

Phase II Study of Erlotinib (Tarceva™) Combined with Chemoradiation and Adjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer

Title: Phase II Study of Erlotinib (Tarceva™) Combined with Chemoradiation and Adjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer

Principal Investigator:

Amol Narang, MD
Weinberg 1440-Oncology
401 North Broadway,
Baltimore MD 21231-2410
(410) 955 7390
Anarang2@jhmi.edu

Co-Investigators:

Ross Donehower, MD	Daniel Laheru, MD
Deborah Frassica, MD	Barish Edil, MD
Michelle Rudek, PharmD/PhD	Joseph Herman, MD, M.Sc.
Richard Schulick, MD	Timothy Pawlik, MD
Christopher Wolfgang, MD	Dung Le, M.D.
Mary E. Griffith, RN	Luis Diaz, MD
Michael Choti, MD	Nilofer Azad, MD
Barbara Biedrzycki, PhD	Lei Zheng, MD, PhD

Protocol Manager:

Helen Kim
Hkim91@jhmi.edu
Phone: 410-614-3950

Terrence Caldwell
caldwte@jhmi.edu
Phone: 443-287-1889

Research Nurses:

Ella-Mae Shupe, R.N.
Eburke4@jhmi.edu
Phone: 410-502-9243

Shirl DiPasquale, R.N.
Sdipasq1@jhmi.edu
Phone: 410-614-3158

Kristi Purcell, R.N.
Kpurcel2@jhmi.edu
Phone: 410-502-9242

Statisticians:

Amanda L. Blackford, ScM
alapide1@jhmi.edu
Phone: 410.614.0361

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IND: Exempt

Phase II Study of Erlotinib (Tarceva™) Combined with Chemoradiation and Adjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer

PROTOCOL SYNOPSIS

Objectives

Primary

1. To seek preliminary evidence of antitumor activity (progression free survival) of Erlotinib in combination with standard adjuvant chemoradiation and chemotherapy in patients with resected adenocarcinoma of the pancreas.

Secondary

1. To characterize the toxicity profile of Erlotinib in combination with adjuvant chemoradiation in patients with resected pancreatic cancer.
2. To evaluate the quality of life of patients receiving Erlotinib based chemoradiation prior to treatment (after surgery), one month following treatment and every 3-4 months thereafter for one year.
3. To seek preliminary evidence of antitumor activity (overall survival) of Erlotinib in combination with standard adjuvant chemoradiation and chemotherapy in patients with resected adenocarcinoma of the pancreas.

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Study Schema: Adjuvant Chemoradiation followed by Adjuvant Chemotherapy

Chemoradiation:

- Baseline EORTC QLQ C-30/ PAN26 QOL
- Capecitabine 800 mg/m² PO BID (1600 mg/m²/day total) (5 days on/ 2 days off regimen) AND
- Erlotinib 100 mg PO QD (1 hour prior to Capecitabine) (both given daily without interruption) AND
- Radiotherapy 50.4 Gy delivered over 28 fractions (Mon-Fri) (*Note: we will have the ability to treat to 54.0 Gy over 30 fractions if a patient presents with close or positive margins after resection)



Four-Eight weeks of recovery from toxicity.



Adjuvant Maintenance Therapy:

- Gemcitabine 1000 mg/m² D1,8, and 15 every 28 days x 4 cycles
- Erlotinib 100 mg PO QD x 4 months

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Trial design:

This study is a phase II trial of erlotinib in combination with chemoradiation in patients with resected stage I/II adenocarcinoma of the pancreas who are candidates for adjuvant chemoradiation. Eligible patients will receive adjuvant treatment with erlotinib 100 mg plus Capecitabine 800 mg/m² PO BID (5 days on/ 2 days off regimen) and External Beam Radiation Therapy (EBRT) at doses of 50.4 Gy in 28 fractions after pancreatectomy (Dosing for capecitabine and erlotinib was amended after considering the toxicity profile of the first 6 patients). Approximately 4-8 weeks after the conclusion of chemoradiation, it is recommended patients will continue treatment with 4 cycles of gemcitabine 1000 mg/m² days 1, 8, and 15 every 28 days plus daily erlotinib 100 mg.

Patient population:

- Resected adenocarcinoma of the pancreas and candidate for adjuvant chemoradiation.
- ECOG performance status 0-1.
- Informed consent and ability to comply with treatment plan.
- Adequate bone marrow, renal and liver function.
- No previous radiation therapy to the abdomen
- No previous chemotherapy for pancreatic cancer

Investigational product, dosage and mode of administration:

Erlotinib 100-mg oral daily dose.

Statistical analysis:

Toxicity will be assessed weekly as mild or severe during chemoradiation using the NCI-CTCAE Version 3 criteria and will be summarized using descriptive statistics.

Progression free and overall survival for patients treated with erlotinib in combination with chemoradiation and chemotherapy will be described using Kaplan-Meier methods. The relationships between these effects and time to disease progression will be tested using Cox proportional hazards model. Quality of life questionnaires will be scored per the EORTC guidelines. A fixed sample size of 40 patients will be enrolled. This number includes 6 patients from the initial portion of the trial which used the same treatment regimen stated in the above design.

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1. OBJECTIVES

This is a phase II study of erlotinib in combination with chemoradiation and adjuvant chemotherapy in patients with resected pancreatic cancer.

The objectives of the trial are:

Primary

1. To seek preliminary evidence of antitumor activity (progression free survival) of Erlotinib in combination with standard adjuvant chemoradiation and chemotherapy in patients with resected adenocarcinoma of the pancreas.

Secondary

1. To characterize the toxicity profile of Erlotinib in combination with adjuvant chemoradiation in patients with resected pancreatic cancer.
2. To evaluate the quality of life of patients receiving Erlotinib based chemoradiation prior to treatment (after surgery), one month following treatment and every 3-4 months thereafter.
3. To seek preliminary evidence of antitumor activity (overall survival) of Erlotinib in combination with standard adjuvant chemoradiation and chemotherapy in patients with resected adenocarcinoma of the pancreas.

2.0 INTRODUCTION:

2.1. Background

2.1.1. Pancreatic Cancer

Pancreatic cancer remains a devastating disease. In 2008, approximately 38,000 patients will be diagnosed with pancreatic cancer and 35,000 will die of their disease(1). At the time of diagnosis, 80% of patients have locally advanced or advanced disease for which no curative therapy exist. Seventy to eighty percent of patients treated with curative intent will recur in the first two years after surgical resection and will succumb to their disease (2, 3). The most recent outcome update from the Johns Hopkins Hospital series (N=616) showed that the median (21.2), 2-year (43.9%), and 5-year (20.1%) were still poor despite aggressive management with adjuvant 5-FU based chemoradiation(4). The standard of treatment for patients with advanced disease or for those who recur after surgical resection is single agent gemcitabine. In phase III studies, treatment with gemcitabine resulted in a response rate of $\approx 5\%$, a median survival less than 6 months, and a 1-year survival of 18 % (5). New therapeutic strategies are clearly needed in this

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disease. The Pancreatic Cancer Research Group at Johns Hopkins has pioneered novel treatments for patients with resectable pancreatic cancer including different regimens of chemoradiation as well as allogeneic vaccines (2)(6).

2.1.2. EGFR as a Target for Anticancer Drug Development(7).

The epidermal growth factor receptor (EGFR) is a member of a large family of growth factor receptor tyrosine kinases that share a common structure composed of an extracellular ligand binding domain, a short transmembrane domain, and an intracellular domain that has tyrosine kinase activity. Binding of the cognate ligand, for example, EGF or transforming growth factor (TGF α) to the extracellular domain of EGFR initiates a signal transduction cascade that can influence many aspects of tumor cell biology; these include growth, survival, metastasis, and angiogenesis, as well as tumor cell sensitivity to chemotherapeutic and radiotherapeutic drugs. Tyrosine phosphorylation provides docking sites on the EGFR for recruitment of proteins that are either direct substrates for EGFR-mediated phosphorylation, or adaptor proteins that link the receptor to a cascade of “downstream” biochemical reactions, for example, the ras-raf-MAPK-*fos* pathway, which drives tumor cell proliferation. Several studies have described amplification of the EGFR gene, mutations of the EGFR gene and overexpression of the EGFR surface protein in a number of tumor types, including up to 80% of pancreatic cancer. Thus EGFR is an attractive target in developing new treatments for cancer. Currently, several agents targeting the EGFR pathway have been approved for lung cancer (gefitinib and erlotinib) and colon cancer (erbitux).

2.1.3. Erlotinib (Tarceva®) (8)

Erlotinib (Tarceva®) is an oral quinazoline derivative that is a signal transduction inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. It has been developed as an oral antitumor agent and has been shown to have human antitumor activity in numerous preclinical and clinical trials. Erlotinib is currently approved for the treatment of patients with chemotherapy refractory non-small cell lung cancer. Details about this agent can be found in the package insert.

In phase I clinical trials, Erlotinib resulted in dose dependant diarrhea and cutaneous toxicity as the more relevant side effects. The maximum tolerated dose of the agent administered on a daily continuous basis was 150 mg. At this dose level, erlotinib was well absorbed resulting in plasma levels above the minimum concentration needed to inhibit the EGFR in preclinical models. In addition, evidence of dose dependent antitumor inhibition of the EGFR was documented in serial skin biopsies (9).

2.1.4. Targeting the EGFR in Pancreatic Cancer

The rationale to target the EGFR in pancreatic cancer is provided by preclinical and clinical studies. In preclinical models, administration of erlotinib to pancreatic cancer xenograft resulted in tumor growth inhibition as well as apoptosis (10). In addition, preclinical investigations have shown that the combination of inhibitors of the EGFR with chemotherapy results in increased antitumor activity in preclinical models of pancreatic cancer (11). In clinical trials, the anti

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EGFR antibody erbitux resulted in 12% response rate in patients with EGFR positive pancreatic cancer in combination with gemcitabine (12). Importantly, a recent randomized phase III clinical trial in which we participated demonstrated a superior survival in patients with advanced pancreatic cancer treated with gemcitabine in combination with erlotinib when compared with gemcitabine alone (13). This study is relevant for several reasons: a) is the first study to show that a targeted agent has activity in pancreatic cancer after a large number of negative trials; b) showed that EGFR targeted agents combined with chemotherapy are superior to chemotherapy alone. This study led to the regulatory approval of erlotinib in patients with pancreatic cancer.

2.1.5. Rationale for adjuvant chemoradiation in pancreatic cancer.

The optimal postoperative treatment of patients with resected pancreatic cancer is still debatable. Based on the results of a trial conducted under the auspices of the GITSG that compare adjuvant chemoradiation with 5-Fluorouracil and radiation therapy versus control and that showed a survival improvement in treated patients. Chemoradiation has been accepted as the standard of care in the USA. The GITSG study has been criticized for different reasons including the small sample size. Subsequent studies have been controversial with regards to the overall impact of chemoradiation in patients with pancreatic cancer. More recent trials have actually shown that chemotherapy is the superior treatment modality in this situation. Once again, methodological flaws limit the acceptability of these results (2)(14).

The Johns Hopkins Hospital is one of the most experienced centers in the treatment of patients with pancreatic cancer. Phase II studies conducted for over the last decade in which different chemotherapy regimens were combined with radiation therapy have resulted in a median survival of ≈ 20 months which is comparable to the best results obtained using other strategies (4). More recently, chemoradiation has been used as a platform to add innovative vaccine strategies developed at Hopkins (6). While there are several regimens available, our standard approach has been a combination of infusional 5-FU administered concurrently with radiation therapy and gemcitabine. This regimen is the control arm of the RTOG 9704 phase III studies which has completed enrollment and was recently reported(15).

2.1.6. Rationale for Capecitabine (Xeloda™) in patients with pancreatic cancer.

Capecitabine (Xeloda™) is an oral pro-drug that is absorbed unchanged in the GI tract and subsequently undergoes a series of enzymatic conversions into 5-FU in tumor cells. It has been approved for use in patients with metastatic breast and colon cancer, and is being investigated in numerous other tumor types. Its activity is felt to be similar to continuous infusion 5-FU, since sustained blood levels are maintained with twice-daily oral dosing. The recommended oral dose is 2500 mg/m² in two divided doses twelve hours apart for 14 days, followed by a 7-day rest period. Several randomized trials have shown that this dose of capcitabine was comparable to 5-FU/leucovorin in patients with advanced or metastatic colorectal cancer (16). Capecitabine either alone or in combination with leucovorin has several advantages including improved response rates, favorable toxicity profiles, and convenience. However, no significant differences in overall survival, median duration of response, and median time to disease progression were seen (17). More recently, capecitabine has demonstrated superior survival as compared to single agent

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5-FU and leucovorin in the adjuvant setting in patients with colorectal cancer. In pancreatic cancer, single agent capecitabine resulted in 7-8 % objective response rate and a 24% clinical benefit response (18).

In addition to simulating continuous infusion 5-FU, which has been shown to be superior to bolus dosing in the post-operative setting, capecitabine has several properties that may enhance its selectivity for tumor cells. Capecitabine has been shown to selectively upregulate thymidine phosphorylase (TP), which releases 5-FU from 5'FUdR in the final enzymatic step of conversion from Capecitabine to 5-FU, in tumor cells (19). Following administration of Capecitabine, 5-FU levels are on average 3 times higher in tumor tissue than in surrounding healthy tissue (20). Correlation between tumor susceptibility to Capecitabine and the TP: dihydropyrimidine dehydrogenase (DPD, which catabolizes 5-FU to its metabolite dihydrofluorouracil) ratio has been shown (21).

Based on preclinical data, using Capecitabine combined with radiation therapy has several theoretical advantages. Radiation may increase the activity of Capecitabine by increasing levels of thymidine phosphorylase (TP) in tumor cells (19). Clinical trials have been conducted with Capecitabine combined with radiation therapy in patients with rectal cancer. A phase I dose-finding trial of Capecitabine combined with pelvic radiotherapy (50.4 Gy) showed the MTD to be 1000 mg/m² BID, with the recommended phase II dose being 825 mg/m² BID (22). A phase II trial combining neoadjuvant Capecitabine 825 mg/m² BID, leucovorin 20 mg/ m²/day, and radiation (50.4 Gy), followed by surgery 6 weeks later, has also been published showing acceptable toxicities (23). The combination is being further investigated in several phase III trials. Similarly, the combination of capecitabine with radiation therapy has been frequently used at doses of 800 mg/m² BID in patients upper GI malignancies with good tolerability (24).

2.1.7. Rationale for adding Erlotinib to Capecitabine and radiation therapy

The combination of inhibitors of the EGFR with chemotherapy and radiation therapy is attractive because the antiproliferative effects of these different therapeutic modalities are, in general, synergistic. The combination of an EGFR inhibitor with radiation therapy is particularly appealing. There is preclinical data indicating that one of the mechanisms by which tumor cells became resistant to the apoptotic and antiproliferative effects of radiation therapy is through paracrine activation of the EGFR by TGF α , which is released after radiation exposure. Inhibition of the EGFR has been demonstrated in preclinical models to block the antiapoptotic effects of TGF alpha shedding and to restore the apoptotic response of tumor cells to radiation (25). In addition, inhibition of the EGFR also been shown to increase TP in human cell lines, which suggests additive activity when combined with Capecitabine. Preliminary results from a trial combining another EGFR inhibitor increased the conversion of capecitabine to 5-fluorouracil and augmented 5-FU AUC_{0- ∞} (unpublished data Laheru, Hidalgo, and Rudek). While these are all preclinical studies, they all show mechanisms by which combining inhibition of the EGFR, Capecitabine, and radiation may have potent and selective antitumor activity.

The initial portion of this protocol enrolled 12 patients which combined erlotinib, capecitabine and radiation therapy. A planned interim analysis of the first 6 patients who completed the course of adjuvant chemoradiation while on study showed increased fatigue and gastrointestinal

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complaints with oral daily capecitabine 800mg/m² bid, erlotinib 150 mg daily, and concurrent radiation. The capecitabine dosage was thus adjusted to 800mg/m² PO bid to be administered on a “5 days on/ 2 days on” regimen with erlotinib changed to 100 mg daily. With this regimen, the subsequent 6 patients have successfully completed the chemoradiation portion of the protocol successfully without any serious adverse events. The next 34 patients will be treated per this regimen to make a total of 40 subjects enrolled.

3.0 ELIGIBILITY CRITERIA

3.1. Inclusion criteria

1. Resection of a stage I/II pancreatic adenocarcinoma of the pancreas (R0/R1) and a candidate to receive postoperative adjuvant chemoradiation. R2 (□acoscopic resection) based on the surgeons operative note will be excluded from the study.
2. Aged 18 years or older.
3. ECOG performance status ≤ 1 .
4. The effects of Erlotinib and Capecitabine on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
5. Patients must have normal organ and marrow function as defined below:

leukocytes	$\geq 3,000/\mu\text{l}$
absolute neutrophil count	$\geq 1,500/\mu\text{l}$
platelets	$\geq 100,000/\mu\text{l}$
total bilirubin	$\leq 2 \text{ mg/dL}$
AST(SGOT)/ALT(SGPT)	$\leq 5 \text{ X institutional upper limit of normal}$
creatinine	$\leq 2 \text{ mg/dL}$
aPTT	$< 40 \text{ seconds,}$
PT	$< 2 \text{ seconds more than ULN.}$

6. Provision of written informed consent
7. Patients must have a working knowledge of English in order to complete the quality of life questionnaires. Patients that do not meet this requirement will be exempt from the QoL assessment, but remain eligible for all other components of the study.

3.2. Exclusion criteria

1. Known severe hypersensitivity to Erlotinib any of the excipient of this product. Hypersensitivity to Capecitabine, doxifluridine, or 5-FU.

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2. Other coexisting malignancies or malignancies diagnosed within the last 5 years, with the exception of basal cell carcinoma, non-invasive early stage bladder cancer (<T1), and cervical cancer in situ.
3. Uncontrolled, intercurrent illness including (but not limited to) ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
4. Concomitant use of phenytoin, carbamazepine, barbiturates, rifampicin, phenobarbital, or St John's Wort. Careful monitoring of PT/INR must be done for patients taking Warfarin.
5. Incomplete healing from previous oncologic or other major surgery.
6. Gastrointestinal tract disease resulting in an inability to take oral medication.
7. Pregnant women are excluded from this study because Erlotinib is an epidermal growth factor inhibitor with the potential for teratogenic or abortifacient effects based on the data suggesting that EGFR expression is important for normal organ development. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Erlotinib, breastfeeding should be discontinued if the mother is treated with Erlotinib. Capecitabine is also potentially teratogenic and its metabolites can be found in breast milk.
8. Patients with known AIDS or who are HIV-positive on anti-retroviral therapy are excluded since patients' immune deficiency are at increased risk of lethal infection when treated with marrow-suppressive therapy, and interactions between Erlotinib and anti-retroviral therapy are unknown. If patients have known risk factors of HIV they should be tested based on the discretion of the treating oncologist.
9. Any evidence of clinically active interstitial lung disease (patients with chronic stable radiographic changes who are asymptomatic need not be excluded).
10. Previous radiation to the abdomen.
11. Previous chemotherapy for pancreatic cancer.

4.0. TREATMENT

4.1. Overview

This combination of therapies, while not previously tested together, is not expected to cause excessive toxicity based on the results of several phase I and II trials. As discussed above, a phase I dose-finding trial of Capecitabine combined with simultaneous irradiation of 50.4 Gy over 5 weeks found the MTD to be 1000 mg/m² BID (2000 mgm² daily total) there where no grade 3 toxicities observed (22). This dose was also well-tolerated in a phase II trial combining Capecitabine and radiation (23). In upper GI malignancies, doses of 1600 mg/m² of Capecitabine are well tolerated. Trials combining Erlotinib and radiotherapy are just beginning to accrue, with no excessive toxicity yet reported. Finally, Erlotinib has been combined with chemotherapy at standard doses without excess toxicity beyond that seen with chemotherapy alone.

This study is a phase II trial of erlotinib in combination with chemoradiation in patients with stage I/II adenocarcinoma of the pancreas who are candidates for adjuvant chemoradiation.

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Eligible patients will receive adjuvant treatment with erlotinib 100 mg plus Capecitabine 800 mg/m² PO BID (5 days on/ 2 days off) and External Beam Radiation Therapy (EBRT) to the tumor bed plus adjacent lymph nodes at doses of 50.4 Gy in 28 fractions after surgery. For patients with close or positive margins after resection, they will be able to receive 54.0 Gy over 30 fractions. Approximately 4-8 weeks after the conclusion of chemoradiation, it is recommended patients will continue treatment with 4 cycles of gemcitabine 1000 mg/m² days 1, 8, and 15 every 28 days plus erlotinib 100 mg/daily.

Schema

Adjuvant Chemoradiation followed by Adjuvant Chemotherapy”

Chemoradiation:

- Baseline collection of EORTC QLQ C-30/ PAN26 QOL
- Capecitabine 800 mg/m² PO BID (1600 mg/m² total) (5 days on/2 days off regimen) AND
- Erlotinib 100 mg PO QD (1 hour prior to Capecitabine) (both given daily without interruption) AND
- Radiotherapy 50.4 Gy delivered over 28 fractions (or 54 Gy delivered over 30 fractions for patients with close or positive margins after resection) (Mon-Fri)



Four to Eight weeks of recovery from toxicity.



Adjuvant:

- Gemcitabine 1000 mg/m² D1,8, and 15 every 28 days x 4 cycles
- Erlotinib 100 mg PO QD x 4 months

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4.2. Treatment Products Description

4.2.1. Erlotinib

Erlotinib will be provided by Genentech and storage and administered as per package insert instructions.

4.2.1.1. Treatment schedule of Erlotinib

Erlotinib will be self-administered to all patients enrolled in the study. During the treatment period, patients will receive single-agent erlotinib 100 mg/day. Tablets should be taken at the same time each day with 200 mL of water at least 1 hour before or 2 hours after a meal. Patients who are unable to swallow tablets may dissolve the tablets in distilled water for administration. If a patient forgets to take a dose, the last missed dose should be taken as soon as the patient remembers, as long as it is at least 12 hours before the next dose is due to be taken. The daily treatment schedule will be resumed the next day with the patient taking the next scheduled dose.

4.2.1.2. Duration of Erlotinib

Discontinue only if indicated by the protocol, disease progression, unacceptable/unmanageable drug-related adverse events occur or the study is closed.

4.2.1.3. Expected Toxicities with Erlotinib

To date, thousands of cancer patients have received Erlotinib at doses of 100-150 mg/day. Common adverse events associated with Erlotinib administration include rash and diarrhea. Other common adverse events include nausea/vomiting, stomatitis, headache, and fatigue.

A common toxicity is a papular, pustular rash manifesting most often on the face and upper trunk. The rash may be associated with erythema, pain, pruritus, dryness, and less commonly, stomatitis, keratitis and nail bed changes. Wearing of contact lenses while receiving Erlotinib therapy is not recommended. The incidence of diarrhea can be as high as 50%. The median time to onset of skin rash was 8 days and median time to occurrence of first diarrheal symptom was 9 days.

There have been infrequent reports of serious interstitial lung disease (ILD) in patients receiving Erlotinib for treatment of NSCLC or other advanced solid tumors. The overall incidence of ILD in Erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Included in this rate of ILD are reported diagnoses of pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, and lung infiltration, irrespective of investigator assessed causality. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, preexisting parenchymal lung disease, metastatic lung disease, or pulmonary infections. Other serious and non-serious adverse events have been reported, and details are provided in the package insert.

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Reversible renal impairment has been reported in association with dehydration associated with nausea, vomiting, and diarrhea. There have been rare reports of renal failure in patients receiving Erlotinib in combination with platinum-containing chemotherapy regimens. Febrile neutropenia has been reported in patients receiving concomitant chemotherapy.

Gastrointestinal perforation (including fatalities) has been reported in patients receiving TARCEVA. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation.

Bullous, blistering and exfoliative skin conditions have been reported, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal. Interrupt or discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions.

Ocular disorders: Corneal perforation or ulceration have been reported during use of TARCEVA. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with TARCEVA treatment and are known risk factors for corneal ulceration/perforation. Interrupt or discontinue TARCEVA therapy if patients present with acute/worsening ocular disorders such as eye pain.

Erlotinib is both protein bound (92%–95%) and metabolized by hepatic cytochromes CYP3A4 and CYP3A5 and pulmonary cytochrome CYP1A1. Therefore, a potential for drug–drug interaction exists when Erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 inhibitors/inducers.

Co-administration of Erlotinib with an inhibitor of CYP3A4 metabolism (ketoconazole, 200 mg po BID for 5 days) resulted in increased exposure to Erlotinib as measured by an 86% increase in median Erlotinib AUC and a 69% increase C_{max} , compared with administration of Erlotinib alone.

Induction of CYP3A4 metabolism by a known enzyme inducer (rifampin, 600 mg po QD for 7 days) resulted in a 69% decrease in the median Erlotinib AUC, compared with administration of Erlotinib alone. However, the effect of rifampin on C_{max} was negligible.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on Erlotinib. Patients taking warfarin or other warfarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

For a comprehensive summary of possible adverse events associated with Erlotinib, please see Appendix F

4.2.1.4 Management of erlotinib toxicity

The following guidelines for holding/discontinuation for erlotinib treatment will be used:

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**Criteria and Guidelines for Management
of Erlotinib-Related Toxicities**

NCI-CTCAE (v 3.0) Grade	Erlotinib Management	Guideline for Management
Diarrhea		
Grade 1	None	Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours)
Grade 2	None (Dose interruption of erlotinib is necessary if diarrhea persists over 48–72 hours despite optimal medical management)	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours)
Grade 3	Hold Erlotinib	Interrupt erlotinib until resolution to Grade ≤1, and then restart. If toxicity does not recover within a week after erlotinib has been stopped it should be discontinued for that phase of treatment. If this toxicity occurs during the maintenance phase then erlotinib will be permanently discontinued.
Grade 4	Discontinue study treatment.	
Pulmonary Events if possibly ILD		
All Grades	Temporarily interrupt erlotinib pending the diagnostic evaluation. If the pulmonary adverse event is assessed as related to erlotinib, discontinue the patient from study treatment.	Unexplained dyspnea, either new or progressive, should be aggressively evaluated.
Rash		
Tolerable rash	None	Any of the following: minocycline ^a , topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course) at discretion of investigator
Intolerable rash	Consider interruption if unresponsive to symptomatic management.	Manage as described above. If rash does not resolve to grade 1 within one week after erlotinib is held, erlotinib will be discontinued until the maintenance phase. If this toxicity occurs during the maintenance phase then erlotinib will be permanently discontinued.
Grade 4	Discontinue study treatment.	Manage as described above

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^a Recommended dose: 200 mg po bid (loading dose) followed by 100 mg po bid for 7–10 days.

Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation.

Interrupt or discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions.

Interrupt or discontinue TARCEVA therapy if patients present with acute/worsening ocular disorders such as eye pain.

4.2.2. Capecitabine

Detailed information regarding Capecitabine can be found in the package insert. Capecitabine will be obtained from commercial sources. Capecitabine will be given by oral administration twice daily concurrently with chemoradiation. Dosing will be as follows:

Capecitabine (Xeloda™) trial treatment

Treatment	Strength	Daily Dose	Tablets per dose
Capecitabine (Xeloda™)	150 mg, 500 mg tablets	800 mg/m ² PO BID on “5 days on/ 2 days off” regimen	Dependent on BSA (m ²) (see dosing table)

Capecitabine tablets should be taken within 30 minutes after the end of a meal and swallowed with water. On study days where both Erlotinib and Capecitabine are given, it is recommended that Erlotinib be taken 60 minutes prior to Capecitabine.

The following tables serve as a general guide for Capecitabine dosing. Exact dose amounts for individual patients should be determined by the study investigator.

Capecitabine Dosing 800 mg/m² BID

Capecitabine dose level = 800 mg/m ²			Number of tablets to be taken at each dose (Morning and evening)	
Surface Area (m ²)	Daily Dose (mg)*		150 mg tablet	500 mg tablet
	Each Dose	Dose		
1.16 – 1.43	1100	2200	4	1
1.44 – 1.71	1300	2600	2	2
1.72 – 1.95	1500	3000	0	3
1.96 – 2.23	1700	3400	8	1
>2.24	1900	3800	6	2

*Total daily dose calculated on mg/m² for the median value and rounded to the nearest 100 mg

4.2.2.1. Expected Toxicities with Capecitabine.

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The most common side effects of Capecitabine are (by system):

GI: diarrhea, nausea, vomiting, stomatitis, abdominal pain, upset stomach, constipation, loss of appetite, and dehydration.

Skin: hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, and hair loss.

Systemic: tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and muscle pain), trouble sleeping, and taste problems.

See Package Insert for details. Dose adjustments will be made as outlined below.

4.2.3 Gemcitabine

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in *in-vivo* and *in vitro* tumors. Gemcitabine should be stored, reconstituted and administered according to the manufacturer's recommendation.

Gemcitabine will be obtained from commercial sources. Vials: 200 mg white, lyophilized powder in a 10 mL size sterile single use vial (No. 7501) NDC 0002-7501-01 1 g white, lyophilized powder in a 50 mL size sterile single use vial (No. 7502) NDC 0002-7502-01 Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defined controlled room temperature as "A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses."

4.2.3.1 Gemcitabine Treatment Schedule

Gemzar should be administered by intravenous infusion at a dose of 1000 mg/m² once weekly for 3 weeks followed by 1 week of rest. The standard infusion is 30 minutes.

The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided. To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200 mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200 mg vial or 1.3 mL for the 1 g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL. Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to

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administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer. When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [See USP]. Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur. The compatibility of Gemzar with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets. Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F). Caution should be exercised in handling and preparing Gemzar solutions. The use of gloves is recommended. If Gemzar solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, two of three rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

4.2.3.2 Expected Toxicities with Gemcitabine

Gemzar can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia, and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy. Hemolytic-Uremic Syndrome (HUS) has been reported rarely with the use of Gemzar. Gemzar is a Pregnancy Category D drug. Gemzar can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m² basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m² basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemzar in pregnant women. If Gemzar is used during pregnancy, or if the patient becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to the fetus.

4.2.4 Radiotherapy

Radiation will be administered by the Department of Radiation Oncology at Johns Hopkins, either in the Weinberg Building of the Sydney Kimmel Comprehensive Cancer Center at John Hopkins (SKCCC), or at the SKCCC Greenspring facilities. All patients will be simulated for radiation therapy at SKCCC.

Patients will receive 50.4 Gy given in 28 fractions (1.8 Gy/fraction) daily for 5 ½ weeks. Patients with close or positive margins after resection may receive up to 54.0 Gy given in 30 fractions. Treatment will be directed at the tumor bed as well as at hepatic, duodenal, celiac, and superior mesenteric artery and periaortic lymph node sites at the same craniocaudal levels using conformal 3-D radiation therapy or intensity-modulated radiation therapy (IMRT).

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4.2.4.1 Treatment Planning Specifications

Patient positioning for radiation therapy:

During radiation therapy simulation and treatment, all patients will be positioned supine with their arms raised above their heads. This will enable the entry of radiotherapy beams from lateral directions. A thoracic immobilization board with hand grips will be used to minimize interfractional motion.

- Equipment:** Greater than or equal to 10 MV photons should be used. The minimal acceptable SAD is 100 cm.
- Dose-Time Factors:** All radiation fields should be treated daily with all external beam schemes.
- Radiation Fields:** Radiation fields include the large field-primary tumor bed plus lymph nodes. A 3-D conformal or IMRT approach is required and will be most appropriate to minimize bowel, spinal cord, liver and kidney dose. The preoperative primary tumor extent (as defined by preoperative imaging and operative findings, PET/CT images, and surgical clip placement, if performed) must be covered with a margin from the field edge of 1.5-2.0 cm, as detailed below in **Large Fields** and in the **Field Edges** table. In addition, the local/regional and para-aortic lymph nodes adjacent to the lower thoracic and upper abdominal vertebral bodies are to be included. Inclusion of the hepaticojejunostomy site is also recommended.
- Large Fields:** As general guidelines, the edges of the large fields are defined as follows (these field edges may be adjusted if 3-D conformal or IMRT planning is used, however adequate coverage with full dose radiation must be confirmed with a dose volume histogram (DVH):
- a) Superior edge: intervertebral space T10-T11 or mid T11.
 - b) Inferior edge: intervertebral space L3-L4, depending on the preoperative studies.
 - c) Right edge: encompassing the preoperative position of the pancreatic duodenum (per preoperative studies).
 - d) Left edge: a margin of 2 cm from the preoperative primary tumor extent or 2 cm from the left edge of the vertebral bodies, whichever is more lateral.

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- e) Posterior edge: should split the anterior vertebral bodies in half. See *Field Diagrams*.
- f) Anterior edge: 1.5-2.0 cm anterior to anterior aspect of the primary tumor as defined on preoperative CT scan, and at least 2.5-3.0 cm anterior to the anterior edge of the vertebral bodies, whichever is most anterior, (or 1.5-2.0 cm anterior to nodal volumes as reconstructed from CT scan information and outlined on simulator films (recommended, but not required).

Boost Fields:

A single field reduction at 45 Gy is required, encompassing only the preoperative primary tumor volume, with a field edge margin of 1.5-2.0 cm on all fields.

Field Edges:

The Target Volume is equivalent to the large field and boost field, as defined in *Radiation Fields* and outlined in *Field Diagrams*.

AP/PA Field(s)	Per Protocol	Variation Acceptable	Deviation Unacceptable
A) Length	Inclusive of 4-5 vertebral bodies		<4 or >5 vertebral bodies
B) Distance from primary tumor	1.5-2 cm	1-3 cm	< 1 or >3 cm
C) Distance from vertebral body*	2 cm	1-3 cm	< 1 or >3 cm

Lateral Fields	Per Protocol	Variation Acceptable	Deviation Unacceptable
A) Length	Same as AP/PA fields		
B) Distance from anterior aspect of primary tumor	1.5-2 cm	0.5-3 cm	<0.5 or >3 cm
C) Distance from remaining aspect of primary tumor	2-3 cm	1-4 cm	<1 or >3 cm
D) Posterior edge	mid-vertebral bodies	+/-1 cm from mid-vertebral bodies	<1 or >3 cm
E) Anterior edge relation to vertebral body	3.5-4 cm	2.5-5 cm	<2.5 or >5 cm

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F) Anterior edge relation to nodal volumes (if reconstructed from CT and outlined on simulator films)	1.5-2 cm	1-3 cm	<1 or >3 cm
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Boost Fields	Per Protocol	Variation Acceptable	Deviation Unacceptable
Distance from primary tumor	1.5-2 cm	1-3 cm	<1 or >3 cm

*May be included at the level of hepaticojejunostomy, if this is included.

NOTE: The above will be reviewed in the context of kidney sparing/shielding as required in *Critical Structure Tolerance* and *Treatment Breaks*.

Physical Parameters

- Beam Energy:** Megavoltage equipment is required, with nominal photon energies ≥ 10 MV.
- Treatment Distance:** Minimum treatment distance to skin for SSD techniques or isocenter for SAD techniques should be at least 100 cm.
- Simulation Films:** Must undergo prospective quality assurance and evaluation as per *Boost Fields* and *Field Edges* during routine quality assurance conference.
- Localization Films:** Obtain for each treatment field per week.
- Isodose Distribution:** Will be reviewed during the routine quality assurance conference. All plans which include the isodose distribution will be stored in IMPAC in the Johns Hopkins Department of radiation oncology. The dose delivered to the target volume must not deviate from the doses specified in *Treatment Fields/Radiation Dose* by more than 5 percent in either direction. Variations will be scored as per *Dose Changes*.
- Dose Specifications:** Doses will be specified as follows:
 - For an arrangement of three or more intersecting beams:* at intersection of the central ray of the beams.
 - Other / complex treatment arrangements:* at the center of the target volume.

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4.2.4.2. Critical Structure Tolerance

Small Bowel /Liver:	Efforts should be made to exclude the small bowel and liver as much as possible by utilizing megavoltage beams and multiple shaped ports. The liver must not have >50% of its volume receiving >30 Gy.
Spinal Cord:	The spinal cord dose will be limited to <40 Gy by use of posterior blocking in the lateral field(s).
Kidneys:	The equivalent of one kidney should receive ≤ 18 Gy or at least the equivalent of two-thirds of one kidney must be spared from the radiotherapy fields. If only a single functioning kidney is present, at least 2/3 of the functioning kidney must be excluded from any radiation port.

4.2.4.3. Radiotherapy toxicity

Common toxicities of radiotherapy include diarrhea, dermatitis, fatigue, nausea, alopecia in involved fields, and sterility (females are more likely to be left sterile than males). Uncommon toxicities include intestinal obstruction and/or intestinal bleeding requiring surgery.

4.3. Other concomitant treatment

Any patients who require ophthalmic surgery during the course of the trial will be temporarily withdrawn. Concomitant use of medications known to affect the conductive system, such as beta-blockers, calcium channel blockers, or digoxin, is allowed under investigator supervision. concomitant use of the following drugs is NOT allowed: phenytoin, carbamazepine, rifampicin, phenobarbital or St John's Wort; these drugs induce CYP3A4 and may decrease levels of Erlotinib. Concomitant use of CYP3A4 inhibitors (eg, itraconazole) may result in increased levels of Erlotinib. This exposure may be clinically relevant, as adverse experiences are related to dose and exposure.

Coadministration of drugs that cause significant sustained elevations in gastric pH greater than or equal to 5 may reduce plasma concentrations of Erlotinib, and therefore may reduce efficacy.

International normalized ratio (INR) elevations, bleeding, or both events have been reported in some patients taking warfarin. Patients taking warfarin should be monitored regularly for changes in prothrombin time (PT) or INR.

Systemic retinoids should not be given because of theoretical concerns about negatively affecting the Erlotinib mechanism of action. Systemic steroids are discouraged for the treatment of skin toxicities. Patients who are taking steroids for reasons other than skin toxicity at trial entry may continue treatment.

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Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator(s).

4.4 Dose modification and management of toxicity

4.4.1 Adjuvant Chemoradiation

Several toxicities of Capecitabine, radiation, and Erlotinib overlap. These include diarrhea, nausea and vomiting and skin toxicity. Dose modifications for Erlotinib are described in table 4.4.2. Capecitabine will be held at the first occurrence of a grade 2 toxicity, then dose-reduced at a second occurrence of a grade 2 toxicity, and held/dose-reduced for first occurrence of grade 3 or greater toxicities (see table 4.4.2). Therapy will be interrupted until the grade 2 or greater toxicity abates to grade 1. Subsequently a dose adjustment will be made unless it is the first occurrence of a grade 2 toxicity where the dose will remain the same. With the second occurrence of grade 2 or greater toxicity, therapy will be interrupted and subsequently restarted at reduced dose level. With a third occurrence, dosing will be interrupted and subsequently restarted at another dose reduction, and will be discontinued if a grade 3 toxicity recurs. It will also be discontinued if a grade 4 toxicity occurs at any time. Patients whose toxicity does not recover after holding the drug for a maximum of 2 weeks will be removed from the study.

Capecitabine dosing (on 5 days on/ 2 days off regimen):

Starting dose = 800 mg/m² po BID (1600 mg/m² daily)
Dose level -1 = 25% dose reduction
Dose level -2 = 50% dose reduction

Since toxic syndromes of severe diarrhea in the setting of neutropenia have been observed with 5-FU based therapy, both Capecitabine and Erlotinib will be held in cases where grade 2 or greater diarrhea is observed in the setting of a rapidly declining ANC (or grade 3 or 4 neutropenia).

This is presented in tabular form below. Note that if radiation therapy is interrupted for toxicity, Erlotinib will be stopped for the duration of radiation therapy and will be resumed in the maintenance phase of treatment if appropriate.

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4.4.2 Toxicities/dose adjustments during adjuvant therapy (radiation)

NCI Grade	% of planned Capecitabine dose ^f	Erlotinib	Radiation
Grade 0-1	100%	Current dose	Current dose
Grade 2^a			
1 st appearance	Hold then return to current dose ^b	Current dose	Current dose
2 nd appearance	Hold then reduce by 25% ^b	Hold, then current dose ^b	Current dose
3 rd appearance	Hold then reduce by 50% ^b	Discontinue	Hold x 1 wk ^c
4 th appearance	Discontinue	Discontinue	Hold x 2 wks ^c
Grade 3^a			
1 st appearance	Hold then reduce by 25% ^b	Hold, then current dose ^b	Current dose ^c
2 nd appearance	Hold then reduce by 50% ^b	Discontinue	Hold x 1 wk ^c
3 rd appearance	Discontinue	Discontinue	Hold x 2 wks ^c
Grade 4	Discontinue permanently, or hold then reduce to 50% of previous level ^d	Discontinue ^d	Hold x 2 wks ^{c, d}

^a Except nausea/vomiting (unless patient is on antiemetic therapy), diarrhea (unless patient is on medical therapy), and neutropenia. Grade ≥ 2 skin toxicity will be treated according to the likely cause. **CTC grade 2, 3, or 4 diarrhea with rapidly or precipitously declining absolute neutrophil count (ANC), or at same time as neutropenia CTC grade 3 or 4.** Erlotinib and Capecitabine should be discontinued for up to a maximum of 14 days until the ANC is $\geq 0.5 \times 10^9/L$, the diarrhea resolves, or the diarrhea has decreased in severity to CTC grade 1.

^b Upon recovery to grade 1 or less within two weeks of stopping (with prophylaxis where possible). Missed doses of Erlotinib and Capecitabine will not be made up.

^c Holding of radiation will be at the discretion of the treating radiation oncologist; missed dosing will be made up at the discretion of the treating radiation oncologist. If radiation therapy is interrupted due to toxicity, erlotinib treatment will be stopped for the duration of radiation therapy and will be resumed in the adjuvant stage of therapy (with capecitabine), if appropriate.

^d All grade 4 discontinuations and/or toxicities will be reviewed by investigator and IRB to determine if patients may continue on study with appropriate dose adjustment.

^e Radiation will be continued unless toxicity is possibly related to radiation treatment; for example, diarrhea, or dermatitis over the radiation area.

^f Capecitabine and erlotinib dose adjustment will not be applied for lymphopenia (Grade 2 or above)

4.4.3 Adjuvant Maintenance Chemotherapy

Adjuvant chemotherapy consists of gemcitabine and erlotinib. Management for Erlotinib toxicities will be as detailed below (Table 4.4.3). For gemcitabine, dose adjustments will be based on the hematological and non-hematological toxicity of the drug and be monitored at the discretion of the treating oncologist. Weekly doses of gemcitabine will not be made up. Weekly dose management of Erlotinib are as follows:

Table 4.4.3

Toxicity	Grade	Erlotinib management*	Guideline for management
Keratitis	1	None	No intervention
	2 (if ≤ 14 days)	None**	Preservative-free artificial tears, ointments, and/or other
	2 (if >14 days)	Hold until recovery to \leq grade	

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		1	therapies as clinically indicated, with a follow-up examination within 2 weeks
	≥ 3	Hold until recovery to ≤ grade 1	
Diarrhea	1	None	No intervention
	2	None**	Loperamide (4 mg at first onset, followed by 2 mg every 2–4 hrs until diarrhea free for 12 hrs)
	≥ 3 (despite optimal use of loperamide)	Hold until recovery to ≤ grade 1	
Rash	1	None	No intervention
	2	None**	Any of the following: monocycline, topical tetracycline or clindamycin, topical silver sulfadiazide, diphenhydramine, oral prednisone (short course)
	≥ 3	Hold until recovery to ≤ grade 1	
Bilirubin	≥ 3 X ULN	Hold until grade ≤ 2	
Liver transaminase	≥ 5 X ULN	Hold until grade ≤ 2	
Signs and symptoms of Interstitial Pneumonitis		Hold pending diagnosis Permanently discontinue if diagnosis is confirmed and considered possibly related to OSI-774	Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated.
Other toxicity	≥ 2 prolonged clinically significant toxicity	Hold until recovery to ≤ grade 1	Treatment as appropriate

* If no recovery after 2 weeks of holding drug, patients should go off study.

** If dose has been previously held for grade 2 rash or diarrhea, and grade 2 symptoms recur, OR if the Patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1

Additional information for erlotinib:

- 1.) GI perforation: In the event of bowel perforation, patient should be removed from erlotinib therapy
- 2.) Ocular AEs: Erlotinib should be interrupted for acute/worsening eye pain and should be discontinued in patients with persistent inflammation or severe eye surface damage.

Patients who develop grade 3-4 toxicity at any time during the study will be dose reduced by 25 % upon recovery and for the rest of the study. Patients who develop recurrent grade 3-4 toxicity can be further dose reduce by 50 % for the remaining treatments. Patients with a third episode of

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toxicity despite 2 dose reduction will be removed from the study permanently. Patients who missed (due to toxicity) more than 3 scheduled doses of gemcitabine will be removed from the study. Erlotinib will be held if patients develop any signs of ILD during the maintenance phase of treatment unless it is determined by the treating physician to not be related to the drug.

Toxicities		Gemcitabine Dose Adjustment
ANC	> 1000 cell/uL	100 % dose
	750-999 cells/uL	50 % dose
	< 750 cells/uL	Hold
Platelets	> 100,000 cells/uL	100 % dose
	75,000-99,999 cells/uL	50 % dose
	< 75,000 cells/uL	Hold
Non Hematologic Toxicity	Grade 0 -1	100 %
	Grade 2 - 4	Hold

Assessment of quality of life: Quality of life will be assessed using The European Organization for Research and Treatment in Cancer quality of life core cancer questionnaire with the pancreatic cancer module (EORTC QLQ C-30/ PAN26). The European Organization for Research and Treatment in Cancer Quality of Life Questionnaire (EORTC QOL-C30) is a multidimensional, 30-item questionnaire which assesses five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), a global health /QOL scale, as well as 6 single items (26)(27). The EORTC QLQ-PAN26 supplements the core questionnaire with 26 items specific for patients with pancreatic cancer (28)(29). The instrument will be administered in English to eligible patients. Questionnaires will be self-reported by the patient at the times outlined in the calendar. Questionnaires should be administered prior to the patient being seen by the doctor. Questions can be read verbatim to patients who are blind or illiterate. For QoL assessment, the primary outcome will be the change in overall QoL score from baseline at 12 months. Changes in QoL from baseline to other time points, and on subscales of both instruments, are secondary endpoints.

5.0 Evaluation of patients: Dose limiting toxicities

Each patient will be evaluated for toxicity weekly during the chemoradiation segment of the protocol and monthly for the maintenance phase of the treatment. Further enrollment will be held if two or more patients of each cohort of six experience any of the following dose limiting toxicities (DLTs):

- Grade 3 or higher nonhematologic toxicity according to CTCAE version 3.0 occurring despite optimal supportive care, if applicable.
- grade 4 neutropenia (ANC <500) for 5 or more days
- febrile neutropenia
- platelet count <25,000/mm³
- grade 3 or higher cutaneous toxicity

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6.0 CRITERIA FOR DISCONTINUATION/WITHDRAWAL OF INFORMED CONSENT.

Patients may be discontinued from trial treatment and assessments at any time, at the discretion of the investigator(s). Specific reasons for discontinuing a patient from this trial are the following:

- Objective local or distant progression of disease
- Patient lost to follow-up (ie, dropouts)
- Unacceptable toxicity
- Protocol noncompliance
- Withdrawal of consent
- Development of intercurrent illness
- Inability to return to Johns Hopkins monthly during the maintenance phase of treatment.

If the reason for withdrawal from the trial is the death of the patient, the 2 options for categorizing withdrawal are either progressive disease or an adverse event (AE; more than 1 AE may be documented as a reason for withdrawal). Only 1 event will be captured as the cause of death. Note that death is an outcome and not an AE.

All deaths that occur within the trial period or within 30 days after administration of the last dose of trial drug must be reported primarily for the purposes of serious adverse event (SAE) reporting; however, deaths due unequivocally to progression are not SAEs. All trial treatment-related toxicities and SAEs must be followed up until resolution or until, in the criteria of the investigator, is unlikely to resolve.

All patients who have new or worsening CTCAE grade 3 or 4 laboratory values at the time of withdrawal must have additional testing performed, and the results must be recorded in the patients' medical records. These patients should be followed up until the laboratory values have returned to CTCAE grade 1 or 2 or until 30 days after the date of withdrawal (whichever comes first), unless these values are not likely to improve because of the underlying disease. In these cases, the investigators must record their opinions in the patients' medical records. Laboratory abnormalities should not be reported as adverse events unless any criterion for a SAE is fulfilled, the laboratory abnormality causes the patient to discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

After withdrawal from treatment, patients must be followed up for existing AEs for 30 calendar days after administration of the last dose of trial drug. All SAEs occurring during that period must be reported to FDA and must be followed up until resolved, unless in the investigator's opinion the condition is unlikely to resolve because of the patient's underlying disease.

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7.0 Study calendar

	Screening	Chemo/XRT Day 1 ⁶	Weekly During Chemo/XRT	Before the start of maintenance Cycle #1	Before the start of maintenance Cycle #2	Before the start of maintenance Cycle #3	Before the start of maintenance Cycle #4	Follow-up every 3-4 Months x 2 years ⁸
Informed consent ¹	X							
Medical history	X ²		X	X	X	X	X	X
Physical exam	X ²		X	X	X	X	X	X
ECOG performance status	X ²		X	X	X	X	X	X
CA 19-9	X ²			X	X	X	X	X
Chemistry panel ³	X ²		X	X	X	X	X	X
Hematology ⁴	X ²		X	X	X	X	X	X
PT/PTT	X ²							
CT scan ⁵	X ²			X		X		X
QOL Questionnaire	X			X		X		X
Erlotinib		X	X	X	X	X	X	
Xeloda		X	X					
Gemcitabine				X	X	X	X	
Radiation		X	X					

¹ To be obtained prior to ANY study-SPECIFIC procedure.

² Within 4 week prior to initiation of chemoradiation. Section 4.3 details use of concomitant medications.

³ Creatinine, total bilirubin, AST, ALT, alkaline phosphatase, LDH, Ca, K, Na, albumin, total protein.

⁴ Hemoglobin, hematocrit, platelets, WBC with differential.

⁵ CT of the chest, abdomen and pelvis with IV and oral contrast. Pancreas protocol (thin slices through the pancreas). Outside CT scans acceptable but must be submitted for review

⁶ Day 1 = Day that Erlotinib/Xeloda/radiation began

⁷ Maintenance chemotherapy will begin 4-8 weeks after completion of chemoradiation, when patient has been deemed by investigator to be sufficiently recovered from chemoradiation. It is recommended that patients receive a total of 4 cycles of gemcitabine (1000 mg/m² weekly 3 doses per month) with daily erlotinib (100 mg/m²). During this period patients have the option of being treated closer to home but must return to Hopkins once a month for follow-up. Gemcitabine/erlotinib administration should include appropriate hematologic, chemistry, and electrolyte monitoring as determined by the patient's oncologist, in consultation with the gemcitabine and erlotinib package inserts

(<http://www.gene.com/gene/products/information/pdf/tarceva-prescribing.pdf> and <http://pi.lilly.com/us/gemzar.pdf>)

At this time all outside records including labs and clinic notes must be submitted to Johns Hopkins for review. Only grade 3 and above AE's will be collected during this maintenance phase of treatment (M1-M4). SAE's will be reported according to institutional guidelines set by Johns Hopkins. Erlotinib will be obtained from the Hopkins pharmacy prior to chemoradiation and monthly during M1-M4. It is required that patients return for a follow-up visit and restaging within 6 weeks of completion of their maintenance therapy (even if the duration is shorter than 4 cycles).

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⁸ Follow-up visits – Following the maintenance phase of therapy patients will be followed every 3 months for 2 years. After 2 years patients will be seen every 6 months for 3 years for a total follow-up of 5 years per standard of care. As in the maintenance phase of the trial only grade 3 AEs will be collected. SAE's will be reported according to institutional guidelines set by Johns Hopkins.

8.0 MEASUREMENT OF EFFECT

The primary clinical endpoint is time to progression determined as the time elapsed from surgical resection to development of tumor recurrence, either local or distant.

8.1 Definitions

Time to progression refers to the time period between surgical resection and detection of recurrence by either clinical exam or radiological exam. Every effort should be made to biopsy suspected disease in order to confirm recurrence. Any recurrence within the pancreatic area will be classified as local recurrence; any failure outside the pancreatic area will be recorded as distant recurrence.

8.2 Monitoring for recurrence

Upon the completion of adjuvant treatment, patients will undergo post-treatment monitoring for 5 years. The following will comprise follow-up:

- History/Exam within 1-3 weeks upon completion of maintenance chemotherapy then every 3 months for 2 years, then every 6 months thereafter; further visits as dictated by patient symptoms.
- CBC, tumor markers, chemistry panel every 3 months for 5 years (total).
- Abd/Pel CT every 3 months for 2 years, then every 6 months for 3 more year.
- Quality of life questionnaire per the study calendar.

Upon detection of local or distant recurrence, patients are off-study; however every attempt will be made to follow patients until death to determine the secondary objective of overall survival.

9.0. ADVERSE EVENTS

9.1. Adverse Event and Reporting Definitions

In the event of an adverse event the first concern will be for the safety of the subject.

Investigators are required to report to Genentech Drug Safety ANY serious treatment emergent adverse event (STEAE) as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during erlotinib treatment or during a post-treatment follow-up period that (1) was not present at the start of erlotinib treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of erlotinib treatment or as part of the patient's medical history but worsened

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in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

9.2. Reporting of Serious Treatment Emergent Adverse Events to Genentech

All treatment emergent SAEs should be recorded on a MedWatch 3500A Form and faxed to:

Genentech Drug Safety Fax:
650-225-4682 or 650-225-4683

(Please use the safety reporting fax cover sheet included in the IST start-up binder for your fax transmission)

AND:

To the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Clinical Research Office.

9.3. MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

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Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B., initials, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report.)

Occasionally, Genentech may contact the reporter for additional information, clarification or current status of the subject for whom an adverse event was reported. For questions regarding STEAE reporting, you may contact the Genentech Drug Safety representative noted above.

9.4. Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that Tarceva caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to Tarceva administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to Tarceva administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

10.0. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

10.1. Study design/endpoints

This is a phase II study of Erlotinib in combination with chemoradiation and adjuvant chemotherapy in patients with resected pancreatic cancer. The objectives of the trial are:

Primary

1. To seek preliminary evidence of antitumor activity (progression free survival) of erlotinib in combination with standard adjuvant chemoradiation and chemotherapy in patients with resected adenocarcinoma of the pancreas.

Secondary

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1. To characterize the toxicity profile of erlotinib in combination with adjuvant chemoradiation in patients with resected pancreatic cancer.
2. To evaluate the quality of life of patients receiving erlotinib based chemoradiation prior to treatment (after surgery), one month following treatment and every 3-4 months thereafter.
3. To seek preliminary evidence of antitumor activity (overall survival) of erlotinib in combination with standard adjuvant chemoradiation and chemotherapy in patients with resected adenocarcinoma of the pancreas.

10.2. Sample size/accrual rate

This is a phase II study evaluating the addition of Erlotinib to 5-FU based chemoradiation and maintenance (gemcitabine and erlotinib) chemotherapy in patients with resectable adenocarcinoma of the pancreas.

The principal endpoint is to estimate the progression free survival for this patient population. The table below shows the power to detect various differences in progression free survival for those treated with erlotinib in combination with standard adjuvant chemoradiation and chemotherapy versus the standard treatment for N=40 and two-sided type I error of 5%. The expected median progression free survival time with 5-FU based chemoradiation alone for an accrual time of 18 months and follow-up period of 60 months is 12 months.

Power	Median Progression Free Survival Difference (months)
0.46	4
0.73	6
0.89	8
0.96	10

We have 89% power to detect an 8 month improvement in progression free survival for those who receive treatment with N=40.

We expect to enroll 2-4 patients per month, with accrual completed in approximately 14-18 months.

10.2.1. Analysis of primary endpoints

Progression free survival will be calculated as the time from surgery to the time of disease progression. Median and overall survival will be estimated and 95% confidence intervals will be reported using Kaplan-Meier methods.

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10.2.2. Analysis of secondary endpoints

Toxicity will be evaluated using the NCI Common Toxicity Criterion for Adverse Events Version 3.0. Toxicities requiring dose-reduction are described in section 4.4. The frequency of toxicities per organ system and grade will be summarized, including time of onset. All patients who receive at least one dose of Erlotinib will be included in the toxicity analysis. Patients who began treatment, patients who are evaluable, and all who required dose reductions will be documented. The toxicity profile of erlotinib will be characterized weekly in patients as mild or severe. The percentage of mild and severe toxicities will be reported separately with 95% confidence intervals. Individual patients' toxicity profiles (frequency of severe reactions) of the course of the entire study will also be summarized.

To determine health related quality of life (QoL) changes following this treatment regimen. For the EORTC QLQ-C30 and QLQ-PAN26, summation results will be reported by subscale. Analysis will be performed using paired t tests/paired ANOVA against baseline values with a 0.05 level of significance (2 tailed). The primary endpoint for QoL assessment is 12 months.

We estimate that 30 patients will have complete data for analysis of this (QOL) secondary endpoint. This conservative estimate of sample size should provide adequate power accounting for additional dropouts.

The overall survival will be calculated as the time from surgery to the time of death. Median and overall survival will be estimated and 95% confidence intervals will be reported using Kaplan-Meier methods.

10.3. Reporting and exclusions

10.3.1. Evaluation of response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. All of the patients who met the eligibility criteria should be included in the main analysis of the outcome parameters. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

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11.0. TRIAL MANAGEMENT

11.1. Audits and inspections

Authorized representatives of Genentech, a regulatory authority, or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of an Genentech audit or inspection is to systematically and independently examine all trial related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements. The investigator should contact Genentech immediately if contacted by a regulatory agency about an inspection at his or her center.

11.2. Changes to the protocol

If it is necessary for the trial protocol to be amended, the amendment or a new version of the trial protocol must be notified to or approved by the IRB. If a protocol amendment requires a change to a particular center's Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

Genentech's willingness to supply Study Drug is predicated upon the review of the protocol. The Investigator agrees to provide prior written notice to Genentech of any modifications to the protocol or informed consent.

11.3. Ethics

The principal investigator(s) is also responsible for providing the IRB with reports of any serious adverse events from any other trial conducted with the investigational product. The trial will be performed in accordance with Good Clinical Practice.

11.4. Procedures in case of overdose

There is currently no known antidote for Erlotinib. The treatment of AEs associated with overdose should be supportive and for the underlying adverse symptoms. To date, no patient has experienced an overdose with Erlotinib.

11.5. Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under trial may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the trial.

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All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs. All outcomes of pregnancy must be reported to Genentech on the pregnancy outcomes report form.

11.6. Trial monitoring

The SKCCC Clinical Trial Monitoring Program (revision 6/16/05) is attached in appendix E. As a phase II IND exempt investigator initiated trial, this trial is assigned a “level 1” plan in the clinical trial monitoring program. Trial Monitor Evaluation and Reporting will be done by the SKCCC Clinical Research Review Committee (CRC).

Trial progress will be discussed at the Johns Hopkins GI Clinical Trial Program weekly meeting, which includes the protocol principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, and retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

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References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71-96.
2. Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. *Curr Probl Cancer* 2002;26:176-275.
3. Abrams RA, Grochow LB, Chakravarthy A, et al. Intensified adjuvant therapy for pancreatic and periampullary adenocarcinoma: Survival results and observations regarding patterns of failure, radiotherapy dose and CA19-9 levels. *Int J Radiat Oncol Biol Phys* 1999;44:1039-46.
4. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol* 2008;26:3503-10.
5. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: A randomized trial. *J Clin Oncol* 1997;15:2403-13.
6. Jaffee EM, Hruban RH, Biedrzycki B, et al. Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: A phase I trial of safety and immune activation. *J Clin Oncol* 2001;19:145-56.
7. Grunwald V, Hidalgo M. Developing inhibitors of the epidermal growth factor receptor for cancer treatment. *J Natl Cancer Inst* 2003;95:851-67.
8. Grunwald V, Hidalgo M. Development of the epidermal growth factor receptor inhibitor OSI-774. *Semin Oncol* 2003;30:23-31.
9. Hidalgo M, Siu LL, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol* 2001;19:3267-79.
10. Ng SS, Tsao MS, Nicklee T, et al. Effects of the epidermal growth factor receptor inhibitor OSI-774, tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. *Mol Cancer Ther* 2002;1:777-83.
11. Bruns CJ, Harbison MT, Davis DW, et al. Epidermal growth factor receptor blockade with C225 plus gemcitabine results in regression of human pancreatic carcinoma growing orthotopically in nude mice by antiangiogenic mechanisms. *Clin Cancer Res* 2000;6:1936-48.
12. Xiong HQ, Rosenberg A, LoBuglio A, et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: A multicenter phase II trial. *J Clin Oncol* 2004;22:2610-6.
13. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25:1960-6.

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14. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004;350:1200-10.
15. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. *JAMA* 2008;299:1019-26.
16. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. *J Clin Oncol* 2001;19:2282-92.
17. Cassidy J, Twelves C, Van Cutsem E, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: A favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol* 2002;13:566-75.
18. Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. *J Clin Oncol* 2002;20:160-4.
19. Sawada N, Ishikawa T, Sekiguchi F, et al. X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (xeloda) in human cancer xenografts. *Clin Cancer Res* 1999;5:2948-53.
20. Schuller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. *Cancer Chemother Pharmacol* 2000;45:291-7.
21. Ishikawa T, Sekiguchi F, Fukase Y, et al. Positive correlation between the efficacy of capecitabine and doxifluridine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase activities in tumors in human cancer xenografts. *Cancer Res* 1998;58:685-90.
22. Dunst J, Reese T, Sutter T, et al. Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer. *J Clin Oncol* 2002;20:3983-91.
23. Kim JS, Kim JS, Cho MJ, et al. Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2002;54:403-8.
24. Vaishampayan UN, Ben-Josef E, Philip PA, et al. A single-institution experience with concurrent capecitabine and radiation therapy in gastrointestinal malignancies. *Int J Radiat Oncol Biol Phys* 2002;53:675-9.
25. Bianco C, Tortora G, Bianco R, et al. Enhancement of antitumor activity of ionizing radiation by combined treatment with the selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (iressa). *Clin Cancer Res* 2002;8:3250-8.
26. Groenvold M, Klee MC, Sprangers MA, et al. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J Clin Epidemiol* 1997;50:441-50.

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27. Aaronson NK, Ahmedzai S, Bergman B, et al. The european organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-76.
28. Fitzsimmons D, Johnson CD. Quality of life after treatment of pancreatic cancer. *Langenbecks Arch Surg* 1998;383:145-51.
29. Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC study group on quality of life. *Eur J Cancer* 1999;35:939-41.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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APPENDIX B

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

“Life threatening” means that the patient was at immediate risk of death from the adverse event as it occurred or it is suspected that use or continued use of the product would result in the patient’s death. “Life threatening” does not mean that had an adverse event occurred in a more severe form it might have caused death (ie, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered adverse events if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in a situation where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Disease Progression

Any events or hospitalization that are unequivocally due to progression of disease must not be reported as a serious adverse event.

Appendix C

**EORTC QLQ-C30
EORTC QLQ-PAN26**

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ENGLISH



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

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ENGLISH

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you <u>financial</u> difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

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ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

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Appendix C

EORTC QLQ-PAN26

Phase II Study of Erlotinib (Tarceva™) Combined with Chemoradiation and Adjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer

ENGLISH/US



EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Were you uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did your arms and legs feel weak?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel a sudden urge to have a bowel movement?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

Phase II Study of Erlotinib (Tarceva™) Combined with Chemoradiation and Adjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer

ENGLISH/US

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Have you worried about what your health might be like in the future?	1	2	3	4
52. Were you limited in planning activities in advance (e.g. meeting friends)?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4

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Phase II Study of Erlotinib (Tarceva™) Combined with Chemoradiation and Adjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer

APPENDIX D

Further Guidance on the Assessment of Casuality

The following factors should be considered when deciding if there is a “reasonable possibility” that an adverse event (AE) may have been caused by the investigational product.

- **Time course of events and exposure to suspect drug:** Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of suspect drug?
- **Consistency with known drug profile:** Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- **De-challenge experience:** Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- **No alternative cause:** The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- **Re-challenge experience:** Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- **Laboratory tests:** Has a specific laboratory investigation confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any de-challenge (if performed) is negative or ambiguous or there is another more likely cause of the AE. In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this.

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Chemotherapy in Patients with Resectable Pancreatic Cancer**

APPENDIX E

**SIDNEY KIMMEL COMPREHENSIVE CANCER
CENTER AT JOHNS HOPKINS**

DATA AND SAFETY MONITORING PROGRAM

(Revised 6/16/2005)

Phase II Study of Erlotinib (Tarceva™) Combined with Chemoradiation and Adjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer

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1. BACKGROUND

NIH policy requires that grantees have in place procedures for the data and safety monitoring of clinical trials¹. This is to ensure the safety of participants, the validity and integrity of the data, and the appropriate termination of trials for which significant benefits or risks have been uncovered or for which, it appears that the trial cannot be concluded successfully. The NIH DSM policy covers clinical trials of all phases funded by the NIH. The Sidney Kimmel Comprehensive Cancer Center (SKCCC) Institutional Data and Safety Monitoring Plan (DSMP) was developed to comply with the NIH policies, the NCI's *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the NCI* guidance document², and FDA regulations for monitoring IND trials.

1.1. NIH Principles of Monitoring Data and Safety

- 1.1.1. All clinical trials require monitoring. Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III), etc.
- 1.1.2. Monitoring should be commensurate with risks. The method and degree of monitoring needed is related to the degree of risk involved. A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. Risk associated with participation in research must be minimized to the extent practical.
- 1.1.3. Monitoring should be commensurate with size and complexity. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator or NIH program staff in a small phase I study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

1.2. National Cancer Institute's Definition of a Clinical Trial

- 1.2.1. The NCI operational definition of a clinical trial is a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.

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- 1.2.2. In the area of molecular or imaging diagnostics, the NCI considers a study to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way, the information from the diagnostic may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach, are not clinical trials and are not covered by this DSM policy, unless performing the diagnostic test itself imposes some risk on study subjects.
- 1.2.3. Behavioral clinical trials include interventions whose goals are to increase behaviors (e.g. cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not clinical trials.

2. MONITORING THE PROGRESS OF TRIALS AND THE SAFETY OF PARTICIPANTS

2.1. SKCCC Data and Safety Monitoring Plan

- 2.1.1. Outlines the general process for data and safety monitoring, including institutional oversight and review procedures important to assure and document compliance. This Plan is comprised of graded oversight mechanisms that comply with NIH/NCI and FDA standards.
- 2.1.2. Monitoring for clinical trials is a continuous, ongoing review of the conduct of the trial, including adherence to study design and documentation of appropriate reporting of protocol events. The responsibilities for monitoring are shared between the Assistant Director for Clinical Research, Clinical Research Review Committee (CRC), SKCCC Data and Safety Monitoring Committee (DSMC), Data and Safety Monitoring Board (DSMB), SKCCC CRO Quality Assurance Program or Sponsor, and the PI.
- 2.1.3. All clinical trials at SKCCC are required to have a Data and Safety Monitoring section in the protocol. If a clinical trial does not have a specific mechanism defined in the protocol for data and safety monitoring, the principal investigator of each trial is required to define a specific clinical research trial monitoring system commensurate with the risks and complexity of the proposed trial.

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- 2.1.4. The SKCCC DSMP utilizes a graded monitoring system as shown in Table 1 below. Level 1 is designed for low risk/low complexity trials, while Level 4 is designed for high risk/high complexity trials including phase III trials. The level of monitoring must be included in the protocol for review and subsequent approval by the SKCCC Clinical Research Review Committee (CRC), the Institutional Review Board (IRB) and, if applicable, the NCI.
- 2.1.5. In all four levels, primary internal data monitoring is performed by the principal investigator. A principal investigator leads a team of data managers and research nurses assigned to the trial. The principal investigator reviews the data on a regular basis and internally monitors the trial performance in a timely manner. PI monitoring is an essential element of all clinical trials.
- 2.1.6. An external data monitor is recommended for higher risk trials. Level 2, 3 and 4 monitoring plans involve an external monitoring process. Such monitoring may be performed by the SKCCC CRO Quality Assurance program monitors or contracted through an external Clinical Research Organization. In addition to data monitoring, all trials covered under the SKCCC DSMP receive periodic quality assurance audits under the SKCCC CRO Auditing Guidelines. Level 1 monitored trials receive an audit after the first subject is enrolled. Subsequent audits are scheduled periodically (usually annually) as long as the trial remains open for accrual. Level 2, 3 & 4 monitored trials are audited at the end of the first year and then periodically every one to three years. Monitoring and auditing reports are reviewed by the DSMC, Medical Expert Committee and/or the DSMB.
- 2.1.7. It is the responsibility of the DSMC, Medical Expert Committee, and/or the DSMB to make recommendations to the PI, Assistant Director for Clinical Research and IRB concerning continuation or conclusion of the trial.

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Table: 1

SKCCC DSMP Schema				
	Level 1	Level 2	Level 3	Level 4
Risk of Trial	Low – Medium	Medium – High	High	High
Complexity of Trial	Low – Medium	Low – High	Medium – High	High
Internal Monitoring Performed by	PI and Study Staff	PI and Study Staff	PI and Study Staff	PI and Study Staff
External Monitoring Performed by	None	CRO QA Program or External	CRO QA Program or External	CRO QA Program or External
SKCCC CRO Auditing	All clinical trials are audited under the SKCCC CRO Auditing Guidelines			
Data and Safety Monitoring Oversight	DSMC	DSMC	DSMC and Medical Expert Committee ^A	DSMC and DSMB ^B
Trial Type	Phase I, II, Behavioral, & Nutritional may select Level 1, 2, or 3			Required for Phase III
		JH Investigator sponsored IND/IDE must use Level 2, 3 or 4		

A When there is conflict between the DSMC and Medical Expert Committee, the DSMC will have final decisional authority.

B When there is conflict between the DSMC and DSMB, the DSMB will have final decisional authority.

2.2. Institutional Oversight and Responsibilities for Monitoring of Clinical Trials

2.2.1. The Assistant Director for Clinical Research (ADCR) has overall responsibility for data and safety monitoring of clinical trials conducted at the SKCCC. The ADCR appoints the Chair and all members of both Clinical Research Review Committee (CRC) and the Data and Safety Monitoring Committee (DSMC).

2.2.2. Clinical Research Review Committee (CRC)

2.2.2.1. The Clinical Research Review Committee is charged with ensuring that protocols meet the Center's standards for Scientific Merit, Scientific Priority, and Adequate Scientific Progress as well as ensuring the inclusion of women and

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minorities and children in research. The CRC is also responsible for approving the monitoring plan for each study.

- 2.2.2.2. CRC membership includes physicians from various Center programs, biostatisticians, epidemiologists, and a patient advocate.
- 2.2.2.3. Clinical trials are reviewed by the CRC in a two-stage process. First, protocols are reviewed all necessary sections are present, adequate, consistent, and complete. Then the study is sent to the full CRC where it receives a review as described in Section 1) a). After discussion, each member votes on the protocol.
- 2.2.2.4. Once studies are approved by the CRC they are forwarded to the IRB for review

2.2.3. Institutional Review Board

- 2.2.3.1. The Johns Hopkins Medicine Institutional Review Boards (JHM IRBs) are responsible for protecting the rights and welfare of the human subjects of research conducted by faculty and staff at Johns Hopkins Institutions. The JHM IRBs review all human subject research projects conducted by Hopkins faculty and staff.
- 2.2.3.2. Monitoring plans are reviewed and approved for each study by the IRB.

2.2.4. Internal Data Monitoring

- 2.2.4.1. The PI has the primary responsibility for continuous internal monitoring for safety, protocol compliance and identification, grading, coding and required reporting of all anticipated and unanticipated protocol events/problems. This responsibility is usually shared between the PI, research nurse and data manager. The PI is ultimately responsible for grading and attribution of all events.

2.2.5. External Data Monitoring

- 2.2.5.1. The SKCCC CRO Quality Assurance Program is responsible for external data monitoring. Alternately, the Sponsor/PI may use external agency for data monitoring. For example, CTEP uses Theradex for Phase I studies.

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- 2.2.5.2. Monitoring visits occur at least annually; but may be as frequent as monthly for rapidly accruing and/or high-risk trials. Monitoring occurs for 100% of subjects enrolled on the trial.

- 2.2.5.3. During routine monitoring visits, the following are generally reviewed:
 - (1) Accrual
 - (2) Consent forms
 - (3) Eligibility
 - (4) Data completeness
 - (5) Data timeliness
 - (6) Data accuracy
 - (7) Anticipated and unanticipated protocol event/problem identification, grading, attribution and appropriate reporting

- 2.2.5.4. Following a monitoring visit, a report is prepared and sent to the PI, study staff and DSMC for review.

- 2.2.5.5. Monitoring SOPs and guidelines have been developed for use, when the external monitor is the SKCCC CRO Quality Assurance Program.

2.2.6. Quality Assurance Auditing

- 2.2.6.1. The Quality Assurance Program is responsible for ensuring protocol compliance and the validity and integrity of data for all Institutional and Externally Peer Reviewed clinical trials. This is accomplished through a comprehensive auditing program. The level of oversight is commensurate with the risk, size and complexity of the clinical trial. Auditors are well trained in the diseases for which they are auditing.

- 2.2.6.2. Two types of audits are routinely performed
 - 2.2.6.2.1. Early audits are scheduled after the first subject has been enrolled. The focus is protocol compliance. Findings are reviewed with the PI and study staff.

 - 2.2.6.2.2. Periodic audits generally occur annually. In addition to a full administrative/regulatory review, three to six subject's research records and corresponding source documents are reviewed.

- 2.2.6.3. Areas of concentration for audits are:

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- (1) Timely submission of continuing review reports, amendments, and reportable protocol events
- (2) Accrual
- (3) Valid signed consent forms
- (4) Eligibility
- (5) Data Quality
- (6) Treatment administration
- (7) Response / Outcome Assessment
- (8) Anticipated and unanticipated protocol event/problem identification, grading, attribution and appropriate reporting
- (9) Study Drug/Instrument Accountability

2.2.6.4. Audit findings are reviewed with the PI and study staff and a final report is sent to the DSMC and/or DSMB for review and approval.

2.2.7. Data And Safety Monitoring Committee

2.2.7.1. The DSMC is charged with ensuring the safety of participants and the validity and integrity of the data and the appropriate termination of studies for which significant benefits or risks have been uncovered. The Committee is responsible for continuous, ongoing review of the conduct of the trial, including adherence to study design and documentation of appropriate monitoring and reporting of protocol events. Inherent in this process is the goal of enhancing the quality of the research by providing the investigator with constructive criticism. The DSMC membership includes physicians from various Center Programs and representatives from biostatistics, data management, nursing, and quality assurance.

2.2.7.2. DSMC members may not have a conflict of interest with any aspect of the trials they monitor. Members must abstain from voting and making recommendations for any trial where they are an investigator or have a conflict of interest. Conflict of interest is defined and managed by the Johns Hopkins University Conflict of Interest Policy.

2.2.7.3. The DSMC reviews:

- 2.2.7.3.1. Reportable anticipated and unanticipated protocol events/problems. The DSMC Chair or designee and QA manager meet at least two times per month to review all events that were submitted to the CRO.

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- (1) Events that may be potentially significant are referred to the DSMC for full review while non-significant events are reviewed in a summary format by the DSMC.
- (2) With respect to subject safety, the Chair may place a temporary hold on any trial pending full DSMC review
- (3) The DSMC may recommend any of the following:
 - (a) No action
 - (b) Request further information/follow-up by PI
 - (c) Temporary hold on accrual
 - (d) Termination of the trial with required reporting to appropriate regulatory agencies
- (4) A Flow Diagram for the reportable protocol events/problems review process is outlined in Appendix A

2.2.7.3.2. Protocol Amendments

- (1) The DSMC Chair or designee and QA manager meet at least two times per month to review all amendments that were submitted to the CRO.
- (2) Administrative or minor amendments do not receive any further consideration by the DSMP committees
- (3) Amendments that may significantly impact the scientific merit of the trial are referred to the CRC for review
- (4) Amendments that may have a significant impact on subject safety are referred to the full DSMC for review
- (5) With respect to subject safety, the Chair may place a temporary hold on any trial pending full DSMC review
- (6) The DSMC may recommend any of the following:
 - (a) No action
 - (b) Request further information/follow-up by PI
 - (c) Temporary hold on accrual
 - (d) Termination of the trial with required reporting to appropriate regulatory agencies
- (7) Flow Diagrams for the Amendment review process is outlined in Appendix B

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2.2.7.3.3. Audit and Monitoring Reports

- (1) Quality Assurance manager presents a synopsis of audit and monitoring findings and recommendations
- (2) The auditor and/or monitor will be present to answer any questions from the Committee
- (3) Committee members may:
 - (a) Accept report as is
 - (b) Recommend QA change report
 - (c) Add, reclassify or delete deficiencies
- (4) Committee members vote on final outcome:
 - (a) Acceptable
 - (b) Acceptable with actions
 - (i) Require a Quality Improvement Plan
 - (ii) Re-audit at a specified time frame for compliance
 - (c) Not acceptable
 - (i) Close the trial with required reporting to appropriate regulatory agencies
 - (ii) Require a Quality Improvement Plan
 - (iii) Re-audit at a specified time frame for compliance

2.2.8. Medical Expert Committee

2.2.8.1. In some clinical trials, the expected outcome may be difficult to assess. This may require oversight by a group with greater expertise in a specific medical area than the DSMC can provide, but less extensive than a DSMB. In such cases, the protocol must specify procedures for an expert medical monitoring process which entail:

2.2.8.1.1. Membership of Monitoring Group

2.2.8.1.2. Content of Review

2.2.8.1.3. Authority of Committee

2.2.8.1.4. Review and reporting frequency

2.2.8.1.5. Reporting Requirements

2.2.8.2. In general, the Medical Expert Committee uses data reported by the internal data monitoring process and the external monitor.

2.2.8.3. If the DSMC and the Medical Expert Committee have differing recommendations, the DSMC will have final decisional authority

2.2.9. Data and Safety Monitoring Board

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- 2.2.9.1. SKCCC has a DSMB available for investigators to utilize. An investigator may assemble a DSMB specific to the trial. The DSMB membership must be approved by the CRC, IRB and NCI.
- 2.2.9.2. The DSMB is charged with monitoring and evaluating three aspects of clinical trials. These Include:
 - 2.2.9.2.1. Safety: By reviewing interim toxicity data for a trial in order to assure the continuing safety of subjects
 - 2.2.9.2.2. Efficacy: By reviewing interim analyses of outcome data, prepared by the study statisticians to assure that the data are consistent with identifying an important clinical efficacy.
 - 2.2.9.2.3. Study Progress: By reviewing outcome data, to assure that the study can be completed in a reasonable time frame to be of significant clinical relevance.
- 2.2.9.3. The DSMB Membership will include voting and nonvoting members. The core DSMB must include five members. These should include at least one experienced oncologist, a statistician and a lay representative. Members should be selected based upon their expertise, experience, reputation for objectivity, knowledge of clinical trial methodology and absence of a significant conflict of interest. Members may not have a conflict of interest with any aspect of the trials they monitor. Conflict of interest is defined by the Johns Hopkins University Conflict of Interest Policy. The DSMB will meet at least twice annually or more frequently as dictated by the requirements of clinical trials under its supervision. Data review dates should be selected so that the committee can prepare a report for the continuing review of supervised trials.
- 2.2.9.4. The formal meeting of the DSMB for each trial shall consist of three parts. The first part is an open session in which members of the clinical team, including the principal investigator and trial statisticians are available to review data with the DSMB. Outcome results must not be discussed during this open session. Following the open session, the DSMB may hold a closed session including members of the board and appropriate members of the coordinating center and the statistician handling the trial. The third phase of each meeting is an executive session involving only voting DSMB members and may be held to allow the DSMB to discuss general conduct of the trial and all outcome results,

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including toxicities, adverse events, and other protocol events/problems, to develop recommendations, and to take votes as necessary. The DSMB recommendation and the SKCCC action plan, if any, will be forwarded together to the IRB, NIH, FDA and sponsor as appropriate, providing the opportunity for their opinions and recommendations. In no cases will the DSMB recommendations be taken as binding, provided reasons for an alternative course of action are endorsed by the CRC and investigator.

2.2.9.5. Following each study review, the DSMB will recommend either:

2.2.9.5.1. Continuation of the trial as is using the current protocol and statistical plan.

2.2.9.5.2. Continuation of the project with modifications as outlined by the board

2.2.9.5.3. Immediate suspension of the trial for safety reasons with a recommended plan of follow-up to minimize subject harm.

2.2.9.5.4. Placing a clinical hold on a trial. Subjects may continue on their assigned treatments until clarifications requested by the board are resolved.

2.2.9.5.5. Termination of the trial because of 1) treatment effectiveness demonstrated earlier than expected ("early stopping"), 2) futility of further accrual to meet the trials goal, 3) discovery of new information that precludes completion of the trial, or 4) structural problems in trial execution that are not amenable to correction.

3. COMPLIANCE WITH PROBLEM/EVENT REPORTING REQUIREMENTS

3.1. Problems and Events include: on-site and off-site adverse events, injuries, side effects, breaches of confidentiality, or other problems that may occur any time during or after the research study

3.2. Reporting of problems/events involving risk to participants or others in all clinical trials at SKCCC is conducted in accordance with all appropriate federal regulations and guidelines as well as Institutional policies and guidelines. In addition, problem/event reporting procedures are specified in detail in each protocol, depending upon the type of study, the severity of the problem/.event, the study sponsor, and the existence of an IND/IDE.

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3.3. Reporting Guidelines followed at SKCCC

3.3.1. NCI

3.3.1.1. [CTEP, NCI Guidelines: Adverse Event Reporting Requirements](#)³

3.3.1.2. [NCI, Data and Safety Monitoring Guidelines](#)⁴

3.3.2. FDA

3.3.2.1. [Information for FDA-Regulated Industry](#)⁵

3.3.2.2. [21 CFR 312.32 IND Safety Reports](#)⁶

3.3.2.3. [21 CFR 812.150 IDE Safety Reports](#)⁷

3.3.3. Johns Hopkins Institutional Review Board (JHM IRB)

3.3.3.1. [Protocol Event And Protocol Deviation Reporting Requirements](#)⁸

3.3.4. Western Institutional Review Board (WIRB)

3.3.4.1. [WIRB Protocol Deviations & Violations / Unanticipated Problems Reporting System](#)⁹

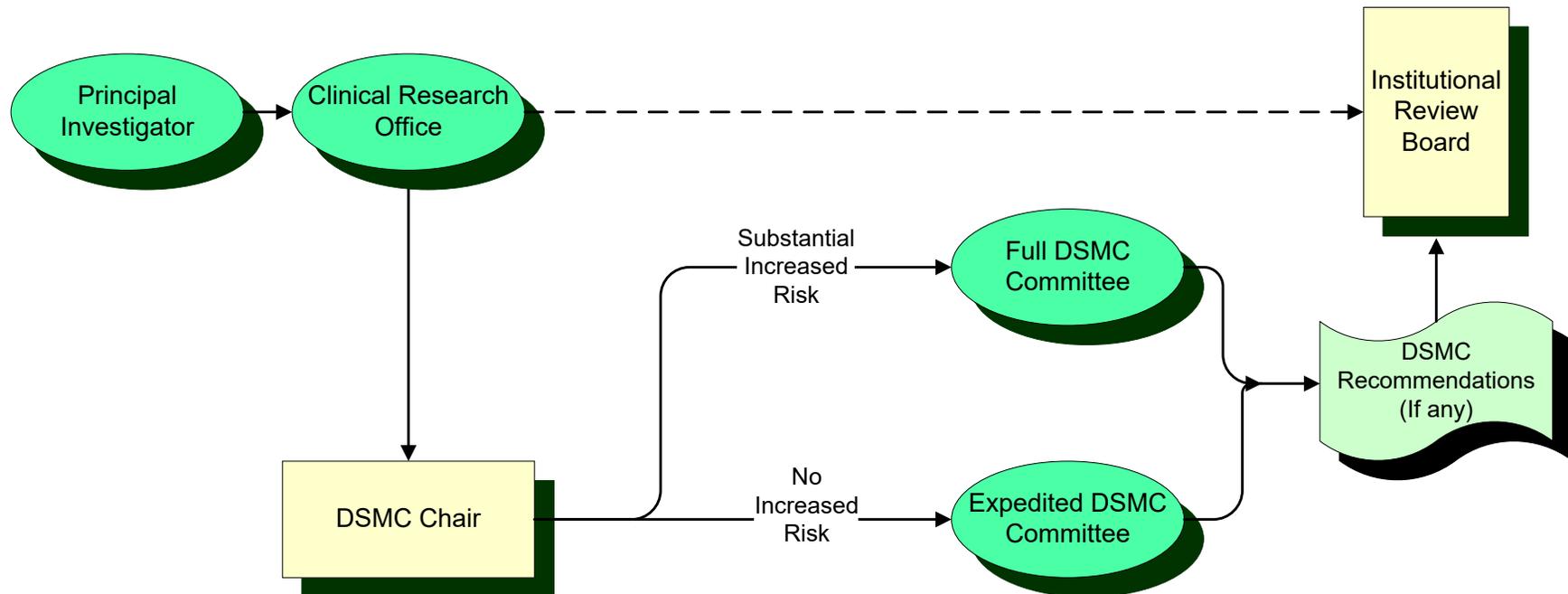
4. MULTI-SITE CLINICAL TRIALS

Principal Investigators from the SKCCC may invite Investigators from other institutions to participate in a clinical trial. In these cases, the Principal Investigator is ultimately responsible for the conduct of the trials at all participating sites, and is required to establish a Coordinating Center to manage all trial related documents and data. The SKCCC Coordinating Center SOPs and Operations Manual were developed to assist investigator when they are responsible for the coordinating center of a clinical.

The Operations Manual is available in Appendix C. The manual describes the processes and oversight that SKCCC coordinating centers have in place for collecting and reporting AEs to all necessary regulatory agencies and co-investigators at participating institutions.

Phase II Study of Erlotinib (Tarceva™) Combined with Chemoradiation and Adjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer
Appendix A: Review of Reportable Protocol Events

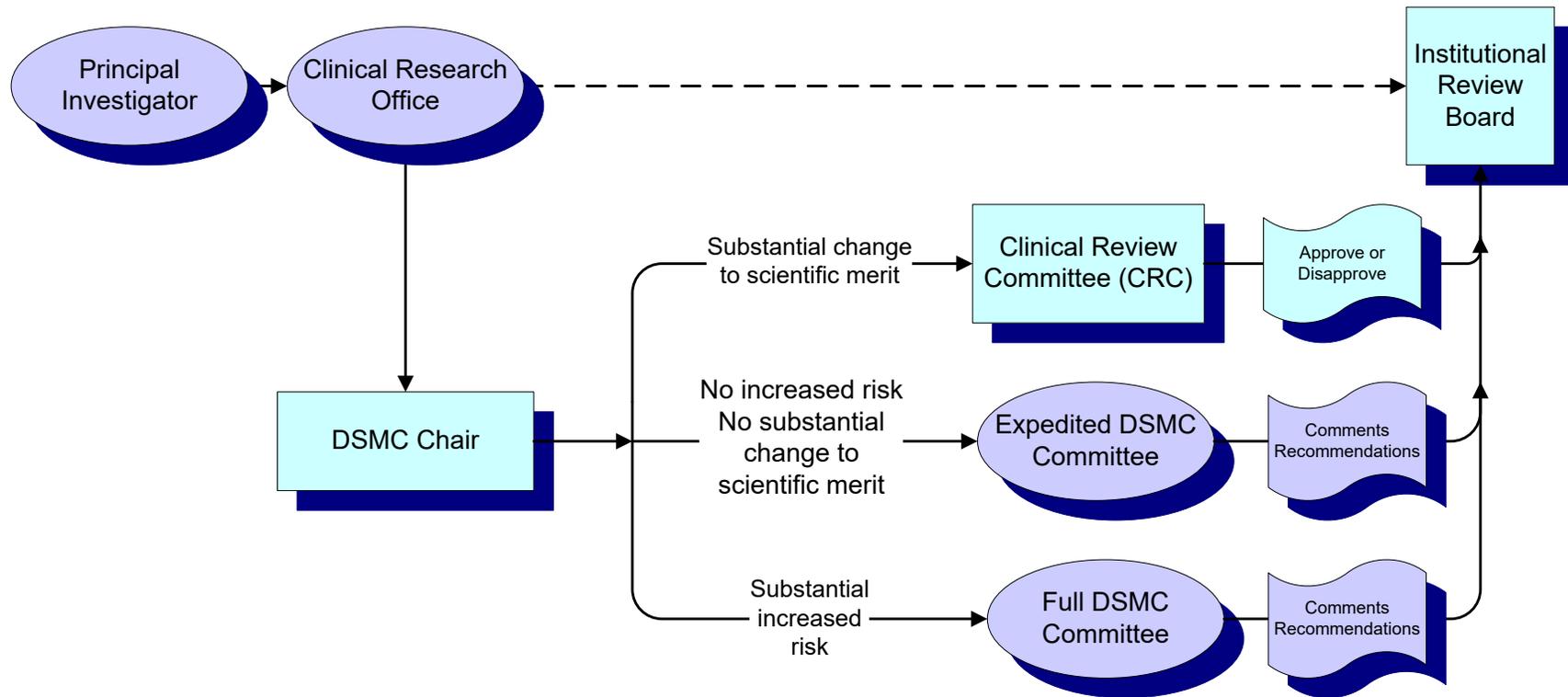
Flow Diagram: Review of Reportable Protocol Events at Sidney Kimmel Comprehensive Cancer Center



Please Note: Copies of Reportable Events will be held in the CRO for DSMC Review. Originals will be forwarded to the IRB for parallel review. DSMC / CRO will notify the IRB of any recommended action.

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Appendix B: Review of Amendments

Flow Diagram: Amendment Reviews at Sidney Kimmel Comprehensive Cancer Center



Please Note: Copies of amendments will be held in the CRO for Committee Review. Originals will be forwarded to the IRB for parallel review. DSMC / CRO will notify the IRB of any recommended action.

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¹ <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>, and
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>

² <http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1>

³ [NCI Reporting Guidelines at http://ctep.gov/reporting](http://ctep.gov/reporting)

⁴ <http://cancertrials.nci.nih.gov/clinicaltrials/conducting/dsm-guidelines/page5>

⁵ <http://www.fda.gov/oc/industry/default.htm>

⁶ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=312.32>

⁷ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=812.150>

⁸ http://irb.jhmi.edu/Guidelines/Event_Deviation_Reporting.html

⁹ http://www.wirb.com/shell.php?content=content/inv_adverse_events