INFORMATION TO PARTICIPANTS INVOLVED IN RESEARCH

You are invited to participate in

The Prostate Cancer Photodynamic Therapy (PDT) Study

Assessing the effectiveness of photo-dynamic therapy (PDT) for local prostate cancer: supplementary fluorescent photography imaging, urinary proteomics and Circulating Tumour Cell (CTC) analyses

The study will be conducted at the National Institute of Integrative Medicine (NIIM), led by Investigators Donald Murphy (Emeritus Urological Surgeon), A/Prof Karin Ried (Director of Research, NIIM), and Prof Avni Sali (Director, NIIM).

Ethics Approval

This research project has been approved by the National Institute of Integrative Medicine Human Research Ethics Committee on 2 June 2021. The HREC Approval no. is [0087N_2021].

Project explanation and objectives

Prostate cancer is the most common cancer in men, and the second leading cause of cancer deaths (25%) in Australia. There is a need for better treatment combined with reliable assessments of treatment effectiveness.
This 3 month intervention study aims to assess the treatment effectiveness and safety of PDT for patients with biopsy proven prostate cancer using fluorescent photography imaging plus pre / post urinary proteomics (analysis of proteins in the urine) and Circulating Tumour Cell (CTC) specimen analyses.

Photodynamic Therapy (PDT)

Session 1: Step 1: Monday: oral administration of photosensitiser = plant based chlorophyll derivative, sourced from algae, taken 15-20 hours before laser therapy
Step 2: Tuesday: 2x Local laser therapy AM and PM, each time for 25 minutes
Session 2: Step 3: Tuesday: oral administration of photosensitiser as above.
Step 4: Wednesday: 2x Local laser therapy AM and PM, each time for 25 minutes
4 week break between 3+4 / 5+6
Sessions 3+4 /5+6: as above Steps 1-4

For more information about the PDT treatment and the CTC analysis go to:
https://niim.com.au/prostatecancerPDTstudy

This Prostate cancer Treatment study aims to

- To assess the effectiveness of PDT by analysis of CTC, proteins in the urine, and real time fluorescent photographic imaging.
- To assess light-bed treatment as an addition to the laser PDT in a subgroup of participants.
- To assess PDT safety and tolerability.

Who can participate in this study?

1. Men between 50-80 years diagnosed with biopsy proven primary prostate cancer
2. Men diagnosed with local prostate cancer relapse after treatment
3. Not planning other treatment in the next 3 months
4. Not presenting with secondary metastatic prostate cancer
5. Not suffering from porphyria
6. Able to provide informed consent

What will I be asked to do?

1. There will be 8 visits to NIIM over 3 months.
2. The first and the last visit will take about 30 min and will involve blood, urine test, and questionnaires.
3. There will be 12 treatment sessions on 6 days. Participants need to consider 3 x 2 full days for treatment.
The morning (AM) PDT laser session of 25 minutes is followed, after a 4 hours break, by the 2nd afternoon (PM) PDT laser session of 25 minutes. PDT treatment involves either a trans-rectal or trans-urethral probe (for details see page 5).
4. A subgroup of participants will be allocated to a 3rd treatment session with the light bed, after the local PDT laser sessions (details to be discussed).

Table 1: PDT treatment schedule

Visit	*Week*	Session	Weekday / Day	Session Details	Treatment
V1 – 30 min	Before Treatment		Mon-Fri	Baseline	CTC Blood test 1 – pre-treatment Blood PSA Urinary proteomics test 1 - pre-treatment Questionnaires: urinary flow Prostate size: by Urologist's examination – pre-treatment
	1		Monday		Patient to take PDT agent (chlorophyll derived agent 15-20 hours before therapy.) Dose 1
V2 – full day		Session Day 1	Tuesday	2x PDT am and pm sessions (n1 and n2)	PDT each laser 25 min duration (book 1 hr / session) PS Agent Dose 2 taken as above
V3 – full day		Session Day 2	Wednesday	2x PDT am and pm sessions (n3 and n4)	PDT laser 25 min session as above Real time photography 1 of Prostate
			Subgroup (n=25) Light bed	+ 3rd lightbed 4 -24 hours after 2nd pm PDT session (LB 1)	PDT light bed 30 min Real time photography LB 1
	4 week interval				
	5		Monday		Patient to take PDT agent (chlorophyll derived agent 15-20 hours before therapy.) Dose 3
V4 - full day		Session Day 3	Tuesday	2x PDT am and pm sessions (n5 and n6)	PDT laser 25 min session as above. PS Agent Dose 4 taken as above.
V5 – full day		Session Day 4	Wednesday	2x PDT am and pm sessions (n7 and n8)	PDT laser 25 min session as above Real time photography 2 of Prostate
			Subgroup (n=25) Light bed	+ 3rd lightbed 4-24 hours after the pm PDT session (LB 2)	PDT light bed 30 min Real time photography LB 2
	4 week interval				
	9		Monday		Patient to take PDT agent (chlorophyll derived agent 15-20 hours before therapy.) Dose 5
V6 – full day		Session Day 5	Tuesday	2x PDT am and pm sessions (n9 and n10)	PDT laser 25 min session as above. PS Agent Dose 6 taken as above.
V7 – full day		Session Day 6	Wednesday	2x PDT am and pm sessions (n11 and n12)	PDT laser 25 min session as above Real time photography 3 of Prostate
			Subgroup (n=25) Light bed	+3rd lightbed 4-24 hours after the pm PDT session (LB 3)	PDT light bed 30 min Real time photography LB 3
V8 – 30 min	Treatment review Week 12		1 month after last treatment		Post-treatment tests: CTC Blood PSA Urinary unlikely test Questionnaires: Urinary flow, tolerability Prostate size: by Urologist's examination – post-treatment

What will I gain from participating?

The PDT laser treatment may be effective in treating your local prostate cancer. Treatment effectiveness will be assessed with the validated CTC Blood Test, photography and urinary protein tests. However, there may be no benefits to you.

How will the information I give be used?

This study will provide data to further evaluate the clinical benefits of the PDT for Prostate Cancer. Results will be available to your doctor. Results will be written up for submission to a peer reviewed journal and presented at conferences.

What are the potential risks of participating in this project?

Blood test: Blood will be taken by a nurse or experienced phlebotomist. There may be some discomfort in having the blood test due to insertion of the needle. There can also be a risk of fainting when some people have blood taken from them. This risk will be minimised by having you lie down during whilst the blood is being taken. There is a risk of bruising at the site where the needle is inserted. This is minimised by applying pressure over the site with a cotton swab after the needle is taken out, then placing a band-aid over it.

Photodynamic therapy (PDT):
Photosensitiser: The dosages and delivery of the green algal-derived photo-sensitiser agent as well as the spectral range of the energies used, have been shown to be safe in previous studies, with over 10 years usage in China. The water soluble photosensitiser has displayed no systemic toxicity or sun sensitivity. Temporary green oral mucus staining may occur, which clears spontaneously within hours.

Ref 1: Meade B, Sali A, Stephens AS, Rainczuk A, Murphy DL. Journal of Cancer Science and Therapeutics 2018; 1 (2):8.
Ref 2: Ried K, Sali A, Wang M, Meade B, Murphy D. Photodynamic therapy with new sublingual sensitiser PhotosoftE4 for cancer: a case seriesF100Research 2013, 2:161; https://f1000research.com/articles/2-161

PDT laser therapy: All equipment will be safety checked. There have been no safety issues with the equipment in previous studies. Eye protection during the treatment will be provided and ambient light precautions advised during the therapy sessions.
There may be discomfort associated with the internal treatments. The unlikelihood of difficulty emptying the bladder and pain will be appropriately managed. Exposure to natural sunlight is not recognized as a problem with the second generation chemical sensitiser used in/during this study, standard light precautions will however be advised.

Adverse event /Side effects
A slight fever and tiredness occurring 7 days after treatment has also been recorded, relating to the cancer tissue destruction. Urinary flow rates have been stable (IPPS Data) and erectile function unchanged.
Risks of trans-rectal and trans-urethral procedures are minimal, and are outlined in detail on page 5.
Participants are encouraged to report any adverse events or side effects to the research team. The investigators on this study will be available for follow-up of participants.

What are the costs?

There are no costs associated with tests (CTC, urine, blood test) and treatments in this study, listed in Table 1.
Any doctor visits outside of the study may incur costs to you.

Privacy and confidentiality

Your personal data will be known only to your doctor and the study team. All data collected will be de-identified before analysis and stored securely in locked files at the NIIM clinic. No personal data will be divulged in publication.

Conflict of interest declaration

One of the three chief investigators DM is a consultant to and share holder in the company sponsoring this study. DM will not be involved in the recruitment, data collection, and primary data analysis. KR and AS declare no conflict of interest.

Who is conducting the study and who should I contact if I have any questions about participating?

AProf Dr Karin Ried
Director of Research, Principal Investigator
Phone: 03 9912 9545
Email: karinried@niim.com.au

Donald Murphy
Emeritus Urological Surgeon

E: donaldmurphy@mertie.com

Queries or complaints

If you wish to discuss with an independent person matters related to making a complaint, or your rights as a participants, contact the Human Research Ethics Committee's Secretary on hrec@niim.com.au.

FREQUENTLY ASKED QUESTIONS

Photodynamic Therapy (PDT) = Photosensitiser based Laser Treatment

1. Can I have other treatments during therapy?

Yes. Concurrent treatments should be maintained on the advice of the doctor.

2. How long will I be light sensitive?

The oral agents will be active in the skin up to 24 hours with direct sunlight precautions suggested for up to one-week post treatment.
In bright light wear a wide brimmed hat and keep the skin covered. Limit direct sun exposure to 10 to 20 minutes. Walking from the house to the car will be fine.

3. Do I Need Protective Equipment during treatment?

Protective glasses /eye masks are provided during treatment. The laser used, is not on its own, in any way harmful to you other than using precautionary eye protection.

4. What additional side effects may I experience?

You may feel tired during therapy especially during the second week when the tumour size may increase due to the induced inflammatory response.

5. How long will the tumour breakdown continue to occur?

This varies between 2 and 12 weeks.

6. What monitoring of the therapy will occur?

Standard blood tests and urinary flow studies will be performed.

7. Why is it important to fast for two hours before and two hours after therapy?

Fasting preferentially increases the uptake of the oral agents into the cancer cell therefore increasing the effect.

8. What circumstances may cause alteration or cessation of therapy?

The decision to alter therapy will be made on clinical grounds and the patient's well-being.

Details and risks and of trans-rectal and trans-urethral procedures

a. Trans-rectal procedures. A digital rectal examination (DRE) is a standard examination procedure in the medical / surgical assessment of the lower gastro-intestinal tract and is performed by trained medical / nursing personnel prior to any rectal procedure: involving a preliminary explanation of the procedure and informed consent and proceeds the Laser Probe passage. The already prepared glove covered and lubricated laser probe, approximates to the examiner's finger dimensions, contrasting the patient's possible prior experience during a trans-rectal ultrasound probe and biopsy procedure. (TRUS) The probe is held in the selected position by an appropriate external clamp. **The risks are minimal and can be considered as local or general**, with both being reduced by the expertise of the examiner with a well lubricated index finger / probe, the former involving possible discomfort depending on any local pathology and the latter mitigated by an adequate explanation, prior to the examination.

b. Transurethral procedures. This standard methodology again involves a preliminary explanation of the procedure and informed consent, as well as knowing any relevant past history. An appropriately sized, well lubricated urethral catheter is passed via the urethra into the bladder by an appropriate trained medical / nursing attendant. The procedure is performed under sterile conditions with anti-septic skin preparation and draping, assisted by urethral installation of a proprietary prepared syringe of Hibitane and local anaesthetic jelly. The much smaller laser probe is subsequently passed into the bladder, through the inner opening of the catheter and subsequently held in place by the use of medical sticky tape attached to the penile skin. **The risks of this procedure are minimal, but may include initial slight urethral discomfort and blood passage, on voiding after removal of the catheter.**

It is anticipated that the patient will have a spontaneous return to normal urination after each of these treatment techniques, with supervision to this effect and management otherwise, as required.

Experience during the phase 1 study describes only one in 37 of the patients requiring trans-urethral laser therapy, that is less than 3%.

Laser light application.

a. **For prostate gland volumes up to 60 cc,** the patient will have trans-rectal, endo-luminal red light laser illumination of the prostate gland performed via a trans-anal probe, a procedure similar to that performed during prostate trans-rectal ultrasound study or biopsy. The illumination will be for a maximum period of 25 minutes.

b. **For prostate gland volumes greater than 60 cc**, the patient will also have alternating supplemental trans-urethral prostatic laser light treatment. Under sterile conditions and local anaesthetic jelly, a laser probe, emitting red light will be inserted to the level of the prostate gland grade. The illumination will be for a maximum period of 25 minutes. The method of the catheter passage is a standard medical / nursing procedure.

The **laser light activates** the plant based **photo-sensitiser agent** that has concentrated in the **prostate gland cancer cells**.

Cancer cells fluorescent during PDT and this will be studied by **external real-time photography**, as quantitative assessment of the treatment on 3 occasions during the study, on visits 3, 5 and 7. (Week 1, 5 and 9.)

Eye protection provided during the treatment.

Supplemental oxygen by nasal tubes or a mask will be provided during treatment. Oxygen levels in the blood will be monitored by a finger-tip pulse oximeter.

The National Institute of Integrative Medicine Human Research Ethics Committee

STANDARD CONSENT FORM
FOR PEOPLE WHO ARE PARTICIPANTS IN A RESEARCH PROJECT

1. I, …… *(please print name)*

   consent to take part in the research project entitled:

   The Prostate Cancer Photodynamic Therapy (PDT) Study

2. I acknowledge that I have read the attached Participant Information Form entitled:

   The Prostate Cancer Photodynamic Therapy (PDT) Study

3. I have had the project, the risks and potential adverse effects, so far as it affects me, fully explained to my satisfaction by the research assistant. My consent is given freely.

4. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.

5. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.

6. I have been informed that, while information gained during the study may be published, I will not be identified and my personal results will not be divulged.

7. I understand that I am free to withdraw from the project at any time and that this will not affect medical advice in the management of my health, now or in the future.

8. I am aware that I should retain a copy of this Consent Form, when completed, and the attached Information Form.

I can be contacted by phone: _____ or by email:_____

Participant: ……
(signature) *(date)*

Investigator: ……...
(to be signed at appointment) *(signature)* *(date)*