Phase Ib Study of Chemoprevention with Green Tea Polyphenon E and Erlotinib in Patients with Advanced Premalignant Lesions (APL) of the Head and Neck

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Phase 1B Study of Chemoprevention with Green Tea Polyphenon E and Erlotinib in Patients with Advanced Premalignant Lesions (APL) of the Head and Neck

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Abstract

Purpose: Based on synergistic effects between green tea polyphenon E (PPE) and epidermal growth factor receptor-tyrosine kinase inhibitor in preclinical studies, we conducted a phase 1b study of the PPE and erlotinib combination in patients with advanced premalignant lesions (APL) of the oral cavity and larynx.

Patients and Methods: Patients were treated with a fixed dose of PPE (200mg 3x day) and dose escalation of erlotinib (50, 75, 100 mg daily) for 6-months (6-M) with tissue biopsy at baseline and 6-M. Primary endpoints were safety and toxicity, secondary endpoints were evaluation of pathologic response, cancer free survival (CFS), overall survival (OS) and biomarker modulation.

Results: Among 21 enrolled patients, 19 began treatment and 17 completed 6 months of treatment with PPE and erlotinib. Main characteristics of treated patients: 15 severe dysplasia or carcinoma in situ; 17 oral cavity. Only skin rash was associated with DLT and MTD. Recommended doses for phase 2 studies are PPE 600mg daily plus erlotinib 100mg daily for 6-M. Pathologic responses in 17 evaluable patients: pCR (47%) and pPR (18%). The 5-year CFS and

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OS were 66.3% and 93%, respectively. Among tested biomarkers, only pERK was correlated with response to treatment.

**Conclusion:** Treatment with PPE and erlotinib combination was well tolerated in patients with APLs of the head and neck, and showed a high rate of pathologic response with excellent CFS. This combination deserves further investigation for the chemoprevention and/or prevention of second primary tumors in early stage head and neck cancer.

**Keywords**
Chemoprevention; green tea PPE; erlotinib; premalignant lesions; phase 1b

**Introduction**

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer worldwide. In the United States, head neck cancer accounts for 3% of all cancers, with approximately 60,000 new cases and more than 12,000 deaths estimated in 2020 (1). Despite advances in conventional therapies, including surgery, radiation, and chemotherapy, molecularly targeted agents, and more recently developed immunotherapy, the overall survival rate for SCCHN has only marginally improved in the past three decades (2, 3). Thus, the development of effectively preventive approaches is highly desirable to reduce the incidence and mortality of SCCHN.

The most studied agents for chemoprevention of head and neck cancer are vitamin A and its analogs. In a double-blind randomized study using either high-dose 13-cis-retinoic acid (13-cRA) or placebo for the treatment of oral premalignant lesions, clinical and pathological responses were observed in more than 50% of those treated with high-dose 13-cRA (4). However, toxicity was significant and the duration of response was limited. Follow up clinical trials attempted to use a long-term low dose of 13-cRA to achieve similar efficacy with reduced toxicity (5, 6), however, the results were disappointingly negative (5–7). Because retinoids and interferons are known to be highly synergistic, a three-drug combination regimen of 13-cRA, interferon-alpha, and alpha-tocopherol (biochemoprevention) was tested in patients with advanced premalignant lesions or locally advanced SCCHN in an adjuvant setting (8–10). The results of these pilot studies were promising, but validation in large-scale clinical trials has not been conducted.

Molecularly targeted agents have also been investigated for their chemopreventive potential. Cyclooxygenase-2 (COX-2) is frequently expressed in neoplastic cells of head and neck, lung, colon, and breast cancer tissues. Almost 100-fold greater expression levels of COX-2 mRNA were found in SCCHN cells compared with normal oral mucosa (11). Thus, selective COX-2 inhibitors have been considered as promising agents for chemoprevention (12), but the cardiovascular side-effects of these agents raise concerns about their use in the preventative setting (13). The epidermal growth factor receptor (EGFR) is also a potential target for chemoprevention given its overexpression in a wide variety of malignant tumors, including SCCHN (39). However, single agent EGFR-TKI erlotinib did not show activity in the prevention of oral cancers in a multi-institutional, placebo-controlled randomized phase 3 study in patients with premalignant lesions of the oral cavity (EPOC) (14).
In general, combination strategies have proven more effective than single agents in the prevention and treatment of cancer, since combination therapies not only enhance clinical responses but also diminish the probability of developing drug resistance (24). Combining lower doses of effective drugs may also reduce the risk of side effects whilst eluding drug resistance and improving efficacy, which is a particularly important strategy in cancer chemopreventive approaches (29). Although there have been some promising results with combination chemoprevention strategies for cancer (10, 26), the use of multiple agents has mainly been studied in the context of cancer treatment. The development of SCCHN is a multi-step process involving multiple signal transduction pathways and complicated cross-talks among the pathways (27). Combined treatments using appropriate multi-targeted agents may be more effective than targeting single molecules in overcoming the variability and complexity of genetic alterations in SCCHN (28).

In preclinical studies, our group found that combined treatment with COX-2 inhibitor (celecoxib, Celebrex) and EGFR-TKI (erlotinib) significantly inhibited tumor cell growth as compared with each single agent both \textit{in vitro} and \textit{in vivo} (15, 16). Based on these results, we conducted a phase I pilot clinical trial to treat premalignant lesions of SCCHN with the combination, which showed promising efficacy but significant toxicity (17, 18). Natural compounds may offer improved safety profiles, a particularly important consideration for chemoprevention approaches. Green tea (\textit{Camellia sinensis}) is one of the most widely consumed beverages worldwide. The cancer preventive activities of green tea have received a great deal of attention from researchers and the general public. We observed in preclinical studies that the combination of green tea polyphenon E (PPE) and EGFR-TKI erlotinib synergistically inhibits tumor growth (54). Epidemiological studies from different countries have reported promising results in reducing human cancer risk (19–22), while other studies, however, are not consistent with these observations (23, 24). Therefore, definitive conclusions on the cancer preventive effects of green tea cannot be reached due to various confounding factors, and further studies in the clinical trial setting are clearly warranted (25).

In the current study, we tested the combination of green tea PPE and EGFR-TKI erlotinib in a phase 1b study. Although toxicity and pharmacokinetics have been studied for either erlotinib or green tea PPE as single agents in humans, no clinical studies have been conducted combining these two agents in the chemoprevention setting in head and neck cancer. Therefore, we conducted a phase 1b clinical trial with dose escalation in patients with advanced premalignant lesions of the oral cavity and larynx along with biomarker studies as a major project of the NCI-funded Head and Neck Cancer SPORE (Specialized Program of Research Excellence) Program.

**Patients and Methods**

**Study design**

This phase 1b chemoprevention study recruited all patients in a single institution at Emory University Winship Cancer Institute and was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS) and performed after approval by the Institutional Review Board (IRB) of Emory University.
Winship Cancer Institute. The primary objectives of the study were to explore dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) and assess safety of the combined treatment with green tea PPE and erlotinib in patients with advanced premalignant lesions of the head and neck. Based on simulation studies of the feasibility parameter alpha, in this study we adopted the Escalation with Overdose Control (EWOC) design, which is an effective means of controlling the frequency of overdosing in a phase 1 trial (30). The secondary objectives were to assess pathologic response, overall survival (OS) and cancer free survival (CFS), and to assess whether relevant biomarkers were modulated by the treatment in tissues or cytobrushed specimens. Pathological response was defined as follows: pathological complete response (pCR) is defined by complete disappearance of dysplasia from the epithelium, pathological partial response (pPR) by improvement of dysplasia at least one degree (i.e., severe dysplasia becomes moderate or mild dysplasia), pathological stable disease (pSD) by minor focal improvement or no changes of dysplasia, and pathological progressive disease (pPD) by worsening of at least one degree of dysplasia or development of invasive squamous cell carcinoma. The final pathological responses were evaluated by pathologists by comparing the biopsied tissues at 6 months to the pre-treatment initial biopsied tissues.

The key eligibility criteria included: documented histology of premalignant lesions of the oral cavity or larynx including advanced premalignant lesions (mild dysplasia, moderate dysplasia, severe dysplasia or carcinoma in situ); definitively treated T1–2N0 with oral premalignant lesions; ECOG performance status of 0 or 1; at least 18 years of age; normal bone marrow, renal and hepatic functions; ability to swallow the pills of green tea PPE and erlotinib; adequate contraception and negative pregnancy test for women of child-bearing potential; consent to have re-biopsy for pathologic responses and biomarker studies using tissue; cytobrushed or blood samples; and signed written informed consent form. For biomarker studies, we recruited non-smoking normal individuals as controls.

**Treatment**

Treatment schedule included a fixed dose of green tea PPE (200 mg) orally administered three times a day, and erlotinib administered orally daily with dose escalation from 50mg [level 1], to 75mg [level 2] to 100mg [level 3] for 6 months. Because of the potential toxicities of erlotinib, such as skin rash and diarrhea, the dose of erlotinib in this study was limited to 100mg per day after consultation with the FDA when the IND was filed. For all enrolled patients, a tissue biopsy was obtained before treatment for diagnosis and a second biopsy was obtained after 6 months of treatment to evaluate pathologic response and biomarker levels, while biopsy at 3 months or 12 months was optional. We also performed cytobrush of the APL lesions and normal buccal mucosa at baseline, 3, 6, and 12 months for biomarker studies.

**Biomarker studies:**

Biopsy specimens were collected at baseline, 6 months and 12 months (optional) intervals. Formalin-fixed paraffin embedded (FFPE) biopsy tissue sections (4-micron thickness) were subjected to immunohistochemical staining, and all sections were pre-heated for 30 minutes and washed through a series of xylene and alcohol treatments, followed by antigen retrieval
using 1X citrate buffer in a microwave. The slides were cooled at room temperature and quenched using 3% hydrogen peroxide in distilled water. The sections were washed and then blocked using 2.5% normal horse serum following the instructions from the manufacturer (Vectastain Kit, Vector Laboratories, Burlingame, CA). Tissue sections were stained using primary antibodies of pERK (4370, Cell Signaling Technology, Danvers, MA), pS6 (4857, Cell Signaling Technology, Danvers, MA) and Ki-67 (ab92742, Cambridge, MA.), and incubated overnight at 4°C. Sections were washed and incubated with corresponding secondary antibodies, visualized by DAB and counterstained with hematoxylin. Positive signals were counted in three random fields under ×200 magnification and were quantified using weighted index (= Intensity × % of positive staining). The intensity of staining was scored as negative (0), weak (1+), intermediate (2+), and strong (3+) positivity. The quantification was determined blindly and independently by two investigators (including the pathologist).

Statistical methods:
Statistical analysis was conducted using SAS Version 9.4, and SAS macros developed by the Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute (31). The significance level was set at P < 0.05. Descriptive statistics for patients’ baseline characteristics and toxicity profile were reported. The univariate association of pathological response was assessed by chi-square test for categorical biomarkers and ANOVA for numerical biomarkers. Kaplan-Meier method and log-rank test were used to estimate 5-year event-free rate with 95% confidence interval.

Results
Patient characteristics and toxicity evaluation
We enrolled 21 patients from February 2011 to November 2017 at Emory Winship Cancer Institute after all eligibility criteria were met and patients signed the IRB-approved informed consent form. We also recruited 6 never smokers with no history of cancer to serve as controls for future studies. After obtaining informed consent, we collected cytobrushed saliva samples from these control subjects and banked them at −80°C for future biomarker studies using next generation sequencing or other molecular studies. Among 21 enrolled patients, 2 were ineligible, 19 patients began treatment, and 17 completed 6 months of treatment (2 patients discontinued treatment due to personal and social reasons within 2 months of treatment). The characteristics of these 19 patients are listed in Table 1. Briefly, there were 9 males and 10 females; median age of 64 years; 10 former or current smokers, 9 never smokers and none had any other risk factors (i.e., betel nut chewing, mal-fitting of denture or any occupational hazards); 15 patients with severe dysplasia or carcinoma in situ (CIS), 2 with moderate dysplasia, 2 with mild dysplasia; 13 prior surgical resections; and 17 patients had APL of the oral cavity and 2 of the larynx. The initial 3 patients were treated with fixed dose of green tea PPE 200mg, three times a day in combination with a dose escalation of erlotinib 50mg a day (level 1), 4 patients received erlotinib 75mg a day (level 2), and 12 patients received erlotinib, 100mg a day (level 3).
The cumulative toxicity of all three doses are tabulated in Table 2. At dose level 1, we observed skin rash and dryness, indigestion, nausea, fatigue, anemia and thrombocytopenia, which were all grade 1 and resolved after treatment, but we did not observe any DLT. Only 1 patient developed grade 3 skin rashes on erlotinib 100mg dose (level 3); the drug was withheld for 2 weeks and restarted at 75mg dose without any further dose reduction. Two patients developed grade 3 hypertension (1 at level 2 and 1 at level 3), which resolved after withholding both green tea PPE and erlotinib for one week and resuming the drug with one dose lower level without further problems. One patient developed grade 2 epistaxis likely related to erlotinib with dryness of the nostril, which resolved without any significant issue. Significant DLTs were skin rash and hypertension (level 3) which were resolved after withholding erlotinib for one week and the MTD may have not been reached (the dose of erlotinib in this study was, however, limited to 100mg per day after consultation with the FDA when the IND was filed). Therefore, the recommended doses for future phase II studies would be erlotinib 100mg per day and green tea PPE 200mg three times a day.

**Pathological response and survival**

Among the 19 patients enrolled, 2 patients dropped out within 2 months of treatment (without undergoing biopsy) and 17 patients completed 6 months of treatment with green tea PPE and erlotinib. All 17 patients underwent repeat biopsy at 6 months for pathologic evaluation and biomarker studies. Pathology specimens from each patient before and after treatment were assessed by the 3 assigned head and neck pathologists and reviewed again by the study designated pathologist (QS) to ensure no discrepancies. In fact there were no disagreements in pathologic grading for all participating subjects. Among 17 pathologically evaluable patients, 8 patients achieved pCR (47%), 3 pPR (18%), 3 pSD (18%) and 3 pPD (18%), with an overall major pathologic response of 65% (11/17). Figure 1 shows examples of complete and partial pathologic responses. In the subset analysis, among 13 patients with severe dysplasia or *carcinoma in situ* histology, 6 patients achieved pCR, 2 had pPR, 2 had pSD and 3 had pPD. For this subset of very advanced APL, we obtained major pathologic responses of 62% (6 pCR and 2 pPR, 8/13 patients) which is remarkable, and a similar rate as in the overall population. The median duration of response was 28 months among all responders, 30 months among subjects with CR (N=8), and 27 months among subjects with PR (N=3) (P=NS). During the follow up period of time, the number of recurrences or PD in the CR group was 2/8 (25%), while that in the PR group was 1/3 (33%) and 2/3 (66%) in the SD group (because of small sample size, the p value was not significant). Two patients developed invasive cancer among all responders. The recurrences (both pre-malignant and invasive cancer) developed in the same sites as the initial premalignant lesions (please see detail for each responder in Figure 2).

The median follow up time was 44.2 months with a 95% CI of (21.3, 59.3) months. The median overall survival has not been reached and only one patient died of non-cancer related diseases (Figure 3A). The median cancer free survival (Figure 3B) has also not been reached. The 5-year cancer free survival and 5-year overall survival were 66.3% (95% C.I., 29.0%, 87.2%) and 92.9% (95% C.I., 59.1%, 99.0%), respectively.

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Biomarker studies

We studied biomarkers in biopsied tissues collected before treatment (baseline samples) and 6 months post treatment (mandatory). Immunohistochemical (IHC) staining was performed based on tissue availability for Ki-67, pERK, and pS6 and quantified by two independent investigators. Positive signals were counted in three random fields as described in the Methods section.

All three biomarkers were analyzed in the baseline tissues, however, no differential expression was observed based on the degree of dysplasia, perhaps related to the small sample size (data not shown). We analyzed the expression of the markers and correlations between the expression of any biomarkers and pathologic response. Interestingly, pERK expression at baseline was significantly correlated with pathologic response \((p=0.014)\) (Figure 4 & Table S1), while expression of Ki-67 and pS6 were not associated with pathologic responses \((p=0.92\) and \(p=0.68\), respectively) (Table S1). We also analyzed whether there was any change in the 3 biomarkers after the treatment for 6-months and any correlation in the change to pathologic responses. It was observed that pERK was clearly reduced particularly in the CR patients and Ki67 was also reduced in most cases after the treatment (Figures 4, S1A, S1B, and Table S1), although we did not obtain a statistically significant correlation between the reductions of ERK and Ki67 and pathologic responses due to the small sample size (Table S1).

Discussion

The concept of chemoprevention in head and neck cancer was born many decades ago (32) and multiple agents including retinoids have been extensively studied. In particular, high dose retinoids have been well documented to effectively prevent invasive cancer in premalignant lesions of the head and neck, but demonstrated significant toxicity (4, 5, 33), while low doses of retinoids did not prevent second primary tumor development when given in an adjuvant setting in early stage head and neck cancer in a large placebo controlled phase III randomized study (34–36). Many other studies with different chemopreventive agents have been conducted in the past without much success (14, 37, 38). Therefore, as of today, no standard approaches have been established for the chemoprevention of head and neck cancer.

As molecularly targeted agents have been extensively developed for cancer therapeutics, orally active agents with limited but tolerable toxicities (i.e., EGFR-TKI [erlotinib]) may be good candidates for chemoprevention in SCCHN. EGFR overexpression has been documented extensively in a wide variety of malignant tumors, including SCCHN (39). Overexpression of EGFR and its ligand TGF-alpha was observed in 80 to 90% of SCCHN specimens. Several studies, including our own, have demonstrated that EGFR overexpression correlates with reduced disease-free and overall survival and increased risk of disease recurrence and metastasis (40). Importantly, we found that EGFR expression was upregulated in a stepwise manner from normal human oral epithelium adjacent to tumor and remained elevated throughout the histologic progression from hyperplasia to dysplasia to carcinoma in situ, and further progressed to squamous cell carcinoma (39), suggesting that EGFR may serve as an excellent target for chemoprevention. There are several potential
approaches to block EGFR signaling pathways in carcinogenesis. Among these studies, many synthetic and semi-synthetic compounds have been identified as EGFR-selective TKIs, which induce significant growth inhibition of human tumor xenografts. Oral administration of erlotinib to mice significantly reduced the level of EGFR autophosphorylation in human tumor xenografts, and daily administration of erlotinib markedly inhibited the growth of the HN5 human head and neck carcinoma, as well as A431 squamous epidermoid carcinoma xenografts (41, 42). However, the chemopreventive activity of erlotinib has only recently been evaluated in human cancers (14, 17, 18). Phase I pharmacokinetic (PK) studies of erlotinib have been conducted in healthy volunteers and in individuals with a variety of solid tumors (43–48) with excellent oral bioavailability. Previously, erlotinib was tested in patients with high-risk oral premalignant lesions (OPLs) defined by specific loss of heterozygosity (LOH) profiles in the Erlotinib Prevention of Oral Cancer (EPOC) study as a multi-institutional randomized, placebo-controlled double-bind trial with erlotinib (150 mg/day) or placebo for 12 months. One hundred and fifty subjects were randomized with 75 each to the placebo and erlotinib groups. The primary study endpoint of 3-year cancer free survival rates in placebo- and erlotinib- treated patients were disappointing similar, 74% and 70%, respectively (P= 0.45). The study, therefore, concluded that single agent erlotinib did not improve cancer free survival in high-risk patients with LOH-positive or high-EGFR-gene-copy-number OPLs, thus this study does not support single agent erlotinib use in this setting (14).

Green tea is a non-fermented product containing four major polyphenols: epigallo-catechin-gallate (EGCG), epicatechin gallate (ECG), epigallo-catechin (EGC), and epicatechin (EC) based on HPLC analysis (49, 50). EGCG is the most abundant and active catechin and has received by far the most attention among the green tea extracts. Several studies have reported the broad inhibitory activity of green tea and its constituents against carcinogenesis (51–55). Multiple signal transduction pathways have been heavily studied in the inhibition of tumor growth and suppression of carcinogenesis by EGCG and other tea polyphenols (51–56). This inhibitory effect of EGCG has also been attributed to the inhibition of AP-1 activity, possibly due to the inhibition of mitogen-activated protein kinase (MAPK) activities (57–59). In our biomarker studies of our phase 1b trial, phosphorylated ERK was shown to be significantly correlated with pathologic response. In fact, this finding is compatible with the findings of preclinical studies: EGCG was shown to inhibit the activation of PI3K/AKT, which represents cellular signaling cascades of MAPK/ERK in cell growth, proliferation and survival (57).

Toxicity is always an important issue when studying cancer chemopreventive agents. When green tea polyphenols are administered orally to animals (mice and rats etc.), no toxicity is observed even at high doses (500mg/kg body weight). However, liver toxicity and thiol conjugates of EGCG can be observed when EGCG is administered in mice (58). In human studies, it was reported that good bioavailability of free EGCG can be achieved by taking green tea PPE capsules, which were well tolerated up to a dose of 800mg EGCG (59). Nevertheless, there have been some concerns regarding the safe use of green tea extracts as a weight reduction aid (60). However, an encouraging report by Bettuzzi, et al., (61) demonstrated that daily oral administration of 600 mg of tea catechins for one year prevented prostate cancer development in subjects with high grade PIN without any toxicity.
profile. Furthermore, our previous study conducted at M.D. Anderson Cancer Center indicated that a phase I trial of oral green tea extract in adult patients with solid tumors led only to tolerable toxicity which was caffeine related (62). These observations strongly support that green tea polyphenols may serve as a good candidate for chemoprevention.

Importantly, green tea polyphenols, particularly, the combination of EGCG and erlotinib may synergistically inhibit carcinogenesis and tumor progression through targeting multiple signal transduction pathway molecules, such as EGFR, AKT, MAPKs, or NF-κB (54, 63). In fact, our current phase 1b trial clearly showed that the combination of green tea PPE and EGFR-TKI (erlotinib) was well tolerated in patients with advanced oral premalignant lesions in the mouth cavity and larynx. After 6 months of intervention, we obtained remarkably high pathologic responses including complete response (47%, 8/17), partial response (18%, 3/17), and stable disease (18%, 3/17), while only 18% (3/17) of patients had progressive disease. In particular, the most advanced premalignant lesions (severe dysplasia or carcinoma in situ) showed also very high pathologic major responses (62%) with excellent median duration of response (33.6 months) in a subset analysis. Therefore, our combined treatment is clearly more active in terms of pathologic response than green tea extract alone, which was reported to yield a pathologic response in 6 of 28 patients (21% with all partial response) (64). As shown in the EPOC study and stated previously, treatment with single agent erlotinib did not show any impact on oral cancer free survival compared to the placebo group (14). Therefore, we believe that our combination of green tea PPE and erlotinib appears to be much more effective and synergistic in preventing the progression of APLs to invasive cancer in the head and neck, although the finding is based on a small pilot phase 1 study. Thus, based on the encouraging results we are convinced that this combination well deserves to move forward in larger chemoprevention studies targeting premalignant lesions of the head and neck, and/or chemoprevention of second primary tumors in an adjuvant setting in early stage (stages I and II) head and neck cancer that is definitively treated with surgery, radiation therapy or both. Currently there are no standard approaches in an adjuvant setting to treat these patients who have developed early stage head and neck cancer, yet there is a good chance of recurrence or development of SPT over the years to come.

Finally, we performed a limited biomarker study using the biopsied tissues, which appears to be a critical component in such chemoprevention studies. Of the markers tested, pERK was the only marker predictive of outcome of response in our pilot study. Based on the small sample size of the current study, however, it is not surprising that the associations of other biomarkers were not statistically significant. Clearly, such biomarker studies should be incorporated into future larger sample sized clinical studies to better understand the biology of chemoprevention studies. Using the collected cytobrushed samples (banked at −80°C) from the enrolled treated and control subjects we plan to conduct additional biomarker studies.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.
Acknowledgements:

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References:


Translational Relevance

We observed in preclinical studies that the combination of green tea polyphenon E (PPE) and epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) synergistically inhibits tumor growth. This report describes the phase I clinical evaluation of the combination, green tea PPE and EGFR-TKI (erlotinib), in patients with advanced premalignant lesions (APLs) of the oral cavity and larynx. The doublet combination with dose escalation of erlotinib and fixed dose of PPE was well tolerated in patients with premalignant lesions and demonstrated a safety profile consistent with that of the individual agents. No unexpected safety concerns were noted. The combination demonstrated promising pathologic responses, including more than 50% of patients with pathologic complete and partial responses after 6 months of treatment. This combination, therefore, deserves further investigation for chemoprevention and/or prevention of second primary tumors in early stage head and neck squamous cell carcinoma.
Figure 1:
Three example cases of pathologic responses of premalignant lesions of the oral cavity before treatment (Pre-Tx) and after 6 months of treatment (Post-Tx) with green tea PPE and erlotinib. Case #16 was moderate dysplasia before treatment (Pre-Tx) that became mild dysplasia (pathologic partial response) after treatment (Post-Tx). Case #3 was mild dysplasia Pre-Tx and improved to no dysplasia Post-Tx (pathologic complete response). Case #24 was severe dysplasia/carcinoma in situ (CIS) Pre-Tx that also improved to no dysplasia Post-Tx (pathologic complete response) (200X Magnification).
Figure 2:
The figure represents duration (months) of response for each responder among 17 pathologically evaluable patients: 8 CRs, 3 PRs and 3 SDs. Five patients developed progressive disease during the follow-up: * Indicates progressive disease without developing invasive cancer (3 cases) and ** indicates progressive disease with developing invasive cancer (2 cases).
Figure 3:
Kaplan-Meier plots of overall survival (OS) (A) and cancer free survival (CFS) (B) of the 19 patients. The 5-year OS was 93% (95% CI, 59.1%–99%) and median OS was not reached. The 5-year CFS was 66.3% (95% CI, 29.0%–87.2%) and median CFS was not reached. The median follow up was 44.2 months.
Figure 4:
Biomarker modulation of Case #24 (severe dysplasia/CIS) at baseline (Pre-Tx) became no dysplasia (pathologic complete response). pERK was highly expressed in the baseline (BL) tissue which was downregulated after 6 months of treatment (6-M). PS6 was not expressed at baseline but increased after 6 months, while Ki-67 was highly expressed at baseline (BL) and was downregulated after 6 months of treatment (6-M) (200X Magnification).
Table 1:

Patient Characteristics

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<td>Never Smokers</td>
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</table>
### Table 2: Toxicity Evaluation

<table>
<thead>
<tr>
<th>Side Effects (N = 19 Patients)</th>
<th>G1 No (%)</th>
<th>G2 No (%)</th>
<th>G3 No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash (skin)</td>
<td>16 (84)</td>
<td>1 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Pruritus/Dry skin</td>
<td>13 (68)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (53)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (53)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Hair thinning</td>
<td>4 (21)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety/sleep disorder</td>
<td>3 (16)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tongue pain</td>
<td>3 (16)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Indigestion</td>
<td>3 (16)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (21)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (16)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SGOT/SGPT elevation</td>
<td>8 (42)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5 (26)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (11)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

G1 - Grade 1, G2 - Grade 2, G3 - Grade 3.