Double-Blind, Randomized Phase III Trial of Low-Dose 13-Cisretinoic Acid in Prevention of Second Primaries in Head and Neck Cancer: Long-Term Follow-up of a Trial of the ECOG-ACRIN Cancer Research Group (C0590)

Running Title: Chemoprevention in head and neck cancer

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Precis:

Effective chemoprevention is an unmet need in head and neck cancers. This study reports on the lowest dose of retinoids ever studied for this indication and provides the longest follow-up to date.

Keywords

Head and neck Cancer, Oral Cancer, Second Primary Cancer, Chemoprevention, Randomized Controlled Trial.

ABSTRACT

Background: 13-Cisretinoic acid (13-CRA) is a synthetic Vitamin A derivative. High-dose 13-CRA in patients with squamous cell cancers of the head and neck (SCCHN) reduces the incidence of second primary tumors (SPT). We report long-term results of a Phase III randomized trial that compared low-dose 13-CRA versus placebo, among patients with early-stage SCCHN in development of SPT and overall survival (OS).

Methods: 176 patients treated for Stage I/II SCCHN were randomized to low-dose 13-CRA (weight-based dose of 7.5 mg or 10 mg) or placebo for two years. Competing-risk approach and log-rank test were used, respectively, to compare time to SPT and OS between groups.

Results: 13-CRA neither significantly reduced cumulative incidence of SPT (p = 0.61) nor improved time to SPT (Hazard ratio (HR, 13-CRA/placebo) 0.86, p= 0.61). Despite limited power, there was a trend to improved OS for the 13-CRA arm (HR 0.75, p = 0.14) particularly among patients whose index tumor was surgically excised (N = 26, HR 0.50, p = 0.057), female patients (N= 39, HR 0.44, p = 0.065) and never/former smokers (N= 129, HR 0.61, p = 0.055), with a median follow-up of 16 years. Main 13-CRA related toxicities were dry skin and cheilitis.

Conclusions: Low-dose 13-CRA for 2 years did not decrease the incidence of SPT; subset analysis indicates a potential survival advantage among female patients 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.

BACKGROUND

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

Vitamin A and its synthetic analogs (retinoids) are potent agents for control of cell differentiation and prevention of carcinogenesis in normal and pre-neoplastic epithelial cells [7]. Sporn et al demonstrated their efficacy in reversing pre-malignant lesions in mouse models [7]. Hong et al reported that 1-2 mg/kg daily dose of 13-cisretinoic acid (13-CRA, isotretinoin), given to patients with oral leukoplakia, significantly decreased the size of the lesions and completely reversed dysplasia in 54% of patients [8]. Relapse occurred in over half of the responders 2-3 months after drug cessation [8]. They then randomized 103 patients curatively treated for stages I-IV SCCHN, to daily high-dose 13-CRA (50-100 mg/m^2 body surface area (BSA)) vs placebo for 12 months [9]. Although there were no significant differences in local or distant recurrence, the

intervention arm had significantly fewer SPT (4% vs 24%, *p*=0.005). However, isotretinoin did not prolong OS [10], with majority of patients in both arms 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 post-surgery/radiation setting for patients with stage I-III squamous cell cancers (SCC) of the oral cavity and oropharynx [11]. With a median follow-up of 41 months, there was no significant difference in SPT between groups, while patients on the treatment arm experienced significantly greater toxicity (33% versus 23%, $p < 0.05$).

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

C0590 tested the lowest dose of isotretinoin ever used in this setting. Here we report the longest follow-up to date of effects of a retinoid in SPT prevention in SCCHN.

OBJECTIVES

C0590 was designed with two aims: first, to confirm that treatment with 13-CRA was more effective than placebo in preventing SPT in SCCHN survivors; second, to determine if lower, weight-based daily dosing (7.5 mg for patients less than 60 kg and 10 mg for patients over 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.

PATIENTS AND METHODS

This was a multi-center, randomized, placebo-controlled, double-blind Phase III Intergroup trial coordinated by the ECOG-ACRIN Cancer Research Group. Affiliated Radiation Therapy Oncology Group (RTOG) and North Central Cancer Treatment Group (NCCTG) institutions also accrued to the study. However, RTOG 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, ECOG performance status of 0 or 1; chest

and bone x-rays within 35 days after definitive treatment, prior to randomization; hematology and chemistries within 2 weeks prior to randomization; adequate marrow, renal and hepatic function (hemoglobin ≥ 10 g/dL, white blood count > 3000/mm^3, platelet count > 100,000/mm^3; transaminases ≤ 1.5 times upper limit of normal [ULN] value; serum creatinine ≤ 1.5 times ULN; 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 prior to randomization, and no evidence of disease. In addition, patients should be able to give written informed consent in compliance with institutional and federal guidelines and be available for long-term follow-up.

Exclusion criteria included: prior chemotherapy; other concurrent malignancies except for localized and resected non-melanoma skin cancer; pregnancy and lactation. Female patients of childbearing potential had to agree to use contraception and to have a negative pregnancy test prior to study initiation.

STUDY DESIGN AND TARGET ACCRUAL

Sample-size calculation was based on an exponential cure-rate model, proposed by Berkson and Gage (1951), with predicted rate of freedom from SPT of 80% and 90% for placebo and 13-CRA arms respectively. The design specified a log-rank test at the one-sided 0.05 significance level, to compare treatment and

placebo groups. 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 one-side 0.05 significance level. Because of 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 equally randomized to treatment (13-CRA) and placebo by using permuted blocks within strata. Stratification factors used were: site of disease (oral cavity, hypopharynx, oropharynx, larynx), smoking history (never-smokers versus former smokers versus current smokers), alcohol history (never-drinkers versus former drinkers versus current drinkers) and weight in kilograms (less than 60 kilograms versus greater than 60 kilograms).

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 dosage. 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 developing limiting toxicities or SPT. Per protocol, follow-up assessments would be administered at one month following study entry and then every six months until five years post-treatment.

ENDPOINTS

The major goal was to compare the effectiveness of 13-CRA treatment to placebo in patients with SCCHN who have a high probability of cure from their primary cancer. Primary endpoints included number of SPT and time to diagnosis of second primary (TSP), with secondary endpoints being OS and toxicity.

STATISTICAL METHODS

Descriptive statistics were used to summarize patient demographic and disease characteristics. Fisher's exact test and Wilcoxon two-sample test were used to compare distribution of frequency data and continuous data between groups as appropriate. TSP was defined as time from randomization to occurrence of SPT. Patients alive without SPT reported were censored at date of last contact. Cumulative incidence rates of SPT and associated 95% confidence intervals (CI) were constructed and compared using the method of Gray [13] by considering death without SPT as a competing risk. OS measured time from randomization to date of all-cause death, censored at date of last contact. OS distributions were

estimated using the Kaplan-Meier method [14] and compared using the log-rank test [15]. Cox proportional hazards (PH) model [16] and computing risk regression model [17] were further used to estimate associations between time-to-event and covariates of interest. *P*-values reported are two-sided.

RESULTS

A total of 189 patients, previously treated 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 CONSORT diagram (Figure 1) illustrates the number assigned to each arm. Utilizing intent-to-treat and excluding ineligible patients, total number of analyzable patients was 176 – 91 allocated to 13-CRA and 85 to placebo.

First interim analysis was performed in November 1998. No significant differences in 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 on 13-CRA and 55 on placebo). Thirty-one patients were lost to or refused follow-up (18%, 15 on 13-CRA and 16 on placebo). Among 61 patients whose cause-of-death information was submitted, 38% were

due to SCCHN and 62% were neither treatment- nor disease-related. Median follow-up time among survivors was 16.1 years (range 1.0 to 25.5 years).

Patient Characteristics

Table 1 shows demographics for 176 randomly assigned eligible patients. Distributions of age, smoking-status, stage of disease, location of primary tumor, prior treatment and performance status were well-balanced between arms (p>0.05).

Toxicity and Adherence

For the 91 patients on 13-CRA, 77% received at least 1 and 52% received 2 years of treatment. For the 85 patients on placebo, 82% and 67%, respectively, completed 1 and 2 years of treatment (p=0.45 and 0.045 for comparison at 1 and 2 years between arms, respectively). Main reasons for premature treatment discontinuation from both arms were patient withdrawal, 21% (18/86) on 13-CRA and 10% (8/80) on placebo (p=0.06) and toxicity, 9% (8/86) on 13-CRA vs. 4% (3/80) on placebo (p=0.21).

All patients receiving 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 (see

Supplementary Material for grading scale). Most common grade 3-4 13-CRA-related toxicity was serum triglycerides > 100% above baseline (11 in 13-CRA, 8 in Placebo, *p*=0.63). Comparisons of other 13-CRA-related toxicities (grade 3+) found no significant differences between arms. However, when we compared grade 1+ toxicities between arms, more adverse events were observed on 13-CRA with respect to skin (38% vs. 21%, p=0.02), cheilitis (23% vs. 5%, p=0.001), and nausea (10% vs. 1%, p=0.02).

With respect to treatment-related toxic events recorded based on Common Toxicity Criteria, majority were grade 1 or 2 (75% on 13-CRA, 79% on placebo, data not shown). Seventeen (18%) 13-CRA patients experienced grade 3 or higher toxicities, compared to 12 (13%) placebo patients (*p*=0.42). Most common ≥ grade 3 toxic events were neuro-clinical (headache, altered consciousness, in-coordination/involuntary movements – 4 in 13-CRA, 3 in placebo), arthralgia (3 in 13-CRA, 0 in placebo), skin (3 in 13-CRA, 1 in placebo), and cardiac (2 in 13-CRA, 2 in placebo).

Efficacy

A primary endpoint was number of SPT. Table 3 lists SPT by site and treatment arm. Of 45 patients who experienced SPT, most common sites were head and neck (11) and lung (10). No significant differences were observed in number of SPT (22/91 for 13-CRA vs. 23/85 for placebo, *p*=0.73).

TSP was another primary endpoint. Table 4 shows cumulative incidence of SPT by treatment arm. The 1-year, 3-year, 5-year, 10-year, and 15-year cumulative SPT rates for 13-CRA patients were 0.04, 0.14, 0.16, 0.18, and 0.21, compared to 0.04, 0.08, 0.18, 0.23, and 0.28 for placebo patients. (p=0.61), exhibiting no significant difference between arms. This conclusion holds with a competing risk regression analysis (HR for 13-CRA/placebo = 0.86, 95% confidence interval (CI) = 0.48, 1.54, p=0.61). Given that the eligibility criterion of completion of primary therapy with surgery and/or radiation was relaxed from within 35 days to within 730 days prior to randomization during study accrual, a secondary analysis was performed on TSP measured from completion of primary therapy (instead of from randomization). Again, no significant benefit in TSP was observed in patients receiving 13-CRA (HR = 0.85, 95% CI = 0.47, 1.52, p=0.58).

A secondary endpoint was OS. The 1-year, 3-year, 5-year, 10-year, and 15-year survival rates on 13-CRA were 0.99, 0.90, 0.79, 0.60 and 0.49, compared to 0.96, 0.91, 0.82, 0.48 and 0.31 on placebo. With a median 16-year follow-up, the two-sided log-rank test gave a p-value of 0.14, with a trend to improved survival on 13-CRA (median: 14.9 vs 9.8 years, HR = 0.75, 95% CI = 0.51, 1.10, p=0.14, see Figure 2B).

Subset analyses were performed to compare treatment effect (13-CRA vs placebo) within each subgroup stratified by gender, race, tumor region, stage,

ECOG PS, prior treatment and smoking status. The analyses demonstrated no significant differences in TSP between arms in each subset. Figure 2C summarizes these results in a forest plot. Figure 2D exhibits a forest plot, showing HR for death along with the corresponding 95% CI. Although not significant (p=0.065), there was a trend to improved OS among patients treated with surgery alone for their index tumor (*n* = 26, HR 0.50, *p* = 0.057), female patients (*n*=39, HR 0.44, *p* = 0.065) and never/former smokers (*n*=129) on low-dose 13-CRA (*p*=0.055).

Multivariable Cox PH regression model and competing risk regression model were fit, respectively, to determine prognostic factors for OS and TSP. Covariates included treatment, patient and disease characteristics listed in Table 1. Only age and smoking history at entry were found significant in the OS model. Controlled for other factors, HR for death comparing never-smokers vs current smokers and former smokers vs current smokers are 0.05 (95% CI = 0.01, 0.36, *p*=0.003) and 0.26 (95% CI = 0.17, 0.39, *p*<0.0001). For every 1-year increase in age, risk of death increased by 5% (95% CI = 1.03, 1.07, *p*<0.0001). With respect to TSP, no factor achieved statistical significance (all *p*>0.05).

To ensure that we are evaluating the impact of 13-CRA on development of new primaries alone, we conducted a second analysis excluding patients whose SPT occurred in the six months following 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 placebo excluded). The original conclusions regarding effect of 13-CRA on number of SPT, TSP and OS hold true (data not shown).

Enrollment on this study predated testing of oropharynx tumors for human papillomavirus (HPV) status. We used oropharynx tumors as a surrogate of HPV-associated disease, although the proportion of HPV-associated cancers in the oropharynx was likely lower at the time this trial accrued, than currently. In this small subset (*n*=19), there were no significant associations between region and SPT (24% in non-oropharynx vs 42% in oropharynx, *p*=0.10).

DISCUSSION

We report a long-term Phase III intervention trial that studied low-dose isotretinoin for benefit and tolerability in patients treated for early-stage SCCHN. Our findings did not confirm findings from the pivotal MD Anderson trial that used high-dose, short-term isotretinoin in patients with stage I-IV SCCHN [9, 10]. There were no statistically significant benefits in either OS or SPT. However, compliance with treatment at 1-year was higher in our study (77% versus 67% in the high-dose trial) presumably due to 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 [18].

Stratification of results by prior treatment, gender and smoking-status, separately, showed a trend toward improved OS for the 13-CRA arm for patients treated with surgery alone, females and for never/former smokers. Statistical significance was not achieved for the 13-CRA arm for females, possibly because of the small size of this subgroup (*n*=39). This finding also was confounded by the fact that 79% of these thirty-nine patients were never/former smokers. Given 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 13-CRA benefit for females is due to the effect of smoking status alone. Khuri et al [12] enrolled a larger female cohort (*n*=250) with early-stage SCCHN but did not present an analysis of benefit from low-dose isotretinoin in them. Further, a trend to 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 enrolled at different institutions had follow-up for disease assessment for differing periods of time after completion of therapy, leading to the possibility of underestimating rate of SPT. To further account for patients who die without SPT reported, we have censored TSP at the point of last contact and considered death as a competing risk in our analysis in order to accurately determine SPT incidence and effect estimates.

It is possible that the lower dose of isotretinoin used in C0590 diminished the benefit previously seen with higher doses of the drug, either when used alone [9, 10] or in combination with interferon α and Vitamin E in patients with locally-advanced SCCHN [19, 20]. It is also possible that excluding the locally-advanced subgroup of patients mitigated a likely benefit, as 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 the difference. Although our small sample-size (due to 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 MD Anderson [12] and we can rather 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 [21]. Final results of the EPOC (Erlotinib Prevention of Oral Cancer) trial are also reported and this study validated the use of loss of heterozygosity (LOH) as a prognostic biomarker [22]. It is imperative therefore, that

future prevention efforts factor in both prognostic (smoking, HPV status and LOH) and predictive molecular markers to optimize responses and resources.

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Table 1: Patient Characteristics

	Treatment				P
	13-CRA (N=91)		Placebo (N=85)		
	N	Col %	N	Col %	
Age (Median [Min, Max])	60 [36, 86]		62 [30, 80]		0.59
Smoking					0.76
Never Smoked	8	9	6	7	
Smoked Previously	57	63	58	68	
Current Smoker	26	29	21	25	
Region					0.74
Oral cavity	29	32	31	37	
Oropharynx	11	12	8	10	
Larynx	51	56	44	53	
Unknown	0	-	2	-	
Sex					0.47
Male	73	80	64	75	
Female	18	20	21	25	
Staging					0.33
1	64	70	51	63	
2	27	30	30	37	
Unknown	0	-	4	-	

	Treatment				
	13-CRA (N=91)		Placebo (N=85)		P
	N	Col %	N	Col %	
Prior Treatment					0.63
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 Performance Status					0.67
0	78	87	70	84	
1	12	13	13	16	
Unknown	1	-	2	-	
NCI Race					0.04
White	75	82	79	93	
Non-white	16	18	6	7	

Table 2: Incidence (N) of Grades 1-4 CRA Toxicities (according to the 13-CRA Grading Scale)

Toxicity	13-CRA (N=92)				Placebo (N=92)			
	Grade*				Grade*			
	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	-	-	-
Neuro – 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	-	-

* Refer to Supplementary Material at end

Table 3: Incidence (N) of Second Primary Cancers by Site and Treatment

Sites	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
Skin cancer not melanoma	2	4	6
Endometrium, Uterine Corpus	1	0	1
Bladder, Urinary Tract	1	1	2
Prostate	1	2	3
Other gyn	1	0	1
Total	22	23	45

Table 4: Cumulative Incidence of Second Primary Tumor (SPT) and Kaplan-Meier Estimate of Overall Survival (OS) by Treatment Arm

Efficacy	Treatment	# of Events/Total	1-year Rate	3-year Rate	5-year Rate	10-year Rate	15-year Rate	HR* (13-CRA/Placebo)	Wald P*
SPT	13-CRA	22/91	0.04	0.14	0.16	0.18	0.21	0.86 (0.48, 1.54)	0. 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)	0.14
	Placebo	55/85	0.96	0.91	0.82	0.48	0.31		

* from univariate analysis

Figure Legends:

Figure 1: CONSORT Diagram

Figure 2A: Cumulative Incidence of Second Primary Tumor by Treatment Arm

Figure 2B: Kaplan-Meier curves for OS by Treatment Arm

Figure 2C: Forest Plot for Treatment Effect on Time to Second Primary (All Analyzable Patients (n=176))

Note: The size of the squares is inversely proportional to the variance of the log hazard ratio (small squares correspond to large variances). Bars represent 95% confidence intervals.

Figure 2D: Forest Plot for Treatment Effect on OS (All Analyzable Patients (n=176))

Note: The size of the squares is inversely proportional to the variance of the log hazard ratio (small squares correspond to large variances). Bars represent 95% confidence intervals.

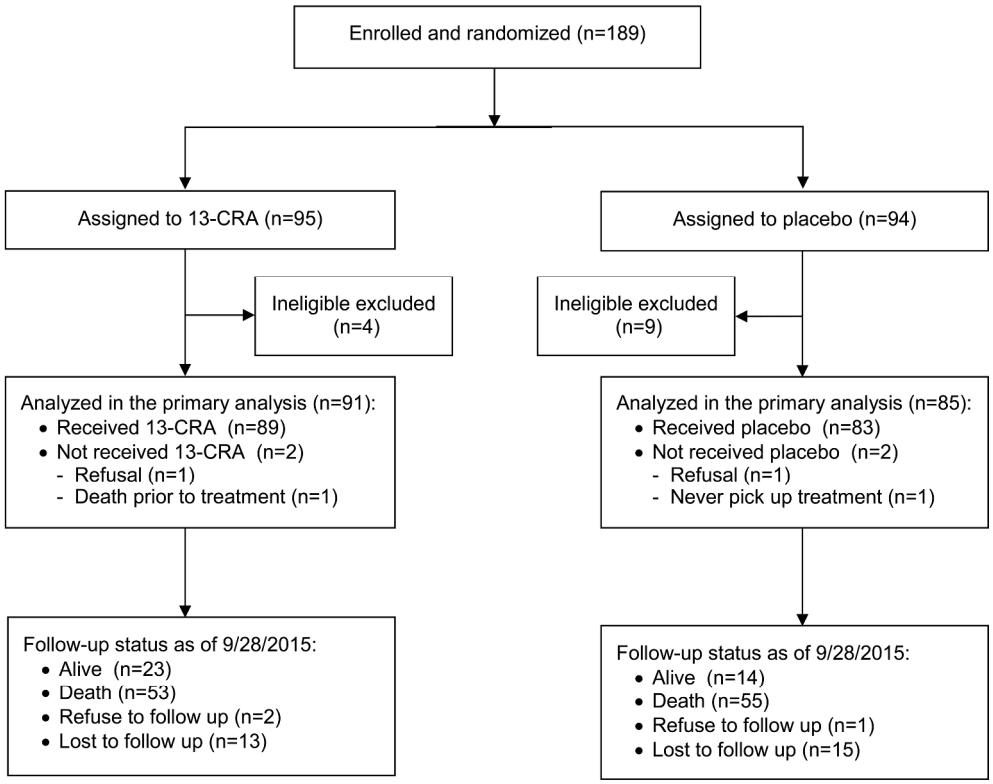

Figure 1: CONSORT Diagram

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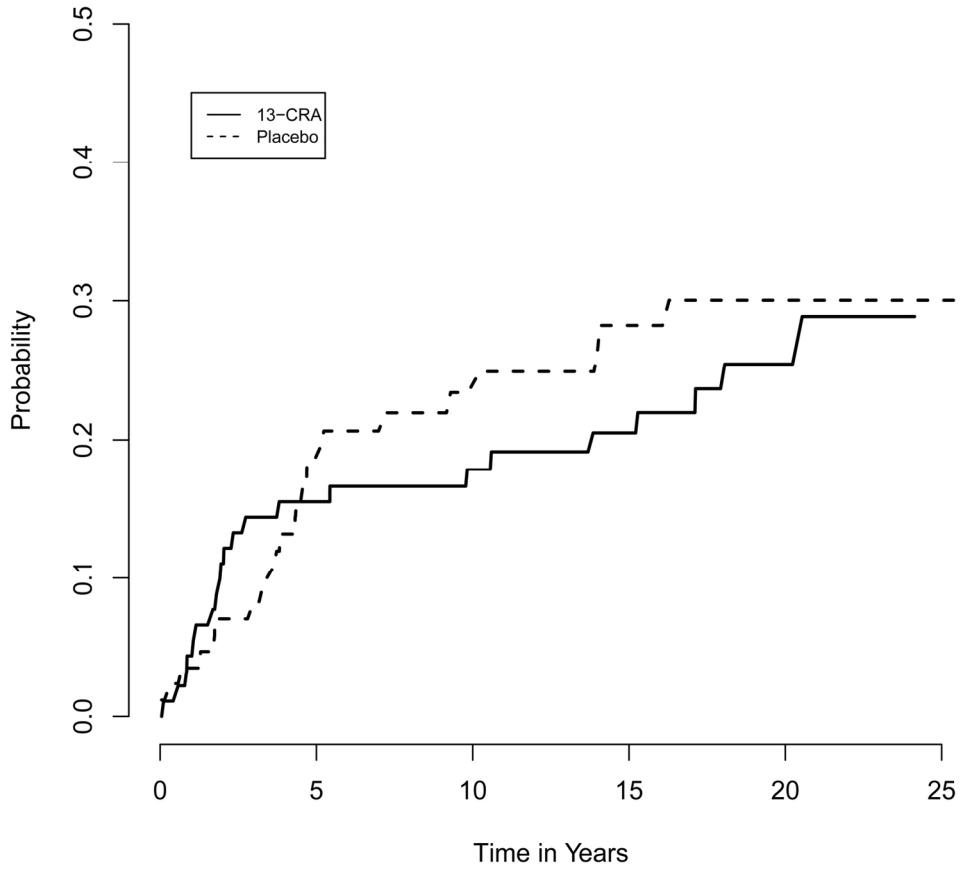

Cumulative Incidence of Second Primary Tumor by treatment arm

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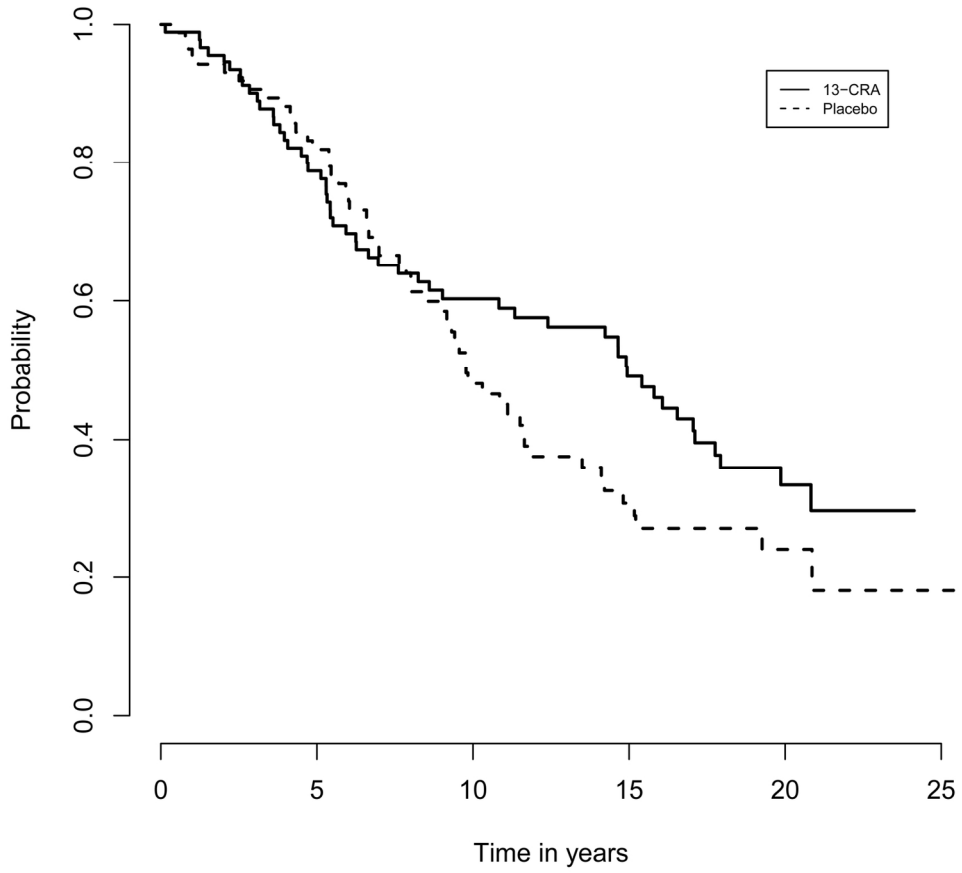
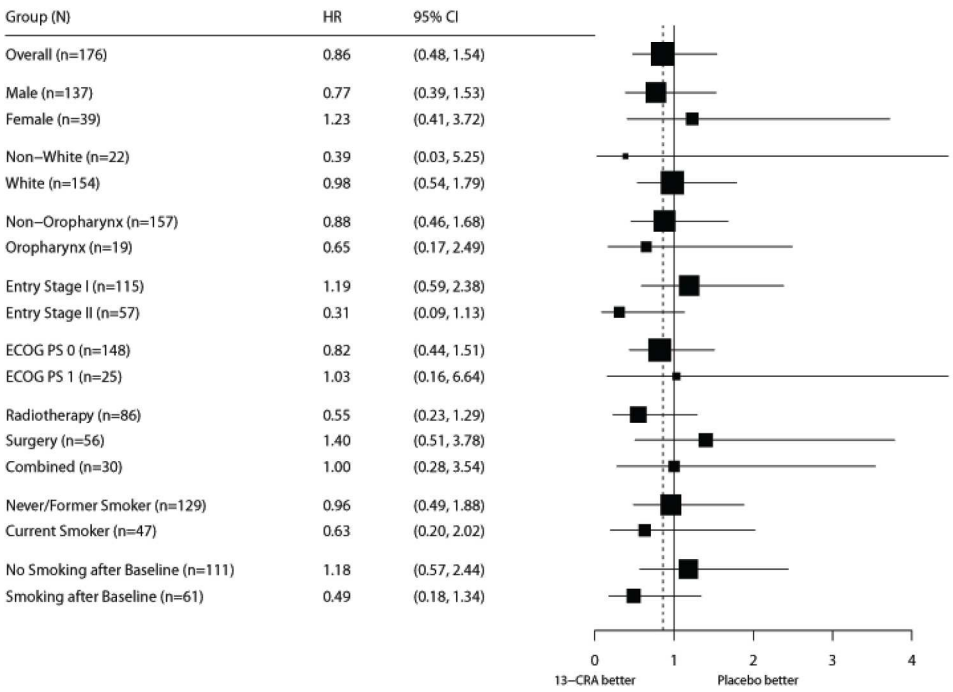


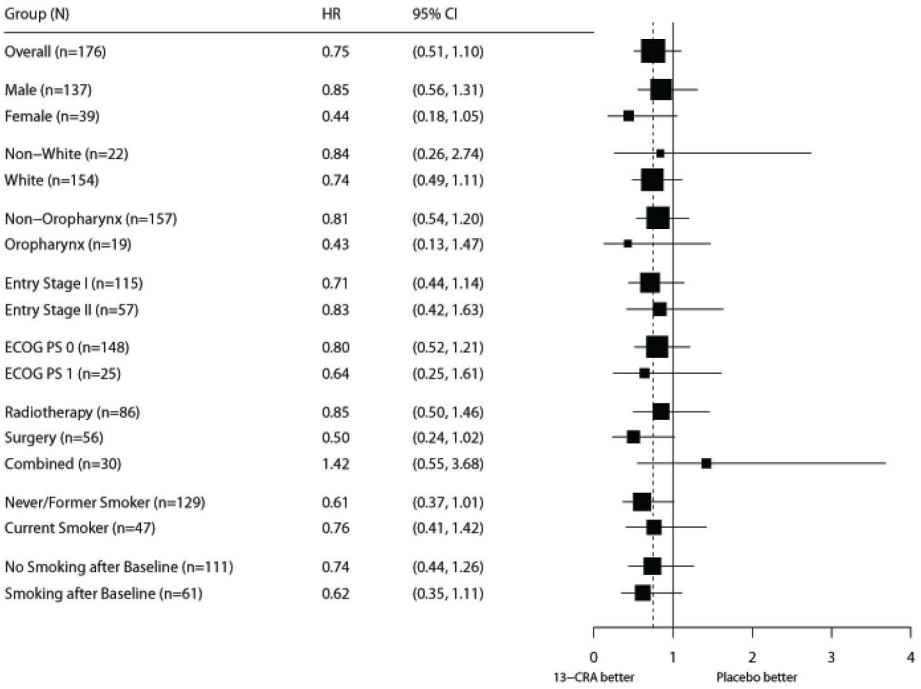
Kaplan Meier curves for OS by treatment arm

149x137mm (300 x 300 DPI)



Forest Plot for Treatment Effect on Time to Second Primary (All Analyzable Patients, n = 176)

203x154mm (300 x 300 DPI)



Forest Plot for Treatment Effect on OS (All Analyzable Patients, n = 176)

203x154mm (300 x 300 DPI)

EST C-0590
Mayo/NCCTG 88-74-51
(REVISED)

EASTERN COOPERATIVE ONCOLOGY GROUP

Double-Blind Phase III Trial of Effects of Low-Dose 13-Cisretinoic Acid on Prevention of Second Primaries in Stages I-II Head and Neck Cancer

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STUDY PARTICIPANTS

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Mayo/NCCTG Entire Group

STUDY ACTIVATED

February 1991

Addendum #1, 7/91 - RTOG deleted; RT summaries requested;bone x-ray requirement clarified; L. Kalis study statistician; WCCC Sample Bank phone number: Index, pp. 3, 4, 6, 11, 12, 14, 21, 22

Addendum #2, 11/91 - René Gonin study statistician; eligibility extended to 180 days after definitive treatment; Forms submission clarified: pp. 3, 4, 14, 21

Addendum #3, 7/92 - Schema eligibility, eligibility criteria 3.110 clarified, and section 4.0 clarified: p. 4

Addendum #4, 2/93 - Address to send correspondence changed from Ops Office to Data Management Office; Stat Ctr, Data Management Office, and NCI telephone number changes; Study Co-Chair added; Treatment assignments preassigned; ECOG Stat Center should be notified by phone; Clarification on drug supply (p. 3, 4, 6, 9, 10, 11, 17, 18).

Addendum #5, 5/94 - Diane Fairclough, Dr.PH. study statistician; eligibility extended to 730 days after definitive treatment; Mega vitamin dose use discontinued; Typo's fixed; Section 7.2 clarified; ECOG ADR reporting reformatted and NCI ADR FAX number added; Address telephone number and instructions for serum sample handling updated; required Retinoic assays eliminated for new enrollees; forms submission schedule revised; sample size reduced; Statistical considerations updated; renumbered sections and pages as needed; revised eligibility checklist.

EST C-0590
Rev. 2/93, Add. #4
Rev. 5/94, Add. #5

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1.0 INTRODUCTION AND BACKGROUND

Patients with localized squamous cancers of the head and neck, that is, stages I and II, have a high rate of cure with appropriate radiation therapy and/or surgery (1). However, their survival is often decreased because of second primary cancers. These cancers may be synchronous or metachronous. In a study from the Boston VA Medical Center of 1,796 patients with head and neck cancers, 401 (22.3%) developed a subsequent malignancy. The median time to development of the second cancer was 2.6 years with a range of 0 to 21 years (2). A compilation of patients from four large series totalling over 1,000 patients has shown that the total incidence of second primaries is approximately 16% (3,4). Approximately 8% of these are other squamous cell cancers of the head and neck, 2% esophagus, 2% lung, and 4% others. The most common histology is a second squamous cell cancer.

In a study by Moore (5) 203 patients with head and neck cancer were followed for an extended period of time. The incidence of second cancers was 6% in patients who stopped smoking and 40% in patients who continued to smoke. The majority of these were cancers of head and neck sites. One obvious way to decrease second primaries is to have patients discontinue smoking, although this is met with little enthusiasm in this patient population. A second approach may be intense screening, although often by the time there is development of symptoms and signs of some head and neck cancers, esophagus cancers and lung cancer, the cancer is often beyond a curable size. Carcinogens are applied over a wide area and thus epithelial changes leading to dysplasia or carcinoma can occur over a wide region. The term "field cancerization" is often used. Retinoids have been shown to stabilize squamous epithelium and may be useful in preventing cancers, particularly those known to have a high likelihood of recurring.

The term "retinoids" is used to include natural compounds with Vitamin A activity and synthetic analogues of retinol (6,7,8). The major source of Vitamin A in the diet is Beta-carotene. This is converted to retinol primarily in the intestinal mucosa. In the mucosal cell retinol is reesterified and retinyl esters are associated with chylomicrons and transported into the circulation. Retinol esters are metabolized by the liver, and it contains the majority of the body's reserves of Vitamin A. When Vitamin A is mobilized from liver storage, it is transported in the plasma as retinol bound to retinol-binding protein. Many tissues in animal and man contain an intracellular protein which can specifically bind retinol. Retinoic acid is absorbed through the portal system and transported in plasma by albumin.

"In vitro" retinoids can reverse keratinization of Vitamin A-deficient trachea in hamsters (6,7,8). In the mouse, retinoids can reverse the hyperplasia and squamous metaplasia induced by carcinogens. Although the exact mechanism of action is unknown, the most likely mechanism is that retinoids can affect the expression of genes involved with cell differentiation and proliferation.

Retinoic acid binding proteins have been studied in human squamous cell carcinomas and normal epithelium (9). The amount of cellular retinol and cellular retinoic acid binding proteins were found to be significantly higher in tumor tissue than in normal tissue. Some have shown that highly differentiated carcinomas contain retinoic acid binding protein whereas less differentiated cancers do not (10). It has been shown that retinol activates a cyclic-AMP dependent protein kinase and that this may be the target for the growth inhibitory effects of retinoic acid (11).

Retinoids have been studied in premalignant lesions by several investigators. Leukoplakia can be a precancerous lesion particularly if it is dysplastic. Retinols have been shown to reduce leukoplakia in humans. Koch treated 90 patients with leukoplakia with either isotretinoin (13-cis retinoic acid), tretinoin or etretinate at 70 mg/kg for 8 weeks (12). The response rates were higher

for isotretinoin (87%) and etretinate (91%) than for tretinoin (59%). Most responses occurred within three weeks. Over half the patients relapsed after discontinuing the drug. In a second study, Koch treated 48 patients with either oral etretinate or oral plus local etretinate paste (13). The overall response rate to the single treatment was 71.5%, to the combined treatment - 83.5%. Approximately half of patients maintained the response at 2 years. Other trials of oral etretinate (14) and topical isotretinoin (15,16) have demonstrated high response rate with acceptable toxicity.

Hong et al (17,18) in a double-blind study randomized patients to 13-cis retinoic acid (13-cRA) versus placebo. 13-cRA was given daily for three months at a dose of 1 to 2 mg/kg. Sixty-seven percent of patients with oral leukoplakia had a partial or complete response to 13-cRA as compared to 10% with the placebo. Adverse side effects included conjunctivitis, cheilitis, and hyperlipidemia, requiring dose reduction in 6 patients. Meyskens et al (19) also noted objective responses in 3 of 5 patients with preneoplastic lesions treated with 13-cRA.

13-cRA has been studied in patients with advanced cancers. Meyskens et al (19) treated patients with a variety of cancers with 13-cRA at 3 mg/kg/day. Of 24 patients with squamous epithelial cancers, 25 percent had a response, including minor responses. Toxicity included mild arthralgias in 15%, cheilitis, dermatitis, and conjunctivitis to a mild degree in 95%, mild emotional changes or headaches in 25%, and increase in triglyceride level in 25%. The headaches and emotional lability were seen mainly in patients who were treated with high doses.

Band et al (20) did a phase I study of 13-cRA in patients with advanced head and neck cancer. Patients received a single daily dose for 3 months in doses ranging from 20 to 120 mg/m^2/day. At drug doses greater than 60 mg/m^2, headaches, urethritis, dermatitis, and ataxia were unacceptable side effects, and the authors recommended utilizing lower doses. In another phase I trial by Gold et al (21) using 13-cRA in advanced germ cell tumors, patients were treated with 100 mg/m^2 daily. Toxicity was minimal and no objective responses were seen in these patients. In a third phase I trial (22) patients with myelodysplastic syndromes were treated with 13-cRA at doses from 20 to 125 mg/m^2/day. The only dose limiting toxicity was hepatotoxicity at the highest dose level. Other side effects which included cheilosis, hyperkeratosis, stomatitis, and elevation of serum triglyceride levels were minimal. Responses were seen in 5 of 17 patients. The authors concluded that the optimal dose was 120 mg/m^2.

Acute and chronic toxicities with varying doses of isotretinoin (13-cis retinoic acid) have been well described (7,23,24). Meyskens has devised a detailed toxicity scale and recommended dose adjustments (7). Strauss et al treated 150 patients with acne at three different dose levels (0.1, 0.5, 1.0 mg/kg/day) (24). There was excellent response at all doses, although 42% of patients at the lower dose required retreatment. The most common toxicities were those previously described to the skin and mucous membranes.

2.0 OBJECTIVES

In this trial we propose to utilize 13-cRA to prevent dysplastic changes and second malignancies in patients with squamous cell carcinoma of the head and neck regions who have a high probability of cure from their primary cancer. Comparisons between patients treated by 13-cRA and patients receiving placebo will include:

2.1 The time to diagnosis of second primary for the treatment versus control groups.

2.2 Survival time for the treatment versus control groups.

2.3 Secondarily, the cost-benefit ratio for 13-cRA will be analyzed by assessing the toxicities of 13-cis retinoic acid treated patients in comparison to those experienced by placebo treated patients.

3.0 SELECTION OF PATIENTS

3.1 Conditions for Eligibility

3.11 Informed consent is obtained, the approved form is signed, and on file at the institution.

3.12 Histologically confirmed squamous cell carcinoma.

Rev. 7/91
Rev. 11/91 3.13 **All chest x-rays and cervical spine x-rays done after definitive treatment within 35 days prior to randomization and all hematology and chemistries done within 2 weeks prior to randomization.**

3.14 The following sites and stages of cancers will be eligible (AJC 1980 Appendix).

3.141 Oral Cavity

1. T1 NO
2. T2 NO

3.142 Oropharynx

1. T1 NO
2. T2 NO

3.143 Hypopharynx

1. T1 NO

3.144 Larynx

1. T1 NO
2. T2 NO

3.15 Age greater than 18 years.

3.16 ECOG performance status 0 or 1.

3.17 Patients must have adequate bone marrow, hepatic and renal function defined as follows:

3.171 WBC $\geq$ 3,500/mm^3, Platelets > 125,000/mm^3.

3.172 Total Bilirubin < 2 mg%, Serum creatinine < 2.5 mg%.

3.173 Serum SGOT < 2x normal, Alkaline Phosphatase < 2x normal.

3.174 Fasting Serum triglyceride levels < 210 mg %.
3.175 Fasting cholesterol < 350 mg %.

3.18 Patient may not be under systemic therapy for hyperlipidemia or have symptomatic arteriosclerotic coronary artery disease or have undergone coronary bypass surgery.

Rev. 11/91 Rev. 5/94 3.19 The patient must have completed primary treatment of their cancer with surgery and/or radiation therapy within **730** days prior to randomization.

Rev. 7/92 3.110 The patient has had surgery and/or radiation therapy as outlined in Sections 5.0 and 6.0, and has been rendered disease-free.

Rev. 5/94 3.111 If currently receiving, patient must discontinue mega vitamin doses

3.2 Conditions for Ineligibility

3.21 Women of child bearing potential.

3.22 Patient with severe coronary artery disease (Class III-IV New York Heart Association.)

3.23 Histology other than squamous cell carcinoma.

3.24 Stages and sites other than those listed in Section 3.14.

3.25 Distant metastases.

Rev. 11/91 Rev. 5/94 3.26 Completion of previous treatment for their primary cancer with radiation, or surgery (except for biopsy) more than **730** days ago.

Rev. 11/91 3.27 Prior, synchronous, or concurrent malignancy except basal cell skin cancer.

Rev. 11/91 3.28 Failure to be rendered disease-free of primary tumor (includes positive surgical margins).

3.29 The patient has had prior therapy other than that outlined in Sections 5.0 and 6.0 of the protocol.

4.0 RANDOMIZATION PROCEDURES

Rev. 7/91 Rev. 5/94 **Note: A signed HHS 596 form for this protocol must be on file at the ECOG Operations Office, at the NCCTG Operations Office (NCCTG members only), or at the Mayo Clinic before any institution may enter a patient.**

Rev. 2/93 **Current FDA 1572 forms (modified version found in Appendix III) must be received by the ECOG Statistical Center Data Management Office for all investigators, regardless of group affiliation, planning to enter patients on study (see Section 10.110). Drug will not be shipped unless the necessary paperwork has been received. Note: This form must be renewed annually while the study is ongoing.**

Rev. 7/92 Rev. 5/94 **Patients will be admitted only after the pretreatment evaluation is completed and the eligibility criteria are met. Randomization must be done within 730 days following completion of surgery and/or radiation. Treatment must begin within 10 days of randomization.**

Rev. 5/94 **A pharmacy agreement form (Appendix VI) must be on file at the ECOG Statistical Center Data Management Office before drug can be shipped.**

4.1 Randomization

Participating patients, medical staff and ancillary medical staff will remain blinded as to the assignment of 13-cisretinoic acid or placebo until completion of the study. The study medication will be sent to the hospital ward by the pharmacist. In the event of an emergency or severe adverse reaction necessitating identification of the medication (13-cisretinoic acid or placebo) for the welfare of the patient, every attempt should be made to notify the ECOG Statistical Center Data Management Office (617-632-3610). Breaking the code will place the patient off study.

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4.11 Identification of Pharmacist

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Patients cannot be randomized to this study unless the ECOG Statistical Center Data Management Office has received the form in Appendix V which contains the following:

4.111 Responsible pharmacist's name

4.112 Pharmacy address

4.113 Pharmacy phone number

4.2 ECOG Randomization

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To randomize a patient, the investigator will telephone the Central Randomization Desk at the ECOG Statistical Center Data Management Office (617) 632-3610. The following information will be requested:

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4.21 Protocol Number

4.22 Investigator Identification

4.221 Institution name and/or affiliate

4.222 Investigator's name

4.23 Patient Identification

4.231 Patient's name or initials; and chart number

4.232 Patient's Social Security number

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4.233 Patient Demographics:
- 4.2331 Gender
- 4.2332 Race
- 4.2333 9-digit zip code
- 4.2334 Method of Payment
- 4.2335 Birthdate (MM/YY)

4.24 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. The randomization specialist will ask all questions from this checklist at the time of randomization.

4.25 Stratification Factors

Patients will be randomly assigned to treatment. Stratification variables, in addition to institution, include the following:

4.251 Region (oral cavity, oropharynx, hypopharynx, larynx)

4.252 Smoking history (never smoked, smoked previously, current smoker)

4.253 Alcohol history (never drank, discontinued drinking, continues to drink)

4.26 An ECOG sequence number will be provided to the institution. This sequence number will appear on all bottles of the drug that the patient will receive.

Rev. 2/93 4.27 Treatment assignments have been preassigned randomly to ECOG sequence numbers. The ECOG Statistical Center will have copies of the list of treatment assignments associated with ECOG sequence numbers.

Rev. 2/93 4.28 The ECOG Statistical Center Data Management Office will ship drug to the responsible pharmacist.

Rev. 7/91 4.3 Mayo/NCCTG Randomization

To randomize a Mayo patient, call the Mayo/NCCTG Randomization Center (4-2753 or 4-3295) Monday through Friday, 8:00 a.m. to 4:00 p.m. (CST). NCCTG investigators will telephone the Mayo/NCCTG Randomization Center (507) 284-4130 (8:00 a.m. to 4:00 p.m. CST Monday through Friday). The Mayo/NCCTG Randomization Center will obtain and confirm all eligibility criteria and information as per Section 4.1, *ECOG Randomization*. The participating group randomization office will then contact the ECOG Statistical Center Data Management Office to enter the patient, after which the group office will contact the institution to relay the ECOG sequence number for that patient. The ECOG Statistical Center Data Management Office will forward a confirmation of treatment assignment to the Mayo Clinic or NCCTG Operations Office for routing to the participating institution.

Rev. 7/91 4.4 Cancellation Guidelines

If a patient does not receive protocol therapy, the patient may be cancelled. Reasons for cancellation should be submitted, as soon as possible, in writing, to the ECOG Statistical Center or NCCTG Operations Office or Mayo Clinic as appropriate. The ECOG Statistical Rev. 2/93 Center should also be notified by phone (617) 632-3610 so that no additional study drug will be shipped. Data will be collected on all cancelled patients (see Section 12.0). **Note: A patient may be cancelled only if no protocol therapy is administered. Once a patient has been given protocol treatment, all forms should be submitted.**

5.0 SURGERY (Prior to randomization)

Table 1 indicates the following surgery that is acceptable for the primary and neck. If a surgical approach is chosen, the extent of surgical resection will be dictated by the extent of the tumor at the time of initial evaluation. The primary lesion must be widely excised using accepted criteria for adequate excision depending on the region involved. The surgical margins must be negative

for the patient to be acceptable for this study. All patients undergoing neck dissection may undergo a radical or a modified radical neck dissection at the discretion of the surgeon.

Table 1: Therapy for stage I, II head and neck cancers prior to cis-retinoic acid

Management of Primary

1. Surgical excision with wide margins
2. External beam irradiation
3. Brachytherapy

Management of Necks

1. No treatment required (optional)	2. Neck dissection or primary irradiation
Oral tongue - T1 < 1.5 cm	Oral tongue - T1 > 1.5 cm, T2
Alveolar ridge - T1, T2	Floor of mouth - T1 > 1.5 cm, T2
Floor of mouth - T1 < 1.5 cm	Buccal cavity - T2
Buccal cavity - T1	Tonsilar pillar - T1 > 1.5 cm, T2
Tonsilar pillar - T1 < 1.5 cm	Tonsil - T1 > 1.5 cm, T2
Tonsil - T1 < 1.5 cm	Base tongue - T1, T2
True cord - T1, T2	Supraglottic larynx - T1, T2
Soft palate - T1 < 1.5 cm	Oropharyngeal wall - T1, T2
	Pyriform sinus - T1
	Soft palate - T1 > 1.5 cm, T2

6.0 RADIATION THERAPY (Prior to randomization)

6.1 Teletherapy

6.11 Physical Factors

Linear accelerator of 4-6 MeV energy is preferred, but up to 10 MeV is acceptable. Electron energies of 6-25 MeV may be utilized as a component of teletherapy treatment. Machines should operate at 80-100 cm SSD or 100 cm SAD. Cobalt 60 unit is acceptable, if operating at 80 cm SSD (Varian Clinic 4-80 SSD). The acceptable dose rate is 180-200 cGy per day. Electron boosts are also allowed.

6.12 Treatment Plan Required

Tumor doses will be expressed in cGy calculated at the center of the tumor volume when lateral opposed portals are used. For elective neck irradiation, the depth for an anterior field will be calculated at 3.0 cm. When "mediastinal-T" portals are used, the depth dose will be calculated at 5.0 cm. When the contour of the neck will result in a significant dose variation, tissue compensators or appropriate field reductions should be used. The radiation dose across the original tumor volume must not vary more than ± 10% within that volume. Spinal cord total radiation doses must not exceed 4500 cGy with 180 rad fractions or 4000 cGy with 200 rad fractions.

6.13 Portal and Treatment Volume Definition

A combination of lateral opposed fields, anterior and lateral wedged fields, or beam-directed multiple fields will be used for the primary tumor site at the discretion of the investigator in the case. A single anterior field will be used to treat the neck below the field for the primary tumor, except for hypopharyngeal lesions, when use of a mediastinal "T" port should be considered. A spinal cord block should be placed either at the mid-line of the anterior lower neck and supraclavicular field or at the lower posterior corners of the lateral field, at the junction of the upper and lower fields. Electron beams or A-P photon beams can be used to boost the neck as needed.

6.14 Dose Definition and Schedule

Tumor doses will be expressed in cGy calculated at the center of tumor volume. The radiation dose to the tumor volume post-operatively will be 5000-6000 cGy in 5 to 6-1/2 weeks. If the neoplasm approaches the surgical margin(s) the tumor dose should be at least 6000 cGy; if the margins are involved, a dose of 6500-7000 cGy is required. The dose to the lower neck if used will be a dose of 5000 cGy at 3.0 cm in 5 to 5-1/2 weeks. Primary radiotherapy alone should deliver from 6500 cGy to 7000 cGy to the primary tumor if using teletherapy alone. If an implant boost is planned, the total tumor dose may be higher (see 7.2).

Five fractions per week of 180 to 200 cGy each will be employed. The total time will depend on whether post-operative irradiation (approximately 5-7 weeks) or primary irradiation (6 to 8 weeks) is used. A continuous course should be maintained if at all possible, but if the radiation reaction requires an interruption of therapy, this should be kept to a minimum and reported.

6.2 Brachytherapy

6.21 Physical Factors

The most commonly used permanent implant source is encapsulated 125 Iodine (T 1/2 60d, Energy 30 KeV) with seed strengths between 0.3 and 0.5MCI. These sources may be used alone with an applicator inserter (MICK, etc.) or in absorbable suture (Vicryl) carriers. The most commonly used removable brachytherapy source is 192 Iridium seeds, regular spaced in nylon ribbon carrier. Both high intensity (^{125}I) and (^{137}CS) may also be used.

6.22 Dose Definition

Tumor dose rate for removable implants should be between 40 and 100 cGy per hour. If the implant is performed near the spinal cord, dose rates at the most proximate spinal cord points should also be calculated and listed.

6.23 Allowable Dose and Dose Rate Modifications

Removable (^{192}Ir, ^{125}I, ^{137}Cs interstitial implants may be used. Permanent (^{125}I) implants at the surgical margins or in the resection bed are also acceptable. In general, total ^{125}I tumor doses in unirradiated patients at one year should be

approximately 10000 cGy, if using the specific gamma ray factor of 1.1 in the calculations.

When preimplant external beam radiation doses of 5000 cGy or more have been used, the total dose from a permanent implant should be limited to approximately 6000-8000 cGy. Removable ^{192}Ir, ^{125}I, or ^{137}Cs interstitial radiation doses when used as a booster after a 4000-5500 cGy external beam radiation course should be limited to 2500 to 3500 cGy (to the implant volume) depending on the external dose, volume implanted, site, and expected tissue tolerance. Doses up to 7000 cGy in 6-7 days may be delivered when an implant alone is used.

6.3 Institution Profile

6.31 Radiotherapy must be given at an institution which has been evaluated and accepted by the Radiologic Physics Center (RPC), in Houston, Texas.

6.4 Expected Toxicities

6.41 Late RT Toxicities should be recorded over the date on which they occur. Space is provided on the Flow Sheet.

7.0 DRUG TREATMENTS

7.1 Drug Administration

13-cis retinoic acid will be dispensed in 3.75 mg and 5 mg gelatin capsules. The placebo will be dispensed in identically appearing capsules and dosage. This will be a double-blind study. **Patients should be instructed to take 2 capsules once daily at bedtime. Treatment must begin within 10 days of randomization.**

Starting dose will be based on patient weight:

Patient's Weight	Starting Dose
≥ 60 kg	10 mg per day *
< 60 kg	7.5 mg per day*

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Starting dose is approximately 0.15 mg/kg/day. It is strongly suggested that patients not take any additional vitamins while on study.

*See Section 7.4 for dose reduction.

7.2 Duration of Therapy

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Therapy will continue daily for a total of 2 years or until toxicity limitations have been met or the patient has developed a second head and neck primary. Recurrence of the first head and neck primary, development of metastatic disease or a second malignancy unrelated to head and neck cancer will not be criteria for discontinuing the drug.

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The ECOG Statistical Center should be notified by phone (617-362-3610) if a patient goes off study prior to 2 years, so that no additional study drug will be shipped.

7.21 Patients who develop diffuse idiopathic skeletal hyperostosis (DISH) syndrome will have assigned treatment discontinued. (See Section 7.41)

7.3 Dose Escalation - None

7.4 Dose Reduction

DRUG MODIFICATION AND TOXICITY

Grade of Toxicity*	Dosage Modification
1	No change.
2 or 3	If positive in one or more categories, dose is reduced by 50%. Dose is to be maintained at 50% for the remainder of the study.
4	Discontinue therapy until toxicity resolves to grade 2 or 3 and then reinstitute drug at 50% of original dose.

Rev. 5/94 * See Toxicity Scale, Appendices IV and V.

7.41 Patients who develop myalgias, arthralgias, or bone pain will have appropriate bone films performed. If DISH is present, the assigned treatment will be discontinued.

Rev. 5/94 7.5 Adverse Reaction Reporting Regulations

ADR Reporting and toxicities should be graded and recorded according to the toxicity scale for 13-Cis Retinoic Acid (Appendix IV). Other toxicities not on the 13-Cis Retinoic Acid scale should be graded and recorded according to the Common Toxicity Scale (Appendix V).

This protocol contains the IND agent 13-Cis Retinoic Acid.

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7.51 The following adverse reactions must be reported to ECOG and DCPC in the manner described below. In addition, your local IRB should be notified.

	Gr 2-3 unusual[2]	Grade 4 & 5 unexpected[2]	Grade 4 expected[3]	Death due to Rx or within 30 days of Rx[1]
Call to DCPC within 24 hours		X		X
Call to ECOG within 24 hours		X		X
ECOG ADR Form to DCPC within 10 days	X	X	X	X
ECOG ADR Form to ECOG DM Office within 10 days	X	X	X	X

1 Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported
2 Any unexpected toxicity not reported in the literature or the package insert must be reported.
3 Grade 4 expected myelosuppression need not be reported but should be documented on flow sheets.

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DCPC Telephone Number: (301) 496-8541

DCPC ADR FAX: (301) 496-8667
DCPC Mailing Address:
National Cancer Institute
DCPC/Corb, Room 300
6130 Executive Boulevard
Bethesda, MD 20892

ECOG telephone number: (617) 632-3610

ECOG Mailing Address:
ECOG Data Management Office
Attn: ADR
303 Boylston Street
Brookline, MA 02146-7215

ECOG required ADRs to be reported on the Adverse Reaction (ADR) Form For Investigational Drugs (#391RF). The form must be signed by the treating investigator.

7.52 Non-Treatment Related Toxicities

If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the ECOG Flow Sheets which are submitted to the ECOG Statistical Center Data Management Office (ATTN: DATA) according to the Records To Be Kept Section (12.0). This does not in any way obviate the need for reporting the toxicities described above.

Mailing address for ECOG ADR reporting is:

ECOG Statistical Center
Data Management Office
303 Boylston Street
Brookline, MA 02146-7215
ATTN: ADR

Rev. 2/93 Rev. 5/94 7.53 NCCTG/Mayo:

NCCTG/Mayo Institutions	Gr 2-3 unusual[2]	Grade 4&5 unexpected[2]	Grade 4 expected[3]	Death due to Rx or within 30 days of Rx[1]
Call DCPC within 24 hours[4]		X		X
Call ECOG within 24 hours		X		X
Call NCCTG within 24 hours[5]		X		X
ADR form to NCCTG within 5 days	X	X	X	X
NCCTG Operations Office will send:				
ADR Form to DCPC within 10 days[4]	X	X	X	X
ECOG ADR Form to ECOG DM Office within 10 days	X	X	X	X

1 Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.
2 Any unexpected toxicity not reported in the literature or the package insert must be reported.
3 Grade 4 expected myelosuppression need not be reported but shoudl be documented on flow sheets.
4 See Section 7.51 for address and phone number.
5 After hours, notify NCCTG the next working day (507) 284-4130.

NOTE: ECOG required ADRs to be reported on the Adverse Reaction (ADR) Form For Investigational Drugs (#391RF). The form must be signed by the treating investigator

7.6 Supportive/Ancillary Therapy

All drugs (including doses) and transfusions given a patient during this protocol study will be recorded on the Flow Sheet.

7.7 Drug Levels

Rev. 5/94 For patients enrolled prior to Addendum #5, serum levels will be drawn prestudy, 6, 12 and 24 months for 13-cRA analysis. This will be done by HPLC (high performance liquid chromatography) under the supervision of Dr. Yei-Mei Peng. **NOTE: Patients randomized to C0590 after activation of Addendum #5 should NOT submit serum levels for 13-cRA analysis.** The goals of the drug level measurements are to:

7.71 Assess compliance.

7.72 Evaluate the relationship between serum level and toxicity.

7.73 Assess the relationship between serum level and response.

7.8 Instructions for serum 13-cRA Specimen Handling

Rev. 5/94 Patients randomized to C0590 after activation of Addendum #5 should NOT submit laboratory samples for 13-cRA analysis. For patients enrolled on C0590 prior to Addendum #5, all samples should be submitted (baseline, 6-month, 12-month, 24-month).

NOTE: APPROPRIATE FREEZER TUBES AND LABELS MUST BE USED. iF YOU DO NOT HAVE THESE AVAILABLE, CONTACT THE ECOG PCO AT (303) 239-3500*.

7.81 1. Draw 10 ml blood in green top (lithium and heparin) tube.

2. Wrap tube in foil ***immediately*** to protect serum from light. *Process sample immediately.*

3. Spin down to separate plasma.

Rev. 5/94 4. Transfer plasma in 1.8-ml aliquots to 2-ml polypropylene freezer tubes (NUNC or similar) wrapped in foil. Label the sample with the labels provided by the ECOG PCO, filling in the patient's name, ECOG sequence number, date and time drawn, and time-point of sample. Wrap the sample in foil.

Note: To ensure integrity of the sample and to allow for adequate storage space, plasma MUST be deparated from sample and submitted in the freezer tubes outlined above.

Rev. 5/94 5. **AGAIN, USING THE LABELS PROVED, LABEL EACH TUBE OVER THE FOIL FILLING IN THE INFORMATION AS INDICATED IN #4, PAGE 14.**. Freeze at -20°C until shipment.

Note: In order to save shipping expenses, samples may be stored at your institution and sent in batches to Dr. Peng's lab. However, in order to store the samples for more than 24 hours, they MUST be stored in a -70°C freezer.

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6. Send *C0590 Serum Sample TransmittalForm* inside the package, with copy sent at the same time to the ECOG Statistical Center Data Management Office. Include the date and time of the serum draw and date and time of the last dose of treatment prior to the draw on the form (if applicable). **Ship Monday - Wednesday via overnight mail or courier**
Samples must be packed in a styrofoam shipping container, completeled filled with dry ice, and sent to:

Dr. Yei-Mei Peng
Arizona Cancer Center
University of Arizona
1515 N. Campbell Avenue
Tucson, AZ 85724

Notify Dr. Peng (602)-626-2332) prior to shipment.

Institutions will make their own shipping arrangements and provide their own supplies. Institutions will be also be responsible for shipping expenses. *Label shipping containers in clearly visible place "FREEZE IMMEDIATELY UPON ARRIVAL".*

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If you have any questions about this change, please contact the Pathology Coordinating Office (303-239-3500)

* If you do not have access to 2-ml freezer tubes, contact the ECOG PCO at (303) 239-3500 to request them. The PCO should be contacted with adequate time to ship the samples regular mail. A Federal Express account number will required from any institution requesting that freezer tubes be shipped overnight mail.

8.0 MEASUREMENT OF EFFECT

8.1 Disease Activity

Disease activity will be recorded in the Disease Activity Section of the Flow Sheet according to the Visit Parameter Table found both in Section 9.0, STUDY PARAMETERS, and on page 7 of the Flow Sheet.

8.11 Disease Activity by Site

8.111 Study Entry

At the time of study entry, the primary site, regional nodes, chest and all other sites evaluated must be free of disease and recorded as:

1 = no evidence of disease,

8.112 Subsequent Evaluation of Organ Site Involvement

After study entry, disease activity evaluations will be made and recorded by using the following criteria and designated codes:

1 = **No evidence of disease**.

2 = **Equivocal Evidence of Disease**. This rating will be assigned where an examination remains abnormal in such a way as to preclude an unequivocal statement that tumor is not present.

6 = **Progressive Disease (P)**. This rating will be assigned where there is the occurrence of a new lesion, or the progression of any osseous lesions. Weight loss of ≥15% from beginning of treatment will also be considered a sign of progression.

8.2 Second Primary

The site and histology of any second primaries will be recorded. All second primaries must be biopsy proven.

8.3 Time to Second Primary

Time to second primary will be measured from the date of randomization to the date of proof of second primary.

8.4 Patterns of Recurrence

The location of and time of each recurrence will be documented.

8.5 Survival

Survival time will be measured from the date of randomization to the date of death. All patients registered will be followed for survival.

8.6 Evaluability

All patients who start treatment will be evaluable for second primary, local recurrence, distant metastases and toxicity.

8.7 Postmortem Examination

Postmortem examination will be carried out whenever possible, and a copy of the autopsy report sent to the *appropriate group data collection center for routing to the ECOG Statistical Center.*

9.0 STUDY PARAMETERS

9.1 The following table indicates the required study parameters to be recorded on the Flow Sheet at patient visits during pretreatment, treatment, and follow-up periods.

Rev. 11/91 All chest x-rays and cervical spine x-rays must be done after definitive treatment within 35 days prior to randomization and all hematology and chemistries done within 2 weeks prior to randomization.

Visit Parameters to be Recorded on Flow Sheet

	PARAMETER	STUDY ENTRY	FOLLOW-UP AT ONE MONTH	FOLLOW-UP[1] VISITS
	Flow Sheet	X	X	X
	Visit date	X	X	X
	Complete history & physical	X	X	X
	Weight	X	X	X
	Alcohol consumption	X	X	X
	Smoking history	X	X	X
	ECOG performance status	X	X	X
	Disease activity by site	X	X	X
	Diagram of primary tumor	X		
	Disease activity - 2nd primary		X	X
Rev. 7/91	Cervical spine x-ray	X		X*
	Chest x-ray	X		q 6 mos.
	WBC	X	X	X
	Hgb	X	X	X
	Hct	X	X	X
	Platelets	X	X	X
	Total Bilirubin	X	X	X
	Calcium	X	X	X
	Alkaline phosphatase	X	X	X
	SGOT	X	X	X
	Creatinine	X	X	X
**	Serum sample for shipping	X		*6, 12 & 24 mos.*
	Triglyceride (fasting)	X	X	X
	Cholesterol (fasting)	X	X	X
	HDL cholesterol	X	X	X
Rev. 5/94	**Toxicity:**			
	Mucous membranes		X	X
	Skin		X	X
	Musculo-skeletal		X	X
	Nausea & Vomiting		X	X
	Diarrhea		X	X
	Hair		X	X
	Bladder		X	X
	Fatigue		X	X
	Headache		X	X
	Other CTC Toxicities		X	X

[1] Follow-up visits will occur at the following intervals: At one month following study entry and then every six monthsuntil five years of post treatment follow-up have been completed. i.e., month 0, month 1, month 6, month 12, month 18,...

* Bone x-ray of lateral cervical spine should be repeated if patients are symptomatic of DISH syndrome.

** Patients randomized to C0590 after activation of Addendum #5 should NOT submit laboratory samples for 13-cRA analysis. For patients enrolled on C0590 prior to Addendum #5, all samples should be submitted. (baseline, 6-month, 12-month, 24-month). Please refer to Section 7.8 for handling and shipping instructions.

10.0 DRUG FORMULATION, TOXICITY, AND PROCUREMENT

10.1 13-Cis Retinoic Acid (NSC 329481)

10.11 Chemistry

13-cis-retinoic acid (13-cis-RA, isotretinoin) is a synthetic retinoid chemically related to vitamin A (retinoic acid). It is the 13-cis isomer of naturally occurring all-trans-retinoic acid. Modification of the terminal carboxyl group of retinoic acid to the cis-configuration resulted in a compound with fewer side effects and enhanced biological activity.

10.12 Mechanism of Action

Vitamin A (retinoids) is required for maintenance of general growth, regulation of proliferation and differentiation of epithelial tissues. Vitamin A and analogues may interact with initiation of cancer by direct interaction with the initiator itself or by enhanced susceptibility to carcinogens during vitamin A deficiency. Antipromotion effects of vitamin A may occur through three mechanisms: (1) inhibition of the enzyme ornithine decarboxylase, a key enzyme in tumor promotion, (2) direct competition with promoting agents for control of cellular differentiation by effects on cellular protein synthesis, or; (3) by blocking the effects of transforming growth factors to prevent expression of malignancy.

10.13 Pharmacokinetics

10.131 Absorption

Following oral administration of 13-cis-RA there is a lag time of 0.5-2 hours before drug is seen in the blood, thought to be a result of slow capsule disintegration. Absorption is rapid after this lag time.

10.132 Distribution

Following absorption, 13-cis-RA is 99.9% bound in plasma to albumin. 13-cis-RA is not stored in the liver.

10.133 Elimination

Following a single oral dose of 3 or 5 mg/kg in patients with advanced cancer, peak plasma concentrations of 200-800 ng/ml and 190-1500 ng/ml, respectively have been noted. Distribution half lives of 1.3-2.4 hours have been noted with a terminal elimination half-life of approximately 25 hours. Area under the curve values are quite variable suggesting variable systemic absorption.

The major metabolite of 13-cis-RA after oral administration is 4-oxo-13-cis-RA. This metabolite may be conjugated with glucuronic acid. Following this oxidative metabolism in the liver the drug and its metabolites appear to be excreted in feces via the bile. Enterohepatic circulation appears to occur.

10.14 Tumor Activity Data

10.141 Animal

Experiments with carcinogen induced neoplasms have shown retinoids to inhibit development of tumors in bladder, esophagus, liver, and oral sites. Data in colon cancer is inconclusive and dependent on the carcinogen used.

10.142 Human

Epidemiological studies in humans have suggested vitamin A (or vitamin A analogues) to be protective in cancers of the head and neck, lung, breast, GI tract, cervix, bladder, prostate.

Preliminary reports have shown some activity of retinoids in the treatment and prevention of basal cell carcinomas, mycosis fungoides, and oral leukoplakia.

10.15 Toxicity

10.151 Animal

Corneal ulcers and opacities, elevated alkaline phosphatase, long bone fractures, focal calcification, fibrosis, inflammation of the myocardium, calcification of coronary and mesenteric arteries, pheochromocytonia, adrenal medullary hyperplasia, teratogenicity.

10.152 Human (approximate incidence)

10.1521 Mucocutaneous. Cheilitis (inflammation of the lips, 90%), dry mouth, epistaxis, pruritus. Hair thinning, skin fragility, and photosensitivity occurs in 5-10%.

10.1522 Metabolic. Hypertriglyceridemia (25%); mean triglyceride level increases of 45-50 mg/dl have been noted during chronic therapy, 17% may have triglyceride levels of 200-600 mg/dl after receiving 1 mg/kg doses for 20 weeks. Effects appear dose related and reverse upon discontinuation of therapy. Significant increases in cholesterol and low-density lipoprotein cholesterol and decreases of high-density lipoprotein cholesterol; it is not known whether these changes in plasma lipoproteins increase the risk of cardiac disease.

10.1523 Musculoskeletal. Bone, joint, or muscle pains occur in about 15% of patients. Hyperostosis (with spine degeneration) has occurred in several patients during long-term (2 years) therapy.

10.1524 Hematologic. Increased erythrocyte sedimentation rate (ESR) occurs in about 40% of patients. About 10-20% of patients

may have a decreased hematocrit or hemoglobin, erythrocyte or leukocyte counts, or a thrombocytosis.

10.1525 Central Nervous System. Lethargy, fatigue, and headache are common. Pseudotumor cerebri associated with headache, visual disturbance, and papilledema has been reported.

10.1526 Gastrointestinal. Anorexia, weight loss, and vomiting have occurred.

10.1527 Hepatic. Hepatic enzyme elevations (10%).

10.1528 Ocular. Conjunctivitis (50%), corneal opacities.

10.1529 Fetal. Fetal abnormalities in women taking 13-cis-RA usually in the first trimester have included: hydrocephalus, microcephaly, malformation of the external ear, cardiac abnormalities, and spontaneous abortions.

10.1530 Overdose. Effects in humans is not known.

10.16 How Supplied

Rev. 2/93

10.161 The active drug will be provided in capsules containing 3.75 mg or 5 mg of 13-cis RA. Placebo capsules will be identical in appearance. Each bottle should contain enough capsules for a 1 month supply.

10.162 One three-part label is attached to each bottle.

10.1621 Description of Label

The label is a three-part label, the first two portions of which are identical. The third portion of the label is masked and contains the identity of that patient's treatment, so that it could be available in emergency situations. **The second and third portions of the label must be removed from each bottle prior to dispensing them to the patient.** The portions should be kept with the patient's study records, then sent, still sealed, with the copies of the flows that correspond with those cycles to the respective group data offices per Section 12.2. Receipt of unsealed labels will put the patient off study. An unsealed label is acceptable only after treatment unblinding.

10.17 Method of Storage

Store at 15-30°C in light resistant containers.

10.18 Preparation, Administration, Stability

Oral administration. The capsules contain parabens as preservatives and are contraindicated in paraben sensitive patients.

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10.19 Method of Procurement

A pharmacy agreement form (Appendix V) must be on file at the ECOG Statistical Center Data Management Office before drug can be shipped.

All drug supplies for this study will be obtained through the ECOG Statistical Center Data Management Office. Drug will be sent out only for patients enrolled in the study. Four six-month (six bottle) batches will be sent. The standard drug ordering system will not be used. In its place is the following:

10.191 Initial Supply

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The Data Management Office is automatically notified of all newly registered patients. Since patients are expected to initiate treatment within 10 days of randomization, this initial supply will need to get to the patient immediately.

10.192 Subsequent Supplies

The other three six-month sets will automatically be sent out a minimum of 2 weeks before the patient will need them.

10.193 Mailing Address

Rev. 2/93

If there is a turnover in the responsible investigational drug pharmacist, please notify the ECOG Statistical Center Data Management Office by resubmitting the Pharmacy Agreement form in Appendix V.

10.194 Disposal of Unused Drug

If a patient goes off-study and has the balance of a six-month supply in their possession, this supply should be returned to:

Mr. Ted Miller
ERC Bioservices Corporation
649J Lofstrand Lane
Rockville, MD 20850
(301) 762-1862

10.110 Availability

To obtain study drug, investigators must submit a current (signed within the last 12 months) Form FDA 1572 (Appendix III) to the ECOG Statistical Center Data Management Office.

Rev. 2/93

Drug will not be shipped unless the necessary paperwork has been received.

Rev. 5/94 **11.0 STATISTICAL CONSIDERATIONS**

11.1 Sample Size

The main endpoints of this study are the number of second primaries and the median time to occurrence of second primary. The sample size requirements are based on a cure rate model first proposed by Berkson and Gage (25). The hypothesized rate in the control arm is an 80% rate of freedom from second primary and, for those who develop a second primary, a 2.4 year median time to second primary. The alternative hypothesis is that the asymptotic rate of freedom from second primary will be 90% in the 13-cis-retinoic acid arm with median time for second primary when it occurs, of four years. *The results obtained for a one-sided logrank test (power=0.8, alpha=0.05) using an asymptotic approximation for the freedom from second primary are that 2.2 years of follow-up will be required after the accrual of 275 patients if the rate of accrual is 50 patients per year The table below estimates the follow-up time for accrual of 35, 50, and 75 patients per year.*

Actual and Follow-up Time for a 50% improvement in Second Primary Incidence and Increase from 2.4 to 4 Years to Occurrence (N=275, Power=0.8, a=0.05).

Accrual Rate (Patient/Year)	Accrual (Years)	Follow-up (Years)	Total (Years)
35	7.24	1.7	8.9
50	5.50	2.1	7.6
75	3.67	2.1	5.8

11.2 Randomization

A compliance problem may cause difficulties in measurement of efficacy. While blinding the patient to drug can be explained in a consent form, local IRBs would not tell the patient they have a 50% chance of receiving the drug when that is false. Randomization after the run-in period appears to have multiple compliance problems and the run-in would make the results difficult to generalize to medical practice. Thus no run-in period is proposed in this study.

11.3 Statistical Analyses

The main statistical analyses will be the determination of the effect of 13-cis-retinoic acid on second primary rates and time to second primary based on the cure rate model, using second primaries per year of observation, a statistic sensitive to both the number of second primaries and delay in second primaries. If this model does not fit the data then standard Cox analyses may be used. In addition to an analysis including all evaluable patients, a second analysis will be done excluding patients whose second primary occurs in the first 6 months following randomization. It is recognized that a portion of the patients will have an existing second primary not observable at time of initial diagnosis. There is a possibility that 13-cis-retinoic acid may affect development of already existing tumors. However, by excluding the second primaries observed early in the study period, we will be more likely to be evaluating the impact on development of new primaries alone. In addition, relapse-free survival, metastatic-free survival, and survival will be evaluated to determine whether the treatment alters these endpoints in this disease. Toxicity rates and compliance rates will be analyzed by multiple logistic methods with covariates (26, 27, 28); stratification variables, including institution and arm, are treated as covariates. The method of analysis for time to second primary, time to local failure, time to distant metastases, and survival time will be patterned after the Cox-Breslow actuarial analysis for censored survival data with covariates (29, 30). Additional analyses will be guided in part by suggestions and questions of the study chairperson, the ECOG Head and Neck, Biological Therapeutics, and Executive Committees.

Cox analysis will be performed on the measurements of serum levels of cis-retinoic acid using time to development of a second primary tumor and time to experience of a toxic event as the endpoints and cis-retinoic acid level as the time-varying covariate. This analysis will be performed with appreciation that there may be uncertainty as to causality in this analysis.

Analysis of the data with regard to the trade off between toxicity and benefit will only arise if the experimental treatment proves relatively more efficacious than placebo.

Rev. 5/94 11.4 Stopping Rules

The study results will be presented to the ECOG Monitoring Committee after the occurrence of 50%, 75% and 100% of the information expected under the aternative hypothesis. If the accrual is 50 patients per year these anlayses would occur at approximately 4.6, 6.0 and 7.7 years. The critical values for the three analyses will be computed using O'Brian/Fleming boundaries. The recommendation for any stopping decision will go to the ECOG Monitoring Committee for approval.

EST C-0590
Rev. 7/91, Add. #1
Rev. 11/91, Add. #2
Rev. 5/94, Add. #5

12.0 RECORDS AND DATA COLLECTION PROCEDURES

12.1 All study forms have been appended to the protocol. Participating institutions will be responsible for copying them.

12.2 The following materials will be required for this study and are to be submitted to the respective groups according to the following schedule:

	Form	To Be Submitted
	*Eligibility Checklist (non-ECOGinstitutions only)	
	*Staging Worksheet	
	Operative Report (if applicable)	Within 1 week of randomization
	Pathology Report	
Rev. 7/91	Narrative Radiotherapy Summary (if applicable)	
	C-0590 Study Specific Flow Sheet (Both on & Off Treatment)	
Rev. 11/91	ECOG Follow-Up Form (#464) (Parts A,B,C,D,E)	On treatment: Months 1, 6, 12, 18, and 24 Off treatment: Every 6 months if patient is < 5 years from study entry
	*ECOG Follow-Up Form (#464) (Parts A and B)	Every 12 months if patient is > 5 years from study entry
Rev. 5/94	**Serum Sample Transmittal Form including time and date of draw and time and date of last dose prior to the draw (if applicable)	At time of sample submission (Submit original form with the serum sample and forward a copy to the ECOG Data Management Office as defined in Section 7.81.)
Rev. 5/94	Bottle Labels (See Sec 10.1621)	With flow sheets after patient finishes bottle of study drug
	Autopsy Report	At time of death
	Adverse Reaction Form for Investigational Drugs (#391R)	Within 10 days of reportable toxic event as defined in Section 7.5
	Narrative Pathology Report	At time of second primary

* These forms are to be submitted for all cancelled patients according to the above schedule.
**Serum Sample Transmittal Forms are not required for patients randomized after activation of Addendum #5.

12.3 Record Transmittal to Study Statistical Center

12.31 The cooperative group headquarters will be responsible for insuring that all materials include the intergroup protocol number and the patient's ECOG sequence number. Upon verifying this, the material will be mailed to:

ECOG Statistical Center
Data Management Office
303 Boylston Street
Brookline, MA 02146-7215
ATTN: DATA

All forms are to be date stamped upon receipt by the cooperative group.

12.32 NCCTG institutions should submit data for routing to ECOG at the required intervals to:

NCCTG Operations Office
200 First Street, S.W.
Rochester, MN 55905

12.33 Mayo institutions should submit data forms at the required intervals to:

ECOG Statistical Center
Data Management Office
303 Boylston Street
Brookline, MA 02146-7215
ATTN: DATA

13.0 PATIENT CONSENT AND PEER JUDGMENT

All institutional, NCI, FDA, state and federal regulations concerning informed consent and peer judgment will be fulfilled.

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APPENDIX I

Suggested Patient Consent Form

RESEARCH STUDY

I, _____, willingly agree to participate in the study which has been explained to me by Dr. _____. This research study is being conducted by the Eastern Cooperative Oncology Group and by _____.

(Institution)

PURPOSE OF THE STUDY

My doctor(s) have informed me that I have had squamous cell carcinoma located in the head and neck region which has been treated by radiation therapy and/or by surgery with the goal of cure. Patients with squamous cell carcinoma in the head and neck region sometimes develop a second cancer. At this time, there is no known method of preventing the occurrence of a second cancer, although the risk can be reduced by stopping smoking. I have been asked to participate in this study which will study the effects of cis-retinoic acid (a synthetic chemical related to vitamin A) in the prevention of second cancers in patients with squamous cell carcinoma of the head and neck. Studies have shown that cis-retinoic acid has been shown to stabilize squamous cell tissue and may be useful in preventing cancer.

DESCRIPTION OF PROCEDURES

I have two choices at this time:

(1) I could choose not to participate in this study.

2) I could consent to participate in this study which will test the effects of cis-retinoic acid vs. placebo in the prevention of second cancers.

If I agree to participate in this study, I will be placed by chance into one of two groups. (This chance selection process is called randomization and is frequently used in experimental studies.) One group will receive cis-retinoic acid. The other group will receive a placebo, which will be identical in appearance to the cis-retinoic acid. Neither my doctors nor I will know whether I will be receiving cis-retinoic acid or placebo. This is called double-blinding of the study.

If I agree to participate in this study, I will receive cis-retinoic acid or placebo by mouth daily for two years, unless I develop a second cancer or I develop intolerable side effects.

RISKS AND DISCOMFORTS

The side effects can be uncomfortable and some are potentially dangerous or even life-threatening, but will usually clear up once the treatments have ended.

Since this is a research study and the treatments are relatively new, there may be additional side effects which are not known or predictable at this time but which occur at the time of treatment or later.

Cis-retinoic acid may cause a dry mouth, inflammation of the lips, hair thinning, and bone or joint pain. Cases of bone thickening on x-rays have been reported. It has been known to cause a rise in the blood

level of cholesterol and triglycerides that may lead to hardening of the arteries (arteriosclerosis). The red cells, white cells, and platelets in my blood might be lowered, making me temporarily more susceptible to infection, bleeding or feeling tired. Fatigue and headache can occur. Loss of appetite, weight loss and vomiting are rare. It can cause irritation of the membranes around the eyes. My doctors can give me medication to relieve some of these effects.

Cis-retinoic acid can cause fetal abnormalities if taken during pregnancy. I am not currently pregnant or able to become pregnant.

There are no side effects from taking the placebo.

My doctors have advised me that they will take measures to lessen complications and side effects. They will very carefully follow my blood counts and will regularly perform physical examinations and laboratory tests that are necessary to determine my progress and toxicity from these treatments. I will receive x-rays of my spine at the beginning of the study and as necessary thereafter to determine if there has been any thickening of my bones. My condition will be monitored closely and appropriate changes in length of therapy will occur, if necessary.

My doctors will go over at any time any questions I may have regarding my disease and the treatment choices. _____ has discussed this study with me. If I have any questions or if I want to report any side effects, I can reach him/her at phone number _____.

The risks of being a part of this study are due to the side effects of the treatment I will receive and the possibility that no benefit may be realized if I am assigned to the placebo. On the other hand, the benefit is that the treatment may prove to be more effective in preventing recurrence of my disease than other, more standard treatments.

If I agree to participate, I will be responsible for the payment of any charges associated with my participation in this study. These costs may or may not be covered by my insurance company and I am encouraged to consult with my insurance carrier as to whether the costs will be covered.

My participation in this study is voluntary, and I can withdraw from it at any time without jeopardy to my further medical care. A goal of the research treatment is to improve my condition; however, no guarantee of effectiveness can be made. Increased discomfort and toxicity from treatments can result. In the event of physical injury resulting from the research procedures, **(STATE WHAT IS AVAILABLE, E.G.,)**

'medical treatment for injuries or illness is available,'/'only acute or immediate or essential medical treatment - including hospitalization - is available'/'monetary compensation is available for wages lost because of injury'; or state what is not available, e.g., 'financial compensation is not available but medical treatment is provided free of charge,' etc.).

The National Cancer Institute will supply investigational drugs only until they become commercially available. Once a drug is commercially available either myself or my insurance company is responsible for payment of the drug.

CONTACT PERSONS

In the event that injury occurs as a result of this research, facilities for treatment of injury [will, will not] be available. I understand, however, I will not automatically be provided with reimbursement for medical care or receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____, the investigator in charge, at _____. In addition, I may contact _____ at
(Telephone)
_____ for information regarding patient's rights in research studies.
(Telephone)

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event that I withdraw from the study, I will continue to be followed and clinical data will continue to be collected from my medical records.

CONFIDENTIALITY

I understand that a record of my progress will be kept in a confidential form at _____ and also in a computer file at the statistical headquarters of the (Institution) Eastern Cooperative Oncology Group. The confidentiality of the central computer records is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI) ***and sponsoring agencies*** may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including slides, may be sent to a central office for review.

* * * * * * * * * * * *

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form, I will receive a copy.

_____ (Patient Signature)	_____ (Date)
_____ (Witness Signature)	_____ (Date)
_____ (Physician Signature)	_____ (Date)

Double-Blind Phase III Trial of Effects of Low-Dose 13-Cisretinoic Acid on Prevention of Second Primaries in Stages I-II Head and Neck Cancer

APPENDIX II

ECOG PERFORMANCE STATUS

Grade	Scale
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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APPENDIX V

COMMON TOXICITY CRITERIA

		0	1	2	3	4
Leukopenia	WBC x 10^3 Granulocytes/Bands Lymphocytes	≥4.0 ≥2.0 ≥2.0	3.0 - 3.9 1.5 - 1.9 1.5 - 1.9	2.0 - 2.9 1.0 - 1.4 1.0 - 1.4	1.0 - 1.9 0.5 - 0.9 0.5 - 0.9	<1.0 <0.5 <0.5
Thrombocyto-penia	Plt x 10^3	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	<25.0
Anemia	Hgb	WNL	10.0 - normal	8.0 - 10.0	6.5 - 7.9	<6.5
Hemorrhage (Clinical)	- - - - -	none	mild, no transfusion	gross, 1-2 units transfusion/episode	gross, 3-4 units transfusion/episode	massive, >4 units transfusion/episode
*Infection	- - - - -	none	mild, no active Rx	Moderate, localized infection requires active Rx	severe, systemic infection requires active Rx, specify site	life-threatening, sepsis, specify site
Fever in absence of infection	- - - - -	none	37.1° - 38.0° C 98.7 °- 100.4° F	38.1 ° - 40.0°C 100.5 ° - 104.0° F	>40.0° C (>104.0° F) for less than 24 hours	>40.0° C (104.0° F) for >24 hrs or fever with hypotension
	• Fever felt to be caused by drug allergy should be coded as allergy. • Fever due to infection is coded under infection only.					
GU	Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	>6.0 x N
	Proteinuria	No change	1+ or <0.3g% or <3g/l	2-3+ or 0.3 - 1.0g% or 3 - 10g/l	4+ or >1.0g% or >10g/l	nephrotic syndrome
	Hematuria	neg	micro only	gross, no clots	gross + clots	requires transfusion
	*BUN	<1.5 x N	1.5 - 2.5 x N	2.6 - 5 x N	5.1 - 10 x N	>10 x N
	• Urinary tract infection should be coded under infection, not GU. • Hematuria resulting from thrombocytopenia should be coded under hemorrhage, not GU.					
GI	Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	- - - - -
	Vomiting	none	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	>10 episodes in 24 hrs or requiring parenteral support
	Diarrhea	none	increase of 2-3 stools/day over pre-Rx	increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	increase of 7-9 stools/day or incontinence, or severe cramping	increase of ≥10 stools/day or grossly bloody diarrhea, or need for parenteral support
	Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers, but can eat	painful erythema, edema or ulcers, and cannot eat	requires parenteral or enteral support
Liver	Bilirubin	WNL	- - - - -	<1.5 x N	1.5 - 3.0 x N	>3.0 x N
	Transaminase (SGOT, SGPT)	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
	Alk Phos or 5'nucleotidase	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	>20.0 x N
	Liver - clinical	no change from baseline	- - - - -	- - - - -	precoma	hepatic coma
	• Viral Hepatitis should be coded as infection rather than liver toxicity.					
Pulmonary	- - - - -	none or no change	asymptomatic, with abnormality in PFTs	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
	• Pneumonia is considered infection and not graded as pulmonary toxicity unless felt to be resultant from pulmonary changes directly induced by treatment.					
Cardiac	Cardiac dysrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring, or hypotension or ventricular tachycardia or fibrillation
	Cardiac function	none	asymptomatic, decline of resting ejection fraction by less than 20% of baseline value	asymptomatic, decline of resting ejection fraction by more than 20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
	Cardiac-- ischemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
	Cardiac-- pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required

		0	1	2	3	4	
Blood Pressure		Hypertension	none or no change	asymptomatic, transient increase by >20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	recurrent or persistent increase by >20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	requires therapy	hypertensive crisis
		Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitalization; resolves within 48 hours of stopping the agent	requires therapy and hospitalization for >48 hours after stopping the agent
Skin		- - - - -	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Allergy		- - - - -	none	transient rash, drug fever <38° C, 100.4° F	urticaria, drug fever ≥ 38°C, 100.4°F, mild bronchospasm	serum sickness, bronchospasm, requires parenteral meds	anaphylaxis
*Phlebitis			none	arm	thrombophlebitis, leg	hospitalization	embolus
Local			none	pain	pain and swelling, with inflammation or phlebitis	ulceration	plastic surgery indicated
Alopecia		- - - - -	no loss	mild hair loss	pronounced or total hair loss	- - - - -	- - - - -
Weight gain/loss		- - - - -	<5.0%	5.0 - 9.9%	10.0 - 19.9%	≥20%	- - - - -
NEUROLOGIC	Sensory	neuro -- sensory	none or no change	mild paresthesias; loss of deep tendon reflexes	mild or moderate objective sensory loss; moderate paresthesias	severe objective sensory loss or paresthesias that interfere with function	- - - - -
		neuro -- vision	none or no change	- - - - -	- - - - -	symptomatic subtotal loss of vision	blindness
		neuro -- hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correct-able with hearing aid	deafness, not correctable
	Motor	neuro -- motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
		neuro -- constipation	none or no change	mild	moderate	severe	ileus >96 hours
	Psych	neuro -- mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
	Clinical	neuro -- cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, agitation, confusion, disorientation or hallucinations	coma, seizures, toxic psychosis
		neuro -- cerebellar	none	slight incoordination, dysdiadokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
		neuro -- headache	none	mild	moderate or severe but transient	unrelenting and severe	- - - - -
Metabolic		Hyperglycemia	<116	116 - 160	161 - 250	251 - 500	>500 or ketoacidosis
		Hypoglycemia	>64	55 - 64	40 - 54	30 - 39	<30
		Amylase	WNL	<1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 x N	>5.1 x N
		Hypercalcemia	<10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	≥13.5
		Hypocalcemia	>8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤6.0
		Hypomagnesemia	>1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤0.5
Coagulation		Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤0.24 x N
		Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	>2.00 x N
		Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	>3.00 x N

* denotes ECOG specific criteria

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APPENDIX VI

Pharmacy Agreement

Please note: This form is required for all participating institutions. If an affiliate uses the main institution as their pharmacy, please indicate that this is the case below. **Patients cannot be randomized to this study until the ECOG Statistical Center Data Management Office has this form on file.**

The ECOG Statistical Center Data Management Office will only ship drugs to the responsible investigational drug pharmacist listed below.

As the responsible investigational drug pharmacist at my institution I agree to the following in the conduct of this clinical trial:

1) Participating patients, medical staff, ancillary medical staff, and data manager will remain blinded as to the assignment of 13-Cisretinoic Acid or placebo until completion of the study. If the responsible investigational drug pharmacist receives a shipment of drug where unblinding has possibly occurred, the ECOG Statistical Center Data Management Office should be contacted immediately.

2) In the event of an emergency or severe adverse reaction necessitating identification of the medication (13-Cisretinoic Acid or placebo) for the welfare of the patients every attempt should be made to notify the ECOG Data Management Office (617-632-3610) before unblinding. Breaking the code will place the patient off study.

3) All copies of parts 2 and 3 of label A will be removed prior to dispensing to patient. These copies will be forwarded to ECOG with appropriate flow sheets.

4) Drug supply will be maintained on a per patient basis and identified by the patient's sequence number.

5) Any unused drug or placebo for a given patient will be returned to the NCI after the patient goes off study.

Pharmacist name: _____

Institution/Affiliate: _____

Address: _____

_____

_____

Phone number: _____

Date: _____

Please fill out the above information and forward the original to the ECOG Data Management Office. Please keep a copy for your records. If there is turnover in the responsible investigational drug pharmacist, please notify the Data Management Office by resubmitting this form.