USC Norris Comprehensive Cancer Center
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Protocol Title: Phase II Study of Oxaliplatin and Xeloda® and Cetuximab as First Line Treatment for Metastatic or Unresectable Gastric or Gastroesophageal Junction Cancer

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**UNIVERSITY OF SOUTHERN CALIFORNIA/KENNETH NORRIS, JR.
COMPREHENSIVE CANCER CENTER AND HOSPITAL
CLINICAL INVESTIGATIONS SUPPORT OFFICE
1441 Eastlake Avenue, Room 7408 MS-74
Los Angeles, California 90089-9177
Telephone (323) 865-0450**

PROTOCOL NUMBER:	3G-03-4
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CO-INVESTIGATORS:	Heinz-Josef Lenz, MD Anthony El-Khoueiry, MD
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1.0 OBJECTIVES

1.1 Primary Objective

1.1.1 To determine the proportion of patients, with advanced gastric or gastroesophageal junction cancer treated with a combination of capecitabine, oxaliplatin and cetuximab that have progressive disease within four months of the start of treatment.

1.2 Secondary Objectives

1.2.1 To determine the time to progression, time to treatment failure, overall response rate and overall survival in patients with advanced gastric or gastroesophageal junction cancer treated with a combination of capecitabine, oxaliplatin and cetuximab.

1.2.2 To assess the toxicity of this regimen.

1.2.3 To identify molecular predictors of response, survival, and toxicity to this combination of chemotherapy.

2.0 BACKGROUND AND HYPOTHESES

2.1 Incidence of Gastric Cancer and Current Treatment Strategies Unresectable or Metastatic Disease

In 2000, there were an estimated 22,800 new cases of gastric carcinoma diagnosed in the United States and 14,000 deaths from this disease.[1] Surgical resection remains the only curative treatment for gastric cancer. Unfortunately, most patients with gastric carcinoma present with either locally advanced or metastatic disease.[2,3]

Various combinations of active drugs have been reported to improve the response rate among patients with unresectable gastric carcinoma. A combination of fluorouracil, doxorubicin, and mitomycin has been associated with a 30 to 40 percent response rate and, until recently, was the most widely prescribed regimen for patients with advanced disease.[4] In another study an initial response rate of 64 percent was seen with a combination of etoposide, doxorubicin, and cisplatin used by German investigators. However, in subsequent trials testing this regimen, it was found to be considerably less effective and extremely toxic.[5-7] Later, a combination of fluorouracil, doxorubicin, and high-dose methotrexate was associated with a significant improvement in the response rate, as compared with either etoposide, doxorubicin, and cisplatin or fluorouracil, doxorubicin, and mitomycin.[6-8] As a result of these latter studies, FAMTX was the standard therapy for much of the past decade.

In a recent study of patients with unresectable or metastatic gastric and esophageal adenocarcinoma, 274 patients were randomized to either 5-FU, doxorubicin, and methotrexate (FAMTX) or epirubicin, cisplatin and continuous infusion 5-FU (ECF).[7,9] ECF was associated with a superior response rate (45% vs. 21%; P = 0.0002), median

survival (8.7 vs. 5.7 mos.; P = 0.00006), and one-year survival (36% vs. 21%). Moreover, ECF was associated with a superior quality of life and less toxicity.

Currently, the standard of care for metastatic gastric cancer patients remains 5-FU/cisplatin type regimens. The most widely investigated single-agent chemotherapy is 5-fluorouracil (5-FU), with reported partial response rates up to 20%. Pilot phase II studies investigating combinations of 5-FU, anthracyclines, mitomycin, methotrexate, and platinums have achieved higher response rates; however, the response rates declined in subsequent larger trials. Furthermore, toxicity was substantially higher in the confirmatory trials, emphasizing the need to develop well-tolerated regimens prior to multi-institutional testing. Although phase III studies of combination regimens have not achieved a clear worldwide standard, the regimen of epirubicin, cisplatin, and continuous-infusion 5-FU has shown a survival benefit, possibly through the increased activity of infusional 5-FU combined with cisplatin.[10] Results from trials in disseminated gancer are summarized below.

Combination	Response Rate (%)	Median Response Duration (Mo)	Median TTP (Months)	Median OS (Months)
FAM (80)	9-42	9		5.6-6
FP (91-'99)	27-45	10.2	4.5	9.0-10.6
FAMTX (82-99)	21-63			6.1-10
ECF (96-2001	42-71	10.1	5.0	8.6-9.0
Cis/Irin	41-58		4.8	9.0
DI	45		4.6	8.2
DC (99-05)	26		3.7-5.0	10.5
DCF (03-05)	43		5.6-5.9	9.6
CAPOX (06)	65		4	6.4
CAP/D (06)	39		4.2	9.0
S-1/cis (04-06)	49		4.9	10.6

The goal of this proposal is to establish the anti-tumor activity of the combination of capecitabine, oxaliplatin and cetuximab in patients with advanced gastric or gastroesophageal junction cancer.

2.2 Capecitabine

Capecitabine is an oral tumor selective fluoropyrimidine carbamate, designed to generate 5-FU selectively in tumor cells. It is converted to 5-FU by three enzymes located in the liver and tumor cells. The final step of the conversion is of 5'-dFUrd to 5-Fura by thymidine phosphorylase in tumor cells.[11,12] Capecitabine is more potent and has a wider spectrum of antitumor activity than other fluoropyrimidines in animal models of human breast, colon, gastric, cervical, bladder, ovarian and prostate cancer.[4-9,11,12] This improved therapeutic index appears to be directly related to the tumor-specific

generation of 5-FU by the tumor associated enzyme thymidine phosphorylase.[4,5] In clinical studies, 5-FU levels were found to be significantly higher in primary colorectal tumor tissues than that found in adjacent normal tissues. This finding can most likely be explained by the four-fold difference in TP activity between primary colorectal tumors and healthy colorectal mucosa (Roche Product Information). In breast cancer a ten-fold difference has been found between breast tumor tissue and adjacent normal tissue (Roche Product Information). Findlay et al reported at ASCO a 20% response rate in advanced colorectal cancer patients receiving capecitabine, which included complete response.[7] *In vitro* and *in vivo* data have shown that capecitabine is still effective in 5-FU resistant cell lines and xenograft models, indicating the high therapeutic potential of this drug.[6-9] The mechanism for drug resistance is similar to that found in 5-FU which include increased levels of thymidylate synthase, low intratumoral levels of TP, and high intratumoral levels of dihydropyrimidine dehydrogenase.

Capectabine is approved for use in metastatic breast cancer in those resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated (e.g., those who have received cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents). Capecitabine is also indicated in combination with docetaxel in metastatic breast cancer. In patients with metastatic colorectal cancer when treatment with fluoropyrimidines alone is preferred, capecitabine monotherapy is approved.

2.2.1 Mechanism of Action

After oral administration capecitabine passes unchanged from the gastrointestinal tract and is metabolized in the liver by 60 Kd carboxylesterase (previously known as acylamidase isoenzyme A), to 5'-deoxy-5-fluorocytidine (5'-DFCR). This is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase located in the liver and also in tumor tissues. Further metabolism of 5'-DFUR then occurs at the site of the tumor under the action of thymidine phosphorylase (dThdPase), to 5-FU. Inactivation of thymidylate synthase (TS) by 2'-deoxy-5-fluorouridine 5'-monophosphate (FdUMP) and interference with RNA processing by 5'-fluorouridine 5'-triphosphate (FUTP) incorporation into RNA are the main mechanisms of action of 5-FU.[7,9] Capecitabine administered orally generates FdUMP and inactivates TS in tumors. Its efficacy is likely mediated by mechanisms similar to those of 5-FU.[8,9]

The efficacy of capecitabine correlates with the activity of dThdPase, the enzyme responsible for the conversion of 5'-DFUR to 5-FU, and dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for the catabolism of 5-FU (Investigator Information, Roche). The intermediate metabolite of capecitabine, 5'-DFUR, is not efficiently converted to 5-FU in the WiDr human colon cancer xenograft, which is refractory to capecitabine (Investigator Information, Roche). Inefficient conversion by dThdPase is a potential mechanism of drug resistance to capecitabine. Tumor susceptibility to capecitabine *in vivo* correlates with the ratio of dThdPase to DPD activity (Investigator Information, Roche). In addition to low intratumoral concentrations of dThdPase, high DPD levels in tumors may represent another mechanism of drug resistance to capecitabine.

2.2.2 Preclinical Studies

In human cancer xenograft models, capecitabine yields substantially higher concentrations of 5-FU within tumors than in plasma or normal tissue (muscle). In addition, capecitabine yields higher levels of 5-FU within tumors than equi-toxic doses of 5-FU (Investigator Information, Roche).

Capecitabine is more potent and has a wider spectrum of antitumor activity than 5-FU, 5'-DFUR, or UFT against human cancer xenograft models of breast, colon, gastric, cervical, bladder, ovarian and prostate cancer. Capecitabine thus shows activity against tumors that are resistant to 5-FU and UFT *in vivo* (Investigator Information, Roche).

2.2.3 Clinical Data

The efficacy of capecitabine as a monotherapy has been evaluated in four phase II studies (one in colorectal cancer patients, three in breast cancer patients) and two phase III studies in colorectal cancer patients.

In a phase II study of previously untreated colorectal cancer patients, 109 patients were randomized to continuous capecitabine treatment, intermittent capecitabine treatment, or combination intermittent capecitabine/leucovorin treatment. The overall response rates in all 3 treatment groups were comparable (21% to 24%). The median time to disease progression was 127 days, 230 days and 212 days, respectively. Leucovorin and capecitabine combination therapy neither increased the overall response rate nor elicited a discernible delay in the median time to disease progression (Investigator Information, Roche).

Phase III Trials in Colorectal Cancer:

SO14796: The efficacy and safety of Xeloda® was compared to that of 5-FU/leucovorin Mayo Clinic regimen was studied in an open label, randomized phase III trial involving 602 previously untreated patients with advanced or metastatic colorectal cancer enrolled globally outside South and North America. Of these, 301 patients were randomized to Xeloda® (twice daily 1250 mg/m^2 given days 1-14 q3w), and 301 patients to 5-FU/LV (5-FU 425 mg/m^2 with LV 20 mg/m^2 given days 1-5, q4w). Overall objective tumor response rates (based on the investigator assessment and all randomized population) were 26.6% vs. 17.9% in the Xeloda® and the 5-FU/LV arms, respectively (p=0.013). In the Xeloda® and 5-FU/LV groups, median times to disease progression were 5.2 and 4.7 months (log-rank p=0.65) and median times to treatment failure were 4.2 and 4.0 months (log rank p=0.89). Xeloda® was at least equivalent to 5-FU/LV in survival, with median overall survival times of 13.2 and 12.4 months (log rank p=0.30) respectively. Treatment with Xeloda® led to significantly lower incidences of neutropenia, stomatitis and alopecia, but a higher incidence of HFS. Xeloda® also resulted in lower incidences of grade 3/4 stomatitis and grade 3/4 neutropenia, leading to a significantly lower incidence of grade 3/4 neutropenic fever and sepsis. Only grade 3 HFS and uncomplicated grade 3/4 hyperbilirubinemia were reported more frequently with Xeloda® than with 5-FU/LV.

SO14695: An identical trial to SO14796 was done in 605 patients with metastatic colorectal cancer enrolled from the USA, Canada, Brazil and Mexico. Of these, 302 were randomized to Xeloda® (twice daily 1250 mg/m^2 given days 1-14 q3w), and

303 to the 5-FU/LV Mayo Clinic regimen (5-FU 425 mg/m^2 with LV 20 mg/m^2 given days 1-5 q4w). The overall objective tumor response rates (based on the investigator assessment and all randomized population) were 24.8% vs 15.5% in the Xeloda® and Mayo Clinic regimen -arms, respectively (p=0.005). In the Xeloda® and 5-FU/LV groups, median times to disease progression were 4.3 and 4.7 months (log-rank p=0.72) and median times to treatment failure were 4.1 and 3.1 months (p=0.19). Xeloda® was at least equivalent to 5-FU/LV in survival, with median overall survival times of 12.5 and 13.3 months (p=0.97), respectively. Xeloda® produced a significantly lower incidence of diarrhea, stomatitis, nausea and alopecia, as compared to 5-FU/LV. Patients treated with Xeloda® also had lower incidences of grade 3/4 stomatitis and grade 3/4 neutropenia, leading to significantly less neutropenic fever/sepsis. Grade 3 HFS (p<0.00001) and grade 3/4 hyperbilirubinemia were the only toxicities more frequently associated with Xeloda® than 5-FU/LV treatment. Patients treated with Xeloda® required fewer hospitalizations (p=0.003) for adverse reactions than did those treated with 5-FU/LV.

XELOX Trials in Esophagogastric cancer:

A multicenter randomized trial has looked at capecitabine and oxaliplatin in combination with epirubicin in patients with oesophagogastric cancer. This trial is ongoing and has four treatment arms: 1)epirubicin, cisplatin, fluorouracil 2) epirubicin, oxaliplatin, fluorouracil 3) epirubicin, cisplatin, capecitabine and 4) epirubicin, oxaliplatin and capecitabine. The doses of each drug were: epirubicin 50 mg/m2, cisplatin 60 mg/m2, oxaliplatin 130 mg/m2, all given iv q 3 weeks. Fluorouracil is being given200 mg/m2/day IV and capecitabine 1,000 mg/m2/day, po, continously. An interim analysis was performed when 80 patients had been randomized. The dose limiting fluoropyrimidine toxicities were stomatitis, palmar plantar erythema and diarrhea, with 5.1% of capecitabine treated patients experiencing grade 3 or 4 toxicity. A protocol planned dose escalation was then instituted, with the capecitabine escalated to 1,250 mg/m2/day. Since then non-haematologic grade 3 or 4 toxicity has effected 10.7% of the 1,250 mg/m2 capecitabine treated patients, making this an optimal dose. With 153 patients evaluable for response, the combined CR +PR rates for each regimen are as follows: epirubicin, cisplatin, fluorouracil 31% (95% CI 17.5-48.7) 2) epirubicin, oxaliplatin, fluorouracil 33% (95% CI 18.6-49.1) 3) epirubicin, cisplatin, capecitabine 35% (95% CI 19.8-53.5) and 4) epirubicin, oxaliplatin and capecitabine 52% (95% CI 34.4-68.1).[13]

2.3 Oxaliplatin

Oxaliplatin (trans-*l*-1,2-diaminocyclohexane oxalatoplatinum), is a novel antineoplastic platinum derivative with a 1,2-diaminocyclohexane [DACH] carrier ligand. Although the precise mechanism of action is unknown, platinum compounds in general are thought to exert their cytotoxic effects through the formation of DNA adducts that block both DNA replication and transcription, resulting in cell death in actively dividing cells as well as the induction of apoptosis. Oxaliplatin is more potent than cisplatin *in vitro*, requiring fewer DNA adducts to achieve an equal level of cytotoxicity. Oxaliplatin has shown efficacy in preclinical studies against many tumor cell lines, including some that are resistant to cisplatin and carboplatin.[14-21] In European clinical trials, oxaliplatin demonstrated

efficacy against colorectal cancer, both as a single agent and in combination with capecitabine or 5-fluorouracil (5-FU) and leucovorin (LV).[21-30]

2.3.1 Mechanism of Action

Like cisplatin, oxaliplatin reacts with DNA, forming mainly platinated intrastrand links with two adjacent guanines or a guanine adjacent to an adenine.[26,31,32] However, DACH-platinum adducts formed by oxaliplatin are apparently more effective at inhibiting DNA synthesis and are more cytotoxic than cis-diammine-platinum adducts formed from cisplatin and carboplatin.[32-34] The 1,2-DACH carrier ligand effects the rate of mono- and diadduct conversion.[35] It also effects the ability of cells to tolerate unrepaired platinum-DNA adducts.[34,36] The latter effect may be responsible for differentiating the antineoplastic activity of oxaliplatin from that of carboplatin or cisplatin.

Two mechanisms that reproducibly discriminate between cisplatin and oxaliplatin are defects in mismatch repair and enhanced replicative bypass.[37] Several studies have demonstrated that the loss of the mismatch repair (MMR) enzyme complex is a contributor to intrinsic resistance to cisplatin, but not oxaliplatin. Computer modeling studies suggest that the MMR complex may be prevented from binding to oxaliplatin adducts due to the steric hindrance of the DACH ring, which is retained after biotransformation.[38] In an *in vivo* study "athymic nude mice with MMR-proficient grafts responded significantly better to cisplatin therapy than did mice with MMR-deficient grafts".[37] However, no difference in sensitivity to oxaliplatin has been found between the groups.[39] Moreover, "colon carcinoma cell lines defective in either *hMLH1* or *hMLH2* display significant resistance to cisplatin but little or no resistance to oxaliplatin".[40] Lastly, both *hMS2* and the *hMutS* complex recognize cisplatin, but not oxaliplatin, diadducts with DNA.[40,41] Further evidence suggests that cisplatin treatment may produce selective pressure for the survival of MMR-deficient cells, implying a role for oxaliplatin in overcoming cisplatin-acquired resistance.[39-42]

Another resistance mechanism that has reproducibly been shown to discriminate between cisplatin and DACH-platinum compounds is enhanced replicative bypass (i.e., the ability of the replication complex to synthesize DNA past the site of DNA damage). "In cisplatin-resistant human ovarian carcinoma cell lines, a two- to six-fold enhanced replicative bypass of cisplatin adducts was observed. However, no difference in replicative bypass of oxaliplatin adducts was observed between the cisplatin-sensitive and -resistant cell lines".[43] Additionally, oxaliplatin adducts have been found to cause greater inhibition of DNA chain elongation than cisplatin adducts in both cisplatin-sensitive and -resistant cell lines.[37]

In summary, the current data indicate that both the alteration of the MMR process and replicative bypass of DNA adducts contribute to cisplatin resistance in ovarian cancer cell lines. However, this resistance can be overcome by a platinum agent with a bulky carrier group, such as oxaliplatin, which can make bypass more difficult and can prevent the binding of the MMR complex.

2.3.2 Preclinical Studies

In vitro, oxaliplatin has shown antiproliferative activity equivalent to or higher than that of cisplatin against murine and human cancer cell lines. These cell lines include murine leukemia L1210 and P388 cell lines, human HT29 colon carcinoma, human HEC59

colon carcinoma), human ovarian carcinoma cell line A2780, non-small cell lung cancer cell lines, epidermal KB cells, breast MCF-7 cells, neuroblastoma cell lines and non-seminomatous germ cell cancer cell lines.[15-20,44] In a study investigating the sensitivity of two cisplatin-resistant cell lines - a clone of ovarian cancer A2780 and the epithelial KB 3-1 cell line - both clones were approximately 10-fold more resistant to cisplatin or carboplatin than to oxaliplatin.[18] Additionally, in nonseminomatous germ cell cancer cell lines with either acquired (H12DDP clone) or intrinsic (1777Nrp Cl-A clone) resistance to cisplatin, oxaliplatin was found to be significantly more cytotoxic than cisplatin.[20] These data suggest that the mechanism of action of oxaliplatin differs from that of cisplatin or carboplatin.

Not all cisplatin-resistant cell lines are sensitive to oxaliplatin. In the human ovarian cancer cell line OVCAR3, which is intrinsically resistant to cisplatin, oxaliplatin was found to be less effective than cisplatin.[45]

2.3.3 Clinical Data

Oxaliplatin in combination with 5-FU/LV has been evaluated in 1106 previously treated patients with refractory metastatic colorectal cancer. Extended-access, compassionate-use programs treated 721 patients who were later assessed by retrospective analyses.[46,47] In one retrospective analysis of 206 patients with advanced colorectal cancer treated with oxaliplatin at 44 European cancer centers, progression on 5-FU/LV schedules was verified in 111 patients.[46] Oxaliplatin was then added to the 5-FU/LV schedules, either as 80 to 100 mg/m^2 per cycle every two weeks (49 patients) or 100 to 135 mg/m^2 per cycle every 3 weeks (62 patients). The objective response rate in 98 evaluable patients was 26% (95% CI, 17.2 to 35.5). These results were confirmed in a second retrospective analysis of a French extended-access program in which 490 patients received oxaliplatin for advanced colorectal cancer.[48] Of 472 patients who received oxaliplatin in combination with 5-FU/LV, 370 proved to be resistant to 5-FU/LV. The cumulative dose of oxaliplatin administered per patient was 600 mg/m^2 (range, 70 to 2300 mg/m^2). Median time to progression was 4.3 months (95% CI, 3.9 to 4.7) and median survival time was 9.7 months (95% CI, 8.5 to 10.8).[46] Similar results were obtained in a small compassionate-use program in which 25 patients received chronomodulated infusions of oxaliplatin/5-FU/LV.[49]

In summary, clinical trials of oxaliplatin combined with 5-FU/LV in both chemotherapy-treated and -untreated patients have shown the effectiveness and tolerability of oxaliplatin when combined with either 5-FU/LV or capecitabine. This proposal is a phase II study to evaluate the role of other thymidylate synthase inhibitors, specifically capecitabine in combination oxaliplatin, in the treatment of gastric and GE junction cancer.

A phase II study of doxifluridine, an intermediate metabolite of capecitabine, was evaluated in gastric cancer. Response rates were reported as approximately 14%, with long median survival times (371 days). The median time to progression and overall survival for patients with objective response or stable disease (> 90 days) were approximately the same.[50]

In a pilot study by Eriguchi et al., oxaliplatin was administered preoperatively in patients with advanced scirrhous type gastric cancer. In this study, preoperative 1-OHP, 67 mg/m2 to 100 mg/m2 was administered every 2-3 weeks, for 2 to 3 cycles, in patients

with stage III and IV disease radiologically and histologically. The platinum concentration in the tissues was measured. Three grade 2 histologic responses and two grade 1 histologic responses were obtained. The mean platinum concentrations in the lesional tissues were 0.98 ppm and 0.5 ppm in patients administered 1-OHP for 2 and 2 cycles respectively. This regimen was tolerated in the neoadjuvant setting and there was no toxicity that prevented surgery.[51]

Louvet and colleagues conducted a phase II study of oxaliplatin, fluorouracil and folinic acid in locally advanced or metastatic gastric cancer patients to evaluate the efficacy and safety of the combination. Fifty-four patients had measurable or assessable disease, 53 received therapy every 2 weeks. 87% had metastatic disease and all had histologically confirmed adenocarcinoma. Of the 49 assessable patients, there were 2 CR's and 20 partial responses, leading to a best response rate of 44.9%. Eight patients underwent complementary treatment with curative intent (6 with surgery and 2 with chemotherapy and radiation therapy). Median time to progression as 6.2 months and overall survival was 8.6 months. The main grade 3/4 toxicity was hematologic and Grade 3 peripheral neuropathy occurred in 21% of patients.

Kim et al performed a Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Due to the activity oxaliplatin has demonstrated in cell lines that are resistant to cisplatin, the combination of 5-FU and oxaliplatin was evaluated in patients with advanced gastric cancer who progressed during or after treatment with 5-FU and platinum compounds. Twenty-six patients with advanced gastric cancer, whose disease progressed while receiving, or after discontinuing chemotherapy with a 5-FU and platinum regimen, were enrolled in this study. Treatment comprised oxaliplatin (85 mg/m(2) on day 1) as a 2-h infusion followed by bolus 5-FU (400 mg/m(2) on day 1), and a 48-h infusion of 5-FU 2.4-3.0 g/m(2) concurrently with LV 150 mg/m(2). Cycles were repeated at 2-week intervals. Of the 23 evaluable patients, there were six partial responses (response rate 26%). All responding patients were among those who entered into this trial immediately after failure of previous chemotherapy with 5-FU and cisplatin. The median time to progression was 4.3 months and the median overall survival was 7.3 months. The most common hematologic toxicity was grade 1-2 anemia in 39 cycles (39%). No grade 4 leukopenia or thrombocytopenia were observed. The most common non-hematologic toxicity was nausea/vomiting (33%). Peripheral neuropathy of grade 1 or 2 was noted (27%), but there was no grade 3 or 4 neurotoxicity. This phase II study of oxaliplatin, 5-FU and LV continuous infusion showed activity in previously platinum-treated patients with advanced gastric cancer, with acceptable toxicities.[52]

In a phase I clinical trial with combination capecitabine and oxaliplatin, 23 patients were entered and the recommended dose was 1000 mg/m2 twice daily (d1-14) with oxaliplatin 130 mgm2 d1 in 21 day cycles. The principle dose limiting toxicity was diarrhea.[53]

Xeloda in monotherapy in 1st line Gastric cancer: Ph II study from South Korea: 44 patients were treated with Xeloda 1250 mg/m2 bid d1-14, q 3 weeks. Results: ORR=34%, SD= 32% and median TTP=3.1 months. The treatment was very tolerable with 9% of Hand Foot syndrome grade 3 and Gastrointestinal AEs grade 3/4< 5%.[54]

Xeloda in combination has been studied in different trials:
- Xeloda + Cisplatin in 1st line Gastric cancer: Ph II study: N=42 patients treated with Cisplatin 60mg/m2 d1 and Xeloda 1000mg/m2 bid d1-14 q3weeks. ORR=55%, median

TTP=6.3 months, and median survival=10.1 months. Grade 3/4 toxicity: neutropenia (32%), thrombocytopenia (10%), HFS (8%), diarrhea (5%) and stomatitis (3%).[55]

- Xeloda + Docetaxel in 1st line Gastric cancer: PhII study: N=35 patients treated with Docetaxel 75mg/m2 and Xeloda 1250mg/m2 bid d1-14, q3weeks. ORR=67%; median TTP=4.8 months and median OS=17.2 months. Toxicity: HFS grade 3 (52%), leucopenia (5% grade 3 and 3% grade 4). [56]

- Xeloda + Oxaliplatin in 2nd line Gastric cancer: ph II study. N=17 patients treated with Oxaliplatin 85mg/m2 d1 and Xeloda 1250mg/m2 d1-14 q3weeks. ORR=24%; SD=35%. Tolerability: grade3/4 neutropenia (18%), thrombocytopenia (12%), HFS (8%), diarrhea (12%) and stomatitis (6%) and neuropathy in 2 patients (12%).[57]

- Xeloda, Cisplatin and Docetaxel (DCX) in 1st line Gastric cancer: Ph I-II study. N=35 patients received total of 168 cycles at 4 dose levels. After dose reductions, final patient cohort treated at: Xeloda 938 mg/m2 bid, d1-14 q3wks + Cisplatin 60 mg/m2 d1 and Docetaxel 60 mg/m2 d1. Results demonstrated activity at all dose levels: ORR of 54% [CR (9%), PR (46%)]. TTP=7.9 months, OS=11.9 months. Toxicity: Neutropenia Grade 4 (17%), asthenia Grade3/4 (8%).[58]

- Xeloda, Cisplatin and Epirubicin (ECX) in 1st line Gastric cancer: Ph II study. N=45 patients treated with Xeloda 1000mg/m2 bid d1-14 qweeks, Cisplatin 60mg/m2 d1 and and Epirubicin 50mg/m2 d1. Results demonstrated ORR (65%) [CR (8%), PR (57%)] with 19% of SD. TTP=5.2 months and OS=13months. 44 patients were evaluable for safety with neutropenia Grade3/4 (30%), Neutroenic fever (3% with 1 death), HFS Grade 3 (2%), Anemia Grade3/4 (8%), N/V and mucositis Grade3/4 (2%) and Neuropathy Grade2 (7%).[59]
-

2.4 Cetuximab

Cetuximab was recently approved as a single-agent in patients with irinotecan-refractory colorectal cancer whose tumors express the epidermal growth factor receptor. The most commonly encountered grade 3 to 4 adverse events, in the 57 patients treated on a recent study were an acne-like skin rash, predominantly on the face and upper torso (86% with any grade; 18% with grade 3), and a composite of asthenia, fatigue, malaise, or lethargy (56% with any grade, 9% with grade 3). [60] Laboratory studies have shown *in vivo* and *in vitro* activity of cetuximab in colorectal cancer, regardless of EGFR level.[61] Early clinical trials with cetuximab required demonstration of the receptor by immunohistochemical (IHC) techniques. Assumptions were made regarding the stability of EGFR expression and the reproducibility of this IHC expression that, are now considered incorrect. It is now thought that current techniques lack the sensitivity and predictability to inform decisions as to the usefulness of cetuximab or other anti-EGFR therapies in the treatment of colorectal or other cancers. Current data do not support the use of the EGFR IHC stain for making any clinical decisions regarding patient management.[62] Further studies of are evaluating the use of cetuximab in conjunction with first-line and adjuvant treatments and in EGFR negative colorectal cancer patients.

Epidermal growth factor receptor (EGFR or HER1) and its homologs HER2 c-erbB-2 or NEU), HER3, and HER4 are glycoproteins that consist of an extracellular domain for binding ligands, a short lipophilic transmembrane domain, and an intracellular domain carrying tyrosine kinase activity.[63-65] The receptors of this family are activated by dimerization that can be between

identical receptors (homodimerization) or between different members of the same family (heterodimerization).[66]

Epidermal growth factor (EGF) and transforming growth factor are produced locally in many tissues as local growth factors rather than as systemic hormones, and through EGFR they stimulate DNA synthesis and cell growth in various systems, including the gastrointestinal tract.[67] EGFR is important not only in cell proliferation, but also in a number of varied processes likely to be important for tumor progression, such as cell motility, cell adhesion, cell invasion, cell survival, and angiogenesis.[68] Laboratory studies suggest that EGFR plays a crucial role in regulating the growth of gastric cancer. Growth inhibition of three human gastric cancer cell lines has occurred, both *in vitro* and *in vivo*, with the suppression of EGFR protein levels via an antisense messenger RNA.[69,70]

High levels of EGFR in gastric cancer have been shown to be associated with shorter survival. A recent prospective study was done in 63 patients with resectable gastric carcinomas who underwent surgical resection of their tumors with no systemic therapy. I n specimens removed during resection membranous EGFR levels were examined by radioligand binding assays, and cytosolic HER2 levels were examined by means of an immunoenzymatic assay. There was a wide variability of EGFR and HER2 levels in tumors. No significant correlation was found between these levels and patient or tumor characteristics. However, high levels of EGFR and HER2 were significantly associated with a shorter overall survival period (P = .03 and P = .02, respectively).[71] Another recent study showed similar results. In this study 65 patients with unresectable gastric cancer, underwent palliative surgery and were followed for survival. Membranous EGFR levels were examined by radioligand binding assays and cytosolic c-erbB-2 levels by means of an immunoenzymatic assay. Median c-erbB2 was significantly higher in tumors of the intestinal type than in tumors of the diffuse type ($p = 0.035$) and in R2 than in R1 tumors ($p = 0.016$). High levels of EGFR were significantly associated with a shorter overall survival ($p = 0.01$). These data suggest a role of both EGFR and c-erbB-2 in the progression of gastric cancer, and their possible future utilization as appropriate biological markers for selecting candidates for treatment based on EGFR and/or c-erbB-2 inhibition.[72]

Another study done in a more heterogenous population did not find a correlation between EGFR levels and survival, but its results also suggest a role for EGFR in tumor progression of gastric cancer. In this study membranous EGFR levels were examined by radioligand binding assays in 110 patients with gastric cancer. EGFR levels were significantly higher ($p<0.0005$) in neoplastic tissue than in paired adjacent mucosa samples (median) (n= 84; 8.7 vs. 3.9 fmol/mg protein). Intratumoral EGFR levels were significantly correlated with tumor stage ($p<0.05$), and were higher in patients with stage III tumors (median) (7.6, 6.4, 12.3 and 7.5 fmol/mg protein for stages I, II, III and IV, respectively). In addition, the tumor/mucosa ratios of the EGFR content were significantly higher ($p<0.05$) in patients with stage III tumors (1, 1.8, 3.9, and 0.92, respectively).[73]

Cetuximab binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha.[74] Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues,

including the skin and hair follicle. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum.

In vitro assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

2.4.1 Human Pharmacokinetics

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics.[74] The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m^2. Cetuximab clearance (CL) decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of distribution (Vd) for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m^2.

Following a 2-hour infusion of 400 mg/m^2 of cetuximab, the maximum mean serum concentration (Cmax) was 184 µg/mL (range: 92-327 µ g/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m^2 produced a mean Cmax of 140 µg/mL (range 120-170 µg/mL). Following the recommended dose regimen (400 mg/m^2 initial dose/250 mg/m^2 weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life was 114 hours (range 75-188 hours).

2.4.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving cetuximab has not been adequately determined. The incidence of antibodies to cetuximab was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-cetuximab antibodies were detected in 5% (28 of 530) of evaluable patients.[74] In patients positive for anti-cetuximab antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or antitumor activity of the molecule.

The observed incidence of anti-cetuximab antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-cetuximab antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cetuximab with the incidence of antibodies to other products may be misleading.

2.4.3 Clinical Studies of Cetuximab in Colorectal Cancer and Head and Neck Cancer : Efficacy

The efficacy and safety of cetuximab in combination with radiation therapy was studies in a randomized controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) versus radiation therapy alone. In addition, cetuximab alone was studied in a single-arm, multi-center clinical trial in 103 patients with recurrent or metastatic SCCHN with documented progression within 30 days after 2-6 cycles of platinum-based chemotherapy.

The efficacy and safety of cetuximab alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). Cetuximab was further evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111 patients treated with single agent cetuximab was also evaluated. All trials studied patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

2.4.3.1 Randomized, Controlled Trial

The efficacy and safety of cetuximab were studied in combination with radiation therapy in a randomized, controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck versus radiation alone. In a multicenter controlled clinical trial, 424 patients with Stage III/IV SCC of the oropharynx, hypopharynx, or larynx with no prior therapy were randomized 1:1 to receive cetuximab plus radiation therapy (211 patients) or radiation therapy alone (213 patients). Stratification factors were Karnofsky Performance Status (60-80 versus 90-100), nodal stage (N0 versus N+), tumor stage (T1-3 versus T4 using American Joint Committee on Cancer 1998 staging criteria), and radiation therapy fractionation (concomitant boost versus once-daily versus twice daily). Radiation therapy was administered form 6-7 weeks as once daily, twice daily, or concomitant boost. The planned radiation therapy regimen was chosen by the investigator prior to enrollment. For patients with $\geq$N1 neck disease, a post-radiation therapy next dissection was recommended. Starting 1 week before radiation, cetuximab was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m ^{2} weekly for the duration of radiation therapy (6-7 weeks). All cetuximab-treated patients treated patients received a 20-mg test dose on Day 1. Cetuximab was administered 1 hour prior to radiation therapy, beginning week 2.

Of the 424 randomized patients, 80% were male and 83% were Caucasian. The median age was 57 years (range 34-83). There were 258 patients enrolled in US sites (61%) and 166 patients (39%) in non-US sites. Ninety percent of patients had baseline Karnofsky Performance Status of 80%. Sixty percent of patients had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. The patient characteristics were similar across the study arms. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen. The main outcome measure of this trial was duration of locoregional control. Overall survival was also assessed. Results are presented below:

Clinical Efficacy in Locoregionally Advanced SCCHN

	Cetuximab + Radiation (n = 211)	Radiation Alone (n = 213)	Hazard Ratio (95% CL[3])	Stratified Log-rank p-value
Locoregional control				

Median Duration	24.4 mo	14.0 mo	0.68 0.52-0.89)	0.005
Overall Survival Median duration	49.0 mo	29.3 mo	0.74 (0.57-0.97)	0.03

a CI = confidence interval.

A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either cetuximab plus irinotecan (218 patients) or cetuximab monotherapy (111 patients).[75] In both arms of the study, cetuximab was administered as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the cetuximab plus irinotecan arm, irinotecan was added to cetuximab using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly times four doses every 6 weeks. An Independent Radiographic Review Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ≥80. Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment. The efficacy of cetuximab plus irinotecan or cetuximab monotherapy was evaluated in all randomized patients. Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with cetuximab, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy. The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen. The objective response rates (ORR) in these populations are presented in the following table.

Objective Response Rates per Independent Review

	Cetuximab + Irinotecan		Cetuximab Monotherapy		Difference (95% CI[a])	
Populations	n	ORR (%)	n	ORR (%)	%	p-value CMH[b]
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
• Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8 - 25.6)	0.09
• Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

[a]95% confidence interval for the difference in objective response rates.
[b]Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to cetuximab

alone, patients randomized to cetuximab and irinotecan experienced a significantly longer median time to disease progression (see Table 2).

Time to Progression per Independent Review

Populations	Cetuximab + Irinotecan (median)	Cetuximab Monotherapy (median)	Hazard Ratio (95% CI[a])	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 – 0.71)	<0.001
• Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
• Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

[a]Hazard ratio of cetuximab + irinotecan: cetuximab monotherapy with 95% confidence interval.

2.4.3.2 Single-Arm Trials

Cetuximab alone was studied in a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN with documented progression within 30 days after 2-6 cycles of a platinum-based chemotherapy. Patients received a 20-mg test dose of cetuximab on Day 1, followed by a 400-mg/m2 initial dose, and 250 mg/m2 weekly until disease progression or unacceptable toxicity. Upon progression, patients were given the option of receiving cetuximab plus the platinum regimen that they failed prior to enrollment. Tumor response and progression were assessed by an Independent Radiographic Review Committee (IRC). The median age was 57 years (range 23-77), 82% were male, 100% Caucasian, and 62% had a Karnofsky performance status of ¡Ý80. The objective response rate on the monotherapy phase was 13% (95% confidence interval (7%-21%). Median duration of response was 5.8 months (range 1.2-5.8 months).

Cetuximab, in combination with irinotecan, was studied in a single-arm, multicenter, open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal cancer who had progressed following an irinotecan containing regimen.[76] Patients received a 20-mg test dose of cetuximab on day 1, followed by a 400-mg/m^2 initial dose, and 250 mg/m^2 weekly until disease progression or unacceptable toxicity. Patients received the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks or 125 mg/m^2 weekly times four doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression to irinotecan as determined by an IRC. This IRC used an identical charter to the IRC which reviewed the randomized trial. The study was initially reported using a different IRC and charter. The overall response rate was 15% for the overall population and 12% for the irinotecan failure population. The median duration of response was 6.5 and 6.7 months, respectively.[74]

Cetuximab was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing metastatic colorectal cancer who progressed following an irinotecan-containing regimen.[60] Of 57 patients enrolled, 28 patients had documented progression to irinotecan. The overall response rate was 9% for the all treated group and 14% for the irinotecan failure group. The median times to progression were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months for both groups.

2.4.3.3 EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit.[74] Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

2.4.4 Safety of Cetuximab in Clinical Studies

2.4.4.1 Anticipated Adverse Events

Squamous Cell Cancer of the Head and Neck

Except where indicated, the data described below reflect exposure to cetuximab in 208 patients with locally or regionally advanced SCCHN who received cetuximab in combination with radiation and as monotherapy in 103 patients with recurrent or metastatic SCCHN. Of the 103 patients receiving cetuximab monotherapy, 53 continued to a second phase with the combination of cetuximab plus chemotherapy. Patients receiving cetuximab plus radiation therapy received a median of 8 doses (range 1-11 infusions). The population had a median age of 56; 81% were male and 84% Caucasian. Patients receiving cetuximab monotherapy, received a median of 11 doses (range 1-45 infusions). The population had a median age of 57; 82% were male and 100% Caucasian. The most **serious adverse reactions** associated with cetuximab in combination with radiation therapy in patients with head and neck cancer were:

- Infusion reaction (3%)
- Cardiopulmonary arrest (2%)
- Dermatologic toxicity (2.5%);
- Mucositis (6%);
- Radiation dermatitis (3%);
- Confusion (2%);
- Diarrhea (2%).

Fourteen (7%) patients receiving cetuximab plus radiation therapy and 5 (5%) patients receiving cetuximab monotherapy, discontinued treatment primarily because of adverse events.

The most common adverse events seen in 208 patients receiving cetuximab in combination with radiation therapy were acneform rash (87%), mucositis (86%), radiation dermatitis (86%), weight loss (84%), xerostomia (72%), dysphagia (65%), asthenia (56%), nausea (49%), constipation (35%), and vomiting (29%).

The most common adverse events seen in 103 patients receiving cetuximab monotherapy were acneform rash (76%), asthenia (45%), pain (28%), fever (27%), and weight loss (27%).

The data in the table below are based on the experience of 208 patients with locoregionally advanced SCCHN treated with cetuximab plus radiation therapy compared to 212 patients treated with radiation therapy alone[1].

Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

	Cetuximab plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
Body System Preferred Term	Grades 1 – 4	Grades 3 and 4	Grades 1 – 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise	56	4	48	5
Fever[1]	29	1	13	<1
Headache	19	<1	8	<1
Infusion Reaction[2]	15	3	2	0
Infection	13	1	9	1
Chills[1]	16	0	5	0
Digestive				
Mucositis/Stomatitis	93	56	94	52
Xerostomia	72	5	71	3
Dysphagia	65	26	63	30
Nausea	49	2	37	2
Constipation	35	5	30	5
Vomiting	29	2	23	4
Anorexia	27	2	23	2
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Respiratory				
Pharyngitis	26	3	19	4
Cough Increased	20	<1	19	0
Skin/Appendages				
Acneform Rash[3]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[1] Includes cases also reported as infusion reactions

[2] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction" or any event on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever" or "dyspnia".

[3] Acneform rash as defined as any event described as "acne", "rash" , "maculopapular rash" , "pustular rash", "dry skin" or "exfoliative dermatitis".

Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in cetuximab in combination with radiation therapy compared with radiation therapy alone. The following

sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%), brain (11% versus 9%), lung (11% versus 8%), spinal cord (4% versus 3%), and bone (4% versus 5%). The incidence of Grade 3 or 4 late radiation toxicities were generally similar between the radiation therapy alone and the cetuximab plus radiation treatment groups.

Colorectal CancerExcept where indicated, the data described below reflect exposure to cetuximab in 774 patients with advanced metastatic colorectal cancer. Cetuximab was studied in combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving cetuximab plus irinotecan received a median of 12 doses [with 88/354 (25%) treated for over 6 months], and patients receiving cetuximab monotherapy received a median of 7 doses [with 36/420 (9%) treated for over 6 months]. The population had a median age of 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving cetuximab plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving cetuximab monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with cetuximab were:

- Infusion reaction (3%);
- Dermatologic toxicity (1%);
- Interstitial lung disease (0.4%);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving cetuximab plus irinotecan, 2% in patients receiving cetuximab monotherapy;
- Diarrhea (6%) in patients receiving cetuximab plus irinotecan, 0% in patients receiving cetuximab monotherapy.

Thirty-seven (10%) patients receiving cetuximab plus irinotecan and 17 (4%) patients receiving cetuximab monotherapy discontinued treatment primarily because of adverse events.
The most common adverse events seen in 354 patients receiving cetuximab plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 420 patients receiving cetuximab monotherapy were acneform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%), constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in Table 3 are based on the experience of 354 patients treated with cetuximab plus irinotecan and 420 patients treated with cetuximab monotherapy.

Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	Cetuximab plus Irinotecan (n=354)		Cetuximab Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	48	10
Abdominal Pain	45	8	26	9
Fever[3]	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction[4]	19	3	21	2
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
Digestive				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea[3]	23	2	17	7
Cough Increased	20	0	11	1
Skin/Appendages				
Acneform Rash[5]	88	14	90	8
Alopecia	21	0	4	0
Skin Disorder	15	1	4	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	11	<1
Conjunctivitis	14	1	7	<1

[1] Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab monotherapy.

[2] Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.

[3] Includes cases reported as infusion reaction.

[4] Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnea”.

[5] Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

2.4.4.2 Infusion Reactions

Severe infusion reactions occurred with the administration of cetuximab in approximately 3% (46/1485) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension, and/or cardiac arrest. Caution must be exercised with every cetuximab infusion, as there were patients who experienced their first severe infusion reaction during later infusions. A 1-hour observation period is recommended following the cetuximab infusion. Longer observation periods may be required in patients who experience infusion reactions.
A 20-mg test dose was administered intravenously over 10 minutes prior to the initial dose to all patients in earlier studies. The test dose did not reliably identify patients at risk for severe allergic reactions.

2.4.4.3 Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced colorectal cancer and in 1 of 796 patients with head and neck cancer receiving cetuximab. Among these four cases, interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one patient with colon cancer. In two of the remaining cases, the patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving cetuximab in combination with irinotecan. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases. In the event of acute onset or worsening pulmonary symptoms, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.[74]

2.4.4.4 Dermatologic Toxicity

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument.[1] At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.
In clinical studies of cetuximab, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was severe (Grade 3 or 4) in 11% (84/774) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Non-suppurative acneform rash described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving cetuximab plus irinotecan and in 90% (8% Grade 3) of patients receiving cetuximab monotherapy.

Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days. **A related nail disorder, occurring in 14% of patients (0.4% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.**

2.4.4.5 Cetuximab Use With Radiotherapy

The safety of cetuximab in combination with radiation therapy and Cisplatin has not been established. Death and serious cardiotoxicity were observed in a 21 patient single-arm study of patients with locally advanced squamous cell cancer of the head and neck. Patients received cetuximab, delayed, accelaerated (concomitant boost) fractionation radiation therapy and Cisplatin (100 mg/m^2).[74]

In a randomized, controlled trial in patients with squamous cell carcinoma of the head and neck (SCCHN), cardiopulmonary arrest and/or sudden death occurred in 4/208 patients (2%) treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab.

2.4.4.6 Electrolyte Depletion

In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of hypomagnesemia, both overall and severe, was increased in patients receiving cetuximab alone or in combination with chemotherapy as opposed to those receiving best supportive care or chemotherapy alone. Approximately one-half of these patients receiving cetuximab experienced hypomagnesemia and 10-15% experienced severe hypomagnesemia.[74]

2.4.4.7 Cardiac Toxicity

Cardiac arrest and / or sudden death occurred in 2% (4/208) of patients with squamous cell carcinoma of the head and neck treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone. Fatal events occurred within 1 to 43 days after the last Cetuximab treatment. Cetuximab in combination with radiation therapy should be used with caution in head and neck cancer patients with known coronary artery disease, congestive heart failure, and arrythmias. Although the etiology of these events is unknown, close monitoring of serum electrolyte, including serum magnesium, potassium and calcium, during and after Cetuximab therapy is recommended.

2.5 Rationale

Capecitabine, an oral prodrug of 5-FU, exhibits a better therapeutic index in CRC than 5-FU/Leucovorin. Clinical trials of oxaliplatin combined with capecitabine in both chemotherapy-treated and -untreated patients have shown the effectiveness and tolerability of the oxaliplatin/capecitabine combination. A recent trial of oxaliplatin and capecitabine in patients with previously untreated advanced gastric carcinoma had promising results. Patients received oxaliplatin 130 mg/m2 on day 1 plus oral capecitabine 1000 mg/m2 twice daily on days 1-14, every 3 weeks. Twenty evaluable patients were enrolled. The overall response rate was 65% (95% confidence interval (CI), 44-86%), with complete responses in two patients and partial responses in 11 patients. Median progression-free survival was 7.5 months (95% CI, 3.2-11.7 months); median overall survival was not reached during the study period. There was no grade 4 and little grade 3 toxicity.[77] Another recent study of oxaliplatin and capecitabine was done in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia. Initially, patients were prescribed 130 mg/m2 intravenously on day 1 and capecitabine 1000 mg/m2 orally twice a day, on days 1-14 of a 21-day cycle. Four treatment-related deaths in the first 24 patients led to a reduction in capecitabine to 850 mg/m2 orally twice a day, days 1-14, for the remainder of the cohort. In the 43 patients enrolled in the study the tumor response rate was 35% [95% confidence intervals (CI) 23% to 50%]. All responses were partial; seven of 24 occurred before the capecitabine dose reduction, and eight of 19 after. Median time to tumor progression was 4 months (95% CI 3.1-4.6), and median survival 6.4 months (95% CI 4.6-10). To date, there have been 36 deaths. Four were treatment-related (one infection, two myocardial infarctions, one respiratory failure), and all occurred before the capecitabine dose reduction.[78] Thus, the combination of oxaliplatin and capecitabine has shown to be of promise in the treatment of patients with advanced gastric cancer.

This proposal is a phase II study to evaluate the role of capecitabine, in combination with oxaliplatin and cetuximab in treatment of advanced gastric cancer, using a schedule of oxaliplatin 130 mg/m2 q week with capecitabine 850 mg/m2 bid on days 1-14, and initial cetuximab 400 mg/m2, followed by weekly cetuximab 250 mg/m2 with oxaliplatin 130 mg/m2 on day 1 (every 3 weeks) with capecitabine 850 mg/m2 bid, daily on days 1-14, every 3 weeks. Each cycle will be administered every three weeks.

This combination of drugs has been extensively studied in colorectal cancer.[79-82] A study of initial cetuximab 400 mg/m2, followed by weekly cetuximab 250 mg/m2 with oxaliplatin 85 mg/m2 on day 1 (every 2 weeks) with capecitabine 1000 mg/m2 bid, daily on days 1-7, every 2 weeks in patients with metastatic colorectal cancer was recently reported. In 40 patients the main toxic effects were grade 3-4 neutropenia (12.5%), grade 3/4 diarrhea (7.5%), grade 3 fatigue (2.5%), and grade 2-3 neurotoxicity (22.5%). One (2.5%) complete and seven (17.5%) partial responses were achieved for an overall objective response rate of 20% in patients that had not previously progressed on an oxaliplatin regimen. The overall objective response rate (ORR) and disease control rate (DCR) were 18.7% and 46.8%, respectively, in patients with oxaliplatin-refractory disease.[79] Heinemann et al recently conducted a randomized study of cetuximab + capecitabine + irinotecan (CCI) vs cetuximab and capecitabine and oxaliplatin (CCO) in patients with metastatic colorectal cancer. This study used cetuximab 400 mg/m2, followed by weekly cetuximab 250 mg/m2 with oxaliplatin 130 mg/m2 on day 1 (every 3 weeks) with capecitabine 1000 mg/m2 bid, daily on days 1-14, every 3 weeks. At the time of report an the ORR in the CCI arm was 41% (11/27), while in the CCO arm an ORR of 71% (15/21) was documented. At the time of report toxicity data were available for 25 patients in each arm. The most common grade 3-4 CTC- toxicities

observed in the CCI and the CCO-arm respectively were skin toxicity (4 vs 5 pts), allergic reactions (0 vs 5 pts), diarrhea (5 vs 3pts), neurotoxicity (1 vs 3 pts), and leucopenia (4 vs 5 pts).[82] Another study using this combination of drugs was recently done in patients with metastatic colorectal cancer refractory tor 5-FU, oxaliplatin and irinotecan. The regimen used was cetuximab 400mg/m² day 1 followed by weekly 250mg/m² and oxaliplatin 70 mg/m² days 1 and 8 plus capecitabine 2000 mg/m² days 1-14, using a three week cycle. Fifteen patients had been treated at time of report. In one patient treatment was stopped due to a grade 4 hypersensitivity reaction. Further NCI-CTC grade 3/4 toxicities were leukopenia 1 patient, sensory neuropathy 1 patient, skin 2 patients, diarrhea 1 patient. At time of report response was as follows: PR 27%, SD 27% (4 pts each), PD 46%.[81] Another recently reported trial randomized patients to two arms. All patients received oxaliplatin 130 mg/m2 day 1 and capecitabine 1000 mg/m2 bid days 1-14 every 21 days. Patients were randomized to receive the capecitabine and oxaliplatin alone or in combination with cetuximab 250 mg/m2 weekly after a loading dose of 400 mg/m2. Treatment was limited to a maximum of 6 cycles. At the time of report the first response data were available in 67 patients (investigators' assessment after 3 cycles) – see table below for results. The study treatment was well tolerated with grade 3/4 toxicities in < 10% of the cycles in each arm. The frequency of side effects was balanced, but with more frequent skin toxicity in the cetuximab arm (6% versus 0% grade 3/4).[80]

	XELOX alone	**plus Cetuximab**
Treatment cycles (median, range)	4 (1-6)	4 (1-6)
OXA dose/cycle (median, mg/m^2)	127	129
CAP dose/administration (median, mg/m^2)	968	984
PR (95% CI)	33% (18-52%)	53% (35-70%)
PR+SD (95% CI)	82% (65-93%)	82% (65-93%)

In clinical practice, prognosis and therapy for patients with gastric cancer depends on clinical/pathological staging. The reasons some patients fail to respond to chemotherapy while others survive and why some patients develop life-threatening toxicities, may be answerable questions. For example, if the associations between measures of drug metabolism and drug resistance in different ethnic groups are established, important genetic determinants of gastric tumor biology might be identified which may lead to more efficient and less toxic therapy. The translational goal of this project is to use specific genetic intratumoral and genomic markers to predict response, survival and clinical toxicity in patients with gastric cancer. If our hypotheses are confirmed, the treatment recommendation for patients with gastric cancer will have to be rewritten.

2.6 Molecular Markers

We have identified molecular correlates for survival after and response to cisplatin/5-FU chemotherapy in patients with locally advanced gastric cancer.[83,84] These molecular correlates are genes relevant to the antitumor-effects of oxaliplatin and capecitabine. These genes are involved in recognition and repair of DNA damage, cell cycle checkpoint control, apoptosis and the metabolic pathway of these drugs. The molecular correlates of the major mechanisms of resistance to platinum are:

1)	Increased DNA repair:	ERCC1, XPA, RR, p53, p21, DNA mismatch repair
2)	DNA adduct formation:	DNA adduct formation
3)	Changes in the metallothioneins.	Gamma GT

2.6.1 DNA repair

2.6.1.1 DNA Repair Enzymes: ERCC1 and XPA.

The capacity of tumor cells to repair DNA damage may play an important role in their resistance to chemotherapy or radiation. The damage recognition/excision step is rate-limiting to the excision repair process which is mainly mediated by genes of the ERCC1 and XP groups.[85] XPA is known to bind to cisplatin-damaged DNA, thereby suggesting that low expression of XPA might cause cells to be more sensitive to cisplatin.[86] In fact, one recent study showed that drug resistance in human ovarian cells was characterized by enhanced expression of XPA.[87] When ERCC1 was transfected into DNA-repair deficient CHO cells**,** ERCC1 conferred cellular resistance to cisplatin along with the ability to repair platinum DNA-adducts.[88] Recent clinical studies have shown that high expression levels of the DNA repair enzyme ERCC1 are significantly associated with resistance to cisplatin in patients with ovarian cancer.[89] Our own recently published data demonstrated that ERCC1 and TS were a significant predictors of response to 5-FU/Cisplatin, with ERCC1 being a predictor independent of TS levels.. Additionally, ERCC-1 was found to be a predictor of survival in these patients.[84] In this study, we will examine whether : a) XPD expression is associated with response to oxaliplatin/capecitabine; b) whether XPA and ERCC1 are regulated independently, and c) if they are, whether using XP groups as a determinant of response to oxaliplatin and capecitabine in conjunction with ERCC1 will increase the power of prediction of response and survival.

Clinically the role of ERCC1 in gastric cancer was demonstrated in a study reported by Metzger et al. The excision repair gene ERCC1 was assessed as a predictive marker for patients receiving 5-FU/cisplatin based chemotherapy. The patients had untreated primary gastric adenocarcinoma and were assessed for ERCC1 mRNA levels. The median ERCC1 mRNA level from 38 primary gastric cancer patients (33 assessable for response) was 5.8 x10(-3) (range, 1.8 x 10(-3) to 19.5 x 10(-3). Of the 17 patients who responded to therapy, 13 (76%) were less than or equal to 5.8 x 10(-3) and four were greater than 5.8 x 10(-3) (p=0.003). The median survival for patients with low TS levels was greater than 5.4 months, which was the median survival for patients with ERCC1 levels greater than 5.8 x 10(-3).[84] These data lead to the suggestion that ERCC1 may be predictive of response to 5-FU/cisplatin based therapy.

A similar study was done in patients with colorectal cancer who received 5-FU/oxaliplatin on a compassionate use protocol after unsuccessful 5-FU and irinotecan chemotherapy. cDNA was derived from paraffin-embedded tumor specimens to determine TS and ERCC1 mRNA expression relative to the internal reference gene beta-actin using fluorescence-based, real-time reverse transcriptase polymerase chain reaction. The median TS gene expression level from 50 metastasized tumors was 3.4 x 10(-3) (minimum expression, 0.18 x 10(-3); maximum

expression, 11.5 x 10(-3)), and the median ERCC1 gene expression level was 2.53 x 10(-3) (minimum, 0.0; maximum, 14.61 x 10(-3)). The gene expression cutoff values for chemotherapy nonresponse were 7.5 x 10(-3) for TS and 4.9 x 10(-3) for ERCC1. The median survival time for patients with TS ≤ 7.5 x 10(-3) (43 of 50 patients) was 10.2 months, compared with 1.5 months for patients with TS > 7.5 x 10(-3) (P < .001). Patients with ERCC1 expression ≤ 4.9 x 10(-3) (40 of 50 patients) had a median survival time of 10.2 months, compared with 1.9 months for patients with ERCC1 expression > 4.9 x 10(-3) (P < .001). In a stratified survival analysis, patients with a high TS expression level were compared to those with a low TS expression level and stratified by high or low ERCC1. TS expression was found to be a significant predictor of survival, independent of ERCC1, with patients having a high TS expression having a hazard ratio of 5.38 (95%CI 1.46-19.92), when compared to those with a low TS expression (p=.002). Similarly, patients with a high ERCC1 expression level were compared to those with a low ERCC1 expression level and stratified by high or low TS. ERCC1 expression was found to be a significant predictor of survival, independent of TS, with patients having a high ERCC1 expression having a hazard ratio of 4.24 (95%CI 1.35-13.29), when compared to those with a low ERCC1 expression (p=.008). A TS of 7.5 x 10(-3) significantly segregated patients into categories of response, stable disease, and progression (P = .02), whereas the association between ERCC1 and response did not reach statistical significance (p = .29). These data suggest that intratumoral ERCC1 mRNA and TS mRNA expression levels are independent predictive markers of survival for 5-FU and oxaliplatin combination chemotherapy in 5-FU-resistant metastatic colorectal cancer.[90]

2.6.1.2 Ribonucleotide Reductase.

Recent evidence suggests that in addition to its essential role in DNA synthesis, ribonucleotide reductase (RR) plays a critical role in DNA repair and is induced by DNA damaging drugs.[91] Furthermore, Fan et al has demonstrated that overexpression of the M2 subunit plays an important role with ras in tumor progression.[92] M2 overexpression, as expected, has been found to produce resistance to hydroxyurea. Our own data suggest that M2 mRNA expression in tumor cells is 10-20 times higher than that in adjacent normal tissue, which indicates that RR may play a role in chemoresistance to DNA damaging drugs (unpublished data).

2.6.1.3 DNA mismatch repair.

One other determinant of DNA repair capacity is the status of DNA mismatch repair enzymes. Loss of DNA mismatch repair due to lack of either hMSH2 or hMLH1 activity results in low-level resistance to cisplatin but not to oxaliplatin, an analogue that produces a different type of DNA adduct.[18,31,40] MSH2-/- tumors are significantly less responsive to cisplatin than MSH2+/+ tumors, but there is no difference in sensitivity to oxaliplatin.[39,93,94] These results demonstrate that the degree of cisplatin resistance conferred by loss of DNA mismatch repair is sufficient to produce both enrichment of mismatch repair-deficient cells during treatment *in vitro* and a large difference in clinical responsiveness *in vivo*).These results also identify loss of DNA mismatch repair as a mechanism of resistance to cisplatin but not oxaliplatin.[39,93,94] The effect of the loss of DNA mismatch repair activity on sensitivity to cisplatin and a panel of analogues has been tested using two pairs of cell lines (colon and

endometrium) proficient or deficient in this function.[39,93,94] In contrast to the cross resistance found in cisplatin and carboplatin, which form the same types of adducts in DNA, no difference in sensitivity was observed between the DNA mismatch repair-proficient and -deficient cell lines for oxaliplatin, tetraplatin, transplatin, JM335, or JM216. *In vitro* results demonstrate a correlation between the failure of DNA mismatch repair proteins to recognize platinum adducts and low-level resistance, suggesting a role for the DNA mismatch repair system in generating signals that contribute to the generation of apoptotic activity. In this study we will determine the status of DNA mismatch repair by screening for microstatellite instability (MIN). If MIN is present (NIH consensus), we will sequence the DNA mismatch repair genes (MSH2, MLH1, PMS1 and PMS2) by cycling sequencing to test whether the presence of MIN and mismatch repair defects will predict chemosensitivity to oxaliplatin/capecitabine *in vivo*.

2.6.1.4 p53 and p21.

Clinically relevant exposures to platinum compounds will lead to a tumor injury response (TIR) that shares characteristics with response produced by many other injurious agents. Although very little is known about the specifics of signal transduction pathway activated by platinum-induced injury, it is possible to identify the general nature of this response. It is believed that the capacity to induce growth arrest in response to injurious conditions arises from the advantages of delaying replication of defective DNA templates until damage has been repaired (G1/S arrest) and delaying the segregation of sister chromatids until DNA breaks have been corrected (G2/M). The function of p53 is to send cells with damaged DNA either into G1 arrest for repair or into programmed cell death through apoptosis.[95,96] Neither G1 arrest nor the apoptotic program is initiated by drug treatment in cells with mutated p53 genes, suggesting that tumors with mutant p53 might be resistant to DNA damaging agents. *In vitro* studies confirmed that p53 is a major modulator of sensitivity to drugs such as 5-FU, etoposide, adriamycin and cisplatin.[97,98] Tumors in mice expressing wt p53 contained a high proportion of apoptotic cells which regressed after radiation or adriamycin, whereas tumors expressing mutated p53 did not respond to treatment. This indicates the relevance of p53 as a predictor of response to chemotherapy.[99] p53 is not only an important predictive marker, but also a possible therapeutic agent. In fact, Fujiwara et al were able to increase the cellular sensitivity to cisplatin by transfection of wt p53 into tumor spheroids of human non-small cell lung cancer cells.[98] These results underscore the role of p53 as a predictor of chemosensitivity, and are of important clinical relevance in GI cancers, 70% of which are associated with p53 mutations. In most cases, the effects of p53 such as G1 cell cycle arrest and apoptosis can be attributed to the biological functions of downstream p53-regulated genes, such as WAF1/CIP1.[100] WAF1/CIP1 plays an important role in p53 induced G1 arrest by coordinately inhibiting the functions of both CDKs and PCNA which arrest DNA replication while permitting active DNA repair.[39,51,93,94,101,102] WAF1/CIP1 has been shown to be directly induced by wt p53 *in vitro*, but its expression is lost when active p53 is absent.[103] While the presence of p53 mutations can be easily established, to date no easily measurable biochemical parameter has been identified that would be indicative of p53 function. WAF1/CIP1 is thought to be a direct mediator of p53 cell-cycle regulation activity and p53-mediated apoptosis.[103,104] These findings suggest that WAF1/CIP1 expression levels can be used as a direct indicator of p53 function in cells. That is, low or

absent expression of WAF1/CIP1 should indicate a lack of p53 function, while partial expression of WAF1/CIP1 should indicate some retention of p53 activity.

2.6.2 DNA adducts formation

The anti-tumor effect of platinum compounds is mediated by the covalent binding of platinum species with DNA or chromatin, which eventually leads to apoptotic cell death. The extent of DNA inter- and intrastand crosslinks seem to correlate with cisplatin cytotoxicity.[31] Furthermore, preclinical data supports a linear relationship between DNA adduct formation and sensitivity to platinum compounds. The major adducts that have been found to be formed *in vitro* are the Pt-GG and Pt-AG intrastrand crosslinks.[31] Platinum concentrations required to achieve 90% cell kill during a 2 h incubation of A2780 cells were 15 microM for cisplatin and oxaliplatin and 22 microM for lobaplatin. Using an anti-serum originally raised against cisplatin-treated DNA, allowed the ability to detect platinum-DNA adducts induced by lobaplatin and oxaliplatin. Maximal nuclear staining for all three compounds was observed after a 4 h post-incubation period. The nuclear staining level induced by cisplatin was about 10-fold higher than after lobaplatin and oxaliplatin treatment. GG and AG adducts, measured by 32P-postlabelling, also showed maximum levels at about 4 h after treatment.[31] Relative GG peak levels were 4:1:3 for cisplatin, lobaplatin and oxaliplatin, respectively. The ratio of GG over AG intrastrand crosslinks in A2780 cells was not significantly different for the various compounds In this study we will determine the formation of DNA adducts in leucocytes and correlate it with PK/PD and clinical outcome.

2.6.3 Metallothioneins

Elevation of glutathione (GSH) is widely observed in cellular resistance to platinum compounds.[45] Previous studies have demonstrated elevated steady-state levels of mRNA and gamma-glutamyl transpeptidase (gamma-GT, EC 2.3.2.2) activity in sublines of human ovarian carcinoma cell line A2780, which exhibited low levels of resistance to oxaliplatin; however the level of gamma-glutamylcysteine synthetase (gamma-GCS, EC 6.3.2.2) was not elevated.[105,106] Single exposures of cells to oxaliplatin induced a time- and concentration-dependent increase in the mRNA of gamma-GT, but not that of gamma-GCS. Cisplatin also induced an elevation in gamma-GT mRNA, but to a lower degree. The gamma-GT enzyme activity increased corresponding to the elevation in mRNA expression. The gamma-GT-induced cells showed an increase in cellular GSH when incubated in medium containing GSH. These data suggest that a) single, brief exposures to pharmacologically relevant concentrations of platinum complexes induce elevation in mRNA of gamma-GT, b) elevation in gamma-GT mRNA translates into elevated gamma-GT activity and an increase in GSH salvage, and c) the degree of induction of gamma-GT mRNA differs between platinum complexes. Elevation of glutathione (GSH) is commonly observed in cellular resistance to a number of anticancer agents. The most frequently reported change in GSH metabolism associated with elevated GSH levels is increased mRNA expression and activity of gamma-glutamyl cysteine synthetase (gamma GCS), the first enzyme of the GSH biosynthetic pathway. Sublines of the A2780 ovarian carcinoma cell line (C10 and C25) demonstrate 8- and 12-fold increases in resistance to oxaliplatin after repeated exposure of the cells to increasing concentrations of the platinum agent. GSH levels in C10 and C25 cell sublines are 3.1- and 3.8-fold higher than in the parent A2780 cell line. The increase in GSH in C10 and C25 has been associated with an elevation in gamma GT mRNA (2.5- and 8-fold) and gamma GT activity (2.7- and 2.8-fold).[107,108] No changes have been

observed in gamma GCS mRNA levels or activity. These data indicate that alterations in GSH metabolism leading to elevations in cellular GSH in A2780 ovarian carcinoma cells selected for low levels of resistance to oxaliplatin are mediated by gamma GT, the "salvage' pathway, rather than an increase in GSH biosynthesis.[105,106] In this study we will test whether mRNA level of gamma glutamyl transpeptidase is a predictor of response to oxaliplatin/capecitabine therapy.

2.7 Mechanisms for resistance to capecitabine

Fluoropyrimidines (FP) are an important group of anti-neoplastic drugs, specifically capecitabine.[109,110] A major mechanism of action of these drugs is the inhibition of thymidylate synthase (TS). This enzyme, the only *de novo* source of thymidine in cells, is essential for DNA synthesis and, therefore, also limiting for cell growth. The sensitivity of tumor cells to FP depends on effective TS inhibition.[111,112] Indeed, one mechanism by which cells acquire resistance to 5-FU is gene amplification.[111-113] We have previously shown that variation in basal TS gene expression levels among patients' tumors is a statistically significant predictor for response to 5-FU. Those tumors with high TS expression are generally non-responsive to protocols that include the TS-directed combination of 5-FU and leucovorin (LV).[107,110,114] However, while high TS expression levels effectively predict non-response, low TS expression do not necessarily predict response: in our study all responding patients had low TS expression, but a subset of patients with low TS expression levels did not respond to treatment.[107] These non-responders therefore may have other mechanisms of resistance that the favorable condition of low TS is insufficient to overcome. These other mechanisms may be decreased thymidine phosphorylase level or increased DPD levels.

2.7.1 Thymidylate Synthase

Regulation of TS gene expression is not very well understood. In *in vitro* studies, hTS gene with triple repeats showed higher expression activity of the reporter gene than the variant with double repeat.[114] Our data in patients with colon cancer demonstrated that patients with triple repeats had a significantly higher TS gene expression, indicating that the regulation of TS gene expression may be directly linked to the polymorphism. To determine the basis for the increase in TS mRNA levels, we will consider two following possibilities. The increase in TS mRNA could either be a result of enhanced transcription, or increased stability of the TS mRNA containing the increased number of repeats. Sequences responsible for the differential expression of TS mRNA have been previously shown to confer differential expression from a heterologous mRNA.[109-111,114]

Preliminary data:

Table 1. TS genotype, TS mRNA levels and pairwise comparison of the TS mean in metastatic tumor tissue.

Genotype	Metastatic liver tissue			Comparison of TS means	
				Genotype	P-value**
	n	TS mean	95% CI*	Overall	0.011

L/L	1	9.42	5.51, 16.12	L/L vs S/S	0.003
S/L	2	5.53	3.68, 8.31	L/L vs S/L	0.12
S/S	1	2.60	1.39, 4.87	S/L vs S/S	0.048

*CI denotes confidence interval.
**P-value for the overall comparison is based on the F-test, all other p-values are based on the LSD method for multiple comparison.

Table 2. TS genotype and response to 5-FU chemotherapy

TS Genotype	Responders	Non-responders
L/L	2(9%)	21 (91%)
S/L	3(14%)	18 (86%)
S/S	4(57%)	3 (43%)

P-value 0.020 (Fisher's Exact test)

A study in gastric cancer assessed Thymidylate synthase mRNA levels as a predictor for primary tumor response and overall survival. Before systemic chemotherapy, the genetic (TSmRNA) level of TS was assessed for patients who were to receive 5-FU continuous infusion chemotherapy. Sixty-five patients with primary gastric cancer had a median TS mRNA level of of 4.6 x 10(-3). Thiry-five percent of patients had measurable responses in their primary tumors. The mean gastric cancer TSmRNA level in responding and resistant patients was a statistically significant predictor of response (P<0.001). The median survival was 43+ months for treated patients with TSmRNA levels less than the median and 6 months for those with TS m-RNA levels more than the median (p=.003). This suggests that genetic expression of TS may be predictive of response to 5-FU based chemotherapy in patients with gastric cancer.

2.7.2 Thymidine Phosphorylase, Dihydropyrimidine Dehydrogenase

We have preliminary data (presented at ASCO) which demonstrate that the gene expression levels of TP and DPD are significant predictors of response and survival in patients with colorectal cancer treated with protracted infusion of 5-FU. However, in patients treated with protracted infusion 5-FU, high TP and not low levels were associated with resistance. One explanation may by the critical role of TP in angiogenesis. We observed a similar pattern of TP to that of TS, that is, high TS expression was associated with non-response to 5-FU/LV. Plotting the TS mRNA content of those tumors against the TP content did not show any correlation between them, indicating that these gene expressions are independent variables. Tumors with

low TS and TP expressions had a response rate of over 80%, while those with high TS and TP had a response rate of zero (see table).

Summary of TS and TP expression data in colorectal tumors in relation to response rate		
		Response Rate
All Patients	10/39	28%
TS≤3	9/18	50%
TS≤3/ p53 wt	4/7	57%
TS≤3/ TP<20	8/10	80%
TS≤3/ TP<20/ p53 wt	6/7	83%

Low DPD levels have been significantly associated with response to 5-FU/LV treatment in patients with colorectal cancer. DPD levels seem to be an independent predictor of outcome which needs to be confirmed in larger studies.[108]

To further explain the resistance to 5-FU in low TS expressing tumors, we became interested in the role of the tumor suppressor gene p53 in relation to the sensitivity of tumor cells to specific chemotherapeutic drugs. Cells with functional wild-type (wt) p53 have been found to be dramatically more sensitive to many of the commonly used anti-cancer-drugs.[97] For example, tumors in immunocompromised mice expressing wt p53 contain a high proportion of apoptotic cells and are sensitive to radiation or doxorubicin, whereas tumors expressing mutant p53 do not respond to treatment.[115] Wt p53 induces cell death after drug treatment by sending cells with extensive DNA into programmed cell death through apoptosis. Neither G1 arrest nor the apoptotic program is initiated by drug treatment in cells with mutated p53 genes, giving these cells a survival advantage in the face of challenges by DNA damaging agents.[97-99] Thus, the ultimate response of a tumor to TS-directed drugs will be determined by the effectiveness of TS inhibition as well as the p53 status of the tumor.

The capability of an almost absolute prediction of non-response as well as identification of a set of patients with very high but not absolute, probability of response could have significant impact on the design of new treatment regimens with fluoropyrimidines. If clinical treatments were to be suggested for individual patients based on these results, it is clear that patients with low TS, low TP, low DPD and wt p53 are most likely to derive benefit from FP-based chemotherapy and therefore should be treated aggressively.

In the above discussion we have presented evidence that it may be beneficial to consider the status and/or levels of the candidate determinants before and during treatment. The ability to obtain small biopsies, and the fact that such biopsies yield sufficient cellular material for PCR quantitation, makes direct clinical application of this concept feasible. The goal of this proposal is to establish 1) the anti-tumor activity of oxaliplatin/capecitabine combination and 2) a profile of chemosensitivity to oxaliplatin/capecitabine among genes relevant to the antitumor effects of these drugs. Findings from this project may provide the basis for prescribing cancer chemotherapy on a more rational basis by establishing the dose of oxaliplatin in combination with

capecitabine with the maximal effect on DNA platination, DNA repair and target enzymes of capecitabine and by identifying patients who will benefit from chemotherapy

The rationale for combination therapy is theoretically and clinically well established. The combination of 5-FU and oxaliplatin has been shown to have a significant anti-tumor activity in multiple phase II studies and has been determined an active agent in colorectal cancer. Capecitabine, as an oral type of 5-FU, has also been shown to have activity in colorectal cancer in both pre-clinical and clinical data. Given these data, we propose to combine oxaliplatin with capecitabine and cetuximab for patients with advanced/metastatic/recurrent gastric or gastroesophageal cancer . We will also propose to evaluate the related molecular correlates, that is predictors of response and survival as described above.

2.8 Mechanisms of Resistance to Oxaliplatin

Glutathione transferases consist of a super-family of phase II metabolic enzymes that catalyze the conjugation of reduced glutathione. The detoxifying character of these reactions is responsible for the protection of cellular macromolecules from damage caused by carcinogenic and cytotoxic agents.[116] GSTP1-1 has been shown to be widely expressed in human epithelial tissues and to be over-expressed in several tumors including colon tumors.[117-121] Increased levels in tumors may be in part responsible for the observed resistance to chemotherapy as it has been found in several tumors, but the mechanism still remains unknown.[122] Factors that influence the expression level of GSTP1 may become important tools to predict therapy response and survival of patients treated with certain drugs or drug combinations.

The following markers will be examined in this study. TS, TP, DPD, ERCC1, XPA, p53 and p21. Gene expression levels will be examined for all markers. Germline polymorphisms will be examined for TS, ERCC1 and XPA.

2.9 Mechanisms of Resistance and Response to Cetuximab

2.9.1 Molecular Determinants of Angiogenesis

The angiogenic factors such as VEGF, TGF-β, IL-8 and IL-10 have been suggested to play an important prognostic role in colorectal cancer and very recently thymidine phosphorylase (TP) has been shown to increase COX activity and COX-2 protein expression in several cell types.[123] There are preliminary data suggesting that COX-2 overexpression increases adhesion to the extracellular matrix. One of the potential molecular effects of COX-2 inhibition is on the integrin family particular $\alpha_v\beta_1$ and β_3 based on the findings that COX-2 expression has been associated with increased attachment to laminin and matrigel. VEGF has been found to be closely associated with microvessel density formation in various cancers.[124,125] A recent study showed that TP and VEGF expression in colon cancer appeared to be anti-coordinated; that is, in tumors with a high vessel density, TP expression was high when VEGF was low and vice versa.[124] These data suggest that VEGF and COX-2 may play a significant role in tumor progression in patients with colorectal cancer. Vessel count and expression of VEGF have been shown to predict distant recurrence in patients with node-negative colon cancer.[125] Thus, if VEGF is also associated with clinical outcome, the use of TP, COX-2 and VEGF expressions simultaneously may identify patients who will more likely

respond to therapy and ultimately may allow the development of more effective treatment strategies.

Our own preliminary data suggest that the gene expression levels of VEGF in the normal and tumor tissue and germline polymorphism of VEGF and TGF-β may be associated tumor recurrence. In addition, the intratumoral mRNA levels of VEGF were significantly higher compared to the normal mucosa ($p<0.001$) indicating that the tumor has a higher angiogenic potential. Our hypothesis is that high gene expression levels of genes involved in angiogenesis will be associated with clinical outcome and toxicity in patients treated with targeted chemotherapy. We will also test whether gene expression profiles will be associated with the pattern of recurrence and progression.

In the future, a combination of novel genes in metabolic and biological pathways might become important predictors of response, survival and toxicity. Angiogenesis is a good example because nucleotide excision is a symphony of enzymes working together to repair DNA defects. Enzymes such as VEGF, TP, COX-2, IL-8 and others all depend on each others' function; alterations of any of these genes can affect clinically relevant angiogenesis.

2.9.2 Epithelial Growth Factor Receptor (EGFR) Pathway

Our primary hypothesis is that gene expression of enzymes involved in the EGFR pathway such as EGFR and EGF are associated with clinical outcome and toxicity to cetuximab based chemotherapy. Our second hypothesis is that gene expression in the EGFR pathway such as IL-8, VEGF and COX-2 and others are associated with clinical outcome and toxicity to cetuximab based chemotherapy.

EGF-R is a commonly expressed transmembrane glycoprotein of the tyrosine kinase growth factor family. EGFR are frequently overexpressed in many types of human cancers, including CRC (colon and rectal cancers) and their overexpression typically confers a more aggressive clinical behavior. The level of EGFR expression is primarily regulated by the abundance of its mRNA and the nature of the EGFR overexpression is believed to be due to an increase in the rate of EGFR transcription. Our data suggest that EGFR-mediated activation of the overall DNA-repair capacity might override the stimulation of tumor proliferation by the receptor in human colorectal cancers. This enhanced DNA-repair may result in an impaired efficacy of the administrated oxaliplatin.

Our preliminary data in patients with metastatic colorectal cancer treated with cetuximab who had low gene expression levels of Cox-2, EGFR and IL-8 showed a significant longer overall survival which was independent from skin toxicity. These data suggest that Cox-2 and IL-8 may be important factors in the EGFR signaling pathway. Cox-2, a rate-limiting enzyme involved in the conversion of arachidonic acid to prostaglandins, is well known to affect tumorigenesis in the colon by the regulation of apoptosis, angiogenesis and tumor cell invasiveness.[126] Pai et al. showed recently that prostaglandin E2, produced by the cyclooxygenase enzymes, transactivates EGFR in gastric epithelial and colon cancer cells, suggesting that Cox-2 induces the pathogenesis of cancer development by the activation of EGFR.[127] Perrotte et al. showed that treatment with cetuximab in human transitional cell carcinoma growing orthotopically in nude mice inhibited mRNA and protein production of IL-8 accompanied by the involution of blood vessels.[128] These data suggest that inhibition of angiogenesis by cetuximab may be by down-regulation of IL-8. Our findings implicate that Cox-2 may be an

important regulator of EGFR, while IL-8 may play a part in cetuximab-related inhibition of angiogenesis.

The most common side-effect of cetuximab treatment is an acneiform follicular or perifollicular dermatitis that generally appears during the first 3 weeks of therapy.[129]In our study, 85% of patients presented with such acne–like rash. Interestingly, study patients with a grade 2-3 cutaneous reaction had significantly lower Cox-2 gene expression levels compared with patients that had grade 0-1 toxicity. Patients with lower EGFR mRNA amount are more likely to have severe skin reactions compared with patients that have higher EGFR expression levels. These results imply that low levels of Cox-2 induce low levels of EGFR, leading to a down-regulated signaling pathway and therefore leading to the acne–like rash. However, it has been suggested that Cox-2, via the up-regulation of prostaglandins, is mainly involved in the pathogenesis of oral mucositis, a common side effect in 5FU and radiation treated patients.[130]

We will test whether gene expression levels of genes involved in the EGFR pathway will predict with response, time to tumor progression and overall survival as well as toxicity. We will, however, review the literature, and refine our choices at the beginning of analyses of this project to incorporate relevant new findings as well as new technologies.

2.9.3 Tumor Angiogenesis and Vascular Endothelial Growth Factor Expression.

New blood vessel formation, termed angiogenesis, is considered a fundamental requirement for tumors to grow beyond a few millimeters in greatest dimension, and to set up new colonies at metastatic sites.[131] VEGF is the most potent known endothelial mitogen and is widely expressed in solid tumors.[132,133] In colorectal cancer, expression of VEGF and its receptors are up-regulated in comparison to normal bowel and inhibition of VEGF activity is a promising addition to chemotherapy for management of metastatic disease.[134,135] Recent retrospective studies have indicated that measures of angiogenesis may be clinically useful as prognostic indicators in colorectal cancer, and that VEGF expression is associated with a poorer treatment outcome.[131 136] Prospective studies to address this issue in stage II and III CRC are underway (CALGB protocols 9581 and 89803).

2.9.4 COX-2 and Prognosis.

COX-2 is an inducible enzyme involved in arachidonic acid metabolism that plays an important role in inflammation and tumorigenesis. COX-2 is highly expressed in both tumor cells and tumor-associated endothelial cells, and its prostaglandin products promote angiogenesis in human tumors.[137,138] These observations led to the hypothesis that COX-2 upregulation supports tumor angiogenesis. Prostaglandin products of COX-2 activity may also be involved in activation of EGFR.[139] COX-2 expression by IHC has been associated with reduced survival in patients undergoing resection of colorectal cancer.[140] Measurement of COX-2 expression by IHC has been challenging, however, due to problems with antibody specificity and consistency of staining.

2.9.5 Markers of Treatment Response for Anti-EGFR Therapies.

EGFR is a transmembrane receptor tyrosine kinase whose activity is stimulated by growth factors such as EGF and TGF-α.[141] Increased expression of this cellular

oncogene is observed in many different types of solid tumors, and is associated with reduced disease-free and overall survival in patients with head and neck, ovarian, bladder, and esophageal carcinomas.[142] Studies of EGFR expression in CRC have suffered from lack of uniform patient populations and variable protein detection methods. By immunohistochemistry (IHC) techniques, EGFR overexpression is observed in approximately 60-80% of CRCs compared to normal intestinal mucosa.[143,144] The relationship between tumor EGFR expression and colon cancer survival is unclear, although a few studies suggest that EGFR overexpression is associated with poor tumor grade and decreased disease-free and overall survival.[145-147] The relationship between EGFR expression and anti-tumor response to antibody blockade of EGFR is likewise not well understood.[148]

An understanding of the relationship between receptor expression and activation of downstream signaling pathways is crucial to improving the results of these targeted therapies. Pre-clinical studies have identified the MAP kinase, PI_3K, and AKT pathways as key signaling mechanisms affected by EGFR activation.[149] Recently, reagents have been developed for use in paraffin sections that can indicate activation of EGFR-associated mediators. These include antibodies recognizing EGFR autophosphorylation (EGFR-p-Y1068), activated AKT (AKT-p-Ser473), and activated MAP kinase (p44/42 MAP kinase).

3.0 DRUG INFORMATION

3.1 Capecitabine (Xeloda®)

3.1.1 Other Names: Xeloda®

3.1.2 Chemical Name: 5'-Deoxy-5-fluro-N-[(pentyloxy) carbonyl]-cytidine

3.1.3 Molecular Formula: $C_{15}H_{22}FN_3O_6$ M.W.: 359.35

3.1.4 How Supplied: Xeloda® (capecitabine) tablets are supplied as 150 mg (light peach) and 500 mg (peach) immediate-release film-coated tablets.

3.1.5 Route of Administration: Oral. Capecitabine should be taken with food every 12 hours (within 30 min after breakfast and dinner with water, not juice)

3.1.6 Storage: Store at room temperature in the container in which they are provided.

3.1.7 Availability: Capecitabine is a commercially available drug.

3.2 Oxaliplatin (Eloxatin™)

3.2.1 Other Names: *l*-OHP, SR 96669

3.2.2 Chemical Name: cis-[(1 R,2R)-1,2-cyclohexanediamine-N,N'] [oxalate(2-)-O,O']platinum

3.2.3 Molecular Formula: $C_8H_{14}N_2O_4Pt$ M.W.: 397.3
Physical Properties: Slightly soluble in water. Very slightly soluble in

methanol. Practically insoluble in ethanol and acetone

3.2.4 Description

Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) with an oxalate ligand as a leaving group.

3.2.5 How Supplied

ELOXATIN is supplied in clear, glass, single-use vials with gray elastomeric stoppers and aluminum flip-off seals containing 50 mg, 100 mg or 200 mg of oxaliplatin as a sterile, preservative-free, aqueous solution at a concentration of 5 mg/ml. Water for Injection, USP is present as an inactive ingredient.

NDC 0024-0590-10: 50 mg single-use vial with green flip-off seal individually packaged in a carton.

NDC 0024-0591-20: 100 mg single-use vial with dark blue flip-off seal individually packaged in a carton.

NDC 0024-0592-40: 200 mg single-use vial with orange flip-off seal individually packaged in a carton.

3.2.6 Solution Preparation

Do not freeze and protect from light the concentrated solution.
A final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions.
The solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.
After dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].**
After final dilution, protection from light is not required.

3.2.7 Route of Administration: intravenous.

3.2.8 Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze and protect from light (keep in original outer carton).

3.2.9 Stability

Use product within eight (8) hours after withdrawing desired dose as the product contains no bacteriostatic agent. Reconstituted solution: in Sterile Water for Injection or Dextrose 5% in Water in the original vial; the solution may be stored for 24 to 48 hours at 2^{o} to 8^{o} C. Infusion solution: after dilution in Dextrose 5% in Water, the shelf life is 24 hours at room temperature.

3.2.10 Incompatibilities

ELOXATIN is incompatible in solution with alkaline medications or media (such as basic solutions of 5-FU) and must not be mixed with these or administered simultaneously through the same infusion line. **The infusion line should be flushed with D5W prior to administration of any concomitant medication.**
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.

Needles or intravenous administration sets containing aluminum parts that may come in contact with ELOXATIN should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

3.2.11 Availability: Oxaliplatin is a commercially available drug.
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3.2.12 Handling and Disposal: As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from ELOXATIN. The use of gloves is recommended. If a solution of ELOXATIN contacts the skin, wash the skin immediately and thoroughly with soap and water. If ELOXATIN contacts the mucous membranes, flush thoroughly with water.

Institutional procedures for the handling and disposal of anticancer drugs should be considered.

3.3 Erbitux (Cetuximab)

3.3.1 Description:

Cetuximab is an anti-EGFR human-to-murine chimeric antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment and nanofiltration. Cetuximab is not known to be a vesicant.

3.3.2 Supplier/How Supplied:

Bristol-Myers Squibb (BMS) will supply cetuximab free of charge to the patient. The product is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42mg/mL sodium phosphate monobasic monohydrate, and Water for injection, USP.

3.3.3 Packaging and Labeling:

Cetuximab for injection will be supplied by BMS in single-use, ready-to-use 50 or 100-mL vials containing 2 mg/mL of product.

3.3.4 Handling and Dispensing of Cetuximab:

Cetuximab must be dispensed only from official study sites by authorized personnel according to local regulations. Cetuximab should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study patients.

3.3.5 Storage Requirement/Stability:

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) or up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

3.3.6 Preparation and Administration:

Cetuximab must not be administered as an iv push or bolus.

Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. **DO NOT SHAKE OR DILUTE.**

Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
- Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with cetuximab before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect up the infusion line and start the infusion after priming the line with cetuximab.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line.

Following the cetuximab infusion, a 1-hour observation period is recommended.

3.3.7 Safety Precautions:

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to BMS for disposal. For questions regarding cetuximab destruction please contact BMS at 800 743-9224.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

3.3.8 Cetuximab Records at Investigational Site(s):

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).

- Amount returned to Sponsor.

BMS will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

3.3.9 Drug Ordering and Accountability

Following submission and approval of the required regulatory documents, a supply of cetuximab may be ordered from BMS. Investigators must complete / download a Drug Request Form and email it to (cetuximab.drug@bms.com) In the absence of email the Form may be faxed to the BMS Clinical Supply Manager at 609 252-7856

Keep in mind that you will need: 7-9 vials for an initial dose, and 4-6 vials for weekly maintenance doses, dependent on patient's BSA. A suggested initial shipment is 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the C225 (Cetuximab) Clinical Supply Shipment Request form. Drug is not patient specific.

All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from BMS on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs.

It is possible that sites may have more than one cetuximab clinical study ongoing at the same time. It is imperative that only product designated for this protocol number be utilized for this study. To help segregate product for this study from other investigational or marketed product, stickers bearing the protocol number will be provided and should be affixed to the front of the outer carton just above the company names so as not to obscure any marking.

Inside each shipping container, a disposable electronic unit (TagAlert™) to ensure the product has remained at the appropriate temperature during shipping may be included. This unit may be attached to an information card. The LCD display will show “OK” (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/alarms have been triggered). Should an alarm be triggered, follow the instructions on the attached information card. Display results should be recorded on the packing list. For questions regarding drug requisitioning or shipment contact Bristol-Myers Squibb at (800) 743-9224.

3.3.10 Important Reorder Instructions:

Reorders should be emailed directly to BMS using cetuximab.drug@bms.com for shipment within 5 days. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose (~7-9 for initial dose, ~4-6 for weekly doses, dependent on patient's BSA), and that shipments may take 5 business days from BMS receipt of request. Drug is not patient specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

3.3.11 Receipt of Drug Shipment:

Study drug shipments may include a TagAlert™ unit and attached information card (see above for description) and a clinical supply packing list (CSPL). If included, the pharmacist/study personnel responsible for the clinical study product will need to

indicate the condition of the shipment, record the TagAlert™ results, and sign the CSPL in the designated areas. The pharmacist/study personnel will keep a photocopy for the site's records, and return the original to BMS, using the enclosed, pre-addressed envelope. The TagAlert™ unit can be discarded after the reading is recorded on the CSPL.

3.3.12 Drug Destruction and Return:

At the end of an infusion for an individual patient, any remaining study drug should be destroyed at the site according to the institution's policy for drug destruction. At the completion of the study, all unused study drugs will also be destroyed at the site as per institutional policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities. If approved procedures are not in place, please contact Bristol-Myers Squibb at (800) 743-9224 for assistance.

3.3.13 Drug Inventory Records:

It is the responsibility of the Investigator to ensure that a current record of study drug disposition is maintained at each study site where the study drug is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

4.0 STAGING CRITERIA

Patients should be staged for their disease by the appropriate, standard TNM staging system of the American Joint Committee on Cancer. Patients must have advanced or disseminated cancer.

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

To be eligible for inclusion, each patient must fulfill each of the following criteria:

5.1.1 Patients with histologically or cytologically confirmed advanced or metastatic gastric or gastroesophageal cancer. Histology must be consistent with adenocarcinoma.

5.1.2 No previous chemotherapy for metastatic or unresectable disease. Prior adjuvant therapy is allowed, as long as it was completed prior to six months of study initiation.

5.1.3 Ability to understand and willingness to sign a written informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw from the study at any time, without prejudice.

5.1.4 Age ≥ 18 years. Because no dosing or toxicity data are currently available on the use of oxaliplatin in patients <18 years of age, children are excluded from this study, but will be eligible for the pediatric phase I single-agent trials now in development.

5.1.5 SWOG performance status ≤ 2.

5.1.6 At least one measurable lesion according to the RECIST criteria which has not been irradiated (i.e. newly arising lesions in previously irradiated areas are accepted). Ascites, pleural effusion, and bone metastases are not considered measurable. Minimum indicator lesion size: ≥ 10 mm measured by spiral CT or ≥20mm measured by conventional techniques.

5.1.7 Have a negative serum or urine pregnancy test within 7 days prior to initiation of chemotherapy (female patients of childbearing potential).

5.1.8 Availability of tumor biopsy (paraffin embedded or fresh frozen) at the time of diagnosis and/or prior to study entry is required.

5.1.9 Patients must agree to have a 20 cc blood sample drawn in addition to routine labs prior to the first cycle of chemotherapy.

5.1.10 Patients must agree to use an effective form of birth control while on study and to continue this contraceptive method for 30 days from the date of the last study drug administration.

5.2 Exclusion Criteria

Patients who fulfill any of the following criteria will be excluded:

5.2.1 Pregnant or lactating woman. Woman of childbearing potential with either a positive or no pregnancy test at baseline. Woman or men of childbearing potential not using a reliable and appropriate contraceptive method. (Postmenopausal woman must have been amenorrheic for at least 12 months to be considered of non-childbearing potential).

5.2.2 Life expectancy < 3 months.

5.2.3 Serious, uncontrolled, concurrent infection(s) or illness(es).

5.2.4 Any prior oxaliplatin treatment.

5.2.5 Prior unanticipated severe reaction to fluoropyrimidine therapy, known hypersensitivity to 5-fluorouracil or known DPD deficiency.

5.2.6 Prior unanticipated severe reaction or hypersensitivity to platinum based compounds.

5.2.7 Completion of previous chemotherapy regimen < four weeks prior to the start of study treatment (within six weeks of study treatment for mitomycin C and nitroureas), or with related toxicities unresolved prior to the start of study treatment.

5.2.8 Treatment for other carcinomas within the last five years, except cured non-melanoma skin and treated in-situ cervical cancer.

5.2.9 Participation in any investigational drug study within 4 weeks preceding the start of study treatment.

5.2.10 Clinically significant cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with

medication), myocardial infarction within the last 6 months, uncontrolled hypertension, unstable angina, and cardiomyopathy with decreased ejection fraction.

5.2.11 History of clinically significant interstitial lung disease and/or pulmonary fibrosis.

5.2.12 History of persistent neurosensory disorder including but not limited to peripheral neuropathy

5.2.13 Evidence of CNS metastases (unless CNS metastases have been stable for > 3 months) or history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance of oral drug intake. Other serious uncontrolled medical conditions that the investigator feels might compromise study participation.

5.2.14 Major surgery within 4 weeks of the start of study treatment, without complete recovery.

5.2.15 Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome.

5.2.16 Any of the following laboratory values:

Abnormal hematologic values (neutrophils < 1.5 x 10^9/L, platelet count < 100 x 10^9/L)

Impaired renal function (estimated creatinine clearance <30ml/min as calculated with Cockroft-Gault equation and serum creatinine > 1.5 x upper normal limit).

Serum bilirubin > 1.5 x upper normal limit.

ALT, AST > 2.5 x upper normal limit (or > 5 x upper normal limit in the case of liver metastases).

Alkaline phosphatase > 2.5 x upper normal limit (or > 5 x upper normal limit in the case of liver metastases or > 10 x upper normal limit in the case of bone disease).

5.2.17 Unwillingness to participate or inability to comply with the protocol for the duration of the study.

5.2.18 Known, existing unctorolled coagulapathy

` 5.2.19 Prior therapy which specifically and directly targets the EGFR pathway.

5.2.20 Prior severe infusion reaction to a monoclonal antibody.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS

This is a phase II, non-randomized, open label study for patients with metastatic or unresectable gastric or gastroesophageal cancer.

7.0 TREATMENT PLAN

7.1 Treatment Plan

Patients will receive initial cetuximab 400 mg/m2, followed by weekly cetuximab 250 mg/m2 with oxaliplatin 130 mg/m2 on day 1 (every 3 weeks) with capecitabine 850 mg/m2 bid, daily on days 1-14, every 3 weeks. Each cycle will be administered every three weeks.

Patients will receive capecitabine 850 mg/m^2, bid, every day on Days 1 through 14. The total daily dose of capecitabine will be divided into two equal doses and given in 12 hour intervals on Days 1 through 14. Capecitabine is available in 500 mg tablets and 150 mg tablets. The dose of capecitabine will be rounded to the nearest dose that can be obtained by using both whole 500 and 150 mg tablets. Patients will receive oxaliplatin 130 mg/m2 IV over 120 minutes on Day 1 of each cycle. Each cycle is to be administered every 3 weeks. Patients will be evaluated on day one of each cycle for toxicity. Any additional monitoring should be done at the treating physician's discretion. Patients will continue on protocol treatment until disease progression or until other reason for removal from protocol treatment (see Section 7.2).

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Cetuximab	400 mg/m^2	I.V. over 120 minutes	Initial	Day 1, Cycle 1
	250 mg/m^2	I.V. over 60 minutes	1, 8,15	Weekly
Capecitabine *	850 mg/m^2 BID	P.O. at 12 hour intervals	1 – 14	Every 21 days
Oxaliplatin	130 mg/m^2	I.V. over 120 minutes	1	Every 21 days

***In patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min), it is recommended that the starting dose of capecitabine be reduced to -1 dose level (see Sections 8.2.9 and 8.4).**

NOTE: Capecitabine is to be administered orally with food every 12 hours. Tablets should be swallowed with water (no fruit juices). Approximately 200 mL of water should be ingested in total.

All patients should be premedicated with diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) by IV given 30-60 minutes prior to the first dose of cetuximab. Premedication may be administered prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine (or a similar agent) may be reduced.

The initial dose of cetuximab is 400 mg/m^2 intravenously administered over 120 minutes, followed by weekly infusions at 250 mg/m^2 IV over 60 minutes. **The**

infusion rate of cetuximab must never exceed 5 mL/min. Patients must be continuously observed during the infusion for signs of anaphylaxis.

Patients will be closely monitored for treatment-related adverse events, especially infusion reactions, during the infusion and the post-infusion observation hour. For the initial cetuximab infusion, vital signs should be monitored pre-infusion, 1/2 hour into the infusion, at the end of the infusion and 1 hour post-infusion. For subsequent infusions, vital signs should be taken pre- and post-infusion; however, it is recommended that the patient be observed for 1 hour post infusion. Longer observation periods may be required in patients who experience infusion reactions.

7.2 Criteria for Removal from Protocol Treatment:

a. Progression of disease (as defined in Section 10.2).

b. Unacceptable toxicity (Irreversible Grade 3-4 toxicity).

c. Delay of treatment ≥ 3 weeks.

d. The patient may withdraw from protocol treatment at any time for any reason.

e. Intercurrent illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment

f. Non protocol chemotherapy or immunotherapy is administered during the study

g. Non compliance with protocol or treatment

h. Patient becomes pregnant

i. Patient is lost to follow-up

Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)

7.3 All reasons for discontinuation of protocol treatment must be documented in the Off Treatment Form.

7.4 All patients will be followed until death or three years after registration, whichever occurs first. This follow-up may occur at the physician's discretion, but at least every 6 months.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 General Approach to Patient Toxicity

All toxicities will be graded according to NCI Common Terminology Criteria for Adverse Events [CTCAE] version 3.0.with the exception that hand-foot syndrome will be graded utilizing Roche Criteria. If multiple toxicities occur the dose administered should be based on the most severe toxicity experienced.

Specific Toxicity – Please note that the frequencies of capecitabine associated toxicities cited below are based on a 1250 mg/m2 bid dose. Please see section 8.4.1.5 for Cetuximab specific dose modifications.

8.2.1 **Diarrhea**: Diarrhea is a common toxicity of fluoropyrimidines, and felt related to an antiproliferative effect on the rapidly dividing epithelial cells of the gastrointestinal mucosa. Diarrhea was the most frequent grade 3/4 toxicity seen with capecitabine treatment, occurring in 15% of patients treated. It was also the most common life-threatening event, the most common serious adverse event, and the most common cause for treatment-related hospitalization. Diarrhea was also a common cause of dose interruption or dose modification (Xeloda® US Package Insert, September 2001, Roche).

Capecitabine can cause diarrhea, and should be *stopped at diarrhea grade* $\geq$ *2*, and treated symptomatically (recommend IV hydration and use of loperamide for diarrhea, observing loperamide dosage recommendation and treatment start, see below). If control takes longer than 2 days, medical evaluation including relevant diagnostic procedures, alternative treatment and possible investigation of DPD deficiency should be considered.

The recommended dosage regimen for loperamide: 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Note: This dosage regimen exceeds the usual dosage recommendations for loperamide. Premedication with loperamide is not recommended.

The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

8.2.2 **Hand-Foot Syndrome**: This syndrome, also known as palmar-plantar erythrodysesthesia and chemotherapy induced acral erythema, is a cutaneous reaction associated with the administration of selected systemic cytotoxic agents. Classically these include fluorouracil, doxorubicin, and cytosine arabinoside, primarily when administered via protracted infusions. The incidence with fluorouracil has ranged from anecdotal reports to 64% in patients receiving a protracted infusion. The pathogenesis of hand-foot syndrome is unknown, but it may be related to antiproliferative damage to the basal-cell layer of the skin or drug elimination by eccrine secretion. Characteristic symptoms include palmoplantar dysthesia, edema, and/or erythema. Severe cases may progress to desquamation, ulceration, blistering or severe pain. The

reaction is self-limited, and typically limited to the palms and soles. Functional consequences may result in the inability of patients to carry out the activities of daily living including hand-gripping activities or walking.

Hand-foot syndrome occurred in 45% of the patients treated with capecitabine. Therapeutic adjuncts included emollients, topical or systemic corticosteroids, and pyridoxine.

8.2.3 **Nausea and vomiting**: Nausea and vomiting are common side effects of capecitabine, occurring in 29% of patients studied. Antiemetics are often successful in these circumstances. Dehydration may happen which can lead to hospitalization.

8.2.4 **Stomatitis**: Stomatitis happened in 20% of patients taking capecitabine. Supportive measures should be given. Severe stomatitis can lead to dehydration and hospitalization.

8.2.5 **Myelosuppression**: Myelosuppression, a frequent problem with 5-FU and other chemotherapies, was rarely reported with capecitabine treatment (<3% of patients).

8.2.6 **Total bilirubin**: In the overall clinical trial safety database of XELODA monotherapy (N=875), grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 3.9% (n=34) of 875 patients with either metastatic breast or colorectal cancer who received at least one dose of XELODA 1250 mg/m^2 twice daily as monotherapy for 2 weeks followed by a 1-week rest period. Of 566 patients who had hepatic metastases at baseline and 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 22.8% and 12.3%, respectively. Of the 167 patients with grade 3 or 4 hyperbilirubinemia, 18.6% (n=31) also had postbaseline elevations (grades 1 to 4, without elevations at baseline) in alkaline phosphatase and 27.5% (n=46) had postbaseline elevations in transaminases at any time (not necessarily concurrent). The majority of these patients, 64.5% (n=20) and 71.7% (n=33), had liver metastases at baseline. In addition, 57.5% (n=96) and 35.3% (n=59) of the 167 patients had elevations (grades 1 to 4) at both prebaseline and postbaseline in alkaline phosphatase or transaminases, respectively. Only 7.8% (n=13) and 3.0% (n=5) had grade 3 or 4 elevations in alkaline phosphatase or transaminases.

In the 596 patients treated with XELODA as first-line therapy for metastatic colorectal cancer, the incidence of grade 3 or 4 hyperbilirubinemia was similar to the overall clinical trial safety database of XELODA monotherapy. The median time to onset for grade 3 or 4 hyperbilirubinemia in the colorectal cancer population was 64 days and median total bilirubin increased from 8 m/L at baseline to 13 m/L during treatment with XELODA. Of the 136 colorectal cancer patients with grade 3 or 4 hyperbilirubinemia, 49 patients had grade 3 or 4

hyperbilirubinemia as their last measured value, of which 46 had liver metastases at baseline.

In 251 patients with metastatic breast cancer who received a combination of XELODA and docetaxel, grade 3 (1.5 to 3 x ULN) hyperbilirubinemia occurred in 7% (n=17) and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 2% (n=5).

If drug-related grade 2 to 4 elevations in bilirubin occur, administration of XELODA should be immediately interrupted until the hyperbilirubinemia resolves or decreases in intensity to grade 1. NCIC grade 2 hyperbilirubinemia is defined as 1.5 x normal, grade 3 hyperbilirubinemia as 1.5 to 3 x normal and grade 4 hyperbilirubinemia as >3 x normal.

8.2.7 **Neurosensory Toxicity:**

Oxaliplatin is known to result in neurosensory symptoms. These can be of two types:

- Cold-related dysesthesias (ie, painful tingling of the hand when exposed to cold) or myotonia (ie, cramping of the hand or jaw soon after oxaliplatin administration). These symptoms usually occur during or within 1-2 days of oxaliplatin administration and resolve within 1 week.
- Cumulative peripheral sensory neuropathy. These symptoms usually occur after 4 to 6 months of therapy and are manifested by decreased sensation to sharp and soft touch and diminished position sense.

8.2.8 **Hypomagnesemia and Hypocalcemia**

Patients should be periodically monitored for hypomagnesemia and accompanying hypocalcemia and hypokalemia during and following the completion of cetuximab therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; i.e., 8 weeks.

8.2.9 **Hypersensitivity reactions: Oxaliplatin, as is the case with all platins, is associated with a low incidence of hypersensitivity reactions, usually after multiple doses of treatment. This can be manifest as bronchospasm, hypotension, and even hemolytic anemia.**

Following a Grade 1 or 2 acute hypersensitivity reaction that is assessed as related to oxaliplatin administration, the following premedication should be administered prior to each subsequent dose of oxaliplatin (patients who have grade 3 or 4 acute hypersensitivity reactions should discontinue oxaliplatin therapy):

Dexamethasone 20 mg PO or IV, <u>12 and 6 hours</u> prior to the oxaliplatin

dose;
Dexamethasone 20 mg PO or IV, as well as diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30-60 minutes prior to oxaliplatin administration.

8.2.10 Warnings:

Renal Insufficiency: Patients with moderate renal impairment **at baseline** require dose reduction (See section 7.1 Treatment plan) Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse events. Prompt interruption of therapy with subsequent dose adjustments will be made if a patient develops a grade 2 to 4 adverse event. Capecitabine is contraindicated in patients with a calculated creatinine clearance of < 30 ml/min.

Coagulopathy: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important Xeloda® -Warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking Xeloda® concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time Xeloda® was introduced. These events occurred within several days and up to several months after initiating Xeloda® therapy and, in a few cases, within one month after stopping Xeloda® . These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

Cardiotoxicity: The cardiotoxicity observed with Xeloda® includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse events may be more common in patients with a prior history of coronary artery disease.

This treatment is foreseen as a self-administered out-patient treatment, and in certain circumstances adverse events that could occur, such as diarrhea, or hand-foot syndrome can rapidly become serious. In the case where a patient experiences any toxicity between scheduled visits, the patient should be encouraged to contact the clinic as soon as possible, for further directions, discontinuation of study medication, and/or treatment.

8.2.11 Concomitant Medications and Treatments

Capecitabine and some of its metabolites are converted principally by liver enzymes (carboxylesterase and cytidine deaminase and TP in tumor tissues). At present, it is unknown whether this metabolism is likely to be

influenced by other treatments or alcohol, which either induce or inhibit certain liver enzymes.

Allopurinol. Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a patient is receiving allopurinol, the need for taking this medicine should be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.

Cimetidine Because cimetidine can decrease the clearance of 5-FU, patients should not enter on this study until the cimetidine is discontinued. Ranitidine or a drug from another anti-ulcer class can be substituted for cimetidine if necessary.

Sorivudine and Brivudine A metabolite of the above two investigational antiviral agents, 5-bromovinyluracil, is a potent inhibitor of dihydropyrimidine dehydrogenase, the enzyme that catabolizes 5-FU. Patients should not receive concurrent therapy with either of these antiviral agents while receiving capecitabine. If a patient has received prior sorivudine or brivudine, then at least four weeks must elapse before the patient receives capecitabine therapy

Anticoagulants: See Warnings and Precautions Section 8.2.9 In a drug interaction study with single dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Phenytoin: Increased phenytoin plasma concentrations have been reported during concomitant use of Xeloda® with phenytoin, suggesting a potential interaction. Patients taking phenytoin concomitantly with Xeloda® should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

The use of drugs with laxative properties should be avoided.

The use of pyridoxine for prevention or treatment of Hand-Foot Syndrome [Palmar/Plantar Erythrodysesthesia] is not allowed.

8.3 This study will utilize the (NCI CTCAE Version 3.0 for toxicity and adverse event with the exception of hand-foot syndrome where Roche criteria will be used for reporting. A copy of the CTC Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). **All appropriate treatment areas should have access to a copy of the CTC Version 3.0.**

8.4. Dosing Delays/Dose Modifications Oxaliplatin, Capecitabine and Cetuximab

Dosing Delay: Each treatment course will begin when hematologic parameters recover to neutrophils ≥ 1,500/μL and platelets ≥ 75,000/μL (≤ grade 1), treatment related diarrhea is baseline or less, any other treatment related GI toxicity has resolved to baseline or grade 1 (if toxicity was not present at baseline) and other toxicities (except neurological toxicity, hypertension, alopecia and asthenia) are ≤ grade 2. If these conditions have not been met, treatment should be delayed for 1 week to allow for recovery. If after a 1-week delay, all of the above conditions are met, then proceed with treatment as outlined in the Day 1 dose modification table. If the above conditions are not met after a 1-week delay, then treatment will be held again, and the patient will be evaluated weekly. During this delay of the cycle cetuximab may continue to be given at the treating physician's discretion on a weekly basis, as long as the patient does not have toxicities described in 8.4.1.5, which require cetuximab to be held.

Dose Modifications: Dose modification for hematologic or GI toxicity will be based on the worst toxicity observed during the previous course. After recovery, standard dose adjustments for oxaliplatin, capecitabine and cetuximab toxicity should be applied.

Levels for dose modification:

Dose Modification for Cetuximab		
Weekly Start Dose	- 1 dose level	-2 dose level
250 mg/m^2	200 mg/m^2	150 mg/m^2

There will be no dose level reductions below a weekly dose of 150 mg/m^2.

Dose Modification for Oxaliplatin		
Start Dose	- 1 dose level	-2 dose level
130 mg/m^2	100 mg/m^2	NA

Dose Modification for Capecitabine		
Start Dose	- 1 dose level	-2 dose level
850 mg/m^2 po bid	725 mg/m^2 po bid	600 mg/m^2 po bid

In patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min), the starting dose will at -1 dose level of capecitabine (725mg/m2 bid) . In case of dose reduction for toxicity, patients will be treated at -2 dose level of capecitabine (600 mg/m2 po bid). If toxicity recurs, the patients should be taken off study.

For toxicities which are considered by the Investigator unlikely to develop into serious or life–threatening events (e.g. alopecia, altered taste etc.), treatment will be continued at the same dose without reduction or interruption. In addition, no dose reductions or interruptions will be required for anemia as it can be satisfactorily managed by transfusions.

For any event Grade 1-3 event which is apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. (e.g. if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of 1 grade and treated as a grade 1 toxicity for dose modification purposes).

If in the opinion of the investigator, a toxicity is considered solely due to one drug (e.g. hand-foot syndrome caused by capecitabine) the dose of the other drug does not require modification.

If the dose is modified to manage an adverse event, it is recommended that the patient be seen by the investigator prior to re-starting study drug. Once a dose has been reduced it will not be increased at a later time. Treatment interruptions are regarded as lost treatment days and missed doses should not be replaced; the planned treatment schedule should be maintained. If a rest period is extended due to toxicity, the “complete" cycle should be given afterwards. If toxicity requires a dosing delay/interruption of both drugs of more than three weeks, the patient will be withdrawn from the study for toxicity reasons. Where several toxicities with different grades or severity occur at the same time, the dose modifications applied should be the greatest reduction applicable.

8.4.1 Dose Modification Recommendations

There are 3 categories of dose-modification recommendations that apply to this study, which are described below:

1. Intra-cycle dose modifications
Adjustment based on the most severe toxicity observed since the start of the cycle and/or upon laboratory values. (Table 1)

2. Dose modifications at the start of a new cycle
Adjustment at the beginning of a new cycle based upon the most severe toxicity encountered in the previous cycle and/or upon laboratory values on the scheduled day of treatment. (Table 2)

3. Oxaliplatin Neurotoxicity Dose Modifications (Table 3)
These recommendations apply to all patients receiving oxaliplatin (Eloxatin™)

8.4.1.1 Intra-cycle dose modifications

Table 1 describes the recommended dose modifications based on the most severe toxicity observed since the start of the cycle and/or upon laboratory values on the day of treatment. All dose modifications are relative to the Day 1 dose of the current cycle.

Table 1: Intra-Cycle Dose Modifications

Oxaliplatin and Capecitabine Dose Modifications <u>During a Cycle</u> Based on the Worst Type of Toxicity Observed

Dose Changes are Relative to the Immediate Prior Dose Given

Toxicity NCI CTCAE Grade *	Capecitabine	Oxaliplatin	Cetuximab
Neutropenia or thrombocytopenia (on day of treatment)			
Grade 0, or 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Maintain dose level
Grade 3	Maintain dose level	Maintain dose level for neutropenia; for thrombocytopenia, omit dose then ↓ 1 dose level	Maintain dose level (do not omit or delay dose)
Grade 4	Omit dose, then ↓ 1 dose level when resolved to ≤ grade 1	Omit dose, then ↓ 1 dose level when resolved to ≥ ANC 1500	Maintain dose level (do not omit or delay dose)
Febrile neutropenia or neutropenic sepsis ♦	Omit dose, then ↓ 1 dose level when resolved	Omit dose, then ↓ 1 dose level when resolved	Maintain dose level (do not omit or delay dose)
Diarrhea (must be resolved ≥ 24 hours of next scheduled dose)			
Grade 0	Maintain dose level	Maintain dose level	Maintain dose level
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 or 3	Omit dose, then ↓ 1 dose level when resolved	Omit dose, then ↓ 1 dose level when resolved	Maintain dose level (do not omit or delay dose)
Grade 4	Omit dose then ↓ 2 dose levels when resolved OR discontinue at investigator discretion	Omit dose, then ↓ 1 dose level when resolved	Maintain dose level (do not omit or delay dose)
Mucositis (since prior treatment)			
Grade 0 or 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Maintain dose level
Grade 3	Omit dose, then ↓ 1 dose level when resolved to grade 2	Maintain dose level	Maintain dose level
Grade 4	Omit dose then ↓ 2 dose levels when resolved to grade 2 OR discontinue at investigator discretion	Omit dose, then ↓ 1 dose level when resolved to ≤ grade 2	Maintain dose level (do not omit or delay dose)
Vomiting (since prior treatment)			
Grade 0, 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 or 3	Maintain dose level; add further antiemetics	Maintain dose level; add further antiemetics	Maintain dose level
Grade 4	↓ 1 dose level; add further antiemetics	↓ 1 dose level; add further antiemetics	Maintain dose level
Thromboembolic Events (since prior treatment)			
Grade 0, 1 or 2	Maintain dose level	Maintain dose level	
Grade 3 or 4	Omit protocol therapy; start therapeutic anticoagulation; resume chemotherapy only at investigator discretion		
All other non-hematological toxicities, except alopecia (since prior treatment)[1]			
Grade 0 or 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Miantain dose level	Maintain dose level	Maintain dose level
Grade 3	Omit dose then ↓ 1 dose level when resolved to grade 2	Omit dose then ↓ 1 dose level when resolved to grade 2	Omit dose, then resume at same dose level when resolved to grade 2
Grade 4	Omit dose then ↓ 2 dose levels when resolved to grade 2 OR discontinue at investigator discretion	Omit dose then ↓ 1 dose level when resolved to grade 2	Omit dose, then resume at same dose level when resolved to grade 2

* NCI CTCAE Version 3.0. ♦Febrile neutropenia: temperature ≥38.5°C concomitant with an ANC 1000/mm^3. [d]

[1]Patients with ≥ grade 2 myocardial ischemia (CTCAE version 3.0), patient off study

8.4.1.2 **Dose Modifications on Day 1 of a new cycle**

A new cycle of treatment may begin on Day 1 of the subsequent cycle when the ANC is ≥1500/mm^3 (grade ≤1) and the platelet count is ≥75,000/mm^3 (grade ≤1), treatment-related diarrhea is baseline or less and other toxicities (except neurological toxicity, hypertension, alopecia and asthenia) are ≤ grade 1. If these conditions have not been met, treatment should be delayed for 1 week to allow for recovery. If after a 1-week delay, all toxicities (except alopecia and asthenia) are grade ≤ 1, then proceed with treatment as outlined in the Day 1 dose modification table. If these toxicities are not resolved to ≤1 grade (diarrhea baseline or less) after a 1-week delay, then treatment will be held again, and the patient will be evaluated weekly.

Table 2 describes the recommended dose modifications on Day 1 of a new cycle based on the most severe toxicity observed in the previous cycle and/or upon laboratory values on the scheduled day of treatment in the new cycle. All dose modifications are relative to the Day 1 dose of the previous cycle.

Table 2 Dose Modifications for Day 1 of New Cycle

Dose Modifications for Day 1 of New Cycle Based on Worst Type Toxicity Observed in the Prior Cycle [Dose Changes are relative to the Day 1 dose of the previous cycle]			
Toxicity NCI CTCAE Grade*	**Capecitabine**	**Oxaliplatin**	**Cetuximab**
Neutropenia or thrombocytopenia (on day of treatment)			
Grade 0, or 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Miantain dose level	Maintain dose level	Maintain dose level
Grade 3	Delay dose, then maintain dose level when resolved to ≤ grade 1	Maintain dose level for neutropenia; for thrombocytopenia, delay dose then ↓ 1 dose level	Maintain dose level (do not omit or delay dose)
Grade 4	Delay dose, then ↓ 1 dose level when resolved to ≤ grade 1	Delay dose, then ↓ 1 dose level when resolved to ≥ ANC 1500	Delay dose, then restart at same dose level l when resolved to ≥ ANC 1500
Febrile neutropenia or neutropenic sepsis♦	Delay dose, then ↓ 1 dose level when resolved	Delay dose, then ↓ 1 dose level when resolved	Delay dose, then restart at same dose level l when resolved to ≥ ANC 1500
Diarrhea (must be resolved ≥ 24 hours of next scheduled dose)			
Grade 0, 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 or 3	↓ 1 dose level	↓ 1 dose level	Maintain dose level
Grade 4	↓ 1 dose level	↓ 1 dose level	Maintain dose level
Mucositis (since prior treatment)			
Grade 0 or 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 or 3	Maintain dose level	Maintain dose level	Maintain dose level
Grade 4	↓ 1 dose level	↓ 1 dose level	Maintain dose level
Vomiting (since prior treatment)			
Grade 0, 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 or 3	Maintain dose level; add antiemetics	Maintain dose level; add antiemetics	Maintain dose level
Grade 4	↓ 1 dose level; add antiemetics	↓ 1 dose level; add antiemetics	Maintain dose level
Thromboembolic Events (since prior treatment)			
Grade 0, 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2, 3 or 4	Delay chemotherapy; start therapeutic anticoagulation; resume chemotherapy only at investigator discretion		
All other non-hematologic toxicities, except alopecia (since prior treatment)[1]			
Grade 0, 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 or 3	↓ 1 dose level	↓ 1 dose level	Maintain dose level
Grade 4	Capecitabine: ↓ 2 dose levels or discontinue at investigator discretion	↓ 1 dose level	Maintain dose level

* NCI CTCAE Version 3.0. ♦Febrile neutropenia: temperature ≥38.5°C concomitant with an ANC 1000/mm^3.
[1]Patients with ≥ grade 2 myocardial ischemia (CTCAE version 3.0), patient off study

8.4.1.3 Management of Oxaliplatin-related Toxicities

Neurotoxicity

For management of neurological toxicity related to oxaliplatin, see Table 3 below:

Table 3 : Neurological Toxicity Scale for Oxaliplatin Dose Adjustments

Toxicity (Grade)	Duration of Toxicity		Persistent
	1 - 7 Days	>7 Days	Between Cycles
Paresthesias/dysesthesias[b] that do not interfere with function (Grade 1)	No change	No change	No change
Paresthesias/dysesthesias[b] interfering with function, but not activities of daily living (ADL) (Grade 2)	No change	No change	65 mg/m^2
Paresthesias/dysesthesias[b] with pain or with functional impairment that also interfere with ADL (Grade 3)	No change	65 mg/m^2	Stop/Off study
Persistent paresthesias/dysesthesias that are disabling or life-threatening (Grade 4)	Stop/Off study	Stop/Off study	Stop/Off study
Grade 3 or 4 acute hypersensitivity or anaphylactic reactions	Stop/Off study		
ACUTE: (during or after the 2 hour infusion) laryngopharyngeal dysesthesias[b]	↑ Duration of next infusion to 6 hours[c]		

[a] Not resolved by the beginning of the next cycle.

[b] May be cold-induced.

[c] May also be pre-treated with benzodiazepines

Laryngopharyngeal dysesthesia

An unusual laryngopharyngeal dysesthesia, a loss of sensation of breathing (acute respiratory distress) without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm), also has been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold.

Should a patient develop laryngopharyngeal dysesthesia, the patient's oxygen saturation will be evaluated via a pulse oximeter and, if normal, an anxiolytic agent or benzodiazepine should be given and the patient should be observed in the clinic until the episode has resolved. The infusion may then be continued at 1/3 the rate. Because this syndrome may be associated with the rapidity of Oxaliplatin infusion, subsequent doses of Oxaliplatin should be administered as 6-hour infusions (instead of the normal 2-hour infusion).

Oral cryotherapy
Patients on Oxaliplatin should not receive oral cryotherapy (such as ice chips) on Day 1 of each cycle as this may exacerbate oral or throat dysesthesia, and laryngopharyngeal dysesthesia.

Allergic reactions
For Grade 1 or 2 acute hypersensitivity reactions, no dose modification of Oxaliplatin is required if, in the Investigator's opinion, it is in the patient's best interest to continue. Pre-medication with dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30 minutes prior to study drug administration is recommended. If an allergic reaction persists into the next cycle, administer 50 mg dexamethasone PO 12 hours and 6 hours prior to administration of Oxaliplatin.

For Grade 3 or 4 acute hypersensitivity reactions, treatment should be discontinued.

Pulmonary fibrosis
In the case of unexplained respiratory symptoms such as nonproductive cough, dyspnea, crackles, or radiological pulmonary infiltrates, Oxaliplatin should be discontinued until further investigations exclude interstitial pulmonary fibrosis.

8.4.1.4 Management of Capecitabine-related Hand foot Syndrome

Hand foot syndrome:

Toxicity and Grade Level	Capecitabine
Hand-foot syndrome (See Appendix 1 Roche Criteria):	
Grade 1	Maintain dose level
Grade 2-3	Reduce to Dose Level -1.

8.4.1.5 Management of Cetuximab related Toxicities

Management of Infusion Reactions

Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In previous clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (eg, diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, see below.

Cetuximab should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions.

Treatment of Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology.

If a patient experiences isolated drug fever, for the next dose, pre treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

Management of Pulmonary Toxicity

In the event of acute onset (grade ≥2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab retreatment should not occur until these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

Management of Dermatologic Toxicity

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (grade 3) acneform rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

If a patient experiences severe acneform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

Cetuximab Dose Modification Guidelines

Grade 3 Acneform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce Dose Level -1
		No Improvement	Discontinue cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce to Dose Level -2
		No Improvement	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Management of Hypomagnesemia

Hypomagnesemia has been reported with Erbitux when administered as a single agent and in combination with multiple different chemotherapeutic regimens. The incidence of hypomagnesemia (both overall and severe [NCI CTC grades 3 & 4]) is increased in patients receiving chemotherapy and Erbitux as compared with those receiving

chemotherapy alone based on controlled clinical trials. Patients receiving Erbitux therapy should be monitored for hypomagnesemia. Magnesium repletion may be necessary based on clinical judgment.

Caution with Radiation Therapy and Cetuximab

Cetuximab in combination with radiation therapy should be used with caution in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, and arrhythmias. Although the etiology of these events is unknown, close monitoring of serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab therapy is recommended.

8.5 Adverse Events (AE)

US Regulations require that a sponsor reports Serious Adverse Events (SAEs) occurring with use of its product in a clinical trial if it is unexpected, and felt to be related to use of the drug. During the conduct of Investigator Initiated Trials (IITs), all SAEs that occur will be evaluated by the investigator for reportability to FDA. An Adverse Event should be identified, Serious Adverse Event and Expectedness determined and causality assessed by the investigator using the definitions that follow:

An **Adverse Event** is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment.

8.5.1 Serious Adverse Event

Bristol-Myers Squibb considers the SAE reporting period to begin with signing of the informed consent.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), or
- Requires in-patient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- results in the development of drug dependency or drug abuse, or
- Is a medically important event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. **For reporting**

purposes, also consider the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events. An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Events).

Note: The term "life-threatening" in the definition of "Serious Adverse Event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

8.5.2 Unexpected Adverse Event

An **Unexpected Adverse Event** is not listed in the current Clinical Investigator's Brochure (CIB) / Package Insert or an event that may be mentioned in the CIB / Package Insert, but differs from the event because of greater severity or specificity.

For SAEs occurring, the Expectedness of an Adverse Event is determined by identifying the term in the table of Expected Adverse Events by Body System, provided in the Clinical Investigator's Brochure SR96669-EN-E05 or an updated version. If the term is not contained in the list under the relevant body system, the term is to be considered UNEXPECTED.

For comparative drugs, expectedness is determined by using the pertinent reference text: the US Package Insert (if marketed drug) or Investigator Brochure (if Investigational New Drug).

Adverse events not listed on the NCI CTCAE version 3.0 grading system will be graded according to the following scale:

Mild: Discomfort noticed but no disruption of normal daily activity
Moderate: Discomfort sufficient to reduce or affect normal daily activity
Severe: Incapacitating with inability to work or perform normal daily activity
Life–threatening: Self–explanatory

The duration, relationship to the trial medication, action taken regarding the drug administration, any treatment given for the adverse event, as well as the intensity and outcome of the adverse event must be reported.

8.5.3 Causality

Causality is a determination of whether there is a reasonable possibility that the drug may have caused or contributed to an adverse event. It includes assessing temporal relationships dechallenge/rechallenge information, association (or lack of association) with underlying diseases, and the presence (or absence) or a lack of one or more likely causes.

8.5.4 Pregnancy Guidance

Sexually active women of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In addition, men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control. All WOCBP MUST have a negative pregnancy test within 7 days prior to first receiving investigational product. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study.

During the course of the trial, all female patients of childbearing potential should be instructed to contact the treating physician immediately if they suspect they might have conceived a child. In addition, a missed or late menstrual period should be reported to the treating physician. If a female patient, or an investigator, suspects a pregnancy prior to administration of study drugs, the study drugs must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed the patient must not receive study medications and must be withdrawn from the study. The Investigator must immediately notify BMS in the event of a confirmed pregnancy in a patient participating in the study.

Throughout the entire pregnancy, additional contact should be made with the patient, and in some cases with the healthcare provider, to identify spontaneous abortions and elective terminations, as well as any medical reasons for elective termination. In addition, the study investigator should include perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

If a male patient is suspected of having fathered a child while on study drugs, the pregnant female partner must be notified and counseled regarding the risk to the fetus. In addition, the treating physician must follow the course of the pregnancy, including prenatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

Upon live-birth delivery, minimum information that should be collected includes date of birth, length of pregnancy, sex of infant, major and minor anomalies identified at birth. Outcomes can be obtained via mailed questionnaires, maternal interviews, medical record abstraction, or a combination of these methods. All serious adverse event reports relating to the pregnancy, including spontaneous abortion, elective abortion and congenital anomalies, should be forwarded to the FDA and a copy sent to Sanofi-Synthelabo and Roche (See Appendix II).

8.5.5 Reporting Guidelines

8.5.5.1 Serious Adverse Events Reportable to the FDA

For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information.

When the principal investigator has determined that a Serious Adverse Event requires reporting to the FDA (unexpected and possibly related to study drug), the following actions must be completed:

Actions towards FDA:

1. TELEPHONE the FDA immediately (day of awareness), in the case of reportable death or life-threatening events.
2. COMPLETE FDA Form 3500.
3. SEND the completed 3500 form to the FDA (preferably by fax) within the timelines mentioned above.
4. ATTACH the photocopy of all examinations that have been carried out as a result of the reportable SAE and the dates on which these examinations were performed. For laboratory results send also the laboratory normal ranges.

Actions towards Sanofi-Synthelabo (oxaliplatin):

5. Concurrently PROVIDE a copy to Sanofi-Synthelabo at New York Safety Surveillance by fax **866-692-7371** at the latest within 24 hours after the FDA submission (initial and follow-up information)

Actions towards other potential investigators/ Ethics Committee (IRB):

6. For this trial, the principal investigator is also responsible for providing all Serious Adverse Events (on form 3500) submitted to the FDA, to the USC IRB via iStar (https://istar-chla.esc.edu), and other investigators (Dear Investigator Letter). This applies to initial and follow-up information.

Actions towards other manufacturers (as relevant)

7. For reportable Serious Adverse Events (completed form 3500) that are reported in patients treated with products other than oxaliplatin, the principal investigator must also transmit the information to the manufacturer of the suspect product within 24 hours.

Actions toward Roche

8. Serious events, whether or not unexpected or considered to be associated with the use of the study drug, must be communicated, by telephone, to the study PI immediately (within 24 hours) upon awareness of the event. The call then must be followed-up with a completed Serious Adverse Event Report. The report must include, at least:

a. site identifiers
b. the patient identifiers
c. description of the event
d. the investigator's opinion of its causality/relationship to study drug
e. onset date of adverse event
f. date event became serious
g. institutional PI's assessment of patient's recovery.

USC will consult with the Roche contact listed below, if appropriate, after which the investigator will be advised regarding the nature of any further information or documentation that is required. Notification and transmission of serious adverse event information should not be delayed to gather additional information. Subsequent information should be communicated to USC as it becomes available.

The Investigator must promptly inform their Institution's IRB in written of any serious, unexpected adverse event that is considered possibly related to the study drug. USC

will submit a quarterly written report to Roche. In addition USC will send Roche a copy of all SAE reports as they are obtained.

ROCHE CONTACT:

Name: Carolyn McGarry
Roche address: 340 Kingsland St.
Nutley, NJ 07110-1199
Telephone number: 973-562-2785
Telefax number : 973-562-3963
USC will send Roche all SAE reports as they are obtained.

Follow-up Reports

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any Serious Adverse Event submitted to the FDA on a 3500 form and complete follow-up forms as necessary. The patient must be followed up until clinical recovery is complete and/or laboratory results have returned to normal. This may mean that follow-up will continue after the patient has completed the trial and that additional investigations may be necessary.

- Any reportable Serious Adverse Events brought to the attention of the Investigator at any time after cessation of the trial and considered by him/her to be reasonably associated with medication administered during the period should also be submitted to the FDA. As for initial reports, a copy is to be provided to Sanofi-Synthelabo New York Safety Surveillance or the appropriate manufacturer of the product. within 24 hours after FDA submission (see above)

- The 3500 form providing follow-up information about a reportable SAE must be submitted to the FDA as soon as possible or within 15 calendar days.

- As with the initial submission to the FDA of the 3500 form, the principal investigator is also responsible for providing all follow-ups for reportable Serious Adverse Events (on form 3500) to the IRB, and other investigators (Dear Investigator Letter).

IND Annual Report

The principal investigator is responsible for preparing and submitting the IND annual reports to the FDA (CFR312.33) within 60 days of the anniversary date that the IND went into effect. A copy of the report shall be provided to New York Safety Surveillance within 24 hours of submission to the FDA.

Roche Quarterly Report

USC will submit a quarterly written report of SAE's to Roche.

Actions towards Bristol-Myers Squibb (cetuximab):

Adverse events classified as "serious" require expeditious handling and reporting to BMS to comply with regulatory requirements.

All serious AEs whether related or unrelated to investigational product, must be immediately reported to BMS (or designee) by confirmed facsimile transmission. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

Bristol-Myers Squibb will be provided with a simultaneous copy via facsimile of all adverse events filed with the FDA

All SAEs should be faxed to Bristol-Myers Squibb at:

Global Pharmacovigilance
Bristol-Myers Squibb Company
Fax Number: 609-818-3804

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed by BMS. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.In BMS supported trials, all SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any SAE that may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

9.0 STUDY CALENDAR

Patients will be evaluated on day one of each cycle for toxicity. Any additional monitoring should be done at the treating physician's discretion. Patients will receive initial cetuximab 400 mg/m2, followed by weekly cetuximab 250 mg/m2 with oxaliplatin 130 mg/m2 on day 1 (every 3 weeks) with capecitabine 850 mg/m2 bid, daily on days 1-14, every 3 weeks. Each cycle is to be administered every 3 weeks.

Parameter	Pre-treatment	Day 1 of Cycle 1 And every other cycle	Day 1 of all cycles	One Day of Week 3 of every other Cycle	Off treatment
History & Physical Exam	X	X			
Weight, Performance Status	X	X			
Vital Signs	X	X[8]	X[8]		
WBC (differential), Hgb, Platelets	X[11]	X	X		
Electrolytes, MG, BUN, Cr	X[11]	X[9]	X[9]		X[9]
LFT (SGOT and Total Bili)	X[11]	X	X		
Urinalysis	X[11]				
CEA	X	X			
EKG	X	X3			
CXR	X[10]			X[1]	
Pregnancy Test	X[7]				
Tumor Biopsy	X[6]				X[4]
Radiology, x-ray or Scans for disease Measurement	X[12]			X	
Blood for Pharmacogenetics[2,5]	X				

1 If used to follow measurable disease.
2 To be done in ancillary pharmacology protocol when active.
3 As clinically indicated.
4 If feasible (endoscopy or CT guided biopsy) and patient consents.
5 Preinfusion
6 Tumor must be accessible for biopsy or paraffin embedded tissue must be available for review.
7 For women of childbearing potential (within 7 days prior to starting study treatment)
8 For the first cetuximab infusion, vital signs should be recorded pre-infusion, 1/2 hours into the infusion, at the end of the infusion and 1 hour post-infusion. For subsequent cetuximab infusions, vital signs should be taken pre- and 1 hour post-infusion.
9 Patients should be periodically monitored for hypomagnesemia and accompanying hypocalcemia and hypokalemia during and following the completion of cetuximab therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; i.e., 8 weeks.
10 May omit in patients that have other radiologic scans of the chest
11 Must be done within 7 days of first receiving study drug.
12 Must be done within 28 days of first receiving study drug.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

All patients who are registered will be accounted for in the report of the results. The outcome status (in terms of toxicity, response, reason off study, progression, and survival) of all eligible patients will be reported. Patients who complete 2 courses of therapy or who experience ≥ grade 2 toxicity, will be evaluable for toxicity. Patients with measurable tumor who complete the first two cycles of treatment, or who terminate treatment for reasons of toxicity, or who progress prior to completion of the first two treatment cycles, will be included in analysis of tumor response. All eligible patients who begin treatment will be included in the analysis of survival and time-to-failure. The Response Evaluation Criteria In Solid Tumors (RECIST) and CTC 3.0 toxicity criteria will be used.

10.1 Measurability of tumor lesions at baseline

At baseline, tumor lesions will be categorized as:

measurable:	lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan

OR

non-measurable:	all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly non-measurable lesions.

All measurements should be recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Lesions that are considered as truly non-measurable include the following: bone lesions; leptomeningeal disease; ascites; pleural / pericardial effusion; inflammatory breast disease; lymphangitis cutis / pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; cystic lesions.

10.2 Specifications by methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

10.2.1 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

10.2.2 Chest X-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Not only should the film be performed in full inspiration in the postero-anterior (PA) projection, but also the film to tube distance should remain constant between examinations. However patients with advanced disease may not be well enough to fulfil these criteria and such situations should be reported together with the measurements.

Lesions bordering the thoracic wall are not suitable for measurements by chest X-ray, since a slight change in position of the patients can cause considerable differences in the plane in which the lesion is projected and may appear to cause a change which is not real. These lesions should be followed by CT or MRI. Similarly, lesions bordering or involving the mediastinum should be documented on CT or MRI.

10.2.3 CT, MRI

CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

10.2.4 Ultrasound

When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

10.2.5 Endoscopy, laparoscopy

The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

10.2.6 Tumor markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

10.2.7 Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.3 Tumor response evaluation

10.3.1 Assessment of overall tumor burden and measurable disease

10.3.1.1 To assess objective response, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as defined in section 10.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

10.3.1.2 Baseline documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions total representative of all involved organs should be identified as ***target lesions*** and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent”.

10.3.2 Response Criteria

At each evaluation (see Study Calendar in Section 9.0), response will be classified as:

10.3.2.1 Evaluation of target lesions

Complete Response (CR)	disappearance of all target lesions.
Partial Response (PR)	at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progression (PD)	at least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

10.3.2.2 Evaluation of non target lesions

Complete Response (CR)	disappearance of all non-target lesions and normalization of tumor marker level.
Non-Complete Response (non-CR) / Non–Progression (non-PD)	persistence of one or more non-target lesion or/and maintenance of tumor marker level above the normal limits.
Progression (PD)	appearance of one or more new lesions. Unequivocal progression of existing non-target lesions (1).

(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the study chair.

10.3.2.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 10.3.3.1 below).

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD

PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

10.3.3 Confirmatory measurement / Duration of response

10.3.3.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after the evaluation done prior to the third course.

Note: If for some reason repeat studies to confirm changes in tumor size are not done in the time period specified above, patients will not have “confirmed response” and this will be made clear when reporting the outcome of such studies.

10.3.3.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

10.3.3.3 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10.4 Endpoint Definitions

10.4.1 Progression-free Survival: Progression-free survival will be measured from the start of treatment until the time the patient is first recorded as having disease progression, or death due to any cause. If a patient has not progressed or died, progression-free survival is censored at the time of last visit for tumor measurement.

10.4.2 Overall Survival: Overall survival will be measured, as the time from start of treatment to the date of death or the last date the patient was known to be alive.

10.4.3: Overall Toxicity: All Grade 2, 3, and 4 hematologic and nonhematologic toxicities will be assessed, as will the need for dose reductions and the need for treatment interruption or discontinuation.

10.4.4 Time to Progression: Time to progression on this regimen will be measured as the time from Study Day 1 to the time the patient is first recorded as having disease progression. If a patient never progresses while being followed, the patient will be censored at the time of last follow-up, by the date of death, or the start of another treatment, whichever comes first.

10.4.5 Time to Treatment Failure: Time to treatment failure will be measured as the time from when the patient started treatment to the time the patient is withdrawn due to: adverse events, progressive disease/insufficient therapeutic response, death, failure to return, and refused treatment/did not cooperate/withdrew consent. The date of last dose of treatment will be used as the date of event in the case that PD was not recorded earlier.

11.0 SPECIAL INSTRUCTIONS

11.1 Experimental Methods and Procedures

11.1.1 **Polymorphism:** We will isolate genomic DNA from whole blood samples. An approximate 230bp region of the gene containing the polymorphic site will be PCR amplified using a P-33 end-labeled forward primer and an unlabeled reverse primer. PCR products will be separated on sequencing gels and autoradiographed, and products will be sized by comparison to known genotypes.

11.1.2 **Quantitation of mRNA levels:** The cDNA library created from each tumor as part of this technology (RT-PCR) contains a quantitative and qualitative record of all of the tumor's expressed genes, and mRNA quantitation as well as mutations screening of 30-40 expressed genes is possible with material obtained from an average tumor biopsy. We have successfully quantitated gene expression in specimens of less than 1 mg and fine needle biopsies only by changing the PCR conditions.[83,107,150-154] The choice of the internal standard is critical for obtaining meaningful results with PCR quantitation. This gene should be one that is expressed constitutively with a level of per cell expression that is constant among different tissues or at least in similar tissues from different individuals.

11.1.3 Samples of blood and tissue should be handled in the following manner:

11.1.3.1 Tissue Specimen collection

We will collect tumor biopsies, prior to initiation of treatment and at time of tumor progression in patients enrolled in this protocol. The tissue specimen

handling will be orchestrated through the Dr Lenz's laboratory at USC. Tumor tissue may be obtained by endoscopic biopsy, radiologic biopsy, or by surgery for correlative studies (including analyses of gene expression, enzyme activity and pharmacodynamics, as appropriate for the specific protocols and the amount of tissue obtainable) and histopathologic examination. We expect these exploratory studies to provide preliminary data, which can be assessed more fully in subsequent trials in a larger patient sample size. Slides require 10 slides of unstained tumor 10 um thick of paraffin embedded tumor blocks or fresh frozen tissue. In lieu of slides, a tumor block may be sent. The tumor block should be large enough to provide the slides described above

11.1.3.2 Blood Sample Collection

Blood will be collected prior to initiation and off study. The blood will be collected to study germline polymorphisms. The blood collection will require 2 tubes of blood (one purple top - EDTA and one red top).

Dr Lenz's laboratory will receive and process information.

Heinz-Josef Lenz, MD Laboratory
USC Norris Cancer Center
1441 Eastlake Avenue, Laboratory Room #5410
Los Angeles, CA 90033
323-865-0572

Contact Dana Agafitei, project specialist: 323-865-0467 for questions about tissue or blood collection.

12.0 STATISTICAL CONSIDERATIONS

This is a two-stage phase II study to evaluate a combination of oxaliplatin, cetuximab and capecitabine as a first line therapy for patients with metastatic or unresectable gastric or gastroesophageal cancer who did not received any previous treatment for their advanced disease. The primary objective is to evaluate the efficacy of this regimen in terms of proportion of patients with progressive disease within the first 4 months of treatment. The secondary objectives are to assess response to chemotherapy, time to progression on this regimen, overall survival, as well as to document the toxicity associated with the chemotherapy and to explore molecular predictors of response, progression, survival, and toxicity to this combination of chemotherapy.

12.1 Hypothesis and Endpoints

The primary endpoint in this study will be proportion of patients with progressive disease within the first 4 months of treatment. The goal is to decide to stop the study early if a combination of oxaliplatin, capecitabine and cetuximab on this schedule shows very little promise. Studies of conventional therapies in this setting have reported median time to progression of about 4 months. Thus a 50% or more chance of progressing within the first 4 months on this regimen, would be discouraging (null hypothesis), while if 30% or less chance of progressing within the first 4 months on this regimen (alternative hypothesis), then this regimen would be promising enough to warrant consideration for further study of a combination of cetuximab, oxaliplatin and capecitabine with this schedule.

This trial accrued fourteen patients to the regimen of oxaliplatin and capecitabine (XELOX) used in the current study. An amendment was then submitted adding cetuximab to the regimen. This amendment was submitted because accrual to the XELOX regimen was poor and several publications have come out since the study was written using this regimen in gastric and gastroesophageal cancer.[77,78] The objectives of the study, besides the change in regimen, remain the same as those before the amendment, with the exception of the addition of the addition of the examination of gene expression levels and polymorphisms thought to be involved in response to cetuximab. The primary endpoint – 50% progression free survival at 4 months has been maintained, as there have been no significant advances in the treatment of gastric cancer since this study was written and 50% progression free survival at 4 months would still indicate a promising regimen. [155] The patients accrued to the regimen using just XELOX will be used to internally document how toxic the addition of cetuximab is to the XELOX regimen by comparing the toxicities between the patients that received XELOX (n=14) and the patients received XELOX + cetuximab. The fourteen patients accrued to the XELOX regimen will not be included in the sample for the the XELOX + cetuximab calculation (i.e. 27 patients will be accrued to XELOX + cetuximab regimen in the first stage and if the trial continues to the second stage and additional 26 will be accrued to the XELOX + cetuximab regimen – the 14 patients accrued to the XELOX only regimen will not be counted toward these totals).

12.2 Sample Size Calculation

A two-stage minimax design, suggested by Simon, will be used.[156] The first interim analysis will be undertaken when 27 evaluable patients are enrolled and followed at least 4 months. If 13 or more (≥ 13) patients have progressed (or go off treatment for unacceptable toxicity) prior to 4 months, then we will terminate the accrual and conclude that this regimen is not sufficiently active to warrant further study. If 12 or fewer (≤ 12) patients progress within 4 months, and if the toxicity is acceptable (see section 12.4 for details), then an additional 26 patients will be accrued, be treated, and be followed at least 4 months in the second stage. If 21 or more (≥ 21) patients in those 53 patients have progressed (or go off treatment for unacceptable toxicity) within the first 4 months, we will not recommend this regimen for further study. If 20 or fewer (≤ 20) patients in those 53 patients have progressed within the first 4 months, then we will conclude that fewer than 50% of patients progressed within 4 months and will be considered as evidence warranting further study of the regimen providing other factors, such as toxicity and survival, also appear favorable.

With the proposed design there is a 5% chance (alpha) that we will recommend this regimen for further study when the probability of progressing within 4 months is 0.5 or greater (equivalently, the median time to progression is 4 months or less) and there is a 90% chance (power) that we will recommend this regimen for further study when the probability of progressing within 4 months is 0.30 or less. If the time to progression follows the exponential distribution (at least approximately), then a decrease in the chance of progressing by 4 months, to 30%, is equivalent to an increase in the median time to progression to about 7.8 months.

The secondary endpoint in this study will be tumor response to this regimen. With 53 patients, the 95% confidence interval for the response rate will have a half-width of ±13.5% or less.

12.3 Analysis of Primary and Secondary Efficacy Parameters

The per protocol analysis will include all patients who:

- received at least 6 weeks of treatment (or who were discontinued due to progressive disease or for reason of toxicity within the first 6 weeks of study)
- had no major protocol violations (see inclusion/exclusion criteria)
- had adequate information about tumor burden at baseline
- had adequate tumor assessment information post-baseline
- received at least 50% of the anticipated treatment during the first 6 weeks.)

1) Clinical Endpoints. The outcome status (in terms of toxicity, response, reason off study, time to progression on this regimen, and survival) of all eligible patients who are registered, will be reported. Patients who complete 2 courses of therapy (i.e., 6 weeks) or who experience any Grade 2 or greater toxicity will be included in the analysis of toxicity. Patients with measurable tumor who complete two cycles of therapy, or who terminate treatment for reasons of toxicity or progression prior to completion of two cycles, will be included in analysis of the proportion of patients with progressive disease within the first 4 months of treatment, time to progression, tumor response, and progression-free survival. Patients who are not evaluable will be replaced. All eligible patients who begin treatment will be included in the analysis of overall survival. The per protocol analysis will be conducted in all patients specified as above.

a) Time to progression on this regimen, time to treatment failure, progression-free survival, and overall survival will be summarized with Kaplan-Meier plots to describe the outcome of patients treated on this protocol. The median time and 95% confidence intervals (CIs) for these time-to-event variables will be calculated. In addition the probability of progression at 4, 6, and 8 months and survival at 6, 12, and 18, months and Greenwood's standard errors will be summarized. The log-rank test will be used to examine whether prognostic factors (e.g. performance status) are associated with time to progression on this regimen, progression-free survival, time to treatment failure, or overall survival. The relative risk and corresponding 95% CIs will be used to summarize the differences in time to event of interest by prognostic factors.

b) Toxicities observed will be summarized in terms of type (organ affected, laboratory determination), severity (by NCI Common Toxicity Criteria and nadir or maximum values for the laboratory measures), time of onset (i.e. course number), duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects by the regimen (with and without cetuximab) and course. Exact tests will be used to compare the differences in the toxicities between two regimens, but as the groups represent two sequential cohorts rather than concurrently randomized arms, any findings we be considered exploratory.[157] Demographic and baseline clinical information will be presented to describe the patients treated in this study.

c) Tumor response to this regimen will be assessed using the RECIST criteria every 2 cycles (each cycle lasting 3 weeks) of a combination of oxaliplatin, cetuximab and capecitabine (with an additional assessment scheduled after 4 weeks to confirm a PR or CR). Patients who receive less than two full courses due to grade 2 or greater toxicity or progressive disease will still be evaluable for response. All responses will be reported. Response rates will be calculated as the percent of evaluable patients whose best response is a CR or PR, and exact 95% confidence intervals will be calculated for this estimate.

2) Analysis of Molecular Markers (genomic polymorphisms and gene expression).

There are two sets of analysis of molecular markers and clinical outcome in patients treated with this regimen. Based on our previous studies[84,90,107], TS, DPD, and ERCC1 mRNA levels in

tumor tissue were associated with clinical outcome in patients with advanced colorectal or gastric cancer. Initially we will verify the association of TS, DPD, and ERCC1 mRNA expression levels in tumor tissue with clinical outcome in terms of time to progression on this regimen, tumor response to this regimen, and overall survival. An established cutpoint for TS, DPD, and ERCC1 expression levels in our previous studies will be used to split patients into good (low expression) and poor prognosis (high expression) group. The cut-off levels (high/low) follows as:

TS/β-actin: 4.1×10^{-3}
DPD/β-actin: 1.2×10^{-3}
ERCC-1/β-actin: 7.4×10^{-3}

A univariate survival analysis (Kaplan-Meier plots and log-rank tests) will be used to examine the association between TS, DPD, and ERCC1 expression levels (low vs. high) and time to progression on this regimen and overall survival. A Fisher's exact test will be used to examine the associations between each of those gene expressions (low vs. high) and tumor response to this regimen (CR+PR vs. PD+SD). A stratified analysis will also be considered to reexamine those associations if baseline demographic characteristics and clinical variables are statistically significantly associated with clinical outcome.

Secondly, we will examine associations between other molecular biomarkers and clinical outcome. Categorical molecular determinants (genomic polymorphisms of VEGF, TGF-β, TS, ERCC1 and XPA) will be summarized overall and by response and presence of toxicity, using contingency tables and percentages. The association of those molecular determinants with time to progression on this regimen or overall survival will be assessed by constructing the Kaplan-Meier curves according to the polymorphisms observed. The log-rank test will be used to test for association formally.

Gene expression levels (VEGF, TGF-β, IL-8, IL-10, Cox-2, EGFR, EGF, TP, XPA, p53 and p21) will be summarized overall and according to response and toxicity (if numbers permit), using plots and medians, quartiles and ranges – or if a transformation is found to render the data compatible with the normal assumptions, with means, standard deviations, and 95% confidence intervals. The associations with time to progression or overall survival will be assessed by categorizing the measures of gene expression at median and optimal cutpoints by constructing Kaplan-Meier plots. Again, the log-rank test will be used to test for association formally.

These analyses of the molecular biomarkers except TS, DPD, and ERCC1 gene expressions in tumor tissue will be descriptive and exploratory, in order to identify questions and patterns for future study. The numbers of patients expected (nearly 100% for the specimens obtained at baseline and once after start of treatment) will not permit formal comparisons of patients according to toxicity and response, but will allow us to estimate the patient-to-patient variability in this well-defined group of patients, as well as the change at the time of progression. These analyses will be descriptive in nature.

3) Analysis of Molecular Markers: Power Analysis

We anticipate that the median time to progression on this regimen is about 8 months, and the median time to survival is about 12 months, and the response rate is about 40% in patients with metastatic or unresectable gastric or gastroesophageal junction cancer receiving this regimen as a first line therapy. We estimate that there will be about 50% of patients with high expression levels of TS, DPD, or ERCC1 in tumor tissue. The percentage of patients with other unfavorable molecular biomarkers including genomic polymorphisms may vary in a greater extent. With 53 patients, we will have at least 74% power to identify the differences of 30% (equivalent to 2.44 in hazard ratio) in proportions of not progressing at 8 months when

the percentage of patients with unfavorable outcome varies from 25% to 75% (Table 1). There is a power of at least 76% that we will observe the difference of 30% (equivalent to 2.44 in hazard ratio) in proportions of survival at 12 months (Table 1). We will also have at least 81% power to detect a difference of 40% (20% vs. 61%) in the response rate between the poor prognosis (about half of patients) and good prognosis groups.

Table 1. Power to Test Differences in Time to Progression or Survival by Prevalence of high TS, DPD, or ERCC1 expression or other molecular biomarkers with Poorer Outcome

% of Patients in the poor prognosis group	Power to Detect a Difference of 0.30 in Proportion of not Progressing at 8 months	Power to Detect a Difference of 0.30 in Proportion Surviving at 12 months
75%	74%	76%
67%	82%	83%
50%	87%	88%
33%	84%	84%
25%	78%	79%

Notes: Power calculations using methods in Rubinstein, Gail, and Santner, as programmed by Buckley[158], are based on a two-sided .05-level logrank test with annual accrual rate of 30 patients per year, 2 years of additional follow-up for time to progression and 4 years of additional follow-up for survival, and at most 2% of patients lost to follow-up annually.

12.4 Monitoring Unacceptable Toxicity

Although we expect that this regimen to be well tolerated, the guidelines listed below will be used to raise a flag if the number of patients who experience unacceptable toxicity is large enough to strongly suggest that the true probability of unacceptable toxicity is > 20%. Unacceptable toxicity will be defined as:

(a) any Grade 3 non-hematologic toxicity not reversible to Grade 1 or less within 96 hours with the exception of Grade 3 diarrhea or
(b) any Grade 4 non-hematologic toxicity or
(c) any Grade 4 hematologic toxicity not resolving to Grade 1 or less within 5 days, despite supportive care or
(d) Grade 4 neutropenia associated with fever or
(e) Grade 4 thrombocytopenia.

An unacceptable toxicity, regardless of attribution, observed during any course, will be used in the decision to suspend accrual.

To be evaluable for excessive toxicity a patient must complete a minimum of 2 courses of treatment (6 weeks) or have experienced unacceptable toxicity. Patients who do not complete 2 courses and who do not experience any unacceptable toxicity will not be used in the decision to continue or suspend accrual to the trials, for reasons for excessive toxicity. Every time unacceptable toxicity is observed, the number of patients (X) who have experienced unacceptable toxicity will be compared to the number of patients (N) who are evaluable for excessive toxicity. If the number of patients, N, is greater than N_X, the number given in column 2 of the Table 2, below, then accrual will not be suspended. If N is less than or equal to N_X, then accrual will be suspended for review of the data.

Table 2: Criteria for Continuing Accrual

X = Total Number of Patients with Unacceptable Toxicity	N_X: Suspend the Trial if Number of Evaluable Patients Is Less Than or Equal to:
4	≤ 7

5	≤ 10
6	≤ 14
7	≤ 17
8	≤ 21
9	≤ 25
10	≤ 29
11	≤ 30
12	≤ 33
13	≤ 37
14	≤ 41
15	≤ 45
16	≤ 49
17	≤ 50
18	≤ 54

Using this rule with 53 patients, the probability of correctly suspending this regimen for review toxicities is 0.84 if the true chance of unacceptable toxicity is 35% or greater. The probability of falsely suspending this regimen for review toxicities is 0.03, if the true chance of unacceptable toxicity is ≤ 15%. Estimations of the probabilities of suspending this regimen are based on 2,000 simulations.

13.0 REGISTRATION, REGULATORY AND DATA SUBMISSION GUIDELINES

All patients will have signed an informed consent for participation in research activities in accord with all institutional, NCI and Federal regulations, and will have been given a copy of the Experimental Subject's Bill of Rights, or the Experimental Subject's Rights required by the state the treating institution is in.

Note: At the time of registration, two copies of a signed and dated patient Informed Consent form with Bill of Rights must be available (an original for patient's medical chart; one copy for the patient; and the other for the CISO office).

13.1 Registration Procedures

All registration will be done centrally through USC Norris Cancer Center (NCC). Patients treated at Norris Cancer Center will be registered according to regular procedure by the research nurse or data manager into the NCC Clinical Trials database. Patients participating at other sites will be registered by contacting the project manager of this protocol at USC Norris. In order to enroll a patient outside institutions should contact:

Sarah Cole, M.S.
Project Manager
1441 Eastlake, Room 3425A (MS 9173)
Los Angeles, CA 90033
Phone: (323) 865-0820
Fax: (323) 865-0061
Pager: (877) 323-8539

Once Ms. Cole is contacted, a completed Eligibility/Registration worksheet along with the signed informed consent should be faxed to Ms. Cole at the fax number listed above. The patient's eligibility will then be confirmed and a confirmation with the patient's study ID will be faxed back to the site.

13.2 Guidelines for the conduct of multi-center trials

13.2.1 Protocol Document and Amendments

Each participating institution will use the protocol document as approved by Roche, Synothofi-Aventis, and Bristol-Myers Squibba and the USC IRB. It should not be re-written or modified by any one other than the Protocol Chairperson at the Coordinating Center who is solely responsible for obtaining USC IRB approval and distributing the protocol to all participants as well as formulating protocol amendments for USC IRB approval and distributing the protocol amendments to all participants. After any amendment or revision has been approved by the USC IRB, the amended version will be distributed to participating institutions for submission to their respective committees.

Informed consents from sites other than USC and LA County must indicate that data and will be sent to USC.

13.2.2 Regulatory Issues

All participating sites will be required to submit the following to USC prior to study activation:

1572
The P.I.'s Curriculum Vita and medical license
IRB approval letter of the protocol and informed consent
IRB stamped informed consent (the informed consent must be submitted to USC for review and approval prior to submission to the local IRB)
HIPAA authorization

All subsequent correspondence to the IRB and approval letters from the IRB must also be submitted to USC. These documents include, but are not limited to:

Continuing Annual Review
Amendments
Serious Adverse Events

All of these regulatory documents should be sent to:

CISO Regulatory Manager
USC/Norris Comprehensive Cancer Center
1441 Eastlake Ave.
LA, CA 90033
323-865-0454
323-865-0089 Fax

13.2.3 Data Submission

All data forms should be mailed to USC project manager (Ms. Cole) at the address listed in section 13.1. The original forms should be retained at the site and a copy mailed to USC.

Once a patient is enrolled, Baseline Records (Including health problems (evaluated using the CTCAE revised version 3.0) at baseline, prior chemotherapy, radiation therapy and surgery) should be mailed to USC within three weeks of registration. Data on treatment (including concomitant measures/medications, cycle records/assessments, changes in treatment, side effect/toxicity forms (evaluated using the CTCAE revised version 3.0) and pill diaries) should be mailed to USC for each cycle, every two cycles, within three weeks of completion of the second cycle. Once a patient comes off treatment, an off treatment form should be completed and mailed within a week to USC. Once off study, patients should be followed every three months for disease status, treatment and survival information. A follow-up form should then be mailed within a week to USC. Copies of the tumor specimen and blood collection forms should be sent with the samples, to the address listed on the form. The original tumor specimen and blood collection form should be retained at the site and one copy sent to Ms. Cole.

13.2.4 Data Quality Monitoring

It is the policy of USC/Norris Cancer Center that 20% of patients accrued to a trial and treated at USC should be audited by the Quality Assurance Committee for data accuracy. A minimum of two patients are required to be audited (if accrual is such that 20% would be less than two).

For this protocol, patients treated at other institutions should be audited according to the data quality monitoring plan for their treating institution.

13.2.5 Adverse Events/Evaluation of Safety.

All Adverse Events will be monitored on an ongoing basis by the protocol chairperson, Dr. Syma Iqbal, 323-865-3907. The adverse events will be tracked via the submission of toxicity forms to the project manager and reporting of SAE's (as specified in sections 8.12 and 8.13). Dr. Iqbal will be responsible for notifying the PI's at other institutions of SAE's experienced at any of the participating institutions.

14.0 MINORITIES AND WOMEN STATEMENT

This study will be open to patients undergoing treatment at USC/Norris Cancer Hospital and LAC+USC Medical Center.

ETHNIC AND GENDER DISTRIBUTION OF NEWLY DIAGNOSED CANCER PATIENTS[1] IN LOS ANGELES COUNTY IN 1999[2]

Primary Site of Tumor	Total # of Patients	Males %	Females %	White %	Black %	Hispanic %	Asian/Other %
ALL INVASIVE TUMORS	**33,194**	**49**	**51**	**61**	**12**	**18**	**10**
ORAL CAVITY/PHARYNX	**749**	**66**	**34**	**64**	**13**	**12**	**11**
DIGESTIVE SYSTEM	**6,727**	**52**	**48**	**56**	**12**	**18**	**13**
Esophagus	294	72	28	61	13	17	10
Stomach	823	60	40	41	12	27	21
Colon	2,677	49	51	62	14	14	11
Rectum/Anus	547	49	51	63	10	17	10
Liver	479	66	34	34	10	29	27
Pancreas	718	50	50	63	11	18	9
RESPIRATORY SYSTEM	**4,341**	**56**	**44**	**64**	**15**	**11**	**10**
Lung and Bronchus	3,949	54	46	65	15	11	10
BONES AND JOINTS	**72**	**58**	**42**	**43**	**11**	**33**	**13**
SOFT TISSUE INCL. HEART	**223**	**54**	**46**	**49**	**14**	**27**	**9**
MELANOMAS OF THE SKIN	**1,101**	**56**	**44**	**91**	**1**	**7**	**1**
BREAST	**5,489**	**1**	**99**	**63**	**11**	**16**	**11**
FEMALE GENITAL SYSTEM	**2,334**	**0**	**100**	**54**	**9**	**26**	**11**
Cervix Uteri	573	0	100	35	10	45	10
Corpus Uteri	954	0	100	63	10	18	9
Ovary	684	0	100	56	8	23	13
MALE GENITAL SYSTEM	**5,404**	**100**	**0**	**59**	**16**	**18**	**7**
Testis	195	100	0	54	2	41	4
Prostate	5,176	100	0	59	17	17	7
URINARY SYSTEM	**1,549**	**65**	**35**	**65**	**11**	**18**	**7**
Invasive Bladder	656	73	27	73	8	12	8
Renal	830	59	41	58	13	23	7
EYE AND ORBIT	**59**	**63**	**37**	**66**	**7**	**24**	**3**
BRAIN /NERVOUS SYSTEM	**481**	**55**	**45**	**61**	**8**	**24**	**6**
ENDOCRINE/THYROID	**656**	**26**	**74**	**53**	**6**	**26**	**15**
HODGKIN'S DISEASE	**245**	**49**	**51**	**53**	**10**	**33**	**4**
NON-HODGKIN'S LYMPHOMA	**1,430**	**55**	**45**	**62**	**8**	**20**	**10**
MULTIPLE MYELOMA	**408**	**57**	**43**	**49**	**23**	**20**	**8**
LEUKEMIA	**841**	**61**	**39**	**56**	**8**	**26**	**9**
Lymphocytic Leukemia	330	60	40	55	10	31	5
Non-Lymphocytic Leukemia	511	61	39	57	8	23	12
***IN SITU* DISEASE**							
in situ Breast	1,063	1	99	67	10	12	11
in situ Bladder	648	77	23	78	6	8	8
in situ Melanoma	658	54	46	92	1	6	1

(1) Invasive cancer with the inclusion of specified *in situ* breast, melanoma and bladder cancer cases.

Data provided by Los Angeles County Cancer Surveillance Program; Department of Preventive Medicine; University of Southern California; 1540 Alcazar St.; LA CA 90033.

15.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional, NCI, and Federal regulations concerning the Informed Consent form will be fulfilled.

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Appendices

Appendix 1: Hand–Foot Syndrome Grading Scale

(Palmar-Plantar Erythrodysesthesia)*

Grade	Clinical Domain	Functional Domain
1	Numbness, dysesthesia / paresthesia tingling, painless swelling or erythema	Numbness, dysesthesia / paresthesia tingling, painless swelling or erythema
2	Painful erythema, with swelling	Discomfort which affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

APPENDIX II **OUTCOME OF PREGNANCY REPORT**

Report number :

PART I : HISTORY AND START OF PREGNANCY

PATIENT

Initials : Surname : _____ First name : _____ Date of birth : _____

Weight : _____ kg Height : _____ cm Profession : _____

FATHER OF CHILD : Age : _____ Profession : _____

Details of any chemotherapy : no yes Details : _____

_____

HISTORY/BACKGROUND (Patient)

Rh : + – Smoking : _____ cig./day Alcohol : _____ glasses/day

Substance abuse : Details : _____

_____

Previous immunizations : Rubella : no yes not known

Toxoplasmosis : no yes not known

Gynaecological details : Contraception : oral local IUD

Normal menstrual cycles : no yes

Treatment for sterility : no yes Details : _____

_____

Obstetric details : Number of pregnancies : _____ Number of births : _____

Miscarriage : _____

Terminations (d ates) : _____ Context : _____

Therapeutic termination : _____ Context : _____

in utero deaths : _____

Number of normal children living : _____ Number of children deceased : _____

Number of children with malformations : _____

Medical details : HBP : no yes Diabetes : no yes

Epilepsy : no yes Psychiatric illness : no yes

Other : _____

Serology : HIV : no yes not known

Hepatitis : Details : _____

_____

FAMILY HISTORY (Mother and Father)

Malformations : no yes not known

Children dying young : no yes not known

Psychomotor retardation : no yes not known

Consanguinity : no yes not known

Hereditary disease : no yes not known

Other : _____

_____

if a « yes » box is ticked, Details : _____

_____

CURRENT PREGNANCY

Details of any medical assistance during pregnancy : _____

_____

LMP : _____ Start of pregnancy : _____ Gestational age : _____ WA or WP : _____

Expected date of delivery : _____ Multiple pregnancy : no yes

Place (with address) : _____

Any drug exposure :

Acute overdose : no yes

Name of medicines	Route of administration	Dose/Day	Start date	End date or Duration	Indication

ADDITIONAL INFORMATION *:* _____

_____

_____

DOCTOR'S STAMP **DATE and SIGNATURE**

OUTCOME OF PREGNANCY REPORT [X]

Report number :

PART II : COURSE AND OUTCOME OF PREGNANCY

PATIENT

Initials : Surname : _____ First name : _____ Date of birth : _____

COURSE OF PREGNANCY

Exposure(s) : Smoking : _____ cig./day Alcohol : _____ glasses/day

Substance abuse : Details : _____

_____

Illness(es) during pregancy : HBP Diabetes Infection Other : _____

Medication taken during pregnancy :

Were treatment at the start of pregnancy continued ? no yes Details : _____

_____

Name of medicines	Route of administration	Dose/Day	Start date	End date or Duration	Indication
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

Hospitalization during pregnancy : no yes Reason(s) : _____

Antenatal check-up : no yes

Ultrasound (dates and results) : _____

Specific tests : Results : _____

Retarded growth in utero : no yes

OUTCOME OF PREGNANCY

Live newborn : no yes see below

Miscarriage : Date : _____ Term : _____ WA

Malformation : no yes Details : _____

Termination : Date : _____ Term : _____ WA

Histopath : no yes Details : _____

Therapeutic termination : Date : _____ Term : _____ WA

Ectopic pregnancy : in utero death : no yes Term : _____ WA

DELIVERY

Date : _____ Term : _____ WA

Normal Induced Caesarian

Fœtal distress : no yes Chronic Acute

Amniotic fluid : Clear Coloured

Medication during labour : no yes not known

if yes, give details : _____

_____

Placenta normal : no yes not known

Post-partum : normal pathological Details : _____

_____

Further information : _____

_____

CONDITION OF NEWBORN

Sex : F M Weight : _____ kg Length : _____ cm

HC : _____ cm Premature : no yes Dysmature : no yes

Apgar : 1 min 5 min

Intensive care : no yes not known

Malformations : no yes Details : _____

Neonatal illness : no yes Details : _____

Transfer to intensive care unit or paediatrics department
no yes Duration : _____

Address of department : _____

Apparent outcome : _____

Infant to be followed up by (Doctor's name and address) : _____

Breast-feeding : no yes

ADDITIONAL INFORMATION *:* _____

_____

_____

DOCTOR'S STAMP **DATE and SIGNATURE**