Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for capecitabine/ oxaliplatin

Proprietary Product Name: Xeloda/ Eloxatin, Oxaliplatin Dakota, Winthrop Oxaliplatin

Submission No: PM-2010-00909-4/2010-02795-4

Sponsor: Roche Products Pty Ltd/Sanofi-Aventis Australia Pty Ltd

March 2011

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation-Extension of indications and New dosage
Decision:	Approved
Date of Decision:	2 February 2011
Active ingredient(s):	capecitabine /oxaliplatin
Product Name(s):	Xeloda /Eloxatin, Oxaliplatin Dakota, Winthrop Oxaliplatin
Sponsor's Name and Address:	Roche Products Pty Ltd/Sanofi-Aventis Australia Pty Ltd. 12-24 Talavera Rd Macquarie Park NSW 2113
Dose form(s):	Film-coated tablets/concentrate or powder for injection
Strength(s):	150 and 500 mg tablets (capecitabine) 50 100 mg and 200 mg concentrated solution (oxaliplatin) or 50 and 100 mg powder (oxaliplatin)
Container(s):	Blister pack (capecitabine) and glass vial (oxaliplatin)
Approved Therapeutic use:	The full indications for Xeloda: ***Colon Cancer*** *Xeloda is indicated for the adjuvant treatment of patients with Dukes' stage C and high-risk stage B colon cancer, either as monotherapy or in combination with oxaliplatin.* ***Colorectal Cancer*** *Xeloda is indicated for the treatment of advanced or metastatic colorectal cancer.* ***Oesophagogastric Cancer*** *Xeloda is indicated for the first-line treatment of patients with advanced oesophagogastric cancer in combination with a platinum-based regimen.* ***Breast Cancer*** *Xeloda is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen unless therapy with these and other standard agents are clinically contraindicated.* *Xeloda in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.* The full indications for Eloxatin, Oxaliplatin Dakota, Winthrop Oxaliplatin: • *Oxaliplatin is indicated for adjuvant treatment of stage III (Duke's C) colon cancer, in combination with a*

	fluoropyrimidine agent. • *Oxaliplatin in combination with fluorouracil and folinic acid is indicated for the treatment of advanced colorectal cancer.* • *Oxaliplatin in combination with capecitabine, with or without bevacizumab, is indicated for the treatment of patients with metastatic colorectal cancer.* • *Oxaliplatin in combination with epirubicin and either capecitabine or fluorouracil, is indicated for the treatment of patients with advanced oesophagogastric cancer*
Route(s) of administration:	Oral (PO) (capecitabine) and IV (oxaliplatin)
Dosage:	For the combination as adjuvant treatment: capecitabine: 1000 mg/m^2 bd[1] Days 1-14 every 21 days oxaliplatin:- 130 mg/m^2 Day 1 every 21 days: with
ARTG Number (s):	75731 and 75732 (Xeloda) and 101658, 101701, 122549, 122550, 125804, 128862, 128864, 75454 and 75455 (Eloxatin, Oxaliplatin Dakota, Winthrop Oxaliplatin)[2].

Product Background

Capecitabine is an orally active anti-neoplastic agent which, following absorption, is converted to 5-fluorouracil (5-FU). It has been registered in Australia since 1999. Oxaliplatin is platinum anti-neoplastic agent which has been registered in Australia since 2001.

Both agents are approved for the adjuvant treatment of colon cancer and each product was approved on the basis of a single randomised controlled trial ('X-ACT' for capecitabine and 'MOSAIC' for oxaliplatin).

The current application seeks approval for use of the two agents in combination (referred to as 'Xelox') for adjuvant use.

Capecitabine was granted a broad indication, which did not limit use to monotherapy, although data to support use in combination was not provided at the time of approval. The current application therefore seeks only to add new information to the 'Clinical Trials' section of the product information (PI) and no amendment to the existing indication is proposed.

For oxaliplatin, the currently approved indication is limited to use in combination with 5-FU and folinic acid (FA). The current application therefore seeks to extend the approved indication. The revised indication proposed is: *"…. for adjuvant treatment of Stage III (Dukes C) colon cancer."*

The Xelox combination has previously been approved, for both drugs, for use in advanced or metastatic colorectal cancer. The proposed dose for the combination as adjuvant treatment is the same as that approved for use in the advanced/metastatic setting (oxaliplatin 130 mg/m^2 Day 1 every 21 days; with capecitabine 1000 mg/m^2 bd Days 1-14 every 21 days).

Regulatory Status

The status of this submission in various countries and regions around the world is as

[1] bd=twice a day.

[2] Eloxatin (oxaliplatin) 50 mg concentrate solution for injection vial (AUST R 101701) 100 mg concentrate solution for injection vial (AUST R 101658) 200 mg concentrate solution for injection vial (AUST R 125804) 50mg powder for injection vial (AUST R 75455) 100mg powder for injection vial (AUST R 75454) Oxaliplatin Dakota (oxaliplatin) 50mg powder for injection vial (AUST R 128862) 100mg powder for injection vial (AUST R 128864) Winthrop Oxaliplatin (oxaliplatin) 50mg powder for injection vial (AUST R 122550) 100mg powder for injection vial (AUST R 122549)

follows:

Country	Submitted	Status
European Union (centralised procedure)	28 November 2009	Approved 31 March 2010
Switzerland*	5 January 2010	Under evaluation
Canada	31 March 2010	Under evaluation

** EU Data package submitted*

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

No new data were submitted with the current Australian submission.

III. Nonclinical Findings

No new data were submitted with the current Australian submission.

IV. Clinical Findings

Introduction

A new study, conducted in the adjuvant setting of colon cancer, Study NO16968, using a combination of capecitabine and oxaliplatin (Xelox) and final results of a previously evaluated meta-analysis (FUM meta-analysis) of six clinical trials in various gastrointestinal cancers were submitted. A post-marketing safety report, Report no. 1034982, has also been reviewed.

At the ADEC meeting of the 1st February 2008, a new study which evaluated the combination of capecitabine and oxaliplatin, that is, Xelox, in patients with previously untreated advanced or metastatic colorectal cancer was approved. Resolution 9157 indicated that there would be no objection to approval of the submission from Roche Products Pty Ltd to register new dosage regimen for the treatment of advanced or metastatic colorectal cancer for Xeloda tablet containing capecitabine 150mg and 500mg for the indication: the dosage regimen in combination with oxaliplatin with or without Bevacizumab (BV) 1000 mg/m^2 twice daily on Days 1-14 of a 21 day cycle.

The pivotal study for the previous approval examined efficacy in first-line treatment in metastatic colorectal cancer by comparing Xelox with Folfox4 (5-FU, Folinic Acid and oxaliplatin) with the aim of establishing non-inferiority and also comparing BV with placebo with the aim of demonstrating superiority of BV. The primary endpoint for the study was progression free survival (PFS) as assessed by the investigator who was not blinded to treatment allocations. Non-inferiority on this endpoint was demonstrated. A secondary endpoint was PFS as assessed by an independent review committee (IRC) who were blinded to treatment allocation. Non-inferiority could not be concluded on this endpoint. There were no differences between Xelox and Folfox4 regimens in the secondary endpoints of overall survival and overall response rates. In regards to safety, the safety profile of Xelox regimen was consistent across the two studies. Overall the toxicity of the Xelox and Folfox4 regimens were comparable with similar incidences of adverse events, serious adverse events (SAEs), Grade III or IV adverse events, discontinuation to adverse events and treatment related deaths. The pattern of toxicity was different for the two regimens with less bone marrow toxicity and stomatitis in the Xelox arms but more gastrointestinal toxicity, particularly diarrhoea and hand/foot syndrome.

On this background, together with the fact that capecitabine has previously been demonstrated to be equivalent in efficacy and safety to 5-FU and folinic acid in the adjuvant setting for colon cancer, a

new study, Study NO16968, an open labelled randomised Phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin (Xelox) versus 5-FU/Leucovorin as adjuvant therapy for patients who have undergone surgery for colon cancer (Duke's Stage C) was undertaken to determine whether better outcome for patients could be achieved if they were offered Xelox as adjuvant treatment.

At the time the trial was initiated, the standard of care for adjuvant treatment for colon cancer was 6-8 months of therapy with either 5-FU or Folinic acid (LV) or Xeloda. It is noteworthy that the regimens of 5-FU/LV utilised in the adjuvant setting internationally included two regimens; the Mayo Clinic regimen which is five days every four weeks of 5-FU/LV and the Roswell Park regimen, which is weekly 5-FU/LV for six consecutive weeks followed by two weeks of rest. Accordingly in the design of Study NO16968 these two regimens were considered to be essentially equivalent and therefore relevant comparators to the study combination of Xelox.

Associated with the approval of the oesophagogastric cancer application in Europe, Roche committed to conducting a safety meta-analysis of the data base representing studies described within the approved Product Information (PI) as well as several ongoing pivotal studies with a total of 13 studies involved. The objective was to investigate factors causing hand/foot syndrome (HFS) and other major adverse events (AEs) as well as correlation of these AEs with efficacy.

The results of this meta-analysis have been previously submitted in earlier applications and this safety meta-analysis has now been updated to include the results of Study in NO16968.

In the context of the above meta-analysis, Roche was also requested to conduct an efficacy meta-analysis on six pivotal gastrointestinal cancer clinical trials. The objective of this analysis was to support the conclusion that capecitabine could replace 5-FU in monotherapy and in combination therapies in gastrointestinal cancer. This data provides a survival update based on a pre-planned analysis.

Review of a post-marketing safety report, Report no. 1034982, which covers the period between the 1st November 2007 and the 31st October 2008, is provided for review.

Good Clinical Practice Aspects:
All requirements for full conformance with Good Clinical Practice (GCP) were undertaken in relation to the pivotal trial NO16968 this included review by Ethics review committees and institutional review board at the participating centres prior to study initiation and appropriate approval for protocol, informed consent forms and accompanying material to be given to patients. Written informed consent was obtained for patients who decided to participate in this study.

An independent drug and safety committee thoroughly reviewed the safety data during the conduct of the study and concluded the study was well conducted and there were no safety concerns.

Pharmacokinetics

There are no data presented in this evaluation in relation to pharmacokinetics.

Drug Interactions

There are no data presented in this evaluation in relation to drug interactions.

Pharmacodynamics

There is no data presented in this evaluation in relation to pharmacodynamics.

Efficacy/Safety

The clinical evaluator considered that the most efficient way of presenting the data for this evaluation is to present separately efficacy and safety data for the pivotal Study NO16968, the FUM meta-analysis and the post-marketing safety report (1034982).

Study NO16968:

Study NO16968 was an open label randomised multicentre multi-national Phase III study designed to assess the efficacy and safety of Xelox as adjuvant treatment of patients who underwent surgery for Stage III colon cancer and were naive to chemotherapy.

Patients eligible for this study were men and women with histologically confirmed colon cancer, Stage III (Duke's Stage C) that was recently resected with curative intent and no macroscopic or microscopic evidence of remaining tumour. Patients would have to be ambulatory (ECOG performance status of 0-1[3]) and should never have had any evidence of metastatic disease nor have received chemotherapy for their colon cancer.

The study was conducted at 226 global investigational sites in 29 countries. The enrolment of approximately 1850 patients was planned. A total of 1886 patients were randomised on a 1:1 basis to receive either Xelox or bolus 5-FU/LV according to the Mayo Clinic or Roswell Park regimens. The randomisation was stratified by geographic region, 5-FU/LV regimen (Mayo Clinic versus Roswell Park), baseline Carcinoembryonic Antigen (CEA) levels (normal versus abnormal), number of positive lymph nodes (=/<3 versus =/>4) and lymph nodes by region interaction (using cross classification of the two factors above).

The patients would have been randomised within 11 weeks of surgical resection of colon cancer. The trial had two main phases: a treatment phase and a follow-up phase. In the treatment phase patients were to be treated for 24 or 32 weeks depending on the regimen chosen. The follow-up phase began when patients either completed or terminated study treatments. Patients were to be followed for recurrence of the original colon cancer or development of a new colon or rectal cancer and survival until death or the last date the patient was known to be alive until two years after primary efficacy analysis took place.

This assessment for recurrence of the original colon cancer, or development of a new colon or rectal cancer, was conducted before randomisation and six months after randomisation. Further assessment time points for recurrence of the original colon cancer or development of a new colon or rectal cancer and survival were at one year, then six monthly to four years after randomisation and yearly thereafter. Non-scheduled assessments for relapse/new occurrence of colorectal cancer occurred as clinically indicated.

Dose modifications including dose reductions, treatment interruptions and cycle delays were prescribed based on adverse events. Those patients who experienced a relapse, developed a new colon or rectal cancer during therapy or experienced unacceptable toxicity were taken off the study treatment. For patients in the Xelox arm, capecitabine could have been administered as monotherapy if oxaliplatin treatment was discontinued due to toxicity or patient refusal.

The primary analysis was to have been conducted when 682 events for the disease free survival (DFS) analysis had been reached in the intent to treat (ITT) population and across both treatment arms. A data cut-off date of April 30, 2009 was chosen based on the estimation that 682 events would be collected; however after closure of the database only 648 events were confirmed. The trial was still sufficiently powered to detect superiority of Xelox. At the time of primary analysis,

---

[3] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction; 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 – Dead.

median observation time was approximately 57 months for DFS and approximately 59 months for overall survival (OS).

The primary efficacy parameter was DFS, which was defined as the time from the data randomisation to the time of first event (relapse from the original colon cancer, development of a new colon or rectal cancer or death due to any cause). Determination of an event was based on tumour assessment, survival and follow-up assessments. Any recurrence of the original cancer or appearance of a new colon or rectal cancer was to be proved by cytology or histology when possible. Isolated events of increased CEA or unexplained clinical deterioration were not considered to be evidence of relapse without support of other objective measurements. The date of relapse was defined as the date of definitive assessment by an objective measurement.

Secondary efficacy parameters included relapse free survival (RFS) which was similar to DFS but included only recurrence of the original colon cancer, development of a new colon or rectal cancer or deaths related to any of the following: treatment, recurrence of the original colon cancer or development of a new colon or rectal cancer. In addition, overall survival (OS) was defined as the time from randomisation to date of death due to any cause or the last day of which a patient was known to be alive.

The primary analysis was based on the ITT population, which included all randomised patients and employed the log rank test for comparing DFS distribution of the two treatment arms with a two-sided significance level 5% covariate. For the secondary analysis of DFS, a Cox-proportional hazards regression model was utilised with treatment as the only covariate to measure the hazard ratio (HR) and its 95% confidence interval (CI). This analysis was also repeated for the per protocol population which excluded randomised patients who did not receive at least one dose of treatment or had a major violation of protocol.

For the analysis of the secondary endpoints, that is, RFS and OS, the same statistical methods were used as for the primary endpoint (DFS).

Sub-group analyses were performed for the three endpoints with the following variables applied; randomisation stratification factors and baseline factors of gender, age, laparoscopic versus open surgery before randomisation, number of lymph nodes reported, geographic region and ethnicity.

Prognostic factor analyses were performed using the Cox-proportional hazard regression analyses (multivariate and univariate) for the three endpoints to confirm the robustness of the results of the primary and secondary analyses.

In relation to safety, safety parameters evaluated included adverse events, laboratory parameters and vital signs. The intensity of adverse events and laboratory parameters were categorised according to National Cancer Institute (NCI) common toxicity criteria for adverse events[4].

The following sub-groups were also evaluated for safety; baseline creatinine clearance; gender; age; Grade III/IV hyperbilirubinanaemia during study (Yes or No) and region, that is, the US, the rest of the world, East Asia.

A total of 1886 patients from 226 centres in 29 countries were randomised to the two treatment arms (944 to Xelox and 942 to 5-FU/LV) between April 2003 and October 2004. Among the patients randomised to receive 5-FU/LV, 664 received the Mayo Clinic regimen and 278 the Roswell Park regimen.

Demographic data were well balanced between Xelox and 5-FU/LV treatment arms. This was consistent with that expected for the target population. The majority of enrolled patients were male (54% and 53% in the Xelox and 5-FU/LV groups, respectively) and Caucasian (85% in both

[4] National Cancer Institute developed the Common Toxicity Criteria (CTC) to aid in the recognition and grading severity of adverse effects.

treatment arms). The median patient age was 61 years in the Xelox arm and 61.5 years in the 5-FU/LV arm. Most patients in both treatment arms entered this study with normal CEAs (92% and 93% in the Xelox and 5-FU/LV groups, respectively), a creatinine clearance of >50mls/minute (97% of patients in both groups) and an ECOG performance status of 0 (75% and 78% in the Xelox and 5-FU/LV groups, respectively).

Other baseline characteristics including nature and date of surgery prior to randomisation and TNM (Tumor, Node, Metastasis) stage of disease were well balanced.

A total of 944 patients were randomised to the Xelox arm and 942 to the 5-FU/LV arm. The majority of patients (>67.2%) were alive at time of clinical cut-off, though more patients in the 5-FU/LV arm were confirmed as having died compared to the Xelox patients (20.9% of Xelox patients compared to 23.9% of 5-FU/LV patients). The percentage of patients who withdrew consent during the treatment phase (2.1%-2.3%) or who were subsequently lost to follow-up (6-6.1%) were balanced between the two treatment arms. When comparing the two 5-FU/LV groups to the Xelox group, the percentage of patients who were confirmed to have died was highest in the 5-FU/LV Mayo Clinic group (26.4%), followed by the Xelox group (20.9%) and the FU/LV Roswell Park group (18%). The percentage of patients who withdrew consent during treatment phase or who were subsequently lost to follow-up were highest in the 5-FU/LV Roswell Park group (4.3% and 7.9%, respectively) and the majority of these were recruited from centres in the USA and lowest in the 5-FU/LV Mayo Clinic group (1.2% and 5.3% respectively versus Xelox 2.3% and 6%, respectively). The results indicate that 32% were withdrawn from treatment during the treatment phase in the Xelox arm as compared with 18% from the 5-FU/LV arm. There were more treatment withdrawals during the treatment phase in the 5-FU/LV Roswell Park group (28%) than in the 5-FU/LV Mayo Clinic group (14%). The most common reason for treatment withdrawal in the Xelox arm was because of recurrent disease or adverse event. When comparing the two 5-FU/LV groups to Xelox group, the rate of treatment withdrawals was higher in the 5-FU/LV Roswell Park group. Within the 5-FU/LV Mayo Clinic group, more patients withdrew from treatment due to adverse events compared with the Roswell Park group. In the latter group, more patients withdrew from treatment because of treatment refusal.

Table 1 summarises the outcome of the primary efficacy parameter DFS, indicating the primary objective of the study was met as Xelox was statistically superior to the 5-FU/LV in terms of DFS for chemotherapy naive patients who underwent surgery for colon cancer with a log rank analysis p=0.0045. In the ITT population, the HR was 0.8 demonstrating a 20% decrease in the risk of relapse of the original colon cancer, development of a new colon or rectal cancer or death due to any causes in the Xelox arm. Following 3, 4 and 5 years of follow-up, the DFS event free rate in the Xelox group was higher (71%, 68% and 66%, respectively) than in the 5-FU/LV arm (67%, 62% and 60%, respectively).

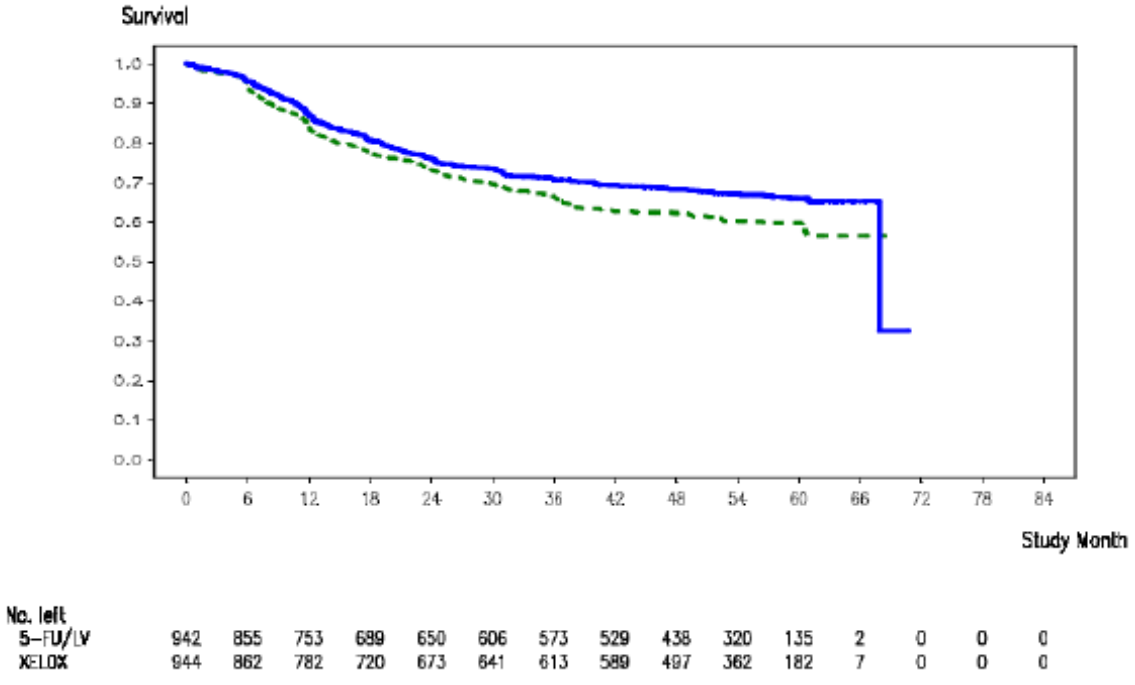
Table 1. Summary of DFS by Trial Treatment (ITT population).

	5-FU/LV (N=942)		XELOX (N=944)
Patients with event	353 (37.5 %)		295 (31.3 %)
Patients without events*	589 (62.5 %)		649 (68.8 %)
Time to event (months)			
Median#	.		67.9
95% CI for Median#	[.;.]		[68;.]
25% and 75%-ile	22;.		25;.
Range##	0 to 68		0 to 71
p-Value (Log-Rank Test)		0.0045	
Hazard Ratio		0.80	
95% CI		[0.69;0.93]	
3 Year Survival			
Number left	573		613
Event Free Rate#	0.67		0.71
95% CI for Rate#	[0.63;0.70]		[0.68;0.74]

* censored
\# Kaplan-Meier estimate
\## including censored observations

The Kaplan-Meier curve of DFS in the ITT population is presented Figure 1.

Figure 1. Kaplan Meier Curve of DFS (ITT Population).



Separation of the curves for the two treatment arms becomes apparent at the first tumour assessment six months after randomisation is maintained for the entire observation period, indicating improved DFS for Xelox treated patients relative to the 5-FU/LV treated patients. The median observation time for DFS was approximately 57 months. It should be noted that a sharp drop in the Xelox curve at Month 66 is represented by the fact that there were only two patients who had an assessment performed after the scheduled 60 month assessment time and for the scheduled Month 72

assessment in the Xelox arm, an event of one of these patients gives a drop of 50% of the remaining DFS rate.

Similar results were obtained for the PP population; p=0.0038 with a HR of 0.80 with 95% CI of 0.68, 0.93.

Table 2 summarises the results of the secondary efficacy parameter RFS by trial treatment. Again it demonstrates statistical superiority for the Xelox arm with a log rank p=0.0024. The HR for the ITT population was 0.78 with 95% CI 0.67-0.92 demonstrating a 22% decrease in the risk of recurrence of the original colon cancer, development of a new colon or rectal cancer or death related to any of the following; treatment, recurrence of original colon cancer or development of a new colon or rectal cancer in Xelox arm. Following 3, 4 and 5 years of follow-up, the RFS event free rate was higher in the Xelox group; 72%, 70% and 68%, respectively, compared to 67%, 63% and 61% respectively, in the 5-FU/LV arm. Figure 2 gives the Kaplan-Meier curve of RFS for the ITT population and is very similar to that seen for the DFS curves. Similar results were obtained from the PP population; p value of 0.0020 and HR of 0.78 with a 95% CI of 0.66-0.91.

Table 2. Summary of RFS by Trial Treatment (IIT Population)

	5-FU/LV (N=942)		XELOX (N=944)
Patients with event	340 (36.1 %)		278 (29.4 %)
Patients without events*	602 (63.9 %)		666 (70.6 %)
Time to event (months)			
Median#	.		67.9
95% CI for Median#	[.;.]		[68;.]
25% and 75%-ile	23;.		29;.
Range##	0 to 68		0 to 71
p-Value (Log-Rank Test)		0.0024	
Hazard Ratio		0.78	
95% CI		[0.67;0.92]	
3 Year Survival			
Number left	572		613
Event Free Rate#	0.67		0.72
95% CI for Rate#	[0.64;0.71]		[0.69;0.75]

* censored
\# Kaplan-Meier estimate
including censored observations

Figure 2. Kaplan Meier Curve of RFS (ITT Population)

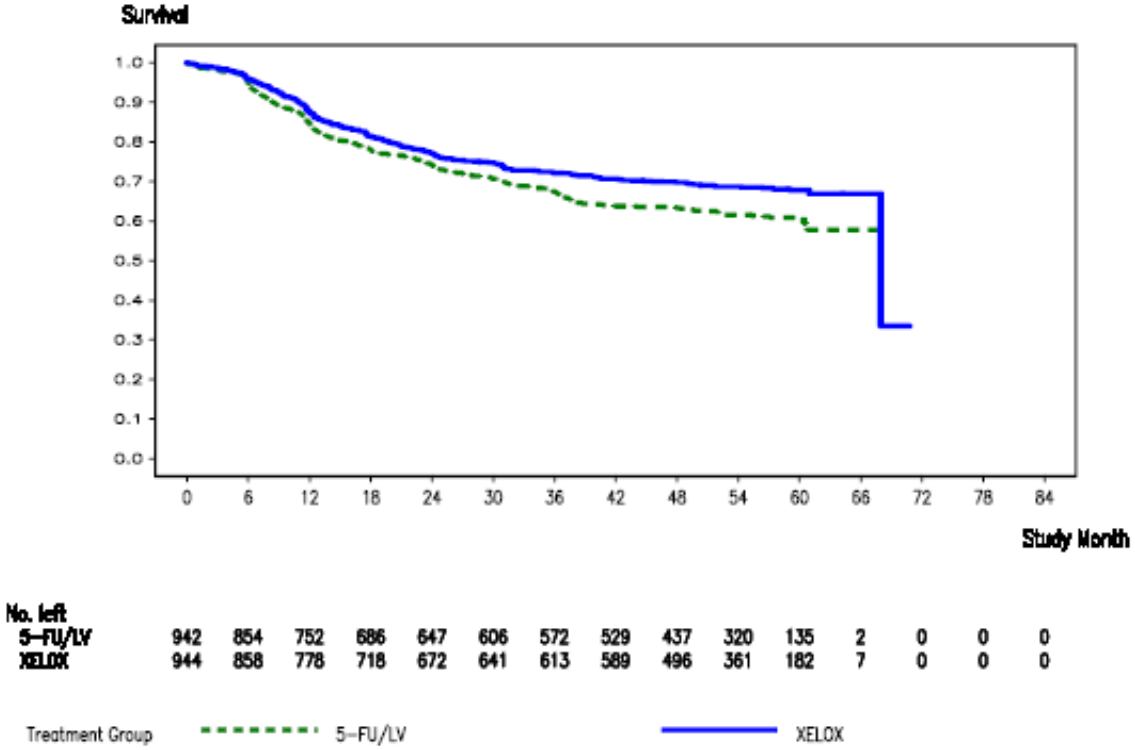


Table 3 summarises the overall survival by trial treatment and indicates that Xelox demonstrated a 13% decrease in the risk of death due to any cause compared to 5-FU/LV in the patient population with a HR of 0.87 95% CI 0.72-1.05. This difference however did not reach statistical significance with a p value of 0.1486. Following 3, 4 and 5 years of follow-up, the OS event free rate was higher in the Xelox group (86%, 80% and 78%, respectively) than in the 5-FU/LV group (84%, 78% and 74%, respectively).

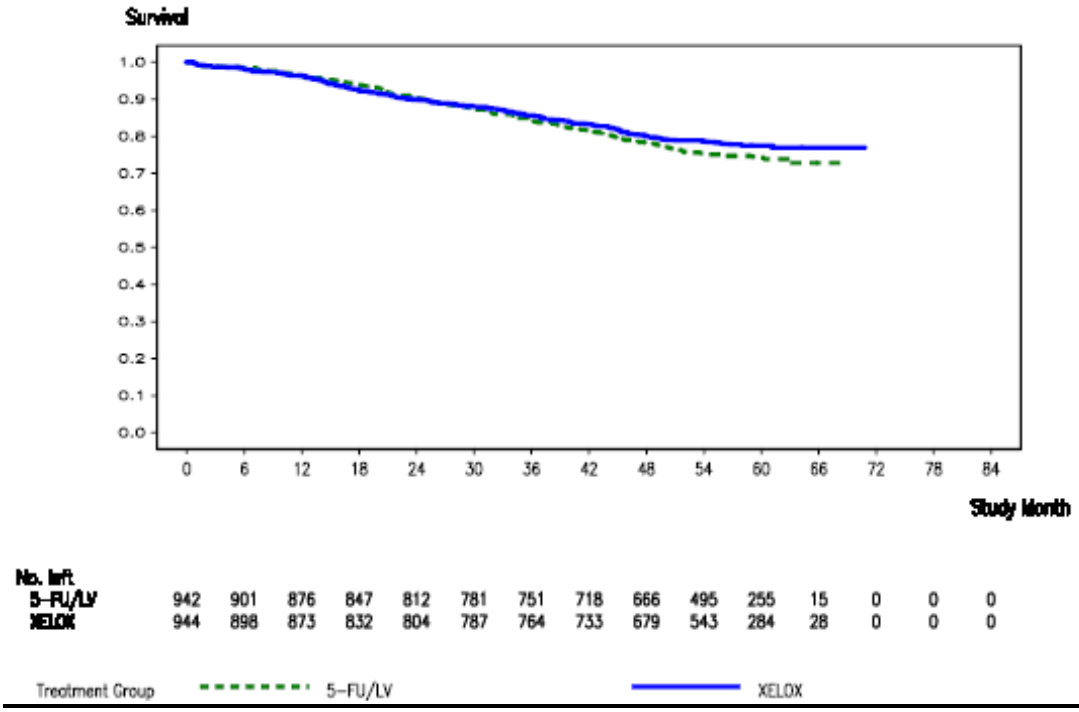
Table 3. Summary of Overall Survival by Trial Treatment (ITT Population).

	5-FU/LV (N=942)		XELOX (N=944)
Patients with event	225 (23.9 %)		197 (20.9 %)
Patients without events*	717 (76.1 %)		747 (79.1 %)
Time to event (months)			
Median#	.		.
95% CI for Median#	[.;.]		[.;.]
25% and 75%-ile	56;.		.;.
Range##	0 to 68		0 to 71
p-Value (Log-Rank Test)		0.1486	
Hazard Ratio		0.87	
95% CI		[0.72;1.05]	
5 Year Survival			
Number left	255		284
Event Free Rate‡	0.74		0.78
95% CI for Rate‡	[0.71;0.77]		[0.75;0.80]

* censored
\# Kaplan-Meier estimate
\## including censored observations

The Kaplan-Meier curve of overall survival for the ITT population is given Figure 3. The median observation time for overall survival is approximately 59 months. Similar results were obtained for the PP population with a p value of 0.1287 and a HR of 0.86 with 95% CI 0.71-1.04.

Figure 3. Kaplan Meier Curve of Overall Survival (ITT Population)



A summary of DFS by stratification factor sub-groups, including number of positive lymph nodes, baseline CEA levels and geographic region and 5-FU/LV regimen used at the study centre is given in Figures 4 and 5. A summary of DFS by the various baseline variable sub-groups is given in Figure 6.

Figure 4. Forest Plot Hazard Ratio for DFS by stratification factor subgroups excluding geographic region (ITT Population).

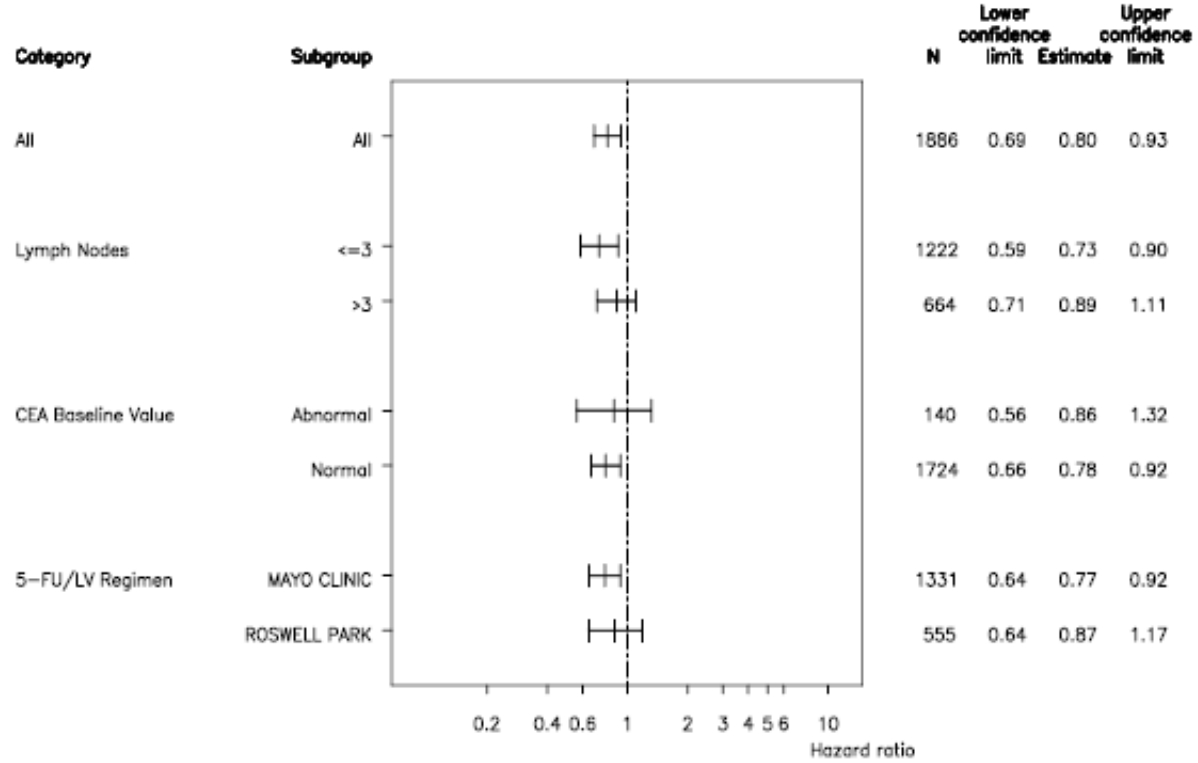


Figure 5. Forest Plot Hazard Ratio for DFS by geographic region stratification factor subgroups (ITT Population).

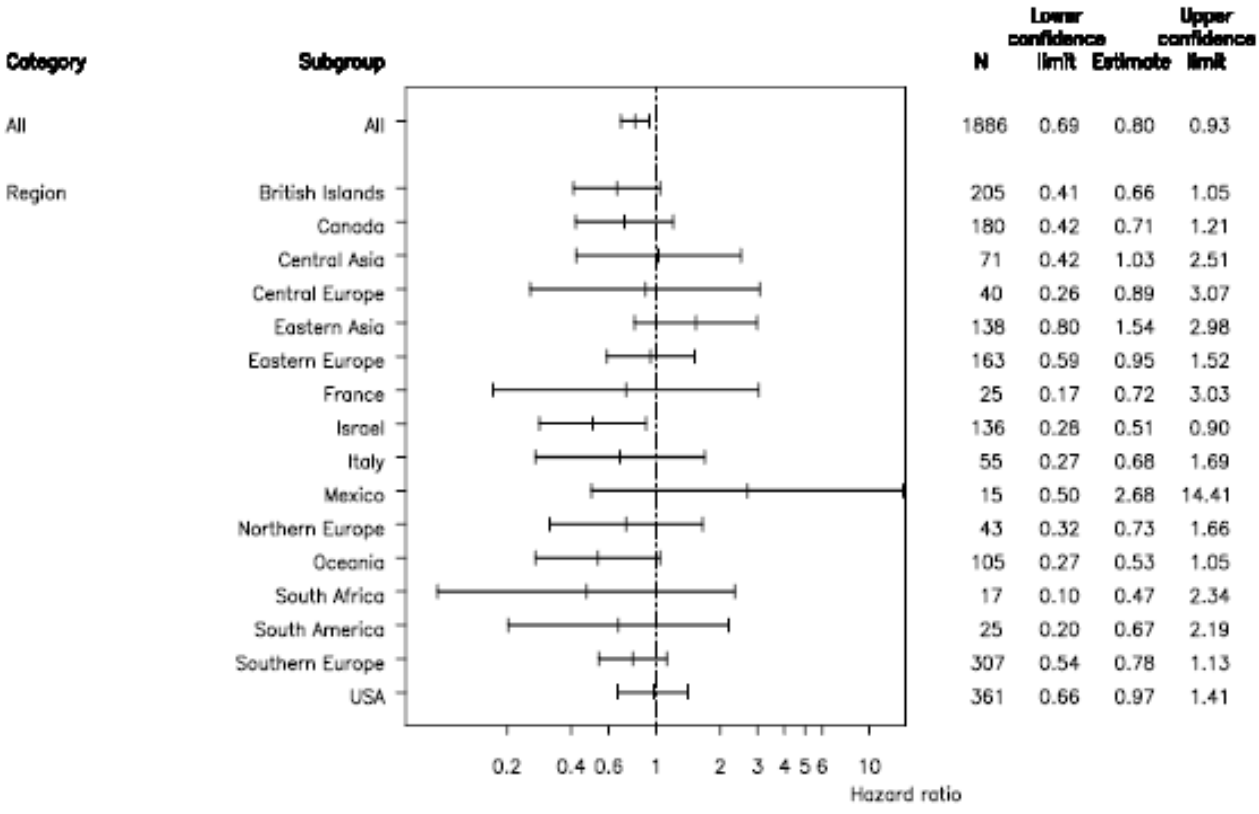
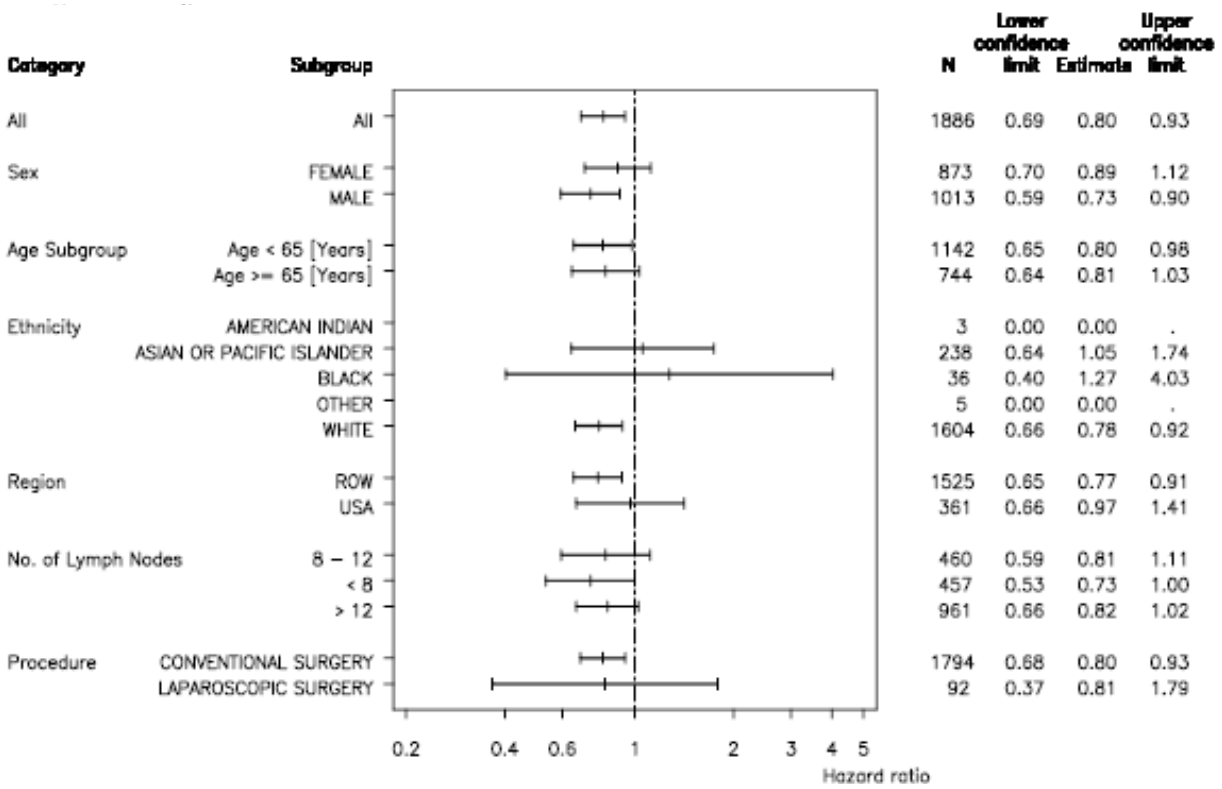


Figure 6. Forest Plot of the Hazard Ratio for DFS by baseline variable subgroups (ITT Population).



In general the point estimates for the HR were <1 in the different sub-groups indicating treatment effect in favour of the Xelox arm with the exception of three geographic regions (central and eastern Asia and Mexico) and two racial groups (Black and Asian or Pacific Islander). The 95% CI around all point estimates were overlapping with each other and with the point estimates in the all subject groups, indicating that treatment effect within each sub-group was consistent with the treatment effect observed for the overall population. It should be noted however, that sample size for a number of the evaluated sub-groups was small, limiting significance.

Nevertheless the results of the sub-groups supported the results of the primary analysis and confirm the robustness of the observed treatment benefit.

As with the DFS analyses there was a fairly consistent treatment effect with a HR of <1 for the RFS and across most sub-groups as indicated in Figures 7 and 8.

Figure 7. Forest Plot Hazard Ratio for RFS by geographic region stratification factor subgroups (ITT Population).

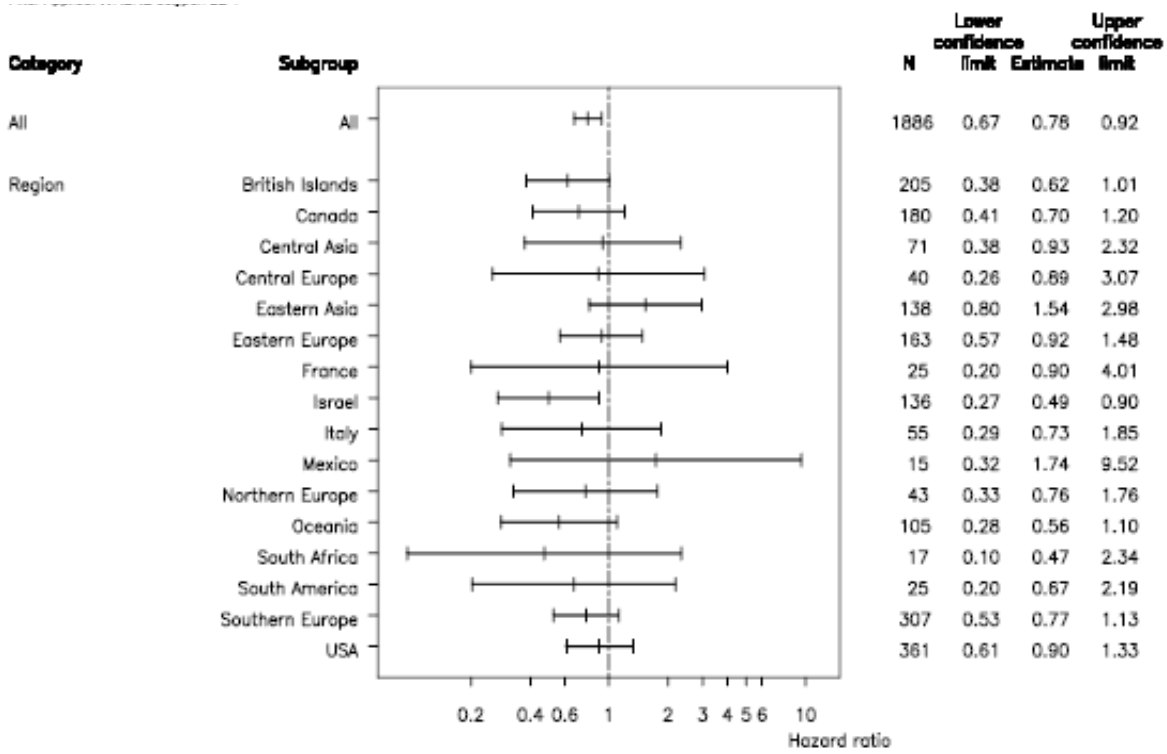
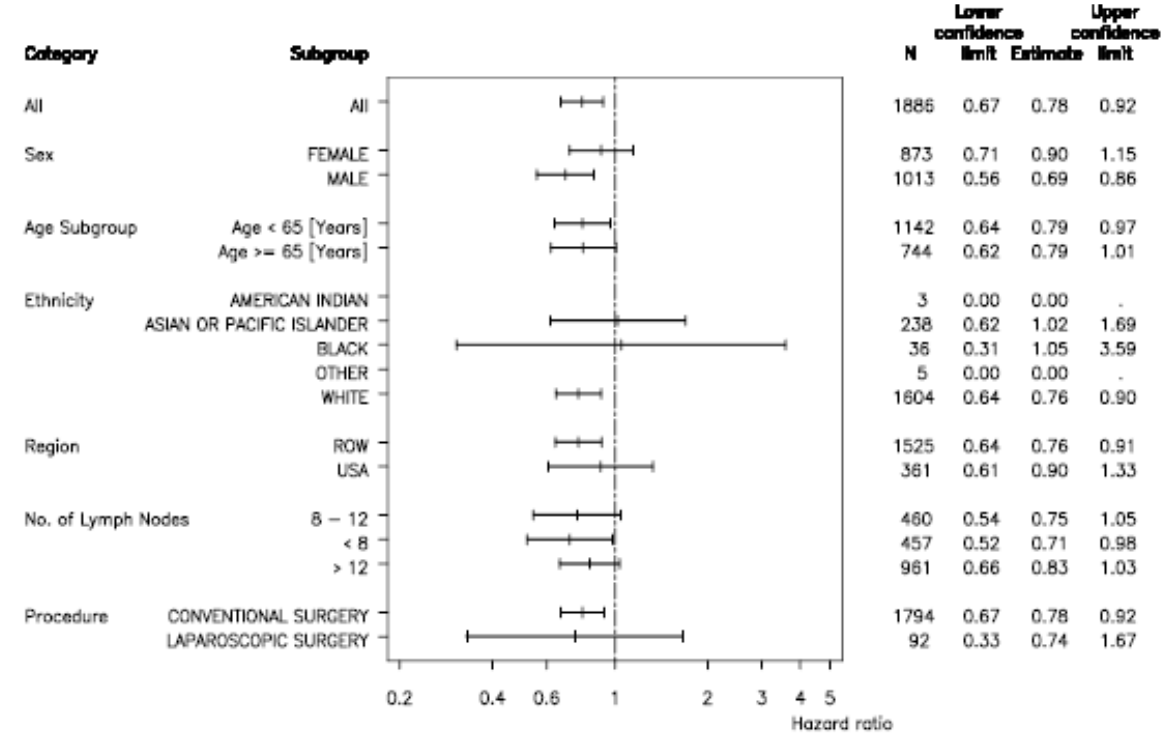


Figure 8. Forest Plot of the Hazard Ratio for RFS by baseline variable subgroups (ITT Population).



Analysis of overall survival by stratification factor sub-groups is presented in Figures 9 and 10. The summary of overall survival by baseline variable sub-groups is given in Figure 11. These various sub-group analyses generally indicated treatment benefits for the Xelox arm over the 5-FU/LV arm but again were small and with the various sub-groups being in themselves relatively small, analyses could not be considered significant.

Review of prognostic factor analyses by univariate Cox-proportional hazard regression and multivariate Cox-proportional hazards regression revealed that differences in terms of stratification and other important prognostic factors did not impact the efficacy endpoint conclusions.

Figure 9. Forest Plot Hazard Ratio for Overall Survival by stratification factor subgroups excluding geographic region (ITT Population).

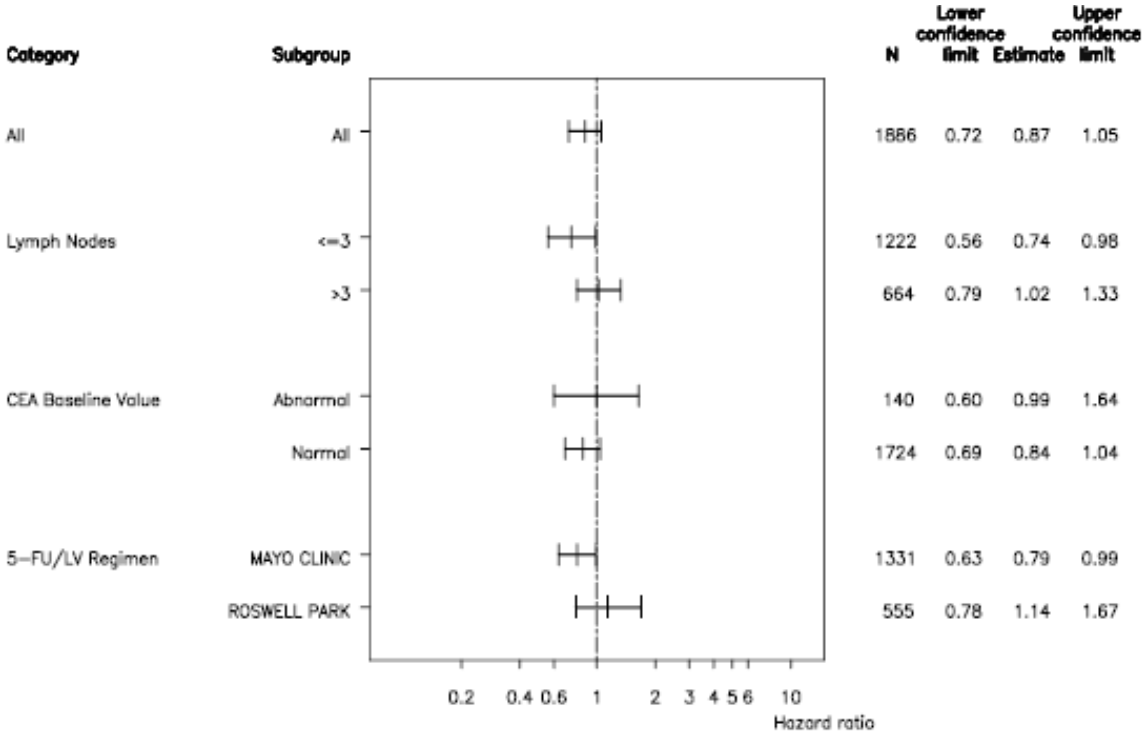


Figure 10. Forest Plot Hazard Ratio for Overall Survival by geographic stratification factor subgroups (ITT Population)

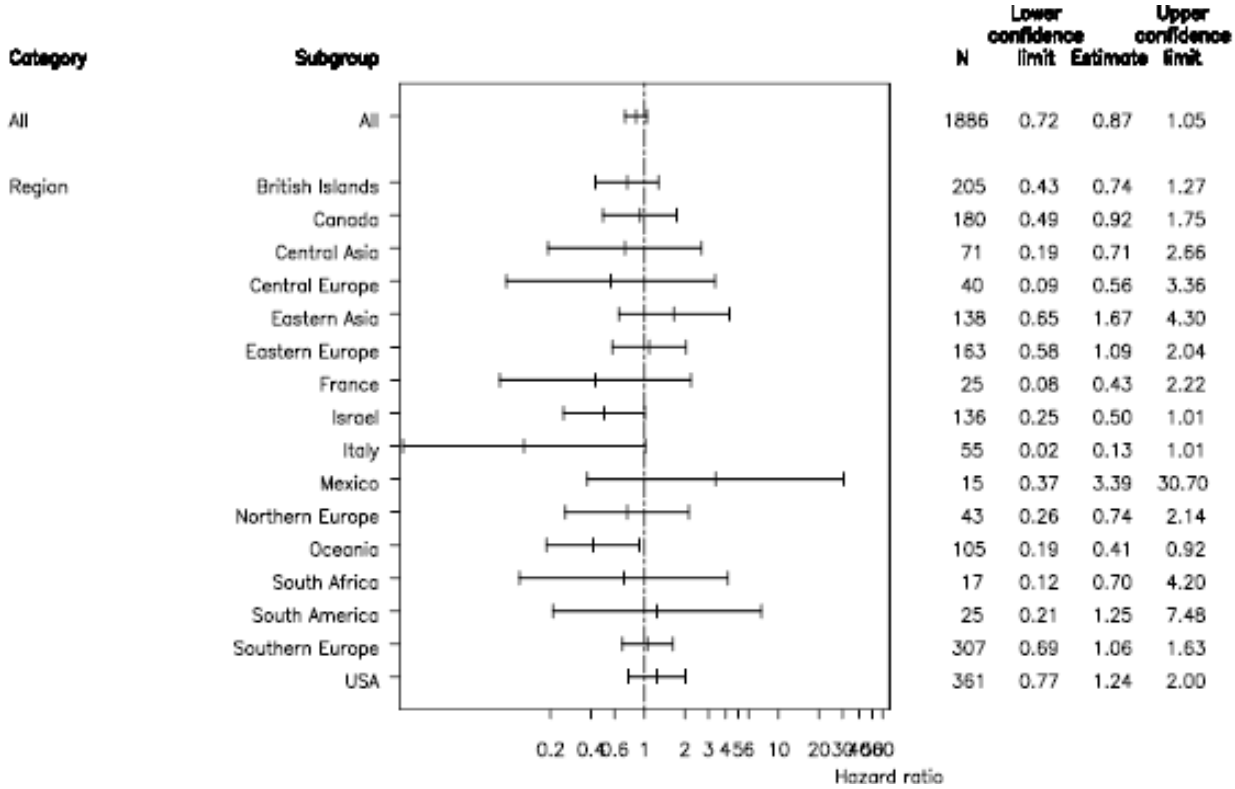


Figure 11. Forest Plot Hazard Ratio for Overall Survival by baseline variable subgroups (ITT Population)

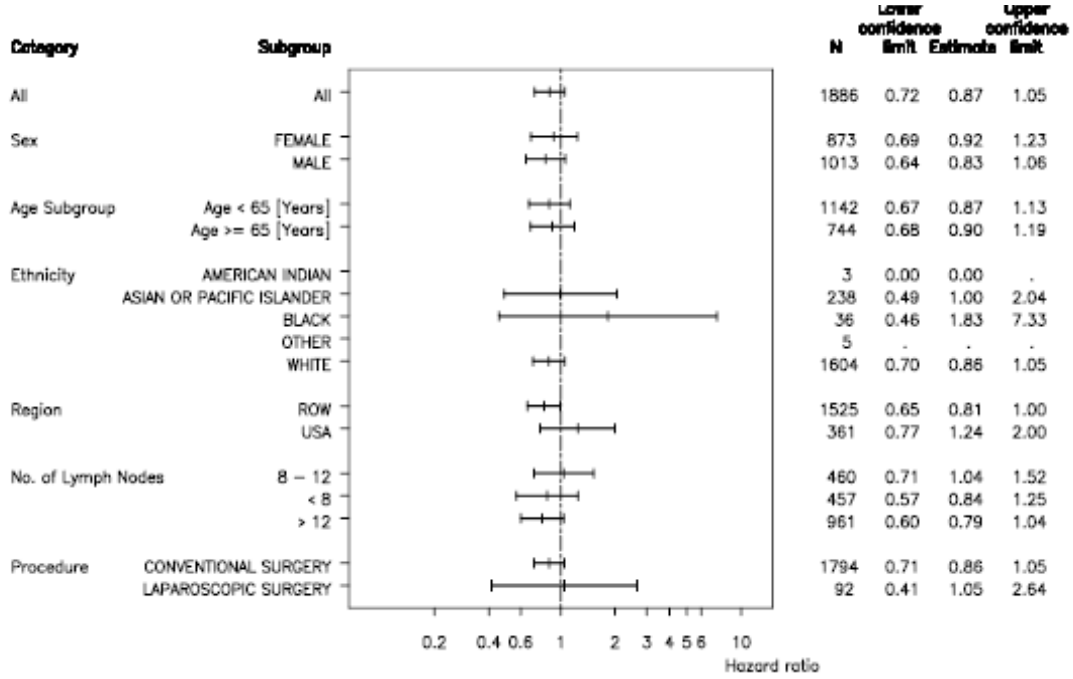


Table 4. Summary of Treatment effect adjusted for each covariate in Cox regression for DFS (ITT Population).

		Covariate Effect*			Treatment Effect Adjusted for Covariate**		
Effect/Covariate	No. of Patients	Hazard Ratio	95% CI for Hazard Ratio	p-Value	Hazard Ratio	95% CI for Hazard Ratio	p-Value
Randomization treatment	1886				0.80	[0.69;0.93]	0.0047
5-FU/LV Regimen (MC Sites vs. RP Sites)	1886	1.12	[0.94;1.34]	0.1894	0.80	[0.68;0.93]	0.0043
British Islands vs. USA	1886	1.15	[0.85;1.55]	0.3551	0.80	[0.68;0.93]	0.0038
Canada vs. USA		0.97	[0.71;1.34]	0.8598			
Central Asia vs. USA		0.97	[0.60;1.56]	0.8928			
Central Europe vs. USA		0.70	[0.37;1.34]	0.2861			
Eastern Asia vs. USA		0.88	[0.60;1.27]	0.4855			
Eastern Europe vs. USA		1.34	[0.99;1.81]	0.0612			
France vs. USA		1.05	[0.51;2.16]	0.8842			
Israel vs. USA		1.27	[0.91;1.77]	0.1677			
Italy vs. USA		1.04	[0.64;1.69]	0.8801			
Mexico vs. USA		1.87	[0.87;4.03]	0.1075			
Northern Europe vs. USA		1.91	[1.21;2.99]	0.0050			
Oceania vs. USA		1.13	[0.77;1.65]	0.5331			
South Africa vs. USA		1.08	[0.48;2.46]	0.8496			
South America vs. USA		1.51	[0.81;2.80]	0.1951			
Southern Europe vs. USA		1.19	[0.92;1.55]	0.1932			
Lymph Nodes (<=3 vs. >3)	1886	0.48	[0.41;0.56]	<.0001	0.80	[0.69;0.94]	0.0051
CEA Baseline Value (Normal vs. Abnormal)	1864	0.40	[0.32;0.50]	<.0001	0.79	[0.68;0.93]	0.0034
Sex (Male vs. Female)	1886	1.11	[0.95;1.29]	0.2045	0.80	[0.68;0.93]	0.0041
Age [10 Years]	1886	1.08	[1.00;1.16]	0.0401	0.80	[0.69;0.94]	0.0056

* Model that includes only the covariate
** Model that includes the covariate and treatment (no interaction term)

Table 4 continued.

Effect/Covariate	No. of Patients	Covariate Effect* Hazard Ratio	95% CI for Hazard Ratio	p-Value	Treatment Effect Adjusted for Covariate** Hazard Ratio	95% CI for Hazard Ratio	p-Value
Time f. Surg. f. Cancer to RND [10 Days]	1886	1.09	[1.01;1.16]	0.0167	0.80	[0.69;0.94]	0.0054

* Model that includes only the covariate
** Model that includes the covariate and treatment (no interaction term)

Review of triggering events of disease free survival appear in only 295 Xelox patients and 353 5-FU/LV patients who contributed events in the analysis DFS and ITT population. Most were recurrence of the original colon cancer or development of a new colon or rectal cancer rather than death (270 Xelox patients and 328 5-FU/LV patients. The percentage of patients who were censored from the analysis was also greater in the Xelox arm (68% versus 62%) and there were fewer DFS events reported for the patients in the Xelox arm. Similar data was apparent when assessing the secondary endpoint RFS.

The most common sites of recurrence were the original colon cancer or development of a new colon or rectal cancer was the liver, with some differences between the Xelox arm and the 5-FU/LV arm as illustrated in Table 5.

Table 5. Summary of location of recurrence/new occurrence of colorectal cancer by trail treatment (ITT Population).

	5-FU/LV (N = 942)		XELOX (N = 944)	
Number of Patients with Recurrence	N = 328		N = 270	
Location of Recurrence	n	(%)	n	(%)
LIVER	129	(39.3%)	99	(36.7%)
OTHER	83	(25.3%)	92	(34.1%)
LUNG	71	(21.6%)	76	(28.1%)
COLON/RECTUM	64	(19.5%)	42	(15.6%)
LYMPH NODE	69	(21.0%)	37	(13.7%)
MISSING	2	(0.6%)	1	(0.4%)

Note: Individual patients may have had more than one location of relapse or new occurrence of colon cancer (NOCC). Consequently, the total number of locations is larger than the number of patients having relapse or NOCC.
Patients with evidence of disease after surgery at screening are counted as recurrence.

Xelox demonstrated a 15% decrease in the risk of death due to any cause compared to the 5-FU/LV arm in patients who experienced a relapse and subsequently had a surgical intervention (HR was 0.85, 95% CI 0.55-1.30) but this difference was not statistically significant (p=0.4468). Following five years of follow-up the overall survival of event free rate in this sub-group was higher in the Xelox group (59%) than in the 5-FU/LV arm (49%).

COMMENT:

This study has demonstrated that in relation to the primary efficacy endpoint, DFS, the drug combination of Xeloda with oxaliplatin (Xelox) is superior to 5-FU/LV alone. This also applies to the secondary endpoint of RFS but importantly while there was some benefit in terms of overall survival for the combination therapy arm this did not reach statistical significance. The study was a relatively large one and the data robust in terms of the primary endpoint. Nevertheless, it is a little disappointing that the study did not include a further single treatment arm (for example Xeloda alone) in order to clearly determine whether or not the drug combination Xeloda plus oxaliplatin is superior to the Xeloda alone. Nevertheless, it is reasonable to anticipate that the addition of

oxaliplatin to the Xeloda in the adjuvant setting of colon cancer is associated with benefit and therefore supports the proposed amendment to the Product Information.

Safety Data for Study NO16968:

The safety population for this study comprised all patients who were randomised and received at least one dose of drug. Given the known differences in the safety profile for the two 5-FU/LV regimens, these were reported separately. Accordingly, comparisons were made with Xelox and the Mayo Clinic regimen of 5-FU/LV and the Roswell Park regimen of 5-FU/LV.

Safety assessments performed included monitoring of the occurrence of adverse events, laboratory assessments, electrocardiogram (ECGs), vital signs, physical measurements and determination of ECOG performance status and monitoring of concomitant medication use.

Standard definitions were used in relation to adverse events and serious adverse events (SAE). The intensity of adverse events was graded according to NCI toxicity criteria.

Consistent with the study protocol and specific regimen the median number of cycles during the treatment phases was eight cycles or 24 weeks in the Xelox group, six cycles or 24 weeks for the 5-FU/LV Mayo Clinic group and four cycles or 32 weeks for the 5-FU/LV Roswell Park group. The percentage of patients who received the protocol specified number of cycles for each treatment regimen was 69% for Xelox, 87% for 5-FU/LV Mayo Clinic and 79% for 5-FU/LV Roswell Park. The median duration of treatment was 163 days for Xelox group, 145 days for 5-FU/LV Mayo Clinic and 204 days for the 5-FU/LV Roswell Park group.

Two Xelox patients did not receive the combination therapy and in addition 85 Xelox patients continued to receive capecitabine monotherapy after withdrawal from oxaliplatin therapy as permitted by the protocol.

Review of dose reductions for the trial revealed that the percentage of patients with dose reduction at any time during treatment was greater in the 24 week 5-FU/LV Mayo Clinic regimen (48.6%) and the 5-FU/LV Roswell Park regimen (43.9%) compared to the Xelox group based on the oxaliplatin component (35.3%) and based on the capecitabine component (29.9% of patients). As more treatment withdrawals occurred in the Xelox arms this lower frequency of dose reductions is not unexpected. Taken as a whole the percentage of patients who experienced dose reduction, treatment delay or interruption of treatment medication was comparable across the treatment medication regimens, ranging between 55.4% and 64.7% of patients.

When summarising the number of cycles that were interrupted by adverse events, the Roswell Park group had the highest percentage of patients in cycles of adverse event treatment interruptions while the 5-FU/LV Mayo Clinic group had the fewest patients with such interruptions.

An overall review of adverse events revealed that the most frequently reported adverse events (in >25% of patients) in Xelox group were nausea (67%), diarrhoea (62%), vomiting (44%), paresthesia (36%), fatigue (35%), peripheral neuropathy (30%), neutropenia (28%) and anorexia (26%). This can be compared to the incidences of these and other toxicities for the two 5-FU/LV regimens in Table 6. This revealed an increase in incidence of diarrhoea, nausea, stomatitis, fatigue, neutropenia, abdominal pain and anorexia in at least one of the two 5-FU/LV treatment groups compared to the Xelox group with more vomiting, paresthesia, peripheral neuropathy and palmar/plantar or hand/foot syndrome in the Xelox group compared to either of the two 5-FU/LV treatment groups.

Table 6. Summary of adverse events with an incidence rate of at least 5% by trial treatment and regimen (Safety Population).

Body System/ Adverse Event	5-FU/LV MAYO CLINIC N = 657 No. (%)	5-FU/LV ROSWELL PARK N = 269 No. (%)	XELOX N = 938 No. (%)
GASTROINTESTINAL DISORDERS			
DIARRHOEA	449 (68)	219 (81)	577 (62)
NAUSEA	350 (53)	190 (71)	625 (67)
*STOMATITIS ALL	419 (64)	57 (21)	195 (21)
VOMITING	142 (22)	103 (38)	415 (44)
ABDOMINAL PAIN	118 (18)	92 (34)	204 (22)
CONSTIPATION	82 (12)	48 (18)	187 (20)
DYSPEPSIA	38 (6)	37 (14)	87 (9)
ABDOMINAL PAIN UPPER	44 (7)	21 (8)	77 (8)
FLATULENCE	21 (3)	29 (11)	47 (5)
DRY MOUTH	23 (4)	14 (5)	26 (3)
NERVOUS SYSTEM DISORDERS			
PARAESTHESIA	16 (2)	10 (4)	339 (36)
NEUROPATHY PERIPHERAL	8 (1)	12 (4)	279 (30)
DYSGEUSIA	86 (13)	40 (15)	126 (13)
HEADACHE	46 (7)	31 (12)	103 (11)
DIZZINESS	34 (5)	34 (13)	99 (11)
PERIPHERAL SENSORY NEUROPATHY	4 (<1)	11 (4)	152 (16)
DYSAESTHESIA	1 (<1)	1 (<1)	104 (11)
LETHARGY	46 (7)	3 (1)	52 (6)
HYPOAESTHESIA	2 (<1)	7 (3)	59 (6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
FATIGUE	148 (23)	170 (63)	332 (35)
ASTHENIA	91 (14)	44 (16)	167 (18)
PYREXIA	60 (9)	43 (16)	108 (12)
TEMPERATURE INTOLERANCE	-	1 (<1)	104 (11)
OEDEMA PERIPHERAL	22 (3)	29 (11)	51 (5)
CHILLS	9 (1)	16 (6)	29 (3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	56 (9)	42 (16)	278 (30)
ALOPECIA	159 (24)	25 (9)	40 (4)
RASH	65 (10)	41 (15)	84 (9)
DRY SKIN	41 (6)	44 (16)	45 (5)
PRURITUS	20 (3)	17 (6)	21 (2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
NEUTROPENIA	232 (35)	36 (13)	260 (28)
THROMBOCYTOPENIA	2 (<1)	4 (1)	167 (18)
ANAEMIA	32 (5)	36 (13)	64 (7)
FEBRILE NEUTROPENIA	36 (5)	3 (1)	4 (<1)
METABOLISM AND NUTRITION DISORDERS			
ANOREXIA	101 (15)	77 (29)	240 (26)
DEHYDRATION	24 (4)	33 (12)	68 (7)
HYPOKALAEMIA	20 (3)	33 (12)	58 (6)
DECREASED APPETITE	16 (2)	15 (6)	27 (3)

Investigator text for Adverse Events encoded using MedDRA version 12.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE13 13JUL2009:08:25:29 (1 of 2)

Table 6 continued.

Body System/ Adverse Event	5-FU/LV MAYO CLINIC N = 657 No. (%)	5-FU/LV ROSWELL PARK N = 269 No. (%)	XELOX N = 938 No. (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
COUGH	15 (2)	35 (13)	47 (5)
OROPHARYNGEAL PAIN	39 (6)	20 (7)	38 (4)
DYSPNOEA	15 (2)	16 (6)	63 (7)
EPISTAXIS	24 (4)	30 (11)	40 (4)
DYSAESTHESIA PHARYNX	-	-	93 (10)
RHINORRHOEA	16 (2)	20 (7)	24 (3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
PAIN IN EXTREMITY	17 (3)	21 (8)	117 (12)
ARTHRALGIA	22 (3)	26 (10)	41 (4)
BACK PAIN	14 (2)	25 (9)	46 (5)
PAIN IN JAW	1 (<1)	-	55 (6)
PSYCHIATRIC DISORDERS			
INSOMNIA	49 (7)	38 (14)	78 (8)
ANXIETY	22 (3)	31 (12)	49 (5)
DEPRESSION	14 (2)	24 (9)	35 (4)
INFECTIONS AND INFESTATIONS			
NASOPHARYNGITIS	20 (3)	15 (6)	32 (3)
UPPER RESPIRATORY TRACT INFECTION	13 (2)	18 (7)	29 (3)
URINARY TRACT INFECTION	14 (2)	20 (7)	22 (2)
EYE DISORDERS			
LACRIMATION INCREASED	53 (8)	49 (18)	45 (5)

Investigator text for Adverse Events encoded using MedDRA version 12.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE13 13JUL2009:08:25:29 (2 of 2)

Table 7 summarises adverse events by intensity. Overall life threatening (Grade IV) adverse events were experienced by more patients in the 5-FU/LV Mayo Clinic group (13%) compared to the Xelox (7%) and 5-FU/LV Roswell Park (8%) groups. More patients in the Xelox group experienced Grade III toxicities (58%) and Grade II toxicities (84%) compared to the Mayo Clinic (46% and 75%, respectively) or Roswell Park group (54% and 81%, respectively). Severe adverse events across all three treatment groups were most commonly gastrointestinal nature (37%, 30% and 29% in the Roswell Park, Xelox and Mayo Clinic groups, respectively) and included diarrhoea and nausea. Severe neutropenia was most common among the Mayo Clinic patients (21%) than among the Xelox (9%) or Roswell Park (4%) of patients. Of these SAEs, the only treatment related SAEs that occurred in greater frequency in Xelox patients compared to patients in 5-FU/LV treatment groups was the hand/foot syndrome (HFS) affecting 5% of Xelox patients compared to 1% of Roswell Park and <1% of the Mayo Clinic patients. Treatment-related severe diarrhoea, nausea and dehydration were all reported at a greater frequency in the Roswell Park patients than Xelox or Mayo Clinic patients. In contrast, treatment related severe stomatitis, neutropenia and febrile neutropenia were most common in the Mayo Clinic patients.

Table 7. Summary of severe adverse events with an incidence rate of at least 5% by trial treatment and regimen (Safety Population).

Body System/ Adverse Event	5-FU/LV MAYO CLINIC N = 657 No. (%)	5-FU/LV ROSWELL PARK N = 269 No. (%)	XELOX N = 938 No. (%)
GASTROINTESTINAL DISORDERS			
DIARRHOEA	110 (17)	80 (30)	182 (19)
NAUSEA	19 (3)	23 (9)	49 (5)
VOMITING	16 (2)	15 (6)	58 (6)
*STOMATITIS ALL	82 (12)	-	6 (<1)
ABDOMINAL PAIN	13 (2)	15 (6)	26 (3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
NEUTROPENIA	136 (21)	11 (4)	82 (9)
FEBRILE NEUTROPENIA	36 (5)	3 (1)	4 (<1)
METABOLISM AND NUTRITION DISORDERS			
DEHYDRATION	8 (1)	19 (7)	37 (4)
HYPOKALAEMIA	9 (1)	15 (6)	32 (3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	3 (<1)	3 (1)	51 (5)

A review of deaths occurring during the treatment phase and within 28 days after last dose of treatment indicates that of the patients who died (26%, 21% and 19% in the Mayo Clinic, Xelox and Roswell Park groups respectively), the most common cause of death was related to recurrence of the original colon cancer or a new recurrence of colorectal cancer. The other most common cause of death occurred in <1% of the patients in each treatment group, and included death of an unspecified cause, pneumonia, myocardial infarction and intestinal ischaemia.

A summary of all deaths that were considered by investigators to be related to study treatment is given in Table 8. The only death that was considered by the investigator to be related to study treatment and which occurred in more than one patient across all treatment groups was pneumonia. As indicated the highest number of treatment related deaths were among the Xelox patients. This was considered by investigators to be related to study treatment that occurred more than 28 days after the last dose of study drug.

Table 8. Summary of deaths related to study drug by trial treatment (Safety population).

Cause of Death	5-FU/LV MAYO CLINIC N = 657 No. (%)	5-FU/LV ROSWELL PARK N = 269 No. (%)	XELOX N = 938 No. (%)
Total No. of Deaths	2 (<1)	4 (1)	7 (<1)
PNEUMONIA	1 (<1)	-	2 (<1)
CLOSTRIDIAL INFECTION	-	1 (<1)	-
HYPOTENSION	-	-	1 (<1)
HYPOVOLAEMIC SHOCK	-	-	1 (<1)
INTESTINAL ISCHAEMIA	-	-	1 (<1)
MYOCARDIAL ISCHAEMIA	-	1 (<1)	-
NEUTROPENIC COLITIS	-	1 (<1)	-
NEUTROPENIC SEPSIS	1 (<1)	-	-
SEPSIS	-	-	1 (<1)
SEPSIS SYNDROME	-	1 (<1)	-
SEPTIC SHOCK	-	-	1 (<1)

Review of individual adverse events revealed that among gastrointestinal disorders these were experienced more often in patients on the Roswell Park regimen (94.4%) compared to the Xelox (87.8%) or Mayo Clinic (87.7%) regimens. The differences were most particularly related to a higher incidence of nausea and vomiting among the Roswell Park patients.

In relation to stomatitis this was experienced more frequently in the Mayo Clinic group (63.8%) compared to the Roswell Park (21.2%) of Xelox (20.8%) treatments. There were significantly more patients who experienced Grade III/IV stomatitis in the Mayo Clinic group (12.5%) compared to patients in the Xelox group (p=0.001).

The highest incidence of neutropenia was experienced among the Mayo Clinic (35.6%) patients (compared to 27.8% and 13.4% in the Xelox and Roswell Park groups, respectively). There were significantly more cases of Grade II – IV neutropenia in the Mayo Clinic group (33%) compared to the Xelox (25.8%) Roswell Park (12.3%) groups (p=0.0011 and p<0.001, respectively). As might be expected febrile neutropenia Grades III and IV was most prevalent among patients in the Mayo Clinic group (5.5%) compared to the Roswell Park (1.1%) and Xelox (0.4%) groups.

Review of the incidence of hand/foot syndrome revealed that 29.6% of patients in the Xelox group experienced this complication compared to 15.6% of the Roswell Park and 8.5% of the Mayo Clinic groups. Significantly more patients in the Xelox group experienced Grade III hand/foot syndrome (5.4%) compared to either of the 5-FU/LV groups (p=0.0025).

The incidence of neuro-sensory toxicities was might be expected clearly higher among the Xelox patients (7.9%) compared to the Roswell Park (5.2%) and Mayo Clinic (5.5%) patient groups. The frequency of Grade II-IV neuro-sensitive toxicity was significantly higher in the Xelox group (3.5%) compared with the Roswell Park (1.1%) and Mayo Clinic (0.6%; p<0.0001) groups.

Review of adverse events requiring dose modification or discontinuation of study treatment indicated that more patients in the Xelox group experienced such adverse events (82% compared to 67% in either of the two 5-FU/LV treatment groups). Most of these patients experienced an adverse event leading to dose modification with (76%, 53% and 53% in the Xelox, Mayo Clinic and Roswell Park groups, respectively) with a lesser number requiring discontinuation from the study (22%, 12% and 8% in the Xelox, Roswell Park and Mayo Clinic groups, respectively).

The most common adverse events requiring dose modification were neutropenia and diarrhoea. The most common adverse event requiring discontinuation from study treatment was diarrhoea across all three treatment groups (5%, 4% and 2% in the Roswell Park, Xelox and Mayo Clinic groups, respectively).

Review of laboratory abnormalities revealed that among the haematological disturbances Grade III and Grade IV abnormalities of neutrophils were less frequent in the Xelox group (10% and 1.3%, respectively) compared with the Mayo Clinic group (28.9% and 12.9%, respectively) and the Roswell Park group (7.1% and 3.3%, respectively). The frequency of patients with Grade III and Grade IV platelet abnormalities was highest in the Xelox group (5.4% and 1%, respectively) compared with the Mayo Clinic (0.3% and 0%, respectively) and Roswell Park (0.4% and 0.4%, respectively) groups.

The incidence of Grade III/IV hyperbilirubinanaemia was <1% in all three groups (0.7%, 0.4% and 0.3% in the Xelox, Roswell Park and Mayo Clinic groups, respectively) with no Grade IV shifts of total bilirubin levels for any group.

The incidence of other liver function enzyme abnormalities was also similar among the three treatment groups (<1.5%).

Review of changes in vital signs among the three treatment groups revealed no evidence of either consistent or clinically significant changes.

Review of safety profiles according to age revealed that the overall incidence of adverse events in each treatment group was similar (that is patients younger than 65 or >65 years) but in regards to serious adverse events the older patients, that is >65 years, experienced a greater incidence (30.4% versus 17.2% in the Xelox group; 36.2% versus 30.1% in the Roswell Park group; and 21.4% versus 19.7% in the Mayo Clinic group) and more deaths were reported in the older sub-groups

(30.8% versus 23.5% in the Mayo Clinic group; 24.8% versus 18.7% in the Xelox group; and 22.4% versus 15.7% in the Roswell Park group). Discontinuation due to adverse events was also higher in the older patients on Xelox (29.9% versus 16.3%).

Review of safety profiles according to gender revealed that overall more female patients than male patients experienced adverse events (99.1% versus 98.4% in the Xelox group; 95% versus 94.4% in the Mayo Clinic group; and 100% versus 94.7% in the Roswell Park group) and serious adverse events (23.9% versus 20% in the Xelox group; 23.1% versus 18.2% in the Mayo Clinic group; and 41.6% versus 23.5% in the Roswell Park group). Fewer males than females also discontinued treatment due to adverse events (5.3% versus 10.7% in the Mayo Clinic group; 8.3% versus 14.6% in the Roswell Park group; and 17.8% versus 25.8% in the Xelox group).

There were no clinically significant differences in adverse events between treatment groups in relation to creatinine clearance levels.

COMMENT:

The safety data from the study essentially indicates the well recognised toxicity profile for the two 5-FU/LV treatment groups with a higher incidence of diarrhoea, nausea, stomatitis, fatigue, neutropenia, abdominal pain and anorexia compared to the Xelox patients, whereas the latter patients experienced more vomiting, paresthesia, peripheral neuropathy and hand/foot syndrome. All of this is in line with the well recognised toxicity profiles for these agents. There were no new adverse events highlighted in the review of safety data from Study NO16968 and accordingly it is considered that Xelox in the adjuvant setting is associated with a toxicity profile well recognised and generally adequately managed.

FUM Meta-analysis:

In March 2007 Roche Pty Ltd received approval in the EU for capecitabine for the treatment of advanced gastric cancers. The study schedule for capecitabine in this trial (ML17032) utilised (in combination with Cisplatin) 1000/m^2 twice daily on Days 1-14 every three weeks and was associated in the study with a frequency of 22-30% of all grades of hand/foot syndrome (HFS). As this was considerably lower than that previously observed with a higher dose regimen of capecitabine (namely 1250mg/m^2 twice daily on Days 1-14 every three weeks with a frequency of 53-60% of HFS), it was mooted that a follow-up meta-analysis (FUM) should be undertaken. Plans were thus made to review 14 registered studies for the incidence of HFS, gastrointestinal adverse events, diarrhoea and Grade III/IV neutropenia. The meta-analysis would include the capecitabine monotherapy trials in metastatic colorectal cancer (Studies S01495 and S014796), the adjuvant colon cancer study (Study M660001), capecitabine combination trials in advanced gastric cancer (Study ML17032) and metastatic colorectal cancer studies (N016966 and N016967).

Update of this approach now includes 14 completed capecitabine registration trials which include four studies of metastatic breast cancer, three studies of metastatic colorectal cancer and one study of adjuvant colon cancer including the most recent Study NO16968. Overall there are eight pool data sets.

Baseline and demographic characteristics for the ITT population were comparable across treatment arms and data sets.

The analyses examined time to first onset, which was calculated as the difference between the date of first onset of the pre-specified adverse event and the date of first study medication plus one day. Factors investigated included starting date of capecitabine, cumulative dose of capecitabine, relative dose intensity between the first six weeks of treatment, treatment duration, gender, age and ECOG score at baseline. Various sub-group analyses were also undertaken in relation to capecitabine combinations and intended indication, that is, adjuvant, first line breast cancer, first line colorectal cancer, second line metastatic colorectal cancer and first line advanced metastatic gastric cancer.

Cox-regression and logistic models were applied.

The covariates most frequently associated with increasing the risk of having HFS included capecitabine starting dose, cumulative capecitabine dose, relative dose intensity of capecitabine, duration of treatment and age. In all studies there was a statistically significant $p<0.05$ association between HFS and the covariates, the higher the capecitabine starting dose, the higher the cumulative capecitabine dose, the higher the relative dose intensity of capecitabine during the first six weeks of treatment, the longer the duration of treatment, the older the patient, male patients and ECOG score of >1.

Review of gastrointestinal adverse events revealed that the co-variates most frequently associated with the increasing risk of having a gastrointestinal (GI) adverse event included capecitabine starting dose, duration of treatment, age and ECOG score.

In all studies there was a statistically significant ($p<0.05$) association between GI adverse events and cumulative capecitabine dose, relative dose intensity in the first six weeks, duration of study treatment and ECOG score.

Review of the adverse event of diarrhoea revealed the covariates most frequently associated with the increasing risk of having diarrhoea included capecitabine starting dose, duration of treatment, age and ECOG score. In all studies combined there was a statistically significant ($p<0.05$) association between diarrhoea and capecitabine starting dose, cumulative capecitabine dose, relative dose intensity in the first six weeks, duration of study treatment, age and gender.

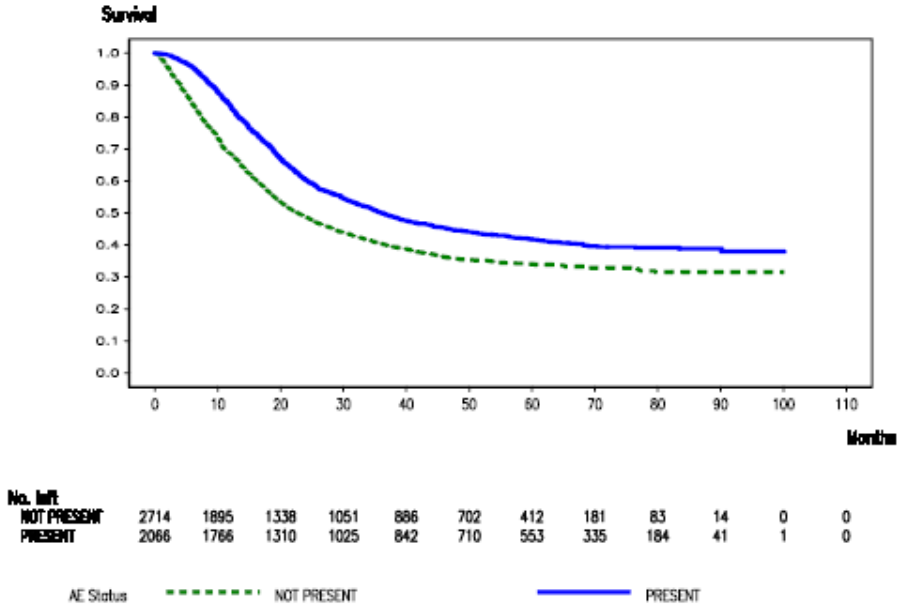
Review of neutropenia revealed the covariates most frequently associated with increasing the risk of having neutropenia included cumulative capecitabine dose, duration of treatment and ECOG score. In all studies combined there was a statistically significant ($p<0.05$) association between neutropenia and capecitabine study dose, cumulative capecitabine dose, duration of study treatment, age, gender and ECOG score.

The next component of the meta-analysis concerned the correlation of the HFS, gastrointestinal adverse events or neutropenia with overall survival in the capecitabine contained treatment arms of the various studies. This involved the administration of capecitabine either as monotherapy or in combination with another agent. The analysis in this section was to evaluate whether the status of a prespecified adverse event (that is HFS, diarrhoea or neutropenia) had an effect on the efficacy parameter of overall survival.

A stratified Cox-regression model was used with prespecified adverse event status as a factor and study indicator as the stratification variable. The log rank test was used to compare survival of functions between patients with or without the prespecified adverse events.

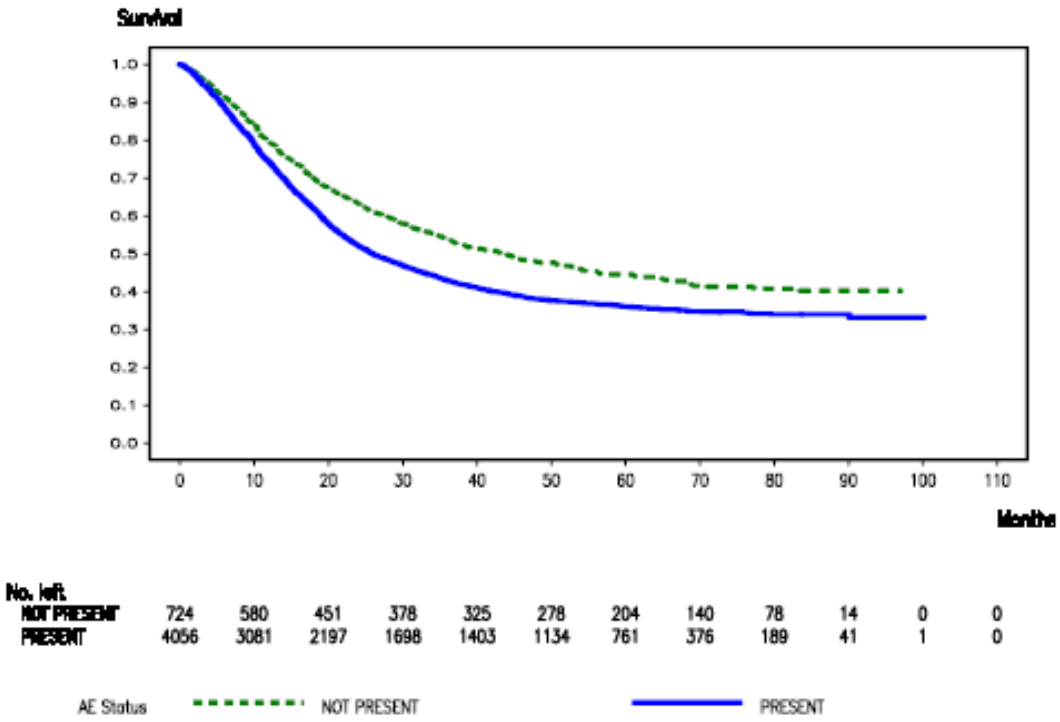
Review of the results in relation to the HFS revealed that among these patients 55.6% (1149 of 2066 patients) died with a median time to death of 1100 days. This can be compared with 61.6% of patients who died who did not have HFS, with a median time to death of 691 days. The risk of dying was significantly lower among patients who had HFS than among those that did not with an HR 0.61 and $p<0.0001$ and this is graphically in Figure 12. Further review of this data revealed that neither treatment duration nor cumulative dose of capecitabine had an impact on the results. The survival benefit having significantly remained irrespective of tumour treatment duration or cumulative dose.

Figure 12. Kaplan Meier Curve of overall survival by HFS status (Safety Population).



Review of the correlation between any grade of GI adverse event and overall survival revealed that among patients who had a GI adverse event, 60.1% (2437 of 4056) of patients died with a median time to death 789 days compared with death among 52.9% (383 of 724) of patients who did not have GI adverse event with a median time to death of 1328 days. There was no statistically significant difference in the risk of dying between patients who had a GI adverse event and those that did not, with an HR 0.93 and p=0.1981 and this is graphically presented in Figure 13.

Figure 13. Kaplan Meier Curve of overall survival by GI adverse event status (Safety Population).

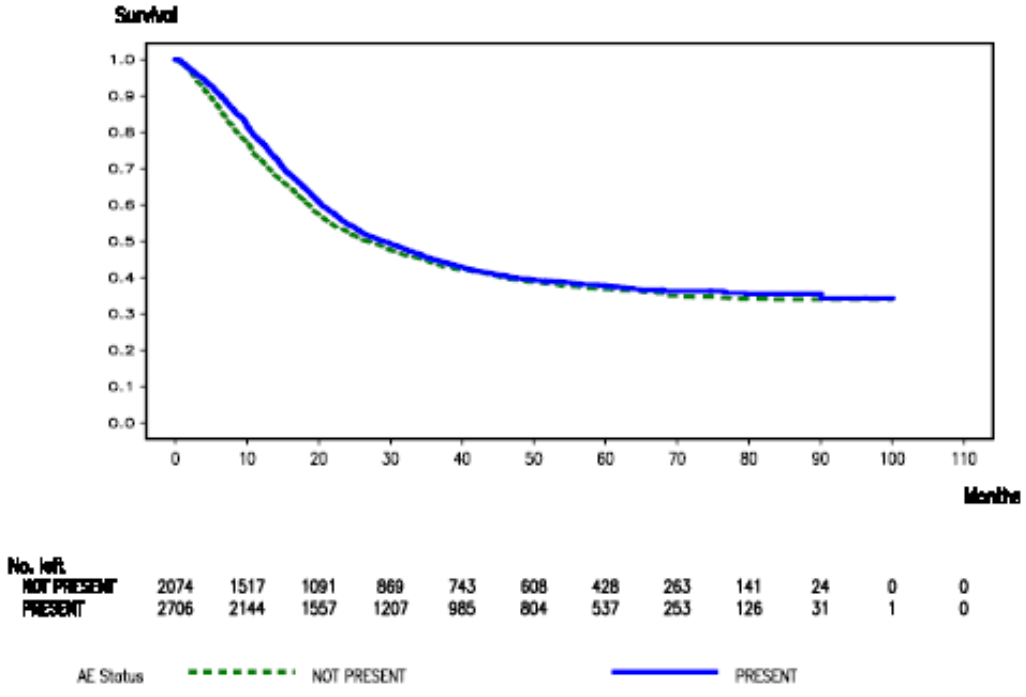


It was noteworthy however that although the risk of dying was not significantly different between the patients who had a GI adverse event and those who did not, there is a clear separation of survival curves which was maintained throughout the evaluation period for patients who had a GI adverse event and those who did not, favouring those who did not have a GI adverse event.

Accordingly further analyses were undertaken splitting the data so that patients with capecitabine contained treatment in the adjuvant setting were separated from those who received it as either first or second line therapy for metastatic disease. It was revealed that a greater percentage of patients who received first or second line treatment with capecitabine than patients who had received adjuvant treatment with capecitabine had a GI adverse event (89% versus 79%). Among patients with a GI adverse event, a greater percentage of patients who received first or second line treatment died compared with those who received adjuvant treatment (81.3% versus 25%). Patients who received capecitabine as first or second line treatment had a less favourable overall survival than patients who received capecitabine as adjuvant treatment regardless of GI adverse events. Therefore, in the set of all patients, the results were driven by the fact that cancer patients who had received capecitabine as adjuvant treatment not only had a better overall survival but a lower percentage of them had GI adverse events compared with patients who received first or second line treatment with capecitabine.

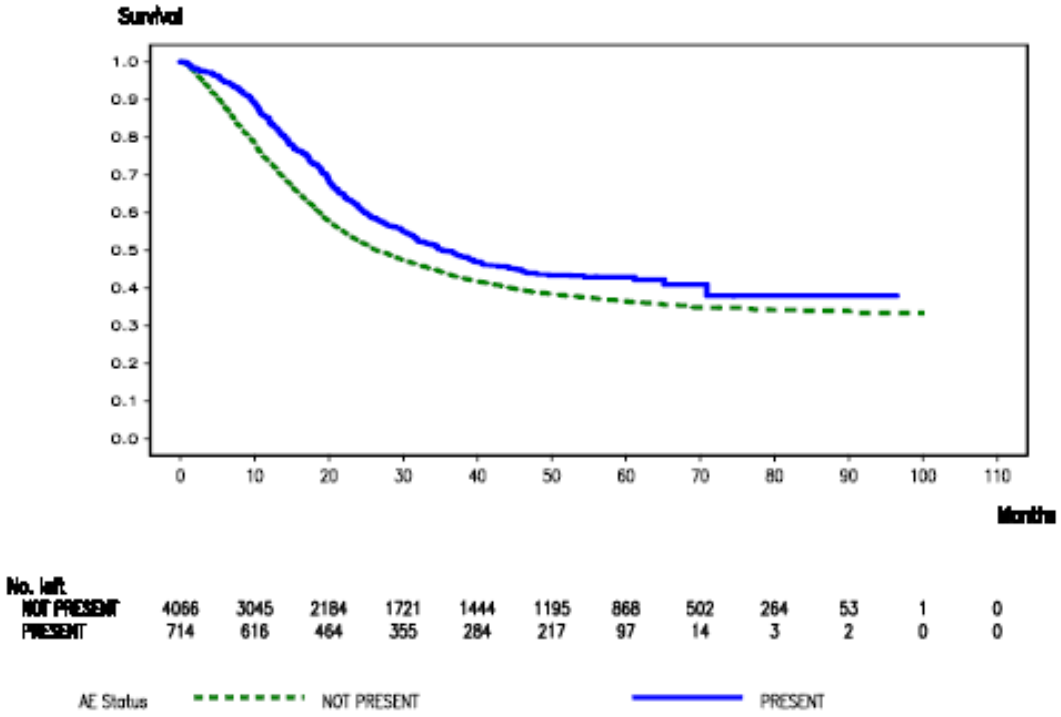
Correlation between any grade of diarrhoea and overall survival revealed that among patients who had diarrhoea, 58.9% (1593 of 2706) patients died with a median time to death of 884 days. This can be compared to 59.2% (1227 of 2074) patients that died who did not have diarrhoea with a median time to death being 822 days. There was a statistically significant lower risk of dying for patients who had diarrhoea compared with those who did not with an HR 0.80 and p<0.0001 this is graphically presented in Figure 14. The data was again reviewed according to separation between those patients receiving adjuvant treatment versus treatment for metastatic disease, the occurrence of diarrhoea provided a small but non-significant survival advantage for the patients receiving adjuvant therapy (HR 0.84 and p=0.0536) and a statistically significant survival advantage for metastatic cancer patients (HR 0.79 and p<0.0001).

Figure 14. Kaplan Meier Curve of overall survival by Diarrhoea status (Safety Population).



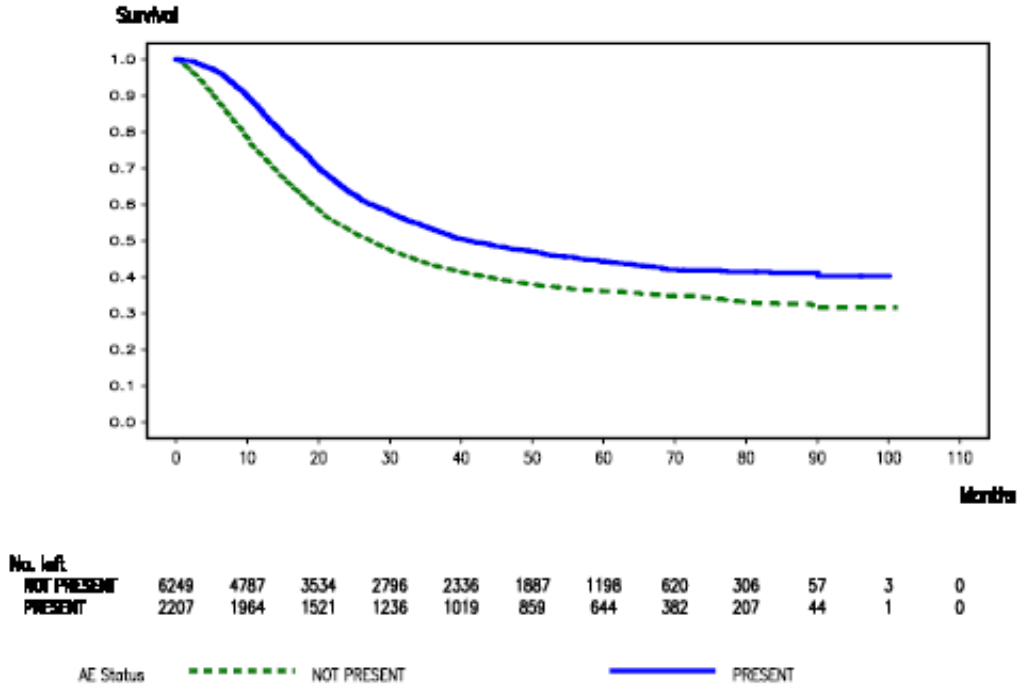
Correlation between any grade of neutropenia and overall survival revealed that most patients did not have neutropenia (85% in all studies). Among those that did have neutropenia, 53.6% died with a median time to death of 1080 days. This can be compared to 59.9% of patients dying who did not have neutropenia, with a median time to death of 804 days. Status of neutropenia appeared to have a statistically significant impact on dying (HR 0.76 and p<0.0001). The presence of neutropenia had a positive effect on overall survival Figure 15.

Figure 15. Kaplan Meier Curve of overall survival by Neutropenia status (Safety Population).



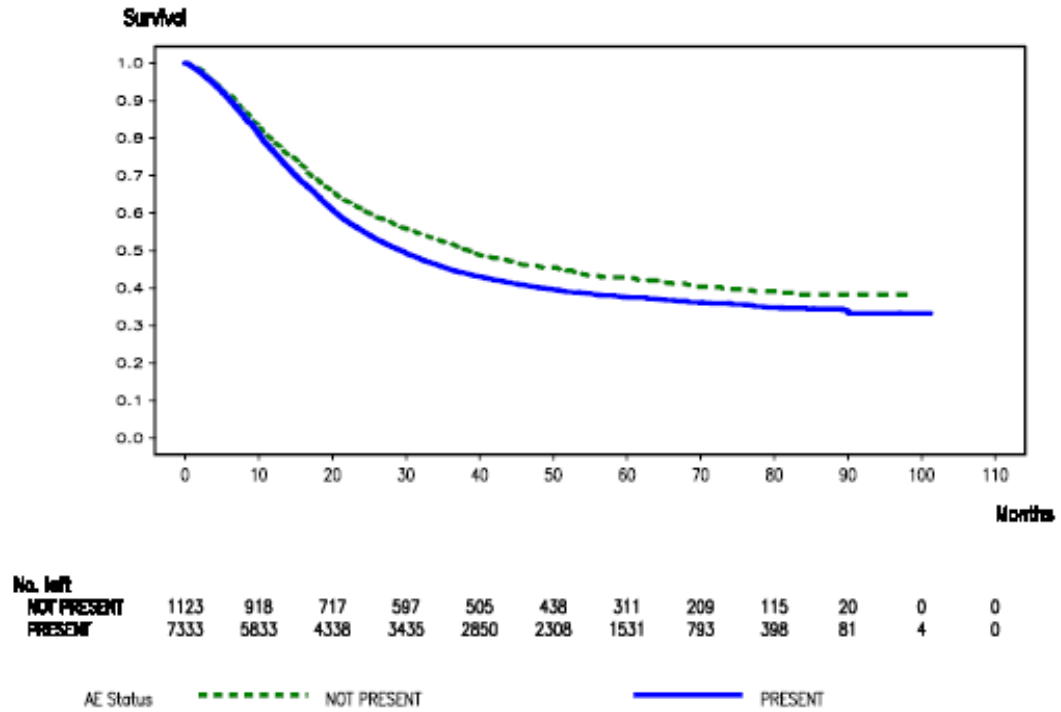
Further analyses were undertaken in which the data was pooled to include both capecitabine containing regimens and those receiving 5-FU/LV as intravenous therapy. With regards to assessment of the correlation between HFS and overall survival, it was revealed that among HFS patients, 55.1% died with a median time to death of 1256 days compared with 61.9% of patients without HFS who died with a median time to death of 831 days. The risk of dying was statistically significantly lower among patients who had HFS than among those that did not (HR 0.69 and $p<0.0001$) Figure 16. These results were similar to those obtained when only the capecitabine patients were included.

Figure 16. Kaplan Meier Curve of overall survival by HFS status, capecitabine and 5-FU/LV treatments pooled (Safety Population).



Among patients who had a GI adverse event, 60.6% died with a median time to death of 894 days. This can be compared to 56.6% of patients dying who did not have a GI adverse event with a median time to death of 1176 days. There was no statistically significant difference in the risk of dying between patients who had a GI adverse event and those who did not (HR 0.93 and p=0.0997) Figure 17. Again, these results were similar to those for GI adverse events when only capecitabine patients were included in the analyses.

Figure 17. Kaplan Meier Curve of overall survival by GI adverse event status, capecitabine and 5-FU/LV treatments pooled (Safety Population).



Among patients who had diarrhoea, 58.1% died with a median time death of 1035 days compared with death among 63% of patients who did not have diarrhoea with a median time to death of 761 days and is indicated in Part B, Section D, Table XXI. There was a statistically significant lower risk of dying for patients who had diarrhoea compared to those who did not with an HR 0.80 and $p<0.0001$ and indicated in Part B, Section D, Figure 7. Again these results were similar to those with only capecitabine patients were analysed.

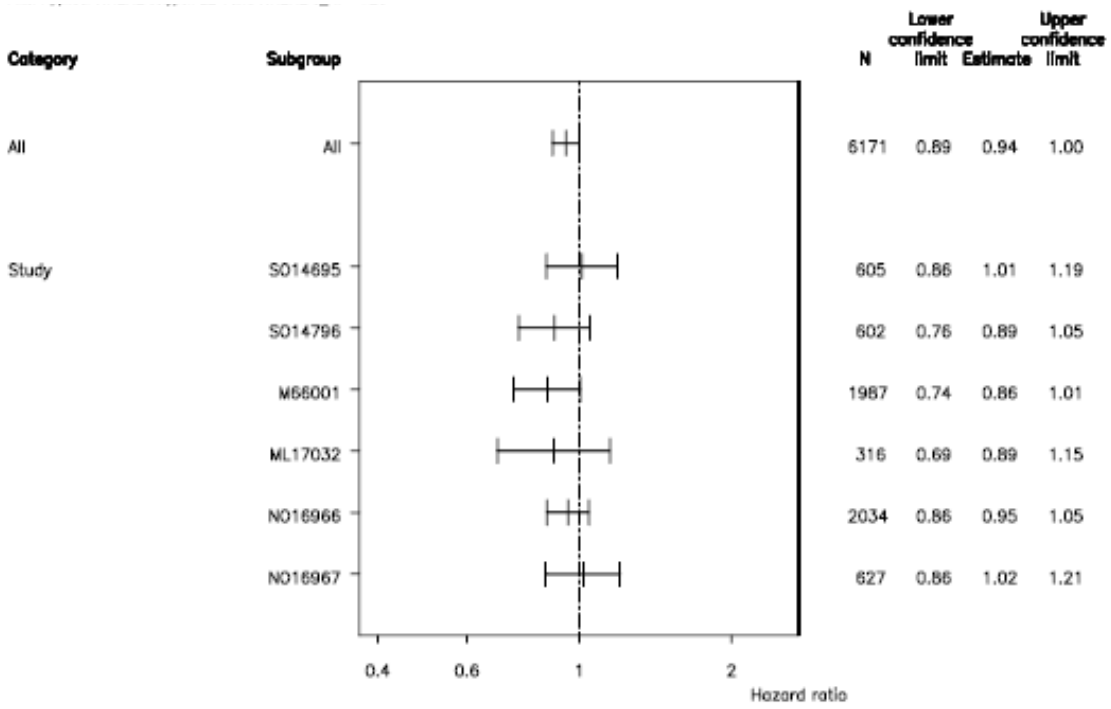
Among patients who had neutropenia, 61.9% died with a median time to death of 854 days compared with 59.6% patients without neutropenia who died with a median time to death of 949 days. Status of neutropenia appeared to have a statistically significant impact on dying (HR 0.81 and $p<0.0001$).

Non-inferiority of capecitabine containing regimens compared with 5-FU containing regimens for overall survival were investigated in a meta-analysis of six Phase III clinical trials in patients with metastatic gastric cancer, colon cancer and metastatic colorectal cancer. The pooled analysis included a total of 6171 patients; 3097 patients treated with capecitabine containing regimens and 3074 patients treated with 5-FU/LV containing regimens. The median overall survival time for patients treated with capecitabine containing regimens was 703 days (23.1 months) and this can be compared with 683 days (22.4 months) for patients treated with 5-FU/LV containing regimens (HR 0.94 and 95% CI 0.98-1.00). The p value of the overall survival difference was 0.0489.

A Cox-regression was used to test the equality of the treatment effects of capecitabine containing regimens versus 5-FU/LV containing regimens. The test for equality of these survival curves was not statistically significant ($p=0.0703$), indicating that there was no evidence of inequality. Of the co-variates included in the model, ECOG score had a significant effect on overall survival.

Sub-group analysis for overall survival, as indicated in Figure 18, examined the capecitabine containing treatment versus 5-FU/LV containing treatments in the six study meta-analysis. The estimates of HRs were similar across the studies and were not significantly different from 1. The majority of estimates of HRs were below one demonstrating a similarity between treatments across sub-groups. The CI overlapped substantially. The similarity of the HRs across the studies showed a strong evidence of a robust result.

Figure 18. Forest Plot Hazard Ratio for subgroup analysis by clinical study for progression-free survival (ITT Population)



COMMENT:

This meta-analysis data effectively confirms the recognised association between the level of capecitabine starting dose, duration of treatment, greater patient age and ECOG score and development of various toxicities associated with capecitabine. This is a well recognised phenomenon and previously appropriately presented in the Australian PI. Of interest is the fact that correlation of common adverse events with efficacy revealed that the presence of HFS was associated with prolonged survival in patients who received treatment with capecitabine. Sub-group analyses showed that the association between the presence of HFS and prolonged survival of patients was independent of treatment duration and of the total cumulative dose of capecitabine. Diarrhoea and neutropenia was also associated with improved clinical efficacy but only the association of diarrhoea was confirmed at the meta-analysis using combined sets of capecitabine and 5-FU treatment.

Meta-analysis comparing within the six clinical trials supported the non-inferiority of capecitabine compared with 5-FU/LV and supported capecitabine replacing 5-FU in mono and combination therapy for gastrointestinal cancer where considered appropriate.

This is important in the context that when discussing this meta-analysis within the proposed revision of the Clinical Trial Section of the Australian PI document, it is stated that the HR for overall survival is 0.946 with a p value = 0.489 and statement that the Xeloda containing regimens are *superior*. This is a change from the previous PI statement which indicates that Xeloda is *comparable* to 5-FU containing regimens. It is this evaluator's view that the previous wording is more appropriate as the survival benefit now demonstrated is borderline and therefore more appropriate to state non-inferiority or *comparable* rather than superior.

Post-marketing data:

A post-marketing Drug Safety Report no. 1034982 is provided in this submission. This report reviews post-marketing adverse event reports received between the 30th April 1998 and 10th July 2009 in which the patient received capecitabine either as monotherapy of in combination with oxaliplatin for colorectal cancer in either the adjuvant or metastatic settings.

This data revealed that capecitabine in combination with oxaliplatin (Xelox) in the adjuvant setting resulted in 88 case reports with a total 122 adverse events in 88 patients who were treated with capecitabine in combination with oxaliplatin. Of these, 118 events were considered serious. The most frequently reported events were diarrhoea (n=19), vomiting (n=6), dehydration (n=6), pyrexia (n=5), small intestinal obstruction (n=5), abdominal pain (n=5) and intestinal obstruction (n=4). These events were considered as expected from the known data base of Xeloda and oxaliplatin. Of note however, is the fact that there was one report of a haemolytic uremic syndrome, one report of an anaphylactic reaction and two of hypersensitivity reactions, two reports of acute myocardial infarction, one of coronary-arteriospasm, and one report of myositis. All of these types of events would benefit from ongoing review.

In relation to capecitabine monotherapy in the adjuvant setting, there were 96 case reports, with a total of 205 adverse events and 11 co-manifestations in 96 patients who were treated with capecitabine monotherapy for colorectal cancer in the adjuvant setting. Of these 157 events were considered serious.

The most frequently reported adverse events were diarrhoea (n=28), HFS (n=12), dehydration (n=7), vomiting (n=5), DVT (n=5), myocardial infarction (n=5) and anaemia (n=5). In general terms, these events are considered expected based on Xeloda data sets. It is certainly important to recognise the issue of coronary artery spasm and potential myocardial infarction which has a well recognised association with 5-FU and which is becoming increasingly apparent with Xeloda.

In the metastatic setting capecitabine in combination with oxaliplatin was involved with 938 adverse events and 12 co-manifestations in 472 patients. Of these 843 events were considered serious. The most frequently reported events were diarrhoea (n=124), vomiting (n=46), pyrexia (n=40), nausea (n=32) and dehydration (n=25). Also noted was one episode of haemolytic anaemia and five of hypersensitivity/anaphylactic reaction. These latter aspects again require appropriate monitoring. In general terms, the events experienced were generally expected, based on the known Xeloda and oxaliplatin toxicity profiles.

With regards to capecitabine monotherapy in the metastatic setting, 483 case reports with a total of 1047 adverse events and 43 co-manifestations in 469 patients treated with capecitabine monotherapy for colorectal cancer in a metastatic setting. Of these, 680 events were considered serious. The most frequently reported events were diarrhoea (n=84), HFS (n=64), vomiting (n=33), nausea (n=30) and disease progression (n=24). Again, these events were considered expected on the basis of the known toxicity profile of capecitabine.

COMMENT:
In essence, a review of this data does not reveal any substantive differences in the safety profile of capecitabine plus oxaliplatin when used in the treatment of colorectal cancer in the adjuvant setting compared with the metastatic setting. It is worth however to again comment on the fact that the potential for hypersensitivity reactions needs monitoring and that the increasing likelihood of an association between coronary artery spasms/myocardial infarction needs to be taken into account.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a “list of questions” to the sponsor is generated.

QUESTIONS:

1. It would also be appropriate to raise with the sponsor the issue of the wording of the proposed alteration in the PI (in the Clinical Trial section) in which the sentence in relation to colon and colorectal advanced gastric cancer meta-analysis now indicates that Xeloda containing regimens are *superior* to the 5-FU containing regimens. As discussed above, the earlier statement indicated that the regimens were *comparable*. Even though it has now been

shown that there may be a borderline statistical benefit for Xeloda, it would still be more appropriate for the statement to remain as *comparable* in the Australian PI.

Sponsor's response

The word *superior* has been replaced with *comparable* In the Australian PI, in line with the clinical evaluator's and Delegate's recommendation (see below).

Clinical Summary and Conclusions

The material provided in this submission is in relation to changes proposed to be made to the Clinical Trial section of the Australian PI. It includes details of a new study undertaken in the adjuvant setting, utilising a comparison between the combination of capecitabine and oxaliplatin (Xelox) to 5-FU containing regimens, that is, the Mayo Clinic regimen and the Roswell Park regimen (Study NO16968). The sponsor would also like to update the Clinical Trial section in relation to final results from a previously submitted and evaluated meta-analysis (called FUM meta-analysis) in relation to both influence of capecitabine on toxicities and comparison of capecitabine and 5-FU containing regimens to overall survival. An updated post-marketing safety report (Report no. 1034892) with dates of assessment from 30th April 1998 – 10th July 2009 was also submitted.

In relation to the Clinical Trial NO16968, which was an open labelled randomised Phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin (Xelox) versus Fluorouracil/Leucovorin as adjuvant therapy for patients who have undergone surgery for colon cancer Stage III (Duke's Stage C). This was a multicentre study involving 225 centres worldwide. The primary objective of the trial was to demonstrate that Xelox was superior to the 5-FU containing regimens in terms of disease free survival (DFS) in chemotherapy naive patients who underwent surgery for colon cancer with Stage III or Duke's Stage C disease. The secondary objectives were to compare RFS and overall survival of the two treatment groups and to compare the safety profiles of the two treatment groups.

Approximately 1850 patients were to be randomised on a 1:1 basis to receive either Xelox or bolus 5-FU/LV according to the Mayo Clinic or the Roswell Park regimens. Patients were to be treated for 24 or 32 weeks depending on the regimen allocated to them, with subsequent assessments at six monthly intervals up to four years and then yearly thereafter. The primary analysis was to be conducted when 682 events for the DFS analysis had been reached in the ITT population across both treatment arms. At the cut-off date of April 30, 2009 the data base consisted of 648 events.

A total of 1886 patients had been enrolled; 944 to Xelox and 942 to 5-FU/LV.

Results from the study revealed that the primary objective was met in that Xelox was statistically superior to 5-FU/LV in terms of DFS in the chemotherapy naïve patient population (p = 0.0045). This was associated with a HR of 0.80 and CI 0.69-0.93, which demonstrated a 20% decrease in the initial recurrence of the original colon cancer or development of a new colon or rectal cancer or death due to any cause. Following 3, 4 and 5 years of follow-up, the DFS event free rate was higher in the Xelox group (71%, 68% and 66%, respectively) than in the 5-FU/LV arms (67%, 62% and 60%, respectively). Similar results were obtained for the per protocol population, with a p value of 0.0038 and a HR of 0.80.

Results of the analysis for the secondary endpoint of RFS again supported the results obtained in the ITT population (p=0.0024 and HR 0.78 with 95% CI 0.67 – 0.92) demonstrating a 22% decrease in the risk in the Xelox arm of recurrence or death. After 3, 4 and 5 years of follow-up the RFS event free rate was higher in the Xelox group (72%, 70% and 68%, respectively) than in the 5-FU/LV arm (67%, 63% and 61%, respectively).

In relation to overall survival, the Xelox group demonstrated a 13% decrease in the risk of death due to any cause compared to the combination of 5-FU/LV (HR of 0.87 and 95% CI 0.72 – 1.05; p=0.1486) but this did not reach statistical significance. Following 3, 4 and 5 years of follow-up the

overall survival event free rate was higher in the Xelox group (86%, 80% and 78%, respectively) than the 5-FU/LV arm (84%, 78% and 74%, respectively). The sub-group analyses essentially confirm the robustness of these results.

In relation to the safety analyses, the safety profile of Xelox and 5-FU/LV were balanced in terms of total amount of toxicities but differed in the type of toxicities reported. Depending on the regimen of 5-FU/LV employed, Xelox had less haematologic toxicity than the 5-FU/LV Mayo Clinic regimen and also less gastrointestinal and cardiac toxins than 5-FU/LV Roswell Park group. The Xelox group did however have more HFS incidences than the IV 5-FU/LV regimen. Patients had slightly more treatment-related serious adverse events in the 5-FU/LV Roswell Park group compared to the 5-FU/LV Mayo Clinic and Xelox groups. The incidence of life-threatening (Grade IV) adverse events was slightly lower in the Xelox group compared to the 5-FU/LV groups.

The toxicity profile demonstrated for the Xelox arm of study was essentially as might be expected for combined treatment of capecitabine and oxaliplatin. It is also essentially similar to that previously demonstrated for Xelox when utilised in the metastatic colorectal cancer setting.

The update of the meta-analysis of the 14 capecitabine registration studies in relation to survival and toxicities associated with capecitabine, as well as a comparison of survival from six of these trials comparing capecitabine either as monotherapy or in combination versus 5-FU/LV regimens, has essentially provided confirmation of previously reported data from the earlier assessments of the meta-analysis. Namely, capecitabine containing regimens are most frequently associated with an increased risk of the prespecified adverse events, namely HFS, gastrointestinal events and neutropenia and this is correlated with higher capecitabine starting dose, longer duration of treatment, greater patient age and a worse ECOG score. Of particular interest was that the presence of HFS was associated with prolonged survival in patients who received treatment with capecitabine. This has been reported previously. Sub-group analyses showed that the association between the presence of HFS and prolonged survival in patients was independent of the treatment duration and the total cumulative dose of capecitabine.

The meta-analysis of the six clinical trials comparing capecitabine as monotherapy or as combination therapy in both the adjuvant and metastatic settings for colon, colorectal and gastric cancers again demonstrated that the survival for capecitabine containing regimens (compared to 5-FU containing regimens) were associated with a HR of 0.94 and a p value of 0.489. This p value is statistically significant and apparently shown for the first time in this update of the meta-analysis. Nevertheless, the statement in the body of the report that the meta-analysis of six clinical trials fits the criteria supporting the non-inferiority of capecitabine compared with 5-FU and Leucovorin is appropriate.

In relation to the post-marketing report, this demonstrates that capecitabine in combination with oxaliplatin (Xelox) has resulted in 88 case reports with a total of 122 adverse events in 88 patients of which 118 events were serious. The most frequently reported events were diarrhoea (n=19), vomiting (n=6), dehydration (n=6), pyrexia (n=6), small intestinal obstruction (n=5), abdominal pain (n=5) and intestinal obstruction (n=4). It was also noted that there was one episode of haemolytic uremic syndrome and three events of hypersensitivity/anaphylactic reaction.

While these events are generally anticipated in the context of the recognised toxicity profile for capecitabine and oxaliplatin, appropriate monitoring for hypersensitivity reactions is worthwhile particularly in the context of the combination treatment. While coronary artery spasm/myocardial infarction is recognised as an associated toxicity with capecitabine and also demonstrated with 5-FU/LV regimens, it is noted that it is appropriately mentioned in the current PI.

With regards to benefit risk assessment for these proposed changes to the Australian PI the clinical evaluator considered that the new study comparing Xelox to 5-FU/LV in the adjuvant setting has demonstrated a benefit in the context of disease free survival but, at this time, without survival

advantage. The toxicity profile for Xelox is as might be anticipated for this drug combination. It is also essentially similar to that previously reported in the metastatic setting. The clinical evaluator considered that there is a likely benefit from the addition of oxaliplatin to capecitabine in the adjuvant setting and there is no evidence of increased risk in the context of adverse effects. It therefore supports a benefit risk ratio for the Xelox combination.

In relation to the update of the meta-analysis, with regards to toxicities and relationship to capecitabine the data are essentially as previously reported and again appropriate in the context of the recognised toxicity profile for capecitabine. In the context of survival comparisons between capecitabine regimens and 5-FU/LV regimens in colorectal cancer, the clinical evaluator considered that a statement regarding non-inferiority for capecitabine versus 5-FU/LV remains pertinent rather than any indication of superiority.

The safety update does not provide any significant new concerns regarding the safety profile for Xelox with the possible exception of careful monitoring for hypersensitivity reactions.

In conclusion therefore, the clinical evaluator supported the proposed changes to the Australian PI along the lines as proposed by the sponsor with the exception of the statement in the Clinical Trial section related to the meta-analysis for gastrointestinal cancers and stating that Xeloda containing regimens are *superior* to 5-FU containing regimens (that is, altering the previous statement of *comparable*). The clinical evaluator feels that the word comparable is still the most appropriate term.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No quality data were included in the current submission.

Nonclinical

No nonclinical data were included in the current submission.

Clinical

The clinical evaluator has recommended approval of the application.

The clinical data to support use of the Xelox combination in the adjuvant setting were reviewed by the clinical evaluator in the context of the application to revise the PI for capecitabine. This application also contained some other data (a meta-analysis of capecitabine studies and a post-marketing safety report).

The Committee's advice was only being sought in relation to the adjuvant Xelox data.

Efficacy

Evidence to support the applications comes from a single randomised controlled trial (Study NO16968). The short-term safety findings from the study have been published[5] and the efficacy findings have been published as a conference abstract[6].

[5]Hans-Joachim Schmoll, H-J *et al* (2007). Phase III Trial of Capecitabine Plus Oxaliplatin As Adjuvant Therapy for Stage III Colon Cancer: A Planned Safety Analysis in 1,864 Patients. *Journal of Clinical Oncology* 25:102-109.

[6] Haller, D.G *et al* (2010). Efficacy findings from a randomized phase III trial of capecitabine plus oxaliplatin versus bolus 5-FU/LV for stage III colon cancer (NO16968): No impact of age on disease-free survival (DFS). 2010 Gastrointestinal Cancers Symposium. Abstract No: 284 .

Subjects enrolled had Dukes C colon cancer which had been completely resected. Subjects were randomised to receive either the proposed Xelox combination (8 cycles/24 weeks) or a bolus 5-fluorouracil / folinic acid (5-FU/FA) regimen. Investigators could choose one of two standard 5-FU/FA regimens - Mayo Clinic (6 cycles/24 weeks) or Roswell Park (4 cycles/32 weeks).

The primary endpoint was disease-free survival (DFS) which is an accepted endpoint for adjuvant trials. Results are summarised in the clinical evaluation. The Xelox combination was associated with a significant reduction in the risk of disease recurrence or death (- 31.3% versus 37.5%); HR was 0.80; (95% CI 0.69 – 0.93 and p=0.0045). There was no difference between the two treatments in overall survival, which was a secondary endpoint.

Safety

A total of 938 subjects were treated with the Xelox regimen in the pivotal study. Of these, 70% received the planned 8 cycles.

The overall safety profiles of Xelox and 5-FU/FA regimens are summarised in the following table (9).

Table 9.

	5-FU/FA Mayo Clinic	**5-FU/FA Roswell Park**	**Xelox**
n	657	269	938
Pts with adverse events (AEs)	94.7 %	97.4 %	98.7 %
Pts with related AEs	92.8 %	97.4 %	98.1 %
Pts with serious AEs (SAEs)	20.4 %	32.7 %	22.2 %
Pts with related SAEs	15.7 %	21.9 %	15.0 %
Pts with Grade 3 or 4 AEs	51.9 %	56.1 %	59.9 %
Pts with Grade 4 AEs	12.6 %	7.8 %	6.7%
Pts discontinued due to AEs	7.8 %	11.5 %	21.4 %
Treatment related deaths	0.3 % (n=2)	1.5 % (n=4)	0.7 % (n=7)

These data suggest that the Xelox regimen has broadly similar overall toxicity compared to the 5FU/FA regimens, although a greater proportion of patients discontinued treatment due to adverse events.

In terms of individual adverse events, Xelox was associated with an increased incidence of neurological toxicity (for example peripheral neuropathy, paresthesia), hand-foot syndrome, vomiting and thrombocytopaenia. It was associated with less severe gastrointestinal toxicity than the Roswell park regimen and less severe haematological toxicity than the Mayo regimen.

Risk Management Plan

Neither sponsor was required to submit a risk management plan as part of the current application.

Risk-Benefit Analysis

Delegate Considerations

1. Overall risk-benefit

Capecitabine monotherapy has previously been demonstrated to have equivalent efficacy to 5FU/FA in the adjuvant setting. Data in this submission indicates that the addition of oxaliplatin to capecitabine results in statistically significant improvement in efficacy. The magnitude of the improvement is comparable to that seen when oxaliplatin is added to 5FU/FA, as in the MOSAIC trial, as shown in the following table (10).

Table 10.

	MOSAIC*		NO16968	
	oxaliplatin + 5-FU/FA (Folfox4)	**5-FU/FA**	**oxaliplatin + capecitabine (Xelox)**	**5-FU/FA**
Median Follow-up	4 years		57 months	
HR (95% CI)	0.75 (0.62 – 0.90)		0.80 (0.69 – 0.93)	
P value	?		0.0045	
3-yr DFS	-	-	71 %	67 %
4-yr DFS	69.7 %	61.0 %	68 %	62 %
5-yr DFS	-	-	66 %	60 %

*Results presented from MOSAIC are for Dukes C patients only.

The safety profile of the Xelox regimen was broadly comparable to the 5FU/FA regimens used in the submitted study. Some increase in peripheral neuropathy and hand-foot syndrome but with decreased toxicity in some other organ systems was noted.

The Delegate therefore considered that both the efficacy and the safety of the new regimen have been satisfactorily demonstrated and the Delegate proposed to approve the application.

2. Choice of comparator

The clinical evaluator has commented that it would have been desirable to have a comparison of the Xelox regimen against capecitabine monotherapy. Another useful comparison would have been the Xelox regimen against the approved oxaliplatin + 5FU/FA (Folfox4) regimen.

The pivotal trial in this submission was commenced in 2003.

- for the Folfox4 regimen, the pivotal study was not published until June 2004 and it was not approved by the TGA until November 2004;
- for capecitabine monotherapy, the pivotal study was not published until June 2005 and it was not approved by the TGA until September 2005.

As neither of these regimens could have been considered as standard therapy at the time the trial commenced, the Delegate considered that the use of 5FU/FA as the comparator is appropriate.

3. Indication - oxaliplatin

The proposed new indication for oxaliplatin is:

> *".. for adjuvant treatment of Stage III (Dukes C) colon cancer".*

The data submitted to date only support use in combination with 5FU/FA or capecitabine. The Delegate therefore proposed to restrict the approved indication as follows:

> *".. for adjuvant treatment of Stage III (Dukes C) colon cancer, in combination with a fluoropyrimidine agent ".*

4. Indication – capecitabine

The existing indication for capecitabine is:

> *"For the adjuvant treatment of Dukes Stage C, and high-risk Stage B, colon cancer"*

No change is being proposed by the sponsor. However, the data submitted to date only support use as monotherapy or in combination with oxaliplatin, and the existing indication suggests that

capecitabine can be used in combination with other agents. The Delegate therefore proposed to amend the indication to read:

> *"For the adjuvant treatment of Dukes Stage C, and high-risk Stage B, colon cancer, either as monotherapy or in combination with oxaliplatin."*

The Delegate proposed to approve the application with amendments to the indications and product information as outlined above. The advice of the Advisory Committee on Prescription Medicines (ACPM) is requested.

Response from Sponsor

Comment on the Delegate's Proposed Action:

Roche Products Pty Limited (Roche) concurs with the Delegate's decision to approve the combination use of Xeloda (capecitabine) with oxaliplatin for the treatment of adjuvant colon cancer.

Indication – oxaliplatin

Sanofi-Aventis concurs with the indication wording as proposed by the Delegate for the oxaliplatin application, the indication to be registered for the oxaliplatin range of products shall read:

oxaliplatin *is indicated for adjuvant treatment of Stage III (Duke's C) colon cancer, in combination with a fluoropyrimidine agent.*

Indication – capecitabine

Roche does not concur with the indication wording as proposed by the Delegate for the Xeloda application. The current indication for adjuvant colon cancer reads as follows:

Xeloda is indicated for the adjuvant treatment of patients with Dukes' Stage C and high-risk Stage B colon cancer.

The proposed wording recommended by the Delegate reads:

Xeloda is indicated for the adjuvant treatment of patients with Dukes' Stage C and high-risk Stage B colon cancer, either as monotherapy or in combination with oxaliplatin.

Roche agrees that the proposed wording reflects the clinical data sets presented to the TGA in support of Xeloda use in the treatment of colon cancer, hence it is a true and exact interpretation of the clinical evidence. However, we believe the current indication wording should not be changed, for the following reasons:

• With this application, Roche requested an update to the Xeloda Product Information (PI) to include new clinical data in support of combination use with oxaliplatin. A change to indication wording was not requested. The Delegate has acknowledged this in the *Overall conclusion and Risk/Benefit Assessment* section above.

• The clinical evaluation report did not recommend a change to the current indication wording, hence the clinical evaluator believes the current indication is still valid.

• The proposed PI clearly presents Xeloda monotherapy and combination treatment options for colon cancer patients under the "Clinical Trials" and "Dosage and Administration" sections, giving clinicians the information they require to appropriately treat their patients with Xeloda.

• The current indication (as worded above) was initially registered in September 2005, based on clinical Study M66001 (X-ACT) supporting the use of Xeloda as monotherapy treatment in colon cancer patients. The indication wording was accepted by the TGA and endorsed by the (then) Australian Drug Evaluation Committee (ADEC), with minor changes to specify the patient

population. The indication was subsequently Pharmaceutical Benefits Scheme listed in November 2005, under Authority script for *Adjuvant treatment of Stage III (Dukes C) colon cancer, following complete resection of the primary tumour*.

• Clinicians have become familiar with this indication and Xeloda is well established in the treatment algorithm for colon cancer as a monotherapy option for patients. Guidelines from the National Comprehensive Cancer Network (NCCN); Colon Cancer version 1.20111[7] endorse this regime as a treatment option.

• With the additional clinical study (NO16968), the evidence is now supporting the alternate treatment option for combination use with oxaliplatin, supplementing the conventional monotherapy treatment, hence the broader clinical evidence further supports the approved indication wording. The recently updated NCCN guidelines have incorporated combination use with oxaliplatin for adjuvant treatment.

• Globally, the European Medicines Agency (EMA) has reviewed similar applications for monotherapy and combination use with oxaliplatin. For both applications, the indication wording remained unchanged and reads as follows:

> *Xeloda is indicated for the adjuvant treatment of patients following surgery of Stage III (Dukes' Stage C) colon cancer.*

• Further, this indication wording is the preferred language used across the globe and is thus included in the company core data sheet for Xeloda. Other countries with the same or similar wording include the European Union states (including the United Kingdom), Canada, Japan, New Zealand and Switzerland.

• Metastatic colorectal indication precedence. As a comparison, Roche wishes to highlight the registration history for the metastatic colorectal cancer applications.

In the original application, Roche requested the following indication wording based on two identical studies comparing Xeloda monotherapy to 5-FU/LV (Mayo regimen) in advanced or metastatic colorectal cancer patients:

> *Xeloda is indicated for the treatment of patients with advanced or metastatic colorectal cancer.*

TGA approved this indication in January 2001. A subsequent application was submitted in support of combination use with oxaliplatin +/- bevacizumab, first-line and second-line treatment in metastatic colorectal patients. This application requested a change to the dosage recommendation with no change to indication wording. The TGA approved the alternate treatment regimen for combination use without a change to indication in April 2008. Considering this circumstance, the applications for adjuvant colon cancer follows the same evaluation path, hence based on this precedence with the metastatic colorectal cancer applications, the sponsor believed the indication wording should not be changed with the subsequent adjuvant application. Roche believes the currently approved indication should remain unchanged with this application. The indication wording succinctly reflects the patient group and disease to be treated and is well established in the mind of the clinician. The treatment options to be used are clearly stated within the PI under the appropriate sections of the document.

Roche trusts the ACPM will consider the indication wording to be appropriate and remain unchanged with this application.

---

[7] NCCN Clinical Practice Guidelines in Oncology (NCCn Guidelines) Colon Cancer, version 1.2011, http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the joint submission from Roche Products Pty Limited and Sanofi-Aventis Australia Pty Ltd to register combination use of capecitabine (Xeloda) and oxaliplatin (Eloxatin) as Xelox.

Xeloda – tablet, 150 mg and 500 mg, for changes to Product Information requiring evaluation of data:

> *For the adjuvant treatment of patients with Dukes Stage C and high-risk Stage B colon cancer, either as monotherapy or in combination with oxaliplatin.*

Eloxatin - concentrate (50mg, 100mg and 200mg) or powder (50 mg and 100 mg) for an extension of indications:

> *For adjuvant treatment of Stage III (Dukes C) colon cancer, in combination with a fluorolpyrimidine agent.*

In making this recommendation the ACPM supported the Delegate in limiting the indication to match the evidence provided in the pivotal trials.

Outcome

Based on a review of quality, safety and efficacy, TGA approved

(1) the registration of Xeloda (tablet, 150 mg and 500 mg) containing capecitabine for the new indication:

For the adjuvant treatment of patients with Dukes' stage C and high-risk stage B colon cancer, either as monotherapy or in combination with oxaliplatin.

and

(2) the registration of Eloxatin/ Winthrop oxaliplatin /Oxaliplatin Dakota (oxaliplatin) concentrate (50mg, 100mg and 200mg) or powder(50 mg and 100 mg) for the new indication:

For adjuvant treatment of stage III (Duke's C) colon cancer, in combination with a fluoropyrimidine agent

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

ELOXATIN®

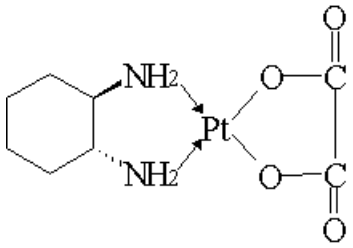
NAME OF THE MEDICINE

Non-proprietary Name

Oxaliplatin concentrated solution for injection.

Chemical Structure

Oxaliplatin has the following chemical structure:



CAS Number

61 825-94-3.

DESCRIPTION

Oxaliplatin is designated chemically as [*SP*-4-2]-(1*R*,2*R*)-(cyclohexane-1,2-diamine-k^2*N,N´*(oxalato(2-)-k^2*O*^{1},*O*^{2}]platinum (II)

The empirical formula of oxaliplatin is $C_8H_{14}N_2O_4Pt$ and its molecular weight is 397.3.

Oxaliplatin is a white to off-white crystalline powder. It is slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol.

Eloxatin concentrated solution for injection also contains water for injections.

PHARMACOLOGY

Pharmacodynamics

Oxaliplatin is an antineoplastic drug belonging to a new class of platinum based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) and an oxalate group. Oxaliplatin is a single enantiomer, the Cis-[oxalato(trans-λ-1,2-DACH) platinum].

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour activity in a variety of tumour model systems, including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin resistant models.

A synergistic cytotoxic action has been observed in combination with fluorouracil both *in vitro* and *in vivo*.

Studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin interact with DNA to form both inter- and intra-strand cross links, resulting in the disruption of DNA synthesis leading to cytotoxic and antitumour effects.

Pharmacokinetics

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two hour infusion of oxaliplatin at 130mg/m² every three weeks for 1 to 5 cycles and oxaliplatin at 85mg/m^2 every two weeks for 1 to 3 cycles are as follows:

Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of Oxaliplatin at 85mg/m^2 Every Two Weeks or at 130mg/m^2 Every Three Weeks

Dose	C_{max} µg/mL	AUC_{0-48} µg.h/mL	AUC µg.h/mL	$t_{1/2}\alpha$ h	$t_{1/2}\beta$ h	$t_{1/2}\gamma$ h	V_{ss} L	CL L/h
85mg/m^2								
Mean	0.814	4.19	4.68	0.43	16.8	391	440	17.4
SD	0.193	0.647	1.40	0.35	5.74	406	199	6.35
130mg/m^2								
Mean	1.21	8.20	11.9	0.28	16.3	273	582	10.1
SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

Mean AUC_{0-48} and C_{max} values were determined on Cycle 3 (85mg/m^2) or Cycle 5 (130mg/m^2).
Mean AUC, V_{ss}, and CL values were determined on Cycle 1.
C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis.
$t_{1/2}\alpha$, $t_{1/2}\beta$ and $t_{1/2}\gamma$ were determined by compartmental analysis (Cycles 1-3 combined).

At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85mg/m^2 every two weeks or 130mg/m^2 every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450 mediated metabolism of the diaminocyclohexane (DACH) ring.

Oxaliplatin undergoes extensive biotransformation in patients, and no intact drug was detectable in plasma ultrafiltrate at the end of a 2 hour infusion. Several cytotoxic biotransformation products including the monochloro, dichloro and diaquo DACH platinum species have been identified in the systemic circulation together with a number of inactive conjugates at later time points.

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours following administration. By day 5, approximately 54% of the total dose was recovered in the urine and <3% in the faeces.

A significant decrease in clearance of ultrafilterable platinum from 17.6 ± 2.18 L/h to 9.95 ± 1.91 L/h in renal impairment (creatinine clearance 12–57mL/min) was observed together with a statistically significant decrease in distribution volume from 330 ± 40.9 to 241 ± 36.1 L. The effect of severe renal impairment on platinum clearance has not been evaluated.

CLINICAL TRIALS

Adjuvant Treatment of Stage III (Duke's C) Colon Cancer

Use in combination with fluorouracil and folinic acid (FU/FA)

EFC3313 (MOSAIC)

EFC3313 (MOSAIC) was an international, multicentre, open-label, randomised phase III study comparing two treatment regimens (FOLFOX4 versus FU/FA) as adjuvant treatment of Duke's stage B2/C colon cancer. FOLFOX4 - Day 1; Oxaliplatin 85mg/m^2 as 2 hour infusion, folinic acid 200mg/m^2 over 2 hours, followed by a FU bolus of 400mg/m^2, then a FU infusion of 600mg/m^2 over 22 hours. Folinic acid and FU repeated on Day 2. FU/FA - the same regimen without oxaliplatin. Both were repeated every two weeks. A total of 1108 patients were treated in the FOLFOX4 arm and 1111 in the FU/FA arm. The median number of cycles received in both arms was 12.

In the ITT population, after a median of 4 years follow-up, patients treated with FOLFOX4 had significantly increased disease-free survival (DFS), the primary endpoint, compared to patients treated with FU/FA (Table 1). In the sub-group analysis by disease stage, only patients with Stage III disease had significantly increased disease-free survival. The trial was not powered to show such a benefit with Stage II disease, but the trend indicated a small benefit is likely. This benefit is not as great as in Stage III patients. The trial was not powered to show significant benefit in overall survival (OS).

Table 1: Disease Free Survival and Overall Survival – ITT Population

	Disease Stage	FOLFOX4	FU/FA	Hazard Ratio [95% CI]
Disease-free Survival - 4 year probability (%) of surviving disease-free [95% CI]	All	75.9 [73.4, 78.5] (n=1123)	69.1 [66.3, 71.9] (n=1123)	**0.76** **[0.65, 0.90]**
	II	85.1 [81.7, 88.6] (n=451)	81.3 [77.6, 85.1] (n=448)	0.80 [0.58, 1.11]
	III	69.7 [66.2, 73.3] (n=672)	61.0 [57.1, 64.8] (n=675)	**0.75** **[0.62, 0.90]**
Overall Survival* - 4 year probability (%) of surviving [95% CI]	All	84.0 [81.7, 86.3] (n=1123)	82.4 [80.0, 84.8] (n=1123)	0.89 [0.72, 1.09]
	II	91.0 [88.1, 93.9] (n=451)	91.1 [88.3, 93.9] (n=448)	0.98 [0.63, 1.53]
	III	79.2 [76.0, 82.5] (n=672)	76.6 [73.2, 80.0] (n=675)	0.86 [0.68, 1.08]

* The trial was not powered to show significant benefit in overall survival.

Use in combination with capecitabine

NO16968

Data from a open-label, multi-centre, randomised, controlled phase III clinical trial in patients with stage III (Dukes' C) colon cancer supports the use of capecitabine in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer (NO16968). In this trial, 944 patients were randomised to 3 week cycles for 24 weeks with capecitabine (1000mg/m^2 twice daily for 2 weeks followed by a 7 day rest period) in combination with oxaliplatin (130mg/m^2 intravenous infusion over 2 hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and leucovorin. In the primary analysis (ITT population), median observation time was 57 months for DFS and 59 months for OS. XELOX group had a statistical significant improvement in DFS compared to 5-FU/LV (HR=0.80, 95% CI=[0.69; 0.93]; p=0.0045). The 3 year DFS rate was 71% for XELOX versus 67% for 5-FU/LV. The analysis for the secondary endpoint of relapse free survival (RFS) supports these results with a HR of 0.78 (95% CI=[0.67; 0.92]; p=0.0024) for XELOX vs. 5-FU/LV. XELOX showed a trend towards superior OS with a HR of 0.87 (95% CI=[0.72; 1.05]; p=0.1486). The 5 year OS rate was 78% for XELOX versus 74% for 5-FU/LV.

Treatment of Advanced Colorectal Cancer

Use in combination with fluorouracil and folinic acid (FU/FA)

A total of 1312 patients have been enrolled in 3 pivotal trials, for untreated (EFC7462/N9741, EFC2962) and pretreated patients (EFC2964). These studies evaluated the efficacy of oxaliplatin at the same dose intensity (85mg/m²/2 weeks) when added to different FU/FA doses and regimens, in terms of overall survival, progression free survival and tumour response.

EFC7462/N9741 was a multicentre open-label randomised, 3-arm phase III study of irinotecan and FU/LV (IFL), or oxaliplatin and irinotecan (IROX), or oxaliplatin and FU/LV (FOLFOX4) as initial treatment of patients with advanced colorectal cancer. Therapy consisted of 2-week FOLFOX4, 6-week IFL, or 3-week IROX treatment cycles.

A total of 795 patients were enrolled and 773 treated from May 1999 in 301 centres in the United States and Canada.

Treatment arms – FOLFOX4 Day 1: oxaliplatin 85mg/m^2 over 2 hours, folinic acid 200mg/m^2 over 2 hours, followed by a FU bolus of 400mg/m^2, then a FU infusion of 600mg/m^2 over 22 hours. Folinic acid and FU repeated on Day 2. Cycle repeated every 2 weeks.

IFL Day 1: irinotecan 125mg/m^2 over 90 minutes, folinic acid 20mg/m^2 over 15 minutes or IV push, FU bolus of 500mg/m^2 weekly x 4. Cycle repeated every 6 weeks.

IROX Day 1: oxaliplatin 85mg/m^2 over 2 hours, irinotecan 200mg/m^2 over 30 minutes. Cycle repeated every 3 weeks.

This study has demonstrated a statistically significant longer TTP (time to progression) and OS, and a significantly higher overall RR (response rate) for oxaliplatin in combination with bolus/infusional FU/LV (FOLFOX4) compared with the IFL control arm. The IROX arm has a significantly longer OS compared with the IFL arm, while TTP and RR on the IROX arm were not significantly different from the IFL arm. Median durations of treatment for each group were 24, 24 and 21 weeks for IFL, FOLFOX4 and IROX (respectively).

Table 2: Summary of Time to Progression – ITT Population

EFC7462/N9741 Time to Progression	IFL N = 264	FOLFOX4 N = 267	IROX N = 264
Number of progressors n (%)	216 (81.8)	221 (82.8)	236 (89.4)
Median TTP (months)	6.9	8.7	6.5
95% confidence interval	(6.0-7.5)	(7.8-9.8)	(5.8-7.6)

P-value (Log-Rank Test) Hazard Ratio (95% confidence interval)

FOLFOX4 vs. IFL: P=0.0014 FOLFOX4 vs. IFL: 0.74 (0.61-0.89)

IROX vs. IFL: P=0.8295 IROX vs. IFL: 1.02 (0.85-1.23)

Table 3: Summary of Overall Survival – ITT Population

EFC7462/N9741 Overall Survival	IFL N = 264	FOLFOX4 N = 267	IROX N = 264
Number of deaths n (%)	192 (72.7)	155 (58.1)	175 (66.3)
Median survival (months)	14.6	19.4	17.6
95% confidence interval	(12.4-16.7)	(17.9-21.0)	(15.8-19.6)

P-value (Log-Rank Test) Hazard Ratio (95% confidence interval)

FOLFOX4 vs. IFL: P<0.0001 FOLFOX4 vs. IFL: 0.65 (0.53-0.80)

IROX vs. IFL: P=0.0252 IROX vs. IFL: 0.79 (0.65-0.97)

Table 4: Summary of Confirmed Overall Response – Patients (N, %) with Measurable Disease

EFC7462/N9741 Overall Response	IFL N = 212	FOLFOX4 N = 210	IROX N = 215
Complete and partial response	69 (32.5)	95 (45.2)	74 (34.4)
95% confidence interval	(26.2-38.9)	(38.5-52.0)	(28.1-40.8)
Complete response	5 (2.4)	13 (6.2)	7 (3.3)
Partial response	64 (30.2)	82 (39.0)	67 (31.2)
Regression[a]	0	3 (1.4)	1 (0.5)
Stable disease	94 (44.3)	75 (35.7)	86 (40.0)

P-value (Chi-Squared Test)

FOLFOX4 vs. IFL: P=< =0.0075

IROX vs. IFL: P=0.6820

[a] Patients with measurable disease at randomisation that became too small to measure during the study were classified as regression and not partial response in this study

Table 5: Number of Deaths – Treated Patients N (%)

EFC7462/N9741	IFL N = 256	FOLFOX4 N = 259	IROX N = 258
Number of deaths within 30 days of last dose	12 (4.7)	8 (3.1)	8 (3.1)
Number of deaths within 60 days of first dose	13 (5.1)	6 (2.3)	8 (3.1)
Number of deaths during the entire study	189 (73.8)	149 (57.5)	170 (65.9)

EFC2962 was a multinational multicentre randomised phase III study in previously untreated patients, comparing two-weekly fluorouracil bolus plus infusion and high dose folinic acid (FU/FA regimen: Day 1; folinic acid 200mg/m^2 over 2 hours, followed by a FU bolus of 400mg/m^2, then a FU infusion of 600mg/m^2 over 22 hours. Repeated on Day 2.) to the same regimen combined with oxaliplatin at the dosage of 85mg/m² every two weeks. A total of 420 patients were enrolled and 417 treated from August 1995 to July 1997 in 35 centres from 9 countries. The median number of treatment cycles was 12 in the FU/FA plus oxaliplatin group and 11 in the FU/FA group. Confirmed responses after independent radiological review (intent to treat analysis n = 420) are as shown in Table 6.

The FU/FA + oxaliplatin group had a statistically significant greater response rate and longer progression free survival. There was no significant difference in OS between the two groups, however, the study was not powered to detect a difference in OS. Additionally, in both groups, post-study treatment with other agents may have influenced survival.

EFC2964 was an open label multicentre study in which patients whose disease had progressed on one of two fluorouracil/folinic acid regimens continued on the same fluorouracil/folinic acid regimen with the addition of oxaliplatin 85mg/m^2 two weekly. The two study regimens were:

Regimen 1: Day 1; folinic acid 200mg/m^2 over 2 hours, followed by a FU bolus of 400mg/m^2, then a FU infusion of 600mg/m^2 over 22 hours. Repeated on Day 2.

Regimen 2: folinic acid 500mg/m^2 over 2 hours, followed by a FU infusion of 1500mg/m^2 over 22 hours, repeated on Day 2.

The results were as shown in Table 7.

Table 6 (EFC2962)	FU/FA + Oxp n = 210	FU/FA n = 210	Difference
Objective Response Rate[1] %%	49.0	21.9	p = 0.0001
[95% CI]	[42, 56]	[16,27]	
Complete	1.4	0.5	
Partial	47.6	21.4	
Median progression free survival (months)[2] [95% CI]	8.2 [7.2, 8.8]	6.0 [5.5, 6.5]	p = 0.0003 (log rank)
Median survival time (months)	16	14.7	p= 0.109
[95% CI]	[14.7, 18.2]	[13.7, 18.2]	(log rank)

Table 7 (EFC2964)	Regimen 1 n =57	Regimen 2 n = 40	All Treated Patients n = 97
Confirmed Responses n(%) [95% CI]			
Expert assessment	13 (23%) [13-36]	7 (18%) [7-33]	20 (21%) [13-30]
Investigator assessment	11 (19%) [10-32]	10 (25%) [13-41]	21 (22%) [14-31]
Median progression free survival (months) [95% CI]	5.1 [3.1 - 5.7]	4.6 [3.0 - 5.5]	4.7 [3.4 - 5.5]
Median overall survival (months) [95% CI]	11.1 [8.3 -13.0]	10.5 [8.6 - 13.4]	11.0 [9.1 - 12.9]

1. Response rate assessed according to WHO-UICC criteria.

2. Independent expert review.

Treatment of Metastatic Colorectal Cancer

Use in combination with capecitabine, with or without bevacizumab

Study NO16966: Data from a multicentre, randomised, controlled phase III clinical study support the use of capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) for the first-line treatment of metastatic colorectal cancer (Study NO16966). The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, XELOX or FOLFOX-4, and a subsequent 2x2 factorial part with four different treatment groups, XELOX + placebo (P), FOLFOX-4+P, XELOX+BV, and FOLFOX-4+BV. The treatment regimens are summarised in Table 8 below.

Table 8: Treatment regimens in Study NO16966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + BV	Oxaliplatin	85 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m^2 IV 2 h	Leucovorin on Day 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	5-fluorouracil IV bolus/infusion, each on Days 1 and 2 , every 2 weeks
	Placebo or bevacizumab	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ BV	Oxaliplatin	130 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 3 weeks
	Capecitabine	1000 mg/m^2 oral bid	Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or bevacizumab	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil:	IV bolus injection immediately after leucovorin		

Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival (PFS) in the eligible per-protocol population (EPP), with progression determined by the study investigators who were not blinded to treatment allocation (see Table 9). The criterion set for concluding non-inferiority was that the upper limit of the 97.5% confidence interval for the hazard ratio for PFS was less than 1.23. The results for OS are similar to those reported for PFS.

Table 9: Key efficacy results for the non-inferiority analysis (EPP population, Study NO16966)

Endpoint Parameter	XELOX/XELOX+P/ XELOX+BV (n = 967)	FOLFOX/FOLFOX+P/ FOLFOX+BV (n = 937)	Hazard Ratio (97.5% CI)
Progression-free survival Median (days) (95% CI)	241 (229; 254)	259 (245; 268)	1.05 (0.94; 1.18)
Overall survival Median (days) (95% CI)	577 (535; 615)	549 (528; 576)	0.97 (0.84; 1.14)

Study NO16966 also demonstrated superiority of the bevacizumab-containing arms over placebo-containing arms.

Study NO16967: Data from a multicenter, randomised, controlled phase III clinical study support the use of capecitabine in combination with oxaliplatin for the second-line treatment of metastatic colorectal cancer. In this trial, 627 patients with metastatic colorectal cancer who have received prior treatment with irinotecan (CPT-11) in combination with a fluoropyrimidine regimen as first-line therapy were randomised to treatment with XELOX or FOLFOX-4 (Study NO16967). The treatment regimens used in study NO16967 are summarised in Table 10 below.

Table 10: Treatment regimens in Study NO16967

	Treatment	Starting Dose	Schedule
FOLFOX-4	Oxaliplatin	85 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m^2 IV 2 h	Leucovorin on Day 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	5-fluorouracil IV bolus/infusion, each on Days 1 and 2 , every 2 weeks
XELOX	Oxaliplatin	130 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 3 weeks
	Capecitabine	1000 mg/m^2 oral bid	Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
5-Fluorouracil: IV bolus injection immediately after leucovorin			

XELOX was demonstrated to be non-inferior to FOLFOX-4 in terms of PFS in the per-protocol population (PPP) (see Table 11). The criterion set for concluding non-inferiority was the upper limit of the 95% confidence interval for the hazard ratio for PFS was less than 1.30. The result for OS was similar to that for PFS.

Table 11: Key efficacy results for the non-inferiority analysis (PPP, Study NO16967)

Endpoint Parameter	XELOX (n = 251)	FOLFOX (n = 252)	Hazard Ratio (95% CI)
Progression-free survival Median (days) (95% CI)	154 (140; 175)	168 (145; 182)	1.03 (0.87; 1.24)
Overall survival Median (Days) (95% CI)	388 (339; 432)	401 (371; 440)	1.07 (0.88; 1.31)

Treatment of Oesophagogastric Cancer

Data from a randomised multicenter, phase III study comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with previously untreated locally advanced or metastatic oesophagogastric cancer supports the use of oxaliplatin for the first-line treatment of advanced oesophagogastric cancer (REAL-2). In this trial, 1002 patients were randomised in a 2x2 factorial design to one of the following 4 arms:

Table 12: Treatment regimens in the REAL-2 Study

Treatment	Starting Dose	Schedule
Epirubicin (E) Cisplatin (C) 5-Fluorouracil (F)	50 mg/m^2 IV bolus 60 mg/m^2 2 hour IV infusion 200 mg/m^2 continuous infusion via a central line	Day 1, every 3 weeks Day 1, every 3 weeks Daily
Epirubicin (E) Cisplatin (C) Capecitabine (X)	50 mg/m^2 IV bolus 60 mg/m^2 2 hour IV infusion 625 mg/m^2 bd orally	Day 1, every 3 weeks Day 1, every 3 weeks Twice daily
Epirubicin (E) Oxaliplatin (O) 5-Fluorouracil (F)	50 mg/m^2 IV bolus 130 mg/m^2 2 hour IV infusion 200 mg/m^2 continuous infusion via a central line	Day 1, every 3 weeks Day 1, every 3 weeks Daily
Epirubicin (E) Oxaliplatin (O) Capecitabine (X)	50 mg/m^2 IV bolus 130 mg/m^2 2 hour IV infusion 625 mg/m^2 bd orally	Day 1, every 3 weeks Day 1, every 3 weeks Twice daily

The primary efficacy analyses in the per-protocol population demonstrated non-inferiority in OS for capecitabine versus 5-FU-based regimens (hazard ratio 0.86, 95% CI: 0.80 to 0.99) and for oxaliplatin versus cisplatin-based regimens (hazard ratio 0.92, 95% CI: 0.80 to 1.10). The median OS was 10.9 months in capecitabine-based regimens and 9.6 months in 5-FU-based regimens. The median OS was 10.0 months in cisplatin-based regimens and 10.4 months in oxaliplatin-based regimens.

INDICATIONS

Oxaliplatin is indicated for adjuvant treatment of stage III (Duke's C) colon cancer, in combination with a fluoropyrimidine agent.

Oxaliplatin in combination with fluorouracil and folinic acid is indicated for the treatment of advanced colorectal cancer.

Oxaliplatin in combination with capecitabine, with or without bevacizumab, is indicated for the treatment of patients with metastatic colorectal cancer

Oxaliplatin in combination with epirubicin and either capecitabine or fluorouracil, is indicated for the treatment of patients with advanced oesophagogastric cancer.

CONTRAINDICATIONS

Oxaliplatin is contraindicated in patients who:

- have a known history of hypersensitivity to oxaliplatin,
- are pregnant,
- are breast feeding,
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils <1.5 x 10^9/L and/or platelet count of <75 x 10^9 /L,
- have a peripheral sensory neuropathy with functional impairment prior to first course,
- have severely impaired renal function (creatinine clearance less than 30mL/min).

If contraindications exist to any of the agents in combination regimens, that agent should not be used.

PRECAUTIONS

General

Oxaliplatin should be administered only by or under the supervision of an experienced clinical oncologist.

Allergic Reactions

Anaphylactic-like reactions to Eloxatin have been reported, and may occur within minutes of Eloxatin administration. Patients with a history of allergic reactions to platinum compounds should be monitored for allergic symptoms. Allergic reactions can occur during any cycle. In case of an anaphylactic-type reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Rechallenge with oxaliplatin is contraindicated.

Neurological Toxicity

Neurological toxicity (see **ADVERSE EFFECTS**) of oxaliplatin should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before initiation of each administration, and periodically thereafter. It is not known whether patients with pre-existing medical conditions associated with peripheral nerve damage have a reduced threshold for oxaliplatin induced peripheral neuropathy.

For patients who develop acute laryngopharyngeal dysaesthesias, during or within 48 hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours. To prevent such dysaesthesia, advise the patient to avoid exposure to cold and to avoid ingesting cold food and/or beverages during or within 48 hours following oxaliplatin administration.

Signs and symptoms of Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension (see **ADVERSE EFFECTS**). Diagnosis of RPLS is based upon confirmation by brain imaging.

Gastrointestinal Toxicity

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic anti-emetic therapy, including 5-HT3 antagonists and corticosteroids. Dehydration, ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis, particularly when combining oxaliplatin with fluorouracil.

Haematological Toxicity

Monitor haematological toxicity with a full blood count and white cell differential count prior to starting therapy and before each subsequent course. Idiosyncratic haematological toxicity may occur, especially in patients who have received previous myelotoxic treatment.

Pulmonary Toxicity

Eloxatin has been associated with pulmonary fibrosis (0.7% of study patients), which may be fatal. In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease or pulmonary fibrosis (see **ADVERSE EFFECTS**).

Hepatic Toxicity

Reactions related to liver sinusoidal obstruction syndrome, including nodular regenerative hyperplasia, have been reported (see **ADVERSE EFFECTS**). In the case of abnormal liver function test results or portal hypertension which could not be explained by liver metastases, reactions related to liver sinusoidal obstruction syndrome should be investigated, and very rare cases of drug induced hepatic vascular disorders should be considered.

Renal Impairment

Oxaliplatin has not been studied in patients with severe renal impairment. It is therefore contraindicated in patients with severe renal impairment.

There is limited information on safety in patients with moderately impaired renal function, and administration should only be considered after suitable appraisal of the benefit/risk for the patient, however, treatment may be initiated at the normally recommended dose. In this situation, renal function should be closely monitored and dose adjusted according to toxicity.

There is no need for dose adjustment in patients with mild renal dysfunction.

Hepatic Insufficiency

Oxaliplatin has not been studied in patients with severe hepatic impairment. No increase in oxaliplatin acute toxicities was observed in the subset of patients with abnormal liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

Paediatric Use

Oxaliplatin is not recommended for use in children as safety and efficacy have not been established in this group of patients.

Use in the Elderly

No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with fluorouracil in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Oxaliplatin was shown to be mutagenic and clastogenic in mammalian test systems *in vitro* and *in vivo*. The carcinogenic potential of oxaliplatin has not been studied, but compounds with similar mechanisms of action and genotoxicity profiles have been reported to be carcinogenic. Oxaliplatin should be considered a probable carcinogen.

In dogs dosed with oxaliplatin, a decrease in testicular weight accompanied with testicular hypoplasia approaching aplasia was seen at doses ≥ 15mg/m². However, no effects on fertility were seen in male and female rats at doses up to 12mg/m²/day for 5 days/cycle.

Use in Pregnancy

Category D. Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Reproductive toxicity studies showed no teratogenic activity in rats or rabbits at intravenous doses up to 6 and 9mg/m²/day respectively (1/20 of the maximum recommended clinical dose, based on body surface area). However, increased embryonic deaths, decreased foetal weight and delayed ossifications were observed in rats. Related compounds with similar mechanisms of action have been reported to be teratogenic. There are no adequate and well- controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus. Oxaliplatin is probably toxic to the human foetus at the recommended therapeutic dose, and is therefore contraindicated during pregnancy.

As with other cytotoxic agents, effective contraceptive measures should be taken in potentially fertile patients prior to initiating chemotherapy with oxaliplatin.

Use in Lactation

There are no data on the excretion of oxaliplatin into milk of animals or humans. Oxaliplatin is contraindicated in breast feeding women.

Interactions with other Medicines

In patients who have received a single dose of 85mg/m^2 of oxaliplatin, immediately before administration of fluorouracil, no change in the level of exposure to fluorouracil has been observed. However, in patients dosed with fluorouracil weekly and oxaliplatin 130mg/m^2 every 3 weeks, increases of 20% in fluorouracil plasma concentrations have been observed.

In vitro little or no displacement of oxaliplatin binding to plasma proteins has been observed with the following agents; erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Oxaliplatin is incompatible with chloride containing solutions and basic solutions (including fluorouracil), therefore oxaliplatin should not be mixed with these or administered simultaneously via the same IV line. There is no data for compatibility with other drugs.

The lack of Cytochrome P450 mediated metabolism indicates that oxaliplatin is unlikely to modulate the P450 metabolism of concomitant medications through a competitive mechanism.

No clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occured when capecitabine and oxaliplatin were administered in combination, with or without bevacizumab.

Advice to Patients

Patients must be adequately informed of the risk of diarrhoea/emesis and neutropenia after oxaliplatin/fluorouracil administration so that they can urgently contact their treating physician for appropriate management.

Patients and caregivers should be informed of the expected side effects of Eloxatin and, in particular, patients should be advised to:

- Avoid cold foods and drinks and cover skin prior to exposure to cold during or within 48 hours following oxaliplatin administration, since neurological effects may be precipitated or exacerbated by exposure to cold.
- Contact their doctor immediately if they develop fever, particularly in association with persistent diarrhoea or evidence of infection since this may indicate low blood count.
- Contact their doctor if persistent vomiting, diarrhoea, signs of dehydration, cough or breathing difficulties or signs of allergic reaction occur.

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patient's ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

ADVERSE EFFECTS

Fluorouracil and folinic acid (FU/FA) in combination with oxaliplatin

Table 13: FU/FA ± Oxaliplatin in Adjuvant Treatment of Colon Cancer - EFC3313 (MOSAIC), all Grades and Grade 3-4 Toxicities - all Cycles - % Patients

	Arm A FOLFOX4 N=1108			Arm B FU/FA N=1111		
	All	**Gr 3**	**Gr 4**	**All**	**Gr 3**	**Gr 4**
Laboratory						
Granulocytopenia	78.9	28.8	12.3	39.9	3.7	1.0
Thrombocytopenia	77.4	1.5	0.2	19.0	0.2	0.2
Anemia	75.6	0.7	0.1	66.9	0.3	-
Adverse effects						
Paraesthesia	92.0	12.4	NA	15.6	0.2	NA
Nausea	73.7	4.8	0.3	61.1	1.5	0.3
Diarrhoea	56.3	8.3	2.5	48.4	5.1	1.5
Vomiting	47.2	5.3	0.5	24.0	0.9	0.5
Stomatitis/mucositis	42.1	2.8	0.1	39.7	2.1	0.2
Skin disorder	31.5	1.4	0.6	35.5	1.7	0.7
Alopecia	30.2	NA	NA	28.1	NA	NA
Fever	27.3	0.7	0.3	12.2	0.4	0.2
Infection	25.2	3.3	0.7	24.9	2.3	0.6
Injection site reaction	11.1	2.6	0.5	10.4	3.1	0.2
Allergic reaction	10.3	2.3	0.6	1.9	0.1	0.1
Thrombosis/phlebitis	5.7	1.0	0.2	6.5	1.7	0.1
Neutropenic sepsis	1.1	0.6	0.4	0.1	-	0.1
Febrile neutropenia	0.7	0.7	-	0.1	0.1	-

Table 14: FU/FA ± Oxaliplatin in Previously Untreated Patients with Advanced Colorectal Cancer, all Grades and Grade 3-4 Toxicities - all Cycles - % Patients

Incidence of Toxicity by Patient %	EFC2962				N9741			
	N=208 Control arm q 2w FU bolus + CIV		N=209 Oxaliplatin 85 q 2w FU bolus + CIV		N=256 Irinotecan 125 q 6w FU bolus x 4 weekly		N=259 FOLFOX4 Oxaliplatin 85 q 2w FU bolus + CIV	
	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4
Paraesthesias†	11.5	0.0	67.0	16.7	15.6	2.3	77.2	17.8
Laryngopharyngeal dysesthesia	NA†	NA†	NA†	NA†	1.2	0	38.2	1.5
Neurosensory	NA†	NA†	NA†	NA†	2.3	0	12.0	0.8
Nausea	53.4	1.9	72.2	5.7	67.2	14.5	71.0	6.2
Vomiting	29.3	1.9	54.1	5.7	43.4	13.3	40.9	3.5
Diarrhoea	43.8	5.3	58.9	12.0	65.2	28.5	56.0	11.6
Stomatitis	35.6	1.4	44.0	5.7	25.0	0.8	37.5	0
Anaemia	80.8	2.4	85.2	3.3	28.1	4.3	27.0	2.7
Neutropenia	30.8	7.2	74.6	43.1	80.1	46.1***	82.2	54.1***
Thrombocytopenia	28.8	0.0	75.6	2.4	26.2	2.7	71.4	4.6
Fever without neutropenia	14.9	0.0	33.0	0.0	8.6	0.4	16.2	0.8
Infection	27.9	1.0	31.6	1.0	5.1	0.8	9.7	3.5
Asthenia	21.6	3.4	23.4	4.3	NA	NA	NA	NA
Fatigue	7.2	0.5	12.9	1.0	58.2	10.5	70.3	6.6
Alopecia	19.2	NA	17.7	NA	44.1	0	37.5	0
Skin	32.2	0.5	28.7	0.0	NA	NA	NA	NA
AST	23.1	0.0	46.4	0.5	2.0	0.4	17.4	1.2
ALT	21.6	0.0	29.2	1.0	2.3	0	6.2	0.8
Alk. phosphatase	39.9	1.4	56.5	1.4	7.0	0	16.2	0
Creatinine increase	8.2	0.5	4.8	0.5	3.5	0.4	4.2	0

NA: Not applicable

CIV – continuous intravenous infusion

*nausea-vomiting are reported together in that study (WHO toxicity grading scale)

** modified WHO toxicity grading scale

*** 14.8% febrile neutropenia reported in the IFL arm and 4.2% in the FOLFOX4 arm

†Various studies used different data convention. Break down data collection by laryngopharyngeal dysesthesia and neurosensory was not done in EFC2962.

Note:

very common	≥1/10 (≥10%)
common	≥1/100 and <1/10 (≥1% and <10%)
uncommon	≥1/1000 and <1/100 (≥0.1% and <1.0%)
rare	≥1/10,000 and <1/1000 (≥0.01% and <0.1%)
very rare	<1/10,000 (<0.01%)

Neurological

	Adjuvant	Advanced
very common:	Sensory peripheral neuropathy, dysgeusia	Primarily sensory peripheral neuropathy (e.g. loss of deep tendon reflexes, dysaesthesia, paraesthesia Lhermitte's sign), dysgeusia
common:		Pharyngolaryngeal dysaesthesia, jaw spasm, abnormal tongue sensation, feeling of chest pressure
rare:		Dysarthria *Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES) (see **PRECAUTIONS**).

Post marketing experience with unknown frequency – convulsion.

Neurological adverse effects are the dose-limiting toxicity. A primarily sensory peripheral neuropathy occurs in 85-95% of patients. These symptoms usually develop at the end of the 2-hour oxaliplatin infusion or within a few hours, abate spontaneously within the next hours or days, and frequently recur with further cycles. They may be precipitated by or exacerbated by exposure to cold temperatures or objects. They usually present as transient paraesthesia, dysaesthesia and hypoaesthesia. There may be functional impairment such as difficulty in executing fine movements. The duration of symptoms increases with the number of treatment cycles. Symptoms usually recede between courses of treatment.

If symptoms persist or pain or functional impairment develops, the dose should be reduced or treatment discontinued (see **DOSAGE AND ADMINSTRATION**).

In the adjuvant setting, for a cumulative dose of 850mg/m^2 (10 cycles) the risk of occurrence of persistent symptoms is 10% and for a cumulative dose of 1020mg/m^2 (12 cycles) the risk of occurrence is 20%.

In the advanced setting, in EFC2962, 16% of patients receiving oxaliplatin + FU/FA developed paraesthesia and associated functional impairment lasting longer than two weeks, after a median cumulative oxaliplatin dose of 874mg/m². Two percent were withdrawn due to persisting paraesthesia (i.e. persisting between treatment cycles), after cumulative oxaliplatin doses of 759-1100mg/m².

In the majority of cases, the neurological signs and symptoms improve when treatment is discontinued. Analysis of patients in EFC2962 showed that of the 34 patients who developed Grade 3 neurotoxicity (the maximum grade in that study), 25 (73.5%) had an improvement of their symptoms in a median time of 13.2 weeks. Eight of the 34 patients (23%) had complete resolution of their symptoms. The mean duration of the Grade 3 neurotoxicity was 13.6 weeks. The mean cumulative oxaliplatin dose at date of onset was 913.6mg/m² (range: 169.7-1713.15mg/m²). The median follow-up time for these 34 patients was 55.71 weeks.

An acute pharyngolaryngeal dysaesthesia syndrome occurs in 1% to 2% of patients. It often occurs on exposure to cold and changes in temperature. It is characterised by subjective sensations of dysphagia and dyspnoea, feeling of suffocation, without evidence of respiratory distress (no cyanosis or hypoxia, laryngospasm or bronchospasm).

Other symptoms occasionally observed, particularly of cranial nerve dysfunction may be either associated with other symptoms, or also may occur in isolation, such as ptosis, diplopia, aphonia/dysphonia/hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, decrease of visual acuity, visual field disorders. In addition, the following symptoms have been observed: jaw spasm/muscle spasm/muscle contractions – involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain.

Vascular Disorders

	Adjuvant	Advanced
very common:	Epistaxis	Epistaxis
common:	Deep vein thrombosis, thromboembolic events, hypertension	Deep vein thrombosis, thromboembolic events, hypertension

Post marketing experience with unknown frequency - haemolytic uremic syndrome

Haematological

	Adjuvant	Advanced
very common:	Epistaxis, anaemia (all grades), neutropenia (all grades), thrombocytopenia (all grades)	Anaemia (all grades), neutropenia (all grades), thrombocytopenia (all grades)

In both adjuvant and advanced cancer treatment, addition of oxaliplatin to fluorouracil and folinic acid:

- Substantially increased the incidence of neutropenia and severe neutropenia (neutrophils $<1.0 \times 10^9$/L) and
- Substantially increased the incidence of thrombocytopenia (Tables 13-14).

Gastrointestinal

	Adjuvant	Advanced
very common:	Diarrhoea, nausea, vomiting, stomatitis, anorexia, abdominal pain, mucositis, constipation	Diarrhoea, nausea, vomiting, stomatitis, anorexia, abdominal pain, mucositis, dehydration, ileus, intestinal obstruction, hypokalemia, metabolic acidosis, constipation
common:	Dyspepsia, gastrointestinal haemorrhage	Gastrointestinal haemorrhage
rare:		Colitis, including Clostridium difficile diarrhoea *Pancreatitis

Addition of oxaliplatin to fluorouracil and folinic acid:

- Increased the incidence of severe nausea, vomiting, diarrhoea and stomatitis in the adjuvant setting (Table 13) and substantially increased these effects in the advanced cancer setting (Table 14).

Hepatobiliary

	Adjuvant	Advanced
very common:		Elevation of transaminases and alkaline phosphatases activities
very rare:	Reactions related to liver sinusoidal obstruction syndrome, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.	Reactions related to liver sinusoidal obstruction syndrome, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Musculoskeletal

	Adjuvant	Advanced
very common:	Arthralgia	Back pain*, arthralgia

* Back pain. If associated with haemolysis, which has been rarely reported, should be investigated.

Hypersensitivity

	Adjuvant	Advanced
very common:	Skin rash (particularly urticaria), conjunctivitis, rhinitis, injection site reactions	Skin rash (particularly urticaria), conjunctivitis, rhinitis, injection site reactions
common:	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock

Sensory

	Adjuvant	Advanced
very common:	Taste perversion	
common:	Conjunctivitis	
uncommon:		Ototoxicity
rare:	Deafness, optic neuritis, loss of visual acuity, visual field disturbances, transient vision loss (reversible following therapy discontinuation)	Deafness, optic neuritis, loss of visual acuity, visual field disturbances, transient vision loss (reversible following therapy discontinuation)

Renal

	Adjuvant	Advanced
common:		Altered renal function
very rare:		Renal tubular necrosis

In clinical and post-marketing setting: *very rare* – Acute tubular necrosis, acute interstitial nephritis, and acute renal failure.

Respiratory

	Adjuvant	Advanced
very common	Cough	cough
common:	Rhinitis, dyspnoea. hiccups	hiccups
rare:		Acute interstitial lung disease (sometimes fatal), pulmonary fibrosis

Immune system

	Adjuvant	Advanced
very common:	Infections, fever, rigors (tremors), fatigue, asthenia	Infections, fever, rigors, (tremors), fatigue, asthenia
common:	Febrile neutropenia	Febrile neutropenia
rare:		Autoimmune haemolytic anaemia and thrombocytopenia

Skin

	Adjuvant	Advanced
very common:	Alopecia, rash	
common:		Alopecia, rash

Moderate alopecia has been reported in 2% of patients treated with oxaliplatin as a single agent; the combination of oxaliplatin and fluorouracil did not increase the incidence of alopecia observed with fluorouracil alone.

Capecitabine in combination with oxaliplatin

Table 15 Summary of ADRs in ≥ 5% of patients who received capecitabine with oxaliplatin for adjuvant colon cancer (Study NO16968)

Body System Adverse drug reaction	**XELOX** **N=938** **All Grades %**	**5-FU/LV MAYO CLINIC** **N=657** **All Grades %**	**5-FU/LV ROSWELL PARK** **N=269** **All Grades %**
Gastrointestinal Disorders			
Diarrhoea	62	68	81
Nausea	67	53	71
*Stomatitis All	21	64	21
Vomiting	44	22	38
Abdominal pain	22	18	34
Constipation	20	12	18
Dyspepsia	9	6	14
Abdominal pain upper	8	7	8
Flatulence	5	3	11
Dry mouth	3	4	5
Nervous System Disorders			
Paraesthesia	36	2	4
Neuropathy peripheral	30	1	4
Dysgeusia	13	13	15
Headache	11	7	12
Dizziness	11	5	13
Peripheral sensory neuropathy	16	<1	4
Dysaesthesia	11	<1	<1
Lethargy	6	7	1
Hypoaesthesia	6	<1	3
General Disorders and Administration Site Conditions			
Fatigue	35	23	63
Asthenia	18	14	16
Pyrexia	12	9	16
Temperature intolerance	11	-	<1
Oedema peripheral	5	3	11
Chills	3	1	6
Skin and Subcutaneous Tissue disordErs			
Palmar-plantar Erythrodysaethesia syndrome	30	9	16
Alopecia	4	24	9
Rash	9	10	15
Dry skin	5	6	16
Pruritus	2	3	6
Blood and Lymphatic System Disorders	28	35	13
Neutropenia	18	<1	1
Thrombocytopenia	7	5	13
Anaemia	<1	5	1
Febrile neutropenia			
Metabolism and Nutrition Disorders			
Anorexia	26	15	29
Dehydration	7	4	12
Hypokalaemia	6	3	12
Decreased appetite	3	2	6
Respiratory, Thoracic and Mediastinal Disorders			
Cough	5	2	13
Oropharyngeal pain	4	6	7
Dyspnoea	7	2	6
Epistaxis	4	4	11
Dysaethesia pharynx	10	-	-
Rhinorrhoea	3	2	7

Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	12	3	8
Arthralgia	4	3	10
Back pain	5	2	9
Pain in jaw	6	<1	-
Psychiatric Disorders			
Insomnia	8	7	14
Anxiety	5	3	12
Depression	4	2	9
Infections and Infestations			
Nasopharyngitis	3	3	6
Upper respiratory tract infection	3	2	7
Urinary tract infection	2	2	7
Eye disorders			
Lacrimation increased	5	8	18

** stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration*

Table 16 shows the most frequent ADRs (≥ 5%) reported in patients with metastatic colorectal cancer who received first-line (Study NO16966) or second-line (Study NO16967) treatment with capecitabine in combination with oxaliplatin (XELOX). In Study NO16966, the pooled XELOX versus FOLFOX-4 comparison includes pooled safety data from the XELOX arm of the initial 2-arm part of the study and the XELOX+placebo (P) arm of the 2x2 factorial part of the study versus the pooled safety data from the FOLFOX-4 arm of the initial 2-arm part of the study and the FOLFOX-4+P arm of the 2x2 factorial part of the study (see **CLINICAL TRIALS**). The intensity of adverse events was graded according to the toxicity categories of the NCI CTCAE grading system.

Table 16: Summary of ADRs in ≥ 5 % of patients who received first-line or second-line capecitabine with oxaliplatin for metastatic colorectal cancer (Study NO16966 and Study NO16967)

	XELOX[a] n=966		FOLFOX-4 [b] n=957	
Body System	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Adverse drug reaction	**%**	**%**	**%**	**%**
Gastrointestinal Disorders				
Nausea	60	4	60	3
Diarrhoea	60	19	53	9
Vomiting	41	4	35	3
Stomatitis	18	<1	34	2
Abdominal pain	18	2	15	2
Constipation	13	<1	18	1
Dyspepsia	8	-	10	<1
Abdominal pain upper	5	<1	5	<1
Nervous System Disorders				
Paraesthesia	36	4	35	3
Neuropathy peripheral	17	3	17	2
Peripheral sensory neuropathy	15	2	16	2
Dysgeusia	11	-	14	-
Neuropathy	13	2	12	2
Dysaesthesia	12	1	13	2

Body System Adverse drug reaction	XELOX[a] n=966		FOLFOX-4[b] n=957	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
Dizziness	9	<1	8	-
Headache	8	<1	8	<1
Lethargy	8	2	8	<1
Hypoaesthesia	8	<1	6	<1
General Disorders and Administration Site Conditions				
Fatigue	36	5	41	7
Asthenia	17	3	18	3
Pyrexia	11	<1	17	1
Temperature intolerance	7	<1	7	<1
Blood and Lymphatic System Disorders				
Neutropenia	24	6	54	40
Thrombocytopenia	19	5	21	3
Anaemia	10	1	10	1
Metabolism and Nutrition Disorders				
Anorexia	26	2	24	2
Hypokalaemia	7	5	5	2
Dehydration	6	3	4	2
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	28	5	9	1
Rash	5	<1	7	<1
Respiratory,Thoracic and Mediastinal Disorders				
Dysaesthesia pharynx	12	2	6	<1
Epistaxis	5	-	10	-
Dyspnoea	7	1	5	1
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	8	<1	3	<1
Pain in jaw	5	<1	4	<1
Investigations				
Weight decreased	7	<1	4	<1
Psychiatric Disorders				
Insomnia	5	<1	5	<1

[a] XELOX: capecitabine (1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period) and oxaliplatin (130 mg/m^2 as a 2-hour infusion on day 1 every three weeks).

[b] FOLFOX-4: leucovorin (200 mg/m^2 as a 2-hour infusion on days 1 and 2 every two weeks), 5-FU (400 mg/m^2 as a bolus injection, 600 mg/m^2 as a 22 hour infusion on days 1 and 2 every two weeks), and oxaliplatin (85 mg/m^2 as a 2 hour infusion on day 1 every two weeks).

Rare or uncommon ADRs reported for the combination of capecitabine with oxaliplatin are consistent with ADRs reported for capecitabine monotherapy or oxaliplatin monotherapy (see Product Information for capecitabine).

Capecitabine in combination with oxaliplatin and bevacizumab

Table 17 shows the most frequent ADRs (≥ 5%) reported in a phase III trial (Study NO16966) of patients with metastatic colorectal cancer who received first-line treatment with capecitabine in combination with oxaliplatin and bevacizumab (XELOX+BV). The comparison of XELOX+BV versus FOLFOX-4+BV includes safety data from the XELOX+BV arm and the FOLFOX-4+BV arm of the 2x2 factorial part of the study. The intensity of adverse events was graded according to the toxicity categories of the NCI CTCAE grading system.

Table 17: Summary of ADRs reported in ≥ 5% of patients with metastatic colorectal cancer who received first-line treatment with XELOX+BV (Study NO16966)

	XELOX+BV[a] (N=353)		FOLFOX-4+BV[b] (N=341)	
Body System	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Adverse drug reaction	**%**	**%**	**%**	**%**
Gastrointestinal Disorders				
Nausea	64	6	62	3
Diarrhoea	62	21	60	12
Vomiting	44	5	37	6
Stomatitis	29	2	40	4
Constipation	14	-	21	-
Abdominal pain	15	3	16	<1
Abdominal pain upper	7	-	6	-
Dyspepsia	6	-	11	<1
Nervous System Disorders				
Paraesthesia	37	5	39	6
Neuropathy peripheral	20	5	18	3
Peripheral sensory neuropathy	18	2	21	5
Neuropathy	14	2	13	3
Dysaesthesia	13	3	12	1
Dysgeusia	12	<1	14	-
Headache	12	<1	13	<1
Dizziness	7	<1	7	<1
Lethargy	8	<1	7	1
General Disorders and Administration Site Conditions				
Fatigue	36	7	37	6
Asthenia	21	7	26	4
Pyrexia	12	-	15	<1
Temperature intolerance	9	-	6	-
Blood and Lymphatic System Disorders				
Neutropenia	20	7	55	40

Body System	XELOX+BV[a] (N=353)		FOLFOX-4+BV[b] (N=341)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Adverse drug reaction	%	%	%	%
Thrombocytopenia	13	3	13	3
Anaemia	7	<1	11	1
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	39	12	13	2
Rash	7	-	10	-
Dry skin	6	-	4	-
Respiratory, Thoracic and Mediastinal Disorders				
Dysaesthesia pharynx	10	1	4	-
Epistaxis	8	-	29	<1
Dyspnoea	6	2	6	<1
Rhinorrhoea	5	-	4	-
Dysphonia	5	-	6	-
Metabolism and Nutrition Disorders				
Anorexia	28	3	26	2
Hypokalaemia	6	3	5	2
Dehydration	6	3	4	1
Vascular Disorders				
Hypertension	12	3	16	3
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	10	-	7	<1
Investigations				
Weight decreased	8	<1	7	-
Psychiatric Disorders				
Insomnia	5	-	4	-

[a] XELOX+BV: capecitabine (1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period) and oxaliplatin (130 mg/m^2 as a 2-hour infusion on day 1 every three weeks), and bevacizumab (7.5 mg/kg on day 1 every three weeks).

[b] FOLFOX-4+BV: leucovorin (200 mg/m^2 as a 2-hour infusion on days 1 and 2 every two weeks), 5-FU (400 mg/m^2 as a bolus injection, 600 mg/m^2 as a 22 hour infusion on days 1 and 2 every two weeks), and oxaliplatin (85 mg/m^2 as a 2 hour infusion on day 1 every two weeks), and bevacizumab (5 mg/kg on day 1 every two weeks).

Rare or uncommon ADRs reported for the combination of capecitabine with oxaliplatin and bevacizumab are consistent with ADRs reported for capecitabine monotherapy or oxaliplatin monotherapy or bevacizumab combination therapy (see Product Information for capecitabine or bevacizumab).

Epirubicin in combination with oxaliplatin and either fluorouracil or capecitabine

Table 18: Summary of the most common Grade 3/4 haematological ADRs reported in patients treated with oxaliplatin and epirubicin in combination with fluorouracil (EOF) or capecitabine (EOX) for advanced oesophagogastric cancer

The table also lists ADRs reported in the other arms of this trial, using cisplatin and epirubicin in combination with fluorouracil (ECF) or capecitabine (ECX).

Body System Adverse Drug Reaction	**ECF n = 236**	**ECX n = 229**	**EOF n = 231**	**EOX n = 232**
	Grade 3/4 %	**Grade 3/4 %**	**Grade 3/4 %**	**Grade 3/4 %**
Blood And Lymphatic System Disorders				
Neutropenia	41.7	51.1	29.9	27.6
Leucopenia	19.5	21.0	13.4	13.8
Anaemia	13.1	10.5	6.5	8.6
Thrombocytopenia	4.7	4.8	4.3	5.2
Febrile neutropenia	9.3	6.7	8.5	7.8

Table 19: Summary of the most common Grade 3/4 non-haematological ADRs reported in patients treated with oxaliplatin and epirubicin in combination with fluorouracil (EOF) or capecitabine (EOX) for advanced oesophagogastric cancer

The table also lists ADRs reported in the other arms of this trial, using cisplatin and epirubicin in combination with fluorouracil (ECF) or capecitabine (ECX).

Body System Adverse Drug Reaction	**ECF n = 234**	**ECX n = 234**	**EOF n = 225**	**EOX n = 227**
	Grade 3/4 %	**Grade 3/4 %**	**Grade 3/4 %**	**Grade 3/4 %**
Infections and infestations				
Infection	11.9	5.1	11.5	8.4
Nervous System Disorders				
Peripheral Neuropathy	0.4	1.7	8.4	4.4
Vascular Disorders				
Thromboembolism	18.1	14.9	8.5	8.4
Gastrointestinal Disorders				
Stomatitis	1.3	1.7	4.4	2.2
Nausea/vomiting	10.2	7.7	13.8	11.4
Diarrhoea	2.6	5.1	10.7	11.9
Skin And Subcutaneous Tissue Disorders				
Palmar-Plantar Erythrodysaesthesia	4.3	10.3	2.7	3.1
Alopecia (grade 1- 2)	44.2†	47.4†	27.7 †	28.8†
General Disorders and Administration Site Conditions				
Lethargy	16.6	15.5	12.9	24.9
Fever	3.4	4.3	2.6	4.4

† grade 2 only

DOSAGE AND ADMINISTRATION

Dosage

In combination with fluorouracil and folinic acid for adjuvant treatment of colon cancer, the recommended dose of oxaliplatin is 85 mg/m^2 intravenously repeated every two weeks for 12 cycles (6 months).

In combination with capecitabine for adjuvant treatment of colon cancer, the recommended dose of oxaliplatin is 130 mg/m^2, administered as an intravenous infusion over 2 hours on day 1 of a three week cycle. For the recommended dose of capecitabine see **CLINICAL TRIALS**.

In combination with fluorouracil and folinic acid for the treatment of advanced colorectal cancer, the recommended dose of oxaliplatin is 85mg/m^2 intravenously repeated every two weeks.

In combination with capecitabine with or without bevacizumab, for the treatment of metastatic colorectal cancer, the recommended dose of oxaliplatin is 130 mg/m^2, administered as an intravenous infusion over 2 hours on day 1 of a three week cycle. For the recommended dose of capecitabine and bevacizumab, see **CLINICAL TRIALS**.

In combination with epirubicin and either fluororuracil or capecitabine, for the treatment of oesophagogastric cancer, the recommended dose of oxaliplatin is 130 mg/m^2, administered as an intravenous infusion over 2 hours on day 1 of a three week cycle. For the recommended doses of epirubicin, capecitabine and fluorouracil, see **CLINICAL TRIALS**.

Dosage Modification

Prior to each treatment cycle, patients should be evaluated for toxicity and the dose of oxaliplatin adjusted accordingly.

Neurological Toxicity

If acute neurological reactions occur e.g. acute pharyngolaryngeal dysaesthesia, increase the oxaliplatin infusion time from 2 hours to 6 hours. This decreases C_{max} by 30% and may lessen acute toxicities.

If sensory loss or paraesthesia persists longer than 7 days or interferes with function (grade 2 toxicity), reduce oxaliplatin dose by 25%.

If sensory loss or paraesthesia interferes with activities of daily living (grade 3 toxicity), oxaliplatin should be discontinued.

Haematological Toxicity

If haematological toxicity (neutrophils <1.5 x 10^9/L or platelets <75 x 10^9/L) is present before starting treatment or prior to the next course:

- Delay treatment until neutrophil count is ≥1.5 x 10^9/L and platelet count is ≥75 x 10^9/L and
- Reduce the 85mg/m^2 oxaliplatin dose to 75mg/m² every two weeks and FU dose by 20% (adjuvant treatment)
- Reduce the 85mg/m^2 oxaliplatin dose to 65mg/m² every two weeks and FU dose by 20% (advanced treatment)

Gastrointestinal Toxicity

If grade 3-4 gastrointestinal reactions occur, as assessed according to US *National Cancer Institute* criteria:

- Delay treatment until resolution of the adverse effects and
- Reduce the 85mg/m^2 oxaliplatin dose to 75mg/m² every two weeks and FU dose by 20% (adjuvant treatment)
- Reduce the 85mg/m^2 oxaliplatin dose to 65mg/m² every two weeks and FU dose by 20% (advanced treatment)

Toxicity associated with fluorouracil

Dose adjustments should also be made for fluorouracil associated toxicities (see relevant Product Information).

Oxaliplatin should be administered before fluorouracil.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500mL of 5% glucose injection.

Toxicity associated with capecitabine, epirubicin and bevacizumab

See relevant Product Information for capecitabine, epirubicin and bevacizumab-associated toxicities.

Dose Modifications for Haematological Toxicity used in Studies NO16966 and NO16967

Table 20: Dose Modifications for Febrile Neutropenia, "XELOX" Arm

	Grade 3 **ANC < 1.0x10^9/L with fever ≥ 38.5˚C**	**Grade 4** **ANC <1.0x10^9/L with fever ≥ 38.5˚C and life threatening sepsis**
1st occurrence	Capecitabine 75% of original dose + oxaliplatin 85 mg/m^2	Treatment was stopped permanently unless it was in the best interest of the patient to be treated with capecitabine at 50% of original dose + oxaliplatin 85mg mg/m^2
2nd occurrence	Treatment was stopped permanently unless it was in the best interest of the patient to be treated with capecitabine at 50% of original dose + oxaliplatin 85 mg/m^2	Treatment stopped permanently

Treatment (including bevacizumab/placebo) was not to start unless toxicity (except anemia) was resolved to grade ≤ 1(eg, ANC ≥ 1.5 x10^9/L, platelets ≥ 75x10^9/L)

Table 21: Dose Modifications for Neutropenia, "XELOX" Arm

	Grade 2 1.0≤ANC<1.5x10^9/L	Grade 3 0.5≤ANC<1.0x10^9/L	Grade 4 ANC<0.5x10^9/L
1st occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 100 mg/m^2	Capecitabine 50% of original dose + oxaliplatin 85 mg/m^2
2nd occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 85 mg/m^2	Treatment stopped permanently
3rd occurrence	No dose adjustment	Treatment was stopped permanently unless it was in the best interest of the patient to be treated with capecitabine monotherapy at 75% of original dose	Not applicable

Laboratory value at start of a treatment cycle: Treatment start was delayed (including bevacizumab/placebo) until ANC ≥ 1.5 x10^9/L, platelets ≥ 75x10^9/L, and the patient had recovered from non-hematologic toxicity to baseline or grade ≤ 1, then treatment was started with doses indicated above.

Table 22: Dose Modifications for Thrombocytopenia and Anemia, "XELOX" Arm

Thrombocytopenia	Platelets ≥ 25 - < 75x10^9/L	Platelets ≥ 10 - < 25x10^9/L	Platelets < 10 x10^9/L
1st occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 100 mg/m^2	Capecitabine 50% of original dose + oxaliplatin 85 mg/m^2
2nd occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 85 mg/m^2	Treatment was stopped permanently unless it was in the best interest of the patient to be treated with capecitabine monotherapy at 50% of original dose
3rd occurrence	No dose adjustment	Capecitabine 50% of original dose + oxaliplatin 85 mg/m^2	Treatment was stopped permanently
Anemia (non-hemolytic) anytime during treatment	Hemoglobin 8.0 - < 10.0 g/dL	Hemoglobin 6.5 - < 8.0 g/dL	Hemoglobin < 6.5 g/dL
any occurrence	No dose adjustment (could be managed by transfusion)	No dose adjustment (could be managed by transfusion)	No dose adjustment (could be managed by transfusion)

Treatment did not start unless toxicity (except anemia) was resolved to grade ≤ 1(eg, ANC ≥ 1.5 x10^9/L, platelets ≥ 75x10^9/L)

Laboratory value at start of a treatment cycle: Treatment start was delayed (including bevacizumab/placebo) until ANC ≥ 1.5 x10^9/L, platelets ≥ 75x10^9/L, and recovery from non-hematologic toxicity to baseline or grade ≤ 1, then treatment was started with doses indicated above.

Dose Modifications for Non-haematological Toxicity used in Study NO16966

Table 23: Dose Modifications for Non-hematologic Adverse Events, "XELOX" Arm

Toxicity	Grade	Dose Adjustment
* Allergic reactions	3 or 4	Stop treatment permanently
* Respiratory symptoms indicative of pulmonary fibrosis	any	Interrupt treatment and investigate cause of symptoms
* Interstitial pulmonary fibrosis not present at baseline	any	Stop treatment permanently
Nausea and/or vomiting despite premedication with an effective antiemetic therapy	3	Oxaliplatin 100 mg/m^2
Nausea and/or vomiting	4	Oxaliplatin 100 mg/m^2
Diarrhoea	3 or 4	Oxaliplatin 100 mg/m^2
Stomatitis	3	No dose reduction
Stomatitis	4	Oxaliplatin 100 mg/m^2
Skin toxicity (retreatment delayed until recovery to Grade ≤ 1)	3 or 4	No dose reduction

* No dose adjustment for capecitabine (if in the best interest of the patient)

Dose Modifications used in the REAL-2 Study

Oxaliplatin was delayed for 1 week if neutrophil count < 1.0 x10^9/L, platelet count < 75 x10^9/L or the patient had persistent grade 1 or 2 neuropathy. After recovery from grade 2-4 thrombocytopenia or grade 3/4 neutropenia, the dose of oxaliplatin was reduced to 100 mg/m^2. On recovery of persistent grade 1/2 neuropathy between cycles or grade 3/4 neuropathy for 7-14 days, the dose of oxaliplatin was reduced to 100 mg/m^2. In the event of persistent grade 3/4 neuropathy, further oxaliplatin was omitted and carboplatin could be substituted at the investigators discretion. If laryngeal dysaesthesia occurred, subsequent oxaliplatin was administered as a 6-h infusion. If grade 3/4 diarrhoea or stomatitis occurred despite appropriate fluoropyrimidine dose reductions, subsequent oxaliplatin was reduced to 100 mg/m^2.

Preparation and Administration

SPECIAL PRECAUTIONS FOR ADMINISTRATION

- DO NOT use any injection material containing aluminium
- DO NOT administer undiluted
- DO NOT mix or administer with sodium chloride injection or any other solution containing chlorides
- DO NOT mix with any other medication or administer simultaneously by the same infusion line (in particular fluorouracil and folinic acid). A Y-tube may be used (see Infusion).
- USE ONLY the recommended diluents (see below).

Any reconstituted solution that shows evidence of precipitation should not be used and should be destroyed.

Handling

As with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin solutions.

The handling of this cytotoxic agent by health care personnel requires every precaution to guarantee the protection of the handler and their surroundings. It is essential to use appropriate protective clothing, including protective goggles, mask and gloves. Pregnant women must be warned to avoid handling cytotoxic agents. If oxaliplatin concentrate, premixed solution or infusion solution should come into contact with skin, mucous membranes or eyes, wash immediately and thoroughly with water.

Preparation of Infusion Solution

Dilution before Infusion

The concentrated solution **MUST** be further diluted in an infusion solution of 250-500mL of 5% glucose injection. After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 8°C and for 24 hours at 25°C. From a microbiological point of view, this infusion preparation should be used immediately.

To reduce microbiological hazard, use as soon as practicable after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C. Reconstitution should take place in controlled and validated aseptic conditions. Inspect visually prior to use. Only clear solutions without particles should be used. Contains no antimicrobial agent. The product is for single use in one patient only. Discard any residue. **NEVER** use sodium chloride solution for dilution.

Infusion

The administration of oxaliplatin does not require prehydration. Oxaliplatin diluted in 250 to 500mL of a glucose 5% injection must be infused either by central venous line or peripheral vein over 2 to 6 hours. When oxaliplatin is administered with fluorouracil, the oxaliplatin infusion should precede that of fluorouracil.

Oxaliplatin can be co-administered with folinic acid infusion using a Y-tube placed immediately before the site of injection. The drugs should not be combined in the same infusion bag. Folinic acid must be diluted using isotonic infusion solutions such as 5% glucose solution but **NOT** sodium chloride solutions or alkaline solutions.

Flush the line after oxaliplatin administration.

While oxaliplatin has minimal to no vesicant potential, extravasation may result in local pain and inflammation which may be severe and lead to complications especially when oxaliplatin is infused through a peripheral vein. In case of oxaliplatin extravasation, the infusion must be stopped immediately and the usual local symptomatic treatment initiated.

Disposal

All materials that have been used for reconstitution, for dilution and administration must be destroyed according to local statutory requirements.

OVERDOSAGE

There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse effects can be expected. Monitoring of haematological parameters should be initiated and symptomatic treatment given. The Poisons Information Centre, telephone number 131 126, should be contacted for advice on the management of an overdosage.

PRESENTATION AND STORAGE CONDITIONS

Eloxatin is a sterile concentrated solution for infusion, available in 50mg/10mL, 100mg/20mL and 200mg/40mL vials. Store below 30ºC. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park
NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

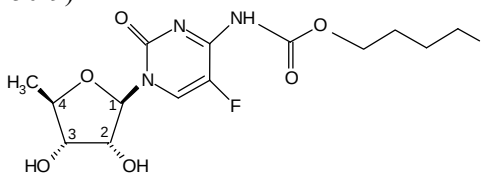
Date of TGA approval: 02 February 2011

® Registered trademark of sanofi-aventis

XELODA®

capecitabine

(CAS Registry Number: 154361-50-9)



The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine with the molecular formula $C_{15}H_{22}FN_3O_6$ and a molecular weight of 359.35.

DESCRIPTION

XELODA (capecitabine) is an oral, antineoplastic agent belonging to the fluoropyrimidine carbamate class. It was rationally designed as an orally administered precursor of 5'-deoxy-5-fluorouridine (5'-DFUR), which is selectively activated to the cytotoxic moiety, fluorouracil, in tumours. Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20°C.

XELODA is supplied as biconvex oblong film-coated tablets for oral administration. Each light peach coloured tablet contains 150 mg capecitabine and each peach coloured tablet contains 500 mg capecitabine. The inactive ingredients in XELODA are anhydrous lactose, croscarmellose sodium, hypromellose, microcrystalline cellulose and magnesium stearate. The peach or light peach film coating contains hypromellose, talc, titanium dioxide and iron oxide yellow CI77492 and iron oxide red CI77491.

PHARMACOLOGY

Capecitabine itself is non-cytotoxic; however, it is selectively activated to the cytotoxic moiety, fluorouracil (5-FU), by thymidine phosphorylase in tumours.

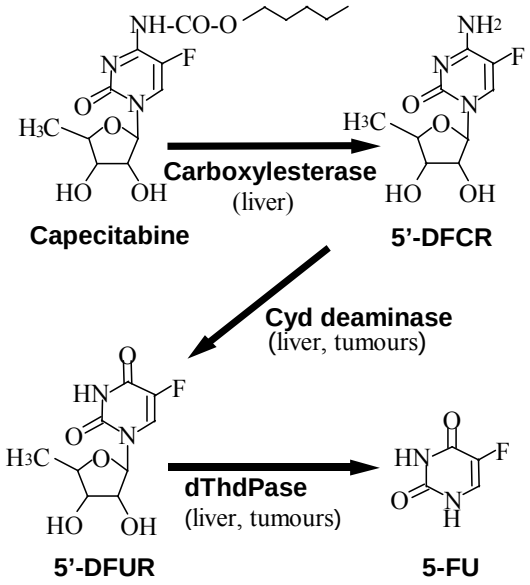
PHARMACODYNAMICS

Bioactivation

Capecitabine is a fluoropyrimidine carbamate derivative that was designed as an orally administered, tumour-activated and tumour-selective cytotoxic agent. Capecitabine is non-cytotoxic *in vitro*.

Capecitabine is absorbed unchanged from the gastrointestinal tract, metabolised primarily in the liver by the 60 kDa carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-DFCR), which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissue. Further metabolism of 5'-DFUR to the pharmacologically active agent 5-FU occurs mainly at the site of the tumour by the tumour-associated angiogenic factor thymidine phosphorylase (dThdPase), which has levels considerably higher in tumour tissues compared to normal tissues. Several human tumours such as breast, gastric, colorectal, cervical and ovarian cancers have a higher level of thymidine phosphorylase than normal tissues. This minimises the exposure of healthy tissues to systemic 5-FU. Catabolism of 5-FU by dihydropyrimidine dehydrogenase (DPD) leads to formation of dihydro-5-fluorouracil (FUH_2), followed by ring cleavage with dihydropyrimidinase (DHP) to 5-fluoro-ureido-propionic acid (FUPA) and finally to α-fluoro-β-alanine (FBAL) by the enzyme β-ureido-propionase (BUP).

Figure 1: Metabolic Pathway of capecitabine to 5-FU



Mechanism of Action

Both normal and tumour cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor N^{5-10} methylenetetrahydrofolate bind covalently to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding prevents formation of thymidylate from uracil, the necessary precursor of thymidine triphosphate that is required for DNA synthesis. A deficiency of thymidine triphosphate can inhibit cell division. The second mechanism results from the incorporation of FUTP into RNA in place of UTP, thereby preventing the correct nuclear processing of ribosomal RNA and messenger RNA. These effects are most marked on rapidly proliferating cells, such as tumour cells, which utilise 5-FU at a higher rate.

PHARMACOKINETICS

Pharmacokinetics in Tumours and Adjacent Healthy Tissue

A pharmacokinetic study in 19 colorectal patients was conducted investigating the tumour selectivity of capecitabine comparing 5-FU concentrations in tumour, healthy tissue and plasma. Following oral administration of capecitabine (1250 mg/m^2 twice daily, 5 to 7 days before surgery), concentrations of 5-FU were significantly greater in primary tumour than in adjacent healthy tissue (geometric mean ratio 2.5; 95% CI: [1.5 to 4.1]) and plasma (geometric mean ratio 14).

Thymidine phosphorylase activity was four times greater in primary tumour tissue (colon) than in normal tissue.

Human Pharmacokinetics

The pharmacokinetics of capecitabine and its metabolites have been evaluated in 11 studies in a total of 213 cancer patients at a dosage range of 502 to 3514 mg/m^2/day. In the dose range of 250 to 1250 mg/m^2 as a single dose, the pharmacokinetics of capecitabine and its metabolites were dose proportional, except for 5-FU. Area under the curve (AUC) of 5-FU was 30% higher on day 14, but did not increase subsequently (day 22). A summary of key data for a dose of 1255 mg/m^2 twice daily is presented below:

Absorption: After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-DFUR. Administration of food decreases the rate of capecitabine absorption but has only a minor effect on the AUC of 5'-DFUR and the subsequent metabolite 5-FU. The absorption of capecitabine is confirmed since 95.5% of an orally administered dose is recovered in urine.

Distribution: *In vitro* human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound respectively, mainly to albumin

Metabolism: Capecitabine is first metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues. Formation of 5-FU occurs preferentially at the tumour site by the tumour-associated angiogenic factor dThdPase, thereby minimising the exposure of healthy body tissues to systemic 5-FU.

The plasma AUC of 5-FU is 6 to 22 times lower than that following an IV bolus of 5-FU (dose of 600 mg/m^2). The metabolites of capecitabine become cytotoxic only after conversion to 5-FU and anabolites of 5-FU. 5-FU is further catabolised to the inactive metabolites dihydro-5-fluorouracil (FUH_2), 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting.

Elimination: After oral administration, capecitabine metabolites are primarily recovered in the urine. Most (95.5%) of administered capecitabine dose is recovered in urine. Faecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL, which represents 57% of the administered dose. About 3% of the administered dose is excreted in the urine as unchanged drug.

Pharmacokinetic Parameters: Table 1 shows the time course of pharmacokinetic parameters for capecitabine and 5-FU in plasma at steady-state (day 14) following administration of the recommended dose (1250 mg/m^2 twice daily) in 8 cancer patients. The peak of plasma concentrations of intact drug and 5-FU are reached within 1.5 and 2 hours, respectively (median times), and the concentrations decline with half-lives of 0.85 and 0.76 hours, respectively.

Table 1: Pharmacokinetic parameters estimated on Day 14 after administration of capecitabine (1250 mg/m^2 twice daily) in 8 cancer patients

Parameter	Capecitabine	5-FU
C_{max} (µg/mL)	3.99	0.709
t_{max} (h)	1.50 (0.78 - 2.17)[#]	2.00 (1.28 - 4.08)[#]
AUC_{0-t} (µg.h/mL)	7.29	1.62
$AUC_{0-\infty}$ (µg.h/mL)	7.40	1.63
$t_{1/2}$ (h)	0.85	0.76

[#] Median values (min-max) are reported for t_{max}

Combination therapy: Phase I studies evaluating the effect of XELODA on the pharmacokinetics of either docetaxel or paclitaxel and vice versa showed no effect by XELODA on the pharmacokinetics of docetaxel or paclitaxel (C_{max} and AUC) and no effect by docetaxel or paclitaxel on the pharmacokinetics of 5'-DFUR.

Pharmacokinetics in Special Populations
See also PRECAUTIONS and DOSAGE AND ADMINISTRATION for recommendations regarding the use of XELODA in (i) the elderly; (ii) patients with hepatic impairment and (iii) patients with renal impairment.

A population pharmacokinetic analysis was carried out after XELODA treatment of 505 patients with colorectal cancer dosed at 1250 mg/m^2 twice daily. Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, AST/ALT had no statistically significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

Elderly: A population pharmacokinetic analysis which included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients greater or equal to 65 years of age, found age has no influence on the pharmacokinetics of 5'-DFUR and 5-FU. The AUC of FBAL increased with age (20% increase in age results in a 15% increase in the AUC of FBAL). This increase is likely due to a change in renal function.

Race: Based on the population pharmacokinetic analysis of 455 white patients (90.1%) 22 black patients (4.4%) and 28 patients of other race or ethnicity (5.5%), the pharmacokinetics of black patients were not different compared to white patients. For the other minority groups the numbers were too small to draw a conclusion. Limited available data suggest that there are no clinically significant differences in capecitabine pharmacokinetics between Caucasians and Oriental subjects.

Hepatic Impairment: XELODA has been evaluated in patients with mild to moderate hepatic impairment due to liver metastases as defined by a composite score including bilirubin, AST/ALT and alkaline phosphatase. C_{max} of capecitabine, 5'-DFUR and 5-FU were increased by 49%, 33% and 28%, respectively. $AUC_{0-\infty}$ of capecitabine 5'-DFUR and 5-FU were increased by 48%, 20% and 15%, respectively. Conversely, C_{max} and AUC of 5'-DFCR decreased by 29% and 35%, respectively. Therefore, bioactivation of capecitabine is not affected.

Renal Impairment: A pharmacokinetic study in cancer patients with mild to severe renal impairment showed that renal impairment significantly increased systemic 5'-DFUR exposure. 5'-DFUR is the direct precursor of 5-FU and is considered an indicator of tissue exposure to 5-FU. A 50% reduction in creatinine clearance increased 5'-DFUR AUC by 35%, 95% CI: [12, 64], on the first day of capecitabine treatment. Exposure to another metabolite, FBAL increased 114%, 95% CI: [73, 165], when creatinine clearance was decreased by 50%. This was expected since most of the capecitabine dose is recovered as FBAL in urine. FBAL does not have anti-tumour activity.

CLINICAL TRIALS

Colon and Colorectal Cancer

Monotherapy - adjuvant colon cancer

Data from an open-label, multicenter, randomised, phase III clinical trial investigated the efficacy and safety of XELODA for the adjuvant treatment in patients who underwent surgery for Dukes' stage C colon cancer (XACT: study M66001). In this trial, 1987 patients were randomised to treatment with XELODA (1250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 week cycles for 24 weeks) or 5-FU and leucovorin (Mayo regimen: 20 mg/m^2 leucovorin intravenous (IV) followed by 425 mg/m^2 IV bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks).

The major efficacy parameters assessed were disease free survival (DFS, primary endpoint) and overall survival (OS). The median follow up at the time of the analysis was 6.9 years. XELODA was shown to be at least equivalent to 5-FU/leucovorin in DFS and OS.

Table 2: Adjuvant colon cancer efficacy results monotherapy[1]

Endpoint Parameter	Number of patients (%) without an Event[2]		Hazard Ratio[3] [95% CI]	p-value[4]
	Capecitabine *n* = 1004	5-FU/leucovorin *n* = 983		
Disease Free Survival	65.3	61.3	0.88 [0.77, 1.01]	0.068
Overall Survival	80.1	76.9	0.86 [0.74, 1.01]	0.060

1 All-randomised population
2 For disease free survival event = death, relapse or new occurrence of colon cancer (NOCC); for relapse free survival event = death related to treatment or to disease progression, relapse or NOCC; for overall survival event = death (all causes)
3 Hazard Ratio capecitabine vs. 5-FU/leucovorin. Non-inferiority criterion: 95% CI upper bound ≤1.25
4 Wald chi-square test

Study M66001 did not include patients with Dukes' stage B disease. However, the findings of the study are considered to support the use of XELODA as adjuvant therapy in patients with high-risk stage B disease, such as those with inadequately sampled nodes, T4 lesions, perforation or poorly differentiated histology.

Combination therapy - adjuvant colon cancer

Data from a multicentre, randomised, controlled phase III clinical trial in patients with stage III (Dukes' C) colon cancer supports the use of XELODA in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer (NO16968). In this trial, 944 patients were randomised to 3 week cycles for 24 weeks with XELODA (1000 mg/m^2 twice daily for 2 weeks followed by a 7 day rest period) in combination with oxaliplatin (130 mg/m^2 intravenous infusion over 2 hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and leucovorin. In the primary analysis (ITT population), median observation time was 57 months for DFS and 59 months for OS. XELOX was shown to be significantly superior to 5-FU/LV (HR=0.80, 95% CI=[0.69; 0.93]; p=0.0045). The 3 year DFS rate was 71% for XELOX versus 67% for 5-FU/LV. The analysis for the secondary endpoint of relapse free survival (RFS) supports these results with a HR of 0.78 (95% CI=[0.67; 0.92]; p=0.0024) for XELOX vs. 5-FU/LV. XELOX showed a trend towards superior OS with a HR of 0.87 (95% CI=[0.72; 1.05]; p=0.1486). The 5 year OS rate was 78% for XELOX versus 74% for 5-FU/LV.

Monotherapy - metastatic colorectal cancer

A phase II open label, multicentre, randomised clinical trial was conducted to explore the efficacy and safety of three different treatment regimens in patients with advanced and/or metastatic colorectal cancer. These were continuous therapy with XELODA (1331 mg/m^2/day, *n* = 39) over 12 weeks; intermittent therapy with capecitabine (1250 mg/m^2 twice daily, *n* = 34) 2 weeks treatment followed by a 1 week rest period, given as 3 week cycles over 12 weeks and intermittent therapy with capecitabine in combination with oral leucovorin (capecitabine 1657 mg/m^2/day; leucovorin 60 mg/day, *n* = 35). The objective response rate was 22% in the continuous arm, 25% in the intermittent arm and 24% in the combination arm.

Data from two identically-designed, multicenter, randomised, controlled phase III clinical trials (SO14695; SO14796) conducted in 120 centres internationally, compared XELODA with 5-FU in combination with leucovorin (Mayo regimen) as first-line chemotherapy in patients with advanced and/or metastatic colorectal cancer. In these trials, 603 patients were randomised to treatment with XELODA at a daily dose of 1250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 week cycles over 30 weeks. A total of 604 patients were randomised to treatment with 5-FU/leucovorin (20 mg/m^2 leucovorin IV followed by 425 mg/m^2 IV bolus 5-FU, on days 1 to 5, every 28 days). The mean duration of treatment was 139 days for capecitabine treated patients and 140 days for 5-FU/leucovorin treated patients.

The major efficacy endpoints assessed were time to disease progression (primary endpoint), objective response rate and OS. The objective response rate included partial and complete responses. The results from the two phase III trials were similar; the pooled efficacy data from both trials are given in the table below.

Table 3: Metastatic colorectal cancer pooled trials efficacy results monotherapy[1]

Endpoint Parameter	**Capecitabine *n* = 603**	**5-FU/leucovorin *n* = 604**	**Difference [95% CI]**
Time to Disease Progression median (range)	140 days (131-161)	144 days (134-164)	HR[2] 1.00 [0.89; 1.12]
Response Rate	25.7%	16.7%	9% [4.3 - 13.5%]
Overall Survival median	392 days	391 days	HR 0.96 [0.85; 1.08]

1 All-randomised population, investigator assessment
2 Hazard Ratio capecitabine/5-FU leucovorin. Non-inferiority criterion: 95% CI upper bound ≤ 1.20

XELODA was equivalent to 5-FU/leucovorin in time to disease progression, equivalent in overall survival and superior in objective response rate.

Combination therapy - first-line treatment of metastatic colorectal cancer

Data from a multicenter, randomised, controlled phase III clinical study (NO16966) support the use of XELODA in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) for the first-line treatment of metastatic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, XELOX or FOLFOX-4, and a subsequent 2x2 factorial part with four different treatment groups, XELOX + placebo (P), FOLFOX-4 + P, XELOX+BV, and FOLFOX-4 + BV. The treatment regimens are summarised in the table below.

Table 4: Treatment regimens in study NO16966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + BV	Oxaliplatin	85 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m^2 IV 2 h	Leucovorin on Day 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	5-fluorouracil IV bolus/infusion, each on Days 1 and 2 , every 2 weeks
	Placebo or Avastin	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX + BV	Oxaliplatin	130 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 3 weeks
	Capecitabine	1000 mg/m^2 oral bd	Capecitabine oral bd for 2 weeks (followed by 1 week off treatment)
	Placebo or BV	7.5 mg/kg IV 30 - 90 min	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil: IV bolus injection immediately after leucovorin			

Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival (PFS) in the eligible per-protocol population (EPP), with progression determined by the study investigators who were not blinded to treatment allocation (see Table 5). The criterion set for concluding non-inferiority was that the upper limit of the 97.5% confidence interval for the hazard ratio for PFS was less than 1.23. The results for OS are similar to those reported for PFS. A comparison of XELOX plus BV versus FOLFOX-4 plus BV was a pre-specified exploratory analysis. In this treatment subgroup comparison, XELOX plus BV was similar compared to FOLFOX-4 plus BV in terms of PFS (hazard ratio 1.01 [97.5% CI 0.84, 1.22]). The median follow up at the time of the primary analyses in the intent-to-treat population was 1.5 years; data from analyses following an additional 1 year of follow up are included in Table 5.

Table 5: Key non-inferiority efficacy results for the primary analysis and 1 year follow-up data (EPP population, Study NO16966)

PRIMARY ANALYSIS			
	XELOX/XELOX+P/ XELOX+BV (EPP[#]: *n* = 967)	**FOLFOX-4/FOLFOX-4+P/ FOLFOX-4+BV (EPP[#]: *n* = 937)**	
Population	**Median Time to Event (Days)**		**HR (97.5% CI)**
Parameter: Progression-free Survival			
EPP (95% CI)	241 (229; 254)	259 (245; 268)	1.05 (0.94; 1.18)
Parameter: Overall Survival			
EPP (95% CI)	577 (535; 615)	549 (528; 576)	0.97 (0.84; 1.14)
ADDITIONAL 1 YEAR OF FOLLOW UP			
Population	**Median Time to Event (Days)**		**HR (97.5% CI)**
Parameter: Progression-free Survival			
EPP	242	259	1.02 (0.92; 1.14)
Parameter: Overall Survival			

EPP	600	594	1.00 (0.88; 1.13)

#EPP=eligible patient population

Study NO16966 also demonstrated superiority of the bevacizumab-containing arms over placebo-containing arms.

Combination therapy - second- line treatment of metastatic colorectal cancer

Data from a multicenter, randomised, controlled phase III clinical study (NO16967) support the use of XELODA in combination with oxaliplatin for the second-line treatment of metastastic colorectal cancer. In this trial, 627 patients with metastatic colorectal cancer who have received prior treatment with irinotecan in combination with a fluoropyrimidine regimen as first-line therapy were randomised to treatment with XELOX or FOLFOX-4. The treatment regimens used in study NO16967 are summarised in the table below.

Table 6: Treatment regimens in Study NO16967

	Treatment	Starting Dose	Schedule
FOLFOX-4	Oxaliplatin	85 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m^2 IV 2 h	Leucovorin on Day 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	5-fluorouracil IV bolus/infusion, each on Days 1 and 2 , every 2 weeks
XELOX	Oxaliplatin	130 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 3 weeks
	Capecitabine	1000 mg/m^2 oral bd	Capecitabine oral bd for 2 weeks (followed by 1 week off treatment)
5-Fluorouracil: IV bolus injection immediately after leucovorin			

XELOX was demonstrated to be non-inferior to FOLFOX-4 in terms of PFS in the per-protocol population (see Table 7). The criterion set for concluding non-inferiority was the upper limit of the 95% confidence interval for the hazard ratio for PFS was less than 1.30. The results for overall survival were similar to those for PFS. The median follow up at the time of primary analyses in the intent-to-treat population was 2.1 years; data from analyses following an additional 6 months of follow up are also included in Table 7.

Table 7: Key non-inferiority efficacy results for the primary analysis and 6-month follow-up data of Study NO16967 (PPP population)

PRIMARY ANALYSIS			
	XELOX (PPP#: *n* = 251)	**FOLFOX-4 (PPP#: *n* = 252)**	
Population	**Median Time to Event (Days)**		**HR (95% CI)**
Parameter: Progression-free Survival			
PPP (95% CI)	154 (140; 175)	168 (145; 182)	1.03 (0.87; 1.24)
Parameter: Overall Survival			
PPP (95% CI)	388 (339; 432)	401 (371; 440)	1.07 (0.88; 1.31)
ADDITIONAL 6 MONTHS OF FOLLOW UP			
Population	**Median Time to Event (Days)**		**HR (95% CI)**
Parameter: Progression-free Survival			

PPP	154	166	1.04 (0.87; 1.24)
Parameter: Overall Survival			
PPP	393	402	1.05 (0.88; 1.27)

[#]PPP = per-protocol population

A pooled analysis of the efficacy data from first-line (study NO16966; initial 2-arm part) and second line treatment (study NO 16967) further support the non-inferiority results of XELOX versus FOLFOX-4 as obtained in the individual studies: PFS in the per-protocol population (hazard ratio 1.00 [95% CI: 0.88; 1.14]) with a median PFS of 193 days (XELOX; 508 patients) versus 204 days (FOLFOX-4; 500 patients). The results also indicate that XELOX is comparable to FOLFOX-4 in terms of OS (hazard ratio 1.01 [95% CI: 0.87; 1.17]) with a median OS of 468 days (XELOX) versus 478 days (FOLFOX-4).

Combination therapy - oesophagogastric cancer

Two multicentre, randomised, controlled phase III clinical trials were conducted to evaluate the safety and efficacy of capecitabine in patients with previously untreated advanced or metastatic oesophagogastric.

Data from a multicentre, open-label, randomised, controlled phase III clinical trial (ML17032,) supports the use of XELODA in this setting. In this trial, 160 patients with previously untreated advanced or metastatic gastric cancer were randomised to treatment with XELODA (1000 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period) and cisplatin (80 mg/m^2 as a 2 hour IV infusion every 3 weeks). A total of 156 patients were randomised to treatment with 5-FU (800 mg/m^2 per day, continuous infusion on days 1 to 5 every 3 weeks) and cisplatin (80 mg/m^2 as a 2 hour IV infusion on day 1, every 3 weeks). Patients received treatment for at least 6 weeks (2 cycles) and were treated until disease progression or unacceptable toxicity.

The primary objective of the study was met, XELODA in combination with cisplatin was at least equivalent to 5-FU in combination with cisplatin in terms of PFS in the per-protocol analysis. Duration of survival (overall survival) with the combination of XELODA and cisplatin was also at least equivalent to that of 5-FU and cisplatin.

Table 8: Summary of results for key efficacy parameters (PPP, Study ML17032)

Endpoint Parameter	Capecitabine/cisplatin n =139	5-FU/Cisplatin n = 137	Hazard Ratio [95% CI] [#]
Progression-Free Survival median (months) [95% CI]	5.6 [4.9, 7.3]	5.0 [4.2, 6.3]	0.81 [0.63, 1.04]
Duration of Survival median (months) [95% CI]	10.5 [9.3, 11.2]	9.3 [7.4, 10.6]	0.85 [0.64, 1.13]

[#] Unadjusted treatment effect in Cox proportional model

Data from a randomised multicenter, phase III study comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with previously untreated locally advanced or metastatic oesophagogastric cancer supports the use of XELODA for the first-line treatment of advanced oesophagogastric cancer (REAL-2). In this trial, 1002 patients were randomised in a 2 x 2 factorial design to one of the following 4 arms:

Table 9: Treatment regimens in the REAL-2 Study

Treatment	Starting Dose	Schedule
Epirubicin (E) Cisplatin (C) 5-Fluorouracil (F)	50 mg/m^2 IV bolus 60 mg/m^2 2 hour IV infusion 200 mg/m^2 continuous infusion via a central line	Day 1, every 3 weeks Day 1, every 3 weeks Daily
Epirubicin (E) Cisplatin (C) Capecitabine (X)	50 mg/m^2 IV bolus 60 mg/m^2 2 hour IV infusion 625 mg/m^2 bd orally	Day 1, every 3 weeks Day 1, every 3 weeks Twice daily
Epirubicin (E) Oxaliplatin (O) 5-Fluorouracil (F)	50 mg/m^2 IV bolus 130 mg/m^2 2 hour IV infusion 200 mg/m^2 continuous infusion via a central line	Day 1, every 3 weeks Day 1, every 3 weeks Daily
Epirubicin (E) Oxaliplatin (O) Capecitabine (X)	50 mg/m^2 IV bolus 130 mg/m^2 2 hour IV infusion 625 mg/m^2 bd orally	Day 1, every 3 weeks Day 1, every 3 weeks Twice daily

The primary efficacy analyses in the per-protocol population demonstrated non-inferiority in OS for capecitabine versus 5-FU-based regimens (hazard ratio 0.86, 95% CI: 0.80 to 0.99) and for oxaliplatin versus cisplatin-based regimens (hazard ratio 0.92, 95% CI: 0.80 to 1.10). The median OS was 10.9 months in capecitabine-based regimens and 9.6 months in 5-FU-based regimens. The median OS was 10.0 months in cisplatin-based regimens and 10.4 months in oxaliplatin-based regimens.

Colon, colorectal and advanced gastric cancer: meta-analysis

A meta-analysis of six clinical trials (studies SO14695, SO14796, M66001, NO16966, NO16967, ML17032) supports XELODA replacing 5-FU in mono- and combination treatment in gastrointestinal cancer. The pooled analysis includes 3097 patients treated with XELODA-containing regimens and 3074 patients treated with 5-FU-containing regimens. The hazard ratio for OS was 0.94 (95% CI: 0.89; 1.00, p=0.0489) indicating that XELODA-containing regimens are comparable to 5-FU containing regimens.

Monotherapy- Breast cancer

Two phase II open label, multicenter trials were conducted to evaluate the efficacy and safety of XELODA in patients with locally advanced and/or metastatic breast cancer who had been previously treated with taxanes. XELODA was administered at a dose of 1250 mg/m^2 twice daily for 2 weeks treatment followed by a 1 week rest period, given as 3 week cycles.

In the first trial, 162 female outpatients were selected from an investigator's current practice or from referred patients. This heavily pre-treated patient population was refractory to previous paclitaxel therapy (77% resistant, 23% failed). Additionally, most patients were resistant (41%) or had failed (26%) previous anthracycline therapy and 82% had been exposed to 5-FU.

In the second trial, 74 patients were treated; all but three had received prior treatment with taxanes (paclitaxel and/or docetaxel). In addition, over 95% had previously been treated with an anthracycline-based chemotherapy.

Table 10: Breast cancer monotherapy efficacy results[1]

Endpoint Parameter	Capecitabine with paclitaxel ***n* = 162**	Capecitabine with paclitaxel /docetaxel ***n* = 74**
Response Rate (95% CI)	20% (13.6 - 27.8)	24.6% (15.05 - 36.49)
Duration of Response median (range)	241 days (97 - 324)	253 days (213 - 301)
Time to Disease Progression median (95% CI)	93 days (84 - 106)	98 days (71 - 130)
Survival median	384 days	373 days

1 Intent to Treat population

A prospectively defined clinical benefit response score (pain, analgesic consumption and Karnofsky Performance Status) was used to assess the effect of treatment on tumour-associated morbidity. The overall clinical benefit response was positive in 29 patients (20%) in the first trial and 8 patients (15%) in the second trial, 45 patients (31%) and 22 patients (41%), respectively, remained stable.

Of the 51 patients with baseline pain ≥ 20 mm on the visual analogue scale in the first trial, 24 patients (47%) had a positive response in pain intensity (greater than or equal to 50% decrease lasting for at least 4 weeks), similar analysis in the second trial showed 7/27 patients (26%) had a positive pain response.

Combination therapy - Breast cancer

The dose of XELODA used in the phase III clinical trial in combination with docetaxel was based on the results of a phase I trial, where a range of doses of docetaxel given every 3 weeks in combination with an intermittent regimen of XELODA (2 weeks treatment followed by a 1 week rest period) were evaluated. The combination dose regimen was selected based on the tolerability profile of docetaxel 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks in combination with 1250 mg/m^2 twice daily for 2 weeks of XELODA administered every 3 weeks for at least 6 weeks. The approved dose of 100 mg/m^2 of docetaxel administered every 3 weeks was the control arm of the phase III study.

XELODA in combination with docetaxel was assessed in an open label, multicenter, randomised trial. A total of 511 patients with locally advanced and/or metastatic breast cancer resistant to, or recurring after an anthracycline containing therapy, or relapsing during or recurring within two years of completing an anthracycline containing adjuvant therapy were enrolled. In this trial, 255 patients were randomised to receive XELODA in combination with docetaxel and 256 patients received docetaxel alone.

XELODA in combination with docetaxel resulted in statistically significant improvements in time to disease progression, overall survival and objective response rate compared to monotherapy with docetaxel as shown in Table 11 and Figures 2 and 3. Health related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC-QLQ; C30 version 2, including Breast Cancer Module BR23). HRQoL was similar in the two treatment groups.

Table 11: Breast cancer combination treatment efficacy results[1]

Endpoint Parameter	Capecitabine/ docetaxel ***n* = 255**	docetaxel ***n* = 256**	Difference	*p*-value
Time to Disease Progression				

median [95% CI]	186 days [165,198]	128 days [105,136]	HR[2] = 0.643 [0.563, 0.770]	0.0001
Survival median [95% CI]	 442 days [374, 492]	 352days [298, 362]	 HR = 0.753 [0.603, 0.940]	 0.0126
Response Rate [95% CI]	41.6 % [35.5, 47.9]	29.7% [24.2, 35.7]	11.9% [3.4, 20.0]	0.0058

1. All-randomised population, Investigator assessment
2. Hazard Ratio

Figure 2. Kaplan-Meier Estimates for Time to Disease Progression XELODA and Docetaxel vs. Docetaxel

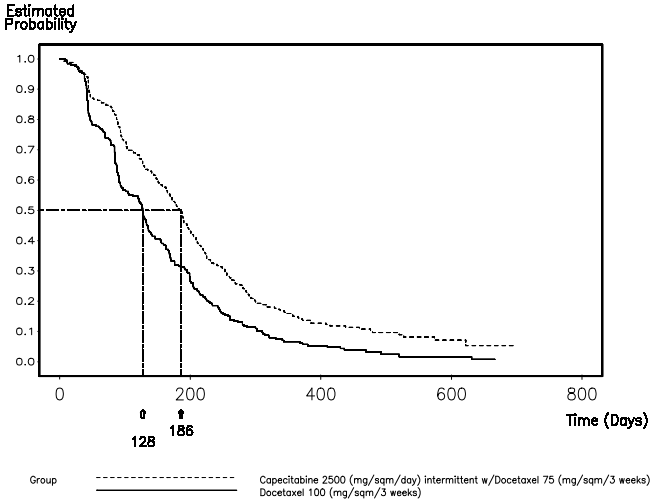
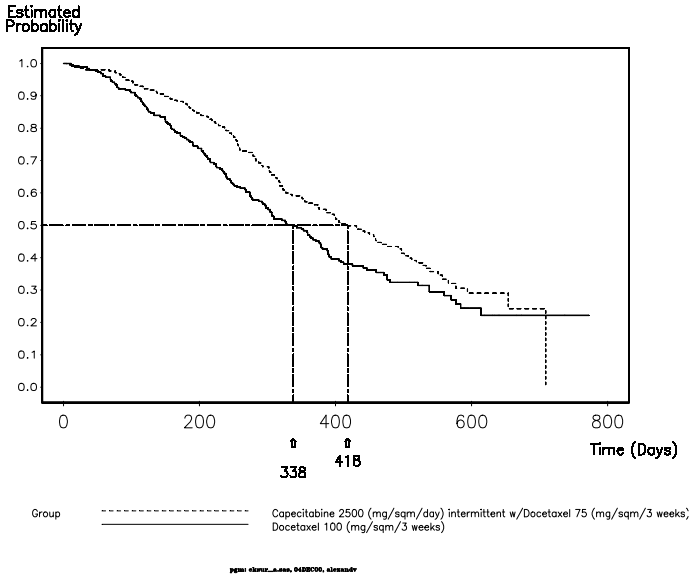


Figure 3. Kaplan-Meier Estimates of Survival XELODA and Docetaxel vs. Docetaxel



INDICATIONS

Colon Cancer
XELODA is indicated for the adjuvant treatment of patients with Dukes' stage C and high-risk stage B, colon cancer, either as monotherapy or in combination with oxaliplatin.

Colorectal Cancer
XELODA is indicated for the treatment of patients with advanced or metastatic colorectal cancer.

Oesophagogastric Cancer
XELODA is indicated for the first-line treatment of patients with advanced oesophagogastric cancer in combination with a platinum-based regimen.

Breast Cancer
XELODA is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen unless therapy with these and other standard agents are clinically contraindicated.

XELODA in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.

CONTRAINDICATIONS

XELODA is contraindicated in patients who have:
- a known hypersensitivity to capecitabine or to any of the excipients contained in the tablets
- a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil
- severe renal impairment (creatinine clearance below 30 mL/min)
- known dihydropyrimidine dehydrogenase (DPD) deficiency
- treatment with sorivudine or its chemically related analogues, such as brivudine

If contraindications exist to any of the agents in combination regimen, that agent should not be used.

PRECAUTIONS

General
Patients receiving therapy with XELODA should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. Patients should be carefully monitored for toxicity. Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced (see DOSAGE AND ADMINISTRATION).

Information for Patients
Patients and patients' caregivers should be informed of the expected adverse effects of XELODA, particularly of nausea, vomiting, diarrhoea and hand-foot syndrome. The frequent oral administration of XELODA allows patient specific dose adaptations during therapy (see DOSAGE AND ADMINISTRATION). Patients should be encouraged to recognise the common toxicities associated with XELODA treatment.

Diarrhoea: Patients experiencing Grade 2 diarrhoea (an increase of 4 to 6 stools/day or nocturnal stools) or greater should be instructed to stop taking XELODA immediately. Standard anti-diarrhoeal treatments (e.g. loperamide) are recommended.

Nausea: Patients experiencing Grade 2 nausea (food intake significantly decreased but able to eat intermittently) or greater should be instructed to stop taking XELODA immediately. Initiation of symptomatic treatment is recommended.

Vomiting: Patients experiencing Grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater should be instructed to stop taking XELODA immediately. Initiation of symptomatic treatment is recommended.

Hand-foot Syndrome: Patients experiencing Grade 2 hand-foot syndrome (painful erythema and swelling of the hands and/or feet that results in discomfort affecting the patient's activities of daily living) or greater should be instructed to stop taking XELODA immediately.

Stomatitis: Patients experiencing Grade 2 stomatitis (painful erythema, oedema or ulcers, but able to eat) or greater should be instructed to stop taking XELODA immediately. Initiation of symptomatic treatment is recommended.

Diarrhoea
XELODA can induce diarrhoea, which can sometimes be severe. In patients receiving XELODA monotherapy, the median time to first occurrence of Grade 2 to 4 diarrhoea was 31 days, and median duration of Grade 3 or 4 diarrhoea was 4.5 days. Patients with severe diarrhoea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. National Cancer Institute of Canada (NCIC) Grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, Grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and Grade 4 diarrhoea as an increase of ≥ 10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Standard anti-diarrhoeal treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary.

Dehydration
Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. If Grade 2 (or higher) dehydration occurs, XELODA treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be applied for the precipitating adverse event as necessary (see DOSAGE AND ADMINISTRATION).

Hand-foot Syndrome
XELODA can induce hand-foot syndrome (palmar-plantar erythrodysaesthesia or chemotherapy induced acral erythema), which is a cutaneous toxicity. For patients receiving XELODA monotherapy in the metastatic setting, the median time to onset was 79 days (range from 11 to 360 days), with a severity range of Grades 1 to 3.

Grade 1 is defined by numbness, dysaesthesia/paraesthesia, tingling, or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activity. Grade 2 hand-foot syndrome is defined as painful erythema and swelling of the hands and/or feet that results in discomfort affecting the patient's activities of daily living. Grade 3 hand-foot syndrome is defined as moist desquamation, ulceration, blistering and severe pain of the hands and/or feet that results in severe discomfort that causes the patient to be unable to work or perform activities of daily living.

If Grade 2 or 3 hand-foot syndrome occurs, administration of XELODA should be interrupted until the event resolves or decreases in intensity to Grade 1. Following Grade 3 hand-foot syndrome, subsequent doses of XELODA should be decreased (see DOSAGE AND ADMINISTRATION).

When XELODA and cisplatin are used in combination, the use of vitamin B6 (pyroxidine) is not advised for symptomatic or secondary prophylactic treatment of hand-foot syndrome because of published reports that it may decrease the efficacy of cisplatin.

Cardiac
The spectrum of cardiotoxicity observed with XELODA is similar to that of other fluorinated pyrimidines. This includes myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure and electrocardiograph changes. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

Hepatic Impairment
Patients with hepatic impairment should be carefully monitored when XELODA is administered. The effect of hepatic impairment not due to liver metastases or of severe hepatic impairment on the disposition of XELODA is not known (see PHARMACOKINETICS and DOSAGE AND ADMINISTRATION).

Renal Impairment
In patients with moderate renal impairment (creatinine clearance 30-50 mL/min) at baseline, a dose reduction to 75% for starting doses is recommended for both monotherapy and combination use. Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3 or 4 adverse reaction with subsequent dose adjustment as outlined in the DOSAGE AND ADMINISTRATION section.

Physicians should exercise caution when XELODA is administered to patients with impaired renal function. As seen with 5-FU, the incidence of treatment related Grade 3 or 4 adverse reactions is higher in patients with moderate renal impairment (creatinine clearance 30-50 mL) (see *Dose Adjustment in Special Populations*). XELODA is contraindicated in patients with creatinine clearance below 30 mL/min (see CONTRAINDICATIONS).

Haematologic
In 949 patients with either advanced or metastatic colorectal cancer or breast cancer who received a dose of capecitabine 1 250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, 3.6, 2.0 and 3.1% of patients had Grade 3 or 4 neutropenia, thrombocytopenia and decreases in haemoglobin respectively.

In 251 patients with metastatic breast cancer who received a dose of XELODA in combination with docetaxel, abnormal laboratory values showed 68%, 2.8 % and 9.6% of patients had Grade 3 or 4 neutropenia/granulocytopenia, thrombocytopenia and haemoglobin respectively. The majority of cases did not require medical intervention.

Dihydropyrimidine Dehydrogenase
Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. A link between decreased levels of DPD and increased potentially fatal toxic effects of 5-FU therefore cannot be excluded.

Hyperbilirubinaemia
XELODA can induce hyperbilirubinaemia. Administration of XELODA should be interrupted if treatment-related elevations in bilirubin of > 3.0 x the upper limit of normal (ULN) or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur. Treatment may be resumed when bilirubin decreases to ≤ 3.0 x ULN or hepatic aminotransfereases decrease to ≤ 2.5 x ULN.

In 949 patients, grade 3 hyperbilirubinaemia occurred in 133 (14.0%) patients and Grade 4 hyperbilirubinaemia occurred in 35 (3.7%) patients. These reactions were rarely associated with significant elevations in alkaline phosphatase or liver transaminases. The majority of these elevations occurred in patients with progressive hepatic metastases.

In 251 patients with metastatic breast cancer who received combination of XELODA and docetaxel, Grade 3 hyperbilirubinaemia occurred in 6.8% (*n* = 17) and Grade 4 hyperbilirubinaemia occurred in 2% (*n* = 5).

Use in Children
The safety and effectiveness of XELODA in persons < 18 years of age has not been established.

Use in the Elderly
In 949 patients assessed for safety, patients were also assessed for the incidence of Grade 3 and 4 reactions in terms of age groups as illustrated in the table below.

Table 12: Summary of the occurrence (%) of treatment related Grade 3 and 4 adverse reactions by age

Age Group (years)	Number of patients at risk	Grade		Diarrhoea	Nausea	Vomiting	Stomatitis	Hand-Foot Syndrome
		3	4					
Total	949	40.7	3.5	13.2	3.7	3.6	4.1	15.9
< 40	46	30.4	0	4.3	2.2	0	6.5	10.9
40 - 59	369	36.3	1.4	13.0	5.1	3.8	3.8	13.6
60 - 69	295	41.7	5.8	14.6	2.7	3.1	3.7	14.6
70 - 79	218	46.8	4.1	11.9	1.8	4.1	4.6	22.9
80 and over	21	61.9	9.5	28.6	14.3	9.5	4.8	14.3

Among patients with colorectal cancer aged 60-79 years receiving XELODA monotherapy in the metastatic setting, the incidence of Grade 3 and 4 toxicity was similar to that in the overall population. In patients aged 80 years or older, a larger percentage experienced reversible Grade 3 or 4 adverse reactions. When XELODA was used in combination with other agents, elderly patients (≥ 65 years of age) experienced more Grade 3 and 4 adverse reactions (ADRs) and ADRs that led to discontinuation than younger patients. An analysis of safety data in patients equal to or greater than 60 years of age treated with XELODA in combination with docetaxel showed an increase in the incidence of treatment-related Grade 3 or 4 adverse reactions, treatment-related serious adverse reactions and early withdrawals from treatment due to adverse reactions compared to patients less than 60 years of age.

Carcinogenicity, Mutagenicity and Impairment of Fertility
Carcinogenicity: In a two year carcinogenicity study in mice, there was no evidence for a carcinogenicity potential of capecitabine at dietary doses up to 90 mg/kg/day (270 mg/m^2/day). In terms of plasma AUC values, systemic exposure to capecitabine and 5'-DFUR at the highest dose was at least 10 times lower than that in humans at the recommended dose.

Mutagenicity: Capecitabine was not mutagenic or clastogenic in the following models: *in vitro* Ames test (bacterial) and V79/HPRT (mammalian) gene mutation assays and *in vivo* mouse micronucleus test. However, consistent with the known chromosome-damaging potential of nucleoside analogs, capecitabine was clastogenic *in vitro* in human peripheral blood lymphocytes in the absence of S9 metabolic activation.

Impairment of Fertility: Impairment of fertility was observed in female mice receiving capecitabine at 760 mg/kg/day (2292 mg/m^2/day) - a disruption in the oestrous cycle occurred with a subsequent failure of mating. A reduction in live litter size, decreased foetal weight and foetal abnormalities were observed in mice dosed at 380 mg/kg/day (1174 mg/m^2/day) before implantation. At the no effect dose of 190 mg/kg/day (587 mg/m^2/day), plasma C_{max} for 5'-DFUR was similar to that observed in humans at the recommended dose, while the AUC value was 4-fold lower than that in humans. The effect of capecitabine on female fertility was reversible after a drug-free period.

In male mice, degenerative changes and a decrease in the number of spermatocytes and spermatids were noted at 760 mg/kg/day (2401 mg/m^2/day). At the no-effect dose of 380 mg/kg/day (1201 mg/m^2/day), plasma C_{max} for 5'-DFUR was slightly greater than that observed in humans at the recommended dose, while the AUC was about half that in humans.

Use in Pregnancy – CATEGORY D

XELODA may cause foetal harm when administered to pregnant women. Women of child bearing potential should be advised to avoid becoming pregnant while receiving treatment with XELODA.

There are no adequate and well-controlled studies in pregnant women using XELODA. If the medicine is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient should be advised of the potential hazard to the foetus.

Studies Conducted in Animals

Mice: Capecitabine and/or its metabolites have been shown to cross the placenta in mice. Capecitabine was shown to be teratogenic and embryolethal when administered orally to mice during organogenesis at a dose of 198 mg/kg/day (676 mg/m^2/day). Teratogenic findings included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilatation of cerebral ventricles. The non-teratogenic dose level in mice was 50 mg/kg/day (approximately 170 mg/m^2/day). Systemic exposure to 5'-DFUR at the 50 mg/kg/day dose level was not assessed in any studies; however, this dose level is estimated to be about 20 times lower than that in patients dosed at 2510 mg/m^2/day, based on plasma AUC values.

Capecitabine administered to mice dams for the period following organogenesis through to weaning at doses up to 400 mg/kg/day (1428 mg/m^2/day) was not associated with any adverse effects on the dams or offspring. In separate studies, this dose produced 5'-DFUR C_{max} and AUC values about 1.4 and 0.43 times, respectively, of the corresponding values in patients administered 2510 mg/m^2/day.

Monkeys: Capecitabine was embryolethal when administered to dams during organogenesis at a dose of 90 mg/kg/day equivalent to 1095 mg/m^2/day. However, no teratogenic effects were observed in those fetuses that did survive at that dose level. The no-effect dose was 45 mg/kg/day (560 mg/m^2/day), which produced a plasma 5'-DFUR AUC value that was about one third of the corresponding value in patients at the recommended dose.

Use in Lactation

It is not known whether capecitabine and its metabolites are excreted in human milk. In a study of single oral administration of capecitabine in lactating mice, a significant amount of capecitabine metabolites was detected in the milk. No effects were observed on the offspring of lactating mice dosed orally with capecitabine at 400 mg/kg/day (1428 mg/m^2/day). However, plasma AUC for 5'-DFUR at this dose was lower than that in patients receiving the recommended dose of the medicine. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving XELODA therapy.

Interaction with Food
The effect of food on the pharmacokinetics of capecitabine was investigated in 11 cancer patients. The rate and extent of absorption of capecitabine is decreased when administered with food. The effect on $AUC_{0-\infty}$ of the 3 main metabolites in plasma (5'DFUR, 5-FU, FBAL) is minor. In all clinical trials, patients were instructed to administer XELODA within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that XELODA be administered with food.

Interactions with Other Medicines
Antacid: The effect of an aluminium hydroxide (220 mg/5 mL) andmagnesium hydroxide (195 mg/5 mL) containing antacid on the pharmacokinetics of capecitabine was investigated in 12 cancer patients. There was a small increase in plasma concentrations of capecitabine and one metabolite (5'DFCR); there was no effect on the 3 major metabolites (5'DFUR, 5-FU and FBAL).

Leucovorin (folinic acid): A phase I study evaluating the effect of leucovorin on the pharmacokinetics of capecitabine was conducted in 22 cancer patients. Leucovorin has no effect on the pharmacokinetics of capecitabine and its metabolites. However, leucovorin has an effect on the pharmacodynamics of XELODA and its toxicity may be enhanced by leucovorin.

Coumarin Anticoagulants: Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. In a clinical interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the AUC of S-warfarin by 57% with a 91% increase in INR value. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolities. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly.

Phenytoin: Increase phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin. Formal interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine (see *Coumarin Anticoagulants*). Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

Cytochrome P450 2C9: No formal interaction studies with capecitabine and other medicines known to be metabolised by the cytochrome P450 2C9 isoenzyme have been conducted. Care should be exercised when XELODA is co-administered with these medicines.

Sorivudine and analogues: A clinically significant medicine interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, XELODA should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. There must be at least a 4 week waiting period between the end of treatment with sorivudine or its chemically related analogues such as brivudine, and the start of XELODA therapy.

Oxaliplatin: No clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occur when capecitabine and oxaliplatin were administered in combination, with or without bevacizumab.

Bevacizumab: There was no clinically significant effect of bevacizumab on the pharmacokinetic parameters of capecitabine or its metabolites.

ADVERSE EFFECTS

CLINICAL TRIALS

Adverse drug reactions (ADRs) considered by the investigator to be possibly, probably, or remotely related to the administration of XELODA have been obtained from clinical studies conducted with XELODA monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer), and clinical studies conducted with XELODA in combination with different chemotherapy regimens for multiple indications. ADRs are added to the appropriate category in the tables below according to the highest incidence from the pooled analysis of seven clinical trials. Within each frequency grouping, ADRs are listed in descending order of seriousness. Frequencies are defined as very common ≥ 1/10, common ≥ 5/100 to < 1/10, and uncommon ≥ 1/1000 to < 1/100.

XELODA in Monotherapy

Safety data of XELODA monotherapy were reported for patients who received adjuvant treatment for colon cancer and for patients who received treatment for metastatic breast cancer or metastatic colorectal cancer. The safety information includes data from a phase III trial in adjuvant colon cancer (995 patients treated with XELODA and 974 treated with IV 5-FU/leucovorin) and from 4 phase II trials in female patients with breast cancer (n = 319) and 3 trials (one phase II and two phase III trials) in male and female patients with colorectal cancer (n = 630). The safety profile of XELODA monotherapy is comparable in patients who received adjuvant treatment for colon cancer and in those who received treatment for metastatic breast cancer or metastatic colorectal cancer. The intensity of ADRs was graded according to the toxicity categories of the NCIC CTC grading system.

Table 13 Summary of ADRs reported in ≥ 5% of patients treated with XELODA monotherapy

Body System ADR	Very Common (≥ 10%)	Common (≥ 5% - < 10%)
Metabolism and nutrition disorders	Anorexia (G3/4: 1%)	Dehydration (G3/4: 3%) Appetite decreased (G3/4: < 1%)
Nervous system disorders		Paraesthesia Dysgeusia (G3/4: < 1%)

		Headache (G3/4: < 1%) Dizziness (excl. vertigo) (G3/4: < 1%)
Eye disorders		Lacrimation increased Conjunctivitis (G3/4: <1%)
Gastrointestinal disorders	Diarrhoea (G3/4: 13%) Vomiting (G3/4: 4%) Nausea (G3/4: 4%) Stomatitis (all) [#] (G3/4: 4%) Abdominal pain (G3/4: 3%)	Constipation (G3/4: < 1%) Abdominal pain upper (G3/4: < 1%) Dyspepsia (G3/4: < 1%)
Hepatobiliary disorders		Hyperbilirubinemia (G3/4: 1%)
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome (G3/4: 17%) Dermatitis (G3/4: < 1%)	Rash, Alopecia Erythema (G3/4: 1%) Dry Skin (G3/4: < 1%)
General disorders and administration site conditions	Fatigue (G3/4: 3%) Lethargy (G3/4: < 1%)	Pyrexia (G3/4: < 1%) Weakness (G3/4: < 1%) Asthenia (G3/4: < 1%)

[#] stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration

Skin fissures were reported to be at least remotely related to XELODA in less than 2% of the patients in seven completed clinical trials (n = 949).

The following ADRs represent known toxicities with fluoropyrimidine therapy and were reported to be at least remotely related to XELODA in less than 5% of patients in seven completed clinical trials (n = 949).

Gastrointestinal disorders: dry mouth, flatulence, oral pain, ADRs related to inflammation/ulceration of mucous membranes such as oesophagitis, gastritis, duodenitis, colitis, gastrointestinal haemorrhage

Cardiac disorders: lower limb oedema, cardiac chest pain including angina, cardiomyopathy, myocardial ischemia/infarction, cardiac failure, cardiac arrest, sudden death, tachycardia, atrial arrhythmias including atrial fibrillation, and ventricular extrasystoles

Nervous system disorders: taste disturbance, insomnia, hypoesthesia, hyperesthesia, confusion, encephalopathy, and cerebellar signs such as ataxia, dysarthria, impaired balance, abnormal coordination, vertigo

Infections and infestations: ADRs related to bone marrow depression, immune system compromise, and/or disruption of mucous membranes, such as local and fatal systemic infections (including bacterial, viral, fungal etiologies) and sepsis

Blood and lymphatic system disorders: anaemia, bone marrow depression, pancytopenia.

Skin and subcutaneous tissue disorders: pruritus, localised exfoliation, skin hyperpigmentation, nail disorders, pigmentation disorders, skin fissures, exfoliative dermatitis, pruritic rash, skin discolouration, photosensitivity reactions, radiation recall syndrome

General disorders and administration site conditions: asthenia, pain in limb, lethargy, chest pain, rigors, malaise

Eye: conjunctivitis, eye irritation

Respiratory: dyspnoea, cough, epistaxis

Musculoskeletal: back pain, myalgia, arthralgia

Metabolic: decreased weight

Psychiatric disorders: depression

Jaundice, hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing exposure. A causal relationship with XELODA has not been established.

XELODA in Combination therapy

Table 14 lists ADRs associated with the use of XELODA in combination therapy with different chemotherapy regimens in multiple indications and occurred in addition to those seen with monotherapy and/or at a higher frequency grouping. The safety profile was similar across all indications and combination regimens. These reactions occurred in ≥ 5% of patients treated with XELODA in combination with other chemotherapies. Adverse drug reactions are added to the appropriate category in the table according to the highest incidence seen in any of the major clinical trials. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin, hypertension seen with bevacizumab); however, an exacerbation by XELODA therapy cannot be excluded.

Table 14 Very common and common ADRs for XELODA in combination with different chemotherapies in addition to those seen for XELODA monotherapy.

Body System Adverse Event	Very Common ≥ 10%	Common ≥ 5% to < 10%
Infections and Infestations		Infection[+] Oral candidiasis
Blood and lymphatic system disorders	Neutropenia [+] Leukopenia [+] Febrile neutropenia[+] Thromboyctopenia [+] Anaemia [+]	
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia Weight Decreased
Psychiatric disorders		Insomnia
Nervous system disorders	Neuropathy peripheral Peripheral sensory neuropathy Neuropathy Taste disturbance Paraesthesia Dysgeusia Dysaesthesia Headache	Hypoaesthesia
Eye disorders	Lacrimation increased	
Vascular Disorders	Thrombosis/embolism Hypertension Lower limb oedema	
Respiratory	Dysaesthesia pharynx Sore throat	Epistaxis Dysphonia

		Rhinorrhoea Dyspnoea
Gastrointestinal disorders	Constipation Dyspepsia	Dry mouth
Skin and subcutaneous tissue disorders	Alopecia Nail disorder	
Musculoskeletal and connective tissue disorders	Arthragia Myalgia Pain in extremity	Pain in jaw Back Pain
General disorders and administration site conditions	Pyrexia Asthenia Weakness Temperature intolerance	Fever [+] Pain

[+] *Frequencies based on all grades except those denoted with [+], which are based on G3/4 ADRs only*

Hypersensitivity reactions (2%) and cardiac ischaemia/infarction (3%) have been reported commonly for XELODA in combination with other chemotherapy but in less than 5% of patients.

Rare or uncommon ADRs reported for XELODA in combination with other chemotherapy are consistent with the ADRs reported for XELODA monotherapyy or the combination product monotherapy (refer to the product information document for the combination product).

Laboratory Abnormalities

The following table displays laboratory abnormalities observed in 995 patients (adjuvant colon cancer) and 949 patients (metastatic breast cancer and colon cancer), regardless of relationship to treatment with XELODA.

Table 15 Laboratory abnormalities[a]: XELODA monotherapy in adjuvant colon cancer and in metastatic breast and colorectal cancer

Parameter [a]	**Xeloda 1250 mg/m^2 twice daily intermittent**
	Patients with Grade 3 / 4 abnormality (%)
Increased ALAT (SGPT)	1.6
Increased ASAT (SGOT)	1.1
Increased alkaline phosphatase	3.5
Increased calcium	1.1
Decreased calcium	2.3
Decreased granulocytes	0.3
Decreased hemoglobin	3.1
Decreased lymphocytes	44.4
Decreased neutrophils	3.6
Decreased neutrophils/granulocytes	2.4
Decreased platelets	2.0
Decreased potassium	0.3
Increased serum creatinine	0.5
Decreased sodium	0.4
Increased bilirubin	20
Hyperglycemia	4.4

[a] *Laboratory abnormalities were graded according to the categories of the NCIC CTC Grading System.*

POST-MARKETING EXPERIENCE

The following adverse reactions have been identified during post-marketing exposure:

Very rare: Lacrimal duct stenosis NOS

Very rare: hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing experience.

DOSAGE AND ADMINISTRATION

Standard Dosage

XELODA tablets should be swallowed with water within 30 minutes after the end of a meal.

Monotherapy - Colon, colorectal, breast cancer

The recommended monotherapy starting dose of XELODA is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 7 day rest period; given as 3 week cycles.

Combination therapy - Breast cancer

In combination with docetaxel, the recommended starting dose of XELODA is 1250 mg/m^2 administered twice daily for 2 weeks followed by a 7 day rest period, combined with docetaxel 75 mg/m^2 administered as a 1 hour intravenous infusion every 3 weeks.

Pre-medication, according to the docetaxel product information, should be started prior to docetaxel administration for patients receiving XELODA plus docetaxel combination.

Combination therapy - Colorectal cancer

In combination with oxaliplatin with or without bevacizumab the recommended starting dose of XELODA is 1000 mg/m^2 twice daily for 2 weeks followed by a 7 day rest period. The first dose of XELODA is given on the evening of day 1 and the last dose is given on the morning of day 15. Given as a 3 week cycle, on day 1 every 3 weeks bevacizumab is administered as a 7.5 mg/kg intravenous infusion over 30 to 90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours.

Combination therapy – Adjuvant colon cancer

In combination with oxaliplatin the recommended starting dose of XELODA is 1000 mg/m^2 twice daily for 2 weeks followed by a 7 day rest period. The first dose of XELODA is given on the evening of day 1 and the last dose is given on the morning of day 15. Given as a 3 week cycle, on day 1 oxaliplatin is administered as a 130 mg/m^2 intravenous infusion over 2 hours.

Premedication to maintain adequate anti-emesis according to the oxaliplatin product information should be started prior to oxaliplatin administration for patients receiving the XELODA plus oxaliplatin combination.

Combination therapy - Oesophagogastric cancer

In triplet combination with epirubicin and cisplatin/oxaliplatin for oesophagogastric cancer, the recommended starting dose of XELODA is 625 mg/m^2 twice daily as a continuous regimen. Epirubicin is administered as a 50 mg/m^2 intravenous bolus on day 1 of a 3 week cycle. Platinum therapy should consist of either cisplatin administered at a dose of 60 mg/m^2 given as a

2 hour intravenous infusion on day 1 of a 3 week cycle; or oxaliplatin administered at a dose of 130 mg/m^2 given as a 2 hour intravenous infusion on day 1 of a 3 week cycle.

In doublet combination with cisplatin for gastric cancer, the recommended starting dose of XELODA is 1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period. The first dose of XELODA is given on the evening of day 1 and the last dose is given on the morning of day 15. Cisplatin is administered at a dose of 80 mg/m^2 as a 2 hour intravenous infusion on day 1 of a 3-week cycle.

Pre-medication to maintain adequate hydration and anti-emesis should be started prior to oxaliplatin/cisplatin administration for patients receiving XELODA in combination with one of these agents.

The XELODA dose is calculated according to body surface area. The following tables show examples of the standard and reduced dose calculations for a starting dose of XELODA of 1250 mg/m^2 or 1000 mg/m^2.

Table 16: Standard and reduced dose calculations according to body surface area for a starting dose of XELODA of 1250 mg/m^2

	Dose level 1250 mg/m^2 (twice daily)				
	Full dose **1250 mg/m^2**	**Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)**		**Reduced dose (75%)** **950 mg/m^2**	**Reduced dose (50%)** **625 mg/m^2**
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1500	-	3	1150	800
1.27 - 1.38	1650	1	3	1300	800
1.39 - 1.52	1800	2	3	1450	950
1.53 - 1.66	2000	-	4	1500	1000
1.67 - 1.78	2150	1	4	1650	1000
1.79 - 1.92	2300	2	4	1800	1150
1.93 - 2.06	2500	-	5	1950	1300
2.07 - 2.18	2650	1	5	2000	1300
≥ 2.19	2800	2	5	2150	1450

Table 17: Standard and reduced dose calculations according to body surface area for a starting dose of XELODA of 1000 mg/m^2

	Dose level 1000 mg/m^2 (twice daily)				
	Full dose **1000 mg/m^2**	**Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)**		**Reduced dose (75%)** **750 mg/m^2**	**Reduced dose (50%)** **500 mg/m^2**
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1150	1	2	800	600
1.27 - 1.38	1300	2	2	1000	600
1.39 - 1.52	1450	3	2	1100	750
1.53 - 1.66	1600	4	2	1200	800
1.67 - 1.78	1750	5	2	1300	800
1.79 - 1.92	1800	2	3	1400	900
1.93 - 2.06	2000	-	4	1500	1000
2.07 - 2.18	2150	1	4	1600	1050
≥ 2.19	2300	2	4	1750	1100

Duration of Treatment

For metastatic disease, XELODA is intended for long-term administration unless clinically inappropriate. In the adjuvant setting, treatment duration is recommended for 24 weeks.

Dosage Adjustment During Treatment

General

Toxicity due to XELODA administration may be managed by symptomatic treatment and/or modification of the XELODA dose (treatment interruption or dose reduction). Once dose has been reduced, it should not be increased at a later time.

Dosage modifications are not recommended for Grade 1 events. Therapy with XELODA should be interrupted if a Grade 2 or 3 adverse experience occurs. Once the adverse event has resolved or decreased in intensity to Grade 1, XELODA therapy may be restarted at full dose or as adjusted according to Table 18. If a Grade 4 experience occurs, therapy should be discontinued or interrupted until resolved or decreased to Grade 1, and therapy can then be restarted at 50% of the original dose. Patients taking XELODA should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of XELODA omitted for toxicity are not replaced.

Haematology: Patients with baseline neutrophil counts of < 1.5 x 10^9/L and/or thrombocyte counts of < 100 x 10^9/L should not be treated with XELODA. If unscheduled laboratory assessments during a treatment cycle show Grade 3 or 4 haematologic toxicity, treatment with XELODA should be interrupted.

The following table shows the recommended dose modifications following toxicity related to XELODA.

Table 18: XELODA dose reduction schedule

Toxicity Grades[#]	During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 0-1	100%
2nd appearance	Interrupt until resolved to Grade 0-1	75%
3rd appearance	Interrupt until resolved to Grade 0-1	50%
4th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
1st appearance	Interrupt until resolved to Grade 0-1	75%
2nd appearance	Interrupt until resolved to Grade 0-1	50%
3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4 1st appearance	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	50%
2nd appearance	Discontinue permanently	Not applicable

[#] According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute (version 3.0). For hand-foot syndrome and hyperbilirubinaemia see PRECAUTIONS.

General combination therapy

Dose modifications for toxicity when XELODA is used in combination with other therapies should be made according to the table above for XELODA, and according to the appropriate product information for the other agent(s).

At the beginning of a treatment cycle, if a treatment delay is indicated for either XELODA or the other agent(s), then administration of all agents should be delayed until the requirements for restarting all medicines are met.

During a treatment cycle for those toxicities considered by the treating physician not to be related to XELODA [for example, neurotoxicity, ototoxicity, neurosensory toxicity, fluid retention (pleural effusion, pericardial effusion or ascites), bleeding, gastrointestinal perforations, proteinuria, hypertension], then XELODA should be continued and the dose of the other agent adjusted according to the appropriate product information.

If the other agent(s) have to be discontinued permanently, XELODA treatment can be resumed when the requirements for restarting XELODA are met.

This advice is applicable to all indications and to all special populations.

Dosage Adjustments in Special Populations

- *Hepatic Impairment due to liver metastases*: Patients with mild to moderate hepatic impairment due to liver metastases, should be carefully monitored when XELODA is administered. No starting dose reduction is necessary. Patients with severe hepatic impairment have not been studied.
- *Renal Impairment*: In metastatic colorectal and breast cancer clinical trials, patients with renal impairment had a greater incidence of Grade 3 or 4 adverse reactions than other patients, the incidence increasing with the degree of renal impairment from 35% in patients

with normal renal function to 55% in patients with moderate renal impairment (creatinine clearance 30-50 mL/min). Based on the pharmacokinetic data, a dose reduction to 75% is recommended in moderate renal impairment for both monotherapy and combination use. No initial dose reduction is recommended in patients with mild renal impairment (creatinine clearance 51-80 mL/min). Further dose reductions should be made if adverse reactions occur (see Tables 18). XELODA is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min). XELODA is contraindicated in patients with creatinine clearance below 30 mL/min (see CONTRAINDICATIONS).

- *Elderly:* For XELODA monotherapy, no adjustment of the starting dose is needed . However, severe Grade 3 or 4 treatment-related adverse reactions were more frequent in patients over 80 years of age compared to younger patients. When XELODA was used in combination with other agents, elderly patients (≥ 65 years of age) experienced more Grade 3 and Grade 4 adverse drug reactions (ADRs), and ADRs that led to discontinuation, compared to younger patients. Careful monitoring of elderly patients is advisable. For treatment with XELODA in combination with docetaxel, an increased incidence of Grade 3 or 4 treatment-related adverse reactions and treatment-related serious adverse reactions were observed in patients 60 years of age or more. For patients 60 years of age or more treated with the combination of XELODA plus docetaxel, a starting dose reduction of XELODA to 75% (950 mg/m^2 twice daily) is recommended. For dosage calculations, see Tables 16 and 17.

OVERDOSAGE

The manifestations of acute overdose include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation and bleeding and bone marrow depression. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

XELODA tablets are available in the following presentations:

- 150 mg light peach, film-coated tablets with “XELODA” on one side and “150” on the other side. In blister packs of 60.
- 500 mg peach, film-coated tablets with “XELODA” on one side and “500” on the other side. In blister packs of 120.

XELODA tablets should be stored below 30 °C. XELODA tablets should not be taken after the expiry date imprinted on the container label.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4–10 Inman Road
Dee Why NSW 2099

Customer Enquiries: 1800 233 950

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF APPROVAL

TGA Approval Date: 2 February 2011