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Clinical Trial Results

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 panitumumab.

Methods. Eligible patients with metastatic adenocarcinoma of the pancreas were randomized to either gemcitabine 1,000 mg/m^2 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 panitumumab 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

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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;24:589–e160

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 α 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).

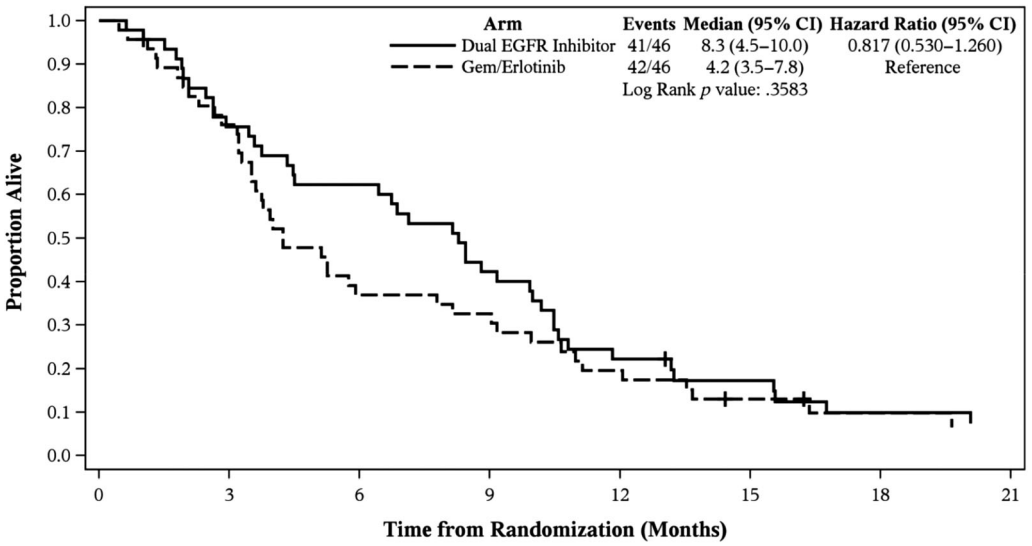

Figure 1. Overall survival by treatment arm.
Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; Gem, gemcitabine.

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
Additional Details of Endpoints or Study Design	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.
Investigator's Analysis	Level of activity did not meet planned endpoint.

Drug Information (Control – Arm A)	
Drug 1	
Generic/Working Name	Gemcitabine
Drug Class	Antimetabolite
Dose	1,000 milligrams (mg) per squared meter (m^2)
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 Information (Experimental – Arm B)	
Drug 1	
Generic/Working Name	Gemcitabine
Drug Class	Antimetabolite
Dose	1,000 milligrams (mg) per squared meter (m^2)
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

Patient Characteristics (Control – Arm A)	
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)	
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)	
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	
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

Response Assessment – PR	*n* = 5 (10.9%)
Response Assessment – SD	*n* = 24 (52.2%)
Response Assessment – PD	*n* = 12 (26.1%)
Response Assessment – Other	*n* = 5 (10.9%)
(Median) Duration Assessments – PFS	2 months; CI, 1.8–3.3 months
(Median) Duration Assessments – OS	4.2 months; CI, 3.5–7.8 months
Outcome Notes	Outcomes are summarized in Table 2.

Adverse Events

Adverse events are summarized in Table 3.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Level of activity did not meet planned endpoint

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 blockage 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

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.

Acknowledgments

The following institutional networks participated in this study: Colorado Cancer Research Program NCORP (National Cancer Institute [NCI] Community Oncology Research Program), Denver, CO, Keren Sturtz, UG1CA189805; Dayton NCI Community Oncology Research Program, Dayton, OH, Howard Gross, UG1CA189957; Geisinger Cancer Institute NCI Community Oncology Research Program, Danville, PA, Srilatha Hosur, UG1CA189847; Hawaii Minority Underserved NCORP, Honolulu, HI, Jeffrey Berenberg, UG1CA189804; Iowa-Wide Oncology Research Coalition NCORP, Des Moines, IA, Robert Behrens, UG1CA189816; Mayo Clinic LAPS, Rochester, MN, Steven Alberts, U10CA180790; Metro Minnesota Community Oncology Research Consortium, Saint Louis Park, MN, Daniel Anderson, UG1CA189863; Michigan Cancer Research Consortium NCORP, Ann Arbor, MI, Philip Stella, UG1CA189971; Missouri Valley Cancer Consortium CCOP (Community Clinical Oncology Program), Omaha, NE, Gamini Soori, U10CA063849; Montana Cancer Consortium NCORP, Billings, MT, Benjamin Marchello, UG1CA189872; Northern Indiana Cancer Research Consortium, South Bend, IN; Michael Method, U10CA086726; Ochsner NCI Community Oncology Research Program, New Orleans, LA, John Cole, UG1CA189870; Pacific Cancer Research Consortium NCORP, Seattle, WA, Alison Conlin, UG1CA189953; Rapid City Regional Hospital, Rapid City, SD, Joshua Lukenbill; Sanford NCI Community Oncology Research Program of the North Central Plains, Sioux Falls, SD, Preston Steen, UG1CA189825; Southeast Clinical Oncology Research Consortium NCORP, Winston-Salem, NC, James Atkins, UG1CA189858; Toledo Clinic Cancer Centers-Toledo, Toledo, OH, Rex Mowat; Toledo Community Hospital Oncology Program CCOP, Toledo, OH, Rex Mowat; Wichita NCI Community Oncology Research Program, Wichita, KS, Shaker Dakhil, UG1CA189808; and Wisconsin NCI Community Oncology Research Program, Marshfield, WI, Anthony Jaslowski, UG1CA189956.

Disclosures

Thorvardur R. Halfdanarson: Advanced Accelerator Applications (institutional), Lexicon (C/A), Ipsen, ThermoFisher Scientific, ArQule, Agios (institutional) (RF); **George P. Kim:** Genentech, Amgen (C/A, H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figure and Tables

Table 1. Trial and patient characteristics

Trial information	
Disease	Pancreatic adenocarcinoma
Stage	Metastatic
Prior therapy	Previously untreated for metastatic disease (adjuvant therapy allowed)
Trial design	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/m^2 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		*p* value
Overall survival, mo	4.2	8.3	.1792 (1-sided)
Progression-free survival, mo	2	3.6	.4190
Confirmed response			
Partial response, *n* (%)	5 (10.9)	5 (10.9)	
Stable disease, *n* (%)	15 (32.6)	24 (52.2)	
Progressive disease, *n* (%)	25 (54.3)	12 (26.1)	
Missing data, *n* (%)	1 (2.2)	5 (10.9)	
Treatment delivery			
No. cycles administered	155	186	
Mean (SD) no. of cycles	3.4 (2.9)	4.0 (2.6)	
Median number of cycles	2.0	4.0	
Range number of cycles	(1.0–13.0)	(1.0–11.0)	

Table 3. Adverse events, grades 3 and 4

Adverse events	Patient subset		*p* value
	Arm A, *n* (%)	Arm B, *n* (%)	
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.

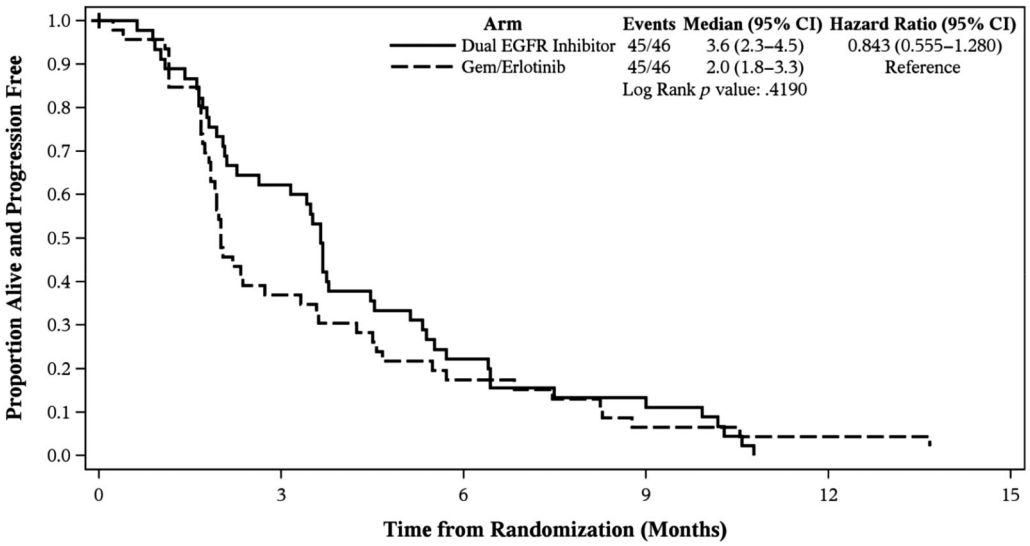

Figure 2. Progression-free survival by treatment arm.
Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; Gem, gemcitabine.