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ORIGINAL REPORT

Phase II Study of Cetuximab in Combination With Chemoradiation in Patients With Stage IIIA/B Non–Small-Cell Lung Cancer: RTOG 0324

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ABSTRACT

Purpose
Non–small-cell lung cancer (NSCLC) commonly expresses the epidermal growth factor receptor (EGFR), which is associated with poor clinical outcome. Cetuximab is a chimerized monoclonal antibody that targets the EGFR and, in preclinical models, it demonstrates radiosensitization properties. We report a phase II trial testing the combination of cetuximab with chemoradiotherapy (CRT) in unresectable stage III NSCLC.

Patients and Methods
Eligibility criteria included unresectable stage III NSCLC, Zubrod performance status ≤ 1, weight loss ≤ 5%, forced expiratory volume in 1 second ≥ 1.2 L, and adequate organ function. Patients received an initial dose of cetuximab (400 mg/m^2) on day 1 of week 1 and then weekly doses of cetuximab (250 mg/m^2) until completion of therapy (weeks 2 through 17). During week 2, patients started CRT (63 Gy in 35 fractions) with weekly carboplatin at area under the [concentration-time] curve (AUC) 2 and six doses of paclitaxel at 45 mg/m^2 followed by carboplatin (AUC 6) and two cycles of paclitaxel (200 mg/m^2) during weeks 12 through 17. Primary end points included safety and compliance of concurrent cetuximab and CRT.

Results
In all, 93 patients were enrolled and 87 were evaluable. Median follow-up was 21.6 months. Response rate was 62% (n = 54), median survival was 22.7 months, and 24-month overall survival was 49.3%. Adverse events related to treatment included 20% grade 4 hematologic toxicities, 8% grade 3 esophagitis, and 7% grade 3 to 4 pneumonitis. There were five grade 5 events.

Conclusion
The combination of cetuximab with CRT is feasible and shows promising activity. The median and overall survival achieved with this regimen were longer than any previously reported by the Radiation Therapy Oncology Group.

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INTRODUCTION

Lung cancer remains the leading cause of cancer-related death in the United States. It is estimated that 215,020 people were diagnosed with lung cancer in 2008, and approximately 161,840 people died as a result of lung cancer during the course of that year.[1]

Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer diagnoses.[2,3] For the 35% to 40% of patients with locally advanced, inoperable disease, the recommended therapeutic approach is combined-modality therapy with thoracic radiation therapy (TRT) and chemotherapy.[4-6] Within the Radiation Therapy Oncology Group (RTOG) standard of care is paclitaxel and carboplatin given concurrently with TRT, followed by consolidation chemotherapy.[7] An area under investigation is the addition of molecularly targeted agents to chemoradiotherapy (CRT) regimens.

The epidermal growth factor receptor (EGFR) pathway is associated with resistance to both cytotoxic chemotherapy and radiation therapy in cancer cell lines and is a validated therapeutic target in NSCLC.[8-12] Cetuximab is an anti-EGFR immunoglobulin G1 monoclonal antibody that targets the extracellular domain of the EGFR and binds to the receptor with an affinity that is 1 log higher than the naturally occurring ligand.[13] Preclinical data indicate that cetuximab can amplify response to chemotherapy and has radiosensitizing properties.[14-21]

Combinations of cetuximab with various chemotherapy regimens have been evaluated in

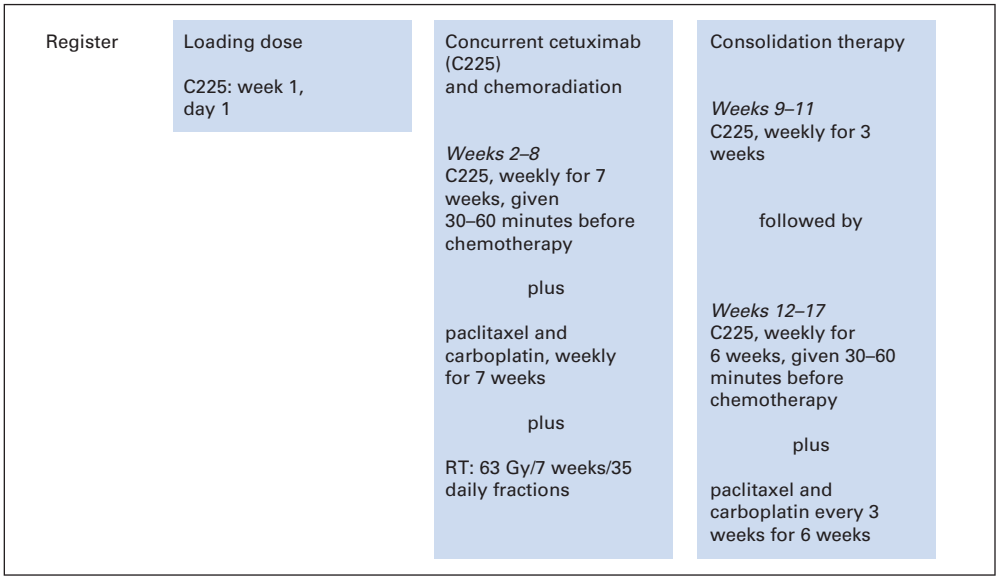

Fig 1. Treatment schema for Radiation Therapy Oncology Group 0324 (RTOG 0324) trial. RT, radiotherapy.

patients with NSCLC in the metastatic setting demonstrating that cetuximab is effective and tolerable with a manageable safety profile.[22-26] Cetuximab is approved for use in patients with squamous cell carcinoma of the head and neck (SCCHN) on the basis of the results of a randomized phase III trial that demonstrated improvement in both survival and locoregional control in those patients who received radiation and cetuximab versus radiation alone.[27]

On the basis of these data, we hypothesized that adding an agent targeting the EGFR pathway to CRT would improve the efficacy of CRT in patients with NSCLC. We now report the results of a phase II feasibility study to evaluate the safety, toxicity, and efficacy of the addition of cetuximab to the standard RTOG CRT regimen in patients with stage IIIA or IIIB NSCLC.

PATIENTS AND METHODS

Patient Selection

Patients were eligible if they were ≥ 18 years of age with untreated pathologically confirmed inoperable stage IIIA or IIIB NSCLC, weight loss of less than 5% over the 3 months before registration, a Zubrod performance status (PS) of 0 to 1, forced expiratory ventilation in 1 second ≥ 1,200 cm^3, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), and adequate organ (bone marrow, kidney, liver, heart) function.[28]

Included in the prestudy evaluation were history and physical examination, assessment of PS, complete blood count, and laboratory profile within 2 weeks before study entry. Patients had to have computed tomography (CT) or magnetic resonance imaging scans of the chest, ECG, bone scan (positron emission tomography could be substituted), CT or magnetic resonance imaging scan of the brain, and pulmonary function tests within 4 weeks before study entry. CT scans were used for all subsequent evaluations and for tumor measurements.

Informed consent was obtained from eligible patients before prestudy assessments, and the protocol was approved by the institutional review board of each participating center in agreement with local regulatory requirements.

Treatment Schedule

Eligible patients received an intravenous (IV) loading dose of cetuximab (400 mg/m^2) week 1 day 1 over 2 hours and then weekly cetuximab 250 mg/m^2 IV over 60 minutes without interruption for the duration of treatment (17 weeks total). Cetuximab was given before the administration of chemotherapy and TRT during the concurrent and consolidation portions of treatment, respectively. During weeks 2 through 8, patients received CRT (63 Gy in 35 fractions) with weekly IV paclitaxel 45 mg/m^2 administered over 1 hour followed by IV carboplatin (target area under the [concentration-time] curve [AUC] of 2 mg/mL · min; administered over 30 minutes) at AUC 2 for seven doses. Beginning at week 9, patients continued to receive weekly doses of single-agent cetuximab and, starting at week 12, after administration of cetuximab, IV paclitaxel at 200 mg/m^2 was administered over 3 hours followed by carboplatin AUC 6 over 30 minutes every 3 weeks for two cycles (weeks 12 through 17; Fig 1). The dose of carboplatin was calculated by using the modified Calvert formula which uses creatinine clearance estimated by the Cockroft-Gault equation.[29]

TRT began at week 2 and all patients received 3D conformal radiotherapy. Patients received a total dose of 63 Gy in 35 fractions over 7 weeks, 1.8

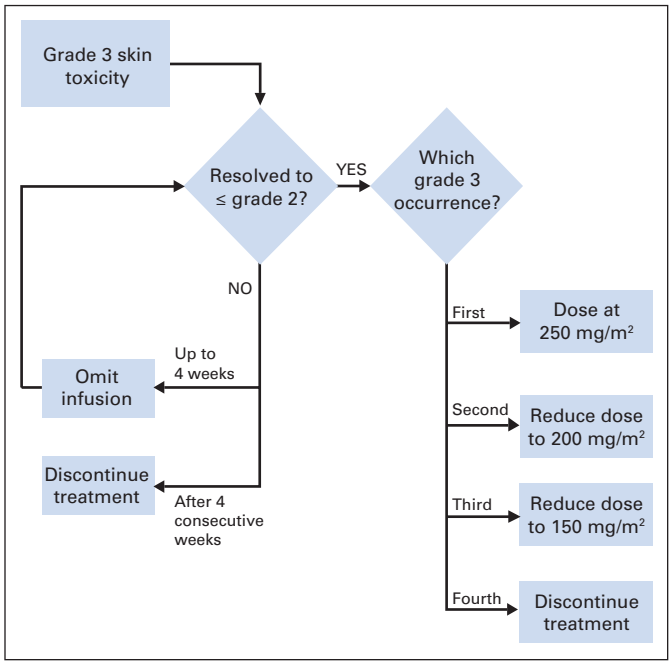

Fig 2. Management of cetuximab (C225) skin toxicity.

Table 1. Pretreatment Characteristics (n = 87)

Characteristic	No.	%
Age, years		
Median	64	
Range	42-85	
Sex		
Male	50	57
Female	37	43
Zubrod performance status		
0	41	47
1	46	53
Stage		
IIIA	40	46
IIIB	47	54

Gy × 25 fractions to an initial target volume, including selective elective nodal irradiation, followed by 1.8 Gy × 10 fractions to a boost volume. The initial target volume treated to 45 Gy included the primary tumor and grossly involved lymph nodes (gross tumor volume) with a 1-cm microscopic margin (clinical target volume 1 [CTV1]) plus the mediastinum and ipsilateral hilum with a 2-cm margin (CTV2). The initial field borders for upper and middle lobe tumors were 3 cm below the carina for CTV2. Contralateral supraclavicular and hilar lymph nodes were not included (unless they were grossly involved). The boost volume (CVT1) included the primary tumor and grossly involved lymph nodes with a 1-cm margin. Radiotherapy and chemotherapy quality assurance was performed by central review for all patients.

Treatment Modifications

CTV for this study was defined as the pretreatment gross tumor volume plus 1 cm. Patients received a total dose of 63 Gy in 35 fractions over 7 weeks, 1.8 Gy × 25 fractions, then 1.8 Gy × 10 fractions using standard fractionated radiotherapy. Standard fractionated radiotherapy was defined as 1.8 to 2.0 Gy once daily radiation to a dose of 70.2 Gy or less, including 2D and 3D conformal radiotherapy. Deviations of up to 5% were allowed for the daily dose. Radiotherapy interruptions or delays were permitted for grade 4 esophagitis/mucositis or skin toxicity and/or grade ≥ 3 pulmonary toxicity; resumption of radiotherapy was allowed once toxicity had resolved to grade ≤ 2. Interruptions in radiotherapy longer than 2 weeks resulted in removal of the patient from protocol treatment.

Chemotherapy

During CRT, paclitaxel, carboplatin, and cetuximab doses were held if the neutrophil level dropped below 1,000/μL or the patient experienced neutropenic fever. Chemotherapy was held if the platelet count dropped below 75,000/μL, and cetuximab was held for platelet counts of less than 25,000/μL. Treatment was resumed once the counts had recovered. Paclitaxel, carboplatin, and cetuximab were held for grade 3 nonhematologic toxicities until the toxicity had resolved to grade ≤ 2. If paclitaxel and/or carboplatin dose was held for more than two consecutive weeks, the drug(s) were held permanently for the duration of concurrent therapy.

For the consolidation treatment, paclitaxel and carboplatin doses were held if the neutrophil or platelet count dropped below 1,500/μL or 75,000/μL, respectively, and were reduced by one dose level if the counts had not fully recovered in 1 week. If the patient had neutropenic fever, a neutrophil count below 500/μL, or platelet count less than 25,000/μL, chemotherapy was reduced by one dose level on recovery of the counts. Cetuximab was not held for hematologic toxicities but the dose was reduced if said toxicities did not resolve after chemotherapy was held. Nonhematologic toxicities were managed as described for the concurrent portion of treatment. Dose delays greater than 2 weeks resulted in suspension of chemotherapy for the consolidation cycles. Cetuximab was discontinued for grade 3 or 4 allergic, hypersensitivity, or cytokine release reaction. Grade 3 skin toxicities induced by cetuximab were managed as outlined in Figure 2.

Assessment of Efficacy and Safety

Data were collected on efficacy, safety, concomitant medications, and therapies until the first follow-up visit to occur 4 weeks after discontinuation of

Table 2. Chemotherapy and Radiotherapy Review (n = 87)

Variable	Loading Dose Cetuximab		Concurrent Cetuximab and Chemoradiation		Consolidation Therapy	
	No.	%	No.	%	No.	%
Chemotherapy review						
Not reviewed	3	3	2	2	2	2
Reviewed	84	97	85	98	85	98
Per protocol	81	96	68	80	58	68
Not specified by reviewer	2	2	3	4	2	3
No modifications and/or delays	72	89	37	54	24	41
Modifications and/or delays	7	9	28	41	32	55
Not per protocol	1	1	12	14	17	20
Modifications and/or delays with ≥ 80% of protocol dose given	1	100	4	44	2	17
Modifications and/or delays with < 80% of protocol dose given	0	0	5	56	10	83
Not evaluable	2	2	5	6	10	12
Radiotherapy review						
Reviewed	87	100				
Per protocol	68	78				
Acceptable variation	7	8				
Unacceptable deviation	3	3				
Incomplete RT/death	4	5				
Incomplete RT/progression	1	1				
No RT given	2	2				
Not evaluable	2	2				

Abbreviation: RT, radiotherapy.

the last study drug. Post-treatment follow-up included an evaluation approximately 30 days after completion of all protocol treatment. All patients were followed for a minimum of 30 days after the last dose of study therapy or every 4 weeks until all study drug–related toxicities resolved, returned to baseline, or were deemed irreversible, whichever was longer. Patients were seen in follow-up every 3 months for 2 years and then every 4 months for 2 years.

Adverse events (AEs) were defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. There were five reviews of the rate of grade 3 or worse of the following nonhematologic toxicities: treatment-related esophagitis and pneumonitis within 90 days of the first day of TRT. These occurred after the 10th, 20th, 30th, 60th, and 80th patients had been treated and followed for at least 90 days from the end of radiation therapy. Response rate (determined 2 months after completion of consolidation chemotherapy) was defined as the proportion of patients who achieved a complete response or partial response by RECIST.[28]

Statistical Analysis

The primary end point of this study was to assess the feasibility of concurrent cetuximab and CRT as measured by safety and compliance; secondary end points included assessment of the treatment response rate, overall survival (OS), and time to disease progression. With 80 evaluable patients, the study provided sufficient power to evaluate both safety and OS. By using a Fleming one-sample multiple test procedure with type I and type II errors of 15% and 14%, the study was able to test the null hypothesis that the true toxicity rate of adding cetuximab to CRT followed by consolidation chemotherapy was greater than 75% versus the alternative hypothesis that the true rate was no more than 60%.[30] If no early stopping rules were met, at the final look, if grade 3 or 4 nonhematologic AEs occurring before the start of consolidation therapy or within 90 days of start of TRT are reported for 55 or fewer patients, the null hypothesis will be rejected and the conclusion will be that the true rate of these AEs is no more than 60%. The sample size also provided 81% power to detect an increase in median survival (MS) time from 17 months to 24 months with a one-sided alpha of .10.[31] Adjusting by 5% to account for ineligibility resulted in a final targeted sample size of 84 patients.

Safety was measured by the rate of grade 3 or worse nonhematologic toxicities occurring before the beginning of consolidation therapy or within 90 days of the start of TRT; compliance was defined as the completion of the treatment regimen with no more than minor variations. A failure event for OS was considered a death due to any cause; OS rates were calculated by using the Kaplan-Meier method. A failure event for time to progression was considered the first of the following: local, regional, or distant progression. Patients without failure were censored at the date of death or last follow-up; death without failure was considered a competing risk. Time to tumor progression was calculated by using the cumulative incidence method.[32,33]

RESULTS

Patient Characteristics

Between March 2004 and June 2005, 93 patients from 42 RTOG centers were enrolled onto the study. Of the 93 patients enrolled, six patients were deemed ineligible (one patient had an forced expiratory ventilation $< 1{,}200\ cm^3$, two patients had weight loss $> 5\%$, one patient's protocol treatment started before registration, one patient's staging workup was not completed, and one patient refused treatment after consenting for therapy). Characteristics and stage subsets of 87 patients are listed in Table 1. The median age was 64 years, 54% of

Table 3. Adverse Events Reported As Definitely, Probably, or Possibly Related to Treatment (n = 87)

	At Any Time								Prior to Beginning Consolidation or Within 90 Days of RT Start									
	Grade								Grade									
		2		3		4		5	1		2		3		4		5	
Category	1	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Allergy/immunology	2	2		3		1		0	2		2		4		1		0	
Auditory/ear	0	1		0		0		0	0		0		0		0		0	
Blood/bone marrow	7	12		31		17		0	13		16		29		6		0	
Cardiac arrhythmia	0	3		2		0		0	1		0		0		0		0	
Cardiac general	3	4		3		2		0	2		3		0		1		0	
Constitutional symptoms	14	40		17		0		0	31		27		11		0		0	
Death	0	0		0		0		1	0		0		0		0		0	
Dermatology/skin	13	40		20		1		0	19		37		19		1		0	
Endocrine	0	2		0		0		0	1		1		0		0		0	
GI	14	47		12		2		0	18		45		8		0		0	
Hemorrhage/bleeding	23	0		0		0		0	19		0		0		0		0	
Hepatobiliary/pancreas	2	1		0		0		0	1		0		0		0		0	
Infection	0	10		9		2		1	0		4		5		2		0	
Lymphatics	5	0		0		0		0	0		0		0		0		0	
Metabolic/laboratory	22	15		13		2		0	26		9		12		0		0	
Musculoskeletal/soft tissue	4	0		1		0		0	3		0		0		0		0	
Neurology	22	18		9		0		1	12		4		6		0		0	
Ocular/visual	6	7		0		0		0	5		2		0		0		0	
Pain	12	24		9		0		0	11		16		8		0		0	
Pulmonary/upper respiratory	20	26		14		1		4	13		12		11		0		3	
Renal/genitourinary	1	2		0		0		0	0		1		0		0		0	
Syndromes	0	0		2		0		0	0		0		2		0		0	
Vascular	0	0		0		2		0	0		0		0		2		0	
Worst nonhematologic	0	24	28	46	53	7	8	6	7	2	2	30	34	44	51	5	6	3	3
Worst overall	0	12	14	44	51	21	24	6	7	0		23	26	48	55	10	11	3	3

patients had stage IIIB, 25% had N3 disease, and 57% of patients were male. Pretreatment positron emission tomography scans were obtained in 84% of patients and used in staging for 64% of patients. All patients had dose volume histograms and Zubrod PS of 0 to 1.

Treatment Delivery and Compliance

Chemotherapy reviews were complete for 84 patients (97%). Eighty-one patients (96%) completed induction cextuximab per protocol, with one patient receiving the induction cextuximab with modifications and/or delays within ≥ 80% of the intended protocol dose; two patients were not evaluable because of lack of documentation.

Sixty-eight patients (80%) completed concurrent cetuximab and CRT per protocol, 12 patients (14%) were not treated per protocol, and five patients were not evaluable. During the consolidation portion of therapy, 58 patients (68%) were treated per protocol with 17 patients (20%) treated outside the parameters described by the study and 10 patients (12%) not evaluable. Details of the chemotherapy review are listed in Table 2.

Seventy-five patients (86%) had TRT delivered per protocol or with an acceptable variation, and three (3%) had unacceptable deviation. Of the remaining nine patients, five (6%) had incomplete TRT because of progression (n = 1) or death (n = 4), and four (4%) had no TRT (n = 2) or were not evaluable (n = 2; Table 2).

Safety

The AEs reported as definitely, probably, or possibly related to treatment are outlined in Table 3. Fifty-two patients (60%) experienced treatment-related grade 3 or worse nonhematologic AEs before the start of consolidation therapy or within 90 days of start of TRT. Since this number is ≤ 55, the safety conclusion is that the true rate of the specified AEs is not more than 60%. Overall, 59 patients (68%) had grade 3 or higher treatment-related nonhematologic AEs. The grade 3 esophagitis rate was 7%, and the grade 3 and higher pneumonitis rate was 9%. There were six grade 5 adverse events that were reported as definitely, probably, or possibly related to treatment. These events included acute respiratory distress syndrome with associated hypoxia 87 days after starting TRT, sepsis 65 days after starting TRT, encephalopathy and hypoxia 99 days after starting TRT, pneumonitis 46 and 84 days after starting TRT, and death not otherwise specified (thought to be a cardiopulmonary arrest) 95 days after the start of TRT. Three of the six grade 5 AEs attributed to study treatment (acute respiratory distress syndrome with hypoxia, encephalopathy and hypoxia, and pneumonitis at 46 days) had unacceptable study deviations in TRT planning, with volume of lung receiving at least 20 Gy of 65%, 40%, and 50%, respectively.

Efficacy

With a median follow-up of 21.6 months, the 24-month progression failure rate was 55.2% (95% CI, 44.6% to 65.7%; Fig 3). The 24-month survival rate was 49.3% (95% CI, 38.3% to 59.3%), and MS was 22.7 months (95% CI, 15.3 to 30.4 months). There were 25 patients (29%) who had a complete response and an additional 29 patients (33%) who had a partial response for an overall response rate of 62%. Fourteen patients had stable disease (16%), and 10 patients (11%) had progressive disease as their best outcome. Nine patients (10%) had no or inadequate reassessment or their records were unavailable for review.

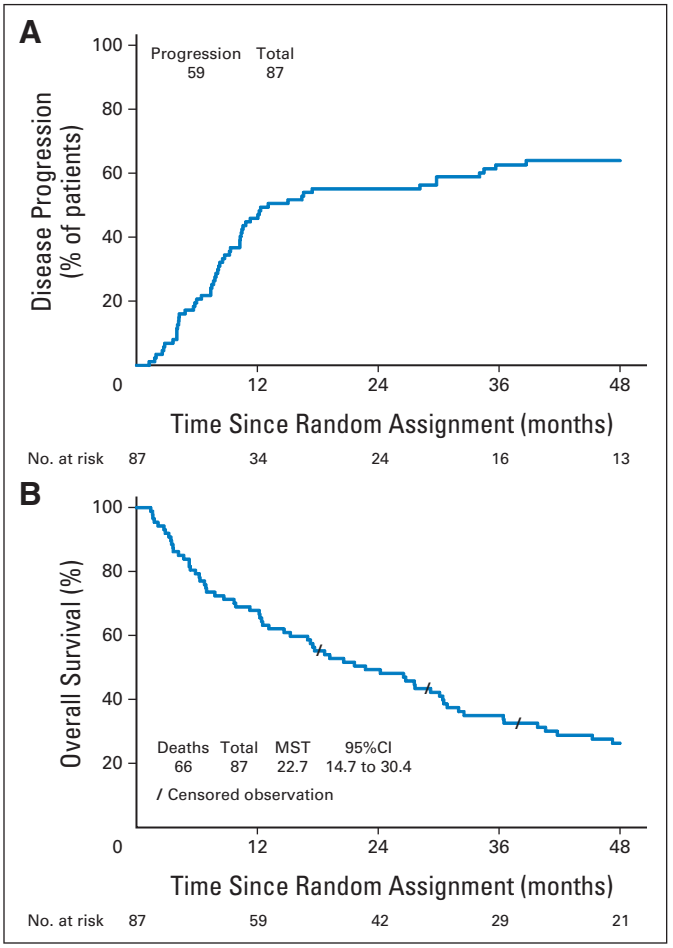

Fig 3. Time to progression. (A) Disease progression; (B) overall survival; best observed response (n = 87). MST, median survival time.

DISCUSSION

This regimen proved to be well tolerated and did not reveal any unexpected safety signals. The incidence of grade ≥ 3 nonhematologic toxicities was 60% (n = 52), which is similar to the rate of 68% reported in arm 3 (CRT followed by consolidation chemotherapy) of the locally advanced multimodality protocol (LAMP)/ACR427 trial, which served as historical control.[7] The most frequently occurring AEs that were attributable to protocol therapy included skin, GI, pulmonary, and metabolic/laboratory toxicities. The rate of grade 3 esophagitis reported in this study is 7%, which is better than the 28% rate reported in arm 3 of LAMP/ACR427 and the 25% rate reported in the concurrent arm of RTOG 9410.[6,7] The 9% rate of grade 3 to 5 pneumonitis in this study is consistent with rates previously reported for CRT alone.[6,34,35]

There were six deaths reported in this trial as potentially related to protocol therapy. Three of these had a respiratory component and unacceptable study deviations in the volume of lung included in the radiation fields. Previous CRT trials have seen grade 5 toxicities of 2% (LAMP), 3.5% (RTOG 9410), and 4% (Southwest Oncology Group [SWOG] 9504).[6,7,34]

The lack of added grade 3 and higher toxicity from the addition of cetuximab to CRT mirrors the findings in a phase III trial in SCCHN

reported by Bonner[27] in which the combination of cetuximab and radiation did not increase local toxicities within the radiation field compared with radiation alone.[27,36]

The trial also met its feasibility end point in regard to compliance because the majority of patients were able to complete the intended therapy. TRT was delivered per protocol or within acceptable variation for 86% of patients treated. The cetuximab-chemotherapy combinations were delivered per protocol in a majority of patients, with 96% of the patients receiving their loading dose of cetuximab per protocol, 80% receiving the concurrent portion of cetuximab and chemotherapy per protocol, and 68% receiving consolidation treatment of cetuximab and chemotherapy per protocol. Delivery of cetuximab-chemotherapy combination therapy was similar to the rates of chemotherapy administered in the CRT-consolidation arm of LAMP/ACR427 (70% for concurrent therapy and 67% for consolidation therapy).[7] There was no increase in toxicity or decline in dose intensity of treatment with the addition of cetuximab to standard CRT.

Although cetuximab has marginal activity as a single agent in metastatic NSCLC, there is strong preclinical rationale for its use in combination with either chemotherapy or RT.[18-21,37] The additive effects of cetuximab to either chemotherapy or radiation have been validated by the results of several large randomized clinical trials in both NSCLC and SCCHN. The FLEX trial, which compared the regimen of vinorelbine and cisplatin with or without the addition of cetuximab in 1,125 chemotherapy-naive patients with metastatic NSCLC, reported a statistically significant improvement in OS when cetuximab was added to platinum-based chemotherapy.[26] The phase III trial by Bonner et al[27] showed an improvement in both local control and OS with the combination of cetuximab and radiation compared with radiation alone, supporting a radiosensitizing effect of cetuximab. The efficacy observed in RTOG 0324 demonstrates a clinical benefit superior to that seen in previously reported RTOG studies. The progression-free survival reported in this trial was 12 months with an MS of 22.7 months and a 2-year survival rate of 49.3%. In comparison, the third arm of the LAMP/ACR427 trial reported a progression-free survival of 8.7 months, an MS of 16.3 months, and 2-year survival rate of 31%.[7] In RTOG 9410, the concurrent arm reported an MS of 17 months and a 2-year survival rate of 37%.[6]

In conclusion, the regimen of cetuximab with the RTOG standard of weekly paclitaxel, carboplatin, and TRT is feasible and can be successfully administered to patients in a cooperative group setting. The efficacy observed in RTOG 0324 appears to be promising when compared with historical data from previous RTOG studies. A confirmatory intergroup trial, RTOG 0617, is currently evaluating the addition of cetuximab to CRT in a phase III setting.

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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