A Phase II Randomized Trial of Panitumumab, Erlotinib, and Gemcitabine Versus Erlotinib and Gemcitabine in Patients with Untreated, Metastatic Pancreatic Adenocarcinoma: North Central Cancer Treatment Group Trial N064B (Alliance)

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TRIAL INFORMATION

- ClinicalTrials.gov Identifier: NCT00550836
- Sponsor(s): Alliance for Clinical Trials in Oncology
- Principal Investigator: George P. Kim
- IRB Approved: Yes

LESSONS LEARNED

- Dual epidermal growth factor receptor (EGFR)-directed therapy with erlotinib and panitumumab in combination with gemcitabine was superior to gemcitabine and erlotinib, but the clinical relevance is uncertain given the limited role of gemcitabine monotherapy.
- A significantly longer overall survival was observed in patients receiving the dual EGFR-directed therapy.
- The dual EGFR-directed therapy resulted in increased toxicity.

ABSTRACT

Background. Gemcitabine is active in patients with advanced pancreatic adenocarcinoma. The combination of erlotinib, an oral epidermal growth factor receptor (EGFR) inhibitor, and gemcitabine was shown to modestly prolong overall survival when compared with gemcitabine alone. The North Central Cancer Treatment Group (now part of Alliance for Clinical Trials in Oncology) trial N064B compared gemcitabine plus erlotinib versus gemcitabine plus combined EGFR inhibition with erlotinib and panitumab.

Methods. Eligible patients with metastatic adenocarcinoma of the pancreas were randomized to either gemcitabine 1,000 mg/m² on days 1, 8, and 15 of a 28-day cycle with erlotinib 100 mg p.o. daily (Arm A) or the same combination with the addition of panitumab 4 mg/kg on days 1 and 15 of a 28-day cycle (Arm B). The primary endpoint of the trial was overall survival. Secondary endpoints included progression-free survival, the confirmed response rate, and toxicity. Comparison between arms for the primary endpoint was done with a one-sided log-rank test, and a p value less than .20 was considered statistically significant. Response rate comparison was done with Fisher’s exact test. All other reported p values are two-sided.

Results. A total of 92 patients were randomized, 46 to each arm. The median overall survival was 4.2 months in Arm A and 8.3 months in Arm B (hazard ratio, 0.817; 95% confidence interval [CI], 0.530–1.260; p = .1792). The progression-free survival was 2.0 months in Arm A and 3.6 months in Arm B (hazard ratio, 0.843; 95% CI, 0.555–1.280; p = .4190). A partial confirmed response was seen in 8.7% of patients on Arm A and 6.5% on Arm B (p = .9999). No patients had a...
complete response. Grade 3 and higher nonhematologic toxicities were more common in patients on Arm B compared with those on Arm A (82.6% vs. 52.2%; \( p = .0018 \)).

**Conclusion.** Dual EGFR-directed therapy resulted in a significant prolongation of overall survival in patients with advanced adenocarcinoma of the pancreas but was associated with substantially increased toxicities. Dual EGFR-directed therapy in combination with gemcitabine alone cannot be recommended for further study, as single-agent gemcitabine is no longer considered an appropriate therapy for otherwise fit patients with metastatic pancreatic cancer. *The Oncologist* 2019;24:1–9

**DISCUSSION**

Single-agent gemcitabine has modest activity in patients with advanced adenocarcinoma of the pancreas. Gemcitabine was shown to be superior to 5-fluorouracil with an improvement in a composite endpoint of pain, performance status, and weight (clinical benefit response) and a modest prolongation of overall survival [1]. Multiple trials have compared gemcitabine alone with combinations of gemcitabine and both cytotoxic and molecularly targeted drugs and failed to show improvement over gemcitabine alone. A large trial conducted by the National Cancer Institute of Canada compared gemcitabine with and without erlotinib in patients with locally advanced or metastatic pancreatic cancer. The overall survival (OS) in the combination arm was statistically superior to the gemcitabine alone arm (6.2 months vs. 5.9 months), but the increase in the overall survival was of questionable clinical importance [2].

Another large trial compared gemcitabine monotherapy with the combination of gemcitabine and cetuximab [3]. Although the combination resulted in a slightly longer overall survival (5.9 months vs. 6.3 months), the difference was not statistically different. Given evidence from preclinical and translational studies suggesting synergistic efficacy of different classes of anti-EGFR agents, this trial was performed [4, 5].

Designed as a randomized phase II trial, evaluating the efficacy of a combined EGFR inhibition using erlotinib and panitumumab in conjunction with gemcitabine with gemcitabine plus erlotinib as a reference arm, 92 patients were enrolled, 46 on each arm. The patient characteristics were balanced between the arms. The primary endpoint was OS, with progression-free survival (PFS), radiographic response rate, and toxicity as secondary endpoints. The trial was designed to detect with 80% power a difference in the primary outcome between arms using a one-sided log-rank test with an \( \alpha \) of .20. A \( p \) value less than .20 was therefore considered significant for OS.

The median OS was longer in the combined EGFR inhibition plus gemcitabine arm (Arm B) compared with gemcitabine with erlotinib (Arm A)—8.3 months versus 4.2 months—and met statistical significance (hazard ratio, 0.817; 95% CI, 0.530–1.260; \( p = .1792 \)) (Fig. 1). A nonsignificant difference in the PFS was seen, favoring Arm B (median: 3.6 months in Arm B and 2.0 months in Arm A; hazard ratio 0.843; 95% CI, 0.555–1.280; \( p = .4190 \)) (Fig. 2). A partial response was seen in 8.7% of patients on Arm A and 6.5% on Arm B (\( p = .9999 \)). No patients had a complete response. Grade 3 and higher nonhematologic toxicities were more common in patients receiving combined EGFR inhibition therapy (82.6% vs. 52.2%; \( p = .0018 \)).

**Figure 1.** Overall survival by treatment arm.

Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; Gem, gemcitabine.
### Trial Information

| Disease            | Pancreatic cancer |
|--------------------|------------------|
| Stage of Disease/Treatment | Metastatic/advanced |
| Prior Therapy       | None             |
| Type of Study - 1   | Phase II         |
| Type of Study - 2   | Randomized       |
| Primary Endpoint    | Overall survival |
| Secondary Endpoint  | Progression-free survival |
| Secondary Endpoint  | Overall response rate |
| Secondary Endpoint  | Toxicity         |

### Drug Information (Control – Arm A)

**Drug 1**
- Generic/Working Name: Gemcitabine
- Drug Class: Antimetabolite
- Dose: 1,000 milligrams (mg) per squared meter (m²)
- Route: IV
- Schedule of Administration: On days 1, 8, and 15 of a 28-day cycle

**Drug 2**
- Generic/Working Name: Erlotinib
- Drug Class: EGFR
- Dose: 100 milligrams (mg)
- Route: Oral (p.o.)
- Schedule of Administration: Daily

**Drug 3**
- Generic/Working Name: Panitumumab
- Drug Class: EGFR
- Dose: 4 milligrams (mg) per kilogram (kg)
- Route: IV
- Schedule of Administration: On days 1 and 15 of a 28-day cycle

### Drug Information (Experimental – Arm B)

**Drug 1**
- Generic/Working Name: Gemcitabine
- Drug Class: Antimetabolite
- Dose: 1,000 milligrams (mg) per squared meter (m²)
- Route: IV
- Schedule of Administration: On days 1, 8, and 15 of a 28-day cycle

**Drug 2**
- Generic/Working Name: Erlotinib
- Drug Class: EGFR
- Dose: 100 milligrams (mg)
- Route: Oral (p.o.)
- Schedule of Administration: Daily

**Drug 3**
- Generic/Working Name: Panitumumab
- Drug Class: EGFR
- Dose: 4 milligrams (mg) per kilogram (kg)
- Route: IV
- Schedule of Administration: On days 1 and 15 of a 28-day cycle

Investigator’s Analysis: Level of activity did not meet planned endpoint.

The trial was opened on December 30, 2009 and was closed to accrual on August 13, 2010. Trial information and patient characteristics are summarized in Table 1.
## Patient Characteristics (Control – Arm A)

| Characteristic                          | Value       |
|----------------------------------------|-------------|
| Number of Patients, Male               | 29          |
| Number of Patients, Female             | 17          |
| Stage                                  | Metastatic  |
| Age                                    | Median (range): 60.5 years |
| Number of Prior Systemic Therapies     | Median (range): 0 |
| Performance Status: ECOG               | 0 — 52.2%   |
|                                        | 1 — 47.8%   |
|                                        | 2 —         |
|                                        | 3 —         |
|                                        | Unknown —   |
| Cancer Types or Histologic Subtypes    | Adenocarcinoma, 46 |

## Patient Characteristics (Experimental – Arm B)

| Characteristic                          | Value       |
|----------------------------------------|-------------|
| Number of Patients, Male               | 31          |
| Number of Patients, Female             | 15          |
| Stage                                  | Metastatic  |
| Age                                    | Median (range): 62 years |
| Number of Prior Systemic Therapies     | Median (range): 0 |
| Performance Status: ECOG               | 0 — 50%     |
|                                        | 1 — 50%     |
|                                        | 2 —         |
|                                        | 3 —         |
|                                        | Unknown —   |
| Cancer Types or Histologic Subtypes    | Adenocarcinoma, 46 |

## Primary Assessment Method (Control – Arm A)

| Characteristic                          | Value       |
|----------------------------------------|-------------|
| Title                                  | Gemcitabine/Erlotinib |
| Number of Patients Enrolled            | 46          |
| Number of Patients Evaluable for Toxicity | 46       |
| Number of Patients Evaluated for Efficacy | 46       |
| Evaluation Method                      | RECIST 1.0  |
| Response Assessment – CR               | n = 0 (0%)  |
| Response Assessment – PR               | n = 5 (10.9%) |
| Response Assessment – SD               | n = 15 (32.5%) |
| Response Assessment – PD               | n = 25 (54.3%) |
| Response Assessment – Other            | n = 1 (2.2%)  |
| (Median) Duration Assessments – PFS    | 2 months; 95% CI, 1.8–3.3 months |
| (Median) Duration Assessments – OS     | 4.2 months; 95% CI, 3.5–7.8 months |
| Outcome Notes                          | Outcomes are summarized in Table 2. |

## Primary Assessment Method for Phase II Experimental

| Characteristic                          | Value       |
|----------------------------------------|-------------|
| Title                                  | Gemcitabine/Erlotinib/Panitumumab |
| Number of Patients Enrolled            | 46          |
| Number of Patients Evaluable for Toxicity | 46       |
| Number of Patients Evaluated for Efficacy | 46       |
| Evaluation Method                      | RECIST 1.0  |
Pancreatic cancer is a highly lethal malignancy, and the survival of patients with advanced disease is less than a year, ranging from 6 to 11 months in patients on clinical trials. Long-term survivors are rare, and even among patients with surgically resected disease, the 10-year overall survival is 3.9% [6]. Most patients who undergo resection will suffer a recurrence within 5 years, which is invariably fatal. Adjuvant therapy improves outcomes following surgery, but even with such therapy, the outcome is poor and recurrences remain very common [7, 8]. Given the high recurrence rate following surgery and the fact that the majority of patients have either metastatic or locally advanced disease at diagnosis, there is a great need for better systemic therapy. Gemcitabine was the standard therapy for advanced pancreatic cancer for more than 10 years, and multiple trials combining cytotoxic or targeted therapy with gemcitabine showed no improvement over gemcitabine alone [9].

The epidermal growth factor receptor (EGFR) pathway has been considered a potential target for therapy in pancreatic cancer. Increased expression of EGFR and its epidermal growth factor ligand are detected in pancreatic cancer tissues and predict for poor prognosis [10, 11]. Blocking the EGFR pathway in preclinical models was shown to suppress pancreatic cancer growth, suggesting a potential therapeutic target [12, 13]. Dual EGFR blockade with a monoclonal antibody and a tyrosine kinase inhibitor was also shown to have effect on tumor growth, suggesting utility in patients with pancreatic cancer [14]. KRAS mutations are very common in pancreatic cancer and may be predictive of an inferior survival, but unlike in colorectal cancer, KRAS mutations do not appear to predict outcomes in patients with pancreatic cancer treated with EGFR inhibitors [15–17].

The combination of gemcitabine and erlotinib showed a very modest and statistically significant prolongation of overall survival in patients with metastatic pancreatic cancer, but the clinical significance was questionable, and the combination never gained traction [2]. It was not until 2011 that substantial improvements were made, when oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) was shown to substantially prolong overall survival compared with gemcitabine alone, from 6.8 months to 11.1 months [18]. Shortly thereafter, the combination of gemcitabine and albumin-bound paclitaxel (nab-paclitaxel) was shown to be superior to gemcitabine alone, prolonging the overall survival of patients from 6.7 months to 8.5 months [19]. Gemcitabine alone is no longer considered an acceptable therapy for metastatic pancreatic cancer except for patients with impaired performance status or for patients who desire to receive less aggressive, and less toxic, albeit less effective, therapy [20].

Our trial was designed before FOLFIRINOX and gemcitabine with nab-paclitaxel were shown to be superior to gemcitabine alone and when there was still a substantial enthusiasm for EGFR-directed therapy. An early phase II trial of gemcitabine with cetuximab suggested a benefit of the combination indicating that EGFR was a potential target in pancreatic cancer [21]. A National Cancer Institute of Canada phase III trial of erlotinib given with gemcitabine, an oral EGFR inhibitor, showed a statistically significant but very modest prolongation of overall survival [2]. These findings, along with preclinical data, led to the design of our trial testing the hypothesis that two EGFR inhibitors of different classes could be superior to gemcitabine and erlotinib, a reasonable therapy standard at that time. Unfortunately, a large phase III trial (Southwest Oncology Group S0205) failed to show improvement of survival in patients treated with gemcitabine and cetuximab over gemcitabine alone [3]. In this large trial, there was no difference in overall survival of patients among the two arms—6.3 months for the combination versus 5.9 months for gemcitabine alone (hazard ratio, 1.06; 95% confidence interval, 0.91–1.23; p = .23)—and a 2-week improvement was seen in the time to treatment failure (p = .006).

The current trial showed a statistically significant difference observed in terms of overall survival favoring the combination of dual EGFR inhibition and gemcitabine. The dual EGFR inhibition therapy was more toxic, as expected. The relevance of this finding is of uncertain clinical significance, as gemcitabine monotherapy can no longer be considered an appropriate chemotherapy backbone for combination therapy with targeted

### Adverse Events

Adverse events are summarized in Table 3.

### Assessment, Analysis, and Discussion

**Completion**

**Investigator’s Assessment**

Outcome Notes

Outcomes are summarized in Table 2.

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agents given the superiority of cytotoxic doublet or triplet therapy, and toxicities, especially dermatological, were substantial. Dual EGFR inhibition may be even more challenging in conjunction with chemotherapy doublets or triplets given the adverse events seen with gemcitabine alone. Further studies of EGFR inhibitors administered concurrently with cytotoxic agents are unlikely to result in a meaningful improvement in the outcome of patients with metastatic pancreatic cancer and cannot be recommended.

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Table 1. Trial and patient characteristics

| Trial information | Pancreatic adenocarcinoma |
|-------------------|---------------------------|
| Disease           | Metastatic                |
| Stage             | Previously untreated for metastatic disease (adjuvant therapy allowed) |
| Prior therapy     | Randomized phase II trial |
| Trial arms        | Arm A: Gemcitabine + erlotinib (GE) |
|                   | Arm B: Gemcitabine + erlotinib + panitumumab (GEP) |
| Primary endpoint  | Overall survival |
| Secondary endpoints | Progression free survival, confirmed response rate, toxicity |

Drug information

- Gemcitabine: 1000 mg/m² on days 1, 8 and 15 of a 28-day cycle
- Erlotinib: 100 mg p.o. daily
- Panitumumab: 4 mg/kg on days 1 and 15 of a 28-day cycle

Patient information

- No. of enrolled patients: 92 (46 in each arm)
- Median age, yr: Arm A: 60.5; Arm B: 62.0
- Male/female: 60/32
- ECOG PS, n (%): PS 0: 47 (51); PS 1: 45 (49)
- Prior adjuvant therapy: 6 (6.5%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 2. Outcomes

| Results                          | Results | p value     |
|----------------------------------|---------|-------------|
| Overall survival, mo             | 4.2     | 8.3         | .1792 (1-sided) |
| Progression-free survival, mo    | 2       | 3.6         | 4.190         |

Confirmed response

- Partial response, n (%): 5 (10.9) vs 5 (10.9)
- Stable disease, n (%): 15 (32.6) vs 24 (52.2)
- Progressive disease, n (%): 25 (54.3) vs 12 (26.1)
- Missing data, n (%): 1 (2.2) vs 5 (10.9)

Treatment delivery

- No. cycles administered: 155 vs 186
- Mean (SD) no. of cycles: 3.4 (2.9) vs 4.0 (2.6)
- Median number of cycles: 2.0 vs 4.0
- Range number of cycles: (1.0–13.0) vs (1.0–11.0)
| Adverse events | Patient subset | Arm A, n (%) | Arm B, n (%) | p value |
|----------------|---------------|--------------|--------------|---------|
| Thrombosis     |               |              |              |         |
| All adverse events | 11 (24) | 10 (22) | .9999 |
| Related to therapy | 4 (9) | 5 (11) | .9999 |
| Nausea         |               |              |              |         |
| All adverse events | 7 (15) | 6 (13) | .9999 |
| Related to therapy | 4 (9) | 5 (11) | .9999 |
| Vomiting       |               |              |              |         |
| All adverse events | 3 (7) | 4 (9) | .9999 |
| Related to therapy | 2 (4) | 3 (7) | .9999 |
| Skin rash      |               |              |              |         |
| All adverse events | 4 (9) | 14 (30) | .0164 |
| Related to therapy | 4 (9) | 13 (28) | .0295 |
| Fatigue        |               |              |              |         |
| All adverse events | 8 (17) | 8 (17) | .9999 |
| Related to therapy | 1 (2) | 7 (15) | .0585 |
| Anorexia       |               |              |              |         |
| All adverse events | 7 (15) | 2 (4) | .1577 |
| Related to therapy | 6 (13) | 2 (4) | .2668 |
| Dyspnea        |               |              |              |         |
| All adverse events | 3 (7) | 6 (13) | .4850 |
| Related to therapy | 1 (2) | 3 (7) | .6166 |
| Dehydration    |               |              |              |         |
| All adverse events | 3 (7) | 4 (9) | .9999 |
| Related to therapy | 3 (7) | 3 (7) | .9999 |
| Abdominal pain |               |              |              |         |
| All adverse events | 9 (20) | 5 (11) | .3846 |
| Related to therapy | 2 (4) | 3 (7) | .9999 |
| Neutropenia    |               |              |              |         |
| All adverse events | 13 (28) | 5 (11) | .0639 |
| Related to therapy | 12 (26) | 5 (11) | .1052 |
| Thrombocytopenia |       |              |              |         |
| All adverse events | 2 (4) | 4 (9) | .6768 |
| Related to therapy | 2 (4) | 3 (7) | .9999 |
| Anemia         |               |              |              |         |
| All adverse events | 5 (11) | 6 (13) | .9999 |
| Related to therapy | 3 (7) | 5 (11) | .7139 |
| Elevated bilirubin |       |              |              |         |
| All adverse events | 7 (15) | 6 (13) | .9999 |
| Related to therapy | 4 (9) | 4 (9) | .9999 |
| Elevated ALT   |               |              |              |         |
| All adverse events | 5 (11) | 5 (11) | .9999 |
| Related to therapy | 1 (2) | 5 (11) | .2031 |
| Elevated alkaline phosphatase | | | | |
| All adverse events | 10 (22) | 5 (11) | .2586 |
| Related to therapy | 3 (7) | 2 (4) | .9999 |
| Hyperglycemia  |               |              |              |         |
| All adverse events | 3 (7) | 3 (7) | .9999 |
| Related to therapy | 1 (2) | 2 (4) | .9999 |

Bold p values indicate statistical significance. Abbreviation: ALT, alanine aminotransferase.
Figure 2. Progression-free survival by treatment arm.
Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; Gem, gemcitabine.