Document Coversheet

Study Title:

A Phase 1 Trial: Porfimer Sodium Mediated Interstitial Photodynamic for the Treatment of Patients with Locally Advanced or Recurrent Head and Neck Cancer

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Confidentiality Statement

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1.0 Objectives

1.1 Primary Objectives

- To determine the safety of porfimer sodium (Photofrin®) mediated interstitial photodynamic therapy (I-PDT) in patients with locally advanced or recurrent head and neck cancer (HNC).
    - To determine the recommended light irradiance dose for a future Phase 2 trial of Photofrin® mediated I-PDT in patients with locally advanced or recurrent HNC.

1.2 Exploratory Objectives

- To assess the objective tumor response rate.

2.0 Background

2.1 Locally Advanced Head and Neck Cancer and Current Treatment Approaches

Recent cancer statistics in the U.S. predicted that 51,540 men and women would be diagnosed with and 10,030 men and women would die of cancer of the oral cavity and pharynx in 2018.(1) These numbers represent an estimate increase of 21% and 19% in incidence and death rate, respectively, when compared to the published statistics in 2014 (i.e., 42,440 and 8,390 incidence and death rate, respectively).(2) These data (and statistics for 2015-2017, (3-5)) suggest that there is a constant increase in incidence and death rates for patients with HNC in the U.S. Although approximately 60–65% of these patients can be cured with surgery, chemoradiation, and targeted therapy, the rest will eventually die of local regional recurrent and/or metastatic disease. Among them, more than 40-60% of the patients will have persistent or recurrent local regional disease.(6) Locally advanced and recurrent head and neck squamous cell carcinoma (HNSCC) are frequently resistant (refractory) to standard chemotherapy and are typically not amenable to receive curative radiation therapy.(7-10) The newest immunotherapy regimens result in encouraging but limited overall response rate of no more than 16%.(11, 12) These aggressive tumors grow to destroy vital structures and patients often die from airway obstruction and uncontrolled local hemorrhage.(13)

Quality of life and survival of these patients are severely compromised due to local effects of recurrent disease. Systemic chemotherapy is a widely used tool for reducing tumor burden, with the assumption that this leads to alleviation of tumor-related symptoms and prolongs survival. Platinum agent (cisplatin or carboplatin) and 5-FU have been considered the most effective first line chemotherapy for these patients. A phase III study (EXTREME study) has shown that the addition of Cetuximab can improve the response to 36% and the median survival from 7 to 10.3 months, in comparison to a regimen that includes only platinum and 5-FU.(10) This SoC therapy, however, is associated with extensive morbidity that relates to the use of the platinum agent and 5-FU, particularly. The potential adverse events include bone marrow suppression, neuropathy, ototoxicity, renal toxicity, mucositis, gastrointestinal and hematologic toxicities.(10) Furthermore, poor tolerability of the aforementioned chemotherapy regimen limits this approach to a relatively small number of patients that can receive this therapy.

Salvage surgery has limited success that is associated with sever disfigurement and morbidity (13). Re-irradiation (Re-RT) with concurrent chemotherapy (Re-CTRT) has been suggested for selected patients with locally advanced, locoregional recurrent HNC in a previously irradiated field.(7)

Several groups have reported their retrospective experiences with Re-RT, and have suggested a feasibility and survival benefit of this approach.(14, 15) A phase III multi-institutional study conducted in France evaluated the efficacy of Re-CTRT after salvage surgery and demonstrated that deaths due to locoregional recurrence were less frequent in the Re-CTRT arm than in the wait and see (WS) arm.(16) However, treatment related deaths were more frequent in the Re-CTRT arm than in the WS arm.(16) Patients with severe toxicity, such as osteonecrosis and trismus from prior radiation have typically been excluded from reported experiences with Re-RT.(17) Therefore, Re-RT is still considered experimental by many, and feasible only in a limited patient population.(17, 18)

2.2 Clinical Use of Porfimer Sodium (Photofrin®)

The U.S. Food and Drug Administration (FDA) approved the use of porfimer sodium mediated PDT for the treatment of esophageal cancer, NSCLC and High-Grade Dysplasia in Barrett's Esophagus.(19, 20) In PDT, systemic administration of porfimer sodium is followed by illumination of the target tissue with visible light that leads to the generation of reactive oxygen species, notably singlet oxygen.(21) Porfimer sodium is being used off label and in clinical studies to treat many other cancers, including HNC.(22-27) These were retrospective studies in patients with early stage (T1, T2) HNSCC. Theses researchers reported complete response rates of 80-85%, suggesting that porfimer sodium mediated PDT can be effective in treating HNSCC.

A detailed description of the specific indications and, discussion of the clinical pharmacology, pharmacokinetics, and toxicology of porfimer sodium can be found in the Photofrin® prescribing information (http://www.photofrin.com/wp-content/uploads/2013/02/prescribing-info.pdf).

2.3 Clinical Use of PDT with Chemotherapy

PDT with photosensitizers (PSs) in combination with chemotherapy has shown promising outcomes in down staging and improve local control, overall all survival and quality of life of patients with advanced non-small cell lung cancer (NSCLC).(28-30) The PDT was done pre or intraoperatively and in one study chemotherapy was administered on day of or day after PDT in patients with stage IIa to IV NSCLC.(28) (30)

Several retrospective studies suggested that Photofrin® mediated PDT with chemotherapy could improve the outcomes for patients with advanced esophageal cancer, and for patients with unresectable cholangiocarcinoma.(31-33) Photofrin® mediated PDT + chemotherapy has been reported to be better than either PDT alone or chemotherapy alone in the treatment of unresectable cholangiocarcinoma and advanced esophageal cancer in a limited number of studies.(31, 33, 34) A relatively large retrospective study by Lindenmann et al. (35) suggested that adding Photofrin® mediated PDT prior to standard of care (n=118) resulted in better overall survival than adding PDT after SoC (n=130) in patients with inoperable esophageal cancer. (35) That report was in agreement with Li et al. 2010(31) who found that Photofrin® mediated PDT before chemotherapy (n=33) is associated with significantly better overall response when compared with either Photofrin® mediated PDT (n=27) or chemotherapy alone (n=30) in patients with advanced esophageal cancer.(31)

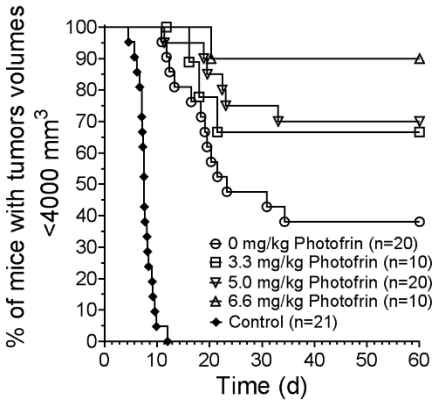
Importantly, the above-mentioned studies did not report of added toxicity or serious adverse events due to the combination of PDT and chemotherapy.

Our preliminary experience suggests that porfimer sodium mediated I-PDT with chemotherapy is safe and may hold promise for patients with locally advanced recurrent HNSCC.(36)

2.4 Preclinical Studies in Photofrin® Mediated I-PDT

Ongoing NCI funded preclinical studies at Dr. Shafirstein's laboratory (Shafirstein PI, RO1CA193610-03) focus on defining the impact of intratumoral light fluence rate (i.e., could also be referred to as irradiance) on response and cure of locally advanced tumors revealed that:

1. Intratumoral light fluence rate appears to govern tumor response to I-PDT with Photofrin®.
2. The clinically approved light intensity (400 mW/cm) for Photofrin® can impede photoreaction. Lower light intensities can be used to administer a safe and effective I-PDT in mice bearing syngeneic locally advanced squamous cell carcinomas (SCCVII), which is appropriate for studying treatments for HNC. (37, 38)
3. Intratumoral 630 ± 3nm laser light at a fluence rate of >8.6 mW/cm^2 and a fluence of >45 J/cm^2 delivered to 100% of the tumor volume will yield significantly ($p<0.05$, see **Figure** 1 below) high cure rate (70%-90%) in C3H mice bearing syngeneic 400-600 mm^3 SCCVII tumors, a size of a locally advanced murine tumor. (39)
4. The finite element modeling (FEM) approach developed in Dr. Shafirstein laboratory (40, 41), and will be use in this study, can be used to compute intratumoral fluence rate and fluence for a range of laser settings to guide Photofrin® I-PDT in C3H mice bearing locally advanced SCCVII tumors and guide safe and potentially effective treatment in New Zealand White rabbits bearing large VX2 tumors in the neck (Figure 2).



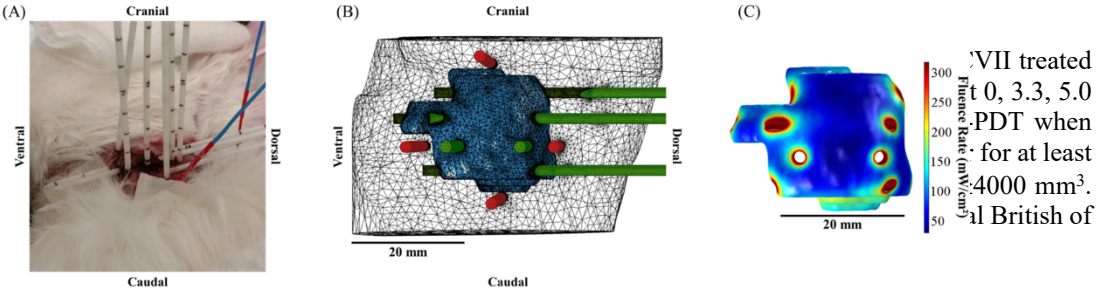


Figure 1 VII treated with 630 t 0, 3.3, 5.0 and 6.6 PDT when compare for at least 60 days. 4000 mm^3. Therefor l British of Cancer,

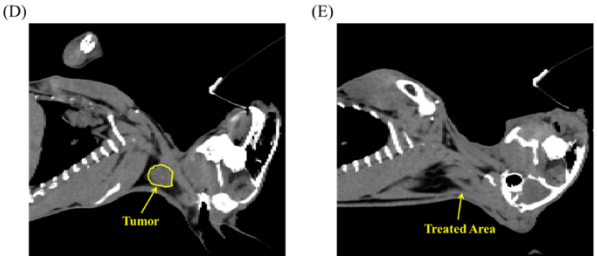


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Figure 2. (A) Image of the rabbit treated with I-PDT. Visible in the image are the transparent close-end sharp catheters where treatment or dosimetry fibers were inserted. The blue probes are the optical thermometers that were placed on the tumor surface at margins. (B) 3-D representation of the treatment plan. The tumor is represented in blue. The intended treatment fibers are in green and the intended location of dosimetry fibers are in red. (C) 3-D representation of the intratumoral fluence rate throughout the tumor. (D) CT scan prior to treatment, and (E) a CT scan 41 days post treatment. (from Shafirstein et al. Journal British of Cancer, (2018) 119, 1191-1199)

In previous publications we demonstrated that FEM could be used to plan and guide interstitial light delivery in models mimicking human tumors (40, 41). This modeling was used in a recent paper to guide I-PDT in the treatment of mice and NZW rabbits with VX2, part of the results are shown in figures 1 and 2 above. (Shafirstein et al. Journal British of Cancer, Accepted for publication July 5, 2018).

We therefore propose to use the treatment planning to administer intratumoral 630 ± 3 nm laser light at >8.6 mW/cm2 and >45 J/cm2 to 100% of the tumor volume, as described in details in Section 10.2.

2.5 Study Rationale

There was a steady increase in incidence and disease related deaths for patients with HNC within the past 5 years in the US.(1-5) Patients die from locally advanced or recurrent HNC that have failed radiation therapy and have no viable treatment.(13, 42) Combination chemotherapy yields objective response rates of 10-36%.(8-10) Re-irradiation has been shown to be associated with significant toxicity.(16, 17, 42, 43) Salvage surgery is associated with prolonged hospitalization, and the cure rates are poor.(44, 45) These tumors are typically very heterogeneous, so theoretically their response to target therapy would be limited, and their response to immunotherapy (5-16%) is still being evaluated.(46)

Several review papers and reports of retrospective studies suggested that adding PDT or I-PDT to SoC targeted and chemotherapy can improve OS and QoL in patients with unresectable cholangiocarcinoma, advanced esophageal cancer, lung cancer, malignant mesothelioma, and pancreatic cancer. (31, 33, 34, 47-49) Non-randomized, single-site, studies of I-PDT with Temoporfin have shown promising results in the treatment of patients with locally advanced and

recurrent HNC that fail standard therapies.(50-52) However, I-PDT with Temoporfin is not approved for clinical use in the U.S. Photofrin® is the only clinically approved PS for treating cancerous tumors in the U.S.A. Our preliminary experience suggests that Photofrin® mediated I-PDT may hold promise for patients with locally advanced and recurrent HNC. (36) While I-PDT has the potential to provide local control, it is acknowledged that patients with locally advanced disease require systematic therapy. And multiples studies suggest that adding PDT to the SoC chemotherapy is safe (as summarized in the above section 2.3). **We hypothesize that Photofrin® mediated I-PDT will be a safe treatment in patients with locally advanced or recurrent head and neck cancer that failed radiation therapy.** The goal of this study is to test the safety and find the recommended light irradiance for porfimer sodium mediated I-PDT in patients with locally advanced or recurrent HNC who are not candidates for standard or salvage surgery or radiotherapy.

2.6 Correlative Studies

2.6.1 QUALITY OF LIFE EVALUATION

Several clinical studies suggested that PDT and I-PDT could improve QoL in patients with locally advanced HNC. (53-56) Few studies reported that I-PDT (with Temoporfin) reduced tumor related bleeding and pain, while improving breathing, speaking, swallowing, and appearance.(50, 51, 57) The impact of Photofrin® mediated I-PDT on QoL has not been evaluated, to date.

In this protocol, participants' QoL will be evaluated with an accepted University of Washington Quality of Life Questionnaire Version 4 (UW-QoLQ v4: see **Appendix E**) (58, 59). It has been tested in several prospective studies and found to be reproducible, reliable, and valid for HNC patients: it is simple to complete, employs a simple algorithm to compute the overall score, and is easy to interpret while yielding objective results.(60) This version includes 12 individual Likert-scale items and 4 global questions. Each participant's overall score on the UW-QoLQ v4 will be calculated at baseline, at 12-16 weeks, and at 30 days post final treatment.

2.6.2 IMMUNE STUDIES (OPTIONAL)

In order to determine whether I-PDT enhances anti-tumor immunity a multi-pronged analysis will be performed. The effect of I-PDT on T cell activity will initially be determined by examining the activation status of participant T cells before and after I-PDT administration. PDT induces a rapid pro-inflammatory response and such responses are associated with T cell activation and proliferation, which are frequently muted in participants with advanced cancer. Furthermore, the effects of I-PDT on patient anti-tumor T cells are unknown. T cell activation will be determined by flow cytometric analysis of peripheral blood T cells. Using T cell subtype and activation specific profiles, this analysis will allow us to determine whether administration of I-PDT alters both the activation status and ratio of T cell subtypes present before and after therapy.

The phenotypic characterization described above will determine whether I-PDT affects T cell activation and subtype ratio but will not discern whether the effects are tumor specific. Most tumors over-express p53 and many head and neck tumors overexpress HPV 16. Examination of changes in the immune response to p53 and/or HPV16 can reveal changes in tumor specific immune responses. To examine whether PDT enhances the immune response to p53 or HPV 16, peripheral blood T cells will be isolated and exposed to p53 and HPV 16 ex vivo. The ability of each participant's T cells to respond will be measured over time and compared against pre-treatment

results and to their ability to respond to antigens they have previously been exposed to, i.e., cytomegalovirus, Epstein-Barr virus and influenza virus (the so-called memory mix).

The third method for examining tumor specific T cells following I-PDT involves adding an additional marker to the flow panels described above. There is a well-defined p53 immune epitope that binds to the human major histocompatibility complex molecule HLAA2. Greater than 40% of the patients at Roswell Park express HLA-A2. HLA-A2 expression status of the trial participants will be determined. T cells isolated from HLA-A2+ participants will be tested for p53 reactivity using a flow cytometry reagent known as a tetramer that allows identification of p53 specific T cells.

Finally, we will examine changes in immune cell infiltrate and T cells activation status in tumors following PDT by comparing infiltrate and immune cell activation in tumors surgically removed from PDT treated patients to those removed non-PDT treated patients.

The mentioned immune studies analysis is optional for study participants with enough tissue for analysis as determined by the treating physician and dependent on amount of tumor, tumor location and if additional samples can be collected, which will vary based on the specifics of the tumor.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. Male or female patients age ≥ 18 years of age.
2. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2. Refer to **Appendix A.**
3. Patients with locally advanced or recurrent head and neck cancer who failed to respond to standard therapy and are not amenable to standard curative treatment.
4. Tumor accessible for unrestricted illumination for interstitial Photodynamic Therapy (PDT) (accessibility as determined by the physician).
5. Life expectancy of at least 6 months, in the judgment of the physician.
6. Subjects of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
7. Subject must understand the investigational nature of this study and sign an Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Refer to **Appendix B** for the **ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA CHECKLIST**.

3.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. High dose curative radiotherapy within 30 days in the area to be treated.
2. Tumor invading a major blood vessel.
3. Tumor is not measurable on a CT or MRI scan according to RECIST v1.1.
4. Location and extension of the tumor precludes a potentially effective I-PDT.
5. Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
6. Patients with porphyria, or with known hypersensitivity to porphyrins or porphyrin-like compounds.
7. Platelet count < 75,000.
8. Patients with impaired renal and/or hepatic function (total serum bilirubin > 2 mg/dL, alkaline phosphatase (hepatic), SGOT or SGPT > 3 times the upper normal limit.

9. Patients with moderately to severely impaired creatinine clearance (CrCl <44) will be excluded.
10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
11. Pregnant or nursing female subjects.
12. Unwilling or unable to follow protocol requirements.
13. Any condition which in the Investigator's opinion deems the subject an unsuitable candidate to receive porfimer sodium.

Refer to **Appendix C** for the **ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA CHECKLIST**.

3.3 Special Populations

The following special populations will be excluded from this study:

- Cognitively impaired adults/adults with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

3.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

4.0 Local and Study-Wide Number of Subjects

In the Phase 1 study, a maximum of 12 (four cohorts of 3) evaluable participants at Roswell Park, will be enrolled. The number of subjects required is a function of the unknown dose-toxicity.

5.0 Local and Study-Wide Recruitment Methods

Participants will be identified/recruited/screened from patients at the Head and Neck Clinic at Roswell Park and participating sites and from multi-disciplinary conference discussion.

6.0 Multi-Site Research

Not applicable-This is a single-site study.

7.0 Study Timelines

A maximum of 12 participants at Roswell Park will be enrolled. Accrual is expected to take 5 years, with follow-up for 24 months from the start of investigational treatment.

8.0 Study Endpoints

8.1 Primary Endpoints

- **Phase 1:**
    - The safety will be determined by recording the occurrence of AE during the first 30 days post final I-PDT day, using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Exploratory Endpoint

- Objective target tumor response rates will be assessed according to RECIST v1.1 at 12 ± 2 weeks post I-PDT as described in section 16.2.

9.0 Study Design

All participants will meet the inclusion and exclusion criteria summarized in Section 3.1 and Section 3.2 prior to taking part in this study.

This study will recruit subjects with HNC who failed to respond to standard therapy and are not candidates for salvage surgery or radiation therapy including re-irradiation. These HNC subjects would otherwise receive SoC chemotherapy, targeted therapy or potentially immunotherapy as first line palliative care treatment options.

All participants will receive I-PDT. All participants will have a standard diagnostic head and neck scan with CT or MRI, with or without contrast. Participants will be followed according to the 2018-NCCN follow-up guidelines (63; Appendix H) for patients with advanced HNC (https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf). The study related visits would be up to 2 years, thus every 1-3 months in the first year, and every 2-6 months in the second year. The routine clinical follow up will be up to 5 years. The study schema is shown in

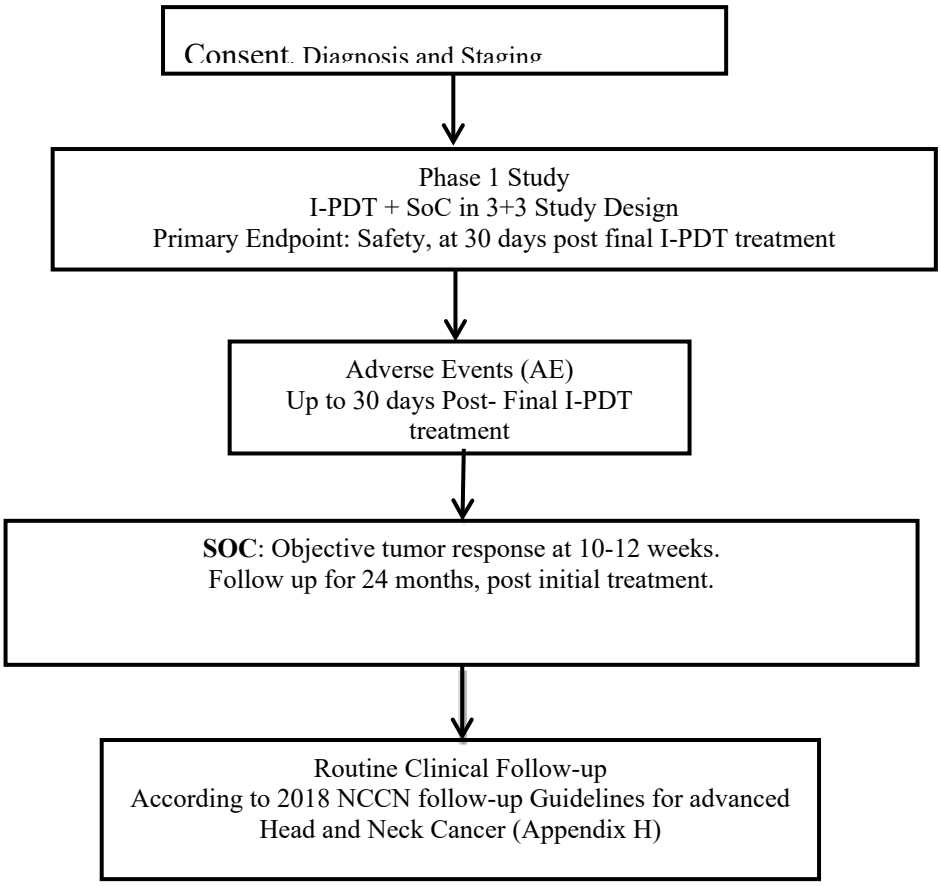
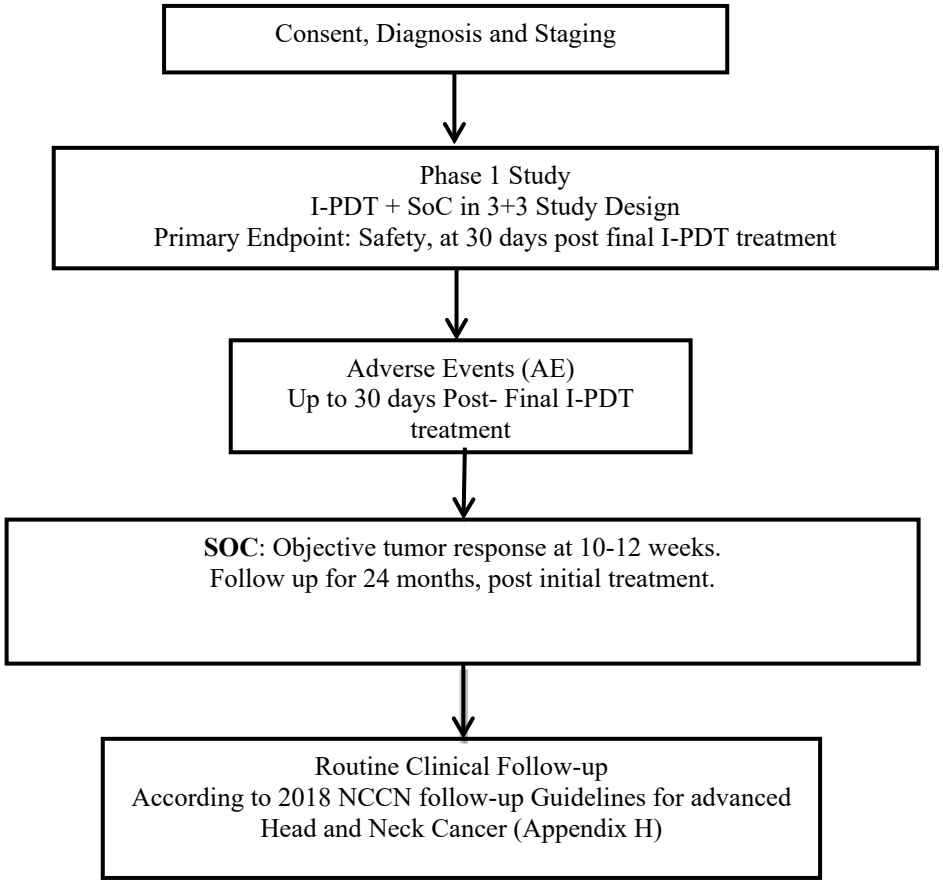

Consent, Diagnosis and Staging
Phase 1 Study
I-PDT + SoC in 3+3 Study Design
Primary Endpoint: Safety, at 30 days post final I-PDT treatment
Adverse Events (AE)
Up to 30 days Post- Final I-PDT treatment
SOC: Objective tumor response at 10-12 weeks.
Follow up for 24 months, post initial treatment.
Routine Clinical Follow-up
According to 2018 NCCN follow-up Guidelines for advanced Head and Neck Cancer (Appendix H)

Figure 3 Study Schema



10.0 Treatment

10.1 The Standard of Care Procedure

All participants will undergo a standard diagnostic head and neck scan with computed tomography (CT) or magnetic resonance imaging (MRI) as clinically indicated.

10.2 Interstitial Photodynamic Therapy (I-PDT)

10.2.1 Porfimer Sodium Administration

Subjects will receive a single intravenous dose of porfimer sodium that will be administered approximately 48 ± 8 hours before the first I-PDT treatment.

Drug administration will take place in a room that has covered windows to protect the subjects from light exposure that can induce phototoxicity (i.e., direct sun light or visible artificial light that is more than 60 W). The Principal Investigator or designee will inject the subjects with porfimer sodium for this study.

A dose of 2 mg/kg of porfimer sodium will be administered by slow intravenous injection into a vein (3-5 minutes). Light-avoidance measures for approximately 30-90 days will be required. The Clinical Research Coordinator and staff nurses will explain the light-avoidance measures to each subject and written instructions will be handed out to the subjects (**Appendix F)**. The subject will be cautioned to protect the site of the infusion from excessive direct sunlight and certain bright lights for up to 3 months. The site may be exposed to normal ambient light.

Vital signs will be done immediately after the end of the injection and 15 minutes after.

10.2.2 Pre-treatment Planning

For all participants receiving I-PDT, a standard diagnostic head and neck scan with CT or MRI, will be obtained within 4 weeks prior to I-PDT. This imaging will be used for pre-treatment planning that will be conducted at Dr. Shafirstein's laboratory at Roswell Park, with the treating physician at each participating site.

<u>The pretreatment planning will be carried out by following these steps:</u>

1. If possible, clinically approved surface fiducial markers (using removal stickers) will be affixed to the skin (at the region of the tumor) prior to CT or MRI, to assist in the guidance of laser fibers, as described in Oakley et al. 2017(40).
2. The scans will be de-identified, linked to a subject ID, and copied on CD or transferred via secure network to Dr. Shafirstein's laboratory, 5-14 business days prior to the scheduled I-PDT.
3. The treating physician will use the CT or MRI scans and the image reconstruction model for defining the clinical target volume (CTV).
4. Image analysis software will be used to reconstruct the CT or MRI scans to generate a computer model of tumors and adjacent anatomy as we described in Oakley et al. 2015 and Oakley et al.2017.(40, 41)
5. The treating physician will also use the computer model to recommend the number and location of closed-end transparent catheters that can be safely placed within the CTV.

6. The computer model (of the CTV) will be imported into a finite element modeling (FEM) software, to calculate the light intensity (mW/cm) and energy (J/cm) that will be required to be delivered by each fiber, so that 100% of the CTV receives the target light dose (i.e. computed fluence rate >8.6 mW/cm^2 and fluence >45 J/cm^2) as much as possible.
7. The FEM simulations will be presented to the treating physician for approval of the treatment plan at least 5 business days prior to the I-PDT.

Note: If subjects are scheduled to receive additional I-PDT courses (at least 30 days from the previous I-PDT, see Section 10.4), per the physician's discretion, pre-treatment planning procedures for additional I-PDT courses are per the physician's discretion.

10.2.3 I-PDT Procedure

The I-PDT will commence by following these steps:

1. An ultrasound system will be used, prior to fiber insertion, to confirm that the close-end sterile catheters can be safely placed into the CTV, according to the approved treatment plan. These catheters will be used to accommodate cylindrical laser fibers that will deliver the therapeutic light. If possible, an intraoperative CT (or other clinically approved radiological imaging) will be used to image the actual location of the inserted catheters.
2. Laser fibers with cylindrical end will be inserted into the close-end sterile catheters, according to the approved treatment plan. Only one laser fiber will be inserted into each catheter.
3. Additionally, dosimetry fibers to measure light will be inserted into other, nearby, close-end sterile catheters to monitor the light delivery.
4. The laser system(s) will be turned on to deliver the therapeutic light (630 ± 3 nm) into the tumor.
5. A light dosimetry system (described in Section 32.2) will be used to monitor the light fluence rate, fluence and tumor during I-PDT, in all participating sites.

The laser treatment and dosimetry fibers could be moved from one close-end sterile catheter to another to deliver the planned light fluence rate and fluence, and monitor the light and thermal dose. At any given time, there will be only one fiber (treatment or dosimetry) in a close-end sterile catheter. The laser fibers and detectors will *not* be in direct contact with patient tissue. Following administration of the laser light, the laser fibers and detectors will be removed, they will be cleaned and disinfected with an acceptable method (e.g., Cidex). The fibers and detectors can be reused, as they must be checked for calibration prior to each procedure.

Light Exposure Precautions

Light precautions will be maintained from the moment the subject enters the hospital and will continue while the subject is in the surgical suite and on the surgical subject care units.

Subjects are instructed to wear their protective eyewear when they travel to the hospital. The surgery will be performed with room lights, which are modified by amber filters to minimize unwanted activation of the photosensitizing drug and inadvertent light exposure to the subjects. Yellow filter paper will be employed over the procedure room lights and the surgeons' headlights

that blocks wavelength below 550 nm, thereby eliminating the light absorption by porphyrin in the UV and blue-green range.

It has been the experience thus far that the surgeons have been able to adapt safely to operating with such filters in place. Incisions, if needed, will be shielded from inadvertent light exposure with sterile blue towels sewn or secured to the skin edges. The remainder of the subject's skin will be draped in the usual surgical/sterile manner and therefore will not be inadvertently exposed to light during the entire procedure. The pulse-oximeter will be rotated between fingers every 15 minutes to avoid nail bed burns. Either disposable clips will be placed on all fingers, and the pulse-oximeter probe will be rotated or non-disposable clips will be rotated by the anesthesiologist.

These light precautions will be maintained throughout the entire hospital stay. Light precaution signs will be displayed above the subject's bed at all times.

Appropriate goggles will be furnished and available for the surgeons and others to operate and function in the operating room when the laser light is on.

10.3 Definition of Dose-Limiting Toxicity

Dose Limiting Toxicities will include:

Any adverse events (AEs) that are ≥ grade 4 that are possibly, probably, or definitely related to the I-PDT, by recording the occurrence of AE during the first 30 days post final I-PDT treatment using the revised the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Dose Limiting Toxicities will be evaluated for 30 days post final I-PDT day.

If participants experience DLTs, further I-PDT sessions will be held until DLT resolution as well as after porfimer sodium clearance.

10.4 Dose Escalation/Finding Schema

The FDA approved porfimer sodium dose (2 mg/kg) will not change. We will aim to deliver light fluence rate of ≥8.6 mW/cm^2 and fluence of ≥45 J/cm^2 to 100% of the CTV (dose level 1), as much as possible. Dose level -1 will ≥5.0 mW/cm^2 and fluence of ≥45 J/cm^2 to 100% of the CTV.

Table 2. The study plan for finding optimal fluence rate in I-PDT with Photofrin in patients with LAHNC.

Dose Level	Number of patients with DLT at a given dose level	Decision rules
Dose Level 1 (Starting): The maximum fluence rate, scaled for human, which induced effective	0 out of 3	Enter 3 patients at **Dose Level 1**: The laser fluence rate and fluence, scaled for human, which induced maximum photoreaction in the animal models
	1 out of 3	Enter 3 more patients at this **Dose Level** .

photoreaction in the animal models.	≥ 2	Enter 3 patients at **Dose Level -1**: The laser fluence rate and fluence, scaled for human, which induced minimal toxicity in the animal models.
	≤ 1 out of 6	This is generally the recommended Phase II dose rate/dose. At least 6 patients must be entered at the recommended Phase II dose.

In participants where their tumors may require more than one course of I-PDT for complete effective illumination of the CTV, up to three sessions of I-PDT may be performed, at the discretion of the treating physician. The FDA approves to administer up to three courses of PDT with Photofrin® each separated by at least 30 days in the treatment of esophageal and endobronchial cancer (http://www.photofrin.com/wp-content/uploads/2013/02/prescribing-info.pdf.). Therefore, treatment sessions in this study will be conducted at least 30-days apart. The porfimer sodium dose (2 mg/kg) will remain the same.

See Appendix D 1 for the Dose Escalation Schedule of Events. The date of the last I-PDT course will be used to determine the scheduling of the follow up SoC related to this study.

10.5 Treatment Discontinuation

All subjects who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the subject's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Treatment-related toxicity
- Toxicity unrelated to treatment
- Investigator judgment
- The Investigator may withdraw a subject if, in his/her judgment, it is in the subject's best interest to do so.
- Noncompliance
- Subject voluntary withdrawal
    - A subject may withdraw from the study at any time, for any reason. If a subject discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Early withdrawal of subject(s)
- Sponsor decision

Subjects who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a subject to be considered lost to follow-up, the investigator must make two attempts to re-establish contact with the subject. The attempts to re-establish subject contact must be documented (e.g., certified letter).
- Death: Date and cause of death will be recorded for those subjects who die within 30 days after treatment (telephone contact is acceptable).

11.0 Procedures Involved

11.1 Participant Registration

Eligibility of each participant will be established prior to enrollment. Patients at Roswell Park will be registered directly by Roswell staff using the web-based registration system.

Informed consent **MUST** be completed prior to receiving any study related procedures.

11.2 Baseline Evaluations

The following will be performed within 8 weeks prior to administration of porfimer sodium:

- Informed consent: Must be completed prior to receiving any study-related procedures
- Medical history
- Physical examination including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, height, and pain assessment using a verbal score of 0 - 10) *
- Hematology (i.e., complete blood count (CBC) with auto differential, absolute neutrophil count (ANC), and platelets) *, **
- Chemistry (i.e., AST, ALT, total bilirubin, alkaline phosphatase, creatinine, potassium, glucose, and calcium) *
- Pregnancy test (urine) in females of childbearing potential **
- ECOG Performance Status **
- UW QoLQ v4 #
- Standard imaging for patients with HNC (i.e., CT and/or MRI) *, at least 10 business days prior to the scheduled I-PDT #
- Pretreatment planning #
- Concomitant Medications (including narcotic and nonnarcotic analgesics) **

*These are standard of care and may be used for baseline evaluation if performed before informed consent but within 4 weeks of porfimer sodium and can be used for the pretreatment planning.

These will be done prior to later 2nd and 3rd later I-PDT sessions (if later I-PDT sessions are required per treating physician's discretion per Section 10.4). Height does not need to be reassessed for later possible I-PDT sessions. **If later I-PDT courses are deemed necessary, previous study treatment adverse events will be reviewed before the start of next I-PDT course.

Performed as per PI discretion if 2nd and 3rd I-PDT courses are deemed necessary as per Section 10.4.

11.3 Pre-operative - Day of Porfimer Sodium Injection

- 48 ± 8 hours before illumination
- Porfimer sodium solution (following the USPI) by a single slow intravenous injection over 3-5 minutes at 2 mg/kg body weight
- Vital signs will be done immediately after the end of the injection and 15 minutes later

11.4 Evaluations Performed on the Day of Each I-PDT Treatment

- ECOG Performance Status
- Concomitant medication (including narcotic and nonnarcotic analgesics)
- Adverse events
- Pre-laser light research bloods (Optional) #
- Intraoperative ultrasound #
- Light dosimetry measurements

Performed per PI discretion if later I-PDT courses are deemed necessary as per Section 10.4.

11.5 Evaluations Performed at 1st Post-Operative Clinic Visit

This visit will be scheduled 1 to 4 weeks post I-PDT and will include:

- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and pain assessment using a verbal score of 0-10)
- Hematology (i.e., CBC (with auto differential), ANC, and platelets)
- Chemistry (i.e., AST, ALT, total bilirubin, alkaline phosphatase, creatinine, potassium, glucose, and calcium)
- ECOG Performance Status
- Adverse events
- UW QoLQ v4
- Research blood draws (Optional) #

Performed as per PI discretion if later I-PDT courses are deemed necessary as per Section 10.4.

11.6 Post-Treatment Follow-Up

Follow-up safety evaluations will occur every 1-3 months during the first year and then every 2-6 months in the second year after I-PDT day.

Follow-up Clinic Visits

Participants will be followed according to the 2018-NCCN follow-up guidelines for patients with advanced HNC(63). The study related visits occur up to 2 years, thus every 1-3 months in the first year, and every 2-6 months in the second year. The efficacy will be determined at 10-12 weeks after the initial study related treatment (see Section 8.1).

If it turns out that a participant will be scheduled to have a routine visit at 10-12 weeks (which is within 1-3 months), we will not schedule another study visit. We will use the routine visit (at 10-12 weeks) to record data for the study. The routine clinical follow up will be up to 5 years.

11.7 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in Appendix D.

11.8 Blood Draws for Immune Marker Analysis

Research blood draws for immune marker analysis is optional for study participants.

Recent work from the Gollnick lab has demonstrated the critical role of the immune system in PDT efficacy. Because of the importance of the immune system for PDT efficacy, along with the potential for the immune system to mount an effective anti-tumor response, it would be beneficial to monitor immune markers (detailed in Section 2.6) for correlation between the I-PDT treatment and local or distant disease recurrence.

Blood samples will be collected via venipuncture for immune marker analysis. Samples will be collected using one 10 mL heparinized green-top collection tube. Tubes will be labeled with the participant's initials, participant's study number, clinical study number, protocol time point (i.e. prior to infusion of porfimer sodium, Day 0), dose, and protocol day.

Samples for immune marker analysis will be obtained on:

- Day of 1st I-PDT prior to laser light illumination
- 7-10 days following 1st I-PDT.

All subsequent follow-up evaluations (if feasible):

- Initial follow-up (approximately 4 weeks ± 1 week following 1st I-PDT

NOTE: For subjects that need later 2nd and 3rd I-PDT sessions (as per Section 10.4), the research blood draws are taken per the physician's discretion.

Whole blood samples collected at RP will be sent at room temperature for processing the same day of collection.

The samples should be sent to:

Roswell Park Comprehensive Cancer Center
Attn: Flow Cytometry – I 67918
Elm & Carlton Streets
Buffalo, New York 14263
716-845 3528 (8:30 am -5 pm)
flowlab@RoswellPark.org

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens.

11.9 Pathology

Standard pathologic analysis of resected head and neck tissue and tumor will be performed.

12.0 Withdrawal of Subjects

Subject Withdrawal

The subject will be withdrawn from the study as described in Section 10.5 and if:

- The I-PDT can't be administered.
- The patient would become hemodynamically unstable during I-PDT.

13.0 Risks to Subjects

This is a Greater Than Minimal Risk study according to IRB criteria. Phototoxicity is the most likely potential risk associated with the systemic administration of the porfimer sodium. Proper shielding from the procedure room lights will be maintained and the pulse oximetry sensor will be rotated every 15 minutes, to minimize this risk. The subjects will be provided with written instructions on how to protect themselves from excessive light exposure.

The site-specific toxicity associated with this therapy includes:

a. **Injection site reaction:** Very common effects include pain at the injection site (12%) which is transient and can be minimized by slowing the injection rate. Common effects include injection site reaction (3%) and burning sensation (3%).

b. **Tumor/local tissue reaction:** Very common effects include pain (15%), hemorrhage (15%) and scaring (12%). Common effects include edema (8%), localized infection (8%), fever (8%), and skin necrosis (2%).

c. **Phototoxicity:** Common effects include sunburn (3%), blisters (5%), erythema (5%), hyper-pigmentation (3%), and cutaneous photosensitivity (3%).

d. **Other systemic events:** Constipation (11%), vomiting (9%), anemia (8%), nausea (6%) and giddiness (2%).

e. **Collection of blood:** Potential rare risks include local bleeding, inflammation and infection at the collection site (<1% of patients).

14.0 Potential Benefits to Subjects

For subjects that will have partial or complete response to I-PDT, the potential benefits include reduction in tumor related side effects (such as bleeding, pain, and dysphagia). Subjects that do not respond to I-PDT may not benefit from this treatment. In addition it has been shown, in other diseases sites, that PDT can improve OS and PFS when added to SoC therapy. Thus, it is possible that subjects that will respond to the experimental arm (I-PDT + SoC) will have increased OS and PFS. There is no guarantee of the outcome nor is it possible to predict whether or not the subject will respond to porfimer sodium-mediated I-PDT.

15.0 Data and Specimen Banking

Any clinical data that is associated with the samples will be stored on a secured server, will be accessible only by the PI, co-investigators and PI-designated data manager and, will be password protected. All computer entry and networking programs will be done using PIDs only.

Upon completion of sample assays the analyzing laboratories will provide results to Biostatistics and to CRS Data Management in a SAS compatible Excel file.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

16.0 Measurement of Effect

16.1 Objective Disease Assessment

History, physical examination and standard CT will be used to monitor disease recurrence every 1-3 months in the first year, and every 2-6 in year 2, following the 2018 NCCN follow-up guidelines for patients with advanced HNC (https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf) (63; Appendix H). Subsequently, the treating physician will continue the usual clinical disease monitoring. Ancillary imaging studies such as PET-CT or MRI will be performed as indicated in the judgment of the treating physician based on findings from the history, physical examination or CT. Biopsy of suspected recurrent disease will be performed when feasible with minimal risk to the patient.

16.2 Target Lesions

The target lesions will be the locally advanced HNC that were treated with I-PDT or the ones that were identified by the principal investigator (or treating physician) as locally advanced and were treated with SoC therapy. Tumors measurements will take place 10-12 weeks after I-PDT or the first SoC in the control ram. Change in the target tumor size will be determine using the methods described in RECIST v1.1 (62). CT with contrast or MRI (when CT is not possible) will be used to determine change in tumor size. The objective response of the target tumor will be determined following these criteria:

- **Complete Response (CR):** Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. A biopsy will be taken from the suspected lesions for histological confirmation.
- **Progressive Disease (PD):** At least a 20% increase in the diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- **Stable Disease (SD):** Neither, sufficient shrinkage to qualify for PR nor, sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study, the response will be listed with stable disease. In this case, a biopsy will be taken from the suspected lesion for histological confirmation.

16.3 Evaluation of Response

Time point response assessments will be performed according to the 2018-NCCN follow-up guidelines for patients with advanced HNC (63), up to 24 months after I-PDT. To determine time point response criteria, refer to **Table 1** below.

Table 1 Time Point Response Criteria (+/- non-target disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 2. Time Point Response Criteria (non-target disease only)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

[1] Non-CR/non-PD is preferred over SD for non-target disease since SD is used as endpoint for assessment of efficacy in trials so to assign this category when no lesions can be measured is not advised.

The best overall response is the best response recorded from the start of study treatment until follow-up is completed or the participant goes off study (the end of treatment taking into account any requirement for confirmation).

- **Symptomatic Deterioration:** Participants with global deterioration of health status requiring study withdrawal without objective evidence of disease progression at that time, and not related to study treatment or other medical conditions should be reported as progressive disease due to "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment due to symptomatic deterioration. Symptomatic deterioration that may lead to study withdrawal includes, but is not limited to, symptoms such as:

- Weight loss > 10% of body weight.
- Worsening of disease-related symptoms (e.g., worsening dyspnea, increasing pain/increasing requirement for narcotic analgesics).
- Decline in performance status of > 1 level on ECOG scale.

16.4 Guidelines for Evaluation of Measurable Disease

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations.

17.0 Safety Evaluation

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of ‘unrelated’, ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’).

An AE is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

17.1.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.1.2 ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.1.3 ABNORMAL LABORATORY VALUES

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.1.4 PREEXISTING MEDICAL CONDITIONS (BASELINE CONDITIONS)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2 Grading and Reporting Adverse Events

17.2.1 GRADING AND RELATIONSHIP TO DRUG

The descriptions and grading scales found in the CTEP Version 5.0 of the NCI Common CTCAE will be utilized for AE reporting. CTEP Version 5.0 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 5.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

17.3 Reporting Adverse Events

Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

Table 1 Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Routine AEs occurring between the start of intervention until 30 days after the last intervention or until the event has resolved, stabilized, death, or a new treatment is started, whichever comes first, will be reported. New information will be reported after it is received.

Pinnacle Biologics, Inc. Bannockburn IL, will be receiving copies of all the reports (de-identified).

17.4 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in ANY of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

17.4.1 REPORTING SERIOUS ADVERSE EVENTS

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs that are unexpected and possibly, probably or definitely related must be reported as an Unanticipated Problem. Please refer to **Section 17.6** for details on reporting Unanticipated Problems.

17.5 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.6 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized or if in relation to an AE is deemed Serious per Section 17.4.

17.6.1 REPORTING UNANTICIPATED PROBLEMS

Unanticipated problem reporting will begin at the time of participant consent. The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1

business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems, whether related or unrelated to the investigational agent(s) to the IRB in accordance with their local institutional guidelines.

17.7 FDA Reporting

When Roswell Park is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening;

Or, meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

17.8 Investigator Reporting: Notifying the Manufacturer of Porfimer Sodium

Investigators MUST report (within 1 business day), upon becoming aware, to Pinnacle Biologics, Inc. ANY Serious Adverse Events, whether or not they are considered related to the investigational agents using the forms supplied by Pinnacle.

Pinnacle reporting contact: fax (+1(905) 689-1465) or email (pinnaclesafety@optum.com).

17.9 Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS QA Office via email to CRS-QA@RoswellPark.org.

18.0 Data Management and Confidentiality

18.1 Data Collection

Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Clinical data management activities are performed using CTMS and EDC systems that enable the collection, cleaning and viewing of clinical trial data. CRS Clinical Data manages, designs and develops the study-specific database Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into Production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.2 Maintenance of Study Documents

Essential documents will be retained per Roswell Park policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

18.3 Revisions to the Protocol

Roswell Park may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.4 Termination of the Study

It is agreed that, for reasonable cause, either the Roswell Park Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, Roswell Park may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

18.5 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and

networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

19.0 Statistical Plan

This is a Phase 1 trial. The primary objective of the Phase 1 component is to test the safety of porfimer sodium mediated I-PDT in patients with locally advanced or recurrent HNC who are not candidates for standard or salvage surgery or radiotherapy.

19.1 Sample Size Determination

The maximum sample size is 12 patients. The actual sample size depends on the unknown dose-toxicity profile of the treatment, see section 10.14 for the dose escalation scheme.

19.2 Demographics and Baseline Characteristics

Descriptive statistics such as frequencies and relative frequencies will be computed for all categorical variables. Numeric variables will be summarized using simple descriptive statistics such as the mean, standard deviation and range. A variety of graphical techniques will also be used to display data such as histograms, boxplots, scatterplots, etc.

19.3 Safety Analysis

The safety will be determined by recording the occurrence of SAE during the first 30 days post first SOC treatment day (or last I-PDT day if no therapeutic SOC is given) using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Sequential boundaries will be used to monitor the SAE rate (64). The accrual will be halted if excessive numbers of SAEs are seen.

19.4 Exploratory

Objective tumor response rates at 10-12 weeks will be summarized with a sample proportion and corresponding 95% confidence interval. Time-to-event endpoints will be examined using a Cox regression model with a factors for I-PDT (yes/no), standard-of-care type (chemotherapy, targeted therapy, immunotherapy) and an interaction term. Survival curves will be estimated per group using Kaplan-Meier estimates. It is assumed a priori that any drop out times will be non-informative in terms of the censoring mechanism.

19.5 Quality-of-Life Analysis

UW-QoLQ v4 will be calculated at baseline and at 30 days post final treatment. The primary analysis will consist of examining the change from baseline to Day 30 using a Wilcoxon sign-rank test.

19.6 Adverse Events

The frequency of toxicities will be tabulated by grade across all dose levels and cycles. All subjects who receive any study treatment will be considered evaluable for toxicity.

19.7 Interim Analysis and Criteria for Early Termination of the Study

A formal stopping rule for safety is given in Section 19.1. In addition, the Phase 1 study will be monitored and discussed by Roswell Park's Early Phase Clinical Trials Committee, which meets on a regular basis per the Roswell Park Data Safety Monitoring Plan. Drug safety will be monitored and evaluated continuously throughout the study including 30-day safety follow-up period by obtaining, reviewing and analyzing data on AEs, changes in laboratory values, vital signs, electrocardiograms (ECGs), and physical examination findings. Potential early termination decisions are an inherent part of the Phase 1 study monitoring.

Specific attention will be paid to incidents of:

1. Life threatening hemorrhaging
2. Airway compromise leading to emergency intubation or tracheostomy

19.8 Correlative Data Analysis

Study metrics will be summarized using simple descriptive statistics such as the mean, standard deviation, range, etc. Ninety-five percent confidence intervals will be computed when appropriate. A variety of graphical techniques will also be used to display data.

Light Dosimetry

In all participating sites, the light dosimetry system, described in Section 32.2, will be used to measure light dose during the entire treatment at several key locations within the treated area. The light dosimetry system will be stored and maintained in Dr. Shafirstein laboratory at Roswell Park. The system will be provided to the site before the procedure and returned to Roswell Park, after the procedure. Dr. Shafirstein or one of his research team members will operate the system during the I-PDT procedure.

During I-PDT, each detector will be marked (with a number) and the data from each location will be saved with information on the location and time of measurement. The primary measurable outputs will be the light fluence (J/cm^2) and fluence rate (mW/cm^2) at each location.

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

All Roswell Park studies will be reviewed at the scheduled Early Phase Clinical Trial Committee meetings.

The Roswell Park Data and Safety Monitoring Committee (DSMC) will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design, (c) suspension of, or (d) or termination of the study.

21.0 Vulnerable Populations

Not applicable.

22.0 Community-Based Participatory Research

Not applicable.

23.0 Sharing of Results with Subjects

Individual response data is shared with the participant as a part of their clinical care.

24.0 Setting

Participants will receive porfimer sodium as an outpatient in the Head and Neck Clinic and PDT will occur at inpatient surgery at Roswell Park and participating sites.

25.0 Provisions to Protect the Privacy Interests of Subjects

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26.0 Resources Available

Not Applicable.

27.0 Prior Approvals

Not Applicable.

28.0 Compensation for Research-Related Injury

For Roswell Patients only, if the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-4094.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor (716-845-3161) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29.0 Economic Burden to Subjects

The participants will not be subject to any economic burden.

30.0 Consent Process

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

31.0 Process to Document Consent in Writing

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

32.0 Drugs or Devices

32.1 Porfimer Sodium

The porfimer sodium will be provided, at no cost, to the patients or their insurance.

32.1.1 ACTIVE SUBSTANCE AND SOURCE

Porfimer sodium for injection is supplied as a freeze-dried cake or powder as follows: NDC 76128-155-75, 75 mg vial.

32.1.2 DRUG SHIPMENT

Porfimer sodium (Photofrin®) will be provided and shipped by Pinnacle Biologics Inc. to all participating sites. The receiving site will document the date of receipt and condition of the shipment. Drug shipment records will be retained by the investigational pharmacist or designee.

Roswell Park will provide the participating sites with instructions whom to contact and how to order the Photofrin® vials from Pinnacle Biologics Inc. The company will provide few vials when the study is approved and prior to open for enrollment at each site. More vials will be provided few days before each participant will be scheduled for treatment. The vials will be labeled and can be used for this study, only.

32.1.3 PREPARATION

Porfimer Sodium will be prepared for injection following the manufacturer instructions: "Reconstitute each vial of porfimer sodium with 31.8 mL of either 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), resulting in a final concentration of 2.5 mg/mL: Shake well until dissolved. Do not mix porfimer sodium with other drugs in the same solution.

Porfimer sodium reconstituted with 5% Dextrose Injection (USP) or with 0.9% Sodium Chloride Injection (USP), has a pH in the range of 7 to 8. Porfimer sodium has been formulated with an overage to deliver the 75 mg labeled quantity. The reconstituted product should be protected from bright light and used immediately. Reconstituted porfimer sodium is an opaque solution, in which detection of particulate matter by visual inspection is extremely difficult. Reconstituted porfimer sodium, however, like all parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit area from light.

32.1.4 STORAGE AND STABILITY

Porfimer sodium freeze-dried cake or powder will be stored at Controlled Room Temperature 20–25°C (68–77°F).

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified by the Sponsor and in accordance with the applicable regulatory requirements.

Drug storage temperature will be maintained and recorded, as applicable.

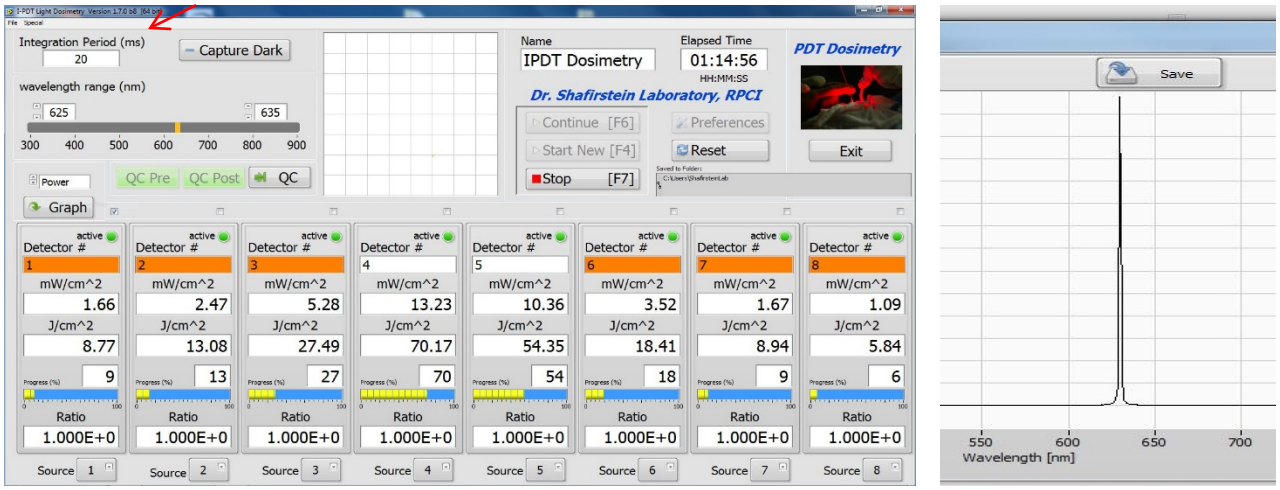
32.1.5 HANDLING AND DISPOSAL

Under no circumstances will the Investigator supply porfimer sodium to a third party or allow it to be used in a manner other than as directed by this protocol.

32.2 Light Dosimetry System

All participating sites will have a light dosimetry system that will be used to measure the light dose [fluence rate (mW/cm^2) and fluence (J/cm^2)]. The dosimetry system (shown in Figure 4) has been developed at Dr. Shafirstein laboratory at Roswell Park. This system has been used to treat patients with head a neck cancer in a compassionate care settings (36), and in ongoing studies to guide intraoperative PDT in the treatment of treat patient with lung cancer. (48) The console of this light dosimetry system is shown in **Figure 4** below. The data is recorded and stored on a password secured personal computer.

Figure 4Dosimetry System screen layout



The light dosimetry system that will be used in this study: The screen layout of the dosimetry system. The light fluence rate (mW/cm^2) and fluence (J/cm^2) are continuously updated during therapy and presented on a LCD screen, so the treating physician can monitor the light delivery in real-time. In this example the integration period (pointed with a red arrow) or acquisition time is 20 milliseconds (ms) to obtain high signal to noise ratio reading as shown on the right, for 630±3 nm laser light.

32.3 Laser Systems

These laser systems will be shipped before the procedure and send back after each procedure. The laser will be shipped at least one day prior to I-PDT, to allow the laser safety officer to examine the laser/s (at each participating site). The laser systems will not stay in any site, they will be shipped back and forth as described above. All participating sites will use the following or comparable laser systems:

1. An experimental medical PDT diode laser (ML7710-630-6W, Modulight Inc. Tampere, Finland). This system emits light with a wavelength of 630 ± 3 nm up to 6 W. It includes SMA-905 connector, fiber sensor, integrated dose calibration unit (for 10-70 mm diffuser fibers), power control, dose calibration, and a foot pedal switch. It is used under IND in another study (I 256814).
2. The Modulight laser (ML7710-630, medical laser system, 630 ± 3 nm, 2 x 2.5 W (400 µm NA=0.22) individually controls laser fiber outputs with a SMA-905 connector and fiber sensors. It includes SMA-905 connector, fiber sensor, integrated dose calibration unit (for 10-70 mm diffuser fibers), power control, dose calibration, and a foot pedal switch.

The Modulight lasers have CE 0537, 93/42 EEC and ISO 13485 certifications to design and manufacture medical laser systems for PDT. The Modulight's ML7710-PDT platform has been specifically designed for illumination in PDT treatment processes, to meet the requirements in dose calibration, power stability and wavelength tolerance. The ML7710-630 version designed specifically for porfimer sodium. It has CB certification and design documentation for CE/FDA. These lasers, owned by Roswell Park, can reduce the treatment time significantly.

3. One or more DIOMED 630 PDT Laser. This laser system emits 630 ± 3 nm up to 2 Watts. The FDA approved the use of this laser for PDT with porfimer sodium. Pinnacle Biologics Inc.

provides this laser system at no cost to physicians that administer PDT with Photofrin®. This service is offered for all customers including Roswell Park. The laser is shipped 1-2 days prior to the procedure. The laser safety officer inspects it prior to treatment. The laser is sent back (to Pinnacle Biologics, Inc.) after treatment. This arrangement has been worked well for the past few years.

32.4 Cylindrical Light Diffuser and Dosimetry fibers

The I-PDT will be accomplished by delivering diffuse red light with fiber with cylindrical light diffuser end that will be connected to one of the lasers systems described above (section 32.3). A general description of these fibers can be found in Shafirstein et al. 2017.(47) In the study described herein, we will use fiber with cylindrical light diffuser end that can have 10, 20, 30, 40 or 50 mm length diffuser end (RD10-RD50, Medlight SA, Ecublens, Switzerland) and/or clinically approved cylindrical diffuser fibers (OPTIGUIDE® DCYL700 series 1, 1.5, 2.0, 2.5 and 5.0 cm, Pinnacle Biologics Inc. Bannockburn, IL).

For light dosimetry, we will use detection fibers with an isotropic probe end (IP, Medlight SA, Ecublens, Switzerland). We use these fibers in another clinical study that utilize PDT for the treatment of lung cancer.(48)

Medlight is ISO 13485 and ISO 9001 certified manufacturer. All their devices are CE marked, and are designed, marketed and used for PDT in the EU, and in many clinical studies. The USA FDA has successfully inspected Medlight on April 10-11, 2000.

33.0 References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30. doi: 10.3322/caac.21442. PubMed PMID: 29313949.

2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29. doi: 10.3322/caac.21208. PubMed PMID: 24399786.

3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30. doi: 10.3322/caac.21387. PubMed PMID: 28055103.

4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30. doi: 10.3322/caac.21332. PubMed PMID: 26742998.

5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29. doi: 10.3322/caac.21254. PubMed PMID: 25559415.

6. Machiels JP, Schmitz S. Management and palliative chemotherapy for metastatic or recurrent squamous cell carcinoma of the head and neck. Expert Rev Anticancer Ther. 2011;11(3):359-71. Epub 2011/05/04. doi: 10.1586/era.10.178. PubMed PMID: 21534878.

7. Salama JK, Vokes EE. Concurrent chemotherapy and re-irradiation for locoregionally recurrent head and neck cancer. Semin Oncol. 2008;35(3):251-61. Epub 2008/06/12. doi: 10.1053/j.seminoncol.2008.03.010
S0093-7754(08)00073-0 [pii]. PubMed PMID: 18544440.

8. Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J, Forastiere AA. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2005;23(15):3562-7. PubMed PMID: 15908667.

9. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol. 2005;23(34):8646-54. PubMed PMID: 16314626.

10. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359(11):1116-27. Epub 2008/09/12. doi: 10.1056/NEJMoa0802656 359/11/1116 [pii]. PubMed PMID: 18784101.

11. Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert J, Saba NF, Weiss J, Wirth L, Sukari A, Kang H, Gibson MK, Massarelli E, Powell S, Meister A, Shu X, Cheng JD, Haddad R. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study. J Clin Oncol. 2017;35(14):1542-9. doi: 10.1200/JCO.2016.70.1524. PubMed PMID: 28328302.

12. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW, Gillison ML. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016;375(19):1856-67. doi: 10.1056/NEJMoa1602252. PubMed PMID: 27718784; PMCID: PMC5564292.

13. Zafereo ME, Hanasono MM, Rosenthal DI, Sturgis EM, Lewin JS, Roberts DB, Weber RS. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. Cancer. 2009;115(24):5723-33. Epub 2009/09/18. doi: 10.1002/cncr.24595. PubMed PMID: 19760612.

14. Platteaux N, Dirix P, Vanstraelen B, Nuyts S. Outcome after re-irradiation of head and neck cancer patients. Strahlenther Onkol. 2011;187(1):23-31. Epub 2011/01/15. doi: 10.1007/s00066-010-2139-9. PubMed PMID: 21234530.

15. Lee N, Chan K, Bekelman JE, Zhung J, Mechalakos J, Narayana A, Wolden S, Venkatraman ES, Pfister D, Kraus D, Shah J, Zelefsky MJ. Salvage re-irradiation for recurrent head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;68(3):731-40. Epub 2007/03/24. doi: S0360-3016(07)00081-8 [pii]
10.1016/j.ijrobp.2006.12.055. PubMed PMID: 17379449.

16. Janot F, de Raucourt D, Benhamou E, Ferron C, Dolivet G, Bensadoun RJ, Hamoir M, Gery B, Julieron M, Castaing M, Bardet E, Gregoire V, Bourhis J. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. J Clin Oncol. 2008;26(34):5518-23. Epub 2008/10/22. doi: 10.1200/JCO.2007.15.0102
JCO.2007.15.0102 [pii]. PubMed PMID: 18936479.

17. McDonald MW, Lawson J, Garg MK, Quon H, Ridge JA, Saba N, Salama JK, Smith RV, Yeung AR, Yom SS, Beitler JJ. ACR appropriateness criteria retreatment of recurrent head and neck cancer after prior definitive radiation expert panel on radiation oncology-head and neck cancer. Int J Radiat Oncol Biol Phys. 2011;80(5):1292-8. Epub 2011/05/03. doi: 10.1016/j.ijrobp.2011.02.014
S0360-3016(11)00247-1 [pii]. PubMed PMID: 21530100.

18. Chen AM, Phillips TL, Lee NY. Practical considerations in the re-irradiation of recurrent and second primary head-and-neck cancer: who, why, how, and how much? Int J Radiat Oncol Biol Phys. 2011;81(5):1211-9. Epub 2011/11/26. doi: 10.1016/j.ijrobp.2011.06.1998
S0360-3016(11)02929-4 [pii]. PubMed PMID: 22115554.

19. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, Moan J, Peng Q. Photodynamic therapy. J Natl Cancer Inst. 1998;90(12):889-905. PubMed PMID: 9637138.

20. Kato H, Harada M, Ichinose S, Usuda J, Tsuchida T, Okunaka T. Photodynamic therapy (PDT) of lung cancer: experience of the Tokyo Medical University. Photodiagnosis Photodyn Ther. 2004;1(1):49-55. doi: 10.1016/S1572-1000(04)00008-0. PubMed PMID: 25048064.

21. Henderson BW, Dougherty TJ. How does photodynamic therapy work? Photochem Photobiol. 1992;55(1):145-57. PubMed PMID: 1603846.

22. Feyh J, Gutmann R, Leunig A. [Photodynamic laser therapy in the field of otorhinolaryngology]. Laryngorhinootologie. 1993;72(6):273-8. doi: 10.1055/s-2007-997899. PubMed PMID: 8333880.

23. Feyh J, Goetz A, Muller W, Konigsberger R, Kastenbauer E. Photodynamic therapy in head and neck surgery. J Photochem Photobiol B. 1990;7(2-4):353-8. PubMed PMID: 2150861.

24. Grant WE, Hopper C, Speight PM, Macrobert AJ, Bown SG. Photodynamic therapy of malignant and premalignant lesions in patients with 'field cancerization' of the oral cavity. J Laryngol Otol. 1993;107(12):1140-5. PubMed PMID: 8289004.

25. Biel MA. Photodynamic therapy of head and neck cancers. Methods Mol Biol. 2010;635:281-93. doi: 10.1007/978-1-60761-697-9_18. PubMed PMID: 20552353.

26. Schweitzer VG. PHOTOFRIN-mediated photodynamic therapy for treatment of early stage oral cavity and laryngeal malignancies. Lasers Surg Med. 2001;29(4):305-13. PubMed PMID: 11746107.

27. Rigual NR, Thankappan K, Cooper M, Sullivan MA, Dougherty T, Popat SR, Loree TR, Biel MA, Henderson B. Photodynamic therapy for head and neck dysplasia and cancer. Arch Otolaryngol Head Neck Surg. 2009;135(8):784-8. doi: 10.1001/archoto.2009.98. PubMed PMID: 19687399; PMCID: PMC2810853.

28. Kimura M, Miyajima K, Kojika M, Kono T, Kato H. Photodynamic Therapy (PDT) with Chemotherapy for Advanced Lung Cancer with Airway Stenosis. Int J Mol Sci. 2015;16(10):25466-75. doi: 10.3390/ijms161025466. PubMed PMID: 26512656; PMCID: PMC4632810.

29. Akopov A, Rusanov A, Gerasin A, Kazakov N, Urtenova M, Chistyakov I. Preoperative endobronchial photodynamic therapy improves resectability in initially irresectable (inoperable) locally advanced non small cell lung cancer. Photodiagnosis Photodyn Ther. 2014;11(3):259-64. doi: 10.1016/j.pdpdt.2014.03.011. PubMed PMID: 24704942.

30. Akopov AL, Rusanov AA, Molodtsova VP, Chistiakov IV, Kazakov NV, Urtenova MA, Rait M, Papaian GV. [Photodynamic therapy in combined treatment of stage III non-small cell lung carcinoma]. Khirurgiia (Mosk). 2013(3):17-20. PubMed PMID: 23612332.

31. Li LB, Xie JM, Zhang XN, Chen JZ, Luo YL, Zhang LY, Luo RC. Retrospective study of photodynamic therapy vs photodynamic therapy combined with chemotherapy and chemotherapy alone on advanced esophageal cancer. Photodiagnosis Photodyn Ther. 2010;7(3):139-43. doi: 10.1016/j.pdpdt.2010.06.002. PubMed PMID: 20728836.

32. Fuks D, Bartoli E, Delcenserie R, Yzet T, Celice P, Sabbagh C, Chatelain D, Joly JP, Cheron N, Dupas JL, Regimbeau JM. Biliary drainage, photodynamic therapy and chemotherapy for

unresectable cholangiocarcinoma with jaundice. J Gastroenterol Hepatol. 2009;24(11):1745-52. doi: 10.1111/j.1440-1746.2009.05915.x. PubMed PMID: 19780885.

33. Hong MJ, Cheon YK, Lee EJ, Lee TY, Shim CS. Long-term outcome of photodynamic therapy with systemic chemotherapy compared to photodynamic therapy alone in patients with advanced hilar cholangiocarcinoma. Gut Liver. 2014;8(3):318-23. doi: 10.5009/gnl.2014.8.3.318. PubMed PMID: 24827630; PMCID: PMC4026651.

34. Zhang NZ, Zhu Y, Pan W, Ma WQ, Shao AL. Photodynamic therapy combined with local chemotherapy for the treatment of advanced esophagocardiac carcinoma. Photodiagnosis Photodyn Ther. 2007;4(1):60-4. doi: 10.1016/j.pdpdt.2006.12.002. PubMed PMID: 25047193.

35. Lindenmann J, Matzi V, Neuboeck N, Anegg U, Baumgartner E, Maier A, Smolle J, Smolle-Juettner FM. Individualized, multimodal palliative treatment of inoperable esophageal cancer: clinical impact of photodynamic therapy resulting in prolonged survival. Lasers Surg Med. 2012;44(3):189-98. doi: 10.1002/lsm.22006. PubMed PMID: 22334351.

36. Mimikos C, Shafirstein G, Arshad H. Current state and future of photodynamic therapy for the treatment of head and neck squamous cell carcinoma. World Journal of Otorhinolaryngology-Head and Neck Surgery. 2016;2(2):126-9. doi: http://dx.doi.org/10.1016/j.wjorl.2016.05.011.

37. Khurana D, Martin EA, Kasperbauer JL, O'Malley BW, Jr., Salomao DR, Chen L, Strome SE. Characterization of a spontaneously arising murine squamous cell carcinoma (SCC VII) as a prerequisite for head and neck cancer immunotherapy. Head Neck. 2001;23(10):899-906. PubMed PMID: 11592238.

38. Suit HD, Sedlacek RS, Silver G, Dosoretz D. Pentobarbital anesthesia and the response of tumor and normal tissue in the C3Hf/sed mouse to radiation. Radiation research. 1985;104(1):47-65. PubMed PMID: 4048394.

39. Lew YS, Kolozsvary A, Brown SL, Kim JH. Synergistic interaction with arsenic trioxide and fractionated radiation in locally advanced murine tumor. Cancer research. 2002;62(15):4202-5. PubMed PMID: 12154019.

40. Oakley E, Bellnier DA, Hutson A, Wrazen B, Arshad H, Quon H, Shafirstein G. Surface markers for guiding cylindrical diffuser fiber insertion in interstitial photodynamic therapy of head and neck cancer. Lasers Surg Med. 2017;49(6):599-608. doi: 10.1002/lsm.22644. PubMed PMID: 28185275; PMCID: PMC5513772.

41. Oakley E, Wrazen B, Bellnier DA, Syed Y, Arshad H, Shafirstein G. A new finite element approach for near real-time simulation of light propagation in locally advanced head and neck tumors. Lasers Surg Med. 2015;47(1):60-7. doi: 10.1002/lsm.22313. PubMed PMID: 25559426; PMCID: PMC4304874.

42. Mendenhall WM, Mendenhall CM, Malyapa RS, Palta JR, Mendenhall NP. Re-irradiation of head and neck carcinoma. Am J Clin Oncol. 2008;31(4):393-8. Epub 2008/10/11. doi: 10.1097/COC.0b013e3181637398

00000421-200808000-00015 [pii]. PubMed PMID: 18846001.

43. Wong SJ, Spencer S. Reirradiation and concurrent chemotherapy after salvage surgery: pay now or pay later. J Clin Oncol. 2008;26(34):5500-1. Epub 2008/10/22. doi: 10.1200/JCO.2008.19.0868
JCO.2008.19.0868 [pii]. PubMed PMID: 18936468.

44. Licitra L, Vermorken JB. Is there still a role for neoadjuvant chemotherapy in head and neck cancer? Ann Oncol. 2004;15(1):7-11. Epub 2003/12/18. PubMed PMID: 14679112.

45. Khuri FR, Shin DM, Glisson BS, Lippman SM, Hong WK. Treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck: current status and future directions. Semin Oncol. 2000;27(4 Suppl 8):25-33. Epub 2000/08/22. PubMed PMID: 10952435.

46. Whiteside TL. Head and Neck Carcinoma Immunotherapy: Facts and Hopes. Clin Cancer Res. 2018;24(1):6-13. doi: 10.1158/1078-0432.CCR-17-1261. PubMed PMID: 28751445; PMCID: PMC5754223.

47. Shafirstein G, Bellnier D, Oakley E, Hamilton S, Potasek M, Beeson K, Parilov E. Interstitial Photodynamic Therapy-A Focused Review. Cancers. 2017;9(2). Epub 2017/01/27. doi: 10.3390/cancers9020012. PubMed PMID: 28125024; PMCID: PMC5332935.

48. Shafirstein G, Battoo A, Harris K, Baumann H, Gollnick SO, Lindenmann J, Nwogu CE. Photodynamic Therapy of Non-Small Cell Lung Cancer. Narrative Review and Future Directions. Ann Am Thorac Soc. 2016;13(2):265-75. doi: 10.1513/AnnalsATS.201509-650FR. PubMed PMID: 26646726; PMCID: PMC5015713.

49. Simone CB, 2nd, Cengel KA. Photodynamic therapy for lung cancer and malignant pleural mesothelioma. Semin Oncol. 2014;41(6):820-30. doi: 10.1053/j.seminoncol.2014.09.017. PubMed PMID: 25499640; PMCID: 4272687.

50. Lou PJ, Jager HR, Jones L, Theodossy T, Bown SG, Hopper C. Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. Br J Cancer. 2004;91(3):441-6. doi: 10.1038/sj.bjc.6601993. PubMed PMID: 15238981; PMCID: PMC2409848.

51. Jager HR, Taylor MN, Theodossy T, Hopper C. MR imaging-guided interstitial photodynamic laser therapy for advanced head and neck tumors. AJNR Am J Neuroradiol. 2005;26(5):1193-200. PubMed PMID: 15891183.

52. Robinson DJ, Karakullukcu BM, Kruijt B, Kanick CS, van Veen RPL, Amelink A, Sterenborg HJCM, Witjes MJ, Tan BI. Optical Spectroscopy to Guide Photodynamic Therapy of Head and Neck Tumors. Selected Topics in Quantum Electronics. 2010(4):854-62. doi: 10.1109/JSTQE.2009.2035930

53. Golusinski P, Szybiak B, Wegner A, Pazdrowski J, Pienkowski P. Photodynamic therapy in palliative treatment of head and neck cancer. Otolaryngol Pol. 2015;69(3):15-20. doi: 10.5604/00306657.1156330. PubMed PMID: 26388245.

54. Nyst HJ, Tan IB, Stewart FA, Balm AJ. Is photodynamic therapy a good alternative to surgery and radiotherapy in the treatment of head and neck cancer? Photodiagnosis Photodyn Ther. 2009;6(1):3-11. doi: 10.1016/j.pdpdt.2009.03.002. PubMed PMID: 19447366.

55. Stranadko EF, Volgin VN, Kagoyants RV. [The use of the method of photodynamic therapy for the treatment of the patients presenting with primary and recurrent laryngeal cancer]. Vestn Otorinolaringol. 2015;80(4):69-73. doi: 10.17116/otorino201580469-73. PubMed PMID: 26525327.

56. Jerjes W, Upile T, Akram S, Hopper C. The surgical palliation of advanced head and neck cancer using photodynamic therapy. Clin Oncol (R Coll Radiol). 2010;22(9):785-91. doi: 10.1016/j.clon.2010.07.001. PubMed PMID: 20829005.

57. Jerjes W, Upile T, Hamdoon Z, Abbas S, Akram S, Mosse CA, Morley S, Hopper C. Photodynamic therapy: The minimally invasive surgical intervention for advanced and/or recurrent tongue base carcinoma. Lasers Surg Med. 2011;43(4):283-92. Epub 2011/04/19. doi: 10.1002/lsm.21048. PubMed PMID: 21500222.

58. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller EA, Jr. The addition of mood and anxiety domains to the University of Washington quality of life scale. Head & neck. 2002;24(6):521-9. PubMed PMID: 12112548.

59. Hassan SJ, Weymuller EA, Jr. Assessment of quality of life in head and neck cancer patients. Head & neck. 1993;15(6):485-96. PubMed PMID: 8253555.

60. Weymuller EA, Jr., Alsarraf R, Yueh B, Deleyiannis FW, Coltrera MD. Analysis of the performance characteristics of the University of Washington Quality of Life instrument and its modification (UW-QOL-R). Arch Otolaryngol Head Neck Surg. 2001;127(5):489-93. PubMed PMID: 11346422.

61. Economidou-Karaoglou A, Opsomer M, Lans M, Taper HS, Deckers C, Roberfroid MB. Predictive value of serum alkaline DNase activity variations in treatment of head and neck cancer. Acta oncologica (Stockholm, Sweden). 1990;29(2):163-6. Epub 1990/01/01. PubMed PMID: 1692227.

62. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. PubMed PMID: 19097774.

63. NCCN Guidelines: Head and Neck Cancers Version 1.2018-February 15, 2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.

64. Ivanova A, Qaqish BF, Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. Biometrics. 2005;61(2):540-5. doi: 10.1111/j.1541-0420.2005.00311.x. PubMed PMID: 16011702.

34.0 Appendices/ Supplements

Appendix A ECOG Performance Status Scores

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

Appendix B Inclusion Criteria Checklist

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA

Participant Name:_____

Medical Record No.:_____

Title: A Phase 1 Trial: Porfimer Sodium Mediated Interstitial Photodynamic for the Treatment of Patients with Locally Advanced or Recurrent Head and Neck Cancer.

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Male or female patients age ≥ 18 years of age.	
☐	☐	☐	2. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 – 2. Refer to Appendix A.	
☐	☐	☐	3. Patients with locally advanced or recurrent head and neck cancer who failed to respond to standard therapy and are not amenable to standard curative treatment	
☐	☐	☐	4. Tumor accessible for unrestricted illumination for interstitial photodynamic Therapy (I-PDT) (accessibility as determined by the physician).	
☐	☐	☐	5. Life expectancy of at least 6 months, in the judgment of the physician.	
☐	☐	☐	6. Subjects of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	7. Subject must understand the investigational nature of this study and sign an Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix C Exclusion Criteria Checklist

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA

Participant Name:_____
Medical Record No.:_____
Title: A Phase 1 Trial: Porfimer Sodium Mediated Interstitial Photodynamic for the Treatment of Patients with Locally Advanced or Recurrent Head and Neck Cancer.

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. High dose curative radiotherapy within 30 days in the area to be treated.	
☐	☐	☐	2. Tumor invading a major blood vessel.	
☐	☐	☐	3. Tumor is not measurable on a CT or MRI scan according to RECIST v1.1.	
☐	☐	☐	4. Location and extension of the tumor precludes a potentially effective I-PDT.	
☐	☐	☐	5. Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.	
☐	☐	☐	6. Patients with porphyria, or with known hypersensitivity to porphyrins or porphyrin-like compounds.	
☐	☐	☐	7. Platelet count < 75,000.	
☐	☐	☐	8. Patients with impaired renal and/or hepatic function (total serum bilirubin > 2 mg/dL, serum creatinine > 2 mg/dL, alkaline phosphatase (hepatic), SGOT or SGPT > 3 times the upper normal limit.	
☐	☐	☐	9. Patients with moderately to severely impaired creatinine clearance (CrCl <44) will be excluded.	
☐	☐	☐	10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	11. Pregnant or nursing female subjects.	
☐	☐	☐	12. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	13. Any condition which in the Investigator's opinion deems the subject an unsuitable candidate to receive porfimer sodium.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix D Schedule of Procedures and Observations if Only I-PDT Course is Necessary

Evaluation	Baseline[1]	Pre-Operative	Day of Treatment	Day 1 Post Treatment	1-week Post-treatment	Optional I-PDT Course 2 Within 2-3 Weeks of Day 0[17]	Clinic Visit[2,2a]	30-Day Post I-PDT [14]	Optional I-PDT Treatment additional 2 or 3 At least 6 Weeks after last I-PDT Session[18]	Follow-Up
Informed Consent	X									
Medical History	X								X	
Physical Exam/ Vital signs & pain assessment using a verbal score 0-10[3]	X				X		X	X	X	X
Hematology[4] and Chemistry[5]	X				X		X	X	X	
Research Blood Draws[6]			X		X		X	X	X	
Pregnancy Test (Urine)	X								X	
ECOG Performance Status	X		X		X		X	X	X	X
UW-QoLQ v. 4[15]	X				X		X	X	X	X
Standard Imaging of the head and neck with CT or MRI, for RECIST v11.1	X[7]								X	X[8]
Treatment planning	X								X	
Porfimer Sodium administration and Vital Signs		X[9]							X	
Intraoperative Ultrasound			X						X	
If possible, intraoperative CT or other clinically approved radiological imaging			X[10]			X[10]			X[10]	
Interstitial PDT (I-PDT) [16]			X[11]			X[11]			X[11]	
Concomitant Medications	X[12]		X							
Adverse Events[13]			X		X		X	X		

Notes:

* The I-PDT procedure is termed a "course".

1. Performed within 8 weeks prior to porfimer sodium.
2. Performed at Day 1of SOC therapy.
   2a: If later 2nd and 3rd I-PDT courses are deemed necessary per the physician (see Section 10.4), please refer to Appendix D 1 for treatment, procedure, and test scheduling.
3. Temperature, heart rate, respiratory rate, blood pressure, body weight and, height, Height collected at baseline only. Refer to Section 11.2.
4. Hematology (i.e., CBC (with auto differential), ANC, and platelets). Refer to Section 11.2.
5. Chemistry (i.e., AST, ALT, total bilirubin, alkaline phosphatase, creatinine, potassium, glucose, and calcium). Refer to Section 11.2.
6. This is optional. Refer to immune markers Section 11.8 (1, 10 mL green-top tube).
7. Standard tumor staging performed within 4 weeks, and at least 14 business days prior to I-PDT. If possible, the imaging will include temporary fiducial markers that will be affixed to skin. Refer to Section 11.2.
8. CT scans at 10 to 12 weeks post SOC therapy and as clinically indicated following the NCNN 2018 guidelines.
9. Infusion will occur 48 hours ±8 h prior to illumination. Vitals are to be taken immediately after injection and after 15 minutes.
10. If possible, intraoperative CT (such as O arm) or another radiological imaging (e.g. C-arm) will be used to image the catheters in the tumor.
11. Refer to Section 10.2.1.
12. Medications ongoing within 1 week prior to porfimer sodium injection.
13. AE reporting period will be for 30 days ± 2 days post first SOC treatment.
14. First SOC treatment day of I-PDT day if no therapeutic SOC treatment is administered.
15. Refer to Section 11.6f patient doesn't come in or quality of life is missed, may be done via telephone.
16. In the event that the tumor size is such that treating the entire tumor could cause a health risk to the patient, the current I-PDT course will be broken up into session/ s. We will illuminate one part of the tumor on the day of I-PDT and another part/s of the tumor in additional I-PDT session/s within 14 days after the initial I-PDT session, at the discretion of the treating physician. If

an I-PDT course is broken up into I-PDT sessions, the I-PDT dosage for each session will remain the same as though sessions were not broken up as dosing is dependent on number of fibers received per session. The patient will not need to receive additional doses of porfimer sodium if having additional I-PDT sessions within 14 days after the previous I-PDT session as porfimer sodium is expected to be in the tumor for at least 30 days.

17. Another (one or two, total of three) laser light treatment(s) only (no additional drug) within 2-3 weeks of the initial administration of Photofrin.
18. Patient may receive a second complete I-PDT treatment that will include drug and light administration. It will be at the discretion of the treating physician to administer this additional treatment. Another CT (charged to the study if it is not SoC) will be done, and all tests will be conducted before and after additional treatment, according to the same schedule parameters as the initial treatment.

Appendix D 1 Schedule of Procedures and Observations (Only for Dose Escalation later I-PDT Sessions if Deemed Necessary by Physician)**

Evaluation	Repeat of Initial Tests and Procedures [A]	Pre-Operative	Day of Treatment	1-week Post-treatment	Clinic Visit	Post-Treatment [p]	Follow-Up
Physical Exam/ Vital signs [B]& pain assessment using a verbal score 0-10	X			X	X	X	X
Hematology [C] and Chemistry [D]	X			X	X	X	
Research Blood Draws [E]			X	X	X	X	X
Pregnancy Test (Urine)	X						
ECOG Performance Status	X		X	X	X	X	X
UW-QoLQ v. 4[p]	X			X	X	X	X
Fresh Tissue Tumor Biopsy[F]	X			X			
Standard Imaging of the head and neck with CT or MRI[G]	X[H]						X[I]
Treatment planning	X						
Porfimer Sodium administration and Vital Signs		X[J]					
Intraoperative Ultrasound [Q]			X				
If possible, intraoperative CT or other clinically approved radiological imaging			X[K]				
Interstitial PDT (I-PDT)			X[L, Li]				
Concomitant Medications	X[M]		X				
Standard of care (SoC) chemotherapy, targeted therapy or potentially immunotherapy as first line palliative care treatment options					X[N]		
Adverse Events [O]	X [Oi]		X	X	X	X	

Notes:

* The I-PDT procedure is termed a “course”. As per later Section 10.4, study participants may have up to 3 I-PDT courses per physician’s discretion, at least 30 days from the previous illumination procedure.

** **NOTE**: 2nd and 3rd I-PDT courses are per the physician's discretion as per Section 10.4, 2nd and 3rd I-PDT courses are **not** required for all study participants. If it is decided participants should receive all 3 I-PDT courses, items from "Repeat of Initial Tests and Procedures" until the completion of I-week Post treatment" are completed twice before the Clinic Visit and start of Standard of Care chemotherapy.

A. Performed within 4 weeks prior to 2nd and 3rd I-PDT courses. Since there may be up to three I-PDT courses, at least 30 days apart (see Section 10.4) per the physician's discretion, the initial procedures, exams, or tests may be completed up to two more times based on the individual participant's study treatment regimen. Research blood draws, standard imaging of head and neck with CT or MRI, and treatment planning for later I-PDT courses are per physician's discretion.
B. Temperature, heart rate, respiratory rate, blood pressure, and body weight. Refer to Section 11.2.
C. Hematology (i.e., CBC (with auto differential), ANC, and platelets). Refer to Section 11.2.
D. Chemistry (i.e., AST, ALT, total bilirubin, alkaline phosphatase, creatinine, potassium, glucose, and calcium). Refer to Section 11.2.
E. This is optional. Research blood draws for any 2nd and 3rd I-PDT courses (all timepoints) are per the physician's discretion. Refer to immune markers Section 11.8 (1 green top tube).
F. If required per physician's discretion, standard tumor staging performed within 4 weeks, and at least 14 business days prior to following I-PDT. If possible, the imaging will include temporary fiducial markers that will be affixed to skin. Refer to Section 11.2.
G. CT scans at 10 to 12 weeks post I-PDT and as clinically indicated following the NCNN 2018 guidelines.
H. If tumor results determine porfimer sodium infusion is needed for later 2nd and 3rd I-PDT sessions, infusion will occur 48 hours ±8 h prior to illumination. Vitals are to be taken immediately after injection and after 15 minutes.
I. If possible, intraoperative CT (such as O arm) or another radiological imaging (e.g. C-arm) will be used to image the catheters in the tumor.
J. Refer to Section 10.2.1.
K. Medications ongoing within 1 week prior to illumination.
L. Refer to Section 10.2.1.
   Li. The later 2nd and 3rd I-PDT study treatments total as per the physician's discretion are at least 30 days apart from each other (see Section 10.4). For additional I-PDT treatments that are 30 days from the previous that require an additional dosage of porfimer sodium the porfimer sodium (2mg/kg) is administered 48 hours prior to illumination.
M. AE reporting period will be for 30 days ± 2 days post first SOC treatment.
   Oi. Since there may be up to three I-PDT courses, at least 30 days apart (see Section 10.4), per the physician's discretion, adverse events review of previous study treatments are reviewed prior of the next additional I-PDT.
N. In Phase 1, patients are off treatment/on follow up as clinically indicated 30 days after the last I-PDT.
O. Refer to Section 11.6 if patient doesn't come in or quality of life is missed, may be done via telephone.

P. In the event that the tumor size is such that treating the entire tumor could cause a health risk to the patient, the current I-PDT course will be broken up into session/s. We will illuminate one part of the tumor on the day of I-PDT and another part/s of the tumor in additional I-PDT session/s within 14 days after the initial I-PDT session, at the discretion of the treating physician. If an I-PDT course is broken up into I-PDT sessions, the I-PDT dosage for each session will remain the same as though sessions were not broken up as dosing is dependent on number of fibers received per session. The patient will not need to receive additional doses of porfimer sodium if having additional I-PDT sessions within 14 days after the previous I-PDT session as porfimer sodium is expected to be in the tumor for at least 30 days.
Q. The intraoperative ultrasound is done for 2nd and 3rd I-PDT courses, as per physician's discretion.

Appendix E University of Washington Quality of Life Questionnaire

Date: ___/___/____ Subject ID#_____

This questionnaire asks about your health and quality of life over the past seven days. Please answer all of the questions by checking one box for each question.

1. Pain (Check one box:)

   I have no pain.

   There is mild pain not needing medication.

   I have moderate pain - requires regular medication (codeine or nonnarcotic).

   I have severe pain controlled only by narcotics.

   I have severe pain, not controlled by medication.

2. Appearance (Check one box:)

   There is no change in my appearance.

   The change in my appearance is minor.

   My appearance bothers me but I remain active.

   I feel significantly disfigured and limit my activities due to my appearance.

   I cannot be with people due to my appearance.

3. Activity (Check one box:)

   I am as active as I have ever been.

   There are times when I can't keep up my old pace, but not often.

   I am often tired and have slowed down my activities although I still get out.

   I don't go out because I don't have the strength.

   I am usually in bed or chair and don't leave home.

4. Recreation (Check one box:)

   There are no limitations to recreation at home or away from home.

   There are a few things I can't do but I still get out and enjoy life.

   There are many times when I wish I could get out more, but I'm not up to it.

   There are severe limitations to what I can do, mostly I stay at home & watch TV.

I can't do anything enjoyable.5.Swallowing (Check one box:)

I can swallow as well as ever.

I cannot swallow certain solid foods.

I can only swallow liquid food.

I cannot swallow because it "goes down the wrong way" and chokes me.

6. Chewing (Check one box:)

I can chew as well as ever.

I can eat soft solids but cannot chew some foods.

I cannot even chew soft solids.

7. Speech (Check one box:)

My speech is the same as always.

I have difficulty saying some words but I can be understood over the phone.

Only my family and friends can understand me.

I cannot be understood.

8. Shoulder (Check one box:)

I have no problem with my shoulder.

My shoulder is stiff but it has not affected my activity or strength.

Pain or weakness in my shoulder has caused me to change my work.

I cannot work due to problems with my shoulder.

9. Taste (Check one box:)

I can taste food normally.

I can taste most foods normally.

I can taste some foods.

I cannot taste any foods.

10. Saliva (Check one box:)

My saliva is of normal consistency.

I have less saliva than normal, but it is enough.

I have too little saliva.

I have no saliva.

11. Mood (Check one box:)

My mood is excellent and unaffected by my cancer.

My mood is generally good and only occasionally affected by my cancer.

I am neither in a good mood nor depressed about my cancer.

I am somewhat depressed about my cancer.

I am extremely depressed about my cancer.

12. Anxiety (Check one box:)

I am not anxious about my cancer.

I am a little anxious about my cancer.

I am anxious about my cancer.

I am very anxious about my cancer.

Which issues have been the most important to you during the past 7 days?

Check up to 3 boxes.

Pain	Swallowing	Taste
Appearance	Chewing	Saliva
Activity	Speech	Mood
Recreation	Shoulder	Anxiety

GENERAL QUESTIONS

Compared to the month before you developed cancer, how would you rate your health-related quality of life? (check one box:)

Much better

Somewhat better

About the same

Somewhat worse

Much worse

In general, would you say your health-related quality of life during the past 7 days has been: (check one box:)

Outstanding

Very good

Good

Fair

Poor

Very poor

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your overall quality of life during the past 7 days. (Check one box:)

Outstanding

Very good

Good

Fair

Poor

Very poor

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).

Signature_____

Printed name_____

Date_____

Appendix F Patient Instructions

Patient Instructions for Photofrin® and Laser Treatment

You should protect yourself from daylight while in the hospital and when you go home. The major danger is severe sunburn of the skin. Photofrin® stays in your body for a long time after you have received treatment. Therefore, you must be careful and limit your exposure to daylight. You are most likely to be burned by daylight for 6 to 8 weeks after receiving the drug. However, you should limit your daylight exposure for about 2 months after the treatment. Several suggestions are listed below:

1. For the first 1 month keep the drapes closed (drawn) so that daylight does not enter your room(s) in the hospital and when you go home. You must remember that there is a danger from direct sunlight even on days that are overcast and cloudy.

2. Your eyes are also sensitive to direct daylight, so you should wear dark sunglasses (100% UV protection) for at least 2 months after receiving Photofrin®.

3. If you must be exposed to daylight, you should wear a hat with a large brim, sunglasses, gloves to protect your hands, a long-sleeved shirt or blouse, slacks, socks, and a scarf to protect your neckline.

4. Poor circulation in any area of your body may result in that area retaining the Photofrin® for a longer period of time than the rest of your body, and this area will need extra protection for a longer time than 2 months.

5. You **may** be exposed to indoor light from a low wattage (60 watt) light bulb for up to ten hours each day. For longer periods of exposure to light, dimly lit rooms are advisable (60 watt). Exposure to Fluorescent lighting is OK. **You may watch TV and use indirect lights such as the lights in the hospital found above your bed, which shine toward the ceiling. Try not to use Ultra-violet or Halogen lights.**
    - For reading, it would be useful to use a small book lamp (example: Itty-bitty Book lamp). The book light will prevent you from having the light shine on you.

6. Do not have your eyes examined for at least 2 months after receiving Photofrin®. This is a precaution to prevent any retina damage that could occur from exposure to the bright exam light used in eye exams.

7. Please also do not go to the dentist in the 2-month period after receiving Photofrin® to prevent any oral/facial skin burning from the bright exam light.

8. Showers and baths are allowed.

9. You must report any redness, swelling, tenderness, blistering, sunburn, or any other event that does not usually happen to you.

10. Remember that your doctor is here to study the usefulness of Photofrin® and photodynamic therapy for the treatment of tumors; your questions, concerns, and symptoms are important.

11. Please help the doctor to learn more about you and your treatment by keeping lists of questions, concerns, and symptoms. Your doctor will address these when you see them. Also, remember that the nurse can aid you at any time.

12. You are welcome to bring any family member or close friend to your appointments to help you in communicating with your doctor.

Skin Testing After Photofrin®

1. *When should I test my skin?*

   Approximately 1 month after receiving the drug Photofrin®.

2. *What do I do?*

   Cut a hole in a paper bag approximately 2-inch diameter. Place the bag over your forearm. Cover all other skin thoroughly. Expose the 2-inch diameter of the forearm skin to direct sunlight for one minute, then examine for evidence of skin reaction, such as redness, blistering or burning sensation. If there is no reaction, expose the skin again, and check it in another minute. Repeat this procedure up to eight more times, provided there is no sign of skin reaction.

3. *What if I see a skin reaction?*

   Immediately cover the exposed skin and stop the skin test. You may retry skin testing in a few days. Contact your doctor or nurse to find out more information.

4. *What if I don't have a skin reaction?*

   If there is no reaction after the above procedure, cover the exposed skin and protect yourself from sunlight for 24 hours. Re-examine the exposed skin at the end of this time. If there is no delayed skin reaction, slowly begin to increase your time in direct light.

5. *Should I use sunscreen?*

   No. A sunscreen will not help protect your skin from the sun when using Photofrin®.

Appendix G Tumor response following irRECIST, according to attachment: "irRECIST-path-PDF Bohnsack et al 2014 ESMO abstract.pdf".

Target Lesion Selection for irRECIST

- Follow the definitions from RECIST 1.1

Non-measurable Lesion Definitions for irRECIST

- Follow the definitions from RECIST 1.1

Response	Criteria for Response per irRECIST
Complete Response (irCR) ☐	**irCR**: complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
Partial Response (irPR) ☐	**irPR**: decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
Stable Disease (irSD) ☐	**irSD**: failure to meet criteria for irCR or irPR in the absence of irPD.
(irNN) ☐	**irNN**: no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.

MD/PI/Co-I Signature _____ Date _____

Printed Name _____

OUTPATIENT PROGRESS RECORD

Protocol Title and Number -

Date of Assessment:

_____

Response	Criteria for Response
Progressive Disease (irPD) ☐	**irPD**: minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.
Non Evaluable (irNE) ☐	**irNE**: used in exceptional cases where insufficient data exists.
No Disease (irND) ☐	**irND**: in adjuvant setting when no disease is detected.

MD/PI/Co-I Signature: _____Date: _____

Printed Name _____

Appendix H NCCN Guidelines Version 1.2018 Follow up Recommendations

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Head and Neck Cancers

NCCN Guidelines Index
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Discussion

FOLLOW-UP RECOMMENDATIONS[1]
(based on risk of relapse, second primaries, treatment sequelae, and toxicities)

- **H&P exam (including a complete head and neck exam; and mirror and fiberoptic examination):[2]**
  - **Year 1, every 1–3 mo**
  - **Year 2, every 2–6 mo**
  - **Years 3–5, every 4–8 mo**
  - **>5 years, every 12 mo**
- **Imaging:**
  - **Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 mo of treatment (category 2B).**
  - **Chest CT with or without contrast as clinically indicated for patients with smoking history (See NCCN Guidelines for Lung Cancer Screening).**
  - **Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history, and areas inaccessible to clinical examination.**
  - **Routine annual imaging (repeat use of pretreatment imaging modality) may be indicated in areas difficult to visualize on exam.**
- **Thyroid-stimulating hormone (TSH) every 6–12 mo if neck irradiated.**
- **Dental evaluation[3] for oral cavity and sites exposed to significant intraoral radiation treatment.**
- **Consider EBV DNA monitoring for nasopharyngeal cancer (category 2B).**
- **Supportive care and rehabilitation:**
  - **Speech/hearing and swallowing evaluation[4] and rehabilitation as clinically indicated.**
  - **Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is stabilized.[4]**
  - **Ongoing surveillance for depression (See NCCN Guidelines for Distress Management).**
  - **Smoking cessation[5] and alcohol counseling as clinically indicated.**
- **Integration of survivorship care and care plan within 1 year, complementary to ongoing involvement from a head and neck oncologist (See NCCN Guidelines for Survivorship).[6]**

[1]Most recurrences are reported by the patient.
[2]For mucosal melanoma and paranasal sinus cancers, a physical exam should include endoscopic inspection for paranasal sinus disease.
[3]See Principles of Dental Evaluation and Management (DENT-A).
[4]See Principles of Nutrition (NUTR-A).
[5]All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be referred to the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[6]Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. CA Cancer J Clin 2016;66:203-239.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Head and Neck Cancers

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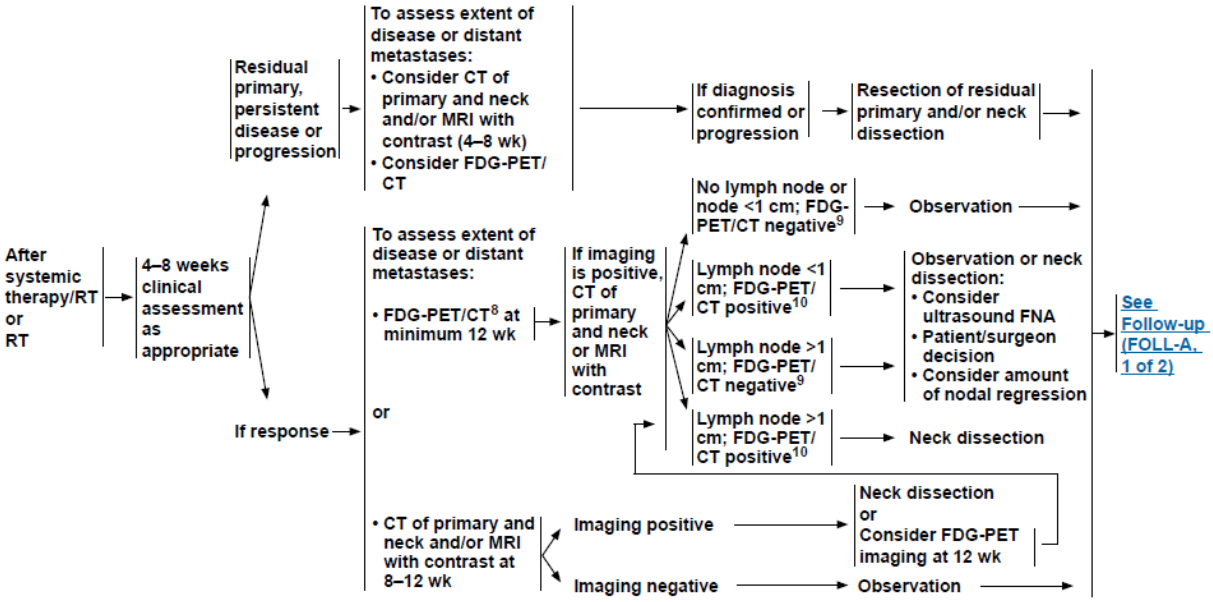
FOLLOW-UP RECOMMENDATIONS POST CHEMORADIATION OR RT NECK EVALUATION[7]



[7]Adapted with permission from Kutler DI, Patel SG, Shah JP. The role of neck dissection following definitive chemoradiation. Oncology 2004;18:993-998.
[8]If a FDG-PET/CT is performed and negative for suspicion of persistent cancer, further cross-sectional imaging is optional.
[9]PET negative = No or low-grade uptake, felt not suspicious for disease.
[10]PET positive = PET suspicious for disease.

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