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ORIGINAL REPORT

# Phase III Randomized, Placebo-Controlled Trial of Docetaxel With or Without Gefitinib in Recurrent or Metastatic Head and Neck Cancer: An Eastern Cooperative Oncology Group Trial

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## ABSTRACT

### Purpose
We hypothesized that the addition of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, to docetaxel would enhance therapeutic efficacy in squamous cell carcinoma of the head and neck (SCCHN).

### Patients and Methods
Patients with recurrent or metastatic SCCHN with Eastern Cooperative Oncology Group (ECOG) performance status of 2, or patients with ECOG performance status of 0 to 2 but were previously treated with chemotherapy, were randomly assigned to receive weekly docetaxel plus either placebo (arm A) or gefitinib 250 mg/d, orally (arm B) until disease progression. At the time of progression, patients in the placebo arm could receive single-agent gefitinib. EGFR, c-MET, and KRAS mutations and polymorphisms in drug metabolizing enzymes and transporters were evaluated by pyrosequencing.

### Results
Two hundred seventy patients were enrolled before the study was closed early at interim analysis (arm A, n = 136; arm B, n = 134). Median overall survival was 6.0 months in arm A versus 7.3 months in arm B (hazard ratio, 0.93; 95% CI, 0.72 to 1.21; $P = .60$). An unplanned subset analysis showed that gefitinib improved survival in patients younger than 65 years (median 7.6 *v* 5.2 months; $P = .04$). Also, there was a trend for improved survival in patients with c-MET wild-type (5.7 *v* 3.6 months; $P = .09$) regardless of treatment. Grade 3/4 toxicities were comparable between the two arms except that grade 3/4 diarrhea was more common with docetaxel/gefitinib. Of 18 eligible patients who received gefitinib after disease progression in arm A, one patient had a partial response.

### Conclusion
The addition of gefitinib to docetaxel was well tolerated but did not improve outcomes in poor prognosis but otherwise unselected patients with SCCHN.

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## INTRODUCTION

Approximately 52,000 new instances of head and neck cancer are diagnosed annually in the United States.[1] Although locally advanced squamous cell carcinoma of the head and neck (SCCHN) is potentially curable with combined-modality therapy, recurrent or metastatic (R/M) disease carries a poor prognosis. Patients with disease progression after first-line therapy for R/M SCCHN or early recurrence after potentially curative chemoradiotherapy have a particularly poor outcome. Performance status (PS) is a strong predictor of survival in SCCHN.[2] There are limited data on therapeutic outcomes in patients with compromised PS.[3] A number of single agents have activity in previously treated patients with R/M SCCHN, including the taxanes and methotrexate, however, there is no standard treatment. Weekly docetaxel was active in a phase II trial in the first-line treatment of R/M SCCHN with a reported a response rate of 42% and median overall survival (OS) of 11.3 months.[4] A phase II randomized study of weekly docetaxel versus methotrexate showed higher response rates for docetaxel but comparable survival rates.[5]

Epidermal growth factor receptor (EGFR) inhibitors have antitumor activity and tolerable toxicity profiles in SCCHN. Cetuximab, a monoclonal antibody against EGFR, has demonstrated efficacy in the management of SCCHN.[6] A randomized Eastern Cooperative Oncology Group (ECOG) study (E5397) in R/M SCCHN showed that adding cetuximab to cisplatin improves objective response rate but not overall survival.[7] In contrast, a larger phase III trial conducted by Vermorken et al[8] showed that adding cetuximab to platinum/fluorouracil prolongs survival in first-line treatment of R/M SCCHN.

Gefitinib, an oral quinazoline, is a highly selective EGFR-tyrosine kinase inhibitor (TKI). Its common adverse effects included rash, diarrhea, and elevated transaminases. Gefitinib resulted in single-agent response rates in phase II trials in R/M SCCHN of 1% to 11%.[9-11] A phase III trial showed that gefitinib at doses of 250 mg or 500 mg was not superior to methotrexate.[3] EGFR-TKIs can potentiate the effect of chemotherapy in a manner that may be tumor type– and schedule-dependent. The combination of docetaxel with gefitinib is supported by preclinical observations in SCCHN models. Simultaneous administration or sequencing gefitinib after chemotherapy was optimal in the laboratory.[12-14]

Clinical data with docetaxel plus gefitinib have been reported in many cancers, including phase II data with cisplatin/docetaxel plus gefitinib in SCCHN.[15] The combination of erlotinib and docetaxel resulted in significant toxicities in a phase I trial in patients with SCCHN necessitating reduction of the erlotinib dose to 50 mg daily.[16] This prompted us to study gefitinib as the EGFR-TKI of choice. Our hypothesis was that the addition of gefitinib to docetaxel will be synergistic and improve the outcome of previously treated and/or compromised performance status patients with recurrent or metastatic SCCHN.

## PATIENTS AND METHODS

### Patient Selection

Eligible patients were at least 18 years old with R/M SCCHN considered incurable with locoregional therapies; adequate hematologic and liver function test parameters; and measurable or nonmeasurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST)[17]; PS 2, if previously untreated (including prior chemotherapy as part of potentially curative therapy $>$ 6 months); or PS 0 to 2, if previously treated for R/M disease or prior chemotherapy as part of potentially curative therapy within 6 months of study enrollment. Any number of prior regimens was permitted except prior treatment with an EGFR inhibitor or docetaxel. Prior paclitaxel was allowed, if disease did not progress while receiving paclitaxel. Patients with peripheral neuropathy of grade 2 or worse, unstable comorbid disease, or hypercalcemia were excluded. Female patients of childbearing potential could not be pregnant or breastfeeding. Patients with major tumor-related hemorrhagic events in the previous 3 months, on therapeutic anticoagulation, or with tumors that invaded major vessels were also excluded. All patients signed informed consent and the protocol was approved by the respective institutional review boards.

### Treatment Plan

Docetaxel was administered as a 60-minute infusion at a dose of 35 mg/m$^2$ on days 1, 8, and 15 of a 28-day cycle. Placebo (arm A) or gefitinib

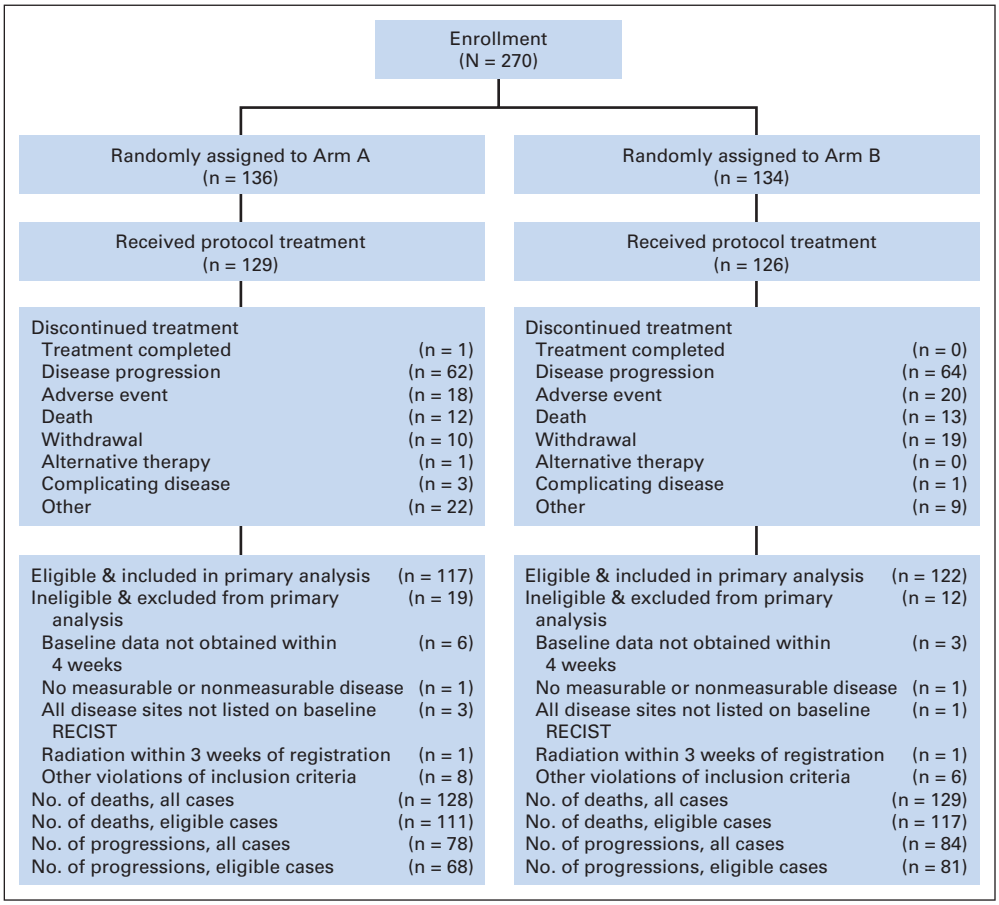


**Fig 1.** CONSORT diagram representing enrollment and outcomes of patients in the docetaxel/placebo (arm A) or docetaxel/gefitinib (arm B) treatment group. RECIST, Response Evaluation Criteria in Solid Tumors.

  

**Table 1.** Patient Characteristics, Disease Status, and Prior Treatment (N = 239)

| Characteristic | Treatment Arm | | | | Total | | *P** |
|---|---|---|---|---|---|---|---|
| | Placebo Arm | | Gefitinib Arm | | | | |
| | No. of Patients | % | No. of Patients | % | No. of Patients | % | |
| Age, years | | | | | | | .57 |
| Median | 61.4 | | 60.8 | | | | |
| Range | 28.0-86.5 | | 41.6-84.4 | | | | |
| < 65 | 72 | 62 | 84 | 69 | 156 | 65 | .28 |
| ≥ 65 | 45 | 38 | 38 | 31 | 83 | 35 | |
| Sex | | | | | | | .75 |
| Male | 92 | 79 | 98 | 80 | 190 | 79 | |
| Female | 25 | 21 | 24 | 20 | 49 | 21 | |
| Race | | | | | | | .59 |
| White | 101 | 86 | 102 | 84 | 203 | 85 | |
| Nonwhite | 16 | 14 | 20 | 16 | 36 | 15 | |
| Performance status | | | | | | | .72 |
| 0 | 15 | 13 | 12 | 10 | 27 | 11 | |
| 1 | 31 | 26 | 31 | 25 | 62 | 26 | |
| 2 | 71 | 61 | 79 | 65 | 150 | 63 | |
| Weight loss in previous 6 months | | | | | | | .82 |
| < 5% of body weight | 64 | 55 | 71 | 58 | 135 | 57 | |
| 5-10% of body weight | 24 | 21 | 24 | 20 | 48 | 20 | |
| 10 to < 20% of body weight | 19 | 16 | 15 | 12 | 34 | 14 | |
| ≥ 20% of body weight | 10 | 9 | 12 | 10 | 22 | 9 | |
| Smoking history | | | | | | | .19 |
| Never smoked | 13 | 12 | 7 | 6 | 20 | 9 | |
| Pipe or cigar smoker only | 1 | 1 | 2 | 2 | 3 | 1 | |
| Cigarette smoker, pack-years | | | | | | | |
| < 20 | 17 | 15 | 10 | 8 | 27 | 11 | |
| 20-40 | 35 | 31 | 46 | 38 | 81 | 34 | |
| > 40 | 47 | 42 | 56 | 46 | 103 | 43 | |
| Unknown | 4 | | 1 | | 5 | | |
| Average alcohol consumption | | | | | | | .89 |
| < 1 drink/month | 6 | 19 | 4 | 14 | 10 | 4 | |
| 1-5 drinks/month | 5 | 16 | 8 | 28 | 13 | 5 | |
| 1-10 drinks/week | 10 | 32 | 8 | 28 | 18 | 7 | |
| 11-30 drinks/week | 7 | 23 | 6 | 21 | 13 | 5 | |
| > 30 drinks/week | 3 | 10 | 3 | 10 | 6 | 2 | |
| Unknown | 5 | | 5 | | 10 | | |
| Histologic grade | | | | | | | .90 |
| Well differentiated | 10 | 9 | 14 | 11 | 24 | 10 | |
| Moderately differentiated | 59 | 50 | 56 | 46 | 115 | 48 | |
| Poorly differentiated | 33 | 28 | 37 | 30 | 70 | 29 | |
| Undifferentiated | 2 | 2 | 3 | 2 | 5 | 2 | |
| Grade cannot be assessed | 13 | 11 | 12 | 10 | 25 | 11 | |
| Disease status at study entry | | | | | | | .53 |
| Eradicated, no recurrence | 32 | 28 | 37 | 31 | 69 | 29 | |
| Eradicated, recurred locally | 58 | 51 | 49 | 42 | 107 | 45 | |
| Residual after prior therapy | 21 | 18 | 27 | 23 | 48 | 20 | |
| Untreated | 3 | 3 | 5 | 4 | 8 | 3 | |
| Unknown | 3 | | 4 | | 7 | | |
| Overall disease status | | | | | | | .82 |
| Locally or locoregionally recurrent/persistent only | 39 | 33 | 44 | 36 | 83 | 35 | |
| Distant metastases only | 29 | 25 | 32 | 26 | 61 | 25 | |
| Both | 49 | 42 | 46 | 38 | 95 | 40 | |
| Regional lymph node status | | | | | | | .15 |
| Unknown | 6 | | 11 | | 17 | | |
| Never involved | 17 | 15 | 19 | 17 | 36 | 15 | |
| Never involved but removed | 1 | 1 | 5 | 5 | 6 | 3 | |

(continued on following page)

**Table 1.** Patient Characteristics, Disease Status, and Prior Treatment (N = 239) (continued)

| Characteristic | Treatment Arm | | | | Total | | *P** |
|---|---|---|---|---|---|---|---|
| | Placebo Arm | | Gefitinib Arm | | | | |
| | No. of Patients | % | No. of Patients | % | No. of Patients | % | |
| Involved nodes, eradicated | 49 | 44 | 32 | 29 | 81 | 34 | |
| Involved nodes eradicated, new involvement | 22 | 20 | 26 | 23 | 48 | 20 | |
| Involved nodes, not treated | 13 | 12 | 14 | 13 | 27 | 11 | |
| Other | 9 | 8 | 15 | 14 | 24 | 10 | |
| Primary site | | | | | | | .40 |
| Oral cavity | 30 | 26 | 23 | 19 | 53 | 22 | |
| Oropharynx | 36 | 31 | 42 | 34 | 78 | 33 | |
| Larynx | 28 | 24 | 33 | 27 | 61 | 26 | |
| More than one | 4 | 3 | 9 | 7 | 13 | 5 | |
| Other† | 19 | 16 | 15 | 12 | 34 | 14 | |
| Prior chemotherapy | | | | | | | .38 |
| No | 33 | 28 | 28 | 23 | 61 | 26 | |
| Yes | 84 | 72 | 94 | 77 | 178 | 74 | |
| Prior radiotherapy | | | | | | | .47 |
| No | 20 | 17 | 16 | 13 | 36 | 15 | |
| Yes | 97 | 83 | 106 | 87 | 203 | 85 | |
| Prior surgery | | | | | | | .24 |
| No | 41 | 35 | 52 | 43 | 93 | 39 | |
| Yes | 76 | 65 | 70 | 57 | 146 | 61 | |
| Prior biologic/targeted therapy | | | | | | | .03 |
| No | 111 | 96 | 122 | 100 | 233 | 98 | |
| Yes | 5 | 4 | 0 | 0 | 5 | 2 | |
| Metastatic site involvement | | | | | | | |
| Lung | | | | | | | .70 |
| Unknown | 2 | | 1 | | 3 | | |
| Not involved | 50 | 43 | 56 | 46 | 106 | 44 | |
| Involved | 65 | 57 | 65 | 54 | 130 | 54 | |
| Liver | | | | | | | .78 |
| Unknown | 4 | | 5 | | 9 | | |
| Not involved | 106 | 95 | 109 | 93 | 215 | 90 | |
| Involved | 6 | 5 | 8 | 7 | 14 | 6 | |
| Bone | | | | | | | .16 |
| Unknown | 0 | | 1 | | 1 | | |
| Not involved | 94 | 80 | 106 | 88 | 200 | 84 | |
| Involved | 23 | 20 | 15 | 12 | 38 | 15 | |

**P* value calculation excludes unknown values.
†Lip and oral cavity, nasopharynx, hypopharynx, salivary glands, paranasal sinuses, no primary identified, other.

(Iressa, AstraZeneca, Wilmington, DE; arm B) at a dose of 250 mg (one tablet) was administered orally each day starting on day 1 and continuing for days 1 to 28 of each cycle. Premedication with dexamethasone was given for a total of three doses: 4 mg orally 12 hours before docetaxel, 4 mg intravenously or orally 30 to 60 minutes before docetaxel, and 4 mg orally 12 hours after docetaxel. Docetaxel plus placebo/gefitinib treatment continued until disease progression. Patients assigned to arm A had the option of unblinding at disease progression and registering (step 2) to receive single-agent gefitinib 250 mg once daily until disease progression. This option was eliminated in September 2007. Docetaxel and gefitinib dose modifications were applied for hematologic and nonhematologic toxicities according to protocol-specified criteria. Gefitinib and matching placebo were provided by AstraZeneca (Wilmington, DE) and distributed by the Pharmaceutical Management Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis of the National Cancer Institute.

### *Patient Assessments and Monitoring*

Patients were evaluated by computed tomography of the chest and abdomen and computed tomography or magnetic resonance imaging of the neck at baseline, within 4 weeks of registration, and after every 2 cycles (8 weeks). Bone scan was performed at baseline and then as clinically indicated. Objective response was evaluated using RECIST version 1.0.[17] Complete blood counts were obtained on days 1 and 8 and serum chemistry tests were administered on day 1 of each cycle. All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

### *Genotyping and Mutation Analyses*

Genotyping studies were performed to identify biomarkers that would correlate with treatment. Genomic DNA was extracted from whole blood or paraffin-embedded tumor blocks for analyses of single nucleotide polymorphisms (SNPs) or mutations, respectively, using standard extraction procedures. SNPs in *CYP3A4, CYP3A5, ABCB1, EGFR Q787*, and *ABCG2* genes, as well as mutations in EGFR exons 18 to 21[18-21]; *c-MET* exons 2, 14, 15, and the tyrosine kinase domain[22-26]; and *KRAS* exons 12 and 13[27-29] were analyzed by pyrosequencing. EGFRvIII was analyzed by polymerase chain reaction–amplifying-specific regions of the *EGFR* gene and visualizing samples on a 2% agarose-ethidium bromide gel for the absence or presence of mutant EGFR.[19]

  

### Statistical Design and Analysis

This was a double blind, placebo-controlled phase III randomized trial. Patients were randomly assigned equally to docetaxel/placebo (arm A) and docetaxel/gefitinib (arm B). Randomization was done using permuted blocks within strata, with dynamic balancing within main institutions and their affiliate networks, with stratification by prior chemotherapy status (treated/untreated), PS (0, 1, or 2), weight loss in the last 6 months ($< 5\%$ *v* $\geq 5\%$), and prior cetuximab (yes *v* no). The study was designed to detect an improvement in median OS from 6 months in the control arm to 8.4 months in the experimental arm. A total accrual of 314 eligible patients and total information of 286 deaths were needed to attain 80% power with 2.5% type I error, using a one-sided log-rank test. To allow for up to 5% of the patients to be ineligible, a total of 330 patients were to be accrued. The trial was monitored according to principles of group-sequential methods using a one-sided O'Brien-Fleming[30] upper boundary. Interim analyses were scheduled beginning at 25% of full information, then semiannually with stopping rules in favor of the null and alternative hypotheses based on repeated CI[31] on the hazard ratio (HR), using the O'Brien-Fleming boundary. In November 2008, the ECOG Data Monitoring Committee recommended study closure to accrual because it was unlikely that the primary end point would be reached.

The analysis of efficacy outcomes excluded ineligible patients, whereas the toxicity summary included all patients who received treatment. OS was defined as the time from registration to death from any cause or censored at the time of last contact. Time-to-progression (TTP) was defined as time from registration to evidence of disease progression or censored at the last disease evaluation. Categorical data were summarized by frequency and percentage. Exact binomial confidence intervals were estimated for response rates.[32] Wilcoxon rank sum and Fisher's exact tests were used to compare continuous and categoric variables, respectively, between groups. The survival data were analyzed using the Kaplan-Meier[33] method and the significance was tested by log-rank tests. Cox's proportional hazards models[34] were used to estimate HR and evaluate interaction effects. All *P* values are two-sided. A level of 5% was considered statistically significant. SNPs were investigated in blood samples and efficacy was compared by genotype (variant *v* nonvariant, including wild-type and heterozygote) for each polymorphism. Mutations were examined in tumor samples and efficacy was compared by mutation status (wild-type *v* mutation, including heterozygote and variant). Because the analysis of correlatives was exploratory, no statistical adjustment was performed for multiple comparisons.

## RESULTS

From August 2004 to November 2008, a total of 270 patients (136 in arm A; 134 in arm B) were enrolled onto the study, of whom 239 were eligible (117 in arm A; 122 in arm B; Fig 1). Fifteen patients (seven in arm A; eight in arm B) never started their assigned treatment.

Twenty-four patients initially assigned to docetaxel plus placebo were registered to step 2 following disease progression; of those patients, 22 were eligible and four patients never started gefitinib. A total of six patients received cetuximab after study treatment completion and before documented disease progression per study criteria (four patients in arm A; two in arm B).

### Patient Characteristics and Treatment Delivery

Table 1 provides baseline patient demographics and disease characteristics for eligible patients (N = 239). Except for the prior biologic/targeted therapy status, there were no statistically significant imbalances between the two arms. The median number of treatment cycles received was two (range, 0 to 10) and two (range, 0 to 18) for arms A and B, respectively. Appendix Table A1 (online-only) presents the reasons for treatment discontinuation, the most common of which was progressive disease. Although a similar number of gefitinib cycles was administered to younger and elderly patients (median, two), a higher proportion of the elderly required gefitinib dose interruptions in arm B (72% *v* 41%; $P < .001$) but not placebo in arm A (47% *v* 46%; $P = 1.00$). No significant association between docetaxel dose modifications and treatment arm was observed for either younger patients or older patients.

### Overall Survival and Time-to-Progression

Seven patients (3%) were alive at the time of the analysis (arm A, four patients; arm B, three), with a median follow-up time of 35 months (range, 24 to 54 months). For all patients, median OS was 6.8 months (95% CI, 5.72 to 7.52 months). The median OS was 6.0 months (95% CI, 4.93 to 7.43) and 7.3 months (95% CI, 5.75 to 8.44) in arms A and B, respectively (HR, 0.93; 95% CI, 0.72 to 1.21; $P = .60$). Median TTP was 2.1 months for arm A and 3.5 months for arm B (HR, 0.81; 95% CI, 0.58 to 1.11; $P = .19$). Figure 2 shows the Kaplan-Meier curves for OS and TTP. The median OS and TTP for the 22 patients who registered for step 2, calculated from the time of cross-over registration, were 6.3 and 2.6 months, respectively.

In an unplanned subgroup analysis, we found that patients younger than 65 years derived survival benefit from combination

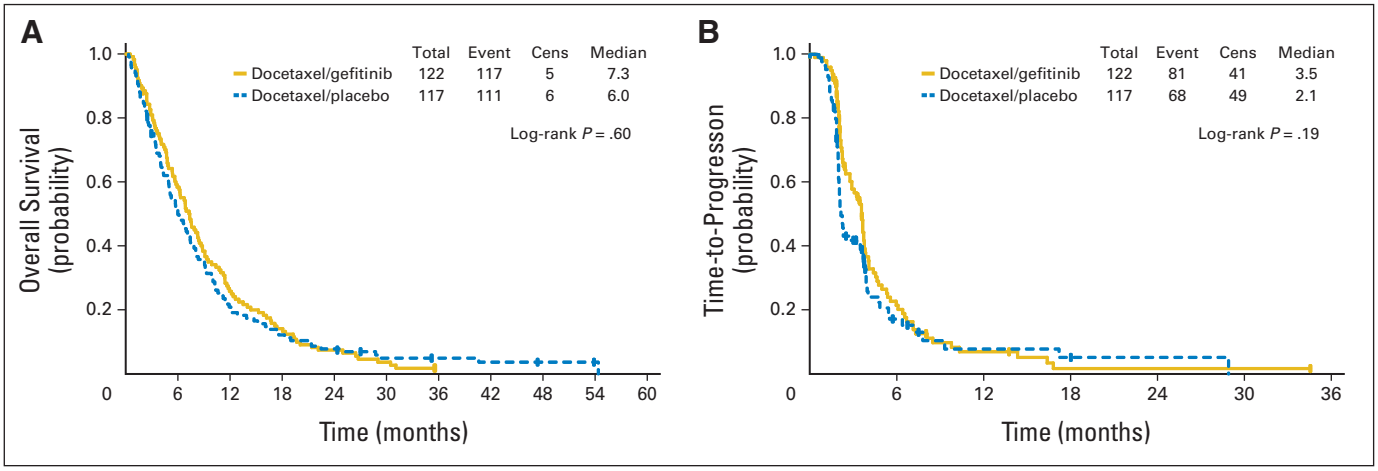


**Fig 2.** Kaplan-Meier estimates of (A) overall survival by treatment arm (n = 239) and (B) time-to-progression by treatment arm (n = 239). Cens, censored.

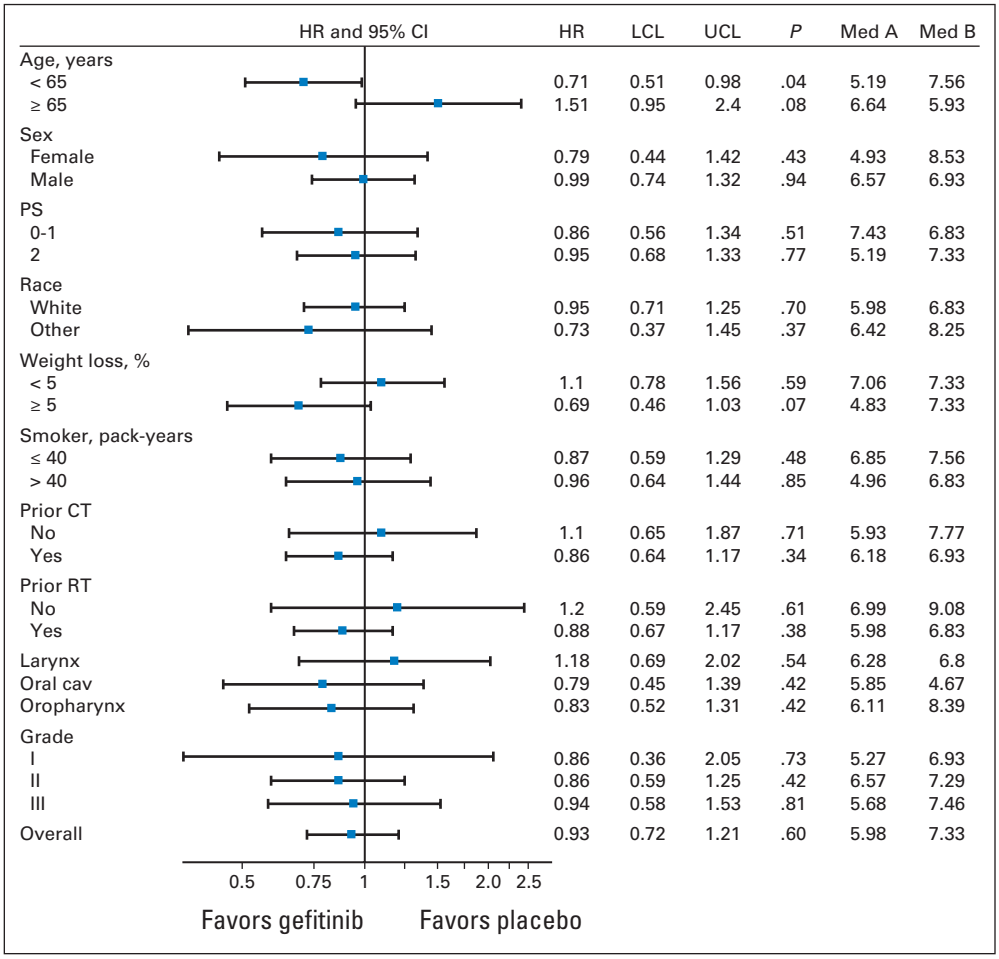


**Fig 3.** Forest plot representing hazard ratios (HRs) with 95% CIs of overall survival in patient subgroups. Cav, cavity; CT, chemotherapy; LCL, lower confidence limit; Med A, median overall survival in arm A; Med B, median overall survival in arm B; PS, performance status; RT, radiotherapy; UCL, upper confidence limit.

therapy (median OS, 7.6 months with docetaxel/gefitinib *v* 5.2 months with docetaxel/placebo; $P = .04$) but patients 65 years or older did not (median OS, 5.9 months with docetaxel/gefitinib *v* 6.6 months with docetaxel/placebo; $P = .08$; Fig 3 shows forest plot of HRs of OS and Fig 4 shows survival curves). The Cox proportional hazards regression analysis showed that the interaction effect by age and treatment arm was highly significant ($P = .007$). There was also improvement in TTP with the addition of gefitinib in younger patients (median, 3.6 *v* 2.0 months; $P = .01$) but not in patients ≥ 65 years (median, 3.4 *v* 3.7 months; $P = .58$).

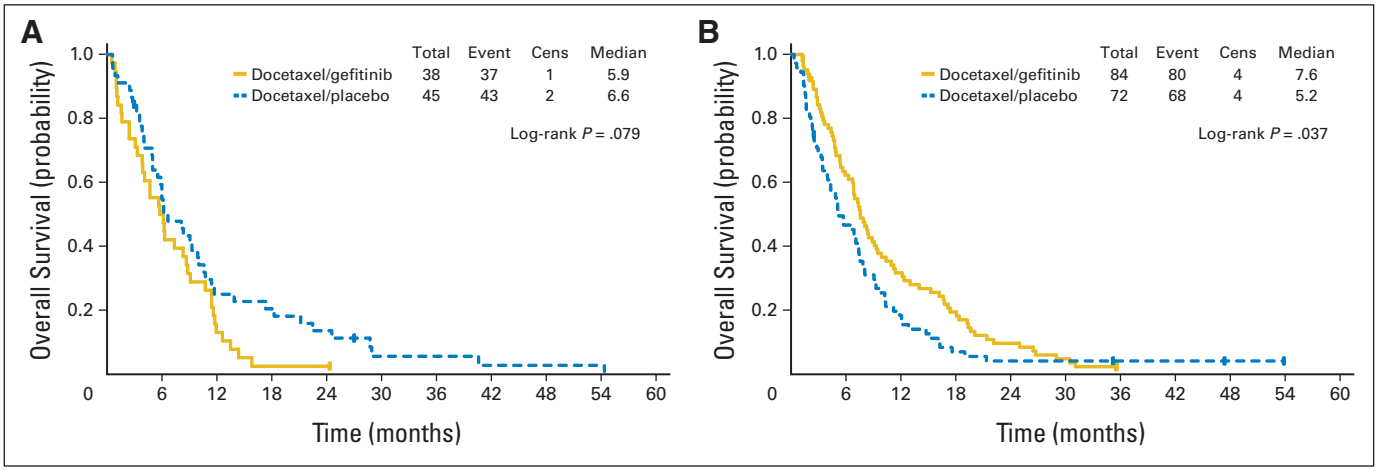


**Fig 4.** Kaplan-Meier estimates of overall survival by treatment arm for (A) patients ≥ 65 years (n = 83) and (B) patients younger than 65 years (n = 156). Cens, censored.

  

**Table 2.** Treatment-Related Adverse Events

| Adverse Event | Gefitinib Arm (n = 124) | | | Placebo Arm (n = 129) | | |
|---|---|---|---|---|---|---|
| | Grade 3 (%) | Grade 4 (%) | Grade 5 (%) | Grade 3 (%) | Grade 4 (%) | Grade 5 (%) |
| Allergic reaction | 1 | | | 2 | | |
| Hemoglobin | | | | 4 | | |
| Leukopenia | 3 | 2 | | 2 | 2 | |
| Lymphopenia | 2 | 1 | | 5 | 2 | |
| Neutropenia | 2 | 1 | | 1 | 2 | |
| Thrombocytopenia | | 1 | | | | |
| Atrial fibrillation | 1 | | | 1 | | |
| Ventricular flutter | | | | 1 | | |
| Hypotension | 2 | | 1 | 2 | 1 | |
| Left ventricular diastolic dysfunction | | | | 1 | | |
| Fatigue | 11 | | | 13 | 3 | |
| Insomnia | | | | 1 | | |
| Weight loss | 1 | | | 2 | | |
| International normalized ratio | | | | 1 | | |
| Partial thromboplastin time | | | | 1 | | |
| Nail changes | 1 | | | 1 | | |
| Pruritus/itching | 1 | | | | | |
| Rash/desquamation | | | | 2 | | |
| Hand-foot reaction | | | | 1 | | |
| Death/sudden death | | | 2 | | | |
| Anorexia | 5 | | | 2 | | |
| Dehydration | 6 | 1 | | 5 | | |
| Diarrhea without prior colostomy | 11 | 2 | | 2 | | |
| Dysphagia | 2 | | | 1 | | |
| Fistula, colon/cecum/appendix | | | | 1 | | |
| Oral mucositis by examination | 2 | | | | | |
| Oral mucositis by symptoms | 2 | | | 2 | | |
| Nausea | 6 | | | 3 | 1 | |
| Perforation, duodenum | | 1 | | | | |
| Vomiting | 2 | 1 | | 3 | | |
| Abdomen, hemorrhage NOS | 1 | | | | | |
| Esophagus, hemorrhage | | | | 1 | | |
| Oral cavity, hemorrhage | | | | | 1 | |
| Bronchus, hemorrhage | | | | | | 1 |
| Colitis, infectious | | | | 1 | | |
| Febrile neutropenia | | | | 1 | | |
| Infection with neutropenia | | | | | | |
| Grade 3-4 | | | | | | |
| Abdomen NOS | 1 | | | | | |
| Bladder | | | | 1 | | |
| Lung | 1 | | | | | |
| Blood | | | 1 | | | |
| Grade 0-2 | | | | | | |
| Abdomen | 1 | | | | | |
| Catheter | | | | 2 | | |
| Colon | | | | | 1 | |
| Lung | 3 | 1 | | 5 | 1 | 1 |
| Neck | 1 | | | | 1 | |
| Skin | 1 | | | 3 | | |
| Urinary tract | 1 | | | | | |
| Wound | 1 | | | | | |
| Blood | 2 | | | | 1 | |
| Infection with unknown neutrophils, lung | 1 | | | | | |
| Infection with unknown neutrophils, skin | 1 | | | 1 | | |
| Opportunistic infection with lymphopenia | 1 | | | | | |
| Infection, other | | | | | 1 | |
| Edema | | | | | | |
| Head and neck | 2 | | | 1 | | |
| Limb | | | | 1 | | |
| Hypoalbuminemia | | | | 1 | | |
| Alkaline phosphatase | | | | 1 | | |
| ALT | | | | 1 | | |
| Creatinine | 1 | | | | | |
| Hyperglycemia | 2 | | | 1 | | |
| Hypophosphatemia | | | | 1 | | |
| Hypokalemia | | | | | 1 | |
| Hyponatremia | 1 | | | 2 | 1 | |
| Non-neuropathic lower extremity muscle weakness | 1 | | | 1 | | |
| Non-neuropathic generalized weakness | 1 | | | 5 | | |
| Trismus | 1 | | | | | |
| Neuropathy, motor | 1 | | | | | |
| Neuropathy, sensory | 3 | | | | | |
| Syncope | 2 | | | | | |
| Abdomen, pain | 1 | | | | | |
| Chest pain NOS | 1 | | | | | |
| Head/headache | | | | 1 | | |
| Adult respiratory distress syndrome | | 1 | | | 1 | |
| Bronchospasm, wheezing | 1 | | | | | |
| Cough | | | | 1 | | |
| Dyspnea | 3 | 1 | | 4 | 1 | |
| Hypoxia | 1 | | | 1 | 1 | |
| Pleural effusion, nonmalignant | 2 | | | 1 | | |
| Pneumonitis/pulmonary infiltrates | | | 1 | 1 | 2 | |
| Renal failure | 1 | | | | | |
| Thrombosis/embolism | 1 | | | | | |
| Vessel injury, carotid | 1 | | | | | |
| Worst degree | 37 | 6 | 5 | 36 | 12 | 2 |

NOTE. Grade 3, severe; grade 4, life threatening; grade 5, lethal.
Abbreviation: NOS, not otherwise specified.

### *Response*

The distribution of response in arm A was: two patients with complete responses, three patients with partial responses, 28 patients with stable disease, 48 patients with progressive disease, and 36 patients unevaluable. In arm B, there were two patients with complete responses, 10 patients with partial responses, 41 patients with stable disease, 43 patients with progressive disease, 26 patients who were unevaluable. In evaluable patients, the overall response rate (ORR) was 6.2% (95% CI, 2.01% to 13.82%) and 12.5% (95% CI, 6.61% to 20.84%), in arms A and B, respectively, a difference that was not statistically significant ($P = .13$). Of 16 evaluable patients registered to step 2, one had an objective response and six had stable disease as best response.

### Toxicity

Toxicities were assessed in a total of 253 patients (129 in arm A; 124 in arm B) in step 1 of the study (Table 2). The incidence of grade 3/4 toxicities was comparable between the two arms, except for a higher incidence of diarrhea with gefitinib (13% *v* 2%; $P < .001$). Two treatment-related lethal toxicities occurred in patients in arm A (lung infection and pulmonary hemorrhage) and six in patients in arm B (pneumonitis, septicemia, hypotension, and three sudden deaths). No statistically significant difference in grade 3 to 5 toxicities was noted between younger (< 65 years) and older patients (≥ 65 years) in either arm, except for a higher rate of grade 3 to 5 infection on the gefitinib arm (8% in older *v* 0% in younger patients; $P = .03$).

Of 19 patients assessed for toxicity in step 2, two experienced grade 3 toxicities (fatigue and dysphagia, respectively). No grade 4 or 5 toxicities were reported.

### Correlative Studies

SNP analysis was performed on germline DNA samples and mutation analysis was performed on somatic DNA samples from tumor tissue. Among the 239 eligible patients, 89 blood samples and 69 tumor samples were available for analysis (Table 3 and Appendix Tables 2-4). No significant difference was found in any patient characteristic between patients who had blood or tumor sample analyzed and those who did not. No association was found between SNP genotypes and toxicity or efficacy. Two *EGFR* mutations were detected, one *EGFRvIII* and one *EGFR A767T* (both in arm B). The patient with an *EGFRvIII* mutation had an objective response, whereas two of 35 patients with wild-type *EGFR* achieved an objective response (100% *v* 6%; $P = .08$) in arm B and had an OS of 19.6 months versus 5.7 months in patients with wild type. The patient with the *EGFR A767T* mutation was not evaluable for response. Regardless of treatment, the presence of *c-MET* mutations tended to predict decreased OS. In 10 patients with *c-MET* mutations, the median OS was 3.6 months (95% CI, 1.1 to 8.6) versus a median OS of 5.7 months (95% CI, 3.5 to 8.3; $P = .09$) in 41 patients with wild-type *c-MET*. TTP was also decreased, although not significantly (median TTP, 2.1 *v* 2.9 months; $P = .07$), in patients with *c-MET* mutations. There were no *KRAS* mutations identified.

## DISCUSSION

This trial was one of the first phase III, placebo-controlled trials in poor PS and/or heavily pretreated patients with R/M SCCHN. For this patient population, we did not demonstrate a survival benefit by adding gefitinib to docetaxel. The median overall survival with or without gefitinib was 7.3 months versus 6.0 months, respectively, a difference that did not reach statistical significance. Moreover, there was no significant difference in TTP between the two arms (median TTP was 2.1 months for arm A and 3.5 months for arm B). The addition of gefitinib to docetaxel resulted in a higher rate of grade 3 or 4 diarrhea but other toxicities were comparable between the two arms.

Unplanned subgroup analysis showed that patients younger than 65 years derived survival benefit with the addition of gefitinib to docetaxel (median, 7.6 *v* 5.2 months), but not patients ≥ 65 years. There were no significant differences in grade 3 to 5 toxicities between younger and elderly patients except a higher incidence of infections with docetaxel and gefitinib in the elderly. However, the elderly required more dose interruptions of gefitinib dosing, which may explain the differential survival outcome by age. It has been previously reported that elderly patients with R/M SCCHN treated with chemotherapy have increased toxicities when compared with younger patients, even though survival outcomes appear comparable.[35,36] With advancing age, there are biologic changes and a higher incidence of comorbidities that may predispose the elderly to increased risks from chemotherapy.[37] Our observation of a potential survival benefit with the addition of gefitinib to docetaxel in younger but not older patients may warrant further validation in clinical studies.

A prior ECOG trial showed poor survival results in previously treated patients with R/M SCCHN dosed with irinotecan and docetaxel resulting in an ORR of 3% and median OS of 5 months.[38] The results seen with single-agent docetaxel in the control arm of the current trial were as expected. Although cross-over to single-agent gefitinib was initially allowed in this trial, only 18 eligible patients received it. This is unlikely to have had any impact on the survival results of our study.

**Table 3.** Efficacy by the Presence of *c-MET* Tumor Mutation

| *cMET* Mutation by Arm | Objective Response | | | | | Overall Survival | | | Time to Progression | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No | | Yes | | | | | | | | |
| | No. of Patients | % | No. of Patients | % | *P* | Median | 95% CI | *P* | Median | 95% CI | *P* |
| Docetaxel (n = 23) | | | | | | | | | | | |
| No | 19 | 95 | 1 | 5 | 1.00 | 5.4 | 2.0 to 14.7 | — | 3.2 | 1.4 to 4.8 | — |
| Yes | 3 | 100 | 0 | 0 | | 2.4 | 1.6 to 3.5 | | 1.5 | 0.8 to 2.2 | |
| Gefitinib (n = 28) | | | | | | | | | | | |
| No | 20 | 95 | 1 | 5 | 1.00 | 5.9 | 3.1 to 10.3 | .44 | 2.4 | 1.5 to 6.1 | .19 |
| Yes | 7 | 100 | 0 | 0 | | 5.7 | 1.1 to 9.1 | | 2.1 | 1.6 to 3.8 | |
| Both (n = 51) | | | | | | | | | | | |
| No | 39 | 95 | 2 | 5 | 1.00 | 5.7 | 3.5 to 8.3 | .09 | 2.9 | 1.8 to 3.7 | .07 |
| Yes | 10 | 100 | 0 | 0 | | 3.6 | 1.1 to 8.6 | | 2.1 | 0.8 to 2.3 | |

NOTE. If tumor mutation was observed on *cMET V1110I* (n = 2), *H1112Y* (n = 5), *H112RL* (n = 0), *T1010I* (n = 1), *R988C* (n = 1), *V1333I* (n = 1), or any *cMET* exon 14 del (n = 2), then *cMET* mutation was coded as "Yes." If wild type was observed in all these biomarkers, then *cMET* mutation status was coded as "No." Otherwise, the status was coded as missing and excluded from data analysis.

  

Two phase II trials explored the addition of an EGFR-TKI to cisplatin and docetaxel in patients with R/M SCCHN.[15,39] Kim et al[39] reported an ORR of 66% in the first 37 patients treated with cisplatin/docetaxel plus erlotinib, whereas Belon et al[15] reported an ORR of 50% in 24 patients treated with cisplatin/docetaxel plus gefitinib. The combination of an EGFR-TKI (erlotinib) and chemotherapy resulted in survival benefit, albeit marginal, in advanced pancreatic cancer[40] but not in advanced non–small-cell lung cancer.[41-44] Whether the lack of efficacy in combined EGFR-TKI and chemotherapy in lung cancer can be attributed to a sequence-dependent effect is the subject of ongoing research.[45]

Our analysis of correlative biomarkers in a rather small fraction of available patient samples indicate that *c-MET* mutations are possible prognostic markers for survival and disease progression but do not predict outcomes after EGFR inhibitor therapy, which is consistent with other reports that suggest the *c-MET* amplification does not predict response to EGFR inhibitors and that *c-MET* is a negative prognostic marker.[46-48] The single patient found to have a tumor with an *EGFRvIII* mutation responded to docetaxel/gefitinib in our study. Although mutations in *EGFR* are rare in SCCHN,[49] the potential benefit with EFGR-TKI treatment for these patients may warrant further study.

In conclusion, the addition of gefitinib to docetaxel was well tolerated but it did not enhance therapeutic efficacy across all patients in this clinical setting. The outcome of patients with SCCHN with previously treated disease or performance status of 2 remains poor and the study of other novel agents in this setting should continue.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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