*** (**)	*** (**)	*** (**)
Site of Non-target lesion[1]			
Abdomen	*** (**)	*** (**)	*** (**)
Adrenals	*** (**)	*** (**)	*** (**)
Bone	*** (**)	*** (**)	*** (**)
Brain	*** (**)	*** (**)	*** (**)
Liver	*** (**)	*** (**)	*** (**)
Lung	*** (**)	*** (**)	*** (**)
Nodes	*** (**)	*** (**)	*** (**)
Pleura	*** (**)	*** (**)	*** (**)
Skin	*** (**)	*** (**)	*** (**)
Subcutaneous Tissue	*** (**)	*** (**)	*** (**)
Other	*** (**)	*** (**)	*** (**)
Number of disease sites			
1	*** (**)	*** (**)	*** (**)
2	*** (**)	*** (**)	*** (**)
3	*** (**)	*** (**)	*** (**)
4	*** (**)	*** (**)	*** (**)
≥5	*** (**)	*** (**)	*** (**)
Procedures for Evaluating Target Lesions			
Imaging [2]	*** (**)	*** (**)	*** (**)
Clinical Exam	*** (**)	*** (**)	*** (**)
Imaging [2] and Physical Exam	*** (**)	*** (**)	*** (**)

(1) Patients may have non-target lesions at more than one site

(2) Bone scan, CT scan, MRI, PET-CT, or X-Ray

Table 13: Baseline Hematology

Data set: All Randomized Patients			
	Number of Patients (%)		
	ARM A N = ***	ARM B N = ***	Total N=***
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)]	** (**)	** (**)	** (**)

[(1)] Not done or outside the 7-day window prior to start of therapy

Table 14: Baseline Chemistry

Data set: All Randomized Patients

	Number of Patients (%)		
	ARM A N = ***	ARM B N = ***	Total N=***
Total bilirubin			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Alkaline phosphatase			
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)]	** (**)	** (**)	** (**)
AST			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
LDH			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Serum Creatinine			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Total Protein			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)

[(1)] Not done or outside the 7-day window prior to start of therapy

Table 15: Baseline Symptoms Status

Data set: All Randomized Patients (ARM A arm)

	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

NOTE: Same table to be made for ARM B arm

Table 16: Prior Concomitant Medications (Baseline)

Data set: All Randomized Patients

	Number of patients (%)		
	ARM A N=***	ARM B N=***	Total N=***
Any prior concomitant medication [(1)]			
No	** (**)	** (**)	** (**)
Yes	** (**)	** (**)	** (**)
Drug Name 1	** (**)	** (**)	** (**)
Drug Name 2	** (**)	** (**)	** (**)
....			

Table 17: Past or Current Major Medical Problems

Data set: All Randomized Patients

	Number of patients (%)		
	ARM A N=***	ARM B N=***	Total 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 18: Number of Patients by Cycle

Data Set: All Treated Patients			
		Number of Patients (%)	
		ARM A N=***	ARM B N=***
Cycle	1	** (**)	** (**)
	2	** (**)	** (**)
	3	** (**)	** (**)
	...		

Table 19: Number of Cycles of Protocol Therapy per Patient

Data Set: All Treated Patients		
	ARM A	ARM B
Number of Cycles:		
N	***	***
Median	*	*
Min – Max	* - *	* - *

Table 20: Total treatment Duration of Protocol Therapy

Data Set: All Treated Patients		
	ARM A	ARM B
Duration in weeks:		
N	***	***
Median	*	*
Min – Max	* - *	* - *

Note: Table will be done for each of protocol treatments.

Table 21: Number of Patients with Modifications of Protocol Therapy

Data Set: All Treated Patients						
	ARM A					
	Reolysin	Bevacizumab	Oxaliplatin	Leucovarin	Bolos Fluorouracil	Continuous Fluorouracil
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	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
...	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)

Note: Similar table will be done for ARM B and each type of dose modification

Table 22: Cumulative Dose

Data Set: All Treated Patients						
	ARM A					
	Reolysin	Bevacizumab	Oxaliplatin	Leucovarin	Bolos Fluorouracil	Continuous Fluorouracil
Cumulative dose per patient (<unit>)						
N	***	***	***	***	***	***
Mean (SD)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Median	**	**	**	**	**	**
Min-Max	** - **	** - **	** - **	** - **	** - **	** - **

Note: Similar table will be done for ARM B

Table 23: Actual Dose Intensity

Data Set: All Treated Patients						
	ARM A					
	Reolysin	Bevacizumab	Oxaliplatin	Leucovarin	Bolos Fluorouracil	Continuous Fluorouracil
Dose intensity						
N	***	***	***	***	***	***
Mean (SD)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Median	**	**	**	**	**	**
Min-Max	** - **	** - **	** - **	** - **	** - **	** - **

Note: Similar table will be done for ARM B

Table 24: Relative Dose Intensity

Data Set: All Treated Patients

	ARM A					
	Reolysin	Bevacizumab	Oxaliplatin	Leucovarin	Bolos Fluorouracil	Continuous Fluorouracil
Relative Dose intensity						
≥ 90% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
≥ 80% - < 90% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
≥ 60% - < 80% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
< 60% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)

Note: Similar table will be done for ARM B

Table 25: Off Protocol Therapy Summary

Data set: All Treated Patients

	Number of patients (%)	
	ARM A N = ***	ARM B N = ***
Patients off (type of) protocol therapy	N = ** (**)	N = ** (**)
Reason off protocol therapy		
Treatment Completed	**	**
Progressive Disease (objective)	**	**
Symptomatic Progression	**	**
Intercurrent Illness – adverse events unrelated to treatment	**	**
Adverse events related to protocol therapy	**	**
Patient Refusal (not related to adverse event)	**	**
Death	**	**
Other Reason	**	**

Note: Table will be done for each of protocol regiments (bevacizumab, FOLFOX6, Reolysin)

Table 26: Log Rank and Cox Regression Model for Progression Free Survival

Data set: All Randomized Patients							
	N	Univariate Analysis[1]				Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors at Baseline		Median PFS (Months)	1 year PFS Rate (95% C. I.)	Hazard Ratio[4] (95% CI)	Log-rank p-value	Hazard Ratio[4] (95% C.I.)	P-value from Cox regression
Treatment arm					0.***		0.***
ARM A	***	**.**	0.*** (0.***-0.***)	**.**		**.**	
ARM B	***	**.**	0.*** (0.***-0.***)	(**.**,**.**)		(**.**,**.**)	
Gender					0.***		0.***
Male	***	**.**	0.*** (0.***-0.***)	NC [3]		**.**	
Female	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	
Age					0.***		0.***
<65	***	**.**	0.*** (0.***-0.***)	NC		**.**	
≥ 65	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	
LDH					0.***		0.***
≤UNL	***	**.**	0.*** (0.***-0.***)	NC		**.**	
>UNL	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	
Alkaline phosphatase					0.***		0.***
≤UNL	***	**.**	0.*** (0.***-0.***)	NC		**.**	
> UNL	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	
Hemoglobin					0.***		0.***
≤LLN	***	**.**	0.*** (0.***-0.***)	NC		**.**	
>LLN	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	

(1) Stratified; (2) Stratified Cox regression with all factors included; (3) NC = not computed
(4) Hazard ratio of first category over second category

Table 27: Progression Summary

Data set: All Randomized Patients

	Number of Patients (%)	
	ARM A N=***	ARM B N=***
Patients who had PFS event	*** (**)	*** (**)
Relapse/Progression on treatment	**	**
Relapse/Progression during follow-up	**	**
Death (without relapse/progression)	**	**
Patients who were censored	*** (**)	*** (**)
Reason Censored		
Received other cancer treatment	**	**
Alive at the clinical cut-off without progression		
Lost to follow-up	**	**

Table 28: Progression-free survival by Subsets

Data set: All Randomized Patients

Factors	Value	N	ARM A Median PFS 95% C.I.	N	ARM B Median PFS 95% C.I.	Hazard Ratio[(1)] 95% C.I.
Performance Status at baseline	ECOG 0-1	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	ECOG 2	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Age	<65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	≥65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Female	Female	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Male	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)

(1) ARM A over ARM B hazard ratio (Unstratified)

Table 29: Summary Baseline CEA values and Change from Baseline at Each Time Period*

	ARM A	ARM B	P Value*
CEA			
Baseline			.
N	***	***	
Mean	***	***	
STD	***	***	
Change from baseline at Week 4 during treatment			.**
N	***	***	
Mean	***	***	
STD	***	***	
…			

**Wilcoxon rank sum test

Table 30: Log Rank and Cox Regression Model for Overall Survival (OS)

Data set: All Randomized Patients

	N	Univariate Analysis[1]				Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors at Baseline		Median OS (Months)	1 year Survival Rate (95% C. I.)	Hazard Ratio[4] (95% CI)	Log-rank p-value	Hazard Ratio[4] (95% C.I.)	P-value from Cox regression
Treatment arm					0.***		0.***
ARM A	***	**.**	0.*** (0.***-0.***)	**.**		**.**	
ARM B	***	**.**	0.*** (0.***-0.***)	(**.**,**.**)		(**.**,**.**)	
Gender					0.***		0.***
Male	***	**.**	0.*** (0.***-0.***)	NC [3]		**.**	
Female	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	
Age					0.***		0.***
<65	***	**.**	0.*** (0.***-0.***)	NC		**.**	
≥ 65	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	
LDH					0.***		0.***
≤UNL	***	**.**	0.*** (0.***-0.***)	NC		**.**	
>UNL	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	
Alkaline phosphatase					0.***		0.***
≤UNL	***	**.**	0.*** (0.***-0.***)	NC		**.**	
> UNL	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	
Hemoglobin					0.***		0.***
≤UNL	***	**.**	0.*** (0.***-0.***)	NC		**.**	
> UNL	***	**.**	0.*** (0.***-0.***)			(**.**,**.**)	

(1) Stratified; (2) Stratified Cox regression with all factors included; (3) NC = not computed (4) Hazard ratio of first category over second category

Table 31: Overall Survival by Subsets

Data set: All Randomized Patients

Factors	Value	ARM A N	ARM A Median OS 95% C.I.	ARM B N	ARM B Median OS 95% C.I.	Hazard Ratio[(1)] 95% C.I.
Performance Status at baseline	ECOG 0-1	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	ECOG 2	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Age	<65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	≥65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Female	Female	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Male	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)

(1) ARM A over ARM B hazard ratio (Unstratified)

Table 32: Treatment Response

Data set: All Randomized Patients

	Number of Patients (%)[a] N=***	
	ARM A N=***	ARM B N=***
Patients with at least one target lesion	N=***	N=***
Response-evaluable	N=***	N=***
Complete response (CR)	** (**)	** (**)
Partial response (PR)	** (**)	** (**)
Stable disease (SD)	** (**)	** (**)
Progressive disease (PD)	** (**)	** (**)
Inevaluable for response (IN)	** (**)	** (**)
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Not response evaluable	N=***	N=***
Never treated	**	**
Not assessed (NA)	**	**
Patients with no target lesions	N=***	N=***
Progressive disease (PD)	**	**
Inevaluable for response (IN)	**	**
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Not assessed (NA)	**	**
Never treated	**	**

[a] percentages are calculated out of the number of randomized patients

Table 33: Cochran Mantel Haenszel and Logistic Regression Model for Response

Data set: All Randomized Patients				
	Univariate Analysis [1]		Multivariate Analysis [2]	
Treatment/ Prognostic Factors	Odds Ratio[4] (95%CI)	CMH p-value	Odds Ratio [4] (95% C.I.)	p-value from logistic regression
Treatment arm		0.***		0.***
ARM A: ARM B	**.** (**.**,**.**)		**.** (**.**,**.**)	
Gender		0.***		0.***
Male: Female	NC		**.** (**.**,**.**)	
Age		0.***		0.***
<65: ≥65	NC		**.** (**.**,**.**)	
LDH		0.***		0.***
≤UNL: >UNL	NC		**.** (**.**,**.**)	
Alkaline phosphatase		0.***		0.***
≤ UNL: >UNL	NC		**.** (**.**,**.**)	
Hemoglobin		0.***		0.***
≤ LLN: >LLN	NC		**.** (**.**,**.**)	

(1) Stratified
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

NOTE: Same table to be made for all response evaluable patients.

Table 34: Response According to Pretreatment Characteristics

Data set: All Randomized Patients

	Number of Responses/Number of Patients (%)	
	ARM A N=***	ARM B N=***
Gender		
Male	**/** (**)	**/** (**)
Female	**/** (**)	**/** (**)
Age		
< 65 years	**/** (**)	**/** (**)
≥ 65 years	**/** (**)	**/** (**)
Baseline performance status		
ECOG 0-1	**/** (**)	**/** (**)
ECOG 2	**/** (**)	**/** (**)

NOTE: Same table to be made for all response evaluable patients.

Table 35: Duration of Response

Data set: All Randomized Patients with CR or PR

	ARM A N=***	ARM B N=***	P-value[(1)]
Median Duration of Response (months) (95% CI)	*** (**-**)	*** (**-**)	.**

(1) Stratified

Table 36: All Acute Non-Hematologic Adverse Events in ARM A

Data set: All Treated Patients in ARM A							
	Number of patients in ARM A (%) 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.

NOTE: Same table to be made on ARM B.

Table 37: Severe Acute Non-Hematologic Adverse Events in ARM A

Data set: All Treated Patients in ARM A				
	Number of patients in ARM A (%) 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.

NOTE: Same table to be made on ARM B.

Table 38: Acute (On-treatment) Adverse Events Related to Bevacizumab

Data set: All Treated Patients in ARM A							
	Number of patients in ARM A (%) 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 ARM B and also adverse events related to FOLFOX6 on both arms and related to Reolysin on ARM A.

Table 39: Severe Delayed Non-Hematologic Adverse Events in ARM A

Data set: All Treated Patients in ARM A				
	Number of patients in ARM A (%) 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.

NOTE: Same table to be made on ARM B.

Table 40: Hematology by arm: Worst Grade per Patient

Data set: All Randomized Patients		
	Number of Patients (%)	
	ARM A N=***	ARM B N=***
WBC		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Lymphocyte		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Platelet		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Anemia (Hemoglobin)		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Neutrophil		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)

Table 41: Biochemistry Tests by Arm: Worst per Patient

Data set: All Randomized Patients		
	Number of Patients (%)	
	ARM A N = ***	ARM B N = ***
Total bilirubin		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Alkaline phosphatase		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
ALT		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
AST		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
LDH		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Creatinine		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)

Table 42: All Deaths

Data set: All Treated Patients

	Number of Patients (%)	
	ARM A N = **	ARM B 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 43: Deaths within 4 Weeks of Last Treatment

Data set: All Treated Patients

	Number of Patients (%)	
	ARM A N = ***	ARM B N = ***
Number of Patients who died within 30 days of last cetuximab treatment	** (**)	** (**)
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 44: Adverse Event leading to Treatment Discontinuation

Data set: All Treated Patients

	Number of patients (%)	
	ARM A N = ***	ARM B N = ***
Number discontinued from adverse events	** (**)	** (**)
<Adverse event 1>[(a)]	**	**
<Adverse event 2>	**	**
....		

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

NOTE: Table will be made for each component of protocol therapy.

Table 45: Hospitalization

Data set: All Treated Patients		
	Arm 1 N=***	Arm 2 N=***
Number (%) cycles with hospitalization	**/*** (**)	**/*** (**)
Number (%) of patients hospitalized	*** (**)	*** (**)

Table 46: Transfusion

Data set: All Treated Patients		
	Number of patients (%)	
	Arm 1 N=***	Arm 2 N=***
Number (%) of patients transfused	*** (**)	*** (**)
Type of transfusion [(1)]		
Number of patients received Red Blood Cells	**	**
Number of patients received Platelets	**	**
Number of patients received Other Transfusions	**	**
[(1)] All cycles		

Table 47: Concomitant Medication

Data set: All Treated Patients

	Number of patients (%)	
	ARM A N = ***	ARM B N = ***
Any concomitant medication during and 4 weeks after protocol treatment		
No	** (**)	** (**)
Yes	** (**)	** (**)
Type of concomitant medications during protocol treatment*		
Medication A	** (**)	** (**)
…	** (**)	** (**)

* one patient may have more than one medication.

Table 48: Anti-Cancer Treatment

Data set: All Randomized patients

	Number of patients (%)	
	ARM A N = ***	ARM B N = ***
Number of patients with any other anti-cancer treatment during and 4 weeks after 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	*** (**)	*** (**)
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 49: Compliance Rate with QoL Assessment by Treatment Arm

	ARM A N = ***		ARM B N = ***	
	N	received (%)	N	received (%)
Baseline	***	** (**)	***	** (**)
During chemotherapy (Day 1 cycle 5)	***	** (**)	***	** (**)
Off treatment (off study or week 4 after completion of protocol treatment)	***	** (**)	***	** (**)

Table 50: QoL: Summary Baseline Scores

	ARM A	ARM B
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	***	***
…	…	…

Table 51: Summary QOL Change Scores from Baseline for Scale/Domain/Item at Each Time Period*

	ARM A	ARM B	P Value**
Scale/Domain/Item			
During Chemotherapy (Day 1 cycle 5)			.**
N	***	***	
Mean	***	***	
STD	***	***	
Off treatment (Off study or week 4 after completion of protocol treatment)			.**
N			
Mean	***	***	
STD	***	***	

* Table will be provided for each EORTC QLQ-C30 scale/domain/item.
** Wilcoxon rank sum test

Table 52: Proportion of Patients with Deterioration, Improvement or Stable EORTC QLQ-C30 domains/items and Global QLQ scales*

	N	ARM A N (%)	ARM B N (%)	P value**
Deterioration				
Physical function				
During Chemotherapy (Day 1 cycle 5)	***	*** (**.**)	*** (**.**)	0.***
Off treatment (Off study or week 4 after completion of protocol treatment)	***	*** (**.**)	*** (**.**)	0.***
Improvement				
Physical function				
During Chemotherapy (Day 1 cycle 5)	***	*** (**.**)	*** (**.**)	0.***
Off treatment (Off study or week 4 after completion of protocol treatment)	***	*** (**.**)	*** (**.**)	0.***
Stable				
Physical function				
During Chemotherapy (Day 1 cycle 5)	***	*** (**.**)	*** (**.**)	0.***
Off treatment (Off study or week 4 after completion of protocol treatment)	***	*** (**.**)	*** (**.**)	0.***

* Table will be provided for each EORTC QLQ-C30 scale/domain/item
**Fisher's exact test