PROTOCOL
Erlotinib Prevention of Oral Cancer (EPOC)

MDACC SPONSOR VERSION #8

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SCHEMA

Erlotinib Prevention of Oral Cancer (EPOC)

Males and females ≥ 18 years of age with a confirmed diagnosis of oral leukoplakia and LOH or confirmed diagnosis of oral leukoplakia, LOH and prior oral cancer (cured)

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Pre-study/ Baseline

Informed consent, smoking status and alcohol usage, epidemiological and nutrition questionnaire, family history of cancer, medical history, physical examination including vital signs and performance status, examination of the oral cavity (including baseline quantitation and bidimensional measurements of visible lesions), hematology, chemistry, β-HCG in women of childbearing potential, blood for biomarker assays, isolation of lymphocytes, plasma trough levels, concomitant medication review. Archival diagnostic tissue sample(s) or biopsy of oral leukoplakia lesions for LOH (Loss of Heterozygosity) status

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Eligible patients with oral leukoplakia and LOH +/- prior oral cancer (cured)

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Randomization

Balanced randomization to one of two arms: Erlotinib (150 mg po QD) or placebo continuous administration for 1 year

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Months 1 thru 3:

Clinic visits at months 1 and 3: Full physical examination including vital signs, smoking status and alcohol usage, examination of the oral cavity, hematology, chemistry, blood for biomarker assays and plasma trough levels (at month 3), concomitant medication review, adverse event and symptom assessment, return of completed pill diaries and unused medication returned, new medication and pill diaries dispensed at months 1 and 3. For patients with visible oral leukoplakia lesions, quantitation of lesions, bidimensional measurements, and biopsy will be obtained at month 3. For patients with no visible oral leukoplakia lesions, a biopsy will be obtained at the site of the previous lesion biopsy or at mucosa adjacent to cancer resection at month 3.

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Months 4 thru 11

Clinic visits at months 6 and 9: Full physical examination including vital signs, smoking status and alcohol usage, examination of the oral cavity, hematology, chemistry, blood for biomarker assays and plasma trough levels (at month 6), concomitant medication review, adverse event and symptom assessment, return of completed pill diaries and unused medication returned, new medication and pill diaries dispensed

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Month 12 or Early Termination

Clinic visit: Full physical examination including vital signs, smoking status and alcohol usage, examination of the oral cavity, hematology, chemistry, blood for biomarker assays and plasma trough levels, concomitant medication review, adverse event and symptom assessment, return of completed pill diaries and unused medication returned. For patients with visible oral leukoplakia lesions, quantitation of lesions, bidimensional measurements, and biopsy will be obtained. For patients with no visible oral leukoplakia lesions, a biopsy will be obtained at the site of the previous lesion biopsy or at mucosa adjacent to cancer resection.

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Follow-Up Clinic Visits Every Six Months

Clinic Visit: Full physical examination including vital signs, smoking status and alcohol usage, examination of the oral cavity, hematology, chemistry, blood for biomarker assays, symptom assessment and epidemiological and nutrition questionnaire (at final visit only)

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1. OBJECTIVES

This study will test the ability of an epidermal growth factor receptor (EGFR) inhibitor (erlotinib) to reduce the incidence of oral cancer in the high-risk setting of oral leukoplakia with LOH in two cohorts, oral IEN (Intraepithelial neoplasia) patients with LOH in 3p and/or 9p and one other specific chromosomal locus but without cancer or oral IEN patients with LOH in 3p and/or 9p associated with curatively treated oral cancer. We will test this treatment in a randomized clinical trial with 2 treatment arms: Erlotinib 150mg po QD or placebo.

1.1 Primary Aim

The primary endpoint of the trial will be the oral cancer-free survival in patients receiving erlotinib as compared with the control or placebo group.

1.2 Secondary Aims

1.2.1 The size, number, and appearance of oral IEN will be assessed and correlated with cancer risk. A $\geq$ 50% reduction in the bidimensional measurements of IEN lesions is considered a treatment response. We hypothesize that patients with IEN lesions and LOH of the oral cavity will respond to erlotinib.

1.2.2 To examine toxicity associated with erlotinib. Our hypothesis is that patients with oral lesions will tolerate treatment with erlotinib.

1.2.3 To assess a panel of molecular markers for correlations with oral cancer development in our oral IEN patients. The markers will include (but are not restricted to):

- 1.2.3.1 EGFR, phospho-EGFR, TGF-alpha, ERK1/2, phospho-ERK1/2, AKT, phospho-AKT, COX-2, STAT3, phospho-STAT3, cyclin D1, HER2, Ki67, TUNEL, RAR-beta, hTERT expression, E-cadherin, P-cadherin, vimentin, Src, phospho-Src, cytokeratin
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- 1.2.3.10 Frequencies of BPDE chromosomal aberrations on 3p12.3, 3p14.2, 3p21.3 and 3p25.2.
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- 1.2.3.12 Genome wide single nucleotide polymorphisms, telomere length, mitochondrial DNA alterations

2. BACKGROUND

2.1 Study Disease—Oral Carcinogenesis

Oral squamous cell carcinoma (OSCC) is a disfiguring, aggressive epithelial malignancy associated with high mortality and severe morbidity in long-term survivors. More than 300,000 annual new cases are diagnosed worldwide. Treating oral leukoplakia, the most common oral IEN and a precursor lesion of oral cancer, varies from watchful waiting to complete resection.[1,2] The prevalence rate of oral IEN ranges from 2%-8% in older persons.[3] Oral cancer incidence is increasing, and oropharyngeal cancer is the sixth most common cancer in adults in western countries. Almost 50% of the patients in the oncology departments of some developing countries suffer from oral cancer. Despite recent advances in screening and treatment, the long-term survival of patients with OSCC has only marginally improved over the past three decades, only 50% of OSCC patients survive 5 years after diagnosis.[1-4]

Etiology

Epidemiologic data established tobacco and alcohol use as the major causes of oral cancer.[4-7] Oral cancer risk is almost 10 times greater in individuals who do than who do not smoke and drink and almost 100 times greater in persons who smoke and drink heavily. A substantial percentage of the people with these risk behaviors, however, do not develop cancer. Other OSCC risk factors are betel quid chewing and possibly marijuana use.[8] These factors, and tobacco and alcohol use, also increase the risk of oral IEN.[9] The risk of oral cancer with any type of unfiltered cigarette is twice that of filtered cigarettes,[6] and the risk associated with hand-rolled unfiltered cigarettes is higher than that of factory-made unfiltered cigarettes.[10]

Although human papilloma virus (HPV) infection has been hypothesized for decades to play a role in the etiology of oral neoplasia, various studies have found different and contradictory frequencies of HPV DNA detection in oral mucosal lesions.[11,12] Recent data from the largest sample size yet analyzed could not establish a link between HPV infection and the development of either regular or more-aggressive verrucous oral IEN.[13] Nevertheless, HPV may be involved in some patients who develop oral neoplasia, for example, in a subset of OSCC patients without tobacco or alcohol risk factors.

Multifocal, Multistep Carcinogenesis

Oral cancer development is a multifocal process due both to multiclonal development and clonal intraepithelial spread.[2,4,14-16] Multifocality likely is a major cause of the failure of local treatment of oral IEN in preventing oral cancer and supports the testing of systemic therapy with agents targeting signaling pathways relevant to oral carcinogenesis such as the EGFR pathways.

Head and neck carcinogenesis is a multistep process requiring the accumulation of multiple genetic alterations.[1,4,17-27] Extensive genetic analysis of oral cancers and oral IEN has identified many common genetic abnormalities. LOH, a result of genetic instability and clonal selection, is one of the major mechanisms to inactivate tumor suppressor genes. Our earlier study showed that IEN with LOH at 3p14 and/or 9p21 regions increases the IEN risk for developing invasive oral cancer.[19] The 3-year oral cancer incidence in the LOH group was approximately 25%. The region 3p14 contains the tumor suppressor gene FHIT, and 9p21 contains the tumor suppressor genes p16/p15/p14, supporting the hypothesis that clones with deletions at these chromosomal

regions are more advanced in the tumorigenic process. Several subsequent studies by other groups had similar results and conclusions.[20,21,23-26]

Rosin *et al.* employed their centralized Oral Biopsy Service and the database of the British Columbia Cancer Registry to identify 116 patients who had oral IEN and who had been followed for a long period.[23] Importantly, only patients whose oral lesions had moderate histological changes (hyperplasia or mild or moderate dysplasia) similar to our earlier study[19] were selected for the study. The 3-year oral cancer incidence in the 3p14 and/or 9p21 LOH group was remarkably similar (25%) to our earlier study. A substantial proportion of lesions with LOH at 3p14 and/or 9p21 did not develop oral cancer, and so this group investigated the additional chromosomal loci 4q, 8p, 11q, 13q, and 17p, which are commonly deleted in oral cancers.[23] They found that LOH at one of these additional loci plus at 3p14 and/or 9p21 significantly improved the ability of LOH to predict oral cancer development. The 3-year cancer rate was 35%, and this expanded LOH profile was found in approximately 28% of the oral lesions. Several tumor suppressor or candidate tumor suppressor genes, such as TRAIL-R1 and TRAIL-R2 at 8p21.3 and p53 tumor suppressor gene at 17p13, are located in these chromosomal regions.

Rosin *et al*. also have retrospectively studied the oral cancer risk of LOH in IEN of patients with a history of curatively treated oral cancer.[27] LOH at 3p14 and/or 9p21 in IEN associated with curatively treated oral cancer has a 69% risk of a subsequent oral cancer in 3 years, and the prevalence of this LOH was approximately 66% among these cancer survivors with IEN. In order to confirm these retrospective data, this research group developed a prospective study in the same setting (R01 DE13124, "Clonal Changes in Oral Lesions of High-Risk Patients"). The preliminary results indicate that the rate of LOH on 3p and/or 9p in IEN and the rate of oral cancer are similar between the ongoing prospective and earlier retrospective studies in these curatively treated cancer patients (Personal communication, M. Rosin, Feb. 2006). LOH is a powerful, feasible risk marker that has been confirmed by multiple research groups and allows for selecting patients at M. D. Anderson Cancer Center and three other U.S. cancer centers for a phase III prevention trial.

High-risk oral IEN and early-stage oral cancer have overlapping molecular targets for intervention agents such as erlotinib. It can be very difficult to determine if a new cancer is an SPT (second primary tumor) or a recurrence in the setting of definitively treated early-stage aerodigestive tract cancer.[28-31] In our phase III SPT chemoprevention trial (NCI P01 CA52051), we examined patients treated curatively for early-stage head and neck cancer and who subsequently developed new cancer that was rigorously determined clinically to be either an SPT or recurrence.[31] Genetic profiling of the initial and subsequent cancers in these patients revealed substantial molecular ambiguity regarding the origins of the subsequent cancers.[32] For example, over 50% of the clinically defined SPTs were molecularly determined to be recurrences (i.e., genetic profiles consistent with clonal spread of the original tumor). We plan to examine distinctions between SPTs and recurrence based on patterns and mathematical modeling of genetic alterations (LOH, specific mutations of p53, and microsatellite instability) within cancers that develop in study patients with a cancer history; this approach also will be applied to determining clonal relationships between IEN and cancer in patients with or without a cancer history. Nevertheless, whether preventing SPT or recurrence, we believe that our trial has a high potential to bring clinical benefit to patients with a critical medical need through an approach that addresses the interfacing challenges presented by cancer prevention and therapy.[33,34]

Systemic Retinoid Approaches

Retinoids are the most-studied cancer preventive agent in oral carcinogenesis, and our collaborative group developed one of the largest programs of retinoid research in this setting in the world. Although largely predating molecular-targeted approaches, the oral IEN model produced seminal clinical and laboratory advances in our understanding of oral carcinogenesis and its response to retinoids, in particular, and of molecular targets for cancer prevention (and therapy) in general. The decades-long history of clinical retinoid trials includes five early randomized trials in oral IEN, one of which presaged another retinoid trial involving second primary tumor (SPT) prevention in head and neck cancer patients that provided a proof of principle for human cancer chemoprevention.[29,35-38] We showed that a high-dose of the retinoid 13-*cis*-retinoic acid (13cRA) can reverse oral IEN in the short term and reduce the SPT risk of definitively resected head and neck cancer patients. However, toxicity was substantial and not acceptable for long-term prevention and activity was reversible with high-dose 13cRA.[29,37-39] These high-dose, short-term results led to a randomized maintenance trial in oral IEN designed to reduce the toxicity of and prolong the response to a 3-month induction course of high-dose 13cRA (1.5 mg/kg/d) via a 9-month maintenance course with low-dose 13cRA (0.5 mg/kg/d) or beta-carotene (30 mg/d) in responding or stable oral IEN patients of the induction phase.[40] The maintenance-phase clinical lesion progression rates were significantly lower in the retinoid group than in the beta-carotene group. Therefore, we tested low-dose 13cRA (versus placebo) in a long-term, large-scale, NCI Intergroup phase III trial to prevent SPTs in early-stage head and neck cancer patients. This trial found no significant difference in SPT rates between the 13cRA and placebo arms.[31] Studies of retinoid-interferon combinations in advanced oral and laryngeal IEN have produced promising results in advanced laryngeal but only limited activity in advanced oral IEN.[41]

Translational studies in the retinoid–oral IEN model have helped to advance the overall understanding of the biology of intraepithelial carcinogenesis, preventive agent molecular targets and mechanisms, and markers for developing drugs, monitoring interventions, and assessing cancer risk and pharmacogenomics. These studies have assessed retinoic acid receptor-beta (*RAR-β*), *p53*, *p16* genetic instability, LOH, and cyclin D1, among other markers of tumorigenesis and/or risk[38]. Extensive studies of nuclear RARs in the retinoid-oral IEN model include a study by Lotan et al[42] that found a selective and progressive loss of *RAR-β* (one of six *RAR*s) in oral carcinogenesis, a striking upregulation of *RAR-β* expression after 3 months of high-dose 13cRA, and a significant association of *RAR-β* upregulation with clinical IEN response. *RAR-β* loss was associated with immortalization in short-term in vitro cultures of oral IEN cells.[43] Recent studies indicate potential mechanisms of *RAR-β* loss, including a defect in intracellular RA metabolism and *RAR-β* silencing by methylation and histone deacetylation.[44,45] *RAR-β* is expressed in three isoforms in humans (*β1*, *β2*, and *β4*). *RAR-β2*, the most abundant and inducible form, has tumor suppressor activity. *RAR-β4* has oncogenic activity. Recent studies also show that the tobacco carcinogen benzo(a)pyrene diolepoxide (BPDE) suppresses *RAR-β2* in vitro and that there is an inverse relationship between *RAR-β* and COX-2 in oral cancer cells in vitro and in oral leukoplakia, and that *RAR-β2* transfection suppresses EGFR and COX-2 in vitro.[46-48] A recent study suggested that the GG genotype of cyclin D1 can mark retinoid sensitivity in patients with advanced head and neck IEN to retinoic acid (likely related to effects on ubiquitin-dependent proteolysis) as indicated by cyclin D1 protein modulation, IEN response, and

progression free survival.[49] The beneficial drug effect in patients with the GG genotype was lost shortly after the 1-year intervention was stopped. Cancer development in patients with the GG genotype began approximately 1 year after stopping the intervention at an annual cancer rate paralleling that of patients with the retinoid-resistant AA or AG genotypes. Studies in advanced oral IEN indicate the importance of molecular confirmation with LOH of IEN response.[50] Molecular-targeted drug development in carcinogenesis of the head and neck or any other region or site has benefited enormously from translational research in the retinoid–oral IEN model, which has helped pioneer rigorous scientific and clinical methodologies, including reliable sampling methods, for clinical and translational studies of oral IEN such as the studies governed by this protocol.[38]

Over the past 10 years, our group and others have conducted molecular studies of genetic instability and loss of heterozygosity for identifying head and neck IEN patients who have a high risk of oral cancer.[19,22-27,38,51] Molecular markers of the varying cancer risks of oral IEN have revolutionized drug development in this setting. Substantial evidence points to genetic instability as a cause rather than as a consequence of malignant transformation. Mutations in genes controlling chromosome segregation during mitosis and centrosome abnormalities play a critical role in the development of chromosome instability in cancer. This high-risk population allows the protocol trial to use cancer as the primary endpoint, the value of which is illustrated by our recent, unpublished data from the largest retinoid trial ever conducted in oral IEN. Oral cancer development did not correlate with retinoid response in this trial, which was sponsored by the NCI and involved lesions with a lower risk than that of IEN with LOH. The present protocol trial will assess IEN response (with LOH) in addition to cancer, allowing an assessment of the potential correlation between lesion response and cancer outcome. In summary, we chose IEN with LOH because it is a powerful known predictor of oral cancer development.

2.2 EGFR Inhibition

The strong rationale for EGFR inhibition in this setting is based on the following constellation of findings: 1) EGFR is overexpressed in virtually all oral IEN;[52,53] 2) levels of EGFR ligands are increased in oral IEN and in the oral mucosa of smokers;[53,54] 3) suppression of EGFR signaling leads to reduced levels of cyclooxygenase-2 (COX-2) and decreased synthesis of prostaglandin E_2 (PGE_2) in a model of oral IEN; PGE_2-mediated activation of EGFR signaling is dampened by an EGFR TKI;[55] 4) EGFR TKIs suppress growth in oral cancer xenografts and IEN cells;[54-59] and 5) suppression of EGFR signaling is active in preclinical (in vivo) and clinical head and neck and lung prevention models.[38,60] Two additional strengths of the rationale, i.e., important clinical findings and the suppression of levels of cyclin D1 and genetic instability, are discussed in detail below.

Our group has found that increased cyclin D1 expression is associated with genetic instability and cancer risk in head and neck IEN.[49] Consistent with recent data of others,[61] our recent studies in cultured IEN cells transfected with an inducible cyclin D1 vector demonstrated that upregulation of cyclin D1 induces genetic instability in a dose-dependent fashion; decreasing cyclin D1 expression leads to decreased genetic instability. Suppressed cyclin D1 is the only biomarker endpoint of drug efficacy that has been shown clinically to correlate with reduced cancer risk in the setting of head and neck IEN. As reviewed earlier, a retinoid-based regimen significantly suppressed cyclin D1 and genetic instability and delayed the onset of cancer in advanced head and neck IEN patients with the GG genotype of cyclin D1 but not with the AA or AG genotype (A

allele).[49] Laboratory data of Dimitrovsky's group suggest why the clinical response differed by cyclin D1 genotype. Retinoids decrease cyclin D1 expression through ubiquitin-mediated protein degradation. The A allele, however, produces an alternatively spliced RNA transcript that encodes a cyclin D1 form that is resistant to ubiquitin-mediated protein degradation.[62] These results, which provide the proof of principle of head and neck cancer prevention via down-regulation of cyclin D1, are extremely relevant rationale for the use of EGFR inhibitors such as erlotinib. Because EGFR can induce the transcription of cyclin D1 via STAT3[63,64] and this pathway can be suppressed by EGFR inhibitors in head and neck cancer, erlotinib can suppress cyclin D1 expression at the level of gene transcription, which may broaden its cancer preventive effects to patients with any cyclin D1 genotype.

Overexpression of EGFR, STAT3 and cyclin D1 have been shown to be poor prognostic factors in head and neck cancer patients.[65,66] Limited clinical data show that erlotinib (150 mg/day) produced pathologic responses in head and neck/lung cancers that correlated with higher concentrations of the drug in tumor tissue and with the suppression of cyclin D1.[67] EGFR can induce Snail to transcriptionally suppress E-cadherin, which is associated with the following events: MMP activation and dysplasia in oral IEN and a highly aggressive phenotype, poor response to EGFR TKIs, and poor prognosis in head and neck cancer.[68-72] In oral IEN cells in vitro, an EGFR TKI downregulates extracellular matrix metalloproteinase inducer, which is important for tumor invasion and angiogenesis and is overexpressed in oral IEN biopsy specimens.[73] Furthermore, PGE_2 also can induce cyclin D1 transcription, either through an EGFR-dependent (positive feedback loop) or -independent mechanism.[73-75] Therefore, erlotinib potentially can decrease cyclin D1 levels, in part, by suppressing PGE_2 synthesis. In preclinical head and neck IEN and cancer models, the activity of a high-dose single-agent EGFR inhibitor is similar to that of combined low-dose EGFR and COX-2 inhibitors.[77,78] This equivalency likely is due to the beneficial impact of the high-dose EGFR inhibitor on interactions between the COX-2 and EGFR signaling pathways as well as on EGFR signaling pathways not known to involve COX-2.

Substantial further clinical support, such as from the following data, also support erlotinib (150 mg/day): patient plasma erlotinib concentrations are equivalent to active concentrations in preclinical head and neck/lung cancer models; recent phase III data led to the FDA approval of erlotinib for treating two tobacco-related cancers, including the approval of single-agent erlotinib for non-small cell lung cancer (NSCLC).[79] Moreover, there are several relevant trials in recurrent/metastatic head and neck cancer patients, including single-agent trials of the EGFR inhibitors gefitinib, cetuximab and erlotinib, which produced promising safety and efficacy results suggesting a dose-response relationship,[80-82] and a phase II trial showing high activity of a chemotherapy combination with an EGFR-inhibitor.[83] There also is a phase III trial showing that an EGFR inhibitor combined with radiation improved survival over that of radiation alone in locally/regionally advance head and neck cancer patients.[84,85] An EGFR inhibitor is more likely to affect growth in oral IEN than in oral cancer because genetic damage and instability have progressed to a lesser degree in IEN than in cancer.

2.3 Study Agent

Erlotinib

One approach to block EGFR activity involves the use of small molecules to inhibit tyrosine kinase activity of erbB-1 receptor.[86-88] Protein kinases are a family of cellular components that regulate signaling for a wide variety of cellular processes such as growth and differentiation. They are divided into subgroups based on the amino acid

substrate for phosphorylation: serine, threonine or tyrosine. Tyrosine kinase was the last to be identified following the discovery of the Rous sarcoma virus *src* gene approximately 20 years ago. Tyrosine kinase activity is considered a hallmark of the transformation of malignant cells. Substantial evidence *in vivo* and *in vitro* points to the close relationship between tyrosine kinase activity and the initiation, growth and metastases of many human tumors.

Tyrosine kinase is the intracellular domain of the EGFR and the other members of the erbB family except the c-erbB-3. As such, it serves as the first step in the EGF signal transduction pathway. The binding of a ligand to the extracellular domain of EGFR activates the intrinsic tyrosine kinase activity, which then, transfers the terminal phosphate group of adenosine triphosphate to the hydroxyl group of specific tyrosine residues of target proteins and of the receptors themselves. Tyrosine kinase has several protein substrates, PLC-γ1, PI-3 kinase, GAP, MAP kinase, *raf* kinase, and lipocortin I. Although growth factors and their receptors vary in structure, tyrosine kinase activity remains the initial step in the mechanism of action for all growth factors. The discovery of small molecules that interfere with ATP binding or utilization represented a major breakthrough in tyrosine kinase-targeted therapy. In the last two decades, enormous efforts have been made to develop compounds that can inhibit tyrosine kinase activity and several kinase inhibitors have been generated and successfully inhibited cell cycle progression and induced apoptosis in both human tumor cell lines *in vitro* and in xenograft models. Inhibitors bind intracellularly to EGFR tyrosine kinase, inhibit kinase activity, and subsequently block the signal transduction cascade. Tyrosine kinase inhibitors (TKIs) targeting the intracellular domain are small molecules that specifically inhibit EGFR tyrosine kinase activity over precise dose ranges. Several different classes of TKIs have been reported after molecular modeling has been employed to develop compounds that can selectively and tightly bind to various kinase targets. The quinazolines and the pyridopyrimidines currently appear to be the most promising classes of the TKIs.

Erlotinib (OSI-774, Tarceva™) is an orally bioavailable EGFR TKI low-molecular weight quinazoline derivative. This novel drug induces cell cycle arrest at the G1 phase and has a high specificity as an inhibitor of the EGFR tyrosine kinase. Erlotinib acts through direct and reversible inhibition of EGFR tyrosine kinase.[89] Erlotinib inhibits human EGFR tyrosine kinase with an IC_{50} of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC_{50} of 20 nM (7.9 ng/mL). This inhibition is selective for EGFR tyrosine kinase in assays of isolated tyrosine kinases and cellular assays. EGFR is overexpressed in a significant percentage of epithelium-derived carcinomas. Erlotinib inhibits the EGF-dependent proliferation of cells at nanomolar concentrations and blocks cell cycle progression at the G1 phase. Oral administration of erlotinib to mice reduced the level of EGFR autophosphorylation in human tumor xenografts by > 70% for more than 12 hours.[90] Daily administration of erlotinib markedly inhibited the growth of HN5 human head and neck tumors and A431 squamous cell carcinoma xenografts in aythymic mice, with near complete inhibition of tumor growth during a 20-day treatment regimen at the highest doses. Many other potential effects of erlotinib in oral cancer prevention and therapy, including the abrogation of EGFR-dependent induction of COX-2 are discussed above in Section 2.2. Erlotinib also has been shown to downregulate cyclin D1,[67] which is upregulated in head and neck lEN and has been reduced by other agents in preventing head and neck carcinogenesis.[49]

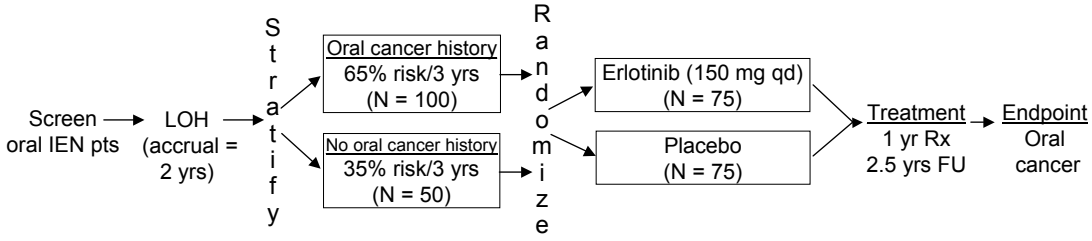
As of February 2005, erlotinib has been studied clinically in more than 6,800 healthy subjects and cancer patients (excluding patients exposed to placebo) in a number of Phase I, II and III studies, including a large phase II study showing modest single-agent activity in advanced squamous cell carcinoma of the head and neck.[91,92] Erlotinib/Tarceva was approved by the US FDA for second- and third-line treatment of advanced or metastatic NSCLC at a dose of 150 mg daily.[79]

Following oral administration in rats and dogs, erlotinib was rapidly absorbed (T_{max} 1 to 2 hours) with an oral bioavailability of 45% to 88%. Erlotinib displayed nonlinear pharmacokinetics, with greater than expected increases in C_{max} and AUC with increasing doses. Repeat-dose studies showed no substantial changes in the pharmacokinetics of erlotinib over time. In vitro measurement of protein binding of erlotinib in animal and human plasma ranged from 85% to 95%. The primary route of metabolism was oxidation by CYP3A4. Erlotinib and its metabolites were excreted predominantly via the feces (> 90%) with a small amount recovered in urine.

Toxicology studies were conducted in mice, rats (up to 6 months), dogs (up to 1 year), and monkeys (1 week). Treatment-related effects observed in at least 1 species or study included effects on the cornea (atrophy and ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (liver necrosis), kidney (renal papillary necrosis and tubular dilatation), and gastrointestinal tract (delayed gastric emptying and diarrhea). Red blood cells (RBC) parameters were decreased, and white blood cells (WBCs) primarily neutrophils, were increased. There were treatment-related increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin; increases in bilirubin were likely caused by treatment-related impairment of bilirubin metabolism.

3. SUMMARY OF STUDY PLAN

The proposed study will be a double-blinded, placebo-controlled randomized study to evaluate the chemopreventive effect of erlotinib in a high-risk group of oral IEN patients. The trial will be conducted at five centers in the United States: M. D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, Emory University, the University of Chicago, and the University of Maryland. There will be two categories of high-risk patients in this study: (a) loss of heterozygosity (LOH) at 3p14 and/or 9p21 in the oral IEN of patients with a history of curatively treated oral cancer and (b) LOH at 3p14 and/or 9p21 plus at one other chromosomal region in the IEN of patients with no oral cancer history. The trial will randomize 150 patients--75 will receive erlotinib (150 mg po QD) and 75 will receive matched placebo (po QD). The trial period is 4.5 years (including one-year treatment)--2 years to complete accrual and 2.5 more years of follow-up (mean of the additional follow-up period from 1.5 to 3.5 years). A summary of the study schema appears below:



Once at the study site, informed consent will be obtained from willing participants, medical history will be obtained, oral lesions (if present) will be examined, blood samples will be taken, collection of archival tissue sample or biopsy of oral leukoplakia lesions for LOH analysis, and the epidemiologic and nutrition questionnaire (included in Appendix A) will be initiated. Patients classified with oral leukoplakia and LOH with or without a prior history of cured oral cancer will be eligible for inclusion in the study and will be randomized into one of two groups.

The primary endpoint of the trial will be the oral cancer-free survival in patients receiving erlotinib as compared with the control group. Multiple secondary endpoints will be assessed as outlined in Section 1.2.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

All the following conditions must be met before a patient can be included in the study:

4.1.1 Male or female patients with one of the following: (a) loss of heterozygosity (LOH) at 3p14 and/or 9p21 in the oral IEN of patients with a history of curatively treated oral cancer or (b) LOH at 3p14 and/or 9p21 plus at one other chromosomal region in the IEN of patients with no oral cancer history.

4.1.2 Participants must have confirmed diagnosis of oral IEN lesion with LOH. (Note:The initial screening biopsy of oral IEN lesion with LOH must be obtained within 12 months of study enrollment. If initial diagnostic biopsy for LOH is > 3 months prior to study enrollment, investigators may use clinical judgment to order an additional screening biopsy to assess histopathological changes).

4.1.3 Age $\geq$ 18 years

4.1.4 ECOG performance status < 2

4.1.5 Participants must have normal organ and marrow function as defined below within 30 days of randomization:

CBC with differential white cell count – acceptable results must include:
WBC $\geq$ 3,000μl, hemoglobin $\geq$ 10 g/dl, platelet count $\geq$ 125,000μl

LFTs - total bilirubin and alkaline phosphatase, AST (SGOT) and ALT (SPGT) all within $\leq$ 1.5xULN. Note: At the discretion of the attending physician, participants with Gilbert's disease may still be eligible to participate in the event the total bilirubin value is > 1.5xULN.

Kidney function - serum creatinine $\leq$ 1.5xULN

Chemistry - Sodium and potassium all within normal institutional limits.

4.1.6 The effects of the study agent on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of active treatment. Negative serum pregnancy test in women of child-bearing potential. Childbearing potential will be defined as women who have had menses within the past 12 months, who have not had tubal ligation or bilateral oophorectomy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.1.7 Ability to understand and the willingness to sign a written informed consent document

4.2 Exclusion Criteria

4.2.1 Patients with active cancer or any cancer within the previous two years, excluding oral and non-melanoma skin cancer.
4.2.2 Patients with acute intercurrent illness or who have had surgery, radiation therapy, or chemotherapy within the preceeding 4 weeks unless they have fully recovered.
4.2.3 Patients with a documented history of coagulopathy and/or those taking warfarin or warfarin-derivative anticoagulants
4.2.4 Women who are pregnant (confirmed by β-HCG if applicable) or breastfeeding
4.2.5 Any medical or psychological condition or any reason that, according to the investigator's judgment, makes the patient unsuitable for participation in the study
4.2.6 Patients who have participated in other experimental therapy studies within 3 months of enrollment to this trial
4.2.7 Patients with a history of inflammatory bowel disease
4.2.8 Patients with a documented history of interstitial lung disease

4.3 Inclusion of Women and Minorities

No patient will be excluded from the study on the basis of ethnicity, race, sex, or older age. Most oral cavity cancers arise in patients above the age of 65, but the incidence in younger patients is increasing, i.e. including patients younger than 50 years. The study subjects will be patients above 18 years of age, since oral IEN/cancer is extremely rare in children and the safety profile of erlotinib is unknown in this age group. Efforts will be made to recruit all minority participants identified with IEN and LOH.

4.4 Recruitment and Retention Plan

Methodology, Infrastructure and Accrual

The 20-years experience of M. D. Anderson Cancer Center (MDACC) in advancing the translational study of head and neck cancer chemoprevention in the settings of head and neck IEN and SPTs[1,2,4,38,93-102] includes 9 trials in oral IEN, the majority of which were randomized, controlled and 5 of which were completed within the past 5 years. With this experience, MDACC has established effective methodologies and a strong clinical, laboratory and accrual infrastructure for translational head-and-neck chemoprevention. The majority of trial patients will be accrued at MDACC, with additional accrual from Memorial Sloan Kettering Cancer Center, Emory University, the University of Chicago, and the University of Maryland. The estimated accrual figures for all participating centers are presented in Table 1 (relevant data and calculations follow the table):

Table 1. Screenings and Randomizations by Quarter (Q).

	Year 1				Year 2				Year 3
	Q1*	Q2†	Q3	Q4	Q1	Q2	Q3	Q4	Q1‡
Screened	26	59	72	72	59	59	59	59	26
Randomized	8	18	22	22	18	18	18	18	8

***** M. D. Anderson alone (while awaiting IRB approval at the 4 other sites); begins with MDACC protocol activation.

† The 4 other sites join M. D. Anderson in this quarter.

‡ Total for 4 other sites; M. D. Anderson finished at end of Year 2.

Quarter 1 (Q1) screenings (26) and accruals (8) in the table reflect trial activation at MDACC alone while the protocol is undergoing IRB review and approval at the other 3 clinical sites. These sites begin screening and accrual in Q2 of Year 1 and will complete accrual in Q1 of Year 3. Each center will have a substantial cohort of potentially eligible patients in follow-up when the trial is activated. These patients will be captured (along with new patients) throughout the first year at each center. We assume that 2/3 of the patients will have oral intraepithelial neoplasia (IEN) and a prior oral cancer and 1/3 will have oral IEN alone (no oral cancer history). Among those with a prior cancer, 67% will have eligible LOH and 60% of these will consent to go on trial. Therefore, the randomization "yield" among screening patients with oral IEN and a prior oral cancer is 0.67 x 0.60 = 0.40. On the other hand, among patients with oral IEN alone, 28% will have eligible LOH and 45% will consent to go on trial. The randomization "yield" of these patients is 0.28 x 0.45 = 0.13. Therefore, the overall yield is 0.67 x 0.40 + 0.33 x 0.13 = 0.31. Based on these assumptions, we will screen approximately 491 patients in order to accrue 150 randomized patients at all 4 participating U.S. clinical sites.

Accrual at MDACC

There are no competing studies for the oral IEN patients in this study at M. D. Anderson Cancer Center, and the trial has the full support of the chairs of the departments of Thoracic/Head and Neck Medical Oncology and Head and Neck Surgery (which includes dental oncology). As part of this collaboration, we have added this clinical protocol to an interactive database managed by the department of Head and Neck Surgery entitled "First Match." This matching database will alert research personnel of new patients with certain characteristics, i.e., oral cancer diagnosis, that have been evaluated in the Head and Neck Surgery clinic. Through this mechanism, these patients may then be approached at the time of their follow-up visit to discuss possible participation in this clinical trial.

Oral IEN/LOH Patients with Curatively Treated Cancer History: MDACC sees 300 oral cancer patients per year (actual average in past 5 years = 309), who are referred primarily by dentists and ear, nose and throat (ENT) specialists. The eligible patients in this cohort are not eligible for any other protocols, have no standard treatment, and are continually followed by M. D. Anderson Cancer Center surgeons over the years. These IEN with oral cancer history estimates are a collaboration of Drs. Lippman (Chair, Thoracic/Head and Neck Medical Oncology), Weber (Chair, Head and Neck Surgery), and Gillenwater (head and neck surgeon), and the Head and Neck Center database manager.

Oral IEN/LOH Patients with No Cancer History: Patients with eligible IEN (based on LOH) and no history of cancer also have no standard treatment. Approximately 80 oral IEN patients (no cancer history) are registered within our current follow-up program within our Head and Neck Cancer SPORE and are available for recruitment to our trial. We also evaluate approximately 50 new oral IEN (no prior cancer) patients per year in the MDACC Head and Neck Center. Screened patients who do not have the eligible LOH profile will be followed observationally (and prospectively) with biopsy as indicated to assess acquisition of LOH; if LOH is acquired, these patients become eligible for the trial. Furthermore, our head and neck team will move in Summer 2006 into a new Head and Neck Center, where Drs. Weber and Lippman will establish a comprehensive oral premalignancy/IEN program since oral IEN is a major research focus of both of their departments.

Accrual at the University of Chicago, Memorial Sloan Kettering, Emory University, and the University of Maryland

As does MDACC, our four partner accrual centers all have pre-eminent programs of head and neck cancer therapy and prevention practice and research, including active programs of chemoprevention in oral IEN. The considerations for estimating accrual at each center are similar to those outlined above for MDACC. The conflicts between this trial and other trials are from none to minimal at these respective centers, and their accrual estimates have taken into account the portfolio of trials at each center.

The University of Chicago Head and Neck program is a world renowned program with published experience in oral IEN trials.[1,80,82,103] The collaborative history of MDACC with the University of Chicago includes a targeted-agent trial in oral IEN.[103] Co-investigator Dr. Ezra Cohen, who will lead our clinical trial at the University of Chicago, is an expert in the area of EGFR targeting in clinical/translational trials in head and neck cancer. Memorial Sloan Kettering has an outstanding Head and Neck cancer program and collaborates already with MDACC in our NCI N01 cancer chemoprevention consortium. Co-investigator Dr. Jay Boyle is a leader in targeted prevention in oral IEN[104] and will lead our clinical trial at Memorial Sloan Kettering. Dr. Boyle is PI of an N01 trial of an PPAR-gamma agonist in oral IEN and is a key collaborator with MDACC on the recently completed RCT of celecoxib in oral IEN. Emory University also has strong experience in head and neck cancer therapy and prevention under the leadership of Co-investigator Dr. Dong Shin, who is Director of the Clinical and Translational Cancer Prevention Program at Emory. Dr. Shin has extensive experience in clinical/translational trials in oral IEN and in the setting of curatively treated head and neck cancer patients and has long-standing collaborations with head and neck investigators at M. D. Anderson Cancer Center, where he was a highly respected member of the faculty.[52,84,95,105,106] Dr. Li Mao is one of the key architects for the current prevention trial and the key player for development of the genetic test used for selection of high risk patients in the clinical trial. Dr. Mao has recently moved to University of Maryland Dental School to serve as Professor and Chairman, Department of Oncology and Diagnostic Sciences.

LOH Screening

Based on the strong data presented above in Molecular Risk and Cohort Selection, the previous section, we propose to use LOH status to select patients to participate in our prevention trial. There will be two selection criteria. IEN

patients with no oral cancer history must have LOH at 3p14 and/or 9p21 plus at least one of the following regions: 17p, 8p, 11p, 4q, or 13q. IEN patients with clinically cured oral cancer must have LOH at either 3p14 and/or 9p21 to be eligible for the study.

Dr. Mao's extensive data derived from small paraffin-embedded tissue samples of oral IENs and oral cancers demonstrate that using 2-3 microsatellite markers for each locus gives a > 95% informative test rate (deletion status could be interpreted). We will use automatic capillary DNA analyzer (AB3100) to separate microsatellite alleles and to quantify peak heights of each alleles. LOH is defined as the ratios of the peak heights of the two alleles in lesion (L1/L2) DNA and in the corresponding normal lymphocytes (N1/N2) DNA ≥1.43 or 0.7. The extensive experience of Drs. Li Mao and Adel El-Naggar in this area of research ensures peak efficiency in the patient screening and selection process. We have established that the LOH status of oral IENs can be determined within 7 business days, which will ensure timely enrollment of patients into our clinical trial.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6.2

5.1 Dose Regimen and Dose Groups

1) Erlotinib, 150 mg po QD
2) Erlotinib placebo

Patients will be on active, continuous treatment for 12 months

5.2 Rationale for Dose Selection

Erlotinib

The dose of 150 mg po QD of the EGFR inhibitor erlotinib was chosen for this trial based on strong supportive preclinical and clinical data including in the head and neck. The standard recommended dose of erlotinib approved by the FDA for treatment of NSCLC, another disease of the upper aerodigestive tract, is 150 mg po QD. This FDA-approved dose was based on the positive results of erlotinib in the BR21 trial, which was a multinational, placebo-controlled, double-blind phase III trial of second- or third-line therapy for advanced or metastatic NSCLC. A total of 731 patients were randomized to erlotinib at 150 mg per day versus placebo in a 2:1 randomization, and a subset of BR21 patients received erlotinib for > 1 year.[79]

Erlotinib at 150 mg/day produces plasma concentrations in patients that are equivalent to active erlotinib concentrations in preclinical head and neck and lung cancer models. A limited clinical study in cancers of the head and neck and lung indicated that erlotinib at 150 mg/day produced pathologic responses that correlated with higher tumor tissue concentrations of erlotinib and suppression of cyclin D1 (which is highly associated with oral cancer development, is upregulated by EGFR, is suppressed by erlotinib in vitro, and can be suppressed in association with oral cancer prevention[49]) and Ki67 in tissue samples of responding patients (versus samples of non-responding patients).[67]

5.3 Study Agent Administration

Each patient will be required to take 1 tablet daily (unless there is a dose reduction, which is described in Section 10.3). Participants should take the study medication (erlotinib or its matched placebo) in the morning at approximately the same time every day. It is to be taken with up to 200 mL (~1 cup or 8 oz) of water, and should be taken 1 hour before or 2 hours after meals, other medications, vitamins and iron supplements. Participants will be instructed not to drink grapefruit juice while on study drug as this is a CYP3A4 inhibitor. If the patient vomits after taking a study dose, the dose is replaced only if the tablet(s) can actually be seen (and counted). The scheme for dose reductions of both agents based on certain toxicity criteria are outlined in Section 10.3.

5.4 Concomitant Medication

Erlotinib is both protein bound (92% to 95% in humans) and metabolized in the liver by CYP3A4 and, to a lesser extent, CYP1A2 and in the lungs by CYP1A1. A potential for drug-drug interactions exists when erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 inhibitors/inducers. (See Appendix D).

For patients who are being concomitantly treated with a potent CYP3A4 inhibitor, a dose reduction should be considered in the presence of severe adverse events. For patients who are being concomitantly treated with a potent CYP3A4 inducer, alternative treatments that lack potent CYP3A4-inducing properties should be considered.

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication source documentation and will include: 1) start and stop date, dose, route of administration, and indication. Medications taken for a procedure (e.g., biopsy) should also be included.

5.5 Compliance

Compliance is defined as number of pills taken divided by number of pills that should have been taken measured by pill count. Patients will also be given a pill diary and will be instructed to keep the diary during the one-year treatment period. During clinical visits at 1, 3, 6, 9 and 12 months, patients will be instructed to bring in the bottles with remaining drugs (for pill count) and pill diary. New study medication will be dispensed and new pill diaries provided at months 1, 3, 6 and 9. Compliance will be based on pill count and plasma trough levels. Information from the pill diary can supplement pill count to have a more accurate assessment of a patient's compliance.

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent

Erlotinib

Chemistry: Erlotinib is chemically designated as N (3-ethynylphenyl)-6,7-bis (2-methoxyethoxy)-4-quinazoliamine, monohydrochloride. The empirical formula for erlotinib is $C_{22}H_{23}N_3O_4 \bullet HCL$. Erlotinib is an off-white to pale yellow powder. The pharmaceutical preparations of erlotinib are formulations containing the hydrochloride (HCl) salt. All clinical evaluations have investigated erlotinib HCl; doses were based on free base equivalents. Erlotinib is currently formulated as

conventional, immediate-release tablets. Excipients in the formulation include lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and magnesium stearate.

Supply: The 150 mg, 100 mg and 25 mg strengths are supplied as white film-coated tablets for daily oral administration. All tablets are round with a biconvex face and straight sides. The 150 mg tablets are 13/32" (10 mm); the 100 mg tablets are 11/32" (9 mm); and the 25 mg tablets are 1/4" (6 mm). The lower doses (100 mg and 25 mg) will be used when dose reductions are necessary. Erlotinib tablets will be supplied in white, high-density polyethylene (HDPE) bottles.

Storage: Erlotinib should be stored at temperatures between 15°C and 30°C (59°F and 86°F).

Drug Accountability
The investigator is ultimately responsible for the maintenance of records regarding the study drug receipt, dispensing, unused drug return by subjects. Institutions participating in this study have the responsibility of establishing a system to ensure that delivery of study medication is correctly received and recorded by a responsible party (e.g., a pharmacist), and that study medication is handled, dispensed and stored safely and properly.

6.2 Reported Adverse Events and Potential Risks

Erlotinib

Based on clinical results, rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache were the most frequently reported toxicities with exposure to single-agent erlotinib. Patients receiving erlotinib in combination with various chemotherapy agents have generally experienced the same type of adverse events as with either agent alone.

Common adverse events (occurring in 10%-25% of subjects) include dry or itchy skin, desquamation, dry eyes, decreased blood counts (which may lead to infection, bleeding and/or fatigue), dry mouth, nausea and vomiting, and anorexia.

Laboratory abnormalities observed infrequently with erlotinib as a single agent primarily involve liver function tests, including elevation of ALT, AST, and/or bilirubin.

There have been infrequent reports of serious interstitial lung disease (ILD)-like events (including fatalities) in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In a single-agent study in patients with NSCLC, the incidence of ILD-like events (0.8%) was the same in the placebo and erlotinib groups. In a combination study with gemcitabine in patients with pancreatic cancer, the incidence of ILD-like events was 2.5% versus 0.4% in the erlotinib plus gemcitabine versus the placebo plus gemcitabine groups, respectively. The overall incidence in erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.7% out of approximately 4,900 patients. Reported diagnoses included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease,

obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, and lung infiltration. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, preexisting parenchymal lung disease, metastatic lung disease, or pulmonary infections. No imbalance was noted in the incidence of ILD-like events between treatment groups in a single-agent, randomized, placebo-controlled or in 2 large 1st line NSCLC studies (Study OSI2298g, Study BO16411), which utilized a standard platinum-based regimen with or without erlotinib. However, that was not the case when erlotinib was used concurrently with gemcitabine in a placebo-controlled study. Therefore, one cannot completely rule out a potential causal relationship between erlotinib exposure and the rare occurrence of ILD.

In the event of acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment instituted as necessary.

Erlotinib is protein bound (92% to 95% in humans). It is metabolized in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent CYP1A2, and the pulmonary isoform CYP1A1. Therefore, a potential for drug-drug interaction exists when erlotinib is coadministered with drugs that are highly protein bound or that are potent CYP3A4 inhibitors/inducers (discussed in Section 5.4; examples listed in Appendix D). In addition to these possibilities, altered coagulation parameters and/or bleeding events (including fatalities) have been reported in patients receiving erlotinib either alone or in combination with other chemotherapeutic agents together with concomitant coumarin-derivative anticoagulants, including warfarin. The mechanism for this is still unknown. Additional information on clinically relevant enzyme inhibitors and enhancers can be found at http://medicine.iupui.edu/flockhart/ or www.drug-interactions.com.

6.3 Availability and Accountability

OSI Pharmaceuticals will provide active substance of erlotinib and matched placebo in tablets. The packaged medication will be sent to the pharmacy at each participating center and each site will be responsible for: storing the trial medication and keeping accounts of all batch numbers in stock; keeping drug accountability records; re-labeling the study medication with required labels; and dispatching labeled medication to the patients while they are attending scheduled clinic visits. Unused study medication will be destroyed at the pharmacies of the study sites.

6.4 Dispensing

Each patient will be provided with the study medication containing the active drug or the matched placebo to the active drug.

6.5 Randomization and Blinding

Stratified randomization with dynamic allocation (see Section 12.2 for details) will be performed via the web-based database system. A randomization algorithm will be developed and implemented by the Biostatistics and Data Management Core at M. D. Anderson Cancer Center. Upon verifying the eligibility criteria and specifying the stratification factors, the research nurse at each site can randomize patients by pushing the “Randomize” button in the web-based database system. Each randomization result will be sent directly to the site’s

pharmacy. Study participants, the sponsor, research nurses, and investigators will be blinded to the assigned treatment. For verification of study randomization procedures, the sponsor may submit a formal request to the study statistician to obtain the blinded treatment assignments for study participants.

The pharmacies will blind the study medication by inserting the name and patient number on the pre-printed labels (on medication bottles) and then by removing the tear-off portion of the label containing the correct information regarding the study medication. This tear-off portion will be transferred to a form (one for each patient) and filed. Only pharmacy personnel and the study monitor will have access to this file. The patient will then be administered blinded medication.

Unblinding

Unblinding of single cases by the sponsor and/or investigator will only be performed if relevant for the safety of the participant. In emergency situations, the investigator would contact the sponsor, who would contact the study statistician and local pharmacy to obtain immediate blinding information for the participant. The sponsor would then pass this information on to the investigator to enable the participant to be treated. In non-emergency situations, the same procedures would apply, however the study statistician and the study sponsor will discuss and evaluate the request, then, would be responsible for making the decision of whether or not to unblind.

Unblinding of all participants will occur at the end of study, whereby the sponsor and investigators will be provided with a list containing data on which arms each of his/her patients were randomized to. All unblinded cases should be reported to the US NCI.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Procedure [a]	Baseline /Pre-Study	Randomization	Month 1	Month 3	Month 6	Month 9	Month 12 or Early Termination	Follow-Up Visits (every 6 months)
Informed Consent	X							
Assess Eligibility	X							
Medical History	X							
Smoking Status, Alcohol Usage	X		X	X	X	X	X	X
Epidemiologic/Nutrition Questionnaires	X							X[k]
Physical Exam[b]	X		X	X	X	X	X	X
Vital Signs: Temperature,BP, Pulse, Respiration	X		X	X	X	X	X	X
Hematology/Chemistry[c]	X		X	X	X	X	X	X
Serum β-HCG Pregnancy Test[d]	X							
Examination of Oral Cavity	X		X	X	X	X	X	X
Biopsies[e]	X			X[m]			X[m]	
Biomarkers[f]	X			X	X		X	X[l]
Plasma Trough Levels[g]	X			X	X		X	
Concomitant Medication Review	X		X	X	X	X	X	X
Dispense Study Agent[h]		X	X	X	X	X		
Collect Study Agent[i]			X	X	X	X	X	
Review Agent Diary/Record[j]		X	X	X	X	X	X	
Adverse Events and Symptom Assessments			X	X	X	X	X	X

a Baseline evaluations should be conducted within 30 days prior to initiating study treatment unless otherwise specified. On-Study evaluations may be conducted within the following timeframes: Months 1 and 3: +/- 7 days of the date specified in the protocol; Months 6, 9, and 12: +/- 14 days of the date specified in the protocol; Follow-Up Visits: within 60 days of the date specified in the protocol.

b Full physical exam to include performance status (at baseline to determine eligibility) and vital signs (including temperature, blood pressure, pulse, and respiration).

c Hematology and chemistry will be done at baseline, months 1, 3, 6, 9, and 12 then Q6 months thereafter until completion of follow-up period. These will include the following: SGPT, SGOT, alkaline phosphatase, bilirubin, creatinine, sodium, potassium, magnesium, albumin, hemoglobin, hematocrit, platelet count, CBC with differential, and WBC.

d Serum β-HCG in women of child-bearing potential at baseline within 14 days of initiating study treatment

e Biopsies of lesions at baseline (Biopsy will only be obtained if initial diagnostic biopsy of LOH is > 12 months prior to study enrollment or unavailable), month 3, and month12 or early termination.

f Baseline blood collection for isolation of lymphocytes and biomarker assays. On-study blood collection for biomarker assays at months 3, 6, and 12 then Q12 months thereafter until completion of follow-up period

g Plasma trough levels will be done at baseline, month 3, month 6 and month 12

h Study medication and pill diaries will be dispensed at randomization and during clinic visits at months 1,3, 6 and 9

i Unused study medication and completed pill diaries will be collected during clinic visits at months 1, 3, 6, 9 and 12

j Review of pill diaries and compliance will be done during clinic visits

k At final clinic visit

l Every Q12 months (Months 24 and 36) during the follow-up period

m For patients with visible oral leukoplakia lesions, quantitation of lesions, bidimensional measurements, and biopsy will be obtained. For patients with no visible oral leukoplakia lesions, a biopsy will be obtained at the site of the previous lesion biopsy or at mucosa adjacent to cancer resection.

7.2 Baseline Testing/Pre-Study Evaluation

Following an introduction to the nature of the study, the study physician and research coordinator will evaluate each individual for enrollment. Baseline evaluations **(with the exception of the study questionnaire**) should be conducted within 30 days prior to initiating study treatment unless otherwise specified.

This will include:

7.2.1 Review of medical records for eligibility

7.2.2 Discussion of the risks, benefits, goals and limitations of the study and any alternate treatments that may be available with the subject.

7.2.3 Review of inclusion and exclusion criteria

7.2.4 Review of the informed consent process and form

7.2.5 Acquisition of informed consent and registration into study

7.2.6 Physical examination and examination of oral cavity (including baseline quantitation and bidimensional measurements of visible lesions)

7.2.7 Mucosal biopsies for histological analysis and LOH status.
Note: Biopsy will only be obtained if initial diagnostic biopsy of LOH is > 12 months prior to study enrollment or unavailable. If initial diagnostic biopsy for LOH is > 3 months prior to study enrollment,

investigators may use clinical judgment to order an additional screening biopsy to assess histopathological changes.

7.2.8 Symptom assessment and concomitant medication review

7.2.9 Study questionnaire (tobacco consumption, alcohol use, demographics, nutrition). Note: The research team will make every attempt to initiate the questionnaire within 30 days of beginning study treatment

7.2.10 Medical history (including smoking status and alcohol usage)

7.2.11 SGPT, SGOT, alkaline phosphatase, bilirubin, creatinine, sodium, potassium, magnesium, albumin, hemoglobin, hematocrit, platelet count, CBC with differential, WBC, and serum ßHCG in females of childbearing potential (within 14 days of randomization).

7.2.12 Plasma drug trough assessment. This will be used as a baseline for each patient on which subsequent trough levels will be compared.

7.2.13 Family history of cancer

7.2.14 Blood collection for isolation of lymphocytes and biomarker analysis

7.3 Randomization

Upon verifying the eligibility criteria, the research nurse at each site can randomize patients by pushing the “Randomize” button in the web-based database system. Each randomization result will be sent directly to the site’s pharmacy. Study participants, the sponsor, research nurses, and investigators will be blinded to the assigned treatment.

7.3.1 Study medication dispensed

7.3.2 Pill diary and instructions dispensed

7.4 On-Study Evaluations (Active Treatment Period)

7.4.1 Months 1-3 (within +/- 7 days) clinic visits at months 1 and 3 to include full physical examination, examination of the oral cavity, hematology and chemistry, smoking status, alcohol usage, blood for biomarker assays and plasma trough levels (at month 3 visit), concomitant medication review, adverse event and symptom assessment, return of completed pill diaries and unused medication returned, new medication and pill diaries dispensed. For patients with visible oral leukoplakia lesions, quantitation of lesions, bidimensional measurements, and biopsy will be obtained at month 3. For patients with no visible oral leukoplakia lesions, a biopsy will be obtained at the site of the previous lesion biopsy or at mucosa adjacent to cancer resection at month 3.

7.4.2 Months 4 – 11 (within +/- 14 days) clinic visits at months 6 and 9 to include full physical examination, examination of the oral cavity, hematology and chemistry, smoking status, alcohol usage, blood for biomarker assays and plasma trough levels (at month 6 visit), concomitant medication review, adverse event and symptom assessment, return of completed pill diaries and unused medication returned, new medication and pill diaries dispensed.

7.4.3 Month 12 (within +/- 14 days) or Early Termination to include full physical examination, examination of the oral cavity, hematology, chemistry, smoking status, alcohol usage, blood for biomarker assays and plasma trough levels, concomitant medication review, adverse event and symptom assessment, return of completed pill diaries and unused medication. For patients with visible oral leukoplakia lesions, quantitation of lesions, bidimensional measurements, and biopsy will be obtained. For patients with no visible oral leukoplakia lesions, a biopsy will be obtained at the site of the previous lesion biopsy or at mucosa adjacent to cancer resection.

7.5 Follow-up (End of the active treatment period until patients are placed off study)

7.5.1 Every six months (within 60 days): Full physical examination, examination of the oral cavity, smoking status, alcohol usage, hematology, chemistry, blood for biomarker assays (at months 24 and month 36) and symptom assessment.

7.5.2 Final visit: Full physical examination, examination of the oral cavity, smoking status, alcohol usage, hematology, chemistry, blood for biomarker assays, symptom assessment and epidemiological/nutrition questionnaires.

7.6 Long-term Follow-up (continued evaluation from initial participation until after the study is completed)

All patients who signed a written informed consent document (or their family members/designees), even if they were not subsequently randomized to one of the treatment arms for any reason, may be contacted by the research team (during clinic visits, by telephone, in writing, by electronic mail or by other method of communication) to confirm or provide clinical information on long-term follow-up. Participants' medical records may also be reviewed to obtain long-term follow-up information. This will allow for a better estimation, for example, of rates of invasive cancer in patients whose lesions harbor LOH or not.

7.7 Methods for Clinical Procedures

Clinical Investigation of Oral Cavity

Examination of the oral cavity will be conducted at each scheduled clinic visit. Leukoplakias that have increased in size or new leukoplakias will be biopsied at the discretion of the investigator. Leukoplakias will be monitored at each scheduled clinic visit and bi-dimensional measurements of the visible lesions will be performed as indicated on the study schema and study schedule of events (section 7).

Epidemiological Data

Baseline and follow-up epidemiologic and nutrition data will be collected by means of a structured questionnaire. Participants at M.D. Anderson Cancer Center will have the questionnaire administered during a 90-minute interview. All interviewers will be trained on specific interviewing techniques concerning the questionnaire, as well as general interviewing techniques (including leading and probing) to ensure accuracy and consistency of collected data.

Five percent of interviews will be re-conducted by a trained back-up interviewer to confirm consistency of collected data. Quality assurance/quality control will be assured by coding the data and removing all personal identifiers; keying coded data into a single password-protected database; utilizing a data edit check program; and by storing hard copies from all recruitment sites at M. D. Anderson Cancer Center.

The Epidemiologic Questionnaire Database will contain entered data from completed epidemiologic and nutrition questionnaires. Hard copies of the epidemiologic and nutrition questionnaires will be filled out during an interview initiated at baseline and at the completion of the follow-up period. Participants at University of Chicago, Memorial Sloan-Kettering, Emory University – Winship Cancer Institute, and the University of Maryland will submit the original questionnaires to Dr. Jie Lin at the following address to be edit checked and entered into the Epidemiologic Questionnaire Database:

Dr. Jie Lin
U.T. M. D. Anderson Cancer Center
Department of Epidemiology
1155 Herman P. Pressler Street, Unit 1340
Houston, Texas 77030
[redacted]

The original will be stored in a locked file at M. D. Anderson Cancer Center following data entry.

Blood and Tissue Samples

If initial diagnostic tissue sample for LOH is > 12 months prior to study enrollment or unavailable, a biopsy sample will be taken from at least one existing lesion. Biopsy samples may be taken from all existing lesions at the discretion of the attending physician. The biopsies should be a minimum of 4-5 millimeters in diameter. If the entire lesion is excised at baseline, subsequent biopsies will be performed on normal appearing mucosa at the same site as clinically indicated. The biopsies will be partitioned for snap freezing and for fixation in 10% formalin immediately. Please note: Archival diagnostic tissue specimens obtained for LOH analysis will not be processed for snap freezing. All biopsy specimens (initial screening biopsy for LOH analysis and subsequent biopsy specimens) from Memorial Sloan Kettering Cancer Center, Emory University, University of Chicago, and the University of Maryland will be **ONLY** prepared for fixation (see Appendix G).

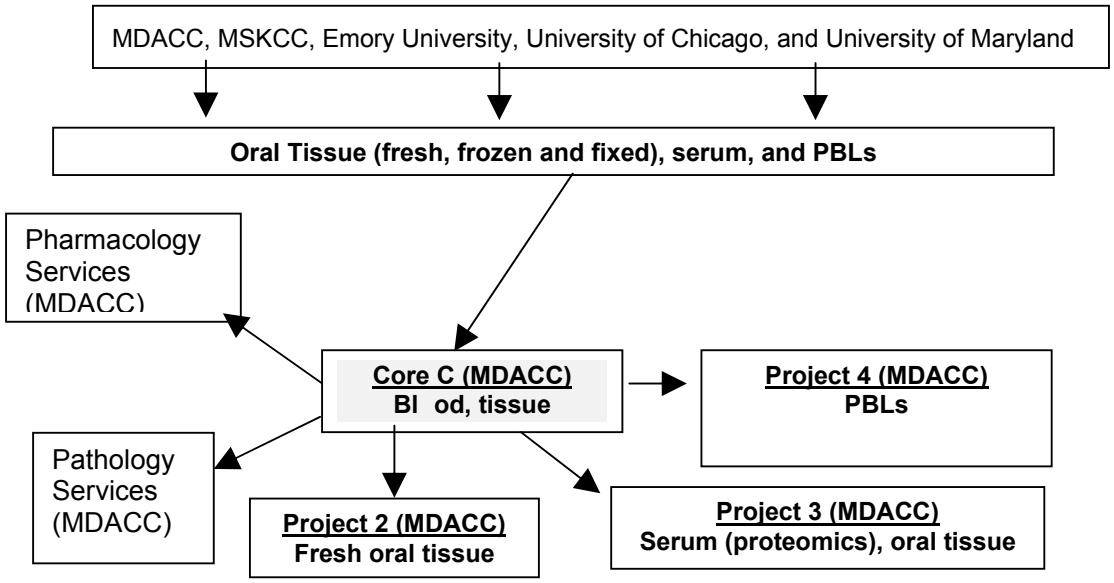
LOH investigations are performed on at least one sample taken (see “LOH Screening” section for details).

Blood - 10 cc’s of blood (1-5cc EDTA tube and 1-5cc SST tube) will be drawn at each baseline, on-study and follow-up visit for analysis of routine laboratory parameters as listed in Section 7. 40 cc’s of blood (3-10 cc heparinized tubes and 1-10cc EDTA tube) will be drawn at the pre-study blood draw for isolation of lymphocytes. 10 cc’s of blood (1-10cc EDTA tube) will also be drawn at specified on-study visits for biomarker analysis and plasma trough levels.

Blood samples and biopsy specimens will be collected and shipped as detailed in Appendix G.

The specimens and data used for clinical patient management and for ascertaining response to treatment on this protocol will also be processed and shipped to support interactive research projects at M. D. Anderson Cancer Center. No data or specimens will be used until the protocol for their use has been submitted to and approved by the Institutional Review Boards at M. D. Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Emory University, University of Chicago, and University of Maryland. No data or specimens will be transferred to any other institution/party without the patient's own consent. Confidentiality and patient anonymity will be assured through the assignment of unique and unrelated pathology numbers to each specimen as it is collected. The name of each subject will be available only in a password-protected database.

The data and specimens to be processed and shipped for research purposes include serum, PBLs, tissue, including surgical specimens of cancer tissue from patients who develop cancer during the clinical trial, and epidemiologic and clinical data, including information regarding patient outcome, survival and treatment. All samples and data will be protected and kept confidential as described above.



8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

An objective clinical response will be considered complete when gross inspection reveals no evidence of lesion(s) and will be considered partial when the product of bidimensional (perpendicular) millimeter measurements of the lesion or, if there are multiple lesions, the sum of the product of bidimensional measurements of all lesions

decreases by at least 50 percent. Lesions will be considered stable when the sum areas of all lesions combined increases by less than 25 percent or decreases by less than 50 percent. Disease progression will be defined as an increase of at least 25 percent in the total area of all lesions combined during treatment or as the appearance of any new lesion. Although we will collect histologic data on oral leukoplakia lesions, these data will not be included in the response assessments but will be available for exploratory analyses.

8.1 Primary Endpoint

The primary endpoint for the randomized trial will be oral cancer-free survival.

8.2 Planned Secondary Endpoints and Analytical Methods

8.2.1 The size (bi-dimensional measurements) of oral IEN will be assessed and will be correlated with reduction in cancer risk. All oral lesions will be numbered and drawn onto a standardized diagram.

8.2.2 Toxicities associated with therapy will be assessed during the active treatment period. We will employ a rigorous monitoring plan for all participants and will include frequent clinic visits, assessment of symptoms, surveillance labs and measurement of drug trough levels.

8.2.3 We will assess molecular markers for correlations with oral cancer development in our oral leukoplakia patients. They will include (but are not restricted to):

8.2.3.1 EGFR, phospho-EGFR, TGF-alpha, ERK1/2, phospho-ERK1/2, AKT, phospho-AKT, COX-2, STAT3, phospho-STAT3, cyclin D1, HER2, Ki67, TUNEL, RAR-beta, hTERT, E-cadherin, P-cadherin, vimentin, Src, phospho-Src, cytokeratin. All these markers will be assessed in oral tissue biopsy specimens via immunohistochemistry laboratory analyses, except for RAR-beta and hTERT, which will be assessed via RNA in situ hybridization.

8.2.3.2 EGFR gene copy number, will be measured by real-time Q-PCR.

8.2.3.3 PGE_2 levels. This marker will be measured by high-performance liquid chromatography (HPLC) mass-spectrometry in frozen oral tissue biopsy specimens.

8.2.3.4 Perform computerized DNA image analysis of DNA content and ploidy evaluation and interpretation

8.2.3.5 Promoter methylation in p16 and in FHIT. These markers will be assessed via methylation-specific PCR (MSP) in oral tissue biopsy specimens.

8.2.3.6 Protein profiling, which will be assessed via SELDI mass-spectroscopy in serum specimens.

8.2.3.7 Chromosome-9–related levels of chromosome polysomy, chromosome index, and fraction of cells involved in subclonal outgrowth. These markers will be determined via chromosomal in situ hybridization (CISH) in oral tissue biopsy specimens.

8.2.3.8 BPDE-induced genetic damage, which will be measured by the Komet 4.0 image system in peripheral blood lymphocytes.

8.2.3.9 Estimated frequencies of polymorphisms in the following DNA–repair genes implicated in the nucleotide excision repair (NER) pathway: ERCC1, XPC, XPD/ERCC2, EXPF/ERC4, XPA, RAD23B, CLNH, ERCC5, LIG1. These polymorphisms will be assessed via DNA extraction and genotyping techniques in peripheral blood lymphocytes.

8.2.3.10 Frequencies of BPDE chromosomal aberrations on 3p12.3, 3p14.2, 3p21.3 and 3p25.2. These markers will be determined by fluorescence in situ hybridization (FISH) with several probes on 3p in peripheral blood lymphocytes.

8.2.3.11 Polymorphisms of CYP1A1, CYP3A4, CCND1, COX-2, EGFR, and ErbB-2. These polymorphisms will be explored via DNA extraction and genotyping techniques in peripheral blood lymphocytes.

8.2.3.12 Genome wide single nucleotide polymorphisms, telomere length, mitochondrial DNA alterations

8.2.4 Other Time-to-Event Endpoints

8.2.4.1 Overall survival. Overall survival is defined as time from randomization to death of any cause. If patients are alive at the end of study, the censoring time is set at the last follow up time.

8.2.4.2 Cancer-specific survival. Cancer-specific survival is defined as time from randomization to cancer specific death. If patients die of non-cancer cause or are alive at the end of study, the censoring time is set at the non-cancer death date or the last follow-up time.

8.3 Off Agent Criteria

Patients who have been included may discontinue the study agent for general reasons (Declaration of Helsinki) or for safety reasons. A patient has the right to discontinue the study agent without having to give an explanation and without any negative effect on further treatment.

All participants discontinuing the study agent prior to normal completion (normal completion will be defined as 12 consecutive months from study treatment initiation) will be asked to return to the study site for all remaining clinic visits and follow-up visits according to the schedule of events (Section 7.1), except for patients discontinuing treatment due to diagnosis of oral cancer.

Patients may stop taking study medications for the following reasons:

- Completed the protocol-prescribed intervention
- Adverse event or serious adverse event that is unacceptable to the patient or physician
- Repeated grade 2 or greater toxicities or grade 4 toxicity that is believed to be possibly, probably or definitely related to study medication
- Disease progression requiring alternative therapy in the opinion of the Principal Investigator

- Pregnancy
- Inadequate agent supply
- Allergic reaction to the study medication(s)
- Noncompliance
- Patient desire to stop taking medication
- Concomitant medications or medical contraindications.

Patients may resume treatment if the following criteria are met:

- Patients are within the normal treatment period (i.e. within 12 consecutive months from treatment initiation)
- The reason for treatment discontinuation was not a grade 4 toxicity determined to be possibly, probably, or definitely related to the study treatment, or diagnosis of oral cancer
- There is no other reason for withholding the study treatment in the Principal Investigator's opinion

8.4 Off-Study Criteria

Patients may go off-study for the following reasons:

- The protocol intervention and any protocol-required follow-up period is completed
- Diagnosis of cancer
- Lost to follow-up
- Withdraw consent
- Death.

Patients that have been placed off study will be asked to return to the study site for an early termination visit according to the schedule of events (Section 7.1).

8.5 Study Termination

The NCI or regulatory agencies may discontinue the investigation at any time.

9. REPORTING ADVERSE EVENTS

Definition: An adverse event (AE) is an untoward medical occurrence in a study participant. An AE does not necessarily have a casual relationship with the treatment or study participant. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that can occur while a participant is on a study. The NCI Common Toxicity Criteria (v3.0CTCAE), Appendix E) will guide grading of adverse events and dose reductions.

A list of adverse events that have occurred or might occur can be found in Section 6.2.

9.1 Adverse Events

9.1.1 Reportable Adverse Events

All adverse events that occur after the informed consent is signed and within 30 days after the last dose of study drug must be recorded on the adverse event source document whether or not related to study agent. Adverse events will be spontaneously reported by the patients,

observed by the investigators, or elicited by the investigator by asking the patients specific questions according to a predefined scheme. The investigator is responsible for assuring that there are procedures and expertise available to deal with emergency situations during procedures related to the study.

9.1.2 AE Data Elements

- Verbatim description of event
- Severity of AE
- Event onset date and ended date of AE (duration)
- Relationship to study drug
- Whether or not the event was reported as a Serious Adverse Event (SAE)

9.1.3 Severity of AEs

Adverse events not listed in the NCI Common Toxicity Criteria (v.3.0) will be assessed according to their impact on the participant's ability to perform daily activities as follows:

Severity	Description
Mild	• Barely noticeable, does not influence functioning • Causing no limitations of usual activities
Moderate	• Makes participant uncomfortable, influences functioning • Causes some limitations of usual activities
Severe	• Severe discomfort, treatment needed • Severe and undesirable, causing inability to carry out usual activities
Life Threatening	• Immediate risk of death • Life threatening or disabling
Fatal	• Causes death of participant

9.1.4 Follow-up of Adverse Events

All adverse events, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

9.2 Serious Adverse Events

9.2.1 Definition: ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997 define serious adverse events as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (*Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner

9.2.2 Reporting Serious Adverse Events

All participating centers will report SAEs to their respective IRBs within 5 working days of knowledge of the event and will simultaneously submit a copy of the SAE report to the IND sponsor (MDACC). Each center will report all deaths to their respective IRBs within 24 hours of knowledge of the event and will simultaneously submit a copy of the SAE report to the IND sponsor (MDACC). The IND sponsor will notify the NCI and OSI Pharmaceuticals within 24 hours of learning of the SAE to the following contacts:

- OSI Pharmaceuticals: fax to OSI Drug Safety at 303-546-7706 (for questions related to safety reporting, call OSI Drug Safety at 303-546-7869)
- NCI: fax [redacted]
- MDACC: Please email the SAE form to mdaccsafetyreports@mdanderson.org
  (E-mail must be sent from the PI's email address or the PI must be copied on the e-mail containing the form).
  For problems sending the form or other questions, please contact [redacted]

The IND sponsor will also process and submit any required safety information to the FDA as required by CFR 312.32 "IND Safety Report."

All adverse events will be followed until the patient outcome has been established. To ensure the safety of study participants, all SAEs will also be reported to the Data and Safety Monitoring Board (DSMB) at M. D. Anderson Cancer Center.

10. MANAGING ADVERSE EVENTS/TOXICITIES/EARLY TERMINATIONS

10.1 Adverse Events

Study participants will be monitored for all adverse events. All adverse events will be recorded in the source documentation.

Persons included in the study will be monitored for adverse events during telephone contacts and clinic visits. Patients will also be provided with a telephone number at which they can reach the study coordinator, research nurse or principal investigator. The range of adverse events possible in any clinical investigation is extensive and patients enrolled in this study will be carefully monitored. Particular attention will be paid to

a) Diarrhea
b) Rash
c) Psychological side-effects as insomnia
d) Signs and symptoms of ILD

e) Eye disorders
f) Anorexia
g) Nausea
h) Vomiting
i) Hepatotoxicity

Potential hepatotoxicity from erlotinib will be monitored with periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase); erlotinib dose reductions, as described in Section 10.3, will be implemented if warranted by changes in liver function.

Management of Adverse Events:
Skin rash or dermatosis has been observed during the first several days of treatment with erlotinib in many patients and has been noted to diminish in severity despite continued treatment. Patients who develop a rash characterized by pustules or raised red areas may be treated with oral minocycline (100 mg BID for 7–10 days to a maximum of 150 mg BID for 7–10 days as clinically indicated) at the discretion of the Investigator. Minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly.

Patients with acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever should have treatment held pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment instituted as necessary.

10.2 Causal Relationship of AE to Study Medication
The causal relationship of the adverse event to the study medication will be assessed as one of the following:

Unrelated:
- does not follow a reasonable temporal sequence following administration of the treatment drug

Unlikely:
- could readily be produced by other medication administered to the patient or other, environmental factors the patient has been exposed to
- has previously been causally related to other drugs the patient is taking
- does not follow a normal response pattern to the treatment drug

Possible:
- follows a reasonable temporal sequence following administration of the treatment drug

Probable:
- follows a typical temporal sequence following administration of the treatment drug

Definite:
- follows a known pattern of response to the treatment drug

10.3 Toxicity Attribution and Dose Reduction
Study medication will be held then restarted for grade 3 or 4 toxicities as outlined in the table below. If the patient experiences grade 3 toxicity on the

lowest doses, the patient will be taken off agent. There will be no dose escalation after dose reduction. Patients will not be taken off agent permanently if the SAE is clearly unrelated to the study medication. Dose reduction or stopping drug is also an option for grades 1 and 2 toxicities, irrespective of attribution to the study medication, that are unacceptable to the participant or physician.

Toxicity Attribution

Grade of Toxicity	Is Toxicity Associated with Drug Treatment				
	Unrelated	Unlikely	Possibly	Probably	Definitely
Grade 0	C	C	C	C	C
Grade 1	C	C	C	C	C
Grade 2	C	C	**C**	**C**	**C**
Grade 3	S-R^0	S-R^0	S-R^{-1}	S-R^{-1}	S-R^{-1}
Grade 4	S-R^0	S-R^0	W	W	W

C = Continue drug

S-R^0 = Stop drug until toxicity reaches grade 1 or lower, then restart drugs at the same doses

S-R^{-1} = Stop drug until toxicity reaches grade 1 or lower, then restart drug at the next lower dose level (100 mg QD for erlotinib). The most common adverse events associated with erlotinib are rash (the most frequent) and diarrhea. If these adverse events do not resolve after the initial dose reduction, second dose reductions of erlotinib to 50 mg po QD are acceptable. After the second dose reductions, no further reductions will be permitted and patients with returning toxicities will be removed from the study.

W = Withdraw from trial

11. STUDY MONITORING

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check completed source documentation, discuss the progress of the study and monitor drug according to good clinical practice (GCP). The monitoring will also include source data verification (SDV).

Source Data Verifications

Monitor and/or regulatory authorities will be allowed audits at the investigation site for the purpose of source data verification, in which a case review of those parts of the hospital records relevant to the study must be required. Data recorded in the CRF must be current at the time of the scheduled monitoring visit.

The Principal Investigator (Scott Lippman,M.D. M.D. Anderson Cancer Center) will be responsible for writing the protocol, ensuring any modifications to the study protocol must be reviewed and approved by the NCI prior to implementation, and for publishing study results.

The Protocol Lead Investigator is responsible for reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Statistician, and for publishing study results. He/She will, together with the study group, be responsible for data cleaning. He/She will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients. He/She is responsible for arranging for the retention of the patient identification and the code list for at least 15 years after completion of the study. Patient files and other source data shall be kept for a maximum period of time permitted by each hospital. All information concerning the study should be stored in safe places inaccessible to unauthorized personnel. Unique study IDs will be assigned to identify the study participants. The cross-reference of study ID and patient ID will be stored in a secure file at each site and will be accessible only to

authorized personnel. All the subsequent study coordination including information sent to M. D. Anderson Cancer Center will be based on study ID to protect the patient confidentiality.

Treatment termination for any reason except completion of the study will be fully documented in the source documentation. Patients leaving the study before end-point should, if possible, go through the same final evaluations as patients completing the study according to the protocol. Every reasonable effort should be made to maintain patient's protocol compliance and participation in the study. The investigator will monitor patient protocol compliance at each follow-up visit.

Should a patient discontinue the study for any reason, the patients should be urged to return for a final visit (with an early termination evaluation preferably performed within 14 days after discontinuation from the study).

The IND sponsor and the National Cancer Institute will approve changes to the protocol or discontinuation of the study. Amendments or discontinuation of the study will be forwarded to each site for review and approval by their respective IRBs.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design

The basic trial design is described earlier. The proposed study will be a double-blinded, placebo-controlled randomized study to evaluate the chemopreventive effect of erlotinib in a high-risk group of oral IEN patients. We plan to recruit a total of 150 patients in 2 years with an additional 2.5 years of follow-up. The total study period will be 4.5 years. Interim analyses will be conducted at the ends of year 2.5 and year 3.5, and the final analysis will be done at the end of year 4.5. We expect a small percentage of early drop out or loss to follow-up (10%) due to the nature of higher compliance of the elevated risk groups, tolerable toxicity profile of the agent, and intense follow up in this population.

12.2 Analysis of Primary Endpoint

The primary endpoint of the study is cancer-free survival defined as time from randomization to the development of histologically confirmed oral cancer. All patients will be analyzed on an intent-to-treat basis (i.e., as randomized). Patients lost to follow-up due to refusal or death from other causes will be censored at their time of last follow-up. The distribution of time to oral cancer development will be estimated by the Kaplan-Meier method. For randomization purposes, eligible patients will be stratified (1) by prior oral cancer status (no prior oral cancer versus prior oral cancer) and (2) broadly by registration site (M. D. Anderson versus non-M. D. Anderson site). Within each stratum, Pocock-Simon dynamic allocation method will be applied to achieve balanced randomization with respect to potentially important factors including current, former and never smoking. Patients will be randomized into the erlotinib arm or the placebo arm with equal probability. Stratified log-rank test will be used to compare cancer-free survival among treatment groups. The Cox (proportional hazards) regression model will be used to incorporate potential prognostic factors and treatment assignment as covariates. Details of the assumptions used for the sample size calculation are listed below.

1. The study has a 2-year period to accrue 100 oral IEN/prior cancer and 50

IEN-alone patients, with an additional 2.5-years follow-up. The total study duration is 4.5 years.

2. The anticipated yield of LOH screening (described earlier) will be approximately 66% in the IEN/LOH-cancer history group and 28% in the IEN/LOH-alone group. Assuming accrual rates of 60% (eligible, cancer history) and 45% (eligible, no cancer history), we will need to screen a total of 253 oral IEN patients with and 365 (accounting for year-2 accruals who were screened, eligible, and did not volunteer in year 1) oral IEN patients without a history of curatively treated oral cancer at all four participating centers in order to reach our total accrual goal.
3. Time-to-oral cancer development follows an exponential distribution. Based on the data described earlier, 65% of the patients with IEN/LOH associated with curatively treated oral cancer will develop oral cancer in three years, and 35% of the IEN/LOH-alone patients will develop oral cancer in three years.
4. Erlotinib, the active treatment, can reduce the 3-yr oral cancer rate by 40% for the IEN/LOH-cancer history group, i.e., 3-year cancer rate will be reduced from 65% to 39%. This corresponds to a hazard ratio of 0.47. We assume the same treatment effect (hazard ratio) in the IEN/LOH-alone group, corresponding to the 3-yr oral cancer rate reduction from 35% to 18%. The parameters, lambda, for the exponential distributions are 0.3499 (control) and 0.1648 (treatment) in IEN/LOH-cancer history patients and 0.1436 (control) and 0.0676 (treatment) in IEN/LOH-alone patients, respectively.
5. We assume the rate of lost-to-follow up, which includes patient refusal, early drop out, or competing risk, etc. is 10%. The distribution of the time to loss to follow-up is assumed to be uniform.
6. Stratified log-rank test **(stratify by the randomization stratification factors)** is used to compare the cancer-free survival between the active and control groups.
7. Two interim analyses are planned – one at the end of year 2.5 and another one at the end of year 3.5. The final analysis will be performed at the end of year 4.5. We will apply the group sequential design with the O'Brien-Fleming boundary to control the overall two-sided type I error rate to 5%. The levels of significance for the first, second, and third tests are 0.0005, 0.014, 0.045, respectively.

Based on the above assumptions, we ran simulation studies with 10,000 replications. The results show that a total of 150 patients will allow us to have 85% power with a two-sided 5% type I error rate.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Ethical Standards and Notifications

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

13.2 IRB Approval

The study will be reviewed by the IRBs at M. D. Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Emory University, University of Chicago, and the University of Maryland. The protocol will also be reviewed by the National Cancer Institute and the FDA.

13.3 Patient Data Protection and Confidentiality

Each study participant will be assigned a unique study ID number to assure confidentiality.

Each investigator is responsible for keeping a master list of all enrolled patients including their name, unique study ID number, phone number(s) and last known address.

The patients will also be informed in the informed consent document about the possibility of audits by authorized representatives of the NCI, FDA, OSI Pharmaceuticals or study monitors, in which case a review of those parts of the hospital records relevant to the study may be required, with due consideration of the patient confidentiality. New pathology accession numbers will be assigned for specimen identification versus patient hospital numbers. Once assigned, these numbers are cross-referenced in a secure database maintained by the study statistician at M. D. Anderson Cancer Center.

In the event of a breach of confidentiality, all investigators and the sponsors will be notified. Appropriate action will be taken following consultation with these representatives, as well as with the involved patient(s). Actions could include but will not necessarily be limited to withdrawal of the patient(s) from the study or recording of the patient(s) data.

13.4 Informed Consent

The investigator is responsible for giving and documenting the patients full and adequate verbal and written information about the nature, purpose, possible risks and benefits of the study. This will include information that (a) this is a placebo controlled trial, (b) the study agent must be taken daily for the 1 year duration of the intervention, (c) they must be willing to have biopsies and give blood at the specified times, (d) specified follow-up visits with physicians and study clinics must be scheduled and kept, and (e) side effects and health risks may occur, as described in the consent form.

The patients will be given the opportunity to refuse to participate in the study, under the assurance that such refusal will in no way affect their treatment at their study center. The patients must also be notified that they are free to withdraw from the study at any time. The investigator and study research nurse are responsible for obtaining signed informed consent from all participants. This consent form fulfills the requirements set by the Institutional Review Board at M. D. Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Emory University, the University of Chicago, and the University of Maryland. It fully describes the procedures, risks, alternatives and potential benefits as required by FDA specifications. A copy of the signed consent form will be placed in the patient's medical record, and a separate copy will be maintained in the research file. Another copy will be given to the patient for his or her own record.

14. FINANCIAL SUPPORT AND DISCLOSURE

14.1 Financial Support

The study is funded by grant P01-CA-106451 from the US National Cancer Institute (NCI). OSI Pharmaceuticals will support the study by providing active drug and matched placebo and provide funds specifically for monitoring this multicenter study. The NCI and OSI Pharmaceuticals will, if requested, have the right to review and comment upon any manuscripts prior to submission for publication.

14.2 Financial Disclosure

None of the investigators listed in this protocol have received or will receive financial support from OSI Pharmaceuticals.

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