Achieving Clinically Proven Treatment Results With Photodynamic Therapy (PDT) and PHOTOFRIN® (porfimer sodium) for Injection

Photodynamic Therapy (PDT) Is a Guideline-Recommended Endobronchial Therapy[1]

PDT is one of the most studied endobronchial treatment modalities[2]

PDT IN DIFFERENT STAGES OF NON-SMALL CELL LUNG CANCER (NSCLC)

- It is one of the modalities for definitive therapy for carcinoma in situ and microinvasive (superficial) NSCLC[3]
- Symptomatic management Stage I or II[4,5]
- Can be used for induction for Stage IIIA or IIIB[5]
- Palliation[6]

THERAPY FOR RECURRENCE[1]

Locoregional Recurrence

Endobronchial Obstruction	Severe Hemoptysis
Laser/Stent/Other Surgery* External-beam RT or Brachytherapy† PDT	External-beam RT or Brachytherapy† Laser or PDT or Embolization Surgery

Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-Small Cell Lung Cancer. Version 7.2015.
** See Principles of Surgical Therapy (NSCL-B).*
† See Principles of Radiation Therapy (NSCL-C).

Important Safety Information About PHOTOFRIN® (porfimer sodium) for Injection

- PHOTOFRIN® should not be used in patients with porphyria
- Photosensitivity and Ocular Photosensitivity: Observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days. Instruct patients when outdoors to wear dark sunglasses which have an average light transmittance of <4% for at least 30 days and until ocular sensitivity resolves.
- Other photosensitizing agents may increase the risk of photosensitivity reaction.

This is not a full list of risks and side effects. See important prescribing and safety information for PHOTOFRIN® (porfimer sodium) for Injection on Page 10. Talk to your health care provider and read the patient labeling for more information on **www.photofrin.com**

References quoted may have used settings not within the prescribing information for PHOTOFRIN® (porfimer sodium) for Injection.

PDT with PHOTOFRIN® [porfimer sodium] for injection

The Three Components of Photodynamic Therapy (PDT)

PDT with PHOTOFRIN® [porfimer sodium] for injection

1. PHOTOFRIN® (porfimer sodium) for Injection

PHOTOFRIN® (porfimer sodium) for Injection is injected several days prior to laser activation, where it's selectively retained in tumor cells. When activated with red laser light, the drug produces a chain reaction of cell death in targeted tissue, with low collateral damage to healthy tissue.

2. Fiber

The Optiguide Fiber Optic Diffuser Series have a range of fiber diffuser lengths which enables the red laser light delivery to multiple tumor sizes. The series includes the Flexible Diffuser, with a flexible yet durable material to ease navigation through instruments and anatomy.

OPTIGUIDE™ FIBER OPTIC

Flexible Diffuser

Rigid Diffuser | Flexible Diffuser

3. Laser

The laser generates 630 nm wavelength red non-thermal laser light necessary for PHOTOFRIN® activation.

PHOTOFRIN®
630 PDT Laser

PHOTOFRIN® (porfimer sodium) for Injection Photodynamic Therapy (PDT) Timeline

DAY 1

Administration
Typically used in an outpatient setting, PHOTOFRIN® (porfimer sodium) for Injection is reconstituted and administered as a single IV injection over 3 to 5 minutes.

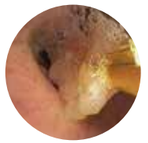
Targeted Retention
PHOTOFRIN® for Injection is selectively retained in cancer cells.

DAY 3

Laser Application
An OPTIGUIDE® Fiber Optic Diffuser is used to administer 630 nm nonthermal light.

Excited PHOTOFRIN® (porfimer sodium) for Injection causes vasoconstriction, which leads to vascular occlusion and additional tumor cell death.[7]

DAY 5



Debridement
Removal of post treatment necrotic tissue.

Important Safety Information About PHOTOFRIN® (porfimer sodium) for Injection (Continued from Page 1)

- Emergency treatment of patients with severe acute respiratory distress caused by an obstructing endobronchial lesion because 40 to 50 hours are required between injection of PHOTOFRIN® and laser light treatment
- Use Before or After Radiotherapy: Allow 2-4 weeks between PDT and subsequent radiotherapy.

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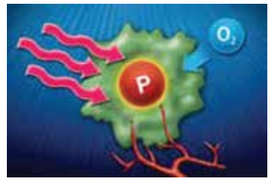
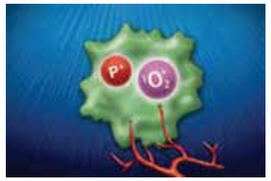
ACTIVATION



Red light permeates tissue (the indicated light dosimetry for endobronchial cancer is 200 J/cm) and activates PHOTOFRIN® to an excited state.[7]



Energy transfer generates reactive singlet oxygen[7] and selective necrosis of the target lesion up to a 6-mm depth.[8]

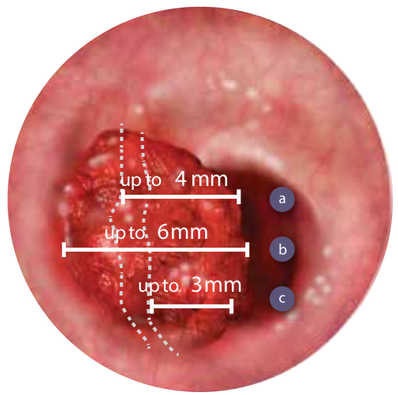
DESTRUCTION OF CANCER CELLS

Excited PHOTOFRIN® causes vasoconstriction, which leads to vascular occlusion and additional tumor cell death.[7]

Treatment results in lysis and ischemic necrosis of cancer cells.[7] Cleanout bronchoscopy is performed to remove obstructive debris.

PDT Makes Selective Treatment of Target Lesions and Tumor Margins Possible Up to a Depth of 6 mm[8]

PDT provides depth of ablation—up to 6 mm.



A. Cryotherapy

B. PDT with PHOTOFRIN® (porfimer sodium) for Injection

C. Argon Plasma (30-90W)

Important Safety Information About PHOTOFRIN® (porfimer sodium) for Injection (Continued from Page 1)

Important Warnings and Precautions using PHOTOFRIN® include:

- Chest Pain: Substernal chest pain can occur
- Airway Obstruction and Respiratory Distress: Administer with caution to patients with tumors in locations where treatment-induced inflammation can obstruct the main airway. Monitor patients closely between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress.
- Hepatic and Renal Impairment: Patients with hepatic or renal impairment may need longer precautionary measures for photosensitivity.
- Thromboembolism: Thromboembolic events can occur.

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ESTIMATED DEPTH OF DAMAGE FOR VARIOUS METHODS OF ENDOSCOPIC MUCOSAL ABLATION[8]

Method of ablation	Approximate depth of ablation (mm)	Author/ref
Argon laser (514 nm)	0.3	Weston 2003
KTP laser (532 nm)	0.4	Dix 1996
Diode laser (805 nm)	1.3	Dix 1996
Nd:YAG laser (1064 nm)	4-6	Dix 1996
APC (30–90 W)	1-3	Barham 1996, Franchimont 2003
MPEC 15–20 W	1.7–4.8	Sampliner 2003
ALA PDT	2	Tan 1999, Gossner 1990
Exogenous PDT	4-6	Barr 1990, Heier 1995
Cryotherapy	1-4	Johnston 2003

KTP, potassium titanyl phosphate; Nd:YAG, neodymium yttrium aluminium garnet; APC, argon beam plasma coagulation; MPEC, multipolar electrocoagulation; ALA PDT, 5-aminolevulinic acid photodynamic therapy.

Benefits of Photodynamic Therapy (PDT)

TUMOR RESPONSE AND ATELECTASIS IMPROVEMENT[7]

Efficacy results from studies in late-stage obstructing endobronchial cancer—all randomized patients*

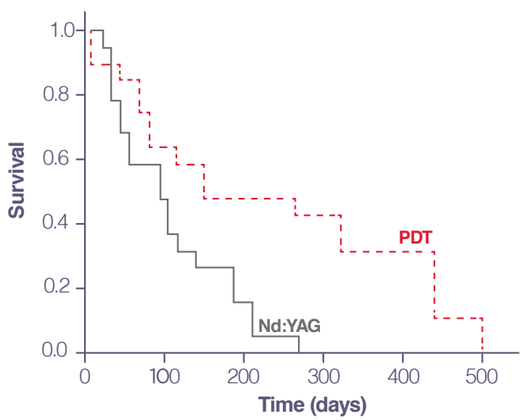
Efficacy parameter	PDT N=102, % patients	Nd:YAG N=109, % patients
Objective tumor response†		
Week 1	59%	58%
Month 1 or later	60%	41%*
Atelectasis improvement‡	**n=60**	**n=71**
Week 1	35%	18%
Month 1 or later	35%	20%

** Statistical comparisons were precluded by the amount of missing data at Month 1 or later (e.g., for tumor response, PDT 28% missing, Nd:YAG 38%).*

† CR+PR where CR=complete response (absence of bronchoscopically visible tumor) and PR=partial response (increase of ≥50% in the smallest luminal diameter; or any appearance of a lumen for completely obstructing tumors).

‡ In patients with atelectasis at baseline.

EXTENDED SURVIVAL AND SYMPTOM IMPROVEMENT COMPARED TO ND:YAG LASER RESECTION[9]



Probability of survival of patients with inoperable non–small cell lung cancer (NSCLC) assigned to photodynamic therapy (---) and Nd:YAG laser resection (—).

Fourteen patients out of 31 with late-stage obstructing endobronchial cancer who were treated with PHOTOFRIN® (porfimer sodium)

- Post treatment survival was significantly longer in the PDT group than in the Nd:YAG laser resection group: 265 days PDT, 95 days Nd:YAG, P=0.007
- Similar improvement in dyspnea, cough, hemoptysis symptoms and sputum production in both groups

IMPROVED PERFORMANCE STATUS AND RESPIRATORY FUNCTION[6]

Stage IIIA-IV Symptom Palliation in Patients With Advanced Inoperable Bronchogenic and Endobronchial Luminal Obstruction

Changes in Bronchial Luminal Obstruction, Pulmonary Ventilation, and Performance Status Following Treatment With PDT[6]*

Parameters	Pre PDT Mean±SD	Post PDT Mean±SD	Changes
% Obstruction	85.8±19.6	18.5±17.3	-67.3%
(% Range)	(30-100)	(0-35)	
FVC (1) L	2.07±0.78	2.50±0.74	+0.43 L
FEV1 (1) L	2.07±0.78	2.50±0.74	+0.43 L
WHO ≤2	N=43	N=87	+44
WHO >2	N=54	N=10	-44

WHO performance status scores summary

0 - Asymptomatic
1 - Symptomatic but completely ambulatory
2 - Symptomatic, <50% in bed during the day
3 - Symptomatic, >50% in bed, but not bedbound 4 - Bedbound
5 - Death

44 patients (81% of WHO >2) move to WHO ≤2

** Study was prospective nonrandomized.*

Multimodality Treatment With Photodynamic Therapy (PDT)

SEQUENCE AND TIMING OF THERAPIES[7,10*]

PDT in combination with	Induction/ Neoadjuvant	Concurrent	Adjuvant	Comments relating to PDT
Nd:YAG/APC	×	×	×	PDT may be beneficial when utilized after Nd:YAG or APC to further enhance local control[10]
Chemotherapy	×	×	×	Avoid overlapping toxicities[10] Ensure/confirm blood cell count normal[10]
Radiation therapy (XRT, EBRT, SBRT, brachytherapy)	×		×	2-4 weeks if PDT is used prior to radiation[7] 4 weeks if radiation is used prior to PDT[7] The timing of PDT is ideal before radiotherapy because of its potential impact on vascular access[7]
Surgery	×		×	Allow 10-12 weeks post PDT for surgical intervention[10]

**PHOTOFRIN® (porfimer sodium) for Injection prescribing information does not include reference to PDT use in conjunction with other treatment modalities besides radiotherapy.*

Important Safety Information About PHOTOFRIN® (porfimer sodium) for Injection (Continued from Page 1)

In clinical studies, the following adverse reactions were reported in at least 10% of subjects receiving PHOTOFRIN® for:

- Obstructing Endobronchial Cancer: Dyspnea, photosensitivity reaction, hemoptysis, pyrexia, cough, pneumonia
- Superficial Endobronchial Tumors: Exudate, photosensitivity reaction, bronchial obstruction, edema, bronchostenosis

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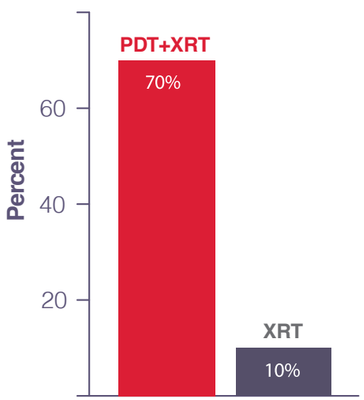
Radiation Treatment and Photodynamic Therapy (PDT)

PDT MAY BE USED WITH RADIATION THERAPY (XRT), WHICH MAY PROVIDE ADDITIONAL BENEFITS[11]

Complete Reopening of Bronchial Lumen
With No Residual Tumor

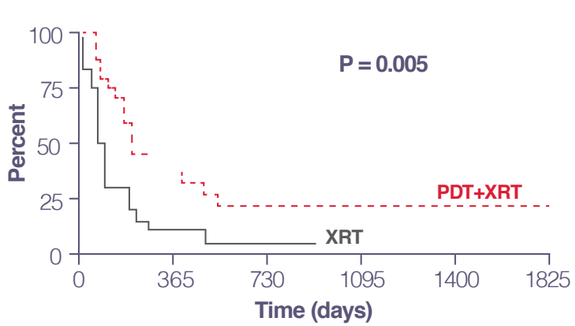


Patients With Inoperable Non–Small Cell Bronchogenic Carcinoma Obstructing a Central Airway

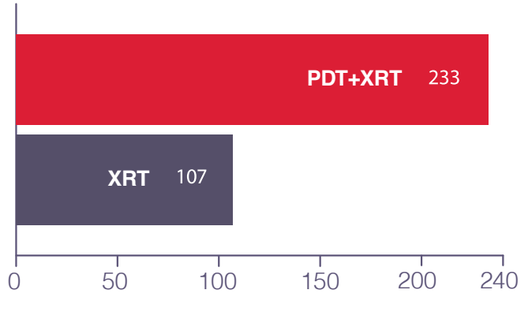
Complete reopening of the bronchial lumen with no gross tumor visible on bronchoscopy was observed in 2 of 21 patients (10%) in the XRT group and 14 of 20 patients (70%) in the PDT+XRT group at 1 and 3 months after treatment (P<0.05).

There were no treatment failures in the PDT+XRT group, but 4 of 21 (19%) patients in the XRT group failed to respond to treatment.

Interval Between Treatment and Local Recurrence



Median Time to Local Recurrence



The median interval between treatment and local recurrence was significantly longer in the PDT+XRT group than in the XRT group (233 days vs 107 days, P=0.005). Palliation of hemoptysis and shortness of breath was significantly better for the PDT+XRT group 3 months after treatment, along with reduction in cough at 1 and 3 months.

Important Safety Information About PHOTOFRIN® (porfimer sodium) for Injection (Continued from Page 1)

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REFERENCES

1. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-Small Cell Lung Cancer. Version 6. 2020. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Published June 15, 2020.

2. 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-e277S. doi:10.1378/chest.12-2358.

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10. PDT Academy, Faculty recommendation, 2020.

11. Lam S, Grafton C, Coy P, Voss N, Fairey R. Combined photodynamic therapy (PDT) using Photofrin and radiotherapy (XRT) versus radiotherapy alone in patients with inoperable obstructive non-small cell bronchogenic carcinoma. Proc. SPIE. 1991;1616:20-28. doi:10.1117/12.137038.

PHOTOFRIN® (porfimer sodium) for Injection Indications

Palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.

Treatment of microinvasive endobronchial non–small cell lung cancer (NSCLC) in patients for whom surgery and radiotherapy are not indicated.

Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial NSCLC.

Ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) patients who do not undergo esophagectomy.

Important Safety Information About PHOTOFRIN® (porfimer sodium) for Injection

PHOTOFRIN® should not be used in patients with porphyria, existing tracheoesophageal or bronchoesophageal fistula, tumors eroding into a major blood vessel, emergency treatment of patients with severe acute respiratory distress caused by an obstructing endobronchial lesion because 40 to 50 hours are required between injection of PHOTOFRIN® and laser light treatment, and esophageal or gastric varices or esophageal ulcers >1 cm in diameter.

IMPORTANT WARNINGS AND PRECAUTIONS USING PHOTOFRIN® INCLUDE:

Gastroesophageal Fistula and Perforation: Do not initiate PHOTOFRIN with photodynamic therapy (PDT) in patients with esophageal tumors eroding into the trachea or bronchial tree or bronchial wall.

Pulmonary and Gastroesophageal Hemorrhage: Assess patients for tumors eroding into a pulmonary blood vessel and esophageal varices. Do not administer light directly to an area with esophageal varices.

High-Grade Dysplasia (HGD) in Barrett's Esophagus (BE): After treatment of HGD in BE, conduct endoscopic biopsy surveillance every 3 months, until 4 consecutive negative evaluations for HGD have been recorded.

Photosensitivity and Ocular Photosensitivity: Observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days. Instruct patients when outdoors to wear dark sunglasses which have an average light transmittance of <4% for at least 30 days and until ocular sensitivity resolves.

Use Before or After Radiotherapy: Allow 2-4 weeks between PDT and subsequent radiotherapy.

Chest Pain: Substernal chest pain can occur

Airway Obstruction and Respiratory Distress: Administer with caution to patients with tumors in locations where treatment-induced inflammation can obstruct the main airway. Monitor patients closely between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress.

Esophageal Strictures: Esophageal strictures can occur

Hepatic and Renal Impairment: Patients with hepatic or renal impairment may need longer precautionary measures for photosensitivity.

Thromboembolism: Thromboembolic events can occur.

Embryo-Fetal Toxicity: May cause embryo-fetal toxicity. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

MOST COMMON ADVERSE REACTIONS reported during clinical trials (>10% of patients) are:

Esophageal Cancer: Anemia, pleural effusion, pyrexia, constipation, nausea, chest pain, pain, abdominal pain, dyspnea, photosensitivity reaction, pneumonia, vomiting, insomnia, back pain, pharyngitis.

Obstructing Endobronchial Cancer: Dyspnea, photosensitivity reaction, hemoptysis, pyrexia, cough, pneumonia.

Superficial Endobronchial Tumors: Exudate, photosensitivity reaction, bronchial obstruction, edema, bronchostenosis.

High-Grade Dysplasia in Barrett's Esophagus: Photosensitivity reaction, esophageal stenosis, vomiting, chest pain, nausea, pyrexia, constipation, dysphagia, abdominal pain, pleural effusion, dehydration.

Other photosensitizing agents may increase the risk of photosensitivity reaction. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with PHOTOFRIN and for 5 months after the last dose.

Please see full Prescribing Information for PHOTOFRIN® (porfimer sodium) for Injection at: www.photofrin.com

FOR MORE INFORMATION about PHOTOFRIN®, or if there are any questions regarding the information provided, visit **www.photofrin.com** or please contact the Medical Information Department at **1-866-248-2039**. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

PDT with PHOTOFRIN® [porfimer sodium] for injection

PINNACLE BIOLOGICS