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Combination Chemotherapy With or Without Bevacizumab in Treating Patients Who Have Undergone Surgery for High Risk Stage II or Stage III Colon Cancer

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	National Cancer Institute (NCI)
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00112918

Purpose

RATIONALE: Drugs used in chemotherapy work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Monoclonal antibodies, such as bevacizumab, can block tumor growth in different ways. Some block the ability of tumor cells to grow and spread. Others find tumor cells and help kill them or carry tumor-killing substances to them. Bevacizumab (Bv) may also stop the growth of tumor cells by blocking blood flow to the tumor. Giving combination chemotherapy together with bevacizumab after surgery may kill any tumor cells that remain after surgery. It is not yet known whether giving combination chemotherapy together with bevacizumab is more effective than combination chemotherapy alone in treating colon cancer in adjuvant setting.

PURPOSE: This randomized phase III trial is studying two different combination chemotherapy regimens with or without bevacizumab to compare how well they work in treating patients who have undergone surgery for high risk stage II or stage III colon cancer.

Condition	Intervention	Phase
Colorectal Cancer	Biological/Vaccine: Bevacizumab Drug: Capecitabine Drug: 5-Fluorouracil (5-FU) Drug: Leucovorin calcium	Phase 3

Condition	Intervention	Phase
	Drug: Oxaliplatin	

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized
Official Title: A Randomized, Three Arm Multinational Phase III Study to Investigate Bevacizumab (q3w or q2w) in Combination With Either Intermittent Capecitabine Plus Oxaliplatin (XELOX) (q3w) or Fluorouracil/Leucovorin With Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 Regimen Alone as Adjuvant Chemotherapy in Colon Carcinoma: The AVANT Study

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Disease-free Survival in Stage III Cancer Patients - Time to Event [Time Frame: From first patient randomized until the data cut-off date of 30 June 2010 (36 months after the last patient randomized).] [Designated as safety issue: No]
  Disease-free survival (DFS) was defined as the time from the date of randomization to the time of a recurrence, a new occurrence of colorectal cancer or death due to any cause, whichever occurred first. Patients without an event were censored at the last date the patient was known to be disease-free. Recurrence and new occurrence of colorectal cancer were based on tumor assessments made by the investigator. Patients with no tumor assessments after baseline but still alive at the time of the clinical cut-off were censored at day 1.
- Disease-free Survival in Stage III Cancer Patients - Number of Events [Time Frame: From first patient randomized until the data cut-off date of 30 June 2010 (36 months after the last patient randomized).] [Designated as safety issue: No]
  A disease-free survival (DFS) event was composed of a recurrence, a new occurrence of colorectal cancer or death due to any cause. Recurrence and new occurrence of colorectal cancer were based on tumor assessments made by the investigator. Triggering events for DFS are reported; a patient can have both recurrence and a new occurrence of colon cancer.

Secondary Outcome Measures:

- Overall Survival in Stage III Cancer Patients - Time to Event [Time Frame: From first patient randomized until the clinical data cut-off date of 30 June 2010 (36 months after the last patient randomized).] [Designated as safety issue: No]
  Overall survival was defined as the time between date of randomization and date of death due to any cause. Patients not reported as having died at the time of the analysis were censored at the date they were last known to be alive.
- Overall Survival in Stage III Cancer Patients - Number of Events [Time Frame: From first patient randomized until the clinical data cut-off date of 30 June 2010 (36 months after the last patient randomized).] [Designated as safety issue: No]
  An overall survival event was death due to any cause.
- Overall Survival in Stage III Cancer Patients - Time to Event: Final Analysis [Time Frame: From first patient randomized until the final data cut-off date of 30 June 2012 (5 years after the last patient randomized).] [Designated as safety issue: No]
  Overall survival was defined as the time between date of randomization and date of death due to any cause. Patients not reported as having died at the time of the clinical cut-off date (30 June 2012) were censored at the date they were last known to be alive.
- Overall Survival in Stage III Cancer Patients - Number of Events: Final Analysis [Time Frame: From first patient randomized until the final data cut-off date of 30 June 2012 (5 years after the last patient randomized).] [Designated as safety issue: No]
  An overall survival event was death due to any cause.

Enrollment: 3451
Study Start Date: December 2004
Primary Completion Date: June 2010
Study Completion Date: June 2012

Arms	Assigned Interventions
Active Comparator: FOLFOX4 Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.	Drug: 5-Fluorouracil (5-FU) Administered as either a bolus injection or continuous intravenous infusion over 22 hours. Drug: Leucovorin calcium Administered as a 200 mg/m^2 infusion over 2 hours. Drug: Oxaliplatin Administered as an intravenous infusion over 2 hours.
Experimental: FOLFOX4 + Bv Weeks 1-24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).	Biological/Vaccine: Bevacizumab Administered as an intravenous infusion over 30 - 90 minutes. Drug: 5-Fluorouracil (5-FU) Administered as either a bolus injection or continuous intravenous infusion over 22 hours. Drug: Leucovorin calcium Administered as a 200 mg/m^2 infusion over 2 hours. Drug: Oxaliplatin Administered as an intravenous infusion over 2 hours.
Experimental: XELOX+Bv	Biological/Vaccine: Bevacizumab

Arms	Assigned Interventions
Weeks 1–24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 – 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25–48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).	Administered as an intravenous infusion over 30 - 90 minutes. Drug: Capecitabine Film-coated tablets Other Names: Xeloda® Drug: Oxaliplatin Administered as an intravenous infusion over 2 hours.

Detailed Description:

This was an open-label Phase III, multicenter, multinational, randomized, 3-arm study designed to evaluate the efficacy and safety of bevacizumab in combination with either intermittent fluorouracil/leucovorin with oxaliplatin (FOLFOX4) or capecitabine plus oxaliplatin (XELOX) versus FOLFOX4 regimen alone, as adjuvant chemotherapy in colon carcinoma.

The treatment phase consisted of two parts of 24 weeks for a total of 48 weeks. The first part (weeks 1 to 24) consisted of treatment with either FOLFOX4, FOLFOX4 in combination with bevacizumab, or XELOX in combination with bevacizumab. The second part (weeks 25 to 48) consisted of single-agent bevacizumab for patients randomized to either bevacizumab-containing arm, but was only an observation period for patients assigned to the FOLFOX4-alone arm.

Patients were to be followed for recurrence/new occurrence of colorectal cancer and survival. Patients who experienced a confirmed recurrence, occurrence of a new colorectal cancer during therapy, or experienced unacceptable toxicity were to be taken off study treatment but remain in study follow-up. Patients that came off therapy due to a confirmed recurrence/appearance of new colorectal cancer, were to be followed for survival until the end of the study follow-up period. The primary analysis was performed 36 months after the last patient has been randomized. After the primary analysis, patients continue to be followed for survival for at least a further 2 years ie, until all patients have been followed-up for at least 5 years following randomization.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria

1. Signed written informed consent obtained prior to any study specific screening procedures.
2. Patient willing and able to comply with the protocol.
3. Age ≥ 18 years-of-age.
4. Histologically confirmed colon carcinoma, American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC) Stage II or Stage III defined as a tumor location ≥ 15 cm from the anal verge by endoscopy or above the peritoneal reflection at surgery. The patient was not to be a candidate for (neo) adjuvant radiotherapy. Note: Stage II patients were to be considered as high-risk patients fulfilling one of the following criteria:
    - T4 tumours,
    - Patients presenting with bowel obstruction or perforation,
    - Histological signs of vascular invasion (i.e. blood and lymphatic vessels) or perineural invasion,
    - Patients aged less than 50 years,
    - Patients with sub-optimal surgery (less than 12 nodes analyzed).
5. Curative surgery not less than 4 and not more than 8 weeks prior to randomization.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
7. Life expectancy of ≥ 5 years.

Exclusion Criteria

1. Macroscopic or microscopic evidence of remaining tumour. Patients should never have had any evidence of metastatic disease (including presence of tumour cells in the ascites). The isolated finding of cytokeratin positive cells in bone marrow is not considered evidence of metastatic disease for purposes of this study.
2. Carcinoembryonic antigen > 1.5 x upper limit of normal (ULN) after surgery (during screening period).
3. For patients with colostomy, unwilling to delay revision until at least 28 days after treatment completion.
4. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study treatment start, not fully healed wounds, or anticipation of the need for major surgical procedure during the course of the study. Any central venous access device (CVAD) for chemotherapy administration must be inserted at least 2 days prior to treatment start.
5. Previous anti-angiogenic treatment for any malignancy; cytotoxic chemotherapy, radiotherapy or immunotherapy for colon cancer.
6. Other malignancies within the last 5 years (other than curatively treated basal cell carcinoma of the skin and/or in situ carcinoma of the cervix).
7. Females with a positive or no pregnancy test (within 7 days before treatment start) unless childbearing potential can be otherwise excluded (postmenopausal i.e. amenorrheic for at least 2 years, hysterectomy or oophorectomy).
8. Lactating women.
9. Fertile women (< 2 years after last menstruation) and men of childbearing potential not willing to use effective means of contraception.
10. History or evidence upon physical examination of central nervous disease (CNS) disease (eg, primary brain tumour, seizure not controlled with standard medical therapy, any brain metastases).
11. History of psychiatric disability judged by the investigator to be clinically significant, precluding informed consent or interfering with compliance for oral drug intake.
12. Clinically significant (ie, active) cardiovascular disease. This includes, but is not limited to, the following examples: cerebrovascular accidents (≤ 6 months prior to randomization), myocardial infarction (≤ 1 year prior to randomization), uncontrolled hypertension (>150/100 mmHg) while receiving chronic medication, unstable angina, New York Heart Association (NYHA) Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, clinically significant electrocardiogram (ECG) findings (e.g. QTc ≥ 440 msecs [male] 460 msecs [female] or ≥ 2º atrioventricular block, etc.).

Patients who suffer from serious cardiac arrhythmia requiring medication can enter the study only if they are considered to be in a stable condition regarding both the arrhythmia and their medication. Patients with pacemakers are allowed to enter the study only if they are considered as being in a stable condition. In case of doubt, the investigator should obtain a consultation with a local cardiologist.

13. Lack of physical integrity of the upper gastro-intestinal tract, malabsorption syndrome, or inability to take oral medication.
14. Interstitial pneumonia or extensive symptomatic fibrosis of the lungs.
15. Known peripheral neuropathy ≥ Common terminology criteria for adverse events (CTCAE) version 3.0 Grade 1. Absence of deep tendon reflexes as the sole neurological abnormality does not render the patient ineligible.
16. Organ allografts requiring immunosuppressive therapy.
17. Serious, non-healing wound, ulcer, or bone fracture.
18. Evidence of bleeding diathesis or coagulopathy.
19. Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agent for therapeutic purposes.
20. Chronic, daily treatment with high-dose aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day).
21. Chronic treatment with corticosteroids (dose of ≥ 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids).
22. Serious intercurrent infections (uncontrolled or requiring treatment).
23. Known dihydropyrimidine dehydrogenase deficiency.
24. Current or recent (within the 28 days prior to randomization) treatment with another investigational drug or participation in another investigational study.
25. Patients with known allergy to Chinese hamster ovary cell proteins or other recombinant human or humanized antibodies or to any excipients of bevacizumab formulation, platinum compounds or to any other components of the study drugs.
26. History or presence of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or patient at high risk from treatment complications.
27. Presence of proteinuria at baseline as defined by:

    - Patients with > 1 g of protein/24 hour by a 24-hour urine collection.
28. Any laboratory values at baseline are as follows:

Haematology:

- Absolute neutrophil count (ANC) < 1.5 x 109/L
- Platelet count < 100 x 10^9/L
- Haemoglobin < 9 g/dL (may be transfused to maintain or exceed this level)
- International normalized ratio (INR) > 1.5
- Activated partial prothrombin time (APTT) ≥ 1.5 x ULN

Biochemistry:

- Total bilirubin > 1.5 x ULN
- aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) > 2.5 x ULN
- Alkaline phosphatase (ALP) > 2.5 x ULN
- Serum creatinine > 1.5 x ULN or creatinine clearance ≤ 50 mL/min (e.g. Cockcroft-Gault formula).

Contacts and Locations

Locations

United States, California

Jonsson Comprehensive Cancer Center at UCLA

Los Angeles, California, United States, 90095-1781

Investigators

Principal Investigator:	Joel Randolph Hecht, MD	Jonsson Comprehensive Cancer Center at UCLA

More Information

Clinical trial summary from the National Cancer Institute's PDQ® database
http://cancer.gov/clinicaltrials/UCLA-0412086-01

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	CDR0000427299 P30CA016042 [US NIH Grant/Contract Award Number] UCLA-0412086-01 ROCHE-BO17920A
Health Authority:	United States: Food and Drug Administration

Study Results

Participant Flow

Pre-Assignment Details	Randomization was stratified according to geographic region and disease stage (high-risk stage II or stage III N1 or stage III N2). The primary analysis population consisted of patients with Stage III disease.

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-fluorouracil (5-FU), given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.

	Description
FOLFOX4 + Bv	Weeks 1-24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).
XELOX+Bv	Weeks 1-24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Overall Study

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
Started	1151	1155	1145
Received Treatment	1126	1145 [1]	1135
Stage III Disease Population	955	960	952
Completed	854 [2]	810 [2]	846 [2]
Not Completed	297	345	299

[1] Includes two patients from FOLFOX4 who received Bv and were assigned to FOLFOX4+Bv safety analysis
[2] Represents patients alive in follow-up at the time of final data cut-off (30 June 2012)

Baseline Characteristics

Analysis Population Description
Baseline Measures are based on the Intent-to-Treat - Stage III Disease Patient Population.

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-fluorouracil (5-FU), given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.
FOLFOX4 + Bv	Weeks 1–24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 – 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25–48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).
XELOX+Bv	Weeks 1–24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 – 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25–48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Baseline Measures

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv	Total
Number of Participants	955	960	952	2867
Age, Customized [units: participants]				
<40	77	74	68	219
40-65	603	625	588	1816
>=65	275	261	296	832
Gender, Male/Female [units: participants]				

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv	Total
Female	425	473	432	1330
Male	530	487	520	1537
Race/Ethnicity, Customized [units: participants]				
American Indian or Alaska Native	1	1	0	2
Asian	139	115	123	377
Black or African American	6	13	14	33
White	791	813	795	2399
Other	18	18	20	56

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Disease-free Survival in Stage III Cancer Patients - Time to Event
Measure Description	Disease-free survival (DFS) was defined as the time from the date of randomization to the time of a recurrence, a new occurrence of colorectal cancer or death due to any cause, whichever occurred first. Patients without an event were censored at the last date the patient was known to be disease-free. Recurrence and new occurrence of colorectal cancer were based on tumor assessments made by the investigator. Patients with no tumor assessments after baseline but still alive at the time of the clinical cut-off were censored at day 1.
Time Frame	From first patient randomized until the data cut-off date of 30 June 2010 (36 months after the last patient randomized).
Safety Issue?	No

Analysis Population Description

The primary population for efficacy analyses was the intent to treat population (ITT; all randomized patients) with stage III disease.

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.

	Description
FOLFOX4 + Bv	Weeks 1-24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).
XELOX+Bv	Weeks 1-24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Measured Values

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
Number of Participants Analyzed	955	960	952
Disease-free Survival in Stage III Cancer Patients - Time to Event [units: months] Median (95% Confidence Interval)	NA (NA to NA) [1]	NA (NA to NA) [1]	NA (NA to NA) [1]

[1] Median time to event and 95% confidence intervals could not be estimated due to the low number of events.

Statistical Analysis 1 for Disease-free Survival in Stage III Cancer Patients - Time to Event

Statistical Analysis Overview	Comparison Groups	FOLFOX4, FOLFOX4 + Bv, XELOX+Bv
	Comments	Adjustments for multiplicity was done using a closed test procedure which tests for differences between all three treatment groups at the 5% alpha level first. Only in case of a significant result, the pair-wise comparison between the control arm and each of the bevacizumab arm will be tested, again at the 5% alpha level.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2024
	Comments	[Not specified]
	Method	Other [Closed test procedure]
	Comments	[Not specified]

2. Primary Outcome Measure:

Measure Title	Disease-free Survival in Stage III Cancer Patients - Number of Events
Measure Description	A disease-free survival (DFS) event was composed of a recurrence, a new occurrence of colorectal cancer or death due to any cause. Recurrence and new occurrence of colorectal cancer were based on tumor assessments made by the investigator. Triggering events for DFS are reported; a patient can have both recurrence and a new occurrence of colon cancer.
Time Frame	From first patient randomized until the data cut-off date of 30 June 2010 (36 months after the last patient randomized).
Safety Issue?	No

Analysis Population Description

The primary population for efficacy analyses was the intent to treat population (ITT; all randomized patients) with stage III disease.

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.
FOLFOX4 + Bv	Weeks 1-24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

	Description
XELOX+Bv	Weeks 1-24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Measured Values

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
Number of Participants Analyzed	955	960	952
Disease-free Survival in Stage III Cancer Patients - Number of Events [units: participants]			
Patients with a DFS event	237	280	253
Recurrence	219	253	223
New Occurrence	3	8	6
Death	17	21	25
Patients without events	718	680	699

3. Secondary Outcome Measure:

Measure Title	Overall Survival in Stage III Cancer Patients - Time to Event
Measure Description	Overall survival was defined as the time between date of randomization and date of death due to any cause. Patients not reported as having died at the time of the analysis were censored at the date they were last known to be alive.
Time Frame	From first patient randomized until the clinical data cut-off date of 30 June 2010 (36 months after the last patient randomized).
Safety Issue?	No

Analysis Population Description

ITT patients with Stage III disease.

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.
FOLFOX4 + Bv	Weeks 1-24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).
XELOX+Bv	Weeks 1-24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Measured Values

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
Number of Participants Analyzed	955	960	952
Overall Survival in Stage III Cancer Patients - Time to Event [units: months] Median (95% Confidence Interval)	NA (NA to NA) [1]	NA (NA to NA) [1]	NA (NA to NA) [1]

[1] Median time to event and 95% confidence intervals could not be estimated due to the low number of events.

4. Secondary Outcome Measure:

Measure Title	Overall Survival in Stage III Cancer Patients - Number of Events

Measure Description	An overall survival event was death due to any cause.
Time Frame	From first patient randomized until the clinical data cut-off date of 30 June 2010 (36 months after the last patient randomized).
Safety Issue?	No

Analysis Population Description

ITT patients with Stage III disease.

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.
FOLFOX4 + Bv	Weeks 1-24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).
XELOX+Bv	Weeks 1-24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Measured Values

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
Number of Participants Analyzed	955	960	952
Overall Survival in Stage III Cancer Patients - Number of Events			

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
[units: participants]			
Patients with events	115	151	145
Patients without events	840	809	807

5. Secondary Outcome Measure:

Measure Title	Overall Survival in Stage III Cancer Patients - Time to Event: Final Analysis
Measure Description	Overall survival was defined as the time between date of randomization and date of death due to any cause. Patients not reported as having died at the time of the clinical cut-off date (30 June 2012) were censored at the date they were last known to be alive.
Time Frame	From first patient randomized until the final data cut-off date of 30 June 2012 (5 years after the last patient randomized).
Safety Issue?	No

Analysis Population Description

ITT patients with Stage III disease.

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.
FOLFOX4 + Bv	Weeks 1-24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

	Description
XELOX+Bv	Weeks 1-24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Measured Values

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
Number of Participants Analyzed	955	960	952
Overall Survival in Stage III Cancer Patients - Time to Event: Final Analysis [units: months] Median (95% Confidence Interval)	NA (NA to NA) [1]	NA (NA to NA) [1]	NA (NA to NA) [1]

[1] Median time to event and 95% confidence intervals could not be estimated due to the low number of events.

6. Secondary Outcome Measure:

Measure Title	Overall Survival in Stage III Cancer Patients - Number of Events: Final Analysis
Measure Description	An overall survival event was death due to any cause.
Time Frame	From first patient randomized until the final data cut-off date of 30 June 2012 (5 years after the last patient randomized).
Safety Issue?	No

Analysis Population Description

ITT patients with Stage III disease.

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.
FOLFOX4 + Bv	Weeks 1-24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).
XELOX+Bv	Weeks 1-24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 - 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25-48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Measured Values

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
Number of Participants Analyzed	955	960	952
Overall Survival in Stage III Cancer Patients - Number of Events: Final Analysis [units: participants]			
Patients with events	161	202	182
Patients without events	794	758	770

Reported Adverse Events

Time Frame	All adverse events occurring between the date of first drug intake and 28 days after last drug intake, regardless of which treatment group the patient was randomized to.
Additional Description	[Not specified]

Reporting Groups

	Description
FOLFOX4	Weeks 1-24: Oxaliplatin was administered as an 85 mg/m^2 intravenous infusion over 2 hours concomitantly with Leucovorin as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion were repeated on day 2. Cycle length was 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25-48: Observation only.
FOLFOX4 + Bv	Weeks 1–24: Bevacizumab 5 mg/kg was administered as an intravenous infusion over 30 – 90 minutes followed by oxaliplatin, administered as an 85 mg/m^2 intravenous infusion over 2 hours (on day 1 only) concomitantly with leucovorin, as a 200 mg/m^2 infusion over 2 hours, followed by 5-FU, given as a 400 mg/m^2 bolus injection, and then as a 600 mg/m^2 continuous infusion over 22 hours. Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection, and 5-FU 600 mg/m^2 continuous infusion are repeated on day 2. Cycle length is 2 weeks and cycles were repeated every second week for a total of 12 cycles (24 weeks). Weeks 25–48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).
XELOX+Bv	Weeks 1–24: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 – 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours (day 1 every 3 weeks) in combination with capecitabine, which was administered orally at a dose of 1000 mg/m^2 twice daily (equivalent to a total daily dose of 2000 mg/m^2), with first dose the evening of day 1 and last dose the morning of day 15, given as intermittent treatment (3-week cycles consisting of 2 weeks of treatment followed by 1 week without treatment), for a total of 8 cycles (24 weeks). Weeks 25–48: Bevacizumab 7.5 mg/kg was administered as an intravenous infusion over 30 minutes. Cycle length was 3 weeks. Cycles were repeated every 3 weeks for a total of 8 cycles (24 weeks).

Serious Adverse Events

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	226/1126 (20.07%)	297/1145 (25.94%)	284/1135 (25.02%)
Blood and lymphatic system disorders			

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Anaemia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Febrile neutropenia [A] †	14/1126 (1.24%)	9/1145 (0.79%)	2/1135 (0.18%)
Idiopathic thrombocytopenia purpura [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Leukopenia [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Neutropenia [A] †	18/1126 (1.6%)	18/1145 (1.57%)	0/1135 (0%)
Thrombocytopenia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Cardiac disorders			
Acute coronary syndrome [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Acute myocardial infarction [A] †	1/1126 (0.09%)	2/1145 (0.17%)	0/1135 (0%)
Angina pectoris [A] †	1/1126 (0.09%)	1/1145 (0.09%)	4/1135 (0.35%)
Angina unstable [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Arteriospasm coronary [A] †	1/1126 (0.09%)	0/1145 (0%)	1/1135 (0.09%)
Atrial fibrillation [A] †	2/1126 (0.18%)	0/1145 (0%)	0/1135 (0%)
Cardiac arrest [A] †	0/1126 (0%)	1/1145 (0.09%)	2/1135 (0.18%)
Cardiac asthma [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Cardiac failure [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Cardiac failure congestive [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Coronary artery disease [A] †	1/1126 (0.09%)	2/1145 (0.17%)	1/1135 (0.09%)
Left ventricular dysfunction [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Mitral valve incompetence [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Myocardial infarction [A] †	1/1126 (0.09%)	5/1145 (0.44%)	1/1135 (0.09%)
Myocardial ischaemia [A] †	2/1126 (0.18%)	1/1145 (0.09%)	1/1135 (0.09%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Palpitations [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Paroxysmal arrhythmia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Pericardial haemorrhage [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Sinus arrest [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Ear and labyrinth disorders			
Vertigo [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Endocrine disorders			
Hypothyroidism [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Eye disorders			
Retinal detachment [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Retinal vein thrombosis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Uveitis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Gastrointestinal disorders			
Abdominal adhesions [A] †	2/1126 (0.18%)	0/1145 (0%)	2/1135 (0.18%)
Abdominal discomfort [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Abdominal distension [A] †	1/1126 (0.09%)	0/1145 (0%)	1/1135 (0.09%)
Abdominal hernia [A] †	2/1126 (0.18%)	0/1145 (0%)	0/1135 (0%)
Abdominal pain [A] †	11/1126 (0.98%)	14/1145 (1.22%)	18/1135 (1.59%)
Abdominal pain lower [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Abdominal pain upper [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Abdominal rigidity [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Acute abdomen [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Anal fissure [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Anal fistula [A] †	0/1126 (0%)	2/1145 (0.17%)	0/1135 (0%)
Caecitis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Colitis [A] †	0/1126 (0%)	1/1145 (0.09%)	5/1135 (0.44%)
Colitis ulcerative [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Constipation [A] †	1/1126 (0.09%)	4/1145 (0.35%)	2/1135 (0.18%)
Crohn's disease [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Diarrhoea [A] †	28/1126 (2.49%)	28/1145 (2.45%)	62/1135 (5.46%)
Duodenitis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Dyspepsia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Enteritis [A] †	3/1126 (0.27%)	0/1145 (0%)	5/1135 (0.44%)
Enterocolitis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	1/1135 (0.09%)
Enterocolitis haemorrhagic [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Erosive oesophagitis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Faecaloma [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Food poisoning [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Gastric ulcer [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Gastric volvulus [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Gastritis [A] †	3/1126 (0.27%)	1/1145 (0.09%)	0/1135 (0%)
Gastrointestinal haemorrhage [A] †	0/1126 (0%)	2/1145 (0.17%)	2/1135 (0.18%)
Gastrointestinal necrosis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Gastrointestinal obstruction [A] †	0/1126 (0%)	3/1145 (0.26%)	1/1135 (0.09%)
Gastrointestinal perforation [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Gastrooesophageal reflux disease [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Haematemesis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Haematochezia [A] †	0/1126 (0%)	0/1145 (0%)	2/1135 (0.18%)
Haemorrhoids [A] †	1/1126 (0.09%)	1/1145 (0.09%)	2/1135 (0.18%)
Hiatus hernia, obstructive [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Ileal perforation [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Ileus [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Ileus paralytic [A] †	0/1126 (0%)	1/1145 (0.09%)	2/1135 (0.18%)
Intestinal angina [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Intestinal dilatation [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Intestinal fistula [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Intestinal ischaemia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Intestinal obstruction [A] †	6/1126 (0.53%)	9/1145 (0.79%)	7/1135 (0.62%)
Intestinal perforation [A] †	1/1126 (0.09%)	2/1145 (0.17%)	0/1135 (0%)
Intestinal prolapse [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Intestinal strangulation [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Large intestine perforation [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Lower gastrointestinal haemorrhage [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Mallory-Weiss syndrome [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Mechanical ileus [A] †	2/1126 (0.18%)	0/1145 (0%)	0/1135 (0%)
Melaena [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Mesenteric vein thrombosis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Nausea [A] †	0/1126 (0%)	4/1145 (0.35%)	7/1135 (0.62%)
Neutropenic colitis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Oesophagitis [A] †	0/1126 (0%)	2/1145 (0.17%)	2/1135 (0.18%)
Pancreatitis [A] †	2/1126 (0.18%)	1/1145 (0.09%)	0/1135 (0%)
Pancreatitis acute [A] †	1/1126 (0.09%)	1/1145 (0.09%)	1/1135 (0.09%)
Peritonitis [A] †	0/1126 (0%)	1/1145 (0.09%)	2/1135 (0.18%)
Rectal haemorrhage [A] †	1/1126 (0.09%)	7/1145 (0.61%)	3/1135 (0.26%)
Rectal perforation [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Small intestinal obstruction [A] †	2/1126 (0.18%)	2/1145 (0.17%)	4/1135 (0.35%)
Small intestinal perforation [A] †	0/1126 (0%)	4/1145 (0.35%)	0/1135 (0%)
Stomatitis [A] †	1/1126 (0.09%)	0/1145 (0%)	2/1135 (0.18%)
Subileus [A] †	1/1126 (0.09%)	4/1145 (0.35%)	2/1135 (0.18%)
Umbilical hernia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Upper gastrointestinal haemorrhage [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Volvulus of small bowel [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Vomiting [A] †	7/1126 (0.62%)	11/1145 (0.96%)	16/1135 (1.41%)
General disorders			
Adhesion [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Asthenia [A] †	0/1126 (0%)	3/1145 (0.26%)	1/1135 (0.09%)
Catheter site pain [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Chest pain [A] †	1/1126 (0.09%)	2/1145 (0.17%)	1/1135 (0.09%)
Chills [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Device leakage [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Device malfunction [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Extravasation [A] †	0/1126 (0%)	0/1145 (0%)	2/1135 (0.18%)
General physical health deterioration [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Hernia obstructive [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Hyperpyrexia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Infusion site thrombosis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Malaise [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Medical device complication [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Multi-organ failure [A] †	2/1126 (0.18%)	0/1145 (0%)	0/1135 (0%)
Non-cardiac chest pain [A] †	1/1126 (0.09%)	2/1145 (0.17%)	5/1135 (0.44%)
Pain [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Performance status decreased [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Pyrexia [A] †	20/1126 (1.78%)	10/1145 (0.87%)	16/1135 (1.41%)
Sudden cardiac death [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Sudden death [A] †	0/1126 (0%)	2/1145 (0.17%)	3/1135 (0.26%)
Thrombosis in device [A] †	1/1126 (0.09%)	0/1145 (0%)	1/1135 (0.09%)
Visceral pain [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Hepatobiliary disorders			
Cholangitis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Cholecystitis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	2/1135 (0.18%)
Cholecystitis acute [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Cholelithiasis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Cytolytic hepatitis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Hepatic function abnormal [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Hepatitis toxic [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Hepatotoxicity [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Hyperbilirubinaemia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Portal vein thrombosis [A] †	1/1126 (0.09%)	2/1145 (0.17%)	1/1135 (0.09%)
Immune system disorders			
Anaphylactic reaction [A] †	0/1126 (0%)	3/1145 (0.26%)	0/1135 (0%)
Anaphylactic shock [A] †	2/1126 (0.18%)	0/1145 (0%)	1/1135 (0.09%)
Anaphylactiod reaction [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Drug hypersensitivity [A] †	5/1126 (0.44%)	3/1145 (0.26%)	1/1135 (0.09%)
Hypersensitivity [A] †	3/1126 (0.27%)	1/1145 (0.09%)	1/1135 (0.09%)
Infections and infestations			
Abdominal abscess [A] †	2/1126 (0.18%)	4/1145 (0.35%)	2/1135 (0.18%)
Abdominal infection [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Abdominal wall abscess [A] †	0/1126 (0%)	2/1145 (0.17%)	1/1135 (0.09%)
Abscess [A] †	0/1126 (0%)	2/1145 (0.17%)	0/1135 (0%)
Anal abscess [A] †	0/1126 (0%)	3/1145 (0.26%)	1/1135 (0.09%)
Appendicitis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Appendicitis perforated [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Aspergillosis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Bacteraemia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Bronchopneumonia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Bronchopulmonary aspergillosis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Campylobacter infection [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Candida sepsis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Catheter site cellulitis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Catheter site infection [A] †	4/1126 (0.36%)	4/1145 (0.35%)	0/1135 (0%)
Cellulitis [A] †	3/1126 (0.27%)	0/1145 (0%)	1/1135 (0.09%)
Cholecystitis infective [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Clostridial infection [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Clostridium difficile colitis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Device related infection [A] †	8/1126 (0.71%)	12/1145 (1.05%)	4/1135 (0.35%)
Device related sepsis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	1/1135 (0.09%)
Diverticulitis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Enteritis infection [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Erysipelas [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Gastroenteritis [A] †	1/1126 (0.09%)	5/1145 (0.44%)	3/1135 (0.26%)
Gastroenteritis norovirus [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Gastroenteritis viral [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Hepatitis viral [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Herpes zoster [A] †	1/1126 (0.09%)	0/1145 (0%)	1/1135 (0.09%)
Herpes zoster ophthalmic [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Incision site cellulitis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Infection [A] †	5/1126 (0.44%)	3/1145 (0.26%)	1/1135 (0.09%)
Intervertebral discitis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Intestinal fistual infection [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Klebsiella bacteraemia [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Klebsiella infection [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Lower respiratory tract infection [A] †	3/1126 (0.27%)	2/1145 (0.17%)	0/1135 (0%)
Lower respiratory tract infection viral [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Neutropenic infection [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Neutropenic sepsis [A] †	4/1126 (0.36%)	1/1145 (0.09%)	1/1135 (0.09%)
Oral candidiasis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Orchitis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Overgrowth bacterial [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Pelvic abscess [A] †	0/1126 (0%)	2/1145 (0.17%)	0/1135 (0%)
Perineal abscess [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Pharyngitis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Pneumonia [A] †	3/1126 (0.27%)	4/1145 (0.35%)	5/1135 (0.44%)
Post procedural infection [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Postoperative abscess [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Psoas abscess [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Puncture site infection [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Respiratory tract infection [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Sepsis [A] †	4/1126 (0.36%)	3/1145 (0.26%)	3/1135 (0.26%)
Septic shock [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Skin infection [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Staphylococcal bacteraemia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Staphylococcal sepsis [A] †	1/1126 (0.09%)	0/1145 (0%)	2/1135 (0.18%)
Subcutaneous abscess [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Tooth abscess [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Tuberculosis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Upper respiratory tract infection [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Urinary tract infection [A] †	2/1126 (0.18%)	5/1145 (0.44%)	4/1135 (0.35%)
Viral infection [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Wound abscess [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Wound infection [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Injury, poisoning and procedural complications			
Accident at work [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Anastomotic stenosis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Brachial plexus injury [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Cervical vertebral fracture [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Drug toxicity [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Fall [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Femur fracture [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Foot fracture [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Head injury [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Incisional hernia [A] †	1/1126 (0.09%)	2/1145 (0.17%)	2/1135 (0.18%)
Joint dislocation [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Multiple fractures [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Post procedural fistula [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Post procedural haemorrhage [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Procedural site reaction [A] †	0/1126 (0%)	0/1145 (0%)	2/1135 (0.18%)
Road traffic accident [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Subdural haematoma [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Thoracic vertebral fracture [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Tibia fracture [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Investigations			
Blood creatinine increased [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Blood glucose fluctuation [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Blood lactate dehydrogenase increased [A] †	1/1126 (0.09%)	0/1145 (0%)	1/1135 (0.09%)
Weight increased [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Metabolism and nutrition disorders			
Decreased appetite [A] †	0/1126 (0%)	1/1145 (0.09%)	2/1135 (0.18%)
Dehydration [A] †	7/1126 (0.62%)	10/1145 (0.87%)	17/1135 (1.5%)
Diabetes mellitus [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Diabetic ketoacidosis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Gout [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Hypercholesterolaemia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Hyperglycaemia [A] †	3/1126 (0.27%)	4/1145 (0.35%)	2/1135 (0.18%)
Hypertriglyceridaemia [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Hypocalcaemia [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Hypokalaemia [A] †	2/1126 (0.18%)	3/1145 (0.26%)	2/1135 (0.18%)
Hypomagnesaemia [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Hyponatraemia [A] †	0/1126 (0%)	2/1145 (0.17%)	0/1135 (0%)
Musculoskeletal and connective tissue disorders			
Intervertebral disc protusion [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Muscle spasms [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Muscular weakness [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Musculoskeletal chest pain [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Musculoskeletal disorder [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Musculoskeletal pain [A] †	1/1126 (0.09%)	1/1145 (0.09%)	1/1135 (0.09%)
Myalgia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Pain in extremity [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign lung neoplasm [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Breast cancer [A] †	1/1126 (0.09%)	0/1145 (0%)	1/1135 (0.09%)
Nervous system disorders			
Cerebral ischaemia [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Cerebrovascular accident [A] †	0/1126 (0%)	2/1145 (0.17%)	1/1135 (0.09%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Convulsion [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Dizziness [A] †	2/1126 (0.18%)	0/1145 (0%)	0/1135 (0%)
Dysaesthesia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Encephalopathy [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Epilepsy [A] †	0/1126 (0%)	0/1145 (0%)	2/1135 (0.18%)
Headache [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Ischaemic stroke [A] †	0/1126 (0%)	0/1145 (0%)	2/1135 (0.18%)
Leukoaraiosis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Loss of consciousness [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Migraine [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Monoparesis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Neuropathy peripheral [A] †	1/1126 (0.09%)	1/1145 (0.09%)	1/1135 (0.09%)
Neurotoxicity [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Orthostatic intolerance [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Paraesthesia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Peripheral sensory neuropathy [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Post herpetic neuralgia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Reversible ischaemic neurological deficit [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Reversible posterior leukoencephalopathy syndrome [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Sensory disturbance [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Somnolence [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Speech disorder [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Syncope [A] †	2/1126 (0.18%)	5/1145 (0.44%)	1/1135 (0.09%)
Transient ischaemic attack [A] †	1/1126 (0.09%)	3/1145 (0.26%)	2/1135 (0.18%)
Psychiatric disorders			
Alcoholism [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Anxiety [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Depression [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Renal and urinary disorders			
Acute prerenal failure [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Calculus ureteric [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Calculus urinary [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Hydronephrosis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	1/1135 (0.09%)
Nephrogenic diabetes insipidus [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Nephrotic syndrome [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Renal failure [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Renal failure acute [A] †	2/1126 (0.18%)	1/1145 (0.09%)	0/1135 (0%)
Renal impairment [A] †	0/1126 (0%)	1/1145 (0.09%)	1/1135 (0.09%)
Ureteric stenosis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Reproductive system and breast disorders			
Female genital tract fistula [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Prostatitis [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Vaginal haemorrhage [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Respiratory, thoracic and mediastinal disorders			

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Acute respiratory distress syndrome [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Bronchospasm [A] †	0/1126 (0%)	1/1145 (0.09%)	2/1135 (0.18%)
Dysaesthesia pharynx [A] †	0/1126 (0%)	0/1145 (0%)	3/1135 (0.26%)
Dyspnoea [A] †	2/1126 (0.18%)	3/1145 (0.26%)	2/1135 (0.18%)
Epistaxis [A] †	0/1126 (0%)	3/1145 (0.26%)	1/1135 (0.09%)
Interstitial lung disease [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Laryngospasm [A] †	0/1126 (0%)	0/1145 (0%)	3/1135 (0.26%)
Organising pneumonia [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Pneumonia aspiration [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Pneumothorax [A] †	1/1126 (0.09%)	2/1145 (0.17%)	0/1135 (0%)
Pulmonary artery thrombosis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Pulmonary embolism [A] †	11/1126 (0.98%)	15/1145 (1.31%)	10/1135 (0.88%)
Pulmonary oedema [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Respiratory failure [A] †	0/1126 (0%)	0/1145 (0%)	2/1135 (0.18%)
Skin and subcutaneous tissue disorders			
Angioedema [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Drug eruption [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Palmar-Plantar [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Swelling face [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Urticaria [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Social circumstances			
Pregnancy of partner [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Surgical and medical procedures			
Central venous catheter removal [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Vascular disorders			
Arterial stenosis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Arterial thrombosis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Arterial thrombosis limb [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Axillary vein thrombosis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Deep vein thrombosis [A] †	9/1126 (0.8%)	16/1145 (1.4%)	12/1135 (1.06%)
Hypertension [A] †	1/1126 (0.09%)	2/1145 (0.17%)	13/1135 (1.15%)
Hypertensive crisis [A] †	0/1126 (0%)	3/1145 (0.26%)	1/1135 (0.09%)
Hypotension [A] †	0/1126 (0%)	2/1145 (0.17%)	1/1135 (0.09%)
Jugular vein thrombosis [A] †	2/1126 (0.18%)	3/1145 (0.26%)	0/1135 (0%)
Pelvic venous thrombosis [A] †	0/1126 (0%)	0/1145 (0%)	1/1135 (0.09%)
Peripheral ischaemia [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Phlebitis [A] †	0/1126 (0%)	1/1145 (0.09%)	0/1135 (0%)
Subclavian vein thrombosis [A] †	1/1126 (0.09%)	2/1145 (0.17%)	2/1135 (0.18%)
Thrombophlebitis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Thrombophlebitis superficial [A] †	1/1126 (0.09%)	0/1145 (0%)	0/1135 (0%)
Thrombosis [A] †	1/1126 (0.09%)	1/1145 (0.09%)	0/1135 (0%)
Venous thrombosis [A] †	3/1126 (0.27%)	5/1145 (0.44%)	1/1135 (0.09%)
Venous thrombosis limb [A] †	0/1126 (0%)	3/1145 (0.26%)	2/1135 (0.18%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (13.0)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	1112/1126 (98.76%)	1127/1145 (98.43%)	1117/1135 (98.41%)
Blood and lymphatic system disorders			
Anaemia [A] †	116/1126 (10.3%)	89/1145 (7.77%)	74/1135 (6.52%)
Leukopenia [A] †	79/1126 (7.02%)	55/1145 (4.8%)	34/1135 (3%)
Neutropenia [A] †	660/1126 (58.61%)	567/1145 (49.52%)	273/1135 (24.05%)
Thrombocytopenia [A] †	331/1126 (29.4%)	115/1145 (10.04%)	99/1135 (8.72%)
Eye disorders			
Lacrimation increased [A] †	70/1126 (6.22%)	69/1145 (6.03%)	35/1135 (3.08%)
Gastrointestinal disorders			
Abdominal pain [A] †	220/1126 (19.54%)	227/1145 (19.83%)	214/1135 (18.85%)
Abdominal pain upper [A] †	86/1126 (7.64%)	118/1145 (10.31%)	113/1135 (9.96%)
Constipation [A] †	308/1126 (27.35%)	324/1145 (28.3%)	219/1135 (19.3%)
Diarrhoea [A] †	620/1126 (55.06%)	699/1145 (61.05%)	699/1135 (61.59%)
Dyspepsia [A] †	126/1126 (11.19%)	162/1145 (14.15%)	84/1135 (7.4%)
Haemorrhoids [A] †	29/1126 (2.58%)	68/1145 (5.94%)	41/1135 (3.61%)
Nausea [A] †	725/1126 (64.39%)	761/1145 (66.46%)	720/1135 (63.44%)
Stomatitis [A] †	310/1126 (27.53%)	360/1145 (31.44%)	246/1135 (21.67%)
Vomiting [A] †	385/1126 (34.19%)	394/1145 (34.41%)	460/1135 (40.53%)
General disorders			
Asthenia [A] †	241/1126 (21.4%)	251/1145 (21.92%)	250/1135 (22.03%)
Fatigue [A] †	404/1126 (35.88%)	425/1145 (37.12%)	355/1135 (31.28%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Mucosal inflammation [A] †	85/1126 (7.55%)	85/1145 (7.42%)	57/1135 (5.02%)
Oedema peripheral [A] †	54/1126 (4.8%)	62/1145 (5.41%)	45/1135 (3.96%)
Pyrexia [A] †	186/1126 (16.52%)	185/1145 (16.16%)	106/1135 (9.34%)
Temperature intolerance [A] †	61/1126 (5.42%)	61/1145 (5.33%)	50/1135 (4.41%)
Immune system disorders			
Drug hypersensitivity [A] †	66/1126 (5.86%)	72/1145 (6.29%)	32/1135 (2.82%)
Infections and infestations			
Nasopharyngitis [A] †	76/1126 (6.75%)	92/1145 (8.03%)	70/1135 (6.17%)
Upper respiratory tract infection [A] †	52/1126 (4.62%)	87/1145 (7.6%)	55/1135 (4.85%)
Investigations			
Weight decreased [A] †	26/1126 (2.31%)	56/1145 (4.89%)	61/1135 (5.37%)
Weight increased [A] †	58/1126 (5.15%)	81/1145 (7.07%)	68/1135 (5.99%)
Metabolism and nutrition disorders			
Decreased appetite [A] †	268/1126 (23.8%)	324/1145 (28.3%)	295/1135 (25.99%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] †	63/1126 (5.6%)	140/1145 (12.23%)	122/1135 (10.75%)
Back pain [A] †	79/1126 (7.02%)	87/1145 (7.6%)	66/1135 (5.81%)
Musculoskeletal pain [A] †	35/1126 (3.11%)	86/1145 (7.51%)	46/1135 (4.05%)
Myalgia [A] †	39/1126 (3.46%)	70/1145 (6.11%)	56/1135 (4.93%)
Pain in extremity [A] †	63/1126 (5.6%)	78/1145 (6.81%)	116/1135 (10.22%)
Nervous system disorders			
Dizziness [A] †	102/1126 (9.06%)	117/1145 (10.22%)	79/1135 (6.96%)
Dysaesthesia [A] †	128/1126 (11.37%)	106/1145 (9.26%)	128/1135 (11.28%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Dysgeusia [A] †	237/1126 (21.05%)	222/1145 (19.39%)	152/1135 (13.39%)
Headache [A] †	169/1126 (15.01%)	284/1145 (24.8%)	219/1135 (19.3%)
Lethargy [A] †	44/1126 (3.91%)	50/1145 (4.37%)	59/1135 (5.2%)
Neuropathy peripheral [A] †	252/1126 (22.38%)	234/1145 (20.44%)	204/1135 (17.97%)
Neurotoxicity [A] †	60/1126 (5.33%)	69/1145 (6.03%)	50/1135 (4.41%)
Paraesthesia [A] †	310/1126 (27.53%)	328/1145 (28.65%)	314/1135 (27.67%)
Peripheral sensory neuropathy [A] †	430/1126 (38.19%)	430/1145 (37.55%)	436/1135 (38.41%)
Psychiatric disorders			
Anxiety [A] †	45/1126 (4%)	60/1145 (5.24%)	61/1135 (5.37%)
Insomnia [A] †	135/1126 (11.99%)	132/1145 (11.53%)	91/1135 (8.02%)
Renal and urinary disorders			
Proteinuria [A] †	19/1126 (1.69%)	73/1145 (6.38%)	69/1135 (6.08%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] †	86/1126 (7.64%)	120/1145 (10.48%)	41/1135 (3.61%)
Dysaesthesia pharynx [A] †	37/1126 (3.29%)	28/1145 (2.45%)	79/1135 (6.96%)
Dysphonia [A] †	17/1126 (1.51%)	91/1145 (7.95%)	74/1135 (6.52%)
Dyspnoea [A] †	57/1126 (5.06%)	74/1145 (6.46%)	73/1135 (6.43%)
Epistaxis [A] †	228/1126 (20.25%)	424/1145 (37.03%)	216/1135 (19.03%)
Oropharyngeal pain [A] †	52/1126 (4.62%)	59/1145 (5.15%)	33/1135 (2.91%)
Skin and subcutaneous tissue disorders			
Alopecia [A] †	231/1126 (20.52%)	241/1145 (21.05%)	73/1135 (6.43%)
Dry skin [A] †	52/1126 (4.62%)	66/1145 (5.76%)	50/1135 (4.41%)

	FOLFOX4	FOLFOX4 + Bv	XELOX+Bv
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Palmar-Plantar Erythrodysaesthesia Syndrome [A] †	98/1126 (8.7%)	119/1145 (10.39%)	435/1135 (38.33%)
Pruritus [A] †	36/1126 (3.2%)	65/1145 (5.68%)	28/1135 (2.47%)
Rash [A] †	114/1126 (10.12%)	112/1145 (9.78%)	110/1135 (9.69%)
Vascular disorders			
Hypertension [A] †	196/1126 (17.41%)	472/1145 (41.22%)	468/1135 (41.23%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (13.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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