Original Article

Pemetrexed in Combination With Cisplatin Versus Cisplatin Monotherapy in Patients With Recurrent or Metastatic Head and Neck Cancer

Final Results of a Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Susan Urba, MD[1]; Carla M. L. van Herpen, MD, PhD[2]; Tarini Prasad Sahoo, MD[3]; Dong M. Shin, MD[4]; Lisa Licitra, MD[5]; Klara Mezei, MD[6]; Christoph Reuter, MD, PhD[7]; Ricardo Hitt, MD, PhD[8]; Francesca Russo, MD[9]; Shao-Chun Chang, MD, PhD[10]; Anwar M. Hossain, MStat[10]; Bente Frimodt-Moller, MSc[11]; Andrew Koustenis, BPharm[10]; and Ruey-Long Hong, MD, PhD[12]

BACKGROUND: Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) is associated with poor survival. Platinum-based chemotherapy is often a first-line treatment. Pemetrexed has shown single-agent activity in SCCHN and in combination with cisplatin for other tumors. This trial examined the efficacy of pemetrexed-cisplatin for SCCHN. **METHODS:** In a double-blind phase 3 trial, patients with recurrent or metastatic SCCHN and no prior systemic therapy for metastatic disease were randomized to pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2; n = 398) or placebo plus cisplatin (75 mg/m^2; n = 397) to assess overall survival (OS) and secondary endpoints. **RESULTS:** Median OS was 7.3 months in the pemetrexed-cisplatin arm and 6.3 months in the placebo-cisplatin arm (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.75-1.02; P = .082). Median progression-free survival (PFS, months) was similar in both treatment arms (pemetrexed-cisplatin, 3.6; placebo-cisplatin, 2.8; HR, 0.88; 95% CI, 0.76-1.03; P = .166). Among patients with performance status 0 or 1, pemetrexed-cisplatin (n = 347) led to longer OS and PFS than placebo-cisplatin (n = 343; 8.4 vs 6.7 months; HR, 0.83; P = .026; 4.0 vs 3.0 months; HR, 0.84; P = .044, respectively). Among patients with oropharyngeal cancers, pemetrexed-cisplatin (n = 86) resulted in longer OS and PFS than placebo-cisplatin (n = 106; 9.9 vs 6.1 months; HR, 0.59; P = .002; 4.0 vs 3.4 months; HR, 0.73; P = .047, respectively). Pemetrexed-cisplatin toxicity was consistent with studies in other tumors. **CONCLUSIONS:** Pemetrexed-cisplatin compared with placebo-cisplatin did not significantly improve survival for the intent-to-treat population. However, in a prespecified subgroup analysis, pemetrexed-cisplatin showed OS and PFS advantage for patients with performance status 0 or 1 or oropharyngeal cancers. ***Cancer*** **2012;118:4694-705.** © *2012 American Cancer Society.*

KEYWORDS: pemetrexed, cisplatin, head and neck cancer, clinical trial, phase 3.

INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common type of cancer worldwide, with an estimated 650,000 new cases and 350,000 deaths reported every year.[1,2] Inoperable recurrent and metastatic SCCHNs are generally incurable, thus treatment focuses on prolonging overall survival (OS) or progression-free survival (PFS), palliating existing symptoms, and preventing new cancer-related symptoms.[3,4] Multiple chemotherapeutic agents have been shown to induce tumor responses; among these, cisplatin chemotherapy is frequently used for inoperable recurrent or metastatic SCCHN, either as a single agent or in combination with other chemotherapeutics.[4,5] The historical median

Corresponding author: Susan Urba, MD, University of Michigan Comprehensive Cancer Center, Division of Hematology/Oncology, 1500 E. Medical Center Drive, C347 MIB, SPC 5848, Ann Arbor, MI 48109; Fax: (734) 936-4940; surba@umich.edu

[1]Division of Hematology/Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan; [2]Department of Medical Oncology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; [3]Jawaharlal Nehru Cancer Hospital & Research Centre, Bhopal, India; [4]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia; [5]Head and Neck Medical Oncology Unit, National Tumor Institute, Milan, Italy; [6]Onkoradiologiai Osztaly Szent Istvan, Nyiregyhaza, Hungary; [7]Department of Hematology, Hannover Medical School, Hemostasis, Oncology and Stem Cell Transplantation, Hannover, Germany; [8]Medical Oncology Service, University Hospital 12th of October, Madrid, Spain; [9]Eli Lilly and Company, Florence, Italy; [10]Eli Lilly and Company, Indianapolis, Indiana; [11]Eli Lilly and Company, Copenhagen, Denmark; [12]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

Some of the results of this study have been previously disclosed at the European Society for Medical Oncology Congress; October 8-12, 2010; Milan, Italy.

We thank all the patients involved in this study, and all the institutions and investigators. We also thank Mary Dugan Wood, PhD, and Svetlana Dominguez, ELS, for writing and editorial assistance.

Registry name: ClinicalTrials.gov; registry identifier number: NCT00415194; registry URL: http://clinicaltrials.gov/ct2/show/NCT00415194?term = head + neck + cancer + pemetrexed + cisplatin&rank = 1

DOI: 10.1002/cncr.27449, **Received:** July 19, 2011; **Revised:** November 16, 2011; **Accepted:** December 27, 2011, **Published online** March 20, 2012 in Wiley Online Library (wileyonlinelibrary.com)

survival with cisplatin-based combination chemotherapy ranges from 6 to 8 months, with a corresponding 1-year survival rate of 20% to 40%.[6,7]

Pemetrexed, an inhibitor of thymidylate synthase and other folate-dependent enzymes,[8-10] has been investigated in a phase 2 study of patients with SCCHN as a single agent.[11] In this study, 9 of the 34 evaluable patients (26.5%) achieved a partial response (median time to treatment failure, 3.9 months; median OS, 7.3 months). These results, together with data from pilot studies investigating pemetrexed with cisplatin for SCCHN (data on file) and data from trials in other solid tumors,[12,13] suggest that pemetrexed may have activity in patients with recurrent or metastatic SCCHN. To explore this hypothesis, a phase 3 trial was undertaken to compare the OS of patients treated with pemetrexed plus cisplatin with that of patients treated with single-agent cisplatin. Cisplatin was chosen as the control arm because at the time of trial initiation (2006), it was considered a standard well-tolerated treatment, and had been used as the comparator arm in the 2005 phase 3 trial examining the combination of cisplatin and the biological agent cetuximab.[6] In addition, single-agent cisplatin was chosen so as not to unnecessarily increase the toxicity of the comparator arm, because at the time, no platinum-based chemotherapy doublet had improved survival time compared with single-agent therapy in this population; rather they had resulted in the expected increased toxicity.[5,6,14-16]

MATERIALS AND METHODS

Patients

Patient eligibility criteria included histological or cytological diagnosis of recurrent SCCHN or newly diagnosed distant metastatic SCCHN, $\geq$6 months since completion of chemotherapy or biological anticancer therapy, and no prior systemic therapy for metastatic disease. Other inclusion criteria were $\geq$18 years of age; life expectancy $\geq$3 months; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2[17]; measurable or nonmeasurable disease status as defined by Response Evaluation Criteria in Solid Tumors (RECIST)[18]; and adequate bone marrow reserve and organ function.

Protocol amendments approved after study initiation included changing the requirement that prior surgery and radiation be completed $\geq$6 months before study enrollment to $\geq$4 weeks before enrollment; this was more in keeping with standard clinical practice. Another protocol change lowered the minimum required creatinine clearance value[19] from 60 to 45 mL/min based on clinical evidence of the tolerability of the pemetrexed-cisplatin regimen used in this study. In addition, a protocol change provided for the collection of tumor tissue samples as formalin-fixed, paraffin-embedded tissue to study genes involved in SCCHN biology and drug activity by microarray gene expression analysis. No results are available to be reported because poor microarray performance yielded no results.

Exclusion criteria included nasopharyngeal, paranasal sinus, lip, or salivary gland cancer; clinically significant third-space fluid that could not be drained; and central nervous system metastases. Patients were also excluded if they were unable to interrupt therapy with aspirin or other nonsteroidal anti-inflammatory drugs, or if they were unable or unwilling to take folic acid, vitamin B_{12}, or corticosteroids.

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by each participating institutional/ethics review board. All patients provided written informed consent before treatment.

Study Design and Treatment Plan

This was a global, double-blind, randomized, placebo controlled phase 3 study. On day 1 every 21 days, patients received pemetrexed 500 mg/m^2 (10-minute infusion) plus cisplatin 75 mg/m^2 or placebo (100 mL saline) plus cisplatin 75 mg/m^2. The cisplatin dose was chosen to yield a dose intensity of 25 mg/m^2/wk, a dose intensity supported by previous randomized trials[5,6,14] and shown to be within the 20 to 40 mg/m^2/wk range found to yield equivalent efficacy in a randomized study comparing a high and standard doses of cisplatin in the treatment of advanced nonsmall cell lung cancer.[20] Randomization (1:1) by the technique of Pocock and Simon[21] was used to minimize imbalances among prognostic factors: baseline ECOG PS (0 or 1 vs 2), prior treatment for SCCHN, distant metastases, prior platinum-based therapy, and country.

Chemotherapy was administered for 6 cycles; patients could be discontinued from the study before the completion of the 6 cycles for disease progression, unacceptable toxicity, or patient/physician decision. Additional cycles were permitted for patients receiving benefit from study treatment. All patients were followed until death or study closure. Patients on both arms received prophylactic dexamethasone, oral folic acid, and vitamin B_{12} injection as per the pemetrexed label. Because pemetrexed, cisplatin, placebo, and vitamin B_{12} were administered at the investigational sites by authorized study personnel, patient compliance was ensured.

The following were allowed per protocol: dose adjustments (as per the pemetrexed label), cycle delays $\leq$42 days (to allow resolution of toxicities), and concomitant supportive therapies (granulocyte colony-stimulating factors or erythropoietin) according to the American Society of Clinical Oncology guidelines.[22]

Baseline and Treatment Assessments

The primary efficacy measure was OS. Secondary endpoints included PFS, tumor response rate, safety, time to worsening, and change from baseline in dimensions of health-related quality of life (HRQL) using the Functional Assessment of Cancer Therapy - Head and Neck scale (FACT-H&N).[23,24]

Baseline tumor measurements were performed within 4 weeks before first treatment dose. Computed tomography or magnetic resonance imaging was preferred, but chest x-ray was acceptable for clearly defined lesions. Any palpable tumors were measured within 2 weeks of first treatment. The baseline assessment method was repeated every other cycle, and every 6 weeks after treatment discontinuation until disease progression. Patients who had baseline imaging and at least 1 scan after starting chemotherapy were considered assessable for tumor response using RECIST 1.0.[18] OS and PFS analyses incorporated all randomized patients on an intention-to-treat (ITT) basis.

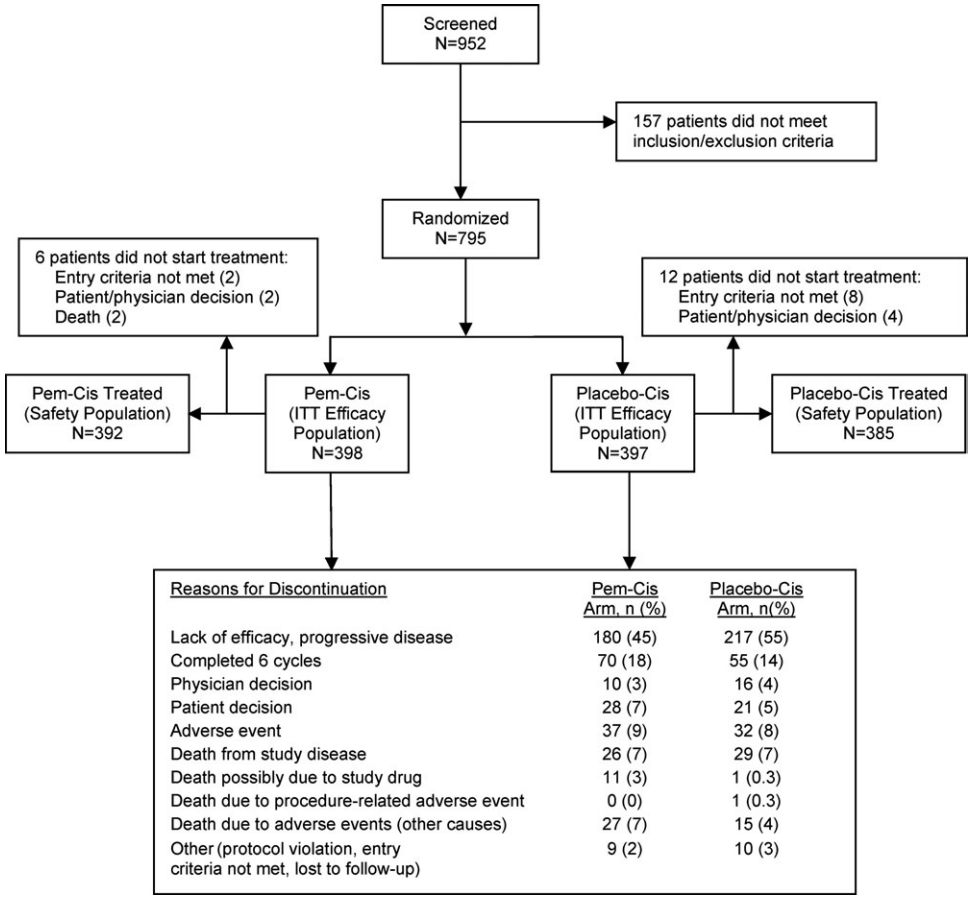
Patients were assessed for toxicity before each cycle according to the Common Terminology Criteria for Adverse Events, version 3.0.[25] All patients who received at least 1 dose of pemetrexed or cisplatin were considered assessable for safety.

The FACT-H&N scale (version 4) was administered at baseline and on day 1 of all cycles to assess and compare changes in HRQL between treatment arms. This reliable and valid instrument[24] consists of a 39-item scale organized into 5 subscales: physical, social/family, functional, and emotional well-being, and additional concerns-head and neck, with higher scores representing better quality of life. The FACT-H&N scores were calculated based on scoring criteria proposed by the developer.[23] Results of the FACT-H&N are reported as follows: the scores for the 5 individual subscales; a FACT-General total score (sum of all subscales excluding the H&N subscale); a Trial Outcome Index-H&N (the sum of the scores of the physical well-being, functional well-being, and H&N cancer subscales); and Total FACT-H&N score (the sum of the scores of all 5 subscales). Prospectively defined minimally important differences were used to calculate time to worsening and to interpret change from baseline results.[26]

Statistical Analyses

The study was designed to enroll approximately 790 patients, with 1:1 randomization between the 2 arms. The median OS with single-agent cisplatin was estimated to be 8 months[6]; the study was powered to detect a 25% improvement in OS by showing a median OS of 10 months with pemetrexed-cisplatin. Assuming the true survival hazard ratio (HR) of pemetrexed-cisplatin to cisplatin alone was 0.80, the study had 80% power to achieve significance at a 2-sided level of .05. An interim analysis based on PFS was planned after approximately 300 patients had died or experienced disease progression to assess safety and futility. An independent statistical analysis group performed the analysis for the Data Monitoring Committee. As reported herein, the final analysis comparing OS between the arms was to be performed after 632 deaths had occurred (20% censoring rate). To compare the time-to-event endpoints (including the primary endpoint, OS), a stratified log-rank test at a 2-sided $\alpha = .05$ was used, with the following prognostic factors as stratification variables: PS (0 or 1 vs 2), previously treated for SCCHN (no vs yes), distant metastasis (no vs yes), and prior platinum-based therapy (no vs yes). The survival distributions were estimated using the Kaplan-Meier method.[27] The Kaplan-Meier estimations included Kaplan-Meier curve, quartiles, and interval estimation using 95% confidence intervals (CIs). Supportive analyses were done to obtain treatment effect after adjusting for the prognostic variables using the Cox regression model.[28]

Prespecified subgroup analyses for OS and PFS were conducted on important subgroups of patients: ECOG PS (0 or 1 vs 2), previously treated SCCHN (no vs yes), prior platinum-based therapy (no vs yes), distant metastasis (no vs yes), age ($<$50 vs $\geq$50 years), sex (male vs female), race (Caucasian vs non-Caucasian), primary site of disease (oral cavity, oropharynx, hypopharynx, larynx, and other), and prior surgery or radiotherapy within 6 months of randomization (no vs yes). An unstratified log-rank test was used to assess the treatment difference within subgroups, and the Cox regression model was used to test the treatment-by-subgroup interaction. Tumor responses were compared between treatments using unadjusted normal approximation for differences in rates. The changes from baseline in the FACT-H&N subscale scores were analyzed using mixed-model repeated-measures analysis with treatment, baseline score, visit, and treatment-by-visit interaction as fixed effects, and with patient nested in treatment as a random effect in the model; missing data were assumed to be missing at random. The incidences of toxicities, hospitalizations, and concomitant medication use were analyzed using the Fisher exact test.



Reasons for Discontinuation	Pem-Cis Arm, n (%)	Placebo-Cis Arm, n(%)
Lack of efficacy, progressive disease	180 (45)	217 (55)
Completed 6 cycles	70 (18)	55 (14)
Physician decision	10 (3)	16 (4)
Patient decision	28 (7)	21 (5)
Adverse event	37 (9)	32 (8)
Death from study disease	26 (7)	29 (7)
Death possibly due to study drug	11 (3)	1 (0.3)
Death due to procedure-related adverse event	0 (0)	1 (0.3)
Death due to adverse events (other causes)	27 (7)	15 (4)
Other (protocol violation, entry criteria not met, lost to follow-up)	9 (2)	10 (3)

Figure 1. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram shows patient disposition. Percentages do not add up to 100 because of rounding. Cis, cisplatin; ITT, intention to treat; Pem, pemetrexed.

RESULTS

Patients

Between December 2006 and March 2010, 114 investigators at 110 study sites in 20 countries (in Asia, Europe, and North America) screened 952 patients. Among these, 795 were randomized (pemetrexed-cisplatin, n = 398; placebo-cisplatin, n = 397; Fig. 1). The baseline patient and disease characteristics were well balanced between the treatment arms, and generally reflected the overall population of patients with SCCHN (Table 1). The distribution of disease sites reflects the global nature of the trial. Within the PS subgroups (0 or 1 and 2), the treatment arms were also balanced. The planned interim analysis was performed in November 2008 after 301 events and resulted in the decision to continue the study as planned. Post-trial analysis showed the number of patients with prior surgery or radiotherapy within 6 months of randomization was balanced between treatment arms (pemetrexed-cisplatin, 20.2%; placebo-cisplatin, 19.8%).

Treatment

Seven hundred seventy-seven patients (97.7%) received study treatment consisting of at least 1 dose of pemetrexed or cisplatin (pemetrexed-cisplatin: n = 392; placebo-cisplatin: n = 385). A median of 4 cycles was administered on the pemetrexed-cisplatin arm and 3 cycles on the placebo-cisplatin arm. More pemetrexed-cisplatin patients completed ≥6 cycles than did placebo-cisplatin patients (126 vs 103, respectively), whereas more patients discontinued from the placebo-cisplatin arm because of lack of efficacy or progressive disease (217 vs 180, respectively; Fig. 1). The dose intensity was similar for both arms; for pemetrexed-cisplatin, it was 94% for pemetrexed and 91% for cisplatin; for placebo-cisplatin, it was 96.0% each. Within the PS 0 or 1 subgroup, similar treatment trends were observed.

Dose adjustments (delays or reductions) were less frequent in patients treated with placebo-cisplatin compared with pemetrexed-cisplatin patients. On the pemetrexed-cisplatin arm, there were 33 pemetrexed and 74

Table 1. Baseline Demographic and Disease Characteristics for ITT Population and PS Subgroups

Characteristic	ITT Population		PS 0 or 1 Subgroup		PS 2 Subgroup	
	Pem-Cis, n=398	Placebo-Cis, n=397[a]	Pem-Cis, n=347	Placebo-Cis, n=343	Pem-Cis, n=51	Placebo-Cis, n=53
Median age, y	57.7	57.9	57.5	57.4	60.4	61.6
Range, y	32-79	21-84	32-79	21-82	33-75	39-84
Sex, No. (%)						
Male	342 (85.9)	344 (86.6)	301 (86.7)	298 (86.9)	41 (80.4)	45 (84.9)
Female	56 (14.1)	53 (13.4)	46 (13.3)	45 (13.1)	10 (19.6)	8 (15.1)
Ethnicity, No. (%)						
Caucasian	243 (61.1)	233 (58.7)	206 (59.4)	195 (56.9)	37 (72.5)	37 (69.8)
Western Asian (Indian subcontinent)	72 (18.1)	70 (17.6)	69 (19.9)	67 (19.5)	3 (5.9)	3 (5.7)
Eastern Asian	55 (13.8)	65 (16.4)	45 (13.0)	55 (16.0)	10 (19.6)	10 (18.9)
African	17 (4.3)	12 (3.0)	16 (4.6)	11 (3.2)	1 (2.0)	1 (1.9)
Hispanic	11 (2.8)	16 (4.0)	11 (3.2)	14 (4.1)	0	2 (3.8)
ECOG PS, No. (%)						
0 or 1	347 (87.2)	343 (86.4)	347 (100)	343 (100)	0	0
2	51 (12.8)	53 (13.4)	0	0	51 (100)	53 (100)
Previously treated for SCCHN, No. (%)						
Received ≥1 previous therapy	363 (91.2)	358 (90.2)	317 (91.4)	310 (90.4)	46 (90.2)	47 (88.7)
Chemotherapy	206 (51.8)	181 (45.6)	179 (51.6)	157 (45.8)	27 (52.9)	23 (43.4)
Radiotherapy	342 (85.9)	322 (81.1)	298 (85.9)	278 (81.0)	44 (86.3)	43 (81.1)
Chemoradiotherapy	162 (40.7)	139 (35.0)	140 (40.3)	122 (35.6)	22 (43.1)	17 (32.1)
Surgery	236 (59.3)	252 (63.5)	200 (57.6)	216 (63.0)	36 (70.6)	36 (67.9)
Prior surgery or radiotherapy, No. (%)						
≤6 months before randomization	81 (20.4)	89 (22.4)	70 (20.2)	68 (19.8)	11 (21.6)	21 (39.6)
>6 months before randomization	281 (70.6)	265 (66.8)	246 (70.9)	239 (69.7)	35 (68.6)	26 (49.1)
Never had radiotherapy or surgery	36 (9.0)	43 (10.8)	31 (8.9)	36 (10.5)	5 (9.8)	6 (11.3)
Prior platinum-based therapy, No. (%)						
Yes	185 (46.5)	169 (42.6)	159 (45.8)	145 (42.3)	26 (51.0)	23 (43.4)
No	213 (53.5)	228 (57.4)	188 (54.2)	198 (57.7)	25 (49.0)	30 (56.6)
Distant metastasis, No. (%)						
Yes	233 (58.5)	242 (61.0)	199 (57.3)	207 (60.3)	34 (66.7)	35 (66.0)
No	165 (41.5)	155 (39.0)	148 (42.7)	136 (39.7)	17 (33.3)	18 (34.0)
Primary site of disease, No. (%)						
Oral cavity	138 (34.7)	123 (31.0)	119 (34.3)	111 (32.4)	19 (37.3)	12 (22.6)
Oropharynx	86 (21.6)	106 (26.7)	79 (22.8)	90 (26.2)	7 (13.7)	16 (30.2)
Hypopharynx	63 (15.8)	59 (14.9)	56 (16.1)	48 (14.0)	7 (13.7)	10 (18.9)
Larynx	103 (25.9)	102 (25.7)	85 (24.5)	89 (25.9)	18 (35.3)	13 (24.5)
Other	8 (2.0)	7 (1.8)	8 (2.3)	5 (1.5)	0	2 (3.8)

Abbreviations: Cis, cisplatin; ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; Pem, pemetrexed; PS, performance status; SCCHN, squamous cell carcinoma of the head and neck.
[a] PS was not available for 1 patient.

cisplatin dose reductions; on the placebo-cisplatin arm, there were 7 placebo and 55 cisplatin dose reductions. The most common reasons for pemetrexed dose reductions were febrile neutropenia and neutropenia; for cisplatin (on both treatment arms), it was decreased creatinine clearance.

Efficacy and HRQL

OS for ITT patients on the pemetrexed-cisplatin arm was not superior to that for patients on the placebo-cisplatin arm (Fig. 2A), with both arms having ~20% censoring and similar use of postdiscontinuation systemic therapy (Table 2). The median OS times were 7.3 and 6.3 months for the pemetrexed-cisplatin and placebo-cisplatin arms, respectively (HR, 0.87; 95% CI, 0.75-1.02; $P = .082$). The 1- and 2-year survival probability rates were as follows: pemetrexed-cisplatin arm, 30.0% and 9.0%; placebo-cisplatin arm, 25.0% and 10.0%. The treatment effect on OS after adjusting for baseline prognostic factors was similar to that observed in the unadjusted analysis (HR, 0.89; 95% CI, 0.76-1.03; $P = .125$).

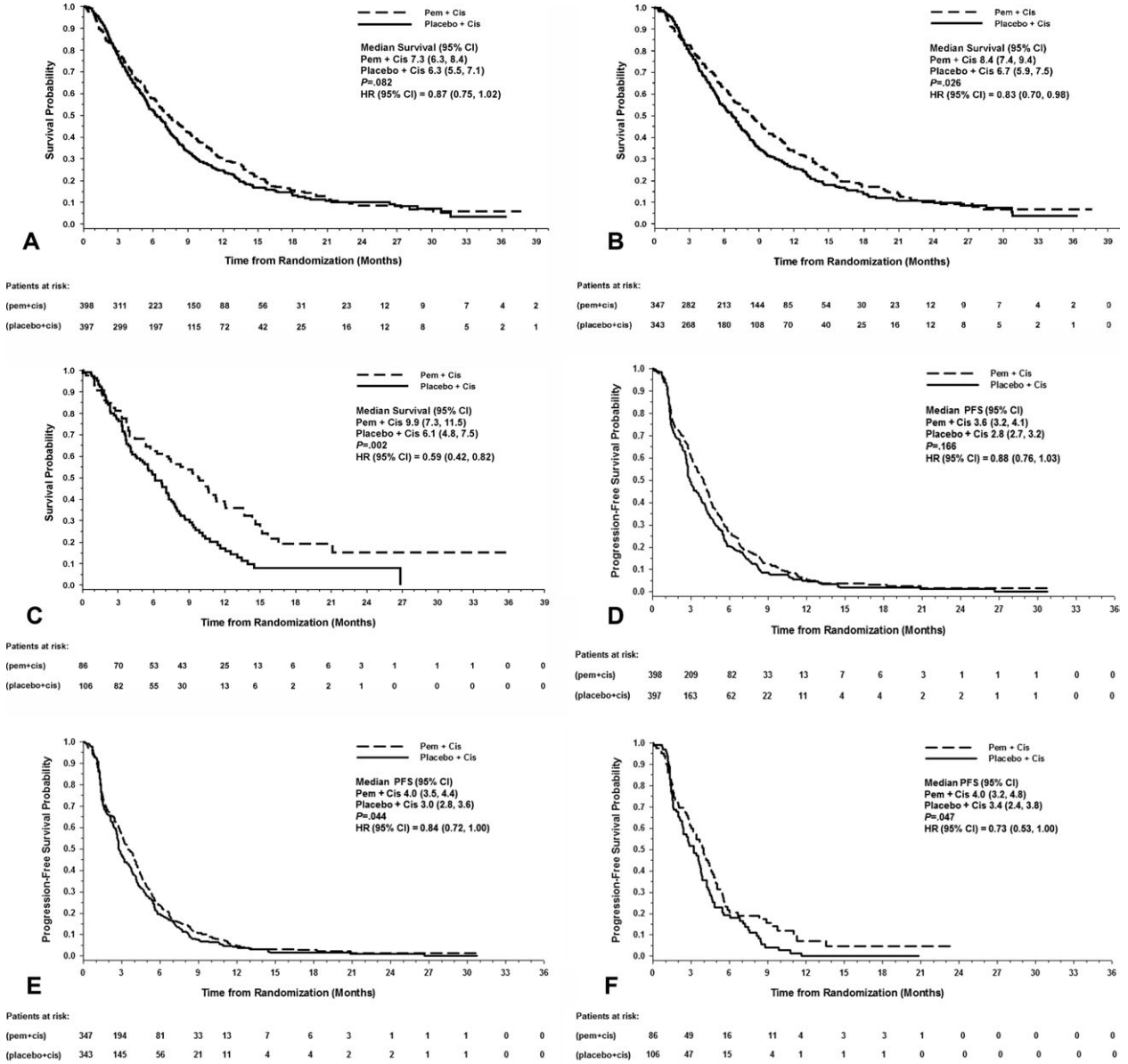


Figure 2. Kaplan-Meier plots show overall survival (OS) and progression-free survival (PFS) for total (intention to treat [ITT]) population, and performance status (PS) 0 or 1 and oropharynx subgroups. (A) Kaplan-Meier plot shows OS for ITT population. (B) Kaplan-Meier plot shows OS for PS 0 or 1 subgroup. (C) Kaplan-Meier plot shows OS for oropharynx subgroup. (D) Kaplan-Meier plot shows PFS for ITT population. (E) Kaplan-Meier plot shows PFS for PS 0 or 1 subgroup. (F) Kaplan-Meier plot shows PFS for oropharynx subgroup. CI, confidence interval; Cis, cisplatin; HR, hazard ratio; Pem, pemetrexed.

Prospectively planned subgroup analyses showed that among patients with PS 0 or 1 (n = 690; 86.8% of the ITT population), those treated with pemetrexed-cisplatin (n = 347) had a median OS of 8.4 months compared with 6.7 months in patients who received placebo-cisplatin (n = 343; HR, 0.83; 95% CI, 0.70-0.98; P = .026; interaction P = .034; Fig. 2B). In contrast, the PS 2 subgroup (n = 104; 13.1% of the ITT population) had a median OS of 3.5 months for the pemetrexed-cisplatin arm and 3.3 months for the placebo-cisplatin arm (P = .243). In addition to the PS 0 or 1 subgroup, there was a median OS advantage in the subgroup of patients with oropharynx cancer (n = 192; 24.2% of the ITT population) of 9.9 months versus 6.1 months (HR, 0.59; 95% CI, 0.42-0.82; P = .002; interaction P = .012), pemetrexed-cisplatin versus placebo-cisplatin, respectively (Fig. 2C). Use of systemic postdiscontinuation therapy was balanced between treatment arms for patients with PS 0 or 1 and oropharynx cancer (Table 2).

Table 2. Postdiscontinuation Therapy for ITT Population and Select Subgroups

Type of Therapy[a]	ITT Population		PS 0 or 1 Subgroup		Oropharynx Subgroup	
	Pem-Cis, n=398, No. (%)	Placebo-Cis, n=397, No. (%)	Pem-Cis, n=347, No. (%)	Placebo-Cis, n=343, No. (%)	Pem-Cis, n=86, No. (%)	Placebo-Cis, n=106, No. (%)
Patients receiving ≥1 poststudy therapy	130 (32.7)	152 (38.3)	122 (35.2)	138 (40.2)	36 (41.9)	41 (38.7)
Patients with no poststudy therapy	268 (67.3)	245 (61.7)	225 (64.8)	205 (59.8)	50 (58.1)	65 (61.3)
Carboplatin	20 (5.0)	19 (4.8)	19 (5.5)	17 (5.0)	8 (9.3)	6 (5.7)
Cetuximab	33 (8.3)	31 (7.8)	30 (8.6)	29 (8.5)	12 (14.0)	9 (8.5)
Cisplatin	36 (9.0)	47 (11.8)	34 (9.8)	43 (12.5)	7 (8.1)	10 (9.4)
Docetaxel	35 (8.8)	33 (8.3)	32 (9.2)	28 (8.2)	8 (9.3)	10 (9.4)
Fluorouracil	28 (7.0)	30 (7.6)	27 (7.8)	28 (8.2)	7 (8.1)	6 (5.7)
Methotrexate	19 (4.8)	31 (7.8)	19 (5.5)	26 (7.6)	5 (5.8)	11 (10.4)
Paclitaxel	22 (5.5)	32 (8.1)	19 (5.5)	31 (9.0)	4 (4.7)	9 (8.5)
Pemetrexed	0	1 (0.3)	0	1 (0.3)	0	0

Abbreviations: Cis, cisplatin; ITT, intention to treat; Pem, pemetrexed; PS, performance status.
No. indicates number of patients with response.
[a] Systemic therapies used in >5% of a treatment arm are listed, along with pemetrexed.

A similar analysis was undertaken among the ITT population for the secondary endpoint PFS. The median PFS was 3.6 months for the pemetrexed-cisplatin arm and 2.8 months for the placebo-cisplatin arm (HR, 0.88; 95% CI, 0.76-1.03; $P = .166$; Fig. 2D), with ~15% censoring on both arms. After adjusting for baseline prognostic factors, the treatment effect on PFS was similar to that observed in the unadjusted analysis (HR, 0.92; 95% CI, 0.79-1.07; $P = .290$). Prospectively planned subgroup analyses identified PFS advantage for the pemetrexed-cisplatin arm compared with the placebo-cisplatin arm in both the ECOG PS 0 or 1 subgroup (Fig. 2E; HR, 0.84; 95% CI, 0.72-1.00; $P = .044$; interaction $P = .017$) and the oropharynx subgroup (Fig. 2F; HR, 0.73; 95% CI, 0.53-1.00; $P = .047$; interaction $P = .205$).

Figure 3 presents the OS and PFS results within the PS 0 or 1 subgroup. OS and PFS both favored pemetrexed-cisplatin over placebo-cisplatin across most of the subgroups (HRs <1).

Tumor response rate (complete plus partial response) was not significantly different between arms in the total population, but was significantly higher for the pemetrexed-cisplatin arm within the PS 0 or 1 subgroup (Table 3).

Patient compliance with the FACT-H&N instrument was similar between treatment groups (range, 60%-89% over 6 cycles). No significant differences in time to worsening were noted for any FACT-H&N subscale or total score (Table 4). Likewise, no significant differences were noted in any change-from-baseline analyses or FACT-H&N parameters analyzed by PS subgroups (data not shown).

Safety

Compared with placebo-cisplatin, patients receiving pemetrexed-cisplatin exhibited significantly greater incidence of drug-related grade 3 or 4 laboratory toxicities (neutropenia, anemia, and leukopenia), drug-related grade 3 or 4 nonlaboratory toxicities (febrile neutropenia and fatigue; Table 5), and need for supportive care (Table 6). Analysis of safety data for various subgroups including PS (Tables 5 and 6), age, and sex (data not shown) found subgroups to be consistent with the safety profile observed in the entire population, with the exception of patients in the PS 2 subgroup. Patients with PS 2 experienced more possibly drug-related serious adverse events, more deaths because of study drug toxicity, and more deaths because of study disease compared with PS 0 or 1 patients.

Ninety-two patients (23.5%) on the pemetrexed-cisplatin arm and 96 patients (24.9%) on the placebo-cisplatin arm died during therapy or within 30 days of treatment discontinuation. The most common cause of death was disease progression (pemetrexed-cisplatin, 46 [11.7%]; placebo-cisplatin, 75 [19.5%]). Adverse events accounted for 33 (8.4%) deaths on the pemetrexed-cisplatin arm and 19 (4.9%) deaths on the placebo-cisplatin arm. On study or within 30 days of discontinuation, 1 patient (0.3%) on the placebo-cisplatin arm died because of possible study drug-related toxicity (cardiorespiratory arrest), compared with 13 (3.3%) deaths on the pemetrexed-cisplatin arm (2 deaths each from agranulocytosis, renal failure, sepsis/septic shock; 1 death each from febrile neutropenia, bone marrow toxicity, gastrointestinal necrosis, diarrhea, respiratory tract hemorrhage, cardiac failure, and multiorgan failure). Further review of patient

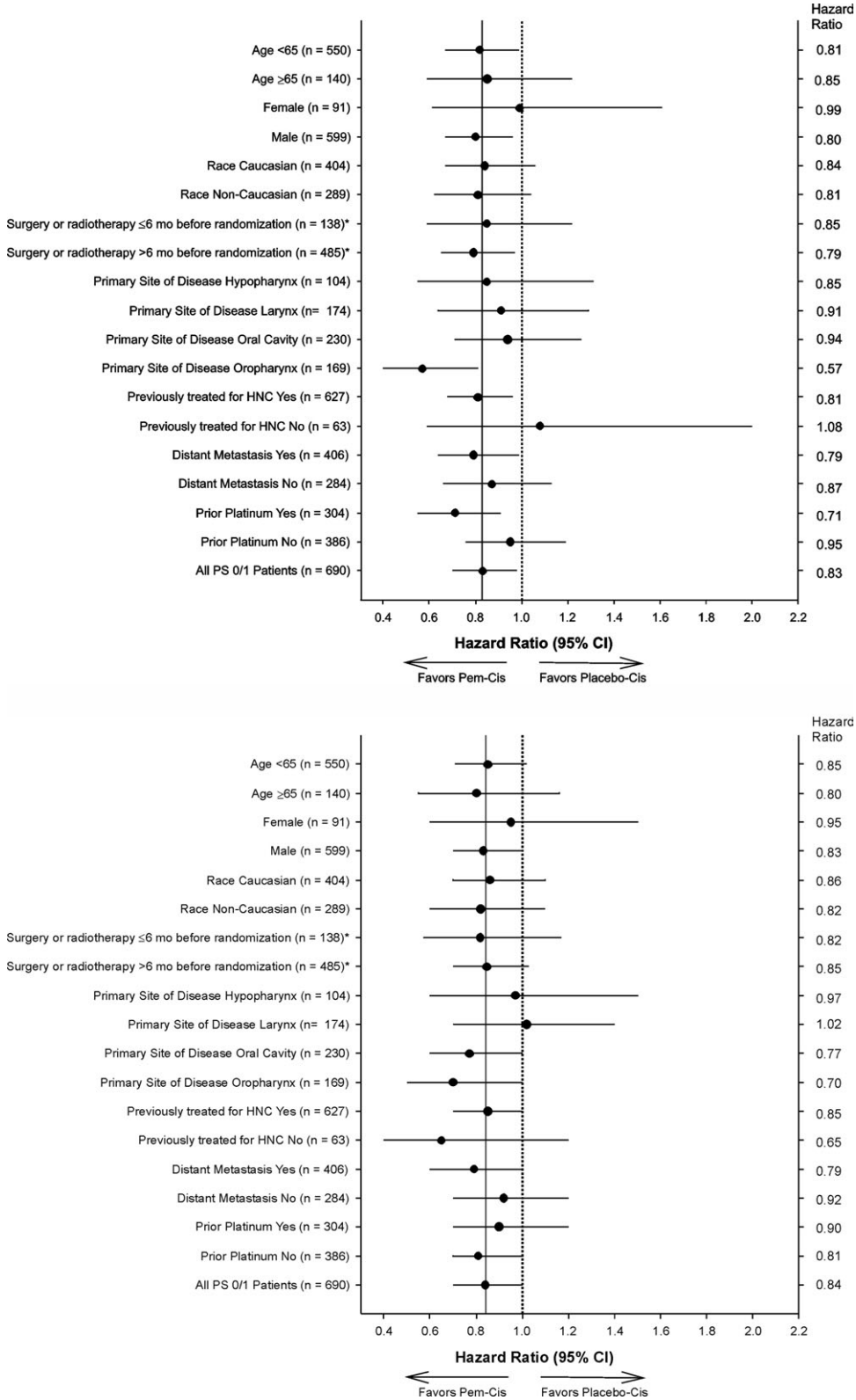


Figure 3. Forest plots show data for patients with performance status (PS) 0 or 1. (*Top*) overall survival; (*Bottom*) progression-free survival. The solid vertical line on both figures represents the hazard ratio associated with overall survival (*Top*) and progression-free survival (*Bottom*) for all PS 0 or 1 patients. *Some patients had not been treated with radiotherapy or surgery. CI, confidence interval; Cis, cisplatin; HNC, head and neck cancer; Pem, pemetrexed.

Table 3. Best Overall Tumor Response for ITT Population and PS Subgroups

Type of Response	ITT Population		PS 0 or 1 Subgroup		PS 2 Subgroup	
	Pem-Cis, n=398, No. (%)	Placebo-Cis, n=397[a], No. (%)	Pem-Cis, n=347, No. (%)	Placebo-Cis, n=343, No. (%)	Pem-Cis, n=51, No. (%)	Placebo-Cis, n=53, No. (%)
CR	2 (0.5)	4 (1.0)	2 (0.6)	3 (0.9)	0	1 (1.9)
PR	46 (11.6)	28 (7.1)	45 (13.0)	26 (7.6)	1 (2.0)	2 (3.8)
CR+PR	48 (12.1)	32 (8.1)	47 (13.5)	29 (8.5)	1 (2.0)	3 (5.7)
	P=.061[b]		P=.033[b]		P=.327[b]	
SD	153 (38.4)	135 (34.0)	143 (41.2)	119 (34.7)	10 (19.6)	16 (30.2)
PD	95 (23.9)	128 (32.2)	76 (21.9)	111 (32.4)	19 (37.3)	17 (32.1)
Unknown/not done[c]	102 (25.6)	102 (25.7)	81 (23.3)	84 (24.5)	21 (41.2)	17 (32.1)

Abbreviations: Cis, cisplatin; CR, complete response; ITT, intention to treat; PD, progressive disease; Pem, pemetrexed; PR, partial response; PS, performance status; SD, stable disease.
No. indicates number of patients with response.
[a] PS was not available for 1 patient.
[b] P value is based on an unadjusted, normal distribution approximation for differences in rates.
[c] Most patients (~95%) without a recorded best overall tumor response were either lost to follow-up or did not have a tumor assessment performed that met Response Evaluation Criteria in Solid Tumors after the one performed at baseline, or tumor assessment was not done due to early death in the study (assessment incomplete or too soon after baseline visit).

Table 4. HRQL

HRQL Measure	Summary of TTW[a]			Change From Baseline in HRQL Dimensions[b]		
	Pem-Cis, Median Score (No. of Events)	Placebo-Cis, Median Score (No. of Events)	HR [P]	Pem-Cis, LS Mean {SE}	Placebo-Cis, LS Mean {SE}	P
FACT-H&N subscales						
Physical well-being	1.77 (256)	2.14 (228)	0.86 [.152]	−2.57 {0.26}	−2.93 {0.27}	.347
Social/family well-being	3.25 (221)	2.76 (201)	0.84 [.122]	−0.67 {0.22}	−0.82 {0.24}	.633
Emotional well-being	3.88 (216)	3.19 (192)	0.86 [.161]	0.03 {0.20}	−0.10 {0.21}	.652
Functional well-being	2.07 (251)	2.33 (202)	1.11 [.311]	−1.61 {0.25}	−1.31 {0.26}	.405
Additional concerns-H&N	3.25 (174)	2.89 (156)	0.84 [.107]	−0.31 {0.32}	−1.15 {0.34}	.072
Trial Outcome Index-H&N	2.76 (196)	2.40 (168)	0.93 [.494]	−4.10 {0.71}	−5.55 {0.75}	.163
FACT-General	2.40 (238)	2.17 (216)	0.88 [.249]	−4.67 {0.64}	−5.22 {0.68}	.560
Total FACT-H&N	3.3 (177)	2.9 (154)	0.86 [.200]	−4.44 {0.99}	−6.25 {1.05}	.210

Abbreviations: Cis, cisplatin; FACT, Functional Assessment of Cancer Therapy; H&N, Head and Neck; HR, hazard ratio; HRQL, health-related quality of life; ITT, intention to treat; LS, least-squares; Pem, pemetrexed; SE, standard error; TTW, time to worsening.
[a] ITT population with at least baseline data.
[b] Qualified ITT population.

files revealed 3 of these deaths were unlikely to be related to study drug toxicity. In addition, 4 of the deaths were in patients with poor PS (PS 2) at study entry, and 2 deaths were in patients who did not receive proper dose reductions and died from agranulocytosis.

DISCUSSION

To our knowledge, this is the largest phase 3, randomized, double-blind study to date in patients with inoperable recurrent or metastatic SCCHN. The primary objective was not achieved, as the ITT analysis of patients on the pemetrexed-cisplatin arm did not show a significant improvement in OS over patients on cisplatin monotherapy. However, in the subgroup of PS 0 or 1 patients, which comprised 87.2% of the 795 study participants, a preplanned analysis showed that pemetrexed-cisplatin treatment led to longer OS and PFS compared with cisplatin monotherapy, whereas no significant efficacy differences were noted for PS 2 patients.

Multivariate analyses from palliative chemotherapy clinical trials have shown that time to progression and OS are influenced by factors other than the specific chemotherapy administered. Poor PS, prior treatment, lack of or minimal response to treatment, and advanced stage or metastatic disease are among those factors associated with worse outcomes in patients with SCCHN treated with

Table 5. Randomized and Treated Patients With CTCAE Grade 3/4 Drug-Related Toxicities (Worst Grade): Total Safety Population and PS Subgroups

Toxicity	Total Safety Population			PS 0 or 1 Subgroup			PS 2 Subgroup		
	Pem-Cis, n=392, No. (%)	Placebo-Cis, n=385, No. (%)	*P*	Pem-Cis, n=343, No. (%)	Placebo-Cis, n=333, No. (%)	*P*	Pem-Cis, n=49, No. (%)	Placebo-Cis, n=52, No. (%)	*P*
Laboratory									
Neutropenia	45 (11.5)	10 (2.6)	<.001	41 (12.0)	10 (3.0)	<.001	4 (8.2)	0	.052
Anemia	40 (10.2)	13 (3.4)	<.001	35 (10.2)	12 (3.6)	.001	5 (10.2)	1 (1.9)	.105
Leukopenia	33 (8.4)	5 (1.3)	<.001	28 (8.2)	3 (0.9)	<.001	5 (10.2)	2 (3.8)	.260
Thrombocytopenia	15 (3.8)	6 (1.6)	.075	9 (2.6)	5 (1.5)	.420	6 (12.2)	1 (1.9)	.055
Nonlaboratory									
Fatigue	19 (4.8)	7 (1.8)	.027	17 (5.0)	4 (1.2)	.006	2 (4.1)	3 (5.8)	>.999
Febrile neutropenia	12 (3.1)	0	<.001	8 (2.3)	0	.008	4 (8.2)	0	.052
Nausea	10 (2.6)	10 (2.6)	>.999	9 (2.6)	6 (1.8)	.604	1 (2.0)	4 (7.7)	.363
Vomiting	8 (2.0)	10 (2.6)	.641	8 (2.3)	8 (2.4)	>.999	0	2 (3.8)	.495
Diarrhea	5 (1.3)	0	.062	5 (1.5)	0	.062	0	0	—
Anorexia	8 (2.0)	6 (1.6)	.789	7 (2.0)	5 (1.5)	.773	1 (2.0)	1 (1.9)	>.999
Renal failure	5 (1.3)	5 (1.3)	>.999	4 (1.2)	5 (1.5)	.749	1 (2.0)	0	.485

Abbreviations: Cis, cisplatin; CTCAE, Common Terminology Criteria for Adverse Events, version 3; Pem, pemetrexed; PS, performance status.

Table 6. Hospitalizations and Other Supportive Care: Total Safety Population and PS Subgroups

Type of Supportive Care	Total Safety Population			PS 0 or 1 Subgroup			PS 2 Subgroup		
	Pem-Cis, n=392, No. (%)	Placebo-Cis, n=385, No. (%)	*P*	Pem-Cis, n=343, No. (%)	Placebo-Cis, n=333, No. (%)	*P*	Pem-Cis, n=49, No. (%)	Placebo-Cis, n=52, No. (%)	*P*
Concomitant medications[a]									
G-CSF or GM-CSF	45 (11.5)	15 (3.9)	<.001	38 (11.1)	14 (4.2)	<.001	7 (14.3)	1 (1.9)	.028
Anti-infectives[b]	2 (0.5)	1 (0.3)	1.00	2 (0.6)	1 (0.3)	1.00	0	0	—
Analgesics	238 (60.7)	221 (57.4)	.381	201 (58.6)	185 (55.6)	.438	37 (75.5)	36 (69.2)	.512
Transfusions, patients with ≥1 transfusion	86 (21.9)	58 (15.1)	.016	70 (20.4)	52 (15.6)	.110	16 (32.7)	6 (11.5)	.015
Hospitalizations, patients with ≥1 hospitalization for drug-related adverse events, all grades	93 (23.7)	43 (11.2)	<.001	79 (23.0)	36 (10.8)	<.001	14 (28.6)	7 (13.5)	.086

Abbreviations: Cis, cisplatin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; Pem, pemetrexed; PS, performance status.

[a] Erythropoietin use was allowed, but it was not administered to any patient.

[b] Anti-infectives = antibiotic, antiviral, and antifungal agents.

systemic chemotherapy.[4] These findings suggest that patient selection can be at least as important as the type of therapy administered.

PS is a valid and reliable parameter that may be used as an inclusion criterion in clinical trials because it not only defines the physical medical condition of the patient, but is also a prognostic factor.[29,30] The same observation was made in patients with SCCHN in the Vermorken et al phase 3 study, in which PS had the greatest prognostic relevance for OS time.[31] In that study, a Karnofsky PS score ≥80 was associated with a reduced risk of death by 49% as compared with a Karnofsky score <80 (HR, 0.51; 95% CI, 0.37-0.69; $P < .001$). Thus, PS 2 patients would be anticipated to have a worse clinical outcome as a group, as was confirmed in this study.

The median OS observed in PS 0 or 1 patients treated with pemetrexed-cisplatin (8.4 months) versus that for patients treated with placebo-cisplatin (6.7 months) contrasts with the median OS of 3.5 months versus 3.3 months observed in PS 2 patients receiving the same treatments. A prespecified interaction test showed a significant treatment-by-PS (0 or 1 vs 2) interaction, suggesting that pemetrexed-cisplatin effect is significantly greater in the PS 0 or 1 population compared with that in PS 2 patients (OS, $P = .034$; PFS, $P = .017$). This is a clinically meaningful difference in this subgroup.

Beyond PS subgroups, other preplanned analyses looked for evidence of differential treatment benefits in other subgroups, including primary site of disease. Patients with oropharyngeal cancer who were treated with

pemetrexed-cisplatin showed improvement in both OS and PFS compared with patients treated with cisplatin monotherapy. We are not aware of preclinical evidence that would have predicted this result, nor are there data to suggest that oropharyngeal tumors express lower levels of thymidylate synthase, an enzyme in the folate pathway associated with sensitivity to pemetrexed. However, human papillomavirus (HPV) has recently been established as a risk factor for oropharyngeal cancer, with emerging data suggesting that HPV-positive tumors are more sensitive to chemotherapy and radiotherapy than HPV-negative tumors.[32] Whereas the greater responsiveness to pemetrexed-cisplatin of the oropharyngeal subgroup within this study may well be because of the HPV-positive status of the patients, data on the HPV status of patients were not collected because this study was initiated before the full current understanding of this association. Tumor tissue collection began midtrial to address this association and others, but no results were obtained because of difficulties in the RNA analysis. Future studies will undoubtedly continue to explore the association between HPV infection and increased sensitivity to chemotherapy of oropharyngeal tumors. For now, the responsiveness of this tumor type to pemetrexed-cisplatin should be considered only as hypothesis generating, given the relatively small number of patients in this subgroup.

The toxicity profile of pemetrexed-cisplatin in this study was consistent with what is already known for this combination in other tumor types. Pemetrexed-cisplatin was associated with a higher rate of drug toxicity than placebo-cisplatin, as expected with combination chemotherapy. There were more study drug-related deaths, as well as grade 3 or 4 neutropenia, anemia, leukopenia, febrile neutropenia, and fatigue, and thus a greater need for supportive care (granulocyte colony-stimulating factor, hospitalization, and transfusion). However, as detailed in Table 5, with the exception of neutropenia (11.5%) and anemia (10.2%), <10% of patients (total safety population) experienced these grade 3 or 4 toxicities. Whereas the FACT-H&N results did not identify any measurable difference in HRQL parameters, they also did not identify any negative HRQL results stemming from the addition of a second chemotherapeutic agent in the pemetrexed-cisplatin arm.

Because SCCHN treatment has evolved since this study was initiated in 2006, cisplatin monotherapy is not used frequently for treatment, and when administered as part of a chemotherapy regimen for SCCHN, is often used at a somewhat higher dose of 100 mg/m^2/3 wk, as in the Vermorken et al study that compared platinum/fluorouracil/cetuximab with platinum/fluorouracil.[31] Although it is difficult to compare these studies because of the difference in treatment arms, the OS of the chemotherapy arm of the Vermorken et al trial (7.4 months) is similar to that of the pemetrexed-cisplatin arm in our study (7.3 months). In addition, within the chemotherapy arm of both studies, the subset of patients with oropharynx cancer had a longer median OS than the median OS of the total population: Vermorken et al trial, 7.9 versus 7.4 months; our trial, 9.9 versus 7.3 months. Because the Vermorken et al study showed that the addition of cetuximab, an antibody targeting the epidermal growth factor receptor, improved OS to 10.1 months, a phase 2 study is underway to examine the PFS after treatment with the combination of cetuximab/pemetrexed/carboplatin or cetuximab/pemetrexed/cisplatin (ClinicalTrials.gov identifier: NCT01087970). Another study is investigating the impact of bevacizumab, an antibody to vascular endothelial cell growth factor, on pemetrexed-cetuximab chemoradiotherapy (ClinicalTrials.gov identifier: NCT00703976).

In conclusion, the results of this study in patients with inoperable recurrent or metastatic SCCHN demonstrate that pemetrexed-cisplatin combination was not more efficacious than cisplatin monotherapy for the whole ITT population. However, it was more efficacious than platinum monotherapy in patients with PS 0 or 1 and patients with oropharyngeal cancers. In light of the efficacy of pemetrexed-cisplatin in this trial and the known mild safety profile of pemetrexed monotherapy, a phase 2 study is investigating the benefits of pemetrexed for treating higher-risk patients who are less likely to tolerate triplet therapy (ClinicalTrials.gov identifier: NCT00293579).

FUNDING SOURCES

This study (H3E-MC-JMHR) was sponsored and funded by Eli Lilly and Company, Indianapolis, Indiana.

CONFLICT OF INTEREST DISCLOSURES

F.R., S.-C.C., A.M.H., B.F.-M., and A.K. are employees of Eli Lilly and Company.

REFERENCES

1. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet.* 2008;371:1695-1709.
2. Gold KA, Lee HY, Kim ES. Targeted therapies in squamous cell carcinoma of the head and neck. *Cancer.* 2009;115:922-935.
3. Haddad RI, Shin DM. Recent advances in head and neck cancer. *N Engl J Med.* 2008;359:1143-1154.

4. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2006;24:2644-2652.
5. Clavel M, Vermorken JB, Cognetti F, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. *Ann Oncol.* 1994;5:521-526.
6. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA; Eastern Cooperative Oncology Group. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol.* 2005;23:8646-8654.
7. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2005;23:3562-3567.
8. Taylor EC, Kuhnt D, Shih C, et al. A dideazatetrahydrofolate analogue lacking a chiral center at C-6, N-[4-[2-(2-amino-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid, is an inhibitor of thymidylate synthase. *J Med Chem.* 1992;35:4450-4454.
9. Schultz RM, Patel VF, Worzalla JF, Shih C. Role of thymidylate synthase in the antitumor activity of the multitargeted antifolate, LY231514. *Anticancer Res.* 1999;19:437-443.
10. Shih C, Habeck LL, Mendelsohn LG, Chen VJ, Schultz RM. Multiple folate enzyme inhibition: mechanism of a novel pyrrolopyrimidine-based antifolate LY231514 (MTA). *Adv Enzyme Regul.* 1998;38:135-152.
11. Pivot X, Raymond E, Laguerre B, et al. Pemetrexed disodium in recurrent locally advanced or metastatic squamous cell carcinoma of the head and neck. *Br J Cancer.* 2001;85:649-655.
12. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2003;21:2636-2644.
13. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26:3543-3551.
14. Morton RP, Rugman F, Dorman EB, et al. 1985. Cisplatinum and bleomycin for advanced or recurrent squamous cell carcinoma of the head and neck: a randomized factorial phase III controlled trial. *Cancer Chemother Pharmacol.* 1985;15:283-289.
15. Jacobs C, Lyman G, Velez-Garcia E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol.* 1992;10:257-263.
16. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol.* 1992;10:1245-1251.
17. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.
18. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205-216.
19. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.
20. Klastersky J, Sculier JP, Ravez P, et al. A randomized study comparing a high and a standard dose of cisplatin in combination with etoposide in the treatment of advanced non-small-cell lung carcinoma. *J Clin Oncol.* 1986;4:1780-1786.
21. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics.* 1975;31:103-115.
22. Ozer H, Armitage JO, Bennett CL, et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *J Clin Oncol.* 2000;18:3558-3585.
23. Cella D (ed). Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System (Version 4.1). Evanston, IL: Center for Outcomes Research and Education, Evanston Northwestern Healthcare and Northwestern University; 2004.
24. List MA, D'Antonio LL, Cella DF, et al. The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. *Cancer.* 1996;77:2294-2301.
25. National Cancer Institute. Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 3.0. 2006. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf Accessed August 3, 2010.
26. Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Prof.* 2005;28:172-191.
27. Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
28. Cox DR. Regression models and life-tables (with discussion). *J R Stat Soc B.* 1972;34:187-220.
29. Conill C, Verger E, Salamero M. Performance status assessment in cancer patients. *Cancer.* 1990;65:1864-1866.
30. Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer.* 1993;67:773-775.
31. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008;359:1116-1127.
32. Gillison M, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst.* 2000;92:709-720.