VOLUME 27 · NUMBER 33 · NOVEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Dose Finding and Early Efficacy Study of Gemcitabine Plus Capecitabine in Combination With Bevacizumab Plus Erlotinib in Advanced Pancreatic Cancer

*Naureen Starling, David Watkins, David Cunningham, Janet Thomas, Janine Webb, Gina Brown, Karen Thomas, Jacqui Oates, and Ian Chau*

See accompanying editorial on page 5487 and articles on pages 5506, 5513, and 5660

From the Departments of Medicine, Radiology, and Computing and Statistics, Royal Marsden Hospital, National Health Service Foundation Trust, Surrey and London, United Kingdom.

Submitted December 18, 2008; accepted March 25, 2009; published online ahead of print at www.jco.org on October 26, 2009.

Supported by Royal Marsden Hospital National Health Service (NHS) Foundation Trust. We acknowledge NHS funding to the National Institute for Health Research Biomedical Research Centre. Hoffman-La Roche provided an educational grant toward running the trial and provided capecitabine, erlotinib, and bevacizumab at no cost.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: David Cunningham, MD, FRCP, Department of Medicine, Royal Marsden Hospital, Downs Rd, Sutton, Surrey, SM2 5PT, United Kingdom; e-mail: david.cunningham@rmh.nhs.uk.

The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).



0732-183X/09/2733-5499/$20.00

DOI: 10.1200/JCO.2008.21.5384

## ABSTRACT

### Purpose
This study evaluated safety and efficacy of chemotherapy (gemcitabine plus capecitabine) plus bevacizumab/erlotinib in advanced pancreatic cancer because dual epidermal growth factor receptor/vascular endothelial growth factor blockade has a rational biologic basis in this malignancy.

### Patients and Methods
Patients with untreated, unresectable, locally advanced or metastatic pancreatic carcinoma were enrolled onto one of the following four sequential dose levels (DLs) of escalating capecitabine doses (days 1 to 21): DL1, 910 mg/m$^2$; DL2, 1,160 mg/m$^2$; DL3, 1,400 mg/m$^2$; or DL4, 1,660 mg/m$^2$. Doses of coadministered gemcitabine (1,000 mg/m$^2$ on days 1, 8, and 15), bevacizumab (5 mg/kg on days 1 and 15), and erlotinib (100 mg/d) every 28 days (up to six cycles) were fixed. Using a 3+3 study design, dose-limiting toxicity (DLT) was assessed in cycle 1.

### Results
Twenty assessable patients were enrolled (DL1, n = 8; DL2, n = 3; DL3, n = 6; and DL4, n = 3); 97 cycles were administered. Median age was 63 years (range, 33 to 77 years), and male-to-female ratio was 10:10. Performance status was 0 and 1 in two and 17 patients, respectively; and nine and 11 patients had locally advanced and metastatic disease, respectively. DLT occurred in one patient at DL1 (grade 3 epistaxis) and two patients at DL4 (grade 3 diarrhea and grade 3 skin rash > 7 days). Common grade 3 and 4 toxicities (10% to 20%) were diarrhea, hand-foot syndrome, stomatitis, and skin rash. Grade 3 lethargy and grade 3 or 4 neutropenia occurred in 40% and 45% of patients, respectively. No GI perforation, grade 3 GI hemorrhage/hypertension, or pneumonitis occurred. Ten partial responses were observed. Median overall and progression-survival times (all patients) were 12.5 and 9.0 months, respectively.

### Conclusion
The maximum-tolerated dose of capecitabine was 1,660 mg/m$^2$. The recommended capecitabine dose in this cytotoxic doublet/biologic doublet regimen is 1,440 mg/m$^2$; this regimen is under evaluation in an ongoing phase II study.

*J Clin Oncol 27:5499-5505. © 2009 by American Society of Clinical Oncology*

## INTRODUCTION

Pancreatic cancer is the eighth most common cause of cancer-related death worldwide[1] and is associated with a dismal prognosis, with a 5-year survival rate of less than 5% to 6%.[2-4] The majority of patients present with advanced unresectable disease, correlating with a median overall survival time of 3 to 4 months if untreated. Gemcitabine monotherapy was established as a palliative option based on improved clinical benefit for gemcitabine compared with bolus fluorouracil and was accompanied by marginal improvement in median overall survival (5.65 *v* 4.41 months, respectively, and 1-year survival rate, 18% *v* 2%, respectively; $P = .0025$). Subsequently, many alternative cytotoxic/biologic agents and gemcitabine doublets containing investigational agents have failed to demonstrate superiority in survival over gemcitabine alone in randomized evaluation. However, a recent meta-analysis of these trials indicated a likely survival benefit for gemcitabine doublets containing either platinum agents or the oral fluoropyrimidine capecitabine.[5]

The epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) receptor pathways are thought to play important roles in the initiation and growth of pancreatic cancer. Both EGFR and VEGF are overexpressed

in pancreatic cancer and are associated with poor prognosis and disease progression,[6-8] and antagonism of their signaling in preclinical models inhibits tumor growth.[9-14] There is commonality and cross talk between the downstream signaling pathways of the EGFR and VEGF receptor. EGFR may modulate angiogenesis via effects on VEGF and vice versa.[15-17] These interactions include EGFR-mediated upregulation of VEGF expression[18] and VEGF-mediated resistance to EGFR inhibition,[16] thereby providing a biologic rationale for dual targeted therapy. This rationale is supported by preclinical studies in gastric, colon, and pancreatic xenograft models, which demonstrate at least additive effects,[19-21] and by early phase clinical studies in colon and non–small-cell lung cancer, which indicate antitumor activity for anti-EGFR/anti-VEGF doublets and favorable safety profiles.[22-24] These trials mostly assessed erlotinib (an EGFR small-molecule tyrosine kinase inhibitor) combined with bevacizumab (an anti-VEGF humanized monoclonal antibody). Both drugs have separately demonstrated clinical activity when administered with gemcitabine in pancreatic cancer, and erlotinib (plus gemcitabine) is licensed for advanced pancreatic cancer.[25,26]

This study was undertaken to evaluate the safety and efficacy of adding a biologic doublet (erlotinib plus bevacizumab) to a cytotoxic platform for treating advanced chemotherapy-naive pancreatic cancer. When this study was initiated, preliminary analysis of the United Kingdom National Cancer Research Institute randomized trial of gemcitabine versus gemcitabine plus capecitabine (GemCap) had reported a significant survival advantage for GemCap,[27] with efficacy further being supported by subsequent meta-analysis.[5] Therefore, GemCap comprised the cytotoxic platform in this study. Because of potential overlapping toxicity between erlotinib and capecitabine, a dose-escalation design was used to increase the dose of capecitabine toward the target daily dose of 1,660 mg/m$^2$, with safety and efficacy as primary and secondary outcome measures, respectively.

## PATIENTS AND METHODS

### Patients

Eligible patients had inoperable histologically/cytologically proven locally advanced or metastatic pancreatic ductal adenocarcinoma/undifferentiated carcinoma. Patients were older than 18 years; had Eastern Cooperative Oncology Group performance status (PS) $\leq 2$; and had adequate renal (creatinine clearance $\geq$ 50 mL/min), bone marrow (platelets $> 100 \times 10^9$/L, leukocytes $> 3.0 \times 10^9$/L, and absolute neutrophil count [ANC] $> 1.5 \times 10^9$/L), and liver (total bilirubin $< 2\times$ the upper limit of normal) function, a serum albumin $\geq$ 26 g/L, and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST).[28] Exclusion criteria included any prior chemotherapy, radiotherapy, or investigational agents; intracerebral/meningeal metastases; uncontrolled hypertension; significant cardiovascular comorbidity; major bleeding diathesis; full-dose anticoagulation before study; aspirin use ($\geq$ 325 mg/d); major surgery/traumatic injury within 28 days; nonhealing wound/fracture; second malignancy; uncontrolled comorbid conditions; and pregnancy/lactation. After a protocol amendment, patients with duodenal invasion were permitted. All patients provided written informed consent, and the study was approved by the local scientific review and research ethics committees.

### Trial Design and Treatment

This was an open-label, single-center study of the safety and tolerability of the gemcitabine, capecitabine, bevacizumab, and erlotinib combination. A 3+3 dose-escalation study design[29] was used to determine the optimal dose of capecitabine in this regimen. All patients received gemcitabine 1,000 mg/m$^2$ (intravenously over 30 minutes) on days 1, 8, and 15 of a 28-day cycle, together with bevacizumab 5 mg/kg intravenously on days 1 and 15 (over 90 minutes, reducing to 60 then 30 minutes for subsequent infusions if tolerated) and erlotinib 100 mg orally daily on days 1 through 28. These were coadministered with oral capecitabine (days 1 to 21), which was administered in escalating doses in sequential patient cohorts as follows: dose level (DL) 1 = 910 mg/m$^2$, DL2 = 1,160 mg/m$^2$, DL3 = 1,400 mg/m$^2$, and DL4 = 1,660 mg/m$^2$, representing 55%, 70%, 85%, and 100%, respectively, of the target dose of capecitabine in the GemCap regimen.[27] The total daily dose was administered in two divided doses. Treatment continued for six cycles or longer in patients deriving clinical benefit.

Each DL comprised a minimum of three patients assessable for cycle 1 dose-limiting toxicities (DLT), expanding to six patients if one DLT occurred. Dose escalation proceeded to the subsequent DL in the absence of DLT in three patients or $\leq$ one DLT among six patients. The maximum-tolerated dose (MTD) of capecitabine in the four-drug regimen was the dose that induced first-cycle DLT in one third or more of patients (ie, at least two of a maximum of six patients), thereby terminating accrual to that DL. The DL below the MTD could be expanded by up to six patients and declared the recommended dose for capecitabine for phase II evaluation (if associated with $\leq$ one DLT among six patients).

DLTs were treatment-related grade 4 neutropenia lasting $\geq$ 7 days, neutropenic fever, grade 4 thrombocytopenia, grade 3 or 4 diarrhea despite optimal supportive care, any nonhematologic toxicity $\geq$ grade 3 lasting $\geq$ 7 days (except for transient increases in liver transaminases), grade 3 or 4 hemorrhage or GI perforation, and treatment delay of more than 4 weeks as a result of toxicity. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

### Dose Modifications

DLT resulted in reduction of capecitabine to the next lower DL. For non–dose-limiting, nonhematologic toxicity, capecitabine therapy was interrupted until toxicity had resolved to $\leq$ grade 1 and then resumed at 75% of the intended dose, and on second occurrence, capecitabine was resumed at 50% of the intended dose. Re-treatment criteria required an ANC of more than $1.0 \times 10^9$/L and platelet count of more than $100 \times 10^9$/L. If the ANC was 0.5 to $1.0 \times 10^9$/L or the platelet count was 50 to $100 \times 10^9$/L, gemcitabine was dose reduced by 25%. Gemcitabine was omitted for a week for an ANC less than $0.5 \times 10^9$/L, platelets less than $50 \times 10^9$/L, or neutropenic sepsis. The latter or recurrent low ANC/platelet counts incurred a 25% dose reduction of gemcitabine. Full-dose gemcitabine was administered for nonhematologic toxicities $\leq$ grade 2, and a 25% dose reduction/omission was considered for grade 3 nonhematologic toxicity.

There were no dose reductions for bevacizumab. Patients developing new proteinuria (2+ on urinalysis) underwent 24-hour urinary protein measurement with $\geq$ 2 g protein/24 hours precluding further administration of bevacizumab until resolution to less than 2 g/24 hours. Bevacizumab was discontinued for grade 4 proteinuria, GI perforation, grade 3 or 4 hemorrhage, grade 4 hypertension, uncontrolled grade 3 hypertension, arterial thromboembolism, or symptomatic grade 4 venous thromboembolism. Erlotinib dosing was interrupted for related grade 3 nonhematologic toxicities and reduced to 50 mg once a day on resolution of toxicities to $\leq$ grade 1 or discontinued for grade 4 toxicities.

### Patient Evaluation

Screening included a clinical history, physical examination, full blood count, biochemistry panel, urinalysis, calculated creatinine clearance, and ECG. At every treatment visit, toxicity and standard laboratory panels were assessed. Tumor response was evaluated by CA 19-9 markers every 4 weeks and by computed tomography of the chest/abdomen/pelvis (RECIST guidelines) at baseline (within 4 weeks of starting protocol therapy) and every 8 weeks thereafter. Responses were confirmed at least 4 weeks after responding scan.

### Study End Points and Objectives

The primary objective was determination of the recommended dose for phase II evaluation of capecitabine in this regimen based on the end point of first-cycle DLT and establishment of the MTD. Response rates and overall and progression-free survival were secondary end points. Survival was calculated from the date of study registration to the date of death (overall survival) or

  

**Table 1.** Patient Demographics and Clinical Characteristics

| Patient Demographics and Clinical Characteristics | No. of Patients | | | | All Patients (N = 20) | |
|---|---|---|---|---|---|---|
| | DL1 (n = 8)* | DL2 (n = 3) | DL3 (n = 6) | DL4 (n = 3) | No. | % |
| Age, years | | | | | | |
| Median | 65 | 71 | 49 | 67 | 63 | |
| Range | 41-74 | 64-76 | 33-69 | 56-77 | 33-77 | |
| Sex | | | | | | |
| Male | 5 | 2 | 3 | 0 | 10 | 50 |
| Female | 3 | 1 | 3 | 3 | 10 | 50 |
| Performance status | | | | | | |
| 0 | 2 | 0 | 0 | 0 | 2 | 10 |
| 1 | 6 | 3 | 6 | 2 | 17 | 85 |
| 2 | 0 | 0 | 0 | 1 | 1 | 5 |
| Extent of disease | | | | | | |
| Locally advanced | 2 | 2 | 2 | 3 | 9 | 45 |
| Metastatic | 6 | 1 | 4 | 0 | 11 | 55 |
| Location of tumor | | | | | | |
| Head of pancreas | 3 | 2 | 4 | 2 | 11 | 55 |
| Body/tail | 5 | 1 | 2 | 1 | 9 | 45 |
| Duodenal/gastric invasion | 0 | 0 | 1 | 1 | 2 | 10 |
| Previous surgery | 0 | 1 | 1 | 0 | 2 | 10 |

Abbreviation: DL, dose level.
*One patient was ineligible (increased bilirubin of 44 $\mu$mol/L), and one patient did not complete the first cycle as a result of disease progression; therefore, both patients were replaced in the cohort. All patients are included for survival and overall toxicity assessment.

progression/death (progression-free survival) using the Kaplan-Meier method, with patients censored at the date of last follow-up if still alive.

## RESULTS

### *Patient Population and Dose Escalation*

Twenty patients were enrolled between December 2005 and December 2007. Data were analyzed at least 6 months after accrual of the final patient. Table 1 lists patient characteristics; 95% of patients had PS of 0 or 1, 50% were male, and approximately half had metastatic disease.

DL1 was expanded to six patients as a result of one dose-limiting occurrence of grade 3 epistaxis that was successfully treated by surgical intervention. Two additional patients were recruited to DL1 to replace two patients who were not fully assessable for first-cycle DLT (disease-related deterioration and ineligibility as a result of increased bilirubin) with no further occurrence of DLT. No DLT was observed in the three patients each at DL2 or DL3. Capecitabine was escalated to the target

**Table 2.** Adverse Events by DL

| Adverse Event | No. of Patients by Grade | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | DL1 (n = 8) | | DL2 (n = 3) | | DL3 (n = 6) | | DL4 (n = 3) | |
| | 1 or 2 | 3 or 4 | 1 or 2 | 3 or 4 | 1 or 2 | 3 or 4 | 1 or 2 | 3 or 4 |
| Neutropenia | 5 | 2 | 1 | 2 | 2 | 3 | 1 | 2 |
| Thrombocytopenia | 5 | 0 | 3 | 0 | 5 | 1 | 3 | 0 |
| Anemia | 6 | 1 | 2 | 0 | 6 | 0 | 3 | 0 |
| Diarrhea | 4 | 1 | 2 | 0 | 4 | 2 | 2 | 1* |
| Stomatitis | 5 | 2 | 2 | 0 | 4 | 0 | 3 | 0 |
| Nausea/vomiting | 7 | 0 | 3 | 0 | 6 | 0 | 1 | 1 |
| Hand-foot syndrome | 3 | 2 | 1 | 1 | 5 | 0 | 2 | 0 |
| Rash (acneiform) | 3 | 0 | 2 | 0 | 3 | 1 | 1 | 1* |
| Lethargy | 5 | 3 | 2 | 1 | 4 | 2 | 1 | 2 |
| Epistaxis | 4 | 1* | 3 | 0 | 4 | 0 | 1 | 0 |
| Other bleeding | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| Thromboembolism | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Hypertension | 1 | 0 | 1 | 0 | 2 | 0 | 1 | 0 |
| Proteinuria | 1 | 0 | 1 | 0 | 3 | 0 | 2 | 0 |

Abbreviation: DL, dose level.
*Indicates dose-limiting toxicity during cycle 1.

therapeutic dose in DL4, wherein two DLTs occurred (grade 3 skin toxicity lasting > 7 days and grade 3 diarrhea despite optimal supportive measures). DL4 was declared the MTD, and DL3 was expanded by three patients, none of whom experienced DLT (zero DLTs among six patients at DL3). Thus, the recommended dose of capecitabine for phase II evaluation was 1,400 mg/m$^2$.

### Safety

Toxicities according to DL are listed in Table 2. In all patients (n = 20) and across all cycles, grade 3 toxicities with rates of 10% to 20% included diarrhea, stomatitis, hand-foot syndrome, and skin rash. Grade 3 lethargy was observed in eight (40%) of 20 patients, and grade 3 or 4 neutropenia was observed in nine (45%) of 20 patients. There were no other grade 4 toxicities or cases of febrile neutropenia, GI perforation, grade 3 GI bleeding, grade 3 hypertension/proteinuria, or interstitial pneumonitis. One patient developed pulmonary embolism (detected by computed tomography) and remained on protocol therapy with anticoagulation, and one patient developed a deep vein thrombosis associated with disease progression and came off study.

There were five treatment-related serious adverse events, including two DLTs (grade 3 diarrhea and grade 3 epistaxis). The other serious adverse events included abdominal pain (etiology unknown), overnight admission with grade 3 neutropenia associated with fatigue but no fever, and skin infection secondary to erlotinib-induced skin rash.

### Treatment Delivery

A total of 97 cycles (median, six cycles; range, one to eight cycles) have been administered. Two patients continue on protocol therapy. Nine patients completed six cycles (four patients at DL3), with one further patient continuing to receive treatment beyond six cycles in DL3. Two patients withdrew as a result of lethargy, one after three cycles and one after five cycles. The numbers of patients requiring at least one dose reduction of gemcitabine were as follows: DL1, n = 2; DL2, n = 3; DL3, n = 4; and DL4, n = 2. The numbers of patients requiring at least one dose reduction of capecitabine were as follows: DL1, n = 4; DL2, n = 2; DL3, n = 3; and DL4, n = 2. Treatment delays of greater than 1 week occurred in 19%, 0%, 9%, and 20% of cycles in DL1 to DL4, respectively. A dose reduction of erlotinib occurred in seven patients (DL1, n = 4; DL3, n =1; DL4, n = 2).

### Efficacy

With a median follow-up time of 9.8 months, 14 patients have died and six remain alive. Median overall survival time (Fig 1A) for all patients was 12.5 months (95% CI, 10.9 to 14.1 months), and 1-year survival rate was 73.7% (95% CI, 47.9% to 88.1%). Survival according to metastatic versus locally advanced disease is shown in Appendix Figure A1 (online only). Progression-free survival time (Fig 1B) was 9.0 months (95% CI, 8.8 to 9.3 months), with a 1-year progression-free survival rate of 31.9% (95% CI, 12.1% to 53.9%). The overall response rate (unconfirmed; Table 3) was 50% (95% CI, 27% to 73%), and the disease control rate was 85% (95% CI, 62% to 97%). Responses by cohort were as follows: four of eight patients in DL1, two of three patients in DL2, three of six patients in DL3, and one of three patients in DL4. The overall confirmed response rate was 35%. CA 19-9 trends during treatment are indicated for all patients in Figure 2. In an exploratory analysis, 63% (95% CI, 38% to 84%) of 19 assessable patients (one nonsecretor) experienced a 50% reduction in CA 19-9 for 8 weeks (three of 20 patients had < 50% decrease; four of 20 patients had increased CA 19-9).

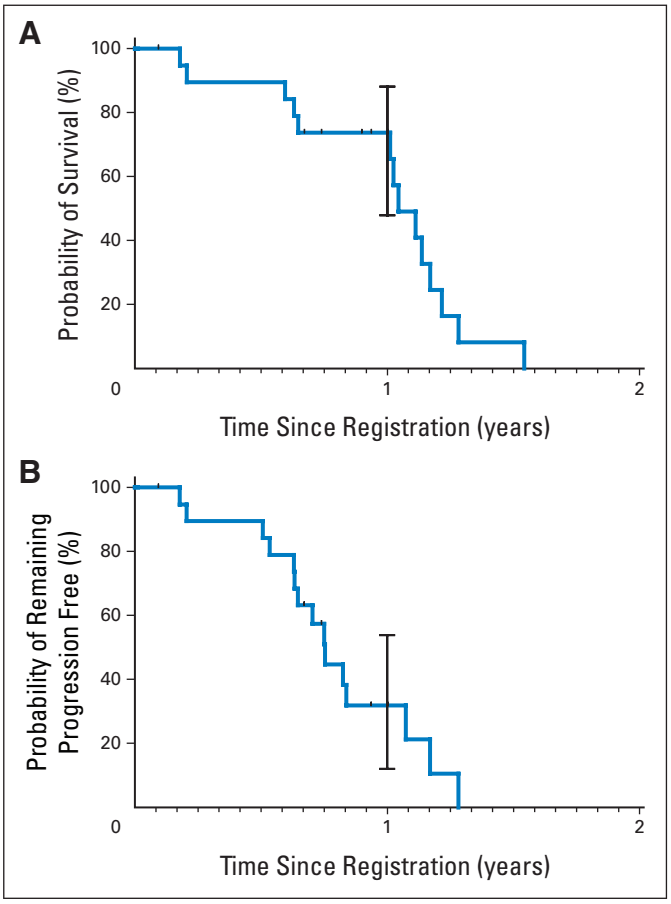


**Fig 1.** (A) With a median follow-up time of 9.8 months, median overall survival was 12.5 months (95% CI, 10.9 to 14.1 months), and 1-year survival rate was 73.7% (N = 20). (B) Progression-free survival was 9.0 months (95% CI, 8.8 to 9.3 months), with a 1-year progression-free survival rate of 31.9% (N = 20).

## DISCUSSION

The primary objective was to establish the toxicity profile and recommended phase II dose of capecitabine in the investigational GemCap plus erlotinib/bevacizumab regimen. The recommended dose of 1,400 mg/m$^2$ represents a 15% dose reduction of the target dose of capecitabine of 1,660 mg/m$^2$ used in the GemCap alone doublet. DLTs were predictably diarrhea and skin rash, occurring in two separate patients in the 1,660 mg/m$^2$ cohort. At the recommend DL, no patients experienced first-cycle DLT, and the frequency of grade 3 or 4 toxicity in any cycle was relatively low, with mostly grade1 or 2 toxicities observed, except for grade 3 or 4 diarrhea and lethargy in two of six patients. Grade 3 or 4 toxicities occurring in 10% to 20% of all patients (n = 20) were diarrhea, skin rash, stomatitis, hand-foot syndrome, and lethargy, consistent with those observed in a phase II study of capecitabine plus erlotinib in chemotherapy-refractory pancreatic cancer.[30] Grade 3 or 4 lethargy was experienced by 40% of patients, and it is not clear to what extent this is disease or treatment related. Grade 3 or 4 neutropenia (with no observed febrile neutropenia)

  

**Table 3.** Summary of Radiologic Responses

| Response | No. of Patients | | | | All Patients (N = 20) | |
|---|---|---|---|---|---|---|
| | DL1 (n = 8) | DL2 (n = 3) | DL3 (n = 6) | DL4 (n = 3) | No. | % |
| Partial response | 4 | 2 | 3 | 1 | 10 | 50 |
| Stable disease | 1 | 1 | 3 | 2 | 7 | 35 |
| Disease control | 5 | 3 | 6 | 3 | 17 | 85 |
| Progressive disease | 2 | — | — | — | 2 | 10 |
| Nonassessable | 1* | — | — | — | 1 | 5 |

Abbreviation: DL, dose level.
*This patient did not complete one cycle of therapy.

occurred in 45% of patients; this toxicity was seen in 36% of patients treated with GemCap alone.[27]

Concerning bevacizumab-specific toxicities, no patients had GI perforation or grade 3 or 4 GI bleeding, but one patient experienced grade 3 epistaxis. A phase II study of gemcitabine in combination with bevacizumab in 52 patients reported an incidence of visceral perforation of 8% and bleeding of 2% and advised caution in administering bevacizumab in the presence of visceral invasion.[26] This was originally an exclusion criterion in our study, but after a protocol amendment, two patients with duodenal/gastric invasion were included without complications. The frequency of grade 1 or 2 hypertension was consistent with other studies of bevacizumab in advanced pancreatic cancer,[26,31,32] but unlike these studies, no patients experienced grade 3 or 4 hypertension. This could reflect the small sample size, but the lower dose of bevacizumab (5 mg/kg as opposed to 10 mg/kg) may be contributory. The incidence of interstitial lung disease with the combination of gemcitabine plus erlotinib is reported to be 2.4%,[25] which is higher than with either drug alone, but no interstitial lung disease occurred in the present study.

A dose-escalation study design was used in the assessment of this four-drug regimen given the potential for overlapping toxicity between capecitabine and erlotinib because several phase II studies adding erlotinib to cytotoxic platforms in other tumors had observed excessive grade 3 or 4 diarrhea, resulting in upfront dose reductions of the cytotoxic drugs. In our study, capecitabine, rather than erlotinib, was dose-escalated to increase the scope for dose titration to toxicity. Pharmacokinetic interactions increasing drug exposure have not been observed with erlotinib plus bevacizumab,[23] gemcitabine plus erlotinib,[33] and capecitabine plus erlotinib,[34,35] and hence, none were expected with the four-drug combination used in this study. Thus, the observed DLTs of grade 3 diarrhea and skin rash are likely to be a consequence of additive toxicity.

In one of the only positive randomized phase III studies to report results in advanced pancreatic cancer, the combination of gemcitabine with erlotinib produced a modest improvement in overall survival compared with gemcitabine alone (median overall time and 1-year survival rate were 6.24 months and 23%, respectively; hazard ratio [HR] = 0.82; 95% CI, 0.69 to 0.99; $P = .038$).[25] However, despite promising activity in phase II evaluation,[26,36] alternative doublets targeting EGFR or VEGF have failed to result in significantly improved survival in advanced pancreatic cancer in phase III evaluation; gemcitabine plus bevacizumab versus gemcitabine alone resulted in median survival times of 5.8 *v* 6.1 months, respectively (HR = 1.03, $P = .78$, 95% CI not reported),[31] and gemcitabine plus cetuximab versus gemcitabine alone resulted in an HR for death of 1.09 (95% CI, 0.93 to 1.27; $P = .14$; median survival not reported).[37]

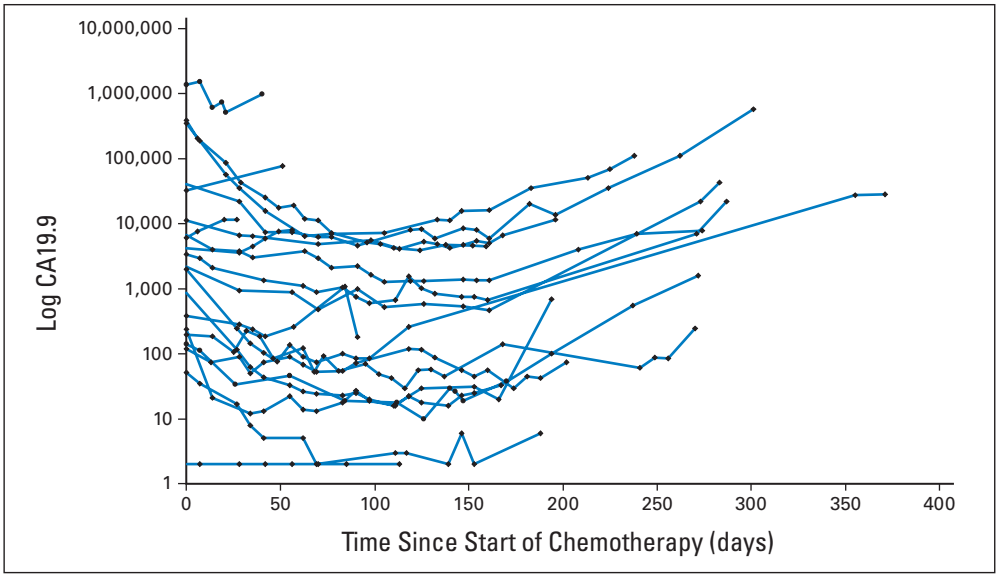


**Fig 2.** CA 19-9 changes according to time after starting chemotherapy are represented for each patient in the trial (N = 20). In an exploratory analysis, the percentage of patients whose CA19-9 levels had been reduced by more than 50% by 8 weeks was calculated.

A third recently published study addressed the issue of dual EGFR/VEGF blockade, randomly assigning patients with metastatic disease between gemcitabine/erlotinib/bevacizumab and gemcitabine/erlotinib; median overall survival times were 7.1 and 6.0 months, respectively (HR = 0.89; 95% CI, 0.74 to 1.07; $P = .21$).[38] In this study, however, progression-free survival, a secondary end point, was significantly better for combined EGFR/VEGF blockade (HR = 0.73; 95% CI, 0.61 to 0.86; $P = .0002$), but there was no significant difference in response rates (13.5% for gemcitabine/erlotinib/bevacizumab *v* 8.6% for gemcitabine/erlotinib). The rates of grade 3 or 4 diarrhea, rash, and neutropenia were 4%, 8%, and 21% for the triplet arm, suggesting that in our study, the addition of capecitabine increased these toxicities. In a randomized phase II study of dual blockade with gemcitabine/bevacizumab/erlotinib versus gemcitabine/bevacizumab/cetuximab, median survival times of 7.2 *v* 7.8 months, respectively, and response rates of 18% *v* 23%, respectively, were observed, leading the investigators to conclude that neither regimen demonstrated sufficient activity to warrant further evaluation.[32]

In our study, median survival, 1-year survival, and median progression-free survival were 12.5 months, 73.7%, and 9 months, respectively. These outcomes are much better than those observed with historical controls. However, the current study comprises a small number of patients with characteristics predictive of a more favorable outcome, including good PS (95% had PS of 0 or 1) and locally advanced disease (45%), which have been previously identified as being associated with better outcomes.[31] The response rate of 50% was encouraging for a multitargeted approach in this patient population, particularly because radiologic response can be difficult to measure in pancreatic neoplasms as a result of associated desmoplastic reaction. Regimens that result in good tumor shrinkage could potentially have application in the neoadjuvant treatment of pancreatic cancer, which is currently an investigational area. The regimen also resulted in a 50% reduction in CA 19-9 for 8 weeks in 63% of patients.

Although the rationale and preclinical data for combined EGFR/VEGF blockade in pancreatic cancer and other tumor types seemed promising, this has not translated into a clear clinical benefit in pancreatic cancer based on the results of phase III evaluation where overall survival remains the standard efficacy measure. Similarly, in renal cell and colorectal cancer, superiority of a dual targeted approach was not demonstrated in randomized evaluation,[39-41] despite encouraging activity in single-arm studies.[22,42] Nonetheless, tumorigenesis in pancreatic cancer is governed by the complex interplay of tumoral, stromal, and host factors; genetic and epigenetic events; and dysregulation of the molecular and growth pathways they control. Therefore, multitargeted approaches still seem logical; several phase III studies assessing gemcitabine plus or minus oral multitargeted tyrosine kinase inhibitors are ongoing, and alternative approaches including vaccine therapy are under investigation.

In conclusion, this study demonstrated that to combine GemCap with erlotinib plus bevacizumab, a 15% dose reduction of capecitabine was required as a result of overlapping toxicities with erlotinib. A follow-up phase II study of this regimen using the recommended dose of capecitabine and with response rate as the primary outcome measure has recently fully accrued.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** None **Consultant or Advisory Role:** David Cunningham, Hoffmann-La Roche (C); Ian Chau, Hoffmann-La Roche (C) **Stock Ownership:** None **Honoraria:** David Cunningham, Hoffmann-La Roche; Ian Chau, Hoffmann-La Roche **Research Funding:** David Cunningham, Hoffmann-La Roche **Expert Testimony:** David Cunningham, Hoffmann-La Roche (U) **Other Remuneration:** None

## AUTHOR CONTRIBUTIONS

**Conception and design:** Naureen Starling, David Cunningham
**Administrative support:** Jacqui Oates
**Provision of study materials or patients:** David Cunningham, Ian Chau
**Collection and assembly of data:** Naureen Starling, David Watkins, David Cunningham, Janet Thomas, Janine Webb, Karen Thomas, Jacqui Oates
**Data analysis and interpretation:** Naureen Starling, David Watkins, David Cunningham, Gina Brown, Karen Thomas, Ian Chau
**Manuscript writing:** Naureen Starling, David Watkins, David Cunningham, Ian Chau
**Final approval of manuscript:** Naureen Starling, David Watkins, David Cunningham, Janet Thomas, Janine Webb, Gina Brown, Karen Thomas, Jacqui Oates, Ian Chau

## REFERENCES


1. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, 2005
2. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. CA Cancer J Clin 58:71-96, 2008
3. Mitry E, Rachet B, Quinn MJ, et al: Survival from cancer of the pancreas in England and Wales up to 2001. Br J Cancer 99:S21-S23, 2008 (suppl 1)
4. Starling N, Cunningham D: Survival from cancer of the pancreas in England and Wales up to 2001. Br J Cancer 99:S24-S25, 2008 (suppl 1)
5. Sultana A, Tudur SC, Cunningham D, et al: Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer: Results of secondary end points analyses. Br J Cancer 99:6-13, 2008
6. Ueda S, Ogata S, Tsuda H, et al: The correlation between cytoplasmic overexpression of epidermal growth factor receptor and tumor aggressiveness: Poor prognosis in patients with pancreatic ductal adenocarcinoma. Pancreas 29:e1-e8, 2004
7. Seo Y, Baba H, Fukuda T, et al: High expression of vascular endothelial growth factor is associated with liver metastasis and a poor prognosis for patients with ductal pancreatic adenocarcinoma. Cancer 88:2239-2245, 2000
8. Itakura J, Ishiwata T, Friess H, et al: Enhanced expression of vascular endothelial growth factor in human pancreatic cancer correlates with local disease progression. Clin Cancer Res 3:1309-1316, 1997
9. 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 6:1936-1948, 2000
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 1:777-783, 2002
11. Overholser JP, Prewett MC, Hooper AT, et al: Epidermal growth factor receptor blockade by antibody IMC-C225 inhibits growth of a human pancreatic carcinoma xenograft in nude mice. Cancer 89:74-82, 2000


  

**12.** Solorzano CC, Baker CH, Bruns CJ, et al: Inhibition of growth and metastasis of human pancreatic cancer growing in nude mice by PTK 787/ZK222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases. Cancer Biother Radiopharm 16:359-370, 2001

**13.** Bockhorn M, Tsuzuki Y, Xu L, et al: Differential vascular and transcriptional responses to anti-vascular endothelial growth factor antibody in orthotopic human pancreatic cancer xenografts. Clin Cancer Res 9:4221-4226, 2003

**14.** Bruns CJ, Shrader M, Harbison MT, et al: Effect of the vascular endothelial growth factor receptor-2 antibody DC101 plus gemcitabine on growth, metastasis and angiogenesis of human pancreatic cancer growing orthotopically in nude mice. Int J Cancer 102:101-108, 2002

**15.** Sandler A, Herbst R: Combining targeted agents: Blocking the epidermal growth factor and vascular endothelial growth factor pathways. Clin Cancer Res 12:4421s-4425s, 2006.

**16.** Tabernero J: The role of VEGF and EGFR inhibition: Implications for combining anti-VEGF and anti-EGFR agents. Mol Cancer Res 5:203-220, 2007

**17.** Ciardiello F, Troiani T, Bianco R, et al: Interaction between the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) pathways: A rational approach for multitarget anticancer therapy. Ann Oncol 17:vii109-vii114, 2006 (suppl 7)

**18.** Niu G, Wright KL, Huang M, et al: Constitutive Stat3 activity up-regulates VEGF expression and tumor angiogenesis. Oncogene 21:2000-2008, 2002

**19.** Jung YD, Mansfield PF, Akagi M, et al: Effects of combination anti-vascular endothelial growth factor receptor and anti-epidermal growth factor receptor therapies on the growth of gastric cancer in a nude mouse model. Eur J Cancer 38:1133-1140, 2002

**20.** Ciardiello F, Bianco R, Damiano V, et al: Antiangiogenic and antitumor activity of anti-epidermal growth factor receptor C225 monoclonal antibody in combination with vascular endothelial growth factor antisense oligonucleotide in human GEO colon cancer cells. Clin Cancer Res 6:3739-3747, 2000

**21.** Baker CH, Solorzano CC, Fidler IJ: Blockade of vascular endothelial growth factor receptor and epidermal growth factor receptor signaling for therapy of metastatic human pancreatic cancer. Cancer Res 62:1996-2003, 2002

**22.** Saltz LB, Lenz HJ, Kindler HL, et al: Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: The BOND-2 study. J Clin Oncol 25:4557-4561, 2007

**23.** Herbst RS, Johnson DH, Mininberg E, et al: Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non–small-cell lung cancer. J Clin Oncol 23:2544-2555, 2005

**24.** Herbst RS, O'Neill VJ, Fehrenbacher L, et al: Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non–small-cell lung cancer. J Clin Oncol 25:4743-4750, 2007

**25.** 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 25:1960-1966, 2007

**26.** Kindler HL, Friberg G, Singh DA, et al: Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol 23: 8033-8040, 2005

**27.** Cunningham D, Chau I, Stocken D, et al: Phase III randomised comparison of gemcitabine with gemcitabine plus capecitabine in patients with advanced pancreatic cancer. Eur J Cancer 3:12, 2005 (abstr)

**28.** Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000

**29.** Ratain MJ, Mick R, Schilsky RL, et al: Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. J Natl Cancer Inst 85:1637-1643, 1993

**30.** Kulke MH, Blaszkowsky LS, Ryan DP, et al: Capecitabine plus erlotinib in gemcitabine-refractory advanced pancreatic cancer. J Clin Oncol 25:4787-4792, 2007

**31.** Kindler HL, Niedzwiecki D, Hollis D, et al: A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis of Cancer and Leukemia Group B (CALGB). J Clin Oncol 25:199s, 2007 (suppl; abstr 4508)

**32.** Kindler HL, Gangadhar T, Karrison T, et al: Final analysis of a randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC). J Clin Oncol 26:213s, 2008 (suppl; abstr 4502)

**33.** Dragovich T, Huberman M, Von Hoff DD, et al: Erlotinib plus gemcitabine in patients with unresectable pancreatic cancer and other solid tumors: Phase IB trial. Cancer Chemother Pharmacol 60: 295-303, 2007

**34.** Twelves C, Trigo JM, Jones R, et al: Erlotinib in combination with capecitabine and docetaxel in patients with metastatic breast cancer: A dose-escalation study. Eur J Cancer 44:419-426, 2008

**35.** Van Cutsem E, Verslype C, Beale P, et al: A phase Ib dose-escalation study of erlotinib, capecitabine and oxaliplatin in metastatic colorectal cancer patients. Ann Oncol 19:332-339, 2008

**36.** 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 22:2610-2616, 2004

**37.** Philip PA, Benedetti J, Fenoglio-Preiser C, et al: Phase III study of gemcitabine (G) plus cetuximab (C) versus gemcitabine in patients (pts) with locally advanced or metastatic pancreatic adenocarcinoma (PC): SWOG S0205 study. J Clin Oncol 25:199s, 2007 (suppl; abstr LBA4509)

**38.** Van Cutsem E, Vervenne WL, Bennouna J, et al: Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic caner. J Clin Oncol 27:2231-2237, 2009

**39.** Bukowski RM, Kabbinavar FF, Figlin RA, et al: Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. J Clin Oncol 25:4536-4541, 2007

**40.** Punt CJ, Tol J, Rodenburg CJ, et al: Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). J Clin Oncol 26:180s, 2008 (suppl; abstr LBA4011)

**41.** Hecht JR, Mitchell T, Chidiac T, et al: An updated analysis of safety and efficacy of oxaliplatin (Ox)/bevacizumab (bev) +/− panitumumab (pmab) for first-line treatment (tx) of metastatic colorectal cancer (mCRC) from a randomized, controlled trial (PACCE). 2008 Gastrointestinal Cancers Symposium, Orlando, FL, January 25-27, 2008 (abstr 273)

**42.** Hainsworth JD, Sosman JA, Spigel DR, et al: Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib. J Clin Oncol 23:7889-7896, 2005



 