Original Article

Double-Blind, Randomized Phase 3 Trial of Low-Dose 13-Cis Retinoic Acid in the Prevention of Second Primaries in Head and Neck Cancer: Long-Term Follow-Up of a Trial of the Eastern Cooperative Oncology Group-ACRIN Cancer Research Group (C0590)

Aarti K. Bhatia, MD, MPH[1]; Ju-Whei Lee, PhD[2]; Harlan A. Pinto, MD[3]; Charlotte D. Jacobs, MD[3]; Paul J. Limburg, MD, MPH[4]; Philip Rubin, MD[5†]; Robert M. Arusell, MD[6]; Eamonn P. Dunphy, MD[7]; Janardan D. Khandekar, MD[8]; Seth A. Reiner, MD[9]; Luis Baez-Diaz, MD[10]; Paul Celano, MD[11]; Shuli Li, PhD[2]; Yi Li, PhD[12]; Barbara A. Burtness, MD[1]; George L. Adams, MD[13†]; and Kishan J. Pandya, MD[14]

BACKGROUND: 13-Cis retinoic acid (13-CRA) is a synthetic vitamin A derivative. High-dose 13-CRA in patients with squamous cell cancers of the head and neck (SCCHNs) reduces the incidence of second primary tumors (SPTs). The authors report long-term results from a phase 3 randomized trial that compared treatment with low-dose 13-CRA versus placebo for patients who had early stage SCCHN, with a focus on the development of SPTs and overall survival (OS). **METHODS:** In total, 176 patients who received treatment for stage I/II SCCHN were randomized to receive either low-dose 13-CRA (weight-based dose of 7.5 mg or 10 mg) or placebo for 2 years. A competing-risk approach and the log-rank test were used to compare the time to SPT and OS, respectively, between groups. **RESULTS:** 13-CRA neither significantly reduced the cumulative incidence of SPT ($P = .61$) nor improved the time to SPT (hazard ratio [HR] for 13-CRA/placebo; 0.86; $P = .61$). Despite limited power, there was a trend toward improved OS for the 13-CRA arm (HR, 0.75; $P = .14$), particularly among patients whose index tumor was surgically excised (N = 26; HR, 0.50; $P = .057$) and among women (N = 39; HR, 0.44; $P = .065$) and never/former smokers (N = 129; HR, 0.61; $P = .055$), with a median follow-up of 16 years. The main 13-CRA related toxicities were dry skin and cheilitis. **CONCLUSIONS:** Treatment with low-dose 13-CRA for 2 years did not decrease the incidence of SPT; subset analysis indicates a potential survival advantage among patients who are women and never/former smokers. More targeted interventions based on clinical risk factors and molecular characterization of tumors may yield greater success in future prevention trials. ***Cancer* 2017;123:4653-62**. *© 2017 American Cancer Society.*

KEYWORDS: chemoprevention, head and neck cancer, oral cancer, randomized controlled trial, second primary cancer.

INTRODUCTION

Over 60,000 cases of head and neck cancers are diagnosed annually in the United States, and approximately 13,000 patients die of their disease.[1] Squamous cell cancers (SSCs) of the head and neck (SCCHNs) remain among the top 10 causes of new cancer cases in men.[1] Although recent decades have witnessed significant improvements in overall survival (OS) for patients diagnosed with early stage (stage I-II) SCCHN, the risk of developing second primary tumors (SPTs) remains significantly increased compared with an age-matched general population[2,3] and is a major cause of increased morbidity and mortality among survivors of early stage SCCHN.[4-6]

Corresponding author: Aarti K. Bhatia, MD, MPH, Yale School of Medicine, Yale Comprehensive Cancer Center, 333 Cedar Street, FMP 128, New Haven, CT 06520; aarti.bhatia@yale.edu

[1]Department of Medical Oncology, Yale University School of Medicine and Yale Cancer Center, New Haven, Connecticut; [2]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Eastern Cooperative Oncology Group-ACRIN Biostatistics Center, Boston, Massachusetts; [3]Division of Oncology, Department of Medicine, Stanford University and Veterans Affairs Palo Alto Health Care System, Stanford, California; [4]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [5]Department of Radiation Oncology, University of Rochester Medical Center, Rochester, New York; [6]Sanford North Fargo Clinic, Fargo, North Dakota; [7]Santa Clara Valley Medical Center, San Jose, California; [8]North Shore University Health System, Evanston, Illinois; [9]Porter Cancer Center, Denver, Colorado; [10]San Juan City Hospital, San Juan, Puerto Rico; [11]Sandra and Malcolm Berman Cancer Institute, Baltimore, Maryland; [12]University of Michigan, Ann Arbor, Michigan; [13]University of Minnesota, Minneapolis, Minnesota; [14]Department of Medicine Hematology/Oncology, University of Rochester Medical Center, Rochester, New York.

Yi Li's current address: University of Michigan, Ann Arbor, Michigan.

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[†]Deceased.

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Vitamin A and its synthetic analogs (retinoids) are potent agents for the control of cell differentiation and prevention of carcinogenesis in normal and preneoplastic epithelial cells.[7] Sporn et al demonstrated the efficacy of retinoids in reversing premalignant lesions in mouse models.[7] Hong et al reported that a 1 or 2 mg/kg daily dose of 13-cisretinoic acid (13-CRA [isotretinoin]) given to patients with oral leukoplakia significantly decreased the size of their lesions and completely reversed dysplasia in 54% of patients.[8] Relapse occurred in greater than one-half of responders from 2 to 3 months after drug cessation.[8] The authors then randomized 103 patients who had received curative treatment for stage I through IV SCCHN to daily, high-dose 13-CRA (50-100 mg/m^2 body surface area) versus placebo for 12 months.[9] Although there were no significant differences in local or distant recurrence, the intervention arm had significantly fewer SPTs (4% vs 24%; $P = .005$). However, isotretinoin did not prolong OS,[10] but majority of patients in both arms remained alive. Toxicities of skin dryness, cheilitis, hypertriglyceridemia, and conjunctivitis proved dose-limiting.[9]

A subsequent European trial used etretinate, a second-generation retinoid, in the postsurgery/radiation setting for patients with stage I through III SCCs of the oral cavity and oropharynx.[11] At a median follow-up of 41 months, there was no significant difference in SPTs between groups, whereas patients in the treatment arm experienced significantly greater toxicity (33% vs 23%; $P < .05$).

The largest intervention trial in patients who received curative treatment for stage I and II SCCHN accrued at the same time as our trial.[12] Given the high toxicity rate with the 50 to 100 mg/m^2 body surface area dose, a lower daily dose of isotretinoin (30 mg) or placebo was received for a longer duration (3 years). Patients were monitored for 4 years beyond treatment completion, and there were no significant differences in SPTs or OS between arms. Considerable toxicity was reported even at this lower dose, with nearly 30% of patients requiring dose reduction or treatment discontinuation.

The Eastern Cooperative Oncology Group (ECOG)-ACRIN Research Group trial C0590 tested the lowest dose of isotretinoin ever used in this setting. Here, we report the longest follow-up to date of the effects of a retinoid in preventing SPTs in patients with SCCHN.

C0590 was designed with 2 objectives: 1) to confirm that treatment with 13-CRA was more effective than placebo in preventing SPTs in SCCHN survivors; and 2) to determine whether lower, weight-based daily dosing (7.5 mg for patients who weighed <60 kg and 10 mg for those who weighed >60 kg) over 2 years would have similar efficacy while improving tolerability and compliance. We also evaluated the association between smoking history and SPT development.

MATERIALS AND METHODS

This was a multicenter, randomized, placebo-controlled, double-blind phase 3 intergroup trial coordinated by the ECOG-ACRIN Cancer Research Group. Affiliated Radiation Therapy Oncology Group and North Central Cancer Treatment Group institutions also accrued to the study. However, the Radiation Therapy Oncology Group discontinued recruitment from July 1991. This study was approved by institutional review boards of all participating institutions and cooperative groups.

Patient Eligibility

Eligibility criteria included: histologically proven, stage I/II SCC of the oral cavity, oropharynx, hypopharynx, or larynx; an ECOG performance status of 0 or 1; chest and bone x-rays within 35 days after definitive treatment, before randomization; hematology and chemistries within 2 weeks before randomization; adequate bone marrow, renal, and hepatic function (hemoglobin $\geq$ 10 g/dL, white blood count >3000/mm^3, platelet count > 100,000/mm^3; transaminases $\leq$ 1.5 times the upper limit of normal; serum creatinine $\leq$ 1.5 times the upper limit of normal; and electrolytes within normal limits); no treatment for hyperlipidemia; no symptomatic coronary arteriosclerotic disease or prior history of coronary bypass surgery; completion of primary therapy with surgery and/or radiation within 730 days before randomization; and no evidence of disease. In addition, patients had to be capable of providing written informed consent in compliance with institutional and federal guidelines and had to be available for long-term follow-up.

Exclusion criteria included: prior chemotherapy; other concurrent malignancies, except for localized and resected nonmelanoma skin cancer; pregnancy; and lactation. Women of childbearing potential had to agree to use contraception and to have a negative pregnancy test before study initiation.

Study Design and Target Accrual

Sample-size calculation was based on an exponential cure-rate model, as proposed by Berkson and Gage,[13] with predicted rates of freedom from SPT of 80% and 90% for the placebo and 13-CRA arms, respectively. The design specified a log-rank test at the 1-sided significance level of

.05 to compare the treatment and placebo groups. The accrual goal was 275 cases. Under the assumptions of the design, 5.5 years of accrual at 50 patients per year and 2.2 years of follow-up would yield 80% power, at a 1-sided significance level of .05. Because of a lower than expected accrual rate, the study did not meet its design specifications and was terminated on January 15, 1999. The last patient was randomized on January 12, 1999.

Treatment Plan

Patients were randomized equally to receive treatment (13-CRA) or placebo by using permuted blocks within strata. Stratification factors used were: disease site (oral cavity, hypopharynx, oropharynx, larynx), smoking history (never-smokers vs former smokers vs current smokers), alcohol history (never-drinkers vs former drinkers vs current drinkers), and weight in kilograms (<60 kg vs >60 kg).

In the treatment group, 13-CRA was dispensed in 3.75-mg and 5-mg gelatin capsules, depending on patient weight. Placebo was dispensed in identical capsules and dosages. Patients took 2 capsules once daily at bedtime. This was a double-blind study, and treatment began within 10 days of randomization. In the event of an emergency or severe adverse reaction, unblinding of the medication would take place.

Therapy would continue daily for a total of 2 years or until patients developed limiting toxicities or SPTs. According to the protocol, follow-up assessments would be administered at 1 month after study entry and then every 6 months until 5 years post-treatment.

Endpoints

The major objective of this study was to compare the effectiveness of 13-CRA treatment versus placebo in patients with SCCHN who had a high probability of cure from their primary cancer. Primary endpoints included the number of SPTs and the time to diagnosis of an SPT (TSP). Secondary endpoints were OS and toxicity.

Statistical Methods

Descriptive statistics were used to summarize patient demographic and disease characteristics. Fisher exact tests and Wilcoxon 2-sample tests were used to compare the distribution of frequency data and continuous data between groups, as appropriate. TSP was defined as the time from randomization to the occurrence of an SPT. Patients who remained alive without reporting an SPT were censored at date of last contact. Cumulative incidence rates of SPT and associated 95% confidence intervals (CIs) were constructed and compared using the method of Gray[14] by considering death without SPT as a competing risk. OS was measured from randomization to the date of all-cause death and was censored at date of last contact. OS distributions were estimated using the Kaplan-Meier method[15] and were compared using the log-rank test.[16] A Cox proportional-hazards model[17] and competing-risk regression model[18] also were used to estimate associations between time-to-event and covariates of interest. The *P* values reported are 2-sided.

RESULTS

In total, 189 patients who received previous treatment for stage I/II SCC of the oral cavity, oropharynx, hypopharynx, or larynx, were enrolled between 1989 and January 1999, with an overall accrual rate of 26 patients per year. The Consolidated Standards of Reporting Trials (CONSORT) diagram (Fig. 1) illustrates the number of patients assigned to each arm. By using an intent-to-treat and excluding ineligible patients, the total number of evaluable patients was 176, with 91 assigned to the 13-CRA group and 85 assigned to the placebo group.

The first interim analysis was performed in November 1998. No significant differences in the SPT rate were noted between arms. Given slow accrual, the data safety monitoring committee recommended closing the study to further registration.

Study follow-up was terminated in April 2015. At the time of this analysis, 108 patients had died (61%; 53 in the 13-CRA arm and 55 in the placebo arm). Thirty-one patients were lost to or refused follow-up (18%; 15 in the 13-CRA arm and 16 in the placebo arm). Among 61 patients who had cause-of-death information submitted, 38% died from SCCHN, and 62% of deaths were neither treatment-related nor disease-related. The median follow-up for survivors was 16.1 years (range, 1.0-25.5 years).

Patient Characteristics

Table 1 provides the demographics for 176 randomly assigned eligible patients. Distributions of age, smoking-status, disease stage, location of primary tumor, prior treatment, and performance status were well balanced between arms ($P > .05$).

Toxicity and Adherence

Of 91 patients in the 13-CRA arm, 77% received at least 1 year and 52% received 2 years of treatment. Of 85 patients in the placebo arm, 82% and 67% completed 1 year and 2 years of treatment, respectively ($P = .45$ and $P = .045$ for the comparison at 1 year and 2 years between

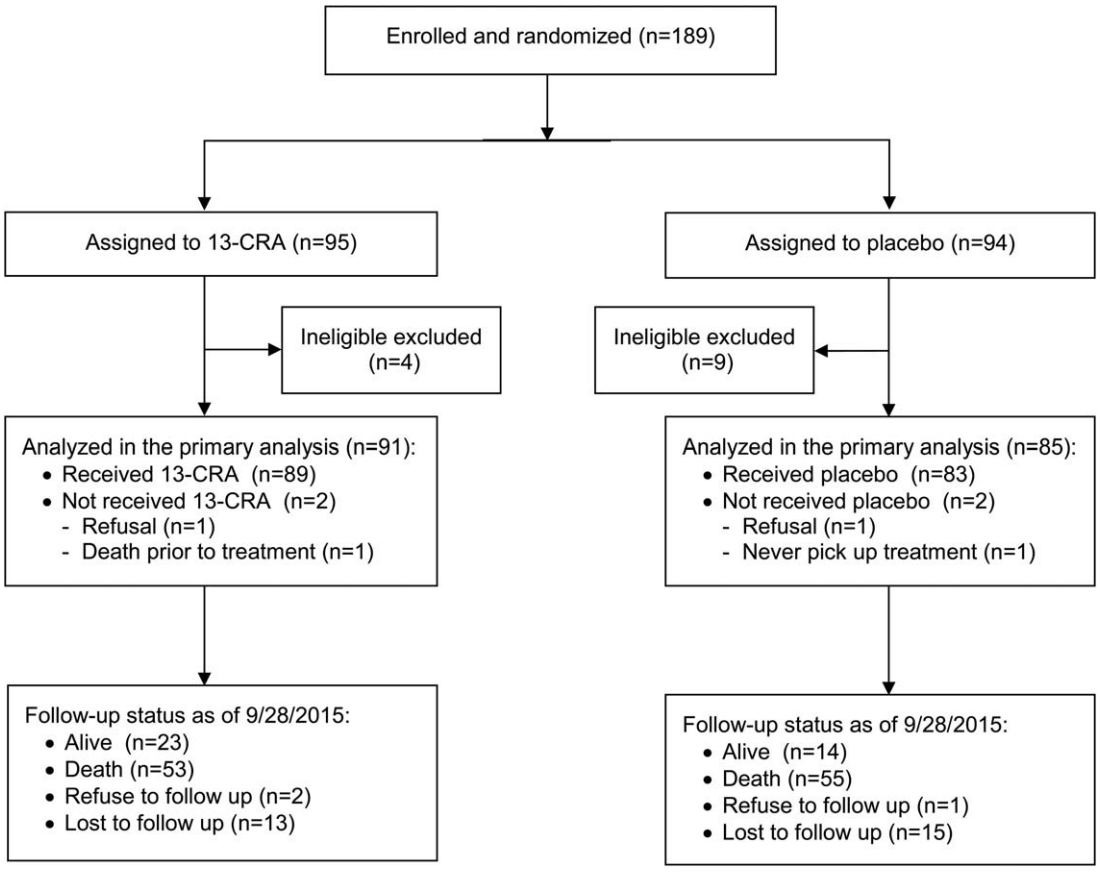


Figure 1. This is a Consolidated Standards of Reporting Trials (CONSORT) diagram of the current study. CRA indicates 13-cis retinoic acid.

arms, respectively). The main reasons for premature treatment discontinuation in both arms were patient withdrawal (21% [18 of 86 patients] in the 13-CRA arm; 10% [8 of 80 patients] in the placebo arm; $P = .06$) and toxicity (9% [8 of 86 patients] in the 13-CRA arm; 4% [3 of 80 patients] in the placebo arm; $P = .21$).

All patients who received protocol treatment were included in the toxicity analysis regardless of eligibility (n = 184). There were 2 deaths (1 cardiac arrest on 13-CRA, 1 infection on placebo). Table 2 summarizes 13-CRA–related toxicities (for the grading scale, see the online supporting information). Most common grade 3 and 4 13-CRA–related toxicity was serum triglycerides >100% above baseline (11 in the 13-CRA arm; 8 in the placebo arm; $P = .63$). Comparisons of other 13-CRA–related toxicities (grade ≥ 3) revealed no significant differences between arms. However, when we compared grade ≥ 1 toxicities between arms, more adverse events were observed in the 13-CRA arm with respect to skin toxicity (38% vs 21%; $P = .02$), cheilitis (23% vs 5%; $P = .001$), and nausea (10% vs 1%; $P = .02$).

With respect to treatment-related toxic events recorded based on Common Toxicity Criteria, most events were grade 1 or 2 (75% in the 13-CRA arm; 79% in the placebo arm; data not shown). Seventeen patients (18%) in the 13-CRA arm experienced grade ≥ 3 toxicities, compared with 12 patients (13%) in the placebo arm ($P = .42$). The most common grade ≥ 3 toxic events were neuroclinical (headache, altered consciousness, incoordination/involuntary movements; 4 in the 13-CRA arm; 3 in the placebo arm), arthralgia (3 in the 13-CRA arm; 0 in the placebo arm), skin (3 in the 13-CRA arm; 1 in the placebo arm), and cardiac (2 in the 13-CRA arm; 2 in the placebo arm).

Efficacy

A primary endpoint was the number of SPTs. Table 3 lists SPTs by site and treatment arm. Of 45 patients who experienced SPTs, the most common sites were the head and neck (n = 11) and lungs (n = 10). No significant differences were observed in the number of SPTs (22 of 91

TABLE 1. Patient Characteristics

Characteristic	Treatment: 13-CRA, N = 91 No. (Column %)	Treatment: Placebo, N = 85 No. (Column %)	*P*
Age: Median [min, max], y	60 [36, 86]	62 [30, 80]	.59
Smoking history			.76
Never smoked	8 (9)	6 (7)	
Smoked previously	57 (63)	58 (68)	
Current smoker	26 (29)	21 (25)	
Disease site			.74
Oral cavity	29 (32)	31 (37)	
Oropharynx	11 (12)	8 (10)	
Larynx	51 (56)	44 (53)	
Unknown	0 (0)	2	
Sex			.47
Men	73 (80)	64 (75)	
Women	18 (20)	21 (25)	
Stage			.33
I	64 (70)	51 (63)	
II	27 (30)	30 (37)	
Unknown	0	4	
Prior treatment			.63
Radiotherapy	46 (52)	40 (48)	
Surgery	26 (29)	30 (36)	
Combined	17 (19)	13 (16)	
Unknown	2	2	
FU smoking status			1.00
No smoking after baseline	57 (64)	54 (65)	
Smoking after baseline	32 (36)	29 (35)	
Unknown	2	2	
ECOG PS			.67
0	78 (87)	70 (84)	
1	12 (13)	13 (16)	
Unknown	1	2	
NCI race			.04
White	75 (82)	79 (93)	
Nonwhite	16 (18)	6 (7)	

Abbreviations: 13-CRA, 13-cis retinoic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, follow-up; max, maximum; min, minimum; NCI, National Cancer Institute.

patients in the 13-CRA arm vs 23 of 85 in the placebo arm; $P = .73$).

The TSP was another primary endpoint. Table 4 details the cumulative incidence of SPT by treatment arm. The 1-year, 3-year, 5-year, 10-year, and 15-year cumulative SPT rates for patients in the 13-CRA arm were 0.04, 0.14, 0.16, 0.18, and 0.21, respectively, compared with 0.04, 0.08, 0.18, 0.23, and 0.28 in the placebo arm. ($P = .61$), exhibiting no significant difference between arms. This conclusion holds with a competing risk regression analysis (hazard ratio [HR] for 13-CRA/placebo, 0.86; 95% CI, 0.48-1.54; $P = .61$). Because the eligibility criterion of completion of primary therapy with surgery and/or radiation was relaxed from within 35 days to within 730 days before randomization during study accrual, a secondary analysis was performed on the TSP measured from the completion of primary therapy (instead of from randomization). Again, no significant benefit in the TSP was observed in patients who were receiving 13-CRA (HR, 0.85; 95% CI, 0.47-1.52; $P = .58$).

A secondary endpoint was OS. The 1-year, 3-year, 5-year, 10-year, and 15-year OS rates for patients in the 13-CRA arm were 0.99, 0.90, 0.79, 0.60, and 0.49, respectively, compared with 0.96, 0.91, 0.82, 0.48, and 0.31, respectively, in the placebo arm. With a median 16 years of follow-up, the 2-sided log-rank test yielded a *P* value of .14, with a trend toward improved survival for the 13-CRA arm (median, 14.9 vs 9.8 years; HR, 0.75; 95% CI, 0.51-1.10; $P = .14$) (see Fig. 2B).

Subset analyses were performed to compare treatment effect (13-CRA vs placebo) within each subgroup stratified by sex, race, tumor site region, disease stage, ECOG PS, prior treatment, and smoking status. The analyses demonstrated no significant differences in the TSP between arms in each subset. Figure 2C summarizes these results in a forest plot. The forest plot in Figure 2D illustrates the HR for death along with the corresponding 95% CI. Although it was not significant ($P = .065$), there was a trend toward improved OS among patients who underwent surgery alone for their index tumor (n = 26; HR, 0.50; $P = .057$), women (n = 39; HR, 0.44; $P = .065$), and never/former smokers (n = 129) on low-dose 13-CRA ($P = .055$).

Multivariable Cox proportional-hazards and competing-risk regression models were fit to determine prognostic factors for OS and TSP, respectively. Covariates included the treatment, patient, and disease characteristics listed in Table 1. Only age and smoking history at entry were identified as significant in the OS model. When controlled for other factors, the HRs for death comparing never-smokers versus current smokers and former smokers versus current smokers were 0.05 (95% CI, 0.01-0.36; $P = .003$) and 0.26 (95% CI, 0.17-0.39; $P < .0001$), respectively. For every 1-year increase in age, the risk of death increased by 5% (95% CI, 1.03-1.07; $P < .0001$). With respect to the TSP, no factor achieved statistical significance (all $P > .05$).

To ensure that we were evaluating the impact of 13-CRA on the development of new primaries alone, we conducted a second analysis excluding patients whose SPT occurred during the 6 months after randomization, anticipating that some patients might have had a subclinical SPT at initial diagnosis. With this criterion, 171 patients were included (2 assigned to 13-CRA and 3 assigned to

TABLE 2. Incidence of Grade 1 through 4 13-Cis Retinoic Acid (13-CRA) Toxicities According to the 13-CRA Grading Scale

	Incidence: No. of Patients							
	13-CRA, N = 92				Placebo, N = 92			
	Grade[a]				Grade[a]			
Toxicity	1	2	3	4	1	2	3	4
Skin	32	2	1	—	15	3	1	—
Cheilitis	17	4	—	—	4	1	—	—
Conjunctivitis	—	1	—	—	—	—	—	—
Epistaxis	1	—	—	—	—	—	—	—
Hair	4	—	—	—	4	—	—	—
Nausea	8	1	—	—	1	—	—	—
Diarrhea	5	—	—	—	3	—	—	—
Neurologic, headache	7	3	1	—	5	1		—
Reproductive function	1	1	—	—	—	—	—	—
Bladder	1	—	—	—	—	—	—	—
Musculoskeletal	5	7	3	—	2	5	1	1
Fatigue	11	4	2	—	7	2	0	1
Liver	16	2	—	—	13	1	1	—
Serum cholesterol	18	9	—	—	14	8	1	—
Serum triglycerides	4	47	11	—	14	32	8	—
HDL cholesterol	23	12	—	—	12	10	—	—

Abbreviations: 13-CRA, 13-cis retinoic acid; HDL, High-density lipoprotein.
[a] For further details, see online supporting information.

TABLE 3. Incidence of Second Primary Cancers by Site and Treatment

	Treatment: No. of Patients		
Second Primary Site	13-CRA	Placebo	Total
Breast	1	2	3
Esophagus	0	1	1
Anal canal	0	1	1
Colorectal	0	3	3
Head and neck	7	4	11
Brain tumor	1	0	1
B-cell lymphoma	1	0	1
Lung	6	4	10
Melanoma	0	1	1
Nonmelanoma skin cancer	2	4	6
Endometrium, uterine corpus	1	0	1
Bladder, urinary tract	1	1	2
Prostate	1	2	3
Other gynecologic site	1	0	1
Total	22	23	45

Abbreviation: 13-CRA, 13-cis retinoic acid.

placebo were excluded). The original conclusions regarding the effect of 13-CRA on the number of SPTs, the TSP, and OS held true (data not shown).

Enrollment on this study predated testing of oropharynx tumors for human papillomavirus (HPV) status. We used oropharyngeal tumors as a surrogate for HPV-associated disease, although the proportion of HPV-associated cancers in the oropharynx was likely lower at the time this trial accrued. In this small subset (n = 19), there were no significant associations between region and SPT (24% in nonoropharynx vs 42% in oropharynx sites; $P = .10$).

DISCUSSION

We report a long-term, phase 3, intervention trial that studied low-dose isotretinoin for benefit and tolerability in patients who received treatment for early stage SCCHN. Our findings did not confirm those from the pivotal MD Anderson Cancer Center trial, in which high-dose, short-term isotretinoin was received by patients with stage I through IV SCCHN.[9,10] There were no statistically significant benefits in either OS or SPT. However, compliance with treatment at 1 year was greater in our study (77% vs 67% in the high-dose trial), presumably because of decreased toxicities with the lower dose. Our findings mirror those of Khuri et al[12] as well as findings from a large European trial reported in 2000.[19]

Stratification of results separately by prior treatment, sex, and smoking status revealed a trend toward improved OS for the 13-CRA arm in patients who underwent with surgery alone, women, and never/former smokers. Statistical significance was not achieved in the 13-CRA arm for women, possibly because of the small size of this subgroup (n = 39). This also was confounded by the finding that

79% of these 39 patients were never/former smokers. Because a similar proportion of male patients (72%) were never/former smokers but no 13-CRA benefit on OS was noted, it is unlikely that the trend of a 13-CRA benefit for women is because of the effect of smoking status alone. Khuri and colleagues[12] enrolled a larger cohort of women (n = 250) with early stage SCCHN but did not present an analysis of benefit from low-dose isotretinoin in them. Furthermore, a trend toward a survival benefit for the never/former smoking group indicates that this group merits further testing, and there may be a role for chemoprevention in the current generation of tobacco-cessation studies.

Patients who enrolled at different institutions had follow-up for disease assessment for differing periods after the completion of therapy, leading to the possibility of underestimating rate the of SPT. To further account for patients who died without an SPT reported, we have censored the TSP at the point of last contact and considered death as a competing risk in our analysis to accurately determine SPT incidence and effect estimates.

It is possible that the lower dose of isotretinoin used in the C0590 trial diminished the benefit previously observed with higher doses of the drug, either when used alone[9,10] or when used in combination with interferon α and vitamin E in patients with locally advanced SCCHN.[20,21] It is also possible that excluding the locally advanced subgroup of patients mitigated a likely benefit, because this would be the subset with the highest risk of recurrence. Another possibility for failing to detect any benefit is the observed higher cumulative incidence rate of SPT in our study (21% for 13-CRA and 28% for placebo at 15 years) than expected (10% vs 20%, respectively, based on a cure rate model), leading to less power to detect

TABLE 4. Cumulative Incidence of Second Primary Tumor and Kaplan-Meier Estimate of Overall Survival by Treatment Arm

Efficacy	Treatment	No. of Events/ Total No.	Rate, %					HR (95% CI): 13-CRA/Placebo[a]	Wald *P*[a]
			1 Year	3 Years	5 Years	10 Years	15 Years		
SPT	13-CRA	22/91	0.04	0.14	0.16	0.18	0.21	0.86 (0.48-1.54)	. 61
	Placebo	22/85	0.04	0.08	0.18	0.23	0.28		
OS	13-CRA	53/91	0.99	0.90	0.79	0.60	0.49	0.75 (0.51-1.10)	.14
	Placebo	55/85	0.96	0.91	0.82	0.48	0.31		

Abbreviations: 13-CRA, 13-cis retinoic acid; CI, confidence interval; HR, hazard ratio; OS, overall survival; SPT, second primary tumor.
[a] These data are from the univariate analysis.

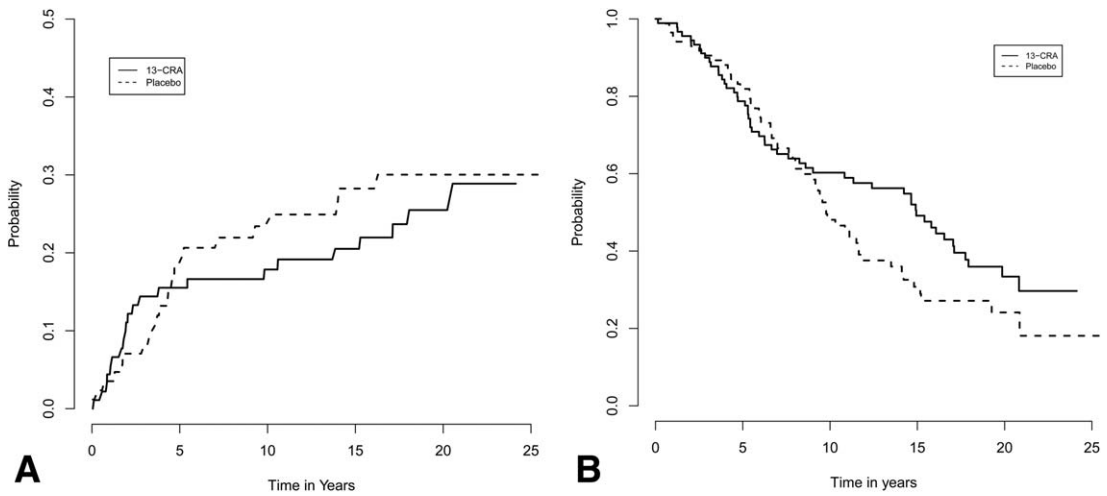
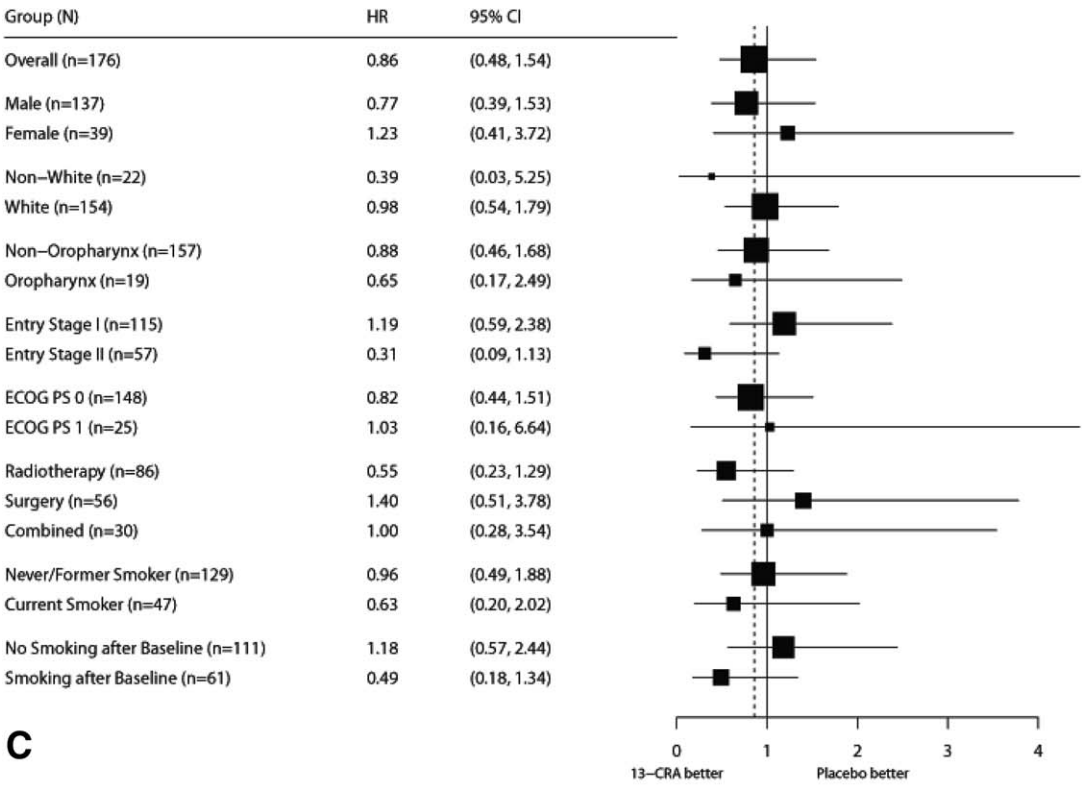


Figure 2. Charts illustrate (A) the cumulative incidence of second primary tumor by treatment arm and (B) Kaplan-Meier curves for overall survival by treatment arm. Forest plots illustrate the treatment effect on (C) time to second primary and (D) overall survival for all analyzable patients (n = 176). Note that the size of the squares is inversely proportional to the variance of the log hazard ratio (HR) (small squares correspond to large variances). Bars represent 95% confidence intervals (CIs). CRA indicates 13-cis retinoic acid; ECOG PS, Eastern Cooperative Oncology Group performance status.



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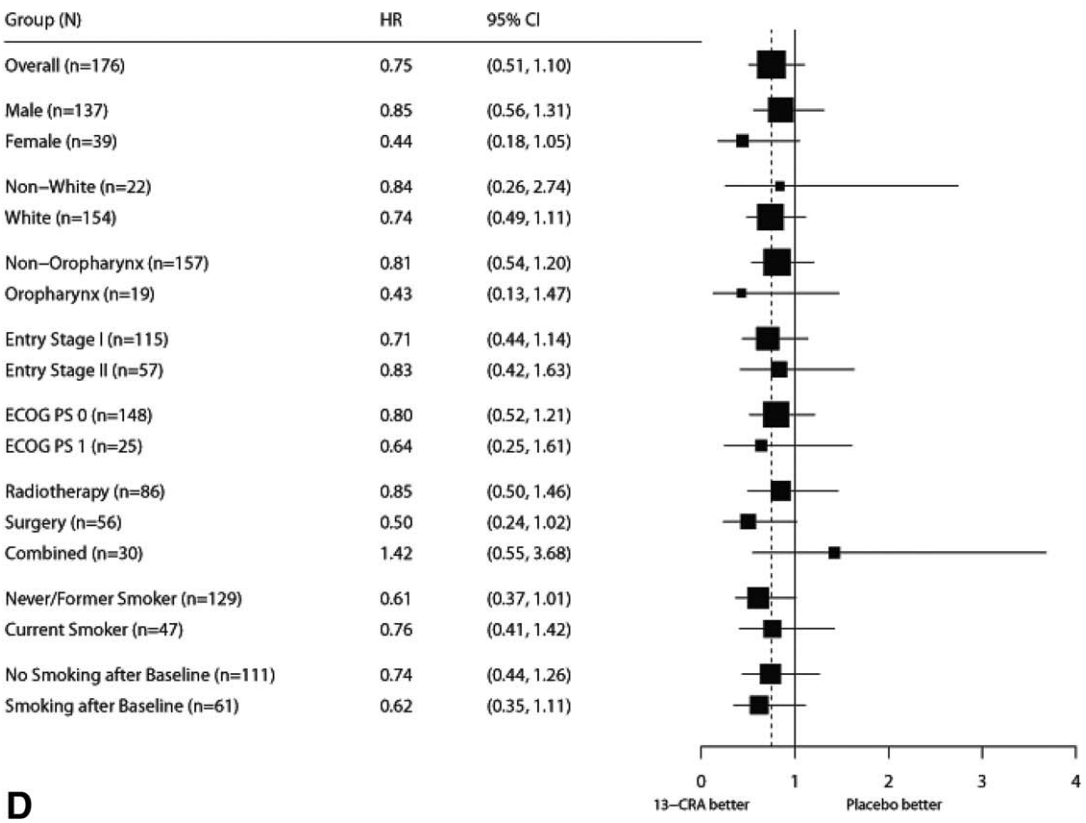

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Figure 2. Continued

the difference. Although our small sample size (because of early termination) might have further limited power to detect a significant difference in endpoints between the arms, our findings follow those from the largest patient sample enrolled in a similar study led by the MD Anderson Cancer Centerm[12] and we can conclusively rest this question of low-dose vitamin A analogues having a substantive chemopreventive role in patients with early stage SCCHN.

These results are reported in an era of personalized medicine, and the lack of molecular characterization of patients' tumors is a limitation in the study design. A wealth of data pertaining to driver mutations in SCCHN has emerged from the Cancer Genome Atlas.[22] Final results of the EPOC (Erlotinib Prevention of Oral Cancer) trial are also reported, and that study validated the use of loss of heterozygosity as a prognostic biomarker.[23] It is imperative therefore, that future prevention efforts factor in both prognostic (smoking, HPV status, and loss of heterozygosity) and predictive molecular markers to optimize responses and resources.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Aarti K. Bhatia: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Ju-Whei Lee**: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Harlan A. Pinto**: Contributed the conception and design of the trial, analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Charlotte D. Jacobs**: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Paul J. Limburg**: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Robert M. Arusell**: Contributed the conception and design of the trial, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Eamonn P. Dunphy**: Contributed the conception and design of the trial, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Janardan D. Khandekar**: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Seth A. Reiner**: Contributed the conception and design of the trial, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Luis Baez-Diaz**: Contributed the conception and design of the trial, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Pal Celano**: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Shuli Li**: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Yi Li**: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Barbara A. Burtness**: Analysis and interpretation of data, writing–initial draft, writing–editing and revisions, and approved the final version for publication. **Kishan J. Pandya**: Contributed the conception and design of the trial, writing–initial draft, writing–editing and revisions, and approved the final version for publication.

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