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ClinicalTrials.gov ID: NCT00069108

Study Identification

Unique Protocol ID:	NO16967
Brief Title:	A Study of Xeloda (Capecitabine) in Patients With Metastatic Colorectal Cancer
Official Title:	An Open-Label Randomized Phase III Study of Intermittent Oral Capecitabine in Combination With Intravenous Oxaliplatin (Q3W) ("XELOX") Versus Bolus and Continuous Infusion Fluorouracil/ Intravenous Leucovorin With Intravenous Oxaliplatin (Q2W) ("FOLFOX4") as Treatment for Patients With Metastatic Colorectal Cancer Who Have Received Prior Treatment With CPT-11 in Combination With 5-FU/LV as First Line Therapy
Secondary IDs:	

Study Status

Record Verification:	March 2016
Overall Status:	Completed
Study Start:	July 2003 []
Primary Completion:	August 2006 [Actual]
Study Completion:	August 2006 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Unapproved/Uncleared Device:	No
U.S. FDA IND/IDE:	Yes
IND/IDE Information:	FDA Center: CDER IND/IDE Number: 45,305 Serial Number: S-412 Has Expanded Access: No
Human Subjects Review:	Board Status: Approved
Data Monitoring:	
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary:	This 2 arm study will assess the efficacy and safety of intermittent oral Xeloda, or iv fluorouracil/leucovorin, in combination with intravenous Eloxatin (oxaliplatin) in patients previously treated for metastatic colorectal cancer. Patients will be randomized to receive either 1)XELOX (Xeloda 1000mg/m2 po bid on days 1-15 + oxaliplatin) in 3 week cycles or 2) FOLFOX-4 (oxaliplatin + leucovorin + 5-FU in 2 week cycles. The anticipated time on study treatment is until disease progression, and the target sample size is 500+ individuals.
Detailed Description:	

Conditions

Conditions:	Colorectal Cancer
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3

Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	627 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: XELOX Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).	Drug: Oxaliplatin As prescribed, in 3 week cycles Drug: capecitabine [Xeloda] 1000mg/m2 po bid on days 1-15 of each 3 week cycle
Active Comparator: FOLFOX-4 Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m^2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).	Drug: 5 FU As prescribed, in 2 week cycles Drug: Leucovorin As prescribed, in 2 week cycles Drug: Oxaliplatin As prescribed, in 2 week cycles

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- adult patients >=18 years of age;
- metastatic colorectal cancer;
- >=1 target lesion;
- failed first-line chemotherapy with 5-fluorouracil and irinotecan.

Exclusion Criteria:

- previous treatment with oxaliplatin;
- progressive or recurrent disease during or within 6 months of completion of first-line chemotherapy;
- >=1 previous chemotherapeutic agent or systemic anticancer regimen for metastatic disease.

Contacts/Locations

Central Contact Person: Reference Study ID Number: NO16967 www.roche.com/about_roche/roche_worldwide.htm
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IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Study Results

Participant Flow

Recruitment Details	The study was conducted from 09 Jul 2003 to 31 Aug 2006 at 87 centers in 19 countries.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Overall Study

	XELOX	FOLFOX-4
Started	313	314
Completed	100	95
Not Completed	213	219
Withdrawal by Subject	5	9
Adverse Event	64	42
Death	6	6
Administration	15	4
Insufficient therapy	117	144

	XELOX	FOLFOX-4
Violation criteria	1	4
Refused treatment	5	10

Baseline Characteristics

Baseline Analysis Population Description

All participants with written informed consent who were randomized to one of the two study arms were included in the Intent-to-treat (ITT) population. Participants in this population were analyzed according to the arm to which they were randomized

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 IV infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Baseline Measures

		XELOX	FOLFOX-4	Total
Overall Number of Participants		313	314	627
Age, Continuous Mean (Standard Deviation) Unit of measure: Years	Number Analyzed	313 participants	314 participants	627 participants
		60.7 (9.91)	59.7 (10.55)	60.2 (10.24)

		XELOX	FOLFOX-4	Total
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	313 participants	314 participants	627 participants
	Female	119 38.02%	123 39.17%	242 38.6%
	Male	194 61.98%	191 60.83%	385 61.4%

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression Free Survival
Measure Description	Progression free survival (PFS) is defined as the time from the date of randomization to the day of documented disease progression or death from any cause. It was based on tumor assessments made according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0, wherein progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter (LD) of the target lesions (TLs), taking as reference the smallest sum LD recorded since the treatment started or appearance of one or more new lesions or unequivocal progression of existing non-target lesions. Participants with neither disease progression nor death were censored at the last date of the last tumor assessment confirming that they had not progressed. Participants with no tumor assessments after baseline but who were still alive at the time of the clinical cut-off were censored at date of randomization
Time Frame	Up to 3 years

Analysis Population Description

The per protocol (PP) population included randomized participants who received at least one dose of capecitabine, 5-FU, or oxaliplatin, or who did not had a major violation of protocol inclusion or exclusion criteria assessments.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).

	Description
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	251	252
Progression Free Survival Median (95% Confidence Interval) Unit of measure: days	154 (140 to 175)	168 (145 to 182)

Statistical Analysis 1 for Progression Free Survival

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Non-Inferiority or Equivalence (legacy)
	Comments	The pre-specified non-inferiority margin (1.30) was compared with the upper limit of the 95% confidence interval (CI) of the hazard ratio (HR, XELOX vs FOLFOX-4) in the population

Statistical Test of Hypothesis	P-Value	0.00584
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.03
	Confidence Interval	(2-Sided) 95% 0.87 to 1.24

	Estimation Comments	The pre-specified non-inferiority margin (1.30) was compared with the upper limit of the 95% confidence interval (CI) of the hazard ratio (HR, XELOX vs FOLFOX-4) in the population

2. Secondary Outcome Measure:

Measure Title	Progression Free Survival Based on Independent Review Committee Assessment
Measure Description	Progression free survival (PFS) is defined as the time from the date of randomization to the day of documented disease progression or death from any cause. It was based on tumor assessments made according to the RECIST version 1.0, wherein PD was defined as at least a 20% increase in the sum of the LD of the TLs, taking as reference the smallest sum LD recorded since the treatment started or appearance of one or more new lesions or unequivocal progression of existing non-TLs. Participants with neither disease progression nor death were censored at the last date of the last tumor assessment confirming that they had not progressed. Participants with no tumor assessments after baseline but who were still alive at the time of the clinical cut-off were censored at date of randomization. This PFS evaluation was based on Independent Review Committee Assessment.
Time Frame	Up to 3 years

Analysis Population Description

PP population excluded randomized participants who did not receive at least one dose of Capecitabine, 5-FU, or Oxaliplatin, or who had a major violation of protocol inclusion or exclusion criteria.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	251	252

	XELOX	FOLFOX-4
Progression Free Survival Based on Independent Review Committee Assessment Median (95% Confidence Interval) Unit of measure: days	168 (139 to 183)	162 (141 to 179)

Statistical Analysis 1 for Progression Free Survival Based on Independent Review Committee Assessment

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Non-Inferiority or Equivalence (legacy)
	Comments	While the study was not designed to demonstrate non-inferiority in PFS based on IRC assessments the pre-specified margin (1.30) was compared with the upper limit of the 95% confidence interval (CI) of the hazard ratio (HR, XELOX vs FOLFOX-4) in the population.

Statistical Test of Hypothesis	P-Value	0.00223
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.93
	Confidence Interval	(2-Sided) 95% 0.74 to 1.17
	Estimation Comments	The pre-specified non-inferiority margin (1.30) was compared with the upper limit of the 95% confidence interval (CI) of the hazard ratio (HR, XELOX vs FOLFOX-4) in the population

3. Secondary Outcome Measure:

Measure Title	Progression Free Survival Based on Treatment Analysis- Intent To Treat Population

Measure Description	Progression free survival (PFS) is defined as the time from date of randomization to day of documented disease progression or death from any cause. It was based on tumor assessments made according to the RECIST version 1.0, wherein PD was defined as at least a 20% increase in the sum of LD of the TLs, taking as reference the smallest sum LD recorded since the treatment started or appearance of one or more new lesions or unequivocal progression of existing non-TLs. Participants with neither disease progression nor death were censored at the last date of the last tumor assessment confirming that they had not progressed. Participants with no tumor assessments after baseline but who were still alive at the time of the clinical cut-off were censored at date of randomization. PFS was analyzed using an on-treatment approach included only disease progression and death that occurred no later than 28 days after the last confirmed intake of study medication in the primary study treatment phase.
Time Frame	Up to 3 years

Analysis Population Description

All participants who were randomized to one of the two study arms were included in the Intent To Treat (ITT) population. Participants were analyzed according to the arm to which they were randomized.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	313	314
Progression Free Survival Based on Treatment Analysis- Intent To Treat Population Median (95% Confidence Interval) Unit of measure: days	145 (137 to 169)	152 (137 to 172)

Statistical Analysis 1 for Progression Free Survival Based on Treatment Analysis- Intent To Treat Population

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.11
	Confidence Interval	(2-Sided) 95% 0.91 to 1.37
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Progression Free Survival Based on Treatment Analysis- Per Population
Measure Description	Progression free survival (PFS) is defined as the time from the date of randomization to the day of documented disease progression or death from any cause. It was based on tumor assessments made according to the RECIST version 1.0, wherein PD was defined as at least a 20% increase in the sum of the LD of the TLs, taking as reference the smallest sum LD recorded since the treatment started or appearance of one or more new lesions or unequivocal progression of existing non-TLs. Participants with neither disease progression nor death were censored at the last date of the last tumor assessment confirming that they had not progressed. Participants with no tumor assessments after baseline but who were still alive at the time of the clinical cut-off were censored at date of randomization
Time Frame	Up to 3 years

Analysis Population Description

The PP population included randomized participants who received at least one dose of Capecitabine, 5-FU, or Oxaliplatin, or who did not had a major violation of protocol inclusion or exclusion criteria assessments.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).

	Description
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	251	252
Progression Free Survival Based on Treatment Analysis- Per Population Median (95% Confidence Interval) Unit of measure: days	153 (139 to 172)	164 (142 to 175)

Statistical Analysis 1 for Progression Free Survival Based on Treatment Analysis- Per Population

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.18
	Confidence Interval	(2-Sided) 95% 0.95 to 1.47
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Best Overall Response, Investigators' Assessments

Measure Description	Best overall response is best response recorded from start of treatment until disease progression/recurrence where responses include complete response (CR), partial response (PR), or stable disease (SD). CR was defined as disappearance of all TLs, non-TLs along with normalization of tumor marker level. PR is at least 30% decrease in sum of the LD of TLs, taking as reference baseline sum LD. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking reference of smallest sum LD since treatment started. It was dependent on achievement of measurement and confirmation criteria. BOR .i.e. CR or PR was confirmed by repeat assessments performed within 4 weeks. For SD, follow-up assessments had to meet the SD criteria at least once after study entry within 6 to 8 weeks.
Time Frame	Up to 3 years

Analysis Population Description

All participants who were randomized to one of the two study arms were included in the ITT population. Participants in this population were analyzed according to the arm to which they were randomized.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	313	314
Best Overall Response, Investigators' Assessments Measure Type: Number Unit of measure: participants		
Investigator Assessed, Responders	63	55
Investigator assessed-CR	0	2

	XELOX	FOLFOX-4
Investigator assessed-PR	63	53

Statistical Analysis 1 for Best Overall Response, Investigators' Assessments

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.4028
	Comments	p-value is for difference between response rates.
	Method	Chi-squared
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.19
	Confidence Interval	(2-Sided) 95% 0.79 to 1.77
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Best Overall Response, Independent Review Committee Assessment
Measure Description	Best overall response is best response recorded from start of treatment until disease progression/recurrence where responses include CR, PR, or SD. CR was defined as disappearance of all TLs, non-TLs along with normalization of tumor marker level. PR is at least 30% decrease in sum of the LD of TLs, taking as reference baseline sum LD. SD defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking reference of smallest sum LD since treatment started. It was dependent on achievement of measurement and confirmation criteria. BOR .i.e. CR or PR was confirmed by repeat assessments performed within 4 weeks, for SD, follow-up assessments had to meet the SD criteria at least once after study entry within 6 to 8 weeks. This PFS evaluation was based on Independent Review Committee Assessment.
Time Frame	Up to 3 years

Analysis Population Description

All participants who were randomized to one of the two study arms were included in the ITT population. Participants in this population were analyzed according to the arm to which they were randomized.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	313	314
Best Overall Response, Independent Review Committee Assessment Measure Type: Number Unit of measure: participants		
IRC Assessed, Responders	48	39
IRC assessed-CR	0	0
IRC assessed-PR	48	39

Statistical Analysis 1 for Best Overall Response, Independent Review Committee Assessment

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2911
	Comments	p-value is for difference between response rates.
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.28
	Confidence Interval	(2-Sided) 95% 0.81 to 2.01
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival was measured as the time from the date of randomization to the date of death. Participant who were not reported to have died at the time of the analysis were censored using the date they were last known to be alive.
Time Frame	Up to 3 years

Analysis Population Description

All participants who were randomized to one of the two study arms were included in the ITT population. Participants in this population were analyzed according to the arm to which they were randomized.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	313	314
Overall Survival Median (95% Confidence Interval) Unit of measure: days	363 (320 to 412)	382 (323 to 418)

Statistical Analysis 1 for Overall Survival

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Non-Inferiority or Equivalence (legacy)
	Comments	The pre-specified non-inferiority margin (1.30) was compared with the upper limit of the 95% CI of the hazard ratio (HR, XELOX vs FOLFOX-4) in the population.

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.03
	Confidence Interval	(2-Sided) 95% 0.87 to 1.23
	Estimation Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Time To Response
Measure Description	Time to response (TOR) (best response of CR or PR) was measured as the time from randomization to the first date on which the measurement criteria for CR or PR (whichever status was recorded first) were met. CR for TLs was defined as disappearance of all TLs and for non-TLs as disappearance of all non-TLs and normalization of tumor marker level. PR was defined as at least 30% decrease in the sum of the LD of TLs, taking as reference the baseline sum LD.
Time Frame	Up to 3 years

Analysis Population Description

All participants who were randomized to one of the two study arms were included in the ITT population. Participants in this population were analyzed according to the arm to which they were randomized.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	313	314
Time To Response Measure Type: Number Unit of measure: participants		
Week 1-6	13	11
Week 7-12	26	23
Week 13-18	22	18
Week 19-24	2	3

9. Secondary Outcome Measure:

Measure Title	Duration Of Response
Measure Description	Duration of response (DOR) is defined as the time when CR or PR was first met up to first date that PD or death is documented. CR is defined as disappearance of all TLs and non TLs, PR is defined as at least 30% decrease in the sum of the LD of TLs, taking as reference the baseline sum LD. PD was defined as at least a 20% increase in the sum of the LD of the TLs, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions for the TLs or the appearance of one or more new lesions and/or unequivocal progression of existing non-TLs.

Time Frame	Up to 3 years

Analysis Population Description

All participants who were randomized to one of the two study arms were included in the Intent-to-treat (ITT) population. Participants in this population were analyzed according to the arm to which they were randomized.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	313	314
Duration Of Response Median (95% Confidence Interval) Unit of measure: days	169 (142 to 192)	190 (161 to 206)

Statistical Analysis 1 for Duration Of Response

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)

	Estimated Value	1.15
	Confidence Interval	(2-Sided) 95% 0.79 to 1.68
	Estimation Comments	[Not specified]

10. Secondary Outcome Measure:

Measure Title	Time To Treatment Failure
Measure Description	Time to treatment failure was defined as the time from the date of randomization to the first occurrence of adverse event (AE), insufficient therapeutic response, death, failure to return, or refusing treatment/being uncooperative/withdrawing consent.
Time Frame	Up to 3 years

Analysis Population Description

All participants who were randomized and received at least one dose of capecitabine, 5-FU, or oxaliplatin were included in the safety population. The safety population was used for the analyses of all safety parameters.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	311	308

	XELOX	FOLFOX-4
Time To Treatment Failure Median (95% Confidence Interval) Unit of measure: days	125 (106 to 139)	121.5 (101 to 137)

Statistical Analysis 1 for Time To Treatment Failure

Statistical Analysis Overview	Comparison Group Selection	XELOX, FOLFOX-4
	Comments	[Not specified]
	Type of Statistical Test	Superiority or Other (legacy)
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.96
	Confidence Interval	(2-Sided) 95% 0.81 to 1.12
	Estimation Comments	[Not specified]

11. Secondary Outcome Measure:

Measure Title	Number of Participants With Marked Post-baseline Laboratory Abnormalities by Trial Treatment
Measure Description	Laboratory abnormalities were defined as those values that were outside the Roche defined reference range and showed a clinically relevant change from baseline. All laboratory parameters were categorized according to the National Cancer Center Common Toxicity Criteria (NCI-CTCAE) grading system. Incidence of Grade 1 to 4 laboratory abnormalities are presented in the table below.
Time Frame	Up to 3 years

Analysis Population Description

All participants who were randomized and received at least one dose of capecitabine, 5-FU, or oxaliplatin were included in the safety population. The safety population was used for the analyses of all safety parameters

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m^2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

Measured Values

	XELOX	FOLFOX-4
Overall Number of Participants Analyzed	311	308
Number of Participants With Marked Post-baseline Laboratory Abnormalities by Trial Treatment Measure Type: Number Unit of measure: participants		
Serum Glutamic-Pyruvic Transaminase (SGPT)	90	110
Serum Glutamic Oxaloacetic Transaminase (SGOT)	193	174
Alkaline Phosphatase	184	201
Calcium (hyper)	7	9
Calcium (hypo)	68	70
Glucose (hyper)	201	207
Glucose (hypo)	12	9
Granulocytes	1	6
Haemoglobin	216	240
Neutrophils	113	199
Neutrophils/Granulocytes	114	202

	XELOX	FOLFOX-4
Platelets	168	212
Potassium (hyper)	17	26
Potassium (hypo)	68	92
Serum Albumin	116	138
Serum Creatinine	18	32
Sodium (hyper)	14	21
Sodium (hypo)	64	73
Total Bilirubin	107	95
White blood cell (WBC)	124	205

Reported Adverse Events

Time Frame	Up to 3 years
Adverse Event Reporting Description	Serious adverse events and non-serious adverse events are reported in Safety Analysis Set, which consists of all participants who were randomized and received at least one dose of capecitabine, 5-FU, or oxaliplatin and had a safety assessment performed post baseline.

Reporting Groups

	Description
XELOX	Participants received XELOX (oxaliplatin and capecitabine). Oxaliplatin was administered 130 mg/m^2 intravenous (IV) infusion over 2 hours (every 3 weeks [Day 1]) before the first dose of capecitabine. Capecitabine was administered orally within 30 minutes after the end of a meal (breakfast and dinner) 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 up to 8 cycles (24-weeks).
FOLFOX-4	Participants received FOLFOX-4 (combination of oxaliplatin, leucovorin [LV] and 5-fluorouracil [5-FU] combination). Oxaliplatin was administered as an 85 mg/m^2 IV infusion over 2 hours (on Day 1 only); with LV infusion as 200mg/m^2 over 2 hours followed by 5-FU, given as 400mg/m^2 bolus injection over 2-4 minutes, and then as a 600 mg/m^2 continuous infusion over 22 hours. On Day 2, Leucovorin 200 mg/m^2 (alone), followed by 5-FU 400 mg/m^2 bolus injection over 2-4 minutes, and 5-FU 600 mg/m^2 continuous infusion was repeated over 22 hours. It was (2-week cycles comprising 48 hours of infusion and 12 days of rest) for up to 12 cycles (24- weeks).

All-Cause Mortality

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Total All-Cause Mortality	/	/

Serious Adverse Events

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Total	94/311 (30.23%)	97/308 (31.49%)
Blood and lymphatic system disorders		
Anaemia [A] †	1/311 (0.32%)	0/308 (0%)
Coagulopathy [A] †	1/311 (0.32%)	0/308 (0%)
Febrile Neutropenia [A] †	0/311 (0%)	11/308 (3.57%)
Neutropenia [A] †	0/311 (0%)	6/308 (1.95%)
Thrombocytopenia [A] †	2/311 (0.64%)	2/308 (0.65%)
Warm type haemolytic anaemia [A] †	0/311 (0%)	1/308 (0.32%)
Cardiac disorders		
Cardiac failure [A] †	0/311 (0%)	1/308 (0.32%)
Myocardial infarction [A] †	1/311 (0.32%)	1/308 (0.32%)
Ear and labyrinth disorders		
Vertigo [A] †	0/311 (0%)	1/308 (0.32%)
Gastrointestinal disorders		
*Stomatitis all [A] †	0/311 (0%)	1/308 (0.32%)
Abdominal pain [A] †	5/311 (1.61%)	4/308 (1.3%)
Abdominal pain upper [A] †	0/311 (0%)	1/308 (0.32%)
Anal fistula [A] †	0/311 (0%)	1/308 (0.32%)

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Colitis [A] †	1/311 (0.32%)	0/308 (0%)
Colonic pseudo-obstruction [A] †	1/311 (0.32%)	0/308 (0%)
Colonic stenosis [A] †	0/311 (0%)	1/308 (0.32%)
Constipation [A] †	2/311 (0.64%)	0/308 (0%)
Diarrhoea [A] †	18/311 (5.79%)	3/308 (0.97%)
Enteritis [A] †	3/311 (0.96%)	0/308 (0%)
Gastrointestinal haemorrhage [A] †	0/311 (0%)	2/308 (0.65%)
Haematemesis [A] †	1/311 (0.32%)	0/308 (0%)
Ileus [A] †	1/311 (0.32%)	0/308 (0%)
Ileus paralytic [A] †	0/311 (0%)	1/308 (0.32%)
Intestinal Obstruction [A] †	8/311 (2.57%)	4/308 (1.3%)
Large intestinal obstruction [A] †	0/311 (0%)	1/308 (0.32%)
Lower gastrointestinal haemorrhage [A] †	0/311 (0%)	1/308 (0.32%)
Melaena [A] †	0/311 (0%)	1/308 (0.32%)
Nausea [A] †	4/311 (1.29%)	0/308 (0%)
Pancreatitis acute [A] †	1/311 (0.32%)	0/308 (0%)
Rectal haemorrhage [A] †	1/311 (0.32%)	1/308 (0.32%)
Small intestinal obstruction [A] †	4/311 (1.29%)	1/308 (0.32%)
Vomiting [A] †	9/311 (2.89%)	1/308 (0.32%)
General disorders		
Asthenia [A] †	1/311 (0.32%)	1/308 (0.32%)
Catheter related complication [A] †	0/311 (0%)	2/308 (0.65%)

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Fatigue [A] †	1/311 (0.32%)	0/308 (0%)
General physical health deterioration [A] †	0/311 (0%)	1/308 (0.32%)
Pain [A] †	0/311 (0%)	1/308 (0.32%)
Pyrexia [A] †	6/311 (1.93%)	9/308 (2.92%)
Hepatobiliary disorders		
Cholelithiasis [A] †	0/311 (0%)	1/308 (0.32%)
Hepatic failure [A] †	1/311 (0.32%)	0/308 (0%)
Hepatic pain [A] †	1/311 (0.32%)	0/308 (0%)
Hyperbilirubinaemia [A] †	2/311 (0.64%)	0/308 (0%)
Jaundice cholestatic [A] †	1/311 (0.32%)	1/308 (0.32%)
Immune system disorders		
Hypersensitivity [A] †	0/311 (0%)	5/308 (1.62%)
Infections and infestations		
Abdominal abscess [A] †	0/311 (0%)	2/308 (0.65%)
Bacteraemia [A] †	1/311 (0.32%)	0/308 (0%)
Bacterial sepsis [A] †	0/311 (0%)	1/308 (0.32%)
Bronchopneumonia [A] †	0/311 (0%)	1/308 (0.32%)
Central line infection [A] †	2/311 (0.64%)	0/308 (0%)
Clostridium difficile colitis [A] †	0/311 (0%)	1/308 (0.32%)
Diarrhoea infectious [A] †	1/311 (0.32%)	0/308 (0%)
Escherichia bacteraemia [A] †	1/311 (0.32%)	1/308 (0.32%)
Gastroenteritis [A] †	1/311 (0.32%)	1/308 (0.32%)
Gastroenteritis salmonella [A] †	0/311 (0%)	1/308 (0.32%)

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Herpes zoster [A] †	0/311 (0%)	1/308 (0.32%)
Infection [A] †	0/311 (0%)	3/308 (0.97%)
Influenza [A] †	0/311 (0%)	1/308 (0.32%)
Parotitis [A] †	0/311 (0%)	1/308 (0.32%)
Pelvic inflammatory disease [A] †	1/311 (0.32%)	0/308 (0%)
Pneumonia [A] †	0/311 (0%)	3/308 (0.97%)
Pneumonia pneumococcal [A] †	0/311 (0%)	1/308 (0.32%)
Postoperative abscess [A] †	0/311 (0%)	1/308 (0.32%)
Pyelonephritis acute [A] †	1/311 (0.32%)	0/308 (0%)
Sepsis [A] †	2/311 (0.64%)	2/308 (0.65%)
Septic shock [A] †	0/311 (0%)	1/308 (0.32%)
Sinusitis [A] †	0/311 (0%)	1/308 (0.32%)
Streptococcal bacteraemia [A] †	1/311 (0.32%)	0/308 (0%)
Upper respiratory tract infection [A] †	0/311 (0%)	1/308 (0.32%)
Urinary tract infection [A] †	0/311 (0%)	1/308 (0.32%)
Urosepsis [A] †	1/311 (0.32%)	0/308 (0%)
Injury, poisoning and procedural complications		
Hand fracture [A] †	0/311 (0%)	1/308 (0.32%)
Post procedural haemorrhage [A] †	1/311 (0.32%)	0/308 (0%)
Subdural haematoma [A] †	0/311 (0%)	1/308 (0.32%)
Thermal burn [A] †	0/311 (0%)	1/308 (0.32%)
Transfusion reaction [A] †	0/311 (0%)	1/308 (0.32%)
Investigations		

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Weight decreased [A] †	1/311 (0.32%)	0/308 (0%)
Metabolism and nutrition disorders		
Anorexia [A] †	0/311 (0%)	1/308 (0.32%)
Dehydration [A] †	7/311 (2.25%)	5/308 (1.62%)
Hyperglycaemic hyperosmolar nonketotic syndrome [A] †	0/311 (0%)	1/308 (0.32%)
Hyponatraemia [A] †	2/311 (0.64%)	0/308 (0%)
Hypovolaemia [A] †	0/311 (0%)	2/308 (0.65%)
Musculoskeletal and connective tissue disorders		
Back pain [A] †	2/311 (0.64%)	2/308 (0.65%)
Intervertebral disc protrusion [A] †	1/311 (0.32%)	0/308 (0%)
Osteoporotic fracture [A] †	0/311 (0%)	1/308 (0.32%)
Spinal disorder [A] †	0/311 (0%)	1/308 (0.32%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Abdominal neoplasm [A] †	1/311 (0.32%)	0/308 (0%)
Rectal neoplasm [A] †	1/311 (0.32%)	0/308 (0%)
Nervous system disorders		
Convulsion [A] †	1/311 (0.32%)	0/308 (0%)
Headache [A] †	0/311 (0%)	1/308 (0.32%)
Lethargy [A] †	1/311 (0.32%)	0/308 (0%)
Loss of consciousness [A] †	1/311 (0.32%)	0/308 (0%)
Peripheral motor neuropathy [A] †	1/311 (0.32%)	0/308 (0%)
Sciatica [A] †	0/311 (0%)	1/308 (0.32%)

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Vocal cord paralysis [A] †	0/311 (0%)	1/308 (0.32%)
Psychiatric disorders		
Confusional state [A] †	1/311 (0.32%)	0/308 (0%)
Mania [A] †	1/311 (0.32%)	0/308 (0%)
Renal and urinary disorders		
Dysuria [A] †	1/311 (0.32%)	0/308 (0%)
Hydronephrosis [A] †	1/311 (0.32%)	0/308 (0%)
Renal failure acute [A] †	1/311 (0.32%)	0/308 (0%)
Reproductive system and breast disorders		
Female genital tract fistula [A] †	1/311 (0.32%)	0/308 (0%)
Pelvic pain [A] †	0/311 (0%)	1/308 (0.32%)
Respiratory, thoracic and mediastinal disorders		
Bronchospasm [A] †	0/311 (0%)	1/308 (0.32%)
Cough [A] †	1/311 (0.32%)	0/308 (0%)
Dysaesthesia pharynx [A] †	1/311 (0.32%)	0/308 (0%)
Dyspnoea [A] †	1/311 (0.32%)	2/308 (0.65%)
Pleural effusion [A] †	0/311 (0%)	1/308 (0.32%)
Pulmonary embolism [A] †	1/311 (0.32%)	5/308 (1.62%)
Surgical and medical procedures		
Analgesic therapy [A] †	0/311 (0%)	1/308 (0.32%)
Urinary tract operation [A] †	1/311 (0.32%)	0/308 (0%)
Vascular disorders		
Deep vein thrombosis [A] †	3/311 (0.96%)	3/308 (0.97%)

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Haematoma [A] †	1/311 (0.32%)	0/308 (0%)
Peripheral ischaemia [A] †	1/311 (0.32%)	0/308 (0%)
Superior vena caval occlusionq [A] †	0/311 (0%)	1/308 (0.32%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (8.0)

Other Adverse Events

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

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Total	302/311 (97.11%)	298/308 (96.75%)
Blood and lymphatic system disorders		
Anaemia [A] †	19/311 (6.11%)	26/308 (8.44%)
Neutropenia [A] †	56/311 (18.01%)	146/308 (47.4%)
Thrombocytopenia [A] †	39/311 (12.54%)	51/308 (16.56%)
Gastrointestinal disorders		
Abdominal pain [A] †	92/311 (29.58%)	73/308 (23.7%)
Abdominal pain upper [A] †	20/311 (6.43%)	18/308 (5.84%)
Constipation [A] †	50/311 (16.08%)	79/308 (25.65%)
Diarrhoea [A] †	168/311 (54.02%)	148/308 (48.05%)
Dyspepsia [A] †	34/311 (10.93%)	23/308 (7.47%)
Nausea [A] †	185/311 (59.49%)	172/308 (55.84%)
Stomatitis all [A] †	42/311 (13.5%)	92/308 (29.87%)
Vomiting [A] †	132/311 (42.44%)	105/308 (34.09%)
General disorders		

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Asthenia [A] †	60/311 (19.29%)	56/308 (18.18%)
Chills [A] †	9/311 (2.89%)	18/308 (5.84%)
Fatigue [A] †	127/311 (40.84%)	129/308 (41.88%)
Oedema peripheral [A] †	16/311 (5.14%)	28/308 (9.09%)
Pyrexia [A] †	64/311 (20.58%)	68/308 (22.08%)
Temperature intolerance [A] †	15/311 (4.82%)	21/308 (6.82%)
Infections and infestations		
Nasopharyngitis [A] †	14/311 (4.5%)	21/308 (6.82%)
Investigations		
Weight decreased [A] †	19/311 (6.11%)	20/308 (6.49%)
Metabolism and nutrition disorders		
Anorexia [A] †	98/311 (31.51%)	84/308 (27.27%)
Hypokalaemia [A] †	24/311 (7.72%)	17/308 (5.52%)
Musculoskeletal and connective tissue disorders		
Back pain [A] †	32/311 (10.29%)	41/308 (13.31%)
Myalgia [A] †	11/311 (3.54%)	21/308 (6.82%)
Pain in extremity [A] †	19/311 (6.11%)	15/308 (4.87%)
Pain in jaw [A] †	16/311 (5.14%)	12/308 (3.9%)
Nervous system disorders		
Dizziness [A] †	32/311 (10.29%)	29/308 (9.42%)
Dysaesthesia [A] †	32/311 (10.29%)	34/308 (11.04%)
Dysgeusia [A] †	22/311 (7.07%)	33/308 (10.71%)
Headache [A] †	32/311 (10.29%)	32/308 (10.39%)

	XELOX	FOLFOX-4
	Affected/At Risk (%)	Affected/At Risk (%)
Hypoaesthesia [A] †	23/311 (7.4%)	20/308 (6.49%)
Lethargy [A] †	18/311 (5.79%)	19/308 (6.17%)
Neuropathy [A] †	36/311 (11.58%)	29/308 (9.42%)
Neuropathy peripheral [A] †	40/311 (12.86%)	30/308 (9.74%)
Paraesthesia [A] †	103/311 (33.12%)	98/308 (31.82%)
Peripheral sensory neuropathy [A] †	40/311 (12.86%)	50/308 (16.23%)
Psychiatric disorders		
Insomnia [A] †	21/311 (6.75%)	37/308 (12.01%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	21/311 (6.75%)	47/308 (15.26%)
Dysaesthesia pharynx [A] †	32/311 (10.29%)	13/308 (4.22%)
Dyspnoea [A] †	27/311 (8.68%)	30/308 (9.74%)
Epistaxis [A] †	10/311 (3.22%)	22/308 (7.14%)
Pharyngolaryngeal pain [A] †	10/311 (3.22%)	16/308 (5.19%)
Skin and subcutaneous tissue disorders		
Alopecia [A] †	4/311 (1.29%)	19/308 (6.17%)
Palmar-plantar erythrodysaesthesia syndrome [A] †	71/311 (22.83%)	18/308 (5.84%)
Rash [A] †	30/311 (9.65%)	22/308 (7.14%)
Vascular disorders		
Flushing [A] †	8/311 (2.57%)	19/308 (6.17%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (8.0)

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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