**Full Title:** *Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II, Single Centre, Randomised, Pilot Study.*

**Project Title: T**opical **I**miquimod or **D**iphenylcyclopropenone for **A**dvanced **Locoregional** Melanoma (TIDAL Melanoma) Pilot Study

**Running Title: TIDAL Melanoma Study**

**Investigational Agents:** Diphenylcyclopropenone (DPCP) and Imiquimod for topical administration

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**Protocol Number**

**TIDAL-M-01**

**Protocol Version**

The amended protocol is TIDAL Melanoma Protocol Version 3.7.

**Date of Protocol**

1 December 2017

**Foreword**

This document describes an investigator-initiated clinical study to be conducted at the Princess Alexandra Hospital, Brisbane. It aims to provide information concerning procedures for patients satisfying strict eligibility criteria and enrolling in the clinical trial. It is not intended that the protocol be used as a guide for the treatment of other patients. This study commenced with institutional Human Research Ethics Committee approval (HREC/15/QPAH/632-SSA/15/QPAH/633).

**Confidentiality Disclosure**

The information contained in this study protocol is intended solely for the use of clinical investigators and members of the research team. It should not be disclosed other than through communication with those directly involved in the execution or ethical review of the study without the prior written authorization from the principal investigator.

**List of Abbreviations**

**AE** Adverse Event

**AJCC** American Joint Committee on Cancer

**ANZCTR** Australian and New Zealand Clinical Trial Registry

**ATP** According-To-Protocol

**Beta-HCG** Beta Human Chorionic Gonadotropin

**BOR** Best Overall Response

**BRAF** B-raf murine sarcoma viral oncogene homolog B1

**BSA** Body Surface Area

**BUN** Blood Urea Nitrogen

**CI** Co-investigator

**CK** Creatinine Kinase

**CMI** Cell-Mediated Immune

**CR** Complete Response

**CRF** Clinical Research Fellow

**CT** Computer Tomography

**CTCAE** Common Terminology Criteria for Adverse Events

**DFS** Disease-free Survival

**DOFT** Day of First Treatment

**DPCP** Diphenylcyclopropenone

**DSMC** Data Safety Monitoring Committee

**ECOG** Eastern Cooperative Oncology Group

**FACT-M** FACT-Melanoma

**HREC** Human Research Ethics Committee

**ICF** Informed Consent Form

**ILI** Isolated Limb Infusion

**ImiQ** Imiquimod

**IRB** Institutional Review Board

**ITM** In-transit Melanoma

**Met** Metastasis

**MR** Mixed Response

**MRI** Magnetic Resonance Imaging

**MSS** Melanoma-specific Survival

**MTD** Maximum Tolerated Dose

**ORR** Objective Response Rate

**OS** Overall Survival

**PAH** Princess Alexandra Hospital

**PD** Progressive Disease

**PET** Positron Emission Tomography

**PI** Principal Investigator

**PR** Partial Response

**PV-10** Rose Bengal

**QMP** Queensland Melanoma Project

**QOL** Quality of Life

**RECIST** Response Evaluation Criteria In Solid Tumors

**SD** Stable Disease

**TE** Tumour Evaluation

**TLR7** Toll-Like Receptor 7

**ULN** Upper Limit of Normal

**US** Ultrasound

**WMA** World Medical Association

**SUPERVISOR SIGNATURE SHEET**

The undersigned have reviewed the format and content of this protocol as official supervisors of Dr Tavis Read during his Doctor of Philosophy candidature. They have approved Protocol No. TIDAL-M-01 (Version 3.7) dated 1 December 2017 for issuance.

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Signature Date

Dr Michael Wagels, Staff Specialist

Department of Plastic and

Reconstructive Surgery PAH

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Signature Date

Prof. B. Mark Smithers, Director

Upper Gastrointestinal and Soft

Tissue Surgery PAH

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Signature Date

Prof. H. Peter Soyer, Director

Department of Dermatology PAH

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Signature Date

Assoc. Prof. Helmut Schaider,

Staff Specialist Department of

Dermatology PAH

**PRINCIPAL INVESTIGATOR SIGNATURE SHEET**

I have read and understand the enclosed protocol. I agree that it contains all the necessary details for performing the study.

I have provided copies of this protocol to all investigators responsible to me who participate in the study. I have discussed this material with the research team to ensure that they are fully informed regarding the article and the conduct of the study.

Once the Human Research Ethics Committee (HREC) and Institutional Review Board (IRB) has approved the protocol, I will not modify this protocol without obtaining the prior written approval of the HREC/IRB. Any protocol amendments and/or informed consent modifications to will be duly submitted to the HREC/IRB, and approval will be obtained before any proposed changes are implemented.

I understand the protocol and will conduct the investigation according to its prescribed instructions, the relevant clinical guidelines and the principles of Good Clinical Practice (espoused in the current ICH guidelines) and the Declaration of Helsinki (1964) including all amendments up to and including the Scotland revision (2000).

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature Date

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Printed Name

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PROTOCOL SYNOPSIS

**Full Title:** *Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II Single Centre Prospective Randomised Pilot Study.*

**Running Title: T**opical **I**miquimod or **D**iphenylcyclopropenone for **A**dvanced **Locoregional** Melanoma (TIDAL Melanoma) Pilot Study

**Short Title: TIDAL Melanoma Trial**

**Study Design**

This is a Phase II, open-label, randomised, dual arm, non-superiority, pilot study. All eligible patients will be enrolled, randomised and treated with either DPCP or ImiQ.

**Study Objectives**

Primary Objective:

The primary objective of this study is to assess the clinical complete response rate. This will be used to measure the effectiveness of topical DPCP or imiquimod for locoregional treatment of cutaneous in-transit melanoma metastases.

Secondary Objectives:

Secondary objectives are to determine patients’: objective response rate, progression-free survival, overall survival, mortality rate, change in quality of life, rate of treatment-related complications and estimated difference in health-related costs.

**Study Population**

Patients older than 18 years of age with multiple, superficial, in-transit melanoma metastases. Patients must be unsuitable, have failed or refuse surgical resection and are referred for ongoing treatment at the PAH. Please refer to specific inclusion and exclusion criteria below for additional details.

**Treatment**

The investigational agents are diphenylcyclopropenone (DPCP) and imiquimod, two dermatological immunotherapies for topical administration to cutaneous in-transit lesions. Up to 20 lesions can be selected for in-field treatment with a surface are of up to 25cm2. Each agent will be administered topically with a 5mm peripheral margin to uniformly treat between 5-20 target lesions.

**Design -** This is an open-label, randomised, dual arm, pilot study. All eligible patients will be enrolled, randomised and treated with either DPCP or ImiQ.

**Intervention** – DPCP or ImiQ topical immunotherapy (refer to treatment schedule).

**Selection** - Patients with ITM treated at the PAH Melanoma Outpatient Clinic that fulfil eligibility criteria who are unable, refuse or have failed surgery will be screened, assessed, consented and randomised to one of two treatment arms (A or B).

**Treatment Arm A –** 5% Topical Imiquimod Cream: Self-application 5 times weekly, regular clinical review, time to best response and formal 12 month assessment, regular clinical surveillance for duration of remaining trial.

**Treatment Arm B –** Topical DPCP Cream: Sensitisation with 2% Solution, Responders commence treatment regimen - self-application once weekly, regular clinical review, titration to effect, time to best response and formal 12 month assessment, regular clinical surveillance for duration of remaining trial.

**Control** **Arm** **(Historical)** – Single group, single centre, retrospective data for ILI treatment. This represents the current standard of care and will be used in an historical ad hoc analysis comparing health-related costs.

**Cross-over:** Nil treatment arm cross-over when one therapy fails.

**Primary endpoint** – The clinical complete response rate of patients randomised to either imiquimod or DCPC.

**Secondary endpoints** – disease-free survival, progression-free survival, overall survival, quality of life assessment, cost-effectiveness analysis, adverse drug reactions and side-effects.

**Follow-up**

Formal assessments at 1, 3, 6, 9, 12, 15, 18, 24 months following commencement of treatment. Design aim for mean duration of 18 months with a minimum of 12 months. Data collection will be continued after 12 months or best response up to 24 months following the commencement of treatment. *N.B. Interval reviews will be accepted at the discretion of the treating clinician as specified in section 12.6*

**Off-label therapeutic approval** – Will be sought from Professor Peter Pillans, Director Clinical Pharmacology.

**Study Duration**

Each subject will be treated for up to 52 weeks after commencing imiquimod or DPCP treatment. The aim is to also achieve a minimum follow-up duration of 12 months. The total study length is estimated to be between 36 months based on recruitment rates.

**Study Site**

Princess Alexandra Hospital

199 Ipswich Road

Queensland, 4102

**1. INTRODUCTION**

**1.1 Background**

Melanoma represents a significant burden of disease in the Australian population. [1] An ageing population, with predominately fair skin types (Fitzpatrick Types I and II) and intermittent exposure to high doses of UV radiation place the Australian population at a high level of risk (incidence 62.7 and 39.9 per 100, 000 males/females respectively). [2-5] Queensland has the highest incidence of melanoma per capita worldwide and this has continued to increase over the past 30 years without gender bias (68.6 per 100, 000 overall). [2] With early detection, the five-year survival rate for melanoma is excellent (> 90%), however the prognosis remains poor in patients diagnosed with advanced primary melanoma or recurrent disease. [3] Survival time decreases steadily as primary tumour thickness and subsequent disease stage increases. [6] In particular, patients with locoregional disease face significant challenges due to high rates of local recurrence and distant metastases.

The overwhelming majority of locoregional disease occurs in the form of subcutaneous or intra-dermal local and in-transit deposits. [7] In-transit melanoma is defined as skin or subcutaneous metastases that are farther than 2 cm from the primary lesion scar but that have not extended beyond the regional lymph node basin as in distant metastatic disease. [8] This is an advanced form of locoregional disease (AJCC 7th Ed. ≥Stage IIIB) and is associated with significant morbidity stemming from both disease-related functional impairment and treatment side-effects. Approximately 12-22% of all melanoma recurrences occur in the form of in-transit disease, with diverse outcomes and the risk of recurrence varying substantially across a heterogenous patient population for unknown reasons. [9]

Complete surgical excision is the accepted standard of treatment, however the location, size, number, distribution and advanced age of patients mean that surgery is not always reasonable or appropriate. [12] Other therapies available in Australia include: surgical debulking, isolated limb infusion and perfusion, intralesional chemoablative therapy, radiotherapy, carbon dioxide laser ablation and systemic chemo-or immunotherapies. Ideally an individualised and evidence-based treatment plan is formulated within a multidisciplinary specialist clinic. Unfortunately, the management of in-transit melanoma currently encompasses a disparate range of options that are often inconsistently selected. Existing treatment algorithms are guided by the staging of disease and target different regions of effect. Often combinations of therapies are given and patients have diverse responses for unidentified reasons. Due to the great variability in patient demographics and treatment responses, a comprehensive review of the professional literature and existing data within our institution has been undertaken to characterise this population and the suitability of available therapeutics.

Topical immunotherapies may provide an alternative when other treatment modalities have failed or are inappropriate. Initially, with the development of immunological-based topical therapies it was unclear which agents and patients should be selected for treatment. Results derived from institutional data have provided evidence that patients can be rationally selected and successfully treated based on patients’ disease phenotype, medical co-morbidities and functional status. Results indicate that while locoregional treatments do not prolong patients’ survival these may improve progression-free survival. Our data suggest patients with multiple, superficial, cutaneous, in-transit deposits can be successfully treated using topical DPCP.

This pilot study will evaluate two immunotherapies: DPCP and imiquimod for the selective management of cutaneous in-transit melanoma metastases. These two immunological agents appear to be durable, safe, well tolerated, easy to (self-) administer and require only intermittent clinician review. Notably, both agents are substantially cheaper than existing treatment options and this will be evaluated using a cost-benefit analysis within this study. These properties make both topical treatments attractive alternatives to more invasive options. A trial-based assessment of the efficacy of these agents has not been undertaken elsewhere to date. The aim is to determine if topical imiquimod or DPCP treatment is an efficacious, well-tolerated and cost-effective alternative to current therapies in patients unable to undergo, refuse or have failed surgery. It is expected that the results of this study will lead to improved patient- rated outcomes through a reduction in disease, fewer serious treatment-related complications, more convenient application, streamlined review and ultimately decreased healthcare-associated expenditure.

In-transit melanoma is a heterogeneous disease and poses a clinical and therapeutic challenge. This has led to the use of multiple treatment modalities and the majority of patients being referred to major tertiary and specialist clinics. While existing treatments provide temporary improvements in disease burden these effects are usually short-lasted and may reduce overall QOL. They fail to improve overall survival outcomes and consume substantial resources, demanding significant patient time and energy, requiring intensive ongoing specialist review and involving heavy financial costs.

The multidisciplinary Melanoma Clinic at the PA Hospital provides a world-class service and presents an environment that facilitates the implementation of novel treatment strategies. The underlying goal of this project is to offer individual patients the best available evidence-based care including novel therapeutics to maximise their quality of life and progression-free prognosis. This should translate into improved patient outcomes through stronger evidence-based recommendations and optimization of existing management strategies. While significant efforts are well-deservedly being directed towards the early detection and management of melanoma at a primary care level and within the nation’s public hospitals, this group of patients requires much greater attention and more sustained focus than they currently receive.

**1.2 Definitions and Nomenclature**

The terminology used to describe in-transit disease is inconsistent and often poorly defined. The terms local recurrence, local metastasis, satellitosis, in-transit or advanced local disease are often interchanged and are hypothesised to be derived from the same biological process representing intra-lymphatic spread of disease. [13] Local recurrence can represent either persistent disease due to inadequate initial surgical excision or reflect disease extending within close proximity of the primary lesion. The term ‘regional non-nodal metastases’, was first applied by Cascinelli et al. and is a simplified yet accurate deﬁnition of the pathological process. [14] By convention, it is accepted that locoregional recurrence includes both in-transit and satellite lesions and that these are both products of the same pathological process. For the purposes of this project the American Joint Commission on Cancer (AJCC) 7th Edition definitions will be applied as follows: [15]

**Local recurrence**: Disease recurrence occurring within the primary excision scar.

**Satellite metastasis**: Disease recurrence located within 5cm of the initial lesion or 2cm of the excision scar.

**In-transit metastasis**: Disease recurrence occurring greater than 5cm of the initial lesion or 2cm of the excision scar.

**1.3 Rationale**

Based on our structured literature review and retrospective institutional treatment results, it appears that ImiQ or DPCP are effective, non-invasive therapies that are useful for treating patients with multiple cutaneous melanoma metastases when surgical is not possible, has failed or is refused by patients. We believe that when patients are selected based on their in-transit phenotype (macular, papular or small nodular disease) treatment with ImiQ or DPCP will result in improved complete response rates. It is also hypothesized that these treatments will cause fewer severe treatment complications, will be more cost effective and that patients will experience an improved overall quality of life compared to other treatments (such as ILI).

**1.4 Research Significance**

Based on a systematic review conducted by the investigators, the literature indicates that current directed locoregional therapies and management strategies for in-transit metastatic melanoma fail to improve melanoma-specific survival. Patients face significant morbidity limiting their quality of life (QOL) with ultimately poor prognoses. This project has the potential to significantly reduce disease burden and healthcare related costs while enhancing QOL and disease-free survival. The stratification of treatment based on disease morphology may facilitate the selection of more efficacious therapies. The results derived from this study will provide additional data that may guide evidence-based recommendations and support non-invasive treatments that reduce disease burden, treatment-related morbidity, time and health expenditure.

**1.5 Overview**

This is the formal experimental protocol for a pilot study designed as a phase II, open-label, single center, randomised trial evaluating the use of non-invasive topical immunotherapies for patients with multiple in-transit cutaneous melanoma metastases. The aim is to determine if independent topical imiquimod or diphenylcyclopropenone (DPCP) treatment is an efficacious, well-tolerated and cost-effective alternative to current locoregional therapies in patients who are unable to undergo, refuse or have failed surgery. While imiquimod and DPCP have been used successfully, the evidence is limited to case reports and small prospective case series and treatment regimens vary between institutions. The results of this study may lead to improved patient rated outcomes compared to current strategies through a reduction in the burden of local disease, fewer serious treatment-related complications, more convenient application, streamlined review and ultimately decreased healthcare-associated expenditure.

**2. STUDY DESIGN**

This is a Phase II, open-label, single center, randomised, non-superiority pilot study. Eligible patients will be enrolled and randomised in a 1:1 ratio to receive either ImiQ (‘Treatment Arm A’) or DPCP (‘Treatment Arm B’) This will allow for the comparison of the clinical complete response rate of multiple cutaneous in-transit melanoma metastases at the time to best response and at 12 months following treatment with ImiQ or DPCP in patients who are unable to undergo surgery, refuse surgery or who have failed surgery (not clinically appropriate). Treatment failure will include both the recurrence, progression or persistence of in-transit melanoma metastases, and will be defined as the presence of malignant melanoma cells within the existing treatment region confirmed by histopathology prior to commencement of treatment.

**3. STUDY POPULATION**

A total of thirty subjects in total, 18 years or older, with biopsy-confirmed Stage III or IV cutaneous in-transit melanoma metastases in at least five measurable lesions will be enrolled for treatment. A minimum of 5 measurable lesions in anatomical locations suitable for topical treatment are required to enable initial and repeat lesion biopsies and the objective assessment of tumour response. The target number of patients successfully completing treatment and follow-up is 10 patients within each treatment arm. An adjustment calculation has been completed and in order to achieve this target number of patients a sample size of 15 patients should be recruited. This accounts for an assumed 10-15% drop-out rate due to discontinuation secondary to severe adverse treatment reactions, loss-to-follow-up and death. This is a pilot non-superiority study and therefore a formal power-calculation has not been applied to determine the number of participants allocated to each treatment arm.

# 3.1 Subject Completion and Withdrawal

# Subjects may withdraw from the study at any time or may be discontinued at the discretion of the treating physician. They may also be withdrawn in the presence of unmanageable toxicity or if the investigator makes a decision to terminate the study. Treatment after the completion of the study duration will be at the discretion of the treating physician.

**4. STUDY AIMS**

To evaluate the clinical efficacy of topical imiquimod and diphenylcyclpropenone (DPCP) as independent non-invasive therapies for cutaneous in-transit melanoma metastases and determine whether these agents can enhance patient-rated outcomes and reduce health-related expenditure.

**5. OUTCOMES**

**5.1 Primary Endpoint**

The number of patients experiencing a complete response (clinical assessment) following treatment.

**5.2 Secondary Endpoints**

* Proportion of patients experiencing partial response, stable disease and local disease progression at 12, 18 and 24 months.
* Length of time patients experience local disease-free or progression-free survival.
* Proportion of patients experiencing overall disease progression including death following the completion of the treatment intervention.
* Differences in time to disease recurrence or progression following complete clinical resolution with DPCP treatment depending on further prophylactic treatment.
* Change in patient-rated outcomes (reported quality of life parameters) before, at 12 months and the time of best response following treatment, assessed using the FACT-M
* Rate of complication(adverse events) secondary to treatment.
* Estimated difference in the health-related costs.

**5.3 Study Duration**

Each subject will be enrolled in the study for 52 weeks after commencing imiquimod or DPCP treatment. The aim is to achieve a minimum follow-up duration of 12 months, continuing up to 24 months after treatment commencement. The total recruitment window will be open for at least 24 months. The total study length is therefore estimated to be between 36 months based on recruitment rates.

**5.4 Study Site and Setting**

The TIDAL Melanoma Study will be conducted through the specialist outpatient setting in conjunction between the Dermatology Department and Melanoma Specialist Outpatient Clinic at Princess Alexandra Hospital.

**6. PATIENT SELECTION**

**6.1 Inclusion Criteria**Patients will only be included in the study if they satisfy all of the following:

* Men or women aged 18 years or older.
* Willing and able to comply with study requirements.
* Capable of providing valid (written and informed) consent.
* Histologically or cytologically proven in-transit melanoma metastases.
* Measurable disease between 2-20mm in diameter that can be accurately assessed by ruler/caliper.
* Between 5 to 20 target lesions.
* ITM present in anatomical locations amenable to imiquimod or DPCP treatment.
* Cutaneous (superficial) macular, papular or small nodular ITM deposits.
* Considered un-suitable for surgery by the treating surgeon due to anatomical location or prohibitive disease factors, previous treatment failure or patient refusal.
* 12 weeks minimum duration between completing other directed locoregional treatments (such as ILI or PV-10) to prevent potentially confounding effects (treatment responses).
* Subjects must have, in the opinion of the investigator, adequate renal, haematopoietic and hepatic function, with no clinically significant impairment or uncontrolled haematological, hepatic or renal disease.

**6.2 Exclusion Criteria**Patients will be excluded from the study for any of the following:

* Considered eligible for concurrent treatment with systemic chemo- or immunotherapies.
* Subjects who have received systemic cancer therapy within 12 weeks of study.
* Subjects who have received local treatment (e.g., surgery, cryotherapy, radiofrequency ablation) to the treatment area within 4 weeks of study treatment - to prevent potentially confounding effects (treatment responses/immunosuppression).
* Life expectancy of less than 6 months or ECOG performance status ≥3 (see Appendix G).
* Medical or psychiatric condition that compromises the patient’s ability to complete the treatment or follow-up assessments as per the protocol.
* Unable or unwilling to provide fully informed consent and participate including patients with intellectual or mental impairment.
* Patients who are pregnant or lactating. Women of child bearing potential must have a confirmed negative urine pregnancy test at study entry.
* Known history of immumodeficiency including HIV, uncontrolled central nervous system metastases, concomitant systemic corticosteroid therapy, previous organ transplant.
* Known severe concurrent or inter-current illness including: cardiovascular, respiratory or immunological) illness, psychiatric disorders, or alcohol or chemical dependence that would, in the opinion of the Investigator, compromise their safety or compliance or interfere with interpretation of study results.
* Previous severe adverse or allergic reaction to either treatment agent.
* Patients unable or unwilling to comply with home application of treatment and the investigational nature of the study.

**Acceptable Haematology Results**

Neutrophil count >2.0 x 109 L-1

White cell count >3.0 x 109 L-1

Platelets >100 x 109 L-1

Haemoglobin > 9 g dLL-1

**7. REGISTRATION**

**7.1 Trial Registration and Support**

To register, a patient must satisfy all eligibility criteria, a registration form must be completed and the PI or trial co-ordinator notified. The TIDAL Melanoma Trial will be appropriately registered under the Australian and New Zealand Clinical Trials Registry. This will facilitate transparency, constructive clinician feedback and foster effective public communication. The Principal Coordinator has prepared the final protocol and all study documents and the Data Coordinator will assist with the collection, storage and management of data derived through the trial.

**7.2 Data Management and Quality Assurance**

Comprehensive data management and quality assurance will be conducted in accordance with ANZMTG standards with strict operating procedures and policies. Quarterly operations meeting will be held to review trial progress, supported by at least annual Trial Management Committee meetings. Patient data will be collected using standardised paper proformae (case report forms) (refer to appendix) and entered onto a secure QMP Database that complies with ICH GCP recommendations. With respect to the primary and secondary endpoints, the first 5 participants will be reviewed by specialist expert dedicated reviewer (some of whom are named study investigators on this grant as well as Trial Management Committee members) thereafter 1 in every 5 patients (20%) will undergo select review. ANZMTG has strict data management protocols. All trial data will be cleaned and entered by clinical trials data coordinator.

**8. STATISTICAL CONSIDERATIONS**

**8.1 Analysis Population**

All subjects who are enrolled and receive either treatment modality will be evaluated for efficacy, safety and progression-free survival using an intention to treat analysis.

**8.2 Patient Recruitment** The Melanoma Specialist Outpatient Clinic at the PAH receives approximately 600 new melanoma patient referrals annually. Additionally, approximately 2000 patients are reviewed per year for ongoing follow-up and further management as required. It is estimated that 3-4 new patients with in-transit disease are referred to the PA Hospital Melanoma Specialist Outpatient Clinic each month. Furthermore, a review of the existing patient database has identified 260 patients with in-transit disease treated through the specialist outpatient department over the past 15 years, many whom continue to return for regular review. To date, sixty patients have been treated with DPCP at our institution and have formed the basis for a retrospective ‘early experience’ sub-group analysis.

**8.3 Randomisation and Blinding**

Randomisation will be provided by a web-based permuted block system available to the QMP. This will be available 24 hours a day in order to facilitate efficient patient recruitment. Patients will be randomised in a 1:1 ratio and allocated to either treatment arm, thereby receiving one of two possible treatments. This study will be open-label and non-blinded in nature.

**8.4 Sample Size and Power Calculations**

This is a proof of concept, pilot study that aims to primarily assess the efficacy of each treatment arm. This will facilitate comparison with the currently accepted standard of care (historical control). ILI is another directed locoregional therapy that has been studied in detail at our institution and the results formally published. [17] The complete response rate for patients undergoing ILI was 24% in a cohort of 74 patients. The pilot study will aim to recruit a total of 15 patients into each treatment arm over the course of an 18-24 month time period at our institution. The actual assessable target sample size for analysis after completing treatment and at least 12 months follow-up is 10 patients in each treatment arm and a larger cohort will allow for expected patient drop-out. This will yield important preliminary data that will facilitate an interim safety and efficacy analysis. On the condition that the preliminary data supports the hypotheses and the safety report is satisfactory the pilot study may be extended and completed as a separate, larger Phase II/III, randomised, adequately powered, comparative, superiority trial.

**8.5 Summary**

This is a pilot, non-superiority proof of concept, phase II study that will aim to recruit 15 participants into each treatment arm over a 24 month period. A standard estimate of 10-15% drop-out and loss to follow-up has been anticipated and these numbers should provide adequate data for the patients completing a minimum of 12 months follow-up. All registered patients will be accounted for in the analysis of the study and patients who commence any therapy will be used to assess the main study endpoints.

**9. OUTCOME MEASURES**

**9.1 Intention to Treat**

All registered patients will be accounted for in the analysis (intention to treat) and patients who commence either treatment will be used to assess the main endpoints.

**9.2 Assessment of Tumour Response**

Baseline documentation of in-field target lesions is required prior to the commencement of treatment. This will be performed using standardised data collection forms and colour photography. All measurable lesions up to a maximum of 20 lesions in total, representative of cutaneous disease, should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repetitive measurements. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD can then be used as a reference measure to characterise the objective tumor response following treatment. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded and measured at baseline. Measurements are not required but the presence or absence of each should be noted throughout follow-up.

**9.3 Efficacy (Primary Outcome Measure)**

Complete response will be determined through clinical disease assessment for palpable or visual lesions at the time to best response or up to 12 months following the commencement of treatment. Progression-free survival will also be monitored by clinical disease assessment for palpable or visual lesions, additionally CT/PET/MRI or similar methodology for systemic disease will be performed according to the standard of care of the study institution. Response assessments will be performed in accordance with RECIST guidelines whenever possible. All subjects will be followed for overall survival until the close of the study. The primary outcome measure will be the complete response rate as per RECIST criteria.

**9.4 Planned Analysis Methods**

Efficacy will be measured using RECIST criteria where possible and clinical benefit by summation of response parameters (e.g. CR, PR, SD and PD) – refer to appendix C. Treatment of emergent adverse experiences will be summarised based on CTCAE severity grade and coded by the MedDRA system organ class and preferred term. Changes in haematology, chemistry and other laboratory values will be summarised using descriptive methods. Changes will be calculated relative to the values collected at baseline of the initial study. Shifts in laboratory toxicity grades will be evaluated for each laboratory parameter by assessing the maximum increase and decrease observed during the course of the study treatment as graded according to the CTCAE criteria v4.03 for adverse events.

**9.5 Other Secondary Outcomes**

Progression-free survival monitored by clinical disease assessment for palpable or visual lesions and CT/MRI or similar methodology for systemic disease will be performed according to the standard of care of the study institution. Response assessments will be performed in accordance with RECIST guidelines. All subjects will be followed for overall survival until the close of the study. Other outcome measures including the objective response rate (ORR) and clinical benefit (CR+PR+SD) of in-field target lesions will also be assessed using RECIST criteria (Appendix C). Changes in patient rated outcomes (reported quality of life parameters) before, at 12 months and the time of best response following treatment, will be assessed using the FACT-M tool, a validated Quality of life measurement subscale for patients with melanoma. An estimated difference in the health-related costs will be performed at the conclusion of the study by comparing the typical expenses incurred by a patient in each treatment arm compared to the existing standard of care (ILI) using a projected economic bootstrapping model.

**9.6. Safety**

Safety will be assessed by documenting toxicity using CTCAE v4.03 and recording other serious adverse events with acceptable safety defined as 80% of patients receiving the treatment without any grade IV toxicity. An interim safety assessment will be performed using adverse event data available four weeks following the 5th patient completing 90 days of treatment with DPCP and ImiQ. An acceptable safety will be defined as 80% of patients receiving the treatment without any grade IV toxicity.

**9.7 Off-label Therapeutic Approval**

Approval for the use of the investigational agents will be sought for the use of imiquimod for the treatment of cutaneous melanoma metastases from Professor Peter Pillans, Director Clinical Pharmacology. Additionally, an application to the Australian Therapeutic Goods Association for the ‘Supply of unapproved therapeutic goods under the Clinical Trial Exemption (CTX) Scheme’ will be completed under the *Therapeutic Goods Act 1989.*

**9.8 Interim Analyses and Early Closure Criteria**

An interim safety assessment will be performed using adverse event data available four weeks following the 5th patient from each treatment modality completing 90 days of treatment. If the Investigator discovers conditions during the study that indicate it should be terminated, a recommendation to terminate the study may be made after consultation between the Principal Coordinator and the HREC. If necessary the study will be terminated under an appropriate schedule designed so as not to jeopardise the health of any subject.

**10. PRE-TREATMENT EVALUATION**

Patients will be evaluated with a complete history, physical examination, complete blood count (CBC), liver functions tests (LFTs), serum creatinine, and pregnancy test (for females of childbearing potential) prior to study entry. Key data including ECOG status, ASA grade, Modified Karnofsky Performance Scale, medical co-morbidities and the FACT-M (QOL) will also be assessed. This will be performed during the screening phase of patient recruitment and will be completed within 28 days of commencing treatment. A second pre-commencement visit will ensure patients are randomised and further pre-treatment evaluation will be undertaken within 14 days of commencing either DPCP or ImiQ.

**10.1 Serum and Saliva Sub-Studies**

The following routine serum studies will be collected periodically (as per the treatment schedule):

* + Chem 20/CMP (ELFTs, RFTs, LDH) – see below\*.
  + Vitamin D
  + FBC
  + Extended T-cell differential (including CD4 and CD8) – full haematology screen inc. B/T cell
  + Inflammatory markers (IFN, TNF, IL-17, prognostic protein S100B)
  + B-hCG

An additional 20mL of ‘research blood’ will be collected and stored for later analysis. Saliva samples will also be collected and stored at the time of routine serum collection for future RNA and DNA analysis. These biological specimens will be stored within the existing Melanoma and Soft Tissue Bank. This repository is located within the TRI complex on site at the PAH campus, and will be conducted in accordance with the appropriate ethical standards approved for this parallel project (HREC-10-QPAH-153).

*The Comprehensive Metabolic Panel (CMP) includes: albumin, ALP (alkaline phosphatase), ALT (alanine amino transferase, also called SGPT), AST (aspartate amino transferase, also called SGOT), bilirubin, calcium, carbon dioxide (bicarbonate), chloride, creatinine, glucose, potassium, total protein, sodium, and BUN (blood urea nitrogen).*

**10.2 Histopathology**

3mm punch biopsies will be used to obtain histological specimens periodically both at baseline (prior to treatment (W-2) and throughout the treatment (as per the treatment schedule). Biopsy targets will include at least 1 in-transit melanoma lesion for diagnosis and BRAF testing and 1 skin specimen within the anticipated treatment field (≤10mm) prior to treatment. After 4 weeks of treatment biopsies will be repeated including both an in-transit melanoma lesion and skin within the surrounding treatment field. Once the diagnosis of in-transit disease has been established, the collected tissue will also be stored for later use within the existing Melanoma and Soft Tissue Bank.

**10.3 Photography**

Digital colour photography of melanoma lesions in the treatment area, including dermoscopy and reflectance confocal microscopy will be taken at baseline and thereafter as per the formal treatment schedule. If considered relevant additional photographs may be taken between these timeframes as required by investigators. These images will be backed-up and stored securely within the Department of Dermatology.

**10.4 Radiology**

Patients will be required to have completed a CT or CT/PET staging scan within 3 months of commencing treatment on the trial to evaluate for distant metastases. This will be repeated at 6, 12 and 24 months into the trial.**11. TREATMENT**

**11.1 Overview**

This is a Phase II, single centre, randomised, open-label, two-agent study. Subjects with at least one cutaneous in-transit melanoma lesion ≥ 2 mm in diameter that can be accurately measured by ruler/caliper will receive topical treatment with either agent treating up to twenty target lesions. Body mapping and digital photography with lesion identification markers and reference scale will be used to accurately identify and track all study lesions. To accurately reflect anticipated clinical use, new lesions presenting after the initial treatment session may be treated as new non-target lesions provided that the limit of 10 non-target lesions is not exceeded. To ensure adequate time is allotted for the development of full response to treatment, subjects should be followed for a minimum of 52 weeks following after commencing treatment. Systemic and locoregional adverse events will be monitored over the study interval. Subjects will be observed for onset of acute adverse effects for 1 hours following the sensitisation process for DPCP treatment.

A subject’s participation in the study will be stopped if progressive disease (based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria) is observed in treated study lesions, or if new systemic lesions or progression of visceral lesions is observed, at 3 months or more following commencement. An interim safety assessment will be performed using adverse event data available at a point four weeks following initial administration to the 5th and 10th subjects treated. No local or systemic cancer therapy, including experiment therapies, may be administered during the study interval unless the patient is excluded due to disease progression or adverse events.

Treatment for concurrent or inter-current illness other than melanoma, and for wound care (including application of absorbent bandages to study lesions) or management of pain, may be prescribed at the Investigator’s discretion. Subjects must avoid exposure of skin and eyes to bright light (especially direct or indirect sunlight) for 48 hours following treatment administration to prevent potential reaction to DPCP or imiquimod.

The investigational agents are DPCP and imiquimod, two dermatological immunotherapies for topical administration to cutaneous in-transit lesions. Up to 20 target lesions can be treated. It is recommended that the total dose for imiquimod treatment should not exceed 25cm2. Each agent will be administered topically with a 5mm peripheral margin to uniformly treat between 5-20 target lesions. Study lesions will be designated at screening, with target lesions selected on the basis of size (≥ 2mm and ≤15mm diameter) and suitability for accurate repeat measurement throughout the study (measurable by ruler/caliper or ultrasound).

**Treatment Arm A –** 5% Topical Imiquimod Cream: Self-application 5 times weekly, regular clinical review, time to best response and formal 12 month assessment, regular clinical surveillance for duration of remaining trial.

**Treatment Arm B –** Topical DPCP Cream: Sensitisation with 2% Solution, Responders commence treatment regimen - self-application once weekly, regular clinical review, titration to effect, time to best response and formal 12 month assessment, regular clinical surveillance for duration of remaining trial.

**Cross-over and Cessation:** Nil treatment arm cross-over when one therapy fails. Following complete response, patients will cease treatment until clinical recurrence or disease progression.

**11.2 Treatment Schedule**

Eligible patients will commence treatment within four weeks of signing informed consent.

1. Patients randomised to treatment arm A will receive topical 5% imiquimod cream that is self-applied to target lesions up to 5 times weekly for the first 16 weeks and then second daily thereafter. The total treatment area is recommended as <25 cm2 with a maximum number of 20 target lesions.

2. Patients randomised to treatment arm B will receive topical DPCP. Patients will be sensitised with 2% solution and responders will commence the treatment regimen. This will involve self-application of 0.005% DPCP once weekly for the first 4 weeks. Regular clinical review as per the treatment schedule will enable titration to appropriate therapeutic effect. A maximum of 20 lesions are to be targeted within the treatment field.

**Imiquimod and DPCP Regimen / Administration Guide**

|  |  |  |
| --- | --- | --- |
| **Week** | **Imiquimod** | **DPCP** |
| **1 - 8** | 5% Imiquimod applied to lesions 5 days per week with 2 rest days. | 0.005% DPCP applied once weekly. |
| **8 - 16** | Imiquimod applied to lesions 5 days per week (as tolerated). If a sustained, moderate treatment reaction is noted then frequency modified to every second day (3 days per week). | DPCP concentration titrated to effect (up to 5% concentration) and applied once per week to lesions. DPCP can be used up to twice per week to achieve moderate treatment reaction. |
| **16-52** | Imiquimod applied on alternate days (3 days per week) to lesions as tolerated. | DPCP applied at maintenance dose as tolerated in order to achieve a moderate erythematous reaction. |

**11.3 Medications**

**Imiquimod**

Patients are treated using 5% topical imiquimod applied as a mixture within an aqueous cream. This concentration remains constant throughout the duration of treatment. An adequate (i.e. mild to moderate) local inflammatory response is produced with application once daily, five days per week, with two rest days. The solution is applied to the treatment area with a 0.5cm margin surrounding lesions and left overnight for 8 hours duration. The treatment is continued so that a mild to moderate dermatitis is maintained following sequential treatments and this includes the provision to titrate the treatment frequency and dose to effect for individual patients.

Most patients develop a clinical response within 1-3 months and experience clinical regression within 6-12 months. If no clinical response is demonstrated within 3 months, treatment with imiquimod is discontinued. If there is complete clinical resolution of target lesions within 3-6 months the treatment can ceased. If a partial or a stable disease response is achieved the treatment be continued at the discretion of the clinician (to a maximum of 24 months within the trial and thereafter off-trial) or until disease recurrence or progression. Topical imiquimod can be self-administered by patients with regular clinical reviews conducted through the outpatient setting as per the formal treatment schedule.

**Preparation, Storage and Dispensing**

Imiquimod will be prepared for dispensing in the Department of Pharmacy, PAH in accordance with the manufacturer’s instructions. A patient specific hospital prescription will be provided by the treating clinician and delivered to the hospital pharmacy so that the appropriate mediation can be dispensed. The imiquimod is delivered pre-packaged as 12 x 2g sachets containing the agent and will be checked and labeled appropriately. The medication will be stored in a cool, dark, secure place. An expiry date of 12 months after packaging will be provided and 30 days once the seal is broken on individual sachets. All requirements including packaging, labeling and dispensing will be performed by the Department of Pharmacy at the PAH and will be overseen by the Clinical Trials Pharmacist.

**Dose Constraints**

It is recommended that the maximum surface area treated by 5% imiquimod topical cream does not exceed 25cm2.

**Dose Titration**

The dose (concentration) of Imiquimod cream applied to the patient will be remain at 5% and the frequency of administration can be determined based on the individual patient’s clinical response. This assessment will include the degree of erythema, pruritis, tenderness, degree of ulceration/erosion of the skin and response of melanoma metastases. The aim of treatment is to maintain mild erythema with tolerable pruritis, discomfort and keratitis. After completing treatment for the first 8 weeks the frequency of administration can be decreased to achieve the desired clinical response at the discretion of the investigators as per the administration guide.

**DPCP**

Patients are initially sensitised to DPCP using a 2% solution applied to a clinically accessible point of contact (e.g. forearm). Two weeks following sensitisation definitive treatment is commenced. The optimal dose of DPCP is based on an individual’s clinical response. Treatments concentrations range from 0.005% to 5% applied as a mixture within an aqueous cream. An adequate (i.e. mild to moderate) local contact dermatitis is produced following application once per week for up to 24-48 hours exposure depending on the intensity of response. The ideal dose is gradually achieved by titrating the dose to effect so that a mild to moderate dermatitis is maintained following sequential treatments.

Most patients develop a clinical response within 3 months and experience clinical regression within 6-12 months. If no clinical response is demonstrated within 3 months, treatment with DPCP is discontinued. If there is complete clinical resolution of target lesions the treatment can ceased or continued as per subgroup randomisation. If a partial or a stable disease response is achieved the treatment be continued at the discretion of the clinician (to a maximum of 24 months within the trial and thereafter off-trial) or until disease recurrence or progression. DPCP can be self-administered by patients once weekly with regular clinical reviews conducted through the outpatient setting as per the formal treatment schedule.

**Continuing Treatment**

Patients with complete clinical response will cease treatment until disease recurrence at which time treatment will be re-commenced as per protocol or as clinically appropriate. There is no substantial evidence continuing treatment is warranted and may confound the calculations of time to recurrence or locoregional progression recorded in this trial. Various regimens have been reported in the literature with no clearly significant advantage.

**Preparation, Storage and Dispensing**

The agent DPCP will be diluted in aqueous cream in the Department of Pharmacy, PAH in order to provide the required dosage for administration ranging between 0.005-5%. A patient specific hospital prescription will be provided by the treating clinician and delivered to the hospital pharmacy so that the appropriate dosage can be dispensed. The DPCP titrations will be packaged for each patient in labeled sterile brown glass containers. They will be stored in a cool, dark, secure place. An expiry date of 3 months after packaging will be provided. All dilutions, packaging, labeling and dispensing will be performed by the Department of Pharmacy at the PAH and will be overseen by the Clinical Trials Pharmacist.

**Dose Escalation and Titration**

The dose (concentration) of DPCP cream applied to the patient will be determined based on the individual patient’s clinical response. This assessment will include the degree of erythema, pruritis, tenderness, degree of ulceration/erosion of the skin and response of melanoma metastases. The aim of treatment is to maintain mild erythema with tolerable pruritis, discomfort and keratitis. Additionally, the frequency of administration can be increased up to twice per week to achieve the desired clinical response at the discretion of the investigators.

**Treatment Rationale - Imiquimod**

Topical imiquimod 5% applied 5-7 times per week (e.g. overnight) for a total contact duration of at least 8 hours. The aim is to produce a ‘moderate inflammatory response’ for the duration of treatment until clinical resolution is achieved. Total treatment lengths vary in the literature from a mean duration of: 3 - 12 months Shi et al. [24, 26, 28, 29, 34, 35]

**Treatment Rationale - DPCP**

Initial sensitisation to DPCP is required for the treatment to work. The clinician applies a small quantity of high concentration DPCP (2%) and this is left intact for 2-3 day to induce a contact allergy. The patient or clinical assistant then applies a lower concentration of DPCP to the affected areas once weekly, using up to 1 ml per session. The solution should remain on the skin for 6 to 24 hours or as directed, and is then washed off. The area of application should be physically covered during the first 24 hours, as DPCP is degraded by sunlight. Great care should be taken to avoid DPCP touching other areas of the body. Gloves are worn by the patient and/or assistant for each application. There is a risk that the patient's partner or healthcare worker may also become sensitised and develop dermatitis. This treatment protocol is derived from the published methodology and results of Damian et al. and the preliminary treatment results at the PA Hospital.

**12. STUDY EVALUATIONS**

**12.1 Screening Visit**

The patient will be evaluated against the relevant inclusion and exclusion criteria. This will involve a standard medical history and examination with photographic documentation and measurement of the target lesions to be treated. Lesions to be treated with either DPCP or imiquimod will be designated at screening. These lesions should be selected on the basis of size (between 2-20mm) and suitability for repeat measurement throughout the study (measurable by ruler/caliper). The target lesions should be in locations that will allow consistent application of the investigational agents. The screening visit should occur within 28 days prior to study treatment and ideally within 2 weeks of beginning treatment. The following procedures/evaluations will occur at screening:

* + - 1. Informed consent.
      2. Subject history (subject demography, current and previous medical history).
      3. Physical exam (general examination, including auscultation of heart and lungs).
      4. Vital signs (resting/reclining heart rate and blood pressure, respiration, temperature, height and weight).
      5. Disease evaluation.
      6. Body mapping of Study Lesions.
      7. Biopsy (3mm punch biopsy or fine needle aspiration biopsy) of at least one Study Lesion if first episode of in-transit disease. Local anaesthetic may be used prior to biopsy at the discretion of the investigator.
      8. Laboratory tests (CBC, CMP, TFT).
      9. Pregnancy test (serum, pre-menopausal female subjects only).
      10. Evaluation of Study Lesions (lesion measurement by ruler/caliper measurement)
      11. CT documentation of visceral lesions (e.g., documentation of absence of lesions in Stage III subjects, location and size of visceral lesions in Stage IV subjects).
      12. Concurrent medications.
      13. Randomisation to either treatment arm A or treatment arm B
      14. Sensitisation using 2% DPCP as per the sensitisation instructions if randomised to the DPCP group.

**12.2 Sensitisation (DPCP)**

Equipment required for sensitisation:

* 2% DPCP in acetone solution in a brown glass bottle – a hospital prescription in the patient’s name is used as the medication order for the DPCP solution.
* Filter paper disc.
* Finn chamber (Epitest: Tuusula Finland)
* Disposable pipette or dropper
* Disposable forceps
* Occlusive dressing

1. A sun-protected area on the medial arm of the patient is selected and cleaned with an alcohol wipe.
2. Two drops of DPCP are applied with a pipette or dropper to a filter paper disc.
3. The filter paper disc is placed on an adhesive Finn chamber with forceps.
4. The filter paper disc and Finn chamber are placed onto the prepared area of skin on the patient’s arm.
5. An adhesive dressing is placed over the Finn chamber apparatus to secure it in place. This is to remain in situ for 48 hours and to be kept dry.
6. After 48 hours, the Finn chamber apparatus is removed from the patient’s arm. An area of erythema +/1 blistering in the sensitised area is expected by not necessary for sensitisation to have taken place.
7. The patient is booked for the initial treatment appointment 2 weeks following sensitisation to DPCP.

**12.3 DPCP Treatment**

Equipment required for DPCP treatment phase:

* 0.005-5% DPCP in aqueous cream to 100 grams – a hospital prescription in the patient’s name is used as the medication for the DPCP cream.
* Disposable gloves

Patient take-home kit:

* Disposable gloves
* Non-soap cleanser
* Topical emollient
* White soft paraffin or equivalent
* Jelonet or equivalent paraffin gauze
* Dressing packs — Melolin/Combine, Micropore and Tubigrip
* Emergency contact number for Dermatology Registrar on-call

DPCP treatment (2 weeks following screening, randomisation and sensitisation):

*NB: if the patient is female of child bearing potential, negative pregnancy status must be confirmed prior to treatment and reliable contraceptive methods must be established.*

1. The patient is provided with the initial concentration of DPCP in aqueous cream and instructed to apply the cream with gloved hand to the agreed treatment area once weekly.
2. The DPCP cream is to remain on the skin and not be washed off until 24-48 hours following application. A non-soap cleanser is used. Simple emollients can be applied to the treatment area alter the 24-48 hour treatment application period.
3. After 2 weeks the patient is reviewed. Moderate erythema +/- mild pruritis is expected at this stage but is variable.
4. Three concentrations of DPCP in aqueous cream are provided to the patient for weekly application in the same manner as detailed above, with titration such as to elicit moderate erythema +/- pruritis to the treatment site. It is recommended that the DPCP be titrated to clinical response by increasing by up to a maximum of 5% DPCP. A typical range of concentrations provided to the patient initially could include 0.005%, 0.01%, 0.1% DPCP.
5. The patient continues treatment in this manner to maintain moderate erythema at treatment site.
6. The patient should he reviewed by clinical staff periodically to ensure appropriate response and to modify treatment according to response. (refer to formal treatment schedule for frequency of clinical reviews)
7. Treatment should continue in this manner indefinitely or until otherwise determined by the treating clinician and in agreement with the patient.
8. If erosion or ulceration of the skin within the treatment site occurs (i.e. an excessive of greater than anticipated reaction), the next lowest concentration of DPCP in aqueous cream necessary to maintain a mild inflammatory response at the treatment site should be used by the patient. The patient is to be provided with a take-home kit for managing these reactions. Simple wound care incorporating saline bathes, simple emollients and clean dressings should be applied. The patient should be reviewed at the earliest opportunity.

For lesions that respond to DPCP, treatment response is usually seen within the first 8 weeks, manifested as lack of, or slowed rate of, lesion growth, flattening of lesions and grey-blue discoloration of lesions as immune-mediated regression occurs. Melanoma metastatses that have been rendered nonviable by DPCP slowly fade in colour over several months as the "pigment tattoo" left by the tumour is digested by macrophages. It is anticipated that many patients will have complete or near-complete responses to DPCP, and that in some patients the DPCP treatment may slow but not halt the rate of disease progression

**12.4 Imiquimod**

Equipment required for imiquimod treatment phase:

* 5% Imiquimod – a hospital prescription in the patient’s name is used as the medication for the DPCP cream.
* Disposable gloves

Patient take-home kit:

* Disposable gloves
* Non-soap cleanser
* Topical emollient
* White soft paraffin or equivalent
* Jelonet or equivalent paraffin gauze
* Dressing packs — Melolin/Combine, Micropore and Tubigrip
* Emergency contact number for Dermatology Registrar on-call

Imiquimod treatment (2 weeks following screening and randomisation):

NB: if the patient is female of child bearing potential, negative pregnancy status must be confirmed prior to treatment and reliable contraceptive methods must be established.

1. The patient is provided with the 5% imiquimod cream and instructed to apply the cream with gloved hand to the agreed treatment area 5 days per week.
2. The Imiquimod cream is to be applied with a 0.5cm periphery around the target lesions. It is to remain on the skin overnight and not to be washed off until after 8 hours following application. A non-soap cleanser is used. Simple emollients can be applied to the treatment area after the treatment application period. It is recommended the patient have 2 ‘rest’ days per week where no treatment is applied and regular skin cares are continued.
3. After 4 weeks the patient is reviewed. Moderate erythema +/- mild pruritis is expected at this stage but is variable.
4. One concentration (5%) Imiquimod cream is provided to the patient for regular application in the same manner as detailed above. This should be continued with titration such as to elicit moderate erythema +/- pruritis to the treatment site. It is recommended that the frequency of application be adjusted following review at 4 weeks and each appointment thereafter to clinical response as per the application guide so that if necessary application every second day be recommended in those with a robust response. The duration of exposure can also be increased from 8 hours if necessary for those not achieving the desired clinical response with 5 days per week applications.
5. The patient is to continue treatment in this manner to maintain moderate erythema at the treatment site.
6. The patient should he reviewed by clinical staff periodically to ensure appropriate response and to modify treatment according to response (refer to formal treatment schedule for frequency of clinical reviews).
7. Treatment should continue in this manner indefinitely or until otherwise determined by the treating clinician and in agreement with the patient.
8. If erosion or ulceration of the skin within the treatment site occurs (i.e. an excessive of greater than anticipated reaction), the next lowest concentration of DPCP in aqueous cream necessary to maintain a mild inflammatory response at the treatment site should be used by the patient. The patient is to be provided with a take-home kit for managing these reactions. Simple wound care incorporating saline bathes, simple emollients and clean dressings should be applied. The patient should be reviewed at the earliest opportunity.

For lesions that respond to Imiquimod, treatment response is usually seen within the first 16 weeks, manifested as lack of, or slowed rate of, lesion growth, flattening of lesions and grey-blue discoloration of lesions as immune-mediated regression occurs. Melanoma metastatses that have been rendered nonviable by treatment slowly fade in colour over several months as the "pigment tattoo" left by the tumour is digested by macrophages. It is anticipated that many patients will have complete or near-complete responses to ImiQ, and that in some patients the treatment may slow but not halt the rate of disease progression

The formal treatment instructions for patients are outlines in Appendix

**12.5 Treatment Failure / Non-responders**

Patients will be formally assessed for clinical response as per the treatment schedule (refer to Appendix B). If patients fail to demonstrate a clinical response, including stable disease within 3 months of commencing treatment they will be excluded from the trial. The definition for locoregionally progressive disease are defined under RECIST (refer to Appendix D) however this must be applied only to target lesions and the development of new disease outside of the previous treatment field does not necessarily disqualify patients from further treatment. Patients with new and untreated lesions should be clinically assessed and these deposits documented as ‘non-target’ lesions. Non-target lesions should be treated for a minimum of 3 months duration. If during this time the target lesions progress in size (as per RECIST) and no clinical benefit is elicited with treatment of non-target lesions that patient should be removed from the trial and offered alternative treatment. Patients that demonstrate a poor clinical response can be monitored more frequently at the discretion of the clinician to ensure they do not develop rapidly progressive disease and to confirm they are being appropriately treated. **12.6 Regular Clinical Follow-Up**

Study evaluations will be performed at screening, study day 0 (day of agent administration), day 14 (2 week follow-up), and at weeks 4, 8, 12, 16, 24, 36 and 52 etc. (or early termination) as per Appendix B. Treatment and follow-up for patients will continue at regular intervals following the first 12-months as per the formal appointment schedule (Appendix B). The size of all study lesions will be assessed at each visit (except those visits occurring in addition to the treatment schedule due to clinical concern or need for additional follow-up) using ruler/caliper or ultrasound imaging. Study lesions that may be a complete response (CR) based on clinical evidence can be biopsy confirmed at final evaluation when a residual mass is present to distinguish potential CR from partial response (PR); biopsy of all other study lesions shall be at the discretion of the Investigator. This schedule will allow comprehensive monitoring of response to DPCP or Imiquimod treatment.

Laboratory tests (complete blood count, blood chemistry and inflammatory measures) and vital signs (temperature, pulse, blood pressure) will be performed at screening and on study days 1 and at week 4, and at final evaluation (week 52 or early termination). Systemic disease will be assessed at screening, at weeks 24 (6 months), 12 months and 24 months (if applicable) or at final follow-up (or early termination) by CT imaging. Subjects for whom final follow-up occurs less than 8 weeks after a prior CT will not undergo additional CT imaging at final follow-up. The survival status of subjects withdrawing early from the study will be assessed by telephone interview conducted at weeks 12, 24, 36 and 52 as appropriate based on time of withdrawal.

Systemic and locoregional toxicity (including abnormal laboratory test results) will be monitored over the study interval. Adverse events will be graded by the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) and coded according to MedDRA terminology.

During the scheduled clinical appointments patients will undergo a review of their progress including history, routine examination and routine blood tests. This will enable adjustments to their treatment and will facilitate the collection of accurate data. The results of clinical findings including examination results, measurements and adverse events will be documented within the patient record. Photographic records will also be taken and stored within the department. A biopsy of a solitary treated lesion will also be performed at week four to enable histopathological sub-studies. The typical review appointment will include the following:

* A review of the patient’s history and progress since their previous appointment.
* A standard physical examination including treatment area / wound review
* Measurement of treated lesions.
* Photographic records.
* A review of any adverse events and adjustment to the treatment plan including new prescriptions.

In order to monitor clinical response or any adverse events and facilitate care the clinician may at their discretion request additional clinical appointments within the scope of the clinical trial.

**12.7 Post-Trial Conclusion and Continuing Treatment**

Following the conclusion of the trial patients will continue to be offered treatment at the appropriate standard of care and this will be funded through the PAH as currently occurs. Patients will continue to be reviewed at regular clinical interviews as per the formal treatment schedule (refer to Appendix B). Patients with complete clinical response will cease treatment until disease recurrence or progression. At that time treatment will re-commence at the appropriate standard. There is no substantial evidence for continuing treatment after a complete response and various regimens have been reported.

**13. PRE-CAUTIONS**

**Pregnancy**

Female patients of child-bearing age must be tested and have a negative pregnancy test prior to commencing treatment with either agent. Appropriate contraception must also be used throughout treatment. At any time during the trial if a patient suspects or is diagnosed as being pregnant they must discontinue treatment and notify the PI.

**Local Inflammation, Swelling, Blistering or Infection**

Localised inflammation, swelling, blistering or infection lasting up to several weeks may be observed following Imiquimod and DPCP administration, possibly related to the occurrence of necrotic tumour tissue at the injection site in subjects having compromised local circulation or immune system function. To preclude onset of cellulitis it may be appropriate to prescribe prophylactic antibiotics prior to or at the time of Imiquimod or DPCP administration on clinical review when patients are considered to be at risk.

**Discomfort and Irritation**

Mild pain at the treatment site has been noted by the majority of patients during and following, DPCP and Imiquimod administration. Subjects should be advised that they may experience discomfort, tenderness or irritation of the treatment lesions for a day or more, and should be offered analgesia if discomfort is severe or persistent.

**Influenza-like Symptoms**

Following treatment with Imiquimod patients may develop mild flu-like symptoms and nausea. These patients should be carefully monitored and if severe and symptoms persist it may be reasonable to temporarily withhold further treatment until their clinical condition improves at the discretion of the clinician.

**Severe Contact Dermatitis**

This reaction may include intense pruritis, local oedema and or desquamation at the site of treatment or areas exposed to the investigational agent. This can be managed with topical corticosteroids but will generally improve spontaneously within 10 days. Patients must take care to use gloves and to accurately apply the agent avoiding application to unintended and sensitive body sites (e.g. eyes, mucous membranes and genitals). Generalised dermatitis may also occur and generally resolves spontaneously – this should prompt the clinician to reduce the total dose or frequency of application as per the administration guide.

**Hypo- or hyperpigmentation**

Intense reactions to the investigational agents can cause post-inflammatory changes in pigmentation. These effects are usually more pronounced in darker-skinned individuals. This side-effect will often improve gradually over months following severe inflammation and should not necessarily prompt the clinician to discontinue treatment although they may reasonably suspend treatment temporarily to ensure the effects improve. Treatment may also trigger vitiligo, regional lymphadenopathy, erosion, ulceration and crusting of the skin.

**Temporary Treatment Interruption / Suspension**

At the discretion of clinicians, treatment can be temporarily withheld due to the development of robust and excessive treatment side-effects. This period can continue for up to 4 weeks without warranting exclusion of the patient from the trial.

**14. WITHDRAWAL**

Subjects may withdraw from the study at any time or may be discontinued at the discretion of the treating physician. They may also be withdrawn in the presence of unmanageable toxicity or if the investigator makes a decision to terminate the study. Treatment after study will be at the discretion of the treating physician.

**14.1 Withdrawal Criteria**

Treatment can be terminated early if any of the following occur:

* There is evidence of a type I allergic reaction (including the development of acute urticarial, wheeze or signs of anaphylaxis) associated with either therapy.
* The patient becomes pregnant during the course of treatment.
* The patient requests to discontinue treatment.
* There is no clinical response within 12 weeks of commencing treatment.
* The patient becomes eligible for systemic therapy and begins further treatment.

**14.2 Concomitant Treatment**

Patients are permitted to continue all routine medications considered essential for their welfare. A record of the patient’s medications will be captured within the patient record including the name of the drug, dose, start date, stop date (if applicable) and the indication. At the time of dispensing either therapeutic agent within the trial the pharmacist will assess the patient’s current medications and ensure there is no adverse cross-reaction or contra-indication. If this occurs the pharmacist will notify the principal investigator and members of the clinical team involved with ongoing review, seek advise regarding continuing the concomitant medication and document the outcome within the patient’s record.

**15. ADVERSE EVENTS**

US Department of Health and Human Services. *Common terminology criteria for adverse events v4. 03*. 2010. Available online: <http://evs.nci.nih.gov/ftp1/CTCAE/>

All adverse events (AE) including adverse drug reactions (ADR) and adverse events from radiotherapy encountered during the clinical study should be followed until resolution. This may require obtaining clinical blood samples for appropriate laboratory tests until their values return to baseline levels or performing follow-up physical examinations until resolution of identified abnormalities.

Any adverse events that are on-going at the time of subject withdrawal from the study should be followed until resolution or for a period of at least 28 days following the last dose of the investigational drug or from radiotherapy.

* All adverse events having an onset within a period of at least 28 days following the last dose of the investigational drug should be reported to the manufacturer of the investigational drug via the manufacturer’s Australian representative.
* Any adverse event deemed to be at least possibly related to administration of the investigational drug should be reported to the manufacturer of the investigational drug via the manufacturer’s Australian representative regardless of interval following the last dose of the investigational drug.
* Any serious adverse events that occur within 28 days following the last dose of the investigational drug or from radiotherapy must be reported to the manufacturer of the investigational drug via the manufacturer’s Australian representative and followed to conclusion.

An adverse event is defined as:

“Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product….” ICH-E6: Good Clinical Practice, Consolidated Guideline (CPMP/ICH/135/95, July 1996)

An adverse drug reaction is any adverse event (AE) associated with the use of a drug in humans, whether or not considered drug related, including the following:

“all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, e.g. the relationship cannot be ruled out.” (CPMP/ICH/135/95)

## 15.1 Adverse Event Reporting

All adverse events, whether or not associated with administration of the investigational drug that occur within the study interval following administration of the investigational drug should be recorded and monitored until:

1. The adverse event resolves and the subject has returned to baseline state of health;

2. The subject is lost to follow-up;

3. The event is otherwise explained; or

4. The Investigator does not expect any further improvement or worsening of the adverse event.

The information to be recorded will include:

1. The specific type of reaction reported in standard medical terminology.
2. The severity/grade of the adverse event. Toxicities will be graded according to the NCI Common Terminology for Adverse Events v4.03 (CTCAE). The CTCAE is delineated in booklet form and is also available on the NCI website at <http://evs.nci.nih.gov/ftp1/CTCAE/About.html> If toxicities are not defined in this scale, the intensity of each adverse event should be graded as follows:

|  |  |  |
| --- | --- | --- |
| **CTCAE Grade** | Severity | **Definition** |
| 1 | Mild | Discomfort noted, but no disruption of normal daily activity |
| 2 | Moderate | Discomfort noted of sufficient severity to reduce or adversely affect normal activity |
| 3 | Severe | Incapacitating, with inability to work or perform normal daily activity |
| 4 | Life-threatening or disabling | Must be reported as a Serious Adverse Event (SAE). See section 6.2. |
| 5 | Death | Must be reported as a Serious Adverse Event (SAE). See section 6.2. |

1. The duration of the adverse event (start and stop dates).
2. The drug/treatment relationship (assessed by the Investigator).

An assessment should be made of the attributability of the adverse event to the investigational drug or treatment, e.g., according to the following definitions:

**Unrelated:** There is evidence that the adverse event definitely has an aetiology other than the assigned investigational drug or treatment

**Possibly Related**: The adverse event follows reasonable temporal relationship to the investigational drug or treatment but could be explained by either the subject’s clinical status or concomitant medication(s).

**Probably Related**: The adverse event follows reasonable temporal relationship to the investigational drug or treatment and is not reasonably explained by either the subject’s clinical status or concomitant medication(s). Confirmations by de-challenge and/or re-challenge is not required.

**Very Likely Related**: The adverse event follows anticipated response to the investigational drug or treatment and alternative aetiology is not apparent. Confirmations by de-challenge and/or re-challenge is not required.

5. The outcome/status, coded:

[1] Recovered from this AE

[2] Not yet recovered

[3] Died due to this AE

6. A description of action taken in treating the adverse event and/or change in investigational drug or treatment.

## 15.2 Serious Adverse Experiences

A serious adverse experience is any event or combination of events that may represent a hazard, contraindication, warning, or precaution. Serious adverse experiences include:

1. All deaths

2. Life-threatening events

3. Events that are persistently or significantly incapacitating or disabling.

4. Events requiring or prolonging hospitalization.

5. Congenital anomalies/birth defects.

6. Any event, based upon appropriate medical judgment, that may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

All fatal or life-threatening experiences deemed at least possibly related to use of the investigational drug must be reported to the manufacturer or manufacturer’s Australian representative immediately (within 24 hours by telephone).

Serious experiences deemed at least possibly related to use of the investigational drug that are non-fatal and non-life threatening must be reported to the manufacturer’s representative within 24 hours by transmitting a completed SERIOUS ADVERSE EVENT REPORT FORM.

The manufacturer must notify the TGA, FDA and other participating trial Investigators in a written safety report of any adverse experience deemed at least possibly related to use of the investigational drug that is both serious and unexpected within 7 working days and unexpected fatal or life-threatening experience deemed at least possibly related to use of the investigational drug within 3 working days after receipt of the information.

The Investigator will maintain in the subject’s files all pertinent clinical data relating to the event including medical records and information and clinical judgments from colleagues who assist in the treatment and follow-up of the subject.

In addition, the Principal Investigator will provide the manufacturer with a complete written history of the adverse experience and keep his/her HREC or IRB informed of all adverse experiences occurring during the course of the study according to their HREC’s or IRB’s rules and regulations.

**16. ETHICAL AND REGULATORY CONSIDERATIONS**

## Institutional Approval

Formal approval for conducting this study will be sought from the PAH Human Research Ethics Committee (HREC) using a web-based National Ethics Application Form (NEAF).

## Guiding Principles

This protocol has been designed to comply with guiding principles of the Declaration of Helsinki and ICH Harmonised Tripartite Guidelines for Good Clinical Practice.

## Informed Consent

Before enrolment into the study, each prospective candidate will be given a full explanation of the study. The informed consent form will be submitted for approval to the Human Research Ethics Committee of the Princess Alexandra Hospital.

## Institutional Ethics Committee

The Coordinating Investigator will submit this protocol to the Institutional Ethics Committee. The date of the review, the trial identifiers (title, protocol number and version) and the documents studied (protocol and informed consent material) will be clearly stated on the approval or advice sheet.

## Confidentiality

All patient information will be treated in strict confidence. Data, which identify any study subject, will not be revealed to anyone not directly involved in the research project or the clinical care of that subject. An exception is where the patient has provided written consent for his/her records to be subject to source document verification.

## Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. Any deviation from the protocol will be recorded and explained.

**Financial Considerations**

The practical costs associated with coordinating and physically running the trial will be absorbed in the budget allocated to the Melanoma Outpatient Clinic. This will include the costs of DPCP treatment, clinical review and routine biochemistry. There is an associated cost using imiquimod for the off-label treatment of patients with in-transit melanoma, approval for this therapeutic indication will be sought from the Director of Clinical Pharmacology, Professor Peter Pillans. The manufacturers of this product have been contact early within the development phase of this trial and have expressed interest in cooperating with researchers.

**Protocol Version**

The final protocol synopsis is version 3.7 and is dated 1 December 2017.

**Additional Documents**

A complete set of supporting documentation relevant to the study including the case report forms, preliminary melanoma database ethics approval and the patient data proforma have been prepared in parallel to this protocol.

**17. GLOSSARY OF TERMS**

Adverse event: Any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a therapeutic agent. An AE is further characterised according to the CTCAE v4.0.

Eligible: Qualified for enrolment into the study based upon strict adherence to inclusion and exclusion criteria.

Investigational study product: The pharmaceutical form of an active ingredient or placebo

undergoing testing in the clinical trial.

Month: One month is defined as four weeks i.e.28 days during the treatment phase. One year is equal to 12 months.

Patient: Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, as a recipient of the investigational agent.

Patient number: A unique number identifying a patient, assigned to each individual consenting to participate in the study after they sign the first informed consent.

Protocol amendment: ICH defines a protocol amendment as: ‘A written description of a change(s) to or formal clarification of a protocol.’

Protocol administrative change: A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of patients, scope of the investigation, study design, or

scientific integrity of the study) MUST be prepared as an amendment to the protocol.

Site Monitor: An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.

Treatment: Term used throughout the clinical study to denote the investigational agent intended to be administered to a patient, identified by a unique number, according to the study randomization or treatment allocation.

Treatment number: A number identifying a treatment to a patient, determined according to the study randomization or treatment allocation.**18. REFERENCES**

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**Appendix A – Introductory Tables and Figures**

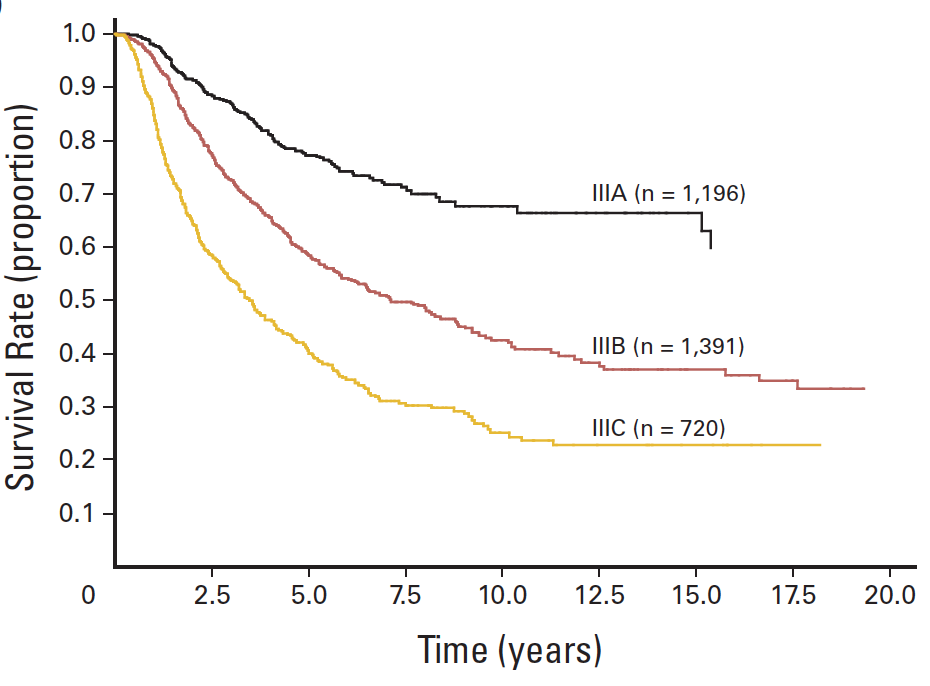
**Table 1: TNM Classification of Stage III and IV Melanoma [8]**

|  |  |  |  |
| --- | --- | --- | --- |
| Stage | T | N | M |
| *IIIA* | Any depth,  Without ulceration | 1-3 regional lymph nodes (not clinically detectable\*) | No distant disease |
| *IIIB* | Any depth,  With ulceration | 1-3 regional lymph nodes (not clinically detectable\*) | No distant disease |
| Any depth,  Without ulceration | 1-3 regional lymph nodes (clinically detectable^) OR  **In-transit lesions** | No distant disease |
| *IIIC* | Any depth,  With ulceration | 1-3 regional lymph nodes (clinically detectable^) OR  **In-transit lesions** OR  Any combination of positive nodes with in-transit disease OR  > 4 positive nodes | No distant disease |
| *IV* | Any depth | Any number of regional lymph nodes | **Distant disease** |

**\*Not clinically detectable = micro-metastases identified after sentinel or elective lymphadenectomy**

**^ Clinically detectable = macro-metastases defined as clinically detectable nodal metastases confirmed by lymphadenectomy or when nodal metastases develop gross extra-capsular extension**

**M1a = Metastases involving the skin, subcutaneous or distant lymph node with normal serum LDH.**

**Figure 1 – Predicted Survival Curves for Melanoma Patients based on Stage III Disease (Balch et al. 2009)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Assessment** | **Screening and Randomisation** | **Treatment Period** | | | | | | | | | | | | | | | | | | | | |
| **Time Point** | **W-2** | **DOFT** | **W1** | **W2** | **W3** | **W4** | **W5** | **W6** | **W7** | **W8** | **W9** | **W10** | **W11** | **W12** | **6M** | **9M** | **12M** | **15M** | **18M** | **21M** | **24M** | **Termination** |
| **Informed Consent** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Inclusion / Exclusion** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **X** |
| **Medical History** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **X** |
| **FACT-M Assessment** | **X** |  |  |  |  | **X** |  |  |  |  |  |  |  | **X** | **X** |  | **X** |  | **X** |  | **X** | **X** |
| **Pregnancy Test** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Routine Blood Tests** | **X** |  |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **Research Blood Tests** | **X** |  |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **Physical Examination** | **X** | **X** |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **CT HNCAP or CT-PET** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  | **X** |  | **X** |  |  |  | **X** | **X** |
| **Measurement of lesions** | **X** | **X** |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **Photography of lesions** | **X** | **X** |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **RCM and Dermoscopy** | **X** | **X** |  |  |  | **X** |  |  |  |  |  |  |  |  |  | **X** |  |  |  |  |  |  |
| **Biopsy of lesions** | **X** |  |  |  |  | **X** |  |  |  |  |  |  |  |  |  | **X** |  |  |  |  |  |  |
| **Randomisation** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Application of 2% DPCP Sensitising Solution** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Prescription for DPCP** |  | **X** |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |  |
| **Application of DPCP Treatment Solution** |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |  |
| **Titration of DPCP** |  |  |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |  |
| **Adverse Events** |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |

**Appendix B – FORMAL SCHEDULE OF EVENTS**

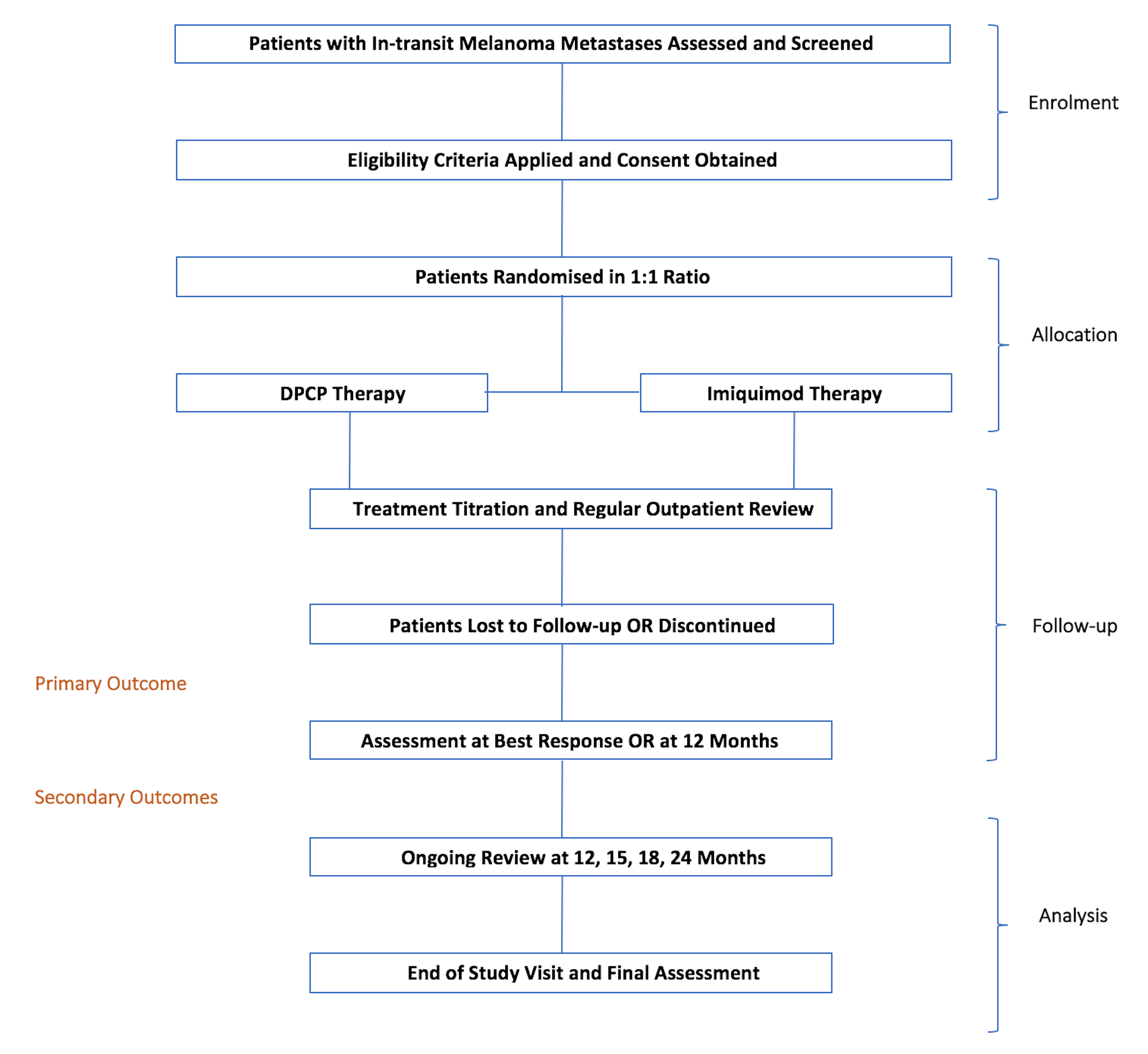
**Table 5 – Treatment Schedule: Topical DPCP**

**Table 6 – Treatment Schedule: Topical Imiquimod**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Assessment** | **Screening and Randomisation** | **Treatment Period** | | | | | | | | | | | | | | | | | | | | |
| **Time Point** | **W-2** | **DOFT** | **W1** | **W2** | **W3** | **W4** | **W5** | **W6** | **W7** | **W8** | **W9** | **W10** | **W11** | **W12** | **6M** | **9M** | **12M** | **15M** | **18M** | **21M** | **24M** | **Termination** |
| **Informed Consent** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Inclusion / Exclusion** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **X** |
| **Medical History** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **X** |
| **FACT-M Assessment** | **X** |  |  |  |  | **X** |  |  |  |  |  |  |  | **X** | **X** |  | **X** |  | **X** |  | **X** | **X** |
| **Pregnancy Test** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Routine Blood Tests** | **X** |  |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **Research Blood Tests** | **X** |  |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **Physical Examination** | **X** | **X** |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **CT HNCAP or CT-PET** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  | **X** |  | **X** |  |  |  | **X** | **X** |
| **Measurement of lesions** | **X** | **X** |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **Photography of lesions** | **X** | **X** |  |  |  | **X** |  |  |  | **X** |  |  |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| **RCM and Dermoscopy** | **X** | **X** |  |  |  | **X** |  |  |  |  |  |  |  |  |  | **X** |  |  |  |  |  |  |
| **Biopsy of lesions** | **X** |  |  |  |  | **X** |  |  |  |  |  |  |  |  |  | **X** |  |  |  |  |  |  |
| **Randomisation** | **X** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Prescription for 5% imiquimod** |  | **X** |  |  |  |  |  |  |  |  |  |  |  |  | **X** |  |  |  |  |  |  |  |
| **Application of 5% imiquimod** |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |  |
| **Adverse Events** |  | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |

**Appendix C – Study Overview**

**Figure 2 - TIDAL Melanoma Study Flowchart**



**APPENDIX D – RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS (RECIST)**

**Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology**.**

**Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

**Methods of Measurement –**

* CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.

**Baseline documentation of “Target” and “Non-Target” lesions**

* All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
* Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
* A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterise the objective tumour.
* All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

**Response Criteria**

**Evaluation of target lesions**

|  |  |
| --- | --- |
| \* Complete Response (CR): | Disappearance of all target lesions |
| \* Partial Response (PR): | At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD |
| \* Progressive Disease (PD): | At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions |
| \* Stable Disease (SD): | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started |

**Evaluation of non-target lesions**

|  |  |
| --- | --- |
| \* Complete Response (CR): | Disappearance of all non-target lesions and normalization of tumour marker level |
| \* Incomplete Response/ Stable Disease (SD): | Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits |
| \* Progressive Disease (PD): | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1) |

1. Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

**Evaluation of best overall response**

The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

|  |  |  |  |
| --- | --- | --- | --- |
| Target lesions | Non-Target lesions | New Lesions | Overall response |
| CR | CR | No | CR |
| CR | Incomplete response/SD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

**Confirmation**

* The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
* To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
* In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

**Duration of overall response**

* The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

**Duration of stable disease**

* SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
* The clinical relevance of the duration of SD varies for different tumour types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

**RECIST CRITERIA REFERENCE TABLES**

**Table 2 – Evaluation of Cutaneous Disease Response**

|  |  |  |  |
| --- | --- | --- | --- |
| **Overall Response** | **Target Lesions** | **Non-Target Lesions** | **New Lesions** |
| **CR** | **CR** | **CR** | **No** |
| **PR** | **CR** | **Incomplete response / SD** | **No** |
| **PR** | **PR** | **Any response other than PD** | **No** |
| **SD** | **SD** | **Any response other than PD** | **No** |
| **PD** | **PD** | **Any** | **Yes or No** |
| **PD** | **Any** | **PD** | **Yes or No** |
| **NE** | **Not all evaluated** | **Any response other than PD** | **No** |
| **PD** | **Any** | **Any** | **Yes** |
| **NE** | **Any response other than PD** | **Not all evaluated** | **No** |

CR: Complete Response, PR: partial response, SD: stable disease, NA: not applicable, NE: non-evaluable

**Table 3 – Evaluation Criteria of Cutaneous Target Lesions**

|  |  |
| --- | --- |
| **Evaluation of Target Lesions** | |
| **Complete Response (CR)** | **Disappearance of all target lesions** |
| **Partial Response (PR)** | **At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD** |
| **Stable Disease (SD)** | **Neither sufficient shrinkage to qualify for PD taking as references the smallest sum LD since the treatment started i.e. ≤20% increase or decrease in size.** |
| **Progressive Disease (PD)** | **At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started OR the appearance of one or more new lesions OR both of these** |

CR: Complete Response, PR: partial response, SD: stable disease, NA: not applicable, NE: non-evaluable

**Table 4 – Evaluation Criteria of Non-Target Lesions**

|  |  |
| --- | --- |
| **Evaluation of Non-Target Lesions** | |
| **Complete Response (CR)** | **Disappearance of all non-target lesions** |
| **Partial Response (PR) / Stable Disease (SD)** | **Persistence of one or more non-target lesion(s)** |
| **Progressive Disease (PD)** | **Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. (Although a clear progression of ‘non-target’ lesions only is exceptional in such circumstances the opinion of the treating physician should prevail.** |

CR: Complete Response, PR: partial response, SD: stable disease, NA: not applicable, NE: non-evaluable

**APPENDIX E: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS version 4.0**

*Attached separately – please request from PI.***APPENDIX F: FACT-M QUALITY OF LIFE MEASUREMENT TOOL**

Below is a list of statements that other people with your illness have said are important**.**

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **PHYSICAL WELL-BEING** | **Not at all** | | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|  |
| GP1 | I have a lack of energy | 0 | | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | | 1 | 2 | 3 | 4 |
|  | | | | | | | |
|  | **SOCIAL/FAMILY WELL-BEING** | **Not at all** | | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|  |
| GS1 | I feel close to my friends | 0 | | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* | |  |  |  |  |  |
| GS7 | I am satisfied with my sex life | | 0 | 1 | 2 | 3 | 4 |

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

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

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

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **ADDITIONAL CONCERNS** | **Not at all** | | **A little bit** | **Some-what** | **Quite**  **a bit** | **Very much** |
|  |
| M1 | I have pain at my melanoma site or surgical site | | 0 | 1 | 2 | 3 | 4 |
| M2 | I have noticed new changes in my skin (lumps, bumps, colour) | | 0 | 1 | 2 | 3 | 4 |
| M3 | I worry about the appearance of surgical scars | | 0 | 1 | 2 | 3 | 4 |
| B1 | I have been short of breath | | 0 | 1 | 2 | 3 | 4 |
| ITU4 | I have to limit my physical activity because of my condition | | 0 | 1 | 2 | 3 | 4 |
| An10 | I get headaches | | 0 | 1 | 2 | 3 | 4 |
| Hep3 | I have had fevers (episodes of high body temperature) | | 0 | 1 | 2 | 3 | 4 |
| C1 | I have swelling or cramps in my stomach area | | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | | 0 | 1 | 2 | 3 | 4 |
| M5 | I have aches and pains in my bones | | 0 | 1 | 2 | 3 | 4 |
| M6 | I have noticed blood in my stool | | 0 | 1 | 2 | 3 | 4 |
| ITU3 | I have to limit my social activity because of my condition | | 0 | 1 | 2 | 3 | 4 |
| MS8 | I feel overwhelmed by my condition | | 0 | 1 | 2 | 3 | 4 |
| M8 | I isolate myself from others because of my condition | | 0 | 1 | 2 | 3 | 4 |
| M9 | I have difficulty thinking clearly (remembering, concentrating) | | 0 | 1 | 2 | 3 | 4 |
| HI7 | I feel fatigued | | 0 | 1 | 2 | 3 | 4 |

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***At the site of my melanoma surgery:*** | **Not at all** | | **A little bit** | **Some-what** | **Quite**  **a bit** | **Very much** |
|  |
| M10 | I have swelling at my melanoma site | | 0 | 1 | 2 | 3 | 4 |
| M11 | I have swelling as a result of surgery | | 0 | 1 | 2 | 3 | 4 |
| M12 | I am bothered by the amount of swelling | | 0 | 1 | 2 | 3 | 4 |
| M13 | Movement of my swollen area is painful | | 0 | 1 | 2 | 3 | 4 |
| M14 | Swelling keeps me from doing the things I want to do | | 0 | 1 | 2 | 3 | 4 |
| M15 | Swelling keeps me from wearing clothes or shoes I want to wear | | 0 | 1 | 2 | 3 | 4 |
| M16 | I feel numbness at my surgical site | | 0 | 1 | 2 | 3 | 4 |
| M17 | I have good range of movement in my arm or leg | | 0 | 1 | 2 | 3 | 4 |

**APPENDIX G - ECOG PERFORMANCE STATUS**

|  |  |
| --- | --- |
| **Grade** | **Definition** |
| 0 | Able to carry out all normal activity without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to do light work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair. |

Oken M., Creech R, Tormey D, Horton J, Davis T et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group*. Am J Clin Oncol. 1982;5:649-655.

**APPENDIX H - SPECIFICATIONS FOR RADIOLOGICAL INVESTIGATIONS**

**Computed Tomography**

* Spiral (helical) CT should be performed using a 5-mm or finer contiguous reconstruction algorithm to allow accurate assessment of 10 mm lesions (maximum diameter in axial plane).
* To achieve sufficient resolution for detection of visceral metastases, use of a 16-slice device is recommended.
* Scanning of the head (brain), neck, thorax, abdomen and pelvis, including the liver and adrenals, is recommended for all patients with Stage IV disease.
* Scanning of the head is strongly recommended for patients with suspected brain metastases.
* A pelvic scan including inguinal sections is recommended in the setting of inguinofemoral lymphadenopathy.
* Intravenous contrast media should be used unless contraindicated for medical reasons such as allergy. Sufficient quantity of contrast should be used to allow detection and measurement of visceral or nodal metastases; this administration should be consistent on subsequent examinations of a particular subject to allow accurate comparison against prior data.
* As with CM administration, window settings should be consistent for each examination of a particular subject to allow accurate comparison of a subject’s data throughout the study interval.
* All images should be included in the resultant data set, along with operational details such as window settings. Data sets are to be provided to the Sponsor in a portable electronic format for review and analysis.

**Positron Emission Tomography**

* PET scanning is recommended for the initial screening of patients with suspected stage IV disease. Once the diagnosis of visceral metastases is made, periodic CT imaging can be used to evaluate tumour response and progression.
* PET scanning is usually performed with a low-dose CT scan for reference at the PAH.
* The use of PET scanning is contingent upon discussion with an investigator and may be performed at the discretion of the medical investigator based on the clinical circumstances.

**Ultrasound**

* Ultrasound should be performed for patients presenting with new lymphadenopathy without evidence of systemic disease. This can be undertaken with fine needle aspiration of lymph nodes based on their sonographic appearance (if concerning features are present).
* Where possible, ultrasound imaging should be used to determine the maximum diameter for each subcutaneous lesion and for the rapid investigation of lymphadenopathy; lesion diameters on orthogonal axes should be determined.
* All images from each assessment should be included in the subject’s data set, and should include a dimensional calibration data. Image data sets are to be stored within institutional for review and analysis, along with copies of all assessment reports.

**APPENDIX I - DECLARATION OF HELSINKI**

**WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**

**Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

And amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

###### INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

**B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14 The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

**C. ADDITIONAL PRICIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering.

Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

**Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

* Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
* Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

**Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

**APPENDIX J: PATIENT TREATMENT INSTRUCTIONS**

The following instructions describe the recommended method for applying your treatment.

**DPCP Treatment**

Equipment required for DPCP treatment:

* 0.005-5% DPCP in aqueous cream to 100 grams – a hospital prescription in the patient’s name is used as the medication for the DPCP cream.
* Disposable gloves

**DPCP Application**

1. You will be provided with the initial concentration of DPCP in aqueous cream and instructed to apply the cream with gloved hand to the agreed treatment area once weekly. This involves using a small quantity of the cream and applying a thin layer over designated melanoma lesions.
2. On the day of treatment shower or bath as normal using a non-soap cleanser and ensure that the area to be treated is clean and free of visible contaminants.
3. Once the skin is dry don a disposable glove and use this to gently massage a small quantity of the DPCP cream over the treatment area until it is no longer visible.
4. Repeat this procedure for each lesion taking care to only apply the treatment to the designated lesions and treatment area.
5. A surrounding area of unaffected skin measuring 0.5cm should also be treated as described by the clinician during your appointment.
6. The DPCP cream should remain on the skin and not be washed off until 24-48 hours following application.
7. A non-soap cleanser is used. Simple emollients can be applied to the treatment area after the 24-48 hour treatment application period.
8. If necessary, a simple dressing can then be applied to the treated area as instructed by a nurse or clinician during your previous review.
9. This process is continued at regular intervals, usually once per week and your progress and any changes will be reviewed during the next outpatient appointment.
10. You will have been provided with a simple wound-care take-home dressing kit for managing minor reactions. Simple wound care incorporating saline bathes, simple emollients and clean dressings should be used as needed.

**Take-home Dressing Kit**

* Disposable gloves
* Non-soap cleanser
* Topical emollient
* White soft paraffin or equivalent
* Jelonet or equivalent paraffin gauze
* Dressing packs — Melolin/Combine, Micropore and Tubigrip
* Emergency contact number for Dermatology Registrar on-call

**Imiquimod Treatment**

Equipment required for imiquimod treatment phase:

* 5% Imiquimod – a hospital prescription in the patient’s name is used as the medication for the imiquimod cream.
* Disposable gloves

**Imiquimod** **Application**

1. You will be provided with the 5% imiquimod cream and instructed to apply the cream with gloved hand to the agreed treatment area 5 days per week (unless otherwise specified). This involves using a small quantity of the cream and applying a thin layer over designated melanoma lesions.
2. On the days of treatment shower or bath as normal using a non-soap cleanser and ensure that the area to be treated is clean and free of visible contaminants.
3. Once the skin is dry, don a disposable glove and use this to gently massage a small quantity of the imquimod cream over the treatment area until it is no longer visible.
4. Repeat this procedure for each lesion taking care to only apply the treatment to the designated lesions and treatment area.
5. A surrounding area of unaffected skin measuring 0.5cm should also be treated as described by the clinician during your appointment.
6. The imiquimod cream is to remain on the skin overnight and not to be washed off until after 8 hours following application. It is recommended the patient have 2 ‘rest’ days per week where no treatment is applied and regular skin cares are continued.
7. A non-soap cleanser should be used to clean the treatment area and simple emollients can be applied to the site after the 8 hour treatment period.
8. If necessary, a simple dressing can then be applied to the treated area as instructed by a nurse or clinician during your previous review.
9. This process is continued at regular intervals, usually once per week and your progress and any changes will be reviewed during the next outpatient appointment.
10. You will have been provided with a simple wound-care take-home dressing kit for managing minor reactions. Simple wound care incorporating saline bathes, simple emollients and clean dressings should be used as needed.

**Take-home Dressing Kit**

* Disposable gloves
* Non-soap cleanser
* Topical emollient
* White soft paraffin or equivalent
* Jelonet or equivalent paraffin gauze
* Dressing packs — Melolin/Combine, Micropore and Tubigrip
* Emergency contact number for Dermatology Registrar on-call