Document Coversheet

Study Title:

Endobronchial Ultrasound Transbronchial Needle guided Interstitial Photodynamic Therapy for Palliation of Locally Advanced Lung Cancer and Advanced Cancers Obstructing the Airway -Phase I/II Study

Institution/Site:	Roswell Park Comprehensive Cancer Center
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Roswell Park Cancer Institute

Study Number: I 279415

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Confidentiality Statement

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INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant initials): _____

Title: Endobronchial Ultrasound Transbronchial Needle Guided Interstitial Photodynamic Therapy for Palliation of Locally Advanced Lung Cancer and Advanced Cancer Obstructing the Airway-Phase I/II Study

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years of age.	
☐	☐	☐	2. Eligibility checklist before registration requires review of case by study surgeon or interventional pulmonologists to approve anatomic feasibility of an airway intervention.	
☐	☐	☐	3. For patients in Cohort B only. Patients are amenable to receive a palliative radiotherapy of 8 Gy x1 48±4 h prior to the I-PDT, as determined by the radiation oncologist.	
☐	☐	☐	4. Patients with an established pathologic diagnosis of small cell and/or non-small cell lung cancer or other malignancies causing airway obstruction > 25% requiring bronchoscopic intervention. Or inoperable malignancies not candidates for curative radiotherapy within the airway.	
☐	☐	☐	5. Have an ECOG Performance Status of ≤ 3. Refer to Appendix A.	
☐	☐	☐	6. Have the following clinical laboratory values: • Platelets ≥ 100,000 cells/mm^3 (SI units100 x 10^9/L)	
☐	☐	☐	7. Participants 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. 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.	
☐	☐	☐	8. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ Date: _____
Print Name of Investigator: _____

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant initials): _____

Title: Endobronchial Ultrasound Transbronchial Needle Guided Interstitial Photodynamic Therapy for Palliation of Locally Advanced Lung Cancer and Advanced Cancer Obstructing the Airway - Phase I/II Study

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Participants who have had curative radiotherapy to the target tumor within 4 weeks prior to the scheduled I-PDT and/or PDT.	
☐	☐	☐	2. 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.	
☐	☐	☐	3. Pregnant or nursing female participants.	
☐	☐	☐	4. Co-existing ophthalmic disease likely to require slit-lamp examination within the next 14 days following I-PDT and/or PDT treatment.	
☐	☐	☐	5. Known hypersensitivity/allergy to porphyrin.	
☐	☐	☐	6. Patients who are not cleared by the anesthesiologist to undergo an advanced bronchoscopy procedure under general anesthesia.	
			7. Patients with target tumor invading into the lumen of the esophagus, confirmed by esophago-gastro-duodenoscopy (EGD) with endoscopic ultrasound.	
☐	☐	☐	8. Patients diagnosed with porphyria.	
☐	☐	☐	9. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	10. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive I-PDT or PDT.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**

If "NO", do not enroll participant in study.

Investigator Signature: _____ Date: _____

Print Name of Investigator: _____

TABLE OF CONTENTS

1 BACKGROUND

1.1.1 Lung Cancer with Airway Obstruction

Lung cancer may be cured in its early stages with surgical resection. Unfortunately, the majority of patients with lung cancer are presented in later stages where chemotherapy, with or without radiation, is the preferred treatment. Advanced disease stage carries poorer prognosis, with low survival rates. (1, 2)

Patients with late-stage lung cancer may be presented with tracheal or bronchial airway obstruction. These patients are at higher risk for respiratory failure, post-obstructive pneumonia, and prolonged hospitalizations. The therapeutic approach for patients with malignant airway obstruction is usually complicated and challenging and, includes bronchoscopic intervention, radiation therapy, or both, in combination with chemotherapy. Some patients resist chemoradiation therapy (CRT) or, are not able to tolerate the CRT because of other medical co-morbidities. In these instances, their disease continues to progress with persistent airway obstruction, requiring palliation and life-saving interventions with one or more bronchoscopic procedures. Bronchoscopic intervention leads to faster improvement but requires an advanced bronchoscopic procedure using laser, cryotherapy, tumor debulking, and ablation with or without airway stenting. Patients at this terminal stage tend to progress with recurrent airway obstruction, which can lead to repetitive palliative bronchoscopic procedures.

Additionally, a variety of malignancies can create malignant central airway obstruction, including lung, breast, colon, thyroid, adenoid cystic, various head and neck malignancies, renal cell, and others. Other non-epithelioid malignancies, including melanoma can also cause central airway obstruction. Intraluminal PDT has been used to treat any malignancy metastatic to the airway. Reddy et al. published a case series treating malignant central airway obstruction due to renal cell carcinoma. (3) Magro et al. published a case series treating a variety of metastatic central airway obstruction using PDT with similar promising results (4) when treating carcinomas of the colon, breast, kidney, and tongue that were metastatic to the airways. Other authors have demonstrated that PDT, when applied to metastatic tumors of the central airways, was able to significantly improve the degree of obstruction and quality of life these patients experienced. (5)

All of the above authors used intraluminal PDT to direct their treatment. Thus, we will use same I-PDT treatment approach for all malignancies that compromise the airway in this study.

1.1.2 Photodynamic Therapy for Bronchogenic and Esophageal Cancer

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.(6, 7) PDT with Photofrin® (porfimer sodium) has been approved for the treatment of non-small cell lung cancer (NSCLC) for over 15 years (6, 7). In PDT, systemic administration of a light sensitive drug (i.e., photosensitizer, PS) is followed by illumination of the target tumor with visible light that leads to the generation of reactive oxygen species, notably singlet oxygen, (8) resulting in the destruction of the tumor by a combination of direct cellular and secondary vascular effects. (9) In addition to local tumor ablation, PDT has been shown to enhance anti-tumor immunity in both clinical and pre-clinical settings. (10-12) PDT is also used as a single-therapy or, in combination with surgery, chemotherapy, or standard radiation therapy. (13-15)

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.(16) 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.(16, 17) A relatively large retrospective study by Lindenmann et al. (18) suggested that adding Photofrin® mediated PDT prior to standard of care (n=118) resulted in better overall survival than adding PDT after standard of care (n=130) in patients with inoperable esophageal cancer. (18) That report was in agreement with Li et al.'s study (2010) (16) which 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.(16)

PDT's primary indication is for obstructive disease and symptom palliation in patients with tumors that are not eligible for standard surgery and radiation therapy. Currently, the most commonly used photosensitizer in PDT is Photofrin® (Pinnacle Biologics Inc. Bannockburn, IL). After intravenous injection, Photofrin® is retained in neoplastic cells and, to a lesser degree, in normal tissue. The therapeutic effect is obtained by illuminating the target tumor and margins with visible light with 630 ± 3 nm wavelength, approximately 48 hours post-administration. (19-21) Photosensitivity is the major complication of PDT with Photofrin®. The photosensitivity usually lasts for 4-6 weeks. During that time, patients are instructed to use sunglasses to protect the eyes and cover the skin with long sleeve shirts and pants, when exposed to direct sunlight or bright indoor light. The development of second-generation PSs has minimized photosensitivity, by having fast accumulation and clearance.

1.1.3 Photofrin® (Porfimer Sodium)

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

1.1.4 Clinical Use of Porfimer Sodium

The US 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 (6, 7). 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 (8). Porfimer sodium is being used off label and in clinical studies to treat many other cancers (10, 22-24).

Porfimer sodium may last for at least 30 days within the primary tumor.

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® User's Guide.

1.1.5 Endobronchial Ultrasound (EBUS)

In the past 10 years, convex-probe endobronchial ultrasound (EBUS) became the procedure of choice for the mediastinal lung cancer staging. (25) It is widely used for evaluation and diagnosis of mediastinal abnormalities such as lymphoma, sarcoidosis, vascular abnormalities, and other

tumors. (26-28) Recently, the therapeutic role of EBUS is cautiously emerging with few reports of its use in placing fiducial markers for central pulmonary nodules to guide stereotactic body radiation (29) and for local injection of chemotherapeutic agents to treat lung cancer. (30-33)

The EBUS scope consists of a fiber optic component for endobronchial airway visualization and a curvilinear ultrasound probe for real-time ultrasound scanning. It also allows the identification of vascular structures using the integrated color Doppler. To allow ultrasound scanning of the extrabronchial structures, the scope looks at a 35-degree forward oblique angle, with an angle of view of 80-degrees. Endobronchial ultrasound with transbronchial needle (EBUS-TBN) is usually performed using a dedicated 25-, 22-, 21- or 19-gauge needle with an echogenic tip. These devices are equipped with a stylet that is kept in place as the transbronchial puncture is performed and used to clean the tip of the needle from any bronchial contamination. The needle can be used to implant a laser fiber with cylindrical diffuser in tissue, as discussed below (Section 1.1.7).

1.1.6 EBUS-TBN Guided I-PDT

1.1.7 EBUS-TBN I-PDT: Phantom Evaluation

The phantom evaluation of optic fiber placement and illumination using EBUS-TBN was performed in Roswell Park's Center for PDT laser laboratory (Dr. Shafirstein, PI) using a solid phantom model that mimics the mechanical properties of soft tissue (Ballistic gel, Clear Ballistics LLC, Fort Smith, AR). A 21-gauge EBUS needle (NA-201SX-4021; Olympus, Tokyo, Japan) was inserted into the phantom model. After cleaning the EBUS needle tip, the stylet was withdrawn, and an optical fiber with a cylindrical diffuser was inserted into the needle: the fiber is made of flexible polymer that is 3 meters long and 0.5 mm in diameter with a cylindrical diffuser end (RD250, Medlight SA, Ecublens, Switzerland). Light is emitted from the cylindrical diffuser. The EBUS needle, with the fiber, was pushed to a distal target region in the phantom. Thereafter, the needle was withdrawn to expose the cylindrical diffuser end of the optical fiber. On the other end, the optical fiber was connected to a diode laser that was used as a light source for delivering laser light from the cylindrical diffuser end to the phantom, as shown in **Figure 1**. This experiment revealed the functional placement of using EBUS-TBN in placing the optical fiber in a phantom model.

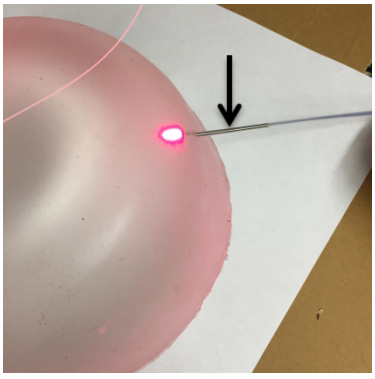

Figure 1: Image showing the EBUS needle-guided (arrow) placement and illumination of the optic fiber inside the phantom model.

1.1.8 In-Vivo EBUS-TBNI for I-PDT

Five female mice (C3H) bearing SCCVII tumors were used to assess the feasibility of guiding the RD250 fiber through a 21-gauge EBUS needle (NA-201SX-4021; Olympus, Tokyo, Japan). The curvilinear probe of the ultrasound (Vevo® 2100, VisualSonics, Toronto, Canada) system was used for real-time ultrasound guidance. Each mouse was anesthetized, using isoflurane by inhalation, and placed on a small solid platform in a decubitus position with the tumor upward. The tumor was covered with a water-based gel and the ultrasound probe was placed in contact with the tumor (**Figure 2**).

Using the jabbing technique, the EBUS needle was inserted into the tumor parallel to the linear ultrasound probe. The needle stylet was used to clean the tip of the needle under real-time ultrasound visualization. The stylet was removed and the optical fiber that was marked for the length of the EBUS needle was introduced up to the needle tip. The fiber was then gently pushed outside the needle successfully under real time ultrasound guidance without any manipulation. The fiber was notably hyperechoic and, was easily adjusted inside the tumor under real-time ultrasound guidance. The fiber's appropriate functionality inside the tumor was successfully tested with illumination. This procedure was performed in the PDT animal laboratory under an IACUC approved protocol.

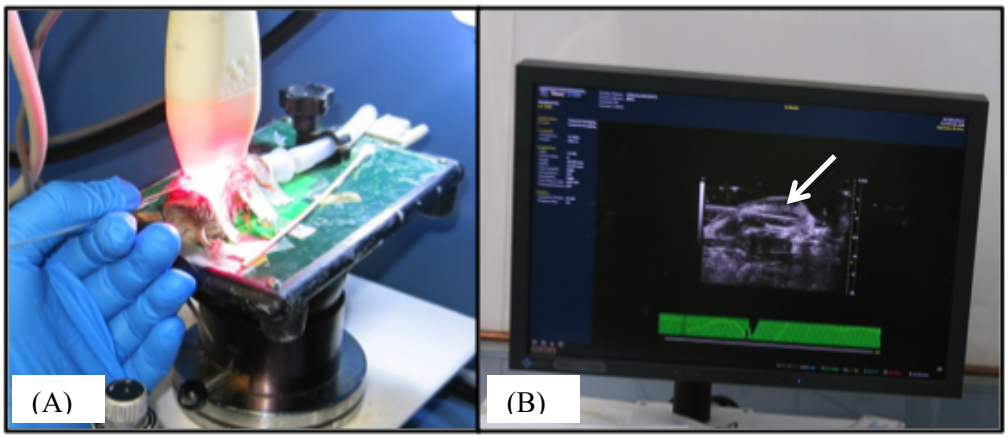

Figure 2: (A) An anesthetized mouse imaged with an ultrasound during interstitial photodynamic therapy using the EBUS needle. (B) The ultrasound image of the laser fiber (arrow) within the tumor.

1.1.9 Treatment Planning for I-PDT in Locally Advanced Lung Cancer or Metastatic Disease to the Airways

Recent advancements in computer simulations enable near real-time planning and dosimetry during I-PDT. (34-39) We have demonstrated that finite element modeling (FEM) can be used to plan the number and location of the optical fibers in the tumor, for an effective illumination of the target tumor. (34) A detailed description of this modeling approach is provided in Oakley et al. 2015. (34) Briefly, an image visualization and analysis software package (Simpleware, Exeter, UK) is used to segment tumor, adjacent normal tissues, blood vessels, and other important anatomical features. The segmented scans are reconstructed to create a 3-D model that is imported

into the FEM software (Comsol Inc., Burlington, MA). The FEM is used to calculate the light propagation and absorption in the 3-D model. **Figure 3** shows the results of a simulation that was conducted on a model created from de-identified CT scans of a patient with locally advanced NSCLC. The de-identified scans were obtained with approval from the Roswell Park Cancer Institute Office of Research Subject Protection. This was a proof-of-concept simulation to assess the possibility of delivering sufficient light dose to a tumor that could be amenable for EBUS-TBN guided I-PDT. The simulations suggest that by interstitial illuminating of the tumor with seven fibers (RD250) with 4 cm cylindrical diffuser end each, we can administer a light dose of 56.5 J/cm^2 to 100% of the tumor. Each fiber delivers the FDA approved laser light intensity of 400 mW/cm and energy of 200 J/cm. In this large tumor, the overall I-PDT treatment time would be about 1 hr, when fiber is illuminated for 500 s each time.

Recent preclinical studies in Dr. Shafirstein's laboratory suggest that the irradiance has an important impact on tumor response, for I-PDT of locally advanced head and neck cancer. (40, 41) We believe that this is also true for I-PDT in LALC. However, in EBUS guided I-PDT for LALC, we are limited in the number and location of fibers that we can insert into the tumor. In this exploratory study we will aim to administer the new light settings to a significant volume of the target tumor. We will administer a 630-nm laser light with the objective to deliver a minimal irradiance of ≥8.6, ≥10.8 or ≥15.3 mW/cm^2 where we reported effective ablation in Oakley et al. 2020. (41) The treatment time will be adjusted to deliver ≥45 J/cm^2 to a significant volume of the target tumor. The research team will present a table showing the light delivery options and percent of tumor volume that will receive the minimal irradiance and fluence for the physician to review.

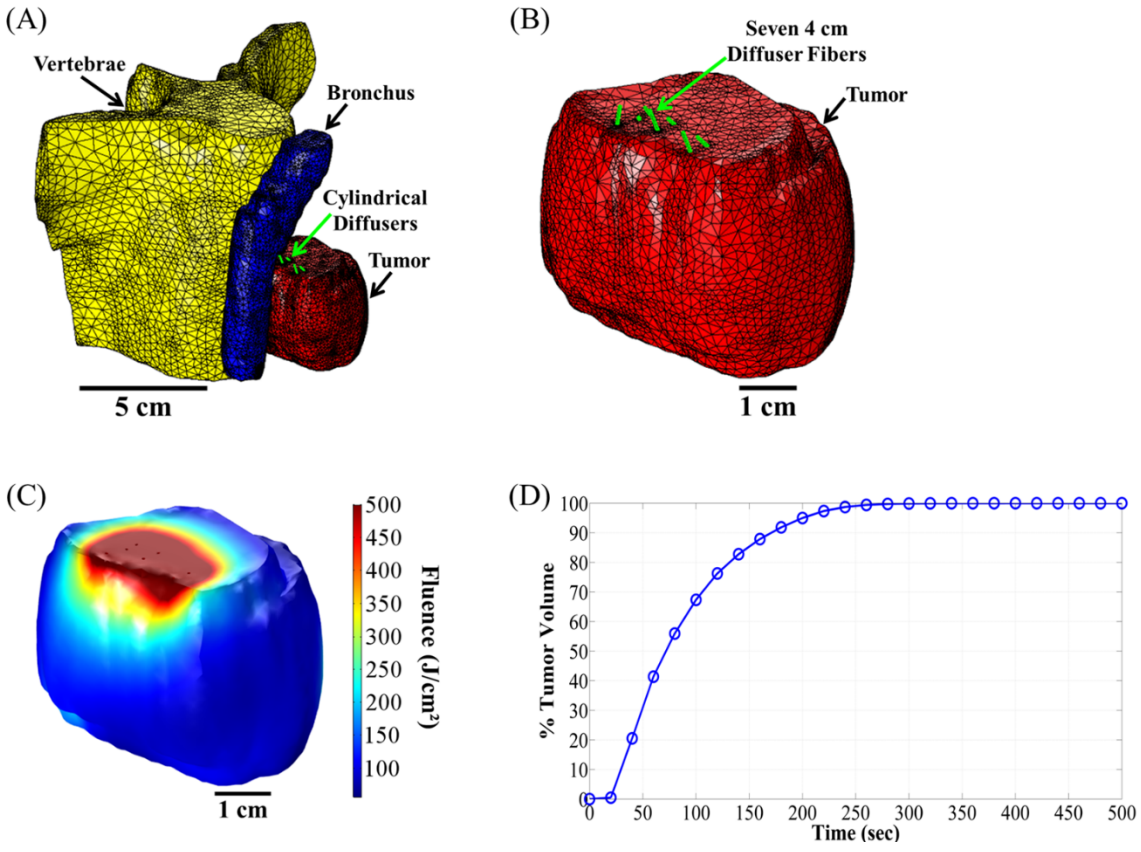

Figure 3: (A) A three-dimensional (3-D) mesh of a geometry that was reconstructed from CT scans of LALC. (B) Close up of 3-D mesh of the tumor with seven 4-cm diffuser fibers (C) The 3-D fluence (J/cm²) distribution on the tumor surface, for laser light wavelength of 630 nm with an input light intensity of 400 mW/cm per fiber and a treatment time of 500 s per fiber that results in 200 J/cm. The total I-PDT treatment time would be 7X500=3500 s or about 1 h. Within the entire tumor, the minimum and maximum fluences would be 56.5 J/cm² and 1273 J/cm², respectively. **(D) Dose volume histogram for the percent of the tumor volume that receives >45 J/cm² as a function of treatment time** per fiber, when all seven fibers were on**.**

COMSOL™ is a commercial non-medical software that we use for treatment planning. An alternative option is to use DOSIE™ (Simphotek Inc., Newark, NJ) a novel image-based treatment planning for PDT and I-PDT.

The significance of testing DOSIE™ in this study is:

1. It will help to address a major unmet need in I-PDT that is the ability to do calculations in near real-time, so that the treatment planning is quickly performed during pre-treatment phase and can be adjusted in the operating room in case some of the original treatment or patient-specific parameters are changed. Currently, simulations are done the day before treatment and real-time adjustments cannot be made during treatment. This proposal will test the ability of DOSIE™ running in near real-time, which is faster than COMSOL™.
2. The currently available commercial simulation software packages, such as COMSOL™, are not tuned for simulations specific to I-PDT and have limited features, which significantly limits its ability to be adopted for the clinic. DOSIE™ was designed with help from scientists and clinicians at Roswell Park, designated for modeling all types of PDT treatments: I-PDT, intracavitary PDT, and external beam PDT (EB-PDT).
3. DOSIE™ entirely owned by Simphotek, collaborator in the NCI/NIH award that will support the study to compare DOSIE™ to COMSOL™. DOSIE™ contains no commercial software that would limit its ability to be modified/customized on clinicians' demand and Simphotek long term goal is to obtain FDA approval for DOSIE™ as a treatment planning for PDT and I-PDT.

DOSIE™ is the first image-based treatment planning that is dedicated for PDT and I-PDT. The following points set DOSIE™ apart from COMSOL™ with respect to provide a novel image-based treatment planning.

1. DOSIE™ is a near real-time system that can be used during clinical treatment in case the original treatment parameters are changed in the operating room.
2. DOSIE™ supports generating treatment plans based not only on the standard light dose, but also on the promising new types of doses: thresholding the light irradiance, PDT-dose, and singlet-oxygen dose. None of the existing commercial packages offers this versatility.
3. DOSIE™ supports simulation of light dose and light irradiance in every cubic millimeter of target tumor volume. Two solvers are available for simulation: finite-element method and Monte Carlo method to estimate the distribution of the light scattered within the target volume and at the margins.

DOSIE's Photokinetics module supports multi-thread simulation of spatially resolved time-dependent PDT dose and singlet oxygen dose (sOxy) dose (42). The modules are tightly integrated: the MC's output fluence rate map is passed to Photokinetics solver to model PDT dose, with modeling photosensitizer's excitation and photobleaching, and singlet oxygen dose (sOxy) dose,

with taking into account oxygen intake and reacted species concentration, that in turn can provide calculated concentration of PS excited state molecules as an input to the FE solver to estimate distribution of the fluorescent light signal, resulted from the induced fluorescence emission during PS radiative relaxation at excitation sites.

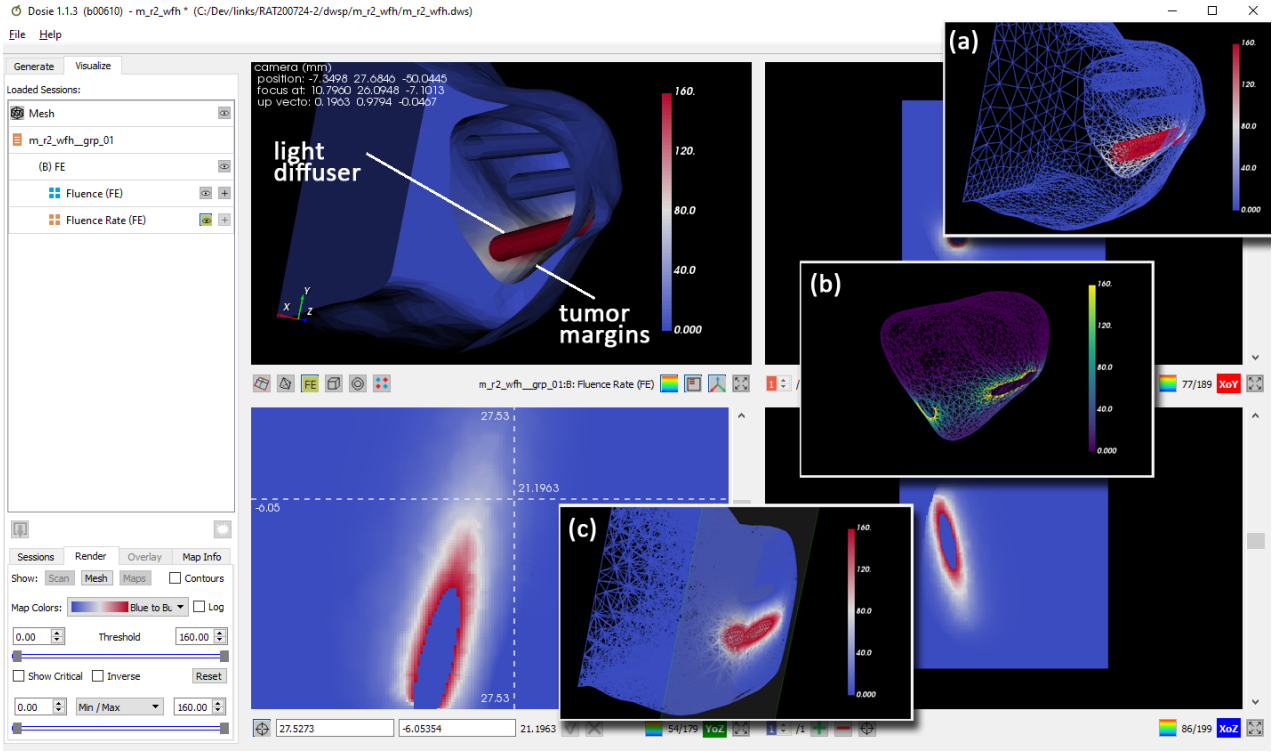

Figure 4. DOSIE™ screenshots: different modes of treatment plan visualization (only one diffuser is on). (a) Tissue and tumor irradiance on wireframe, (b) Tumor margins only, (c) Clipping the target volume to visualize interior of the tumor.

1.1.10 EBUS Guided I-PDT Preceded by Standard of Care Palliative Radiotherapy

Following the completion of Cohort 0, we have recently reported that Photofrin® mediated interstitial photodynamic therapy (I-PDT), delivered via our image-guided light dosimetry planning platform, is safe with promising outcomes in the treatment of extrabronchial MCAO with 3 out of 10 patients alive at 8.3, 12, and 26.5 months (56). This study included patients with stage IIb-IVb of either non-small cell lung cancer, large cell neuroendocrine, melanoma, or endometrial cancer that metastasize to the airway causing extrabronchial MCAO. The Photofrin® was retained in all these tumors and responses did not seem to be affected by the cancer pathology. Our computer modelling suggests that we delivered the maximum safe light dose rate (irradiance) and dose (fluence). Careful analysis of the clinical outcomes indicates that further improvement in tumor control requires augmenting I-PDT with additional therapy.

We propose to improve the response to I-PDT with palliative radiotherapy (*p-XRT)*. P-XRT is standard of care treatment for patients with refractory lung cancer (57, 58), and several groups have reported that it can increase tumor oxygenation and alter tumor vasculature for 1-2 days after the last radiation fraction (59-63). Our group and others have reported that increases in tumor hemoglobin oxygen saturation and vascular perfusion will increase tumor oxygenation and

penetration of the Photrofrin®-exciting 630-nm illumination laser light (64-68). This is accompanied by improvement in tumor response to PDT.

Preliminary preclinical data demonstrate that p-XRT followed by I-PDT provide for constructive cooperation between the modalities. In studies investigating this approach, we evaluated the preclinical response of two murine models to a regimen of p-XRT followed in 24 h by I-PDT (**Figure 5**). To demonstrate that p-XRT improves tumor response, we used low dose I-PDT in mice with locally advanced murine tumors (400-600 mm^3). An X-radiation dose of 10 Gyx2 on consecutive days induced slight tumor growth delay, establishing it as a palliative regimen (palliative X-Radiation, p-XRT). As a standalone modality, the low dose I-PDT produced minimal to modest tumor control as a function of tumor model, as expected. When p-XRT is followed by I-PDT, there is significant ($p<0.05$) improvement in durable complete response in both models (**Figure 5).** This establishes the benefit of preceding I-PDT with p-XRT.

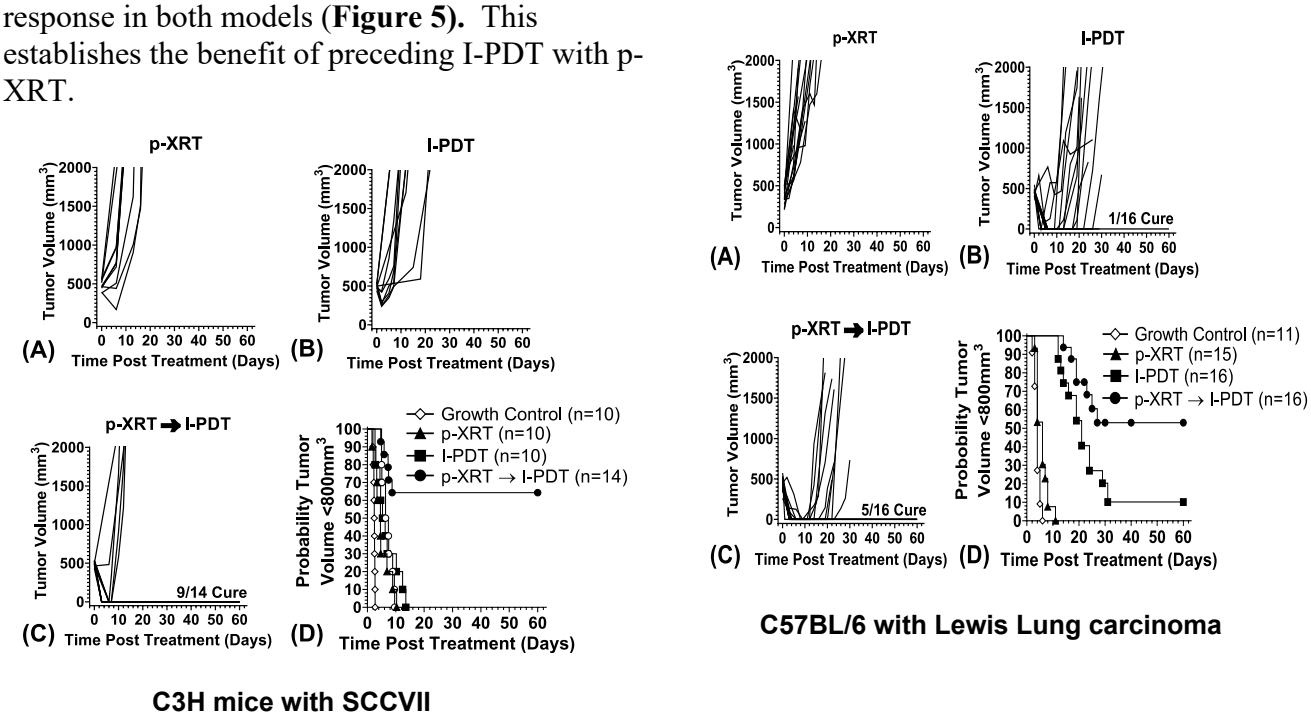

Figure 5. C3H mice with SCCVII: Tumor growth delay and Kaplan Meier plots for eight- to twelve-week-old C3H mice with locally advanced (400-600 mm^3) subcutaneous squamous cell carcinoma VII (SCCVII). **C57BL/6 with Lewis Lung carcinoma (LLC)**: Eight- to twelve-week-old C57BL/6 mice with locally advanced (400-600 mm^3) subcutaneous LLC. Both models treated with I-PDT and palliative radiotherapy (p-XRT) **(A)** mice treated with p-XRT, **(B)** mice treated with I-PDT, **(C)** mice treated with p-XRT followed by I-PDT. Cure is defined as no palpable tumor at 60 days (i.e., a complete response) as described in Shafirstein et al. 2018. **(D)** Kaplan Meier plot including control growth, p-XRT, I-PDT, and p-XRT followed I-PDT. The Log-rank (Mantel-Cox) test found that p-XRT followed by I-PDT resulted in significantly ($p <0.05$) better tumor control when compared to p-XRT only and I-PDT only. The p-XRT regimen was 10 Gy x2 consecutive daily fractions. The Photofrin® was administered 1-2 h after the second dose of the p-XRT. The I-PDT was administered with 630-nm light 24±2 h after the Photofrin® injection. The laser settings were such that the irradiance and fluence were 6.9 mW/cm^2 and 62.5 J/cm^2 at the margins and 195 mW/cm^2 and 1754 J/cm^2 at the fiber surface.

In further studies, we considered the mechanisms behind p-XRT sensitization of tumor to I-PDT. Cytotoxic effects of low dose, palliative radiation manifest as temporary control of tumor growth and/or partial reduction of tumor burden. This can be accompanied by vascular effects that include transient, acute increases in vascular volume and permeability, as well as temporary increases in tumor oxygenation. We used photoacoustic imaging to assess the effect of p-XRT on tumor hemoglobin and blood oxygenation (**Figure 6**). At 24 h after p-XRT there was a slight increase in hemoglobin compared to the control (no p-XRT in **Figure 6 B).** In mice treated with p-XRT the tumor blood oxygenation saturation was significantly ($p<0.05$) higher in comparison to the control **(Figure 6 C).** Relative high blood oxygenation is expected to improve the response to PDT due to high oxygen supply and decrease absorption at 630-nm light which will result in better light penetration that will allow for treatment of larger tumors (67, 68). Together, these data provide initial evidence that the addition of p-XRT prior to I-PDT can greatly improve I-PDT outcomes.

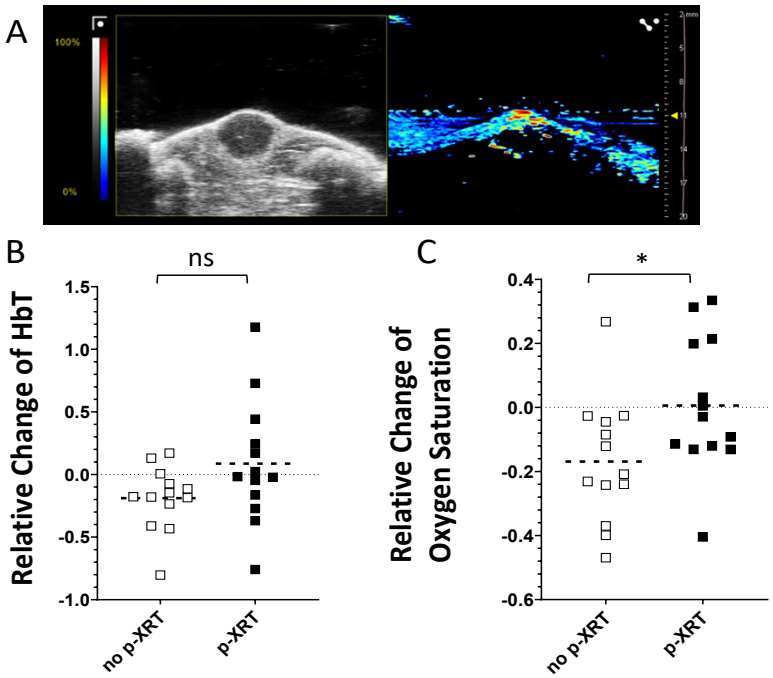

Figure 6. Photoacoustic imaging suggests that the p-XRT did not change total hemoglobin and oxygenated blood with time. While no treatment resulted in reduction of blood oxygenation when compared to baseline. **(A)** Representative ultrasound and photoacoustic image of LLC tumor. **(B)** Relative change in hemoglobin (HbT) and **(C)** relative change in percent oxygen saturation of LLC tumors in control (no p-XRT) mice and mice treated with p-XRT (10 Gyx2 over two days). Relative change is defined as the difference of photoacoustic HbT or percent oxygen saturation signal before and after p-XRT divided by the baseline (before p-XRT). Untreated mice had imaging performed at the same treatment volume and same time interval, 48 hours apart (n=13 mice per group). C57BL/6 mice with 200-400 mm^3 LLC subcutaneous tumors (n=13 per group).

In assessing the feasibility of using p-XRT followed by I-PDT to treat very large tumors, we recently employed this treatment in a compassionate care exemption setting with Roswell Park IRB approval (CE- 22-14). This patient had unusually large extrabronchial MCAO induced by

metastatic renal cell carcinoma of 9.5 cm (**Figure 7**). In the treatment of this patient, we used p-XRT (at 8 Gy x1) that 48 h later was followed by our image-guided I-PDT. This single-patient treatment was safe and provided benefit in improved breathing and functionality (as seen in the CT scan **Figure 7B**) at 40 days post I-PDT. These results demonstrate the feasibility of using p-XRT and I-PDT, and suggest that it can provide benefits**.**

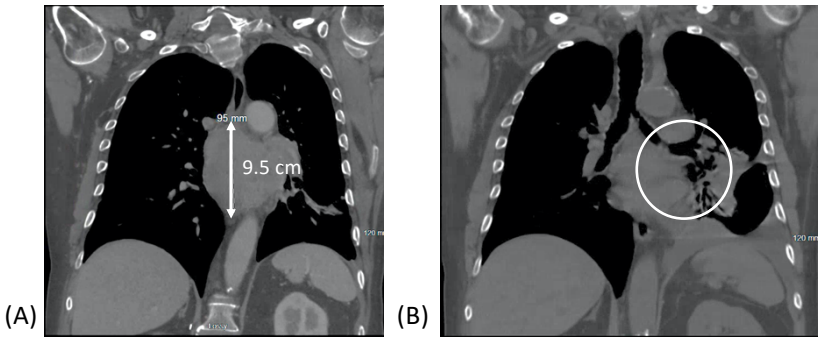

Figure 7. Treatment outcomes for a patient with locally advanced extrabronchial MCAO induced by metastatic renal cell carcinoma treated with 8 Gy x1 followed by our image-guided I-PDT 48 h after the p-XRT. (A) CT scan 13 days prior to treatment showing a 9.5 cm extrabronchial tumor blocking the airway. (B) CT scan 40 days after the I-PDT showing open left mainstem airway (marked with a circle) resulting in significant improvement in breathing.

Palliative radiotherapy in patients. In consultation with the treating radiation oncologist (Dr. Malik) who treated the patient on CE 22-14 we propose to treat patients with a standard of care single dose of 8 Gy x1 that is expected to be safe, with effective palliation and no significant tumor response. This p-XRT regimen was also reported to be safe and induce similar responses when compared to other p-XRT regimens for palliation in patients with NSCLC (57, 69).

1.1.11 Correlative Studies

Many NSCLC are infiltrated with immunosuppressive immune cells and these tumor cells are known to secrete immunosuppressive cytokines (70, 71) and express immunoregulatory, checkpoint molecules that impair anti-tumor immunity. The two best characterized immune checkpoints are cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1). (72) CTLA4, through interaction with its receptor, CD28, regulates the amplitude of the early stages of T cell activation and enhances Treg cell immunosuppressive activity. (73, 74) The primary role of PD1 is to limit T cell activity in the periphery. (75, 76) PD1 is highly expressed on Treg cells and is associated with increased Treg cell proliferation. PD1 mediates its effects on T cells upon interaction with its ligands PDL1 (B7-H1) and PDL2 (B7-DC). PDL1 is expressed by numerous cancer cells (77) and by myeloid cells within the tumor microenvironment (78). Numerous clinical trials have been performed using antibodies that inhibit immune checkpoints. Blockade of CTLA4 has shown promise in melanoma, but is associated with significant immune related toxicities. (72) Blockade of PD1/PDL1 axis has proven to be effective in clinical trials of NSCLC with an overall response rate of 20%; PD1/PDL1 blockade also resulted in fewer immune toxicity than blockade of CTLA4. (70, 79-82) While extremely encouraging and

promising, 80% of patients did not respond to checkpoint blockade, suggesting that additional optimization, patient selection and development of combination therapies are needed.

Several recent studies have indicated that treatment of human tumors with photodynamic therapy (PDT) can stimulate the host anti-tumor immune response (10, 11, 83) and potentially overcome tumor induced immunosuppression allowing for enhanced survival and opening a window for the use of immunotherapy. The purpose of these correlative studies is to assess whether treatment with biophysical modalities, such as PDT, affects the immune contexture of NSCLC patients. These patients tend to have an immunosuppressed immune contexture, which is associated with lower overall lymphocytes counts in the periphery, leading to higher neutrophil to lymphocyte ratios (NLR) that can be prognostic for treatment outcome (84), elevated levels of circulating regulatory T cells, myeloid derived suppressor cells (MDSC), PD1 expressing T cells, and PD-L1 expressing MDSCs. (71, 84, 85)

To assess the effect of I-PDT and/or PDT on the immune contexture of study patients we will use flow cytometry to examine changes in circulating levels of neutrophils, total lymphocytes ($CD45^+$), MDSCs ($CD45^+$, $CD11b^+$, $CD33^+$, $HLADR^{lo}$, $CD14^+$ or $CD15^+$ and $PD\text{-}L1^+$), cytotoxic T lymphocytes ($CD45^+$, $CD3^+$, $CD8^+$, Granzyme B^+, $Perforin^+$). Tumor tissue will be collected and used as antigenic material for analysis of tumor specific T cell function (ELISPOT) and examined by flow cytometry for changes in PD-L1+ MDSCs and cytotoxic T lymphocytes similarly as above in the circulation.

We will use de-identified CT scans from each patient to fabricate 3-D phantoms with 3-D printing technology of the airway and tumor. This model will be used to make a mold where we will fabricate a phantom with optical properties that mimic the calculated optical properties of the tumor. These phantoms will be used to test the accuracy of a new algorithm to compute optical properties, and if found accurate it will be considered in future clinical studies.

1.1.12 Optical and Oxygenation Measurements (optional)

It has been reported that oxygenated blood has lower absorption coefficient in comparison to deoxygenated blood (68). Our group and others have reported that increases in tumor hemoglobin oxygen saturation and vascular perfusion will increase tumor oxygenation and penetration of the Photrofrin®-exciting 630-nm illumination laser light (64-68). An increase in light penetration and tumor oxygenation are expected to be accompanied by improvement in tumor response to I-PDT.

Therefore, prior to and immediately after delivering the therapeutic 630-nm laser light, we will measure tumor tissue partial oxygen pressure (pO2), and we will perform in-vivo spectral interstitial transmittance measurements that will provide data that can be used to assess optical properties.

Tumor pO2 will be measured with a validated commercial system (OxyLite™ Pro, Oxford Optronix North America, London, ON, Canada; Oxford Optronix Ltd, Abingdon, UK) (86, 87) with a sterile pO2 sensor (pO2 'Large Area' sensor, sterile, 5 m length; 1 mm2 sampling area, Oxford Optronix North America, London, ON, Canada; Oxford Optronix Ltd, Abingdon, UK). The sterile pO2 sensor will be placed into a sterile catheter (Bronchial Tube sterile, Best Medical International, Inc. Springfield, VA) to achieve rigidity. The end of the bronchial tube will be open (prior to treatment) to expose the end of the pO2 sensor that can be

inserted into the target tumor for 2-3 min to measure the tumor pO2. The sensor and the catheter will then be removed. The sensor and the catheter will be of single use.

The change in optical properties will be reflected in changes in light irradiance that we have shown to affect tumor response and we can measure with a light dosimetry system (40, 41). We will measure the transmission of the laser light (for 10-30 s) with an isotropic dosimetry fiber (IP, Medlight S.A. Ecublens, Switzerland) that will be connected to our customized light dosimetry to measure the transmitted laser light irradiance and fluence. This system is being used in several other Roswell Park IRB approved studies (I 67918, I 62118 and I 767720). The isotropic dosimetry fiber is a 3 m long and 1 mm in diameter optical fiber with 0.85 mm in diameter distal tip. This fiber will be attached to the outer surface of endoscope so that the detection end is at the end of the endoscope. The isotropic dosimetry fiber must be calibrated prior to each use. Consequently, the fiber will be submitted to high-level disinfection before and after use, following the clinical procedure used to disinfect the endoscope. Then the isotropic dosimetry fiber can then be reused in multiple patients.

In addition, we will use the standard endoscope camera to measure the light transmission. To that end, we will use a video capture device (USB 3.0 HD Video Capture Device, StarTech, Groveport, Ohio) to connect a video output port on the endoscope to a USB port on a password secured computer. The streaming software Stream Catcher Pro (StreamCatcherPro, StarTech, Groveport, Ohio) will be used in unison with the Startech system to allow for the recording of the endoscope video feed. Live feed from the endoscope camera is displayed on the software interface. This interface allows the user to name their recording, select the file format the video will be saved as, and then start and stop recording. All videos will be taken during treatment. Recordings save automatically with the given name and file type immediately upon stopping a recording. *This process does not interfere with the routine EBUS procedure.* It has been tested in Dr. Shafirstein's laboratory using a research clinical system (an Olympus endoscope) that is same as the system being used in the clinic. The recoded data will be saved and analyzed on a password secured computer in Dr. Shafirstein's laboratory.

2 RATIONALE

Chemotherapy remains the mainstay of treating inoperable malignant airway obstruction. Despite chemotherapy with one or more regimens, most patients will suffer recurrent disease and may present with airway obstruction. Some patients may develop respiratory symptoms (e.g., dyspnea, hemoptysis, post-obstructive pneumonia, respiratory failure) secondary to tracheal or bronchial obstruction. Palliation of their symptoms is usually accomplished by tumor irradiation or bronchoscopic intervention. For some patients, palliative radiation results in clinical improvement after partial or complete resolution of the airway obstruction. However, other patients may have no response to radiation, which results in disease progression and worsening of respiratory symptoms.

Bronchoscopic intervention leads to faster improvement but requires an advanced bronchoscopic procedure using laser, cryotherapy, tumor debulking, and ablation with or without airway stenting. Patients at this terminal stage tend to progress with recurrent airway obstruction, which can lead to repetitive palliative bronchoscopic procedures. There is an urgent need to offer these frail patients a treatment with minimal toxicity and morbidity, and that can reduce tumor-induced symptoms with a chance to improve their quality of life and perhaps their survival.

Multiple studies have shown that PDT can lead to tumor regression in lung cancer and other malignancies when the tumors are less than 1 cm in thickness. However, I-PDT is required to treat large tumors. In recent review papers, we highlighted future directions using I-PDT with treatment planning as a possible modality to treat patients with locally advanced cancer including intrinsic and extrinsic cancer that compromise the airway and are larger than 1 cm (22, 23). In these tumors, EBUS can be used to guide the insertions of the TBN into the tumor and the RD250 laser fiber can be inserted through that needle for intra-tumor illumination (Figure 1 and Figure 2). Recently, Dr. Shafirstein (Co-Investigator) and his research team published the concept of using EBUS-TBN to guide I-PDT in the treatment of locally advanced lung cancer. (90) In addition, I-PDT and/or PDT can be used to treat endobronchial tumors. (22)

Our overall hypothesis is that EBUS-TBN guided I-PDT and/or I-PDT and preceded by p-XRT are safe and have the potential to treat the bulk of locally advanced lung cancer or other malignancies in the central airway, which may lead to tumor regression or slower progression and therefore a longer palliation period.

3 OBJECTIVES

3.1.1 Primary Phase I Objective (Cohort 0, data collection completed)

- For patients with locally advanced lung cancer (LALC) and malignancies causing airway obstructions: To evaluate the safety and potential efficacy of EBUS-TBN guided I-PDT and/or I-PDT and/or PDT, using porfimer sodium as a photosensitizer.

3.1.2 Primary Phase II Objectives (Cohort A and Cohort B)

- To assess the tumor response to treatment.
- To observe changes in well-being.

3.1.3 Secondary Objectives (Cohort A and Cohort B)

- To evaluate PFS.
- To compare the treatment planning in DOSIE™ with the plan generated in COMSOL™ in Cohort A only.
- To measure changes in tumor pO2, optical properties, and irradiance and fluence in relationship to response.
  -

3.1.4 Exploratory Objectives (Cohort A and Cohort B)

- Examine porfimer sodium retention in the target tumor tissue.
- Examine the relationship between immune biomarkers and response.

4 METHODOLOGY

4.1 Study Design

This is a multi-center, multi-arm, Phase I (Cohort 0; data collection complete) to monitor the safety and Phase II study (Cohort A and Cohort B described below) to monitor the efficacy of EBUS-

TBN guided I-PDT and/or I-PDT and/or PDT in patients with malignant airway obstructions that are refractory to curative chemoradiation or, who are not candidates for curative chemoradiation. Participants will be treated on an outpatient or inpatient basis, and the treating physician will make this decision on a case-by-case basis.

Cohort 0 is closed to accrual and fulfilled the Phase 1 safety monitoring requirements. Cohort 0 provided the safety monitoring component for Cohort A of this Phase II study. Cohort 0 consisted of patients with the diagnosis of lung cancer that received porfimer sodium with EBUS I-PDT and participated in all of the study procedures except the Quality of Life Questionnaires and Six Minute Walk Test.

Cohort A (n=18, Phase II) consists of patients with a diagnosis of lung cancer or other malignancies causing airway obstruction or inoperable malignancies not candidates for curative radiotherapy within the airway; and that receive EBUS I-PDT and all of the study procedures. Subjects treated in Cohort 0 are considered the Phase I part of Cohort A.

Cohort B (n=39) will consist of patients with the diagnosis of lung cancer or other malignancies causing airway obstruction, or inoperable malignancies not candidates for curative radiotherapy within the airway. Subjects in Cohort B will receive the EBUS-guided I-PDT 48±4 h after standard of care palliative radiotherapy of 8 Gy x1.

NOTE: *Given the nature of this advanced airway procedure, only the physician performing the procedure will be the consenter for the procedure as well as for the study.*

All participants will undergo the standard of care interventional bronchoscopy procedure with an attempt to treat and resolve the airway obstruction using conventional methods such as mechanical debulking, tumor ablation, and/or airway stenting. Airway stenting will be performed before or after I-PDT and/or PDT, as necessary. Curvilinear EBUS with Color Doppler will be used to guide the intra-tumor fiber insertion.

In each procedure, the estimated percentage of obstruction will be documented before and after endobronchial debulking and ablation. Tumor debulking and ablation will be performed before EBUS-TBN with I-PDT and/or I-PDT and/or PDT. The airway obstruction severity is usually estimated based on the size of scope that can be passed through an obstructed airway and based on the size of the balloon used to dilate the obstructed airway.

Airway obstruction severity will be classified as(91): mild (<50%), moderate (50-70%), and severe (>70%).

The baseline obstruction to be used in the study will be the airway obstruction that was established before the I-PDT and/or PDT.

It is considered standard of care, and a commonly used approach, to use the Endobronchial Ultrasound (EBUS) in combination with therapeutic bronchoscopy. It is useful for diagnostics, as well as a tool to guide therapeutic bronchoscopy. EBUS helps demarcate the anatomy of the bronchial and peri-bronchial structures such as vascular and cardiac organs and thus, making the therapeutic procedure safer. (92)

For Cohort B participants only, standard of care palliative radiotherapy of 8 Gy x1 will be administered to the target tumor at day -2 just before systemic administration of 2 mg/kg porfimer sodium. This will be coordinated with the radiation oncologist.

Standard of care blood work and a repeat bronchoscopy and endobronchial ultrasound are completed within four weeks (± 2 week) after the airway intervention, depending on the severity of the disease and the clinical condition of the patient. A chest CT scan will be performed prior to the repeat bronchoscopy to evaluate the airway obstruction and the disease progression.

4.1.1 Primary Phase I Endpoint (Cohort 0, data collection completed)

- For patients with LALC or other malignancies in the central airway that may extend and involve the esophagus: The primary outcome is the safety of the I-PDT using EBUS-TBN and/or I-PDT and/or PDT, as measured by toxicity and adverse events (AEs). The AEs will be evaluated and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

4.1.2 Primary Phase II Endpoints (Cohort A and Cohort B)

- Objective tumor response (CR, PR, PD, and SD)
- The FACT-L Total Score related subscale
- 6-minute walk measures.

4.1.3 Secondary Endpoints (Cohort A and Cohort B)

- The number of bronchoscopies
- Evaluate progression free survival (PFS)
    - Compare the treatment planning in DOSIE™ with the plan generated in COMSOL™ in Cohort A only.
- To measure changes in tumor pO2, optical properties, and irradiance and fluence in relationship to response.

All participants will sign an informed consent prior to study related tests and interventions. All participants will meet the inclusion and exclusion criteria summarized in **Section 5.1** and **Section 5.2**.

4.1.4 Target Accrual and Study Duration

Eight patients in the Phase I (Cohort 0), and 18 patients will be enrolled in the Phase II Cohort A (8 already enrolled under Phase 1 portion of Cohort A from previous protocol version) and 39 in Cohort B (65 patients total). It is expected to have up to 32 patients enrolled from accompanying external sites and the remainder enrolled from Roswell Park. Accrual is expected to take up to 10 years.

Patients will be drawn from the interventional pulmonology practice and from referrals from medical oncologists. All patients will come off study at 24 weeks.

Enrolled patients who do not receive the I-PDT and/or PDT for any reason (such as patient withdrawal, safety or inability to deliver the I-PDT) will be replaced.

4.1.5 Multi-Site Research

All sites have the most current version of the protocol, consent document, and HIPAA authorization.

All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).

All modifications have been communicated to sites and approved (including approval by the site' s IRB of record) before the modification is implemented.

All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.

All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.

All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Refer to Appendix C: Instructions for Multi-Site Studies.

5 PARTICIPANT SELECTION

5.1 Inclusion Criteria

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

1. Age ≥ 18 years of age.
2. Eligibility checklist before registration requires review of case by study surgeon or interventional pulmonologists to approve anatomic feasibility of an airway intervention.
3. For patients in Cohort B only. Patients are amenable to receive a palliative radiotherapy of 8 Gy x1 48±4 h prior to the I-PDT, as determined by the radiation oncologist.
4. Patients with an established pathologic diagnosis of small cell and/or non-small cell lung cancer or other malignancies causing airway obstruction > 25% requiring bronchoscopic intervention. Or inoperable malignancies not candidates for curative radiotherapy within the airway.
5. Have an ECOG Performance Status of ≤ 3. Refer to Appendix A.
6. Have the following clinical laboratory values:

   -Platelets ≥ 100,000 cells/mm^3 (SI units100 x 10^9/L)
7. Participants 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. 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.
8. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

5.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Participants who have had curative radiotherapy to the target tumor within 4 weeks prior to the scheduled I-PDT and/or PDT.
2. 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.
3. Pregnant or nursing female participants.
4. Co-existing ophthalmic disease likely to require slit-lamp examination within 14 days following I-PDT and/or PDT treatment.
5. Known hypersensitivity/allergy to porphyrin.
6. Patients who are not cleared by the anesthesiologist to undergo an advanced bronchoscopy procedure under general anesthesia.
7. Patients with target tumor invading into the lumen of the esophagus, confirmed by esophago-gastro-duodenoscopy (EGD) with endoscopic ultrasound.
8. Patients diagnosed with porphyria.
9. Unwilling or unable to follow protocol requirements.
10. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive I-PDT or PDT.

5.2.1 Special Populations

The following special populations are excluded from this study:

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

5.2.2 Inclusion of Women and Minorities

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

6 TREATMENT PLAN

Dosing, Administration and Intervention

The following table summarizes the treatment plan for each study cohort.

Cohort	Participant disease	Treatment	Additional therapy or intervention
Cohort A	Cancer causing airway narrowing.	Participants will be treated with PDT or I-PDT using treatment planning developed by Dr. Shafirstein and the treatment	None.

	Or Cancer is not a candidate for surgery or curative radiation therapy.	planning developed by a company (Simphotek Inc.).	
Cohort B	Cancer causing airway narrowing. Or Cancer is not a candidate for surgery or curative radiation therapy	Participants will be treated with PDT or I-PDT using treatment planning developed by Dr. Shafirstein.	Participants will receive one treatment of palliative radiotherapy two days before the PDT or I-PDT.

6.1.1 Porfimer Sodium Administration

The intended drug dose of porfimer sodium is 2 mg/kg body weight, administered as a single IV dose 48 ± 4 hours prior to the delivery of the therapeutic light (630 ± 3 nm), as clinically approved.

Drug administration will take place in the Infusion center or the Clinical Sciences Center or 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).

A dose of 2 mg/kg of porfimer sodium will be administered by slow intravenous injection into a vein (3-5 minutes).

6.1.2 EBUS and Light Delivery for I-PDT

Treatment will be administered in the Endoscopy suite at Roswell Park Cancer Institute.

All patients will undergo bronchoscopy under general anesthesia, which is the standard of care procedure for advanced airway management. The patients will be ventilated using laryngeal mask airway (LMA) or endotracheal tube (ETT). The flexible bronchoscope will be used first for airway inspection for obstruction evaluation and, images of the airway obstruction will be taken and saved. Depending on the nature and characteristic of airway obstruction, rigid bronchoscopy may be used during the procedure. When indicated, the airway obstruction will be managed using argon plasma coagulation (APC), laser, electrocautery or mechanical debulking. In cases where the airway obstruction is solely resulting from extrinsically compressing tumor, the airway will be dilated using a controlled radial expansion (CRE) balloon. After establishing airway patency, the EBUS scope will be used to identify extrabronchial tumor (tumor that cannot be visualized in the airway) around the site of airway obstruction. Color-Doppler will be used to demarcate the tumor vasculature.

The pre-treatment plan will follow these steps:

- Obtain high-resolution chest CT scan within 2 weeks ± 1-week prior to planned treatment with EBUS guided I-PDT.
    - A CT scan with 0.625-1.25 mm slice thickness and slice interval of 0.5-1 mm. The CT will be conducted with or without contrast due to known allergy.

- The CT scan will be deidentified to remove all PHI and will only be associated with subject study ID.
- The treating physician will use the deidentified CT scan to mark the target tumor and define the sensitive structure,
- The marked scan will be provided to Dr. Shafirstein laboratory for treatment planning.
- The team in Dr. Shafirstein's laboratory will use computer software (Simpleware) to generate a 3-D reconstruction of the tumor, airway, blood vessels, and all clinically relevant anatomies.
    - When necessary, Dr. Shafirstein's laboratory will send the 3-D deidentified reconstruction models of the tumor anatomy and adjacent tissues to Simphotek Inc. for meshing. These files with meshes will be returned to Dr. Shafirstein's laboratory at Roswell Park, for use in the DOSIE™ simulations.
- The 3-D model will be presented to the treating physician for review, and to indicate where fibers can be placed, including maximum depth and angles of insertion, relative to the surface of the airway.
- At Dr. Shafirstein's laboratory, both DOSIE™ and COMSOL™ will be used to generate treatment planning for 630-nm laser. Each plan will use the same number and location of the fiber placement, diffuser length, and intensity (W/cm). The software packages will be used to compute the irradiance and fluence required to administer our target irradiance of ≥ 8.6 mW/cm^2 in a significant volume of the target tumor. The plans will also suggest the treatment time to deliver ≥ 45 J/cm^2 to a significant volume of the target tumor.
- For each plan, the research team will generate a table showing the light delivery options and percent of tumor volume that will receive the minimal and maximal irradiance and fluence for the physician to review.
- The research team will compare the DOSIE™ computation with the COMSOL™. Although both use same input, the differences in the mesh generation and the solvers used in the simulations could impact the resulted irradiance and fluence. The comparison will include percent of tumor that receive ≥ 8.6 mW/cm^2 and ≥ 45 J/cm^2, the irradiance and fluence at the margins, the minimum, average, and maximum irradiance and fluence in 100% of the tumor. If there is disagreement (more than 5% difference) we will use COMSOL™ computation.

- The treating physician will review the plan and either approve or request changes.
    - Several iterations (typically 1-3) may be required until the treating physician approves the plan. The review will be in-person or via secured web-based communication (e.g., password protected Microsoft Teams).
    - Once approved, a detailed description of the plan will be provided via secured e-mail.
- The I-PDT procedure will follow the plan as much as possible, taking into consideration patient safety, and treatment time.
    - Our previous studies suggest that fiber placement within ≤ 10 mm from the planned placement will have insignificant impact on the total light irradiance and fluence in the target tumor.

- The difference between the planned and actual placement of the fibers will be recorded (using EBUS imaging and measurements). These data will be used for post analysis, to calculate the actual light distribution by DOSIE™ and COMSOL™.

Extrabronchial tumors that are identified by EBUS will be treated with I-PDT. The laser fiber will be inserted into the tumor using the EBUS-TBN. The I-PDT procedure will follow these steps:

- Curvilinear Endobronchial Ultrasound will be used to identify the tumor.
- The EBUS-color Doppler will be used to identify and locate the vasculature inside and adjacent to the tumor.
- EBUS guided transbronchial needle aspiration (Olympus America, Center Valley, PA) will be used to obtain tumor tissue specimen, prior to and after I-PDT. The specimen will be sent to cytology for analysis as per standard of care. Another specimen (tissue obtained prior to light delivery) will be sent to Dr. Shafirstein's laboratory as described in Section 8.2 below. The electronic health records (I) will be used to review and collect information from the cytology report.
- In this study we will use fiber optics with cylindrical diffuser end that will be obtained from either Pinnacle Biologics Inc. Chicago, IL or Medlight SA, Ecublens, Switzerland. Both fibers will deliver same laser power output that will be checked and confirmed prior to treatment. **The preference will be to use the Pinnacle fiber (Micro Diffuser Fiber that is the PB900 model) because it is stiff enough to be placed into the tumor through the 19 G EBUS needle (NA-201SX-4021; Olympus, Tokyo, Japan).** This fiber will be provided at no cost to the study.
- In the event that the Pinnacle PB900 will not be available, we will continue to use the Medlight RD250 using a 19 G Cook endoscopic ultrasound needle (Cook Medical LLC, Bloomington, IN). The needle will be shortened to facilitate its use through an Olympus endobronchial ultrasound bronchoscope (Olympus America, Center Valley, PA). The shortened cook endoscopic ultrasound needle will only be used to deliver the PDT laser into the lesion. Shortening will be performed in the Roswell Park Laser Room. Once complete, the needle will be mounted on a specially designed laser fiber holding device.
- The RD250 laser fiber preparation will be performed by inserting the laser fiber into a Progreat® Microsheath Catheter (Terumo Medical Corporation, Somerset, NJ). The microsheath catheter has a clear plastic distal end with Tungsten coil reinforcement. This laser/microsheath catheter will be inserted through the above mentioned shortened endoscopic ultrasound needle. The rationale for this is to provide sufficient stiffness to allow the laser fiber to be held in place within the lesion while the needle is withdrawn from the lesion. The laser power output (from the fiber/catheter end) will be checked and confirmed prior to treatment.
- The laser fiber will be placed within the target tumor under EBUS guidance in one to 10 locations, sequentially. The number and location of the fiber placement will be according to a pre-treatment planning (as much as possible), as the example shown in **Figure 3.**

- If possible (i.e., optional), optical measurement of light transmission and tumor pO2 will be performed before and after I-PDT as described in **section 1.1.13**
- Using either fiber, a 630-nm laser light will be administered with the objective to deliver a minimal irradiance of ≥ 8.6, ≥ 10.8 or ≥ 15.3 mW/cm^2 to a significant volume of the target tumor, based on Oakley et al. 2019. The treatment time will be adjusted to deliver ≥ 45 J/cm^2 to a significant volume of the target tumor. The research team will present a table showing the light delivery options and percent of tumor volume that will receive the minimal irradiance and fluence for the physician to review.
- The pre-treatment plan will be presented to the treating physician (the investigator) for review and approval. The investigator will decide how many insertions will be made and where the fiber(s) will be inserted, using clinical judgment and taking into account the patient's safety.
- The I-PDT procedure should be complete within a few hours.
- Airway stenting will be performed after I-PDT, as needed.
    - For cases where airway stenting is indicated to secure the airway, EBUS will be performed before or after airway stenting, as necessary, and the identified portion of the tumor will be evaluated and treated with I-PDT.

At least one tumor will be treated during the I-PDT. The treating physician will determine how many tumors will be treated, taking into account the patient’s safety.

6.1.3 Endobronchial tumors that are identified with endoscopy and prior CT or MRI will be treated with I-PDT and/or PDT

- The laser fiber will be placed in the tumor for I-PDT or in the airway for PDT.
- A 630-nm laser light will be administered with the objective to deliver a minimal irradiance of ≥ 8.6, ≥ 10.8 or ≥ 15.3 mW/cm^2 to a significant volume of the target tumor, based on Oakley et al. 2020. (41) The treatment time will be adjusted to deliver ≥ 45 J/cm^2 to a significant volume of the target tumor. The research team will present a table showing the light delivery options and percent of tumor volume that will receive the minimal irradiance and fluence for the physician to review.
- The pre-treatment plan will be presented to the treating physician (the investigator) for review and approval. The investigator will decide how many insertions or placements will be made and where the fiber(s) will be positioned, using clinical judgment and taking into account the patient's safety.
- The I-PDT and/or PDT procedure/s should be complete within few hours.
- Airway stenting will be performed after I-PDT and/or PDT, as needed.
    - For cases where airway stenting is indicated to secure the airway, EBUS will be performed before or after airway stenting, as necessary, and the identified portion of the tumor will be evaluated and treated with I-PDT and/or PDT.

6.1.4 Criteria for Retreatment

Retreatments with porfimer sodium are allowed per the approved indication. The retreatments will take place at the discretion of the treating physician, if an incomplete response is observed, and the participant had no SAEs from the first I-PDT and/or PDT treatment. Since the porfimer sodium is retained in the disease tissue for at least 3-4 weeks, there is no need for additional drug administration. Therefore, the retreatment will consist of an additional light administration only.

6.1.5 Dose Modification/ Reduction

There will be no dose modification or reduction of the porfimer sodium. The light dose may be reduced, at the discretion of the treating physician, in the retreatment sessions.

6.1.6 General Concomitant Medication and Supportive Care

Withholding of anticoagulation and antiplatelet agents prior to bronchoscopy/I-PDT and/or PDT will be determined per investigator discretion and the anesthesia preoperative team, as per Roswell Park standard of care (e.g., warfarin for 5 days, clopidogrel for 5 days, etc.).

Participants may be pre-treated for nausea and vomiting with appropriate anti-emetics.

There is a potential for an exacerbation of skin photosensitivity if porfimer sodium is used with other photosensitizing drugs. No drug interactions have been investigated.

The concomitant use of local anesthetics (infiltration anesthesia) is recommended and concomitant use of analgesics is also possible.

The use of antioxidants, including vitamin preparations, should be terminated on the day before treatment.

6.1.7 Precautions When Using Porfimer Sodium

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 a written instructions leaflet will be handed out to the subjects (**Appendix B**). 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 taken immediately after the end of the injection and 15 minutes after.

6.1.8 Duration of Treatment

The porfimer sodium photosensitizing drug will be given as a single dose 48 ± 4 hours (Day -2) before the EBUS I-PDT. The treatment is expected to be completed within a few hours.

6.1.9 Compliance

Any participant, who undergoes at least the EBUS-TBN guided I-PDT and/or I-PDT and/or PDT procedure and returns for the study follow-ups, is considered compliant when the treatment is administered.

6.1.10 Risks and Benefits

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 operating room lights will be maintained and the pulse oximetry sensor will be rotated every 20 – 30 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:

- 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%).
- Tumor/local tissue reaction: Very common effects include pain (15%), hemorrhage (15%) and scarring (12%). Common effects include edema (8%), localized infection (8%), fever (8%), and skin necrosis (2%).
- Phototoxicity: Common effects include sunburn (3%), blisters (5%), erythema (5%), hyper-pigmentation (3%), and cutaneous photosensitivity (3%).
- Other systemic events: Constipation (11%), vomiting (9%), anemia (8%), nausea (6%), and giddiness (2%).

Potential Procedural Risks of EBUS-TBN Guided I-PDT and/or I-PDT and/or PDT

- Bronchial bleeding from the insertion site
- Extension of the bronchoscopic procedure duration
- Minimal risk of pneumothorax, infection, mediastinitis, allergic reaction to porfimer sodium
- Airway perforation

Standard of care palliative radiotherapy followed by I-PDT. It is not known what the risk is for administering the I-PDT two days after standard of care palliative radiotherapy.

Potential Benefits of the Proposed Research

For participants that have partial or complete response to I-PDT and/or PDT, the potential benefits include a significant reduction in tumor mass and symptoms. There is no guarantee of the outcome, nor is it possible to predict whether or not any specific participant will respond to porfimer sodium I-PDT and/or PDT.

The data that will be collected in this study will allow the research team to evaluate the safety and provide indication on the potential efficacy of this treatment. If shown to be safe, we will use this data to design Phase I/II studies to confirm safety and test the efficacy of EBUS-TBN guided I-PDT with porfimer sodium.

7 INVESTIGATIONAL PRODUCT

7.1.1 Active Substance and Source

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

7.1.2 Drug Shipment

Pinnacle Biologic, Inc. will ship porfimer sodium (Photofrin®) vials to Roswell Park to the Investigational Drug Service as per Roswell Park policy or to other enrolling study site. The receiving site will document the date of receipt and condition of the shipment. The investigational pharmacist or designee will retain drug shipment records.

The Photofrin® will be provided to the participants at no cost.

7.1.3 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."

7.1.4 Storage and Stability

Porfimer sodium freeze-dried cake or powder will be stored at Controlled Room Temperature 20–25°C (68–77°F). The porfimer sodium vials will be dispensed by the pharmacy of Roswell Park.

Documentation: A careful record of each vial dispensed (including lot number) will be maintained. This record will also include the date of drug administration and the patient ID for whom the drug was made available.

7.1.5 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Pinnacle Biologics, Inc. exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the study staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug) will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

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

7.1.6 The Treatment Laser System

We will use one of the following laser systems for EBUS guided I-PDT

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 Watts. The system includes a port for integrated light dose calibration unit. It is used under an IND from other studies (I 256814 and I 67918).
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. This laser is used in protocol I 67918.

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 mediated PDT. It has CB certification and design documentation for CE/FDA. Modulight Inc. has CE 0537, 93/42 EEC and ISO 13485 certifications to design and manufacture medical laser systems for PDT. These lasers are owned by Roswell Park:

3. A 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 porfimer sodium. 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) after treatment. This arrangement has been worked well for the past few years.

8 STUDY PROCEDURES

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

Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with Roswell Park Clinical Research Services Standard Operating Procedures.

8.1.1 Disease Evaluation

Patients with the diagnosis of lung cancer or other malignancies causing airway obstruction with and without involvement of the esophagus will be evaluated for enrollment in this study.

- Standard of care radiological imaging scans will be provided to the study team prior to EBUS-TBN I-PDT and/or I-PDT and/or PDT. These scans will be used for pre-treatment planning, with computer simulations of light propagation in the target tumor and margins.

8.1.2 Baseline Evaluations

The following will be performed as standard of care procedures for the therapeutic bronchoscopy procedure within 4 weeks prior to scheduled I-PDT and/or PDT, *unless otherwise indicated*:

- Medical history and pre-existing conditions (including type of lung cancer and all prior anti-tumoral therapy related to lung cancer)
- Physical examination: including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure), body weight, and height
- Hematology: Complete blood count (CBC) with automated differentials (routinely performed before bronchoscopy under general anesthesia in all cases). CBC with automated differentials includes: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).
- Chemistry: Complete metabolic panel (CMP) (routinely performed before bronchoscopy and general anesthesia in all cases). CMP includes: chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap.
- Pregnancy test (urine or serum HCG will be obtained if urine is not available) in females of childbearing potential: to be performed *within 7 days prior to treatment*. Females who have undergone surgical sterilization or, who have been postmenopausal for at least 2 years are not considered to be of childbearing potential. The standard operating procedure for all females of childbearing potential in the Ambulatory Surgical Center (ASC) pre-op holding area is to obtain a urine HCG (or a serum HCG if urine is unable to be obtained). As per standard of care procedures, if the pregnancy test is positive, the patient is excluded from the study.
- ECOG Performance Status (Appendix A)
- Quality of Life Questionnaire (Cohorts A and, B): Quality of life will be assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale. The 36 self-report items on the FACT-L measure six domains of quality of life (physical well-being, social/family well-being, relationship with doctor, emotional well-being, functional well-being, and additional concerns). FACT-L is written at a sixth grade reading level and takes an average of 7 minutes to complete. It is based upon recall over the last seven days of time. FACT-L was chosen because multiple studies support its validity and use in clinical trials of lung cancer (73, 74, 88, 89). It has been used across Phase 1-Phase 3 clinical trials. Additionally, prior research has quantified the minimal clinically important difference, and has been used to distinguish complete responders from non-responders in other studies (54). Study subjects will be given the questionnaire (see Appendix D) at time of study enrollment and at each follow up visit until study completion via tablet (or paper questionnaire if tablets are unavailable at that time).

- Six-Minute Walk Test (Cohorts A and B): The Six-Minute Walk Test is the most used measure of functional capacity in lung cancer (55, 70). As the pathophysiology of central airflow obstruction is similar regardless of the underlying malignancy, authors have evaluated change in 6-minute walk distance across a range of malignancies, including sarcomas, breast, colon, esophageal, and thyroid cancers (71). Additionally, the effect of treatment will hopefully be evident in differences in exercise tolerance, oxygen saturation, and dyspnea.
- Tumor/Disease Assessment: Chest CT scan - to be performed *within 2 weeks ± 1 week treatment.* These CT scans will be used for the pre-treatment planning.
- Concomitant Medications: List any current medications taken within 1 week of study treatment.

8.1.3 Days Prior to the EBUS Guided I-PDT Procedure

- All participants will have a blood draw for CBC with automated differentials and CMP within 2 days prior to administration of porfimer sodium. Additionally, patients on chemotherapy will have a blood draw within 2 days for CBC and CMP prior to PDT.
- **For all participants**: systemic administration of 2 mg/kg porfimer sodium 48 ± 4 hours (Day -2) prior to I-PDT as described in Section **6.1.1**.
  - Blood draw for immune biomarkers prior to the administration of the porfimer sodium.
  - For Cohort B participants only: standard of care palliative radiotherapy of 8 Gyx1 will be administered to the target tumor at day -2 just before systemic administration of 2 mg/kg porfimer sodium. This will be coordinated with the radiation oncologist.

8.1.4 Evaluations Performed on Day of EBUS guided I-PDT Procedure (Day 0)

- On the day of the EBUS guided I-PDT procedure (Day 0), all participants will start fasting at midnight per current recommended preparation for the procedure. Participants are allowed to resume their diet after the procedure (according to the standard clinical instructions).
  - Physical examination including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure) and oxygen saturation, as per SOC. Note: on the day of scheduled bronchoscopy, weight is not needed at the preoperative and postoperative physical exam.

  Note: *Pre- and post-op physical is required (even if there has been an exam within 30 days prior to procedure). Because of the acuity and severity typical to this particular patient population, patients require a physical pre- and post-surgical intervention.*

  - Review of Concomitant Medication
  - Tumor debulking, ablation, or stenting (as part of standard of care for therapeutic bronchoscopy)
  - I-PDT and/or PDT using standard endoscopy to guide the therapy.
  - Tumor/disease assessment by bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

- EBUS-color Doppler to identify vasculature.
- From the EBUS 1 to 5 biopsies are collected prior to I-PDT for drug uptake. See Section 8.2 for testing and processing details.
- From the EBUS 1 to 5 biopsies are collected prior to I-PDT for immune markers. See section 8.11 for testing and processing details.
- If possible, take optical measurements and tumor pO2 immediately before and after EBUS I-PDT.
- EBUS-TBN guided I-PDT
- From the EBUS 1 to 5 tumor tissue biopsies are collected from the treated area immediately (within minutes) after I-PDT. See Section 8.3 for testing and processing details.
- Immune marker blood sampling: Day of EBUS-TBN guided I-PDT and/or I-PDT and/or PDT prior to laser light illumination

The following evaluations will be performed **on the same day *following* bronchoscopy/EBUS-TBN procedure**:

- Physical examination (including vital signs), oxygen saturation
- Adverse events

8.1.5 EBUS-TBN guided I-PDT and/or I-PDT and/or PDT

Day of scheduled bronchoscopy (Day 0):

- I-PDT will be administered with a 630±3 nm laser light that will be delivered through optical laser fiber with cylindrical diffuser end.
- The EBUS will be used to image the insertion of the laser fiber into the tumor prior to treatment, and changes in blood flow and volume during treatment.
- The endoscope will be used to guide the fiber location when I-PDT and/or PDT will be used to treat the target tumor.
- All patients will undergo an interventional bronchoscopy procedure with an attempt to treat and resolve the airway obstruction using conventional methods such as balloon dilation, mechanical debulking, tumor ablation and/ or airway stenting. Airway stenting will be performed before or after I-PDT and/or PDT, if deemed necessary.
- 1 to 5 tumor tissue biopsies are collected from the treated area immediately (within minutes) after EBUS.

8.1.6 Days Post EBUS Guided I-PDT Procedure

- For Cohorts A and B, standard of care bronchoscopy will be performed if clinically indicated at 48 ± 4 h post therapy. If additional I-PDT will be conducted, optical measurements will be performed before and after I-PDT.

8.1.7 7 – 10 Days Post-Procedure

- Blood draw for immune biomarkers

8.1.8 Initial Follow-Up Evaluation

The following evaluations will be performed **4 weeks (± 1 week)** after the last study I-PDT and/or PDT (*unless otherwise indicated**):

- Physical examination (including vital signs)
- Hematology: Complete blood count (CBC) with automated differentials.
- Chemistry: Complete metabolic panel (CMP).
- Blood draw for immune markers
- ECOG Performance Status (Appendix A)
- Tumor/Disease Assessment: Chest CT scan
- Concomitant medications
- Quality of Life Questionnaire (Cohorts A and B; Appendix D)
- Adverse events (will be followed for 30 days following treatment/procedure)
- Schedule date/time for follow-up bronchoscopy with EBUS (without TBNA). TBNA will be performed only if clinically indicated outside the scope of this study. If a tumor is visible, tumor tissue biopsies (about 50-300 mg per biopsy, if feasible) will be collected for immune markers. NOTE: The bronchoscopy will not be performed at this visit.
- If EBUS is performed and a tumor is visible, tumor tissue biopsies (about 50-300 mg per biopsy, if feasible) will be collected for immune markers.

*Bronchoscopic and ultrasound images that are routinely obtained during therapeutic procedures will be used to evaluate the airway initially and during follow up. *Note: Initial follow-up bronchoscopy will be performed within 4 weeks following the first follow-up visit. Additional bronchoscopies will be performed as clinically indicated.*

8.1.9 Long Term Follow-Up Evaluations

The following evaluations will be performed at **8 weeks (± 2 weeks), 12 weeks (± 2 weeks) and 24 weeks (± 4 weeks)** after last study I-PDT and/or PDT (or when clinically indicated):

Physical examination (including vital signs)

ECOG Performance Status (Appendix A)

Concomitant medications: Required as indicated throughout the long-term follow-up period so that any medications that may interfere with immune function are documented.

Chest CT scan

Quality of Life Questionnaire at 12 and 24 weeks (Cohorts A and B; Appendix D)

Six-Minute Walk Test at 12 weeks and 24 weeks (Cohorts A and B)

8.1.10 Patients coming off the study:

- Patients will be taken off the study and no data will be collected after the follow-up visit at 24 weeks (± 4 weeks) after the last I-PDT and/or PDT.

- All patients, including those that progress prior to 24 weeks, will continue to be followed for disease and survival status for the full 24 weeks.

Progression of disease will not cause the patients to be off study. We will continue to collect response data as it will be part of standard of care for these patients. We will use modified RECIST 1.1 to determine response.

8.1.11 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in **Table 1** below.

Table 1 Schedule of Procedures and Observations

Evaluation	Baseline[1]	Day -3	Day -2	Day -1	Scheduled EBUS I-PDT (Day 0)	Days 1 through 3	Days 2 through 10[22]	7-10 Days Post-Procedure	Initial Follow-Up[2] Evaluation	Long Term Follow-Up[3] Evaluations
Medical History	X									
Pre-Existing Conditions	X									
Physical Examination, including vital signs[4]	X				X[5]		X[5,22b]		X	X
Hematology[6]	X		X[24]		X[24]				X	
Blood Chemistry/creatinine clearance[7]	X		X[24]		X[24]				X	
Pregnancy Test (Urine/Serum)	X[8]									
ECOG Performance Status (Appendix A)	X								X	X
Tumor/Disease Assessment: Contrast Enhanced CT scan (chest)[9] (non-contrast CT if the patient has allergy to the contrast agent)	X[9]								X[9]	X[9]
Injection of porfimer sodium			X							
Diet prior to I-PDT procedure					X[20]		X[20a]			
Cohort B Only: SOC palliative radiotherapy			X[22]							
SOC Bronchoscopy/EBUS-TBNA					X[10]				X[11]	
EBUS color Doppler to identify vasculature					X					
Tumor Debulking, Ablation and/or Airway Stenting					X		X			

Evaluation	Baseline[1]	Day -3	Day -2	Day -1	Scheduled EBUS I-PDT (Day 0)	Days 1 through 3	Days 2 through 10[22]	7-10 Days Post-Procedure	Initial Follow-Up[2] Evaluation	Long Term Follow-Up[3] Evaluations
If possible, optical and pO2 measurements immediately before and after I-PDT					X[23]					
I-PDT [12] guided with EBUS-TBN and/or I-PDT and/or PDT					X					
Immune marker blood and tumor tissue sampling[13]			X		X			X	X	
Pre-I-PDT and/or PDT tissue sample					X[14,14a]		X[14b]		X[14]	
Concomitant Medications	X[15]				X		X[22b]		X	X[16]
Adverse Events					X		X[22b]		X	
Quality of Life Questionnaire (Appendix D)[17]	X								X	X[18]
Six-Minute Walk Test[21]	X									X[18]
Survival Status										X[19]

1 Performed within 4 weeks prior to scheduled EBUS I-PDT, as part of standard of care for the therapeutic bronchoscopy, unless otherwise indicated.

2 Initial Follow-Up evaluation at 4 ± 1 weeks after the last I-PDT and/or PDT treatment (dependent on severity of disease and clinical condition of patient).

3 Long-Term Follow-Up routine will be performed only when clinically indicated, at these visits: 8 weeks (± 2 weeks), 12 weeks (± 2 weeks), and 24 weeks (± 4 weeks) after the last I-PDT and/or PDT.

4 Vital signs: temperature, heart rate, respiratory rate, blood pressure, body weight, and height. *Height collected at baseline only*.

5 To be performed prior to procedures as SOC and at post-operative evaluation after undergoing treatment. Note: on the day of scheduled bronchoscopy, weight is not needed at the preoperative and postoperative physical exam. Oxygen saturation to be measured pre- and post-operatively.

6 Standard of care - will be performed if indicated by the anesthesia pre-op assessment: Complete blood count (CBC) with automated differentials: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated).

7 Standard of care - will be performed if indicated by the anesthesia pre-op assessment: Complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap.

8 Within 7 days prior to study treatment. Serum HCG will be obtained if urine is not available.

9 CT scan will be within 2 weeks ± 1 week prior to study treatment. CT scan in Follow-Up, will be performed only when clinically indicated, at these visits: 4 weeks (±1 week), 8 weeks (± 2 weeks), 12 weeks (± 2 weeks), and 24 weeks (± 4 weeks) after the last I-PDT and/or PDT.

10 Bronchoscopy (SOC) **with** EBUS-TBNA. The details of the interventional bronchoscopy procedure described in Section 6.1.2 are standard of care and, do not need to be documented in the Case Report form.

11 Schedule date/time for initial follow-up SOC bronchoscopy **without** EBUS-TBNA: TBNA will be performed only if clinically indicated outside the scope of this study. *Note*: Initial follow-up bronchoscopy will be performed within 4 weeks following the initial follow-up visit.

12 I-PDT and/or PDT will be performed with 630-nm light delivered through a cylindrical diffuser that will be inserted into tumor through a TBN with EBUS guided imaging. Endobronchial tumors can be treated with I-PDT and/or PDT. An endoscope will be used to guide the fiber placement.

13 Refer to Section 8.12

14 Refer to Section 8.13 for standard of care Pathology procedures.

14a.Tissue is taken **before and after** I-PDT during the EBUS I-PDT. For the Tissue Immune Markers and Drug Uptake processing, tissue is taken **prior** to EBUS I-PDT, see Section 8.4. For the Tissue Sample for the STAT3 Crosslinking processing, tumor tissue is collected from the treated area immediately (within minutes) after EBUS I-PDT procedures, see Section 8.3

15 Required as indicated throughout the long-term follow-up period so that any medications that may interfere with immune function are documented.

16 List any ongoing medications with an onset within 1 week of study treatment.

17 Survey data will be stored in REDCap. Quality of Life Questionnaires do not apply to Cohort 0 participants.

18 Only required at 12 and 24 weeks.

19 For all patients, (including those with disease progression prior to 24 weeks), survival status will continue to be collected until 24 weeks. After 24 weeks they will come off study.

20 For day of EBUS I-PDT bronchoscopy (Day 0), starting at midnight, all participants are fasting at home per normal preparation procedures. Participants can eat after the procedure (according to the standard clinical instructions).

21 The Six Minute Walk Test does not apply to Cohort 0 participants.

22 Palliative radiotherapy of 8 Gyx1 will be administered to the target tumor at day -2 just before systemic administration of 2 mg/kg porfimer sodium. This will be coordinated with the radiation oncologist. This only applies to participants in Cohort B.

23 Optical measurements and tumor pO2 will be conducted as described in section 1.1.13, optional. The data will be saved on password secured computer in Dr. Shafirstein laboratory. The CRF will only document that these measurements were done.

24 All participants will have a blood draw for CBC and CMP within 2 days prior to administration of porfimer sodium. Additionally, patients on chemotherapy will have a blood draw for CBC and CMP within 2 days prior to PDT.

If there are multiple PDT treatments for patients on chemotherapy, CBC and CMP will be done within 2 days prior to each treatment.

8.2 Tissue Sample for Drug Uptake and Immune Markers

If possible, before I-PDT and/or PDT, tissue samples (about 100-300 mg per biopsy if feasible) from the primary lung tumor (or other tumor to be treated) will be collected intraoperatively for measurement of optical properties and porfimer sodium concentration levels **prior** to light delivery (EBUS I-PDT).

These tissue samples will be sent from the operating room via the Clinical Research Laboratory Services to Dr. Shafirstein's laboratory in the Roswell Park PDT center, even for procedures performed after hours. The specimens will be labeled with the subject's MR number, initials, study number, protocol time point, dose, and protocol day.

Note: PDT center laboratory personnel will be notified by tissue procurement when the sample is available for pick-up. Tissue is to be wrapped in an opaque, sterile surgical towel, placed in a biosafety bag and transported on ice to Dr. Shafirstein's laboratory.

Samples will immediately be frozen at -70ºC until analyzed. Samples will be processed, stored and analyzed in Dr. Shafirstein's laboratory:

Gal Shafirstein, D.Sc.
Roswell Park Comprehensive Cancer Center PDT Center
Medical Research Complex (MRC) M-156
Attn: Study Number I 279415
Elm & Carlton Streets
Buffalo, NY 14263
Office phone: 716-845-4025
Laboratory phone: 716-845-4893
Off hours contact number (cell): 716-698 0467
Gal.Shafirstein@RoswellPark.org

EXTERNAL (NETWORK) SITES: Follow directions above for sample collection and processing (Note: External sites will process samples as personnel will be cross trained for uniform sample processing.). The cryogenic tubes will be labeled with the Subject ID #, initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will immediately be frozen at -70ºC or below (samples are to be stored until requested for batch mailing). Samples are to be batch shipped, frozen, on dry ice.

Roswell Park External Site Coordinators must be notified by email on the day prior to sample shipment at CRS-QA@RoswellPark.org.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon.-Fri., NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Address shipments to the address provided above. For any questions regarding specimen processing contact Dr. Gal Shafirstein, (716)-845-4025 or email: Gal.Shafirstein@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. This is required for both observational and interventional clinical studies collecting clinical samples.

Porfimer sodium levels in tissues will be monitored using a fluorescence assay because of the high quantum fluorescence yield of the drug and the inherent increased sensitivity of spectrofluorometry over absorption-based methods (e.g., spectrophotometry, HPLC). Concentrations of porfimer sodium will be determined by admixture with Solvable™ (Packard Bioscience, Meriden, CT) and heating at 53°C followed by analysis of fluorescence emission spectra. Briefly, following treatment with Solvable™ and heat, each sample will be placed in a quartz cuvette and a fluorescence emission spectrum (λex = 412 nm) will be obtained using a commercial fluorometer. If sufficient sample is available, 2 - 3 replicate determinations of porfimer sodium concentration will be obtained. The amplitude of the fluorescence emission maximum (λem = 670 nm), following baseline correction, will be compared to a standard curve obtained by processing known amounts of porfimer sodium in Solvable™.

8.3 Tissue Sample for STAT3 Crosslinking

If possible, we would like to quantify the photoreaction using an assay that will evaluate the signal transducer and activator of transcription 3 (STAT3) crosslinking that we have shown to be associated with durable response of early stage HNSCC treated with external beam PDT (1). For performing the STAT3 assay, the treating physicians will use the EBUS (if performed as well) to collect 1 to 5 tumor tissue biopsies (about 100-300 mg per biopsy, if feasible) from the treated area immediately (within minutes) **after** I-PDT. These research biopsies will be snap-frozen on dry ice and processed for determining STAT3 cross-linking as previously described (2, 3). Immunoblot signals for STAT3 will be quantified and expressed as percent conversion of monomeric into covalently cross-linked dimeric STAT3.

Samples will immediately be frozen at -70°C until analyzed. Samples will be processed, stored, and analyzed in Dr. Shafirstein's laboratory (same location).

Dr. Gal Shafirstein, D.Sc.
Roswell Park Comprehensive Cancer Center PDT Center
Medical Research Complex (MRC) M-156
Attn: Study Number I 279415
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Buffalo, NY 14263
Office phone: 716 845-4025
Off hours contact number (cell): 716 698-0467
Gal.Shafirstein@RoswellPark.org

EXTERNAL (NETWORK) SITES: Follow directions above for sample collection and processing (Note: External sites will process samples as personnel will be cross trained for uniform sample processing.). The cryogenic tubes will be labeled with the Subject ID #, initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will immediately be frozen at -70ºC or below (samples are to be stored until requested for batch mailing). Samples are to be batch shipped, frozen, on dry ice.

Roswell Park External Site Coordinators must be notified by email on the day prior to sample shipment at CRS-QA@RoswellPark.org.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon.-Fri., NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Address shipments to the address provided above. For any questions regarding specimen processing contact Dr. Gal Shafirstein, (716-845-4025) or email: Gal.Shafirstein@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. This is required for both observational and interventional clinical studies collecting clinical samples.

8.4 Blood Draw and Tissue Samples for Immune Markers

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 the last paragraph of **Section 1.9**) for correlation between the I-PDT and/or PDT treatment and local or distant disease recurrence.

Blood samples will be collected via venipuncture for immune marker analysis. Samples will be collected using 3, 10 mL heparinized green-top collection tubes. Tumor tissue samples (50-300 mg per biopsy) will be collected during the endoscopy procedure using the EBUS needle.

Samples for immune marker analysis will be obtained on:

- Blood samples prior to the administration of the porfimer sodium and on the day of porfimer sodium administration.
- Tumor tissue and blood sample prior to the laser light illumination and on the day of I-PDT and/or PDT.
- 7-10 days following I-PDT and/or PDT with bronchoscopy procedure.
- Initial follow-up (approximately 4 weeks ± 1 week following last I-PDT and/or PDT with bronchoscopy)

Whole blood samples (3 tubes) and fresh tissue samples (in saline) will be sent the same day of collection, to the Flow Cytometry Department for processing.

Joseph Tario, PhD
Department of Flow and Image Cytometry
Cancer Cell Center C-311
Attn: Study Number I 279415
Elm & Carlton Streets
Buffalo, NY 14263
Office phone: 716-845-8418
Laboratory fax: 716-845-8806
flowlab@RoswellPark.org

EXTERNAL (NETWORK) SITES: Follow directions above for sample collection and processing (Note: External sites will process samples as personnel will be cross trained for uniform sample processing.). The cryogenic tubes will be labeled with the Subject ID #, initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will immediately be frozen at -80ºC or below (samples are to be stored until requested for batch mailing). Samples are to be batch shipped, frozen, on dry ice.

Roswell Park External Site Coordinators must be notified by email on the day prior to sample shipment at CRS-QA@RoswellPark.org.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon.-Fri., NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Address shipments to the address provided above. For any questions regarding specimen processing contact Dr. Joseph Tario, (716)-845-8418 or email: 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. This is required for both observational and interventional clinical studies collecting clinical samples.

8.4.1 Pathology

Standard pathologic analysis of resected lung tissue will be performed. The electronic health records (EHR) will be used to review and collect information from the cytology report.

9 EFFICACY EVALUATIONS

9.1 Objective Tumor Response

All protocol-defined imaging studies must be performed at the investigative site or sponsor-approved facility using protocol-defined parameters. 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. A modified RECIST 1.1 criterion will be used to assess objective tumor response of the I-PDT and/or PDT treated tumor.

RECIST 1.1 will be used for tumor response assessment at time of continuing review and will be used for IRB reporting and formal analysis.

Along with tumor size and volume, percent of airway obstruction (in cases where an airway stent is not placed) measured by bronchoscopy, will also be used as a measure of tumor response.

9.2 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size. Lesions with the longest diameter (short axis for lymph nodes) and are ≥ 10 mm (CT and MRI), ≥ 15 mm lymph nodes, > 20 mm CXR and are for accurate repetitive measurements (either by imaging techniques or clinically) will be chosen. A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be

calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

The above standard RECIST technique will be used for measurement of the longest diameter of the target lesion.

NOTE: We will use I-PDT and PDT to treat *extrabronchial and endobronchial tumors.* The *extrabronchial* will be treated with EBUS-TBN I-PDT. *The endobronchial tumors (inside the airway) can be treated with* I-PDT and/or PDT. All treated tumors will be measured by CT scans (baseline and follow-up).

Tumors that are *inside* the airway that will be treated with laser, rigid bronchoscopy or ablation (see Section 6), *will not be measured on CT scan.*

Therefore, the volume of the tumor that will be treated with either EBUS-TBN I-PDT or with I-PDT and/or PDT will be measured on CT that was performed within 2 weeks ± 1 week before the procedure (refer to Section 8.1: Baseline Evaluations) will be compared to the volume of the I-PDT and PDT treated tumor on CT that is taken at initial follow-up bronchoscopy (refer to Section 8.1.5).

9.2.1 Evaluation of Target Lesions

Tumor response assessments will be performed at 4 weeks (± 1week) following I-PDT and/or PDT (refer to Section 8.1.8**).**

- Complete Response (CR): Disappearance of all target lesions.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of 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 a sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study.

9.2.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. 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.

- Contrast-Enhanced CT: 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 (e.g., for body scans). Non-contrast CT can be used if the patient has allegory to the contrast agent.

- Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

9.2.3 Evaluation of Airway Obstruction

The estimated percentage of obstruction will be documented before and after endobronchial debulking and ablation. Tumor debulking and ablation will always be performed before EBUS-TBNA. The airway obstruction severity is usually estimated based on the size of scope that can be passed through an obstructed airway and based on the size of the balloon used to dilate the obstructed airway.

Airway obstruction severity will be classified as follows (51):

- Mild (<50%),
- Moderate (50-70%) and,
- Severe (>70%).
- The baseline obstruction to be used in the study will be the airway obstruction that was established after debulking and ablation and, before the EBUS-TBN guided I-PDT, and/or I-PDT and/or PDT.

9.2.4 Progression-Free Survival

PFS, using modified RECIST 1.1 criteria, is defined in this study as the time from date of study treatment to the time of first observed disease progression at the treated tumor site or, death due to any cause.

10 SAFETY EVALUATION

Adverse Events

10.1.1 Definition

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.

10.1.1.1 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.

10.1.1.2 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.

10.1.1.3 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.

10.1.1.4 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”).

10.1.2 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 5 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5 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 5.0.

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.

10.1.3 Reporting Adverse Events

Table 2 Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

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

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.

Adverse events will be graded from 1 to 5. Mild and moderate side effects are common after therapeutic bronchoscopy for central airway tumors. Therefore, grade 3 or above will be included in safety analysis, and grades 1 and 2 will be collected and reported.

Serious Adverse Events

10.1.4 Definition

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.

10.1.5 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 principal investigator or designee will inform Roswell (via email using both the Oncore SAE form and MEDWATCH 3500A form) within twenty-four (24) hours of first awareness of any event that meets the above criteria. Forms will be submitted to SafetyEventReporting@RoswellPark.org. See Appendix C for Multi-site reporting instructions. 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 0** for details on reporting Unanticipated Problems.

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.

Unanticipated Problems

10.1.6 Definition

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 0.

10.1.7 Reporting Unanticipated Problems

Unanticipated problem reporting will begin at the time of participant consent. The Reportable New Information Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, the 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 to the **IRB in accordance with their local institutional guidelines**.

11 DATA AND SAFETY MONITORING

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 annually 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) termination of the study.

12 STATISTICAL METHODOLOGY

This is a multi-center, multi-arm, Phase I (Cohort 0, data collection completed) and Phase II study [Cohort A (8 already enrolled under Phase 1 portion of Cohort A from previous protocol version) and Cohort B]. Cohort 0 is closed to accrual and fulfilled the Phase 1 safety monitoring requirements. Cohort 0 provided the safety monitoring component for Cohort A of this Phase II study. Cohort 0 consisted of patients with the diagnosis of lung cancer that received porfimer sodium with EBUS I-PDT and all of the study procedures with the exception of the Quality of Life Questionnaires and Six Minute Walk Test. Cohort A consists of patients with the diagnosis of lung cancer or other malignancies causing airway obstruction, or cancer that is not a candidate

for surgery or curative radiation therapy; EBUS I-PDT; and all of the study procedures. Cohort B will consist of patients with the diagnosis of lung cancer or other malignancies causing airway obstruction, or cancer that is not a candidate for surgery or curative radiation therapy. Subjects in Cohort B will receive the EBUS guided I-PDT 48±4 h after standard of care palliative radiotherapy of 8 Gy x1.

The primary safety endpoints for Cohort 0 for this study are:

- AEs that are ≥ Grade 4.

The primary efficacy endpoints for Cohort A and Cohort B portion of this study are:

- Objective tumor response (CR, PR, PD, and SD)
- The FACT-L Total Score related subscale
- 6-Minute walk measures

The secondary endpoints for Cohort 0+A and Cohort B of this study are:

- The number of bronchoscopies
- Progression free survival
- Compare the treatment plan in DOSIE™ with the plan generated in COMSOL™ in Cohort A only.
- Measure changes in optical properties and irradiance and fluence and relationship to response.

The exploratory endpoints are for Cohort 0+A and Cohort B of this study:

- Porfimer sodium retention in the target tumor tissue
- The relationship between immune biomarkers and response

12.1.1 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, minimum, and maximum) will be used to summarize demographic and baseline characteristics.

12.1.2 Primary Cohort 0 Phase I Safety Analysis

For patients LALC or other malignancies in the central airway that may extend and involve the esophagus. For Cohort 0, the safety profile will be measured by recording I-PDT and/or PDT treatment related AEs that are ≥ grade 4 with attribution of 'possible', 'probable', or 'definite', according to the NCI CTCAE v5.0. The safety measures will be evaluated in all patients who received I-PDT and/or PDT following bronchoscopic intervention for malignant airway obstruction. Let p represent the proportion of the evaluable population of interest who experience an AE≥ grade 4. A true response of more than p_0=0.20 is considered unacceptable and evidence of such will deem the treatment unsafe for further study.

The null and alternative hypotheses to be tested are:

$$H_0 : p \leq p_0,$$
$$H_a : p > p_0.$$

The study design stops early for evidence of safety and will proceed in two stages:

- Stage 1: If 0 out of the first 3 evaluable participants have an I-PDT and/or PDT treatment related AE≥ grade 4 (with attribution of 'possible', 'probable', or 'definite'), it will be concluded that the therapy is safe and the study will enter the Phase II component. Otherwise, the study will progress to the second stage.
- Stage 2: We will accrue 3 additional evaluable participants. If 3 or more of the total of 6 evaluable participants will have I-PDT and/or PDT treatment related AE≥ grade 4 (attribution of 'possible', 'probable', or 'definite'), it will be concluded that p exceeds and that the therapy is unsafe; otherwise, it will be concluded that the therapy is safe and enter the Phase II component.

The nominal significance level of this design is α=0.10.

12.1.3 Primary Phase II Efficacy Analysis

The primary endpoint for Cohort A and Cohort B is the proportion of complete responders (CR) and partial responders (PR) as measured by RECIST v1.1 at 12±1 week after DOSIE™ (Cohort A) and COMSOL™ guided I-PDT.

For Cohort A, we hypothesize that the objective tumor response for CR+PR will be at least 29%. We also want to investigate the impact of variation in optical properties, Photofrin® retention, and fiber location perturbation on the objective tumor response. The primary analysis will consist of a one-sided exact binomial test of H_0: π=0.05 versus H_a: π>0.05 at level α=0.05, where π is the proportion of CR+PR responders. For Cohort B, the primary analysis will consist of a one-sided exact binomial test of H_0: π=0.30 versus H_a: π>0.30 at level α=0.05.

Additional clinical efficacy endpoints are: (1) changes from baseline to 3 months in the FACT-L Total Score related subscales (physical well-being, social/family well-being, emotional well-being, functional well-being); (2) the 6-minute walk measures (distance, VO2max, shortness of breath scores). All key clinical efficacy outcomes will be considered suitably continuous will be analyzed with an analysis-of-covariance (ANCOVA) approach regressing change from baseline to three months on the baseline value of the respective measure adjusted for baseline tumor volume, age, and sex.

12.1.4 Secondary Analysis

For both Cohort 0+A combined and Cohort B progression free survival (PFS) will be defined as the time from date of study treatment to the time of first observed disease progression (modified RECIST 1.1 criteria) at the treated tumor site or death due to any cause. PFS will be summarized using standard Kaplan-Meier methods, with median PFS and specified PFS rates estimated with 95% confidence intervals. The number of bronchoscopies will be summarized descriptively.

For Cohort A only we will measure agreement between DOSIE™ and COMSOL™ treatment planning measures in n=18 subjects consisting of light intensity from each fiber (mW, and mW/cm), percent of tumor that receives ≥8.6 mW/cm^2 and ≥45 J/cm^2, the irradiance and fluence at the margins, the min, average and maximum irradiance and fluence in 100% of the tumor using the concordance correlation coefficient (76)(CCC) and Bland-Altman plots (77) for visual displays of agreement. We will calculate the one-sided 95% confidence interval for the CCC using a percentile bootstrap-t approach for each endpoint and we will calculate the 95% confidence interval for the paired differences relative to the Bland-Altman graphical display. Disagreement on a given measure will be inferred if the estimated CCC is below the lower bound of the one-sided 95% percentile confidence interval.

Tumor response as a function of STAT3 tumor conversion percentages (if possible) will be analyzed using logistic regression adjusted for age and sex.

The data from this trial will inform the design of a prospective Phase IIb randomized trial.

12.1.5 Exploratory Analysis

Porfimer sodium retention in the target tumor tissue will be descriptively summarized with mean ± standard deviations. We will correlate immune biomarkers and tumor response measures using the Spearman correlation of ±0.63 or larger differences from 0, at 0.80 power and alpha=0.05 (two-sided).

12.1.6 Phase II Sample Size Justification (Cohort A and Cohort B)

Let π equal the proportion of CR+PR responses. The primary analysis, for Cohort A and Cohort B , will consist of a one-sided exact binomial test of H_0: π=0.05 versus H_a: π>0.05 at level α=0.05. Given n=18 subjects and setting power at 0.80 we will be able to detect an alternative response rate of π>0.29. The primary analysis for Cohort B will consist of a one-sided exact binomial test of H0: π=0.30 versus Ha: π>0.30 at level α=0.05. Given n=39 subjects (including n=6 from the Phase I) and setting power at 0.80 we will be able to detect an alternative response rate of π>0.50. A secondary analysis of efficacy will utilize an ordinal regression of response (CR, PR, SD, PD) as a function of baseline tumor volume. All key secondary outcomes will be considered suitably continuous will be analyzed with an analysis-of-covariance (ANCOVA) approach regressing change from baseline to three months on the baseline value of the respective measure adjusted for baseline tumor volume, age, and sex. The null hypothesis of interest is H_0: β_0=0,β_1=0 versus H_a: β_0≠0,β_1≠0, where β_0 is the ANCOVA intercept and β_1 is the regression slope, respectively. All tests will be at level α=0.05. Since both the FACT-L based measures and the 6-minute walk measures are likely to be highly cross correlated no adjustments for multiple testing will be considered a priori. For Cohort A and Cohort B , each continuous endpoint and given n=18 subjects we will have 0.80 power to reject the joint null hypothesis if the slope and intercept account for 39% of the overall variation or larger in the given endpoint. For Cohort B, each continuous endpoint and given n=39 subjects we will have 0.80 power to reject the joint null hypothesis if the slope and intercept account for 20% of the overall variation or larger in the given endpoint.

12.1.7 Interim Analysis and Criteria for Early Termination of the Study

A futility analysis of efficacy will be carried out for Cohort B after n=20 subjects have completed the trial. A conditional power calculation will inform the decision to continue accrual.

12.1.8 Safety Monitoring (Cohort A and Cohort B)

Safety and tolerability will be assessed by incidence, severity, and changes from baseline of all relevant parameters including adverse events (AEs), laboratory values and vital signs.

Vital sign results (systolic and diastolic blood pressure, pulse, respiration, and temperature) will be summarized descriptively for each scheduled and unscheduled protocol time point. Changes will be calculated relative to the assessments at baseline.

The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled and unscheduled protocol assessment time point. Changes will be calculated relative to the values collected at baseline. Data listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified in data listings and will include flags for high and low values.

The frequency of toxicities will be tabulated by grade. All participants who receive any study treatment will be considered evaluable for toxicity.

12.1.9 Safety Monitoring Lead-In (Cohort B)

The safety profile will be measured by recording treatment related AEs that are ≥ grade 4 with attribution of 'possible', 'probable', or 'definite', according to the NCI CTCAE v5.0. The safety measures will be evaluated in all patients who received image-guided I-PDT preceded by standard of care p-XRT of 8 Gy x1 for the treating their MCAO. The following decision rules will be followed: (i) If 0/3 AE≥ grade 4's are observed it will be concluded the therapy is safe. (ii) If 1/3 AE≥ grade 4's are observed, enroll 3 more patients for safety evaluation. If 1/6 AE≥ grade 4's are observed, it will be concluded the therapy is safe. If ≥2/3 or ≥2/6 AE≥ grade 4's are observed it will be concluded that therapy is unsafe. We calculated via Monte Carlo simulation that if the AE≥ grade 4 rate is 20%, 30% and 40% the respective probabilities of declaring the treatment unsafe are 0.26, 0.51 and 0.70.

13 ETHICAL AND REGULATORY STANDARDS

13.1.1 Ethical Principles

Roswell Park will be the IRB of record for this multi-site study. Accruals will occur at Roswell Park Cancer Institute and accompanying external sites. Any participating site will enter into a reliance agreement with the Roswell Park IRB and proper IRB approval of each site will be given prior to participation in the study.

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.

13.1.2 Informed Consent

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 research file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

14 STUDY RESPONSIBILITIES

14.1.1 Data Collection

Cohorts A and B patient-reported outcomes from questionnaires will be stored using the secure Roswell Park REDCap database, while the CTMS will be used to collect physician-assessed clinical outcomes.

Patient survey data will be kept on the secure Roswell Park REDCap database, and will be accessible only by the PI, Co-Investigator, and the CRS representative. Patient clinical data will be kept in CRS CTMS. The REDCap database will be password protected. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only.

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.

Data management activities will be performed using eClinical. eClinical is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the eClinical Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be 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.

14.1.2 Maintenance of Study Documents

Essential documents will be retained per Roswell Park's 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.

15 ADMINISTRATIVE RULES

15.1.1 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.

15.1.2 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.

15.1.3 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.

Completed Cohort A and B participant questionnaire data will be entered into a secure REDCap Database on the Roswell Park server via tablet by the patient, or the usage of paper questionnaires when tablets are unavailable (paper questionnaire information will then be entered by the study Clinical Research Coordinator). This will be accessible only to investigators on the study. For analysis, data will be entered into OnCore which will only be accessible to authorized individuals. Any paper files containing identifiers will not be taken off Roswell Park premises. PHI will not be reused or disclosed to any other person or entity.

16 APPENDICES

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 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 C Instructions for Multi-Site Studies – can enroll patients into Cohorts A and B only

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Comprehensive Cancer Center
CRS Quality Assurance (QA) Office
CRS-QA@RoswellPark.org
Elm and Carlton Streets
Buffalo, New York 14263
Telephone:
Monday - Friday; 8:00 AM to 4:30 PM EST
716-845-8084
After hours, weekends, and holidays request the Roswell Park Investigator
716-845-2300

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any procedures or treatment**.
- An informed consent template is provided by Roswell Park and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by Roswell Park CRS QA Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the Roswell Park CRS QA Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

Roswell Park does not grant exceptions to eligibility criteria.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be emailed (CRS-QA@RoswellPark.org) to the Roswell Park CRS QA Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and email it to the Roswell Park CRS QA Coordinator at CRS-QA@RoswellPark.org.

Protocol Randomization Instructions

Patients at Roswell Park Cancer Institute will be registered directly by Roswell staff using the web-based registration system. For patients at institutions outside Roswell Park Cancer Institute,

the local site staff will contact the appropriate coordinator to register the patient using the web-based registration application as developed by the GOG Foundation Statistical & Data Management Center in conjunction with the study biostatistician. Within 24 hours the QA Coordinator will email the randomization arm assignment and participant ID # back to the site PI. The site PI will send a confirmation email back to the QA Coordinator verifying the randomization arm for the specified network participant. Questions regarding randomization issues can be emailed to alan.hutson@roswellpark.org.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the Roswell Park CRS QA department, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principal Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The Roswell Park CRS QA Coordinator must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of Roswell Park to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to Roswell Park upon written agreement between the Investigator and Roswell Park.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific; they are study source documents and will be used to verify compliance with the study.

- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the Roswell Park CRS QA Coordinator within 1 business day of being made aware of the SAE. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- Roswell Park Oncore SAE form
- Notify Pinnacle Biologics Inc. (Contact: Sherry Swint, swints@pinnaclebiologics.com)

  Name, address, phone, e-mail

The principal investigator or designee will inform Roswell (via email using both the Oncore SAE form and MEDWATCH 3500A form) within twenty-four (24) hours of first awareness of any event that meets the above criteria. Both forms should include all available information, including a brief narrative describing the SAE, attributions, and any other relevant information. Upload all related (redacted) source information into OnCore along with the completed forms signed by the PI. Forms will be submitted to the CRS QA Office via email to SafetyEventReporting@RoswellPark.org.

A complete follow-up report must be sent to the Roswell Park CRS QA Coordinator when new information becomes available.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 17.7**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the Roswell Park CRS QA Coordinator **within 1 business day** of being made aware of the Unanticipated Problem by completing the **Roswell Park Unanticipated Problem Report Form** and emailing it to the Roswell Park CRS QA Coordinator to SafetyEventReporting@roswellpark.org.

Appendix D FACT-L Quality of Life Questionnaires

FACT-L (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-L (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-L (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4

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