CLINICAL STUDY PROTOCOL

A MULTICENTER, PROSPECTIVE, OPEN-LABEL, SINGLE-ARM CLINICAL STUDY OF THE SAFETY AND FEASIBILITY OF USING NAVIGATIONAL BRONCHOSCOPY TO PERFORM INTERSTITIAL PHOTODYNAMIC THERAPY USING PHOTOFRIN® AS TREATMENT IN SUBJECTS WITH UNRESECTABLE SOLID TUMOR IN PERIPHERAL LUNG

Protocol Number: CLI-PHO1601

Type of Study: Feasibility

NCT02916745

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PROTOCOL/PROTOCOL AMENDMENT APPROVAL PAGE

Protocol Number: CLI-PHO1601

A Multicenter, Prospective, Open-Label, Single-Arm Clinical Study of the Safety and Feasibility of using Navigational Bronchoscopy to Perform Interstitial Photodynamic Therapy using Photofrin® as Treatment in Subjects with Unresectable Solid Tumor in Peripheral Lung

STUDY SPONSOR

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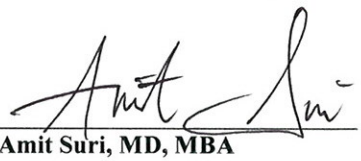

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INVESTIGATOR'S AGREEMENT

I have read the study protocol titled "A Multicenter, Prospective, Open-Label, Single-Arm Clinical Study of the Safety and Feasibility of Using Navigational Bronchoscopy to Perform Interstitial Photodynamic Therapy using Photofrin® as Treatment in Subjects with Unresectable Solid Tumor in Peripheral Lung", and agree to:

- Conduct this study in accordance with the design and provisions of this protocol.
- Await IRB/REB approval for the protocol and informed consent before initiating enrollment into the study.
- Ensure that the requirements for obtaining informed consent are met according to FDA requirements of 21 CFR 50.20 and to obtain informed consent from subjects before their enrollment into the study.
- Provide sufficient and accurate financial disclosure and update information if any relevant changes occur during the investigation and for one year following the completion of the study.
- Collect and record data as required by this protocol into the case report form.
- Maintain the confidentiality of all information received or developed in connection with this protocol.
- Conduct this study in accordance with the *International Council for Harmonisation* (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable regulatory requirements.
- Permit study-related monitoring, audits, Institutional Review Board (IRB)/Research Ethics Board (REB) review, and regulatory inspection(s) by providing direct access to source data/documents.
- Ensure that requirements for reporting are met per FDA requirements of 21 CFR 312.64.
- Maintain study documentation for the period of time required.
- Report all adverse events within the specified timeframe to Concordia Laboratories Inc.
- Report all serious adverse events/incidents within 24 hours after becoming aware of the event to Mapi Group and enter the data into the Electronic Data Capture (EDC) system.
- Adhere to the publication policy of Concordia Laboratories Inc. for data collected during this study.

I acknowledge the study protocol contains all necessary details for me and my staff to conduct the study as described. I will conduct this study in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me.

Signature of Principal Investigator	Date (dd/mmm/yyyy)
Print Name	Site Number

1. PROTOCOL SYNOPSIS

NAME OF SPONSOR: Concordia Laboratories Inc.	
PROTOCOL NUMBER: CLI-PHO1601	**IND NUMBER:** 25,064
NAME OF FINISHED PRODUCT: Photofrin®	
LIST OF ACTIVE INGREDIENTS: Porfimer sodium	
TITLE OF STUDY: A Multicenter, Prospective, Open Label, Single-Arm Clinical Study of the Safety and Feasibility of Using Navigational Bronchoscopy to Perform Interstitial Photodynamic Therapy using Photofrin® as Treatment in Subjects with Unresectable Solid Tumor in Peripheral Lung	
OBJECTIVES: **Primary Objective:** To assess the safety and feasibility of using navigational bronchoscopy to perform interstitial photodynamic therapy (iPDT) in subjects with primary lung cancer or solid tumor metastases located in the peripheral lung (including oligometastasis). **Secondary Objectives:** To assess the overall safety and effectiveness of iPDT in subjects with solid tumor in peripheral lung by assessing tumor response and to explore iPDT-induced effects on immune system.	
DEVELOPMENT PHASE: Feasibility study	
STUDY POPULATION: Subjects with histological or cytological confirmation (if subject's condition permits) of primary lung cancer or solid tumor metastases located in the peripheral lung (including oligometastasis) who are inoperable or refused surgery. Tumor size will be ≤ 3 cm based on official radiology report. Peripheral tumor location will be defined by the Radiation Therapy Oncology Group protocols as the primary tumor not touching a 2-cm volume in all directions around the proximal bronchial tree (distal 2 cm of the trachea, main stem bronchi, and lobar bronchi) and includes tumors beyond the 3rd generation airways.	
NUMBER OF PLANNED SUBJECTS AND SITES: Approximately 20 subjects from up to 10 sites in the United States (US) and Canada.	
PLANNED STUDY ENROLLMENT DATES: January 2017 to March 2018 (6-month follow-up until September 2018).	
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION: Porfimer sodium (Photofrin®) 2.0 mg/kg delivered intravenously.	
DURATION OF TREATMENT: This study is a one-time administration of Photofrin® and one-time use of navigational bronchoscopy-iPDT. **Duration of Follow-Up**: Study Exit is at the 6-month visit.	

MAIN CRITERIA FOR INCLUSION:

1. Male or female subject is eighteen years of age and older.
2. Subject is diagnosed, if condition permits, with histologically confirmed primary lung cancer or discrete solid tumor metastases with any confirmed malignant histology located in the peripheral lung (including oligometastasis).
3. Subject is not a candidate for surgery, is unfit for surgery, or does not wish to undergo surgical resection.
4. Subject may be candidate for, has failed, or does not wish to undergo radiation therapy (e.g., SABR).
5. The tumor is ≤ 3 cm in size and clearly observable in computerized tomography (CT).
6. The tumor is accessible for unrestricted illumination of iPDT.
7. Subject is deemed likely to survive for at least 3 months.
8. Non-menopausal or non-sterile female subject of childbearing potential has a negative serum β–HCG at the time of entry into the study.
9. Non-menopausal or non-surgically sterilized female subject of childbearing potential uses a medically acceptable form of birth control.
10. Subject is willing to remain in a controlled light exposure environment for at least 30 days and for as long as deemed necessary as per the investigator's clinical judgment.
11. Subject is able and willing to provide written informed consent to participate in the study, which must comply with the *International Council for Harmonisation (ICH)* guidelines and local requirements.

MAIN CRITERIA FOR EXCLUSION:

1. Subject diagnosed with small cell lung cancers.
2. Subject with solid tumor in central lung defined by the Radiation Therapy Oncology Group protocols as located within 2 cm of the proximal bronchial tree or within 2 cm of a major structure (e.g., aorta, heart, trachea, pericardium, superior vena cava, pulmonary artery, esophagus, vertebral body, spinal canal).
3. Subject with concurrent non-solid malignancy.
4. Subject with blood parameters of Grade 3 or higher on the Common Terminology Criteria for Adverse Events (CTCAE) 5-point scale; parameters of Grade 2 will be excluded if judged clinically significant by the investigator.
5. Subject has had chemotherapy/immunotherapy in the last four weeks.
6. The tumor invades a major blood vessel.
7. Subject with known porphyria or known hypersensitivity to Photofrin® or porphyrin-like compounds or to any of its excipients.
8. Subject with a planned surgical procedure within the next 90 days.
9. Subject with a coexisting ophthalmic disease likely to require slit-lamp examination within the next 90 days.
10. Subject with any acute or chronic medical or psychological illnesses as judged clinically significant by the investigator to preclude bronchoscopy procedures.
11. Female subject who is breastfeeding or intends to breastfeed during the study.
12. Subject has received prior PDT during 3 months prior to the date of the ICF signature.
13. Subject who participates or intends to participate in another investigational study (other than observational studies) during the study.

CRITERIA FOR EVALUATION:

Primary Endpoints:

Safety and feasibility evaluations will include incidence of adverse events following navigational bronchoscopy-iPDT and ability to perform the procedure.

Secondary Endpoints:

Effectiveness evaluations will include

- Tumor response
- Performance status
- Quality of life

Overall safety evaluation will include adverse events, serious adverse events, laboratory data, physical examination, vital signs, pulmonary function tests, and concomitant medication.

Exploratory Endpoints:

- Immune parameters

DATE OF PROTOCOL: 26 October 2017 (Version 3)

2. TABLE OF CONTENTS

3. ABBREVIATIONS

Abbreviation or Term	Definition
ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
aPPT	Absolute partial thromboplastin time
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CL	Confidence Limit
CRA	Clinical Research Associate
CRF	Case Report Form
CRX	Chest X-ray
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Diffusing capacity of lung for carbon monoxide
DSMB	Data Safety Monitoring Board
EBUS	Endobronchial ultrasonography
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ENB	Electromagnetic navigation bronchoscopy
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FEV	Forced expiratory volume
GCP	Good Clinical Practices
HPFB	Health Products and Food Branch
HRQoL	Health-related quality of life
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ILP	Interstitial laser photocoagulation
INR	International normalized ratio
iPDT	Interstitial photodynamic therapy
IRB	Institutional Review Board
irRC	Immune-related Response Criteria
IV	Intravenous
J/cm	Joules/centimeter
Kg	Kilogram
LD	Lesion diameter
LLN	Lower limit of normal

mg	Milligram
NCCN	National Comprehensive Cancer Network
NOS	Not otherwise specified
NSCLC	Non-small-cell-lung cancer
PDT	Photodynamic therapy
PET	Positron Emission Tomography
PT	Preferred term
QLQ-LC13	Quality of Life Questionnaire for cancer patients-Lung cancer module
QLQ-C30	Quality of Life Questionnaire for cancer patients
REB	Research Ethics Board
REBUS	Radial probe endobronchial ultrasonography
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency ablation
RP	Radiation pneumonitis
SABR	Stereotactic ablative radiation therapy
SAE	Serious adverse event
SBRT	Stereotactic body radiation therapy
SF36	The Short Form (36) Health Survey
SoC	Standard of Care
SOC	System organ class
SUV	Standardized uptake value
TBNA	Transbronchial needle aspiration
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
WHO	World Health Organization

4. ETHICS

4.1. Ethical Conduct of the Study

This study will be conducted in compliance with Institutional Review Board (IRB)/Research Ethics Board (REB), and *International Council for Harmonisation (ICH)* Good Clinical Practice (GCP) Guidelines; United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR § 50, 56, 312); the Declaration of Helsinki, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). This study will also adhere to the US Food and Drug Administration (FDA), Health Products and Food Branch (HPFB) at Health Canada, and applicable local laws and regulations, as well as requirements for data protection. To ensure that the study conduct is according to the principles above mentioned, an inspection may occur at any time by the sponsor, sponsor's designee, and/or other representatives (e.g., site representatives, etc.). The investigator must agree to the inspection of study-related records when requested. The investigator must adhere to the following principles, in addition to any applicable or local requirements.

4.2. Institutional Review Board/Research Ethics Board Review

Before study initiation, the investigator and institution must have written and dated approval from the IRB/REB for the study protocol/amendment(s), written informed consent form (ICF), any consent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects. Appropriate reports on the progress of the study will be made to the IRB/REB and Concordia Laboratories Inc. by the investigator in accordance with applicable regulatory regulations. When necessary, an extension or renewal of the IRB/REB approval must be obtained and copy forwarded to the sponsor. Upon approval and before the study start, the following IRB/REB approval documentation must be sent to the sponsor:

- A letter documenting the IRB/REB approval of the protocol and the ICF (indicating its title, protocol number and version).
- A letter documenting the IRB/REB approval of amendment(s) to the protocol and/or the ICF, if applicable (indicating its title, protocol number and version).
- A list of the IRB/REB members, their representative capacities, and their affiliations. Should this list be unavailable due to local regulations of the institution, a letter to this effect must be provided to the sponsor with a copy remaining in the study file.

The ICH guidelines for GCP specify that the committee should include persons of varying backgrounds (including peers of the responsible investigator and lay people) and must exclude the responsible investigator as a voting member.

4.3. Subject Information and Informed Consent

Information in simple terms will be provided to explain the risks and the benefits of the subject's participation in the study, the procedures involved and other relevant details. Written informed consent must be obtained from the subject by the investigator (or designee) before the subject takes

part in the study or before altering the medical regimen of the subject for the purpose of enrolling the subject in the study. The investigator must adopt a standardized approach for obtaining informed consent from each subject. The following items must be described fully to each subject prior to obtaining consent.

1. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures involved and the identification of any procedures which are experimental.
2. A description of any foreseeable risk or discomfort to the subject.
3. A description of the benefits for the subject, which may reasonably be expected.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing to what extent, if any, the confidentiality of records identifying the subject will be maintained and noting the possibility that the records will be inspected by the sponsor and/or other representatives.
6. An explanation of whom to contact for answers to pertinent questions about the research and subject's rights, and whom to contact in the event of a research-related injury to the subject.
7. A statement that participation is voluntary, that refusal to participate will not involve any penalty or loss of benefits to which the subject is otherwise entitled and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
8. Any anticipated circumstances under which the subject's participation may be terminated by the investigator without the need of the subject's consent.
9. Any additional costs to the subject that may result from participation in the research.
10. The consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject.
11. A statement explaining that significant new findings developed during the course of the research which may influence the subject's willingness to continue participation will be provided to the subject.
12. The approximate number of subjects involved in the study.
13. Any other country-specific and ICH/GCP requirements.

Should the investigator decide to modify the Informed Consent document, the modified version must be approved by the sponsor or designee prior to its submission to the IRB/REB. Should the IRB/REB request modifications, the IRB/REB's version must be submitted to the sponsor or designee for approval prior to study initiation. The original signed Informed Consent document is to be maintained with the source documents. The subject should receive a copy of the signed Informed Consent document. All signed and dated Informed Consent documents will be inspected by the study monitor or designee.

5. INTRODUCTION

5.1. Current Treatment Approaches for Solid Tumor in the Lung

5.1.1. Current Treatment Approaches for Non-Small Cell Lung Cancer

Lung cancer accounts for almost one-third of cancer deaths. Cancer screening strategies have the potential to achieve a 20% reduction in deaths rates. Screening for lung cancer with low dose computerized tomography (CT) will result in the identification of an increasing number of peripherally located lung cancers with the majority being stage I (Detterbeck *et al.*, 2013). Early stage (T1-2 N0) primary non-small cell lung cancer (NSCLC) has been traditionally managed with surgical resection. Nevertheless, many subjects may decline surgery or may not be surgical candidates because of pulmonary or cardiovascular comorbidities. For these subjects, stereotactic ablative radiation therapy (SABR) has become an accepted alternative based on results from studies that showed 3-year local control rates of 70% to 90% with 2-year survivals of approximately 50% (Zimmermann *et al.*, 2005; Fritz *et al.*, 2008, Detterbeck *et al*., 2013).

Published series using SABR have reported local recurrence ranging from 10% to 30% (similar to that reported with limited surgical resection) with most recurrence occurring within the first year after treatment. However, tissue diagnosis was not obtained in several SABR studies and benefits of SABR thus may have been slightly overestimated (Howington *et al.*, 2013) considering that previous studies in subjects with early-stage NSCLC in the Western European population have shown that the risk of finding benign lesions during surgery is less than 4.3% (Lagerwaard *et al.*, 2012). Radiation pneumonitis (RP), while less common than with conventional radiation, can occur after SABR and is a limitation of this treatment modality. In a multicenter prospective single-arm study of subjects with inoperable stage I NSCLC receiving SABR, the rate of grade 3 or 4 pulmonary or respiratory tract-specific toxicity was 16%, and the rate of protocol-specified hypoxia or pneumonitis was 8% (Timmerman *et al.*, 2010). This risk was even higher (26%) in subjects with interstitial lung disease (Takeda *et al.*, 2014). Symptomatic RP is characterized by cough or dyspnea, often accompanied with fever, chest discomfort, and pleuritic pain, occasionally requiring oxygen supplementation or hospitalization. Other SABR-induced acute or sub-acute adverse effects can include skin toxicity, chest wall pain, and nausea, whereas late effects can include chronic chest wall pain, rib fracture, and less commonly, injury to the mediastinal structures when SABR is delivered to centrally located tumors including obliterative bronchitis and “vanishing airway” syndrome. In addition, three randomized trials comparing lobectomy or wedge resection to SABR have prematurely closed because of a lack of accrual. As a result, randomized comparisons with surgery will unlikely be available in the near future. These data led the guidelines from national societies to only suggest (not recommend) SABR for subjects with clinical stage I NSCLC who cannot tolerate a lobectomy or sublobar resection (level of evidence 2C based on GRADE system) (Howington *et al.*, 2013; NCCN Clinical Practice Guidelines 2015).

The use of SABR as primary treatment for early stage NSCLC or for ablation of metastases has increased rapidly in the past decade. Nevertheless, alternative treatment strategies should be investigated because of the local recurrence (10-30%) and pneumonitis rates (2-16%), and

considering that the patient population is becoming increasingly older and potentially unfit for surgery or radiation.

One such alternative is percutaneous radiofrequency ablation (RFA) of peripheral cancers. This is the most studied of the ablative modalities which has been used in medically inoperable patients with small (< 3 cm) peripheral stage 1 NSCLC (Howington *et al*., 2013). Although, there is currently no comparative studies, the local control rates seem lower than those reported with SABR or sublobar resection (Howington *et al.*, 2013; Donington *et al.*, 2012). Tumors larger than 3 cm had the highest local recurrence rate (50%) and thus ideal lesions for this treatment should include lesions less than 3 cm in size (Lanuti *et al.*, 2009). Studies show a consistent local control rate of 60%, with a 30% to 40% overall survival at 3 years and a cancer-specific survival of 30% to 40% at 5 years. These outcomes are better than those seen in untreated patients with clinical stage I NSCLC but worse than those reported with SABR or sublobar resection. In the studies specifically addressing the inoperable stage I NSCLC, the primary tumor relapse rate after percutaneous RFA ranges from 8% to 43% (Donington *et al.*, 2012). The most common reported complications were pneumothorax (18%-62%), pleural effusion (7%-21%), and hemoptysis (4%-11%). Chest tube drainage was required in 5%-25% of subjects. There are also reports of bronchopleural fistula and massive hemoptysis. Considering the unfavorable safety profile and the modest local control rate, alternatives to SABR and RFA are therefore warranted for subjects with inoperable peripheral stage I NSCLC.

5.1.2. Current Treatment Approaches for Metastatic Lung Lesions

Although metastasis is responsible for up to 90% of all cancer-associated mortality it is still poorly understood (Chaffer and Weinberg, 2011). The lung is one of the primary targets of several cancers. Twenty to 50% of primary extrapulmonary solid malignancies demonstrate pulmonary metastases. Solid metastatic tumors of the endobronchial area are most commonly from breast, kidney, and colon-rectum. Other primary tumors such as prostate cancer, melanoma, thyroid cancer, account for less than 5% of lung metastasis (Marchioni *et al.*, 2014). Generally, distant metastasis from breast cancer remains common and incurable (Kennecke *et al.*, 2010) with bone metastases being the most common site and lung as the next most common site for metastases. The exception is the basal-type tumor which has a high rate of lung metastasis of 18.5% (Berman *et al.*, 2013). Metastasis to the lung occurs in 50-60% of patients with renal cell carcinoma (NCCN Guidelines®, Kidney Cancer, V2.2017, 2016) while approximately 4-9% of patients with colon or rectal cancer will have lung metastases (NCCN Guidelines®, Colon cancer, V1.2017, 2016). Because more colorectal cancer patients are surviving longer, lung metastasis is more frequent. It increased from 8.9% between 1990 and 1999 to 11.9% between 2000 and 2009. It is assumed it will continue to increase (Nozawa *et al.*, 2012).

Metastases is generally considered to require new blood vessel growth thus anti-angiogenic drugs are utilized. However, these drugs have shown limited efficacy for patients with metastatic disease. It is understood that some tumors incorporate pre-existing blood vessels found in surrounding normal tissue. This process is known as vessel co-option or vascular co-option and

has been frequently observed in metastases to the lung. There are at least three distinct mechanisms for vessel co-option that occur in lung metastases. One mechanism is the growth of cancer cells only in the alveolar air spaces permitting intact alveolar walls to be incorporated into the tumor which allows the tumor to co-opt the alveolar capillaries contained within those alveolar walls. This is known as alveolar co-option. There is also interstitial co-option and perivascular cuffing co-option. As a result, these tumors are generally resistant to anti-angiogenic therapy. Some tumors have a mixture of growth patterns with both angiogenesis and vessel co-option present in the same lesion. It appears for NSCLC, the tumors at the periphery permit vessel co-option but a switch to angiogenesis may occur in the center of the tumor. Tumors of diverse primary origin (breast, colon and kidney) all can utilize vessel co-option when they metastasize to the lung suggesting an active role of the lung environment in inducing cancer cells to use vessel co-option. It was observed that vessel co-option does occur less frequently with renal cell lung metastases compared to breast cancer lung metastases (Bridgeman *et al.*, 2016).

Much of the literature surrounding management and clinical outcomes of endobronchial lesions is limited to case reports and retrospective reviews of small cohorts. There is some data suggesting that these lesions respond poorly to systemic therapy and can lead to median survivals as low as 9 months (Katsimbri *et al*., 2000). Hamamoto and colleagues (Hamamoto *et al.*, 2010) demonstrated that metastatic lung lesions rather than NSCLC primary lesions tend to have higher rates of local recurrence. Most lung lesions are recommended to be treated with resection. When resection is not feasible, image guided ablation or stereotactic body radiation therapy (SBRT) are considered reasonable options (NCCN Guidelines®, Colon cancer, V1.2017, 2016). Tumor ablation therapy is also used when there are lung oligometastases (NCCN Guidelines®, Rectal cancer, V2.2017, 2016).

First line treatment for metastatic disease has traditionally been systemic therapy (Lischalk *et al*., 2016). Although chemotherapy is typically first-line treatment for metastatic disease it is unlikely to provide durable local control for such lung metastases (Okunieff *et al.*, 2006). However, recently local therapy has been utilized. Radiotherapeutic ablation of larger tumor sites is an option. In a retrospective study (Lischalk *et al*., 2016). Lischalk and colleagues (Lischalk *et al*., 2016) retrospectively examined 20 consecutive patients with a median age of 66 years (range, 24 to 82 years) treated with SBRT from November 2008 to November 2011. All patients presented with inoperable metastatic lung lesions localized to the central pulmonary tree. Most metastatic lung lesions were confirmed pathologically prior to treatment when clinically judged safe for the patient (safe accessibility and biopsy of the lesion, performance status of the patient, and/or lack of previous pathologic confirmation of metastatic disease). Most metastatic lesions (35%) were adenocarcinoma, with squamous cell accounting for 20%, renal cell for 15% and the remaining tumor sites accounted for 10% each (sarcoma, carcinoid, other). Patients with primary localized lung cancers or those with previous in-field thoracic irradiation were excluded from this study. Of the patients who had symptomatic lesions prior to treatment the majority (64 %) had significant symptomatic palliation after SBRT. At a median follow up of 19 months, the 1- and 2-year Kaplan-Meier local control was 70.1 and 57.4 %, respectively. The median Kaplan-Meier local

control was estimated to be 27.9 months. The 1- and 2-year Kaplan-Meier overall survival was 75 and 40 %, respectively, with a median overall survival estimated to 16.3 months. Acute grade 2 or higher toxicity was noted in one patient who developed medically manageable esophagitis (grade 2). Late grade 2 or higher radiation toxicity occurred in 30 % of treated patients and included the following: grade 2 atelectasis (3), grade 2 bronchitis (1), grade 3 pneumonitis (1), and grade 4 atelectasis (1).

5.2. Newly Developed Bronchoscopic Technologies

Newly developed bronchoscopic technologies such as navigational bronchoscopy, including the electromagnetic navigation bronchoscopy (ENB) system, and radial endobronchial ultrasonography (REBUS) have shown that reaching peripheral lung lesions and obtaining diagnosis in humans is both feasible and safe (Eberhardt et al., 2007; Wang Memoli et al., 2012; Brownback et al., 2102; Jensen et al., 2012; Loo et al., 2014; Al-Jaghbeer et al., 2016). In a retrospective chart review of 98 ENB procedures in 92 patients, the diagnostic yield was 60% with a 6% pneumothorax rate (Al-Jaghbeer *et al.*, 2016).

In 2015, Zhang and collaborators (Zhang *et al.* 2015) performed a systematic review to summarize the overall diagnostic yield and accuracy of ENB-based targeted biopsies in detecting peripheral lesions. Several databases were searched from inception to 2015 for studies that included more than ten patients and reported the diagnostic for peripheral lung nodules or lesions without any restriction with confirmation of peripheral nodules by radiographic evidence. The results of this meta-analysis (19 studies, 1,106 patients with peripheral lung nodules) indicated that electromagnetic-guided bronchoscopy has good sensitivity (82%) and excellent specificity (100%) in diagnosing peripheral pulmonary lesions, suggesting a hugely potential diagnostic value. A total of 40 (6%) pneumothoraces occurred in 681 procedures, in which two cases were induced using transbronchial biopsy, otherwise, no pneumothorax was ENB procedure-related. In addition, minor or moderate bleeding was reported in seven cases, and two post-procedure respiratory failure cases were recorded, none of them requiring specific treatment. Other adverse events included two of chest drainage, five of chest pain, three of fever, seven of sore throat, four of hemoptysis, and four of emesis, attributed to sedation or biopsy procedure.

The navigational bronchoscopy system is a minimally invasive technology that allows thoracic surgeons not only to localize small deep lesions but to biopsy these lesions intra-operatively when combined with on-site cytological evaluation. It provides a three-dimensional virtual “roadmap” that enables the physician to maneuver through multiple branches of the bronchial tree to reach targeted lesions in distal regions of the lung, obtain diagnosis, and potentially offer simultaneous bronchoscopic therapeutic interventions.

5.3. Navigational Bronchoscopy Photodynamic Therapy

Photodynamic therapy (PDT) is a technique for local destruction of tissue with light after prior administration of a photosensitizing agent. Complete response rates of 85% can be achieved in non-surgical candidates with early (microinvasive, superficial) central airway lung cancer (Furuse

et al., 1993; Kato *et al.*, 2003). Photodynamic therapy can reduce the degree of central airway obstruction, often leading to better respiratory function. In addition, PDT may help resolve acute hemoptysis and post-obstructive pneumonia and improve performance status (Kato *et al.*, 2012; Wisnivesky *et al.*, 2013).

The approved treatment with PDT in lung cancer involves the systemic administration of a photoreactive drug known as a photosensitizer, which is inert until activated by the light of a specific wavelength. The only approved photosensitizer agent for treatment of lung cancer in US and in Canada is porfimer sodium (Photofrin®). Photodynamic therapy with Photofrin® is indicated for 1) the treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated, and 2) for the reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial NSCLC. Treatment selectivity is achieved by directed light delivery obtained by the placement of optical fibers at the tumor site for intraluminal activation or by interstitial fiber placement to produce better efficacy with less exposure of the normal bronchial mucosa to light (US Package Insert, Canadian Product Monograph). Light activation of the photosensitizer leads to the production of reactive oxygen species, direct tumor cell death, and vascular shutdown.

The biological effect of this treatment is photochemical rather than thermal and thus normal tissue injury is less than with thermal ablative techniques (Fielding *et al.*, 2001). There is remarkably little effect on connective tissue like collagen, hence maintaining the basic mechanical integrity of organs. The PDT-necrotized areas heal well with less scarring than most other forms of localized necrosis and without cumulative toxicity (Fielding *et al.*, 2001). Photofrin® followed by PDT can cause treatment-induced inflammation and obstruct the main airway. In patients with superficial endobronchial tumors, the most common reaction to therapy was a mucositis reaction in one-fifth of the patients, which manifested as edema, exudate, and obstruction. The obstruction (mucus plug) was easily removed with suction or forceps. Mucositis can be minimized by avoiding exposure of normal tissue to excessive light. Stent placement was required in 3% of the patients due to endobronchial stricture.

Although PDT was initially considered a local treatment, several studies have indicated that local PDT can result in systemic neutrophilia, induction of acute phase proteins, increased circulating levels of complement proteins, and systemic release of proinflammatory cytokines, all of which indicate the presence of a systemic inflammatory response with T-cell mediated anti-tumor immune response. Studies demonstrate that local PDT of murine tumors could lead to the induction of anti-tumor immunity, which may control distant, untreated disease sites (Gollnick and Brackett, 2010). Friedberg and collaborators reported an increased survival for subjects with NSCLC with malignant pleural disease who receive surgery and PDT when compared to historical controls of subjects receiving surgery alone (Friedberg *et al.*, 2004). These results suggest that local PDT of tumors may lead to induction of an anti-tumor immune response capable of controlling the growth of tumors outside the treatment field and indicate that this modality has potential in the treatment of distant disease sites (Kabingu *et al.*, 2007; Pizova *et al.*, 2012).

In the last decade, two pulmonary procedures have been used with PDT to treat peripheral early-stage lung cancer: transthoracic robotic needle PDT and navigational bronchoscopy PDT (Kato *et al.*, 2012). To date, several subjects have been treated with transthoracic robotic needle PDT (Kato *et al.*, 2012). The tumors in these subjects were on average larger than those treated in the RFA studies (range 1.2 to 8.0 cm *versus* 0.7-5 cm, respectively) (Fanucchi *et al.*, 2016). Partial response was obtained in 78% of these subjects (Kato *et al.*, 2012). The efficacy of RFA is limited by tumor size as it is commonly difficult to achieve complete ablation of cancerous lesions in tumors with diameter larger than 3 cm (Hataji *et al.*, 2005). The transthoracic approach *via* CT guidance using 19 gauge needles has been reported to result in partial remission in 7/9 (78%) subjects. Partial response was defined as a reduction in tumor volume greater than 50% but with the cancer still recognizable on biopsy or brushing for at least 4 weeks after therapy. There were two cases of pneumothorax (Okunaka *et al.*, 2004). Furthermore, an animal study in nine normal pigs suggests that interstitial PDT (iPDT) necrosis lesions, large enough to cover a small tumor similar to those found in humans, can be made safely in the lung parenchyma (Fielding *et al.*, 2001). The authors compared interstitial laser photocoagulation (ILP) where the laser energy heats the tissue *versus* iPDT performed at a light dose of 100 J/cm at 50-100 mW/cm. On Day 3 post injection of the photosensitizer, well-defined, localized treated areas, typically 3.5 x 2 x 2 cm, were observed. Histology showed hemorrhagic necrosis after iPDT but no late cavitation as seen after ILP. The PDT treated lung areas healed with preservation of larger arteries and bronchi. The few small pneumothoraces resolved spontaneously and were probably related to the chest wall puncture used for the placement of the fibers (Fielding *et al.*, 2001).

5.4. Rationale

Cancer screening strategies have the potential of detecting an increasing number of peripherally located lung cancers with the majority being stage 1. While early stage (T1-2 N0) primary NSCLC has been traditionally managed with surgical resection, SABR and RFA are currently the therapeutic approaches used for subjects who decline surgery or are not surgical candidates because of pulmonary or cardiovascular comorbidities. Published series using SABR have reported local recurrence ranging from 10% to 30% with an overall radiation pneumonitis rates ranging from 2-16%. The most common reported complications of RFA were pneumothorax (18%-62%), pleural effusion (7%-21%), and hemoptysis (4%-11%). Bronchopleural fistula and massive hemoptysis were also reported. Considering the unfavorable safety profile and the modest local control rate, alternatives to SABR and RFA are therefore warranted for subjects with inoperable peripheral NSCLC and lung metastasis. Considering the advances in bronchoscopic technologies, PDT applied *via* navigational bronchoscopy may be a reasonable alternative to RFA and SABR for inoperable solid tumor in the lung for a variety of reasons. The bronchoscopic approach rather than CT-guided biopsy could prevent the occurrence of complications associated with more invasive methods and possibly reduce the risk of pneumothorax and bronchopleural fistula. A single treatment session is needed with PDT contrary to SABR where several sessions are required. There is no radiation involved in PDT, therefore, if PDT fails, a subject can still undergo salvage radiation therapy. Based upon these findings, this study is designed to evaluate

the safety and feasibility of using navigational bronchoscopy to perform iPDT as a therapeutic approach.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to assess the safety and feasibility of using navigational bronchoscopy to perform iPDT in subjects with primary lung cancer or solid tumor metastases located in the peripheral lung (including oligometastasis).

6.2. Secondary Objectives

The secondary objectives are to assess the overall safety and effectiveness of iPDT in subjects with solid tumor in peripheral lung by assessing tumor response and to explore iPDT-induced effects on immune system.

7. STUDY DESCRIPTION

7.1. Overall Study Description

This is a prospective, multicenter, uncontrolled, non-randomized, open-label, feasibility clinical study. A Time and Procedures Schedule for the overall conduct of the study is outlined in Appendix 17-1.

The primary diagnosis will be obtained prior to consent signature. The primary diagnosis will involve, when applicable, invasive staging of the tumor *via* endobronchial ultrasonography (EBUS) - transbronchial needle aspiration (TBNA) or mediastinoscopy to allow systematic nodal evaluation and accurate staging, and, if subject's condition permits, biopsy or cytology confirmation of any malignant histology type of the tumor.

Upon consent signature, all eligible subjects will undergo a Pretreatment Procedures evaluation conducted during the 60 days prior to enrollment. This phase will involve general medical evaluations and thorough review of all reports that led to the primary diagnosis. Upon successful baseline evaluations, subjects will be enrolled to the open label treatment group and will be assigned a unique participation number.

Treatment Procedures will consist of one iPDT-Photofrin® course performed through navigational bronchoscopy. One course will consist of an intravenous (IV) injection of Photofrin® 2 mg/kg over 3-5 minutes followed by one laser light application. The end of injection will be Study Hour 0. Photodynamic laser therapy will be performed on Study Hour 40-50. Laser light (630 nm wavelength) will be applied at a dose of 200 J/cm. Follow-up assessments will include some or all the following procedures: physical exam; vital signs evaluation; body weight measurement; spirometry with diffusing capacity of lung for carbon monoxide (DLCO); chest CT; performance status; HRQoL questionnaires; and clinical laboratory testing. All subjects will be asked general questions about the occurrence of adverse events, concurrent medical conditions, use of adjunctive therapy/procedure, and intake of concomitant medication.

Data will be analyzed to evaluate the safety and effectiveness of the modality up to 6 months.

7.2. Scheduling of Visits

Screening assessments will be performed during the 14 days prior to enrollment. After enrollment, study visits will be as follows:

- Study Day 0 will be the day the subject is enrolled.
- Study Day 1 will be the day of the PHO injection. Study Hour 0 will be the time of the end of PHO injection.
- Study Day 3 will be the day of PDT. Study Hour 40-50 will be calculated from Study Hour 0.
- Study Day 9 to Day 11 will be the 10-day post enrolment visit.
- Study Day 27 to Day 33 will be the 30-day post enrolment visit.
- Study Day 42 to Day 48 will be the 45-day post enrolment phone call.
- Study Day 83 to Day 97 will be the 90-day (3 months) post enrolment visit.

- Study Day 173 to Day 187 will be the 180-day (6 months) post enrolment last study visit.

7.3. Estimated Duration of the Study

Time permitted for enrollment will be 9 months. Therefore, the clinical part of the study has an estimated duration of approximately 15 months.

Enrollment at all sites will be reviewed on an ongoing basis. After six months, if enrollment at any site falls below 50% of the projected total, the sponsor can exercise the right to terminate the study at that site.

The end of the clinical part of the study at any site will be defined as the date of the last visit of the last active subject at that site. The official end of the clinical part of the study at all sites will be defined as the date of the last visit of the last active subject in the study. At the end of the clinical part of the study, subjects will be treated as per the investigator's judgment.

8. STUDY POPULATION

8.1. Primary Diagnosis

This study plans to enroll subjects with primary lung cancer or solid tumor metastases located in the peripheral lung (including oligometastasis). When applicable, subjects will be staged with chest CT and positron emission tomography (PET) scanning (NCCN Guidelines®, Non-small cell lung cancer, V3.2016, 2015) or as per local practice. Ideally subjects should have undergone an initial integrated whole body PET CT scan as part of their standard of care (SoC) staging protocol. All procedures performed to confirm the primary diagnosis will be considered SoC and not research-related activities.

Primary diagnosis will be based on the following assessments performed no more than 60 days prior to ICF signature with results available at screening.

1. Confirmed primary lung cancer or solid tumor metastases located in the peripheral lung (including oligometastasis) via EBUS-TBNA or mediastinoscopy, when applicable and if subject's condition permits.
2. Either biopsy- or cytology-proven confirmation of any confirmed malignant histology type, if subject's condition permits.
3. Peripheral tumor location as defined by the Radiation Therapy Oncology Group protocols as the primary tumor not touching a 2-cm volume in all directions around the proximal bronchial tree (distal 2 cm of the trachea, main stem bronchi, and lobar bronchi). Tumors beyond the 3rd generation airways are included.
4. Tumor size ≤ 3 cm based on official radiology report that would include both solid and semi-solid lesions, and no evidence of interlobar, hilar or mediastinal adenopathy on CT or PET scanning, or negative mediastinal and hilar lymph nodes by EBUS-TBNA or mediastinoscopy, when performed. Chest CT will have to be performed within 60 days of ICF signature, as longer delays may result in upstaging of tumors.
5. Medical inoperability defined as not being a candidate for curative surgery or as refusal of surgery because of elevated risk profile. Guidelines for inoperability will be determined by the thoracic surgeon and typically include:
   - compromised pulmonary function measured as forced expiratory volume in 1 second (FEV_1) less than 40% predicted, diffusion capacity of carbon monoxide less than 50% predicted, or oxygen desaturation with climbing one flight of stairs;
   - severe vascular disease;
   - high cardiac risk, including unstable angina or ejection fraction less than 30%;
   - poor performance status (Eastern Cooperative Oncology Group [ECOG] > 2, Appendix 17-2).

8.2. Number of Subjects

This study plans to enroll up to approximately 20 subjects from up to 10 North-American clinical research sites experienced in navigational bronchoscopy.

8.3. Selection Criteria

8.3.1. Inclusion Criteria

In order to be eligible to participate in the study, potential subjects must meet all of the following inclusion criteria.

1. Male or female subject is eighteen years of age and older.
2. Subject is diagnosed with primary lung cancer or solid tumor metastases located in the peripheral lung (including oligometastasis) of any malignant histology type (if subject's condition permits).
3. Subject is not a candidate for surgery, is unfit for surgery, or does not wish to undergo surgical resection.
4. Subject may be a candidate for, has failed, or does not wish to undergo radiation therapy (e.g., SABR).
5. The tumor is ≤ 3 cm in size and clearly observable in CT without contrast.
6. The tumor is accessible for unrestricted illumination of iPDT.
7. Subject deemed likely to survive for at least 3 months.
8. Non-menopausal or non-sterile female subject of childbearing potential must have a negative serum β–HCG at the time of entry into the study.
9. Non-menopausal or non-surgically sterilized female subject of childbearing potential must use a medically acceptable form of birth control.
10. Subject is willing to remain in a controlled light exposure environment for at least 30 days and for as long as deemed necessary as per the investigator's clinical judgment.
11. Subject is able and willing to provide written informed consent to participate in the study, which must comply with the ICH guidelines and local requirements.

8.3.2. Exclusion Criteria

Potential subjects who meet any of the exclusion criteria will not be allowed to enroll into the study.

1. Subject diagnosed with small cell lung cancers.
2. Subject with solid tumor in central location defined by the Radiation Therapy Oncology Group protocols as located within 2 cm of the proximal bronchial tree or within 2 cm of a major structure (aorta, heart, trachea, pericardium, superior vena cava, pulmonary artery, esophagus, vertebral body, spinal canal) (Timmerman *et al.*, 2010; Chang *et al.*, 2008).
3. Subject with concurrent non-solid malignancy.

4. Subject with blood parameters of Grade 3 or higher on the Common Terminology Criteria for Adverse Events (CTCAE) 5-point scale; parameters of Grade 2 will be excluded if judged clinically significant by the investigator.
5. Subject has had chemotherapy/immunotherapy in the last four weeks.
6. The tumor invades a major blood vessel.
7. Subject with known porphyria or known hypersensitivity to Photofrin® or porphyrin-like compounds or to any of its excipients.
8. Subject with a planned surgical procedure within the next 90 days.
9. Subject with a coexisting ophthalmic disease likely to require slit-lamp examination within the next 90 days.
10. Subject with any acute or chronic medical or psychological illnesses as judged clinically significant by the investigator to preclude endoscopy procedures.
11. Female subject who is breastfeeding or intends to breastfeed during the study.
12. Subject has received prior PDT during 3 months prior to the date of the ICF signature.
13. Subject who participates or intends to participate in another investigation study (other than observational studies) during the study.

8.4. Concomitant Medication

Subjects may receive medication that is clinically indicated, such as pain prophylaxis, as per the investigator's clinical judgement. The brand name (or, if unknown, the generic name), dose, dose unit (or dosage form if compound), frequency, route of administration, duration of use (start date and, if applicable, stop date) and indication for all previous medications (taken 30 days prior to the date of the ICF signature) and concomitant medications (taken at the time of the ICF signature and during the course of the study) must be documented altogether in the concomitant medication record section of the case report form (CRF). Concomitant medications include intravenous fluids, herbal products, vitamins, and any over-the-counter medicines.

8.5. Adjunctive Therapy/Procedure

An adjunctive therapy/procedure is defined as any procedure or intervention (e.g., psychotherapy, surgery, dental work, acupuncture, physiotherapy, chiropracty, osteopathy) used to treat an illness. Diagnostic tests or procedures (e.g., chest X-rays, ECG) are not considered as a therapy, these will not be recorded unless the test or procedure may have played a role in the occurrence of an adverse event or was performed to assess an adverse event.

As per labelling, if PDT is to be used before or after radiotherapy, sufficient time should be allotted between the two therapies to ensure that the inflammatory response produced by the first treatment has subsided before commencing the second treatment. The inflammatory response from PDT will depend on tumor size and extent of surrounding normal tissue that receives light. It is recommended that 2 to 4 weeks be allowed after PDT before commencing radiotherapy. Similarly,

if PDT is to be given after radiotherapy, the acute inflammatory reaction from radiotherapy usually subsides within 4 weeks after completing radiotherapy, after which PDT may be given.

The adjunctive therapy/procedure (type, duration of use [start date and, if applicable, stop date], and indication) received during 30 days prior to the date of the ICF signature and throughout the study must be recorded in the adjunctive therapy record of the CRF.

8.6. Acceptable Contraceptive Regimens

Current regulations and guidelines pertaining to pharmaceutical industry require properly documenting and monitoring exposure to any drugs, whether investigational or not, under clinical research during pregnancy of study human subjects and/or their partner.

8.6.1. Female Study Subjects

During the study, it is expected that females of childbearing potential will have to take appropriate measures to prevent pregnancy during the study (Study exit) or for 3 months after iPDT if early termination, such as the use of medically acceptable contraceptive regimens namely:

- systemic contraceptives (e.g., transdermal patch, birth control pills, injectable or implantable or insertable hormonal birth control products);
- double-barrier method (e.g., diaphragm with intravaginal spermicide, cervical cap with intravaginal spermicide, condom with intravaginal spermicide, condom with diaphragm); or
- Intrauterine or intravaginal methods (e.g., vaginal contraceptive ring, intrauterine system with hormone release, copper intrauterine device).

Female subjects will be instructed to inform the investigator should a change in the contraceptive regimen occur during the study. Females of childbearing potential will be informed about this requirement in the ICF. Abstinence will not be considered as a medically acceptable contraceptive method.

Females who do not use an acceptable contraceptive regimen will be allowed to participate in this study only if they are not considered to be of childbearing potential: female who has had a hysterectomy, bilateral ovariectomy, or tubal ligation (performed during at least six months prior to enrollment), is clinically diagnosed infertile, or is in a menopausal state (minimum of one year without menses). A female subject engaged with a vasectomized partner will not require an additional contraceptive method.

Should a case of pregnancy in female subject occur during the course of the study, the female subject will be monitored for the pregnancy outcome at birth, 6 months and 12 months following birth.

8.6.2. Male Study Subjects

Contraceptive methods will be required for the male subject in the study as well as for the partner of the male subject in the study during the study (Study exit) or for 3 months after iPDT if early

termination. Contraceptive methods will not be required if the male subject in the study is vasectomized or if the partner of the male subject in the study is not considered to be of childbearing potential.

Cases of pregnancy in partner of male subject in the study will be monitored during the course of the study. Should a case of pregnancy in the partner of the male subject occur during the course of the study, the male subject will remain in the study and the partner of the male subject will be monitored for the pregnancy outcome (at birth, 6 months and 12 months following birth) after giving consent.

8.7. Early Discontinuation Criteria

Early discontinuation from study will not, on its own, invalidate a subject for the safety analyses.

An investigator may choose to remove a subject from the study for any variety of reasons. Below is a list of possible reasons for removal of a subject; however, it does not include all possible justifiable reasons for removing a subject from the study.

1. The subject has been included in violation of the inclusion / exclusion criteria (as described under Section 8.3).
2. The subject chooses to discontinue participation for personal reasons (e.g., moving away, no time).
3. The subject chooses to discontinue, or is discontinued by the investigator or the sponsor due to intolerable, serious or unexpected adverse event or laboratory values judged to be clinically significant.
4. The investigator or the sponsor discontinues the subject for a significant protocol violation (e.g., pregnancy, current participation in another clinical study, etc.).
5. An illness newly develops as determined by the physician in charge that compromises continued participation.
6. The subject is uncooperative or does not comply with the protocol requirements (e.g., failure to return for scheduled visits at the enrolling study site, failure to complete study evaluation tools, failure to follow instructions).
7. In the investigator's or sponsor's judgment, withdrawal from the study would be in the subject's best interest (e.g., an immediate medical or surgical procedure is required that would compromise the subject's continued participation, lack of adequate therapeutic response resulting in intolerable symptoms or unacceptable risk).
8. The study is terminated by the sponsor.

For any subject who leaves the study, the investigator must complete the CRF up to the time study treatment is terminated. Every effort should be made to ascertain the reason for discontinuation and to perform the early discontinuation procedures (Section 9.5). All reasonable effort must be made to contact subjects who fail to return for scheduled visits and to encourage them to comply with the procedure. All attempts to contact subjects must be clearly documented. The investigator will advise the sponsor immediately of every dropout by telephone, facsimile, or E-mail.

In case of withdrawal of consent, the date of and the reason for withdrawing consent will be collected. No additional data will be collected from the time of consent withdrawal.

9. STUDY PROCEDURES

This is a multicenter, prospective, open-label, single-arm clinical study of the safety and feasibility of using navigational bronchoscopy to perform iPDT using Photofrin® (porfimer sodium). A detailed description of the time and events schedule of planned study assessments and visit procedures is outlined in Appendix 17-1.

9.1. Screening Procedures

The diagnosis of histologically confirmed-solid tumor in peripheral lung considered to be medically inoperable (Section 8.1) must have been obtained prior to signing the ICF (Section 4.3).

Before any study-specific procedures are performed, informed consent will be obtained. All subjects will undergo the following evaluations at the screening visit:

1. Collection of demographic data;
2. Collection of medical and oncological history, including concurrent medical conditions;
3. Comprehensive physical examination as per SoC (excluding genital/gynecologic and urogenital unless indicated);
4. Skin phototype according to Fitzpatrick Classification (Appendix 17-3);
5. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate), body weight (SoC), and height assessment;
6. Chest X-ray if has not been performed up to 90 days prior to ICF signature;
7. A 5-minute resting 12-lead ECG;
8. Clinical laboratory as per Appendix 17-4;
9. Serum β–HCG (only for female subjects of childbearing potential);
10. Pulmonary function tests, including DLCO if not performed prior to ICF signature (SoC);
11. Chest CT, PET scanning, or as per local practice if not performed prior to ICF signature (SoC);
12. ECOG Performance Status (SoC);
13. Collection of all adjunctive therapies/procedures and medication information including over-the-counter and phytomedicinal products currently taken by the subject as well as up to 30 days prior to the date of the ICF signature;
14. Collection of adverse events;
15. Review of eligibility criteria.

9.2. Enrollment Procedure

Along with the reports confirming the subject's primary diagnosis (Section 8.1), the investigator will check all the admission criteria (Section 8.3) of the subject based on all screening procedure results. This requires the availability and evaluation of the results of all screening procedures (Section 9.1). The investigator will then submit the Eligibility Verification Form (EVF) to the sponsor-designated medical monitor to approve the enrollment of the subject. Subjects will be provided with instructions on how to manage light exposure upon enrollment (Day 0).

9.3. Treatment Procedures

9.3.1. Day 1 (Photofrin® Injection)

At the Day 1 visit, Photofrin® injection will be administered and the following assessments will be performed.

Prior to Photofrin® injection

1. Reevaluate eligibility criteria.
2. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
3. Body weight.
4. Brief Physical Examination.
5. ECOG Performance Status.
6. Quality of Life Assessments (SF-36 and EORTC QLQ-C30/LC13).
7. Blood samples for the immunology marker testing.
8. Remind instructions on how to manage light exposure.
9. Record concomitant medications and adverse events.

Photofrin® injection

1. Subjects will receive Photofrin® at a dose of 2 mg/kg as a single, slow IV injection lasting 3–5 minutes corresponding to approximately 5 mL every 15 seconds. It may be administered through the "Y" tube of an IV administration set. It cannot be mixed with other drugs. Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, care must be taken to protect the area from light. There is no known benefit from injecting the extravasation site with another substance. Further information on reconstitution and administration of PHO can be found in Section 10.1.3 and in the Pharmacy Manual.
2. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate) at 15 minutes, 30 minutes, 1, 2, 4, and 8 hours after the injection.
3. After the injection, subjects will be asked general questions about how they feel. Any occurrence of adverse events and need of concomitant medication will be recorded.

9.3.2. iPDT Bronchoscopy (40-50 Hours post Photofrin® injection)

Subjects will return at Day 3 (40-50 hours post Photofrin® injection) for the iPDT bronchoscopy procedure and the following assessments will be performed.

1. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
2. Brief Physical Examination.
3. ECOG Performance Status.
4. Under general anesthesia or deep sedation
   a. Subjects will undergo a flexible bronchoscopy with navigation guidance to confirm the location and the size of the lesion as per usual practice (e.g., with the use of radial probe endobronchial ultrasonography [REBUS]). This will be captured by video or photos to document the relationship between the probe and the lesion.
   b. The investigator will select the optical fiber diffuser length to match the tumor length.
   c. Once the desired placement of the probe is confirmed, the investigator will proceed with the placement of the selected optical fiber under fluoroscopy guidance.
      i. Tumor size ≤ 2 cm
         - The selected optical fiber will be inserted into the tumor (interstitial fiber placement [concentric or eccentric pattern]). Exceptionally, the placement of the diffuser in a location adjacent to the tumor for intraluminal activation will be done if the interstitial fiber placement has been unsuccessful.
         - After the placement (interstitial or adjacent) of the optical fiber, photoactivation will be performed at a light dose of 200 J/cm as per labeling.
      ii. Tumor size > 2 cm-≤ 3 cm
         - PDT is to be performed on all areas of the tumor (if feasible) which will require multiple fiber placements.
         - The optical fiber will first be inserted into the tumor (concentric or eccentric pattern) or placed adjacent to the tumor. After the placement, photoactivation will be performed at a light dose of 200 J/cm as per labeling.
         - The optical fiber will then be repositioned at about 1 cm apart from the previous location to minimize the overlap of illumination. After each repositioning, photoactivation will be performed at a light dose of 200 J/cm as per labeling.
   d. Up to two lesions, on either or both sides, would be treated if oligometastatic or multiple metastases.
5. Re-educate the subject on how to manage light exposure.
6. Record concomitant medications and adverse events.
7. Admit subject for a 48-hour hospitalization period.

9.3.3. Day 5 (Hospital Discharge Evaluation)

Approximately 48 hours after iPDT bronchoscopy, the following safety evaluations will be performed to determine if subjects are medically stable to be discharged from the hospital.

1. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
2. Brief Physical Examination.
3. Clinical labs (Appendix 17-4).
4. Chest X-ray.
5. Record concomitant medications and adverse events.

9.3.3.1. Subject medically stable

Discharge subject and provide instructions on how to manage light exposure.

9.3.3.2. Subject non medically stable (Day 6 to Day 10 -Extended hospitalization as required)

The subject's 48-hour hospitalization can be extended to 72 hours (or longer) at the discretion of the investigator if the subject is deemed medically unstable. During this extended hospitalization, the following assessments should be performed daily until the subject is considered stable and able to be discharged.

1. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
2. Brief Physical Examination.
3. Record concomitant medications and adverse events.

The day of the discharge, the following assessments should be performed.

1. Clinical labs (Appendix 17-4).
2. Chest X-ray.

The prolongation of hospitalization after 72 hours due to subject being medically unstable is to be reported to the sponsor as a serious adverse event. In the event that a subject is still hospitalized at Day 10, the sponsor should be notified promptly.

9.4. Follow-Up Period

9.4.1. Day 10

Subjects will return to the site on Day 10 to have the following evaluations performed.

1. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
2. Brief Physical Examination.
3. Chest X-ray.
4. Blood samples for the immune response.
5. Re-educate the subject on how to manage light exposure.
6. Record concomitant medications and adverse events.

9.4.2. Day 30

Subjects will return to the site on Day 30 to have the following evaluations performed.

1. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
2. Brief Physical Examination.
3. ECOG Performance Status.
4. Chest X-ray.
5. Re-educate the subject on how to manage light exposure.
6. Study coordinator will train subject on how to perform the Light Challenge procedures at home on Day 44 (Section 11.1).
7. Record concomitant medications and adverse events.

9.4.3. Day 45 (Phone Call)

The study coordinator will call the subject at Day 45 to ensure the Light Challenge was performed on Day 44 and will record the Light Challenge results.

- If the subject passes the Light Challenge, the subject will be instructed to gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure.
- If the subject does not pass the Light Challenge, the subject will be instructed to continue adhering to light restrictions and repeat the Light Challenge in 14 days. The Light Challenge should be repeated every 14 days until passed.

During Phone Visit, the study coordinator will:

1. Record the results of the Light Challenge;
2. Re-educate the subject on how to manage light exposure;
3. Record concomitant medications and adverse events.

9.4.4. Month 3

Subjects will return to the site on Month 3 to have the following evaluations performed.

1. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
2. Comprehensive Physical Examination.
3. CT scan without contrast and evaluation.
4. Pulmonary Function Tests, including DLCO.
5. Clinical labs (Appendix 17-4).
6. Serum β–HCG (only for female subjects of childbearing potential).
7. ECOG Performance Status.
8. Quality of Life Assessments (SF-36 and EORTC QLQ-C30/LC13).

9. Re-educate the subject on how to manage light exposure, if needed.
10. Record concomitant medications and adverse events.

9.4.5. Month 6 (Study Exit)

Subjects will return to the site at Month 6 to have the following study exit procedures performed.

1. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
2. Comprehensive Physical Examination.
3. CT scan without contrast and evaluation.
4. Pulmonary Function Tests, including DLCO.
5. ECOG Performance Status.
6. Quality of Life Assessments (SF-36 and EORTC QLQ-C30/LC13).
7. Record concomitant medications and adverse events.

9.5. Study Early Discontinuation

9.5.1. Early discontinuation due to consent withdrawal

In case of withdrawal of consent, the date of withdrawing consent will be collected. If possible, the reason for withdrawing consent will be collected to exclude safety reason. No additional data will be collected from the time of consent withdrawal.

9.5.2. Early discontinuation for reason other than withdrawing consent

The investigator will make every effort to complete the following at the time of study discontinuation.

1. Reason for early discontinuation.
2. Comprehensive Physical Examination.
3. Vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate).
4. ECOG Performance Status.
5. Quality of Life Assessments (SF-36 and EORTC QLQ-C30/LC13).
6. Clinical labs (Appendix 17-4) if discontinuation before the Month 3 visit.
7. Serum β–HCG (only for female subjects of childbearing potential) if discontinuation before the Month 3 visit.
8. Concomitant medications and adverse events.

9.6. Exploratory Immunology Markers

The following immunomodulatory proteins will be quantified.

- T-helper cells (Th cells): CD3, CD4, HLADR
  - CD3, CD4, HLADR Ki67 (Proliferating Th cells)
  - CD3, CD4, HLADR PD1 (Tolerized/exhausted Th cells)
  - CD3, CD4, HLADR, CD25, CD39, CD127 (Treg Cell)

- Cytotoxic T-Lymphocyte (CTLs): CD3, CD8
  - CD3, CD8, perforin (activated CTLs)
  - CD3, CD8, PD1 (exhausted CTLs)
- Myeloid-derived suppressor cells (MDSCs): CD11b, CD45, CD33, HLADR, CD14, CD15, CD16, PDL1

Blood sampling will be taken on two separate occasions:

- Prior to Photofrin® injection;
- Day 10.

Procedures for acquisition and shipment of blood samples will be performed as per laboratory instructions provided to participating sites. Samples will be sent to Dr. Sandra Gollnick's laboratory at Roswell Park Cancer Institute (Buffalo, NY, USA).

10. MATERIALS

10.1. Photofrin®

10.1.1. Supply

Photofrin® 75 mg (porfimer sodium) for injection will be supplied by Concordia Laboratories Inc. (St. Michael, Barbados).

10.1.2. Packaging and Labelling

10.1.2.1. Primary Packaging (Vial)

A label will be affixed to each vial. The label will comply with local regulations and will reflect the following, but not be limited to, pertinent study information: pharmaceutical dosage form, route of administration, the name/identifier and strength/potency, protocol number, lot number, re-assay/expiry date, subject number, investigator name, sponsor identification, storage conditions.

10.1.2.2. Secondary Packaging (Box)

A label will be affixed to each box. The label will comply with local regulations and will reflect the following, but not be limited to, pertinent study information: pharmaceutical dosage form, route of administration, the name/identifier and strength/potency, protocol number, lot number, re-assay/expiry date, subject number (or space provided), investigator name (or space provided), sponsor identification, storage conditions, caution statement, direction for use.

10.1.3. Reconstitution and Administration of Photofrin®

10.1.3.1. Reconstitution

Reconstitute each 75-mg vial of Photofrin® with 31.8 mL of 5% Dextrose Injection (USP) which will result in a final concentration of 2.5 mg/mL. Shake well until dissolved. Do not mix Photofrin® with other drugs in the same solution. Porfimer sodium, reconstituted with 5% Dextrose Injection, has a pH in the range of 7 to 8 and 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 Photofrin® is an opaque solution, in which detection of particulate matter by visual inspection is extremely difficult. Reconstituted Photofrin®, however, like all parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

10.1.3.2. Administration

Photofrin® dose will be 2 mg/kg body weight.

For conversion from subject's weight in pounds to kilograms multiply by 0.454 (e.g., 200 lbs x 0.454 = 91 kg).

The "mg/kg" will be converted in "mL" to be administered as follows:

$$\text{Total volume of Photofrin}^{®}\text{ (mL)} = \frac{\text{Subject's weight (kg) x 2 mg/kg}}{\text{2.5 mg/mL}}$$

10.1.3.3. *Spillage and Disposal*

Any spillage of Photofrin® should be wiped up with a damp cloth. Contact to the skin and eyes should be avoided due to the potential of photosensitivity reactions upon exposure to light. It is recommended that rubber gloves and eye protection be used. All contaminated materials should be disposed of in a polyethylene bag in compliance with local regulations.

10.1.3.4. *Compliance*

Assessment of compliance with the dosing regimen is not applicable as Photofrin® will not be provided to subjects for self-administration. Any variance of administration with the intended dose will be recorded.

10.1.3.5. *Storage, Dispensing and Reconciliation*

Prior to reconstitution, vials must be stored at controlled room temperature of 20°C-25°C (68-77°F) or as per local labelling in a secure, locked facility accessible only to the investigator or authorized personnel. Reconstituted solutions must be protected from bright light and used immediately. The storage area must be free of environmental extremes. Prior to the study start, the drug storage area will be inspected by a Concordia Laboratories Inc. monitor or designee.

A qualified individual (pharmacist or authorized study personnel) designated by the investigator will dispense Photofrin® only to subjects enrolled in this study. Photofrin® supplies must not be loaned or dispensed by the investigator to another investigator or site or used for any purpose other than the study.

Upon receiving Photofrin® supplies, the qualified individual must complete, sign and return to the sponsor the form acknowledging the receipt of Photofrin®. Each vial will be identified by a reference number, which will be recorded in the inventory/dispensing record to document its use per subject. It is the responsibility of the qualified individual designated by the investigator to maintain and keep current the inventory/dispensing record for all drugs withdrawn and dispensed. A copy of the Photofrin® inventory/dispensing record must be kept at the investigator's site and be available to the sponsor's monitor or designee who will visit the site. Any discrepancy and deficiency are to be recorded and explained.

10.2. Optical Fibers

10.2.1. Supply

Sterile Optiguide™ cylindrical diffusers (DCYL700 series) manufactured for Concordia Laboratories Inc. are available in several lengths for single use and will be supplied in sufficient quantities to allow for the treatment of subjects on the study. The choice of the diffuser length

will depend on the length of the tumor to avoid exposure of nonmalignant tissue to light and to minimize overlapping of previously treated malignant tissue.

10.2.2. Packaging and Labelling

Labeling of the primary and secondary packaging will comply with all local regulations of the receiving country.

Optical fibers will be mechanically protected in a dispenser tray. The primary packaging will consist of a sealed pouch. The loaded tray will be placed into the pouch. The secondary packaging will consist of an individual box and will contain the primary packaging and the instructions for use. A label will be affixed to the primary and secondary packaging. The label will comply with local regulations and will reflect the following, but not be limited to, pertinent study information: device name/identifier, protocol number, subject number (or space provided), investigator name (or space provided), lot number, re-assay/expiry date, caution statement as per local regulations, manufacturer or manufactured for identification, storage conditions.

10.2.3. Storage, Dispensing, and Reconciliation

Optical fibers must be stored in its original individual box and in a secure, dry location, away from temperature extremes, accessible only to authorized study personnel.

Upon receiving the optical fibers, the authorized study personnel will complete, sign and return to the sponsor the form acknowledging the receipt of the optical fibers. Each optical fiber will be identified by a reference number, which will be recorded in the inventory/dispensing record to document its use per subject. A copy of the device inventory/dispensing record must be kept at the study site and be available to the sponsor's monitor or designee who will visit the site. Any discrepancies and deficiencies are to be recorded.

Optical fibers must not be loaned or dispensed by the investigator to another investigator or site or used for any purpose other than the study.

10.2.4. Inspection of Optical Fibers

Fiber optic diffusers must be checked for gross defects, proper functioning and power output prior to use. Optical fibers should visually be inspected by placing the optical fiber into the laser calibration port. Using the trace light emitted during about 10-20 sec when the laser is preparing for calibration, the fiber can be inspected for irregularities such as "hotspots" or nicks in the cylinder or coating on the fiber itself, which would interfere with the proper administration of the light dose. If such defects are detected a new fiber should replace the defective fiber. Likewise, the new fiber must be tested for defects prior to use. In the event of damage, the damaged optical fiber diffuser must be returned to the sponsor using the provided event form.

10.3. Disposition of Photofrin® and Optical Fibers

During the study, the sponsor's monitor or designee will periodically check the inventory/dispensing record for the complete accountability of Photofrin® vials and optical fibers. At the end of the study, the sponsor's monitor or designee will perform a last check of the inventory/dispensing record. Any discrepancies will be explored and documented.

10.3.1. Disposition of Unused Photofrin® and Optical Fibers

At the end of the study, all unused Photofrin® vials and optical fibers, along with the inventory/dispensing records, will be returned to the sponsor or designee who will perform the final reconciliation; any discrepancies will be explored and documented.

The sponsor may grant permission for the destruction of unused Photofrin® vials on site. In such case, Photofrin® vials shall be disposed as per institution's guidelines for biohazard medical waste with written documentation. The record shall include the following:

- A copy of the institution's Standard Operating Procedures;
- The name and signature of the person who destroyed the supplies;
- The identity and quantity of destroyed product;
- Method and date of destruction.

A copy of the destruction record will be provided to the sponsor.

10.3.2. Disposition of Used Photofrin® and Optical Fibers

All used Photofrin® vials and optical fibers shall be disposed as per institution's guidelines for biohazard medical waste with written documentation. The record shall include the following:

- A copy of the institution's Standard Operating Procedures;
- The name and signature of the person who destroyed the supplies;
- The identity and quantity of destroyed product;
- Method and date of destruction.

A copy of the destruction record will be provided to the sponsor.

11. WARNINGS AND PRECAUTIONS

11.1. Phototoxicity Reactions

All subjects who receive Photofrin® will be photosensitive and must observe precautions to avoid exposure of eyes and skin to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, etc.) for at least 30 days or longer as per local labelling.

The level of phototoxicity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the subject should perform the Light Challenge to test the skin for residual phototoxicity. A small area of skin (e.g., hand) should be exposed to sunlight for 10 minutes. If no phototoxicity reaction (erythema, edema, blistering) occurs within 24 hours, the subject can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If a phototoxicity reaction occurs with the limited skin test, the subject should continue the existing precautions for another 2 weeks before re-testing. As the tissue surrounding the eyes may be more sensitive, it is therefore not recommended that the face be used for testing. If subjects travel to a different geographical area with greater sunshine, they should retest their level of phototoxicity. Ultraviolet (UV) sunscreens are of no value in protecting against phototoxicity reactions because photoactivation is caused by visible light.

Some subjects may remain photosensitive for up to 90 days or more. The photosensitivity is due to residual drug, which will be present in all parts of the skin. Exposure of the largest possible area of skin to ambient indoor light is, however, beneficial because the remaining drug will be inactivated gradually and safely through a photobleaching reaction. Therefore, subjects should not stay in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light.

11.2. Ocular Sensitivity

Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in subjects who received Photofrin®. Subjects should wear dark sunglasses when outdoors, which have an average white light transmittance of < 4% for at least 30 days or longer as per local labelling. Subject should be advised to consult their ophthalmologist if they notice any change in vision after iPDT.

11.3. Training and Instructions

Members at each site will be trained by the sponsor-designated representatives to ensure knowledge of subject safety issues prior to recruitment of the first subject. All subjects will be seen in clinic prior to scheduling the procedure and will be educated on the risks and benefits of the intervention and educated on the preventive measures to avoid cutaneous phototoxicity. Subjects will also be given a “Patient Kit”, which includes gloves, sunglasses, hat with neck protection, and instructions on how to manage light exposure. Subjects will be encouraged to

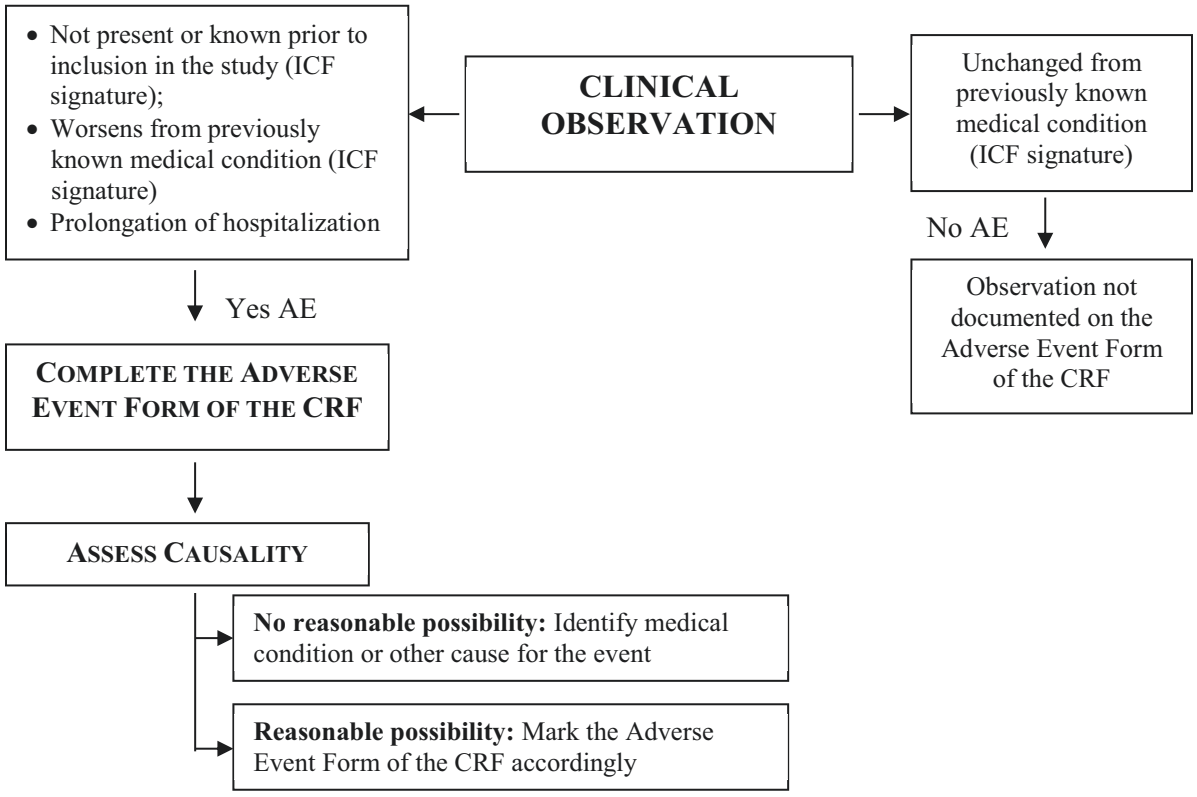
expose their skin to ambient indoor light. Subjects will not be considered for the study if the clinician deems that the subject is not mentally capable of following instructions to prevent phototoxicity.

12. ASSESSMENT OF SAFETY

Any adverse event/concurrent illness experienced by a subject during any portion of the study must be described in detail and be fully evaluated by the investigator. The investigator is responsible for recording and reporting all adverse events observed or reported during the study from informed consent signature until date of completion/discontinuation, regardless of drug-related assessment and/or clinical significance. Any pertinent information must be recorded in the CRF and additional comments describing the course and outcome of these events should be provided as appropriate.

12.1. Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a subject or clinical investigation subject during the course of a clinical study regardless of the causal relationship. The following flow chart illustrates the decision making process the investigator should follow in determining how to document an AE in the study.



An **Unexpected Adverse Event** is defined as an adverse drug event, the nature or incidence of which is not consistent with applicable product information (US Package Insert, Canadian Product Monograph).

A **Serious Adverse Event** (SAE) is defined as any untoward medical occurrence that at any drug dose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization excepting hospital admissions due to administrative reasons (e.g., the subject has no transportation home) or hospitalization for elective treatment of a pre-existing condition that did not worsen during the study unless a complication occurs during the hospitalization;
- Results in permanent or significant disability/incapacity; or
- Results in congenital anomaly/birth defect.

Other important medical adverse events may also be considered serious, depending on the judgment of the investigator or the sponsor (e.g., from ICH guidelines, intensive treatment in an emergency room or at home to prevent one of the outcomes listed in this definition, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse). In addition, suspected transmission of infectious agents should always be considered as a SAE.

Note that as defined, serious events (expected or not) are not necessarily causally associated with the study treatment.

12.2. Pre-existing Medical Conditions

Any pre-existing medical condition (including findings from physical examination), which does not worsen in duration, intensity or frequency during the study, is not an AE. These pre-existing medical conditions should be adequately documented in the medical history/current illnesses of the CRF and any other appropriate ancillary documents. Pre-existing medical conditions which worsen after ICF signature will be recorded as an AE on the Adverse Event Form of the CRF.

12.3. Laboratories Abnormalities

During the course of the study, the investigator will be required to comment on any laboratory values outside the normal reference range. A laboratory abnormality should be regarded as an AE and recorded on the Adverse Event Form of the CRF if, according to the investigator's judgment, the value is significantly worse than at pretreatment (where "significantly worse" is defined as Grade 3 or 4 by the CTCAE and has been confirmed by repeat testing, when applicable. In addition, a clinically significant abnormal laboratory test value discovered after ICF signature and that was not previously known should be considered as an AE.

12.4. Guidelines and Evaluation

To promote consistency between assessments, the following guidelines should be taken into consideration along with good clinical judgment when documenting and recording AEs.

12.4.1. Assessment and Recording

An AE, whether or not considered to be causally related to the treatment, must be promptly documented and recorded. At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the appropriate open questions. In addition to straightforward subject observation (e.g., headache, nausea, etc.), AEs will also be documented from any data collected in the CRF (e.g., laboratory values, physical examination findings, ECG changes, etc.) or other documents that are relevant to the safety of the subject.

At each follow-up visit or assessment by phone or otherwise, all AEs, whether observed by the investigator or other professional collaborators, or reported by the subject spontaneously or in response to an open question, will be recorded on the Adverse Event Form included in the CRF with the following information.

- Name of the AE: Name should be a medical term. When possible, the investigator should differentiate an illness entity from isolated symptoms or signs. For instance, the term "flu" should be recorded instead of listing all the flu-related symptoms. Where a differentiation is not possible, symptoms and signs should be separately recorded and evaluated as adverse events.
- Date of onset of the AE.
- Intensity: Event intensity will be assessed according to the CTCAE. If not described in the CTCAE, the intensity should be assessed according to the following categories: *Mild* (noticeable to the subject, does not interfere with the subject's daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study); *Moderate* (interferes with the subject's daily activities, possibly requires additional therapy, but does not require discontinuation of the study); *Severe* (severely limits the subject's daily activities and may require discontinuation of the study); *Life-threatening*; *Death*.
- Date of resolution (or statement that the event is continuing).
- Action taken (e.g., concomitant medication or adjunctive therapy given will be recorded on the Concomitant Medications Form or the Adjunctive Therapy Form of the CRF, respectively).
- Outcome defined as resolved, resolving, ongoing, worsening, death, or unknown.
- Whether the event meets the definition of a SAE (see Section 12.1).

Wherever possible, all AEs, regardless of the seriousness, must be followed through resolution. The completeness and accuracy of the Adverse Event Form will be checked by the study monitor who visits the site.

12.4.2. Causality Assessment

Part of the adverse event documentation will involve the investigator making a causality assessment. To promote consistency between investigators, the following guidelines should be taken into consideration along with good clinical judgment when determining the relationship of Photofrin®, devices and laser light application to adverse event.

The following criteria can be used in order to evaluate the causal relationship between iPDT-Photofrin® and the AE.

NO REASONABLE POSSIBILITY

- The AE is definitely not associated with iPDT-Photofrin®;
- The AE does not follow a reasonable temporal sequence from iPDT-Photofrin® administration;
- The AE does not disappear or decrease on discontinuation of iPDT-Photofrin® (dechallenge) and/or does not reappear or increase on repeated exposure (rechallenge);
- The AE is reasonably explained by known characteristics of the subject's clinical state, history, environment, other therapy administered to the subject (drug or non-drug); and/or
- The AE may be caused by reasons other than administration of iPDT-Photofrin®.

REASONABLE POSSIBILITY

- The AE follows or may follow a reasonable temporal sequence from iPDT-Photofrin® administration;
- The AE disappears or abates upon discontinuation of iPDT-Photofrin® (dechallenge) and/or reappears or worsens on repeated exposure (rechallenge);
- The AE cannot be reasonably explained by known characteristics of the subject's clinical state, history, environment, other therapy administered to the subject (drug or non-drug); and/or
- The AE is a known effect of iPDT-Photofrin®.

12.4.3. Reporting Requirements

12.4.3.1. Serious Adverse Events

All SAEs, regardless of relationship to study treatment, must be reported by the investigator to the sponsor-designated third party, Mapi Group (UK), by completing the SAE form within 24 hours of awareness. This includes SAEs occurring as soon as the subject signs the informed consent (i.e., pre-treatment SAEs). Serious Adverse Events which could be associated with the study procedures and which could modify the conduct of the study are reportable within 24 hours. In addition, any spontaneously reported SAE that occurs within 30 days after the last study procedure for subjects who completed the study protocol or within 90 days after the Photofrin® injection for subjects who prematurely discontinued study treatment should be reported using the SAE form.

The SAE form should be completed as thoroughly as possible, given the information available and time constraints. Upon completion, the SAE form should be signed by the investigator or sub-investigator and faxed or emailed to the designated drug safety group.

Conventional paper-based SAE Form will be provided in the Investigator Study File (ISF). The form will also be electronically available.

Death and surgery should not be reported as an event. Death and surgery are viewed as an outcome of an event, rather than the event itself. In cases where the cause of death is unknown, death may be initially reported as an event. Every attempt should be made to submit a follow-up report identifying the cause of death.

All SAEs will be monitored by Concordia Laboratories Inc. or designee in real time throughout the study.

12.4.3.2. *Adverse Events*

All AEs will be reported on the Adverse Events Form of the CRF.

12.4.3.3. *Pregnancy*

Pregnancy will be recorded and reported within 24 hours to the sponsor designee. Any pregnancy that occurs to study subjects or their partners during the study should be recorded and reported using the appropriate pregnancy surveillance form provided in the ISF. Pregnancy's outcome should also be reported. When the newborn is healthy, additional follow-up is not needed. In case of health problem in the newborn, follow-up must be performed and the investigator will provide follow-up information concerning the outcome of pregnancy within 24 hours of awareness.

12.4.3.4. *Other Reportable Events*

The following should be recorded and reported on the appropriate form provided in the ISF:

- Drug abuse and overdose with or without AEs. An overdose is a dose higher than that prescribed by a health care professional for clinical reasons. It is up to the participating investigator to decide whether a dose was an overdose;
- Inadvertent or accidental exposure to Photofrin® with or without an AE;
- Any other medication errors (including dispensing errors such as inadvertent use of expired medication and dosing errors) with or without an AE;
- Suspected transmission of an infectious agent.

12.5. Follow-Up and Final reports

The clinical condition of subjects who have had a SAE must be followed until all parameters, including laboratory values, have either returned to normal or to baseline value or are otherwise explained or judged acceptable by the investigator. Follow-up and/or Final Reports, including information on the action taken and the outcome, must be sent to the sponsor.

In the event of death, any post-mortem findings (including histopathology and an autopsy report) must be provided to the sponsor.

If the follow-up information is received after the last study procedure or last Photofrin® administration, this information will not be recorded in the CRF but should be provided to the sponsor using the SAE form provided in the ISF.

12.6. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be formed of four experts (three clinicians and one statistician) all of whom are independent of the sponsor and the investigators conducting the study. The DSMB will independently review safety data and, if needed, recommend any changes to the conduct of the study for safety reasons. The DSMB will also review the final analyses.

12.7. Regulatory Aspects

Concordia Laboratories Inc. has a legal responsibility to notify the Health Products and Food Branch (HPFB) of Canada, the FDA of the USA, European Medicines Agency (EMA), National Competent Authorities and Central Ethics Committees of European Union, and all other foreign regulatory agencies as well as all study sites about the safety of Photofrin®.

The investigator has the responsibility to notify the local Ethics Committee about SAEs. Copies of the notification to the ethics committee must be sent to the sponsor.

13. UNANTICIPATED PROBLEMS

13.1. Definition

An unanticipated problem is defined as any occurrence that may negatively affect the subject and/or the study conduct and that is not in accordance with the approved study documents. The unanticipated problem can be related to a specific subject or to the whole site.

13.2. Categories of Unanticipated Problems

Unanticipated problems should be classified in at least one of these categories:

Categories of Unanticipated problems

Risk	Definition	Example
Physical risk	Unanticipated problem that may jeopardize the physical health of the subject.	Potential physical hazard associated with the participation of subject(s) to the study such as building refection and/or use of dysfunctional medical material.
Psychological risk	Unanticipated problem that may jeopardize the psychological health of the subject.	Pressure coming from another health professional and/or subject(s) relative regarding the participation of subject(s) to the study.
Economic risk	Unanticipated problem that may negatively impair the economic status of the subject.	Unplanned financial burden for subject(s) due to loss of income or expenses related to the study conduct (e.g., travelling to another site for a study procedure, etc.)
Social risk	Unanticipated problem that may negatively impair the social behavior of the subject.	More frequent and/or unplanned follow-up visit(s) and/or procedure(s) affecting subject(s) social life.
Other	Unanticipated problem that may represent a risk to the subject (other than physical, psychological, economic and/or social) or that may jeopardize the study conduct.	Partial or total loss of subject(s) confidential information.

13.3. Reporting of Unanticipated Problems

Unanticipated problems identified during the course of the clinical study should be reported to the sponsor within 24 hours of awareness using the appropriate form of the CRF. Occurrences meeting the definition of adverse event (see Section 12.1) should be reported as an adverse event (Adverse Event form of the CRF) and not as unanticipated problem. For site-related unanticipated problem, the data will be entered under only one subject and will be identified as site-specific on the unanticipated problem form of the CRF.

14. MEASUREMENT OF EFFECTIVENESS

Tumor response, measured according to international criteria proposed by the Modified Response Evaluation Criteria in Solid Tumors (Modified RECIST) criteria (Pennathur *et al.*, 2007) and the immune-related Response Criteria (irRC, Wolchok *et al.*, 2009), will be assessed at Months 3 and 6. Lobar recurrences will be defined as local recurrences. Metastatic recurrence will be defined as both regional nodal recurrence (N1 or N2) and distant systemic metastases. Distant recurrence will be determined by imaging (CT) and confirmed pathologically unless the procedures are considered at high risk.

14.1. Modified RECIST Criteria

Modified RECIST Criteria

Response	CT scan mass size	CT scan mass quality	PET scan*
Complete (2 of the following)	Lesion disappearance (scar) or < 25% original size	Cyst cavity formation; low density	SUV < 2.5
Partial (1 of the following)	> 30% Decrease in the sum LD of target lesions	Mass central necrosis or central cavity with liquid density	Decreased SUV or area of FDG uptake
Stable lesion (1 of the following)	< 30% Decrease in the sum LD of target lesions	Mass solid appearance, no central necrosis or cavity	Unchanged SUV or area of FDG uptake
Progression (2 of the following)	Increase of > 20% in sum LD of target lesions	Solid mass, invasion adjacent structures	Higher SUV or larger area of FDG uptake

CT, Computed tomography; PET, positron emission tomography; SUV, standardized uptake value of fluorodeoxyglucose F18; FDG, fluorodeoxyglucose F18; LD, lesion diameter. *Positron emission tomographic scan done selectively.

14.2. Best Overall Response (irRC)

The irRC are derived from WHO criteria. The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
- irPR, decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden ≥ 25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

15. DATA MANAGEMENT AND STATISTICS

15.1. Sample Size/Power Considerations

This study is designed to explore the safety and feasibility of using navigational bronchoscopy for iPDT and to perform secondary, non-statistical, evaluation of effectiveness, overall morbidity/mortality, and effects on the immune system. The intent of this study is to enroll 20 subjects. This sample size has the following precision for estimation of rates of AE's of special interest (AESI). The following table shows historical AE rates for RFA ranging from <1 to ~50%.

AESI	Rate observed with RFA
Pneumothorax	11-52%
Pleural effusion	6-19%
Hemorrhage	6-18%
Pulmonary artery pseudoaneurysm	0.2%
Needle tract seeding	0.3-0.7%
Cavitation	14%
Bronchopleural fistula	0.6%
Pneumonitis	0.4%

The sample size of N=20 has precision for estimation of AE rates for estimates ranging from <0.01 to ~0.5 as shown in the following list. Precision is measured by 1-sided 95% upper confidence limit (CL) on the estimated AE rate via exact binomial distribution. PDT is expected to have lower AE rates than RFA, so, for example, for a RFA historical rate of 0.15 (15%), if no such AE's are observed on PDT, then the TRUE underlying PDT rate is lower than 0.15 with 95% confidence since the upper 95% CL is 0.14 - indicated by "*" in the list below.

No. of AESIs	Rate	Upper 1-sided 95% confidence limit
0	0.00	0.14*
1	0.05	0.22
2	0.10	0.28
3	0.15	0.34
4	0.20	0.40
5	0.25	0.46
6	0.30	0.51
7	0.35	0.56
8	0.40	0.61
9	0.45	0.65
10	0.50	0.70

For assessment of feasibility, the above calculations also apply to precision for estimating feasibility rate. In addition, the success criterion for assessment of feasibility will be at least 40% (8 of 20 subjects) cases yielding feasibility. If the TRUE underlying feasibility rate is 50%, which is the minimum target, then observing 7 or fewer feasible cases out of 20 would have a probability

0.13 or less. Observing 8 or more would have a probability of at least 0.25. Hence, this feasibility success criterion has adequate statistical performance characteristics.

Minor hemoptysis or expectoration of blood, is an expected complication following bronchoscopy. Massive hemoptysis is defined as expectoration of a blood volume that equals or exceeds the anatomical dead space of the airway, which is estimated to be 150 mL. By definition, massive hemoptysis represents a grade 4 toxicity, which is life-threatening. Grade 4 (life-threatening) or grade 5 (fatal) hemoptysis will result in immediate discontinuation of the entire clinical study.

15.2. Data Collection and Case Report Form Monitoring

In the USA, prior to CRF and chart review, the study monitor will confirm that each subject has signed a Health Insurance Portability and Accountability Act (HIPAA)-compliant consent form or a HIPAA supplement to the consent form.

All data will be collected using ProtocolFirst (P1) Electronic Data Capture (EDC) system. The Web-based system will be in compliance with regulations and will consist of an electronic CRF to handle collection of all data. The set-up of the Web-based system will be executed by P1. A completion guideline will be developed to provide guidance to study site personnel on how to record data in the electronic case report form (eCRF).

A detailed monitoring plan will be developed to ensure the quality of the data. The progress of the study will be monitored by on-site and telephone communications between the investigator and personnel from the sponsor and/or designee. On-site visits would be performed at intervals deemed necessary to ensure compliance with the study protocol, to review the subject CRFs against the source documents as described below, to ensure that adequate records of clinical study supplies are maintained and to assess the continued suitability of the site. The investigator will permit direct access to paper/electronic source data/documents. If access to electronic Medical Records not granted due to institution's policy, the investigator will print and provide paper source bounded and signed.

The CRFs must be kept up-to-date, always reflecting the latest observations on the subjects enrolled in the study.

15.3. Source Documents

All individual entries in the source need signature and date by the authors. All typed or dictated documents and computer printouts must be signed and dated by the investigator to confirm review.

Preliminary and/or fax copies of laboratory reports must be initialed and dated, and need to be retained. Final laboratory reports should be signed and dated by the investigator to confirm review. Original laboratory reports should be kept in file.

The following are considered to be source documents, but not limited to:

- Medical charts, clinic charts, nurses' notes, medical correspondence regarding the subject;
- Subject progress notes;
- ECG tracing, X-ray reports, CT scans;
- Pathology reports;
- Quality of life questionnaires;
- Laboratory reports;
- Study worksheets; and/or
- Electronic (paperless) hospital reporting systems – the investigator must sign and date a hard copy of this data for this to be considered a source document.

15.4. Data Validation

A detailed validation plan will be developed to ensure the quality of the data. The Web-based system will integrate data discrepancy management and resolution with audit trails. The CRF will be validated through extensive data checking and query processing capabilities. Capabilities will include generating open queries and routing answers.

15.5. Data Analysis

15.5.1. Samples for Analysis

15.5.1.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will be defined as all enrolled subjects.

15.5.1.2. Safety Population

The Safety Population will be defined as all enrolled subjects who received the Photofrin® injection.

15.5.2. Analysis of Baseline, Disposition, and Demographic Data

Baseline and subject demographic information will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum) for quantitative variables (e.g., weight) and counts and percentages for categorical variables (e.g., sex). Subject demographics and selected baseline information will be summarized for the Safety Population.

The frequency and percent of subjects who enroll in the study, complete the study, or discontinue the study prior to completion will be summarized.

15.5.3. Safety Analysis

Safety analysis will be performed on the Safety Population.

The number and percentage of subjects with normal and abnormal findings will be provided for each physical examination in a shift table comparing screening and the end of study evaluation.

Vital signs will be summarized descriptively (mean, standard deviation, median, minimum and maximum). Change from baseline will also be summarized.

Skin photosensitivity is an adverse event of special interest and will be summarized separately from other adverse events at each safety assessment. Changes in skin will be assessed by grade of erythema, edema and blistering. The data will be tabulated by CTCAE grade in the Dermatology/Skin category.

Descriptive statistics for each clinical laboratory test will be presented for the baseline and the end of study assessment. Change from baseline will also be summarized. According to the laboratory normal ranges, laboratory test results will be categorized as low (< lower limit of normal, LLN), normal (within normal range), and high (> ULN). Shift tables, comparing the distributions of these three categories at baseline versus the end of study assessment, will be presented.

Concomitant medications will be coded using the WHO Drug dictionary. Medications initiated prior to start of treatment and maintained during the study, or taken during the course of the study will be considered as concomitant medications. Concomitant medications will be summarized according to the preferred terms only.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who experienced any AEs as well as serious AEs will be presented by system organ class (SOC) and by preferred term (PT) within SOC. All AEs will be similarly presented by intensity (mild, moderate, severe or using the CTCAE grading system) and by relationship to treatment (reasonable possibility/no reasonable possibility). One-sided 95% confidence limit will be computed for each AE percentage via exact binomial method (Clopper-Pearson, 1934).

15.5.4. Effectiveness Analysis

The secondary efficacy endpoints will involve the assessment of the tumor response, performance status, and quality of life.

15.5.4.1. Objective tumor response rate

The objective tumor response rate will be estimated based on the crude proportion of subjects who achieve an objective response (a Complete Response [CR] or a Partial Response [PR]) during the study using the Modified RECIST criteria and the irRC. The estimate will be accompanied by an exact 2-sided 95% confidence interval. All ITT subjects will be included in the analysis of the response rate.

15.5.4.2. Performance status

The performance status will be assessed using the ECOG score. The number and percent of subjects under each ECOG category and change from baseline will be tabulated at each time point.

15.5.4.3. Quality of Life

The quality of life will be assessed using the SF-36 score, the QLQ-C30, and the QLQ-LC13.

Descriptive statistics on the actual values and the change from baseline will be summarized at each time point.

15.5.5. Exploratory Analysis

Quantification of each immunology marker will be tabulated, graphically displayed, and used to assess whether there is a correlation between the immunological change and the treatment. The exploratory analysis will be conducted with results addressed through an addendum to the main report once they are available.

16. STUDY ADMINISTRATION

The study will be administered by and monitored by employees or representatives of Concordia Laboratories Inc. Designated Clinical Research Associates (CRAs) will visit each site on a periodic basis and perform verification of source documentation for each subject. The sponsor will be responsible for ensuring timely reporting of expedited SAE reports to regulatory agencies, IRB/REBs, and investigators, as applicable by local regulations.

16.1. Investigator Responsibilities

The investigator undertakes to perform the study in accordance with ICH Guidelines per GCPs and the applicable regulatory requirements. It is the investigator's responsibility to ensure that adequate time and appropriate resources are available at the investigational site prior to commitment to participate in this study. The investigator should also be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the investigator and sub-investigator(s) will be provided to the sponsor (or its designee) before starting the study.

Before study initiation, each investigator must provide the protocol signature page and a fully executed and signed Form FDA 1572 to the sponsor or their representative. Financial Disclosure Forms must be completed by all investigators and sub-investigators who will be directly involved in the treatment or evaluation of research subjects in this study. The investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study following information; any significant payments of other sorts from Concordia Laboratories Inc. such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in Photofrin®; any significant equity interest in Concordia Laboratories Inc. as defined in the US Code of Federal Regulations (21 CFR 54 2(b)).

In consideration of participation in the study, Concordia Laboratories Inc. will pay the investigator, or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

16.2. Protocol Adherence and Investigator Agreement

The investigator must adhere to the protocol as detailed in this document. The investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. The investigators will be required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

It is the investigator's responsibility to communicate with their local IRB/REB to ensure accurate and timely information is provided at all phases during the study. In particular, the

appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB/REB must be informed of study completion. The reason for any deviation in the visit schedule must be documented in the CRFs.

16.3. Subject Confidentiality

Subjects will be identified by unique identification code. Their names will not be disclosed in any publication or presentation of results.

16.4. Study Files and Source Documents

The investigator must maintain adequate and accurate clinical trial documentation to ensure protocol procedures were adequately performed and provide documentation that study data was appropriately collected and accurately entered into the eCRF. The investigator will ensure that all study files are maintained, including IRB/REB-approved study protocol and amendments, IRB/REB-approved consent forms, inventory records, and all other required regulatory documents.

All individual entries in the source need signature and date by the authors. All typed or dictated documents and computer printouts must be signed and dated by the investigator to confirm review. Preliminary and/or fax copies of laboratory reports must be initialed and dated, and need to be retained. Final laboratory reports should be signed and dated by the investigator to confirm review. Original laboratory reports should be kept in file. Examples of source documents are provided in Section 15.3.

16.5. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, a quality assurance audit may be conducted. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by Concordia Laboratories Inc., its designees, and/or auditor/inspector. In signing this protocol, the investigator understands and agrees to give access to the necessary documentation and files.

16.6. Publications

All information concerning the study and related to Concordia Laboratories Inc. operations, such as patent applications, manufacturing processes, basic scientific data, assay methods, and formulation information supplied by Concordia Laboratories Inc. and not previously published, is considered confidential by Concordia Laboratories Inc. and shall remain the sole property of Concordia Laboratories Inc. The investigator agrees to only use this information for the purpose of undertaking this study and will not use it for any other purpose without prior written consent

from Concordia Laboratories Inc.

Concordia Laboratories Inc. is committed to ensure that publications of all of its clinical study results in biomedical journals are done in a timely manner, regardless of the Results. Publications should follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals (http://www.icmje.org). Concordia Laboratories Inc. is committed to ensuring that authorship for all publications comply with the criteria defined by the ICMJE.

Since this is a multicenter study, a study publication group composed of different investigators with a key involvement in the Study and representatives of Concordia Laboratories Inc.'s Clinical Department (the "Study Publication Group"), will be created and it will be the Study Publication Group's responsibility to identify the individuals who accept direct responsibility for the primary abstract and/or manuscript (the "Primary Manuscript"). These individuals should fully meet the criteria for authorship referred to above. Other members of the Study Publication Group should be listed in the acknowledgments if and as appropriate. The development, review and submission of the Primary Manuscript will be done in accordance with Concordia Laboratories Inc.'s Standard Operating Procedure. Presentation or publication of data subsets from individual institutions participating in the multicenter studies ("Individual Manuscripts") should not precede the Primary Manuscript, without Concordia Laboratories Inc.'s prior written consent, unless the Primary Manuscript is not published within twenty four (24) months after the Site close-out visit. All proposed Individual Manuscripts will be submitted to Concordia Laboratories Inc. at least sixty (60) days prior to submission, for prior review by Concordia Laboratories Inc.

- to allow Concordia Laboratories Inc. to identify any Confidential Information, excluding Results, which must be removed from the Individual Manuscript prior to publication or presentation;
- to ensure accuracy of the data and analyses being published or presented, and
- to allow Concordia Laboratories Inc. to identify any information requiring intellectual property protection prior to publication or presentation.

In the event Concordia Laboratories Inc. identifies any information requiring intellectual property protection, Institution and/or Principal Investigator agrees to delay publication or presentation of the Individual Manuscript for an additional period not to exceed ninety (90) days in order for Concordia Laboratories Inc. to secure appropriate intellectual property protection. Except as otherwise provided under this Section, the Principal Investigator will be under no obligation to modify the Individual Manuscript and will retain full control over its publication, including where it is published. Concordia Laboratories Inc. is authorized to freely use and distribute the Primary Manuscript and Individual Manuscripts as needed, after their publication, without any other obligation. Insofar as required, Concordia Laboratories Inc. is therefore granted a free license for an unlimited duration and territory.

17. APPENDICES

Appendix 17-1 Time and Procedures Schedule

Procedures/Examinations	STUDY TIME									
	S	E	Photofrin® PDT Course		Hospital Discharge[f]	Follow-up				
	Days -14 to -1	Day 0	Injection Day 1	PDT/iPDT 40-50 H		Day 10 (±1 day)	Day 30 (± 3 days)	Phone Call Day 45 (± 3 days)	3 Months (±1 week)	Study Exit 6 Months (±1 week)
Informed Consent	X									
Assess primary diagnosis [a]	X									
Eligibility criteria	X		X							
Demography	X									
Medical and oncologic history	X									
Skin phototype	X									
Vital signs [b]	X		X	X	X	X	X		X	X
Height	X									
Body weight	X		X							
Comprehensive physical examination	X								X	X
Brief physical examination			X	X	X	X	X			
ECOG Status	X		X	X			X		X	X
Chest X-ray [c]	X				X	X	X			
12-lead ECG	X									
CT scan without contrast and evaluation									X	X
Pulmonary function tests and DLCO	X								X	X
Clinical labs [d]	X				X				X	
Serum β-HCG [e]	X								X	
Enrolment		X								
Photofrin® injection			X							
Instructions to subjects		X	X	X	X	X	X	X	X	
iPDT & 48-hour hospitalization				X						
Light Challenge								X		
Quality of Life assessments			X						X	X
Record Adverse Events [g]	X		X	X	X	X	X	X	X	X
Medication/Therapy Assessment [h]	X		X	X	X	X	X	X	X	X
Immunology marker testing			X [i]			X				

S=Screening; E=Enrolment; [a] Radiology/pathology reports must confirm solid tumor and thoracic surgeon must confirm the tumor unresectability; [b] On Day 1, vital signs (pulse, blood pressure, temperature, pulse oximetry, and respiration rate) to be performed prior to Photofrin® injection and repeated at 15 and 30 minutes, 1, 2, 4, and 8 hours after injection. After Day 1, vital signs to be assessed once, prior to all other procedures being performed; [c] If not done up to 90 days prior to ICF signature; [d] Clinical labs to include hematology and chemistry as specified in Appendix 17-4; [e] For females of childbearing potential only, who must agree to use acceptable contraceptive method for 90 days post Photofrin® injection; [f] Subject to be discharged from the 48-hour hospital stay after the Chest X-ray and other safety evaluations indicating that the subject is stable and able to be discharged; otherwise, the subject's hospital stay may be extended to 72 hours or until the subject is stable for discharge; [g] All AEs to be recorded from the time of ICF signature; [h] All medications and adjunctive therapies/procedures to be recorded 30 days prior to screening and throughout the study; [i] Prior to injection.

Appendix 17-2 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Appendix 17-3 Fitzpatrick Skin Type Classification

FITZPATRICK SKIN TYPE	COLOR	SKIN DESCRIPTION
I	Caucasian; blond or red hair, freckles, fair skin, blue eyes	Extremely fair skin Always burns, never tans
II	Caucasian; blond or red hair, freckles, fair skin, blue or green eyes	Fair skin Always burns, sometimes tans
III	Darker Caucasian, light Asian	Medium skin Sometimes burns, always tans
IV	Mediterranean, Asian, Hispanic	Olive skin Rarely burns, always tans
V	Middle Eastern, Latin, light-skinned black, Indian	Moderately pigmented brown skin Never burns, always tans
VI	Dark-skinned black	Markedly pigmented black skin Never burns, always tans

Appendix 17-4 Clinical Laboratory

HEMATOLOGY	CHEMISTRY
Hemoglobin (Hb)	Glucose (random)
Hematocrit (Hct)	Blood urea nitrogen (BUN)
White blood cell (WBC)	Electrolytes: sodium, potassium, chloride
Red blood cell (RBC)	Creatinine
Platelet count	Alkaline Phosphatase (AP)
Prothrombin time (ProT)	Aspartate Aminotransferase (AST)
	Alanine Aminotransferase (ALT)
	Total bilirubin
	Albumin
	Total protein

Appendix 17-5 References

Al-Jaghbeer M, Marcus M, Durkin M, McGuire FR, Iftikhar IH. Diagnostic yield of electromagnetic navigational bronchoscopy. Ther Adv Respir Dis 2016 Mar (Epub ahead of print)

Berman AT, Thukral AD, Hwang WT, Solin LJ, Vapiwala M. Incidence and Patterns of Distant Metastases for Patients With Early-Stage Breast Cancer After Breast Conservation Treatment. Clin Breast Cancer 2013;13(2): 88-94.

Bridgeman VL, Vermeulen PB, Foo S, Bilecz A, Daley F, Kostaras E, Nathan MR, Wan E, Frentzas S, Schweiger T, Hegedus B, Hoetzenecker K, Renyi-Vamos F, Kuczynski EA, Vasudev NS, Larkin J, Gore M, Dvorak HF, Paku S, Kerbel RS, Dome B, Reynolds AR. Vessel co-option is common in human lung metastases and mediates resistance to anti-angiogenic therapy in preclinical lung metastasis models. J Pathol 2016 Nov doi: 10.1002/path.4845.

Brownback KR, Quijano F, Latham HE, Simpson SQ. Electromagnetic navigational bronchoscopy in the diagnosis of lung lesions. J Bronchology Interv Pulmonol 2012;19(2):91-7.

Canadian Product Monograph, 2005.

Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science 2011;25;331(6024):1559-64.

Chang JY, Balter PA, Dong L, Yang Q, Liao Z, Jeter M, Bucci MK, McAleer MF, Mehran RJ, Roth JA, Komaki R. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:967-71.

Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika XXVI, 1934.

Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd Ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5) Suppl:e78S-e92S.

Donington J, Ferguson M, Mazzone P, Handy J Jr, Schuchert M, Fernando H, Loo B Jr, Lanuti M, de Hoyos A, Detterbeck F, Pennathur A, Howington J, Landreneau R, Silvestri G, for the Thoracic Oncology Network of the American College of Chest Physicians and the Workforce on evidence-based surgery of the Society of Thoracic Surgeons. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. Chest 2012;142(6):1620-35.

Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions. Am J Respir Crit Care Med 2007;176(1):36-41.

Fanucchi O, Ambrogi MC, Aprile V, Cioni R, Cappelli C, Melfi F, Massimetti G, Mussi A. Long-term results of percutaneous radiofrequency ablation of pulmonary metastases: a single institution experience. Interac Cardiovasc Thorac Surg 2016;1-8.

Fielding DI, Buonaccorsi G, Cowley G, Johnston AM, Hughes G, Hetzel MR, Bown SG. Interstitial laser photocoagulation and interstitial photodynamic therapy of normal lung parenchyma in the pig. Lasers Med Sci 2001;16(1):26-33.

Friedberg JS, Mick R, Stevenson JP, Zhu T, Busch TM, Shin D, Smith D, Culligan M, Dimofte A, Glatstein E, Hahn SM. Phase II trial of pleural photodynamic therapy and surgery for patients with non-small-cell lung cancer with pleural spread. J Clin Oncol 2004;22(11):2192-201.

Fritz P, Krausa HJ, Blaschke T, Werner Mühlnickel W, Strauch K, Engel-Riedel W, Chemaissani A, Stoelben E. Stereotactic, high single-dose irradiation of stage I non-Small cell lung cancer (NSCLC) using four-dimensional CT scans for treatment planning. Lung Cancer 2008;60(2):193-9.

Furuse K, Fukuoka M, Kato H, Horai T, Kubota K, Kodama N, Kusunoki Y, Takifuji N, Okunaka T, Konaka C, et al. A prospective phase II study on photodynamic therapy with photofrin II for centrally located early-stage lung cancer. The Japan Lung Cancer Photodynamic Therapy Study Group. J Clin Oncol 1993;11(10):1852-7.

Gollnick SO, Brackett CM. Enhancement of anti-tumor immunity by photodynamic therapy. Immunol Res 2010;46(1-3): 216-26.

Hataji O, Yamakado K, Nakatsuka A, Murashima S, Fujimoto H, Nishii Y, Nakahara H, Kobayashi H, Gabazza EC, Taguchi O. Radiological and pathological correlation of lung malignant tumors treated with percutaneous radiofrequency ablation. Intern Med 2005;44(8):865-9.

Hamamoto Y, Kataoka M, Yamashita M, Shinkai T, Kubo Y, Sugawara Y, Inoue T, Sakai S, Aono S, Takahashi T, Semba T, Uwatsu K. Local control of metastatic lung tumors treated with SBRT of 48 Gy in four fractions: in comparison with primary lung cancer. Jpn J Clin Oncol 2010;40(2):125-9.

Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd Ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5) Suppl:e278S-313S.

Jensen KW, Hsia DW, Seijo LM, Feller-Kopman DJ, Lamb C, Berkowitz D, Curran-Everett D, Musani AI. Multicenter experience with electromagnetic navigation bronchoscopy for the diagnosis of pulmonary nodules. J Bronchology Interv Pulmonol 2012;19:195-9.

Kabingu E, Vaughan L, Owczarczak B, Ramsey KD, Gollnick SO. Cd8(+) T cell-mediated control of distant tumours following local photodynamic therapy is independent of Cd4(+) T cells and dependent on natural killer cells. British Journal of Cancer 2007;96(12):1839-48.

Kato H, Furukawa K, Sato M, Okunaka T, Kusunoki Y, Kawahara M, Fukuoka M, Miyazawa T, Yana T, Matsui K, Shiraishi T, Horinouchi H. Phase II clinical study of photodynamic therapy using mono-L-aspartyl chlorin e6 and diode laser for early superficial squamous cell carcinoma of the lung. Lung Cancer 2003;42(1):103-11.

Kato H. Our experience with photodynamic diagnosis and photodynamic therapy for lung cancer. JNCCN 2012;10 (Suppl 2): S3-S8.

Katsimbri PP, Bamias AT, Froudarakis ME, Peponis IA, Constantopoulos SH, Pavlidis NA. Endobronchial metastases secondary to solid tumors: report of eight cases and review of the literature. Lung Cancer. 2000;28(2):163–70.

Kennecke H, Yerushalmi R, Woods R, Cheang MCU, Voduc D, Speers CH, Nielsen TO, Gelmon K. Metastatic behavior of breast cancer subtypes. J Clin Oncol 2010;28(20):3271-7.

Lagerwaard FJ, Verstegen NE, Haasbeek CJA, Slotman BJ, Paul MA, Smit EF, Senan S. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiation Oncol Biol Phys 2012;83(1):348-53.

Lanuti M, Sharma A, Digumarthy SR, Wright CD, Donahue DM, Wain JC, Mathisen DJ, Shepard JO. Radiofrequency ablation for treatment of medically inoperable stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2009;137(1):160-66.

Lischalk JW, Malik RM, Collins SP, Collins BT, Matus IA, Anderson ED. Stereotactic body radiotherapy (SBRT) for high-risk central pulmonary metastases. Rad Oncology 2016;11: 28-37.

Loo FL, Halligan AM, Port JL, Hoda RS. The emerging technique of electromagnetic navigation bronchoscopy-guided fine-needle aspiration of peripheral lung lesions: promising results in 50 lesions. Cancer Cytopathol 2014;122(3):191-9.

Marchioni A, Lasagni A, Busca A, Cavazza A, Agostini L, Migaldi M, Corradini P, Rossi G. Endobronchial metastasis: An epidemiologic and clinicopathologic study of 174 consecutive cases. Lung Cancer 2014;84: 222-8.

National Comprehensive Cancer Network (NCCN). Breast cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Version 2.2016, 2016.

National Comprehensive Cancer Network (NCCN). Colon cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Version 1.2017, 2016.

National Comprehensive Cancer Network (NCCN). Kidney cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Version 2.2017, 2016.

National Comprehensive Cancer Network (NCCN). Non-small cell lung cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Version 2.2017, 2016. V3.2016, 2015.

National Comprehensive Cancer Network (NCCN). Rectal cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Version 2.2017, 2016.

Nozawa H, Sunami E, Nakajima J, Nagawa H, Kitayama J. Synchronous and metachronous lung metastases in patients with colorectal cancer: A 20-year monocentric experience. Exp Ther Med 2012;3(3): 449-56.

Okunaka T, Kato H, Tsutsui H, Ishizumi T, Ichinose S, Kuroiwa Y. Photodynamic therapy for peripheral lung cancer. Lung Cancer 2004;43(1):77-82.

Okunieff P, Petersen AL, Philip A, Milano MT, Katz AW, Boros L, Schell MC. Stereotactic Body Radiation Therapy (SBRT) for lung metastases. Acta Oncol. 2006;45(7):808-17.

Pennathur A, Luketich JD, Abbas G, Chen M, Fernando HC, Gooding WE, Schuchert MJ, Gilbert S, Christie NA, Landreneau RJ. Radiofrequency ablation for the treatment of stage I non-small cell lung cancer in high-risk patients. J Thorac Cardiovasc Surg 2007;134(4):857-64.

Pizova K, Tomankova K, Daskova A, Binder S, Bajgar R, Kolarova H. Photodynamic therapy for enhancing antitumour immunity. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2012;156(2):93-102.

Takeda A, Enomoto T, Kunieda E. Subclinical interstitial lung disease: Is it a risk factor for fatal radiation pneumonitis following stereotactic body radiotherapy? Lung Cancer 2014;83(1):112.

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92(3):205-16.

Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303(11):1070-6.

US Package Insert, 2011.

Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest 2012;142(2):385-93.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res 2009;15(23):7412-20.

Wisnivesky JP, Yung RC, Mathur PN, Zulueta JJ. Diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways: Diagnosis and management of lung cancer, 3rd Ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5) Suppl:e263S-77S.

Zhang W, Chen S, Dong X, Lei P. Meta-analysis of the diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules. J Thorac Dis 2015;7(5):799-809.

Zimmermann FB, Geinitz H, Schill S, Grosu A, Schratzenstaller U, Molls M, Jeremic B. Stereotactic hypofractionated radiation therapy for stage I non-small cell lung cancer. Lung Cancer 2005;48(1):107-14.