PROTOCOL TITLE: Utilization of Low Level Laser Therapy (LLLT) for Radiation-Induced Dermatitis in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC)

PRINCIPAL INVESTIGATOR:

David Weksberg, MD, PhD

VERSION DATE: 12DEC2022

CLINICALTRIALS.GOV REGISTRATION: NCT02384434

Table of Contents

1.0 Study Summary 3
2.0 Objectives 4
3.0 Background 4
4.0 Study Endpoint 6
5.0 Study Intervention/Investigational Agent 6
6.0 Procedures Involved 7
7.0 Study Timelines 8
8.0 Inclusion and Exclusion Criteria 8
9.0 Withdrawal of Subjects 8
10.0 Risks to Subjects 9
11.0 Potential Benefits to Subjects 10
12.0 Data Management 10
13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects 10

1.0 Study Summary

Study Title	Utilization of Low Level Laser Therapy (LLLT) for Radiation-Induced Dermatitis in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC)
Study Design	Single-arm, Phase I/II
Primary Objective/Endpoint	Assess the safety and efficacy of low level laser therapy (LLLT) in mitigating radiation-induced dermatitis in patients undergoing radiation therapy for head and neck squamous cell carcinoma (HNSCC) Endpoint: Documented Grade 3 or higher Adverse Events as per CTCAE v4.0
Secondary Objective(s)/Endpoints	assessment of patient-reported quality of life data, pain parameters and dermatologic quality of life responses Endpoints: • quality of life data measured using the University of Washington Quality of Life Questionnaire (UW-QOL) • pain parameters assessed using Brief Pain Inventory (BPI) • dermatologic quality of life responses measured using the Dermatology Life Quality Index (DLQI)
Research Intervention(s)/ Investigational Agent(s)	THOR Laser system
IND/IDE #	N/A
Study Population	patients with histologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx who are candidates for either definitive or adjuvant therapy consisting of a chemotherapy regimen and concurrent radiation therap
Sample Size	75 planned
Study Duration for individual participants	15 months

2.0 Objectives

2.1 The study aims to assess the safety and efficacy of the utilization of low level laser therapy to mitigate radiation-induced dermatitis in patients undergoing definitive or adjuvant radiation therapy with head and neck squamous cell carcinoma.

2.2 The hypothesis is that low level laser therapy given prior to and during the course of treatment will decrease the rate of grade III dermatitis, a common finding seen in patients undergoing radiation therapy with head and neck squamous cell carcinoma. An additional goal of low level laser therapy is to increase wound healing.

3.0 Background

3.1 There are approximately 43,000 cases of head and neck squamous cell carcinoma (HNSCC) diagnosed annually in the United States of which approximately two-thirds will present with locally-advanced disease (Stage III or IV). For these patients, traditional treatment options including surgical resection and adjuvant radiotherapy have been largely supplanted by non-operative approaches. The success of non-operative approaches has been made possible through both refinement of radiotherapy (RT) techniques as well as an increased understanding of the biology of the disease and the subsequent introduction of targeted agents including cetuximab, an inhibitor of the epidermal growth factor (EGFR) (Kabolizadeh et al, 2012).

Much has been learned about the biology of HNSCC including the role of EGFR. This receptor is expressed at high levels in the majority of HNSCC. Furthermore, pre-clinical data indicate that it is intimately associated with the malignant phenotype of HNSCC. EGFR activation in response to its ligand results in phosphorylation of its intracytoplasmic tyrosine kinase domain, leading to a cascade of signal transduction within the cell and ultimately alternations in DNA synthesis, cell proliferation, anti-apoptosis, and transcription of growth factors such as pro-angiogenic molecules. Blockade of this pathway serves as an effective anti-neoplastic as well as radiosensitization strategy.

The anti-neoplastic properties and radiosensitization of EGFR blockade was proven in a landmark randomized trial in patients with locally-advanced, non-operative HNSCC in which patients were randomized to RT alone or RT with weekly cetuximab (Bonner JA, et al., 2010). The investigators found that locoregional control and survival were significantly improved with cetuximab. Specifically, the 3-year rate for freedom from local-regional progression and overall survival were 47% and 55% for RT with cetuximab compared with 34% and 45% for RT alone. The relative reduction in the risk of local-regional progression and death were 32% (p=0.005) and 26% (p=0.03), respectively (Bonner JA, et al., 2010). Interestingly, improved outcomes were associated with the

development a drug-induced acne-like rash, a common side effect of this class of medications.

In this respect, cetuximab appears to have a different toxicity profile than that of traditional chemotherapy such as cisplatin. The most commonly reported side effect is the development of skin reactions including macular, papular, and pustular rashes, xerosis, fissures, telangiectasias, and hyperpigmentation of the hair and nails (Bernier et al., 2008). The most frequent of these reactions is an acne-like rash that predominately appears in areas rich in sebaceous glands. The acne-like rash comprises itchy erythematous follicular papules that evolve into pustules. Other presentations include diffuse erythema with follicular papulopustules and telangiectasia, a seborrhoeic dermatitis-like rash or, occasionally, an edematous facial erythema. In the absence of radiation, the acne-like rash can be seen within a few days of the initiation of treatment and peaks 2–3 weeks after starting therapy (Bernier et al., 2008).

The effect on the skin during the combination of cetuximab and radiation is of considerable interest, as it might require special care to reduce symptoms and severity. It appears that radiation may delay the onset of the cetuximab-induced rash as it typically appears within irradiated fields 3–5 weeks after initiation of treatment (Bernier et al., 2008). There appears to be no obvious relationship between the severity of cetuximab-associated acne-like rash outside irradiated fields and the severity of radiation dermatitis. The aforementioned Phase III trial (Bonner JA et al., 2010) revealed no statistically significantly increase in the incidence or severity of radiation dermatitis compared with radiotherapy alone. The incidence of grade 3 radiation dermatitis was 18% with RT alone and 23% with RT with cetuximab ($p = 0.27$). There was a slight increase in the median duration of radiation dermatitis in the cetuximab arm (11.1 weeks) compared with the RT-alone arm (9.4 weeks).

While the majority of skin reactions seen with cetuximab are grade 1 or 2 (80%), there is certainly an effect on quality of life (QoL) as well as treatment continuity. A survey of EGFR inhibitor use by oncologists found that 76% of clinicians interrupted treatment due to skin toxicity and 32% discontinued therapy altogether (Boone et al., 2006). However, its prevalence presents an opportunity to explore novel modes of symptom reduction as well as to assess modalities that may improve pain and patient-reported quality of life (PR-QoL). Currently, the most utilized treatments include anti-inflammatory agents, antibiotics, antihistamines, and saline compresses (Bernier et al., 2008). A potential novel strategy to influence both the cetuximab as well as radiation-induced dermatitis is the implementation of low level laser light therapy (LLLT).

3.2 LLLT is potentially effective in wound healing by producing an anti-inflammatory response by promoting cellular metabolism and increasing circulation and lymphatic flow. The mechanism of action may be related to a decrease in interstitial edema and an increase in the healing

process. Its clinical utility in reducing oral mucositis was assessed prospectively and was recently discussed in a Cochrane review (Clarkson et al., 2010; Guatuam AP et al., 2012; Migliorati et al., 2013). Here, LLLT showed a reduction in severe mucositis when compared with the sham procedure (risk ratio: 5.28, 95% confidence interval: 2.30 to 12.13). While these studies support an improvement in oral mucositis with LLLT, the clinical experience addressing an improvement in cetuximab-induced rashes and radiation-dermatitis is limited. An Italian case series (Gobbo et al., 2011) reported that in 4 patients with metastatic colorectal cancer and two patients with HNSCC, LLLT reduced cetuximab-related skin toxicities. Here, patients were treated with two 8-minute long consecutive sessions/day over a 4-day treatment. Patients were evaluated weekly for up to 3 weeks and after 180 days. Follow-up evaluations including a questionnaire about the onset and progression of the acneiform rash and visual analog scales were reported. The authors reported that after the fourth session of LLLT, the patients showed a decrease in both cetuximab-related toxicity and visual analog scales, up to complete regression of the lesions in all treated areas (Gobbo et al., 2011). No adverse effects from treatment were reported. These findings suggest that LLLT may be an effective way of managing cetuximab- and radiation-induced skin toxicities. Herein we propose a pilot study to assess the efficacy of LLLT to mitigate and ameliorate the acneiform-rash, radiation dermatitis, and pain while assessing its impact on PR-QoL measures.

4.0 Study Endpoints

4.1 Primary Endpoint: The primary endpoint is to characterize the rate of any Grade 3 or higher Adverse Events as per CTCAE v4.0 (Common Terminology Criteria for Adverse Events).

4.2 Secondary Endpoints: Several patient reported QOL metrics will be collected as secondary endpoints.

- quality of life data measured using the University of Washington Quality of Life Questionnaire (UW-QOL)
- pain parameters assessed using Brief Pain Inventory (BPI)
- dermatologic quality of life responses measured using the Dermatology Life Quality Index (DLQI)

5.0 Study Intervention/Investigational Agent

THOR Laser system: MASCC/ISOO Clinical Practice Guidelines for mucositis (May 2014) recommend LLLT to prevent oral mucositis. In addition, the following studies have indicated that LLLT in the setting of RT alone or chemo-RT, appears to confer a benefit in reducing the rates of mucositis when compared to placebo or supportive care and is suggested for the prophylaxis of mucositis: -Phase III trial of low-level laser

therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation. -Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. -Effect of low level helium-neon (He-Ne) laser therapy in the prevention & treatment of radiation induced mucositis in head & neck cancer patients. -Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. -Low-energy He/Ne laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer. Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - a triple blinded randomized controlled trial. -Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. -Use of 660-nm diode laser in the prevention and treatment of human oral mucositis induced by radiotherapy and chemotherapy. -Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis. -Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers.

6.0 Procedures Involved

6.1 Screening / Pre-treatment:

- Medical history
- Physical examination, including Karnofsky Performance Status and vital signs.
- Signed informed consent
- Subject body weight and height
- Quality of Life Assessments (UW QoL, BPI, DLQI)

6.2 Evaluation during Treatment

- Patients will be treated with the 69 diode LED cluster probe. The wavelength utilized are both 660 nm and 850 nm. The average power density is 100 mW/cm2 and the spot size is 0.2 cm2. Treatment time is 60 seconds to each site. There are a minimum of nine treatment sites: (1) left forehead, (2) right forehead, (3) left upper cheek/malar region, (4) right upper cheek/malar region, (5) right lower cheek / trigeminal nerve mandibular division distribution, (6) left lower cheek / trigeminal nerve mandibular division distribution, (7) submental region, (8) left neck, (9) right neck. Patients will be pretreated with a minimum of 3 sessions over 7 days before starting radiotherapy. Patients will receive LLLT at least twice the week prior to initiation of radiation and then at least three times per week during the course of radiation treatment.

- Adverse Event Assessment (Grading of skin toxicity and mucositis by patient)
- Completion of patient reported DLQI during treatment week 5 and at end of treatment

6.3 Evaluation following Treatment

- Patients will be seen in follow-up at least every three months in the first year following completion of treatment.
    - Observer reported mucositis and skin reaction every three months for one year
    - Patient reported QoL assessments (UQ QoL, BPI, DLQI) every three months for one year

7.0 Study Timelines

- The expected duration of an individual subject's participation is approximately 15 months.

8.0 Inclusion and Exclusion Criteria

8.1 Inclusion Criteria:

- Male or female patients ≥ 18 years of age
- Karnofsky performance status > 70
- Histologic proof of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx
- No prior radiotherapy to the head and neck region.
- No previous systemic chemotherapy or targeted therapy
- Must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the nature of the therapy, alternatives, potential benefits, side-effects, risks and discomforts.
- Patients using standard therapies for cetuximab-induced acne-form rash will be included.

8.2 Exclusion Criteria:

- Evidence of distant metastasis on upright chest x-ray (CXR), computed tomography (CT) or other staging studies
- Any co-morbidity or condition of sufficient severity to limit full compliance with the protocol per assessment by the investigator
- Concurrent serious infection
- Continued use of Niacin

9.0 Withdrawal of Subjects

9.1 Patients are to discontinue therapy in the event of:

- Disease progression
- Development of a serious medical illness
- Evidence of dose-limiting toxicity
- Major protocol violation
- Discretion of the principal investigator

9.2 Patients may withdraw from study participation voluntarily.

10.0 Risks to Subjects

10.1 There are few risks associated with low-level laser therapy. This treatment is non-invasive and uses a cold laser output. Infrequently, eye damage has occurred with prolonged visual contact with the laser. Further, patients using concomitant supplemental niacin may experience, facial flushing.

10.2 Although no reported grade 3 or greater toxicities for LLLT have been published, patients will be closely monitored by a certified nurse prior to each delivery. Patients will be instructed to seek alternatives to niacin if taking this medication at the time of enrollment to the study. Additionally, eye protection is provided to all patients and staff present in the examination room during delivery of LLLT to prevent any eye damage. Significant mucositis from radiation is expected. Appropriate supportive care will be provided including analgesia, local therapies, and potentially low level laser therapy. Patients will be monitored weekly by the treating physicians to appropriately manage and record potential toxicities. Patients developing dermatologic adverse events will be monitored for the development of inflammatory or infectious sequelae. Supportive therapies other than the investigational intervention may include the following:

- Antibiotics: The benefit of routine antibiotics in uncomplicated (uninfected) rash is unclear. Some clinicians have used oral minocycline (Minocin), mupirocin (Bactroban), or topical clindamycin (Cleocin). Rash complicated by cellulitis should be treated with appropriate antibiotics based on clinical judgment or microbial sensitivity analysis.
- Antihistamines: Benadryl or Atarax may be helpful to control itching.
- Topical Steroids: The benefit of topical steroids is unclear.
- Retinoids: No data to support use. Use is not advised.

- Benzoyl peroxide: Should NOT be used--may aggravate rash.
- Makeup: Rash can be covered with makeup; this should not make it worse (use a dermatologist-approved cover-up, e.g., Dermablend, or any other type of foundation). Remove makeup with a skin-friendly liquid cleanser, e.g., Neutrogena, Dove, or Ivory
- Skin Cleansing Liqui-Gel.
- Moisturizers: Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena Norwegian Formula Hand Cream or Vaseline Intensive Care Advanced Healing Lotion.
- Sunlight: It is recommended that patients wear sunscreen and hats and limit sun exposure during treatment as sunlight can exacerbate any skin reactions that may occur.
- Over-the-counter medications: Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) are not advised. This rash is not like acne vulgaris and these treatments could make it worse.

11.0 Potential Benefits to Subjects

11.1 Taking part in this study may or may not make the subject's health better. While doctors hope that this study treatment will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about this drug as a treatment for cancer. This information could help future cancer patients.

12.0 Data Management

12.1 This prospective observational study seeks to describe the toxicities of patients undergoing this intervention. Rates of Grade 3 CTCAE toxicities will be documented, along with PR-QOL secondary endpoints, and will be compared to historical reports of toxicity in the literature.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

13.1 Data will be monitored internally by the research manager. Any considerable deviations or concerns are to be addressed with the research manager and the principal investigator.

Expected adverse events from each intervention (radiotherapy and LLLT) are listed in the research protocol and are to be managed accordingly. For all adverse events, sufficient information should be obtained by the investigator to determine the causality, (i.e., study

drug or other illness). The investigator is required to assess causality and indicate that assessment on the CRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator. Adverse events that continue, or emerge within 30 days, after the patient's discontinuation or completion of the study will be followed until the events resolve, are considered stable, or can be ascribed to causes other than study treatment.

All serious AE meeting criteria for reporting will be reported per the University of Pittsburgh Institutional Review Board's policies. In the event of such adverse event, the investigator must report the event(s) via phone within 24 hours and a written report filed within 24 hours to the Principal Investigator.

14.0 Statistical Considerations

14.1 Study Design/Endpoints

This is a phase I/II clinical trial aiming to assess the safety and efficacy of low level laser therapy (LLLT) in mitigating radiation-induced dermatitis in patients undergoing radiation therapy for head and neck squamous cell carcinoma (HNSCC). The primary endpoint is documented Grade 3 or higher Adverse Events as per CTCAE v4.0. The secondary objectives are the assessment of patient-reported quality of life data, pain parameters and dermatologic quality of life responses. The secondary endpoints are:

• Quality of life data measured using the University of Washington Quality of Life Questionnaire (UW-QOL)

• Pain parameters assessed using Brief Pain Inventory (BPI)

• Dermatologic quality of life responses measured using the Dermatology Life Quality Index (DLQI)aimed at the evaluation of the safety and clinical activity of tiragolumab in combination with atezolizumab, carboplatin, and pemetrexed in the 1st line treatment of non-squamous NSCLC patients with untreated brain metastases.

14.2. Statistical Analysis Plan

14.2.1 Analysis of the Primary Endpoint

The main goal of this study is to descriptively estimate grade 3 or higher adverse events as per CTCAE v4.0. The frequency and percentage will be calculated along with its exact 95% CI.

All patients who enroll in the study, and received at least 1 dose of the study treatment are evaluable for safety analysis. As per NCI

CTCAE Version 5, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. The incidence of treatment-emergent AEs and SAEs will be summarized by system organ class and/or preferred term, severity, and relationship to study treatment determined.

14.2.2 Analysis of Secondary Endpoints

University of Washington Quality of Life questionnaire (UW-QOL): The UW-QOL consists of 12 single question domains focusing on current patient health and quality of life within the past 7 days. These domains have between 3 and 6 response options that are scaled evenly from 0 (worst) to 100 (best) according to the hierarchy of response. The domains are pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety; patient choice of up to three of these domains that have been the most important to them. There are also three global questions, one about how the patient feel relative to before they developed their cancer, one about their health-related QOL and one about their overall QOL. In regard to their overall QOL, patients are asked to consider not only physical & mental health, but also many other factors, such as family, friends, spirituality or personal leisure activities that were important to their enjoyment of life.

Brief Pain Inventory (BPI): The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function.

Dermatology Life Quality Index (DLQI): The DLQI is a ten-question questionnaire designed to measure the health-related quality of life of adult patients suffering from a skin disease. Each question is scored from 0 to 3, giving a possible score range from 0 (meaning no impact of skin disease on quality of life) to 30 (meaning maximum impact on quality of life).

For all these QoL measures, descriptive statistics (mean, SD, median, and inter-quartile range) will be primarily used to summarize the scored scales at each scheduled assessment time point. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. Mixed effect model for repeated measures (MMRM) will be used to examine the change of Qol measures with time and treatment.

14.3. Sample Size/Accrual Rate

As stated in Section 14.2, the main goal of this descriptive study is not for hypothesis testing. We plan to accrue 75 patients. With this sample size, the exact 95% CI for the grade 3 AE has a maximum width of 24%. For example, if the observed rate is 15/75 (20%), then the 95% CI will be (12%, 31%) . The following is a table for the CI.

Observed proportion of grade 3 AE	Exact 95% CI for the grade 3 AE rate
5/75 (7%)	(2%, 15%)
10/75 (13%)	(7%, 23%)
15/75 (20%)	(12%, 31%)
20/75 (27%)	(17%, 38%)
25/75 (33%)	(23%, 45%)
30/75 (40%)	(29%, 52%)