SYLVESTER COMPREHENSIVE CANCER CENTER
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MILLER SCHOOL OF MEDICINE
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Randomized pilot study of treatment for basal cell carcinoma using the multiplex 595/1064 nm laser

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SCHEMA:

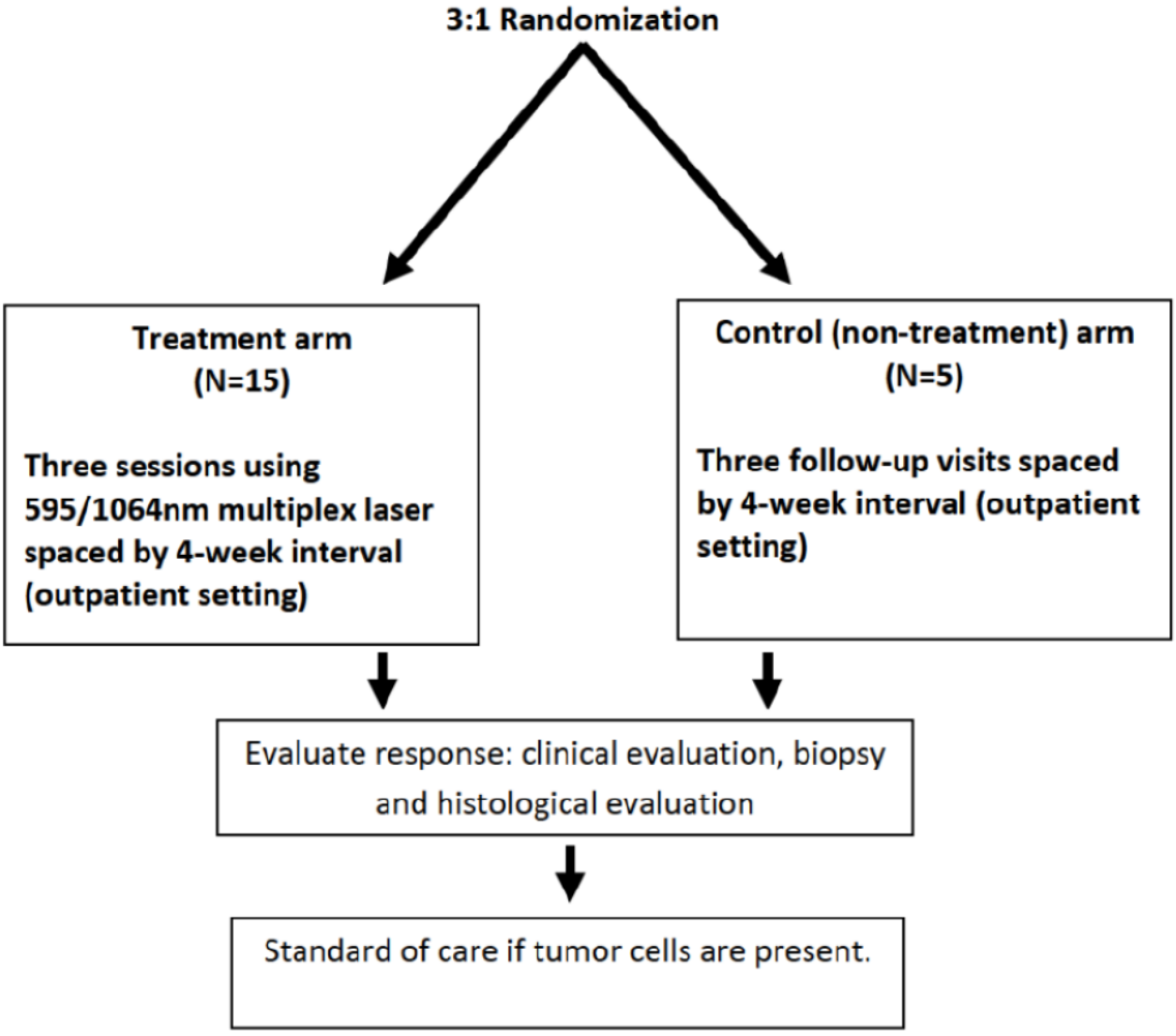
Basal cell carcinoma is a malignancy with significant prevalence that rarely metastasizes but can be locally destructive. Laser therapy for this type of lesion may be a superior option for patients who do not wish to or cannot tolerate other modalities such as topical chemotherapeutics or surgery.

In this pilot study, we will preliminarily assess the efficacy and safety of the 595/1064 nm Multiplex laser when treating superficial and nodular basal cell carcinomas less than 1.5 cm in size. Eligible patients with biopsy-proven superficial or nodular BCCs less than 1.5 cm in size will have the opportunity to enroll in this study. This is an unblinded study in which patients will be randomized to either a treatment arm or a control arm. Patients in the treatment arm will receive three treatments with the 595/1064 nm multiplex laser spaced four weeks apart. In addition to assessing the presence of any adverse effects, photographs will be taken at each visit. One month after the last treatment session, patients in this group will return for evaluation of 1) clinical clearance and 2) histological clearance of their BCC. In order to assess clinical clearance, a dermatologist will grossly examine, measure, and document any residual lesion. Afterwards, a deep excisional biopsy encompassing the entire region will be taken and histological clearance will be determined by a microscopic examination for any residual tumor cells. Follow-up for wound care of the biopsy will occur one week later. Tumor burden will be calculated by change in surface area of the lesion.

After standard diagnostic biopsy, patients in the control arm will be followed for three regular visits, spaced 4 weeks apart. One month after the third follow-up visit, control patients will return for final photography and evaluation of clinical and histological clearance, just as the treatment arm. Although extremely rare[1], if any clinical signs of progression are visible during this period (what we will consider greater than 10% growth), the patient will be withdrawn from the study and will undergo standard of care treatment.

Eligible patients (N=20)

Adult patients with superficial or nodular basal cell carcinoma less than 1.5cm in size on either trunk or extremities.



HYPOTHESIS:

The 595/1064 nm Multiplex laser is a potentially safe and effective treatment of superficial and nodular basal cell carcinomas less than 1.5 cm in size.

1.0 BACKGROUND

1.1 Study Disease

Basal cell carcinoma (BCC) is the most common malignant tumor in humans and its incidence is increasing.[2-4] In the United States alone, approximately 1 million new cases of BCC are diagnosed annually.[4]Basal cell carcinomas rarely metastasize but can be locally destructive and invasive over a long period of time.[5,6]Rates of growth, however, are small and successful treatment has been found to not be compromised by waiting an average of 10 weeks for elective excision.[1] Superficial (17.4%) and nodular (21%) subtypes, moreover, are considered very common.[7] Numerous treatments such as surgical excision, cryotherapy, topical imiquimod, 5-fluorouracil, curettage and electrodessication, and Mohs micrographic surgery currently exist.[3]A number of patients, however, cannot tolerate the inflammatory response associated with topical immunomodulators nor the surgical approaches that are known to lead to high clearance rates.[8] Furthermore, some of the current treatment alternatives for BCC, most notably including surgical excision and Mohs micrographic surgery, have a high risk of pain, scarring, or increased healing time, as well as greater risk for infection.

Basal cell carcinomas are considered highly vascular lesions. Basal cell tumor beds have been found to be enclosed by a dense capillary network and basal cell carcinomas are very often characterized by superficial telangiectasias.[9] In addition, superficial and nodular basal cell carcinomas may contain melanin, possibly giving these lesions a brown, blue or black hue.[3]

1.2 Study Agent

The Cynosure 595/1064 nm Cynergy multiplex laser is a combination laser emitting both 595 nm and 1064 nm wavelengths, corresponding to visible and infrared regions of the electromagnetic spectrum, respectively. It is capable ofdelivering one wavelength pulse alone or sequentially delivering two pulses, one of each wavelength.The laser's "MultiPlex technology" allows the wavelengths to be sequentially administered in a controlled and safe manner.

The 595 nm aspect of this laser is currently indicated for benign vascular and vascular dependent lesion removal. The 1064 nm wavelength is currently indicated for the coagulation and hemostasis of benign and vascular lesions such as, but not limited to, port wine stains, hemangiomas, warts, telangiectasias, rosacea, venus lakes, leg veins, spider veins and poikiloderma of civatte, in addition to treatment of benign cutaneous lesions such as age and solar lentigos, café au lait macules, seborrheic keratoses, nevi, chloasma, verruca, skin tags, keratoses, tattoos, and plaques.

Using the 595 nm and 1064 nm lasers sequentially creates a synergistic effect. The first pulse with the 595 nm wavelength laser generatesthe chromophore methemoglobin, which diffuses more deeply into the dermis and is readily targeted by light from the second pulse (1064 nm wavelength laser). This allows for both increased efficacy and the ability to use lower fluences for each wavelength, increasing safety.

1.3 Other Agent(s)

N/A

1.4 Rationale

Due to the fact that basal cell carcinomas are highly vascular lesions and tumors on the whole are known to be dependent on blood supply, we propose that using the 595/1064 nm Multiplex laser, with wavelengths known to target both superficial and dermal blood vessels, will result in clearance of the basal cell carcinoma by destroying the lesion's blood supply. In addition, these wavelengths are also able to target pigment, which may be present within basal cell carcinoma as well.

1.5 Gender and Ethnicity

N/A

2.0 OBJECTIVES

This is a pilot study to determine whether there is potential for the development of a larger clinical trial to properly evaluate whether the 595/ 1064 nm multiplex laser is a safe and effective treatment for superficial and nodular basal cell carcinomas less than 1.5 cm in size.

2.1 Primary objectives

The primary objective of the study is to preliminarily assess the efficacy of the 595/1064 nm multiplex laser for the treatment of superficial and nodular basal cell carcinomas less than 1.5 cm in size.

Efficacy will be measured both clinically and histologically. This will first be determined by clinical dermatologic evaluation for the gross appearance of residual lesion. Residual tumor burden will be calculated by change in surface area of the lesion. Histological clearance will be determined by absence of residual tumor cells on histopathology of biopsy following treatment. The primary endpoint is response, defined as CR or PR. (see Section 9).

2.2. Secondary objectives

The secondary objective of this study is to assess the safety and side effect profile of the multiplex laser for this indication.

Although the 595/1064 nm multiplex laser has been deemed safe when used for other dermatologic conditions, this will be the first time this combination laser will be used specifically in the context of treatment for superficial and nodular basal cell carcinomas. We do not anticipate an increased risk of adverse effects in this clinical context, however, we intend to thoroughly monitor for and document any new and/or concerning adverse reactions to the multiplex laser. During treatment, any adverse events that occur will be documented. Furthermore, at each visit, patients will be questioned about whether any side effects occurred after treatment and in the period leading up to the next session.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Adults age 18 years or older

3.1.2 Diagnostic biopsy must be no later than three months prior to enrollment

3.1.3 Lesion is biopsy-proven nodular or superficial BCC

3.1.4 BCC is 1.5 cm or less in diameter

3.1.5 BCC is on trunk or extremities

3.1.6 Fitzpatrick skin types I, II, III, or IV

3.1.7 Female subjects should either be:

- Post-menopausal as defined by 12 months with no menses without an alternative medical cause.

    - Surgically sterile, by means of a hysterectomy, or

    - Females of child bearing potential must agree to use “highly effective” method of birth control as defined by FDA that result in low failure rate (i.e. <1% per year) and include:

        - Intrauterine device

        - Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring)

- Sexual abstinence

- Vasectomized partner

3.1.8 Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

3.2.1 BCC is greater than 1.5 cm in size

3.2.2 If location of BCC is on the face.

3.2.3 Patients whose biopsy shows a subtype other than superficial or nodular, or has characteristics of a more aggressive nature, such as:

- Basosquamous basal cell carcinoma

- Morpheaform/ infiltrative basal cell carcinoma

- Sclerosing basal cell carcinoma

- Recurrent basal cell carcinomas

3.2.4 Patients who may not be able to tolerate light therapy, such as:

- Patients with seizure disorders triggered by light

- Patients who have or are currently receiving gold therapy

- Patients with any light sensitive disorder

- Patients taking medication that increases sensitivity to light (see appendix VI)

- Patients with Systemic Lupus Erythematous

3.2.5 Fitzpatrick skin types V or VI

3.2.6 Patients who are taking certain oral medications such as:

- Isotretinoin (currently or within last 6 months)

- Medications that alter wound healing (see appendix VI)

3.2.7 Patients who have a history of Herpes Simplex Virus outbreak in the area to be treated

3.2.8 Patients whose lesion has been previously, or is currently being, treated by another modality (topical immunomodulators/ chemotherapeutics, cryotherapy, curretage and electrodessication, surgical excision, or Mohs micrographic surgery)

3.3 Recruitment, enrollment, and randomization

3.3.1 Recruitment

Patients that present to Dr. Nouri's clinic for follow-up of their biopsy who have biopsy proven superficial or nodular basal cell carcinoma will be approached to participate in the study. We will identify patients who have biopsy proven superficial or nodular basal cell carcinoma via medical records (via partial waiver of authorization approval).

3.3.2 Enrollment

To enter a patient, the investigator or study team member will contact the assigned study coordinator at the respective study site. All eligibility requirements must be reviewed by the study coordinator or the Principal Investigator, and the eligibility checklist must be completed and signed by the Principal Investigator or designated Sub-PI prior to initiating registration to enter the patient on study. Once the eligibility checklist is signed, the patient will be enrolled in Velos. The research staff will then randomize the patient. The following information will be retained in the patient's study chart:

1) Completed and signed protocol-specific eligibility checklist;
2) All pages of the original signed informed consent forms (ICFs), including HIPAA Form B and photo consent form.
3) Relevant source documents such as: subject medical history and physical exam, admission or discharge notes, diagnostic reports,

pathologic confirmation of diagnosis, and relevant subject-specific written communication.

3.3.2.1 Cancellation Guidelines

If a subject does not complete protocol therapy or no longer wishes to receive therapy, the subject may withdraw. Dr. Nouri may also

withdraw patients if it is in their best interest. Subjects who are enrolled on study but not treated will be excluded from all analyses.

3.3.2.2Emergency Registration

None

3.3.3. Randomization

Randomization of study subjects will be done in 3:1 ratio to the treatment arm and control arm. Due to the nature of study treatment, this is an unblinded study. A randomization list will be prepared by the SCCCBiostatistics and implemented by the research staff.

After each patient's study eligibility is confirmed and the informed consent is signed, the research staff will enter the required subject information into the CIERRA system in order to register the subject. The coordinator of the PI will receive the designated patient ID, study arm, randomization number, and randomization date. Coordinator will print the randomization confirmation form from the CIERRA system and place it in the subject's research chart and then notify the requesting member of the study team of the treatment assignment for the new randomized subject.

4.0 TREATMENT PLAN

Subjects in the treatment arm will receive 3 treatments using the 595/1064 multiplex laser spaced by a four week interval (+/- 7 days), administered in an outpatient clinic setting. If a subject in the treatment arm has multiple BCCs satisfying inclusion criteria, all BCCs will be treated. The treatment settings for this laser will be as follows:

595 nm PDL at a fluence of 10 J/cm^2, a 10 ms pulse duration, and a 10 mm spot size, followed by 500 ms multiplex interpulse delay, followed by 1064 nm laser at a fluence of 40 J/cm2, 10 ms pulse duration, and 10 mm spot size; the BCC lesion will be treated using 10% overlap with a single pass, along with 4 mm of normal skin. Dynamic cooling feature (cool air being blown onto treatment area) will be provided.

Subjects in the control arm will receive 3 regular study visits spaced 4 weeks (+/- 7 days) apart. If a subject in the control arm has multiple BCCs satisfying inclusion criteria, all BCCs will not be treated.

Four weeks (+/- 7 days) after the last (Day 84) both treatment and control patients will be assessed for final clinical appearance, measurement, and evaluation of the lesion by a dermatologist. Perpendicular diameters of the lesion will be measured with a ruler, as on initial evaluation, and surface area will be calculated. Residual tumor burden will be calculated based on change in surface area of the lesion.

Subjects will also undergo deep excisional biopsy encompassing the entire lesion to determine residual tumor cell presence. If histologic examination of the tissue reveals residual BCC, then the subject will receive standard of treatment.

A digital camera will be used to photograph the BCC immediately before, during and after treatment.

Note: If any clinical signs of progression are visible during this period (what we will consider greater than 10% growth), the subject in either treatment arm or control arm will be withdrawn from the study and undergo standard of care. Such a subject will be considered non- responder for the efficacy analysis.

4.1 Agent Administration

Subjects in the treatment arm will receive 3 treatments using the 595/1064 multiplex laser spaced by a four-week interval (+/- 7 days), administered in an outpatient clinic setting. Prior to treatment, the area will be cleaned and dried. Application of a topical anesthetic will not be necessary but is available upon request.

The treatment settings for each laser session will be as follows:

595 nm PDL at a fluence of 10 J/cm^2, a 10 ms pulse duration, and a 10 mm spot size. After a 500 msec interpulse delay, a second pulse with1064 nm laser at a fluence of 40 J/cm^2, 10 ms pulse duration, and 10 mm spot size will be administered; the BCC lesion will be treated using 10% overlap with a single pass, along with 4 mm of normal skin. Dynamic cooling feature (cool air) will be provided.

Subjects in the control arm will not receive any treatment; however they will receive 3 regular study visits spaced 4 weeks (+/- 7 days).

4.2 Supportive Care Guidelines

The 595/1064 nm multiplex laser has a cooling feature (Smart cool 6-air cooling system) available for patient comfort during laser sessions. If the subject is concerned about being uncomfortable during the laser treatment session, an additional topical anesthetic may be applied before each treatment.

After treatment, should the subject experience any expected or unexpected adverse side effects, supportive care will be offered. These include:

- Skin pain: The subject may experience discomfort during and immediately after laser treatment. This typically resolves within 24-48 hours. Administration of topical and/or oral pain care will be determined on a case-by-case basis.

- Skin ulceration or bullous dermatitis: The laser may cause slight cutaneous disruption that can take several days to heal. The disruption may lead to mild swelling or crusting that may remain photosensitive for 2-12 weeks following treatment. Subjects will be informed of the potential risk and will be advised to wear sunscreen before and after treatment. Any blistering or crusting that occurs after therapy will be treated with washing the site with soap and water followed by topical application of Vaseline and tefla/gauze dressing.

- Skin hyperpigmentation or hypopigmentation: The site of laser application may heal with some post-treatment pigment changes. This adverse effect is more common in darker-skinned individuals, who will be excluded from this study for this reason. It may also occur following sun exposure. Subjects will be urged to wear sunscreen before and after treatment. Pigment alterations that do arise will generally fade in 3-6 months

- Scarring: A small chance of scarring exists. Rarely, hypertrophic scars or keloids may form in response to laser treatment. If this unusual complication should occur, intralesional triamcinolone acetonide in concentration of 10-40mg/mL at 4-6week intervals will be used to diminish the appearance.

- Skin infections: Cutaneous infection can occur with the use of laser therapy, although rare, and would require antibiotic treatment. In such circumstances, antibiotics will be given according to standard of treatment for cutaneous infection.

- Erythema/Purpura: Immediately post-laser, the treated skin is expected to become red and splotchy. This is followed by a purpuric response, where the affected area becomes purple or violaceous. This response

is expected and may worsen in the 24-48 hours immediately post-treatment and may last as long as 10 days. Reassurance will be given to subjects.

4.2.1 Concurrent Medication (if applicable)

The following are part of eligibility criteria and as such we prohibitpatients from starting any of the following medications:

- Medications that increase sensitivity to light

- Medications that alter wound healing

- Isotretinoin

- Gold therapy

Should the subject be required, or desire to, begin treatment with any of the above medications, they will either be removed from the study or considered inevaluable for response.

Resources for examples of these agents may be seen in appendix VI.

4.3 Duration of Therapy

The laser therapy will take place in three sessions with 4-week intervals between sessions. A final biopsy will occur four weeks later after the last treatment with one-week follow-up for biopsy wound care and check-up. Thus, study involvement will require approximately 13 weeks of commitment.

5.0 CLINICAL AND LABORATORY EVALUATIONS

5.1 Baseline/pretreatment evaluation

Prior to involvement in the study

Prior to consideration of being a possible participant in the study, patients will receive a diagnostic biopsy as is the standard practice for evaluation of lesions that are suspicious for BCC.

Patients that present to Dr. Nouri's clinic for follow-up of their biopsy who have biopsy proven superficial or nodular basal cell carcinoma will be approached to participate in the study. We will identify patients who have biopsy proven superficial or nodular basal cell carcinoma on the trunk or extremities that is less than 1.5 cm in size via medical records (partial waiver

of authorization approval). If patients have more than one BCC that satisfy inclusion criteria, they will also be treated.

After signing informed consent, patients will be fully evaluated for eligibility criteria. Patients will be randomly assigned in either a control arm or treatment arm. Patients will be advised that if placed in control arm, there is an extremely low risk of serious progression during the short time needed for the study and that should any clinical signs of progression be seen, they would be withdrawn from the study and receive immediate surgical excision.

Patients will be entered into Velos system and completed HIPAA forms will be sent to HIPAA privacy office as per University of Miami policy.

5.2 Evaluations during treatment

After enrollment (day 0), subjects in both control and treatment arms will receive standard baseline photographs of their lesion. Subjects in the treatment arm will receive their first laser treatment. Lesions will be assessed by Dr. Nouri and documented, as well as monitoring for adverse effects and reviewing "prohibited" medications.

Days 28 and 56 (+/- 7 days) correspond to treatment sessions #2 and #3 for the treatment arm, and study visits #2 and #3 for the control arm. At these visits, patients will be asked of any side effects, reactions, or adverse events that occurred since the last visit as well as any other concerns. These will all be documented. If any serious adverse events have occurred, they will be reported to the IRB as per University of Miami policy.

Photographs and measurements of the lesion will be taken at each study visit. Subjects in the treatment arm will then receive laser treatment and patients in the control arm will receive a standard study visit.

5.3 Post-treatment evaluation

Four weeks after the last of the 3 treatment sessions or follow-up visits (day 84 +/- 7 days) subjects will asked about any side effects, reactions or adverse events that have occurred since the last visit. In the treatment arm, a dermatologist will then evaluate for any gross residual lesion as per protocol defined response criteria (see section 9.0) and a deep excisional biopsy encompassing entire region will be performed. Biopsy specimen will be evaluated for histopathologic clearance of tumor. If tumor cells are present, standard of care will be performed. In the control arm, biopsy specimen will be evaluated for histopathologic clearance of tumor and after gross evaluation and measurement of lesion by a dermatologist, standard of care will be performed.

5.4 Early discontinuation of therapy

Grading for adverse events as determined by US Department of Health Common Terminology Criteria for Adverse Events (CTCAE version 4.0)

Any subject with a non-laboratory Grade III or higher toxicity that is possibly, probably or definitely related to involvement in our study will be considered for removal.

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6.0 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Study Agent

There are no expected dosing delays or dosing modifications for this study. Due to the fact we are testing specific laser parameters for the potential efficacy of clearing certain types of basal cell carcinomas, we will not be adjusting the settings.

However, should the subject experience any adverse effects secondary to the use of the multiplex laser, they will immediately be provided with supportive care tailored to the nature of the adverse effect (see section 4.2). In addition, there are no expected systemic toxicities. If the expected and unexpected effects are not tolerable, the subject may also withdraw from the study at any point.

In our study, early termination will be based on presence of intolerable side effects and desire to withdraw from studies. Should our treatment prove ineffective, all patients will receive standard treatment of care immediately.

6.2 Other Agent(s)

N/A

7.0 AGENT FORMULATION AND PROCUREMENT

7.1 Agent

7.1.1 Other names

CYNERGY VASCULAR WORKSTATION

7.1.2 Classification

Dual wavelength 595 nm / 1064 nm laser

7.1.3 Mode of action

Selective photothermolysis

7.1.4 Storage and stability

N/A

7.1.5. Dose specifics

595 nm:
Fluence = 10 J/cm^2
Pulse duration = 10 ms
Spot size = 10 mm

Interpulse delay: 500 ms

1064 nm:
Fluence = 40 J/cm^2
Pulse duration = 10 ms
Spot size = 10 mm

10% overlap with a single pass, along with 4 mm of normal skin.

Dynamic cooling.

7.1.6 Preparation

N/A

7.1.7 Administration

Single pass of 595 nm wavelength followed by a single pass of 1064 nm wavelength. Administration of wavelengths separated by a 500 ms delay. Each pass is composed of pulses of laser that will have 10% overlap between pulses. Treated area will include a 4 mm margin of normal skin. Dynamic cooling feature will be provided.

7.1.8 Incompatibilities

There are no direct incompatibilities, however, contraindications have been included in exclusion criteria.

7.1.9 Availability

In office

7.1.10 Side effects

- Pain of the skin

- Edema

- Erythema and/or purpura

- Temporary hypo- or hyperpigmentation

7.1.11 Nursing implications

None

7.1.12 Reported Adverse Events and Potential Risks

Likely:

- Pain of the skin

- Edema

- Erythema and/or purpura

- Temporary skin hypopigmentation or hyperpigmentation

Unlikely:

- Hematoma

- Scarring

- Herpes Simplex Virus outbreak if treating an area with past recurrent outbreaks, usually around the mouth

- Skin infection

- Skin ulceration/ bullous dermatitis

8.0 CORRELATIVE/SPECIAL STUDIES*(if applicable to this study)*

N/A

9.0 MEASUREMENT OF EFFECT

9.1 Guidelines for Evaluation of Measurable Disease

We will measure disease both clinically and histologically. Clinically, a dermatologist will visually inspect for the lesion and measure the size of any residual tumor with perpendicular diameters (d_1 and d_2).Surface area(SA) will be calculated as that for an ellipse, by SA = $\pi r_1 r_2$, where $r_1 = d_1/2$and $r_2=d_2/2$. Residual tumor burden will be calculated by change is surface area of the lesion. Histologically, an excisional biopsy will be performed in order to examine for any residual tumor cells in the lesion. We will classify response according to our criteria below.

9.2 Response Criteria

For determination of response, we will consider:

- Complete response (CR):

    1) Both clinical and histological disappearance of the target lesion or

    2) Positive clinical assessmentof the “lesion” but negative histology.

- Partial response (PR):

    1) At least 10% decrease in the size of lesion on clinical evaluation and positive histology or

    2) Complete clinical clearance of the lesion and positive histology.

- Progression of disease [10]: At least 10% increase in the size of the lesion on clinical evaluation.

- Stable disease (SD): Clinically, neither sufficient reduction to qualify for PR nor sufficient increase to qualify for PD.

The following table summarizes the above response criteria.

		Clinical assessment			
		No lesion	Lesion ≤90% baseline size	Lesion >90 but <110% baseline size	Lesion ≥110% baseline size
Histology	Positive	PR	PR	SD	PD
	negative	CR	CR	SD*	PD*

* not expected to occur.

9.3 Confirmatory Measurement/Duration of Response

Biopsy will be performed for confirmatory measurement.

9.4 Progression-Free Survival

N/A

9.5 Response Review

Final response review will be conducted four weeks after the last of 3 treatment sessions for the treatment arm or the last of 3 study visits for controls.

10.0 ADVERSE EVENT REPORTING

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

10.1 Definitions

10.1.1 ***Adverse events***(AE's) will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE v 4.0) in Appendix II.

Adverse events: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

10.1.2 A ***serious adverse event*** (SAE) is defined by the federal regulations as any adverse event that:

- Results in death; or is
- Life threatening; or
- Results in permanent impairment of body function or permanent damage to a body structure; or
- An event requires medical or surgical intervention to prevent permanent impairment or damage to a body function or body structure.

SAE's are defined by FDA and therefore seriousness (not severity) serves as a guide for defining regulatory reporting obligations for patient/subject safety. **Serious** is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

The definition of serious adverse event (experience) also includes ***important medical events***. Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or **may require intervention** to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.1.3 **Expected events** are those that have been previously identified as resulting from administration of the agent. For this study, these include:

Likely:

- Pain of the skin

- Edema

- Erythema and/or purpura

- Temporary skin hypopigmentation or hyperpigmentation

Unlikely:

- Hematoma

- Scarring

- Herpes Simplex Virus outbreak if treating an area with past recurrent outbreaks, usually around the mouth

- Skin infection

- Skin ulceration/ bullous dermatitis

Any of these key adverse events that are greater than grade III according to CTCAE, are not expected.

10.1.4 An adverse event is considered ***unexpected*** when either the type of event or the severity of the event is *not* listed in: the device brochure, or the device information section of this protocol.

10.1.5 The definition of ***related*** is that there is a reasonable possibility that the device caused the adverse experience.

10.2 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please follow directions for routine reporting provided in the Data Reporting Section). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

Events resulting from concurrent illnesses and reactions to concurrent medications must be reported as adverse events.

Any worsening of the patient's clinical condition while the patient is on study will be considered to be an adverse event unless it is within the normal range of disease fluctuation for that patient.

10.2.1 Determination of Reporting Requirements

Reporting requirements may include the following considerations:

1) whether the patient has received an investigational or commercial agent;
2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event;

3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

10.2.2 Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.*

The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).*

Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.*

Step 5: *Review Table 10.1to determine if there are any protocol-specific requirements for reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

NOTE:If the subject received at least one treatment with the investigational device serious adverse events will be reported as indicated in section 10.3.

10.3 Reporting Methods

All AEs and SAEs will be reported as per as per University of Miami's Human Subject Research Office Policy and Procedures. Any suspected medical device-related death will be reported to the manufacturer no later than three work days from the day that the PI or designee became aware of the event. All medical device-related serious injuries will be reported to

the manufacturer no later than three work days from the day that the PI or designee became aware of the event. At the discretion of the Sponsor, a malfunction may be reported to the FDA by using the voluntary Med Watch program to advise FDA of problems with medical devices.

10.3.2 **FDA Reporting**

10.3.2.1 Investigational Agent reporting

All serious, unexpected adverse events must be reported to the manufacturer within three work days.

Fatal or life-threatening adverse events must be reported to the manufacturer within three work days from being made known to the Principal Investigator or designee.

10.3.3 **IRB Reporting**

All adverse events will be reported as per University of Miami's Human Subject Research Office Policy and Procedures.

10.3.3.1

All adverse events that are serious adverse events **and** are unexpected **and** are related or possibly related IRB **and** suggest that the research places subjects or others at greater risk of harm or discomfort than known or anticipated must be reported within ten (10) working days of being made known to the Principal Investigator. Events that are more frequent than anticipated or more severe than expected must be reported to the IRB within ten (10) working days of being made known to the Principal Investigator.

All unanticipated life-threating events or deaths must be reported to the IRB within 24 hours of being made known to the Principal Investigator if the event is a direct outcome or possibly an outcome of the study intervention.

10.3.4 **Follow-up Reporting**

For all SAE's, the investigator is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached or the patient is lost to follow-up.

11.0 CRITERIA FOR DISCONTINUATION OF THERAPY

Should any of the following occur, the will be immediately be withdrawn from the study and receive timely supportive or standard care if necessary.

11.1 Disease progression

Superficial and nodular basal cell carcinoma subtypes are considered less aggressive than other subtypes of BCC such as morpheaform or infiltrative. In addition, the rate of invasion is lower with smaller lesions. However, should there be obvious disease progression (10% increase in size) in either group throughout the short duration of the study, they will be immediately withdrawn and receive standard of care.

11.2 Unacceptable Adverse Events

Likely side effects to treatment with this laser may include pain of the skin, erythema, purpura, or temporary hypo or hyperpigmentation of the skin. Unlikely reported side effects include hematoma, scarring, mild skin ulceration or bullous dermatitis, and skin infection. See section 7.1.12.

Any grade III non-lab toxicities that are possible, probably or definitely related to involvement in the study are unacceptable and subjects will receive immediate supportive care and be withdrawn from the study.

11.3 Patient wishes

Should the subject wish to withdraw from the study, he/she may do so at any time. The subject may then continue to receive standard of care.

11.4 Investigator discretion

Should the subject no longer meet eligibility criteria, or should Dr. Nouri deem the treatment inappropriate for the subject, he may elect to withdraw the subject at any time.

12.0 DATA REPORTING

Screening:

Approved, watermarked ICFs will be used to consent patients prior to enrollment in the study.

At the screening visit the subject will sign ICFs (main and photo) and HIPAA forms. An investigator will also assess eligibility using source documents provided (see

appendix VII). Patient will be entered into Velos as per University of Miami policyand HIPAA forms will be faxed to the UM Office of HIPAA Privacy & Security.

During Therapy:

At each treatment session, the investigator will complete the appropriate source documents relevant to each visit. The data from these source sheets may be entered into master document (excel spreadsheet on locked computer) up to 21 days from time of visit. Source documents can be seen in Appendix VII.

Follow-up:

One week after final excisional biopsy, subjects will return for wound check and final follow-up. Follow-up source document will be completed at that time. (see Appendix VII).

Completion:

After the final follow-up visit, subjects' completion of involvement in study will be documented in Velos, as per University of Miami Policy.

All paper documents listed above will be stored in a labeled binder that will be kept in a locked filing cabinet within our office. Only people listed on eProst will have access. Computer data will be kept in an excel file in a locked computer in our office. Only people listed on eProst will have access.

Data must be submitted according to the protocol requirements for ALL subjects receiving treatment. Subjects for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

A list of forms to be submitted, as well as expectation dates, may be found in Appendix IV.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design/Objectives

This is a prospective, unblinded, randomized, two-arm (treatment arm vs Control/non-treatment arm) pilot study to determine whether the 595/1064 nm laser merits further study forefficacy in the treatment of basal cell carcinoma. The primary objective of the study is to preliminarily assess the efficacy of the 595/1064 nm multiplex laser for the treatment superficial and

nodular basal cell carcinomas less than 1.5 cm in size. Our primary endpoint will be the overall response rates (CR+PR), as defined in section 9.0.

The secondary objective of this study is to assess the safety and side effect profile of the multiplex laser for this indication.

13.2 Sample Size Justification/Accrual Rate

The analysis set (evaluable subjects) consist of study-eligible subjects who either complete three treatments/three study visits and the biopsy visitor are withdrawn from the study due to showing evidence of PD during the study (non-responder). Subjects will be non-evaluable when they do not wish to continue in the study, are unable to continue in the study, or they cannot complete treatments or study visits for any reason other than PD. There will be 15 evaluable subjects in the treatment arm and 5 evaluable subjects in the control (non-treatment) arm. We expect that three to four subjects in both treatment arm and control arm will be non-evaluable. Therefore, the planned maximum number of enrolled subjects will be 28.The number of subjects is small due to the preliminary nature of the study, yet similar in size to previous studies (Konnikov et al 2011 and Shah et al 2009), which only used the 595 nm laser. Out of our 15 subjects in the treatment arm, we expect eleven or more subjects will respond to proposed treatment (either CR or PR). The table below shows significance (p-value) of hypothetical study findings assuming one BCC per subject. As shown in the second row, if one out of five subjects in the control arm shows either CR or PR and twelve or more out of fifteen subjects in the treatment arm show either CR or PR then test of comparing proportions of two arms is statistically significant (p-value < 0.05). If none in the control arm show either CR or PR and nine or more out of fifteen subjects in the treatment arm have either CR or PR, we also get a statistically significant difference indicating a better response rate in the treatment arm.

Number of subjects (CR or PR) among 15 subjects in the treatment arm vs. 5 in control arm	p-value*
11 (73.3%) vs. 1 (20%)	0.058
12 (80%) vs.1 (20%)	0.031
9 (60%) vs 0 (0%)	0.030

* one-sided Fisher's exact test (assuming every subject has one BCC)

One to two subjects will be accrued per week secondary to availability of the laser.

13.3 Planned statistical analyses

13.3.1 Subject characteristics

Subject demographics (age, sex, race/ethnicity) and disease characteristics (type of BCC, size of BCC, site of BCC, number of BCCs per subject, Fitzpatrick skin types, etc,) will be summarized using descriptive statistics: counts and percentages, range, median, mean, and standard deviation, as appropriate. Descriptive statistics will also be provided for size of BCC at baseline and subsequent visits and displayed as box plots for each study arm. We will also calculate percentage change in size of BCC from baseline and display in a spider plot.

13.3.2 Efficacy

Each BCC will be assessed for response as specified in Section 9.0.

If all subjects have one BCC, the overall response rates (CR or PR) for treatment and control arms will be estimated by the percentage of subjects achieving these criteria and compared using one-sided Fisher's exact test. The corresponding two-sided 95% confidence intervals will be estimated by the exact binomial method.

If some study subjects have more than one BCC, response rate will be defined as the number of BCCs achieving CR or PR divided by total number of BCCs for all subjects in each arm. We will use Donner's adjusted χ^2test with one degree of freedom to compare response rates between the treatment and control arms. The corresponding two-sided 95% confidence intervals will be estimated using Jung and Ahn's method. We also report percentage change in lesion size for both treatment and control arms.

13.3.3 Safety

We will tabulate adverse events possibly, probably or definitely related to treatment as counts and percentage according to NCI Common Terminology Criteria for Adverse Events version 4.0 in Appendix II (see Section 10.1.1-10.1.5).

13.4 Data and Safety Monitoring

13.4.1 Role of the Research Team and the DSMC

The Research Team will continually monitor study accruals, toxicities, and responses to treatment with 595/1064 nm laser. In addition, the UM/Sylvester Comprehensive Cancer Center's Data and Safety Monitoring Committee (DSMC) will monitor this protocol according to the Cancer Center's DSM plan.

13.4.2 Early stopping rule for lack of efficacy

We do not intend to stop the study early since this is a small study with the objective of gathering preliminary evidence of efficacy of the treatment arm.

13.5 Reporting and Exclusions

All non-identifying relevant study data will be reported to an appropriate scientific journal. Any data that meets the predefined requirements for study exclusion will be reported as long as it does not contain subject specific identification.

14.0 INVESTIGATOR'S RESPONSIBILITIES

14.1 Investigator Responsibility/Performance

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects.

The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

14.2 Confidentiality

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

14.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in

lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian.

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

14.4 Source Documentation and Investigator Files

The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents would include hospital/clinic patient records; physician's and nurse's notes; appointment book; original laboratory, ECG, EEG, radiology, pathology, and special assessment reports; pharmacy dispensing records; subject diaries; signed informed consent forms; and consultant letters. When the CRF or any form is used as the source document, this must be clearly stated in the investigator study file.

Minimally, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit
- Documentation of treatment
- Laboratory test results
- Adverse events (action taken and resolution)

- Condition and response of subject upon completion of or early termination from the study

14.5 Recording and Processing of Data

If using hard copies of CRF's, study center personnel will complete individual CRF's in black ink. All corrections to entered data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. **Do not use "white-out" or obscuring correction tape.** A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries.

14.6 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

14.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

14.8 Essential documents for the conduct of a clinical trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

The following documents should be on file:

- CV's and license of all investigators
- IRB documentation/correspondence
- Documentation of IRB and CITI certification

15.0 REFERENCES

1. Kirkup ME, De Berker DA. Clinical measurement of dimensions of basal cell carcinoma: effect of waiting for elective surgery. The British journal of dermatology 1999;141:876-9.
2. Diffey BL, Langtry JA. Skin cancer incidence and the ageing population. The British journal of dermatology 2005;153:679-80.
3. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. The New England journal of medicine 2005;353:2262-9.
4. Neville JA, Welch E, Leffell DJ. Management of nonmelanoma skin cancer in 2007. Nature clinical practice Oncology 2007;4:462-9.
5. Shriner DL, McCoy DK, Goldberg DJ, Wagner RF, Jr. Mohs micrographic surgery. Journal of the American Academy of Dermatology 1998;39:79-97.
6. Nagler RM, Laufer D. Invading basal cell carcinoma of the jaw: an under-evaluated complex entity. Anticancer research 2001;21:759-64.
7. Sexton M, Jones DB, Maloney ME. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. Journal of the American Academy of Dermatology 1990;23:1118-26.
8. Shah SM, Konnikov N, Duncan LM, Tannous ZS. The effect of 595 nm pulsed dye laser on superficial and nodular basal cell carcinomas. Lasers in surgery and medicine 2009;41:417-22.
9. Grunt TW, Lametschwandtner A, Staindl O. The vascular pattern of basal cell tumors: light microscopy and scanning electron microscopic study on vascular corrosion casts. Microvascular research 1985;29:371-86.
10. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. The New England journal of medicine 2001;344:1031-7.

APPENDIX I:
STUDY CALENDAR

Procedure	Screening	Randomization[1]	Day 0	Day28 (+/- 7 days)	Day 56 (+/- 7 days)	Day 84 (+/- 7 days)	Day 91 (+/- 7 days)/ Follow up visit
Written Informed Consent	X						
HIPAA	X						
Photo consent	X						
Eligibility checklist[2]	X						
Velos	X						
Randomization		X					
Pt and lesion characteristics [3]			X	X	X	X	

Treatment #1 [4]			X				
Treatment #2 [4]				X			
Treatment #3 [4]					X		
Photographs are taken			X	X	X	X	
Monitoring of adverse events and concomitant medication			X	X	X	X	X
Dermatologic eval for clearance						X	
Excisional biopsy						X	

[1]Within 3 months of initial diagnostic biopsy and within 1 week of enrollment (+ 3 days)
[2] Source document titled "Enrollment"
[3] Source document titled "Patient information"
[4] Or regular study visit for control arm

APPENDIX II:

NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) version 4.0

The NCI CTCAE can be viewed on-line at the following NCI web site:

http://ctep.cancer.gov/reporting/ctc.html

APPENDIX III:

DATA AND SAFETY MONITORING PLAN

The Sylvester Comprehensive Cancer Center (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the Cancer Center's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study.

DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event data, and periodic review of the safety and efficacy of the 595/1064 nm laser in treating superficial and nodular basal cell carcinomas less than 1.5 cm in size. The guidelines appearing in Sections 7.1.12 and 11.0 are offered for DSMC consideration in assessing adverse events safety. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action.

APPENDIX IV:

DATA SUBMISSION SCHEDULE

FORM	TO BE COMPLETED
Screening	
Consent Forms Signed/dated	Prior to enrollment
Photo consent form	At enrollment
Eligibility Checklist	
Velos registration	Within 24 hours of consent
HIPAA	
DURING PROTOCOL THERAPY	
Source documents	At time of visit
Data entered into excel spreadsheet	Within 21 days of visit
FOLLOW-UP	
Follow-up source document	Within 1 week (+/- 7 days) of final excisional biopsy
COMPLETION	
Registration of completion into Velos	Within 24 hours of final follow-up visit

NOTE: FORMS WILL BE CONSIDERED PAST DUE 21 DAYS AFTER THE DUE DATE.

APPENDIX V:

ADDITIONAL ITEMS

For the safety of our patients, please refrain from using the following prohibited and/or misleading abbreviations in the treatment and dose modification sections of the protocol.

Abbreviation	Definition	Term to Use
U	For unit	Unit
IU	For international unit	International unit
Pharmacy abbreviations	Example, qd for daily	Daily
1.0 mg	Trailing zero	1 mg
.1 mg	Lack of leading zero	0.1 mg
Drug name abbreviations	Example, MS for morphine sulfate	Write out drug name
µg	microgram	mcg
d/c	Discharge	Discharge
Cc	cubic centimeter	ml (milliliter)
>	Greater than	Write out meaning
<	Less than	Write out meaning

APPENDIX VI:

INFORMATION ON RELEVANT MEDICATIONS

Agents that increase photosensitivity:

http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=7&ved=0CFYQFjAG&url=http%3A%2F%2Fwww.wellnesspharmacy.net%2Fphotosensitivity.pdf&ei=G1N0UKjBM4rM9QTksoHADw&usg=AFQjCNGQnMqju1CSwjyvq8Oc1PH2hQUwoq

Agents that may affect wound healing:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2903966/

Agents listed in the above resources are subject to change and to be considered under the discretion of Dr. Nouri