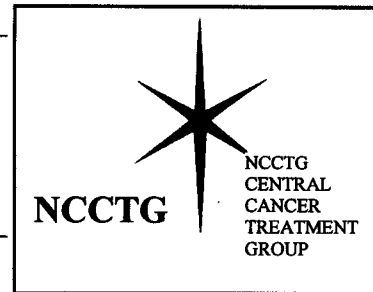

Operations Office

Telephone (507) 266-3853



Date: August 29, 2003

To: NCCTG Primary Clinical Research Associates

From: Linda S. Long

Re: N0177, Pilot and Phase II Trial of OSI-774 and Radiation in Glioblastoma Multiforme Patients

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with OSI-774 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_105114_F1

Please note that all risks currently cited in the NCCTG consent form can not be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Linda S. Long at 507-266-3853.

lsl
enclosure

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting
Genentech, Inc.

Relays International, Inc.
FDA Facsimile Approval: 11-JUN-1999

Mfr report #	105114
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FDA Use Only	

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A. Patient information

1. Patient identifier in confidence	2. Age at time of event 66 Years or Date of birth:	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight 155.0 lbs or 70.4 kgs
--	---	---	--

B. Adverse event or product problem

1. <input checked="" type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)	
2. Outcomes attributed to adverse event (check all that apply)	
<input type="checkbox"/> death	<input type="checkbox"/> disability
<input type="checkbox"/> life-threatening	<input type="checkbox"/> congenital anomaly
<input checked="" type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
<input type="checkbox"/> other:	
3. Date of event (month/day/yr) 11/26/2002	4. Date of this report (month/day/yr) 08/01/2003

5. Describe event or problem
small bowel obstruction[SMALL INTESTINAL OBSTRUCTION NOS]

Case Description:
IND SAFETY REPORT - FOLLOW-UP #1
SMALL BOWEL OBSTRUCTION (PREVIOUSLY REPORTED AS BOWEL PERFORATION)

This case, manufacturer control number 105114, is a report from the United States referring to a 66-year-old female. An investigator reported this case from study OSI2298g, a Genentech, Inc. sponsored phase III, randomized, double-blind, multinational trial of erlotinib plus paclitaxel and carboplatin versus chemotherapy alone in subjects with advanced (stage IIIb or IV) non-small cell lung cancer (NSCLC) who have not received prior chemotherapy.

continued in additional info section...

6. Relevant tests/laboratory data, including dates
NI

7. Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
NI

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)	
#1. ERLOTINIB OR PLACEBO(Erlotinib) (continued)	
#2. PACLITAXEL(PACLITAXEL) Soluti (continued)	
2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) <small>how/No (or best estimate)</small>
#1. 150 mg, qd, Oral	#1. 01/25/2002 to 11/13/2002
#2. 368 mg, (continued)	#2. 01/25/2002 to 05/10/2002
4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1. NON-SMALL CELL (continued)	#1. <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply
#2. NON-SMALL CELL (continued)	#2. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK
6. Lot # (if known)	7. Exp. date (if known)
#1. NO(continued)	#1. UNK
#2. NO(continued)	#2. UNK
9. NDC # - for product problems only (if known)	
8. Event reappeared after reintroduction	
#1. <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
#2. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK	

10. Concomitant medical products and therapy dates (exclude treatment of event)
CALCIUM (CALCIUM NOS) UNK to UNK
FERROUS SULFATE (FERROUS SULFATE) UNK to UNK
continued in additional info section...

G. All Manufacturers

1. Contact office - name/address (& mfring site for devices) Genentech, Inc. James Nickas Pharm.D. Mailstop: 84, 1 DNA Way South San Francisco, CA 94080 UNITED STATES	2. Phone number
	3. Report source (check all that apply)
	<input type="checkbox"/> foreign
	<input checked="" type="checkbox"/> study
	<input type="checkbox"/> literature
	<input type="checkbox"/> consumer
	<input checked="" type="checkbox"/> health professional
	<input type="checkbox"/> user facility
	<input type="checkbox"/> company representative
	<input type="checkbox"/> distributor
	<input type="checkbox"/> other:
4. Date received by manufacturer (month/day/yr) 07/18/2003	5. (A)NDA # IND # 61,874 PLA # pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes
6. If IND, protocol # OSI2298G	7. Type of report (check all that apply)
	<input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day
	<input type="checkbox"/> 10-day <input type="checkbox"/> periodic
	<input type="checkbox"/> initial <input checked="" type="checkbox"/> follow-up.# 1
9. Mfr. report number 105114	8. Adverse event term(s) SMALL INTESTINAL OBSTRUCTION NOS

E. Initial reporter

1. Name & address	phone #
2. Health professional ? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation Physician
4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> unk	



3500A - Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

**Medication and Device
Experience Report**
(continued)

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Genentech, Inc.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration

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C. Suspect medication(s)	
1. Name (give labeled strength & mfr/labeler, if known) # 3. CARBOPLATIN Solu (continued) # 4.	
2. Dose, frequency & route used # 3. 557 mg, (continued) # 4.	3. Therapy dates (if unknown, give duration) <small>from to (or best estimate)</small> # 3. 01/25/2002 to 05/10/2002 # 4.
4. Diagnosis for use (indication) # 3. NON-SMALL CELL (continued) # 4.	5. Event abated after use stopped or dose reduced # 3. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK # 4. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
6. Lot # (if known) 7. Exp. date (if known) # 3. NO(continued) # 3. UNK # 4. # 4.	8. Event reappeared after reintroduction # 3. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply UNK # 4. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
9. NDC # - for product problems only (if known) NA	
10. Concomitant medical products and therapy dates (exclude treatment of event) NA	

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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**Medication and Device
Experience Report**
(continued)

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Additional Information

B5. EVENT DESCRIPTION (cont.)

Past medical history was significant for a hiatal hernia, an episode of severe hives attributed to an imbalance between estrogens and progestins, colonic polyps and congenital left ureteral stenosis, which was temporarily stented. She was diagnosed with bronchoalveolar cell carcinoma in July 1995 initial treatment included a thoracotomy. In December 2001, she presented with a left upper lobe infiltrate associated with a superior mediastinal/supraclavicular mass, hilar adenopathy and a 2.0 cm lesion in the liver. Concomitant medications included calcium, ferrous sulfate, vitamin E, a multivitamin, alendronate, raloxifene, levothyroxine, ranitidine, cyanocobalamin, folic acid and ascorbic acid.

On 25 Jan 2002, the subject received erlotinib (150 mg by mouth QD), paclitaxel (368 mg IV Q3W) and carboplatin (557mg IV Q3W). The most recent infusions of paclitaxel and carboplatin were administered on 10 May 2002.

On 15 Nov 2002, the subject was seen in the office as a follow up to previous complaints of abdominal pain, cramping and diarrhea. At the time of the visit she denied any diarrhea. Upon examination, her abdomen was described as soft, minimal tenderness and no guarding or rebound. It was recommended that she stop erlotinib to allow her abdomen to recover. The patient refused to stop taking erlotinib.

On 21 Nov 2002, the subject was again seen in the office for follow up. She had recently been treated with antibiotics for possible diverticulitis. Her abdominal symptoms had regressed significantly but she still had residual cramping. Bowel movements were reported to be normal. Upon examination, her abdomen was described as soft but distended with gas and no areas of tenderness were noted. It was again recommended that she stop erlotinib therapy.

On 26 Nov 2002, the subject had increasing abdominal pain and was admitted to the hospital for a possible small bowel obstruction. Upon admission, a study of the abdomen/pelvic with contrast was performed, which revealed a stable large hiatal hernia, marked dilatation of the small bowel to the level of the ileocecal region but no evidence of diverticulitis. A repeat small bowel film was obtained on 29 Nov 2002, which revealed a small bowel obstruction, probably involving the distal ileum with a mild to moderate degree of proximal jejunal dilatation. On 30 Nov 2002, the subject was taken to the operating room where she underwent an ileocelectomy and left oophorectomy. Findings included diffuse inflammation in the abdomen/pelvis mostly small bowel secondary to multiple abscess cavities, which appear to originate from what likely represented an old undiagnosed perforated appendicitis. A left ovarian mass that was suspicious for malignancy was resected. It was noted there was no appendix visible and it was suspected that it may have ruptured giving rise to a large abscess. Additionally it was noted there was a sizable hole in the cecum communicating with an abscess cavity. The pathology report confirmed the findings of the abscess adjacent to the terminal ileum and cecum. The ovarian mass was found to be a benign fibroma. Further clinical course and treatment not reported.

On 11 Dec 2002, the subject was discharged from the hospital and the event was reported as resolved.

The investigator assessed the event of NCI CTC grade 4 perforated bowel as related to erlotinib.

Upon unblinding (11 Dec 2002), it was determined the subject was receiving erlotinib.

Additional information has been requested.

Additional information received on 18 Jul 2003 indicated that the subject's last dose of erlotinib was administered on 13 Nov 2002; the investigator re-assessed the event as not related to erlotinib, but related to a concurrent illness; and the primary event term of bowel perforation was changed to small bowel obstruction (NCI-CTC grade 4).

No further information is expected.

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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**Medication and Device
Experience Report**
(continued)

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C1. Name (cont.)

Suspect Medication #1: ERLOTINIB OR PLACEBO(ERLOTINIB OR PLACEBO) Tablet

Suspect Medication #2: PACLITAXEL(PACLITAXEL) Solution for injection

Suspect Medication #3: CARBOPLATIN(CARBOPLATIN) Solution for injection

C2. Dose, frequency & route used (cont.)

Suspect Medication #2: 368 mg, Q3W, Intravenous

Suspect Medication #3: 557 mg, Q3W, Intravenous

C4. Diagnosis for use (cont.)

#1: NON-SMALL CELL LUNG CANCER

#2: NON-SMALL CELL LUNG CANCER

#3: NON-SMALL CELL LUNG CANCER

C6. lot#(if known) (cont.)

Suspect Medication #1: NOT REPORTED

Suspect Medication #2: NOT REPORTED

Suspect Medication #3: NOT REPORTED

C10. CONCOMITANT MEDICAL PRODUCTS

VITAMIN E (VITAMIN E) UNK to UNK

MULTIVITAMIN (MULTIVITAMINS NOS) UNK to UNK

FOSAMAX (ALENDRONATE SODIUM) UNK to UNK

EVISTA (RALOXIFENE HYDROCHLORIDE) UNK to UNK

LEVOXYL (LEVOTHYROXINE SODIUM) UNK to UNK

ZANTAC (RANITIDINE) UNK to UNK

VITAMIN B12 (CYANOCOBALAMIN) UNK to UNK

FOLIC ACID (FOLIC ACID) UNK to UNK

VITAMIN C (ASCORBIC ACID) UNK to UNK

MED WATCH	A.1. Patient Identifier	G.9. Mfr. report number 105114	Addendum
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Follow-Up IND SAFETY REPORT

Additional information received on 18 Jul 2003 indicated that the subject's last dose of erlotinib was administered on 13 Nov 2002. The investigator re-assessed the event as not related to erlotinib, but related to concurrent illness. Also the primary event term was changed to small bowel obstruction. See FOLLOW-UP ASSESSMENT OF RELATIONSHIP.

CASE SUMMARY: Genentech MCN 105114

This IND safety report of INTESTINAL PERFORATION refers to a 66-year-old female enrolled in OSI2298g, a phase III, randomized, double-blind trial of paclitaxel / carboplatin with or without erlotinib/placebo in advanced non-small cell lung cancer (NSCLC). She was diagnosed with bronchoalveolar cell carcinoma in July 1995; initial treatment included a thoracotomy. In December 2001, recurrence of NSCLC was identified.

Trial medication, begun in January 2002, consisted of erlotinib administered as 150 mg PO QD with paclitaxel (368 mg IV Q3W) and carboplatin (557 mg IV Q3W). The last cycle of paclitaxel and carboplatin prior to the event was administered on 10 May 2002.

During early November 2002, the subject was evaluated at least twice for diarrhea and abdominal pain. She was treated with antibiotics for diverticulitis. The treating physician recommended discontinuation of study drug; however, it was unclear whether the subject followed this medical advice. *In follow-up, it was determined that the subject's last dose of erlotinib was administered on 13 Nov 2002.*

On 26 Nov 2002, the subject was admitted to the hospital for increasing abdominal pain. On 29 Nov 2002, a small bowel x-ray revealed a small bowel obstruction, probably involving the distal ileum. She was taken to the operating room where she underwent an ileocelectomy and left oophorectomy. The operative and pathology reports noted a large multifocal abscess in the ileocecal area, as well as a secondary small bowel obstruction and an ovarian fibroma. The appendix was not visible and "may have ruptured and given rise to the large abscess" per the pathology report.

The investigator assessed the intestinal perforation as related to erlotinib based on the recent history of diarrhea; *follow-up indicated that the investigator re-assessed the event as not related to erlotinib, but related to concurrent illness.*

Upon unblinding, it was determined the subject was receiving erlotinib.

ANALYSIS OF SIMILAR EVENTS

The Roche, OSI-P, and Genentech Safety Databases for erlotinib were searched for all serious events with the primary or linking preferred term of intestinal perforation.

Previous Reports of Intestinal Perforation:

There were 8 previously reported serious adverse events (SAEs) of gastrointestinal perforation, all of which were assessed as not related to erlotinib/placebo (Table 1).

Events of Gastrointestinal Perforation (Table 1)

Roche ID Study Age/Sex	Indication/ Chemotherapy	Preferred Term	Causality	Outcome	Comments
309575 BO16411 73 yr/male	NSCLC Cisplatin Gemcitabine	Gastric Perforation	Not related	Resolved	Confounders included the use of steroids and history of peptic ulcer disease
319340 OSI2298g 73 yr/female	NSCLC Carboplatin Paclitaxel	Gastric Ulcer Perforation	Not related	Died	
320027 OSI2298g 60 yr/male	NSCLC Carboplatin Paclitaxel	Diverticular Perforation	Not related	Resolved	Laparotomy - perforated sigmoid diverticulum with walled off abscess
320225 OSI2298g 71 yr/female	NSCLC Carboplatin Paclitaxel	Duodenal Ulcer Perforated	Not related	Resolved	Confounders included the use of steroids
320356 OSI2298g 53 yr/male	NSCLC Carboplatin Paclitaxel	Perforated Bowel	Not related	Resolved	Path report: poorly differentiated carcinoma; Confounders included the use of steroids
321113 BO16411 71 yr/male	NSCLC Cisplatin Gemcitabine	Duodenal Ulcer Perforation	Not related	Resolved	Confounders included the use of steroids
324322 BO16411 52 yr/male	NSCLC Cisplatin Gemcitabine Docetaxel	Stomach Perforation	Not Related	Resolved	Confounders included the use of steroids
318117 BO16411 64 yr/male	NSCLC Cisplatin Gemcitabine	Gastric Ulcer Perforation	Not Related	Not reported (Patient died after experiencing a cerebral accident)	Confounders included the use of steroids

Initial Assessment of Relationship

Regarding the index case, limited information was available, eg, erlotinib dosing administration and history of concurrent diverticulitis; hence it is difficult to assess a cause and effect relationship to erlotinib. Chronic appendicitis is a possible confounding factor. The concomitant medications ranitidine, raloxifene and alendronate may also be contributory. Regarding the 8 similar events of gastrointestinal perforation, most (6) involved gastric or duodenal perforation and were likely related to underlying ulcer disease. In the remaining 2 cases, a jejunal perforation was attributed to malignancy and a sigmoid perforation was attributed to diverticulitis.

Based on the review of available data, the sponsor cannot establish or exclude the possibility of a cause and effect relationship between administration of erlotinib and the occurrence of intestinal perforation. Ongoing randomized controlled trials, such as the current Phase III trial OSI2298g, will allow a comparison of the rates of such events in erlotinib treatment arms to those in chemotherapy alone treatment arms.

After review of the clinical details and investigators' comments pertaining to this adverse event and based upon the experience of erlotinib to date, the sponsor does not believe that changes to the conduct of this clinical trial are warranted. However, Genentech, Inc., intends the submission of this IND Safety Report of INTESTINAL PERFORATION to represent a safety amendment to the OSI-774 (erlotinib; Tarceva) Investigator Brochure.

Follow-up Assessment of Relationship

Given the change in investigator causality assessment from related to not related, this case is now classified as "not related" to Tarceva and INTESTINAL PERFORATION is not considered to be an expected event. Genentech, Inc., intends the submission of this follow-up report to represent a safety amendment to the OSI-774 (erlotinib; Tarceva) Investigator Brochure.