

Randomized Phase II Study of Pemetrexed, Carboplatin, and Thoracic Radiation With or Without Cetuximab in Patients With Locally Advanced Unresectable Non–Small-Cell Lung Cancer: Cancer and Leukemia Group B Trial 30407

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A B S T R A C T

Purpose

Cancer and Leukemia Group B conducted a randomized phase II trial to investigate two novel chemotherapy regimens in combination with concurrent thoracic radiation therapy (TRT).

Patients and Methods

Patients with unresectable stage III non–small-cell lung cancer (NSCLC) were randomly assigned to carboplatin (area under the curve, 5) and pemetrexed (500 mg/m²) every 21 days for four cycles and TRT (70 Gy; arm A) or the same treatment with cetuximab administered concurrent only with TRT (arm B). Patients in both arms received up to four cycles of pemetrexed as consolidation therapy. The primary end point was the 18-month overall survival (OS) rate; if the 18-month OS rate was $\geq 55\%$, the regimen(s) would be considered for further study.

Results

Of the 101 eligible patients enrolled (48 in arm A and 53 in arm B), 60% were male; the median age was 66 years (range, 32 to 81 years); 44% and 35% had adenocarcinoma and squamous carcinoma, respectively; and more patients enrolled onto arm A compared with arm B had a performance status of 0 (58% v 34%, respectively; $P = .04$). The 18-month OS rate was 58% (95% CI, 46% to 74%) in arm A and 54% (95% CI, 42% to 70%) in arm B. No significant difference in OS between patients with squamous and nonsquamous NSCLC was observed ($P = .667$). The toxicities observed were consistent with toxicities associated with concurrent chemoradiotherapy.

Conclusion

The combination of pemetrexed, carboplatin, and TRT met the prespecified criteria for further evaluation. This regimen should be studied further in patients with locally advanced unresectable nonsquamous NSCLC.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in the United States for both men and women, and 87% of lung cancers are non–small-cell lung cancer (NSCLC).^{1,2} Approximately one third of patients with NSCLC will present with unresectable stage III disease.³ Concurrent administration of chemotherapy with thoracic radiation therapy (TRT) is the standard of care for appropriate patients.⁴ The standard therapy used in this setting involves systemic doses of cisplatin and etoposide concurrent with TRT.^{5,6} It has been challenging to administer systemically active doses of docetaxel, gemcitabine, or vinorelbine in combination with TRT.⁷⁻⁹ A novel chemotherapy regimen that could

be administered in systemically active doses yet tolerable in combination with TRT would be of interest because a majority of relapses after treatment with concurrent chemotherapy and TRT are distant. Pemetrexed was initially approved for the treatment of metastatic NSCLC in the second-line setting¹⁰ and was subsequently approved for patients with nonsquamous NSCLC as first-line and maintenance therapy.^{11,12}

Systemic doses of carboplatin and pemetrexed and TRT were delivered with acceptable toxicities in a phase I trial.¹³ Phase II studies in advanced NSCLC suggested improved outcomes with the addition of cetuximab, a monoclonal antibody against the epidermal growth factor receptor, to platinum-based chemotherapy.¹⁴⁻¹⁶ A phase III trial in patients

with squamous cancer of the head and neck revealed a significant improvement in overall survival (OS) with cetuximab and radiation therapy compared with radiation therapy alone.¹⁷ Cancer and Leukemia Group B (CALGB) conducted a randomized phase II study (CALGB 30407) that incorporated [¹⁸F]fluorodeoxyglucose (FDG) positron emission tomography (PET) staging before therapy and three-dimensional conformal TRT with the intention of developing a novel systemic therapy regimen to be used concurrent with TRT (ClinicalTrials.gov identifier: NCT00117962). We elected to use carboplatin-based therapy because the phase I trial and recent CALGB chemoradiotherapy trials have used carboplatin, and we decided not to use any induction chemotherapy based on our previous experience.^{13,18,19} The fact that pemetrexed is inactive in squamous NSCLC was not known at the time the study was developed.^{11,12}

PATIENTS AND METHODS

Eligibility

Patients were required to have histologic or cytologic diagnosis of NSCLC, inoperable stage IIIA or stage IIIB disease, measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST),²⁰ an Eastern Cooperative Oncology Group performance status of 0 to 1, age \geq 18 years, and weight loss \leq 10% in the past 3 months. Laboratory requirements were as follows: an absolute neutrophil count (ANC) of \geq 1,500/ μ L, platelets \geq 100,000 μ L, a calculated creatinine clearance (CrCl) of \geq 45 mL/min, bilirubin 1.5 \times upper limit of normal (ULN), AST and ALT less than 3 \times ULN, and alkaline phosphatase less than 3 \times ULN. Patients were required to undergo FDG-PET imaging, computed tomography (CT) scan of the chest and abdomen, and pulmonary function tests before enrollment. Patients were required to have a mediastinal lymph node (LN) of \geq 2 cm by CT scans; if the mediastinal LN was less than 2 cm, then biopsy confirmation of malignant involvement in mediastinal LN was required (regardless of the results of PET imaging). Patients with contralateral mediastinal LN disease (N3) were eligible if disease could be encompassed within a single radiation field. Patients with scalene, supraclavicular, and contralateral hilar LN involvement based on assessment of the treating physician; direct invasion of vertebral body; or exudative, bloody, or cytologically malignant pleural effusions were not eligible. Prior chemotherapy for NSCLC, chest irradiation therapy, or therapy directed at the epidermal growth factor receptor pathway was not allowed. Patients who were pregnant or nursing; with known hypersensitivity to carboplatin, pemetrexed, or a monoclonal antibody; or who were HIV positive were ineligible. This trial was approved by the institutional reviews boards of the participating institutions, and patients were required to provide informed consent before enrollment.

Chemotherapy Treatment Plan

The first 19 patients in arms A and B received carboplatin area under the curve (AUC) of 6 using the Calvert equation²¹ over 30 minutes and pemetrexed 500 mg/m² over 10 minutes every 21 days for four cycles. Patients randomly assigned to arm B received cetuximab 400 mg/m² over 120 minutes on day 1 of week 1 and then 250 mg/m² over 60 minutes weekly for 6 weeks during the radiation therapy (for a total of 7 weeks). Radiation therapy started on day 1 of therapy. After 19 patients had been treated, the trial was amended, and the dose of carboplatin was reduced to an AUC of 5 because five patients had experienced grade 4 thrombocytopenia. In the absence of disease progression or unacceptable toxicity, patients in both arms were treated with four additional cycles of pemetrexed 500 mg/m² administered every 21 days. Patients received folic acid, vitamin B₁₂, and dexamethasone as recommended in the pemetrexed package insert.²² Patients received diphenhydramine 50 mg intravenously 30 to 60 minutes before the first dose of cetuximab, and dose could be repeated before subsequent doses.

Patients received carboplatin and pemetrexed if the ANC was \geq 1,500/ μ L and platelet count was \geq 100,000/ μ L; if ANC or platelet counts

were less than these levels, the treatment was held, and a CBC was checked on a weekly basis. Febrile neutropenia resulted in a dose reduction of both agents. Both agents were held for a CrCl of less than 45 mL/min, and if CrCl remained less than 45 mL/min after 1 week, the protocol therapy was discontinued. Patients who experienced a grade \geq 3 infusion reaction as a result of carboplatin were removed from protocol therapy. Patients who experienced grade \geq 3 infusion reactions as a result of cetuximab discontinued cetuximab and continued other protocol therapy. Dermatologic toxicity related to cetuximab was managed according to the package insert.²³ For the consolidation therapy, guidelines for dose adjustment were similar to those used during initial concurrent chemoradiotherapy. For patients experiencing radiation-related esophagitis of grade \geq 3, chemotherapy was held, patients were re-evaluated on a weekly basis, and therapy was resumed when dysphagia had improved to grade less than 3; carboplatin and pemetrexed were reduced one dose level for subsequent cycles. Radiation was held for grade 4 esophagitis and then resumed when dysphagia had improved to grade \leq 2.

Radiation Treatment Plan

All patients were assigned to receive a cumulative dose of 70 Gy in 35 daily fractions of 2 Gy. Three-dimensional conformal TRT planning was required, although the use of intensity-modulated radiotherapy was not allowed. Photon beam energies of 4 to 25 MV could be used, and tissue heterogeneity factors were used for bone, soft tissue, and lung in dose calculations. The gross tumor volume included the primary lung tumor on the planning CT scan and staging FDG-PET, and LN metastases included LNs that were pathologically proven, were greater than 1.0 cm in short axis measurement on CT or magnetic imaging, had a necrotic center, or demonstrated activity on FDG-PET. PET imaging guidelines were included in the protocol, but determination of FDG-PET–active disease was left to the discretion of the treating radiation oncologist, and a specific standardized uptake value cutoff point was not specified. The clinical target volume included the primary tumor volume and nodal volume with a 1.0-cm margin, except at the tumor/lung interface, where a 0.5-cm margin was used. The planning target volume (PTV) included the clinical target volume with a minimum margin of 0 to 0.5 cm and was adjusted for respiration visualized under treatment simulation. Clinically uninvolved LNs were not targeted. A single PTV was used for the entire treatment course, and the 95% isodense line was required to encompass the entire PTV. Normal tissue constraints limited the volume of lung receiving 20 Gy to 40% (calculated based on lung volume not involved with tumor), and the maximum spinal cord point dose allowed was 50 Gy. Specific esophageal dose constraints were not mandated by protocol. Radiotherapy data, including treatment planning CT images, portal images, and the three-dimensional data set, were reviewed by Quality Assurance Review Center during the first week of treatment, and a final review of all radiotherapy data was performed by the radiotherapy study chair in conjunction with Quality Assurance Review Center. The use of image-guided radiotherapy or respiratory gating was not specified. An analysis of the radiation treatment planning parameters and toxicity is pending and will be published separately.

Efficacy and Toxicity Evaluation

The response was assessed according to RECIST after every two cycles while on therapy; after completion of therapy, disease status was assessed every 4 months for 1 year, and then every 6 months for the next 2 years, and then annually for the next 3 years. Toxicity assessments according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) were performed weekly for the first four cycles, and then every 3 weeks during single-agent pemetrexed.

Statistical Methods

This was a single-stage randomized phase II trial with the primary objective of estimating the OS for patients treated with carboplatin and pemetrexed with or without cetuximab in combination with TRT of 70 Gy. On the basis of the estimated 18-month OS probability of 35% from the previous CALGB trial, it was determined that if an 18-month OS probability of \leq 35% was observed, then the combination was not worthy of further investigation. If the 18-month OS probability was \geq 55%, the combination would be worthy of further investigation. Using a one-sided binomial exact test with a significance level of $P = .10$, the study, with 50 patients in each arm, had 90% power to

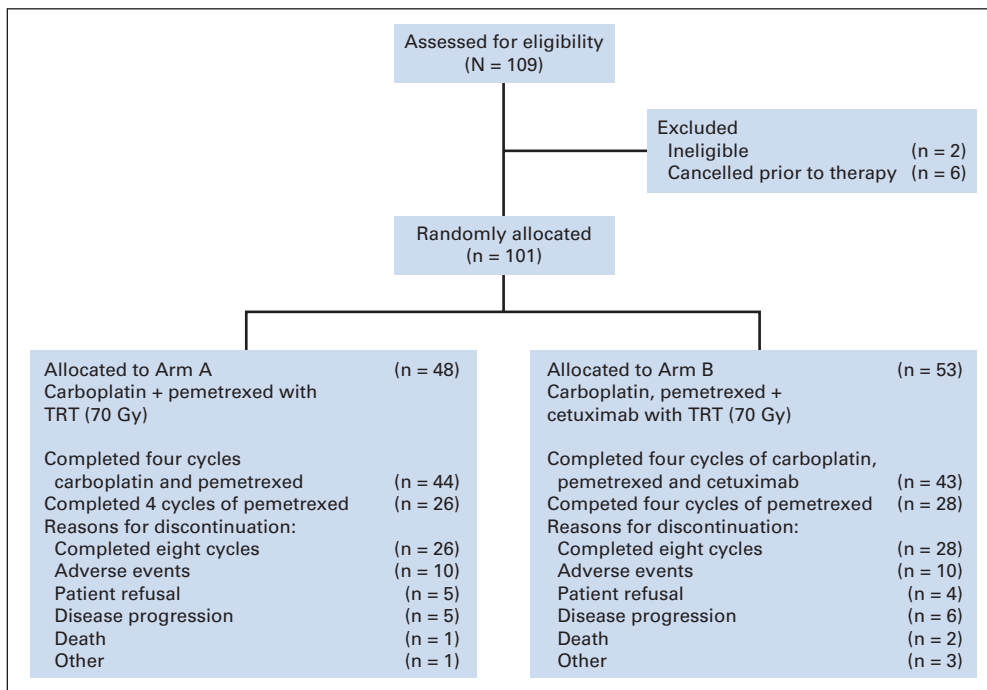


Fig 1. CONSORT diagram. TRT, thoracic radiation therapy.

differentiate the hypotheses. The probability of erroneously concluding that the treatment regimen was worthy of further investigation when the survival probability was truly $\leq 35\%$ was 0.071, and the probability of erroneously concluding the treatment was not worthy of further investigation when the survival probability was $\geq 55\%$ was 0.078. The trial was not designed to have adequate power to compare the two treatment arms.

OS is defined as the time from patient random assignment until death from any cause. The Kaplan-Meier²⁴ product-limit estimator was used to estimate the median OS and the OS probability at 18 months, as well as the 95% CIs. A similar analytic method was used to characterize the failure-free survival, which is the time between patient random assignment and a failure event, defined as disease progression or death from any cause (whichever occurred first). The proportion of patients who experienced a response (partial or complete) to each combination was estimated, and binomial 95% CIs were calculated. Toxicity was assessed for both combinations. For each type of toxicity, a patient's worst treatment-related toxic episode was used to summarize distribution of toxicity grade experienced.

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairman. CALGB statisticians performed statistical analyses.

As part of the quality assurance program of the CALGB, members of the Audit Committee visit all participating institutions at least once every 3 years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 27 patients (25%) of the 109 patients enrolled onto this study.

RESULTS

Patients

The trial was activated in September 2005, and 109 patients were registered between November 2005 and January 2008 (Fig 1). Of the 109 patients enrolled, six patients were cancelled before receiving any protocol-related therapy as a result of myocardial infarction (n = 1),

lack of adequate radiation planning equipment (n = 1), physician decision (n = 1), and determination of ineligibility after enrollment but before starting protocol therapy (n = 3); two patients were found to be ineligible after starting protocol therapy. The patient characteristics are listed in Table 1. An imbalance in performance status was observed between the two treatment arms.

Treatment Administration

Forty-eight patients initiated chemoradiotherapy in arm A, and 26 patients completed the eight cycles (Table 2). The most common reasons for treatment discontinuation before completion in arm A were adverse events (AEs; n = 10), disease progression (n = 5), patient refusal (n = 5), and death (n = 1; Fig 1). Fifty-three patients initiated chemoradiotherapy in arm B, and 28 patients completed the eight cycles. The most common reasons for treatment discontinuation before completion in arm B were AEs (n = 10), disease progression (n = 6), patient refusal (n = 4), and death (n = 2). The median three-dimensional conformal TRT for all patients with initiated radiotherapy was 70 Gy (range, 10.53 to 76.92 Gy); 14 patients experienced a radiation treatment interruption, and the median number of days of treatment interruption was 2 (range, 1 to 9 days).

Toxicity

In arms A and B, 50 and 53 patients, respectively, were evaluable for toxicity. The most common grade 3 and 4 hematologic AEs observed in arms A and B are listed in Table 3. The common ($\geq 10\%$) grade 3 to 5 nonhematologic toxicities observed in arms A and B (Table 3) were esophagitis, dysphagia, fatigue, pneumonitis, dehydration, and nausea/vomiting. The rates of observed grade 3 and 4 hematologic AEs were 42% and 28%, respectively, in arm A and 38% and 32%, respectively, in arm B. No grade 5 hematologic AEs were observed in either arm. The rates of observed grade 3 and 4 nonhematologic AEs were 46% and 6%, respectively, in arm A and 53% and 9%,

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Arm A (n = 48)		Arm B (n = 53)		Overall (N = 101)		P
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Sex							.42
Male	27	56	24	64	61	60	
Female	21	44	19	36	40	39	
Age, years							.74
Median	65		66		66		
Range	41-79		32-81		32-81		
Race							.04
White	39	81	50	94	89	88	
Black	8	17	2	4	10	10	
Asian	0	0	1	2	1	1	
Unknown	1	2	0	0	1	1	
Histology							.78
Adenocarcinoma	22	46	22	42	44	44	
Squamous	17	35	18	34	35	35	
NSCLC, undifferentiated	8	17	10	19	18	18	
Large cell	0	0	2	4	2	2	
Missing	1	2	1	2	2	2	
Performance status							.01
0	28	58	18	34	46	46	
1	20	42	35	66	55	54	
Stage							.34
IIIA	29	60	27	51	56	55	
IIIB	18	38	24	45	42	42	
Missing	1	2	2	4	3	2	

Abbreviation: NSCLC, non-small-cell lung cancer.

Table 3. Grade ≥ 3 Toxicities Observed on Cancer and Leukemia Group B Trial 30407

Toxicity	Arm A: Carboplatin + Pemetrexed (n = 50)		Arm B: Carboplatin + Pemetrexed + Cetuximab (n = 53)	
	No. of Patients	%	No. of Patients	%
Hematologic toxicity				
Anemia	9	18	7	13
Neutropenia	21	42	25	47
Thrombocytopenia	18	36	18	34
Febrile neutropenia	4	8	3	6
Maximum hematologic	35	70	37	70
Nonhematologic toxicity occurring at ≥ 10% in one or both treatment arms				
Dehydration	6	12	5	9
Dysphagia	8	16	6	11
Dyspnea	5	10	3	6
Esophagitis	8	16	7	13
Fatigue	11	22	9	17
Hypokalemia	0	0	6	11
Nausea/vomiting	4	8	5	9
Pneumonitis	6	12	6	11
Rash (acneiform)	0	0	7	13
Maximum adverse events*	38	76	45	85

*Two treatment-related deaths were observed on arm A (one as a result of pneumonitis and one as a result of pulmonary hemorrhage), and three were observed on arm B (two as a result of pneumonitis and one as a result of grade 3 respiratory toxicity complicated by pulmonary embolism and intrathoracic recurrence).

respectively, in arm B. Two patients in arm A experienced grade 5 AEs (pulmonary hemorrhage and pneumonitis), and three patients in arm B experienced grade 5 AEs (two experienced pneumonitis, and one experienced grade 3 pneumonitis complicated by intrathoracic recurrence and pulmonary embolism leading to respiratory failure).

Efficacy

The efficacy data are listed in Table 4 and Appendix Table A1 (online only). With a median follow-up of 32 months (range, 11.7 to

48.4 months), 59 of 101 patients have died; the 18-month OS rates observed in arms A and B were 58% (95% CI, 46% to 74%) and 54% (95% CI, 42% to 70%), respectively (Table 4; Fig 2). The median failure-free survival times observed in arms A and B were 12.6 months (95% CI, 7.9 to 17.2 months) and 12.3 months (95% CI, 8.8 to 18.7 months), respectively (Fig 3).

An unplanned analysis of OS by histology revealed that among patients with squamous and nonsquamous histology in both arms, the median OS was 22.2 months (95% CI, 12.1 months to not available) and 22.4 months (95% CI, 16.6 to 36.2 months), respectively; no significant difference in OS between the squamous and nonsquamous patients was observed ($P = .667$). The efficacy results of patients with squamous and nonsquamous histology in treatment arms A and B are listed in Table 5.

Of 101 patients, 59 patients have experienced progression. Fourteen patients (24%) experienced local and distant progression, 19 patients (32%) experienced local disease progression alone, 26 patients (44%) experienced distant disease progression alone, and 12 patients developed brain metastases.

DISCUSSION

The OS observed in this study is significantly better than many of our previous CALGB studies in patients with locally advanced unresectable NSCLC.^{18,25} It is tempting to attribute these results to the novel chemotherapy regimen and higher doses of TRT, but a number of others factors could have contributed to the results. The mandatory

Table 2. Treatment Administration

Treatment	No. of Patients	
	Arm A: Carboplatin + Pemetrexed (n = 48)	Arm B: Carboplatin + Pemetrexed + Cetuximab (n = 53)
Completed all planned treatment	26	28
Chemoradiotherapy		
Completed 1 cycle	1	3
Completed 2 cycles	2	5
Completed 3 cycles	1	2
Completed 4 cycles	44	43
Postchemoradiation chemotherapy		
Completed 0 cycles	7	16
Completed 1 cycle	3	2
Completed 2 cycles	8	6
Completed 3 cycles	4	1
Completed 4 cycles	26	28

Table 4. Efficacy of Treatment Arms A and B

Efficacy	Arm A: Carboplatin + Pemetrexed (n = 48)		Arm B: Carboplatin + Pemetrexed + Cetuximab (n = 53)	
	No. of Patients	%	No. of Patients	%
Best Response				
Complete response	4	8	2	4
Partial response	33	69	36	68
Stable response	11	23	12	23
Progressive disease	0	0	2	4
Not evaluable	0	0	1	2
Overall response rate, %	77		72	
95% CI	63 to 88		58 to 83	
Median failure-free survival, months	12.6		12.3	
95% CI	7.9 to 17.2		8.8 to 18.7	
18-month failure-free survival, %	29		33	
95% CI	19 to 45		23 to 49	
Median overall survival, months	21.2		25.2	
95% CI	17.5 to NA		14.4 to NA	
18-month overall survival, %	58		54	
95% CI	46 to 74		42 to 70	

Abbreviation: NA, not available.

use of FDG-PET scans for staging purposes and the exclusion of patients with significant pretreatment weight loss may have contributed to the selection of patients with a better prognosis than those enrolled in CALGB 39801. The use of a higher dose of TRT could have contributed to the improved survival. The CALGB 30105 study of high-dose TRT produced a median survival similar to CALGB 30407.¹⁹

The toxicities observed were similar to previous CALGB trials, although rates of severe esophagitis were lower in this study presumably related to absence of radiation to the uninvolved mediastinal nodes.¹⁸ The fact that the efficacy of pemetrexed is limited to patients with nonsquamous histology was not known when this study was designed and conducted. The OS among patients with squamous and nonsquamous histology was similar, but the number of patients in each of the histologic subgroups was small, which reduced our ability

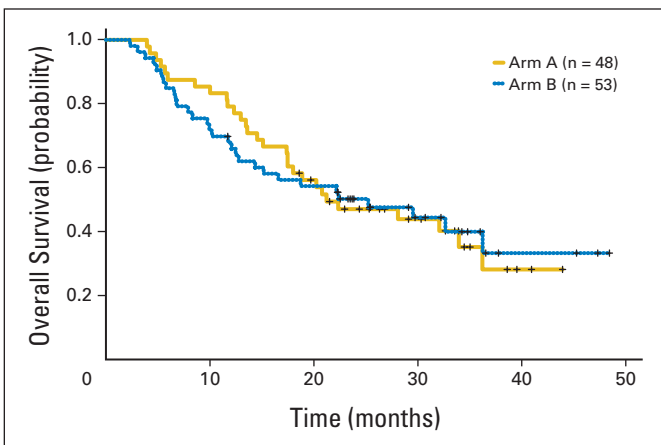


Fig 2. Kaplan-Meier curve of overall survival by treatment arm.

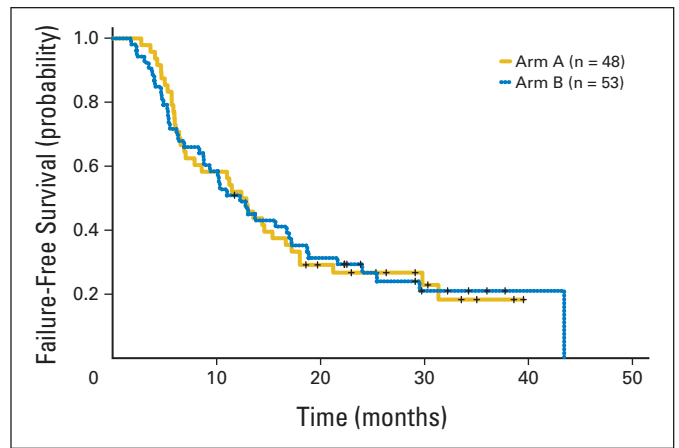


Fig 3. Kaplan-Meier curve of failure-free survival by treatment arm.

to detect an established treatment interaction. The ongoing international phase III study sponsored by Eli Lilly is investigating pemetrexed and cisplatin in combination with TRT to 66 Gy compared with cisplatin, etoposide, and TRT in patients with nonsquamous NSCLC.²⁶

In metastatic NSCLC, a phase III trial of cisplatin and vinorelbine with or without cetuximab revealed an improvement in OS with the addition of cetuximab.²⁷ The addition of cetuximab to paclitaxel, carboplatin, and radiation resulted in an encouraging median survival of 23 months in a single-arm phase II study conducted by the Radiation Therapy Oncology Group (RTOG).²⁸ It is not clear whether the observed improvement in survival (compared with prior RTOG studies) is a result of the addition of cetuximab or patient selection. We would like to emphasize that CALGB 30407 was not designed to compare the two different systemic therapy regimens (arm A without cetuximab and arm B with cetuximab) but was designed only to identify the arm(s) that would meet a predefined end point for further exploration. Unlike arm A, arm B narrowly missed the predefined criterion for further study. The ongoing RTOG phase III trial 0617 will address the utility of cetuximab in addition to the role of an escalated dose of TRT in the management of patients with unresectable stage III NSCLC.

We should await the results of these two large trials before incorporating pemetrexed or cetuximab in routine clinical practice for the treatment of patients with locally advanced NSCLC.

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.

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Provision of study materials or patients: Ramaswamy Govindan, Thomas Stinchcombe, Jennifer Garst, Timothy Brotherton, Everett E. Vokes
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Manuscript writing: All authors
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